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Nonhalogenated organic molecules from *Laurencia* algae

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Abstract The marine red algae of the genus *Laurencia* have produced more 700 secondary metabolites and exhibited high molecular diversity and intriguing bioactivity. Since the halogenated structures have been comprehensively reviewed previously, this review, covering up to the end of 2012, mainly focuses on the source, structure elucidation, and bioactivity of nonhalogenated organic molecules from *Laurencia* spp. as well as the relationship between nonhalogenated and halogenated products. Overall, 173 new or new naturally occurring compounds with 58 skeletons, mainly including sesquiterpenes, diterpenes, triterpenes, and C_{15}-acetogenins, are described.

Keywords *Laurencia* · Secondary metabolites · Nonhalogenated compounds · Terpenes · C_{15}-acetogenins

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Introduction

Secondary metabolites from marine algae have attracted much attention for phytochemical researches (Blunt et al. 2013). The marine red algae of the genus *Laurencia* (family Rhodomelaceae, order Ceramiales) have been established to be rich sources of halogenated and nonhalogenated organic molecules, mainly including sesquiterpenes, diterpenes, triterpenes, and C_{15}-acetogenins, which were reviewed in detail by Erickson (1983) 30 years ago. After that, a large number of other interesting structures have been characterized along with the improvement of isolation, identification, and bioassay techniques, and overall more than 700 organic molecules were reported from this genus so far (Blunt et al. 2013; Faulkner 1977). Among them, the halogenated compounds (more than 500) were often the subjects of previous reviews, and they really exhibited high molecular diversity and intriguing bioactivity (Wang et al. 2013). However, the nonhalogenated products with diverse skeletons also occurred widely in *Laurencia* species, and some of them related to the halogenated ones in biogenesis and showed potent biological activities. This review focuses on the source, structure elucidation, and bioactivity of nonhalogenated organic molecules from *Laurencia* as well as their relationship with halogenated ones.

Nonhalogenated sesquiterpenes

To date, a total of 94 nonhalogenated sesquiterpenes containing 31 skeletons (Fig. 1) have been isolated

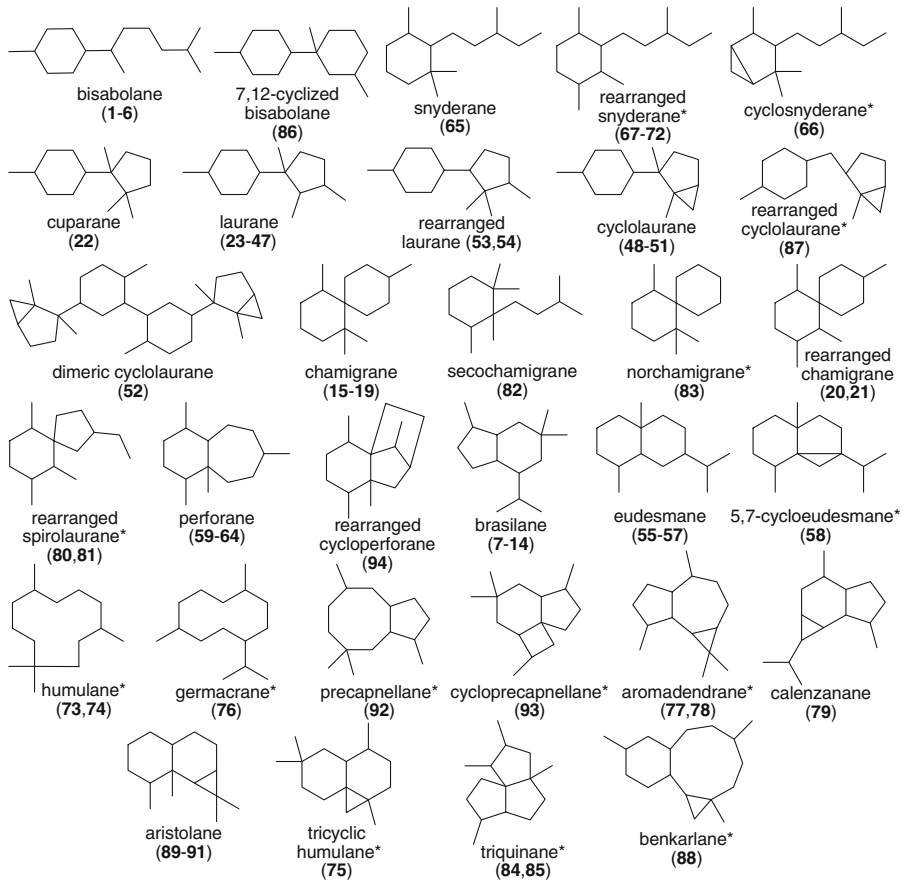


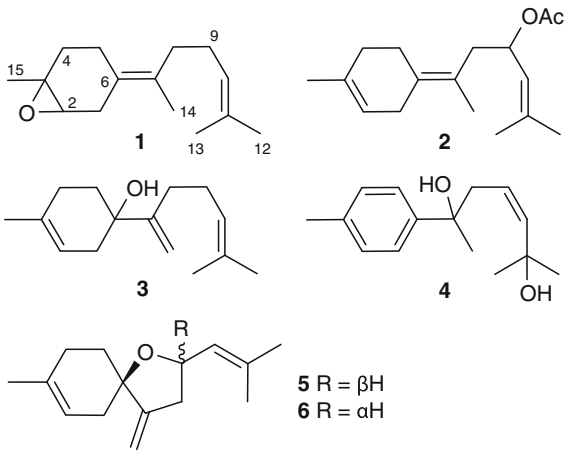
Fig. 1 Carbon skeletons of the nonhalogenated sesquiterpenes from *Laurencia* (*devoid of halogenated members)

and identified originally from 25 *Laurencia* species, which accounted for almost one forth of the whole *Laurencia*-derived sesquiterpenes and comprised bisabolanes, brasilanes, chamigranes, cuparanes, lauranes, eudesmanes, perforanes, snyderanes, and some other rarely occurring sesquiterpenes.

Bisabolanes

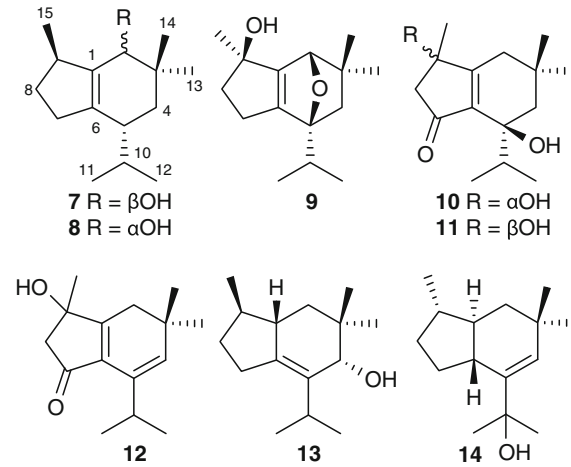
Six nonhalogenated bisabolane sesquiterpenes (**1**–**6**) have been characterized from five *Laurencia* species. A 2,3-epoxy bisabolane sesquiterpene **1** was isolated from Japanese *L. nipponica*, which has been determined by 1D NMR and IR spectroscopic methods as well as chemical degradation to (*E*)-γ-bisabolene. Unfortunately, the stereochemistry of oxirane ring remained unresolved, although a stereocontrolled synthesis with neighboring group participation was performed later (Suzuki et al. 1980; Martin et al. 1985). 9-Acetoxy-*E*-γ-bisabolene (**2**) with moderate antialgal activity against *Chlorella fusca* (inhibition zone 0.3 cm) was obtained from Australian *L. rigida*, and only a planar structure was assigned by spectroscopic analysis due to its instability (König and Wright 1997). A hydroxyl derivative **3** of β-bisabolene from Greek *L. microcladia* and an aromatic bisabolane sesquiterpene **4** from Chinese *L. tristicha* were also identified grossly, and the latter was reported to be inactive (IC_{50} >10 μg/mL) against A549, BGC-823, Bel 7402, HCT-8, and Hela tumor cell lines (Kladi et al. 2007; Sun et al. 2005b). Epimers **5** and **6**, two possible cyclic derivatives of **3** in biogenesis, were obtained as a 2:1 mixture from Chinese *L. okamurai* and displayed moderate or weak brine shrimp lethality (Liang et al. 2012). Overall, the geometries of double bonds in **1**–**6** were determined, but the absolute configurations of chiral centers were not assigned. Most of the halogenated bisabolane sesquiterpenes featured halogens at C-2 and C-3 (Wang et al. 2013), but the majority of the nonhalogenated ones were

