

Natural Halogenated Sesquiterpenes from Marine Organisms

VALERY M. DEMBITSKY¹ and GENRICH A. TOLSTIKOV²

¹Department of Pharmaceutical Chemistry and Natural Products, School of Pharmacy,
The Hebrew University of Jerusalem, P. O. Box 12065, Jerusalem 91120 (Israel)

E-mail: dvalery@cc.huji.ac.il

²Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy
of Sciences, Pr. Akademika Lavrentyeva 9, Novosibirsk 630090 (Russia)

E-mail: gtolstik@nioch.nsc.ru

(Received June 6, 2002)

Abstract

Natural halogenated sesquiterpenes from marine organisms form a large group of natural compounds. The structures of more than 200 compounds are considered, and their biological activity is described.

Contents

Introduction...	1
Monocyclic and other simple sesquiterpenes	–
Chamigrene type sesquiterpenes and related compounds	3
Sesquiterpenes of eudesmane and miscellaneous other types	7
Aromatic sesquiterpenes and related compounds	8

INTRODUCTION

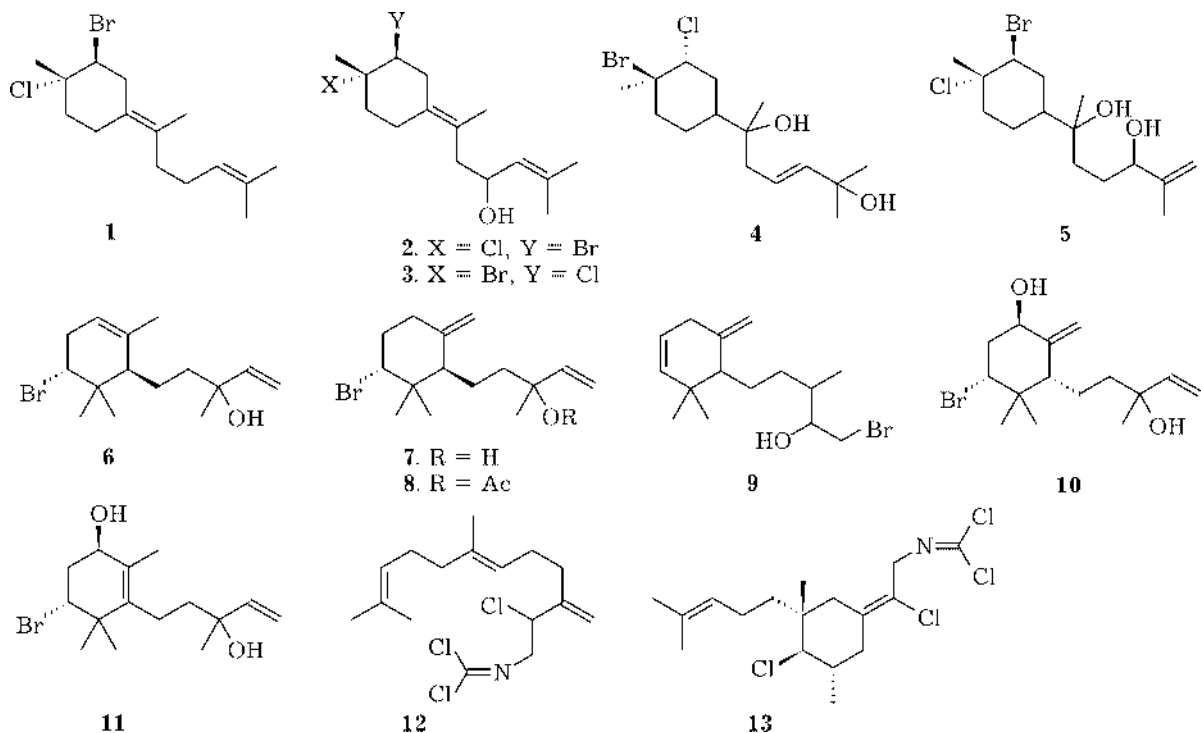
Sesquiterpenes from marine organisms constitute a large group of natural compounds [1–3], but only some of them contain halogen atoms in the molecule [4, 5]. Most halogenated sesquiterpenes are produced by the algae of the genus *Laurencia* (family Ceramiales, type Rhodophyta) [2]. They were also found in extracts from some species of the green algae, soft corals, mollusks, and sponges. Many of these metabolites possess biological activity.

Halogenated sesquiterpenes from plants were treated in one of our previous communications [6]. This paper is a continuation of our works dealing with halogenated sesquiterpenes.

Sesquiterpenes from algae of the genus *Laurencia* cover 18 structural types, only some of which are halogenated.

MONOCYCLIC AND OTHER SIMPLE SESQUITERPENES

A number of monocyclic and other simple sesquiterpenes were found in extracts from the algae *Laurencia* [2] and marine invertebrates. Preintricatol (**1**), believed to be a precursor of halogenated sesquiterpenes of chamigrene type, was found in *Laurencia intricata* [7], *Laurencia* sp. and *L. gracilis* [8], inhabiting the sea off the coast of New Zealand. Puertitols A (**2**) and B (**3**) (isolated from *L. obtusa* [9]), as well as metabolites (**4**) and (**5**) (isolated from



L. caespitosa [10]), are present in algae living around the Canary Islands.

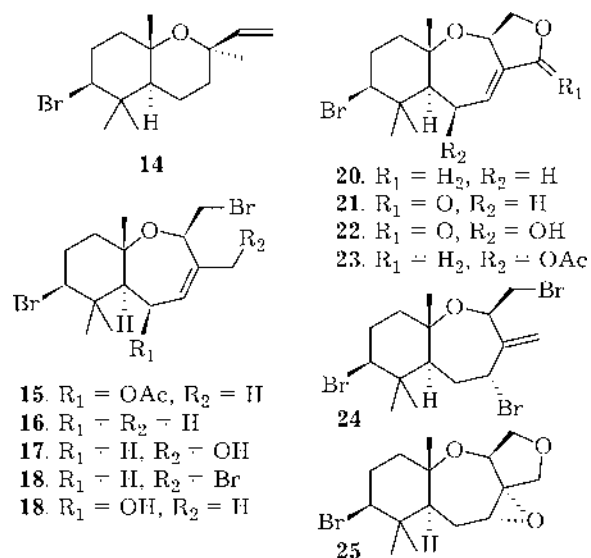
Isomeric α - (**6**) and β -snyderols (**7**) were isolated from *L. obtusa*, growing off the coast of Spain, and from *L. snyderae*, whose habitat is the sea off the Californian coast of USA [11], respectively. β -Snyderol (**7**) and its acetate (**8**) are contained in the alga *L. obtusa* from the Red Sea [12]. Palisiol (**9**) was found as a minor component in *Laurencia* cf. *palisada* [13], and two metabolites, (**10**) and (**11**), are produced by *L. caespitosa* [14].

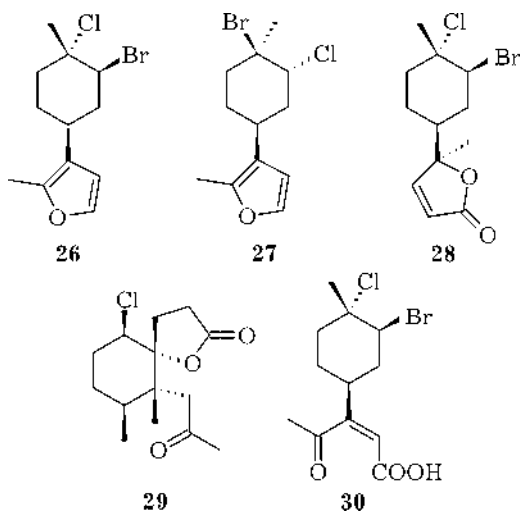
Halogenated isonitriles (**12**) and (**13**) were isolated from the sea sponge *Pseudaxinyssa pitys* [15]. Natural isonitriles are rather rarely occurring compounds; their structures and metabolism were recently considered in [16].

Sesquiterpene (**14**) was detected in the alga *Laurencia obtusa* inhabiting the English Channel. It is believed to be a derivative of α - and β -snyderols (**6**) and (**7**) [16]. The red alga *L. af. palisada* contains bi- and tricyclic ethers: acetoxypalisadine B (**15**), palisadine B (**16**), (**17**), and palisadine A (**20**) as the major component [13]. Aplysiatane (**21**) was shown [13] to be an oxidized product of palisadine A (**20**). Nevertheless, (**21**) was previously isolated from the mollusk *Aplysia angasi* [17]. Me-

tabolite (**21**) and its 6b-hydroxy derivative (**22**) were isolated from the alga *Laurencia filiformis* [18]. The alga *L. flexilis*, which is widespread off the coast of the Philippine Islands, produces a series of new palisadines: (**18**), (**19**), (**23**)–(**25**) [19, 20].

