Progress in the Chemistry of Organic Natural Products

A. Douglas Kinghorn
Heinz Falk
Simon Gibbons
Jun'ichi Kobayashi *Editors*

102

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A. Douglas Kinghorn • Heinz Falk •
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Editors

Progress in the Chemistry of Organic Natural Products

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With contributions by

G. Appendino
M. Harizani · E. Ioannou · V. Roussis

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Editors
A. Douglas Kinghorn
Div. Medicinal Chemistry & Pharmacognosy
The Ohio State University
College of Pharmacy
Columbus, Ohio
USA

Heinz Falk
Institute of Organic Chemistry
Johannes Kepler University Linz
Linz, Austria

Simon Gibbons
Research Department of Pharmaceutical and Biological Chemistry
UCL School of Pharmacy
London, United Kingdom

Jun'ichi Kobayashi
Graduate School of Pharmaceutical Science
Hokkaido University
Sapporo, Japan

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Ingenane Diterpenoids

Giovanni Appendino

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G. Appendino (✉)
Dipartimento di Scienze del Farmaco, Largo Donegani 2, 28100 Novara, Italy
e-mail: giovanni.appendino@uniupo.it

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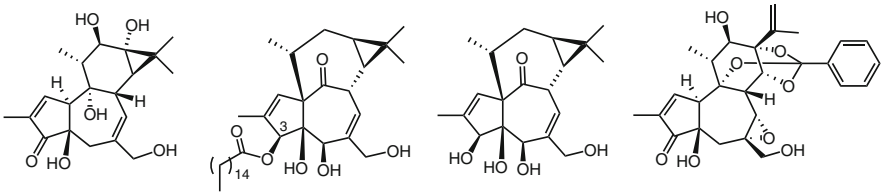
1 Introduction

Ingenane diterpenoids are a biogenetically advanced group of phorboids, a family of polycyclic diterpenoids structurally related to the tigliane skeleton of phorbol (**1**) that also includes the tiglianes and daphnanes. A combination of limited distribution, very low concentration in plant tissues, chemical instability, and difficulty of detection delayed the discovery of ingenane derivatives (ingenoids) compared to the tiglianes, the major class of phorboids. Thus, while phorbol (**1**), the archetypical tigliane, was first obtained in pure form in 1934 [1], the first ingenol derivative (ingenol-3-hexadecanoate = ingenol 3-palmitate, **2**) was only reported in 1968 [2, 3]. On the other hand, while phorbol went into a long series of constitutional and configurational revisions before its structure was clarified unambiguously by X-ray crystallography in 1967 [4], the basic ingenane polyol ingenol (**3**), just like the archetypical daphnane daphnetoxin (**4**) [5], benefited from an early (two years after the isolation) crystallographic determination of its relative and absolute configuration [6]. In retrospect, the early structure elucidation of ingenol, along with the lack of an abundant plant source, is responsible for the limited information still available on its chemistry compared to phorbol, for which the reactivity was

thoroughly investigated in attempts to elucidate its structure by classic studies of chemical degradation [7].



1 (phorbol) **2** (ingenol-3-palmitate) **3** (ingenol) **4** (daphnetoxin)

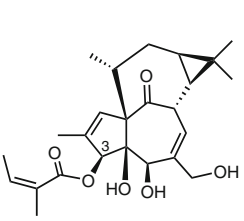
To detect the presence, often in trace amounts, of ingenol derivatives in crude extracts and chromatographic fractions, the early studies relied extensively on non-selective bioassays common also to other types of phorboids (e.g. cytotoxicity, fish toxicity, skin irritancy). The improvements in analytical techniques and the introduction of hyphenated chromatographic techniques like HPLC-MS have now simplified the detection and the isolation of ingenol esters. Despite these advancements and the growth of the natural products chemistry community, the diversity of ingenol derivatives has not expanded significantly in terms of chemotypes or euphorbiaceous sources since the pioneering work of the groups of Erich Hecker (Plate 1) in Heidelberg and Fred J. Evans (Plate 2) in London during the seventies and the eighties of the past century [8], suggesting that

Plate 1 Erich Hecker (taken from the brochure "Cancer Research and Cooperation, German-Israeli Cooperation in Cancer Research – The first 20 years". Deutsches Krebsforschungszentrum (1999)

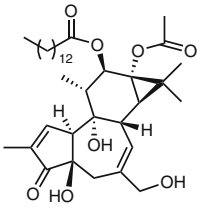
Plate 2 Fred J. Evans (1943–2007) (photograph provided courtesy of Prof. Elizabeth M. Williamson)

this class of compounds has a very narrow distribution in Nature and a limited structural diversity.

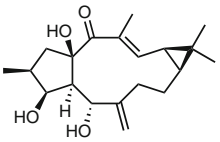
After an initial interest for the oxymoronic tumor-promoting and anticancer properties of ingenol derivatives, activities remained for a long time limited to the chemical synthesis community and the total synthesis of the parent alcohol. On the other hand, the successful and paradoxical development of the (weak) rodent tumor promoter ingenol mebutate (= ingenol-3-angelate, I3A, **5**) into a topical human chemopreventive drug (Picato®) (see Sect. 4.3), has rekindled a multidisciplinary interest for this compound and its biological potential.



5 (ingenol-3-angelate, I3A)



6 (phorbol-12-myristate-13-acetae, PMA)



7 (lathyrol)

Just like phorbol, ingenol does not occur in Nature as a free polyol, but only in esterified form, and its direct isolation from plant extracts is associated with the facile hydrolysis of the 3- and 20-monoesters. The first member of the class was reported in 1968 as part of a screening for co-carcinogenic diterpenoids in euphorbiaceous plants and the products obtained thereof [2, 3]. This systematic search for the distribution of co-carcinogenic compounds was undertaken by the German Cancer Research Centre in Heidelberg in the wake of the identification of phorbol 12-myristate-13-acetate (PMA, **6**) (= tetradecanoylphorbol acetate, TPA) as the major tumor-promoting principle of croton oil (*Croton tiglium* L.) by Hecker [7]. The purification of the compound later structurally elucidated as ingenol 3-hexadecanoate (**2**) was reported in 1968 from the seeds of the caper spurge (*Euphorbia lathyris* L.) [2] and from the latex of the African candelabra tree (*E. ingens* E. Mey.) [3]. Just like croton oil, a major source of phorbol esters, also the sap of the candelabra tree and the oil from caper spurge seeds have long been known for their high irritancy and skin-blistering properties, and the sap of the candelabra tree was also known to display co-carcinogenic properties [9]. Unexpectedly, both sources lacked phorbol esters, containing rather a complex mixture of ingenol esters and macrocyclic diterpenoids. Hecker, who pioneered studies in this field, assigned codes to diterpenoid constituents obtained in his laboratory, possibly to cope with the delay before isolation and structure elucidation that used to plague phytochemistry in the decades before pre-high-field NMR spectroscopic techniques became available. These codes were related to the plant source and to the chromatographic elution order, and the major irritant and co-cocarcinogenic constituents of *E. ingens* and *E. lathyris* respectively, dubbed Factors I_5 and L_1, turned out to be the same compound, namely, ingenol-3-hexadecanoate (**2**), with the structure of the parent polyol being eventually clarified by X-ray analysis of its crystalline triacetate [6]. Ingenol was named after *E. ingens*, possibly because

laboratory work on this plant actually predated that on *E. lathyris*, or, alternatively, because the name lathyrol (**7**) was already being used, as epoxylathyrol [10], for the major macrocyclic diterpenoid polyol of caper spurge oil, a compound previously known as *Euphorbia*-steroid and first reported in 1937 [11].

The total synthesis of ingenol is well covered in the secondary literature (see Sect. 3.2), while the other aspects of its properties have not been comprehensively reviewed since the chapter on ingenoids by Evans and Taylor in Volume of 42 of this Series [8] and the monographic book on phorboids edited by Evans [12]. This work aims at filling this gap, providing a platform for further investigation and the full exploitation of the pharmacological potential of this remarkable and fascinating parent diterpene natural product.

2 Phytochemistry

2.1 Structure and Spectroscopic Properties

The ingenane skeleton is based on a 5/7/7/3 tetracyclic system featuring a *trans*-bridgeheaded bicyclo[4.4.1] undecane core. The two-dimensional structural representation of ingenol is not straightforward, and several formulas have been used in the literature. The formula A (Fig. 1) is based on the azulenoid A,B ring system, and avoids the ambiguities associated with the two-dimensional representation of the *trans*-bridge, even though it depicts with a wedge/broken line endocyclic bonds

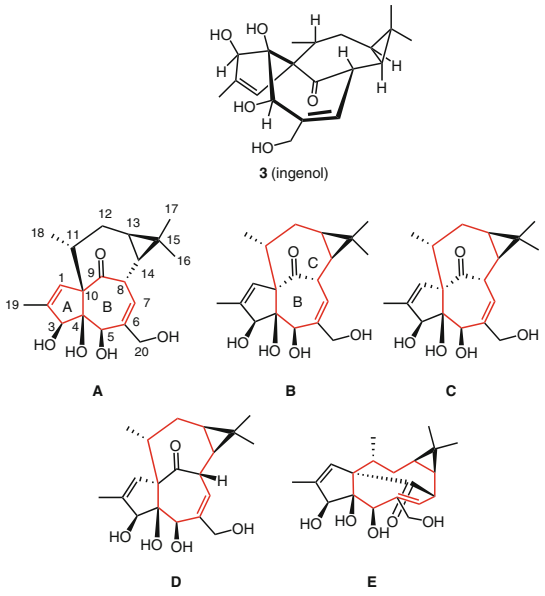


Fig. 1 Three-dimensional and two-dimensional representations of ingenol (**3**)

centered on stereogenic carbons. Thus, C-11 and C-14 of the cycloheptane C-ring bear an endocyclic wedge/broken line descriptor in addition to the one of their exocyclic substituent. The cyclodecane-based formulas B-D are also documented in the literature, but are ambiguous in terms of *(R),(S)* descriptors for the stereogenic centers at the bridge. As a consequence of this, *Chemical Abstracts Service* (Columbus, Ohio, USA) uses a different cyclodecane-based representation (*E*) for ingenol, unambiguous from the standpoint of translation in *R,S* configurational descriptors, but rather unfamiliar in the chemical literature, ambiguous in terms of configuration of the ring B double bond, and reminiscent of an Escher painting in the way the bridge is drawn. In conformational terms, the cyclodecane rim of the B, C-ring system approaches a sofa conformation, with C-10 upwardly oriented outside the mean plane through the other atoms, while the C-9 bridge and ring A are oriented toward the opposite (α-) face of the molecule.

The *trans*-bridge between C-8 and C-10 is an example of a conformationally locked *in,out*-bridge junction [13], a very rare structural element within the pool of natural products of which the major examples among the isoprenoids belong to the *seco*-trinervitane class of insect diterpenoids [14, 15]. The configuration is *in* at C-8 (angle C-10/C-8/H-8 $< 90°$, Fig. 1) and *out* at C-10 (angle C-8/C-10/C-11 $> 90°$, Fig. 1), and the bridge results, when referred to the de-apicalized cyclodecane system, from the merging on the C-9 methylene of a β-bond at C-8 and of an α-bond at C-10 (Fig. 2). The homeomorphic interconversion [13] of the *in*/*out* and the *out*/*in* forms is impossible in ingenol because of the small size of the ring system and because of the presence of the junction with the cyclopentane A-ring and the cyclopropane D-ring. Models show angular strain at several carbon atoms, with flattening at C-5, C-8 and C-11. Although the original X-ray data on ingenol triacetate [6] were not made available, the X-ray structural analysis of 20-deoxyingenol (**3**) found indeed that the bond angles of these carbons are significantly larger than the tetrahedral value (125.0°, 126.4° and 119.5°, respectively) [16].

In general, the relative stabilities of isomeric bicyclic [x.1.y] ring systems depend on their size. Isomers of the *out,out*-type are only possible in rings up to cyclononane, and they are also the most stable form up to cycloundecane, with the *in,out* becoming the preferred form for cyclotridecane and larger rings [13]. Unsurprisingly, the C-8 epimer of ingenol, the *out,out*- stereoisomer **8**, is significantly (24.7 kJ/mol) more stable than the natural polyol, and is characterized by a reduced angular strain [17]. The esters of this isomer, at least in the tris-*nor* version lacking the D ring (**9**), are devoid of tumor-promoting properties, and have been assumed to

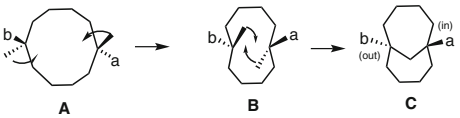
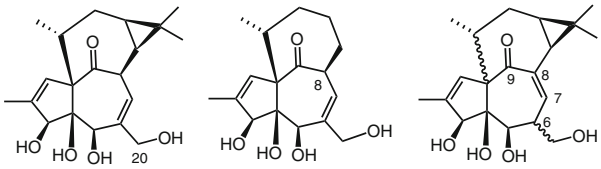


Fig. 2 Effect of de-apicalization on the configurational descriptors of the bridgehead carbons in a cyclodecane bearing a 1,6-*trans* bridge (bold and hashed wedges are used to indicate the orientation of the substituents a and b compared to the mean plane through the cyclodecane ring)

be biologically inactive [18]. The parent tris-*nor* polyol was synthesized by Paquette in 1988 [18], 20 years after the isolation of ingenol and 14 years before the first total synthesis of the natural product by Winkler [19]. In the light of the articulated and multifaceted nature of the biological profile of ingenol esters and of the lack of ring D, this assumption should be better evaluated before generalization.



8 (8-epi-ingenol) **9** (8-epi-tris-*nor*ingenol) **10** (isoingenol)

The isomerization of ingenol does not lead to 8-epi-ingenol (**8**), but to iso-ingenol (**10**), a compound where the double bond has shifted to the bridgehead carbon and is formally conjugated with the C-9 carbonyl, although the two π-systems cannot achieve planarity [20]. There is, unfortunately, a certain confusion in the literature between epi-ingenol (**8**) and isoingenol (**10**), and the situation is further compounded by confusion between epi-ingenol (**8**), a compound so far unknown, and its synthetic tris-*nor* derivative **9**. Isomerization of ingenol to isoingenol (**10**) leads to total loss of tumor-promoting properties of its 3-esters, and iso-ingenol 3-esters have been used as negative controls in biological assays just like 4-epi-phorbol (4α-phorbol) esters have been used for the activity of tumor-promoting phorbol esters [20].

The ^{1}H- and ^{13}C-NMR features of ingenol are summarized in Fig. 3 [21]. The most remarkable features of the NMR spectra are the downfield resonance of the non-oxygenated carbon C-10 (δ 72.6) and of the H-8 methine (δ 4.13), and the upfield resonance (δ 3.80) of the 5-proton, presumably because of its location in the anisotropy cone of the C-9 carbonyl. Although the ^{1}H NMR spectrum of the *out,out* isomer **9** was not assigned, all oxymethines resonated at $\delta > 4$ ppm [18], as expected from a different orientation of the C-9 carbonyl and H-5. Esterification causes predictable α,γ-downfield and β-upfield shifts in the proton and carbon resonances of the parent polyol. Remarkable differences were noticed between

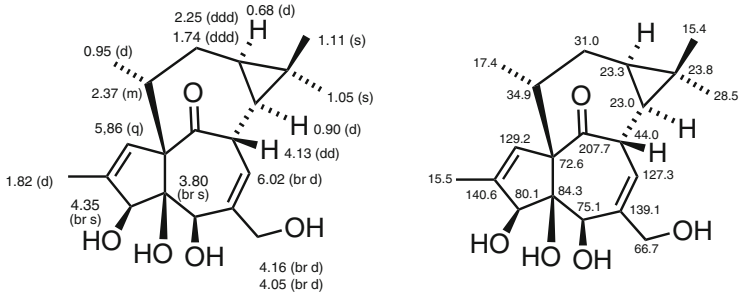


Fig. 3 ^{1}H- and ^{13}C NMR data for ingenol (**3**) ($CDCl_3$, 400 and 100 MHz, respectively). *J* values: 1,19 = 1.5 Hz; 7,8 = 4.5 Hz; 8,14 = 12.5 Hz; 11,12 = 3.0 Hz; 11,12′ = 8.5 Hz, 12,12′ = 15; 12,13 = 6.0 Hz; 12′,13 = 8.5 Hz; 13,14 = 8.5 Hz, 20,20′ = ca. 7 Hz [21]

the IR carbonyl frequencies of ingenol and its *out,out* model analog **9** ($v = 1705$ and 1675 cm^{-1}), presumably because of different degrees of deviation from planarity, of ground-state strain energy, or of a combination of both [18]. An extensive compilation of ^{13}C NMR data for ingenol esters has been published, facilitating the characterization of the acyl decoration of its esters [22].

The MS fragmentation of ingenol is significantly different from those of phorbol and deoxyphorbol, and this makes it possible to selectively detect its derivatives in complex extracts using MS-MS techniques [23]. The mass spectra of ingenol esters are characterized by the stepwise loss of the ester groups, and their fragmentation profile has been investigated in the positive-ion mode, which readily ionizes them [23]. While the nature of the acyl moiety can be inferred from the pattern of mass fragmentation loss, the elimination order is of limited general value for the establishment of the esterification profile, since it was found to be dependent on the experimental conditions and the nature of the ester group [23].

Ingenol triacetate and ingenol-3-angelate (I3A, **5**) [24] have been investigated by X-ray diffraction, and such data on several semi-synthetic analogs obtained during various total synthesis campaigns are also available [16]. Crystalline forms of I3A were obtained from ethanol by addition of water, and from acetonitrile by cooling. Apparently, the crystalline forms are easier to formulate than the amorphous form, and their preparation has been patented [24]. In accordance with observations made on 20-deoxyingenol, angular strain was particularly evident at the angles C4–C5–C6 (123.0°) and C10–C13–C14 (119.3°). Angular strain was also present at the carbonyl bridge, with the angle C8–C9–C10 being only 111.2°. Linear strain was especially marked at the bond C4–C10, which is considerably longer than normal [1.602 (5) Å] [24].

Ingenol was originally reported as dextrorotatory ($[\alpha]_D^{25} = +41° cm^2 g^{-1}$, methanol) [21], and further studies confirmed a positive optical rotation also for the synthetic product. Nevertheless, a high-purity sample prepared in the course of a large-scale isolation of the product at LEO Pharma, the company that developed Picato®, showed a negative optical rotation ($[\alpha]_D^{25} = -18° cm^2 g^{-1}$, methanol), confirmed with an ad hoc prepared synthetic sample ($[\alpha]_D^{25} = -13° cm^2 g^{-1}$, methanol), with the absolute configuration of the levorotatory sample supported by X-ray analysis of a heavy-atom containing derivative (3-(4-bromobenzoate) of the 5,20-acetonide) [16]. More than the presence of impurities, for which the profiles should be different between samples of natural and of synthetic origin, it is possible that the reversal of the optical rotation might be related to degradation, since ingenol is not stable (see Sect. 2.3). Ingenol esters are mostly dextrorotatory, while those of 13-hydroxyingenol show an opposite optical rotation [8]. Some exceptions are known, but, since the purification of ingenol esters is difficult and the observed optical rotations are sometimes small, this could be related to the presence of impurities. Similar considerations hold also for the CD spectra. Ingenol esters show a positive Cotton effect at 300 nm, while 13-hydroxyingenol esters show a negative Cotton effect at 290 nm [8]. No systematic study has been done so far on the chiroptical properties of ingenoids.

2.2 Biogenesis

Euphorbiaceous plants are prolific producers of diterpenoid skeletal types, many of which, like the ingenanes, are unique to this large plant family [25]. According to their derivation from a linear tetraprenyl phosphate, *Euphorbia* diterpenoids can be broadly divided into compounds derived from the cascade cyclization and those derived from the head-to-tail cyclization of a tetraprenyl phosphate precursor through the effects of type II and type I cyclases, respectively (Fig. 4).

The first cyclization mode is at the origin of the so-called polycyclic diterpenoids, represented in euphorbiaceous plants mainly by abietanes, pimaranes, kauranes, atisanes, and trachylobanes, while the second one generates, in a stepwise fashion and with the cation processes typical of the isoprenoid cyclizations, macrocyclic diterpenoids, namely, the monocyclic cembranes, the bicyclic casbanes, and the tricyclic lathyrane derivatives (Fig. 5). Alternatively, cyclopropane ring opening generates jatrophanes from lathyranes (Fig. 5).

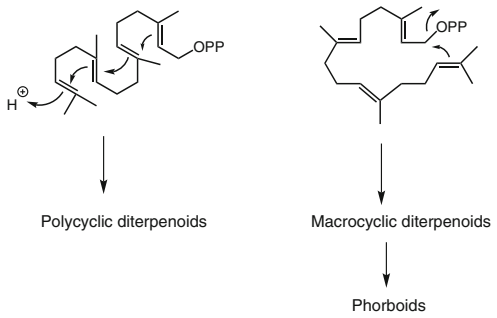


Fig. 4 Cascade and head-to-tail cyclization mode of a tetraprenyl phosphate

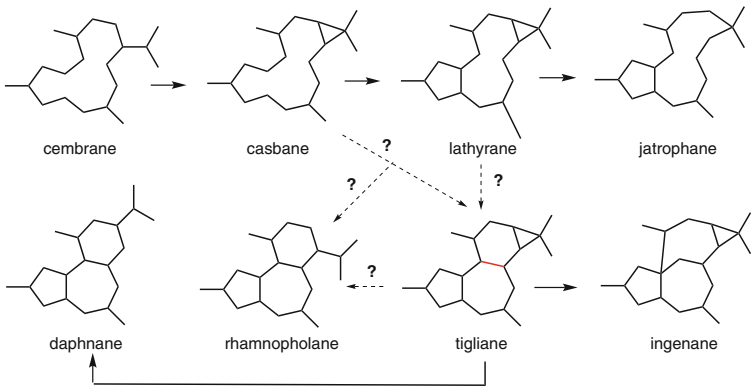


Fig. 5 Topological relationship between the macrocylic diterpenoid skeleta (upper line) and those of phorboids (lower line), and their possible biogenetic relationship via lathyrane derivatives (topological proposal) or via casbane derivatives (Jakupovic proposal)

From a structural standpoint, phorboids are polycyclic diterpenoids, but are biogenetically derived by macrocyclic diterpene precursors. Therefore, they are considered products of a "head-to-tail" cyclization mode of a tetraprenyl phosphate, in one of the many oxymoronic relationships between biogenesis and structure that plague natural products chemistry, as exemplified by the isoquinoline alkaloid quinine, an indole alkaloid from a biogenetic standpoint. The relationship between macrocyclic diterpenoids and phorboids has long remained a mechanistic black box, despite obvious structural similarities between the lathyrane and tigliane skeleta. Tiglianes can next, at least formally, be converted to the other structural types of phorboids by cationic rearrangements typical of isoprenoid chemistry, and the present mechanistic uncertainties on the biogenesis of phorboids center, therefore, on the relationship between lathyranes and tiglianes and, in particular, on the formation of the single bond that differentiates compounds representative of these two classes.

Despite the structural similarity between the carbon-carbon connectivity of the lathyrane and tigliane skeleta, several issues make questionable a direct relationship between compounds of the two classes:

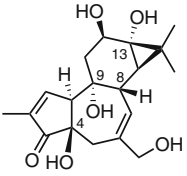
(a) While tiglianes have a broad distribution, occurring in several species of Euphorbiaceous plants, lathyranes have a much more limited distribution, exclusive to only a few species of the genus *Euphorbia*. If compounds from the two types were biogenetically related, one would expect a better overlapping occurrence, and not a "traceless" biogenetic relationship.

(b) As exemplified by phorbol (**1**) and lathyrol (**7**), the cyclopropyl carbon C-13 (tigliane numbering, C-11 in terms of lathyrane numbering) is hydroxylated in all natural tiglianes, as well as in many ingenanes, while no lathyrane discovered so far in Nature is hydroxylated at the cyclopropane carbons. In biological systems, C-H functionalization is basically an iron-mediated radical process [26], and the direct hydroxylation of a cyclopropane ring would therefore be biased toward the formation of a cyclopropylalkyl radical rather than a cyclopropyl radical [26]. In turn, the cyclopropylalkyl radical would rapidly generate the 3-butenyl radical, with eventual opening of the cyclopropane ring [27]. These considerations suggest distinct mechanisms of formation for the cyclopropane ring in lathyranes and tiglianes.

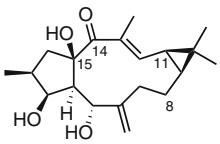
(c) In topological terms, the conversion of lathyranes to tiglianes involves the formation of a bond between the carbons 8 and 14 (corresponding to the carbons 8 and 9 of the tiglianes, cf. **1** and **7**), but no lathyrane derivative isolated so far bears the correct functionalization for this cyclization, which would require complementarity in terms of nucleophilic and electrophilic properties between these two carbons. Thus, C-14 of the lathyranes is generally a carbonyl, while C-8 is either hydroxylated, and therefore electrophilic, or is part of an unfunctionalized sequence of methylenes, as exemplified by lathyrol (**7**). Furthermore, most lathyranes contain at least one endocyclic (*E*)-double bond [25], which, apart from preventing a spatial interaction between the functionalities at C-8 and C-14, makes the cyclization to tiglianes impossible, since (*E*)-double bonds can only exist in eight-membered or higher ring systems. Unsurprisingly, the cationic cyclization of lathyranes has provided a wealth of

rearranged diterpenoid skeleta, with none of these, however, bearing any resemblance with the tigliane skeleton [28].

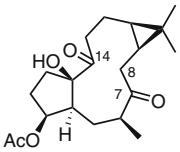
A high-yield lathyrane-to-tigliane conversion was reported via an anionic process that involved the intramolecular aldol reaction of an ad hoc prepared semi-synthetic lathyrane 7,14-diketone devoid of unsaturations on the eleven-membered ring (**11**) [29]. The resulting tigliane (**12**) was assumed tentatively to have the same configuration as natural phorbol esters at the stereogenic carbons at the B,C ring-junction, but the functionalization of these two rings was completely different from that of the naturally occurring compounds of this class. Furthermore, aldol-type anionic cyclizations, although well documented in the chemistry of isoprenoids [30], are rarely involved in their biogenesis.



1 (phorbol)



7 (lathyrol)



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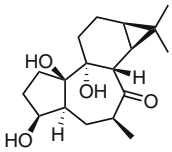

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(d) Naturally occurring lathyranes and tiglianes show an opposite hydroxylation at the A,B ring junction, as exemplified by comparison of phorbol (**1**) and lathyrol (**7**).

Owing to these differences, and the implausibility of the hydroxylation of a cyclopropane carbon under biomimetic conditions, the biogenetic relationship between lathyranes and tiglianes has been questioned, without, however, proposing a possible biogenetic alternative [31]. As a result, tiglianes and ingenanes may be added to the thapsane family of sesquiterpenoids, the ryanodane family of diterpenoids, and the *Iboga* alkaloids as veritable biogenetic enigmas.

The late Jasmin Jakupovic (Plate 3) (1949–2005) of the Technische Universität Berlin and later Analyticon elaborated an elegant biogenetic proposal to solve this

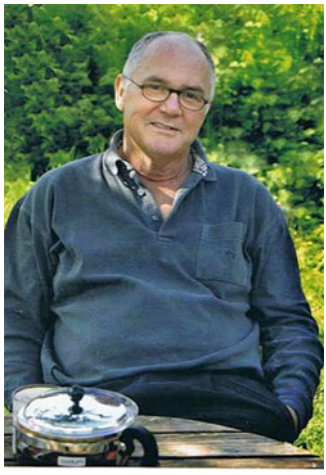


Plate 3 Jasmin Jakupovic (1949–2005) (photograph provided courtesy of Fotini Tsichrtzis)

riddle, providing a unifying mechanistic setting for the generation of lathyranes and tiglianes from casbanes that explains the differences in the functionalization pattern of these two class of compounds. This proposal has important implications for the biogenesis of ingenol, and is also capable of shedding light on the biogenesis of rhamnofolanes, another biogenetically enigmatic class of phorboids. The premature death of Jasmin Jakupovic has precluded the dissemination of his ideas within the natural products community, and his views remained confined to laboratory meetings, private discussions, and a Ph.D. thesis [32]. Thanks to the help of the Jakupovic family and his collaborator Frank Jeske, as well as to ideas and comments exchanged during personal discussions before Jakupovic's death, sufficient material has been retrieved to present in an organic fashion what will be referred to as the "Jakupovic biogenetic proposal" for phorboids. Despite radically deviating from some current ideas in the area, this proposal is the only one capable of rationalizing the biogenetic derivation and the functionalization pattern of phorboids in light of the isoprenoid rule.

The starting point for the elaboration of this proposal is a retrosynthetic analysis of the tigliane skeleton according to the isoprenoid rule. Thus, the reversal of the cyclopropane ring closure by protonation of the C-13 α-carbon unambiguously connects the tigliane skeleton (**13**) to the cembranyl cation **14** (Fig. 6). The alternative opening of the cyclopropane by protonation at C-14 is, in fact, incompatible with the isoprenoid rule, which sets the relative location of the alkyl substituents on isoprenoid chains. Conversely, the topologically symmetric cembranyl cation **14** could be generated by two distinct foldings of the acyclic tetraprenyl precursor. The folding **15** of pathway A seems more obvious, since it leads to tiglianes with the correct location of the cyclopropane on ring C. Conversely, the folding **17** of pathway B is apparently counterintuitive, since, by (formal) insertion

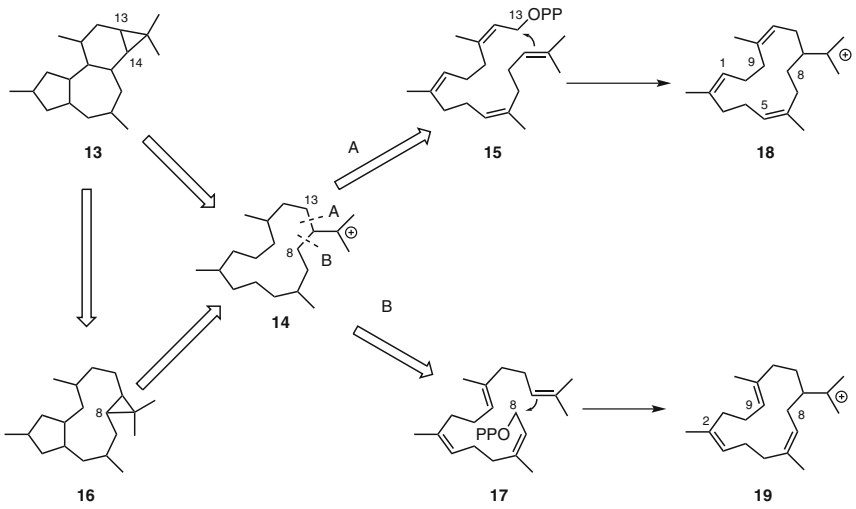


Fig. 6 Retro-biogenetic analysis of the tigliane skeleton

of the side-chain cation center into a C(8)-H sigma bond, it would generate compounds with the unnatural location of the other cyclopropane bond at C-8 (represented in **16** in its lathyrane version), and a rearrangement would be needed to bring it to its natural location at C-13. This rearrangement is, indeed, at the core of the Jakupovic biogenetic proposal, and provides a mechanistic explanation for all the "unknowns" of the biogenesis of phorboids. Thus, pathway A requires the triply-isomerized all-(*Z*) tetraprenyl precursor **18**, and will lead to the "functionalization" "cul-de-sac" discussed before, since neither C-8 nor C-9 are properly functionalized to form the critical B, C ring junction. Furthermore, it leaves unresolved the issue of the hydroxylation of the cyclopropane carbon.

The configuration issue for the double bond located in what will become the cyclopentane ring A (Δ^1 in **18** and Δ^2 in **19**) is irrelevant, since the isomerization can be associated with functionalization and the generation of the five-membered A-ring, with a similar argument holding also for the allylic C-9 methylene of **18**. However, this issue is difficult to resolve by simply advocating functionalization for the Δ^5 double bond of **18**, since this occurs as an unfunctionalized methylene in most tiglianes. Conversely, in **19** the configuration of the endocyclic double bond is not an issue, since the Δ^9 double bond can be accommodated in an (*E*)-configuration, and the Δ^6 double bond is allylic to the phosphate group, and therefore can isomerize via the classic rearrangement of primary γ,γ-dimethylallyl phosphates to tertiary α-dimethylvinyl phosphates [33]. In general, the isomerization of the pyrophosphate starter from a terpenyl-geranyl to the terpenyl-linalyl type (Fig. 7,

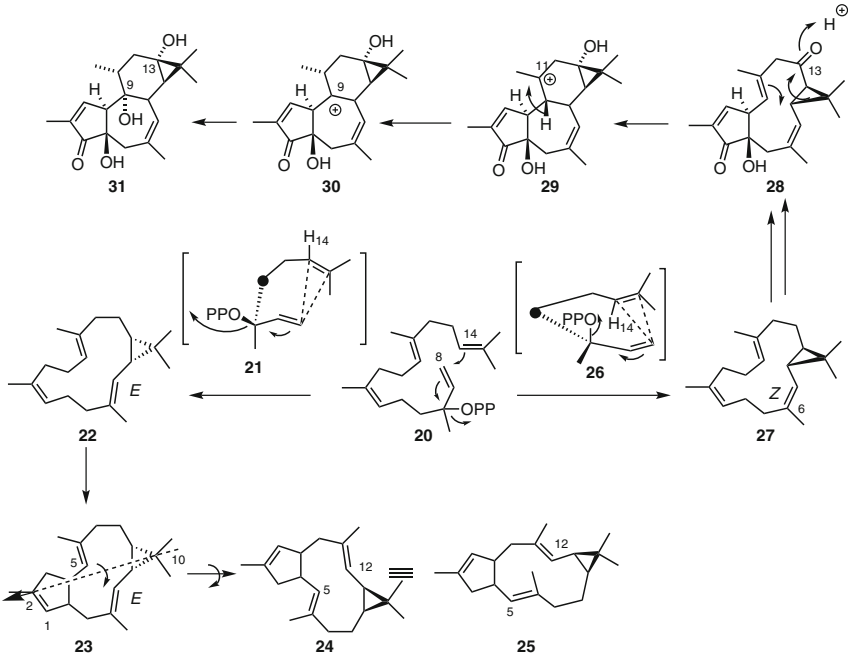


Fig. 7 The Jakupovic proposal for the biogenesis of phorboids and lathyranes

20) is associated with an increase of the possibility of cyclization modes, and this conformational diversity (Fig. 7, **21** and **26**) might ultimately be responsible for the generation of both lathyranes and tigliane from the same precursor. Thus, electrophilic attack on the *re*-face (H-14 "up") of the terminal double bond from the vinyl antiperiplanar to the phosphate leaving group, would translate into an *E*-configuration of the newly generated trisubstituted double bond, and, when the resulting casbene derivative is viewed in a tigliane orientation, an α-orientation of the cyclopropane ring (Fig. 7, **22**). Conversely, attack on the *si*-face of the terminal double bond (H-14 "down") from the vinyl group *synclinal* to the phosphate leaving group will generate an opposite configuration of the double bond and the cyclopropane ring [27]. After formation of the cyclopentane ring A, rotation around the C-2–C-10 axis (lathyrane numbering) of the casbene **23** generates a lathyrane with the double bond locations (Δ^5 and Δ^{12}) and configuration typical of this class of products. Conversely, the casbene **27** has the correct double bond configuration and location to generate, after closure of the A-ring, the phorboid skeletal of tiglianes, ingenanes and rhamnofolanes. Thus, introduction of a carbonyl function at C-13 (tigliane numbering) triggers the formation of a stable non-classic cyclopropylmethyl cation, which is then quenched by the C-9 (tigliane numbering) endocyclic double bond and closure of the cyclopropane ring at C-13 (see **28**), with formation of the critical C-8—C-9 bond and of the hydroxylated version of the cyclopropane D ring. Hydride migration and quenching by water will eventually provide a tigliane (**31**) with hydroxy groups at C-9 and C-13, the hallmark of all natural compounds of this class (Fig. 7).

For ingenanes that lack a 13-hydroxy group, like the parent polyol ingenol, the electrophilic trigger for the migration of the cyclopropane could be provided by the generation of an oxonium ion at C-13 (Fig. 8), while their rearranged skeleton might, in principle, derive from an alternative quenching of the C-9 cation **34**.

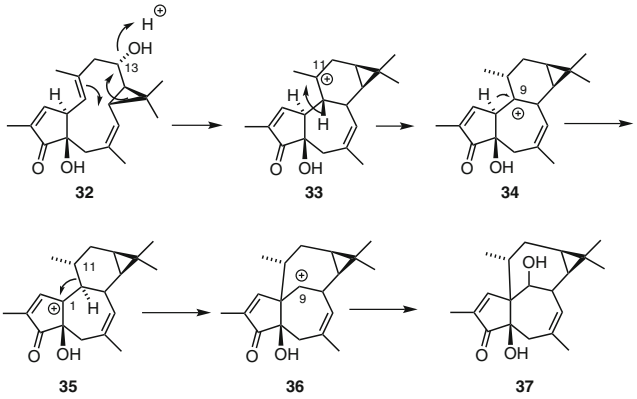


Fig. 8 Possible direct biogenetic derivation of the ingenane skeleton from a C-13 hydroxylated (tigliane numbering) bicyclic precursor

Rather than directly undergoing water trapping like the cation **30**, quenching could occur after a 1,2 hydride shift to generate a C-1 cation that next undergoes a 1,2-alkyl shift, eventually rearranging to the ingenyl cation **36**. A detailed study on the tigliane-to-ingenane rearrangement during the Baran synthesis of ingenol [16] has highlighted the role of the presence of a hydroxy substituent at C-9 to overcome the thermodynamic barrier involved in the reaction, suggesting that a direct derivation of the ingenane skeleton from a lathyrane-type bicyclic precursor seems unlikely.

Finally, oxidation of the casbene **27** at C-16 (tigliane numbering) and the generation of lathyranes like **38** (Fig. 9) may trigger a different mode of transannular opening of the cyclopropane ring, generating the typical ring C functionalization of rhamnofolanes (**25**) via the backside attack of the double bond to the cyclopropane C-8 carbon.

The two different retro-biogenetic disconnections of the tigliane skeleton according to the isoprenoid rule (Pathways A and B in Fig. 6) could be distinguished easily by labeling experiments. Thus, labeling C-1 of geranyl-geraniol will lead, via the phosphate **40**, to a tigliane labeled at C-13 according to pathway A (**41**), but, via the phosphate **42**, to a tigliane labeled at C-8 (**43**), if pathway B is indeed the one occurring in Nature (Fig. 10).