unsaturated at the same positions. Thus, some of these nonhalogenated bisabolane sesquiterpenes were speculated to be the possible precursors not only for the halogenated analogues but also for the other skeletons, such as chamigrane, cuparane, laurane, and perforane (Wang et al. 2013).



Brasilanes

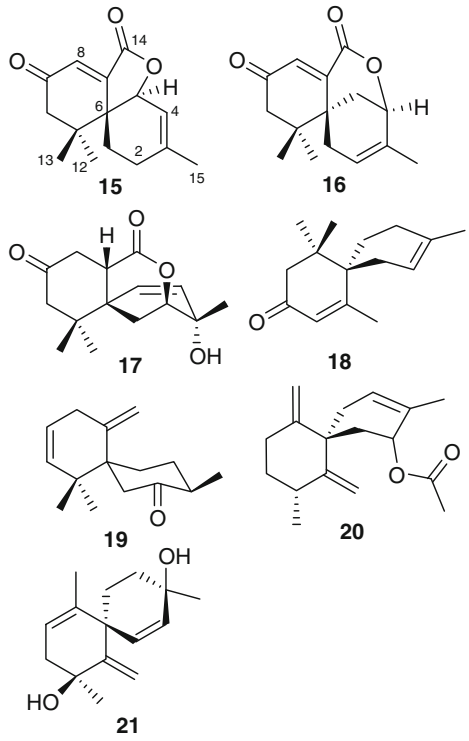
Eight nonhalogenated brasilane sesquiterpenes (**7**–**14**) from two *Laurencia* species were identified, which were more common than the halogenated ones (Wang et al. 2013). Brasilenol (**7**) and epibrasilenol (**8**) occurred as epimers in both sea hare *Aplysia brasiliana* and alga *L. obtusa*, with the latter (*Laurencia* species) might be their true origin (Stallard and Fenical 1978). From the same *Laurencia* species collected from Italy, five brasilane sesquiterpenes **9**–**13** were identified and the relative configurations of **10**, **11**, and **13** were assigned with the aid of molecular mechanics calculations using the MacroModel program (MM2 force field) (Caccamese et al. 1990; Amico et al. 1991). Simultaneously, **13** was also obtained from Australian *L. implicata* together with **14** (Wright et al. 1991), which was revised and assigned the absolute configuration by synthesis of its isomers and by analysis of the electronic circular dichroism (ECD) spectrum of its keto derivative (Tori et al. 1994). Given the lower number of halogenated brasilane sesquiterpenes and the devoid of bromine atoms in most of them, this backbone might not take shape through a bromonium ion-induced cyclization (Wang et al. 2013). Unfortunately, the bioactivity of **7**–**14** was not reported.



Chamigranes and rearranged chamigranes

Although a wide variety of halogenated chamigrane and rearranged chamigrane sesquiterpenes were discovered from the genus *Laurencia* (Wang et al. 2013), only five nonhalogenated chamigrane sesquiterpenes (**15**–**19**) and two rearranged ones (**20** and **21**) were obtained from five *Laurencia* species. Among them, lactones **15** and **16** were isolated from Spanish *L. majuscula*, and their absolute configurations were established by the aid of Pirkle's reagents (Díaz-Marrero et al. 2009). Another lactone **17** was identified from Caribbean *L. obtusa* with only the relative configuration being assigned by coupling constants and NOESY experiments (Dorta et al. 2004). Two chamigrane sesquiterpenes **18** and **19**, each containing a keto group, were isolated from Jamaican *L. obtusa* and Philippine *L. flexilis*, respectively (Kennedy et al. 1988; de Nys et al. 1993). A rearranged chamigrane sesquiterpene **20** possessing the brine shrimp toxicity (LC_{50} 51.1 μg/mL) was obtained from Chinese *L. composita*, and its relative configuration was confirmed by a combination of NOE correlations and quantum chemical calculations of the energy-minimized conformer (Li et al. 2012a). Scopariol (**21**) with a rearranged chamigrane skeleton was identified from Brazilian *L. scoparia*, which demonstrated no effect on the parasitant stage of *Nippostrongylus brasiliensis* (Davyt et al. 2001). Based the high degrees (at least

five) of unsaturation and the key role of bromonium ion in the assembly of chamigrane backbone (Wang et al. 2013), compounds **15**–**17** might be formed by the debromonation at C-10.

