14.02 Eight-Membered Rings With One Oxygen Atom

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14.02.1 Introduction

This chapter appears as a complement of the material and information previously published in *Comprehensive Heterocyclic Chemistry* II (CHEC-II)[1] and CHEC-III,[2] providing a privileged point of entry to the eight-membered ring oxygen heterocycle systems chemistry.

Throughout the last decade, the numerous reviews on the synthesis of naturally occurring derivatives have highlighted the importance of this heterocycle moiety. Reviews describing the synthesis of brevetoxins (PbTxs) and ciguatoxins (CTXs),[3] on the most recent developments on the synthesis of maitotoxin (MTX)[4] and CTX,[5] on the synthesis of brevetoxin A (PbTx-1) on the 1990s[6] and on the isolation and synthesis of heliannuols, namely A, G, H, K, and L,[7] have appeared. Nicolaou reviewed their work on the total synthesis of several natural compounds, including the synthesis of PbTx-1, which subunits B and G were obtained through lactonization and dithioketal cyclization reactions, respectively, and of brevetoxin B (PbTx-2), which subunit H was synthesized via hydroxyl dithioketal cyclization reaction.[8] The synthesis of subunit H of PbTx-2 proposed by Nicolaou was also reviewed by T. Nakata.[9]

The importance of specific reagents, namely SmI_2-promoted cyclizations applied to the synthesis of some cyclic ethers of PbTx-2[10,11] and oxiranyl anions as building blocks in the construction of CDEFGHIJ-ring system of yessotoxin (YTX) and adriatoxin[12] have been disclosed.

H. Oguri studied the absolute configuration of CTX using an approach which combined partial structure synthesis, microscale chemical transformations, and the CD exciton chirality method. In addition, the partial structures of CTXs were synthesized as haptens for the preparation of anti-ciguatoxin antibodies.[13]

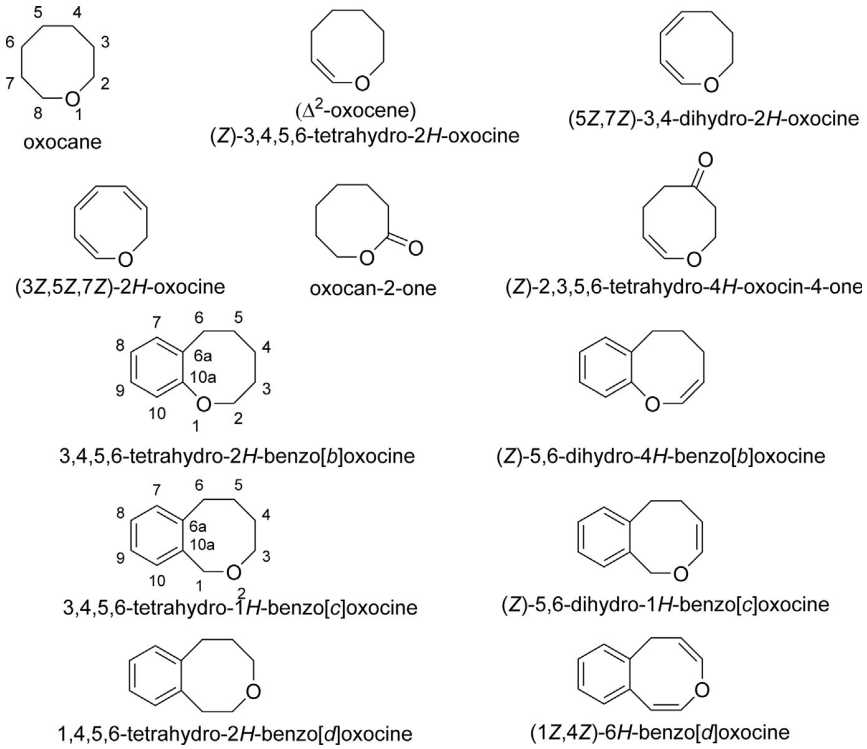
Reviews dedicated to toxic naturally occurring seafood contaminants have appeared, including the biosynthesis of PbTxs and YTX,[14] biosynthesis of PbTxs and CTXs,[15] monitoring and toxicity assessment of PbTxs in molluscan shellfish,[16] inflammatory and immune effects of PbTxs and CTXs.[17]

A critical overview on the chemistry, toxicity, distribution and fate of CTX derivatives has appeared.[18] Friedman and a large group of collaborators of different scientific areas published in 2017 an update review on the effects of exposure to CTXs on human health, diagnosis, human pathophysiology of Ciguatera Fish Poisoning (CFP), treatment, detection of CTXs in fish, epidemiology of the illness, global dimensions, prevention, future directions, and recommendations not only for clinicians but also for patients.[19] In the same year, reviews on the mechanism of action of CTXs and PbTxs, both activators of the same target, voltage-gated Na^+ channels,[20]

and on the quantification of five CTXs [ciguatoxin-1B (CTX-1B), 52-*epi*-54-deoxyciguatoxin-1B (52-*epi*-54-deoxyCTX-1B), ciguatoxin-3C (CTX-3C), 51-hydroxyciguatoxin-3C (51-hydroxyCTX-3C) and ciguatoxin-4A (CTX-4A)] (see structures in Section 14.02.3.1) in the Pacific area using Quantitative NMR Spectroscopy[21] have appeared.

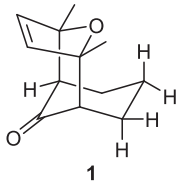
Details on the origin, structure and clinical symptoms of YTX and its analogs can be seen in a brief review.[22] In addition to these topics, the metabolism, biosynthetic origin, toxicological properties, potential risks to human health and advances in detection methods of YTXs have been overviewed.[23]

Until now, specific names have been given to the natural compounds bearing an *O*-8-membered heterocycle without referring the ring itself. As recommended by IUPAC, a proper nomenclature is associated to this heterocycles. Thus, eight-membered rings with one oxygen atom are named as oxocanes (fully saturated), oxocenes (one double bond) or oxocines (more than one double bond in the cyclic system). When a benzene is fused to the eight-membered ring, benzoxocines are formed.



14.02.2 Theoretical models

Berry et al. reported an unusual long-range Perlin effect in the conformationally constrained oxocane **1**. They assigned this high Perlin effect to the proposed boat like conformation of the structure, which was proved by NMR (NOE effects and *J* analysis) and that agreed with the solved crystal structure and with the DFT-calculated, energy minimized, and gas-phase structure. They also reported the largest $(1)J_{C\text{-}H}$ Perlin effect.[24] Salome and Tormena revisited this long-range Perlin effect by theoretical calculations and experimental results, based on their high resolution NMR data, and proved that the difference between $(1)J_{CHax}$ and $(1)J_{CHeq}$ (used to calculate Perlin effect) actually comes from the increase in the $(1)J_{CHax}$ and not from the decrease in the $(1)J_{CHeq}$. Thus, the reported largest Perlin effect are not real.[25]



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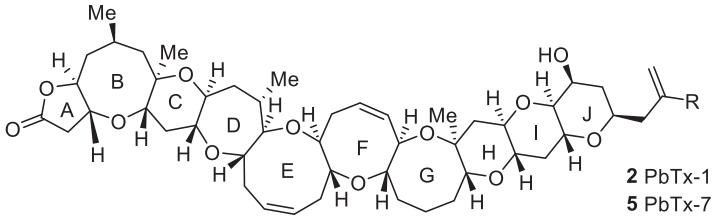
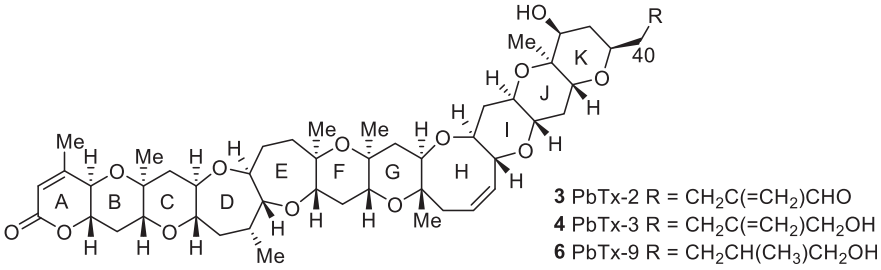
14.02.3 Experimental structural methods

14.02.3.1 Natural products

Many marine natural products, including marine toxins, possess complex and unusual chemical structures containing at least one 8-*O*-membered ring. Brevetoxins (PbTxs) are one of most popular examples of toxins, produced by marine dinoflagellates belonging to the genus *Karenia*. These neurotoxins are associated to the harmful algal blooms and responsible for the deaths of several marine organisms or for their accumulation in the marine food chain with consequent intoxication in human consumers, known as neurotoxic shellfish poisoning (NSP). In the previous chapter of CHC-III dedicated to 8-*O*-membered rings, the identification and characterization of numerous brevetoxins has been assigned, due to the intense and challenging marine discovery programs back in the 1980s but also to the development of the analytical techniques for their structural assignment.[26]

In 2007, Twiner et al. extracted from *K. brevis* of Texas Gulf coast using a C18 solid-phase extraction disc (SPEC) methodology, a series of brevetoxins and made their quantification by four independent methods: receptor binding assay (RBA), radioimmunoassay (RIA), neuroblastoma (N2A) cytotoxicity assay, and liquid chromatography/mass spectrometry (LC/MS). In addition, LC/MS analysis also provided the identification of several individual congeners (PbTx-1 (also known as brevetoxin A) **2**, PbTx-2 (also known as brevetoxin B) **3**, PbTx-3 **4**, PbTx-7 **5**, and PbTx-9 **6**) and of their hydrolyzed products (resulting from the lactone A ring opening).[27]

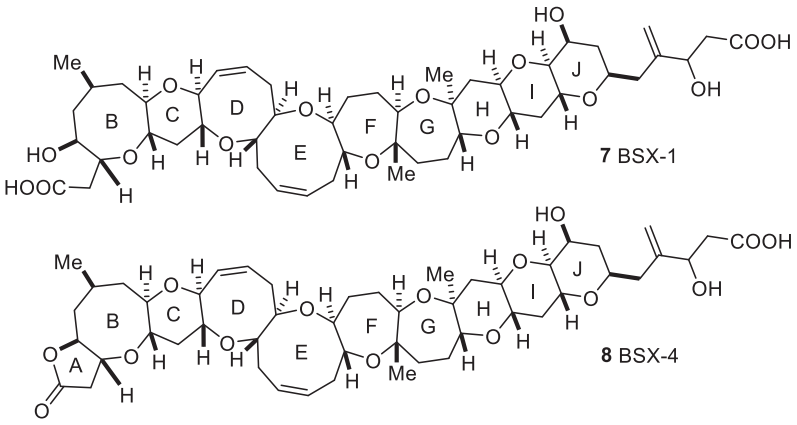




Studies on the conformational analysis of a model structure for the *trans*-fused FGH ether rings in PbTx-1 **2**, involving several classical force field-solvent combinations provided ensembles containing 30–60 structures with the central G-ring, the ring that plays an important role in the ion channel active binding site, adopting the crown, twist-crown, boat-chair, and boat conformations. Moreover, quantum mechanical calculations showed that twist-crown and boat-chair conformers were typically lowest in energy, in agreement with other reports describing the need for the 8-membered G-ring of PbTx-1 **2** to adopt the boat-chair conformation in order to bind to the ion channel active site. Other calculations including solvation indicated that solvent does not play a major role in the conformational preferences.[28]

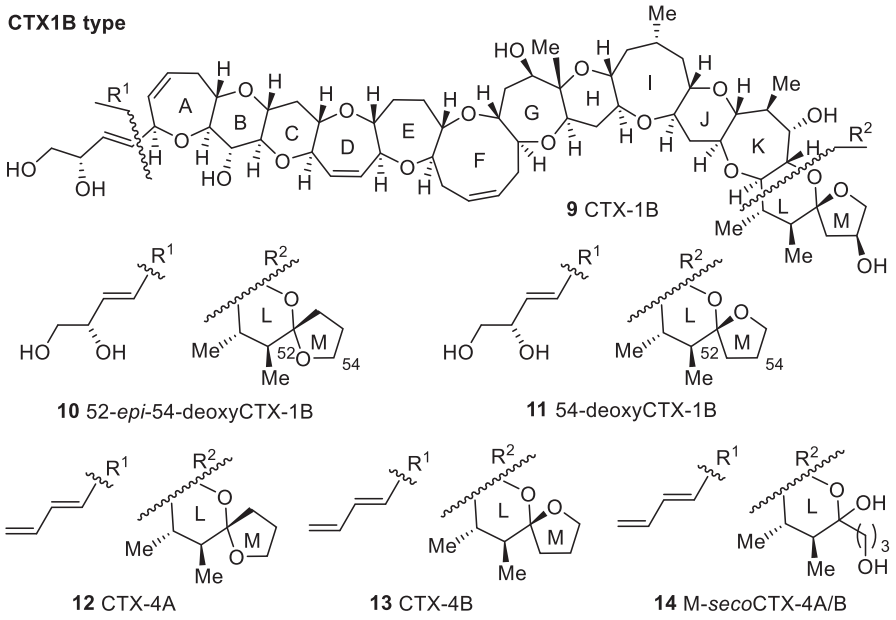
PbTx-2 **3** was isolated for the first time from New Zealand and Delaware strains of *K. papilionacea*, being produced 25 times more in the former strain than in the latter. The toxin production also increased in response to hypoosmotic stress, as previously reported in *K. brevis*. The structural assignment of PbTx-2 **3** was carried out by mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopy. Indeed, a strong overlap was observed in ^{1}H NMR spectra of the New Zealand extract with the PbTx-2 **3** standard, namely in the signals corresponding to the aldehyde proton, the exomethylene protons and to the protons on the unsaturated bonds in the A and H-rings.[29]

Two novel marine ladder-frame polyethers named brevisulcatic acid-1 (BSX-1 **7**, $C_{49}H_{72}O_{16}$, $[M + H]^+$ calcd 917.4899) and brevisulcatic acid-4 (BSX-4 **8**, $C_{49}H_{70}O_{15}$, $[M + H]^+$ calcd 899.4793) were isolated from red tide dinoflagellate *K. brevisulcata* in New Zealand. These molecules are similar to PbTx-1 **2** ($C_{49}H_{70}O_{13}$) and their structural elucidation was obtained after detailed analysis of low-temperature NMR spectra and high-energy MALDI TOF MS/MS spectra. The β-hydroxy-γ-methylene valeric acid side chain and the ether ring skeleton of both brevisulcatic acids are common to both acids, but BSX-4 **8**, has a γ-lactone as the 5-membered A-ring while BSX-1 **7** is the *seco* acid analog. BSX-4 **8** has structural and bioactivity similarities to PbTx-1 **2**.[30]

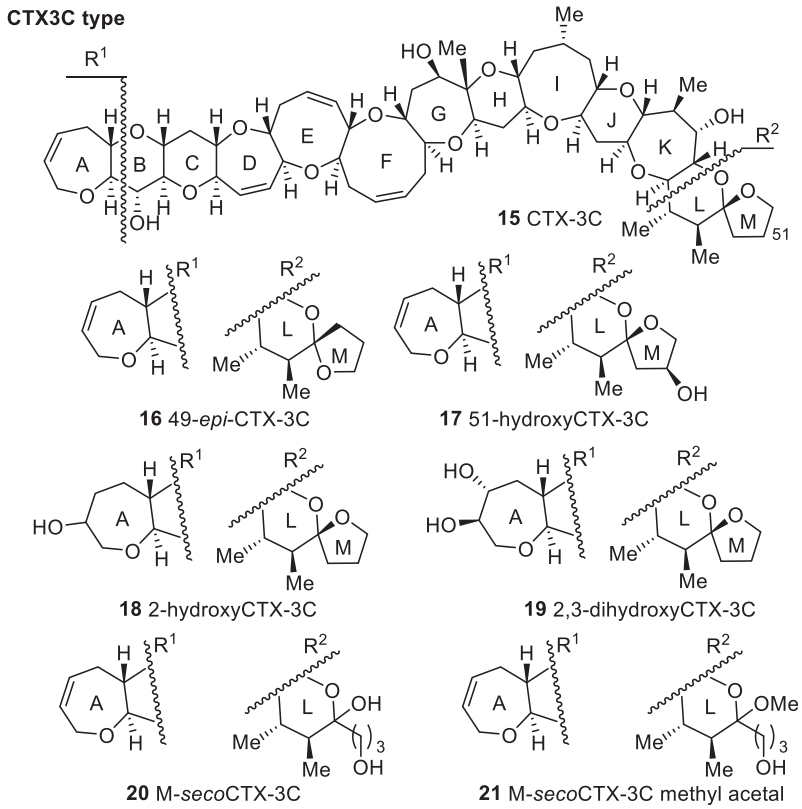


Ciguatoxins (CTXs) are synthesized by microalgae of the dinoflagellate genus *Gambierdiscus* and composed by a ladder shaped structure made by 13 or 14 ether rings. Soliño and Costa suggested a classification of this class of compounds according to the differences in the number and substitution of the rings as well as their regional occurrence: Pacific Ocean, Caribbean Sea and Indian Ocean.[18] Pacific CTXs possess 13 rings with main differences in E ring, lack of the side-chain substituent and can be separated into CTX-I (CTX1B type) and CTX-II (CTX3C type). Caribbean and Indian CTXs have a structure similar to CTX-II with an extra fused ring. Humans of isolated island communities which depends mainly on fishing for their food supply can eat fish containing these naturally occurring CTXs and develop Ciguatera Fish Poisoning (CFP) illness. It is characterized by gastrointestinal, neurologic, and cardiovascular symptoms.[18]

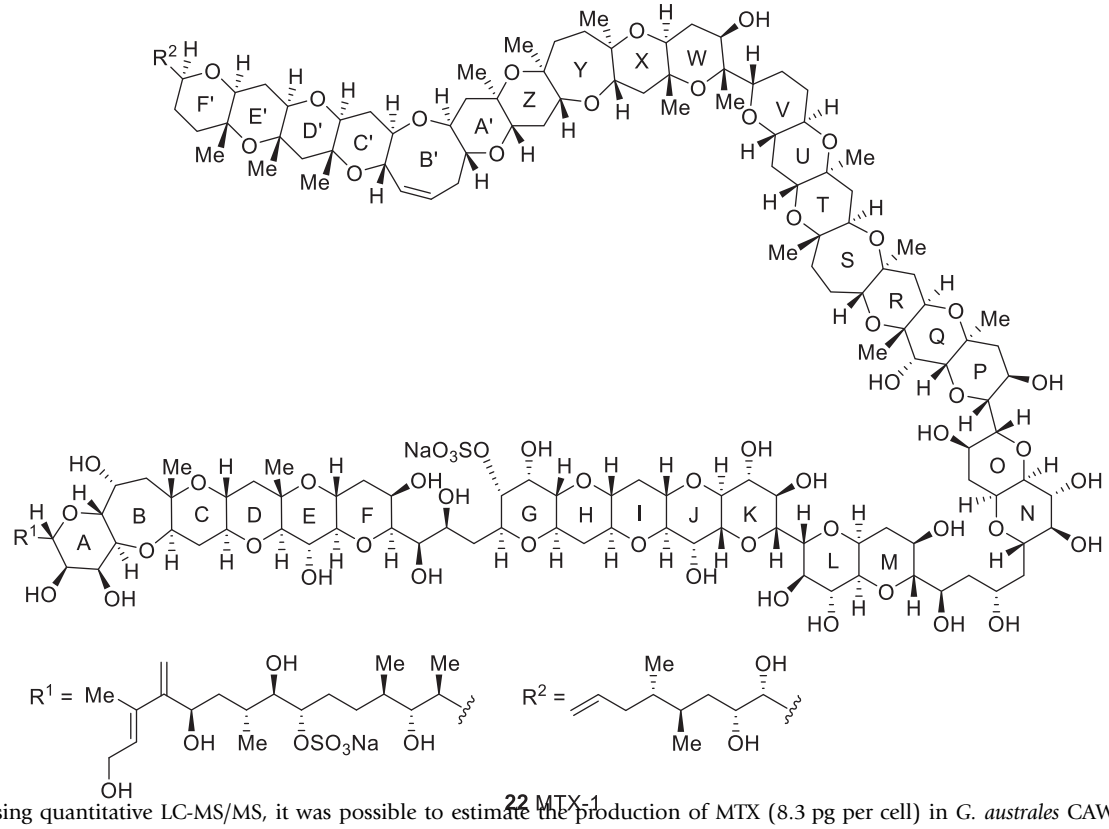
Using high-performance liquid chromatography tandem mass spectrometry (LC-MS/MS), the identification and quantification of 13 CTXs (CTX-1B **9**, 52-*epi*-54-deoxyCTX-1B **10**, 54-deoxyCTX-1B **11**, CTX-4A **12**, CTX-4B **13**, M-*seco*-CTX-4A/B **14**, CTX-3C **15**, 40-*epi*-CTX-3C **16**, 51-hydroxyCTX-3C **17**, 2-hydroxyCTX-3C **18**, 2,3-dihydroxyCTX-3C **19**, M-*seco*-CTX-3C **20** and M-*seco*-CTX-3C methyl acetal **21**) in fish flesh collected at different locations of Japan were accomplished. Regional differences were also possible to be made: ciguatoxin-1B-type were found in snappers and groupers from Okinawa, ciguatoxin-3C-type were found in a spotted knifejaw, *Oplegnathus punctatus*, from Miyazaki and both types of toxins were found in a red snapper, *Lutjanus bohar*, from Minamitorishima (Marcus) Island. In addition, 10 CTXs (compounds **10–17**, **20**, **21**) were identified in the dinoflagellate *Gambierdiscus toxicus* collected in French Polynesia. This technique revealed high sensitivity, specificity, and rapidity in monitoring CTXs in these type of specimens.[31] Using quantitative LC-MS/MS, it was possible to estimate the production of CTX (18.2 pg per cell) in *G. polynesiensis* CAWD212, isolated from samples of seawater of Rarotonga, Cook Islands.[32]



