CHEMICAL REVIEWS

Review

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Halogenated Organic Molecules of Rhodomelaceae Origin: Chemistry and Biology

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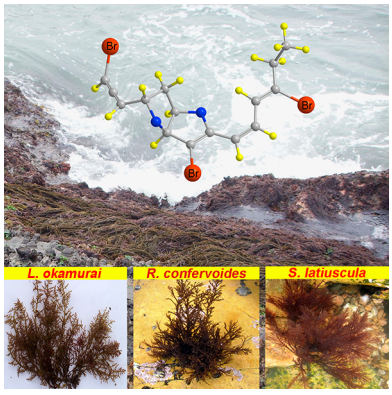
S *Supporting Information*



CONTENTS

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1. INTRODUCTION

It is sometimes assumed that halogenated organic molecules, organic chemicals containing one or more carbon−chlorine, carbon−bromine, carbon−iodine, or carbon−fluorine bonds, are generally rare in nature.[1] For example, the presence of bromine as an algal constituent in some form has long been recognized. As early as the 1920s, many algae were known to concentrate it, but the chemical nature of the accumulated bromine was the subject of some dispute.[2] Eventually, studies of *Polysiphonia fastigiata* (also known as *P. lanosa*), a marine red algal species of the family Rhodomelaceae, provided unequivocal evidence for covalently bound bromine in algae.[2] More recent studies indicated that halogenated natural products are actually common in some sources. In fact, more than 5000 halogenated natural products had been discovered as of 2011.[3]

The Rhodomelaceae (order Ceramiales, class Rhodophyceae, and phylum Rhodophycota) is estimated to be the largest marine red algal family, with about 125 genera and some 700 species recognized worldwide.[4] Chemical investigations of species of this family have resulted in the isolation and structure elucidation of many interesting halogenated molecules. According to a recently released version of MarinLit (version vpc 15.5, March 2012), a marine literature database produced and maintained by the Department of Chemistry, University of Canterbury, New Zealand,[5] a total of 1058 naturally occurring compounds were isolated and characterized from species in the Rhodomelaceae from the 1960s until early 2012. Of these, 808 (76%) were halogenated (760 brominated, 262 chlorinated, 218 brominated and chlorinated, and 4 iodinated). These molecules account for 20% of the 4079 halogenated compounds that were characterized from all marine organisms during this period.[5]

Halogen-containing organic molecules from the Rhodomelaceae represent unique secondary metabolites in terms of structural and biological diversity, and the widespread occurrence of such compounds in these organisms has implications for their potential ecological significance. The biodiversity of algal species of this family provided a useful resource for extending the chemodiversity of known halogenated molecules, as well as for finding new interesting structures for medicinal chemistry studies.

This review attempts to give a comprehensive survey and highlight the diversity of halogenated organic molecules produced by marine red algal species in the family Rhodomelaceae. A total of 697 structures published up to the end of 2011 are included and 525 references are cited in this review. However, simple halogenated hydrocarbons, phenols, and volatile organic molecules are generally not included. It should be noted that some of the earliest reports of structures of this type unfortunately contained limited spectroscopic data and lacked firm evidence for the proposed stereochemistry. In addition, the collection sites for some of the studied algal materials were not described in some reports. While every effort was made to be comprehensive within the topic, we apologize in advance for any oversights.

2. REVIEWS

Although no review on the many halogenated molecules derived from marine red algae of the family Rhodomelaceae appeared in the literature up to now, a number of excellent reviews on various aspects of naturally occurring halogenated molecules were published. A series of excellent reviews by Gribble provided an extensive coverage of various halogenated organic compounds of both biotic and abiotic origin.[1,3,6−16] Specific classes of compounds are evaluated in "Halogenated and/or sulfated phenols from marine macroalgae"[17] and "Natural halogenated fatty acids: their analogues and derivatives".[18] Other related topics reviewed are "Nature's inventory of halogenation catalysts: oxidative strategies predominate",[3] "Marine haloperoxidases",[19] "Halogenated

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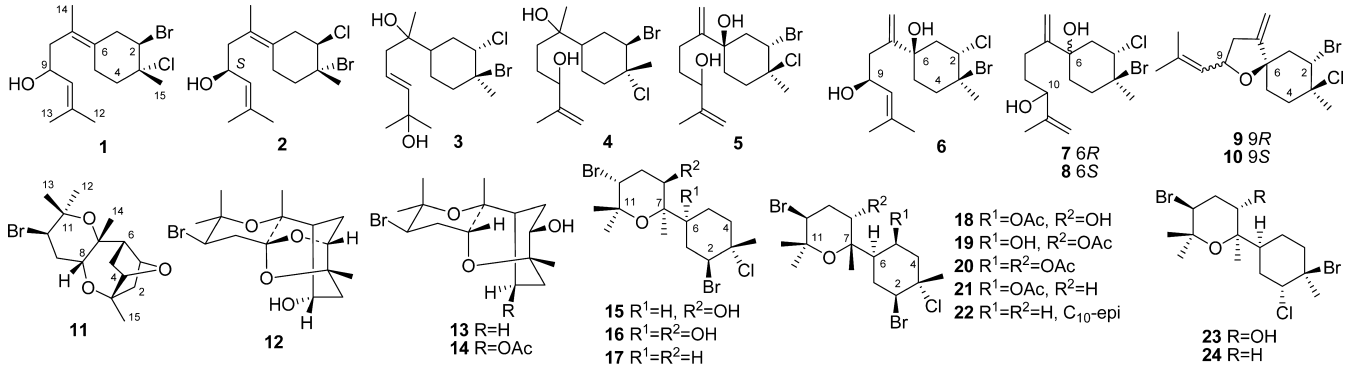

Figure 1. Bisabolane sesquiterpenes (**1**−**24**).

metabolites from marine animals and plants",[20] and "Halogenation in the Rhodophyta".[21] A series of timely reviews entitled "Marine natural products" provided comprehensive surveys of all natural products that were isolated and reported from marine resources annually.[22,23] In addition to the above listed reviews, a book chapter entitled "Constituents of *Laurencia*" appeared in 1983[24] and provided a consolidated review covering all types of compounds, both halogenated and nonhalogenated, reported from species of the genus *Laurencia*, the most heavily studied algal genus within the family Rhodomelaceae. However, none of the above-mentioned reviews provided a full-aspect and in-depth view on the array of halogenated organic molecules from the algal family Rhodomelaceae. The present review aims to give a comprehensive coverage of all naturally occurring halogenated organic molecules of the Rhodomelaceae origin and to provide a general overview of both chemical and biological aspects of these compounds. In general, the occurrence/distribution and structure/substitution features, as well as the chemotaxonomic significance of these molecules are discussed. Approaches toward the synthesis and biosynthesis of these halogenated organic molecules, especially studies employing a new methodology or a new strategy, are summarized. Biological activities and potential functions of these molecules are also discussed.

3. CLASSIFICATION

Halogenated molecules can most simply be classified as fluorinated, chlorinated, brominated, or iodinated compounds. Most halogenated compounds of Rhodomelaceae origin are brominated or chlorinated. Only four were iodinated and no fluorinated compounds were discovered from these sources to date. Since most of these compounds contain only bromine or chlorine atoms, it is not particularly useful to classify the halogenated compounds only according to the halogen they contain. Instead, the halogenated organic molecules from the family Rhodomelaceae are generally categorized in this review on the basis of their structural characteristics into terpenoids, nonterpenoid C_{15}-acetogenins (ACGs), indoles, and phenols/aromatics. The halogenated terpenoids, nonterpenoid ACGs, and indoles were mainly discovered from the genus *Laurencia*, while the halogenated phenols/aromatics were reported primarily as metabolites from other genera of the family, such as *Polysiphonia*, *Rhodomela*, and *Symphyocladia*.

4. STRUCTURE AND OCCURRENCE

4.1. Halogenated Monoterpenes

Although algal species of the family Rhodomelaceae were the most prolific producers of halogenated organic molecules, up to date no halogenated monoterpene was reported from a member of this family. Thus far, the isolation of halogenated monoterpenes is restricted to two families of marine red algae, the Plocamiaceae and Rhizophyllidaceae.[25]

4.2. Halogenated Sesquiterpenes

Species of the Rhodomelaceae especially from the genus *Laurencia*, produce sesquiterpenoids, either regular or irregular, in far greater numbers than any other structural class of secondary metabolites. Up to now, 275 halogenated sesquiterpenes (**1**−**275**, Figures 1−19) were identified as metabolites of Rhodomelaceae. Detailed and tabulated information for each of these halosesquiterpenes, including compound name (synonym, if applicable), molecular formula, halogenation/structure features, source species, sample collection locality, and reference, was provided in Tables S1−S7 in the Supporting Information.

4.2.1. Bisabolane Sesquiterpenes. Twenty-four halogenated bisabolane sesquiterpenes (**1**−**24**, Figure 1 and Supporting Information Table S1) were identified from the algal family Rhodomelaceae, and all of them from the genus *Laurencia*.[26−38] Compounds of this class occurred in seven species including *L. aldingensis*,[31,32] *L. caespitosa*,[27,33−35,37,38] *L. catarinensis*,[36] *L. composita*,[28] *L. obtusa*,[26] *L. saitoi*,[30] and *L. scoparia*.[29] These metabolites are usually characterized by containing monocyclohexanyl motif (**1**−**8**), or possessing 6,9-epoxy (**9** and **10**) or 7,11-epoxy (**11**−**24**) ring system, or having multiple oxacyclic rings (**11**−**14**) in the molecules. With few exceptions (**11**−**14**), these compounds are both brominated and chlorinated at C_2 and C_3 and generally possess 2,3-*trans*-halide conformation. The structures of these metabolites were mainly determined by interpretation of spectral data, and the S configuration at C_9 of puertitol B (**2**) was established by use of the CD allylic benzoate method.[26] For compounds **6**, **15**−**17**, and **23**, their structures were confirmed by single-crystal X-ray crystallographic experiments. Among them, compounds **6**[29] and **15**[33,34] are remarkable. The X-ray crystallographic analysis of compound **6** was nontrivial since the allylic-homoallylic system present in the side chain of **6** was found to be very reactive and a rapid decomposition was observed upon irradiation.[29] To determine the structure and absolute configuration of all stereocenters in the molecule, several single crystals were required and were protected from air by embedding them in a droplet of wax to reduce the decomposition rate. A complete

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data set which is suitable for determining both the structure and the absolute configuration of the entire molecule was obtained by combining results from two different crystals.[29] As for caespitol (**15**), it was originally reported as a chamigrane sesquiterpene as determined by spectroscopic analysis[33] but the structure was subsequently revised to a bisabolane sesquiterpene **15** based on the results of X-ray studies of isocaespitol (**23**), a coexisting sesquiterpene in the same species of *L. caespitosa*, as well as by chemical correlation between the two isomers.[34]

4.2.2. Brasilane Sesquiterpenes. To date, only two papers describing four halogenated brasilane derivatives (**25**−**28**, Figure 2 and Supporting Information Table S1) were

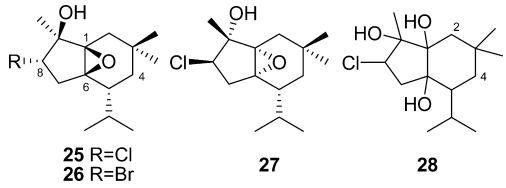

Figure 2. Brasilane sesquiterpenes (**25**−**28**).

published, with all of them from *L. obtusa* collected either from Greece[39] or from Turkish waters.[40] These sesquiterpenes share common characteristics of 8-Cl (**25**, **27**, and **28**) or 8-Br (**26**) halogenation and a 9-OH substitution in the five-membered ring, with three of them, **25**−**27**, possessing an unprecedented 1,6-epoxy moiety in the brasilane skeleton.[39] While the structures and relative configurations of **25**−**27** were fully established by means of spectral data analysis along with molecular modeling calculations,[39] the relative stereochemistry of the various asymmetric centers in **28** could not be determined.[40] However, the magnitude of the vicinal coupling constants and the four-bond coupling of H-4a and H-2b indicated that the six-membered ring assumes a regular chair conformation with the isopropyl group adopting an equatorial orientation.[40]

4.2.3. Chamigrane Sesquiterpenes. Halogenated and spiro-fused sesquiterpenoids containing the spiro[5,5]undecane skeleton as exemplified by the chamigrane class are the most frequently encountered types of marine natural products from the genus *Laurencia*. Halochamigranes distributed in a wide range of species of the genus, and four species (*L. nidifica*, *L. nipponica*, *L. majuscula*, and *L. obtusa*) are especially abundant sources of this class of compounds (Supporting Information Table S2). A total of 93 halochamigranes (**29**−**121**, Figures 3−6 and Supporting Information Table S2), with 33 brominated, 6 chlorinated, and 54 bromochlorinated (with 26 and 28 of them containing BrCl and Br_2Cl, respectively), were described up to the end of 2011.[28,30,41−105] On the basis of the oxidation state at C_5 and C_{10}, halochamigranes can be further divided into two subclasses, that is, with or without a 5,10-epoxide ring system. Twelve of them (**29**−**40**, Figure 3) that contain a 5,10-epoxide ring system fall into the first subclass and the others (**41**−**121**, Figures 4−6), possessing various halogen- and oxygen-substitution as well as dehydrogenations at different positions in the skeleton, form the second subclass. Among these, pacifenol (**29**) was the first natural product reported to contain both Br and Cl in the structure.[41] As can be seen from Figure 3, the bromine atom is usually located on the secondary carbon (C_2) whereas the chlorine is often attached to the tertiary center (C_3) on the opposite face of Br-atom,

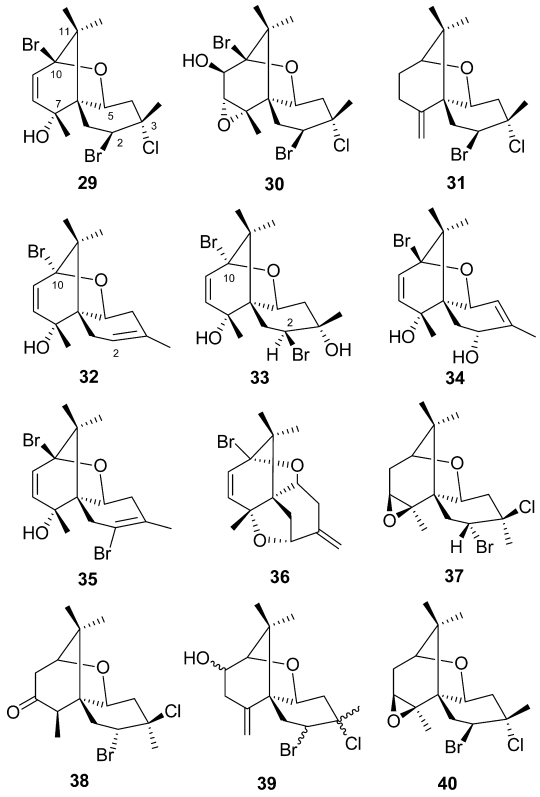

Figure 3. Chamigrane sesquiterpenes (**29**−**40**).

representing a characteristic 2,3-*trans*-halide arrangement observed for 5,10-epoxychamigrane sesquiterpenes (**29**−**31** and **37**−**40**). This halogenation pattern is also commonly observed in other chamigrane sesquiterpenes, as shown in Figures 4−6, which indicates that C_2 and C_{10} are the most favored positions for Br-substitution, whereas C_3 appears to be favored for Cl-substitution. However, the secondary carbon C_2 tends to be the preferred position for the Cl-atom when a chamigrane sesquiterpene contains Cl as the only halogen atom in the molecule (**56**,[64] **83**,[80] **86**,[81] **109**, and **110**[95]). Some other unique structural features, such as the unusual *cis*-relationship of the heteroatoms at C_2 and C_3 (**68**[72] and **85**[81]), the unusual occurrence of halogenation on a double bond (**41**−**43**,[28,55] **52**,[43] **53**,[62] **55**,[63] **56**,[64] **60**,[67] **70**, **71**,[74] **83**,[80] **88**,[30] **89**,[82] **92**,[85] and **94**−**98**[49,86−88]), and the rare conjugated bromodiene system (**76**, **77**,[76] **107**, **108**,[93,94] and **114**[98]), were observed among the halochamigranes of *Laurencia* origin.

With regard to structure determination, it should be noted that NMR spectroscopic techniques are sometimes not enough to unambiguously determine the positions of the Br and Cl atoms in chamigranes as well as in other polybromochlorinated natural products because NMR signals because of protons/carbons α to oxygen, bromine, and chlorine often occur in the same region of the spectrum. This is exemplified by the fact that the locations of Br and Cl atoms in a number of halochamigranes were misplaced in initial structure assignments.[46,69,105] Therefore, the X-ray crystallographic analysis should be used for structure confirmation of such metabolites, especially when a new compound with an unprecedented halogenation pattern is discovered.[69] For noncrystalline compounds, NMR data calculation and comparison with experimental results, chemical correlation with known compounds, or independent partial or total synthesis can also

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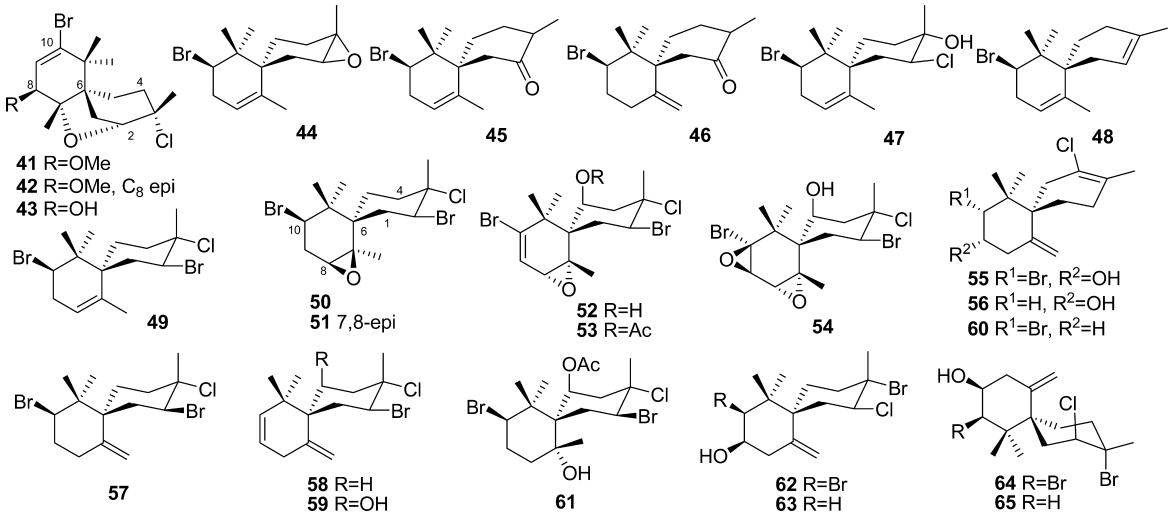

Figure 4. Chamigrane sesquiterpenes (**41**–**65**).

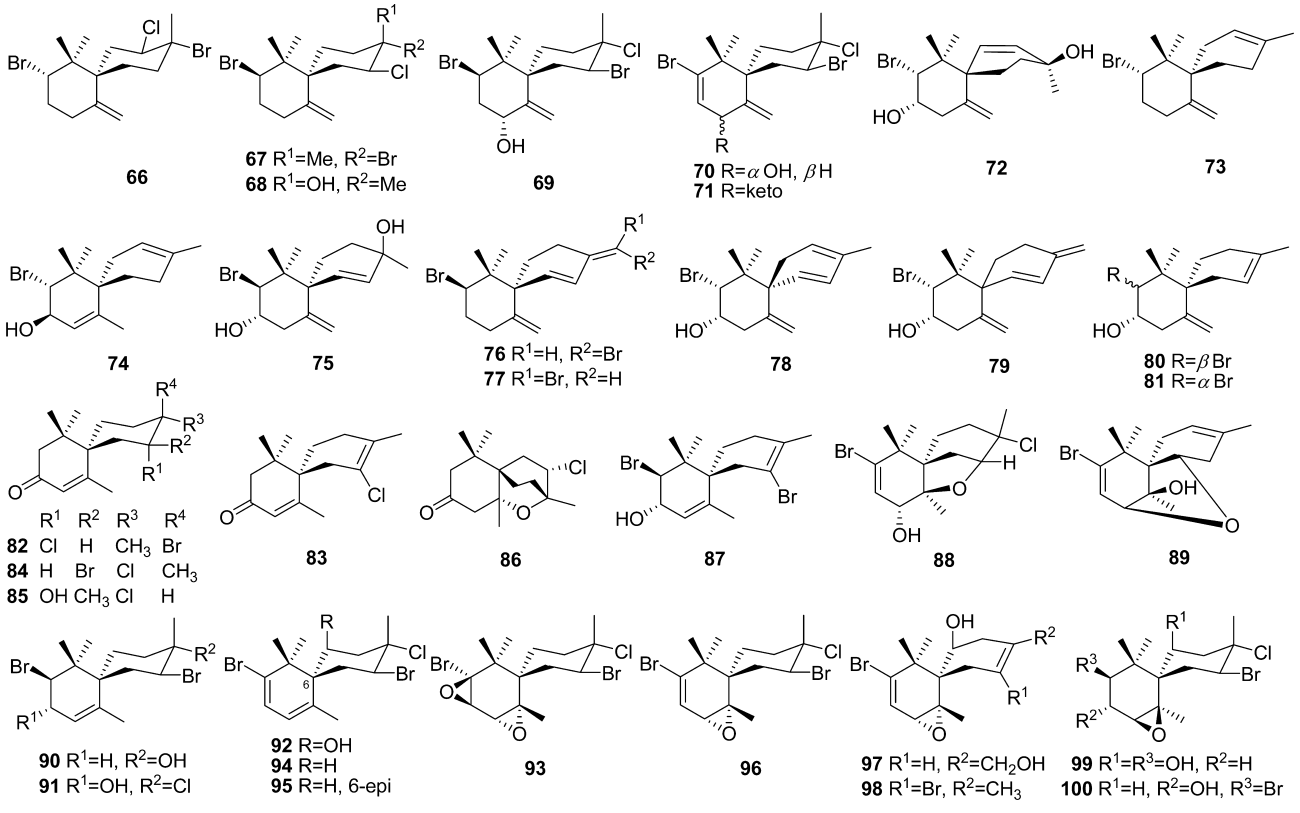

Figure 5. Chamigrane sesquiterpenes (**66**–**100**).

become particularly important for structure determination and confirmation.

4.2.4. Cuparane Sesquiterpenes. Although a wide variety of sesquiterpenes were discovered from the algal species of the family Rhodomelaceae, cuparane sesquiterpenes are occasionally encountered. To date, only seven representatives of this class (**122**–**128**, Figure 7 and Supporting Information Table S3) were reported from the family, with four of them having Br-atom at C_3 (**122**–**125**)[106−108] and three at C_{10} (**126**–**128**).[109,110] α-Bromocuparene (**122**) and α-isobromocuparene (**123**) appeared to be the first representatives of cuparane sesquiterpenes isolated from seaweeds.[106] Compound **126** contains a 3,7-epoxy moiety in the molecules, while **127**[109] and **128**[110] reflect a migration of the C_1 methyl group that is unprecedented among members of the cuparane class of sesquiterpenes. Cuparane sesquiterpenes were recorded from five species of the genus *Laurencia* including *L. glandulifera*,[106] *L. implicata*,[108] *L. majuscula*,[107] *L. microcladia*,[109] and *L. okamurai*.[110]

4.2.5. Eudesmane and 6,8-Cycloeudesmane Sesquiterpenes. Like cuparane sesquiterpenes, eudesmane (selinane), and 6,8-cycloeudesmane sesquiterpenes are also rarely encountered from these algae. To date, only seven representatives (**129**–**135**, Figure 8 and Supporting Information Table S3) were reported from members of the Rhodomelaceae, mainly from *Laurencia filiformis*, *L. intricata*,

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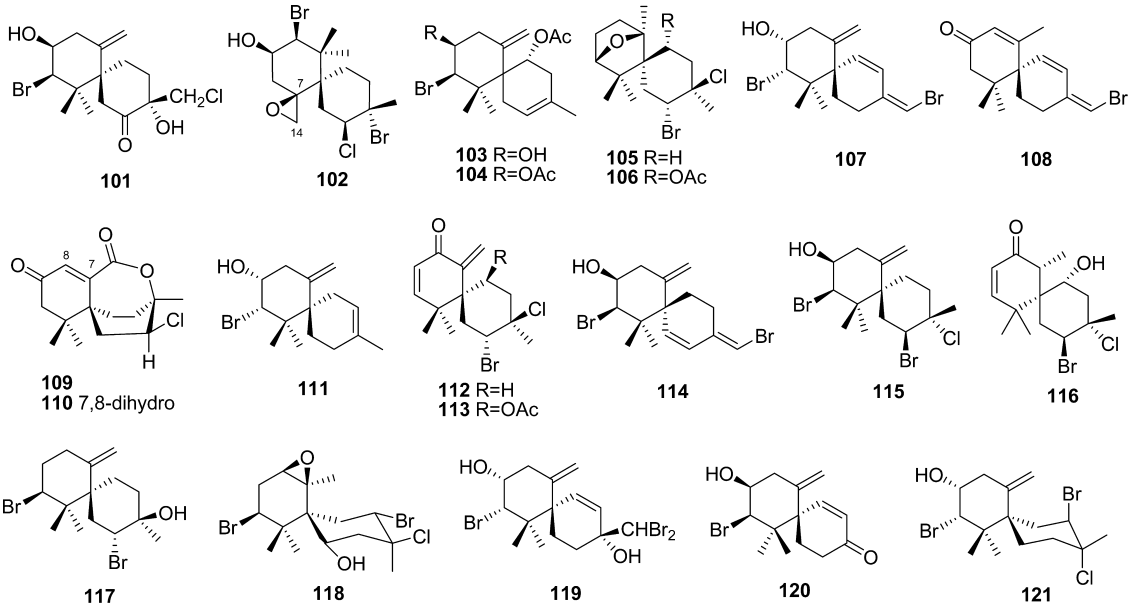

Figure 6. Chamigrane sesquiterpenes (**101**−**121**).

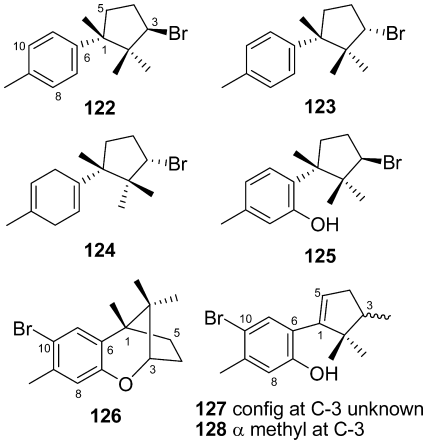

Figure 7. Cuparane sesquiterpenes (**122**−**128**).

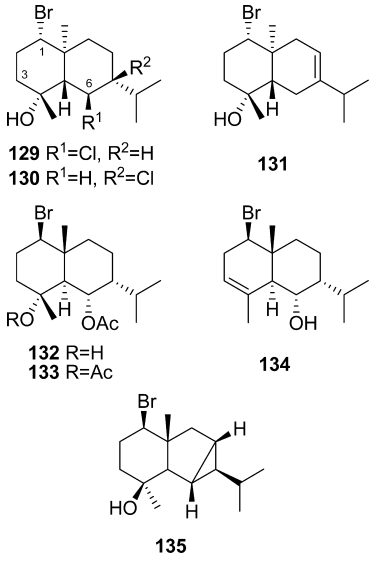

Figure 8. Eudesmane (**129**−**134**) and 6,8-cycloeudesmane (**135**) sesquiterpenes.

and *L. microcladia*.[111−117] Among them, heterocladol (**129**), which was characterized in 1977 from *L. filiformis* f. *heteroclada* collected near Cape Jervis of South Australia, represents the first example of a eudesmane sesquiterpene from the family Rhodomelaceae.[111] Its structure, including absolute configuration, was determined by spectroscopic methods as well as by an X-ray crystallographic study.[111] A similar compound, 1*S*-bromo-4*R*-hydroxy-(−)-selin-7-ene (**131**), was independently reported by two groups from unidentified *Laurencia* spp. from the Gulf of California[113] and from Australia.[114] Eudesmane sesquiterpenes of Rhodomelace origin display a 1-bromo substituent, with **129** and **130** containing a Cl-atom at C_6 and C_7, respectively, while 1-bromo-6,8-cyclo-4-eudesmanol (**135**), isolated from *L. microcladia* collected in the Bay of Calenzana, Elba Island,[117] represents the first 6,8-cyclo-eudesmane sesquiterpene of marine origin.

4.2.6. Laurane and Cyclolaurane Sesquiterpenes. A total of 30 laurane (**136**−**165**)[110,118−138] and six cyclolaurane (**166**−**171**)[125,126,130,131,137,139,140] sesquiterpenes were identified from the algal family Rhodomelaceae (Figure 9 and Supporting Information Table S4). These molecules are generally constituted by a substituted aromatic/phenyl group connecting a 1,2,3-trisubstituted cyclopentane moiety, with only one exception, compound **163**, as a nonaromatic triene obtained from a Spanish specimen of *L. pinnatifida*.[127] Some of these sesquiterpenes contain 2,7-epoxy (**147**−**151**),[110,130−133] 3,7-epoxy (**152**−**158**,[120−123,134,135] **161**,[137] and **162**[138]), 4,7-epoxy (**160**),[136] or 5,7-epoxy (**164**)[134] units. As for halogenation, each compound contains a Br-substituent, with the majority at C_{10} and/or C_{12}, and three of them display iodine substitution at C_8 (**169**),[137] C_{11} (**140**), and C_{12} (**157**).[123] The latter two compounds represent the first examples of naturally occurring iodinated sesquiterpenes.[123] Laurane and cyclolaurane sesquiterpenes are mainly characterized from the species *L. filiformis*,[120,134] *L. glandulifera*,[121,122] *L. microcladia*,[137,140] *L. nipponica*,[118] *L. okamurai*,[110,130−132] and *L. tristicha*.[129,133,135]

4.2.7. Snyderane Sesquiterpenes. Following chamigranes, a total of 38 halogenated snyderane sesquiterpenes form the next largest major group of halosesquiterpenes

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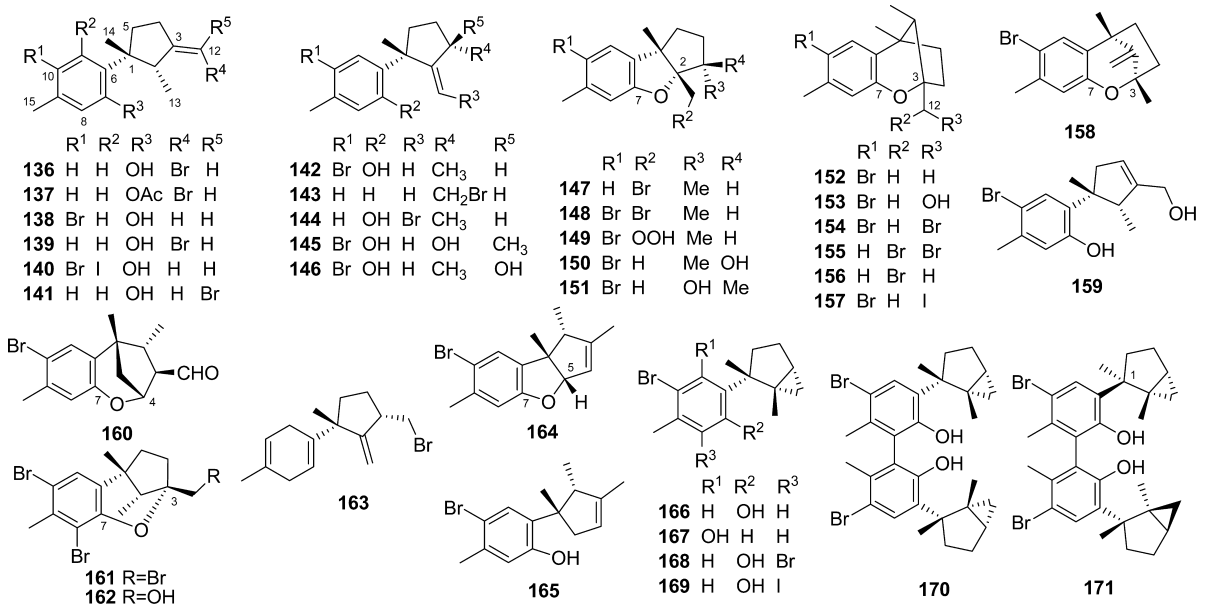

Figure 9. Laurane (**136**–**165**) and cyclolaurane (**166**–**171**) sesquiterpenes.

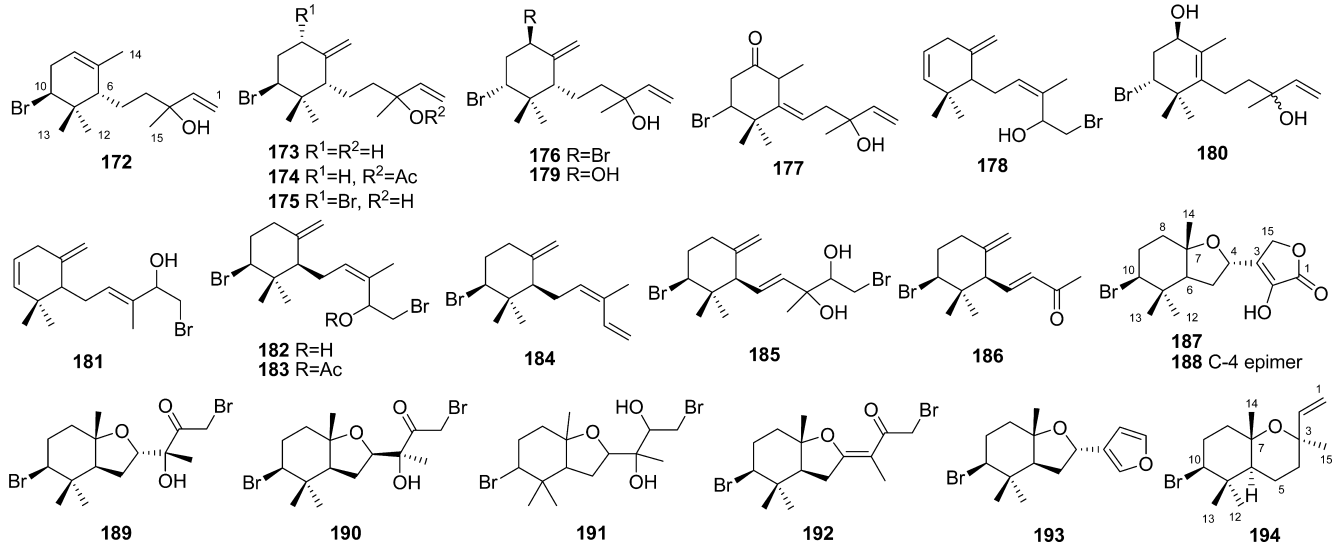

Figure 10. Snyderane sesquiterpenes (**172**–**194**).

characterizd from the genus *Laurencia* (**172**–**209**, Figures 10 and 11 and Supporting Information Table S5).[72,141−154] These sesquiterpenes generally contain a cyclohexane or cyclohexene moiety, with seven (**187**–**193**,[147−149] Figure 10) and fifteen (**195**–**209**,[143,147,149,151−154] Figure 11) of them containing additional 4,7-epoxy and 2,7-epoxy ring systems, respectively. 3β-Bromo-8-epicaparrapi oxide (**194**) is the only halogenated snyderane sesquiterpene having a 3,7-epoxy unit,[150] while luzofuran (**193**) was the first furan-containing derivative to be encountered among the snyderane-type sesquiterpenes from the genus *Laurencia*.[149] α-Snyderol (**172**) and β-snyderol (**173**) are the first examples of the snyderane class of sesquiterpenes, and were isolated from *L. obtusa* collected at Tossa de Mar, Spain, and *L. snyderae* collected at La Jolla, California, respectively,[141] while 8-hydroxy-γ-snyderol (**180**) is the first example of a γ-snyderol derivative isolated from marine sources[144] and 2-bromo-γ-ionone (**186**) is the only brominated dinor-snyderane sesquiterpene characterized from *Laurencia* species.[147] Each of the snyderane derivatives of *Laurencia* origin is monobrominated at C_{10} or dibrominated at C_{10} and C_1, with only two exceptions, palisol (**178**)[143] and isopalisol (**181**),[145] which are monobrominated at C_1. Among the dibromiated snyderane derivatives, C_1 and C_{10} were the most favored positions for Br-atoms (**182**, **183**,[145] **185**,[146] **189**–**192**,[148,149] **196**–**198**,[143] **202**, **203**,[149] and **206**–**209**,[147,153] Figures 10 and 11). As indicated in Supporting Information Table S5, seven species were reported to produce snyderane sesquiterpenes, with *L. luzonensis*[145,148,149] and *L. obtusa*[72,141,142,150] being the most abundant sources of this compound type.

4.2.8. Sesquiterpenes with New Carbon Skeletons. To date, thirty-seven different sesquiterpenoid carbon skeletons have been described from members of the algal family Rhodomelaceae, with twenty of them being new or rare structural types (see below in section 4.2.10). Four halogenated acetal derivatives, laureacetals A (**210**),[155,156] B (**211**),[156] D (**212**), and E (**213**),[157] which possess a new (secochamigrane)

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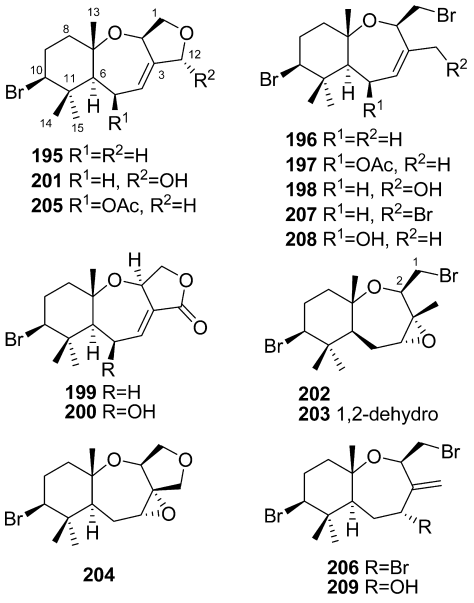

Figure 11. Snyderane sesquiterpenes (**195**–**209**).

carbon skeleton that appears to be generated from a 10-bromochamigrene derivative by oxidative cleavage of the C_1–C_2 bond, followed by acetal formation, were identified from *L. nipponica* collected from Hokkaido, Japan (Figure 12 and

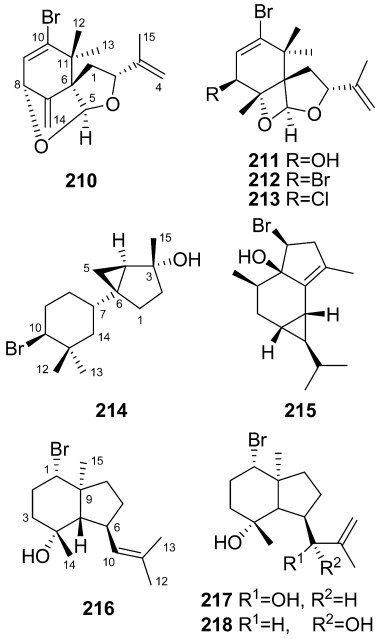

Figure 12. Sesquiterpenes with new carbon skeletons (**210**–**218**).

Supporting Information Table S6). While **210** featured two five-membered ether rings, **211**–**213** had a four-membered ether ring fused to a five-membered ether ring to form the acetal. The structure and absolute configuration of **210** were determined by spectroscopic methods and by X-ray diffraction analysis.[155] Bromocyclococanol (**214**), a sesquiterpene containing fused cyclopropane–cyclopentane rings leading to a novel carbon skeleton, was discovered from *L. obtusa* collected from Cayo Coco, Cuba.[158] The trivial name cyclococane was proposed for the skeleton. Calenzanol (**215**), a sesquiterpene possessing the novel calenzanane carbon skeleton, was isolated as a major metabolite of *L. microcladia* collected from the Bay of Calenzana at Elba Island.[159] This compound features a fused 3/6/5-membered tricyclic ring system. It was very unstable and underwent thermal decomposition at 40 °C to give a novel indene derivative.[159] A species of *L. subopposita* collected at La Jolla, California, contained the major metabolite oppositol (**216**)[160] and its two congeners, the epimeric diols **217** and **218**,[161] which comprise another class of sesquiterpenes having a novel carbon skeleton (oppositane). Spectral and X-ray diffraction analysis of oppositol **216** led to the determination of its structure and absolute configuration.[160]

Perforatone (**219**, Figure 13 and Supporting Information Table S6), a sesquiterpene with a new carbon skeleton

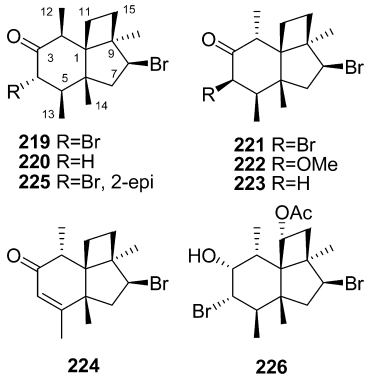

Figure 13. Sesquiterpenes with new carbon skeletons (**219**–**226**).

(cycloperforane) featuring a fused 4/5/6-membered tricyclic unit, was obtained from *L. perforata* collected at the Canary Islands.[162] Following extensive analyses of NOESY correlations, the stereochemistry of **219** was revised in a recent report, which also described the structures of four similar compounds **220**–**223** from *L. obtusa* collected at Milos Island in the Aegean Sea, Greece.[163] *L. obtusa* (Serifos Island in the central Aegean Sea, Greece) was the source of the sesquiterpene 8-bromo-9,11-cyclo-4-perforen-3-one (**224**),[140] while *L. tenera* (Townsville region of the Great Barrier Reef, Australia) produced 2-epi-perforatone (**225**)[164] and tenerol acetate (**226**).[165] The structure of 2-epi-perforatone (**225**) was determined by single-crystal X-ray diffraction.[164]

Perforenone B (**227**)[162] and perforenol (**228**)[166] isolated from *L. perforata* and perforenol B (**229**)[140] isolated from *L. obtusa* were three halosesquiterpenes with a new carbon skeleton (perforane), which might be derived from perforatone **219** by cleavage of the C_1–C_9 bond (Figure 14 and Supporting Information Table S6). *L. perforata* was also the source of

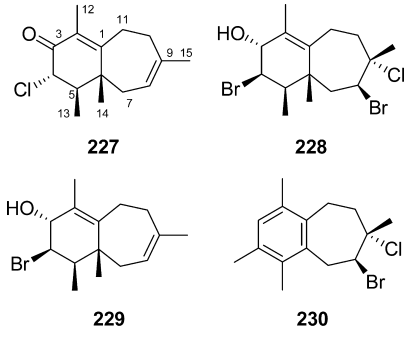

Figure 14. Sesquiterpenes with new carbon skeletons (**227**–**230**).

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another bromochlorosesquiterpene, perforene (**230**),[167] possesses another new carbon skeleton (friedoperforane) that might be derived from the bromocarbenium ion of the corresponding chamigrene sesquiterpenes through a stereospecific pathway.[167] The structures and the relative configurations of these compounds were proposed on the basis of their spectral data, and the structure of perforenol (**228**), including its absolute configuration, was confirmed by X-ray crystallographic analysis.[166]

Three new bromochlorosesquiterpenes including rhodolaureol and rhodolauradiol (**231** and **232**)[168] and 1(12)-isorhodolaureol (**233**)[98] (Figure 15 and Supporting Information Table S6), which have a new tricyclic carbon skeleton (rhodolaurane) not found previously among naturally occurring terpenoids, were isolated from an unidentified alga of the genus *Laurencia* and from *L. majuscula*, respectively. Gomerones A–C (**234**–**236**), recently reported from *L. majuscula*, are new chlorosesquiterpenes representing a novel tricyclic carbon skeleton given the name gomerane.[169] Both the rhodolaurane and gomerane skeletons are likely derived from a *β*-chamigrene precursor by ring closure from C_{14} to C_3 and C_2,[169] respectively. Güimarediol (**237**) is also a tricyclic bromosesquiterpene with a new rearranged isoprenoid skeleton (designated as güimarane, derived from the location where the seaweed was collected) and was obtained from a species of the genus *Laurencia* collected off Güimar, Tenerife, Canary Islands,[170] while **238** is an additional bromosesquiterpene having a new tricyclic carbon framework (rearranged cycloperforane) and was isolated from *L. tenera* (Townsville, Australia).[164] The crystalline sample of **238** was unstable and the bulk of the specimen decomposed on storage at −10 °C and thus precluded a single-crystal X-ray study of this interesting molecule.[164]

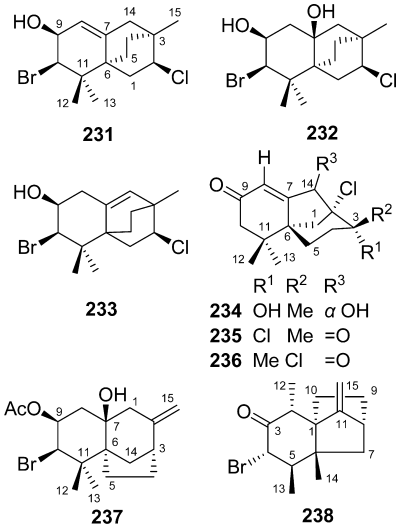

Figure 15. Sesquiterpenes with new carbon skeletons (**231**–**238**).