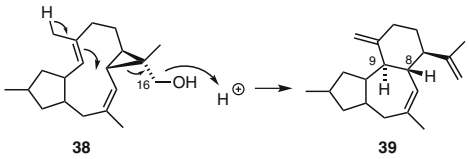


Fig. 9 Generation of the rhamnofolane skeleton by rearrangement of a C-16 hydroxylated lathyrane precursor (tigliane numbering throughout)

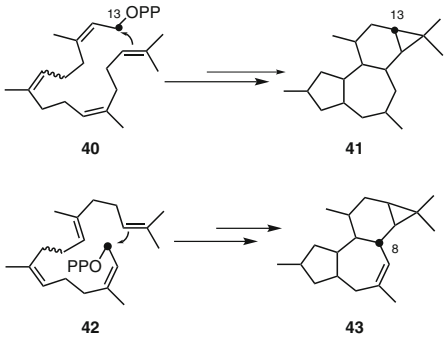


Fig. 10 Location of the labeling of the C-1 carbon of a tetraprenyl phosphate precursor according the two possible retro-biogenetic disconnections of the tigliane skeleton

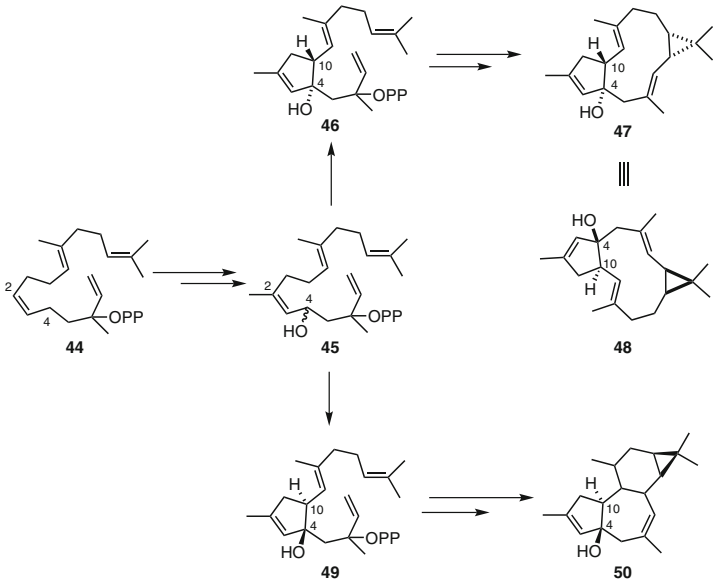


Fig. 11 Possible rationalization of the opposite hydroxylation of the A,B-ring junction in lathyranes and tiglianes (tigliane numbering throughout)

According to the Jakupovic biogenetic proposal, lathyranes and tiglianes have, in biogenetic terms, a different location of the cyclopropane ring. The conventional representation of this class of compounds hides this, and generates inconsistencies between the functionalization pattern of these compounds and phorboids. Regarding the opposite functionalization of the cyclopentane A-ring in lathyranes and tiglianes, it is tempting to imagine that the allylic oxidation of the Δ^2 double bond (tigliane folding) of a tetraprenyl precursor like **44** could trigger formation of the cyclopentane A ring, and that the different configuration of this hydroxy group, which generates diastereoisomers in a tetraprenyl starter of the geranyl-linalyl type, might be involved in the pre-organization of the cyclization step involving the pyrophosphate group (Fig. 11), thus explaining the apparently different hydroxylation of the A, B ring junction in lathyranes and tiglianes.

The Jakupovic proposal provides a mechanistic framework to relate biogenetically the functionalization pattern of lathyranes and phorboids, elegantly by-passing the "cul-de-sac" represented by the apparently unrelated configuration and location of the double bonds within these compounds and providing a mechanistic rationale for the oxygenation of the cyclopropane ring in tiglianes and ingenanes. Since it rationalizes all the many "unknowns" of the biogenesis of phorboids, its wider appreciation will, hopefully, trigger studies aimed at its confirmation or invalidation.

2.3 Isolation

Many ingenol esters are potent irritant and vesicant agents as well as tumor promoters, and during their extraction and purification great care has to be taken to avoid contact with the skin, mucous membranes, and the eyes. Accidental eye contact is characterized by massive lacrimation and acute pain, and may require hospital treatment to be managed correctly. In turn, skin contact induces within 2–3 h the formation of an erythema that can persist for well over 24 h, but which if the exposed area is limited, can be soothed by topical treatment with local anesthetics and ice blocks [34], or with a solution of a polyamphoteric detergent [35]. Hospitalization might, however, be necessary in case of the accidental contamination of a large skin area [34]. Based on observations done with I3A, the inflammatory response to ingenoids is transient and resolves spontaneously without scarring within 2–4 weeks, during which topical treatment with corticosteroids may be recommended to control pain and inflammation [34]. Severe allergic reactions, including throat tightness, difficulty in breathing, feeling faint, or swelling of the lips or tongue, have been reported with Picato® [36], and they might well result also from contact with other ingenoids. Facial, especially the eyes, and skin protection is therefore mandatory during the laboratory manipulation of ingenol esters, as well as of plant material, extracts, and chromatographic fractions containing compounds of this type. Glassware should be treated with bases before washing, and contaminated laboratory spaces should be treated in the same way. It is known that 5% KOH in methanol quickly hydrolyzes ingenol esters, and is preferred to washing with aqueous solutions that can not quickly penetrate fatty matrices [37].

The literature is rife with exaggerated statements on the difficulties involved in the isolation of ingenol esters, and, in general, of phorboids. Thus, the claim that "*the isolation (of phorboids) must be conducted in oxygen-free conditions; solvents must be degassed and extraction should be conducted under continuous flow of nitrogen or argon*" [38] is exaggerated, even though ingenol derivatives are unstable toward hydrolysis and transesterification, and are easily oxidized by atmospheric oxygen. Undoubtedly, their isolation in the native form requires care and the need to avoid acidic and basic conditions, which even if mild, can promote degradation and/or isomerization reactions, but these features are not exclusive to this class of natural products, and do not preclude working under normal laboratory conditions. Although no systematic study has yet been done, ingenoids are probably also easily degraded by heating, explaining the edible uses of the seeds of the caper spurge (*E. lathyris*), which after roasting, were used as a coffee replacement during the shortages associated with World War I [39]. Heating is also use to detoxify this oil from this species before its technical uses may be applied [39].

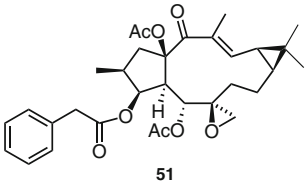
Ingenane polyols do not occur as free alcohols, but only in the esterified form. Ingenol esters are lipophilic and insoluble in water. They are extracted from plant material with organic solvents, and, depending upon their degree of acylation and the nature of the ester groups, they show different polarities and therefore partition differently between hydrocarbon and more polar solvent phases. Extraction from a plant biomass typically involves the use of solvents like ethanol, acetone or

chloroform, evaporation, and next partition between hexane and water-methanol, with ingenol esters ending up in the more polar and hydrophilic phase. Conversely, when the primary extract is partitioned between water and chloroform, or between water and ethyl acetate, ingenol esters end up in the organic phase. Partition is especially critical to recover long-chain ingenol esters from fatty matrices like seed oils. In this case, the system acetonitrile-cyclohexane was found to work much better than other partition systems [21]. Crude ingenoid mixtures can then be partially resolved by various chromatography techniques, namely, gravity chromatography on silica gel (both in the normal and in the RP mode) or Sephadex. For final purification, HPLC is generally necessary, since ingenol esters often represent minor constituents of the diterpenoid bouquet of the plant under investigation. During solid-liquid chromatographic separation, acyl rearrangement can take place, and ingenoids having a free hydroxy group at C-3 and ester groups at C-5 and C-20 are most likely to be isolation artifacts (see Sect. 3.1). The early phytochemical work on ingenoids made extensive use of droplet counter-current chromatography for their purification [8], a technique that minimizes acyl rearrangements. While now obsolete in its original form, this method could benefit from many recent rapid developments in the field [40], and holds potential especially for large scale purifications. However, this possibility is still largely unexploited for the phorboids.

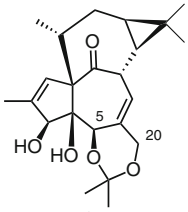
The isolation of ingenol has been detailed from the seed oil of *E. lathyris*, an agricultural commodity (Plate 4), and the methods developed could be applied also to other oily sources. The original method by Hecker [41] involved a series of liquid-liquid and solid-liquid partitions. Thus, a methanolic extract from the seeds

Plate 4 *Euphorbia lathyris* L. at the time of fruit maturation (photograph provided courtesy of Dr. Gianpaolo Grassi, Cra, Rovigo, Italy)

(9.7% yield) was first partitioned between a half saturated NaCl solution and ethyl acetate to remove the polar fractions containing mono- and dimeric coumarins and other polar constituents. The organic phase was then evaporated, and the residue (7.7%) was emulsified with methanol. An oily phase made up by glycerides separated from the emulsion, and, after evaporation, the methanol phase (3.2%) was adsorbed onto silica gel. The cake was then washed sequentially with petroleum ether, to further remove glycerides, and with ethyl acetate, to recover the diterpenoid fraction (0.58%). Zemplén methanolysis of the latter and partitioning between water and ethyl acetate of the residue of the hydrolysis eventually gave a polyol fraction (0.5%) that was adsorbed onto silica gel and then washed with chloroform to remove the ester fraction. Washing with ethyl acetate afforded a purified polyol fraction (0.13%) that was subjected to a sequence of gravity column chromatographic purifications, eventually affording ingenol in an overall 0.025% yield (250 mg/kg of seeds).



51
(Euphorbia Factor L1))



52
(ingenol 5.20-acetonide)

A simplified method was later developed [21], based on the possibility of directly separating the diterpene fraction of the oil by partition of a methanolic extract between acetonitrile and cyclohexane, a system originally devised to remove lipophilic tin derivatives in the work-up of Bu_3SnH reductions [42]. The diterpenoid fraction was then treated with 8% KCN in methanol to hydrolyze selectively the macrocyclic diterpenoid esters, of which the major member, the epoxylathyrol ester L_1 (**51**), directly precipitated from the reaction mixture. Ingenol, a more polar compound, could then be easily separated from the macrocyclic esters by gravity column chromatography on silica gel, with an overall isolation yield of ca. 250–600 mg/kg of seeds [21]. The rationale for the chemoselectivity of the hydrolysis is that the presence of nearby free hydroxy groups catalyzes the deacylation of ester groups [43], a condition holding for ingenol esters but not for lathyrol and epoxylathyrol esters. Zemplén methanolysis with freshly prepared sodium methylate in methanol gave lower yields and was less selective for ingenol vs. lathyrol and epoxylathyrol esters, but would, undoubtedly, be more practical for a large-scale process. When obtaining macrocyclic polyesters is not important, a further simplification is possible, directly extracting the crushed seeds with methanolic sodium methylate. In this step, a significant precipitation of the highly crystalline macrocyclic polyols lathyrol and epoxylathyrol takes place, and, after filtration, neutralization, and evaporation, a fraction containing a mixture of ingenol and the partially hydrolyzed macrocyclic diterpene moiety is obtained. This can then be purified by gravity colum chromatography on silica gel [44]. This method minimizes the exposure to ingenol esters, since the crude crushed seeds are

extracted with an active solvent that "detoxifies" them, and, comparative experiments with other procedures have highlighted the superiority of this protocol, with yields consistently in the range of 500 mg/kg of seeds [44].

Other sources of ingenol, like the latex of *E. ingens*, turned out not not to be reliable due to large variations in their concentrations [41]. Since all succulent African *Euphorbia* species are now included in the CITES list [45], the trade of *E. ingens* would, in any case, be subjected to severe regulatory limitations. The latex of a South-American chemotype of *E. tirucalli* L., a plant known as "Aveloz" in Brazilian folk medicine, has also been claimed to be an excellent source of ingenol, and used for the development of semi-synthetic antiviral agents (see Sect. 4.2), without, however, disclosing details of the yield and the isolation protocol [46]. "Aveloz" is a popular medicinal plant in Brazil, but in 2011 the Brazilian Agency for Sanitary Vigilance (ANVISA) prohibited its use in herbal medical products because of the presence of co-carcinogenic diterpenoids [47].

Ingenol obtained by hydrolysis of its esters occurs as an amorphous glass, which degrades easily even in the cold, and is better stored as its crystalline 5,20-acetonide, **52**. Alternatively, it has been stored as such in frozen DMSO or in benzene.

2.4 Distribution and Diversity

The distribution of ingenoids is limited to three closely related genera within the Euphorbiaceace family (*Euphorbia*, *Elaeophorbia* and *Mabea*) [48]. The tropical genera *Elaeophorbia* and *Mabea* are small (less than 100 species each), with the genus *Elaeophorbia* often being included in the genus *Euphorbia* [48]. The latter, with 1600–2000 species, depending on the classification system, is the second largest among higher plants after the genus *Astragalus* [49]. Most ingenoids have therefore been reported from plants belonging to the genus *Euphorbia*, to the point that this genus is often quoted as the only source of ingenoids in Nature. For comparison, tigliane derivatives have been reported from twenty-three genera belonging to two families (Euphorbiaceae and Thymelaeaceae) [50]. Ingenol esters occur both in spurges and in cactus-like members of the genus, and no clear trend associating their presence to certain morphological features is evident from the phytochemical literature. Just like phorboids in general, ingenol esters are absent in the New World species of the genus *Euphorbia*. The concentration of ingenoids in plants is generally rather low, often in ppm (mg/kg of) of fresh biomass. The best source of ingenol remains the caper spurge (*E. lathyris*), one of its two original sources, where it occurs in the seeds at a concentration up to ca. 0.5–0.8 g/kg [44]. For comparison, the concentration of phorbol esters in croton oil is an order of magnitude higher [7]. A systematic study on the concentration of ingenol in the latex of various *Euphorbia* species was carried out after hydrolysis of the diterpenoid mixture and GC analysis of the triacetate [51]. Typical concentration levels in the latices analyzed ranged between 1% and 3% [51].

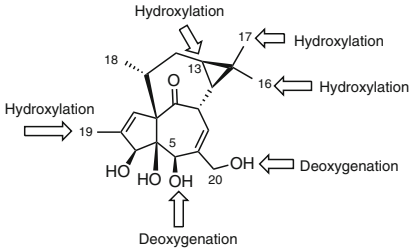


Fig. 12 Functionalization diversity within ingenol esters

Chemical diversity within ingenol derivatives is associated with modification of the hydroxylation pattern of the parent polyol and/or to the nature of the acyl decoration. The latter can include, apart from fatty acids and their derivatives, also reasonably complex anthranilate-derived oligopeptides. Deoxygenation can occur at C-5 and C-20, and hydroxylation at C-13, C-16, and C-19, with the possibility also of combining deoxygenation and hydroxylation, as in 20-deoxy-16-hydroxyingenol derivatives (Fig. 12). It is, however possible that the structure of all 16-hydroxyingenoids should actually be revised to their corresponding 17-hydroxy derivatives (see Sect. 2.4.8).

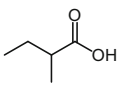
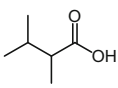
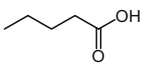
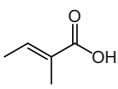
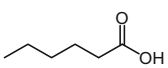
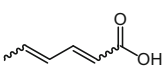
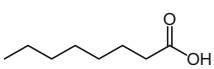
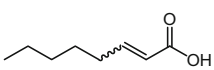
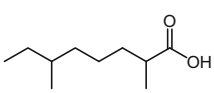
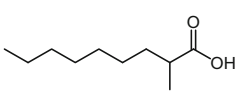
In some species of *Euphorbia*, ingenol esters occur in a mutually exclusive manner with phorbol esters, but the co-occurrence of ingenane, tigliane and daphnanes has been reported in some species, in particular in *E. resinifera* O. Berg. [52], with tiglianes and ingenanes co-occurring in few other species. Ingenol derivatives are sometimes isolated as very complex mixtures of homologous polyunsaturated esters that could not be individually characterized. The compounds listed in Tables 2–19 might therefore only represent the tip of a much larger "iceberg" of compounds of this type that still await complete structure elucidation.

Some acyl groups are unique to ingenol esters. The most interesting case is that of the anthranilate-based tripeptides occurring in milliamines (sic) and related compounds isolated from *E. milii* Des Moul., an ornamental plant native to Madagascar and popularly known as "crown of thorns" (Table 1). 2,6-Dimethyl substitution as well as polyunsaturation (up to five conjugated double bonds) are not uncommon in the acyl decoration of ingenol esters (Table 1). The configuration of these acyl chains has not generally been assigned, but in some cases isomeric forms of polyunsaturated acids have been isolated.

Tables 2–19 report all the known ingenol esters, along with their plant source. Authority abbreviations for the binomial were assigned using the International Plant Name Index (http://www.ipni.org/ipni/plantnamesearchpage.do). Authority abbreviations are not included in the Tables for the species mentioned in the text. Compounds are sorted out into six basic chemotypes:

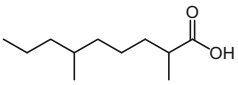
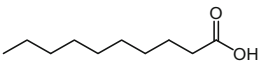
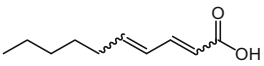
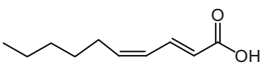
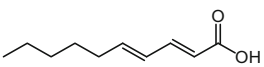
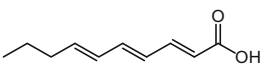
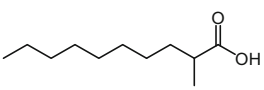
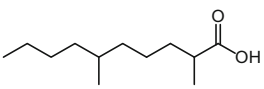
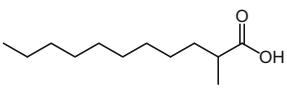
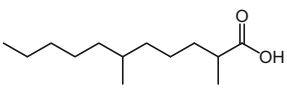
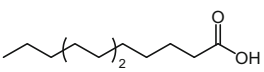
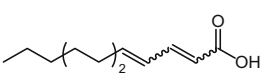
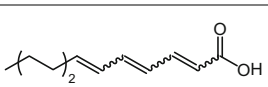
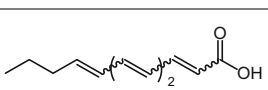
(a) ingenol esters
(b) ingenol mono (13-hydroxy-, 16-hydroxy-, 17-hydroxy-, 19-hydroxyingenol) and dihydroxy (13,16-dihydroxy-, 13,17-dihydroxyingenol) esters
(c) tetrahydroingenol esters

Table 1 Ester groups found in ingenoids

Abbreviation	Name	Formula
Ac	Acetic acid	
Prop	Propionic acid	
*i*Bu	Isobutyric acid	
2Me-C_4	2-Methylbutyric acid	
2,3-Me-C_4	2,3-Dimethylbutyric acid	
C_5	Pentanoic acid	
Ang	Angelic acid	
Tigl	Tiglic acid	
C_6	Hexanoic acid	
$\Delta^{2,4}$-C_6	2,4-Hexadienoic acid	
C_8	Octanoic acid	
Δ^{2}-C_8	2-Octenoic acid	
2,6-Me-C_8	2,6-Dimethyloctanoic acid	
2-Me-C_9	2-Methylnonanoic acid	

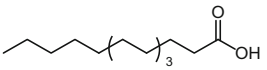
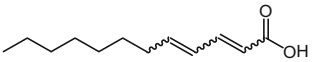
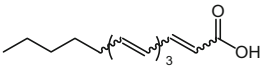
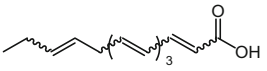
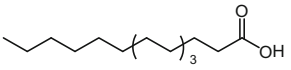
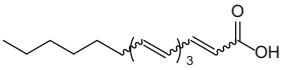
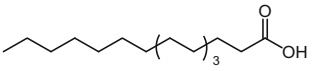
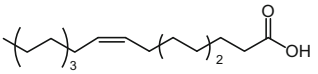
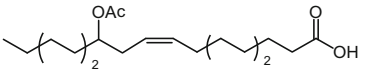
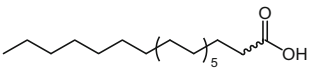
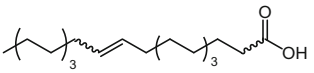
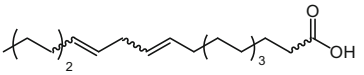
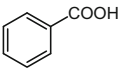
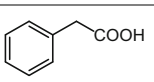
(continued)

Table 1 (continued)

Abbreviation	Name	Formula
2,6-Me-C_9	2,6-Dimethylnonanoic acid	
C_{10}	Decanoic acid	
D2,4-C_{10}	2,4-Decadienoic acid	
(*E*,*Z*)-D2,4-C_{10}	(2*E*,4*Z*)-Decadienoic acid	
(*E*,*Z*)-D2,4-C_{10}	(2*E*,4*E*)-Decadienoic acid	
D2,4,6-C_{10}	(2*E*,4*E*,6*E*)-Decatrienoic acid	
2-Me-C_{10}	2-Methyldecanoic acid	
2,6-Me-C_{10}	2,6-Dimethyldecanoic acid	
2-Me-C_{11}	2-Methylundecanoic acid	
2,6-Me-C_{11}	2,6-Dimethylundecanoic acid	
C_{12}	Dodecanoic (lauric) acid	
$\Delta^{2,4}$-C_{12}	2,4-Dodecadienoic acid	
$\Delta^{2,4,6}$-C_{12}	2,4,6-Dodecatrienoic acid	
$\Delta^{2,4,6,8}$-C_{12}	2,4,6,8-Dodecatetraenoic acid	

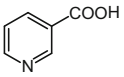
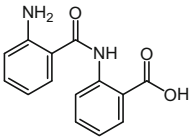
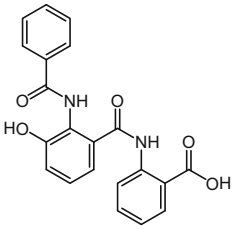
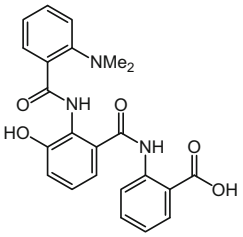
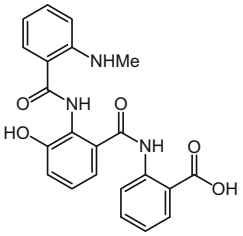
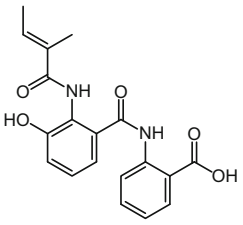
(continued)

Table 1 (continued)

Abbreviation	Name	Formula
C_{14}	Tetradecanoic (myristic) acid	
(*E*,*Z*)-$\Delta^{2,4}$-C_{14}	(*E*,*Z*)-2,4-Tetradecadienoic acid	
$\Delta^{2,4,6,8}$-C_{14}	2,4,6,8-Tetradecatetrienoic acid	
$\Delta^{2,4,6,8,10}$-C_{14}	2,4,6,8,10-Tetradecapentaenoic acid	
C_{15}	Pentadecanoic acid	
$\Delta^{2,4,6,8}$-C_{15}	2,4,6,8-Pentadecatetraenoic acid	
C_{16}	Hexadecanoic (palmitic) acid	
(*Z*)-Δ^{9}-C_{18}	Oleic acid	
12-OAc-(*Z*) −Δ^{9}-C_{18}	12-*O*-Acetylricinoleic acid	
C_{20}	Eicosanoic acid	
Δ^{11}-C_{20}	11-Eicosenoic acid	
$\Delta^{11,14}$-C_{20}	11,14-Eicosadienoic acid	
Bz	Benzoic acid	
PhAc	Phenylacetic acid	

(continued)

Table 1 (continued)

Abbreviation	Name	Formula
Nic	Nicotinic acid	
P1	2-(2-Aminobenzamido)benzoic acid	
P2	2-(2-(Benzamido)-3-hydroxybenzamido)benzoic acid	
P3	2-(2-(2-(Dimethylamino)benzamido)-3-hydroxybenzamido)benzoic acid	
P4	2-(3-Hydroxy-2-(2-methylamino)benzamido)benzamido)benzoic acid	
P5	(*E*)-2-(3-Hydroxy-2-(2-methylbut-2-enamido)benzamido)benzoic acid	

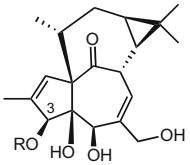
(d) 20-deoxyingenol esters
(e) mono (13-hydroxy-, 16-hydroxy-, 17-hydroxy)- and dihydroxy (13,17-dihydroxy-) 20-deoxyingenol esters
(f) 5-deoxyingenol esters.

Within each class, compounds are ordered according to increasing acylation, from monoesters to tetraesters, and with an increasing number of carbons of the longest linear sequence of their side chains. Abbreviations are used for the acyl group (Table 1). Thus, Δ is used to indicate the presence of an unsaturation, and Me for methyl branching, while the chain length is indicated using a "Cn" code, where n is the number of the longest linear carbon sequence of the acyl group. Irritancy data, mostly from the mouse ear erythema assay, are the only data available for most of these compounds, and will be discussed briefly, in an anticipation of the general coverage in Sect. 4.4.1.

2.4.1 Ingenol 3-Monoesters

Compounds of this type are by far the largest group of ingenoids. The acyl group is generally aliphatic, sometimes extensively unsaturated, and with methyl branching at the α(2)- and the ε(6)-carbons. The configuration at the stereogenic double bonds and carbons of these side chain has, in general, not been assigned, and it is not clear if diastereomeric forms occur, as shown for unsaturated acids like 2,4-decadienoic acid, which has been found to occur both in the (2*E*,4*Z*) and (2*E*,4*E*) diastereomers. Many individual esters could not be obtained in pure form, but were only isolated as mixtures, and the nature of the acyl groups was identified by GC analysis of the methyl esters obtained by transesterification of the mixture of the corresponding 5,20-acetonides. Of special taxonomic relevance is the occurrence of the structurally unique anthranilate-base tripeptides named milliamines. The biogenesis of these tripeptides, especially the derivation of the 2-amino-3-hydroxybenzoyl moiety, is unknown. While esterification with acyl long chains is associated with both irritancy and tumor-promoting activity, these properties can be dissected, since unsaturation decreases tumor promotion, which is completely absent in the highly irritant tripeptide esters [52]. Interestingly, unsaturation as well as shortening of the acyl moiety accelerate the attainment of the peak of irritancy in the mouse ear erythema assay. For instance, this is ca. 24 h for ingenol 3-tetradecanoate, but only ca. 5 h for ingenol 3-angelate (**5**) [52].

Table 2 Naturally occurring ingenol 3-esters



53a–53w

Compound	R	Source	Ref
53a (= **5**)	Ang	*E. antiquorum* L.	[53]
		E. canariensis	[54]
		E. drummondii Boiss.	[55]
		E. hirta L.	[55]
		E. helioscopia	[56]
		E. paralias	[57]
		E. peplus	[58, 59]
		E. virgata Waldst. & Kit	[60]
53b	C_8	*E. peplus*	[61]
53c	2,6-Me-C_8	*E. resinifera*	[52]
53d	2-Me-C_9	*E. resinifera*	[52]
53e	2,6-Me-C_9	*E. resinifera*	[52]
53f	C_{10}	*E. kamerunica* Pax	[62]
53g	2-Me-C_{10}	*E. resinifera*	[62]
		E. virgata	[60]
53h	$\Delta^{2,4}$-C_{10}	*E. esula*	[56]
		E. helioscopia	[56]
		E. lathyris	[60]
		E. tirucalli	[63]
53i	(*E*,*E*)-$\Delta^{2,4}$-C_{10}	*E. kansui*	[64, 65]
53j	(*E*,*Z*)-$\Delta^{2,4}$-C_{10}	*E. helioscopia*	[56]
		E. kansui	[65, 66]
53k	$\Delta^{2,4,6}$-C_{10}	*E. ingens*	[67, 68]
		E. esula	[56]
		E. lathyris	[60]
		E. tirucalli	[63]
53l	2,6-Me-C_{10}	*E. resinifera*	[52]
53m	2-Me-C_{11}	*E. resinifera*	[52]
53n	2,6-Me-C_{11}	*E. resinifera*	[52]
53o	C_{12}	*E. kamerunica*	[62]
		E. esula	[56]
53p	$\Delta^{2,4}$-C_{12}	*E. lathyris*	[60]
53q	$\Delta^{2,4,6}$-C_{12}	*E. esula*	[56]
		E. lathyris	[69, 70]
		E. tirucalli	[63]

(continued)

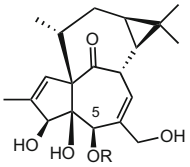
Table 2 (continued)

Compound	R	Source	Ref
53r	$\Delta^{2,4,6,8}$-C_{12}	*E. esula*	[56]
		E. tirucalli	[63]
53t	C_{14}	*E. broteri* Daveau	[71]
		E. wallichii Hook.f.	[72]
53u	(*E,Z*)-$\Delta^{2,4}$-C_{14}	*E. petiolata*	[73, 74]
53v	$\Delta^{2,4,6,8}$-C_{14}	*E. nematocypha* Hand.-Mazz	[75]
		E. tirucalli	[63]
53w	$\Delta^{2,4,6,8,10}$-C_{14}	*E. lathyris*	[69, 70]
		E. esula	[56]
		E. jolkini Boiss.	[76]
		E. tirucalli	[63]
53x	$\Delta^{2,3,6,8}$-C_{15}	*E. nematocypha*	[75]
53y (=2)	C_{16}	*E. ingens*	[3]
		E. lathyris	[2]
		E. serrata L.	[77]
		E. wallichii	[72]
53z	P2	*E. milii*	[78, 79]
53aa	P3	*E. milii*	[78, 79]

2.4.2 Ingenol 5-Monoesters

Ingenol 3-monoesters rearrange to their corresponding 20-esters with the intermediate formation of 5-monoesters (for a mechanistic discussion of the reaction, see Sect. 3.1.6), and represent therefore essentially extraction and/or fractionation artefacts. Ingenol 5-monoesters are not stable, and rapidly generate ingenol 20-esters under acidic or basic conditions. Mild treatment of the ingenol 20-esters

Table 3 Naturally occurring ingenol 5-monoesters



54a–54d

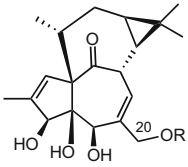
Compound	R	Source	Ref
54a	$\Delta^{2,4}$-C_6	*E. kamerunica*	[62]
54b	Δ^{2}-C_8	*E. kamerunica*	[62]
54c	(*E,Z*)−$\Delta^{2,4}$-C_{10}	*E. kansui*	[64]
54d	C_{14}	*E. broteri*	[71]

can, however, lead to the generation of 5-esters, at least with saturated acyl groups [53]. Interestingly, ingenol-5-decanoate shows irritant activity, possibly related to partial retro-equilibration to its corresponding 3-decanoate [52], but the general instability of these compounds, and their difficult preparation, have precluded a systematic investigation of their biological profile.

2.4.3 Ingenol 20-Monoesters

Compounds of this type are the stable final products of the acyl rearrangement of ingenol 3-monoesters, and are, most probably, isolation artifacts, devoid of the significant irritancy associated with their corresponding 3-esters. Since they are

Table 4 Naturally occurring ingenol 20-monoesters



55a–55l

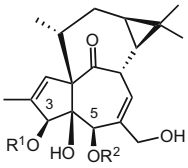
Compound	R	Source	Ref.
55a	Ac	*E. segetalis* L.	[199]
		E. kansui	[64]
55b	*i*Bu	*E. cotinifolia* L.	[200]
55c	C_6	*E. serrata*	[77]
55d	C_8	*E. peplus*	[61]
55e	(*E*,*E*)-$\Delta^{2,4}$-C_{10}	*E. kansui*	[64]
55f	(*E*,*Z*)-$\Delta^{2,4}$-C_{10}	*E. kansui*	[64]
55g	C_{14}	*E. broteri*	[71]
		E. wallichii	[72]
55h	C_{16}	*E. ingens*	[67, 68]
		E. lathyris	[69]
		E. nematocypha	[201]
		E. quinquecostata Volkens	[202]
		E. serrata	[77]
		E. sieboldiana Morren & Decne.	[203]
		E. wallichii	[72]
55i	C_{20}	*E. iberica* Boiss.	[204]
		E. kansui	[64]
55j	Bz	*E. virgata*	[60]
55k	PhAc	*E. virgata*	[60]
55l	P3	*E. milii*	[77]

generated under physiological conditions, it would, nevertheless, be interesting to investigate their biological profile and evaluate if, and to what extent, they contribute to the complex biological profile of ingenol 3-esters.

2.4.4 Ingenol 3,5-Diesters

Compounds of this type are unstable towards acyl rearrangement and quickly generate their corresponding 5,20- and 3,20-diesters.

Table 5 Naturally occurring ingenol 3,5-diesters



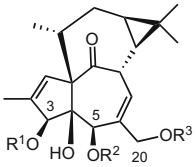
56a–56g

Compound	R^1	R^2	Source	Ref
56a	P2	Ac	*E. milii*	[79]
56b	P3	Ac	*E. milii*	[78, 79]
56c	Prop	*i*Bu	*E. cotinifolia*	[205]
56d	Prop	2-Me-C_4	*E. cotinifolia*	[205]
56e	*i*Bu	*i*Bu	*E. cotinifolia*	[205]
56f	(*E*,*E*)-$\Delta^{2,4}$-C_{10}	Ac	*E. kansui*	[64]
56g	(*E*,*Z*)$\Delta^{2,4}$-C_{10}	Ac	*E. kansui*	[64]

2.4.5 Ingenol 3,20-Diesters and 5,20-Diesters

It is not clear if compounds of this type are genuine natural products, or if, conversely, they are the result of acyl rearrangement from the corresponding and, sometimes co-occurring, 3,5-diesters. The 5,20-diesters are stable to transesterification, and acyl rearrangement is slow in 3,20-diesters, highlighting the relevance of a free primary 20-hydroxy group as an anchor for the migration of secondary acyl groups from the 3- and 5-hydroxy functionalities. The most representative member of the 3,20-diesters is the antitumor agent ingenol dibenzoate, which was subjected to a structure-activity study for this type of effect (see Sect. 4.1.4).

Table 6 Naturally occurring ingenol 3,20-diesters and 5,20-diesters



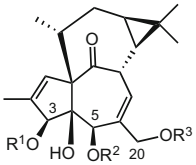
57a–57s

Compound	R^1	R^2	R^3	Source	Ref.
57a	Ang	H	Ac	*E. canariensis*	[54]
				E. helioscopia	[56]
				E. hermentiana Lem.	[105]
				E. kamerunica	[62]
				E. peplus	[59]
				E. trigona Mill.	[206]
57b	Tigl	H	Prop	*E. cotinifolia*	[200]
57c	2-Me-C_4	H	Prop	*E. cotinifolia*	[200]
57d	Prop	H	*i*Bu	*E. cotinifolia*	[200]
57e	*i*Bu	H	*i*Bu	*E. cotinifolia*	[200]
57f	Δ^2-C_8	H	Ac	*E. kamerunica*	[62]
57g	(*E*,*E*)-$\Delta^{2,4}$-C_{10}	H	Ac	*E. broteri*	[71]
				E. kansui	[83, 207]
57h	(*E*,*Z*)-$\Delta^{2,4}$-C_{10}	H	Ac	*E. kansui*	[64]
				E. petiolata	[74]
57i	$\Delta^{2,4}$-C_{10}	H	Ac	*E. biglandulosa* Desf.	[208]
57j	$\Delta^{2,4,6}$-C_{10}	H	Ac	*E. biglandulosa*	[208]
57k	Bz	H	Bz	*E. esula*	[145]
57l	P1	H	Ac	*E. milii*	[79]
57m	H	P1	Ac	*E. milii*	[79]
57n	P4	H	Ac	*E. milii*	[79]
57o	P3	H	Ac	*E. leuconeura* L.	[209]
				E. milii	[103]
57p	P3	Ac	H	*E. milii*	[103]
56q	P2	H	Prop	*E. leuconeura*	[209]
57r	H	P2	Ac	*E. milii*	[79]
57s	H	P3	Ac	*E. milii*	[79]

2.4.6 Ingenol 3,5,20-Triesters

Many compounds of this class contain anthranilate-based short peptides and come from *E. milii* and a few closely related species. Remarkably, all the statistical possibilities of the combination of three acyl groups may be present in the same plant, suggesting a randomized biogenetic strategy of acylation, in sharp contrast to glycerides, where a preference for a specific position exists depending upon the nature of the acyl group.

Table 7 Naturally occurring ingenol 3,5,20-triesters



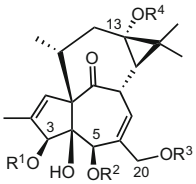
58a–58o

Compound	R^1	R^2	R^3	Source	Ref.
58a	Ac	Ac	C_{14}	*E. broteri*	[71]
58b	Ang	Ac	Ac	*E. acrurensis* N.E. Br.	[210]
				E. canariensis	[54]
				E. esula	[73, 74]
				E. petiolata	[73, 74]
58c	C_{14}	Ac	Ac	*E. broteri*	[71]
58d	Ac	C_{14}	Ac	*E. broteri*	[71]
58e	Ac	(*E*,*Z*)-$\Delta^{2,4}C_{14}$	Ac	*E. petiolata*	[74]
58f	(*E*,*Z*)-$\Delta^{2,4}$-C_{14}	Ac	Ac	*E. petiolata*	[74]
58g	P1	Ac	Ang	*E. cornigera*	[160]
58h	P1	Ang	Ac	*E. cornigera*	[160]
58i	Ac	P1	Ang	*E. cornigera*	[160]
58j	Ac	P1	Ac	*E. milii*	[79]
58k	Ac	Ang	P1	*E. cornigera*	[160]
58l	Ang	Ac	P1	*E. cornigera*	[160]
58m	Ang	P1	Ac	*E. cornigera*	[160]
58n	Ac	P1	Ac	*E. cornigera*	[160]
58o	P1	Ac	Ac	*E. cornigera*	[160]

2.4.7 13-Hydroxyingenol Esters

In this relatively small group of compounds, for which the first member was reported in 1974 from *E. kansui* Liou ex S.B. Ho the tertiary 13-hydroxy group is generally acylated, and the acylation profile shows the variation expected from the possibility of intramolecular migration of acyl groups from the 3- to the 5- and 20-hydroxy groups. It is therefore not clear what compounds are genuine natural products, and so they have consequently been grouped in one single class.

Table 8 Naturally occurring 13-hydroxyingenol esters



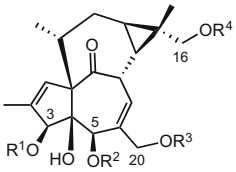
59a–59o

Compound	R^1	R^2	R^3	R^4	Source	Ref.
59a	H	H	H	C_{12}	*E. kansui*	[211]
59b	2,3-Me-C_4	H	H	C_8	*E. esula*	[212]
59c	2,3-Me-C_4	H	H	C_{10}	*E. cyparissias*	[213]
					E. kansui	[207, 214]
59d	2,3-Me-C_4	H	H	C_{12}	*E. cyparissias*	[213]
					E. kansui	[207]
59e	2,3-Me-C_4	H	Ac	C_{12}	*E. kansui*	[214]
59f	H	2,3-Me-C_4	H	C_{12}	*E. cyparissias*	[213]
59g	H	H	C_6	C_{12}	*E. kansui*	[104]
59h	H	H	Ang	Ac	*E. cornigera*	[82]
59i	H	Ang	H	Ac	*E. cornigera*	[82]
59j	H	H	2,3-Me-C_4	C_{12}	*E. cyparissias*	[213]
					E. kansui	[214]
59k	C10	H	C6	H	*E. esula*	[212]
59l	Bz	H	H	Bz	*E. esula*	[212]
59m	2,3-Me-C_4	Ac	C_6	C_{12}	*E. cornigera*	[82]
59n	Bz	H	H	C_8	*E. esula*	[212]
59o	2,3-Me-C_4	Ac	Ac	C12	*E. kansui*	[211]

2.4.8 16-Hydroxyingenol Esters and 17-Hydroxyingenol Esters

In the early studies on ingenoids, hydroxylation at C-16 was established based exclusively on considerations of chemical shift differences with the parent polyol ingenol. Whenever rigorous 2D-NMR measurements were done, the hydroxylation site on the geminal methyls was, however, always located at C-17. Since the chemical shift considerations underlying the location of the ester group at C-16 also hold for their 17-isomers, the structure of the C-16 esters should be probably revised to their corresponding C-17 isomers. Indeed, the ^{1}H NMR spectroscopic data of compounds from the two series are very similar, although the spectra of the 16-esters have not been fully assigned and a comparison of the whole NMR spectrum is therefore not possible. Interestingly, phorbol esters are indeed generally hydroxylated at the 16-methyl [3], and this might have biased the original structure assignment of the ingenol esters. Hydroxylation at C-16 of ingenol esters was found detrimental for both irritancy and tumor promotion [67].