Maitotoxin (MTX-1, **22**) is the largest non-polymeric natural compound known so far. It is a polycyclic ether isolated from the marine dinoflagellate *G. toxicus*, and similarly to CTXs, that are responsible for CFP illness. A critical review on the biosynthesis of



marine polyether ladders, points out some mechanistic hypotheses for the contiguous rings formation that questioned the well-established structure of maitotoxin.[33] Meanwhile, based on NMR studies, the conformation of maitotoxin and yessotoxin (described later), mode of action and their interactions in biomembranes, have been briefly reviewed by Murata et al.[34]



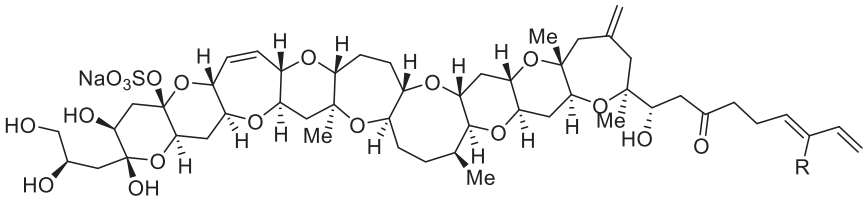
Using quantitative LC-MS/MS, it was possible to estimate the production of MTX (8.3 pg per cell) in *G. australes* CAWD149 isolated from samples of seawater of Rarotonga, Cook Islands. Moreover, the production of MTX-3 **23**, a MTX analog, was also monitored in three species of *Gambierdiscus*: *G. pacificus* CAWD213, *G. australes* CAWD149 and 216.[32] LC-MS analysis of G. cf.

yasumotoi CAWD210 isolated from the Bay of Islands, Northland, New Zealand revealed the production of MTX-3 **23** but not of MTX-1 **22** or CTXs by this species.[35] Years later, the isolation of two *Gambierdiscus* species, *G. australes* and a previously unknown *Gambierdiscus* species named as CAWD242, collected from North Meyer Island, Kermadec Islands, was accomplished. The production of MTX-1 **22** in 10 of the isolates from *G. australes* ranged from detectable to 36.6 pg per cell while the presence of MTX-3 **23** was detected in all isolates of *G. australes*. In addition, for the *Gambierdiscus* species CAWD242 was detected the production of MTX-3 **23** but not of MTX-1 **22**.[36] The structural identification of MTX-3 **23** (initially reported as 44-methylgambierone) was assigned, by comparison of its NMR and MS data with those of gambierone **24**, for the first time in 2019 by Boente-Juncal et al. from *G. belizeanus* collected in the Caribbean Sea[37] and by Murray et al. from *G. australes* collected at Raoul Island (Rangitahua/Kermadec Islands).[38]

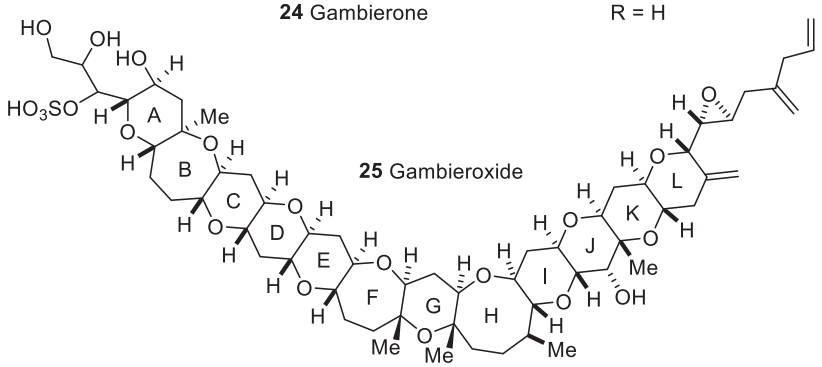
A new MTX analog named as MTX-4, isolated from two Canary Islands *G. excentricus* strains VGO791 and VGO792, was reported by Pisapia et al. in 2017, which HRMS/MS spectra analysis allowed their identification (accurate mono-isotopic mass of 3292.4860 Da, as free acid form). In addition, the authors screened the identification and quantification of four MTX analogs (MTX-1 **22**, putative MTX-2, MTX-3 **23** and MTX-4) in the extracts of two strains of *Fukuyoa ruetzleri* and 42 *Gambierdiscus* strains using LC-LRMS (low resolution mass spectrometry)/MS analysis. To note that MTX-4 was detected and quantified (13.0–72.8 pg MTX equiv. cell^{-1}) in all seven strains of *G. excentricus* analyzed, independently of their origin (Brazil, Canary Islands, and Caribbean) but not detected in any other species under study. Unfortunately, the structural elucidation of MTX-4 was not provided by the authors.[39]

Very recently, MTX and two MTX-like compounds from Caribbean strains of *Gambierdiscus* spp. were isolated by liquid chromatography: one from *G. belezianus*, isolate CCMP 399 from St. Barthelemy Island, Greater Antilles, Caribbean Sea; and the second from both *Gambierdiscus* ribotype-2, isolate CCMP 1655 from Martinique, Lesser Antilles, Caribbean Sea, and *Gambierdiscus* sp., isolate SIU 350 from Virgin Gorda, British Virgin Islands, Caribbean Sea. Besides MTX, HRMS analysis suggested that the first unknown compound is a desulfo-MTX congener and the second one is a didehydro-demethyl-desulfo-MTX congener. Furthermore, the authors used the Advanced Chemistry Development program, "ACD/C+H NMR Predictors and Data Base," to predict the ^{13}C chemical shifts of some carbons.[40]

In 2013, Watanabe et al. identified a novel epoxy polyether compound named gambieroxide **25**, isolated from *G. toxicus* (GTP2 strain) collected at Papeete, Tahiti, French Polynesia. The assignment of this structure was based on the analysis of NMR and MS spectroscopic data and comprises 12 contiguous *trans*-fused ether rings, a sulfate ester group, an epoxide and two olefins in side chains.[41]



23 MTX-3 (44-methylgambierone) R = Me
24 Gambierone R = H

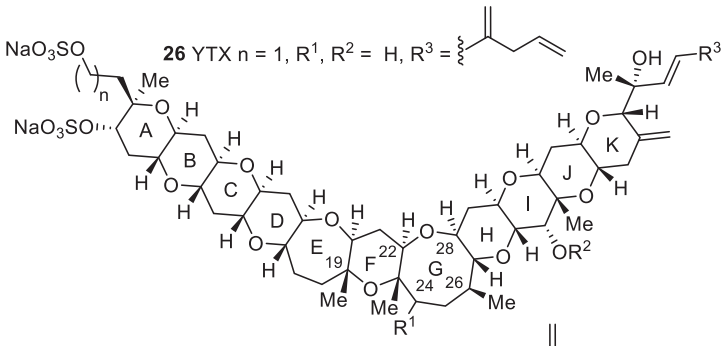


25 Gambieroxide

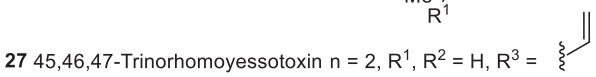
Yessotoxin (YTX, **26**) is a disulfated polyether compound with a characteristic ladder-shape formed by 11 adjacent ether rings of different sizes, with two sulfate ethers in one terminus of the chain and an acyclic unsaturated side chain constituted by nine carbons in the opposite side. This compound was firstly isolated in 1987 from the scallop *Pecten yessoensis* and since then, several metabolites have been found in shellfish from throughout the world. Various YTX analogs have also been isolated from three dinoflagellate algae *Protoceratium reticulatum*, *Lingulodinium polyedrum*, and *Gonyaulax spinifera*.

In 2006 a new YTX analog, 45,46,47-trinorhomoyessotoxin **27**, was isolated from cultures of *P. reticulatum* collected at Yamada Bay, Iwate in Japan.[42] YTX and a novel yessotoxin analog (furanoyessotoxin **28**) containing a furan ring in the side chain have been isolated (by filtration followed by solid-phase extraction) and purified from a large-scale culture (226 L) of *P. reticulatum* strain CAWD129 from the western coast of South Island, New Zealand.[43] All these structures have been established by 1D and 2D NMR experiments and MS studies.

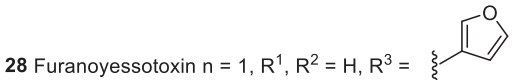
From the GG1AM strain of *P. reticulatum* collected from phytoplankton cultures at the *Centro Oceanográfico de Vigo*, YTX, glycoyessotoxin (G-YTXA **29**) and a novel polyether named adriatoxin-B **30** were isolated. The latest compound is a C_{13} terminal truncated YTX analogous metabolite and was characterized using a combination of NMR spectroscopy experiments and conformational analysis.[44] Very recently, Rajotte et al. identified YTX and the analog (24*R*)-24-hydroxyyessotoxin **31** from a Namibian isolate of *Gonyaulax spinifera*. The configuration at C-24 of **31** was based on the correlations observed in the ROESY NMR experiment. Thus, the signal of H-24 correlated with the signals of H-22α, H-25α and H-26α. In addition, on the α-face, the signal of H-28α correlated with the signals of H-22α and H-26α; on the β-face, the signal of H-25β correlated with the signals of 23-Meβ and H-27β.[45]



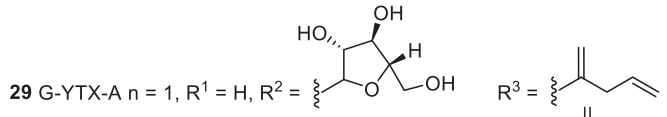
26 YTX n = 1, R^1, R^2 = H, R^3 =



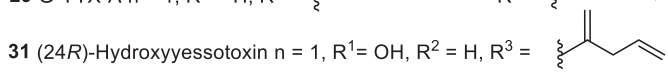
27 45,46,47-Trinorhomoyessotoxin n = 2, R^1, R^2 = H, R^3 =



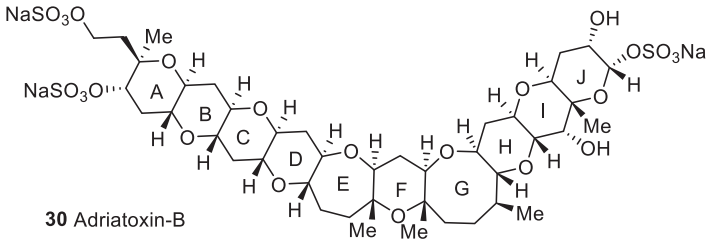
28 Furanoyessotoxin n = 1, R^1, R^2 = H, R^3 =



29 G-YTX-A n = 1, R^1 = H, R^2 = R^3 =



31 (24*R*)-Hydroxyyessotoxin n = 1, R^1= OH, R^2 = H, R^3 =



30 Adriatoxin-B

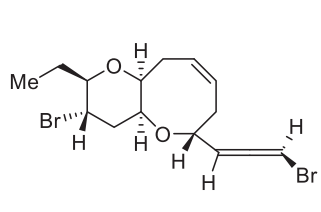
The analysis of ethyl acetate extract obtained from the marine organism *Laurencia obtusa*, collected in Corsica, France, allowed the identification of the known microcladallene A **32**.[46] Chromatographic fractionations of the extract were made and spectroscopic analysis (NMR and MS experiments) supported the assignment of this compound.

The assignment of structure of ansellone B was a challenging task. Wang et al. isolated from the marine sponge *Phorbas* sp. collected in Gageodo Island, southwestern Korea this sesterterpenoid and proposed a molecular formula established by the high-resolution FABMS of $C_{29}H_{40}O_6$ **33a** (calcd for $[M + Na]^+$ $C_{29}H_{40}O_6Na$, 507.2723).[47] However, Daoust et al., collected specimens of *Phorbas* sp. at Ansell Point in Howe Sound, British Columbia and identified ansellone B as a tetracyclic ether bearing an eight-membered ring **33b**. The high-resolution ESIMS was consistent with a molecular formula of $C_{27}H_{40}O_5$ (calcd for $[M + Na]^+$ $C_{27}H_{40}O_5Na$, 467.2773) and the structure fully characterize by extensive NMR studies.[48]

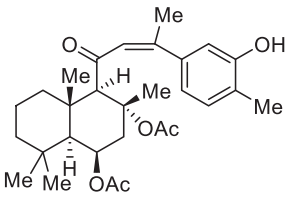
Ansellone C **34** was identified as a novel sesterterpene isolated from the marine sponge *Clathria gombawuiensis* collected from Korean waters. NMR studies confirmed a tetracyclic compound containing an eight-membered oxocane moiety and the relative configuration was assigned by NOESY experiments as 5*S**, 6*R**, 8*R**, 9*R**, 10*S**, 14*R** and 19*R**. Despite the presence of a secondary 6-hydroxyl group, the attempts to determine its absolute configuration by Mosher's method were unsuccessful.[49]

The novel amaroxocane A **35**, a dimeric sulfated sterol bridged by an oxocane moiety, was isolated from *Phorbas amaranthus* collected on shallow coral reefs off Key Largo, Florida. Full assignment of all protons and carbons was accomplished after extensive analysis of NMR spectra and the molecular formula proposed by HRESI-TOF/MS was $C_{55}H_{85}Na_2O_{17}S_3$ ($[M–Na]^-$ calcd for 1159.4744). The relative configuration of the different heterocyclic rings was possible due to the interpretation of the NOESY spectra and of the coupling constant data. The absolute configuration of the different heterocyclic rings in amaroxocane A **35** was

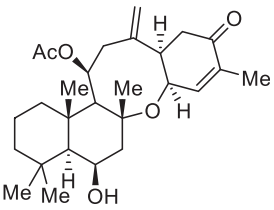
based on the natural (*R*)-configuration of C-20, assumed based on the biogenetic principles, and also on the NOESY data. However, the absence of scalar coupling between H-20 and H-22 (dihedral angle of 90 degrees) was compensated by the NOESY correlations observed between H-17 and H-23 eq and of H-16ax/eq and H-22.[50]



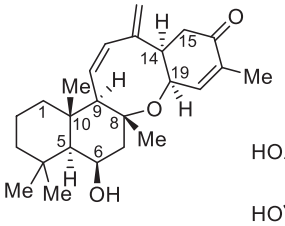
32 Microcladallene A



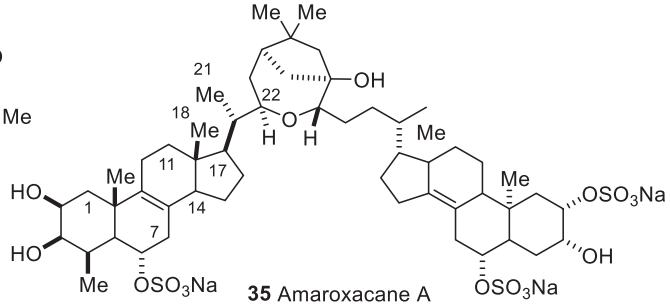
33a Ansellone B
(Wang et al.)



33b Ansellone B
(Daoust et al.)

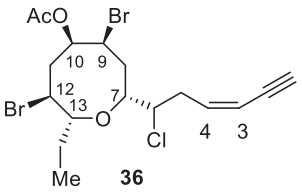


34 Ansellone C

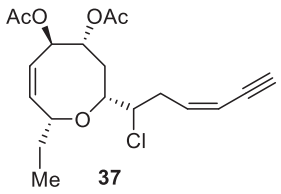


35 Amaroxacane A

Five new C_{15} eight-membered cyclic ethers **36–40** along with the acetylenic chloro diol **41** were isolated from a 3:1 mixture of dichloromethane:methanol extract of the red alga *Laurencia glandulifera*, collected at Crete Island in South Greece. The assignment of all protons and carbon resonances were established by 1D and 2D NMR studies. The coupling constant ($J = 10.8$ Hz) between H-3 and H-4 as well as the chemical shift of the acetylenic proton (3.11–3.13 ppm) indicated the (*Z*)-configuration of the C3═C4 double bond. The relative stereochemistry was assigned on the basis of NOESY experiments as: (3*Z*,7*R**,9*S**,10*R**,12*S**,13*R**)-10-acetoxy-6-chloro-9,12-dibromolauthisa-3-en-1-yne **36**; (3*Z*,7*R**,9*R**,10*R**,13*R**)-9,10-diacetoxy-6-chlorolauthisa-3,11-dien-1-yne **37**; (3*Z*,7*R**,9*R**,10*R**,13*R**)-10-acetoxy-9-hydroxy-6-chlorolauthisa-3,11-dien-1-yne **38**; (3*Z*,7*R**,9*R**,10*R**,13*R**)-9-acetoxy-10-hydroxy-6-chlorolauthisa-3,11-dien-1-yne **39**; (3*Z*,7*R**,9*R**,10*R**,13*R**)-10-acetoxy-6-chloro-9-bromolauthisa-3,11-dien-1-yne **40** and (3*Z*,7*R**,9*R**,10*R**,13*R**)-6-chlorolauthisa-3,11-dien-1-yne-9,10-diol **41**.[51]



36



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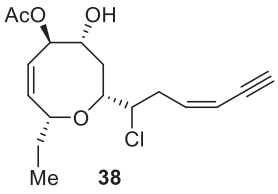
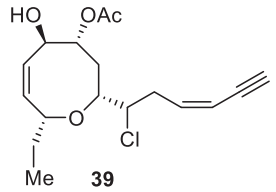


38



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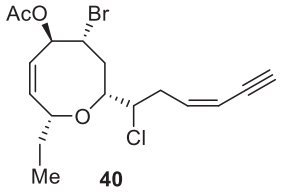

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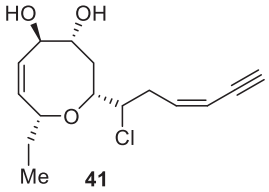
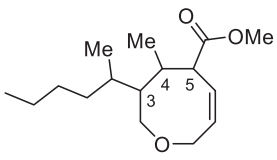


41

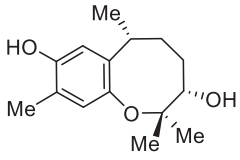
A new cyclic ether assigned as methyl (3*S*,4*R*,5*S*,6*Z*)-3-[(*R*)-hex-2-yl]-4-methyl-3,4,5,8-tetrahydro-2*H*-oxocine-5-carboxylate **42** was isolated from a 1:1 mixture of ethyl acetate:methanol extract of the red seaweed *Kappaphycus alvarezii*. Their structural elucidation and relative stereochemistry was based on the detailed analysis of NMR spectroscopy and MS data.[52]

A non-marine natural compound bearing an eight-*O*-membered ring isolated in the past decade was heliannuol A **43**, obtained from dried leaves of sunflower (*Helianthus annuus* L. var. Arianna) and extracted with pure supercritical CO_2[53] or in combination with high-pressure techniques.[54] This structure was elucidated based on a detailed interpretation of 1D and 2D NMR spectra

and MS.

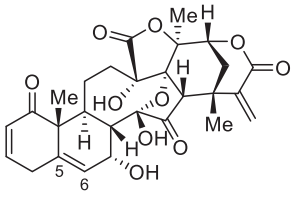


42

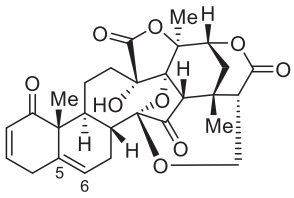


43 Heliannuol A

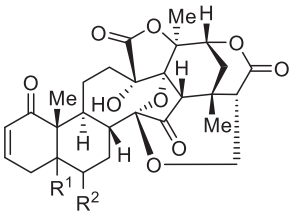
The genus Physalis belongs to the Solanaceae family and includes about 120 species widely distributed around tropical and subtropical regions of the world. Some of these species are used as food as well in folk medicine for the treatment of several illnesses such as malaria, hepatitis, hyperglycemia, rheumatism, asthma, among others. There was a series of *seco*-steroid compounds named physalins that have been isolated from this plant family, since the firstly isolation of physalin A **44** in 1969.[55] In this article, we will only present the characterization of novel physalins reported after 2006, since the other derivatives have been characterized by NMR and MS techniques in the previous CHC chapters. Nevertheless, many of them have been isolated from different species and geographic regions for their biological evaluation, namely physalins B **45**, D **46**, E **47**, F **48**, G **49**, H **50**, I **51**, J **52** and U **53** from *Physalis angulata* L. plant collected in Brazil,[56–63] Republic of China[64–68] or Republic of Congo.[69] For physalins B and F, crystallization of the dichloromethane extract from acetone allowed the structural determination of both compounds by X-ray crystallography.[69] From the whole *Physalis angulata* L. plant collected in Tainan Hsien, Taiwan, Republic of China a new physalin, physalin W **54**, was isolated and fully characterized by a combination of 1D and 2D NMR and MS studies. The relative configuration assignments were based on NOESY correlations and coupling constants data.[64] A novel physalin, 25-hydroxylisophysalin B **55**, were isolated from whole plant of *Physalis angulata* collected in Hainan Province, China. The structure of such compound was based on the analysis of their spectroscopic data.[65]



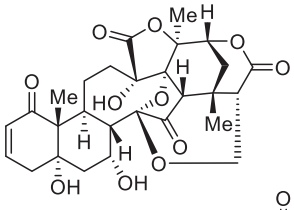
44 Physalin A



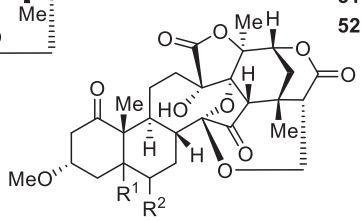
45 Physalin B



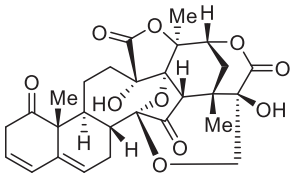
46 Physalin D, R^1 = α–OH, R^2 = β–OH
48 Physalin F, R^1, R^2 = β–epoxy
49 Physalin G, Δ^4, R^2 = β–OH
50 Physalin H, R^1 = α–Cl, R^2 = β–OH
51 Physalin I,R^1 = α–OMe, R^2 = β–OH
52 Physalin J, R^1, R^2 = α–epoxy



47 Physalin E

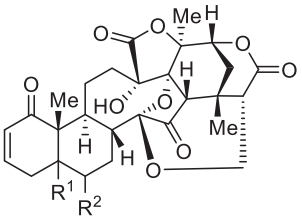


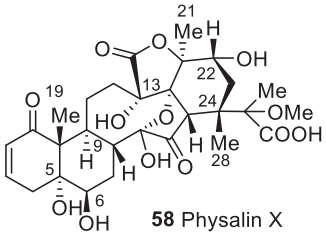
53 Physalin U, R^1, R^2 = β–epoxy
54 Physalin W, R^1 = α–H