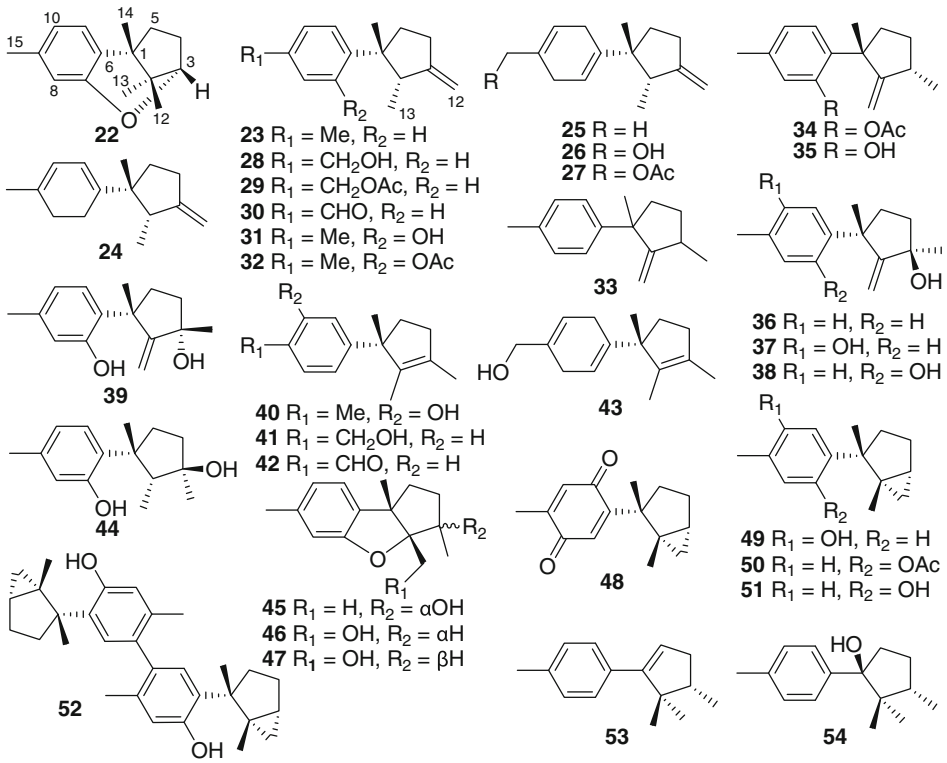


Cuparanes, lauranes, and cyclic/rearranged lauranes

This cuparane/laurane-derived class consisted of cuparane (**22**), laurane (**23**–**47**), cyclolaurane (**48**–**51**), dimeric cyclolaurane (**52**), and rearranged laurane (**53** and **54**) members from ten *Laurencia* species. Nine (**22**, **32**, **35**, **40**, **47**, **49**, **50**, **53**, and **54**) of these 33 sesquiterpenes were identified from Chinese or Japanese *L. okamurai* (Suzuki and Kurosawa 1978, 1979; Li et al. 2012b; Feutrill et al. 1973; Mao and Guo 2005, 2006, 2010), and **40** was also reported as a new constituent from Greek *L. microcladia* simultaneously (Kladi et al. 2005). The absolute configuration of **53** was established by an enantioselective total synthesis starting from (*S*)-campholenaldehyde (Srikrishna et al. 2008), and one of the intermediates afforded a valuable reference to confirm the absolute configuration of **54** (Srikrishna et al. 2008; Mao and Guo 2010). *L. nipponica* from Japan was the source of laurane sesquiterpenes **25**–**30** (Suzuki et al. 1982), and the absolute configurations of these compounds as well as **24** (from Australian *L. filiformis* f. *heteroclada*) were established based on the chemical conversion to laurene (**23**) (Kazlauskas et al. 1976), which was obtained originally from Japanese *L. glandulifera* with the absolute configuration being assigned by a series of chiral syntheses (Irie et al. 1965, 1967, 1969; Oh et al. 2000; Nemoto et al. 1992, 1993; Kulkarni and Pendharkar 1997; Bailey et al. 1995; Srikrishna and Sunderbabu 1989, 1990). A hydroxylated derivative (**31**) and an isomer (**33**) of laurene were identified from Californian *L. subopposita* and Greek *L. microcladia*, respectively (Kladi et al. 2007; Wratten and Faulkner 1977), and the latter was previously reported to be a byproduct in the synthesis of laurene using two palladium-catalyzed cycloreduction strategies (Oh et al. 2000). Compounds **31** and **32** exhibited higher antibacterial activity and brine shrimp toxicity than laurene, which suggested that the hydroxyl and acetoxyl groups at C-7 could be crucial to these activities (Liang et al. 2012; Wratten and Faulkner 1977; Li et al. 2012b). An acetoxylated derivative (**34**) and four hydroxylated derivatives (**36**–**39**) of **33** were identified from Japanese *L. intermedia* and Chinese *L. tristicha*, respectively (Sun et al. 2005b; Irie et al. 1970; Ji et al. 2008a), and **34** was isolated later as a pure constituent from Chinese *L. okamurai* (Mao and Guo 2005). Apart from **40**, three new isolaurene derivatives **41**–**43** with a source of Saudi Arabian *L. obtusa* were also identified (Alarif et al. 2012). Compounds **40**, **42**, and **43** showed potent cytotoxic activities, and **41**–**43** exhibited antibacterial and antifungal activities (Kladi et al. 2005; Alarif et al. 2012). A laurane sesquiterpene **44** with a saturated five-membered ring was obtained from Greek *L. microcladia* and showed weak cytotoxicity against four human tumor cell lines MCF7, PC3, Hela, and A431 with IC_{50} values of 121.3–201.7 μM (Kladi et al. 2006). Two cycloethers **45** and **46** and a diketone **48** were isolated from Chinese *L. tristicha* and Japanese *L. nidifica*, respectively (Sun et al. 2005a, 2007; Shizuri et al. 1984), and **48** was synthesized through combining the intramolecular Heck reaction and carbene insertion (Takahashi et al. 1998). The only nonhalogenated dimeric sesquiterpene, laurebiphenyl (**52**), and its monomer, debromolaurinterol (**51**), were identified from Japanese *L. nidifica* and

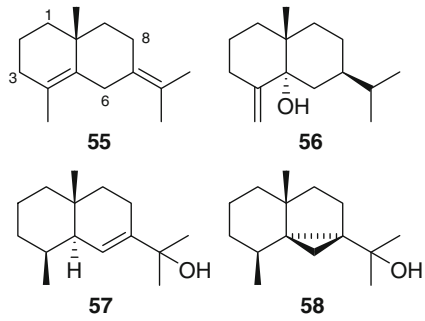
L. intermedia, respectively (Irie et al. 1966, 1970; Shizuri and Yamada 1985). When culturing *L. okamurae*, Kuwano et al. (1998) found that the concentration of **51** increased with the increase of salinity, which evidenced the influence of environmental conditions on the metabolism of *Laurencia* products. In biogenesis, bromonation at C-3 accompanied the assembly of cuparane backbone in *Laurencia* (Wang et al. 2013), and debromonation followed by rearrangement or cyclization might result in the production of these nonhalogenated cuparane/laurane derivatives.

(Sun and Erickson 1978). The other two eudesmane sesquiterpenes **56** and **57** were identified from Japanese *L. nipponica*, and their absolute configurations were also established by conversion to (+)-*δ*-selinene with *p*-toluene sulphonic acid (Suzuki et al. 1985a; Fukuzawa et al. 1990c). The only nonhalogenated cycloeudesmane sesquiterpene **58** also occurred in *L. nipponica*, which was identified to be an isomer of cycloeudesmol and named isocycloeudesmol originally (Suzuki et al. 1980). However, a detailed comparison of ^{1}H NMR data and optical rotations revealed that **58** was



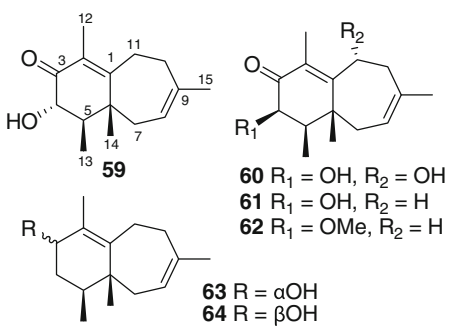
Eudesmanes and cycloeudesmanes

Like the halogenated eudesmane and cycloeudesmane sesquiterpenes, the nonhalogenated ones were also rarely encountered in *Laurencia* (Wang et al. 2013). Up to date, only four representatives (**55**–**58**) were reported from two members of this genus. Selin-4,7(11)-diene (**55**) represented the first example of nonhalogenated eudesmane sesquiterpenes, which was characterized from Hawaiian *L. nidifica* by 1D NMR and mass spectral data as well as isomerization to (+)-*δ*-selinene identical with cycloeudesmol isolated from *Chondria oppositiclada*, and the absolute configuration was determined by analysis of the CuKα X-ray diffraction of its acetoxylated derivative (Suzuki et al. 1981), which was further confirmed by total syntheses via two different stereospecific routes (Chen 1982; Ando et al. 1985). All the halogenated eudesmane and cycloeudesmane sesquiterpenes had a bromine atom at C-1 (Wang et al. 2013), but it was saturated with hydrogen atoms in these nonhalogenated ones. Additionally, the bioassay results for **55**–**58** were devoid.