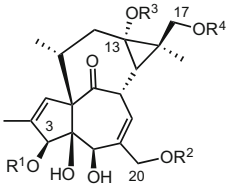
Table 9 Naturally occurring 16-hydroxyingenol esters



60a–60g

Compound	R^1	R^2	R^3	R^4	Source	Ref.
60a	Ang	H	H	Bz	*E. canariensis*	[215]
60b	$\Delta^{2,4,6}$-C_{10}	H	H	Ang	*E. hermentiana*	[105]
					E. ingens	[67]
60c	Ang	H	Ac	H	*E. hermentiana*	[105]
60d	Ang	H	Ac	Ac	*E. hermentiana*	[105]
60e	Ang	H	Ac	Bz	*E. cornigera*	[82]
60f	Ang	Ac	Ac	Ac	*E. hermentiana*	[105]
60g	Ac	H	Ang	Bz	*E. canariensis*	[215]

Table 10 Naturally occurring 17-hydroxyingenol esters



62a–62l

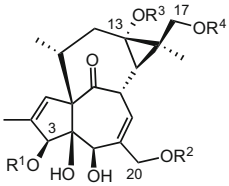
Compound	R^1	R^2	R^3	R^4	Source	Ref.
61a	H	H	C16	H	*E. quinquecostata*	[202]
61b	H	H	H	$\Delta^{2,4,6}$-C10	*E. caducifolia* Haines	[216]
61c	Ang	H	H	$\Delta^{2,4,6}$-C_{10}	*E. caducifolia*	[216]
61d	Ac	H	Ang	H	*E. caducifolia*	[216]
61e	Ang	H	H	Ac	*E. caducifolia*	[216]
61f	Ang	H	Ac	H	*E. caducifolia*	[216]
					E. canariensis	[54]
61g	Ang	H	H	Bz	*E. caducifolia*	[216]
					E. canariensis	[54]
61h	H	Ang	H	Bz	*E. canariensis*	[54]
61i	Ang	H	Ac	Bz	*E. canariensis*	[54]
					E. caducifolia	[216]
61j	Ang	Ac	Ac	Ac	*E. trigona*	[206]
					E. kamerunica	[217]
61k	Ac	Ang	H	Bz	*E. caducifolia*	[216]
61l	Ac	Ac	Ac	Ac	*E. kamerunica*	[217]

Some data on the chemical behavior of these compounds have been reported. Thus, in basic conditions, hydrolytic removal of the secondary ester at C-3 is often easier than that of the neopentylic primary ester at C-16, while the opposite holds when the reaction is carried out under acidic conditions, so that selective hydrolyses are possible. Also worth mentioning is the hydroxylation of I3A to its 16-hydroxy derivative by cell cultures of barley (*Hordeum vulgare* L.) [81]. Interestingly, activity against melanoma cells was retained by hydroxylation of the 16-methyl group [82]. Furthermore in this case, however, the location of the hydroxylation needs confirmation.

2.4.9 13,17-Dihydroxyingenol Esters

Most compounds from this type were isolated from a single Chinese collection of *E. esula* L., but are, otherwise, very rare in spurges. What is also remarkable is the replacement of the angelate residue with its reduced version. Interestingly, other collections of *E. esula* gave instead less hydroxylated ingenol esters (see Sect. 4.4).

Table 11 Naturally occurring 13,17-dihydroxyingenol esters



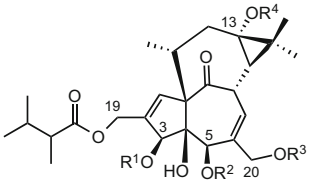
62a–62m

Compound	R^1	R^2	R^3	R^4	Source	Ref.
62a	Bz	H	Ac	H	*E. segetalis* L.	[199]
62b	Ang	H	Ac	H	*E. segetalis*	[199]
62c	2,3-Me-C_4	H	2,3-Me-C_4	Bz	*E. esula*	[212]
62d	H	2,3-Me-C_4	2,3-Me-C_4	Bz	*E. esula*	[212]
62e	H	H	C_8	Bz	*E. esula*	[212]
62f	Bz	H	C_8	Bz	*E. esula*	[212]
62g	H	Bz	C_8	Bz	*E. esula*	[212]
62h	2,3-Me-C_4	H	C_8	Bz	*E. esula*	[212]
62i	H	2,3-Me-C_4	Bz	Bz	*E. esula*	[212]
62j	H	2,3-Me-C_4	C8	Bz	*E. esula*	[212]
62k	Bz	H	Bz	Bz	*E. esula*	[212]
62l	2,3-Me-C_4	H	Bz	Bz	*E. esula*	[212]
62m	Bz	H	2,3-Me-C_4	Bz	*E. esula*	[212]

2.4.10 13,19-Dihydroxyingenol Esters

Hydroxylation at the allylic C-19 methyl is very rare, and has so far been observed only in a single species (*E. cyparissias* L.). All compounds bear a 2,3-dimethylbutanoyl residue of unknown configuration at C-19.

Table 12 Naturally occurring 13,19-dihydroxyingenol esters



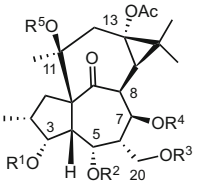
63a–63c

Compound	R^1	R^2	R^3	R^4	Source	Ref.
63a	2,3-Me-C_4	H	H	2,3-Me-C_4	*E. cyparissias*	[213]
63b	H	2,3-Me-C_4	H	2,3-Me-C_4	*E. cyparissias*	[213]
63c	H	H	2,3-Me-C_4	2,3-Me-C_4	*E. cyparissias*	[213]

2.4.11 Tetrahydroingenol Esters

Ingenoids of this type have so far only be isolated from *E. erythradenia* Boiss., a spurge endemic to Iran. These compounds are characterized by hydroxylation at C-7, C-11, and C-13, and represent a unique class of phorboids. Also remarkable is the esterification pattern, which includes nicotinic acid, a residue common in the *Euphorbia* macrocyclic diterpenoids, but uncommon in phorboids. Some spectroscopic features of these compounds are also unusual for ingenoids,

Table 13 Naturally occurring tetrahydroingenol esters



64a–64d

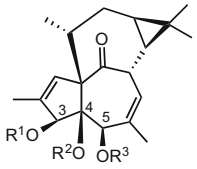
Compound	R^1	R^2	R^3	R^4	R^5	Source	Ref.
64a	But	Ang	Nic	H	H	*E. erythradenia*	[218]
64b	Prop	Ang	Nic	Ac	H	*E. erythradenia*	[218]
64c	Prop	Ac	Nic	Bz	H	*E. erythradenia*	[218]
64d	But	Ang	H	H	Nic	*E. erythradenia*	[218]

especially the relatively upfield shift of C-10 (δ 48.6, vs. ca. δ 70 ppm in ingenol esters). The nature of the bridge was not clearly evaluated, and was suggested to be of the *out,out*-type. Further investigation on these compounds is surely warranted, owing to the marked deviation from the basic structural chemotype of the class also in terms of configuration of the C-3 and C-5 hydroxy groups, and in terms of deoxygenation at C-4.

2.4.12 20-Deoxyingenol Esters

This type of ingenoids was first reported in 1974 from *E. kansui* [83], and is of considerable interest because of the potent irritancy still exerted by its 3-esters, a surprising observation because the primary 20-hydroxy group was previously considered essential for the irritancy of ingenane derivatives. Thus, **65a**, the 20-deoxy derivative of I3A (**5**), was reported to be one order of magnitude more potent as a skin-irritant than **5** in the mouse ear erythema assay [57, 84], and even showed a more rapid onset of activity. The molecular targets involved in the potent irritancy induced by these compounds are unknown, and the activity might, indeed,

Table 14 Naturally occurring 20-deoxyingenol esters



65a–65l

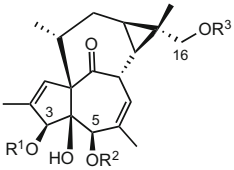
Compound	R^1	R^2	R^3	Source	Ref.
65a	Ang	H	H	*E. helioscopia*	[56]
				E. paralias	[84]
				E. peplus	[61]
65b	Ac	Ang		*E. kansui*	[219]
65c	C_6	H	H	*E. paralias*	[84]
65d	(*E*,*Z*)-$\Delta^{2,4}$-C_{10}	H	H	*E. kansui*	[214]
65e	(*E*,*E*)-$\Delta^{2,4}$-C_{10}	H	H	*E. kansui*	[214]
65f	$\Delta^{2,4,6}$-C_{10}	H	H	*E. biglandulosa*	[208]
65g	H	H	$\Delta^{2,4,6}$-C_{10}	*E. biglandulosa*	[208]
				E. palustris	[220]
65h	Bz	H	H	*E. kansui*	[83]
65i	H	H	Ang	*E. peplus*	[61]
65j	H	H	Bz	*E. kansui*	[83]
				E. palustris	[220]
65k	Bz	H	Bz	*E. palustris*	[220]
65l	H	Ac	Bz	*E. palustris*	[220]

be independent from PKC. The Baran synthesis of ingenol (see Sect. 3.2) can provide an expeditious access to this type of compounds, and could make possible the clarification of this important issue.

2.4.13 16- and 17-Hydroxy-20-deoxyingenol Esters

The same considerations referred to above for the 16- and 17-esters of ingenols also hold for the corresponding esters of 20-deoxyingenol, namely, that the structure of the 16-hydroxy derivatives probably need revision, and location of the neopentyl

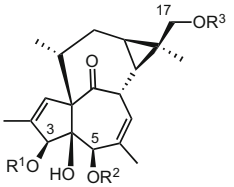
Table 15 Naturally occurring 16-hydroxy-20-deoxyingenol esters



66a–66c

Compound	R^1	R^2	R^3	Source	Ref.
66a	Ang	H	Ac	*E. quadrialata* Pax	[220]
				E. hermentiana	[105]
66b	Bz	H	Bz	*E. quadrialata*	[220]
66c	H	Bz	Bz	*E. quadrialata*	[220]

Table 16 Naturally occurring 17-hydroxy-20-deoxyingenol esters



67a–67i

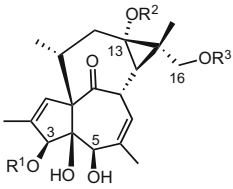
Compound	R^1	R^2	R^3	Source	Ref.
67a	Ang	H	Ac	*E. trigona*	[206]
67b	Ang	H	Ang	*E. esula*	[212]
67c	Bz	H	Bz	*E. esula*	[212]
67d	Ang	H	Bz	*E. esula*	[212]
67e	2,3-Me-C_4	H	Bz	*E. esula*	[212]
67f	H	Ang	Tigl	*E. neriifolia* L.	[221]
67g	Ac	Ang	H	*E. neriifolia*	L. [221]
67h	Bz	H	Bz	*E. quadrialata*	[220]
67i	H	Bz	Bz	*E. quadrialata*	[220]

hydroxylated residue should be moved to C-17. In fact, the spectroscopic data of compounds **66a** and **66b** are very similar to those of the 17-hydroxyingenol esters **67a** and **67c**.

2.4.14 16- and 17-Hydroxy-20-deoxy-13-hydroxyingenol Esters

Esters of 13,16-dihydroxy-20-deoxyingenol have so far been isolated from a single plant source (*E. palustris* L.), and probably need revision to the corresponding derivatives of 13,17-dihydroxy-20-deoxyingenol derivatives.

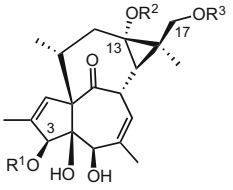
Table 17 Naturally occurring 13,16-dihydroxy-20-deoxyingenol esters



68a–68d

Compound	R^1	R^2	R^3	Source	Ref.
68a	Bz	H	Bz	*E. palustris*	[220]
68b	Bz	Bz	Bz	*E. palustris*	[220]
68c	Bz	PhAc	Bz	*E. palustris*	[220]
68d	Bz	Ac	Bz	*E. palustris*	[220]

Table 18 Naturally occurring 13,17-dihydroxy-20-deoxyingenol esters



69a–69c

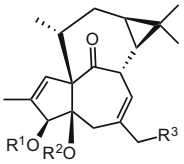
Compound	R^1	R^2	R^3	Source	Ref.
69a	2,3-Me-C_4	2,3-Me-C_4	Bz	*E. esula*	[212]
69b	Bz	C_8	Bz	*E. esula*	[212]
69c	2,3-Me-C_4	Bz	Bz	*E. esula*	[212]

2.4.15 5-Deoxyingenol Esters and Miscellaneous Ingenoids

The major source of these compounds is Chechum (*Mabea excelsa* Standl. & Steyerm.), a Central American highly irritant and toxic plant that was related to the development of a debilitating inflammatory condition experienced by British soldiers in Belize [85]. The toxic principle of the plant was named "Chechum toxin", and turned out to be a complex mixture of 5-deoxy-16-hydroxyingenol esters that can potently activate PKC [85]. There is also a report on the occurrence of a 5-deoxyingenol derivative in the latex of *E. canariensis* L. [54]. The presence of 5-deoxyingenol esters has been suggested as being typical of *Euphorbia* species from the section *Tithymalus* [48].

The 5,20-acetonides of some 3-esters of ingenol (tetradecanoate, 3-*O*-(2*E*,4*Z*)-tetradecadienoate, palmitate) were reported as natural products from *E. petiolata* Banks & Sol. [74] and *E. eubracteolata* Hayata [86], but are most probably isolation artifacts since acetone was used in their extraction and/or purification.

Table 19 Naturally occurring 5-deoxyingenol esters



70a–70g

Compound	R^1	R^2	R^3	Source	Ref.
70a	H	H	O-C_5	*Mabea excelsa*	[80]
70b	H	H	O-C_{14}	*Mabea excelsa*	[80]
70c	H	H	O-(*Z*)-Δ^9C_{18}	*Mabea excelsa*	[80]
70d	H	H	O-12OAc-Δ^9-C_{18}	*Mabea excelsa*	[80]
70e	H	H	O-Δ^{11}-C_{20}	*Mabea excelsa*	[80]
70f	H	H	O-$\Delta^{11,14}$-C_{20}	*Mabea excelsa*	[80]
70g	Ang	Ac	H	*E. canariensis*	[54]

2.5 Ecology

The skin-irritant properties of most ingenoids makes it reasonable that they play an ecological role as feeding deterrents, complementing the physical protection of spines in the succulent species of the genus *Euphorbia*. This strategy is successful with cattle, but goat and sheep can feed on spurges, while camels, dromedaries and rhinos can also consume the thorny succulent species with impunity [87]. The physiological basis for the insensitivity to oral irritation by phorboids observed in these animals is unknown, but excretion in milk represents a major detoxification route in lactating animals, making the milk and the dairy products derived

therefrom unsuitable for human consumption [87]. Ingenoids often co-occur with large amounts of macrocyclic diterpenoid esters [88, 89]. These, by inhibiting transport proteins like P-gp that are overexpressed in lactating mammary tissues [88, 89] could interfere with the transfer of diterpenoids from plasma to milk, potentially exacerbating the toxicity of spurges (see Sect. 4.4).

Also the larvae of some moths can feed with impunity on *Euphorbia* species, accumulating toxic phorboids in their body and carrying them into adult life as a protection against predators [90]. The hawk moth (*Hyles euphorbiae*) is capable of accumulating ingenol esters [91], and was even considered for the biological control of the leafy spurge (*Euphorbia esula*), a highly invasive species in the North American plains (see Sects. 4.2.4 and 4.4.2).

3 Chemistry

3.1 Reactivity

Ingenol, the parent polyol of ingenoids, is unstable to basic conditions as well as to atmospheric oxidation, but is relatively stable in mildly acidic media (pH 3–5), undergoing, however, skeletal rearrangements at more acidic values of pH [92]. No specific degradation product of treatment of ingenol with bases has been characterized, but the instability in these conditions might be related to the presence of the aldol motif (a carbonyl at C-9 and a hydroxy group at C-4), which makes possible retro-aldol equilibration at low pH values. This, rather than eventually leading to epimerization at C-4 as observed for phorbol [7], triggers a massive degradation process, presumably due to the instability of the bridged polycyclic system of ingenol. Quite remarkably, the 4,5-carbonate of synthetic 20-deoxyingenol (**71**) can, however, be deprotected to the parent polyol (**72**) under strong basic conditions (1 h stirring in 1:1 THF-10% NaOH) [16] (Fig. 13).

Reversible acyl migration to the primary 20-hydroxy group takes place in 3-acyl ingenol derivatives, scrambling the acylation pattern and potentially dramatically affecting the biological profile. These changes might underlie the practice of

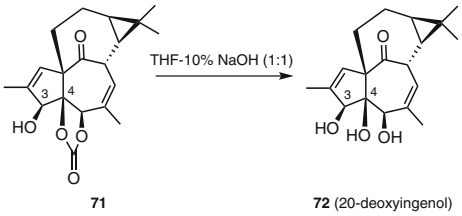


Fig. 13 Successful removal of the carbonate protection in 20-deoxyingenol carbonate under strongly basic conditions. (The reaction was part of a telescoped three-step process that gave an overall yield of 43%) [17]

vinegar baking associated with the medicinal use of certain plants like Kansui (*E. kansui*), a celebrated east Asian medicine for edema and asthma but also a rich source of ingenol esters [93].

Much data on the reactivity of ingenol has been obtained in the course of studies on its total synthesis rather than by modification of the natural polyol, but the development of ingenol mebutate (I3A, **5**) as a drug has rekindled systematic studies on the reactivity of the natural product.

3.1.1 Epimerization and Isomerization

Interest in the epimerization α- to the C-9 carbonyl was spurred by the availability of the totally synthetic C-8 epimerized analog **9**, potentially amenable of conversion to the natural product [18]. However, the epimerization to **73** never materialized, presumably because of its counter-thermodynamic trait, while ingenol is rapidly degraded in basic media, in accordance with the presence of a sugar-like string of adjacent hydroxy groups susceptible to retro-aldolization. On the other hand, the 5,20-acetonide **52** was converted in good yield into iso-ingenol 5,20-acetonide (**75**) by refluxing with NaH in anhydrous THF (Fig. 14) [20]. Surprisingly,

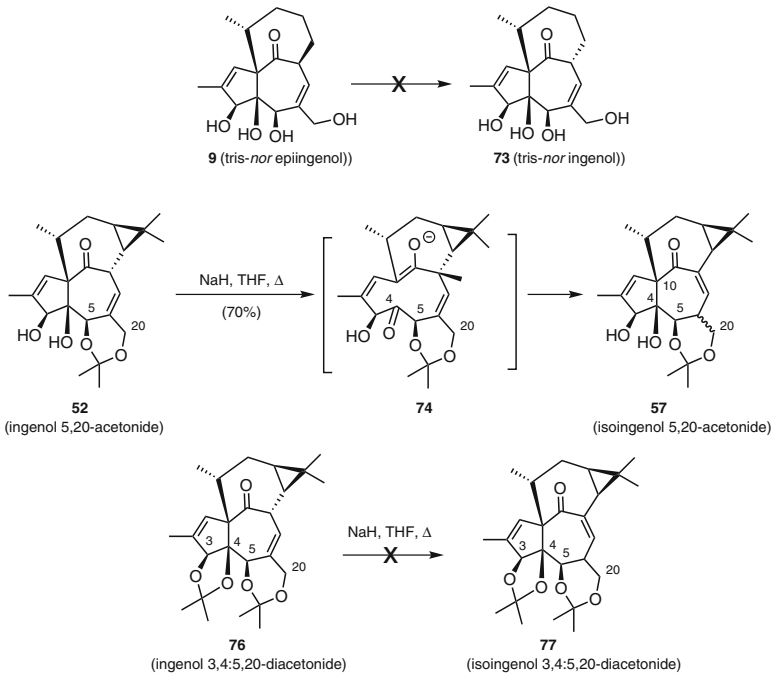


Fig. 14 Reaction of ingenoids with bases

the 3,4:5,20-bis acetonide **76** was stable under these conditions, as well as under a variety of other basic treatments used to epimerize carbonyl derivatives [41]. This observation suggests that epimerization takes place after retro-aldolization of **52** to **74**, and is next followed by aldolization. If so, the configuration of isoingenol at C-4 and C-10 should be confirmed. Esterification of isoingenol (**10**) led to 3-esters substantially devoid of irritancy [20], an observation reminiscent of the effect of epimerization at C-4 in phorbol esters [7]. The isomerization of ingenol to iso-ingenol is surprising, owing to the generation of an anti-Bredt, yet "isolable" olefin [94]. Apparently, the partial pyramidalization is compensated by a reduction of angular strain in the undecane cyclic core, but the generation of an anti-Bredt olefin by isomerization of a non-bridgehead double bond is nevertheless unusual, although not unprecedented [95].

3.1.2 Skeletal Rearrangements

On account of its considerable angular strain, the bridged tetracyclic skeleton of ingenol can rearrange to more stable polycyclic skeletons devoid of the transannular bridge. The first rearrangement of this type was observed with the (9*R*) reduction product of ingenol diacetonide (**78**), which, upon treatment with mesyl chloride in pyridine, afforded the trienic tigliane **82** [41]. The mechanism of the reaction involves activation of the 9-hydroxy group by mesylation, followed by its diplacement triggered by the anionotropic migration of C-11 and, eventually, by proton loss. The concerted nature of the rearrangement, which involves the back-side displacement of the mesylate, was confirmed by the results observed with the (9*S*) epimer **83**, where migration of C-4 and formation of the isomeric naphthalenyl diene **86** were observed instead [41] (Fig. 15).

A more direct rearrangement was discovered serendipitously while investigating the chemoselective deacylation of ingenol polyesters. Thus, overnight treatment of ingenol and its esters in 10^{-2} *N* $HClO_4$ in methanol triggered a retro-pinacol rearrangement initiated by protonation of the 9-carbonyl and terminated in a vinylogous fashion by stereoselective methanol trapping of a C-2 cation [92] (Fig. 16). The reaction is interesting since it provides access to uniquely functionalized ingenane derivatives, and, apart from ingenol esters, it could also be carried out on the native polyol itself. Its facile nature means that the acidic deprotection of ingenol acetonides, important synthetic intermediates, should be carefully controlled in terms of conditions and duration.

Remarkably, the opposite rearrangement, the formation of a C-9 oxo-ingenane from a C-10 hydroxylated tigliane, was critical in the Baran synthesis of ingenol (Fig. 17) [16]. This fundamentally counter-thermodynamic transformation could be steered into kinetic control and the generation of the ingenane derivative **90** by judicious choice of the reaction conditions (temperature, Lewis acid activation, quenching) and by exploiting the pre-organizing effect of carbonate protection of

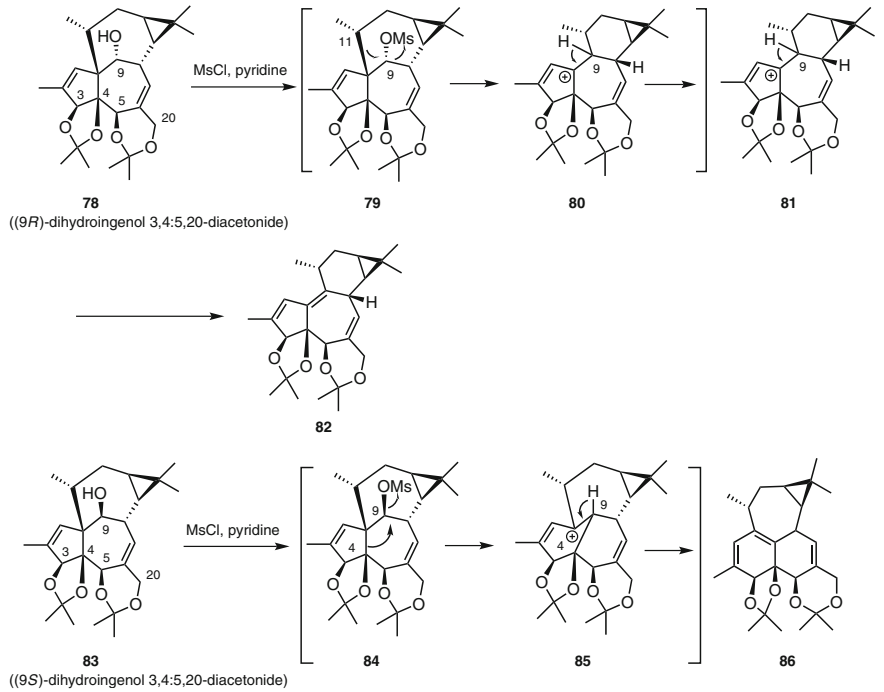


Fig. 15 Rearrangement of C-9 epimeric dihydroingenol esters

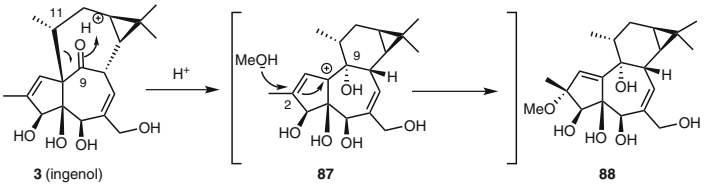


Fig. 16 Acidic rearrangement of ingenol to a tigliane derivative

the 4,5-diol group, with silylation of the C-10 hydroxy group being also critical to avoid oxygen trapping of the C-10 cation **88**. DFT calculations were used to rationalize some of these observations. Thus, the anionotropic migration of C-11 to C-10 in the vinylogous pinacol rearrangement is favored by silylation of the C-9 hydroxy group because of the possibility of hyperconjugative silyl β-stabilization of the resulting oxonium ion [96]. A plausible mimic of this process could be associated to Brønsted base activation of the 10-hydroxy group, for instance, by the ω-amino group of a lysine or by the basic imidazole nitrogen of a terpenoid cyclase. In this way, the positive charge on the oxonium ion generated by the anionotropic

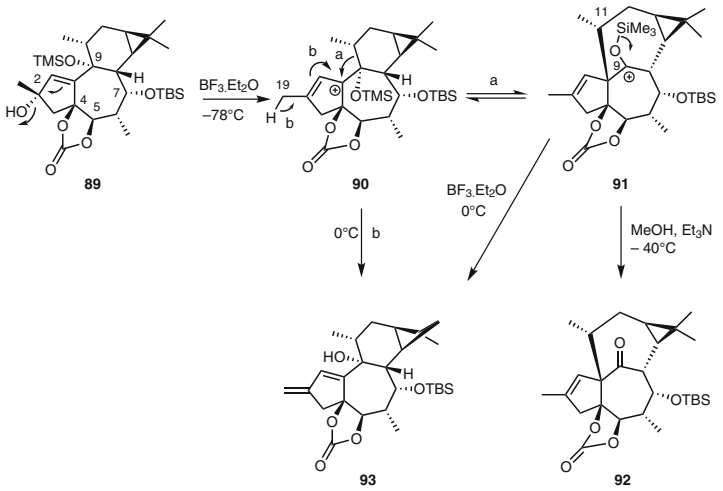


Fig. 17 The tigliane-to-ingenane rearrangement involved in the Baran synthesis of ingenol [16]

migration of the carbon-carbon bond could be stabilized by proton transfer to the Brønsted base, *overall turning an oxonium ion in a more stable ammonium ion,* an interesting and potentially general concept for the mechanism of activity of isoprenoid cyclases. Calculations also highlighted the stabilizing effect of oxygenated functions on ring A to favor the generation of an allyl cation by Lewis acid-promoted activation of the C-2 hydroxy group, presumably because of the associated inductive effect that tends to move the positive charge on the adjacent ring. The calculations showed that in the rearrangement of **89** to **92**, the effects of β-silyl stabilization, the presence of oxygenated functions on ring A, and the pre-organization effect of the carbonate, all combine to make the vinylogous pinacol rearrangement of the allylic cation on ring A favored in terms of both thermodynamics and in kinetics. On the other hand, the rearrangement is fundamentally reversible, and quenching at 0°C produced the thermodynamically favored exomethylene tigliane olefin **93**, while treatment of the ingenane **92** with $BF_3{\cdot}Et_2O$ at 0°C afforded the same tigliane olefin. Low-temperature quenching with methanol-triethylamine at −40°C eventually proved optimal to isolate the ingenane product of vinylogous pinacol rearrangement [16].

A different type of rearrangement of the bridged system was discovered in 13-hydroxyingenol esters by Hirata [97]. Since the 13-ester group could not be removed hydrolytically, a reductive removal with an excess $LiAlH_4$ was attempted. This triggered, via the cyclopropylogous version of a 1,3-sigmatropic rearrangement, the formation of a 12,13-enol ester (**95**), which then, after reductive cleavage, collapsed via an intramolecular aldol reaction, eventually affording the cyclobutane derivative **96**, characterized as a triacetate. This 9,12-cycloingenoid could be further rearranged after reduction of the C-13 carbonyl. Activation of

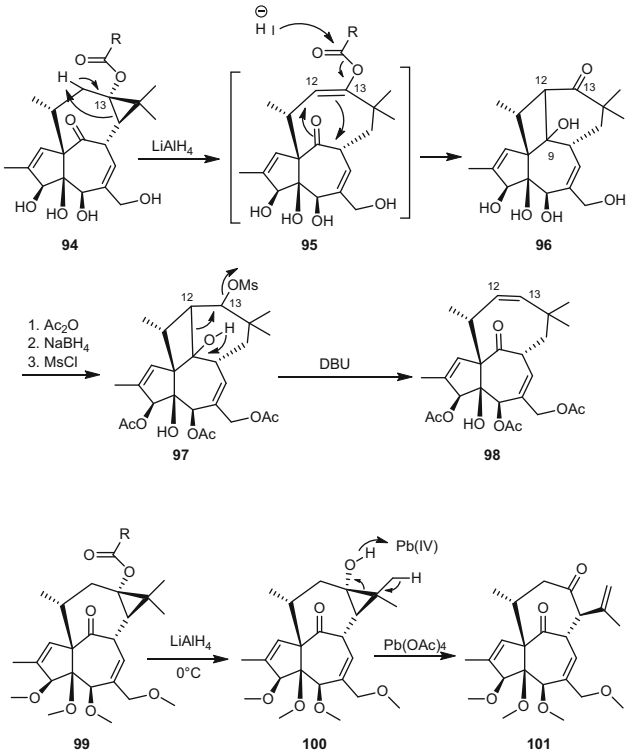


Fig. 18 Rearrangement of 13-hydroxyingenol

the resulting alcohol by mesylation, and treatment with diazabicycloundecane (DBU) triggered a Grob fragmentation that regenerated the 9-keto group and expansion of ring C to an eight-membered ring, eventually affording the D-*seco*-derivative **96**. With only a moderate excess of $LiALH_4$ and at low temperature, the permethylated derivative **99** afforded the expected C-13 alcohol, which, when treated with lead tetraacetate, underwent oxidative opening of the cyclopropane ring to generate the isopropenyldiketone **101** (Fig. 18).

3.1.3 Reduction

Reduction of the C-9 ketone carbonyl was investigated under several reaction conditions using the diacetonide **76** as a substrate since the natural polyol proved unstable to basic conditions. In general, this hindered keto group proved resistant to mild reducing agents, like $NaBH_4$, and stronger reducing agents were necessary [41]. The configuration of the resulting C-9 hydroxy group was found to be

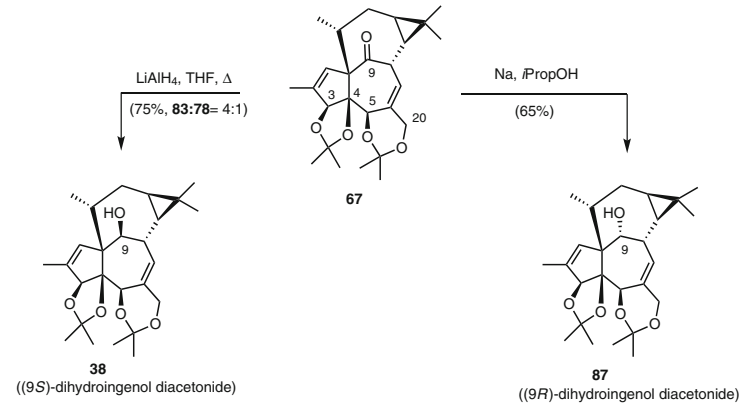


Fig. 19 Reduction of the C-9 carbonyl of ingenol diacetonide (**76**)

dependent on the reducing agent, with stereo-complementary results being obtained on hydride ($LiAlH_4$) and dissolving metal (Na/isopropanol, Bouveault-Blanc reduction) reductions (Fig. 19). The C-9 carbonyl was also not reduced by sodium amalgam (Na-Hg), and the chemoselective desulfurization of an ingenol 20-sulfone is featured in the final steps of the Wood total synthesis of ingenol [98]. Oxidation of the allylic hydroxy group at C-3 in ingenol 5,20-acetonide led to a 3-dehydro derivative that could not be reduced back to ingenol with hydrides or boranes [99]. The difficulty of reducing the C-9 carbonyl is predictable from its orientation on the concave and sterically encumbered α-face of the bridged system, but the situation with the C-3 carbonyl is unexpected, since this group can be easily reduced in phorbol. On the other hand, reduction of a C-3 carbonyl is featured in advanced ingenane intermediates in the total syntheses of ingenol by Winkler [19] and Wood [98].

Hydrogenation of ingenol triacetate led to the exclusive non- stereoselective saturation of the Δ^6 double bond, and was accompanied by hydrogenolysis of the primary 20-hydroxy group, with the Δ^1 double bond being unaffected [83].

3.1.4 Oxidation

The oxidation of the allylic 3-hydroxylated group was investigated in ingenol 5,20-acetonide (**52**). MnO_2 afforded a mixture of unidentified compounds, but the reaction succeeded with Cr(VI)-based reagents. The best results (80% yield) [99] were obtained with the Snatzke reagent (CrO_3-H_2SO_4 in DMF) [100].

The allylic oxidation of a 20-deoxyingenol (**103**) is a critical step in two total syntheses of ingenol, and is indeed the final step of the Baran synthesis [16], where it was efficiently carried out in terms of regiochemistry (exclusive formation of the

primary 20-alcohol) and chemoselectivity (avoidance of over-oxidation to a carbonyl derivative) under the Shibuya conditions (SeO_2-formic acid) [101].

Epoxidation of I3A (**5**) occurred chemo- and stereoselectively on the β-face of the Δ^6 double bond even with an excess of *meta*-chloroperbenzoic acid (MCPBA), affording the epoxide **104** as the only reaction product [102]. The oxidation of the allylic 20-hydroxy group of ingenol 3,5-dibenzoate (**57j**) failed with a variety of reagents (MnO_2, PCC, PDC). Using CrO_3 in the presence of 18-crown-6, the 20-enal **105** could be obtained, but as an inseparable mixture with the exomethylene enone **106** resulting from the [3]-sigmatropic rearrangement of the intermediate chromate ester [92]. A similar rearrangement occurred also during the reaction of an ingenyl 20-chloride with NaN_3, affording via the 20-azide **109**, the rearranged azide **110** as the only reaction product [92] (Figs. 20 and 21).

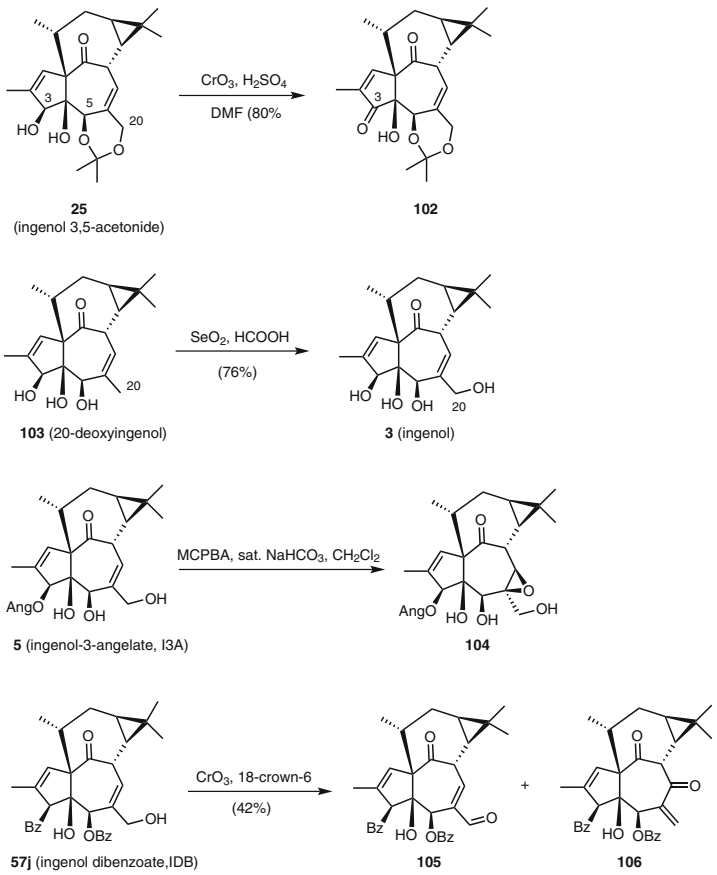


Fig. 20 Oxidative modifications of ingenoids

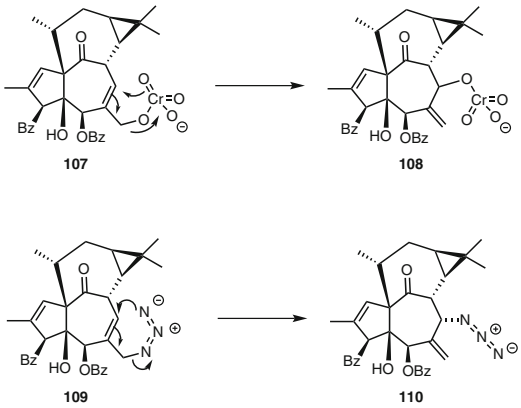


Fig. 21 [3.3] Sigmatropic rearrangement of ingenoids derivatized at C-20

3.1.5 Etherification and Acetalization

The primary 20-hydroxy group of ingenol (**3**) can be chemoselectively silylated and tritylated with, respectively, TBDMS-Cl (*tert*-butyldimethylsilyl chloride)-imidazole in DMF or trityl chloride in pyridine [92]. Removal of these protecting groups under controlled acidic conditions did not trigger acyl rearrangement from 3- and 5-esters to the 20-hydroxy group position [92]. Conversely, removal of the 20-silyl protection by fluoridolysis triggered acyl migration [92]. Reaction of ingenol with acetone in the presence of acids affords chemoselectively the seven-membered 5,20-acetonide **52** and only traces of the regio-isomeric 3,4-acetonide (**111**) [99]. The acetonide **52** is a stable and crystalline compound, and is a suitable storage form for the natural polyol, which is otherwise rapidly degraded in the solid state. Reaction of ingenol or its 5,20-acetonide (**52**) with the more reactive acetalizating agent isopropenyl methyl ether affords a 3,4:5,20-bis acetonide (**76**) [99]. The protection of the hydroxy groups with carboinyldimidazole gave similar results, with easier formation of the 5,20-carbonate compared to the 3,4-carbonate [103] (Fig. 22).

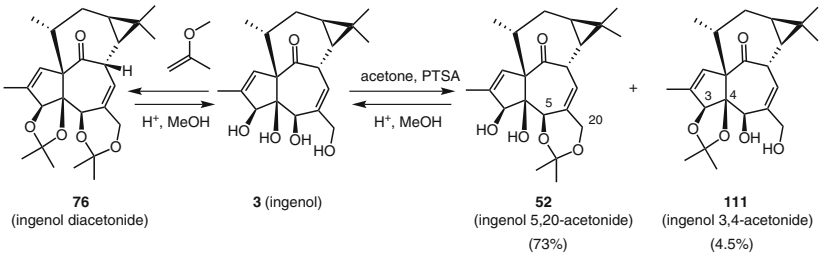


Fig. 22 Acetalization-deacetalization of ingenol

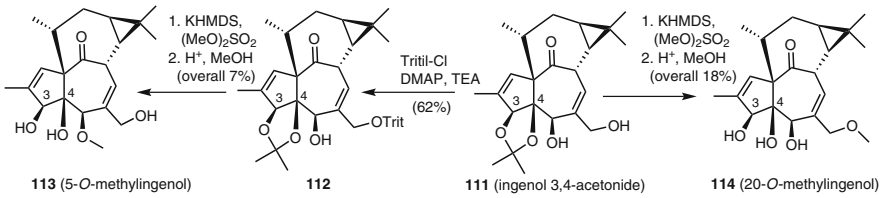


Fig. 23 Synthesis of ingenol 5- and 20-methyl ethers **113** and **114**

The chemoselectivity of the acetalization (formation of a seven-membered ring rather than a five-membered ring) is probably related to the strain induced by formation of an acetonide involving the tertiary hydroxy group at the A,B-ring junction. The acetonides could be hydrolyzed in acidic methanol [0.34% $HClO_4$ (70% *w*/*w*) in methanol] [92]. Starting from the minor 3,4-acetonide **111** formed as a side-product in the acetalization reaction, the primary hydroxy group could be selectively methylated by treatment with dimethyl sulfate and KHMDS. Methylation of the 5-hydroxy group could be achieved in the same conditions after protection of the 20-hydroxy group as trityl ether [102] (Fig. 23).

