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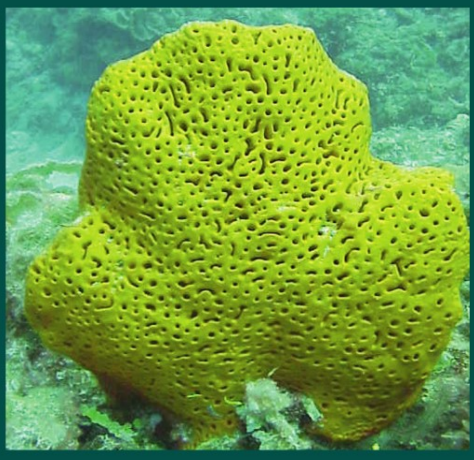
Progress in the Chemistry of Organic Natural Products
91

Gordon W. Gribble

Naturally Occurring Organohalogen Compounds – A Comprehensive Update



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Naturally Occurring Organohalogen Compounds – A Comprehensive Update

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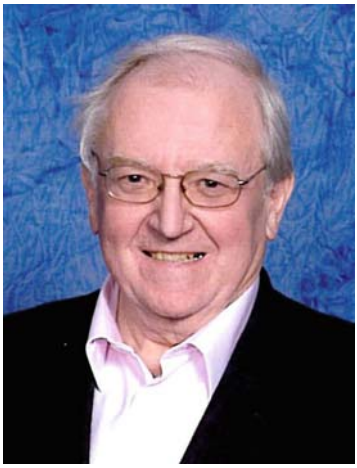
Dedicated to the memory of my mother, Jane Adena Gribble, 1917–2007.

Brief CV – Gordon W. Gribble



Gordon W. Gribble is a native of San Francisco, California, and completed his undergraduate education at the University of California at Berkeley, in 1963. He earned a Ph.D. in organic chemistry at the University of Oregon, in 1967. Following a Postdoctoral Fellowship at the University of California, Los Angeles, he joined the faculty of Dartmouth College, in 1968, where has been Full Professor of Chemistry since 1980. He served as Department Chair from 1988 to 1991. In 2005, he was named to the newly endowed Chair as "The Dartmouth Professor of Chemistry." Dr. Gribble has published 320 papers in natural product synthesis, synthetic methodology, heterocyclic chemistry, natural organohalogen compounds, and synthetic triterpenoids. Since 1995, he has coedited the annual series *Progress in Heterocyclic Chemistry*, and the 2nd edition of *Palladium in Heterocyclic Chemistry*, coauthored with Jack Li, was published in 2008. Dr. Gribble has had a long-standing interest in organic chemical toxicity, chemical carcinogenesis, environmental chemistry, and naturally occurring organohalogen compounds. As an award winning home winemaker for the past 30 years, he has a strong interest in the chemistry of wine and winemaking.

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Contents

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1 Introduction

The previous survey documented 2,448 naturally occurring organohalogen compounds, both biogenic and abiotic (*1*). In the intervening years an additional 2,266 compounds have been identified from a myriad of natural sources, which include chlorine-, bromine-, iodine-, and fluorine-containing organic compounds. The organization herein follows that used earlier so as to provide continuity. Numerous reviews covering natural organohalogens, both very general and highly specialized, have appeared since 1994 (*2–72*). Others will be cited in the appropriate section.

While the furor over "chlorine" has abated to some extent, there remains an underlying "chlorophobia" – an irrational fear of chlorine and organochlorine compounds. It is hoped that the present review along with the references cited herein will help to balance the need to regulate persistent organic organohalogen pollutants (e.g., "POPs") against the clearly demonstrated important role of organohalogens – both natural and anthropogenic – in our society and in the environment.

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2 Origins

The ubiquitous abundance of the four halides (Table 2.1) has resulted in the evolution of organohalogens in all regions of our earth, both biogenic and abiotic (*73–77*).

2.1 Marine Environment

As will be seen, most naturally occurring organohalogen compounds are unique to individual marine organisms and are not widely dispersed in the environment. However, the more volatile haloalkanes, which have several marine sources, are important contributors to the atmosphere. The salinity of Earth's early ocean was probably twice that of the present value (*77*), and sea-salt spray is the major atmospheric source of reactive halogens (Cl_2, Br_2, BrCl, HOCl, HOBr) that are subsequently converted to chlorine oxide and bromine oxide. This atmosphere chemistry is exceedingly complex and beyond the scope of this review (*78–85*). The formation of reactive chlorine and bromine in sea-salt aerosols, for which there is compelling evidence, may explain the low ozone concentrations that are often observed above the oceans (*86–94*). The importance of bromine oxide to both tropospheric and stratospheric bromine-ozone chemistry has been stressed (*95–100*). Not surprising is the observation of similar bromine oxide-ozone interactions over the Dead Sea (*101*), and both bromine oxide and chlorine oxide chemical reactions with ozone over the Great Salt Lake (*102*), with concomitant ozone depletion in both areas. Although less studied, iodine in the marine boundary layer is well known and can involve the photolysis of marine biogenic organoiodine compounds (*103, 104*). Moreover, it appears that the global aerosol load has a major contribution from marine organohalogen aerosols with the inevitable formation of reactive halogens (*105*).

As abundantly illustrated in the first survey, marine organisms produce and sequester an enormous number of organohalogens. It is estimated that more than 15,000 marine natural products of all types have been described (*106*). This author

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Table 2.1 Distribution of halides/mg kg^{-1} in the environment

Halide	Oceans (*73, 74*)	Sedimentary rocks (*66, 74*)	Fungi (*75*)	Wood pulp (*218*)	Plants (*74, 76*)
Cl^-	19,000	10–320		70–2100	200–10,000
Br^-	65	1.6–3	100		
I^-	0.05	0.3			
F^-	1.4	270–740			

has determined from the published literature (1998–2005) that 15–20% of all newly discovered marine natural products are organohalogens (*107*). Given the salinity of the world's oceans, which occupy more than 70% of the earth's surface and over 90% of the volume of the crust (*108*), it is not surprising that organohalogens are plentiful in the 500,000 estimated species of marine organisms spread over 30 phyla (*109*). This figure includes 100,000 marine invertebrates (*110*), 80,000 molluscs (*111*), 15,000 sponges (*112*), and 4,000 species of bryozoa (moss animals) (*113*).

Perhaps due to their accessibility (and visibility!), sponges – the simplest and earliest multicellular organisms that evolved about one billion years ago (*114*) – have been widely examined for their chemical content, and new sponge species are still being discovered (*115*). However, to acquire significant quantities of biologically active sponge metabolites, it is necessary to develop "farming" methods (*116, 117*) or to employ cell culture and gene cluster tactics (*118*). A major sponge research area has been to explore the now well-established sponge-bacteria symbiosis (*119–123*). Such studies of sponges include *Aplysina cavernicola* (*124–126*), *Aplysina aerophoba* (*126–128*), *Theonella swinhoei* (*128*), *Rhopaloeides odorabile* (*129, 130*), and *Xestospongia muta* and *X. testudinaria* (*131*), all of which have associated active bacterial communities that may produce the metabolite.

Even older than sponges are cyanobacteria (blue-green algae, Fig. 2.1), which date back 2.8 billion years (*132*). As will be seen in Chap. 3 (Occurrence), the 2,000 species of cyanobacteria produce a multitude of organohalogen and other metabolites (*133–135*), which are often highly toxic to humans (*136–138*). The cyanobacterium *Oscillatoria spongeliae* is a common symbiont of the sponges *Dysidea herbacea* and *Dysidea granulosa* (Fig. 2.2) (*139–144*), but the actual producer of the organohalogen metabolites remains uncertain.

As will be presented in Chap. 3 (Occurrence), other marine organisms such as molluscs (*145*), sea hares (*146*), mussels (*147*), bryozoans (*148*), tunicates, and soft corals (*149*) produce a myriad of organohalogen metabolites. Interestingly, symbiotic bacteria can also be associated with these organisms (*123*). Marine phytoplankton (*150*) and macroalgae (*151, 152*) are rich sources of organohalogens, particularly volatile haloalkanes. Two relatively new areas for ocean exploration are marine bacteria and fungi (*108, 153–155, 178*). Finally, as more remote and deeper regions of the oceans are explored, new marine species are being discovered; for example, the new genus, *Osedax*, of marine worms (*156*).

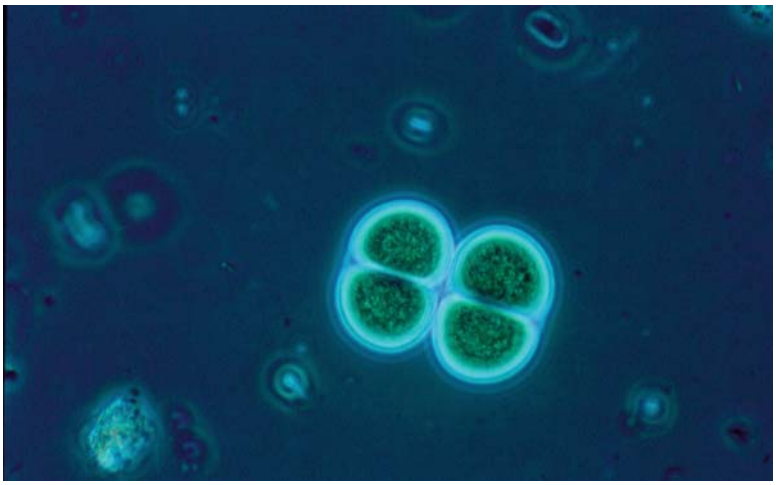

Fig. 2.1 *Chroococcus turgidus*, a species of cyanobacteria, which are prolific producers of organohalogens (Photo: A. D. Wright)

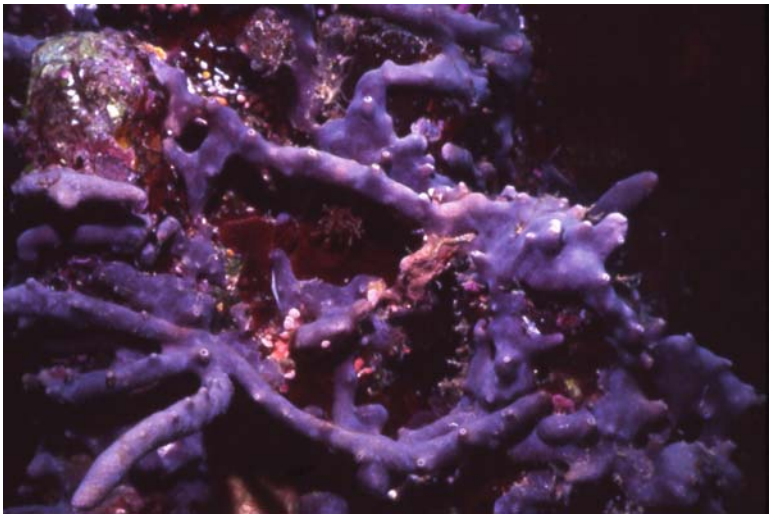

Fig. 2.2 *Dysidea granulosa*, a cyanobacterium containing sponge (Photo: F. J. Schmitz)

2.2 Terrestrial Environment

Organohalogens are present in many terrestrial environments: sediments, soils, plants, fungi, lichen, volcanoes, biomass combustion, bacteria, insects, and higher organisms. The high concentration and dispersal of chloride in minerals, soils,

and plants results in a multitude of both biogenic and abiotic organochlorine compounds in these terrestrial environments (*37, 157–167*). Humic forest lake sediments (*168*) and peatlands (*169–171*) contain large quantities of organohalogens, including organoiodines that form during humification in peatlands (*171*). Peatlands that comprise 2% of the earth's continental surface are a major reservoir of organically bound iodine in the terrestrial environment (*171*), accumulating 280–1,000 million tons of organochlorines during the postglacial period (*169*). Likewise, 91% of the bromine found in peat is organically bound (*170*).

X-ray absorption spectroscopy has revealed the formation of organochlorine compounds from chloride and chloroperoxidase in "weathering" plant material (*172–174*). Moreover, this technique has uncovered the bromide-to-organobromine conversion in environmental samples (*174*). In addition to chloroperoxidase mediated chlorination, the abiotic chlorination in soils and sediments involving the alkylation of halides during Fe(III) oxidation of natural organic phenols in soils and sediments has been discovered (*175–177*).

Other terrestrial organisms frequently contain organohalogens. Lichens dating back 400 million years are a rich source of chlorinated phenolics (*1, 178, 179*). The even older fungi, which date back one billion years (*180*), perhaps number 1.5 million species of which only 70,000 are described (*181*). Basidiomycetes fungi are ubiquitous producers of organohalogens (*182*), and fungi, bacteria, and lichen engage in symbiosis (*183, 184*). Tundra fungi under snow-cover (*185*) and insect pathogenic fungi (*186*) are of recent interest and undoubtedly will yield novel natural products. Slime molds (myxomycetes) (*187*) and bryophytes (liverworts, mosses, hornworts) (*188, 189*) possess a rich assortment of natural products, including organohalogens, but terrestrial bacteria remain king of the biosynthesizers (*190*).

Volcanoes have been comparatively little studied for their chemical content. However, a few studies have provided some astonishing results as will be described later in Chap. 3 (Occurrence) (*1*). The origin of volcanic organohalogens may simply be a result of the halides present in sediments and minerals reacting with organic matter within the volcano at the high temperatures and pressures during eruptions and outgassing. The four halides are known to be entombed in rocks and sediments (*190–199*), and also in the ocean mantle (*200, 201*). Volcanic emissions invariably contain massive quantities of HCl and HF (*1*). Recent studies of Mt. Etna (*202–205*), Mt. Pinatubo (*206*), Soufriere Hills (*207, 208*), Popocatépetl (*209*), Villarrica (*210*), Satsuma-Iwojima (*211*), Sakurajima (*212*), and Laki (*213*) confirm their ubiquity of gaseous HCl and HF. Reactive bromine (BrO) and iodine emissions are also reported (*206, 208, 211, 212*). The largest known point source of both HCl and HF is the 1997 Mt. Etna eruption, with emission rates of 8.6 and 2.2 kg s^{-1}, respectively (*203*). Newer detection techniques such as solar occultation spectroscopy (*203*) and remote infrared spectroscopy (*214*) will obviously lessen the hazards of sampling. The role that these halogens play in depleting ozone has been discussed (*215*).

Only two studies of organohalogen volcanic gases were reported since the last survey, those of Vulcano (Fig. 2.3) (*216*) and Kuju, Satsuma-Iwojima, Mt. Etna,

Fig. 2.3 A volcano on Stromboli, an island in the Tyrrhenian Sea off the north coast of Sicily (Photo: F. M. Schwandner)

and Vulcano (*217*). These results will be described in Chap. 3 (Occurrence). The mysterious chemistry that occurs in volcanoes has been addressed with regard both to halogen (*218*) and hydrocarbon formation (*219*). An interesting personal account of the Kamchatka hot springs, which are a rich source of organohalogens (*1, 218*), has appeared (*220*). A novel volcanic source of HCl stems from the heating and evaporation of seawater by molten lava from the Hawaiian volcano Kilauea, which has been in continuous eruption since 1986, leading to highly acidic plumes ("acid rain") estimated at 3–30 tons of HCl daily (*221*).

A related pyrolytic source of HCl, HBr, and low molecular weight haloalkanes is biomass combustion. Human controlled fires may date back 790,000 years (*222*), but natural forest and grass fires presumably date from the time vegetation first appeared on earth (350–400 million years ago), and continue unabated today (*223–225*). Recent massive fires include those in Indonesia 1997 (*226*), Northern Alberta 1998 (*227*), Alaska 2004 (*228*), and Russia 2002–2005 (*229*). In Canada alone some 10,000 forest fires occur annually (*230*), and forest fires have plagued the Western United States for decades (*225, 231*). The 1988 Yellowstone fire, which burned more than 3 months, consumed 600,000 ha (*225*). Interestingly, a model study revealed that heating a mixture of methane, hydrogen chloride, and oxygen forms haloalkanes, chlorinated aromatics, dioxins, and many other organochlorines (*232*), indicating the plausibility of finding such compounds in volcanic

plumes and biomass combustion fires. Cigarette smoke contains 30–66 mg kg^{-1} of unidentified organochlorines (*233*).

2.3 Extraterrestrial Environment

Although both HCl (*234*) and HF (*235*) are present in interstellar space, it came as a stunning surprise when meteorites were found to contain organohalogen compounds (*236*). The several earlier claims of meteoritic organochlorines were only cautiously advanced and perhaps even viewed with skepticism (*237–240*). In various forms, chlorine has been detected in and around Io, Jupiter's largest moon (*241–245*).

3 Occurrence

3.1 Simple Alkanes

No other class of natural organohalogens has the wide diversity of sources, as do the simple halokanes – marine, terrestrial biogenic, terrestrial abiotic, biomass combustion, and volcanoes. However, since the previous survey, only a few newly discovered natural simple halogenated alkanes have been reported.

3.1.1 Chloromethane

Chloromethane is the most abundant organohalogen – anthropogenic or natural – in the atmosphere. The myriad natural sources of CH_3Cl dwarf the anthropogenic contribution (Table 3.1). Subsequent to the previous survey (*1*) a number of new natural sources of CH_3Cl have been identified, and other reviews have appeared (*42, 246, 247*).

3.1.1.1 Marine

Laboratory cultures of marine phytoplankton (*Phaeodactylum tricornutum*, *Phaeocystis* sp., *Thalassiosira weissflogii*, *Chaetoceros calcitrans*, *Isochrysis* sp., *Porphyridium* sp., *Synechococcus* sp., *Tetraselmis* sp., *Prorocentrum* sp., and *Emiliana huxleyi*) produce CH_3Cl, but in relatively insignificant amounts (*248, 249*). Similarly, low production of CH_3Cl was observed from several macroalgae (*Fucus vesticulosus*, *Enteromorpha compressa*, *Ulva lactuca*, and *Corallina officinalis*) but not for two others (*250*). Another laboratory study of micro- and macroalgae failed to detect CH_3Cl in 58 species, although CH_3Br and CH_3I were observed (*251*). An extensive study of 30 species of polar macroalgae revealed the release of significant amounts of CH_3Cl in only *Gigartina skottsbergii* and *Gymnogongrus antarcticus* (*152*). In contrast to these studies, ten species of salt marsh (notably

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Table 3.1 Sources and estimated amounts[a,b] of chloromethane/Gg y^{-1}

Source	Best estimate	Range[c]	References
Biomass combustion	910	650–1,120	(*285, 286*)
Biomass combustion	611 ± 38	–	(*295*)
Biomass combustion	515	226–904	(*283*)
Savanna fires	420	–	(*285*)
Asian tropical plants[c]	910	820–8,200	(*268*)
Oceanic	650	325–1,300	(*253*)
Oceanic	–	200–400	(*300*)
Salt marshes	170	65–440	(*252*)
Wood rotting fungi	160	43–470	(*271, 295*)
Industrial incineration	162	–	(*296*)
Coal combustion	105	5-205	(*287*)
Conifer forest floor	84.7	38.7–130.8	(*267*)
Leaf litter	–	75–2,500	(*281*)
Fossil fuel combustion	75	5–145	(*296*)
Wetlands	48	6–270	(*270*)
Waste incineration	32	15–75	(*296*)
Other industry	7	–	(*296*)
Peatlands	5.5	0.9–43.3	(*267*)
Macroalgae	0.14	–	(*250*)
Volcanoes	0.074 ± 0.045	–	(*216*)
Volcanoes	0.012	–	(*217*)

[a]1 Gg (gigagram) = 10^9 g ≅ 1,000 tons

[b]For excellent compilations of these data and discussions of the missing CH_3Cl, see (*279, 280, 287, 295, 297*)

[c]Some of these ranges (uncertainties) were taken from those cited in (*280*)

Salicornia sp., *Batis maritima*, and *Frankenia grandifolia*) produce large amounts of CH_3Cl, perhaps constituting the largest natural terrestrial source (Table 3.1) (*252*).

Chloromethane has a strong atmospheric presence, particularly over the oceans and ice packs (*253–259*). A new technique has been reported for the determination of CH_3Cl in ice cores (*260*). The measured CH_3Cl concentration of 528 ± 26 pptv in pre-industrial and/or early industrial ice cores is similar both to present day concentrations in the remote atmosphere and to concentrations measured from ice cores dating back 300 years. These results support previous conclusions that the CH_3Cl concentration has remained relatively constant over the past few hundred years. Interesting is the finding that a strong source of CH_3Cl is warm coastal areas, such as tropical islands (*261*).

3.1.1.2 Terrestrial Biogenic

Both new and preexisting terrestrial sources of CH_3Cl have been reported since the previous survey. Rice paddies (*262–266*), peatlands (Fig. 3.1) (*267*), tropical plants (*268*), shrublands (*269*), wetlands (*270*), woodrot fungi (*271, 272*), root fungi (*273*), forest leaf litter (*274*), and coastal wetlands (*275*) are significant and, in some cases, major sources of atmospheric CH_3Cl (Table 3.1). Higher plants such as potato

Fig. 3.1 A peatbog in Ireland that is a rich source of natural organohalogens (Photo: H. Falk)

tubers (*Solanum tuberosum*) (*276, 277*) and the saltwort (*Batis maritima*) (*277*) (also mentioned in Sect. 3.1.1.1) yield CH_3Cl, as do other terrestrial plants (*278–280*). It is quite possible that the "missing" CH_3Cl source may have its origin in tropical green plants (*278, 280*).

3.1.1.3 Terrestrial Abiotic

It is proposed that the CH_3Cl missing source (vide supra) may be the abiotic methylation of chloride in plants and soils (*280, 281*). This methylation by plant pectin in senescent and dead leaves efficiently produces CH_3Cl and shows a positive correlation with temperature. Plants studied include Norway maple, horse chestnut, cherry, oak, beech, a *Eucalyptus* sp., and a salt marsh (*Batis maritima*) (*281*). This important study complements that of *Myneni* (*172–174*) and *Keppler* et al. (*175, 176*), cited earlier, and *Öberg* (*298, 299*).

3.1.1.4 Biomass Combustion

Biomass combustion is a major global source and may even be the major source of atmospheric CH_3Cl (*223, 282–288*). These studies indicate that CH_3Cl production is maximized in low intensity fires, from incomplete combustion, and by increased chloride concentration. It is estimated that six billion tons of biomass are consumed

by fire per year (*282*). The actual mechanism of CH_3Cl formation during biomass combustion may be similar to the abiotic formation of CH_3Cl in plants (*281*).

3.1.1.5 Volcanic Emissions

As described previously, volcanoes liberate a myriad of organic chemicals including CH_3Cl (*1*) and two recent studies confirm the earlier findings (*216, 217*). Thus, Vulcano, Mt. Etna, Kuju, and Satsuma-Iwojima all emit CH_3Cl from both the fumaroles and the lava gas.

3.1.1.6 Biogenesis

In addition to the abiotic mechanism suggested for CH_3Cl formation (vide supra), there is compelling evidence for biosynthetic pathways (*289–292*). The salt marsh plant *Batis maritima* contains the enzyme methyl chloride transferase that catalyzes the synthesis of CH_3Cl from *S*-adenosine-L-methionine and chloride (*291*). This protein has been purified and expressed in *E. coli*, and seems to be present in other organisms such as white rot fungi (*Phellinus pomaceus*), red algae (*Endocladia muricata*), and the ice plant (*Mesembryanthemum crystallium*), each of which is a known CH_3Cl producer (*291, 292*).

A vexing factor in understanding CH_3Cl sources is the observation that the bacterial conversion of CH_3Br to CH_3Cl with chloride has been reported in a biotranshalogenation S_N2 reaction (*293*). Since bromide is a better nucleophile than chloride in aqueous media (*294*), the reverse biotranshalogenation reaction is plausible.

3.1.2 Dichloromethane

Dichloromethane is a widely used industrial and academic laboratory solvent. New natural sources are recognized subsequent to the previous review, although the amounts are small compared to industrial emissions (Table 3.2). These include estimates of biomass combustion (*256, 283, 286*), oceanic sources (*250, 253, 256, 275, 302*), wetlands (*275*), and volcanoes (*216, 217*). Macroalgae (*Desmarestia*

Table 3.2 Sources and estimated amounts[a,b] of dichloromethane/Gg y^{-1}

Source	Best estimate	Range[c]	References
Industry[c]	650	–	(*259*)
Biomass combustion	60	50–70	(*256*)
Oceanic	190	100–290	(*256*)
Macroalgae	0.32	–	(*250*)
Volcanoes	0.021 ± 0.013	–	(*216*)

[a]The latest estimates are provided
[b]See (*253, 283, 286, 287, 301*)
[c]See also (*301*)

Table 3.3 Sources and estimated amounts[a] of trichloromethane/Gg y^{-1}

Source	Best estimate	Range	References
Oceanic	360	210–510	(*256*)
Soil/fungi	235	110–450	(*256, 259*)
Termites	100	10–100	(*327*)
Peatlands	4.7	0.1–151.9	(*267*)
Biomass combustion	2	0.9–4	(*283*)
Rice paddies	23	7.7–50	(*304*)
Volcanoes	0.095	0.067–0.12	(*216*)
Microalgae	23	7.9–49	(*304*)
Macroalgae (non-kelp)	0.25	–	(*250*)
Macroalgae (non-kelp)	10	–	(*308*)
Macroalgae (non-kelp)	0.06	–	(*306*)
Macroalgae (kelp)	0.17	–	(*306*)
Macroalgae	0.84	0.009–3.1	(*304*)
Industry	66	40–100	(*256, 259*)

[a]See also (*253, 286, 287, 303–305*)

antarctica, *Lambia antarctica*, *Laminaria saccharina*, and *Neuroglossum ligulatum*) release substantial amounts of CH_2Cl_2, surpassing bromoform in some cases (*302*). Interestingly, CH_2Cl_2 forms when CH_4 and HCl are heated in the presence of oxygen (*232*).

3.1.3 Trichloromethane

Trichloromethane (chloroform) is a widely used industrial and academic laboratory solvent. In contrast to CH_2Cl_2, $CHCl_3$ has a multitude of natural sources, both biogenic and abiotic (*1*), and several excellent reviews are available (*303–305*). Noteworthy is the estimate that greater than 90% of atmospheric $CHCl_3$ is of natural origin (Table 3.3).

3.1.3.1 Marine

Trichloromethane is produced by brown seaweeds (*Laminaria digitata*, *Laminaria saccharina*, *Fucus serratus*, *Pelvetia canalicuta*, *Ascophyllum nodosum*), red seaweeds (*Gigartina stellata*, *Corallina officinalis*, *Polysiphonia lanosa*), and green seaweeds (*Ulva lactuca*, *Enteromorpha* sp., *Cladophora albida*) (*306*). Similarly, the macroalga *Eucheuma denticulatum*, which is cultivated and harvested on a large scale for carrageenan production, produces $CHCl_3$ (*307*), as do *Hypnea spinella*, *Falkenbergia hillebrandii*, and *Gracilara cornea* along with seven indigenous macroalgae inhabiting a rock pool (*308*). These studies show increased $CHCl_3$ production with increased light intensity, presumably when photosynthesis is at a maximum. Trichloromethane is also produced by the brown alga *Fucus vesiculosus*, the green algae *Cladophora glomerata*, *Enteromorpha ahlneriana*,

Enteromorpha flexuosa, and *Enteromorpha intestinalis*, and the diatom *Pleurosira laevis* (*309*). Other studies observe $CHCl_3$ in *Fucus serratus*, *Fucus vesiculosis*, *Corallina officinalis*, *Cladophora pellucida*, and *Ulva lactuca* (*250*), and *Desmarestia antarctica*, *Lambia antarctica*, *Laminaria saccharina*, *Neuroglossum ligulatum* (*302*). The yields of $CHCl_3$ often vary widely in these studies. Microalgae are also emitters of $CHCl_3$, as first found with laboratory cultures of *Porphyridium purpureum* and *Dunaliella tertiolecta* (*310, 311*). Oceanic atmospheric trichloromethane measurements provide the estimate of 320–360 Gg y^{-1} for ocean emissions (*253, 256, 259, 287, 312*) (Table 3.3). A new source of $CHCl_3$ arises from the sediments of salt lakes that harbor halobacteria capable of biosynthesizing volatile chloroalkanes (*312*).

3.1.3.2 Terrestrial Biogenic

Subsequent to the seminal work of *Asplund* and *Grimvall* (*313*), it is now well established that $CHCl_3$, trichloroacetic acid, and other simple organochlorides are naturally produced in soil, perhaps involving both biogenic and abiotic pathways (*278, 303–305, 314–323*). A study with $Na^{37}Cl$ demonstrated isotopic enrichment in the $CHCl_3$ (*316*), and numerous worldwide remote forest sites (spruce, beech, Douglas fir, grasslands) all generate trichloromethane, a process believed to involve a microbial enzymatic origin (*317–322*). One particular spruce forest was found to liberate $CHCl_3$ at a rate of 12 μg m^{-2} day^{-1} (*319*). Another forest site with a rich humic layer emits 24 μg m^{-2} day^{-1} (*321*). As will be presented in later sections, $CHCl_3$ formation is believed to involve chloroperoxidase-mediated chlorination of phenolic structures in soil humic acid, followed by ring rupture, and degradation to afford both $CHCl_3$ and trichloroacetic acid, along with other organic products (*317, 324*). The laboratory chlorination of resorcinol yielding $CHCl_3$ is an undergraduate experiment (*325*).

Other terrestrial biogenic sources of $CHCl_3$ exist. The fungi *Mycena metata*, *Peniophora pseudopini*, and *Caldariomyces fumago* produce 0.07–70 μg L^{-1} culture per day for the latter fungus and 0.7–40 ng L^{-1} culture per day for the first two fungi. The fungi *Agaricus arvensis*, *Bjerkandera* sp. BOS55, and *Phellinus pini* produce $CHCl_3$, but only in incidental cases (*326*). Nevertheless, the authors of this latter study conclude that fungi are important sources of soil air $CHCl_3$. Coastal wetlands and grassland areas in Tasmania produce $CHCl_3$, and a major contributor is the eucalypt soil-plant material site, probably due to the high chloride content of eucalyptus leaves (*275*). Irish peatlands are significant sources of $CHCl_3$ (*267*), as is leaf litter from aspen and willow trees (*274*). It is estimated that termites worldwide produce less than 15% (<100 Gg y^{-1}) of the atmospheric $CHCl_3$. Six termite species (*Coptotermes lacteus*, *Amitermes laurensis*, *Nasutitermes magnus*, *Nasutitermes triodiae*, *Drepanotermes perniger*, *Tumulitermes pastinator*) produce $CHCl_3$ within their mounds, and in the mound of one species, *Coptotermes lacteus*, the $CHCl_3$ concentration is 1,000 times higher than the ambient concentration (*327*).

3.1.3.3 Biomass Combustion

The combustion of biomass, which invariably contains carbon and chloride, produces $CHCl_3$, although the amount is much less than that recorded for CH_3Cl and CH_2Cl_2 (*283, 286*) and is a minor emission source of $CHCl_3$ (<1%) (*303–305*) (Table 3.3). The high temperature (700°C) reaction of methane, HCl, and oxygen furnishes trichloromethane (*232*).

3.1.3.4 Volcanic Emissions

Following the pioneering studies of Isidorov (*218*), other investigations find $CHCl_3$ in several Italian (Vulcano, Mt. Etna) and Japan (Kuju, Satsuma-Iwojima) volcanoes (*216, 217*), but the amounts are relatively small (*216*).

3.1.4 Tetrachloromethane (Carbon Tetrachloride)

Tetrachloromethane (carbon tetrachloride, CCl_4) is a toxic industrial chemical with several natural sources (*1*). The solfataras and hydrothermal vents of Kamchatka (*328*) and the thermal springs in Ashkhabad (Turkmenia) and Tskhaltubo (Georgia) (*329*) emit CCl_4. The carbonaceous black shales from Central Asia contain CCl_4 (*330*), consistent with earlier studies of similar abiotic sources (*218*). Volcanic emissions contain CCl_4 (*216, 217*), and one study determined a global volcanic emission rate of 0.00341 Gg y^{-1} (*216*). A larger global emission rate is estimated for biomass combustion of 3 Gg y^{-1} on the average (*283*). Thermolysis of a mixture of CH_4, HCl, and O_2 also produces CCl_4 (*232*). Forest soil has been reported to emit CCl_4 at low levels or not at all (*274, 278, 318, 319*), but it has been suggested that the presence of CCl_4 in these studies "is probably due to an equilibrium with atmospheric concentrations of anthropogenic origin" (*278*). The commercially important seaweed *Eucheuma denticulatum*, which is used to make the food thickener carrageenan, emits CCl_4 (*307*). Other studies of marine algae and salt lakes are inconclusive with regard to CCl_4 (*308, 312, 392*).

3.1.5 Bromomethane

Unlike other simple haloalkanes, bromomethane (methyl bromide, CH_3Br) has very large natural and anthropogenic sources. Indeed, CH_3Br is an outstanding pesticide (e.g., soil fumigant) for which there are no suitable alternatives (*331–334*). Although CH_3Br is now banned in the United States because of its presumed toxicity (*335*), it is still used by some farmers for selective applications (*334*).

Table 3.4 Distribution of halides/mg kg^{-1} in the environment

Halide	Oceans (*73, 74*)	Sedimentary rocks (*66, 74*)	Fungi (*75*)	Wood pulp (*218*)	Plants (*74, 76*)
Cl^-	19,000	10–320		70–2,100	200–10,000
Br^-		65	1.6–3	100	
I^-		0.05	0.3		
F^-		1.4	270–740		

Table 3.5 Sources and estimated amounts[a] of bromomethane/Gg y^{-1}

Source	Best estimate	Range	References
Oceanic	60	–	(*531*)
Biomass burning	20	10–50	(*285*)
Salt marshes	14	7–29	(*252*)
Macroalgae	0.056	–	(*250*)
Rice paddies	–	0.5–0.9	(*266*)
Litter decomposition (fungi)	1.7	0.5–5.2	(*350*)
Wetlands	4.6	–	(*270*)
Peatlands	0.9	0.1–3.3	(*267*)
Automobiles	1.5	–	(*352*)
Creosote bush (*Larrea tridentata*)	0.2	–	(*269*)
Brassica plants[b]	7	–	(*347*)
Fumigation	47	–	(*42*)
Phytoplankton	–	2.6–47.0	(*340*)
Volcanoes	0.00098 ± 0.00047		(*216*)

[a]See also (*288, 353*)
[b]Rapeseed and cabbage

In previous years some 20,000 metric tons of CH_3Br was used annually in the US as a soil pesticide (*331*).

Despite the low abundance of bromide relative to chloride in sediments, soil, and the ocean (Table 3.4), the ease with which nature can manipulate bromide (reduction potentials: $E^\circ = 1.09$ V for Br^- vs. 1.36 V for Cl^-, 0.54 V for I^-, and 2.87 V for F^- (*2671*)) results in a multitude of natural organobromine compounds especially in the oceans (*41, 45*) (Table 3.5).

3.1.5.1 Marine

Perhaps because of its volatility (boiling point, 4°C), CH_3Br has not been identified in marine organisms (i.e., algae) as frequently as bromoform and other bromoalkanes. Nevertheless, CH_3Br is released from both Antarctic and Arctic cultivated macroalgae, including brown algae, red algae, and green algae (*152, 336–338*). Several macroalgae from the north coast of Norfolk, England, yield CH_3Br (*250*). Methyl bromide is also found in cultures of marine microalgae (*248, 249, 251, 311, 339, 340*). The several reported atmospheric measurements of CH_3Br are consistent with oceanic sources (*252, 254, 255, 259, 341–346*). Methyl bromide originates from the vegetation zones of coastal salt marshes (*252*), and CH_3Br is

supersaturated over part of the northeast Atlantic due in large measure to the phytoplankton *Phaeocystis* (*343*).

3.1.5.2 Terrestrial Biogenic

In addition to the emission of CH_3Br from coastal salt marshes (vide supra) (*252*), which could be considered a terrestrial source, shrublands and wetlands near coastal sites also emit CH_3Br (*269, 270, 275*). Extraordinary is the observation that higher plants (e.g., rapeseed, mustard, cabbage, broccoli, turnip, radish, alyssum, etc.) produce significant amounts of CH_3Br from natural soil bromide, estimated to be 6.6 Gg y^{-1} CH_3Br from rapeseed worldwide (*347*). It might be noted that plants are also a sink for both CH_3Br (*348*) and bromide (*347, 349*). Peatlands are a source of CH_3Br (*267*) as are rice paddies (*262–266*) and fungi (*273*). Wood-rotting fungi are another source of CH_3Br, but of low significance (*350*) (Table 3.5).

3.1.5.3 Terrestrial Abiotic

The abiotic bromination involving the alkylation of bromide during Fe(III) oxidation of natural organic phenols in organic matter is a pathway to CH_3Br that has been demonstrated in the laboratory (*175*).

3.1.5.4 Biomass Combustion

Where there is halide, carbon, oxygen, and fire there will be organohalogens. Such is the case with bromide giving rise to CH_3Br in forest fires (*223, 284, 285, 288*). Indeed, vegetation fires are a major source of CH_3Br (*285*).

3.1.5.5 Volcanic Emissions

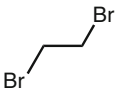
Studies of volcanoes (Vulcano, Mt. Etna, Kuju, and Satsuma-Iwojima) have found CH_3Br in the fumarolic emissions (*216, 217*).

3.1.6 Other Simple Bromoalkanes

3.1.6.1 Marine

Marine algae biosynthesize and emit several other simple bromoalkanes, including dibromomethane (CH_2Br_2), tribromomethane (bromoform, $CHBr_3$), bromoethane

(CH_3CH_2Br), and 1,2-dibromoethane ($BrCH_2CH_2Br$) (*1*). Indeed, $CHBr_3$ is a promiscuous marine metabolite and is invariably produced by both macro- and microalgae (*152, 250, 302, 306–309, 336–339, 342, 344–346, 354–370*), and is the major contributor of organic bromine to the atmosphere. Bromoform may supply reactive bromine (e.g., BrO) to the upper troposphere and lower stratosphere for reaction with and destruction of ozone (*371, 372*). Macroalgae may contribute 70% of the world's $CHBr_3$ (*373*). An estimate of a global emission rate of 220 Gg y^{-1} (*50–390*) is proposed for $CHBr_3$ (*373*). Studies of brown, red, and green macroalgae from the polar region show that $CHBr_3$ is released by all 30 species examined (*152*). Dibromomethane frequently accompanies $CHBr_3$ in marine algae emissions, although usually with lower release rates (*152, 250, 302, 306, 308, 309, 336, 337, 339, 342, 345, 346, 354–366, 368–370*). In one polar algae study cited above, only 12 of 30 species were reported to emit CH_2Br_2 (*152*). Likewise, bromoethane is only occasionally reported as a marine algae volatile (*152, 250, 336, 337, 345*). The previous survey listed 1,2-dibromoethane as a tentative marine algae metabolite (*1*), but subsequent independent studies clearly establish 1,2-dibromoethane ($BrCH_2CH_2Br$, **1**) as a bona fide natural product (*359, 362*). This organobromine, which has anthropogenic sources (*359*), is emitted by several algae species (*152, 250, 336, 337, 359, 360, 362*).



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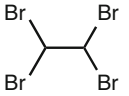

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4

3.1.6.2 Volcanic Emissions

Several simple organobromines are emitted from Mt. Etna, Vulcano, Kuju, and Satsuma-Iwojima, including CH_2Br_2, $CHBr_3$, CH_3CH_2Br, each of which has large biogenic (marine algae) contributions, and the new compound bromobutane (**2**, isomer unknown) (*217, 216*). 1,1,2,2-Tetrabromoethane (**3**) is present in carbonaceous black shale (*330*).

3.1.7 Mixed Bromochloromethanes

The mixed bromochloromethanes, chlorobromomethane (CH_2BrCl), chlorodibromomethane ($CHBr_2Cl$), and bromodichloromethane ($CHBrCl_2$), often accompany $CHBr_3$ and CH_2Br_2 in marine algae (*1*). Both macro- and microalgae produce CH_2BrCl (*152, 250, 309, 336, 337, 346, 358, 365*), $CHBr_2Cl$ (*152, 250, 306–309, 336, 342, 344, 345, 346, 354–362, 364, 365, 368, 373*), and $CHBrCl_2$ (*152, 250, 302, 306, 309, 336, 337, 342, 346, 356, 357–362, 365*). Volcanic emissions of bromochloromethanes include the known CH_2BrCl, $CHBr_2Cl$, and $CHBrCl_2$, along with the previously unreported $CBrCl_3$ (**4**) (*217*).

3.1.8 Iodomethanes

3.1.8.1 Marine

The widely used organic chemical reagent, iodomethane (CH_3I, methyl iodide), has a large biogenic source in worldwide marine algae (*1*). Like CH_3Br and $CHBr_3$, CH_3I is often detected in emissions from algae and in the oceanic atmosphere (*152, 248–251, 255, 302, 306–311, 338, 339, 342, 344–346, 356, 357, 359, 361, 365*). Diiodomethane also has numerous marine algae sources (*152, 307, 309, 336, 337, 339, 342, 344, 345, 356, 357, 359–362, 365, 367, 369*), but iodoform (CHI_3) has not been described in nature following its report in *Asparagopsis taxiformis* (*1*). Diiodomethane is a more significant source of iodine in the atmosphere than CH_3I (*365*).

3.1.8.2 Terrestrial

Iodomethane has several terrestrial biogenic and abiotic sources (Table 3.6). It is emitted from volcanoes (*216, 217*), fungi (*273*), wetlands (*275*), peatlands (*267*), rice paddies (*262–266, 374*), and oat plants (*374*). Biomass combustion also accounts for some CH_3I (*284, 285, 288*). The abiotic soil source cited earlier can also produce CH_3I (*175*).

3.1.9 Other Simple Iodoalkanes

Given the dearth of iodide in the ecosystem relative to chloride and bromide (Table 3.4), it is perhaps surprising that several other alkyl iodides are found in the environment.

3.1.9.1 Marine

Marine algae are a rich source of iodoethane (CH_3CH_2I) (*152, 250, 309, 336, 337, 339, 344, 357, 365, 367*), 1-iodopropane ($CH_3CH_2CH_2I$) (*152, 309, 342, 356, 357, 365, 367*), 2-iodopropane ($(CH_3)_2CHI$) (*152, 308, 309, 356, 357, 365, 367*),

Table 3.6 Sources and estimated amounts[a] of iodomethane/Gg y^{-1}

Source	Best estimate	Range	References
Oceanic	–	128–335	(*375*)
Biomass burning	< 10	–	(*285*)
Rice paddies	–	16–29	(*266*)
Peatlands	1.4	0.1–12.8	(*267*)
Macroalgae	–	0.00092–0.011	(*365*)
Macroalgae	0.28	–	(*250*)

[a]See also (*42*)

1-iodobutane ($CH_3(CH_2)_3I$) (*152, 307–309, 357, 361, 365, 367*), 2-iodobutane ($CH_3CH_2CH(CH_3)I$) (*152, 307, 309, 357, 365*), and the new 1-iodo-2-methylpropane (**5**) (*152, 365*).

3.1.9.2 Volcanic Emissions

An examination of the emissions from Mt. Etna, Vulcano, Kuju, and Satsuma-Iwojima has revealed the presence of ethyl iodide (*217*).

3.1.10 Mixed Iodomethanes

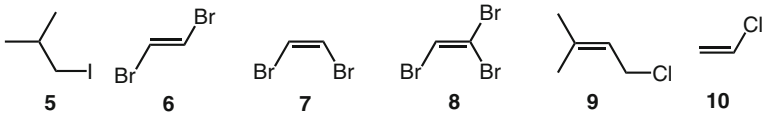
By unknown biogenetic mechanisms (perhaps nucleophilic substitution reactions?), marine algae produce several iodomethanes containing chlorine or bromine (*1*). Recent studies confirm the oceanic presence of chloroiodomethane (CH_2ClI) (*152, 250, 307–309, 336, 337, 339, 342, 344, 345, 355–357, 359, 360, 362, 365, 367, 369*), bromoiodomethane ($BrCH_2I$) (*339, 344, 345*), dibromoiodomethane ($CHBr_2I$) (*345*), and the new dichloroiodomethane (Cl_2CHI) (**6**) (*345*). Volcanic emissions from Mt. Etna, Vulcano, Kuju, and Satsuma-Iwojima are reported to contain CH_2ClI (*217*).

3.1.11 Simple Alkenes

While the carbon–carbon double bond is a common functional group in complex natural products, it is far rarer in simple natural compounds.

3.1.11.1 Marine

The chemically productive red algae *Asparagopsis taxiformis* and *Asparagopsis armata*, which are prized by Hawaiians for flavor and aroma ("limu kohu", supreme seaweed) (*1*), contain the novel (*E*)-1,2-dibromoethylene (**7a**), (*Z*)-1,2-dibromoethylene (**7b**), and tribromoethylene (**8**) (*364*). Trichloroethylene (TCE) (*301, 307–309, 312, 361, 376, 377*) and tetrachloroethylene (PERC) (*307–309, 312, 376, 377*) continue to be found in marine algae in concentrations larger than anticipated, but their origin remains controversial (*253, 278, 301, 307–309, 376–378*). Initially, TCE and PERC were found in 27 species of macroalgae (*376*).



5 **6** **7** **8** **9** **10**

3.1.11.2 Terrestrial Biogenic

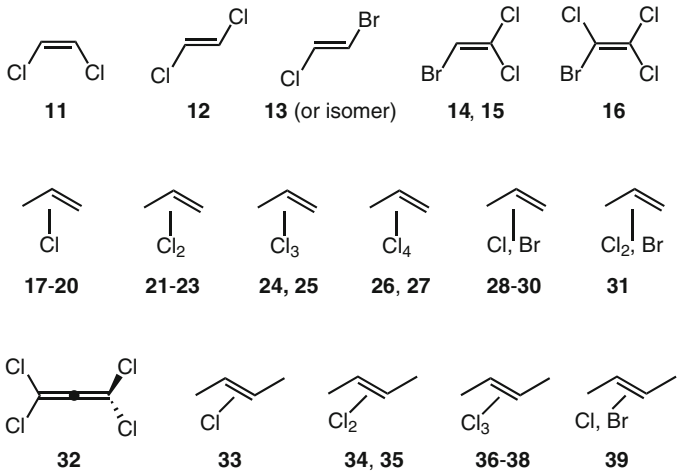
One of the most intriguing newly discovered natural organohalogens is 1-chloro-3-methyl-2-butene (**9**) from a secretion of a male flying fox (*Pteropus giganteus*) (*380*). Since this compound is known to be a powerful lachrymator (personal experience), it may function as a chemical defensive agent ("allomone") for the fox.

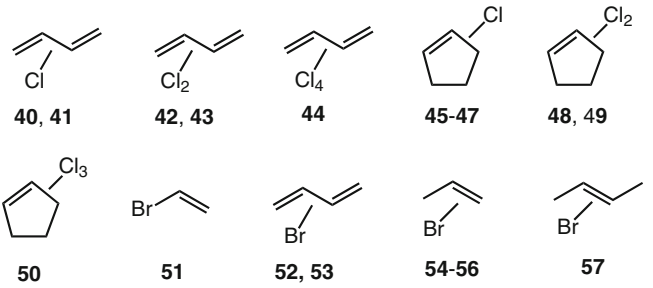
3.1.11.3 Terrestrial Abiotic

Vinyl chloride is obviously essential for the manufacture of poly(vinyl chloride) polymer (PVC), and is a known human liver carcinogen. Therefore, it is surprising that vinyl chloride (**10**) (CH_2 = CHCl) is produced abiotically in soil, during the oxidative degradation of soil matter (*381*), similar to the proposed abiotic soil formation of CH_3Cl (vide supra). Model experiments with catechol (1,2-dihydroxybenzene), Fe(III), and chloride yield both vinyl chloride and CH_3Cl. It might be noted that CH_3CCl_3, TCE, and PERC are not formed under these conditions (*381*). The latter observations are consistent with field studies of spruce forests (*319, 322*); for a review, see (*278*). Both TCE and PERC are reported in biomass fires (*283*).

3.1.11.4 Volcanic Emissions

Several chlorinated and brominated alkenes are present in emissions of Mt. Etna, Vulcano, Kuju, and Satsuma-Iwojima (*217*). In addition to vinyl chloride (**10**), TCE, PERC, and 1,1-dichloroethylene, compounds **11**–**57** were detected in these emissions. For many of these compounds, exact structures remain unknown.





40, **41** **42**, **43** **44** **45-47** **48**, 49

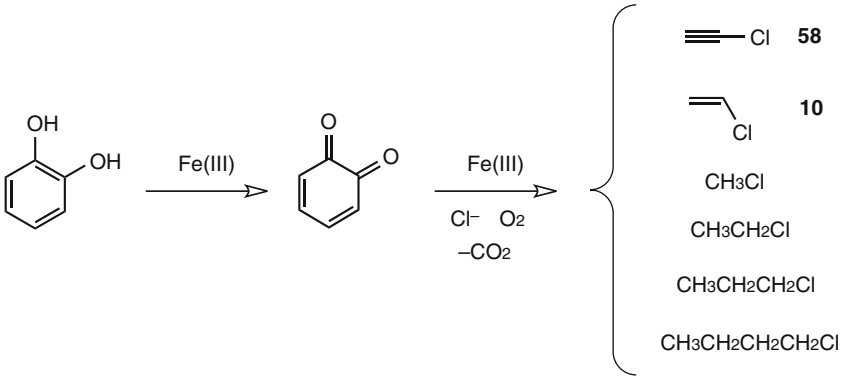
50 **51** **52**, **53** **54-56** **57**

3.1.12 Simple Alkynes

Although acetylenes are widely used in organic synthesis, and are present both in pharmaceuticals and in interstellar space, simple halogenated acetylenes are virtually unknown in nature.

3.1.12.1 Terrestrial Abiotic

In model experiments with catechol, Fe(III), and chloride, and in soil emission studies, it is found that chloroethyne (chloroacetylene) (**58**) is produced (*382*). The natural formation of **58** parallels that of vinyl chloride, which is also found in these experiments. The in vitro and in vivo mechanisms are unknown, but the authors propose the path shown in Scheme 3.1 (*382*). Both chloroethyne and vinyl chloride are emitted from three soil types (coastal salt marsh, peatland, and a deciduous forest).

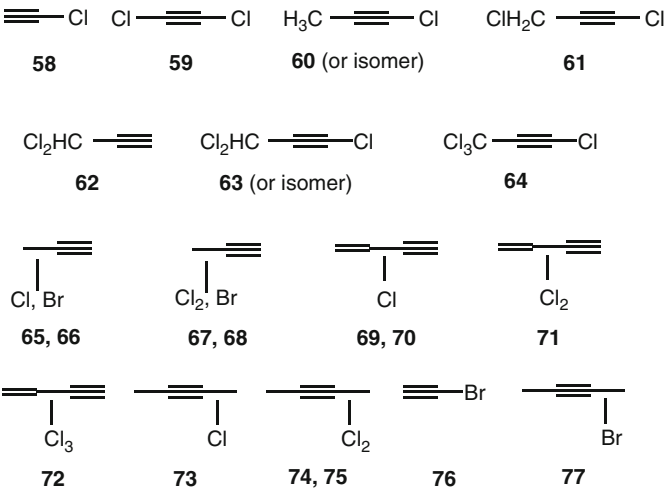


Abiotic formation of organochlorines from catechol (*382*).

Scheme 3.1

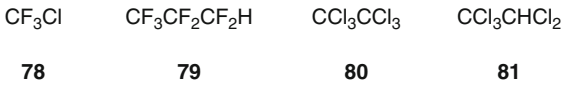
3.1.12.2 Volcanic Emissions

A study of Mt. Etna, Vulcano, Kuju, and Satsuma-Iwojima volcanoes reveals the presence of several halogenated alkynes **59**–**77** (*217*).



3.1.13 Simple Organofluorines

Following the early reports of chlorofluorocarbons (CFCs) in volcanic and drill well emissions (*1*), more recent work confirms these studies (*216, 217*), although the emission rates of $CFCl_3$ and CF_2Cl_2 are very small compared to the anthropogenic sources of these compounds (*383*). Tetrafluoromethane occurs in natural fluorites and granites (*384, 385*) and has been detected in natural gas (*385*). The global emission rate from cold degassing from the Earth's crust is negligible at 0.0001–0.01 Gg y^{-1} compared to anthropogenic emissions (*383*), but, because it has the very long atmospheric lifetime of 200,000 years, about half of the present CF_4 is from natural sources (*384, 385*). In this study, tetrafluoroethylene was also found (*384*), which had been previously found in volcanic emissions (*1*). Further study of fluorites, plutonites, and other rocks reveals the presence of CF_4, CF_2Cl_2, $CFCl_3$, and SF_4, along with CHF_3 and the previously unreported CF_3Cl (**78**) (*386*). Both $CFCl_3$ and CF_2Cl_2 are emitted from the Kamchatka solfataras and hydrothermal vents (*328*) and other thermal springs (*329*). The novel $CF_3CF_2CF_2H$ (**79**) is found in carbonaceous black shales (*330*).

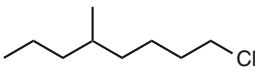


3.1.14 Other Simple Organochlorines

Another controversial compound is 1,1,1-trichloroethane (methyl chloroform, CH_3CCl_3), which may or may not have significant natural sources (*253, 286, 287*). A few studies reveal emissions of CH_3CCl_3 from marine algae (*307*) and halobacteria (*312*), but studies of biomass burning (*283, 286, 387*) and forest soil emissions (*318*) do not indicate a significant natural source for CH_3CCl_3. The carbonaceous black shales from Central Asia are reported to contain the novel CCl_3CCl_3 (**80**) and CCl_3CHCl_2 (**81**) (*330*). The meteorites, Orgueil and Cold Bokkeveld, have yielded the long-chain chloroalkanes, 1-chlorododecane (**82**), 1-chlorotridecane (**83**), 1-chlorotetradecane (**84**), 1-chloropentadecane (**85**), 1-chlorohexadecane (**86**), 1-chloroheptadecane (**87**), and 1-chlorooctadecane (**88**) (*388*). The closely related long-chain chloroalkanes, 1-chlorononadecane (**89**), 1-chloroicosane (**90**), 1-chlorohenicosane (**91**), 1-chlorodocosane (**92**), 1-chlorotricosane (**93**), 1-chlorotetracosane (**94**), 1-chloropentacosane (**95**), 1-chlorohexacosane (**96**), 1-chloroheptacosane (**97**), 1-chlorooctacosane (**98**), and 1-chlorononacosane (**99**), are found in three salt marsh plants (*Suaeda vera*, *Sarcocornia fruticosa*, *Halimione portulacoides*) (*389*).

n-$C_{12}H_{25}Cl$	*n*-$C_{13}H_{26}Cl$	*n*-$C_{14}H_{29}Cl$	*n*-$C_{15}H_{31}Cl$	*n*-$C_{16}H_{33}Cl$	*n*-$C_{17}H_{35}Cl$
82	**83**	**84**	**85**	**86**	**87**
n-$C_{18}H_{37}Cl$	*n*-$C_{19}H_{39}Cl$	*n*-$C_{20}H_{41}Cl$	*n*-$C_{21}H_{43}Cl$	*n*-$C_{22}H_{45}Cl$	*n*-$C_{23}H_{47}Cl$
88	**89**	**90**	**91**	**92**	**93**
n-$C_{24}H_{49}Cl$	*n*-$C_{25}H_{51}Cl$	*n*-$C_{26}H_{53}Cl$	*n*-$C_{27}H_{55}Cl$	*n*-$C_{28}H_{57}Cl$	*n*-$C_{29}H_{59}Cl$
94	**95**	**96**	**97**	**98**	**99**

An examination of several marine worms (*Marenzellaria viridis*, *Polydora socialis*, *Scolelepsis squamata*, *Spiophanes bombyx*, and *Streblospio benedicti*) has tentatively identified alkyl and alkenyl halides **100**–**105** (*390*).



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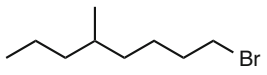

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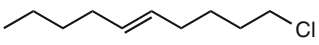

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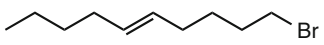

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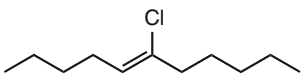

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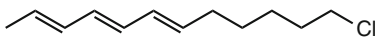
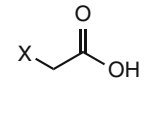


105

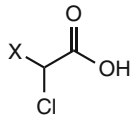
3.2 Simple Functionalized Acyclic Organohalogens

Several simple functionalized natural organohalogens do not reasonably fit into categories such as terpenes, alkaloids, or fatty acids (*1*) and are therefore included here.

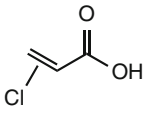
The prolific red seaweed *Asparagopsis taxiformis* has afforded eight new halogenated carboxylic acids **106–113** (*391*) in addition to several already described (*1*). In some cases the double bond stereochemistry or the exact location of the halogens has not been established. Another study of this seaweed has identified the two heavily brominated enol esters **114** and **115**, the structures of which were confirmed by synthesis (*392*). These compounds, which are aldose reductase inhibitors, are two of the most heavily halogenated natural compounds known. This brings to over 100 the number of halogenated compounds found in this alga (*1*). An Antarctic collection of the red alga *Delisea fimbriata* yielded two new brominated acetates **116** and **117**, in addition to four brominated furanones and two bromooctenones that were previously known from this alga (*393*). Five Antarctic sponges (*Phorbas glaberrima*, *Kirkpatrickia variolosa*, *Artemisina apollinis*, *Halichondria* sp., and *Leucetta antarctica*) contain the known 1,1,2-tribromooct-1-en-3-one (*394*). The Okinawan alga *Wrangelia* sp. has afforded the simple tribromoacetamide (**118**), which displays potent biofilm inhibition against *Rhodospirillum salexigens* and cytotoxicity towards P388 leukemia (*395*). An unidentified fungus on the surface of the red alga *Gracillaria verrucosa* has furnished the novel brominated keto esters **119** and **120** (*396*).



106 X = Br
107 X = I



108 X = Br
109 X = I



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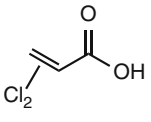

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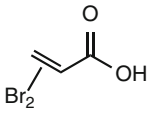

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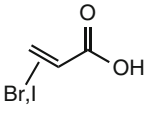

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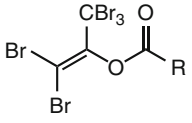
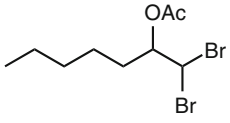


114 R = CBr_3
115 R = $CHBr_2$



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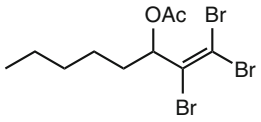

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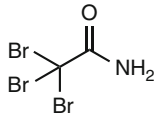
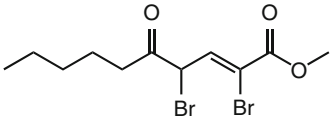


118



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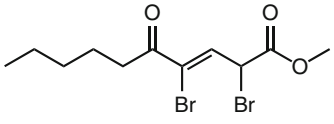
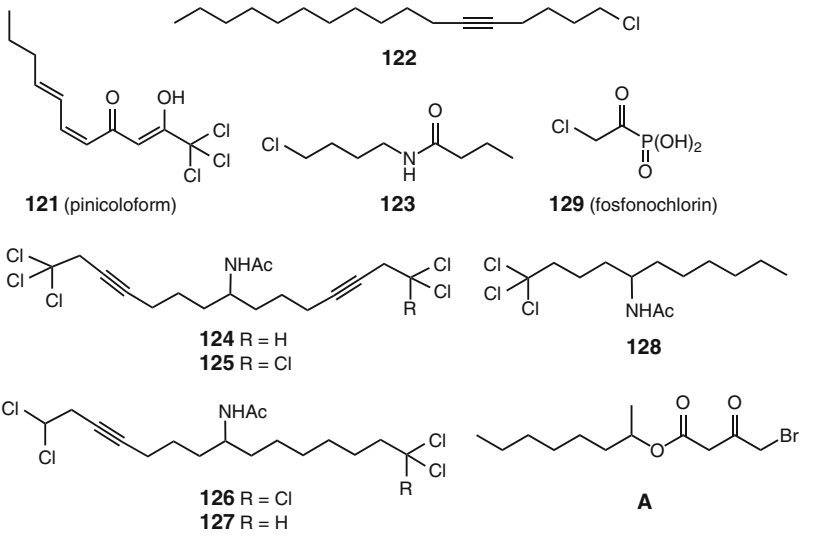


120

Pinicoloform (**121**), which has antibiotic and cytotoxic activities, was isolated from the fungus *Resinicium pinicola* (*397*). The edible wild milk cap (*Lactarius* spp.) contains 1-chloro-5-heptadecyne (**122**) (*398*). In addition to containing the toxic alkaloid coniine, the Yemenese plant *Aloe sabaea* has afforded the novel *N*-4′-chlorobutylbutyramide (**123**), which is the first report of a chlorinated compound in the Aloeaceae family (*399*). Several polychlorinated acetamides (**124**–**128**) were characterized from the cyanobacterium *Microcoleus lyngbyaceus* (*400*). The novel fosfonochlorin (chloroacetylphosphonic acid) (**129**) was isolated from four fungi (*Fusarium avenaceum*, *Fusarium oxysporum*, *Fusarium tricinctum*, and *Talaromyces flavus*) (*401*). The remarkable previously known bromoester **A** [2-octyl 4-bromo-3-oxobutanoate], which is present in mammalian cerebrospinal fluid and is involved in REM-sleep (*1, 402*), has been synthesized and investigated further in comparison with synthetic analogues (*403, 404*).

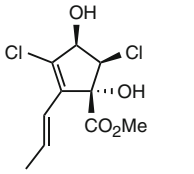


All three chloroacetic acids (chloroacetic acid [MCA], dichloroacetic acid [DCA], and trichloroacetic acid [TCA]) are naturally occurring (*1*), with TCA being identified in the environment most frequently (reviews: (*278, 405–408*)). However, these chlorinated acetic acids also have anthropogenic sources. The major source of natural TCA appears to be the enzymatic (chloroperoxidase) or abiotic degradation of humic and fulvic acids, which ultimately leads to chloroform and TCA. Early studies (*409*) and subsequent work confirm both a biogenic and an abiotic pathway. Model experiments with soil humic and fulvic acids, chloroperoxidase, chloride, and hydrogen peroxide show the formation of TCA, chloroform, and other chlorinated compounds (*317, 410–412*). Other studies reveal an abiotic source of TCA (*412, 413*).

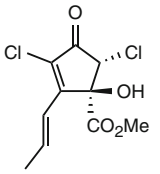
3.3 Simple Functionalized Cyclic Organohalogens

3.3.1 Cyclopentanes

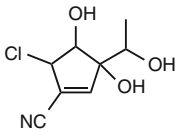
The previously known cryptosporiopsinol (**B**) (*1*) is also found in the marine fungus *Coniothyrium* sp. living on the sponge *Ectyplasia perox* (*414*), and its biosynthesis has been investigated (*415, 416*). These results reveal that chlorination occurs early in the sequence and a ring contraction from an isocoumarin seems to be involved. An asymmetric synthesis of (–)-cryptosporiopsin (**130**), the antipode of the previously described natural product (*1*), has been reported (*417*). The known (+)-cryptosporiopsin was found in cultures of the fungus *Pezicula livida* (*418*). The chlorinated isonitrile MR566A (**131**) is a melanin synthesis inhibitor produced by *Trichoderma harzianum* (*419, 420*). This same fungus found on the sponge *Halichondria okadai* has yielded trichodenones B (**132**) and C (**133**), which show significant cytotoxicity against P388 leukemia (*421*); total syntheses have established their stereochemistry (*422*). Metabolite **134** was isolated from a culture of the ascomycete A23-98 (*423*). The diastereomeric cyclopentenones VM 4798-1a (**135**) and VM 4798-1b (**136**) were obtained from the fungus *Dasyscyphus* sp. A47-98 found growing on tree bark (*424*). The pentachlorinated cyclopentenone A11-99-1 (**137**) was isolated from cultures of the ascomycete *Mollisia melaleuca* and displays inhibition of human TNF-α promoter activity and synthesis (*425*). The Madagascan plant *Samadera madagascariensis* contains the quassinoid 2-chlorosamaderine A (**138**), which has a 2-chlorocyclopentenone ring (*426*).



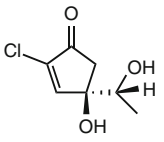
B (cryptosporiopsinol)



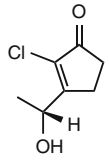
130 ((–)-cryptosporiopsin)



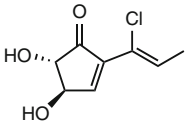
131 (MR566A)



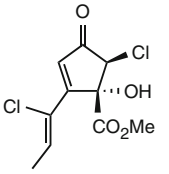
132 (trichodenone B)



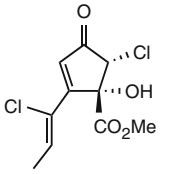
133 (trichodenone C)



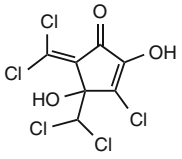
134



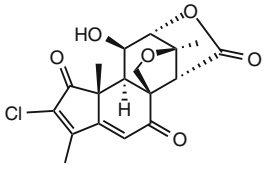
135 (VM 4798-1a)



136 (VM 4798-1b)



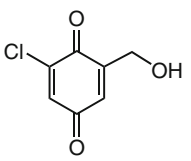
137 (A11-99-1)



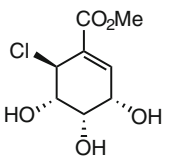
138 (2-chlorosamaderine A)

3.3.2 Cyclitols and Benzoquinones

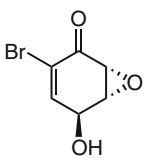
The halogenated natural products in this section are mainly fungal metabolites that are cyclohexene derived via a shikimate or polyketide pathway (*1*). The simple inhibitor of rat brain neutral sphingomyelinase activity, chlorogentisylquinone (**139**), is produced by the marine fungus FOM-8108 found on beach sand in Japan (*427*). The structure of the cytotoxic (+)-pericosine A (**140**), which was isolated from a marine fungus (*Periconia byssoides*) in a sea hare (*Aplysia kurodai*) (*428*), was revised by total synthesis (*429, 430*). Because of its pronounced antitumor activity, the previously reported Maui acorn worm (*Ptychodera*) (+)-bromoxone (**C**) (*1*) has been of synthetic interest (*431–433*; review, *434*). The antipode (–)-mycorrhizin A (**141**) of the previously reported (+)-mycorrhizin A was isolated from the fungi *Pezicula carpinea* and *Pezicula livida* (*418*). Some "forced" brominated metabolites of mycorrhizin A, chloromycorrhizin A, and the related lachnumons were characterized from cultures of *Lachnum papyraceum* (e.g., **D**) (*435, 436*), but these are not counted as natural products. Chlovalicin (**142**) from *Sporothrix* sp. inhibits interleukin 6 (*437, 438*), and a *Cytospora* sp. produces cytosporin B (**143**) an antagonist of angiotensin II (*439*).



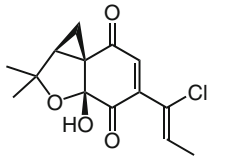
139 (chlorogentisylquinone)



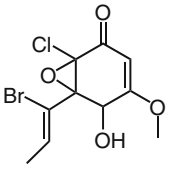
140 (pericosine A)



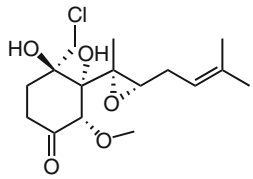
C (bromoxone)



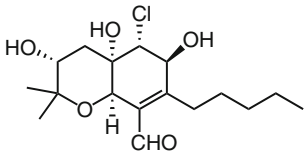
141 ((–)-mycorrhizin A)



D (lachnumon B2)

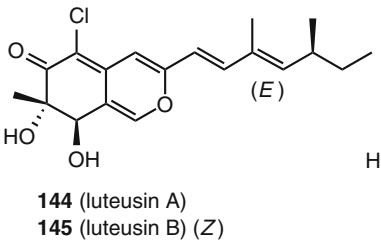


142 (chlovalicin)

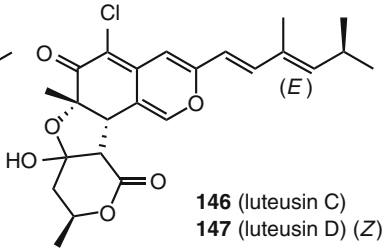


143 (cytosporin B)

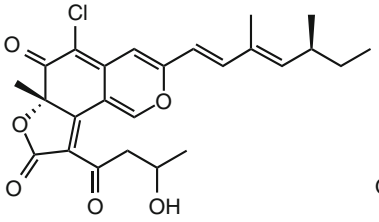
Several new fungal metabolites ("azaphilones", having an affinity for nitrogen nucleophiles) related to the well-known sclerotiorin (*1*) have been reported in recent years. Studies of the fungus *Talaromyces luteus* have uncovered luteusins A–E (**144**–**148**) (*440–443*). Luteusins A and B were originally named TL-1 and TL-2, and the stereochemistry of C and D was later revised (*443*). These metabolites have monoamine oxidase inhibitory properties. The related fungus *Talaromyces helicus* has furnished helicusins A–D (**149**–**152**) (*444*).



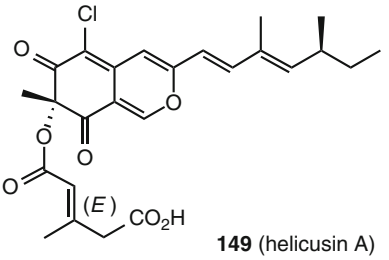
144 (luteusin A)
145 (luteusin B) (*Z*)



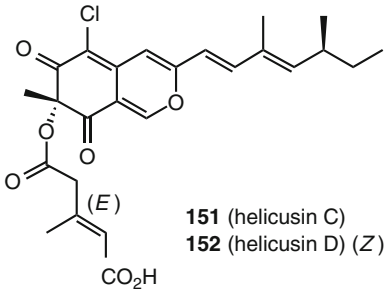
146 (luteusin C)
147 (luteusin D) (*Z*)



148 (luteusin E)

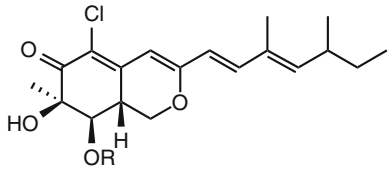


149 (helicusin A)
150 (helicusin B) (*Z*)

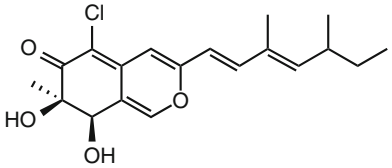


151 (helicusin C)
152 (helicusin D) (*Z*)

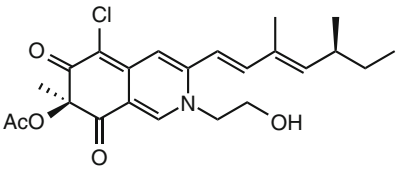
A full account and structures are reported for isochromophilones I (**E**) and II (**F**) from *Penicillium multicolor* FO-2338 (*445, 446*). The latter study also confirms the structure of sclerotiorin. The ACAT inhibitors isochromophilones III-VI (**153–156**) are found in cultures of *Penicillium multicolor* FO-3216 (*447*) and isochromophilones VII and VIII (**157**, **158**) are produced by *Penicillium* sp. FO-4164 (*448*). These azaphilones inhibit cholesteryl ester transfer protein (CETP), which promotes the exchange and transfer of neutral lipids between plasma lipoproteins, and is involved in atherosclerosis. Thus, CETP is a logical target for anti-atherosclerotic drugs (*449*). A study of *Penicillium sclerotiorum* has reported 5-chloroisorotiorin (**159**), which may be isochromophilone III (**153**) (*450*). Unnatural brominated azaphilones ("forced metabolites") are produced when bromide is added to the cultures (*451*). The novel GABA-containing isochromophilone IX (**160**) is found in cultures of *Penicillium* sp. (*452*).



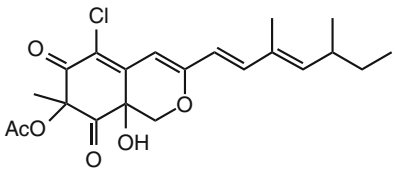
153 R = H (isochromophilone III)
154 R = Ac (isochromophilone IV)



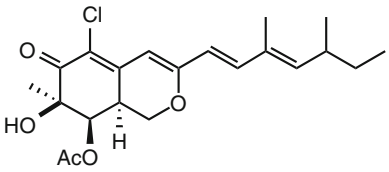
155 (isochromophilone V)



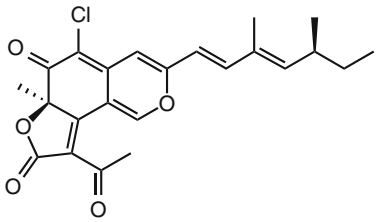
156 (isochromophilone VI)



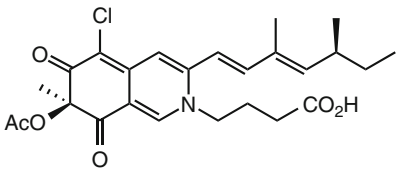
157 (isochromophilone VII)



158 (isochromophilone VIII)

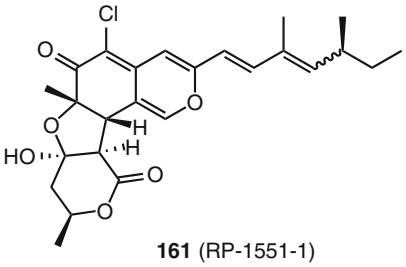


159 (5-chloroisorotiorin)

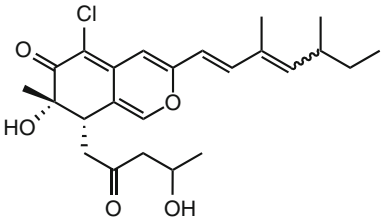


160 (isochromophilone IX)

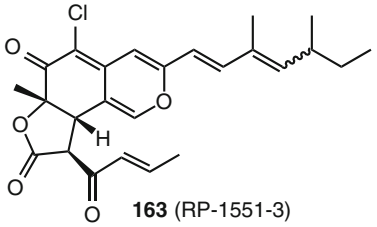
A new family of azaphilones, the RP-1551s (**161**–**168**), is produced by *Penicillium* sp. SPC-21609 and they inhibit the binding of PDGF to its receptor (*453*). RP-1551-7 is identical to luteusin A (**144**). RP-1551-1 (**161**) and RP-1551-6 (**166**) are diastereomers and are different stereoisomers from luteusins C (**146**) and D (**147**).



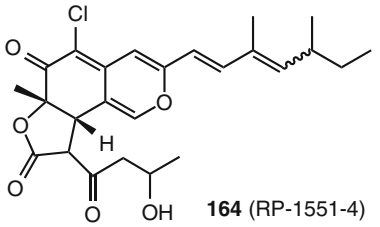
161 (RP-1551-1)



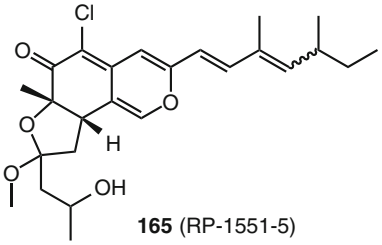
162 (RP-1551-2)



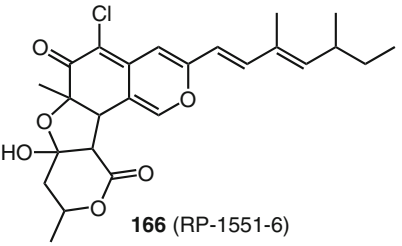
163 (RP-1551-3)



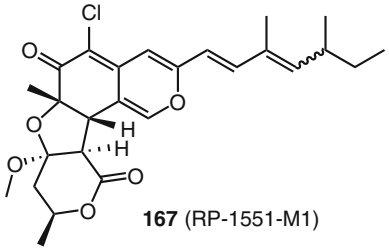
164 (RP-1551-4)



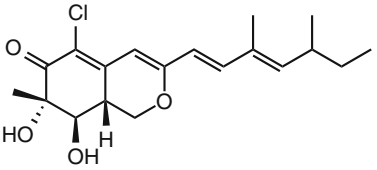
165 (RP-1551-5)



166 (RP-1551-6)

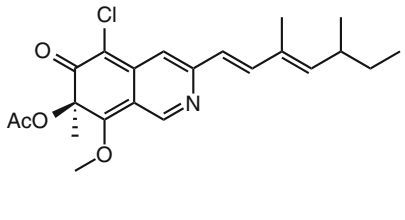


167 (RP-1551-M1)

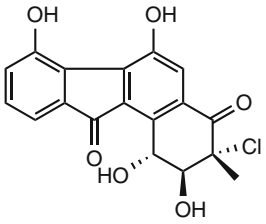


168 (RP-1551-M2)

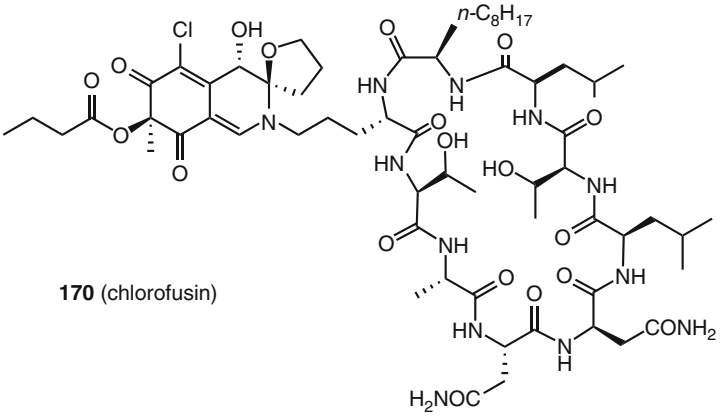
The novel 8-*O*-methylsclerotiorinamine (**169**) was isolated from a strain of *Penicillium multicolor* and is a strong antagonist of the Grb2-SH2 domain (*454*). A *Fusarium* sp. fungus has yielded the cyclopeptide chlorofusin (**170**), which is a p53-MDM2 antagonist (*455*). The biosynthesis of chlorofusin involves an acetogenic origin coupled with an aminodecanoic acid piece (*456*). A total synthesis has established the absolute configuration (*2657*). Fluostatin E (**171**) is a minor member of the fluostatin family of metabolites from *Streptomyces* sp. (*457, 458*). The epoxide (fluostatin C) corresponding to **171** is also isolated; the authors cannot exclude fluostatin E as an artifact arising from HCl ring opening of fluostatin C.



169 (8-*O*-methylsclerotiorinamine)



171 (fluostatin E)



170 (chlorofusin)

3.4 Terpenes

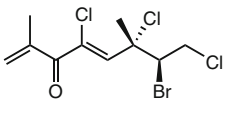
The first survey of natural organohalogens documented 570 halogenated terpenes (*1*). The present update describes many additional new members of this important class of marine and terrestrial natural products.

3.4.1 Monoterpenes

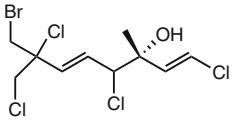
3.4.1.1 Acyclic Monoterpenes

A review on halogenated monoterpenes has appeared (*459*). The structure of the previously known plocamenone (incorrectly named plocamenone A in (*1*)) from a *Plocamium* red alga has been revised to **G** (*460*). A collection of *Plocamium cartilagineum* from the Antarctic has yielded the new monoterpene **172** along with two known halogenated compounds (*461*). The previously isolated **H** (now named halomon) from *Portieria hornemannii* (*1*) has been fully characterized (*462*) and synthesized from myrcene (*463*). Halomon has broad range activity against human cancer cell lines and has undergone clinical evaluation. A subsequent study of this seaweed afforded isohalomon (**I**), which was isolated previously but with

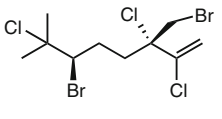
undefined stereochemistry (*1*), and the new metabolites **173** and **174**. In addition, the stereochemistry of the known metabolites **J** and **K** was established (*464*). A Portuguese collection of *Plocamium cartilagineum* contains the novel **175** and **176** (*465*); the former is the first natural halogenated dimethyloctadiene with a (*Z*)-alkene.



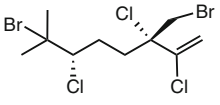
G (plocamenone)



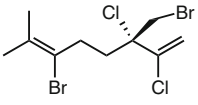
172



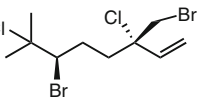
H (halomon)



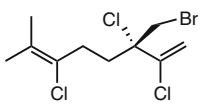
I (isohalomon)



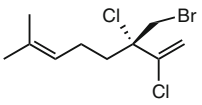
173



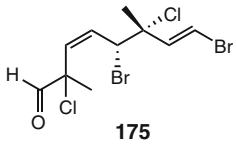
174



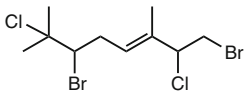
J



K

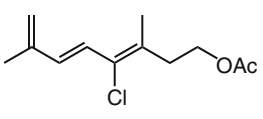


175

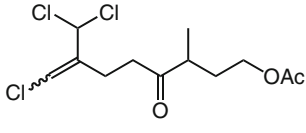


176

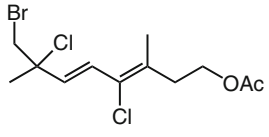
The Spanish sea hare *Aplysia punctata* contains the four novel acetates **177**–**180**, which are perhaps biotransformation products of dietary algae compounds (*466*). A study of the Antarctic red alga *Pantoneura plocamioides* uncovered the novel pantoneurotriols (**181**, **182**) and **183**, in addition to establishing the stereochemistry of the previously isolated **172** (*467*). A Tasmanian collection of *Plocamium costatum* yielded the new **184** and three known halogenated monoterpenes, some of which deter barnacle larvae settlement (*468*). A detailed survey of six samples of *Plocamium hamatum* from the Great Barrier Reef identified 11 known halogenated monoterpenes, the occurrence of which differed significantly between locations. In this study the previously reported monoterpene **L** (*1*) was obtained for the first time in pure form (*469*). A collection of *Plocamium cartilagineum* from Tasmania uncovered two new polyhalogenated monoterpenes **185** and **186** (*470*).



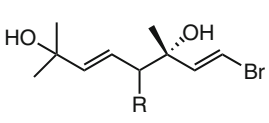
177



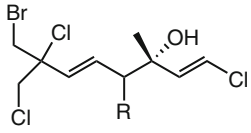
178 (*Z*)
179 (*E*)



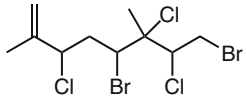
180



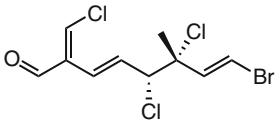
181 R = *β*-OH
182 R = *α*-OH



183 R = *β*-Cl
172 R = *α*-Cl



184



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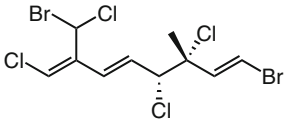
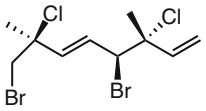
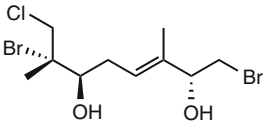


186

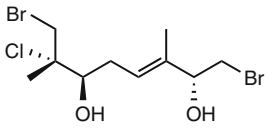


L

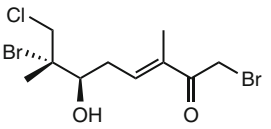
Three plocamenols A–C (**187**–**189**) were isolated from a Chilean collection of *Plocamium cartilagineum* (*471*), and this seaweed also yielded prefuroplocamioid (**190**) (*472*), **191** (*473*), **192**, and **193** (*474*). The alga *Plocamium corallorhiza* from Cape Town, South Africa, has afforded plocoralides A–C (**194**–**196**), which display some cytotoxicity toward esophageal cancer cells (*475*). Anverene (**197**) was found in an Antarctic collection of *Plocamium cartilagineum* (*476*). The Madagascar red alga *Portieria hornemannii* has yielded the new monoterpenes **198–200** along with halomon and two other known compounds (*477*). The known marine alga metabolite **M** (*1*) is found in several fish, monk seals, hooded seals, and harp seals, presumably as a bioaccumulative compound (*478*). It is also present in Norwegian predatory bird eggs (white-tailed eagle, osprey, goshawk, golden eagle, and merlin) (*479*).



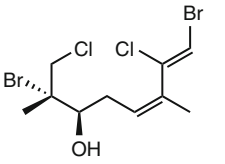
187 (plocamenol A)



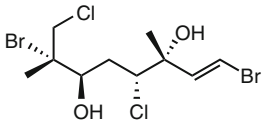
188 (plocamenol B)



189 (plocamenol C)



190 (prefuroplocamioid)



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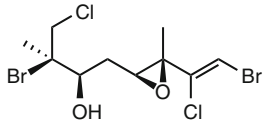
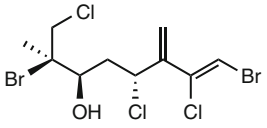
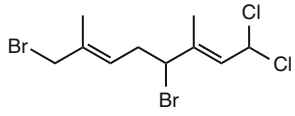


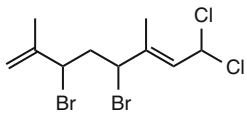
192



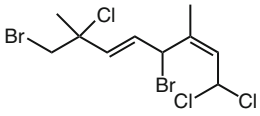
193



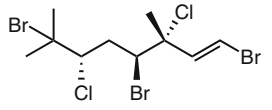
194 (plocoralide A)



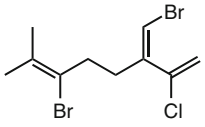
195 (plocoralide B)



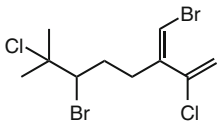
196 (plocoralide C)



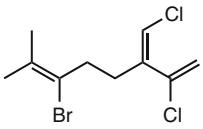
197 (anverene)



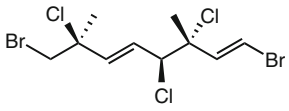
198



199



200



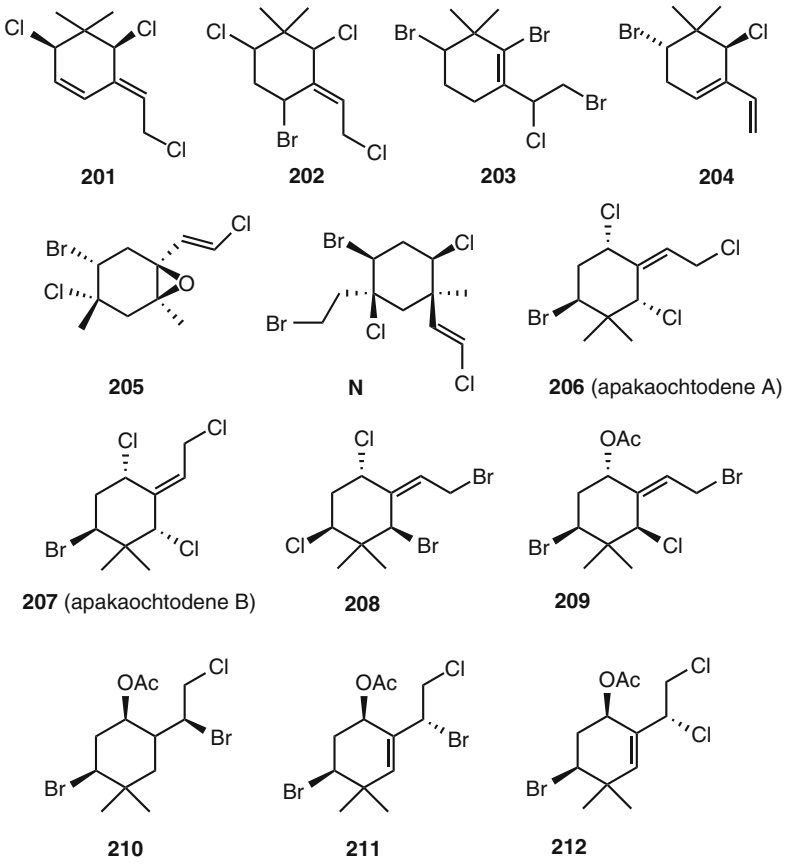
M (or isomer)

Many polyhalogenated monoterpenes have potent biological activity (*1*). In addition to cytotoxic activity, several compounds display insect repellent and antifeedant activity, and selective insect cell toxicity (*480*). To acquire sufficient quantities of these and other target metabolites for biological evaluation, the laboratory cultivation of marine algae – "bioprocess engineering" – is under intense exploration (*481–483*).

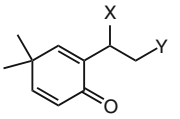
3.4.1.2 Alicyclic Monoterpenes

The halogenated acyclic marine monoterpenes are often considered to be the biogenetic precursors of the alicyclic monoterpenes that are presented in this section. Many of the preceding algae species also contain cyclic monoterpenes. As was the case in preceding sections only newly characterized compounds are numbered and the reader is referred to the first survey for structures of previously isolated compounds (*1*).

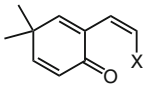
The halomon-containing red alga *Portieria hornemannii* contains the new cyclic trichloro metabolite **201** (*462*), and another study of this seaweed has furnished **202–205** (*464*). The prolific *Plocamium cartilagineum* from the Portuguese coast produces epoxide **205**, which is the first natural alicyclic polyhalogenated epoxy-monoterpene to be isolated (*484*). The absolute configuration of the previously known **N** (*1*) was determined (*469*). A Guam collection of *Portieria hornemannii* contains the novel apakaochtodenes A (**206**) and B (**207**) (*485*), which are effective feeding deterrents toward herbivorous reef fish (*486*). The Japanese red seaweed *Carpopeltis crispata* contains the new ochtodenes **208–212** (*487*). Several known antifeedant alicyclic monoterpenes are found in the sea hare *Aplysia punctata* that are apparently diet derived and used for chemical defense (*488*). An alicyclic polyhalogenated monoterpene (as yet unidentified) has been detected in fish, seal, and birds (*478, 479, 489*). The known monoterpenes mertensene and violacene, and some synthetic derivatives, found in *Plocamium cartilagineum* have insecticidal activity (*490*).



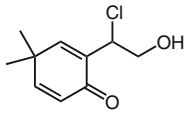
Two different Okinawan collections of *Portieria hornemanni* have yielded the novel cyclohexadienones **213**–**217** (*491*). The previously known *Portieria hornemanni* metabolite **O** has been characterized from the cyanobacterium *Lyngbya majuscula* (*492*). Several cyclic monoterpene ethers are seaweed metabolites, presumably derived by cyclization of a proximate hydroxyl group (i.e., "neighboring group participation"). For example, the Antarctic *Pantoneura plocamioides* has yielded pantofuranoids A–F (**218**–**223**) (*493*) and pantoisofuranoids A–C (**224**–**226**) (*494*). The Antarctic *Plocamium cartilagineum* contains furoplocamioids A–C (**227**–**229**), which possess the unusual bromochlorovinyl moiety (*495*), and also **230a** and **230b** (*473*).



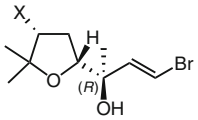
213 X = Y = Br
214 X = Cl, Y = Br
215 X = Y = Cl



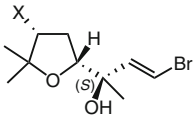
216 X = Br
217 X = Cl



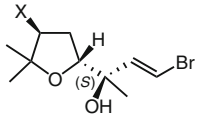
O



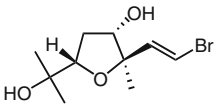
218 X = Br (pantofuranoid A)
222 X = OH (pantofuranoid E)



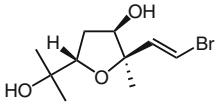
219 X = Br (pantofuranoid B)
221 X = OH (pantofuranoid D)



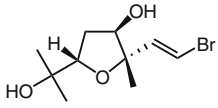
220 X = Br (pantofuranoid C)
223 X = OH (pantofuranoid F)



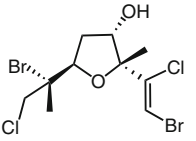
224 (pantoisofuranoid A)



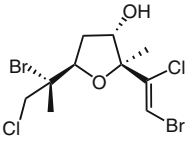
225 (pantoisofuranoid B)



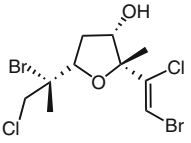
226 (pantoisofuranoid C)



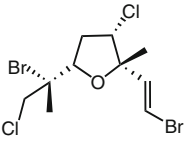
227 (furoplocamioid A)



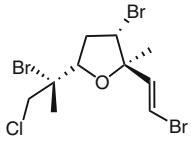
228 (furoplocamioid B)



229 (furoplocamioid C)

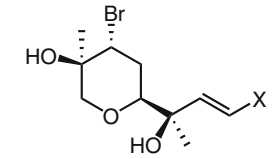


230a

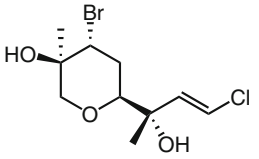


230b

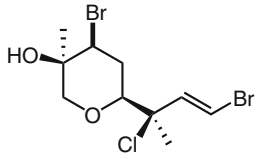
The pyran metabolites, pantopyranoids A–C (**231**–**233**), have been isolated from the Antarctic alga *Pantoneura plocamioides* (*494*). This seaweed and *Plocamium cartilagineum* contain plocamiopyranoid (**234**) and **235**, and pantoneurines A (**236**) and B (**237**) (*496*). The Pakistani herb *Mentha longifolia* has yielded the novel chlorinated menthone longifone **238** (*497*), one of the few known terrestrial halogenated monoterpenes.



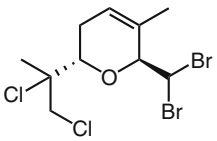
231 X = Br (pantopyranoid A)
233 X = Cl (pantopyranoid C)



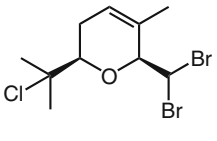
232 (pantopyranoid B)



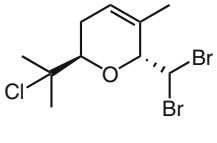
234 (plocamiopyranoid)



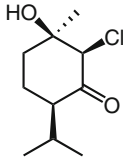
235



236 (pantoneurine A)



237 (pantoneurine B)



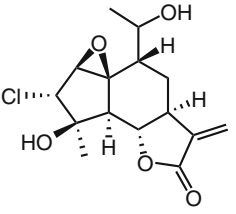
238

3.4.2 Sesquiterpenes

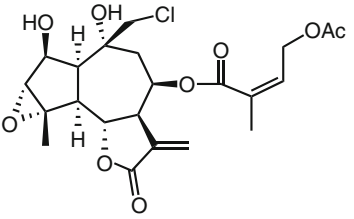
In addition to the myriad natural marine halogenated sesquiterpenes (vide infra), the terrestrial plant kingdom is also a major source of halogenated (chlorinated) sesquiterpenes, most of which possess the guaianolide skeleton (*498*).

3.4.2.1 Terrestrial Sesquiterpene Lactones

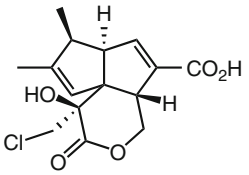
Although the first survey listed 45 natural chlorinated sesquiterpene lactones, several such compounds were omitted in that coverage (*1*) and are described here. The novel sesquiterpene lactone chlorochrymorin (**239**) was isolated from *Chrysanthemum morfolium* (*499*), and the chlorohydrin graminichlorin (**240**) is found in *Liatris graminifolia* (*500*). The antibacterial AA-57 (**241**), which is related to pentalenolactone, is produced by a *Streptomyces* sp. (*501*). The plant *Eupatorium chinense* var. *simplicifolium* has yielded eupachifolin D (**242**) (*502*) (side-chain double bond stereochemistry revised (*518*)), and the new guaianolide andalucin (**243**) was characterized from *Artemisia lanata* (*503*). The previously known chlorohyssopifolins (*1*) have been studied for cytostatic activity, and the presence of one and even two chlorine atoms amplifies this activity (*504*).



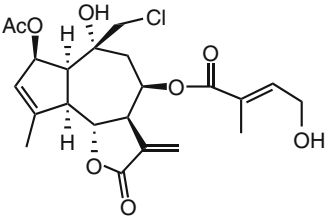
239 (chlorochrymorin)



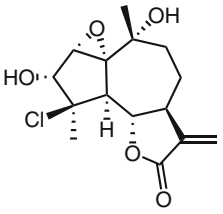
240 (graminichlorin)



241 (AA-57)

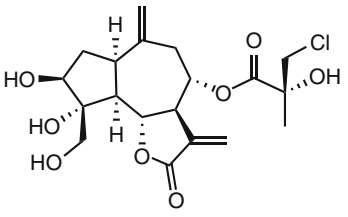


242 (eupachifolin-D)

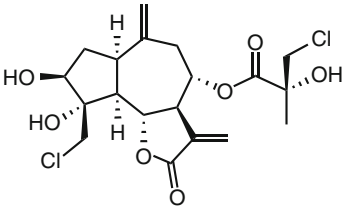


243 (andalucin)

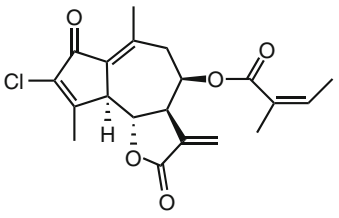
It should be noted that at least some of these chlorohydrin sesquiterpenes could be artifacts (*505*) formed by epoxide ring opening during isolation. It is essential that acid and acid-forming reagents (e.g., $CHCl_3$) be avoided during isolation of these compounds when epoxides might also be present, and that investigators be cognizant of this potential problem. Unless otherwise indicated, the following new compounds were isolated in the absence of chlorinated solvents.



244 (epicebellin J)



245 (epicentaurepensin)



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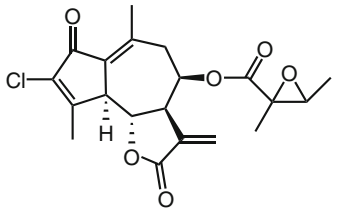

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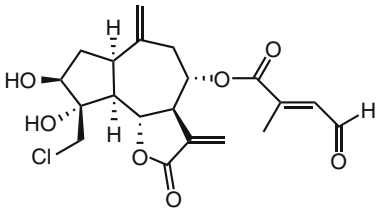

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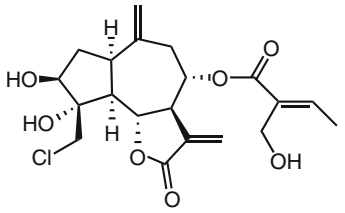

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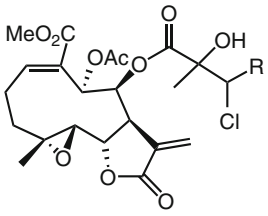
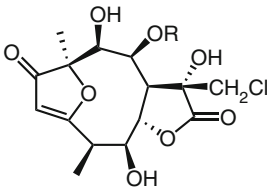
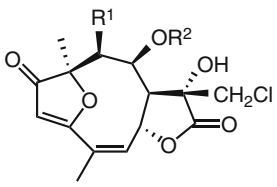


250 R = H
251 R = Me



252 R = tiglyl
253 R = angelyl

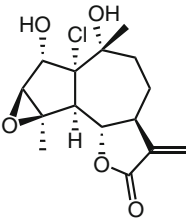


254 R^1 = OH, R^2 = tiglyl
255 R^1 = H, R^2 = 5-OAc-tiglyl

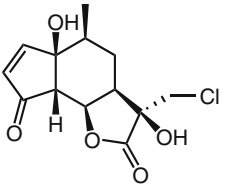
The new epicebellin J (**244**) was isolated from *Centaurea glatifolia* along with several known guaianolides (*506*). *Centaurea conifera* has yielded the C-17 epimer of the previously known chlorohyssopifolin A (centaurepensin) (**245**), and the previously described chlorohyssopifolin A and chlorojanerin (*507*). The high altitude Argentinean plant *Stevia sanguinea* contains the new **246** and **247** (*508*). Another study of *Centaurea scoparia* has identified the new **248** and **249** (*509*). The eastern India medicinal plant *Enhydra fluctuans* has yielded two new chlorinated melampolides **250** and **251** (*510*). The South American plant *Bejaranoa balansae* contains the novel furanoheliangolides **252**–**254**, and *Bejaranoa semistriata* has afforded **255** (*511*).

The plant *Achillea clusiana* from the mountains of Bulgaria contains the new 2-*epi*-chloroklotzchin (**256**), which is the first report of a halogenated sesquiterpene lactone from *Achillea* genus (*512*). Chloroform was used to process the plant. The Egyptian medicinal plant *Ambrosia maritima*, which is still used to treat renal colic and other aliments, has afforded 11β-hydroxy-13-chloro-11,13-dihydrohymenin (**257**) (*513*). Eupaglehnins E (**258**) and F (**259**) are novel germacranolides isolated

from the Japanese plant *Eupatorium glehni* (*514, 515*). In addition to containing the new guaianolide **260**, a Greece collection of *Achillea ligustica* has uncovered the seco-tanapartholide **261** (*516*). The first chlorinated sesquiterpene lactone glucoside to be isolated is **262**, 13-chloro-3-*O*-β-D-glucopyranosylsolstitialin, from *Leontodon palisae* (*517*).



256 (2-*epi*-chloroklotzchin)



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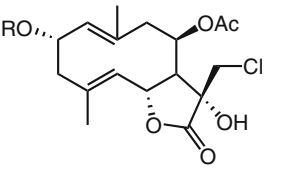
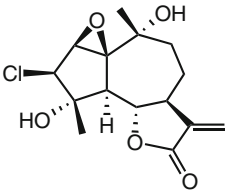


258 R = H (eupaglehnin E)
259 R = Ac (eupaglehnin F)



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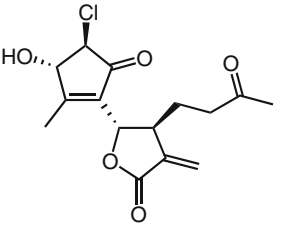

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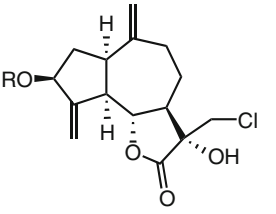
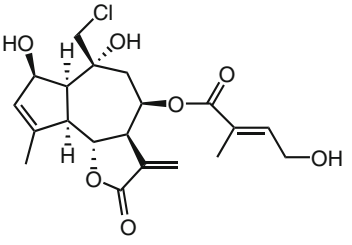
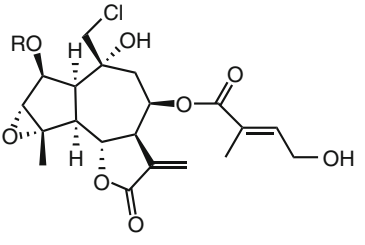


262 R = β-D-glucose

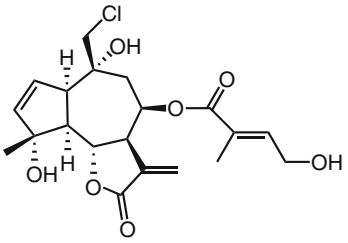
The Chinese *Eupatorium chinense* has afforded ten new sesquiterpenoids, three of which are chlorinated, eupachinilides C (**263**), E (**264**), and F (**265**) (*518*). The Chinese medicinal plant *Eupatorium lindleyanum* contains the chlorinated guaianes eupalinilides A (**266**), D (**267**), E (**268**), and H (**269**), amongst other non-chlorinated eupalinilides and nine known sesquiterpenoids (*519*). The Oregon coastal perennial plant *Artemisia suksdorfii* contains four novel chlorinated sesquiterpene lactones **270**–**273** (*520*).



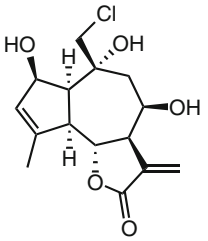
263 (eupachinilide C)



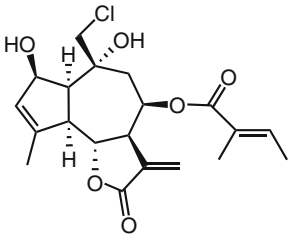
264 R = H (eupachinilide E)
265 R = Ac (eupachinilide F)



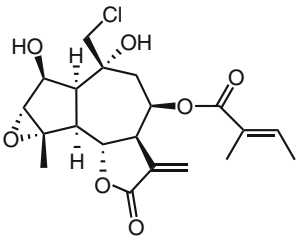
266 (eupalinilide A)



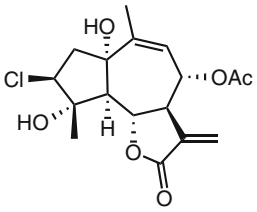
267 (eupalinilide D)



268 (eupalinilide E)



269 (eupalinilide H)



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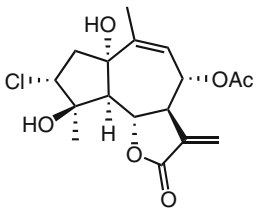

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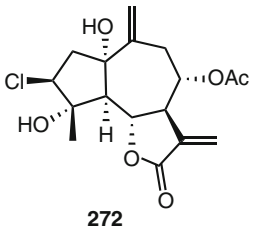

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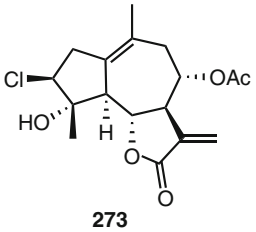
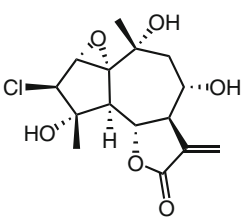


273

The Balkan Peninsula plant *Achillea depressa* contains the previously discussed **260** and its novel hydroxy derivative **274** (*521*), which is apparently a diastereomer of the known bibsanin (*1*). *Centaurea acaulis* from Algeria has afforded 14-chloro-10β-hydroxy-10(14)-dihydrozaluzanin D (**275**) (*522*). The widely distributed medicinal herbaceous perennial plant *Cynara scolymus* contains the new cynarinin B (**276**) as one of nine related sesquiterpenoids (*523*).

Examination of the Montenegro *Achillea clavennae* reveals the presence of three new chlorine-containing guaianolides **277–279** in addition to several known analogues (*524*). The first investigation of the Chinese medicinal plant *Vernonia chinensis* has uncovered the new chlorinated sesquiterpene lactones vernchinilides A (**280**), B (**281**), C (**282**) and E (**283**) (*525*). Vernchinilides B and E exhibit potent cytotoxic activity against the P-388 and A-549 cell lines. The structurally similar vernolide C (**284**) was found in the Cambodian traditional medicinal plant *Vernonia cinera* (fever, colic, malaria) (*526*). Indeed, vernolide C could be identical with vernchinilide A.



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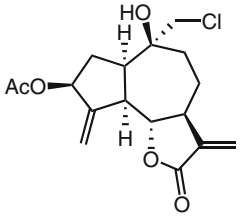

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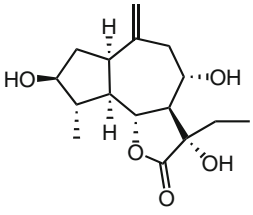
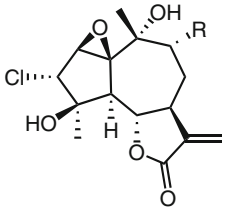
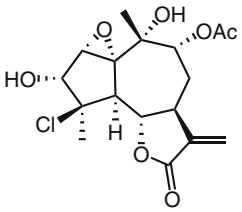


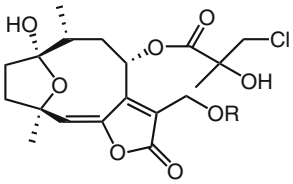
276 (cynarinin B)



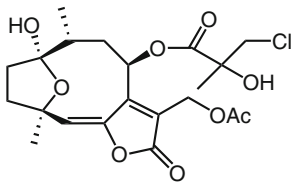
277 R = H
278 R = OAc



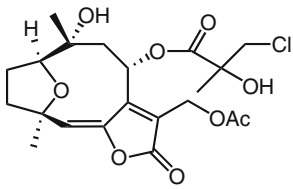
279 (9α-acetoxyanadalucin)



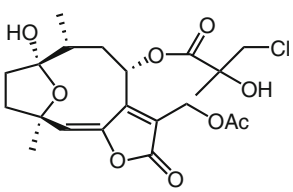
280 R = Ac (vernchinilide A)
282 R = H (vernchinilide C)



281 R = Ac (vernchinilide B)



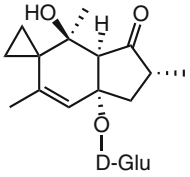
283 R = Ac (vernchinilide E)



284 (vernolide C)

3.4.2.2 Indanone Sesquiterpenes

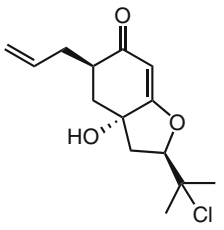
A review on the isolation, chemistry, and biochemistry of the bracken fern (*Pteridium aquilinum*) carcinogen ptaquiloside (**P**) has been published (*527*). This fern and others contain the pterosins that were summarized previously (*1*). No new examples were reported in the interim.



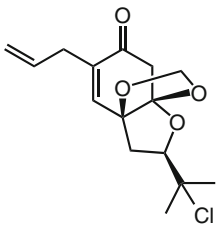
P (ptaquiloside)

3.4.2.3 Other Terrestrial Sesquiterpenes

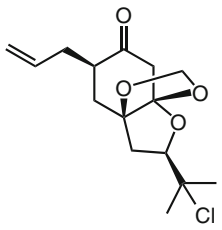
The toxic plant *Illicium tashiroi* is the source of many novel sesquiterpenes and one new chlorine derivative, 12-chloroillifunone C (**285**) (*528*). A subsequent investigation of this plant revealed 12-chloroillicinone E (**286**) and (2*R*)-12-chloro-2,3-dihydroillicinone E (**287**) (*529*). The latter metabolite increases choline acetyltransferase activity and thus may find use in the treatment of Alzheimer's disease. The common Pakistani weed *Pluchea arguta* has yielded 3,4-di-*epi*-3′-chloro-2′-hydroxyarguticinin (**288**) (*530*), which is a diastereomer of a compound previously reported in this plant (*1*), and *Pluchea carolonesis* from Haiti contains the eudesmane **289** (*531*). Five novel chlorinated bisabolanes **290**–**294** were characterized from the Himalayan plant *Cremanthodium discoideum*, the genus of which is used as a Tibetan traditional herbal medicine for the treatment of fever, pain, inflammation, and other ailments. Compound **290** shows antibacterial activity against *Bacillus acidilatici* and *Bacillus subtilis* (*532*). The related bisabolane **295** was isolated from the roots of *Ligularia cymbulifera* (*533*). As with the previous studies in this section, no chloroform or HCl was employed in the isolation process, which might otherwise convert the corresponding epoxides to these chlorohydrins. The fungus *Phomopsis* sp., which was found growing on the plant *Adenocarpus foliolosus*, produces the sesquiterpene acid **296** (*534*).



285 (12-chloroillifunone C)



286 (12-chloroillicinone E)



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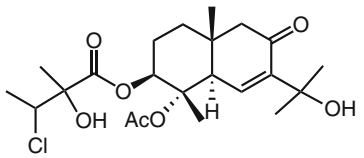

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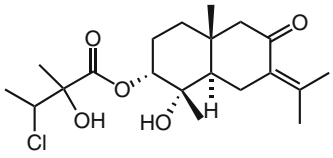

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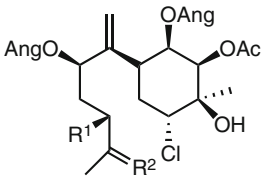
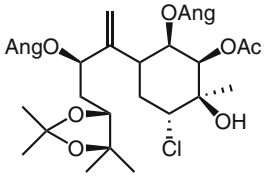


290 R^1 = OH, R^2 = Me/OMe
291 R^1 = OH, R^2 = Me/OH
292 R^1 = OH, R^2 = CH_2
293 R^1 = Cl, R^2 = Me/OH



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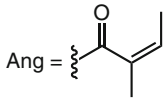

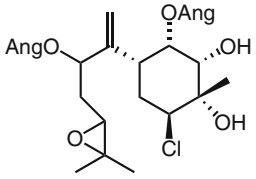

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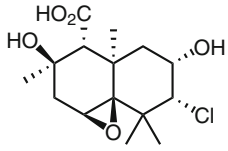
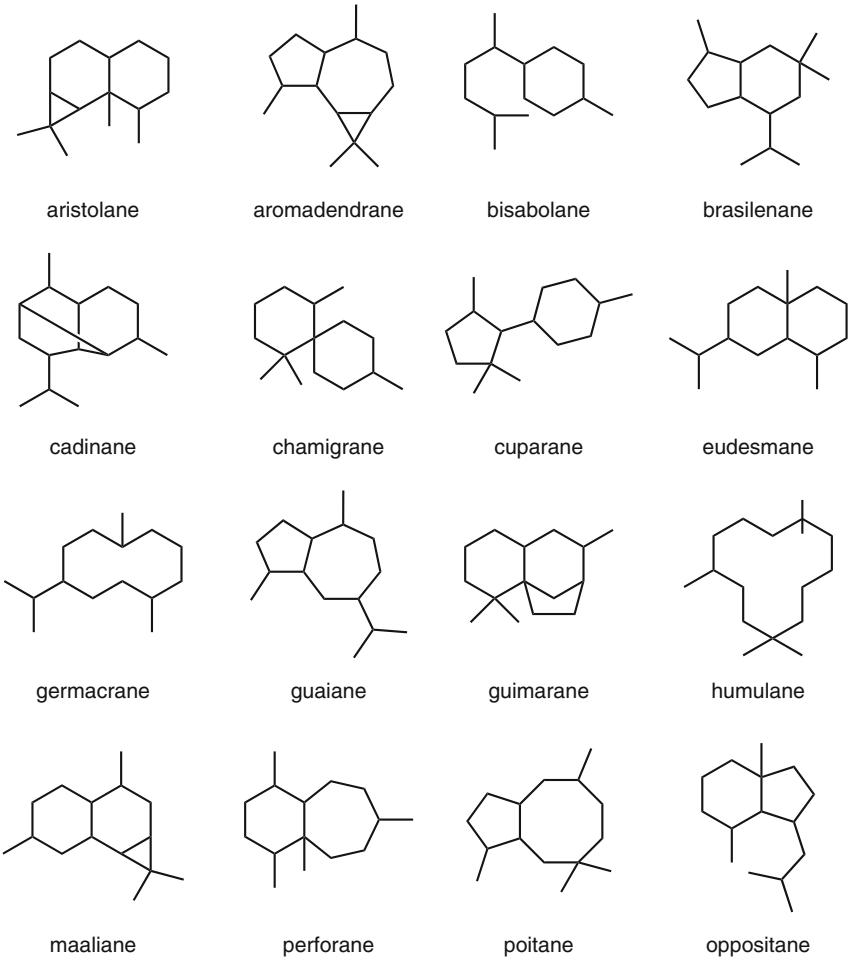


296

Fig. 3.2 *Laurencia subopposita*, an example of the widespread red alga genus *Laurencia* (Photo: W. Fenical)

3.4.2.4 Marine Sesquiterpenes

The first survey covered more than 200 halogenated marine sesquiterpenes (*1*), and these extraordinarily structurally diverse natural products continue to be discovered from marine organisms. The red algal genus *Laurencia* (*Rhodomelaceae*, *Ceramiales*) is a large genus comprising at least 140 species distributed throughout the world's oceans, but mainly in warm waters. *Laurencia* is a treasure trove of halogenated (i.e., brominated) metabolites, and the morphology of this genus is of great interest (Fig. 3.2) (*535–538*).



