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Review Article

C_{15} acetogenins from the *Laurencia* complex: 50 years of research – an overview

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ABSTRACT

Acetogenins are secondary metabolites derived from the polyketide pathway and their potential role as chemotaxonomical markers for red algae belonging to the *Laurencia* complex has been long pointed out. C_{15} acetogenins from algae are quite different from plant acetogenins: they are usually halogenated, and have an enyne or a bromoallene terminal group. Since they were first reported, laurencin and other algal acetogenins have inspired great curiosity among natural product chemists and also those working with synthesis. This paper reviews the literature about C_{15} acetogenins, focusing on their distribution, chemical and biological aspects, including their reported biological activities.

Introduction

Acetogenins are a large group of nonterpenoid molecules that originate in the polyketide pathway (Dembitsky et al., 2003). They are relatively common in certain plant families, especially Annonaceae, and are well known for their biological activities. Annonaceous acetogenins are larger molecules (C_{35} or C_{37}) bearing ether groups, but usually no halogen (Liaw et al., 2010). Among marine algae, acetogenins are mostly halogenated, and are generally thought to originate from a common C_{15} precursor derived from a C_{16} fatty acid (Wang et al., 2013). Acetogenins are recognized as chemotaxonomic markers for red algae belonging to the family Rhodomelaceae, in particular, to the genus *Laurencia* (Stout and Kubanek, 2010).

It is well known that halogenated metabolites are abundant in red algae, especially in *Laurencia* (Fenical, 1981). Nevertheless, its taxonomy is considered a challenge, and has undergone substantial revision. This genus has been substantially divided since its original description in the 19th century, and the different genera accepted as components of the *Laurencia* complex have been distinguished as: *Laurencia* sensu stricto, *Palisada*, *Chondrophycus*, *Yuzurua* and *Osmundea* (Furnari et al., 2001). A further monospecific genus was recently added: *Laurenciella* (Cassano et al., 2012).

Despite of a few linear compounds, most algal C_{15} acetogenins are cyclic ether metabolites with different ring sizes and a conjugated enyne (C=C–C≡CH) or bromoallene (C=C=CHBr) terminus. Until the 1960s, alkyne groups were considered to be rare in the nature, but nowadays, it is well known that compounds with the acetylenic group are also prevalent in marine organisms, particularly microrganisms and sponges, such as *Petrosia* polyacetylenes ranging from C_{44} to C_{47} (Minto and Blacklock, 2008).

Currently there are more than 22,000 compounds derived from marine macro- or microrganisms and some molecules are quite stunning in their complexity (Carter and Crews, 2011). There have been comprehensive reviews of marine natural products organized phylogenetically, which are published annually (Blunt et al., 2015 and previous reports in this series). There are also reviews in the literature on marine polyacetylenes (Legrave et al., 2015), bioactive compounds from marine invertebrates (Datta et al., 2015), and halogenated metabolites from *Laurencia* (Cabrita et al., 2010), but these do not focus on acetogenins, or else they omit some important points about this group of metabolites. Nevertheless, some intriguing acetogenin structures have inspired several groups of chemists to explore this field, through both

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biosynthetic and synthetic approaches, with the two approaches frequently converging. Dembitsky et al. (2003) reviewed the literature on acetogenins up to 1999, but since then, a number of new acetogenins have been described in the literature, and the structures of some known compounds have been revised (Suyama et al., 2011). Wang et al. (2013) included acetogenins in their review of halogenated metabolites from Rhodomelaceae, but excluded the non-halogenated metabolites and did not consider the taxonomic review of the genus *Laurencia*. The present review aims to provide a general overview of 50 years of chemical and biological research on algal acetogenins, including their distribution, structural features, biological activities and potential ecological roles, highlighting new compounds isolated in the last 15 years, as well as the taxonomic aspects of the *Laurencia* complex.

First reports

Laurencin (**1**) was isolated from an alga identified as *Laurencia glandulifera* collected in Japan, and it was the first C_{15} acetogenin to be reported (Irie et al., 1965). Since its isolation, 50 years ago, more than 200 acetogenins have been described, mostly of the family Rhodomelaceae (Dembitsky et al., 2003; Wang et al., 2013), which includes the *Laurencia* complex, but also from sea hare (in this case, a dietary origin is assumed).

It is noteworthy that the structure elucidation of the first acetogenin was based on careful and systematic analysis, with combination of partial structures deducted from relatively few spectral data (by today's standards): ^{1}H NMR, MS, infrared (IR) and strongly on derivatization procedures with analysis of successive reaction adducts to eliminate other possible hypotheses (Irie et al., 1965, 1970).

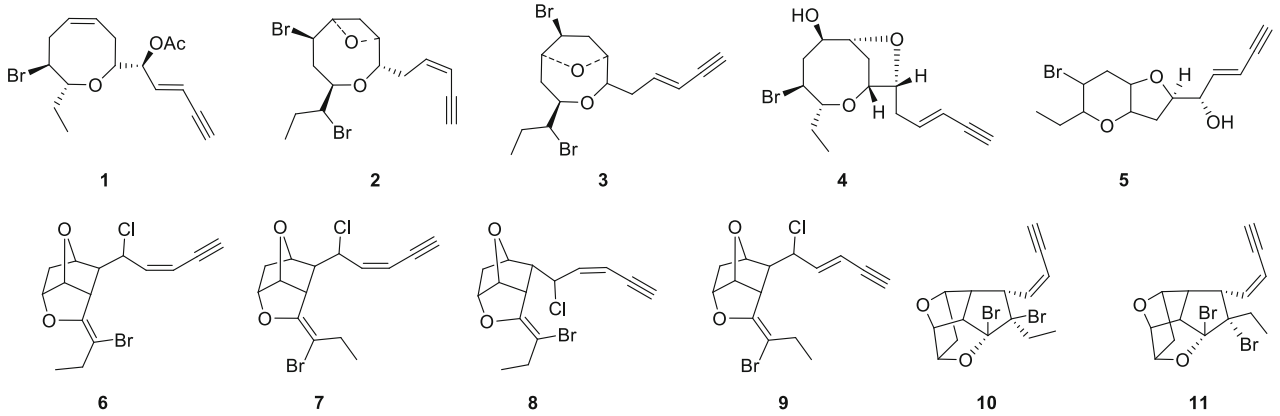
The characteristic bands in the infrared (IR) spectra are still useful for diagnosis: about 3300 cm^{-1} for (≡C—H) and from 2000 to 2300 cm^{-1} for (C≡C) of enyne or about 2000 cm^{-1} for (=C=C) of allenic compounds. The NMR signals for the enyne are also characteristic, ranging from 2.7 to 3.1 ppm for the alkyne proton and about 75–83 ppm for the carbons on the triple bond (Rücker et al., 2001; Gutiérrez-Cepeda et al., 2011a,b). The bromoallenic partial structure (BrHC=C=CH—) can be recognized by the characteristic chemical shifts of the carbon atoms: approximately 70 ppm for C-1, about 200 ppm for C-2, and about 100 ppm for C-3; the hydrogen atoms of C-1 and C-3 correlate with a coupling constant of about 6 Hz (Gutiérrez-Cepeda et al., 2011a,b).

In the 1960s, these structural features were not common, therefore it is not surprising that laurencin (**1**) and the subsequent isolated acetogenins attracted great curiosity from natural product chemists. Besides spectral data from natural compounds and their derivatives, total synthesis became a common approach to structure confirmation, and some Japanese groups developed expertise in acetogenin chemistry. Irie et al. (1970) reported also the isolation of laureatin (**2**) and isolaureatin (**3**) a few years later, with a similar approach to the one used for laurencin (**1**).

Some difficulties emerged concerning the new natural product class after the structure of laurefucin, isolated from *Laurencia nipponica* Yamada (Fukuzawa et al., 1972), was revised 1 year later (Furusaki et al., 1973), when X-ray crystallography established the absolute configuration, and showed that the molecule has an oxolane ring (**4**) instead of the initially proposed structure (**5**).

In a very interesting review, Faulkner (1977, p. 1423) commented about the acetylenes isolated from red algae: "...it is not surprising that several incorrect structures were corrected using X-ray analysis... Because the signals due to protons α to oxygen, bromine and chlorine often occur in the same region of the spectrum, it is difficult to assign signals in this region, even though it may be possible to determine all vicinal and geminal relationships between protons through careful spin decoupling. ... the major problem was to determine which four of six possible methine carbon atoms were involved in ether linkages and to determine the ring sizes".

The maneonenes (**6**–**9**) and isomaneonenes (**10** and **11**) groups were reported in the 1970s (Waraszkiewicz et al., 1976; Sun et al., 1976). By the early 1980s, there were about 25 described acetogenins, including some discovered out of Japan, like that of a *Laurencia* species from the Gulf of California, Mexico (Fenical, 1981). When Erickson (1983) reviewed constituents of *Laurencia*, she dedicated about a quarter of her chapter to acetogenins that were already considered chemical markers of this genus. It was recently estimated that acetogenins represent 26% (180) of 697 halogenated molecules of Rhodomelaceae origin (Wang et al., 2013) and about 18% (32) of 173 non-halogenated metabolites from the complex *Laurencia* (Ji and Wang, 2014).



Classification of acetogenins

Acetogenins are generally classified based on structural features such as the presence of rings and their size, or the nature of the terminal group (enyne or bromoallene). Besides the C_{15} acetogenins, a few C_{12} acetogenins have also been reported in algae so far (Li et al., 2012; Liang et al., 2012).

Since most acetogenins bear bromine and chlorine atoms, the presence of one or another type of halogen as a criterion for classification is not useful, but bromine atoms are more

prevalent. One of the few exceptions is the class of linear acetogenins.

Linear

This class of compounds was reported in just a few species, and includes non-halogenated (Kigoshi et al., 1986; Ji and Wang, 2014) and halogenated metabolites (Ji et al., 2009). Most halogenated linear acetogenins bear a chlorine at C-6, an oxygenated group at C-7, and *Z*-geometry at the isolated double bonds (Wang et al., 2013).

Tetrahydrofuran

This class was reported mainly for *L. nipponica*, *Chondrophycus glandulifer* (as *L. glandulifera*) and *L. obtusa*. Most compounds in this group present a *cis*- or *trans*-enyne as terminus, like in laureepoxide (**12**), but some bromoallenes are also seen. The compounds are generally brominated, but some have chlorine as the only halogen atom, while others are bromochlorinated. Because the side chain bears small rings it is easier, in this group (than in more complex acetogenins), to identify the original acyclic compound that could be the precursor before the cyclization through the hydroxyl groups in the side chain.

Bis-tetrahydrofuran

This class was reported for *Laurencia* species distributed from the Mediterranean Sea to the Pacific Ocean. Again, most compounds are brominated, and enynes are more prevalent than bromoallenes. The structure of at least three compounds of this group was revised after achieving total synthesis, *e.g.* elatenyne (previously reported as **13**, had its structure revised to **14**) (Suyama et al., 2011). It is notable that acetogenins with partial structures 2,2′-bis-tetrahydrofuran and 2,7-dioxabicyclo[4.4.0]decane present the same C and H connectivity, therefore unambiguous structure elucidation by NMR analysis alone is quite a challenge (Faulkner, 1977).