55 25-Hydroxyisophysalin B

The known 6α-chloro-5β-hydroxy-5,6-dihydrophysalin B **56** and the new 5α-ethoxy-6β-hydroxy-5,6-dihydrophysalin B **57** were obtained from the whole *Physalis angulata* L. plant collected in Guangdong, Republic of China, and their structures assigned through MS, IR, NMR spectroscopy analyses and X-ray crystallography.[68] The structural elucidation of novel physalin X **58** was accomplished by spectral analysis of NMR and MS data and the configuration was based on NOESY experiments which showed correlations of 5-OH with H-9, 6-OH with 19-CH_3, 13-OH with H-9/21-CH_3, and of H-22 with 28-CH_3, giving α-orientations for 5-OH and 13-OH and β-orientations for 6-OH and H-22. The absolute configuration was deduced as 5*R*,6*R*,8*R*,9*S*,10*R*,13*S*,14*R*,16*S*, 17*R*,20*S*,22*R*,24*S* from the X-ray structure of physalin P, the skeletal structure of physalins, and their biosynthetic background.[70]





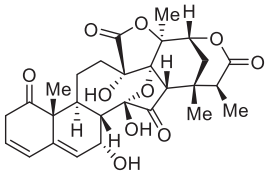
58 Physalin X

56 6α-Chloro-5β-hydroxy-5,6-dihydrophysalin B, R^1 = β–OH, R^2 = α–Cl

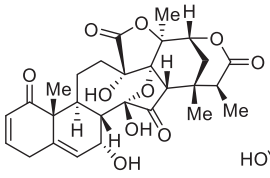
57 5α-Ethoxy-6β-hydroxy-5,6-dihydrophysalin B, R^1 = α–OEt, R^2 = β–OH

Similarly, to *Physalis angulata* L. plant, a number of known physalins have been isolated mainly from the calyces of *P. alkekengi* var. *Franchetii* for pharmacological purposes. Examples are physalins A **44**, B **45**, D **46**, E **47**, F **48**, G **49**, J **52**, L **59**, O **60** and X **58**,[71–79] which structures were elucidated on the basis of NMR and MS studies and confirmed by comparison with a reference sample and spectroscopic data already published. More details on the ethnomedical, phytochemical and pharmacological properties of *Physalis alkekengi* L. var. *Franchetii* (Mast.) Makino can be seen in the review of Li et al. published in 2018.[80]

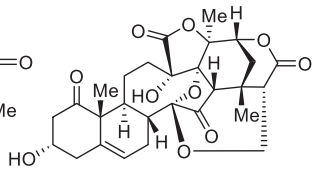
A study reported the quantification of physalin D in methanolic extracts of fruit (mature and immature) and calyx of *P. alkekengi* collected from wild plants growing in the Mures district, Romania. The quantification was determined by RP-HPLC-UV method, being their content in a relation of immature calyx > mature calyx > immature fruits > mature fruits.[81] Qiu et al. isolated from *P. alkekengi* var. *Franchetii* calyces hydroalcoholic extract two new physalins, physalin Y **61** and Z **62**, along with the already known 3β-hydroxy-2,3-dihydro-4,7-didehydrophysalin B **63**.[71] From the same type of extracts, Li et al. isolated three new physalins which structures were elucidated by UV, MS, 1D and 2D NMR spectroscopy as 5α,6β-dihydroxy-25,27-dihydro-7-deoxyphysalin A **64**, 5α,6β-dihydroxyphysalin R **65** and 3β-hydroxy-2-hydrophysalin A **66**.[82] Two years later, from the fruits of *P. alkekengi* L. var. *Franchetii* (Mast.) Makino collected in Qiqihar City, China, was identified a novel physalin, 5α,6α-dihydroxyphysalin D. This compound is an epimer of physalin D, and the authors named it as physalin D_1 **67**. Their structural assignment was based on 1D and 2D NMR, IR and MS spectroscopic data. Thus, the main differences in ^{13}C NMR spectra of physalin D_1 **67** and D **46** are the changes of the chemical shift of C-4, C-19 and C-11 due to the space field effect of the 6-α (equatorial) hydroxy group in physalin D_1 instead of the 6-β (axial) hydroxy group in physalin D. The equatorial orientation of 6-OH in physalin D_1 **67** was further confirmed by NOESY correlations of H-6 with 19-Me and of H-28.[78]



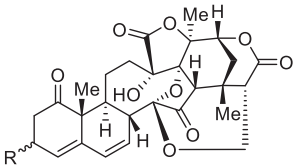
59 Physalin L



60 Physalin O

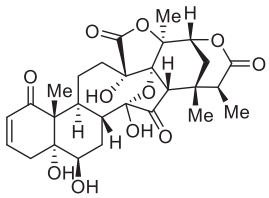


61 Physalin Y

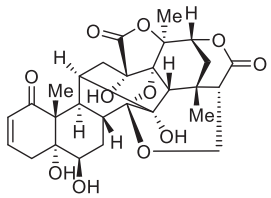


62 Physalin Z, R = α-OH

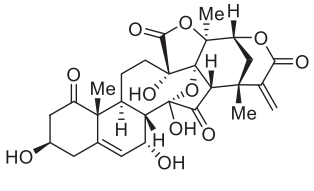
63 3β-Hydroxy-2,3-dihydro-4,7-didehydrophysalin B, R = β-OH



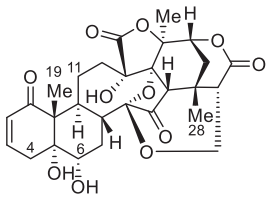
64 5α,6β-Dihydroxy-25,27-dihydro-7-deoxyphysalin A



65 5α,6β-Dihydroxyphysalin R



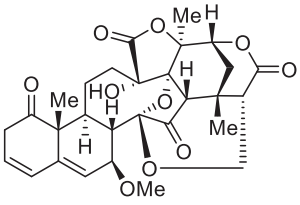
66 3α-Hydroxy-2-hydrophysalin A



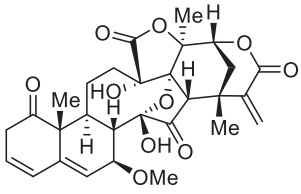
67 Physalin D_1

More recently, seven new physalins (7β-methoxylisophysalin B **68**, 7β-methoxylphysalin C **69**, physalin V **70**, physalin VII **71**, isophysalin I **72**, 7β-ethoxylisophysalin C **73** and 3β-ethoxyl-2,3-dihydro-4,7-didehydrophysalin B **74**) were also isolated from a Chinese *P. alkekengi* var. *Franchetii* calyces hydroalcoholic extract and identified by NMR and MS studies, along with 18 already known physalins, elucidated by comparison of the literature spectral data.[83,84] A novel and efficient HPTLC (High Performance Thin-Layer Chromatography)-MS/(MS) methodology was developed for the first time for the analysis of physalins in crude plant extracts of different parts of *P. alkekengi* L. collected in Slovenia and harvested at different stages of maturity. This method proved to be more selective, sensitive and with higher resolution in the separation of physalin L standard and its impurity (2,3,25,27-tetrahydrophysalin A).[85]

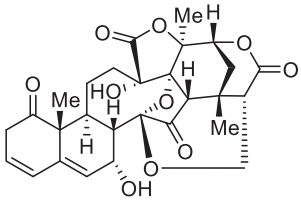
More examples of physalins were collected from other plants of the genera *Physalis* and *Withania*. Thus, physalin F was isolated form *P. minima* L. whole plant collected in Arau-Perlis, Malaysia,[86] while from that collected in Guangdong, Republic of China,[87] five derivatives was isolated using a ultra-performance liquid chromatographic (UHPLC) method: isophysalin B **75**, physalin G **49**, physalin D **46**, physalin I **51** and 5α,6β-dihydroxyphysalin R **65**. Physalins A **44**, B **45**, D **46**, F **48** and H **50** were also isolated from the extracts of the aerial parts of *P. divericata* D. Don[88,89] while from the leaves of *Witheringia solanacea* were isolated physalins B, D, and F.[90] All structures were elucidated based on ultraviolet spectrophotometry, NMR and MS studies and confirmed by comparison with spectroscopic data already published.



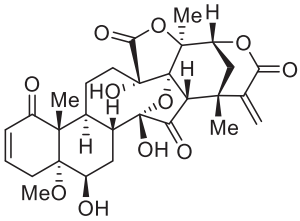
68 7β-Methoxylisophysalin B



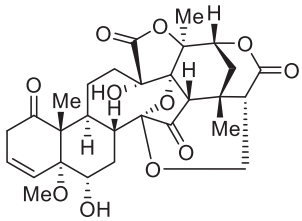
69 7β-Methoxylphysalin C



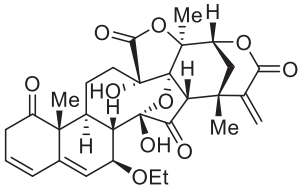
70 Physalin V



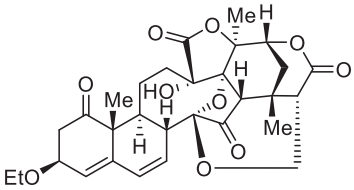
71 Physalin VII



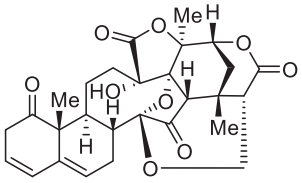
72 Isophysalin I



73 7β-Ethoxylisophysalin C



74 3β-Ethoxyl-2,3-dihydro-4,7-didehydrophysalin B

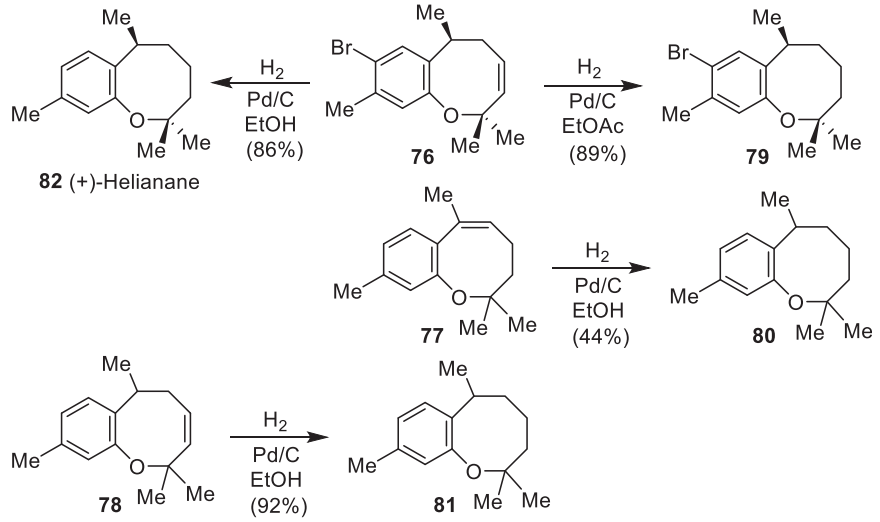


75 Isophysalin B

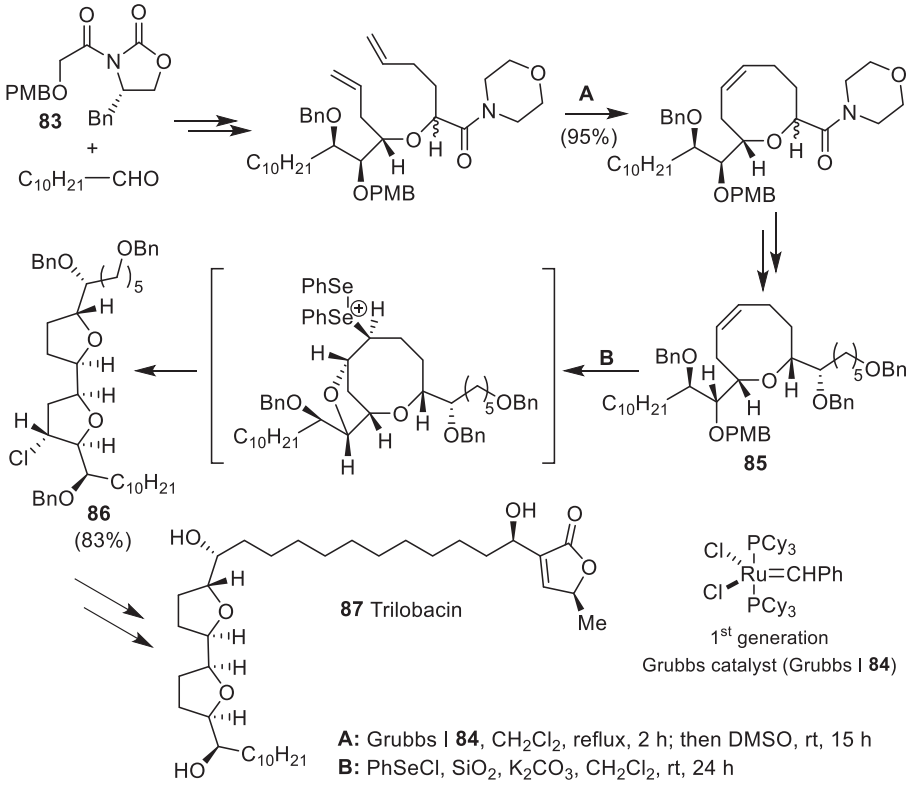
14.02.4 Reactivity of substituents attached to ring carbon atoms

Several hydrogenation reactions of benzoxocines **76–78** over Pd/C have been reported to prepare benzoxocanes **79–81**. One of them discloses the preparation of the natural compound helianane **82** (Scheme 1).[91–93]

Asymmetric total synthesis of trilobacin **87** was achieved through a multistep strategy starting from glycolate oxazolidinone **83** and undecanal. Initially, it involves a 13-step sequence for the formation of the α,α′-*cis*-oxocene **85** that includes a ring-closing metathesis promoted by 1st generation Grubbs catalyst [bis(tricyclohexylphosphine)benzylidene ruthenium (IV) dichloride] (Grubbs I, **84**). Then, additional 5-steps including an organoselenium-mediated oxonium ion formation/SiO_2-promoted fragmentation to form *erythro*-bis(2,2′)-tetrahydrofuran moiety **86** are required for the total synthesis of **87**, in a 14% overall yield (Scheme 2).[94]

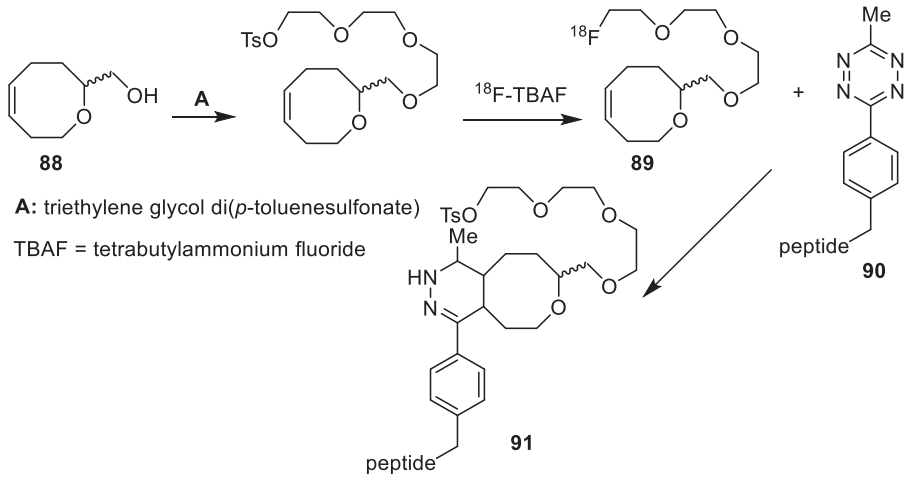


Scheme 1



Scheme 2

In order to construct the PET probe **91** with improved tumor-to-background ratios in neurotensin receptor (NTR) imaging, a diastereomeric mixture of *trans*-5-oxocene **88** reacted with triethylene glycol di(*p*-toluenesulfonate), followed by treatment with ^{18}F-TBAF to provide ^{18}F-labeled *trans*-5-oxocene **89**, which after mixing a few seconds with tetrazine-peptide conjugate **90**, afforded the desired probe **91** (Scheme 3).[95] The computational guided synthesis of **90** was previously reported in seven steps from the commercially available glycidol and involves Sakurai allylation, olefin metathesis and flow enabled photoisomerization as key steps. Wallace et al. also demonstrated the potential use of *trans*-5-oxocene in studies where hydrophilicity and bioconjugation are required. Thus they showed the rapid and quantitative inverse electron-demand Diels-Alder (IED-DA) reaction of *trans*-5-oxocene



Scheme 3

with a water-soluble tetrazine derivative and with a green fluorescence protein encoded with an unnatural tetrazine containing amino acid.[96]

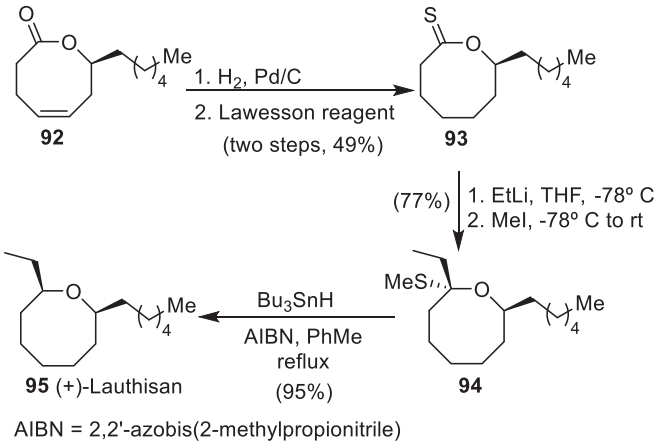
Stereoselective synthesis of (+)-*cis*-lauthisan **95** is accomplished in a three-step approach starting from eight-membered lactone **92** (the synthesis of **92** is described in Section 14.02.6.3). It involves saturation of the oxocene ring and conversion to thionolactone **93** by using Lawesson reagent, treatment with ethyl lithium followed by iodomethane to form intermediate **94** and finally reductive removal of sulfur in the presence of tributyltin hydride and a catalytic amount of 2,2′-azobis(2-methylpropionitrile) (AIBN) in refluxing toluene (Scheme 4).[97]

The synthesis of oxocene Holmes intermediate **102**, which is involved in the formal synthesis of natural (+)-laurencin **103** can be achieved through a multistep transformation of bridged cyclic ether **96** (the synthesis of **96** is described in Section 14.02.6.2). It starts by the removal of the sulfur bridge via Raney nickel reduction in the presence of acetate buffer (pH = 4.6); decarboxylation of the oxocane formed **97** via microwave heating in aqueous DMF to afford ketone **98**; reducing with L-selectride to form a 2:1 epimeric mixture of alcohols **99**; formation of xanthate **100** by reaction with NaH, CS_2 and MeI; elimination reaction carried out by microwave heating in *O*-dichlorobenzene giving a 9:1 mixture of oxocene regioisomers (C5═C6 and C6═C7) **101**; and finally acetate cleavage to provide Holmes intermediate **102** (Scheme 5).[98]

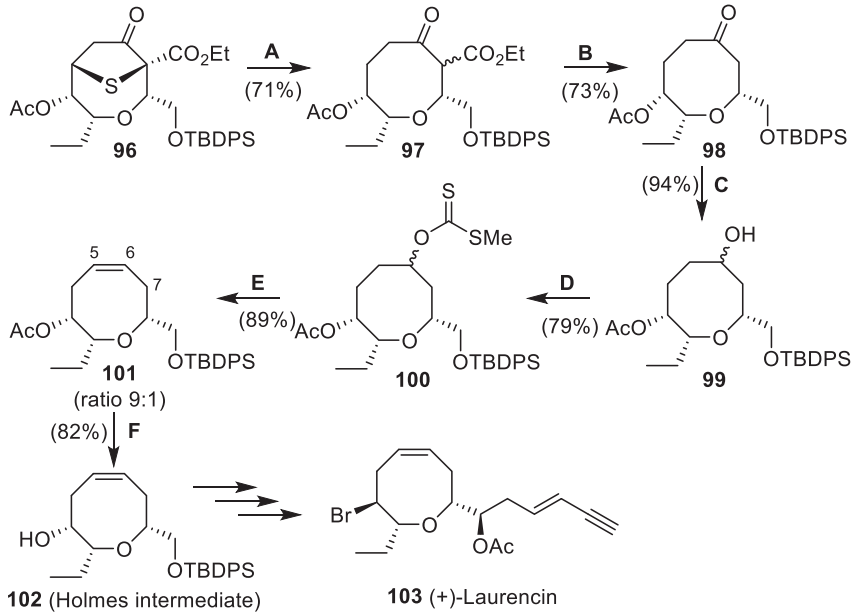
14.02.5 Ring syntheses classified by number of ring atoms in each component

14.02.5.1 Hydroxydithioketal cyclization

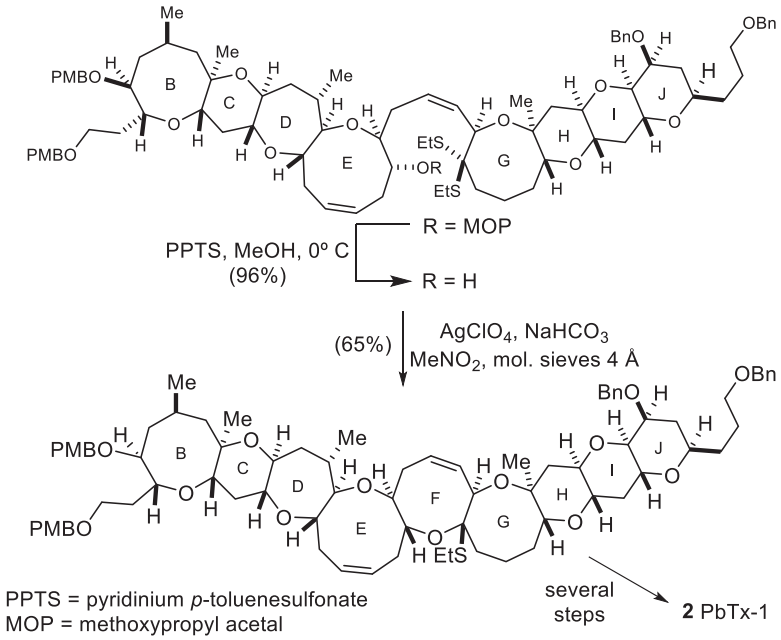
The hydroxydithioketal cyclization approach was applied in the construction of the oxocene ring in some natural fused polycyclic ethers isolated from marine sources. Examples are the formation of the F-ring in the total synthesis of PbTx-1 **2** (Scheme 6)[99,100] and of the B′-ring in the convergent synthesis of the *ent*-ZA′B′C′D′-ring system of MTX-1 **22** (Scheme 7).[101,102]