Sesquiterpene skeletons from *Laurencia* spp. (*553*).

Scheme 3.2

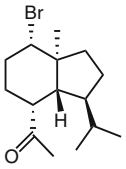
The diversity of ring systems found in *Laurencia* is shown in Scheme 3.2 (*553*), although the present organization of marine sesquiterpenes does not follow these categories, but rather continues the previous one (*1*).

Monocyclic and Other Simple Sesquiterpenes

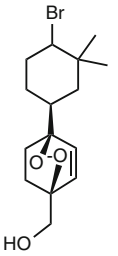
The new red algal species *Laurencia mariannensis* from the Great Barrier Reef provides the novel sesquiterpene **297**, along with the known pacifenol and deoxyprepacifenol, which are now fully characterized by NMR for the first time (*539*). The Philippine *Laurencia majuscula* has furnished 13 novel halogenated sesquiterpenes **298**–**310**, of which the major components are the majapolenes A (**298**, **299**) (two diastereomers), which are also found in *Laurencia caraibica* (*540*). Most of these compounds occur as inseparable diastereomers. A collection of *Laurencia majuscula* from the South China Sea has yielded the cedrene-type sesquiterpene majusin (**311**) (*541*). A new sesquiterpene dichloroimine, stylotellane A (**312**), was isolated from the sponge *Stylotella aurantium* (Fig. 3.3) (*542*).

Feeding experiments with carbon-14 reagents revealed the incorporation of both cyanide and thiocyanate into **312**. Three new dichloroimines were isolated from the sponge *Axinyssa* sp., axinyssimides A–C (**313**–**315**), and possess strong larval settlement inhibitory activity against the infamous barnacle *Balanus amphitrite* (*543*). The Australian sponge *Ulosa spongia* has furnished the new carbonimide dichlorides ulosins A (**316**) and B (**317**) (*544*), and **316** was isolated independently from the sponge *Stylotella aurantium* along with the new **318** (*545*). This sponge has also yielded the novel stylotellane D (**319**) (*546*). Biosynthetic labeling studies have been performed with these dichloroimine sesquiterpenes (*542, 547, 548*).

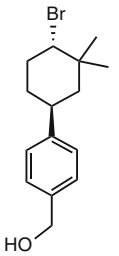
Fig. 3.3 *Stylotella aurantium*, a sponge that produces the dichloroimine stylotellane A (**312**) (Photo: A. Flowers)



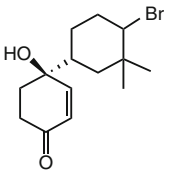
297



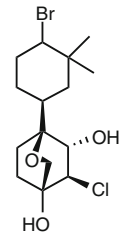
298, **299** (majapolene A)



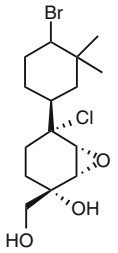
300 (majapolene B)



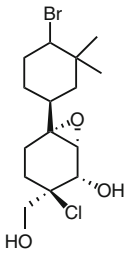
301, **302** (majapolene)



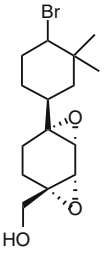
303, **304** (majapol A)



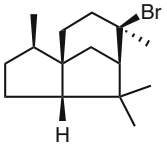
305, **306** (majapol B)



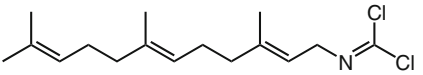
307, **308** (majapol C)



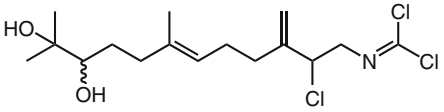
309, **310** (majapol D)



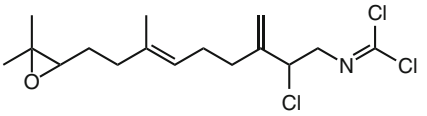
311 (majusin)



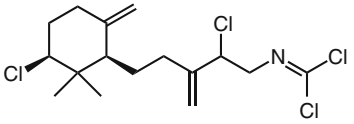
312 (stylotellane A)



314 (axinyssimide B)
315 (axinyssimide C)



313 (axinyssimide A)



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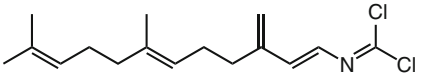
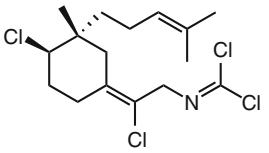
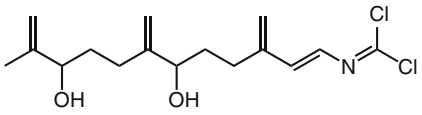


316 (ulosin A)

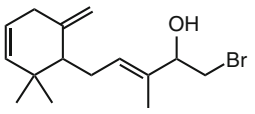


319 (stylotellane D)

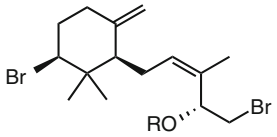


317 (ulosin B)

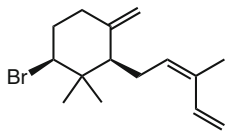
Laurencia seaweeds continue to be a rich source of brominated sesquiterpenes. The Okinawan *Laurencia luzonensis* contains the new isopalisol (**320**), luzonensol (**321**), luzonensol acetate (**322**), luzonensin (**323**), and triene bromohydrin **324** (*549*). A collection of *Laurencia obtusa* from Turkey has furnished the β-snyderol analogues **325** and **326** and ketone **327** (*550*), whereas *Laurencia scoparia* from Brazil contains the novel β-bisabolenes **328**–**330**, the first β-bisabolenes from the genus *Laurencia* (*551*). Bromocyclococanol (**331**) from *Laurencia obtusa* in Cuba, has a novel fused cyclopropane-cyclopentane ring system (*552*). The authors propose a biogenesis involving an interesting cyclopropyl carbinyl cation intermediate (**332**).



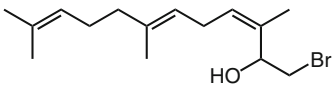
320 (isopalisol)



321 R = H (luzonensol)
322 R = Ac (luzonensol acetate)



323 (luzonensin)



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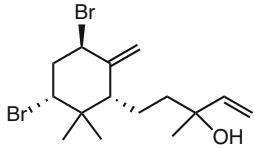

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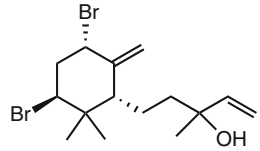

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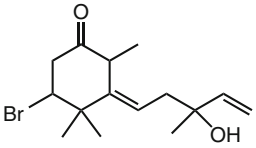

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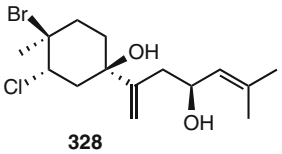

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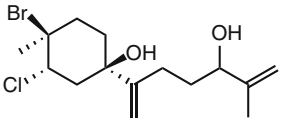

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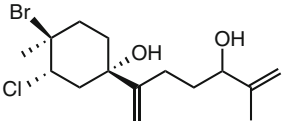

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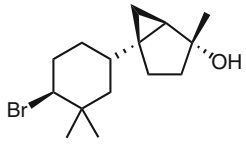
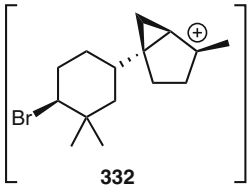
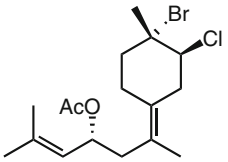


331 (bromocyclococanol)

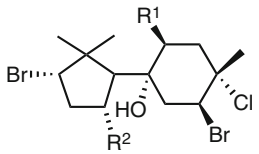


332

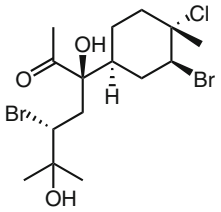
Sea hares and nudibranchs feed on seaweeds to acquire their chemicals for defense. The common sea hare *Aplysia dactylomela* from Spain contains puertitol-B acetate (**333**) (*554*), whereas this animal collected off the coast of South Africa affords the new algoane (**334**), 1-deacetoxyalgoane (**335**), 1-deacetoxy-8-deoxyalgoane (**336**), and ibhayinol (**337**) (*555, 556*). Investigation of this sea hare from La Palma has uncovered the new **338** along with two other halogenated compounds shown in section "Eudesmane and Other Types" (*557*).



333 (puertitol-B acetate)



334 R^1 = OAc, R^2 = OH (algoane)
335 R^1 = H, R^2 = OH
336 R^1 = R^2 = H



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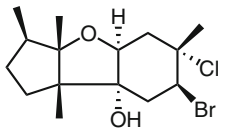
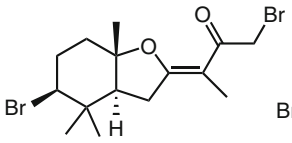
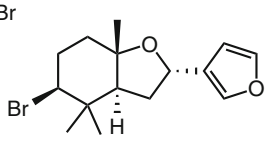


337 (ibhayinol)

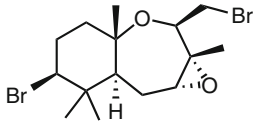
An Okinawan collection of *Laurencia luzonensis* has yielded five new sesquiterpenes, luzonenone (**339**), luzofuran (**340**), 3,4-epoxypalisadin B (**341**), 1,2-dehydro-3,4-epoxypalisadin B (**342**), and 15-hydroxypalisadin A (**343** (*558*). In addition, the relative stereochemistry of luzonensol (**321**) (vide supra) (*549*) was assigned by conversion to the known palisadin B (**P**) (*1*). The novel fused bisabolene aldingenins A (**344**), B (**345**), C (**346**), and D (**347**) were isolated from *Laurencia aldingensis* (*559, 560*). The interesting chlorotriol **348** was found in a Turkish *Laurencia obtusa* (*561*).



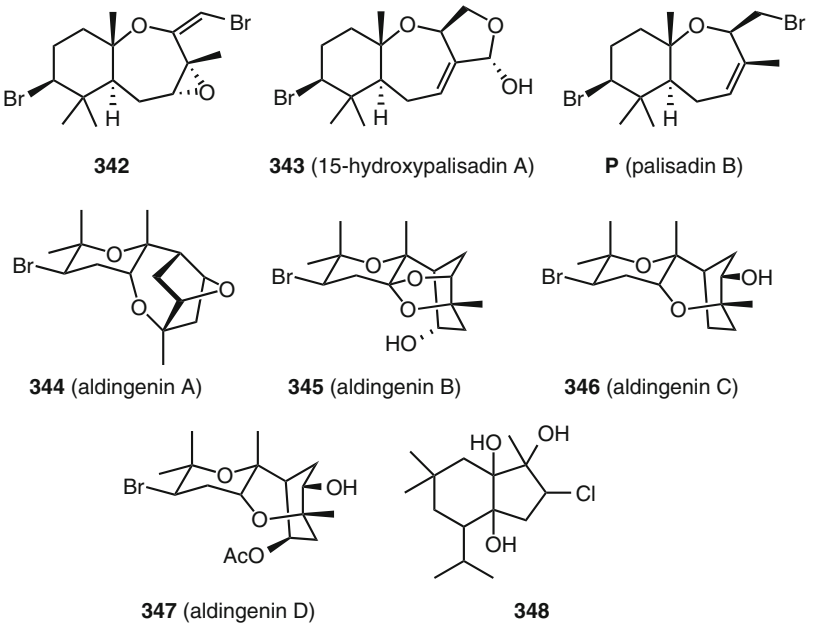
339 (luzonenone)



340 (luzofuran)



341 (3,4-epoxypalisadin B)



342 **343** (15-hydroxypalisadin A) **P** (palisadin B)

344 (aldingenin A) **345** (aldingenin B) **346** (aldingenin C)

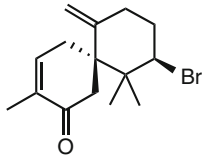
347 (aldingenin D) **348**

Chamigrene and Related Types

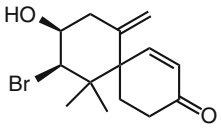
The halogenated spiro-chamigrene, and related metabolites represent a huge class of marine natural products, mainly from *Laurencia* seaweeds. The initial survey documented 85 examples (*1*).

Many of these chamigrenes are found in sea hares, presumably from their diet of algae, and the new 10-bromo-β-chamigren-4-one (**349**) was isolated from an *Aplysia* sp. (*562*). The Hawaiian red alga *Laurencia cartilaginea* has yielded the new ma'ilione (**350**) and *allo*-isoobtusol (**351**) (*563*). The latter is a diastereomer of isoobtusol. However, this assignment has been questioned and *allo*-isoobtusol should be reassigned as **Q** and renamed as cartilagineol (*564*), a correction that has now been confirmed (*565*). An Australian collection of *Laurencia rigida* contains the new (–)-10α-bromo-9*β*-hydroxy-α-chamigrene (**352**), rigidol (**353**), and (+)-(10*S*)-10-bromo-*β*-chamigrene (**354**) (*566*), for which the latter metabolite was subjected to detailed NMR analysis (*567*). It should be noted that extensive NMR studies have been performed on several known halogenated chamigrenes (e.g., prepacifenol epoxide, johnstonol, pacifenediol, pacifidiene, pacifenol, etc.) (*568–570*). Furthermore, dynamic NMR conformational analysis studies have been described with the polyhalogenated α-chamigrenes (*571, 572*). *Laurencia claviformis*, which is endemic to Easter Island, has afforded the new claviol (**355**) in addition to a suite of known halogenated chamigrenes (*573*). The Oahu red seaweed *Laurencia nidifica* contains the new **356** and **357**, along with ten known

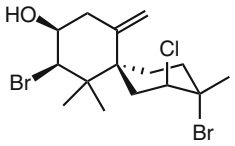
halogenated chamigranes (*574*). Tribrominated ma'iliohydrin (**358**) was isolated from a Philippine *Laurencia* sp. (*575*). Mailione (**359**) and isorigidol (**365**), which are found in *Laurencia scoparia*, were subjected to X-ray crystallography (*576*). It is not clear if **350 = 359** from the data provided (*563, 576*). *Laurencia mariannensis* contains 9-deoxyelatol (**360**) (*2658*).



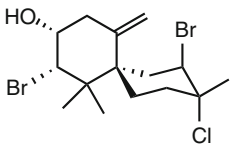
349 (10-bromo-β-chamigren-4-one)



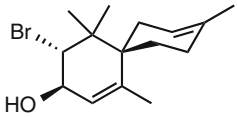
350 (ma'ilione)



351 (*allo*-isoobtusol)



Q (cartilagineol = "*allo*-isoobtusol")



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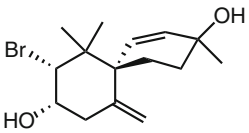
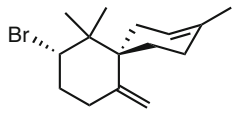


353 (rigidol)



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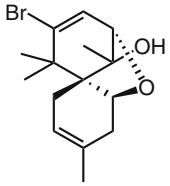
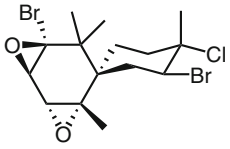


355 (claviol)



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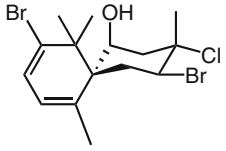

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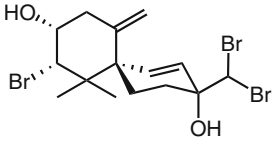
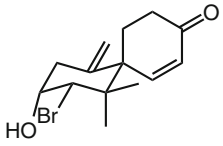
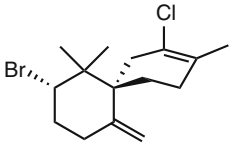


358 (ma'iliohydrin)



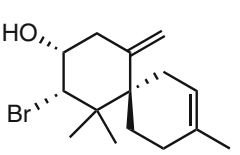
359 (mailione)



360 (9-deoxyelatol)

Whereas Okinawan *Laurencia cartilaginea* and *Laurencia concreta* yielded no halogenated metabolites, *Laurencia majuscula* from these waters afforded (6*R*,9*R*,10*S*)-10-bromo-9-hydroxychamigra-2,7(14)-diene (**361**) (*577*), which

appears to be an epimer of the known deschloroelatol (*1*). A Malaysian *Laurencia pannosa* contains the new pannosanol (**362**) and pannosane (**363**) (*578*). The new 5-acetoxy-2,10-dibromo-3-chloro-7,8-epoxy-α-chamigrene (**364**) is found in both *Laurencia filiformis* and the sea hare *Aplysia parvula* from Tasmania (*579*). The NMR spectra of the known 2,10-dibromo-3-chloro-7-chamigrene are assigned for the first time. A Brazilian collection of *Laurencia scoparia* has yielded three new halogenated chamigrenes, isorigidol (**365**), (+)-3-(*Z*)-bromomethylidene-10*β*-bromo-β-chamigrene (**366**), and (–)-3-(*E*)-bromomethylidene-10*β*-bromo-β-chamigrene (**367**) (*580*). A South China Sea collection of *Laurencia majuscula* afforded the simple 8-bromo-chamigren-1-en (**368**) (*581*). Oxachamigrene (**369**) and 5-acetoxyoxachamigrene (**370**) were found in *Laurencia obtusa* from Cuba, metabolites that are proposed to arise from a γ-bisabolene (*582*). The sea hare *Aplysia dactylomela* contains the novel and highly strained aplydactone (**371**) (*583*). The authors propose a biosynthesis of **371** via a formal (*2* + *2*) cycloaddition from **349**, which is also found in this sea hare (*562*). Sea hares from La Palma Island have furnished the new compounds **372–374** (*584*). It should be noted that several of these chamigrenes have both cytotoxic and antibacterial activity (*584–586*). The chemical diversity of halogenated chamigrenes within four Japanese *Laurencia* species has been compared and contrasted (*587*).



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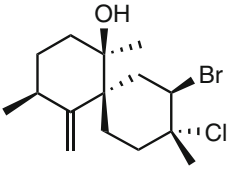
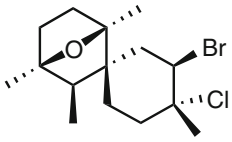
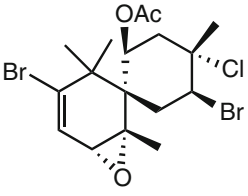


362 (pannosanol)



363 (pannosane)



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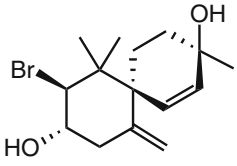
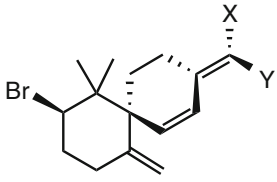
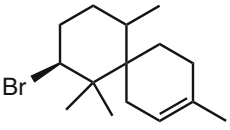


365 (isorigidol)



366 X = H, Y = Br
367 X = Br, Y = H



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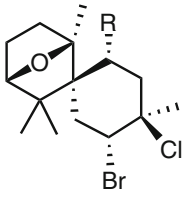
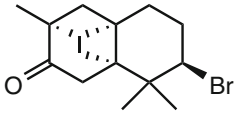
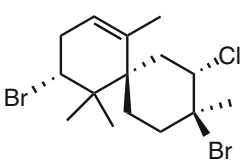


369 R = H (oxachamigrene)
370 R = OAc



371 (aplydactone)



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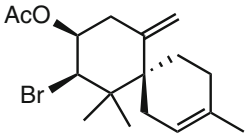
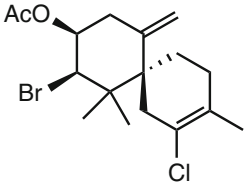


373 (acetyldeschloroelatol)

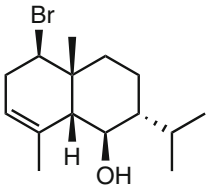


374 (acetylelatol)

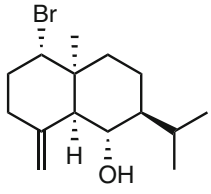
Eudesmane and Other Types

Nearly 40 halogenated eudesmanes and related halogenated sesquiterpenes were documented in the first survey (*1*), and terrestrial eudesmanes of all types are well represented with some 100 known examples (*588*).

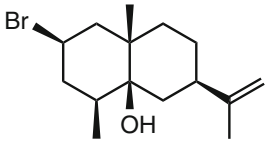
The sea hare *Aplysia dactylomela* contains lankalapuols A (**375**) and B (**376**), which interestingly have opposite absolute configurations (*589*). The tropical green alga *Neomeris annulata* has yielded the three novel brominated sesquiterpenes **377–379**, which are effective feeding deterrents (*590*), and an Okinawan collection of *Laurencia intricata* contains itomanol (**380**), which is a diastereomer of lankalapuol A (**375**) (*591*). The Elba Island *Laurencia microcladia* has afforded the novel 6,8-cycloeudesmanes calenzanol (**381**) (*553, 592*) and **382** (*592, 593*), which feature the new sesquiterpene skeleton, calenzanane (*553, 592*). A study of *Laurencia obtusa* from the Aegean Sea, Greece, has revealed the presence of four new perforatone analogs **383–386** (*594*), and, from a different location in the Aegean Sea, the new perforenol B (**387**) and **388** (*595*). The sea hare *Aplysia punctata* contains the new perforatol (**389**) (*596*).



375 (lankalapuol A)



376 (lankalapuol B)



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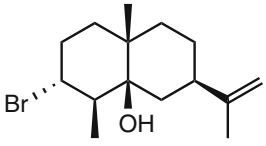

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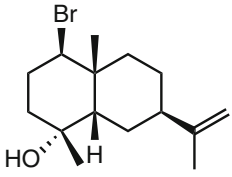

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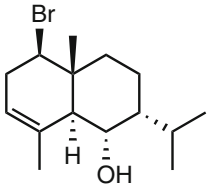
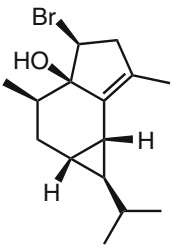
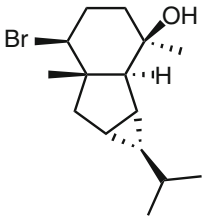


380 (itomanol)



381 (calenzanol)



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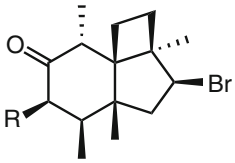
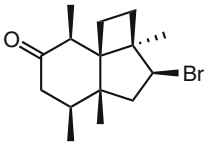


383 R = Br
384 R = OMe
385 R = H



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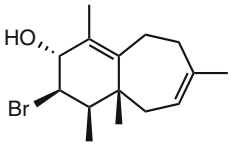
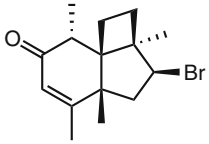


387 (perforenol B)



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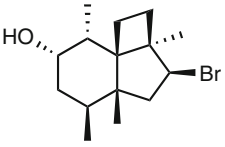
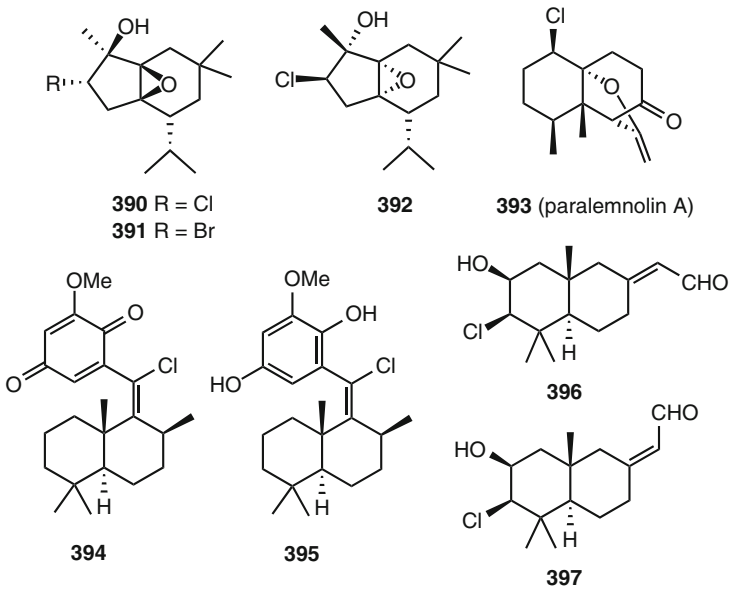
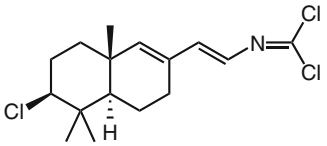


389 (perforatol)

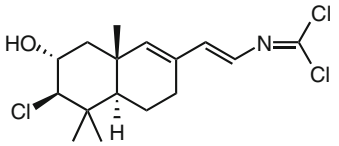
An examination of the red seaweed *Laurencia obtusa* from Symi Island in the Aegean Sea has uncovered the brasilanes **390**–**392** (*597*). The soft coral *Paralemnalia thyrsoides* from Taiwan has afforded the chlorinated norsesquiterpenoid paralemnolin A (**393**) (*598*), and the Australian sponge *Euryspongia* sp. provides the sesquiterpene quinone (*E*)-chlorodeoxyspongiaquinone (**394**) and related hydroquinone (*E*)-chlorodeoxyspongiaquinol (**395**) (*599*). Several new sesquiterpene chlorohydrins and carbonimidic dichlorides (*600*) have been found in the sponge *Stylotella aurantium* (Fig. 3.3), **396**–**398** (*545, 546*), and from the nudibranch *Reticulidia fungia* (Fig. 3.4), reticulidins A (**399**) and B (**400**) (*601*). A biosynthetic pathway to these sesquiterpene dichloroimines involving farnesyl isocyanide and isothiocyanate is supported by labeling experiments (*548*). The sea hare *Aplysia dactylomela* contains caespitenone (**401**) and 8-acetylcaespitol (**402**) (*554*), and *Aplysia punctata* has yielded punctatol (**403**) (*596*). The former mollusc also contains deschlorobromocaespitol (**404**) and furocaespitanelactol (**405**) (*557*).

Fig. 3.4 *Reticulidia fungia*, a nudibranch collected in Manza, Okinawa, that contains reticulidins A and B (**399** and **400**) (Photo: J. Tanaka)

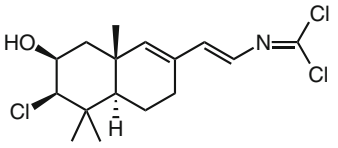




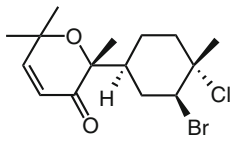
398 (deoxyisoreticulidine B)



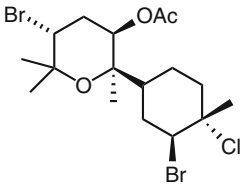
399 (reticulidin A)



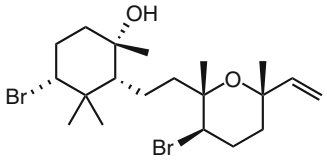
400 (reticulidin B)



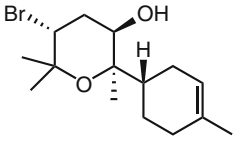
401 (caespitenone)



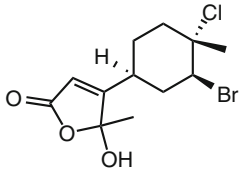
402 (8-acetylcaespitol)



403 (punctatol)



404 (deschlorobromocaespitol)



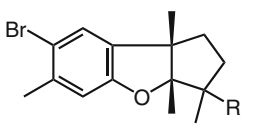
405 (furocaespitanelactol)

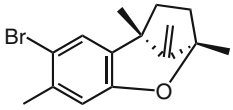
Cuparene, Laurene, and Other Aromatic Types

Some 50 marine aromatic halogenated sesquiterpenes were documented in the first survey (*1*). In the interim a number of new examples have been reported, mainly from *Laurencia* red algae.

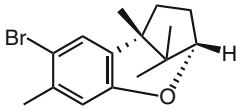
A study of *Laurencia tristicha* from the South China Sea has discovered the hydroxylated aplysins, 10-hydroxyepiaplysin (**406**) and 10-hydroxyaplysin (**407**) (*602*), and 4-bromo-1,1-epoxylaur-11-ene (**408**), which was previously synthesized but not found naturally (*603*). *Laurencia microcladia* from the North Aegean Sea has yielded the new **409** and **410**, which exhibit significant cytotoxicity against two lung cancer cell lines (*604*). This red alga also contains the dimeric cyclolaurane **411** (*595*). An East China Sea collection of *Laurencia okamurai* has led to the isolation of the novel laureperoxide (**412**) and 10-bromoisoaplysin (**413**)

(*605*), and "3β-hydroxyaplysin" and "laurokamurene A" (*606*), which would appear to be identical to 10-hydroxyaplysin (**407**) and **410**, respectively. Specimens of the sea hare *Aplysia kurodai* from the Sea of Japan have afforded the new laurinterol acetate (**414**) (*607*). It should be noted that syntheses of these halogenated cuparane and asplysin sesquiterpenes are known (*608, 609*). The previously known laurinterol, isolaurinterol, aplysinal, and aplysin (*1*) show pronounced cytotoxicity against the A549, SK-OV-3, SK-MEL-2, XF498, and HT15 cell lines (*610*).





406 R = α–OH (10-hydroxyepiaplysin) **408** (4-bromo-1,10-epoxylaur-11-ene)
407 R = β–OH (10-hydroxyaplysin)



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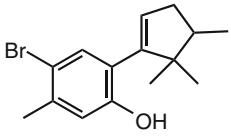

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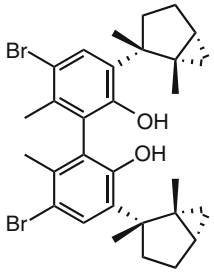

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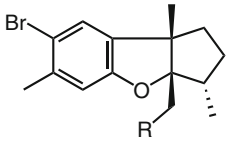
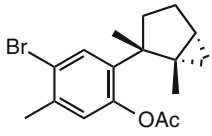
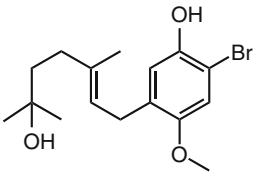




412 R = OOH (laureperoxide) **414** (laurinterol acetate)
413 R = Br (10-bromoisoaplysin)

The green alga *Cymopolia barbata* from Cuba contains the new prenylated hydroquinones 3′-methoxy-7-hydroxycymopol (**415**), 3-hydroxycymopolone (**416**), 3,7-dihydroxycymopolone (**417**), 7-hydroxycymopochromanone (**418**), 7-hydroxycymopochromenol (**419**), 6-hydroxycymopochromenol (**420**) (*611*), and a Jamaican collection of this alga yielded 7-hydroxycymopol (**421**) (*612*). The latter compound was previously described as a synthetic intermediate (*613*). The structurally similar known brominated cacoxanthenes from the sponge *Cacospongia* are found in the blubber of monk seal, in commercial fish samples and mussels (*489*). The sponge *Spirastrella hartmani* from Martinique has yielded the two halogenated heliananes **422** and **423** (*614*). The New Zealand sponge *Hamigera tarangaensis* produces hamigeran A (**424**), hamigeran B (**425**), 4-bromohamigeran B (**426**), hamigeran C (**427**), hamigeran D (**428**), and hamigeran E (**429**) (*615*). The structure of hamigeran E was revised from that reported earlier (*616*), and the structures of **424**, **425**, and **426** have been confirmed by total synthesis (*617, 618*).



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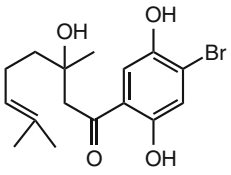

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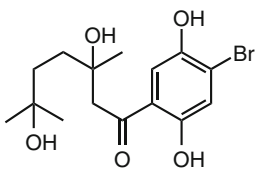

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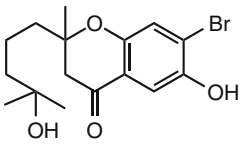

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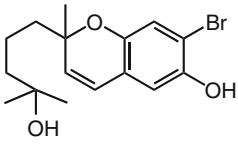

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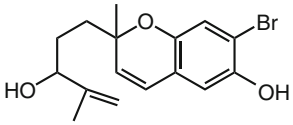

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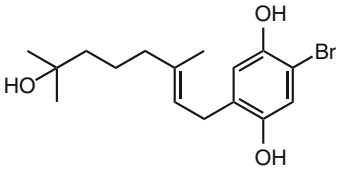

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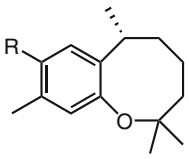
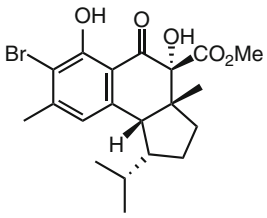
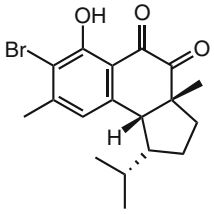


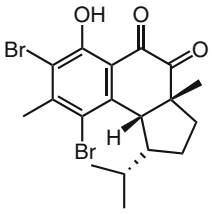
422 R = Cl
423 R = Br



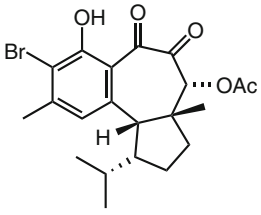
424 (hamigeran A)



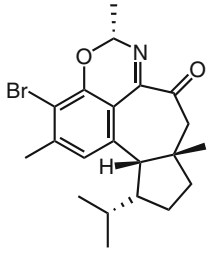
425 (hamigeran B)



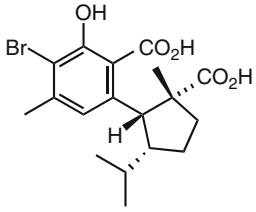
426 (4-bromohamigeran B)



427 (hamigeran C)

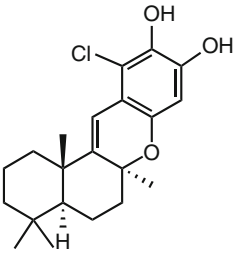


428 (hamigeran D)

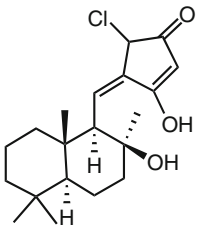


429 (hamigeran E)

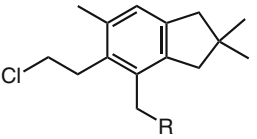
The Hawaiian sponge *Hyrtios* sp. from Oahu has furnished 21-chloropuupehenol (**430**), while the same sponge from Maui contains molokinenone (**431**) (*619*). The absolute configuration of these drimane-phenolic metabolites has been assigned as shown based on that of puupehenone (*620*). The South Georgia Island soft coral *Alcyonium paessleri* produces several novel illudalane sesquiterpenoids, including the chlorinated alcyopterosins A (**432**), D (**433**), K (**434**), and L (**435**) (*621*).



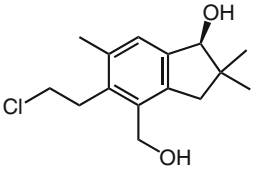
430 (21-chloropuupehenol)



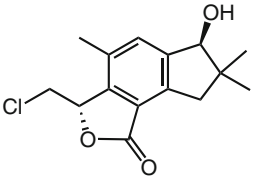
431 (molokinenone)



432 R = H (alcyopterosin A)
433 R = OH (alcyopterosin D)



434 (alcyopterosin K)



435 (alcyopterosin L)

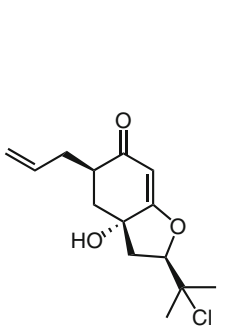
3.4.3 Diterpenes

3.4.3.1 Terrestrial Diterpenes

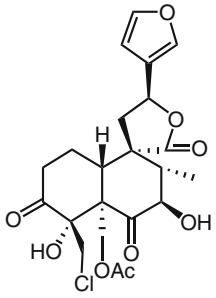
As was illustrated in the first survey, all known halogenated terrestrial diterpenes are chlorohydrins (*1*), and that continues to be mainly the case. Obviously, one must be alert to the possibility of artifact formation from ring opening of the corresponding epoxide during isolation. Many nonhalogenated terrestrial diterpenoids also continue to be isolated (*622*).

The Brazilian plant *Vellozia bicolor* contains the isopimarane diterpene 12-chloroillifunone C (**436**). The corresponding epoxide, which is also found in this plant, is not converted to **436** under the isolation conditions (*623*). Teuracemin (**437**), a novel *neo*-clerodane diterpene, was isolated from *Teucrium racemosum* and is the 7-hydroxy derivative of the known tafricanin A (*624*). Examination of fresh plant material revealed the presence of **437**. The new *neo*-clerodane ajugarin-I chlorohydrin (**438**) has been characterized from the Indian plant *Ajuga parviflora*

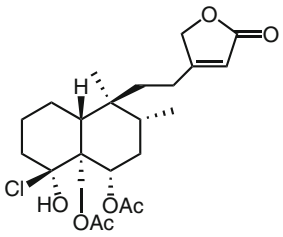
(*625*). The wood resin of *Excoecaria agallocha* has furnished several labdane-type diterpenes including the chlorinated excoercarin F (**439**), which is the first example of a chlorine-containing metabolite from this "shore plant" (*626*). Another investigation of this mangrove plant from India revealed the labdanes agallochins A (**440**), B (**441**), and C (**442**) in the roots (*627*). Another mangrove plant, *Bruguiera gymnorrhiza*, from China contains the *ent*-kaurane **443** (*628*).



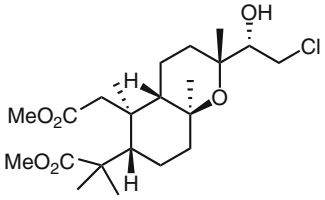
436 (12-chloroillifunone C)



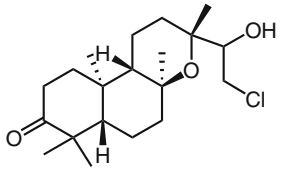
437 (teuracemin)



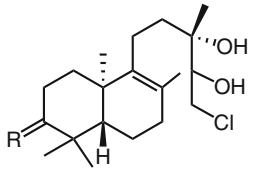
438



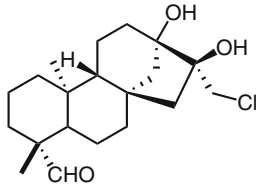
439 (excoercarin F)



440 (agallochin A)

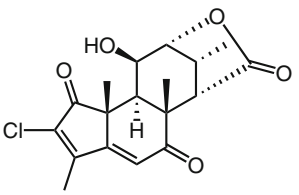


441 R = O (agallochin B)
442 R = βOH, H (agallochin C)

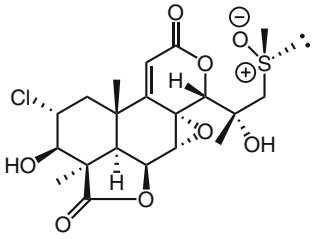


443

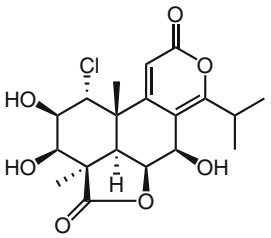
The novel chloroenone quassinoid eurycolactone B (**444**) was characterized from the roots of *Eurycoma longifolia* from Malaysia (*629*). This is the first halogenated quassinoid discovered in a plant. A series of norditerpene dilactones, including the chlorinated rakanmakilactones E (**445**), G (**446**), and **447**, were isolated from the leaves of *Podocarpus macrophyllus* from Japan (*630, 631*). These represent the first halogenated norditerpene dilactones found in the Podocarpaceae.



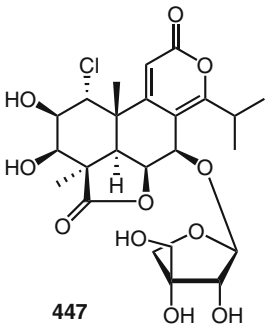
444 (eurycolactone B)



445 (rakanmakilactone E)



446 (rakanmakilactone G)



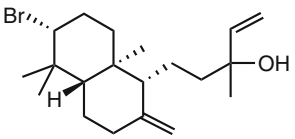
447

3.4.3.2 Marine Diterpenes

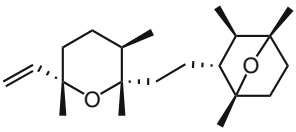
In contrast to the small number of known halogenated (chlorinated) terrestrial diterpenes (vide supra), the number of marine diterpenes is very large, and more than 130 were documented in the initial survey (*1*).

Diterpenes of Aplysia

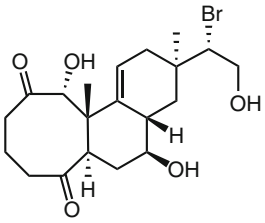
Sea hares of genus *Aplysia* continue to be the source of new halogenated and nonhalogenated diterpenes, and a review of diterpenes from marine opisthobranch molluscs has appeared (*632*). The Tenerife *Aplysia dactylomela* contains isopinnatol B (**448**) and dactylopyranoid (**449**) (*554*). *Aplysia punctata* from Sardinia has afforded the novel neoparguerol dione (**450**), which may arise from the previously known isoparguerol, and deacetylparguerol (**451**) (*596*). Most probably all of these brominated diterpenes originate from the *Laurencia* and other algae diet of the sea hare.



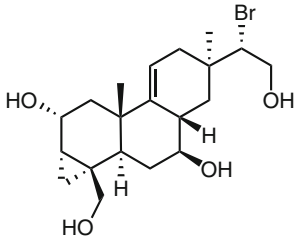
448 (isopinnatol B)



449 (dactylopyranoid)



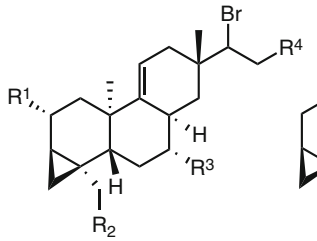
450 (neopargueroldione)



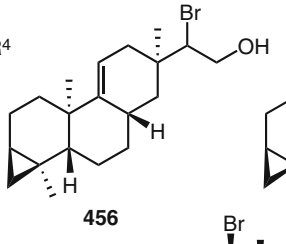
451 (deacetylparguerol)

Diterpenes of Laurencia

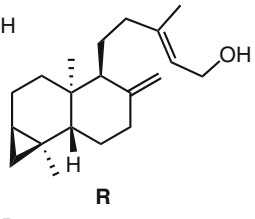
Laurencia red seaweeds produce a large and varied assortment of halogenated (mainly brominated) diterpenes (*1*), and this trend continues with the present survey. Five new parguerenes, **452**–**456**, are found in the Southern Australian *Laurencia filiformis*, along with a plausible biogenic precursor **R** (*633*). A collection of *Laurencia nipponica* from Russian waters in the Sea of Japan has identified the new pargueranes **457** and **458**, where the former metabolite appears to be a diastereomer of **455** (*634*). The new *Laurencia japonensis* species contains anhydroaplysiadiol (**459**) along with the known aplysiadiol and a halogenated chamigrene (*635*). A collection of *Laurencia paniculata* from the Arabian Gulf furnished the *ent*-labdane paniculatol (**460**), which contains an unusual tetrahydropyran ring and is closely related to the known *ent*-isoconcinndiol isolated from *Aplysia kurodai* (*636*). The closely related *ent*-labdanes **461** and **462** were found in an Okinawan *Laurencia* sp. collection, and are the first labdane bromoditerpenoids to be functionalized at C-1 (*637*). Two collections of *Laurencia* sp. in different locations in Japanese waters have yielded **463**, closely related to paniculatol (**460**) (*638*).



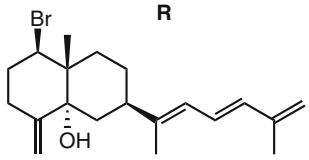
452 $R_1 = R^3 = R^4 = OAc$, $R^2 = H$
453 $R_1 = R^3 = OAc$, $R_2 = H$, $R^4 = OH$
454 $R_1 = OAc$, $R^2 = R^3 = H$, $R^4 = OH$
455 $R_1 = R^2 = R^3 = H$, $R^4 = OH$



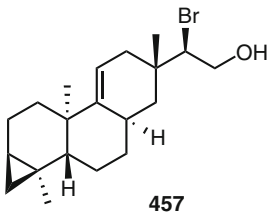
456



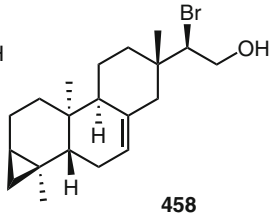
R



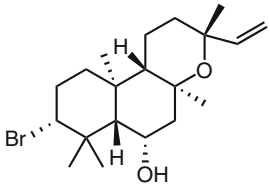
459 (anhydroaplysiadiol)



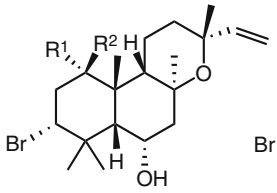
457



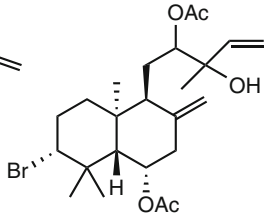
458



460 (paniculatol)

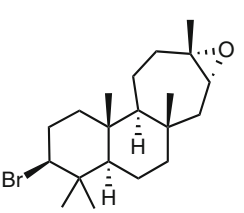


461 $R^1 = OAc$, $R^2 = H$
462 $R^1 = R^2 = O$

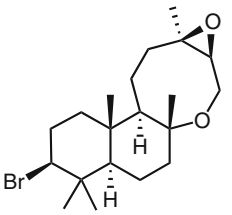


463

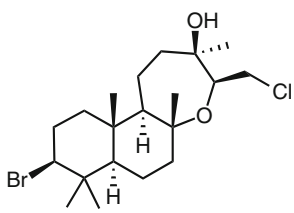
The Okinawan *Laurencia luzonensis* contains 3-bromobarekoxide (**464**), a novel seven-membered ring diterpene (*549, 639*). Equally unprecedented are the labdanes **465** and **466** from *Laurencia obtusa* gathered in the Ionean Sea (*640*). This source of *Laurencia obtusa* has also yielded the new prevezols A (**467**) and B (**468**), which are marginally related to the known obtusadiol and rogioldiol A (vide infra) (*641*). This red alga also contains the new prevezols C-E (**469**–**471**) and neorogioldiol B (**472**) (*642*). Prevezol B (**468**) was revised (*642*) from the original assignment (*641*).



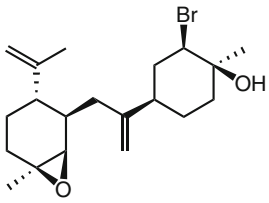
464 (3-bromobarekoxide)



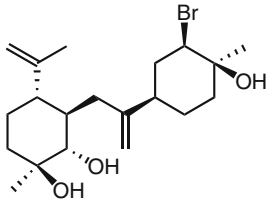
465



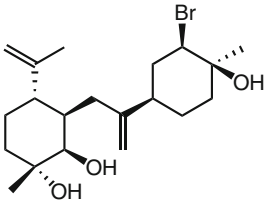
466



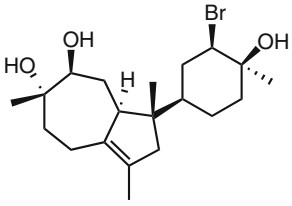
467 (prevezol A)



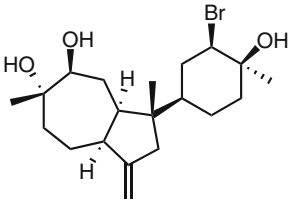
468 (prevezol B)



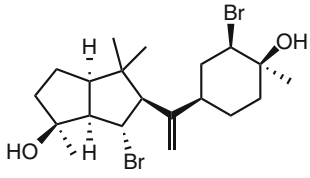
469 (prevezol C)



470 (prevezol D)

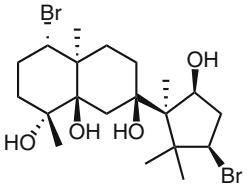


471 (prevezol E)

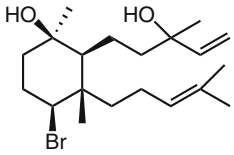


472 neorogioldiol B)

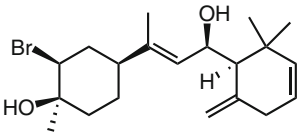
The neoirieane diterpene neoirietetraol (**473**) is found in the new *Laurencia yonaguniensis* species (*643*), and the novel luzodiol (**474**) was isolated from *Laurencia luzonensis* found in Okinawa (*558*). A study of *Laurencia microcladia* from the coast of Tuscany has yielded rogioldiol A (**475**), rogiolal (**476**), isorogiolal **477** (*644*), rogioldiols B (**478**), and C (**479**) (*645*). Further studies of this seaweed identified neorogioldiol (**480**), rogioldiol D (**481**), and **482** (*646*).



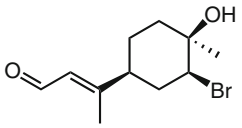
473 (neoirietetraol)



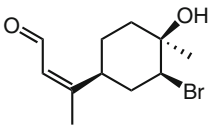
474 (luzodiol)



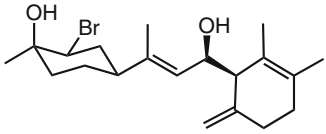
475 (rogioldiol A)



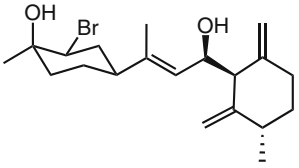
476 (rogiolal)



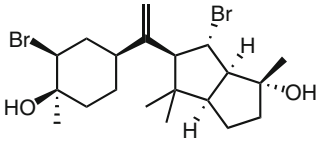
477 (isorogiolal)



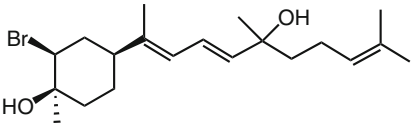
478 (rogioldiol B)



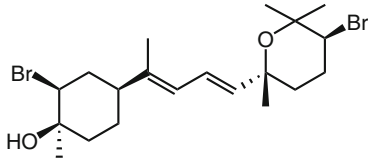
479 (rogioldiol C)



480 (neorogioldiol)



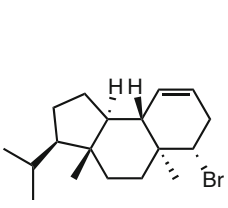
481 (rogioldiol D)



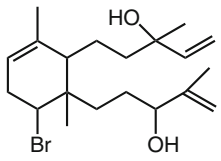
482

Sphaerococcus and Other Red Algae Diterpenes

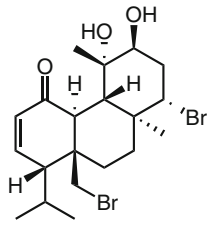
The Mediterranean red alga *Sphaerococcus coronopifolius*, which was seen to be a rich source of novel bromine-containing diterpenes in the first survey (*1*), has furnished some new examples. A Naples collection of this seaweed has afforded norsphaerol (**483**), and sphaerolabdadiene-3,14-diol (**484**) and bromosphaerone (**485**) were characterized from a Morocco version of this alga (*648*). The novel and unprecedented iodinated diterpenes tasihalides A (**486**) and B (**487**) were isolated from a *Symploca* cyanobacterium associated with an unidentified red alga (*649*). The Fijian red alga *Callophycus serratus* produces the nine novel bromophycolides A–I (**488**–**496**), which contain a diterpene-benzoate skeleton (*650, 651*).



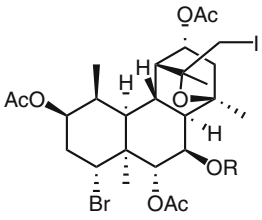
483 (norsphaerol)



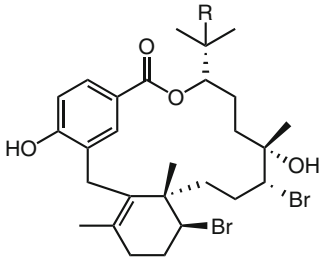
484 (sphaeroladadiene-3,14-diol)



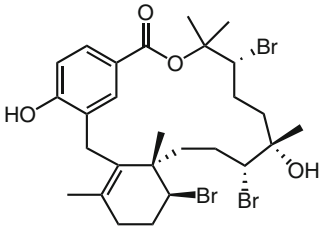
485 (bromosphaerone)



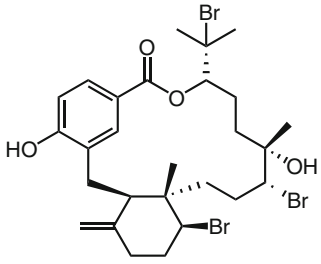
486 R = H (tasihalide A)
487 R = Ac (tashalide B)



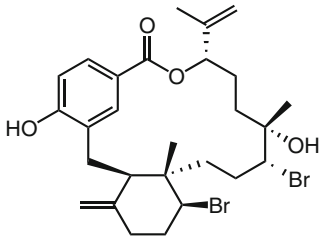
488 R = Br (bromophycolide A)
490 R = OH (bromophycolide C)



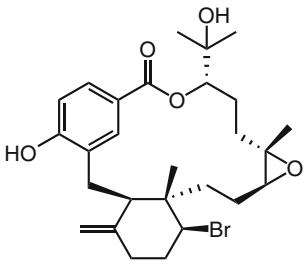
489 (bromophycolide B)



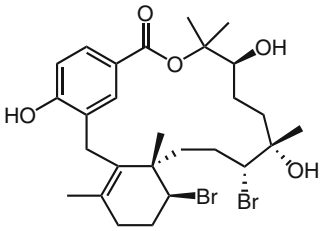
491 (bromophycolide D)



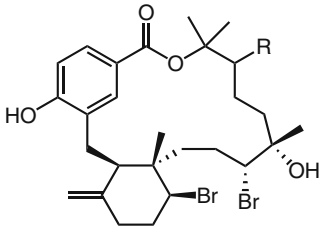
492 (bromophycolide E)



493 (bromophycolide F)



494 (bromophycolide G)

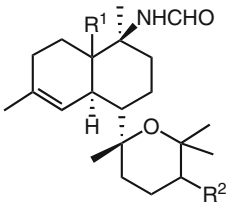


495 R = α–Br (bromophycolide H)
496 R = β–OH (bromophycolide I)

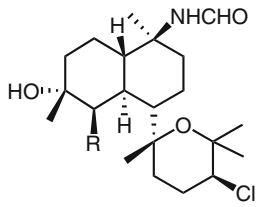
Sponge Diterpenes

Relatively few sponge diterpenes are known and these are typified by the isocyano kalihinanes (*600, 652*), such as the kalihinols that were presented in the first survey (*1, 653, 654*). The absolute configuration of kalihinol A has been determined (*655*) and it is correct as shown in the first survey (*1*). Sponges of genus *Acanthella* from the Pacific Ocean are the producers of the kalihinanes. Investigations of *Acanthella cavernosa* in Pacific waters south of Tokyo (Yakushima Island) have uncovered the new kalihinenes X (**497**), Y (**498**), and Z (**499**) (*656*), and a total synthesis of kalihinene X (**497**) has established its relative and absolute configuration (*657*). A collection from a slightly different location revealed 10β-formamidokalihinol-A (**500**), 10β-formamidokalihinol-E (**501**), 10β-formamido-5-isocyanatokalihinol-A (**502**), and 10β-formamido-5β-isothiocyanatokalihinol-A (**503**) (*658*). The Yakushima sample also yielded kalihipyran B (**504**) (*659*). All of these metabolites display potent antifouling activity against larvae of the barnacle *Balanus amphitrite*, suggesting a natural function for these compounds in the sponge. An Okinawan collection of *Acanthella* sp. contains the new Δ^9-kalihinol Y (**505**) and 10-epikalihinol I (**506**) (*660*). This paper also describes the powerful antimalarial activity of kalihinol A. The Philippines sponge *Phakellia pulcherrima*, which is

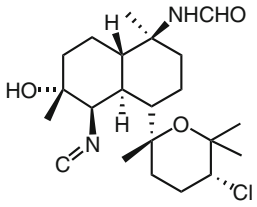
in the same family as *Acanthella cavernosa*, contains several known kalihinols, including **505** (*661*).



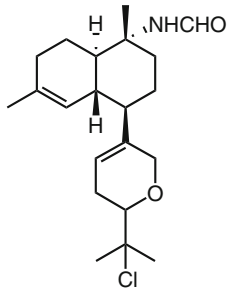
497 $R^1 = \alpha$-H, $R^2 = \beta$-Cl (kalihinene X)
498 $R^1 = \beta$-H, $R^2 = \beta$-Cl (kalihinene Y)
499 $R^1 = \alpha$-H, $R^2 = \alpha$-Cl (kalihinene Z)



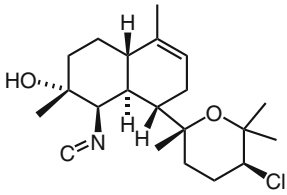
500 R = NC
502 R = NCO
503 R = NCS



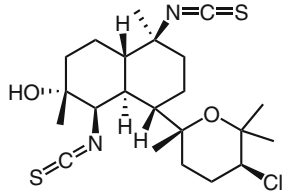
501



504 (kalihipyran B)

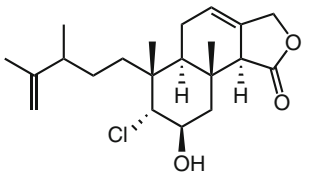


505 (Δ^9-kalihinol Y)

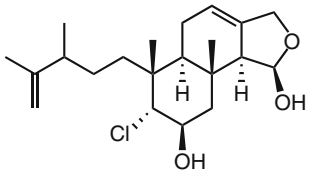


506 (10-epikalihinol I)

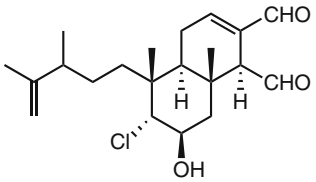
The first report of isocyanide diterpenes occurring in nudibranchs (sea slugs) has appeared, which describes the known kalihinol A and kalihinol E, along with nonchlorinated metabolites, in *Phyllidiella pustulosa* from the South China Sea (*662*). This supports the notion that nudibranchs feed on sponges and thereby acquire metabolites for their own purposes, giving new meaning to the term "lazy slugs". A nudibranch from South Africa, *Chromodoris hamiltoni*, contains the novel hamiltonins A–D (**507**–**510**) (*663*). The Mediterranean dorid nudibranch *Doris verrucosa* has afforded several novel diterpene isocopalane verrucosins, including the chlorinated verrucosins-7 (**511**) and -9 (**512**) (*664*).



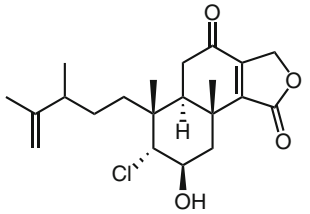
507 (hamiltonin A)



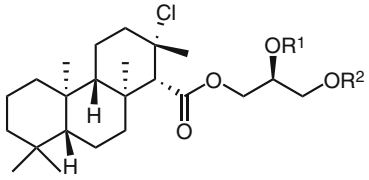
508 (hamiltonin B)



509 (hamiltonin C)



510 (hamiltonin D)

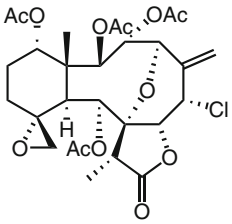


511 R^1 = H, R^2 = Ac (verrucosin-7)
512 R^1 = Ac, R^2 = H (verrucosin-9)

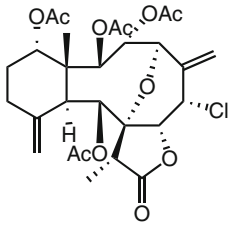
Gorgonian Diterpenes

Gorgonians produce the largest complement of chlorine-containing marine metabolites – more than 50 were illustrated in the first survey (*1*) – and many more nonchlorinated gorgonian diterpenes are known (*665–667*). There is evidence to indicate that these gorgonian diterpenoids are feeding deterrents to reef fishes. Gorgonian corals can achieve densities of up to 20 colonies per square meter on the reef (*668, 669*).

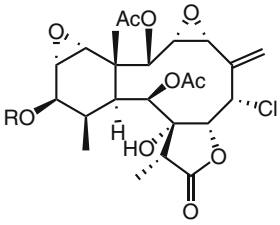
The stereochemistry of the diterpenoid praelolide, which was originally isolated from *Plexaureides praelonga* from the South China Sea (*1*) and subsequently from the Indian Ocean gorgonian *Gorgonella umbraculum* (*670*) and the Taiwanese *Junceella fragilis* and *Junceella juncea* (*671*), has now been confirmed as **S** (*670, 671*). Likewise the structure of junceellin, which was incorrect in the first survey (*1*), is corrected as **T** (*670, 671*). The stereochemistry of the previously known solenolides C and D are proposed to be revised as **U** and **V** (*672*). Several new chlorinated briareins have been identified from the common Caribbean gorgonian *Briareum asbestinum*, including briareins B (**513**), C (**514**), D (**515**), E (**516**), F (**517**), G (**518**), and J (**519**) (*673*). Although briarein B was isolated some years previously, its structure was not positively established at that time (*674, 675*).



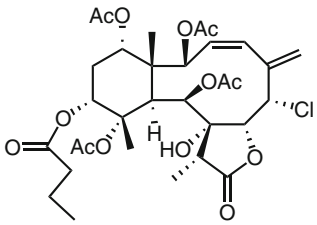
S (praelolide)



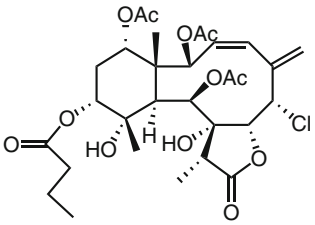
T (junceellin)



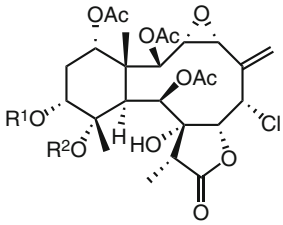
U R = H (solenolide C)
V R = Ac (solenolide D)



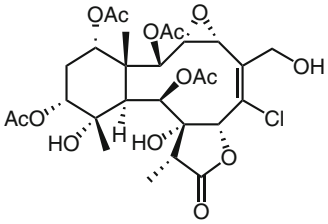
513 (briarein B)



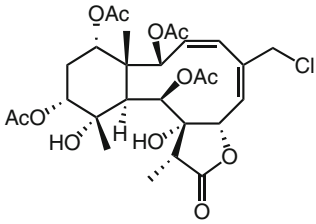
514 (briarein C)



515 $R^1 = R^2 = Ac$ (briarein D)
516 $R^1 = Ac$, $R^2 = H$ (briarein E)
518 $R^1 = COPr$, $R^2 = Ac$ (briarein G)



517 (briarein F)



519 (briarein J)

A Bahamian collection of *Briareum asbestinum* (Fig. 3.5) has provided the new 11-hydroxybrianthein V (**520**), 11-hydroxybrianthein U (**521**), 11-hydroxybrianthein Y (**522**), 3,4-dihydro-11-hydroxybrianthein V (**523**), and 3,4-dihydro-

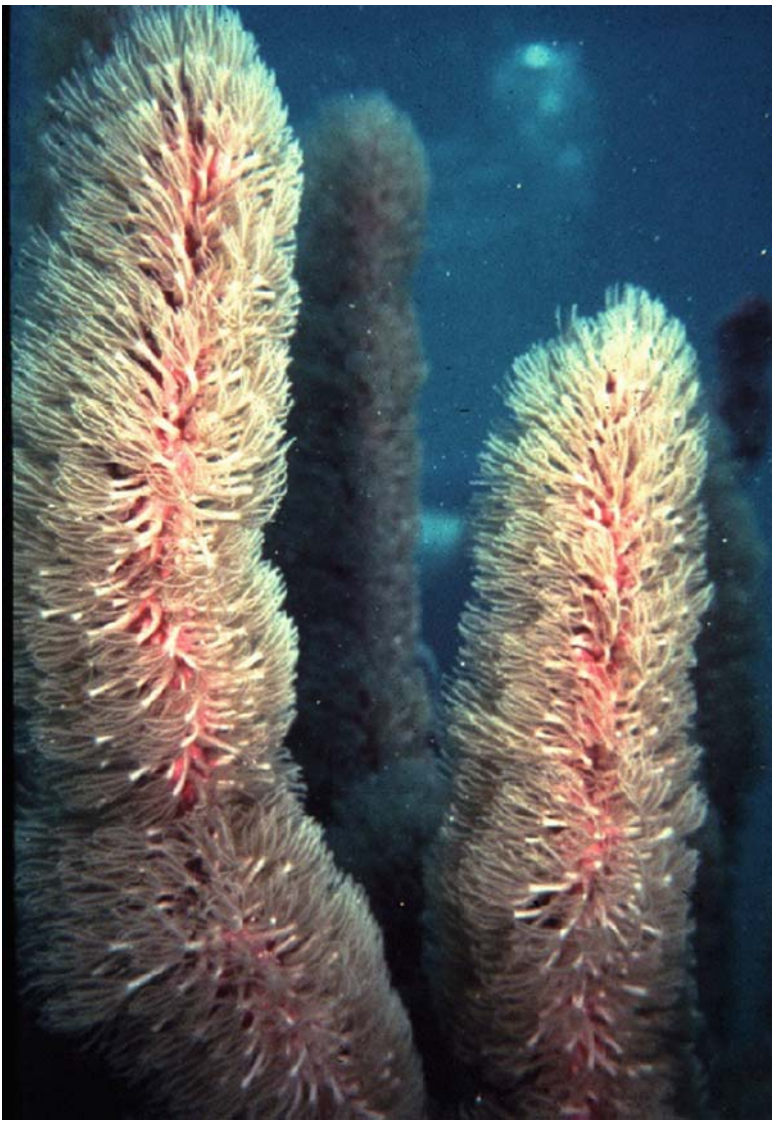
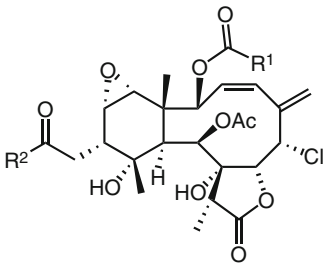
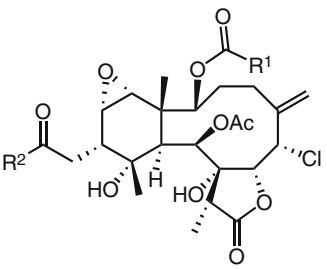


Fig. 3.5 *Briareum asbestinum*, a Caribbean gorgonian soft coral that produces numerous chlorinated diterpenes such as the briareins (**513–519**) and briantheins (**520–524**) (Photo: W. Fenical)

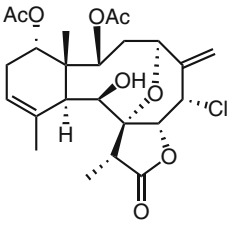
11-hydroxybrianthein U (**524**) (*676*), whereas a study of *Briareum excavatum* from Taiwan yielded a series of excavatolides, one of which is chlorinated, excavatolide A (**525**) (*677*). This latter gorgonian collection also contains seven chlorinated briaexcavatolides E (**526**), F (**527**), G (**528**), H (**529**), I (**530**), J (**531**) (*678*), and M (**532**) (*679*).



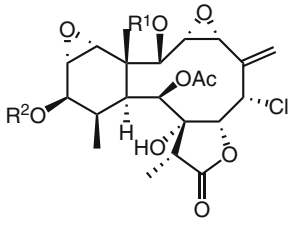
520 $R^1 = R^2 = n$-Pr
521 R^1 = Me, $R^2 = n$-Pr
522 $R^1 = n$-Pr, R^2 = Me



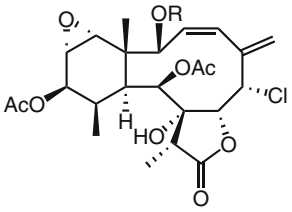
523 $R^1 = R^2 = n$-Pr
524 R^1 = Me, $R^2 = n$-Pr



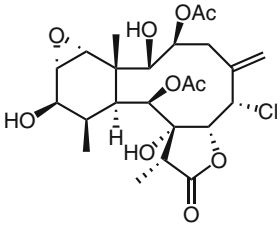
525 (excavatolide A)



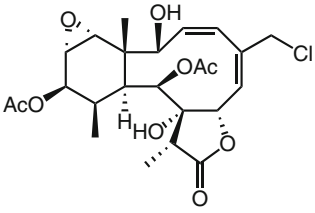
526 $R^1 = R^2$ = Ac (briaexcavatolide E)
527 R^1 = H, $R^2 = COCH_2CH_2CH_3$ (briaexcavatolide F)
528 $R^1 = R^2$ = H (briaexcavatolide G)



529 R = H (briaexcavatolide H)
530 R = Ac (briaexcavatolide I)



531 (briaexcavatolide J)

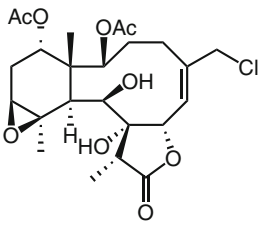


532 (briaexcavatolide M)

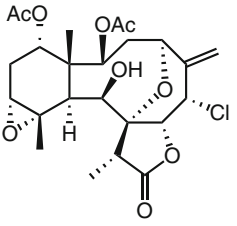
The Micronesian soft coral *Briareum stechei* (Fig. 3.6) has furnished a series of milolides, including 16-chloromilolide B (**533**), milolide C (**534**), 4-hydroxymilolide C (**535**), milolide D (**536**), milolide E (**537**) (*680*), and milolide L (**538**) (*681*).

Fig. 3.6 *Briareum stechei*, a Western Pacific octocoral that produces the milolides (**533–538**) (Photo: F. J. Schmitz)

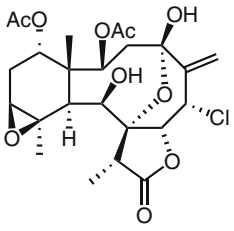
The stereochemistry of solenolide C (**U**) is also revised in this study (*680*). The new briviolides B (**539**) and C (**540**) were characterized from a Japanese collection of *Briareum* sp. (*682*). A study of octocorals from Pohnpei and Ant atoll in Micronesia led to the novel nui-inoalides A–D (**541–544**) (*683*). The absolute configuration of juncin E (**W**) was also established by these researchers.



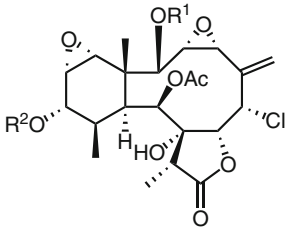
533 (16-chloromilolide B)



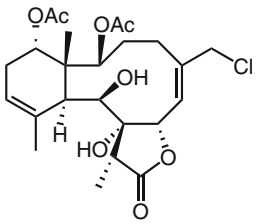
534 (milolide C)



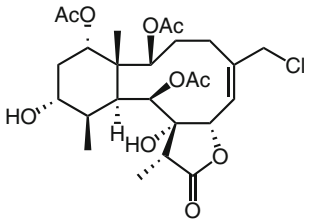
535 (4-hydroxymilolide C)



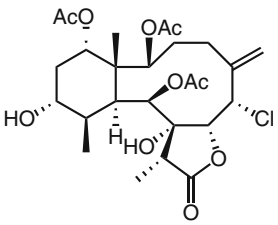
536 R^1 = H, R^2 = COC_3H_7 (milolide D)
537 R^1 = Ac, R^2 = COC_5H_{11} (milolide E)



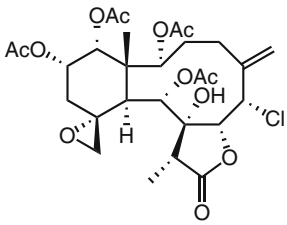
538 (milolide L)



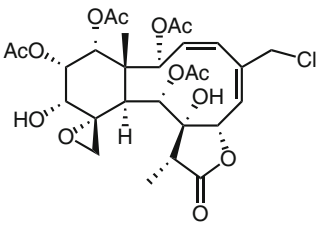
539 (briviolide B)



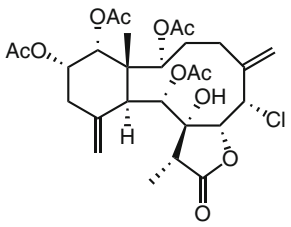
540 (briviolide C)



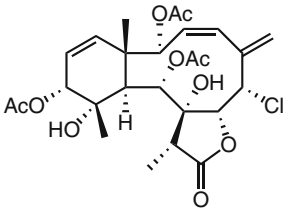
541 (nui-inoalide A)



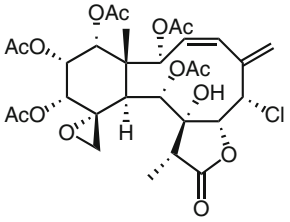
542 (nui-inoalide B)



543 (nui-inoalide C)



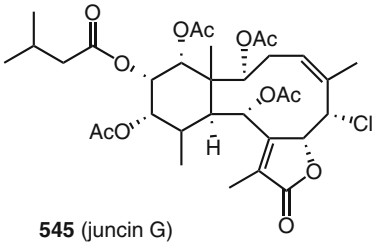
544 (nui-inoalide D)



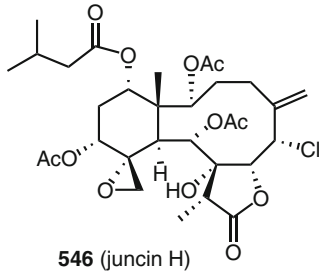
W (juncin E)

Another prolific gorgonian is *Junceella*, and these animals contributed 15 chlorinated briarane diterpenoids to the first survey. A series of juncins A–F from the Red Sea *Junceella juncea* were presented earlier, although C and F were not

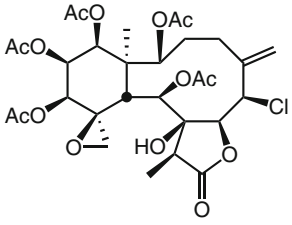
precisely defined (*1*). The Indian Ocean *Junceella juncea* contains the new juncins G (**545**) and H (**546**), along with the antipodes of the previously known gemmacolides A (**547**) and B (**548**) (*684*). The same research group isolated chlorinated juncins L (**549**) and M (**550**) from this collection of *Junceella juncea* (*685*). Chemical extraction of this octocoral living in Taiwan waters furnished juncin N (**551**) (*686*), and the chlorine-containing juncins O (**552**) and P (**553**) were characterized from a South China Sea *Junceella juncea* (*687*), which also afforded juncins R (**554**), S (**555**), and ZI (**556**), along with seven new non-chlorinated briaranes (*688*). The Taiwanese *Junceella juncea* is also the source of juncenolides A (**557**) (*689*), F (**558**), and G (**559**) (*690*).



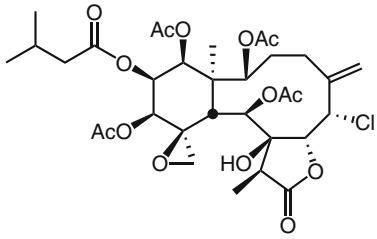
545 (juncin G)



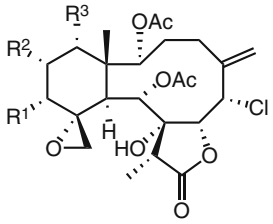
546 (juncin H)



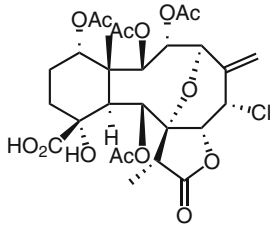
547 (gemmacolide A)



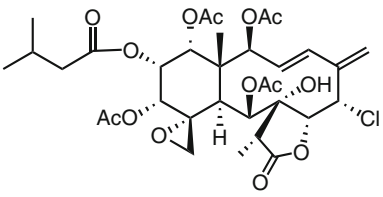
548 (gemmacolide B)



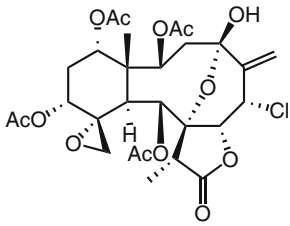
549 $R^1 = R^2 = OCOCH_2CH(CH_3)_2$, $R^3 = OAc$ (juncin L)
550 $R^1 = R^3 = OCOCH_2CH(CH_3)_2$, $R^2 = H$ (juncin M)



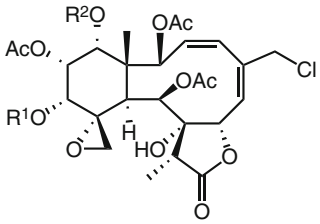
551 (juncin N)



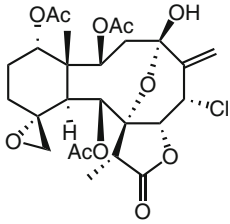
552



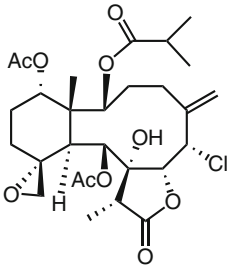
553 (juncin P)



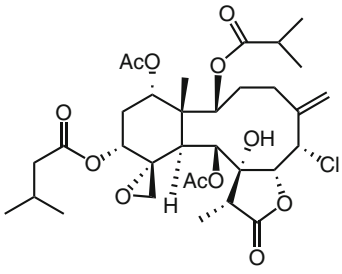
554 R^1 = Ac, R^2 = $COCH_2CH(CH_3)_2$ (juncin R)
555 R^2 = Ac, R^1 = $COCH_2CH(CH_3)_2$ (juncin S)



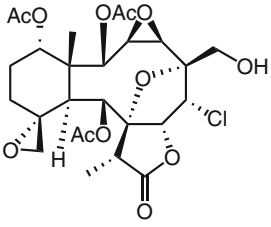
556 (juncin ZI)



557 (juncenolide A)



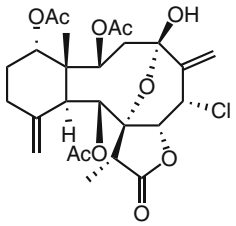
558 (juncenolide F)



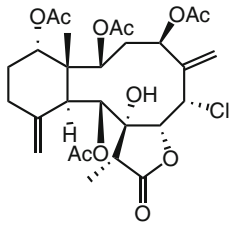
559 (juncenolide G)

Junceella fragilis from Indonesia contains the novel antipode (+)-junceelloide A (**560**) of the known (–)-junceelloide A (drawn incorrectly in (*1*)) (*691*). A collection of *Junceella fragilis* from the South China Sea yielded junceellonoid A (**561**) (*692*)

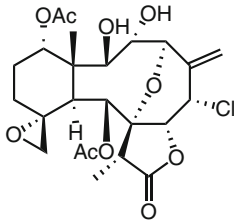
and junceellonoids C–E (**562**–**564**) (*693*), and a Papuan sample of this coral led to (–)-2-deacetyljunceellin (**565**) and (–)-3-deacetyljunceellin (**566**) (absolute configuration shown) (*694*).



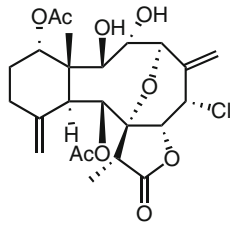
560 ((+)-junceellolide A)



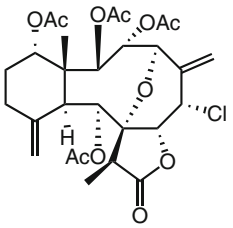
561 (junceellonoid A)



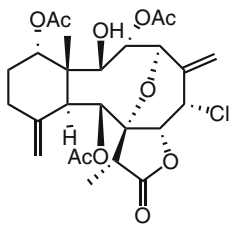
562 (junceellonoid C)



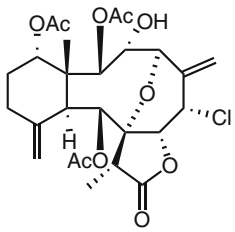
563 (junceellonoid D)



564 (junceellonoid E)



565 ((–)-2-deacetyljunceellin)



566 ((–)-3-deacetyljunceellin)

The common Caribbean octocoral *Erythropodium caribaeorum* has yielded several additional chlorinated diterpenes since the first survey (*1*).

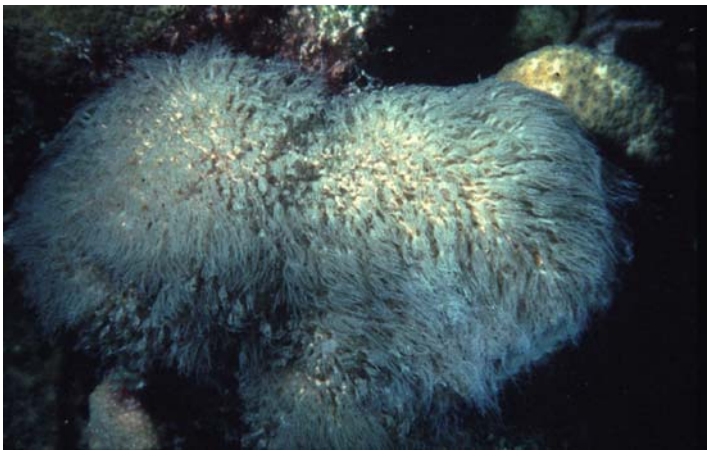
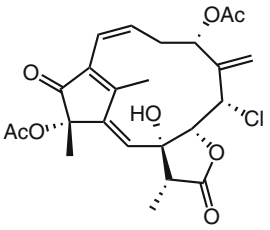
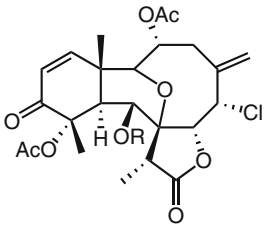


Fig. 3.7 *Erythropodium caribaeorum*, a common Caribbean octocoral that produces chlorinated diterpenes such as the erythrolides and aquariolides (**567**–**574**) (Photo: W. Fenical)

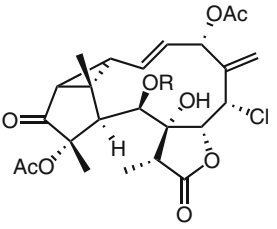
The structure of the novel erythrolide K (**567**), which was isolated from *Erythropodium caribaeorum* (Fig. 3.7) collected in Tobago, was confirmed by synthesis from the known erythrolide A (*695*). A Jamaican source of this soft coral has afforded the new **568** and **569** in addition to six known erythrolides (*696*). These two new compounds are acetyl derivatives of erythrolides E and I. The Tobagoan *Erythropodium caribaeorum* also contains the three new chlorinated erythrolides L (**570**), P (**571**), and Q (**572**) (*697*). A survey of *Erythropodium caribaeorum* from Dominica has revealed the new erythrolides R (**573**), T (**574**), U (**575**), V (**576**), and aquariolides B (**577**) and C (**578**) (*698*). Aquariolide A (**579**) was earlier isolated from cultured (aquarium grown) *Erythropodium caribaeorum* (*699*). On the basis of these studies, the authors suggest a biogenesis of: briaranes to erythranes (i.e., erythrolides) then to aquarianes (i.e., aquariolides), involving sequential di-π-methane and vinyl cyclopropane rearrangements (*699*), the first transformation of which was mentioned previously (*1*).



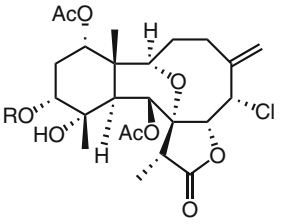
567 (erythrolide K)



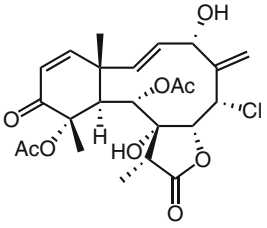
568 R = Ac
569 R = $COCH_2OAc$



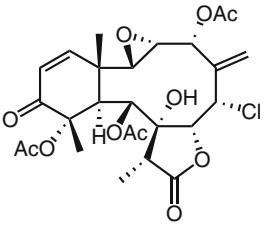
570 R = $COCH_2OAc$ (erythrolide L)



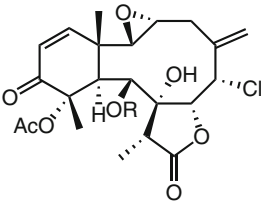
571 R = H (erythrolide P)
572 R = Ac (erythrolide Q)



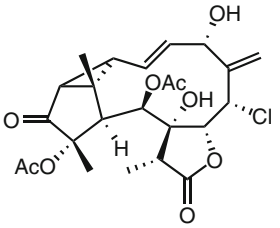
573 (erythrolide R)



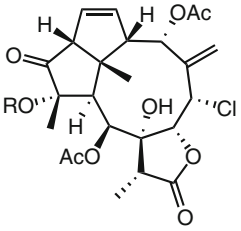
574 (erythrolide T)



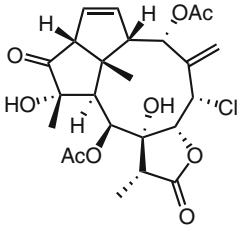
575 R = $COCH_2OH$ (erythrolide U)



576 (erythrolide V)



577 R = Me (aquariolide B)
578 R = Ac (aquariolide C)



579 (aquariolide A)

The Indian Ocean gorgonian *Gorgonella umbraculum* has yielded the new umbraculolides C (**580**) and D (**581**) (*700*). The Okinawan sea whip *Ellisella* sp. (Fig. 3.8) furnished the four new briaranes **582**–**585**, and the sea pen *Pteroeides* sp. (Fig. 3.9) was likewise found to contain the novel **586** and **587** (*701*). Renillins A (**588**) and B (**589**) were isolated from the sea pansy *Renilla reniformis* (*702*). These

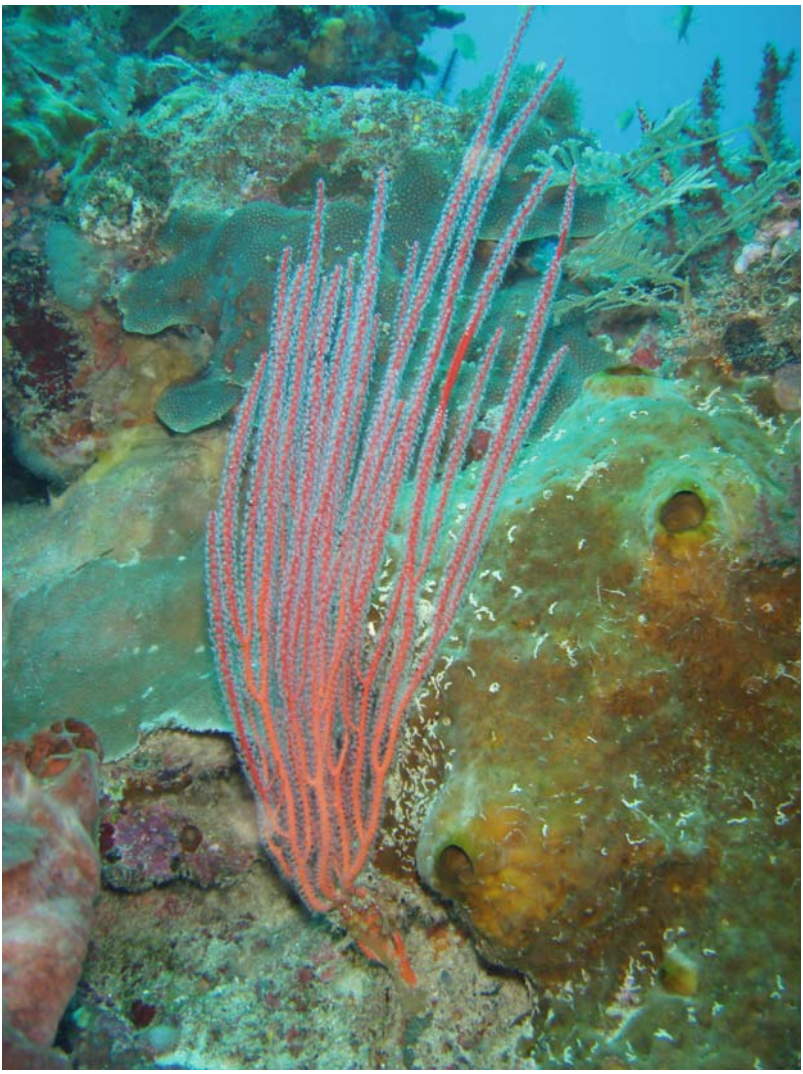
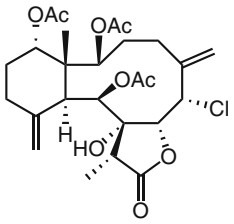


Fig. 3.8 *Ellisella* sp., a briarane-containing sea whip, collected in Alor, Indonesia (Photo: J. Tanaka)

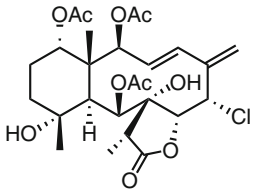
new compounds with an unprecedented oxygenation pattern deterred feeding by the predatory blue crab, *Callinectes similis*, and two nonchlorinated renillins were deterrents to the predatory mummichog fish, *Fundulus heteroclitus*. The soft coral *Pachyclavularia violacea* has furnished pachyclavulide D (**590**) along with three nonchlorinated analogs (*703*). The sponge *Psammaplysilla purpurea* contains bis (deacetyl)solenolide D (**591**) (*704*). Examination of the Pohnpei octocoral

Fig. 3.9 *Pteroeides* sp., a sea pen from Flores, Indonesia, that contains the novel diterpenes **586** and **587** (Photo: J. Tanaka)

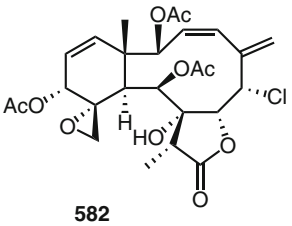
Eleutherobia sp. led to several known briareins. This study also found that minabien-6 is identical to 11-hydroxyptilosarcenone and that minabein-4 and nui-inoalide D are the same except they are epimeric at C-2 (*705*).



580 (umbraculolide C)



581 (umbraculolide D)



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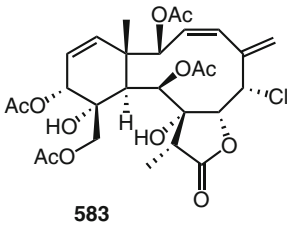

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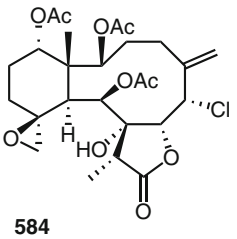

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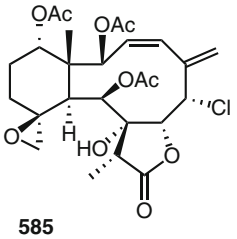

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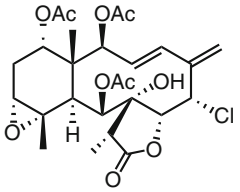

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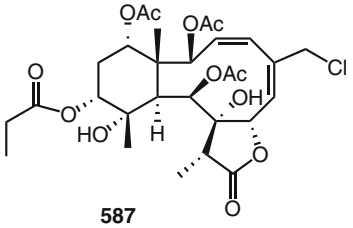

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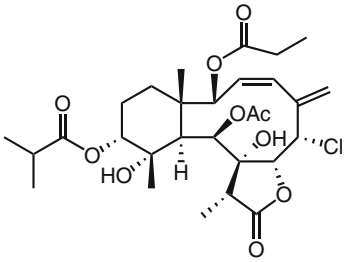
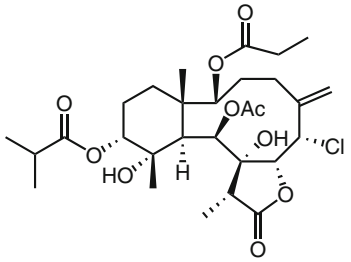
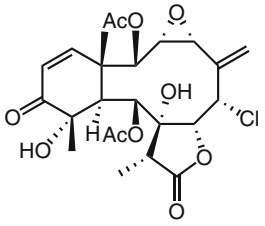


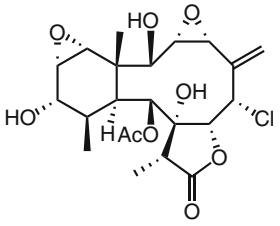
588 (renillin A)



589 (renillin B)

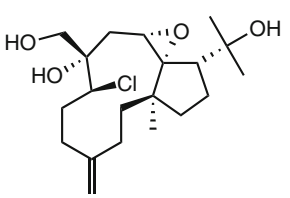


590 (pachyclavulide D)

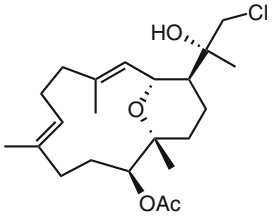


591

New diterpenoids of the dolabellane class have been reported, such as clavinflol B (**592**) from the Taiwanese soft coral *Clavularia inflata* (*706*). This metabolite has comparable cytotoxicity against the KB cell line to doxorubicin. A sea whip of the genus *Eunicea* has yielded the cembrane **593** (*707*). Both **592** and **593** are considered to be natural since no chlorinated solvents were used in the isolation process, and in both metabolites the chlorine is attached to the less substituted carbon, opposite to what is expected for acid-induced epoxide ring opening. A Kenyan soft coral, *Sinularia erecta*, contains the norcembrane sinularectin (**594**) (*708*).



592 (clavinflol B)



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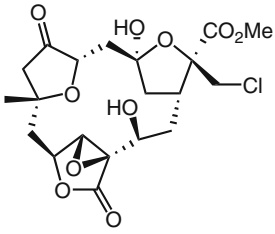
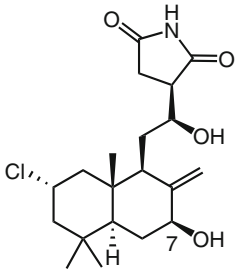
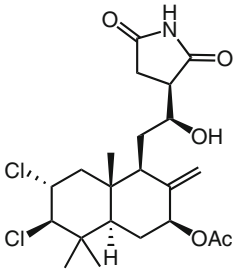


594 (sinularectin)

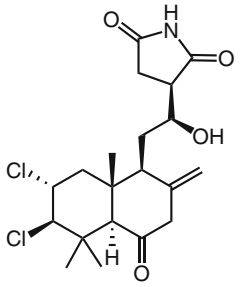
The New Caledonian ascidian *Lissoclinum voeltzkowi* has yielded several cytotoxic labdane diterpenes. Dichlorolissoclimide was described earlier (*1*) and the related chlorolissoclimide (**595**) was isolated subsequently (*709*). The C-7 hydroxy stereochemistry was more recently revised as shown for both **595** and dichlorolissoclimide (*710*). The antiproliferative activity of these compounds on a non-small-cell bronchopulmonary carcinoma cell line has been investigated (*711*). The lissoclimides are believed to be involved in human food poisoning from the consumption of oysters contaminated by *Lissoclinum voeltzkowi* (*709*). An Okinawan *Lissoclinum* sp. has yielded an array of chlorinated lissoclimide-type diterpenoids, the haterumaimides (*712–715*). This collection includes haterumaimides A–E (**596–600**) (*712*). Both C (**598**) and D (**599**) were detected in the animal and are not considered to be artifacts of B (**597**). Haterumaimides F-I (**601–604**) are also present, and both collections also produced the known chloro- (**595**) and dichlorolissoclimides (*713*). Heating G (**602**) and treating H (**603**) with *p*-toluenesulfonic acid resulted in no conversion to H (**603**) or I (**604**), respectively, supporting the natural origin of H and I. Haterumaimides J (**605**) and K (**606**) (*714*), and N (**607**), O (**608**), and P (**609**) (*715*) complete this metabolite collection. Only one compound in this set, haterumaimide Q, is not chlorinated. Some of the haterumaimides have sub-nanogram cytotoxicity and a structure–activity relationship is known; e.g., a chlorine atom at C-2 is essential for maximum activity (*715*). Haterumaimides L (**610**) and M (**611**), and 3β-hydroxychlorolissoclimide (**612**) were isolated from the molluscs *Pleurobranchus albiguttatus* (**610–612**) and *Pleurobranchus forskalii* (**610**, **611**) from the Philippines (*716*). The mechanism of cytotoxicity ascribed to the chlorolissoclimides seems to involve protein synthesis inhibition (*717*).



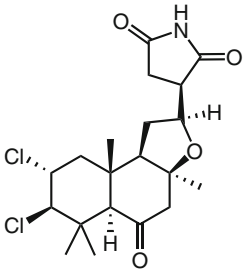
595 (chlorolissoclimide)



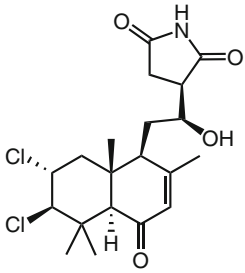
596 (haterumaimide A)



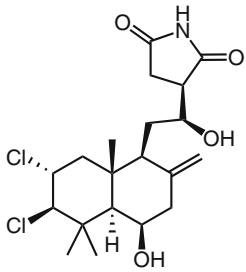
597 (haterumaimide B)



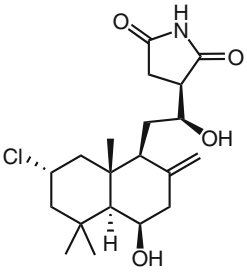
598 (haterumaimide C)



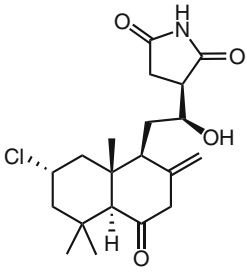
599 (haterumaimide D)



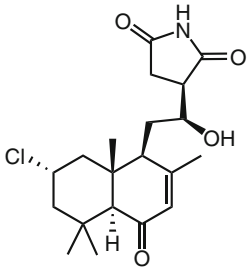
600 (haterumaimide E)



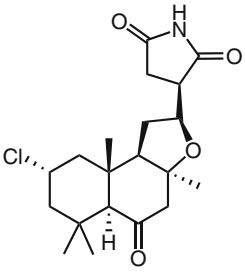
601 (haterumaimide F)



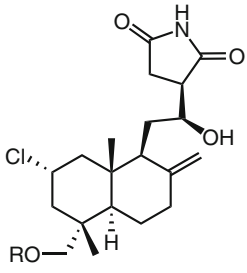
602 (haterumaimide G)



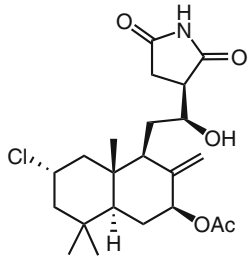
603 (haterumaimide H)



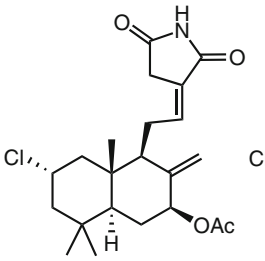
604 (haterumaimide I)



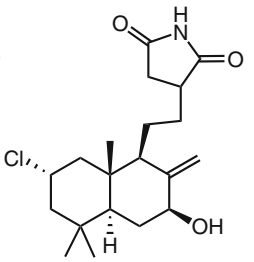
605 R = H (haterumaimide J)
606 R = Ac (haterumaimide K)



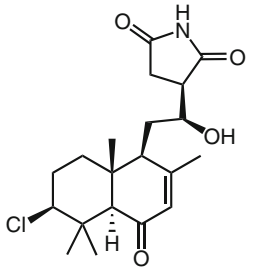
607 (haterumaimide N)



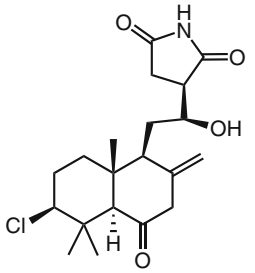
608 (haterumaimide O)



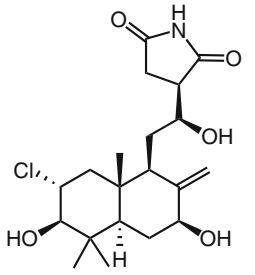
609 (haterumaimide P)



610 (haterumaimide L)



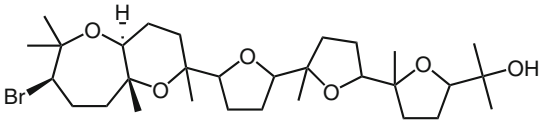
611 (haterumaimide M)



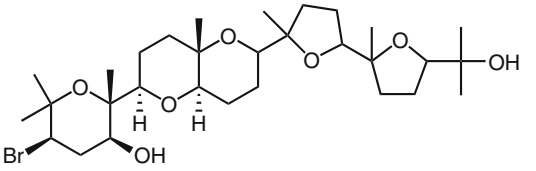
612

3.4.4 Higher Terpenes

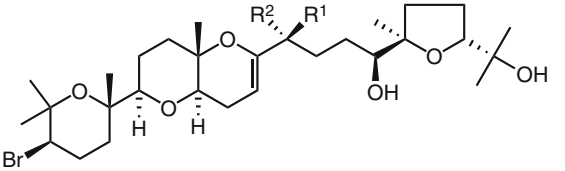
Although the numbers are relatively small, several new halogenated triterpenes and other higher terpenes have been described since the earlier review (*1*). Accounts of marine polyether triterpenes (*718*) and heterocyclic triterpenes (*719*) have been published. The novel pentacyclic triterpene squalene-derived enshuol (**613**) is found in the new species *Laurencia omaezakiana* from central Japan Pacific waters (*720*). The first study of *Laurencia* living in Vietnamese waters has led to callicladol (**614**) from *Laurencia calliclada* (*721*). The Canary Islands *Laurencia viridis*, also a new species, has yielded several novel brominated polyether squalene-derived metabolites (*722–724*). These include thyrsenols A (**615**) and B (**616**) (*722*), isodehydrothrysiferol (**617**) and 10-epidehydrothyrsiferol (**618**) (*723*), and dehydrovenustatriol (**619**), 15,16-dehydrovenustatriol (**620**), 16-hydroxydehydrothyrsiferol (**621**), and 10-*epi*-15,16-dehydrothyrsiferol (**622** (*724*). The Canary Islands *Laurencia pinnatifida* contains dehydrothyrsiferol (**623**) (*725*). Two later collections of *Laurencia viridis* from around the Canary Islands revealed the presence of dioxepandehydrothyrsiferol (**624**), 16-*epi*-hydroxydehydrothyrsiferol (**625**) (*726*), clavidol (**626**), and 3-*epi*-dehydrothyrsiferol (**627**) (*727*).



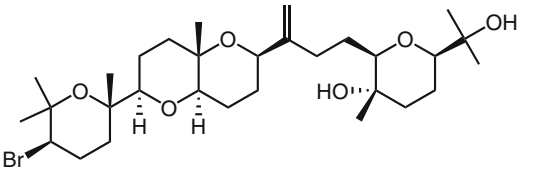
613 (enshuol)



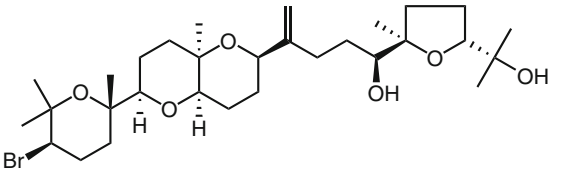
614 (callicladol)



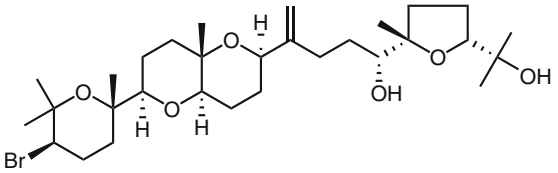
615 R^1 = OH, R^2 = CH_2OH (thyrsenol A)
616 R^1 = CH_2OH, R^2 = OH (thyrsenol B)



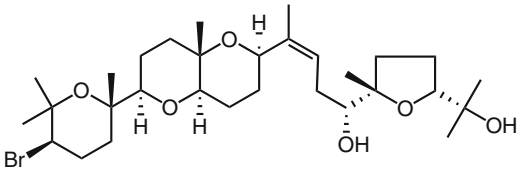
617 (isodehydrothyrsiferol)



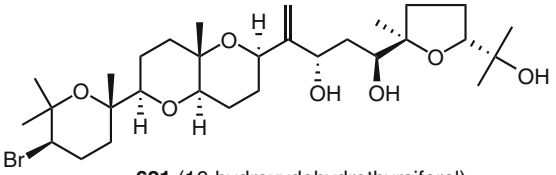
618 (10-epidehydrothyrsiferol)



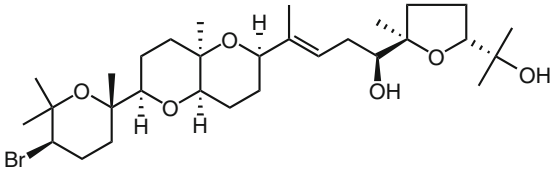
619 (dehydrovenustatriol)



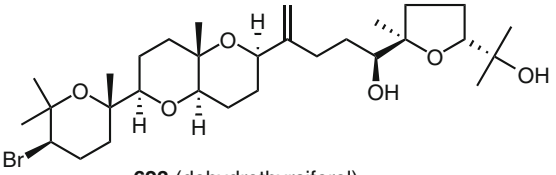
620 (15,16-dehydrovenustatriol)



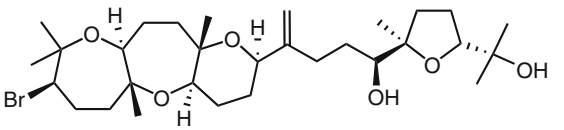
621 (16-hydroxydehydrothyrsiferol)



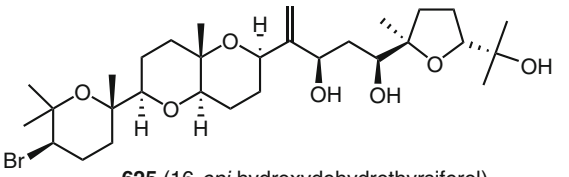
622 (10-*epi*-15,16-dehydrothyrsiferol)



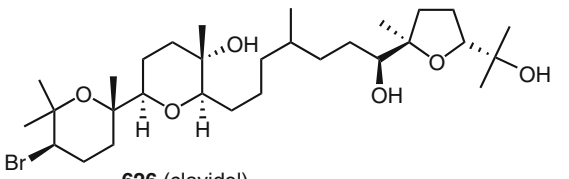
623 (dehydrothyrsiferol)



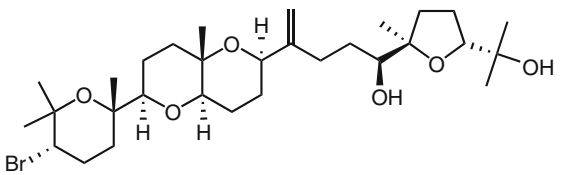
624 (dioxepandehydrothyrsiferol)



625 (16-*epi*-hydroxydehydrothyrsiferol)

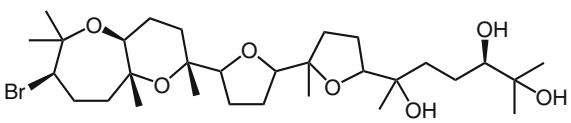


626 (clavidol)

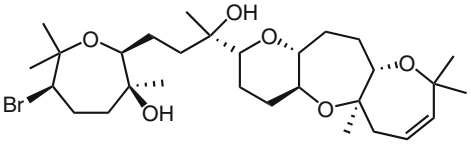


627 (3-*epi*-dehydrothyrsiferol)

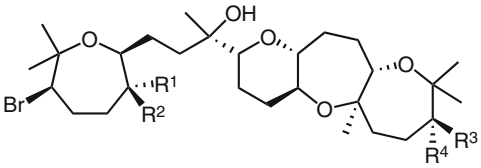
The sea hare *Dolabella auricularia* has furnished aurilol (**628**), which is cytotoxic (*728*) and for which the structure has now been fully assigned by total synthesis (*729*). The Indian Ocean red alga *Chondria armata*, a member of the *Laurencia* family, contains armatols A–F (**629**–**634**) (*730*).



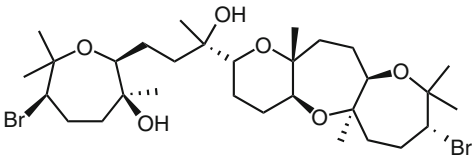
628 (aurilol)



629 (armatol A)

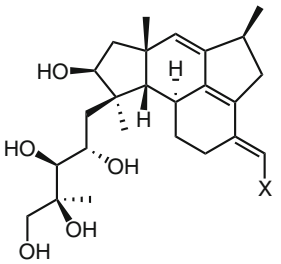


630 R^1 = Me, R^2 = OH, R_3 = H, R^4 = Br (armatol B)
631 R^1 = OH, R^2 = Me, R^3 = H, R^4 = Br (armatol C)
632 R^1 = Me, R^2 = OH, R^3 = Br, R^4 = H (armatol D)
633 R^1 = OH, R^2 = Me, R^3 = Br, R^4 = H (armatol E)

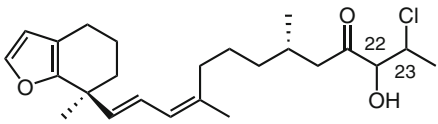


634 (armatol F)

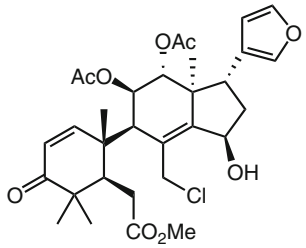
Despite their stereochemical complexity, a few brominated polyethers have succumbed to total synthesis. In addition to aurilol (**628**), discussed above (*728*), the previously described thyrsiferol and thyrsiferyl 23-acetate (*1*) have been synthesized (*731*), as has (unnatural) 7,11-*epi*-thyrsiferol (*732*). Several other synthetic studies are known (*733*). The cytotoxicity of thyrsiferyl 23-acetate and some of the other *Laurencia* polyether terpenoids has generated considerable interest into the biological mechanisms and possible drug development (*734–738*). A marine fungus of the genus *Fusarium* found on driftwood in a Bahamas mangrove habitat produces the halogenated sesterterpenes neomangicols A (**635**) and B (**636**), which have some activity against several human cancer cell lines (*740*). These compounds are the first natural halogenated sesterterpenes. A subsequent study tentatively identified this fungus as *Fusarium heterosporum* (*741*). The medicinal terrestrial plant *Turraea pubescens* has yielded turrapubesin A (**637**) (*742*), and the Okinawan sponge *Ircinia* sp. contains the new furanosesterterpenes **638** and **639** (*743*). An *Aspergillus* sp. culture has yielded ICM0301C (**640**) and ICM0301D (**641**), along with several nonchlorinated analogs (*744, 745*).



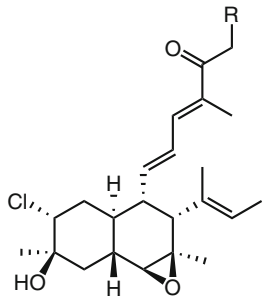
635 X = Cl (neomangicol A)
636 X = Br (neomangicol B)



638 (22, 23 *anti)*
639 (22, 23 *syn)*

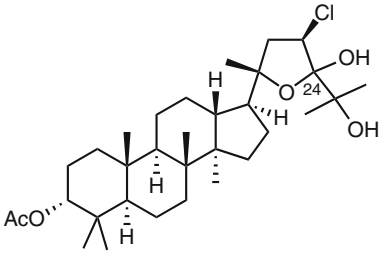


637 (turrapubesin)

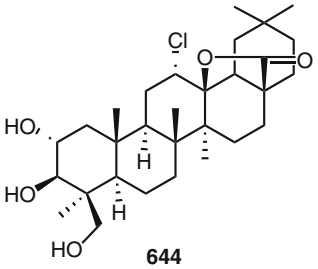


640 R = Me (ICM0301C)
641 R = H (ICM0301D)

The Chinese plant *Amoora yunnanensis* contains dammaranes **642** and **643** (*746*), and oleanane **644** was isolated as a triacetate from *Mentha villosa* (*747*). It is conceivable that **644** is an artifact formed by HCl acting on the corresponding unsaturated carboxylic acid, since this type of acid-catalyzed lactone formation is well known (*748*).



642, 643 (isomeric at C-24)

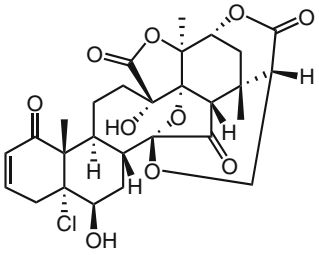


644

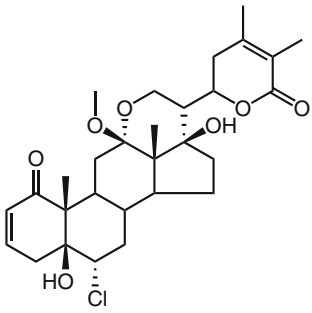
3.5 Steroids

Because most natural halogenated steroids are chlorohydrins, which are usually accompanied by the corresponding epoxide, one must ensure that the former are not artifacts formed during the isolation process.

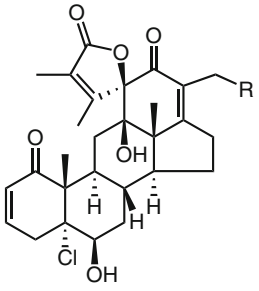
The structure of physalin H (**645**) from the plant *Physalis angulata* has been revised to the chlorohydrin shown (*749*). The Argentinian *Jaborosa sativa* has afforded the new jaborosalactone T (**646**) (*750*), and *Jaborosa runcinata* contains jaborosalactones 3 (**647**) and 6 (**648**) (*751*). Another Argentina collection of *Jaborosa odonelliana* revealed jaborosalactone 10 (**649**), which was present in plants collected in December but not in April (*752*). The Argentinian *Jaborosa bergii* contains chlorohydrins **650–652** in addition to nonchlorinated withanolides (*753*). As a group these steroids and the corresponding chlorohydrins display interesting biological activity. Several withanolides induce quinone reductase (*754*) and inhibit the growth of human cancer cell lines (*755*). Physalin H (**645**) has potent leishmanicidal activity (*756*).