2,6-Dioxabicyclo[3.3.0]octane and 2,7-dioxabicyclo[4.3.0]nonane

Obtusin (**15**) was the first member to be described for the dioxabicyclooctane class, which includes just over ten compounds, mostly bromoallenic compounds, and was mainly found in *L. obtusa* and *L. intricata*. The second class includes the very unstable japonenynes A–C (**16**–**18**) from *L. japonensis* (Takahashi et al., 1999).

Tetrahydropyran

Just few members of this six-membered cyclic ether class have been reported for the *Laurencia* complex to date: scanlonenyne (**19**) from *L. obtusa* (Suzuki et al., 1997) and bisezakyne B (**20**) from an undescribed Japanese *Laurencia* (Suzuki et al., 1999). Some acetogenins belonging to this class have been reported for *Aplysia* species, such as the dactylyne-related compounds (see *Acetogenins of sea hare*).

Seven-membered cyclic ethers

These acetogenins may be monocyclic (oxepane) or bear an additional 6,9-epoxide ring, as in isoprelaurefucin (**21**). Most compounds are dihalogenated and have an enyne as the terminal group (Kurosawa et al., 1973).

Eight-membered cyclic ethers

This class is the most abundant, including the first reported acetogenin, laurencin (**1**), as well as more than 70 other metabolites. According to the ring closure system (which might include epoxy rings in different positions and different terminal groups), it can be divided into seven subclasses (Wang et al., 2013).

Nine- to 12-membered cyclic ethers

Acetogenins of these classes may also contain epoxy ring systems, and have been found among other species in *L. obtusa*, *L. okamurae*, *L. nipponica*, *Osmundea pinnatifida* (as *L. pinnatifida*) and *Laurencia intricata* (as *L. implicata*), which afforded the only known 10-membered cyclic ether (**22**) (Coll and Wright, 1989 apud Wang et al., 2013). Most 12-membered cyclic ethers were reported for *L. obtusa*, but so far, there have been no reports of 11-membered cyclic ethers (Wang et al., 2013).

Maneonenes and isomaneonenes

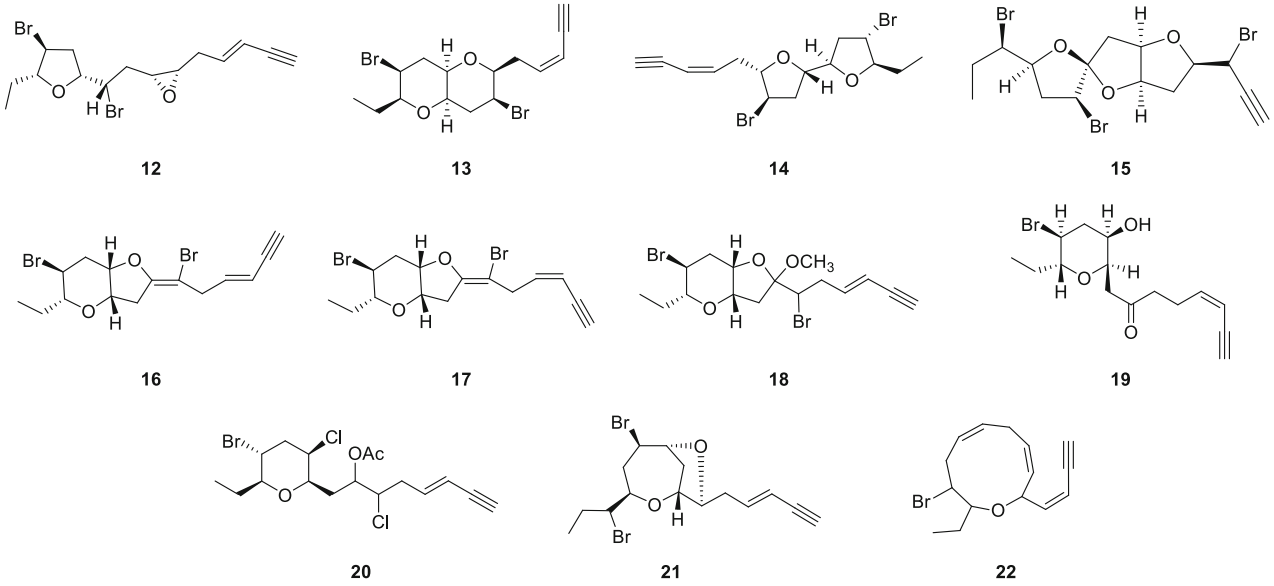
This class differs from the other because the carbon chain cyclises back on itself to form a carbocyclic ring in maneonenes (**6**–**9**) (Waraszkiewicz et al., 1976, 1978; Sun et al., 1976) and biscarbocyclic rings in isomaneonenes (**10**–**11**) (Waraszkiewicz et al., 1978). Both classes were first described for *L. nidifica* from Hawaii.

Branched

These acetogenins have been so far reported just for *L. microcladia* from Il Rogiolo, Italy, and the compounds were named after it as “rogiolenynes” (Guella et al., 1992b; Guella and Pietra, 1991).

Miscellaneous

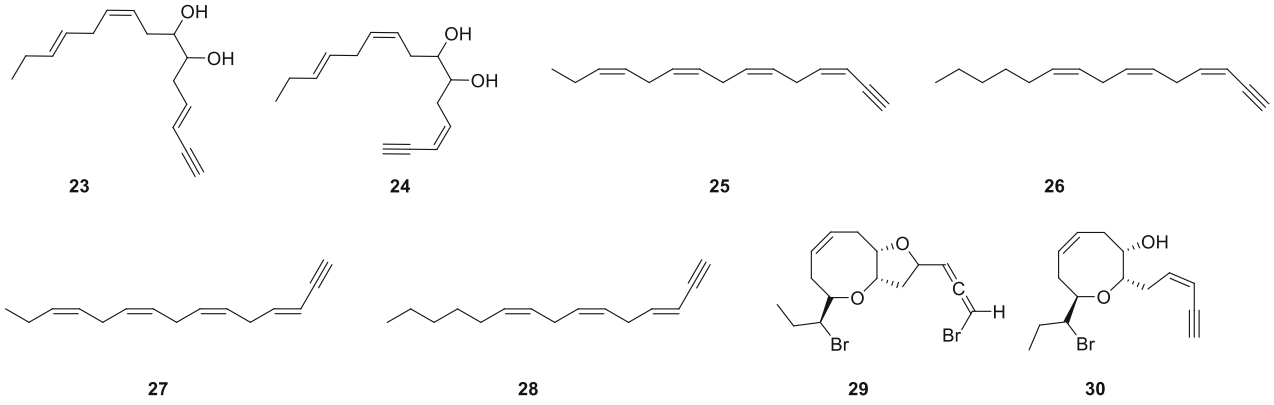
This class includes a few compounds with unusual bicyclic structures, such as the ones that have been isolated from *L. obtusa* collected in the Canary Islands, and from *L. dendroidea* (as *L. majuscula*) collected in Australia (Norte et al., 1989a,b; Wright et al., 1993).



Biosynthesis

Kurosawa et al. (1972) isolated from *L. nipponica* the nonhalogenated *trans*- and *cis*-laurediols (**23** and **24**), which were regarded as biosynthetic precursors of various nonterpenoid C_{15} metabolites. Four acetylenic polyenes (**25**–**28**) closely related to laurediols (**23** and **24**) were isolated from *L. okamurae* (Kigoshi et al., 1986) and were also found to be of biogenetic significance.

Due to the complex variations that acetogenins may present, each structural group required specific studies, but those early findings were essential to establish the first common steps of the biosynthetical process.



Eight-membered cyclic ethers are the most abundant and structurally diverse C_{15} acetogenins. They can be divided into two subclasses: lauthisan type, as laurencin (**1**) and laurenan type, as laureatin (**2**) and laurallene (**29**) (Sugimoto et al., 2007). A series of studies by the Murai group led to the proposal of a biogenetic pathway for laurenan compounds, including the bromo-cationic cyclization of an acyclic precursor *cis*-laurediol (**24**) to afford prelaureatin (**30**), which is converted to laureatin (**2**) and several bicyclic compounds by the subsequent bromo-cationic cyclization (Murai et al., 1977). Fukuzawa and Murai's proposed biosynthesis of various bromoethers stemming from bromonium ion is shown in Scheme 1. Murai has also shown that lactoperoxydase can catalyze the formation of 5-membered ethers from linear polyenes, as in Scheme 2 (Taylor and Fox, 2015). The idea that a transient bromonium species could be the intermediary key for the biosynthesis of several acetogenins, through intramolecular bromoetherification inspired other groups. According to this biogenetic pathway, the first total synthesis of laureatin (**2**) was proposed some years later (Sugimoto et al., 2007). Bromonium ions were also used recently to propose a bromine-induced skeletal rearrangement of an oxocene precursor to obtain the epoxy tetrahydrofuran laureepoxide (**12**) (Taylor and Fox, 2015).

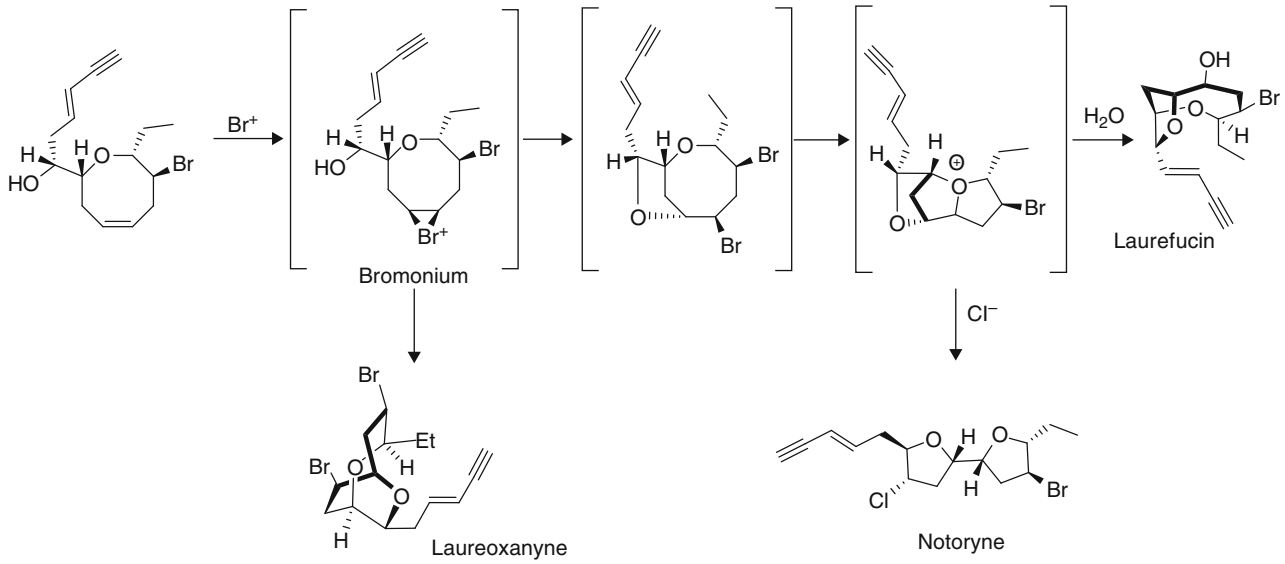
Distribution by species

Some algae species are particularly proficuous on the synthesis of acetogenins, like the ones highlighted above. Species not clearly identified, but that also contain interesting structures, are included on the topic "*Other species*".