A specimen of *L. nipponica* collected off the Pacific Coast of Hokkaido contained the minor sesquiterpene laurencial (**239**, Figure 16 and Supporting Information Table S6), which possesses a new spiro[4,5]decane skeleton and *α*,*β*-unsaturated aldehyde moiety.[171] The carbon skeleton might be derived from the chamigrene framework involving with an interesting modification of ring-contraction.[171] Spirolaurenone (**240**), which possesses a new carbon skeleton (spirolaurane), is

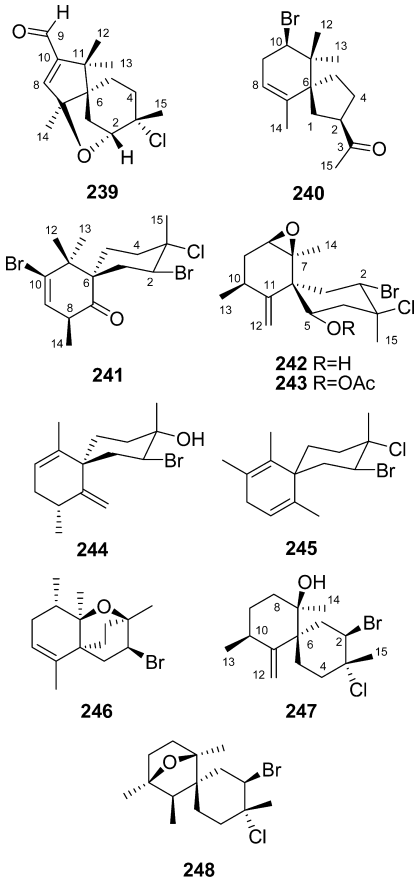

Figure 16. Sesquiterpenes with new carbon skeletons (**239**–**248**).

another novel sesquiterpene that is considered to be a ring contraction product of the corresponding chamigrene epoxide,10-bromo-3,4-epoxy-*α*-chamigrene (**44**), with which it co-occurs in the species *L. glandulifera*.[172] Its absolute configuration was established by chemical correlation with glanduliferol (**47**), a halo-chamigrene derivative isolated from the same alga.[173] Kylinone (**241**), which was obtained from *L. pacifica* collected at Stillwater Cove on the Monterey Peninsula, California and possesses a new spirobicycloundecane skeleton assigned the trivial name kylinane (in honor of the Swedish phycologist Kylin, who first described *L. pacifica*), appears to be derived from rearrangement of the corresponding chamigrene epoxide, deoxyprepacifenol (**96**).[174] Other rearranged sesquiterpenes (**242**–**248**) possessing a new carbon skeleton which appears to result from a methyl migration from C_{11} to C_{10} of chamigrene framework, were isolated from a new species of the genus *Laurencia* (**242**),[101] from *L. pinnatifida* (**243**, pinnatifate),[175] from *L. okamurai* (**244**, laurenokamurin),[176] from *L. composita* (laurencomposidiene **245** and 2-bromospironippol **246**),[177] as well as from *L. pannosa* (pannosanol **247** and pannosane **248**).[178] The positions of Br and Cl in **247** were confirmed by the halogen-induced ^{13}C isotope shifts in the ^{13}C NMR measurement.[178]

Eleven halosesquiterpenes (**249**–**259**, Figure 17 and Supporting Information Table S6) representing a new class of cyclohexylcyclohexane-containing carbon skeleton that may be rationalized as arising from C_{11}–C_{14} cyclization of a bisabolene derivative, were identified from several species of the genus *Laurencia*.[179–181] One of them, dibromoether **249**, was isolated from *L. obtusa* collected at Graciosa Island and its

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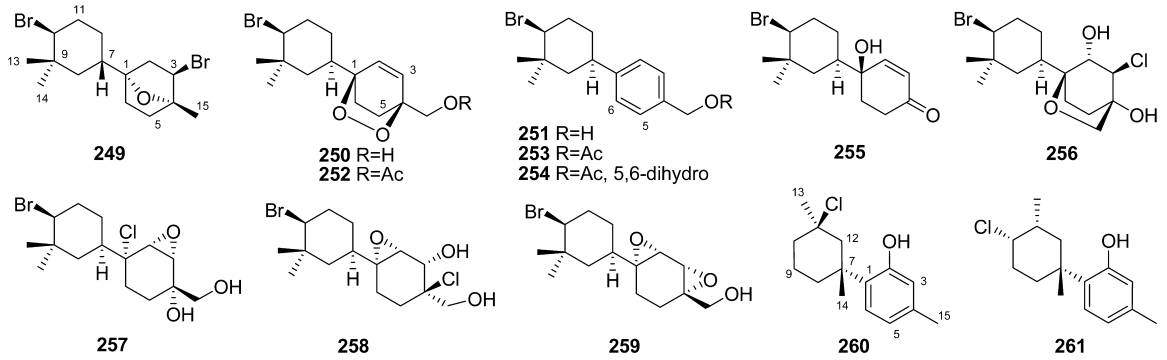

Figure 17. Sesquiterpenes with new carbon skeletons (**249**–**261**).

structure, including absolute configuration, was determined by X-ray crystallographic techniques.[179] Seven structurally related compounds, majapolenes A (**250**) and B (**251**), majapolone (**255**), and majapols A–D (**256**–**259**), were obtained from a Philippine collection of *L. majuscula*.[180] The three congeners acetylmajapolene A (**252**), acetylmajapolene B (**253**), and tiomanene (**254**) were recently isolated from an unidentified *Laurencia* species that was collected from Pulau Tioman, Malaysia.[181] With the exceptions of **249**, **251**, **253**, and **254**, all of these compounds were obtained as inseparable diastereomeric mixtures. A sample of *L. majuscula* collected from Geoffrey Bay, Magnetic Island, afforded two new aromatic sesquiterpenes, **260** and **261**, which feature a cyclohexylphenol ring system that might be derived from C_7–C_{12} cyclization of a bisabolene derivative, thus representing another previously undescribed natural occurring carbon skeleton.[182]

The first members of a new class of irregular rearranged sesquiterpenes related to bisabolanes, laucapyranoids A–C (**262**–**264**, Figure 18 and Supporting Information Table S6),

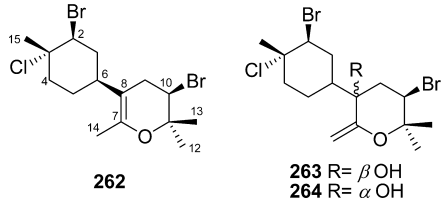

Figure 18. Sesquiterpenes with new carbon skeletons (**262**–**264**).

were obtained from *L. caespitosa* collected at Punta del Hidalgo, Tenerife, and near the Island of La Graciosa.[35] While the structure of laucapyranoid B (**263**) including the absolute configuration was confirmed by X-ray crystallographic analysis, the identity of the extremely unstable laucapyranoid C (**264**) was established by analysis of its hydrodebrominated derivatives, whose structures were determined by spectroscopic analysis and X-ray crystallographic experiment.[35]

4.2.9. Miscellaneous Sesquiterpenes. In addition to the halosesquiterpenes discussed above, eleven additional C_{15} or C_{12} terpenoids (**265**–**275**, Figure 19 and Supporting Information Table S7) were also identified from *Laurencia* species.[36,71,145,183–188] Among these, majusin (**265**) is a halogenated sesquiterpene with a rare cedrene skeleton isolated from *L. majuscula* (Xisha Islands, South China Sea),[183] while bromoketone (**266**) is a rare friedooppositane sesquiterpene characterized from *L. marianensis* (the Great Barrier Reef).[184] Aristolan-1α-bromo-9β,10β-epoxide (**267**), isolated from *L. similis* (Hainan Islands, China), is the only halogenated

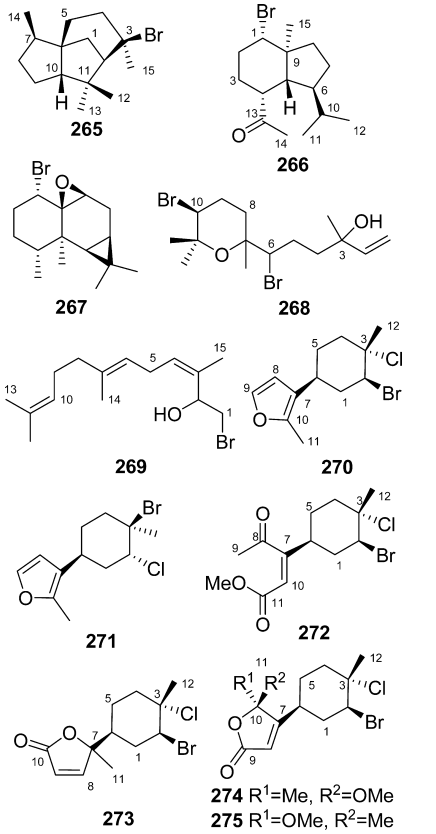

Figure 19. Miscellaneous sesquiterpenes/norsesquiterpenes (**265**–**275**).

aristolane derivative so far characterized from the genus *Laurencia*.[185] A cyclic ether, obtusenol (**268**),[186] and an acyclic bromohydrin-containing sesquiterpene (**269**)[145] were obtained from *L. obtusa* (Gökceada Island, Aegean Sea) and from *L. luzonensis* (Okinawa), respectively. Two new C_{12} terpenoids, furocaespitane (**270**),[187,188] and isofurocaespitane (**271**),[71] considered to be degraded bisabolanes, were isolated from *L. caespitosa* and their structures were elucidated by interpretation of spectral data, while two additional congeners (**272** and **273**) were obtained from the same species as minor components.[182] The structures of compounds **272** and **273**, including their absolute configurations, were determined by X-ray diffraction analysis.[188] Very recently, two additional C_{12} terpenoids, (10*R**)- and (10*S**)-10-*O*-methylfurocaespitanelactol (**274** and **275**), which possess a ketal unit associated with the butenolide moiety, were characterized from the first chemical

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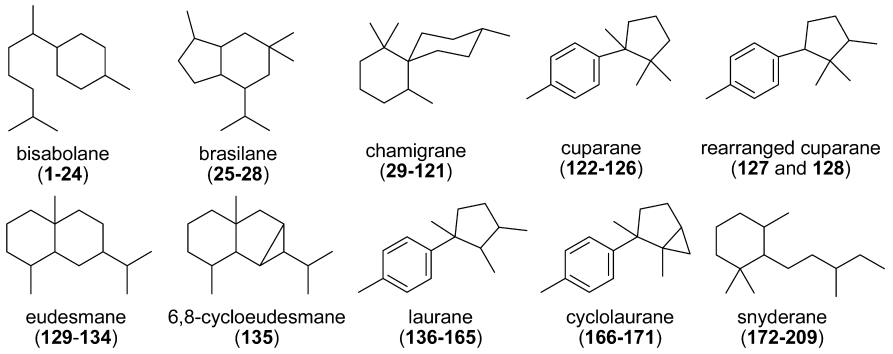


Figure 20. Ten known sesquiterpenoid skeletons with halogenated representatives characterized from Rhodomelaceae.

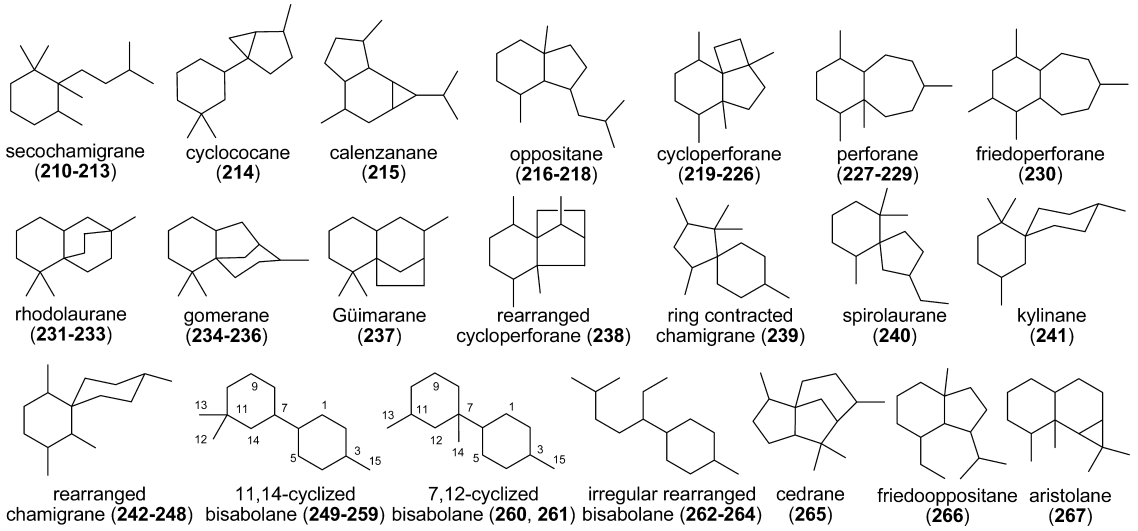


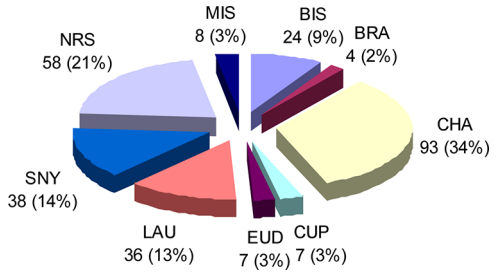
Figure 21. Twenty new or rare sesquiterpenoid skeletons with halogenated representatives characterized from Rhodomelaceae.

investigation of the species *L. catarinensis* (Santa Catarina, Brazil). The structure of **274** was confirmed by X-ray crystallographic analysis.[36]

4.2.10. Summary of the Occurrence of Halogenated Sesquiterpenes. The 275 halogenated sesquiterpenes and norsesquiterpenes (**1**–**275**) reported from the Rhodomelaceae, as discussed above, belong to 10 known (Figure 20, **1**–**209**) and 21 new/rare carbon skeletons (Figure 21, **210**–**267**). Most of them consist of fused- or spiro-ring systems (Figures 20 and 21) and their possible biogenetic correlations will be discussed in section 7.1. In general, compounds with chamigrane, snyderane, and laurane skeletons are the most frequently occurring sesquiterpenoid types, respectively accounting for 93 (**29**–**121**, 34%), 38 (**172**–**209**, 14%), and 36 (**136**–**171**, 13%) of the 275 halogenated sesquiterpenes that were characterized from marine algal species of the family Rhodomelaceae (Chart 1). On the other hand, only four examples of halogenated brasilane sesquiterpenes (**25**–**28**) and only a single example of a halogenated 6,8-cycloeudesmane (**135**) were described. Among the 21 new/rare carbon skeletons, only single examples were reported for 11 of them, namely, cyclococane (**214**), calenzanane (**215**), friedoperforane (**230**), Güimarane (**237**), rearranged cycloperforane (**238**), ring-contracted chamigrane (**239**), spirolaurane (**240**), kylinane (**241**), cedrane (**265**), friedooppositane (**266**), and aristolan-1α-bromo-9β,10β-epoxide (**267**) (Figure 21).

In addition to the sesquiterpenes with 10 known and 21 new/rare different carbon skeletons discussed above, sesquiterpene derivatives with seven other skeletons (oplopane, 4,15-cycloeudesmane, isocycloeudesmane, guaiane, aromadendrane, poitane, and germacrane), were also reported from the Rhodomelaceae (Figure 22). However, no halogenated examples of these skeletons were reported to date. Such nonhalogenated examples are beyond of the scope of this review, but interested readers might refer to an excellent review of this area by Erickson.[24]

Chart 1. Distribution of the 275 Halogenated Sesquiterpenes of Rhodomelaceae Origin by Structural Class[a]



[a]BIS, bisabolane; BRA, brasilane; CHA, chamigrane; CUP, cuparane; EUD, eudesmane; LAU, laurane; SNY, snyderane; NRS, new/rare skeletonal sesquiterpenes; MIS, miscellaneous sesquitperpenes.

4.3. Halogenated Diterpenes

Compared to the high number and great diversity of sesquiterpenes already discussed above, and the nonterpenoid

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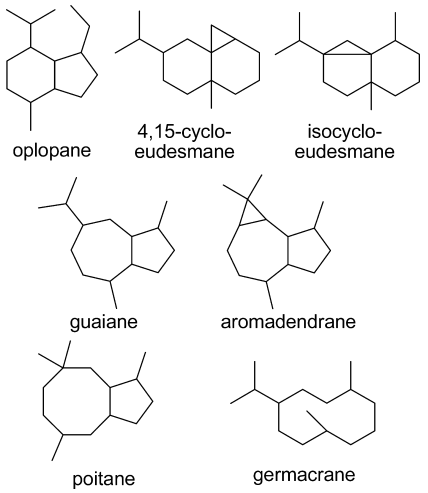

Figure 22. Seven sesquiterpenoid skeletons found among Rhodomelaceae metabolites for which halogenated representatives have not been reported.

C_{15}-acetogenins that will be discussed later, the list of Rhodomelaceae-derived diterpenes is relatively short. However, several different diterpene structural types, including members of the irieane, labdane, and parguerane classes, are present in species of the family, and were reported mainly from the genus *Laurencia*. To date, at least 71 halogenated diterpenoids were identified from the Rhodomelaceae.

4.3.1. Irieane Diterpenes. Diterpenes of the irieane class contain a new tricyclic carbon skeleton consisting of a cyclohexylmethyl unit coupled with an octahydroindene system. The first examples of this class, irieol A (**276**) and iriediol (**277**) (Figure 23 and Supporting Information Table S8), were identified from an undescribed *Laurencia* species collected at Puerto Peñasco, Mexico in 1975 by Fenical and co-workers, and their structures were determined by spectral and X-ray crystallographic analysis.[189] This species was later assigned the name *L. irieii* based upon pioneering research in *Laurencia* chemistry of Professor Toshi Irie at Hokkaidao University.[190] To date, a total of 14 diterpenes of the irieane class corresponding to compounds **276**–**289** (Figure 23 and Supporting Information Table S8),[189−194] with irieol A (**276**) being regarded as the archetypal compound of this class, were isolated from three species of the genus *Laurencia* (*L. irieii*,[189,190] *L. pinnata*,[191] and *L. decumbens*),[192,193] with *L. irieii* being the major producer (**276**–**284**).[189,190] Without exception, irieane diterpenes are all dibrominated at C_1 and C_{14} and each Br-substituent possesses the α-configuration (Figure 23). In addition, compounds of this class generally possess a free 4α-OH, with the only exceptions being pinnaterpene C (**287**),[191] 11-*O*-deacetylpinnaterpene C (**288**),[192,193] and 10-acetoxyangasiol (**289**),[194] which contained 4,18-epoxy and 18-hemiacetal functionalities (**287** and **288**) or 4,18-lactone unit (**289**) in their structures. Another feature of these molecules is C_{11}-oxygenation, but for **277** and **278** each contain a C_{10}-double bond.[189,190]

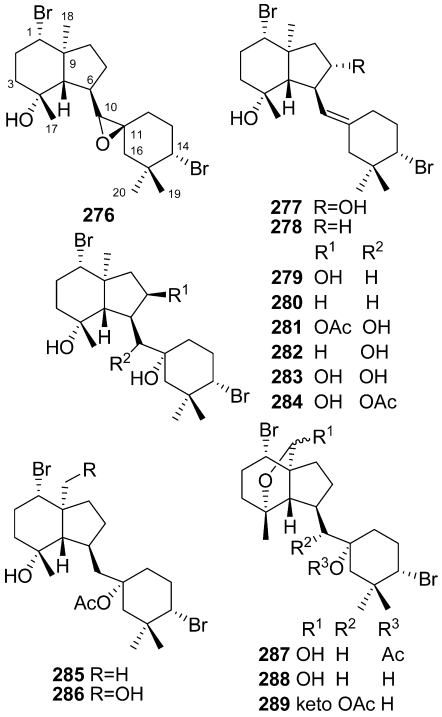

Figure 23. Irieane diterpenes (**276**–**289**).

4.3.2. Labdane Diterpenes. Concinndiol (**290**),[195] a labdane diterpene identified from *L. concinna*, was the second example of a bromoditerpene that found to occur naturally (The first was aplysin-20 from the sea hare *Aplysia kurodai*,[196] which consumes red algae, especially *Laurencia* species, and thus the true source of aplysin-20 appears likely to be a *Laurencia* species). A total of twelve halogenated labdane diterpenes (**290**–**301**, Figure 24 and Supporting Information Table S9) were isolated from members of the family Rhodomelaceae.[195,197−205] Without exception, each of them is brominated at C_3, with one compound, **300**,[205] containing an additional Cl-substitution at C_{15}. Compounds of this class generally have OH groups at C_8, C_9, or C_{13}. While (−)-paniculatol (**299**) possesses an unusual tetrahydropyran unit,[204] compounds **300** and **301** respectively contain oxepane and oxocane moieties previously unprecedented in this type of metabolites.[205] In the original report of isoconcinndiol (**291**), the C_8 configuration was incorrectly assigned and the C_{13} configuration was undetermined,[197] and these were clarified in a latter report by synthesis.[198] As indicated in Supporting Information Table S9, at least seven species of the genera *Chondria* and *Laurencia* were found to produce halogenated labdane diterpenes, with *L. pinnata* being the most abundant source of this compound type.

4.3.3. Parguerane, Isoparguerane, Neoparguerane, and Pimarane Diterpenes. The parguerane skeleton, a new carbocyclic framework comprising a 3,18-cyclopimarane system, was named by Schmitz and co-workers in 1981 when parguerol and a series of related derivatives were first isolated from the sea hare *Aplysia dactylomela* collected near La Parguera, Puerto Rico.[206,207] As mentioned above, sea hares are known to consume large quantities of red algae, so it was not surprising that several diterpenes of this type were subsequently isolated and reported from marine red algae, including *Laurencia* species. In 1982, the first example of a brominated parguerane diterpene of algal origin, 15-bromo-2,16-diacetoxy-7-hydroxy-9(11)-parguerene (**302**, Figure 25 and Supporting Information Table S10), was obtained from *L. obtusa* that was collected from the English Channel at Kimmeridge Bay, Dorset.[208] Subsequently, 12 additional halogenated parguerane derivatives (**303**–**314**, Figure 25 and Supporting Information Table S10) were isolated from *L.*

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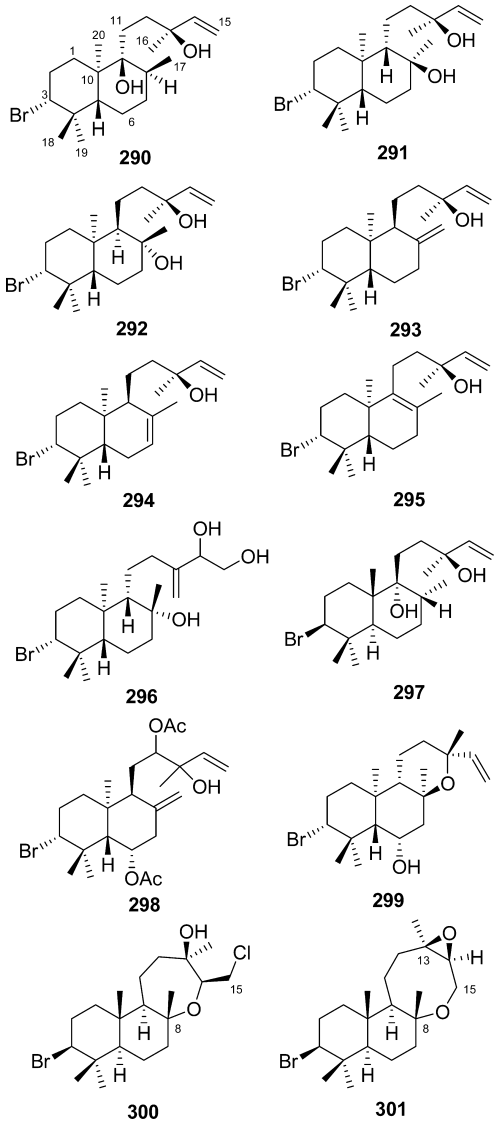

Figure 24. Labdane diterpenes (**290**–**301**).

filiformis, *L. nipponica*, and *L. obtusa* collected from Australian, Russian, and Japanese waters,[209−212] respectively, with *L. filiformis* being the most prolific producer (**307**–**312**).[211] Apart from the parguerane diterpenes, two related isomeric bromoditerpenes, deacetylisoparguerol (**315**)[210] and 2α-acetoxy-15*S*-bromo-7α,16-dihydroxy-3β-palmitoyloxy-4(19),9-(11)-neoparguerdiene (**316**),[210,213] which possess isoparguerane and neoparguerane skeletons, respectively, were identified from *L. obtusa* by Suzuki's group in 1990. From a biogenetic point of view, the isoparguerane skeleton appears to be derived from rearrangement of cyclopropane and C_{19} units in the parguerane framework, while the neoparguerane skeleton is likely generated through cleavage of the cyclopropane ring between C_3 and C_4 of the parguerane skeleton. In addition to parguerane, isoparguerane, and neoparguerane diterpenes, two new brominated pimarane diterpenes, 3,15-dibromo-9(11)-isopimarene-7,16-diol (**317**), and 3,15-dibromo-9(11)-isopimarene-7,12,16-triol (**318**) were also characterized from *L. perforata* collected at the Canary Islands.[214]

The diterpenes discussed in this section are all brominated and the Br-substitution is restricted to C_{15}, while C_{16} is oxygenated. Another feature of these derivatives is the presence

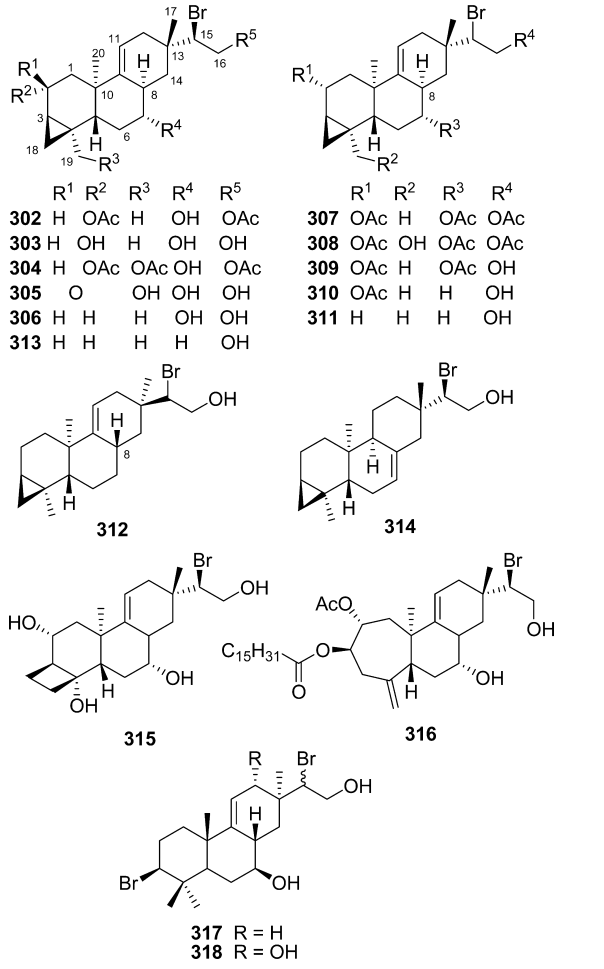

Figure 25. Parguerane (**302**–**314**), isoparguerane (**315**), neoparguerane (**316**), and pimarane (**317** and **318**) diterpenes.

of a double bond at $C_{9(11)}$, with only one exception, compound **314**, which has this functional group at C_7.[212]

4.3.4. Miscellaneous Diterpenes with New or Rarely Reported Skeletons. In addition to the halogenated diterpenes discussed above, 28 diterpenes (**319**–**346**, Figures 26 and 27 and Supporting Information Table S11) with 14 new or rarely reported carbon skeletons were also discovered from species of the family Rhodomelaceae.[67,145,149,192,193,214−229] These diterpenes, as summarized in Supporting Information Table S11, possess a diverse array of ring systems including mono- (**319**–**324**), bis- (**325**–**334**), and tricarbocyclic systems (**335**–**346**), with some of them containing spiro- (**339**–**341**) or cyclic ether/epoxide (**320**, **323**, **324**, **329**, **338**, and **339**) systems. All of these diterpenes are brominated, with two of them, dactylomelol (**320**)[215] and laurencianol (**324**),[217] also containing a chlorine atom. Some of these diterpenes possessing a rigid *cis*-1,2-bromohydrin (**322**, **323**, **325**–**331**, and **342**–**346**) or chlorohydrin (**324**) unit. *L. microcladia*[216,219] and *L. obtusa*[217,218,220,221] are the two most prolific producers of haloditerpenes having new or rarely reported skeletons (Supporting Information Table S11).

4.4. Halogenated Triterpenes/Polyethers

Rhodomelaceae-derived triterpenes also comprise a relatively small group of metabolites compared to the number of sesquiterpenes and nonterpenoid C_{15}-acetogenins obtained from this family. All of the halogenated triterpenes found to

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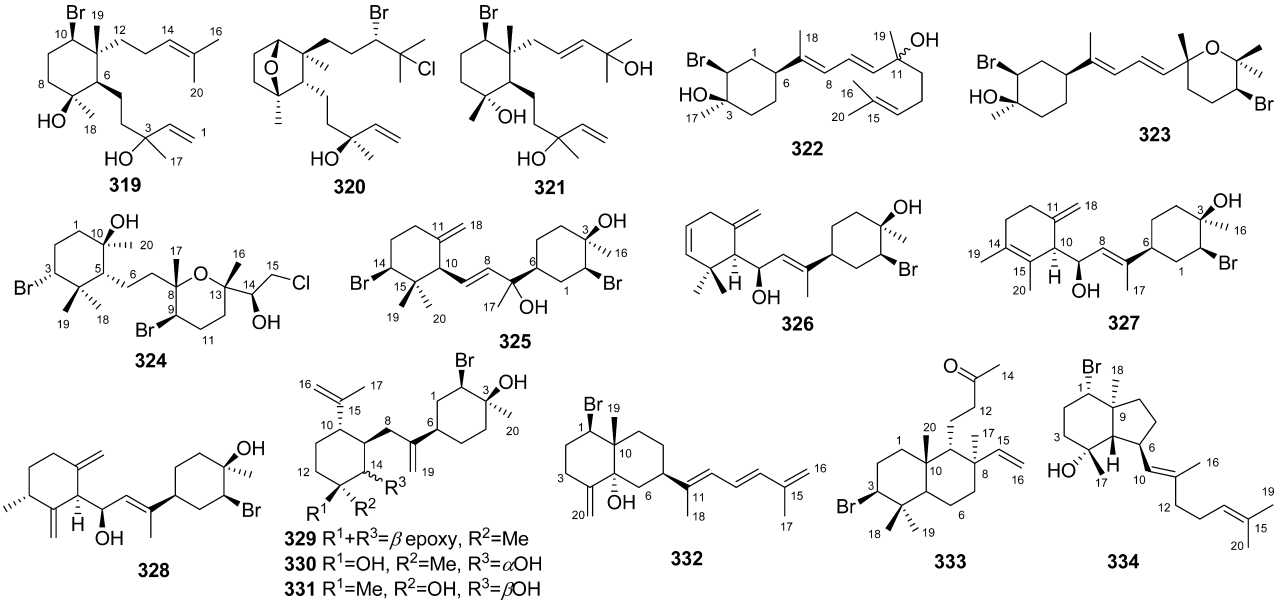

Figure 26. Miscellaneous diterpenes with new or rarely reported skeletons (**319**–**334**).

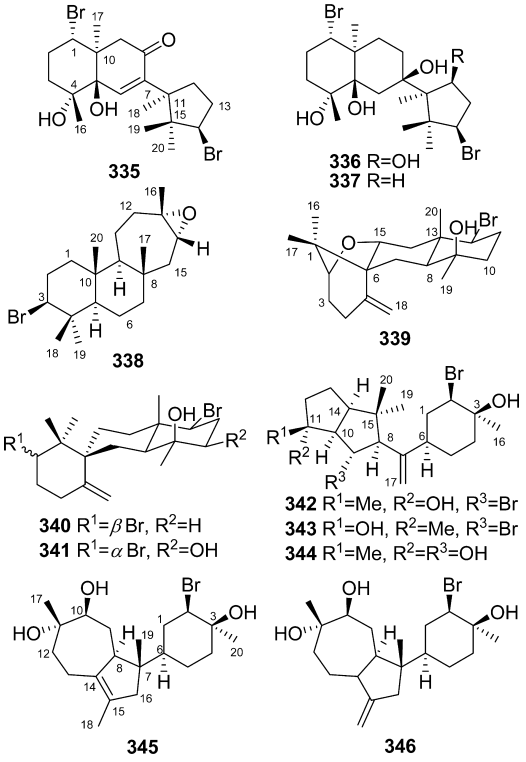

Figure 27. Miscellaneous diterpenes with new or rarely reported skeletons (**335**–**346**).

date from the family are noncarbocyclic polyethers that are biogenetically derived from squalene. An excellent review dealing with the structures, biogenetic considerations, and biological activities of both halogenated and nonhalogenated polyethers from red algae and sponges appeared in 2000.[230] On the basis of their structural characteristics, the halogenated triterpenes of Rhodomelaceae origin can be divided into three different classes including those with a 2,7-dioxabicyclo[4.4.0]-decane skeleton, those with a 2,8-dioxabicyclo[5.4.0]undecane skeleton, and one having a distinctive C_2 symmetry element.

4.4.1. Triterpenes Possessing a 2,7-Dioxabicyclo[4.4.0]decane Skeleton. The 2,7-dioxabicyclo[4.4.0]decane moiety is a typical feature in most of the triterpenes reported from the Rhodomelaceae. A total of 33 halogenated triterpenes that possess a 2,7-dioxabicyclo[4.4.0]decane unit are known from this family (**347**–**379**, Figure 28 and Supporting Information Table S12).[127,231−248] This unit is generally connected to an oxane moiety by a single bond in the left side, while in the right side it connected to a side chain differing at C_{15} through C_{24} either in the configuration of the chiral centers (e.g., thyrsiferol **347**[231−233] and venustatriol **348**),[233] in the degree of oxidation (e.g., thyrsiferol **347** and dehydrothyrsiferol **350**),[127] or in the number and size of cyclic ether ring(s) (e.g., magireol A **353**,[235] thyrsiferol **347**, callicladol **356**,[236] and isodehydrothyrsiferol **365**).[241] Among these, isodehydrothyrsiferol (**365**) is the only example containing an oxane unit in the right side chain,[241] while thyrsenols A and B (**376** and **377**)[248] and 15-dehydroxythyrsenol A (**378**)[246] each possesses an unusual enol-ether moiety. In addition, clavidol (**372**),[242] prethyrsenol A (**373**), 13-hydroxyprethyrsenol A (**374**),[246] and 14-keto-dehydrothyrsiferol (**375**)[247] are the only examples in this series without a 10,14-cyclic ether ring. Without exception, each compound in this category is C_3 brominated with β-configuration implying the strict biogenetic bromination pathway for this kind of compounds. The archetypal compound of this class is thyrsiferol (**347**), which was the first squalene-derived halogenated triterpenes to be described, and was isolated from *L. thyrsifera* collected at Seal Reef, Kaikoura, New Zealand.[231] The structure of **347** was determined on the basis of spectroscopic methods, as well as X-ray crystallographic analysis of its 18-acetate,[231] and the ^{1}H and ^{13}C NMR data for this compound was fully assigned in a subsequent report.[232] Compounds of this class occur mainly in species of *L. obtusa*[234,235] and *L. viridis*,[237−242,246−248] as well as in *L. calliclada*,[236] *L. mariannensis*,[243] *L. pinnatifida*,[127] *L. thyrsifera*,[231] and *L. venusta*[233] (Supporting Information Table S12). It should be noted that 21α-hydroxythyrsiferol (**367**) and laurenmariannol (**368**) were reported as new compounds from *L. mariannensis* in 2008.[243] However, the spectroscopic

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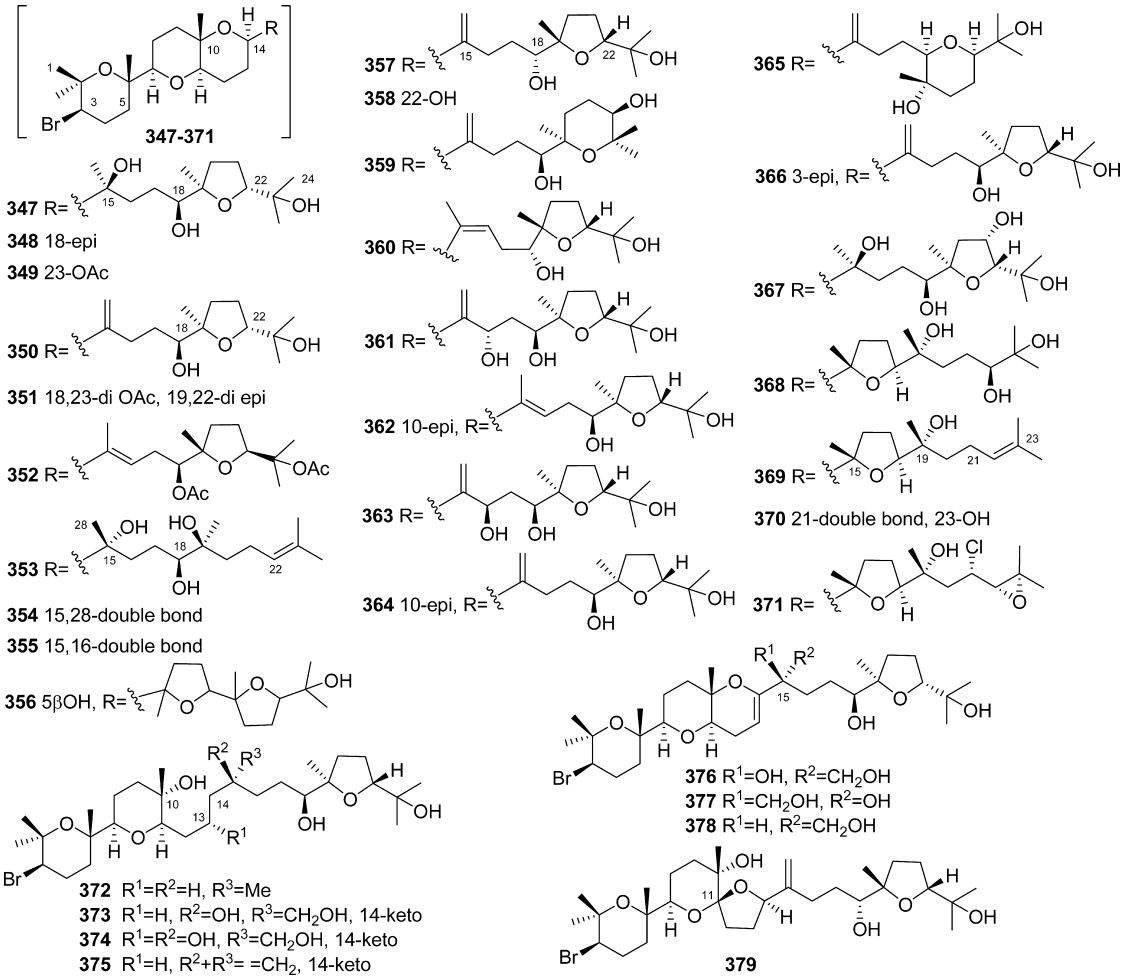

Figure 28. Triterpenes/polyethers of 2,7-dioxabicyclo[4,4,0]decane class (**347**−**371**) and the related congeners (**372**−**379**).

data of these two compounds were very similar to those of aplysiols A and B, which were isolated from the sea hare *Aplysia dactylomela* in 2007.[244] Sea hare are known to feed upon *Laurencia* species, and it thus seems likely that the true origin of these compounds is dietary algae. Recently, the relative configuration of laurenmariannol (aplysiol B, **368**) was revised with the aid of a 1D gradient selective NOESY experiment.[245]

4.4.2. Triterpenes Possessing a 2,8-Dioxabicyclo[5.4.0]undecane Skeleton. Compounds **380**−**388** fall into a class of halogenated triterpenes/polyethers having a 2,8-dioxabicyclo[5.4.0]undecane unit (Figure 29 and Supporting Information Table S12).[240,249−253] Seven of them, **380**−**386**,[240,249] feature an oxepane ring fused to the 2,8-dioxabicyclo[5.4.0]undecane unit thereby affording a 7/7/6-ring system, which further connects via single bonds either to an oxolane ring (**380**)[240] or to an oxepane ring (**381**−**386**).[249] In contrast, two other triterpenes, enshuol (**387**)[250,251] and aurilol (**388**),[252,253] possess a 2,8-dioxabicyclo[5.4.0]undecane unit connected via a single bond to three and two isolated oxolane rings, respectively. These triterpenes are all brominated at C_3, but not for armatol A (**381**, with C_{22} bromination), and usually possess β-configuration (except for **382** and **383**). Armatols B−F (**382**−**386**)[249] have additional bromine substitution at C_{22} with β-configuration. Compounds of this class of triterpenes were found in samples of *Chondria armata*,[249] *Laurencia omaezakiana*,[250,251] and *L. viridis*,[240] as well as in the sea hare *Dolabella auricularia*,[252,253] which is known to feed on marine algae like *Laurencia* species.

4.4.3. Triterpenes Possessing Symmetric Element(s). The chlorinated bromotriterpene intricatetraol (**389**, Figure 29 and Table S12) was identified from *Laurencia intricata* collected from three different sites near Hokkaido, Japan.[254] This compound is the only example of a halogenated triterpene with a C_2 symmetrical structure and was the first example of a chlorine-containing triterpene found from a species of the family Rhodomelaceae.

4.5. Halogenated Nonterpenoid C_{15}-Acetogenins (ACGs)

The C_{15}-acetogenins (ACGs) are a large group of halogenated organic molecules that are commonly found in species of the family Rhodomelaceae. It is generally accepted that these ACGs arise from a common C_{15} precursor, which is in all probability derived from a C_{16} fatty acid. In addition to a few linear ACGs, most of these ACG derivatives are characterized as cyclic ether metabolites varying in ring sizes and usually contain a conjugated enyne or bromoallene terminus. Since the isolation of laurencin, the first Rhodomelaceous ACG derivative, from *Laurencia glandulifera* in 1965,[255] reports of such molecules have rapidly grown in number. On the basis of data in hand, 180 Rhodomelaceae-derived halogenated ACGs (**390**−**569**) were described to date. In the discussion below, these ACGs are grouped into linear and cyclic ether classes, with the latter

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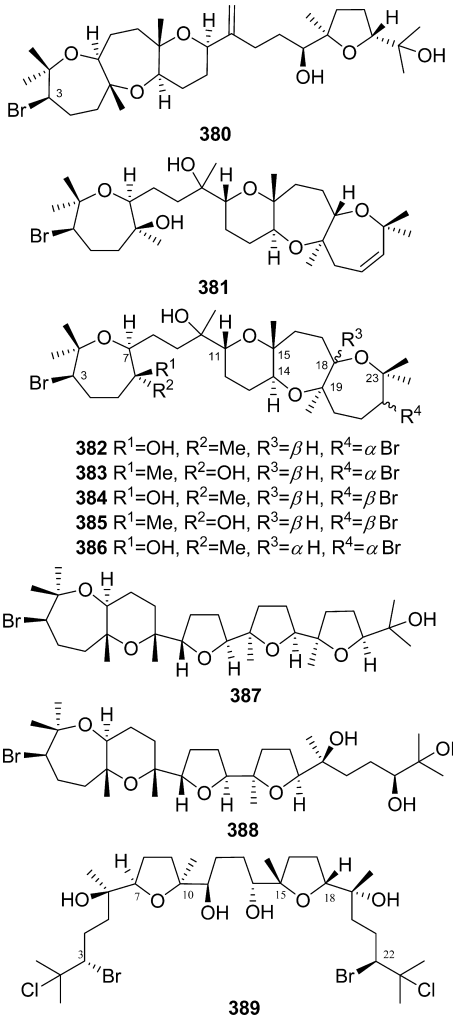

Figure 29. Triterpenes/polyethers of 2,8-dioxabicyclo[5,4,0]undecane class (**380**–**388**) and one possessing symmetric element (**389**).