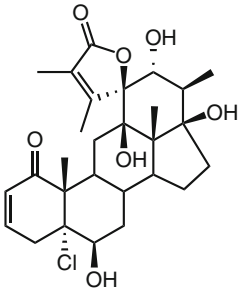
645 (physalin H)



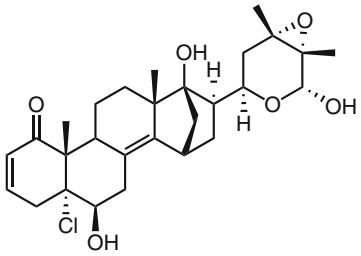
646 (jaborosalactone T)



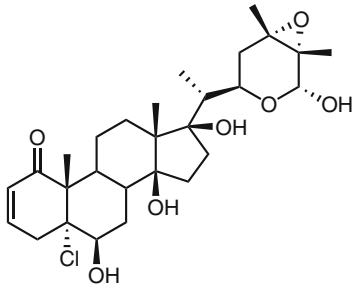
647 R = H (jaborosalactone 3)
648 R = OH (jaborosalactone 6)



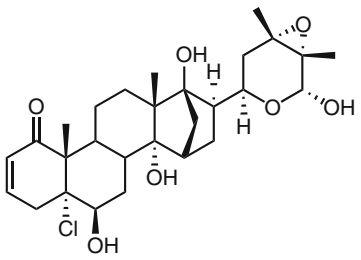
649 (jaborosalactone 10)



650 (jaborosalactol 21)

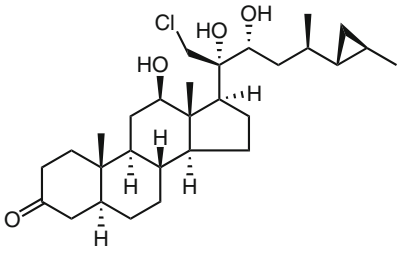


651 (jaborosalactol 23)

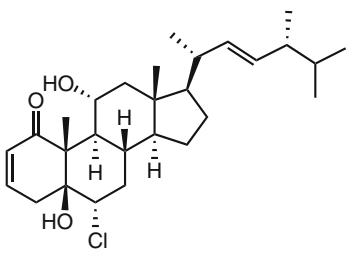


652

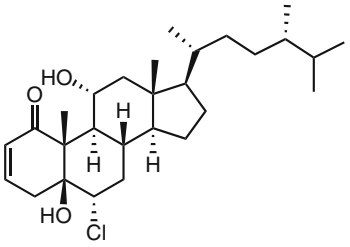
Several new halogenated marine steroids have been characterized. An Okinawan marine sponge of *Xestospongia* sp. contains aragusteroketal C (**653**), which has nanogram activity against KB cells (*757*). Since methanol was not used in the isolation procedure, this compound, along with the corresponding nonchlorinated epoxide, are rare examples of natural dimethylketals. Yonarasterols G (**654**), H (**655**), and I (**656**) were isolated from the Okinawan soft coral *Clavularia viridis* (*758*). The epoxide corresponding to chlorohydrin **655** was heated in methanol for 3 days in the presence of NaCl with and without silica gel, but remained unaffected. Another Okinawan sponge, *Terpios hoshinota*, contains nakiterpiosin (**657**) and nakiterpiosinone (**658**), novel mixed bromochloro nor-steroids that show potent cytotoxicity against P388 leukemia cells (*759, 760*). It might be noted that CH_2Cl_2 was not employed in the isolation and purification process.



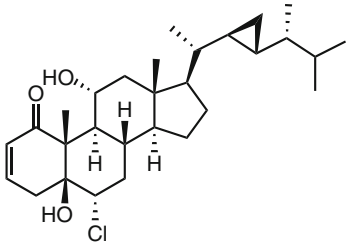
653 (aragusteroketal C)



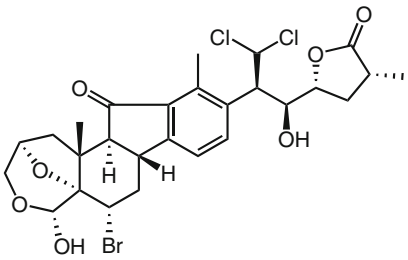
654 (yonarasterol G)



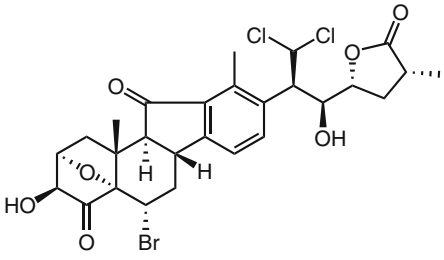
655 (yonarasterol H)



656 (yonarasterol I)

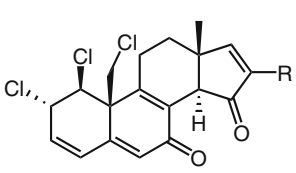


657 (nakiterpiosin)

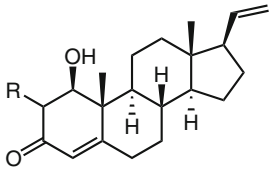


658 (nakiterpiosinone)

The polychlorinated androstanes clionastatins A (**659**) and B (**660**) were isolated from the burrowing sponge *Cliona nigricans* (Fig. 3.10) collected in two locations along the Italian coast (*761*). These unique metabolites have good cytotoxic activity against murine and human cancer cell lines. The eastern Pacific octocoral *Carijoa multiflora* has yielded the unusual chlorinated pregnanes **661** and **662** in a chloroform-free isolation process (*762*).

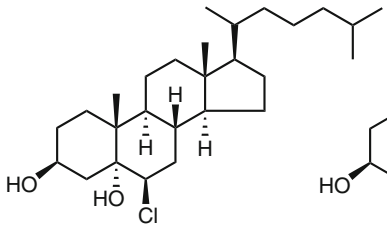


659 R = H (clionastatin A)
660 R = Cl (clionastatin B)



661 R = α-Cl
662 R = β-Cl

Another group of natural chlorinated steroids are the products of enzymatic (or anthropogenic) chlorination of cholesterol, estrone, and other natural steroids. Thus, the well known myeloperoxidase–H_2O_2–chloride system in white blood cells (*763, 764*) targets cholesterol leading to at least three chlorohydrins (*765–769*), the structures of which have now been confirmed (**663–665**) (*769*). These studies also show that the same chlorohydrins are produced when HOCl and cholesterol are allowed to react. Interestingly, three chlorinated estrones have been identified in wastewater effluents treated with hypochlorous acid (*770*), although these products are not considered to be naturally occurring for the present survey.



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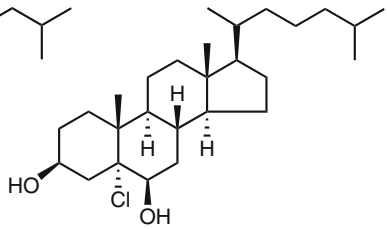
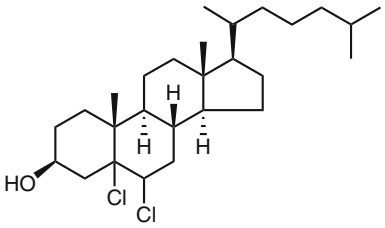


664



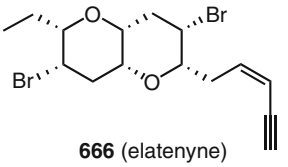
665

Fig. 3.10 *Cliona nigricans*, a boring sponge found in the Ligurian Sea, Italy, that contains the clionastatins A and B (**659** and **660**). The brown color is due to symbiotic zooxanthellae (Photo: C. Cerrano)

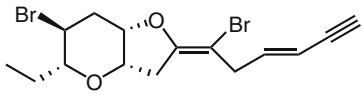
3.6 Marine Nonterpenes: C_{15} Acetogenins

When chemists began to explore the oceans for novel natural products, halogenated C_{15} acetogenins were an unknown class of compounds. But since the initial discovery of laurencin from *Laurencia glandulifera* in 1965, a large number of these compounds have been found – 130 examples in the first survey (*1*). This number continues to grow, especially as produced by the prolific *Laurencia* red algae. The biological properties and synthesis of allenic natural products, of which many are bromoallene C_{15} acetogenins, have been published (*771*).

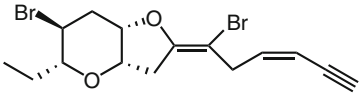
A collection of *Laurencia elata* from the coast of Victoria has provided the pyrano[3,2-*b*]pyranyl vinyl acetylene elatenyne (**666**) (*772*), which is related to the known (*Z*)-dactomelyne (*1*). Japonenynes A (**667**), B (**668**), and C (**669**), which possess a furo[3,2-*b*]pyranyl framework, were isolated from *Laurencia japonensis* (*773*). Compound **669** may be an isolation (methanol) artifact although it is isolated as a single compound. The report of "aplysiallene" from the sea hare *Aplysia kurodai* (*774*) is erroneous and this compound is actually a known bromoallene (*775*) described earlier (*1*). The Vietnamese *Laurencia pannosa* contains pannosallene (**670**), which is closely related to the known laurallene (*776*). During this investigation the authors discovered that their earlier proposed structure of epilaurallene must be incorrect. A new isomer of pannosallene, nipponallene (**671**), along with the novel neonipponallene (**672**) was isolated from *Laurencia nipponica* collected off the Russian shore of the Sea of Japan (*777*). The sea hare *Aplysia parvula* has yielded aplyparvunin (**673**), which has potent fish toxicity (*778*). *Laurencia intricata* has furnished itomanallenes A (**674**) and B (**675**); the former is an epimer of the known neolaurallene (*591*). Chinzallene (**676**) was characterized from a Japanese *Laurencia* sp. (*638*). The stereochemistry of chinzallene is not fully established.



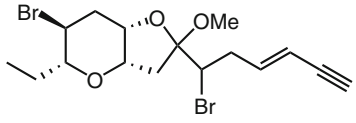
666 (elatenyne)



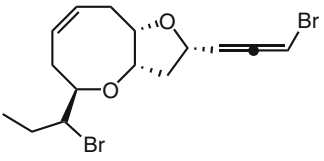
667 (japonenyne A)



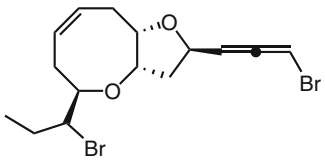
668 (japonenyne B)



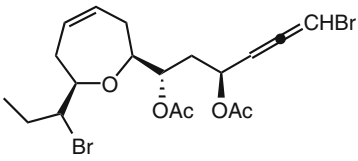
669 (japonenyne C)



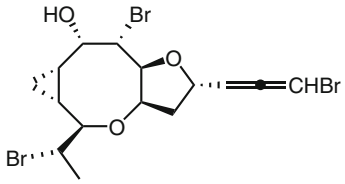
670 (pannosallene)



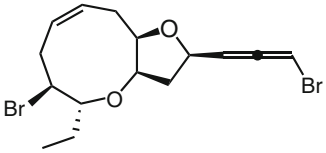
671 (nipponallene)



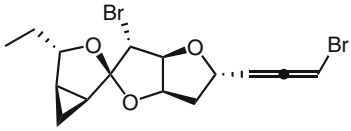
672 (neonipponallene)



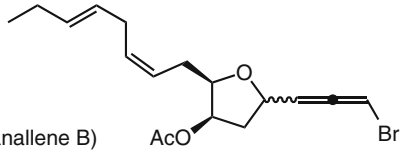
673 (aplyparvunin)



674 (itomanallene A)

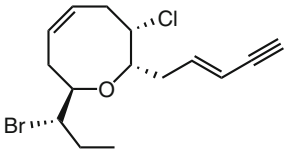


676 (chinzallene)

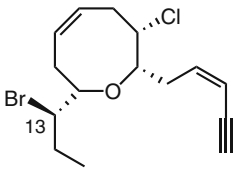


675 (itomanallene B)

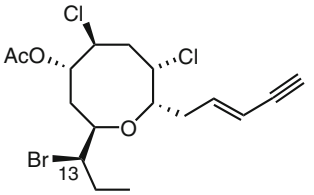
The C_{15} acetogenin (*E*)-dihydrorhodophytin (**677**), an isomer of the previously known (*Z*)-isomer (*1*), is found in *Laurencia pinnatifida* from the Canary Islands (*779*). An Easter Island variety of *Laurencia claviformis* has afforded (3*Z*)-13-epipinnatifidenyne (**678**) (*780*). Likewise, an epimer of the previously known laurencienyne, 13-epilaurencienyne (**679**), is found in *Laurencia obtusa* from the Aegean coast (*781*). This same seaweed and locale yielded laurencienyne B (**680**), the *cis* isomer of laurencienyne (*782*), and the acetate **681** (*783*). This Aegean Sea *Laurencia obtusa* has also provided (3*Z*)-13-epilaurencienyne (**682**), (3*E*)-13-epi-pinnatifidenyne (**683**) (revised in (*785*)), **684**, and **685** (*784*). The (*Z*)-diastereomers **682** and **685** showed very potent insecticidal activity. Three enantiomers of known compounds were identified in the sea hare *Aplysia dactylomela*, (–)-(3*E*,6*R*,7*R*)-pinnatifidenyne (**686**), (+)-(3*E*,6*R*,7*R*)-obtusenyne (**687**), and (+)-(3*Z*,6*R*,7*R*)-obtusenyne (**688**) (*785*).



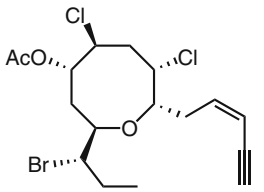
677 ((*3E*)-dihydrorhodophytin)



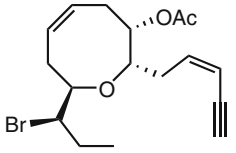
678 ((3*Z*)-13-*epi*-pinnatifidenyne)



679 (13-*epi*-laurencienyne)



680 (laurencienyne B)



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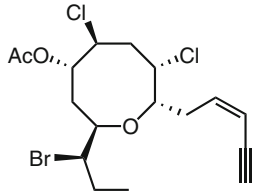
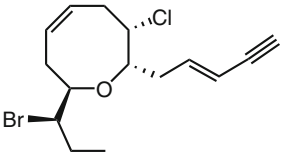
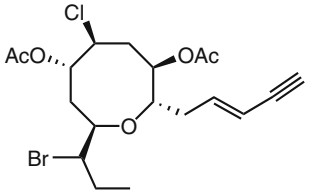


682 ((3*Z*)-13-*epi*-laurencienyne)



683 ((3*E*)-13-*epi*-pinnatifidenyne)



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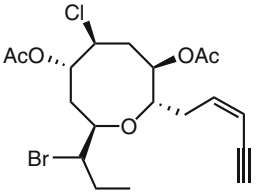

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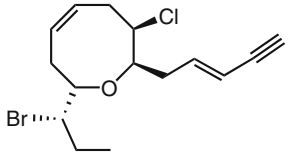
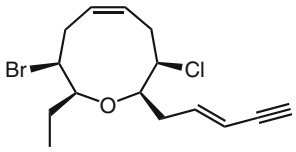
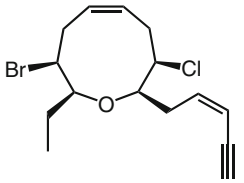


686 ((3*E*,6*R*,7*R*)-pinnatifidenyne)

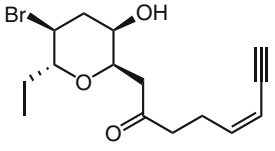


687 ((3*E*,6*R*,7*R*)-obtusenyne)

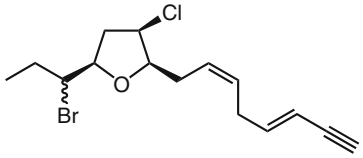


688 ((3*Z*,6*R*,7*R*)-obtusenyne)

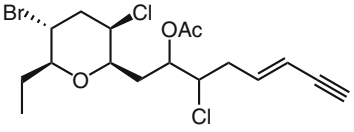
Laurencia obtusa from the western coast of Ireland has afforded scanlonenyne (**689**), the first reported study of *Laurencia* red algae from Irish waters (*786*). A Japanese *Laurencia* sp. contains the new bisezakyne-A (**690**) and -B (**691**) (*787*). The red alga *Ptilonia magellanica* is the source of pyranosylmagellanicus A–C (**692–694**) and the linear **695**, a possible biogenetic precursor (*788*).



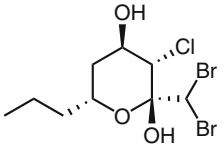
689 (scanlonenyne)



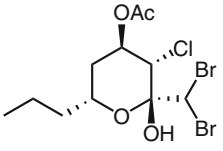
690 (bisezakyne-A)



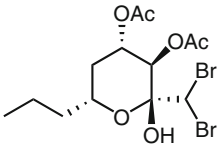
691 (bisezakyne-B)



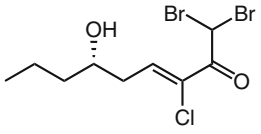
692 (pyranosylmagellanicus A)



693 (pyranosylmagellanicus B)



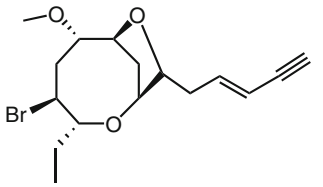
694 (pyranosylmagellanicus C)



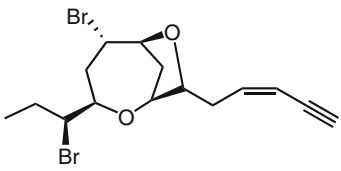
695

Several new halogenated bicyclic acetogenins of the laurefucin type have been discovered in marine organisms since the first survey (*1*). Thus, the Coral Sea red seaweed *Dasyphila plumariodes* contains the new isolaurefucin methyl ether (**696**) (*789*). Neoisoprelaurefucin (**697**) was characterized from a Japanese

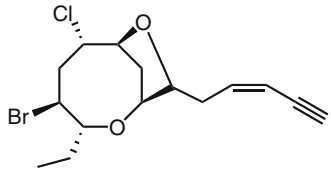
Laurencia nipponica (*790*), and the structure and absolute configuration were confirmed by total synthesis (*791*). This new compound is a stereoisomer of the known (3*Z*)-isoprelaurefucin. A Malaysian *Laurencia pannosa* has yielded (3*Z*)-chlorofucin (**698**) (*578*), and (3*Z*)-bromofucin (**699**), which is also a new C_{15}-acetogenin, is found in a South African sea hare, *Aplysia parvula* (*792*). The (3*E*)-neoisoprelaurefucin (**700**) was found in *Laurencia obtusa* collected in Turkish waters (*557*).



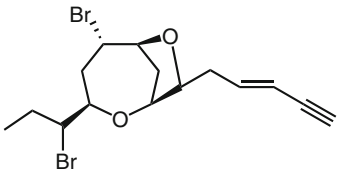
696



697 (neoisoprelaurefucin)

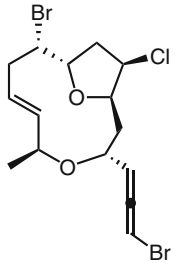


698 R = Cl ((3*Z*)-chlorofucin)
699 R = Br ((3*Z*)-bromofucin)

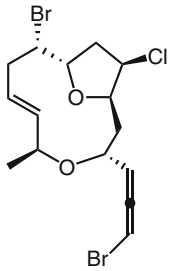


700 ((3*E*)-neoisoprelaurefucin)

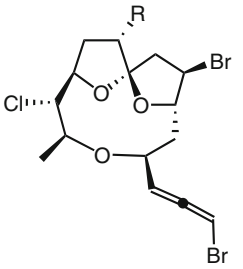
The sea hare *Aplysia dactylomela* from the Canary Islands contains dactylallene (**701**), which is highly toxic to the mosquito fish (*Gambusia affinis*) at 10 ppm and deters feeding by the golden fish (*Carassius auratus*) at low concentrations (*793*). Dactylallene is a stereoisomer of the known obtusallene II. Obtusallene IV (**702**) was isolated from *Laurencia obtusa* collected in Turkish waters (*794*). This study also describes the conformational properties of several obtusallenes as does a subsequent investigation, which reports the isolation of five new obtusallenes from *Laurencia obtusa*, V–IX (**703–707**) (*795*). An unrecorded Malaysian *Laurencia* species has afforded the novel lembyne-A (**708**) and lembyne-B (**709**), the former of which is a (*Z*)-diastereomer of the known *cis*-maneonene C, while the latter is a stereoisomer of isomaneonene A (*796*). The related (12*E*)-lembyne A (**710**) has been isolated from an Okinawan *Laurencia mariannensis* (*577*). This metabolite appears to be a stereoisomer of *cis*-maneonene C.



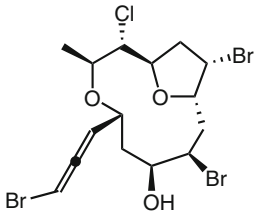
701 (dactylallene)



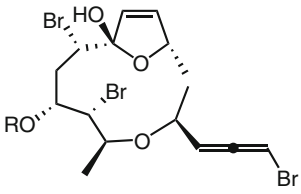
702 (obtusallene IV)



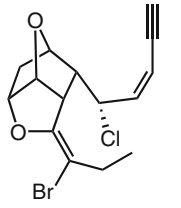
703 R = Br (obtusallene V)
704 R = H (obtusallene VI)



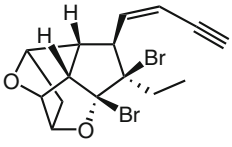
705 (obtusallene VII)



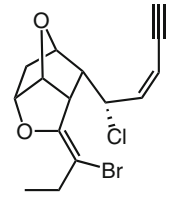
706 R = H (obtusallene VIII)
707 R = Ac (obtusallene IX)



708 (lembyne-A)

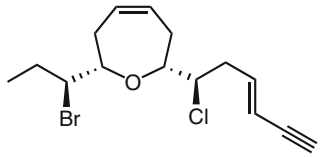


709 (lembyne-B)

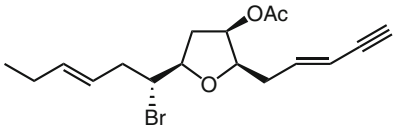


710 ((12*E*)-lembyne-A)

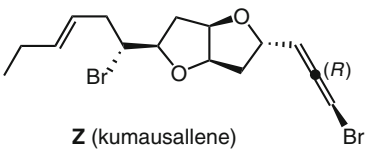
Only a few of the many reported total syntheses of the halogenated C_{15} acetogenins are listed here. The first total synthesis of (+)-isolaurepinnacin (**X**) confirms the proposed structure, notably the (*S*)-configuration at C-3, and corrects the rotation of natural **X** as being dextrorotatory (*797*). Total syntheses of (–)-*trans*-kumausyne (**Y**) (*798*) and (–)-kumausallene (**Z**) (*799*) support the proposed structures and absolute configurations of these compounds. Several syntheses of (+)-obtusenyne (**AA**) have been described (*800*), and the absolute configurations were established for "Norte's obtusenynes" (**BB**) and (**CC**) (*801*). Several syntheses of (+)-laurencin (**DD**) have been described (*802*), as has the first total synthesis of (+)-(*Z*)-laureatin (**EE**), which confirms its absolute configuration (*803*). Likewise, the first total syntheses of (+)-rogioloxepane A (**FF**) (*804*) and (–)-isolaurallene (**GG**) (*805*) validate the proposed structures of these *Laurencia* metabolites. Although the antipode (**HH**) was synthesized earlier, the first total synthesis of (+)-laurenyne (**II**) was described later (*806*). A second total synthesis of (+)-rogioloxepane A (**FF**) (*807*) and syntheses of both (+)-(3*E*)- (**JJ**) and (+)-(3*Z*)-pinnatifidenyne (**KK**) (*808*) confirm the proposed structures. An asymmetric synthesis of (–)-panacene (**LL**) has corrected its relative configuration as shown (*809*). In contrast to these and other successful syntheses, some synthetic efforts expose incorrectly proposed structures for natural products. Total syntheses of elatenyne (**MM**) and **NN** reveal that the proposed structures for these pyrano[3,2-*b*]pyrans are probably incorrect (*810*). The authors suggest a 2,2′-bifuranyl core for **MM** and **NN**. Unfortunately, space does not permit a full presentation of the many other elegant total syntheses of the halogenated C_{15} acetogenins.



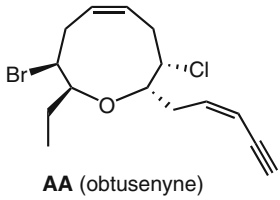
X (isolaurepinnacin)



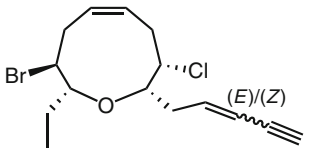
Y (*trans* - kumausyne)



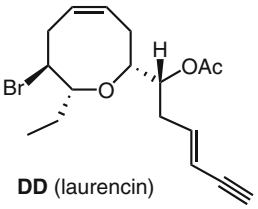
Z (kumausallene)



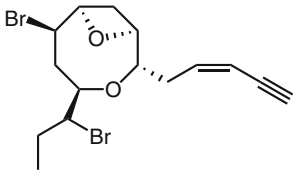
AA (obtusenyne)



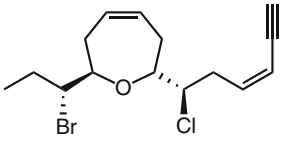
BB ((*E*)-isomer)
CC ((*Z*)-isomer)



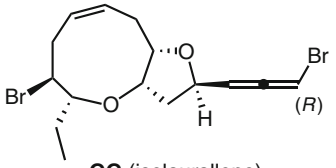
DD (laurencin)



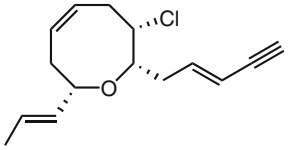
EE ((*Z*)-laureatin)



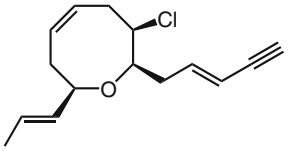
FF (rogioloxepane A)



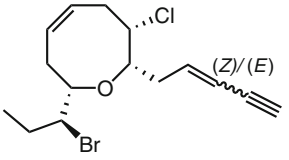
GG (isolaurallene)



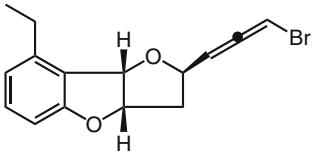
HH



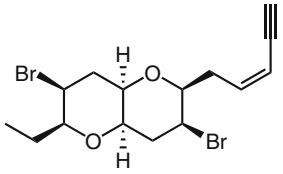
II (laurenyne)



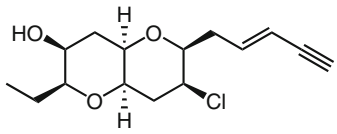
JJ ((*E*)-pinnatifidienyne)
KK ((*Z*)-pinnatifidienyne)



LL (panacene)



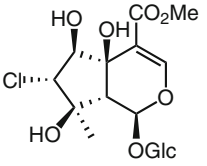
MM (elatenyne)



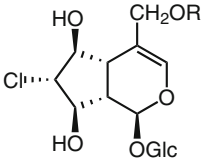
NN

3.7 Iridoids

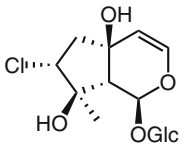
Iridoids are a large group of plant metabolites that are mevalonate-derived in origin and isoprenoid in carbon skeleton (*811*). A dozen chlorinated iridoids were cited in the first review (*1*), all of which are chlorohydrins. Phloyoside II (**711**) was isolated from the roots of *Phlomis younghusbandii* from Tibet (*812*). The South American shrub *Mentzelia cordifolia* contains the novel mentzefoliol (**712**) and glucosylmentzefoliol (**713**) in addition to the known 7-chlorodeutziol (*813*). The full paper describing the isolation, characterization of the previously reported glutinoside has appeared (*814*). Stegioside I (**714**) is found in *Physostegia virginiana* ssp. *virginiana*, and is a dehydroxylinarioside (*815*). The Okinawan plant *Premia subscandens* has furnished the four novel 10-*O*-acyl derivatives of the known asystasioside E (**715**–**718**) (*816*). Likewise, **719** and **720** from *Calalpae fructus* are 4-hydroxybenzoyl esters of known iridoid glucosides (*817*). Urphoside B (**721**), which is closely related to **719**, was isolated from a Turkish collection of *Veronica pectinata* var. *glandulosa* (*818*). Similarly, piscroside A (**722**) is a methoxy analogue of **720** and was characterized from the roots of the Chinese plant *Neopicrorhiza scrophulariiflora* (*819*). Globularioside (**723**), with a unique beta-chlorine atom, has been isolated from the Moroccan plant *Globularia alypum* (*820*). A collection of the parasitic plant *Cistanche tubulosa* has yielded kankanoside C (**724**) and kankanol (**725**) along with several other new nonchlorinated iridoids (*821*). A ^{13}C NMR analysis of iridoids is available (*822*).



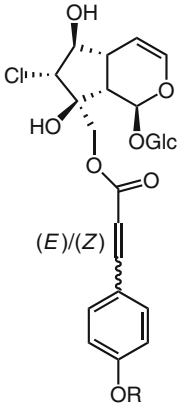
711 (phloyoside II)



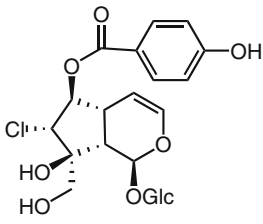
712 R = H (mentzefoliol)
713 R = Glc



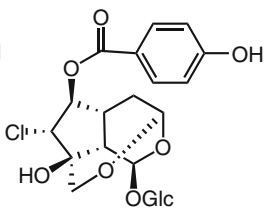
714 (stegioside I)



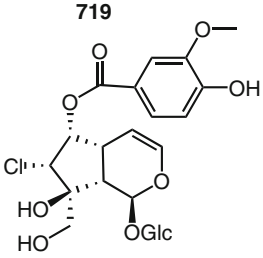
715 R = Me, (*E*)
716 R = Me, (*Z*)
717 R = H, (*E*)
718 R = H, (*Z*)



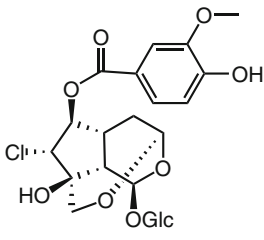
719



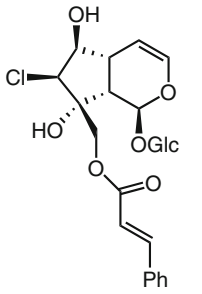
720



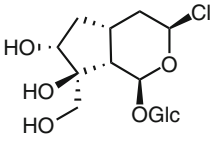
721 (urphoside B)



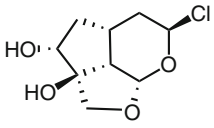
722 (piscroside A)



723 (globularioside)



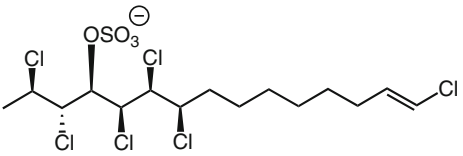
724 (kankanoside C)



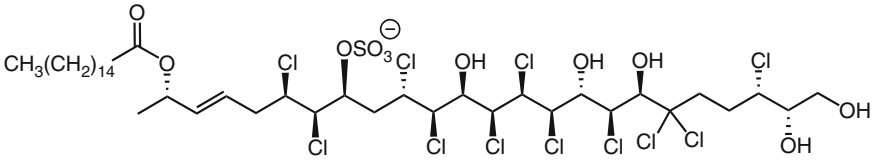
725 (kankanol)

3.8 Lipids and Fatty Acids

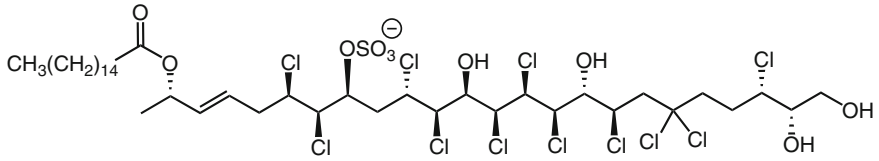
The evaluation of halogenated lipids and fatty acids is rendered difficult because many examples of chlorinated fatty acids are indisputably man-made and do not have clear natural sources. The order of presentation follows that adopted in the first survey. As before, only newly isolated and characterized compounds are numbered. Studies of the toxic (contaminated) edible mussel *Mytilus galloprovincialis* from the Adriatic Sea have led to the isolation of three novel chlorosulfolipids **726**–**728** (*823*–*825*). These cytotoxic compounds are found in the digestive glands of the animals and are antiproliferative against several cell lines (J774, WEHI164, P388).



726

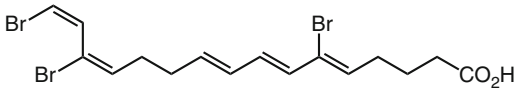


727



728

Halogenated fatty acids have both anthropogenic and natural sources (*826–830*), and the distinction is not always unambiguous, particularly with chlorinated fatty acids (*826–829*). Nevertheless, an abundance of natural halogenated fatty acids is beyond dispute (*830*). Several new members of the class of bromine-containing fatty acids, which numbered 14 in the first survey (*1*), have been identified from both marine and terrestrial sources. An Indonesian sponge, *Oceanapia* sp., has furnished the two novel bromo acids **729** and **730** (*831*), and the Australian sponge *Amphimedon terpenensis* contains 6-bromo-(5*E*,9*Z*)-tetracosadienoic acid (**731**) and 6-bromo-(5*E*,9*Z*)-pentacosadienoic acid (**732**) (*832, 833*). In addition to the latter two bromoacids, the Caribbean sponge *Agelas* (Fig. 3.11) has afforded **733** and **734** (*834*). The sea anemone *Stoichactis helianthus* contains 6-bromo-(5*E*,9*Z*)-heneicosadienoic acid (**735**) and 6-bromo-(5*E*,9*Z*)-docosadienoic acid (**736**) (*835*). The phospholipid extracts of both the sea anemone *Condylactis gigantea* and the zoanthid *Palythoa caribaeorum* furnished the novel 6-bromo-(5*E*,9*Z*)-eicosadienoic acid (double bond stereochemistry assumed) (**737**) (*836*).



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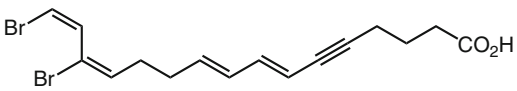

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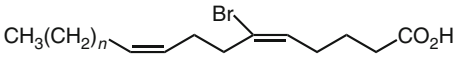
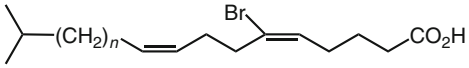


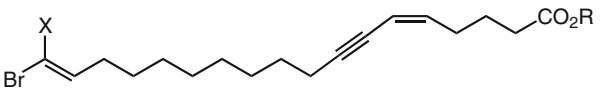
731 $n = 13$
732 $n = 14$
735 $n = 10$
736 $n = 11$
737 $n = 9$



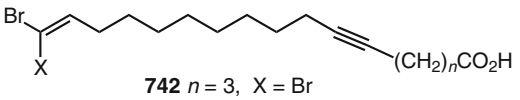
733 $n = 12$
734 $n = 13$

Fig. 3.11 *Agelas* sp. An example of a very common marine sponge that produces a wide variety of halogenated metabolites such as the brominated fatty acids **733** and **734** (Photo: J. R. Pawlik)

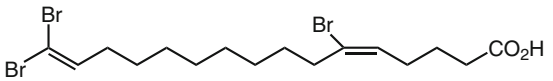
Sponges of genus *Xestospongia* are rich suppliers of brominated fatty acids. An Okinawan sampling of this sponge yielded 14 new brominated fatty acids (**738**–**751**), along with three previously identified examples (*837*). A study of this sponge from the Indian Ocean characterized the novel **752**–**754** (*838*). The new xestosterol esters **755** and **756** were discovered in *Xestospongia testudinaria* from Australia, which had previously been found to contain xestosterol (*839*).



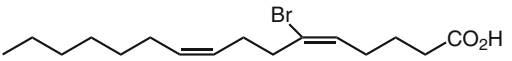
738 R = H, X = Br
739 R = X = H
740 R = Me, X = H
741 R = Me, X = Br



742 *n* = 3, X = Br
743 *n* = 3, X = H
744 *n* = 5, X = Br
745 *n* = 5, X = H



746



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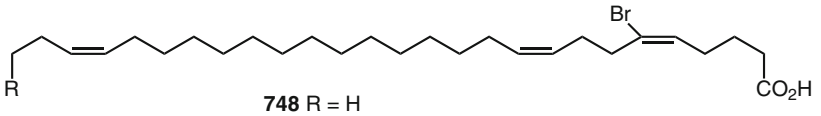
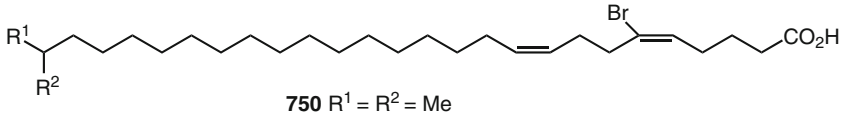
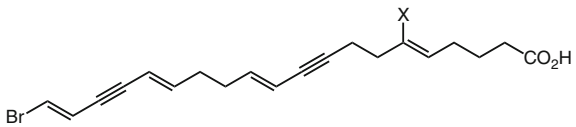


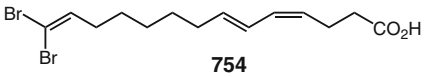
748 R = H
749 R = Me



750 $R^1 = R^2 = Me$
751 $R^1 = H$, $R^2 = i\text{-Pr}$

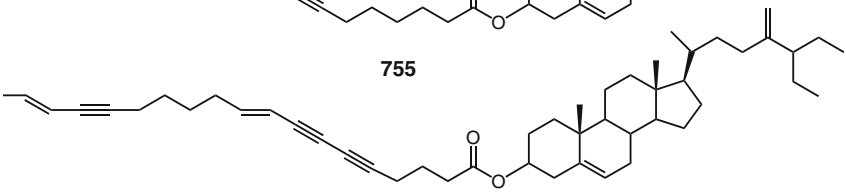


752 X = H
753 X = Br



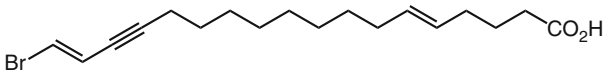
754

755

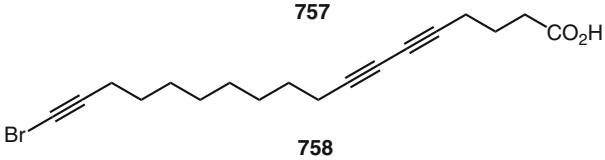


756

Surrounding a fresh water lake in Central Asia, which has a high salt content (up to 5,800 ppm), is the lichen *Acorospora gobiensis*. This lichen yielded the novel bromo acids **757** and **758** (*840*). Further study of this lichen and others collected around Lake Issyk-Kul in Central Asia (*Cladonia furcata*, *Lecanora fructulosa*, *Leptogium saturninum*, *Parmelia linctina*, *Parmelia comtseliadalis*, *Peltigera canina*, and *Xanthoria* sp.) uncovered six additional new brominated fatty acids, **759–764** (*841*). Another study of these and other lichens around this lake led to the first natural bromoallenic fatty acids **765** and **766** (*842*). The new lichens examined were *Rhizoplaca peltata*, *Xanthoparmelia camtschadalis*, *Xanthoparmelia tinctina*, and *Xanthoria elegans*.



757



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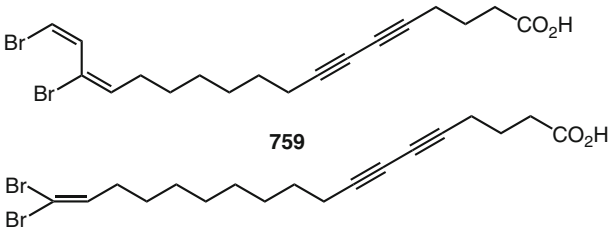
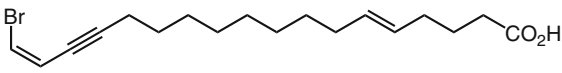


759

760



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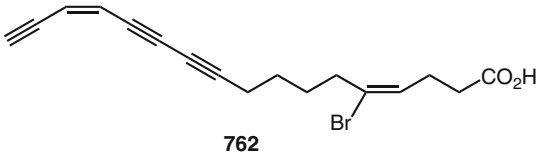

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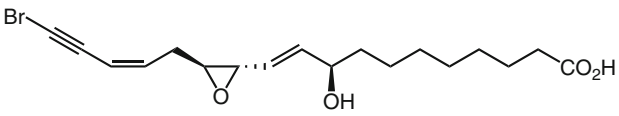

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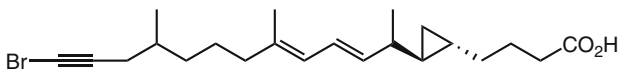

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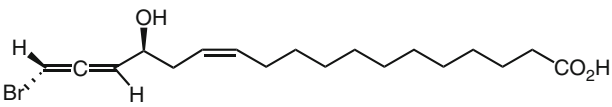

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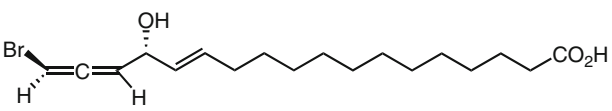
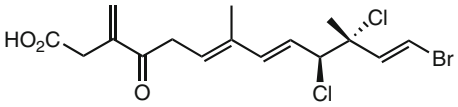


766

A collection of the red alga *Plocamium cartilagineum* from Corsica and the Maltese Islands has yielded the four new halogenated homosesquiterpenic fatty acids **767**–**770** (*843*). The Pohnpei sponge *Dysidea fragilis* contains the novel (4*E*)-

(*S*)-antazirine (**771**) and (4*Z*)-antazirine (**772**) (*844*). Majusculoic acid (**773**) is a novel metabolite isolated from a Bahamian cyanobacterial mat microbial community (*845*). A further cyclopropane fatty acid, grenadadiene (**774**), was found in the marine blue-green alga (cyanobacterium) *Lyngbya majuscula* from Grenada (*846*), a seaweed implicated in causing contact dermatitis ("swimmer's itch") (*847, 848*). Another genus of cyanobacteria, *Nostoc*, can also cause severe health problems (*849*).



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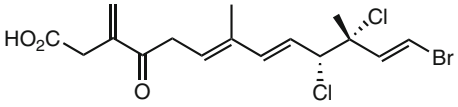

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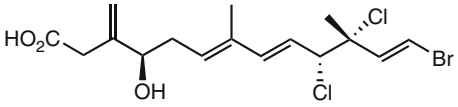

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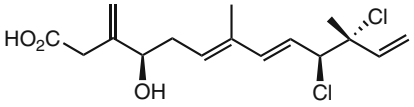

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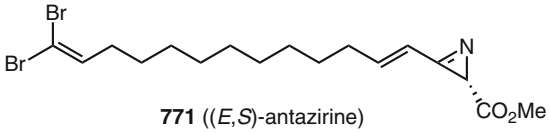
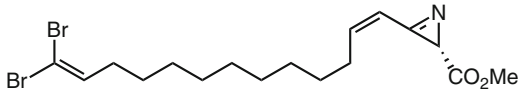
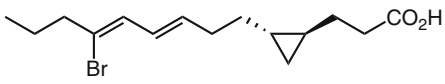


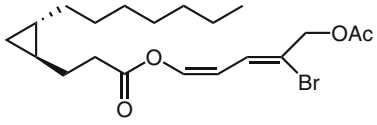
771 ((*E,S*)-antazirine)



772 ((*Z,S*)-antazirine)

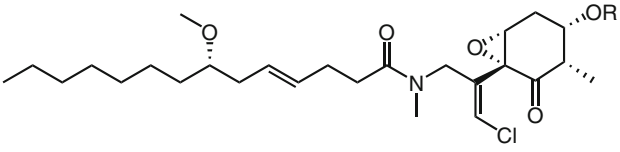


773 (majusculoic acid)

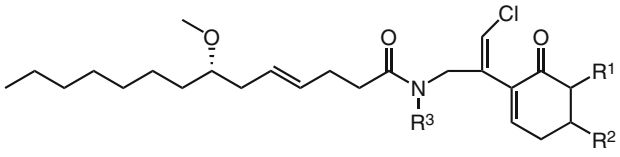


774 (grenadadiene)

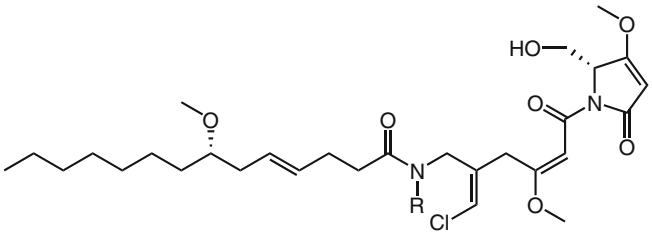
In addition to producing grenadadiene (**774**), *Lyngbya majuscula* is an amazingly prolific source of diverse fatty acid metabolites (*1*). An Okinawan collection of this cyanobacterium has yielded the novel malyngamide I (**775**), and this study led to the revision of the previously reported stylocheilamide as the acetate **OO** (*850*). The latter metabolite was originally isolated from the sea hare *Stylocheilus longicauda*, which feeds on *Lyngbya majuscula* (*1*). An assemblage of this blue-green alga from Curacao contains malyngamides K (**776**) and L (**777**) (*851*), a Madagascan sample yielded malyngamides Q (**778**) and R (**779**) (*852*), and a Puerto Rican specimen afforded malyngamide T (**780**) (*853*). The Hawaiian sea hare *Stylocheilus longicauda*, which feeds on *Lyngbya majuscula*, contains malyngamides O (**781**) and P (**782**) (*854*), and the New Zealand sea hare *Bursatella leachii* has yielded malyngamide S (**783**), which displays some antiinflammatory and cytotoxic activity (*855*). This animal is also known to feed on *Lyngbya majuscula*. The Hawaiian red alga *Gracilaria coronopifolia*, known as the source of the toxic aplysiatoxin, contains malyngamides M (**784**) and N (**PP**), the latter of which is a revised structure of deacetoxystylocheilamide (*856*), a compound described earlier (*1*). Malyngamide M is the first natural aromatized malyngamide. The authors suggest that an associated cyanobacterium actually produces the malyngamides.



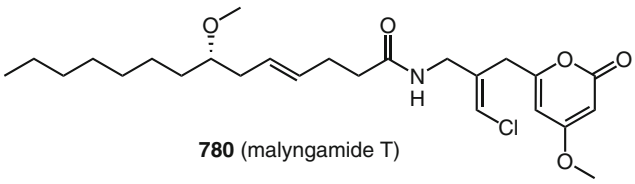
775 R = H (malyngamide I)
OO R = Ac (stylocheilamide)



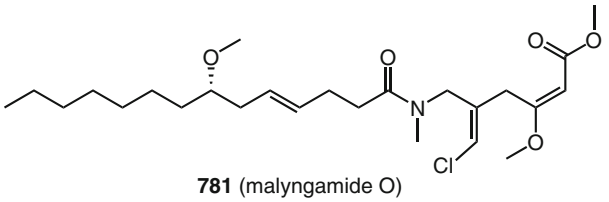
776 $R^1 = R^2 = R^3 = H$ (malyngamide K)
777 $R^1 = R^3 = Me$, $R^2 = OH$ (malyngamide L)



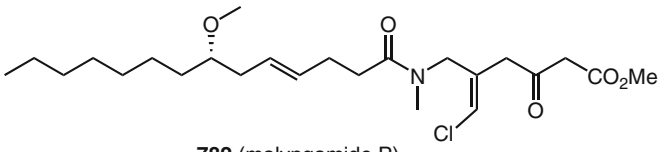
778 R = H (malyngamide Q)
779 R = Me (malyngamide R)



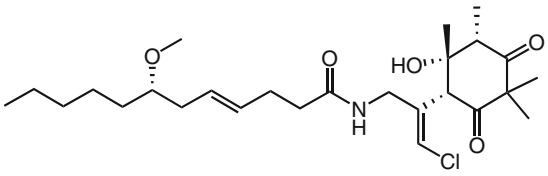
780 (malyngamide T)



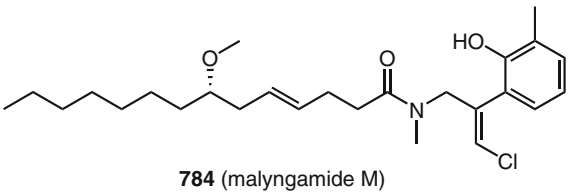
781 (malyngamide O)



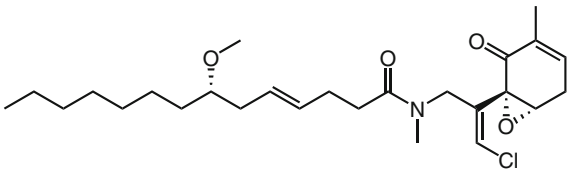
782 (malyngamide P)



783 (malyngamide S)



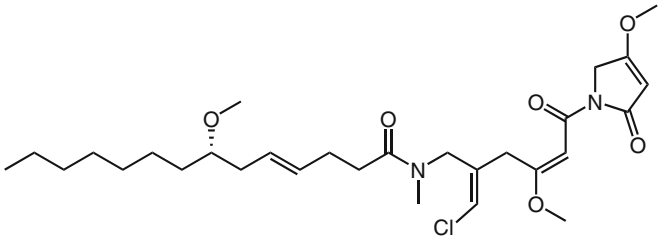
784 (malyngamide M)



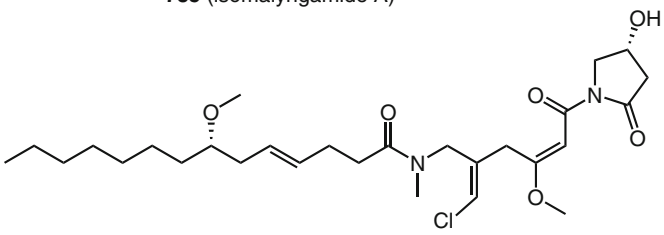
PP (malyngamide N = deacetoxystylocheilamide)

The Hawaiian *Lyngbya majuscula* has afforded isomalyngamides A (**785**) and B (**786**) (*857*), isomeric with the known malyngamide A, and the previously unreported malyngamide B (**787**) (*858*). The novel pitiamide A (**788**) was isolated from

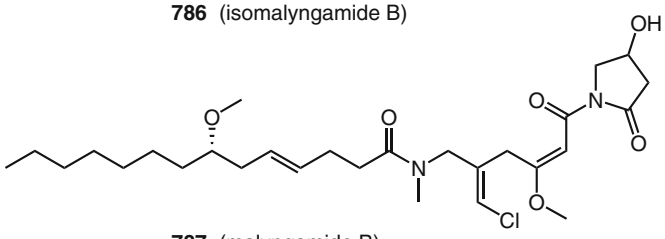
a mixed cyanobacterial sample of *Lyngbya majuscula* and *Microcoleus* sp. growing on the hard coral *Porites cylindra* from Guam (*859*). The structure and absolute configuration were confirmed by total synthesis (*860*). A homologue, pitiamide B, with one additional methylene group remains unidentified (*859*). A Jamaican strain of *Lyngbya majuscula* has yielded jamaicamides A (**789**), B (**790**), and C (**791**) (*861, 862*). The sea hare *Stylocheilus longicauda* from Oahu contains the unprecedented makalika ester (**792**) and makalikone ester (**793**) (*863*). The South African red alga *Gracilaria verrucosa* has furnished the two chlorohydrins **794** and **795** (*864*), and the related α-chloro divinyl ethers, maracens A (**796**), B (**797**), C (**798**), and D (**799**), were isolated from *Sorangium cellulosum* and display some activity against mycobacteria, related to the cause of tuberculosis (*865*).



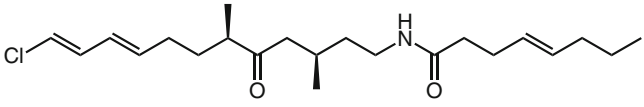
785 (isomalyngamide A)



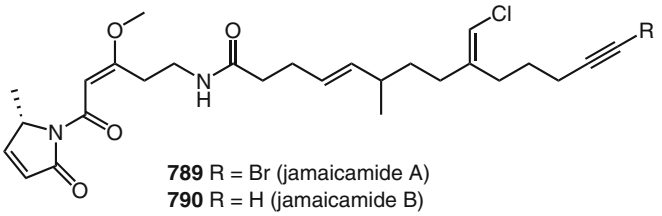
786 (isomalyngamide B)



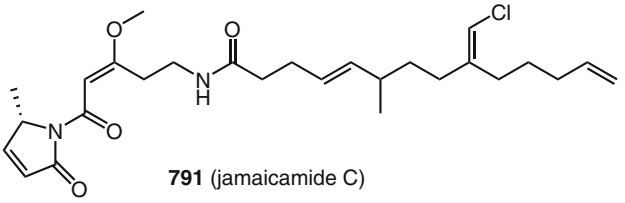
787 (malyngamide B)



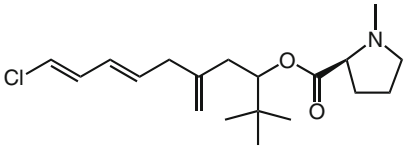
788 (pitiamide A)



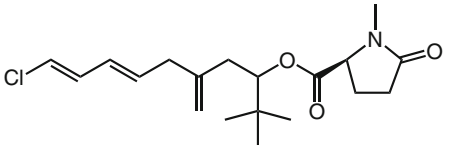
789 R = Br (jamaicamide A)
790 R = H (jamaicamide B)



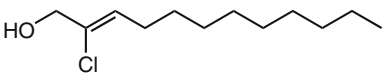
791 (jamaicamide C)



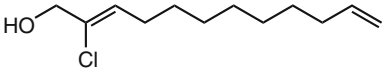
792 (makalika ester)



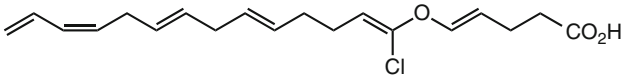
793 (makalikone ester)



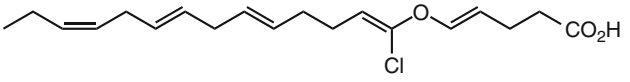
794



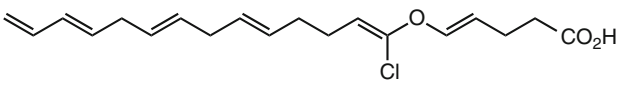
795



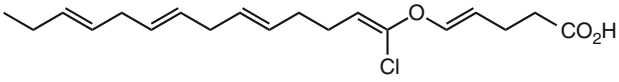
796 (maracen A)



797 (maracen B)

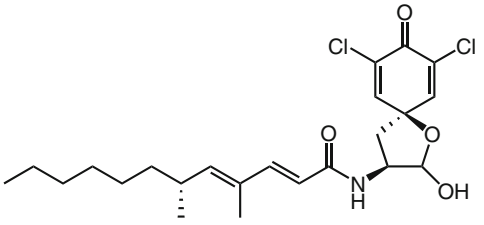


798 (maracen C)

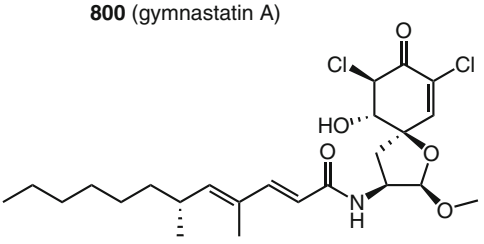


799 (maracen D)

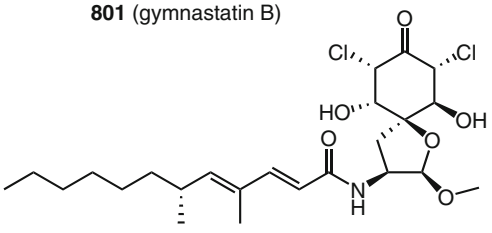
Blue-green algae are not the sole producers of halogenated fatty acid metabolites; several marine sponges and associated fungi have furnished new examples. The fungus *Gymnasella dankaliensis* from the sponge *Halichondria japonica* has supplied the novel gymnastatins A–H, most of which are chlorinated (A, **800**; B, **801**; C, **802**; D, **803**; E, **804**; F, **805**; G, **806**) (*866–868*). Gymnastatin A (**800**) has been synthesized (*869*). Several of these metabolites have pronounced cytotoxic and cytostatic activity. It should be noted that gymnastatins A, D, and E are each mixtures of two hemiacetals. The related aranochlors A (**807**) and B (**808**) were isolated from the fungus *Pseudoarachniotus roseus* (*870*). It seems possible that these hemiacetals also each exist as two epimers.



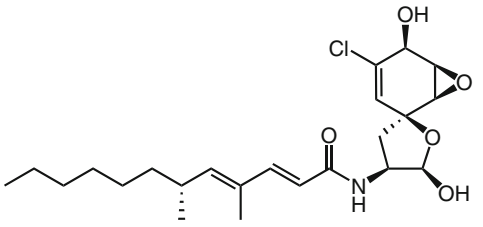
800 (gymnastatin A)



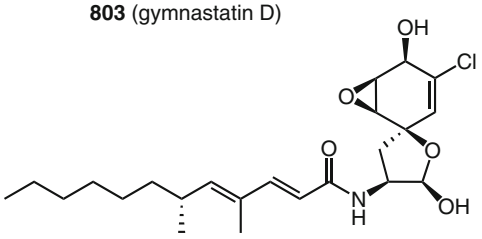
801 (gymnastatin B)



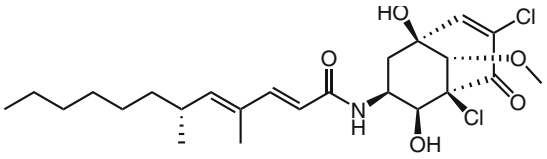
802 (gymnastatin C)



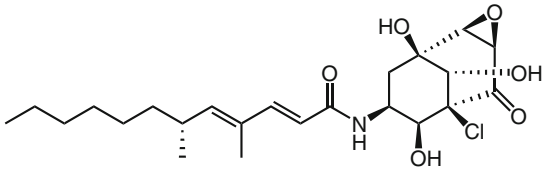
803 (gymnastatin D)



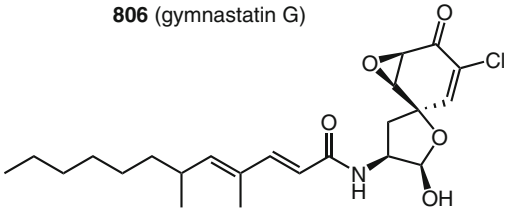
804 (gymnastatin E)



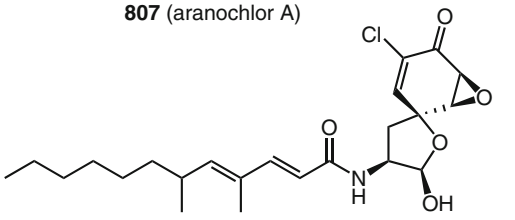
805 (gymnastatin F)



806 (gymnastatin G)

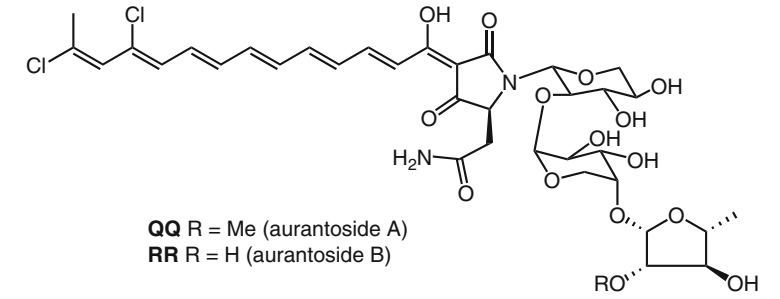


807 (aranochlor A)

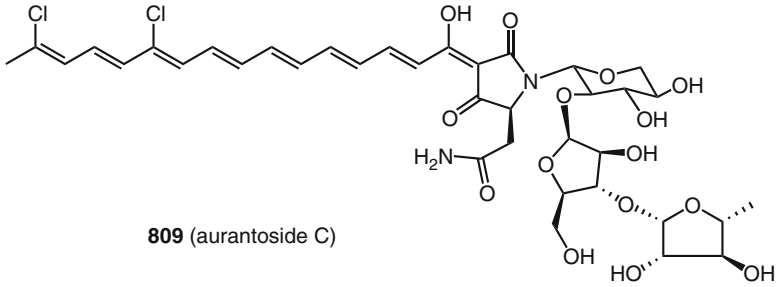


808 (aranochlor B)

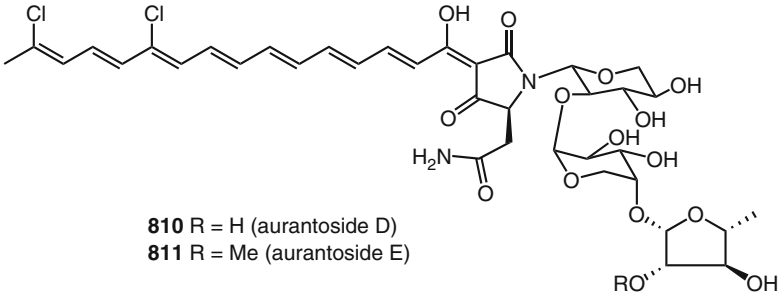
The sponge metabolites aurantosides A (**QQ**) and B (**RR**) were described in the first survey (*1*); subsequently, several new aurantosides have been isolated. Thus, aurantoside C (**809**) is found in the sponge *Homophymia conferta* and has the same absolute configuration as aurantosides A and B (*871*). The stereochemistry about the terminal double bond in the latter two compounds was revised as shown (**QQ**, **RR**) in a report that described the isolation of the new aurantosides D (**810**), E (**811**), and F (**812**), which have both antifungal and cytotoxic activity, from the sponge *Siliquariaspongia japonica* (*872*). The Papua New Guinea sponge *Theonella swinhoei* has afforded aurantosides G (**813**), H (**814**), and I (**815**) (*873*). A series of related tetramic acid glycosides, rubrosides A–H (**816–823**), was characterized from the Japanese sponge *Siliquariaspongia japonica* (*874*). Several of these rubrosides have antifungal (*Aspergillus fumigatus*, *Candida albicans*) and cytotoxic (P388) activity.



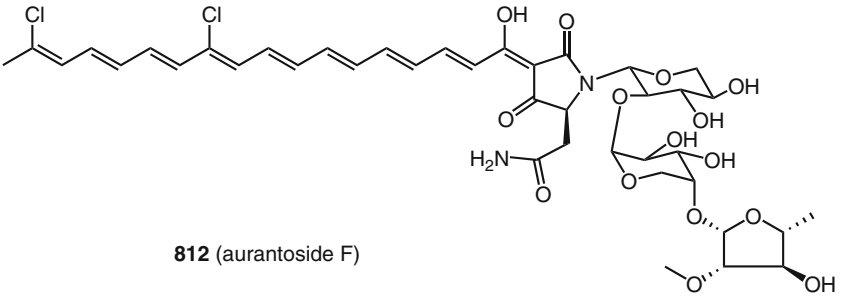
QQ R = Me (aurantoside A)
RR R = H (aurantoside B)



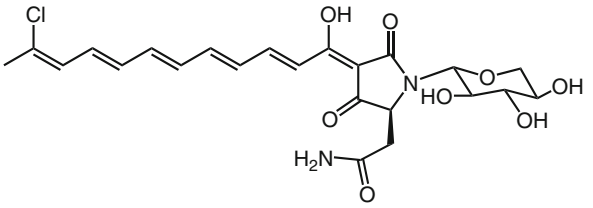
809 (aurantoside C)



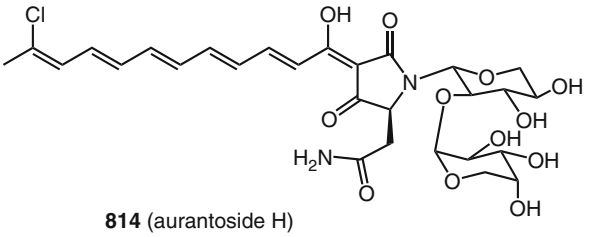
810 R = H (aurantoside D)
811 R = Me (aurantoside E)



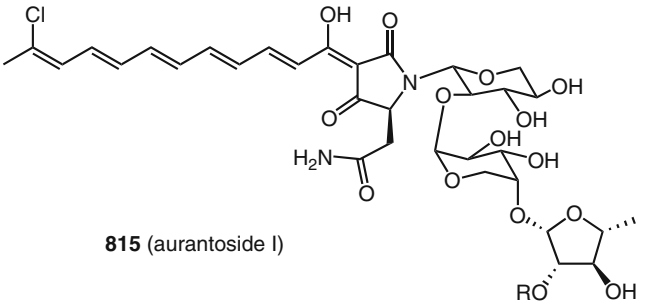
812 (aurantoside F)



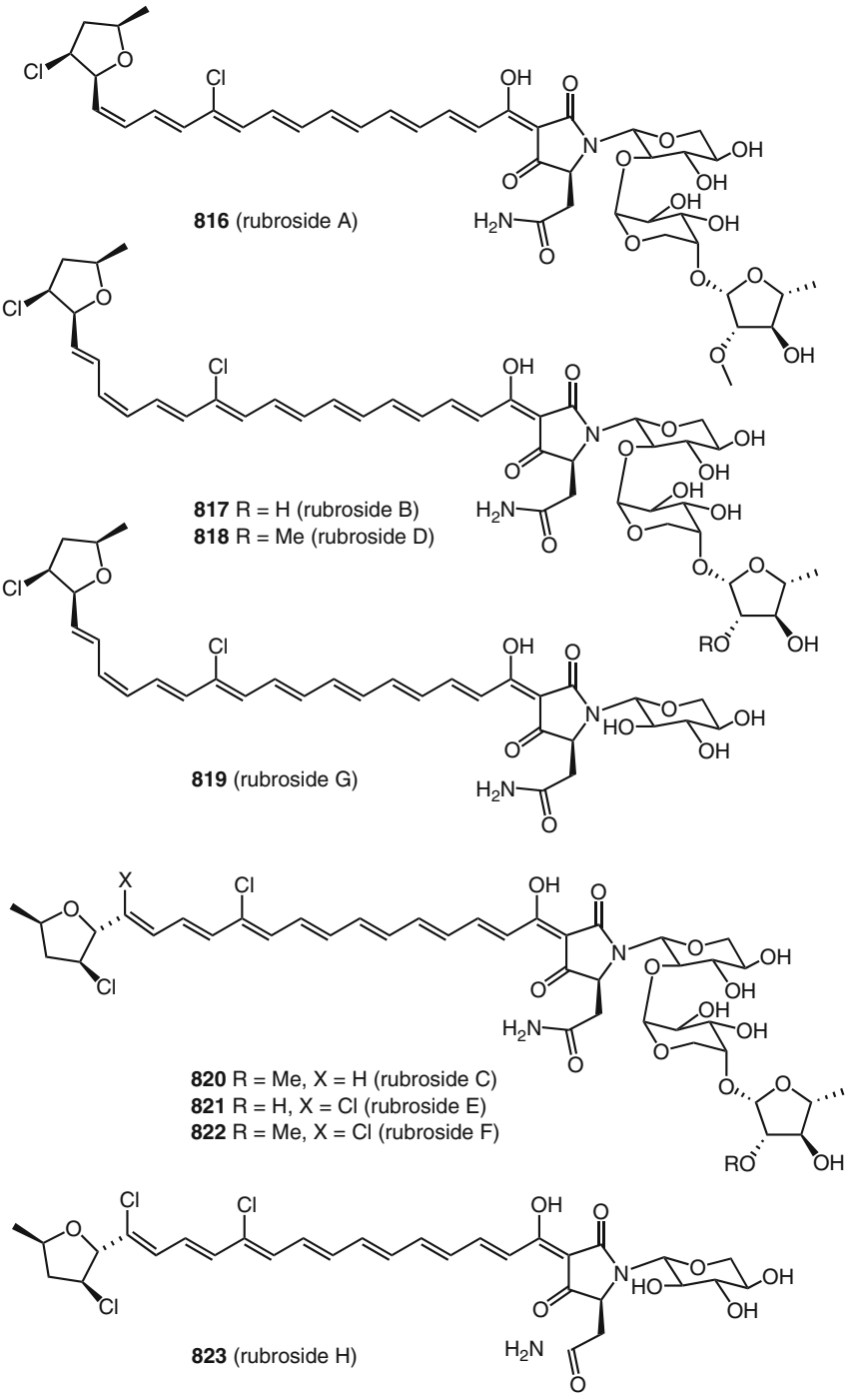
813 (aurantoside G)



814 (aurantoside H)



815 (aurantoside I)



816 (rubroside A)

817 R = H (rubroside B)
818 R = Me (rubroside D)

819 (rubroside G)

820 R = Me, X = H (rubroside C)
821 R = H, X = Cl (rubroside E)
822 R = Me, X = Cl (rubroside F)

823 (rubroside H)

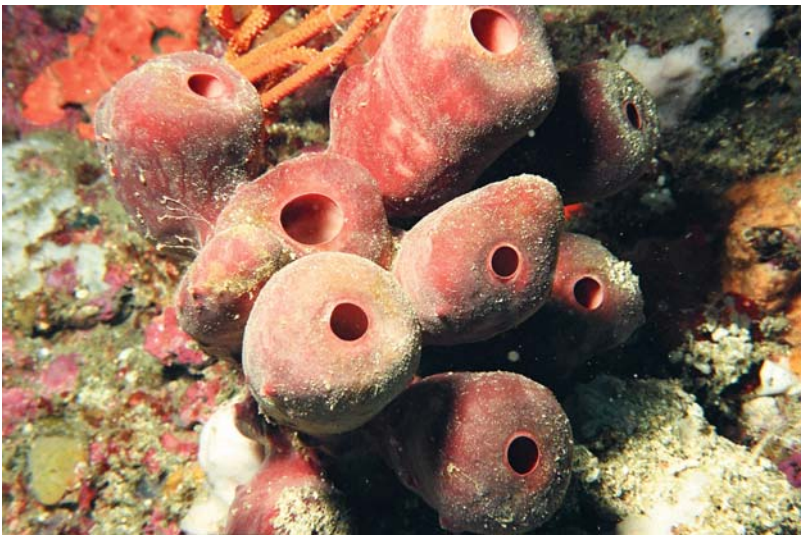
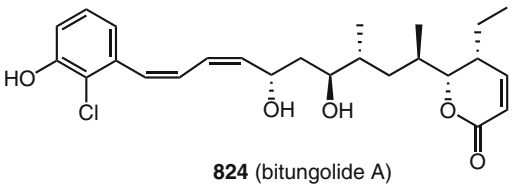
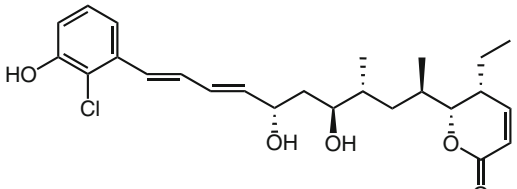


Fig. 3.12 *Theonella* cf. *swinhoei*, a sponge collected at Bitung, Indonesia, that contains the bitungolides A–D (**824**–**827**) (Photo: J. Tanaka)

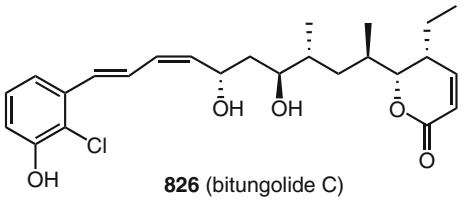
The novel polyketides, bitungolides A–D (**824**–**827**), were characterized from the Indonesian sponge *Theonella* cf. *swinhoei* (Fig. 3.12), compounds that inhibit dual-specificity phosphatase VHR (*875*). The first chlorine-containing compound found in a Caribbean *Plakoris* sponge (*Plakoris simplex*) is plakortether C (**828**), along with several non-halogenated analogs (*876*). In addition to the known clathrynamide A, the Okinawan sponge *Psammoclemma* sp. has afforded the new (6*E*)-clathrynamide A (**829**) (*877*). Moreover, the absolute stereochemistry of clathrynamide A was established as shown for **829**. The marine bacterium *Pseudoalteromonas* sp. F-420 produces korormicin analog **830** (*878*).



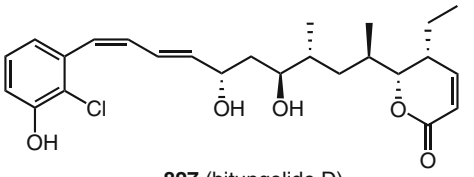
824 (bitungolide A)



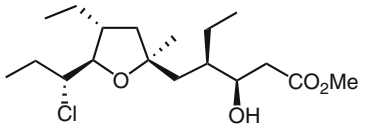
825 (bitungolide B)



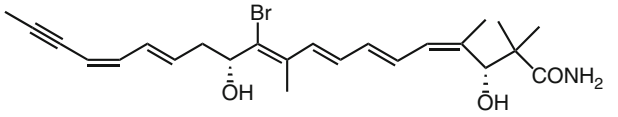
826 (bitungolide C)



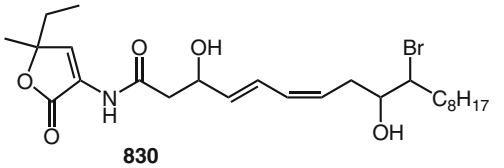
827 (bitungolide D)



828 (plakortether C)

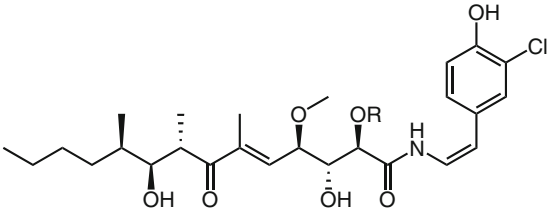


829 ((6*E*)-clathrynamide A)

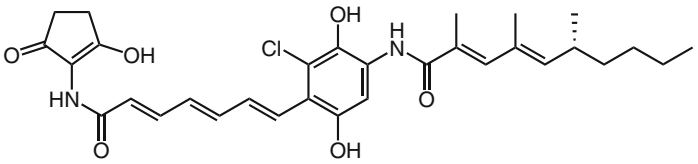


830

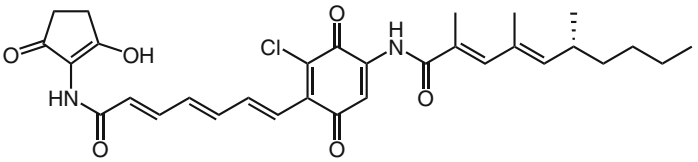
The myxobacterium *Chondromyces crocatus* contains the novel chondrochlorens A (**831**) and B (**832**) (*879*). A marine *Streptomyces* species has afforded the manumycin antibiotics chinikomycins A (**833**) and B (**834**) (*880*). While inactive in antiviral, antimicrobial, and phytotoxicity screens, these chinikomycins display some cytotoxic activity.



831 R = Me (chondrochloren A)
832 R = Et (chondrochloren B)

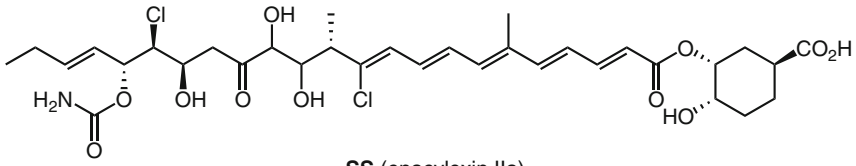


833 (chinikomycin A)

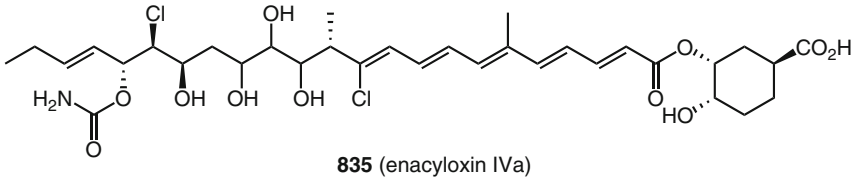


834 (chinikomycin B)

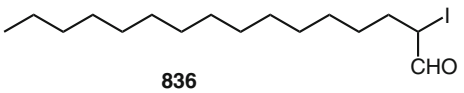
The absolute configuration of the previously described enacyloxin IIa (formerly named enacyloxin II) (*1*) has now been partially established as **SS** (*881*), following earlier structural studies (*882*). This same bacterium *Frateuria* sp. W-315 produces enacyloxin IVa (**835**) (*883*). Several studies on the biological activity of enacyloxin IIa reveal that it inhibits protein biosynthesis (*884–887*). Two iodolactones found in the thyroid gland of dogs were presented in the first survey (*1*). The novel 2-iodohexadecanal (**836**) is present in the horse, dog, and rat thyroid (*888*). Studies indicate that **836** serves as a "mediator of some of the regulatory actions of iodide on the thyroid gland" (*889, 890*). The aforementioned iodolactones (*1*) seem to have a different role than **836** in the thyroid gland (*891, 892*).



SS (enacyloxin IIa)



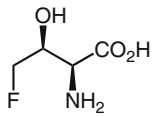
835 (enacyloxin IVa)



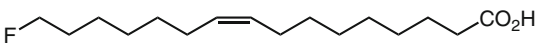
836

3.9 Fluorine-Containing Carboxylic Acids

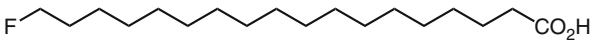
The infamous fluoroacetic acid and the equally toxic naturally occurring even-numbered ω-fluorinated fatty acids were discussed in detail earlier (*1*), and several reviews are available (*34, 44, 66*). Although not counted as being natural in the earlier survey (*1*), 4-fluorothreonine (**837**) is now considered to be a bona fide natural metabolite of *Streptomyces cattleya* (*893*), the stereochemistry of which has been confirmed by synthesis (*894*). In addition to the five ω-fluorinated fatty acids presented earlier (*1*), new studies of the seed oil of *Dichapetalum toxicarium* have uncovered 16-fluoropalmitoleic acid (**838**), 18-fluorostearic acid (**839**), 18-fluorolinoleic acid (**840**), 20-fluoroarachidic acid (**841**), 20-fluoroeicosenoic acid (**842**), 18-fluoro-9,10-epoxystearic acid (**843**) (*895*), (*Z*)-16-fluorohexadec-7-enoic acid (**844**), (*Z*)-18-fluorooctadec-9-enoic acid (**845**), and (*Z*)-20-fluoroicos-9-enoic acid (**846**) (*896*).



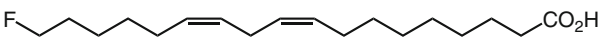
837



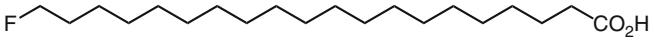
838 (16-fluoropalmitoleic acid)



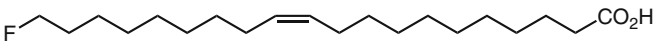
839 (18-fluorostearic acid)



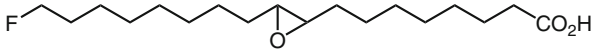
840 (18-fluorolinoleic acid)



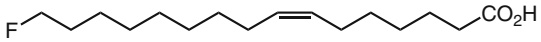
841 (20-fluoroarachidic acid)



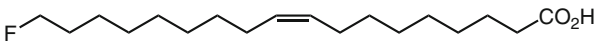
842 (20-fluoroeicosenoic acid)



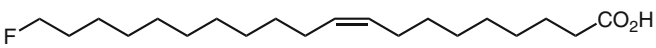
843 (18-fluoro-9,10-epoxystearic acid)



844 ((*Z*)-16-fluorohexadec-7-enoic acid)



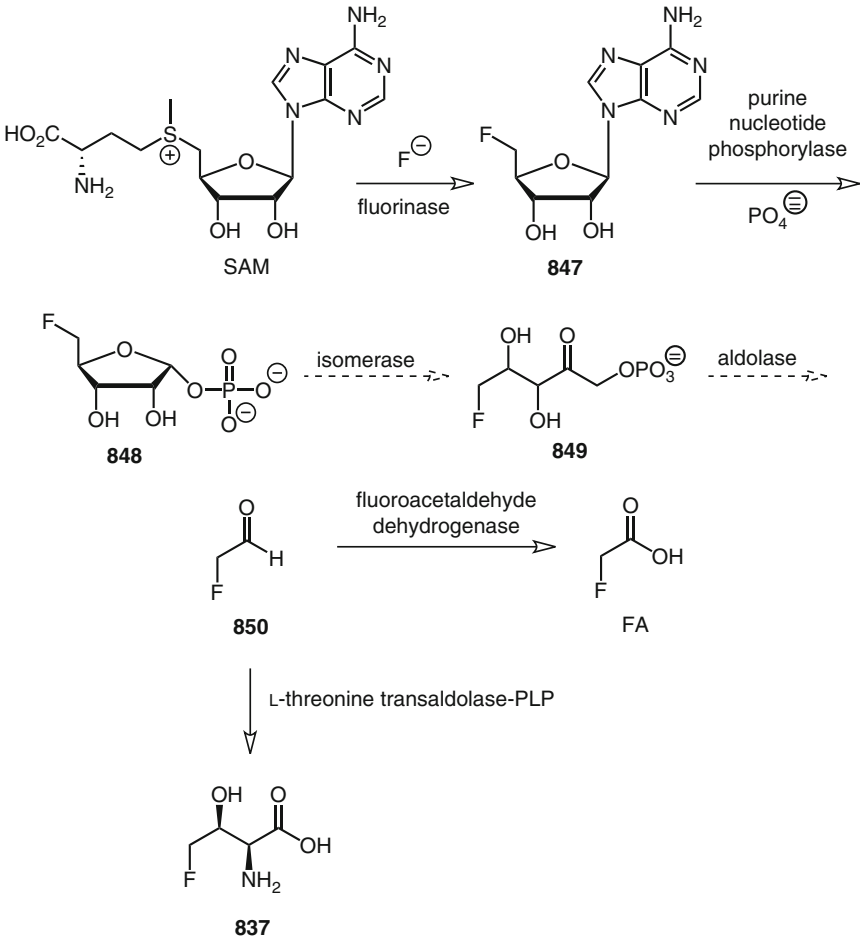
845 ((*Z*)-18-fluorooctadec-9-enoic acid)



846 ((*Z*)-20-fluoroicos-9-enoic acid)

Extensive and elegant biosynthetic studies on these fluorine-containing metabolites have revealed some additional natural organofluorines produced by *Streptomyces cattleya*, and, more importantly, provide a comprehensive understanding of the biosynthesis of fluoroacetate and 4-fluorothreonine (*895, 897–913*). A summary of this biosynthesis is shown in Scheme 3.3 and reviews are available (*914, 915*).

The first step in this pathway involves S_N2 displacement by fluoride on *S*-adenosine-L-methionine (SAM) catalyzed by the newly discovered enzyme fluorinase (*905–910*), which also can function as a chlorinase (*912*). Fluorinase has been isolated and characterized, and the gene has been cloned (*916*). Both 5′-fluoro-5′-deoxyadenosine (**847**) and 5′-fluoro-5′-deoxy-D-ribose-1-phosphate (**848**) have been identified as intermediates (*905–908*). Fluoroacetaldehyde (**850**) is the immediate precursor, presumably via fluororibulose-1-phosphate (**849**) (*915*), to both fluoroacetate and 4-fluorothreonine (**837**) (*901*). The requisite enzymes fluoroacetaldehyde dehydrogenase (*902*) and L-threonine transaldolase-PLP (*903*) have been isolated and purified. The steps from **848** to **850** remain to be established but are based on known biochemistry. The pronounced toxicity of fluoroacetic acid



Proposed abbreviated biosynthesis of fluoroacetic acid and 4-fluorothreonine (*909, 915, 2395*).

Scheme 3.3

(fluoroacetate) is still of major concern, especially with the realization that it is a metabolite of several fluorinated drugs, pesticides, and other industrial chemicals, and thus may pose an environmental threat to aquatic organisms (*917*). A study of genetically modified ruminal bacteria, with a gene encoding fluoroacetate dehalogenase, indicates promise in protecting sheep against fluoroacetate poisoning (*918*). The mechanism of fluoroacetate toxicity, which is known to involve conversion to fluorocitrate, has been shown to entail further transformation to 4-hydroxy-(*E*)-aconitate, which then binds to aconitase (*919*). While it has been known as an

anthropogenic atmospheric pollutant for a long time, trifluoroacetic acid (**851**) is now considered to have (unknown) natural sources with an ocean concentration of about 200 ng L^{-1} (*920*).

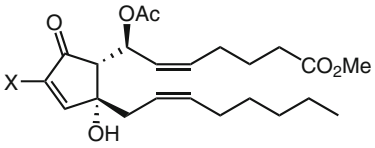
CF_3CO_2H

851

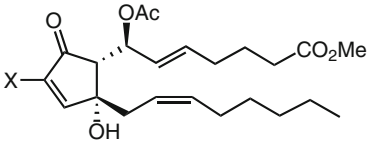
3.10 Prostaglandins

The first survey identified 15 marine halogenated prostaglandins, some of which display striking biological activity (*1*), and a review is available on the occurrence, biological activity, and biogenesis of these interesting organohalogen compounds (*921*).

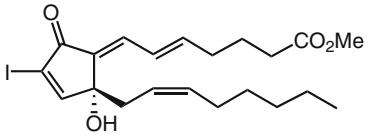
A practical racemic synthesis of the known chlorovulone II from the Okinawan soft coral *Clavularia viridis* has been accomplished (*922*). This coral has more recently afforded the new prostanoids **852**–**856** (*923*), **857**–**871** (*924*), and, from a Taiwanese collection, **872**, **873** in addition to **857** and **858** (*925*). The absolute configuration of the previously known punaglandin 8 (**852**, X = Cl) was determined as shown (*923*). This soft coral also contains several non-halogenated possible biosynthetic precursors to these halogenated metabolites (*926*).



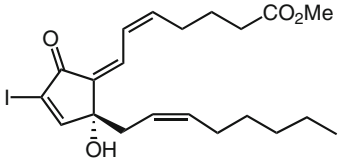
852 X = I
853 X = Br



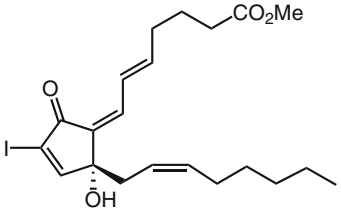
854 X = I
855 X = Br
856 X = Cl



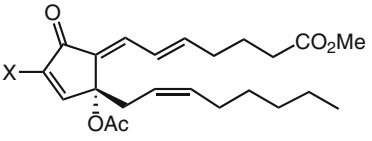
857 (iodovulone II)



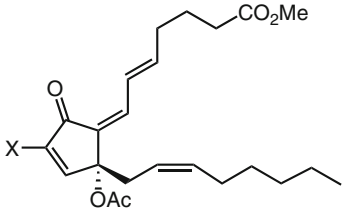
859 (iodovulone IV)



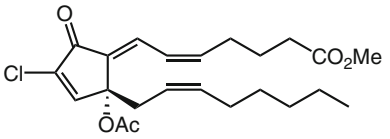
858 (iodovulone III)



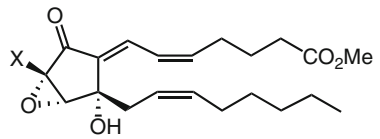
860 X = I (12-*O*-acetyliodovulone II)
861 X = Br (12-*O*-acetylbromovulone II)
862 X = Cl (12-*O*-acetylchlorovulone II)



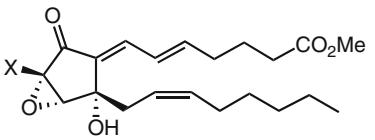
863 X = I (12-*O*-acetyliodovulone III)
864 X = Br (12-*O*-acetylbromovulone III)
865 X = Cl (12-*O*-acetylchlorovulone III)



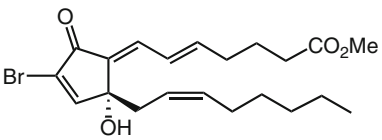
866 (12-*O*-acetylchlorovulone I)



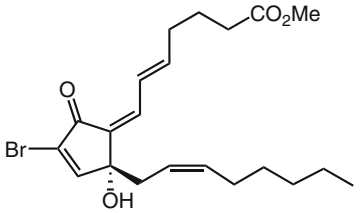
870 X = I (10,11-epoxyliodovulone I)
871 X = Br (10,11-epoxybromovulone I)



867 X = I (10,11-epoxyliodovulone II)
868 X = Br (10,11-epoxybromovulone II)
869 X = Cl (10,11-epoxychlorovulone II)

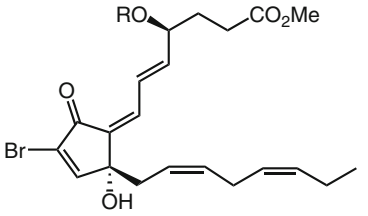


872 (bromovulone II)

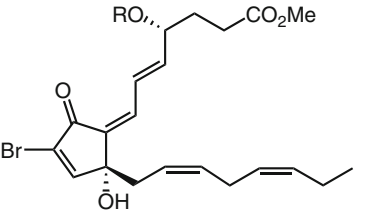


873 (bromovulone III)

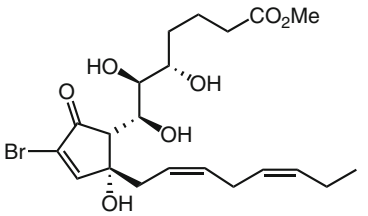
A Red Sea collection of the soft corals *Dendrophyllia* sp., *Dendronephthya* sp. (red variety), *Dendronephthya* sp. (yellow variety), and *Tubipora musica* revealed the eight new brominated oxylipins **874–881** (*927*). The brown alga *Eisenia bicyclis*, which was gathered around the coast of Japan, has afforded eiseniachlorides A–C (**882–884**), eiseniaiodides A (**885**) and B (**886**), and **887** (*928*). The eastern Pacific octocoral *Carijoa multiflora* contains the novel prostanoid carijenone (**888**) (*929*). Both natural punaglandins and synthetic analogs can function as Michael reaction acceptors to inhibit ubiquitin isopeptidase activity, which may represent a target for anticancer agents (*930, 931*).



874 R = H
875 R = α-D-glucopyranosyl



876 R = H
877 R = β-D-glucopyranosyl



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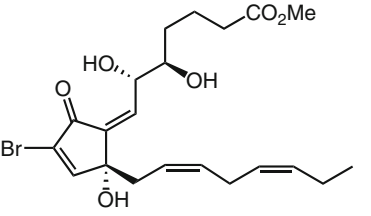

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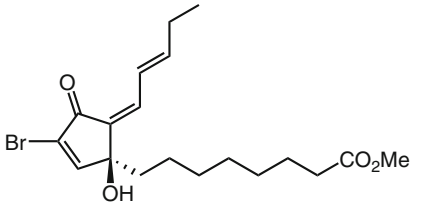

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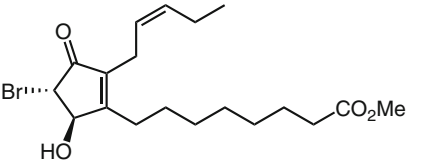
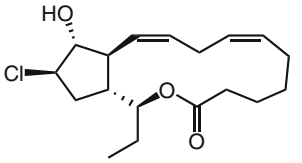
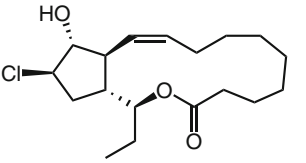


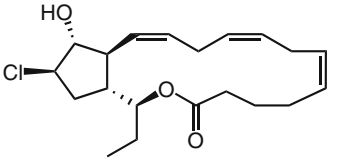
881



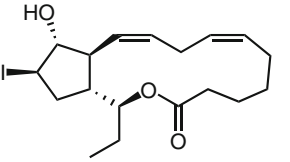
882 (eiseniachloride A)



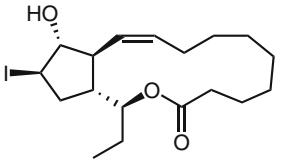
883 (eiseniachloride B)



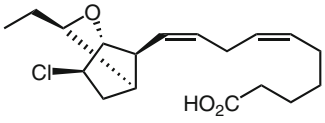
884 (eiseniachloride C)



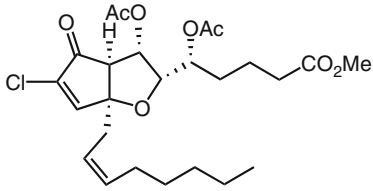
885 (eiseniaiodide A)



886 (eiseniaiodide B)



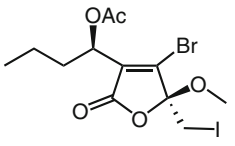
887



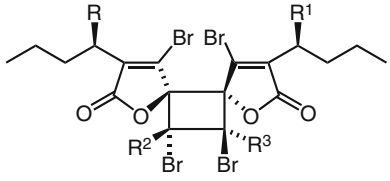
888 (carijenone)

3.11 Furanones

Red algae of the genus *Delisea* enriched the first survey with 40 mainly brominated furanones, some of which have powerful antibacterial activity (*1*). The absolute configuration of the previously known *Delisea pulchra* furanone **TT**, and others by extension, has been determined (*932*). While the only new examples of these heavily brominated furanones appear to be the pulchralides A–C (**889**–**891**) from an Antarctic collection of *Delisea pulchra* (*476*), these compounds have been extensively studied from a biological standpoint (*933–945*). Most notably, these halogenated furanones inhibit bacterial colonization (*933–942, 944*), and this quorum-sensing inhibitory activity may lead to drugs for the treatment of bacterial infections. These furanones also display feeding deterrence to herbivores (*943*) and show cytotoxic, antimicrobial, and antiplasmodial activity (*945*). The sea hare *Aplysia parvula* feeds on *Delisea pulchra* to acquire halogenated furanones for chemical defense (*946*).

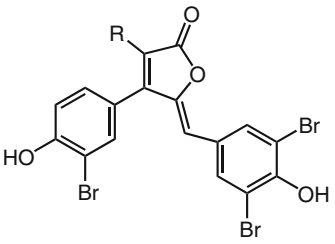


TT

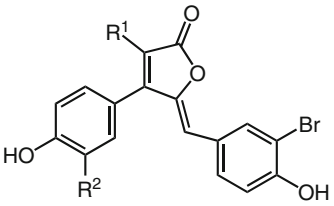


889 R = R^1 = OAc, R^2 = R^3 = H (pulchralide A)
890 R = R^1 = R^2 = R^3 = H (pulchralide B)
891 R = OAc, R^1 = R^2 = R^3 = H (pulchralide C)

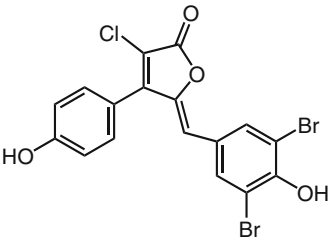
Six new halogenated rubrolides I (**892**), J (**893**), K (**894**), L (**895**), M (**896**), and N (**897**) were characterized from the Spanish ascidian *Synoicum blochmanni* (*947*). Several of these compounds exhibit significant cytotoxicity against these tumor cell lines: HT-29, MEL-28, P-388, and A-549, with rubrolide M (**895**) showing the greatest activity. A New Zealand variety of *Synoicum* sp. has provided rubrolide O as a mixture of *Z* (**898**) and *E* (**899**) isomers, which display some antiinflammatory activity (*948*). The previously known rubrolides C and E have been efficiently synthesized (*949*).



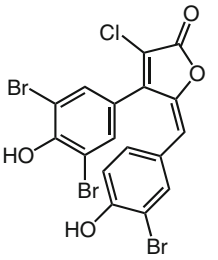
892 R = Cl (rubrolide I)
893 R = H (rubrolide J)



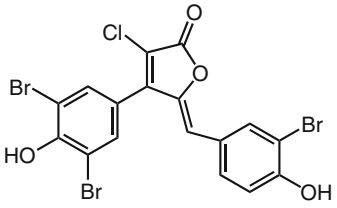
894 R^1 = Cl, R^2 = Br (rubrolide K)
895 R^1 = Cl, R^2 = H (rubrolide M)
896 R^1 = Br, R^2 = Cl (rubrolide N)



897 (rubrolide L)

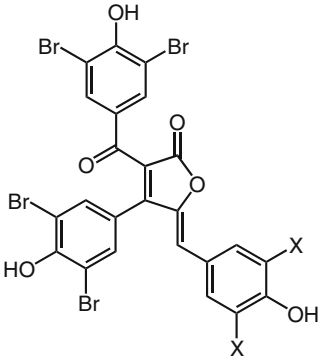


899 ((*E*)-rubrolide O)

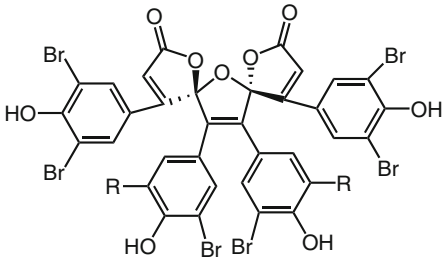


898 ((*Z*)-rubrolide O)

An Indonesian ascidian of the genus *Botryllus* contains the novel cadiolides A (**900**) and B (**901**) (*950*). The tetraphenolic bis-spiroketals prunolides A (**902**, **903**) and B (**904**, **905**) were characterized from an Australian ascidian *Synoicum prunum* (*951*).

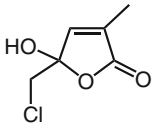


900 X = H (cadiolide A)
901 X = Br (cadiolide B)

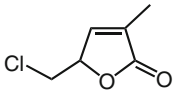


902, 903 R = Br (prunolide A; racemic mixture)
904, 905 R = H (prunolide B; racemic mixture)

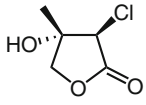
The ant-cultivated fungus *Lepiota* sp. produces the antibacterial lepiochlorin (**906**), which is racemic, perhaps due to ring-opening tautomerism (*952*). The mushroom *Clitocybe flaccida* (Fig. 3.13), which is repugnant to the banana slug (*Ariolimax columbianus*) (Fig. 3.14), secretes clitolactone (**907**) (*953*). Control experiments clearly demonstrate the potent antifeedant properties of clitolactone to these slugs (Fig. 3.15). The Asian shrub *Prinsepia utilis* affords lactone **908** (*954*). An *Aspergillus* sp. fungus from the sponge *Jaspis* cf. *coriacea* has yielded chlorocarolides A (**909**) and B (**910**) (*955*). Another marine-derived fungus, *Aspergillus ostianus*, from Pohnpei has provided chlorinated furanones **911** and **912** (*956*). A related pyrone from this organism is shown later in Sect. 3.14.8 (Pyrones and Chromones).



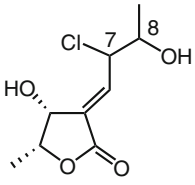
906 (lepiochlorin)



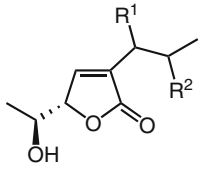
907 (clitolactone)



908



909 ((7*R*,8*R*)-chlorocarolide A)
910 ((7*S*,8*S*)-chlorocarolide B)



911 R^1 = Cl, R^2 = OH
912 R^1 = OH, R^2 = Cl

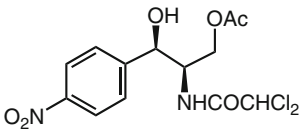
Fig. 3.13 *Clitocybe flaccida*, the mushroom that contains the antifeedant clitolactone (**907**) (Photo: W. F. Wood)

Fig. 3.14 The banana slug (*Ariolimax columbianus*) feeding on the mushroom *Russula roscea* (= *R. sanguinea*) (Photo: W. F. Wood)

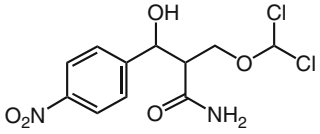
Fig. 3.15 The banana slug (*Ariolimax columbianus*) tasting and being repelled by clitolactone-treated lettuce (Photo: W. F. Wood)

3.12 Amino Acids and Peptides

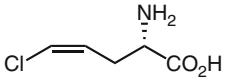
Halogenated amino acids and peptides represent an enormous class of natural products. The first survey counted nearly 100 such examples of marine and terrestrial bacterial origin (*1*). One of the first halogenated natural products to be characterized, chloramphenicol, continues to draw attention (*2656*). The new analog 3′-*O*-acetylchloramphenicol (**913**), which is a possible intermediate in the biosynthesis of chloramphenicol, has been isolated from *Streptomyces venezuelae* (*957*). The antifungal acrodontiolamide (**914**) is produced by *Acrodontium salmoneum* (*958, 959*). The dichloromethyl ether moiety is unique amongst natural products and is expected to be a potent alkylating agent, assuming that this structure is correct. An enantioselective synthesis of (–)-(1*R*,2*R*)-chloramphenicol has been reported (*960*), and the genes required for its biosynthesis by *Streptomyces venezuelae* have been identified (*961, 962*), including those required for the dichloroacetyl unit (*962*). Synthetic derivatives of bactobolin (*1*), which also contains a dichloromethyl group, show less activity than the natural product in various cytotoxicity and antibacterial assays (*963*).



913



914 (acrodontiolamide)

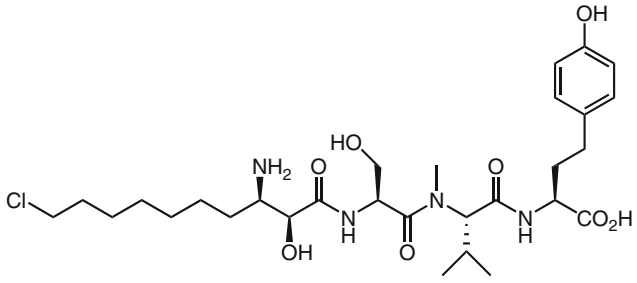


915

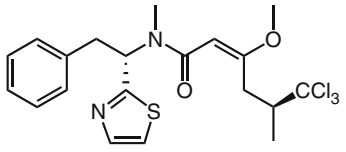
Mushrooms are a source of simple chlorinated amino acids (*1*), and several new examples are known. Thus, *Amanita vergineoides* has furnished (2*S*,4*Z*)-2-amino-5-chloro-4-pentenoic acid (**915**) (*964*), and a full account of the isolation of (2*S*)-2-

amino-5-chloro-4-hydroxy-5-hexenoic acid from *Amanita gymnopus* (*1*) and other *Amanita* species has been published (*965, 966*). Likewise, a full report on the isolation of 2-amino-5-chloro-5-hexenoic acid from *Amanita miculifera* (*1*) has appeared (*967*). Interestingly, the related amino acid **915** was isolated as a racemate from *Amanita castanopsidis* (*968*). The biosynthesis of the known armentomycin (2-amino-4,4-dichlorobutyric acid) from *Streptomyces armentosus* var. *armentosus* was studied using radiolabelling and the results support a pathway of pyruvate to acetyl-CoA and perhaps dichloropyruvate, followed by condensation and conversion to armentomycin along known amino acid pathways (*969*).

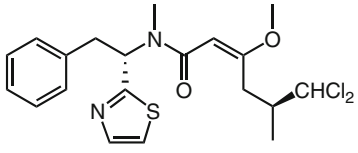
Cyanobacteria blooms can pose an extremely serious threat to human health (*970–972*), and some of the causative toxins contain halogen. The fresh water toxic cyanobacterium *Oscillatoria agardhii* produces oscillaginin A (**916**), which features the novel 3-amino-10-chloro-2-hydroxydecanoic acid, and is the source of the microcystins, which are heptatoxins (*973*). The prolific cyanobacterium *Lyngbya majuscula* from Curacao has furnished the novel barbamide (**917**) (*974*) and dechlorobarbamide (**918**) (*975*). Extensive biosynthetic studies show that the amino acids leucine, cysteine, and phenylalanine are involved in barbamide production (*976–982*). The chlorination of leucine is of great interest and may involve a radical mechanism (*976, 980–983*).



916 (oscillaginin A)



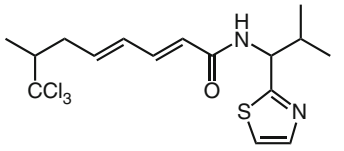
917 (barbamide)



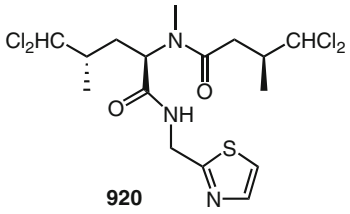
918

The marine sponge *Dysidea herbacea*, perhaps in association with its cyanobacterial symbiont *Oscillatoria spongeliae*, is responsible for furnishing some 20 polychlorinated amino acid-derived metabolites (*1*). A Papua New Guinea sample of *Dysidea herbacea*, which contains *Oscillatoria spongeliae*, has yielded the novel herbamide A (**919**) (*984*), whereas a collection of this sponge from the Great Barrier

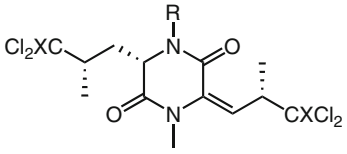
Reef provided **920–922**, and the absolute configuration of the latter metabolite was established as shown (*985*). *Dysidea fragilis* from the South China Sea has yielded dysamide D (**923**) (*986*), and *Dysidea chlorea* from Micronesia afforded 12 new polychlorinated diketopiperazines, dysamides I-T (**924–935**) (*987*). In addition, this study (*987*) confirmed the structure of dysamide E (**936**) (*988*). Based on previous assignments the absolute configurations of **924–936** are believed to be those indicated. A Pacific Ocean collection of *Dysidea* sp. provided dysamide U (**937**), which is the first trichlorinated member of the diketopiperazine family to be identified (*989*).



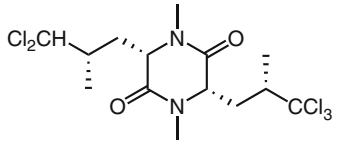
919 (herbamide A)



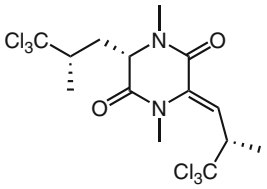
920



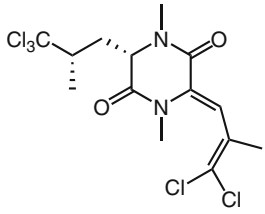
921 R = Me, X = H
922 R = H, X = Cl



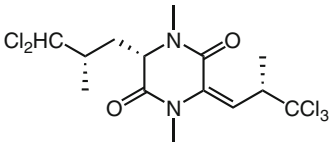
923 (dysamide D)



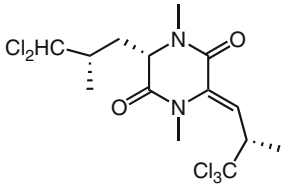
924 (dysamide I)



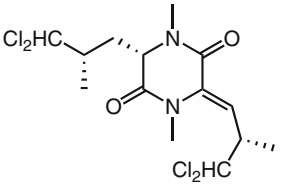
925 (dysamide J)



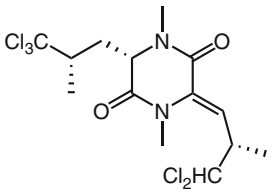
926 (dysamide K)



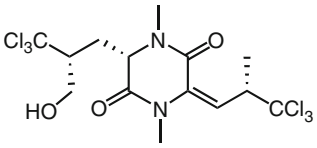
927 (dysamide L)



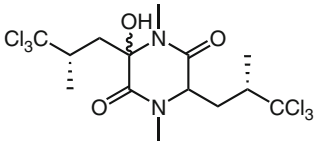
928 (dysamide M)



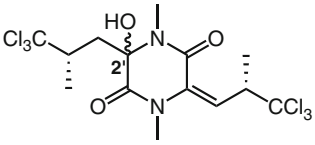
929 (dysamide N)



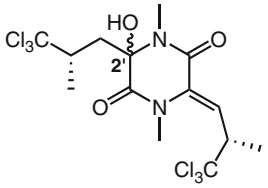
930 (dysamide O)



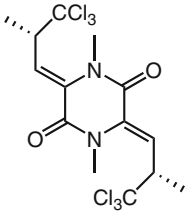
931 (dysamide P)



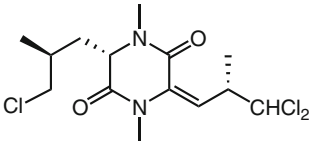
932, 933 (dysamide Q and R)
(epimers at C-2')



934, 935 (dysamide S and T)
(epimers at C-2')



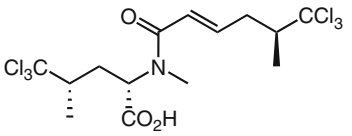
936 (dysamide E)



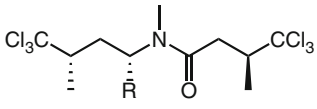
937 (dysamide U)

The simple herbacic acid (**938**) was isolated from *Dysidea herbacea* from the Great Barrier Reef, and may be a precursor to more complex trichloromethyl metabolites (*990*). Another collection of *Dysidea* sp. from Australia's Great Barrier Reef yielded five new metabolites (**939**–**943**) for which the absolute stereochemistry was determined by correlation with (–)-(*S*)-4,4,4-trichloro-3-methylbutanoic acid (*991*). *Dysidea herbacea* from the Great Barrier Reef contains (–)-neodysidenin (**944**), which is an isomer of the well-known and often isolated dysidenin.

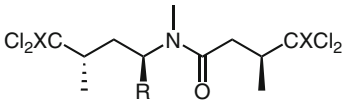
This new metabolite belongs to the L-series of trichloroleucine peptides and is a rare example of a non-*N*-methylated trichloroleucine amino acid (*992*). Another sample of this sponge from the same locale has yielded the new thiazoles **945** and **946**, which are also related to dysidenin (*993*). The Panamanian *Lyngbya majuscula* has afforded the new dysidenamide (**947**), pseudodysidenin (**948**), and nordysidenin (**949**), which is the first report of dysidenin-like compounds from a free-living cyanobacterium (*994*).



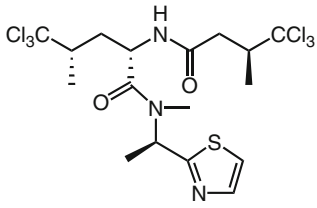
938 (herbacic acid)



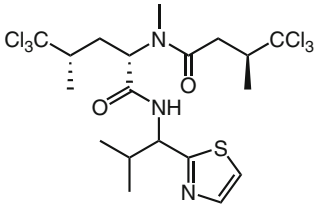
939 R = CO_2Me
940 R = CO_2H



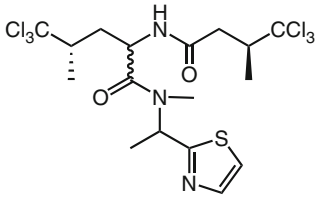
941 X = Cl, R = CO_2Me
942 X = H, R = CO_2Me
943 X = Cl, R = CO_2H



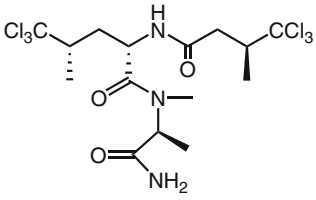
944 (neodysidenin)



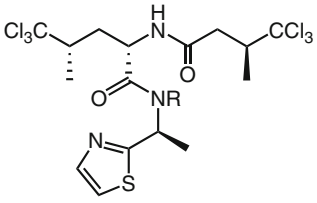
945



946

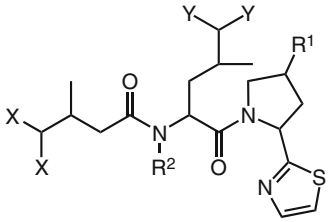


947 (dysidenamide)

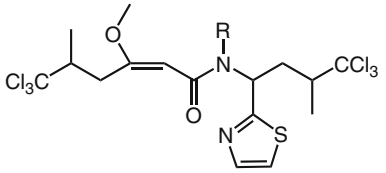


948 R = Me (pseudodysidenin)
949 R = H (nordysidenin)

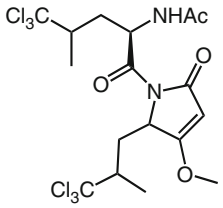
A study of a Philippines *Dysidea* sp. has yielded the novel proline analogs of dysidenin, dysideaprolines A–F (**950**–**955**) and barbaleucamides A (**956**) and B (**957**), which are reminiscent of barbamide (*995*). Also from the Philippines was isolated the novel pyrrolidone **958** from the nudibranch *Asteronotus cespitosus* (*996*), which is the first example of a *Dysidea*-type polychlorinated metabolite found in a carnivorous mollusc. An Indonesian collection of *Dysidea* sp. has furnished dysithiazolamide (**959**), having the suggested absolute configuration shown (*997*).



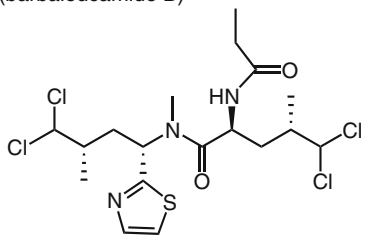
950 R^1 = H, R^2 = Me, X = Y = Cl (dysideaproline A)
951 R^1 = R^2 = Me, X = Y = Cl (dysideaproline B)
952 R^1 = R^2 = H, X = Y = Cl (dysideaproline C)
953 R^1 = H, R^2 = Me, X = H, Y = Cl (dysideaproline D)
954 R^1 = H, R^2 = Me, X = Cl, Y = H (dysideaproline E)
955 R^1 = H, R^2 = Me, X = Cl, Y = H,Cl (dysideaproline F)



956 R = H (barbaleucamide A)
957 R = Me (barbaleucamide B)

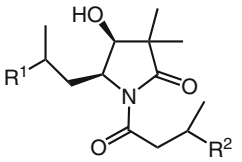


958

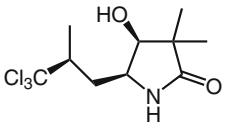


959 (dysithiazolamide)

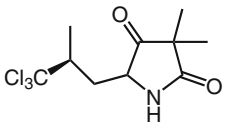
The Red Sea sponge *Lamellodysidea herbacea* contains the new dysidamides D–H (**960–965**) and ring-opened analogs **966** and **967** (*998*). As has been pointed out several times (*999*), the determination of absolute stereochemistry of the *Dysidea* polychlorinated peptides has been difficult and revisions are not uncommon. The X-ray crystal structure of a zinc chelate of dechlorinated dysidenin has confirmed its absolute configuration as (5*S*,13*S*) as shown in **UU** (*999*).