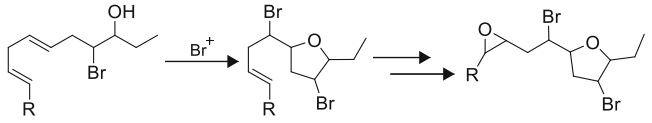
Chondrophycus glandulifer (as Laurencia glandulifera)

Laurencia glandulifera (Kützing) Kützing is a taxonomic synonym for *Chondrophycus glandulifer* (Kützing) Lipkin & P.C. Silva (current accepted name according to the Algaebase). It is reported mainly in Europe, but also in the Atlantic Islands (Canary and Madeira), Indian and Pacific Oceans, and Asia. In the Algaebase, there is just one record of this species collected in Japan (Guiry and Guiry, 2015).

Interestingly, Furnari et al. (2001, p. 351) reports concerning *L. glandulifera:* "According to Saito (1985) records of this species from Japan and adjacent areas should be referred to *L. nipponica* Yamada". Irie reported the first acetogenin from a sample identified



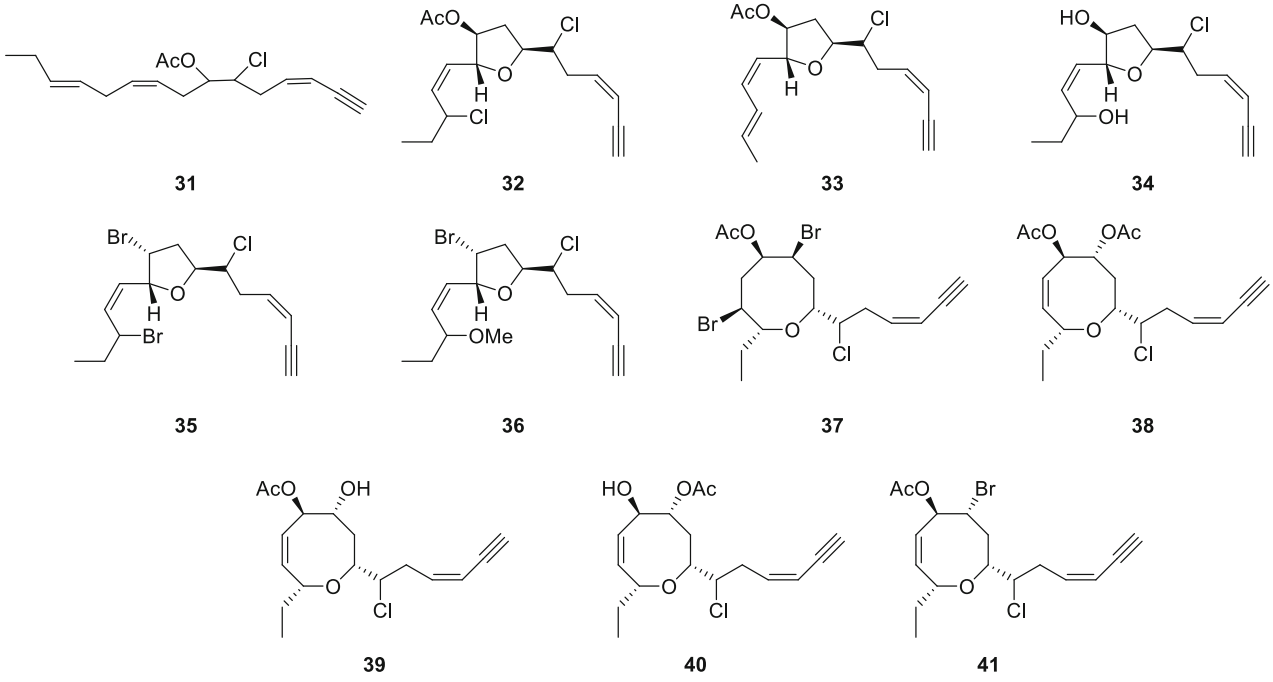
Scheme 1. Fukuzawa and Murai's proposed biosynthesis of various bromoethers stemming from bromonium.



Scheme 2. Proposed biosynthesis of brominated THF's from linear polyenes.

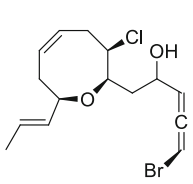
as *L. glandulifera*, collected in Oshoro Bay, Hokkaido, Japan (1965). In a paper on the biosynthesis of brominated metabolites, Suzuki and coauthors (2009) affirm that laurencin (**1**) was isolated from a chemical race of *L. nipponica* Yamada that was identified as *L. glandulifera* Kützing (see *Laurencia nipponica*). The sample afforded laurencin (**1**) in relatively high quantities (4.5 g from 8.5 kg dried alga according to Irie et al., 1968c), which allowed the scientists to perform several reactions until its structure elucidation (Irie et al., 1965, 1968c). Investigation of this compound with X-ray crystallography enabled its stereochemistry to be established (Cameron et al., 1965), and the first total synthesis of laurencin (**1**) in a racemic form was achieved in 1977 by Murai et al. (1977). Biological investigations showed that laurencin (**1**) prolonged pentobarbitone-induced sleep time in mice (Kaul et al., 2011).

From *Laurencia glandulifera* collected in the Mediterranean Sea (Crete Island, Greece), different acetogenins were reported: one linear (**31**), and a group of five tetrahydrofuran derivatives (**32**–**36**) (Kladi et al., 2009), as well as five other compounds (**37**–**41**) belonging to the same class as laurencin (**1**). Most exhibited significant antistaphylococcal activity against a panel of multi-drug and methicillin resistant *Staphylococcus aureus* (MRSA), with minimum inhibitory concentrations (MIC) in the range of 8–256 μg/mL (Kladi et al., 2008).



Laurencia chondrioides

L. chondrioides Børgesen is reported in Europe (mostly Mediterranean Sea), Atlantic Islands, Caribbean Islands, Israel and Philippines (Guiry and Guiry, 2015). The material collected in Kefalonia Island (Greece) was submitted to a dereplication approach using UHPLC-PDA-HRMS and 2D HSQC NMR. Two new bromoallene acetogenins were isolated: marilzallene B (**42**) and chondrioallene (**43**) along with known acetogenins 3-*E*-laurenyne (**44**), *trans*-pinnatifidenyne (**45**), obtusenyne (**46**) and obtusallenes II (**47**), III (**48**), V (**49**) and VI (**50**) (Kokkotou et al., 2014).



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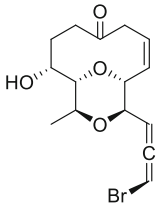

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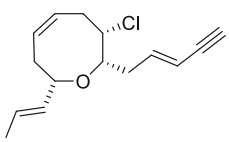

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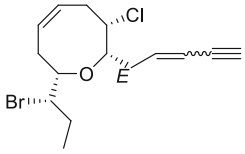

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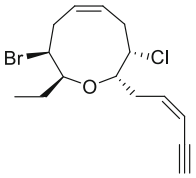

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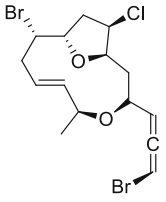

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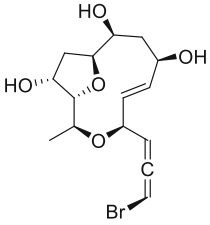

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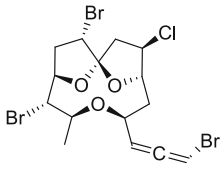

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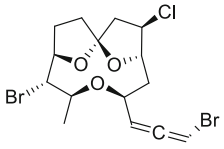

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Laurencia decumbens

L. decumbens Kützing (syn. *L. pygmaea* Weber – van Bosse) is reported in several locations of America, Africa, Asia and Oceania, but not in Europe (Guiry and Guiry, 2015).

According to Stout and Kubanek (2010) it is not common to see bromoallene and enyne metabolites co-occurring, but this was reported for *L. decumbens* from China, that besides elatenyne (**14**) presents laurendecumenynes A (**51**) and B (**52**) as well as laurendecumallenes A (**53**) and B (**54**) (Ji et al., 2007, 2010). Their structures and relative stereochemistry were established by spectroscopic analysis including 1D and 2D NMR techniques, but two compounds had their structures revised (Ji et al., 2010).

Laurencia elata

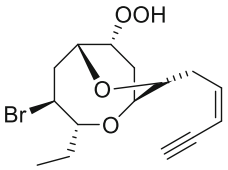
Laurencia elata (C. Agardh) J.D. Hooker & Harvey was reported in Africa, South-West Asia, Australia and New Zealand (Guiry and Guiry, 2015). Elatenyne was isolated in 1986 from *L. elata* and its structure deduced as **13** on the basis of ^{1}H and ^{13}C NMR spectroscopic analysis (Hall and Reiss, 1986). However, more recently elatenyne was isolated from sample of *L. elata* collected in St. Paul's Beach, Sorrento, Victoria (Australia), with 3-*Z*-chlorofucin (**55**) (Dias and Urban, 2011). In this case, the elucidation of elatenyne was performed in comparison with data reported by Hall and Reiss (1986); the relative configuration was revised to **14** using synthesis of several derivatives together with on and off resonance decoupling, double resonance and lanthanide shift NMR experiments (Brkljaca and Urban, 2013; Wright et al., 1993). Moreover, elatenyne has also been reported from the marine red algae *L. majuscula* (Wright et al., 1993) and *L. decumbens* (Ji et al., 2007).

Laurencia filiformis

Laurencia filiformis (C. Agardh) Montagne is found mainly in Australia and New Zealand, but it is also reported from Europe, Florida, Brazil, Belize (Central America), Tanzania, Pakistan, Japan, Indonesia and Pacific Islands (Guiry and Guiry, 2015). From *L. filiformis* collected along the western coast of Australia, eight-membered ether ring acetogenins were isolated, such as *cis*-dihydrorhodophytin (**56**) (Brennan and Erickson, 1982), also found in *Osmundea pinnatifida* (as *L. pinnatifida*) (Norte et al., 1989a), *Laurencia nangii* (Vairappan and Tan, 2009) and from mollusk species *Aplysia brasiliana* (Kinnel et al., 1979). The related metabolite *cis*-epi-dihydrorhodophytin (**57**) also was isolated from this species (Brennan and Erickson, 1982).

Laurencia intricata

Laurencia intricata J.V. Lamouroux occurs in the Pacific Islands, Asia, Australia, Europe and America (Guiry and Guiry, 2015). The acetogenin bermudenynol (**58**) and its acetate (**59**) were isolated from a sample collected in Castle Harbour, Bermuda; they are eight-membered cyclic ethers (Cardellina et al., 1982) as well as intricenyne (**60**), obtained from a sample collected at Key Largo, Florida (White and Hager, 1978).



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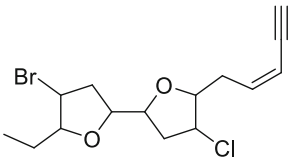

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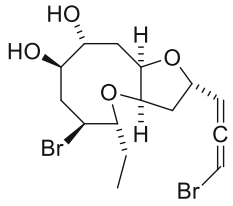

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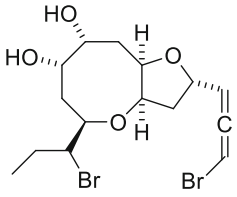

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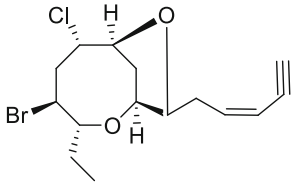

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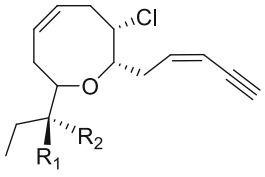
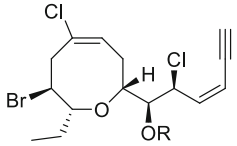


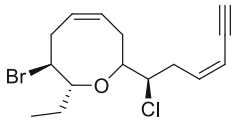
56 R_1 = Br, R_2 = H
57 R_1 = H, R_2 = Br

The samples collected in Japan presented acetogenins belonging to three different classes: tetrahydrofuran derivatives such as itomanallene B (**61**) and nine-membered cyclic ethers such as itomanallene A (**62**) (Suzuki et al., 2002). The total synthesis for itomanallene A (**62**) was obtained through intermolecular amide enolate alkylation and ring-closing metathesis (Jeong et al., 2010).