3.1.6 Hydrolysis, Acylation, and Acyl Rearrangements

Acyl groups can be easily removed from the 3-, 5- ,16-, and 20-hydroxy groups by basic hydrolysis, while hydrolysis of the 13-ester unit is more difficult and much slower [104]. This observation is in sharp contrast to what is observed for phorbol esters, where the tertiary 13-hydroxy group can be easily deacylated (as well as re-esterified) [7]. The difficulties encountered in the hydrolysis of 13-acyl ingenols are not uncommon for hindered tertiary hydroxy groups, while the unusual reactivity of the tertiary 13-hydroxy functionalities of phorbol might be mediated by acyl migration to the adjacent secondary C-12 hydroxy group.

Acyl groups at the primary and allylic 20-hydroxy group can be selectively removed by solvolysis in acidic methanol [105]. The rate of the reaction is critically dependent on the size of the ester group, sharply decreasing with the growing length of the acyl group. Mild basic conditions can remove the ester group at the primary 20-hydroxy group, then promoting next the migration of a 3-acyl group to the secondary 5-hydroxy unit, and next to the primary 20-hydroxy group, affording mixtures dominated by the 20-ester (Fig. 24). This rearrangement plagued the early studies on the structural elucidation of ingenol esters, leading to a wrong assignment of the acylation pattern. Acyl migration is indeed a major stability issue for all ingenol 3-esters having free hydroxylated substituents at C-3 and C-20, and is reversible, as shown by the observation that acetylation has been reported to afford the same 5,20-diacetate from both ingenol 3-ester and ingenol 20-esters [64].

The primary 20-hydroxy group is only slightly more reactive than the two secondary hydroxy groups, but could be chemoselectively esterified with the Steglich protocol at low temperature [92], as exemplified by the synthesis of

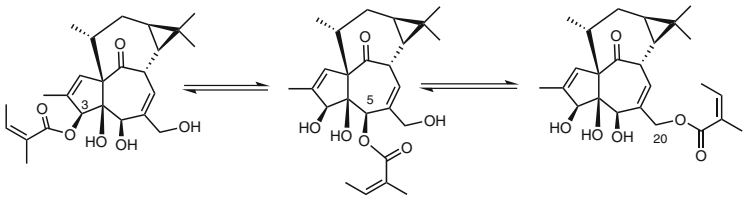


Fig. 24 Acyl rearrangement of 3-acyl ingenol derivatives as exemplified by the equilibrium mixture of ingenol monoangelates at pH 7.4 (water-DMSO) and room temperature

ingenol-20-benzoate by treatment of ingenol in the Steglich esterification conditions [benzoic acid, 1-ethyl-3-(3-dimethylaminopropylcarbodiimide (EDC) and 4-dimethylaminopyridine (DMAP), 41% yield] [92]. The modest difference of reactivity between the two secondary and the tertiary hydroxylated units of ingenol is reminiscent of the situation in sugars, and is presumably due to hydrogen-bonding network effects. Esterification of the 3-hydroxy could be accomplished only after protection of the 20-hydroxy, for instance by treatment of ingenol 5,20-acetonide with an acid in the presence of a carbodiimide and a hypernucleophilic species like DMAP (Steglich esterification), or by treatment with an acyl chloride in the presence of pyridine and DMAP. Acidic deprotection can next be controlled, to avoid acyl rearrangement. The esterification of ingenol with angelic acid is the key step in the semisynthesis of Picato®, and has been thoroughly investigated [106]. The reaction is plagued by two problems, one general to ingenol 3-esters, and the other specifically associated with angelic acid. 3-Acylingenol derivatives are unstable toward acyl rearrangement, which eventually affords the corresponding and more stable 20-acyl isomers via transient 5-acyl derivatives (Fig. 24). At equilibrium, a 1:1:18 mixture of 20-, 3-, and 5-esters is generated from I3A. The acyl rearrangement is promoted by acids and bases, with complementary mechanisms, namely, ester carbonyl activation in acidic medium and alcoholate formation under basic conditions. Stability peaks at mildly acidic pH values, around 3–4, and rapidly declines outside this range of values, and is faster in basic media than in acidic ones. Stability is also solvent-dependent, being favored by aprotic media, and this issue been the subject of proprietary research [107]. Picato® is indeed a gel with a limited shelf life, and an analogous problem of acyl migration, for instance, once plagued the development of topical 17-esters of corticosteroids [108]. The stability of ingenol-3-acylates was investigated as a water emulsion at pH 7.4, measuring recovery after 16 h. Recovery for ingenol mebutate (I3A) was 60%, and the rate of the acyl migration was dependent from the acidity and the bulkiness of the acyl group. With acids stronger than angelic acid ($pK_a = 4.3$) the acyl rearrangement was faster, while steric hindrance had a stabilizing effect [106]. Thus, replacement of angelic acid with its *nor*-analog (*E*)-crotonic acid led to complete degradation, while addition of an extra methyl increased recovery to 75%. Aliphatic acids were less stable due to their higher

acidity, while the recovery of the benzoate was only 30% presumably on account of the lack of an α-methyl, as suggested by the increased stabilizing effect of *ortho*-substitution [102, 106, 109].

The second issue is the facile isomerization of angelic acid to tiglic acid upon activation of the carboxylate group. Angeloylation is a notorious synthetic problem because of the unreactivity of angelic anhydride (**117**) and its propensity to undergo isomerization to tiglic acid by reversible Michael addition with the nucleophilic agents used to accelerate acyl substitution reactions (pyridine, DMAP). Given the hydrolytic stability of angelic anhydride, a compound that can be purified by column chromatography, it is not unconceivable that nucleophilic alcohol attack only occurs after Michael addition, which removes the transmission of the electron-donating inductive effects of the methyl and the mesomeric electron-donation of the double bond to the carbonyl of the anhydride (Fig. 25). Various literature strategies were evaluated to overcome this difficulty, and, eventually, the best results were obtained with LiHMDS (lithium hexamethyldisilazide). The reaction can be carried out at room temperature in THF, affording in ten minutes a complete conversion of ingenol 5,20-acetonide to its angeloyl ester, with a very rewarding 86% isolation yield. The corresponding sodium and potassium amides gave lower yields, suggesting that lithium, on account of a higher oxyphilicity, can activate the anhydride by behaving as a Lewis acid. Therefore, LiHMDS co-activates in a complementary fashion both the 3-hydroxylated site of ingenol 5,20-acetonide, by acting as a Brønsted base, and the acyl carbonyl of angelic anhydride, by behaving as a Lewis acid. Removal of the acetonide protection was uneventful, and I3A (**5**) was eventually obtained in 62% yield (Fig. 26).

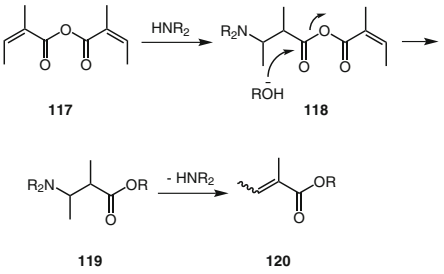


Fig. 25 Possible mechanism of the angelate to tigliate isomerization during acylation reactions

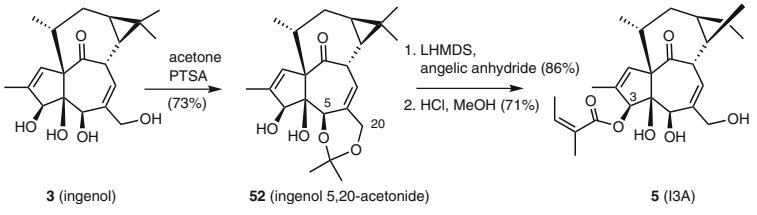


Fig. 26 Semisynthesis of ingenol mebutate

3.1.7 Other Functional Group Modifications

The two double bonds of ingenol show a different type of reactivity, and the ring B Δ^6-double bond of 3-acyl ingenols can be reacted selectively with electrophilic reagents like MCPBA [102]. Substitution reactions at the 5-hydroxy group substituent tend to proceed in a vinylogous fashion, and 3-benzoyl-20 trityl ingenol and 20-acetyl I3A were shown to react with DAST (diethylaminosulfur trifluoride) to give the corresponding Δ^5-7α-fluorides, as observed for the 20-azide (Fig. 21 [102]).

The primary 20-hydroxy unit of ingenol 3,5-dibenzoate (**121**) may be replaced by a fluorine by reaction with DAST at low temperature, while, using Mitsunobu-type chemistry, the 20-hydroxy group of ingenol can be substituted with an amino group via the corresponding 20-phthalimide (**123**) (Fig. 27) [92]. 20-Deoxy-20-aminoingenol (**124**) was not found to be stable, but can be trapped as an amide or an urea by acylation or reaction with isocyanates, respectively [92].

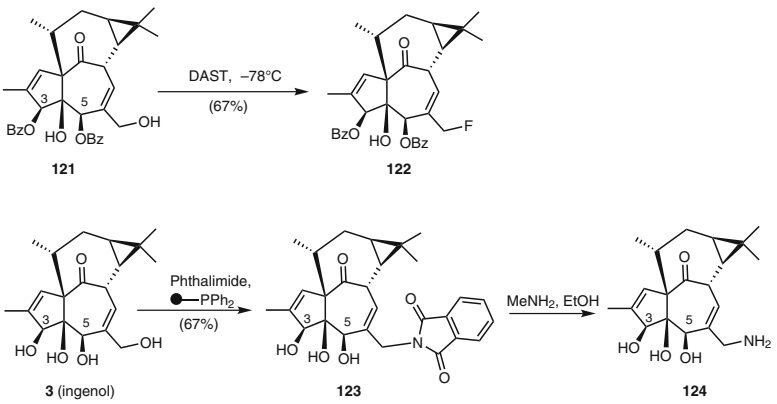


Fig. 27 Functional group modification of ingenoids

3.2 Total Synthesis

The challenging structure of ingenol has long fascinated organic chemists, and this compound has been a favored target for total synthesis ever since its isolation. Four decades of efforts have culminated in four total syntheses of ingenol, one synthesis of its 13-hydroxylated derivative, and countless frustrated efforts, which, despite missing the final target, nevertheless represent a monumental treasure-trove of ingenuity to serve as a source of inspiration for synthetic chemists. There is no shortage of reviews on the synthetic approaches to ingenol [110–112], and only the successful total syntheses will be discussed, focusing on the generation of the tricyclic core of ingenol and its functionalization to the natural product.

A comparative analysis of the published ingenol syntheses exemplifies some important concepts of general relevance for natural products synthesis. The first one is the clash between the brilliant generation of a scaffold and the tribulations of its functionalization that characterizes the pre-Baran approaches. The generation of the scaffold did not succeed, or was beyond control in terms of stereochemistry, with functionalized precursors, and its decoration with functional groups had therefore to be carried out in a painfully linear strategy plagued by the unpredictability of functional group manipulation in the strained ingenoid framework. The tribulations of the syntheses of Winkler, Wood, Kuwaijima, and Kigoshi with the sugar-like lower part of ingenol are instructive for the ingenuity of the solutions eventually found to get the synthesis "out of the swamps" of functional group manipulation and to pave the way to the final target. The second concept relates to the logic underlying the choice of a natural product as a synthetic target. Until recently, ingenol was simply a curiosity, a minor relative of phorbol of little practical relevance. Its derivatives never surged to the status of biological tools like the more stable and easily available phorbol esters, and there was little really exciting in the biomedical literature to justify the titanic efforts of the synthetic community to achieve a total synthesis of this compound. Indeed, apart from phytochemical reports of occurrence of specific esters, until recently the literature on ingenol was dominated by studies on its synthesis. One therefore wonders why ingenol has so long fascinated synthetic organic chemists. The answer is probably the challenges associated by its synthesis, in particular the presence of an exotic scaffold with an unconventional *in,out* rather than *out,out* configuration at the bridge, and the clash between its hydrocarbon-like northern sector and the sugar-like nature of the lower rim, with three contiguous and *cis*-oriented hydroxylated functionalities. In this context, ingenol became an iconic compound, a sort of chemical "Mount Everest" waiting to be conquered.

3.2.1 The Winkler Synthesis (2002)

This synthesis was the first one described for ingenol [19]. The key step is the intramolecular dioxenone-alkene photoisomerization of the bicyclic allylic chloride **125**. The [2+2] photocycloaddiction (De Mayo reaction) was followed by a base-induced retro-Claisen fragmentation that generated the cyclopentane-fused *trans*-bridged cycloundecane skeleton of the natural product (**126**). The missing carbons from the cyclopropane ring could be installed after chloride elimination to **127** and stereoselective addition of the dibromocarbene followed by halogen-methyl exchange via a mixed cuprate (Corey-Posner reaction), a sequence also featured in the Kuwajima-Tanino synthesis (see Sect. 3.2.2). The following functionalization of the lower rim had to rely only on the C-6 hydroxymethyl of **128** to functionalize a string of seven adjacent carbons, in a real tour-de-force of ingenuity. The final missing carbon (C-14) was introduced after carboxyallylation of the ketone **129**, which made possible α-monoalkylation and the palladium-catalyzed oxidative

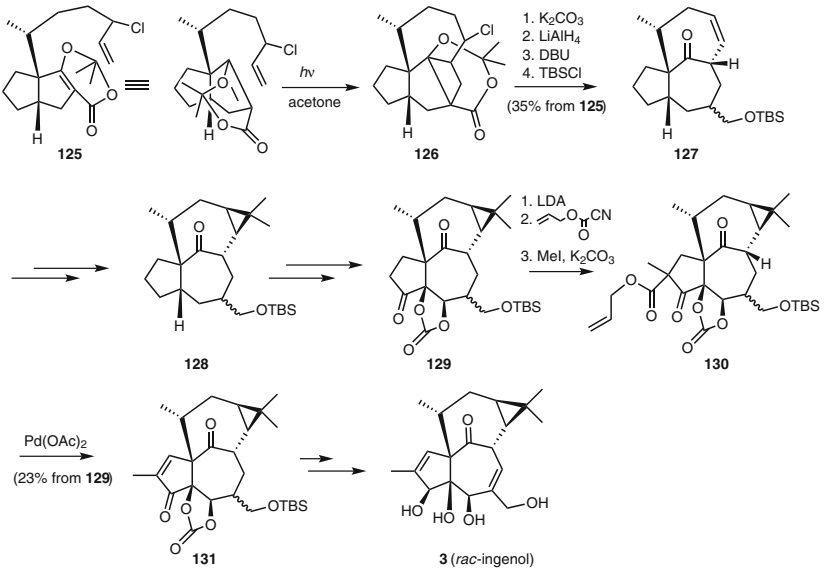


Fig. 28 The Winkler synthesis of ingenol (DBU: diazabicycloundecene, TBSCl: *tert*-butyldimethylsilyl chloride, TBS: *tert*-butyldimethylsilyl, LDA lithium diisopropylamide)

deallylation to a C-3 enone. This could then be reduced stereoselectively with $NaBH_4$-$CeCl_3$ according to the Luche protocol, delivering, after global deprotection, the racemic natural polyol. Overall, the synthesis required 45 linear steps. Even though the average yield per step was high (ca. 80%), the final yield was exceedingly low <0.1%. The asymmetric synthesis of one intermediate from the Winkler synthesis was reported by Kigoshi based on a ring-closing metathesis approach [113] (Fig. 28).

3.2.2 The Kuwajima-Tanino Synthesis (2003)

This racemic synthesis was published only a few months after that by Winkler [114], and relies on a completely different approach to build the *trans*-intrabridgehead tricyclic core, generated via the type-3 semi-pinacol rearrangement of the epoxyalcohol **132** promoted by the Lewis acid $AlMe_3$. Just like in the synthesis of Winkler, the functionalization of the tricyclic compound also proved tricky, especially the introduction of the 20-carbon, which required eight steps from the *nor*-ingenoid **136**, and was eventually achieved by dissolving a metal (Zn, NH_4Cl) for the reduction of the bromoepoxide **137**. The number of steps was similar to the synthesis by Winkler, and the overall yield similar (<0.1%). Within the many remarkable reactions involved, the bis-dihydroxylation of the diene **134** to **135** is remarkable for its efficiency (59% yield) and stereoselectivity (Fig. 29).

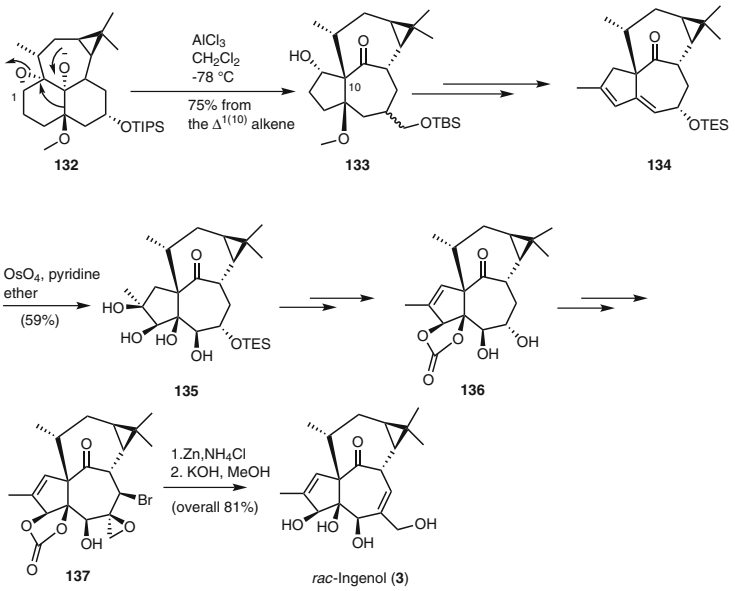


Fig. 29 The Kuwajima-Tanino synthesis of ingenol (TBS: *tert*-butylddimethylsilyl TES: triethylsilyl)

3.2.3 The Wood Synthesis (2004)

This synthesis, the first asymmetric such method [98], is considerably shorter than the two previous ones, and relies on an olefin metathesis reaction to assemble the tricyclic core of ingenol from the optically active diene precursor **140**. The resulting adduct was already better functionalized than those involved in the previous syntheses, and this explains the shortening of the whole sequence, now reduced to 32 linear steps from the so called Funk's keto-ester (**139**), a compound available in five steps from (+)-carene (**138**). In spite of this, the overall yield remained around 0.1%. A critical reaction found was the regio- and stereoselective allylic oxidation of the diene **142**, which afforded in almost 50% yield only one of the four possible regioisomeric products of allylic oxidation (**143**). The functionalization of ring B was achieved in a quite remarkable way. The enone **144** was stereoselectively α-hydroxylated and the 4-hydroxy group next served as a handle to stereoselectively epoxidize, via the $VO(acac)_2$-*t*-BuOOH protocol, the Δ^5 double bond, to afford **145**. The epoxide ring, as observed also in the Kuwaijima synthesis, proved recalcitant to opening, and this could eventually be effected only in a rather roundabout way. After functional group modulation that involved reduction of the enone and acetal protection of the 3,4-diol system, the 20-hydroxy group of **146** was replaced by a phenylsulfonyl function by mesylation, reaction with thiophenol, and oxidation to **147**. The epoxide ring was then opened via an E_2 reaction that capitalized on the sulfur-induced acidity of the 20-methylene, and the resulting exomethylene olefin easily isomerized to the endocyclic isomer, and was eventually

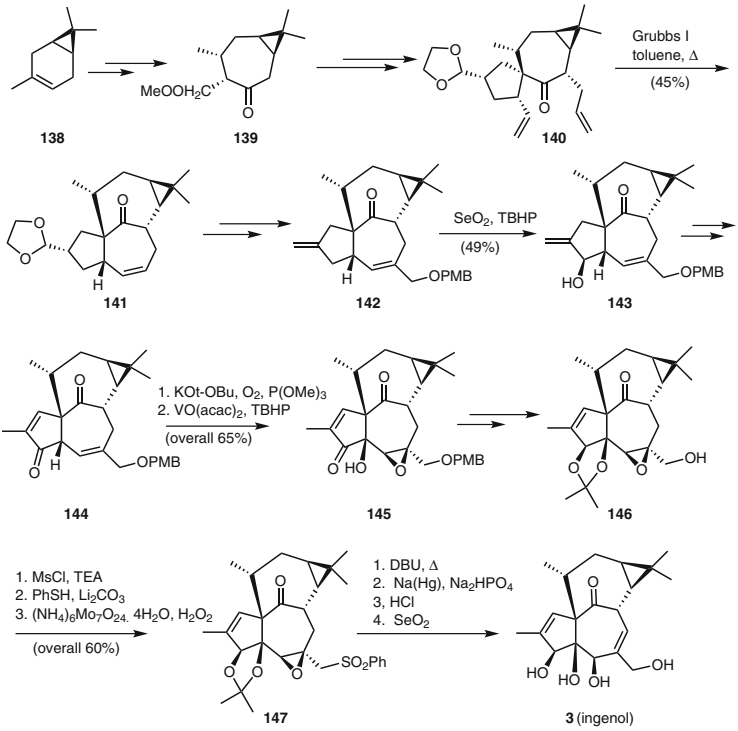


Fig. 30 The Wood synthesis of ingenol (PMB: *p*-methoxybenzyl, TBHP: *tert*-butyl-hydroperoxide, MsCl: mesyl chloride, DBU: diazabicycloundecene)

desulfurized by treatment with sodium amalgam. After deprotection to 20-deoxyingenol, allylic oxidation delivered the natural product **3** in an optically active form (Fig. 30).

3.2.4 The Kigoshi Synthesis of 13-Hydroxyingenol (2012)

This synthesis is conceptually similar to the one of Wood, relying on a ring-closing metathesis to assemble the tricyclic carbon system of the target [115]. The reaction gave the best yields when carried out on the exomethylene enone **148** under the catalysis of the second-generation Hoveyda-Grubbs catalyst. The corresponding alcohols and acetate gave lower yields, suggesting that the presence of an additional sp^2-hybridized carbon has a stabilizing effect on the adduct. The Wood and Kigoshi metathesis approaches each generated a Δ^5-ingenoid that could not be directly converted into their Δ^6-natural isomers, suggesting that Δ^6 ingenoids are inherently less stable than their Δ^5 isomers. To overcome this issue, functionalization at C-7 (ingenol numbering) was included in the metathesis precursor. After ring A-modification, reduction of the C-7 ketone to alcohol, change of the protecting

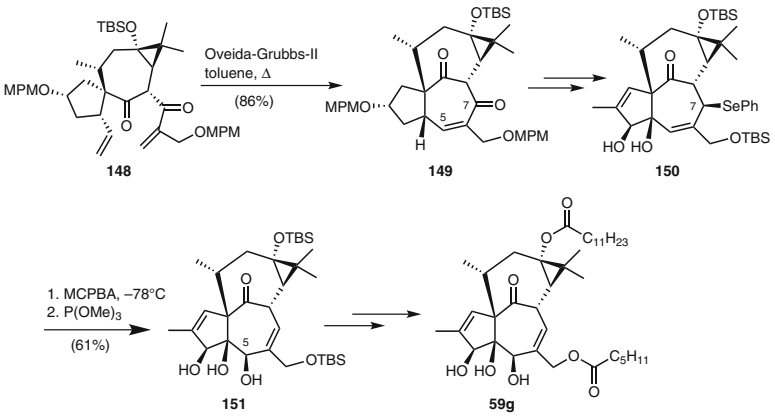


Fig. 31 The Kigoshi synthesis of the 13-hydroxyingenol ester **59g** (MCPBA: *meta*-chloroperoxybenzoic acid, MPM: 4-methoxyphenylmethyl, TBS: *tert*-butyldimethylsilyl)

group at the 20-hydroxy group site, and oxygen-to selenium exchange, the selenide **150** was chemoselectively oxidized to a selenoxide, that underwent 1,5-sigmatropic rearrangement establishing oxygenation at C-5 and the correct location of the double bond. After protection of the lower-rim hydroxy groups as the diacetonide, the tertiary 13-hydroxy unit was esterified with dodecanoic acid, and, after deprotection, the primary 20-hydroxy group was chemoselectively esterified by treatment with hexanoic anhydride and triethylamine at low temperature, giving the natural 20-hexanoyl-13-dodecanoyl ester (**59g**) occurring in *E. kansui* [104] (Fig. 31).

3.2.5 The Baran Synthesis (2013)

Comparison of this synthesis with the previous ones highlights the current trend in natural products synthesis toward brevity and scalability. In a certain sense, this synthesis is a sort of manifesto for a novel era in compound total synthesis, where the virtuosistic duplication of a natural product is aimed at both increasing its availability and exploring the chemical space around its scaffold, and, in general, at improving our knowledge on a specific class of compounds. Unlike all the previous syntheses, the Baran synthesis relies on a biogenetic strategy to assemble the tetracyclic core of the natural product, following the logic of isoprenoid synthesis, where a polycyclic core (cyclase stage) is first assembled from a precursor that can be oxidatively decorated (oxidase stage). This logic is exemplified by the biosynthesis of taxol (paclitaxel) in the yew tree [116], and might be of general relevance for oxygenated terpenoids, if not because oxygenated functionalities can interfere with cyclization reactions, affording oxygen bridges and ether bonds rather that carbon-carbon bonds and polycyclic scaffolds.

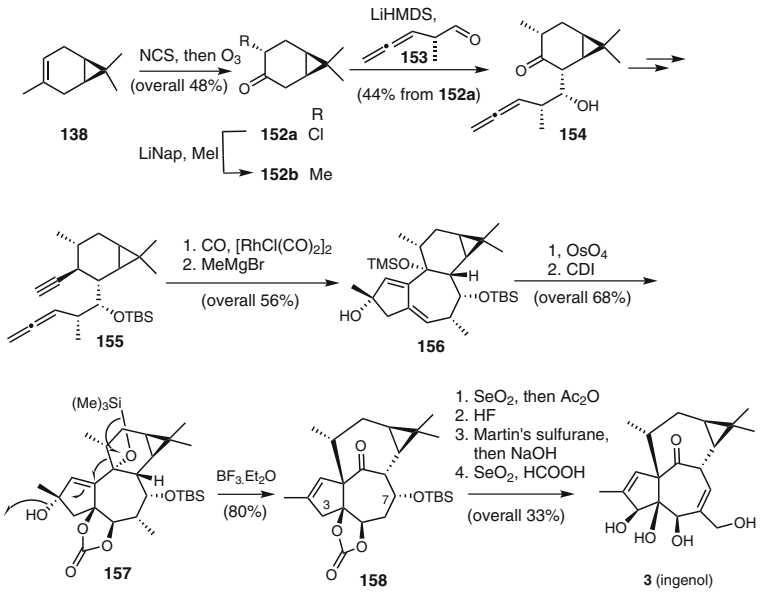


Fig. 32 The Baran total synthesis of ingenol (CDI carbonyldimidazole, NCS *N*-chlorosuccinimide, LiHMDS lithium hexamethyldisylamide, TBS *tert*-butyldimethylsilyl, TMS trimethylsilyl)

The cyclase phase (Fig. 32) begins with a form of configurational inversion of the naturally occurring monoterpene olefin, (+)-3-carene (**138**), a commodity chemical available in crude form from Indian turpentine. (+)-3-Carene is also the starting material for the synthesis of Funk ketone, a precursor for the C,D rings in the Wood synthesis of ingenol [98], as well as of the C,D rings of heterocyclic analogs of phorbol [117]. However, rather than directly expanding it into a seven-membered analog of rings C,D of an ingenoid, the six-membered ring architecture is maintained, and is elaborated into a mimic of the C,D rings of a tigliane precursor of ingenol, that is, a compound capable of generating the C-10 cation that triggers the migration of C-11 from a hydroxylated C-9 carbon. This is accomplished by re-shuffling the location of the methyl substituent of the cyclohexene ring by electrophilic chlorination of the natural product to an exomethylene olefin, which is next ozonized and methylated to **152b**. This compound proved difficult to purify and, in the final process, was only a transient intermediate in the one-pot telescoped process that reductively alkylated the chloroketone **152a** by methyl-chlorine exchange and next aldolized it on the other α-side by reaction with the allenyl aldehyde **153**. After installation of the acetylenic group and protection of the hydroxy group functions to allenylacetylene **155**, the tigliane derivative **156** was obtained by treatment of **155** with carbon monoxide and a Rh (I) catalyst. The allenyl Pauson-Khand carbonylation had to be carried out at a high-dilution (5 m*M*), but could, nevertheless, be scaled up at gram level. The availability of the resulting tigliane **156** is per se a remarkable achievement, since it could be used

to explore the many areas of the phorbol pharmacophore that are non-accessible from the pool of natural diterpenoids.

The oxidative phase was easier and more straightforward than in the previous syntheses, because of the presence of a hydroxy group at C-7 which, after rearrangement to the ingenane skeleton, served to generate the Δ^6 double bond, a difficult step in the functionalization of the lower rim of ingenol precursors. After dihydroxylation of the Δ^4 double bond and carbonation of the resulting diol, the C-2 allylic hydroxy group of **157** was used to trigger the tigliane-to-ingenane rearrangement discussed in Sect. 4.1, with allylic oxidation at C-3 and C-20 completing the synthesis.

Compared to the previous syntheses, the extraordinary abbreviation achieved by Baran is the result of the generation of the ingenane skeleton in a highly functionalized form that could be converted to the final target in a straightforward way. With the exception of galantamine [118], the total synthesis of complex natural products has been industrialized essentially when no other alternative source existed, as exemplified by the active moiety of the marine polyether halichondrin B (eribulin mesylate) [119]. Given the availability of ingenol from a cheap and renewable agricultural source (the seeds of the caper spurge), the synthesis by Baran probably will never become competitive with isolation. Nevertheless, it might be modulated to generate ingenoid chemotypes not available by modification of the natural polyol, via exploring the chemical space around the ingenol chemotypes through avenues unavailable from the natural polyol. Undoubtedly, it will remain in the history of chemistry to testify how ingenuity and judicious synthetic planning can overcome apparently insurmountable difficulties.

4 Bioactivity

4.1 Molecular Targets

The successful introduction to therapy of ingenol-3-acetate (I3A) (**5**, Picato®) in 2012 has fostered studies on all aspects of the pharmacology of ingenol derivatives, revitalizing investigation of phorboids, a field that had stagnated substantially after the great interest in their tumor-promoting properties in the second half of the past century and the substantial deflation of the prostratin anti-HIV hype at the beginning of the present century. Many, but not all, bioactivities identified so far for phorboids are downstream to the activation of PKC, a heterogeneous family of serine/threonine kinases that can be modulated selectively in terms of activation and/or inhibition by these compounds [120]. The ensuing picture is complicated and has still substantially eluded full rationalization, since different phorboid esters show distinct profiles of isoform activation, while compounds apparently devoid of any affinity for PKC still maintain activity in certain bioassays. This suggests that further high-affinity targets might exist, of which some are starting to surface [121].

4.1.1 Protein Kinase C (PKC)

This multifamily of lipid-regulated enzymes, consisting of fifteen members in humans, phosphorylates a variety of cellular proteins and plays an essential role in the mechanism of signal transduction [120]. Protein kinases C have been classified into several distinct subfamilies depending on their specific requirements for activation. Classical [(c)PKC] isoforms (α, βI, βII, and γ) require calcium (II) and diacylglycerol (*sn*-1,2-diacylglycerol, DAG); novel [(n)PKC] isoforms (δ-, ε-, η-, and θ) require DAG but not calcium for activation, while activation of the atypical isoforms [(a)PKCs] (Mζ- ι/λ isoforms) is independent from calcium and DAG. The PKC-related kinases (PRK) are the most recent addition to the family. All classical and novel PKC isoforms are sensitive to phorboids, which bind to their regulatory domain acting as ultra-potent biological analogs of DAG [121], eliminating the requirement for DAG for activation, and, for (c)PKC, decreasing the concentration of calcium needed for activation. Considerable uncertainty exists, however, on the binding mode and the selectivity profile of phorboids for the activation of various PKC isoforms, and even the stoichiometry of the interaction is debated [120]. More than a single-binding mode is probably possible within the same phorboid-recognition site of the various PKCs, since phorboids, and especially ingenoids, are remarkably plastic in their interaction with PKC isoforms. A further issue of confusion is that there is incomplete overlapping between biochemical experiments on PKC activation and structure-activity relationships for phenotypic end-points sensitive to PKC modulation, such as cytotoxicity, skin-irritancy, tumor promotion, and reversal of HIV-1 latency. More than three decades after the seminal discovery by Nishizuka that PKC is the target of phorbol esters [122], the details and the implications of this interaction are still largely to be clarified.

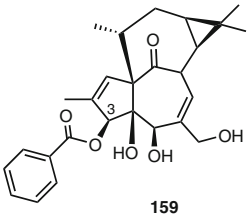
The interaction of phorboid polyols with PKC is critically dependent on their type of ester decoration, and requires a combination of optimal hydrogen bondings and hydrophobic contacts for high potency. A lipophilic ester group and a free hydroxy group at a specific position are required for binding, which relies on a network of complementary hydrogen bonding donor and acceptor sites between the two partners. The net result is the replacement of a hydrophilic surface with a hydrophobic one, and this polarity transfer promotes membrane association of cytoplasmatic PKC and implementation of its enzymatic activity. While there is substantial agreement on this general view, the identification of the network of hydrogen bondings that triggers the transfer of polarity has raised considerable controversy, and is still an unsettled issue for both phorbol and ingenol.

Unlike phorbol, ingenol has an intrinsic affinity for PKC, with overall effects in cellular assays in a similar, but less intense, way than those associated with its esters [123]. Activity for this polyol can be demonstrated both at the level of isolated enzymes and of intact cells, with a Ki value around 30 μ*M*, four orders of magnitude

higher than phorbol esters like TPA or phorbol dibutyrate, for which the Ki is sub-nanomolar, but not too different from that of the physiological activator DAG (K_i 0.56 μ*M*) [123]. The lipophilic element of phorboids is credited with a dual role, entropic and enthalpic, promoting affinity by increasing the concentration at the membrane interface, and providing an ester carbonyl oxygen function suitably located to be able to act as a hydrogen-bonding acceptor. The surprising activity of ingenol suggests that the lipophic upper part of the molecule can meet the hydrophobic requirements, and that the string of oxygenated functions on rings A and B can somewhat compensate for the lack of a carbonyl ester, providing an extra hydrogen-bonding acceptor site. Phorbol is apparently unable to do so, also because the 12-hydroxy unit is, basically, a deactivating structural element for PKC binding [124].

These observations suggest that ingenol is a more versatile molecule than phorbol for the modulation of PKC activity, but limited information exists on the structure-activity relationships of ingenol esters as PKC ligands. A large body of the literature uses indirect, downstream biochemical end-points of PKC modulation or phenotypical assays (tumor promotion, skin irritation, HIV-1 latency reversal) that are not directly or exclusively related to the activation of PKC. Finally, most studies on the interaction of ingenoids with purified isoforms of PKC have been carried out with I3A (**5**) and it is not clear to what extent the conclusions of these studies can be applied to other esters as well [125].

The most detailed molecular modeling investigation on the interaction of ingenoids with PKC was performed on ingenol 3-benzoate (**159**), an anticancer compound and potent PKC modulator [126]. A combination of complementary



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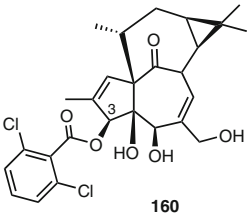

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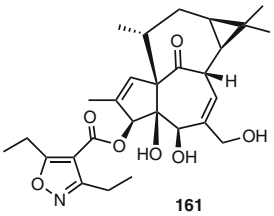

161

molecular dynamic and site-directed mutagenesis methods was employed, using as a reference the X-ray data of phorbol-13-acetate bound to one of the two cysteine-rich regulatory domains (C1b) of PKCδ, a classic isozyme, and the Blumberg model of binding derived thereof [127]. When fitted into the binding pocket defined by the interaction of phorbol-13-acetate with the phorboid binding element of PKCδ, the interaction of ingenol-3-benzoate involves a dual role of H-bonding donor and acceptor for the 20-hydroxy group, and as a donor for the 4- and 5-hydroxy groups, and as an acceptor for the ester carbonyl, with lipophilic interactions with the hydrophobic pocket of PKC (Pro11, Leu20, and Leu24) limited to rings C and D, and with the 9-keto group essentially acting as an inert unit (Fig. 33).

This binding mode is very similar to that of the daphnane orthoester thymeleatoxin, a weaker ligand, with the ester carbonyl at position 3 taking the

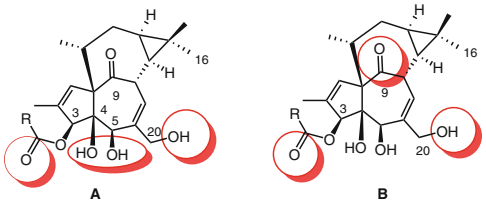

Fig. 33 Pharmacophoric models for the interaction of ingenol esters with PKC. A: the Blumberg (B) model; B: the Hecker-Rando-Kishi (HRK) model. The red circles represent the oxygen functions involved in binding

place of the carbonyl group at position 3 of phorbol esters as a hydrogen bond acceptor for the amide group of Gly23 of PKC. When compared to the other high-affinity ligands considered in this study (phorbol dibutyrate, thymeleatoxin, and indolactam V), ingenol-3-benzoate was the least sensitive to structural perturbation associated with site-directed mutagenesis, suggesting a noteworthy degree of plasticity to accommodate changes in the phorboid pocket to PKC. This observation might be related to the presence of a closer proximity of the hydroxy groups in ingenol esters compared to phorbol esters, resulting in a better capacity to reorganize the hydrogen bonding network required for PKC binding. For docking calculations, the need to assume that the binding site is rigid and interacts with the various ligands in essentially the same conformation despite the inherent flexibility of the hydrophobic binding domain, was partially compensated for by the adoption of a molecular dynamics technique based on generalized statistic-mechanics theory (q-jumping MD method) [128].

The major limitation of this study is that it relies on the interaction of a very low affinity pseudo-agonist, for which the location in the cysteine-rich domain of PKC might be an artifact, representing a special case of complementarity with little relevance for the higher affinity ligands, or else providing just a hint of how more potent ligands might interact.

A rather different binding mode has emerged from the investigation of the structure-activity relationships of ingenol esters as tumor-promoters [129]. This model, proposed by Hecker, assumes that the ester carbonyl at C-3 and the primary 20-hydroxy group are involved in the interaction, but the 9-carbonyl, and not the hydroxy units at C-4 and C-5, represents the third element of the oxygen triangulation required for binding, as a hydrogen-bonding acceptor (Fig. 33). According to this model, the 9-carbonyl plays the role of hydrogen-bonding acceptor that in phorbol esters is associated with the 4-hydroxy group, and the major lipophilic interactions are associated with the acyl group, and not the hydrophobic moiety of the diterpenoid scaffold, as proposed for phorbol esters. By molecular modeling, it was possible to superimpose the minimum-energy conformation of TPA and ingenol 3-palmitate with *sn*-1,2-diacylglycerol.

The pharmacophore model associate to this binding mode fits with the Rando-Kishi model of PKC activation, which requires the presence of three hydrophilic atoms separated by approximately 6 Å for a significant affinity [130]. The limitation

of this approach is that it is based on a phenotypic end-point (tumor-promoting activity) downstream to PKC activation, and therefore sensitive to modulation also by other factors, and, at least for the limited data available, not fully superimposable with the primary molecular event of PKC activation.

The B-model is structure-based, while the HRK-model is ligand-based, and, unsurprisingly, the two models also differ in the identification of the pharmacophore of phorbol esters [131]. Both models emphasize the relevance of the 20-hydroxy group and the ester carbonyl at C-3 of ingenol esters, as well as on the need for a third oxygen functionality and of hydrophobic interactions, but they differ in the location of these elements. Some observations are more in line with the HRK model than with the B-model. Thus, photo-cross linking experiments have highlighted the relevance of the hydrophobic interactions associated to the acyl moiety for the interaction of phorboids with PKC [132], while the HRK model seems better suited to explain the tumor-promoting activity, and therefore PKC affinity, of the 3-esters of 16-hydroxy-20-deoxyingenol and of those of 13-hydroxyingenol, where the hydrophobic moiety of the diterpenoid skeleton is perturbed by the introduction of the oxygen functions [129]. On the other hand, the activity of the 3-esters of both epimers of 9-dihydroingenol can be accommodated in both models [129]. In the B-model, C-9 is located into a space not involved in binding, while the HRK model assumes that both configurations of the 9-hydroxy group can function as a H-bonding acceptor. The similar bioactivity (at least in terms of tumor-promoting properties) of the diastereomeric dihydroingenols parallels a similar observation for the 3-dihydrophorbol esters [129]. The occurrence of ingenol esters based on different oxygenation and acylation patterns from those considered in the modeling studies (16-hydroxy-20-deoxy-, 13,19-dihydroxy-, and 13-hydroxy esters) provides an interesting opportunity to investigate the binding of ingenol esters to PKC, but the biological profile of these compounds is still largely unexplored, apart from information on their tumor-promoting properties [129].