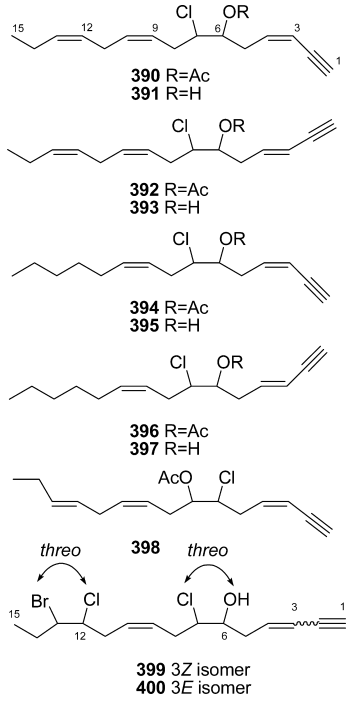

Figure 30. Linear acetogenins (**390**–**400**).

further divided according to the size of the largest ether ring present.

4.5.1. Linear ACGs. The first example of a halogenated linear ACG, 6-acetoxy-7-chloro-3*Z*,9*Z*,12*Z*-pentadecatrien-1-yne (**390**), was isolated from *Laurencia pinnatifida* in 1982.[256] A total of eleven members of this metabolite class were identified so far, with eight (**390**–**397**)[256,257] from *L. pinnatifida*, one (**398**)[258] from *L. glandulifera*, and very recently, two (**399** and **400**)[259] from a newly described species, *L. marilzae* (Figure 30 and Supporting Information Table S13). These ACGs are all oxygenated at C_6 and chlorinated at C_7, with only one exception, **398**, which is chlorinated at C_6 and oxygenated at C_7. Each of these ACGs contains a *cis*- or *trans*-enyne terminal moiety and one or two isolated double bond(s), and all these isolated double bonds possess Z-geometry, except for the case of **398**.[258]

4.5.2. ACGs of the Five-Membered Cyclic Ether Class (Tetrahydrofuran ACGs, THF ACGs). Sixteen halogenated compounds (**401**–**416**, Figure 31 and Supporting Information Table S13) fall into the class of five-membered cyclic ether ACGs (or tetrahydrofuran ACGs, THF ACGs) of Rhodomelaceae origin.[72,116,258,260–264] They all possess an ethyl group as one terminus, while four different units may be present as the other terminus: one has a bromopropargylic unit (**412**),[263] two have bromoallenic groups (**413**[263] and **414**),[116] and the other thirteen have a *cis*- or *trans*-enyne moiety. Compounds of this class are generally brominated, with three of them chlorinated (**407**–**409**)[258] and four bromochlorinated (**410**, **411**,[258] **415**,[72] and **416**).[264] The first halogenated THF ACG to be reported was laureepoxide (**401**), which was isolated from *L. nipponica* collected from Hokkaido, Japan.[260] This compound is also the first example of a brominated ACG derivative containing both oxolane and oxirane rings. The THF ACGs occur mainly in *L. glandulifera*,[258] *L. nipponica*,[260–262] and *L. obtusa*.[72,263]

4.5.3. ACGs of the Bis-Tetrahydrofuran Class (Bis-THF ACGs). Seven compounds (**417**–**423**), including five derivatives possessing a 2,2′-bis-tetrahydrofuran substructure (**417**–**421**)[107,265–270] and two having isolated oxolane rings (**422**[271] and **423**),[272] comprise the class of halogenated bis-THF ACGs (Figure 32 and Table S13), which were found among five algal species (*L. decumbens*,[269,270] *L. elata*,[267,268] *L. majuscula*,[107,265,268] *L. nipponica*,[266] and *L. obtusa*).[271,272] Each of these ACGs also has an ethyl group as one terminus. Six of them possess *cis*- or *trans*-enyne moieties at the other terminus, while the seventh, **423**,[272] has a bromoallenic unit. All of these bis-THF-ACGs are brominated and compounds **418**,[266] **420**,[107,268] and **421**[269,270] also contain a Cl-atom. Compound **423** is the only tetrabrominated derivative among all of the ACGs isolated from Rhodomelacese.[272] Among the bis-THF ACGs, the presence of two 2,2′-bis-tetrahydrofuran derivatives, **419** (elatenyne) and **420**, are perhaps most noteworthy. These two compounds were originally characterized as 2,7-dioxabicyclo[4.4.0]decane metabolites of *L. elata*[267] and *L. majuscula*,[107] respectively. However, their structures were later revised to 2,2′-bis-tetrahydrofuran derivatives by total synthesis.[268] Similar revision was made to the structure of laurendecumenyne B (**421**),[270] which was originally isolated from *L. decumbens* and its structure was elucidated solely by NMR comparison with that of originally assigned for **419**.[269] ACGs having 2,2′-bis-tetrahydrofuran and 2,7-dioxabicyclo[4.4.0]decane units possess the same carbon and

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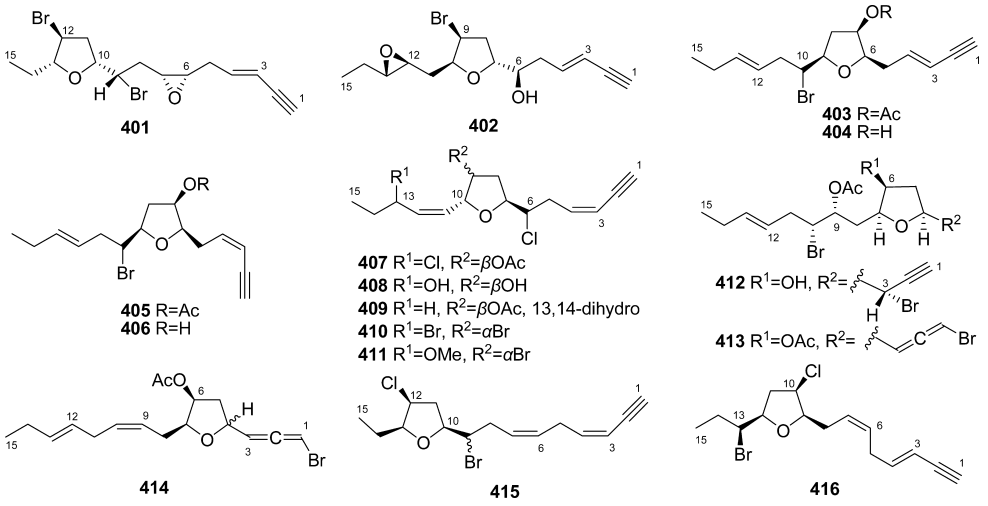

Figure 31. ACGs of the tetrahydrofuran class (**401**−**416**).

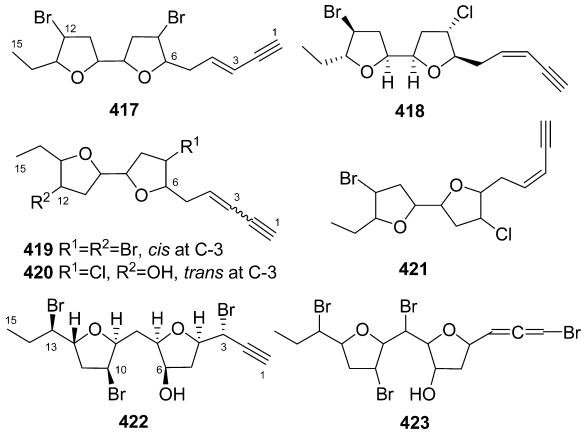

Figure 32. ACGs of the 2,2′-bis-tetrahydrofuran class (**417**−**423**).

proton connectivity, making unambiguous structure assignment solely by NMR analysis challenging.[268] Therefore, other evidence, such as chemical transformation, total synthesis, computation modeling, or X-ray crystallographic data are particularly important for structure confirmation in these cases.

4.5.4. ACGs of the 2,6-Dioxabicyclo[3.3.0]octane Class. Thirteen ACGs of the 2,6-dioxabicyclo[3.3.0]octane class, which contain two five-membered ether rings derived either from C_4−C_7 and C_6−C_9 etherification (**424**−**433**)[67,203,273−280] or from C_7−C_{10} and C_9−C_{12} etherification (**434**−**436**),[281,282] were isolated from the Rhodomelaceae (Figure 33 and Supporting Information Table S13), with obtusin (**424**), which was isolated and reported by Howard and co-workers from a Mediterranean variety of *L. obtusa* in 1979, was the first example of this class.[273] The structure of obtusin (**424**) was determined by analysis of spectral data as well as by X-ray crystallographic studies of its 3-OH derivative, obtusinol, which was obtained by treatment of obtusin (**424**) with an excess of silver acetate in glacial acetic acid, followed by saponification of the resulting acetate with methanolic KOH.[273] This compound as well as two other congeners, neoobtusin (**425**)[274] and chinzallene (**426**),[203] contain an additional five-membered cyclic ether ring derived from C_9−C_{12} etherification, and thus forming a unique and unprecedented bicyclic ketal motif. All halogenated ACGs of the 2,6-dioxabicyclo[3.3.0]-octane class are brominated, with one compound, **430**, also containing a Cl-atom as part of a chlorohydrin moiety in the structure.[276] The bromoallenic unit is the most frequently occurring terminus among this group of ACGs, although bromopropargylic- (**424**[273] and **425**[274]) and *cis*-enyne (**434**−**436**)[281] termini are also present in some of these compounds.

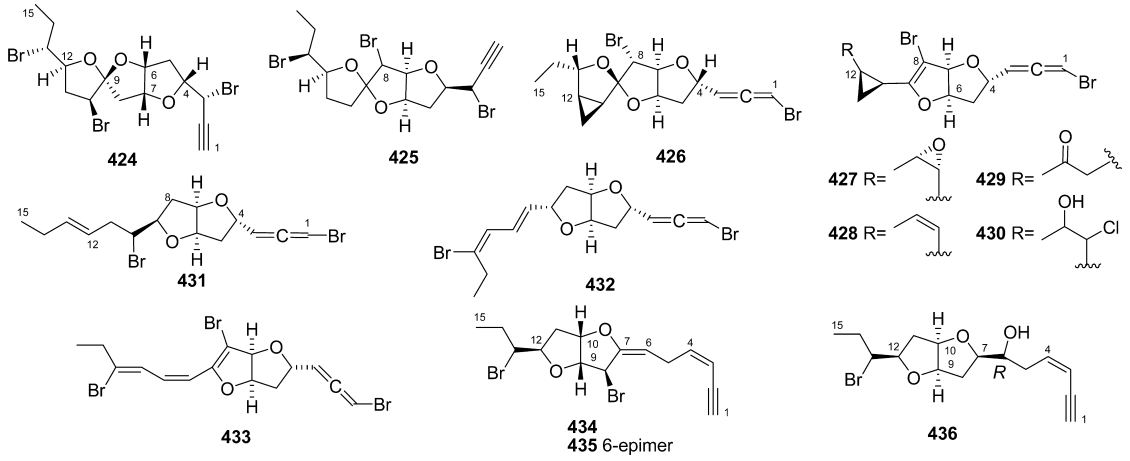

Figure 33. ACGs of the 2,6-dioxabicyclo[3.3.0]octane class (**424**−**436**).

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ACG derivatives of this 2,6-dioxabicyclo[3.3.0]octane class are mainly found from species of *L. intricata*[275−278] and *L. obtusa*,[273,274] but also occur in *L. mariannensis*,[67] *L. nidifica*,[282] *L. nipponica*,[279] *L. okamurai*,[280] and some undescribed *Laurencia* species.[281]

4.5.5. ACGs of the Six-Membered Cyclic Ether Class (Tetrahydropyran ACGs, THP ACGs). Surprisingly, only two tetrahydropyran (THP) ACG derivatives were identified from the Rhodomelaceae to date. Scanlonenyne (**437**)[283] was isolated from *L. obtusa* that was collected at Scanlon Islands, Ireland, and bisezakyne B (**438**)[264] was obtained from an undescribed *Laurencia* species collected at Bisezaki, Okinawa, Japan (Figure 34 and Supporting Information Table S13).

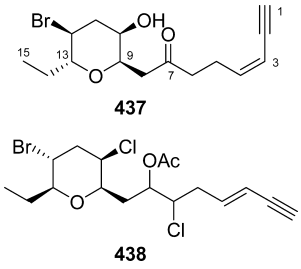

Figure 34. ACGs of the six-membered cyclic ether class (**437** and **438**).

Compound **437** is brominated and possesses a *cis*-enyne terminus, while **438** is bromochlorinated and has a *trans*-enyne terminus. The former represents the first halogenated C_{15}-acetogenin with a ketone functionality at the C_7 position from a *Laurencia* species. This compound was very unstable and a large amount of the sample decomposed despite refrigerated storage.[283]

4.5.6. ACGs of the 2,7-Dioxabicyclo[4.3.0]nonane Class. Thus far, only three ACGs containing a 2,7-dioxabicyclo[4.3.0]nonane skeleton, japonenynes A−C (**439**−**441**, Figure 35 and Supporting Information Table S13), all

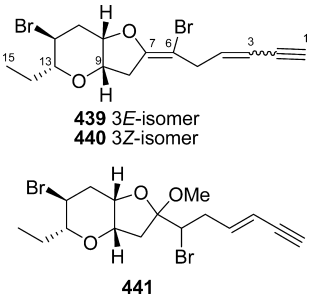

Figure 35. ACGs of the 2,7-dioxabicyclo[4.3.0]nonane class (**439**−**441**).

brominated at C_6 and C_{12} and having either a *cis*- or a *trans*-enyne terminus, were described.[284] These compounds were isolated from a Japanese *L. japonensis* and their structures were deduced from spectral evidence. They were observed to be very unstable and decomposed even when stored at −18 °C for a few days. Japonenyne C (**441**) may be an artifact formed during the extraction process.[284]

4.5.7. ACGs of the Seven-Membered Cyclic Ether Class. *4.5.7.1. Seven-Membered Monocyclic Ether (Oxepane) ACGs.* ACGs of the monocyclic oxepane class share common a cyclic ether ring that is formed by C_7−C_{12} etherification. Five compounds including one brominated (**442**)[285] and four bromochlorinated derivatives (**443**−**446**)[286,287] fall into this class, with the former having a bromoallenic terminus and the latter possessing *cis*- or *trans*-enyne termini (Figure 36 and

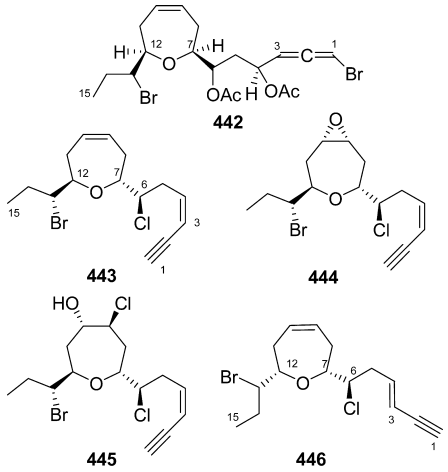

Figure 36. ACGs of the seven-membered cyclic ether class (**442**−**446**).

Supporting Information Table S13). The C_9 and C_{10} positions in these ACGs are usually functionalized, either as part of a double bond (**442**,[285] **443**,[286] and **446**),[287] an epoxy unit (**444**),[286] or a chlorohydrin moiety (**445**),[286] while the C_6 position is either oxygenated (**442**)[285] or chlorinated (**443**−**446**).[286,287] Compounds of this class reported so far are present in species of *L. microcladia*,[286] *L. nipponica*,[285] and *L. pinnata*[287] collected either from Mediterranean or from Japanese waters.

4.5.7.2. Seven-Membered Cyclic Ether ACGs with Additional 6,9-Epoxide Ring. Four oxepane ACGs coupled with a 6,9-epoxide ring including isoprelaurefucin (**447**),[288] (3*Z*)-isoprelaurefucin (**448**),[289] and (3*Z*)-neoisoprelaurefucin (**449**)[290] from *L. nipponica*, and (3*E*)-neoisoprelaurefucin (**450**) from *L. obtusa*,[40] were reported from members of the Rhodomelaceae (Figure 37 and Supporting Information Table

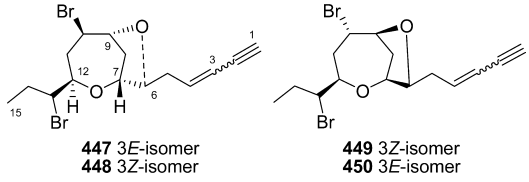

Figure 37. ACGs of the seven-membered cyclic ether class (**447**−**450**).

S13). All these compounds are dibrominated at C_{10} and C_{13} and have the same planar structure, differing only in their stereochemistry. Each compound has 1-bromopropanyl- and enyne-termini, in the left and right sides, respectively.

4.5.8. ACGs of the Eight-Membered Cyclic Ether Class. The first eight-membered cyclic ether ACG derivative, laurencin (**451**, Figure 38), was identified from a Hokkaido specimen of *L. glandulifera* in 1965,[255] and its isolation and structure determination were reported in detail in 1968.[291] The structure was determined by spectroscopic and chemical methods and was confirmed by X-ray crystallographic analysis.[292,293] To date, a total of 75 halogenated derivatives of eight-membered cyclic ether ACGs (**451**−**525**, Figures 38−

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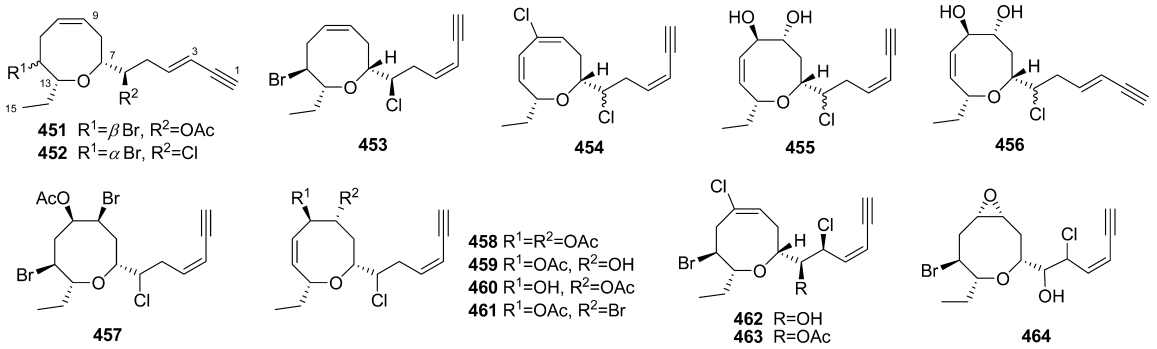

Figure 38. ACGs of the eight-membered cyclic ether class (**451**−**464**).

42 and Supporting Information Table S13) were described from members of the family Rhodomelaceae, making it the most abundant class of halogenated organic molecules found in this taxonomic group. Based on the ring closure system in the structures, this class of ACGs can be further divided into seven subclasses including those with 7,13-epoxy (**451**−**464**, Figure 38),[255,287,291−299] 6,9:7,13-bisepoxy (**465**−**471**, Figure 39),[108,178,299−302] 6,10:7,13-bisepoxy (**472**[269] and **473**,[303]

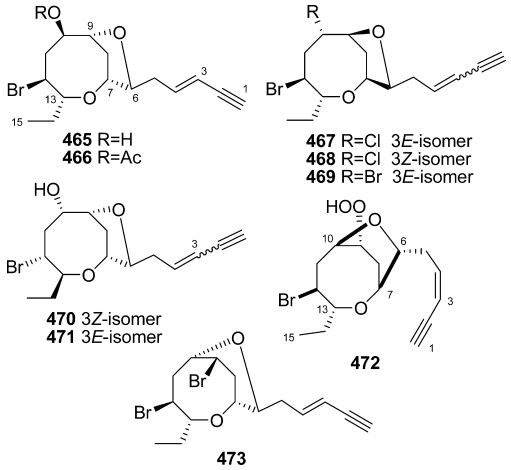

Figure 39. ACGs of the eight-membered cyclic ether class (**465**−**473**).

Figure 39), 6,12-epoxy (**474**−**509**, Figure 40),[124,175,225,256,259,304−323] 4,7:6,12-bisepoxy (**510**−**518**, Figure 41),[269,271,276,285,324−328] 4,10:9,13-bisepoxy (**519**−**521**, Figure 42),[329] and 4,14:6,12-bisepoxy (**522**−**525**, Figure 42)[330] frameworks.

All members of the first three subclasses (**451**−**473**, Figures 38 and 39) feature an ethyl unit at one terminus and a *cis*- or *trans*-enyne moiety at the other. As for the fourth and fifth subclasses (**474**−**518**, Figures 40 and 41), a bromopropyl unit frequently occurs at one terminus, with the other consisting of either a *cis*- or *trans*-enyne moiety for the fourth subclass (**474**−**506**, Figure 40) or a bromoallenic or bromopropargylic units for the fifth subclass (**510**−**518**, Figure 41). Microcladallenes A−C (**519**−**521**, Figure 42) identified from *L. microcladia* (off the French coast at Cape Ferrat)[329] and marilzabicycloallenes A−D (**522**−**525**, Figure 42) isolated from a newly described species *L. marilzae* (Canary Islands, Spain),[330] are the only representatives of the sixth and seventh subclasses of ACG derivatives to be reported so far. Each of these compounds contains a bromoallenic unit at one terminus and an ethyl- (**519** and **521**), or olefinic (**520**), or methyl (**522**−**525**) unit at the other.

The C_9 and C_{10} positions in the eight-membered cyclic ether ACGs are usually functionalized as a double bond (**451**−**444**, **462**, **463**, **474**, **476**−**480**, **485**, **487**, **491**, **494**−**497**, **499**, **502**−**505**, **507**−**509**, **510**−**512**, and **517**), a diol (**455**, **456**, and **518**), an epoxy (**464**, **475**, **488**, **500**, and **501**), or a halohydrin unit (**457**, **461**, **486**, **489**, **490**, **492**, **493**, **506**, and **513**−**515**), while the C_6 position in the first subclass is either chlorinated (**452**−**461**) or oxygenated (**451**, **462**−**464**). Eight-membered cyclic ether ACGs have most often been found in *L. glandulifera*,[255,291,297] *L. intricata*,[276,294,295,298] *L. marilzae*,[259,330] *L. nipponica*,[285,300,301,303,308−313,324,325] and *L. obtusa*.[271,314−319,326]

4.5.9. ACGs of the Nine- and Ten-Membered Cyclic Ether Classes. The first ACG of the nine-membered cyclic ether class, obtusenyne (**526**, Figure 43 and Supporting Information Table S13), was isolated independently by two research groups from *L. obtusa* with samples collected from Positano, Italy[299] and from Gökceada in the Aegean Sea.[331] So far, 10 nine-membered cyclic ether ACG derivatives including those containing 6,13-epoxy (**526**−**528**),[257,299,331,332] 4,7:6,13-bisepoxy (**529**−**534**),[108,116,269,327,333−335] and 5,12-epoxy (**535**)[108] ring systems, were reported from the Rhodomelaceae. These ACGs are all brominated, usually at C_{12}, with three members, the 6,13-epoxy ACGs **526**−**528**, having additional chlorine substitution at C_7.[257,299,331,332] Each of these ACGs (**526**−**534**) features an ethyl unit at one terminus, except for the 5,12-epoxy ACG derivative **535**, which has a bromopropyl unit.[108] As for the other terminus, the 6,13-epoxy (**526**−**528**) and 5,12-epoxy (**535**) ACGs possess either a *cis*- or *trans*-enyne group, while the 4,7:6,13-bisepoxy ACGs (**529**−**534**) possess a bromoallenic moiety. The C_9 and C_{10} positions of these ACGs are also functionalized either as a double bond (**526**−**531** and **535**) or a diol (**534**) or are oxygenated and brominated (**532** and **533**). It is worth mentioning that a recently reported asymmetric total synthesis of itomanallene A indicated that the initially proposed *α,α′-cis*-tetrahydrofuran moiety should be corrected to *α,α′-trans*-configuration (**531**),[336] which is a common feature for ACGs of 4,7:6,13-bisepoxy series (**529**−**534**). ACGs of the nine-membered cyclic ether class were found in *L. decumbens*,[269] *L. implicata*,[108,327] *L. intricata*,[116] *L. nipponica*,[333,334] *L. obtusa*,[299,331] *L. okamurai*,[334,335] and *L. pinnatifida*.[257,332]

Thus far only one ten-membered cyclic ether ACG, compound **536** (Figure 44 and Supporting Information Table S13), was described from the Rhodomelaceae.[108] This brominated compound was isolated from *L. implicata* collected

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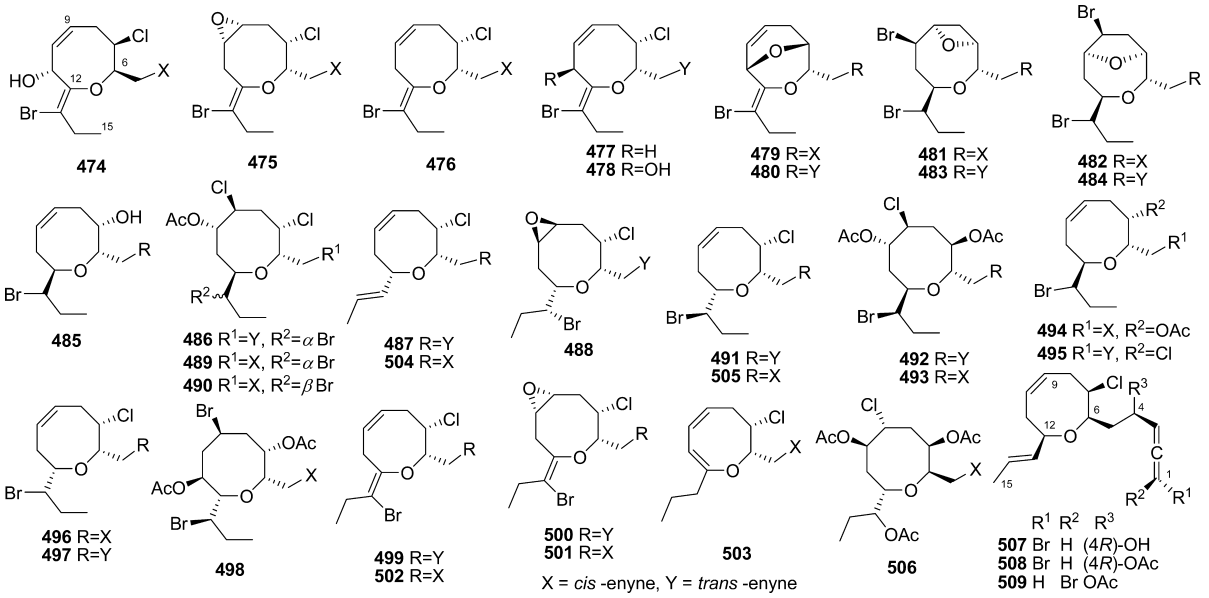

Figure 40. ACGs of the eight-membered cyclic ether class (**474**−**509**).

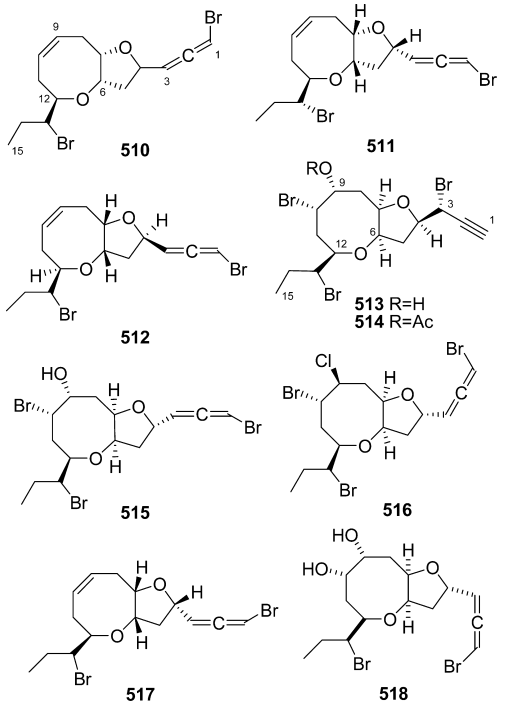

Figure 41. ACGs of the eight-membered cyclic ether class (**510**−**518**).

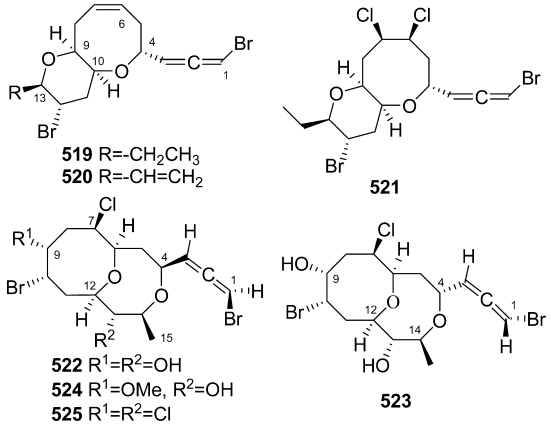

Figure 42. ACGs of the eight-membered cyclic ether class (**519**−**525**).

from Florence Bay, Magnetic Island, and possesses normal ethyl and *cis*-enyne units as termini. The absolute configurations of the stereocenters in **536** were not defined.

4.5.10. ACGs of the Twelve-Membered Cyclic Ether Class. The first twelve-membered cyclic ether ACG to be described was obtusallene I (**537**) that was isolated from *L. obtusa* collected at Gökceada in the Aegean Sea.[337] To date, a total of 14 ACG metabolites of this class (**537**−**550**, Figure 45 and Supporting Information Table S13) were obtained from Rhodomelaceae, with 11 of them were isolated from *L. obtusa* (**537**−**541** and **545**−**550**),[337−343] and three of them were recently identified from a newly described species, *L. marilzae*.[259] These ACGs feature a 4,14-epoxy linkage to form the twelve-membered cyclic ether ring and each of them have methyl and bromoallenic termini. In addition to the twelve-membered ring, these ACG derivatives usually contain an additional O-bridged five- or six-membered ring in the structures, with two of them, obtusallenes V and VI (**545** and **546**), containing two five-membered cyclic ether rings that derived from C_6−C_9 and C_9−C_{12} etherification, thereby forming a unique and unprecedented spiro-ketal motif in each case.[341,342] The members of this group are all brominated and some are bromochlorinated (**537**−**539**[337−339] and **541**−**547**).[259,340−342] The placement of the bromine atom at C_7 and chlorine atom at C_{13} for obtusallenes V−VII (**545**−**547**) was originally assigned by NMR spectroscopic analysis.[341] However, the results from GIAO-based density functional prediction revealed that the positions of the halogen atoms at C_7 and C_{13} in these compounds should be reversed.[342] These results again indicated the challenge for the structure assignment by NMR spectral analysis of bromochlorinated metabolites. In addition, the assignment of relative configurations for the macrocyclic ether ACGs such as obtusallene V (**545**) is also troublesome because of the superimposition of the ^{1}H NMR signals and conformational flexibility in the functionalized portion of the macrocycle.[341] Collecting ^{1}H NMR spectra in different NMR

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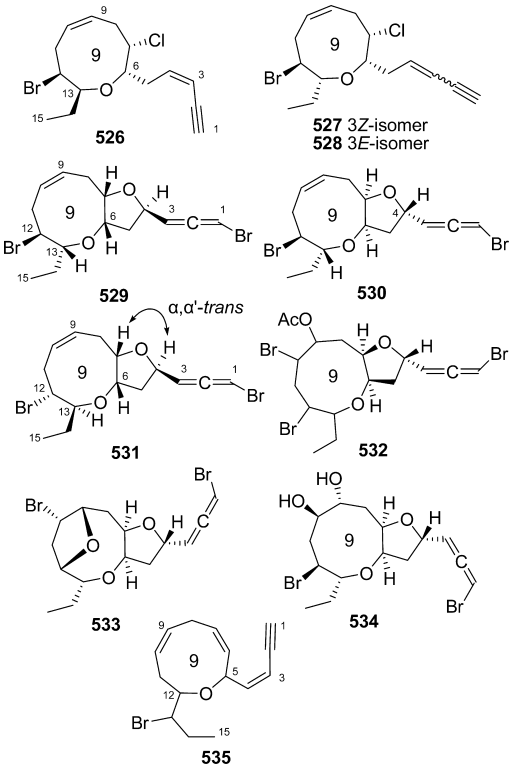

Figure 43. ACGs of the nine-membered cyclic ether class (**526**–**535**).

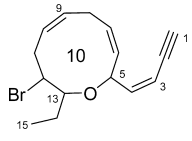

Figure 44. ACG of the ten-membered cyclic ether class (**536**).

solvents might be a solution of the problem of signal superimposition.[341]

4.5.11. ACGs of the Maneonene and Isomaneonene Classes. Two other sets of ACG derivatives from the Rhodomelaceae, **551**–**559**[96,344–349] and **560**–**562** (Figures 46 and 47 and Supporting Information Table S13),[345,346,349] were named as maneonene and isomaneonene classes,

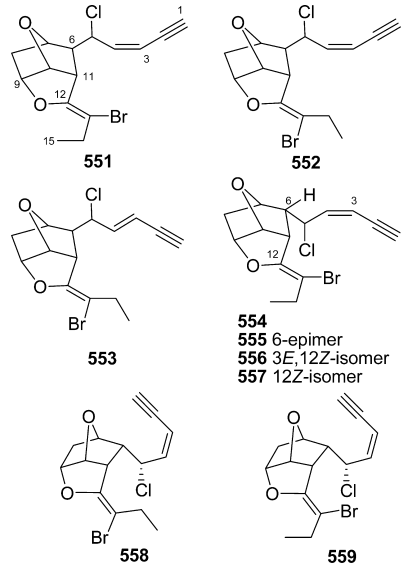

Figure 46. ACGs of the maneonene class (**551**–**559**).

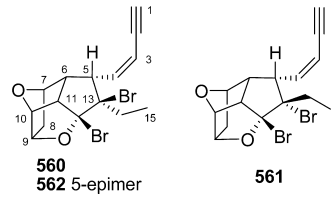

Figure 47. ACGs of the isomaneonene class (**560**–**562**).

respectively. These compounds differ from the other ACGs discussed above in that the carbon chain cyclized back on itself to form a carbocyclic ring in maneonenes (C_6–C_{11} bond, **551**–**559**) and biscarbocyclic rings in isomaneonenes (C_5–C_{13} and C_6–C_{11} bonds, **560**–**562**). Each of the maneonene and isomaneonene ACG derivatives features terminal ethyl and *cis*- or *trans*-enyne units. All maneonene ACGs (**551**–**559**) are bromochlorinated, with chlorine at C_5 and bromine at C_{13}, while the isomaneonenes (**560**–**562**) are all dibrominated at C_{12} and C_{13}. The first examples of maneonene derivatives were *cis*-maneonenes A (**551**) and B (**552**), and *trans*-maneonene B (**553**) (Figure 46), which were isolated from a green variety of *L. nidifica* collected off the south coast of Oahu, Hawaii.[344,345]

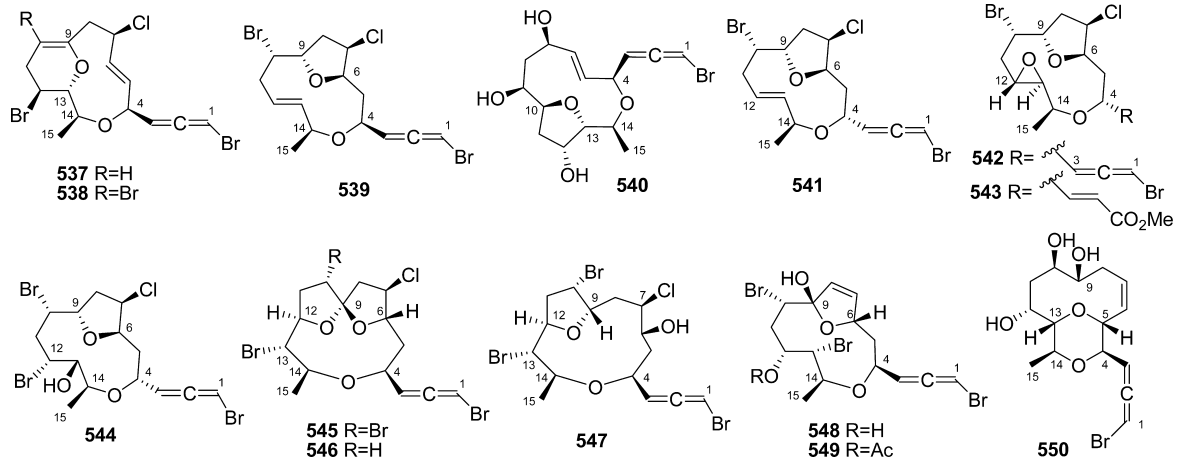

Figure 45. ACGs of the twelve-membered cyclic ether class (**537**–**550**).

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Recently, (12*E*)-*cis*-maneonene E (**555**) was isolated from two *Laurencia* species, *L. papillosa*[347] and *L. obtusa*,[348] and was reported twice by the same group in 2011.[347,348] Confusingly, a different configuration at C_6 was described in the reports, although the assignment in the latter report seems more reasonable.[348] As for the isomaneonene class, the only three ACGs of this type reported so far are isomaneonenes A (**560**) and B (**561**) from a Hawaiian collection of *L. nidifica*[345,346] and the C_5-isomer of **560**, lembyne B (**562**), from an unidentified Malaysian *Laurencia* species (Figure 47).[349]

4.5.12. Branched ACGs. All of the ACG derivatives discussed above incorporate a linear C_{15} chain, with the chain either modified or folded to form cyclic ethers or carbocycles, and, most terminate with an enyne or bromoallene function. In 1991, however, the first ACGs found to contain a branched C_{15} chain, rogiolenynes A–C (**563**–**565**, Figure 48 and Supporting

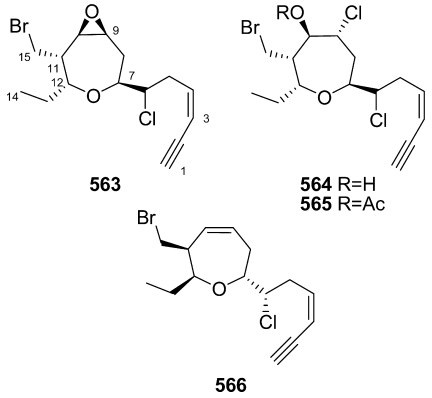

Figure 48. Branched ACGs (**563**–**566**).

Information Table S13), were reported from the alga *L. microcladia* and the sponge *Spongia zimocca*.[350] These two organisms occur in the same small area in the Mediterranean off the Torrent Il Rogiolo, south of Livorno. It is suggested that rogiolenynes B (**564**) and C (**565**) might be derived by transferring rogiolenyne A (**563**) from the alga *L. microcladia* to the sponge *S. zimocca* where it undergoes epoxide opening by Cl^- to give **564**, followed by acetylation to give **565**.[350] Another study of the same algal sample afforded rogiolenyne D (**566**), a novel branched ACG that was hypothesized to be the parent compound in this series.[351] All of these branched ACGs have terminal ethyl and *cis*-enyne units, and all are bromochlorinated, with a bromine atom at C_{15} and a chlorine atom at C_6. Two of them, rogiolenynes B (**564**) and C (**565**), have additional chlorine substitution at C_9.[350] The structures of these compounds were established by extensive spectral analysis as well as by chemical transformation, and the absolute configuration was assigned via the Mosher's NMR method applied to the MTPA esters of rogiolenyne B (**564**).[350]

4.5.13. Miscellaneous ACGs. Two novel ACGs, (3*E*,6*R**,7*R**,9*R**,10*S**)-6,9:7,10-bisepoxy-13-chloro-12-hydroxypentadeca-3,14-dien-1-yne (**567**) and (3*E*,6*R**,7*R**,9*R**,10*S**,13*E*)-6,9:7,10-bisepoxy-15-chloro-12-hydroxypentadeca-3,13-dien-1-yne (**568**), both possessing the rare 2,5-dioxabicyclo[2,2,1]heptane ring system (Figure 49 and Supporting Information Table S13), were identified from *L. majuscula* collected from Holmes Reef, Queensland, Australia.[107] Another novel ACG derivative (**569**) containing isolated tetrahydrofuran and tetrahydro-2*H*-pyran rings was obtained

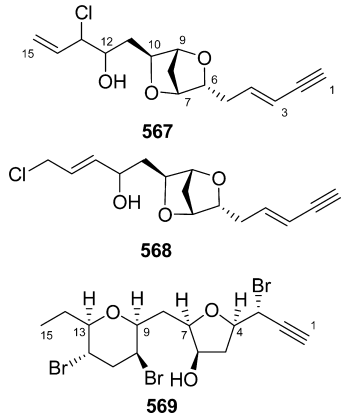

Figure 49. Miscellaneous ACGs (**567**–**569**).

from *L. obtusa* collected off the Island of La Graciosa of Canary Island.[271]

4.6. Halogenated Indoles

Twenty-seven haloindoles (all brominated) were described so far from the family Rhodomelaceae (**570**–**596**, Figure 50 and Supporting Information Table S14). These compounds can be classified into three subclasses: the monoindoles (**570**–**580**),[352–356] the *N*-methylmonoindoles (**581**–**587**),[185,192,354,355,357] and the bisindoles (**588**–**596**).[353,356–358] All of these compounds contain at least two bromine atoms. Except for three *N*-methylmonoindoles **582**,[354] **585**,[357] and **587**,[192] these indoles generally possess a bromine substituent at C_6. In addition to the bromine substitutions, fourteen of them contain sulfur (**570**, **571**,[352] **574**,[353] **578**–**580**,[356] and **589**–**596**).[353,356,358] All of the brominated indoles reported to date were found in the species *L. brongniartii*[352–354,356,358] *L. decumbens*,[192] and *L. similis* (Supporting Information Table S14).[355,357]

4.7. Halogenated Phenols/Aromatics

The number of halogenated phenols/aromatic compounds obtained from members of the Rhodomelaceae has grown considerably in recent years. A total of 92 halophenols (**597**–**688**, Figures 51–55 and Supporting Information Table S15) were isolated and identified from these sources, with 66 of them were described since 2000. On the basis of the number of benzene rings in the molecules, these halophenols can be divided into mono- (**597**–**648**,[2,359–381] Figures 51 and 52), di- (**649**–**683**,[363,365–369,373,375,380–394] Figures 53 and 54), tri- (**684**–**687**,[363,368,386,395,396] Figure 55), and tetra-aryl classes (**688**,[397] Figure 55). All of these compounds are brominated or polybrominated. Among these, 2,3-dibromobenzyl alcohol 4,5-disulfate dipotassium salt (**597**, Figure 51), isolated from *Polysiphonia lanosa* in 1966, was the first aromatic metabolite isolated from a natural source that contains bromine on contiguous carbon atoms.[359] The 2,3-dibromobenzyl moiety appears the most commonly occurring structural unit in the bromophenols of Rhodomelaceae origin, with 63 such representatives having been identified so far (**597**, **600**–**603**, **608**–**615**, **617**–**621**, **623**, **624**, **629**–**635**, **637**, **638**, **642**–**646**, **649**–**666**, **669**–**671**, **673**–**677**, and **685**–**687**, Figures 51–55 and Supporting Information Table S15). Most of them were characterized from the species of the genera *Rhodomela*[2,361–369,382–384] and *Symphyocladia*.[370–374,380,390] Bromophenols from the genus *Symphyocladia* usually contain an additional bromine atom at C_6, thereby forming a 2,3,6-

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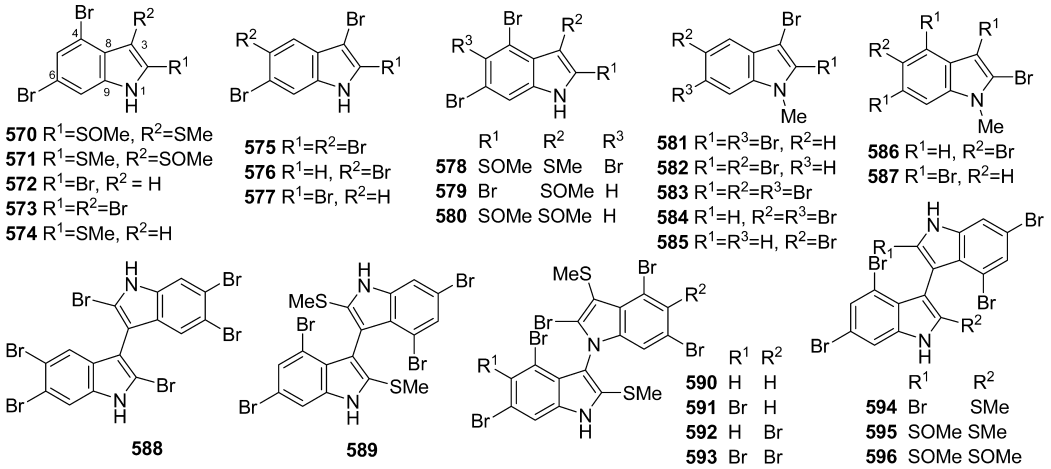

Figure 50. Indole derivatives (**570**–**596**).