L. implicata J. Agardh is regarded as a taxonomic synonym of *L. intricata* J.V. Lamouroux, which is the correct name according to the Algaebase (Guiry and Guiry, 2015). There are two reports of studies under the non-correct epithet, both from Australia. The samples collected in Magnetic Island, Australia, presented acetogenins belonging to two different classes: eight-membered cyclic ethers such as 3-*Z*-bromofucin (**63**) and nine-membered cyclic ethers such as **64** (Coll and Wright, 1989 apud Wang et al., 2013). Two other acetogenins were isolated from material collected from Britomart Reef, Australia, also presenting eight- and nine-membered cyclic ethers such as **65** and **66** (Wright et al., 1991).



58 R=H
59 R= Ac



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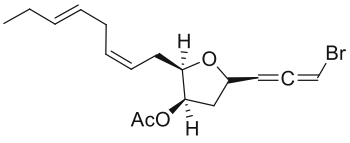

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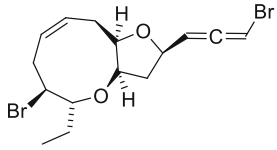

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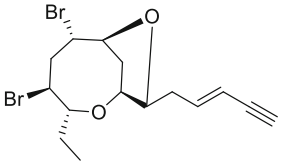

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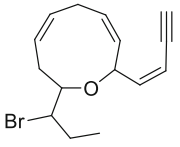

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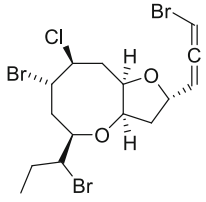

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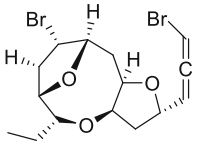

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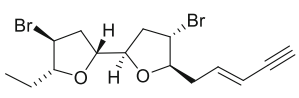
Laurencia majuscula

Laurencia majuscula (Harvey) A.H.S. Lucas is regarded as a taxonomic synonym of *L. dendroidea* J. Agardh, which is the currently accepted name, according to the Algaebase. This species was described in Europe; Atlantic Islands, Africa, Indian Ocean Islands; Asia (China, Japan, Korea); South-east Asia (Indonesia, Malaysia, Philippines, Vietnam); Australia, New Zealand and Pacific Islands (Guiry and Guiry, 2015).

For the species collected off the North coast of Oahu, Hawaii and the Holmes Reef, Queensland, Australia, at least seven acetogenins were reported. The material from Australia afforded an

acetogenin, **67** (Kim et al., 1989) which was totally synthesized through an efficient synthetic route for halogenated pyrano[3,2-b]pyrans (Sheldrake et al., 2006). Material from Hawaii afforded acetogenins belonging to the 2,2-bis-tetrahydrofuran class (**68),** two linear acetogenins (**69–70)** and three belonging to miscellaneous acetogenins (**71**–**73**) (Wright et al., 1993).



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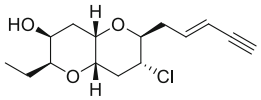

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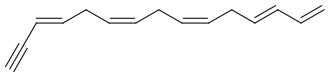

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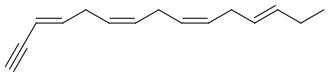

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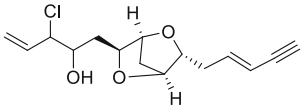

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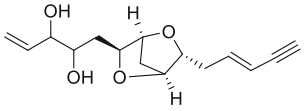

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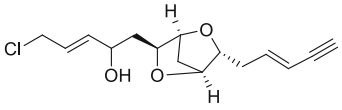
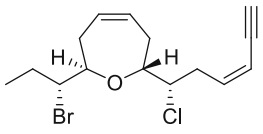


73

Laurencia microcladia

Laurencia microcladia Kützing occurs in the Atlantic Ocean, Pacific Islands, Asia, and Mediterranean Sea (Guiry and Guiry, 2015). The samples collected at Torrent Il Rogiolo, Italy, in the Mediterranean Sea presented acetogenins of the seven-membered cyclic ether class such as rogioloxepanes A–C (**74**–**76**) (Guella et al., 1992a), and branched acetogenins like rogiolenyne A–D (**77**–**80**) (Guella et al., 1992b; Guella and Pietra, 1991). Curiously, the rogiolenynes A–C (**77**–**79**) were also identified for a sponge species in the same area, which feed on the algae (Guella and Pietra, 1991). The sample collected in the French coast at Cape Ferrat, Mediterranean Sea presents the eight-membered cyclic ethers microcladallenes A and B (**81**–**82**) (Kennedy et al., 1984).



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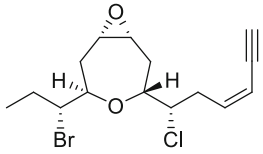

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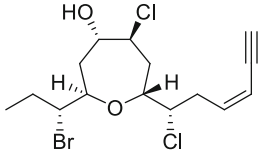

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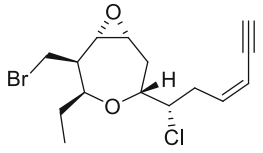

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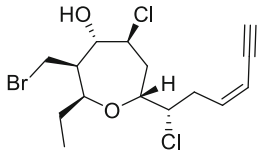

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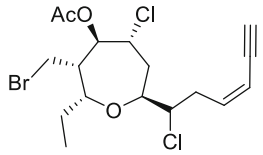

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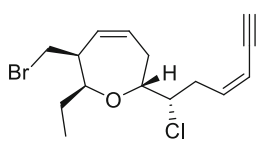

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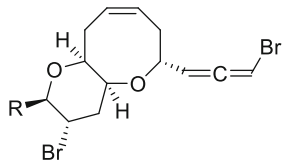


81 R= Et
82 R= CH=CH_2

Laurencia nidifica

Laurencia nidifica J. Agardh occurs mainly in the South Pacific and Indian Ocean, especially in Hawaii, but also in the Atlantic Islands, China, Australia and New Zealand (Guiry and Guiry, 2015). The sample collected from the Island of Oahu, Hawaii, presented *cis*-maneonene A (**6**) (Waraszkiewicz et al., 1976; Sun et al., 1976), *cis*-maneonene B (**7**) (Waraszkiewicz et al., 1976), *cis*-maneonene C (**8**) (Waraszkiewicz et al., 1978), *trans*-maneonene B (**9**) (Waraszkiewicz et al., 1976, 1978) and isomaneonenes A and B (**10** and **11**) (Waraszkiewicz et al., 1978). Holmes et al. (1983) reported the total synthesis of **10** and **11**; 1 year later, the same group synthesized **9** (Holmes et al., 1984). Laurenidificin (**83**) was reported for the species collected in Hainann Island, China, and belong to the 2,6-dioxabicyclooctane class (Liu et al., 2010).

Laurencia nipponica

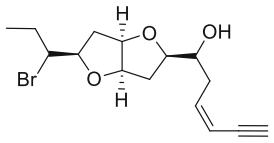
Laurencia nipponica Yamada, known in Japan by the name "Urasozo" (Irie et al., 1970) is reported only in Asian countries (Guiry and Guiry, 2015). Samples collected in Hakodate Bay Japan, presented specially acetogenins belonging to the eight-membered cyclic ether class, such as laureatin (**2**) and isolaureatin (**3**), which were obtained in relatively high quantities from the same extract and had their structures elucidated also by a combination of ^{1}H NMR, IR, MS and chemical reactions (Irie et al., 1970; Kurosawa et al., 1972). As occurred with laurencin (**1**), the structures were reported first (Irie et al., 1968a,b), and then more complete details of the isolation and structural elucidation were published (Irie et al., 1970). Total synthesis of both was achieved by Kim et al. (2007).

Further investigations led to the isolation of the eight-membered cyclic ethers deacetyllaurencin (**84**) (Kurosawa et al., 1972), prelaureatin (**30**) (Fukuzawa et al., 1991), laurefucin (**4**), acetyllaurefucin (**85**), (Fukuzawa et al., 1972) and laurallene (**29**) (Fukuzawa and Kurosawa, 1979).

L. nipponica also contains acetogenins belonging to the tetrahydrofuran class: laureepoxide (**12**) (Fukuzawa and Kurosawa, 1980), *trans*- and *cis*-kumausyne (**86** and **87**), *trans*- and

cis-deacetylkumausyne (**88** and **89**) (Suzuki et al., 1983c), laureoxolane (**90**) (Fukuzawa et al., 1989).

Some other acetogenins have also been reported: the seven-membered isoprelaurefucin (**21**) (Kurosawa et al., 1973) and neoisoprelaurefucin (**91**) (Suzuki et al., 1996a); the nine-membered isolaurallene (**92**) (Kurata et al., 1982; Furusaki et al., 1985); notoryne (**93**) belonging to the 2,2′-bis-tetrahydrofuran class (Kikuchi et al., 1991); the 2,6-dioxabicyclo[3.3.0]octane kumausallene (**94**) (Pradilla et al., 1998; Suzuki et al., 1983b); and the linear acetogenins *trans*- and *cis*-laurediols (**23** and **24**) (Kurosawa et al., 1972).



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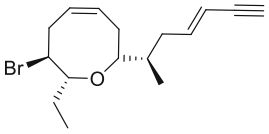

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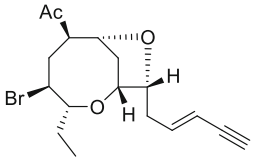

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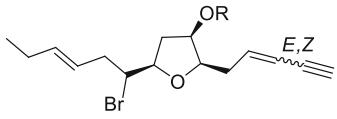
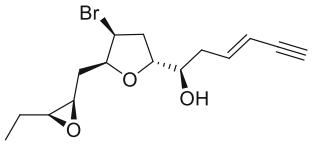


86 R = Ac, C3, *E*
87 R = Ac, C3, *Z*
88 R = H, C3, *E*
89 R = H, C3, *Z*



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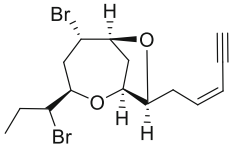

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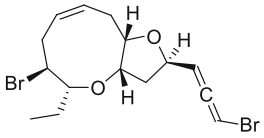

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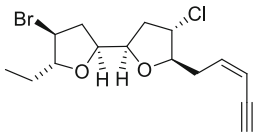

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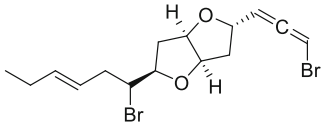


94

Pacific Islands (Guiry and Guiry, 2015). This species is the one with the highest number of isolated compounds for the genus *Laurencia*, including more than thirty acetogenins. These include compounds belonging to the tetrahydrofuran class, isolated from material collected in the Canary Islands, Spain, such as graciosin (**95**), graciosallene (**96**) (Norte et al., 1988) and also from the Red Sea, Egypt, such as hurgadenyne (**97**) (Ayyad et al., 1990). Two belong to the 2,2′-bis-tetrahydrofuran class: **98** from material collected in La Graciosa, Canary Islands, Spain (Norte et al., 1989b) and **99** from algae collected in Güvercinlik, near Bodrum, in the Mediterranean (Imre et al., 1995). Obtusin (**15**) was obtained from material collected in Tossa de Mar, in the Mediterranean, and belongs to the 2,6-dioxabicyclo[3.3.0]octane class; its structure was established by X-ray crystallography (Howard et al., 1979) and contains a bromoproparglyc terminus, a structural feature that was reported so far just for acetogenins from *L. obtusa* (as **95**, **98**, **106** and **107**).