Taken together, these studies evidence an unsettled situation regarding the binding mode of ingenoids to PKC. Unsurprisingly, a confusing situation exists also on their selectivity of isoform activation, with growing evidence that different esters target different isoforms, and that this issue can only be addressed in terms of systems biology, since PKC is essentially a target mix with similar but non-equivalent ligand-binding domains, different phospholipid requirements, and specific intracellular localizations. The largest body of information concerns I3A, a broad-range activator of both classical and novel PKC isoforms first reported as a highly inflammatory and weak tumor-promoting agent [129]. The phenotypic response of I3A (**5**) was, however, basically different from that of PMA, since the inflammatory response induced in mouse skin was transient, and reminiscent of that of the short chain esters of deoxyphorbol, which, although very powerful skin irritants, actually inhibit tumor promotion by long-chain phorbol esters like PMA [129]. Despite the lack of a long-chain hydrophobic moiety and a lower overall lipophilicity compared to PMA, **5** is remarkably potent in the activation of PKC, in line with the suggestion that the hydrophobic diterpenoid core of ingenol can act as a surrogate for a long-chain acyl moiety. On the other hand, the overall profile of

activation was functionally distinct from that of PMA and DAG, the physiological activator of PKC, with more emphasis on PKC-δ for **5** and on PKC-α for PMA. Rather than having a different binding mode for the ligands, these differences might be associated with their different polarities, since, with a calculated log P of 3.89, **5** is much less lipophilic than TPA, for which the calculated log P is 6.65. A polarity swap between the hydrophilic surface of PKC and the lipophilic moiety of phorboids is critical for the translocation of PKC to the lipid membrane and its functional activity, rationalizing the conclusion that **5** is not simply another phorbol ester with a different potency. Interestingly, PKC-δ is overexpressed in tumors, and plays an important role in the generation and proliferation of malignant cells, possibly explaining the major emphasis on anticancer therapy for ingenol esters compared to phorbol esters. Selective interaction with PKCβII is also critical for the activation of neutrophils involved in the clinical activity of I3A [133].

Another ingenol derivative with an interesting profile of interaction with PKC is ingenol 3,20-dibenzoate (IDB, **57k**), which has been reported to activate selectively the so-called "novel" forms of PKC, in sharp contrast to the 3-acyl esters of ingenol and phorbol esters, that also activate the classical isoforms [134]. This finding has significant clinical potential for cancer supporting care. Thus, while activation of the classical PKC isoforms inhibits megakaryocyte differentiation, activation of the novel forms is associated with megakaryopoietic and thrombopoietic effects in vivo. The possibility therefore exists to promote early megakaryocyte and platelet reconstitution in conditions associated with therapy-related marrow damage, as in cancer chemotherapy, and IDB was assayed with positive results in a murine model of this condition [134].

4.1.2 Topoisomerase II

Many ingenol esters can induce cell cycle arrest in the G2/M phase, potently inhibiting cell proliferation and inducing the DNA-decatenation checkpoint, a typical profile of topoisomerase (topo) inhibitors [135]. Limited structure-activity relationship work has been done, with 3-*O*-((2′*E*,4′*Z*)-decadienoyl)-20-*O*-acetylingenol (3*EZ*,20Ac-ingenol, **57h**) emerging as a lead compound [136], endowed with catalytic (class II) topo-I inhibitory activity similar to that of the thiobarbiturate merbarone [137]. From the database of ingenoids included in these studies, the presence of a 20-ester group seems critical, while a 3-ester group alone is not sufficient for significant activity. In light of these findings, it is tempting to assume that ingenol 3-esters, originally PKC modulators and cytostatic agents, could be transformed by spontaneous acyl migration into cytotoxic compounds.

4.1.3 Other Targets

IDB (**57k**) has been shown to directly bind the erythropoietin receptor (EpoR) and mimic the activity of the endogenous hormone, stimulating the proliferation of EPO-dependent cell lines [138]. In animal experiments, IDB can attenuate anemia

induced by the cytotoxic drug 5-fluorouracil, showing a synergistic effect on EPO at low concentrations, but an antagonistic effect at higher concentrations. Erythropoietin promotes tumor angiogenesis, and dysregulation of EpoR may affect the growth of certain tumors. Since IDB shows antitumor properties, it qualifies as a potential agent to counteract anemia in cancer patients [138]. Interaction of IDB with tubulin with inhibition of its polymerization, has also been described for ingenol esters, but this preliminary report needs confirmation [139].

4.1.4 Target-Based Structure-Activity Relationship Studies

Given the complex pharmacology of ingenoids, it is difficult to summarize their profile in a single molecular- or phenotypic assay and optimize their clinical potential accordingly, as exemplified by the medicinal chemistry of I3A. Aberrant keratinocyte death and lesion-directed immunological responses seem critical for the clinical activity of this compound, and both actions are to a various extent dependent on the activation of PKC isoforms, and especially PKCδ. In terms of cell-based assays, this could be translated into the induction of necrotic cell death in cancer cells and the stimulation of oxidative burst and cytokine release in immune cells and keratinocytes. In practice, cell death was investigated in HeLa cells, and the generation of reactive oxygen species (ROS) in polymorphonuclear leukocytes, and cytokine (IL8 and TNF-α) release in human primary epidermal keratinocytes. Since ingenol-3-esters are not stable toward acyl rearrangement, the bioactivity assays were complemented by stability determinations, evaluating the kinetic of degradation in an aqueous buffer at pH 7.4 and 37°C. Despite the maintenance of the critical angeloylation at C-3 and the presence of a free hydroxy group at C-20, massive loss of activity was observed upon modification of the diterpenoid scaffold (epoxidation of the Δ^6 double bond, methylation of the 5-hydroxy group, fluoridative rearrangement of the 5-hydroxy group) [102]. This suggested that the diterpenoid core of I3A is already substantially optimized for activity, refocusing activities on the nature of the ester group at C-3. Starting from ingenol 5,20-acetonide, various esters were prepared from all of the saturated, unsaturated and aromatic series [102]. Within the set of bioassays investigated, the most critical factor turned out to be the stability to acyl rearrangement. Thus, all compounds that outperformed I3A in the biological end-points also showed an increased chemical stability, suggesting an intrinsically flat SAR, dominated by the concentration of the active species in the assay. These considerations could rationalize the lower potency of ingenol-3-tiglate when compared to ingenol-3-angelate. The carbonyl of tiglic acid is less encumbered by I-strain because of the lack of the *cis*-methyl group, which is replaced by a hydrogen atom, and is therefore more prone to attack from the nearby 4- or 5-hydroxy group and rearrangement. The comparative recovery of the 3-tiglate was, in fact, 30% lower than that of the angelate [102].

These considerations were confirmed in a series of benzoyl derivatives [108]. Ingenol-3-benzoate (**159**) is more easily degraded when compared to I3A (**5**), but stability may be improved by the introduction of substituents at the two

ortho-positions. On the other hand, this was not accompanied systematically by a substantial increase of potency in the various biological end-points investigated. In particular, a partial dissection between the induction of necrosis, the immune-boosting activity and the affinity for PKCδ was observed. For instance, the 2,6-dichlorobenzoate (**160**) was stable toward rearrangement (>95% recovery), but had less than half of the potency of I3A in terms of cytokine-releasing properties, and was also less potent than I3A in terms of PKC-δ activation ($EC_{50} = 19.8$ n*M* vs. 4.1 n*M*). Nevertheless, it was considerably more potent in terms of necrotic properties than I3A ($LC_{50} = 59$ vs. 230 μ*M*). A dissection between PKC activation and cytotoxicity had already been observed in analogs of ingenol-3-benzoate [109]. A further issue to consider in cell-based studies of bioactivity optimization is the potential increase of tumor-promoting properties with the lipophilicity of the acyl group at C-3, an observation clearly observed in linear esters but of unknown relevance in branched esters. In a parallel series of investigation not yet disclosed, ingenol disoxate (LEO 43204) (**161**) has emerged as an interesting analog of I3A, and this compound is currently undergoing clinical development with promising phase IIa clinical data, where it outperformed I3A without a corresponding increase in side-effects [140–142].

As indicated earlier, the development of an expeditious total synthesis of ingenol has made possible the exploration of areas of its chemical space unavailable by chemical modification of the natural product [133]. This has afforded interesting information on the relationship between the immunostimulating activity and the specificity of PKC isoform activation. Thus, the neutrophil oxidative burst parameter may be better correlated with the activation of PKCβII rather than PKCδ. Since PKCβII is expressed very little in keratinocytes, the availability of ingenol-based selective probes will make it possible to dissect the activity at keratinocytes and at neutrophils, paving the way for new pharmacological applications of these analogs.

Taken together, the results of these medicinal chemistry studies show a complex scenario, where readings in bioassays are dominated by selectivity of PKC isoform expression but are complicated by the need to consider chemical stability. There is little doubt that the clinical potential of I3A could never have been discovered in a mainstream medicinal chemistry campaign.

4.2 Preclinical Pharmacology

Ingenol was discovered because of the tumor-promoting properties of some of its esters. In general, ingenol derivatives are less potent tumor promoters compared to phorbol esters, but fully retain their potent inflammatory activity. Cytotoxicity was also observed in the early studies, in part paving the way to the eventual development of ingenol 3-angelate (**5**) and Picato®.

4.2.1 Tumor Promotion

Despite intense research even since its discovery in 1941 [143], the human relevance of tumor promotion, a mostly rodent process, is still unclear. The process can be demonstrated on mouse skin, but may not applicable to the human situation. Nevertheless, research on ingenol was fueled paradoxically by an interest in these negative properties rather than in the anticancer potential of this class of phorboids. Ingenol 3-hexadecanoate (*Euphorbia* factor $L_5 = I_1$, **2**) is an order of magnitude weaker as a tumor-promoting agent than phorbol-12-tetradecanoate-13-acetate (TPA = PMA), the reference compound for this type of activity [67]. An interesting dissection between irritancy and tumor- promoting properties was observed in the corresponding 2,4,6-dodecatrienoate (*Euphorbia* factor I_6, **53q**), that was more irritant but less potent as a tumor-promoter than ingenol-hexadecanoate (**2**), in line with the observation that among phorbol derivatives polyunsaturated and short-chain acyl groups induce strong inflammatory activities, but weak tumor-promoting properties [144]. The tumor-promoting activity of ingenol-3-esters is strongly dependent upon their acyl decoration. Location is critical, since migration of the ester group from the 3-hydroxy to the 20-hydroxy position completely abolishes the tumor-promoting properties [144]. Short chain (C_2–C_6) esters are weak or very weak promoters, while activity peaks with at with a chain-length of C_{14}, with ingenol 3-myristate being almost as potent as PMA [67]. Ingenol 5-monoesters are unstable, and rearrange very quickly to their corresponding and inactive 20-esters, and could not be included in the analysis of the SAR. The presence of both a free 20-hydroxy functionality and of a medium-chain linear acyl moiety are also critical for the tumor-promoting activity of phorbol esters, despite the different topological relationships between these elements. Remarkably, deletion of the 20-hydroxy group can be compensated for by the presence of a hydroxy unit at C-16, since the 3-esters of 20-deoxy-16-hydroxyingenol are potent tumor promoters [144].

4.2.2 Anticancer and Immunostimulating Activity

Ingenol-3,20-dibenzoate (IDB, **57k**), a non-tumor promoting ester, was identified as the potent antileukemic principle of *E. esula* by Kupchan in 1976 [145], fostering considerable interest in the anticancer properties of ingenol esters. The same bioactivity-directed fractionation scheme afforded phorbol 12-tiglate-13-decanoate, a moderately potent tumor promoting ester, as the antileukemic principle of croton oil. This early finding suggested that the anticancer and cytotoxic properties of phorboids could, in principle, be dissected from their skin-irritancy and the tumor-promoting properties. On the other hand, ingenol-3-hexadecanoate, the major irritant and tumor-promoting constituent of the caper spurge was also identified as its antitumor constituent [146], suggesting that a clear-cut distinction

between these various biological properties is difficult, and that our predictive power in this area is limited.

Some ingenol esters, and I3A (**5**) in particular, show a surprising association of cytotoxicity against leukemia cells with the stimulation of immune cells [147]. This pharmacological oxymoronic profile has been related to the expression of different PKC isoforms in myeloid and immune cells, with apoptosis being induced by activation of PKCδ, and suppressed by activation of PKCθ, an isoform expressed selectively in T cells but absent from myeloid cells. Depending on the cell type, I3A can therefore suppress or, alternatively, promote cell growth, and this might indeed represent one important mechanism of its clinical activity. In addition to PKCδ, I3A can also directly bind to a subset family (RasGRP) of Ras modulators, eventually inducing apoptosis [148]. Both ingenol and phorbol esters can induce senescence in selected cell lines from solid tumors (e.g. melanoma, breast, colon) with permanent growth arrest [149]. This activity was inhibited by the PKC inhibitor bisindoleylmaleimide-I, showing that this type of activity was related to the modulation of these kinases.

A systematic study on the structure-activity relationship of IDB as a potential anticancer agent, using the induction of apoptosis in Jurkat cells as the end point, showed strict structure-activity relationships [150]. Benzoylation of the 20-hydroxy group was required to trigger apoptosis through a pathway that involved caspase-3, which occurred at the specific cell cycle checkpoint that controls the S-M phase transition, and was insensitive to treatment with PKC pan-inhibitors like GF 109130XO. In this series of compounds, activation of PKC was evaluated indirectly, measuring the induction of the transcription factors AP-1 and NF-κB. The caspase-3 and the PKC activation pathway were substantial orthogonal in terms of structure-activity relationships, suggesting that a complete dissection could, in principle, be possible [150].

Taken together, the available biochemical and cellular data suggest that ingenol derivatives have the potential to be developed as anticancer agents. Their activity depends on their profile of PKC isoform modulation, but can also involve other targets unrelated to the PKC pathway. Although the anticancer and tumor-promoting properties may be dissected, phorboids, and ingenol esters in particular, have a complex pharmacology that seems to substantially transcend the current paradigm of anticancer drug discovery, making it difficult to optimize activity, and investigate structure-activity relationships using in vitro and cellular assays that bear a direct relationship with in vivo activity, and overall to be able to qualify a specific compound as a lead based exclusively on cellular and preclinical data.

4.2.3 Antiviral Activity

Ingenol triacetate (ITA) potently inhibits the replication of human type 1-immunodeficiency virus (HIV-1) in acutely infected cells [151]. This antiviral activity was observed at nanomolar dosages that are three orders of magnitude lower than the cytotoxic ones, and was associated with the downregulation of CD4,

a major HIV-1 receptor on host cells. Although interesting, this therapeutic index is three orders of magnitude lower than that of zidovudine, a clinically useful anti-HIV-1 agent [151]. Activation of PKC and/or its downstream-related transcription factors like NF-κB are known to downregulate the expression of CD4, but ITA showed no affinity for PKC, suggesting that ingenoids have an intrinsic capacity to downregulate the expression of CD4 independently from PKC activation. This was confirmed by the observation that anti-HIV-1 activity was not affected by staurosporine, a PKC inhibitor [151]. Very limited information is, however, available on the structure-activity relationships of ingenol esters as inhibitors of HIV replication. Activity was tolerated by acylation of the 20-hydroxy group, but was substantially lost by methylation of this functionality [152]. From these studies, a diester of 13-hydroxyingenol (3α-methylbutyrate, 13-dodecanoate; RD4-2138) emerged as a sub-nanomolar HIV-1 inhibitor [153]. The potency of this compound was higher than that of the reverse transcriptase and the protease inhibitors used currently in the management of HIV-1, and RD4-2138 was also active against viral strains resistant to reverse transcriptase- and protease inhibitors. Since RD4-2138 was also relatively well tolerated in animals, its lack of further development is surprising, and might be related to the danger of chronic administration of a compound that potentially could affect the expression of oncogenes.

Quite different results were observed in chronically infected cells, where many ingenol derivatives potently enhanced the replication of the HIV virus at nanomolar concentrations, effectively reverting, in a PKC-dependent way, HIV-1 latency [153]. HIV-1 delatentization in T-lymphocytes is an unmet need in the current management of this type of infection, and a major barrier to achieve the complete viral eradication in HIV-1 positive patients on highly active antiretroviral therapy (HAART) [154]. By enhancing the transcriptional activity of latent HIV-1 without inducing the polyclonal activation of non-infected cells, the viral reservoirs potentially could be purged of the virus. Reversal of latency is related to the binding of NF-κB and related transcription factors to HIV-1 LTR (long terminal repeat) promoter, with triggering of viral RNA transcription [154]. Thus, I3A (**5**) [155], IDB (**57k**) [156] and ingenol 3-hexanoate (ingenol-B) [154, 157] showed outstanding reactivation properties, fully comparable to CD3/28 antibody stimulation, and, because of a lower toxicity profile when compared to other PKC modulators like bryostatin, all qualified as excellent latency-reversing agents. A remarkable synergism was observed between ingenol-B and histone deacylase inhibitors like SAHA (suberoylanilidenehydroxamic acid), an effect not observed with IDB [157]. Ingenol-B (**162**) is a semi-synthetic ester developed in Brazil starting from a mixture of ingenol esters isolated from *E. tirucalli*, which is simplified to the parent polyol and then re-esterified with caproic (hexanoic) acid [157]. Surprisingly, while the 3-cinnamate and the 3-hexadecanoate of ingenol showed considerable cytotoxicity, the 3-caproate (= hexanoate) was not cytotoxic [157], and its reactivation properties were coupled to downregulation of the expression of the surface proteins necessary for the replication of HIV (CD4, CXCR4, CCR5), confirming the early reports of a similar activity for ingenol triacetate [151]. In comparison experiments, ingenol-B outperformed a series of HIV-1 latency disruptors of the phorboid

type (TPA, IDB) as well as the histone deacylase (HDAC) inhibitor suberoylanilidenehydroxamic acid (SAHA, vorinostat), the PI3K/Akt pathway activator HMBA (hexamethylenebisacetamide), and even TNF-α itself. Ingenol B was well tolerated and efficacious in a simian model of HIV reactivation, with low toxicity upon oral administration in various animal species (rats, mice, dogs, monkeys) [157]. The similarity of activity of IDB, I3A (**5**), and ingenol-B is remarkable, since their profile of PKC activation is not overlapping.

Taken together, these studies show that ingenol esters have the potential to be developed as HIV-1 latency-reversal agents to be used along with retroviral drugs for viral eradication [154]. A surprising diversity between ingenol esters, however, seems to exist in terms of cytotoxicity and synergism with other delatentizing agents [157]. The reasons for the dissection of latency reversal and cytotoxicity are unknown, as are those underlying the synergy with other mechanistically unrelated reversal agents. Undoubtedly, this represents an obstacle for a systematic optimization of pre-clinical profiles, which is thus far based on a very limited database of compounds.

Phorboids have also been at the forefront of research on another RNA virus, the Chikungunya virus (CHIKV), and several phorbol and deoxyphorbol esters show outstanding inhibitory activity on the replication of this RNA virus [158]. However, I3A, IDB, and ingenol itself showed only weak activity, a remarkable example of differentiation between the biological profile of tigliane and ingenane lead compounds [159].

4.2.4 Pesticide Activity

Ingenol esters are remarkably potent pesticide agents. It is, however, unclear as to what extent their activity is selective and therefore of practical relevance, while their use could eventually lead to contamination of crops. On the other hand, their substantial potencies could make them interesting probes to discover new mechanisms of action against pests of agricultural relevance and noxious animals, and some pests seem exquisitely sensitive to these compounds. Thus, milliamines and related dipeptide ingenol esters from *E. cornigera* Boiss. [160] and *E. milii* [161, 162] are among the most potent molluscicidal compounds ever reported, outperforming by two orders of magnitude the potency of niclosamide (Bayluscide®) when assayed against the snail *Biomphalaria glabrata*, one important intermediate snail host for the schistosoma trematode (*Schistosoma mansoni*). Milliamines are only mildly irritant and are not tumor-promoting, and, since snails are sensitive to these compounds at nanomolar concentrations non toxic for other animals, the crude latex of *E. milii* was used successfully used in field experiments at a concentration of ca 1 mg/L as part of a control project on schistosomiasis [161]. Of relevance is also the observation that ingenol 3-(2′*E*,4′*Z*)-decadienoate (**53j**), its 20-acetyl derivative, and its 5,20-isomer, show impressive activity (5 μg/cotton ball!) against the pine-wood nematode *Bursaphelenchus xylophilus* [163]. This pest, present in Asia and America and recently discovered also in Europe, is the causal agent of pine wilt disease, and is

one of the worst pest for forest trees and the cause of a major economic loss for the timber industry [163].

4.3 Clinical Pharmacology

The only clinical data on ingenol derivatives are those of I3A (**5**), successfully introduced onto the pharmaceutical market as a gel for the management of actinic keratosis (Picato®). The discovery of the clinical potential of I3A is rather unusual and almost at complete odds with the current mainstream paradigm of drug discovery. Rather than emanating from the sophistication of the molecular screening on the cancer receptor "du jour", the discovery of I3A can be traced to the curiosity and motivation of James Aylward, an ex-scientist from the Commonwealth Scientific and Industrial Research Organisation (CSIRO), and to the open-mindness and ingenuity of a small group of Australian researchers based at the Queensland Institute of Medical Research (QIMR) in Brisbane [164]. Overall, the discovery of this agent is a remarkable example of cutting-edge modern "reverse pharmacology", where preliminary clinical validation related to folkloric use was obtained before pharmaceutical development.

4.3.1 Discovery of the Anticancer Activity of the Sap from *Euphorbia peplus*

Australia has one of the highest rates of skin cancer in the world, accounting for about 80% of all new cancers diagnosed each year [165]. With the estimate that two in three Australians will be diagnosed with skin cancer by the age of 70 [166], this condition gains a great deal of media attention, and in the 1970s Aylward's mother read in an article that the sap of the petty spurge (*E. peplus* L., known as "radium weed" in Australia) was used by farmers to treat skin cancer and related conditions. She then started to treat her own sun spots, a type of pre-cancerous lesions known more formally as actinic keratosis, and those of other members of her family, with amazing results. In 1996, Aylward contacted Peter Parsons, a Professor at QIMR, with the idea of investigating the potential of the sap to be developed as a mainstream anticancer drug. Parsons evaluated the antiproliferative activity of the sap against five cell lines, documenting a noteworthy degree of selectivity between cancer cells and normal fibroblasts, and discovering a curious effect on the melanoma cell line MM96L, for which the phenotype had lost the polydendritic pattern, back-differentiating into the bipolar shape of the melanocytes from which it had derived [164]. This morphological change was used as the cellular end-point for the activity-guided fractionation of the sap that ultimately led to the discovery of I3A (**5**) as the active anticancer agent in *E. peplus* sap. In light of the confirmation of

cytotoxic activity for a wide panel of cancer cell lines, the biotechnology company Peplin was eventually established two years later, in 1998.

Peplin was instrumental in coordinating and funding a network of multidisciplinary collaborations that in the following two years provided further evidence for the anticancer activity of the sap, including the critical observations that activity was fully retained by sap extracts, as well as using in vivo experiments on nude (Foxn1nu) mice injected with melanoma cells [164]. Much of this early stage research was by, at that time, a junior postdoctoral researcher, Steven Ogbourne, who, having won a prestigious National Health and Medical Research, Industry Research Fellowship, was able to focus his research efforts under the mentorship of Parsons at QIMR and Aylward at Peplin on the isolation, anticancer activity determination, and mechanism of action of I3A (**5**). Ogbourne was ultimately employed by Peplin, and was closely involved in all aspects of the development of this compound.

4.3.2 Identification of I3A as the Major Active Constituent from the Sap of *Euphorbia peplus*

In the wake of the promising pre-clinical data on the sap, Peplin went on a public offering in September 2000, raising almost five million euros, which fueled studies aimed at clinically validating the activity of the plant sap and initiating a drug development program. The topical administration of the sap showed remarkable activity when evaluated against a small cohort of cancer patients suffering from basal cell-, squamous cell-, and intraepidermal-carcinomas. This study, carried out in 2000–2002 but published later [166], provided a strong rationale for turning the sap into a mainstream drug. Given the lack of information on the molecular mechanism of activity of the sap and its molecular target(s), bioactivity-directed fractionation was carried out using a combination of three phenotypic assays, namely, cytotoxicity, morphological transformation of the melanoma line MM96L to a bipolar state, and mouse xenografts. The active fraction purified from the sap contained a mixture of three ingenoids, all featuring a 3-angeloyl moiety: ingenol-3-angelate (PEP005, **5**) and its 20-deoxy (PEP006, **65a**) and 20-acetyl (PEP008, **57a**) derivatives. Ingenol-3-angelate (**5**) was the most potent of the three, and a patent was filed in 2001 on its uses as an anticancer agent [167], with the first one gram batch being manufactured at QIMR in 2004. Ingenol-3-angelate (**5**) had first been isolated from the petty spurge in 2000 [58], and had already been described in several other species (see Table 2), but not until the discoveries of Aylward and Parsons had **5** been associated with cancer treatment.

4.3.3 Development of I3A

A supply chain for the production of the starting biomass (dried aerial parts) of the petty spurge was implemented successfully, and production then moved from QIMR

to a custom-built GMP manufacturing facility in the Gold Coast area of Queensland. A deal struck in November 2002 gave the U.S. company Allergan exclusivity of the product for skin diseases in North and South America, but, in the wake of budgetary constraints at Allergan, Peplin re-acquired the product rights in October 2004. Positive phase I results were reported in 2005 [168], and Peplin went on to validate clinically a gel formulation of PEP005 in phase II studies and initiated phase III trials. On September 3, 2009, Peplin was eventually purchased by the Danish company LEO Pharma, a globally recognized dermatology leader, for approximately US $ 287.5 million. The Danish LEO Pharma continued the clinical development of **5** and eventually received U.S. FDA approval for a gel formulation of the compound in January 2012 [169]. Derivative PEP005 was renamed ingenol mebutate, and the formulation received the brand name of Picato®. Approval in the EU was granted in November 2012 [170], and the product is now commercialized worldwide. Ingenol-3-angelate (**5**) is currently obtained by isolation from farmed *E. peplus*. The supply chain directly employs over 60 manufacturing specialists and approximately ten farmers, directly injecting over $30 million into Australia's economy each year.

4.3.4 Molecular and Clinical Pharmacology of Picato®

The molecular mechanism of the anticancer activity of I3A (**5**) is unclear, and it has been suggested to be twofold, involving a combination of necrotic and immunostimulating effects [171]. Depending on the concentration and cell type, I3A shows necrotic or apoptotic properties, the latter seemingly dependent upon the activation of PKCδ and its translocation from the cytoplasm into the nuclear membrane. Conversely, interaction with PKCβII is critical for the activation of neutrophils involved in the immunostimulating activity [133]. Ingenol-3-angelate (**5**) also shows immunostimulatory effects, increasing the release of chemokines by a range of cell types inclusive of malignant cells, and promoting, after topical application, the local infiltration of neutrophils, and the development of specific anticancer immune responses by CD8(+) T cells [133].

Ingenol-3-angelate (**5**) shows an impressive potential to be used as a systemic anticancer agent, especially against leukemia [172], but little information exists on its systemic toxicity and therapeutic window, and similar considerations apply for its use as HIV-1 latency-reversal agent [173].

So far, the only clinically approved use of I3A (**5**) is for the treatment of actinic keratosis (AK), a focal area of abnormal keratinocyte proliferation associated with chronic exposure to the sun (sun spots) and considered an early step in a continuum of alterations that leads from normal skin to invasive and metastatic squamous cell carcinoma (SCC). The likelihood of development of an invasive SCC from a single AK lesion is around 0.075–0.096% per lesion per year, meaning that for an individual with an average of 7.7 lesions, the probability of at least one transforming into SCC, within a ten-year period, is almost 10% [174]. The removal of sun spots is therefore, an important form of cancer chemoprevention. The topical treatment of multiple actinic keratosis lesions by application of a pharmaceutical

product to a specific area of the skin is referred to in medical terminology as "field therapy", and, before the introduction of **5**, required weeks or months of treatment, alone or in association with surgical operations like laser removal, cryosurgery, electrodesiccation, shave excision, or laser ablation. Before the introduction of **5** the pharmacological treatment was based on 5-fluorouracil, imiquimod, retinoids, or diclofenac [174].

For topical application, two formulations of **5** have been developed. The lower concentration product (0.015%, 150 ppm) is used daily for three consecutive days for actinic keratosis on the face or scalp, while the more concentrated product (0.05%, 500 ppm) is used daily for two consecutive days for actinic keratosis on the trunk or limbs [175]. Complete and sustained clearance is observed in a significant percentage (ca. 50%) of patients, with outstanding quality of life and satisfaction [176]. Ingenol-3-angelate (**5**) has also been proposed as a treatment for genital warts [177], another application in line with the use of the sap of *E. peplus* in folkloric medicine.

4.4 Toxicity

4.4.1 Skin Irritancy

Ingenol esters are potent skin irritants, as most tumor promoters are, but they are generally less potent tumor promoters when compared to phorbol esters [178]. Thus, irritancy is a necessary but per se insufficient prerequisite for tumor-promoting activity, and these two types of activities can be dissected as in phorbol 12-retinoate-13-acetate, a compound almost as irritant as TPA but only marginally active as a promoter [179]. The detrimental effect of polyunsaturation on tumor promotion is quite general in phorboids, and has been observed also in ingenol-3-esters. Short-chain esters like I3A are highly irritant for the skin, but, unlike TPA and long-chain esters, induce a transient, and not long lasting, response [7]. From a mechanistic standpoint, co-carcinogenicity is related to the activation of various isoforms of PKC, while it has been suggested that irritancy can be mediated by the activation of specific isoforms of PKC [7] and or by phospholipase A2 and the liberation of arachidonic acid from biological membranes [179].

4.4.2 Animal and Human Exposure

Animal exposure to ingenoids is direct, via consumption of their plant food sources or with fodder contaminated with these compounds. Conversely, human exposure is mostly indirect, via the food chain and products (e.g. milk, honey, cheese) obtained from animals exposed to ingenoids, with direct exposure being limited to the medicinal uses of euphorbiaceous species or to gardening activities [180]. Many spurges have a high protein content and low fiber levels, qualifying as a potential

highly nutritive food source for animals, comparable to alfalfa, and better than most grasses [87]. However, the presence of ingenol esters triggers aversive responses in cattle after ingestion of even small amounts of ingenoid-containing plants, with a negative impact on the productivity of agricultural areas. The situation is especially severe in the Great Plains of North America, where millions of acres of pasture lands are heavily contaminated by the leafy spurge (*E. esula*), a creeping perennial of Eurasian origin first imported to the U.S. as a seed impurity in the first half of the nineteenth century [87, 181].

Phytochemical studies have established the presence in the leafy spurge of 3-acyl derivatives of ingenol, of which the nature seems to depend on location, due to the presence of distinct chemotypes characterized by the presence of aromatic (benzoyl) [103] or polyunsaturated aliphatic acyl moieties [56], with both chemotypes having been detected in U.S. collections of the plant [87]. Due to their irritancy, these compounds are the most likely candidates as the aversive constituents of the leafy spurge. On the other hand, the concentration of ingenol esters in the leafy spurge is very small, overall in the range of 5–10 ppm, and in vivo experiments in cattle have shown significant activity for ingenol itself and for a compound tentatively identified as 3-acetyl-20-dodecanoylingenol, suggesting a complex situation, not exclusively accounted for by the presence of any single 3-acyl ingenol derivative or by its irritancy [87]. A toxification role for the rumen microbiota has also been suggested, possibly related to the selective hydrolysis of the 3,20-diesters to the more irritant 3-esters, and vegetable tannins (plant polyphenols) might also play a role [182]. Despite a negative economic impact estimated at more than $ 200 million a year [87], the molecular basis for the aversion of cattle to leafy spurge is still not entirely clear. The aggressive diffusion of the plant in the prairies suggests that most wildlife avoids it, and the plant has not only an economic impact but also a negative effect on the overall quality of the natural habitat, replacing native plants and failing to support their associated animal community. Furthermore, the avoidance of the leafy spurge by large herbivores means that non-contaminated area will be intensely browsed, creating additional opportunities for further encroachment by *E. esula*, which can thus spread both by seed dispersal and through its rhizomes. Additionally, other spurges are invasive plants, and they can contaminate fodder, as detected in Egypt for *E. helioscopia* L., a plant containing short- and medium-chain ingenol esters [183, 184].

Lactating animals fed with spurges excrete diterpenoid esters in the milk, rationalizing the observation that milk from animals fed in areas contaminated by these plants is toxic [185]. Contamination from ingenol derivatives was indeed detected in lactating goats fed *E. peplus* [186]. Both the native esters and ingenol itself were isolated from the milk, explaining certain case reports of acute human poisoning from milk contaminated by spurge constituents [186]. The toxicological implications of the chronic consumption of milk contaminated by diterpenoid esters are unknown, but it has been suggested that the unusually high incidence of esophageal cancer observed in certain areas of the Caspian littoral of Iran, where consumption of goat milk is very high, might be related to chronic exposure to diterpenoid esters [187, 188].

In general, rumen microbes cannot degrade phorboids [189], and nor is the rumen biota is affected adversely by them, and it has been suggested that little difference exists in the toxicity of these compounds between ruminants and monogastric animals. Mammary excretion seems therefore an important detoxification pathway for phorboids, and it is interesting to observe that they generally co-occur with macrocyclic diterpenoid esters. These non-irritant compounds are potent inhibitors of transport proteins of the ATP cassette [16], a class of transporters highly expressed in mammary tissues during lactation [190], and it does not seem unreasonable to assume that their evolutionary role might be related to the block of this major detoxification route in herbivorous animals.

Ingenol derivatives have been detected in honey obtained from spurges [191]. Although the pollen of spurges is per se devoid of toxic diterpenoids, pollinators get contaminated during their browsing activity. Transfer of ingenol esters to honey has been documented for *E. seguieriana* Neck. in Iran [192], and honeys from ingenoid-containing plants like *E. marginata* Pursh are generally toxic [192]. Since the flowers of *E. ingens* are a major source of nectar, also the (in) famous toxic and irritant South-African noors honeys might contain ingenol derivatives [193].

Taken together, these studies show that a human dietary exposure to ingenol esters is, overall, possible, but, given the trace amounts involved, poisoning seems limited to the chronic consumption of goat milk contaminated with trace amounts of ingenol esters. Goats, as well as sheep, can feed with impunity on many spurges, and have even been proposed as a "green" alternative to pesticides and insects for the control of invasive spurge like *E. esula* [87].

In Western medicine, the use of spurges in folk medicine is mostly topical, for the removal of warts, and skin cancers, and they are only occasionally used internally as cathartics [180]. Exposure to ingenoids is therefore limited. On the other hand, several *Euphorbia* species are used in traditional Chinese Medicine (TCM), with four of them being included in the Chinese Pharmacopoeia [194]. Among these plants, *E. kansui* is a major source of ingenol esters. This plant is a prolific producer of ingenol and 16-hydroxyingenol esters, and is a popular treatment for edema, ascites, and asthma. However, the roots are processed by stir-baking with vinegar, a procedure that causes a considerable degradation of the ingenol esters [93, 195]. Some homeopathic products are based on ingenoid-containing plants, and, indeed, trace amounts of ingenol and its derivatives were detected in homeopathic tinctures [196]. Concentrations of ingenol in the range of 5–17 mg/L were, in fact, detected in the tincture of *E. resinifera*, while other popular homeopathic tinctures like those from *E. amygdaloides* L. and *E. pilulifera* L. only contained traces amount of this compound. Unfortunately, the presence of deoxyphorbol esters, which often co-occur with ingenols in spurges, was not evaluated [196]. Given the low level of consumption of these products, it seems unlikely that these trace amounts of ingenol ester might be bioactive.

Professional exposure to ingenoids is limited to the species grown for the production of oils or for horticultural purposes. The seeds of *E. lathyris* are mass-cultivated for the production of lamp oil, especially in mainland China, and contain

large amounts (>0.1%) of ingenol esters [2]. The oil is detoxified by heating, which degrades the irritant diterpenoids. It is also commonly planted in domestic gardens for an alleged capability of deterring moles (hence its nickname of "mole plant") [2]. *Euphorbia milii* (crown of thorns), a species native to Madagascar, is a popular indoor plant in temperate zones, and is used extensively used as an ornamental in warmer areas [180]. As mentioned earlier, this plant contains peptide conjugates of ingenol based on *N*-methyl anthranilate, a unique type of natural product [78, 79]. Also, *E. marginata* (snow-on-the-mountain), a North American plant of which the type specimen was collected by William Clark during his famous expedition with Lewis, has been reported to contain ingenol esters, but the only phytochemical investigation on this plant actually afforded an ingol ester [197]. Finally, some ingenoid-containing succulent Euphorbias (*E. ingens*, *E. tirucalli*) are used as border plants in warm areas, acting not only as a physical, but also as a veritable chemical barrier [180].

5 Conclusions

Phorboids have provided valuable tools to study cell metabolism and neural activity, as exemplified by the tigliane PMA and the daphnane resiniferatoxin (RTX), but ingenoids are the only class of phorboids to have so far been subjected to clinical development. This is surprising not only on account of the instability of ingenol esters to both skeletal and acyl rearrangement, but also because of their low concentrations in plant biomass. Clinical research of ingenol-3-angelate (I3A, **5**) is expected to provide a better comprehension of the biological profile of this class of compounds, clarifying the differences, if any, with the analogous parameters of phorbol esters, while the increased availability of the parent polyol will expand the resultant knowledge on their chemical reactivity and the medicinal chemistry.

Several issues are still unresolved and will be important to address. From the phytochemical standpoint, the structure of two groups of ingenoids, the tetrahydroingenol esters and the 16-hydroxyingenol esters, need confirmation. The nature of the ingenol derivatives occurring in plants from the genus *Elaeophorbia* is still unknown, and the distribution of ingenoids in neo-tropical euphorbiaceous species should be worth a systematic evaluation. Most important, the Jakupovic biogenetic proposal for the formation of phorboids should be rigorously evaluated in labeling experiments. From the biological standpoint, the profiles of several classes of ingenoids substantially transcend the interaction with PKC, and is still incompletely understood in terms of their molecular targets. Thus, the extraordinary systemic toxicity of milliamines ($LD_{50} = <1$ mg/kg in mice for milliamine A hydrochloride (**57o**), a value lower than that of strychnine [198]), with the former compound representing a class of non-irritant and tumor-promoting ingenoids, hints to interference with some basic but yet unknown physiological process. In turn, the kinetics of skin irritancy of several classes of ingenoids differ greatly from the phorbol esters, in being more similar to the daphnane

resiniferatoxin, a non-PKC targeting compound. Even within the realm of PKC-activating ingenoids, there is a surprising profligacy of diterpenoid templates (ingenol, 20-deoxyingenol, 5-deoxyingenol, 13-hydroxyingenol), whose acyl decoration is capable of inducing powerful kinase-activating properties. Undoubtedly, ingenoids exemplify vividly the concept that the larger our body of knowledge grows, the longer the interface is extended where current knowledge meets our ignorance of this topic.

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Giovanni Appendino is Professor of Organic Chemistry at the Università del Piemonte Orientale, Department of Pharmaceutical Sciences, Novara, Italy. He graduated from the University of Torino (Italy) and did postdoctoral work in organic synthesis at the University of Gent (Belgium) with Prof. Pierre De Clercq. He is Editor-in-Chief of the journal *Fitoterapia*, and is a member of the Advisory Board of *Progress in the Chemistry of Organic Natural Products*. For his work on the chemistry of bioactive natural products, he was awarded the Quilico Medal of the Italian Chemical Society in 2009 and the Bruker Prize of the Phytochemical Society of Europe in 2014.