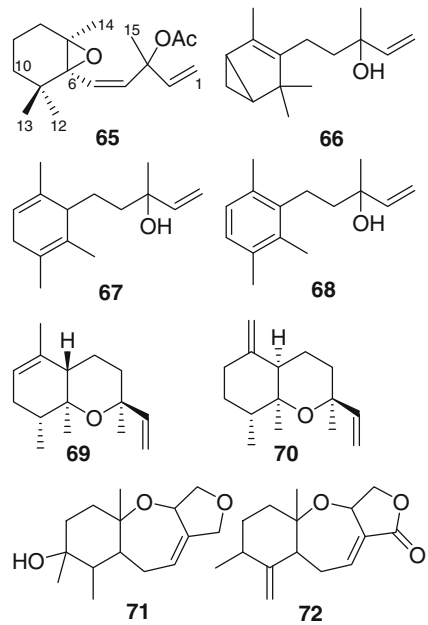
Perforanes

The nonhalogenated perforane sesquiterpenes comprised **59**–**64** with sources of *L. perforata* from Canary Islands and Australia (**59**–**61**) (González et al. 1975; Wright et al. 2003), *L. obtusa* from Greece (**62**) (Iliopoulou et al. 2002), and *L. synderiae* var. *guadalupensis* from Mexico (**63** and **64**) (Howard and Fenical 1979). Their structures and relative configurations were mainly determined by spectroscopic analysis, but the absolute configurations remained unresolved. In the biological evaluation for **60**–**62**, no significant bioactivities were found (Wright et al. 2003; Iliopoulou et al. 2002). Although the number was higher than that of halogenated perforanes (Wang et al. 2013), the biosynthesis of this backbone was speculated from a C-10 brominated chamigrane intermediate (González et al. 1975).



Snyderanes and cyclic/rearranged synderanes

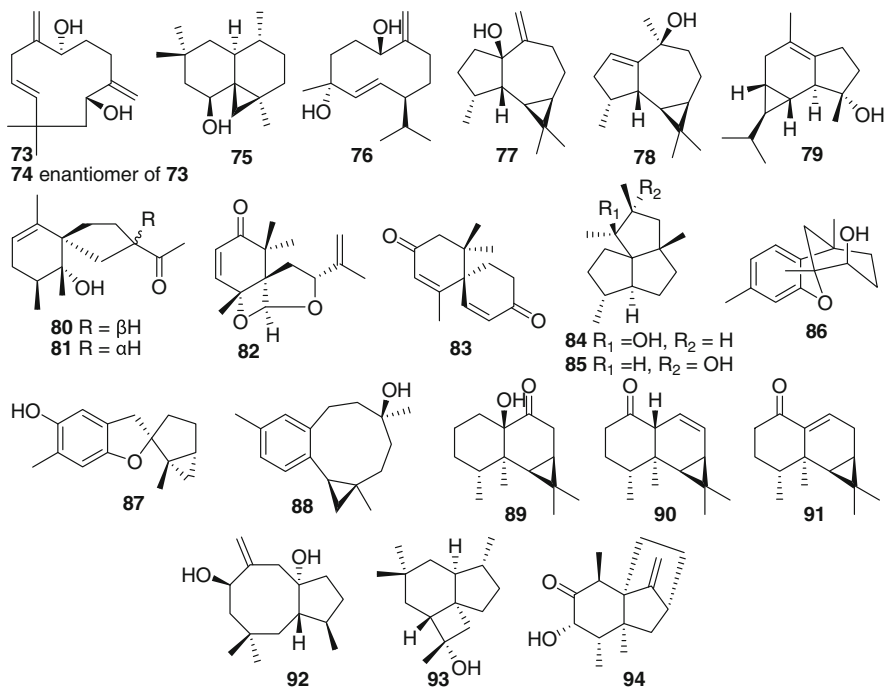
This class was represented by eight members (**65**–**72**) from five *Laurencia* species. The only snyderane sesquiterpene **65** was identified from Terkish *L. obtusa*, and no significant activities were found in the antimalarial assay (Topcu et al. 2003). A cyclosynderane **66** was isolated from Bermudan *L. intricata*, and no other halogenated and nonhalogenated molecules with this skeleton were reported from this genus so far (Horsley et al. 1981). Two rearranged synderanes **67** and **68** with an acyclic side chain were identified from Hawaiian *L. nidifica*, and the latter was the only example featuring a phenyl group in snyderane derivatives from *Laurencia* (Sun et al. 1976). Four epoxy sesquiterpenes with a rearranged synderane backbone were characterized from Chinese *L. mariannensis* (**69**) (Ji et al. 2007b), Egyptian *L. obtusa* (**70**) (Ayyad et al. 1994), and Japanese *L. luzonensis* (**71** and **72**) (Makhanu et al. 2006), and the missing methyl group at C-7 of **72** was added here according to its ^{13}C NMR data (Makhanu et al. 2006). Overall, the structure elucidation of **65**–**72** was preliminary, and the absolute configurations and even some relative ones remained unresolved. Most of the synderane sesquiterpenes were brominated at C-10 (Wang et al. 2013), but the rearranged derivatives were devoid of halogens. It was likely that the debromination at C-10 resulted in the rearrangement of a methyl group at C-11.



Miscellaneous sesquiterpenes

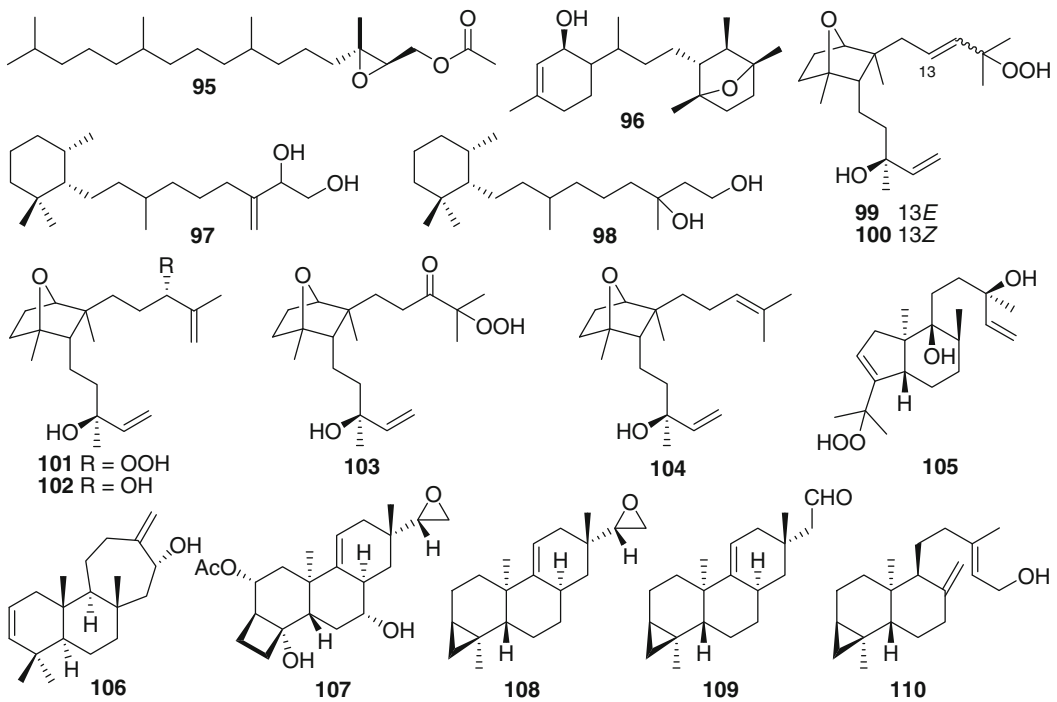
In addition to the typical nonhalogenated sesquiterpenes discussed above, 22 additional sesquiterpenes with new or rare skeletons were also identified from the genus *Laurencia*. Two humulane sesquiterpenes **73** and **74**