This extraordinary chemical diversity may be explained by the occurrence of several races, which produce different major metabolites (sesquiterpenes or acetogenins) with a distinct range of geographical distribution (Masuda et al., 1997). The different populations were studied, also in crossability experiments, which also showed that . . .”occurrence of mixed types of metabolites between experimental interpopulation hybrids and several wild plants at the sympatric locality strongly suggests that the latter plants are natural hybrids between two chemically different populations”. Furthermore, the authors consider this finding “an answer to the question posed by Erickson (1983) . . . that species of *Laurencia* producing different sets of halogenated secondary metabolites may include several different species or varieties”. Based on Masuda’s group results (Masuda et al., 1997), Suzuki et al. (2009) used laurencin- and laureatin-producing races in their biosynthesis studies on *L. nipponica*.

Regarding the eight-membered cyclic ether class, some compounds, laureatin (**2**) and isolaureatin (**3**), showed insecticidal activity against mosquito larvae (*Culex pipiens pallens*) (Watanabe et al., 1989); isolaureatin (**3**) and laurefucin (**4**) prolonged sleep-time in mice induced by pentobarbitone (Kaul et al., 2011).

Laurencia obtusa

Laurencia obtusa (Hudson) J.V. Lamouroux is a species with widespread distribution worldwide. It was described in Europe, the Atlantic Islands, Central America, the Caribbean Islands, the Western Atlantic, South America, Africa, the Indian Ocean Islands, South-West Asia, South-East Asia, Australia, New Zealand and the

Obtusin (**15**) was obtained from material collected in Tossa de Mar, in the Mediterranean, and belongs to the 2,6-dioxabicyclo[3.3.0]octane class; its structure was established by X-ray crystallography (Howard et al., 1979) and contains a bromoproparglyc terminus, a structural feature that was reported so far just for acetogenins from *L. obtusa* (as **95**, **98**, **106** and **107**).

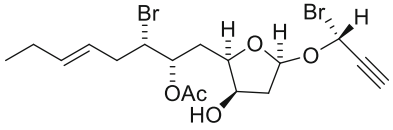
Scanlonenyne (**19**) was isolated from *Laurencia obtusa* collected in the Scanlon Islands, Ireland and belongs to the six-membered cyclic ether class (Suzuki et al., 1997). Eight-membered cyclic ether acetogenins were reported from algae collected in Sicily, in the Mediterranean, including laurencienyne (**100**), which was active against *Bacillus subtilis* and *Escherichia coli* (Caccamese et al., 1980); 3-*Z*-laurenyne (**44**), from material collected in Gökceada, in the Aegean Sea (Falshaw et al., 1980); epoxyisodihydrorhodophytin (**101**) was isolated from organisms found in the Sea of Marmara, Turkey, in the Mediterranean (Imre et al., 1987). From a collection in Symi Island, in the Aegean Sea, Greece, compounds **102**–**105** were obtained (Iliopoulou et al., 2002); from La Graciosa, in the Canary Islands, Spain, compounds **106** and **107** were reported (González et al., 1984; Norte et al., 1989b).

Obtusenyne (**46**) belongs to the nine-membered cyclic ether class and was obtained from two different collections in the Mediterranean Sea (King et al., 1979; Howard et al., 1980). More than 10 acetogenins of the 12-membered cyclic ether class were reported, mostly from collections in the Mediterranean: among them, obtusallene I (**108**) (Cox et al., 1982), obtusallenes II-IX (**47**–**50** and **109**–**112**) and kassallene (**113**) (Öztunç et al., 1991b; Guella et al., 1997, 2000).

Laurencia obtusa collected in the Saudi Arabia Red Sea Coast at Jeddah also afforded acetogenins from the maneonene class: 12-*Z*-*cis*-maneonene D (**114**), 12-*E*-*cis*-maneonene E (**115**), and 12-*Z*-*trans*-maneonene C (**116**); compounds **114** and **115** inhibited apoptosis of blood neutrophils, suggesting that they may be involved in regulation of programmed death in the initiation and propagation of inflammatory responses (Ayyad et al., 2011). Compound **117** belongs to the miscellaneous acetogenins and it was isolated from algae collected in La Graciosa, in the Canary Islands, Spain (Norte et al., 1989b).

Laurencia okamurae

Laurencia okamurae Yamada is found in Asia, Europe and some Pacific Islands (Guiry and Guiry, 2015). Most articles use the epithet name "*okamurai*", which is not considered correct. The main acetogenins found in samples collected in Hokkaido, Japan, belong to the 2,6-dioxabicyclo[3.3.0]octane class, such as okamurallene (**118**) (Suzuki and Kurosawa, 1981; Suzuki et al., 1989), deoxykamurallene (**119**) (Suzuki and Kurosawa, 1982), isookamurallene



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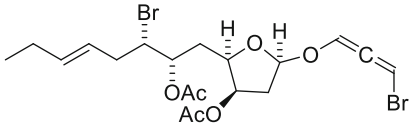

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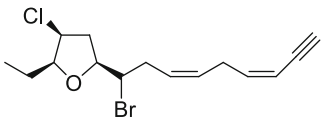

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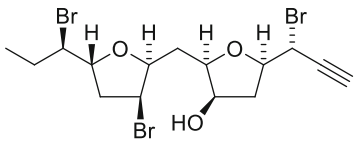

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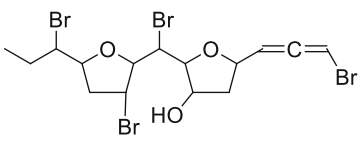

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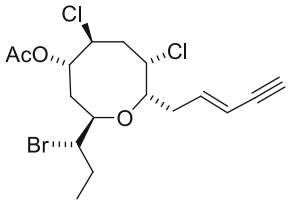

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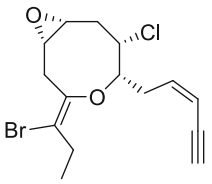

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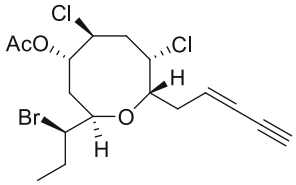

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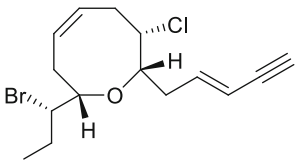

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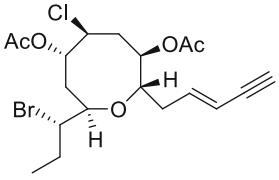

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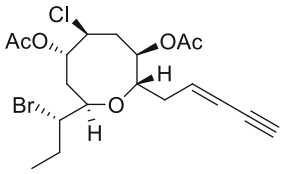

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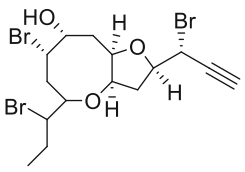

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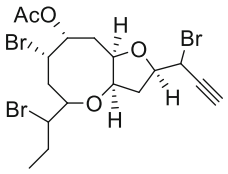

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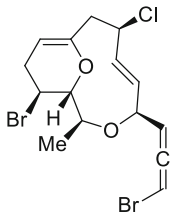

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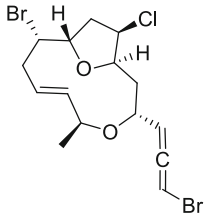

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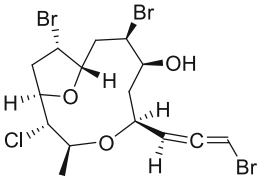

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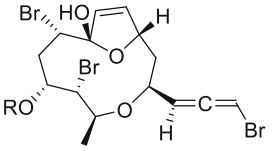
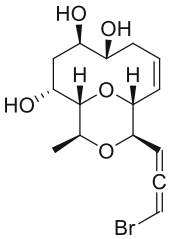


111 R= OH
112 R= Ac



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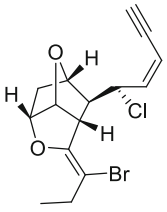

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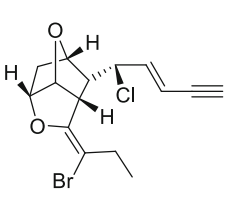

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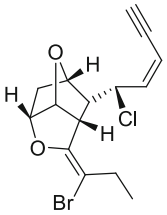

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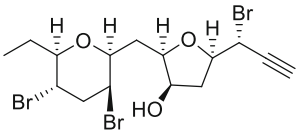
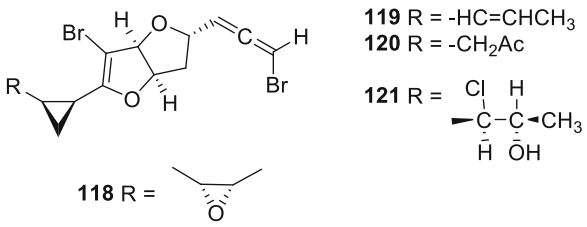


117

(**120**) (Suzuki and Kurosawa, 1982), and a chlorohydrin (**121**) that is an analogue of kamurallene (Suzuki et al., 1989). Their structures (**118**–**121**) were subsequently confirmed (Suzuki et al., 1991). Other metabolites were isolated from *L. okamurae*, also collected in Hokkaido Bay, Japan: neolaurallene (**122**) belongs to the nine-membered cyclic ether class (Suzuki et al., 1984; Ji et al., 2008), compound **123** is an eight-membered cyclic ether (Suzuki et al., 1989) and four acetylenic polyenes (**25**–**28**) considered to be of biogenetic significance (Kigoshi et al., 1986).



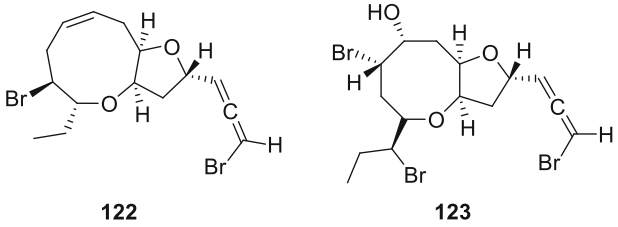
Laurencia pannosa

Laurencia pannosa Zanardini is reported in Asia (India, Taiwan, Indonesia) and Australia (Guiry and Guiry, 2015). Some acetogenins belonging to the eight-membered ether ring class were isolated in this species. From *L. pannosa* collected at An Thoi, Phu Quoc Island (Vietnam) 3-*E*-chlorofucin (**124**) and its dibromo-containing analogue (**125**) were isolated, together with the bromoallene pannosallene (**126**) (Suzuki et al., 1996b). The latter was subsequently reported in *L. okamurae* (Li et al., 2012) and *L. nipponica* as epilaurallene (Abe et al., 1999) and it was also reported for *L. nangii* (Kamada and Vairappan, 2012). Recently, compound **125** was also obtained by synthesis (Kim et al., 2012).