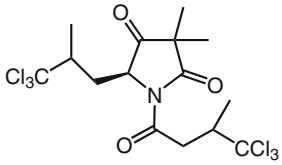
960 $R^1 = CCl_3$, $R^2 = CHCl_2$ (dysidamide D)
961 $R^1 = CHCl_2$, $R^2 = CCl_3$ (dysidamide E)



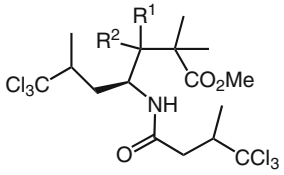
962 (dysidamide F)



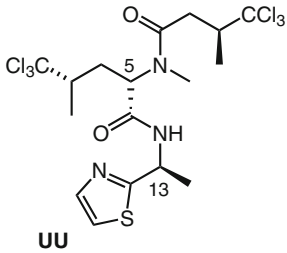
963 (dysidamide G)
964 (5-epidysidamide G)



965 (dysidamide H)



966 $R^1 = H$, $R^2 = OH$
967 $R^1 = R^2 = O$

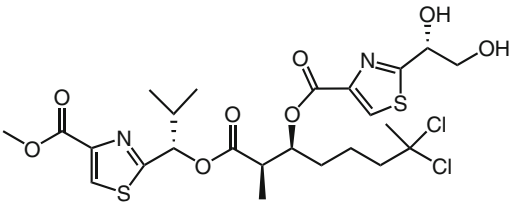


UU

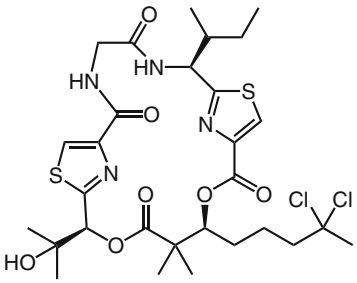
Dysidenin is a strong inhibitor of iodide transport in dog thyroid, and the trichloromethyl group is recognized by the binding site (*1000, 1001*). Interestingly, the configuration at C-5 has no influence on this biological activity. The relationship between *Dysidea* and other sponges and the cyanobacterium *Oscillatoria spongeliae* continues to be studied (*1002, 1003*), revealing that only certain strains of this cyanobacterium are capable of producing either polychlorinated metabolites or polybrominated diphenyl ethers but not both (*1003*).

Several other, more complex cysteine-derived polychlorinated peptide metabolites are known to arise in marine organisms. Dolabellin (**968**) was characterized from the Japanese sea hare *Dolabella auricularia* (*1004*). The absolute

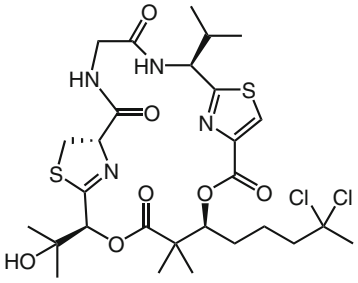
configuration was established by chemical degradation and a total synthesis of dolabellin. A Guamanian strain of the cyanobacterium *Lyngbya majuscula* has yielded lyngbyabellins A (**969**) (*1005*) and B (**970**) (*1006*). The latter metabolite was independently isolated from a collection of this alga in Florida (*1007*). Lyngbyabellin A has been synthesized (*1008*) and the absolute configuration of lyngbyabellin B is as shown (*1006*). A Palauan variety of *Lyngbya* sp. contains lyngbyabellin C (**971**) (*1009*), and the structurally related hectochlorin (**972**) was isolated from a Panamanian sample of *Lyngbya majuscula* and its absolute configuration was determined (*1010*). Hectochlorin has been synthesized (*1011*) and has potent inhibitory action against the fungus *Candida albicans* and displays inhibition of cell growth (*1010*). The Thai sea hare *Bursatella leachii* contains deacetylhectochlorin (**973**), which is more potent than hectochlorin against human carcinoma cell lines (*1012*).



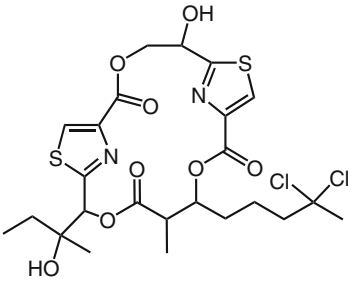
968 (dolabellin)



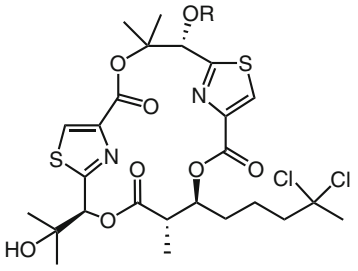
969 (lyngbyabellin A)



970 (lyngbyabellin B)

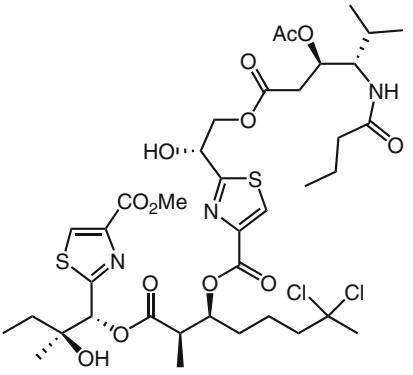


971 (lyngbyabellin C)

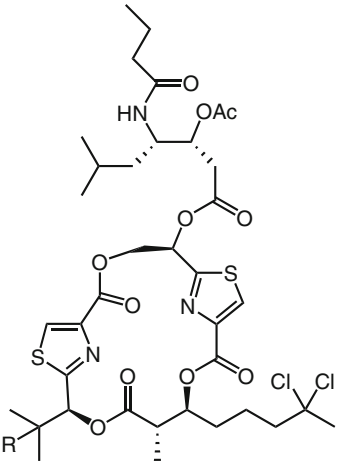


972 R = Ac (hectochlorin)
973 R = H (deacetylhectochlorin)

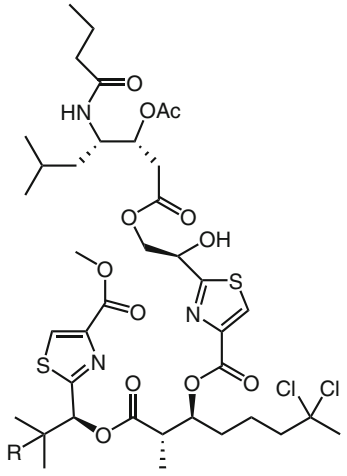
Additional collections of Guamanian *Lyngbya* sp. led to the discovery of lyngbyabellin D (**974**), having the absolute configuration shown and which displays good cytotoxicity against the KB cell line (*1013*). Lyngbyabellins E-I (**975–979**), which exhibit significant cytotoxicity against cancer cell lines, were characterized from *Lyngbya majuscula* from Papua New Guinea (*1014*). The absolute configurations of E (**975**) and H (**978**) were established via degradation products.



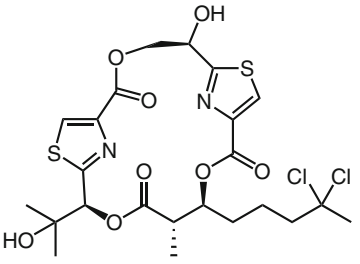
974 (lyngbyabellin D)



975 R = OH (lyngbyabellin E)
978 R = H (lyngbyabellin H)

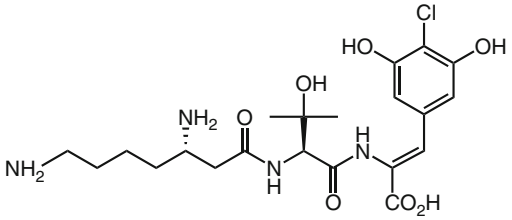


976 R = OH (lyngbyabellin F)
979 R = H (lyngbyabellin I)

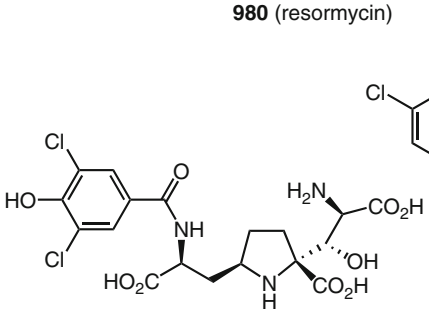


977 (lyngbyabellin G)

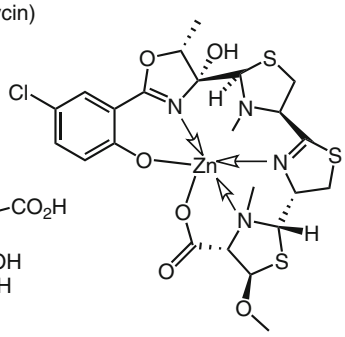
The chlorophenolic peptide resormycin (**980**), which was isolated from cultures of *Streptomyces platensis*, displays herbicidal and fungicidal activities (*1015, 1016*). Kaitocephalin (**981**) is produced by the fungus *Eupenicillium shearii* and is a glutamate receptor antagonist (*1017, 1018*). The original structure has been slightly revised (*1019*) and confirmed by total synthesis (*1019–1022*). The unique zinc-containing antibiotic transvalencin A (**982**) was isolated from *Nocardia transvalensis* found in a human clinical patient (*1023, 1024*).



980 (resormycin)

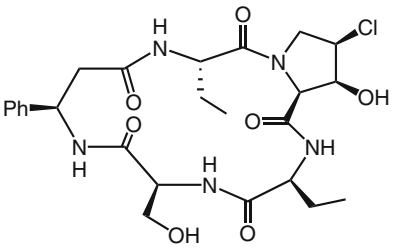


981 (kaitocephalin)

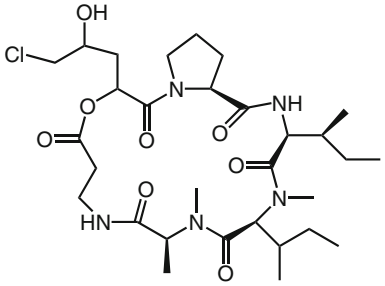


982 (transvalencin A)

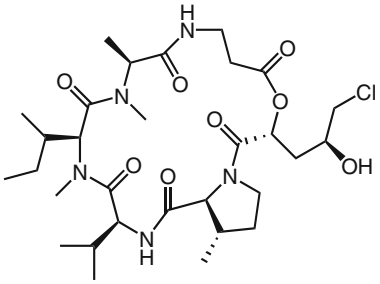
A series of proline-containing cyclopentapeptides was disclosed in the first review (*1*), and subsequent work has shown that islanditoxin and cyclochlorotine are identical metabolites; the latter is the correct structure (*1025*). A new member of this group, astin I (**983**), has been isolated from *Aster tataricus* (*1026*), which is the source of several previously known astins (*1*). A full account of the structure determination of the known astins A–C has appeared (*1027*), and the antitumor activity of the astins seems to be related to the conformation of the dichloroproline unit in astins A–C (*1028, 1029*). A total synthesis of astin G, which is the only non-chlorinated astin, has been reported (*1030*). A cyclic pentapeptide related to the astins is destruxin-A4 chlorohydrin (**984**), which was found in the fungal culture OS-F68576 (*1031*). This chlorohydrin induces erythropoietin gene expression. The marine-derived fungus *Beauveria felina* has afforded [β-Me-Pro] destruxin E chlorohydrin (**985**) (*1032*).



983 (astin I)

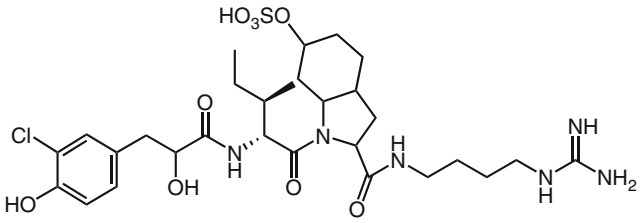


984 (destruxin-A4 chlorohydrin)

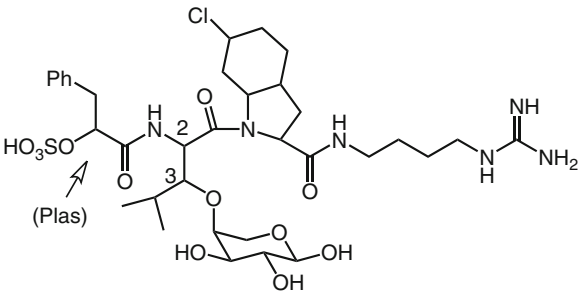


985

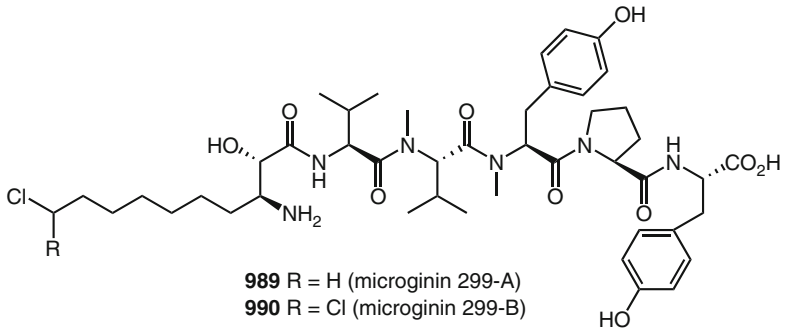
The freshwater blue-green alga *Microcystis aeruginosa* is the source of novel peptides, several of which contain chlorine. Aeruginosin 98-A (**986**) was isolated from *Microcystis aeruginosa* (NIES-98), and this compound inhibits trypsin, plasmin, and thrombin (*1033*). The cyanobacterium *Oscillatoria agardhii* produces glycopeptides aeruginosins 205A (**987**) and 205B (**988**), which are also potent inhibitors of trypsin and thrombin (*1034*). A Japanese bloom of *Microcystis aeruginosa* (NIES-299) yielded microginins 299-A (**989**) and 299-B (**990**), which are leucine aminopeptidase inhibitors. The absolute stereochemistries are indicated (*1035*). From another strain of *Microcystis aeruginosa* (NIES-478) there were isolated micropeptins 478-A (**991**) and 478-B (**992**), which inhibit plasmin but not trypsin, thrombin, papain, chymotrypsin, or elastase at 10 μg mL^{-1} (*1036*).



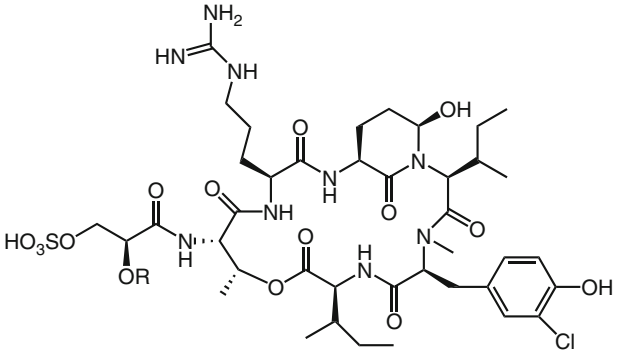
986 (aeruginosin 98-A)



987 (2*R*,3*S*) L-Plas (aeruginosin 205A)
988 (2*S*,3*R*) D-Plas (aeruginosin 205B)

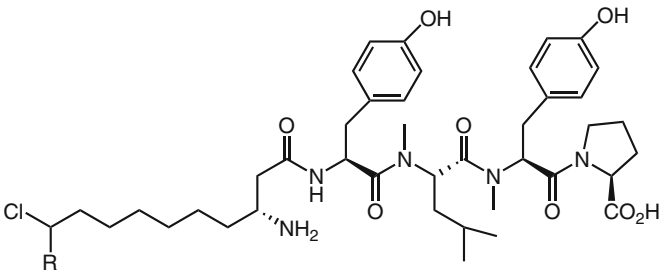


989 R = H (microginin 299-A)
990 R = Cl (microginin 299-B)

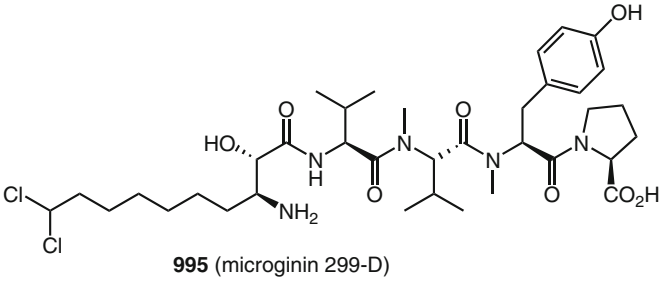


991 R = H (micropeptin 478-A)
992 R = SO^3H (micropeptin 478-B)

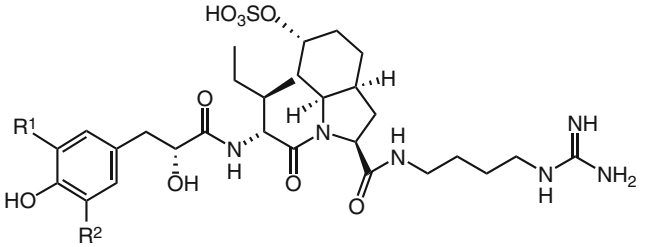
The new chlorinated microginins 99-A (**993**), 99-B (**994**), and 299-D (**995**) were isolated from two blooms of *Microcystis aeruginosa* (*1037*). Structurally similar to aeruginosin 98-A (**986**), the new aeruginosins 98-C (**996**), 101 (**997**), 89-A (**998**), and 89-B (**999**) were isolated from different strains of *Microcystis aeruginosa* (*1038*). The absolute configurations are as shown. A subsequent investigation of this blue-green alga revealed the presence of the new microginins 91-A (**1000**), 91-B (**1001**), 91-D (**1002**), and 91-E (**1003**) (*1039*). The total synthesis of the non-chlorinated aeruginosin 298-A has corrected a stereocenter; thus, D-leucine and not L-leucine is incorporated in this compound (*1040*), which may apply to other aeruginosins.



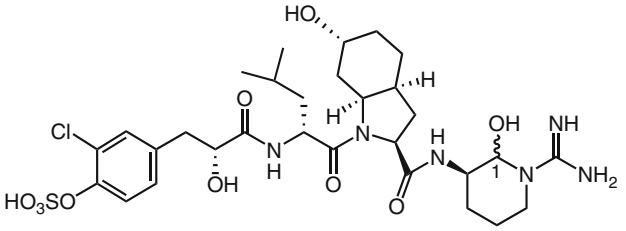
993 R = H (microginin 99-A)
994 R = Cl (microginin 99-B)



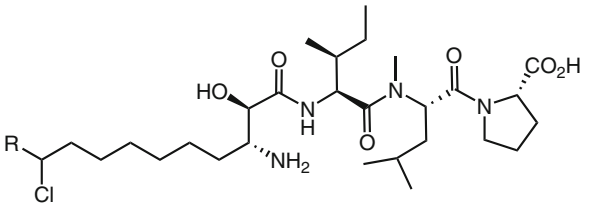
995 (microginin 299-D)



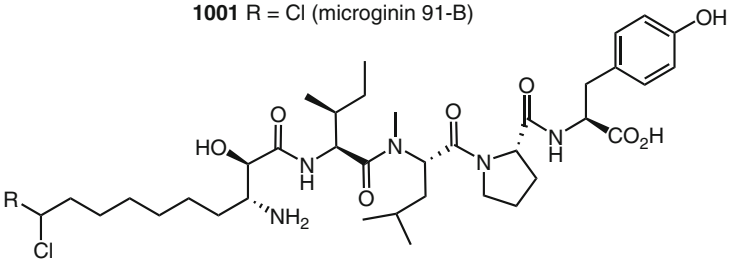
996 R^1 = Br, R^2 = H (aeruginosin 98-C)
997 R^1 = R^2 = Cl (aeruginosin 101)



998 (aeruginosin 89-A) (epimeric at C-1)
999 (aeruginosin 89-B)

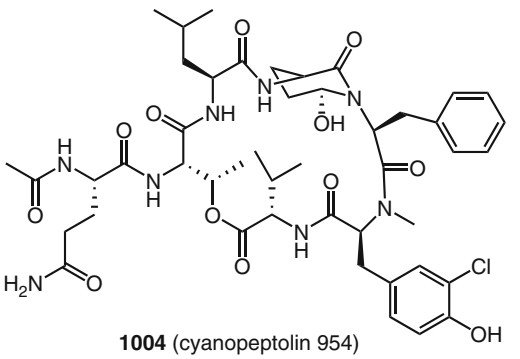


1000 R = H (microginin 91-A)
1001 R = Cl (microginin 91-B)

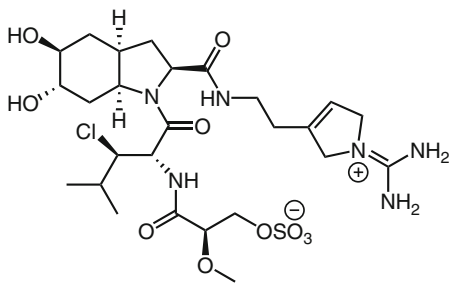


1002 R = H (microginin 91-D)
1003 R = Cl (microginin 91-E)

Another cultivation of *Microcystis aeruginosa* NIVA Cya 43 yielded the new cyanopeptolin 954 (**1004**), which is a chymotrypsin inhibitor (*1041*). The newly isolated chlorodysinosin A (**1005**), from a *Dysidea* sponge, has been synthesized and its structure confirmed (*1042*).

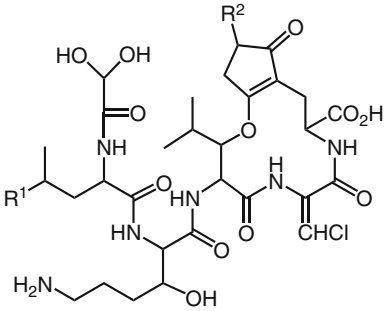


1004 (cyanopeptolin 954)

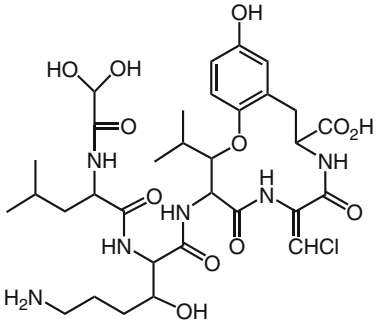


1005 (chlorodysinosin A)

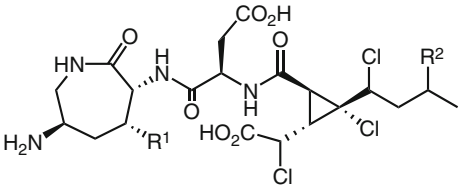
A disease of oats in North America is caused by the fungus *Cochliobolus victoriae* (*Helminthosporium victoriae*) and the major causal agent is victorin C. After considerable work on degradation products (*1043, 1044*) the structure of victorin C (**1006**) was finally established (*1045*). Additional study of this fungus has afforded the minor victorins B, D, and E (**1007**–**1009**) and victoricine (**1010**) (*1046*). The victorin binding protein from oats has been identified (*1047, 1048*). The fungal pathogen *Periconia circinata*, which causes milo disease of grain, produces peritoxins A (**1011**) and B (**1012**), and periconins A (**1013**) and B (**1014**) (*1049*).



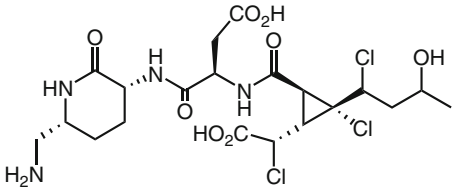
1006 $R^1 = CHCl_2$, $R^2 = OH$ (victorin C)
1007 $R^1 = CH_2Cl$, $R^2 = OH$ (victorin B)
1008 $R^1 = CHCl_2$, $R^2 = H$ (victorin D)
1009 $R^1 = CCl_3$, $R^2 = OH$ (victorin E)



1010 (victoricine)

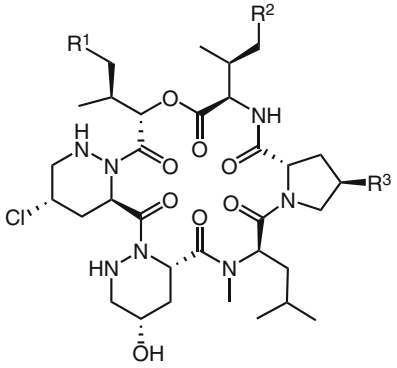


1011 $R^1 = R^2 = OH$ (peritoxin A)
1012 $R^1 = OH$, $R^2 = H$ (peritoxin B)
1013 $R^1 = H$, $R^2 = OH$ (pericinin A)



1014 (pericinin B)

The monamycins are a group of 15 antibiotic cyclodepsipeptides from *Streptomyces jamaicensis*. After much structural elucidation work on the hydrolysis and degradation products (*1050, 1051*), the structures of the six chlorine-containing monamycins G_1 (**1015**), G_2 (**1016**), G_3 (**1017**), H_1 (**1018**), H_2 (**1019**), and I (**1020**) were determined (*1052*).



1015 $R^1 = R^2 = H$, $R^3 = Me$ (monamycin G_1)
1016 $R^1 = R^3 = H$, $R^2 = Me$ (monamycin G_2)
1017 $R^1 = Me$, $R^2 = R^3 = H$ (monamycin G_3)
1018 $R^1 = R^3 = Me$, $R^2 = H$ (monamycin H_1)
1019 $R^1 = H$, $R^2 = R^3 = Me$ (monamycin H_2)
1020 $R^1 = R^2 = R^3 = Me$ (monamycin I)

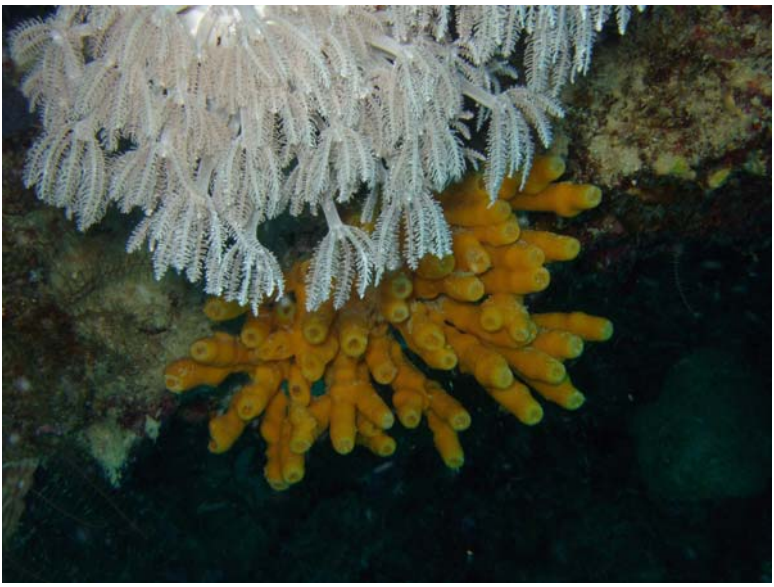
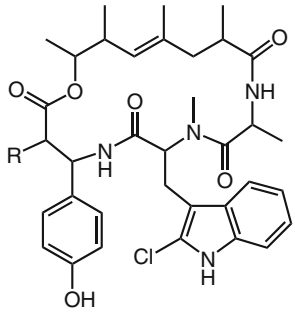
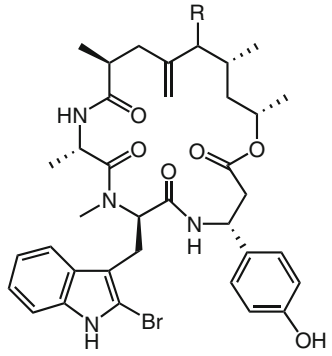


Fig. 3.16 *Auletta* cf. *constricta*, a brownish sponge that contains jasplakinolide, which is related to jasplakinolides B and C (**1023** and **1024**)–to make sure which of the two organisms of the picture are addressed (Photo: P. Crews)

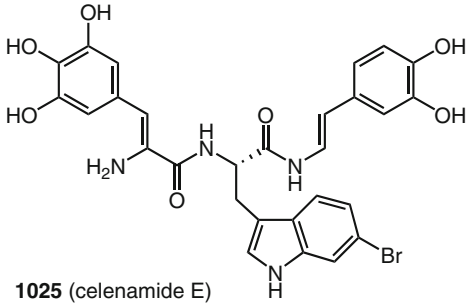
Some 15 halogenated tryptophan-derived peptides were described in the first account (*1*), and several new examples have been discovered in the interim. Chondramides A–D, two of which are the chlorinated B (**1021**) and D (**1022**), were isolated from a strain of myxobacteria (*Chondromyces crocatus*), and possess antifungal and cytostatic activity (*1053, 1054*). The chondramides, which are structurally related to jasplakinolide (= jaspamide) but which can be produced in large quantities by fermentation, exhibit antiproliferative activity against carcinoma cell lines (*1055*). Two new jasplakinolides, B (**1023**) and C (**1024**) (Fig. 3.16), have been characterized from the Vanuatu sponge *Jaspis splendans* (*1056*). The well-known jasplakinolide has been the object of biological studies (e.g., actin cytoskeleton disruptor) (*1057, 1058*), conformational studies with and without lithium (*1059*), and synthesis and biological evaluation of analogs (*1060, 1061*). A new celenamide, celenamide E (**1025**), was found in the Patagonian sponge *Cliona chilensis* (*1062*). This metabolite may be the biosynthetic precursor of the known celenamides A–C (*1*), as it contains an unusual *N*-terminal dehydroamino acid.



1021 R = OMe (chondramide B)
1022 R = H (chondramide D)



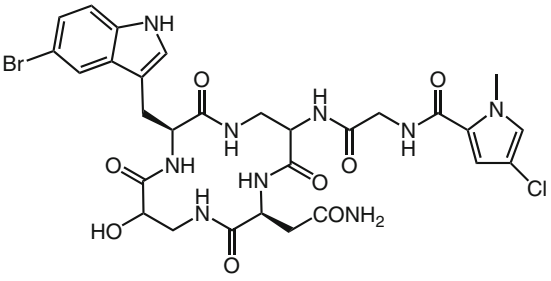
1023 R = =O (jasplakinolide B)
1024 R = OH (jasplakinolide C)



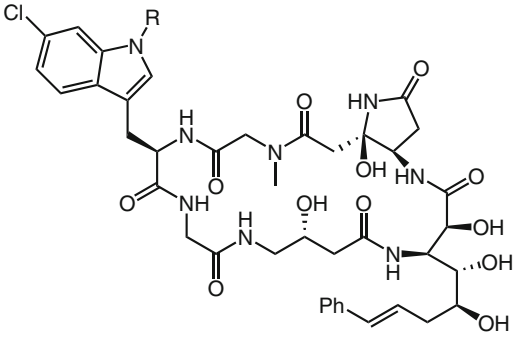
1025 (celenamide E)

Fig. 3.17 *Psammocinia* aff. *bulbosa*, a Papua New Guinea sponge that produces cyclocinamide A (**1026**) (Photo: P. Crews)

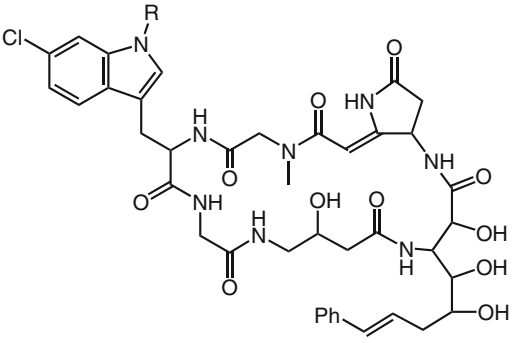
A *Psammocinia* sp. (Fig. 3.17) sponge from Papua New Guinea has yielded the potent cytotoxic cyclocinamide A (**1026**) (*1063*). The novel 6-chlorotryptophan derivatives, microsclerodermins C (**1027**) and D (**1028**), were characterized from a Philippines *Theonella* sp. sponge (*1064*). The related dehydromicrosclerodermins C (**1029**) and D (**1030**) are found in the sponge *Theonella cupola* from Okinawa (*1065*).



1026 (cyclocinamide A)

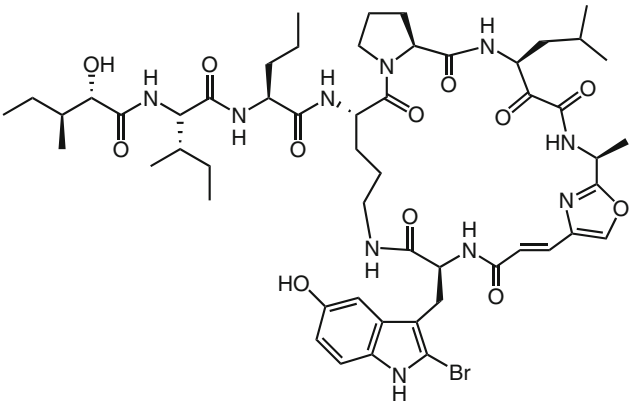


1027 R = $CONH_2$ (microsclerodermin C)
1028 R = H (microsclerodermin D)

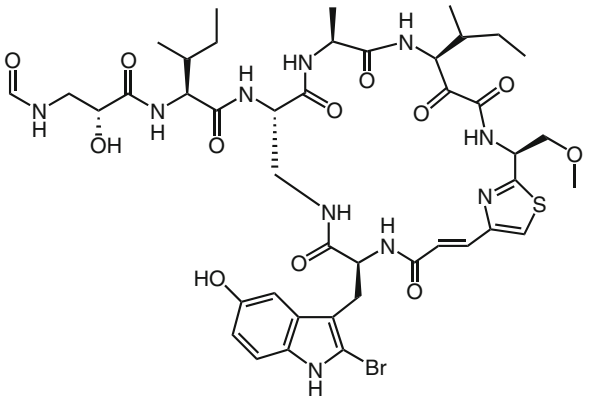


1029 R = $CONH_2$ (dehydromicrosclerodermin C)
1030 R = H (dehydromicrosclerodermin D)

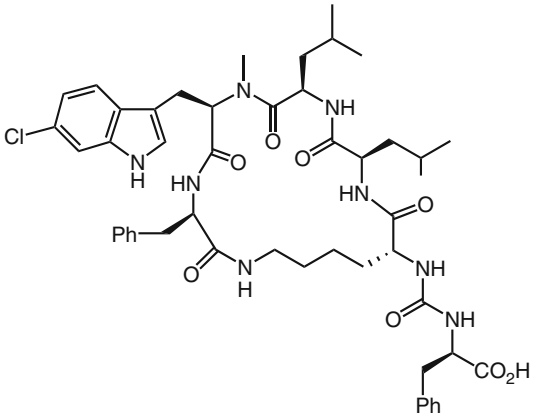
The stereochemistry of the modified tryptophan amino acids in the previously known konbamide and keramamide A sponge metabolites (*1*) has been determined to be L for both 2-bromo-5-hydroxytryptophan and 6-chloro-5-hydroxy-*N*-methyltryptophan, respectively (*1066*). However, based on synthetic studies, doubt has been raised as to the structure of konbamide (*1067*). A series of investigations of Okinawan *Theonella* sp. sponges has uncovered the new halogenated keramamides, E (**1031**), H (**1032**) (*1068*), L (**1033**) (*1069*), M (**1034**), and N (**1035**) (*1070*).



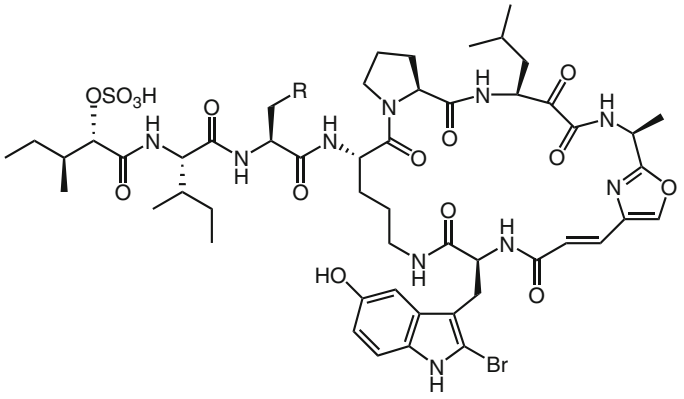
1031 (keramamide E)



1032 (keramamide H)



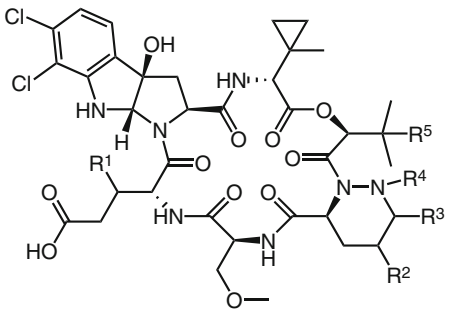
1033 (keramamide L)



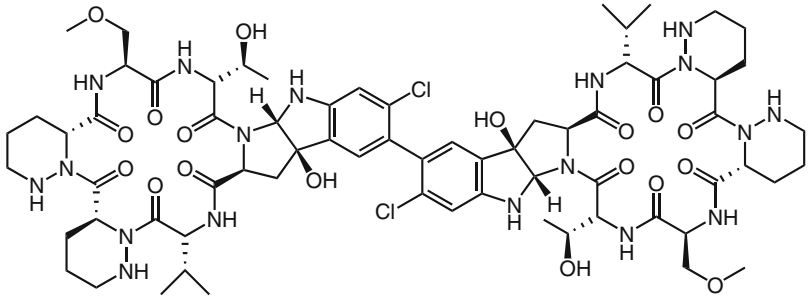
1034 R = Me (keramamide M)
1035 R = Et (keramamide N)

The polychlorinated cyclic hexadepsipeptides kutznerides 1–9 (**1036**–**1044**), which contain both the novel 6,7-dichlorohexahydropyrrolo[2,3-β]indole core and several unusual amino acids, are found in the actinomycete *Kutzneria* sp. 744 inhabiting the roots of *Picea abies* (*1071, 1072*). These compounds show moderate activity against root-rotting fungi. Another chlorinated hexahydropyrrolo[2,3-*b*] indole cyclohexapeptide is the dimeric chloptosin (**1045**) isolated from a *Streptomy-*

ces strain (*1073*). This unique metabolite induces apoptosis and shows strong antimicrobial activity against Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus*.



1036 R^1 = α-OH, R^2 = R^3 = R^4 = H, R^5 = Me (kutzneride 1)
1037 R^1 = α-OH, R^2 = Cl, R^3 = R^4 = H, R^5 = Me (kutzneride 2)
1038 R^1 = β-OH, R^2 = R^3 = R^4 = H, R^5 = Me (kutzneride 3)
1039 R^1 = β-OH, R^2 = H, R^3 = R^4 = π bond, R^5 = Me (kutzneride 4)
1040 R^1 = β-OH, R^2 = R^3 = R^4 = R^5 = H (kutzneride 5)
1041 R^1 = β-OH, R^2 = OH, R^3 = R^4 = π bond, R^5 = Me (kutzneride 6)
1042 R^1 = α-OH, R^2 = R^3 = R^4 = R^5 = H (kutzneride 7)
1043 R^1 = β-OH, R^2 = Cl, R^3 = R^4 = H, R^5 = Me (kutzneride 8)
1044 R^1 = α-OH, R^2 = H, R^3 = R^4 = π bond, R^5 = Me (kutzneride 9)



1045 (chloptosin)

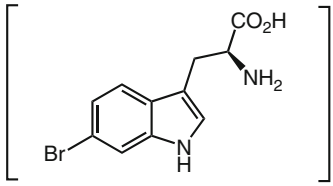
One major recent development in the area of natural products is the discovery and subsequent medicinal application of the toxic peptides from cone snails. These *Conus* peptides, several of which contain a 6-bromotryptophan amino acid, are finding utility for the treatment of neuropathic pain and other neurological conditions (*1074–1078*). For example, ω-conopeptide MVIIA (Ziconotide, trade name Prialt) has been approved by the US FDA since 2004 for the treatment of severe pain. It is estimated that the 500–700 species of cone snails (*Conus* genus) contain

more than 50,000 distinct toxins, since the venom in each snail consists of 40–200 individual peptides with a specific biological action (*1074, 1077, 1080*). However, relatively few of these toxic peptides have been characterized. The venomous worm-hunting cone snail *Conus imperialis* contains the heptapeptide **1046** in which 6-bromotryptophan is present, and *Conus radiatus* produces a 33-amino acid peptide **1047** that also contains 6-bromotryptophan (*1081, 1988*). The venom from this latter snail has also furnished the octapeptide bromocontryphan (**1048**) (*1082*). Numerous conotoxins contain 6-bromotryptophan, such as a 31-amino acid peptide (**1049**) and others from *Conus textile* (*1083, 1984–1987*), and several peptides from other *Conus* species (*1084*), including *Conus delessertii* (*1989*) and *Conus monile* (*1990*).

Pca–cys–gly–gln–ala–Brtrp–cys–NH_2

1046

[Pca = pyroglutamic acid]



Brtrp

1047 (33-amino acid peptide) **1049** (31-amino acid peptide)

gly–cys–hyp–D-trp–glu–pro–Brtrp–cys-NH_2

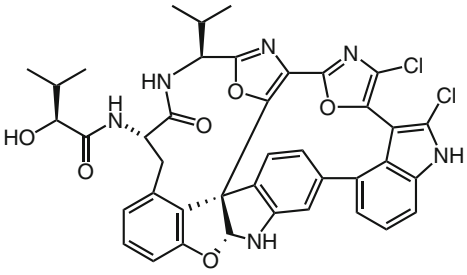
1048 (bromocontryphan) [hyp =*trans*-4-hydroxyproline]

(**1050-1054** are not shown)

Other marine organisms contain peptides and proteins with 6-bromotryptophan. The ascidian *Phallusia mammillata* has a polypeptide morulin Pm (**1050**) that includes 6-bromotryptophan (*1085*). In fact, this amino acid is the major residue in the peptide. Similarly, the solitary ascidian *Styela clava* produces styelin D (**1051**), another 6-bromotryptophan-containing 32-amino acid peptide (*1086, 1087*). Styelin D shows excellent activity against marine bacteria and human pathogens (*1087*). Three cathelicidins, HFIAP-1 (**1052**), HFIAP-2 (**1053**), and HFIAP-3 (**1054**), each containing one or two 6-bromotryptophans, were isolated from the Atlantic hagfish (*Myxine glutinosa*) (*1088*). This report suggests that the role of 6-bromotryptophan in these and other peptides (vide supra) is to block proteolytic degradation. Thus, the large bromine atom makes the peptide a poor fit for chymotrypsin, which normally would cleave tryptophan residues (*1088*).

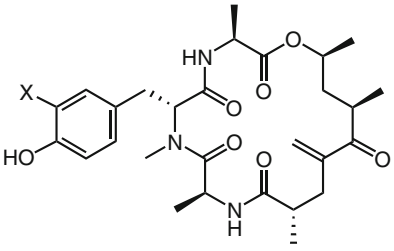
One of the more interesting and structurally complex indole-containing peptides is the previously described diazonamide (A and B) from the ascidian *Diazona*

chinensis, which is now named *Diazona angulata* (*1*). However, as shown by synthesis, the originally proposed structure of the diazonamides (*1*) is incorrect (*1089*). Reevaluation of the data, X-ray analysis, and biogenetic considerations led to structure **VV** for diazonamide A (*1090, 1091*), which has been confirmed by total synthesis (*1092–1094*). Diazonamide A and synthetic analogs continue to find interest as potential anticancer agents (*1095*).

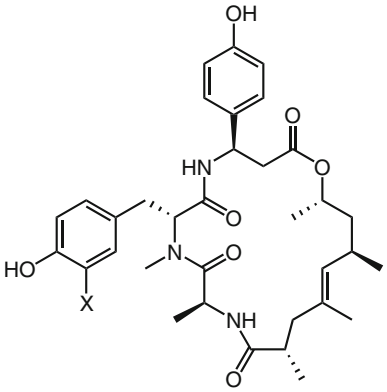


VV (diazonamide A)

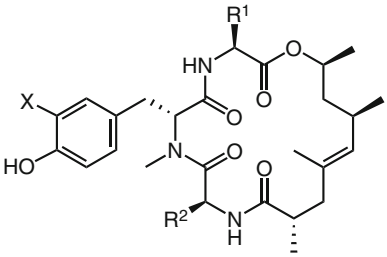
Although iodine-containing natural products are exceedingly rare, the previously described geodiamolides A–F are a group of marine sponge cyclic peptides containing chlorine, bromine, and iodine (*1*). Several new examples are known, such as geodiamolide G (**1055**) from a *Cymbastela* sp. Papua New Guinea sponge (*1096*), H (**1056**) and I (**1057**) from the sponge *Geodia* sp. in Trinidad (*1097*), and from a Papua New Guinea *Cymbastela* sp. J (**1058**), K (**1059**), L (**1060**), M (**1061**), N (**1062**), O (**1063**), P (**1064**), and R (**1065**) (*1098*). Five of these new metabolites contain iodine, and several are cytotoxic (*1096–1098*). The related geodiamolide TA (**1066**) was isolated from the sponge *Hemiasterella minor*, and it has the same configuration as the geodiamolides (*1099*). It is also quite cytotoxic against P388. Related to the geodiamolides (i.e., D) is the iodinated neosiphoniamolide A (**1067**) from the New Caledonian sponge *Neosiphonia superstes* (*1100*).



1055 X = I (geodiamolide G)
1058 X = Br (geodiamolide J)
1059 X = Cl (geodiamolide K)

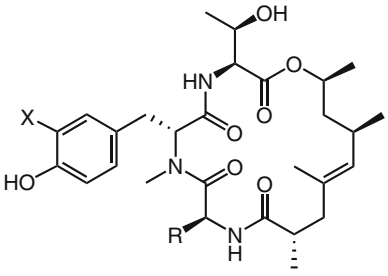


1056 X = I (geodiamolide H)
1057 X = Br (geodiamolide I)

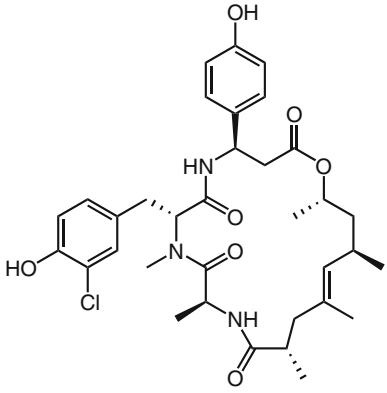


1060 X = I, R^1 = CH_2OH, R^2 = Me (geodiamolide L)
1061 X = Br, R^1 = CH_2OH, R^2 = Me (geodiamolide M)
1062 X = Cl, R^1 = CH_2OH, R^2 = Me (geodiamolide N)
1063 X = I, R^1 = Me, R^2 = CH_2OH (geodiamolide O)
1064 X = Br, R^1 = Me, R^2 = CH_2OH (geodiamolide P)
1065 X = I, R^1 = CH_2OH, R^2 = H (geodiamolide R)
1066 X = I, R^1 = $CHMe_2$, R^2 = Me (geodiamolide TA)
1067 X = I, R^1 = $CHMe_2$, R^2 = H (neosiphoniamolide A)

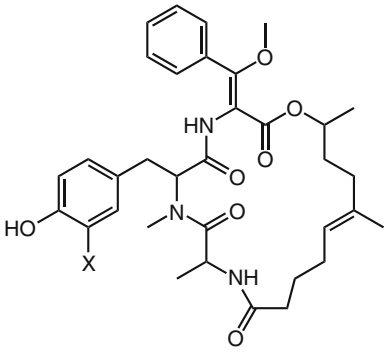
Closely related to the geodiamolides are the seragamides A–F (**1068–1073**) isolated from the Okinawan sponge *Suberites japonicus* (Fig. 3.18) (*1101*). Seragamide A promotes G-actin polymerization and stabilizes F-actin filaments. A different group of cyclic depsipeptides, miuraenamides A (**1074**) and B (**1075**), are produced by the halophilic myxobacterial strain, SMH-27-4, and are potent and selective inhibitors of the phytopathogenic *Phytophthora* sp. (*1102*). Interest in the previously known chlorine-containing pepticinnamin E, which is an inhibitor of farnesyl-protein transferase isolated from a *Streptomyces* strain (*1*), has extended to its total synthesis, and the synthesis of diastereomers (*1103*) and compound libraries (*1104–1106*).



1068 X = I, R = Me (seragamide A)
1069 X = Br, R = Me (seragamide B)
1070 X = Cl, R = Me (seragamide C)
1071 X = I, R = H (seragamide D)
1072 X = I, R = CH_2OH (seragamide E)



1073 (seragamide F)

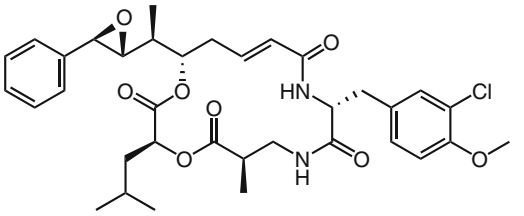


1074 X = Br (miuraenamide A)
1075 X = I (miuraenamide B)

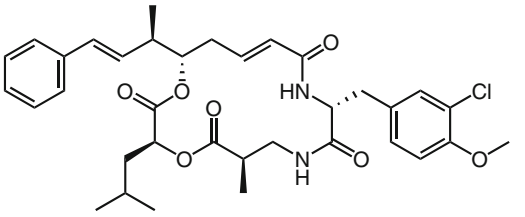
Fig. 3.18 *Suberites japonicus*, a sponge collected in Zampa, Okinawa, that contains seragamides A–F (**1068–1073**) (Photo: J. Tanaka)

The extraordinarily biologically active and clinically promising cryptophycins, which were discovered in a *Nostoc* sp. terrestrial blue-green alga (*1*), continue to be isolated from this genus of filamentous cyanobacteria (*1107–1109*). The ecology of *Nostoc* has been reviewed (*849*). The previously recorded cryptophycins A (**WW**) and C (**XX**) (*1*) have been shown by total synthesis to have the absolute configuration corresponding to the D-series of 3-chloro-*O*-methyltyrosine (*1110*). A study of *Nostoc* sp. GSV 224 has uncovered 22 new chlorine-containing cryptophycins

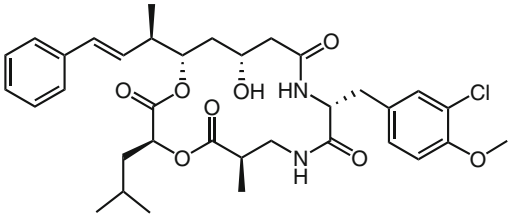
(which are now designated by numbers): cryptophycin-30 (**1076**), -28 (**1077**), -16 (**1078**), -23 (**1079**), -31 (**1080**), -17 (**1081**), -45 (**1082**), -175 (**1083**), -46 (**1084**), -29 (**1085**), -21 (**1086**), -176 (**1087**), -40 (**1088**), -326 (**1089**), -38 (**1090**), and -18 (**1091**), -49 (**1092**), -50 (**1093**), -54 (**1094**), -19 (**1095**), -26 (**1096**), and -327 (**1097**) (*1111–1113*).



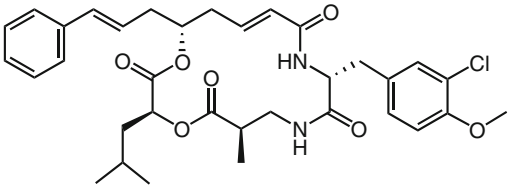
WW (cryptophycin A)



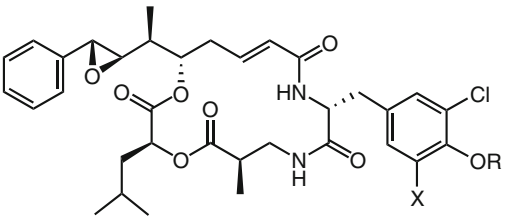
XX (cryptophycin C)



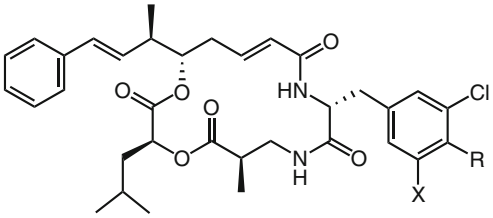
1076 (cryptophycin-30)



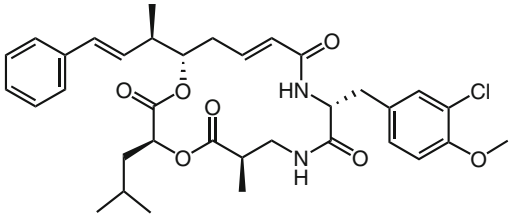
1077 (cryptophycin-28)



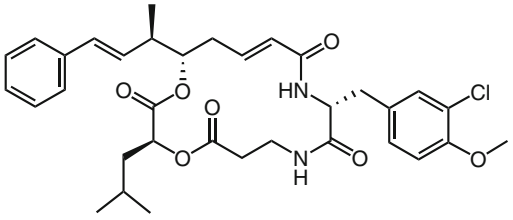
1078 R = H, X = H (cryptophycin-16)
1079 R = H, X = Cl (cryptophycin-23)
1080 R = Me, X = Cl (cryptophycin-31)



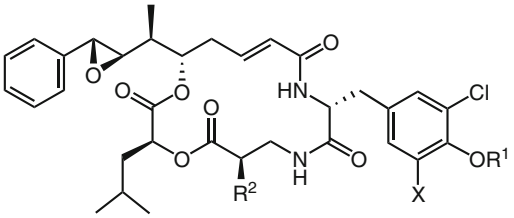
1081 R = H, X = H (cryptophycin-17)
1082 R = H, X = Cl (cryptophycin-45)
1083 R = Me, X = Cl (cryptophycin-175)



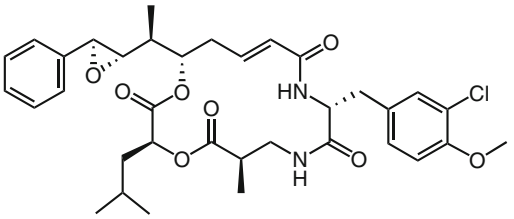
1084 (cryptophycin-46)



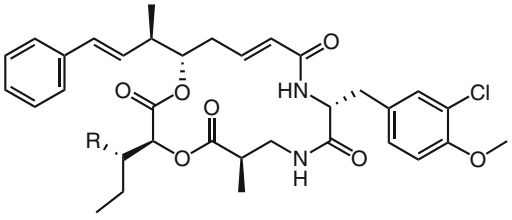
1085 (cryptophycin-29)



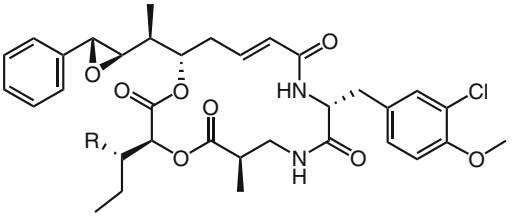
1086 R^1 = Me, R^2 = X = H (cryptophycin-21)
1087 R^1 = R^2 = X = H (cryptophycin-176)
1088 R^1 = R^2 = Me, X = H (cryptophycin-40)
1089 R^1 = Me, R^2 = H, X = Cl (cryptophycin-326)



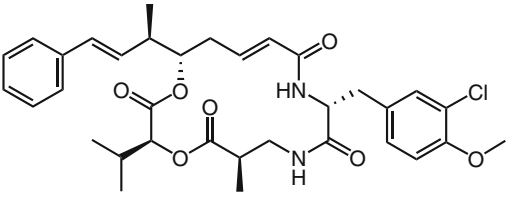
1090 (cryptophycin-38)



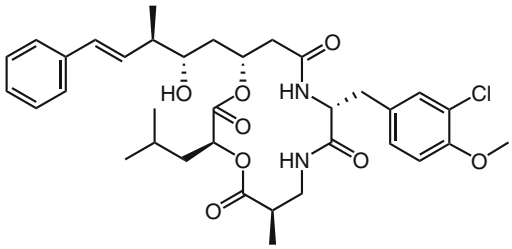
1091 R = Me (cryptophycin-18)
1092 R = H (cryptophycin-49)



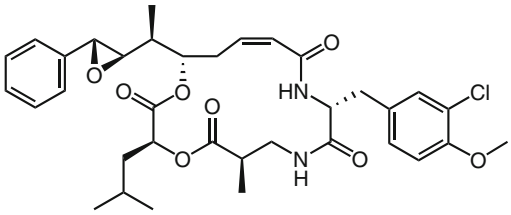
1093 R = H (cryptophycin-50)
1094 R = Me (cryptophycin-54)



1095 (cryptophycin-19)

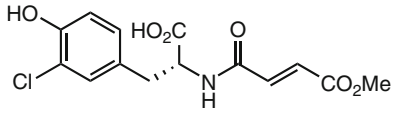


1096 (cryptophycin-26)



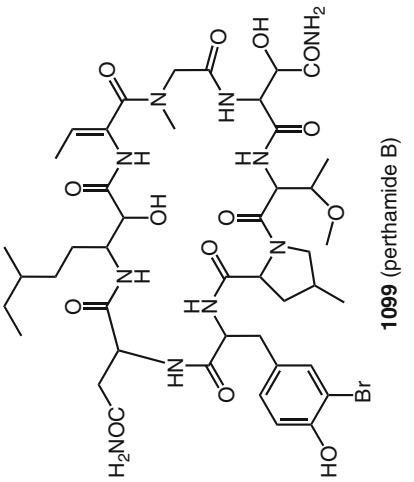
1097 (cryptophycin-327)

The striking cytotoxic activity of some cryptophycins, comparable or superior to taxol and vincristine in some cell lines, has generated intense synthetic interest (*1107, 1109, 1114, 1115*). A synthetic analog, cryptophycin-52 (the C6 *gem*-dimethyl analog of cryptophycin 1 (= cryptophycin A); not shown), has been selected for clinical evaluation (*1116–1119*). Unfortunately, neurotoxicity may preclude further development of cryptophycin-52 (*1118, 1119*). The simple fungal metabolite (–)-xylariamide A (**1098**), which resembles the "right-half" of the cryptophycins, is produced by the terrestrial fungus *Xylaria* sp. (*1120*). The structure of **1098** has been confirmed by synthesis (*1121*).

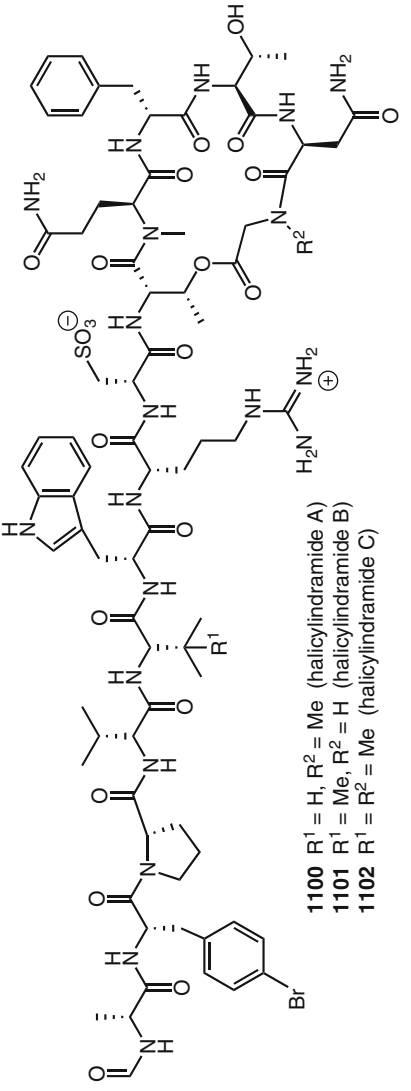


1098 (xylariamide A)

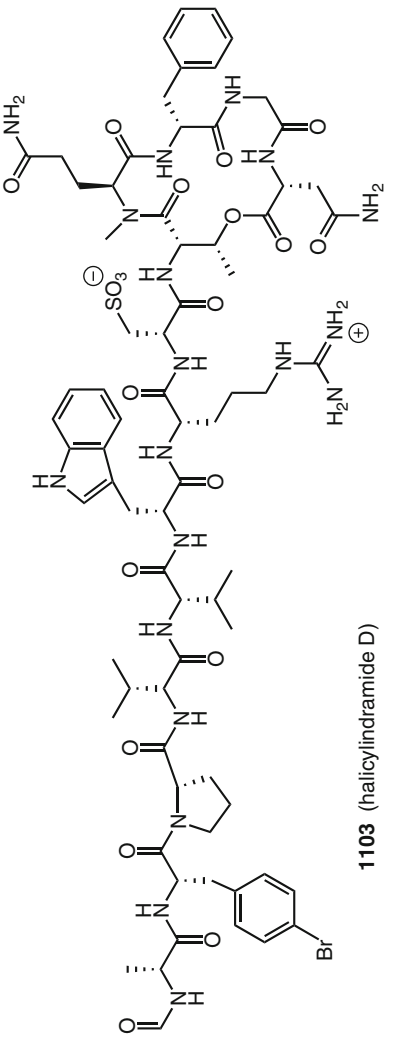
Perthamide B (**1099**) is a novel cyclic octapeptide found in a *Theonella* sp. sponge near Perth, Australia (*1122*). A collection of the Japanese sponge *Halichondria cylindrata* has afforded halicylindramides A–E (**1100–1103**), and the absolute configurations are shown (*1123, 1124*). Each compound features a 4-bromophenylalanine residue.



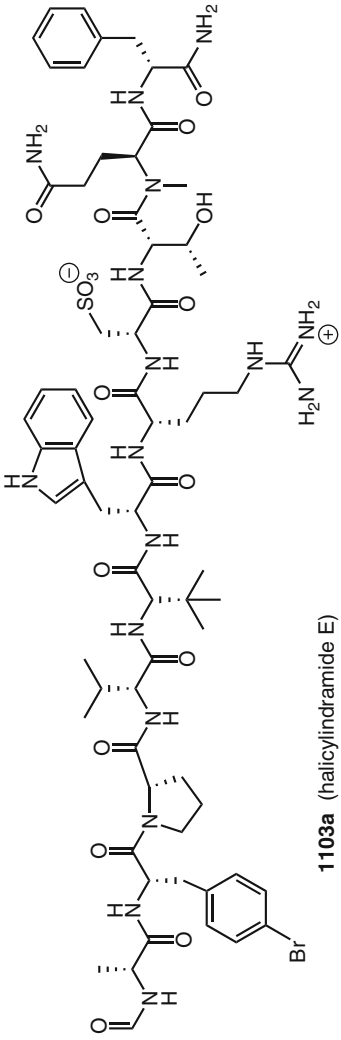
1099 (perthamide B)



1100 R^1 = H, R^2 = Me (halicylindramide A)
1101 R^1 = Me, R^2 = H (halicylindramide B)
1102 R^1 = R^2 = Me (halicylindramide C)

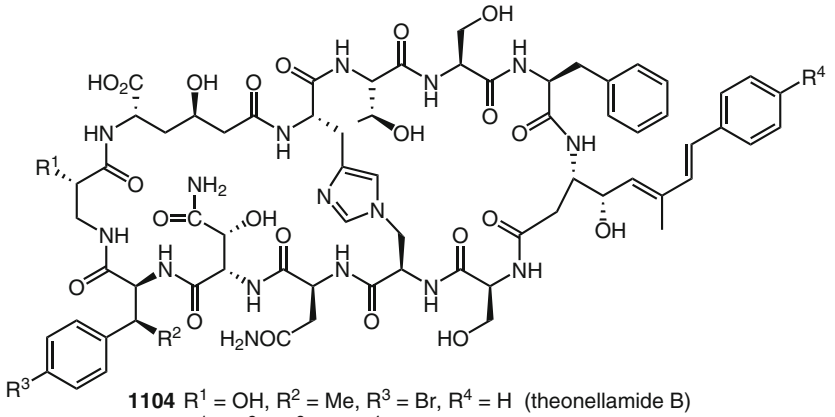


1103 (halicylindramide D)

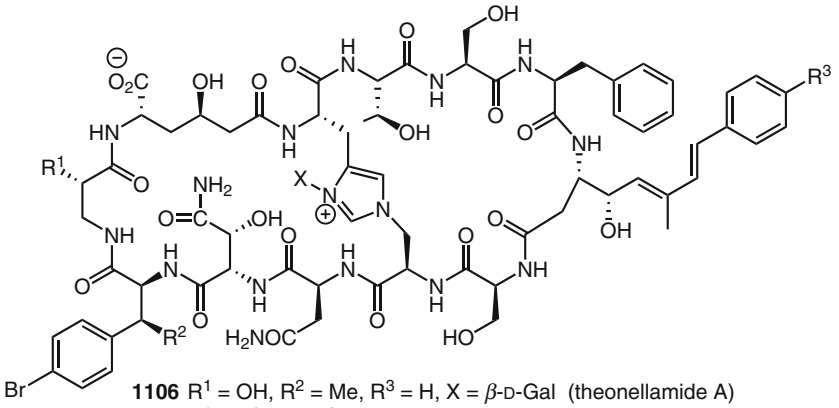


1103a (halicylindramide E)

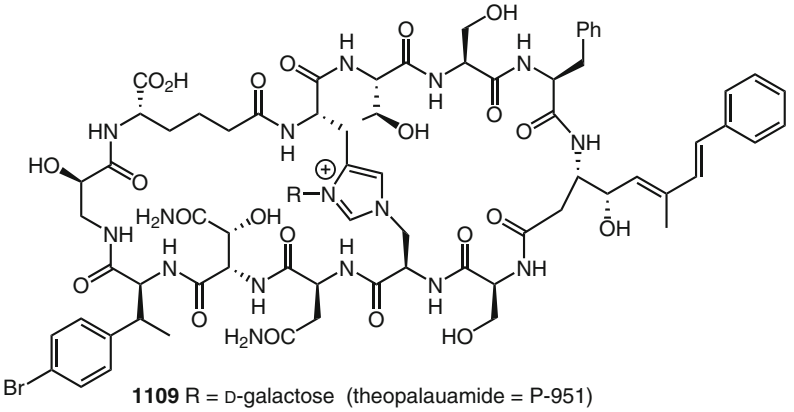
Theonellamides A–E (**1104**–**1108**), which are analogs of the previously isolated theonellamide F (*1*), were characterized from the Japanese sponge *Theonella* sp. (*1125*). The related theopalauamide (= P951) (**1109**) was isolated from *Theonella swinhoei* found in both Palau and Mozambique (*1126, 1127*). It should be noted that a minor structural correction (misplaced methyl group) has been reported for the previously known theonegramide (*1128*).



1104 R^1 = OH, R^2 = Me, R^3 = Br, R^4 = H (theonellamide B)
1105 R^1 = R^2 = R^3 = H, R^4 = Br (theonellamide C)

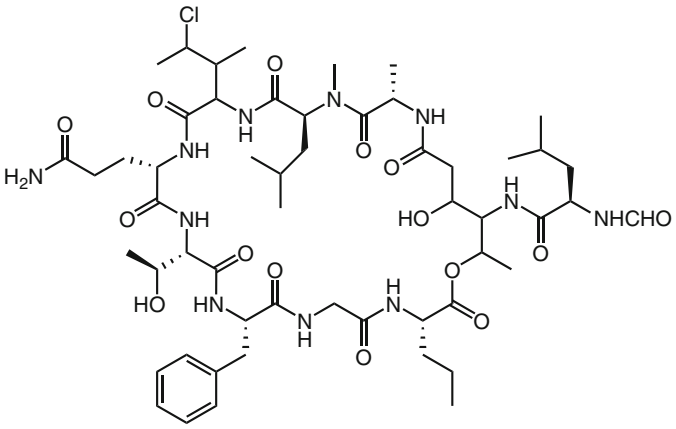


1106 R^1 = OH, R^2 = Me, R^3 = H, X = β-D-Gal (theonellamide A)
1107 R^1 = R^2 = H, R^3 = Br, X = β-L-Ara (theonellamide D)
1108 R^1 = R^2 = H, R^3 = Br, X = β-D-Gal (theonellamide E)

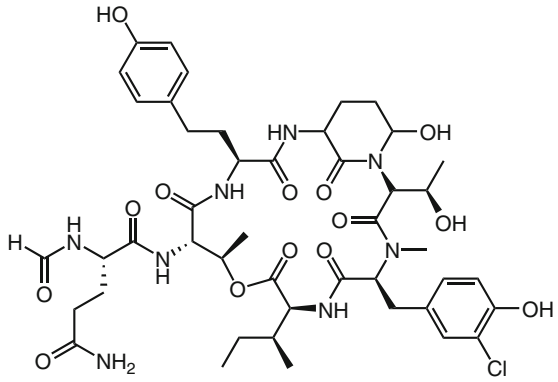


1109 R = D-galactose (theopalauamide = P-951)

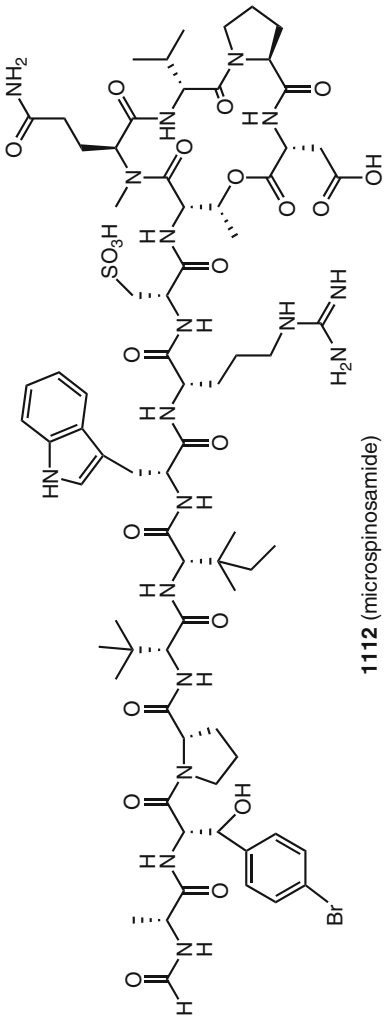
Studies of *Theonella swinhoei* sponges from Papua New Guinea and Indonesia revealed the presence of the chloroleucine-containing cyclolithistide A (**1110**) (*1129*). Anabaenopeptilide 90B (**1111**) is a cyclic depsipeptide produced by the cyanobacterium *Anabaena* strain 90 (*1130*). An Indonesian collection of the sponge *Sidonops microspinosa* yielded microspinosamide (**1112**), a novel HIV-inhibitory cyclic depsipeptide (*1131*). Structurally similar to cyclolithistide A (**1110**) are phoriospongins A (**1113**) and B (**1114**) found in the Australian sponges *Phoriospongia* sp. and *Callyspongia bilamellata* (*1132*).



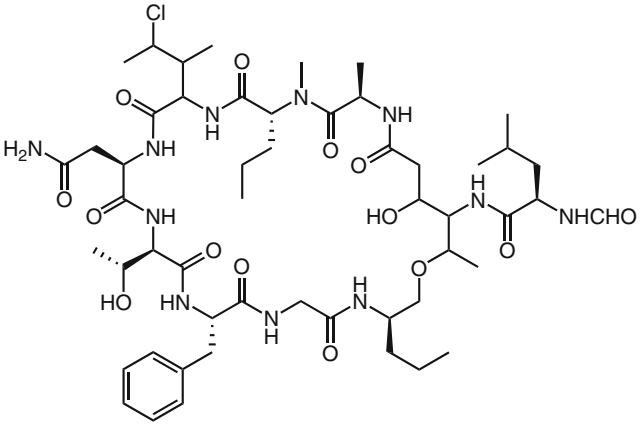
1110 (cyclolithistide A)



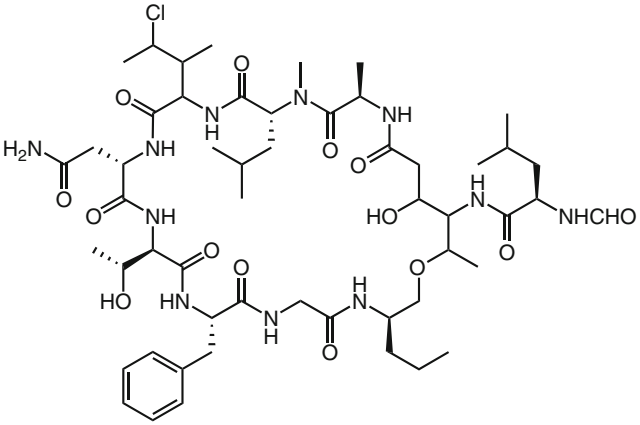
1111 (anabaenopeptilide 90B)



1112 (microspinosamide)

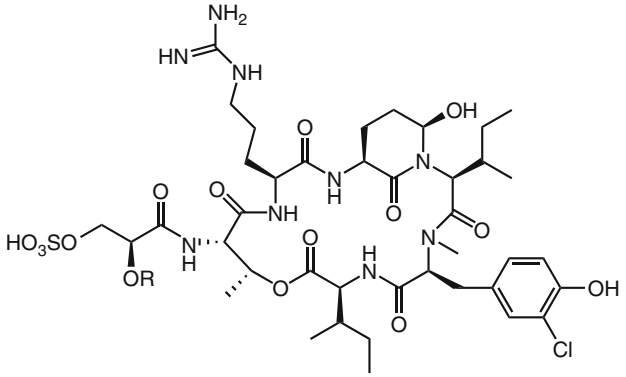


1113 (phoriospongin A)

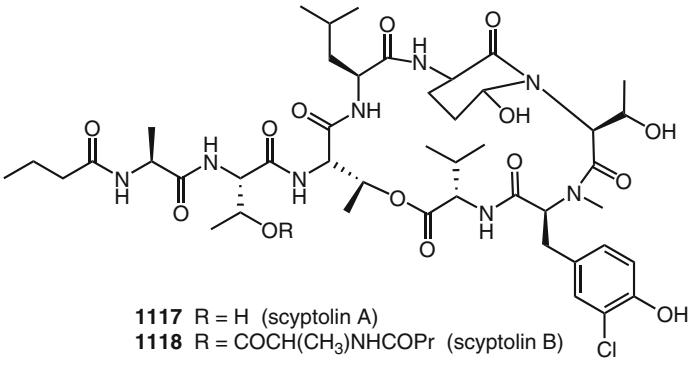


1114 (phoriospongin B)

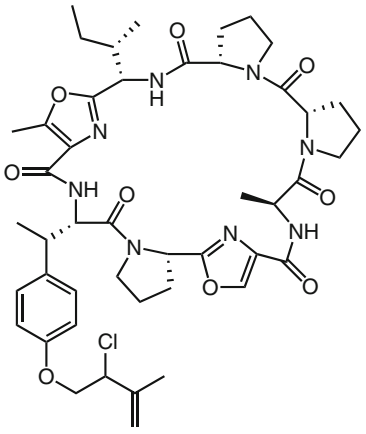
The prevalent *Microcystis aeruginosa* has afforded the plasmin inhibitors micropeptins 478-A (**1115**) and 478-B (**1116**) (*1133*). The terrestrial cyanobacterium *Scytonema hofmanni* PCC 7110 gives rise to scyptolins A (**1117**) and B (**1118**), which contain the 3-chloro-*N*-methyltyrosine residue (*1134*). The binding of **1117** to pancreatic elastase has been determined by X-ray crystallography (*1135*). Myriastramide B (**1119**) was isolated from the Philippine sponge *Myriastra clavosa* and features a novel chlorinated ether moiety (*1136*).



1115 R = H (micropeptin 478-A)
1116 R = SO_3H (micropeptin 478-B)

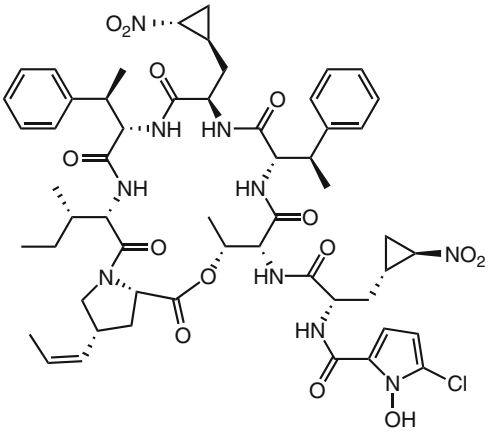


1117 R = H (scyptolin A)
1118 R = $COCH(CH_3)NHCOPr$ (scyptolin B)

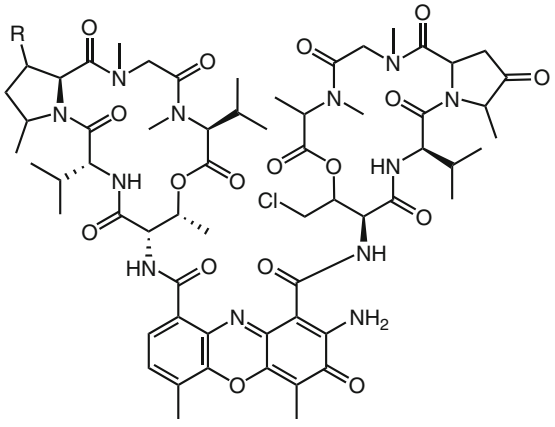


1119 (myriastramide B)

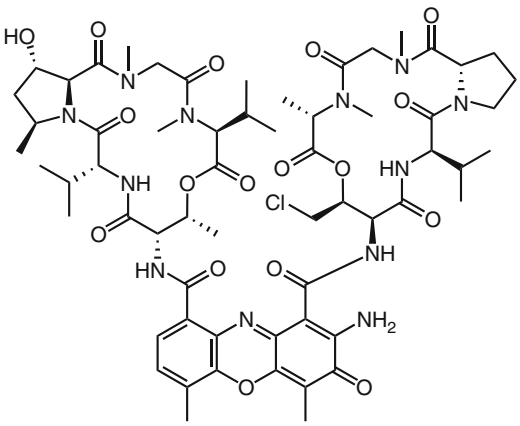
The novel peptide takaokamycin (**1120**) was isolated from a *Streptomyces* sp. culture (*1136*), but it subsequently became clear that this antibiotic was identical to hormaomycin (= **1120**) (*1137*), which was isolated independently from *Streptomyces griseoflavus* (*1138, 1139*). The structure of hormaomycin was later confirmed (*1140*), and it has been synthesized (*1141*). Two chlorinated actinomycins, Z_3 (**1121**) and Z_5 (**1122**), were isolated from cultures of *Streptomyces fradiae* and are more active than the non-chlorinated actinomycin D (*1142*). *Streptomyces iakyrus* provides the new actinomycin G_2 (**1123**), which is the major component of this family of actinomycins and the most biologically active (*1143*). Although no new examples of syringomycins and syringtoxins have been described, the synthesis and study of synthetic analogs reveal the importance of 4-chlorothreonine residues for antibiotic activity (*1144*). The biological chlorination of threonine in syringomycin involves a non-haem halogenase, SyrB2 (*1145, 1146*), and a mechanism is presented in Chap. 4 (Biohalogenation).



1120 (takaokamycin = hormaomycin)

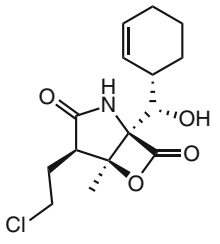


1121 R = OH (actinomycin Z_3)
1122 R = H (actinomycin Z_5)

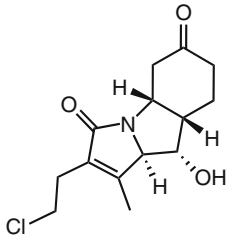


1123 (actinomycin G_2)

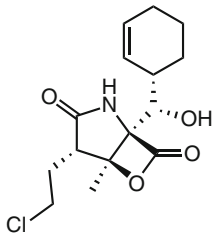
An exciting development in the area of halogenated natural products is the isolation and characterization of salinosporamide A (**1124**) from a new genus of marine bacteria, *Salinospora* (*1147*) (subsequently renamed *Salinispora*). Salinosporamide A displays potent cytotoxicity against a number of human cell lines (HCT-116 colon, NCI-H226 non-small cell lung, SK-MEL-28 melanoma, and others) and is now in phase I clinical trials (as NPI-0052) for the treatment of cancer (*1148*). Additional studies of *Salinispora tropica* yielded salinosporamides C (**1125**) (*1149*), F (**1126**), I (**1127**), and J (**1128**) (*1150*). Several degradation products and non-chlorinated salinosporamides were also isolated in both studies. Cytotoxicity data indicate that the chloroethyl substituent is crucial for activity (*1149–1151*). The mechanism of action of salinosporamide A seems to involve nucleophilic addition of a threonine in the 20S proteasome to the lactone carbonyl group followed by attack on the chloroethyl group leading to a cyclic ether and irreversible binding (*1152*). As anticipated, synthetic interest in the salinosporamides has been intense (*1153, 2655*).



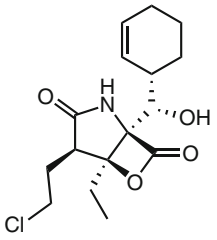
1124 (salinosporamide A)



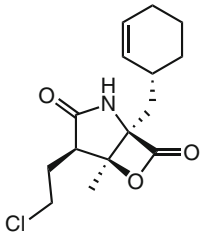
1125 (salinosporamide C)



1126 (salinosporamide F)

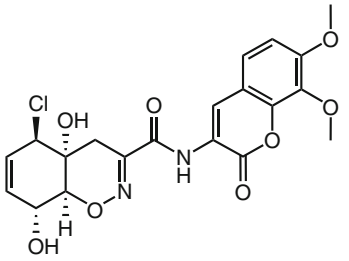


1127 (salinosporamide I)

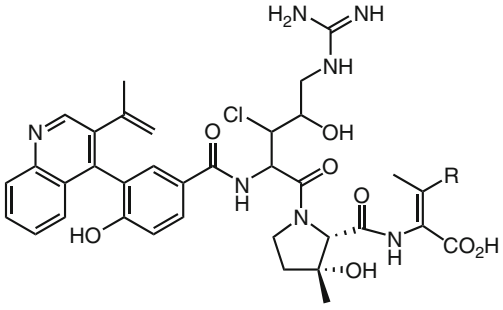


1128 (salinosporamide J)

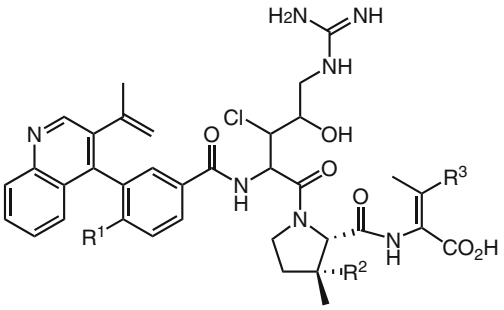
A marine-derived fungus, *Trichoderma virens*, has yielded the novel chlorinated trichodermamide B (**1129**), which displays significant cytotoxicity towards HCT-116 human colon carcinoma (*1154*). Interestingly, trichodermamide A is devoid of both chlorine and biological activity in all of the assays tested. A *Helicomyces* fungal strain (No. 19353) produces the gluconeogenesis inhibitors FR225659 (**1130**), FR225656 (**1131**), and the related **1132**–**1134** (*1155*–*1158*).



1129 (trichodermamide B)



1130 R = Me (FR225659)
1131 R = Et (FR225656)

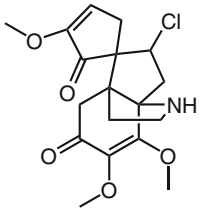


1132 R^1 = OH, R_2 = H, R^3 = Me
1133 R^1 = OMe, R^2 = OH, R^3 = Et
1134 R^1 = OMe, R^2 = OH, R^3 = Me

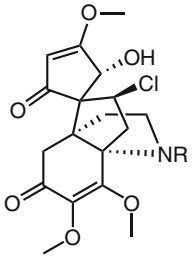
3.13 Alkaloids

This section and the section on alkaloids in the first survey (*1*) are artificially small since many halogenated alkaloids are presented in the sections on pyrroles, indoles, carbolines, tyrosines, and other nitrogen heterocycles. It might be noted that the very large number of brominated alkaloids that are obviously tyrosine-derived are now included in Sect. 3.22.3 (Tyrosines).

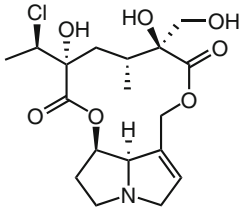
The previously known novel frog alkaloid epibatidine (*1*), continues to be of pharmacological (*1159, 1160*) and synthetic interest (*1161*), including the synthesis of many analogs (*1162*). The new clolimalongine (**1135**), a hasubanan type alkaloid related to the previously described chlorine-containing acutumine (*1*), was characterized from *Limacia oblonga* (*1163*). Two new epimers of known alkaloids are dauricumine (**1136**) and dauricumidine (**1137**) isolated from plant cultures of *Menispermum dauricum* (*1164*). The known acutumine (*1*), which is an epimer of **1136**, incorporates ^{14}C-labelled L-tyrosine (*1165*), and it along with **1136** and **1137** incorporate ^{36}Cl when this radiolabel is fed to the roots (*1164*). An extraction of the Brazilian plant *Senecio selloi* yielded 18-hydroxyjaconine (**1138**) (*1166*). Plants of this genus are infamous for their armament of poisonous pyrrolizidine alkaloids; five chlorinated examples were cited earlier (*1*).



1135 (clolimalongine)

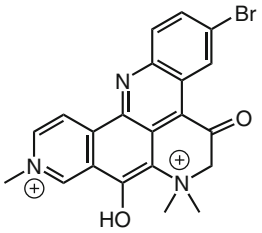


1136 R = Me (dauricumine)
1137 R = H (dauricumidine)

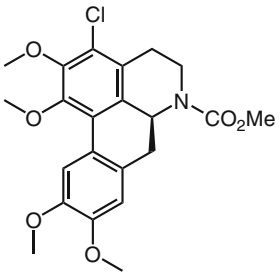


1138 (18-hydroxyjaconine)

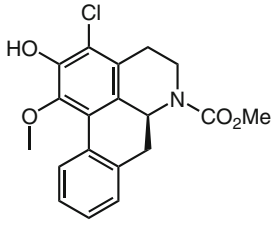
Petrosamine B (**1139**), an isomer of the known petrosamine (*1*), was characterized from the Australian sponge *Oceanapia* sp. (*1167*). The structure of the tetracyclic brominated alkaloid pantherinine (*1*) has been confirmed by total synthesis (*1168*). The novel aporphine alkaloids romucosine F (**1140**) from *Annona purpurea* (*1169*) and romucosine B (**1141**) from *Rollinia mucosa* (*1170*) have antiplatelet aggregation activity. Interestingly, synthetic halogenated boldine (*1171*) and protoberberine alkaloids (*1172*) show enhanced biological activity (monoamine receptor selectivity and cytotoxicity, respectively) over their non-halogenated counterparts. For boldine the order of activity is I > Br > Cl, and it is suggested that both increased lipophilicity and interaction with aromatic residues are involved in the mode of action (*1171*).



1139 (petrosamine B)

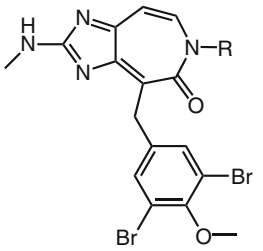


1140 (romucosine F)

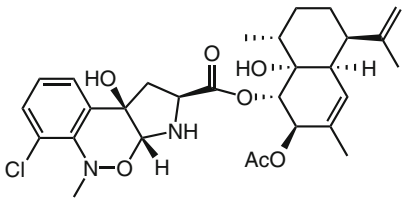


1141 (romucosine B)

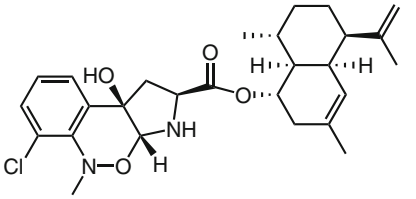
A Papua New Guinea sponge, *Pseudoceratina* sp., contains the unusual alkaloids ceratamines A (**1142**) and B (**1143**), and a biogenesis involving histidine and tyrosine is proposed (*1173*). The fermentation broth from *Aspergillus fischeri* var. *thermomutatus* has yielded CJ-12662 (**1144**) and UK-88051 (**1145**) (*1174*). The former metabolite was confirmed by X-ray spectroscopy and partial synthesis. A marine-derived *Streptomyces* sp. produces the novel pyrrolizidine 5-chlorobohemamine C (**1146**), which was shown not to be an isolation artifact (*1175*). The Chinese medicinal plant *Huperzia serrata* has furnished 2-chlorohyperzine E (**1147**) (*1176*).



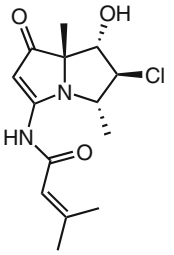
1142 R = Me (ceratamine A)
1143 R = H (ceratamine B)



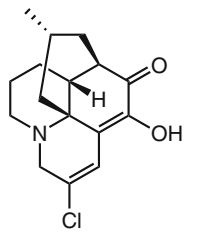
1144 (CJ-12662)



1145 (UK-88051)

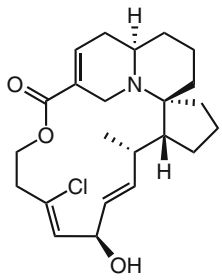


1146 (5-chlorobohemamine C)

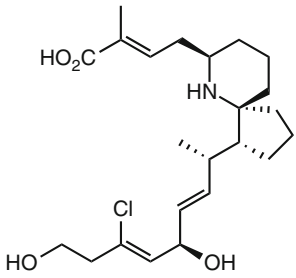


1147 (2-chlorohyperzine E)

Three novel related marine alkaloids, halichlorine (**1148**) from the sponge *Halichondria okadai* (*1177, 1178*) and pinnaic acid (**1149**) and tauropinnaic acid (**1150**) from the bivalve *Pinna muricata* (*1179*), have been the objects of much synthetic interest in view of their pronounced biological activity (inhibition of the vascular cell adhesion molecule-1) (*1180*). Synthesis of these alkaloids led to both revision and confirmation of the original structures (*1181, 1182*). The syntheses of the previously known chlorine-containing cylindricines have been reviewed (*1183*).



1148 (halichlorine)



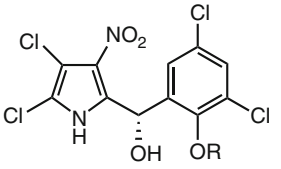
1149 R = OH (pinnaic acid)
1150 R = $NHCH_2CH_2SO_3H$ (tauropinnaic acid)

3.14 Heterocycles

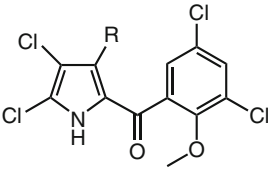
3.14.1 Pyrroles

The abundance of proline (and therefore pyrroles) in the biosphere, coupled with the enormous reactivity of pyrrole towards electrophilic substitution (i.e., halogenation), portends an abundance of naturally occurring halogenated pyrroles (*2668*). The first survey documented more than 70 such compounds (*1*), including the prototypical pyoluteorin and pyrrolnitrin, which continue to receive attention. The latter metabolite is produced by both *Pseudomonas* bacteria and, as recently discovered, *Enterobacter agglomerans* (*1184*). Pyrrolnitrin is active against a wide range of bacteria and fungi (*1184*), such as *Mycobacterium tuberculosis* (*1185*). The biological activity of pyrrolnitrin involves blocking the electron-transport system of the respiratory chain (*1186*), and this metabolite seems to play an important role in the biocontrol of pathogenic fungi (*1187*). Pyrrolnitrin is also used clinically to treat dermatophytosis (*1188*).

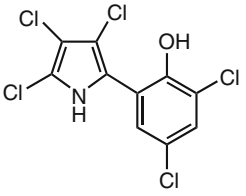
The biosynthesis of pyrrolnitrin has been extensively investigated for 40 years and the current state of affairs is summarized in Chap. 4 (Biohalogenation) (*1189*). Noteworthy is that the chlorination of tryptophan by tryptophan 7-halogenase is the first step in the sequence (*1190, 1191*). Although less well studied, the biosyntheses of other members of this family (pyoluteorin, dioxapyrrolomycin, and pentabromopseudilin) will be briefly presented in Chap. 4 (Biohalogenation). A culture of *Streptomyces fumanus* has yielded the new pyrrolomycin G (**1151**), H (**1152**), I (**1153**), and J (**1154**) (*1192*). The absolute configuration of G and H was determined as (*S*). A compound missed in the earlier survey is pentachloropseudilin (**1155**) (*1193*), the chlorine analog of the known pentabromopseudilin (*1*).



1151 R = H (pyrrolomycin G)
1152 R = Me (pyrrolomycin H)

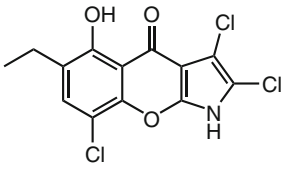


1153 R = H (pyrrolomycin I)
1154 R = Cl (pyrrolomycin J)

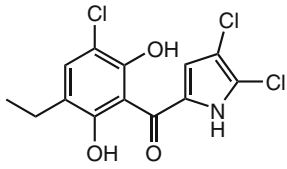


1155 (pentachloropseudilin)

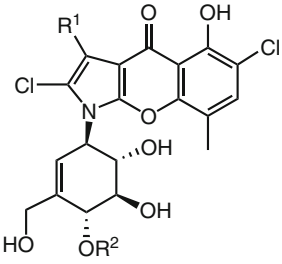
A *Streptomyces* sp. has yielded the novel TAN-876 A (**1156**) and TAN-876 B (**1157**), where the former compound is a unique example of the chromeno[2,3-*b*] pyrrole ring system (*1194*). These metabolites exhibit strong antibacterial activity against Gram-positive and Gram-negative bacteria and fungi. The pyralomicins 1a (**1158**), 1c (**1159**), 1d (**1160**), 1b (**1161**), 2a (**1162**), 2c (**1163**), and 2b (**1164**) were isolated from cultures of *Microtetraspora* (formerly *Actinomadura*) *spiralis* (*1195–1198*). Cultures of *Streptomyces armeniacus* produce streptopyrrole (**1165**) (*1199*), and *Streptomyces rimosus* has afforded an additional six streptopyrroles **1166–1171** (*1200*).



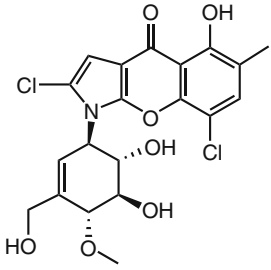
1156 (TAN-876 A)



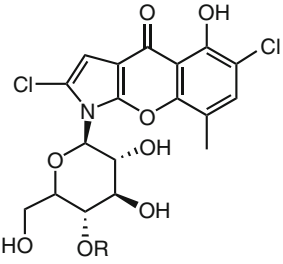
1157 (TAN-876 B)



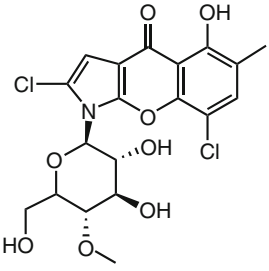
1158 R^1 = H, R^2 = Me (pyralomicin 1a)
1159 R^1 = R^2 = H (pyralomicin 1c)
1160 R^1 = Cl, R^2 = H (pyralomicin 1d)



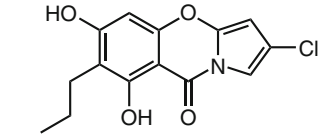
1161 (pyralomicin 1b)



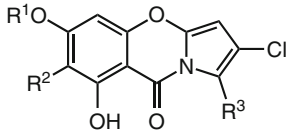
1162 R = Me (pyralomicin 2a)
1163 R = H (pyralomicin 2c)



1164 (pyralomicin 2b)



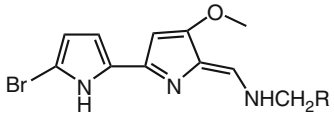
1165 (streptopyrrole)



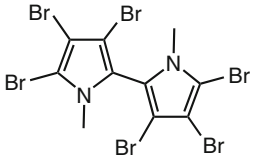
1166 R^1 = R^3 = H, R^2 = Et
1167 R^1 = H, R^2 = Pr, R^3 = Cl
1168 R^1 = Me, R^2 = Pr, R^3 = H
1169 R^1 = R^3 = H, R^2 = Bu
1170 R^1 = Me, R^2 = Et, R^3 = H
1171 R^1 = Me, R^2 = Pr, R^3 = Cl

The sodium sulfamate salt **1172** of the previously known marine acorn worm metabolite 2,3,4-tribromopyrrole was isolated from *Saccoglossus kowalevskii* (*1201*). This compound may serve as the stable, non-toxic, and non-volatile precursor to 2,3,4-tribromopyrrole, which is probably the actual deterrent to predators. The Tasmanian bryozoan *Bugula dentata* has afforded the new bipyrroles tambjamines G-J (**1173–1176**) (*1202*). Several new analogs of the polybrominated 2,2′-bipyrrole that was described earlier (*1*) have been isolated from seabird eggs (gulls, petrel, albatross, puffin, bald eagle) (*1203*). As the isolated amounts were too small to be identified, total synthesis verified the two major compounds as **1177** and **1178** (*1204*). Further confirmation was provided by X-ray crystallography (*1205*). Subsequent studies reveal that **1177**, **1178** and other analogs (**1179–1184**) are ubiquitous in the marine environment, being present in zooplankton, fish, seabirds, seal, porpoise, dolphin, and whale (*1206–1209*). Porpoise and whale blubber also contain the less heavily halogenated **1181–1184**, which have not yet been fully characterized (*1209*). Given their structural similarity to polychlorinated biphenyls (PCBs), it is not surprising that these polyhalogenated bipyrroles bioaccumulate in the food chain.

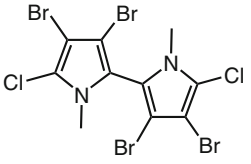
1172



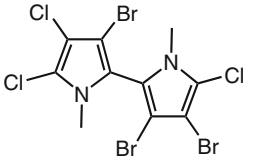
1173 R = CH_3 (tambjamine G)
1174 R = CH_2CH_3 (tambjamine H)
1175 R = $CH(CH_3)_2$ (tambjamine I)
1176 R = $CH(CH_3)CH_2CH_3$ (tambjamine J)



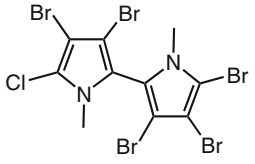
1177



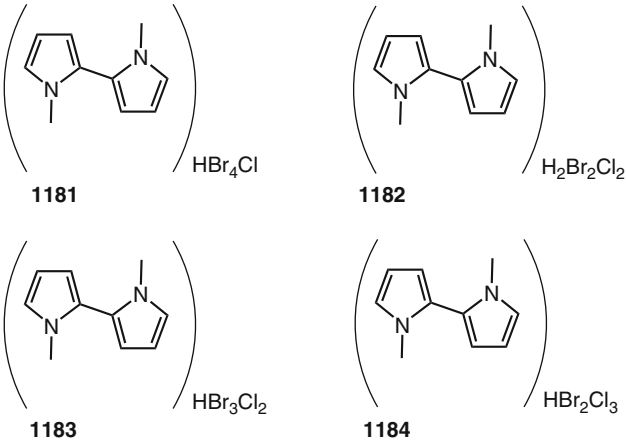
1178



1179 (or isomer)

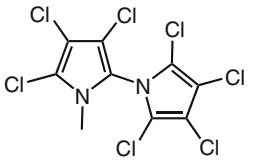


1180 (or isomer)

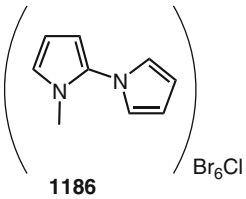


An investigation of marine samples (penguin and skua eggs, in whale and seal blubber, deep sea fish, and human milk) from Antarctica and Africa uncovered "Q1", a novel heptachloro-1′-methyl-1,2′-bipyrrole (**1185**) (*1210–1213*), which was confirmed by total synthesis (*1214*). The discovery of Q1 in human milk samples from women of the Faeroe Islands who consume whale blubber indicates that Q1 is the first natural bioaccumulative compound to move up the food chain to humans, in levels up to 230 μg kg^{-1} (*1213*). Examination of worldwide marine samples shows that Q1 is widespread in the environment, particularly in marine mammals and birds, but also in a green turtle and a python in Australia (*1215*). Q1 is also present in the eggs of five different Norwegian predatory birds (white-tailed sea eagle, golden eagle, merlin, osprey, and goshawk) (*479*). The environmental occurrence and structure of Q1 are reviewed (*1216, 1217*). The highest concentration measured to date is 14 mg kg^{-1} in an Australian dolphin (*1217*). As might be expected for a nonplanar PCB-like compound, Q1 has low biological activity and only modest affinity as an AHR ligand (*1218*). Three brominated derivatives (**1186–1188**) of Q1 have been isolated from the blubber of nine New England marine mammals (species of dolphin, porpoise, whale, seal, and a squid) (*1219, 1220*). Concentrations of **1186–1188** in a squid (*Loligo pealei*) were measured up to 2.7 mg kg^{-1} (*1219*). Marine samples from Australia and Antarctica (melon-headed whale, pygmy sperm whale, common dolphin, bottlenose dolphin) contain 22 new polyhalogenated Q1 analogs in addition to **1186** and **1187** (*1221*). These are **1189–1210**, with varying numbers of bromines and chlorines and different isomers. An important complementary finding is that Q1, several brominated analogs (**1186–1188**), and the new **1211** were discovered in archived whale oil collected in 1921 from the last voyage of the whaling ship *Charles W. Morgan*, a sample of oil that predates large-scale industrial manufacture of organohalogen compounds (*1222*). This oil was found not to contain PCBs, DDT, or DDE. Equally noteworthy is that

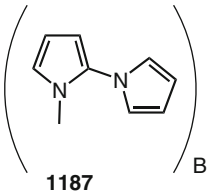
radiocarbon analysis of both Q1 (**1185**) and **1178** reveals that these compounds originate naturally and are not anthropogenic (petroleum-derived) (*1223*). It is highly likely that Q1 and brominated Q1s have been isolated and misidentified in the past. A case in point could be the "halogenated naphthols" isolated from a white-sided dolphin (*1224*).



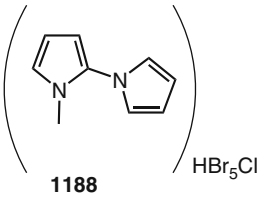
1185 (Q1)



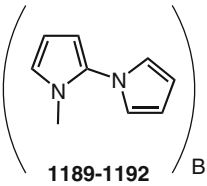
1186 Br_6Cl



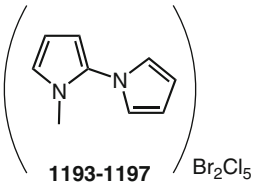
1187 Br_7



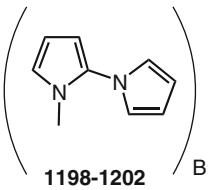
1188 HBr_5Cl



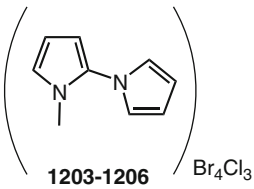
1189-1192 $BrCl_6$



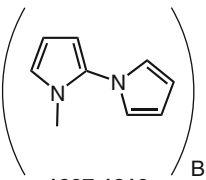
1193-1197 Br_2Cl_5



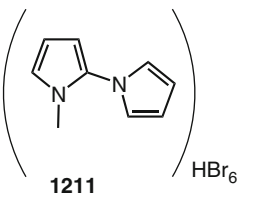
1198-1202 Br_3Cl_4



1203-1206 Br_4Cl_3

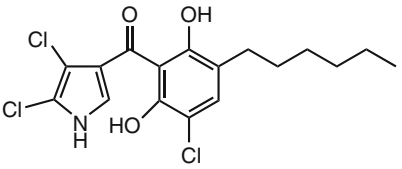


1207-1210 Br_5Cl_2

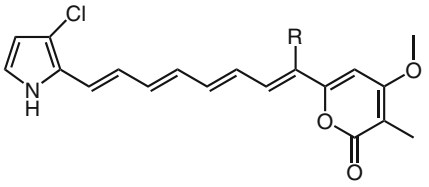


1211 HBr_6

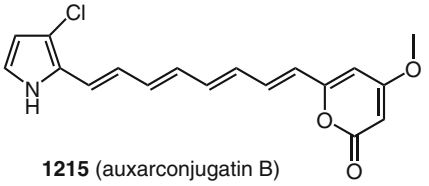
A *Streptomyces* strain isolated from Brazilian (*Maytenus aquifolia*) and South African (*Putterlickia retrospinosa*, *Putterlickia verrucosa*) plants has furnished celastramycin A (**1212**) (*1225*). A new isomer of the known rumbrin (*1*) was isolated from an Australian soil ascomycete, *Gymnoascus reessii*, and named (12*E*)-isorumbrin (**1213**) (*1226*). Somewhat earlier, the three related auxarconjugatins A, B, and (3′*Z*)-A (**1214**–**1216**) were characterized from an Arizona soil microorganism *Auxarthron conjugatum* (*1227*). A basidiomycete fungus from a New Zealand forest, *Chamonixia pachydermis*, produces pachydermin (**1217**) (*1228*).



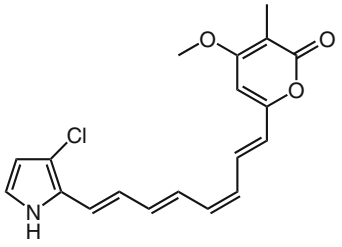
1212 (celastramycin A)



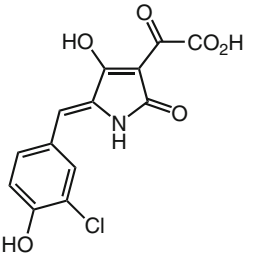
1213 R = Me ((12*E*)-isorumbrin)
1214 R = H (auxarconjugatin A)



1215 (auxarconjugatin B)

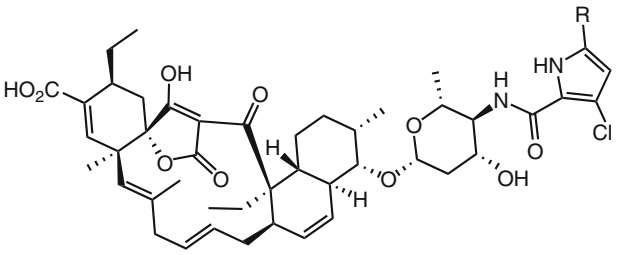


1216 (3'-*cis*-auxarconjugatin A)

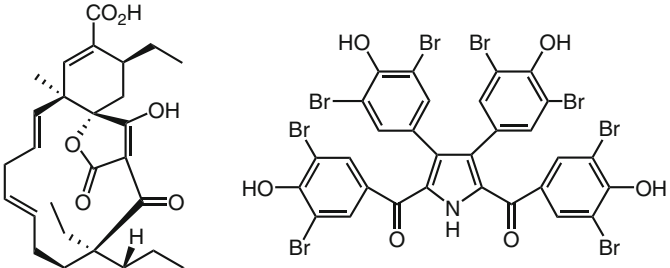


1217 (pachydermin)

Decatromicins A (**1218**) and B (**1219**) are produced by an *Actinomadura* sp. and are active against Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (*1229, 1230*). These compounds are closely related to pyrrolosporin A (**1220**) from *Micromonospora* sp. (*1231, 1232*). The ascidian *Polycitor africanus* from Madagascar has afforded the new polycitone B (**1221**) (*1233*), which is related to the known polycitone A (*1*), a potent inhibitor of retroviral reverse transcriptases and cellular DNA polymerases (*1234*). The known polycitrin B was synthesized for the first time (*1235*).



1218 R = H (decatromicin A)
1219 R = Cl (decatromicin B)

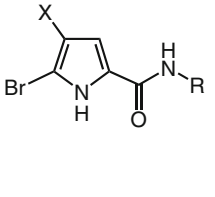


1221 (polycitone B)

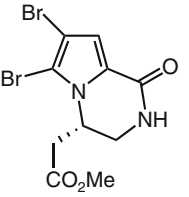
1220 (pyrrolosporin A)

Most of the known natural brominated pyrrole alkaloids are found in sponges, and several new examples were isolated since the first survey (*1*). Reviews are available that discuss the occurrence and syntheses of these metabolites (*1236–1238*). The Papua New Guinea sponge *Agelas nakamurai* has yielded the new simple pyrroles **1222** and **1223** (*1239*). The dibromo analog (**1224**) of **1223** along with enantiomeric lactams **1225/1226**, which were separated by chiral HPLC, and

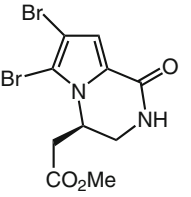
racemic longamide, previously isolated as the (+)-isomer (vide infra), were all characterized from the Japanese sponge *Homaxinella* sp. (*1240*). Interestingly, lactam ester (+)-(*S*)-**1225** was isolated from *Agelas ceylonica* collected in India (*1241*), and (+)-(*S*)-longamide (**1227**) was first described from *Agelas longissima* (*1242*). The (racemic) ethyl ester of methyl esters **1225/1226** is known as hanishin (**1228/1229**), and was isolated from the Red Sea (Hanish Islands) sponge *Acanthella carteri*, along with amide **1230** (*1243*), an isomer of **1222**. A debromo analog (**1231**) of **1225** was isolated from the Indian sponge *Axinella tenuidigitata* (*1244*). Longamide B (**1232**) was found in the Caribbean sponge *Agelas dispar* (*1245*). Debromolongamide **1233** was isolated from the Micronesian *Axinella carteri* (*1246*), and the same compound as "mukanadin C" was found in *Agelas nakamurai* (*1247*). Total syntheses of hanishin (**1228**), longamide B (**1232**), and longamide B methyl ester (**1225**) show that the *levorotary* enantiomers of these natural products have the (*S*)-configuration (*1267*).



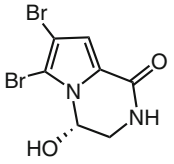
1222 R = X = H
1223 R = CH_2OMe, X = H
1224 R = CH_2OMe, X = Br



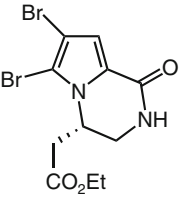
1225



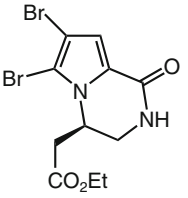
1226



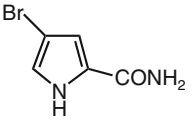
1227 (longamide)



1228 (hanishin)



1229 (hanishin)



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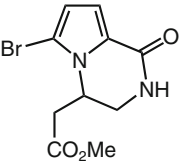
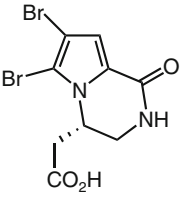
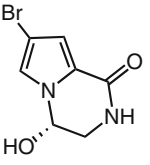


1231

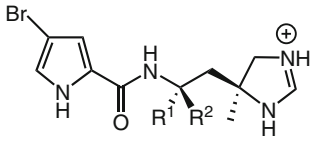


1232 (longamide B)

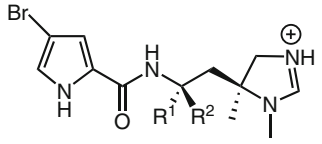


1233 (debromolongamide = mukanadin C)

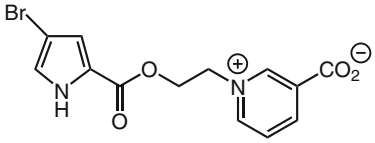
The aforementioned Caribbean collection of *Agelas dispar* affords the novel clathramides C (**1234**) and D (**1235**) (*1245*), which are demethylated examples of the earlier isolated clathramides A (**1236**) and B (**1237**) (*1248*). The zwitterionic alkaloid agelongine (**1238**) was isolated from the Caribbean sponge *Agelas longissima* and displays antiserotonergic activity (*1249*). This sponge and three others from the Caribbean (*Agelas conifera*, *Agelas clathrodes*, and *Agelas dispar*) have afforded dispacamide (**1239**) and its monobromo analog (dispacamide B) **1240** (*1250*). These two metabolites are the first of many new bromopyrroles to be isolated that are related to oroidin. These same four *Agelas* sponges produce dispacamides C (**1241**) and D (**1242**) (*1251*). The latter bromopyrrole was also isolated from *Agelas nakamurai* as "mukanadin A" with the new mukanadin B (**1243**) (*1247*). Along with the latter compound, mukanadin D (**1244**) was found in the Jamaican sponge *Didiscus oxeata* (*1252*).



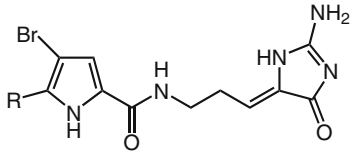
1234 R^1 = H, R^2 = $CO_2^{\ominus}$ (clathramide C)
1235 R^1 = $CO_2^{\ominus}$, R^2 = H (clathramide D)



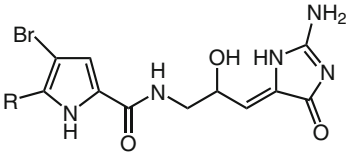
1236 R^1 = H, R^2 = $CO_2^{\ominus}$ (clathramide A)
1237 R^1 = $CO_2^{\ominus}$, R^2 = H (clathramide B)



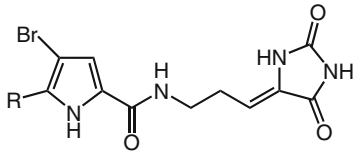
1238 (agelongine)



1239 R = Br (dispacamide)
1240 R = H (dispacamide B)



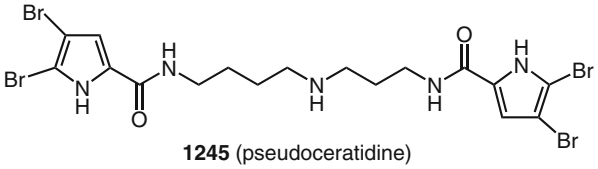
1241 R = Br (dispacamide C)
1242 R = H (dispacamide D)



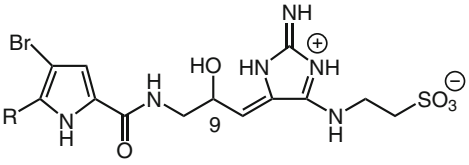
1243 R = H (mukanadin B)
1244 R = Br (mukanadin D)

The antifouling sponge metabolite pseudoceratidine (**1245**) was characterized from the Japanese *Pseudoceratina purpurea* (*1253*). This spermidine derivative has excellent larval settlement and metamorphosis inhibitory activity against the barnacle *Balanus amphitrite* (ED_{50} = 8.0 μg cm^{-3}), and is the first example of an antifouling spermidine derivative. The four tauroacidins A (**1246/1247**) and B (**1248/1249**), with tyrosine kinase inhibitory activity, were isolated from the

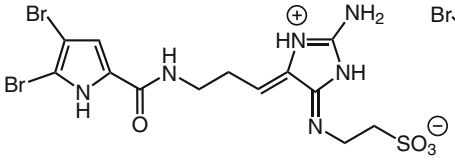
Okinawan sponge *Hymeniacidon* sp. (*1254*). The closely related taurodispacamide A (**1250**) is found in the Mediterranean sponge *Agelas oroides* (*1255*). This compound exhibits good antihistaminic activity. A Florida collection of *Agelas wiedenmayeri* contains the bromopyrrole homoarginine **1251**, which may be a biosynthetic precursor to hymenidin and oroidin derivatives (*1256*). The decarboxylated version of **1251**, laughine (**1252**), was isolated from the Dominican sponge *Eurypon laughlini* (*1257*). The arginine (**1253**) and lysine (**1254**) analogs of **1251** were found in the Bahamanian sponge *Stylissa caribica* (*1258*). A total synthesis of **1251** confirms its structure (*1259*). Sventrin (**1255**) (*N*-methyloroidin) is present in the Bahamanian sponge *Agelas sventres*, and is a feeding deterrent to the reef fish *Thalassoma bifasciatum* (*1260*). Four analogs of known bromopyrrole alkaloids (**1256**–**1259**) were isolated from the Corsican sponge *Axinella verrucosa* (*1261*). Thus, compound **1256** is 9-hydroxymukanadin B, **1257** is 9-methoxydispacamide B, **1258** is 2-debromotaurodispacamide A, and **1259** is the 2-debromo analog of **1224**.