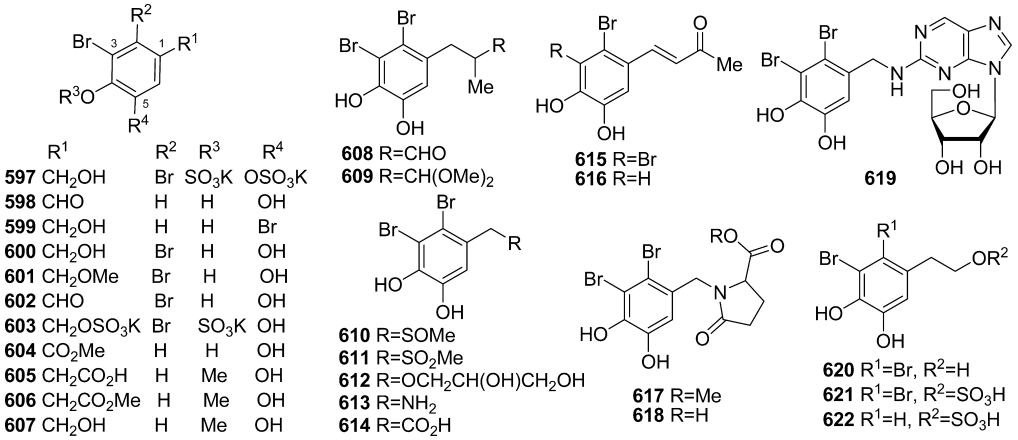

Figure 51. Monoaryl bromophenolic derivatives (**597**–**622**).

tribromobenzyl moiety (**629**–**635**, **645**, **646**, **659**–**661**, **666**, **675**, and **676**).[370−374,380,390] Other bromophenols isolated from Rhodomelaceae including compounds **610** from *R. confervoides*[365] and **646** from *S. latiuscula*[380] containing unique sulfoxide and methyl sulfone moieties, respectively, while compounds **617**–**619** from *R. confervoides* appear to be the first examples of bromophenols coupled with an amino acid or nucleoside unit through a C–N bond,[367] and compound **623** represents the first report of a bromophenol coupled with a γ-ureidobutyrate unit.[368]

Compared to the large number of mono- and diaryl bromophenols found from the Rhodomelaceae, only four triaryl (**684**–**687**)[363,368,386,395,396] and one tetra-aryl (urceolatin, **688**)[397] brominated aromatic compounds were reported to date (Figure 55 and Supporting Information Table S15). Among these, cyclotribromoveratrylene (**684**) is a unique symmetrical trimer isolated from *Halopytis pinastroides* (Syn. *H. incurvus*).[395] Conformational studies of this compound revealed that the bromine atoms force the nine-membered ring from the crown conformation into a "flexible boat" conformation.[396]

The genera *Polysiphonia*, *Rhodomela*, and *Symphyocladia* are the most prolific sources of bromophenols to date, with 15, 46, and 15 such compounds, respectively, isolated and characterized from species of these three genera, accounting for 76 of the 92 bromophenols isolated from this algal family (Supporting Information Table S15).

4.8. Other Halogenated Organic Molecules

Nine other halogenated organic molecules, 3,4-dibromo-5-methylenecyclopent-3-ene-1,2-diol (**689**) from *V. spiralis*,[398] poitediene (**690**) from *L. poitei*,[399] (*Z*)-2-chloropentadec-2-enal (**691**) from *L. flexilis*,[100] 2-(tetrahydro-4-iodo-2-methyl-6-oxo-2*H*-pyran-4-yl)ethyl stearate (**692**) from *L. majuscula*,[400] adejens A and B (**693** and **694**) from *L. viridis*,[247] and highly brominated aromatic derivatives **695**–**697** from *L. similis*,[385] were also characterized from members of the Rhodomelaceae (Figure 56 and Supporting Information Table S16). Among these, compound **690** is an unusual 15-carbon nonterpenoid metabolite containing a previously unreported twelve-membered ring system with a 1,2-dibromoethylenyl group,[399] while compounds **691**[100] and **692**[400] contain unusual chloroenal and iodolactone units, respectively. Recently, Blunt and co-workers indicated that the structures for the highly brominated derivatives **695**–**697** should be re-examined because of inconsistencies in the published NMR data for these compounds.[401]

4.9. Summary to the Occurrence of Halogenated Organic Molecules

This review presents a total of 697 halogenated organic molecules originating from members of the algal family Rhodomelaceae. These compounds are generally classified into sesquiterpene, diterpene, triterpene/polyether, acetogenin, indole, and phenolic classes, with the majority (618, 89%)

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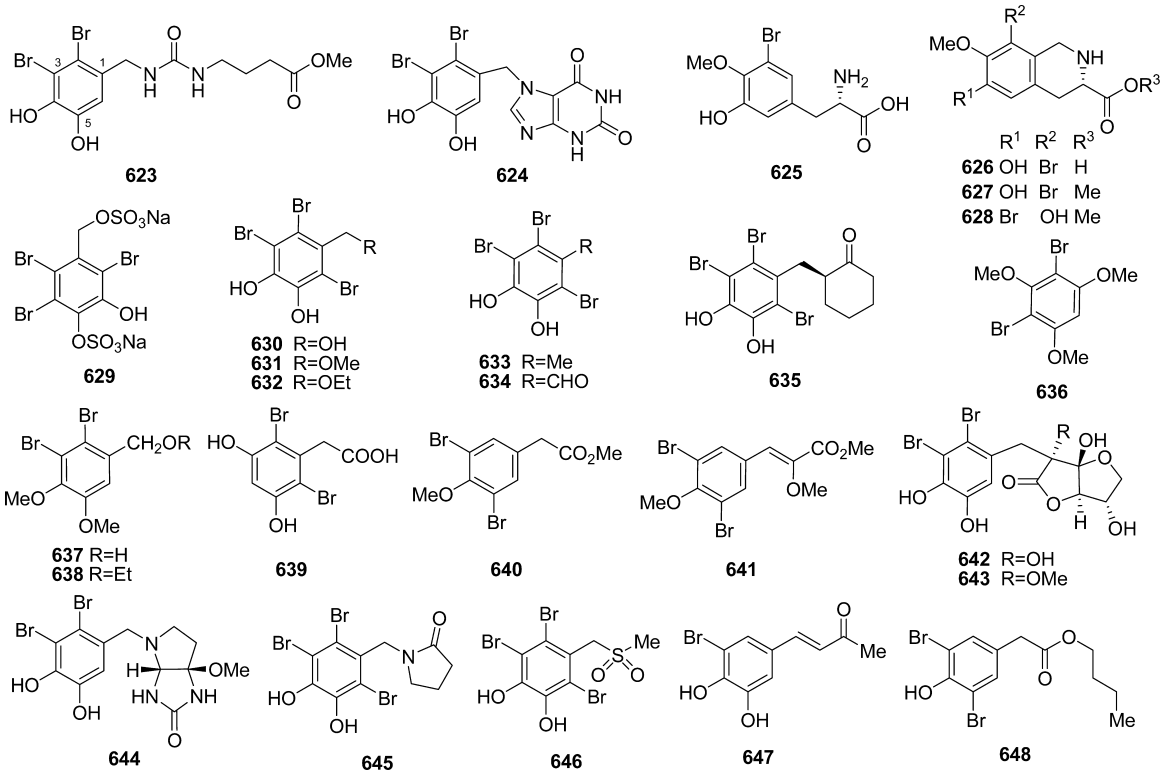

Figure 52. Monoaryl bromophenolic derivatives (**623**–**648**).

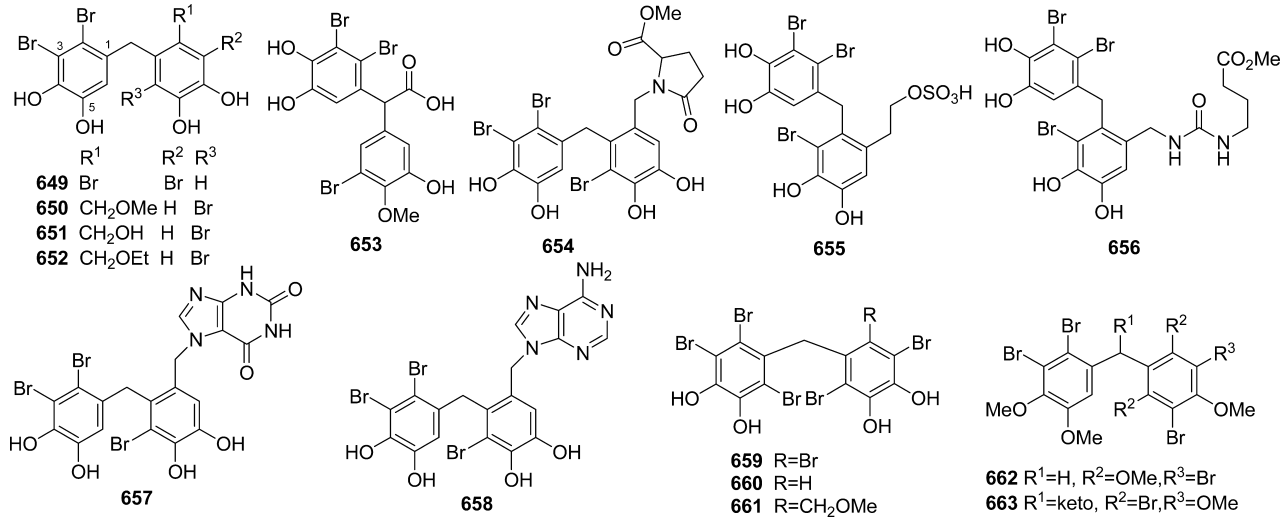

Figure 53. Diaryl bromophenolic derivatives (**649**–**663**).

being sesquiterpenes (275, 40%), acetogenins (180, 26%), phenols/aromatics (92, 13%), or diterpenes (71, 10%) (Chart 2 and Supporting Information Tables S1–S16). The geographical origins of all 697 compounds described in this review are summarized in Chart 3, as well as in Supporting Information Tables S1–S16. Although the sampling sites were not given in some of the earliest references, thus making the data somewhat imprecise, Japan (161, 23%), China (115, 17%), the Eastern Atlantic (112, 16%), and the Mediterranean (91, 14%) stand out as the major sources (479 in total, 69%) for reports of halogenated organic molecules from these sources (Chart 3). Table 1 presents the distribution of halogenated organic molecules produced by the ten most productive species of the family. These species have produced a total of 345 halogenated compounds, accounting for 50% of those reported so far from the family. The species *Laurencia obtusa* was the most prolific producer to date. A total of 98 halogenated molecules, accounting for 14% of all 697 compounds described in this review, were documented as metabolites of this species, including sesquiterpenes, diterpenes, triterpenes/polyethers, and ACGs (Table 1), demonstrating the presence of many versatile enzymatic systems and biosynthetic pathways in this species. *Laurencia nipponica* and *Rhodomela confervoides* stand as the second and third most prolific sources for production of halogenated molecules, from which 45 and 41 halo-compounds were reported, respectively. In contrast to *L. obtusa*, however, species of *Rh. confervoides* appears to be narrower in their biosynthetic capabilities, as all 41 compounds discovered from

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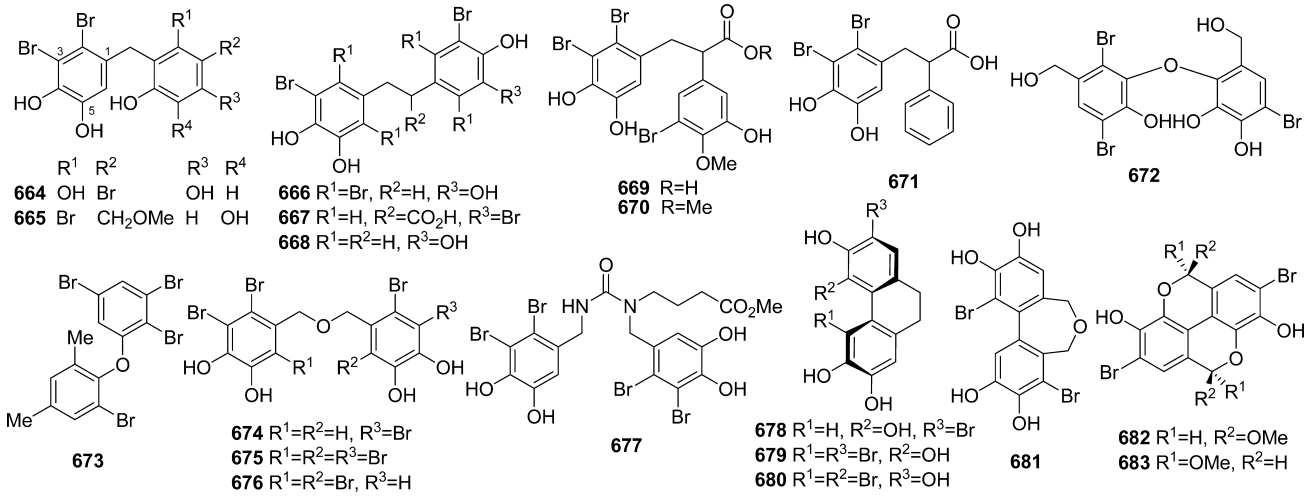


Figure 54. Diaryl bromophenolic derivatives (**664**−**683**).

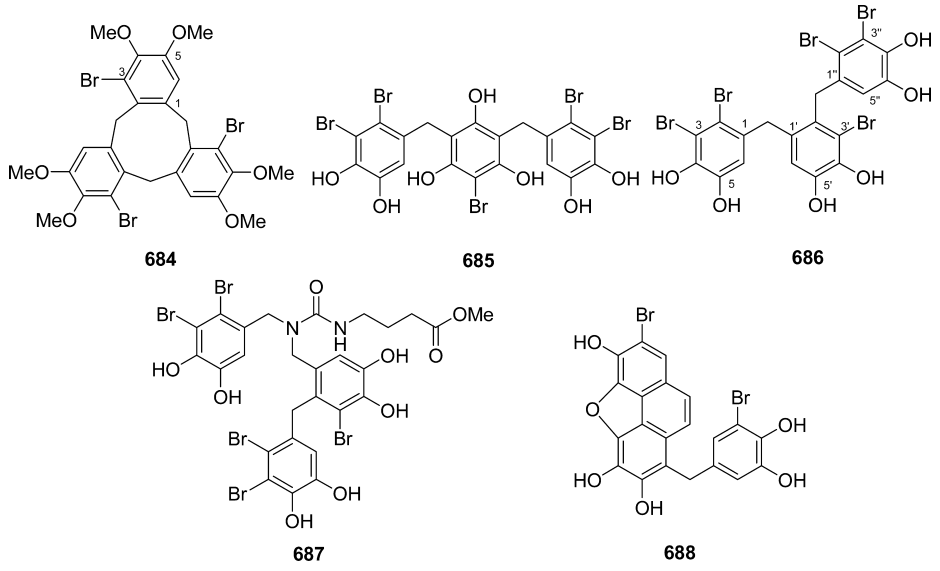


Figure 55. Triaryl (**684**−**687**) and tetra-aryl (**688**) bromophenolic derivatives.

this species in this review are halogenated phenolic derivatives (Supporting Information Table S15). Among other species, it is worthy of note that the halogenated organic molecules produced by *L. viridis* and *L. brongniartii* are restricted to triterpenes and indoles, respectively (Supporting Information Table S15), which implies the presence of strict biosynthetic pathways in these two species.

5. CHEMOTAXONOMIC SIGNIFICANCE

As noted earlier, the Rhodomelaceae is estimated to be the largest red algal family with about 125 genera and some 700 species recognized worldwide.[4] The taxonomy of this family was widely studied, but is often complicated by high morphological variability within individual species. However, some morphological features are closely associated with halogenated chemical constituents. The intracellular refractile inclusion known as *Corps en cerise* (cherry body) that is usually observed in superficial cortical and trichoblast cells of *Laurencia* species is a good example. *Corps en cerise* is recognized as a site for the synthesis or storage of halogenated molecules,[178,402,403] and it was reported that *Laurencia* species without *Corps en cerise* do not produce halogenated metabolites.[116] It was also reported that most species in the genus *Laurencia* produce at least one compound that is not found from any of the others.[32] On the other hand, the occurrence of halogenated molecules in a species is not random because chemical characteristics are determined by its genome and corresponding enzymes,[404,405] and halogenated metabolites of *Laurencia* origin were shown to be under strict genetic control.[264,405] Therefore, halogenated organic molecules may be useful taxonomic markers for the discrimination of species within the genus *Laurencia*.[32,406] The chemotaxonomic significance of using these metabolites as markers in place of heterosides, which were also used for this purpose, is supported by the observation of a correlation between the presence of terpenes and floridosides and between the presence of bromophenols and digeneaside.[407]

The occurrence of halogenated molecules in the Rhodomelaceae varies with genus and species, as discussed above. Species of the genera *Laurencia* and *Chondria* mainly produce terpenes, while members of the genera *Halopytis*, *Odonthalia*, *Polysiphonia*, *Rhodomela*, *Symphyocladia*, and *Vidalia* tend to form bromophenols. In addition, *Laurencia* species also metabolize a variety of C_{15}-acetogenins.

dx.doi.org/10.1021/cr9002215 | *Chem. Rev.* 2013, 113, 3632−3685

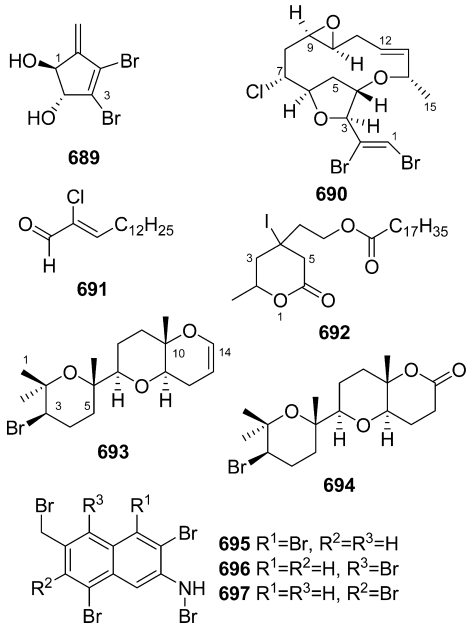
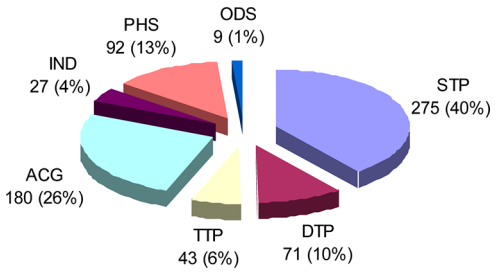


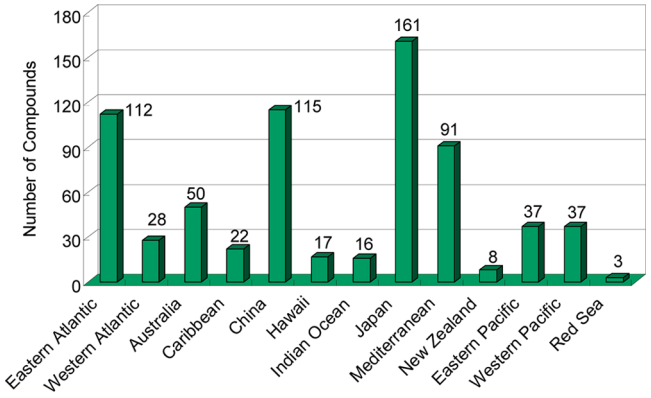
Figure 56. Other halogenated organic molecules (**689**–**697**).

Chart 2. Distribution of the 697 Halogenated Organic Molecules of Rhodomelaceae Origin as Shown by Structural Classes[a]



[a]STP, sesquiterpenes; DTP, diterpenes; TTP, triterpenes/polyethers; ACG, acetogenins; IND, indoles; PHS, phenols/aromatics; ODS, other derivatives.

Chart 3. Geographic Distribution of the 697 Halogenated Organic Molecules of Rhodomelaceae Origin As Shown by Sampling Sources



Chamigrane sesquiterpenes and C_{15}-acetogenins are almost ubiquitous in species of the genus *Laurencia*, but they have never been reported from other genera of the family.[24] *L. composita*, similar to *L. okamurai* in gross morphology and difficult to distinguish, mainly produces halogenated bisabolane (**5**)[28] and chamigrane/rearranged chamigrane sesquiterpenes (**43**, **245**, and **246**),[28,177,405] but *L. okamurai* can produce both chamigrane/rearranged chamigrane (**51**, **94**, **95**, and **244**)[61,86,176,408] and laurane/cuparane sesquiterpenes (**128**, **147**–**150**, **167**, and **168**),[110,130–132,408] as well as acetogenins (**432** and **530**).[280,334,335] Additionally, no oxygenated/halogenated acetogenins have been described to date as metabolites of *L. composita*.[177] It is also difficult to distinguish *L. tristicha* from *L. okamurai* morphologically, but *L. tristicha* produces only chamigrane (**145** and **146**)[129] and laurane/cuparane sesquiterpenes (**150**, **151**, and **158**).[133,135]

Table 1. Distribution of Halogenated Organic Molecules Produced by the Ten Most Productive Species of the Algal Family Rhodomelaceae

	structural class[c]							
species[a,b]	STP	DTP	TTP	ACG	IND	PHS	ODS	total
L. obtusa	42	17	6	33				98
L. nipponica	19	2		24				45
Rh. confervoides						41		41
L. majuscula	26	2		4			1	33
L. microcladia	8	6		10				24
L. glandulifera	11	1		12				24
L. pinnatifida	7		1	14				22
L. viridis			19				2	21
L. brongniartii					20			20
L. filiformis	11	6						17
total	124	34	26	97	20	41	3	345

[a]The table was sorted using the total column on the basis of the number of compounds produced by each species. [b]Abbreviation for the genera: *L.* = *Laurencia*; *Rh.* = *Rhodomela*. [c]Abbreviation for the compound classes: STP, sesquiterpenes; DTP, diterpenes; TTP, triterpenes/polyethers; ACG, acetogenins; IND, indoles; PHS, phenols/aromatics; ODS, other derivatives.

While chamigrane sesquiterpenes are commonly isolated from *Laurencia* species, rearranged structures with a methyl migration from C_{11} to C_{10} have been found only in *L. pinnatifida* (**243**),[175] *L. okamurai* (**244**),[176] *L. composita* (**245** and **246**),[177] *L. pannosa* (**247** and **248**),[178] and an undescribed *Laurencia* species (**242**).[101] Sesquiterpenes with bisabolane skeleton are abundant constituents of some *Laurencia* species, such as *L. scoparia* (**6**–**8**),[29] *L. aldingensis* (**11**–**14**),[31,32] and *L. caespitosa* (**18**–**22**),[36] and may be used as effective chemotaxonamic markers. In contrast, snyderane sesquiterpenes are generally present in *L. obtusa* (**172**, **174**–**177**, and **194**),[72,141,142,150] *L. saitoi* (**186**–**188** and **209**),[147] *L. flexilis* (**204**–**208**),[153,154] and *L. luzonensis* (**181**–**184**, **189**–**193**, and **201**–**203**).[145,148,149] As for halogenated brasilane sesquiterpenes, so far they have been isolated only from *L. obtusa* (**25**–**28**),[39,40] whereas halogenated eudesmanes (selinanes) are unique to *L. filiformis* (**129**, **132**, and **133**),[111,115] *L. intricata* (**134**),[116] and *L. microcladia* (**135**).[117] The above characteristic sesquiterpene classes from various *Laurencia* species might be useful as chemotaxonamic markers.

Diterpenes with unique skeletons are often characteristic of certain *Laurencia* species.[67,149,221,225,228] Irieane diterpenes were solely isolated from *L. irieii* (**276**–**284**),[189,190] *L. pinnata* (**285**–**287**),[191] *L. decumbens* (**288**),[192,193] and more recently, from an unrecorded *Laurencia* species (**289**),[194] while parguerane diterpenes having a modified pimarane skeleton were only reported in *L. obtusa* (**302**–**306**),[208–210] *L. filiformis* (**307**–

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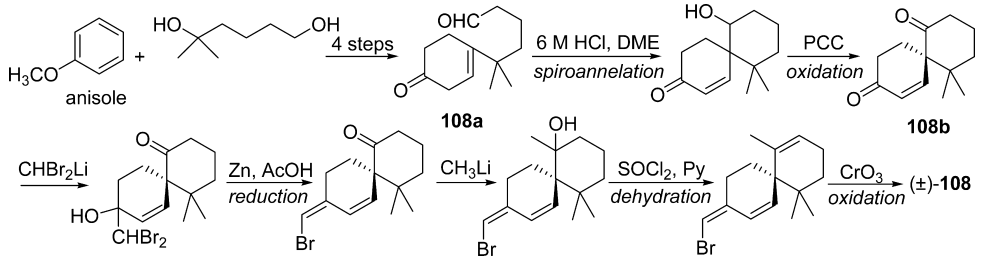
Table 2. Synthesis of Halogenated Sesquiterpenes

	compound	synthetic strategy	research group	ref
chamigrane	(−)-2,10-dibromo-3-hydroxy-α-chamigrene ((−)-**90**)	bromonium-initiated intramolecular carbocyclization	Martín	432
	15-bromo-1,3(15),7-chamigrren-9-one ((±)-**108**)	spiroannelation from anisole	Niwa	440
laurane	allolaurinterol (**138**)	controlling the regiochemistry by using of metalated phenyl methoxymethyl ethers	Ronald	441
	isolaurinterol (**142**) and isoaplysin (**147**)	diastereoselective radical-to-polar crossover sequence	Harrowven	442, 443
	filiforminol (**153**) and bromoether A (**154**)	copper-catalyzed conjugate addition and subsequent metylation, epoxidation, and spontaneous cyclization	Yoo	444
snyderane	β-snyderol (**173**)	bromonium ion-induced cyclization of methyl farnesate	González	411
	palisadins A (**195**), B (**196**), and 12-hydroxypalisadin B (**198**)	formation of *trans-anti*-cyclogeranyl-oxepene systems by stereoselective coupling and ring-closing metathesis	Couladouros	445
sesquiterpenes with new carbon skeletons	(±)-oppositol ((±)-**216**)	doubly diastereodifferentiating "folding and allylic strain-controlled" intramolecular ester enolate alkylation	Kim	425
	(±)-spirolaurenone ((±)-**240**)	efficient cyclization of geranonitrile promoted by boron trifluoride-acetic acid	Masamune	446

Scheme 1. Total Synthesis of (±)-15-Bromo-1,3(15),7-Chamigratrien-9-one ((±)-108) by Niwa et al.[440]



312),[211] *L. nipponica* (**313** and **314**),[212] and *L. saitoi* (**304** and **308**).[409] Additionally, labdane diquiterpenes are mainly found in *L. pinnata* (**292**−**295**).[200]

Polyether triterpenes were found in several *Laurencia* species,[230] such as *L. thyrsifera* (**347**),[231−233] *L. venusta* (**348**),[233] *L. obtusa* (**349** and **351**−**355**),[234,235] *L. pinnatifida* (**350**),[127] *L. calliclada* (**356**),[236] *L. viridis* (**357**−**366** and **372**−**380**),[237−242,246−248] *L. mariannensis* (**367** and **368**),[243] *L. intricata* (**389**),[254] and *L. omaezakiana* (**387**),[250,251] as well as in *Chondria armata* (**369**−**371** and **381**−**386**),[245,249] while polybromoindoles were reported only from *L. brongniartii* (**570**−**575**, **578**−**583**, and **589**−**596**)[352−354,356,358] *L. decumbens* (**587**),[192] and *L. similis* (**576**, **577**, and **584**−**586**, **588**),[185,355,357] with those from *L. brongniartii* often containing sulfur (**570**, **571**, **574**, **578**−**580**, and **589**−**596**).[352,353,356,358,410]

Bromophenols with a 3-bromo-4,5-dihydroxybenzyl unit (**598**,[360] **647**, **667**,[381] **668**,[194] **678**−**683**,[391−394] and **688**[397]) are predominant in the genus *Polysiphonia*, especially in *P. urceolata* (**647**, **667**, **668**, **678**−**683**, and **688**),[194,381,391−394,397] while those with a 2,3-dibromo-4,5-dihydroxybenzyl unit are characteristic of *Rhodomela* (**608**−**615**,[363−366] **617**−**624**,[367−369] **651**−**658**,[363,365−369,383,384] **669**−**671**,[365] **677**,[368] **686**,[363] and **687**[368]) and *Odonthalia* (**600**,[2] **665**,[387] and **674**[389]), and those with a 2,3,6-tribromo-4,5-dihydroxybenzyl unit are typical of *Symphyocladia* (**629**−**635**,[370−374] **645**, **646**,[380] **659**−**661**,[373,380] **675**,[390] and **676**[373]).

Despite of some of the characteristic metabolites were found in certain species of the Rhodomelaceae family, it is interesting to note that recollection of the same algal species at the same site and the same season over the consecutive years does not guarantee that only the same metabolites will be obtained.[98] It thus should be noted that, although the presence of these halogenated molecules can be informative, it is not advisable to rely solely on them to make taxonomic assignments, but instead to combine consideration of chemical composition with examination of morphological and cytological features.

6. SYNTHESIS

Because they possess a variety of novel structures and often display potent biological activities, halogenated organic molecules have attracted considerable attention as challenging targets for partial and total synthesis. A number of elegant synthetic strategies and methodologies were developed and employed for the synthesis of such compounds. Pioneering work in synthetic chemistry related to halogenated organic molecules of Rhodomelaceae origin was carried out by the Martín group for the synthesis of β-snyderol (**173**)[411] and the Masamune group for the synthesis of (±)-laurencin (**451**)[412−414] in the 1970s. Several research groups including those of Crimmins,[415−420] Holmes,[421−424] Kim,[425−430] Martín,[411,431,432] and Overman[433−439] also made great contributions to the synthesis of halogenated organic molecules of Rhodomelaceae origin. To keep this review to a reasonable length, it is not possible to describe all of the synthetic work that could be considered relevant to this topic. In general, only the first total synthesis, or syntheses employing a new methodology or a new strategy, are included in the present review (Tables 2−5). These approaches are discussed in the following sections.

6.1. Synthesis of Sesquiterpenes

6.1.1. Synthesis of Chamigrane Sesquiterpenes. The spirobicarbocyclic chamigranes obtained from red algae of the family Rhodomelaceae, especially from the genus *Laurencia*, are the largest and most varied group among halogenated marine

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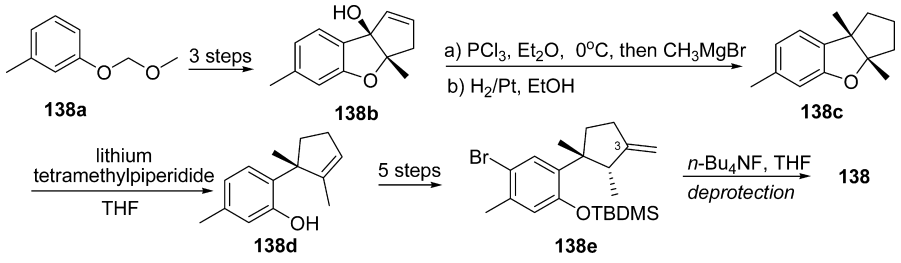
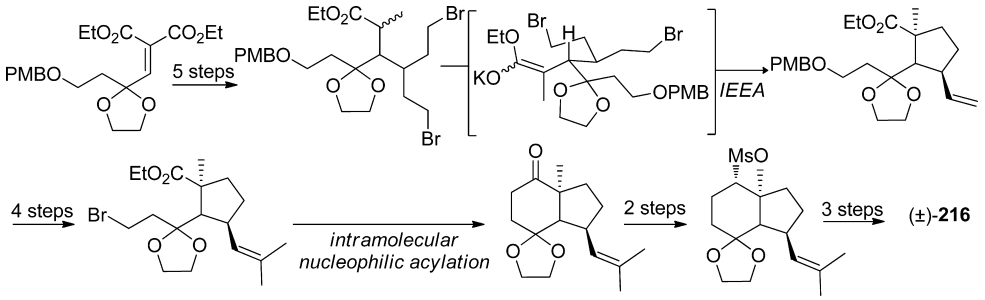
Scheme 2. Total Synthesis of Allolaurinterol (138) by Gewali and Ronald[441]



Scheme 3. Stereoselective Total Synthesis of (±)-Oppositol (216) by Kim et al.[425]



natural products. Spirocycles represent challenging synthetic targets, and installation of a quaternary carbon adjacent to the spirocenter offers an excellent fundamental test of synthetic methodology.[411]

In 1986, Martín and colleagues accomplished the enantioselective total synthesis of (−)-2β,10β-dibromo-α-chamigren-3α-ol (**90**) (Table 2).[432] The synthesis features asymmetric induction in the bromonium-initiated intramolecular carbocyclization reaction as the key strategy which was achieved by generation of exocyclic alkylidienes containing two stereogenic atoms located on the cyclohexene ring. This asymmetric methodology represents a general strategy for the enantioselective construction of spiro[5,5]undecane systems containing a chiral quaternary center, which is useful for the synthesis of a wide variety of six-membered spirocycle-containing natural products.

In 1991, Niwa and co-workers described the total synthesis of (±)-15-bromo-1,3(15),7-chamigratrien-9-one ((±)-**108**) using anisole as starting material (Scheme 1).[440] The desired intermediate 5-(4-methoxyphenyl)-5-methylhexan-1-ol was prepared efficiently by Friedel−Crafts reaction of anisole with 5-methyl-1,5-hexanediol in nearly quantitative yield with a single step. Upon Birch reduction and Swern oxidation, 5-methyl-5-(4-oxocyclohex-1-enyl)hexanal (**108a**) was obtained as a key intermediate, which was then subjected to spiroannelation and oxidation to afford a spiro diketone as a second key intermediate **108b** that possessed the spiro[5.5]-undecane skeleton. The target compound **108** was finally obtained by a series of further reactions including alkylation, reduction with Zn in AcOH, dehydration with $SOCl_2$-pyridine, and oxidation in the presence of CrO_3 (Scheme 1).[440] The key step in the synthesis was construction of the spiro[5.5]-undecane skeleton.

6.1.2. Synthesis of Laurane and Snyderane Sesquiterpenes. *6.1.2.1. Synthesis of Laurane Sesquiterpenes.* In 1982, Gewali and Ronald accomplished the first synthesis of allolaurinterol (**138**) starting from 3-(methoxymethoxy)toluene (**138a**) using metalated phenyl methoxymethyl ethers to control the regiochemistry as the key strategy (Scheme 2).[441] The key tricyclic carbinol **138b** was synthesized from **138a** and then the hydroxyl group of **138b** was replaced by a methyl group to afford **138c** through three conversion steps, with first to be the chlorination with PCl_3 to yield the highly reactive and sensitive tricyclic chloride, which was followed immediately by alkylation with CH_3MgBr, and the resulting olefin was then hydrogenated over platinum to yield the tricyclic ether **138c**. The furanoid ring of **138c** was opened with lithium tetramethylpiperidide in refluxing THF, which was proved to be the best procedure to induce clean elimination to afford the phenolic olefin **138d**. Subsequent functionality at C_3 in the cyclopentane ring yielding the olefin **138e** in five steps and deprotection of **138e** with n-Bu_4NF in THF afforded the target compound allolaurinterol (**138**).[441]

In 1999, isolaurinterol (**142**) and a series of related sesquiterpenes were synthesized by Harrowven and colleagues.[442] The synthesis features a diastereoselective radical-to-polar crossover sequence to transform the diene into debromoisolaurinterol. This methodology was successfully used to the total synthesis of (±)-isoaplysin (**147**) and other related sesquiterpenes of the laurane class.[443] In 1998, Yoo and co-workers described the concise total synthesis of (±)-filiforminol (**153**) and (±)-bromoether A (**154**) starting from 3-methylcyclopent-2-en-1-one through the use of a bromonium ion-initiated cyclization strategy.[444] Key methodology and steps used in the synthesis included copper-catalyzed conjugate addition and subsequent methylation, epoxidation, and spontaneous cyclization.

6.1.2.2. Synthesis of Snyderane Sesquiterpenes. Martín and co-workers developed an approach to selective C−Br bond formation with concomitant ring closure in 1976.[411] As a result, a simple synthesis of β-snyderol (**173**) was carried out involving bromonium ion-induced carbocyclization of an acyclic polyene. In 2004, palisadins A (**195**) and B (**196**) and 12-hydroxypalisadin B (**198**) were efficiently generated by Couladouros and Vidali using a general stereocontrolled strategy for the construction of cyclogeranyl-oxepenes employing a process involving epoxide opening by a tertiary alcohol and subsequent ring-closing metathesis.[445]

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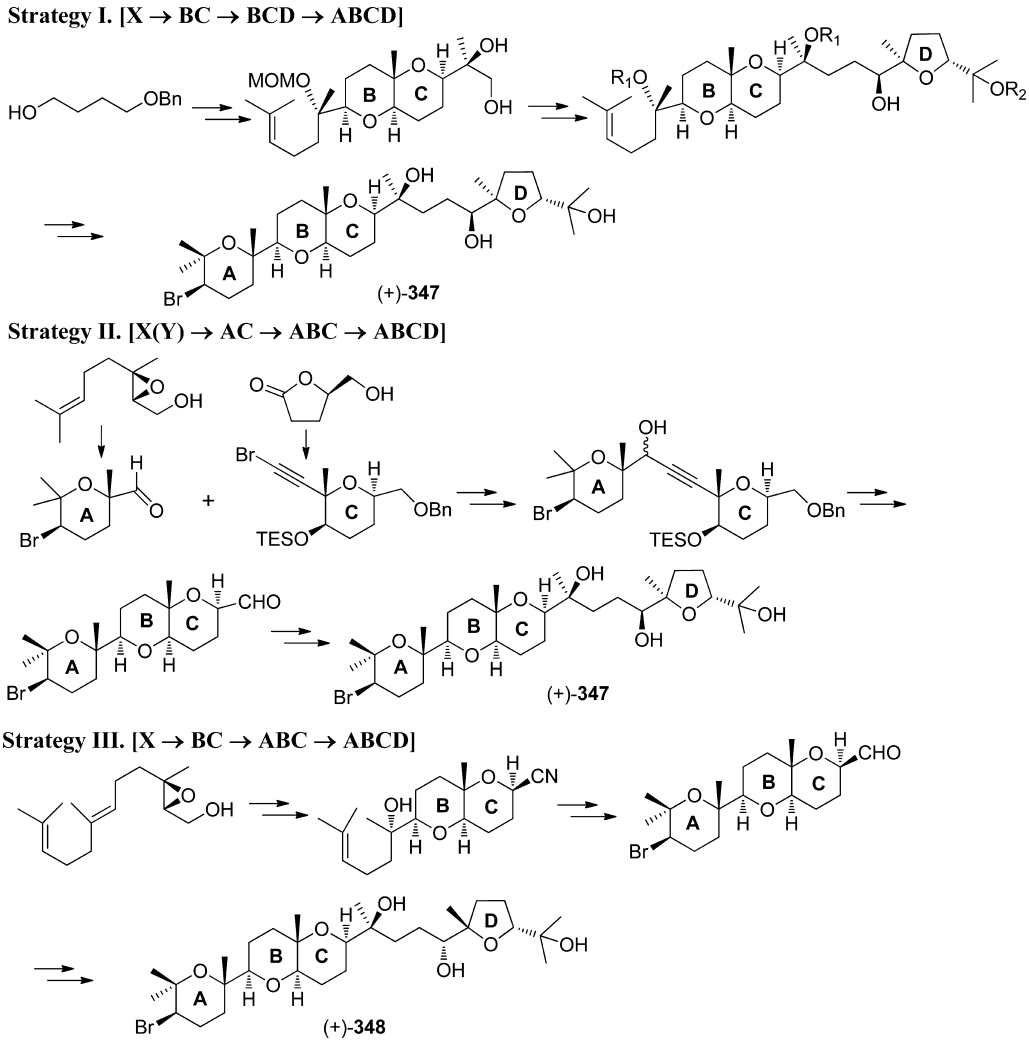
Table 3. Synthesis of Diterpenes and Triterpenes

	compound	synthesis strategy	research group	ref
diterpenes	(±)-prepinnaterpene (**334**)	construction of the brominated bicyclic skeleton involves acid-catalyzed epimerization of a *cis*-hydrindane system to the corresponding trans isomer and a pivotal Finkelstein reaction for bromine introduction as key steps, then installation of the respective diene units through Wittig reaction.	Masamune	447
triterpene/ polyethers	(+)-thyrsiferol (**347**), (+)-venustatriol (**348**), and (+)-thyrsiferyl 23-acetate (**349**)	stereoselective epoxidation of the 4-en-1-ol system and successive cyclization to form the D ring, with construction of the A ring by bromonium ion-induced cyclization of the 4-en-ol system	Shirahama	448
	thyrsiferol (**347**) and thyrsiferyl 23-acetate (**349**)	early joining of intermediates containing the A and C rings followed by formation of the B ring; construction of the D ring by a highly stereoselective Re(VII)-promoted *syn*-oxidative cyclization of bis-homoallylic alcohol	Forsyth	451
	venustatriol (**348**)	stereospecific formation of the tetrahydrofuran ring (the D ring) by PCC oxidation	Corey	452
	ent-dioxepandehydrothyrsiferol (**380**)	construction of the 7,7,6-fused tricyclic polyether framework by a single bromonium-initiated epoxide-openings	Jamison	453
	(+)-intricatetraol (**389**)	enantioselective construction of the vicinal bromochloro functionality	Morimoto	454

Scheme 4. Three Strategies for the Syntheses of Halogenated Triterpenes/Polyethers



6.1.3. Synthesis of Sesquiterpenes with New Carbon Skeletons. In 1997, Kim's group accomplished a stereoselective total synthesis of (±)-oppositol (**216**) involving 16 steps starting from an α,β-unsaturated ester.[425] The synthesis featured a novel, doubly diastereodifferentiating "folding and allylic strain-controlled" intramolecular ester enolate alkylation (Scheme 3). In 1982, Murai and co-workers achieved the first total synthesis of (±)-spirolaurenone (**240**) in 13 steps with an overall yield of 2.4% from the bromohydrin of homogeranonitrile.[446] The synthesis, which was based on the efficient cyclization of geranonitrile, also confirmed the *R*-configuration at C_2 for the compound.

6.2. Synthesis of Diterpenes

Compared to the synthesis of sesquiterpenes, much less work was described regarding the synthesis of diterpenes of Rhodomelaceae origin. In 1987, Masamune and co-workers described a stereoselective synthesis of the bromditerpene

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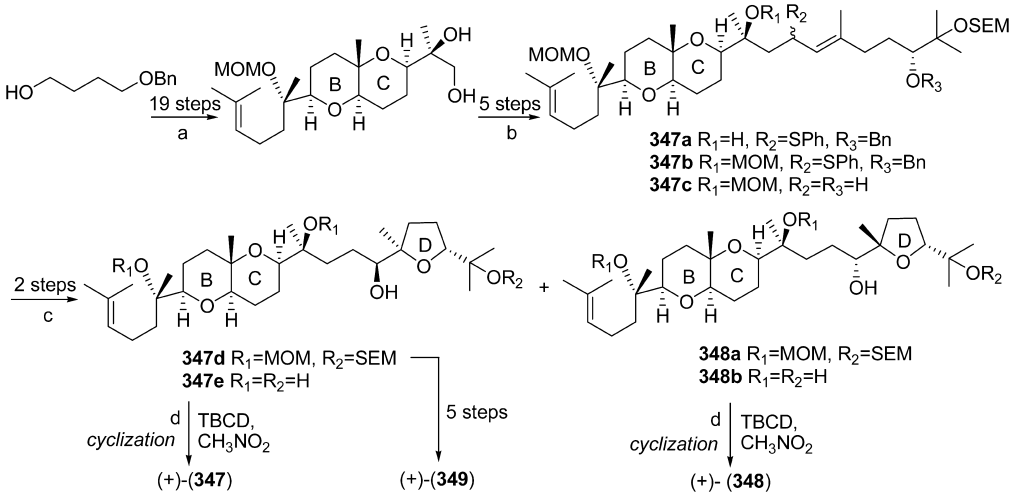
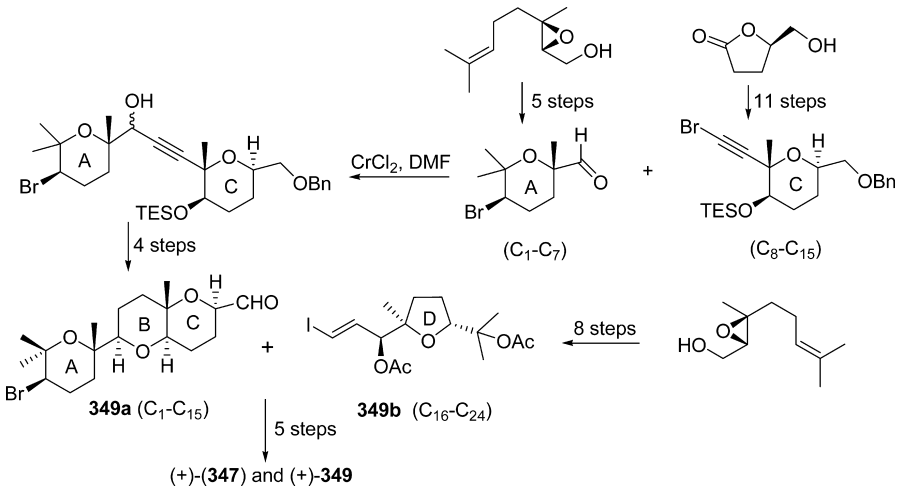
Scheme 5. Total Synthesis of (+)-Thyrsiferol (347), (+)-Venustatriol (348), and (+)-Thyrsiferyl 23-acetate (349) by Shirahama et al.[448]



Scheme 6. Total Syntheses of Thyrsiferol (347) and Thyrsiferyl 23-Acetate (349) via Strategy II, by González and Forsyth[451]



(±)-prepinnaterpene (**334**) in 32 steps with 2.6% overall yield starting from readily available *trans*-octalin-1,4-dione (Table 3).[447] A synthesis of the structurally related sesquiterpene oppositol ((±)-**216**) was also described in the same report. The synthesis of **334** features an acid-catalyzed epimerization of a *cis*-hydrindane system to the corresponding trans isomer and a pivotal Finkelstein reaction for bromine introduction as key steps.