The isomer 3-*Z*-chlorofucin (**55**) was reported for this species in a sample collected in Pulau Talang-Talang Kecil (Kuching, Sarawak, Malaysia) (Suzuki et al., 2001). It was previously reported for *L. snyderae* (Howard et al., 1980; Young et al., 1980), red alga *Dasyphila plumariodes* (Denys et al., 1993), and also for unrecorded species collected at Pulau Nyireh, Terengganu (Malaysia) (Vairappan et al., 2008). Compound **55** was also isolated from *L. elata* (Dias and Urban, 2011) and showed antibacterial activity against *Chromobacterium violaceum* (Suzuki et al., 2001), but no appreciable antitumor activity (Dias and Urban, 2011).

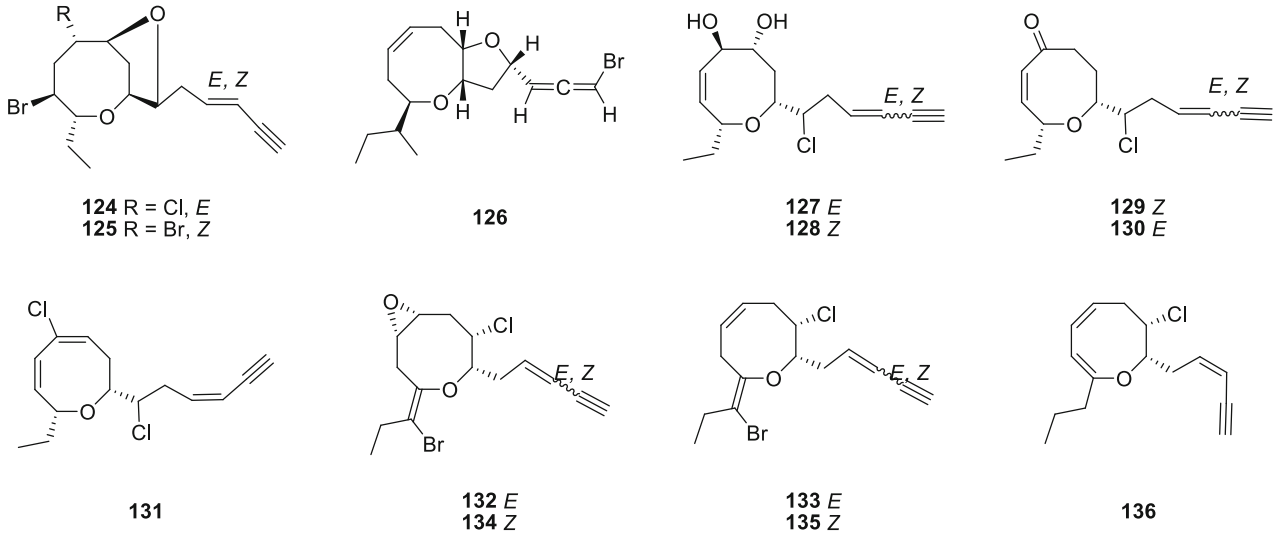
Laurencia snyderae

Laurencia snyderae E.Y. Dawson occurs in North America and South-West Asia (Guiry and Guiry, 2015). The eight-membered cyclic ether 3-*E*-chlorofucin (**124**) was isolated from a sample collected in La Jolla, California (Howard et al., 1980); it was also reported for *L. elata* (Dias and Urban, 2011), *L. pannosa* (Suzuki et al., 1996b) and other *Laurencia* species collected in Malaysia (Vairappan et al., 2008).



Laurencia thyrsifera

Laurencia thyrsifera J. Agardh was reported only in New Zealand (Guiry and Guiry, 2015) and some acetogenins belonging to the eight-membered ether rings class were isolated, as the vinyl acetylenic chloro diols isomers *trans* (**127**) and *cis* (**128**) from *L. thyrsifera* collected in coasts of the southern island of New Zealand (Blunt et al., 1981). These compounds differ from previously reported *Laurencia* cyclic ethers, since they are diols, and chlorine is the sole halogen. In addition, another unusual feature is that the chlorine is present as a side chain substituent at C-6 (Blunt et al., 1981). The isomer **128** was also reported from *Chondrophycus glandulifer* (as *L. glandulifera*), collected on the Island of Crete (Greece), and showed antibacterial activity against a panel of multi-drug and methicillin-resistant *Staphylococcus aureus* (MRSA) (Kladi et al., 2008). In addition, the isomeric keto ethers *cis*- (**129**) and *trans*-chloroketone (**130**) and a dichlorotrienyne (**131**) were reported for a sample collected in New Zealand (Blunt et al., 1984).

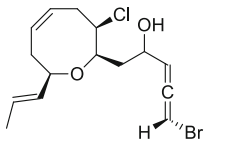


Laurencia venusta

Laurencia venusta Yamada was reported in America (Mexico, Brazil), Africa, Asia, Australia and New Zealand, and also in Pacific Islands (Fiji) (Guiry and Guiry, 2015). All acetogenins isolated so far from this species belong to the eight-membered cyclic ether class. The first reported acetogenins were venustin A (**132**) and B (**133**) (Suzuki and Kurosawa, 1980) obtained from a sample collected at Moheji, Hakodate Bay, Hokkaido (Japan). These metabolites were renamed as 3-*E*-epoxyvenustin and 3-*E*-venustin (Suzuki et al., 1983a), respectively. A related metabolite 3-*Z*-epoxyvenustin (**134**), major component comprising 10% of the extract, and also 3-*Z*-venustin (**135**) and 3-*Z*-venustinene (**136**) were reported in Japan for a sample collected at Moura, near Asamushi, Aomori Prefecture (Suzuki et al., 1983c).

Laurenciella marilzae (as Laurencia marilzae)

Laurencia marilzae was described some years ago as a new species of the genus *Laurencia* (Gil-Rodríguez et al., 2009), but after phylogenetic analyses it was reclassified as a new genus (*Laurenciella*), which is so far monospecific (Cassano et al., 2012). Therefore, the currently accepted name according to Algaebase (Guiry and Guiry, 2015), is *Laurenciella marilzae* (Gil-Rodríguez, Sentíes, Díaz-Larrea, Cassano & M.T. Fujii) Gil-Rodríguez, Sentíes, Díaz-Larrea, Cassano & M.T. Fujii. It has been identified in the Canary Islands, Southeastern Brazil and in the Mexican Caribbean (Cassano et al., 2012).



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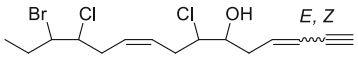
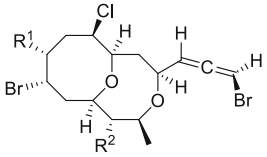
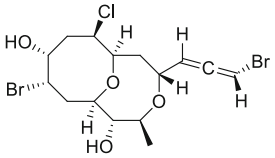


138 *Z* - isomer

139 *E* - isomer



140 $R^1 = R^2 = OH$
142 $R^1 = OCH_3$, $R^2 = OH$
143 $R^1 = R^2 = Cl$



141

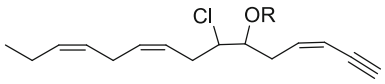
Co-occurrence of enyne and allenes was reported for *Laurenciella marilzae* collected in Tenerife (Canary Islands). Gutiérrez-Cepeda et al. (2011a) reported the isolation of eight new acetogenins (mostly eight- and 12-membered cyclic ethers), besides the known obtusallene IV (**109**). New compounds included marilzallene (**137**) and two acetoxy derivatives of it, besides linear acetogenins *Z*- (**138**) and *E*-adrienyne (**139**). The structural elucidation was obtained by the authors using HECADE experiment. A second report described new 12-membered cyclic ethers, marilzabicycloallenes A–D (**140**–**143**). The framework of these metabolites reinforced the hypothesis that biosynthesis of obtusallenes occurs through electrophilic bromination (Gutiérrez-Cepeda et al., 2011b).

Osmundea pinnatifida (as Laurencia pinnatifida)

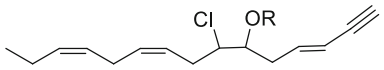
According to the Algaebase, the current accepted name for *L. pinnatifida* is *Osmundea pinnatifida* (Hudson) Stackhouse (Guiry and Guiry, 2015). This species was reported under its previous name in all continents, notably in the countries of Europe (Guiry and Guiry, 2015). In addition to linear acetogenins (**144**–**151**) (González et al., 1982; Norte et al., 1991), some acetogenins belonging to the eight-membered ether rings class were isolated from algae collected on the Island of Tenerife (Canary Islands), as the isomers *cis*- (**152**) and *trans*-pinnatifidenyne (**45**) (González et al., 1982; Norte et al., 1991) and *trans*- (**153**) and *cis*-dihydrorhodophytin (**56**) (Norte et al., 1989a), as well as structures with a nine-membered ether ring (**154** and **155**) (Norte et al., 1991). The absolute configurations of **152** and **45** have been reassigned on the basis of X-ray analysis (Norte et al., 1991), and **45** was isolated also from *Aplysia dactylomela* collected in the South China Sea (Manzo et al., 2005). Pinnatifidine (**156**) has been isolated from sample collected near Karachi, and represents the first diacetylated dibromo belonging to the eight-membered ether ring class (Atta-ur-Rahman, 1989). Metabolite *cis*-dihydrorhodophytin (**56**) presented antifeedant activity (Kinnel et al., 1979) and significant antibacterial activity against the tested food pathogens (Vairappan and Tan, 2009). Recently, the total synthesis of **152** (Kim et al., 2003) and **56** (Kim et al., 2011) was performed.

Yuzurua poiteaui (as Laurencia poitei)

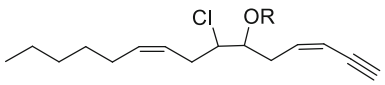
Laurencia poitei is regarded as a taxonomic synonym of *Palisada poiteaui* (J.V. Lamouroux) K.W. Nam, and of *Yuzurua poiteaui* (J.V. Lamouroux) Martin-Lescanne var. *poiteaui*; the latter is currently accepted taxonomically according to the Algaebase (Guiry and Guiry, 2015). *Yuzurua* (Nam) Martin-Lescanne was recognized as a genus in 2010 (Martin-Lescanne et al., 2010). *Y. poiteaui* is distributed in America, the Caribbean Islands, Africa, the Indian Ocean, Asia, Australia and New Zealand (Guiry and Guiry, 2015). There have been few investigations on it, but no report of chemical studies was found in the literature under this name up to date. The eight-membered cyclic ether poiteol (**157**) was isolated from a sample collected in Harris Park, Florida (Howard et al., 1980).