Interesting furans (**26**)–(**30**) were found in the red algae of the genus *Laurencia* [21–23]. The first halogenated norsesquiterpene named "napalilactone" (**29**) was isolated from the soft coral *Lemnalia africana*, growing off





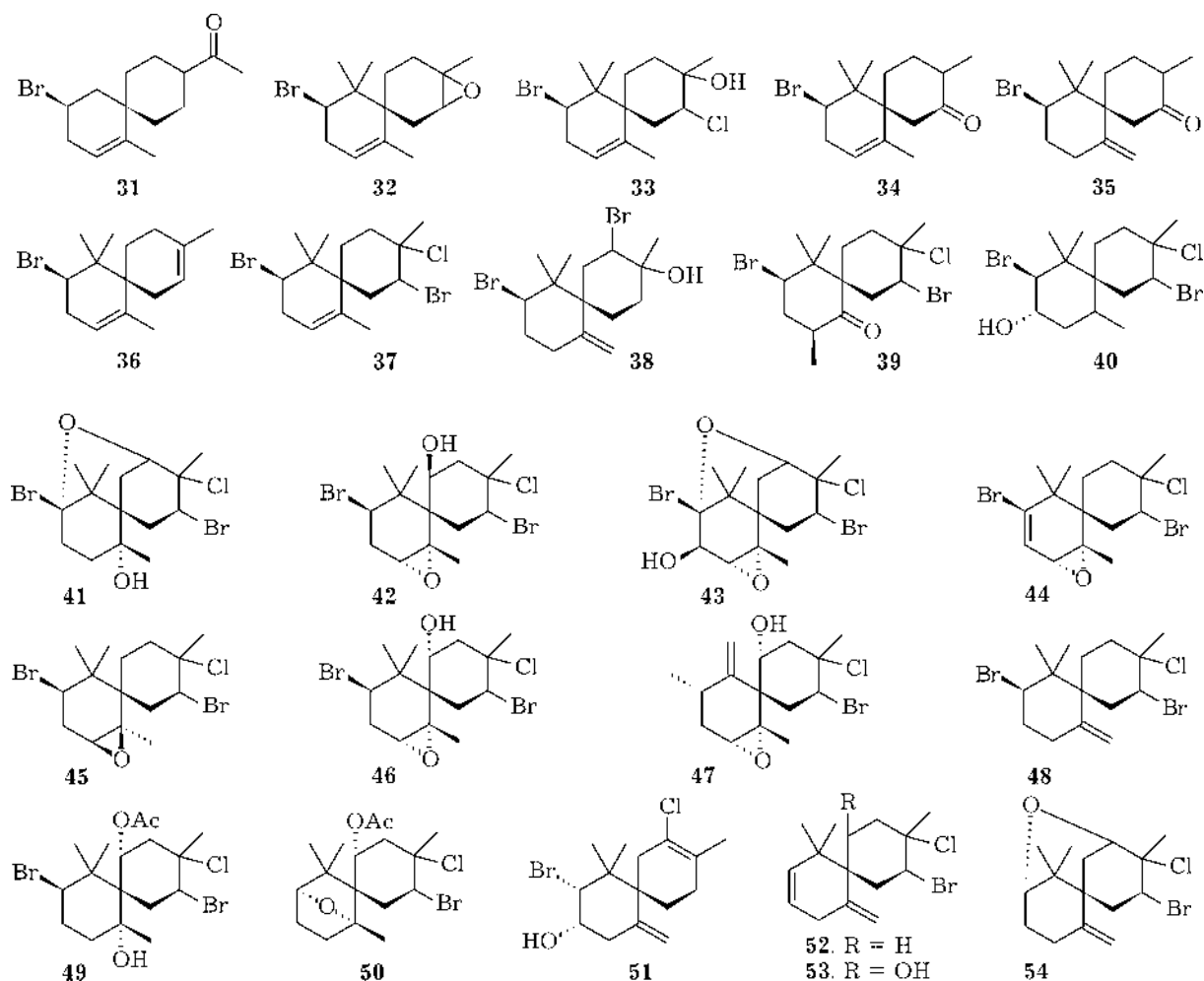
Cambodia [21]. Furocaespitane (**27**) and isofurocaespitane (**28**), as well as C₁₂ metabolites (**28**) and (**30**) (the latter isolated as methyl ether), were found in the alga *Laurencia caespitosa* [22–24].

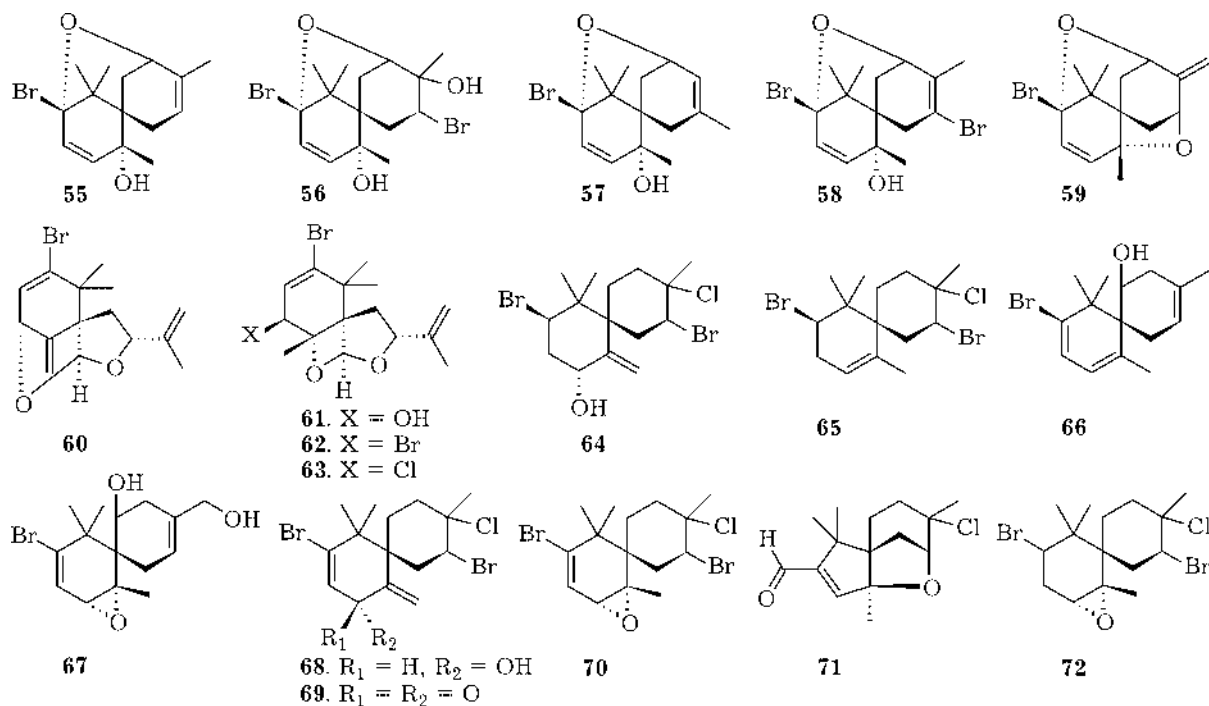
CHAMIGRENE TYPE SESQUITERPENES AND RELATED COMPOUNDS

Spirane type sesquiterpenes – chamigrenes – are probably the most widespread sesquiterpenes from the red algae of the genus *Laurencia* [1, 2]. Spirolaurenone (**31**), the first metabolite from this series, was isolated from *L. glandulifera* [25, 26]. Compounds (**32**)–(**37**) [27–31] were also found in extracts from this alga.

Metabolite (**38**) is contained in the alga *L. flexilis* [32], while kylinone (**39**) [33] and compound (**40**) were isolated from *L. pacifica* [34, 35].