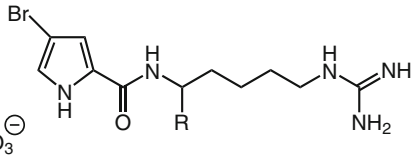
1245 (pseudoceratidine)



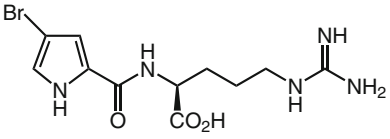
1246 R = Br (9*S*-tauroacidin A)
1247 R = Br (9*R*-tauroacidin A)
1248 R = H (9*S*-tauroacidin B)
1249 R = H (9*R*-tauroacidin B)



1250 (taurodispacamide A)



1251 R = CO_2H
1252 R = H (laughine)



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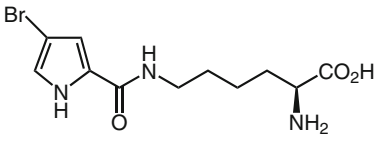
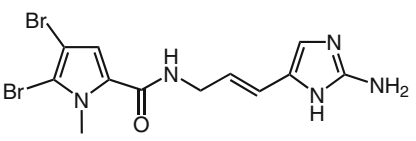
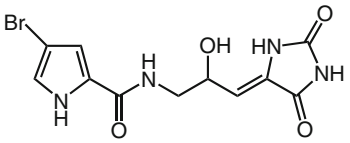


1254



1255 (sventrin)



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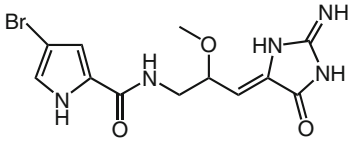

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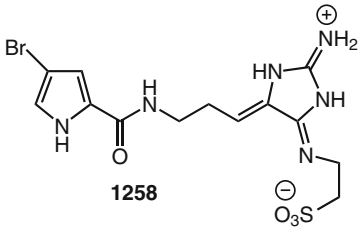
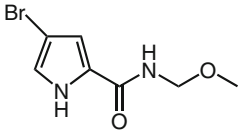
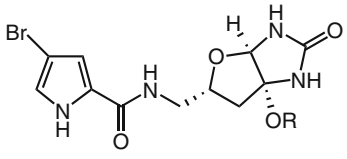


1258

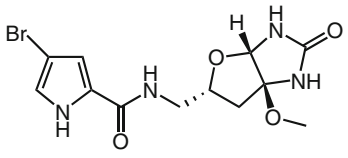


1259

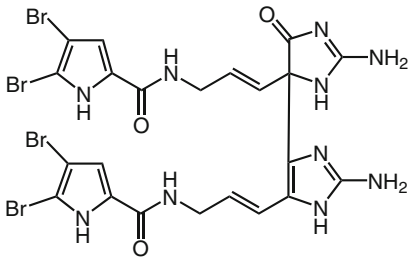
The cyclized slagenins A–C (**1260–1262**) were discovered in the sponge *Agelas nakamurai* living in Okinawan waters (*1262*). Slagenins A and B are active in the L1210 murine leukemia screen. The absolute configurations of **1260–1262** were established by total synthesis (*1263*). A Japanese collection of *Agelas mauritiana* yielded mauritiamine (**1263**) (*1264*). This novel oroidin dimer inhibits barnacle growth (*Balanus amphitrite*). Cyclooroidin (**1264**) was isolated from the Mediterranean *Agelas oroides* (*1255*), and ugibohlin (**1265**) was found in the Philippines sponge *Axinella carteri* (*1265*). Total synthesis confirms the assigned structure of **1264** and establishes its absolute configuration as shown (*1266*). Ageladine A (**1266**) was isolated from the sponge *Agelas nakamurai*, and is a potent inhibitor of matrix metalloproteinases (*1268*). Ageladine A has been synthesized (*1269, 1270*).



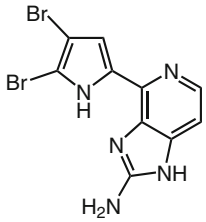
1260 R = H (slagenin A)
1261 R = Me (slagenin B)



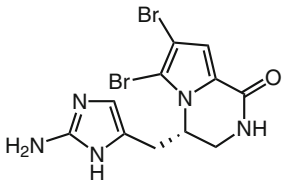
1262 (slagenin C)



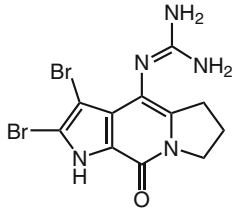
1263 (mauritiamine)



1266 (ageladine A)

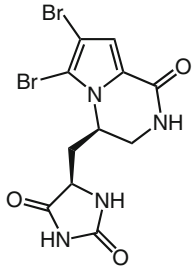


1264 (*S* - cyclooroidin)

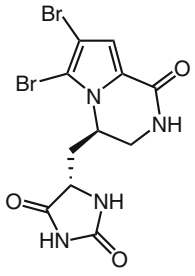


1265 (ugibohlin)

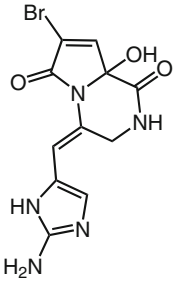
Agesamides A (**1267**) and B (**1268**) were isolated from an Okinawan sponge *Agelas* sp. (*1271*), and the interesting oxocyclostylidol (**1269**) was found in the Bahamian sponge *Stylissa caribica*, and is structurally related to cyclooroidin (*1272*). Some new examples of the hymenialdisine-axinohydantoin bromopyrrole class have been discovered since the first survey (*1*). The prolific sponge *Axinella carteri* from Indonesia contains 3-bromohymenialdisine (**1270**) (*1273*). The Palauan sponge *Stylotella aurantium* has furnished the (10*E*)-diastereomer of hymenialdisine (**1271**) (*1274*), and the (10*Z*)-diastereomer of axinohydantoin (**1272**) was also isolated from the sponge *Stylotella aurantium* (*1275*). An Okinawan sponge *Hymeniacidon* sp. has afforded the new spongiacidins A (**1273**) and B (**1274**), along with **1272** ("spongiacidin D") (*1276*). Spongiacidin A is the (10*E*)-diastereomer of **1270**. The Indonesian sponge *Stylissa carteri* yielded 2-debromostevensine (**1275**) and 2-debromohymenin (**1276**) (*1277*). Syntheses of several axinohydantoins (*1278*) and hymenialdisines (*1279*) have been reported.



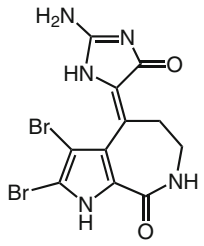
1267 (agesamide A)



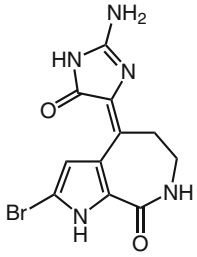
1268 (agesamide B)



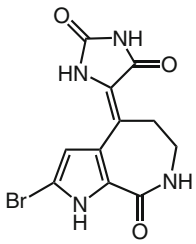
1269 (oxocyclostylidol)



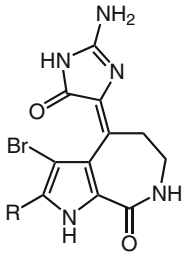
1270 (3-bromohymenialdisine)



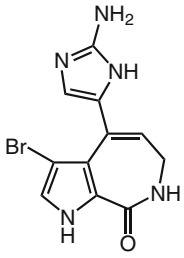
1271 ((*E*)-hymenialdisine)



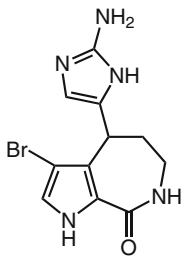
1272 ((*Z*)-axinohydantoin)



1273 R = Br (spongiacidin A)
1274 R = H (spongiacidin B)

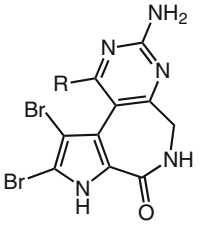


1275 (debromostevensine)

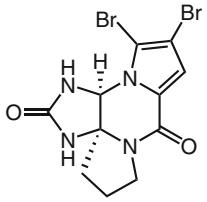


1276 (debromohymenin)

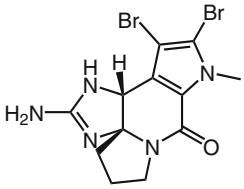
Latonduines A (**1277**) and B (**1278**), which have a novel ring system, were isolated from the Indonesian sponge *Stylissa carteri* and the structures confirmed by total synthesis (*1280*). Some new phakellin-type bromopyrroles have been characterized. The Indian Ocean sponge *Phakellia mauritiana* contains dibromophakellstatin (**1279**), which is the principal antineoplastic component of this sponge and shows activity against ovarian, brain, kidney, lung, colon, and melanoma human cell lines (*1281*). The sponge *Stylissa caribica* from the Bahamas produces *N*-methyldibromoisophakellin (**1280**), which displays excellent feeding deterrent activity against the common reef fish *Thalassoma bifasciatum* (*1282*). This metabolite is more active than oroidin in this assay. The related monobromoisophakellin (**1281**) was identified in an *Agelas* sp. sponge from the Bahamas (*1283*). Syntheses of dibromophakellstatin (*1284–1286*) and dibromoisophakellin (*1284*) confirm the proposed structures. The Japanese sponge *Axinella brevistyla* produces four new pyrrole-derived alkaloids (*1287*). In addition to the simple 3-bromomaleimide (**1282**) and 3,4-dibromomaleimide (**1283**), *N*-methylmanzacidin C (**1284**) and 12-chloro-11-hydroxydibromoisophakellin (**1285**) were characterized from this sponge. The two new phakellin alkaloids, (–)-7-*N*-methyldibromophakellin (**1286**) and (–)-7-*N*-methylmonobromophakellin (**1287**), are present in the Papua New Guinea sponge *Agelas* sp. (*1288*).



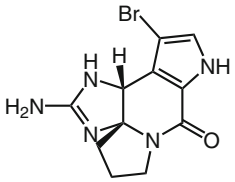
1277 R = H (latonduine A)
1278 R = CO_2H (latonduine B)



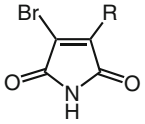
1279 (dibromophakellstatin)



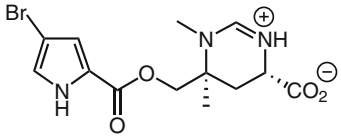
1280 (*N*-methyldibromoisophakellin)



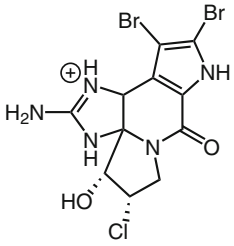
1281 (monobromoisophakellin)



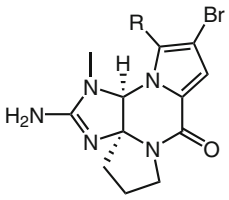
1282 R = H
1283 R = Br



1284 (*N*-methylmanzacidin C)



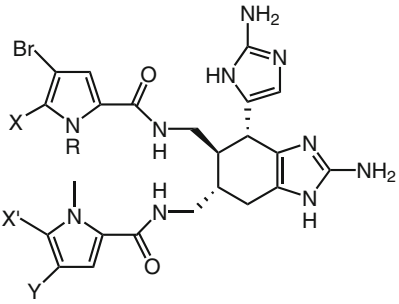
1285



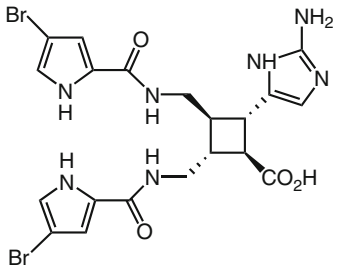
1286 R = Br
1287 R = H

The Pohnpei sponge *Astrosclera willeyana* has furnished seven new *N*-methylageliferins: *N*(1′)-methylageliferin (**1288**), *N*(1),*N*(1′)-dimethylageliferin (**1289**), *N*(1′)-methylisoageliferin (**1290**), *N*(1),*N*(1′)-dimethylisoageliferin (**1291**), *N*(1′)-methyl-2-bromoageliferin (**1292**), *N*(1′)-methyl-2′-bromoageliferin (**1293**), and *N*(1′)-methyl-2,2′-dibromoageliferin (**1294**) (*1289*). The Indonesian sponge *Agelas nakamurai* contains the sceptrin-related nakamuric acid (**1295**) and the corresponding methyl ester, which is considered to be an isolation artifact (*1290*). The new bromosceptrin (**1296**) was characterized from the Florida sponge *Agelas*

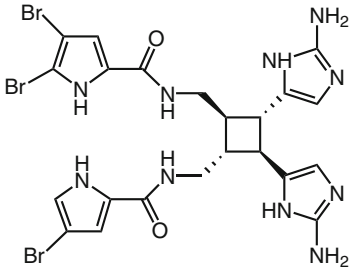
conifera (*1291*). The ageliferin and sceptrin families of bromopyrroles have been of synthetic interest (*1292, 1293*).



1288 R = X = X' = H, Y = Br
1289 R = Me, X = X' = H, Y = Br
1290 R = X = Y = H, X' = Br
1291 R = Me, X = Y = H, X' = Br
1292 R = X' = H, X = Y = Br
1293 R = X = H, X' = Y = Br
1294 R = H, X = X' = Y = Br

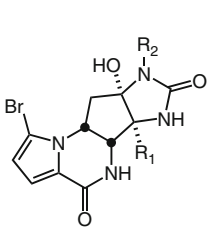


1295 R = H (nakamuric acid)

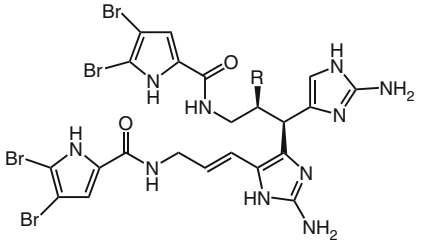


1296 (bromosceptrin)

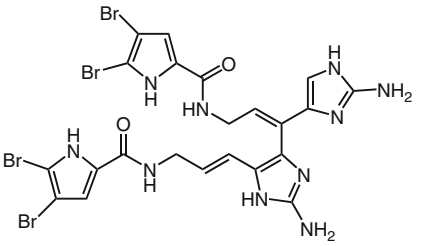
The new agelastatins C (**1297**) and D (**1298**) were discovered in the Indian Ocean sponge *Cymbastela* sp. (*1294*). The absolute configurations are as shown. The known agelastatin A, which has been the object of synthesis (*1295–1298*), was also isolated in this study and shown to have insecticidal activity against larvae of beet army worm and corn rootworm (*1294*). A series of nagelamides A–H (**1299–1306**) was characterized in the Okinawan sponge *Agelas* sp., along with the new 9,10-dihydrokeramadine (**1307**) (*1299*). All of the nagelamides display antibacterial activity and nagelamide G (**1305**) inhibits protein phosphatase 2A. The structurally complex stylissadines A (**1308**) and B (**1309**) were isolated from the sponge *Stylissa caribica* collected in the Bahamas (*1300*). The stylissadines appear to be dimers of massadine (**1314**).



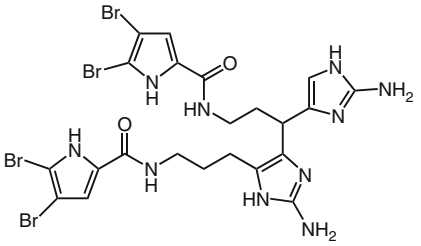
1297 R_1 = OH, R_2 = Me (agelastatin C)
1298 R_1 = R_2 = H (agelastatin D)



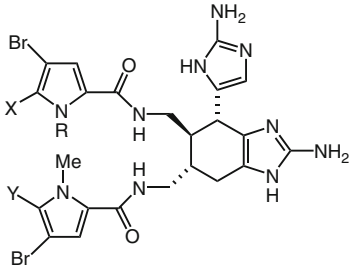
1299 R = H (nagelamide A)
1300 R = OH (nagelamide B)



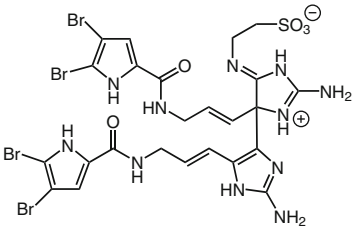
1301 (nagelamide C)



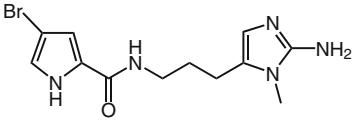
1302 (nagelamide D)



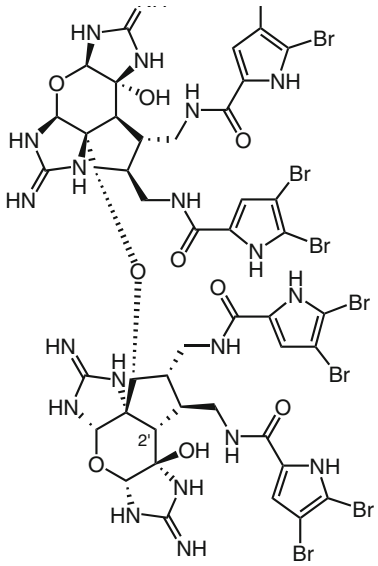
1303 X = Y = H (nagelamide E)
1304 X = Br, Y = H (nagelamide F)
1305 X = Y = Br (nagelamide G)



1306 (nagelamide H)

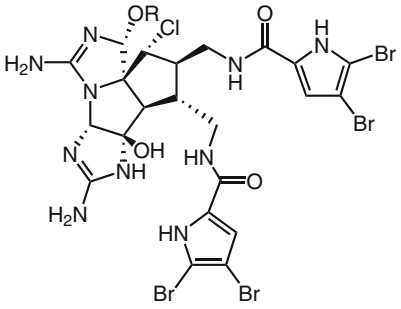


1307 (9,10-dihydrokeramadine)

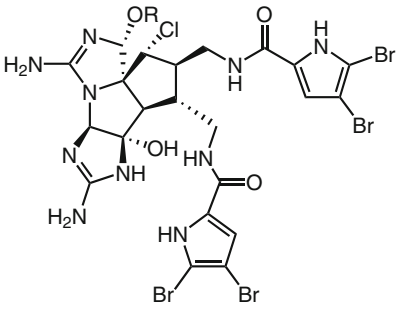


1308, 1309 (stylissadines A and B) (epimeric at C-2')

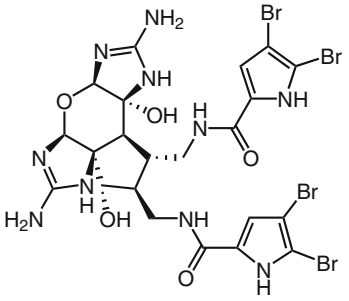
An Australian sponge *Axinella* sp. has afforded the novel axinellamines A–D (**1310**–**1313**), which exhibit activity against *Helicobacter pylori* (*1301*). The similar massadine (**1314**) from the Japanese sponge *Stylissa* aff. *massa* inhibits geranylgeranyltransferase type I and the fungus *Candida albicans* (*1302*). Like many of these 2-aminoimidazole alkaloids, **1310**–**1314** were isolated as acid salts; trifluoroacetic acid salts in these cases.



1310 R = H (axinellamine A)
1312 R = Me (axinellamine C)

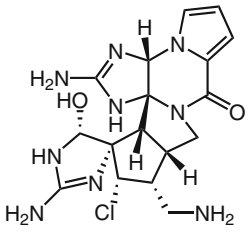


1311 R = H (axinellamine B)
1313 R = Me (axinellamine D)

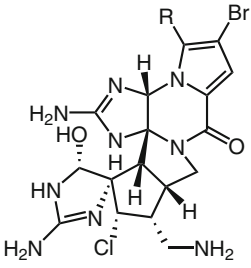


1314 (massadine)

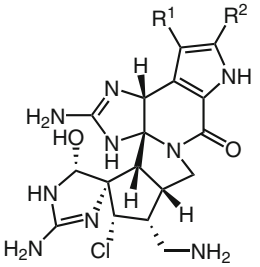
The stunningly complex and intricate palau'amine (**1315**) was isolated from the South Pacific sponge *Stylotella agminata* (renamed as *Stylotella aurantium*) (*1303, 1304*), along with 4-bromopalau'amine (**1316**) and 4,5-dibromopalau'amine (**1317**) (*1304*). This sponge has also yielded styloguanidine (**1318**), 3-bromostyloguanidine (**1319**), and 2,3-dibromostyloguanidine (**1320**), which are potent antifouling compounds against barnacles (*1305*). These three compounds were also identified in a previous examination of *Stylotella aurantium* as "isopalau'amines" (*1304*). The related konbu'acidin A (**1321**), having cyclin dependent kinase activity, was isolated from the Okinawan sponge *Hymeniacidon* sponge (*1306*).



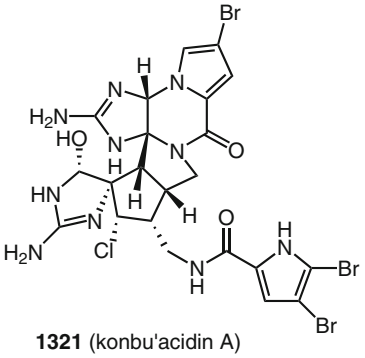
1315 (palau'amine)



1316 R = H
1317 R = Br

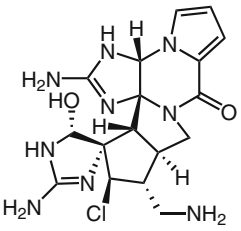


1318 $R^1 = R^2 = H$ (styloguanidine)
1319 $R^1 = Br$, $R^2 = H$
1320 $R^1 = R^2 = Br$

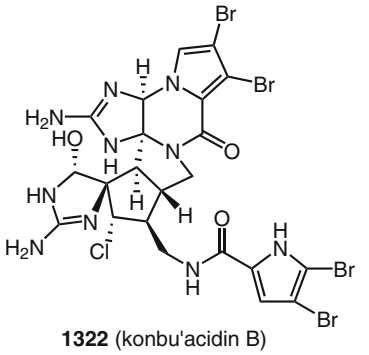


1321 (konbu'acidin A)

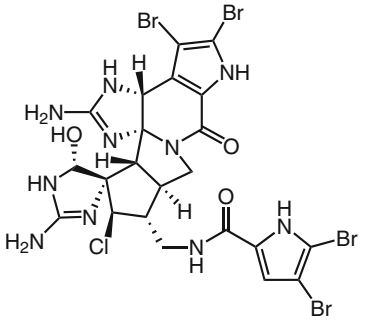
Three independent studies present evidence that palau'amine, styloguanidine, and derivatives need to be revised at three stereocenters (i.e. (12*R*,7*S*,20*S*) (*1307–1309*)). Based on these studies the revised structure of palau'amine is shown as **YY**, and the other structures (**1316–1321**) may need to be reconsidered as well. The Australian sponge *Stylissa flabellata* contains stylissadines A (**1308**) and B (**1309**), which were initially named "flabellazoles A and B", respectively (*1307*). This study also uncovered the new konbu'acidin B (**1322**), and reported that **1308** and **1309** are the most potent natural product $P2X_7$ antagonists to be isolated to date (*1307*). The Bahamaian sponge *Stylissa caribica* contains tetrabromostyloguanidine (**1323**) (*1308*), and *Stylissa carteri* has yielded carteramine A, which appears to be **1323** (same optical rotation) (*1309*). Related to nagelamides A–H (**1299–1300**), the new nagelamide J (**1324**) was isolated from an Okinawan *Agelas* sponge (*2659*).



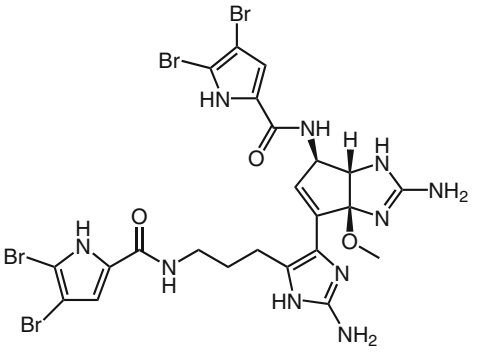
YY (palau'amine) (revised)



1322 (konbu'acidin B)



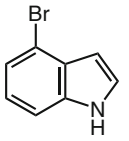
1323 (tetrabromostyloguanidine) (= carteramine A?)



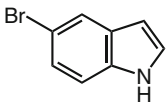
1324 (nagelamide J)

3.14.2 Indoles

Like pyrrole, the enormous reactivity of indole guarantees a large number of natural halogenated indoles. The earlier survey documented nearly 200 halogenated indoles, not including halogenated carbazoles, carbolines, and related fused indoles (*1*). Simple halogenated indoles, both previously known and new, continue to be identified in natural sources. The Palauan ascidian *Distaplia regina* contains 3,6-dibromoindole (*1310*), which was earlier misidentified (*1*). The previously known 1-methyl-2,3,5-tribromoindole was identified in the Indian red alga *Nitophyllum marginata* (*1311*), and the marine acorn worm metabolite 3-chloroindole (*1*) has now been found in the mushroom *Hygrophorus paupertinus* (*1312*). The common oyster *Crassostrea virginica* contains two dibromoindoles and one tribromoindole, which are not yet identified (*1313*). In addition to the previously reported 3,6- and 4,6-dibromoindoles (*1*), both the open ocean and sediments from the North and Baltic Seas contain 4-bromoindole (**1325**), 5-bromoindole (**1326**), 6-bromoindole (**1327**), and 3,4-dibromoindole (**1328**) (*1314*). Three new bromoindoles, 3,5,6-tribromoindole (**1329**), 1-methyl-3,5,6-tribromoindole (**1330**), and 2,3,6-tribromoindole (**1331**) were isolated from the red alga *Laurencia similis* collected off the coast of Hainan Island, China (*1315*). The muricid gastropod *Drupella fragum*, a predator of Madreporaria corals, contains in its mid-intestinal gland novel brominated hydroxyindoles, 6-bromo-5-hydroxyindole (**1332**), 6-bromo-4,5-dihydroxyindole (**1333**), and 5-bromo-4,7-dihydroxyindole (**1334**) (*1316*). Indole **1332** is comparable to BHT and superior to α-tocopherol for antioxidative activity, and the structure of **1332** is confirmed by synthesis. The unusual sulfate-sulfamate indoles ancorinolates A (**1335**) and C (**1336**) were isolated from the sponge *Ancorina* sp. (*1317*). These indoles show weak HIV-inhibitory activity. The Formosan red alga *Laurencia brongniartii* has yielded three new sulfur-containing polybromoindoles, **1337**–**1339**, and two related dimeric polybromoindoles, **1340** and **1341** (*1318*).



1325



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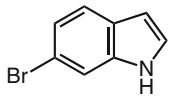

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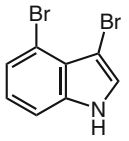

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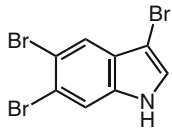

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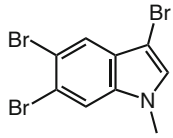

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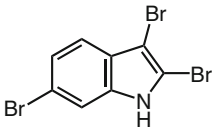

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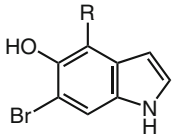
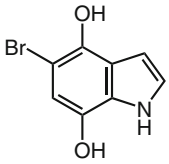


1332 R = H
1333 R = OH



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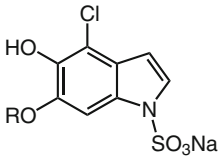
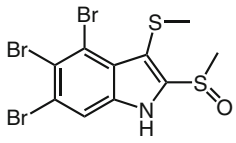
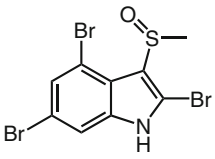


1335 R = SO_3Na (ancorinolate A)
1336 R = H (ancorinolate C)



1337



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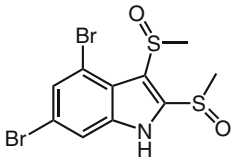

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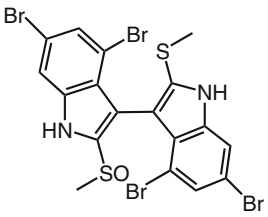

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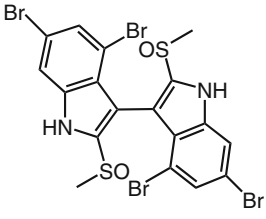
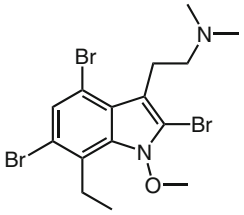


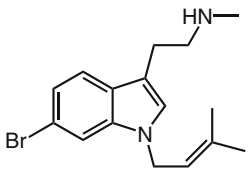
1341

Several new brominated tryptamines and tryptophans have been described. The Tasmanian bryozoan *Amathia convoluta* contains convolutindole A (**1342**) (*1319*), and the North Sea bryozoan *Flustra foliacea* (Fig. 3.19) has afforded deformylflustrabromine B (**1343**) (*1320*), **1344**, **1345**, and deformylflustrabromine (**1346**) (*1321*). A Philippine sponge *Smenospongia* sp. contains 5-bromotryptophan (**1347**), 5-bromoabrine (**1348**), 5,6-dibromoabrine (**1349**), and 5-bromoindole-3-acetic acid (**1350**) (*1322*). A study of the sponge *Thorectandra* sp. has furnished 5-bromo-*N*,*N*-dimethyltryptophan (**1351**), 5-bromohypaphorine (**1352**), and aplysinopsin **1353** (*1323*), while the Papua New Guinea sponge *Smenospongia* sp. produces methyl 6-bromoindole-3-carboxylate (**1354**) (*1323*). The novel iodinated

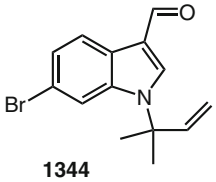
plakohypaphorines A–F (**1355–1360**) were isolated from the Caribbean sponge *Plakortis simplex* (*1324, 1325*). These novel compounds are the first examples of naturally occurring iodine-containing indoles. The Pacific Coast snail *Calliostoma canaticulatum* secretes the disulfide-linked dimer of 6-bromo-2-mercaptotryptamine (**1361**) that repels the predatory starfish *Pycnopodia helianthoides* (*1326*).



1342 (convolutindole A)



1343 (deformylflustrabromine B)



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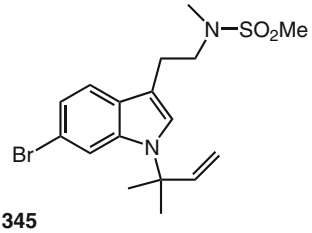

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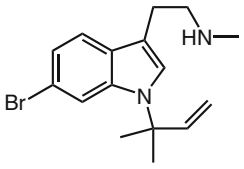
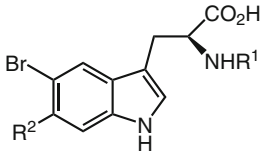
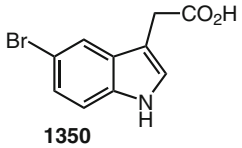


1346 (deformylflustrabromine)



1347 $R^1 = R^2 = H$
1348 R^1 = Me, R^2 = H (5-bromoabrine)
1349 R^1 = Me, R^2 = Br (5,6-dibromoabrine)



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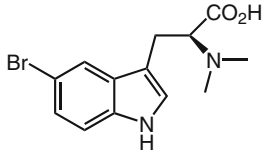

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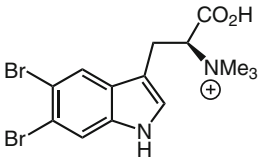
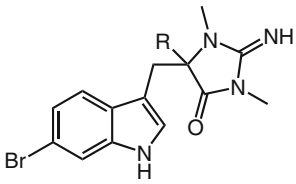
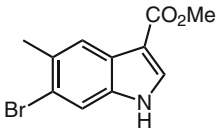


1352 (5-bromohypaphorine)



1353 (aplysinopsin)



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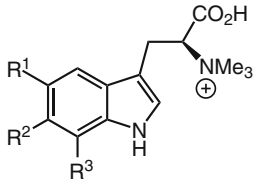
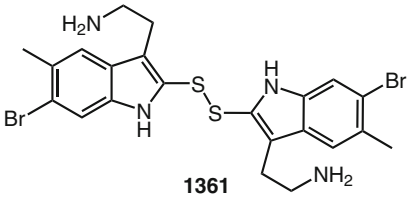


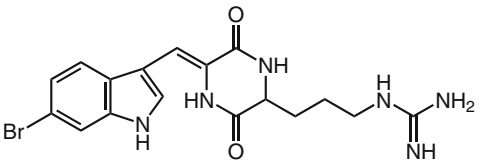
1355 $R^1 = R^2 = H$, $R^3 = I$ (plakohypaphorine A)
1356 $R^1 = H$, $R^2 = R^3 = I$ (plakohypaphorine B)
1357 $R^1 = R^3 = I$, $R^2 = H$ (plakohypaphorine C)
1358 $R^1 = I$, $R^2 = I$, $R^3 = H$ (plakohypaphorine D)
1359 $R^1 = I$, $R^2 = I$, $R^3 = I$ (plakohypaphorine E)
1360 $R^1 = I$, $R^2 = H$, $R^3 = Cl$ (plakohypaphorine F)



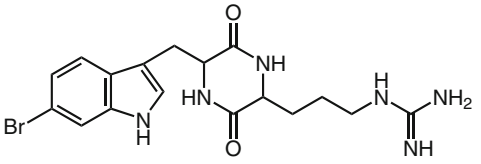
1361

Fig. 3.19 *Flustra foliacea*, a North Sea bryozoan and a producer of many bromotryptamines and brominated indole alkaloids, such as **1343–1346** (Photo: A. D. Wright)

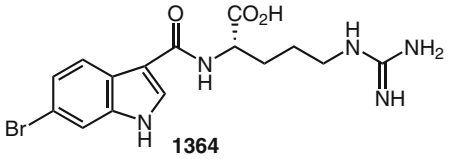
Barettin (**1362**) was isolated from the Swedish sponge *Geodia baretti* (*1327*), and the structure was subsequently revised (*1328*) after a synthesis of the proposed structure proved it incorrect (*1329*). Dihydrobarettin (**1363**) is also found in this sponge (*1330*). The three novel amino acid derivatives **1364–1366** were identified in the New Caledonian ascidian *Leptoclinides debius* (*1331*). The latter metabolite features the rare amino acid enduracididine. Four new bromotryptamine peptides, alternatamides A (**1367**), B (**1368**), C (**1369**), and D (**1370**), were characterized from the bryozoan *Amathia alternata* collected along the North Carolina coast (*1332*). The absolute stereochemistry of the previously known chelonin B (*1*) has been determined as (*S*) by total synthesis (*1333*). The sponge *Hyrtios erecta* contains the new (*Z*)-5,6-dibromo-2′-demethylaplysinopsin (**1371**) and (*E*)-5,6-dibromo-2′-demethylaplysinopsin (**1372**) (*1334*). The New Zealand ascidian *Pycnoclavella kottae* has furnished the four kottamides A–D (**1373–1376**), which display antiinflammatory, antimetabolic, and antitumor activity to varying degrees (*1335*). This same marine animal also contains kottamide E (**1377**), which incorporates an unusual 1,2-dithiolane moiety (*1336*).



1362 (barettin)



1363 (8,9-dihydrobarettin)



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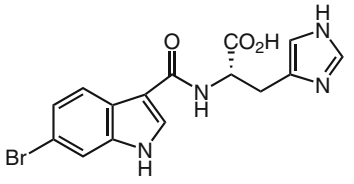

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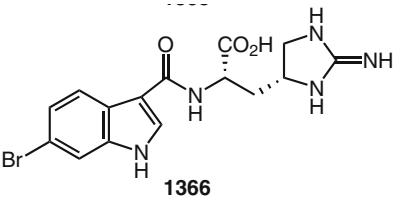

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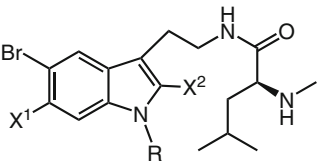
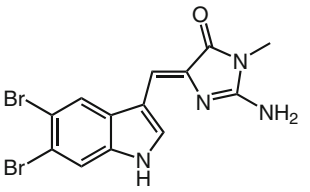
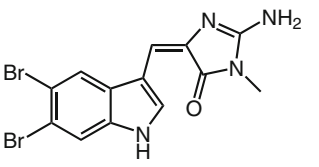


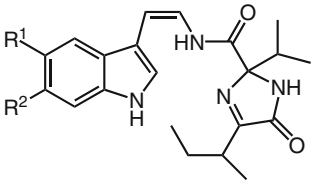
1367 R = Me, $X^1 = X^2 = Br$ (alternatamide A)
1368 R = H, $X^1 = X^2 = Br$ (alternatamide B)
1369 $R = X^1 = H$, $X^2 = Br$ (alternatamide C)
1370 $R = X^2 = H$, $X^1 = Br$ (alternatamide D)



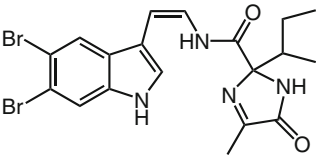
1371



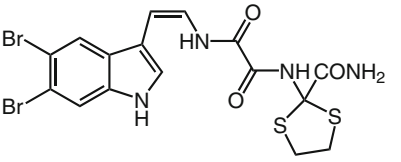
1372



1373 $R^1 = R^2 = Br$ (kottamide A)
1374 $R^1 = Br$, $R^2 = H$ (kottamide B)
1375 $R^1 = H$, $R^2 = Br$ (kottamide C)

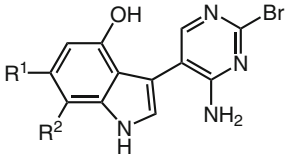


1376 (kottamide D)

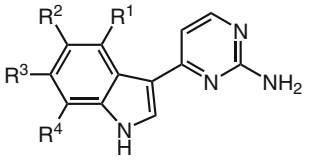


1377 (kottamide E)

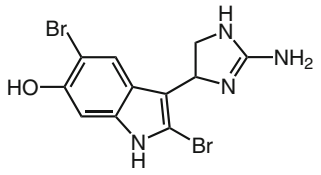
An Antarctica collection of the sponge *Psammopemma* sp. has yielded the new 4-hydroxyindole alkaloids, psammopemmins A (**1378**), B (**1379**), and C (**1380**), which embody the unique 2-bromopyrimidine unit (*1337*). The related meridianins B (**1381**), C (**1382**), D (**1383**), E (**1384**), and F (**1385**) were found in the tunicate *Aplidium meridianum* collected at 100 m near the South Georgia Islands (*1338, 1339*). These protein kinase inhibitors have been synthesized (*1340*). The sponge *Discodermia polydiscus* has afforded 6-hydroxydiscodermindole (**1386**) (*1341*).



1378 $R^1 = R^2 = H$ (psammopemmin A)
1379 $R_1 = H$, $R^2 = Br$ (psammopemmin B)
1380 $R^1 = Br$, $R^2 = H$ (psammopemmin C)



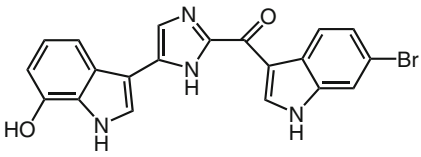
1381 $R^1 = OH$, $R^2 = R_4 = H$, $R^3 = Br$ (meridianin B)
1382 $R^1 = R^3 = R^4 = H$, $R^2 = Br$ (meridianin C)
1383 $R^1 = R^2 = R^4 = H$, $R^3 = Br$ (meridianin D)
1384 $R^1 = OH$, $R^2 = R^3 = H$, $R^4 = Br$ (meridianin E)
1385 $R^1 = R^4 = H$, $R^2 = R^3 = Br$ (meridianin F)



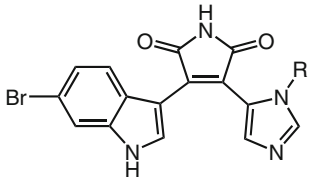
1386 (6-hydroxydiscodermindole)

Numerous halogenated bis-indole natural products have been described since the early discovery of Tyrian purple, the dibrominated analog of indigo (*1*). A new example of the topsentin family has been isolated, isobromotopsentin (**1387**), from the deep water Australian sponge *Spongosorites* sp. (*1342*). The Caribbean mangrove ascidian *Didemnum conchyliatum* (Fig. 3.20) has provided four new didemnimides, two of which, didemnimides B (**1388**) and D (**1389**), contain bromine

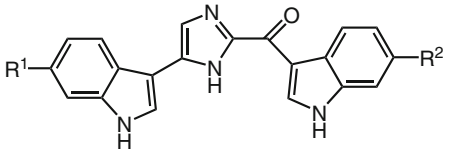
(*1343*). The latter is a potent feeding deterrent against mangrove-specific carnivorous fish. The structure of **1388** is confirmed by total synthesis (*1344*). The Korean sponge *Spongosorites genitrix* has afforded the new bromodeoxytopsentin (**1390**) and isobromodeoxytopsentin (**1391**), which display moderate cytotoxicity against human leukemia K-562 (*1345*). The Okinawan tunicate *Rhopalaea* sp. has yielded four rhopaladins, two of which, rhopaladins A (**1392**) and C (**1393**), are brominated (*1346*), and all four rhopaladins have been synthesized (*1347*). The Mediterranean sponge *Rhaphisia lacazei* produces seven new bis-indoles of the topsentin and hamacanthin classes, *cis*-3,4-dihydrohamacanthin B (**1394**), 6′-debromo-*cis*-3,4-dihydrohamacanthin B (**1395**), 6"-debromo-*cis*-3,4-dihydrohamacanthin B (**1396**), *cis*-3,4-dihydrohamacanthin A (**1397**), *trans*-3,4-dihydrohamacanthin A (**1398**), 6′-debromo-*trans*-3,4-dihydrohamacanthin A (**1399**), and 6"-debromo-*trans*-3,4-dihydrohamacanthin A (**1400**) (*1348*). A Korean collection of the sponge *Spongosorites* sp. has afforded (*R*)-6"-debromohamacanthin A (**1401**), (*R*)-6′-debromohamacanthin A (**1402**), dibromodeoxytopsentin (**1403**) (*1349*), (*R*)-6"-debromohamacanthin B (**1404**) (*1350*), (*R*)- and (*S*)-6′-debromohamacanthin B (**1405**, **1406**), spongotine A (**1407**), spongotine B (**1408**), and spongotine C (**1409**) (*1351*). The previously reported "(*S*)-6"-debromohamacanthin B" (*1349*) has been reassigned as spongotine B (**1408**) (*1351*). The absolute configuration of spongotine A (**1407**) is established as (*S*) by total synthesis (*2670*) (and assumed for **1408** and **1409**). Some of these bis-indoles have significant antibacterial activity against methicillin-resistant *Staphylococcus aureus* and pathogenic fungi (*1352*). Syntheses of the hamacanthins have been accomplished (*1353, 1354*).



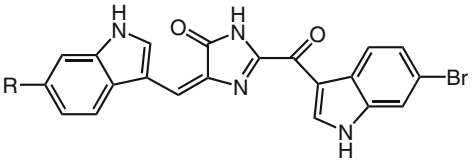
1387 (isobromotopsentin)



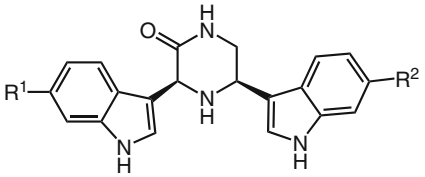
1388 R = H (didemnimide B)
1389 R = Me (didemnimide D)



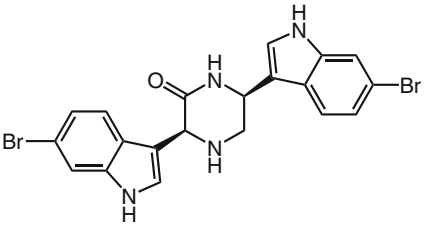
1390 R^1 = Br, R^2 = H (bromodeoxytopsentin)
1391 R^1 = H, R^2 = Br (isobromodeoxytopsentin)



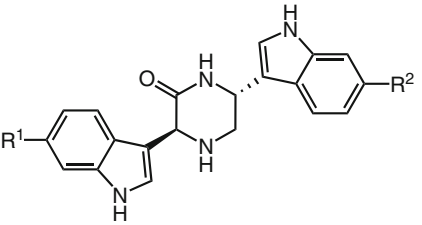
1392 R = OH (rhopaladin A)
1393 R = H (rhopaladin C)



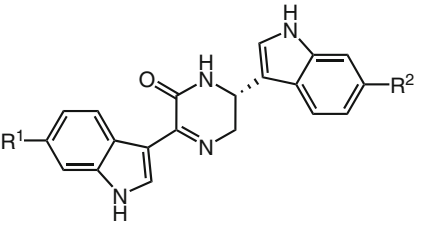
1394 $R^1 = R^2 = Br$ (*cis* - 3,4-dihydrohamacanthin B)
1395 $R^1 = H$, $R^2 = Br$ (6'-debromo-*cis*-3,4-dihydrohamacanthin B)
1396 $R^1 = Br$, $R^2 = H$ (6''-debromo-*cis*-3,4-dihydrohamacanthin B)



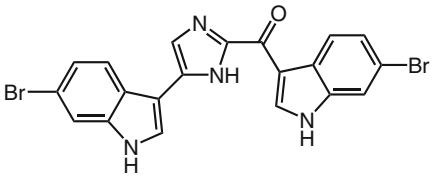
1397 (*cis*-3,4-dihydrohamacanthin A)



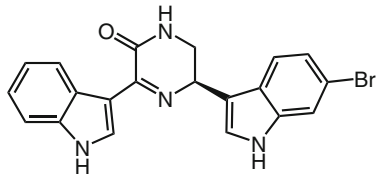
1398 $R^1 = R^2 = Br$ (*trans*-3,4-dihydrohamacanthin A)
1399 $R^1 = H$, $R^2 = Br$ (6'-debromo-*trans*-3,4-dihydrohamacanthin A)
1400 $R^1 = Br$, $R^2 = H$ (6''-debromo-*trans*-3,4-dihydrohamacanthin A)



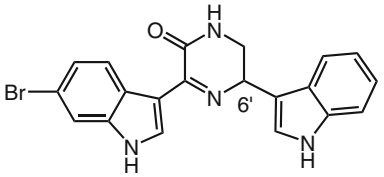
1401 $R^1 = Br$, $R^2 = H$ ((*R*)-6''-debromohamacanthin A)
1402 $R^1 = H$, $R^2 = Br$ ((*R*)-6'-debromohamacanthin A)



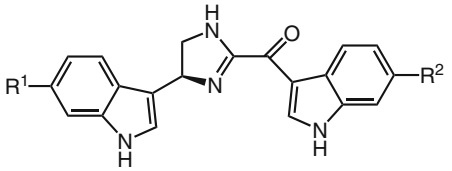
1403 (dibromodeoxytopsentin)



1404 ((*R*)-6''-debromohamacanthin B)

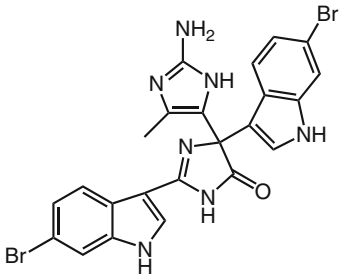


1405 ((*R*)-6'-debromohamacanthin B)
1406 ((*S*)-6'-debromohamacanthin B)

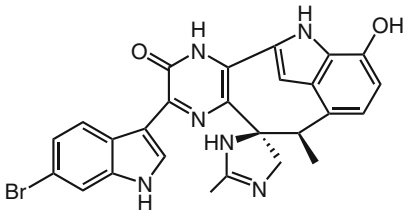


1407 R^1 = Br, R^2 = H (spongotine A)
1408 R^1 = H, R^2 = Br (spongotine B)
1409 R^1 = R^2 = Br (spongotine C)

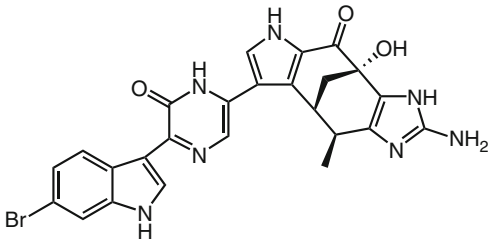
The deep water New Caledonian sponge *Dragmacidon* sp. contains the novel nortopsentin D (**1410**), which is inactive on KB cancer cells (*1355*). However, a polymethylated synthetic derivative (seven methyl groups) is highly cytotoxic. Another deep-water sponge, *Spongosorites* sp., collected from the southern coast of Australia, has provided dragmacidin E (**1411**) (*1356*). Dragmacidin F (**1412**) was isolated from the Mediterranean sponge *Halicortex* sp. (*1357*). This complex metabolite, as well as other dragmacidins, has yielded to total synthesis (*1358*). One of the few calcareous hard corals to be investigated for secondary metabolites is *Tubastraea* sp. from Japan, and this stony coral has yielded tubastrindole A (**1413**), a novel bis-indole (*1359*).



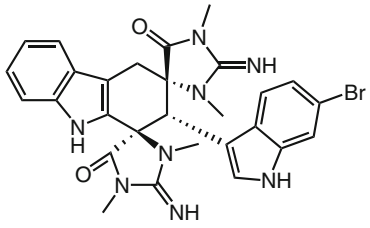
1410 (nortopsentin D)



1411 (dragmacidin E)



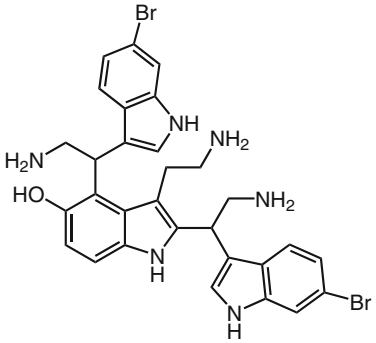
1412 (dragmacidin F)



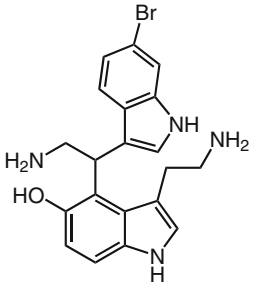
1413 (tubastrindole A)

Several new halogenated polyindole gelliusines were isolated from the deep-water New Caledonian sponge *Orina* sp. (*1360*). These include the racemic (±)-gelliusine C (**1414**, **1415**), (±)-gelliusine D (**1416**, **1417**), (±)-gelliusine E (**1418**, **1419**), and (±)-gelliusine F (**1420**, **1421**). Echinosulfonic acids B

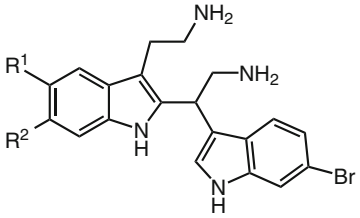
(**1422**) and C (**1423**) along with echinosulfone A (**1424**) are produced by the Southern Australian sponge *Echinodictyum* sp. (*1361*). Echinosulfonic acid A (**1422**, ethoxy in place of methoxy) is probably an artifact produced during storage of the sponge in ethanol. The New Caledonian sponge *Psammoclemma* sp. has afforded echinosulfonic acid D (**1425**) along with echinosulfonic acid B (**1422**) (*1362*). The Papua New Guinea sponge *Coscinoderma* sp. contains coscinamides A (**1426**) and C (**1427**), which are the first reported alkaloids from this genus (*1363*).



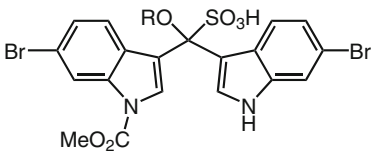
1414, 1415 (gelliusine C)



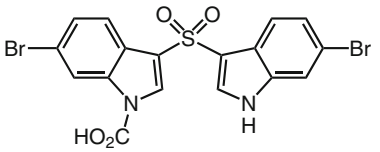
1416, 1417 (gelliusine D)



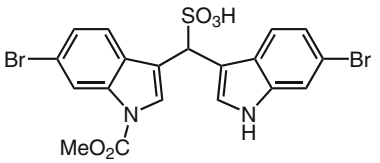
1418, 1419 R^1 = OH, R^2 = H (gelliusine E)
1420, 1421 R^1 = H, R^2 = Br (gelliusine F)



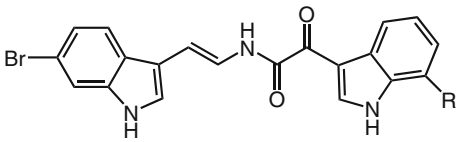
1422 R = Me (echinosulfonic acid B)
1423 R = H (echinosulfonic acid C)
R = Et (echinosulfonic acid A)



1424 (echinosulfone A)

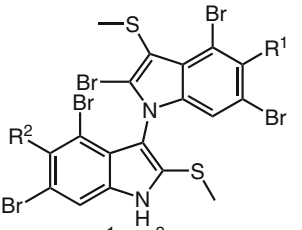


1425 (echinosulfonic acid D)

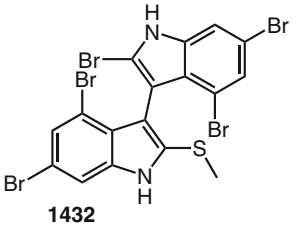


1426 R = H (coscinamide A)
1427 R = OH (coscinamide C)

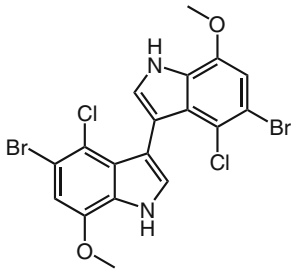
An Okinawan collection of the red alga *Laurencia brongniartii* yielded the five new polybromoindoles **1428**–**1432** (*1364*); the latter compound is similar to **1340** and **1341**. Halogenated biindole **1433** was isolated from the South China Sea green alga *Chaetomorpha basiretorsa* (*1365*). The Okinawan sponge *Dictyodendrilla* sp. provided the novel brominated bis-tryptamine dendridine A (**1434**) (*1366*). The colonial Philippine ascidian *Perophora namei* produces the complex fused indole perophoramidine (**1435**), which is the first metabolite to be reported from the genus *Perophora* (*1367*). The Antarctica tunicate *Aplidium cyaneum* (Fig. 3.21) produces aplicyanins A–F (**1436**–**1440**) (*1368*), which are related to the meridianins (**1381**–**1385**). Aplicyanins B (**1437**), D (**1439**), E (**1440a**), and F (**1440b**) exhibit cytotoxic and antimiotic activities. Aplicyanin E (**1440a**) was readily acetylated to aplicyanin F (**1440b**).



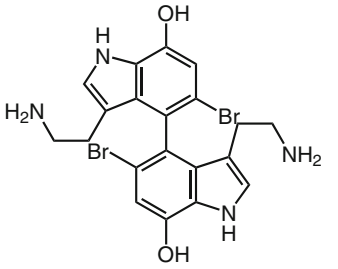
1428 $R^1 = R^2 = H$
1429 $R^1 = H$, $R^2 = Br$
1430 $R^1 = Br$, $R^2 = H$
1431 $R^1 = R^2 = Br$



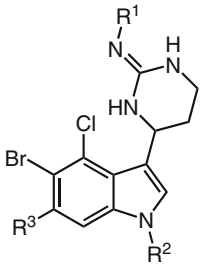
1432



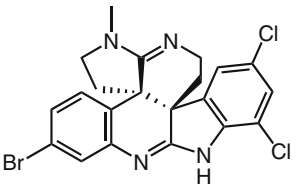
1433



1434 (dendridine A)



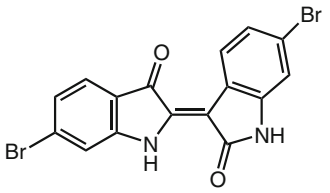
1436 $R^1 = R^2 = R^3 = H$ (aplicyanin A)
1437 $R^1 = Ac$, $R^2 = R^3 = H$ (aplicyanin B)
1438 $R^1 = R^3 = H$, $R^2 = OMe$ (aplicyanin C)
1439 $R^1 = Ac$, $R^2 = OMe$, $R^3 = H$ (aplicyanin D)
1440a $R^1 = H$, $R^2 = OMe$, $R^3 = Br$ (aplicyanin E)
1440b $R^1 = Ac$, $R^2 = OMe$, $R^3 = Br$ (aplicyanin F)



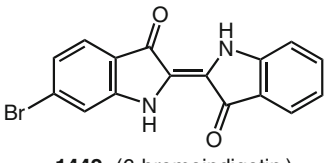
1435 (perophoramidine)

The most famous halogenated bis-indole is Tyrian purple, the dibromo analog of indigo (*1*). This colorful mollusc metabolite, which was the major component of the ancient dye, continues to receive attention (*1369–1374*). Additional studies of Tyrian purple from various molluscs have revealed the presence of 6,6′-dibromoindirubin (**1441**) (*1375*), 6-bromoindigotin (**1442**) (*1375, 1376*), 6-bromoisatin (**1443**) (*1377, 1378*), 6-bromoindoxyl (**1444**) (*1378*), **1445** (*1378*), **1446** (*1378*), 6-bromoindirubin (**1447**) (*1379*), and 6′-bromoindirubin (**1448**) (*1379*). The brominated indirubins are potent and selective kinase inhibitors (*1379*). A direct-exposure

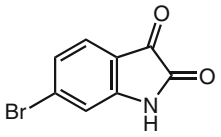
mass spectrometry technique has been developed to characterize the constituents of indigo and Tyrian purple extracts (*1380*). A *Streptomyces* sp. has furnished the chlorinated indigo glycosides akashins A–C (**1449**–**1451**), which display significant antitumor activity against various human cell lines (*1381*).



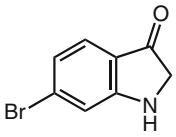
1441 (6,6'-dibromoindirubin)



1442 (6-bromoindigotin)



1443



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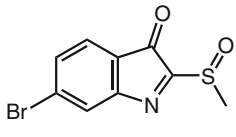

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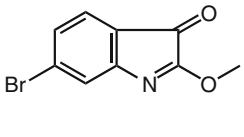

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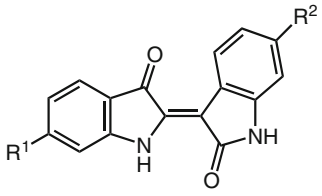
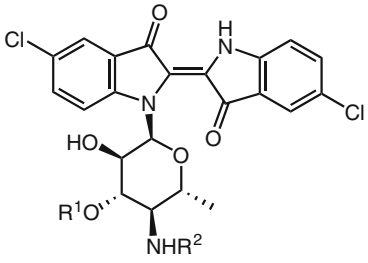
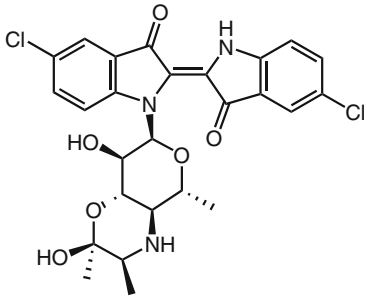


1447 R^1 = H, R^2 = Br (6-bromoindirubin)
1448 R^1 = Br, R^2 = H (6-bromoindirubin)



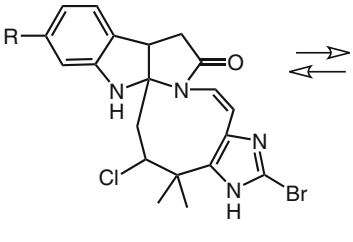


1449 R^1 = R^2 = H (akashin A)
1450 R^1 = H, R^2 = $COCH_3$ (akashin B)

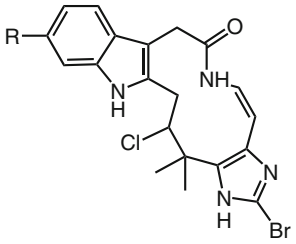
1451 (akashin C)

As illustrated in the first survey, marine bryozoans ("moss animals") are preeminent practitioners of organic synthesis, particularly in the production of halogenated indoles. Thus, the North Sea bryozoan *Securiflustra securifrons* produces

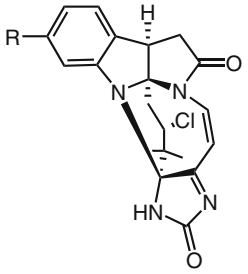
securamines A-G (**1452**–**1458**). Compounds A (**1452**) and B (**1453**) are in equilibrium with their tautomers, securines A and B, as shown (*1382, 1383*). The prolific North Sea bryozoan *Flustra foliacea* (Fig. 3.19) has yielded the new hexahydropyrrolo[2,3-*b*]indole **1459** (*1321*). Total syntheses of the structurally related and previously known flustramines A–C and flustramides A and B have been achieved (*1384–1386*), as has the total synthesis of the known chartelline C (*1387, 1388*).



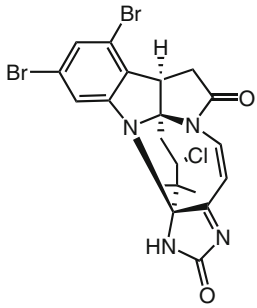
1452 R = H (securamine A)
1453 R = Br (securamine B)



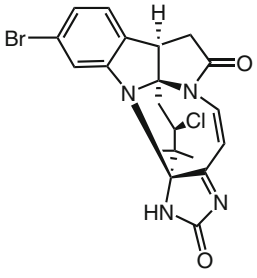
R = H (securine A)
R = Br (securine B)



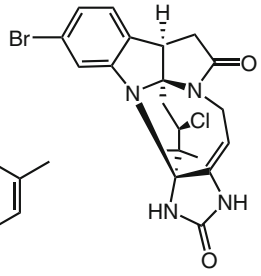
1454 R = Br (securamine C)
1455 R = H (securamine D)



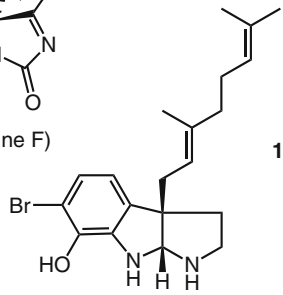
1456 (securamine E)



1457 (securamine F)

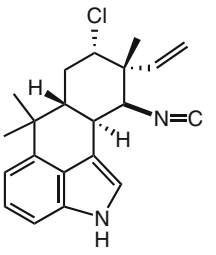


1458 (securamine G)

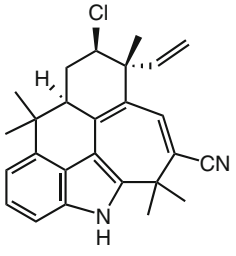


1459

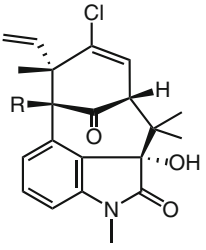
Several species of blue-green algae contain four groups of complex halogenated (and nonhalogenated) indoles: hapalindoles, ambiguines, fischerindoles, and welwitindolinones (*1*). New examples of these interesting metabolites have been discovered, such as 12-*epi*-hapalindole G (**1460**) from the blue-green alga *Hapalosiphon laingii* (*1389*) and ambiguine G nitrile (**1461**) from *Hapalosiphon delicatulus*, the first nitrile found in the Stigonemataceae (*1390*). The terrestrial *Fischerella muscicola* contains 3-hydroxy-*N*-methylwelwitindolinone C isonitrile (**1462**) and 3-hydroxy-*N*-methylwelwitindolinone C isothiocyanate (**1463**) (*1391*). The welwitindolinones can reverse P-glycoprotein mediated multiple drug resistance (*1392, 1393*). Total syntheses of the previously known welwitindolinone A and fischerindoles I and G have been accomplished (*1394, 2648*). The first ergoline marine alkaloids, pibocins A (**1464**) and B (**1465**), were isolated from the Far Eastern ascidian *Eudistoma* sp. (*1395, 1396*).



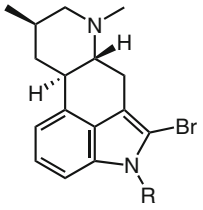
1460 (12-*epi*-hapalindole G)



1461 (ambiguine G nitrile)

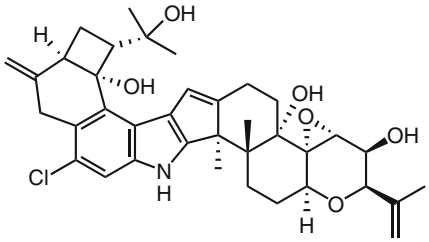


1462 R = NC
1463 R = NCS

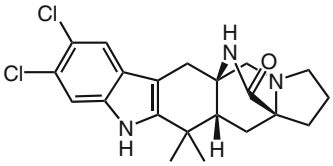


1464 R = H (pibocin A)
1465 R = OMe (pibocin B)

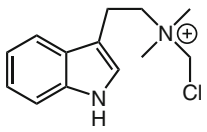
A new halogen-containing member of the penitrem family of indole-diterpenoids, which have insecticidal activity (*1397*), is thomitrem A (**1466**) from *Penicillium crustosum* (*1398*). The novel dichlorinated calmodulin inhibitor, malbrancheamide (**1467**), was characterized from the fungus *Malbranchea aurantiaca* (*1399*). The microbe *Streptomyces rugosporus* produces pyrroindomycin B (**1468**), which is active against both methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococci* (*1400*). The Chinese shrub *Acacia confusa* has yielded the unusual chlorotryptamine alkaloid **1469**, which does not appear to be an artifactual dichloromethane adduct (*1401*).



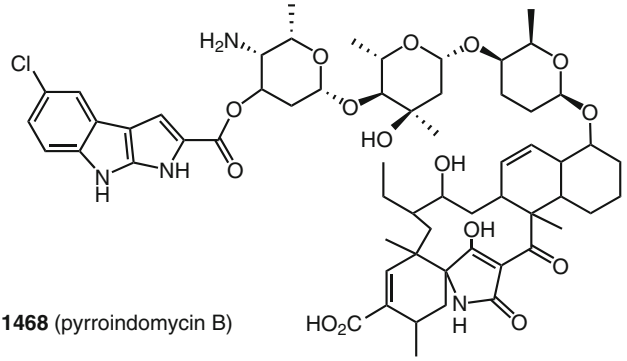
1466 (thomitrem A)



1467 (malbrancheamide)



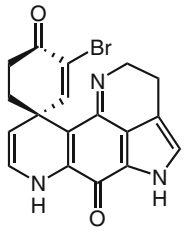
1469



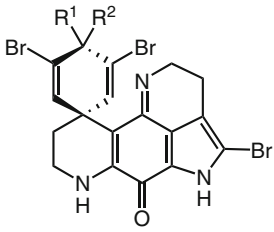
1468 (pyrroindomycin B)

The earlier survey documented a number of indoloquinones and related compounds, the discorhabins, makaluvamines, and batzellines (*1*), which have anticancer activity and are DNA topoisomerase II inhibitors (*1402*). Several new examples of these fused indoles have been uncovered in the interim (*1403, 1404*). The Antarctic sponge *Latrunculia apicalis* contains the novel discorhabdin G (**1470**), which is a feeding deterrent towards the sea star *Perknaster fuscus*, the major Antarctic sponge predator (*1405, 1406*). A South African undescribed latrunculid sponge has afforded 14-bromodiscorhabdin C (**1471**) and 14-bromodihydrodiscorhabdin C (**1472**), which are the first discorhabdins having a 2-bromoindole unit (*1407*). Discorhabdin P (**1473**) is present in the Bahamian sponge *Batzella* sp., and inhibits phosphatase activity (*1408*). The Australian sponges *Latrunculia purpurea*, *Zyzzya massalis*, *Zyzzya fuliginosa*, and *Zyzzya* spp. contain discorhabdin Q (**1474**) (*1409*). Discorhabdins S (**1475**), T (**1476**), and U (**1477**) were isolated from the deep-water Caribbean sponge *Batzella* sp. (*1410*). The newly classified South African sponges *Tsitsikamma pedunculata*, *Tsitsikamma favus*, *Latrunculia bellae*, and *Strongylodesma algoensis* yielded 3-dihydro-7,8-dehydrodiscorhabdin C

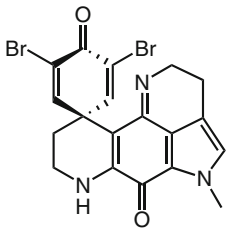
(**1478**), 14-bromo-3-dihydro-7,8-dehydrodiscorhabdin C (**1479**), discorhabdin V (**1480**), and 14-bromo-1-hydroxydiscorhabdin V (**1481**) (*1411*). The novel dimeric discorhabdin W (**1482**) is present in the New Zealand sponge *Latrunculia* sp. and exhibits potent cytotoxicity against the P388 murine leukemia cell line (*1412*). The total synthesis of the previously known discorhabdin A has been achieved (*1413, 1414*), as have semi-syntheses of discorhabdins P (**1473**) and U (**1477**) (*1415*).



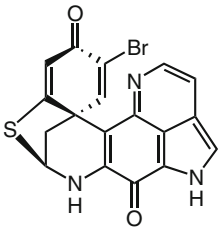
1470 (discorhabdin G)



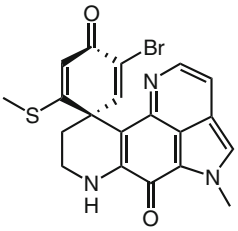
1471 R^1,R^2 = O
1472 R^1 = OH, R^2 = H



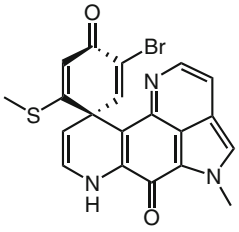
1473 (discorhabdin P)



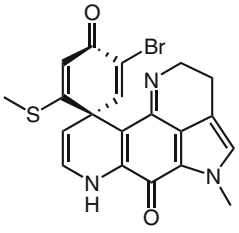
1474 (discorhabdin Q)



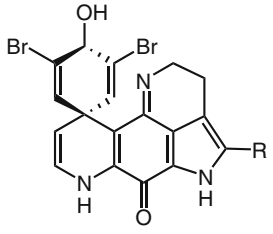
1475 (discorhabdin S)



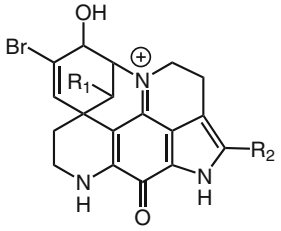
1476 (discorhabdin T)



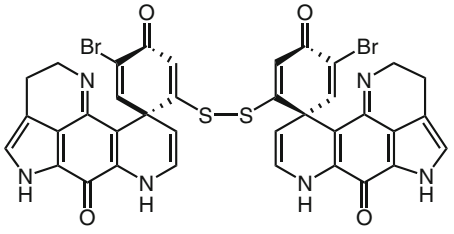
1477 (discorhabdin U)



1478 R = H
1479 R = Br

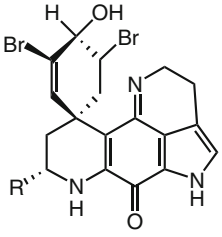


1480 (discorhabdin V)
1481

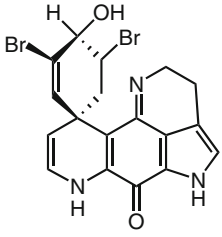


1482 (discorhabdin W)

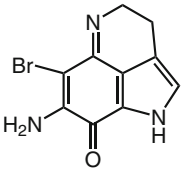
Related to the discorhabdins are epinardins B–D (**1483–1485**), which were isolated from undetermined deep-water green demosponges from pre-Antarctic Indian Ocean waters (*1416*). Epinardin C (**1485**) is strongly cytotoxic towards doxorubicin-resistant L1210/DX tumor cells. The Philippino sponge *Zyzzya fuliginosa* contains makaluvamine N (**1486**) in addition to five related known compounds (*1417*). A study of this sponge from Papua New Guinea has yielded batzelline D (**1487**) and isobatzelline E (**1488**) (*1418*). Four collections of *Zyzzya* were analyzed for antitumor activity and three nonhalogenated makaluvamines were the most potent (*1419*). A deep-water *Batzella* sponge from the Bahamas has furnished secobatzelline A (**1489**), which is a potent inhibitor of the phosphatase activity of calcineurin and the peptidase function of CPP32 (*1420*). The Jamaican sponge *Smenospongia aurea* contains makaluvamine O (**1490**) (*1421*).



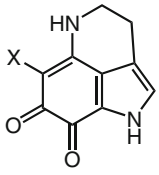
1483 R = H (epinardin B)
1484 R = OMe (epinardin D)



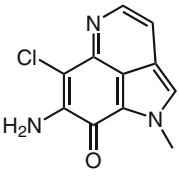
1485 (epinardin C)



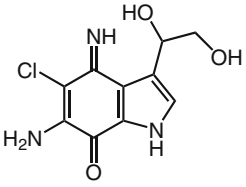
1486 (makaluvamine N)



1487 X = Cl (batzelline D)
1490 X = Br (makaluvamine O)



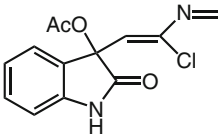
1488 (isobatzelline E)



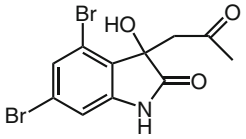
1489 (secobatzelline A)

Several halogenated metabolites with an oxidized indole ring have been discovered since the first survey (*1*). Indisocin (**1491**) was isolated from cultures of the actinomycete *Nocardia blackwellii* and displays strong antimicrobial activity against a range of both Gram-positive and Gram-negative bacteria and fungi (*1422*). The Floridian bryozoan *Amathia convoluta* produces convolutamydines A–E (**1492–1496**) (*1423–1425*), and total syntheses of convolutamydines A and B

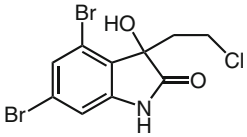
established their absolute configuration (*1426–1428*). The Indian Ocean sponge *Iotrochota purpurea* contains matemone (**1497**), which inhibits division of sea-urchin eggs (*1429*). Cynthichlorine (**1498**) was isolated from the Moroccan tunicate *Cynthia savignyi* and displays both antifungal and antibacterial activity (*1430*).



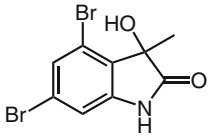
1491 (indisocin)



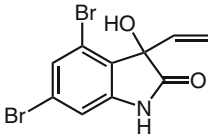
1492 (convolutamydine A)



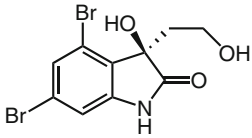
1493 (convolutamydine B)



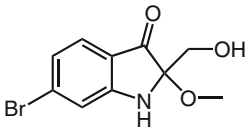
1494 (convolutamydine C)



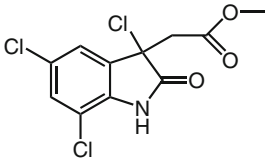
1495 (convolutamydine D)



1496 (convolutamydine E)



1497 (matemone)



1498 (cynthichlorine)

3.14.3 Carbazoles

Newly discovered halogenated carbazoles will be presented in a future volume.

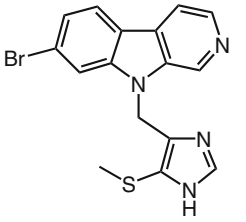
3.14.4 Indolocarbazoles

Although no new natural halogenated indolocarbazoles were reported following the 1996 survey (*1*), an enormous effort has focused on the discovery of synthetic analogs of the chlorine-containing rebeccamycin (*1431, 1432*), comprising fluoro-indolocarbazoles (*1432, 1433*), sugar analogs (*1434*), and others (*1435, 1436*),

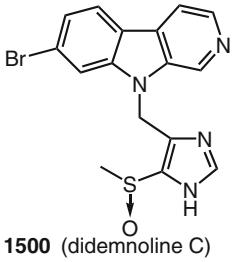
including combinatorial biosynthesis (*1437*). A synthetic rebeccamycin analog is in phase II trials for metastatic renal cell cancer (*1438*). The biosynthesis of rebeccamycin is also of interest (*1439–1441*).

3.14.5 Carbolines

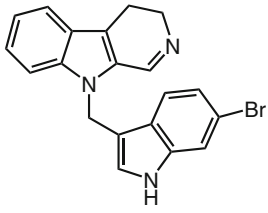
The previous survey presented more than 20 halogenated carbolines from ascidians of genus *Eudistoma*, *Ritterella*, and others (*1*). The Mariana Islands ascidian *Didemnum* sp. has afforded didemnolines A (**1499**) and C (**1500**), along with two nonhalogenated analogs (*1442*). A Western Australia *Eudistoma* sp. ascidian contains 19-bromoisoeudistomin U (**1501**) (*1443*), and the Australian ascidian *Pseudodistoma aureum* provided eudistomin V (**1502**) (*1444*). A Palau *Eudistoma gilboverde* has afforded 2-methyleudistomin D (**1503**), 2-methyleudistomin J (**1504**), and 14-methyleudistomidin C (**1505**) (*1445*). The latter metabolite displays excellent cytotoxicity towards four different human tumor cell lines. The Palauan sponge *Plakortis nigra*, which was collected at a depth of 380 feet, contains plakortamines A–D (**1506–1509**). These compounds are active against the HCT-116 human colon cell line with **1507** being the most active (*1446*). Total syntheses of several eudistomins are known (*1447, 1448*).



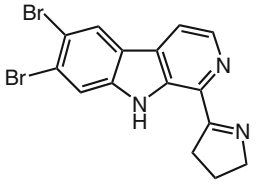
1499 (didemnoline A)



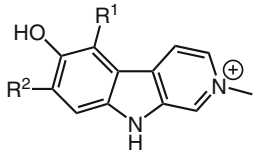
1500 (didemnoline C)



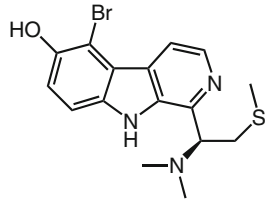
1501 (19-bromoisoeudistomin U)



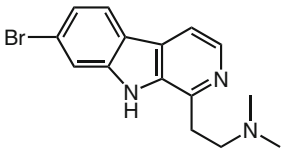
1502 (eudistomin V)



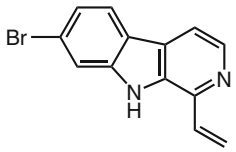
1503 R^1 = Br, R^2 = H (2-methyleudistomin D)
1504 R^1 = H, R^2 = Br (2-methyleudistomin J)



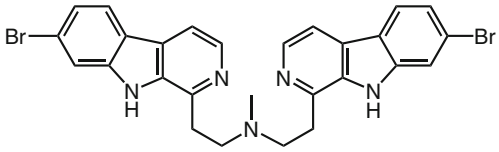
1505 (14-methyleudistomidin C)



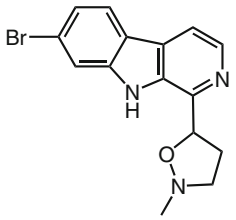
1506 (plakortamine A)



1507 (plakortamine B)

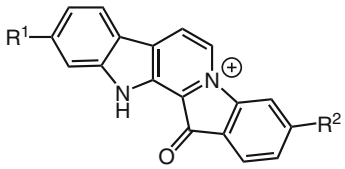


1508 (plakortamine C)

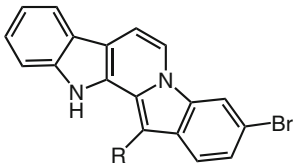


1509 (plakortamine D)

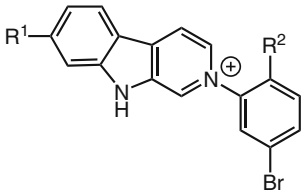
Studies of the sponge *Fascaplysinopsis reticulata* and the tunicate *Didemnum* sp. (Fig. 3.20) have identified several brominated derivatives of the previously known nonbrominated fascaplysin and reticulatine, including 3-bromofascaplysin (**1510**), 14-bromoreticulatine (**1511**), and 14-bromoreticulatate (**1512**) (*1449*). Further investigation of these organisms uncovered 10-bromofascaplysin (**1513**), 3,10-dibromofascaplysin (**1514**), 3-bromohomofascaplysin B (**1515**), 3-bromohomofascaplysin B-1 (**1516**), 3-bromohomofascaplysin C (**1517**), 7,14-dibromoreticulatine (**1518**), 14-bromoreticulatol (**1519**), 3-bromosecofascaplysin A (**1520**), and 3-bromosecofascaplysin B (**1521**) (*1450*). The fresh water cyanobacterium *Nostoc* 78-12A has provided nostocarboline (**1522**), which was synthesized for structural confirmation (*1451, 1452*). Nostocarboline is a potent butyrylcholinesterase inhibitor, comparable to the Alzheimer's disease drug galanthamine. This β-carboline and some derivatives are also potent algicides (*1452*).



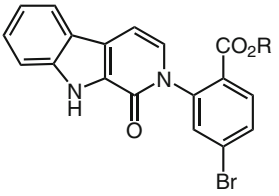
1510 R^1 = H, R^2 = Br (3-bromofascaplysin)
1513 R^1 = Br, R^2 = H (10-bromofascaplysin)
1514 R^1 = R^2 = Br (3,10-bromofascaplysin)



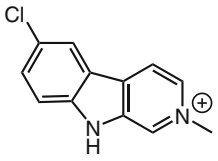
1515 R = $COCO_2Me$ (10-bromohomofascaplysin B)
1516 R = $COCO_2Et$ (3-bromohomofascaplysin B-1)
1517 R = CHO (3-bromohomofascaplysin C)



1511 R^1 = H, R^2 = CO_2Me (14-bromoreticulatine)
1512 R^1 = H, R^2 = CO_2 (14-bromoreticulatate)
1518 R^1 = Br, R^2 = CO_2Me (7,14-dibromoreticulatine)
1519 R^1 = H, R^2 = OH (14-bromoreticulatol)



1520 R = Me (3-bromosecofascaplysin A)
1521 R = H (3-bromosecofascaplysin B)



1522 (nostocarboline)

3.14.6 Quinolines and Other Nitrogen Heterocycles

Unlike π-excessive nitrogen heterocycles (pyrroles, indoles), π-deficient nitrogen heterocycles are much less reactive towards electrophilic halogenation, and relatively few halogenated π-deficient heterocycles are found naturally (*1*). The Thai spiny herb *Acanthus ilicifolius* contains several benzoxazinoid glucosides, including the chlorine-containing **1523** (*1453*). This medicinal plant is distributed in the mangroves of southern Thailand. The *N*-hydroxy derivative, **1524**, of **1523** is found in the medicinal mangrove plant *Acanthus ebracteatus* (*1454*). The sponge *Hyrtios erecta* has furnished the novel quinolones **1525** and **1526** (*1334*). A collection of a Puerto Rican *Lyngbya majuscula* cyanobacterium has yielded **1527** (*853*), and three novel tetrahydroquinolines, **1528**–**1530**, were characterized from the red alga *Rhodomela confervoides* (*1455*). The Palau bryozoan *Caulibugula intermis*

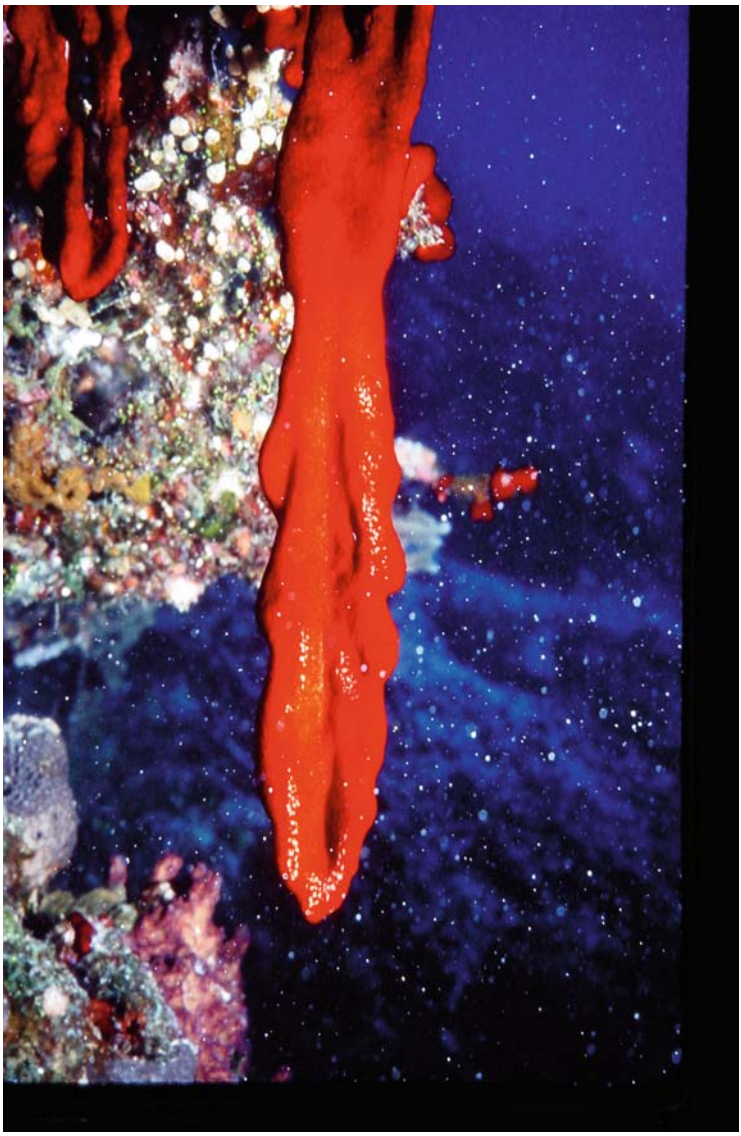
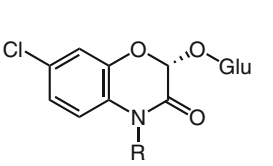


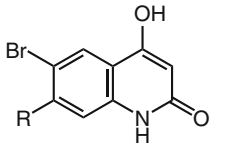
Fig. 3.20 *Didemnum* sp., a tunicate that contains the fascaplysin alkaloids **1510–1521** (Photo: F. J. Schmitz)

contains caulibugulones B (**1531**) and C (**1532**), along with four nonhalogenated analogs (*1456*). These structures were confirmed by chemical interconversion (*1456*) and total synthesis (*1457*), and the compounds display cytotoxicity (*1456*)

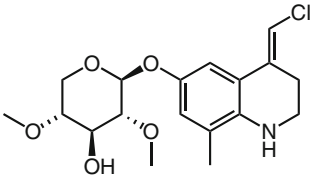
and potent phosphatase inhibitory activity (*1457*). The amide of the previously known virantmycin (*1*), benzastatin C (**1533**), is produced by *Streptomyces nitrosporeus* (*1458, 1459*). This compound is a potent free radical scavenger. The relative and absolute stereochemistry of (–)-virantmycin have been established by synthesis (*1460, 1461*). The New Zealand bryozoan *Euthyroides episcopalis* contains the novel quinone methides, euthyroideones A–C (**1534**–**1536**) (*1462*). Chlorodesnkolbisine (**1537**) was characterized from the African traditional medicine plant *Teclea nobilis* (*1463*). This chlorohydrin is detected in crude hexane extracts of the plant and is excluded as an artifact. Likewise, the new acridone alkaloid A6 (**1538**), which is found in several *Ruta* plants (*Ruta bracteosa*, *Ruta macrophylla*, *Ruta chalepensis*), is not formed when the corresponding allylic alcohol (gravacridonol) is heated with HCl, and, therefore, **1538** is judged not to be artifactual (*1464*).



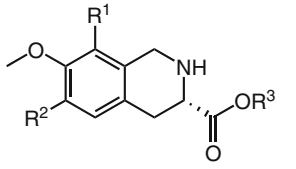
1523 R = H
1524 R = OH



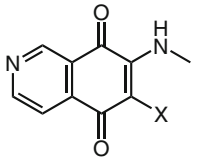
1525 R = H
1526 R = Br



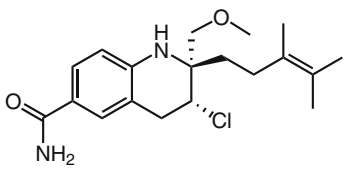
1527



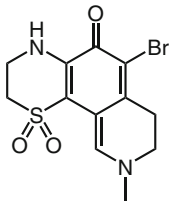
1528 R^1 = Br, R^2 = OH, R^3 = H
1529 R^1 = Br, R^2 = OH, R^3 = Me
1530 R^1 = OH, R^2 = Br, R^3 = Me



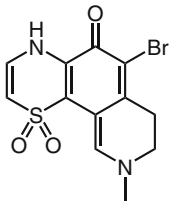
1531 X = Br (caulibugulone B)
1532 X = Cl (caulibugulone C)



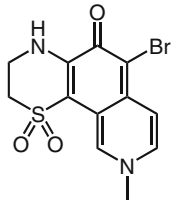
1533 (benzastatin C)



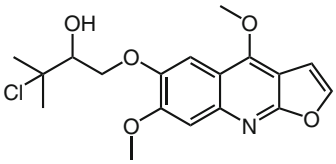
1534 (euthyroideone A)



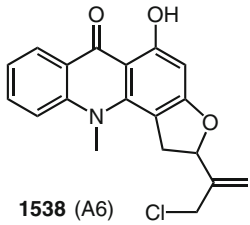
1535 (euthyroideone B)



1536 (euthyroideone C)

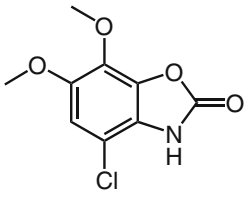


1537 (chlorodesnkolbisine)



1538 (A6)

The simple auxin inhibitor, 4-chloro-6,7-dimethoxy-2-benzoxazolinone (**1539**), was isolated from maize (*Zea mays*) (*1465*), as was the related 5-chloro-6-methoxy-2-benzoxazolinone (**1540**), which causes growth inhibition of crabgrass, ryegrass, lettuce, and oats (*1466*). The egg masses of three muricid molluscs (*Trunculariopsis trunculus*, *Ceratostoma erinaceum*, *Trophon geversianus*) contain 2,4,5-tribromo-1*H*-imidazole (**1541**) (*1467*), and the Indian medicinal plant *Jatropha curcas* has afforded chlorinated imidazole **1542** (*1468*). The structure of the *Streptomyces griseoluteus* metabolite 593A is incorrectly shown in the first survey ((*1*), compound "**1553**") and should be revised as shown **ZZ** (*1469*). The extraordinary cyclic *N*-bromoimide **1543** is claimed to be produced by the sponge *Rhaphisia pallida* (*1470*). The novel antifungal antibiotics atpenins A4 (**1544**) and A5 (**1545**) are produced by a *Penicillium* sp. and possess unique chloroalkane side chains (*1471*). X-ray crystallography supports the 2-hydroxypyridine tautomer.



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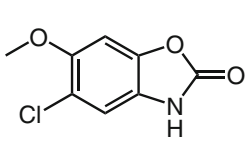

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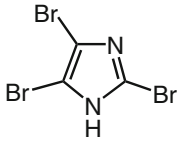

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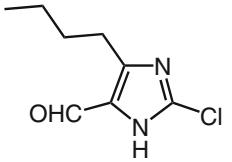

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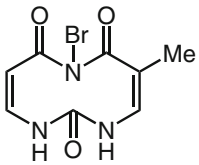

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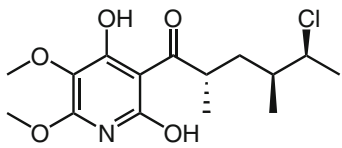
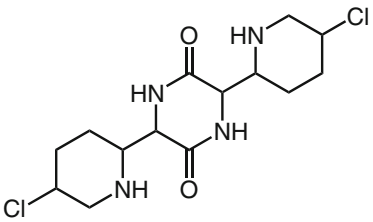
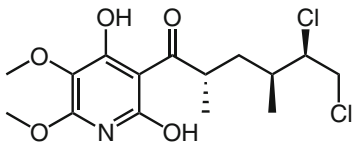


1544 (atpenin A4)

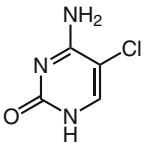


ZZ (593A)



1545 (atpenin A5)

As reported in the first survey, several halogenated nucleic acid bases and nucleosides have been isolated from natural sources. These compounds are generally thought to arise from the action of myeloperoxidase on halide in the presence of DNA (*1*). New examples of halogenated nucleic acid bases and nucleosides include 5-chlorocytosine (**1546**) and 5-chlorodeoxycytidine (**1547**) from salmon sperm (*1472*). Kumusine (**1548**) was isolated from the Indonesian sponge *Theonella* sp. (*1473*), and as "trachycladine A" from the Western Australian sponge *Trachycladus laevispirulifer* (*1474*), and later from the sponge *Theonella cupola* (*1475*). The ascidian *Didemnum voeltzkowi* contains 5′-deoxy-3-bromotubercidin (**1549**) along with the previously known iodo analog (*1476*). The sponge *Phakellia fusca* has yielded five 5-fluorouracil derivatives **1550–1554** (*1477*). The action of myeloperoxidase on human inflammatory tissue produces 5-chlorouracil (**1555**) (*1478, 1479*), 5-bromouracil (**1556**) (*1478, 1480*), and 8-chloroadenine (**1557**) (*1481*), each of which is considered as being natural. It has been suggested that these halogenated nucleic acid bases, which are products of inflammation, may exert cytotoxic and mutagenic effects (*1478–1480, 1482, 1483*). Thus, the incorporation of 5-bromouracil into DNA results in mutagenesis (*1482*).



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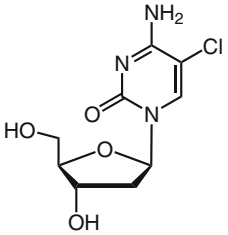

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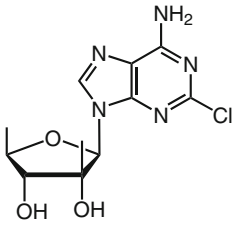
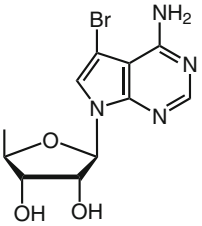


1548 (kumusine)



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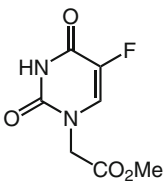

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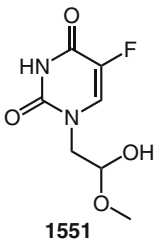

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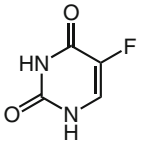

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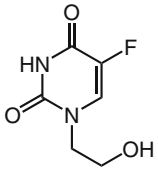

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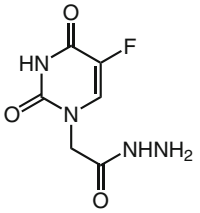

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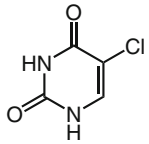

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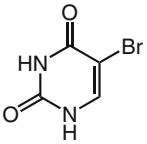

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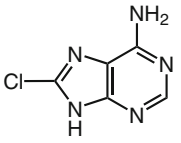
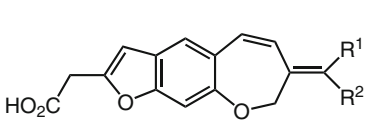


1557

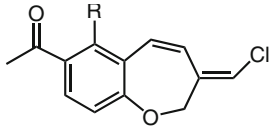
While there are no newly reported naturally occurring benzodiazepines since the first survey (*1*), the interest in this area remains high. The current status of research and clinical implications has been reviewed (*1484*). It is noted that natural benzodiazepines, including seven known halogenated examples (*1*), are found in soil, plants, animal and human tissues, and are chemically identical to their pharmaceutical counterparts. The endogenous formation of benzodiazepines by plant cells (*Artemisia dracunculus* and *Solanum tuberosum*) has been demonstrated for delorazepam, temazepam, and diazepam (*1485*).

3.14.7 Benzofurans and Related Compounds

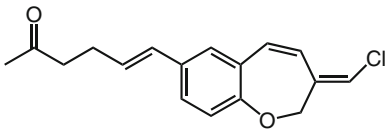
The novel heterocycles pterulinic acids (**1558** and **1559**) and pterulone (**1560**) were isolated from a *Pterula* sp. fungus (*1486, 1487*). These compounds are inhibitors of NADH:ubiquinone oxidoreductase (complex I). Pterulone B (**1561**) was characterized from cultures of *Pterula* sp. 82168 living on wood (*1488*). The wood-rotting fungus *Mycena galopus* has yielded the chlorinated 2,3-dihydro-1-benzoxepins **1562**–**1564** (*1489*). The two aldehydes **1565** and **1566** appear to be minor components in *Mycena galopus*, and several of these metabolites (**1559**, **1563**–**1566**) have been synthesized (*1490*). The novel dimeric polybrominated benzofurans, iantherans A (**1567**) and B (**1568**) are produced by the Australian sponge *Ianthella* sp., and display Na,K-ATPase inhibitory activity (*1491, 1492*). The aurones **1569** and **1570** were isolated from the brown alga *Spatoglossum variabile*, collected along the coast of Pakistan (*1493*). These metabolites are rare examples of the halogen atom residing on an unactivated benzene ring.



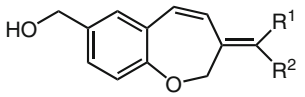
1558 R^1 = Cl, R^2 = H ((*E*)-pterulinic acid; major)
1559 R^1 = H, R^2 = Cl ((*Z*)-pterulinic acid; minor)



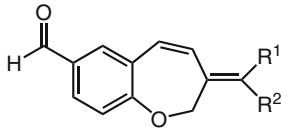
1560 R = H (pterulone)
1562 R = OH



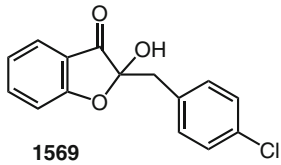
1561 (pterulone B)



1563 R^1 = Cl, R^2 = H
1564 R^1 = H, R^2 = Cl



1565 R^1 = Cl, R^2 = H
1566 R^1 = H, R^2 = Cl



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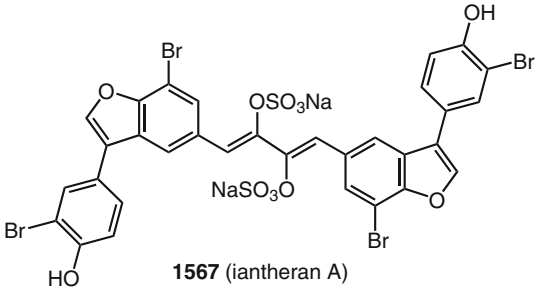
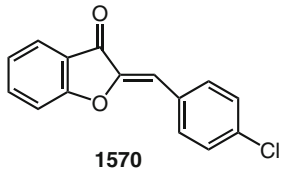


1567 (iantheran A)



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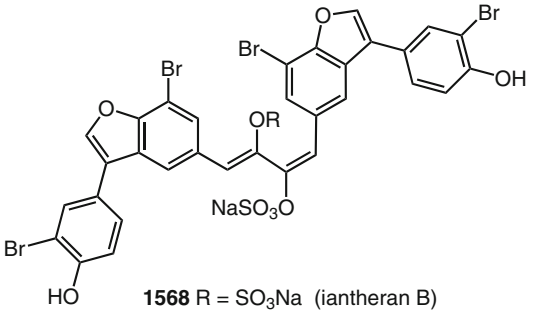
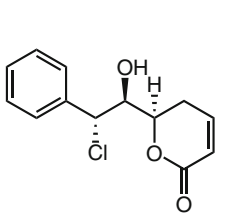


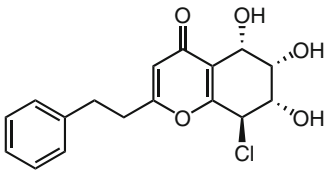
1568 R = SO_3Na (iantheran B)

3.14.8 Pyrones and Chromones

The medicinal plant *Goniothalamus amuyon* from Taiwan contains the pyrone 8-chlorogoniodiol (**1571**) with the absolute configuration shown (*1494*). A Taiwanese collection of withered wood of *Aguilaria sinensis* ("Agarwood"), which is used as incense and for medicinal purposes, has yielded the novel chromone **1572** (*1495*). Cultures of *Aspergillus candidus* F1484 produce the antifungal compound F1484 (**1573**) (*1496*).



1571 (8-chlorogoniodiol)



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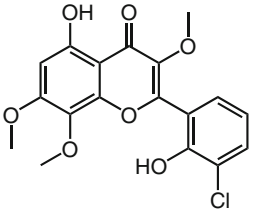
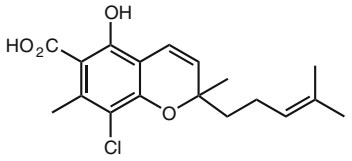


1573 (F1484)

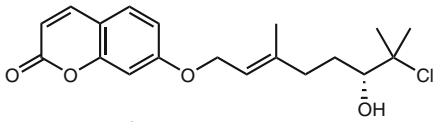
3.14.9 Coumarins and Isocoumarins

Cylindrocarpon olidum, a fungus isolated from the root knot nematode *Meloidogyne incognita*, contains the antifungal 8-chlorocannabiorcichromenic acid (**1574**) (*1497*).

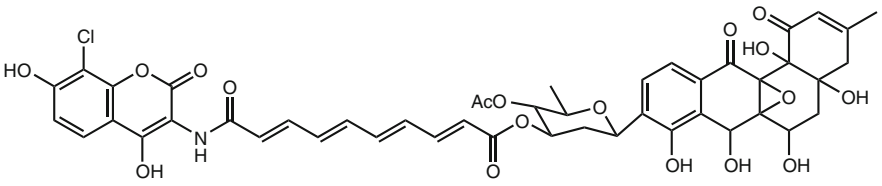
Bark from the Indonesian medicinal plant *Aegle marmelos* has provided chloromarmin (**1575**), having the absolute configuration shown (*1498*). The novel aminocoumarin simocyclinone D8 (**1576**) was isolated from cultures of *Streptomyces antibioticus* Tii 6040 and displays antibiotic activity on Gram-positive bacteria and cytotoxicity against various tumor cell lines (*1499, 1500*). A biosynthetic study of **1576** in an oxygen-18 rich atmosphere reveals the incorporation of four oxygen atoms (*1501*). The well-studied clorobiocin (chlorobiocin, RP 18,631) is one of many aminocoumarins from *Streptomyces* strains (*1502*), and a biosynthesis has been proposed (*1503*). The Western United States plant *Harbouria trachypleura* ("whiskbroom parsley") has yielded (±)-trachypleuranin B (**1577**), confirmed by total synthesis (*1504*). The rare folk medicinal Colombian herb *Niphogeton ternata* contains the new psoralen **1578** (8-methoxysaxalin) (*1505*), and the Tanzanian medicinal plant *Mondia whitei* ("Mbombongazi") has afforded 5-chloropropacin (**1579**), which is the first chlorinated example of the coumarinolignan family (*1506*).



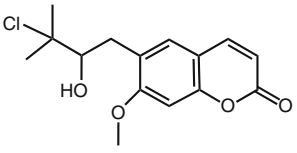
1574



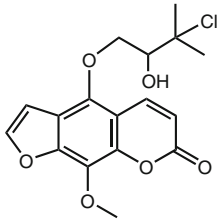
1575 (chloromarmin)



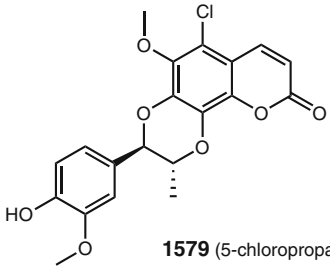
1576 (simocyclinone D8)



1577 (trachypleuranin-B)

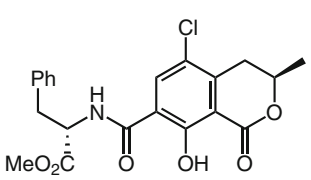


1578 (8-methoxysaxalin)

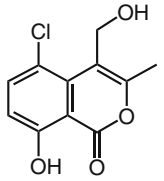


1579 (5-chloropropacin)

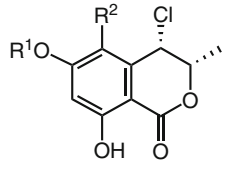
Several new chlorinated isocoumarins have been isolated since the first review (*1*), and an early review of naturally occurring isocoumarins is available (*1507*). The methyl ester (**1580**) of the notorious ochratoxin A was isolated from *Aspergillus ochraceus*, and is not considered being an artifact (*1508*). The wood-rotting fungus *Heterobasidion annosum* (= *Fomes annosus*) yielded isocoumarin **1581** (*1509*), and **1582–1584** were characterized from the ascomycete *Lachnum papyraceum* (*1510*). The fungus *Plectophomella* sp. has yielded the two mellein derivatives, 5-chloro-6-hydroxymellein (**1585**) and 5-chloro-4,6-dihydroxymellein (**1586**) (*1511*). The fungus *Periconia macrospinosa* is the source of several metabolites, which are of biosynthetic interest (*415, 416*), and this organism also produces the new **1587** (*416*). The absolute configuration of the previously known bromine-containing isocoumarin, hiburipyranone, has been established as (*R*) by total synthesis (*1512*). The cheese-associated fungus *Penicillium nalgiovense* produces dichlorodiaportin (**1588**) (*1513*), while the related methylated diaportins **1589** and **1590** are found in the cultured lichen mycobiont of *Graphis* sp. from a Philippines tree (*1514*). Avicennin A (**1591**) is a novel isocoumarin isolated from a mangrove entophytic fungus in the South China Sea (*1515*).



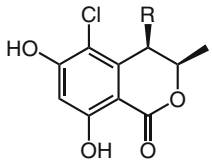
1580



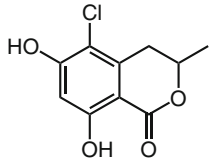
1581



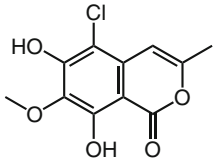
1582 R^1 = H, R^2 = H
1583 R^1 = H, R^2 = OH
1584 R^1 = Me, R^2 = H



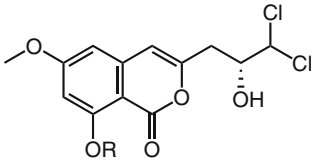
1585 R = H
1586 R = OH



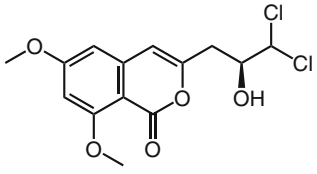
1587



1591 (avicennin A)

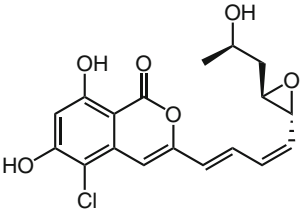


1588 R = H (dichlorodiaportin)
1589 R = Me

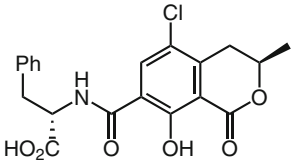


1590 ((10*S*)-8-methyldichlorodiaportin)

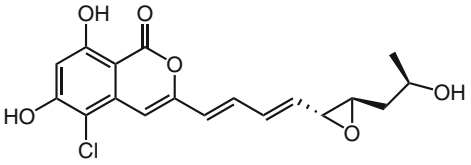
The novel chaetochiversins A (**1592**) and B (**1593**) were identified in the fungus *Chaetomium chiversii* living in association with the Sonoran desert plant *Ephedra fasciculata* (*1516*). The absolute configuration of **1592** was established by synthesis from the known radicicol. Tricyclic TMC-264 (**1594**) was isolated from the fungus *Phoma* sp. TC 1674 (*1517, 1518*), and graphislactone G (**1595**) was identified in the endophytic fungus *Cephalosporium acremonium* IFB-E007 residing in the roots of *Trachelospermum jasminoides* (*1519*).



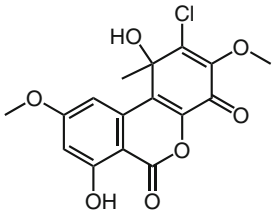
1592 (chaetochiversin A)



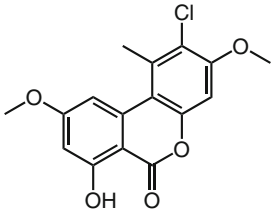
AAA (ochratoxin A)



1593 (chaetochiversin B)



1594 (TMC-264)

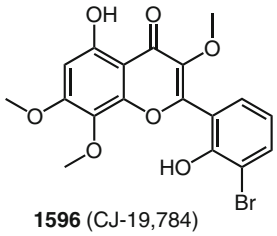


1595 (graphislactone G)

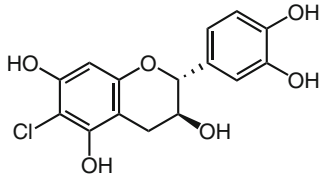
The mycotoxin ochratoxin A (**AAA**) (*1*), which is a possible human carcinogen, continues to receive extensive attention due to its presence in a myriad of foods and beverages (*1520, 1521*) and its well-established toxicity (teratogenicity, mutagenicity, immunotoxicity, genotoxicity, and carcinogenicity) (*1522–1524*). Major sources of ochratoxin A are grapes, must, and wine (*1525–1533*), cereals (*1534*), beer (*1535, 1536*), dried fruit (*1537*), roasted coffee (*1538*), and cocoa products and chocolate (*1539*).

3.14.10 Flavones and Isoflavones

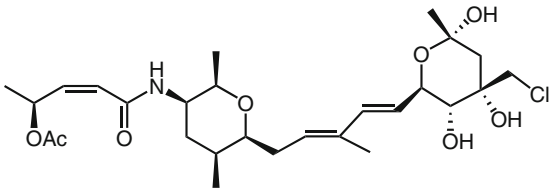
The bromine analog of chlorflavonin, CJ-19,784 (**1596**), is produced by the fungus *Acanthostigmella* sp. in the absence of added bromide ion in the culture medium (*1540*). This metabolite inhibits the growth of the pathogenic fungi *Candida albicans*, *Cryptococcus neoformans*, and *Aspergillus fumigatus*. The roots of the Turkish traditional plant *Rumex patientia* contain 6-chlorocatechin (**1597**), which is the first reported natural halogenated flavan-3-ol (*1541*).



1596 (CJ-19,784)



1597 (6-chlorocatechin)



1598 (FR 901463)

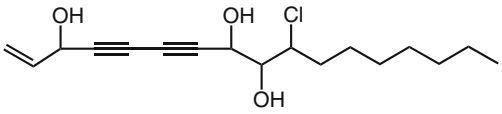
3.14.11 Carbohydrates

Despite the wide spread use of the artificial sweetener, "Splenda", which is a synthetic chlorinated carbohydrate, Nature has provided very few halogenated carbohydrates. The antitumor metabolite FR 901463 (**1598**) was isolated from a *Pseudomonas* sp. along with two nonchlorinated epoxides. FR 901463 is not an isolation artifact, being present in the culture medium prior to extraction and isolation (*1542–1544*).

3.15 Polyacetylenes

3.15.1 Terrestrial Polyacetylenes and Derived Thiophenes

The Colombian medicinal plant *Niphogeton ternata* contains the new polyacetylene **1599** (*1505*).



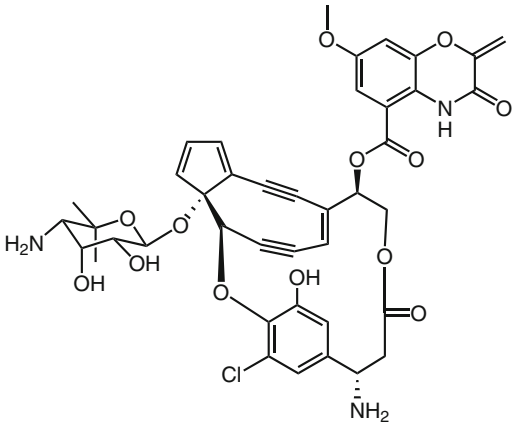
1599

3.15.2 Marine Polyacetylenes

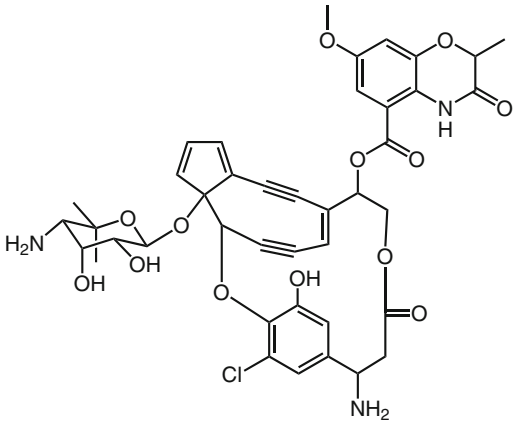
The reader is referred to the section on fatty acids (**3.8**), which includes brominated fatty acids containing multiple acetylene groups.

3.16 Enediynes

Although only a few new members of the extraordinary enediyne class of natural products have been discovered since the first survey (*1*), the powerful biological activity of these natural products, several of which contain halogen, has spurred intensive investigation of their biological activity (*1545–1548*). For example, the calicheamicin family of enediyne antitumor antibiotics continues to be a highlight in this area of natural products (*1549, 1550*). Similarly, the previously known C-1027 is of great interest (*1551*) with regard to its biosynthesis (*1552*), synthesis (*1553*), analog preparation (*1554*), mechanism of action (*1555*), and biological activity (*1556*). The absolute configuration of the C-1027 chromophore (**BBB**) has been established as shown (*1557*), and the new neoC-1027 chromophore (**1600**) was characterized from *Streptomyces globisporus* (*1558*).

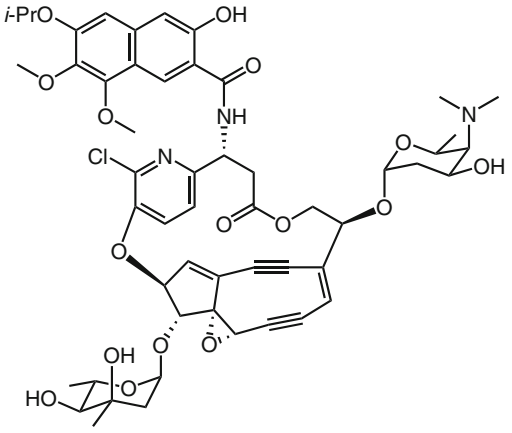


BBB (C-1027 chromophore)

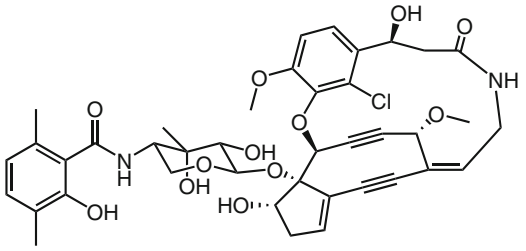


1600 (neoC-1027 chromophore)

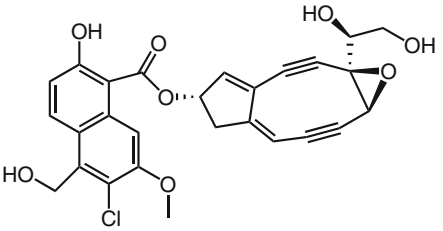
The previously known kedarcidin chromophore (*1*) is revised to **CCC** (*1559*), and the mechanism of action of this enediyne has been studied (*1560*). The new maduropeptin chromophore **1601** was isolated from *Actinomadura madurae*, which is associated with a protein of 14 amino acids (*1561–1563*). The non-protein associated enediyne N1999A2 (**1602**) was characterized from *Streptomyces* sp. AJ 9493 (*1564*), and confirmed by synthesis (*1565, 1566*).