6.3. Synthesis of Triterpenes

6.3.1. Synthesis of Thyrsiferol and Its Derivatives. The structurally complex and densely functionalized nature of the triterpenoid polyether thyrsiferol (**347**) and its derivatives, which possess common structural features including a bromotetrahydropyran unit (A ring), a core pyranopyran moiety (BC rings), and a tetrahydrofuran segment (D ring), makes the construction of the corresponding skeleton a very challenging task. Although the tactical details are distinctive to each synthetic team (Table 3), most of the synthetic efforts directed toward these compounds can be categorized, based on the sequence of constructing the four rings, into three major strategies (Strategies I–III), as illustrated in Scheme 4. "Strategy I" features initial construction of the central BC ring system, followed by elongation of the side-chain to form the D ring, and finally formation of the A ring, while "Strategy II" involves connection of two tetrahydropyran-containing units representing the functionalized A and C rings, annulation of the B ring to form the ABC tricyclic system, and then attachment of the D ring through installation of the C_{15}–C_{16} carbon–carbon bond via coupling an aldehyde with an iodide. "Strategy III" adopts construction of the central BC ring system, followed by formation of the A ring, and installation of the side-chain to form the D ring.

In 1990, Shirahama's group accomplished the first total synthesis of (+)-thyrsiferol (**347**), (+)-venustatriol (**348**), and (+)-thyrsiferyl 23-acetate (**349**) in a stereoselective manner via "Strategy I" (Scheme 5).[448−450] The processes for these syntheses included (1) construction of the BC ring system with a C_1–C_6 carbon unit, (2) elongation of the C_{17}–C_{24} carbon side-chain, (3) formation of the D ring through stereoselective epoxidation of the 4-en-1-ol system and successive cyclization, and finally, (4) construction of the A ring by bromonium ion-induced cyclization of the 4-en-ol system.

"Strategy II", developed by González and Forsyth, was also applied to the total syntheses of thyrsiferol (**347**) and thyrsiferyl 23-acetate (**349**) (Scheme 6).[451] The synthesis

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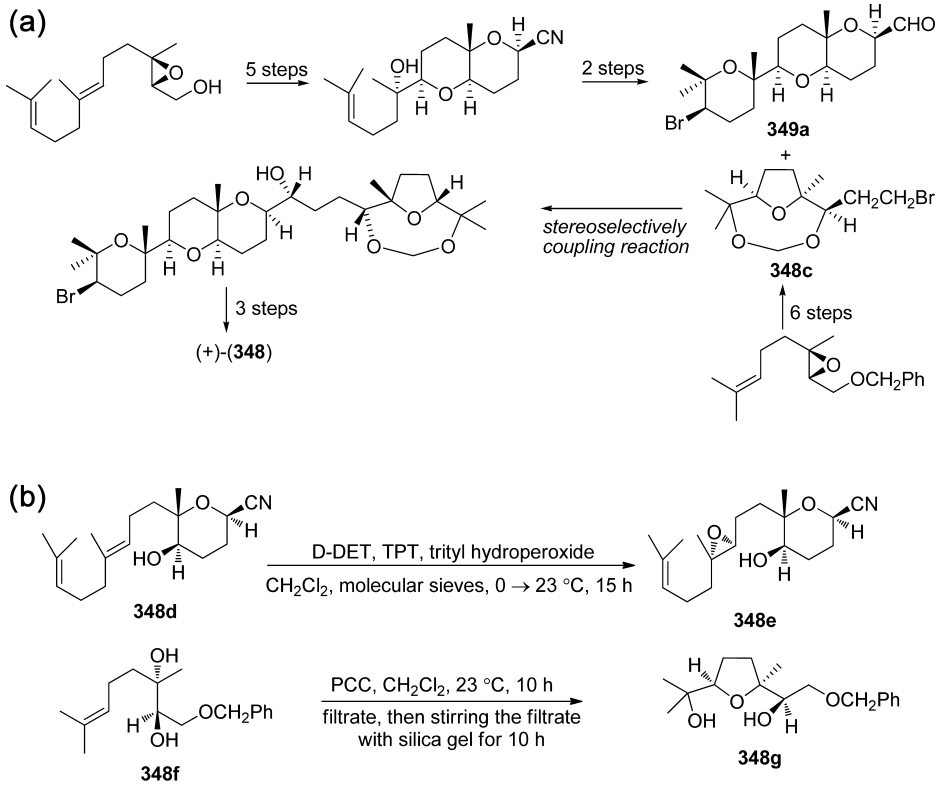
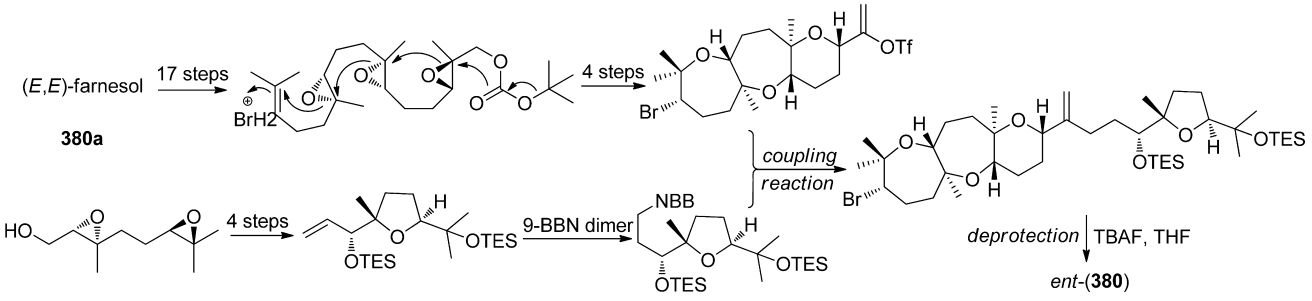
Scheme 7. (a) Total Synthesis of Venustatriol (348) via Strategy III, by Corey and Ha[452] and (b) Highly Stereoselective Reactions Reported in Total Synthesis of Venustatriol (348) by Corey and Ha[452]



Scheme 8. Enantioselective Total Synthesis of (*ent*)-Dioxepandehydrothyrsiferol ((*ent*)-380) by Jamison et al.[453]



features the separate construction of two advanced intermediates representing the C_1–C_{15} (**349a**) and C_{16}–C_{24} (**349b**) domains, followed by their organochromium-mediated coupling, installation of the tertiary alcohol at C_{15}, and manipulation of the C_{18} and C_{23} acetate moieties. The early incorporation of intermediates containing the A and C rings, followed by an efficient annulation of the B ring, as well as convergent attachment of the D ring intermediate and minimal manipulation of hydroxyl-protecting groups, reflects the flexibility and efficiency of the synthesis.

In 1988, Corey and Ha employed "Strategy III" to accomplish an enantioselective and convergent total synthesis of venustatriol (**348**) via key intermediates **349a** and **348c** (Scheme 7a).[452] The synthesis involves a number of highly stereoselective steps, with the tris-homoallylic epoxidation from **348d** to **348e** and the conversion of **348f** to **348g** by PCC being especially noteworthy (Scheme 7b).

In 2009, Jamison and co-workers described an enantioselective total synthesis and absolute configuration confirmation of *ent*-dioxepandehydrothyrsiferol (**380**) starting from (*E*,*E*)-farnesol (**380a**).[453] The synthesis features the only example to date of the construction of the 7,7,6-fused tricyclic polyether framework by a single bromonium-initiated epoxide-opening cascade, which incorporates both endo- and exo-selective epoxide openings (Scheme 8). This work also represents the first total synthesis of any natural product with the trans-anti-trans fused tricyclic motif.

6.3.2. Synthesis of (+)-Intricatetraol. In 2007, Morimoto and co-workers described the first asymmetric total synthesis of the symmetrical bromochlorotriterpene (+)-intricatetraol (**389**).[454] The synthesis, which enabled the absolute configuration of this compound to be unambiguously assigned, features the enantioselective construction of the vicinal bromochloro functionality in an approach that may be applicable to the synthesis of other bromochloro compounds.

6.4. Synthesis of C_{15}-Acetogenins (ACGs)

In addition to the synthetic efforts directed toward the production of halogenated terpenes, syntheses of halogenated ACGs also attracted considerable attention from synthetic

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Table 4. Synthesis of Acetogenins (ACGs)

	compound	synthesis strategy	research group	ref
five-membered cyclic ACGs	(±)-*trans*-Kumausyne (**403**)	assembly of *cis*-hydrobenzofuranones by enlarging tetrahydrofuran annulation of cyclopentanediol precursor, followed by Baeyer–Villiger oxidation and alcohol oxidation to form the pivotal bicyclic lactone aldehyde intermediate	Overman	434
		construction of tetrahydrofurans by electrophilic 5-*exotrig* cyclizations of homoallylsilane derivatives	Landais	455
		tandem ring-opening-ring-closing and ring-opening-ring-closing cross metathesis of simple ring system	Phillips	456
	(−)-*trans*-Kumausyne (**403**)	stereoselective formation of substituted tetrahydrofurans involving the BF_3-promoted reaction of 2,3-*O*-isopropylidene derivatives of *aldehydo*-aldose with allylsilanes via cyclization of β-silyl cation intermediates	Sugimura	457
		radical cyclization of β-alkoxyacrylate as a key step to form the tetrahydrofuran template	Lee	458
		construction of the tetrahydrofuran template by Pd(II)-mediated intramolecular alkoxycarbonylation-lactonization of an enediol	Boukouvalas	459
		Wittig olefination–lactonization–Michael addition of a lactol to construct the corresponding bicyclic lactone as a key intermediate	Mereyala	460
		using enantiomerically enriched β-hydroxy-γ-lactones obtained via Sharpless asymmetric dihydroxylation of the suitable β, γ-unsaturated ester as key precursors, target compound obtained by additional enantioselective Katsuki-Sharpless asymmetric epoxidation	Martín	461
	(+)-*trans*-Kumausyne (**403**)	construction of a 2,3,5-trisubstituted tetrahydrofuran unit via regioselective hydride ring-opening of the epoxide moiety in the readily accessible methyl 2,3-anhydro-5-*O*-benzyl-α-D-lyxofuranoside	Lowary	462
		remote nucleophilic epoxidation of a sulfinyl diene moiety to construct the tetrahydrofuran template	Fernández de la Pradilla	463
	(+)-*trans*-deacetylkumausyne (**404**)	bromonium ion-induced cyclization of a suitable hydroxy alkene	Martín	464
	(±)-kumausallene (**431**)	formation of 2,6-dioxabicyclo[3.3.0]octane ring system through *cis*-hydrobenzofuranone as a key intermediate obtained from 1-vinylcyclopentane-1,2-diol and α-(benzyloxy)-acetaldehyde via Prins cyclization-pinacol rearrangement	Overman	437
	(−)-kumausallene (**431**)	formation of the 2,6-dioxabicyclo[3.3.0]octane ring system via two concomitant radical cyclizations of β-alkoxyacrylates	Lee	465
		preparation of key bicyclic lactone from optically enriched 1,3-butanediol	Evans	466
seven-membered cyclic ACGs	(+)-rogioloxepane A (**443**)	stereoselective construction of the α,ϕ-*trans*-disubstituted oxepene core via cyclization of the hydroxy epoxide promoted by the $(Bu_3Sn)_2O/Zn(OTf)_2$ system	Suzuki	467
		construction of the trans-disubstituted oxepene core by asymmetric glycolate alkylation and a ring-closing metathesis	Crimmins	419
	isolaurepinnacin (**446**)	Lewis acid-promoted cyclizations of β-chloro- (or β-bromo-) acetals	Overman	435
	(+)-isolaurepinnacin (**446**)	acetal-vinylsilane cyclization to stereoselectively form the *cis*-2,7-disubstituted oxepene ring and introduce Δ^4 unsaturation	Overman	436, 439
		$(Bu_3Sn)_2O/Zn(OTf)_2$-promoted hydroxy-epoxide cyclization for the stereoselective construction of substituted oxepane skeleton	Suzuki	468
	(−)-isoprelaurefucin (**447**)	construction of oxepene core by "protecting group-dependent" alkylation and ring-closing metathesis	Kim	429
	(+)-neoisoprelaurefucin (**449**)	regio- and stereocontrolled internal alkylation of amide to form the oxepene core	Kim	427
eight-membered cyclic ACGs	(+)-laurencin (**451**)	formation of 9-aza-3-oxabicyclo[3.3.1]nonane framework by Robinson-Schöf condensation and ring-expansion employing Hoffman elimination	Masamune	412–414
		elaboration of eight-membered lactone as precursor	Holmes	423
		construction of the oxocene core by an acetal-vinyl sulfide cyclization	Overman	438
		formation of the oxocene core from the corresponding lactone precursors by methylenation and subsequent enol-ether functionalization.	Holmes	424
		rapid construction of medium-ring cyclic ethers by merging the asymmetric aldol addition of glycolates with a ring-closing metathesis reaction	Crimmins	415
		asymmetric alkylation-ring-closing metathesis for the synthesis of the medium-ring ether core	Crimmins	416
		conversion of *C*-galactoside derivative arising from ring expansion of the oxane part of the starting material into an eight-membered ring ether	Fujiwara	469
		construction of the oxocene core by efficient internal olefin alkylation	Kim	428
	(+)- and (−)-laurencin (**451**)	facile formation of the medium-sized ether ring from a Diels–Alder adduct	Palenzuela	470
	(−)-laurefucin (**465**)	organoselenium-mediated intramolecular hydroxyetherification to form the 2,8-dioxabicyclo[5.2.1]decane skeleton	Kim	471
	(+)-(*Z*)-laureatin (**481**)	construction of 3,8-dioxabicyclo[5.1.1]nonane skeleton via formation of the oxetane arising from 4-exo cyclization of hydroxy epoxide unit present on the oxocene core	Suzuki	472
	(+)-3-(*Z*)-laureatin (**481**) and (+)-3-(*Z*)-isolaureatin (**482**)	intramolecular amide enolate alkylation to construct the α,α'-*cis*-oxocene skeleton; novel "lone pair-lone pair interaction-controlled" epimerizations to the α,α'-*trans*-oxocenes	Kim	430

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Table 4. continued

	compound	synthesis strategy	research group	ref
	(+)-prelaureatin (**485**)	formation of the oxocene core by asymmetric glycolate aldol addition following a ring-closing metathesis	Crimmins	473
		construction of oxocene core by combination of selective ring-closing metathesis and C-glycoside-ring-cleavage	Murai	475
	(−)-laurenyne (**487**)	construction of functionalized eight-membered cyclic ether core by acetal-initiated cyclizations	Overman	433
	(+)-laurenyne (**487**)	metal ion-templated S_N2' cyclization affording a highly functionalized chiral vinyl cyclobutane and retro-Claisen rearrangement for the construction of the eight-membered ring ether core	Boeckman	476
	(+)-3-(*Z*)- and (+)-3-(*E*)-pinnatifidenyne (**496** and **497**)	construction of oxocene core by a stereo- and regioselective internal alkylation and direct ketone synthesis from the α-alkyloxy amide moiety in the oxocene	Kim	426
	(+)-laurallene (**510**)	construction of the key oxocene skeleton via the cyclization of the corresponding hydroxy epoxide promoted by $Eu(fod)_3$	Suzuki	477
nine-membered cyclic ACGs	(+)-obtusenyne (**526**)	construction of the oxonene core by formation of cyclic enol ether from the corresponding lactone, regio- and stereoselective epoxidation of the cyclic enol ether, and stereoselective DIBAL-H reduction of the epoxide	Murai	478
		establishment of the α,α'-disubstituted ether linkage by Sharpless kinetic resolution and asymmetric glycolate alkylation, and construction of the oxonene core by a ring-closing metathesis	Crimmins	420
		construction of oxonene core via cyclization of the corresponding hydroxy epoxide promoted by $Eu(fod)_3$	Suzuki	479
	(−)-isolaurallene (**529**)	formation of core structure through asymmetric glycolate alkylation, Brown asymmetric allylation, and ring-closing metathesis, with bromoallene formation by S_N2' displacement with $LiCuBr_2$	Crimmins	417, 418
	itomanallene A (**531**)	construction of the dioxabicyclic skeleton through intermolecular amide enolate alkylation and ringclosing metathesis, then installation of the respective bromoallene units	Kim	336
maneonene and isomaneonene ACGs	*cis*-maneonenes A (**551**) and B (**552**), *trans*-maneonene B (**553**)	selective catalytic hydrogenation of a silylated butadiyne derivative	Holmes	421, 422

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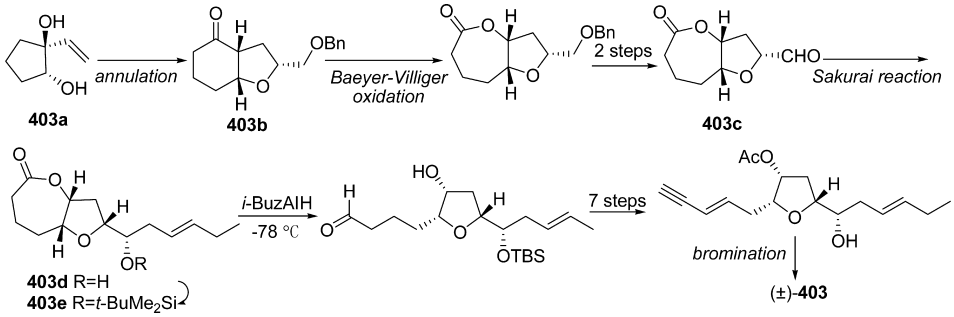
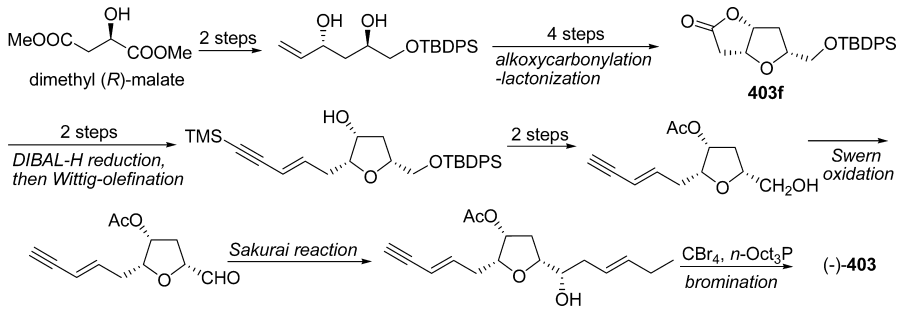
Scheme 9. Total Synthesis of (±)-*trans*-Kumausyne (403) Starting from (1*R,2*S**)-1-Vinylcyclopentane-1,2-diol (403a) by Overman et al.[434]**



Scheme 10. Synthesis of (−)-*trans*-Kumausyne (403) Starting from Dimethyl (*R*)-malate by Boukouvalas et al.[459]



chemists due to distinctive structural features such as the medium- to large-sized ether ring skeleton, substitution of halogen atoms adjacent to an ether oxygen atom, and a bromoallene or an enyne side-chain.[412−421,429,430,434−439] Various strategies were explored with particular attention to construction of the entropically disfavored medium ring ether(s), and a number of ACGs having medium-sized ring cores were successfully synthesized (Table 4). However, syntheses of ACGs possessing larger-ring ether systems such as obtusallene derivatives (**537**−**549**) were not reported.

6.4.1. Synthesis of ACGs Containing Tetrahydrofuran Structural Units. Kumausyne (**403**) was selected as the most important target compound for the synthesis of tetrahydrofuran-containing ACGs and many research groups have reported elegant strategies/methodologies for the synthesis of this compound (Table 4).[434,456−463] In 1991, Overman and co-workers accomplished the landmark total synthesis of (±)-*trans*-kumausyne (**403**). Starting from (1*R**,2*S**)-1-vinylcyclopentane-l,2-diol (**403a**), the synthetic sequence afforded (±)-**403** in 15 steps and 2.7% overall yield, and employed a novel Prins cyclization-pinacol rearrangement for elaborating the tetrahydrofuran core (Scheme 9).[434] The key *rac*-hydrobenzofuranone intermediate **403b** was conveniently formed on a large scale and with complete stereocontrol via a "ring-enlarging tetrahydrofuran annulation", by the acid-catalyzed condensation of **403a** and α-(benzyloxy)acetaldehyde, while intermediate **403c** was conjoined with the six-carbon side chain, and the lactone function of **403e** was then manipulated to elaborate the five-carbon side chain to construct the main skeleton. In 1997, Landais' group approached the total synthesis of (±)-*trans*-kumausyne (**403**) via another strategy featuring the construction of tetrahydrofurans in good yield and diastereoselectivities with excellent 1,3-stereocontrol using electrophilic 5-exo-trig cyclizations of 2-silyl-4-alkenols.[455] The synthesis led to the formation of four chiral centers with excellent diastereoselectivities. Chandler and Phillips later described a different, concise 19-step synthesis of (±)-**403** in 2005.[456] Noteworthy features of the latter synthesis include a tandem ring-opening-ring-closing reaction that converts a structure derived from furan and methyl acrylate by Diels−Alder reaction into an advanced intermediate, a highly selective Baeyer−Villiger reaction, and the use of cross metathesis for the elaboration of a homoallylic alcohol into the pentenyl side-chain.

In 1998, Boukouvalas and co-workers accomplished a more concise and efficient synthesis of (−)-**403** starting from dimethyl (*R*)-malate in 13 steps and 6.2% overall yield (Scheme 10).[459] The synthesis features Pd(II)-mediated intramolecular alkoxycarbonylation-lactonization of an enediol to afford the bicyclic lactone core of the key intermediate (**403f**) in an atom-economical fashion.

In 2001, Gadikota and co-workers developed a concise route for the total synthesis of (+)-*trans*-kumausyne (**403**) and other related marine natural products from D-arabinose using a general strategy for the construction of a 2,3,5-trisubstituted tetrahydrofuran unit via a regioselective hydride ring-opening of the epoxide moiety in the readily accessible methyl 2,3-anhydro-5-*O*-benzyl-α-D-lyxofuranoside.[462] In contrast, Fernández de la Pradilla and co-workers described a unified formal synthesis of enantiopure (+)-**403** in 1998 employing a highly stereoselective remote nucleophilic epoxidation of a sulfinyl diene moiety to construct the tetrahydrofuran template.[463] This methodology was successfully applied to the preparation of (+)-kumausallene (**431**), one of the 2,6-dioxabicyclo[3.3.0]-octane-containing ACGs.[463]

In 1997, Martin and co-workers described a convergent and stereocontrolled 22-step synthesis of (+)-*trans*-deacetylkumausyne (**404**).[464] The approach started with propargyl alcohol and employed brominative cyclization as a key step to obtain the tetrahydrofuran core.

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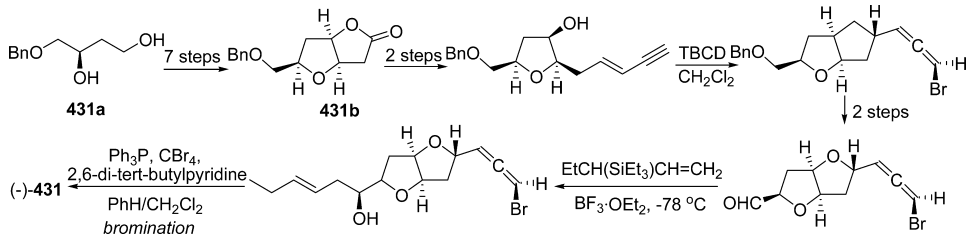
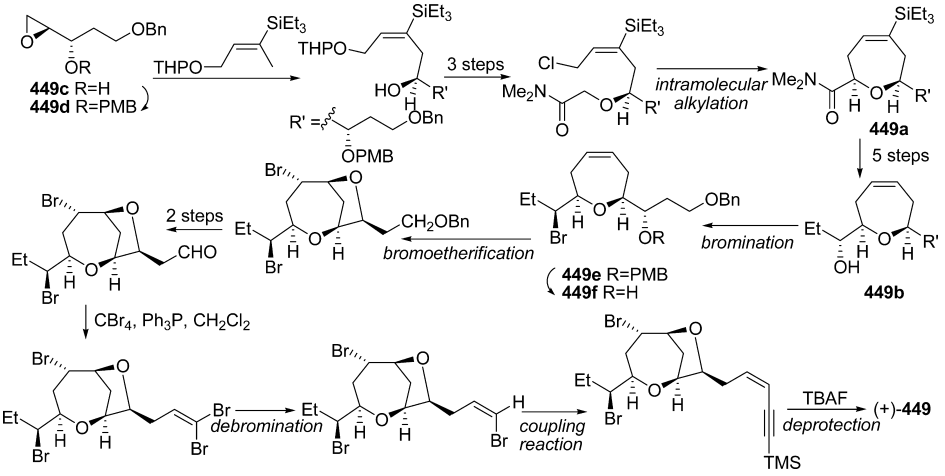
Scheme 11. Enantioselective Synthesis of (−)-Kumausallene (431) by Evans et al.[466]



Scheme 12. Asymmetric Total Synthesis of (+)-Neoisoprelaurefucin (449) by Kim et al.[427]



In 1993, Overman's group reported the first total synthesis of (±)-kumausallene (**431**), a 2,6-dioxabicyclo[3.3.0]octane-containing ACG, employing *cis*-hydrobenzofuranone as a key intermediate obtained from 1-vinylcyclopentane-1,2-diol and α-(benzyloxy)-acetaldehyde via Prins cyclization-pinacol rearrangement strategy.[437] The synthesis proceeded in 17 steps and 2% overall yield from hydrobenzofuranone. In 1998, Lee and co-workers described a formal synthesis of (−)-**431** in 16 steps starting from (−)-diethyl D-tartrate via enantiomerically pure 2,6-dioxabicyclo[3.3.0]octane as the key intermediate,[465] and completing the final portion of the synthesis following Overman's route.[437] This procedure provided an interesting example of the radical cyclization of β-alkoxyacrylates. The first enantioselective synthesis of (−)-**431** was accomplished by Evans and co-workers in 1999 involving 14 steps through the intermediacy of a bicyclic lactone prepared from enantiomerically enriched 1,3-butanediol (Scheme 11).[466] This synthesis demonstrated that the bromoallene moiety is compatible with multiple synthetic operations and led to unambiguous assignment of the absolute configuration of the bromoallene. A similar strategy could, in principle, be adapted to facilitate the preparation of other related tetrahydrofuran-containing ACGs.[446]

6.4.2. Synthesis of Seven-Membered Cyclic ACGs. In 2001, Suzuki and co-workers achieved the first total synthesis of (+)-rogioloxepane A (**443**) with high stereoselectivity.[467] This synthesis showed that the cyclization of hydroxy epoxides promoted by the $(Bu_3Sn)_2O/Zn(OTf)_2$ system is an efficient methodology for the preparation of highly functionalized seven-membered oxacyclics. In addition, the synthesis confirmed the 6*R* and 13*R* configurations for **443**. In 2003, Crimmins and DeBaillie disclosed the enantioselective total synthesis of (+)-**443** in 21 steps starting from 1,5-hexadien-3-ol.[419] The establishment of the trans-disubstituted oxepene ring through the use of a combination of asymmetric glycolate alkylation and a ring-closing metathesis comprise the key steps in the synthesis.

In 1992, Berger and Overman described the efficient synthesis of isolaurepinnacin (**446**) by Lewis acid-promoted cyclizations of β-chloro- (or β-bromo-) acetals starting from 1-methoxy-1-heptene and silylpentenol.[435] The first total synthesis of (+)-**446** was later reported by the same group with high stereoselectivity in 12 steps and 15% overall yield from *cis*-2-penten-1-ol.[436,439] The synthesis features an acetal-vinylsilane cyclization to stereoselectively form the *cis*-2,7-disubstituted oxepene ring and introduce Δ^4 unsaturation. This synthesis rigorously established the *S* configuration of **446** at C_{13}, and the report also corrected the rotation of the natural **446** to be dextrorotatory. In 2001, Suzuki's group accomplished a formal synthesis of (+)-**446** with high stereoselectivity.[468] The approach featured stereoselective construction of the oxepene core employing cyclization of a hydroxy epoxide promoted by the $(Bu_3Sn)_2O/Zn(OTf)_2$ system.

In 2005, Kim's group accomplished a highly stereoselective and concise total synthesis of (−)-isoprelaurefucin (**447**) from oxirane in 14 steps and 12% overall yield. The approach employed a strategy involving a novel "protecting group-dependent" alkylation and ring closing metathesis to form the oxepene core.[429] The first asymmetric total synthesis of (+)-neoisoprelaurefucin (**449**) was developed in 2003 by Kim's group in 20 steps and 2.9% overall yield (Scheme 12).[427] The key intermediate **449b** was obtained by using a novel five-step sequence involving bromolactonization of α,β-unsaturated amide **449a** with NBS, stereoselective debromination with *n*-Bu_3SnH, addition of EtMgBr to the γ-lactone, stereoselective reduction of the resulting hemiketal-ketone mixture (3:1), and

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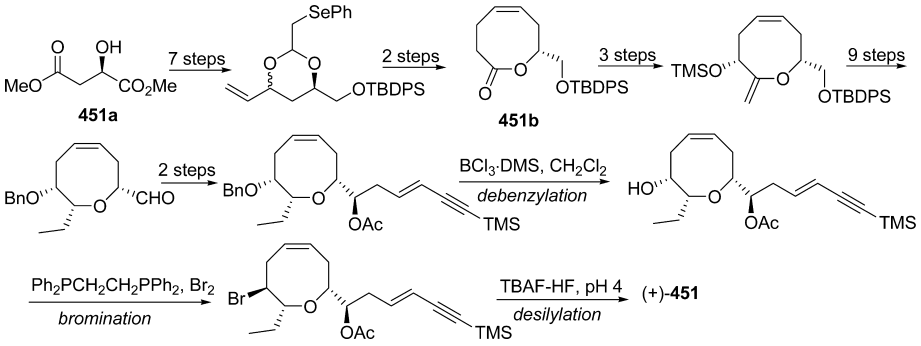
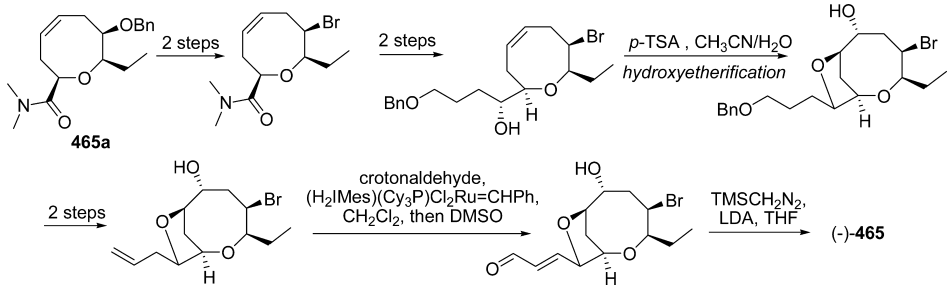
Scheme 13. Enantioselective Synthesis of (+)-Laurencin (451) by Holmes et al.[423]



Scheme 14. Asymmetric Total Synthesis of (−)-Laurefucin (465) by Kim et al.[471]



finally, elimination of *syn*-silyl alcohol by treatment with potassium *t*-butoxide in THF. The approach features an efficient internal alkylation of an amide to form the oxepene skeleton with good regio- and stereocontrol, a novel sequence for removal of a triethylsilyl group from a vinylsilane, and a stereoselective bromoetherification of an alcohol. The synthesis also established the absolute configuration of the natural (+)-**449**.

6.4.3. Synthesis of ACGs Containing Eight-Membered Cyclic Ether Cores. Two strategies were commonly used for the synthesis of ACGs containing an eight-membered cyclic ether unit, with one route employing the cyclization of an acyclic precursor and another (the more popular one) relying on elaboration of eight-membered lactone precursors.[398]

Starting in 1977, much attention was focused on efficient approaches toward the synthesis of (±)- and (+)-laurencin (**451**). The interesting structure of this compound made it an attractive target for synthetic organic chemists on which to test new strategies for stereoselective construction of eight-membered ring ethers. Pioneering work in this area was carried out by Masamune and co-workers as exemplified by the first total synthesis of (±)-laurencin (**451**).[412−414] The synthesis was based on Robinson-Schöf condensation to form a 9-aza-3-oxabicyclo[3.3.1]nonane framework and subsequent ring-expansion employing a Hoffman elimination.

In 1993, Holmes' group described the enantioselective synthesis of (+)-**451** in 26 steps from dimethyl (*R*)-malate (**451a**) using a Claisen rearrangement approach to a key lactone intermediate (**451b**).[423] Noteworthy steps include the reagent-controlled diastereoselective enolate oxidation, the carbon homologation sequence involving Tebbe methylenation of **451b** and diastereoselective intramolecular hydrosilation, the stereocontrolled introduction of the pentenynyl side-chain, and a remarkably high-yielding displacement of the secondary alcohol by bromide ion (Scheme 13).[423] Later in 1997, the Holmes group achieved another enantioselective synthesis of (+)-**451** in 27 steps from (*R*)-malic acid.[424] The key steps involved methylenation of the corresponding lactone followed by intramolecular hydrosilylation of the enol ether and one-carbon homologation of the related diol to give an ethyl-substituted cyclic ether core as the key intermediate. The lactone, in turn, was obtained by two efficient routes including those of a Claisen-ring-expansion followed by α-hydroxylation, and a Yamaguchi lactonization.

In 1995, Overman's group accomplished the enantioselective total synthesis of (+)-**451** from allyl alcohol in 24 steps and 2% overall yield.[438] The synthesis features an acetal-vinyl sulfide cyclization that forms the oxocene ring directly, and introduces, with complete control, the Δ^4 unsaturation and requisite functionality at C_3, C_4, and C_9.

In 1999, Crimmins and Choy reported a method for asymmetric construction of medium-ring cyclic ethers by merging the asymmetric aldol addition of glycolates with a ring-closing metathesis reaction which provided efficient entry to a variety of cyclic ethers.[415] Application of this strategy led to a short formal synthesis of (+)-**451**. The Crimmins' group also developed an original route for the enantioselective total synthesis of (+)-**451** in the same year, where three of the four stereocenters of **451** were provided by asymmetric alkylation and aldol reactions.[416] The synthesis involves 18 steps from *S*-(+)-4-benzyl-3-benzyloxyacetyl-2-oxazolidinone and the key steps included an asymmetric glycolate alkylation leading to an acyl oxazolidinone and a subsequent ring-closing olefin metathesis to construct the oxocene core. The strategy utilized in this synthesis provides a general and efficient route to medium-sized cyclic ether cores of other marine natural products. In 2005, Fujiwara and co-workers achieved the efficient synthesis of (+)-**451** starting from a *C*-galactoside derivative, based on the ring expansion of the oxane part of the starting material into an eight-membered ring ether via a ring-cleavage/ring-closing metathesis process, followed by stereoselective introduction of a bromo group at C_4, and, finally,

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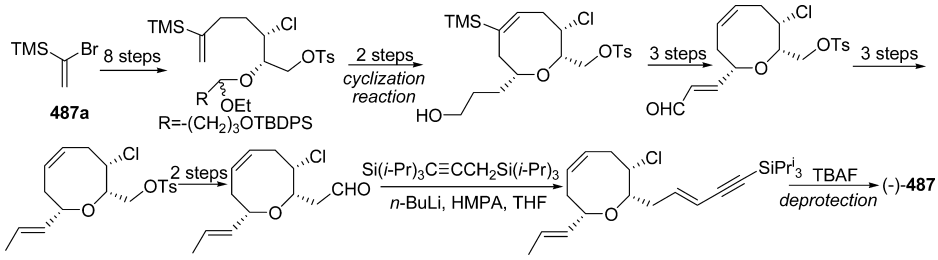
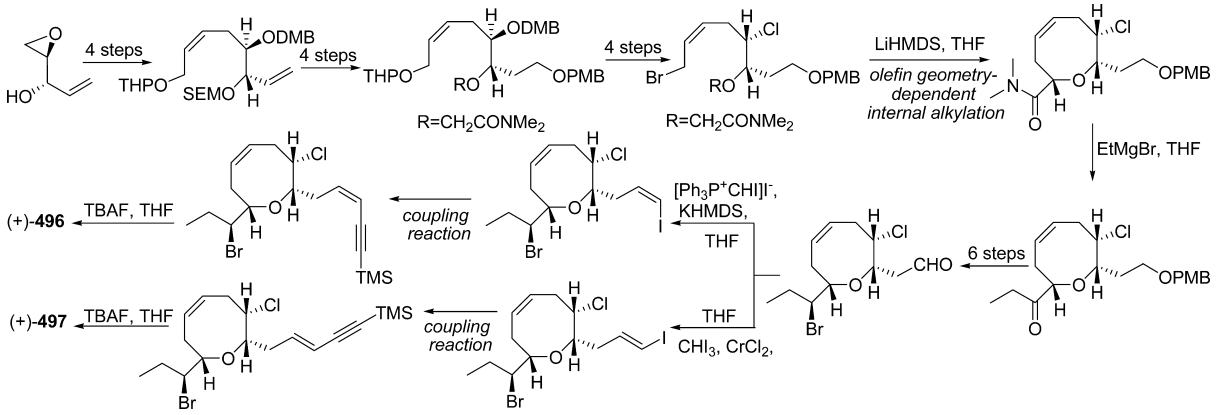
Scheme 15. Total Synthesis of (−)-Laurenyne (487) by Overman and Thompson[433]



Scheme 16. Asymmetric Synthesis of (+)-(3*Z*)- and (+)-(3*E*)-Pinnatifidenyne (496 and 497) by Kim et al.[426]



convergent construction of the side-chain using a lithiated enyne unit.[469] In the same year, Kim and co-workers described a new, efficient, and highly stereoselective total synthesis of (+)-**451** from the known oxazolidinone in 15 steps and 5.4% overall yield. The approach features an efficient olefin geometry-dependent internal alkylation methodology for the construction of eight-membered ether rings and a novel use of acetonitrile anion as an acetaldehyde equivalent for the direct synthesis of a ketone from an α-alkoxy *N*,*N*-dimethylamide.[428] In 1996, Palenzuela and co-workers described a formal synthesis of (+)- and (−)-**451** using a hetero Diels−Alder reaction between a monoactivated diene and (*S*)-(−)-2,3-*O*-isopropylidene-glyceraldehyde (or its enantiomer) as the key step.[470]

Recently, Kim and co-workers accomplished the first and highly stereoselective total synthesis of (−)-laurefucin (**465**) in nine steps with 31% overall yield from known oxocene **465a**.[471] The key step in the synthesis features a novel and efficient organoselenium-mediated biomimetic-type intramolecular hydroxyetherification (Scheme 14).

In 2007, Suzuki and co-workers reported the first total synthesis of (+)-(*Z*)-laureatin (**481**) with high stereoselectivity.[472] The 3,8-dioxabicyclo[5.1.1]nonane skeleton possessing *trans*-oriented alkyl substituents at the α,α'-positions to the ether linkage was stereoselectively constructed by formation of the oxetane via 4-exo cyclization of a hydroxy epoxide unit on the oxocene core. In the same year, Kim's group accomplished the first highly stereo-, regio-, and chemoselective asymmetric total syntheses of (+)-3-(*Z*)-laureatin (**481**) and (+)-3-(*Z*)-isolaureatin (**482**) in a completely substrate-controlled manner.[430] The syntheses feature an intramolecular amide enolate alkylation to construct the α,α'-*cis*-oxocene skeleton, novel "lone pair-lone pair interaction-controlled" epimerizations to give the α,α'-*trans*-oxocenes, various strategies for the stereoselectively demanding introduction of halogen atoms, and novel olefin cross-metatheses for construction of the (*Z*)-enyne systems.

Crimmins and Tabet achieved the first total synthesis of (+)-prelaureatin (**485**) in 2000.[473] The versatile and efficient strategy for the synthesis involved asymmetric glycolate aldol addition following by a ring-closing metathesis to form the eight-membered ring, allowing construction of the oxocene core. Treatment of (+)-**485** with tetrabromocyclohexadienone according to the procedure described by Murai[474] yielded (+)-laurallene (**510**).[473] In 2002, Fujiwara and co-workers also described a total synthesis of **485** featuring stereoselective introduction of two allyl groups starting from galactose pentaacetate, cleavage of the hexose ring, and transformation of an acyclic triene into an oxocene by selective ring-closing metathesis.[475]

In 1988, Overman and Thompson approached the first total synthesis of (−)-laurenyne (**487**) via a linear sequence that proceeded in 20 steps and 0.6% overall yield starting from (1-bromovinyl)trimethylsilane **487a** (Scheme 15).[433] The synthesis is both enantioselective and highly stereocontrolled. The key step was acetal-initiated cyclization to prepare the functionalized eight-membered cyclic ether core, together with the introduction of the Δ^4-unsaturation and the cis-oriented side-chain. The total synthesis also corrected the absolute configuration of natural **487** to be 2R, 7R, and 8R. In 2002, Boeckman and co-workers disclosed a novel asymmetric total synthesis of the natural enantiomer (+)-**487**.[476] The key methodologies applied in the synthesis were a completely diastereoselective metal ion-templated S_N2' cyclization affording a highly functionalized chiral vinyl cyclobutane, and a retro-Claisen rearrangement of the derived homochiral cyclobutane dicarboxaldehyde yielding the eight-membered ring ether core.

In 2003, Kim's group achieved the first and highly stereoselective asymmetric total syntheses of (+)-3-(*Z*)-pinnatifidenyne (**496**) and (+)-3-(*E*)-pinnatifidenyne (**497**)

dx.doi.org/10.1021/cr9002215 | *Chem. Rev.* 2013, 113, 3632−3685

Scheme 17. Substrate-Controlled Asymmetric Total Synthesis and Structure Revision of (+)-Itomanallene A (531) by Kim et al.[336]

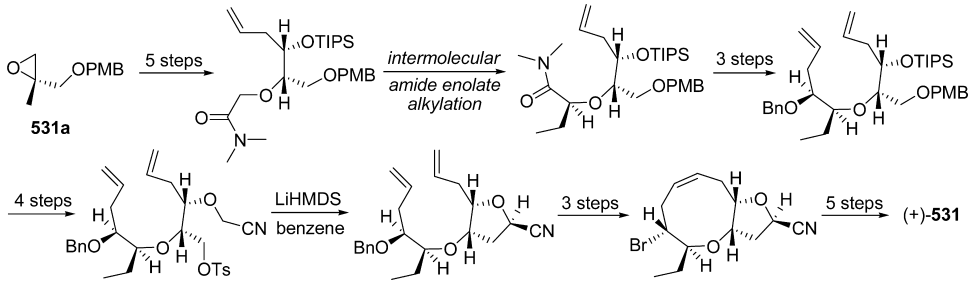


Table 5. Synthesis of Halogenated Indoles and Phenols/Aromatics

	compound	synthetic strategy	research group	ref
bromoindoles	2,3,5,6-tetrabromoindole (**575**)	sequential one-pot bromination-aromatization-bromination reactions to yield the key intermediate, *N*-carbomethoxy-2,3,5-tribromoindole	Suárez-Castillo	481
	N-methyl-2,3,6-tetrabromoindole (**581**)	selective bromination of the key intermediate, 2,3-dibromo-1-methylindole, which was prepared from indole in a one-pot operation	Gribble	480
		incorporation of bromine atoms at C2, C3, and C6 via bromination of *N*-carbomethoxyindole	Suárez-Castillo	481
	N-methyl-2,3,5-tetrabromoindole (**582**)	sequential one-pot bromination-aromatization-bromination reactions to yield the key intermediate, N-carbomethoxy-2,3,5-tribromoindole	Suárez-Castillo	481
	N-methyl-2,3,5,6-tetrabromoindole (**583**)	selective bromination of the key intermediate, 2,3-dibromo-1-methylindole, which was prepared from indole in a one-pot operation	Gribble	480
bromophenols	(±)-polysiphenol (**680**)	highly regioselective intramolecular oxidative coupling	Braddock	482
	cyclotribromoveratrylene (**684**)	coupling reaction promoted by trifluoro-acetic acid	Keehn	484

in 23 steps starting from the known epoxy alcohol (2*R*,3*S*)-1,2-epoxy-4-penten-3-ol with 9.5% and 7.1% overall yields, respectively (Scheme 16).[426] Notable features of the syntheses include novel and efficient construction of the oxocene core via a highly stereo- and regioselective internal alkylation, and direct ketone synthesis from an α-alkyloxy amide moiety in the oxocene.