Pacifenol (**41**) is the first natural metabolite with chlorine and bromine atoms in the molecule. It was found in the alga *L. pacifica* [36]. More recently, compounds (**41**) and (**42**) were extracted from the algae *L. tasmanica* and *L. filiformis* [3] inhabiting the sea around Australia. Johnstonol (**43**), structurally related



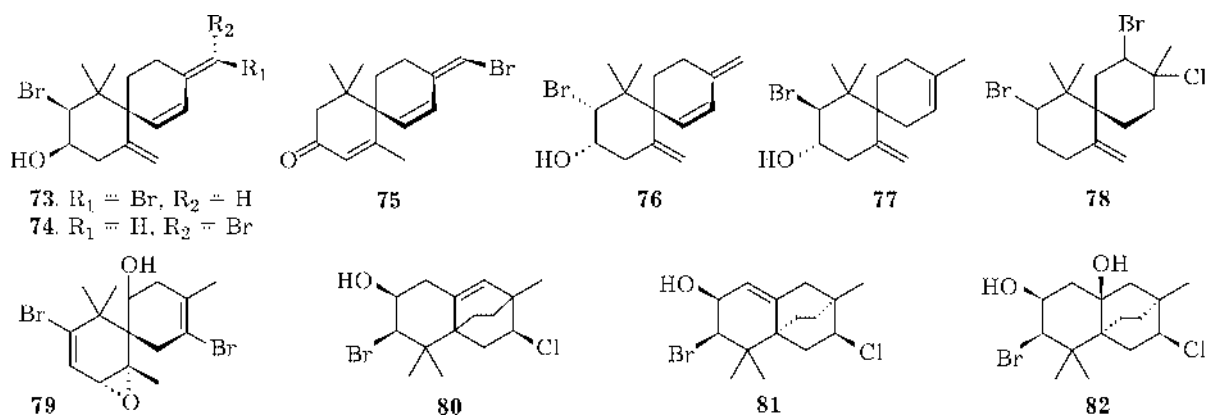


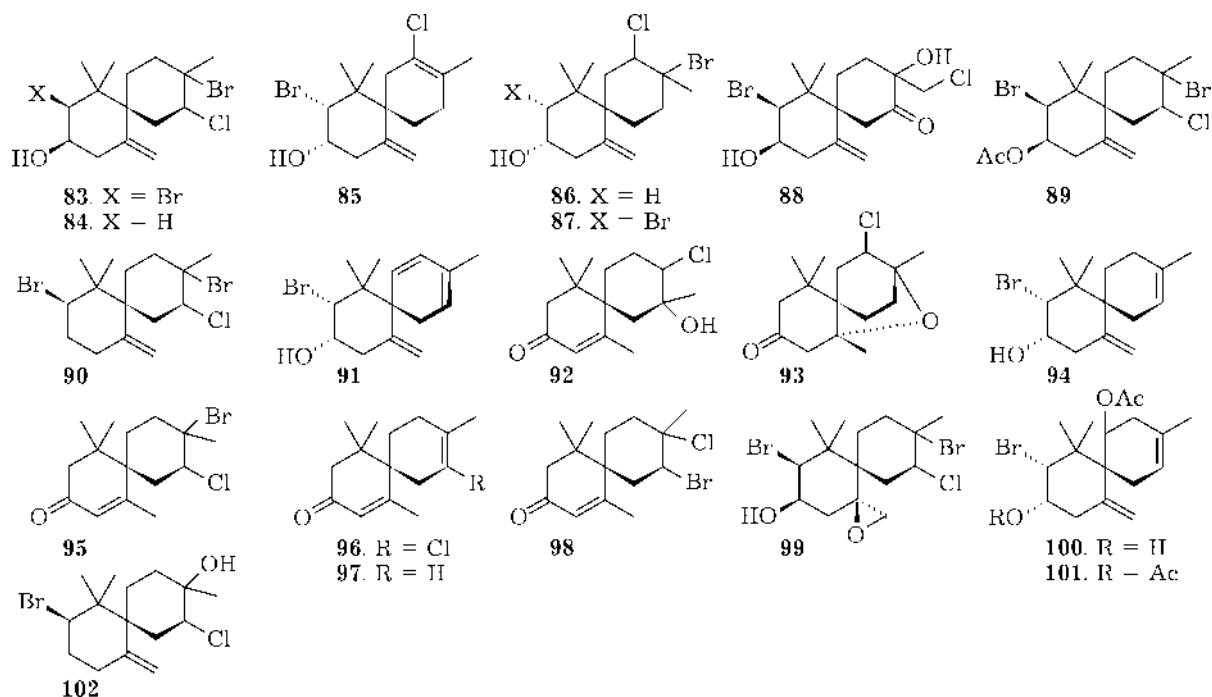
to (41), was found in extracts from the algae *L. johnstonii* and *L. okamurai* [38].

Desoxyprepacifenol (44) was first isolated from the mollusk *Aplysia californica* (sea hare), feeding on seaweeds [39]. The new metabolite (45) and the aforementioned terpene (37) were found in extracts from the alga *Laurencia* sp. from the Gulf of California and Florida Strait (USA) [31, 40]. The alga *L. intricata* contains three halogenated chamigrenes: intricatene (48), acetoxynintricatol (49), and cyclodebromointricatol (50) [7, 41]. Elatol (51) was isolated from *L. elata*. The alga *L. nidifica*, growing off the Hawaiian Islands, contains metabolites nidifiadiene (52) [43], nidifiadienol (53) [44], and nidificene (54) [45].

The alga *Laurencia nipponica* Yamada from the Sea of Japan produces a series of halogenated metabolites (55)–(72), most of which were discovered by Suzuki *et al.* [46–58]. Metabolites of unusual structure – (60)–(63), (71) – were found along with compounds (37) [48], (41) [46], (45) [48], and (48) [49] in extracts from this alga. Sesquiterpenes (45) and (72) were also found in the alga *L. okamurai* [59]. According to [59], each alga species contains a number of unique sesquiterpenes inherent in this particular species along with ordinary sesquiterpenes.

Another red alga – *Laurencia majuscula* Harvey from the Sea of Japan – contains chamigrenes (73)–(75) [30, 60, 61]. The structurally related isoobtusadiene (76) was found in the

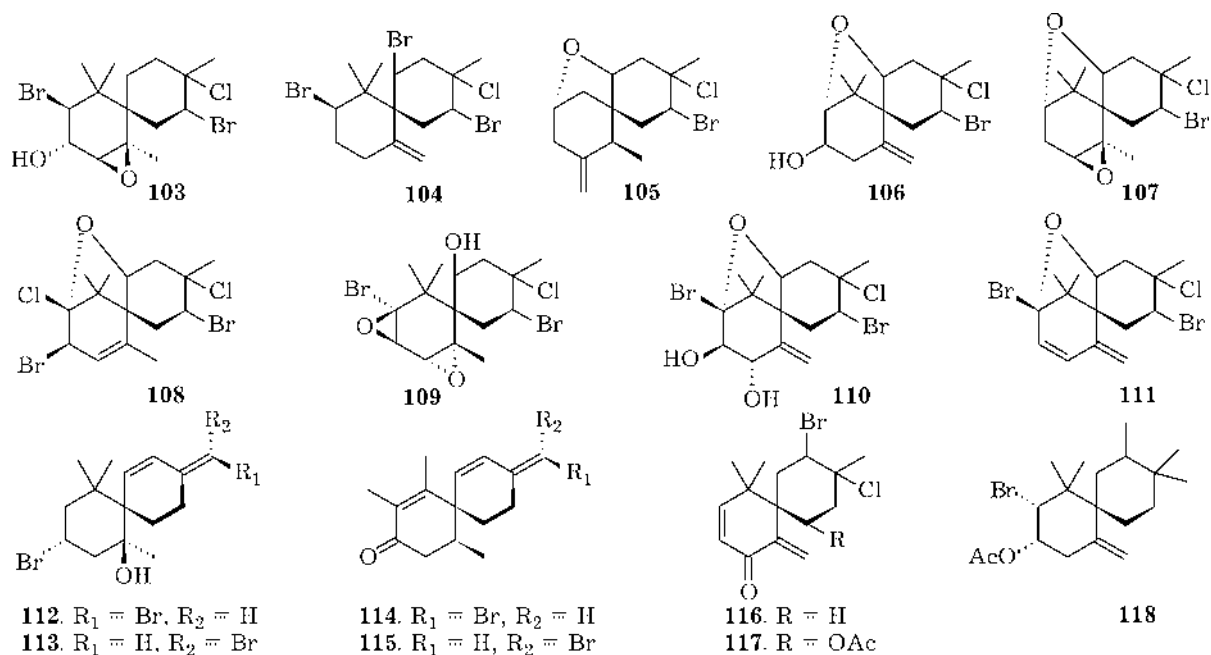


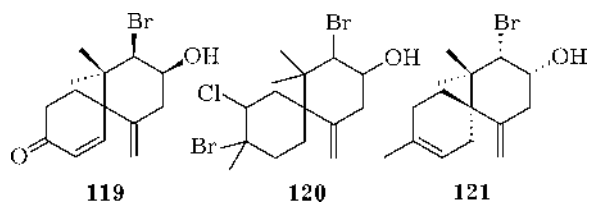


Australian alga *L. obtusa* [62, 63]. The alga *L. majuscula*, growing on the Great Barrier Reef off the coast of Northern Queensland of Australia, contains metabolite (**77**) [64]. Sesquiterpene (**78**), dehydrochloroprepacifenol (**79**), and isorhodolaureol (**80**) were found in the alga *L. majuscula*, growing on the Great Barrier Reef [65, 66]. Rhodolaureol (**81**) and rhodolauradiol (**82**) were found in extracts from the

algae *L. majuscula* [65], *L. obtusa* [66] and unidentified alga *Laurencia* sp. [67].