CCC (kedarcidin chromophore)



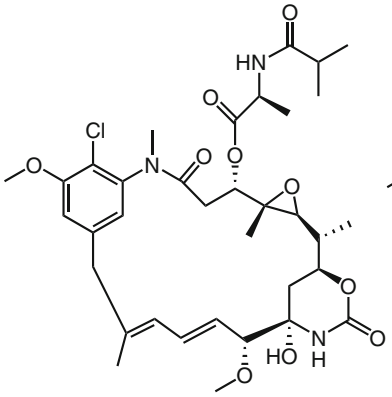
1601 (maduropeptin apoprotein methanol adduct)



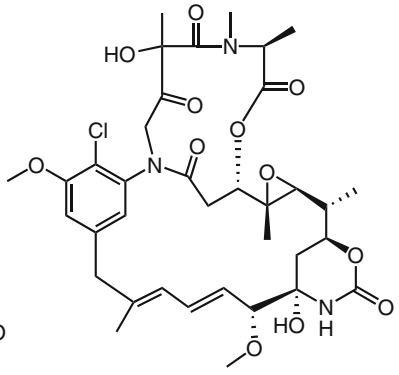
1602 (N1999-A2)

3.17 Macrolides and Polyethers

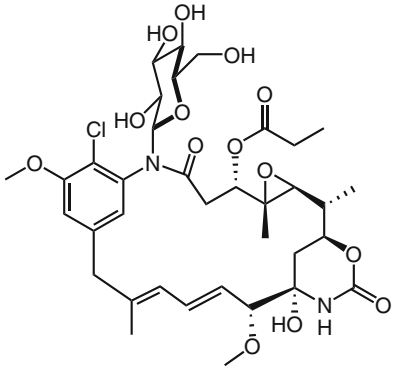
The large and diverse group of naturally occurring biologically active macrolides includes a number of halogenated examples (*1*). The chlorine-containing maytansinoids, which were once promising anticancer agents, nevertheless continue to receive attention (*1567*), and semisynthetic maytansines show promise as new anticancer agents (*1568*). The two new maytansinoids 2′-*N*-demethylmaytanbutine (**1603**) and maytanbicyclinol (**1604**) were isolated from the Kenyan plant *Maytenus buchananii* (*1569*), and the new ansamitocin ansamitocinoside P-2 (**1605**) is produced by *Actinosynnema pretiosum* ssp. *auranticum* (*1570*).



1603 (2′-*N*-demethylmaytanbutine)

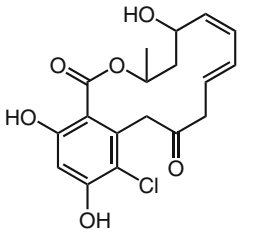


1604 (maytanbicyclinol)

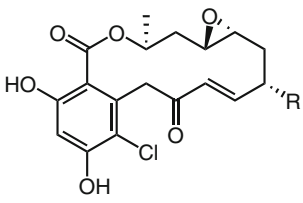


1605 (ansamitocinoside P-2)

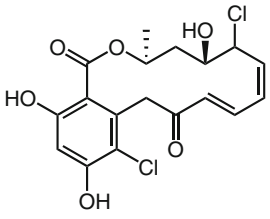
The previously known macrolide radicicol (= monorden A) (*1*) continues to be of interest for its multiplicity of biological activities, such as suppression of oncogene transformation (*1571, 1572*) and inhibition of the human malaria parasite *Plasmodium falciparum* (*1573*). The former activity has been of particular scrutiny, and several novel HSP90 synthetic radicicol analogs are promising anticancer agents (*1574–1576*). The new radicicol **1606** was isolated from the mycoparasite *Humicola fuscoatra* from *Aspergillus flavus* (*1577*). Two groups independently isolated a series of the new pochonins (*1578*) and monordens (*1579, 1580*), which are identical in some cases. Thus, whereas the fungus *Pochonia chlamydosporia* var. *catenulata* produces pochonins A (**1607**), B (**1608**), C (**1609**), D (**1610**), E (**1611**), and tetrahydromonorden (= tetrahydroradicicol) (**1612**) (*1578*), the fungus *Humicola* sp. FO-2942 yields monorden C (= pochonin A, **1607**), monorden D (= pochonin D, **1610**), and monorden E (**1613**) (*1579, 1580*). Diversity-oriented synthesis of the pochonins in a search for ATPase and kinase inhibitors has been reported (*1581*).



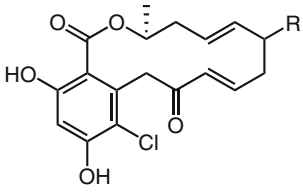
1606



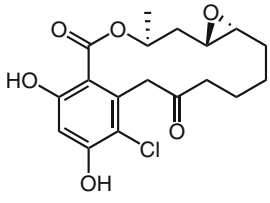
1607 R = H (pochonin A)
1608 R = OH (pochonin B)



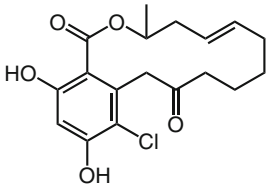
1609 (pochonin C)



1610 R = H (pochonin D)
1611 R = OH (pochonin E)



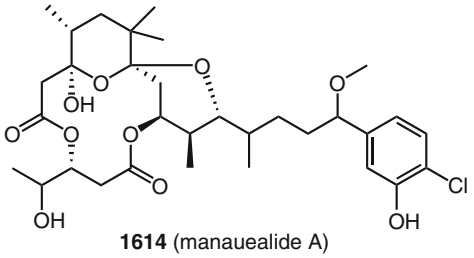
1612 (tetrahydromonorden)



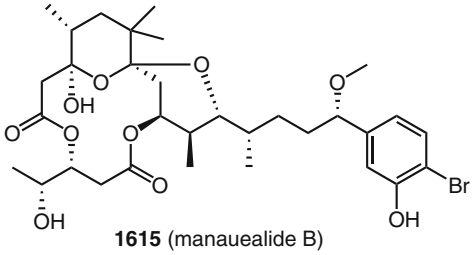
1613 (monorden E)

The previously known and notorious aplysiatoxin (a cause of "swimmer's itch") (*1*) is a protein kinase C inhibitor and has been the object of a structure–activity study (*1582*). The causative agents of a red alga *Gracilaria coronopifolia* poisoning

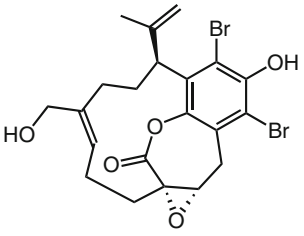
episode in Hawaii are reported to be manauealides A (**1614**) and B (**1615**), compounds that may be associated with a cyanobacterium (*1583*). Manauealide B is an isomer of aplysiatoxin. The novel metacyclophane floresolide C (**1616**) is found in the Indonesian ascidian *Aplidium* sp. (Fig. 3.21) (*1584*). The two macrolides, sporolides A (**1617**) and B (**1618**), were characterized from the marine actinomycete *Salinispora tropica* and have the absolute stereochemistry shown (*1585*).



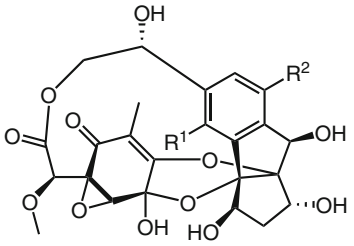
1614 (manauealide A)



1615 (manauealide B)

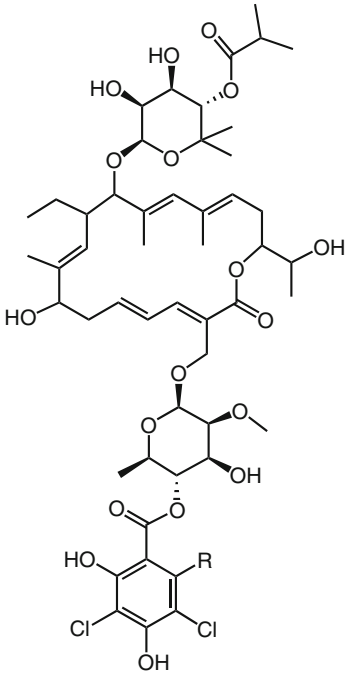


1616 (floresolide C)

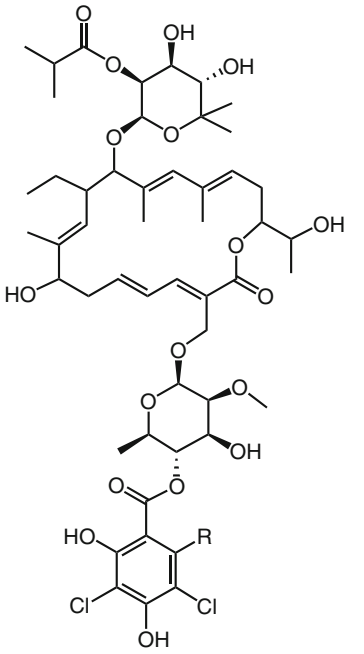


1617 R^1 = Cl, R^2 = H (sporolide A)
1618 R^1 = H, R^2 = Cl (sporolide B)

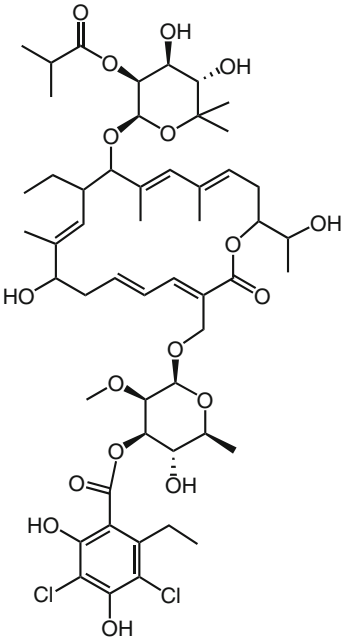
The extraordinarily complex and biologically important altohyrtins and spongistatins (*1*) have been the object of intense synthetic efforts that have clarified previous stereochemical ambiguities (*1586–1588*). The strain of *Actinoplanes deccanensis* produces lipiarmycins A3 (**1619**), A4 (**1620**) (*1589*), B3 (**1621**), and B4 (**1622** (*1590*). A group of very similar (or identical) metabolites to the lipiarmycins was isolated from both *Micromonospora echinospora* subsp. *armeniaca* called clostomicins A, B_1 (= lipiarmycin A_3, **1619**), B_2 (= lipiarmycin B_3, **1621**), C, and D (structures undetermined but each has two chlorines) (*1591, 1592*) and from *Dactylosporangium aurantiacum* subsp. *hamdenensis* named tiacumicins B (= lipiarmycin A_3, **1619**), C (= lipiarmycin B_3, **1621**), D (**1623**), E (**1624**), and F (**1625**, = clostomicin A) (*1593, 1594*).



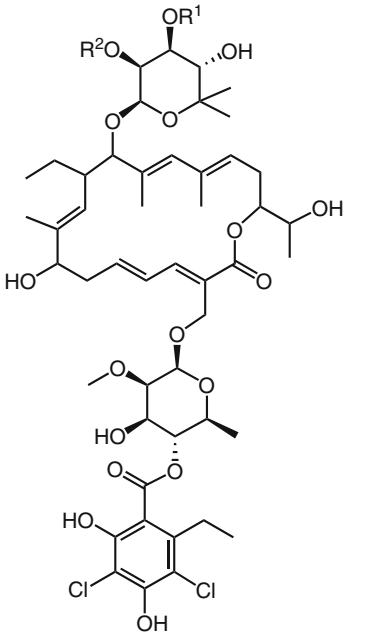
1619 R = Et (lipiarmycin A_3)
1620 R = Me (lipiarmycin A_4)



1621 R = Et (lipiarmycin B_3 = tiacumicin C)
1622 R = Me (lipiarmycin B_4)

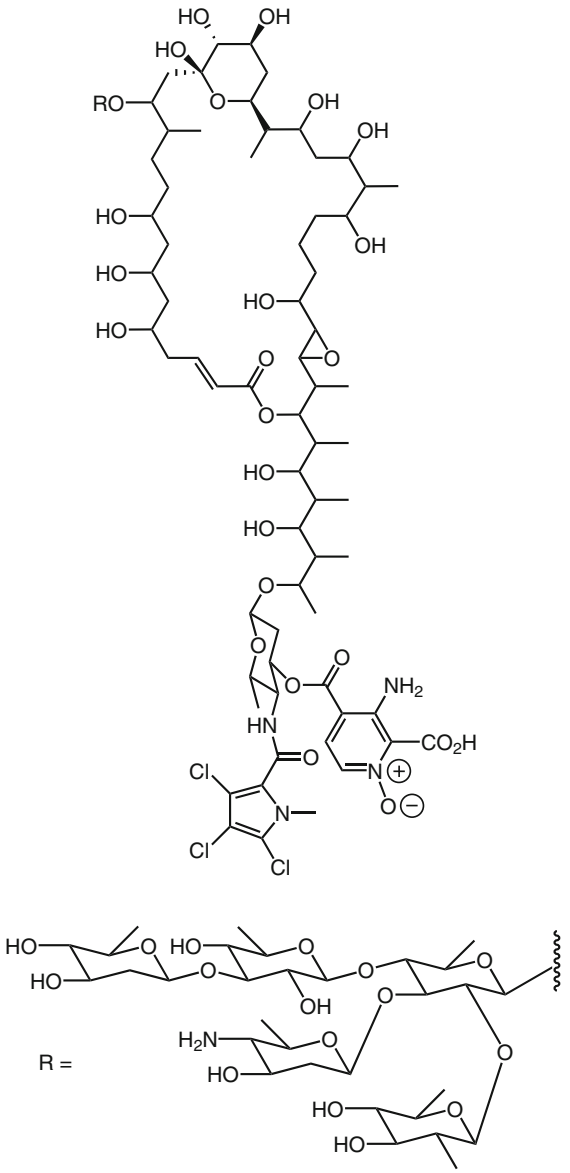


1623 (tiacumicin D)

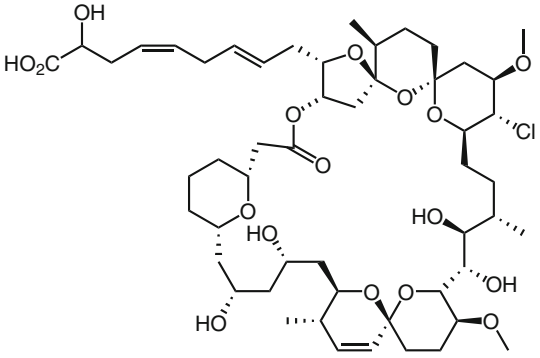


1624 R^1 = H, R^2 = COEt (tiacumicin E)
1625 R^1 = CO*i*-Pr, R^2 = H (tiacumicin F)

The highly complex chlorinated pyrrole-containing macrolide colubricidin A (**1626**) is produced in cultures of an unidentified *Streptomyces* species (*1595*). This metabolite displays excellent activity against Gram-positive bacteria. The Dominican sponge *Spirastrella coccinea* produces spirastrellolide A (**1627**), which is a potent and selective inhibitor of protein phosphatase 2A (*1596*) (revised later (*1597*)).



1626 (colubricidin A)

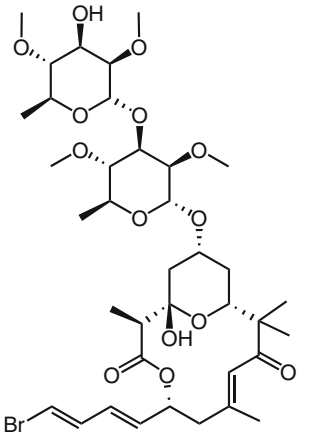


1627 (spirastrellolide A)

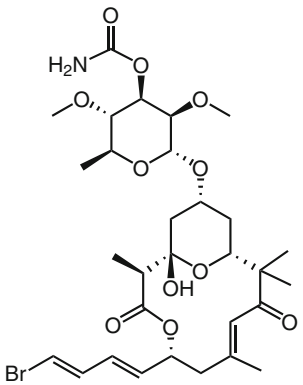
Fig. 3.21 This Indonesian ascidian *Aplidium* sp. produces the novel metacyclophane floresolide C (**1616**) (Photo: J. Tanaka)

The Japanese sea hare *Dolabella auricularia* contains the cytotoxic aurisides A (**1628**) and B (**1629**) (*1598*), which have the absolute stereostructures shown as confirmed by total synthesis (*1599*). Both compounds display excellent cytotoxicity against HeLa S_3 cells (0.17–1.2 μg mL^{-1}). Structurally similar to the aurisides are callipeltosides A (**1630**), B (**1631**), and C (**1632**), which were isolated from the sponge *Callipelta* sp. collected in New Caledonia (*1600, 1601*) and are the targets of several total syntheses (*1586, 2652*). Closely related to the callipeltosides are phorbasides A (**1633**) and B (**1634**) from a Western Australian *Phorbas* sp. sponge (*1602*). The first example of a cyanobacterium glycoside macrolide to be isolated is lyngbyaloside (**1635**) from a Papua New Guinea *Lyngbya bouillonii* (*1603*).

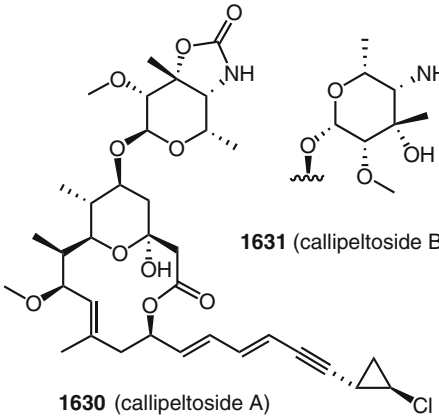
Another Palauan sample of this blue-green alga identified the related bromine-containing lyngbyaloside B (**1636**) (*1604*).



1628 (auriside A)

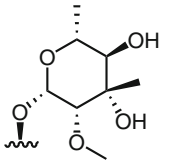


1629 (auriside B)

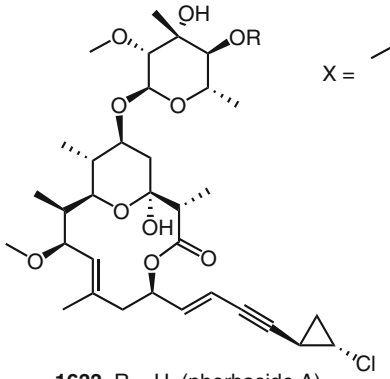


1630 (callipeltoside A)

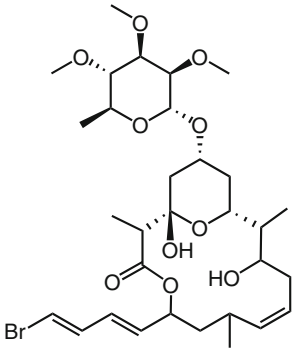
1631 (callipeltoside B)



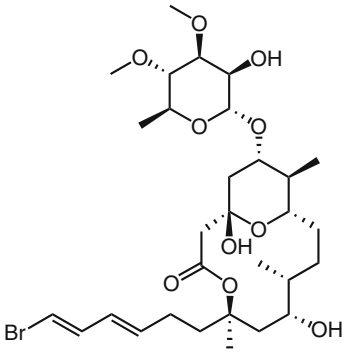
1632 (callipeltoside C)



1633 R = H (phorbaside A)
1634 R = X (phorbaside B)

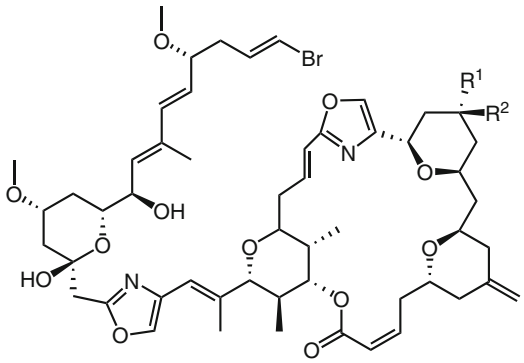


1635 (lyngbyaloside)

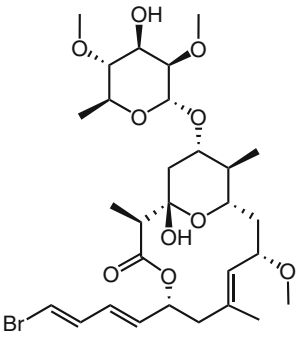


1636 (lyngbyaloside B)

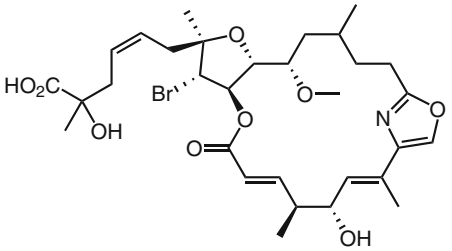
The Indian Ocean sponge *Phorbas* sp. has furnished phorboxazoles A (**1637**) and B (**1638**), which display extraordinary cytostatic activity against human cancer cell lines, comparable to spongistatin 1, and, therefore, are among the most potent cytostatic compounds known (*1605*). Extensive spectral work on model compounds has established the absolute configuration of the phorboxazoles (*1606–1608*), which was confirmed by several elegant total syntheses (*1609–1612*). The sea hare *Dolabella auricularia* from the Gulf of California has afforded dolastatin 19 (**1639**), which is structurally related to the aurisides (*1613*). Total synthesis corrected the stereochemistry and established the absolute configuration of dolastatin 19 (*1614, 2651*). A deep-water (740 feet) Palauan sponge, *Leiodermatium* sp., has yielded leiodelide B (**1640**), along with a non-brominated analog (*1615*). This is the first report of secondary metabolites from the rare genus *Leiodermatium*.



1637 R^1 = OH, R^2 = H (phorboxazole A)
1638 R^1 = H, R^2 = OH (phorboxazole B)

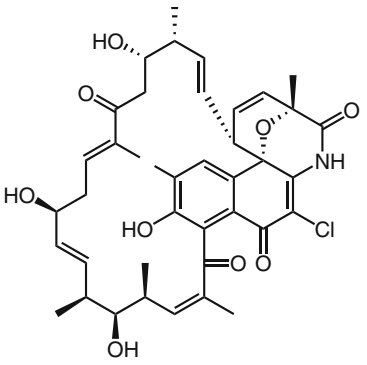


1639 (dolastatin 19)

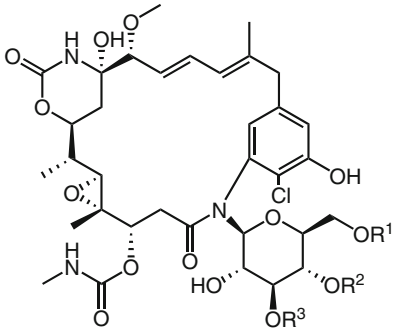


1640 (leiodelide B)

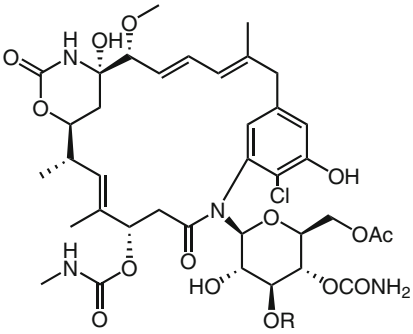
A novel ansamycin, naphthomycin K (**1641**), was isolated from a *Streptomyces* strain of the medicinal plant *Maytenus hookeri* (*1616*). This compound was cytotoxic (P388 and A-549 cell lines) but inactive against *Staphylococcus aureus* and *Mycobacterium tuberculosis*. An *Amycolatopsis* sp. has furnished the ansacarbamitocins A–F, A1, B1 (**1642**–**1649**), which are similar to the ansamitocins (*1617*).



1641 (naphthomycin K)



1642 R^1 = Ac, R^2 = $CONH_2$, R^3 = Me (ansacarbamitocin A)
1643 R^1 = Ac, R^2 = $CONH_2$, R^3 = H (ansacarbamitocin B)
1644 R^1 = H, R^2 = $CONH_2$, R^3 = Me (ansacarbamitocin C)
1645 R^1 = H, R^2 = $CONH_2$, R^3 = H (ansacarbamitocin D)
1646 R^1 = R^2 = H, R^3 = Me (ansacarbamitocin E)
1647 R^1 = R^2 = R^3 = H (ansacarbamitocin F)

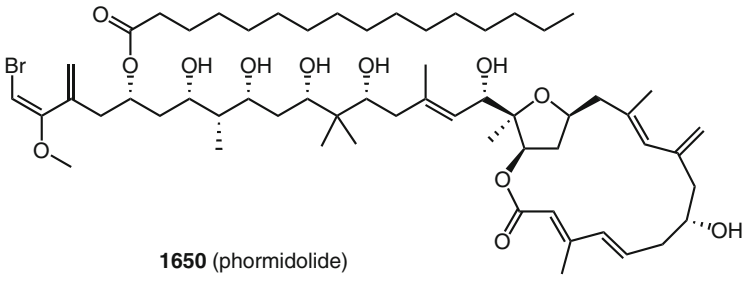


1648 R = Me (ansacarbamitocin A1)
1649 R = H (ansacarbamitocin B1)

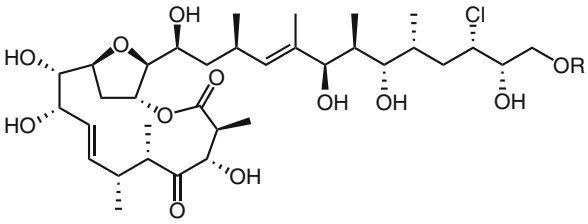
An Indonesian marine cyanobacterium, *Phormidium* sp., has provided the toxic phormidolide (**1650**) (*1618*), which is structurally similar to the previously known cyanobacterium metabolite oscillariolide (*1*). Three chlorine-containing macrolides, lytophilippines A–C (**1651–1653**), were isolated from the Red Sea hydroid *Lytocarpus philippinus* ("fireweed") (*1619*), and the Red Sea sponge *Leucetta chagosensis* (Fig. 3.22) contains chagosensine (**1654**) (*1620*). Several novel chlorinated macrolides have been found in both the Okinawan ascidian *Lissoclinum* sp. and the Okinawan sponge *Ircinia* sp. These metabolites are haterumalide B (**1655**) (*1621*) and haterumalides NA-NE (**1656–1660**) (*1622*). Two total syntheses of 15-*epi*-haterumalide NA methyl ester result in a revision of the absolute stereochemistry of haterumalide NA (**1656**) (*1623, 1624*), which was also isolated independently as "oocydin A" from a strain of *Serratia marcescens* growing on the aquatic plant *Rhyncholacis pedicillata* in Venezuela (*1625*) and from the soil bacterium *Serratia plymuthica* in Sweden (*1626*). This revision is depicted for all haterumalides for

Fig. 3.22 *Leucetta chagosensis*, a Red Sea sponge that contains the novel macrolide chagosensine (**1654**) (Photo: T. Rezanka)

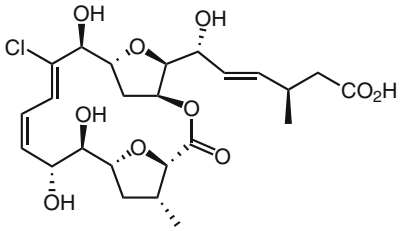
convenience. Closely related to the haterumalides are biselides A–E (**1661**–**1665**), which were characterized from the Okinawan ascidian of the family Didemnidae (*1627, 1628*). A compound FR177391 (**1666**) is produced by *Serratia liquefaciens* and reported to be the enantiomer of haterumalide NA (*1629*).



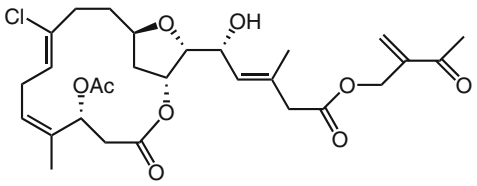
1650 (phormidolide)



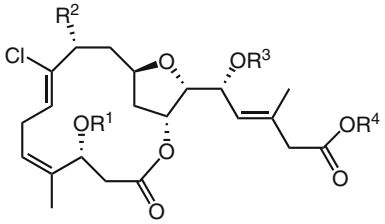
1651 R = H (lytophilippine A)
1652 R = $CO(CH_2)_{14}CH_3$ (lytophilippine B)
1653 R = (*Z*)-$CO(CH_2)_7CH{=}CH(CH_2)_7CH_3$ (lytophilippine A)



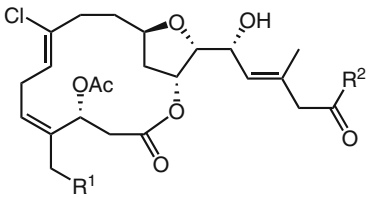
1654 (chagosensine)



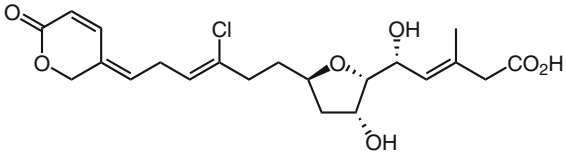
1655 (haterumalide B)



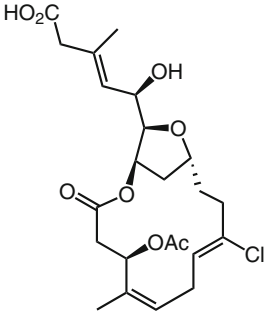
1656 R^1 = Ac, R^2 = R^3 = R^4 = H (haterumalide NA)
1657 R^1 = Ac, R^2 = R^3 = H, R^4 = *n*-Bu (haterumalide NB)
1658 R^1 = Ac, R^2 = OH, R^3 = H, R^4 = *n*-Bu (haterumalide NC)
1659 R^1 = Ac, R^2 = OH, R^3 = R^4 = H (haterumalide ND)
1660 R^1 = R^2 = R^3 = R^4 = H (haterumalide NE)



1661 R^1 = OAc; R^2 = OH (biselide A)
1662 R^1 = OAc; R^2 = $OCH_2C(=CH_2)COCH_3$ (biselide B)
1663 R^1 = R^2 = OH (biselide C)
1664 R^1 = H; R^2 = $NHCH_2CH_2SO_3H$ (biselide D)

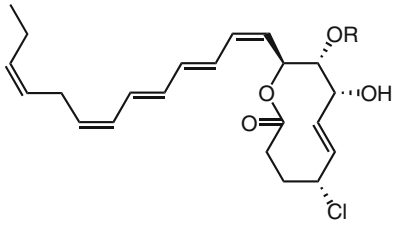


1665 (biselide E)



1666 (FR177391)

The Red Sea sponge *Latrunculia corticata* (Fig. 3.23) has afforded latrunculinosides A (**1667**) and B (**1668**), which contain the unusual saccharides *β*-D-olivose, *β*-L-digitoxose, α-L-amicetose, and *β*-D-oliose (*1630*).



1667 R = *β*-L-Dig–*β*-D-Olv–*α*-L-Ami (latrunculinoside A)
1668 R = *β*-D-Oli–*β*-D-Oli (latrunculinoside B)

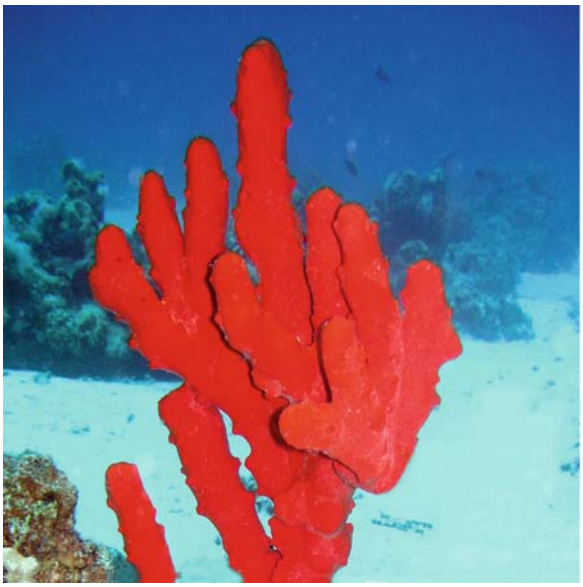
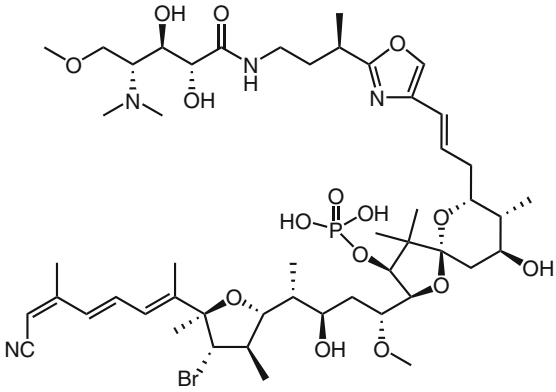
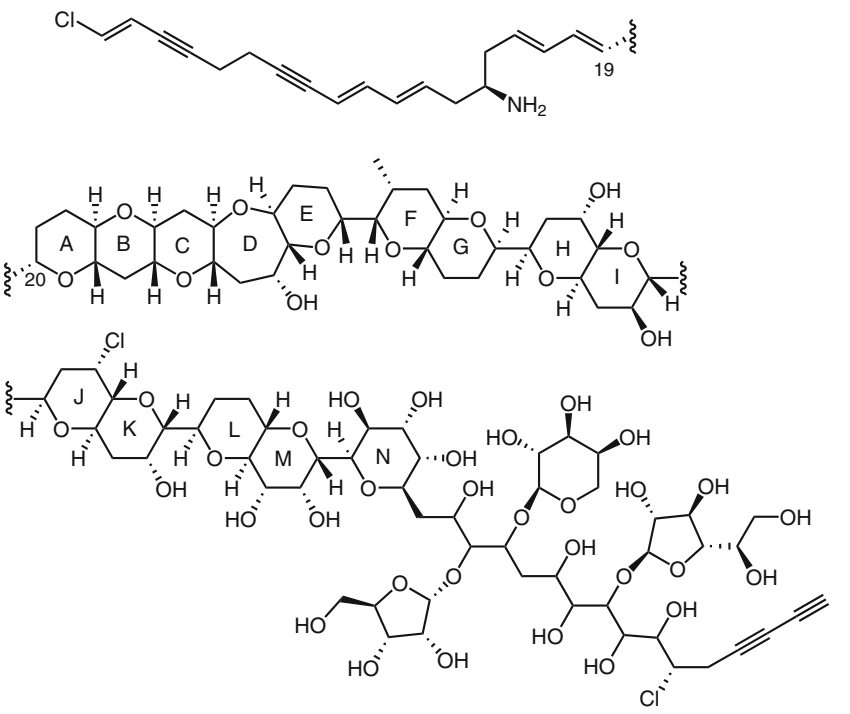


Fig. 3.23 *Latrunculia corticata*, a Red Sea sponge that contains the latrunculinosides A and B (**1667** and **1668**) (Photo: T. Rezanka)

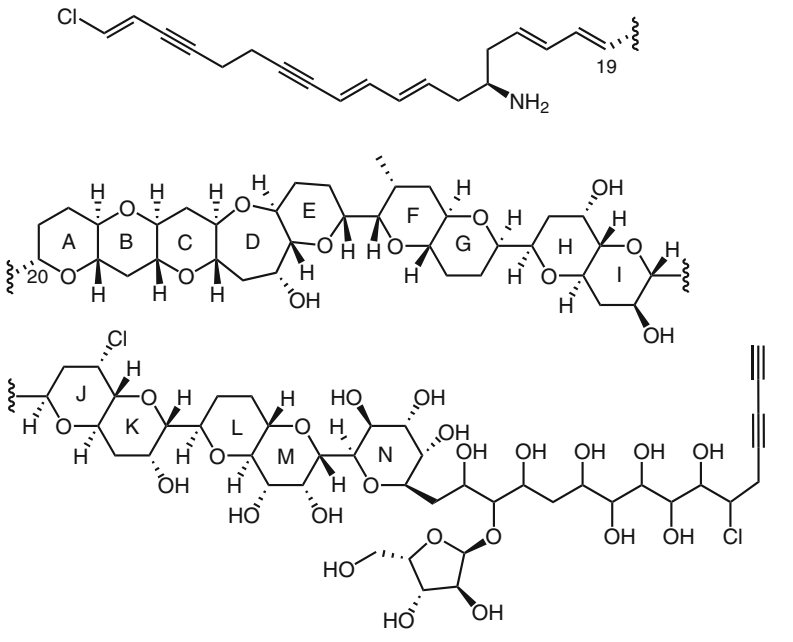
The Japanese sponge *Discodermia calyx* has yielded the new calyculin, calyculin J (**1669**) (*1631*). The highly toxic (ichthyotoxicity, hemolytic activity) prymnesin-1 (**1670**) and -2 (**1671**), possessing unprecedented structural complexity, were characterized from the red tide alga *Prymnesium parvum* (*1632–1634*).



1669 (calyculin J)



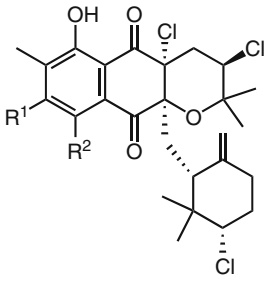
1670 (prymnesin-1)

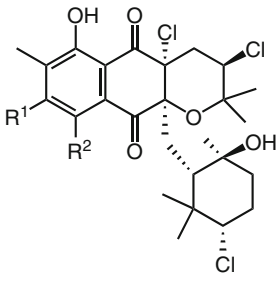


1671 (prymnesin-2)

3.18 Naphthoquinones, Higher Quinones, and Related Compounds

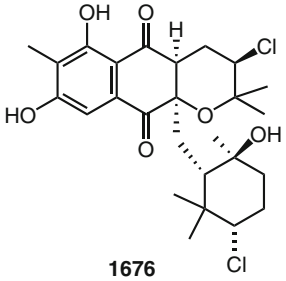
The relatively large group of previously known napyradiomycins and related bacterial metabolites has been augmented by the discovery of A80915-A (**1672**), -B (**1673**), -C (**1674**), and -D (**1675**) from cultures of *Streptomyces aculeolatus* from a Palauan soil sample (*1635*). A deep-sea marine actinomycete has afforded the related **1676–1678**, which exhibit significant antibacterial activity towards drug-resistant *Staphylococcus aureus* and *Enterococcus faecium*, and cytotoxicity toward HCT-116 human colon carcinoma (*1636*). An X-ray structure establishes the absolute configuration of A80915C (**1674**) (*1637*).



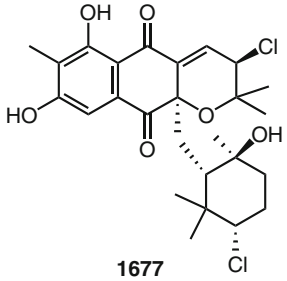


1672 R^1 = OH, R^2 = H (A80915-A)
1673 R^1 = O$^{\ominus}$, R^2 = $N_2^{\oplus}$ (A80915-B)

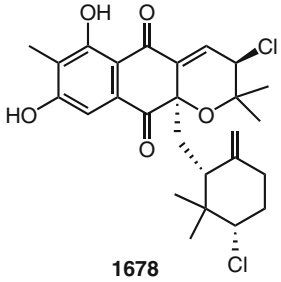
1674 R^1 = OH, R^2 = H (A80915-C)
1675 R^1 = O$^{\ominus}$, R^2 = $N_2^{\oplus}$ (A80915-D)



1676

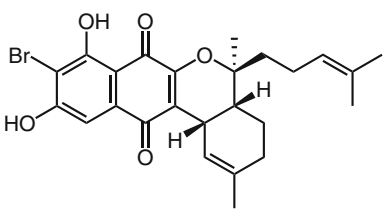


1677

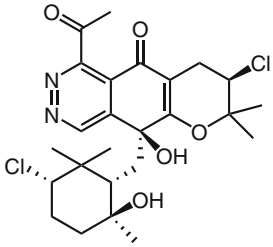


1678

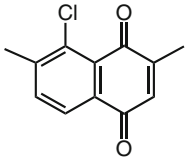
Isomarinone (**1679**), an isomer of the previously known marinone (*1*), was isolated from the same tropical sediment bacterium (*1638*). Another marine-derived bacterium related to the genus *Streptomyces* has yielded the novel azamerone (**1680**) (*1639*). The British Columbian medicinal plant *Moneses uniflora* contains the antibiotic 8-chlorochimaphilin (**1681**), which is more active than chimaphilin (*1640*). Sesame roots (*Sesamum indicum*) have yielded the red chlorinated naphthoquinone chlorosesamone (**1682**) (*1641*). Cultures of *Streptomyces* strain *LL*-A9227 produce chloroquinocin (**1683**), which has some antibacterial activity against Gram-positive bacteria (*1642*). The two xestoquinones **1684** and **1685** were characterized from the Philippino sponge *Xestospongia* sp., and display topoisomerase II activity (*1643*).



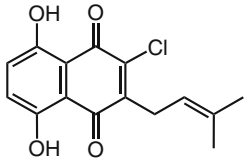
1679 (isomarinone)



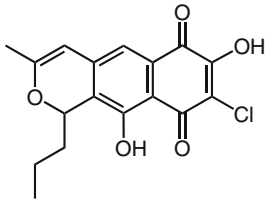
1680 (azamerone)



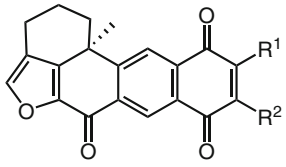
1681 (8-chlorochimaphilin)



1682 (chlorosesamone)



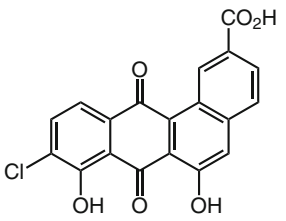
1683 (chloroquinocin)



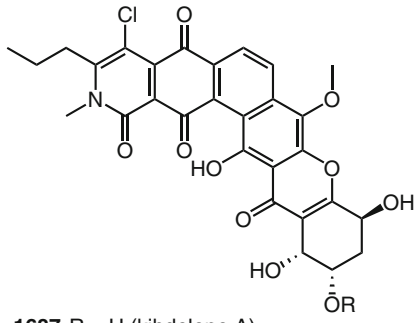
1684 R^1 = Cl, R^2 = OH
1685 R^1 = OH, R^2 = Cl

A synthesis of the chlorinated angucycline antibiotic BE-23254 (**1686**), which was isolated from *Streptomyces* sp. A 23254, has confirmed the structure of this benz[*a*]anthraquinone derivative (*1644, 1939, 1940*). Two detailed examinations of the rare Australian soil actinomycete *Kibdelosporangium* sp. uncovered a series of

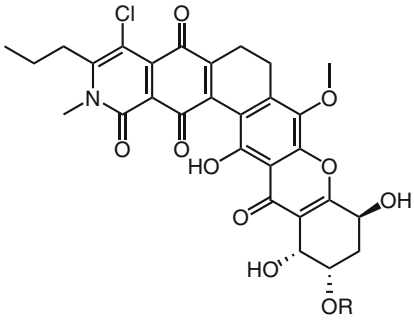
kibdelones (*1645*) and isokibdelones (*1646*) with novel structures. The former study includes kibdelone A (**1687**), kibdelone A rhamnoside (**1688**), kibdelone B (**1689**), kibdelone B rhamnoside (**1690**), kibdelone C (**1691**), kibdelone C rhamnoside (**1692**) and 13-oxokibdelone A (**1693**) (*1645*), while the latter study includes isokibdelone A (**1694**), isokibdelone A rhamnoside (**1695**), isokibdelone B (**1696**), and isokibdelone C (**1697**) (*1646*).

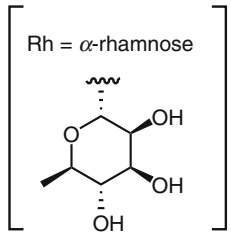


1686 (BE-23254)

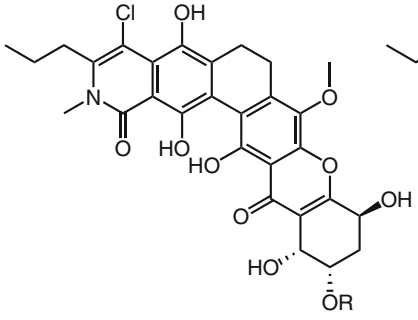


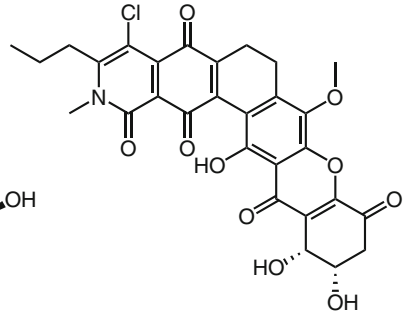
1687 R = H (kibdelone A)
1688 R = α-Rh (kibdelone A rhamnoside)





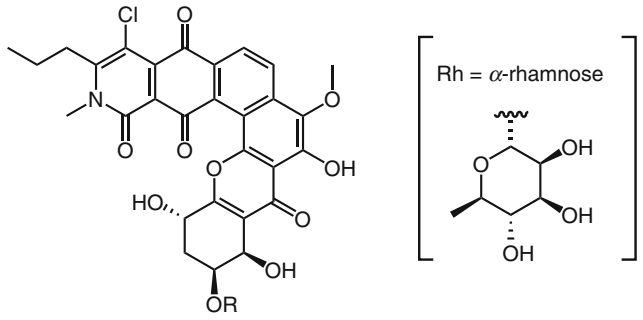
1689 R = H (kibdelone B)
1690 R = α-Rh (kibdelone B rhamnoside)



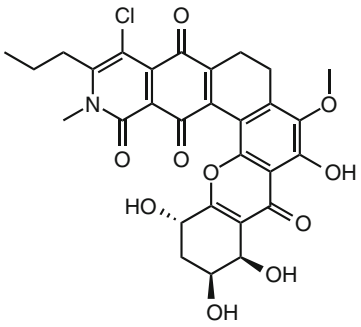


1691 R = H (kibdelone C)
1692 R = α-Rh (kibdelone C rhamnoside)

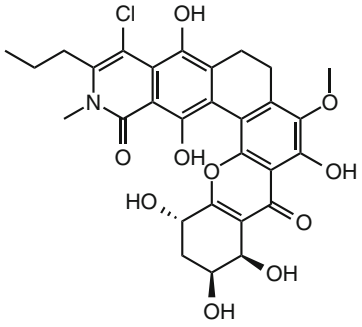
1693 (13-oxokibdelone A)



1694 R = H (isokibdelone A)
1695 R = α-Rh (isokibdelone A rhamnoside)

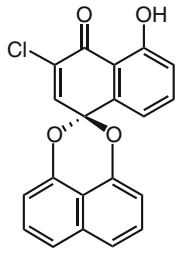


1696 (isokibdelone B)

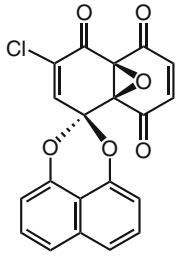


1697 (isokibdelone C)

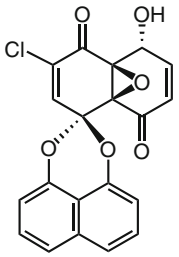
Four novel antibacterial, antifungal, and herbicidal palmarumycins have been isolated from the West Borneo forest soil microbe *Coniothyrium* sp. (*1647*). These are palmarumycins C_1 (**1698**), C_4 (**1699**), C_7 (**1700**), and C_8 (**1701**), along with several nonchlorinated analogs. The palmarumycins have attracted the interest of synthetic chemists (*434*), as have related naphthalenoid natural products (*2669*). The DNA-cleaving antitumor antibiotics spiroxins A (**1702**), B (**1703**), and E (**1704**) are found in a Vancouver Island soft coral containing an associated fungus LL-37H248 (*1648, 1649*). The absolute configuration of **1702** was determined (*1649*), and a synthesis of the nonchlorinated spiroxin C has been described (*1650*).



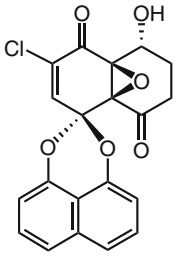
1698 (palmarumycin C_1)



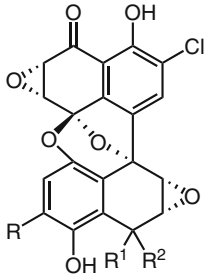
1699 (palmarumycin C_4)



1700 (palmarumycin C_7)



1701 (palmarumycin C_8)



1702 R = H, R^1,R^2 = O (spiroxin A)
1703 R = Cl, R^1,R^2 = O (spiroxin B)
1704 R = Cl, R^1 = OH, R^2 = H (spiroxin E)

3.19 Tetracyclines

Although no new halogen-containing tetracyclines have been reported since the first survey (*1*), the gene responsible for the chlorination of tetracycline in *Streptomyces aureofaciens* (Fig. 3.24) has been cloned and the sequence of nucleotides determined (*1651*). The gene product is a 452 amino acid chlorination enzyme.

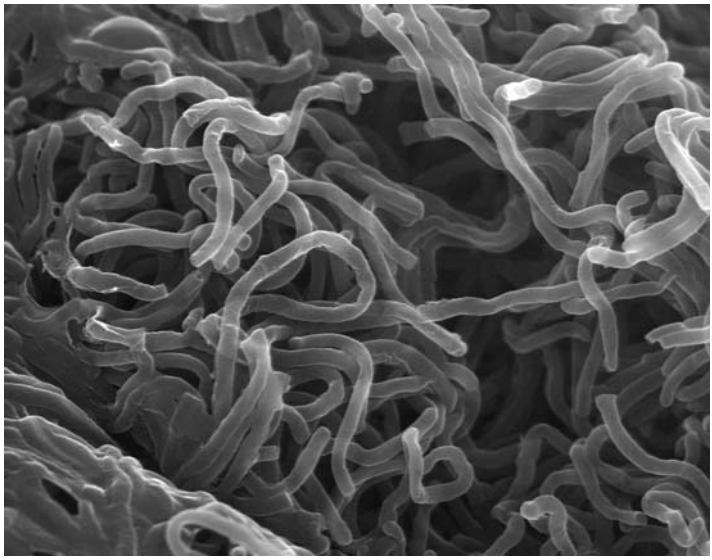
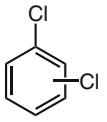


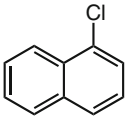
Fig. 3.24 *Streptomyces aureofaciens*, the microorganism that produces the tetracyclines (Photo: T. Rezanka)

3.20 Aromatics

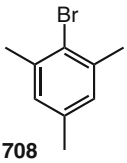
Compared to their more reactive phenol counterparts in electrophilic halogenation, simple unactivated halogenated aromatic rings occur rarely in Nature (*1*). However, several notable examples exist. The high temperatures present in volcanoes and during the formation of meteorites leads to the production of the previously known chlorobenzene and a dichlorobenzene (**1705**) in Orgueil and Cold Bokkeveld meteorites, respectively (*388*), and 1-chloronaphthalene (**1707**) and bromomesitylene (**1708**) in carbonaceous black shales (*330*). Studies of emissions from Vulcano, Mt. Etna, Kuju, and Satsuma Iwojima reveal the presence of chlorobenzene, two dichlorobenzenes (**1705**, **1706**), 1,4-dichlorobenzene, fluorobenzene (**1709**), tetrafluorobenzene (**1710**), fluorochlorobenzene (**1711**), chlorostyrenes (**1712–1714**), trichlorobenzenes (**1715**, **1716**), chlorotoluenes (**1717–1719**), the previously known bromobenzene, and chloroethylbenzene (**1720**) (*216, 217*). It should be noted that heating (400–950°C) a mixture of methane, hydrogen chloride, and oxygen results in the formation of a plethora of chlorinated aromatics (benzenes, toluenes, xylenes, styrenes, naphthalenes, biphenyls, anisoles, acenaphthylenes, phenanthrenes, fluoranthenes) (*232*). Several chlorinated benzoic acids have natural origins. The meteorites Murray, Murchison, Cold Bokkeveld, and Orgueil contain 4-chlorobenzoic acid (**1721**), 2,4-dichlorobenzoic acid (**1722**), and 2,6-dichlorobenzoic acid (**1723**) to varying degrees (*1652*). These chlorobenzoic acids are also found in remote bogs and sediments, particularly 2,4-dichlorobenzoic acid (**1722**) (*1653*). In all samples, trichloroacetic acid was also detected. Laboratory experiments involving benzoic acid and chloroperoxidase give rise to chlorobenzoic acids, in agreement with their natural production (*1653*). Another biogenic source of 2,4-dichlorobenzoic acid (**1722**) is the terrestrial cyanobacterium *Fischerella ambigua*, which is the first report of this compound from a living organism (*1654*). Along with **1722**, three different tetrachlorobiphenyl carboxylic acids (**1724–1726**) are present in dissolved seawater, and, based on their isomer distribution and global inventory, these compounds are suggested to have a natural source (*1655*). The *de novo* formation of 3,4-dichlorophenylacetic acid (**1727**), 3,4-dichlorobenzoic acid (**1728**), and 3,4,5-trichlorobenzoic acid (**1729**) in a sewage treatment plant were reported, along with several other known chlorinated benzoic acids and phenols (*1656*). Garden compost also produces **1727–1729** and 3,4,5-trichlorophenylacetic acid (**1730**) (*1657*). Acid **1727** has also been identified in fungi (*1656*).



1705, 1706



1707



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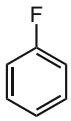
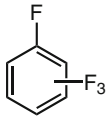
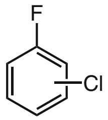


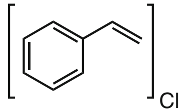
1709



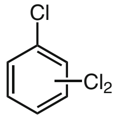
1710



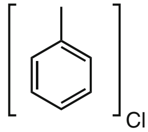
1711



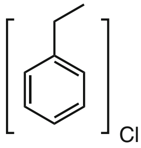
1712-1714



1715, 1716



1717-1719



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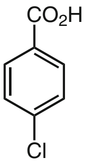

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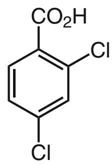

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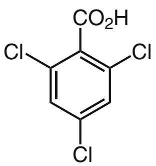
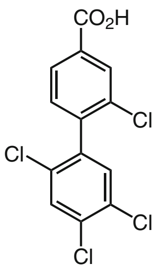


1723



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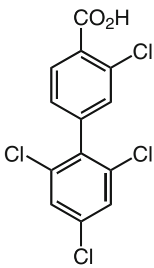
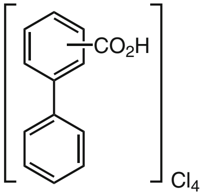
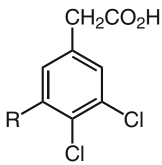


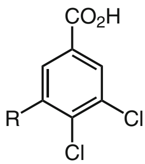
1725



1726

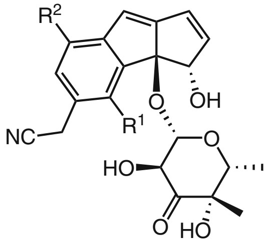


1727 R = H
1730 R = Cl

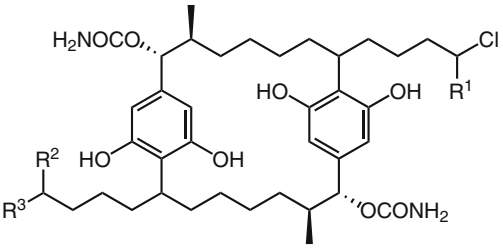


1728 R = H
1729 R = Cl

The Palauan deep-water (500 m) marine actinomycete *Salinispora pacifica* has yielded cyanosporasides A (**1731**) and B (**1732**), which feature a chlorine on an unactivated benzene ring (*1658*). The authors suggest a novel biosynthesis from an enediyne precursor. Related to the previously known nostocyclophanes (*1*) are the new carbamidocyclophanes A–E, of which A (**1733**), B (**1734**), C (**1735**), and D (**1736**) are chlorinated, being isolated from the Vietnamese cyanobacterium *Nostoc* sp. (*1659*). These compounds exhibit cytotoxicity against MCF-7 (breast) and F1 (amniotic epithelial) human cancer cells.

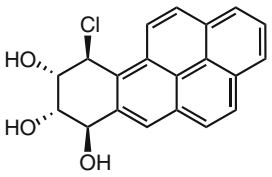


1731 R^1 = Cl, R^2 = H (cyanosporaside A)
1732 R^1 = H, R^2 = Cl (cyanosporaside B)



1733 $R^1 = R^2 = R^3 = Cl$ (carbamidocyclophane A)
1734 $R^1 = R^2 = Cl$, $R^3 = H$ (carbamidocyclophane B)
1735 $R^1 = Cl$, $R^2 = R^3 = H$ (carbamidocyclophane C)
1736 $R^1 = R^2 = R^3 = H$ (carbamidocyclophane D)

Polycyclic aromatic hydrocarbons (PAH), which are ubiquitous in the environment, including surface waters, undergo facile chlorination by hypochlorite when dissolved in humus-poor water to give a suite of chlorinated PAH (*1660*). It is therefore conceivable that this chlorination can occur under natural conditions, but this is yet to be determined. Another new possible source of natural chlorinated PAH is the reported in vitro reaction of benzo[*a*]pyrene diol epoxide, the ultimate carcinogen of benzo[*a*]pyrene with chloride ion to give chlorohydrin **DDD**, which has been isolated and identified as an intermediate en route to a benzo[*a*]pyrene-DNA adduct (*1661*). However, **DDD** is not considered to be a natural compound at this time.



DDD

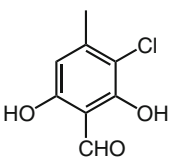
3.21 Simple Phenols

The enormous reactivity of the phenolic ring towards electrophilic halogenation has led to a multitude of natural halogenated phenols, both terrestrial and marine (*1*).

3.21.1 Terrestrial

The previously reported 2,6-dichlorophenol, which is a sex pheromone of several species of tick (*1*), is also produced by the African tick *Amblyomma hebraeum* (*1662, 1663*). This pheromone has been used to control the African bont tick on

cattle in Zimbabwe (*1664*) and the American dog tick (*Dermacentor variabilis*) (*1665*). Neurons in the legs of male ticks (*Amblyomma americanum*) are sensitive to 2,6-dichlorophenol (*1666*). In addition to this well-known chlorophenol, a number of new chlorinated phenols were reported since the first survey, including some that were overlooked by the author (*1*). Oakmoss (*Evernia prunastri*), which contributed bromobenzene to the first survey (*1*), also contains chlororesorcinol **1737** (*1667*). The fungus *Hericium erinaceus* has furnished 4-chloro-3,5-dimethoxybenzoic acid (**1738**) and related esters **1739** and **1740** (*1668*). Another study of this fungus revealed the presence of the related orcinols **1741–1743** (*1669*). Cultures of the basidiomycete *Stropharia* sp. have yielded 3,5-dichloro-4-methoxybenzyl alcohol (**1744**), and 3,5-dichloro-4-methoxybenzaldehyde (**1745**) occurs in *Hypholoma subviride* (*1670*). *Hypholoma elongatum* has provided the new 2,4,6-trichloro-3-methoxyphenol (**1746**), 3,5,6-trichloro-2,4-dimethoxyphenol (**1747**), and 3,4,6-trichloro-2,5-dimethoxyphenol (**1748**) (*1671*). The Japanese mushroom *Russula subnigricans* contains 2,6-dichloro-4-methoxyphenol (**1749**) (*1672*). The basidiomycete strain *Kuehneromyces mutabilis* produces methyl 3,6-dichloro-2-methylbenzoate (**1750**) (*1673*). Chlorinated lactone **1751** was characterized from *Leucoagaricus carneifolia* (*1674*). Metabolites **1744** and **1745** were also isolated from the fungus *Pholiota destruens* (*1675*) and from the American matsutake mushroom *Tricholoma magnivelare* (*1676*).



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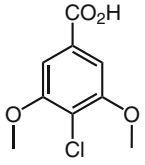

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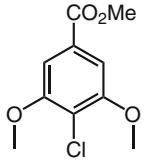
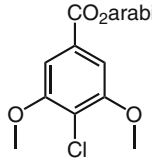
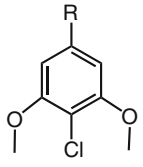


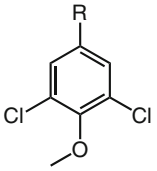
1739



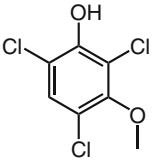
1740



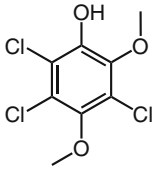
1741 R = Me
1742 R = CH_2OH
1743 R = CHO



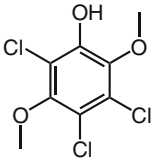
1744 R = CH_2OH
1745 R = CHO



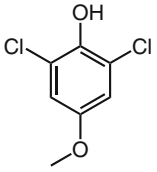
1746



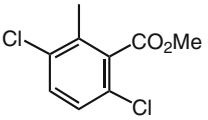
1747



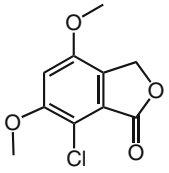
1748



1749



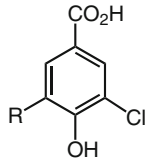
1750



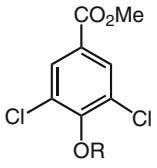
1751

The wood-rotting fungi of genus *Bjerkandera* produce a number of chlorinated phenols and derivatives (*398, 1677*).

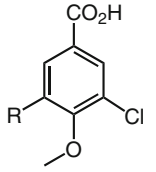
Thus, *Bjerkandera* sp. BOS55 has yielded 3-chloro-4-hydroxybenzoic acid (**1752**), 3,5-dichloro-4-hydroxybenzoic acid (**1753**), methyl 3,5-dichloro-4-hydroxybenzoate (**1754**), methyl 3,5-dichloro-4-methoxybenzoate (**1755**), 3-chloro-4-methoxybenzoic acid (**1756**), and 3,5-dichloro-4-methoxybenzoic acid (**1757**) (*1678*). The latter two metabolites and several other new halogenated phenols were discovered in soil around the fungus *Lepista nuda* (wood blewitt): 5-chloro-3,4-dimethoxybenzaldehyde (**1758**), 3-bromo-5-chloro-4-methoxybenzaldehyde (or isomer) (**1759**), 5-bromo-3,4-dimethoxybenzaldehyde (**1760**), 3-bromo-4-methoxybenzaldehyde (**1761**), 4-chloroanisole (**1762**), 2,6-dichloroanisole (**1763**), 2-chloro-1,4-dimethoxybenzene (**1764**), 2,6-dichloro-1,4-dimethoxybenzene (**1765**), a dichlorodimethoxybenzaldehyde isomer (**1766**), and a few other known compounds (*1679*). The simple phenols tetrachlorocatechol (**1767**) and monomethyl ether (**1768**) were isolated from a *Mycena* fungal species (*1680*). *Mycena alcalina* has furnished alcalinaphenols A–C (**1769–1771**) (*1681*). Veratryl chloride (**1772**) (3,4-dimethoxybenzyl chloride) has been reported in *Bjerkandera* sp. BOS55 (*1682*). In view of the enormous reactivity to be expected for this compound (facile S_N1 and S_N2 reactions), this report is surprising. This same fungus and *Bjerkandera fumosa* contain **1773** and **1774** (*1683*). The related trametol (**1775**) was isolated from the fungus *Trametes* sp. (*1684*). The microfungus *Xylaria* sp. contains 3-chloro-4-hydroxyphenylacetamide (**1776**) (*1685*). The chlorinated anisyl metabolites are produced by a wide range of basidiomycete genera including *Mycena*, *Peniophora*, *Phellinus*, *Phylloporia*, *Bjerandera*, *Hypholoma*, and *Pholiota* (*1686*). An excellent summary of chlorometabolite production by *Bjerkandera adusta* has been published (*1687*).



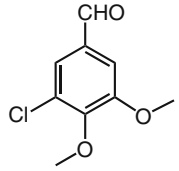
1752 R = H
1753 R = Cl



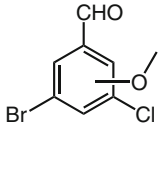
1754 R = H
1755 R = Me



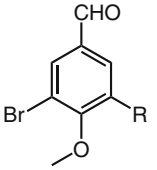
1756 R = H
1757 R = Cl



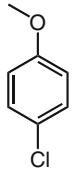
1758



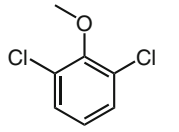
1759



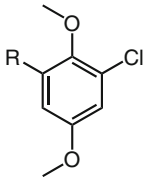
1760 R = OMe
1761 R = H



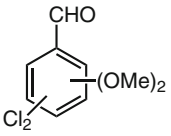
1762



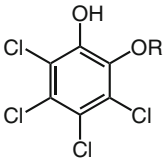
1763



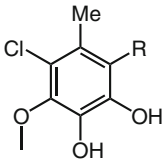
1764 R = H
1765 R = Cl



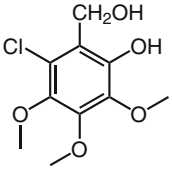
1766



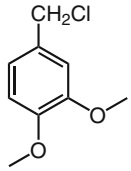
1767 R = H
1768 R = Me



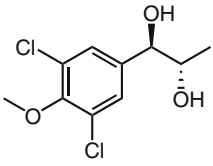
1769 R = H (alcalinaphenol A)
1770 R = OMe (alcalinaphenol B)



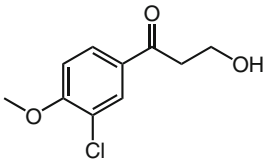
1771 (alcalinaphenol C)



1772



1773 R = Cl
1775 R = H (trametol)



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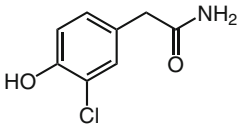
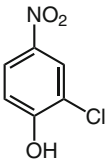
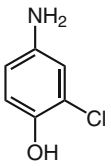


1776

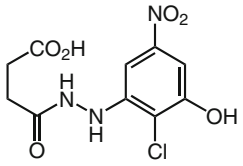
A collection of the carrot truffle, *Stephanospora caroticolor* (Fig. 3.25), from Germany has led to 2-chloro-4-nitrophenol (**1777**), 4-amino-2-chlorophenol (**1778**), and stephanosporin (**1779**) (*1688*). Phenol **1777** is also present in the fruit bodies of *Lindtneria trachyspora* (*1688*). The New Zealand liverwort *Riccardia marginata* has afforded the novel chlorinated bibenzyls **1780–1782** (*1689*). These metabolites have antimicrobial and antifungal activity against *Bacillus subtilis*, *Trichophyton mentagrophytes*, *Candida albicans*, and *Cladosporium resinae*. In response to attack by the pathogenic fungus *Fusarium oxysporum f.* sp. *lilii*, the edible Japanese lily *Lilium maximowiczii* (Fig. 3.26) produces seven chlorinated orcinols **1783–1789** as natural fungicides (*1690*). The Pakistani medicinal lichen (*Usnea longissima*, "Old Man's Beard"), which has been used for pain relief and fever control, contains longissiminone B (**1790**) along with the nonchlorinated analog, which has potent antiinflammatory activity (*1691*). The Canary Islands lichen *Lethariella canariensis* features the new chloroatranol (**1791**), chlorohematommic acid (**1792**), methyl chlorohematommate (**1793**), and ethyl chlorohematommate (**1794**) (*1692*).



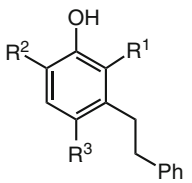
1777



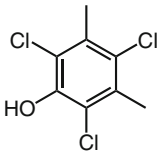
1778



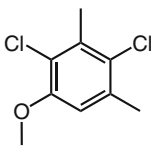
1779 (stephanosporin)



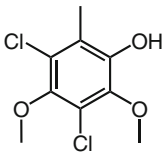
1780 $R^1 = R^2 = R^3 = Cl$
1781 $R^1 = R^2 = Cl$, $R^3 = H$
1782 $R^1 = Cl$, $R^2 = R^3 = H$



1783



1784



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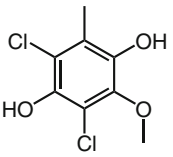

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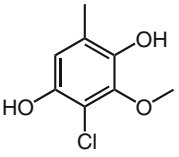
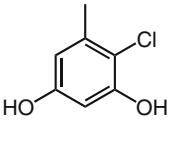
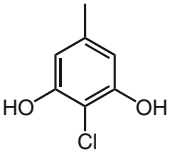


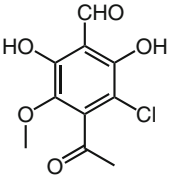
1787



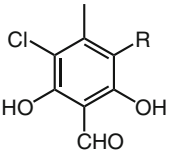
1788



1789

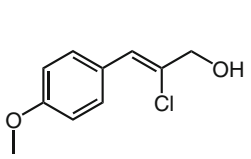


1790 (longissiminone B)

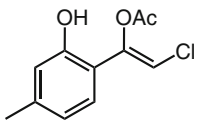


1791 R = H (chloroatranol)
1792 R = CO_2H (chlorohematommic acidl)
1793 R = CO_2Me (methyl chlorohematommate)
1794 R = CO_2Et (ethyl chlorohematommate)

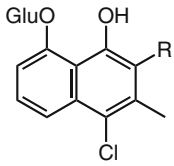
Cultures of *Lentinellus cochleatus* yield chlorostyrene **1795** (*1693*), and the related compound **1796** occurs in *Arnica sachalinensis* (*1694*). The sulfur-oxidizing bacterium *Thialkalivibrio versutus* contains the membrane-bound chloronatronochrome (**1797**) (*1695*). The terrestrial plant *Rumex patientia* from Turkey, which is used in traditional medicine, has yielded the naphthalene glycosides patientosides A (**1798**) and B (**1799**) (*1696*). The Turkish folk medicine plant *Geranium pratense* subsp. *finitimum* contains 6-chloroepicatechin (**1800**) (*1697*). The Indian tree *Gmelina arborea*, which is of commercial importance, has afforded the first bromine-containing lignan **1801** (*1698*).



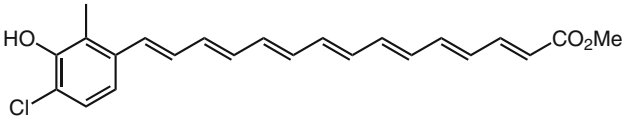
1795



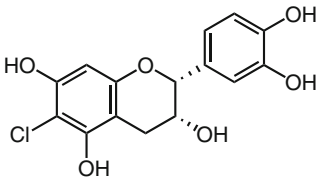
1796



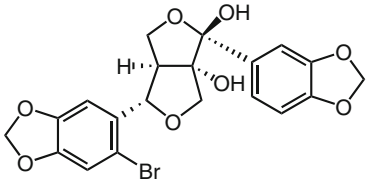
1798 R = Ac (patientoside A)
1799 R = Cl (patientoside B)



1797 (chloronatronochrome)



1800 (6-chloroepicatechin)

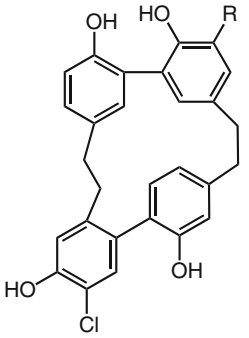


1801

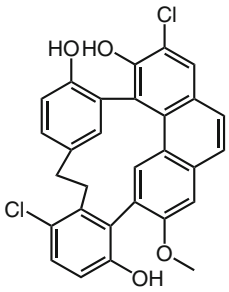
Fig. 3.25 *Stephanospora caroticolor*, the carrot truffle that contains novel chlorophenols **1777** and **1778**, and stephanosporin (**1779**) (Photo: W. Steglich)

Fig. 3.26 *Lilium maximowiczii*, the edible Japanese lily that produces the seven chlorinated fungicides **1783–1789**; the brown portion indicates disease by a *Fusarium* fungus (Photo: K. Monde)

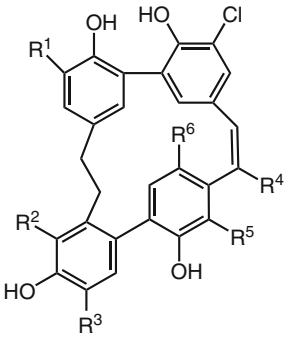
The liverwort genera consisting of 400–500 species have been the source of a large number of chlorinated 'bis-bibenzyls' and related polyphenols (*1699*). The first example appears to be 12-chloroisoplagiochin D (**1802**) found in the Costa Rican liverwort *Plagiochila* sp. (*1700*). In an isolation and identification *tour de force*, a research group has characterized ten chlorinated bridged biphenyls, bazzanins A-J (**1803–1812**), and the novel phenanthrene bazzanin K (**1813**) from the liverwort *Bazzania trilobata* (*1701*). The Japanese liverwort *Herbertus sakuraii* has afforded 2,12-dichloroisoplagiochin D (**1814**), 12,7′-dichloroisoplagiochin D (**1815**), and 12,10′-dichloroisoplagiochin C (**1816**) (*1702, 1703*). The liverwort *Mastigophola diclados* also contains **1802** and **1814** (*1703*). The Taiwanese liverwort *Plagiochila peculiaris* contains bazzanin J and 12-chloroisoplagiochin D (*1704*). Bazzanins L-R (**1817–1823**) and S (**1824**) have been characterized from the liverworts *Lepidozia incurvata* (*1705*) and *Bazzania trilobata* (*1706*), respectively. Several of these bazzanins are optically active, but are not enantiomerically pure in the liverworts (*1706*). The liverwort *Jamesoniella colorata* has furnished the "ring-opened" bis-bibenzyl 6,6′,10,10′,12,12′-hexachloroisoperrottetin (**1825**) (*1707*). That these chlorinated phenols are not isolation artifacts is supported by their presence in the crude liverwort extracts as detected by mass spectrometry (MALD1-TOF and LDI-TOF) (*1708, 1709*). Moreover, a chloroperoxidase enzyme (which will be discussed in detail in Sect. 4.2 (Chloroperoxidase)) has been detected in *Bazzania trilobata* further supporting the natural occurrence of these unusual chlorinated phenols (*1710*).



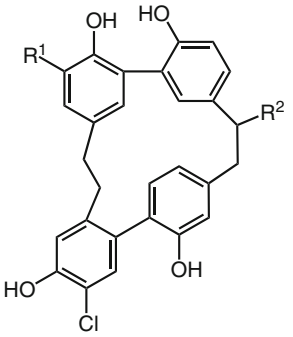
1802 R = H (12-chloroisoplagiochin D)
1812 R = Cl (bazzanin J)



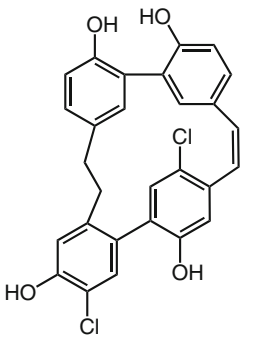
1813 (bazzanin K)



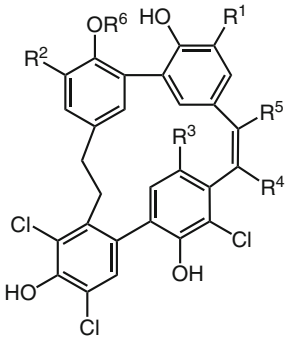
1803 R^1 = H, R^2 = H, R^3 = H, R^4 = H, R^5 = H, R^6 = H (bazzanin A)
1804 R^1 = H, R^2 = H, R^3 = H, R^4 = Cl, R^5 = H, R^6 = H (bazzanin B)
1805 R^1 = H, R^2 = H, R^3 = Cl, R^4 = Cl, R^5 = H, R^6 = H (bazzanin C)
1806 R^1 = H, R^2 = H, R^3 = H, R^4 = Cl, R^5 = Cl, R^6 = H (bazzanin D)
1807 R^1 = H, R^2 = H, R^3 = Cl, R^4 = Cl, R^5 = Cl, R^6 = H (bazzanin E)
1808 R^1 = H, R^2 = Cl, R^3 = H, R^4 = Cl, R^5 = H, R^6 = Cl (bazzanin F)
1809 R^1 = Cl, R^2 = Cl, R^3 = H, R^4 = Cl, R^5 = Cl, R^6 = H (bazzanin G)
1810 R^1 = H, R^2 = Cl, R^3 = H, R^4 = Cl, R^5 = Cl, R^6 = Cl (bazzanin H)
1811 R^1 = Cl, R^2 = H, R^3 = Cl, R^4 = Cl, R^5 = Cl, R^6 = Cl (bazzanin I)



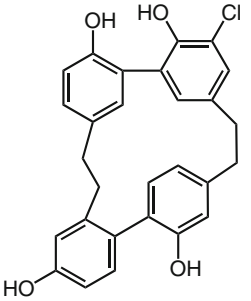
1814 R^1 = Cl, R^2 = H
(2,12-dichloroisoplagiochin D)
1815 R^1 = H, R^2 = Cl
(12,7'-dichloroisoplagiochin D)



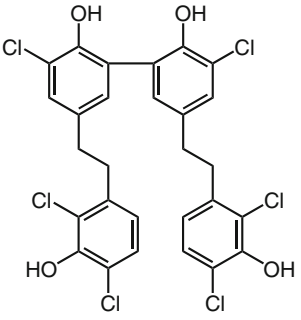
1816 (12,10'-dichloroisoplagiochin C)



1817 R^1 = H, R^2 = H, R^3 = H, R^4 = H, R^5 = H, R^6 = Me (bazzanin L)
1818 R^1 = H, R^2 = H, R^3 = H, R^4 = H, R^5 = H, R^6 = H (bazzanin M)
1819 R^1 = H, R^2 = Cl, R^3 = H, R^4 = H, R^5 = H, R^6 = H (bazzanin N)
1820 R^1 = Cl, R^2 = H, R^3 = Cl, R^4 = H, R^5 = H, R^6 = Me (bazzanin O)
1821 R^1 = Cl, R^2 = Cl, R^3 = H, R^4 = H, R^5 = H, R^6 = H (bazzanin P)
1822 R^1 = Cl, R^2 = Cl, R^3 = Cl, R^4 = H, R^5 = H, R^6 = H (bazzanin Q)
1823 R^1 = Cl, R^2 = Cl, R^3 = Cl, R^4 = Cl, R^5 = Cl, R^6 = H (bazzanin R)



1824 (bazzanin S)

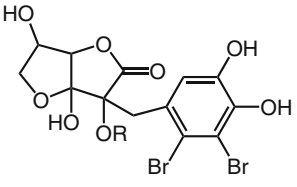


1825

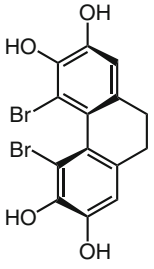
Other sources of chlorophenols are *de novo* formation in a sewage treatment plant (*1656*), composting of organic household waste (*1711*), and production in remote forest soil (*1712*) and by the litter-degrading fungus *Lepista nuda* (*1713*). All composts studied produce a chloromethoxybenzaldehyde in amounts between 5.6 and 73.4 μg kg^{-1} dry matter (*1711*). The chlorophenols detected in rural Douglas fir forest soil are the known 4-chlorophenol, 2,4-, 2,5-, and 2,6-dichlorophenol, and 2,4,5-trichlorophenol, although anthropogenic contributions could not be eliminated (*1712*).

3.21.2 Marine

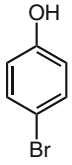
Most of the known marine-derived halogenated phenols are brominated, in accord with the widespread presence of bromoperoxidase in marine organisms, and 45 simple bromophenols were tabulated in the first survey (*1*). Most of these metabolites were found in red algae and, to a lesser extent, marine acorn worms. The red alga *Polysiphonia lanosa* from Brittany, which is the source of several simple bromophenols, also contains the new rhodomelol (**1826**) and methylrhodomelol (**1827**) (*1714*). A collection of the Senegalese red alga *Polysiphonia ferulacea* has yielded the optically active polysiphenol (**1828**), which is the first 9,10-dihydrophenanthrene found in a marine organism (*1715*). This hindered biphenyl analog is optically active and the absolute configuration was determined from its CD spectrum. Surprisingly, the simple 4-bromophenol (**1829**) was characterized for the first time in the acorn worms *Notomastus lobatus*, *Saccoglossus kowalevskii*, and *Arenicola cristata*, along with the previously known 2,6-dibromophenol and 2,4,6-tribromophenol (*1716, 1717*). The major organobromine metabolite in *Notomastus lobatus* is **1829**. Study of the Indo-Pacific *Dysidea* sp. sponge reveals the presence of a mixture of the new metabolites 2,3-dibromo-5-hydroxyphenol (**1830**) and 3,5-dibromo-2-hydroxyphenol (**1831**) (*1718*). A deep-water (113 m) Bahamian sponge *Aplysina fistularis fulva* has afforded the novel disulfate aplysillin A (**1832**) (*1719*). The sponge *Didiscus* sp. contains 3,5-dibromo-2-methoxybenzoic acid (**1833**) (*1720*). The marine ascidian *Aplidiopsis* sp. from Western Australia has yielded aplidiamine (**1834**), a unique zwitterionic adenine derivative (*1721*). The structure of **1834** was confirmed by synthesis and the original tautomeric structure was reassigned as shown (*1722, 1723*).



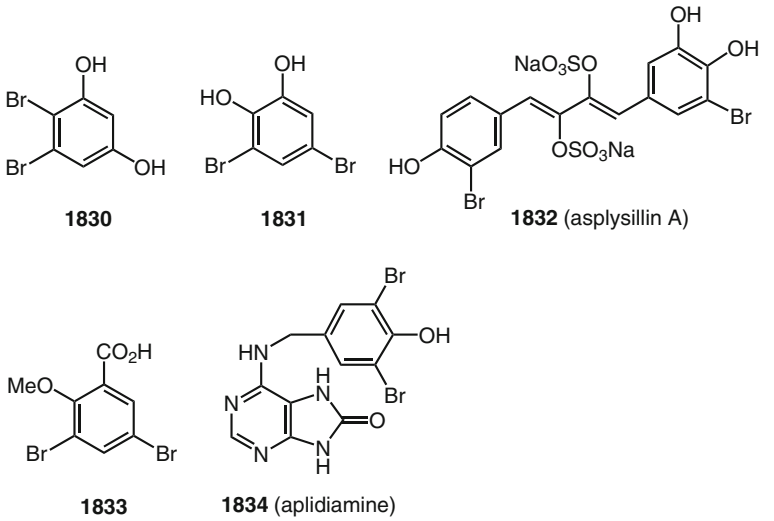
1826 R = H (rhodomelol)
1827 R = Me (methylrhodomelol)



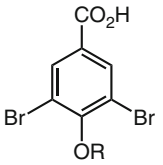
1828 (polysiphenol)



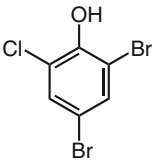
1829



The simple 3,5-dibromo-4-hydroxybenzoic acid (**1835**) and 3,5-dibromo-4-methoxybenzoic acid (**1836**) occur in the green alga *Ulva lactuca* (*1724*) and the Indian Ocean sponge *Psammaplysilla purpurea* (*1725*), respectively. The novel 6-chloro-2,4-dibromophenol (**1837**) was characterized from cultures of the marine bacterium *Pseudoalteromonas luteoviolacea* and displays antibacterial activity against methicillin-resistant *Staphylococcus aureus* and the cystic fibrosis associated pathogen *Burkholderia cepacia* (*1726*). The red alga *Polysiphonia sphaerocarpa* has furnished several previously unreported simple bromophenols, including 2-bromophenol (**1838**), 2,4-dibromoanisole (**1839**), 2,4,6-tribromoanisole (**1840**), and 2-bromo-4-methylphenol (**1841**) (*1727*). Bromoanisole **1840** is ubiquitous in the marine environment (*1728*) and is a compound responsible for the musty aroma of "corked" wine (*1729*). Brominated phenols and anisoles are also found in marine mammals (e.g., Arctic hooded seal and Antarctic Weddell seal) and Antarctic sponges (e.g., *Phorbas glaberrima*) (*394*), and in Norwegian predatory bird eggs (*479*). These compounds are mainly 2,4,6-tribromophenol and 2,4,6-tribromoanisole (**1840**). The flavor and aroma properties of marine bromophenols have been reviewed (*1730*). The Korean red alga *Symphyocladia latiuscula* has provided the new symphyoketone (**1842**), which has radical-scavenging activity (*1731*). Parasitenone (**1843**) was characterized from the Korean marine-derived fungus *Aspergillus parasiticus* and also exhibits radical-scavenging activity (*1732*). A Chinese specimen of the red alga *Rhodomela confervoides* has afforded the new **1844** and **1845** (*1733, 1734*). The isolated dimethyl acetal of **1844** may be an isolation artifact. Further study of this seaweed has uncovered nine new bromophenols, **1846**–**1854** (*1735*).



1835 R = H
1836 R = Me



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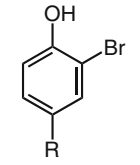
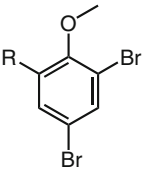
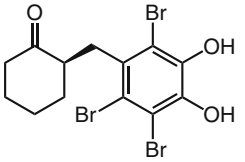


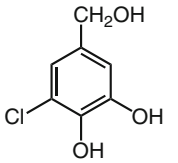
1838 R = H
1841 R = Me



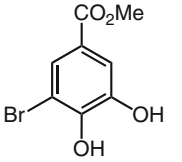
1839 R = H
1840 R = Br



1842 (symphyoketone)



1843 (parasitenone)



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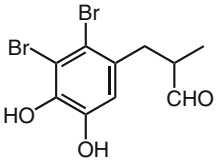

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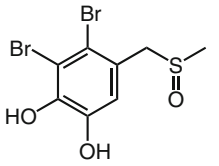

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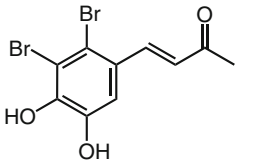

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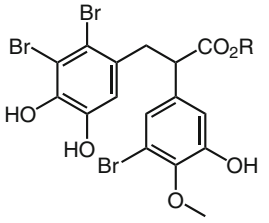
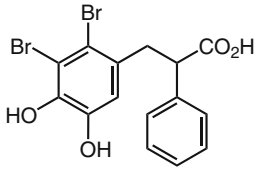


1848 R = H
1849 R = Me



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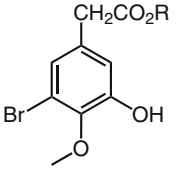
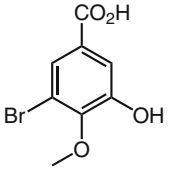


1851 R = H
1852 R = Me



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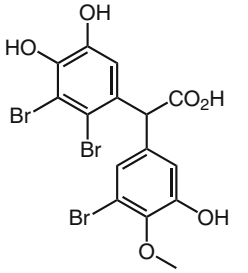
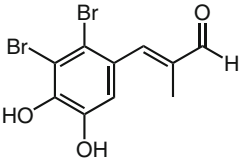
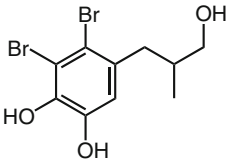


1854

The brown alga *Leathesia nana* from the gulf of the Yellow Sea in China has yielded the new bromophenols **1855** and **1856** (*1736–1738*), and the Chinese red alga *Rhodomela confervoides* contains the five novel brominated catechols **1857**–**1861**, in addition to several brominated diphenylmethanes discussed in Sect. 3.22.1 (Diphenylmethanes and Related Compounds) (*1739*). The Brazilian red alga *Osmundaria obtusilobu* has yielded the two novel sulfated oligobromophenols **1862** and **1863** (*1740*). The luminous acorn worm *Ptychodera flava* produces 2,3,5,6-tetrabromohydroquinone (**1864**), 2,3,5-tribromohydroquinone (**1865**), and tetrabromo-1,4-benzoquinone (**1866**) (*1741*).



1855



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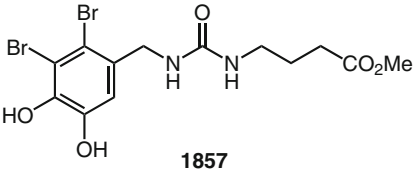
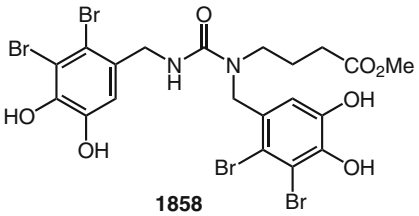
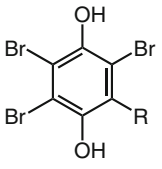


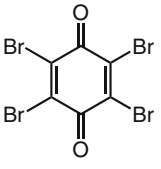
1857



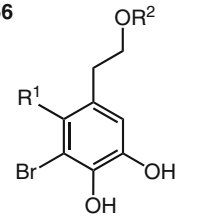
1858



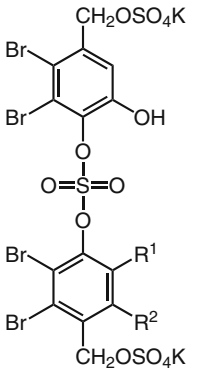
1864 R = Br
1865 R = H



1866

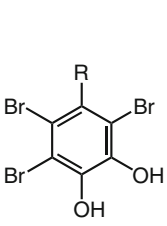


1859 R^1 = Br, R^2 = H
1860 R^1 = Br, R^2 = SO_3H
1861 R^1 = H, R^2 = SO_3H

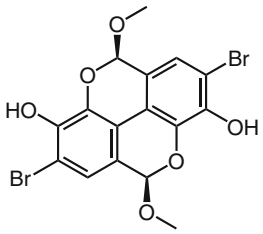


1862 R^1 = OH, R^2 = H
1863 R^1 = H, R^2 = OH

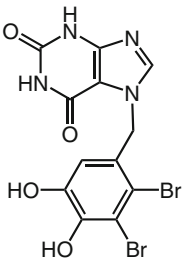
The red alga *Symphyocladia latiuscula* has afforded the new tribromophenols **1867** and **1868** (*1742*), and the red alga *Polysiphonia urceolata* contains urceolatol (**1869**), a novel bromobenzaldehyde dimer having C_2 symmetry (*1743*). The red alga *Rhodomela confervoides* has yielded lanosol-purine metabolite **1870** (*1455*) and lanosol-deoxyguanosine **1871**, along with the new simpler metabolites **1872** and **1873** (*1744*). Poipuol (**1874**) occurs in a Hawaiian *Hyrtios* sp. sponge (*1745*). It is interesting to note that poipuol is a rare halogenated phenol having halogen (chlorine) *meta* to the *ortho*, *para*-directing hydroxy groups.



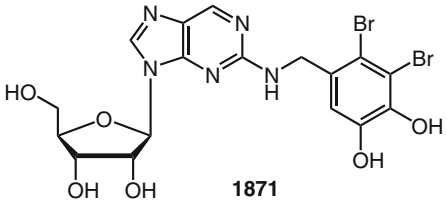
1867 R = Me
1868 R = CHO



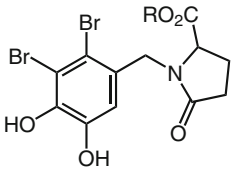
1869 (urceolatol)



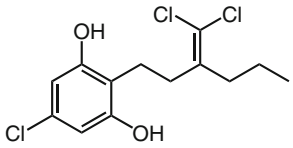
1870



1871



1872 R = Me
1873 R = H



1874 (poipuol)

A study of the natural radiocarbon (^{14}C) in the acorn worm *Saccoglossus bromophenolosus*, which was collected off the Maine coast, revealed that the 2,4-dibromophenol produced by these worms is of recent origin, in contrast to that from petroleum-derived anthropogenic 2,4-dibromophenol (*1746*). Thus, this result combined with the earlier study (*1223*) supports a natural source of 2,4-dibromophenol in these animals. It should be noted that the more recent radiocarbon work utilizes improved methodology (*1746*).

In closing this section, it should be mentioned that simple bromophenols (2-bromophenol, 4-bromophenol, 2,4-dibromophenol, 2,6-dibromophenol, and 2,4,6-

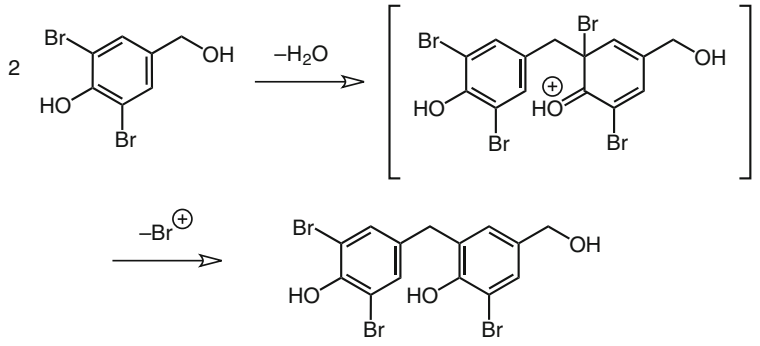
tribromophenol) are ubiquitous in the marine environment, particularly in fresh and saltwater seafood (*1747–1751*). There is compelling evidence for a dietary origin of these compounds, from both marine algae (*1748, 1749, 1751–1753*) and marine polychaetes and bryozoans (*1748–1750*).

3.22 Complex Phenols

3.22.1 Diphenylmethanes and Related Compounds

The several known polybrominated diphenylmethanes (*1*) may arise via a pathway analogous to the known dimerization of benzyl alcohols (*1754*). For example, the red algal known metabolite 3,5-dibromo-4-hydroxybenzyl alcohol may condense to give the known thelephenol (**EEE**) via (non-enzymatic) *ipso* electrophilic substitution (Scheme 3.4). These condensations can occur under mild acidic conditions (*1754*).

Several new polybrominated diphenylmethanes have been discovered since the first survey. The Japanese red alga *Odonthalia corymbifera* contains several known bromophenols and the novel diphenylmethane **1875**, which is a potent feeding deterrent towards abalone (*Haliotis discus hannai*) and sea urchin (*Strongylocentrotus intermedius*) (*1755*). Since methanol was used in the isolation process, the actual metabolite may be the corresponding benzylic alcohol. The red alga *Rhodomela confervoides* is a rich source of bromophenols including new brominated diphenylmethanes, such as **1876** (*1733*), **1877** (*1744*), **1878–1880** (*1739*), and **1881** and **1882** (*1455*). The brown alga *Leathesia nana* has yielded **1883–1886** (*1738*), the latter two of which represent very interesting structures.

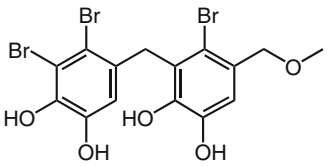


EEE (thelephenol)

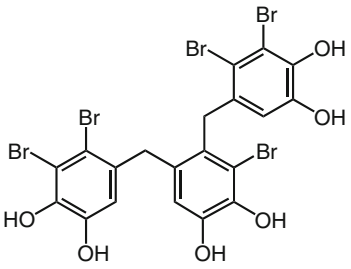
Proposed formation of thelephenol (**EEE**)*(1754)*

Scheme 3.4

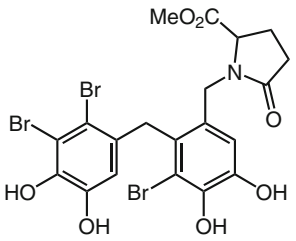
The red alga *Symphyocladia latiuscula* has afforded the two heavily brominated **1887** and **1888** (*1742*).



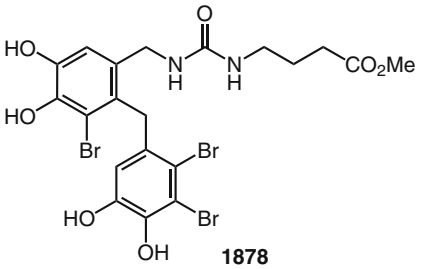
1875



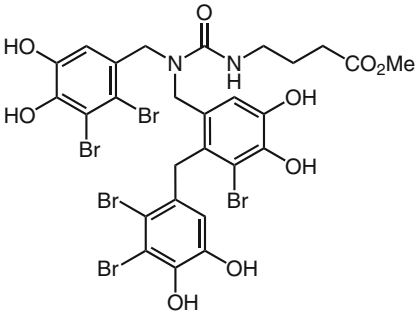
1876



1877



1878



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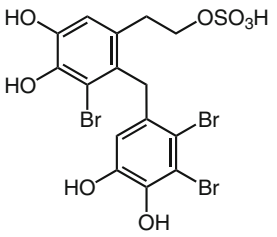
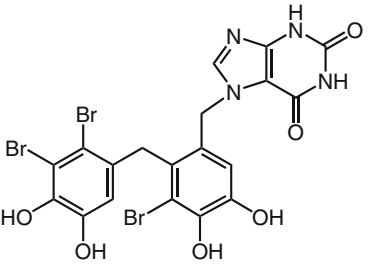
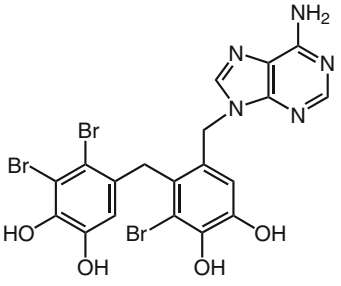


1880



1881



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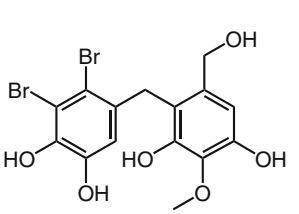
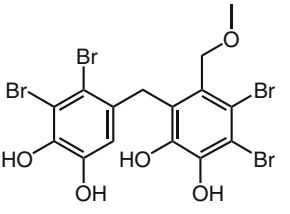


1883



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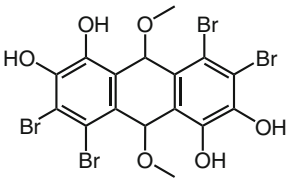

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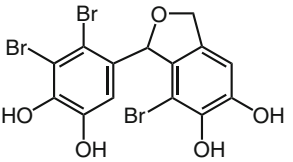

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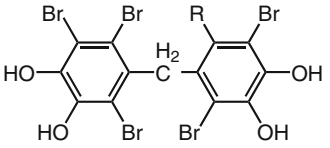
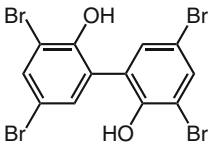
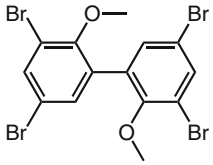


1887 R = Br
1888 R = H

Although not diphenylmethanes, two unique brominated biphenyls were isolated from a marine bacterium and marine mammals. Thus, *Pseudoalteromonas phenolica*, a new marine bacterium, produces MC21-A (**1889**), which appears to be the first naturally occurring polybrominated biphenyl (*1756*). This dimer of 2,4-dibromophenol, 2,2′-dihydroxy-3,3′,5,5′-tetrabromobiphenyl (2,2′-diOH-BB80), has comparable antibacterial activity to vancomycin against methicillin-resistant *Staphylococcus aureus*, and has a higher killing rate than vancomycin. The dimethoxylated version of MC21-A, 2,2′-dimethoxy-3,3′,5,5′-tetrabromobiphenyl (2,2′-diMeO-BB80) (**1890**), is found in several marine mammals, Striped dolphin (*Stenella coeruleoalba*), Bottlenose dolphin (*Tursiops truncatus*), Minke whale (*Balaenoptera acutorostrata*), and Baird's beaked whale (*Berardius bairdii*) (*1757, 1758*). Both of these polybrominated biphenyls (PBBs) are considered to be natural products, as no relevant PBB congener precursor is present in industrial products, no other PBBs are present in the mammalian samples, and the high concentration of **1890** (12–800 ng g^{-1} lipid) represents one of the most abundant compounds analyzed in these samples, which included polybrominated diphenyl ethers (PBDEs), hexabromocyclododecane (HBCDD), and methoxylated PBDEs (*1757, 1758*).



1889 (MC21-A)



1890

3.22.2 Diphenyl Ethers

Given the abundance of phenols in the oceans – halogenated or not – and the ease with which they undergo oxidative dimerization (*1759*), it is hardly surprising that halogenated diphenyl ethers are abundant in the marine environment (Fig. 3.27). More than 30 such natural brominated diphenyl ethers were documented in the first survey (*1*), and several new examples have been subsequently identified. It is worth noting that all of the previously identified natural (sponge-derived) brominated diphenyl ethers have at least one additional oxygen atom (hydroxy or methoxy), whereas the industrial fire retardant polybrominated diphenyl ethers do not.

A study of South Pacific marine invertebrates has revealed the new **1891** in the sponge *Dysidea herbacea* (*1760*). The new **1892** was isolated from *Sagaminopteron bilealbum* molluscs feeding on the sponge *Dysidea herbacea* from Guam waters (*1761*). Four samples of *Dysidea* sponges from the Indo-Pacific yielded the

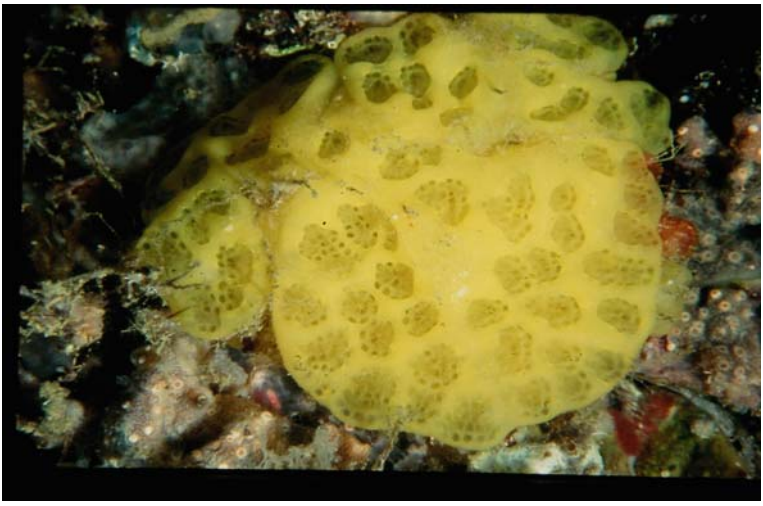
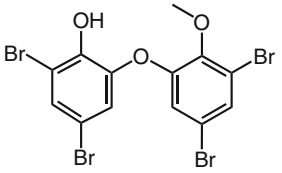


Fig. 3.27 *Aplidium longithorax*, a tunicate that produces polybrominated diphenyl ethers (Photo: F. J. Schmitz)

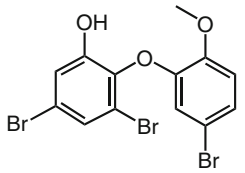
new polybrominated diphenyl ethers **1893–1896**, in addition to several known analogs (*1718, 1762*). These metabolites inhibit inosine monophosphate dehydrogenase, guanosine monophosphate synthetase, and 15-lipoxygenase. An Indian Ocean collection of *Dysidea herbacea* has afforded the new **1897** (*1763*), and this sponge from West Sumatra, Indonesia, contains **1898–1901**, which show activity against *Bacillus subtilis* and the phytopathogenic fungus *Cladosporium cucumerinum* (*1764*). The novel lanosol-type dimers **1902** and **1903** were isolated along with the known lanosol from the red alga *Odonthalia corymbifera*, and all three bromophenols inactivate α-glucosidase (*1765*). Examination of *Dysidea herbacea* from the Great Barrier Reef reveals the presence of the new polybrominated diphenyl ether **1904** (*1766*). The Palauan sponge *Phyllospongia dendyi* has yielded the new **1905–1907** and the known **1892** (*1767*). Another study of this sponge has uncovered the new **1908** and **1909**, in addition to nine previously identified polybrominated diphenyl ethers (*1768*). The brown alga *Leathesia nana* contains **1910**, which was isolated as the bis-ethoxy ether since ethanol was used in the isolation process (*1738*). The red alga *Symphyocladia latiuscula* contains bis-benzyl ether **1911** (*1742*), and acorn worms of genus *Thelepus* produce the novel bis-benzyl ether **1912** (*1793*). Okinawan crustose coralline red algae have yielded corallinaether (**1913**), along with a novel brominated dibenzofuran described later (*1769*). Further examination of a Great Barrier Reef *Dysidea herbacea* has uncovered the new **1914** (*1770*). The Indonesian sponge *Lamellodysidea herbacea* (Fig. 3.28) has afforded the new **1915–1918** along with ten

Fig. 3.28 *Lamellodysidea herbacea*, a sponge from Sunda Strait, Indonesia, that contains the new diphenyl ethers **1915–1918** and several previously known analogues (Photo: J. Tanaka)

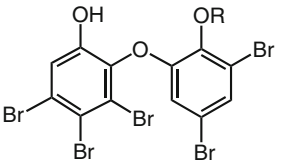
previously known analogs (*1771*). A Solomon Islands sponge *Phyllospongia* sp. has yielded the tribrominated diphenyl ether **1919** (*1772*). This compound, other brominated diphenyl ethers, and related brominated phenolics inhibit various lipoxygenases (*1772*). The methoxylated **1920** occurs both in the red alga *Ceramium tenuicorne* and blue mussels (*Mytilus edulis*) in the Baltic Sea (*1773*). Several other previously known polyhalogenated diphenyl ethers were found in these organisms.



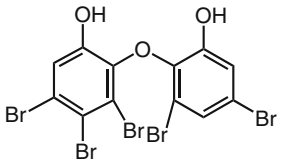
1891



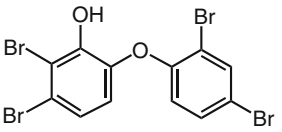
1892



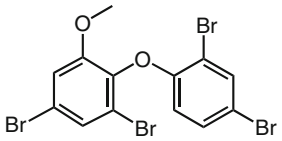
1893 R = H
1894 R = Me



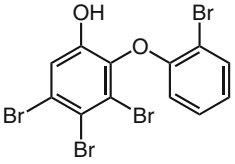
1895



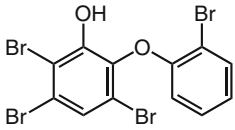
1896



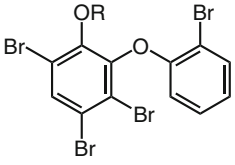
1897



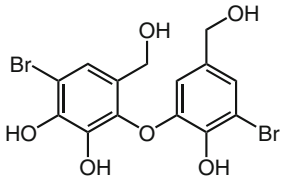
1898



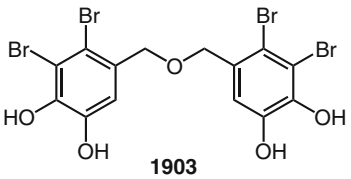
1899



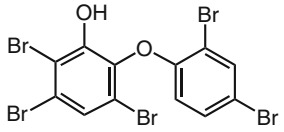
1900 R = H
1901 R = Me



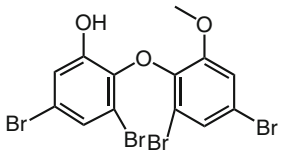
1902



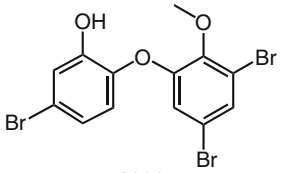
1903



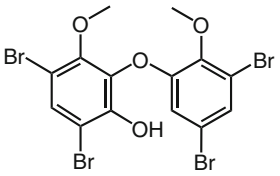
1904



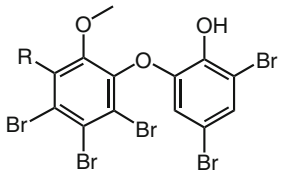
1905



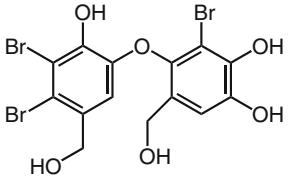
1906



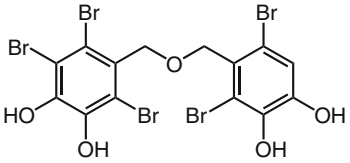
1907



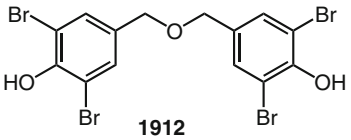
1908 R = Br
1909 R = H



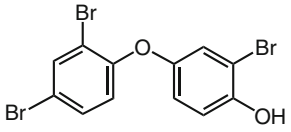
1910



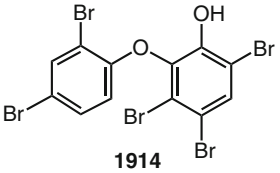
1911



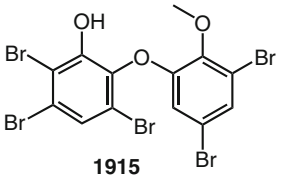
1912



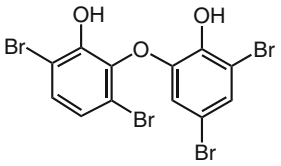
1913



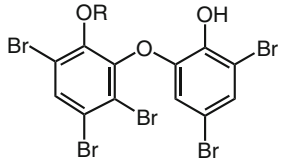
1914



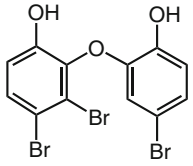
1915



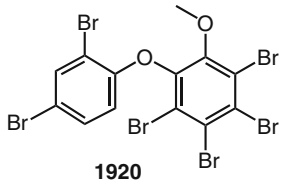
1916



1917 R = H
1918 R = Me



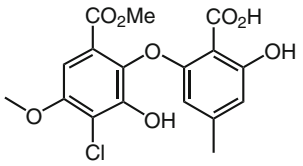
1919



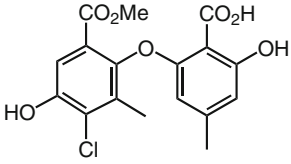
1920

These and other polybrominated diphenyl ethers, along with other halogenated compounds, whether natural marine metabolites or anthropogenic fire retardants (*1774–1776*) have been identified in tunicates (*1777*), nudibranchs (*996, 1778*), cyanobacteria (*1003*) (which may be the actual source of these polybrominated diphenyl ethers), and other marine life such as salmon (*1779, 1780*), other fish (*1781–1783*), several marine mammals (*1215, 1784–1787*), crocodile eggs (*1786*), and human milk from women who consume whale blubber (*1788*). Evidence as to the origin of these polybrominated diphenyl ethers is provided by the observation that some nine halogenated compounds, including polybrominated diphenyl ethers, were discovered in archived whale oil collected in 1921 from the final voyage of the whaling ship *Charles W. Morgan*, obviously predating the large-scale industrial synthesis of brominated fire retardants (*1222*). Noteworthy is that DDT, its metabolites (e.g., DDE), and polychlorinated biphenyls (PCBs) were not detected in this whale oil. Moreover, an analysis of the ^{14}C content of **1897** and two previously described polybrominated diphenyl ethers (*1*) isolated from marine mammals confirms their natural origin (*1223, 1789*). The synthesis of polybrominated diphenyl ethers has been of great interest in view of their biological activity and the need for pure analytical standards (*1790–1792*).

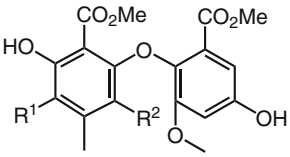
Several other non-marine halogenated diphenyl ethers are newly described. For example, the fungus *Pestalotiopsis* sp. has yielded RES-1214-2 (**1921**) (*1794*), while a fungus of genus *Xylaria* also produces **1921** ("dihydromaldoxin") along with the new isodihydromaldoxin (**1922**) (*1795*). The new methyl dichloroasterrate (**1923**) and methyl chloroasterrate (**1924**) were independently isolated from an *Aspergillus* sp. culture broth (*1796*) and from an unidentified fungal strain B 90911 (*1797*). The corresponding acids **1925** and **1926** were earlier characterized from *Penicillium citrinum* (*1798*). The Brazilian tree *Byrsonima microphylla* contains the novel chlorinated diphenyl ether **1927**, the presence of which in the heartwood was confirmed by HPLC and TLC (*1799*).



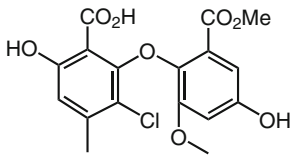
1921 (RES-1214-2)



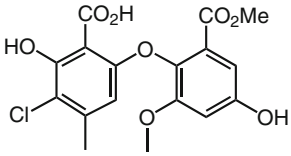
1922 (isodihydromaldoxin)



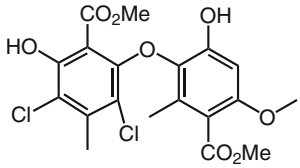
1923 $R^1 = R^2 = Cl$ (methyl dichloroasterrate)
1924 $R^1 = Cl$, $R^2 = H$ (methyl chloroasterrate)



1925

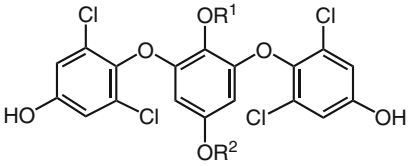


1926

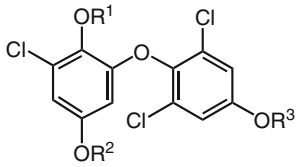


1927

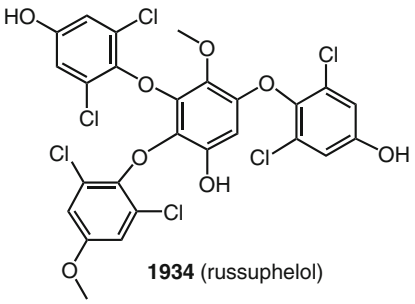
The toxic mushroom *Russula subnigricans* produces the novel polychlorinated phenyl ethers, russuphelins A–F (**1928–1933**), some of which (B, C, D) exhibit cytotoxicity against P388 leukemia cells (*1672, 1800*). Further study of this mushroom uncovered the presence of the optically active russuphelol (**1934**) (*1801*). The terrestrial cyanobacterium *Fischerella ambigua* has afforded ambigol C (**1935**) (*1654*), which is an isomer of the previously described ambigols A and B (*1*).