Scheme 4



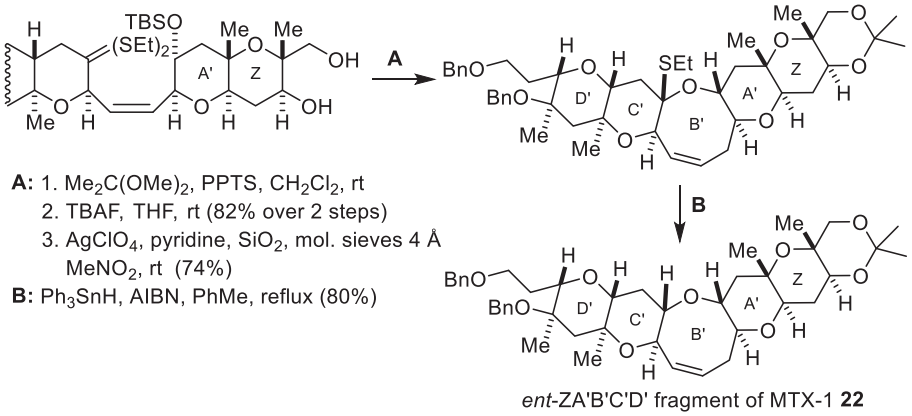
Scheme 5



Scheme 6

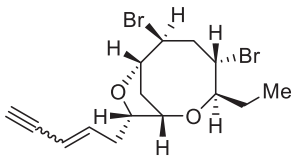
14.02.5.2 Ring-closing metathesis (RCM)

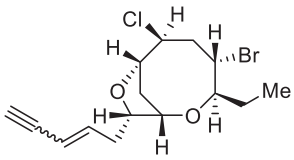
A wide range of natural products bearing an oxocane or oxocene unit were synthesized through RCM approach to obtain their eight-membered heterocycle precursor namely in the synthesis of subunit B of PbTx-1 **2**,[103] subunits B and F of PbTx-1 **2**,[104] subunit H of PbTx-2 **3**,[105,106] subunit B′ of MTX-1 **22**,[107,108] subunit G of YTX **26**,[108–110] subunit E of CTX-3C **15**,[111,112] oxocane unit in the total

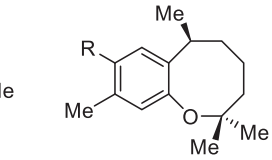


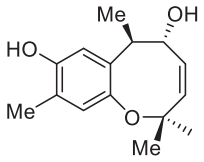
Scheme 7

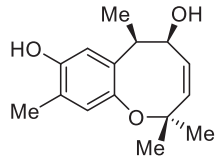
synthesis of natural (3*E* and 3*Z*)-bromofucins **104**, (3*E* and 3*Z*)-chlorofucins **105**,[113] (+)-helianane **82**,[91,114–116] (+)-5-chloro-7,11-helianane **106**,[115] heliannuol A **43**,[117–120] heliannuol G **107**,[117] heliannuol H **108**,[117] heliannuol K **109**,[117–120] (+)-laurencin **103**,[121,122] (+) laurallene **110**,[123,124] (+)-*cis*-lauthisan **95**,[121,125,126] (−)-*trans*-lauthisan **95**,[126] microcladallene B **111**,[127] (+)-pannosallene **112**[123] and also the lactone ring of the natural octalactins A **113** and B **114**.[128]

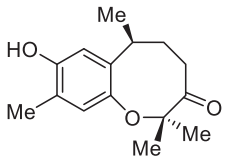

(3*E* and 3*Z*)- **104** Bromofucin

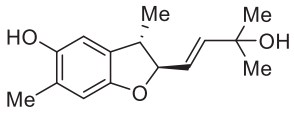

(3*E* and 3*Z*)-**105** Chlorofucin

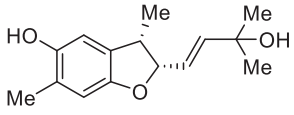

R = H **82** (+)-Helianane
R = Cl **106**
(+)-5-Chloro-7,11-helianane

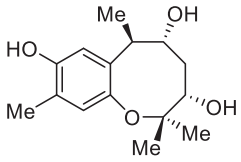

107 Helianuol G
(original structure)

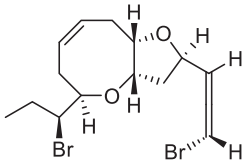

108 Helianuol H
(original structure)

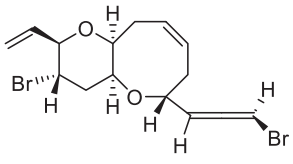

109 Helianuol K

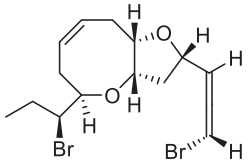

107a Helianuol G
(revised structure)

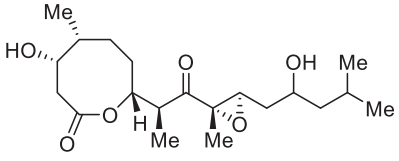

108a Helianuol H
(revised structure)

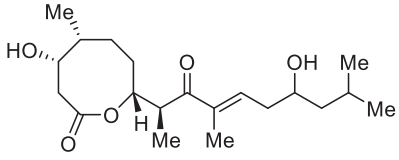

115 Helianuol L


110 (+)-Laurallene


111 (+)-Microcladallene B


112 (+)-Pannosallene


113 Octalatin A


114 Octalatin B

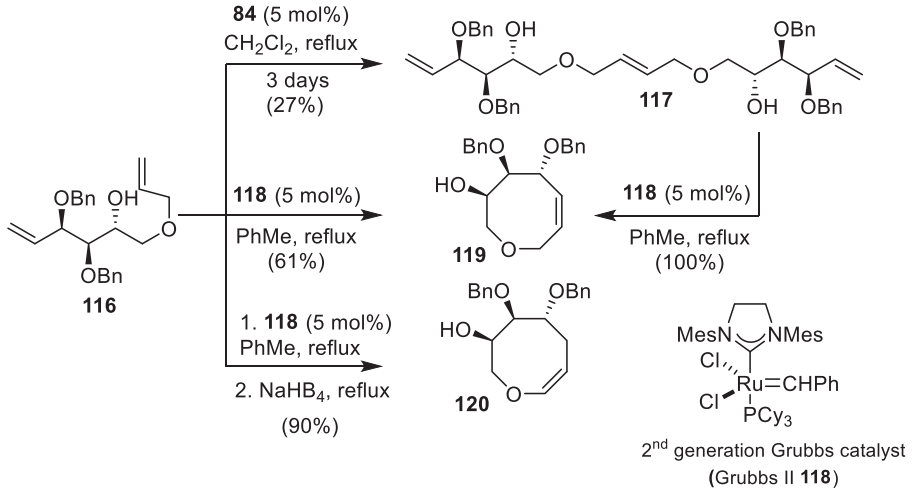
In addition, RCM and other different strategies for the total synthesis of the eight-membered core of heliannuols A **43**, K **109** and L **115** have been reviewed by Chen et al.[129] Another important aspect to refer is that Shishido group has assigned in 2005 benzoxocane structures for heliannuols G **107** and H **108** and in 2006 revised them to substituted dihydrobenzofurans **107a** and **108a**, respectively, with an external *trans*-olefin intact.[130]

Using Grubbs I catalyst **84**, 2-(but-3-en-1-yl)-1-(prop-2-en-1-yloxy)benzenes in dichloromethane at room temperature under argon atmosphere gave 5,6-dihydro-2*H*-benzo[*b*]oxocines[131]; while under refluxing conditions and nitrogen atmosphere 7-(but-3-en-1-yloxy)-8-(prop-2-en-1-yl)flavones gave a couple of oxocine-fused flavones[132] and 3-(but-3-en-1-yloxy)-2-(prop-2-en-1-yl) pyran in argon atmosphere afforded pyran-fused oxocene.[133] Treating hex-5-en-1-yl prop-2-en-1-yl ether **116** with Grubbs I catalyst **84** in refluxing dichloromethane provides only dimer **117** as a single isomer. However, using 2nd generation Grubbs catalyst (Grubbs II, **118**) in refluxing toluene, RCM occurs to give oxocene **119**. Using these conditions, dimer **117** can be converted in oxocene **119**. Additionally, treatment of ether **116** with Grubbs II catalyst **118** followed by treatment with sodium boron hydride, a tandem RCM-isomerization took place to give oxocene **120** (Scheme 8).[134] Biswas et al. also reported that Grubbs I catalyst **84** was not able to promote RCM of 2-(but-3-en-1-yl)-1-(prop-2-en-1-yloxy)benzene derivatives but Grubbs II catalyst **118** provided benzo[*b*]oxocines in good yields. These precursors were used in the synthesis of sesquiterpenes helianane **82**, heliannuol A **43** and heliannuol K **109**.[135]

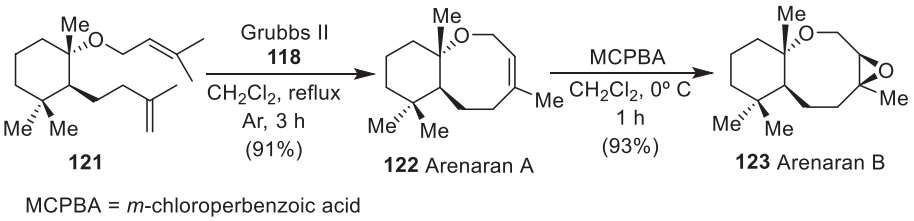
The natural oxocene terpene arenaran A **122** was obtained from the reaction of 1,1,3-trimethyl-2-(3-methylbut-3-en-1-yl)-3-[(3-methylbut-2-en-1-yl)oxy]cyclohexane **121** with Grubbs II catalyst **118** in refluxing dichloromethane under an argon atmosphere for 3 h. Subsequent epoxidation with MCPBA (*m*-chloroperoxybenzoic acid) leds to arenaran B **123** (Scheme 9).[136] Using a catalytic amount of Grubbs II catalyst **118** in refluxing dichloromethane, a couple of 2-allyl-3-(pent-4-en-1-yloxy)pyran derivatives furnished pyran-fused oxocenes.[137]

The diastereoselectivity of RCM of penta-1,4-dien-3-yl ether derivative **124** depended on the ruthenium catalyst used. The reaction occurred for a prolonged reaction time (22 h) and high catalyst loading (30 mol%) for consumption of the starting material. Thus, precursor **124** in the presence of Grubbs I **84** gave rise to *trans*-**125** as the major product (*cis*/*trans* 33:67). In contrast, treatment of **124** with Grubbs II **118** or **126** afforded *cis*-**125** with good diastereoselectivity (**118**: *cis*/*trans* 79:21; **126**: *cis*/*trans* 82:18). Moreover, no diastereoselectivity was found in the RCM of **124** with catalyst **127** (Scheme 10).[138]

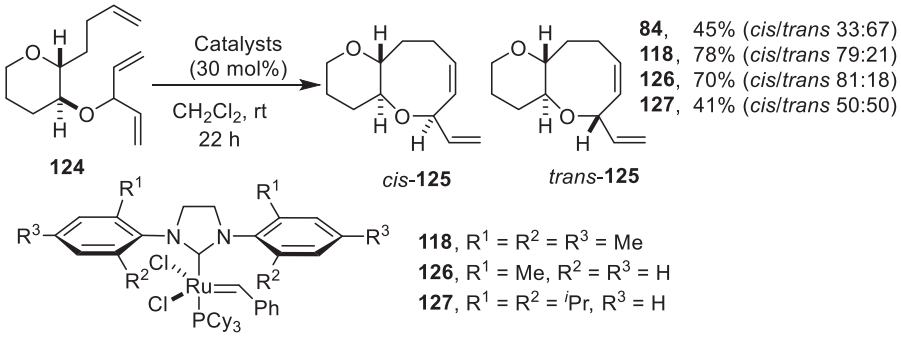
Under nitrogen atmosphere, RCM of 2,4-dimethylquinoline dienes **128** and **129** in toluene occurred efficiently to produce benzoxocenes **130** and **131** in the presence of Grubbs I **84** or II **118** catalysts, respectively, without deactivation of the basic quinoline nitrogen (Scheme 11).[139]



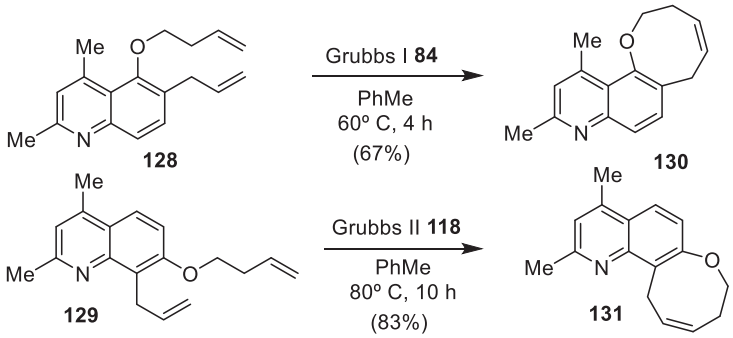
Scheme 8



Scheme 9



Scheme 10



Scheme 11

Two-directional double RCM was used to synthesize bis-oxocine-fused naphthalene **133** starting from 2,6-bis(prop-2-en-1-yloxy)-1,7-bis(but-3-en-1-yloxy)naphthalene **132** in the presence of Grubbs I catalyst **84** in dichloromethane at room temperature under nitrogen atmosphere (Scheme 12).[140]

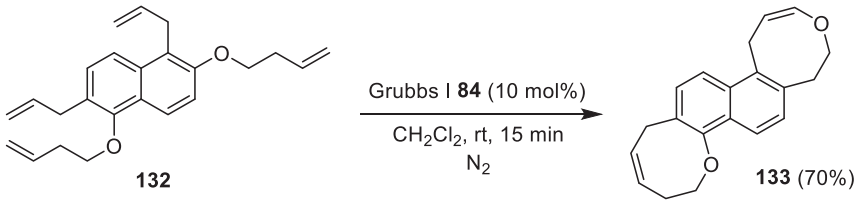
RCM was also used to prepared eight-membered lactones. Protected ester **134** undergo RCM in the presence of Grubbs I catalyst **84** at room temperature overnight, to give the unsaturated lactone **135** in quantitative yield. Meanwhile, RCM of unprotected derivative **136** was only possible with Grubbs II catalyst **118** leading to unsaturated lactone **137**. However, the best conditions for the cyclization process of triene **138** was using Grubbs II **118** as catalyst and $Ti(O^iPr)_4$ as cocatalyst in refluxing dichloromethane producing unsaturated lactone **139** (Scheme 13).[141]

14.02.5.3 Haloetherification of unsaturated alcohols

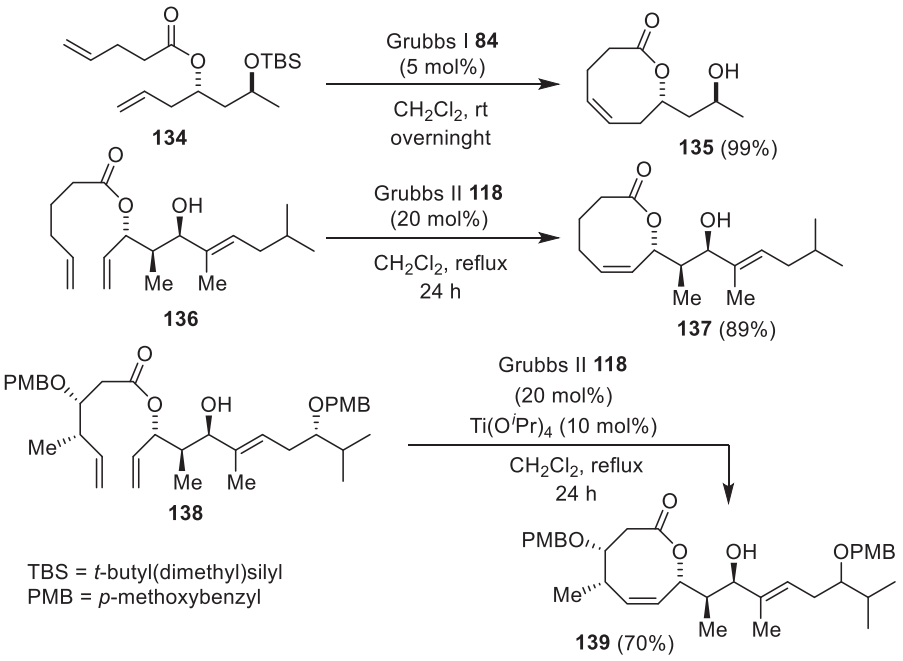
A single study reported iodine-promoted 8-*endo*-oxacyclizations of several dienyl alcohols **140** carried out in the presence of sodium bicarbonate in THF to provide iodinated oxocenes **141** in moderate yields (Scheme 14).[142]

14.02.5.4 Titanocene-promoted cyclizations

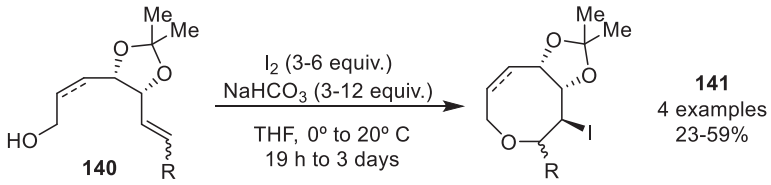
There was a single report studying the radical cyclization of epoxides using titanocene (III) chloride, as the radical source, to construct eight-membered ring ethers. Thus, treating propargyl ether epoxides **142** with Cp_2TiCl (prepared in situ from commercially available Cp_2TiCl_2 and activated zinc dust) in THF under argon gave mainly (5,6-dihydro-2*H*-benzo[*b*]oxocin-5-yl)methanols **143** along with a minor amount of the reduced product **144**. Using the naphthyl analog **145**, only the corresponding naphthyl ether **146** was obtained. Moreover, the reductive opening of allyl epoxide **147** afforded (3,4,5,6-tetrahydro-2*H*-benzo[*b*]oxocin-3-yl) methanol **148** along with the reduced product **149** (Scheme 15).[143]



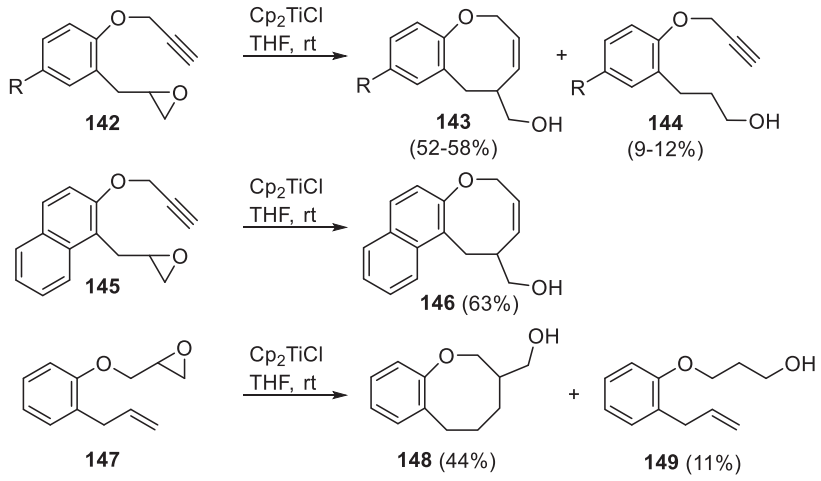
Scheme 12



Scheme 13



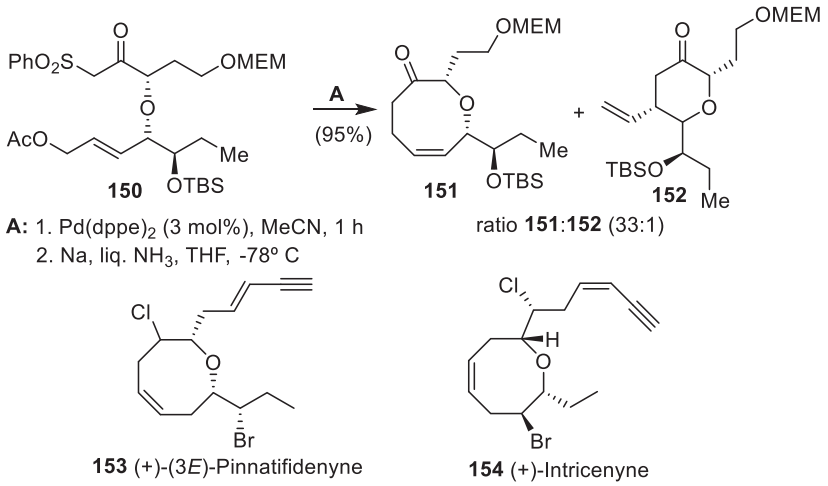
Scheme 14



Scheme 15

14.02.5.5 Palladium-promoted cyclizations

Regioselective intramolecular allylic alkylation of derivative **150** mediated by a palladium(0) catalyst led to the cyclization to an oxocene ring **151** along with small amounts of six-membered cyclic ether **152** (Scheme 16). This strategy was applied in the asymmetric total synthesis of (+)-(3*E*)-pinnatifidenyne **153**.[144] A similar approach was used in the asymmetric total synthesis of (+)-intricenyne **154**.[145]