The alga *Laurencia obtusa* produces great numbers of halogenated sesquiterpenes, including chamigrene type metabolites (**83**)–(**102**) [12, 23, 68–75]. The alga *L. obtusa* from the Island of Jamaica produces *cis*-chlorohydrin (92), which is formed from oxide (**93**) when the latter is treated with an alkali [73]. Lauren-





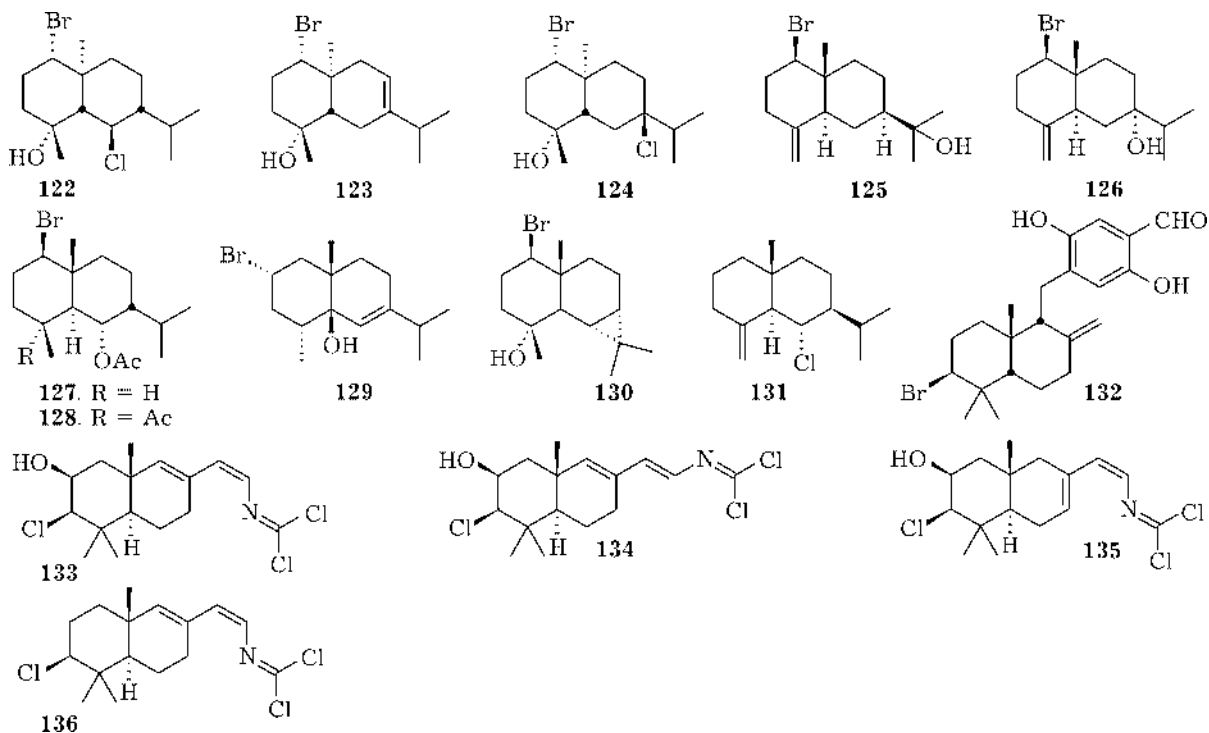
cenones A (**95**), B (**96**), C (**97**), and D (**98**) were found in the alga *L. obtusa* from another collection [74]; metabolites (**99**)–(**101**) were discovered in the alga *L. obtusa* from the Canary Islands [75]. The alga *L. obtusa*, inhabiting the Red Sea, synthesizes hurgadol (**102**).

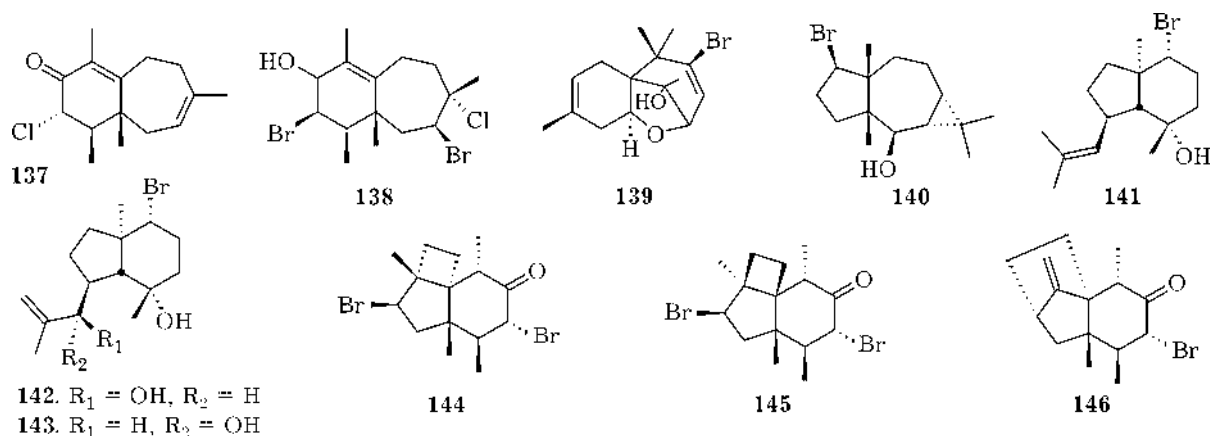
These alga *Laurencia glomerata* from South Africa contains a new epoxide, (**103**), as well as the aforementioned metabolites (**37**), (**40**), and (**72**) [76]. The alga *L. pinnatifida*, which is widespread off the city of Karachi (Pakistan), yields halogenated metabolites (**45**) [77], (**72**) and (**104**) [78], pinnatifidone (**105**), pinnatifinol (**106**) [79], (**47**) [80], ichthyotoxin (**46**), and pinnatazane (**107**) [81].

In the foregoing discussion, it was mentioned that halogenated sesquiterpenes are produced not only by the red algae of the genus *Laurencia*. A number of these compounds were found in marine invertebrates. For example, the mollusk *Aplysia californica* was found to produce new metabolites (**108**), prepacifenol

epoxides (**109**) [82] and (**110**) [83], and known compounds: pacifenol (**41**) [82] and johnstonol (**43**). Moreover, the digestive system of *Aplysia californica* was found to contain pacifidiene (**111**) [82], which can be obtained from pacifenol (**41**). Johnstonol (**43**), which was found earlier in the algae *Laurencia johnstonii* and *L. okamurai* (*vide supra*) and can be obtained from prepacifenol epoxide (**109**) [82], is also met in the digestive system of the mollusk *Aplysia californica* [83]. The mollusk *Aplysia dactylomela* produces sesquiterpenes (**112**) and (**113**) [84], chamigrenes (**114**)–(**117**) [85], and the known metabolite (**56**) [86]. The sponge *Aplysia dactylomela* contains rogiolol acetate (**118**) and metabolites (**78**), (**112**), and (**113**), previously found in the algae of the genus *Laurencia* [87].

Two new derivatives from the chamigrane series – maillione (**119**) and *allo*-isoobtusal (**120**) – were isolated from the alga *Laurencia cartilaginea* [88]. The metabolites showed a high anticancer activity against HT-29 human carcinoma [88]. A new sesquiterpene, (**121**), was isolated from the alga *L. majuscula* [89]. It was found to have a high antibacterial activity with respect to bacteria *Aicaligenes aquamartinus*, *Azomonas agilis*, *Azobacter beijerinckii*, *Erwinia amylovora* and *Escherichia coli* [89].