The *Laurencia* Paradox: An Endless Source of Chemodiversity

Maria Harizani, Efstathia Ioannou, and Vassilios Roussis

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M. Harizani • E. Ioannou (✉) • V. Roussis (✉)
Department of Pharmacognosy and Chemistry of Natural Products, Faculty of Pharmacy, National and Kapodistrian University of Athens, Panepistimiopolis Zografou, Athens 15771, Greece
e-mail: mariachariz@pharm.uoa.gr; eioannou@pharm.uoa.gr; roussis@pharm.uoa.gr

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1 Introduction

Nature, the most prolific source of biological and chemical diversity, has provided mankind with remedies for health problems since ancient times, and continues to be the most promising reservoir of bioactive chemicals for the development of modern drugs. The terrestrial flora and fauna has served as the basis of local pharmacopoeias from as early as 2600 BC and some of the earliest documentation comes from inscriptions found in Mesopotamia. Records from the ancient Egyptians and Chinese show that plants were used for the formulation of a large number of life-saving drugs.

As early as 300 BC, the Greek philosopher and naturalist Theophrastus compiled the botanical characteristics and medicinal properties of herbs in a series of nine

books named "History of Plants". Four centuries later, the physician Dioscorides developed and recorded a wealth of complex prescriptions and formulas using medicinal herbs.

Even though the biomedical and pharmaceutical sciences, through the development of technology, have led to many milestones and hundreds of efficient drugs have become available in the medical armamentum, plant-based remedies are still essential components of the healthcare systems of many communities in developing countries. According to the World Health Organization approximately 80% of the world's population uses traditional medicines in its primary healthcare [1, 2]. Nature is equally important for the healthcare systems of developed countries, since almost 25% of the prescribed drugs contain plant extracts or metabolites and an additional significant percentage of the commercial drugs has been developed through studies employing natural products as the lead molecules [3, 4].

In addition to the terrestrial organisms that still remain a promising source of new bioactive metabolites, the marine environment, covering approximately 70% of the Earth's surface and hosting a largely unexplored biodiversity, offers an enormous resource for the discovery of novel compounds. Due to the wide range of competitive ecosystems they survive in, marine organisms have developed unique defense strategies and bioactive compounds that, in some cases, are unparalleled by their terrestrial counterparts.

Systematic investigations of marine organisms were initiated 60 years ago with the pioneering work of Bergmann and Burke, initially on bivalves and later on sponges, especially those of the genus *Cryptotethya* that paved the way to the development of the antiviral and antileukemic drugs Ara-A and Ara-C [5].

The development of SCUBA (Self-Contained Underwater Breathing Apparatus) and underwater technology made the marine biota relatively easily accessible to marine biologists and chemists and the number of investigated organisms increased exponentially in the last 50 years. According to *MarinLit* [6], more than 27,000 metabolites from marine macro- and microorganisms have been isolated to date providing material and key structures for the development of new products in the pharmaceutical, food, cosmeceutical, chemical, and agrochemical sectors.

Algae, as photosynthetic organisms, thrive in the euphotic zone and were among the first marine organisms that were investigated as sources of food, nutrition supplements, soil fertilizers, and bioactive metabolites. The early attempts to distinguish separate groups of algae relied on pigmentation and characteristics, such as the presence or absence of flagella, cell wall composition, and type of photosynthetic products. It is evident though that at least ultrastructural features, especially details of chloroplast structure, are indispensable taxonomic characters for the safe identification of algae [7].

Seaweeds, as macroscopic algae are frequently called, are divided into three classes known as green (Chlorophyceae), brown (Phaeophyceae), and red (Rhodophyceae) algae. Most of the red algae share the surface of the coastal rocks with green and brown algae and are usually smaller and more delicate than brown algae. Red algae tend to be more abundant in subtropical and tropical waters and their populations in deeper waters are denser than those of green and brown

algae [8]. Among phycologists, red algae are notable for the complexity of their life cycles and the difficulties encountered in their taxonomy.

Among all marine macroalgae, red algae are the most prolific producers of secondary metabolites. Although these molecules are not involved in the basic machinery of life and often account for only a very small fraction of the total biomass of the organism, their contribution to survival is frequently comparable to constituents resulting from primary metabolism.

Red algae of the genus *Laurencia* are accepted unanimously as one of the richest sources of new secondary metabolites [9]. The plasticity of the morphoanatomical characters of *Laurencia* species has resulted in frequent taxonomic revisions of the genus that along with the genera *Chondrophycus*, *Osmundea*, *Palisada*, *Yuzurua*, and *Laurenciella*, are now included in the so called "*Laurencia* complex". The cosmopolitan distribution, along with the chemical variation influenced to a significant degree by environmental and genetic factors, have resulted in an almost endless array of metabolites, often featuring multiple halogenation sites.

Comprehensive and copious reviews have been reported previously, focusing on the chemistry of *Laurencia*, on specific chemical classes of secondary metabolites isolated from the family Rhodomelaceae or on halogenated compounds from natural sources [10–14].

The present contribution, including the chemical diversity and the bioactivity of the secondary metabolites isolated from species of the genus *Laurencia*, covers the literature until August 2015 and offers a comprehensive view of the chemical wealth and the taxonomic problems currently impeding chemical and biological investigations. Mollusks feeding on *Laurencia* are, in many cases, bioaccumulating, and utilize algal metabolites as chemical weaponry against natural enemies. For this reason, metabolites from *Laurencia*-feeding sea hares with such a postulated dietary origin are also included in the present review. In some cases, the frequently unique structures of *Laurencia* metabolites, originally proposed on the basis of their spectroscopic data, were later proven to be incorrect and were revised utilizing additional data provided by chemical synthesis, X-ray crystallographic analysis, or sophisticated spectroscopic techniques. In the present literature review, when chemical structures have been revised, only the currently accepted structure is depicted.

2 The Genus *Laurencia*

The genus *Laurencia*, currently including 146 taxonomically accepted species, belongs to the order Ceramiales, family Rhodomelaceae, tribe Laurencieae and is mainly found in tropical, subtropical, and temperate coastal waters [15]. It is considered one of the most prolific genera and even though it has been investigated intensively over the last 50 years, many new molecules are being reported continuously [6, 9, 16].

The Rhodomelaceae is estimated to be the largest marine red algal family, with approximately 125 genera and 700 species recognized worldwide [15]. According to *MarinLit* [6], more than 1200 naturally occurring compounds have been isolated and characterized from species belonging to this family, with the vast majority of them being halogenated [12].

The tribe Laurencieae is comprised of eight genera, six of which, under the current taxonomic status, are included in the "*Laurencia* complex" (or *Laurencia* sensu lato). These genera are *Chondrophycus* (Tokida et Saito) Garbary et J.T. Harper, *Laurencia* J.V. Lamouroux, *Laurenciella* Cassano, *Osmundea* Stackhouse, *Palisada* (Yamada) K.W. Nam, and *Yuzurua* (K.W. Nam) Martin-Lescanne [17].

2.1 The "Laurencia Complex"

The frequently observed color morphs within single interbreeding populations, the color adaptation mainly affected from the levels of irradiation and the color change through aging of individual specimens, co-existing in most cases on the same substrate, renders species discrimination very difficult for the untrained eye (see Fig. 1).

The genus *Laurencia*, as classified by Lamouroux in 1813, included eight species in its original description, but in the subsequent years the taxonomic hierarchy of the genus underwent a number of revisions [18].

Fig. 1 Different color morphs co-occuring within a *Laurencia* population

Thorough anatomical studies in the last few decades have revealed that *Laurencia* is a highly diverse genus, encompassing species that display distinctive features, usually diagnostic at the generic level [19–23]. Saito in 1967 was the first to divide *Laurencia* into the subgenera, *Laurencia* and *Chondrophycus* and the genus has thereafter been referred to as the "*Laurencia* complex" [19]. Successive detailed studies on the vegetative and reproductive structures of the included species led to the addition of the genera *Osmundea*, *Chondrophycus*, and *Palisada* to the "*Laurencia* complex" to reflect its morphological diversity [21, 22]. These genera share the typical and superficial Rhodomelacean morphology with apical cells sunk in apical pits of branchlets, a recognizable axial cell row only near the apical cell and an extensive cortex [24]. *Osmundea* is easily distinguished from *Laurencia* and *Chondrophycus* as it has a filament-type, rather than a trichoblast-type, spermatangial development and tetrasporangial production from random epidermal cells, rather than particular pericentral cells [20, 22]. *Laurencia* is delimited from *Chondrophycus* by the vegetative axial segment feature of four instead of two pericentral cells [25]. In 1999, Nam proposed an infrageneric classification scheme for *Chondrophycus* that included the subgenus *Yuzurua*. Subsequently, Martin-Lescanne and co-workers in 2010 proposed the elevation of this subgenus to generic rank and *Yuzurua* was recognized as the fifth member of "*Laurencia* complex" [18, 22]. More recent studies on the basis of morphological characters, especially the reproductive traits, and molecular sequences of the plastid-encoded gene *rbcL* (RuBisCO, Ribulose-1,5-Bisphosphate Carboxylase Oxygenase, Large chain) have led to a further division of the "*Laurencia* complex". This phylogenetic analysis by Cassano and co-workers identified the genus *Laurenciella*, which is morphologically identical with the genus *Laurencia*, but differs in the *rbcL* sequence [17].

Of these genera, *Laurencia* has a worldwide distribution (see Fig. 2), although the majority of species are found in the Southern Hemisphere [25]. *Osmundea* occurs in the North American Pacific Ocean, Brazil, the Mediterranean Sea, the

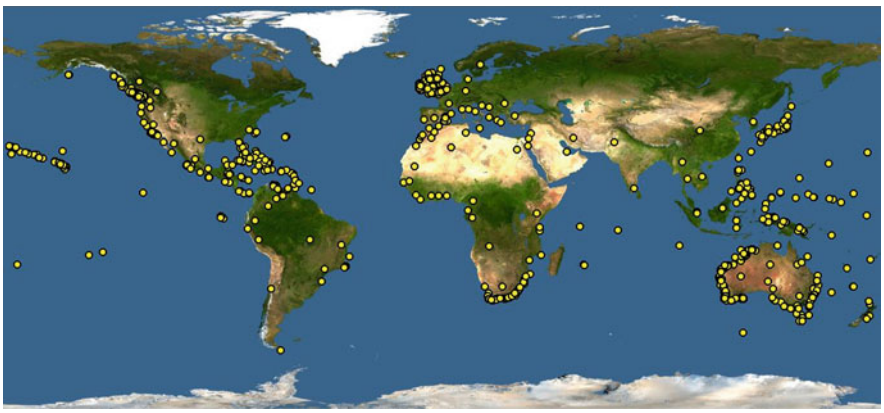


Fig. 2 Global distribution map for the genus *Laurencia*

European Atlantic Ocean, India, Australia, and North Africa [26–29]. *Chondrophycus* has been reported mainly in regions of the Pacific Ocean [21, 22]. Species of *Palisada* have been collected from Asia, Europe, America, Africa, the Atlantic islands, the Caribbean islands, the Indian Ocean islands, Australia, New Zealand, the Pacific islands, and the Western Atlantic Ocean [15]. Reports on the occurrence of *Yuzurua* include the Caribbean islands, the Atlantic islands, North America, Africa, Queensland (Australia), Indonesia, the Western Atlantic, the Arabian Gulf, and the Philippines [15]. The range of *Laurenciella* distribution is relatively narrower, including the Canary Islands, the Azores, Mexico, Brazil, and the Western Atlantic Ocean [15].

The vegetative and reproductive characters used for the distinction of the genera in the "*Laurencia* complex" are the: (1) number of pericentral cells per vegetative axis; (2) position of the first pericentral cell relative to the trichoblast; (3) origin of the tetrasporangia; (4) presence or absence of fertility in the second pericentral cells; (5) number of sterile pericentral cells in the tetrasporangial axis; (6) origin of the spermatangial branches; (7) formation pattern of the spermatangial branches on trichoblasts; (8) number of pericentral cells in procarp-bearing segments of female trichoblasts; and (9) post-fertilization features associated with the timing of auxiliary cell formation [22, 23]. It is worth noting that among the genera comprising the complex, *Laurencia* is the only genus that possesses four pericentral cells per vegetative axial segment [17].

The extensive morphological plasticity, in combination with the difficulty in defining diacritical characters for the morphology and anatomy makes species discrimination within the complex extremely difficult when utilizing only traditional characters. It is now evident that the morphological, anatomical, and reproductive characters have a diagnostic value only at the generic level in the taxonomy of the "*Laurencia* complex".

In an alternative approach, as species separation in "*Laurencia* complex" is complicated by the high degree of morphological variation within the genus, the secondary metabolites have been considered as a useful taxonomic tool [30, 31]. However, the plasticity in morphoanatomical characters has led frequently in the past to the wrong species identification and therefore to serious confusion when recognition of chemotaxonomic markers was attempted. For example, in a chemosystematic study performed by Barrow and co-workers on *Laurencia* species, digeneaside, which was previously suggested as a characteristic photoassimilatory product found only in representatives of the order Ceramiales, was not detected in any of the investigated species, including five species in which it was identified in previous studies. Accordingly, the proposed high diagnostic value of digeneaside was negated and its occurrence in these species is questioned [32].

Therefore, the use of molecular markers seems indispensable in delimiting taxa and inferring their phylogenetic relationships. The promises and perils of DNA barcoding are now well-known, but no systematic investigations have been performed to reveal the extent of taxonomic misidentification of algal specimens available in primary DNA sequence repositories. An attempt towards the reassignment of the taxonomic status of chemically investigated *Laurencia* species

was reported in 2011 by Fujii and co-workers, but unfortunately included only *Laurencia* species that had been collected in Brazilian waters [33].

2.2 Botanical Description of *Laurencia*

Specimens of *Laurencia* species (see Fig. 3) display erect thalli that in some cases can reach 40 cm and are attached by discoidal to rhizoidal appendages on encrusting holdfasts. Branching of thalli can extend to a different degree either bilaterally or in all directions. The branches can be either cylindrical or flat and the branchlets, which are not much narrower than the branches, vary between being blunt and truncate and in some cases are claviform.

Many species appear iridescent when alive. Individuals are polysiphonous, but soon form several layers of pseudoparenchymatous cortication masking the polysiphonous axes. The apical cells are always immersed at the bottom of the apical pit, from which dichotomously branched colorless trichoblasts develop. Stoloniferous propagation is common in some species [15]. The surface cortical cells can display secondary pit connections between them and this character is used for separating groups of species. In fresh material of some species, refringent intracellular "corps en cerise" with discoid to spheroid inclusions are present in the cortical and trichoblast cells [15]. The cortical cells contain photosynthetic pigments arranged in the thylakoids, while other internal cells are colorless [34].

In some species, unequal lenticular thickening of medullary cell walls is observed. The reproductive structures are developed usually on the branchlets, but sometimes are observed on the main branches as well. The procarps are formed in apical pits and the cystocarps protrude from the surface of the thallus. The

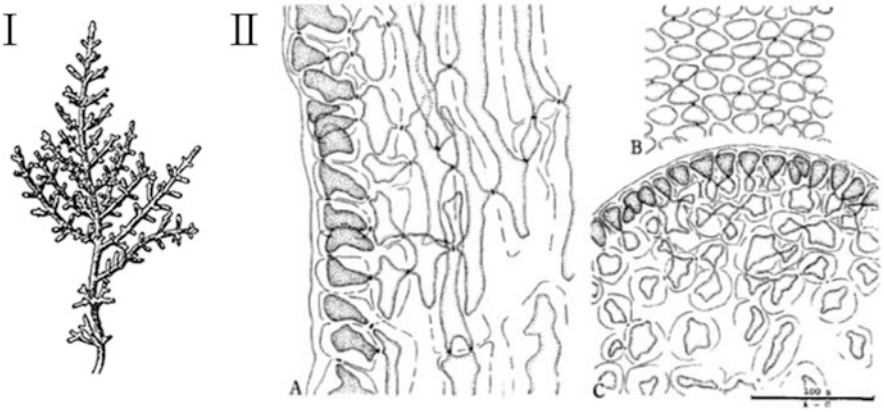


Fig. 3 (I) Drawing of a *Laurencia obtusa* specimen; (II) (A) Longitudinal section through a branch, (B) Surface view of the cortical cell arrangement in the upper part of the ultimate branchlet, (C) Transverse section through a branchlet [18]

spermatangial capitula are cylindrical with a cup-shaped to a more deeper shape exhibiting conceptacle-like pockets at lateral or terminal apices. The tetrasporangia on subcortical cells, products of divisions of elongated fertile pericentral cells [19], occur parallel to the central axis or at right angles to the central axis. This character is important for the separation of groups within species. The tetrasporangial initially is cut off adaxially or abaxially from the pericentral cell product. This characteristic is also used to separate groups of species [15].

2.3 Growth and Population Dynamics of Laurencia

Laurencia species are found in variable population densities in temperate to tropical shores of the world, inhabiting littoral to sublittoral zones, spreading to depths reaching 65 m. The growth of *Laurencia* and frequently the content of the secondary metabolites are influenced by various factors. Nutrients and temperature exert the most significant impact on the growth rate and maturity of the algae, whereas changes in the day length and salinity influence the growth rate to a smaller degree. For *Laurencia okamurae* (syn. *L. okamurai*) the optimum growth was observed at 25°C regardless of the day length. The algae were able to grow at salinities of 14–50‰ with maximum growth observed at 26‰. Variation in temperature between 15 and 25°C did not result in any obvious change in the content of the major metabolites laurinterol and debromolaurinterol [35]. The lower survival temperatures for *Laurencia cartilaginea* and temperature requirements for growth, ranging between 15 and 30°C with an optimum of 25–30°C, are mostly similar to those of tropical west Atlantic and amphi-Atlantic sub-tropical macroalgae [36]. A recent study on Brazilian algae reported that climate change associated with variations in the frequency and intensity of extreme temperatures and precipitation events on the local and regional scale can lead to the disappearance or to expansion of the distribution range of major algal groups [37].

The distribution and abundance of 87 species of macrophytes, including *Laurencia* species, on the intertidal reef flat at Agatti atoll (Lakshadweep, India) was recorded showing that species diversity increased with distance from the shore, while the percentage coverage and species richness exhibited the reverse trend. Herbivory with sea urchins as the major grazers appeared to significantly affect the population density [38].

Comparative studies on *Laurencia cruciata* growing in Indian Ocean sites affected from variable industrial and urban pollution indicated significant adaptability for this particular species [39]. Contradictory results from the Gulf of Antalya (north-eastern Mediterranean), showed that the highest values of biomass were found within the unpolluted stations, while a progressive decrease was observed as the effects of the anthropogenic pressure were more marked [40]. The intertidal vegetation of the "Abra de Bilbao" (on the Basque coast in northern Spain) was studied, following a pollution gradient to show that the richness of the species and the algal abundance suffer a parallel reduction, easily

observed under the most degraded environmental conditions. Pollution altered the zonation pattern, reducing the number of vegetation belts, and algae were gradually replaced by filter-feeders (mussels and barnacles). *Laurencia obtusa*, which requires high quality environmental characteristics, disappeared in the most polluted stations [41].

2.4 Ecological Relations of Laurencia

Laurencia algae, having multiple ecological roles, can grow in dense populations and form "forests" where several animals seek refuge. They host microorganisms and parasitic algae, such as species of *Janczewskia* (belonging to the same tribe), but can also grow as parasites on other marine organisms [42]. Even though they are in general rejected by the majority of grazing organisms due to their deterrent/toxic chemical defense, there is a number of marine invertebrates selectively feeding on *Laurencia* that have developed mechanisms for the detoxification of the bioactive molecules.

Chemical defenses can vary dramatically among geographic regions, habitats, individuals within a local habitat, and within different portions of the same individual. Factors affecting this variance include physical stresses and induction due to previous attack. Further studies are needed though to assess which consumers induce prey defenses, how responses vary in environments with differing physical characteristics and whether the "induced" responses are a direct response to consumer attack or a defense against microbial pathogens invading via feeding wounds [43].

Crabs of the genus *Microphrys* use *Laurencia papillosa* as a food source and as a camouflage [44, 45], whereas the queen conch *Strombus gigas* consumes *Laurencia* algae not only as a source of nutrients, but also for the provision of chemical cues that induce the metamorphosis of its larvae [46, 47].

Competition for space is also an imperative necessity for species survival. In field experiments conducted on declined coral reefs showing predominance of macroalgae, the presence of *Laurencia* species resulted in inhibition of coral larvae recruitment and increased coral larvae mortality [48].

Shell-less sea hares, which are slow-moving marine invertebrates, in many cases exhibit surprising survival rates, even in the most competitive habitats. These animals are postulated to have developed chemical defense mechanisms based on a wide variety of bioactive compounds [49]. Is well known that marine mollusks obtain and bioaccumulate secondary metabolites from their food sources and for this reason are investigated intensely as a rich source of new natural products [50]. Among the invertebrates feeding on *Laurencia*, sea hares of the genus *Aplysia* are the most frequent grazers. They obtain their means of chemical defense from the algae in forms that can be used for their protection either directly or usually after minor structural modifications.

In a study focusing on the patterns and dynamics of algal secondary metabolites in mollusks, *L. obtusa* metabolites were detected in the mucous and opaline secretions of *Aplysia parvula* feeding on this alga species. The loss of *L. obtusa* metabolites from *A. parvula* was found to be faster than predicted for growth alone, suggesting that metabolites were actively metabolized or excreted. The deployment of sequestered metabolites in the secretions of *A. parvula* may explain the more rapid loss of these compounds and is consistent with a possible defensive role for the acquired metabolites [51].

Since in many cases the bioaccumulated molecules are found in higher quantities in the consumers than in the producing organisms, many minor algal metabolites have been isolated only from the grazing mollusks. It is noteworthy that the brominated aromatic sesquiterpene aplysin, the first *Laurencia* metabolite reported, was isolated in 1963 from *Aplysia kurodai* mollusks and later traced to the *Laurencia* substrates [52].

Symbiotic or parasitic host-microbe interaction is a well-recognized driving force for co-evolution in the terrestrial and marine environment. Nonetheless, molecular studies of seaweed-associated microbial communities are still rare. Despite the high number of research studies describing the chemical composition of *Laurencia* species, the genetic knowledge regarding this genus is currently restricted to taxonomic markers and general genome features. In recent work, de Oliveira and co-workers analyzed the transcriptomic profile of *Laurencia dendroidea*, aiming to unveil the genes involved in the biosynthesis of terpenoid compounds in this seaweed and the interactions between this host and its associated microbiome, and showed bacteria to be the dominant active group in its microbiome [53].

2.5 *"Corps en cerise"*

Laurencia is renowned for its unique ability to biosynthesize a large variety of secondary metabolites, frequently featuring uncommon carbocycles and a high degree of halogenation. The phenotypic plasticity of the genus is to a large degree reflected on the insurmountable chemical diversity and the endless number of new natural products constantly reported, especially when the investigated specimens are collected from different geographic regions. The extended chemodiversity can also be seen as a consequence of the halogenated nature of *Laurencia* metabolites, a characteristic permitting intramolecular reactions and generation of new derivatives.

The most striking feature of *Laurencia* metabolites and marine natural products in general is the frequency with which halogenated compounds are described. The majority of the halogenated *Laurencia* metabolites contain one or more bromine atoms, with some of them containing both bromine and chlorine and in some cases even iodine. Since seawater is a halogen-rich environment, it is not surprising that marine organisms are capable of biosynthesizing halogenated metabolites. It is

curious, however, that brominated compounds are more abundant than chlorinated ones, even though seawater contains a much higher concentration of chloride (559 m*M*) than bromide (0.86 m*M*) ions. A plausible explanation can be the relative ease of oxidation of bromide ions resulting in bromonium ions that can undergo electrophilic addition to alkenes and aromatic systems [54]. Despite the fact that halogenated metabolites represent the prevalent group of natural products isolated from red algae, their biosynthesis is still poorly understood, even though biomimetic syntheses and enzyme-catalyzed halogenation reactions have provided useful insights into the biogenesis of these molecules.

The abundance of halogenated metabolites and their important biological activities have intrigued marine natural product chemists, who more than 30 years ago predicted the presence of haloperoxidase enzymes. Since that time, FeHeme- and vanadium-haloperoxidases have been discovered and characterized in many marine organisms [55, 56].

Vanadium-dependent haloperoxidases contain a vanadate prosthetic group and utilize hydrogen peroxide to oxidize a halide ion into a reactive electrophilic intermediate. These metalloenzymes, having been exclusively characterized in eukaryotes, show a large distribution in Nature, including macroalgae, fungi, and bacteria [57].

The production of labeled brominated metabolites with radioactive ^{82}Br in *Laurencia* was investigated by TLC and TLC–autoradioluminography, when several *Laurencia* species were cultured in artificial seawater medium ($ASP_{12}NTA$ including $Na^{82}Br$) under 16:8 h light:dark illumination cycles to show the production of specific ^{82}Br-containing metabolites. Furthermore, when *Laurencia* spp. specimens were cultured in the dark, the production rates of brominated metabolites were diminished [58].

In *Laurencia*, the halogenated metabolites, following their biosynthesis in the chloroplasts by haloperoxidases are stored in the intensively osmiophilic intracellular organelles, called “corps en cerise” (or cherry body) that transport them to the outer surface of the thallus [55, 59]. These organelles occur as intracellular membrane-bound vesicles in trichoblasts and in the outermost cortical cells and have a spherical, reniform to claviform shape [34]. The cellular distribution of halogenated compounds has been demonstrated by fluorescence microscopy that showed them to be stored mainly in the “corps en cerise” and to a lesser degree in vesicles found along the cytoplasm and within the chloroplasts [59].

When these organelles are not observed in the algae specimens, then halogenated metabolites are not detected [60–62]. For chemical defense at the surface level, these metabolites are intracellularly mobilized through vesicle transport from the “corps en cerise” to the cell periphery for their posterior exocytosis. The cell structures involved in this specific vesicle traffic, as well as the cellular structures related to the positioning and anchoring of the “corps en cerise” within the cell are not well known [63].

The transportation of the halogenated metabolites from the "corps en cerise" is affected by changes in temperature and irradiation, desiccation and bacterial fouling. Traffic of vesicles was induced by exposing *L. obtusa* to low temperatures and variations in irradiance. Under high temperatures and desiccation, the membranous tubular connections were lost and transport of vesicles was not observed [64]. Degradation of the "corps en cerise" and release of the halogenated compounds leads to cell death [59]. It has been reported that the number and size of the "corps en cerise" are constant within a species, independent of the geographical distribution, corroborating their use for taxonomical purposes to differentiate groups of species that present a lower number from those that have a higher number of these vesicles [15].

Investigation of *L. obtusa* specimens has revealed that the concentrations of elatol at the algal surface is not sufficient for inhibition of herbivory (sea urchins) and fouling (settlement of barnacle larvae and mussel attachment), whereas the natural within-thallus concentration is sufficient for exhibition of activity. Therefore, transport between the "corps en cerise", where elatol is probably stored, and the cell wall of *L. obtusa* was proposed through channel-like membranous connections that shift vesicles from the "corps en cerise" to the cell wall region. Finally, it was suggested that the natural concentration of defensive chemicals on the surface of *L. obtusa* is probably not absolute, but may be variable according to environmental conditions [65–67].

2.6 Chemical Variation in Laurencia

The frequently observed marked chemical variation of *Laurencia*, even within morphologically homogeneous species and populations, has been the subject of numerous studies that have not reached a unanimous conclusion. Possible explanations include the effects of environmental factors and/or genetic variables. Cultivation of *Laurencia pacifica* under different physical environmental factors has had little or no effect on the chemical profile of the extracts. In parallel, the interfertility between four sympatric populations of *L. pacifica*, which were morphologically similar, but chemically distinct, was investigated. Crossbreeding experiments showed that sympatric, but chemically distinct populations of *L. pacifica* did not interbreed in culture. From these results, it seems reasonable that the unique chemical profiles of the populations reflect genetic differences that are sufficient to cause reproductive isolation [68].

Another research group two decades later investigated a number of morphologically similar, but chemically distinct populations of *Laurencia nipponica* growing in Japan. The selected chemical types were characterized by specific halogenated secondary metabolites that remained the same in the wild and under various cultivation conditions. Experimental crosses between representative individuals

of the chemical types showed that such chemically distinct populations are not reproductively isolated. Thus, the diverse chemical types can be referred to as races (chemical races) [69].

A recent study on *Laurencia dendroidea* showed high inter- and intrapopulation variability in the amount of the sesquiterpene elatol, caused by genetic variation, as well as environmental factors. The concentration of elatol varied from two to ten times among the *L. dendroidea* individuals, but was approximately three orders of magnitude broader among the different populations ranging from 0.001% to 1.24% of the dry weight. The results indicated that abiotic factors, as well as genetic factors clearly take part in fostering chemical variations observed in natural populations and can promote differential susceptibility of algae specimens to natural enemies [70, 71].

The majority of *Laurencia* species from which diterpenes have been isolated occurs in the Northern Hemisphere and the greatest diversity is found in the Pacific Ocean and Sea of Japan (Japan, China). This observation indicates that diterpene-producing species emerged in the Pacific Ocean and were later radiated to other regions [72].

3 Structures and Occurrence

The majority of secondary metabolites isolated from species of the genus *Laurencia*, as well as from mollusks grazing on them, fall into the chemical classes of sesquiterpenes, diterpenes, triterpenes, and C_{15} acetogenins. Moreover, there are a number of metabolites that belong to the relatively small classes of indoles, aromatic compounds and steroids, as well as compounds that either constitute a rather small class or cannot readily be classified and in the present review are included as miscellaneous metabolites.

Besides the chemical structures of the metabolites, detailed information in tabular form, including the name of compound and the corresponding references for isolation sources or synthetic efforts, are provided.

It should be emphasized that extensive analysis of NMR spectroscopic data is sometimes not enough to establish unequivocally the chemical structure of a given compound, especially in regard to the placement of heteroatoms or the assignment of the relative or absolute configurations of stereocenters. Indeed, there are a number of cases in the genus *Laurencia* where the initial structure elucidation was incorrect, e.g. in the positioning of halogen substituents. In this regard, it is to be noted that efforts should be paid to support the structure proposed either with an X-ray crystallographic analysis when possible or with the use of chemical derivatization, partial or total synthesis, or NMR data calculation and comparison with experimental results.

3.1 Sesquiterpenes

Sesquiterpenes, C_{15} compounds consisting of three isoprene units, arise from the common precursor farnesyl pyrophosphate by various modes of cyclizations, followed in many cases by skeletal rearrangement, such as methyl group migration. Sesquiterpenes are by far the largest group of secondary metabolites isolated from species of the genus *Laurencia*, as well as mollusks grazing on them. Chemical investigations have yielded up to now 512 sesquiterpenes and related metabolites (**1–512**, Table 1) belonging to more than 50 carbon frameworks (see Figs. 4 and 5). Most of these feature mono-, bi-, or tri-carbocyclic skeletons, often consisting of fused- or *spiro*-ring systems.

Table 1 Sesquiterpenes from *Laurencia* spp.

No.	Name	Source of isolation/synthesis
1	(–)-(10*R*)-10-Bromo-α-chamigrene	*L. chondrioides* [73], *L. mariannensis* [74], *L. nipponica* [75, 76[d], 77, 78], *L. okamurai* [79], *L. pacifica* [80[a]], *L. rigida* [81]; Synthesis [82]
***ent*-1**	(+)-(10*S*)-10-Bromo-α-chamigrene	*L. obtusa* [83[d]]
2	Laurecomin C	*L. composita* [84]
3	2,10*β*-Dibromochamigra-2,7-dien-9*α*-ol	*L. saitoi* [85]
4	–	*A. dactylomela* [86]
5	2,10-Dibromo-3-chloro-α-chamigrene	*L. claviformis* [87], *L. composita* [69, 88], *L. filiformis* [89], *L. glomerata* [90], *L. implicata* [91], *L. japonensis* [92, 93], *L. nangii* [94], *L. nidifica* [95], *L. nipponica* [76[d], 78, 96, 97], *L. obtusa* [98], *L. okamurai* [99, 100], *L. papillosa* [101], *L. scoparia* [102], *Laurencia* sp. cf. *L. gracilis* [103], *Laurencia* sp. [104[a], 105, 106], *A. parvula* [89]
6	9-Hydroxy-4,10-dibromo-3-chloro-α-chamigrene	*L. claviformis* [87, 107], *L. composita* [69, 88], *L. glomerata* [90], *L. nidifica* [95], *L. nipponica* [108[c,d]], *L. okamurai* [99, 100, 109], *L. pacifica* [110[a]], *L. saitoi* [85]
7	2,10-Dibromo-3-chloro-7-chamigren-9-ol acetate	*L. composita* [84[d]]
8	2,10-Dibromo-3-hydroxy-α-chamigrene	*L. nipponica* [97, 111[a,d]]
9	Glanduliferol	*L. nipponica* [76[d], 112[a]]
10	Okamurene E	*L. okamurai* [109]
11	10-Bromo-α-chamigren-4-one	*L. nipponica* [76[d], 113[a]]
12	Laurocamin C	*L. okamurai* [79]
13	10-Bromo-α-chamigren-3,4-epoxide	*L. nipponica* [75, 76[c,d], 113[a]]

(continued)

Table 1 (continued)

No.	Name	Source of isolation/synthesis
14	10*α*-Bromo-9*β*-hydroxy-α-chamigrene	*L. rigida* [81]
15	–	*L. implicata* [114]
16	9-Acetoxy-3-chloro-4,10-dibromo-α-chamigrene	*A. dactylomela* grazing on *L. claviformis* [115]
17	(6*S*)-2,10-Dibromo-3-chloro-7,9-chamigradiene	*L. okamurai* [100]
18	2,10-Dibromo-3-chloro-chamigrane-7,9-diene-5-ol	*L. composita* [88], *L. nidifica* [95[a]]
19	(6*R*)-2,10-Dibromo-3-chloro-7,9-chamigrediene	*L. okamurai* [100]
20	–	*L. majuscula* [116[a], 117[d], 118], *A. dactylomela* [118]; Synthesis [119[f], 120[f], 121[f]]
21	–	*L. majuscula* [122]; Synthesis [121[f]]
22	Laurencenone C	*L. obtusa* [102]; Synthesis [123[f]]
23	Laurencenone B	*L. obtusa* [102]
24	Laurencenone A	*L. obtusa* [102]
25	Laurencenone D	*L. obtusa* [102]
26	2-Chloro-3-hydroxy-α-chamigren-9-one	*L. obtusa* [124]
27	2,10-Dibromo-3-chloro-8-hydroxy-β-chamigrene	*L. nipponica* [111[a,d]], *A. dactylomela* [125]
28	Obtusol	*L. dendroidea* [126], *L. majuscula* [127, 128], *L. obtusa* [129[a], 130[b,d], 131–133, 136[c]], *L. scoparia* [134], *A. dactylomela* [50, 135]
29	Nidificene	*L. composita* [88], *L. mariannensis* [74], *L. nidifica* [95, 137[a]], *L. nipponica* [111[d], 138], *L. obtusa* [139], *L. okamurai* [79, 99], *A. dactylomela* [140]
30	1*β*,4*β*,10*β*-Tribromo-3-chloro-7(14)-en-α-chamigrene	*L. pinnatifida* [141]
31	Cartilagineol (*allo*-Isoobtusol)	*L. cartilaginea* [83[b], 142[a]], *L. dendroidea* [126], *Laurencia* sp. [143[b,c,d]], *A. dactylomela* [50]
32	–	*A. dactylomela* [144[d]]
33	Hurgadol	*L. obtusa* [145[c,d]]
34	Dendroidiol	*L. dendroidea* [146[c,d]]
35	Isorigidol	*L. scoparia* [134[a], 147[c,d]]
36	Ma'iliohydrin	*Laurencia* sp. [148]
37	Laurecomin B	*L. composita* [84]
38	4-Bromo-β-chamigren-8-one	*L. flexilis* [149], *L. nipponica* [113[a]], *L. snackeyi* [50]
39	Dactylone	*A. dactylomela* [151[a,c,d]]
40	Dendroidone	*L. dendroidea* [146]
41	10-Bromo-β-chamigren-8-ol	*L. okamurai* [152]
42	(1*Z*,8*R**,9*R**)-8-Bromo-chamigra-1,11(12)-dien-9-ol	*L. majuscula* [114[a], 153], *L. scoparia* [134]

(continued)

Table 1 (continued)

No.	Name	Source of isolation/synthesis
43	(+)-(3*Z*)-Bromomethylidiene-10*β*-bromo-β-chamigrane	*L. scoparia* [34]
44	(*Z*)-10,15-Dibromo-9-hydroxy-chamigra-1,3(15),7(14)-triene	*L. cartilaginea* [142], *L. majuscula* [62, 69, 116[a], 117[c,d], 154, 155], *L. scoparia* [134], *Laurencia* sp. [143], *A. dactylomela* [118, 156]
***ent*-44**	–	*L. chondrioides* [157], *L. majuscula* [153, 158[a,d]]
45	(–)-(3*E*)-Bromomethylidiene-10*β*-bromo-β-chamigrane	*L. scoparia* [134]
46	(*E*)-10,15-Dibromo-9-hydroxy-chamigra-1,3(15),7(14)-triene	*L. cartilaginea* [142], *L. majuscula* [62, 122, 153–155, 158[d]], *L. scoparia* [134], *Laurencia* sp. [143], *A. dactylomela* [118, 156[a]]
47	(–)-Obtusane	*L. nipponica* [159[d]]
***ent*-47**	Obtusane	*L. composita* [88], *L. decumbens* [160], *L. dendroidea* [126, 146], *L. majuscula* [127], *L. mariannensis* [74], *L. obtusa* [132, 145, 161[a]], *L. okamurai* [79], *L. scoparia* [134]
48	Rogiolol	*L. majuscula* [118, 158[a], 162], *L. microcladia* [163, 164[b,d]], *L. obtusa* [83], *A. dactylomela* [118]
49	Isoobtusol	*L. majuscula* [127, 153, 162, 165], *L. obtusa* [102, 129[a], 130[b,c,d], 132], *A. dactylomela* [50, 135], *A. parvula* [166]
50	Isoobtusol acetate	*A. dactylomela* [50, 156[a,d]]
51	Epiobtusane	*A. oculifera* [167]
52	(2*S**,6*R**,8*R**,9*R**)-2,8-Dibromo-9-hydroxy-β-chamigrene	*L. flexilis* [149]; Synthesis [168[g]]
53	Rigidol	*L. rigida* [81]
54	–	*L. obtusa* [169[c,d]]
55	(+)-(10*S*)-10-Bromo-β-chamigrene	*L. mariannensis* [74], *L. nipponica* [97], *L. obtusa* [83], *L. okamurai* [79], *L. pacifica* [10[a]], *L. rigida* [81, 170[d]]; Synthesis [171[g]]
56	Deschlorelatol	*L. mariannensis* [74], *L. obtusa* [102[a,d]], *L. rigida* [81], *A. dactylomela* [86]
***ent*-56**	(6*R*,9*R*,10*S*)-10-Bromo-9-hydroxy-chamigra-2,7(14)-diene	*L. majuscula* [62]
57	Acetyldeschlorelatol	*A. dactylomela* [86[d]]
58	9-Deoxyelatol	*L. mariannensis* [74]
59	Elatol	*L. cartilaginea* [142], *L. chondrioides* [157], *L. decumbens* [160], *L. dendroidea* [172, 173], *L. elata* [174[a,c,d]], *L. majuscula* [118, 127, 128, 162, 165], *L. mariannensis* [74], *L. microcladia* [175], *L. obtusa* [102, 124, 129, 131, 132], *L. pacifica* [30], *L. rigida* [81], *L. scoparia* [102], *L. similis* [176], *Laurencia* sp. [165, 177], *A. dactylomela* [50, 86, 118, 135, 156, 178], *A. parvula* [166]

(continued)

Table 1 (continued)