Scheme 16

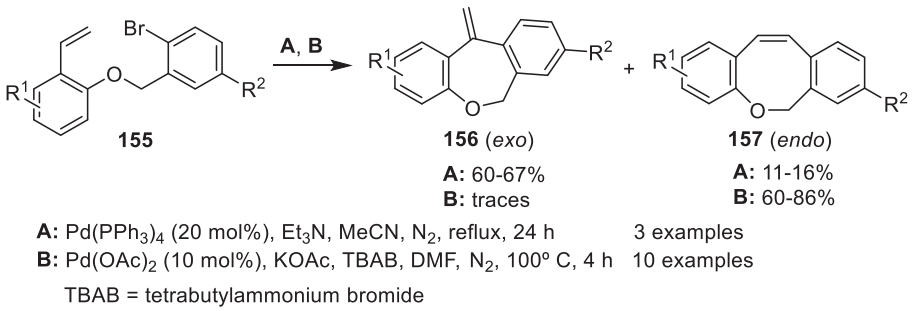
Intramolecular Heck reaction of 1-bromo-2-[(2-vinylaryloxy)methyl]benzene derivatives occurred via 8-*endo-trig* cyclization in the presence of palladium(II) acetate as catalyst, potassium acetate as base, tetrabutylammonium bromide (TBAB) as additive in dry DMF under nitrogen atmosphere to form eight-membered dibenzoxocine compounds.[146] Using similar starting benzene derivatives **155**, cyclization took place in the presence of tetrakis(triphenylphosphine)palladium(0), trimethylamine in refluxing acetonitrile for 24 h, to afford mainly via *exo-trig* mode of cyclization the seven-membered ring derivatives **156** and also 8-*endo-trig* derivatives **157**, as minor products. Using palladium(II) acetate as catalyst, potassium acetate and TBAB as additive in DMF, only the *endo* products were obtained **157** (Scheme 17).[147] Lactone **162** or few dibenzoxocenes **163–166** were synthesized through Heck-type arylation reaction of 2-halo ether (or ester)-tethered 2-(prop-2-en-1-yloxy)benzenes **158–161**, carried out in the presence of palladium(II) acetate, tri-*O*-tolylphosphine and triethylamine in refluxing acetonitrile (Scheme 18).[148]

A series of alkylidendibenzo[*c,f*]oxocines were prepared via Heck-Suzuki tandem reaction of 1-bromo-2-{[2-(alkynyl)benzyloxy]methyl}benzenes with phenyl boronic acid, $Pd_2(dba)_3$●$CHCl_3$ (3 mol%) and Xantphos in a 5:1 mixture of DMF:water for 2.5 h.[149] Further derivatives arise from regioselective reductive Heck 8-*exo-dig* cyclization reaction of the same substrates carried out in the presence of $Pd(PPh_3)_4$ (2 mol%), HCOONa (3 equiv.) at 100 °C in a 5:1 mixture of DMF:water for 3 h[149] or in the presence of $Ni(PPh_3)_2Cl_2$ (10 mol%), HCOONa (3 equiv.) at 90 °C in a 4:1 mixture of DMF:water for 4 h.[150]

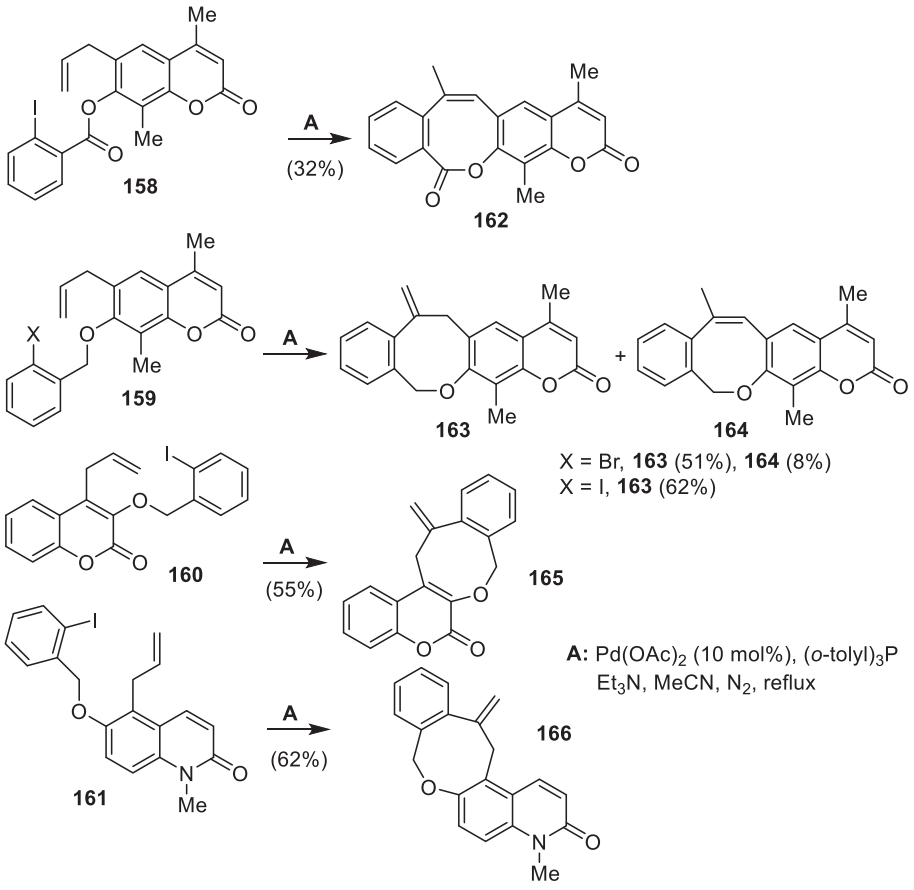
Intramolecular Buchwald-Hartwig etherification of bromoalcohol **167** catalyzed by $Pd(dba)_2$ with Q-Phos and sodium *t*-butoxide provided benzoxocine **168** in very low yield along with debrominated **169** as major product (Scheme 19).[92]

The synthesis of the eight-membered ring of natural (+)-laurendecumallene B **172** involved palladium-catalyzed cyclization of cyclic propargyl carbonate **170** using $Pd_2(dba)_3$ and dppf in the presence of 3 equiv. of water in DMF. This protocol was applied to the synthesis of the precursor **171** of the referred natural product (Scheme 20).[151] Oxidative cyclization of β-citronellol carried out under palladium(II) acetate and hydrogen peroxide catalysis in acetonitrile for 4 h afforded (*Z*)-4,8,8-trimethyl-3,4,5,8-tetrahydro-2*H*-oxocine with high selectivity and conversion (*ca.* 79% and 83%, respectively).[152]

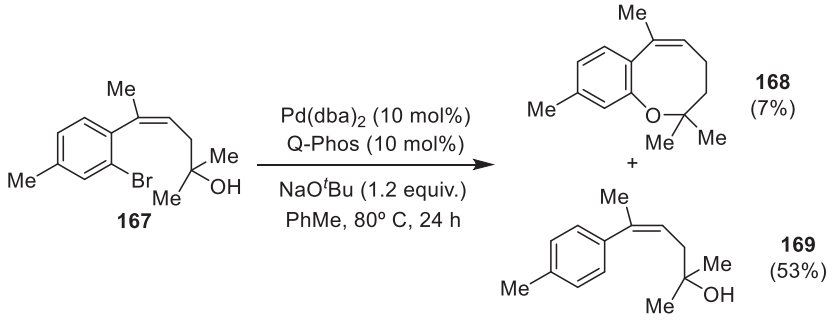
Palladium-mediated cyclizative coupling reaction of γ,δ-allendiols **173** with allyl bromide or 2,3-dibromoprop-1-ene in DMF at room temperature produced β-lactam-fused oxocines **174** in moderate to good yields. It involves 8-*endo* cyclization by attack of the primary hydroxy group to the terminal allene carbon. In addition, oxybromination of γ,δ-allendiols **175** with lithium bromide promoted by a dual catalytic system of palladium(II) and copper(II) in acetonitrile gave brominated β-lactam-fused oxocines **176** (Scheme 21). These reactions occurred in a chemo-, regio-, and diastereoselective way.[153]



Scheme 17



Scheme 18

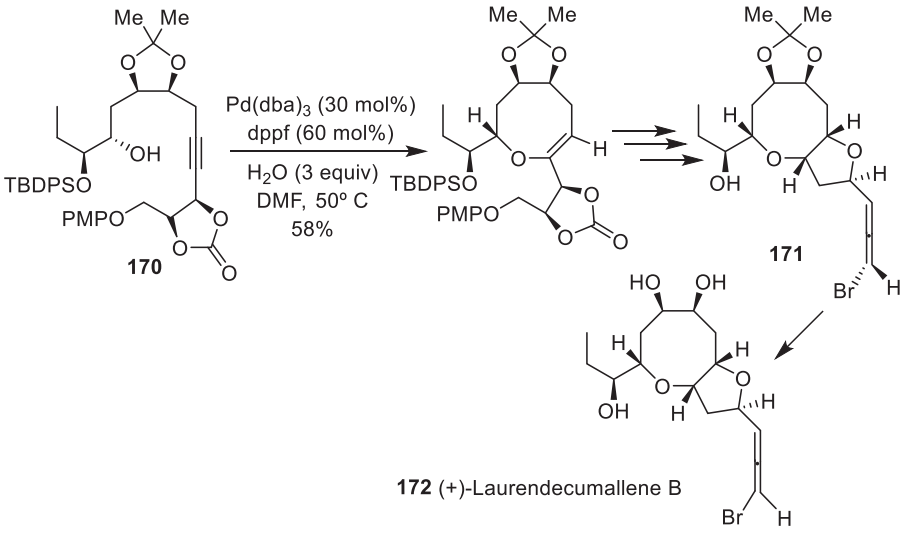


Scheme 19

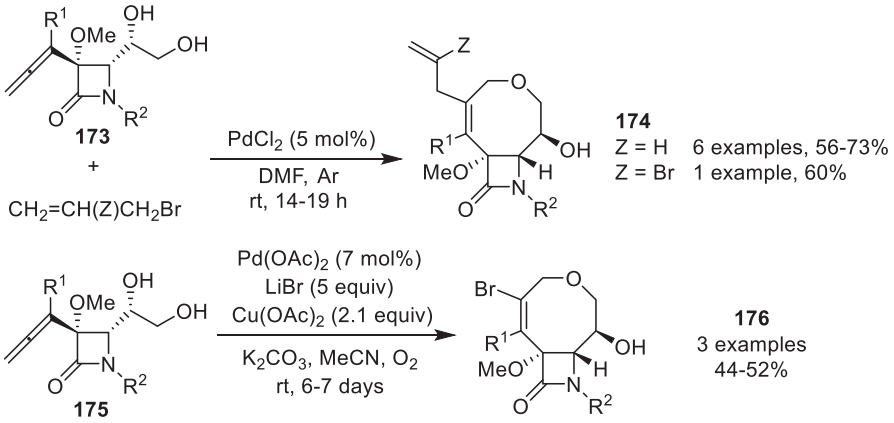
14.02.5.6 Lactonization

The synthesis of the lactone core of natural (−)-octalactin A **113** was accomplished by two different approaches starting from α-diazoketone **177**: (1) treatment with silver benzoate and 4-(dimethylamino)pyridine (DMAP) in dilute tetrahydrofuran to give lactone **178** in 26% yield; (2) photolytic Wolff rearrangement in aqueous tetrahydrofuran provided *seco*-acid **179** which suffered lactonization, after treatment with benzoic anhydride (Scheme 22).[154]

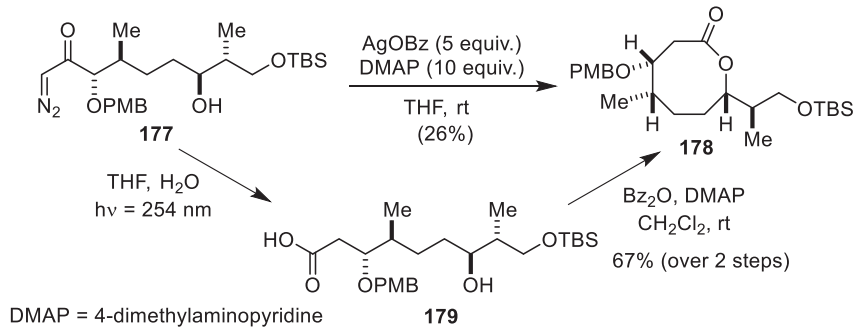
An efficient lactone formation reaction was developed through the use of 2-methyl-6-nitrobenzoic anhydride (MNBA) as a coupling reagent and nucleophilic catalysts, namely acyl-transfer catalysts such as DMAP, 4-pyrrolidinylpyridine and 4-(dimethylamino)pyridine *N*-oxide (DMAPO).[155] Octalactin B **113** was synthesized from the commercially available methyl 3-butenoate and isobutyraldehyde, being the lactonization reaction one of the key-steps. Thus, the eight-membered ring **181** was obtained from the reaction of *seco*-acid **180** with MNBA and DMAP in toluene at room temperature (Scheme 23).[156] This reaction



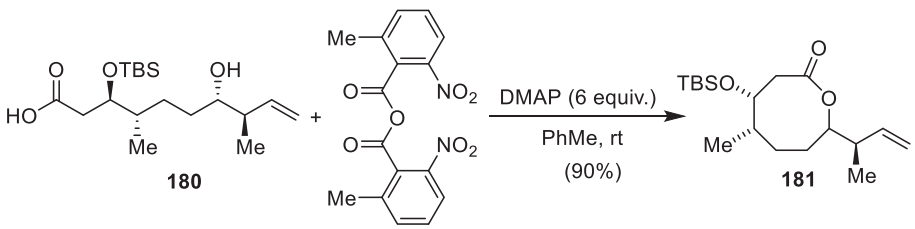
Scheme 20



Scheme 21

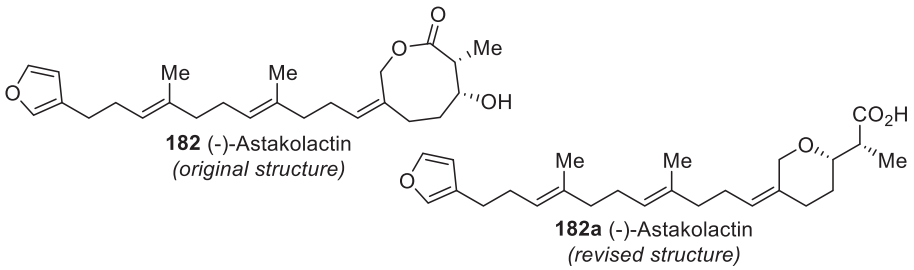


Scheme 22



Scheme 23

conditions were also applied for the synthesis of the lactone core of astakolactin **182**.[157] Meanwhile, 3 years later, the same group revised the structure of astakolactin to a pyran derivative **182a**.[158]



Yamaguchi lactonization was the key step in the stereoselective synthesis of the eight-membered lactone (+)-cephalosporolide D **185**. It involved the reaction of acid **183** in the presence of *N*,*N*-diisopropylethylamine (DIPEA), 2,4,6-trichlorobenzoyl chloride and DMAP in benzene for the construction of the macrolactone **184** and subsequent removal of the protecting group in acid conditions (Scheme 24).[159]

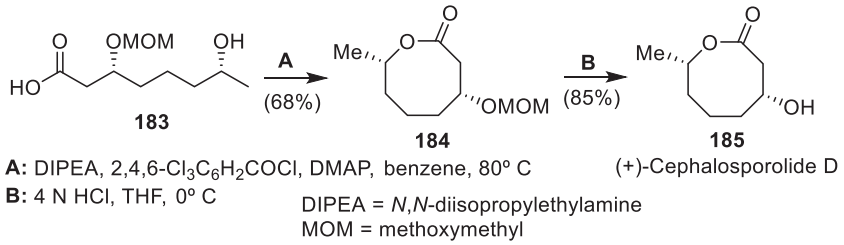
A series of eight-membered lactones **188** were accomplished via [6 + 2] cyclization reaction of (1,6)-amphoteric systems, 2-(oxetan-3-yl)arylaldehydes **186**, with siloxy alkynes **187** mediated by triflimide ($HNTf_2$) in dichloromethane at room temperature (Scheme 25).[160] Oxidative lactonization of 1,7-diol **189** carried out in the presence of a catalytic amount of TEMPO and $PhI(OAc)_2$ afforded eight-membered lactone **190**. This strategy was applied in a concise total synthesis of (±)-isolaurepan **191** (Scheme 26).[161]

14.02.5.7 Intramolecular cyclization methods

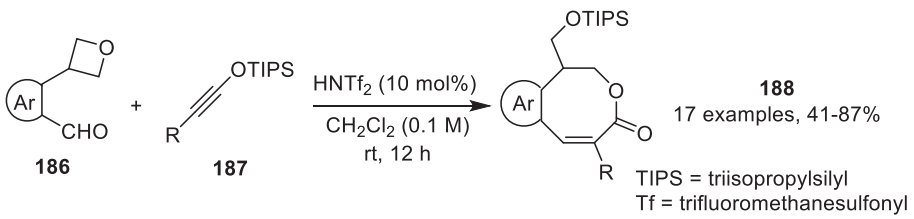
Anodic oxidation of 3,4-dimethoxystilbene bearing *O*-substituted nucleophilic groups (OH or $OSiMe_3$) **192** involved both direct and crossover intramolecular cation-nucleophile reactions to give fused bisbenzopyran **193**, bisbenzofurans **194** and **195** and the unexpected bridged oxocine **196** (Scheme 27).[162]

Total synthesis of natural sesquiterpenoid ansellone B **33b** was accomplished in a 23 steps starting from (+)-sclareolide **197** and (*S*)-carvone **198**. After regioselective protection of the secondary alcohol **199** and regioselective epoxidation substitution in the presence of dimethyldioxirane (DMDO), unstable product **200** was formed which suffered 8-*exo*-*trig* cyclization promoted by PPTS to give the epoxide rearranged side product **201** along with small amounts of the desired oxocane **202**. Finally, oxidation of oxocane **202** mediated by 2-iodoxybenzoic acid (IBX) and desilylation by TBAF furnished ansellone B **33b** (Scheme 28).[163]

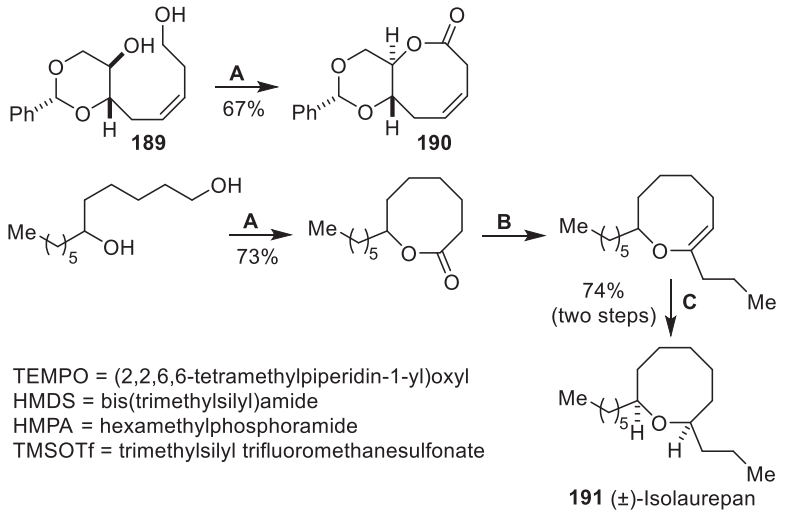
Parent oxocane was obtained in 65% yield from intramolecular dehydration of hepta-1,7-diol promoted by $CuBr_2$ (2 mol%) at 190 °C for 3 h, under argon atmosphere.[164] Intramolecular [4 + 2] cycloaddition reaction of tertiary benzyl alcohols **203** in the



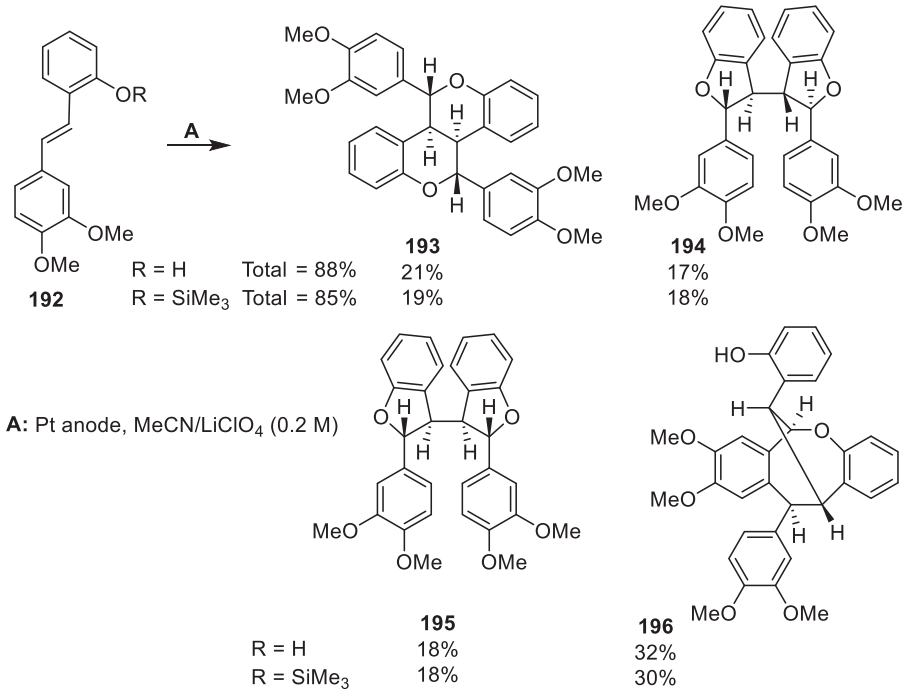
Scheme 24



Scheme 25



Scheme 26

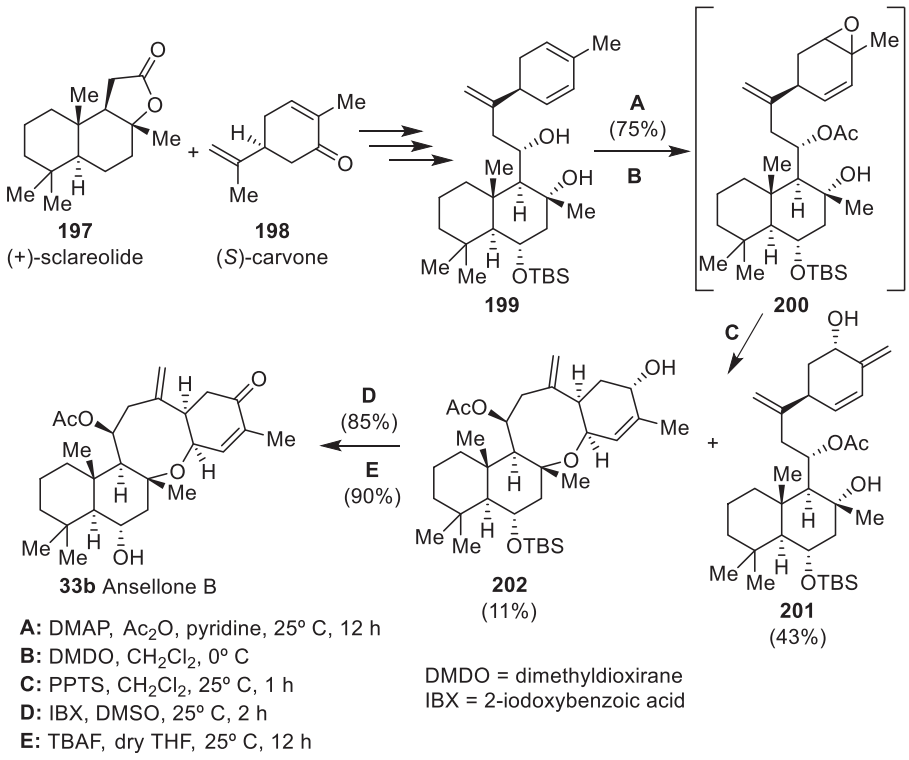


Scheme 27

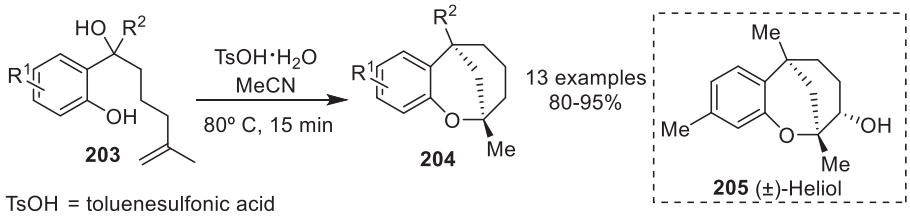
presence of equimolar amount of toluenesulfonic acid hydrate provided adducts **204** in good to excellent yields (Scheme 29). This strategy was used to the first total synthesis of (±)-heliol **205**.[165]