SESQUITERPENES OF EUDESMAE AND MISCELLANEOUS OTHER TYPES

A number of halogenated sesquiterpenes of eudesmane or related types were found in extracts from the red and green algae, mollusks, and sponges. Heterocladol (**122**) and its dechlorinated analog (**123**) were isolated from the algae *Laurencia filiformis* f. *heteroclad* and *Laurencia* sp. inhabiting the Gulf of California [90, 91]. The bromine chloride derivative (**124**) was found in various algae *Laurencia* sp. [92]. The alga *L. filiformis* from the Western Coast of Australia contained austradiol acetate (**127**) and diacetate (**128**) [93].

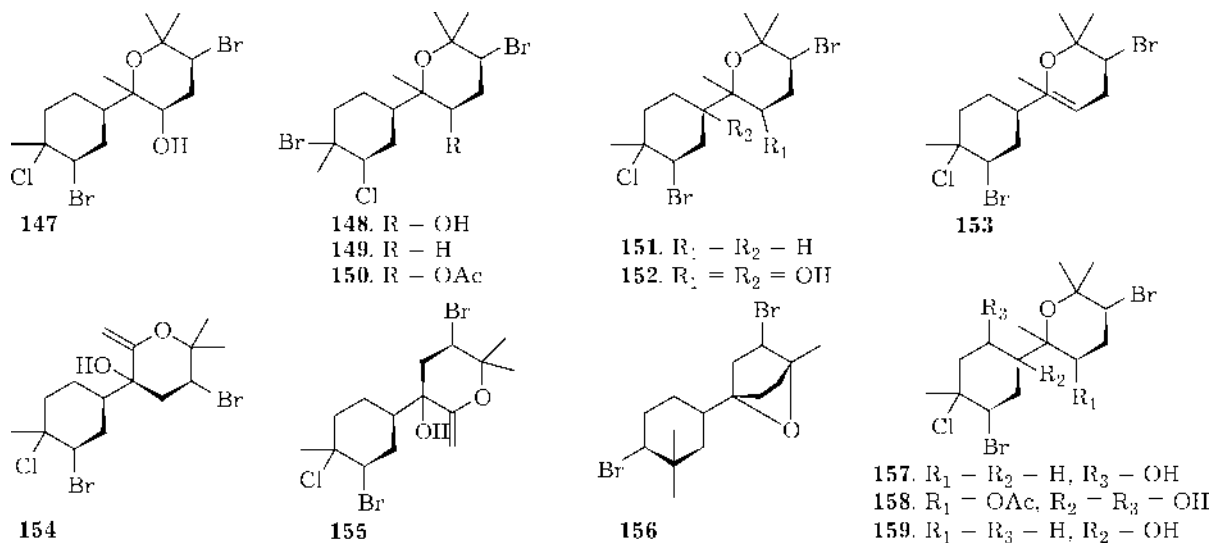
Brasudol (**125**) and isobrasudol (**126**) produced by the mollusk *Aplysia brasiliana* possess antifidant activity [94].

The first communication reporting the isolation of halogenated sesquiterpenes from the green alga *Neomeris annulata* was published in

1989 [95]. Eudesmane (**129**) and cycloeudesmane (**130**) exhibited cyto- and phytotoxic activities [95].

The sponge *Acanthella* sp., living off the coast of British Columbia, produces acanthene A (**131**) [96], while *Hyatella intestinalis* [97] yields peyssonol A (**132**). Metabolite (**132**) was also found in the alga *Peyssonnelia* sp. [97]. Four structurally related dichloroisocyanides (**133**)–(**136**) were found in the sponge *Pseudaxinyssa pitys* [98, 99].

Perforenone B (**137**), perforenol (**138**), and perforatone (**144**) are metabolites of the alga *Laurencia perforata* living off the Canary Islands [100]. A new sesquiterpene, claviol (**139**), inhibiting cytokinesis in the sea-hedgehog *Tetrapygus niger*, was isolated from *Laurencia claviformis* [101]. This alga is an endemic found on the island of West Waiho (Chile) and is not met in any other place of the world's ocean [101]. Neomeranol (**140**) was found in the green



alga *Neomeris annulata* [95]; oppositol (**141**) and two structurally related metabolites, (**142**) and (**143**), were isolated from the extracts of *Laurencia subopposita* [102, 103]. Sesquiterpenes (**145**) and (**146**), as well as the related compound perforatone (**144**), occur in *L. tenera* [104].

The alga *Laurencia caespitosa* produces a number of bisabolenes (**147**)–(**155**); some of these received their individual names: caespitol (**147**), isocaespitol (**148**), caespitane (**151**), and laucapyranoids A (**153**), B (**154**), and C (**155**) [105–108]. These compounds exhibited antibacterial activity. Bicyclic ether (**156**) was found in the alga *Laurencia obtusa* [109].

The mollusk *Aplysia dactylomela* contained three bisabolene sesquiterpenes: deodactols (**157**) and (**158**) and isodeodactol (**159**) [110–113]. Compounds (**157**)–(**159**) possess antibacterial and cytostatic activities [111–113].

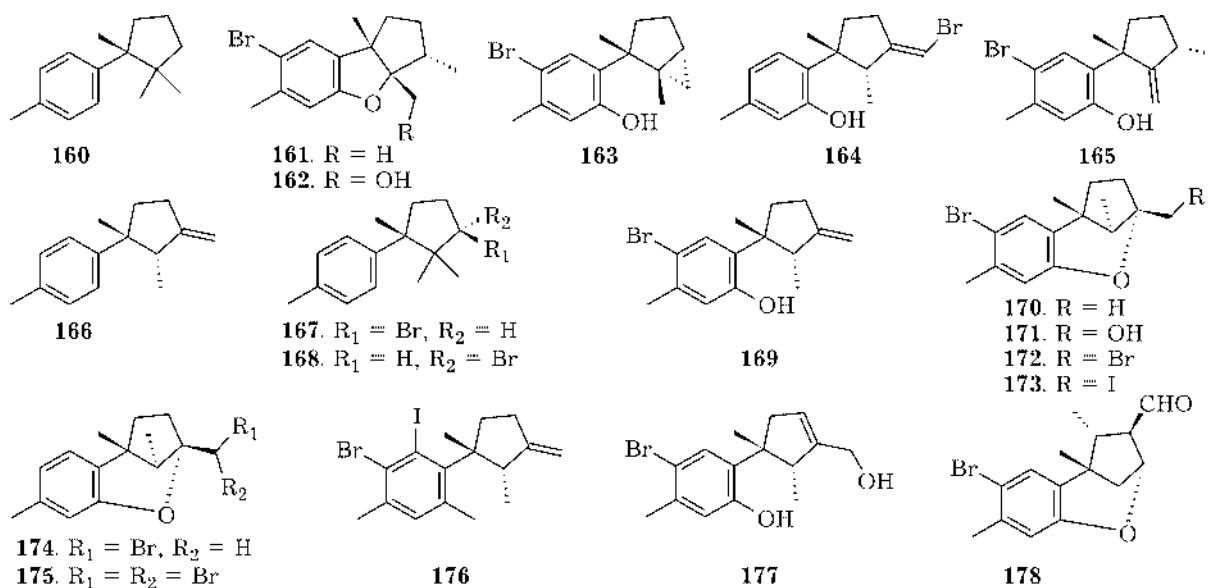
AROMATIC SESQUITERPENES AND RELATED COMPOUNDS