occurred as a racemate in Japanese *L. obtusa*, and the absolute configurations were confirmed by chiral separation and X-ray crystallographic analysis of a levorotary epoxy derivative (Takeda et al. 1990). A Mediterranean *L. obtusa* produced a unique tricyclic-humulane sesquiterpene, laurobtusol (**75**). Its relative configuration was inferred from the quantitative simulation of $Eu(fod)_3$ doped ^1H NMR data and MM2 calculation, which was further supported by total synthesis (Caccamese et al. 1991; Blanchfield et al. 2004). The only germacrane sesquiterpene **76** along with two aromadendrane derivatives (**77** and **78**) was identified from Californian *L. subopposita* (Wratten and Faulkner 1977), and a unique calenzanane sesquiterpene **79** was characterized from Italic *L. microcladia* (Guella et al. 2003). Laurenones A (**80**) and B (**81**) possessing an unusual backbone were identified from Japanese *L. nipponica*, which were regarded as transformed derivatives of a brominated analogue, spirolaurenone (Fukuzawa et al. 1984). The only secochamigrane (**82**) and norchamigrane (**83**) sesquiterpenes were identified from Japanese *L. nipponica* and *L. majuscula*, respectively, which were also possibly derived from the oxidation of their brominated congeners (Kurata et al. 1983; Suzuki et al. 1987b). Two triquinane isomers (**84** and **85**) from Australian *L. majuscula* were typical representatives of rarely occurring frameworks without any halogenated derivatives, and **84** exhibited the leishmanicidal activity (Coll and Wright 1989; da Silva Machado et al. 2011; Wright and Coll 1990). Three aromatic sesquiterpenes were characterized from Australian *L. majuscula* (**86**) and Chinese *L. tristicha* (**87**) and *L. karlae* (**88**), which featured unprecedented 7,12-cyclized bisabolane, rearranged cyclolaurane, and benkarlane skeletons, respectively (Sun et al. 2005b, 2008; de Nys et al. 1992; Zeng et al. 1996). From Chinese *L. similis*, three sesquiterpenes **89–91** with a rarely occurring aristolane skeleton in this genus were identified (Ji et al. 2007a). A precapnellane sesquiterpene **92** and its possible cyclic derivative **93** were obtained from *L. poitei* (Florida Keys) and *L. viridis* (Canary Islands), respectively, and the relative configuration of **92** was established by X-ray diffraction and evidenced by total synthesis (Fenical et al. 1978; Gadwood et al. 1984; Norte et al. 1994; Gil-Rodriguez and Haroun 1992). Apart from perforanes, Australian *L. perforata* produced a tricyclic sesquiterpene (**94**), which was probably derived from the rearrangement of perforenone A (**59**) (Wright et al. 2003). Totally, 16 new or rare sesquiterpene skeletons were found from 11 species of the genus *Laurencia*, and more than two-third of them did not contain any halogenated members, which further added to the molecular diversity of secondary metabolites from this genus.



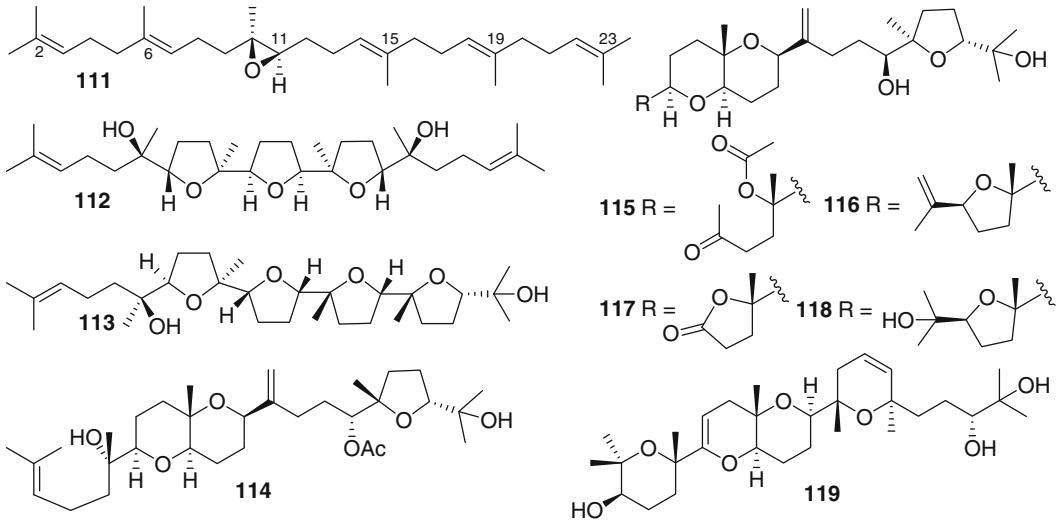
Nonhalogenated diterpenes

Compared to the large amounts of nonhalogenated sesquiterpenes discussed above, only a small number of *Laurencia*-derived nonhalogenated diterpenes have been discovered to date. Among these, a phytol derivative, 2,3-epoxyphytyl acetate (**95**), was identified from Chinese *L. composita* (Ji et al. 2010), and a novel diterpene, laurenditerpenol (**96**), from Jamaican *L. intricata* was evidenced to be a potent agent to inhibit hypoxia-activated HIF-1 (IC_{50} 0.4 μM) and hypoxia-induced VEGF in T47D cells (Mohammed et al. 2004). Two rare 10,15-cyclophytane-type diterpenes, viridiols A (**97**) and B (**98**), were obtained from *L. viridis* (Canary Islands), which showed remarkable activity against P388, A549, HT-29, and MEL-28 tumor cells with IC_{50} values of 1–2.5 μg/mL (Gil-Rodriguez and Haroun 1992; Norte et al. 1996). Six dactylomelane diterpenes **99**–**104** occurred in an unidentified *Laurencia* species collected from Canary Islands, which were deduced to be formed via a bromonium ion intermediate in biogenesis (Fernández et al. 2005). A diterpene hydroperoxide **105** with a novel framework was reported from *L. snyderiae* (Catalina Island), which was proposed to be derived from the debromination and rearrangement of its brominated precursor (Howard et al. 1977). From Chinese *L. karlae*, a novel diterpene **106** featuring a ring system of a cycloheptane *trans*-fused to a *trans*-decalin was identified (Su et al. 1995), and its hydroxyl group was revised to be α-oriented from the original β orientation by chemical synthesis via the free-radical reaction (Justicia et al. 2005). Three diterpenes possessing isoparguerane (**107**) and parguerane (**108** and **109**) backbones along with their possible biogenic precursor **110**, originally identified from Australian *L. filiformis*, were isolated from Japanese *L. saitoi*, which exhibited moderate feeding-deterrent activity against young abalone *Haliotis discus hannai* with electivity indexes ranging from 0.42 to 0.63 (Kurata et al. 1998; Rochfort and Capon 1996). Overall, 16 nonhalogenated diterpenes (**95**–**110**) with nine skeletons were characterized from eight *Laurencia* species, which accounted for almost one-fifth of the total *Laurencia*-derived diterpenes. The molecular diversity was quite lower than that of the halogenated diterpenes.