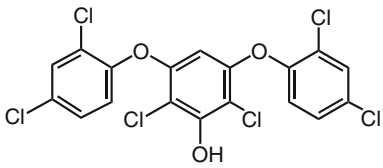
1928 $R^1 = R^2 = Me$ (russuphelin A)
1929 $R^1 = Me$, $R^2 = H$ (russuphelin B)
1930 $R^1 = R^2 = H$ (russuphelin C)



1931 $R^1 = R^2 = Me$, $R^3 = H$ (russuphelin D)
1932 $R^1 = R^3 = Me$, $R^2 = H$ (russuphelin E)
1933 $R^1 = H$, $R^2 = R^3 = Me$ (russuphelin F)

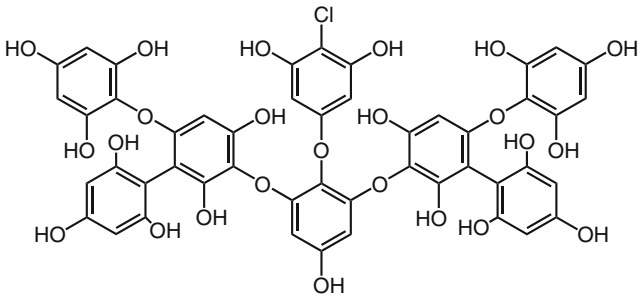


1934 (russuphelol)

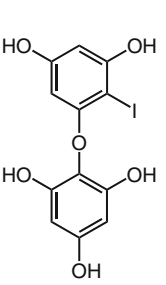


1935 (ambigol C)

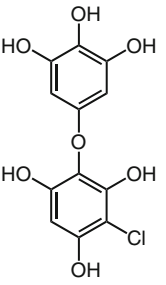
The New Zealand brown algae *Sargassum spinuligerum* and *Cystophora torulosa* produce several fucophlorethols including chlorobisfucopentaphlorethol-A (**1936**) (isolated as the peracetate) (*1802*). The brown alga *Carpophyllum angustifolium*, collected in New Zealand, has furnished 45 phloroglucinols including halogenated 2[D']iododiphlorethol (**1937**), 3[A]chlorobifuhalol (**1938**), and 3[A_4]chlorodifucol (**1939**) (isolated as peracetates) (*1818*). An examination of the New Zealand brown alga *Cystophora retroflexa* has identified 17 halogenated phlorethols and fucophlorethols, including 12 new compounds, all isolated as peracetates: $2_{[B]}$-bromotriphlorethol-A (**1940**), $2_{[D]}$-bromotriphlorethol-A (**1941**), $2_{[B]}$,$2_{[D]}$-dibromotriphlorethol-A (**1942**), $2_{[D]}$-bromotetraphlorethol-C (**1943**), $3_{[A1]}$,$5_{[A1]}$-dichlorotriphlorethol-A (**1944**), $3_{[A1]}$,$4_{[D]}$-dichlorotriphlorethol-A (**1945**), $3_{[A1]}$-chloro,$4_{[D]}$-bromotriphlorethol-A (**1946**), $2_{[B]}$,$4_{[D]}$-dichlorotriphlorethol-A (**1947**), $2_{[D]}$,$3_{[A1]}$-dibromotriphlorethol-A (**1948**), $3_{[A1]}$-bromo,$2_{[D]}$-chlorotriphlorethol-A (**1949**), $4_{[D]}$-chlorofucotriphlorethol-B (**1950**), and $4_{[D]}$-chlorobisfucotetraphlorethol-A (**1951**) (*1803*). These fascinating polyphenolic phloroglucinols have been reviewed (*1804*).



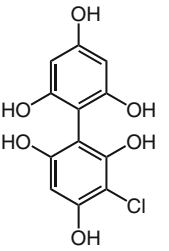
1936



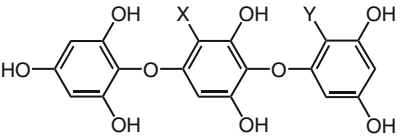
1937



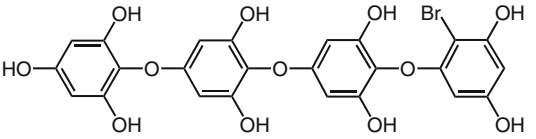
1938



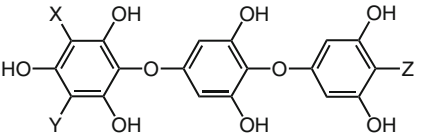
1939



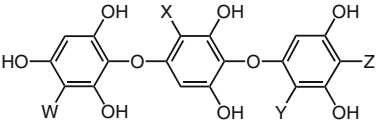
1940 X = Br, Y = H
1941 X = H, Y = Br
1942 X = Y = Br



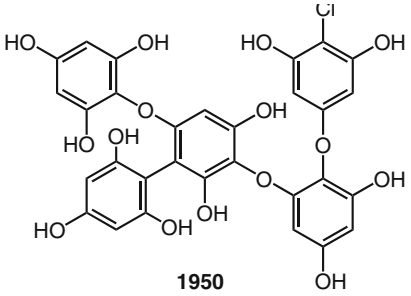
1943



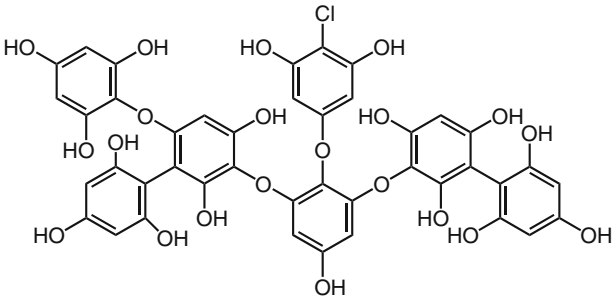
1944 X = Y = Cl, Z = H
1945 X = H, Y = Z = Cl
1946 X = H, Y = Cl, Z = Br



1947 W = Y = H, X = Z = Cl
1948 W = Y = Br, X = Z = H
1949 W = Br, Y = Cl, X = Z = H



1950



1951

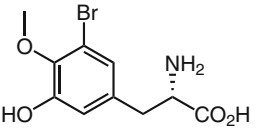
3.22.3 Tyrosines

Although relatively few simple halogenated tyrosines are found naturally, many "transformed" tyrosines are produced by marine organisms and these are covered in Sects. 3.22.3.2–3.22.3.4.

3.22.3.1 Simple Tyrosines, Thyroxine, and Related Compounds

3-Chlorotyrosine, which was previously found to occur in the cuticle of locusts (*1*), is the product of the reaction of tyrosyl residues in albumin (*1805*) and in red blood cells (*1806*) with the human neutrophil myeloperoxidase-hydrogen peroxide-chloride system. The latter study provides evidence that free chlorine gas is involved in this chlorination reaction, rather than hypochlorous acid (*1806*). Furthermore, 3-chlorotyrosine is found in human atherosclerotic tissues, with the highest concentrations present in patients with coronary heart disease, indicating that 3-chlorotyrosine is a specific marker for low-density lipoprotein (LDL) oxidation by myeloperoxidase (MPO) (*1807*). This amino acid forms in dialysis patients as a result of oxidative stress by activated neutrophils. Thus, hemodialysis increases plasma MPO and hypochlorous acid leading to elevated levels of 3-chlorotyrosine (*1808*). This amino acid is also present in high concentrations in cystic fibrosis patients, who have high levels of MPO (*1809*). Consistent with these observations is

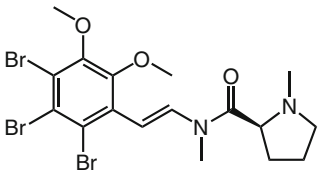
that MPO-deficient mice fail to generate 3-chlorotyrosine and to kill the fungus *Candida albicans* in vivo (*1810*). Infants who develop chronic lung disease contain high levels of 3-chlorotyrosine, suggesting that MPO and neutrophil oxidants contribute to the pathology of these diseases (*1811*). Likewise, both 3-bromotyrosine and 3,5-dibromotyrosine, which were previously isolated from marine organisms and insects (*1*), appear to be major products of protein oxidation by eosinophil peroxidase (EPO) (*1812*). This EPO-promoted bromination may contribute to the tissue damage that accompanies asthma (*1813*). The red alga *Rhodomela confervoides* has yielded the new bromotyrosine **1952** (*1455*).



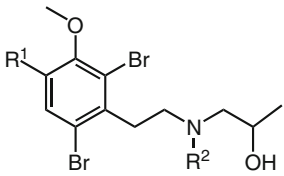
1952

3.22.3.2 Transformed Tyrosines, Tyramines, Phenethylamines and Related Compounds

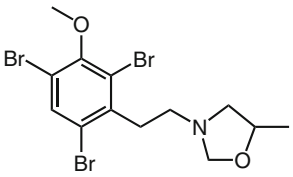
Tyrosine-derived metabolites in this section do not include spiro-cyclohexadienyl-isoxazolines and related compounds (Sect. 3.22.3.3) or bastadins (Sect. 3.22.3.4), but they do include tyrosine-derived alkaloids that were covered in the Alkaloids section in the first survey (*1*). The prolific bryozoan *Amathia convoluta*, collected in Tasmania, has yielded amathamide G (**1953**) (*1814*), the latest of several amathamide alkaloids from the genus *Amathia* (*1*). A Florida collection of this animal furnished the new convolutamines A–E (**1954–1958**) (*1815*), F (**1959**), and G (**1960**) (*1425*), and a Tasmanian sample of this bryozoan afforded convolutamine H (**1961**) (*1319*). A study of *Amathia convoluta* from the North Carolina coast has yielded volutamides A–E (**1962–1966**) (*1816*). Volutamides B and C reduce feeding by the pinfish (*Lagodon rhomboids*) and the urchin (*Arbacia punctulata*), respectively, and volutamides B and D are toxic toward larvae of the hydroid *Eudendrium carneum*. The New Zealand *Amathia wilsoni* contains the six novel amathaspiramides A–F (**1967–1972**) (*1817*).



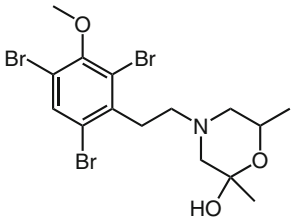
1953 (amathamide G)



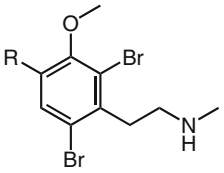
1954 R^1 = Br, R^2 = Me (convolutamine A)
1955 R^1 = H, R^2 = Me (convolutamine B)
1956 R^1 = Br,R^2 = H (convolutamine C)



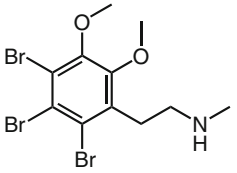
1957 (convolutamine D)



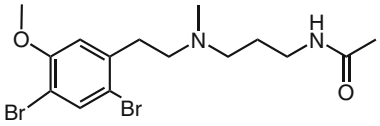
1958 (convolutamine E)



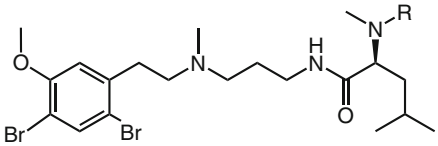
1959 R = Br (convolutamine F)
1960 R = H (convolutamine G)



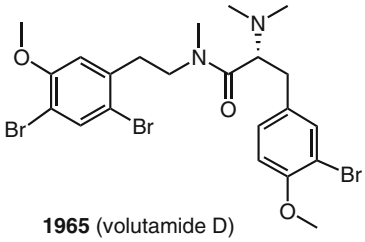
1961 (convolutamine H)



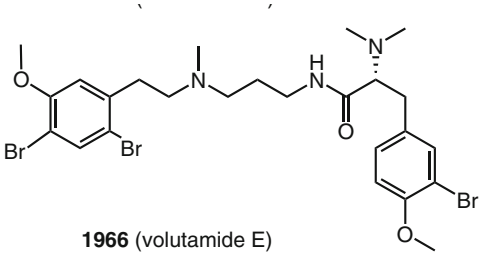
1962 (volutamide A)



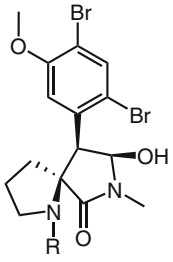
1963 R = H (volutamide B)
1964 R = Me (volutamide C)



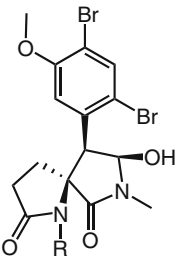
1965 (volutamide D)



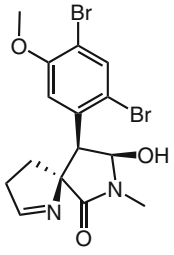
1966 (volutamide E)



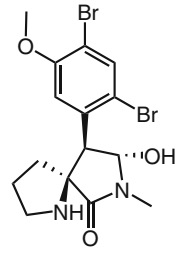
1967 R = Me (amathaspiramide A)
1969 R = H (amathaspiramide C)



1968 R = Me (amathaspiramide B)
1970 R = H (amathaspiramide D)

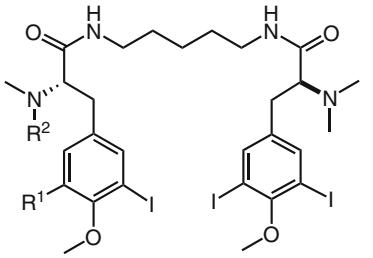


1971 (amathaspiramide E)

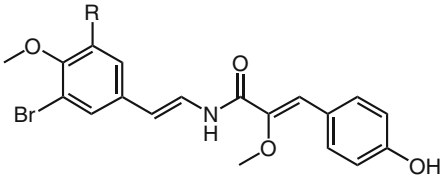


1972 (amathaspiramide F)

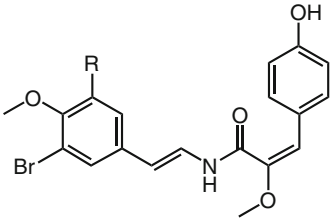
Marine tunicates are also a source of brominated tyrosine derivatives. The colonial ascidian *Aplidium* sp., which was collected in Australia, yielded the novel iodinated tyrosine alkaloids **1973–1975** (*1819*). Collections of *Botryllus* sp. and *Botryllus schlosseri* from the Philippines and the Great Barrier Reef, respectively, have afforded botryllamides A–D (**1976–1979**) (*1820*). A Palauan ascidian *Botrylloides tyreum* produces several new botryllamides, including the brominated botryllamide G (**1980**) (*1821*). The simple brominated tyramines **1981** and **1982** were isolated from the New Zealand ascidian *Cnemidocarpa bicornuta* (*1822*) and an Indonesian *Eudistoma* sp. ascidian (*1823*).



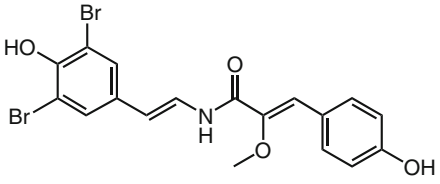
1973 R^1= H, R^2= Me
1974 R^1= I, R^2= Me
1975 R^1= R^2= H



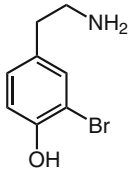
1976 R = Br (botryllamide A)
1978 R = H (botryllamide C)



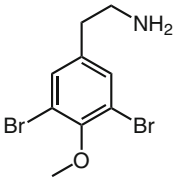
1977 R = Br (botryllamide B)
1979 R = H (botryllamide D)



1980 (botryllamide G)

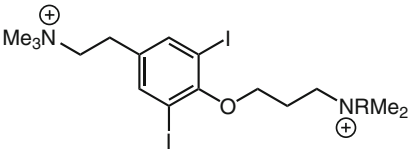


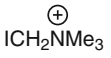
1981



1982

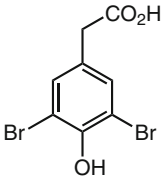
The toxic Japanese gastropod *Turbo marmorata* contains the two toxins, turbotoxins A (**1983**) and B (**1984**), isolated as bis-trifluoroacetates (*1824, 1825*). The turbotoxins A and B show $LD_{99} = 1.0$ and 4.0 mg kg^{-1} in mice. The simple iodinated ammonium salt **1985** is also found in this animal (*1826*). The red alga *Halopytis incurvus* contains the simple brominated phenols **1986** and **1987**, which were isolated as the methyl esters and methyl ethers (*1827*). These presumed degradation products of tyrosine are related to earlier reported brominated metabolites (*1*).



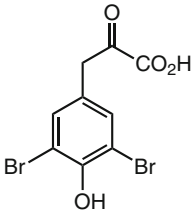


1985

1983 R = Me (turbotoxin A)
1984 R = H (turbotoxin B)



1986



1987

The largest number of brominated tyrosines is found in marine sponges, and more than 100 were documented in the first survey (*1*). The organization in this section is by sponge genus and species, rather than by type of metabolite. The Caribbean sponge *Pseudoceratina crassa* has yielded the new brominated phenylacetonitrile **1988** and imidazole **1989** (*1828*), both of which are close analogs of previously described sponge metabolites, verongamine in the case of **1989** (*1*). In addition to containing several known bromotyrosines, the New Caledonian *Pseudoceratina verrucosa* has afforded pseudoceratinine B (**1990**), in addition to two spirocyclohexadiene isoxazoles reported in the following section (*1829*). A Caribbean *Pseudoceratina* sp. contains 5-bromoverongamine (**1991**), which inhibits the settlement of barnacle larvae at 10 mg cm^{-3} (*1830*). Ceratinamine (**1992**), which was isolated from the Japanese *Pseudoceratina purpurea*, is also an antifouling compound against the barnacle *Balanus amphitrite* and contains the novel cyanoformamide functionality (*1831*). The novel tokaradines A–C (**1993–1995**) are found in the sponge *Pseudoceratina purpurea* (Fig. 3.29) collected in Southern Japan waters (*1832*). These bromotyrosines are lethal to the crab *Hemigrapsus sanguineus* at 20–50 μg g^{-1} (**1993** and **1994**). A Papua New Guinea collection of this sponge yielded the six new psammaplins E-J (**1996–2001**) (*1833*). Psammaplin

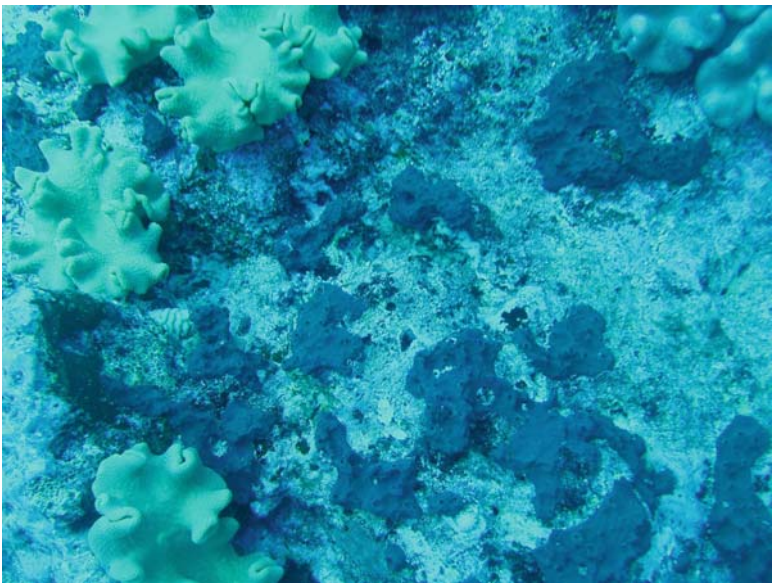
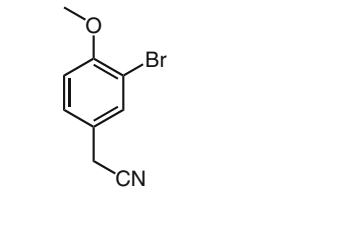
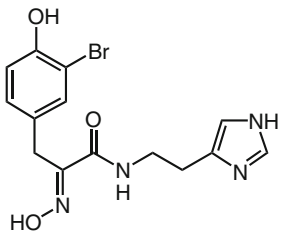


Fig. 3.29 *Pseudoceratina purpurea*, a Papua New Guinea sponge that contains several psammaplins such as **1996–2001** (Photo: P. Crews)

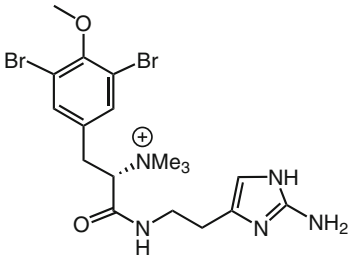
F (**1997**) is a potent histone deacetylase inhibitor, and psammaplin G (**1998**) is a potent DNA methyltransferase inhibitor. A Southern Japanese version of *Pseudoceratina purpurea* has yielded pseudoceratins A (**2002**) and B (**2003**) (*1834*).



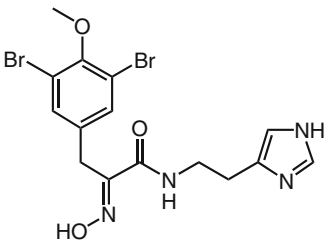
1988



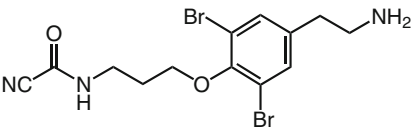
1989



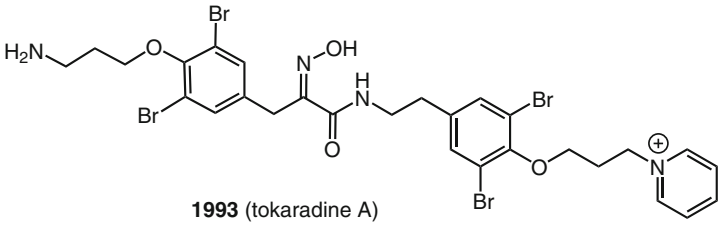
1990 (pseudoceratinine B)



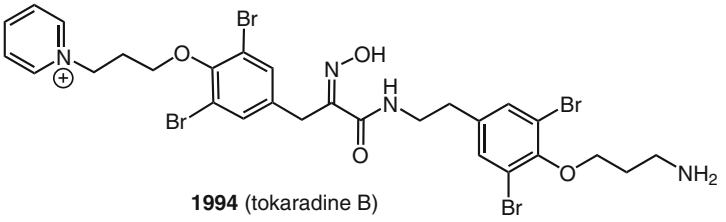
1991 (5-bromoverongamine)



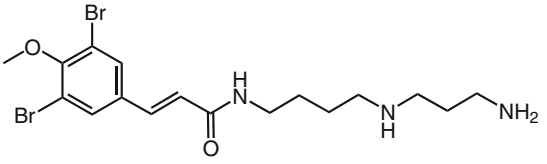
1992 (ceratinamine)



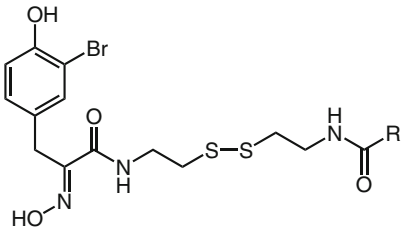
1993 (tokaradine A)



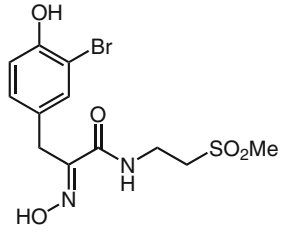
1994 (tokaradine B)



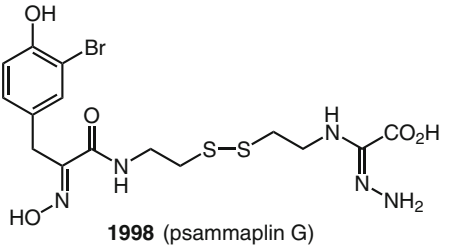
1995 (tokaradine C)



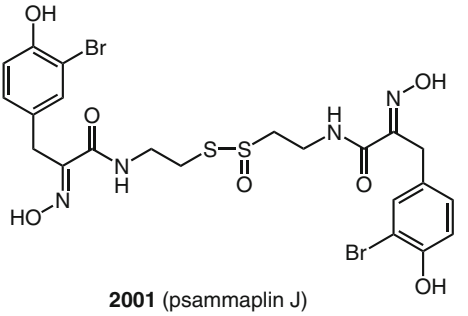
1996 R = $CONH_2$ (psammaplin E)
1997 R = CO_2H (psammaplin F)
1999 R = OEt (psammaplin H)



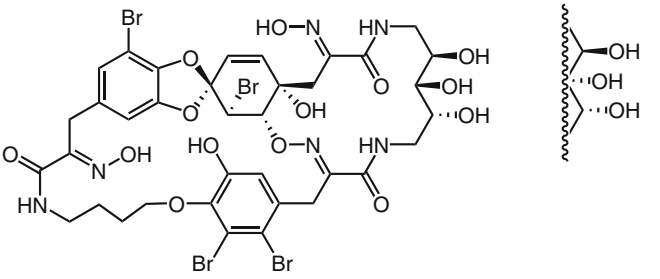
2000 (psammaplin I)



1998 (psammaplin G)

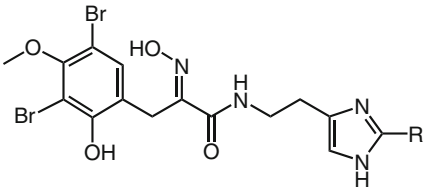


2001 (psammaplin J)

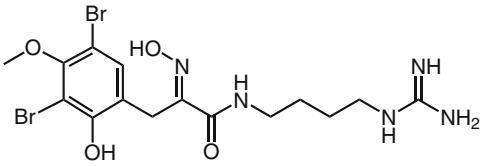


2002 (pseudoceratin A) **2003** (pseudoceratin B)

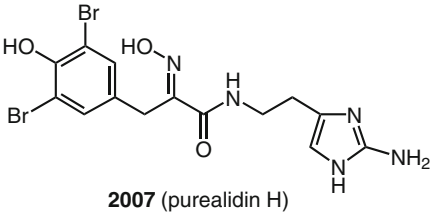
Sponges of the genus *Psammaplysilla* have been a rich source of bromotyrosine metabolites (*1*), and that trend continues for the present survey. An examination of the Okinawan *Psammaplysilla purea* has revealed the presence of purealidins M–O (**2004**–**2006**) (*1835*), and purealidin H (**2007**) and lipopurealins D (**2008**) and E (**2009**) (*1836*). Several collections of *Psammaplysilla purpurea* from India have yielded new bromotyrosines and related compounds. These include the simple **2010** and **2011** (*1837*), **2012** (*1838*), **2013** and **2014** (*1839*), purpuramines K (**2015**) and L (**2016**) (*1840*), **2017** (*1841*), and purpurealidins F (**2018**), G (**2019**), and H (**2020**) (*1842*).



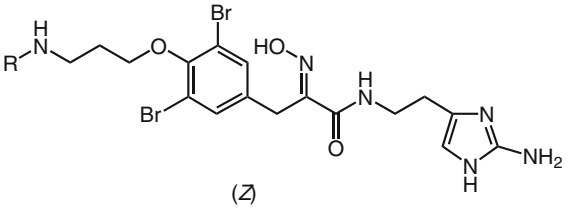
2004 R = NH_2 (purealidin M)
2005 R = H (purealidin N)



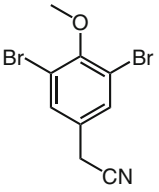
2006 (purealidin O)



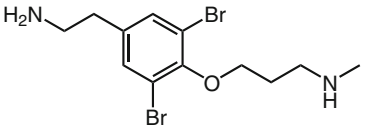
2007 (purealidin H)



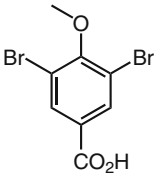
(*Z*)
2008 R = $CO(CH_2)_7CH{=}CH(CH_2)_4CHMe_2$ (lipopurealin D)
2009 R = $CO(CH_2)_{17}CH_3$ (lipopurealin E)



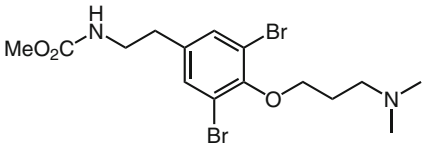
2010



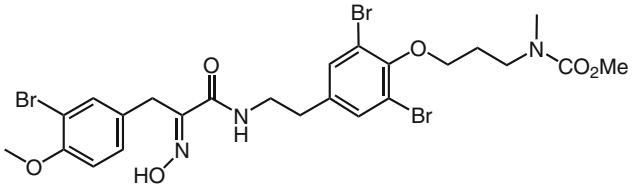
2012



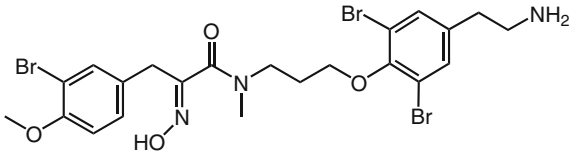
2011



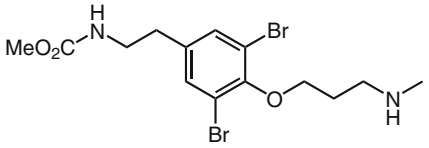
2013
2014 HX salt



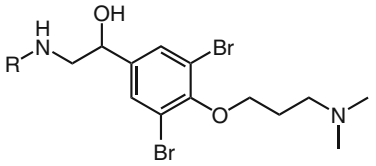
2015 (purpuramine K)



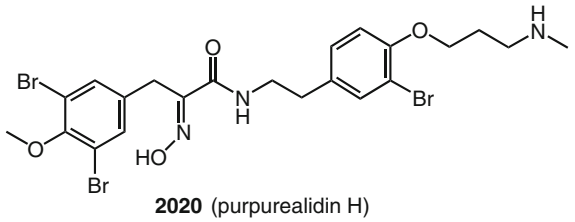
2016 (purpuramine L)



2017

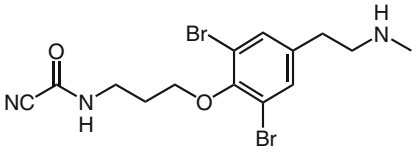


2018 R = H (purpurealidin F)
2019 R = CO_2Et (purpurealidin G)

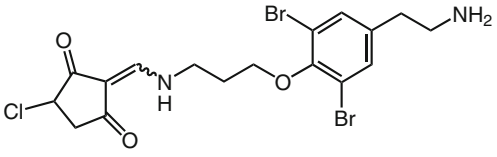


2020 (purpurealidin H)

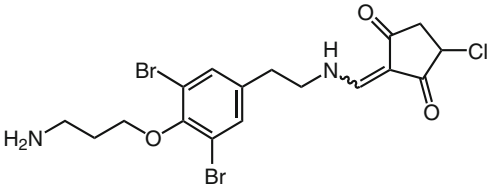
An undescribed Verongid sponge from Molokai, Hawaii, has yielded *N*-methylceratinamine (**2021**) and the moloka'iamine derivatives, wai'anaeamines A (**2022**) and B (**2023**) (*1843*). This sponge is most likely of the genus *Psammaplysilla* or *Pseudoceratina*. Another collection of a Verongid sponge from Molokai has furnished a series of mololipids, **2024**–**2036**, which display anti-HIV activity. These amides are derivatives of the previously known moloka'iamine, also present in this sponge (*1844*). A collection of *Psammaplysilla* sp. from the Indian Ocean has provided the new psammaplysenes A (**2037**) and B (**2038**), which are inhibitors of the FOXO1a nuclear export (*1845*).



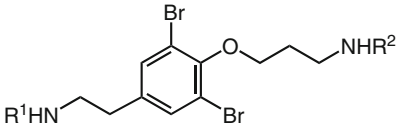
2021 (*N*-methylceratinamine)



2022 (wai'anaeamine A)

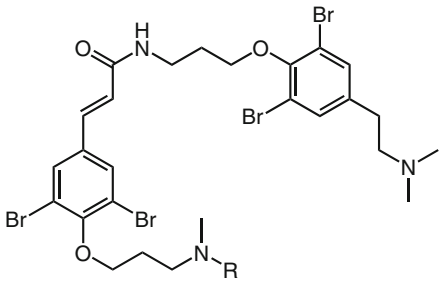


2023 (wai'anaeamine B)



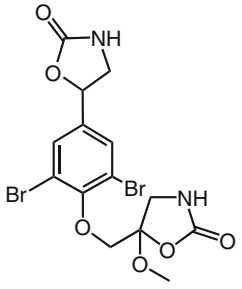
2024 - 2036 (mololipids)

R^1, R^2 = myristic, palmitic, margaric, oleic, stearic, arachidic, pentadecanoic, hexadecanoic (2), heptadecanoic, nondecanoic, unknown (2)

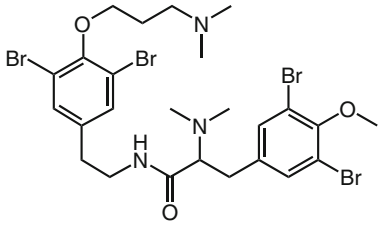


2037 R = Me (psammaplysene A)
2038 R = H (psammaplysene B)

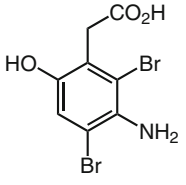
Sponges of the genus *Aplysina* are abundant in the Caribbean and Mediterranean Seas and have yielded a variety of bromotyrosine metabolites (*1*). The Caribbean *Aplysina insularis* affords **2039** (*1846*), and an Indo-Pacific *Aplysina* sp. sponge has yielded aplyzanzine A (**2040**) (*1847*). A study of the Brazilian sponges *Aplysina cauliformis* and *Pachychalina* sp. has led to compounds **2041** and **2042**, respectively (*1848*). An *Aplysinella* sp. sponge from Micronesia contains 7-hydroxyceratinamine (**2043**) and dibromotyramine **2044** (*1849*). An Australian collection of *Aplysinella rhax* has furnished psammaplin A 11′-sulfate (**2045**) and bisaprasin 11′-sulfate (**2046**) (*1850*). An independent study of this sponge, which was collected in Guam, Palau, and Pohnpei, identified **2045** (as the *N*,*N*-dimethylguanidium salt) along with the new psammaplin A_2 (**2047**), aplysinellins A (**2048**) and B (**2049**) (*1851*). A Fijian version of *Aplysinella rhax* has yielded the new psammaplins K (**2050**) and L (**2051**) (*1852*).



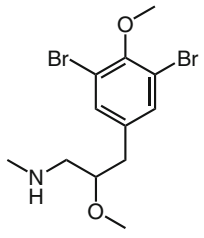
2039



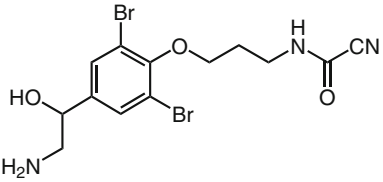
2040 (aplyzanzine A)



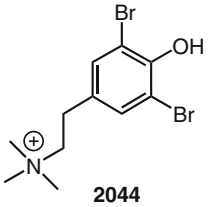
2041



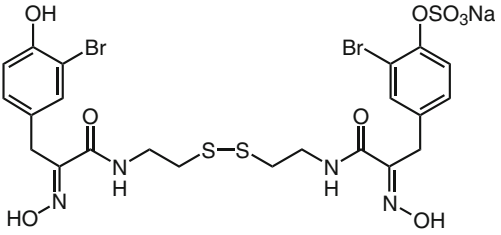
2042



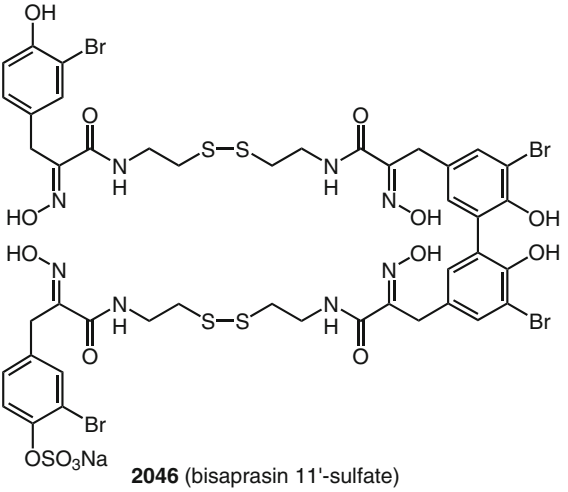
2043 (7-hydroxyceratinamine)



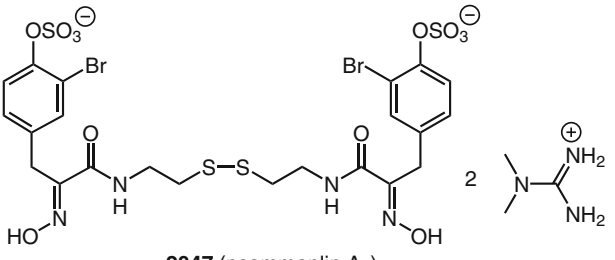
2044



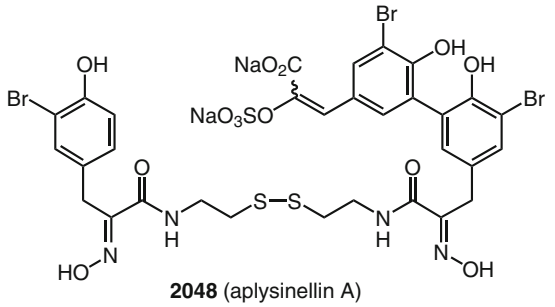
2045 (psammaplin A 11'-sulfate)



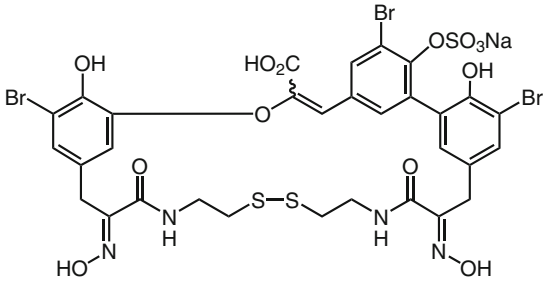
2046 (bisaprasin 11'-sulfate)



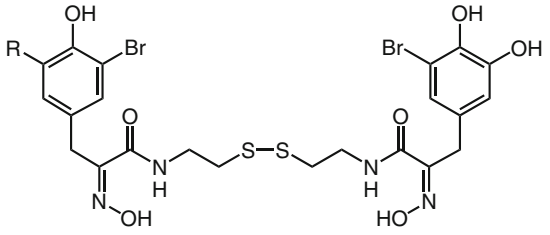
2047 (psammaplin A_2)



2048 (aplysinellin A)

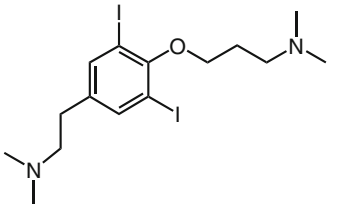


2049 (aplysinellin B)

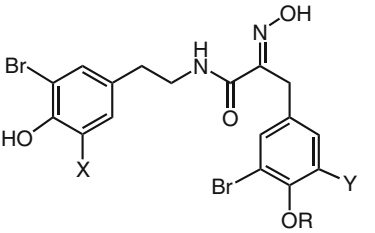


2050 R = H (psammaplin K)
2051 R = OH (psammaplin L)

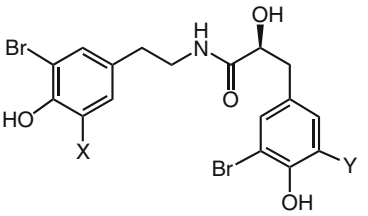
The novel iodinated tyrosine derivative dakaramine (**2052**) is present in the Senegalese sponge *Ptilocaulis spiculifer* (*1853*). A Papua New Guinea sponge *Ianthella basta* (Fig. 3.30) has furnished nine new bromotyrosine compounds, hemibastadins 3 (**2053**), **2054**–**2056**, and hemibastadinols 1 (**2057**), 2 (**2058**), and 3 (**2059**) (*1854*). The previously known hemibastadins 1 and 2 were also isolated. A Guamanian collection of this sponge has afforded 1-*O*-sulfatohemibastadins-1 (**2060**) and -2 (**2061**) (*1855*). The Caribbean sponge *Verongula gigantea* ("Netted Barrel Sponge") contains the novel bromotyrosine metabolite **2062** (*1856*). An unidentified Okinawan sponge of order Verongid has afforded nakirodin A (**2063**) (*1857*).



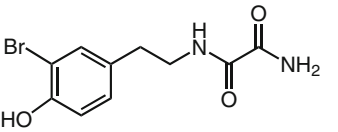
2052 (dakaramine)



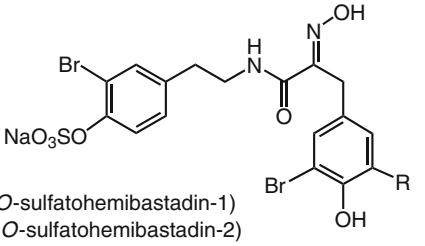
2053 Y = R = H, X = Br (hemibastadin 3)
2054 X = Y = H, R = Me
2055 X = H, R = Me, Y = Br



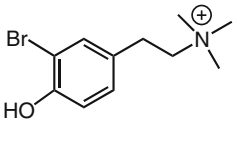
2057 X = Y = H (hemibastadinol 1)
2058 X = H, Y = Br (hemibastadinol 2)
2059 Y = H, X = Br (hemibastadinol 3)



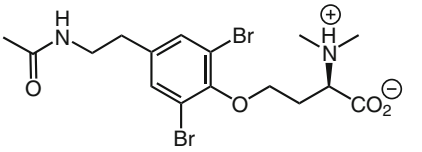
2056



2060 R = H (1-*O*-sulfatohemibastadin-1)
2061 R = Br (1-*O*-sulfatohemibastadin-2)



2062

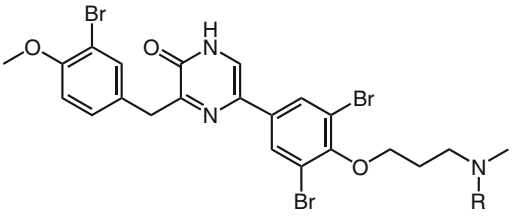


2063 (nakirodin A)

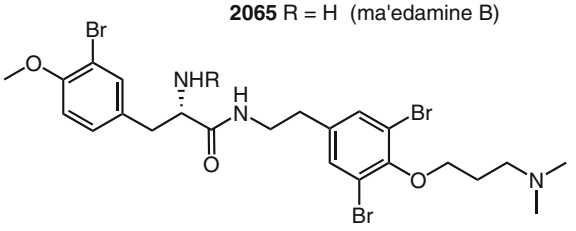
The novel pyrazinone bromotyrosines ma'edamines A (**2064**) and B (**2065**) were characterized from an Okinawan sponge *Suberea* sp. (*1858*). It is proposed that the pyrazinone ring may be derived from a dehydro form of the known aplysamine-2 or purpuramine H, which are also present in this sponge. A separate study of this sponge revealed the presence of the new suberedamines A (**2066**) and B (**2067**) (*1859*). An Australian non-Verongid sponge, *Oceanapia*

Fig. 3.30 *Ianthella basta*, a sponge rich in the bastadins **2053–2061** (Photo: F. J. Schmitz)

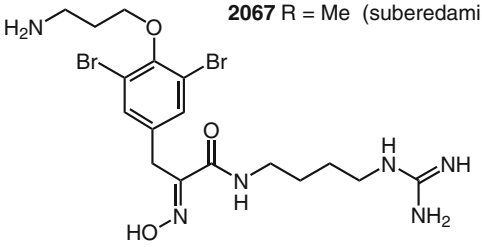
sp., has yielded **2068**, which is the first example of an inhibitor of the mycobacterial enzyme mycothiol *S*-conjugate amidase, found in *Mycobacterium* sp. (*1860*). The Fijian sponge *Druinella* sp. has afforded purpuramine J (**2069**), the first bromotyrosine *N*-oxide alkaloid to be discovered (*1861*). This metabolite is the *N*-oxide of aplysamine-2. The novel trisulfide **2070** and the two disulfides (*E, E*)-bromopsammaplin A (**2071**) and bispsammaplin A (**2072**) were found in a combined extract of the sponges *Jaspis wondoensis* and *Poecillastra wondoensis* (*1862*).



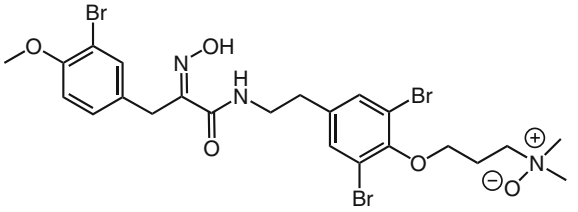
2064 R = Me (ma'edamine A)
2065 R = H (ma'edamine B)



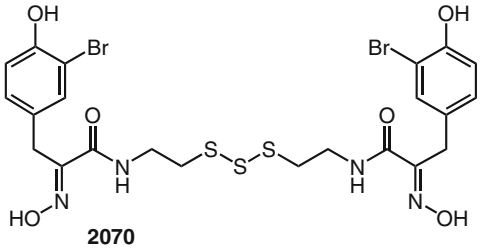
2066 R = H (suberedamine A)
2067 R = Me (suberedamine B)



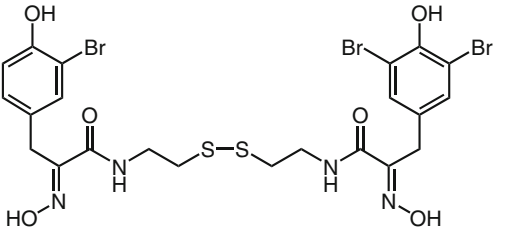
2068



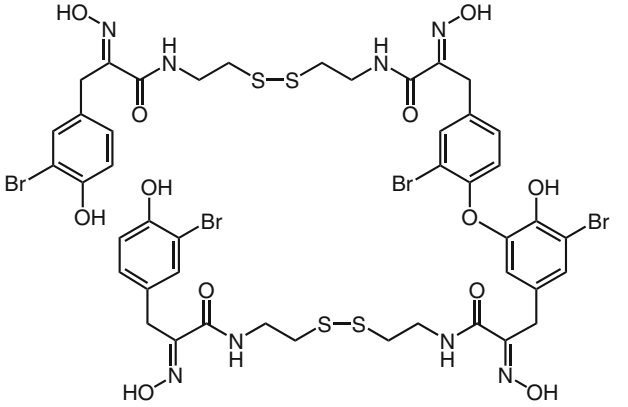
2069 (purpuramine J)



2070

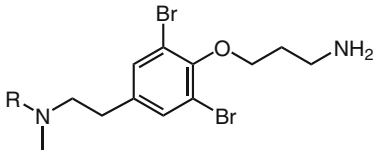


2071 ((*E*, *E*)-bromopsammaplin A)

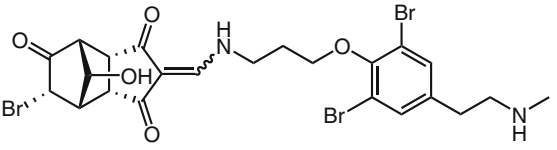


2072 (bispsammaplin A)

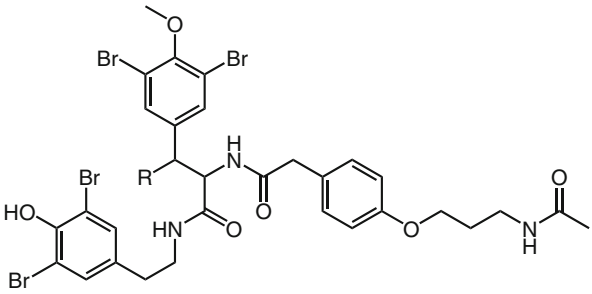
A southern Japan *Hexadella* sp. sponge has furnished the new moloka'iamines **2073** and **2074** and kuchinoenamine (**2075**), the latter having a unique tricyclo [5.2.1.$0^{2,6}$]decane skeleton (*1863*). These metabolites display antibacterial activity against the fish pathogenic bacterium *Aeromonas hydrophila*. A Madagascan sponge *Iotrochota purpurea* contains itampolins A (**2076**) and B (**2077**), which are comprised of three separate units including D-bromotyrosine (*1864*).



2073 R = H
2074 R = CN



2075 (kuchinoenamine)



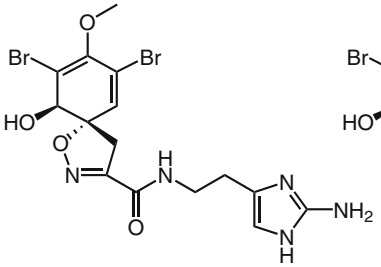
2076 R = H (itampolin A)
2077 R = OH (itampolin B)

While there exist too many syntheses of bromotyrosine alkaloids to delineate here, two illustrative examples are those of moloka'iamine (*1865*) and the mycothiol-*S*-conjugate amidase inhibitor **2068** (*1866*).

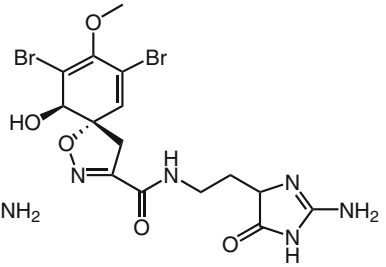
3.22.3.3 Transformed Multiple Tyrosines

As presented in the first survey (*1*), a large number of brominated tyrosines that contain a spirocyclohexadienyl isoxazoline ring are known, and 34 examples were described in the first survey (*1*). The first two such metabolites to be identified, aerothionin and homoaerothionin (*1*), are localized in the spherulous cells of the sponge *Aplysina fistularis*, which may suggest their release into the ectosome matrix and surrounding seawater as antifouling agents (*1867*).

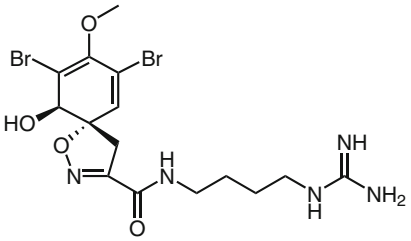
The Okinawan sponge *Psammaplysilla purea* that contains purealidins M–O (**2004**–**2006**) also yields purealidins J (**2078**), K (**2079**), L (**2080**), P (**2081**), Q (**2082**), and R (**2083**) (*1835*). Purealidin J (**2078**) is the antipode of pseudoceratinine A (**2089**). The Indian sponge *Psammaplysilla purpurea*, which is the source of purpurealidins F–H (**2018**–**2020**) and other bromotyrosines (vide supra), also contains purpurealidins A (**2084**), B (**2085**), C (**2086**), and D (**2087**) (*1842*). A Caribbean *Pseudoceratina* sponge has afforded the simple carboxylic acid **2088** (*1868*). The New Caledonian sponge *Pseudoceratina verrucosa*, which is the source of pseudoceratinine B (**1990**), also contains pseudoceratinines A (**2089**) and C (**2090**), the absolute configurations of which are shown (*1829*).



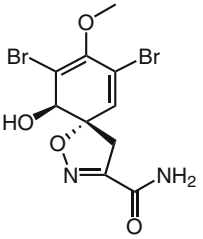
2078 (purealidin J)



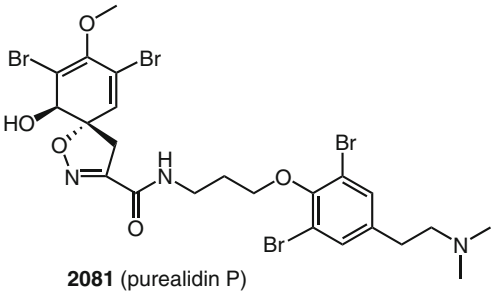
2079 (purealidin K)



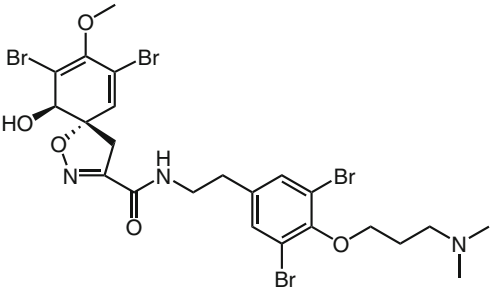
2080 (purealidin L)



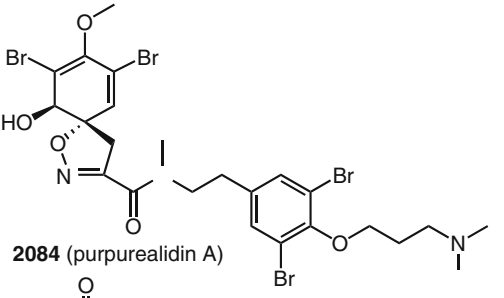
2083 (purealidin R)



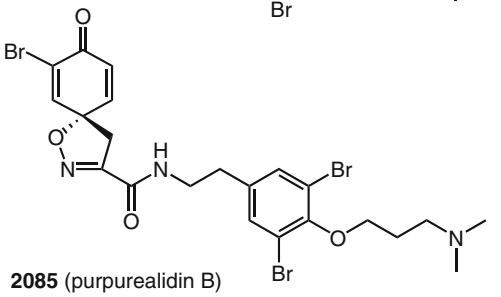
2081 (purealidin P)



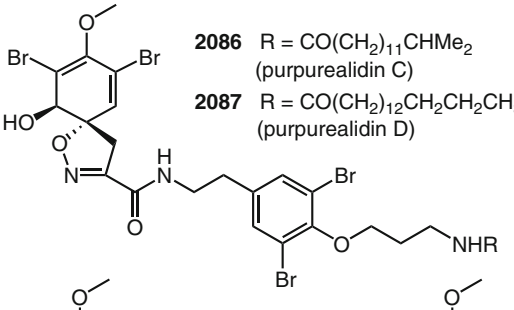
2082 (purealidin Q)



2084 (purpurealidin A)

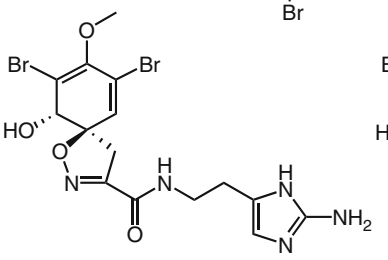


2085 (purpurealidin B)

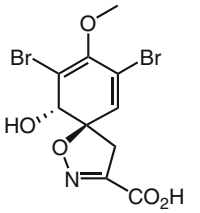


2086 R = $CO(CH_2)_{11}CHMe_2$ (purpurealidin C)

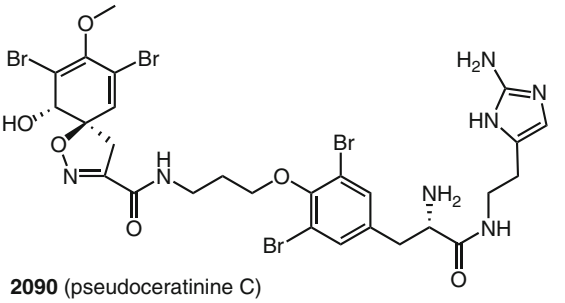
2087 R = $CO(CH_2)_{12}CH_2CH_2CH_3$ (purpurealidin D)



2089 (pseudoceratinine A)

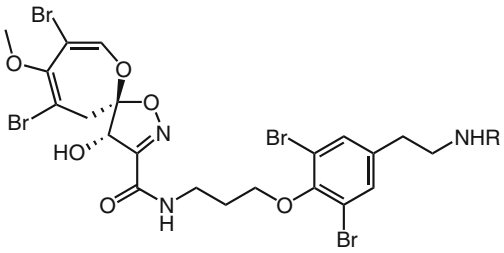


2088

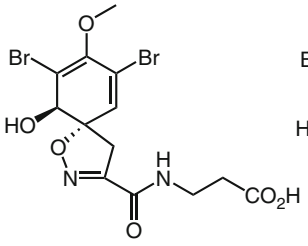


2090 (pseudoceratinine C)

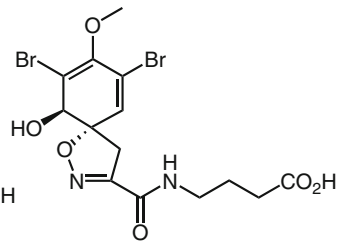
A Japanese collection of *Pseudoceratina purpurea* has uncovered the presence of ceratinamides A (**2091**) and B (**2092**) in this sponge (*1869*). These new compounds are acyl derivatives of psammaplysin A (*1*), which is also present in this sponge. The closely related psammaplysin F (**2093**) was identified in an *Aplysinella* sp. from Chuuk (*1870*). A Gulf of Thailand sponge, *Pseudoceratina purpurea*, has yielded purpuroceratic acids A (**2094**) and B (**2095**) (*1871*). In contrast to the aforementioned simple bromotyrosines, the complex zamamistatin (**2096**) was isolated from an Okinawan collection of *Pseudoceratina purpurea* (*1872*) (revised in *1873*). This novel zamamistatin exhibits significant antibacterial activity against the marine bacterium *Rhodospirillum salexigens*, which has adhering properties (*1872*).



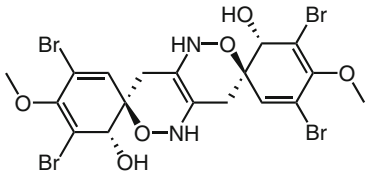
2091 R = CHO (ceratinamide A)
2092 R = $CO(CH_2)_{11}CHMe_2$ (ceratinamide B)
2093 R = Me (psammaplysin F)



2094 (purpuroceratic acid A)

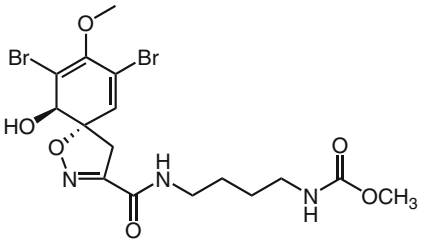


2095 (purpuroceratic acid B)

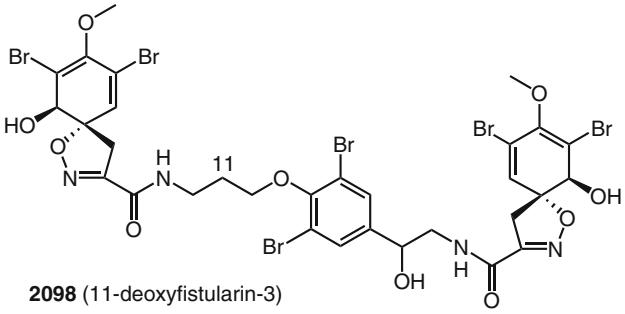


2096 (zamamistatin)

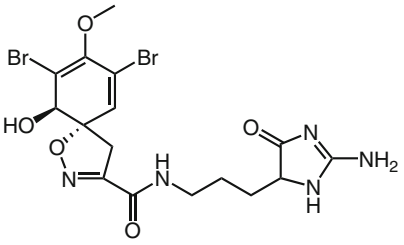
The Caribbean sponge *Aplysina insularis* has furnished **2097** (*1846*), 11-deoxyfistularin-3 (**2098**) (*1874*), and 14-oxoaerophobin-2 (**2099**) (*1875*), along with numerous previously known compounds. Similarly, the Verongida sponge *Aplysina archeri* (Fig. 3.31) contains a number of known bromotyrosine alkaloids in addition to the novel **2100** (*1876*). This Caribbean sponge has also afforded archerine (**2101**), a new metabolite that displays significant antihistamine activity (*1877*). The Mediterranean sponge *Aplysina cavernicola* has provided the new oxohomoaerothionin (**2102**) and 11-hydroxyfistularin-3 (**2103**) (*1878*). *Aplysina cauliformis*, from the Caribbean, has yielded the isomeric carbamates **2104** and **2105**, the latter of which inhibits mammalian protein synthesis and cell proliferation (*1879*).



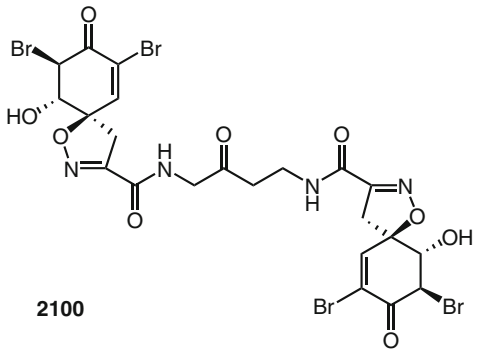
2097



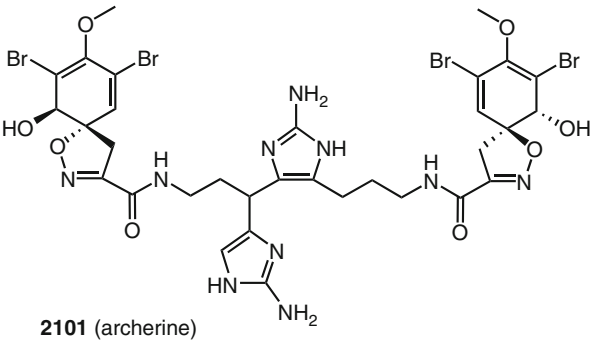
2098 (11-deoxyfistularin-3)



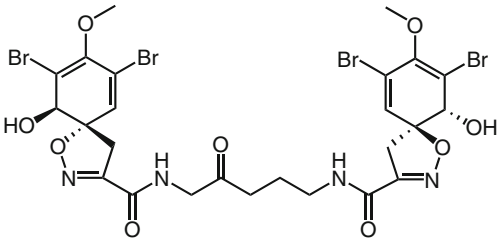
2099 (14-oxoaerophobin-2)



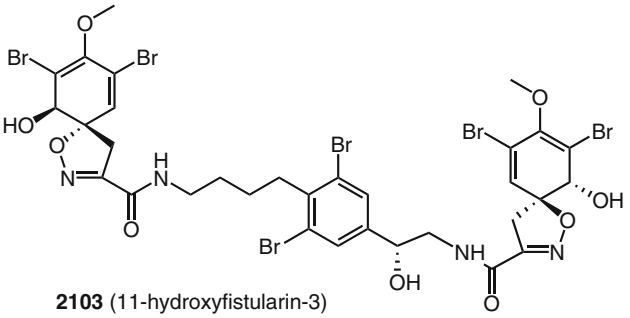
2100



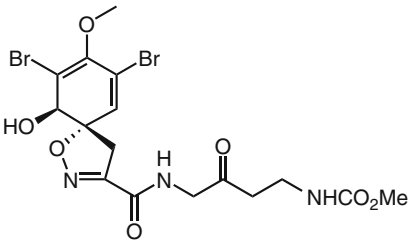
2101 (archerine)



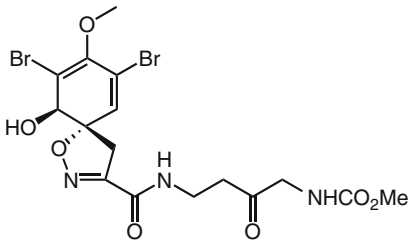
2102 (oxohomoaerothionin)



2103 (11-hydroxyfistularin-3)



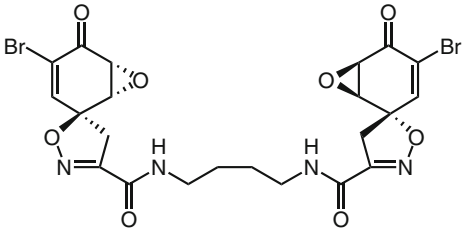
2104



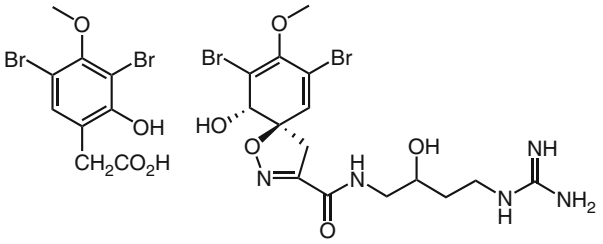
2105

Fig. 3.31 *Aplysina archeri*, a Caribbean sponge containing several bromotyrosines, including **2100** and archerine (**2101**) (Photo: J. R. Pawlik)

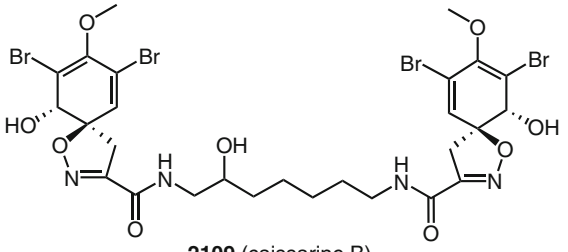
The Mexican sponge *Aplysina gerardogreeni* contains calafianin (**2106**) (*1880*) (structure revised and confirmed by total synthesis, (*1881–1883*)), the known aerothionin, and the new phenylacetic acid **2107** (*1880*). These studies confirm that calafianin (**2106**) and aerothionin have the same absolute configuration (*1883*). Whereas aerothionin displays antibacterial activity against *Mycobacterium tuberculosis*, calafianin does not (*1884*). The Brazilian sponge *Aplysina caissara* contains the new caissarines A (**2108**) and B (**2109**) (*1885*).



2106 (calafianin)



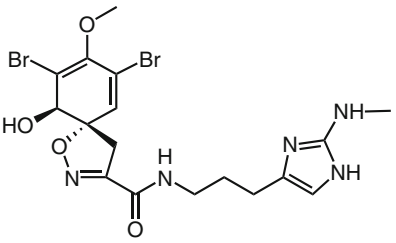
2107 **2108** (caissarine A)



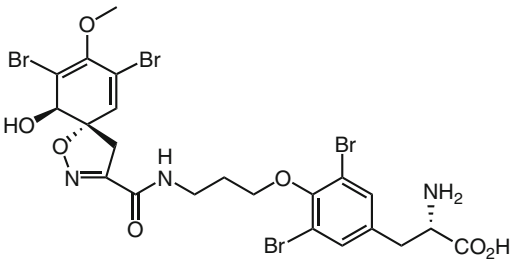
2109 (caissarine B)

A specimen of the Caribbean sponge *Aiolochroia crassa* has yielded the new *N*-methylaerophobin-2 (**2110**) (*1886*). Another collection of this sponge from Belize has afforded araplysillin III (**2111**) and hexadellin C (**2112**) (*1887*). This study established their absolute configurations as shown. A new stereoisomer, **FFF**, of fistularin-3 was reported from an Aegean Sea sample of the sponge *Verongia aerophoba* (*1888*). However, a determination of the absolute configuration of (+)-fistularin-3 and (+)-11-*epi*-fistularin-3 also reveals

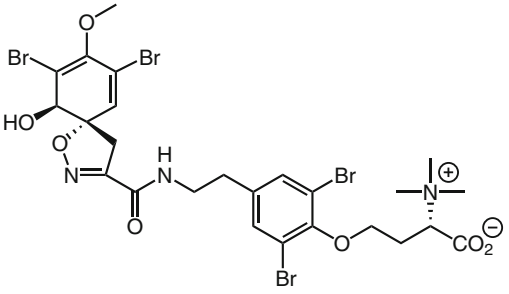
that **FFF** is, in fact, identical to the previously known 11-*epi*-fistularin-3 (*1892*). A Micronesian specimen of *Aplysinella* sp. has furnished (+)-aplysinillin (**2113**), which showed growth inhibition against the MCF-7 breast cancer cell line (*2649*).



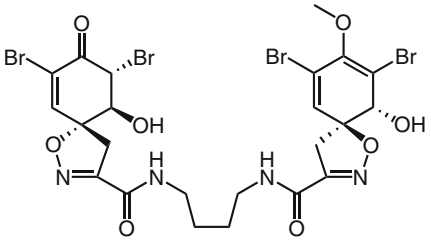
2110 (*N*-methylaerophobin-2)



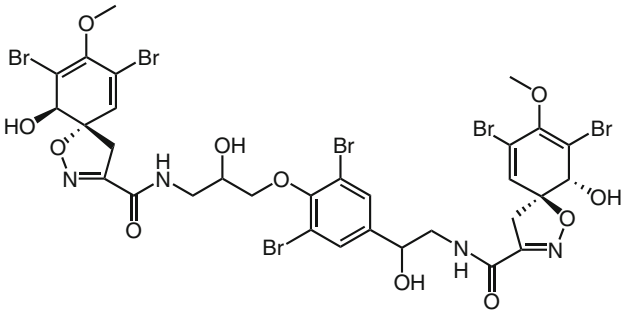
2111 (araplysillin III)



2112 (hexadellin C)

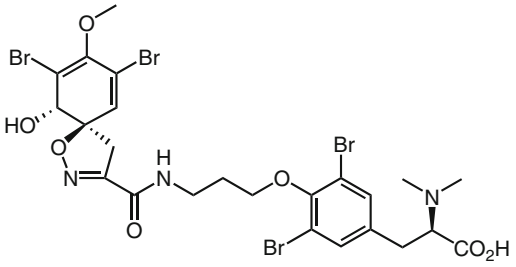


2113 (aplysinillin)

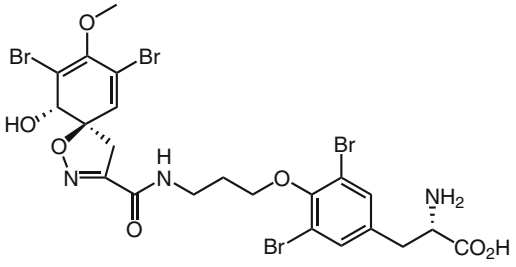


FFF (an epimer of fistularin-3)

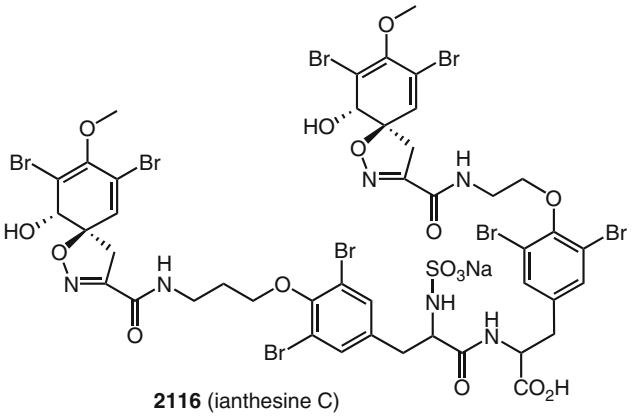
A Great Barrier Reef *Ianthella* sp. sponge has yielded ianthesines A–D (**2114**–**2117**) (*1889*). Ianthesines B–D display Na,K-ATPase inhibitory activity in the range 50–440 μM. The isolation of **2118** from an Australian *Oceanapia* sp. sponge has been described, including determination of its absolute configuration (*1860*).



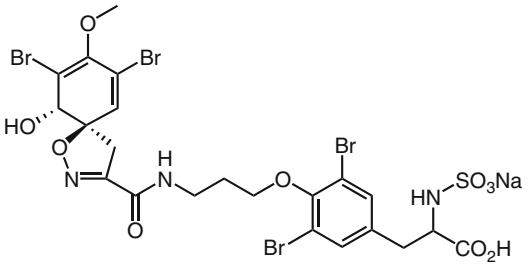
2114 (ianthesine A)



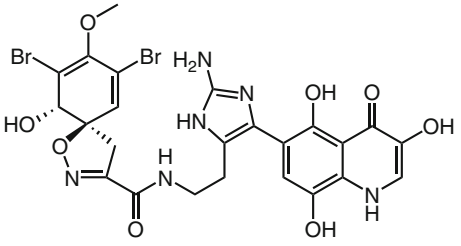
2115 (ianthesine B)



2116 (ianthesine C)

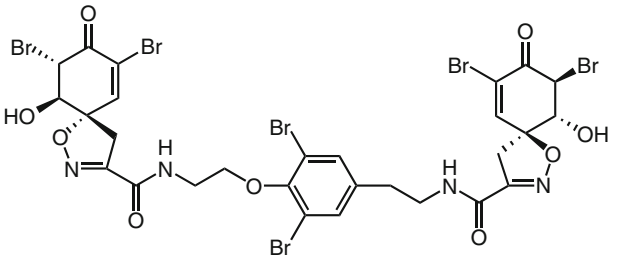


2117 (ianthesine D)

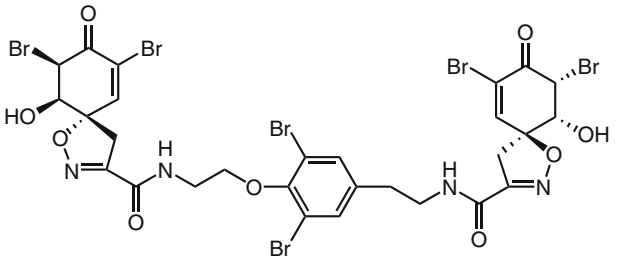


2118

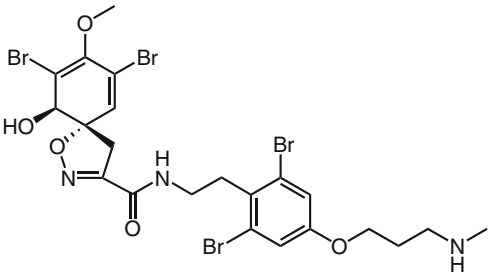
A collection of the sponge *Suberea* aff. *praetensa* from the Gulf of Thailand contains 11,17-dideoxyagelorins A (**2119**) and B (**2120**) (*1890*), and the Fijian sponge *Druinella* sp. has afforded purealidin S (**2121**) (*1861*). The Malaysian crinoid *Himerometra magnipinna* has furnished (+)-12-hydroxyhomoaerothionin (**2122**) (*1891*).



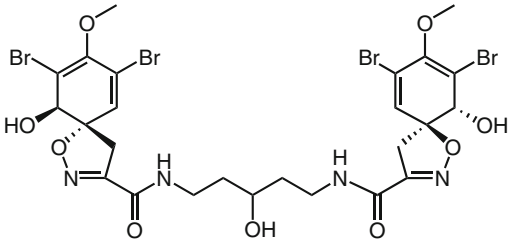
2119 (11,17-dideoxyagelorin A)



2120 (11,17-dideoxyagelorin B)



2121 (purealidin S)

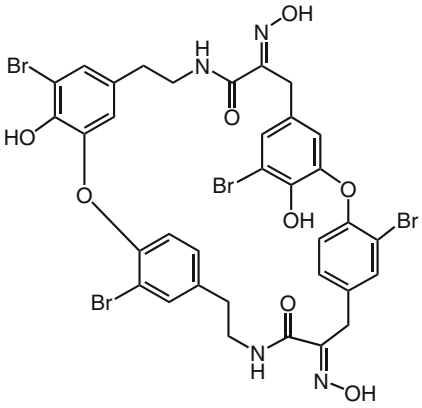


2122 (12-hydroxyhomoaerothionin)

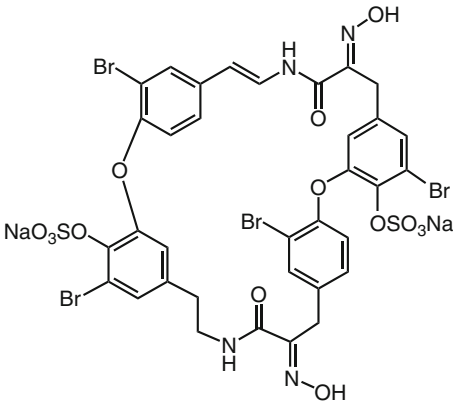
Several syntheses of the bromotyrosine spiroisoxazolines have been described (*1893–1895*), but a full survey of these synthetic efforts cannot be covered here.

3.22.3.4 Bastadins

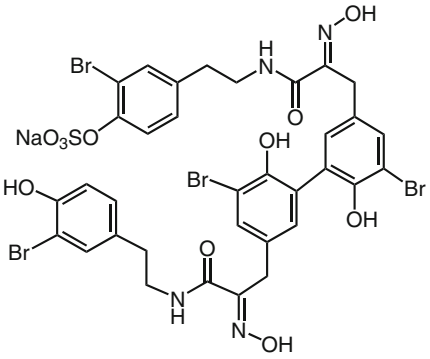
A study of the known bastadins-8, -10, and -12 from the Papua New Guinea sponge *Ianthella basta* has established the absolute configuration of these metabolites (*1896*). Bastadins-10 and -12 significantly inhibit the growth of several human cancer cell lines, and all three of these bastadins inhibit growth of *Staphylococcus aureus* and *Enterococcus faecalis*. Several new bastadins have been described since the first survey (*1*). A Western Australian *Ianthella basta* contains bastadin-20 (**2123**), 15,34-*O*-disulfatobastadin-7 (**2124**), and 10-*O*-sulfatobastadin-3 (**2125**) (*1897*). The Great Barrier Reef *Ianthella quadrangulata* has afforded bastadin-21 (**2126**) (*1898*).



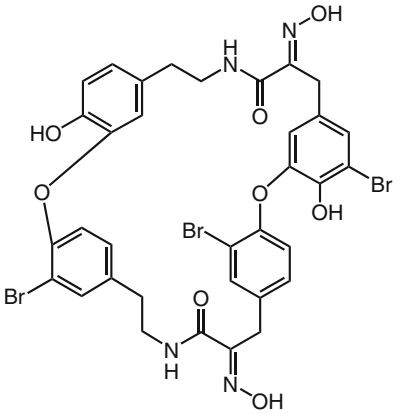
2123 (bastadin-20)



2124 (15,34-*O*-disulfatobastadin-7)

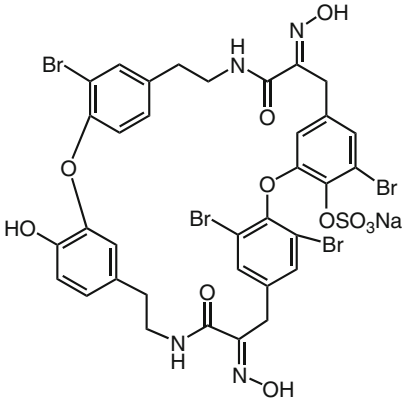


2125 (10-*O*-sulfatobastadin-3)

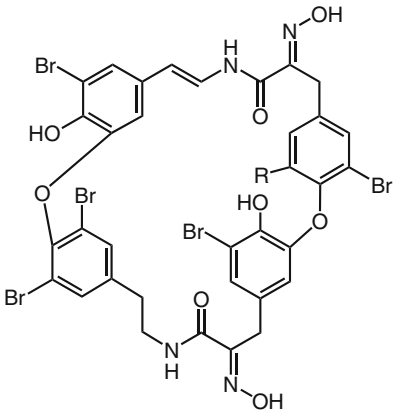


2126 (bastadin-21)

A Guam specimen of *Ianthella basta* has afforded the novel 34-*O*-sulfatobastadin-9 (**2127**) (*1855*), and the sponge *Dendrilla cactos* from India has yielded bastadins-22 (**2128**) and -23 (**2129**) (*1899*).



2127 (34-*O*-sulfatobastadin-9)

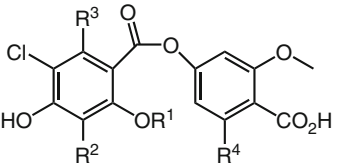


2128 R = Br (bastadin-22)
2129 R = H (bastadin-23)

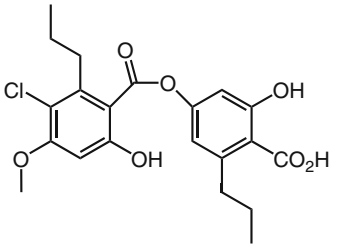
These novel tetrameric bromotyrosine metabolites display a range of biological activities, including effects on calcium channels (*1900*), lipoxygenase inhibition (*1772*), tumor angiogenesis inhibition (*1901*), and endothelial cell anti-proliferation (*1902*). Syntheses of several bastadins have been accomplished (*1903, 1904*).

3.22.4 Depsides

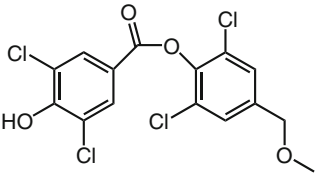
The polyketide-derived depsides are ubiquitous lichen metabolites and some 15 chlorinated examples were cited in the first survey (*1*). A collection of the lichen *Lecanora jamesii* from England has yielded the new 2-*O*-methylsulphurellin (3,5-dichloro-4-*O*-demethylplanaic acid) (**2130**) (*1905, 1906*), while *Lecanora lividocinerea* from Spain has afforded 3,5-dichloro-2′-*O*-methylnorstenosporic acid (**2131**), 5-chloro-2′-*O*-methylanziaic acid (**2132**), and 3,5-dichloro-2′-*O*-methylnorhyperlatolic acid (**2133**) (*1906*). This latter study also confirmed the structure of **2130** by total synthesis. A Mexican sample of the lichen *Dimelaena* cf. *radiata* has yielded the new 5-chlorodivaricatic acid (**2134**) (*1907*). The wood-decaying fungus *Hypholoma fasciculare* contains **2135** (*1908*), and a marine fungus, *Emericella unguis*, which was collected from a Venezuelan mollusc (unidentified) and a medusa (*Stomolopus meliagris*; "Cannonball Jelly"), has afforded guisinol (**2136**) (*1909*). Another marine fungus, *Pestalotia* sp., found on the surface of the brown alga *Rosenvingea* sp. in the Bahamas, produces the novel antibiotic pestalone (**2137**), which displays potent antibacterial activity against both methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium* (*1910*).



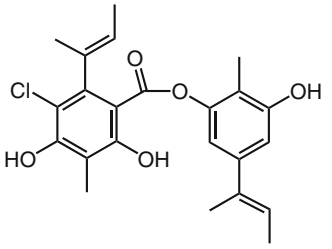
2130 $R^1 = CH_3, R^2 = Cl, R^3 = n\text{–}C_5H_{11}, R^4 = n\text{–}C_5H_{11}$
2131 $R^1 = H, R^2 = Cl, R^3 = n\text{–}C_3H_7, R^4 = n\text{–}C_5H_{11}$
2132 $R^1 = H, R^2 = H, R^3 = n\text{–}C_5H_{11}, R^4 = n\text{–}C_5H_{11}$
2133 $R^1 = H, R^2 = Cl, R^3 = n\text{–}C_5H_{11}, R^4 = n\text{–}C_7H_{15}$



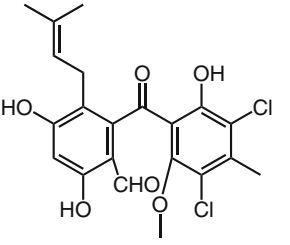
2134 (5-chlorodivaricatic acid)



2135



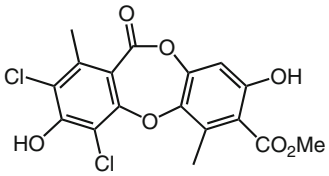
2136 (guisinol)



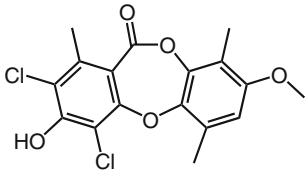
2137 (pestalone)

3.22.5 Depsidones

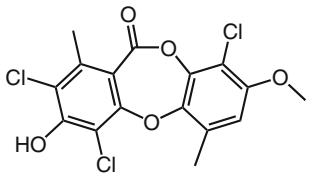
Depsidones are cyclized depsides that also seem to be confined to the world of lichens. Nearly 50 chlorinated depsidones were identified in the first survey (*1*). A study of *Lecanora chlarotera*, a lichen collected in southeast Scotland, contains the new norgangaleoidin (**2138**) (*1911*). Several collections of *Fulgensia fulgida* (France, Spain, and Israel) yield fulgoicin (**2139**) (*1912*), the structure of which is confirmed by total synthesis (*1913*). The related fulgidin was described earlier from this lichen (*1, 1912*), although a subsequent investigation showed, by synthesis, that fulgidin has the revised structure **GGG** (*1914, 1915*). Ironically, the incorrectly proposed structure of fulgidin, now named "isofulgidin" (**2140**), is a depsidone found in the lichens *Rinodina dissa*, *Hafellia parastata*, and *Fulgensia canariensis* (*1914*).



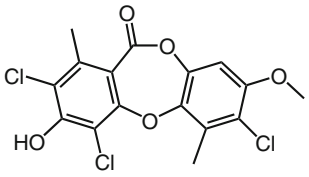
2138 (norgangaleoidin)



2139 (fulgoicin)

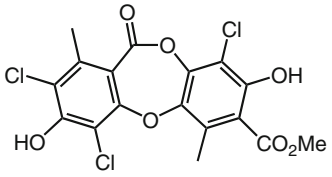


GGG (fulgidin)

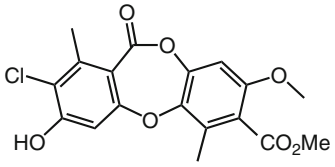


2140 (isofulgidin)

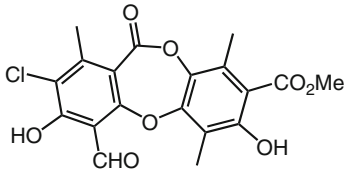
The new chlorolecideoidin (**2141**) is a minor depsidone from the lichens *Lecanora leprosa* and *Lecanora sulphurescens* (*1916*), and the novel 4-dechlorogangaleoidin (**2142**) has been identified in *Lecanora argentata* and *Lecanora californica* (*1917*). The Fijian lichen *Catarraphia dictyoplaca* has yielded cyclographin (**2143**) (*1918*). Cultures of the ascomycete *Coniochaeta tetraspora* have furnished CT-1 (**2144**) (*1919*). An unidentified *Xylaria* fungus contains maldoxone (**2145**) (*1795*), and the two brominated depsidones, acarogobiens A (**2146**) and B (**2147**), were characterized from the Central Asian lichen *Acarospora gobiensis* (Fig. 3.32) (*1920*). These compounds are the first brominated lichen metabolites to be discovered.



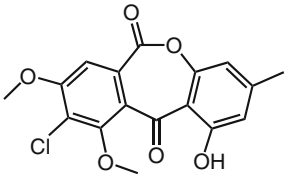
2141 (chlorolecideoidin)



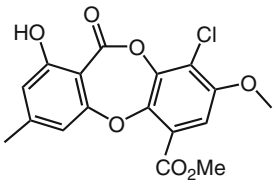
2142 (4-dechlorogangaleoidin)



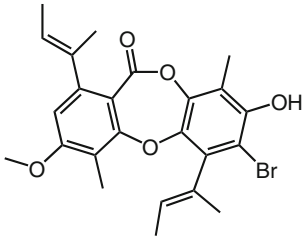
2143 (cyclographin)



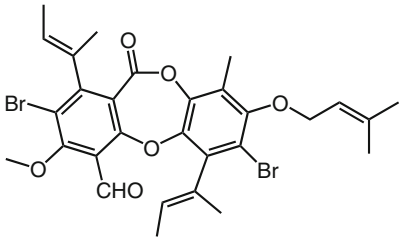
2144 (CT-1)



2145 (maldoxone)



2146 (acarogobien A)



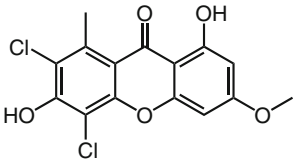
2147 (acarogobien B)

Fig. 3.32 *Acarospora gobiensis*, a Central Asian lichen that contains the novel brominated depsidones, acarogobiens A and B (**2146** and **2147**) (Photo: T. Rezanka)

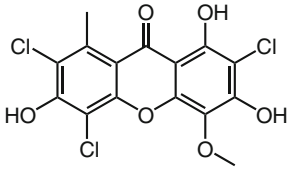
3.22.6 Xanthones

Like depsides and depsidones, most chlorinated xanthones are found in lichens, and more than 50 such compounds were described in the first survey (*1*). The lichen

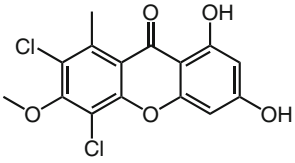
Lecanora broccha contains the new 5,7-dichloro-3-*O*-methylnorlichexanthone (**2148**) (*1921*). The synthesis of 17 chlorinated xanthones, which were listed in the first survey (*1*), has been reported (*1922*). Demethylchodatin (**2149**) occurs in the lichen *Lecanora pachysoma* (*1923*), and *Byssoloma subdiscordans* has furnished the new 5,7-dichloro-6-*O*-methylnorlichexanthone (**2150**) (*1924*). *Sporopodium citrinum* contains 4-chlorolichexanthone (**2151**) and 4-chloro-3-*O*-methylnorlichexanthone (**2152**) (*1924*). The previously known vinetorin (*1*) is the first chloroxanthone to be isolated from a higher plant, *Hypericum ascyron* (*1925*). The new xanthone **2153** has been characterized from the Italian plant *Polygala vulgaris* (*1926*).



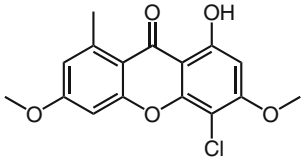
2148 (5,7-dichloro-3-*O*-methylnorlichexanthone)



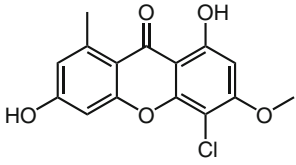
2149 (demethylchodatin)



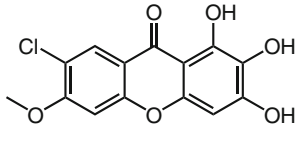
2150 (5,7-dichloro-6-*O*-methylnorlichexanthone)



2151 (4-chlorolichexanthone)

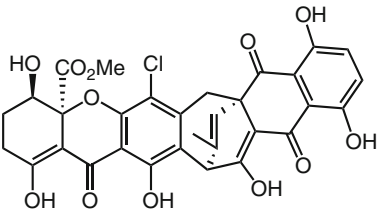


2152 (4-chloro-3-*O*-methylnorlichexanthone)

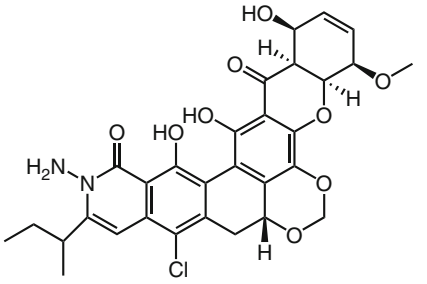


2153

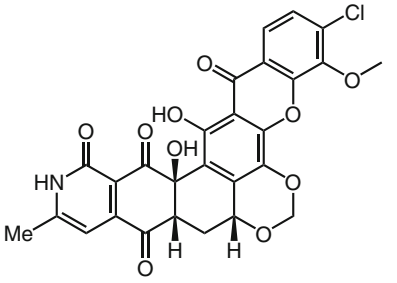
The structures of the previously isolated beticolins 2 and 4 (*1*) have now been confirmed by X-ray crystallography (*1927*). A new isolate from the fungus *Cercospora beticola*, which is a highly destructive disease of sugar beets, is beticolin 0 (**2154**) (*1928*). The polycyclic xanthone Sch 54445 (**2155**) is produced by an *Actinoplanes* species, and is a very active antifungal agent (MIC, 0.00038 $\mu g\ mL^{-1}$) (*1929*). Xantholipin (**2156**) is a related substance from a *Streptomyces* sp. (*1930*), and is structurally similar to the previously known lysolipins from *Streptomyces violaceoniger* (*1*).



2154 (beticolin 0)



2155 (Sch 54445)

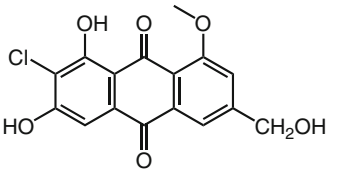


2156 (xantholipin)

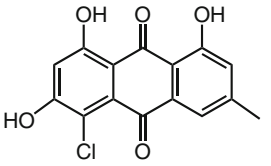
3.22.7 Anthraquinones and Related Compounds

Most of the previously identified 25 chlorinated anthraquinones are found in lichen and fungi (*1*). The newly discovered examples have a wider range of sources. Studies of the lichen *Nephroma laevigatum* from the British Columbia coast have identified the new anthraquinone, 7-chloro-1-*O*-methyl-ω-hydroxyemodin (**2157**), and the two novel hypericins, 7,7′-dichlorohypericin (**2158**) and 2,2′,7,7′-tetrachlorohypericin (**2159**) (*1931*), as well as 5-chloroemodin (**2160**), 5-chloro-1-*O*-methyl-ω-hydroxyemodin (**2161**), and 5-chloro-ω-hydroxyemodin (**2162**) (*1932*). In addition to containing several known chlorinated anthraquinones, the Scandinavian fungus *Dermocybe sanguinea* has afforded the new 5,7-dichloroendocrocin (**2163**) (*1933*). The novel tetracyclic anthraquinones

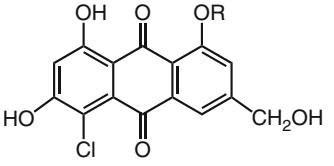
topopyrones A (**2164**) and B (**2165**), and two non-chlorinated analogs, were isolated from cultures of the fungi *Phoma* sp. and *Penicillium* sp. (*1934, 1935*). These compounds are topoisomerase I inhibitors and topopyrone B has activity comparable to that of camptothecin. Topopyrone B is also potent against herpes virus VZV, and is 24 times more active than acyclovir. Syntheses of topopyrones have been described (*1936, 2650*).



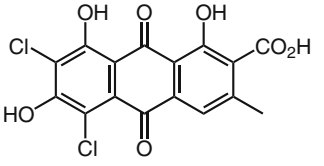
2157



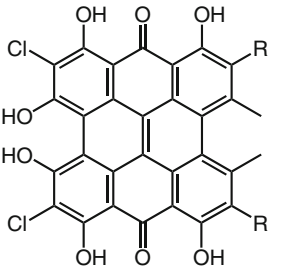
2160



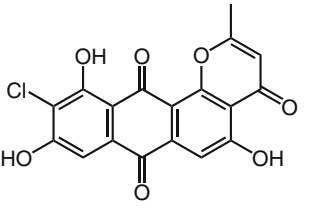
2161 (R = H)
2162 (R = Me)



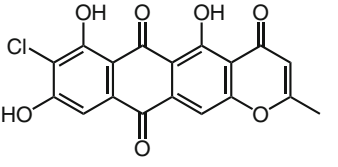
2163 (5,7-dichloroendocrocin)



2158 R = H (7,7'-dichlorohypericin)
2159 R = Cl (2,2',7,7'-tetrachlorohypericin)



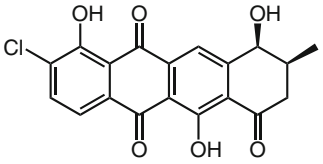
2164 (topopyrone A)



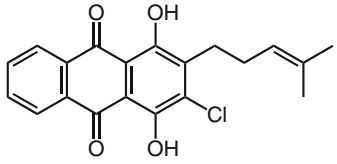
2165 (topopyrone B)

The *Streptomyces* strain that produces celastramycin A (**1212**) has also yielded celastramycin B (**2166**) (*1225*). Another *Streptomyces* sp. has afforded bischloroanthrabenzoxocinone ((–)-BABX) (**2167**), which has antibacterial activity and inhibits ligand-binding activity of liver X receptors (*1937*). An example of a rare chlorinated anthraquinone is anthrasesamone C (**2168**), which was characterized in the Japanese plant *Sesamum indicum* (*1938*). The angucycline-type marmycin B

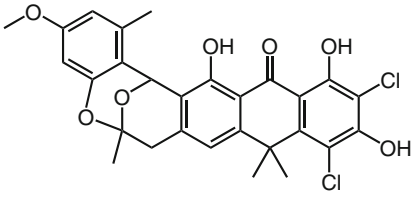
(**2169**) was isolated from cultures of a *Streptomyces* strain, along with the dechloro marmycin A, which was more cytotoxic against several human cancer cell lines than marmycin B (*1941*). A Gram-positive strain of a *Bacillus* bacterium from Californian soil has yielded the novel fluorescent pyrene, chlorxanthomycin (**2170**), which has selective antibiotic activity (*1942*). The antitumor antibiotic BE-19412A (**2171**) is produced by a Streptomycete (*1943*).



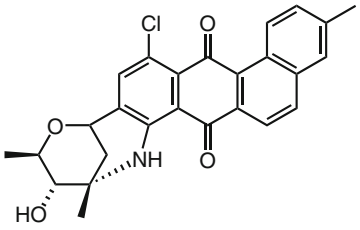
2166 (celastramycin B)



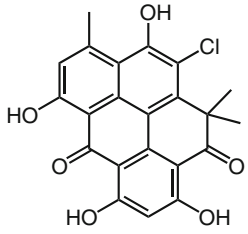
2168 (anthrasesamone C)



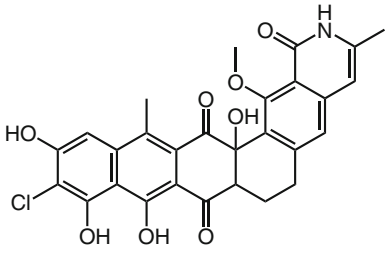
2167 (bischloroanthrabenzoxocinone; (–)-BABX)



2169 (marmycin B)



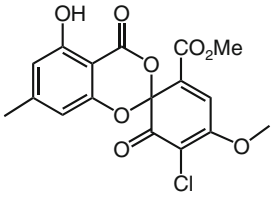
2170 (chlorxanthomycin)



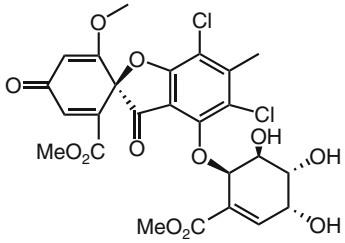
2171 (BE-19412A)

3.22.8 Griseofulvin and Related Compounds

One of the earliest recognized naturally occurring organohalogen compounds is griseofulvin (*1*), and this fungal metabolite is still used clinically to treat tinea pedis (athlete's foot) and, more recently, may have anticancer activity (*1944, 1945*). The new spirocyclohexadienone, maldoxin (**2172**), was isolated from a member of the fungus genus *Xylaria* (*1795*). A fermentation broth of *Aspergillus* sp. has afforded Sch 202596 (**2173**), which displays inhibitory activity in the galanin receptor GALR1 assay (*1946*). This fungus was isolated from the tailing piles of an abandoned uranium mine in California.



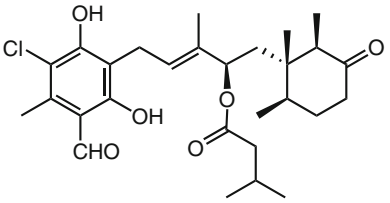
2172 (maldoxin)



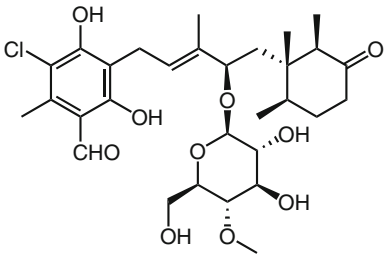
2173 (Sch 202596)

3.22.9 Miscellaneous Fungal Metabolites and Other Complex Phenols

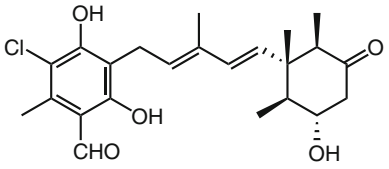
A large number of natural organohalogen compounds, mainly found in fungi, do not fit into the structural categories defined earlier and are presented here. Some new analogs of the well-known prenyl-phenol antibiotic ascochlorin have been reported. The literature on this class of fungal metabolites is confusing since several of the same compounds have been named differently in separate investigations. Thus, ascochlorin is also known as LL-Z1272γ and ilicicolin D, and the known cylindrochlorin (= ilicicolin E) was isolated more than 20 years after its initial discovery and named as 8′,9′-dehydroascochlorin from a *Verticillium* sp. (*1949*). Ilicicolin E is also found in the canker disease phytopathogenic fungus *Nectria galligena* (*1950*). Cylindrol A_4 (**2174**) was isolated from *Cylindrocarpon lucidum* (*1951*) and is related to the known corresponding acetate, chloronectrin (*1*). The insect pathogenic fungus *Verticillium hemipterigenum* from Thailand has yielded vertihemipterin A (**2175**), a glucoside of the previously known aglycone, along with 8′-hydroxyascochlorin (**2176**) (*1952*). Ascochlorin derivatives display significant biological activity such as antidiabetes (*1953, 1954*). The first synthesis of (–)-ascochlorin has been reported (*1955*).



2174 (cylindrol A_4)

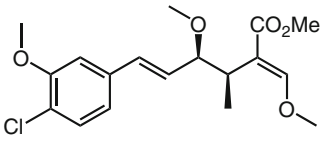


2175 (vertihemipterin A)

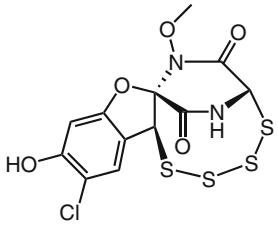


2176 (8'-hydroxyascochlorin)

The previously described antifungal strobilurin B, which has been synthesized (*1956*), is joined in kind by the discovery of oudemansin B (**2177**) from *Xerula longipes* and *Xerula melantricha* (*1957*). This class of substances holds promise for the development of new fungicides (*1958*). Like ascochlorin, the previously known aspirochlorine (*1*) has been frequently isolated (= A30641 = oryzachlorine), and displays potent antifungal activity (*1959*). The new analog tetrathioaspirochlorine (**2178**) and possibly the trisulfide derivative (not counted here) are found in extracts of *Aspergillus flavus* along with aspirochlorine (*1960*).

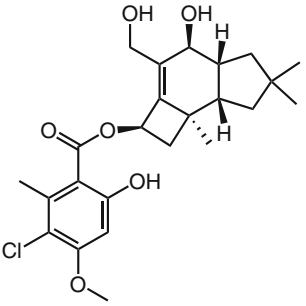


2177 (oudemansin B)

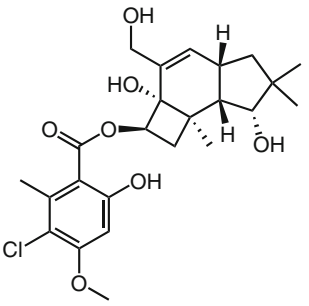


2178 (tetrathioaspirochlorine)

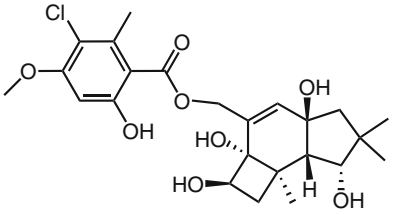
As reported in the first survey, several fungi produce novel cyclobutane-containing metabolites, such as armillaridin, melleolides, and melledonals (*1*). Newly isolated members of this class include arnamiol (**2179**) from *Armillaria mellea* (*1961*), *Armillaria ostoyae* (*1962*), *Armillaria tabescens*, *Armillaria monadelpha*, *Armillaria gallica*, and *Armillaria cepestipes* (*1963*), armellide B (**2180**), melleolides I (**2181**) and J (**2182**) from *Armillaria novae-zelandiae* (*1964*), and melledonal D (**2183**) from *Clitocybe elegans* (*1965*). Melleolide J (**2182**) may be identical to armillarikin isolated from *Armillaria mellea* (*1966*). The pathogenic fungus *Armillaria novae-zelandiae* has also afforded 6′-chloro-10α-hydroxymelleolide (**2184**) (*1967*). Melleolides K (**2185**), L, and M (**2186**) were isolated from *Armillariella mellea* (*1968*), but melleolide L appears to be the same as **2184**.



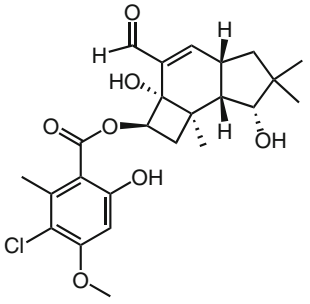
2179 (arnamiol)



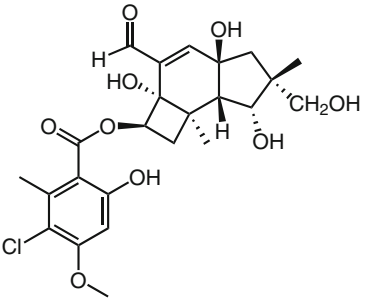
2181 (melleolide I)



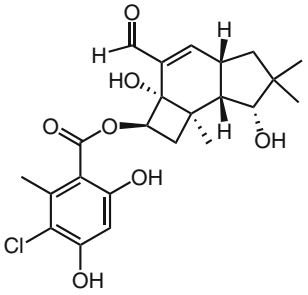
2180 (armellide B)



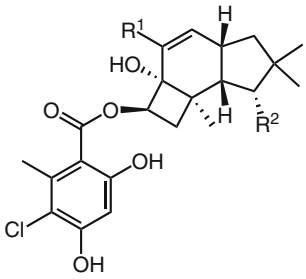
2182 (melleolide J)



2183 (melledonal D)

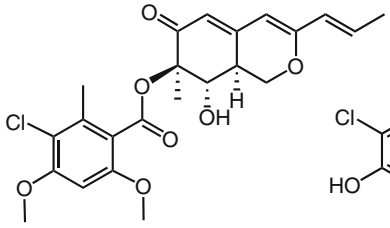


2184

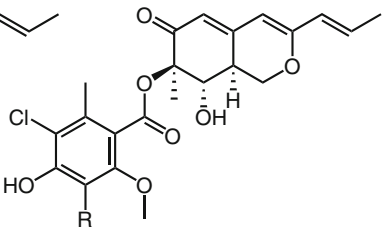


2185 R^1 = CHO, R^2 = H (melleolide K)
2186 R^1 = CH_2OH, R^2 = OH (melleolide M)

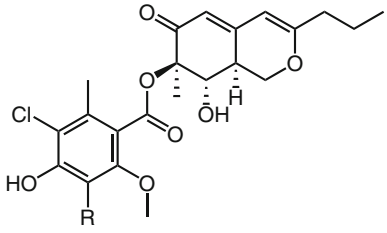
The fungus *Emericella falconensis* is the source of several azaphilones, the falconensins (*1*), and the new falconensin E (**2187**) has been identified in a Venezuelan soil sample containing this fungus (*1969*). The absolute configuration of the falconensins was established in this study. This fungus and *Emericella fruticulosa* have furnished the new falconensins K (**2188**), L (**2190**), M (**2189**), and N (**2191**) (*1970*). The culture broth of an *Amycolatopsis* strain produces the chlorine-containing epoxyquinomicins A and D (**2192**, **2193**) (*1971–1975*). The non-chlorinated epoxyquinomicins B and C are more active than A and D in inhibiting rat embryo histidine decarboxylase (*1975*). An unidentified *Coniothyrium* fungus has furnished coniothyriomycin (**2194**), which shows fungicidal and herbicidal activity (*1976, 1977*). This metabolite is related to **1776** from a *Xylaria* fungus. Cultures of *Actinoplanes* sp. yield BE-40665D (**2195**), a novel brominated antibacterial antibiotic (*1978*).



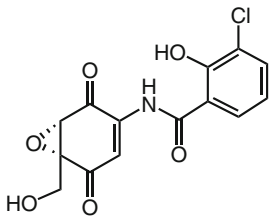
2187 (falconensin E)



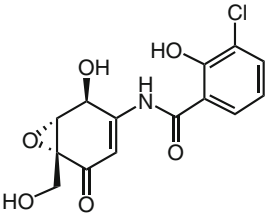
2188 R = H (falconensin K)
2189 R = Cl (falconensin M)



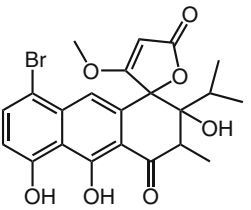
2190 R = H (falconensin L)
2191 R = Cl (falconensin N)



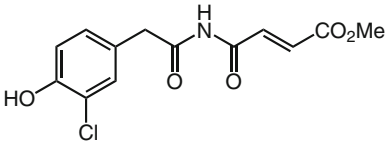
2192 (epoxyquinomicin A)



2193 (epoxyquinomicin D)

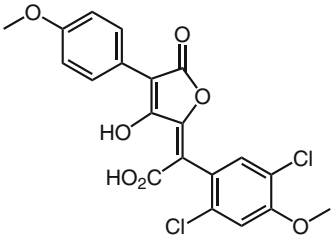


2195 (BE-40665D)

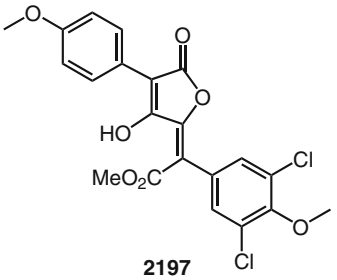


2194 (coniothyriomycin)

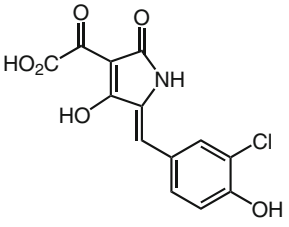
The tropical fungus *Scleroderma sinnamariense* has afforded methyl 2′,5′-dichloro-4,4′-di-*O*-methylatromentate (**2196**) (*1979*), and the related pulvinic acid derivative methyl 3′,5′-dichloro-4,4′-di-*O*-methylatromentate (**2197**) was isolated from the fruiting body of a *Scleroderma* sp. (“poison puff ball”) (*1980*). A New Zealand *Chamonixia pachydermis* has yielded pachydermin (**2198**) (*1981*).



2196

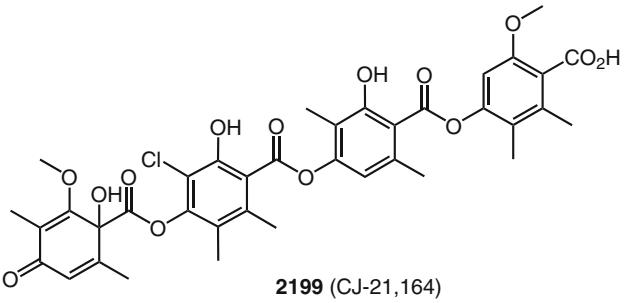


2197

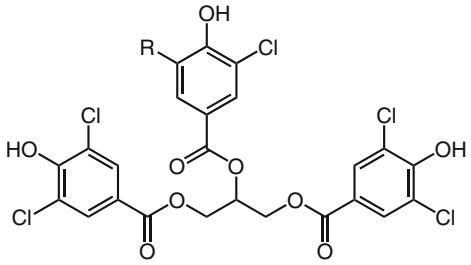


2198 (pachydermin)

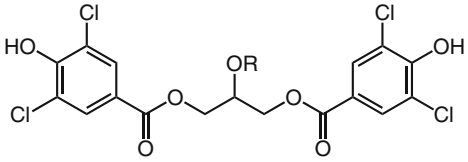
The fungus *Chloridium* sp. produces CJ-21,164 (**2199**), a novel D-glucose-6-phosphate phosphohydrolase inhibitor (*1982*). The edible mushroom *Agaricus macrosporus* has yielded agaricoglycerides A (**2200**), B (**2201**), C (**2202**), D (**2203**), agaricic ester (**2204**), and monoacetylagaricoglycerides A (**2205**, **2206**) (*1983*).



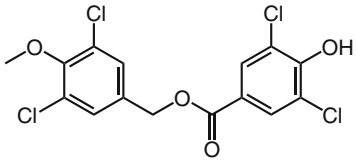
2199 (CJ-21,164)



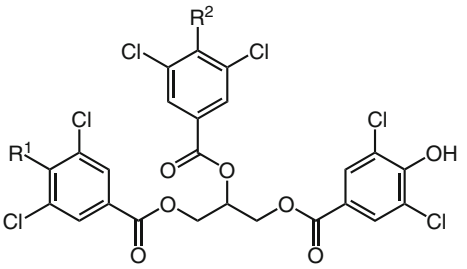
2200 R = Cl (agaricoglyceride A)
2201 R = H (agaricoglyceride B)



2202 R = H (agaricoglyceride C)
2203 R = Ac (agaricoglyceride D)



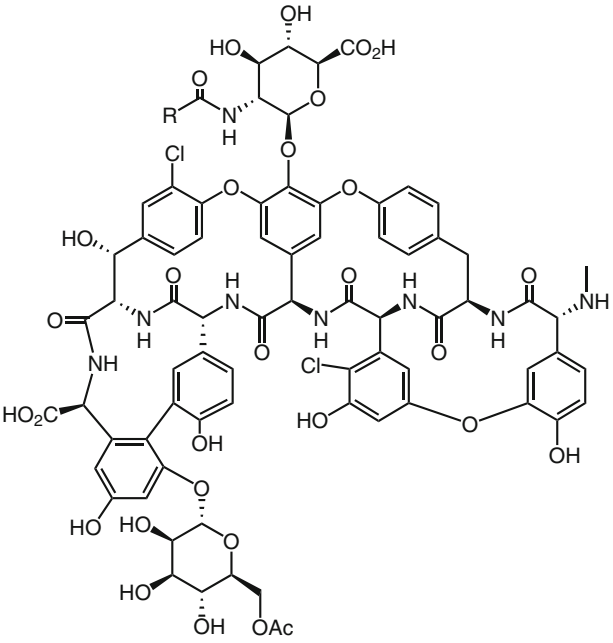
2204 (agaricic ester)



2205 R^1 = OAc, R^2 = OH (monoacetylagaricoglycerides A)
2206 R^1 = OH, R^2 = OAc

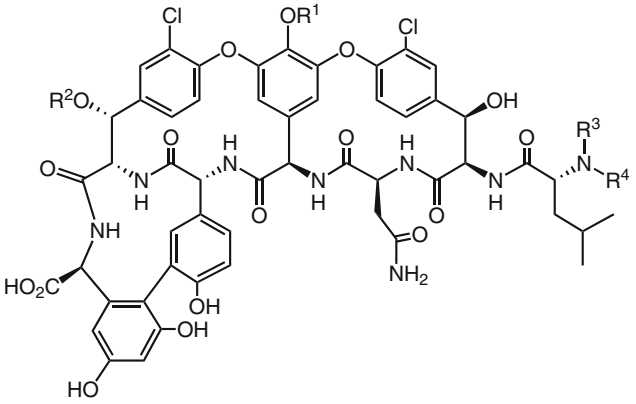
3.23 Glycopeptides

Probably no class of natural products with therapeutic potential has received more attention than the vancomycin glycopeptide antibiotics. In clinical use for more than 40 years, vancomycin – the antibiotic of "last resort" – has been extensively investigated regarding its mechanism of action (*1991–1997*), analog development to combat resistant bacteria (*1993, 1994, 1996–2001*), biosynthesis (*2002*), and total synthesis (*1993, 1997, 2003*). The enormity of the vancomycin and related glycopeptide literature renders full coverage not feasible here, but excellent general reviews are available (*1993, 1996, 1997, 1998, 2004, 2005*). A crystal structure of vancomycin was only relatively recently obtained (*2006*). Some 75 naturally occurring chlorinated glycopeptides were documented in the previous review (*1*), and several new examples have been described subsequently. The new A-40926-PA (**2207**) and A-40926-PB (**2208**), acetates of two previously known glycopeptides A-40926-A and -B (*1*), are produced by an *Actinomadura* strain (*2007*). All four of these metabolites are active against *Neisseria gonorrhoeae* and may offer a treatment for gonorrhea.



2207 R = *n*-$C_{10}H_{21}$ (A-40926-PA)
2208 R = $(CH_2)_8CH(CH_3)_2$ (A-40926-PB)

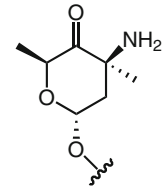
Cultures of *Amycolatopsis* sp. have yielded six new 4-oxovancosamine-containing glycopeptides, ureido-balhimycin (**2209**), rhamnosyl-balhimycin (**2210**), methylbalhimycin (**2211**), demethylbalhimycin (**2212**), balhimycin V (**2213**), devancosamine-vancomycin (**2214**), M43C (**2215**), and degluco-balhimycin (**2216**), along with the known balhimycin (*2008*). A crystal structure of ureido-balhimycin has been reported (*2009*).