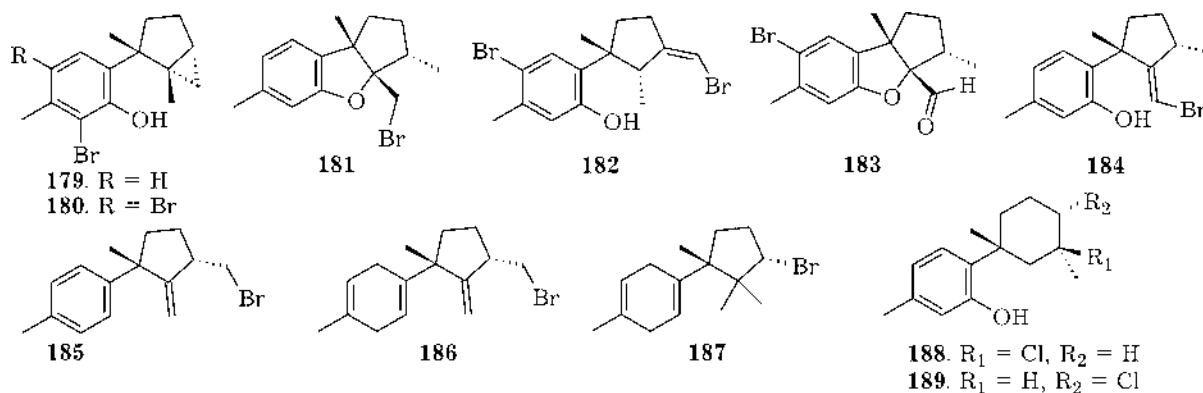
Cuparene (**160**) is the basic structural type of aromatic sesquiterpenes; it was first isolated from mollusks of the class *Anaspidea*. These gastropods are herbivorous invertebrates, feeding on plants swallowing them whole. Sea hare (aplysia) is a typical representative of this class, most comprehensively studied as a producer of mono-, sesqui-, and diterpenoids. Aplysine

(**161**) and aplysinol (**162**) are the first members of the series of halogenated aromatic sesquiterpenes found in *Aplysia kurodai* [114]. More recently, these metabolites, as well as laurinterol (**163**), were found in the algae *Laurencia okamurai* [115] and *L. majuscula* [89]. Metabolites (**161**) and (**163**) were found in the digestive system of the mollusk *Aplysia californica* [116]. Laurenisol (**164**) and isolaurentinol (**165**) were isolated from the methanolic extracts from the algae *Laurencia nipponica* [117] and *L. intermedia* [118].

Laurene (**166**) is the basis of another type of aromatic sesquiterpenes. It was first isolated from the alga *Laurencia glandulifera* [119]. α -Bromocuparene (**167**) was isolated from the same kind of alga, while α -isobromocuparene (**168**) was isolated from the alga *L. nipponica* [120].

10-Bromo-7-hydroxy-laurene (allolaurinterol) (**169**), filiformine (**170**), and filiforminol (**171**) were found in the alga *Laurencia filiformis* f. *heteroclada* living off the coast of South Australia [62, 121, 122]. Allolaurinterol (**169**) was also isolated from the alga *L. subopposita* [103]. Related compounds (**172**), (**174**), and (**175**) were found in *Laurencia glandulifera* [123, 124]. Investigations of extracts from the alga *Laurencia nana* (alternatively, *L. caraibica*) led to the discovery of sesquiterpenes (**173**) and (**176**) containing iodine atoms. Apart from the iodides, researchers found known metabolites such as





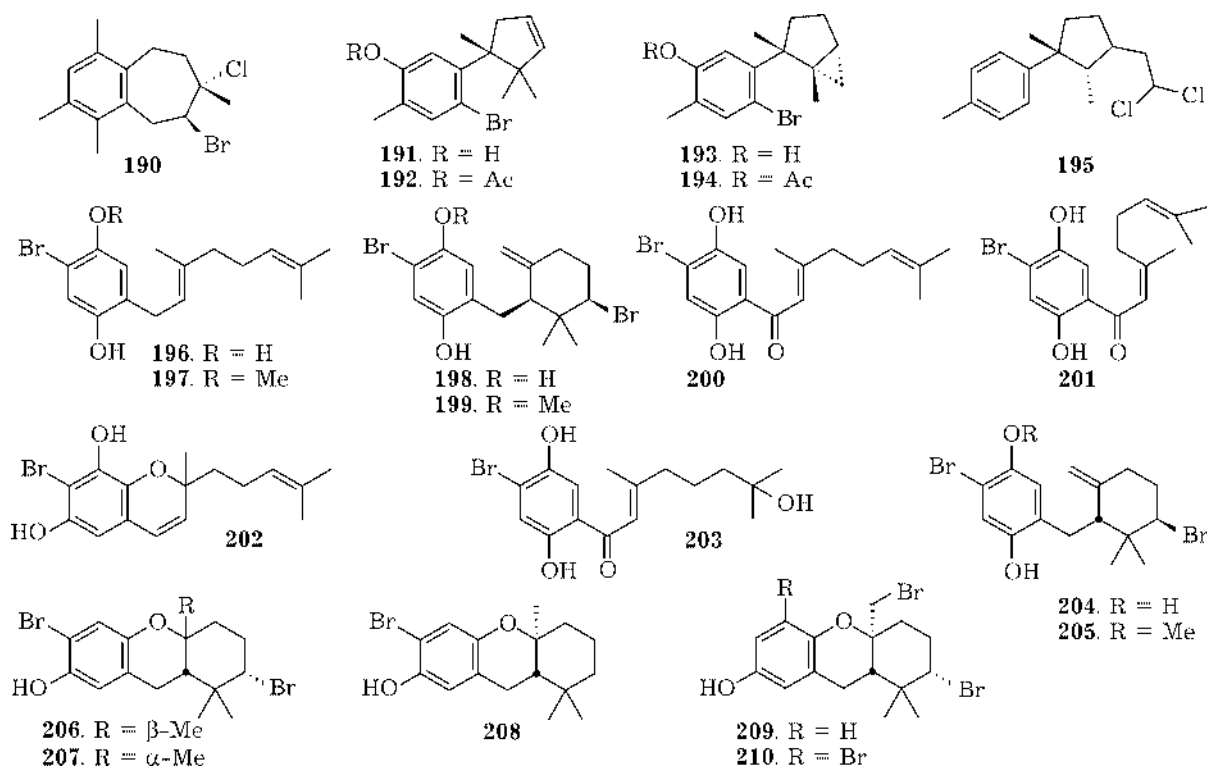
(167), (169), and (170) and new ones, (177) and (178) [125].

The alga *Laurencia okamurai* from the Sea of Japan produces halogenated terpenes in great numbers. Apart from known metabolites, they contain several new laurines: neolaurinterol (179), isoaplysine (181), as well as compounds (180), (182), and aplysinal (183) [126]. The alga *L. distichophylla* living off the coast of New Zealand produces isolaurenisol (184) [127], which was also isolated from *L. gracilis* [8]. *Laurencia pinnatifida* from the Atlantic Ocean contains metabolites (185) and (186) [128]. *L. majuscula*, growing on the Great Barrier Reef, produces new sesquiterpenes (187)–(189) [63, 129, 130].

The aromatic metabolite perforene (190) was found in the alga *Laurencia perforata* [130].

The mollusk *Aplysia dactylomela* contains new metabolites such as cupalaurenol (191), its acetate (192), cyclolaurenol (193), and its acetate (194). These compounds show antibacterial and ichthyotoxic activities [131]. The same kind of mollusk from the Indian Ocean produces dichloride (195) [86].

The green calcined alga *Cymopholia barbata* produces metabolites cymopol (196), its methoxy derivative (197), cyclocymopol (198), its methoxy derivative (199), cymopolone (200), isocymopolone (201), cymopochromenol (202), and compounds (203)–(205) [132–134]. The same



kind of alga, growing off the coast of Florida, contains cymoisobarbatol (**206**), 4-isobarbatol (**207**), and debromoisocymobarbatol (**208**) [135, 136]. The sponge *Cacospongia* produces metabolites: tribromocacoxanthene (**209**) and tetrabromocacoxanthene (**210**) [137].