In 2003, Suzuki's group accomplished a high stereoselective total synthesis of (+)-laurallene (**510**).[477] The oxocene core possessing trans-oriented alkyl substituents at the α,α'-positions was stereoselectively constructed via the cyclization of the corresponding hydroxy epoxide promoted by $Eu(fod)_3$.

6.4.4. Synthesis of ACGs Containing Nine-Membered Cyclic Ether Cores. In 1999, Murai and co-workers accomplished the first total synthesis of (+)-obtusenyne (**526**).[478] The synthesis employs cyclic enol ether formation from the corresponding lactone, regio- and stereoselective epoxidation of the cyclic enol ether, and stereoselective DIBAL-H reduction of the epoxide as the key steps for the construction of the nine-membered cyclic ether core. In 2003, Crimmins and Powell completed a concise and highly diastereoselective synthesis of (+)-**526** in 20 linear steps from commercially available 1,5-hexadiene-3-ol.[420] The key steps were a Sharpless kinetic resolution and an asymmetric glycolate alkylation to establish the stereochemical relationship of the α,α'-disubstituted ether linkage, and a ring-closing metathesis to construct the nine-membered oxocene. In 2007, Suzuki and co-workers accomplished the highly stereoselective total synthesis of (+)-**526** starting from (+)-diethyl tartrate.[479] The synthesis features stereoselective construction of the oxonene core via cyclization of the corresponding hydroxy epoxide promoted by $Eu(fod)_3$.

In 2001 and 2002, Crimmins and co-workers accomplished the total synthesis of (−)-isolaurallene (**529**) starting from a glycolic acid derivative.[417,418] The core structure, a nine-membered cyclic ether ring fused with a bromoallene-substituted tetrahydrofuran, was constructed by a series of reactions including asymmetric glycolate alkylation, Brown asymmetric allylation, ring-closing metathesis, and bromoallene formation via S_N2' displacement with $LiCuBr_2$.

In 2010, Kim and co-workers reported a substrate-controlled approach leading to the first asymmetric total synthesis and structure revision of (+)-itomanallene A (**531**).[336] The key steps involved in this approach were ring-closing metathesis (RCM) and a highly stereoselective intermolecular amide enolate alkylation (IAEA) to form the nine-membered-ring ether. In this approach, known PMB-protected (*S*)-glycidol **531a** was chosen as the starting material. After construction of the dioxabicyclic skeleton using the RCM/IAEA strategy, the bromoallene unit was installed via five steps (Scheme 17). This approach provides a general strategy for the synthesis of both α,α'-*cis*- and α,α'-*trans*-tetrahydrofurans in dioxabicyclic oxonene marine natural products and related structures. Some inefficiency in the ring-closing metathesis step was overcome by modifying the synthetic route to incorporate the tetrahydrofuran ring at an earlier stage.[336]

6.4.5. Synthesis of Maneonene and Isomaneonene ACGs. Holmes and co-workers reported the first total synthesis of *cis*-maneonenes A (**551**) and B (**552**) employing selective catalytic hydrogenation of a silylated butadiyne derivative, which was, in turn, derived from bis(trimethylsily)butadiyne.[421] Later, in 1984, *trans*-maneonene B (**553**) was prepared by the same group using a similar route.[422]

6.5. Synthesis of Bromoindoles

In 2002, Liu and Gribble reported simple syntheses of bromoindoles **581** and **583** starting from indole in 72% and 60% overall yields, respectively (Table 5).[480] The syntheses

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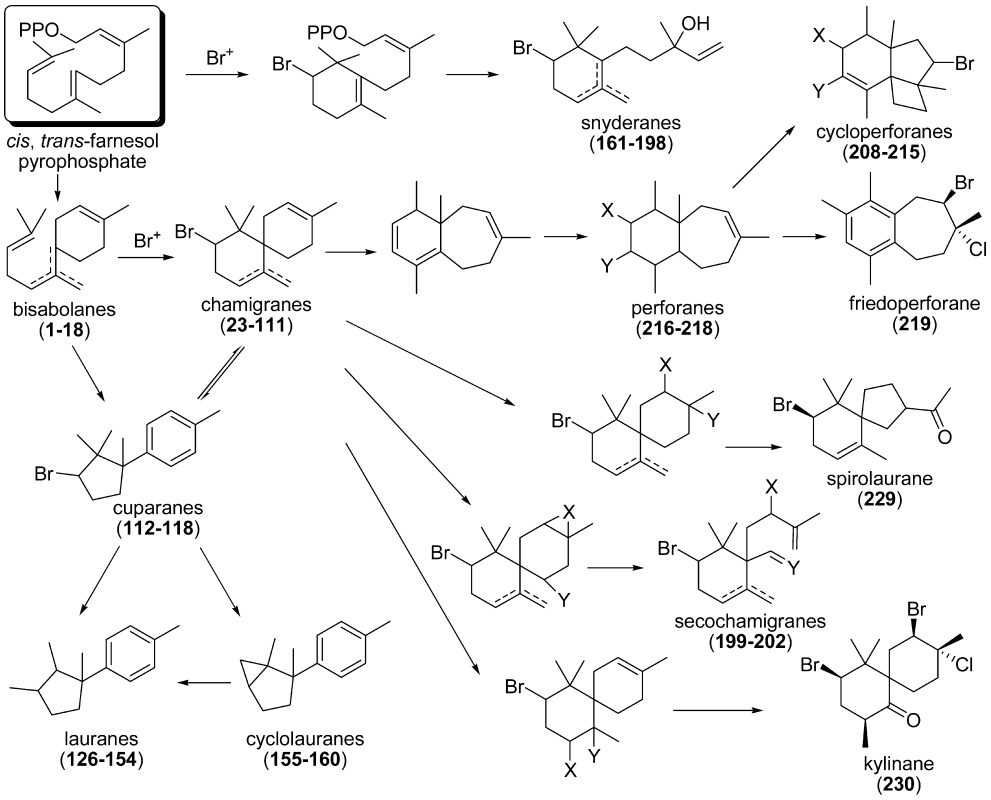
Scheme 18. Plausible Biogenesis of Rhodomelaceae-Derived Sesquiterpenes (Group I)[24,486]



were readily achieved by selective bromination of the key intermediate, 2,3-dibromo-1-methylindole, which in turn was prepared from indole in a one-pot operation in 92% yield. In 2006, Suárez-Castillo and co-workers described a high-yielding and regioselective synthesis of polybrominated indoles **575**, **581**, and **582**.[481] *N*-Carbomethoxyindoline was utilized as starting material to synthesize **575** and **582** via sequential one-pot bromination-aromatization-bromination reactions to yield *N*-carbomethoxy-2,3,5-tribromoindole as the key intermediate. Bromination of *N*-carbomethoxyindole employing excess Br_2 in CCl_4 allowed the incorporation of bromine atoms at C_2, C_3, and C_6 in **581**.

6.6. Synthesis of Bromophenols

Compared to the synthesis of halogenated terpenes and ACGs, relatively limited attention was devoted to the synthesis of algal bromophenols. Recently, Braddock and co-workers reported the first total synthesis of (±)-polysiphenol **680**, a naturally occurring and atropisomerically stable 4,5-dibrominated 9,10-dihydrophenanthrene, in four steps with 70% overall yield using commercially available 5-bromoveratraldehyde as starting material.[482] The installation of the two bromine atoms prior to oxidative coupling prevented further oxidation to a planar aromatized phenanthrene. In this strategy, the key step was realized through highly regioselective oxidative coupling of a dibrominated dihydrostilbene, which was inspired by the probable biogenesis of polysiphenol. In 1983, Amiya and co-workers reported a simple synthesis of a series of methyl esters of tribromophenols from the red alga *Symphyocladia latiuscla*.[483] The syntheses involved a one-step bromination procedure starting from 3,4-dimethoxybenzyl acetate, which, in turn, was prepared by a standard method from commercially available vanillin. In 1992, Keehn and co-workers accomplished the first synthesis of the cyclic trimer cyclotribromoveratrylene (**684**).[484] Treatment of the readily available 5-bromoveratryl alcohol with trifluoroacetic acid at ambient temperature over 3 days yielded **684** as a major product which was readily isolated with no need for chromatographic separation (Table 5).

7. BIOSYNTHESIS

As discussed above, the marine red algae of the Rhodomelaceae family have furnished a variety of structurally unique and sometimes bizarre halogenated metabolites. Understanding of the metabolic processes leading to these halogenated organic molecules is still very limited and the biosynthetic pathways for most of them were not fully elucidated.[404,485] There was a great deal of speculation regarding the biogenesis of these metabolites,[24,486,487] but corroborative experimental evidence to support most of these hypotheses is limited.

7.1. Biosynthesis of Sesquiterpenes

On the basis of biogenetic considerations, sesquiterpenes derived from the Rhodomelaceae family can be classified into two main groups. The first group seems to be arising from six-membered-ring monocyclic farnesane derivatives, such as bisabolanes and snyderanes, for which *cis*,*trans*-farnesol pyrophosphate is a logical precursor (Scheme 18).[24,486] The chamigrane skeleton clearly seems to be a key intermediate system in the construction of the other more complex sesquiterpenes with various carbon frameworks in this group (Scheme 18). The second group of the Rhodomelaceae-derived sesquiterpenes more likely arises from the ten-membered-ring monocyclic farnesane derivatives, such as germacranes, with *trans*,*trans*-farnesol pyrophosphate as the logical precursor (Scheme 19).[24,486] It is interesting that all seven sesquiterpenoid skeletons for which halogenated representatives were not reported (Figure 22) fall into this group (Scheme 19).

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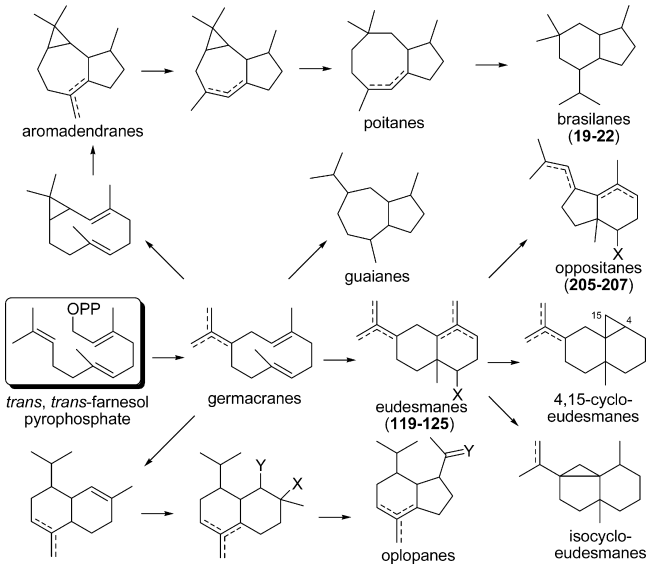
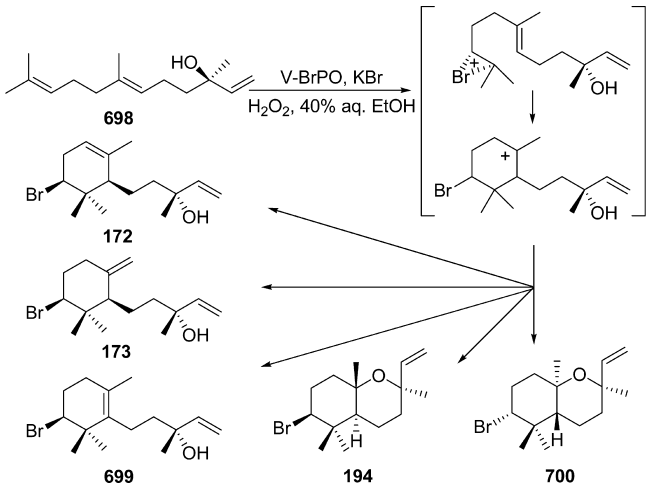
Scheme 19. Plausible Biogenesis of Rhodomelaceae-Derived Sesquiterpenes (Group II)[24,486]



Scheme 20. Proposed Mechanism for V-BrPO-Catalyzed Biosynthesis of α-, β-, and γ-Snyderol (172, 173, and 699), as well as (+)-3β-Bromo-8-epicaparrapi Oxide (194) and Its Stereoisomer 700[493]



Although the proposed transformation processes shown (Schemes 18 and 19) generally appear to be mechanistically rational, they are only hypothetical, and alternate pathways are also possible.

Biogenetic studies have suggested that most brominated cyclic sesquiterpenes are biosynthesized by a bromonium ion-induced cyclization of an acyclic terpene precursor, for example, farnesol, as illustrated in Schemes 18 (or a biological equivalent thereof).[404,431,488] However, except for some biomimetic studies,[489−492] no direct biosynthetic evidence was reported for metabolic pathways leading to formation of Rhodomelaceae-derived halo-sesquiterpenes. In contrast, recent studies of enzyme-catalyzed halogenation reactions provided some useful insight into the biogenesis of Rhodomelaceae-derived metabolites.[429] Among these, vanadium bromoperoxidase (V-BrPO) is an abundant enzyme that was isolated from many algal species, including members of the genus *Laurencia*, and plays a key role in the biosynthesis of brominated molecules.[404] In 2004, the Butler group reported the first V-BrPO-catalyzed asymmetric bromination and cyclization of the sesquiterpene (*E*)-(+)-nerolidol (**698**) to produce α-, β-, and γ-snyderol (**172**, **173**, and **699**), as well as the (+)-3β-bromo-8-epicaparrapi oxide (**194**) and its stereoisomer **700** (Scheme 20).[493] All of these brominated molecules were isolated from *L. obtusa*, as well as from other marine algae, except γ-snyderol (**699**), which is a proposed intermediate in the formation of other bicyclic natural products. This report established for the first time the likely biosynthetic role of V-BrPOs in the production of brominated cyclic sesquiterpenes from marine red algae.[493]

7.2. Biosynthesis of C_{15}-Acetogenins

The biosynthesis of C_{15}-acetogenins (cyclic bromoethers) from red algae was summarized in an excellent review by Murai[494] and pioneering works in biosynthetic studies related to halogenated C_{15}-acetogenins of Rhodomelaceae origin were carried out by Murai and co-workers.[494−498] This biosynthetic work was outlined in detail in the previous review,[494] so the current review only briefly highlights the most important progress in this area.

In 1990, the Murai group reported the first biosynthetic in vitro evidence for brominated acetogenins (ACGs) by using commercially available lactoperoxidase (LPO) and demonstrated that the linear-chained and highly unstable *trans*- and *cis*-laurediols isolated from *Laurencia* species were likely to be the biosynthetic precursors of brominated eight-membered ACGs of *Laurencia* origin.[495,496] In 1992, the same group described a single-step, LPO-catalyzed intramolecular cyclization of (3*Z*,6*S*,7*S*)-laurediol to produce laureatin (**481**) and its key intermediate prelaureatin (**485**).[497] The result also suggests that laurediols are the precursors of *Laurencia* derived ACGs, and that LPO has very low substrate specificity. However, the configurations of the vicinal diol units (3*E*,6*S*,7*S* or 3*Z*,6*R*,7*R*) of laurediols control the pathways leading to either the laurencin- or laureatin-type products.[404] Later in 1994, Murai and co-workers accomplished the cyclization of (3*E*,6*R*,7*R*)- and (3*Z*,6*S*,7*S*)-laurediols catalyzed by partially purified bromoperoxidase (BrPO) from *L. nipponica*, in the presence of H_2O_2 and NaBr, to produce deacetyllaurencin and prelaureatin (**485**) (Scheme 21),[498] respectively. Further reaction of deacetyllaurencin with BrPO yielded bicyclic ACGs such as laurefucin (**465**) and laureoxanyne (**473**) (Scheme 21).[498] These results demonstrated that BrPO is the enzyme that catalyzes the direct bromo-ether cyclization of (3*E*,6*R*,7*R*)-laurediol to deacetyllaurencin, and this was the first direct experimental evidence for the possible biosynthetic pathway leading to the laurencin skeleton.[498] These results also revealed that the geometry of the enyne unit in the substrate (3*E*- or 3*Z*-laurediol) plays an important role in the production of acetogenins with 7,13-epoxy (e.g., laurefucin **465**) or 6,12-epoxy (e.g., prelaureatin **485**) framework (Scheme 21). The Murai group also investigated the electrophilic bromination of prelaureatin (**485**).[474] The enzymatic reaction of (*Z*)-prelaureatin (**485**) with LPO or BrPO afforded laureatin (**481**) and isolaureatin (**482**), whereas the reaction of the (*E*)-isomer with LPO gave laurallene (**510**). Although the yields of brominated ACGs were extremely low, these reactions established a mechanism of bromonium ion-initiated cyclization of an acyclic precursor to the eight-membered bromoether functionality.[404]

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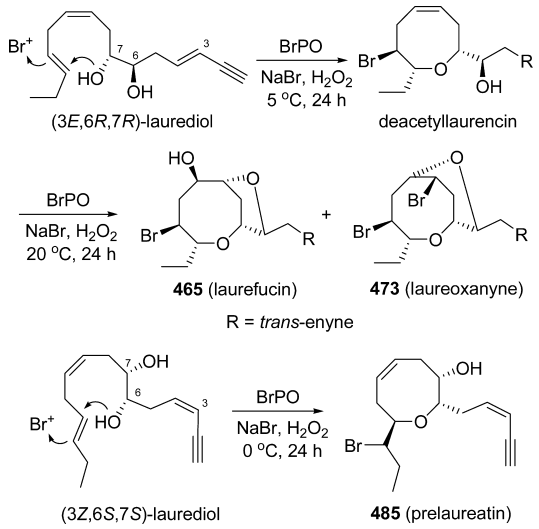
Scheme 21. BrPO-Catalyzed Bromination and Cyclization of Laurediol to ACGs Laurefucin (465), Laureoxanyne (473), and Prelaureatin (485).[498]



Very recently, radioactive ^{82}Br was used by Seki and co-workers in an experimental approach to the biosynthetic study of *Laurencia*-derived brominated metabolites including laurencin (**451**) and laureatin (**481**).[485] When cultured in artificial seawater medium under 16:8 h (light/dark) illumination cycles for 24 h, each of the cultured *Laurencia* strains produced the species-specific ^{82}Br-containing metabolites. The work demonstrated that the use of ^{82}Br provides an effective approach to investigating the biosynthesis of brominated metabolites in *Laurencia* species, though the half-life of ^{82}Br is very short (35.3 h) as compared with those of the more commonly used tracers ^{14}C (5730 y) and ^{3}H (12.3 y).[485]

8. BIOLOGICAL ACTIVITIES AND FUNCTIONS

8.1. Biological Activities

Halogenated organic molecules from members of the family Rhodomelaceae not only possess unique structural features but also exhibit interesting and noteworthy biological properties. Although no molecules of Rhodomelaceae origin have yet been successfully developed as commercial medicinal or agrochemical agents, some of them exhibit potent biological activities, such as cytotoxic, antimicrobial, enzyme−inhibitory, antihelmintic, and antioxidant effects.

8.1.1. Cytotoxic Activity. Cytotoxicity is the most commonly reported kind of biological activity for halogenated organic molecules from the family Rhodomelaceae. A considerable number of such compounds were found to be cytotoxic to a wide range of cancer cell lines. Bisabolane sesquiterpenes (5*S*)-5-acetoxycaespitol (**18**), (5*S*)-5-hydroxyacetylcaespitol (**19**), and (5*S*)-5-acetoxydeoxycaespitol (**20**), and the related norterpene (10*S**)-10-*O*-methylfurocaespitanelactol (**275**), showed weak cytotoxicity against HT-29, MCF-7, and A-431 cancer cells, with IC_{50} values ranging from 11.7 to 91.7 μM.[36] The 11,14-cyclized bisabolane peroxide majapolene A (**250**) exhibited cytotoxicity toward all 60 cell lines in the NCI panel with an average GI_{50} of 0.4 μM, an average TGI of 0.9 μM, and an average LC_{50} of 2.8 μM.[180] Elatol (**55**) is a cytotoxic halosesquiterpene of a type that is characteristic of this family. This compound exhibited IC_{50} values of 1.0 μg/mL to P-388 and 0.1 μg/mL to A-549, HT-29, and MEL-28 cells,[103] and values less than 1.0 μg/mL against HM-02, HEP G2, and MCF-7 cancer cell lines.[499] Although **55** is known to be produced by *Laurencia* spp.,[63] this metabolite, along with several other similar halosesquiterpenes, was recently isolated from the sea hare *Aplysia dactylomela*, which feeds upon *Laurencia*. These compounds were evaluated for their in vitro cytotoxic effects against HeLa and HEP-2 cancer cell lines, and against nontumoral VERO cells, during both lag- and log-phase cell growth.[500] Elatol (**55**) was the most active among the tested compounds under both sets of conditions, with IC_{50} values of 4.1 and 1.3 μM to HeLa, 2.4 and 2.0 μM to HEP-2, and 2.3 and 25.0 μM to VERO cells, in lag- and log-phase, respectively.[500] It was also observed that when the cells are exponentially grown, the activity increases considerably against HeLa, but not against HEP-2 cells.[500] The deschlorinated and acetylated derivatives of elatol (**55**), deschloroelatol (**81**), and acetyldeschloroelatol (**701**) (Figure 57) were found to be inactive in these assays, indicating the relevance of the chlorine atom to the activity.[500] Obtusol (**62**), an HBr adduct of elatol (**55**), was found to be cytotoxic toward MCF-7 and HEP G2 cancer cell lines with IC_{50} values of 1.5 and <1.0 μg/mL, respectively.[499] Five chamigrane sesquiterpenes isolated from *Laurencia cartilaginea* (**79**, **107**, **114**, **120**, and **121**) exhibited cytotoxicity against four tumor cell lines (P-388, A-549, HT-29, and MEL-28) with IC_{50} values ranging from 0.025 to 10 μg/mL.[103] Especially potent activity was observed against HT-29 cells, with IC_{50}'s ranging from 0.025 to 0.5 μg/mL (Table 6).[103]

Table 6. Cytotoxicity (IC_{50}, μg/mL) of Chamigrane Sesquiterpenes 79, 107, 114, 120, and 121[103]

no.	P-388	A-549	HT-29	MEL-28
79	1.0	1.0	0.25	1.0
107	1.0	1.0	0.025	1.0
114	1.0	1.0	0.025	1.0
120	5.0	5.0	0.5	10.0
121	5.0	1.0	0.25	1.0

Representatives of two structurally related classes of halosesquiterpenes, lauranes **144**, **166**,[140] **161**, **168**, **168**,[137] and **702**[140] (Figure 57), and cuparanes **122**−**123**[137] and **126**−**127**[109] that were isolated from *Laurencia microcladia* by Kladi and co-workers, were extensively studied for their cytotoxic

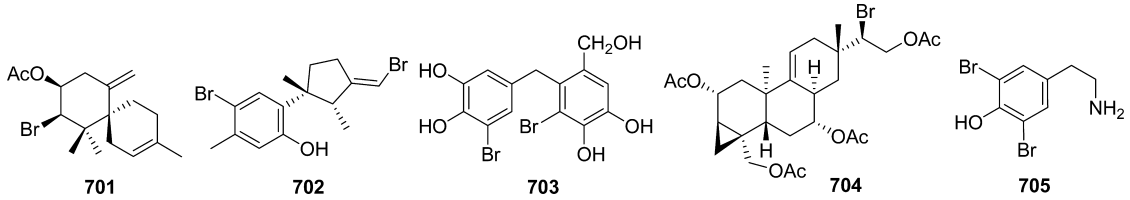


Figure 57. Additional halogenated organic molecules for biological evaluation (**701**−**705**).

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activity against several tumor cell lines, and were found to display a wide range of potency levels.[109,137,140] Analysis of the data indicated that, for laurane and cuparane sesquiterpenes, neither the cyclopropyl ring nor the trisubstituted double bond are essential for cytotoxicity. However, the absence of bromine or hydroxyl functionalities can greatly reduce the activity.[140] Although these results are intriguing, more experiments would be necessary for a detailed SAR analysis of these two classes of halosesquiterpenes.

The cytotoxicity of brominated parguerane (**304**−**306**), isoparguerane (**315**), and neoparguerane (**316**) diterpenes, along with several chemically derived analogues, was evaluated.[210] These compounds display potent activity against HeLa and P-388 cells, with IC_{50} values ranging from 0.3 to 25 μg/mL. It appears that an acetoxy group at C_2 and a bromine at C_{15} are important for activity, while other acetyl groups are not.[210]

Fernández and co-workers evaluated 22 halogenated polyether triterpenes of *Laurencia* origin for their cytotoxic activity against tumor cell lines A-549, P-388, HT-29, and MEL-28.[230] Of these, thyrsiferyl 23-acetate (**349**) displayed the most potent activity against P-388 cells, with an ED_{50} of 0.3 ng/mL,[234] while 16-hydroxydehydrothyrsiferol (**361**) showed the strongest activity against A-549, HT-29, and MEL-28 cells with an IC_{50} of 1.2 μg/mL against each.[230] In addition, 15(28)-anhydrothyrsiferyl diacetate (**351**), 15-anhydrothyrsiferyl diacetate (**352**), and magireols A−C (**353**−**355**) demonstrated potent cytotoxicity against P-388 tumor cells, with ED_{50} values of 50 and 100 ng/mL respectively, for **351** and **352**, and 30 ng/mL for **353**−**355**.[235] Callicladol (**356**) displayed in vitro cytotoxic activity against P-388 murine leukemia cells with an IC_{50} of 1.75 μg/mL.[236] 21α-Hydroxythyrsiferol (**367**) and laurenmariannol (**368**) also showed cytotoxicity toward P-388 with IC_{50} values of 6.6 and 0.60 μg/mL, respectively.[243] Further examination revealed that thyrsiferyl 23-acetate (**349**) induced rapid cell death in various leukemic T- and B-cell lines, and that the cell death follows a typical apoptotic process.[501] Thyrsiferol (**347**) inhibited hypoxia-inducible factor-1 (HIF-1) activation in T47D human breast tumor cells.[502] Moreover, dehydrothyrsiferol (**350**), 22-hydroxy-15(28)-dehydrovenustatriol (**358**), iubol (**359**),[239] prethyrsenol A (**373**), 15-dehydroxythyrsenol A (**378**), and 13-hydroxyprethyrsenol A (**374**)[246] were found to be toxic to Jurkat, MM-144, HeLa, and CADO-ES-1 cancer cell lines with IC_{50} values ranging from 2.0 to 30.0 μM.

The halogenated C_{15}-acetogenin laurefurenyne F (**471**) exhibited moderate nonselective cytotoxicity against three solid tumor cell lines (murine colon 38, human colon H116, and human lung H125), leukemia L1210, and human normal cells CFU-GM.[302] Structure−activity relationship analysis showed that laurefurenyne F (**471**) was more active than its C_3 cis isomer, laurefurenyne E (**470**), which showed very weak cytotoxicity against murine colon 38 only. Additionally, bromoine-substitution at C_{12} was deduced to be a key feature for the cytotoxicity of laurefurenyne F (**471**), as evidenced by comparison with its C_{12}-hydroxylated derivative, which showed no activity against the tested cells.[302]

Apart from the cytotoxic haloterpenes and C_{15}-acetogenins, some haloindoles from these algae also proved to be active in cytotoxicity assays. 2,3,5,6-Tetrabromoindole (**573**) showed cytotoxicity against L1210 tumor cells (ID_{50} 3.6 μg/mL),[354] while the sulfur-containing polybromobisindoles **595** and **596** were reported to possess cytotoxicity against HT-29 and P-388 tumor cells, respectively.[356] Additionally, some phenylethanol-derived bromophenols (**620**−**622** and **655**) showed moderate cytotoxicity against five tumor cell lines (A-549, A-2780, Bel-7402, BGC-823, and HCT-8) with IC_{50} values ranging from 9.4 to 20.8 μg/mL.[368] Bromophenols **649** and **650** showed activity against Hela cancer cell line, with IC_{50} values of 8.71 and 9.61 μg/mL, respectively.[503]

8.1.2. Antibacterial Activity. The halosesquiterpene elatol (**55**) inhibited six species of human pathogenic bacteria, with particularly potent effects against *Staphylococcus epidermis*, *Klebsiella pneumoniae*, and *Salmonella* sp. The potency observed was as good as or better than six standard, commercial available antibiotics (augmentin, latamoxef, ceflaclor, ceftriaxone, kanamycin, and netilmicin).[504] In the same study, iso-obtusol (**64**) exhibited antibacterial activity against four bacteria with especially noteworthy activities against *K. pneumoniae* and *Salmonella* sp.[504] Further experiments demonstrated that both compounds displayed bacteriostatic rather than bactericidal effects.[504] While brominated diterpene 10-acetoxyangasiol (**289**) exhibited antibacterial activity against *Vibrio cholerae* with MIC 100 μg/mL,[194] the bromoditerpene 10-hydroxykahukuene B (**341**) displayed weak antibacterial activity against *Staphylococcus aureus*, and this compound as well as the ACG derivative laurenmariallene (**433**) exhibited weak activity against *Escherichia coli*.[67] Recently, ACG derivatives **455** and **458**−**460** were reported to have antistaphylococcal activity against a panel of multidrug and methicillin-resistant *S. aureus* strains with MICs ranging from 8 to 256 μg/mL.[297] Among these compounds, **458** was found to be the most active, with MIC values of 8−16 μg/mL. The presence of two acetyl groups in **458** may play a key role in improving its cellular bioavailability by making the species more lipophilic.[297]

Bromophenols **649**−**652** and **674** were evaluated for antibacterial activity against eight strains of Gram-positive (*S. aureus* ATCC29213, *S. aureus* 02-60, *S. epidermidis* ATCC12228, and *S. epidermidis* 02-4) and Gram-negative (*E. coli* ATCC25922, *E. coli* 02-26, *Pseudomonas aeruginosa* ATCC27853, and *P. aeruginosa* 02-29) bacteria.[384] Of these, compound **674** showed potent inhibitory activity against seven out of eight strains, especially against *S. epidermidis* ATCC12228, whereas **650** displayed moderate activity against four strains.[384] More recently, bromophenol **649** was reported to have activity against five bacterial strains (*S. aureus* ATCC6538p, *Bacillus subtilis* ATCC 6633, *Micrococcus luteus* IFC 12708, *Proteus vulgaris* ATCC3851, and *S. typhimurium* ATCC 14028) with MIC values ranging from 25 to 50 μg/mL.[505] At a level of 100 μg per 12.7 mm disc, 2,3,5,6-tetrabromoindole (**573**) displayed an inhibition zone of 16 mm against *Bacillus subtilis* after 24 h of growth.[354]

The crude extract of *Laurencia pannosa* exhibited antibacterial activity against three out of 13 species of marine bacteria isolated from algal habitats in Malaysian waters. Three of these species (*Chromobacterium violaceum*, *Proteus mirabilis*, and *Vibrio cholerae*) were then used to evaluate the antibacterial activity of two halosesquiterpenes, pannosanol (**247**) and pannosane (**248**), as well as an ACG derivative, (3*Z*)-chlorofucin (**468**), that were isolated from *L. pannosa*.[178] The major metabolite pannosanol (**247**) exhibited antibacterial activity against all of the tested bacteria with MIC values of 60 μg/disc against *P. mirabilis* and 100 μg/disc against *C. violaceum* and *V. cholerae*, while pannosane (**248**) and (3*Z*)-chlorofucin (**468**) displayed activity only against *C. violaceum* with MIC values of 60 and 100 μg/disc, respectively.[178] A subsequent

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report by the same authors indicated that the halosesquiterpene elatol (**55**) from *L. majuscula* displayed activity against all 13 marine bacteria, with MIC values of 5, 5, and 10 μg/disc against *Clostridium cellobioparum*, *P. mirabilis*, and *Flavobacterium helmiphilum*, and 15−30 μg/disc against the remaining bacteria.[349] In addition, the halosesquiterpene iso-obtusol (**64**) showed MIC values of 10 and 15 μg/disc against *C. cellobioparum* and *P. mirabilis* and 40−60 μg/disc against the other bacteria, whereas the acetogenin lembyne A (**558**) displayed weaker antibacterial activity with MIC values ranging from 20 to 60 μg/disc.[349]

Halogenated organic molecules from several Okinawan *Laurencia* species were evaluated for activity against eight marine bacteria, and the results indicated that the sesquiterpenes deschloroelatol (**81**), iso-laurinterol (**142**), and laurinterol (**166**), as well as the acetogenin (12*E*)-lembyne (**559**), displayed activity when tested in the range of 3−30 μg/disc.[96] The brominated diterpene neoirietetraol (**336**) exhibited inhibitory activity against two of six species of bacterial isolates tested, *Alcaligenes aquamarinus* and *E. coli*, at 100 μg/disc.[225] The halochamigranes elatol (**55**), iso-obtusol (**64**), 10,15-dibromo-1,3(15),7(14)-chamigratrien-9-ol (**107**), and (3*E*)-bromomethylidene-10*β*-bromo-*β*-chamigrene-9*β*-ol (**114**) displayed antibacterial activity against"ice-ice" disease pathogens *Alteromonas* sp1., *Alteromonas* sp2., *Proteus mirabilis*, *Proteus* sp., *Cytophaga*−*Flavobacterium*, and *Vibrio* sp..[506] The above results suggest that halogenated molecules may play ecological roles in defending the algae against the intrusion of pathogenic marine bacteria.

8.1.3. Antifungal Activity. The halosesquiterpenes elatol (**55**) and deschloroelatol (**81**) displayed moderate antifungal properties toward *Mycotypha microspora* and *Eurotium repens*.[75] In addition, the bromophenol bis(2,3,6-tribromo-4,5-dihydroxybenzyl)ether (**675**) exhibited *in vitro* activity below the 50 μg/mL level against *Aspergillus niger* and four other fungal species.[390] At a level of 100 μg per 12.7 mm disc, 2,3,5,6-tetrabromoindole (**573**) displayed an inhibition zone of 16 mm against *Saccharomyces cerevisiae* after 24 h of growth.[354] More recently, bromophenol **649** was reported to have potent activity against four fungal strains with MIC values ranging from 0.78 to 1.56 μg/mL.[505]

8.1.4. Antiviral Activity. Various halosesquiterpenes including pacifenol (**29**), johnstonol (**30**), nidificene (**57**), and nidifidienol (**59**) from *L. nidifica*, were found to possess antiviral activity against Herpes 1-type (HSV-1).[85] Of these, compounds **57** and **59** have good activity with IC_{50} values of 1.5 and 2.4 μg/mL, respectively. The *exo*-methylene group was suggested to be a factor in the antiviral activity.[85] The crude extract of *L. venusta* displayed significant activity against HSV-1 and vesicular stomatitis virus (VSV). Activity-guided fractionation led to the separation of the active components, which included thyrsiferol (**347**), venustatriol (**348**), and thyrsiferyl-23 acetate (**349**).[233]

8.1.5. Enzyme−Inhibitory Activity. The polyether triterpene thyrsiferyl 23-acetate (**349**) displayed potent and selective inhibitory activity against serine/threonine protein phosphatase 2A (PP2A) with IC_{50} values of 4−16 μM depending on the enzyme concentration.[507] Bromophenols **600**, **672**, and **674** from *Odonthalia corymbifera* were found to be inactivators of α-glucosidase.[389] Bromophenols **633**−**634**, **659**−**660**, and **676** exhibited significant aldose reductase inhibitory activity with IC_{50} values ranging from 0.11 to 1.15 μg/mL, and the effect was similar to (**633**) or higher than (**634**, **659**−**660**, and **676**) that of the positive control (quercetin).[373] The bromophenols vidalols A (**664**) and B (**685**) are anti-inflammatory agents that act through inhibition of phospholipase A_2, causing 96% inactivation at 1.6 μg/mL.[386] However, it was difficult to maintain the purity of vidalols A and B during the bioassay, so it was not clear whether the inhibitory activity was caused by the compounds themselves or by degradation products thereof.[386] The bromophenol 5′-hydroxyisoavrainvilleol (**703**) (Figure 57), isolated from both a green alga *Avrainvillea nigricans*[508] and the red alga *Polysiphonia urceolata*,[509] exhibited potent inhibition of protein tyrosine phosphatase 1B (PTP1B) with an IC_{50} of 4.9 μM.[509] Bromophenols **631**, **659**, and **666** obtained from *Symphyocladia latiuscula* also displayed strong activity against PTP1B with IC_{50} of 3.9, 4.3, and 3.5 μM, respectively.[510] Brominated derivatives **663** and **673** from *L. similis* also inhibited PTP1B with IC_{50} values of 2.66 and 2.97 μM, respectively.[385]

8.1.6. Radical Scavenging Activity. A number of bromophenols reportedly display significant antioxidant and radical scavenging activity. Compounds **630** and **635** showed scavenging activities of DPPH radicals with IC_{50} values of 7.5 and 8.5 μM, respectively, and were approximately 2-fold more potent than L-ascorbic acid in the assay.[374] Polybrominated mono- and bis-phenols, including **631**, **633**, **634**, **645**, **646**, **659**, **661**, **666**, and **675** from *Symphyocladia latiuscula*[380] and **647**, **648**, **667**,[381] **678**, **679**, **681**,[391] **682**,[393] and **688**[397] from *Polysiphonia urceolata* were also evaluated for the ability to scavenge DPPH free radicals. All were found to show potent activity, with IC_{50} values ranging from 6.1 to 24.7 μM, compared to the known positive control BHT, which had an IC_{50} 83.8 μM in the assay (Table 7). More recently, six new brominated monophenols (**607**, **611**−**614**, and **616**) isolated from *Rhodomela confervoides* were reported to possess potent antioxidant activity against DPPH (with IC_{50} 7.4−50.6 μM, Table 7) and ABTS radicals (with TEAC 1.60−3.68 *m*M).[366] Generally, the DPPH radical-scavenging effects of the bisphenols are stronger than those of the monophenols, suggesting that the free-radical-scavenging activities of these phenolic compounds are correlated with the number of

Table 7. DPPH Radical Scavenging Activity (IC_{50} values in μM) of Brominated Mono- and Bisphenols

no.	IC_{50}	ref	no.	IC_{50}	ref
600	42.3	366	**634**	24.7	460
601	40.5	366	**645**	18.5	460
602	32.0	366	**646**	24.0	460
605	26.3	366	**647**	9.7	381
606	30.2	366	**648**	16.1	381
607	50.6	366	**659**	8.1	440
608	18.6	366	**661**	10.5	440
611	9.5	366	**666**	10.2	440
612	7.4	366	**667**	21.9	381
613	20.5	366	**675**	8.5	440
614	19.8	366	**678**	6.8	391
615	7.6	366	**679**	6.1	391
616	8.7	366	**681**	8.1	391
620	30.9	366	**682**	15.1	391
625	50.9	366	**688**	7.9	397
631	15.5	440	BHT[a]	83.8	391, 397
633	14.0	440			

[a]BHT = butylated hydroxytoluene (positive control).

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hydroxyl groups in the molecules.[380] Replacement of an OH group with an OMe group on the aromatic ring significantly decreased the activity.[366] Meanwhile, the number and position of the bromine atoms are also important factors contributing to the variation in DPPH scavenging activity observed for the compounds in this class.[366]

8.2. Biological Functions

Halogenated molecules from Rhodomelaceae were speculated to possess multiple biological functions based on laboratory assay results. Numerous reports have shown that such metabolites can act as antifeedant, insecticidal, antifouling, and allelopathic agents, implying possible roles in the defense systems of Rhodomelaceae.

8.2.1. Antifeedant Activity. Chemical defense against herbivores is proposed to be the most important role among all the biological functions of halogenated molecules.[410] Sea hares of the genus *Aplysia* (phylum Mollusca) are well-known to feed on *Laurencia* species. Numerous dietary halogenated structures, such as the sesquiterpenes prepacifenol acetate (**53**),[62] prepacifenol epoxide (**54**),[44] laurenisol acetate (**137**),[119] and aplysistatin (**199**),[151] as well as the triterpene derivative aurilol (**388**),[252] were reported from both sea hares and their algal diets, and some of these compounds display toxicity to cell lines and/or brine shrimp in laboratory assays.[62,500,511] The occurrence of algal dietary toxins in sea hares does not prove a defensive function. However, it is interesting that some of these halogenated molecules were found in less toxic acetylated forms in sea hares.[500] This observation led to a hypothesis that sea hares use acetylation as a simple means of storing toxic metabolites acquired through the diet.[397] Additionally, some grazers such as sea hares may be partly acclimatized to these active molecules, for example, palisadins A (**195**) and B (**196**) from *L. obtusa*,[512] and even use them to defend against their own predators.[511,512]

Defensive effects of halogenated molecules have also been suggested by direct antifeedant assays. A halosesquiterpene of the chamigrane class, pacifenol (**29**), exhibited antifeedant activity against the aphid *Schizaphis graminum*,[513] while the halogenated diterpenes deoxyparguerol (**302**), 2-deacetoxy-deoxyparguerol (**306**), and parguerol triacetate (**704**) (Figure 57) displayed potent feeding-deterrent activity against the young abalone *Huliotis discus hannai*.[409] A series of bromophenols including **600**, **601**, **649**, **650**, and **665** was also revealed to have potent feeding-deterrent activity in the same assay.[387] Further experiments revealed that **302**, **704**,[409] and **649**–**650**[387] significantly deterred feeding by two different species of young sea urchins (*Strongylocentrotus nudus* and *S. intermedius*). When coated on the palatable sea grass *Thalassia testudinum* and placed on coral reefs, the bromophenol vidalol A (**664**) significantly reduced grazing by Caribbean herbivorous fishes, suggesting that it is a potent defensive agent against marine herbivores.[386] The natural concentration of the crude organic extract of *L. obtusa* significantly inhibited feeding by two herbivores (the crab *Pachygrapsus transversus* and the urchin *Lytechinus variegates*).[514] This apparent defensive action was found to be due to elatol (**55**), which was the major constituent of the extract.[514] Further experiments demonstrated that the antifouling property of chemicals produced by *L. obtusa* could make this alga less attractive to fish grazing. Other experimental evidence reinforces the idea that marine natural products may have a variety of similar functions in the sea.[514]

8.2.2. Insecticidal Activity. The chamigrane sesquiterpene deoxyprepacifenol (**96**) and the acetogenins (*Z*)-laureatin (**481**) and (*Z*)-isolaureatin (**482**) exhibited strong insecticidal activity against larvae of the mosquito *Culex pipiens pallens* with IC_{50} values of 0.06–0.50 ppm and LC_{50} values of 2.86–6.83 ppm,[87] while the chamigrane sesquiterpenes pacifenol (**29**), 2,10-dibromo-3-chloro-α-chamigrene (**49**), prepacifenol acetate (**53**), and deoxyprepacifenol (**96**), displayed strong to moderate toxicity to brine shrimp (*Artemia salina*).[62] Similarly, the haloditerpene neoirietetraol (**336**) and the acetogenin (3*Z*)-laurenyne (**499**) showed toxicity toward brine shrimp with LC_{50} values of 40.1 and 467.0 μM, respectively.[225]

The acetogenins (3*Z*)-13-epilaurencienyne (**490**), (3*E*)-epipinnatifidenyne (**491**), (3*E*)-9-chloro-13-bromo-6:12-epoxy-7,10-diacetoxypentadec-3-en-1-yne (**492**), and its 3Z isomer (**493**) exhibited toxicity to ants (*Pheidole pallidula*), with the cis isomers (**490** and **493**) showing stronger activity than the trans isomers (**491** and **492**).[318] More recently, the acetogenin (12*E*)-*cis*-maneonene E (**555**) was reported to have larvicidal activity against two economically important pests, *Tribolium confusum* and *Culex pipiens*.[347]

8.2.3. Antifouling Activity. The chamigrane sesquiterpenes elatol (**55**) and deschloroelatol (**81**) were found to be responsible for the observed antifouling activity of the CH_2Cl_2 extract of *L. rigida*.[75,515] At a concentration of 100 ng/cm^2, elatol (**55**) completely inhibited the settlement of larvae of the barnacle *Balanus amphitrite*, and deschloroelatol (**81**) reduced it by 90%. Both compounds also deterred settlement of larvae of the bryozoan *Bugula neritina* at low concentrations. However, these metabolites act by being toxic and severely affecting the survival rate of nauplii larvae of *B. amphitrite*. Thus, commercial development of **55** or **81** as antifouling agents is unlikely.[75,515] The crude extract of *L. caduciramulosa*, from which the three halosesquiterpenes pacifenol (**29**), filiformin (**152**), and allolaurinterol (**138**) and two nonhalosesquiterpenes were identified, exhibited significant antifouling activity against mussel attachment.[516]

8.2.4. Allelopathic Activity. Two halosesquiterpenes, (−)-10α-bromo-9β-hydroxy-α-chamigrene (**74**) and deschloroelatol (**81**), from the red alga *L. rigida* showed moderate antialgal activity against the green alga *Chlorella fusca*.[75] The bromophenols 5-bromoprotocatechualdehyde (**598**) and lanosol (**600**) were also toxic to some unicellular marine algae, such as *Skeletonema costatum* and *Olisthodiscus* species,[517] while another report indicated that lanosol (**600**) could strongly stimulate the growth of the red algae *Goniotrichum alsidii* and *Polysiphonia urceolata*, but inhibited the growth of *P. urceolata* at a higher concentration of 0.2 mM.[518] Dibromocatechol α-*O*-methyllanosol (**601**) exhibited a stimulating effect on the growth and elongation of terrestrial plants in both in vivo and in vitro systems.[519]

8.3. Miscellaneous Activity

In vitro anthelmintic assays revealed that halosesquiterpenes of the bisabolane class (**6**)[29] and the chamigrane class (**67**, **75**–**77**, **80**, and **120**)[76] displayed moderate antiparasitic activity against *Nippostrongylus brasiliensis*, while snyderane sesquiterpene **176** exhibited moderate antimalarial activity against the D6 and W2 clones of *Plasmodium falciparum* with IC_{50} values of 2700 and 4000 ng/mL, respectively.[142] Halosesquiterpenes elatol (**55**) and obtusol (**62**) were recently reported to have in vitro and in vivo antileishmanial activity against promastigote and amastigote forms of *Leishmania amazonensis*.[520,521] After 72 h of

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treatment, elatol (**55**) showed significant antileishamanial activity, with IC_{50} values of 4.0 and 0.45 μM for promastigote and intracellular amastigote forms of *L. amazonensis*, respectively, and the compound also induced notable changes in the ultrastructure of the mitochondrion of the parasite.[521] These results suggested that elatol (**55**) may have important advantages for the development of new antileishamanial chemotherapies. Recently, the bromoditerpene neorogioltriol (**344**) was reported to possess analgesic and in vitro and in vivo anti-inflammatory activities,[229,522] while acetogenins (12*E*)-*cis*-maneonene E (**555**) and (12*Z*)-*cis*-maneonene D (**557**) were found to have potential to regulate programmed death in the initiation and propagation of inflammatory responses.[348] Several bromophenols including **600**, **601**, **649**−**651**, and **705** (Figure 57) isolated from *Odonthalia corymbifera* were demonstrated to possess potent inhibitory activity against isocitrate lyase (ICL), a key enzyme in the glyoxylate cycle, as well as in the rice fungal pathogen *Magnaporthe grisea*.[523] In addition, as ICL inhibitors, these compounds may be promising candidates for crop protection, particularly to protect rice plants against *M. grisea*.[523]

8.4. Summary of Biological Activities and Functions

As discussed above, many halogenated organic molecules not only have intriguing molecular structures but also possess a variety of biological activities including cytotoxic, antimicrobial, enzyme−inhibitory, and radical scavenging effects, as well as potential ecological relevant functions, such as antifeedant, insecticidal, antifouling, and allelopathic activity. Despite the above positive results, however, biological evaluations of these molecules have typically been limited to one or two bioassay models, and many of them, especially the diterpenes and acetogenins, lack any reported bioassay data. Therefore, much more extensive testing of these molecules seems warranted. Further investigation of the structure−activity relationships, especially the effects of the halogen atoms on the bioactivity as well as mode-of-action studies, could result in the discovery of more promising analogues with potential clinical application. For safety considerations, however, the possible toxicity of these halogenated organic molecules or analogues should be evaluated before implementing any use as a drug candidate or as a dietary supplement.