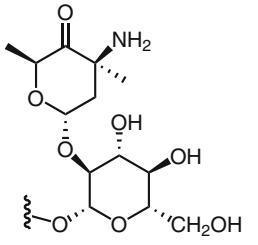
2209 R^1 = glc, R^2 = urvcn, R^3 = H, R^4 = Me (ureido-balhimycin)
2210 R^1 = rha-glc, R^2 = urvcn, R^3 = H, R^4 = Me (rhamnosyl-balhimycin)
2211 R^1 = glc, R^2 = ovcn, R^3 = R^4 = Me (methylbalhimycin)
2212 R^1 = glc, R^2 = ovcn, R^3 = R^4 = H (demethylbalhimycin)
2213 R^1 = ovcn-glc, R^2 = ovcn, R^3 = H, R^4 = Me (balhimycin V)
2214 R^1 = glc, R^2 = H, R^3 = H, R^4 = Me (devancosamine-vancomycin)
2215 R^1 = R^2 = H, R^3 = R^4 = Me (M43C)
2216 R^1 = R^3 = H, R^2 = ovcn, R^4 = Me (degluco-balhimycin)

glc = glucosyl-1

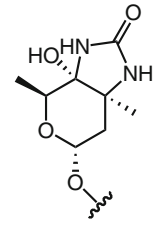
rha-glc = rhamnosyl-(1-2)-glucosyl



ovcn = 4-oxovancosaminyl-1



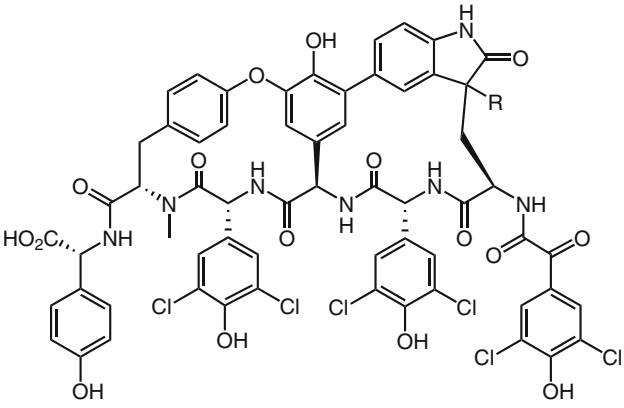
ovcn-glc = 4-oxovancosaminyl-(1-2)-glucosyl



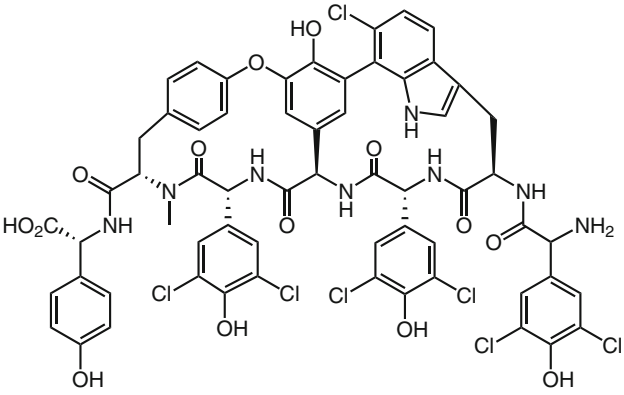
urvcn = ureido-4-oxovancosaminyl-1

The previously known chloropeptin 1 and complestatin (= chloropeptin II) have been the object of synthetic and stereochemical studies and structural revisions (*2010–2012, 2653*). The new complestatins A (**2217**) and B (**2218**) were characterized from a *Streptomyces* sp. MA7-234 (*2013*), and these two compounds would appear to be the same as neuroprotectins A and B isolated from *Streptomyces* sp. Q27107 (*2014, 2015*). Another *Streptomyces* sp. has

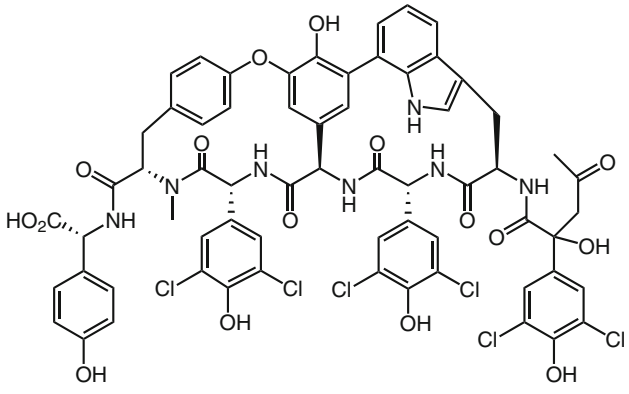
furnished SCH 212394 (**2219**), which incorporates a 6-chloroindole unit (*2016*), and SCH 204698 (**2220**), which is a formal acetone addition product of chloropeptin I (*2017*).



2217 R = H (complestatin A = neuroprotectin A)
2218 R = OH (complestatin B = neuroprotectin B)

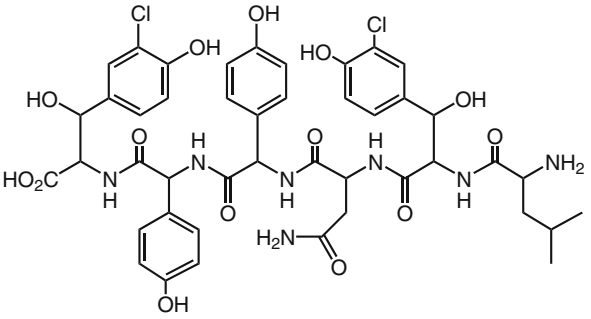


2219 (SCH 212394)

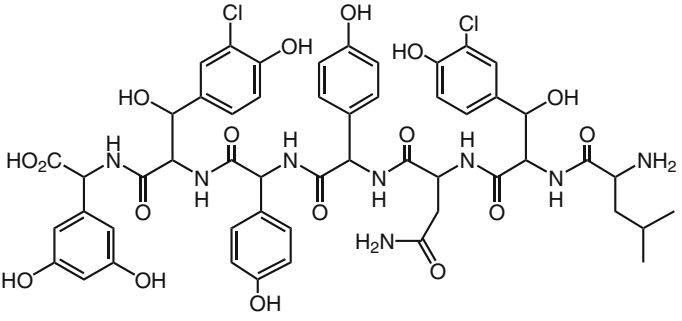


2220 (SCH 204698)

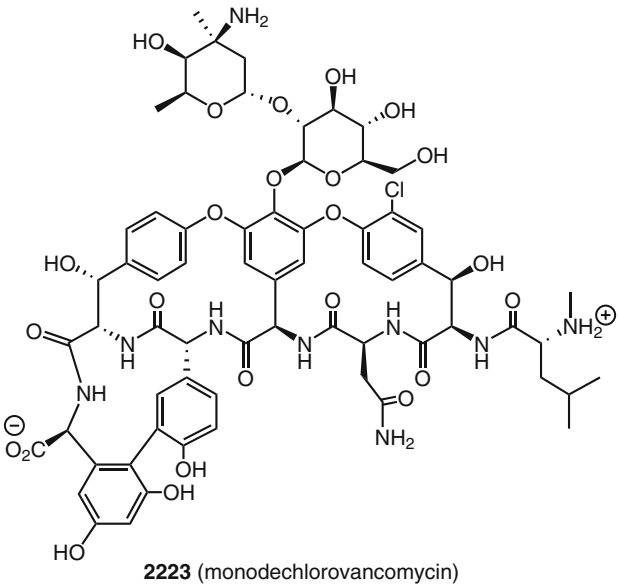
Two biosynthetic intermediates of the vancomycin glycopeptides, SP-969 (**2221**) and SP-1134 (**2222**), are found in cultures of *Amycolatopsis mediterranei* (*2018*). This is the first reported isolation of linear biosynthetic intermediates of the vancomycin family. Monodechlorovancomycin **2223** is found for the first time in fermentation broths of *Amycolatopsis orientalis* (*2019*). The other monodechlorovancomycin was synthesized for comparison with **2223**.



2221 (SP-969)



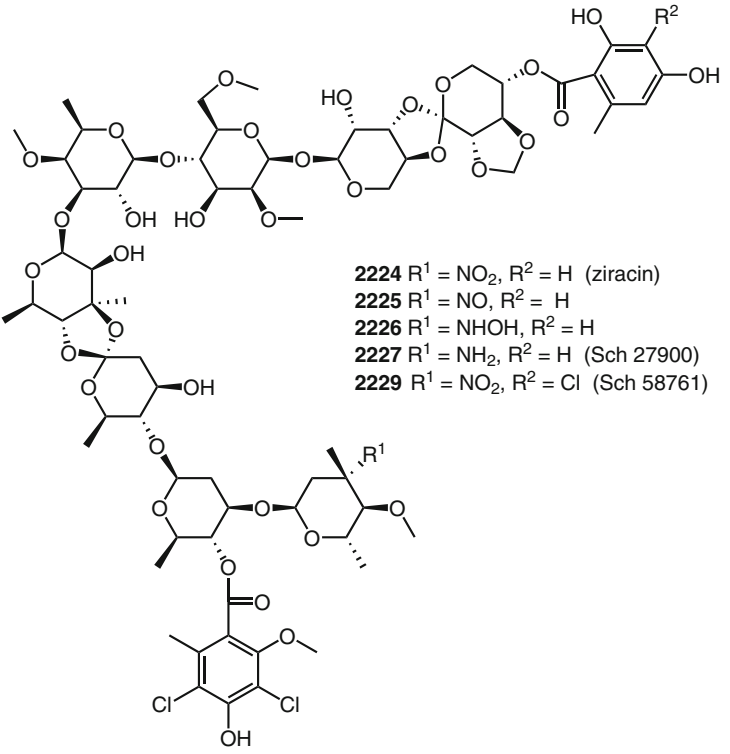
2222 (SP-1134)



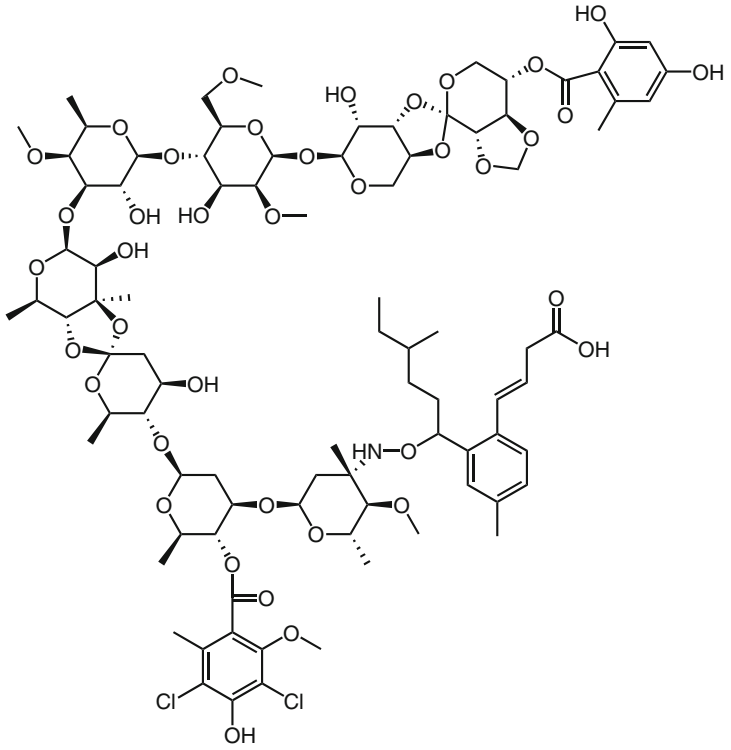
2223 (monodechlorovancomycin)

3.24 Orthosomycins

The small number of novel chlorophenol-oligosaccharide antibiotics (orthosomycins) presented in the earlier survey (*1*) has been expanded to include a few new examples. However, the highlight in this area is the total synthesis of everninomicin 13,384-1 (ziracin; Sch 27899) (**2224**) (*2020–2022*), which is found in cultures of *Micromonospora carbonacea var. africana* (*2023–2025*). This organism has also furnished the related everninomicins **2225**, **2226**, 13,384-5 (Sch 27900) (**2227**), Sch 49088 (**2228**) (*2023–2026*), and Sch 58761 (**2229**) (*2027*).

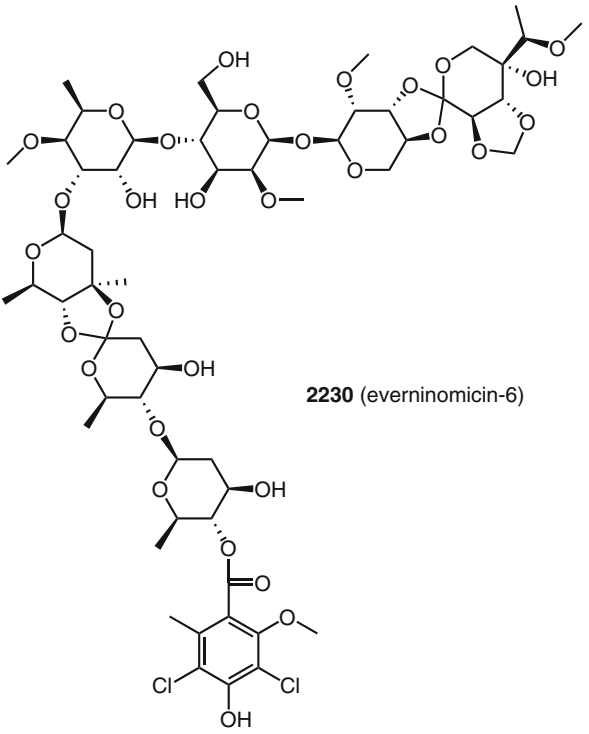


2224 $R^1 = NO_2$, $R^2 = H$ (ziracin)
2225 $R^1 = NO$, $R^2 = H$
2226 $R^1 = NHOH$, $R^2 = H$
2227 $R^1 = NH_2$, $R^2 = H$ (Sch 27900)
2229 $R^1 = NO_2$, $R^2 = Cl$ (Sch 58761)

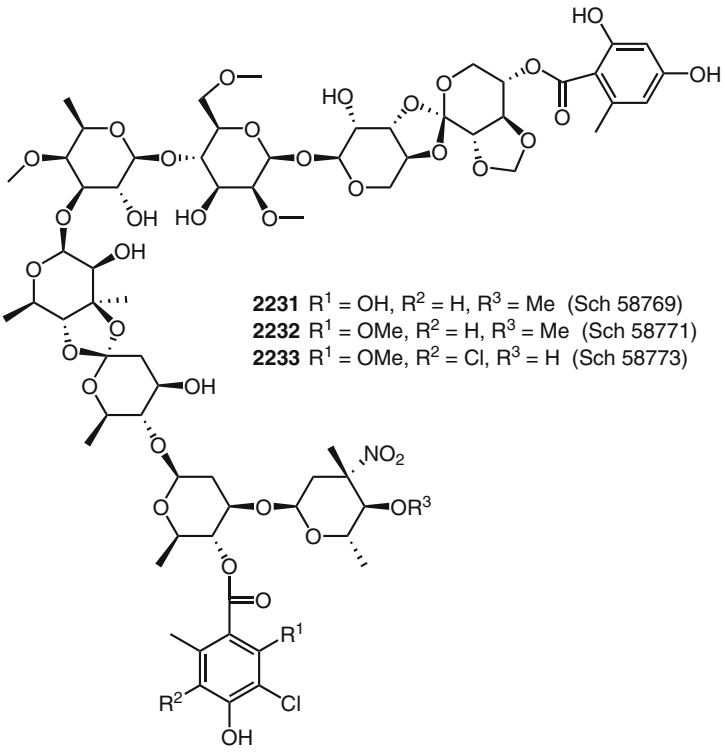


2228 (Sch 49088)

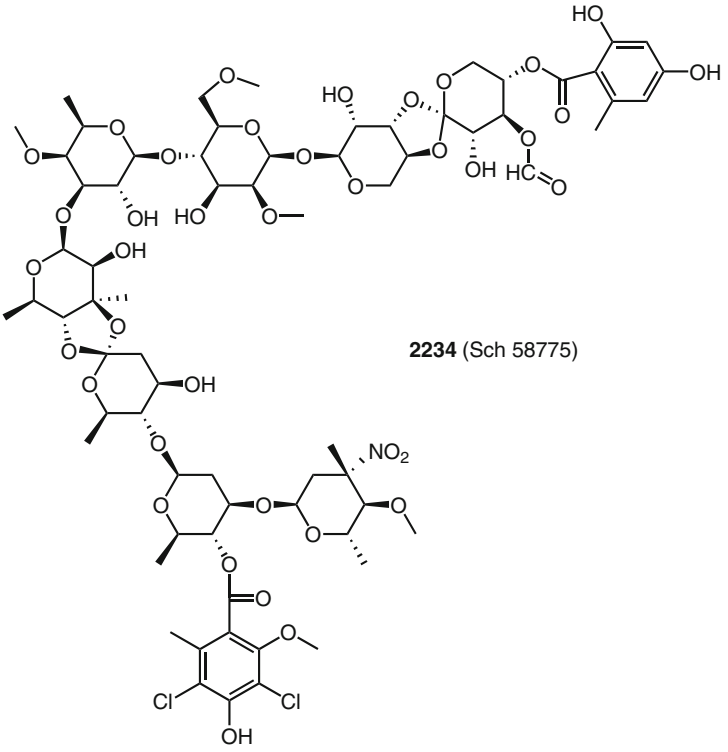
Additional studies of *Micromonospora carbonacea* have revealed the presence of everninomicin-6 (**2230**) (*2028*), and Sch 58769 (**2231**), Sch 58771 (**2232**), Sch 58773 (**2233**), and Sch 58775 (**2234**) (*2029*).



2230 (everninomicin-6)



2231 R^1 = OH, R^2 = H, R^3 = Me (Sch 58769)
2232 R^1 = OMe, R^2 = H, R^3 = Me (Sch 58771)
2233 R^1 = OMe, R^2 = Cl, R^3 = H (Sch 58773)



2234 (Sch 58775)

3.25 Dioxins and Dibenzofurans

For more than 30 years, the class of halogenated dibenzo-*p*-dioxins – "dioxin" – and the related dibenzofurans have probably received more attention by the lay press, the public, politicians, policy regulators, and environmental scientists than all other halogenated chemicals combined. The anthropogenic origins and biological effects of dioxins are summarized in the earlier survey (*1*). The intervening years since 1996 have clearly identified several new natural sources of both halogenated dioxins and dibenzofurans, both biogenic and abiotic, and confirmed previously discovered sources.

Given the huge number of polybrominated diphenyl ethers in marine sponges (vide supra, Sect. 3.22.2 (Diphenyl Ethers)) and the ubiquity of bromoperoxidase in these animals, it is not surprising that several polybrominated dibenzo-*p*-dioxins are found in sponges. Two examples were cited earlier (*1*). The Australian sponge *Dysidea dendyi* (Fig. 3.33) has yielded the new brominated dioxins spongiadioxin A (**2235**), the previously reported (*1*) spongiadioxin B (**2235a**) (*2030*),

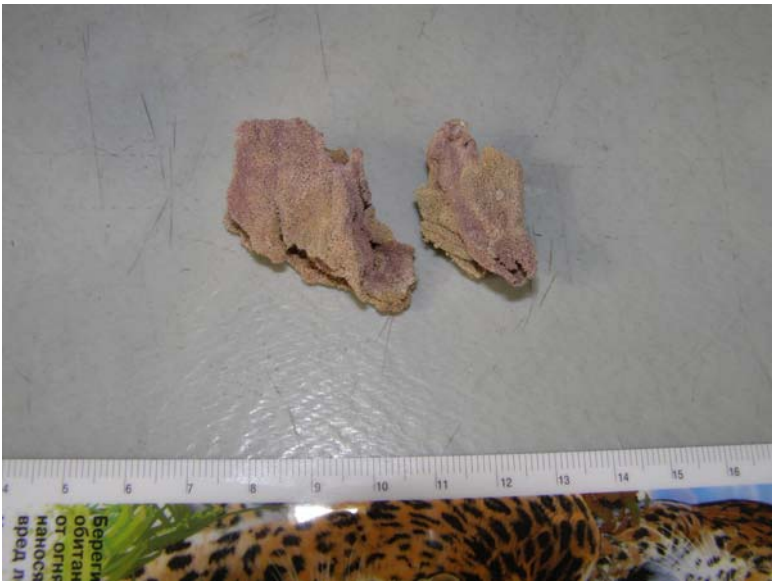
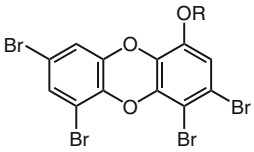
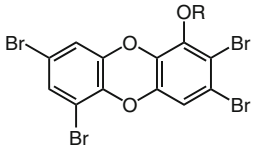


Fig. 3.33 *Dysidea dendyi*, an Australian sponge that contains the brominated dioxins, spongiadioxins A–C and related methyl ethers (**2235**–**2239**) (Photo: N. Utkina)

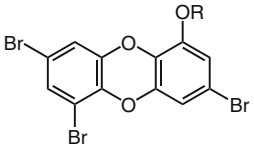
spongiadioxin C (**2236**), and methyl ethers **2237**–**2239** (*2031*). These five brominated dioxins inhibit the cell division of fertilized sea urchin eggs. Methyl ethers **2237**–**2239** are less active (IC_{50} 166, 141, and 94 μ*M*, respectively) than the hydroxy-containing spongiadioxins A, B (**2235**), and C (**2236**) (IC_{50} 5.7, 4.8, and 1.1 μ*M*, respectively). The highest activity of spongiadioxin B is consistent with the lateral arrangement of halogens on the dioxin framework, which is known to impart high biological activity (toxicity) to dioxins (*2032*). A study of three *Dysidea* sponge collections from Indonesia has also uncovered the presence of spongiadioxins A (**2235**) and C (**2236**) (*2033*). The first examples of non-hydroxylated dioxins, 1,3,7- (**2240**) and 1,3,8-tribromodibenzo-*p*-dioxin (**2241**) were characterized from blue mussels (*Mytilus edulis*) from the Baltic Sea (*2034*). A natural source is assumed for these two dioxins and five other brominated dioxins and one brominated dibenzofuran that are only tentatively identified. All of these polybrominated compounds are present in high levels in blue mussels and fish and are widely distributed in the Baltic environment (*2034, 2035*). A biosynthesis of these polybrominated dioxins from bromophenols has been advanced (*2035*). The Yellow Sea brown alga *Leathesia nana* contains the novel **2242** (*1738*). Interestingly, several novel phlorotannins, e.g., eckol (**HHH**), 2-phloroeckol (**III**), and dieckol, which are nonhalogenated dioxins, are found in the brown alga *Ecklonia kurome* Okamura (*2036*). This again illustrates that biohalogenation of electron-rich aromatic rings in the marine environment is not *fait accompli*.



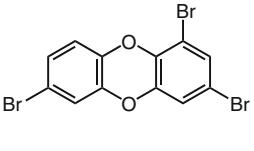
2235 R = H (spongiadioxin A)
2237 R = Me



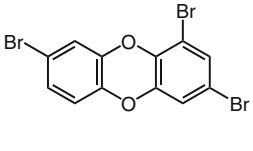
2235a R = H spongiadioxin B
2239 R = Me



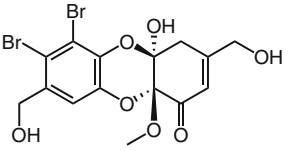
2236 R = H (spongiadioxin C)
2238 R = Me



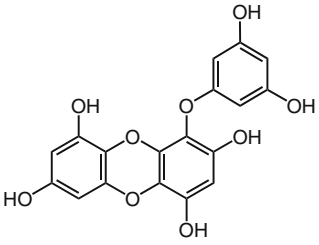
2240



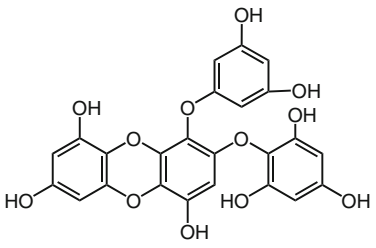
2241



2242



HHH (eckol)

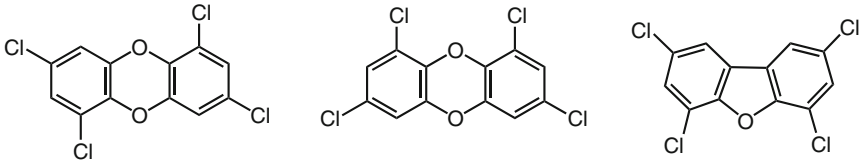


III (2-phloroeckol)

Whereas the earlier survey mentioned that polyhalogenated dibenzo-*p*-dioxins have myriad industrial and combustion sources (*1*), more recent studies have confirmed and extended the fact that natural sources of dioxins and the related polychlorinated dibenzofurans do exist. Thus, Canadian peat bogs are shown to produce several dioxins and dibenzofurans, including 1,3,6,8-tetrachlorodibenzo-*p*-dioxin (**2243**), 1,3,7,9-tetrachlorodibenzo-*p*-dioxin (**2244**), and 2,4,6,8-tetrachlorodibenzofuran (**2245**), along with several minor analogues (Fig. 3.34) (*2037*). Labeling studies with $^{36}Cl^{-}$-chloride demonstrated incorporation into the dioxins and dibenzofurans via 2,4-dichlorophenol, which was also identified in the peat, along with chloroform, a chlorocresol, chloromethoxybenzoic acids, and chlorocinnamic acids. Other dioxins and furans that are minor components in the peat samples are mono- through octachlorinated dioxins and furans. In one sample of the Richibucto, New Brunswick, bog there were identified four monochlorinated furans, nine dichlorinated furans, and six trichlorinated furans. These dioxin and furan isomer patterns are unique to these peat systems and differ from the patterns

Fig. 3.34 New Brunswick peat that produces the dioxins **2243**–**2245** and several chlorophenols, chloroform, and other organochlorines (Photo: P. Silk)

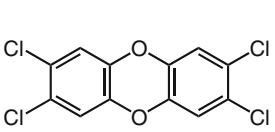
observed from atmospheric deposition associated with anthropogenic sources of dioxins and furans. The same peat dioxin and furan pattern is duplicated when 2,4-dichlorophenol is allowed to react with the fungal enzyme chloroperoxidase (*2037*).



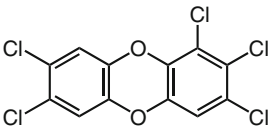
2243 **2244** **2245**

A study of the soil of a *Douglas* fir forest in The Netherlands spiked with $^{37}Cl^{-}$-chloride demonstrated that chlorinated phenols, dibenzo-*p*-dioxins, and dibenzofurans are produced naturally in the humic soil layer probably via chloroperoxidase chemistry (Scheme 3.5) (*1712*). Twenty polychlorinated dioxins and furans were found to be produced naturally in this study, including the highly toxic 2,3,7,8-tetra- (**2246**), 1,2,3,7,8-penta- (**2247**), and 1,2,3,7,8,9-hexachlorodibenzo-*p*-dioxin (**2248**). The major congeners found are 4-chloro- (**2249**), 1,7-dichloro-

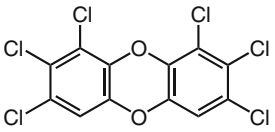
(**2250**), 1,2,3,4,6,8,9-heptachlorodibenzofuran (**2251**), and 1-chloro- (**2252**), 1,2,3,4,6-pentachloro- (**2253**), and 1,2,4,7-/1,2,4,8-/1,3,6,9-tetrachlorodibenzo-*p*-dioxin (**2254**) (isomers not distinguished) (*1712*).



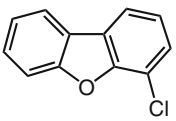
2246



2247



2248



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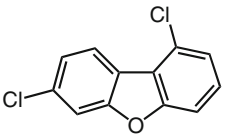
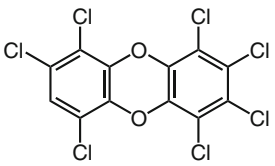
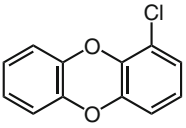


2250



2251



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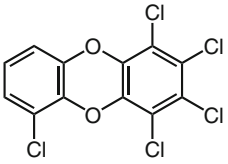
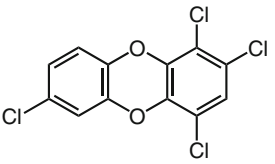
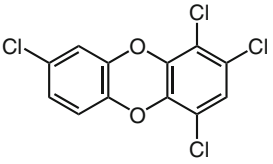


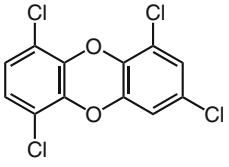
2253



2254a

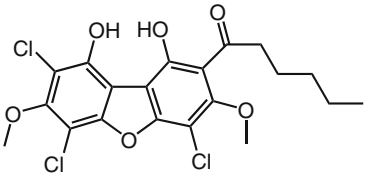


2254b

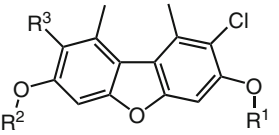


2254c

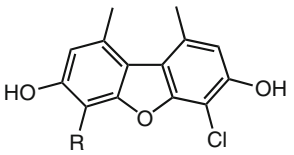
The cellular slime mold *Dictyostelium purpureum* K1001 contains AB0022A (**2255**), a novel antibacterial dibenzofuran, the structure of which was confirmed by total synthesis (*2038*). The lichen *Lecanora cinereocarnea* has yielded several new dibenzofurans, including three chlorinated analogues (**2256–2258**) (*2039*), and *Lecanora iseana* contains **2259** and **2260** (*2040*). The first naturally occurring polybrominated dibenzofuran, corallinafuran (**2261**), is present in a crustose coralline red alga that also contains corallinaether (**1913**) cited earlier (*1769*).



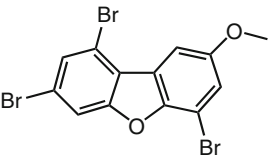
2255 (AB0022A)



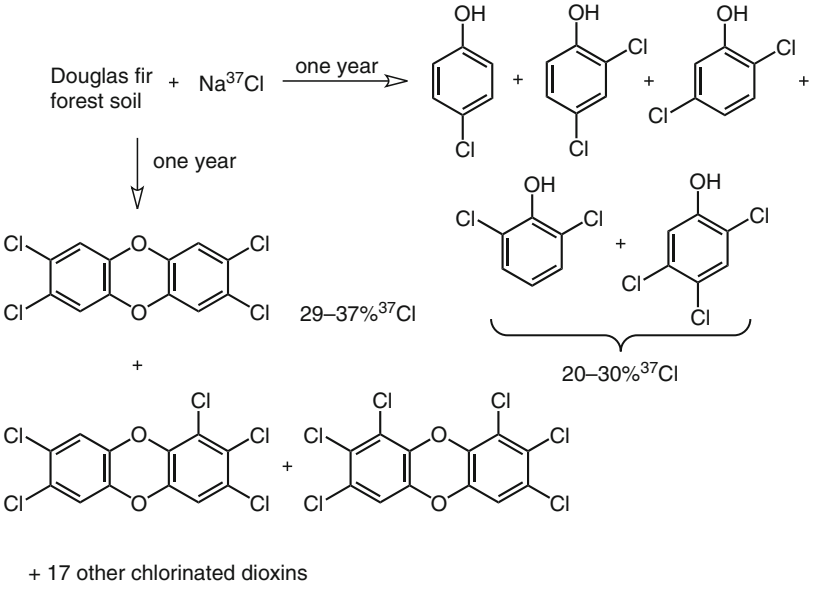
2256 $R^1 = R^2 = R^3 = H$
2257 $R^1 = R^2 = H$, $R^3 = Cl$
2258 $R^1 = Me$, $R^2 = R^3 = H$



2259 R = H
2260 R = Cl



2261 (corallinafuran)

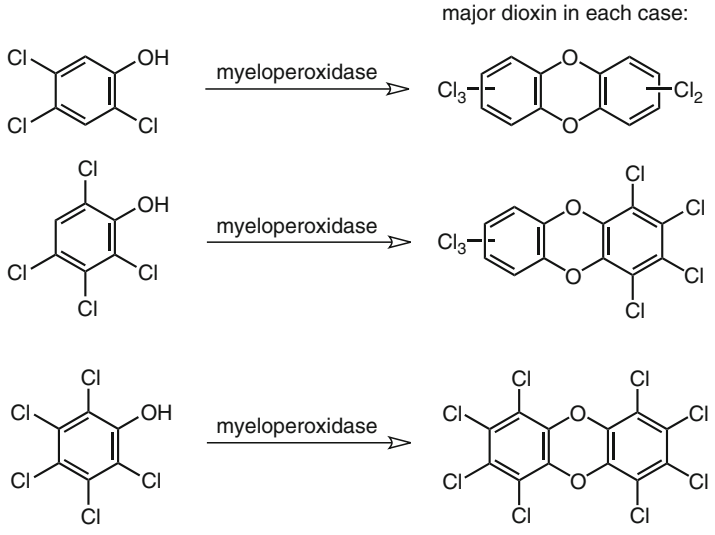


Formation of dioxins and chlorophenols in soil (*1712*)

Scheme 3.5

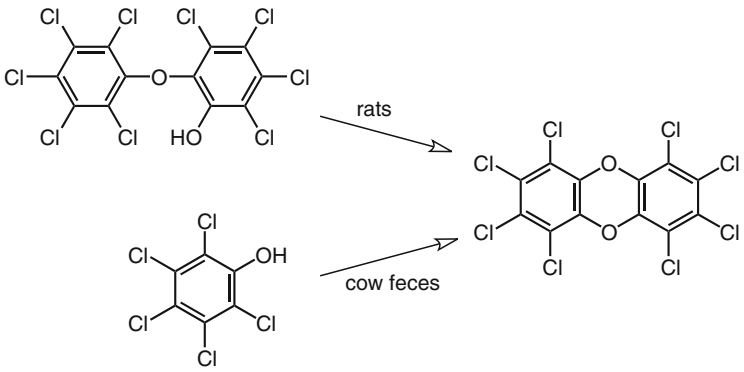
As discussed in the earlier survey (*1*), a biogenic source of polychlorinated dibenzo-*p*-dioxins and dibenzofurans is peroxidase-catalyzed transformation of chlorophenols as first reported by *Öberg* and *Rappe* (*2041–2044*). More recent studies confirm these observations (*2045–2048*). In addition to lactoperoxidase and horseradish peroxidase, human leukocyte myeloperoxidase catalyzes in vitro formation of dioxins and dibenzofurans from chlorophenols (*2046, 2047*). Formation rates are in the μmol/mol range (Scheme 3.6) demonstrating that a human biosynthesis of dioxins and furans is not only possible but also likely. These observations are reinforced by the reported in vivo (rats) conversion of the pre-dioxin nonachloro-2-phenoxyphenol to octachlorodibenzo-*p*-dioxin (OCDD) (*2049*), and the production of hepta- and octachlorodibenzo-*p*-dioxin in the feces of cows fed pentachlorophenol-treated wood (Scheme 3.7) (*2050, 2051*).

Similarly, polychlorinated dioxins and furans form in both compost and sewage sludge (*1*), but the major congeners in both systems are heptachloro- and octachlorodibenzo-*p*-dioxins and their origin is not understood (*2052–2056*). Several studies have attempted to elucidate the importance of natural combustion events as a source of polychlorinated dioxins and furans (*1*), but recent reports indicate that forest fires may not be a significant source of these compounds (*227, 2057*) despite earlier suggestions to the contrary (*1, 2058, 2059*). Nevertheless, numerous studies (wood stoves, control burns, etc.) clearly demonstrate that the combustion of wood



Myeloperoxidase-induced dioxin formation from chlorophenols (*2046, 2047*).

Scheme 3.6



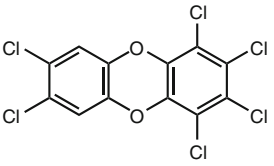
Octachlorodibenzo-*p*-dioxin formation in mammals (*2049-2051*)

Scheme 3.7

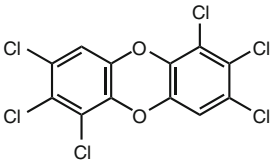
does lead to PCDDs and PCDFs (*1, 2060–2062*). Other reports reveal that the combustion of domesite lignite (*2063*), household waste (*2064*), and chemical waste (*2065*) produces PCDDs and PCDFs, and emissions from landfill fires (*2066*), bonfires and fireworks (*2067*), and crematories (*2068*) are sources of these chlorinated compounds. Quite astonishing is the observation that heating a mixture of methane, hydrogen chloride, and oxygen produces PCDDs and PCDFs containing up to three chlorine atoms (*232*).

Subsequent studies to those reported earlier (*1*) of preserved and ancient soil and sediment samples consistently reveal the presence of presumed naturally occurring PCDDs and (sometimes) PCDFs, but not PCBs. Thus, examination of ancient sediments (estimated at 1–10 million years old) from the Yellow Sea, the East China Sea, and the Pacific Ocean uncovered PCDDs but not PCDFs, the major compound being OCDD (*2069*). A study of Baltic Sea sediments detected both PCDDs and PCDFs "in small but significant levels during the period 1882–1962", including sediments from 1882, 1906, 1922, 1938, 1954, and 1962. Increased levels of these compounds were found in sediments from the period 1970–1985 as expected from anthropogenic contributions (*2070*). A natural origin is indicated for PCDDs and PCDFs found in sediments and clays in the southern United States, compounds that were also detected in catfish and chicken feed adulterated with these clays (*2071–2083*). Carbon and chlorine isotope studies suggest that these PCDDs form abiotically in situ in the sediments and clays (*2082, 2083*). The highest concentration of any congener in most samples is OCDD, and PCDFs are found in much lower amounts, if at all. Examination of ancient clays and sediments in Germany (*2084*), Queensland, Australia (*2085–2088*), and in ceramics and pottery produced from ball clay mined in the United States (*2089*) all reveal the presence of PCDDs, mainly OCDD with lesser amounts of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) (**2246**), **2247**, 1,2,3,4,7,8-hexachlorodibenzo-*p*-dioxin (**2262**), 1,2,3,6,7,8-

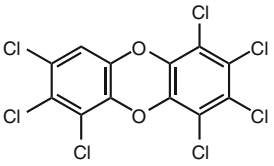
hexachlorodibenzo-*p*-dioxin (**2263**), **2248**, 1,2,3,4,6,7,8-heptachlorodibenzo-*p*-dioxin (**2264**), and several other PCDDs (*2089*).



2262



2263

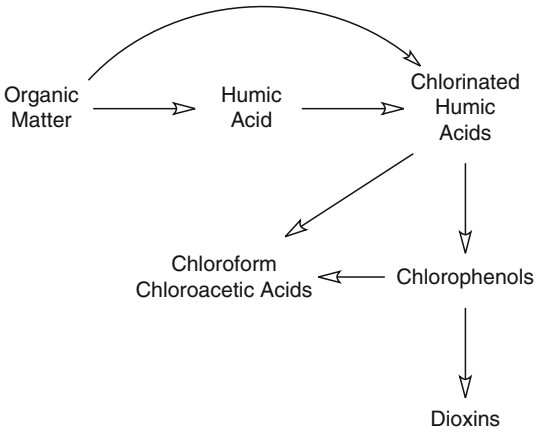


2264

Likewise, 8,000-year old sediments from a Finland lake show a similar PCDD profile to the clay samples (*2090*), as do sediments from Hong Kong (*2091*), and archived soil samples from the UK from the late 1800s and early 1900s (*2092–2094*). No PCBs were found in these latter preserved soil samples. A possible pre-industrial origin of these UK PCDDs is the burning of coastal peat, which is rich in chloride, over the millennia (*2095*). A sealed 1933 sample of municipal sewage sludge exhibits a suite of PCDDs, proposed to arise by in situ formation and condensation of chlorophenols (*2096*). Whether or not these myriad sources of PCDDs and PCDFs are formed biogenically or abiotically, the inescapable conclusion is that they have a natural origin. An excellent review of the occurrence of PCDDs and PCDFs in the environment is available (*22*).

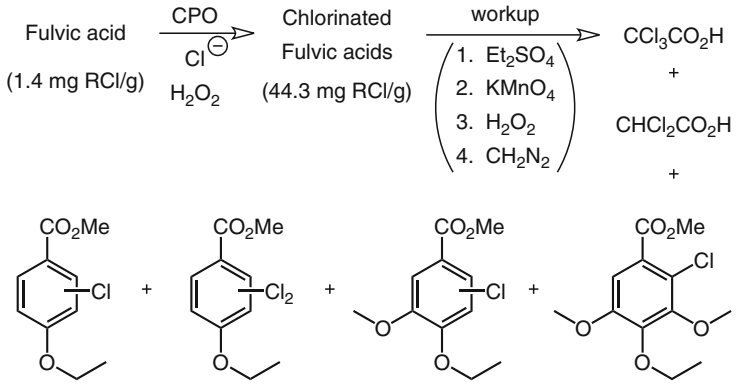
3.26 Humic Acids

Numerous studies support the notion that organohalogen compounds originate on a massive scale via the natural in situ chlorination of humic and fulvic acids and their subsequent breakdown to chlorophenols, chloroacetic acids, chloroform, and other chlorinated and halogenated compounds (*1*). More recent investigations substantiate this ubiquitous route to natural organohalogens (Scheme 3.8) (*172, 2097–2109*). The electron-rich phenolic rings in humic acids (*2666*) are extremely susceptible to both biogenic and abiotic halogenation chemistry, and it is estimated that up to 10% of the aromatic rings in humic acids can be halogenated (*2097*). Evidence shows that the chlorination of humic and fulvic acids facilitates their further decomposition to nonaromatic compounds (*2107, 2109*), and that chloride (i.e., ^{36}Cl) is incorporated into humic acids (*2108*). Furthermore, presumed natural halogenation of humic material also occurs in Baltic Sea marine sediments leading to brominated and iodinated phenolic units in high molecular weight matter (*2110*). Several laboratory studies point to a chloro- or haloperoxidase-promoted halogenation of terrestrial humic and fulvic acids, e.g., (Scheme 3.9) (*315, 412, 2111, 2112*). Moreover, compelling evidence exists for the subsequent formation of chloroacetic acids and chloroform from chlorinated phenolic humic material (*278, 317, 324, 407, 410, 412, 2113, 2654*), including a novel abiotic pathway (Scheme 3.10) (*412*).



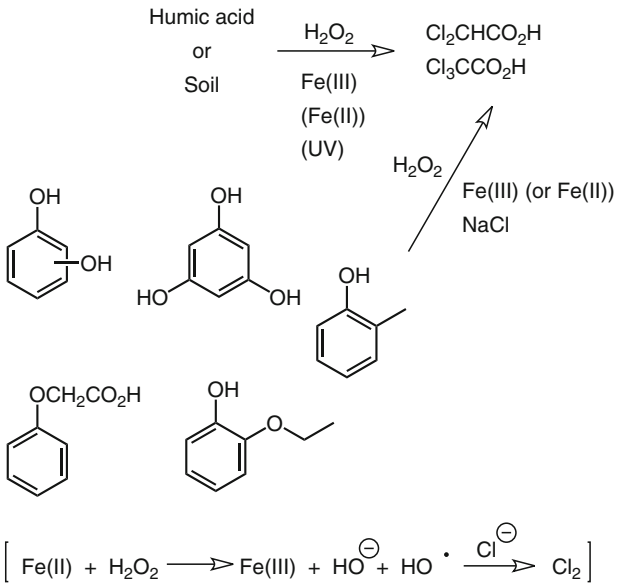
The possible natural formation of organochlorines from humic acid substances.

Scheme 3.8



Chloroperoxidase-induced chlorination of fulvic acid (*412*).

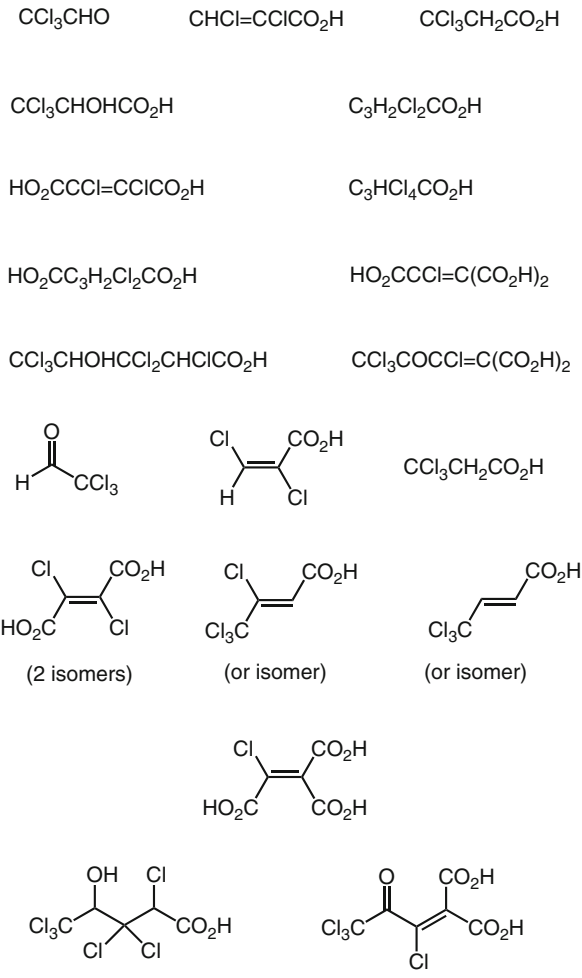
Scheme 3.9



Abiotic formation of chloroacetic acids in soil (*412*).

Scheme 3.10

More than 100 organochlorines have been identified and structurally characterized in the laboratory chlorination of terrestrial humic acid, although the major products are chloroform and trichloroacetic acid, followed by dichloroacetic acid and chlorinated C-4 dicarboxylic acids (*324*). In addition, other products that form in the chlorination of both humic acid and the model compound 3,4-dihydroxybenzoic acid are shown in Scheme 3.11. A more recently discovered source of natural organically bound chlorine is peat, reaching to 0.2% of the dry weight, and estimated to have accumulated globally to the extent of 280–1,000 million tons (*169*).



Products formed in the chlorination of humic acid and 3,5-dihydroxybenzoic acid (*324*).

Scheme 3.11

4 Biohalogenation

4.1 Introduction

While the question of how nature produces organohalogens lagged far behind their discovery, this situation has dramatically changed since the first review (*1*). Numerous excellent reviews of biohalogenation are available (*17, 59, 2114–2122, 2323*), and, as will be seen, several new halogen peroxidases, halogenases, and other enzymes capable of introducing halogen into organic compounds are known, including fluorine.

Specialized reviews on biohalogenation involving vanadium haloperoxidases (*2123–2126*), biochlorination (*2127*), biohalogenation by Basidiomycetes fungi (*2128*), haloperoxidases in organic synthesis (*2129–2131, 2327*), biohalogenation enzymatic mechanisms (*2132*), and halomethane biosynthesis (*2133*) are available. The role of hydrogen peroxide in defining the function of haloperoxidases and other plant enzymes has also been investigated (*2134–2137*).

4.2 Chloroperoxidase

The ubiquitous hemoprotein chloroperoxidase (CPO) (*1*) continues to be of great mechanistic and practical interest following its isolation more than 40 years ago from *Caldariomyces fumago* (*2138*). The CPO gene from this filamentous fungus has been isolated and sequenced (*2139*), an active recombinant CPO has been produced (*2140*), and the crystal structure of this CPO has been determined (*2141, 2142*). The fungus *Curvularia inaequalis* contains a vanadium CPO, which has been characterized (primary and X-ray structure) (Fig. 4.1) (*2143–2147*), as has the vanadium haloperoxidase from *Corallina officinalis* (*2324*). This enzyme has also been studied by density functional theory lending support to the proposed mechanism of action (Scheme 4.1) (*2325*). A related vanadium CPO, which shares 68% primary structural identity with the *Curvularia inaequalis* CPO, is produced

G.W. Gribble, *Naturally Occurring Organohalogen Compounds – A Comprehensive Update*, Progress in the Chemistry of Organic Natural Products, Vol. 91,
DOI 10.1007/978-3-211-99323-1_4, © Springer-Verlag/Wien 2010

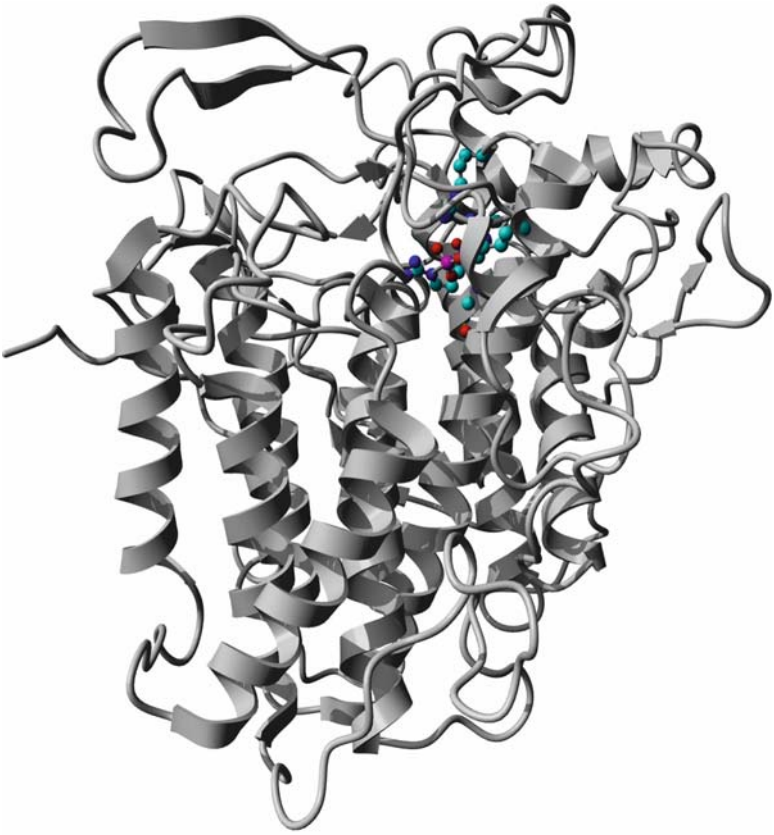
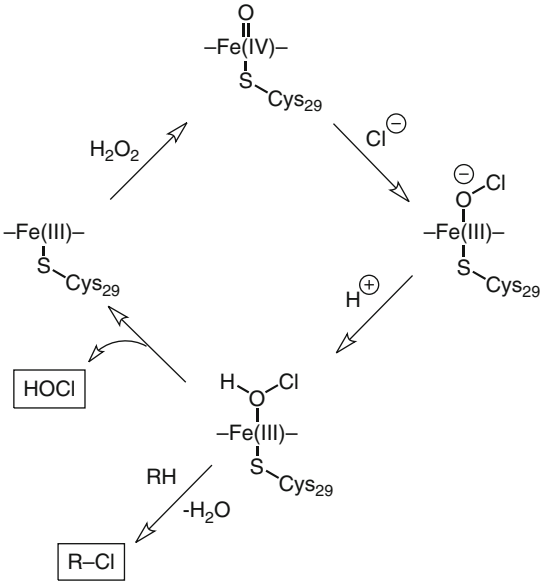


Fig. 4.1 A ribbon diagram of vanadium chloroperoxidase from the fungus *Curvularia inaequalis* (Photo: T. van Herk)

by the fungus *Embellisia didymospora* (*2148*). Some 10 *Caldariomyces* cultures produce CPOs with variable carbohydrate content but identical enzymatic activity (*2149*). CPO enzymes are found in bryophytes (liverworts) (*1710*), the marine worm *Notomastus lobatus* (*2150–2152*), and the bacteria *Streptomyces lividans* (*2153*) and *Serratia marcescens* (*2154*). The latter two CPOs do not contain a metal ion and the *Notomastus lobatus* CPO is the smallest hemoprotein known. Immobilized silica-supported heme-CPO from *Caldariomyces fumago* retains biological activity (*2155, 2156*), and CPO from this fungus also serves as a dehaloperoxidase in the dehalogenation of halophenols (*2157, 2158*).

The mechanism of CPO-induced halogenation has been of interest since the discovery of this extraordinary set of heme proteins, which exhibit catalase, peroxidase, and cytochrome P450 activities in addition to biohalogenation (*2159–2171*). A general consensus mechanism has been proposed that does not involve free



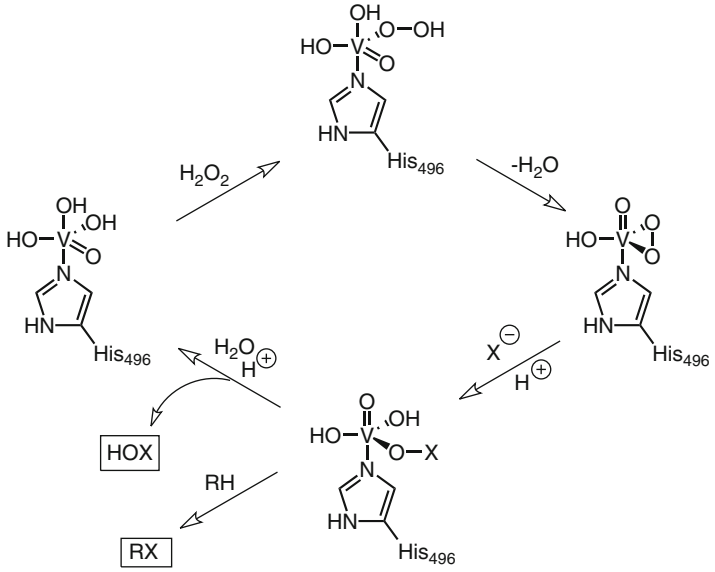
Abbreviated proposed mechanism of heme-chloroperoxidase-catalyzed chlorination (*2163, 2165, 2168, 2202, 2303*).

Scheme 4.1

chlorine or hypochlorite but rather an Fe(III)–OCl species that transfers chlorine to the organic substrate (Scheme 4.1).

Vanadium CPO from *Curvularia inaequalis* has also been the object of both experimental (*2146, 2172–2175, 2329*) (for an X-ray structure see Fig. 4.1) and theoretical studies (*2176*) to understand the biohalogenation operation of this enzyme. A reasonable mechanism has emerged from these data (Scheme 4.2) (active site amino acids and H-bonds are deleted for clarity). The nature of the halide-vanadium intermediate is unknown.

The CPO from *Caldariomyces fumago* has seen extensive use as a synthetic reagent *par excellence* (*1, 2129–2131, 2177, 2178*) and new applications are known. For example, the enantioselective CPO oxidation of sulfides to (*R*)-sulfoxides has been intensely pursued (*2179–2193*) in some cases displaying 100% enantiomeric excess and quantitative yields (Scheme 4.3). Another important and versatile reaction with CPO involving oxygen transfer is epoxidation (*2194–2207*) and some examples are shown in Scheme 4.3. The mechanism of these CPO-catalyzed oxygen insertion reactions has been examined (*2208*). Oxidation reactions that are catalyzed by heme CPO are benzylic hydroxylation (*2209*), propargylic oxidation (*2210, 2211*), benzylic alcohol oxidation (*2212*), cyclopropylmethanol oxidation (*2213*), 5-hydroxymethylfurfural oxidation (*2214*), the enantioselective oxidation of



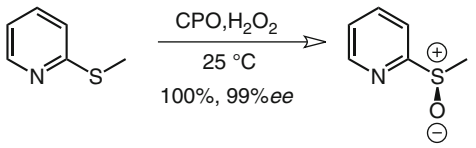
Abbreviated proposed mechanism of vanadium chloroperoxidase-catalyzed halogenation (*2123, 2124, 2146, 2172, 2173, 2175*).

Scheme 4.2

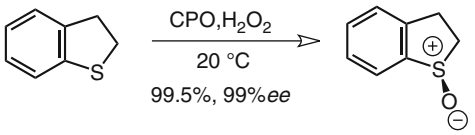
epoxyalcohols (*2215*), and phenol oxidation (*2216*). Indoles are oxidized to oxindoles in excellent yield (*2184, 2189, 2217–2219*), and both benzofurans and benzothiophenes are oxidized to various products (*2219*). CPO converts oximes to halonitro compounds (*2220*) and phosphorothioate pesticides to phosphates (*2221*), chlorinates aromatic hydrocarbons (*2222, 2223*), and effects polymerization of polychlorinated phenols (*2224*). A selection of these reactions is presented (Scheme 4.3).

Although less studied as a synthesis reagent, vanadium-CPO effects similar oxidation reactions to those of heme-CPO (*2225, 2226, 2326*). The CPO from *Streptomyces aureofaciens* can brominate pyrroles in the presence of bromide (*2227*). The synthesis performance of CPO has been improved by controlling the hydrogen peroxide delivery rate (*2228*), engineering CPO mutants resistant to deactivation (*2229–2231*), designing active site analogues (*2232*), and optimizing the role of organic solvents in these reactions (*2233*).

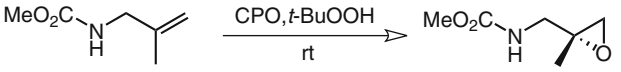
Despite the enormous versatility and efficiency of CPO in organic synthesis, the natural functions of this enzyme are no less important. In addition to its role in the biosynthesis of caldariomycin and other metabolites (*1*), CPO is involved in the degradative recycling of humic and fulvic acids (*315, 412, 2100, 2108, 2111–2113, 2234, 2235*). Both *Caldariomyces fumago* and *Curvularia inaequalis* CPO, which



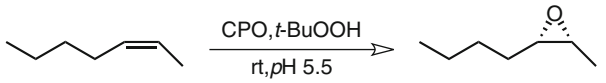
(*2180*)



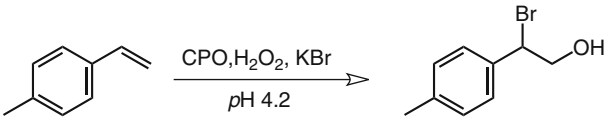
(*2183*)



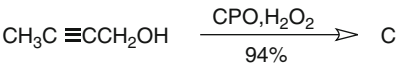
(*2199*)



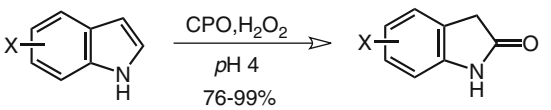
(*2201*)



(*2202*)

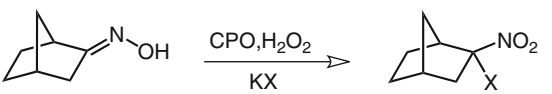


(*2210*)



(*2217*)

X = H, 4-Cl, 5-Cl, 6-Cl, 5-Br, 5-Me, 5-MeO, 7-aza



(*2220*)

X = Cl, Br

Oxidations with chloroperoxidase.

Scheme 4.3

occur in soils, chlorinate and cleave lignin structures (*2234, 2235*), results augmented by the specific incorporation of $^{36}Cl^{-}$ into humic acid (*2108*). A fern (*Athyrium filix-femina*) and a moss (*Polytrichum commune*) take in $^{36}Cl^{-}$ that is released as radiolabelled $CHCl_3$, CCl_4, and CH_3CCl_3, suggesting CPO activity in these forest plants (*2236*). Earlier studies also support the CPO production of $CHCl_3$ and trichloroacetic acid in soil and fungi (*317, 326, 410*), and chlorophenols and dioxins in peat (*2037*). It is estimated that global peatlands contain 280–1,000 million tons of peat-bound organochlorines, perhaps formed via humification by CPO (*169*). Likewise, CPO could play a role in the production of organochlorines in

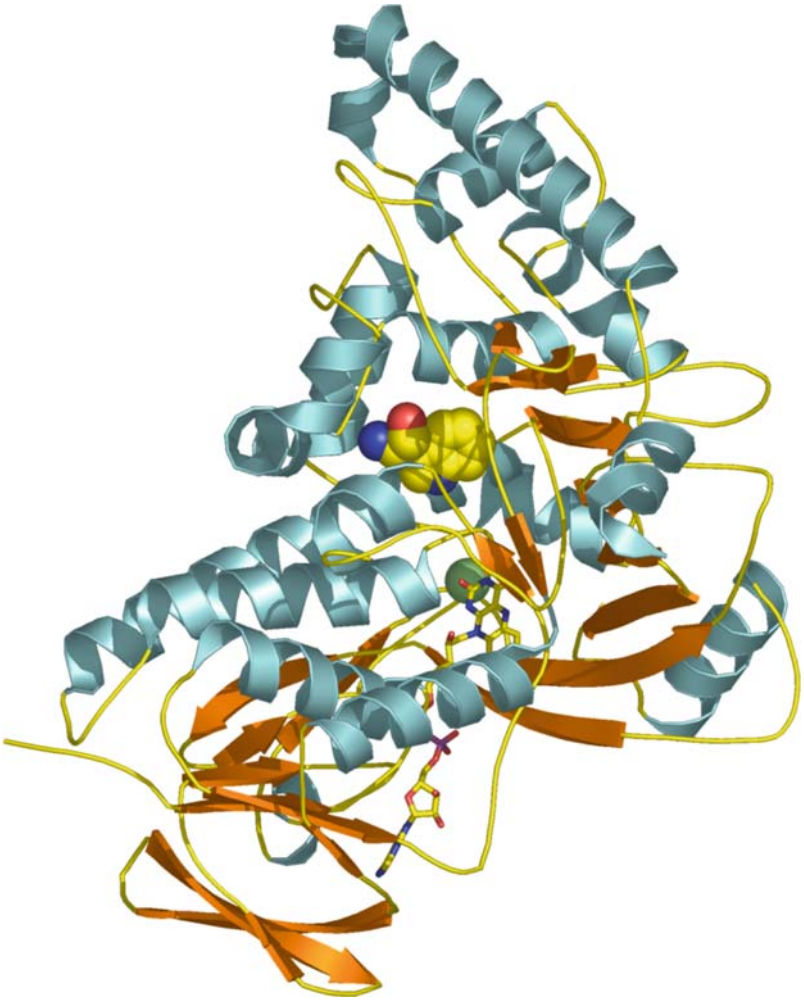


Fig. 4.2 A ribbon diagram of tryptophan 7-halogenase, an enzyme important in the biosynthesis of pyrrolnitrin and rebeccamycin. (Photo: K.-H. van Pée and J. H. Naismith)

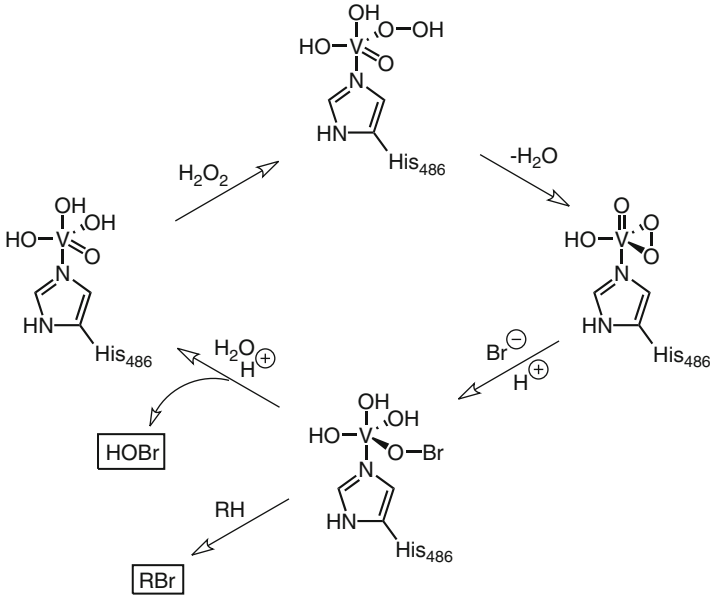
weathering plant material (*172, 173*), and CPO-induced chlorination of surface water in a Swedish peat bog (Fig. 4.2) affords organochlorines such as 2,4,6-trichlorophenol (*2237*). CPO activity in *Laminaria digitata* seems to account for the formation of $CHCl_3$ in this macroalga (*306*), for the biosynthesis of chlorinated orcinols (**1783–1789**) in the Japanese lily *Lilium maximowiczii* (*1690*), and for chlorinated anthraquinones in the lichen *Nephroma laevigatum* (*1932, 2238*). The flavanones naringenin and hesperetin are chlorinated (and brominated) by CPO, although the resulting products are unnatural (*2239*).

4.3 Bromoperoxidase

As noted previously, bromoperoxidase (BPO) is a ubiquitous enzyme that brominates a wide variety of organic substrates (*1*). Both heme and vanadium BPOs are known and these enzymes are probably the main actor in the biosynthesis of the myriad marine organobromine metabolites (*2240–2242, 2329*).

In addition to the organisms cited earlier that contain BPO (*1*), new discoveries of BPO or BPO activity include the green algae *Ulva lactuca* (*2243*) and *Ulvella lens* (*366*), the red algae *Kappaphycus alvarezii* and *Eucheuma serra* (*2244*) and *Ochtodes secundiramea* (*2245*), and the Arctic brown algae *Laminaria saccharina* (*2246, 2247*) and *Laminaria digitata* (*2247, 2248*). A BPO has been isolated from the marine snail *Murex trunculus* (*2249*), and the nonheme BPO found in the bacterium *Pseudomonas putida* has been purified and characterized (*2250*). BPO genes have been cloned and expressed from *Streptomyces aureofaciens* (*2251–2253*), *Streptomyces venezuelae* (*2254*), *Corallina pilulifera* (*2255, 2256*), and *Corallina officinalis* (*2257*). X-ray crystal structure determinations have been reported for BPOs from *Streptomyces aureofaciens* (*2258*), *Corallina officinalis* (*2259, 2260*), and *Ascophyllum nodosum* (*2261–2263*). Based on these crystal structures and extensive model studies (*2124, 2264–2269*), a plausible mechanism for the *Ascophyllum nodosum* vanadium BPO bromination chemistry can be formulated (Scheme 4.4) (active site amino acids and H-bonds are deleted for clarity) (*2124, 2261, 2263, 2264, 2269*).

The synthetic utility of BPO is immature relative to that of CPO, but is showing promise as both a bromination reagent and a source of oxygen (*2131, 2326*). A vanadium-containing BPO from *Corallina officinalis* oxidizes sulfides to sulfoxides with the *S*-configuration, opposite to that observed with CPO (*2270–2273*), and forms bromohydrins from alkenes (*2194*). The indole ergot alkaloid agroclavine is oxidized to the corresponding oxindole and other products with BPO (*2274, 2275*). Several biomimetic studies with BPO have demonstrated the conversion of laureddiols and related precursors to marine natural products (*2276–2278*), the cyclization of terpenes to brominated marine metabolites (*2279, 2280*), and the bromination of bromophenols (*1724, 2281*), examples of which are shown in Scheme 4.5. Interestingly, BPO from *Ascophyllum nodosum* contains brominated tyrosines at the surface of this enzyme (*2328*).



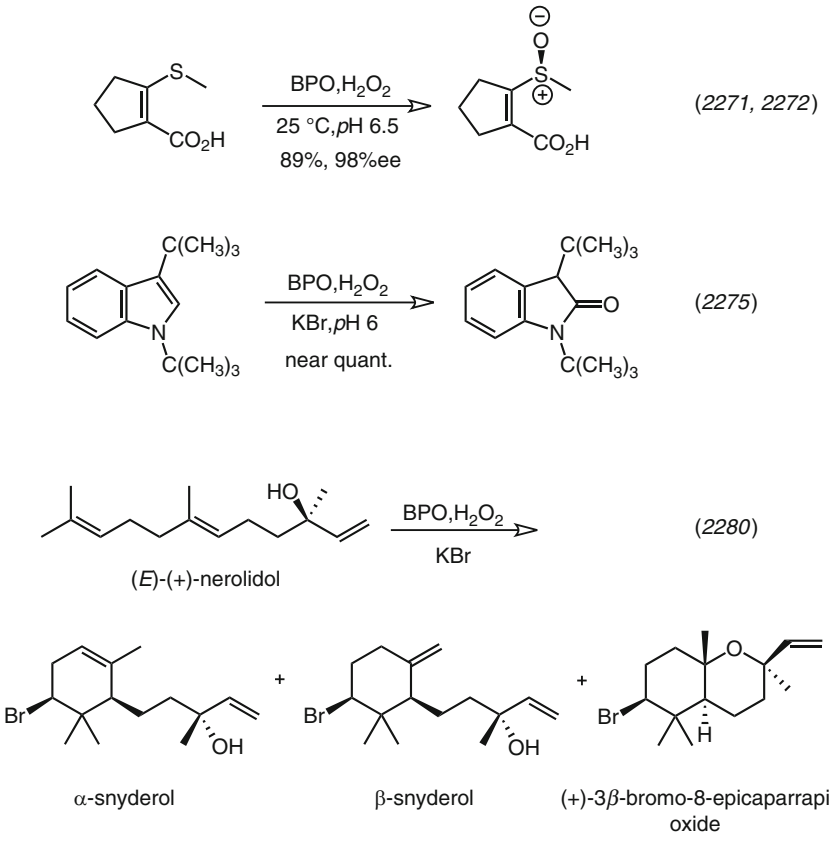
Abbreviated proposed mechanism of vanadium bromoperoxidase-catalyzed bromination (*2123, 2124, 2175, 2261, 2263, 2269, 2280, 2328*).

Scheme 4.4

In marine organisms, notably algae, the normal function of BPO is the production of brominated alkanes, such as $CHBr_3$, CH_2Br_2, $CHClBr_2$, and other bromoalkanes as has been established in studies of marine phytoplankton (*Nitzschia arctica*, *Porosira glacialis, Navicula* sp.) (*339*), *Corallina pilulifera* (*354, 2282*), and the red alga *Asparagopsis* sp. (*370*).

4.4 Halogenases, Other Haloperoxidases and Peroxidases

Several new enzymes capable of biohalogenation have been identified since the first review (*1*). Thus, given the significant number of naturally occurring organoiodine compounds, it is not surprising that iodoperoxidases (IPO) are known. For example, one species of *Navicula* marine phytoplankton produces CH_2I_2 and $ClCH_2I$ via an iodoperoxidase, an enzyme capable of oxidizing iodide but not bromide or chloride (*339*). A vanadium-dependent IPO has been purified and characterized from the brown alga *Saccorhiza polyschides* (*2283*), and also isolated from the brown alga *Phyllariopsis brevipes* (*2284*), and *Laminaria saccharina*, *Laminaria hyperborea*, *A. n. lusitanica*, *Pelvetia canaliculata*, and *Laminaria ochroleuca* (*2285, 2286,*



Oxidations with bromoperoxidase.

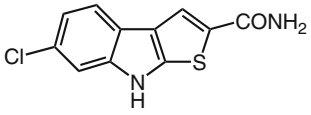
Scheme 4.5

2302). Other studies of *Laminaria digitata* and *Laminaria saccharina* indicate the presence of IPO (*2246, 2247, 2287*), as do studies of the marine microalga *Porphyridium purpureum* (*2288*) and the alga *Ascophyllum nodosum* (*2289*). The Arctic green algae *Acrosiphonia sonderi* and *Enteromorpha compressa* have high IPO activity (*2247*). Two peroxidase enzymes (*2290*) that catalyze the iodination of tyrosine are horseradish peroxidase (HRP) and lactoperoxidase (LPO) (*2291*). The latter enzyme is dominant for the iodination of tyrosine in mammals. The heme-containing HRP, which has been studied for more than one hundred years (*2292*), can also effect the oxidation of pentachlorophenol (*2293*). Similarly, a lignin peroxidase (LP) from *Phanerochaete chrysosporium* that is capable of oxidatively degrading lignin (*2294, 2295*) exhibits haloperoxidase activity (*2296*). This is the first report of biohalogenation in a white rot fungus, and this fungal LP and a related manganese peroxidase (MP) oxidize both bromide and iodide, thus functioning as a

BPO and IPO (*2296, 2297*). The basidiomycetous fungus *Agrocybe aegerita* also contains a haloperoxidase (*2298*), and a model oxomanganese (V) porphyrin is a haloperoxidase mimic (*2299*). The fresh water alga *Cladophora glomerata* contains a heme-haloperoxidase that oxidizes iodide to iodine and iodinates tyrosine and other phenols (*2300*). The actinomycete *Rhodococcus erythropolis* NI 86/21 produces a nonheme haloperoxidase that degrades thiocarbamate herbicides, and is the first such enzyme to be identified in a nocardioform actinomycete (*2301*). The importance of the occurrence and properties of heme peroxidases and their potential as biocatalysts with both biological and environmental applications has been succinctly summarized (*2303*).

A recent development is that of flavin-dependent halogenases discovered during studies of pyrrolnitrin biosynthesis from tryptophan (i.e., tryptophan 7-halogenase) (Fig. 4.2) (*1189–1191, 2122, 2304–2308, 2320*), which is discussed in Sect. 4.8 (Biosynthesis). Tryptophan 7-halogenase requires $FADH_2$ for halogenation and is the first member of this new type of halogenating enzyme. A similarly regioselective tryptophan 5-halogenase is present in *Streptomyces rugosporus* that produces pyrroindomycin B (**1468**) (*2309*), and a tryptophan 6-halogenase was found in the thienodolin (**2265**) producer *Streptomyces albogriseolus* (*2310, 2330, 2331*). A theoretical evaluation of flavin-dependent halogenase biohalogenation with oxidants such as O_2 or N_2O show that this reaction is thermodynamically feasible even without NADH (*2311*). Another halogenase has been isolated from the actinomycete *Actinoplanes* sp. ATCC 33002, a producer of pentachloropseudilin (**1155**) (*2312*), and the role of tryptophan 7-halogenase in the biosynthesis of rebeccamycin has been demonstrated (*1440*). The production of syringomycin E by *Pseudomonas syringae* pv. *syringae* B302D involves chlorination of a threonine (unactivated) methyl group by a novel halogenase, SyrB2, that is a nonheme Fe(II) protein utilizing α-ketoglutarate, O_2, and Cl^- to effect chlorination (*1145, 1146, 2313, 2323*) (Scheme 4.6). A similar enzyme chlorinates an unactivated methyl group of a L-*allo*-isoleucine residue en route to the biosynthesis of coronatine (*2314, 2315, 2323*).

Other enzymes capable of halogenation processes include a bacterial esterase from *Pseudomonas fluorescens* (*2316*), acid phosphatases from the bacteria *Shigella flexneri* and *Salmonella enterica* ser. *typhimurium* (*2317*), a lactonohydrolase from *Acinetobacter calcoaceticus* F46 (*2318*), and hydroperoxide halolyse from the marine diatom *Stephanopyxis turris* (*2319*). The biosynthesis of the ubiquitous methyl halides seems to involve methyl transferase enzymes, which have been isolated and purified in the plant *Brassica oleracea* (*S*-adenosyl-L-methionine:



2265 (thienodolin)

Abbreviated proposed mechanism of non-heme iron halogenase chlorination (*1145, 1146, 2127, 2313, 2323*).

Scheme 4.6

halide/bisulfide methyltransferase) (*2321, 2322*), and in the halophytic plant *Batis maritima*, a robust generator of CH_3Cl (*291, 292*).

4.5 Myeloperoxidase

The biohalogenating mammalian enzyme myeloperoxidase was extensively reviewed in Chap. 3 (*1*). Subsequent studies confirm and extend the importance of this white blood cell (neutrophil) enzyme and the related eosinophil peroxidase in the infection fighting process via, respectively, the generation of hypochlorous (HOCl) and hypobromous (HOBr) acid. Excellent reviews are available (*763, 764, 2332–2336*). The antimicrobial activity of HOCl is revealed by the fact that it is at least 10^3 times more effective than H_2O_2 and hydroxyl radical in killing *Escherichia coli* (*764*). The heme-containing myeloperoxidase, which is the most abundant protein in neutrophils amounting up to 5% of the dry weight (*2337*), has been characterized by X-ray crystallography (*2338*). This protein is the only human enzyme known to produce HOCl at physiological chloride concentrations (100 mM in plasma) (*2339*). Further reaction with cellular amino constituents such as taurine leads to taurine chloramine and other *N*-chloramines that are longer lived and less reactive (and potentially less destructive) chlorinating agents than HOCl (*2340–2343*). This early-demonstrated property of myeloperoxidase has been supported and amplified by many recent studies (*2344–2352*). Free chlorine gas is also implicated in some biochlorination reactions involving myeloperoxidase (*768, 1806, 2353*).

The active chlorinating species produced by the MPO–Cl^-–H_2O_2 system react with a myriad of biological targets including cholesterol (*766–769*), plasmalogens (*2354*), phospholipids (*2355, 2356*), amino acids (*2357–2362*), nucleosides (*2363*), and DNA (*1479, 2364*), accompanied by an array of chlorinated and oxidized by products (3-chlorotyrosine, 5-chlorouracil (**1555**), and others). Of great interest has been the role of MPO in the oxidation of both low- and high-density lipoprotein and implications in atherogenesis (*1807, 1810, 2365–2372*), although the function of MPO in atherosclerosis remains controversial (*2373*). Interestingly, vitamin C is reported to protect and reverse the HOCl- and chloramine-induced oxidation of low-density lipoprotein that may be involved in atherosclerosis (*2374*). In any event, it is clear that a deficiency of MPO can lead to severe fungal infection such as that from *Candida albicans* (*2375*).

In contrast to MPO, eosinophil peroxidase (EPO) prefers to oxidize plasma level bromide (20–100 μM) to hypobromous acid (HOBr) and several biological targets are implicated, including nucleic acids and nucleosides (*1480, 1482, 2376*), proteins (*1812, 1813, 2377, 2378*), unsaturated fatty acids (*2379*), and low-density lipoprotein (*2380, 2381*). This EPO-dependent bromination is suggested to be involved in the pathogenesis of asthma (*2382*). Accordingly, both 3-bromotyrosine and 3,5-dibromotyrosine (*1812, 1813*) are produced by EPO-induced bromination of tyrosine residues in lung tissue (*1813, 2382*).

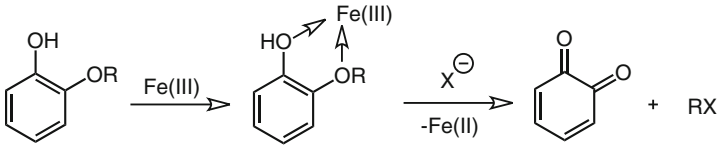
The question posed by Winterton in 1997, "Are Organochlorine Compounds Created in the Human Body?" (*2383*), can now be answered with an authoritative "Yes".

4.6 Abiotic Processes

A major development since the previous review is the discovery that some organohalogen compounds can form in soils by a purely abiotic mechanism involving a Fenton oxidation pathway and the concomitant reduction of Fe(III) to Fe(II) (*2384–2386*). The formation of alkyl halides by this mechanism is shown in Scheme 4.6 (*2387*). The rates of production from soils decreased in this order: $CH_3X > CH_3CH_2X > CH_3CH_2CH_2X \gg CH_3CH_2CH_2CH_2X$, where X = Cl, Br, I. Subsequent studies show that iodoalkanes of 1–4 carbons (*2388*) and chloroacetic acids form abiotically in soil (*413*), in addition to their well-known biogenic enzymatic formation. An abiotic source of CH_3Br is suggested for the emission of this gas from ash (*Fraxinus excelsior*) and saltwort (*Batis maritima*), plants having known bromine content (*2389*). The emissions are a function of both temperature increase and bromine concentration. The natural formation of chloroethyne (**58**) in soil is also proposed to involve a Fenton reaction (*382*), as is the production of dichloroacetic and trichloroacetic acids from phenols and soil humic acid (*413*).

4.7 Biofluorination

Although few in number, fluoroacetic acid and the other naturally occurring ω-fluoro fatty acids (*34, 66, 2390, 2391*) are unsurpassed for their biogenetic intricacy, which has inspired enormous scientific interest, most notably from *O'Hagan* and his colleagues (*898–909, 911–913, 916, 2392–2394*). As noted earlier



X = Cl, Br,I

R = CH_3, CH_3CH_2, $CH_3CH_2CH_2$, $CH_3CH_2CH_2CH_2$

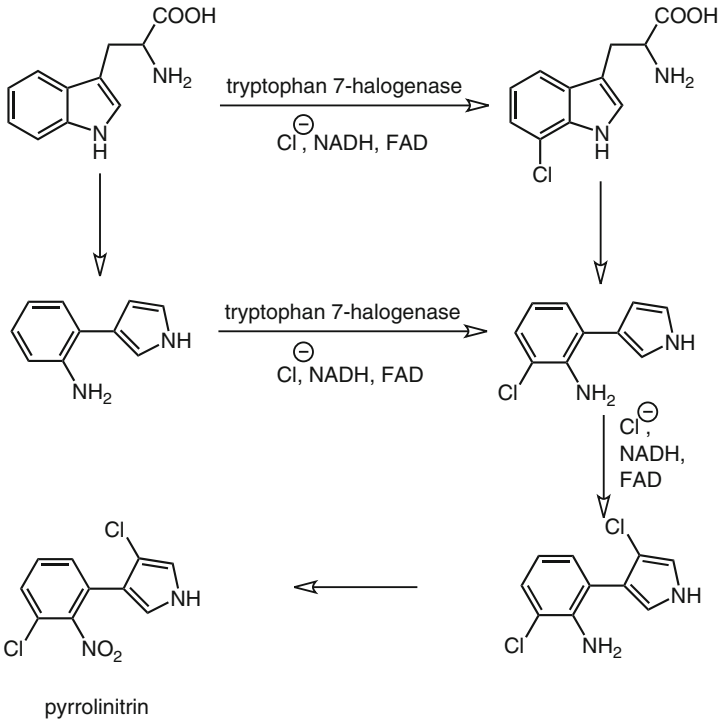
Proposed abiotic formation of alkyl halides (*2386, 2388*).

Scheme 4.7

(Sect. 3.1.13 (Simple Organofluorines)), several reviews are available (*895, 914, 915, 2390, 2391, 2395*). Based on the available evidence, a proposed biosynthetic pathway for the formation of fluoroacetic acid and 4-fluorothreonine is shown in Scheme 4.7. Fluorinase has also served as a catalyst for the incorporation of [^{18}F]-fluoride into nucleosides (*2396, 2397*).

4.8 Biosynthesis

The biosynthesis of organohalogens has seen enormous interest since the first survey, and several examples are mentioned earlier in the present review. Space does not allow for full coverage of this topic, but some additional examples are presented here. The reader is also directed to general reviews on the biosynthesis of marine natural products, many of which contain halogen (*2398–2401*), terrestrial fungal (basidiomycetes) metabolites (*2402*), and halogenated alkaloids (*2403*).



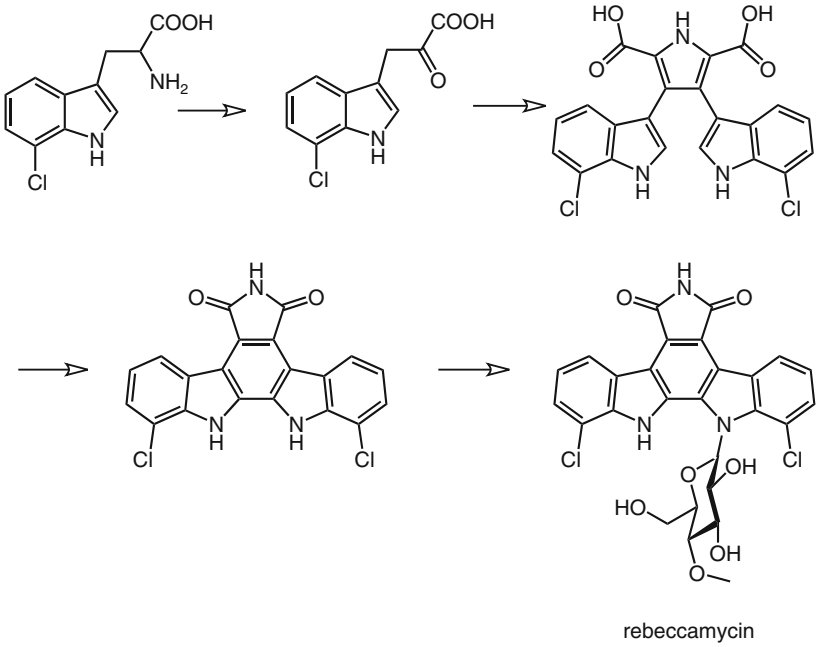
Proposed biosynthesis of pyrrolnitrin (*1189, 2310*).

Scheme 4.8

The biosynthesis of halogenated pyrroles has been of particular interest (*1189, 2404*). Extensive labeling experiments (^{13}C and ^{15}N) support acetate, propionate, proline, glucose, and methionine as the precursors of pyralomicin 1a (**1158**) (*2405, 2406*). A proline and polyketide origin is also established for the biosynthesis of streptopyrrole (**1165**) (*2407*). In both cases the timing of the chlorination step is unknown. Carbon-13 labelling studies show that the benzene ring in pentabromopseudilin evolves via 4-hydroxybenzoic acid and the shikimate pathway (*2408*), while the pyrrole ring is derived from proline (*2409*). Histidine, ornithine, and proline are incorporated into the brominated oroidin sponge alkaloid stevensine (*2410*). The biogenesis of the numerous pyrrole-imidazole alkaloids has received special attention (*2411, 2412*). Dioxapyrrolomycin also features a proline-polyketide pathway (*2413*), and other studies have explored the formation of the pyrrole ring in related metabolites (*2414, 2415*).

The biosynthesis of pyrrolnitrin and related phenylpyrroles has been extensively studied by van Pée (*1189, 2304, 2306, 2307, 2310*), and a proposed biosynthesis from tryptophan is illustrated in Scheme 4.8 (*1189, 2310*).

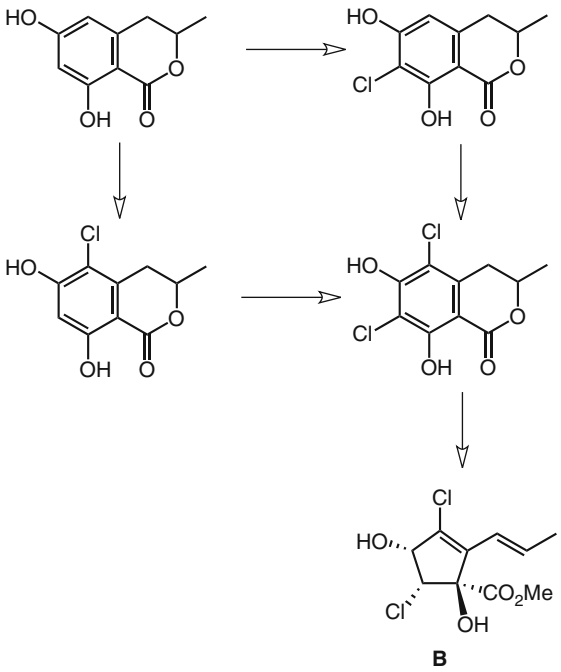
The anticancer indolocarbazole alkaloid rebeccamycin has been the subject of several biosynthetic studies (*1439–1441, 2416*), which is also proposed to involve the chlorination of tryptophan (Scheme 4.9).



Proposed biosynthesis of rebeccamycin (*1439, 1440, 2416*).

Scheme 4.9

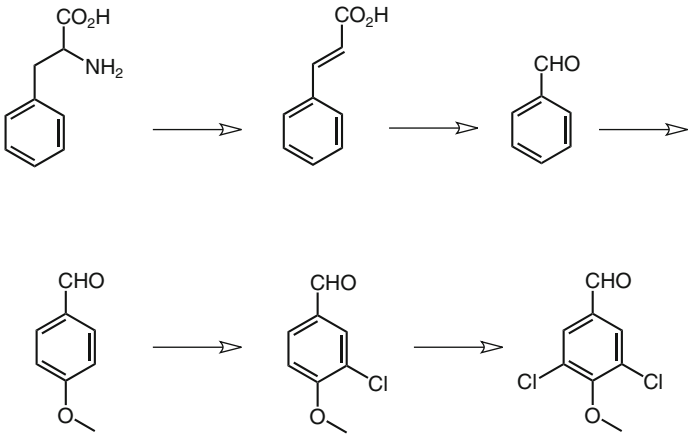
The biogenesis of vancomycin, the vanguard antibiotic of more than 200 naturally occurring glycopeptides, has been exhaustively studied (*2002, 2417*), as have been the venerable antitumor antibiotic maytansinoids (e.g., **1603–1605**), such as ansamitocin (*2418–2422*). In addition to a polyketide sequence, 3-amino-5-hydroxylbenzoic acid is the precursor to the chlorine-containing benzene ring of ansamitocin (*2421*). Similarly, the chlorine-containing benzene ring in the enediyne antitumor antibiotic C-1027 arises from (*S*)-3-chloro-4,5-dihydroxy-β-phenylalanine (*1552, 2423*). The biosynthesis of the mixed polypeptide-polyketide barbamide (**917**) was mentioned in Sect. 3.12 (Amino Acids and Peptides). The trichloromethyl group originates by chlorination of the pro-*R* methyl group of L-leucine, and subsequent conversion to trichloroisovaleric acid (*2424*). Biochlorination of a tyrosine derivative leads to the chlorine-containing coumarin ring of chlorobiocin (*1503*), and tyrosine is the precursor to several brominated tyrosines (*2425*). Likewise, tyrosine and several subsequent intermediates have been identified in the biosynthesis of thyroxine (*2426, 2427*). A polyketide pathway is implicated in the formation of numerous lichen chlorinated anthraquinones (e.g., **2157–2165**) and this lichen (*Nephroma laevigatum*) is able to chlorinate preexisting anthraquinones (*1932*). The origin of the chlorinated cyclopentene ring



B

Proposed abbreviated biosynthesis of cryptosporiopsin (**B**) (*415, 416*).

Scheme 4.10



Proposed biosynthesis of 3-chloro- and 3,5-dichloro-4-methoxybenzaldehyde (*2430, 2431*).

Scheme 4.11

of the *Periconia macrospinosa* metabolites seems to involve an isocoumarin (Scheme 4.10).

The biosynthesis of the white rot fungus *Bjerkandera adusta* chlorinated aryl metabolites has been extensively studied by Silk and others (*1687, 2428–2431*), an abbreviated version of which is shown in Scheme 4.11 for 3-chloro- and 3,5-dichloro-4-methoxybenzaldehyde.

5 Biodegradation

An essential component of the biogenic halogen cycle is the degradation of organohalogens into their constitutive elements when an organism dies. Following the style of the earlier review (*1*), coverage here will be brief since biodegradation of organohalogens, both natural and anthropogenic, is an enormous topic and excellent reviews are available (*2119, 2432–2442*).

Several organisms are capable of degrading methyl halides, including *Methylobacterium chloromethanicum* (*2443, 2444*), *Hyphomicrobium chloromethanicum* (*2444*), *Aminobacter* spp. (*2444*), and others (*2445*), including marine bacteria (*2446, 2447*). The biodegradation of 1,2-dichloroethane has received particular interest, and the haloalkane dehalogenase from *Xanthobacter autotrophicus* has been extensively investigated (*2448–2452*). The key step in this degradation is an S_N2 displacement of chloride that is supported by chlorine isotope effect studies (*2453*). Other bacterial enzymes also biodegrade 1,2-dichloroethane and related haloalkanes and haloacetic acids (*278, 2454–2458*). The dry cleaning agents, trichloroethylene (TCE) and perchloroethylene (PERC), which also have a natural source, are degraded by bacterial enzymes (*2459–2462*), as are dichloroethylenes (*2462, 2464*) and vinyl chloride (*2464*). The white-rot fungus *Trametes versicolor* also mineralizes TCE (*2465*). Transgenic plants degrade TCE, 1,2-dibromoethane, and other organohalogens (*2466*).

Another large group of naturally occurring organohalogen compounds are the halogenated phenols. Both terrestrial and marine versions are readily degraded enzymatically. Marine worms (*Amphitrite ornata* and *Notomastus lobatus*) employ a haloperoxidase to degrade halophenols including fluorophenols (*2151, 2152, 2467–2469*). The enzyme from *Amphitrite ornata* has been purified and crystallized for an X-ray determination (*2469*). Bacteria associated with the marine sponge *Aplysina aerophoba* (*2470*), and the venerable *Caldariomyces fumago* fungal enzyme chloroperoxidase effect dehalogenation of halophenols (*2157, 2158*), as does a marine anaerobic *Desulfovibrio* bacterium strain (*2471*). The ubiquitous chlorophenols are degraded by a wide range of microorganisms, including fungi (*Paxillus involutus*, *Suillus variegatus*) (*2472*), (*Pycnoporus cinnabarinus*) (*2473*), anaerobic bacteria (*Desulfitobacterium* sp.) (*2474–2477*), horseradish peroxidase

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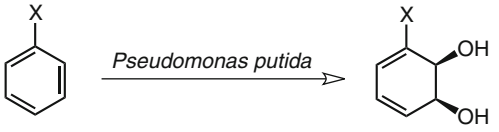

Microbial oxidation of halobenzenes (*2482-2485*).

Scheme 5.1

(*2293, 2478*), and the marine microalga *Tetraselmis marina* (*2479*). The latter organism converts 2,4-dichlorophenol to 2,4-dichlorophenyl-β-D-glucopyranoside for detoxification. Polychlorinated dibenzo-*p*-dioxins and dibenzofurans are biodegraded by an array of organisms, and this important area has been summarized (*2480, 2481*). Both aerobic bacteria (*Sphingomonas*, *Pseudomonas*, *Burkholderia*) and anaerobic sediments are capable of these biotransformations.

The microbial oxidation of halobenzenes to the corresponding *cis*-1,2-dihydrocatechols (Scheme 5.1) has proven to be a treasure trove for organic synthesis (*2482–2485*), most notably utilized by Hudlicky (*2483*). Thus, a myriad of natural products and analogs have been synthesized starting from the biooxidation of halobenzenes: vitamin C (*2486, 2487*), (+)-pericosine B (*2488*), *N*-acetylneuraminic acid (*2489*), combretastatins (*2490*), pancratistatin (*2491*), (–)-patchoulenone (*2492*), (–)-hirsutene (*2492*), (–)-cladospolide B (*2493*), (–)-cladospolide C (*2494*), shikimic acid analogs (*2495*), (–)-conduritol E (*2496*), (–)-conduramine C-4 (*2497*), phenylthioconduritol F (*2498*), (+)-codeine (*2499*), (+)-nangustine (*2500*), the anti-influenza agents Tamiflu and Tamiphosphor (*2501*), inositols (*2502, 2503*), and several other oxygenated benzene compounds (*2504–2513*). The power and versatility of the *Pseudomonas putida* oxidation of halobenzenes is beyond dispute.

6 Natural Function

The question that can be asked about all natural products, including naturally occurring halogenated compounds, is "Why do organisms produce organohalogens?" The first review provided evidence that seems to answer this question for several halogenated metabolites (*1*). For example, in the case of sessile marine organisms, a chemical defense function for these compounds seems paramount, and excellent reviews on this topic are available (*39, 2514–2520*). Nevertheless, a clear function for most of the identified biogenic organohalogens is presently unknown.

While natural chloromethane may have several functions (*42*), in Basidiomycetes wood-rot fungi (*Phellinus*, *Inonotus*, *Fomitosporia*, *Hymenochaete*, *Phaeolus*, and *Fomitopsis*) (*59*) chloromethane is a methyl donor in the biosynthesis of veratryl alcohol, the first step of which is methylation of 4-hydroxybenzoic acid. A second methylation of isovanillic acid affords ultimately veratryl alcohol, the function of which in these fungi is to stabilize lignin peroxidase thus promoting lignin degradation (*2521*).

A spectacular example of host defense involves the Japanese lily *Lilium maximowiczii* (Fig. 3.26) that produces seven chlorinated fungicides (**1783–1789**) in response to attack by the pathogenic fungus *Fusarium oxysporum* (*1690*).

It seems without argument that sponges, tunicates, algae, and other sessile marine organisms produce metabolites, halogenated and not, to prevent bacterial and barnacle overgrowth – "biofouling" – lest these animals be fatally smothered (*2522*), a plague of the shipping industry (*2523*). This antifouling activity is clearly expressed in sponges, such as *Acanthella cavernosa* (and/or their associated bacteria (*2524*)), against larvae of the barnacle *Balanus amphitrite*, most especially due to the action of chlorinated isocyanoterpenoids (*600, 2525*). This bacterial "cleansing" is reported for other organohalogens from many sponges (*2526*), such as the bromine-containing ianthellin (*2527*). The associated marine bacteria genus *Pseudoalteromonas* produces antifouling compounds (*2528*), and the sponge *Geodia barretti* displays antifouling properties from the secretion of barettin (**1362**), 8,9-dihydrobarettin (**1363**), and the new cyclopeptide **2266**, which inhibit larvae of the barnacle *Balanus improvisus* (*2529, 2530*). Coatings of these compounds on artificial surfaces inhibit fouling by this barnacle and by the blue mussel *Mytilus*

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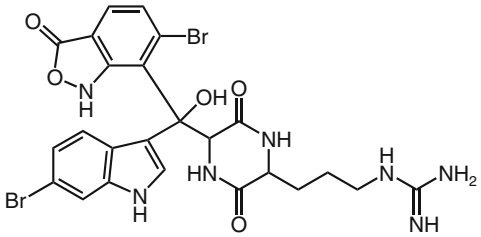
edulis. Zebra mussel antifouling is also inhibited by moloka'iamine and other dibromotyramines on sponges of the order Verongida (*2531*).

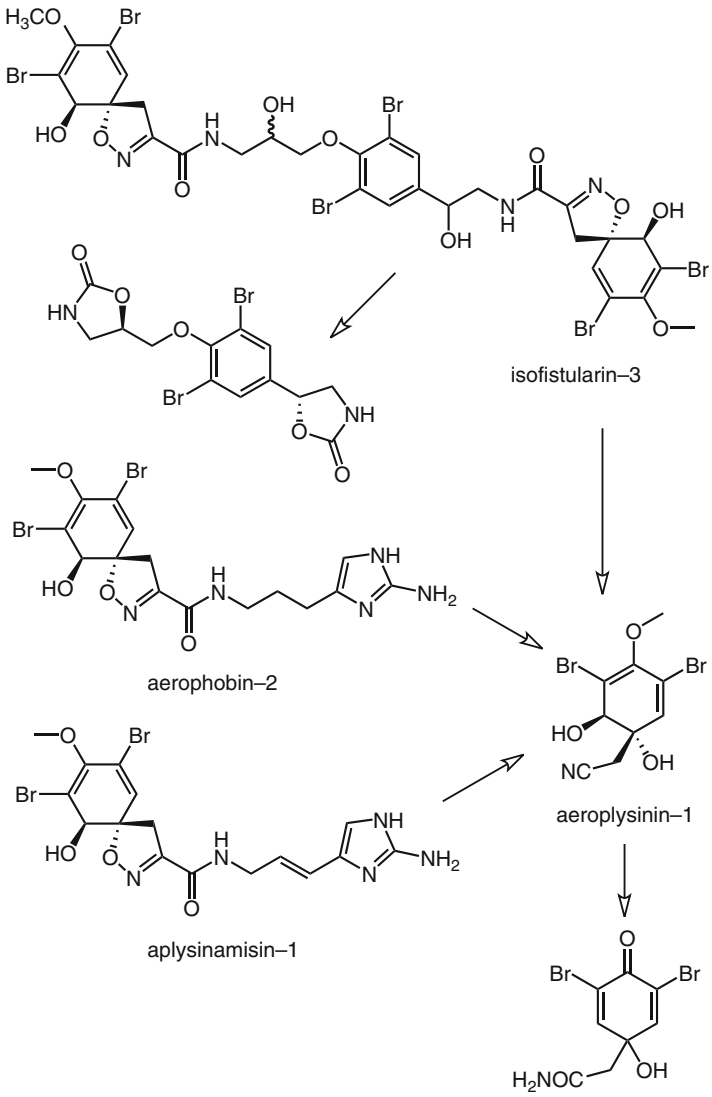


2266

Sponges and their associated bacteria possess other chemical defense mechanisms that have evolved over 600 million years involving antibacterial, antiviral, and cytostatic compounds, many of which contain halogen (*118*). When *Aplysina* (Fig. 6.1) sponges are wounded or otherwise mechanically damaged, brominated isoxazoline alkaloids within the sponge are transformed to a potent fish-deterrent dienone compound (Scheme 6.1) (*2532–2535*). It is suggested that this biotransformation protects the damaged sponge from invasion by foreign bacteria, although contrary results have been claimed (*2536*).

Purealin, another brominated tyrosine metabolite of the sponge *Psammaplysilla purea*, blocks the sliding movement of sea urchin *Anthocidaris crassispina* sperm flagella (*2537*). Numerous sponge metabolites are feeding deterrents to predatory

Fig. 6.1 *Aplysina fistularis,* a sponge rich in bromophenols and bromotyrosines (Photo: F. J. Schmitz)



Proposed bioconversion in the sponge *Aplysina aerophoba* (*2535*).

Scheme 6.1

reef fishes, including the brominated pyrrole stevensine from *Axinella corrugata* (Fig. 6.2) (*2538*), and several other brominated pyrrole alkaloids (i.e., dispacamide (**1239**), keramadine, oroidin, midpacamide, 4,5-dibromopyrrole-2-carboxylic acid, 4,5-dibromopyrrole-2-carboxamide) present in *Agelas* spp. along with some

Fig. 6.2 *Axinella corrugata,* a sponge containing the previously known antifeedant bromopyrrole alkaloid stevensine (Photo: J. R. Pawlik)

synthetic analogs (*2539, 2540*). A pyrrole ring is required for activity and bromine increases it further. In contrast to other *Agelas* spp., Caribbean *Agelas conifera* contains a mixture of antifeedant dimeric bromopyrrole alkaloids, sceptrin, dibromosceptrin, bromoageliferin, dibromoageliferin, ageliferin, bromosceptrin (**1296**), but dominated by sceptrin (*2540*). In addition to providing a purely defensive role for the sponge, brominated metabolites from *Aplysina fistularis* (Fig. 6.1) such as aerothionin and homoaerothionin may act to clump bacteria together for retention as a food source (*2541*).

Bromophenols represent an enormous class of marine natural products, particularly from acorn worms of families Polychaete and Hemichordata. These sediment dwelling animals can live anywhere from the intertidal zone to a depth of 1,400 m (*2542, 2543*). Thus, one function of 2,4,6-tribromophenol produced by the deep-sea

acorn worm *Stereobalanus canadensis* living in the Norwegian Sea is to prevent encroachment by other organisms and to inhibit bacterial growth in the worm's burrow wall (*2543*). Bromophenols from worms of the genus the *Thelepus* may protect the mucous cocoon formed by the tentacles during reproduction and be an antiseptic in wound healing in those protruding and exposed body parts (*1793*). The worm *Notomastus lobatus* lives head down in marine sediments and has the highest concentration of bromophenols in the tail, the animal part first encountered by potential predators (*2150*). Interestingly, 4-bromophenol is also present in this worm, but is not antibacterial against marine sediment bacteria (*2544, 2545*). The worm *Saccoglossus kowalevskii* produces 2,3,4-tribromopyrrole (0.2% of worm dry weight), and this worm is highly unpalatable to predatory fishes (*2546*). Similarly, the burrow tubes of *Sabella pavonia* and *Spirographis spallanzanii* are thought to be strengthened by a halogenation tanning process involving iodination of tyrosine. Iodine can comprise 0.8% of the dry weight of these tubes (*2547*).

The gastropterids *Sagaminopteron nigropunctatum* and *S. psychedelicum*, which contain the diphenyl ether 3,5-dibromo-3-(2′,4′-dibromophenoxy)phenol, acquired through feeding on the sponge *Dysidea granulosa*, deters feeding by the sharpnose pufferfish (*Canthigaster solandri*). This metabolite is transferred to the egg masses of *S. nigropunctatum* where it may offer protection from bacteria (*2548*). The highly toxic cone snail toxin σ-conotoxin GVIIIA, a 41-amino acid peptide, is a highly selective inhibitor of the 5-HT_3 serotonin receptor. It is suggested that a 6-bromotryptophan residue is an important determinant of the pharmacological specificity of this peptide since the endogenous ligand for the 5-HT_3 receptor is 5-hydroxytryptamine, and the 6-bromotryptophan is perhaps situated within a constrained loop of the peptide and assumes a conformation favoring interaction with the 5-HT_3 binding site leading to inactivation of this receptor (*2549*).

A field study of the marine algae organohalogen terpenoids elatol, isolaurinterol, and cymopol, when coated on the palatable seagrass *Thalassia testudinium*, showed significant antifeeding activity towards the herbivorous sea urchin *Diadema antillarum* and reef fishes (*2550*). The brominated furanones present in the red alga *Delisea pulchra*, and acquired by the sea hare *Aplysia parvula* through feeding, not only seem to function as predator deterrents but also may serve as chemical camouflage, since the color of this sea hare closely mimics that of the alga (*2551*). This unique defensive strategy may be more common than commonly thought (*2552*). These furanones are strong inhibitors of both the acyl homoserine lactone and the AI-2 bacterial quorum sensing systems, thus preventing bacterial fouling on *Delisea pulchra* (*2553–2557, 2660*). The sea hare *Aplysia parvula* feeds on this red alga so as to acquire these furanones for apparent chemical defense (*2558*). The deactivation of these bacterial quorum sensing systems by natural haloperoxidases and oxidized halogen species has been reported (*2559*).

The red alga *Plocamium hamatum* produces a metabolite, chloromertensene, that exhibits allelopathy towards the octocoral *Sinularia cruciata*, causing tissue necrosis upon direct contact and dissuading overgrowth by local soft corals (*2560*). Other marine plants seem to generate chemical defenses in response to challenge by aggressors (*2561*), and this induced chemical defense is seen in other macroalgae

(*2562*). Whereas biofouling in the cultivation of *Gracilaria* spp. is a major, global problem (*2563*), the production of bromoform and dibromoacetaldehyde by the red algae *Corallina pilulifera* (*2282*) and *Kappaphycus alvarezii* (*2244*), respectively, seem to play an important role in preventing overgrowth by microalgae, at least with *Corallina pilulifera*. Antifeeding organohalogens have been identified in *Laurencia saitoi* (against young abalone and young sea urchin) (*2564*), and in *Laurencia obtusa* (against crab and sea urchin) (*2565*). Several halogenated monoterpenes, including furoplocamioid C (**229**), are efficient aphid repellents (*2566*), and four hapalindoles, two of which are chlorinated (hapalindole L and 12-*epi*-hapalindole E isonitrile), from the freshwater cyanobacterium *Fischerella* ATCC 43239 are potent insecticides against a dipteran (*2567*).

A role of natural haloalkanes is to cycle halogen/halide between the ocean, atmosphere, and land. This massive global halogen cycle is well established, and excellent reviews are available covering chlorine (*37, 85, 298, 299, 2568*), bromine (*96, 99*), and iodine (*104*). Chloromethane has a major impact on atmospheric ozone (*2569, 2576*) and recent studies suggest that abiotic (and biogenic) methylation of chloride in plants and soil produces the majority of atmospheric chloromethane (*2236, 2569–2571*). Thus, laboratory studies of ferns, a moss, and halophilous plants emit significant amounts of chloromethane (*2236, 2571*), and exhibit uptake of ^{36}Cl-chloride and release of ^{36}Cl-chloromethane (*2236*). It has been suggested that the biosynthesis of halomethanes is the result of "accidents of metabolism" and that the main function of haloperoxidases is to remove hydrogen peroxide (*2133*). Sea salt spray is known to be a source of atmospheric chlorine (Sect. 2.1 (Marine Environment)). A new mechanism for the oxidation of sea salt chloride to chlorine involves reaction with dinitrogen pentoxide (N_2O_5) to nitryl chloride (NO_2Cl) and then to chlorine (*2572*). A newly proposed role of sea spray is as a "cleansing agent" for air pollution over the ocean (*2573*). The relatively new role of natural bromine and iodine, particularly bromine oxide and iodine oxide, in atmospheric processes was mentioned in Sect. 2.1 (Marine Environment) (*90, 97, 98, 100, 103, 2574, 2575*). The highest concentration of iodine oxide (20 ppt) was recorded off the Antarctic coast, and is likely a photolysis-oxidation product of the marine algae metabolites CH_2I_2 and CH_2IBr (*2575*).

7 Significance

Combined with those presented in the first review (*1*), the number of naturally occurring organohalogens – biogenic and abiotic – is more than 4,700. Despite this staggering figure, the quantities of individual organohalogens present in the environment at any given time are largely unknown. A few examples were cited earlier (*1*).

Like other natural products, naturally occurring organohalogens can display a plethora of biological activities (*12, 2577*). In particular, marine natural products – 15–20% of which contain halogen – are of great interest and show enormous potential for the treatment of human disease (*2578–2587, 2667*), against cancer (*2588*), inflammation (*2589*), malaria (*2590*), tuberculosis (*2591*), and others (*1187, 2586, 2587, 2592, 2604*). Marine algae are a treasure trove of biologically active natural products (*2593–2595*), as are symbiotic bacteria in sponges (*121, 2596*). Marine organisms have also furnished numerous insecticidal agents, several examples of which are shown earlier (**682**, **685**, **1466**) (*2597, 2598*). Terpene isonitriles from sponges exhibit antimalarial activity (*2599*), and sponge-derived terpenoids are potent and selective lipoxygenase inhibitors, such as chloropuupehenone (*2600*). The organohalogen-rich sponges *Aplysina aerophoba* and *Aplysina cavernicola* possess antimicrobial activity (*2601*), and *Verongia aerophoba* displays both antibiotic and cytotoxic activity from aeroplysinin-1 and the dienone metabolite (Scheme 6.1) (*2602*). Hymenialdisine, a bromopyrrole from several sponges, is a novel cyclin-dependent kinase inhibitor (GSK-3β and CK1) (*2603*). The bryozoan *Flustra foliacea* metabolite deformylflustrabromine (**1346**) potentiates the human $\alpha 4\beta 2$ neuronal nicotinic receptor (*2605*). Certain natural organohalogens are calmodulin inhibitors, including eudistomidines A and B, malbrancheamide, konbamide, and several KS-504 compounds (*2606*). Maytansinoids have been conjugated with various agents for specific cell targeting and improved antitumor activity (*2607, 2608*). Several marine sponge metabolites, including the organohalogens bromotopsentin, bastadins 4, 8, and 9, and hymenialdisine display anti-inflammatory activity (*2589*). The chlorine-containing radiciol is a promising lead compound for new anticancer agents (*2609*), and dichloroacetate is in clinical use for the treatment of lactic acidosis (*2610*). Bromophenols from the red alga *Odonthalia corymbifera* are highly fungicidal against the rice pathogen *Magnaporthe grisea*

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(*2611*). New vancomycin-type glycopeptide antibiotics are in clinical trials to combat methicillin-resistant bacteria (*2612, 2613*) such as the deadly *Staphylococcus aureus* (*2614*). For the first time, extracts of marine algae indigenous to Japan have shown activity against methicillin-resistant *Staphylococcus aureus* bacteria (*2615, 2661*). The therapeutic use of iodine has been rejuvenated (*2616*). For example, in the treatment of cyclic mastalgia (*2617*).

Cyanobacteria – the Jekyll and Hyde of marine organisms – are a novel source of potential new pharmaceutical compounds (*2618–2620, 2662*). On the other hand, toxic cyanobacterial blooms in lakes, rivers, and water storage reservoirs have occurred worldwide (*2621, 2663, 2664*). For example, 60 patients in a Brazil hemodialysis unit died after drinking water from a lake contaminated with cyanobacterial microcystins (*2622*), not unlike the toxicity of "red tides" (*2623*). Cyanobacteria also produce the highly toxic neurotoxin, β-*N*-methylamino-L-alanine, which may be produced by all cyanobacteria (*2624, 2665*).

There are many examples of the positive, beneficial effects of halogen substitution on organic compounds (*1*), and excellent reviews on this topic are available (*19, 2625*). A chlorinated imidazobenzodiazepinone is 20 times more active than the nonchlorinated analog and three times more active than AZT towards HIV-I (*2626*). Likewise, halogenated (chlorine-, bromide-, and iodine-substituted) gomisin J derivatives are more effective than the natural product itself as HIV-1 reverse transcriptase inhibitors (*2627*). Halogen substitution on aromatic rings greatly stabilizes cross-strand aromatic rings in model β-hairpin peptides (*2628*), which is similar to the iodine-aromatic ring interaction between the thyroid hormone triiodothyroxine, T_3, and the thyroid hormone receptor.

8 Outlook

The dozen years since the publication of the first survey of naturally occurring organohalogens (*1*) has seen an approximate doubling of these new natural compounds, from 2,448 to 4,715, with no sign of abatement. This increase parallels the revitalization of natural products research in general, and is a consequence of improved collection, isolation, and identification techniques. An awareness of ethnobotany and folk medicine leads natural products scientists to potentially biologically active organisms. Multidimensional nuclear magnetic resonance spectroscopy, and improved X-ray crystallography and high-resolution mass spectrometry methods allow for the characterization of minute quantities of compounds. Cultivation techniques like marine bioprocessing (*116, 117, 2629*) permit the harvesting of target marine organisms without plundering the ocean. Remote submersibles can access otherwise inaccessible ocean depths for new marine organisms, such as a new Woods Hole Oceanographic Institution vessel capable of diving to 6,500 m (*2630*). This will allow for the sampling of marine bacteria and other organisms on the ocean floor; for example, the iron-oxidizing bacteria living around deep-sea thermal vents (*2631*) and other deep-sea organisms (*2632, 2633*). Moreover, marine bacteria, in general, are a new field of natural products exploration with enormous possibilities for the discovery of new natural halogenated compounds (e.g., salinosporamide A (**1124**)) (*2634–2636*), especially considering that seawater contains as many as 10^6 bacteria cm^{-3} (*2634*). Marine and terrestrial fungi are also a relatively untapped source of natural products. Indeed, of the 1.5 million estimated terrestrial fungal species on Earth, only 70,000 have been described, let alone examined for their chemical content (*181, 186*). Similarly, marine fungi and terrestrial mosses (bryophytes) are virtually unexplored for their metabolites (*188*). New species of sponges continue to be discovered (*115, 2637*), and it has been suggested that in the oceans sponges can undergo comparatively rapid evolution leading to new species with novel metabolites (*2638*). Furthermore, with bacterial densities as high as 10^{10} bacteria g^{-1} of sponge wet weight, sponges are "microbial fermenters" (*2639*), and only a fraction of the 12,000 extant sponges have been studied for their chemical composition (*112*). The ocean crust is also an abundant repository of microbes (*2640*) and has been for 3.5 billion years (*2641*).

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Abiotic sources of organohalogens will continue to be a major contributor to the environment. Global warming may be leading to more wildfires, adding 3.5×10^{15} g of carbon to the atmospheric carbon budget annually (40% of fossil fuel carbon emissions) (*225*). The world's volcanoes continue to be active, producing massive quantities of HCl and HF as they have done for eons (*2642*). Likewise, the interaction of lava with seawater produces significant quantities of HCl (*221*). Ancient sediments continue to reveal the presence of organohalogens presumably of natural origin (*e.g., 157, 2069–2091*), and the abiotic formation of simple organohalogens in soil is a rapidly developing area of research (*175, 177*). Of academic interest are the observations of HCl and HF on Venus (*2643*) and chloride salts on Mars (*2644*). A potentially highly significant newly discovered source of organohalogens is the abiotic (or biogenic) decomposition of leaf litter leading to as yet unidentified organohalogen compounds (*172–174*). Human breath contains a number of aliphatic and aromatic chlorine compounds that are suggested to be exogenous in origin (*2645*).

A major technical advance in the study of organohalogen compounds is the use of ^{14}C radiocarbon analysis to distinguish natural (high ^{14}C content) from anthropogenic (low or no ^{14}C content) organohalogens (*1223, 1746, 1789, 2646, 2647*). Given sufficient material for analysis, this technique would unequivocally identify the origin of chloroform, chlorophenols, bromophenols, dioxins, brominated diphenyl ethers, and several other compounds that have both natural and anthropogenic sources.

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Author Index

E

G

K

M

T

W

Z

Subject Index

B

C

E

F

I

M

N