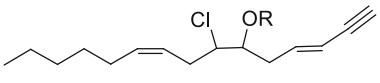
144 R = Ac
145 R = H



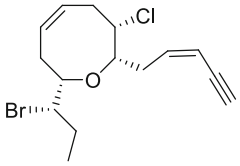
146 R = Ac
147 R = H



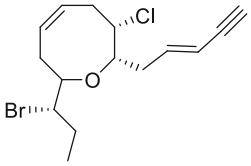
148 R = Ac
149 R = H



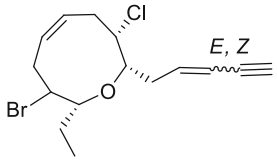
150 R = Ac
151 R = H



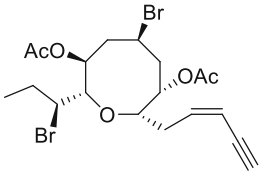
152 *Z*



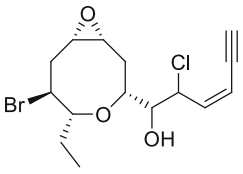
153



154 *E*
155 *Z*



156



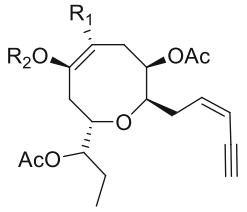
157

Other species

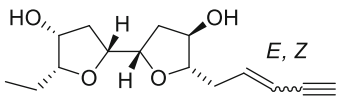
Investigations on *Laurencia* sp. cf. *L. gracilis* collected in New Zealand waters allowed the isolation of the first examples from *Laurencia* species of nonhalogenated C_{15} acetogenins (**158** and **159**) belonging to the eight-membered cyclic ether class (König and Wright, 1994). The related chlorine-containing metabolite **160** was also reported (König and Wright, 1994). No report under this name was found in the Algaebase (Guiry and Guiry, 2015).

A sample of *Laurencia* sp. from Philippines was reported to contain three diasteromeric pairs of cyclic ether acetogenins named laurefurenynes A–F (**161**–**166**). The structures were assigned on the basis of extensive 1D and 2D NMR experiments, NOESY and molecular modelling. The material was provided through collaboration with the American NCI (National Cancer Institute); laurefurenynes C (**163**) and F (**166**) were moderately cytotoxic against solid tumors and leukaemia L1210 cells, but non-selective (Abdel-Mageed et al., 2010). According to the authors, it was the first report of cytotoxicity for vinyl acetylenic acetogenins. Nevertheless, structures of laurefurenynes A (**161**) and B (**162**) were revised after new evidences based on DFT calculations and total synthesis (Shepherd et al., 2013; Holmes and Britton, 2013).

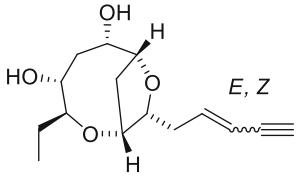
A non-identified *Laurencia* sp. from Malaysia afforded 12-*Z*-lembyne A (**167**) and lembyne B (**168**) (maneonene and isomaneone group, respectively), which were tested against 13 species of marine bacteria. 12-*Z*-Lembyne A (**167**) was active against some of them, such as *Chromobacterium violaceum*, *Clostridium cellobioparum* and *Vibrio parahaemolyticus* (Vairappan et al., 2001a). From another non-identified *Laurencia* sp from Malaysia, collected in a different place by the Vairappan group, about 2 years later, 3-*Z*-chlorofucin (**55**) and a bromoallene (**169**) were isolated (Vairappan et al., 2008).



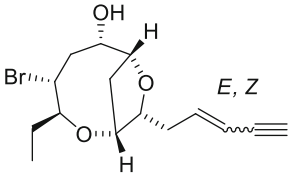
158 R_1 = OAc, R_2 = H
159 R_1 = OH, R_2 = Ac
160 R_1 = Cl, R_2 = Ac



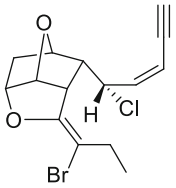
161 *Z* - isomer
162 *E* - isomer



163 *Z* - isomer
164 *E* - isomer



165 *Z* - isomer
166 *E* - isomer



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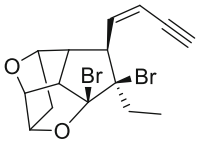
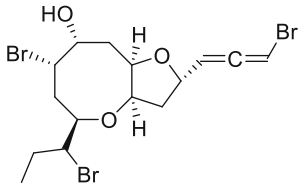


168



169

Acetogenins of sea hare

The sea hares, opistobranch mollusks belonging to the order Aplysiomorpha, are soft-bodied and slow-moving benthic marine animals. They are strictly herbivorous, usually feeding on a variety of marine algae, and with wide distribution in both temperate and tropical waters (Manzo et al., 2005; Ioannou et al., 2009). These mollusks have been proven to act as source of bioactive compounds that are often considered to be of dietary origin. The accumulation of secondary metabolites may play a role as a defense mechanism against predators, and this chemical relationship between sea hares and algae has been the object of interest among scientists (Manzo et al., 2005; Ioannou et al., 2009; Palaniveloo and Vairappan, 2014). Species belonging to the family Aplysiidae, including the genera *Aplysia*, have been studied, resulting in the identification of a large number of dietary metabolites, typically algal halogenated compounds (Blunt et al., 2015 and previous reports of this series).

Aplysia spp. are usually grazing species of the *Laurencia* complex, therefore a wide range of halogenated metabolites have been isolated from this mollusk. Different species collected from various locations have afforded new and known halogenated compounds, mainly terpenes and acetogenins (Ioannou et al., 2009), the latter being the focus of this review.

From specimens of *A. dactylomela* collected in the Bahamas, two acetogenins of the nine-membered cyclic ether class, 3-*Z*- and 3-*E*-12-*epi*-obtusenyne (**170** and **171**) have been isolated along with 3-*Z*- and 3-*E*-dactomelyne (**172** and **173**) (Gopichand et al., 1981). The *trans*-isomer (**173**) has been found as a metabolite of *L. obtusa* collected in Turkey (Aydoğmuş et al., 2004). Investigation of another collection, also in the Bahamas, afforded acetogenins of the hydropyran subclass: 3-*Z*-dactylyne and 3-*E*-isodactylyne (**174** and **175**) (McDonald et al., 1975; Vanderah and Schmitz, 1976); 3-*Z*-dactylyne has also been isolated from a *Laurencia* species from Japan (Suzuki et al., 1999) and has presented pronounced activity in increasing blood levels of pentobarbital in a dose-dependent manner. It increased both the half-life and the duration of action of the drug, possibly due to the inhibition of metabolic elimination of pentobarbital caused by 3-*Z*-dactylyne itself, or perhaps by a metabolite (Kaul and Kulkarni, 1978).

From specimens of *A. dactylomela* collected in Hainan Island, in the China Sea, other nine-membered cyclic ethers were reported, such as 3-*Z*- and 3-*E*-6R,7R-obtusenyne (**176** and **177**) (Manzo et al., 2005). Isomers of pinnatifidenyne (**152**, **153** and **178**), representatives of eight-membered cyclic ether acetogenins, were isolated from *A. dactylomela* (Manzo et al., 2005; Palaniveloo and Vairappan, 2014) and also from the algae *Osmundea pinnatifida* (as *L. pinnatifida*) (González et al., 1982) and *L. claviformis* (Norte et al., 1991). Some of the isomers were tested as feeding-deterrents against gold fish *Carassius auratus*, **178** presenting activity, as well as 3-*Z*-laurenyne (**44**), the last one being also toxic towards brine shrimp, but inactive when tested for antibacterial activity against marine bacteria (Manzo et al., 2005; Takahashi et al., 2002). The acetogenin **44** has been reported for *A. dactylomela* (Manzo et al., 2005) and for the alga *L. yanoguniensis* found in Japan (Takahashi et al., 2002). The latter was presented as a new species of *Laurencia*, but no report was found under this name at the Algaebase (Guiry and Guiry, 2015).

Palaniveloo and Vairappan (2014) collected samples of *A. dactylomela* from different islands of Malaysia, and isolated 12-*Z*-lembyne A (**167**), which was also reported for a non-identified *Laurencia* sp. from Malaysia (Vairappan et al., 2001a) and 12-*E*-lembyne A (**179**) which was also isolated from *L. mariannensis* from Japan (Vairappan et al., 2001b). Both presented prominent antibacterial activity against marine bacteria (Vairappan et al., 2001a,b). Dactylallene (**180**) was first reported for *A. dactylomela* from the Canary Islands; this compound has not been found in algae, but its diastereoisomer obtusallene II (**47**) has previously been isolated from *L. obtusa* (Ciavatta et al., 1997). Another compound found in *A. dactylomela* is *cis*-maneonene C (**8**) (Sakai et al., 1986), a metabolite first reported for *L. nidifica* (Waraszkiewicz et al., 1978).

Ioannou et al. (2009) investigated the chemical profile of the species *A. fasciata*, collected in Alfacs Bay, Catalonia, Spain. Two linear acetogenins (**182**) and (**144**) were identified; the first one is a new natural product and the latter was previously reported for *L. pinnatifida* from the Canary Islands (González et al., 1982; Norte et al., 1991). Ioannou et al. (2009) also identified three acetogenins of the eight-membered cyclic ether class: 3-*Z*-venustinene (**136**), previously isolated from *L. venusta* (Suzuki et al., 1983a); 3-*Z*-13-*epi*-pinnatifidenyne (**182**), previously mentioned for *A. dactylomela*, and 3-*E*-laurenyne (**44**), also isolated from *L. obtusa* (Öztunç et al., 1991a).

Aplysia brasiliana is considered a synonym for *A. fasciata* (accepted name according to the database WoRMS). Four acetogenins were reported for the species described as *A. brasiliana* collected in the Gulf of Florida, USA. Two of them are the diastereoisomers *cis*-dihydrorhodophytin (**56**) and *cis*-isodihydrorhodophytin (**183**) (Kinnel et al., 1979). Acetogenin **56** has already been identified as secondary metabolite of some *Laurencia* species (Brennan and Erickson, 1982; Norte et al., 1989a; Vairappan and Tan, 2009), and has shown antifeedant properties in bioassays with swordtail fish (*Xiphophorus helleri*) (Kinnel et al., 1977) and significant antibacterial activity against food pathogens, besides *Vibrio cholerae*, *Staphylococcus aureus*, *Escherichia coli*, *Salmonella enteritidis*, *S. typhi* and *S. thyphimurium* (Vairappan and Tan, 2009). Metabolite **183** has also been isolated from *L. obtusa* (Imre et al., 1981). Another two metabolites were isolated from material identified as *A. brasiliana*: brasilenyne (**184**) (Kinnel et al., 1979) and panacene (**185**) (Kinnel et al., 1977), whose complete structural elucidation was started by Feldman (1982) with the assignment of relative stereochemistry of the bromoallene portion achieved by Boukouvalas et al. (2006), when the first pathways for an asymmetric total synthesis were established. Brasilenyne (**184**) is a nine-membered cyclic ether and presented antifeedant activity in a bioassay with swordtail fish (Kinnel et al., 1979).

Other species of *Aplysia* presented acetogenins as secondary metabolites. Investigation of specimens of *A. oculifera* found in Sri Lanka and Oahu Island, Hawaii led to the isolation of three acetogenins, srilankenyne (**186**), *Z*- and *E*-ocellenyne (**187** and **188**) (Schulte et al., 1981; Silva et al., 1983). From *A. parvula* it was possible to identify a new acetogenin, aplyparvunin (**189**), a compound that presents ichthyotoxic activity, with LC_{100} of 3 ppm in 24 h (Myiamoto et al., 1995). The metabolite 3-*Z*-bromofucin (**63**) was also reported for *A. parvula* (McPhail and Davies-Coleman, 2005) and previously for *L. intricata* (as *L. implicata*) (Coll and Wright, 1989 apud Wang et al., 2013). For the species *A. kurodai* from the coast of Fukui, Japan, a new bromoallene with promising activity as Na, K-ATPase inhibitor has been reported and named as aplysiallene (**190**) (Okamoto et al., 2001). Its structure has been reviewed by Okamoto et al. (2003), and was found to be the same as a bromoallene isolated from *L. okamurae* (Suzuki and Kurosawa, 1985). In 2007, Wang and Pagenkopf achieved the total synthesis of aplysiallene, therefore its stereochemistry could be unambiguously reassigned.