REFERENCES

- J. D. Martin and J. Darias, Marine Natural Products, in P. J. Scheuer (Ed.), vol. 1, chapter 3, Acad. Press, New York, 1978.
- K. L. Erickson, Marine Natural Products, in P. J. Scheuer (Ed.), vol. 5, chapter 4, Acad. Press, New York, 1983.
- S. S. Roberts, Chemistry of Terpenes and Terpenoids, in A. A. Newman (Ed.), Acad. Press, London & New York, 1972, p. 88.
- S. L. Neidleman and J. Geigert, Biohalogenation: Principles, Basic Roles and Applications, Ellis Horwood Ltd., J. Wiley & Sons, New York, 1986.
- G. W. Gribble, *Prog. Chem. Org. Nat. Prod.*, 68 (1996) 1.
- V. M. Dembitsky, A. G. Tolstikov and G. A. Tolstikov, *Chemistry for Sustainable Development*, 10 (2002) 253. <http://www-psb.ad-sbras.nsc.ru/csde.htm>.
- R. H. White and L. P. Hager, Dahlem Workshop on the Nature of Seawater, in F. D. Goldberg (Ed.), Dahlem Conference, Berlin, 1975, pp. 633–650.
- G. M. König and A. D. Wright, *J. Nat. Prod.*, 57 (1994) 477.
- J. T. Vazquez, M. Chang, K. Nakanishi *et al.*, *Ibid.*, 51 (1988) 1257.
- M. North, J. J. Fernandez and A. Padilla, *Phytochemistry*, 31 (1992) 326.
- B. M. Howard and W. Fenical, *Tetrahedron Lett.*, 17 (1976) 41.
- S.-E. N. Ayyad, A.-A. M. Dawidar, H. W. Dias *et al.*, *Phytochemistry*, 29 (1990) 3193.
- V. J. Paul and W. Fenical, *Tetrahedron Lett.*, 21 (1980) 2787.
- M. Norte, R. Gonzalez, A. Padilla *et al.*, *Can. J. Chem.*, 69 (1991) 518.
- S. J. Wratten and D. J. Faulkner, *J. Am. Chem. Soc.*, 99 (1977) 7367.
- P. J. Scheuer, *Acct. Chem. Res.*, 25 (1992) 433.
- D. J. Faulkner, *Phytochemistry*, 15 (1976) 1992.
- G. R. Pettit, C. L. Herald, M. S. Allen *et al.*, *J. Am. Chem. Soc.*, 99 (1977) 262.
- R. Capon, E. L. Ghisalberti, P. R. Jefferies *et al.*, *Tetrahedron*, 37 (1981) 1613.
- R. de Nys, A. D. Wright, G. M. König *et al.*, *J. Nat. Prod.*, 56 (1993) 877.
- G. M. König, A. D. Wright and F. R. Fronczek, *Ibid.*, 57 (1994) 151.
- J. R. Carney, A. T. Pham, W. Y. Yoshida and P. J. Scheuer, *Tetrahedron Lett.*, 33 (1992) 7115.
- A. G. Gonzalez, J. Darias and J. D. Martin, *Ibid.*, 14 (1973) 3625.
- D. M. Estrada, J. D. Martin, R. Perez *et al.*, *Ibid.*, 28 (1987) 687.
- M. Suzuki, E. Kurosawa and T. Irie, *Ibid.*, 11 (1970) 4995.
- M. Suzuki, N. Kowata and E. Kurosawa, *Tetrahedron*, 36 (1980) 1551.
- M. Suzuki, E. Kurosawa and T. Irie, *Tetrahedron Lett.*, 15 (1974) 821.
- M. Suzuki, A. Furusaki and E. Kurosawa, *Tetrahedron*, 35 (1979) 823.
- M. Suzuki, E. Kurosawa and T. Irie, *Tetrahedron Lett.*, 14 (1974) 1807.
- M. Suzuki and E. Kurosawa, *Chem. Abstr.*, 92 (1980) 215566z.
- B. M. Howard and W. Fenical, *Tetrahedron Lett.*, 16 (1975) 1687.
- R. de Nys, G. M. König, A. D. Wright and O. Sticher, *Phytochemistry*, 34 (1993) 725.
- S. J. Selover and P. Crews, *J. Org. Chem.*, 45 (1980) 69.
- W. Fenical, *Phytochemistry*, 15 (1976) 511.
- M. Suzuki, E. Kurosawa and A. Furusaki, *Bull. Chem. Soc. Japan*, 61 (1988) 3371.
- J. J. Sims, W. Fenical, R. M. Wing and P. Radlick, *J. Am. Chem. Soc.*, 93 (1971) 3774.
- J. J. Sims, W. Fenical, R. M. Wing and P. Radlick, *Ibid.*, 95 (1973) 972.
- J. J. Sims, W. Fenical, R. M. Wing and P. Radlick, *Tetrahedron Lett.*, 13 (1972) 195.
- C. Ireland, M. O. Stallard, D. J. Faulkner *et al.*, *J. Org. Chem.*, 14 (1976) 2461.
- M. L. Bittner, M. Silva, V. J. Paul and W. Fenical, *Phytochemistry*, 24 (1985) 987.
- J. A. McMillan, I. C. Paul, R. H. White and L. P. Hager, *Tetrahedron Lett.*, 15 (1974) 2039.
- J. J. Sims, G. H. Y. Lin and R. M. Wing, *Ibid.*, 15 (1974) 3487.
- S. M. Waraszkiewicz and K. L. Erickson, *Ibid.*, 15 (1974) 2003.
- S. M. Waraszkiewicz and K. L. Erickson, *Ibid.*, 16 (1975) 281.
- S. M. Waraszkiewicz and K. L. Erickson, *Ibid.*, 17 (1976) 1443.
- T. Suzuki, *Chem. Lett.*, (1980) 541.
- K. Kurata, A. Furusaki, C. Katayama *et al.*, *Ibid.*, (1981) 773.
- T. Suzuki, H. Kikuchi and E. Kurosawa, *Bull. Chem. Soc. Japan*, 55 (1982) 1561.
- M. Suzuki, M. Segawa, T. Suzuki and E. Kurosawa, *Ibid.*, 56 (1983) 3824.
- K. Kurata, T. Suzuki, M. Suzuki *et al.*, *Chem. Lett.*, (1983) 557.
- K. Kurata, T. Suzuki, M. Suzuki *et al.*, *Ibid.*, (1983) 561.
- M. Suzuki, M. Segawa, T. Suzuki and E. Kurosawa, *Bull. Chem. Soc. Japan*, 58 (1985) 2435.
- H. Kikuchi, T. Suzuki, M. Suzuki and E. Kurosawa, *Ibid.*, 58 (1985) 2437.
- K. Watanabe, K. Umeda and M. Miyakado, *Agric. Biol. Chem.*, 53 (1989) 2513.
- K. Kurata, T. Suzuki, M. Suzuki *et al.*, *Chem. Lett.*, (1983) 299.
- A. Furusaki, C. Katayama, T. Matsumoto *et al.*, *Bull. Chem. Soc. Japan*, 55 (1982) 3398.
- T. Suzuki, A. Furusaki, N. Hashiba and E. Kurosawa, *Tetrahedron Lett.*, (1977) 3731.
- T. Suzuki and E. Kurosawa, *Chem. Lett.*, (1979) 301.
- W. Fenical and J. N. Norris, *J. Phycol.*, 11 (1975) 104.
- M. Suzuki and E. Kurosawa, *Tetrahedron Lett.*, 19 (1978) 4805.
- M. Suzuki, A. Furusaki, N. Hashiba and E. Kurosawa, *Ibid.*, 20 (1979) 879.
- R. J. Capon, E. L. Ghisalberti, T. A. Mori and P. R. Jefferies, *J. Nat. Prod.*, 51 (1988) 1302.