Nonhalogenated triterpenes

At least 40 *Laurencia*-derived triterpenes have been discovered to date, and more than three forth of them were halogenated (Wang et al. 2013; Fernández et al. 2000). There were only nine members (**111**–**119**) of nonhalogenated triterpenes identified from four *Laurencia* species. Among them, (10*R*,11*R*)-(+)-squalene-10,11-epoxide (**111**) from Japanese *L. okamurai* was proposed as a common precursor of squalene-derived triterpene polyethers (Fernández et al. 2000; Kigoshi et al. 1982a, 1986a), but our work on Chinese *L. decumbens* really resulted in the isolation of squalene (unpublished). Teurilene (**112**) and omaezakianol (**113**) containing three and four tetrahydrofuran rings, respectively, were identified from Japanese *L. obtusa* and *L. omaezakiana*, which attracted much attention for asymmetric syntheses due to their complicated stereochemistry (Suzuki et al. 1985b; Hashimoto et al. 1988, 1991; Morimoto et al. 1999, 2009; Matsuo et al. 2008; Xiong et al. 2010). Algal samples of *L. viridis* collected from Canary Islands were proven to be the largest reservoir not only for the halogenated triterpene polyethers but also for the nonhalogenated ones (Wang et al. 2013; Fernández et al. 2000). From this species, six nonhalogenated triterpene polyethers (**114**–**119**) with a 2,7-dioxabicyclo[4,4,0]decane system were identified, and **114**, **115**, and **118** displayed remarkable cytotoxicity against several tumor cell lines, including P388, A549, HT29, MEL28, Jurkat, MM144, Hela, and CADO-ES1 (Norte et al. 1997; Fernández et al. 1998; Pacheco et al. 2011; Souto et al. 2002; Manríquez et al. 2001). Biogenetically, the intermediates with 1,2-epoxy groups, rather than bromonium ions, might play a key role in the formation of nonhalogenated triterpene polyethers (Fernández et al. 2000).



Nonhalogenated C_{15}-acetogenins

Totally, 32 nonhalogenated C_{15}-acetogenins (**120**–**151**), each featured an enyne terminus, have been reported from six *Laurencia* species so far, which accounted for less than one-fifth of the entire *Laurencia*-derived C_{15}-acetogenins. Some of them were proposed as precursors or dehalogenated derivatives of the halogenated C_{15}-acetogenins in biogenesis, and the devoid of allene terminus further supported the key role of a bromine anion in the conversion from an enyne to an allene group (Ji et al. 2007c).

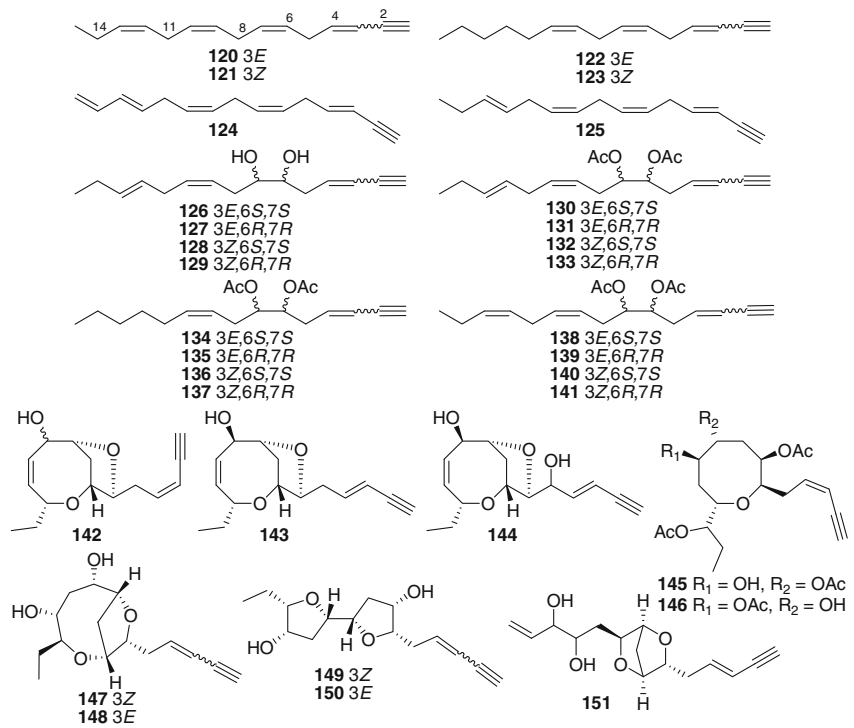
Linear C_{15}-acetogenins

22 Nonhalogenated linear C_{15}-acetogenins were obtained from Japanese *L. okamurai* (**120**–**123**) (Kigoshi et al. 1981, 1982b, 1986b; Holmeide et al. 2001), Australian *L. majuscula* (**124** and **125**) (Wright et al. 1993), and Japanese *L. nipponica* (**126**–**141**) (Kurosawa et al. 1972; Fukuzawa et al. 1986, 1993; Añorbe et al. 1986; Martín and Martín 2000), which were identified on the basis of spectral data and chemical conversion/synthesis. They all featured a *cis*- or *trans*-enyne group, and the compounds (**126**–**141**) with a

dihydroxyl or diacetoxyl group always occurred as a racemate of 6*S*,7*S* and 6*R*,7*R* enantiomers. The biogenic roles of these linear acetogenins were interpreted by a series of enzyme-catalyzed reactions (Fukuzawa et al. 1990a, 1990b, 1992, 1994; Ishihara et al. 1995). When treated with lactoperoxidase in the presence of H_2O_2 and NaBr, (6*R*,7*R*)-*trans*-laurediol (**127**) directly transformed to a deacetylated derivative of laurencin along with bromohydrins and an unknown cycloether (Fukuzawa et al. 1990a). Under similar conditions, (*Z*)-laureatin and a key intermediate, (*Z*)-prelaureatin, was formed from (6*S*,7*S*)-*cis*-laurediol (**128**) by a single-step enzymatic reaction (Fukuzawa et al. 1992), yet the same reaction with (6*S*,7*S*)-*trans*-laurediol (**126**) yielded a less amount of (*E*)-prelaureatin due to a possible stereoselectivity for the geometries of C-3 double bond (Ishihara et al. 1995). The occurrence of linear C_{15}-acetogenins and preliminary enzymatic reactions further supported the previous biogenic hypothesis for halogenated C_{15}-acetogenins (Wang et al. 2013).