No.	Name	Source of isolation/synthesis
***ent*-59**	(–)-Elatol	*L. dendroidea* [126[a,d]]
60	Acetylelatol	*A. dactylomela* [86[d]]
61	–	*A. dactylomela* [144[d]]
62	–	*A. dactylomela* [144[d]]
63	Obtusadiene	*L. obtusa* [131[d]]
64	Isoobtusadiene	*L. cartilaginea* [142], *L. majuscula* [153, 154, 158], *L. obtusa* [131[a]]
65	2-Bromo-3-hydroxy-11-acetoxy-β-chamigrene	*L. obtusa* [132]
66	2-Bromo-3,11-diacetoxy-β-chamigrene	*L. obtusa* [132]
67	–	*L. mariannensis* [74]
68	–	*L. nipponica* [179]
69	(2*S*,3*S*,8*R*)-2,10-Dibromo-3-chlorochamigra-7(14),9-dien-8-ol	*L. nipponica* [179]
70	–	*L. obtusa* [129[a], 130[b,d]]
71	–	*L. obtusa* [129[a], 130[b,d]]
72	Debromoelatol	*L. dendroidea* [146], *L. obtusa* [129[a,d]]
73	Nidifidienol	*L. nidifica* [95, 180[a]]
74	Nidifidiene	*L. nidifica* [137]
75	–	*L. majuscula* [181], *A. dactylomela* [182[a,c,d]]
76	–	*L. majuscula* [181], *L. mariannensis* [62], *A. dactylomela* [182[a,c,d]]
77	(2*Z*,6*S**,9*R**)-Chamigra-2,5(14)-dien-8-one	*L. flexilis* [149[a]], *L. snackeyi* [150]
78	Acetoxy-intricatol	*L. intricata* [183[c,d]]
79	4,10-Dibromo-3-chloro-7*β*,8*β*-epoxy-α-chamigrene	*L. glomerata* [90], *L. nidifica* [95], *L. pinnatifida* [141, 185], *L. scoparia* [102], *Laurencia* sp. [104[a], 184[c,d]]
80	4,10-Dibromo-3-chloro-7,8-epoxy-9-hydroxy-α-chamigrane	*L. glomerata* [90]
81	4,10-Dibromo-3-chloro-7*α*,8*α*-epoxy-α-chamigrene	*L. composita* [88], *L. nipponica* [96[a], 186[c,d]], *L. okamurai* [99, 100], *L. pinnatifida* [141], *Laurencia* sp. [187]
82	10-Bromo-7*α*,8*α*-epoxy-chamigr-1-en-3-ol	*L. okamurai* [152]
83	5,12-Epoxy-obtusol	*L. obtusa* [132[c,d]]
84	–	*L. flagellifera* [188[a]], *L. scoparia* [102]
85	Dehydroxyprepacifenol epoxide	*L. nidifica* [95], *A. dactylomela* [140, 189[a]]
86	Prepacifenol epoxide	*L. composita* [31, 69], *L. johnstonii* [190[a,d], 191], *L. nidifica* [95], *L. okamurai* [99, 192], *Laurencia* sp. [193], *A. californica* [190[a,d], 191], *A. dactylomela* [140, 189, 194]

(continued)

Table 1 (continued)

No.	Name	Source of isolation/synthesis
87	Deoxyprepacifenol	*L. caduciramulosa* [195], *L. claviformis* [87, 107], *L. composita* [84], *L. elata* [196], *L. filiformis* [89], *L. majuscula* [197], *L. mariannensis* [198], *L. nangii* [94], *L. nidifica* [95], *L. nipponica* [78, 97, 199, 200], *L. okamurai* [99, 100, 109, 192, 201], *L. pacifica* [68], *Laurencia* sp. cf. *L. gracilis* [103], *A. californica* [191[a,c,d]], *A. parvula* [89]
88	Prepacifenol	*L. claviformis* [87, 107], *L. composita* [31], *L. filiformis* [202[a,d]], *L. nidifica* [95], *L. nipponica* [97, 203], *L. okamurai* [99, 204], *L. pacifica* [30], *Laurencia* sp. cf. *L. gracilis* [103], *Laurencia* sp. [193]
89	5-Acetoxy-2,10-dibromo-3-chloro-7,8-epoxy-α-chamigrene	*L. filiformis* [89[c,d]], *A. parvula* [89]
90	–	*L. nipponica* [205[c,d]]
91	Dehydrochloroprepacifenol	*L. majuscula* [206[c,d]]
92	–	*L. microcladia* [163], *A. dactylomela* [50, 207[a,c,d]]
93	–	*L. microcladia* [163], *A. dactylomela* [207[a]]
94	Laurecomin D	*L. composita* [84]
95	–	*L. scoparia* [102]
96	Pinnatifinone	*L. pinnatifida* [141, 208[a]]
97	Oxachamigrene	*L. obtusa* [139]
98	5-Acetoxy-oxachamigrene	*L. obtusa* [139]
99	Cyclodebromoacetoxyintricatol	*L. intricata* [209]
100	–	*A. californica* [210]
101	Pacifidiene	*L. pacifica* [211], *A. californica* [210, 212[a,d]], *A. dactylomela* [194, 213]
102	Pacifinediol	*L. composita* [214], *L. nidifica* [95], *A. californica* [190[a,d], 191], *A. dactylomela* [194, 213]
103	Nidifocene	*L. nidifica* [215[a], 216[b,c,d]]; Synthesis [217[f], 218[f]]
104	Pinnatifenol	*L. pinnatifida* [141, 219[a]]
105	Pacifenol	*L. caduciramulosa* [220], *L. claviformis* [87, 107], *L. composita* [31, 69, 88], *L. elata* [196, 221], *L. filiformis* [89], *L. majuscula* [222, 223[c,d]], *L. mariannensis* [198], *L. nidifica* [95, 137], *L. nipponica* [75, 97, 200, 224], *L. okamurai* [99, 192], *L. pacifica* [68, 211, 225[a,c,d]], *L. tasmanica* [202], *Laurencia* sp. cf. *L. gracilis* [103], *Laurencia* sp. [193], *A. californica* [212], *A. dactylomela asymmetrica* [226, 227], *A. dactylomela* [194, 213], *A. parvula* [89]
106	4,10-Dibromo-1,10-epoxy-chamigra-8-ene-4,7-diol	*L. nipponica* [199, 224[a]]
107	10-Bromo-1,10-epoxy-chamigra-8-ene-7-ol	*L. nipponica* [224[d]]

(continued)

Table 1 (continued)

No.	Name	Source of isolation/synthesis
108	–	*L. nipponica* [205[c,d]]
109	–	*L. nipponica* [199, 203[a,c,d]]
110	Bromochlorohydroxy-oxidochamigradiene	*A. dactylomela* [228]
111	Yicterterpene A	*L. composita* [229[d]]
112	Yicterterpene B	*L. composita* [229[d]]
113	Johnstonol	*L. composita* [31, 69, 88], *L. johnstonii* [230[a,c,d]], *L. nidifica* [95], *L. okamurai* [99, 192, 231], *L. pacifica* [230], *L. tristicha* [232], *A. californica* [190], *A. dactylomela* [194, 213]
114	Pinnatazane	*L. pinnatifida* [141, 233[a,c]]
115	Almadioxide	*L. intricata* [234[c,d]]
116	Pinnatifidone	*L. pinnatifida* [141, 235[a,d]]
117	–	*L. nipponica* [199[d]]
118	Cycloelatanene B	*L. elata* [221[a]], *L. nangii* [94]
119	Cycloelatanene A	*L. elata* [221]
120	Laurokamin B	*L. okamurai* [79]
121	10-Bromo-3-chloro-2,7-epoxy-chamigr-9-en-8β-ol	*L. composita* [214]
122	10-Bromo-3-chloro-2,7-epoxy-chamigr-9-en-8α-ol	*L. okamurai* [109], *L. saitoi* [85[a]]
123	–	*L. obtusa* [124]
124	Claviol	*L. claviformis* [87]
125	Gomerolactone A	*L. majuscula* [128]
126	Gomerolactone B	*L. majuscula* [128]
127	Gomerolactone C	*L. majuscula* [128]
128	Gomerolactone D	*L. majuscula* [128]
129	Chamigrenelactone	*L. obtusa* [133]
130	Majusculone	*L. majuscula* [122[a], 128], *L. scoparia* [134]; Synthesis [121[f], 236[d,g]]
131	Ma'ilione	*L. cartilaginea* [142[a]], *L. majuscula* [118], *L. scoparia* [134, 147[c,d]], *Laurencia* sp. [143], *A. dactylomela* [118]
132	–	*A. dactylomela* [144[d]]
133	–	*A. dactylomela* [182]; Synthesis [237[b,f]]
134	–	*A. dactylomela* [182]; Synthesis [237[b,f]]
135	Laurencomposidiene	*L. composita* [88]
136	Scopariol	*L. scoparia* [134]
137	Pannosane	*L. pannosa* [238]
138	Laurenokamurin	*L. okamurai* [239]
139	Laurokamin A	*L. okamurai* [79]
140	Laurecomin A	*L. composita* [84]
141	–	*A. dactylomela* [240[d]]
142	Pannosanol	*L. pannosa* [238]

(continued)

Table 1 (continued)

No.	Name	Source of isolation/synthesis
143	–	*L. flagellifera* [188[a]], *L. pinnatifida* [141, 219], *L. scoparia* [102]
144	Pinnatifate	*L. pinnatifida* [241]
145	Spironippol	*L. nipponica* [97, 242[a]]
146	2-Bromo-spironippol	*L. composita* [88]
147	Kylinone	*L. pacifica* [211]
148	Laurene	*L. elata* [196], *L. filiformis* f. *heteroclada* [243], *L. glandulifera* [244[a], 245[d]], *L. nipponica* [77, 78, 96, 138, 246], *L. okamurai* [109, 152, 247], *L. subopposita* [68, 248], *Laurencia* sp. cf. *L. gracilis* [103], *A. punctata* [249]; Synthesis [250[h], 251[f], 252[f], 253[f], 254[g]]
149	Debromoallolaurinterol (7-Hydroxy-laurene)	*L. caduciramulosa* [220], *L. nipponica* [138], *L. obtusa* [255], *L. okamurai* [109], *L. subopposita* [248[a]], *A. punctata* [249]
150	Debromoallolaurinterol acetate	*L. okamurai* [152]
151	Allolaurinterol (10-Bromo-7-hydroxy-laurene)	*L. caduciramulosa* [220], *L. caraibica* [256], *L. filiformis* f. *heteroclada* [127, 243[a,d], 257], *L. glandulifera* [258], *L. majuscula* [69], *L. obtusa* [259], *L. subopposita* [248], *A. dactylomela* [178, 260]; Synthesis [261[f]]
152	Allolaurinterol acetate	*L. okamurai* [152], *A. dactylomela* [156[a,d], 260]
153	10,11-Dibromo-7-hydroxy-laurene	*L. majuscula* [69]
154	10-Bromo-7-hydroxy-11-iodolaurene	*L. caraibica* [256]
155	Laurenol	*L. nipponica* [96[d]]
156	Laurenol acetate	*L. nipponica* [96[d]]
157	Laurenal	*L. nipponica* [96[d]]
158	–	*L. microcladia* [262]
159	Debromoisolaurinterol	*L. decidua* [60, 263], *L. distichophylla* [264], *L. majuscula* [181], *L. okamurai* [60[d], 192, 201, 247, 265[a]], *L. pacifica* [68]; Synthesis [266[f]]
160	Debromoisolaurinterol acetate	*L. okamurai* [267[d]]
161	Isolaurinterol	*L. decidua* [60, 263], *L. filiformis* f. *heteroclada* [127], *L. nidifica* [62], *L. okamurai* [60, 99, 192, 201, 247, 265[a,d], 268], *L. pacifica* [60, 68], *L. tristicha* [269], *A. dactylomela* [270]; Synthesis [266[f]]
162	Isolaurinterol acetate	*L. okamurai* [267[d]]
163	Laur-11-en-10-ol	*L. tristicha* [232]
164	Laur-11-en-2,10-diol	*L. tristicha* [232]
165	Laur-11-en-1,10-diol	*L. tristicha* [232]

(continued)

Table 1 (continued)

No.	Name	Source of isolation/synthesis
166	4-Bromo-laur-11-en-1,10β-diol	*L. tristicha* [269]
167	Laur-2-ene-3,12-diol	*L. obtusa* [271]
168	Laur-11-en-1,10α-diol	*L. tristicha* [269]
169	4-Bromo-laur-11-en-1,10α-diol	*L. tristicha* [269]
170	–	*L. pinnatifida* [272]
171	Laurenisol	*L. claviformis* [107], *L. filiformis* f. *heteroclada* [127], *L. glandulifera* [258], *L. nipponica* [273[a,d]], *A. punctata* [249]
172	Laurenisol acetate	*A. dactylomela* grazing on *L. claviformis* [115]
173	–	*L. glandulifera* [258[d]]
174	*iso*-Laurenisol	*L. chondrioides* [73], *L. obtusa* [255[a]], *L. saitoi* [85], *Laurencia* sp. cf. *L. gracilis* [103[a]]
175	Bromolaurenisol	*L. filiformis* f. *heteroclada* [127[a], 257], *L. microcladia* [255]
176	Isolaurenisol	*L. distichophylla* [264[a]], *A. dactylomela* [260]
177	Isolaurenisol acetate	*A. dactylomela* [260]
178	Isoallolaurinterol	*L. filiformis* f. *heteroclada* [257]
179	10-Bromo-7,12-dihydroxy-$\Delta^{2.3}$-laurene	*L. caraibica* [256]
180	Isolaurene	*L. elata* [196], *L. glandulifera* [258], *L. nipponica* [60], *L. okamurai* [60, 192, 247[a]], *L. tristicha* [269]; Synthesis [244[d], 245, 246]
181	10-Hydroxy-isolaurene	*L. microcladia* [274[a]], *L. okamurai* [267[a]]
182	12-Hydroxy-isolaurene	*L. obtusa* [98]
183	Isolauraldehyde	*L. obtusa* [98]
184	3,7-Dihydroxy-dihydrolaurene	*L. obtusa* [255]
185	Laurepoxyene	*L. okamurai* [275]
186	Laurol	*L. pinnatifida* [276]
187	Isodihydrolaurene	*L. nipponica* [78, 96[a,d], 97, 138]
188	Isodihydrolaurenol	*L. nipponica* [96[d]]
189	Isodihydrolaurenol acetate	*L. nipponica* [96[d]]
190	–	*L. pinnatifida* [272]
191	8,11-Dihydro-12-hydroxy-isolaurene	*L. obtusa* [98]
192	Dihydrolaurene	*L. filiformis* f. *heteroclada* [243[a,d]], *Laurencia* sp. cf. *L. gracilis* [103]
193	16,16-Dichlorohomolaurane	*A. dactylomela* [277]
194	Debromoaplysin	*L. distichophylla* [264], *L. nidifica* [278], *L. okamurai* [99, 231, 279], *L. pacifica* [211], *L. tristicha* [269], *A. californica* [212], *A. kurodai* [52[a,d]]; Synthesis [266[f], 280[f], 281[h], 282[f], 283[f], 284[f], 285[g], 286[d,g], 287[g], 288[g], 289[g]]

(continued)

Table 1 (continued)

No.	Name	Source of isolation/synthesis
195	Aplysin	*L. decidua* [263], *L. nidifica* [137, 278], *L. okamurai* [99, 231, 268, 275], *L. pacifica* [211, 263], *L. tristicha* [232, 290], *A. californica* [212], *A. kurodai* [52[a], 292[d], 293], *A. parvula* [291]; Synthesis [266[f], 280[f], 281[h], 282[f], 283[f], 284[f], 285[g], 286[g], 287[g], 288[g], 289[g]]
196	10-Hydroxy-aplysin	*L. okamurai* [275, 279], *L. tristicha* [290, 294[a]]
197	3β-Hydroperoxyaplysin	*L. okamurai* [275[d]]
198	10-Hydroxy-debromo-*epi*-aplysin	*L. okamurai* [279], *L. tristicha* [290, 294[a]]
199	10-Hydroxy-*epi*-aplysin	*L. okamurai* [275], *L. tristicha* [290, 294[a]]
200	3α-Hydroperoxy-3-*epi*-aplysin	*L. okamurai* [275[d]]
201	Aplysin-9-ene	*L. tristicha* [290]
202	Debromoaplysinol	*L. okamurai* [60[a], 201], *L. tristicha* [269, 295]; Synthesis [266[f], 283[f]]
203	Isoaplysin	*L. okamurai* [60, 247[a,d], 267, 296]; Synthesis [266[f], 283[f]]
204	Aplysinol	*L. decidua* [263, 297[c,d]], *L. okamurai* [60, 231, 267, 298], *L. pacifica* [263], *L. tristicha* [232, 269, 290], *A. kurodai* [52[a], 292[d], 293]; Synthesis [266[f], 283[f]]
205	Aplysinol acetate	*L. okamurai* [201[d]]
206	Laureperoxide	*L. okamurai* [267]
207	10-Bromoisoaplysin	*L. okamurai* [267[a], 275]
208	8,10-Dibromoisoaplysin	*L. okamurai* [275]
209	Aplysinal	*L. okamurai* [268[d]]; Synthesis [266[f]]
210	Debromo-*epi*-aplysinol	*L. tristicha* [290]
211	*epi*-Aplysinol	*L. tristicha* [290]
212	Ibhayinol	*A. dactylomela* [140, 299[c,d]]
213	Debromofiliformin	*L. caduciramulosa* [220[a]], *L. okamurai* [109]; Synthesis [284[f]]
214	Filiformin	*L. caduciramulosa* [220], *L. caraibica* [256], *L. filiformis* f. *heteroclada* [127, 243[a], 257], *L. okamurai* [109, 201]; Synthesis [284[f], 300[d,g]]
215	Isofiliformin	*L. glandulifera* [258[d], 301[a]], *L. pinnatifida* [272], *A. punctata* [249]
216	12-Bromo-filiformin	*L. caraibica* [256], *L. glandulifera* [258[d], 301[a]], *L. okamurai* [109], *L. pinnatifida* [272]; Synthesis [302[f]]
217	–	*L. microcladia* [262]
218	Filiforminol	*L. filiformis* f. *heteroclada* [243[a], 257]; Synthesis [302[f]]
219	8,10-Dibromo-3,7-epoxy-laur-13-ol	*Laurencia* sp. [303]
220	–	*L. caraibica* [256]
221	–	*L. glandulifera* [258, 301[a]]

(continued)

Table 1 (continued)

No.	Name	Source of isolation/synthesis
222	4-Bromo-1,10-epoxy-laur-11-ene	*L. tristicha* [232]
223	Caraibical	*L. caraibica* [304]
224	Cycloisoallolaurinterol	*L. filiformis* f. *heteroclada* [257]
225	Cyclolaurene	*A. dactylomela* [305[d]]; Synthesis [306[f]]
226	Debromolaurinterol	*L. decidua* [263], *L. flexilis* [149], *L. nidifica* [278], *L. okamurai* [31, 60, 192, 247, 265, 307[a,d]], *L. pacifica* [68, 211, 263], *L. tristicha* [269], *A. californica* [212], *A. kurodai* [308], *A. parvula* [291]; Synthesis [281[h]]
227	Debromolaurinterol acetate	*L. okamurai* [267], *A. kurodai* [309[a,d]]; Synthesis [281[f]]
228	Cyclolauren-2-ol	*L. tristicha* [232]
229	Isodebromolaurinterol	*L. okamurai* [267]
230	Neolaurinterol	*L. okamurai* [247[d]]
231	Laurinterol	*L. decidua* [263], *L. microcladia* [255], *L. nidifica* [62, 137, 278], *L. okamurai* [31, 60, 99, 192, 247, 265, 268, 279, 292[c,d], 293, 298, 307[a]], *L. pacifica* [68, 225, 263], *L. tristicha* [269], *Laurencia* sp. [105], *A. californica* [212], *A. dactylomela* [270], *A. kurodai* [308], *A. parvula* [291], *A. punctata* [249]; Synthesis [281[h]]
232	Laurinterol acetate	*L. okamurai* [267], *A. kurodai* [292[c,d], 293, 309[a]]; Synthesis [281[h]]
233	Cyclolaurenol	*L. calliclada* [310], *L. venusta* [69], *A. dactylomela* [305[a,d]]
234	Cyclolaurenol acetate	*A. dactylomela* [305[d]]
235	Bromolaurinterol	*L. decidua* [263], *L. microcladia* [262], *L. okamurai* [60[a,d]], *L. tristicha* [269]
236	8-Iodolaurinterol	*L. microcladia* [262]
237	Laurequinone	*L. nidifica* [278[a,d]], *L. okamurai* [192]; Synthesis [311[g]]
238	–	*L. microcladia* [262]
239	Laurebiphenyl	*L. nidifica* [312[a,d]], *L. tristicha* [232]
240	–	*L. microcladia* [255[a]], *L. tristicha* [269]
241	Laurokamurene B	*L. okamurai* [279]; Synthesis [313[f], 314[d,g]]
242	Laurokamurene A	*L. microcladia* [274[a]], *L. okamurai* [275, 279], *Laurencia* sp. [118], *A. dactylomela* [118]
243	Laurokamurene C	*L. okamurai* [201[a], 275]
244	Laurokamurene D	*L. okamurai* [275]
245	8,11-Dihydro-1-methoxy-laurokamuren-12-ol	*L. obtusa* [271]
246	Laurentristich-4-ol	*L. tristicha* [232[a], 315[b]]; Synthesis [316[b]]
247	α-Snyderol	*L. nangii* [94], *L. obtusa* [317[a], 318, 319]
248	α-Snyderol acetate	*L. obtusa* [319, 320[a]]

(continued)

Table 1 (continued)

No.	Name	Source of isolation/synthesis
249	β-Snyderol	*L. obtusa* [145, 321], *L. snyderae* [317[a]], *A. punctata* [249]; Synthesis [322[f]]
250	β-Snyderol acetate	*L. obtusa* [145]
251	Luzonensin	*L. luzonensis* [323]
252	Luzonensol	*L. luzonensis* [323[a], 324[b,d]], *L. similis* [325]
253	Luzonensol acetate	*L. luzonensis* [323[d]]
254	–	*L. similis* [325]
255	6-*epi*-β-Snyderol	*A. fasciata* [326]
256	(8*S**)-8-Bromo-β-snyderol	*L. obtusa* [319]
257	8-Hydroxy-β-snyderol	*L. caespitosa* [327[d]]
258	(8*R**)-8-Bromo-10-*epi*-β-snyderol	*L. obtusa* [319]
259	–	*L. implicata* [91], *L. snackeyi* [118], *A. dactylomela* [118]
260	Palisol	*L. flexilis* [149], *L. implicata* [91, 114], *L. luzonensis* [323], *L. snackeyi* [118, 328[a,d], 329, 330], *A. dactylomela* [118]
261	Isopalisol	*L. luzonensis* [323[a]], *L. similis* [325]
262	8-Oxo-10-dehydrobromo-β-snyderol	*L. caespitosa* [327[d]]
263	8-Hydroxy-γ-snyderol	*L. caespitosa* [327[d]]
264	–	*L. obtusa* [319]
265	–	*L. obtusa* [319]
266	Palisadin B	*L. flexilis* [331, 332], *L. implicata* [91, 114], *L. karlae* [333], *L. luzonensis* [323, 334], *L. saitoi* [335], *L. similis* [325], *L. snackeyi* [118, 150, 328[a], 336], *A. dactylomela* [118, 337]; Synthesis [338[d,g]]
267	5*β*-Hydroxy-palisadin B	*L. flexilis* [331[a]], *L. snackeyi* [150]
268	5*β*-Acetoxy-palisadin B	*L. flexilis* [331], *L. karlae* [333], *L. saitoi* [335], *L. similis* [325], *L. snackeyi* [118, 150, 328[a], 329, 330, 339], *A. dactylomela* [118, 337, 339]
269	12-Hydroxy-palisadin B	*L. flexilis* [331], *L. karlae* [333], *L. snackeyi* [328[a,d]], *A. dactylomela* [337]; Synthesis [338[g]]
270	12-Acetoxy-palisadin B	*L. snackeyi* [118], *A. dactylomela* [118]
271	12-Bromopalisadin B	*L. flexilis* [331]
272	4-Hydroxy-palisadin C	*L. saitoi* [335[a]], *L. similis* [325]
273	Palisadin C	*L. flexilis* [331]
274	3,4-Epoxy-palisadin B	*L. luzonensis* [324[a], 334, 340]
275	1,2-Dehydro-3,4-epoxy-palisadin B	*L. luzonensis* [324]
276	Aplysistatin	*L. filiformis* [341], *L. flexilis* [331], *L. implicata* [91, 114], *L. karlae* [333], *L. luzonensis* [334], *L. saitoi* [335], *L. similis* [325], *L. snackeyi* [118, 150, 328–330, 339], *C. papillosus* [342], *A. angasi* [343[a,c,d]], *A. dactylomela* [118, 337, 339]; Synthesis [338[g], 344[f], 345[f], 346[f], 347[g]]

(continued)

Table 1 (continued)

No.	Name	Source of isolation/synthesis
277	6*β*-Hydroxy-aplysistatin	*L. filiformis* [341[a,c,d]], *L. implicata* [91, 114]
278	Palisadin A	*L. flexilis* [331], *L. implicata* [91, 114], *L. karlae* [333], *L. luzonensis* [323, 334], *L. saitoi* [335], *L. similis* [325], *L. snackeyi* [118, 150, 328[a,d], 329, 330, 339], *A. dactylomela* [118, 337, 339], *A. parvula* [166]; Synthesis [338[g]]
279	15-Hydroxy-palisadin A	*L. luzonensis* [324[a], 340]
280	5*β*-Acetoxy-palisadin A	*L. flexilis* [331]
281	3,4-Epoxy-palisadin A	*L. flexilis* [331, 332[c,d]]
282	3*β*-Bromo-8-epicaparrapi oxide	*L. obtusa* [145, 348[a], 349]
283	Luzonenone	*L. luzonensis* [324[a], 340]
284	(3*R**,4*S**)-Luzonolone	*L. luzonensis* [334]
285	(3*S**,4*R**)-Luzonolone	*L. luzonensis* [334]
286	Luzondiol	*L. luzonensis* [334]
287	Luzofuran	*L. luzonensis* [324[a], 340]; Synthesis [350[f]]
288	2-Hydroxy-luzofuranone	*L. saitoi* [335]
289	2-Hydroxy-luzofuranone B	*L. saitoi* [335]
290	Bicyclolaurencenol	*L. intricata* [351]
291	Dactylenol	*L. intricata* [351], *A. dactylomela* [352[a]]
292	Dactylenol acetate	*A. dactylomela* [352]
293	–	*L. nangii* [94], *A. punctata* [249[a]]
294	–	*L. nangii* [94], *A. punctata* [249[a]]
295	–	*L. intricata* [351], *L. nidifica* [353[a]], *L. snyderae* [354]; Synthesis [355[f]]
296	–	*L. intricata* [351], *L. nidifica* [353[a]]
297	–	*L. luzonensis* [334]
298	–	*L. luzonensis* [334]
299	Dactyloxene B	*A. dactylomela* [352, 356[a]]; Synthesis [357[b], 358[d,g], 359[g], 360[g], 361[h]]
300	Dactyloxene C	*A. dactylomela* [352[a]]; Synthesis [357[b], 358[d,g], 359[g], 360[g], 361[h]]
301	Dactyloxene A	*L. nangii* [94], *A. dactylomela* [352[a]]
302	Isodactyloxene A	*L. mariannensis* [74]
303	Dactyloxene D	*L. obtusa* [362]
304	(*E*)-γ-Bisabolene	*L. nipponica* [363]
305	3-Acetoxy-(*E*)-γ-bisabolene	*L. rigida* [81]
306	–	*L. microcladia* [262]
307	(5*S*)-5-Acetoxy-β-bisabolene	*L. okamurai* [275[d]]
308	(*E*)-γ-Bisabolene 8,9-epoxide	*L. nipponica* [363]; Synthesis [171[d,g], 364[f]]
309	Preintricatol	*L. intricata* [209[a]], *Laurencia* sp. cf. *L. gracilis* [103]
310	Puertitol A	*L. obtusa* [365[d]]
311	Puertitol B	*L. obtusa* [365[d]]
312	Puertitol B acetate	*A. dactylomela* [50[d]]

(continued)

Table 1 (continued)

No.	Name	Source of isolation/synthesis
313	–	*L. scoparia* [366[c,d]]
314	2-Bromo-3-chloro-bisabola-7(14),11-diene-6,10-diol	*L. composita* [214]
315	–	*L. scoparia* [366]
316	–	*L. scoparia* [366]
317	–	*L. caespitosa* [367]
318	–	*L. caespitosa* [367]
319	Gossonorol	*L. tristicha* [232]
320	α-Bisabol-9-en-7,11-diol	*L. tristicha* [232]
321	Okamurene D	*L. okamurai* [109]
322	Okamurene C	*L. okamurai* [109]
323	(9*R*)-2-Bromo-3-chloro-6,9-epoxy-bisabola-7(14),10-diene	*L. saitoi* [85]
324	(9*S*)-2-Bromo-3-chloro-6,9-epoxy-bisabola-7(14),10-diene	*L. saitoi* [85]
325	–	*L. scoparia* [366]
326	–	*L. scoparia* [366]
327	7,10-Epoxy-α-bisabol-11-ol	*L. tristicha* [232]
328	10-*epi*-7,10-Epoxy-α-bisabol-11-ol	*L. tristicha* [232]
329	Deschlorobromocaespitol	*A. dactylomela* [368[d]]
330	Deschlorobromocaespitenone	*A. dactylomela* [368[d]]
331	Okamurene A	*L. okamurai* [109]
332	Okamurene B	*L. okamurai* [109]
333	Caespitane (Deoxycaespitol)	*L. caespitosa* [369[a,c,d]], *L. catarinensis* [370], *A. dactylomela* [50, 135, 368]
334	Deodactol	*A. dactylomela* [371[c,d]]
335	(5*S*)-5-Acetoxy-deoxycaespitol	*L. catarinensis* [370]
336	Isodeodactol	*A. dactylomela* [372]
337	Caespitol (Aldingenin C)	*L. aldingensis* [373, 374[b]], *L. caespitosa* [375[a], 376[b]], *L. caespitosa* [369[d]], *L. catarinensis* [370], *L. intricata* [377], *L. obtusa* [129, 318], *A. dactylomela* [50, 368]
338	8-Acetylcaespitol	*L. catarinensis* [370], *A. dactylomela* [50[a,d], 368]
339	6-Hydroxy-caespitol	*L. caespitosa* [369[c,d]]
340	Aldingenin A	*L. aldingensis* [378, 379[b]]
341	(5*S*)-5-Hydroxy-acetylcaespitol	*L. catarinensis* [370]
342	(5*S*)-5-Acetoxy-caespitol (aldingenin D)	*L. aldingensis* [373[a], 374[b], 379], *L. catarinensis* [370[d]]
343	(5*S*)-5-Acetoxy-acetylcaespitol	*L. catarinensis* [370]
344	Dihydroxy-deodactol monoacetate	*A. dactylomela* [380]
345	8-Desoxy-isocaespitol	*L. caespitosa* [381[a]], *L. catarinensis* [370]; Synthesis [381[f]]
346	Isocaespitol	*L. caespitosa* [369[d], 376[b], 382[a]], *L. catarinensis* [370], *L. obtusa* [318]; Synthesis [383[g]]

(continued)

Table 1 (continued)

No.	Name	Source of isolation/synthesis
347	Isocaespitol acetate	*A. dactylomela* [384]
348	10-*epi*-Deoxycaespitol	*L. catarinensis* [370]
349	Caespitenone	*L. catarinensis* [370], *A. dactylomela* [50[a], 135, 368]
350	Aldingenin B	*L. aldingensis* [373, 379[b]]; Synthesis [385[e], 386[b]]
351	–	*L. caespitosa* [387[c,d]]
352	Furocaespitane	*L. caespitosa* [161, 387[b,d], 388[a]], *A. dactylomela* [50, 368]
353	Isofurocaespitane	*L. caespitosa* [161]
354	Furocaespitanelactol	*L. catarinensis* [370], *A. dactylomela* [368[a]]
355	(10*R**)-10-*O*-Methyl-furocaespitanelactol	*L. catarinensis* [370]
356	(10*S**)-10-*O*-Methyl-furocaespitanelactol	*L. catarinensis* [370]
357	–	*L. caespitosa* [387[c,d]]
358	–	*L. majuscula* [153]
359	–	*L. majuscula* [153]
360	–	*L. majuscula* [153]
361	–	*L. obtusa* [389[c,d]]
362	Majapolene A	*L. caraibica* [390], *L. majuscula* [390[a]], *Laurencia* sp. [193]
363	Acetylmajapolene A	*Laurencia* sp. [193]
364	Majapolene B	*L. majuscula* [390[a], 391[d]], *Laurencia* sp. [193]
365	Acetylmajapolene B	*Laurencia* sp. [193, 391[d]]
366	Tiomanene	*Laurencia* sp. [193]
367	Majapolone	*L. majuscula* [390]
368	Majapol A	*L. majuscula* [390]
369	Majapol B	*L. majuscula* [390]
370	Majapol C	*L. majuscula* [390]
371	Majapol D	*L. majuscula* [390]
372	Laucapyranoid A	*L. caespitosa* [369[a]], *A. dactylomela* [50, 368]
373	Laucapyranoid B	*L. caespitosa* [369[c,d]]
374	Laucapyranoid C	*L. caespitosa* [369[c,d]]
375	Aplysiadactydiol	*A. dactylomela* [368[a], 392]
376	Perforenone	*L. obtusa* [393], *L. perforata* [394[a]], *L. snyderae* var. *guadalupensis* [395], *A. punctata* [249]; Synthesis [396[f], 397[f]]
377	Perforenone A	*L. obtusa* [255], *L. perforata* [398[a]]
378	Perforenone B	*L. perforata* [398]
379	Perforenone C (3-*epi*-Perforenone A)	*L. obtusa* [255], *L. perforata* [394[a], 399]
380	Perforenone D	*L. obtusa* [393]
381	9-Hydroxy-3-*epi*-perforenone A	*L. perforata* [399]
382	Perforenol	*L. obtusa* [255], *L. perforata* [400[a,c,d]]
383	Guadalupol	*L. snyderae* var. *guadalupensis* [395]

(continued)

Table 1 (continued)

No.	Name	Source of isolation/synthesis
384	Perforenol B	*L. obtusa* [255]
385	Epiguadalupol	*L. snyderae* var. *guadalupensis* [395]
386	Perforene	*L. perforata* [401[a]]
387	Debromoperforatone	*L. obtusa* [393[b]]; Synthesis [396[f], 398[f]]
388	Perforatone	*L. obtusa* [393], *L. perforata* [398[a]]
389	–	*L. tenera* [402[c,d]]
390	–	*L. obtusa* [393]
391	–	*L. obtusa* [393]
392	–	*L. obtusa* [393]
393	–	*L. obtusa* [255]
394	Perforatol	*A. punctata* [249]
395	Tenerol acetate	*L. tenera* [403]
396	–	*L. tenera* [402]
397	4-Hydroxy-1,8-*epi*-isotenerone	*L. perforata* [399]
398	Brasilenol	*L. implicata* [114], *L. obtusa* [320, 404, 405], *A. brasiliana* [406[a]], *A. dactylomela* [407], *A. fasciata* [326]; Synthesis [408[d,g], 409[f]]
399	Brasilenol acetate	*A. brasiliana* [406[a,d]], *A. fasciata* [326]
400	Epibrasilenol	*L. obtusa* [320, 405, 410, 411], *A. brasiliana* [406[a,d]], *A. fasciata* [326]
401	Epibrasilenol acetate	*A. fasciata* [326[d]]
402	4-Hydroxy-5-brasilene	*L. implicata* [91], *L. obtusa* [410[a], 411], *A. fasciata* [326]
403	4-Acetoxy-5-brasilene	*A. fasciata* [326]
404	–	*L. implicata* [114]
405	–	*L. implicata* [91, 412[d]]
406	6-Hydroxy-1-brasilene	*A. fasciata* [326]
407	*epi*-5,9-Dihydroxy-brasil-1(6)-en-7-one	*L. obtusa* [410]
408	5,9-Dihydroxy-brasil-1(6)-en-7-one	*L. obtusa* [404]
409	9-Hydroxy-brasil-1(6),4-dien-7-one	*L. obtusa* [410]
410	–	*L. obtusa* [413]
411	–	*L. obtusa* [405]
412	–	*L. obtusa* [405]
413	–	*L. obtusa* [405]
414	2,5-Epoxy-brasil-1(6)-en-9-ol	*L. obtusa* [404]
415	(+)-α-Bromocuparene	*L. caraibica* [256, 304], *L. chondrioides* [73], *L. distichophylla* [264], *L. flexilis* [149], *L. glandulifera* [76, 414[a,d]], *L. okamurai* [60, 192, 247], *A. punctata* [249]
***ent*-415**	(–)-α-Bromocuparene	*L. filiformis* f. *heteroclada* [127[a,d]], *L. microcladia* [262], *Laurencia* sp. [83]
416	–	*L. implicata* [415]

(continued)

Table 1 (continued)

No.	Name	Source of isolation/synthesis
417	α-Isobromocuparene	*L. glandulifera* [76, 414[a,d]], *L. majuscula* [416], *L. microcladia* [262], *L. nipponica* [414[a,d]], *L. okamurai* [60, 109, 201, 247], *Laurencia* sp. [83], *A. punctata* [249]
418	Cupalaurenol	*L. venusta* [69], *Laurencia* sp. [187], *A. dactylomela* [305[a,d]]
419	Cupalaurenol acetate	*A. dactylomela* [305[d]]
420	–	*L. obtusa* [271]
421	–	*L. distichophylla* [264], *L. microcladia* [255], *L. okamurai* [60, 201, 247[a]]
422	–	*L. microcladia* [274]
423	–	*L. majuscula* [416]
424	10-Bromo-3-chloro-cupar-5-en-2-ol	*L. okamurai* [152]
425	1-Deacetoxy-8-deoxyalgoane	*A. dactylomela* [140]
426	1-Deacetoxy-algoane	*A. dactylomela* [140]
427	Algoane	*A. dactylomela* [140[c,d]]
428	Oculiferane	*A. oculifera* [167]
429	(+)-Selin-4,7(11)-diene	*L. nidifica* [417[a,d]], *L. nipponica* [363]
430	(4*S*,5*R*,10*R*)-Selin-6(7)-en-11-ol	*L. nipponica* [418[d]]
431	(5*S*,7*R*,10*R*)-Selin-4(14)-en-5α-ol	*L. nipponica* [78[a,d], 418]
432	Brasudol	*A. brasiliana* [419[d]]
433	Isobrasudol	*A. brasiliana* [419[d]]
434	1-Bromo-selin-4(14),11-diene	*L. composita* [84]
435	9-Bromo-selin-4(14),11-diene	*L. composita* [84]
436	–	*A. dactylomela* [277]
437	Austradiol	*L. filiformis* f. *heteroclada* [420[a,d], 421]
438	Austradiol acetate	*L. filiformis* f. *heteroclada* [420[a,d], 421]
439	Itomanol	*L. intricata* [422]
440	Eudesma-4(15),7-diene-5,11-diol	*L. obtusa* [423]
441	(1*S*)-Bromo-(4*R*)-hydroxy-7-chloroselin-7-ene	*Laurencia* sp. [177[a,d], 424[a,d]]
442	(1*S*,4*R*,7*R*)-1-Bromo-4-hydroxy-7-chloroselinane	*Laurencia* sp. [425[c,d]]
443	Heterocladol	*L. filiformis* f. *heteroclada* [426[c,d]]
444	Lankalapuol A	*A. dactylomela* [427[c,d]]
445	Lankalapuol B	*A. dactylomela* [427]
446	Cycloeudesmol	*L. nipponica* [77, 199, 363, 428[b,d]], *Laurencia* sp. [429[a]]
447	–	*L. microcladia* [430]
448	Chabrolidione B	*L. obtusa* [423]
449	Teuhetenone A	*L. obtusa* [423]
450	1(10)-Aristolene	*L. decumbens* [160]

(continued)

Table 1 (continued)