9. PROSPECTS FOR FUTURE DISCOVERIES AND CONCLUDING REMARKS

A total of 697 halogenated organic molecules isolated in the past several decades from algal species of the family Rhodomelaceae were covered in this review. The majority of these compounds contain bromine, with some of them containing both bromine and chlorine. Relatively few contain only chlorine and even fewer contain iodine. Since seawater is a halogen-rich environment, it is not surprising that marine algal species are capable of incorporating halogen atoms into the organic molecules that they produce. However, it is remarkable that brominated compounds reported from the Rhodomelaceae to date are more abundant than chlorinated compounds from such sources, in spite of the fact that seawater contains a much higher concentration of chloride ion (19 000 mg/L) than bromide ion (65 mg/L).[524] The selective incorporation of bromine during the biosynthesis of halogenated metabolites in these algal species offers a very interesting topic for future study. Resolving questions about the biosynthetic pathways of halogenated organic molecules remains an important challenge, as it is intimately connected to understanding the evolutionary and natural roles of such compounds in these algae. On the other hand, marine algae are directly exposed in the marine environment and are affected by symbiotic and/or ambient microorganisms, such as bacteria, fungi, or viruses. However, the impact of these microorganisms on the production of the halogenated organic molecules by marine algae remains unclear so far. A deeper insight in mutualistic symbiosis involving the metabolites of marine algae is therefore of a great interesting subject for the future study.

Although the biological activities and ecological functions of halogenated organic molecules were studied to some degree, little is known regarding their structure−activity relationships. Further studies in this area could contribute to a better understanding of their mechanisms of action at the cellular and molecular level, which would be beneficial in the ongoing development and structure optimization of this class of compounds, and could lead to the discovery of novel pharmacophores and heretofore unidentified mechanisms of drug action. On the other hand, development of new strategies and efficient methods for the synthesis of halogenated organic molecules are also necessary in light of the fascinating structures and intriguing biological properties displayed by such compounds, as well as the difficulties in obtaining large quantities of them from the natural sources.

The Rhodomelaceae constitute a large algal family, and species in this family are distributed worldwide.[525] On the basis of hit rates in the species of the family so far examined, and, as a fact that, the chemical constituents of the species in the family especially in the genus *Laurencia* displayed a marked variation, which often seems to be dependent upon the growth locality and collection season, it could be predicted that hundreds or thousands of new halogenated organic molecules with significant biological activity await discovery. Although at present we cannot comment further on the importance of halogenated organic molecules from the Rhodomelaceae, given their many biological activities, it would be not surprising if some of these compounds or their synthetic analogues eventually find practical application in medicine or agriculture.

ASSOCIATED CONTENT

Supporting Information

Comprehensive tables (Tables S1−S16) containing detailed information for each halomolecule including compound name (synonyms, if applicable), molecular formula, halogenation/structural features, source species, sample collection locality, and references. This information is available free of charge via the Internet at http://pubs.acs.org/.

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Notes

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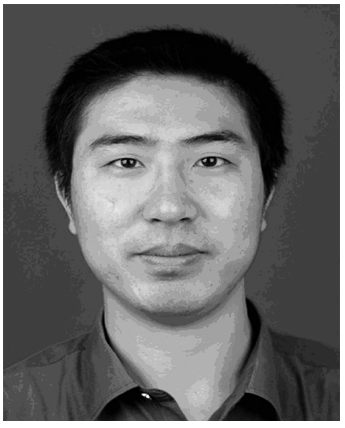

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ABBREVIATIONS

A-2780	human ovarian cancer cell line
A-431	human epidermoid carcinoma cell line
A-549	human lung carcinoma cell line
ABTS	2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonic acid)diammonium salt
ACG	acetogenin
9-BBN	9-borabicyclo[3.3.1]nonane dimer
t-BDMS-Cl	*tert*-butyldimethylsilyl chloride
Bel-7402	hepatoma cell line
BGC-823	stomach cancer cell line
BHT	butylated hydroxytoluene
BrPO	bromoperoxidase
CADO-ES-1	Ewing's sarcoma cell line
CD	circular dichroism
D-DET	D-(−)-diethy tartrate
DIBAL-H	diisobutylaluminium hydride
DME	1,2-dimethoxyethane
DMS	dimethylsulfide
DPPH	α,α-diphenyl-β-picrylhydrazyl
ED_{50}	median effective dose
GI_{50}	50% growth inhibition
HCT-8	human colon cancer cell line
HeLa	human carcinoma of the cervix cell line
HEP-2	human carcinoma of the larynx cell line
HEP G2	liver carcinoma cell line
HIF-1	hypoxia-inducible factor-1
HM-02	gastric carcinoma cell line
HMPA	hexamethylphosphoramide
HT-29	human colon carcinoma cell line
IEEA	intramolecular ester enolate alkylation
Jurkat	T-cell acute leukemia cell line
L1210	mouse lymphocytic leukemia cell line
LC_{50}	50% cell death
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
LPO	lactoperoxidase
MCF-7	breast carcinoma cell line
MEL-28	human melanoma cell line
MIC	minimum inhibitory concentration
MM-144	multiple myeloma cell line
MOMCl	chloromethyl methyl ether
MTPA	2-methoxy-2-(trifluoromethyl)phenylacetic acid
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
n-Oct_3P	tri*n*-octylphosphine
NOESY	nuclear Overhauser enhancement spectroscopy
P-388	murine lymphoid neoplasm
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PMB	*p*-methoxybenzyl
p-TSA	*p*-toluenesulfonic acid
SAR	structure−activity relationship
SEM	2-(trimethylsilyl)ethoxymethyl
T47D	human breast tumor cell line
TBAF	tetrabutylammonium fluoride
TBCD	2,4,4,6-tetrabromocyclohexa-2,5-dienone
TBDPS	*tert*-butyldiphenylsilyl
TEAC	trolox equivalent antioxidant capacity
TES	triethylsilyl
TGI	total growth inhibition
THP	tris(hydroxy-methyl)phosphine
TIPS	triisopropylsilyl
TPT	titanium isopropoxide
V-BrPO	vanadium bromoperoxidase
VERO	African green monkey kidney cell line

REFERENCES

(1) Gribble, G. W. *J. Nat. Prod.* **1992**, *55*, 1353.
(2) Craigie, J. S.; Gruenig, D. E. *Science* **1967**, *157*, 1058 and references cited therein.
(3) Gribble, G. W. *Heterocycles* **2012**, *84*, 157.
(4) Kraft, G. T. In *The Biology of Seaweeds, Rhodophyta, Morphology and Classification*; Lobban, C. S., Wynne, M. J., Eds.; Blackwell Scientific Publications: Oxford, U.K., 1981, p 6.
(5) *MarinLit, A Marine Literature Database*, version vpc 15.5; Department of Chemistry, University of Canterbury: Christchurch, New Zealand, 15 March, 2012; http://www.chem.canterbury.ac.nz/research/marinlit.htm.
(6) Gribble, G. W. *J. Chem. Educ.* **2004**, *81*, 1441.
(7) Gribble, G. W. *Am. Sci.* **2004**, *92*, 342.
(8) Gribble, G. W. *Chemosphere* **2003**, *52*, 289.
(9) Gribble, G. W. *Environ. Sci. Pollut. Res* **2000**, *7*, 37.
(10) Gribble, G. W. *Chem. Soc. Rev.* **1999**, *28*, 335.
(11) Gribble, G. W. *Acc. Chem. Res.* **1998**, *31*, 141.
(12) Gribble, G. W. In *Progress in the Chemistry of Organic Natural Products*; Springer: Wien, 1996; Vol. *68*, p 1.
(13) Gribble, G. W. *Pure Appl. Chem.* **1996**, *68*, 1699.
(14) Gribble, G. W. *Environ. Sci. Technol.* **1994**, *28*, 310A.
(15) Gribble, G. W. *Today's Chemist Work* **1994**, *3*, 64.
(16) Gribble, G. W. *Nucleus* **1994**, *72*, 15.
(17) de Carvalho, L. R.; Roque, N. F. *Quim. Nova* **2000**, *23*, 757.
(18) Dembitsky, V. M.; Srebnik, M. *Prog. Lipid Res.* **2002**, *41*, 315.
(19) Butler, A.; Walker, J. V. *Chem. Rev.* **1993**, *93*, 1937.
(20) Thomson, R. H. *J. Indian Chem. Soc.* **1978**, *55*, 1209.
(21) Fenical, W. *J. Phycol.* **1975**, *11*, 245.
(22) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, *19*, 1 and previous reviews in this series.
(23) Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2010**, *27*, 165 and previous reviews in this series.
(24) Erickson, K. L. In *Marine Natural Products*; Scheuer, P. J., Ed.; Academic Press: New York, 1983; Vol. *5*, p 131.
(25) Coll, J. C.; Wright, A. D. *Aust. J. Chem.* **1987**, *40*, 1893.
(26) Vazquez, J. T.; Chang, M.; Nakanishi, K.; Martin, J. D.; Martin, V. S.; Perez, R. *J. Nat. Prod.* **1988**, *51*, 1257.

(27) Norte, M.; Fernández, J. J.; Padilla, A. *Phytochemistry* **1992**, *31*, 326.
(28) Ji, N. Y.; Li, X. M.; Wang, B. G. *Helv. Chim. Acta* **2010**, *93*, 2281.
(29) Davyt, D.; Fernandez, R.; Suescun, L.; Mombrú, A. W.; Saldaña, J.; Domínguez, L.; Fujii, M. T.; Manta, E. *J. Nat. Prod.* **2006**, *69*, 1113.
(30) Ji, N. Y.; Li, X. M.; Li, K.; Wang, B. G. *Helv. Chim. Acta* **2009**, *92*, 1873.
(31) de Carvalho, L. R.; Fujii, M. T.; Roque, N. F.; Kato, M. J.; Lago, J. H. G. *Tetrahedron Lett.* **2003**, *44*, 2637.
(32) de Carvalho, L. R.; Fujii, M. T.; Roque, N. F.; Lago, J. H. G. *Phytochemistry* **2006**, *67*, 1331.
(33) González, A. G.; Darias, J.; Martín, J. D. *Tetrahedron Lett.* **1973**, *14*, 2381.
(34) González, A. G.; Darias, J.; Martín, J. D.; Pérez, C. *Tetrahedron Lett.* **1974**, *15*, 1249.
(35) Chang, M.; Vazquez, J. T.; Nakanishi, K.; Cataldo, F.; Estrada, D. M.; Fernandez, J.; Gallardo, A.; Martin, J. D.; Norte, M.; Perez, R.; Rodriguez, M. L. *Phytochemistry* **1989**, *28*, 1417.
(36) Lhullier, C.; Falkenberg, M.; Ioannou, E.; Quesada, A.; Papazafiri, P.; Horta, P. A.; Schenkel, E. P.; Vagias, C.; Roussis, V. *J. Nat. Prod.* **2010**, *73*, 27.
(37) González, A. G.; Darias, J.; Martín, J. D.; Pérez, C.; Sims, J. J.; Lin, G. H. Y.; Wing, R. M. *Tetrahedron* **1975**, *31*, 2449.
(38) González, A. G.; Martín, J. D.; Pérez, C.; Ramírez, M. A.; Ravelo, F. *Tetrahedron Lett.* **1980**, *21*, 187.
(39) Iliopoulou, D.; Vagias, C.; Galanakis, D.; Argyropoulos, D.; Roussis, V. *Org. Lett.* **2002**, *4*, 3263.
(40) Aydogmus, Z.; Imre, S.; Ersoy, L.; Wray, V. *Nat. Prod. Res.* **2004**, *18*, 43.
(41) Sims, J. J.; Fenical, W.; Wing, R. M.; Radlick, P. *J. Am. Chem. Soc.* **1971**, *93*, 3774.
(42) Sims, J. J.; Fenical, W.; Wing, R. M.; Radlick, P. *Tetrahedron Lett.* **1972**, *13*, 195.
(43) Sims, J. J.; Fenical, W.; Wing, R. M.; Radlick, P. *J. Am. Chem. Soc.* **1973**, *95*, 972.
(44) Faulkner, D. J.; Stallard, M. O.; Ireland, C. *Tetrahedron Lett.* **1974**, *15*, 3571.
(45) Waraszkiewicz, S. M.; Erickson, K. L. *Tetrahedron Lett.* **1976**, *17*, 1443.
(46) Waraszkiewicz, S. M.; Erickson, K. L.; Finer, J.; Clardy, J. *Tetrahedron Lett.* **1977**, *18*, 2311.
(47) Suzuki, T. *Chem. Lett.* **1980**, *9*, 541.
(48) Kurata, K.; Furusaki, A.; Katayama, C.; Kikuchi, H.; Suzuki, T. *Chem. Lett.* **1981**, *10*, 773.
(49) Kurata, K.; Suzuki, T.; Suzuki, M.; Kurosawa, E.; Furusaki, A.; Suehiro, K.; Matsumoto, T.; Katayama, C. *Chem. Lett.* **1983**, *12*, 561.
(50) Kikuchi, H.; Suzuki, T.; Suzuki, M.; Kurosawa, E. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2437.
(51) Atta-ur-Rahman; Ahmad, V. U.; Bano, S.; Abbas, S. A.; Alvi, K. A.; Ali, M. S.; Lu, H. S. M.; Clardy, J. *Phytochemistry* **1988**, *27*, 3879.
(52) Bano, S.; Ali, M. S.; Ahmad, V. U. *Z. Naturforsch.* **1988**, *43b*, 1347.
(53) Ahmad, V. U.; Ali, M. S. *Phytochemistry* **1991**, *30*, 4172.
(54) Aknin, M.; Ahond, A.; Chiaroni, A.; Poupat, C.; Riche, C.; Kornprobst, J. M. *Tetrahedron Lett.* **1989**, *30*, 559.
(55) Dias, D. A.; Urban, S. *Phytochemistry* **2011**, *72*, 2081.
(56) Suzuki, M.; Kurosawa, E.; Irie, T. *Tetrahedron Lett.* **1974**, *15*, 821.
(57) Suzuki, M.; Furusaki, A.; Kurosawa, E. *Tetrahedron* **1979**, *35*, 823.
(58) Suzuki, M.; Kurosawa, E.; Irie, T. *Tetrahedron Lett.* **1974**, *15*, 1807.
(59) Howard, B. M.; Fenical, W. *Tetrahedron Lett.* **1976**, *17*, 2519.
(60) Howard, B. M.; Fenical, W. *Tetrahedron Lett.* **1975**, *16*, 1687.
(61) Ojika, M.; Shizuri, Y.; Yamada, K. *Phytochemistry* **1982**, *21*, 2410.
(62) Jongaramruong, J.; Blackman, A. J.; Skelton, B. W.; White, A. H. *Aust. J. Chem.* **2002**, *55*, 275.
(63) Sims, J. J.; Lin, G. H. Y.; Wing, R. M. *Tetrahedron Lett.* **1974**, *15*, 3487.
(64) González, A. G.; Darias, J.; Díaz, A.; Fourneron, J. D.; Martín, J. D.; Pérez, C. *Tetrahedron Lett.* **1976**, *17*, 3051.
(65) Waraszkiewicz, S. M.; Erickson, K. L. *Tetrahedron Lett.* **1974**, *15*, 2003.
(66) Waraszkiewicz, S. M.; Erickson, K. L. *Tetrahedron Lett.* **1975**, *16*, 281.
(67) Ji, N. Y.; Li, X. M.; Li, K.; Ding, L. P.; Gloer, J. B.; Wang, B. G. *J. Nat. Prod.* **2007**, *70*, 1901.
(68) McMillan, J. A.; Paul, I. C.; White, R. H.; Hager, L. P. *Tetrahedron Lett.* **1974**, *15*, 2039.
(69) González, A. G.; Martín, J. D.; Martín, V. S.; Martínez-Ripoll, M.; Fayos, J. *Tetrahedron Lett.* **1979**, *20*, 2717.
(70) Furusaki, A.; Matsumoto, T.; Kurata, K.; Suzuki, T.; Suzuki, M.; Kurosawa, E. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3501.
(71) González, A. G.; Martín, J. D.; Martín, V. S.; Norte, M. *Tetrahedron Lett.* **1979**, *20*, 2719.
(72) Ayyad, S. E. N.; Dawidar, A. A. M.; Dias, H. W.; Howie, R. A.; Jakupovic, J.; Thomson, R. H. *Phytochemistry* **1990**, *29*, 3193.
(73) Suzuki, M.; Segawa, M.; Suzuki, T.; Kurosawa, E. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3824.
(74) Suzuki, M.; Segawa, M.; Suzuki, T.; Kurosawa, E. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2435.
(75) König, G. M.; Wright, A. D. *J. Nat. Prod.* **1997**, *60*, 967.
(76) Davyt, D.; Fernandez, R.; Suescun, L.; Mombru, A. W.; Saldana, J.; Dominguez, L.; Coll, J.; Fujii, M. T.; Manta, E. *J. Nat. Prod.* **2001**, *64*, 1552.
(77) Suescun, L.; Mombrú, A. W.; Mariezcurrena, R. A.; Davyt, D.; Fernández, R.; Manta, E. *Acta Crystallogr.* **2001**, *57c*, 286.
(78) Gerwick, W. H.; Lopez, A.; Davila, R.; Albors, R. *J. Nat. Prod.* **1987**, *50*, 1131.
(79) Wright, A. D.; Coll, J. C.; Price, I. R. *J. Nat. Prod.* **1990**, *53*, 845.
(80) Kennedy, D. J.; Selby, I. A.; Thomson, R. H. *Phytochemistry* **1988**, *27*, 1761.
(81) Brennan, M. R.; Erickson, K. L.; Minott, D. A.; Pascoe, K. O. *Phytochemistry* **1987**, *26*, 1053.
(82) Rovirosa, J.; Soto, H.; Cueto, M.; Dárias, J.; Herrera, J.; San-Martín, A. *Phytochemistry* **1999**, *50*, 745.
(83) Fenical, W. *Phytochemistry* **1976**, *15*, 511.
(84) Suzuki, M.; Kurosawa, E.; Furusaki, A. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3371.
(85) Kimura, J.; Kamada, N.; Tsujimoto, Y. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 289.
(86) Ji, N. Y.; Li, X. M.; Zhang, Y.; Wang, B. G. *Biochem. Syst. Ecol.* **2007**, *35*, 627.
(87) Watanabe, K.; Umeda, K.; Miyakado, M. *Agric. Biol. Chem.* **1989**, *53*, 2513.
(88) Caccamese, S.; Compagnini, A.; Toscano, R. M.; Nicolo, F.; Chapuis, G. *Tetrahedron* **1987**, *43*, 5393.
(89) Elsworth, J. F.; Thomson, R. H. *J. Nat. Prod.* **1989**, *52*, 893.
(90) González, A. G.; Martín, J. D.; Martín, V. S.; Norte, M.; Fayos, J.; Martínez-Ripoll, M. *Tetrahedron Lett.* **1978**, *19*, 2035.
(91) Martin, J. D.; Caballero, P.; Fernandez, J. J.; Norte, M.; Perez, R.; Rodriguez, M. L. *Phytochemistry* **1989**, *28*, 3365.
(92) Brito, I.; Cueto, M.; Díaz-Marrero, A. R.; Darias, J.; San Martín, A. *J. Nat. Prod.* **2002**, *65*, 946.
(93) Suzuki, M.; Kurosawa, E. *Tetrahedron Lett.* **1978**, *19*, 4805.
(94) Suzuki, M.; Furusaki, A.; Hashiba, N.; Kurosawa, E. *Tetrahedron Lett.* **1979**, *20*, 879.
(95) Díaz-Marrero, A. R.; Brito, I.; de la Rosa, J. M.; D'Croz, L.; Fabelo, O.; Ruiz-Pérez, C.; Darias, J.; Cueto, M. *Eur. J. Org. Chem.* **2009**, *2009*, 1407.
(96) Vairappan, C. S.; Suzuki, M.; Abe, T.; Masuda, M. *Phytochemistry* **2001**, *58*, 517.
(97) Masuda, M.; Itoh, T.; Matsuo, Y.; Suzuki, M. *Phycol. Res.* **1997**, *45*, 59.
(98) Coll, J. C.; Wright, A. D. *Aust. J. Chem.* **1989**, *42*, 1591.
(99) Ahmad, V. U.; Ali, M. S. *Sci. Pharm.* **1991**, *59*, 243.

(100) deNys, R.; König, G. M.; Wright, A. D.; Sticher, O. *Phytochemistry* **1993**, *34*, 725.
(101) Bittner, M. L.; Silva, M.; Paul, V. J.; Fenical, W. *Phytochemistry* **1985**, *24*, 987.
(102) Francisco, M. E. Y.; Erickson, K. L. *J. Nat. Prod.* **2001**, *64*, 790.
(103) Juagdan, E. G.; Kalidindi, R.; Scheuer, P. *Tetrahedron* **1997**, *53*, 521.
(104) Guella, G.; Öztunç, A.; Mancini, I.; Pietra, F. *Tetrahedron Lett.* **1997**, *38*, 8261.
(105) Francisco, M. E. Y.; Turnbull, M. M.; Erickson, K. L. *Tetrahedron Lett.* **1998**, *39*, 5289.
(106) Suzuki, T.; Suzuki, M.; Kurosawa, E. *Tetrahedron Lett.* **1975**, *16*, 3057.
(107) Wright, A. D.; König, G. M.; de Nys, R.; Sticher, O. *J. Nat. Prod.* **1993**, *56*, 394.
(108) Coll, J. C.; Wright, A. D. *Aust. J. Chem.* **1989**, *42*, 1685. It should be noted that the structure for 2′-hydroxy-α-isobromocuparene (compound **14** in this literature) was incorrectly drawn. The methyl group at $C_{5'}$ should be replaced at $C_{1'}$.
(109) Kladi, M.; Vagias, C.; Furnari, G.; Moreau, D.; Roussakis, C.; Roussis, V. *Tetrahedron Lett.* **2005**, *46*, 5723.
(110) Mao, S.; Guo, Y. *J. Nat. Prod.* **2006**, *69*, 1209.
(111) Kazlauskas, R.; Murphy, P. T.; Wells, R. J.; Daly, J. J.; Oberhänsli, W. E. *Aust. J. Chem.* **1977**, *30*, 2679.
(112) Rose, A. F.; Sims, J. J.; Wing, R. M.; Wiger, G. M. *Tetrahedron Lett.* **1978**, *19*, 2533.
(113) Howard, B. M.; Fenical, W. *J. Org. Chem.* **1977**, *42*, 2518.
(114) Rose, A. F.; Sims, J. J. *Tetrahedron Lett.* **1977**, *18*, 2935.
(115) Brennan, M. R.; Erickson, K. L. *J. Org. Chem.* **1982**, *47*, 3917.
(116) Suzuki, M.; Takahashi, Y.; Mitome, Y.; Itoh, T.; Abe, T.; Masuda, M. *Phytochemistry* **2002**, *60*, 861.
(117) Guella, G.; Skropeta, D.; Mancini, I.; Pietra, F. *Z. Naturforsch.* **2002**, *57b*, 1147.
(118) Irie, T.; Fukuzawa, A.; Izawa, M.; Kurosawa, E. *Tetrahedron Lett.* **1969**, *10*, 1343.
(119) Rovirosa, J.; Astudillo, L.; Ramirez, M. E.; San-Martín, A. *Bol. Soc. Chil. Quim.* **1991**, *36*, 153; *Chem. Abstr.* **1991**, *115*, 252378.
(120) Kazlauskas, R.; Murphy, P. T.; Quinn, R. J.; Wells, R. J. *Aust. J. Chem.* **1976**, *29*, 2533.
(121) Suzuki, M.; Kurosawa, E. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3349.
(122) Suzuki, M.; Kurosawa, E. *Tetrahedron Lett.* **1976**, *17*, 4817.
(123) Izac, R. R.; Sims, J. J. *J. Am. Chem. Soc.* **1979**, *101*, 6136.
(124) König, G. M.; Wright, A. D. *J. Nat. Prod.* **1994**, *57*, 477.
(125) Irie, T.; Suzuki, M.; Kurosawa, E.; Masamune, T. *Tetrahedron* **1970**, *26*, 3271.
(126) Irie, T.; Suzuki, M.; Kurosawa, E.; Masamune, T. *Tetrahedron Lett.* **1966**, *7*, 1837.
(127) Gonzalez, A. G.; Arteaga, J. M.; Fernandez, J. J.; Martin, J. D.; Norte, M.; Ruano, J. Z. *Tetrahedron* **1984**, *40*, 2751.
(128) Blunt, J. W.; Lake, R. J.; Munro, M. H. G. *Phytochemistry* **1984**, *23*, 1951.
(129) Ji, N. Y.; Li, X. M.; Li, K.; Ding, L. P.; Wang, B. G. *Nat. Prod. Res.* **2008**, *22*, 715.
(130) Suzuki, M.; Kurosawa, E. *Tetrahedron Lett.* **1978**, *19*, 2503.
(131) Suzuki, M.; Kurosawa, E. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3352.
(132) Mao, S.; Guo, Y. *Helv. Chim. Acta* **2005**, *88*, 1034.
(133) Sun, J.; Han, L. J.; Shi, D. Y.; Fan, X.; Wang, S. J.; Li, S.; Yang, Y. C.; Shi, J. G. *Chin. Chem. Lett.* **2005**, *16*, 1611.
(134) Dias, D. A.; White, J. M.; Urban, S. *Nat. Prod. Commun.* **2009**, *4*, 157.
(135) Sun, J.; Shi, D. Y.; Ma, M.; Li, S. A.; Wang, S. J.; Han, L. J.; Yang, Y. C.; Fan, X.; Shi, J. G.; He, L. *J. Nat. Prod.* **2005**, *68*, 915.
(136) Izac, R. R.; Drage, J. S.; Sims, J. J. *Tetrahedron Lett.* **1981**, *22*, 1799.
(137) Kladi, M.; Vagias, C.; Papazafiri, P.; Furnari, G.; Serio, D.; Roussis, V. *Tetrahedron* **2007**, *63*, 7606.
(138) Su, S.; Sun, W. S.; Wang, B.; Cheng, W.; Liang, H.; Zhao, Y. Y.; Zhang, Q. Y.; Wu, J. *J. Asian Nat. Prod. Res.* **2010**, *12*, 916.
(139) Cameron, A. F.; Ferguson, G.; Robertson, J. M. *Chem. Commun.* **1967**, *6*, 271.
(140) Kladi, M.; Xenaki, H.; Vagias, C.; Papazafiri, P.; Roussis, V. *Tetrahedron* **2006**, *62*, 182.
(141) Howard, B. M.; Fenical, W. *Tetrahedron Lett.* **1976**, *17*, 41.
(142) Topcu, G.; Aydogmus, Z.; Imre, S.; Gören, A. C.; Pezzuto, J. M.; Clement, J. A.; Kingston, D. G. I. *J. Nat. Prod.* **2003**, *66*, 1505.
(143) Paul, V. J.; Fenical, W. *Tetrahedron Lett.* **1980**, *21*, 2787.
(144) Norte, M.; González, R.; Padilla, A.; Fernández, J. J.; Vázquez, J. T. *Can. J. Chem.* **1991**, *69*, 518.
(145) Kuniyoshi, M.; Marma, M. S.; Higa, T.; Bernardinelli, G.; Jefford, C. W. *J. Nat. Prod.* **2001**, *64*, 696.
(146) Su, H.; Shi, D. Y.; Li, J.; Guo, S. J.; Li, L. L.; Yuan, Z. H.; Zhu, X. B. *Molecules* **2009**, *14*, 1889.
(147) Su, H.; Yuan, Z. H.; Li, J.; Guo, S. J.; Deng, L. P.; Han, L. J.; Zhu, X. B.; Shi, D. Y. *Helv. Chim. Acta* **2009**, *92*, 1291.
(148) Makhanu, D. S.; Yokoyama, M.; Miono, T.; Maesato, T.; Maedomari, M.; Wisespongpand, P.; Kuniyoshi, M. *Bull. Fac. Sci., Univ. Ryukyus* **2006**, *81*, 115.
(149) Kuniyoshi, M.; Wahome, P. G.; Miono, T.; Hashimoto, T.; Yokoyama, M.; Shrestha, K. L.; Higa, T. *J. Nat. Prod.* **2005**, *68*, 1314.
(150) Faulkner, D. J. *Phytochemistry* **1976**, *15*, 1993.
(151) Pettit, G. R.; Herald, C. L.; Allen, M. S.; Von Dreele, R. B.; Vanelle, L. D.; Kao, J. P. Y.; Blake, W. *J. Am. Chem. Soc.* **1977**, *99*, 262.
(152) Capon, R.; Ghisalberti, E. L.; Jefferies, P. R.; Skelton, B. W.; White, A. H. *Tetrahedron* **1981**, *37*, 1613.
(153) de Nys, R.; Wright, A. D.; König, G. M.; Sticher, O. *J. Nat. Prod.* **1993**, *56*, 877.
(154) König, G. M.; Wright, A. D. *J. Nat. Prod.* **1994**, *57*, 151.
(155) Suzuki, T.; Furusaki, A.; Hashiba, N.; Kurosawa, E. *Tetrahedron Lett.* **1977**, *18*, 3731.
(156) Suzuki, T.; Kurosawa, E. *Chem. Lett.* **1979**, *8*, 301.
(157) Kurata, K.; Suzuki, T.; Suzuki, M.; Kurosawa, E.; Furusaki, A.; Matsumoto, T. *Chem. Lett.* **1983**, *12*, 557.
(158) Brito, I.; Cueto, M.; Dorta, E.; Darias, J. *Tetrahedron Lett.* **2002**, *43*, 2551.
(159) Guella, G.; Skropeta, D.; Breuils, S.; Mancini, I.; Pietra, F. *Tetrahedron Lett.* **2001**, *42*, 723.
(160) Hall, S. S.; Faulkner, D. J.; Fayos, J.; Clardy, J. *J. Am. Chem. Soc.* **1973**, *95*, 7187.
(161) Wratten, S. J.; Faulkner, D. J. *J. Org. Chem.* **1977**, *42*, 3343.
(162) González, A. G.; Aguiar, J. M.; Martín, J. D.; Norte, M. *Tetrahedron Lett.* **1975**, *16*, 2499.
(163) Iliopoulou, D.; Roussis, V.; Pannecouque, C.; de Clercq, E.; Vagias, C. *Tetrahedron* **2002**, *58*, 6749.
(164) Coll, J. C.; Skelton, B. W.; White, A. H.; Wright, A. D. *Aust. J. Chem.* **1989**, *42*, 1695.
(165) Wright, A. D.; König, G. M.; Sticher, O.; Rüegger, H. *Phytochem. Anal.* **1992**, *3*, 263.
(166) González, A. G.; Aguiar, J. M.; Darias, J.; González, E.; Martín, J. D.; Martín, V. S.; Pérez, C.; Fayos, J.; Martínez-Ripoll, M. *Tetrahedron Lett.* **1978**, *19*, 3931.
(167) González, A. G.; Aguiar, J. M.; Martín, J. D.; Rodríguez, M. L. *Tetrahedron Lett.* **1976**, *17*, 205.
(168) González, A. G.; Martín, J. D.; Martín, V. S.; Pérez, R.; Tagle, B.; Clardy, J. *J. Chem. Soc., Chem. Commun.* **1985**, *5*, 260.
(169) Díaz-Marrero, A. R.; Brito, I.; de la Rosa, J. M.; Darias, J.; Cueto, M. *Tetrahedron* **2008**, *64*, 10821.
(170) Gonzalez, A. G.; Martin, J. D.; Martin, V. S.; Perez, R.; Drexler, S. A.; Clardy, J. *Chem. Lett.* **1984**, *13*, 1865.
(171) Kurata, K.; Suzuki, T.; Suzuki, M.; Kurosawa, E.; Furusaki, A.; Matsumoto, T. *Chem. Lett.* **1983**, *12*, 299.
(172) Suzuki, M.; Kurosawa, E.; Irie, T. *Tetrahedron Lett.* **1970**, *11*, 4995.
(173) Suzuki, M.; Kowata, N.; Kurosawa, E. *Tetrahedron* **1980**, *36*, 1551.
(174) Selover, S. J.; Crews, P. *J. Org. Chem.* **1980**, *45*, 69.
(175) Atta-ur-Rahman. *Pure Appl. Chem.* **1989**, *61*, 453.

(176) Liang, Y.; Li, X. M.; Cui, C. M.; Li, C. S.; Wang, B. G. *Chin. Chem. Lett.* **2009**, *20*, 190.
(177) Ji, N. Y.; Li, X. M.; Li, K.; Gloer, J. B.; Wang, B. G. *Biochem. Syst. Ecol.* **2008**, *36*, 938.
(178) Suzuki, M.; Daitoh, M.; Vairappan, C. S.; Abe, T.; Masuda, M. *J. Nat. Prod.* **2001**, *64*, 597.
(179) González, A. G.; Martín, J. D.; Norte, M.; Pérez, R.; Rivera, P.; Ruano, J. Z.; Rodríguez, M. L.; Fayos, J.; Perales, A. *Tetrahedron Lett.* **1983**, *24*, 4143.
(180) Erickson, K. L.; Beutler, J. A.; Gray, G. N.; Cardellina, J. H. I.; Boyd, M. R. *J. Nat. Prod.* **1995**, *58*, 1848.
(181) Vairappan, C. S.; Suzuki, M.; Ishii, T.; Okino, T.; Abe, T.; Masuda, M. *Phytochemistry* **2008**, *69*, 2490.
(182) de Nys, R.; Coll, J. C.; Bowden, B. F. *Aust. J. Chem.* **1992**, *45*, 1611.
(183) Xu, X.; Zeng, L.; Su, J. *Chem. Res. Chin. Univ.* **1997**, *13*, 176.
(184) de Nys, R.; Coll, J. C.; Bowden, B. F. *Aust. J. Chem.* **1993**, *46*, 933.
(185) Li, C. S.; Li, X. M.; Cui, C. M.; Wang, B. G. *Z. Naturforsch.* **2010**, *65b*, 87.
(186) Imre, S.; Islimyeli, S.; Öztunc, A.; Thomson, R. H. *Phytochemistry* **1981**, *20*, 833.
(187) González, A. G.; Darias, J.; Martín, J. D. *Tetrahedron Lett.* **1973**, *14*, 3625.
(188) Estrada, D. M.; Martín, J. D.; Pérez, R.; Rivera, P.; Rodríguez, M. L.; Ruano, J. Z. *Tetrahedron Lett.* **1987**, *28*, 687.
(189) Fenical, W.; Howard, B.; Gifkins, K. B.; Clardy, J. *Tetrahedron Lett.* **1975**, *16*, 3983. It should be noted that the stereochemistry of the C_7 hydroxyl in iriediol (**277**) is corrected as drawn in Figure 23. The structure was incorrectly drawn as transposed from the X-ray photograph in the original communication and was corrected in a later report by the same group.[190]
(190) Howard, B. M.; Fenical, W. *J. Org. Chem.* **1978**, *43*, 4401.
(191) Fukuzawa, A.; Kumagai, Y.; Masamune, T.; Furusaki, A.; Matsumoto, T.; Katayama, C. *Chem. Lett.* **1982**, *11*, 1389.
(192) Ji, N. Y.; Li, X. M.; Cui, C. M.; Wang, B. G. *Helv. Chim. Acta* **2007**, *90*, 1731.
(193) Ji, N. Y.; Li, X. M.; Cui, C. M.; Wang, B. G. *Chin. Chem. Lett.* **2007**, *18*, 957.
(194) Vairappan, C. S.; Ishii, T.; Lee, T. K.; Suzuki, M.; Zhan, Z. Q. *Mar. Drugs* **2010**, *8*, 1743.
(195) Sims, J. J.; Lin, G. H. Y.; Wing, R. M.; Fenical, W. *J. Chem. Soc., Chem. Commun.* **1973**, *14*, 470. The structure for concinndiol in this literature appeared incorrectly drawn. A double bond should be present in position C_{14}.
(196) Yamamura, S.; Hirata, Y. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 2560.
(197) Howard, B. M.; Fenical, W. *Phytochemistry* **1980**, *19*, 2774.
(198) Fujiwara, S.; Takeda, K.; Uyehara, T.; Kato, T. *Chem. Lett.* **1986**, *15*, 1763.
(199) Rodríguez, M. L.; Martín, J. D.; Estrada, D. *Acta Crystallogr.* **1989**, *45c*, 306.
(200) Fukuzawa, A.; Miyamoto, M.; Kumagai, Y.; Abiko, A.; Takaya, Y.; Masamune, T. *Chem. Lett.* **1985**, *14*, 1259.
(201) Suzuki, M.; Kurosawa, E.; Kurata, K. *Phytochemistry* **1988**, *27*, 1209.
(202) Öztunç, A.; Imre, S.; Lotter, H.; Wagner, H. *Phytochemistry* **1989**, *28*, 3403.
(203) Suzuki, M.; Kawamoto, T.; Vairappan, C. S.; Ishii, T.; Abe, T.; Masuda, M. *Phytochemistry* **2005**, *66*, 2787.
(204) Briand, A.; Kornprobst, J. M.; Aleasa, H. S.; Rizk, A. F. M.; Toupet, L. *Tetrahedron Lett.* **1997**, *38*, 3399.
(205) Iliopoulou, D.; Mihopoulos, N.; Roussis, V.; Vagias, C. *J. Nat. Prod.* **2003**, *66*, 1225.
(206) Schmitz, F. J.; Gopichand, Y.; Michaud, D. P.; Prasad, R. S.; Remaley, S.; Hossain, M. B.; Rahman, A.; Sengupta, P. K.; van der Helm, D. *Pure Appl. Chem.* **1981**, *51*, 853.
(207) Schmitz, F. J.; Michhaud, D. P.; Schmidt, P. G. *J. Am. Chem. Soc.* **1982**, *104*, 6415.
(208) Higgs, M. D.; Faulkner, D. J. *Phytochemistry* **1982**, *21*, 789.
(209) Suzuki, T.; Takeda, S.; Hayama, N.; Tanaka, I.; Komiyama, K. *Chem. Lett.* **1989**, *18*, 969.
(210) Takeda, S.; Kurosawa, E.; Komiyama, K.; Suzuki, T. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3066.
(211) Rochfort, S. J.; Capon, R. J. *Aust. J. Chem.* **1996**, *49*, 19.
(212) Lyakhova, E. G.; Kalinovsky, A. I.; Kolesnikova, S. A.; Vaskovsky, V. E.; Stonik, V. A. *Phytochemistry* **2004**, *65*, 2527.
(213) Takeda, S.; Matsumoto, T.; Komiyama, K.; Kurosawa, E.; Suzuki, T. *Chem. Lett.* **1990**, *19*, 277.
(214) González, A. G.; Ciccio, J. F.; Rivera, A. P.; Martín, J. D. *J. Org. Chem.* **1985**, *50*, 1261.
(215) Estrada, D. M.; Ravelo, J. L.; Ruiz-Pérez, C.; Martín, J. D.; Solans, X. *Tetrahedron Lett.* **1989**, *30*, 6219.
(216) Guella, G.; Pietra, F. *Helv. Chim. Acta* **2000**, *83*, 2946.
(217) Caccamese, S.; Toscano, R. M.; Cerrini, S.; Gavuzzo, E. *Tetrahedron Lett.* **1982**, *23*, 3415.
(218) Howard, B. M.; Fenical, W. *Tetrahedron Lett.* **1978**, *19*, 2453.
(219) Guella, G.; Pietra, F. *Chem.—Eur. J.* **1998**, *4*, 1692.
(220) Mihopoulos, N.; Vagias, C.; Mikros, E.; Scoullos, M.; Roussis, V. *Tetrahedron Lett.* **2001**, *42*, 3749.
(221) Iliopoulou, D.; Mihopoulos, N.; Vagias, C.; Papazafiri, P.; Roussis, V. *J. Org. Chem.* **2003**, *68*, 7667.
(222) Takahashi, Y.; Suzuki, M.; Abe, T.; Masuda, M. *Phytochemistry* **1998**, *48*, 987.
(223) Fukuzawa, A.; Takaya, Y.; Matsue, H.; Masamune, T. *Chem. Lett.* **1985**, *14*, 1263.
(224) Howard, B. M.; Fenical, W.; Donovan, S. F.; Clardy, J. *Tetrahedron Lett.* **1982**, *23*, 3847.
(225) Takahashi, Y.; Daitoh, M.; Suzuki, M.; Abe, T.; Masuda, M. *J. Nat. Prod.* **2002**, *65*, 395.
(226) Takahashi, H.; Takahashi, Y.; Suzuki, M.; Abe, T.; Masuda, M. *Acta Crystallogr.* **2010**, *66e*, o1795.
(227) Kuniyoshi, M.; Marma, M. S.; Higa, T.; Bernardinelli, G.; Jefford, C. W. *Chem. Commun.* **2000**, *13*, 1155.
(228) Brennan, M. R.; Kim, I. K.; Erickson, K. L. *J. Nat. Prod.* **1993**, *56*, 76.
(229) Chatter, R.; Kladi, M.; Tarhouni, S.; Maatoug, R.; Kharrat, R.; Vagias, C.; Roussis, V. *Phytochem. Lett* **2009**, *2*, 25.
(230) Fernández, J. J.; Souto, M. L.; Norte, M. *Nat. Prod. Rep.* **2000**, *17*, 235.
(231) Blunt, J. W.; Hartshorn, M. P.; McLennan, T. J.; Munro, M. H. G.; Robinson, W. T.; Yorke, S. C. *Tetrahedron Lett.* **1978**, *19*, 69.
(232) Blunt, J. W.; McCombs, J. D.; Munro, M. H. G.; Thomas, F. N. *Magn. Reson. Chem.* **1989**, *27*, 792.
(233) Sakemi, S.; Higa, T.; Jefford, C. W.; Bernardinelli, G. *Tetrahedron Lett.* **1986**, *27*, 4287.
(234) Suzuki, T.; Suzuki, M.; Furusaki, A.; Matsumoto, T.; Kato, A.; Imanaka, Y.; Kurosawa, E. *Tetrahedron Lett.* **1985**, *26*, 1329.
(235) Suzuki, T.; Takeda, S.; Suzuki, M.; Kurosawa, E.; Kato, A.; Imanaka, Y. *Chem. Lett.* **1987**, *16*, 361.
(236) Suzuki, M.; Matsuo, Y.; Takahashi, Y.; Masuda, M. *Chem. Lett.* **1995**, *24*, 1045.
(237) Gil-Rodríguez, M. C.; Haroun, R. *Bot. Mar.* **1992**, *35*, 227.
(238) Norte, M.; Fernández, J. J.; Souto, M. L. *Tetrahedron* **1997**, *53*, 4649.
(239) Cen-Pacheco, F.; Villa-Pulgarin, J. A.; Mollinedo, F.; Martín, M. N.; Fernández, J. J.; Daranas, A. H. *Mar. Drugs* **2011**, *9*, 2220.
(240) Manríquez, C. P.; Souto, M. L.; Gavín, J. A.; Norte, M.; Fernández, J. J. *Tetrahedron* **2001**, *57*, 3117.
(241) Norte, M.; Fernández, J. J.; Souto, M. L.; García-Grávalos, M. D. *Tetrahedron Lett.* **1996**, *37*, 2671.
(242) Souto, M. L.; Manríquez, C. P.; Norte, M.; Fernández, J. J. *Tetrahedron* **2002**, *58*, 8119.
(243) Ji, N. Y.; Li, X. M.; Xie, H.; Ding, J.; Li, K.; Ding, L. P.; Wang, B. G. *Helv. Chim. Acta* **2008**, *91*, 1940.
(244) Manzo, E.; Gavagnin, M.; Bifulco, G.; Cimino, P.; di Micco, S.; Ciavatta, M. L.; Guo, Y. W.; Cimino, G. *Tetrahedron* **2007**, *63*, 9970.
(245) Ola, A. R. B.; Babey, A. M.; Motti, C.; Bowden, B. F. *Aust. J. Chem.* **2010**, *63*, 907.