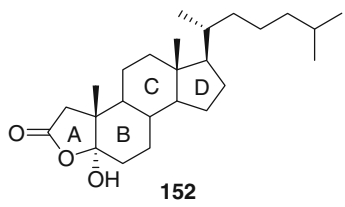
Epoxy C_{15}-acetogenins

Four papers reported the isolation and structure elucidation of ten nonhalogenated epoxy C_{15}-acetogenins (**142**–**151**) (Wratten and Faulkner 1977; Wright et al. 1993; König and Wright 1994; Abdel-Mageed et al. 2010). The first two compounds were obtained from Californian *L. subopposita* as a 1:1 mixture of *cis*- (**142**) and *trans*-isomer (**143**) (Wratten and Faulkner 1977), and the hydroxyl group of **143** was assigned as β orientation based on the pure isolate from Zelanian *Laurencia* sp. cf. *L. gracilis* (König and Wright 1994). The latter species also produced three other eight-membered cyclic ethers (**144**–**146**) (König and Wright 1994). Additionally, four bicyclic ethers **147**–**150** were characterized from an unidentified *Laurencia* species collected from Philippines, and **147** showed moderate cytotoxicity against L1210, Colon 38, H-116, and H-125 tumor cell lines (Abdel-Mageed et al. 2010). Another bicyclic ether **151** with a rare 2,5-dioxabicyclo[2.2.1]heptane ring system was identified from Australian *L. majuscula* (Wright et al. 1993). Based on biogenic considerations, the co-occurence of **143** and its brominated analogue, laurefucin, suggested that **143** was likely formed by the debromination of laurefucin (König and Wright 1994). On the other hand, the intermediates with 1,2-epoxy groups might play a key role in the biosyntheses of these nonhalogenated epoxy C_{15}-acetogenins (Abdel-Mageed et al. 2010).



Nonhalogenated steroids

Steroids represented a rarely encountered type of *Laurencia*-derived secondary metabolites, and to date only four nonhalogenated members from Indian *L. obtusa* (**152**) (Kobayashi et al. 1992), Japanese *L. pinnata* (**153** and **154**) (Fukuzawa et al. 1981), and Chinese *L. majuscula* (**155**) (Xu et al. 2001) were identified. Among them, **152** was the first natural ring A-dinorsteroid, and **153** and **154** with the biological activity as moulting hormones were the first marine ecdysone-like structures.



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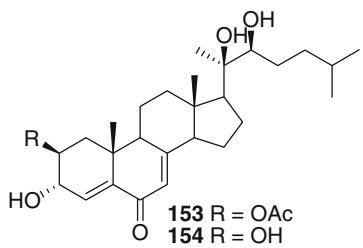
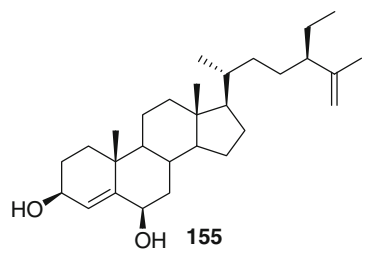


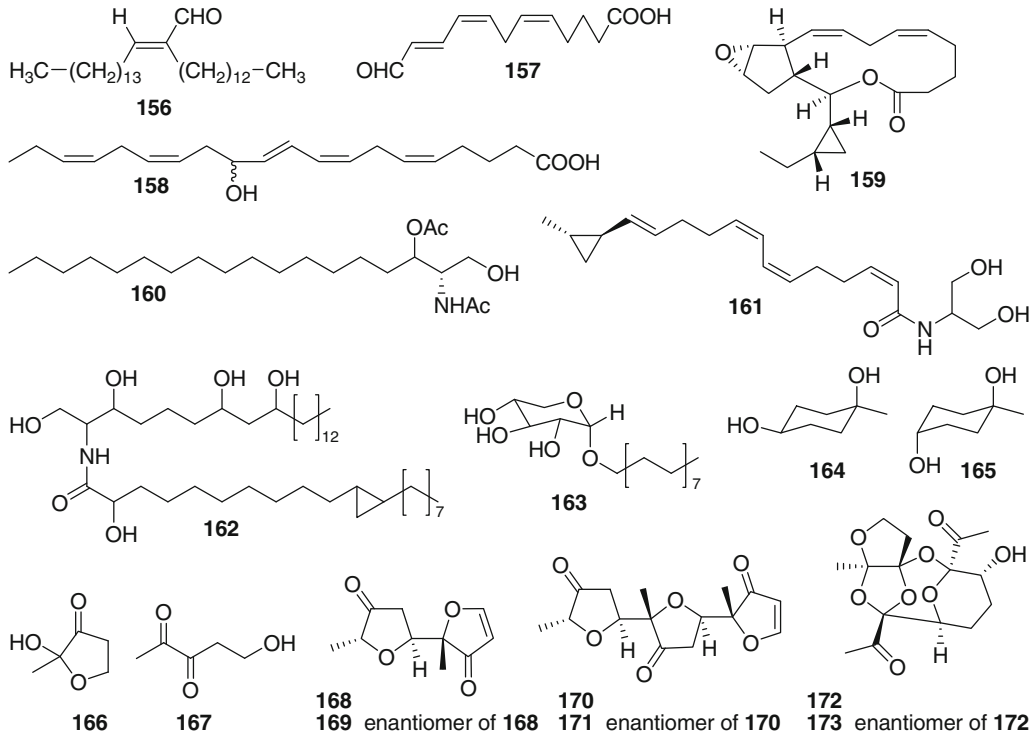
153 R = OAc
154 R = OH



155

Miscellaneous nonhalogenated products

Apart from the nonhalogenated organic molecules discussed above, there were additional 18 nonhalogenated products (**156–173**) with atypical frameworks occurring in the genus *Laurencia*. Among these, an unusual α,β-unsaturated aldehyde **156** was identified from Japanese *L. undulata* and *L. papillosa* (Suzuki et al. 1987a; Basavaiah and Hyma 1996), and three fatty acid derivatives **157–159** were characterized from British *L. hybrida* (Higgs 1981; Bernart and Gerwick 1988; Higgs and Mulheirn 1981; Corey et al. 1984; Hickmann et al. 2011; Corey and De 1984; Ota et al. 2012). Compound **157** was named 11-formyl-undeca-(5*Z*,8*E*,10*E*)-trienoic acid, but its structure was drawn as (8*Z*) (Higgs 1981). Compound **158** was originally assigned as 9-hydroxyeicosa-(2*Z*,5*Z*,7*E*,11*Z*,14*Z*)-pentaenoic acid (Higgs 1981), but its structure was corrected later by comparison of its spectral data with those of (12*S*)-HEPE from *Murrayella periclados* (Bernart and Gerwick 1988). Compound **159**, possibly derived from **158** in biogenesis, represented the first marine-derived oxylipin containing a cyclopropane and a macrolactone ring, and its structure and relative/absolute configuration were extensively elucidated by spectroscopic methods including X-ray diffraction, molecular mechanics calculations, chemical derivation, and total synthesis (Higgs and Mulheirn 1981; Corey et al. 1984; Hickmann et al. 2011; Corey and De 1984; Ota et al. 2012). Three nitrogen-containing constituents were identified from Hawaiian *L. nidifica* (**160**) (Cardellina and Moore 1978), Japanese *L. papillosa* (**161**) (Maru et al. 2010), and Chinese *L. cartilaginea* (**162**) (Xu et al. 2005). In addition to a sesquiterpene **88** and a diterpene **106**, Chinese *L. karlae* yielded another new nonhalogenated compound **163** (Zhong et al. 1996). Two simple epimers **164** and **165** with a methylcyclohexane backbone occurred as natural products in Chinese *L. composita* (Ji et al. 2010). Laurencione existing as a labile mixture of tautomers **166** and **167** was identified from Oregonian *L. spectabilis* by spectral analysis and chemical synthesis (Bernart et al. 1992; de Kimpe et al. 1995, 1996). Three pairs of enantiomers **168/169**, **170/171**, and **172/173** were identified from Chilean *L. chilensis*, and their structures were determined with the aid of X-ray crystallographic techniques (San-Martin et al. 1983, 1987; Bittner et al. 1987). These miscellaneous nonhalogenated constituents also exhibited high molecular diversity, which accounted for more than one tenth of the *Laurencia*-derived nonhalogenated organic molecules. Biogenetically, these nonhalogenated products were deduced to be formed without the participation of halogens.