Gold(I)-catalyzed intramolecular dehydrative alkoxylation of ω-hydroxy allylic alcohol **206** led to the formation of α,α′-*cis*-oxocene **207**, which were applied in the formal synthesis of (+)-laurencin **103** (Scheme 30).[166]

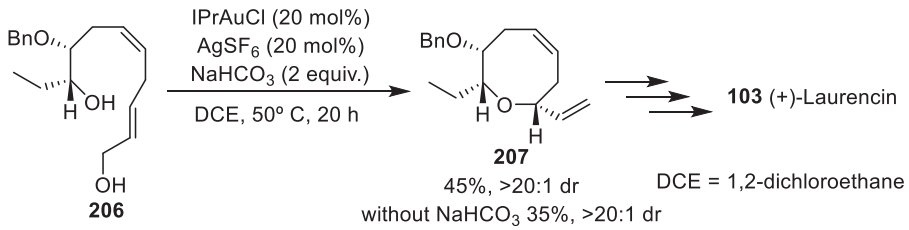
The synthesis of oxocane unit **209** applied in the total synthesis of (±)-lauthisan **95** was achieved through *endo*-cyclization reaction of 1-(5-hydroxyhept-1-yl)-3-pentyl-1-phenylsulfonylallene **208** carried out in the presence of potassium *t*-butoxide in *t*-butanol (Scheme 31).[167]



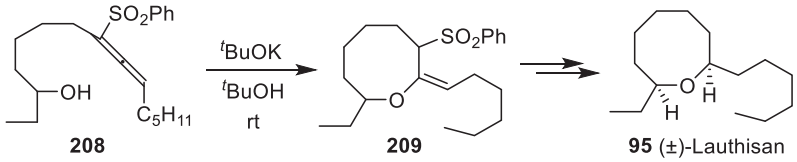
Scheme 28



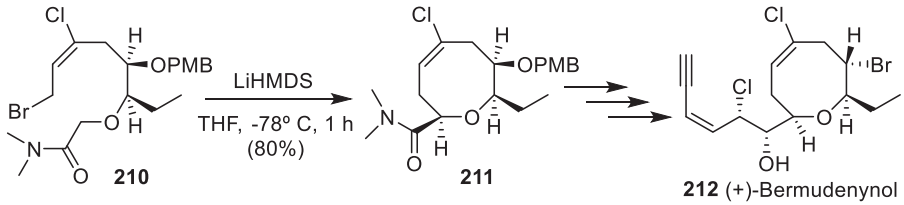
Scheme 29



Scheme 30

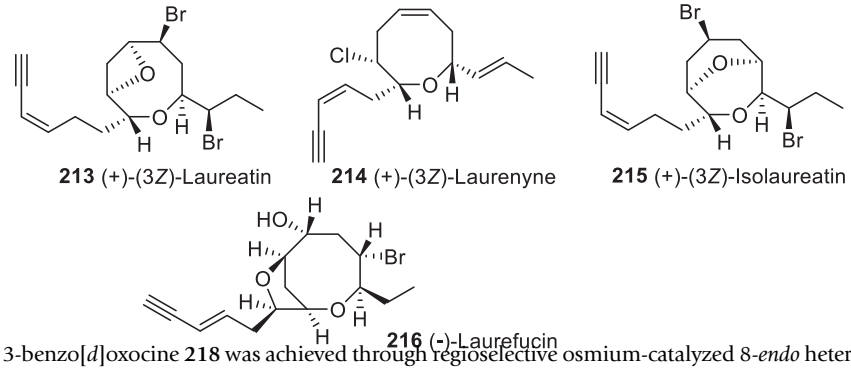


Scheme 31



Scheme 32

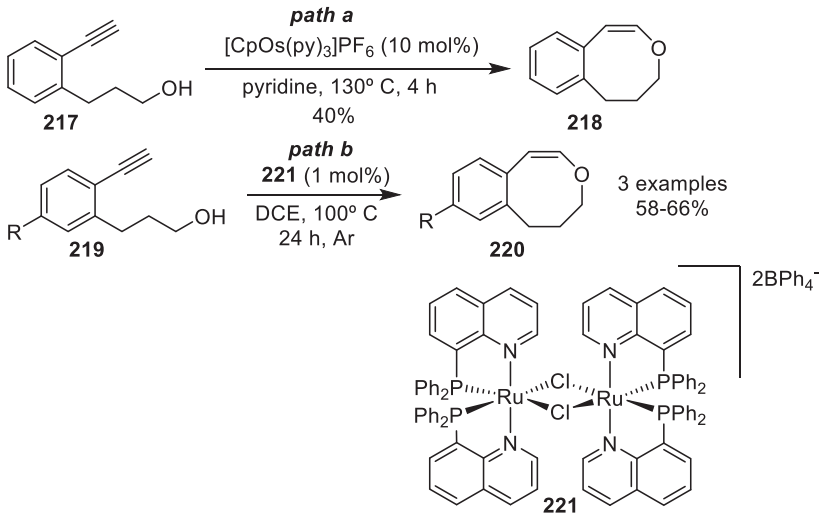
It is through stereoselective intramolecular amide enolate alkylation reaction that (*E*)-allylic bromide **210** cyclize to give the corresponding oxocenes **211**, used in the asymmetric total synthesis of (+)-bermudenynol **212** (Scheme 32).[168] This type of transformation was also applied in the asymmetric total synthesis of (+)-(3*Z*)-laureatin **213**, (+)-(3*Z*)-laurenyne **214**,[169] (+)-(3*Z*)-isolaureatin **215**,[170] and (−)-laurefucin **216**.[171]



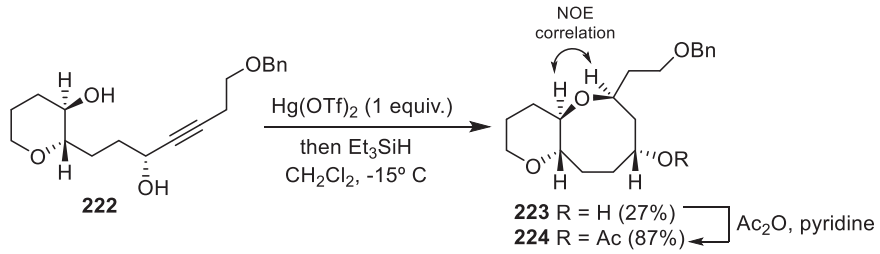
The synthesis of 3-benzo[*d*]oxocine **218** was achieved through regioselective osmium-catalyzed 8-*endo* heterocyclization of 3-(2-ethynylphenyl)propan-1-ol **217** in pyridine at 130 °C for 4 h, in moderate yield (40%) (Scheme 33, path a).[172,173] Further derivatives **220** were obtained from similar substrates **219** under the presence of low loading of a ruthenium complex **221** (Scheme 33, path b).[174]

Regioselective reductive cyclization of alkynyl diol **222** using stoichiometric amount of $Hg(OTf)_2$ and triethylsilane prompted pyran-fused oxocane **223**, via 8-*endo* oxacyclization process (Scheme 34). The structural elucidation of the corresponding acetate derivative **224** was possible through NMR spectroscopy, including COSY, HMBC, HMQC and NOESY correlations of the protons at the C–O–C portion of the oxocane ring.[175]

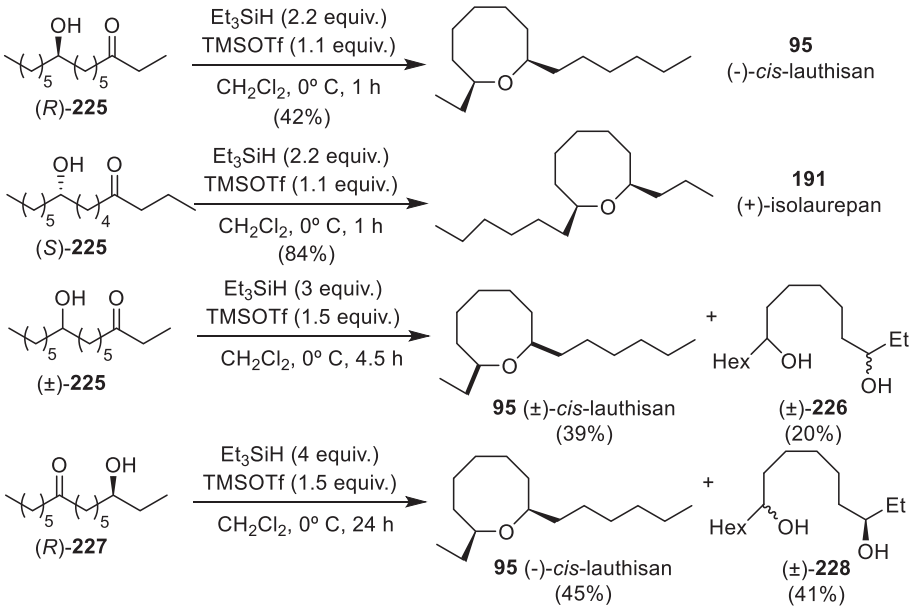
(*R*)-9-Hydroxypentadecan-3-one (*R*)-**225** underwent a diastereoselective reductive cyclization mediated by Et_3SiH and TMSOTf in dichloromethane to furnish exclusively the cyclic eight-membered ether (−)-*cis*-lauthisan **95**. Similarly (*S*)-9-hydroxypentadecan-4-one (*S*)-**225** produced (+)-isolaurepan **191** (Scheme 35).[176] Interestingly, using a similar strategy in the synthesis of (±)-*cis*-lauthisan **95** starting from (±)-9-hydroxypentadecan-3-one (±)-**225**, a mixture of (±)-*cis*-lauthisan **95** and



Scheme 33



Scheme 34



Scheme 35

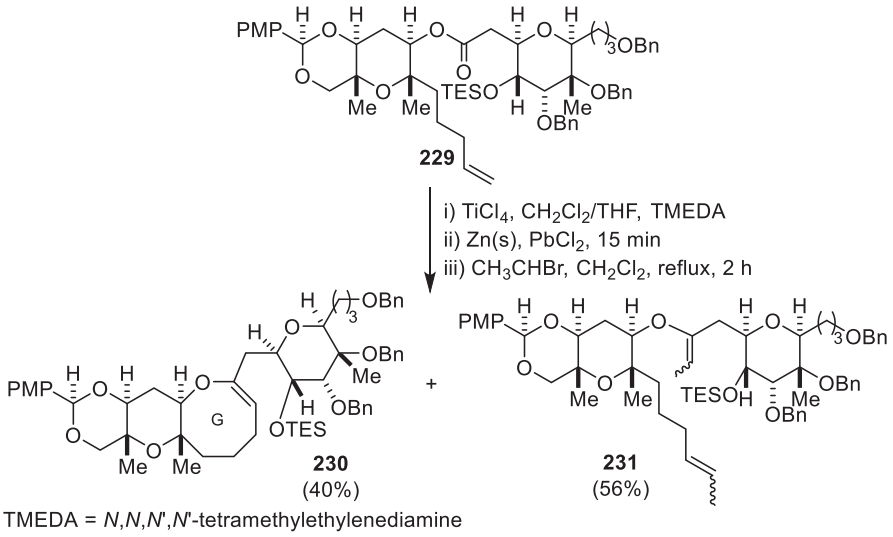
diastereomeric diols (±)-**226** were obtained. Starting from (*R*)-13-hydroxypentadecan-7-one (*R*)-**227**, reductive cyclization provided a mixture of (−)-*cis*-lauthisan **95** and diastereomeric diols **228** (Scheme 35).[177,178]

Olefin-ester cyclization reaction of ester **229**, in a multistep strategy, gave a mixture of the eight-membered ring **230** in 40% yields and the ether **231** in 56% yield (Scheme 36). This synthetic approach was used in the synthesis of the FGHI-ring system of YTX **26** and adriatoxin **30**.[179]

A couple of oxocanes **235** and **236** bearing an exocyclic methylene unit was synthesized via cycloisomerization reaction of 1,8-oxadienes **233** and **234** under catalysis of NHC-Ni complexes, prepared from $Ni(cod)_2$ [bis(cyclooctadienyl)nickel(0)] and [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene] (IPr) or [1,3-bis(2,6-diisopropylphenyl)-imidazolidin-2-ylidene] (SIPr), 1-octene, triethylamine, *p*-anisaldehyde and triethylsilyl trifluoromethanesulfonate (TESOTf) in toluene under nitrogen and anhydrous atmosphere (Scheme 37).[180]

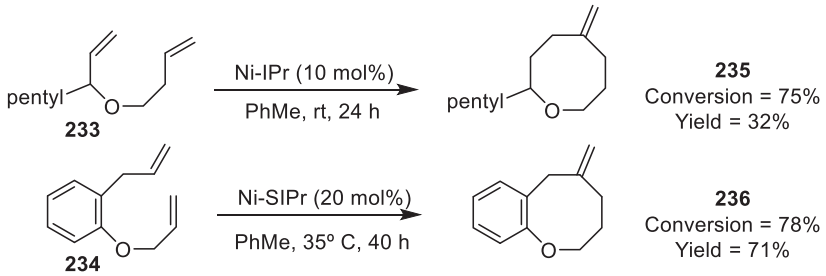
A wide range of methyl 7*H*-dibenz[*b*,*g*]oxocine-6-carboxylates **240** were obtained from a multistep synthesis involving: (i) -solvent-free Morita-Baylis-Hillman (MBH) reaction of 2-phenoxybenzaldehydes **237** with methyl acrylate in the presence of 1,4-diazabicyclo[2,2,2]octane (DABCO) and triethanolamine at room temperature; (ii) treatment of MBH adducts **238** with *N*-bromosuccinimide/dimethyl sulfide (NBS/DMS) in dichloromethane to produce MBH allyl bromides **239**; (iii) Friedel-Crafts cyclization with aluminum chloride in dichloromethane at reflux temperature for 10 min to 2 h (Scheme 38).[181]

One-pot, two-step protocol was applied to the synthesis of benzene-fused eight-membered ketones starting from inactivated terminal alkynes. It involves gold-catalyzed additions of protonated pyridine *N*-oxide to the alkyne triple bonds, generating *N*-alkenoxypyridinium salts, and oxidative cyclization under heating conditions. Thus, using 2-arylethyl propargyl ethers **241** as substrate, the expected ketones **242** were obtained. With naphthyl substrates **243–244**, cyclization can occur in adjacent positions of the aromatic ring giving a mixture of isomers **245–248**. With (pent-4-yn-1-yloxy)benzene **249**, ketone **250** was obtained (Scheme 39).[182]



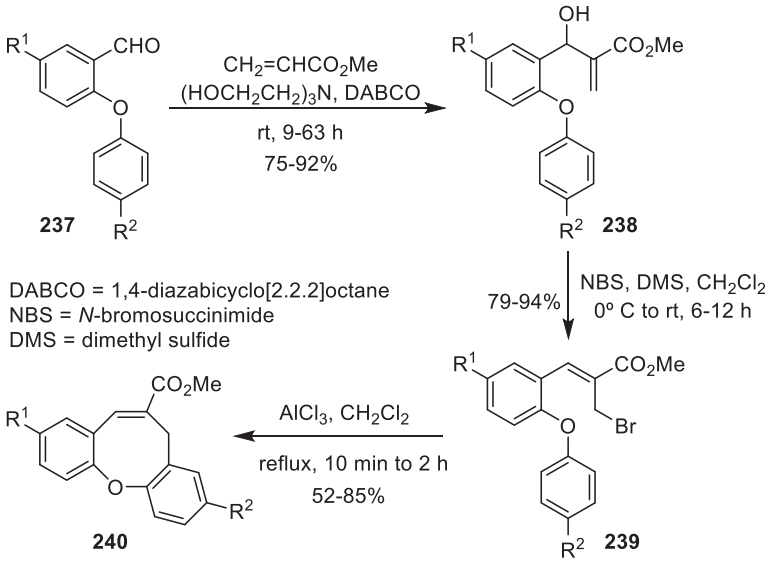
TMEDA = *N*,*N*,*N*',*N*'-tetramethylethylenediamine

Scheme 36



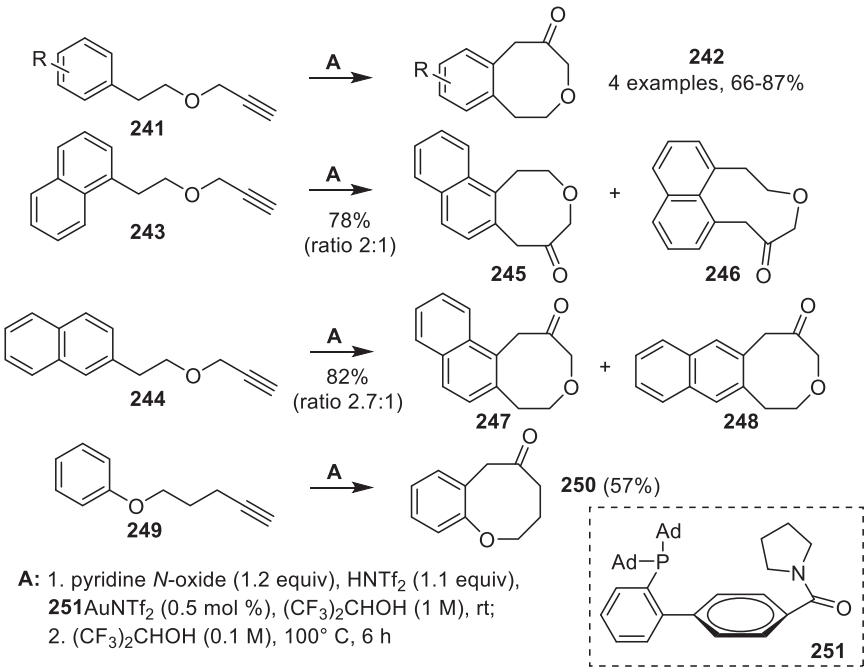
Ni-IPr: 1) $Ni(cod)_2$ [bis-(cyclooctadienyl)nickel(0)], [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene] (IPr), PhMe, N_2, rt, 1 h; 2) 1-octene, triethylamine, *p*-anisaldehyde and triethylsilyl trifluoromethanesulfonate (TESOTf), rt, 45 min.
Ni-SIPr: 1) $Ni(cod)_2$ [bis-(cyclooctadienyl)nickel(0)], [1,3-bis(2,6-diisopropylphenyl)-imidazolidin-2-ylidene] (SIPr), PhMe, N_2, rt, 1 h; 2) 1-octene, triethylamine, *p*-anisaldehyde and triethylsilyl trifluoromethanesulfonate (TESOTf), rt, 45 min.