(246) Cen-Pacheco, F.; Villa-Pulgarin, J. A.; Mollinedo, F.; Norte, M.; Daranas, A. H.; Fernández, J. J. *Eur. J. Med. Chem.* **2011**, *46*, 3302.
(247) Cen-Pacheco, F.; Nordström, L.; Souto, M. L.; Martín, M. N.; Fernández, J. J.; Daranas, A. H. *Mar. Drugs* **2010**, *8*, 1178.
(248) Norte, M.; Fernández, J. J.; Souto, M. L.; Gavin, J. A.; García-Grávalos, M. D. *Tetrahedron* **1997**, *53*, 3173.
(249) Ciavatta, M. L.; Wahidulla, S.; D'Souza, L.; Scognamiglio, G.; Cimino, G. *Tetrahedron* **2001**, *57*, 617.
(250) Matsuo, Y.; Suzuki, M.; Masuda, M. *Chem. Lett.* **1995**, *24*, 1043.
(251) Morimoto, Y.; Yata, H.; Nishikawa, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 6481.
(252) Suenaga, K.; Shibata, T.; Takada, N.; Kigoshi, H.; Yamada, K. *J. Nat. Prod.* **1998**, *61*, 515.
(253) Morimoto, Y.; Nishikawa, Y.; Takaishi, M. *J. Am. Chem. Soc.* **2005**, *127*, 5806.
(254) Suzuki, M.; Matsuo, Y.; Takeda, S.; Suzuki, T. *Phytochemistry* **1993**, *33*, 651.
(255) Irie, T.; Suzuki, M.; Masamune, T. *Tetrahedron Lett.* **1965**, *6*, 1091.
(256) González, A. G.; Martín, J. D.; Martín, V. S.; Norte, M.; Pérez, R.; Ruano, J. Z.; Drexler, S. A.; Clardy, J. *Tetrahedron* **1982**, *38*, 1009.
(257) Norte, M.; González, A. G.; Cataldo, F.; Rodríguez, M. L.; Brito, I. *Tetrahedron* **1991**, *47*, 9411.
(258) Kladi, M.; Vagias, C.; Papazafiri, P.; Brogi, S.; Tafi, A.; Roussis, V. *J. Nat. Prod.* **2009**, *72*, 190.
(259) Gutiérrez-Cepeda, A.; Fernández, J. J.; Gil, L. V.; López-Rodríguez, M.; Norte, M.; Souto, M. L. *J. Nat. Prod.* **2011**, *74*, 441.
(260) Fukuzawa, A.; Kurosawa, E.; Tobetsu, I. *Tetrahedron Lett.* **1980**, *21*, 1471.
(261) Fukuzawa, A.; Aye, M.; Takaya, Y.; Fukui, T. M.; Murai, A.; Masamune, T. *Tetrahedron Lett.* **1989**, *30*, 3665.
(262) Suzuki, T.; Koizumi, K.; Suzuki, M.; Kurosawa, E. *Chem. Lett.* **1983**, *12*, 1643.
(263) Norte, M.; Fernández, J. J.; Ruano, J. Z.; Rodríguez, M. L.; Pérez, R. *Phytochemistry* **1988**, *27*, 3537. It should be noted that the OR^3 group in compounds **1**−**5** presented in this literature should be replaced by R^3.
(264) Suzuki, M.; Nakano, S.; Takahashi, Y.; Abe, T.; Masuda, M. *Phytochemistry* **1999**, *51*, 657.
(265) Kim, K.; Brennan, M. R.; Erickson, K. L. *Tetrahedron Lett.* **1989**, *30*, 1757.
(266) Kikuchi, H.; Suzuki, T.; Kurosawa, E.; Suzuki, M. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1763.
(267) Hall, J. G.; Reiss, J. A. *Aust. J. Chem.* **1986**, *39*, 1401.
(268) Sheldrake, H. M.; Jamieson, C.; Burton, J. W. *Angew. Chem., Int. Ed.* **2006**, *45*, 7199.
(269) Ji, N. Y.; Li, X. M.; Li, K.; Wang, B. G. *J. Nat. Prod.* **2007**, *70*, 1499.
(270) Ji, N. Y.; Li, X. M.; Li, K.; Wang, B. G. *J. Nat. Prod.* **2010**, *73*, 1192.
(271) Norte, M.; Fernández, J. J.; Runao, J. Z. *Tetrahedron* **1989**, *45*, 5987.
(272) Imre, S.; Aydogmus, Z.; Güner, H.; Lotter, H.; Wagner, H. *Z. Naturforsch.* **1995**, *50c*, 743.
(273) Howard, B. M.; Fenical, W.; Arnold, E. V.; Clardy, J. *Tetrahedron Lett.* **1979**, *20*, 2841.
(274) Caccamese, S.; Toscano, R. M. *Gazz. Chim. Ital.* **1986**, *116*, 177.
(275) Suzuki, M.; Kurosawa, E. *Tetrahedron Lett.* **1981**, *22*, 3853.
(276) Suzuki, M.; Sasage, Y.; Ikura, M.; Hikichi, K.; Kurosawa, E. *Phytochemistry* **1989**, *28*, 2145.
(277) Suzuki, M.; Kondo, H.; Tanaka, I. *Chem. Lett.* **1991**, *20*, 33.
(278) Suzuki, M.; Kurosawa, E. *Chem. Lett.* **1982**, *11*, 289.
(279) Suzuki, T.; Koizumi, K.; Suzuki, M.; Kurosawa, E. *Chem. Lett.* **1983**, *12*, 1639.
(280) Suzuki, M.; Kurosawa, E. *Phytochemistry* **1985**, *24*, 1999.
(281) Suzuki, M.; Matsuo, Y.; Masuda, M. *Tetrahedron* **1993**, *49*, 2033.
(282) Liu, X.; Li, X. M.; Li, C. S.; Ji, N. Y.; Wang, B. G. *Chin. Chem. Lett.* **2010**, *21*, 1213.
(283) Suzuki, M.; Takahashi, Y.; Matsuo, Y.; Guiry, M. D.; Masuda, M. *Tetrahedron* **1997**, *53*, 4271.
(284) Takahashi, Y.; Suzuki, M.; Abe, T.; Masuda, M. *Phytochemistry* **1999**, *50*, 799.
(285) Lyakhova, E. G.; Kalinovsky, A. I.; Dmitrenok, A. S.; Kolesnikova, S. A.; Fedorov, S. N.; Vaskovsky, V. E.; Stonik, V. A. *Tetrahedron Lett.* **2006**, *47*, 6549.
(286) Guella, G.; Mancini, I.; Chiasera, G.; Pietra, F. *Helv. Chim. Acta* **1992**, *75*, 310.
(287) Fukuzawa, A.; Masamune, T. *Tetrahedron Lett.* **1981**, *22*, 4081.
(288) Kurosawa, E.; Fukuzawa, A.; Irie, T. *Tetrahedron Lett.* **1973**, *14*, 4135.
(289) Suzuki, M.; Kurata, K.; Suzuki, T.; Kurosawa, E. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2953.
(290) Suzuki, M.; Mizuno, Y.; Matsuo, Y.; Masuda, M. *Phytochemistry* **1996**, *43*, 121.
(291) Irie, T.; Suzuki, M.; Masamune, T. *Tetrahedron* **1968**, *24*, 4193.
(292) Cameron, A. F.; Cheung, K. K.; Ferguson, G.; Robertson, J. M. *Chem. Commun.* **1965**, *24*, 638.
(293) Cameron, A. F.; Cheung, K. K.; Ferguson, G.; Monteath Robertson, J. *J. Chem. Soc. B* **1969**, *12*, 559.
(294) White, R. H.; Hager, L. P. *Phytochemistry* **1978**, *17*, 939.
(295) Blunt, J. W.; Lake, R. J.; Munro, M. H. G. *Aust. J. Chem.* **1984**, *37*, 1545.
(296) Blunt, J. W.; Lake, R. J.; Munro, M. H. G.; Yorke, S. C. *Aust. J. Chem.* **1981**, *34*, 2393.
(297) Kladi, M.; Vagias, C.; Stavri, M.; Rahman, M. M.; Gibbons, S.; Roussis, V. *Phytochemistry Lett.* **2008**, *1*, 31.
(298) Cardellina, J. H.; Horsley, S. B.; Clardy, J.; Leftow, S. R.; Meinwald, J. *Can. J. Chem.* **1982**, *60*, 2675.
(299) Howard, B. M.; Schulte, G. R.; Fenical, W.; Solheim, B.; Clardy, J. *Tetrahedron* **1980**, *36*, 1747.
(300) Fukuzawa, A.; Kurosawa, E.; Irie, T. *Tetrahedron Lett.* **1972**, *13*, 3.
(301) Furusaki, A.; Kurosawa, E.; Fukuzawa, A.; Irie, T. *Tetrahedron Lett.* **1973**, *14*, 4579.
(302) Abdel-Mageed, W. M.; Ebel, R.; Valeriote, F. A.; Jaspars, M. *Tetrahedron* **2010**, *66*, 2855.
(303) Fukuzawa, A.; Aye, M.; Nakamura, M.; Tamura, M.; Murai, A. *Tetrahedron Lett.* **1990**, *31*, 4895.
(304) Fenical, W.; Sims, J. J.; Radlick, P. *Tetrahedron Lett.* **1973**, *14*, 313.
(305) Fenical, W.; Gifkins, K. B.; Clardy, J. *Tetrahedron Lett.* **1974**, *15*, 1507.
(306) Howard, B. M.; Fenical, W.; Hirotsu, K.; Solheim, B.; Clardy, J. *Tetrahedron* **1980**, *36*, 171.
(307) Fenical, W. *J. Am. Chem. Soc.* **1974**, *96*, 5580.
(308) Irie, T.; Izawa, M.; Kurosawa, E. *Tetrahedron Lett.* **1968**, *9*, 2091.
(309) Irie, T.; Izawa, M.; Kurosawa, E. *Tetrahedron* **1970**, *26*, 851.
(310) Kurosawa, E.; Furusaki, A.; Izawa, M.; Fukuzawa, A.; Irie, T. *Tetrahedron Lett.* **1973**, *14*, 3857.
(311) Irie, T.; Izawa, M.; Kurosawa, E. *Tetrahedron Lett.* **1968**, *9*, 2735.
(312) Suzuki, M.; Kurosawa, E. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3791.
(313) Fukuzawa, A.; Takasugi, Y.; Murai, A. *Tetrahedron Lett.* **1991**, *32*, 5597.
(314) Caccamese, S.; Azzolina, R.; Duesler, E. N.; Paul, I. C.; Rinehart, K. L. *Tetrahedron Lett.* **1980**, *21*, 2299.
(315) Falshaw, C. P.; King, T. J.; Imre, S.; Islimyeli, S.; Thomson, R. H. *Tetrahedron Lett.* **1980**, *21*, 4951.
(316) Imre, S.; Lotter, H.; Wagner, H.; Thomson, R. H. *Z. Naturforsch.* **1987**, *42c*, 507.
(317) Mihopoulos, N.; Vagias, C.; Scoullos, M.; Roussis, V. *Nat. Prod. Lett.* **1999**, *13*, 151; *Chem. Abstr.* **1999**, *131*, 85528.
(318) Iliopoulou, D.; Vagias, C.; Harvala, C.; Roussis, V. *Phytochemistry* **2002**, *59*, 111.

(319) Aydogmus, Z.; Imre, S. *Acta Pharm. Turc.* **1999**, *41*, 93; *Chem. Abstr.* **1999**, *132*, 178047.
(320) Norte, M.; Fernandez, J. J.; Cataldo, F.; Gonzalez, A. G. *Phytochemistry* **1989**, *28*, 647.
(321) Suzuki, M.; Kurosawa, E. *Chem. Lett.* **1980**, *9*, 1177.
(322) Suzuki, M.; Kurosawa, E.; Furusaki, A.; Matsumoto, T. *Chem. Lett.* **1983**, *12*, 779.
(323) San-Martín, A.; Darias, J.; Soto, H.; Contreras, C.; Herrera, J. S.; Rovirosa, J. *Nat. Prod. Lett.* **1997**, *10*, 303; *Chem. Abstr.* **1997**, *128*, 1763.
(324) Fukuzawa, A.; Kurosawa, E. *Tetrahedron Lett.* **1979**, *20*, 2797.
(325) Suzuki, M.; Koizumi, K.; Kikuchi, H.; Suzuki, T.; Kurosawa, E. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 715.
(326) González, A. G.; Martín, J. D.; Norte, M.; Rivera, P.; Ruano, J. Z. *Tetrahedron* **1984**, *40*, 3443.
(327) Wright, A. D.; König, G. M.; Sticher, O. *J. Nat. Prod.* **1991**, *54*, 1025.
(328) Suzuki, M.; Takahashi, Y.; Matsuo, Y.; Masuda, M. *Phytochemistry* **1996**, *41*, 1101.
(329) Kennedy, D. J.; Selby, I. A.; Cowe, H. J.; Cox, P. J.; Thomson, R. H. *J. Chem. Soc., Chem. Commun.* **1984**, *3*, 153.
(330) Gutiérrez-Cepeda, A.; Fernández, J. J.; Norte, M.; Souto, M. L. *Org. Lett.* **2011**, *13*, 2690.
(331) King, T. J.; Imre, S.; Öztunç, A.; Thomson, R. H. *Tetrahedron Lett.* **1979**, *20*, 1453.
(332) Awakura, D.; Fujiwara, K.; Murai, A. *Chem. Lett.* **1999**, *28*, 461.
(333) Kurata, K.; Furusaki, A.; Suehiro, K.; Katayama, C.; Suzuki, T. *Chem. Lett.* **1982**, *11*, 1031.
(334) Furusaki, A.; Katsuragi, S.-I.; Suehiro, K.; Matsumoto, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 803.
(335) Suzuki, M.; Kurosawa, E.; Furusaki, A.; Katsuragi, S. I.; Matsumoto, T. *Chem. Lett.* **1984**, *13*, 1033.
(336) Jeong, W.; Kim, M. J.; Kim, H.; Kim, S.; Kim, D.; Shin, K. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 752.
(337) Cox, P. J.; Imre, S.; Islimyeli, S.; Thomson, R. H. *Tetrahedron Lett.* **1982**, *23*, 579.
(338) Öztunç, A.; Imre, S.; Wagner, H.; Norte, M.; Fernández, J. J.; González, R. *Tetrahedron* **1991**, *47*, 2273.
(339) Öztunç, A.; Imre, S.; Lotter, H.; Wagner, H. *Phytochemistry* **1991**, *30*, 255.
(340) Guella, G.; Chiasera, G.; Mancini, I.; Öztunç, A.; Pietra, F. *Chem.—Eur. J.* **1997**, *3*, 1223.
(341) Guella, G.; Mancini, I.; Öztunç, A.; Pietra, F. *Helv. Chim. Acta* **2000**, *83*, 336.
(342) Braddock, D. C.; Rzepa, H. S. *J. Nat. Prod.* **2008**, *71*, 728.
(343) Öztunç, A.; Imre, S.; Wagner, H.; Norte, M.; Fernández, J. J.; González, R. *Tetrahedron Lett.* **1991**, *32*, 4377.
(344) Waraszkiewicz, S. M.; Sun, H. H.; Erickson, K. L. *Tetrahedron Lett.* **1976**, *17*, 3021.
(345) Waraszkiewicz, S. M.; Sun, H. H.; Erickson, K. L.; Finer, J.; Clardy, J. *J. Org. Chem.* **1978**, *43*, 3194.
(346) Sun, H. H.; Waraszkiewicz, S. M.; Erickson, K. L. *Tetrahedron Lett.* **1976**, *17*, 4227.
(347) Abou-Elnaga, Z. S.; Alarif, W. M.; Al-Lihaibi, S. S. *Clean: Soil, Air, Water* **2011**, *39*, 787.
(348) Ayyad, S. E. N.; Al-Footy, K. O.; Alarif, W. M.; Sobahi, T. R.; Bassaif, S. A.; Makki, M. S.; Asiri, A. M.; Al Halawani, A. Y.; Badria, A. F.; Badria, F. A. A. *Chem. Pharm. Bull.* **2011**, *59*, 1294.
(349) Vairappan, C. S.; Daitoh, M.; Suzuki, M.; Abe, T.; Masuda, M. *Phytochemistry* **2001**, *58*, 291.
(350) Guella, G.; Pietra, F. *Helv. Chim. Acta* **1991**, *74*, 47.
(351) Guella, G.; Mancici, I.; Chiasera, G.; Pietra, F. *Helv. Chim. Acta* **1992**, *75*, 303.
(352) Tanaka, J.; Higa, T.; Bernardinelli, G.; Jefford, C. W. *Tetrahedron Lett.* **1988**, *29*, 6091.
(353) Tanaka, J.; Higa, T.; Benardinelli, G.; Jefford, C. W. *Tetrahedron* **1989**, *45*, 7301.
(354) Carter, G. T.; Rinehart, K. L.; Li, L. H.; Kuentzel, S.; Connor, J. L. *Tetrahedron Lett.* **1978**, *19*, 4479.
(355) Ji, N. Y.; Li, X. M.; Ding, L. P.; Wang, B. G. *Helv. Chim. Acta* **2007**, *90*, 385.
(356) El-Gamal, A. A.; Wang, W. L.; Duh, C. Y. *J. Nat. Prod.* **2005**, *68*, 815.
(357) Su, H.; Yuan, Z. H.; Li, J.; Guo, S. J.; Deng, L. P.; Han, L. J.; Zhu, X. B.; Shi, D. Y. *Chin. Chem. Lett.* **2009**, *20*, 456.
(358) Kubota, N. K.; Iwamoto, H.; Fukazawa, Y.; Uchio, Y. *Heterocycles* **2005**, *65*, 2675.
(359) Hodgkin, J. H.; Craigie, J. S.; McInnes, A. G. *Can. J. Chem.* **1966**, *44*, 74.
(360) Saito, T.; Ando, Y. *J. Chem. Soc. Jpn. (Nippon Kagaku Zasshi)* **1955**, *76*, 478.
(361) Katsui, N.; Suzuki, Y.; Kitamura, S.; Irie, T. *Tetrahedron* **1967**, *23*, 1185.
(362) Weinstein, B.; Rold, T. L.; Harrell, C. E., Jr.; Burns, M. W., III; Waaland, J. R. *Phytochemistry* **1975**, *14*, 2667.
(363) Fan, X.; Xu, N. J.; Shi, J. G. *J. Nat. Prod.* **2003**, *66*, 455.
(364) Fan, X.; Xu, N. J.; Shi, J. G. *Chin. Chem. Lett.* **2003**, *14*, 1045.
(365) Zhao, J. L.; Fan, X.; Wang, S. J.; Li, S. A.; Shang, S. Q.; Yang, Y. C.; Xu, N. J.; Lu, Y.; Shi, J. G. *J. Nat. Prod.* **2004**, *67*, 1032.
(366) Li, K.; Li, X. M.; Gloer, J. B.; Wang, B. G. *J. Agric. Food Chem.* **2011**, *59*, 9916.
(367) Zhao, J. L.; Ma, M.; Wang, S. J.; Li, S.; Cao, P.; Yang, Y. C.; Lu, Y.; Shi, J. G.; Xu, N. J.; Fan, X.; He, L. *J. Nat. Prod.* **2005**, *68*, 691.
(368) Ma, M.; Zhao, J. L.; Wang, S. J.; Li, S.; Yang, Y. C.; Shi, J. G.; Fan, X.; He, L . *J. Nat. Prod.* **2006**, *69*, 206.
(369) Ma, M.; Zhao, J.; Wang, S.; Li, S.; Yang, Y.; Shi, J.; Fan, X.; He, L. *J. Nat. Prod.* **2007**, *70*, 337.
(370) Kurata, K.; Amiya, T. *Chem. Lett.* **1980**, *9*, 279.
(371) Lim, C.; Lee, J.; Cho, Y. *Han'guk Susan Hakhoechi* **2000**, *33*, 280; *Chem. Abstr.* **2000**, *134*, 204943.
(372) Xu, X. L.; Song, F. H.; Fan, X.; Fang, N. Q.; Shi, J. G. *Chem. Nat. Compd.* **2009**, *45*, 811.
(373) Wang, W.; Okada, Y.; Shi, H. B.; Wang, Y. Q.; Okuyama, T. *J. Nat. Prod.* **2005**, *68*, 620.
(374) Choi, J. S.; Park, H. J.; Jung, H. A.; Chung, H. Y.; Jung, J. H.; Choi, W. C. *J. Nat. Prod.* **2000**, *63*, 1705.
(375) Chevolot-Magueur, A. M.; Cave, A.; Potier, P.; Teste, J.; Chiaroni, A.; Riche, C. *Phytochemistry* **1976**, *15*, 767.
(376) de Nanteuil, G.; Mastagli, P. *Phytochemistry* **1981**, *20*, 1750.
(377) Chantraine, J. M.; Combaut, G.; Teste, J. *Phytochemistry* **1973**, *12*, 1793.
(378) Glombitza, K. W.; Sukopp, I.; Wiedenfeld, H. *Planta Med.* **1985**, *51*, 437.
(379) Popplewell, W. L.; Northcote, P. T. *Tetrahedron Lett.* **2009**, *50*, 6814.
(380) Duan, X. J.; Li, X. M.; Wang, B. G. *J. Nat. Prod.* **2007**, *70*, 1210.
(381) Li, K.; Li, X. M.; Ji, N. Y.; Wang, B. G. *Bioorg. Med. Chem.* **2007**, *15*, 6627.
(382) Kurata, K.; Amiya, T. *Chem. Lett.* **1977**, *6*, 1435.
(383) Fan, X.; Xu, N. J.; Shi, J. G. *Chin. Chem. Lett.* **2003**, *14*, 939.
(384) Xu, N. J.; Fan, X.; Yan, X. J.; Li, X. C.; Niu, R. L.; Tseng, C. K. *Phytochemistry* **2003**, *62*, 1221.
(385) Qin, J.; Su, H.; Zhang, Y.; Gao, J.; Zhu, L.; Wu, X.; Pan, H.; Li, X. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7152.
(386) Wiemer, D. F.; Idler, D. D.; Fenical, W. *Experientia* **1991**, *47*, 851.
(387) Kurata, K.; Taniguchii, K.; Takashima, K.; Hayashi, I.; Suzuki, M. *Phytochemistry* **1997**, *45*, 485.
(388) Kurata, K.; Amiya, T.; Nakano, N. *Chem. Lett.* **1976**, *5*, 821.
(389) Kurihara, H.; Mitani, T.; Kawabata, J.; Takahashi, K. *J. Nat. Prod.* **1999**, *62*, 882.
(390) Kurata, K.; Amiya, T. *Phytochemistry* **1980**, *19*, 141.
(391) Li, K.; Li, X. M.; Ji, N. Y.; Wang, B. G. *J. Nat. Prod.* **2008**, *71*, 28.
(392) Aknin, M.; Samb, A.; Mirailles, J.; Costantino, V.; Fattorusso, E.; Mangoni, A. *Tetrahedron Lett.* **1992**, *33*, 555.
(393) Liu, Q.; Tan, C.; Zhang, T.; Zhang, S.; Han, L.; Fan, X.; Zhu, D. *J. Asian Nat. Prod. Res.* **2006**, *8*, 379.

(394) Liu, Q. W.; Qiao, Q. A.; Zhang, T.; Sun, L. X.; Wang, M. S. *J. Mol. Struct.* **2009**, *929*, 1.
(395) Combaut, G.; Chantraine, J. M.; Teste, J.; Glombitza, K. W. *Phytochemistry* **1978**, *17*, 1791.
(396) Combaut, G.; Chantraine, J. M.; Teste, J.; Soulier, J.; Glombitza, K. W. *Tetrahedron Lett.* **1978**, *19*, 1699.
(397) Li, K.; Li, X. M.; Ji, N. Y.; Gloer, J. B.; Wang, B. G. *Org. Lett.* **2008**, *10*, 1429.
(398) Kazlauskas, R.; Murphy, P. T.; Wells, R. J. *Aust. J. Chem.* **1982**, *35*, 219.
(399) Wright, A. E.; Wing, R. M.; Sims, J. J. *Tetrahedron Lett.* **1983**, *24*, 4649.
(400) Su, J. Y.; Xu, X. H.; Zeng, L. M.; Wang, C. J. *Gaodeng Xuexiao Huaxue Xuebao* **1997**, *18*, 1333.
(401) Blunt, J. W.; Copp, B. R.; Keyzers, R. A.; Munro, M. H. G.; Prinsep, M. R. *Nat. Prod. Rep.* **2012**, *29*, 144.
(402) Salgado, L. T.; Viana, N. B.; Andrade, L. R.; Leal, R. N.; Da Gama, B. A. P.; Attias, M.; Pereira, R. C.; Filho, G. M. A. *J. Struct. Biol.* **2008**, *162*, 345.
(403) Young, D. N.; Howard, B. M.; Fenical, W. *J. Phycol.* **1980**, *16*, 182.
(404) Butler, A.; Carter-Franklin, J. N. *Nat. Prod. Rep.* **2004**, *21*, 180.
(405) Masuda, M.; Abe, T.; Sato, S.; Suzuki, T.; Suzuki, M. *J. Phycol.* **1997**, *33*, 196.
(406) Fujii, M. T.; Cassano, V.; Stein, E. M.; Carvalho, L. R. *Braz. J. Pharmacogn.* **2011**, *21*, 268.
(407) de Carvalho, L. R.; Roque, N. F. *Biochem. Syst. Ecol.* **2004**, *32*, 337.
(408) Masuda, M.; Abe, T.; Suzuki, T.; Suzuki, M. *Phycologia* **1996**, *35*, 550.
(409) Kurata, K.; Taniguchi, K.; Agatsuma, Y.; Suzuki, M. *Phytochemistry* **1998**, *47*, 363.
(410) Hay, M. E. *Ann. Rev. Ecol. Syst.* **1988**, *19*, 111.
(411) González, A. G.; Martín, J. D.; Pérez, C.; Ramírez, M. A. *Tetrahedron Lett.* **1976**, *17*, 137.
(412) Murai, A.; Murase, H.; Matsue, H.; Masamune, T. *Tetrahedron Lett.* **1977**, *18*, 2507 and references cited therein.
(413) Masamune, T.; Matsue, H.; Murase, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 127.
(414) Masamune, T.; Murase, H.; Matsue, H.; Murai, A. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 135.
(415) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653.
(416) Crimmins, M. T.; Emmitte, K. A. *Org. Lett.* **1999**, *1*, 2029.
(417) Crimmins, M. T.; Emmitte, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 1533.
(418) Crimmins, M. T.; Emmitte, K. A.; Choy, A. L. *Tetrahedron* **2002**, *58*, 1817.
(419) Crimmins, M. T.; DeBaillie, A. C. *Org. Lett.* **2003**, *5*, 3009.
(420) Crimmins, M. T.; Powell, M. T. *J. Am. Chem. Soc.* **2003**, *125*, 7592.
(421) Holmes, A. B.; Jennings-White, C. L. D.; Kendrick, D. A. *J. Chem. Soc., Chem. Commun.* **1983**, *8*, 415.
(422) Holmes, A. B.; Jennings-White, C. L. D.; Kendrick, D. A. *J. Chem. Soc., Chem. Commun.* **1984**, *23*, 1594.
(423) Robinson, R. A.; Clark, J. S.; Holmes, A. B. *J. Am. Chem. Soc.* **1993**, *115*, 10400.
(424) Burton, J. W.; Clark, J. S.; Derrer, S.; Stork, T. C.; Bendall, J. G.; Holmes, A. B. *J. Am. Chem. Soc.* **1997**, *119*, 7483.
(425) Kim, D.; Kim, I. H. *Tetrahedron Lett.* **1997**, *38*, 415.
(426) Kim, H.; Choi, W. J.; Jung, J.; Kim, S.; Kim, D. *J. Am. Chem. Soc.* **2003**, *125*, 10238.
(427) Lee, H.; Kim, H.; Baek, S.; Kim, S.; Kim, D. *Tetrahedron Lett.* **2003**, *44*, 6609.
(428) Baek, S.; Jo, H.; Kim, H.; Kim, H.; Kim, S.; Kim, D. *Org. Lett.* **2005**, *7*, 75.
(429) Lee, H.; Kim, Y.; Yoon, T.; Kim, B.; Kim, S.; Kim, H. D.; Kim, D. *J. Org. Chem.* **2005**, *70*, 8723.
(430) Kim, H.; Lee, H.; Lee, D.; Kim, S.; Kim, D. *J. Am. Chem. Soc.* **2007**, *129*, 2269.
(431) Martín, J. D.; Palazon, J. M.; Pérez, C.; Ravelo, J. L. *Pure Appl. Chem.* **1986**, *58*, 395.
(432) Martín, J. D.; Pérez, C.; Ravelo, J. L. *J. Am. Chem. Soc.* **1986**, *108*, 7801.
(433) Overman, L. E.; Thompson, A. S. *J. Am. Chem. Soc.* **1988**, *110*, 2248.
(434) Brown, M. J.; Harrison, T.; Overman, L. E. *J. Am. Chem. Soc.* **1991**, *113*, 5378.
(435) Berger, D.; Overman, L. E. *Synlett* **1992**, *1992*, 811.
(436) Berger, D.; Overman, L. E.; Renhowe, P. A. *J. Am. Chem. Soc.* **1993**, *115*, 9305.
(437) Grese, T. A.; Hutchinson, K. D.; Overman, L. E. *J. Org. Chem.* **1993**, *58*, 2468.
(438) Bratz, M.; Bullock, W. H.; Overman, L. E.; Takemoto, T. *J. Am. Chem. Soc.* **1995**, *117*, 5958.
(439) Berger, D.; Overman, L. E.; Renhowe, P. A. *J. Am. Chem. Soc.* **1997**, *119*, 2446.
(440) Niwa, H.; Yoshida, Y.; Hasegawa, T.; Yamada, K. *Tetrahedron* **1991**, *47*, 2155.
(441) Gewali, M. B.; Ronald, R. C. *J. Org. Chem.* **1982**, *47*, 2792.
(442) Harrowven, D. C.; Lucas, M. C.; Howes, P. D. *Tetrahedron Lett.* **1999**, *40*, 8271.
(443) Harrowven, D. C.; Lucas, M. C.; Howes, P. D. *Tetrahedron* **2001**, *57*, 791.
(444) Yoo, S.; Suh, J. H.; Yi, K. Y. *Synthesis* **1998**, *1998*, 771.
(445) Couladouros, E. A.; Vidali, V. P. *Chem.—Eur. J.* **2004**, *10*, 3822.
(446) Murai, A.; Kato, K.; Masamune, T. *Tetrahedron Lett.* **1982**, *23*, 2887.
(447) Fukuzawa, A.; Sato, H.; Masamune, T. *Tetrahedron Lett.* **1987**, *28*, 4303.
(448) Hashimoto, M.; Kan, T.; Nozaki, K.; Yanagiya, M.; Shirahama, H.; Matsumoto, T. *J. Org. Chem.* **1990**, *55*, 5088.
(449) Hashimoto, M.; Kan, T.; Nozaki, K.; Yanagiya, M.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1988**, *29*, 1143.
(450) Kan, T.; Hashimoto, M.; Yanagiya, M.; Shirahama, H. *Tetrahedron Lett.* **1988**, *29*, 5417.
(451) González, I. C.; Forsyth, C. J. *J. Am. Chem. Soc.* **2000**, *122*, 9099.
(452) Corey, E. J.; Ha, D. C. *Tetrahedron Lett.* **1988**, *29*, 3171.
(453) Tanuwidjaja, J.; Ng, S. S.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, 12084.
(454) Morimoto, Y.; Okita, T.; Takaishi, M.; Tanaka, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 1132.
(455) Andrey, O.; Glanzmann, C.; Landais, Y.; Parrarapado, L. *Tetrahedron* **1997**, *53*, 2835.
(456) Chandler, C. L.; Phillips, A. J. *Org. Lett.* **2005**, *7*, 3493.
(457) Osumi, K.; Sugimura, H. *Tetrahedron Lett.* **1995**, *36*, 5789.
(458) Lee, E.; Yoo, S. K.; Cho, Y. S.; Cheon, H. S.; Chong, Y. H. *Tetrahedron Lett.* **1997**, *38*, 7757.
(459) Boukouvalas, J.; Fortier, G.; Radu, I. I. *J. Org. Chem.* **1998**, *63*, 916.
(460) Mereyala, H. B.; Gadikota, R. R. *Tetrahedron: Asymmetry* **2000**, *11*, 743.
(461) García, C.; Martín, T.; Martín, V. S. *J. Org. Chem.* **2001**, *66*, 1420.
(462) Gadikota, R. R.; Callam, C. S.; Lowary, T. L. *J. Org. Chem.* **2001**, *66*, 9046.
(463) Fernández de la Pradilla, R.; Montero, C.; Priego, J.; Martínez-Cruz, L. A. *J. Org. Chem.* **1998**, *63*, 9612.
(464) Martín, T.; Soler, M. A.; Betancort, J. M.; Martín, V. S. *J. Org. Chem.* **1997**, *62*, 1570.
(465) Lee, E.; Yoo, S. K.; Choo, H.; Song, H. Y. *Tetrahedron Lett.* **1998**, *39*, 317.
(466) Evans, P. A.; Murthy, V. S.; Roseman, J. D.; Rheingold, A. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 3175.

(467) Matsumura, R.; Suzuki, T.; Hagiwara, H.; Hoshi, T.; Ando, M. *Tetrahedron Lett.* **2001**, *42*, 1543.
(468) Suzuki, T.; Matsumura, R.; Oku, K. I.; Taguchi, K.; Hagiwara, H.; Hoshi, T.; Ando, M. *Tetrahedron Lett.* **2001**, *42*, 65.
(469) Fujiwara, K.; Yoshimoto, S.; Takizawa, A.; Souma, S.; Mishima, H.; Murai, A.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2005**, *46*, 6819.
(470) Mujica, M. T.; Afonso, M. M.; Galindo, A.; Palenzuela, J. A. *Synlett* **1996**, *1996*, 983.
(471) Kim, B.; Lee, M.; Kim, M. J.; Lee, H.; Kim, S.; Kim, D.; Koh, M.; Park, S. B.; Shin, K. J. *J. Am. Chem. Soc.* **2008**, *130*, 16807.
(472) Sugimoto, M.; Suzuki, T.; Hagiwara, H.; Hoshi, T. *Tetrahedron Lett.* **2007**, *48*, 1109.
(473) Crimmins, M. T.; Tabet, E. A. *J. Am. Chem. Soc.* **2000**, *122*, 5473.
(474) Ishihara, J.; Shimada, Y.; Kanoh, N.; Takasugi, Y.; Fukuzawa, A.; Murai, A. *Tetrahedron* **1997**, *53*, 8371.
(475) Fujiwaraa, K.; Souma, S. I.; Mishima, H.; Murai, A. *Synlett* **2002**, *2002*, 1493.
(476) Boeckman, R. K.; Zhang, J.; Reeder, M. R. *Org. Lett.* **2002**, *4*, 3891.
(477) Saitoh, T.; Suzuki, T.; Sugimoto, M.; Hagiwara, H.; Hoshi, T. *Tetrahedron Lett.* **2003**, *44*, 3175.
(478) Fujiwara, K.; Awakura, D.; Tsunashima, M.; Nakamura, A.; Honma, T.; Murai, A. *J. Org. Chem.* **1999**, *64*, 2616.
(479) Uemura, T.; Suzuki, T.; Onodera, N.; Hagiwara, H.; Hoshi, T. *Tetrahedron Lett.* **2007**, *48*, 715.
(480) Liu, Y.; Gribble, G. W. *J. Nat. Prod.* **2002**, *65*, 748.
(481) Suárez-Castillo, O. R.; Beiza-Granados, L.; Meléndez-Rodríguez, M.; Álvarez-Hernández, A.; Morales-Ríos, M. S.; Joseph-Nathan, P. *J. Nat. Prod.* **2006**, *69*, 1596.
(482) Barrett, T. N.; Braddock, D. C.; Monta, A.; Webb, M. R.; White, A. J. P. *J. Nat. Prod.* **2011**, *74*, 1980.
(483) Mori, T.; Bando, H.; Kanaiwa, Y.; Amiya, T.; Kurata, K. *Chem. Pharm. Bull.* **1983**, *31*, 1754.
(484) Al-farhan, E.; Falana, O. M.; Keehn, P. M.; Stevenson, R. *Tetrahedron Lett.* **1992**, *33*, 5885.
(485) Suzuki, M.; Takahashi, Y.; Nakano, S.; Abe, T.; Masuda, M.; Ohnishi, T.; Noya, Y.; Seki, K. *Phytochemistry* **2009**, *70*, 1140.
(486) Xu, R. S. *Natural Products Chemistry*; Science Press: Beijing, 1993; p 762.
(487) Braddock, D. C. *Org. Lett.* **2006**, *8*, 6055.
(488) Faulkner, D. J. *Pure Appl. Chem.* **1976**, *48*, 25.
(489) Wolinsky, L. E.; Faulkner, D. J. *J. Org. Chem.* **1976**, *41*, 597.
(490) Kato, T.; Ichinose, I.; Kamoshida, A.; Kitahara, Y. *J. Chem. Soc., Chem. Commun.* **1976**, *13*, 518.
(491) Kato, T.; Ishii, K.; Ichinose, I.; Nakai, Y.; Kumagai, T. *J. Chem. Soc., Chem. Commun.* **1980**, *23*, 1106.
(492) Shieh, H. M.; Prestwich, G. D. *Tetrahedron Lett.* **1982**, *23*, 4643.
(493) Carter-Franklin, J. N.; Butler, A. *J. Am. Chem. Soc.* **2004**, *126*, 15060.
(494) Murai, A. In *Comprehensive Natural Products Chemistry*; Barton, D., Nakanishi, K., Meth-Cohn, O., Eds.: Elsevier Academic Press: Amsterdam, 1999; Vol. *1*, p 303.
(495) Fukuzawa, A.; Aye, M.; Nakamura, M.; Tamura, M.; Murai, A. *Chem. Lett.* **1990**, *19*, 1287.
(496) Fukuzawa, A.; Aye, M.; Murai, A. *Chem. Lett.* **1990**, *19*, 1579.
(497) Fukuzawa, A.; Takasugi, Y.; Murai, A.; Nakamura, M.; Tamura, M. *Tetrahedron Lett.* **1992**, *33*, 2017.
(498) Fukuzawa, A.; Aye, M.; Takasugi, Y.; Nakamura, M.; Tamura, M.; Murai, A. *Chem. Lett.* **1994**, *23*, 2307.
(499) Wessels, M.; König, G. M.; Wright, A. D. *J. Nat. Prod.* **2000**, *63*, 920.
(500) Dias, T.; Brito, I.; Moujir, L.; Paiz, N.; Darias, J.; Cueto, M. *J. Nat. Prod.* **2005**, *68*, 1677.
(501) Matsuzawa, S.; Kawamura, T.; Mitsuhashi, S.; Suzuki, T.; Matsuo, Y.; Suzuki, M.; Mizuno, Y.; Kikuchi, K. *Bioorg. Med. Chem.* **1999**, *7*, 381.
(502) Mahdi, F.; Falkenberg, M.; Ioannou, E.; Roussis, V.; Zhou, Y. D.; Nagle, D. G. *Phytochem. Lett.* **2011**, *4*, 75.
(503) Sun, X.; Xu, N. J.; Guo, J. M.; Yan, X. J. *Chin. J. Chin. Mat. Med. (Zhongguo Zhongyao Zazhi)* **2010**, *35*, 1173.
(504) Vairappan, C. S. *Biomol. Eng.* **2003**, *20*, 255.
(505) Oh, K. B.; Lee, J. H.; Chung, S. C.; Shin, J.; Shin, H. J.; Kim, H. K.; Lee, H. S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 104.
(506) Vairappan, C. S.; Anangdan, S. P.; Tan, K. L.; Matsunaga, S. *J. Appl. Phycol.* **2010**, *22*, 305.
(507) Matsuzawa, S.; Suzuki, T.; Suzuki, M.; Matsuda, A.; Kawamura, T.; Mizuno, Y.; Kikuchi, K. *FEBS Lett.* **1994**, *356*, 272.
(508) Colon, M.; Guevara, P.; Gerwick, W. H.; Ballantine, D. *J. Nat. Prod.* **1987**, *50*, 368.
(509) Liu, Q. W.; Xu, H.; Zhang, T.; Fan, X.; Han, L. J. *Huaxue Tongbao* **2006**, *69*, 807.
(510) Liu, X.; Li, X. M.; Gao, L. X.; Cui, C. M.; Li, C. S.; Li, J.; Wang, B. G. *Chin. J. Oceanol. Limnol.* **2011**, *29*, 686.
(511) Faulkner, D. J. *Nat. Prod. Rep.* **1984**, *1*, 251.
(512) Rogers, C. N.; de Nys, R.; Charlton, T. S.; Steinberg, P. D. *J. Chem. Ecol.* **2000**, *26*, 721.
(513) Argandoña, V. H.; San-Martín, A.; Rovirosa, J. *Phytochemistry* **1993**, *32*, 1159.
(514) Pereira, R. C.; Dagama, B. A. P.; Teixeira, V. L.; Yoneshigue-valentin, Y. *Braz. J. Biol.* **2003**, *63*, 665.
(515) de Nys, R.; Leya, T.; Maximilien, R.; Afsar, A.; Nair, P. S. R.; Steinberg, P. *Biofouling* **1996**, *10*, 213.
(516) Cassano, V.; De-Paula, J. C.; Fujii, M. T.; Da Gama, B. A. P.; Teixeira, V. L. *Biochem. Syst. Ecol.* **2008**, *36*, 223.
(517) McLachlan, J.; Craigie, J. S. *J. Phycol.* **1966**, *2*, 133.
(518) Fries, L. *Experientia* **1973**, *29*, 1436.
(519) Kubo, I.; Ochi, M.; Shibata, K.; Hanke, F. J.; Nakatsu, T.; Tan, K. S.; Taniguchi, M.; Kamikawa, T.; Yamagiwa, Y.; Arizuka, M.; Wood, W. F. *J. Nat. Prod.* **1990**, *53*, 50.
(520) da Silva Machado, F. L.; Pacienza-Lima, W.; Rossi-Bergmann, B.; de Souza Gestinari, L. M.; Fujii, M. T.; Campos de Paula, J.; Costa, S. S.; Lopes, N. P.; Kaiser, C. R.; Soares, A. R. *Planta Med.* **2011**, *77*, 733.
(521) dos Santos, A. O.; Veiga-Santos, P.; Ueda-Nakamura, T.; Filho, B. P. D.; Sudatti, D. B.; Bianco, E. M.; Pereira, R. C.; Nakamura, C. V. *Mar. Drugs* **2010**, *8*, 2733.
(522) Chatter, R.; Ben Othman, R.; Rabhi, S.; Kladi, M.; Tarhouni, S.; Vagias, C.; Roussis, V.; Guizani-Tabbane, L.; Kharrat, R. *Mar. Drugs* **2011**, *9*, 1293.
(523) Lee, H. S.; Lee, T. H.; Lee, J. H.; Chae, C. S.; Chung, S. C.; Shin, D. S.; Shin, J.; Oh, K. B. *J. Agric. Food Chem.* **2007**, *55*, 6923.
(524) Fenical, W. *Science* **1982**, *215*, 923.
(525) Tseng, C. K. *Common Seaweeds of China*; Science Press: Beijing, 1983; p 43.