Relationship between halogenated and nonhalogenated products

As discussed above and by Wang et al. (2013), some nonhalogenated organic molecules were possible precursors of halogenated products in biogenesis. They might be converted to halogenated derivatives by bromoperoxidase via a bromonium ion-initiated cyclization (Butler and Carter-Franklin 2004). If the corresponding enzymes were devoid, these nonhalogenated procursors were accumulated. For example, the polyenynes occurred in *L. composita*, but no oxygenated/halogenated C_{15}-acetogenins existed therein (Ji et al. 2008b). However, both of them were reported from *L. okamurai* and *L. nipponica*. On the other hand, some nonhalogenated products might be derived from the simple dehalogenation of their halogenated analogues, such as the nonhalogenated chamigrane and cuparane sesquiterpenes. Additionally, the dehalogenation process might be followed by cyclization and rearrangement to result in the transformation of some skeletons (González et al. 1975), exemplified by laurane, perforane, cyclolaurane, rearranged snyderane, etc. For some oxygenated nonhalogenated triterpenes and C_{15}-acetogenins, they might be derived from the same precursors as their halogenated analogues through the key 1,2-epoxy intermediates (Fernández et al. 2000; Abdel-Mageed et al. 2010). Except for the rearranged and cyclized skeletons from their possible halogenated precursors, those devoid of any halogenated members, represented by germacrane, humulane, precapnellane, aromadendrane, triquinane, steroid, and miscellaneous products, were likely produced without the participation of halogens and halidases. Thus, the nonhalogenated products from the genus *Laurencia* could be roughly divided into four goups according their relationship with halogenated ones, i.e. precursors, dehalogenated derivatives, analogues produced through 1,2-epoxy intermediates, and structures devoid of halogenated members. Experimental evidences to support the above speculation were limited so far (Butler and Carter-Franklin 2004), and the other biological techniques, such as isotopic labeling and genetic engineering, may be efficient to elucidate the relationship between halogenated and nonhalogenated metabolites.

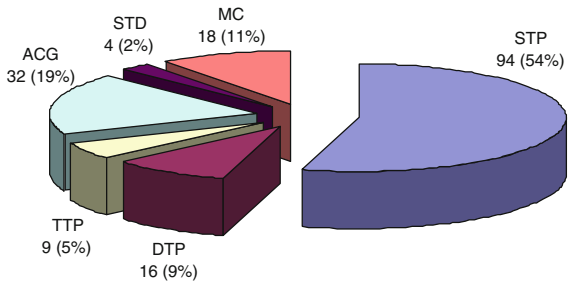


Fig. 2 Distribution of the 173 nonhalogenated organic molecules of *Laurencia* origin as shown by structural classes (*STP* sesquiterpenes, *DTP* diterpenes, *TTP* triterpenes, *ACG* C_{15}-acetogenins, *STD* steroids, *MC* miscellaneous compounds)

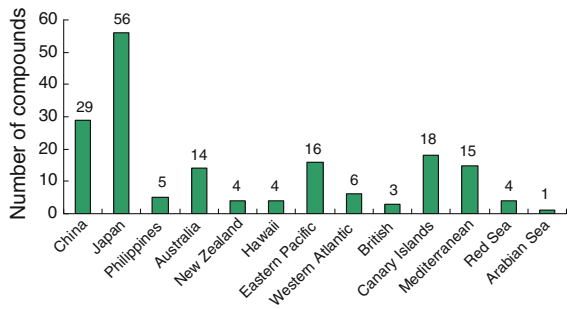


Fig. 3 Geographic distribution of the 173 nonhalogenated organic molecules of *Laurencia* origin as shown by sampling sources (**13** was reported from Italy and Australia simultaneously, and **40** was reported from China and Greece simultaneously)

Concluding remarks

Overall, 173 nonhalogenated organic molecules with 58 frameworks have been produced by 34 *Laurencia* species and three unidentified ones. Sesquiterpenes represented the most prolific type (94, 54 %) with 14 backbones devoid of any halogenated members (Fig. 1), followed by C_{15}-acetogenins (32, 19 %), miscellaneous compounds (18, 11 %), diterpenes (16, 9 %), triterpenes (9, 5 %), and steroids (4, 2 %; Fig. 2). Geographically, algal samples collected from Japanese and Chinese seawater produced almost half of the total nonhalogenated organic molecules (85, Fig. 3), and ten species led by *L. nipponica* stood out as the major sources (115, 66 %; Table 1). Additionally, the same species collected from different locations often exhibited varied metabolic profiles. Spectroscopic techniques including NMR, X-ray, IR, UV, ECD, and mass spectra and chemical methods involving simple transformation and total synthesis as well as computational simulations based on MM2 force field and quantum chemistry were applied to the structure elucidation of these nonhalogenated products, and more than fifty of them were assigned absolute configurations. Additionally, almost a quarter of these compounds were biologically assayed, and several have been found to possess potent activities, such as cytotoxic, antimicrobial, feeding-deterrent, brine shrimp lethal, and antialgal properties.

Table 1 Distribution of nonhalogenated organic molecules produced by the ten most productive species of the genus *Laurencia*

Species	Structural class						
	STP	DTP	TTP	ACG	STD	MC	Total
L. nipponica	13	–	–	16	–	–	29
L. obtusa	18	–	1	–	1	–	20
L. okamurai	10	–	1	4	–	–	15
L. majuscula	6	–	–	3	1	–	10
L. viridis	1	2	6	–	–	–	9
L. tristicha	8	–	–	–	–	–	8
L. subopposita	4	–	–	2	–	–	6
L. nidifica	5	–	–	–	–	1	6
L. chilensis	–	–	–	–	–	6	6
Laurencia sp.[a]	–	6	–	–	–	–	6
Total	65	8	8	25	2	7	115

STP sesquiterpenes, *DTP* diterpenes, *TTP* triterpenes, *ACG* C_{15}-acetogenins, *STD* steroids, *MC* miscellaneous compounds

[a] Collected from Canary Islands

These nonhalogenated organic molecules have played an important role in understanding the procedure and significance of biosynthesis for the halogenated ones as well as the molecular diversity of the genus *Laurencia*. It is interesting that some backbones of the halogenated and nonhalogenated organic molecules are assembled by preceding or following halogenations, but most of the biosynthetic pathways are only limited to speculation nowadays. Given the high number (at least 135) of *Laurencia* species (Masuda et al. 1996), a large amount of other organic molecules will continue to be characterized from this genus in future. They are hopeful to provide more candidates for the development of new marine drugs and functional agents, and unambiguous structure elucidation and extensive bioassay using updated spectroscopic techniques and pharmacological models will be the key points. What is more, the exploration of biosynthetic pathways, environmental influence, and commercial application will highlight the research on the seonday metabolism of *Laurencia* algae.

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