Chemotaxonomy

Species discrimination within the *Laurencia* complex is considered very complicated, due to the high degree of phenotypic variation within species, and also to the fact that morphological features among the genera may be difficult to recognize even for specialists. It is no coincidence that many specimens have been misidentified and reported incorrectly. One such example is the algae that afforded laurencin for the first time, which was initially

identified as *L. glandulifera*, but was, in fact, *L. nipponica*, according to Suzuki et al. (2009). Therefore, halogenated secondary metabolites may be a useful taxonomic tool at the species level, after the investigation of the natural variability factors (Stengel et al., 2011). Fujii et al. (2011) reviewed the taxonomy and the major metabolites of the *Laurencia* complex from Brazil, and no acetogenin was reported for the species cited in the review, but those must be considered preliminary data.

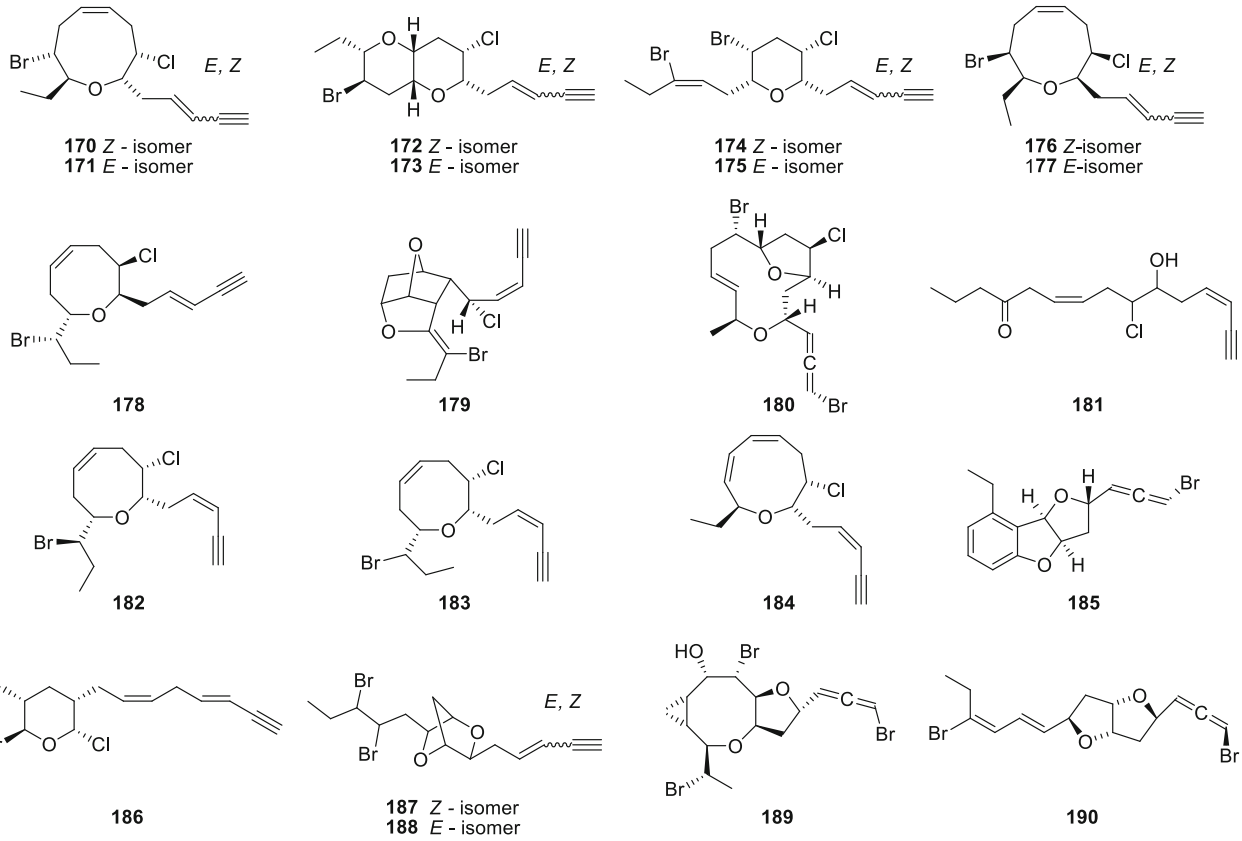
The confirmation of different races for *L. nipponica* could explain the extreme high chemical diversity observed for this species within the same geographical area.

The chemical differences between *L. okamurae* and *L. composita* have proven to be useful as an aid to the identification of these species. These two species are considered difficult to differentiate based on their morphological features alone; however, it was observed that the latter is not able to synthesize oxygenated and halogenated acetogenins (possibly due to the lack of the enzyme activity necessary for oxygenating/halogenating enynes), while *L. okamurae* afforded several complex acetogenins (Ji et al., 2009).

Investigations performed in the last 5 years with the species *L. chondrioides* and *Laurenciella marilzae* suggest that the co-occurrence of enynes and bromoallenes might be more common than was first thought, therefore the type of linear or cyclic structure may be more relevant in a chemotaxonomical approach than the type of terminus. Nevertheless, it is noteworthy that compounds with bromoparglyc terminus have been reported so far just for *Laurencia obtusa*.

and sequester halogenated secondary metabolites from their diet (Kladi et al., 2014). Curiously, many of them were first reported for sea hare, and some later found in algae. This may suggest these metabolites are not very efficient as feeding-deterrent for mollusks, but it is not clear whether they are active against other potential predators. The natural function of most marine secondary metabolites remains uninvestigated, but it has been demonstrated that many secondary metabolites, such as alkaloids, sterols and terpenes, among other metabolites, can play a role in the defenses against consumers, competitors, fouling organisms, etc. (Hay, 1996; Maia et al., 1999; Coutinho et al., 2002; Epifanio et al., 2006). It must be established whether acetogenins are included or not among these chemical defenses for the algae, but they seem to be for *Aplysia* spp (Kinnel et al., 1977, 1979; Vairappan and Tan, 2009).

In a general way, the biological activities were assayed just for a few compounds, probably due to the relatively low amounts usually isolated in the studies reported here. Laurencin, laureatin and isolaureatin were exceptions, but in these cases, the amount of algal material used as the basis for the investigations was over 10 kg of dried algae (Irie et al., 1965, 1970), considering that the available structure elucidation methods at that time consumed up to grams of isolated compounds. Another point is that some acetogenins, such as elatenyne, are unstable (Dias and Urban, 2011).



Biological activities

Metabolites isolated from algae belonging to the *Laurencia* complex have exhibited marked antibacterial, insecticidal, antifungal, and antiviral activity, but the activity of terpenes is more widely investigated than that of acetogenins. Sea hares of the genus *Aplysia* (Anaspidea, Aplysiidae) are known to prey on *Laurencia*,

The most common biological activities described for acetogenins include antibacterial activity towards different microorganisms. Chart 1 presents some biological activities reported for acetogenins primarily isolated from algae, while Chart 2 summarizes the main biological activities reported for acetogenins primarily isolated from sea hare.

Species	Compounds	Biological activities
Chondrophycus glandulifer = L. glandulifera	133-36	Prolongs sleep-time by pentobarbitone (Kaul et al., 2011)
		Antistaphylococcal (MRSA) (Kladi et el., 2008)
L. elata	55, also isolated from *L. pannosa*	Antibacterial activity against *C. violaceum* (Suzuki et al., 2001) but no appreciable antitumour activity (Dias et al., 2011)
L. obtusa	100	Antibacterial activity against *Bacillus subtilis* and *E. coli* (Caccamese et al., 1980)
L. obtusa	114 and 115	Apoptosis inhibition of blood neutrophils (Ayyad et al., 2011)
L. nipponica	2 and 3	Insecticidal against mosquito larvae (Watanabe et al., 1989)
	3 and 4	Prolongs sleep-time by pentobarbitone (Kaul et al., 2011)
Laurencia sp	168	Antibacterial activity against *C. violaceum, Clostridium cellobioparum* and *Vibrio parahaemolyticus* (Vairappan et al., 2001a).
Laurencia sp	163 and 166	Cytotoxic against solid tumours and leukaemia L1210 cells (Abdel-Mageed et al., 2010)
Osmundea pinnatifida = L. pinnatifida	56	Antibacterial activity against food pathogens (Kinnel et al., 1979); antifeedant activity (Vairappan and Tan, 2009)

Chart 1. Reported biological activities of acetogenins isolated from algae belonging to the *Laurencia* complex.

Species of *Aplysia*	Compounds	Biological activities
A. dactylomela	174 also isolated from *Laurencia* (Suzuki et al., 1999)	Activity in increasing blood levels of pentobarbital in a dose-dependent (Kaul and Kulkarni, 1978)
A. dactylomela	178 and 45	Antifeedant against *Carassius auratus* (Manzo et al., 2005); toxicity to brine shrimp but inactive against marine bacteria (Takahashi et al., 2002)
A. dactylomela	167 and 179, also isolated from *Laurencia* sp (Vairappan et al., 2001)	Antibacterial activity against marine bacteria (Vairappan et al, 2001a,b)
A. fasciata = A. brasiliana	56, also isolated from *Laurencia* sp (Brennan and Erickson, 1982; Norte et al., 1989; Vairappan and Tan, 2009)	Antifeedant against *Xiphophorus helleri* (Kinnel et al., 1977); antibacterial activity against *Salmonella enteritidis*, *Vibrio cholerae*, *Staphylococcus aureus*, *E. coli*, *S. typhi* and *S. thyphimurium* (Vairappan and Tan, 2009)
A. fasciata = A. brasiliana	184	Antifeedant activity (Kinnel et al., 1979)
A. kurodai	190	Inhibitor Na, K-ATPase (Okamoto et al., 2001)
A. parvula	189	Ichthyotoxic activity (Myiamoto et al., 1995)

Chart 2. Reported biological activities of acetogenins isolated primarily from sea hare.

Conclusion and perspectives

After 50 years of research on the *Laurencia* complex, hundreds of metabolites have been isolated, mainly terpenes and acetogenins and many more are expected to be found in a near future, since the new dereplication approaches that are being used presently are able to detect unknown compounds even in low concentrations. Our poor knowledge about taxonomical aspects might be a key limitation for the success of these efforts, so more attention must be given to the identification of the algae. Some acetogenins structures are really amazing and a large number of them may have pharmacological potential, but there are also many questions considering their functional role both in the algae and in *Aplysia* spp. The answers may help us to understand a little more the fascinating underwater world and also point to medical applications that may contribute to improve human health.

Authors' contributions

All authors contributed in collecting and analyzing data besides drafting parts of the paper. TW (PhD student), ACP (Master student), GAZ (MSc), LFOV (Undergraduate student) and CL (postdoc fellowship) contributed also drawing the structures. MF (Professor) organized the data and contributed to critical reading of the manuscript. All the authors have read the final manuscript and approved the submission.

Conflicts of interest

The authors declare no conflicts of interest.

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