- 63 R. de Nys, J. C. Coll and B. F. Bowden, *Aust. J. Chem.*, 45 (1992) 1611.
- 64 A. D. Wright, J. C. Coll and I. R. Price, *J. Nat. Prod.*, 53 (1990) 845.
- 65 S. Caccamese, A. Compagnini, R. M. Toscano *et al.*, *Tetrahedron*, 43 (1987) 5393.
- 66 J. C. Coll and A. D. Wright, *Aust. J. Chem.*, 42 (1989) 1591.
- 67 A. G. Gonzalez, J. D. Martin, V. S. Martin *et al.*, *J. Chem. Soc., Chem. Commun.*, (1985) 260.
- 68 A. G. Gonzalez, J. Darias, A. Diaz *et al.*, *Tetrahedron Lett.*, 17 (1976) 3051.
- 69 A. G. Gonzalez, J. D. Martin, V. S. Martin *et al.*, *Ibid.*, 19 (1978) 2035.
- 70 A. Perales, M. Martinez-Ripoll and J. Fayos, *Acta Cryst.*, B35 (1979) 2771.
- 71 A. G. Gonzalez, J. D. Martin, V. S. Martin *et al.*, *Tetrahedron Lett.*, 20 (1979) 2717.
- 72 W. H. Gerwick, A. Lopez, R. da Vila and R. Albers, *J. Nat. Prod.*, 50 (1987) 1131.
- 73 M. R. Brennan, K. L. Erickson, D. A. Minott and K. O. Pascol, *Phytochemistry*, 26 (1987) 1053.
- 74 D. J. Kennedy, I. A. Selby and R. H. Thomson, *Ibid.*, 27 (1988) 1761.
- 75 J. D. Martin, P. Caballero, J. J. Fernandez *et al.*, *Ibid.*, 28 (1989) 3365.
- 76 J. F. Elsworth and R. H. Thomson, *J. Nat. Prod.*, 52 (1989) 893.
- 77 S. Bano, M. S. Ali and V. U. Ahmad, *Planta Med.*, 53 (1987) 508.
- 78 S. Bano, M. S. Ali and V. U. Ahmad, *Sci. Pharm.*, 56 (1988) 125.
- 79 S. Bano, M. S. Ali and V. U. Ahmad, *Z. Naturforsch.*, 43B (1988) 1347.
- 80 V. U. Ahmad and M. S. Ali, *Phytochemistry*, 30 (1991) 4172.
- 81 Atta-Ur-Rahman, V. U. Ahmad, S. Bano *et al.*, *Ibid.*, 27 (1988) 3879.
- 82 M. O. Stallard and D. J. Faulkner, *Comp. Biochem. Physiol.*, 49B (1974) 37.
- 83 D. J. Faulkner, M. O. Stallard and C. Ireland, *Tetrahedron Lett.*, 15 (1974) 3571.
- 84 A. G. Gonzalez, J. D. Martin, M. Norte *et al.*, *Ibid.*, 24 (1983) 847.
- 85 R. Sakai, T. Higa, C. W. Jefford and G. Bernardinelli, *Helv. Chim. Acta*, 69 (1986) 91.
- 86 C. B. Rao, C. Satyanarayana, D. V. Rao *et al.*, *Indian J. Chem.*, B28 (1989) 322.
- 87 G. Guella, I. Mancini, G. Chiasera and F. Pietra, *Helv. Chim. Acta*, 73 (1990) 1612.
- 88 E. G. Jeagdan, R. Kalidindi, P. Scheuer, *Tetrahedron*, 53 (1997) 521.
- 89 C. S. Vairappan, M. Suzuki, T. Abe and M. Masuda, *Phytochemistry*, 58 (2001) 517.
- 90 B. M. Howard and W. Fenical, *J. Org. Chem.*, 42 (1977) 2518.
- 91 A. F. Rose and J. J. Sims, *Tetrahedron Lett.*, 18 (1977) 2935.
- 92 A. F. Rose, J. J. Sims, R. M. Wing and G. M. Wiger, *Ibid.*, 19 (1978) 2533.
- 93 M. R. Brennan and K. L. Erickson, *J. Org. Chem.*, 47 (1982) 3917.
- 94 R. K. Dieter, R. Kinnel, J. Meinwald and T. Eisner, *Tetrahedron Lett.*, 20 (1979) 1645.
- 95 D. E. Barnekow, J. H. Cardellina II, A. S. Zektzer and G. E. Martin, *J. Am. Chem. Soc.*, 111 (1989) 3511.
- 96 D. L. Burgoyne, E. J. Dumdei and R. J. Andersen, *Tetrahedron*, 49 (1993) 4503.
- 97 R. Talpir, A. Rudi, Y. Kashman *et al.*, *Ibid.*, 50 (1994) 4179.
- 98 S. J. Wratten, D. J. Faulkner, D. van Engen and J. Clardy, *Tetrahedron Lett.*, 19 (1978) 1391.
- 99 S. J. Wratten and D. J. Faulkner, *Ibid.*, 19 (1978) 1395.
- 100 A. G. Gonzalez, J. M. Aguiar, J. Darias *et al.*, *Ibid.*, 19 (1978) 3931.
- 101 J. Roviroso, H. Soto, M. Cueto *et al.*, *Phytochemistry*, 50 (1999) 745.
- 102 S. S. Hall, D. J. Faulkner, J. Fayos and J. Clardy, *J. Am. Chem. Soc.*, 95 (1973) 7187.
- 103 S. J. Wratten and D. J. Faulkner, *J. Org. Chem.*, 42 (1977) 3343.
- 104 J. C. Coll, B. W. Skelton, A. H. White and A. D. Wright, *Aust. J. Chem.*, 42 (1989) 1695.
- 105 A. G. Gonzalez, J. Darias, J. D. Martin and C. Perez, *Tetrahedron Lett.*, 15 (1974) 1249.
- 106 A. G. Gonzalez, J. Darias, J. D. Martin *et al.*, *Tetrahedron*, 31 (1975) 2449.
- 107 A. G. Gonzalez, J. D. Martin, C. Perez *et al.*, *Tetrahedron Lett.*, 21 (1980) 187.
- 108 M. Chang, J. T. Vazquez, K. Nakanishi *et al.*, *Phytochemistry*, 28 (1989) 1417.
- 109 A. G. Gonzalez, J. D. Martin, M. Norte *et al.*, *Tetrahedron Lett.*, 24 (1983) 4143.
- 110 K. H. Hollenbeak, F. J. Schmitz, M. B. Hossain and D. van der Helm, *Tetrahedron*, 35 (1979) 541.
- 111 F. J. Schmitz, D. P. Michaud and K. H. Hollenbeak, *J. Org. Chem.*, 45 (1980) 1525.
- 112 Y. Gopichand, F. J. Schmitz, J. Shelly *et al.*, *J. Org. Chem.*, 46 (1981) 5192.
- 113 A. G. Gonzalez, V. Darias and E. Estevez, *Planta Med.*, 44 (1982) 44.
- 114 S. Yamamura and Y. Hirata, *Tetrahedron*, 19 (1963) 1485.
- 115 T. Irie, M. Suzuki and Y. Hayakawa, *Bull. Chem. Soc. Japan*, 42 (1969) 843.
- 116 M. O. Stallard and D. J. Faulkner, *Comp. Biochem. Physiol.*, 49B (1974) 25.
- 117 T. Irie, A. Fukuzawa, M. Izawa and E. Kurosawa, *Tetrahedron Lett.*, 10 (1969) 1343.
- 118 T. Irie, M. Suzuki, E. Kurosawa and T. Masamune, *Tetrahedron*, 26 (1970) 3271.
- 119 T. Irie, Y. Yasunari, T. Suzuki, N. Imai *et al.*, *Tetrahedron Lett.*, 6 (1965) 3619.
- 120 T. Suzuki, M. Suzuki and E. Kurosawa, *Ibid.*, 16 (1975) 3057.
- 121 R. Kazlauskas, P. T. Murphy, R. J. Wells *et al.*, *Aust. J. Chem.*, 30 (1977) 2679.
- 122 R. Kazlauskas, P. T. Murphy, R. J. Quinn and R. J. Wells, *Ibid.*, 29 (1976) 2533.
- 123 M. Suzuki and E. Kurosawa, *Tetrahedron Lett.*, 17 (1976) 4817.
- 124 M. Suzuki and E. Kurosawa, *Bull. Chem. Soc. Japan*, 52 (1979) 3349.
- 125 R. R. Izak, J. S. Drage and J. J. Sims, *Tetrahedron Lett.*, 22 (1981) 1799.
- 126 M. Suzuki and E. Kurosawa, *Bull. Chem. Soc. Japan*, 52 (1979) 3352.
- 127 J. W. Blunt, R. J. Lake and M. H. G. Munro, *Phytochemistry*, 23 (1984) 1951.
- 128 A. G. Gonzalez, J. M. Arteaga, J. J. Fernandez *et al.*, *Tetrahedron*, 40 (1984) 2751.
- 129 A. D. Wright, G. M. Konig, R. de Nys and O. Sticher, *J. Nat. Prod.*, 56 (1993) 394.

- 130 A. G. Gonzalez, J. M. Aguiar, J. D. Martin and M. L. Rodriguez, *Tetrahedron Lett.*, 17 (1976) 205.
- 131 T. Ichiba and T. Higa, *J. Org. Chem.*, 51 (1986) 3364.
- 132 S. Afaq-Husain, M. Shameel, K. Usmanhali *et al.*, *J. Appl. Phycol.*, 3 (1991) 111.
- 133 H. E. Högberg, R. H. Thomson and T. J. King, *J. Chem. Soc., Perkin Trans I*, (1976) 1696.
- 134 O. J. McConnel, P. A. Hughes and N. M. Targett, *Phytochemistry*, 21 (1982) 2139.
- 135 D. M. Estrada, J. D. Martin and C. Perez, *J. Nat. Prod.*, 50 (1987) 735.
- 136 M. E. Wall, M. C. Wani, G. Manikumar and D. R. McPhail, *Ibid.*, 52 (1989) 1092.
- 137 M. Park, W. Fenical and M.E. Hay, *Phytochemistry*, 31 (1992) 4115.