Scheme 37



DABCO = 1,4-diazabicyclo[2.2.2]octane
NBS = *N*-bromosuccinimide
DMS = dimethyl sulfide

Scheme 38

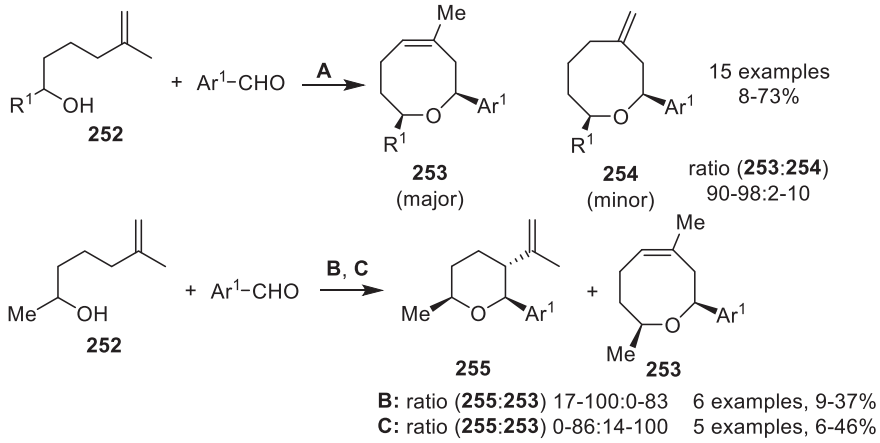


Scheme 39

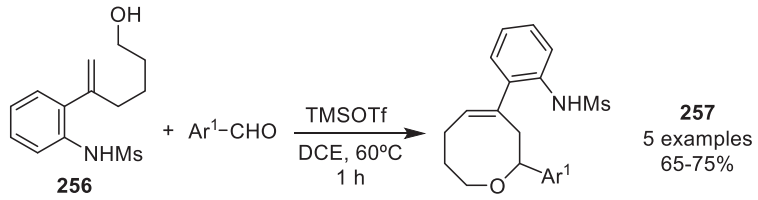
14.02.5.8 Domino/cascade reactions

Several examples of Lewis acids were applied as cyclization promoters for the diastereoselective synthesis of oxocene derivatives. Thus, intermolecular Prins-type cyclization reaction of 1-alkyl-5-methylhex-5-en-l-ols **252** with aromatic aldehydes mediated by TMSOTf provided a range of *endo*-oxocenes **253** as major products along with small amounts of the *exo*-derivatives **254** (Scheme 40).[183] Using the same starting materials **252** in the presence of a combination of *p*-toluenesulfonic acid (*p*-TsOH) (30 mol%) and scandium or dysprosium(III) triflates (10 mol%) afforded a mixture of tetrahydropyrans **254** and few examples of the corresponding oxocene derivatives **253** (Scheme 40).[184]

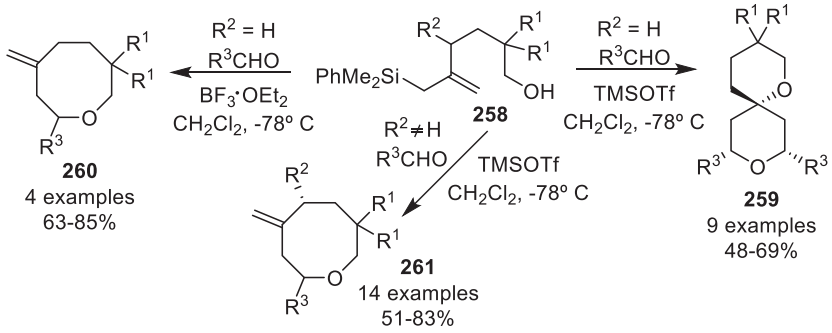
Few examples of benzoxocenes **257** are obtained from aza-ene/Prins cyclization reaction of *O*-aminoaryl alkenols **256** with electron-deficient aryl aldehydes promoted by TMSOTf in DCE (Scheme 41).[185]



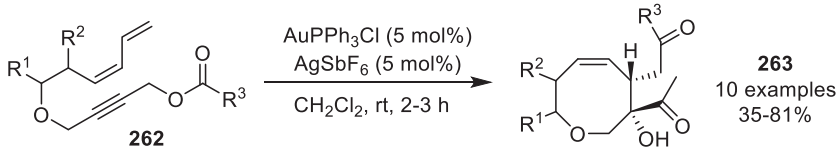
Scheme 40



Scheme 41



Scheme 42



Scheme 43

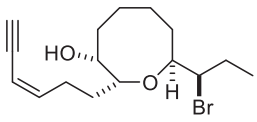
Allylsilyl alcohols ($R^2 = H$) **258** undergo tandem Sakurai-Prins cyclization with aldehydes in the presence of TMSOTf to give mainly dioxaspiroundecane **259** while in the presence of $BF_3{\bullet}OEt_2$ direct silyl-Prins cyclization took place to afford selectively oxocanes **260**. Using substituted allylsilyl alcohols ($R^2 \neq H$) **258** in the presence of TMSOTf, similar oxocanes **261** were obtained (Scheme 42).[186]

A series of (2*Z*,7*Z*)-6-oxo-5,6-dihydro-4*H*-oxocine-3-carbonitriles were obtained in moderate to good yields through DABCO-mediated [4 + 4] domino annulation reactions of ynones with α-cyano-α,β-unsaturated ketones carried out in a 2:1 mixture of ethylene glycol:toluene at 60 °C.[187] Several (*Z*)-1-(3-hydroxy-3,4,7,8-tetrahydro-2*H*-oxocin-3-yl)ethan-1-one derivatives **263** were prompted from cascade reaction of enynyl esters **262** in the presence of $PPh_3AuCl/AgSbF_6$ in dichloromethane at room temperature, involving enynyl ester isomerization and intramolecular [3 + 2] cyclization reactions (Scheme 43).[188]

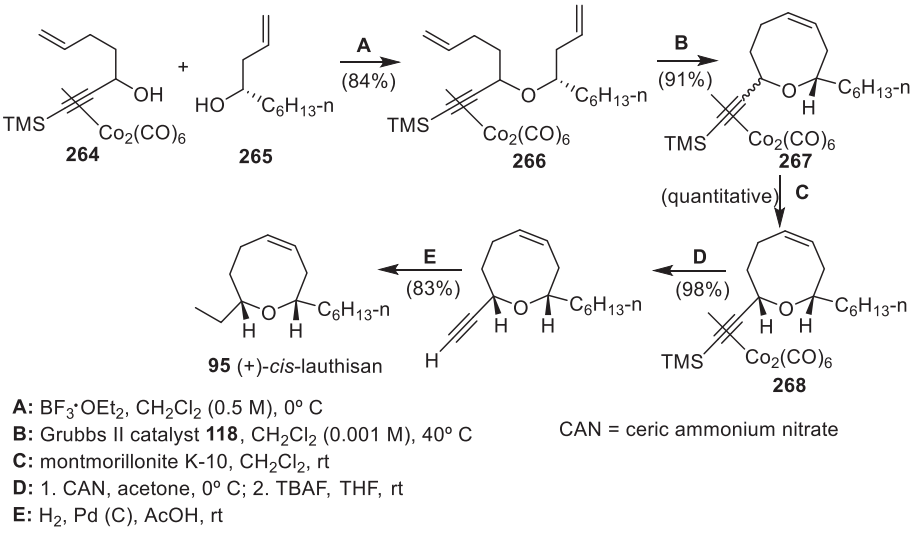
An oxacene $Co_2(CO)_6$-acetylenic complex **268** was prepared by a multistep strategy involving: (1) intermolecular Nicholas reaction of cobalt complex **264** with homoallylic alcohol **265** to obtain unsaturated branched linear ether **266**, (2) RCM to form the cobalt complex cyclic ether **267**, and (3) isomerization mediated by montmorillonite K-10. In addition, cleavage of the TMS protecting group with TBAF and subsequent catalytic hydrogenation provided the natural (+)-*cis*-lauthisan **95** (Scheme 44).[121,125,126] This protocol was also extended to the synthesis of (−)-*trans*-lauthisan **95**[126] and to the eight-membered core of the natural derivative (+)-laurencin **103**.[121]

Other cobalt complexes **270** and **272** were involved in the construction of the eight-membered I-ring in the synthesis of HIJ-fragment[189] and HIJKLM-fragment[190] of natural CTX-1B **9**. Thus, the cyclization of acetylene cobalt complexes **269** and **271** occurs via intramolecular 1,4-hydroxy addition carried out in the presence of $BF_3{\bullet}OEt_2$ in dichloromethane (Scheme 45).

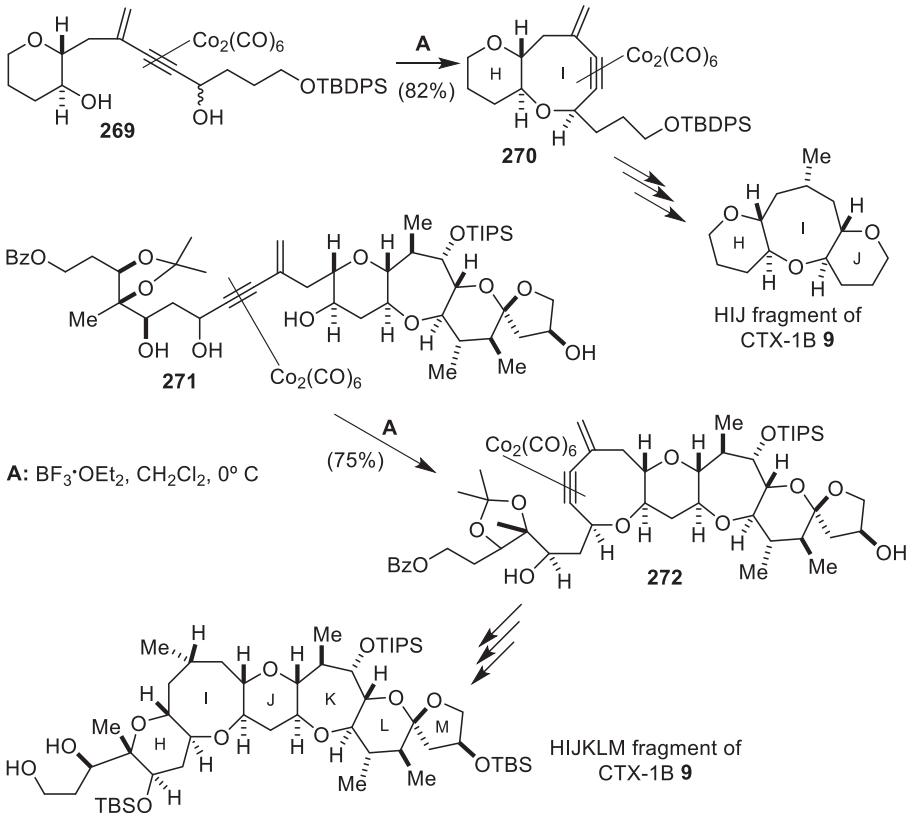
Diastereoselective Brook rearrangement-mediated [3 + 4] annulation reaction of acryloylsilane **273** with 6-oxacyclohepten-2-one derivative **274** and subsequent oxidation (using Davis' oxaziridine) of the enolate formed provided α-hydroxyketone **275**, which suffered oxidative cleavage of the two-atom internal tether to give *trans*-α,α′-disubstituted oxocene **276** (Scheme 46). This strategy was applied in the formal synthesis of (+)-laurallene **110**[191,192] and (+)-prelaureatin **277**.[192]



277 Prelaureatin

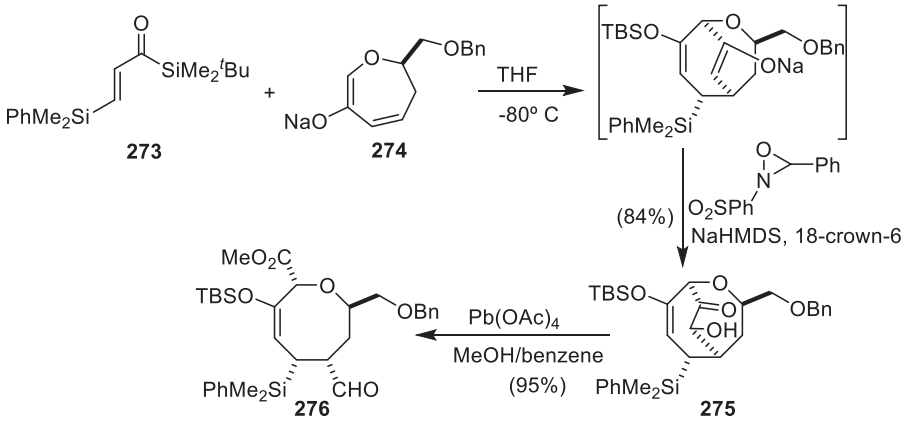


Scheme 44

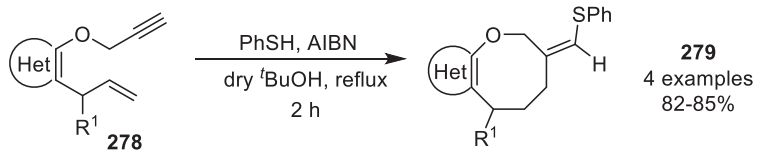


Scheme 45

A wide range of 2-phenylpyrazolo[3,4-*b*]-4,5-dihydrooxocin-4-ones were synthesized via DBU-mediated [4 + 4] domino annulation reactions of ynones with 4-benzylidene-2-phenylpyrazol-3-ones in dichloromethane at room temperature for 10–120 min.[193] Few examples of oxocine-annulated heterocycles **279** arise from sulfanyl radical addition and intramolecular 8-*endo* radical cyclization reactions of enynes **278** with 2 equiv. of thiophenol and the radical initiator AIBN in refluxing dry *t*-butanol (Scheme 47).[194]



Scheme 46



Scheme 47

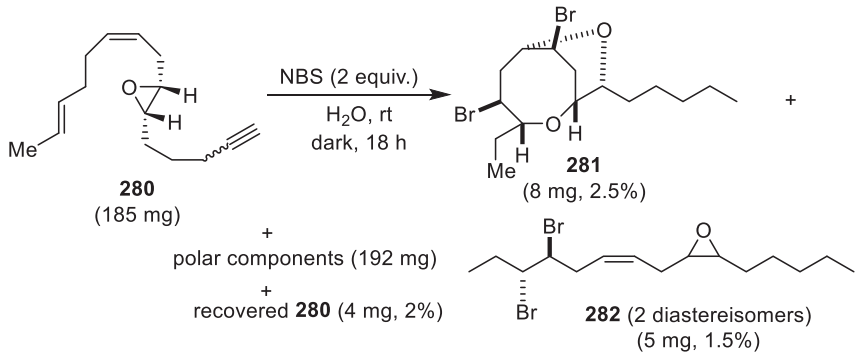
Treating (6*S*,7*R*)-epoxide **280** with two equiv. of NBS under high dilution conditions in water led to (±)-hexahydrolaureoxanyne **281** as a bicyclic medium-ring ether, dibromoepoxides **282**, several polar compounds and recovered of some starting epoxide **280** (Scheme 48). The reaction occurs via intramolecular bromonium ion assisted epoxide ring-opening (IBIAERO) reaction and subsequent bromoetherification of the remaining unsaturation.[195]

Cascade reaction of 2-[(1-methyl-4-oxocyclohexa-2,5-dien-1-yl)oxy]acetaldehyde **283** with 2 equiv. of anilines in dichloromethane furnished highly functionalized 2-oxabicyclo[3.3.1]non-7-en-6-ones **284** (Scheme 49). It involves: (1) condensation of the first equiv. of the amine with aldehyde to form an imine, (2) aza-Michael addition of the second equiv. of the amine, (3) Mannich transannular reaction completed the cyclization process to give the oxocane unit.[196]

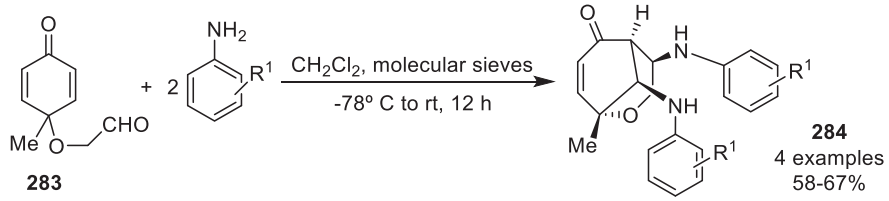
14.02.6 Ring syntheses by transformation of another ring

14.02.6.1 Ring expansions of one atom

BF_3●OEt_2-mediated ring expansion reaction of ketone **285** with TMS-diazomethane at −80 °C followed by to mild acid treatment afforded mainly the eight-membered ketone derivative **286**, along with the regioisomer ketone **287** and spiroepoxide **288**.



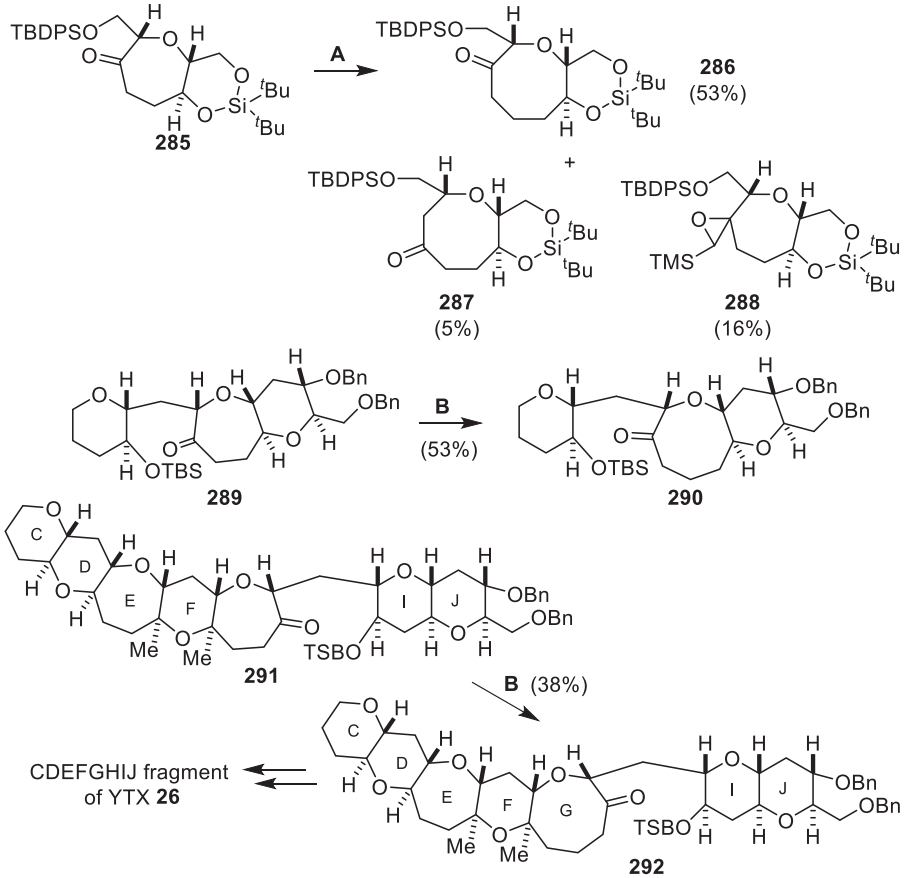
Scheme 48



Scheme 49

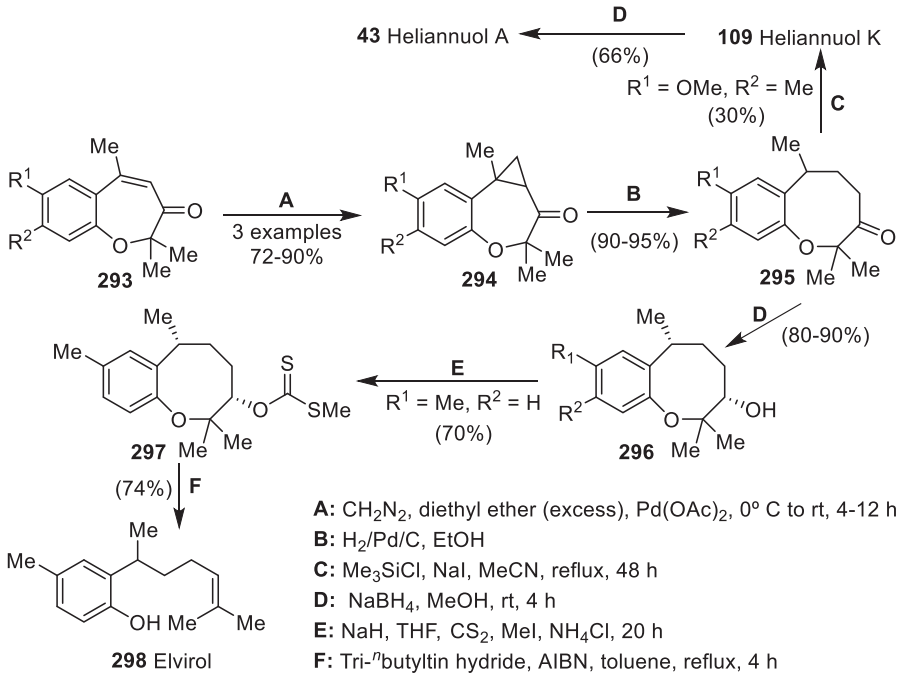
Expansion reaction of ketones **289** and **291** required higher temperature (–40 °C) to achieved the corresponding ketones **290** and **292** (Scheme 50). This methodology was involved in the synthesis of the CDEFGHIJ-ring system of YTX **26**.[197,198]

A study reported the benzoxepane ring enlargement, applied in the synthesis of sesquiterpenes heliannuols A **43** and K **109**. Thus, benzoxopinenones **293** reacted with diazomethane in presence of a catalytic amount of palladium(II) acetate to give cyclopropyl ketones **294**, subsequent catalytic hydrogenation afforded benzoxocanones **295**, which can suffer demethylation (R^1 = OMe, R^2 = Me) promoted by in situ generated iodotrimethyl silane to give heliannuol K **109**. Reduction of **109** with sodium borohydride in methanol afforded heliannuol A **43** (Scheme 51).[93] These transformations were also used for the synthesis of other natural products, namely the bisabolene sesquiterpene elvirol **298**, after reduction of benzoxocanones **295** to benzoxocanols **296**, subsequent transformation into the thionocarbonate **297** and final fragmentation of the eight-membered ring (Scheme 51).[199]



A: 1. $TMSCHN_2$, $BF_3{\cdot}OEt_2$, mol. sieves 4 Å, CH_2Cl_2, -80° C
2. PPTS, CH_2Cl_2/MeOH, rt, then 60°C
B: 1. $TMSCHN_2$, $BF_3{\cdot}OEt_2$, mol. sieves 4 Å, CH_2Cl_2, -40° C
2. PPTS, CH_2Cl_2/MeOH, rt, then 60°C

Scheme 50



Scheme 51

14.02.6.2 Ring expansions of two atoms

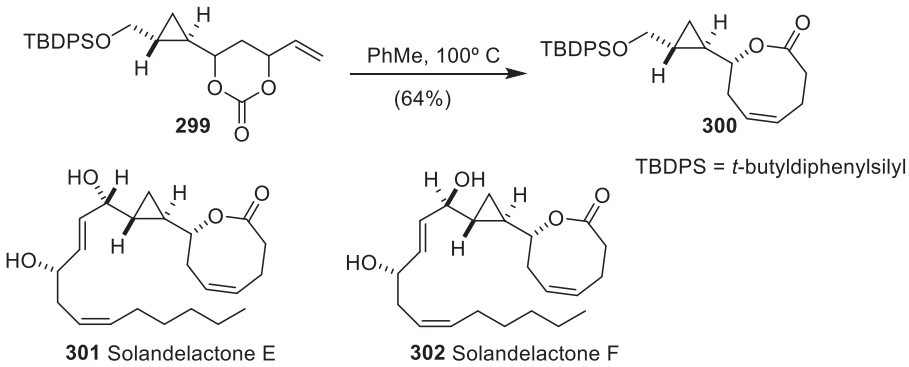
4-[2-(*t*-Butyldiphenylsilanyloxymethyl)cyclopropyl]-6-vinyl-[1,3]-dioxan-2-one **299** underwent Holmes-Claisen rearrangement in hot toluene to afford lactone **300**, intermediate in the total synthesis of natural solandelactones E **301** and F **302** (Scheme 52).[200]

Few examples of sulfur bridged cyclic ethers **304** were prompted via Stevens [1,2]-shift of sulfonium ylides derived from six-membered mixed-monothioacetal precursors **303**, carried out in the presence of a catalytic amount of $Cu(hfacac)_2$ and using toluene or dichloromethane as solvent (Scheme 53). This strategy was applied to the synthesis of Holmes intermediate **102**, involved in the formal synthesis of natural (+)-laurencin **103**.[98]

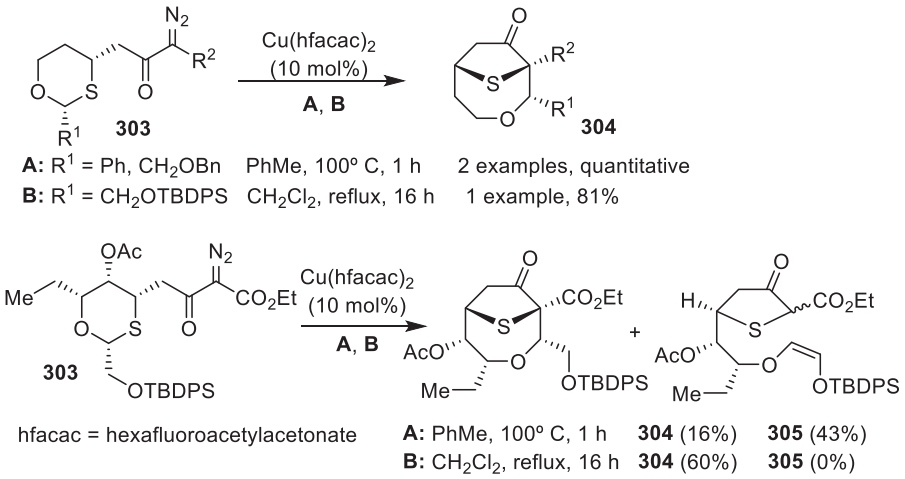
14.02.6.3 Ring expansions of three or more atoms

Regio- and enantiospecific domino reaction of camphor-derived bis(spiroepoxide)-substituted 1-norbornyl triflate **306** in refluxing aqueous ethanol buffered with trimethylamine for 30 days furnished cyclobutane-fused eight-membered cyclic ether **307** (Scheme 54). It involves (1) the formed 1-norbornyl cation undergo an epoxide-based pinacol-type rearrangement to give an hydroxyl epoxide; (2) hydroxy-epoxide cyclization to generate tricyclic β-hydroxy ketone, (3) retro-aldol condensation reaction to form a bicyclic enol and finally keto-enol equilibration to the more-stable trans-fused tautomer.[201]

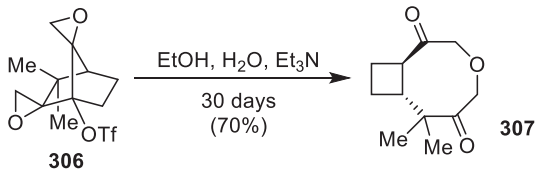
Polycyclic cyclohexadienone **309**, obtained through oxidative dearomatization of bicyclic phenol **308** in the presence of $PhI(OAc)_2$ and potassium carbonate in trifluoroethanol, underwent ring-expansion in the presence of Tf_2O and DTBMP in



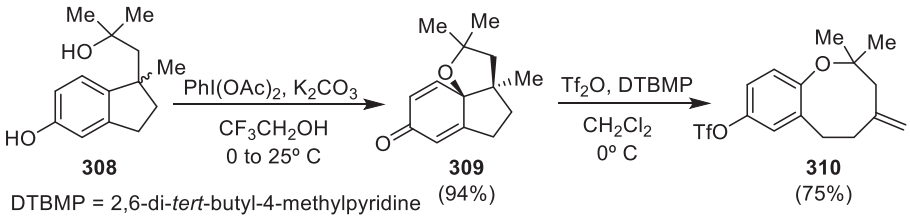
Scheme 52



Scheme 53



Scheme 54

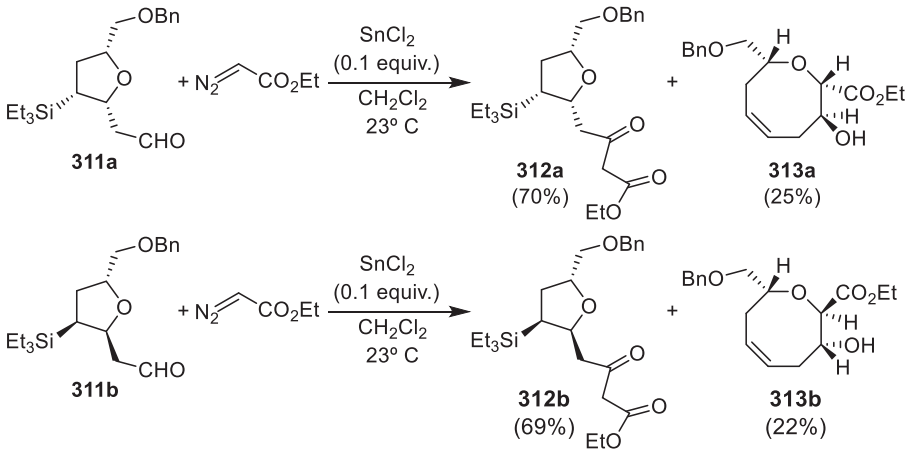


Scheme 55

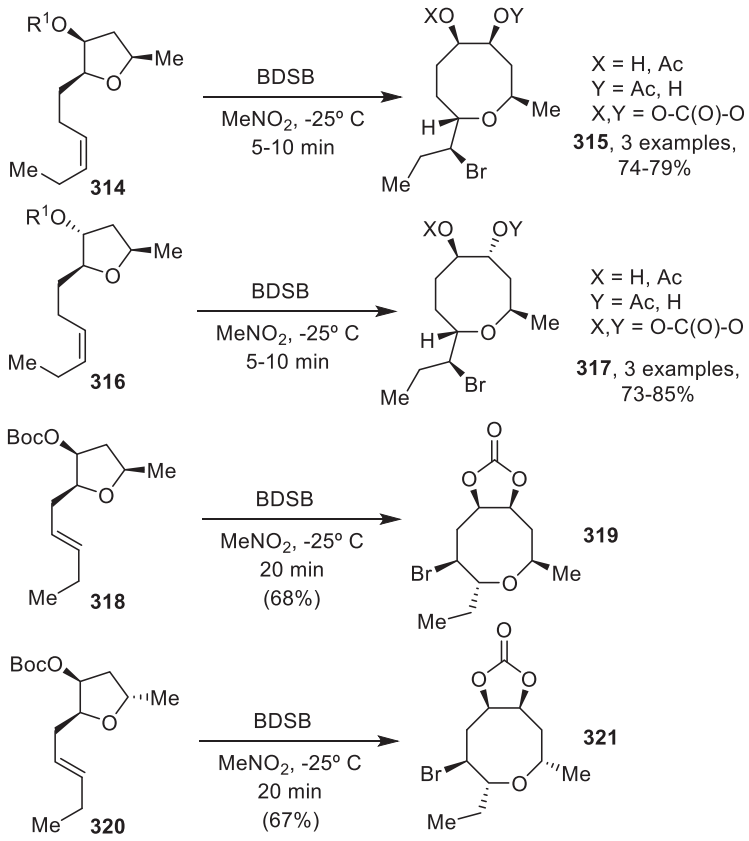
dichloromethane to provide eight-membered derivative **310** (Scheme 55). Low yields were obtained (<25%) when TsOH or Cu $[BF_4]_2$ were used as ring-expansion promoters.[202]

It is through a ring formation-fragmentation-expansion cascade reactions that aldehydes bearing a tetrahydrofuran ring **311a**,**b** reacted with ethyl diazoacetate in the presence of a catalytic amount of anhydrous $SnCl_2$ in dichloromethane at room temperature to provide β-keto esters **312a**,**b** as major products along with small amounts of oxocenes **313a**,**b**, as single diastereomers (Scheme 56).[203]

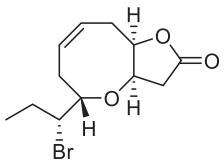
Various 8-membered bromoethers **315**, **317**, **319** and **321** were regio- and stereocontrolled prepared through a ring-expanding bromoetherification protocol, using 1-(3-alkoxy-5-methylfuran-2-yl)hex-3-enes **314** and **316** or 1-(3-OBoc-5-methylfuran-2-yl) pent-2-enes **318** and **320** and bromodiethylsulfonium bromopentachloroantimonate (BDSB) in nitromethane (Scheme 57).[204] This methodology was used in the racemic formal total syntheses of laurefucin **216** and (*E*- and *Z*-)-pinnatifidenyne **153**[205] and in the concise asymmetric total syntheses of microcladallenes A **32** and B **111**, desepilaurallene **322**, laurallene **110**, and prelaureatin **277**.[206]



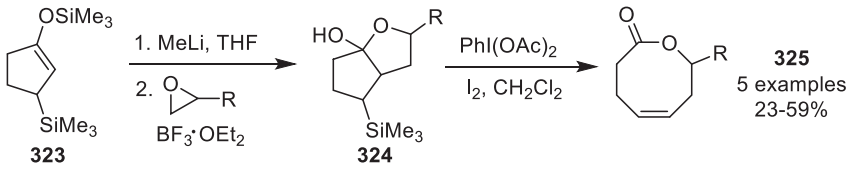
Scheme 56



Scheme 57



322 Desipilaurallene



Scheme 58

Eight-membered lactones **325** were synthesized in moderate yields from the reaction of β-silyl ketone enolates **323** with MeLi in THF, subsequent treatment with epoxides and $BF_3{\bullet}OEt_2$ in THF to yield the desired hemiketals **324** and finally, addition of $PhI(OAc)_2$ and iodine in dichloromethane (Scheme 58). One of these lactones was applied in the stereoselective total synthesis of (+)-*cis*-lauthisan **95**, previously described in Section 14.02.4.[97]

14.02.7 Syntheses of particular classes of compounds and critical comparison of the various routes available

As described along this chapter, a huge number of publications have emerged during the last decade focusing the eight-*O*-membered heterocyclic chemistry. Among the impressive number of methodologies developed, we can mention those dedicated to the synthesis of several marine natural products with unusual and complex structures such as PbTxs, MTX, CTXs and YTXs as well as some natural derivatives extracted from terrestrial origin, namely, heliannuols, pysalins, lauthisan and related derivatives. In fact, seven different routes have been established concerning the total synthesis of natural oxocane derivative lauthisan.

RCM was the most popular approach to construct the eight-membered ring and used as the key reaction in the synthesis of many types of natural compounds, or their precursors. Several reactions promoted by palladium catalysts also deserved special attention in the synthesis of several natural eight-membered oxacycles. Regio- and diastereoselectivity were achieved in the three-carbon ring-enlargement of tetrahydrofuran derivatives assisted by metals such as tin and antimony.

14.02.8 Important compounds and applications

The pharmacological importance of eight-*O*-membered heterocycles among the scientific community is demonstrated by the large number of reviews and original papers related to this topic, published every year.

Extensive studies have been devoted to the toxicology of dinoflagellate toxins such as PbTxs, MTX, CTXs and YTXs, with environmental and human impact. Their molecular mechanisms of action were compiled and described in several reviews (see Section 14.02.1), which can be complemented with the information provided in CHEC III. Here, it is our intention to give a brief presentation on the main therapeutic applications of natural eight-*O*-membered heterocyclic compounds, providing some of the most relevant results. It is noteworthy to mention that no synthetic derivative was evaluated in any biological assay.

Ansellone C **34** showed moderate antitumor activity against A549 (non-small cell lung cancer) and K562 (human leukemia) cell lines with LC_{50} values of 3.9 and 4.5 μM, respectively, when compared with the positive control doxorubicin (LC_{50} of 1.1 and 1.5 μM, respectively). No antibacterial activity was observed against *Staphylococcus aureus* and *Proteus hauseri*.[49]

Antistaphylococcal activity against a panel of multidrug and methicillin-resistant *S. aureus* was tested for eight-membered cyclic ethers **36–41**. Derivatives **36** and **40** did not show any activity at 128 mg/mL, although the remaining compounds exhibited significant antistaphylococcal activity, with minimum inhibitory concentrations (MICs) in the range of 8–256 mg/mL. Derivative **37** was the most active one (MIC 8–16 mg/mL) probably due to the presence of the two acetyl groups that improves its cellular bioavailability by being more lipophilic.[51]

The antioxidant activity of methyl 3,4,5,8-tetrahydro-2*H*-oxocine-5-carboxylate **42** were evaluated and compared to α-tocopherol and the synthetic antioxidants butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA). Similar 1,1-diphenyl-2-picrylhydrazyl (DPPH) and 2,2′-azino-bis-3-ethylbenzothiozoline-6-sulfonic acid (ABTS) radical scavenging activities were observed for compound **42**, BHA and BHT but slightly higher than α-tocopherol. For the anti-inflammatory assays, compound **42** exhibited higher inhibitory activity against cyclooxygenase-1 (COX-1, IC_{50} 0.92 mg/mL) than cyclooxygenase-2 (COX-2, IC_{50} 1.05 mg/mL) isoform. No significant differences were recorded for the in vivo 5-lipoxidase (5-LOX) inhibitory activity of derivative **42** (IC_{50} 0.95 mg/mL) and the control ibuprofen (IC_{50} 0.93 mg/mL).[52]

Some studies have been carried out on the isolation of sunflower constituents with biological activity, with special emphasis on phytotoxicity, an indication for the possible allelopathic activity of sunflower. Heliannuol A **43** have been tested in the etiolated wheat coleoptile bioassay and showed high inhibitory activity on coleoptile elongation at 10^{-3} M, with a value of 85% (very close to the value of the commercial herbicide logran, 93%), and of 50% at 3×10^{-3} M concentration, but the activity decreased significantly with dilution. Derivative **43** was also selected for the evaluation of phytotoxicity on tomato seed growth, in terms of percentage inhibition of germination and shoot and root length, revealing strong inhibitory effects, with activities similar to that of the herbicide logran.[53,54]

A great number of *seco*-steroids named physalins are widely used in folk medicine in many tropical countries around the world. Its known pharmacological applications are antioxidant, anti-inflammatory, antimicrobial, antitumor, sedative, among others. Herein, we will describe the therapeutic potential of the eight-*O*-membered physalins evaluated during the last decade.

Immunomodulatory activities of physalins B **45**, F **48** and G **49** in lymphocyte proliferation, cytokine production and in transplantation were studied. The addition of physalins B **45**, F **48** and G **49** to concanavalin A-activated splenocyte cultures induced a concentration-dependent inhibition of proliferation. Physalin B **45** also inhibited IL-2 production by concanavalin A-activated spleen cells. Rejection of allogeneic heterotopic heart transplant was delayed in mice treated with physalins B **45**, F **48** or G **49**.[56]

The immunosuppressive effect of physalin H **50** on T cells both in vitro and in vivo were also evaluated. The results point out that the immunosuppressive activity might be attributed to the suppression of T cell activation and proliferation, the modulation of Th1/Th2 cytokine balance and the induction of HO-1 in T cells.[66]

The activity of physalin F **48** was investigated in mice models of collagen-induced arthritis and allergic airway inflammation. Oral treatment caused a marked decrease in paw edema and joint inflammation while no effects were observed in mice with allergic airway inflammation. In addition, a different inhibitory mechanism is proposed for physalin F **48** when compared with that of glucocorticoids.[58]

Topic anti-inflammatory potential of physalin E **47** was demonstrated in acute and chronic models of dermatitis induced in mouse ear.[62]

The antimalarial activity of pysalins B **45**, D **46**, F **48** and G **49** was evaluated using in vitro assays against *Plasmodium falciparum*. Although these physalins exhibited antiplasmodial activity, lower cytotoxicity was recorded when compared to the standard antimalarial drug, mefloquine.[59]

The inhibitory effects of some physalins on nitric oxide (NO) production induced by lipopolysaccharide (LPS) in macrophages were tested. Physalin X **58** exhibited a significant inhibitory effect against NO production with an IC_{50} value of 68.50 ± 1.51 μM (positive control hydrocortisone, IC_{50} 58.79 ± 3.32 μM).[70] Another study indicated that physalin F **48** possessed the strongest effect, with an IC_{50} of 0.33 ± 0.17 μM. Pysalins A **44**, B **45**, and O **60** also showed strong inhibition with IC_{50} ranging from 0.84 to 17.11 μM. Moderate activities were observed for physalins Y **61** and Z **62** and 3β-hydroxy-2,3-dihydro-4,7-didehydrophysalin B **63**, which were close to hydrocortisone (IC_{50} 64.34 ± 7.49 μM).[71] Other papers reported the anti-inflammatory potential of physalins A **44**, G **49**, L **59**, O **60**[74] and of physalins B **45** and F **48**.[90]

The antileishmanial activity of physalins B **45**, D **46**, F **48** in vitro and in vivo in models of cutaneous leishmaniasis was evaluated. For the in vitro assays, physalins B **45** and F **48** were able to reduce the percentage of leishmania-infected macrophages and the intracellular parasite number at concentrations non-cytotoxic to macrophages. For the in vivo assays, physalin F **48** reduced the lesion size, the parasite load and histopathological alterations in the infected mice.[63]

An interesting study was undertaken to evaluate a new pharmacological property of physalins B **45**, D **46**, F **48** and G **49** in inflammatory and centrally mediated pain tests in mice. The results suggested that physalins present antinociceptive properties associated with central but not anti-inflammatory events.[60]

Several in vitro and in vivo antitumor activity studies were performed for physalins. Thus, physalin B **45** and D **46** displayed considerable cytotoxicity against several cancer cell lines [B-16 (murine skin), HCT-8 (human colon), PC3 (human prostate), MDA-MB-435, MDA-MB-231 and MCF-7 (human breast), K562, CEM and HL-60 (human leukaemia)], showing IC_{50} values of 0.58–15.18 μg/mL for physalin B **45**, and 0.28–2.43 μg/mL for physalin D **46**. The antitumor activity of both compounds was confirmed in vivo using mice bearing sarcoma 180 tumor cells.[61] Physalins B **45**, D **46**, F **48**, J **52**, U **53** and W **54** were tested against a panel of human cancer cell lines [A549, ZR751 (estrogen receptor positive breast cancer), A431 (EGFR overexpressing skin cancer), LNCAP (AR-dependent prostate cancer), HCT-8, PC-3, KB (nasopharyngeal carcinoma), KB-VIN (vincristine-resistant KB subline)]. The results showed that physalins B **45**, D **46**, F **48** displayed strong cytotoxicity against most of the cell lines with EC_{50} values lower than 3 μg/mL. However, physalin B **45** showed moderate activity against LNCAP and A549, and physalin D **46** against KB-VIN tumor cell lines. In addition, physalin W **54** was only slightly active against 1A9 and physalin J **52** only against A431 cell lines. Physalin U **53** showed modest activity against all human tumor cell line panel.[64] Other paper reported that physalin B **45** showed the highest cytotoxic activities against HeLa (human cervical), SMMC-7721 (human hepatoma) and HL-60 tumor cell lines while physalins A **44**, D **46**, D_1 **67**, L **58** and X **58** show moderate cytotoxic activities.[78] Physalins B **45**, F **48** and J **52** were evaluated for cytotoxicity against human HL-60, SMMC-7721 (hepatoma cell line), A-549, MCF-7 and SW-480 (colon cancer cell line) and displayed potent cytotoxicity ($IC_{50} < 5$ μM) while physalin V **70** exhibited a modest cytotoxicity.[83] High cytotoxicity was observed for physalin H **50** against HXT-116 (human colorectal carcinoma) and NCI-H460 (human non-small cell lung cancer) cells but weak activity for physalins A **44**, B **45**, D **46** and F **48**.[88]

Physalins A **44** and B **45** significantly inhibited the growth of two androgen-independent cell lines CWR22Rv1 and C42B, induced apoptosis and decreased androgen receptor expression.[73] Other studies referred that physalin A **44** also induced cytotoxic effects in human melanoma A375-S2 cells[75] and human fibrosarcoma HT1080 cells[76] and the selective cytotoxicity of physalin B **45** for human melanoma A375 cells[67] and HXT-116 cells,[89] of physalin F **48** for human breast T-47D carcinoma[86] and of 7β-ethoxylisophysalin C **73** for PC-3 cancer cell lines.[84]

The phase II enzyme quinone reductase plays an important role in anticancer, detoxification pathways and antioxidant defense. From the tested compounds, physalin H **50** exhibited strong quinone reductase inhibitory activity while physalin G **49**, 5β-hydroxy-6α-chloro-5,6-dihydrophysalin B **56** and 5α-ethoxy-6β-hydroxy-5,6-dihydrophysalin B **57** showed weak inhibitory activity.[68] The inhibitory effects on quinone reductase activity by physalin A **44**[79] and isophysalin B **75**[87] were also reported.

Physalin D **46** showed low antioxidant potential in the DPPH radical and thiobarbituric acid (TBA) assays. Low antibacterial and antifungal activity was also recorded for physalin D **46**.[72] Further antibacterial assays indicated that physalins B **45** and J **52** showed high antibacterial activities against *Bacillus subtilis* and *Escherichia coli*.[83]

Acknowledgments

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