No.	Name	Source of isolation/synthesis
451	Aristol-1(10)-en-9β-ol	*L. similis* [176[a], 325, 431], *Laurencia* sp. [303], *C. papillosus* [342]
***ent*-451**	–	*L. similis* [432]
452	Aristol-1(10)-en-9-one	*L. similis* [176, 325]
453	–	*L. similis* [432]
454	Aristolone	*L. similis* [325, 432], *Laurencia* sp. [303], *C. papillosus* [342]
455	Axinysone B	*L. similis* [432]
456	Debilone	*L. complanata* [433]
457	Aristol-9-en-1-one	*L. similis* [176[a], 325, 431]
458	Aristol-8-en-1-one	*L. similis* [176[a], 325, 431, 434]
459	Aristol-1(10),8-diene	*L. similis* [176, 325]
460	1(10),8-Aristoladien-2-one	*C. papillosus* [342]
461	Aristol-1,9-diene	*L. similis* [176, 325]
462	10β-Hydroxy-aristolan-9-one	*L. similis* [176[a], 325, 434]
463	Aristolan-1α-bromo-9β,10β-epoxide	*L. similis* [431]
464	–	*L. luzonensis* [323]
465	Obtusenol	*L. obtusa* [413, 435[a]], *A. punctata* [249]; Synthesis [436[b,f]]
466	–	*L. subopposita* [248]
467	Humulene	*L. saitoi* [437]
468	–	*L. saitoi* [437[c,d]]
***ent*-468**	–	*L. saitoi* [437[c,d]]
469	*seco*-Laurokamurone	*L. okamurai* [275[d]]
470	Lauracetal A	*L. nipponica* [75[a], 199]
471	Lauracetal B	*L. nipponica* [199, 438[a]]
472	Lauracetal D	*L. nipponica* [439[c,d]]
473	Lauracetal E	*L. nipponica* [439[c,d]]
474	Lauracetal C	*L. nipponica* [440]
475	(–)-δ-Cadinene	*L. microcladia* [430]
476	(+)-α-Cadinol	*L. microcladia* [430]
477	Oplopanone	*L. subopposita* [248]
478	Dactylol	*L. poitei* [441[d]], *A. dactylomela* [442[a,d]]; Synthesis [443[f], 444[f], 445[g], 446[g]]
479	Poitediol	*L. poitei* [441[c]]; Synthesis [447[f]]
480	Guaiazulene	*L. obtusa* [320]
481	Oppositol	*L. subopposita* [448[c,d]]; Synthesis [449[f], 450[f]]
482	–	*L. subopposita* [248]
483	–	*L. subopposita* [248]
484	–	*L. mariannensis* [198]

(continued)

Table 1 (continued)

No.	Name	Source of isolation/synthesis
485	Pacifigorgiol	*L. flexilis* [149], *L. luzonensis* [323], *L. saitoi* [335], *L. snackeyi* [118, 451], *A. dactylomela* [118]
486	Laurencial	*L. nipponica* [452[c,d]]; Synthesis [453[f]]
487	Spirolaurenone	*L. nipponica* [78, 199, 454[a], 455[d]]; Synthesis [456[f,d]]
488	Laurenone A	*L. nipponica* [457[c,d]]
489	Laurenone B	*L. nipponica* [457[d]]
490	–	*L. dendroidea* [126, 146, 458], *L. majuscula* [153, 158[a]], *L. rigida* [81], *L. scoparia* [366]
491	–	*L. majuscula* [114], *L. scoparia* [366]
492	–	*L. dendroidea* [458]
493	Viridianol	*L. viridis* [459]
494	Majusin	*L. majuscula* [460]
495	Isoafricanol	*L. mariannensis* [74]
496	(–)-Aromadendrene	*L. filiformis* [421]
497	1-Hydroxy-alloaromadendrene	*L. subopposita* [248[d]]
498	10β-Hydroxy-$\Delta^{1(2)}$-aromadendrene	*L. subopposita* [248]
499	Bromocyclococanol	*L. obtusa* [461]
500	Calenzanol	*L. microcladia* [462, 463]
501	Debromoisocalenzanol	*L. microcladia* [463]
502	Laurobtusol	*L. obtusa* [464]; Synthesis [465[b,f]]
503	Guimarediol	*L. obtusa* [132], *Laurencia* sp. [466[a,c,d]]
504	Dactylomelatriol	*A. dactylomela* [135]
505	Gomerone A	*L. majuscula* [467]
506	Gomerone B	*L. majuscula* [467]; Synthesis [468[b]]
507	Gomerone C	*L. majuscula* [467]; Synthesis [468[b,f]]
508	Rhodolauradiol	*L. obtusa* [132], *Laurencia* sp. [469[a,c]]; Synthesis [470]
509	Rhodolaureol	*L. obtusa* [132], *Laurencia* sp. [469[a,c]]; Synthesis [470]
510	Isorhodolaureol	*L. majuscula* [158]
511	–	*L. mariannensis* [74]; Synthesis [470]
512	Aplydactone	*A. dactylomela* [471[c,d]]

[a]The isolation and structure elucidation of this compound was reported for the first time
[b]The structure of this compound has been revised
[c]The structure of this compound or of a derivative has been confirmed by X-ray crystallographic analysis
[d]The absolute stereochemistry of this compound has been established
[e]Partial synthesis
[f]Stereoselective total synthesis
[g]Enantioselective total synthesis
[h]Formal synthesis

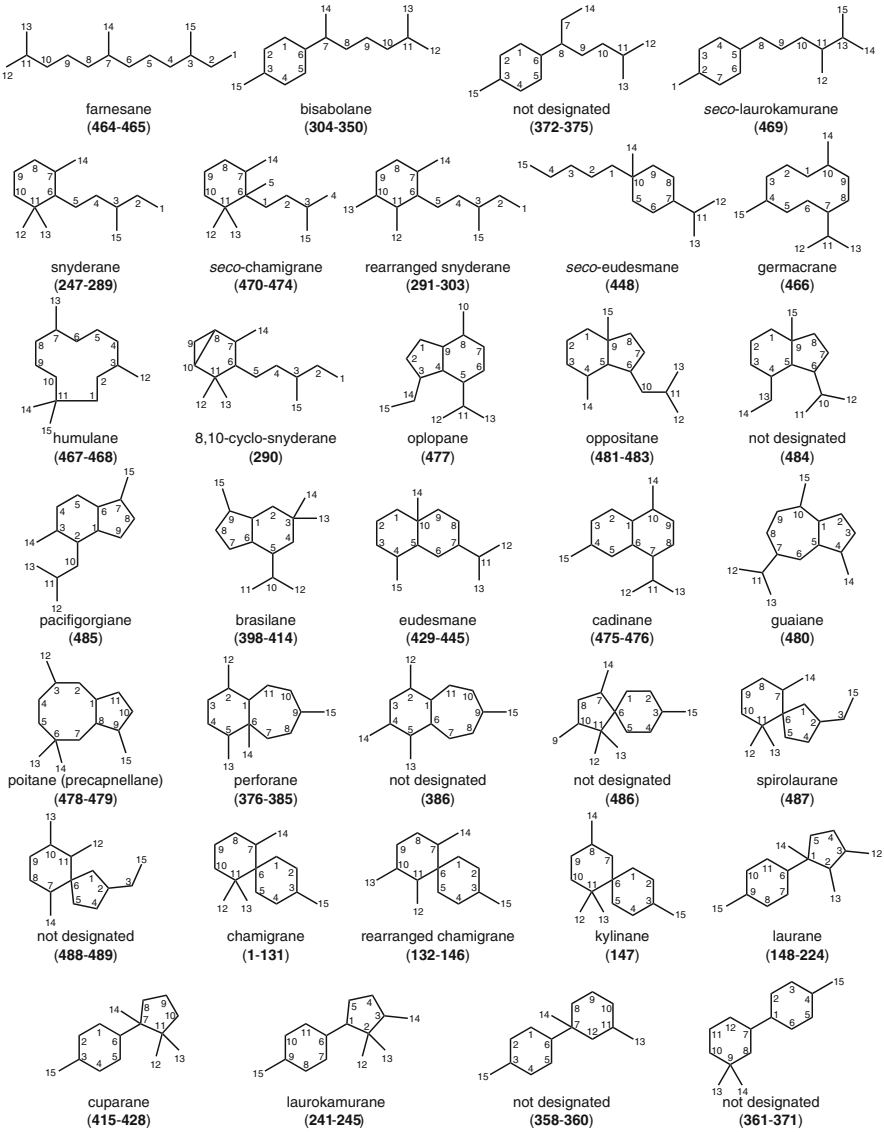


Fig. 4 Acyclic, monocyclic, and bicyclic carbon skeletons of sesquiterpenes isolated from *Laurencia* species

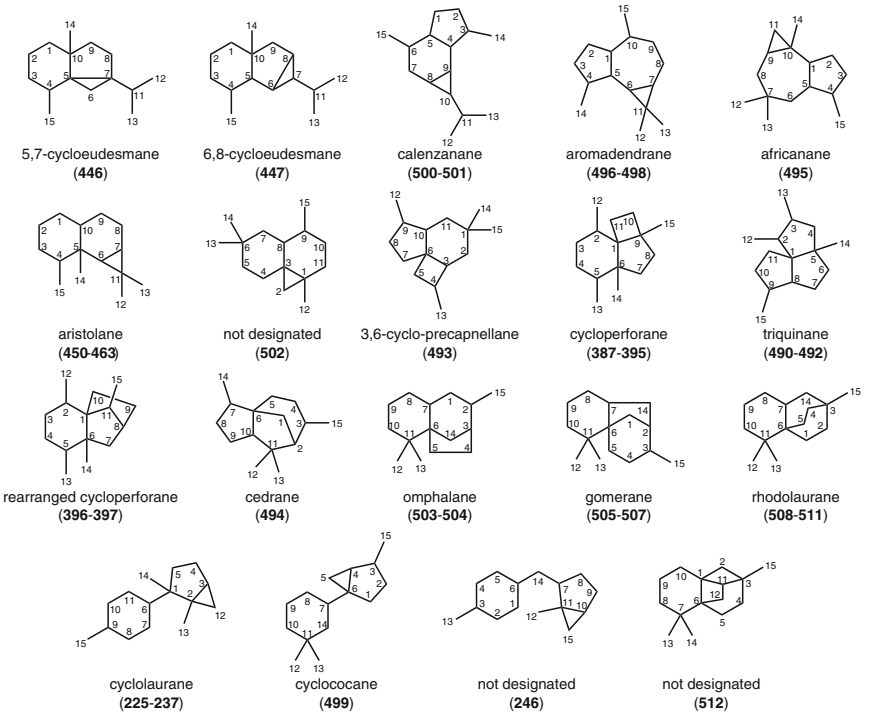
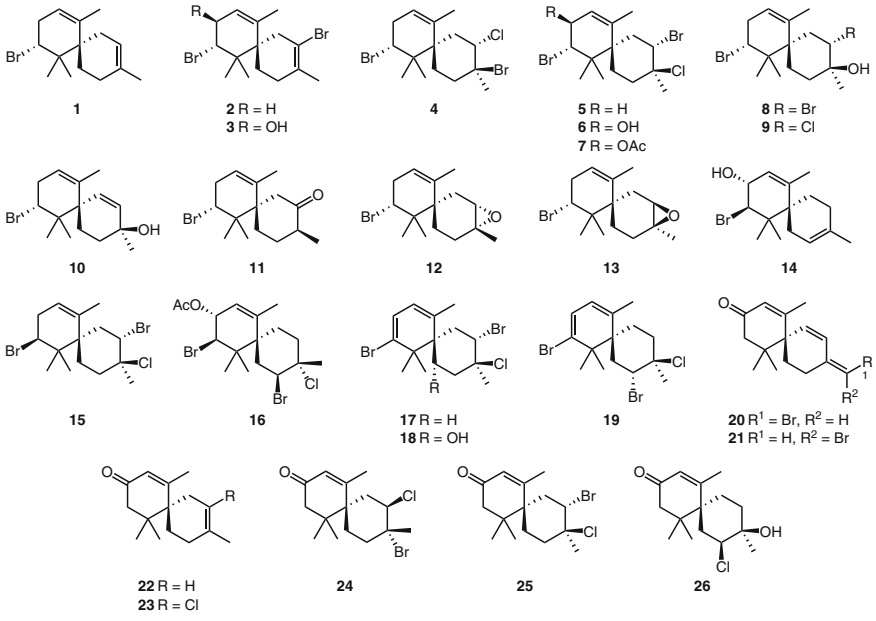


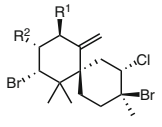
Fig. 5 Tricyclic and tetracyclic carbon skeletons of sesquiterpenes isolated from *Laurencia* species

3.1.1 Chamigranes and Related Sesquiterpenes

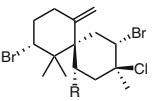
Chamigranes and related metabolites are the most frequently occurring class of sesquiterpenes isolated from *Laurencia* species or sea hares feeding on them, with a total of 147 (**1**–**147**) having been reported in the literature up to now. Structurally, sesquiterpenes of the chamigrane class (**1**–**131**) are characterized by a *spiro*[5.5]undecane skeleton bearing a stereogenic quaternary carbon at the spirocycle junction (C-6). The first six-membered ring, which is moderately to densely functionalized, contains a second non-stereogenic quaternary carbon (C-11) that is vicinal to the spirocycle junction and bears a *gem*-dimethyl group, whereas the second six-membered ring often possesses a tri- or tetrasubstituted olefin or presents a dihalogenation pattern at C-2 and C-3 usually in a 2,3-*trans*-halide arrangement. They can be divided roughly into four subclasses, namely: (1) those belonging to the α-chamigrene series possessing a trisubstituted double bond between C-7 and C-8 (**1**–**26**); (2) those belonging to the β-chamigrene series

possessing an exomethylene group at C-7 (**27**–**77**); (3) those featuring an oxygenation site at C-7 (**78**–**99**); and (4) those with either a 5,10-epoxide ring system (**100**–**117**) or another epoxide (**118**–**124**) or a lactone ring connecting the two six-membered rings (**125**–**129**). Most chamigranes possess various halogen and oxygen substitutions, with C-10 being a favored position for a Br substitution. Often, a bromine atom is located at the secondary carbon C-2 and a chlorine atom is attached to the tertiary carbon C-3 on the opposite face of the former, while seldom a *cis*-arrangement of the two halogens can be observed. Moreover, less frequently halogenation on a double bond or a conjugated bromodiene system is incorporated into the second six-membered ring. In the 1990s, Guella and co-workers undertook thorough conformational studies of α- and β-chamigrenes using temperature-dependent NMR spectra [164, 472, 473]. Majusculone (**130**) and mailione (**131**) are the only two known nor-chamigranes isolated from a number of different *Laurencia* species [118, 122, 128, 134, 142, 143, 147]. Compounds **132**–**146** possess a rearranged chamigrane carbocycle that arises from a methyl migration from C-11 to C-10 of the chamigrane skeleton, whereas kylinone (**147**), isolated as a constituent of *L. pacifica* from the Monterey Peninsula, California [211], is the sole representative of another rearranged chamigrane framework, in all probability derived from a methyl migration from C-7 to C-8.

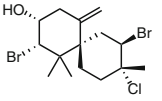




27 R^1 = OH, R^2 = H
28 R^1 = H, R^2 = OH



29 R = H
30 R = Br



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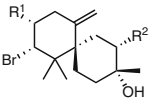
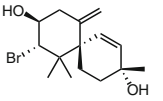


32 R^1 = H, R^2 = OH
33 R^1 = H, R^2 = Cl
34 R^1 = OH, R^2 = Cl



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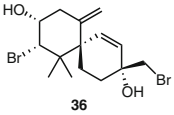

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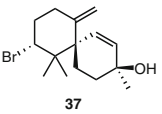

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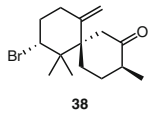

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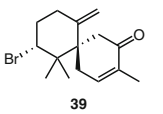

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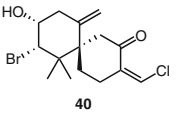

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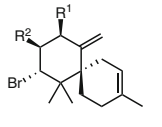
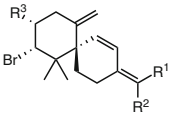
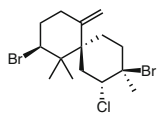


41 R^1 = OH, R^2 = H
42 R^1 = H, R^2 = OH



43 R^1 = Br, R^2 = R^3 = H
44 R^1 = Br, R^2 = H, R^3 = OH
45 R^1 = R^3 = H, R^2 = Br
46 R^1 = H, R^2 = Br, R^3 = OH



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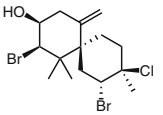

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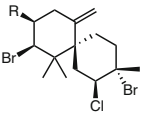
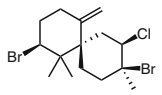


49 R = OH
50 R = OAc



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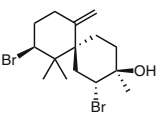

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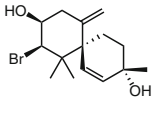

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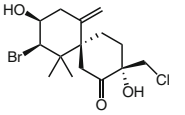

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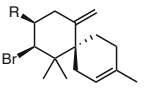
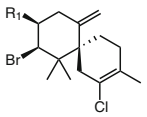
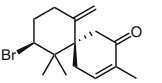


55 R = H
56 R = OH
57 R = OAc



58 R = H
59 R = OH
60 R = OAc



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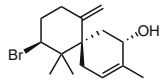

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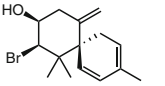

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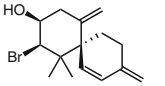

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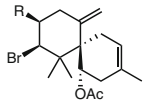
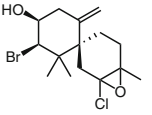


65 R = OH
66 R = OAc



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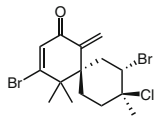

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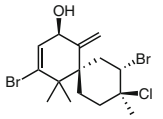

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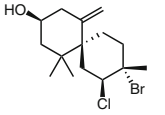

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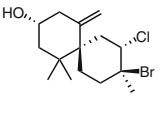

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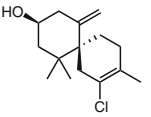

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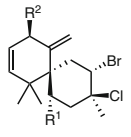
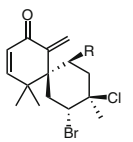
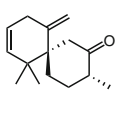


73 R^1 = OH, R^2 = H
74 R^1 = H, R^2 = OH



75 R = H
76 R = OAc



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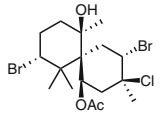
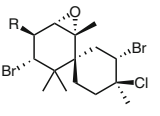
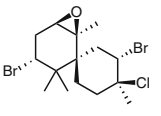


78



79 R = H
80 R = OH



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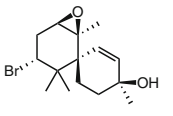

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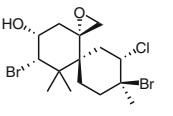
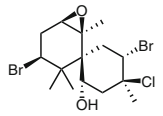
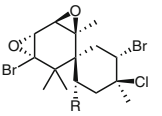


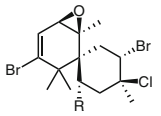
83



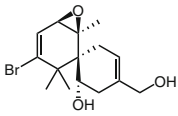
84



85 R = H
86 R = OH



87 R = H
88 R = OH
89 R = OAc



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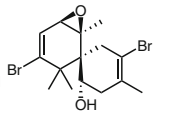

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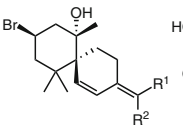
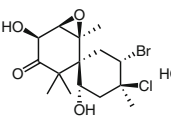


92 R^1 = Br, R^2 = H
93 R^1 = H, R^2 = Br



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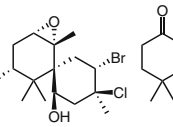

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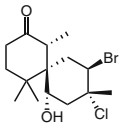

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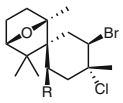
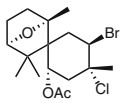


97 R = H
98 R = OAc



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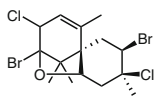

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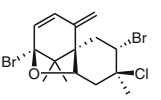

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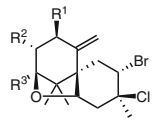
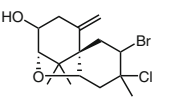


102 R^1 = R^2 = OH, R^3 = Br
103 R^1 = R^2 = R^3 = H



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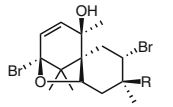
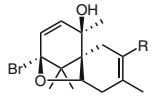
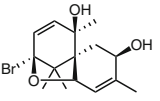


105 R = Cl
106 R = OH



107 R = H
108 R = Br



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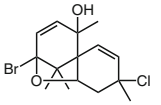

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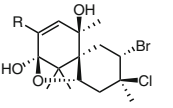
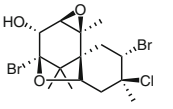


111 R = Cl
112 R = Br



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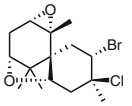
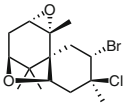


114



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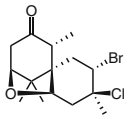

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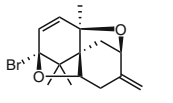

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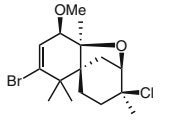

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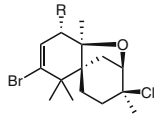
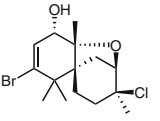


119 R = OMe
120 R = Cl



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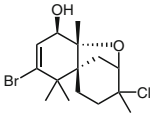

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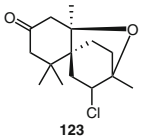

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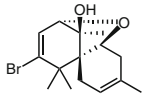
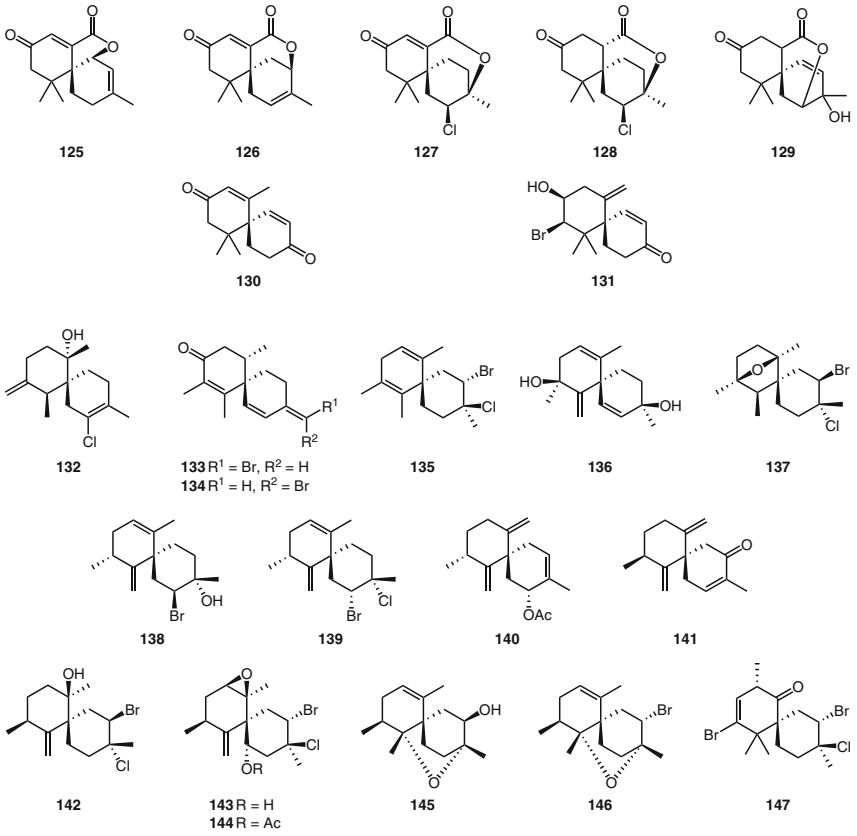


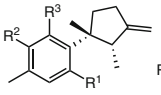
124



3.1.2 Lauranes, Cyclolauranes, and Related Sesquiterpenes

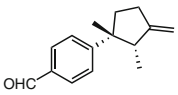
Taken together, lauranes, cyclolauranes, and related metabolites consist the second most often encountered class of sesquiterpenes characterized from *Laurencia* spp. and gastropods feeding on them, amounting to 99 compounds in total (**148**–**246**). Lauranes (**148**–**224**) and cyclolauranes (**225**–**237**) possess a 1,2,3-trisubstituted cyclopentane moiety and a 1,2-dimethylbicyclo[3.1.0]hexane system, respectively, connected through a single bond to a six-membered ring, usually aromatic. Frequently, C-10 and/or C-12 are brominated, whereas C-3 is oxygenated. In addition, several of these sesquiterpenes contain 2,7-epoxy (**194**–**212**), 3,7-epoxy (**213**–**222**), 4,7-epoxy (**223**), or 5,7-epoxy (**224**) rings. Among them, 16,16-di-chloro-homolaurane (**193**), isolated from *Aplysia dactylomela*, is the only known C_{16} derivative of this carbocycle [277]. Attention should be paid to the case of the isomeric metabolites *iso*-laurenisol (**174**), isolated initially from *Laurencia* sp. cf. *L. gracilis* [103], and isolaurenisol (**176**), obtained initially from

Laurencia distichophylla [264], to avoid confusion due to the rather similar common names given. In addition to monomeric cyclolauranes, three dimeric derivatives (**238**–**240**) have been reported to date from various *Laurencia* species. Metabolites **241**–**245** feature a rearranged laurane skeleton arising from a methyl migration from C-1 to C-2, while laurentristich-4-ol (**246**), isolated from a Chinese *Laurencia tristicha* [232, 315], possesses an irregular isoprenoid carbocycle, proposed biogenetically to result from the rearrangement of cyclolaurane skeleton. Total synthesis of the originally proposed structure led to its revision [316].



148 $R^1 = R^2 = R^3 = H$
149 $R^1 = OH$, $R^2 = R^3 = H$
150 $R^1 = OAc$, $R^2 = R^3 = H$
151 $R^1 = OH$, $R^2 = Br$, $R^3 = H$
152 $R^1 = OAc$, $R^2 = Br$, $R^3 = H$
153 $R^1 = OH$, $R^2 = R^3 = Br$
154 $R^1 = OH$, $R^2 = Br$, $R^3 = I$

155 R = H
156 R = Ac



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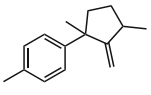

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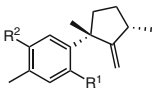
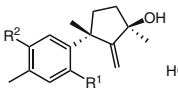
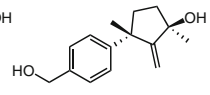


159 $R^1 = OH$, $R^2 = H$
160 $R^1 = OAc$, $R^2 = H$
161 $R^1 = OH$, $R^2 = Br$
162 $R^1 = OAc$, $R^2 = Br$



163 $R^1 = R^2 = H$
164 $R^1 = H$, $R^2 = OH$
165 $R^1 = OH$, $R^2 = H$
166 $R^1 = OH$, $R^2 = Br$



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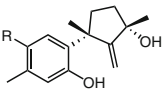
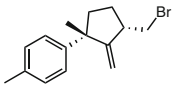


168 R = H
169 R = Br



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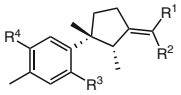
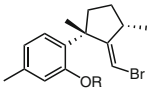
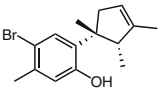


171 $R^1 = R^4 = H$, $R^2 = Br$, $R^3 = OH$
172 $R^1 = R^4 = H$, $R^2 = Br$, $R^3 = OAc$
173 $R^1 = H$, $R^2 = R^4 = Br$, $R^3 = OH$
174 $R^1 = Br$, $R^2 = R^4 = H$, $R^3 = OH$
175 $R^1 = R^4 = Br$, $R^2 = H$, $R^3 = OH$



176 R = H
177 R = Ac



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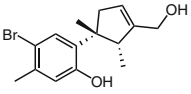

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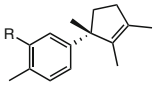
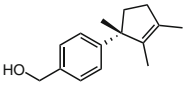


180 R = H
181 R = OH



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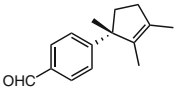

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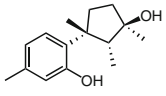

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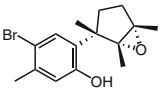

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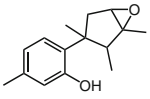

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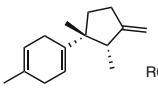

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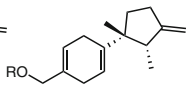
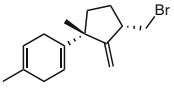


188 R = H
189 R = Ac



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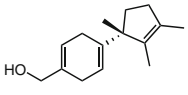

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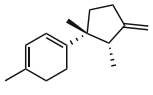

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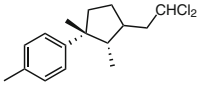

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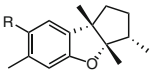
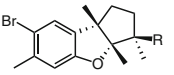
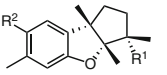


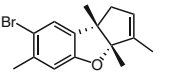
194 R = H
195 R = Br



196 R = OH
197 R = OOH



198 R^1 = OH, R^2 = H
199 R^1 = OH, R^2 = Br
200 R^1 = OOH, R^2 = Br



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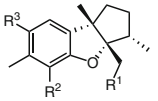
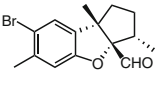


202 R^1 = OH, R^2 = R^3 = H
203 R^1 = Br, R^2 = R^3 = H
204 R^1 = OH, R^2 = H, R^3 = Br
205 R^1 = OAc, R^2 = H, R^3 = Br
206 R^1 = OOH, R^2 = H, R^3 = Br
207 R^1 = R^3 = Br, R^2 = H
208 R^1 = R^2 = R^3 = Br



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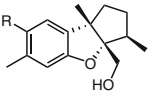
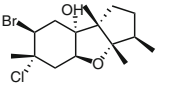


210 R = H
211 R = Br



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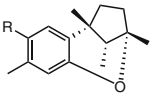
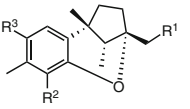
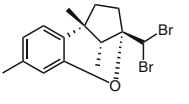


213 R = H
214 R = Br



215 R^1 = Br, R^2 = R^3 = H
216 R^1 = R^3 = Br, R^2 = H
217 R^1 = R^2 = R^3 = Br
218 R^1 = OH, R^2 = H, R^3 = Br
219 R^1 = OH, R^2 = R^3 = Br
220 R^1 = I, R^2 = H, R^3 = Br



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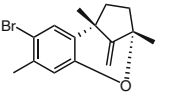

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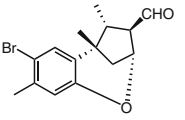

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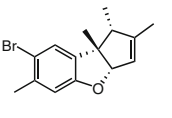

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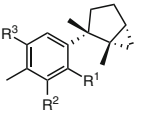
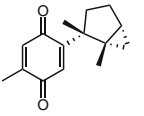


225 R^1 = R^2 = R^3 = H
226 R^1 = OH, R^2 = R^3 = H
227 R^1 = OAc, R^2 = R^3 = H
228 R^1 = R^3 = H, R^2 = OH
229 R^1 = R^2 = H, R^3 = OH
230 R^1 = OH, R^2 = Br, R^3 = H
231 R^1 = OH, R^2 = H, R^3 = Br
232 R^1 = OAc, R^2 = H, R^3 = Br
233 R^1 = Br, R^2 = H, R^3 = OH
234 R^1 = Br, R^2 = H, R^3 = OAc
235 R^1 = OH, R^2 = R^3 = Br
236 R^1 = OH, R^2 = I, R^3 = Br



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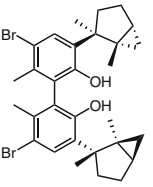

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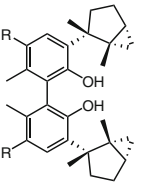
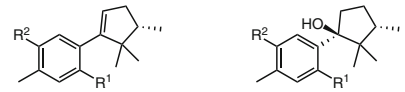
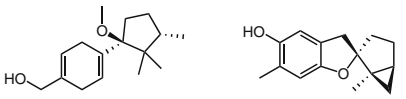


239 R = H
240 R = Br



241 $R^1 = R^2 = H$
242 $R^1 = OH$, $R^2 = Br$

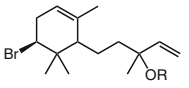
243 $R^1 = R^2 = H$
244 $R^1 = OH$, $R^2 = Br$



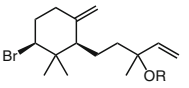
245 **246**

3.1.3 Snyderanes and Related Sesquiterpenes

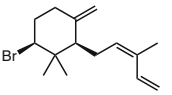
Snyderanes and related metabolites constitute the third largest class of sesquiterpenes isolated from species of the genus *Laurencia* or the sea hares grazing on them, including up to the present 57 members (**247**–**303**). They are monocarbocyclic sesquiterpenes arising from the formation of a six-membered ring between carbons C-6 and C-11 of farnesane. Many snyderanes contain a cyclohexane ring with an acyclic side chain (**247**–**265**), while some of them feature 2,7-epoxy (**266**–**281**), 3,7-epoxy (**282**), or 4,7-epoxy (**283**–**289**) rings in their structures, thus forming 6,7-, 6,6-, or 6,5-fused systems. Most often, they are characterized by bromine incorporation at C-10, whereas less frequently they are brominated at C-1. The cyclohexane ring is commonly unsaturated featuring a Δ^7 double bond, as in α-snyderol (**247**), a $\Delta^{7,14}$ double bond, as in β-snyderol (**249**), a Δ^6 double bond, as in 8-hydroxy-γ-snyderol (**263**) or even an additional Δ^9 double bond, as in **259**–**262**. Bicyclolaurencenol (**290**), obtained from *Laurencia intricata* from Castle Harbour, Bermuda [351], possesses a related bicyclic framework resulting from cyclization between C-8 and C-10 of the snyderane skeleton. Rearranged snyderanes that are derived from a methyl migration from C-11 to C-10, either containing an acyclic side chain (**291**–**296**), or featuring a 2,7-epoxy (**297** and **298**), or a 4,7-epoxy (**299**–**303**) ring, have also been isolated from a number of *Laurencia* species. The synthesis of the natural enantiomers of dactyloxenes B (**299**) and C (**300**) from (–)-(*R*)-linalool in seven steps via a common intermediate has been reported [359, 360], while another route based on a stereoselective iodoetherification reaction of a carvone-derived hydroxyalkene unit was also proposed in 2005 [361].



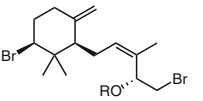
247 R = H
248 R = Ac



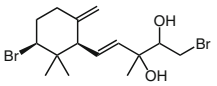
249 R = H
250 R = Ac



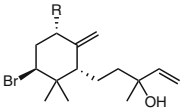
251



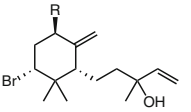
252 R = H
253 R = Ac



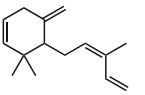
254



255 R = H
256 R = Br



257 R = OH
258 R = Br



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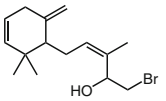

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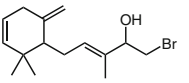
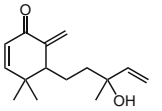


261



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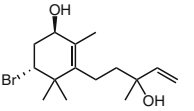

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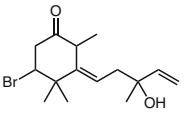
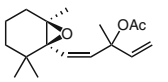
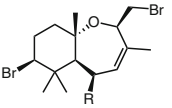


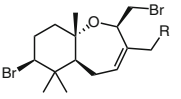
264



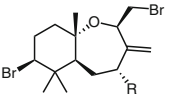
265



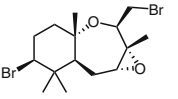
266 R = H
267 R = OH
268 R = OAc



269 R = OH
270 R = OAc
271 R = Br



272 R = OH
273 R = Br



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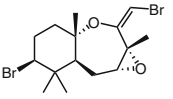

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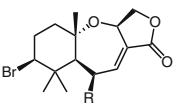
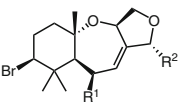
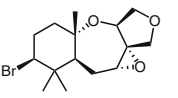


276 R = H
277 R = OH



278 $R^1 = R^2 = H$
279 $R^1 = H$, $R^2 = OH$
280 $R^1 = OAc$, $R^2 = H$



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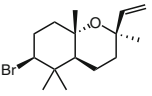

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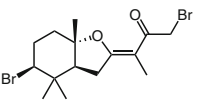

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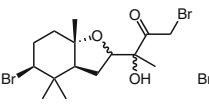
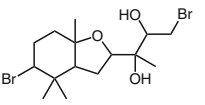
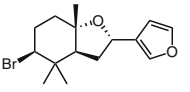


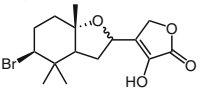
284 (3*R**,4*S**)
285 (3*S**,4*R**)



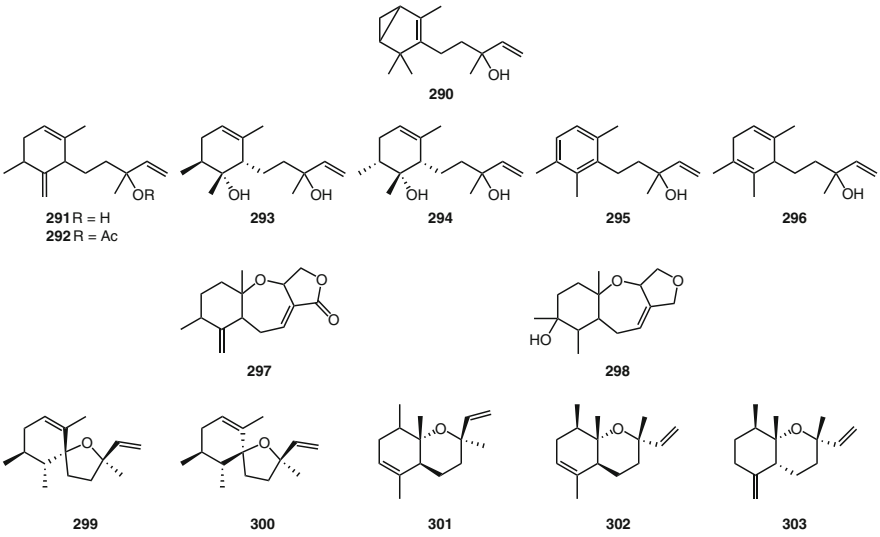
286



287



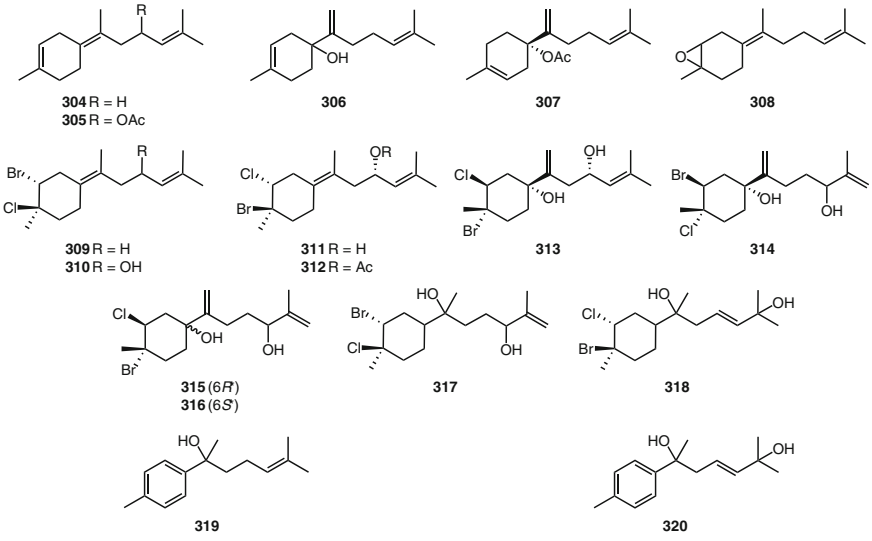
288 (4*S**)
289 (4*R**)

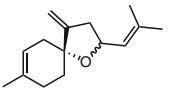


3.1.4 Bisabolanes and Related Sesquiterpenes

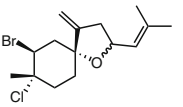
Bisabolanes and related metabolites are a fairly large class of sesquiterpenes found mainly as constituents of higher plants. Nonetheless, up to now there are 72 bisabolanes and related sesquiterpenes (**304**–**375**) identified from *Laurencia* species and their grazers. As with snyderanes, bisabolanes are also monocarbocyclic sesquiterpenes arising, however, by the formation of a six-membered ring between carbons C-1 and C-6 of farnesane. Often members of this class are monocyclic (**304**–**320**), but there are also representatives possessing 6,9-epoxy (**321**–**326**), 7,10-epoxy (**327** and **328**), or 7,11-epoxy (**329**–**350**) ring systems, the latter of which are commonly known as caespitanes. Usually, bisabolanes are both brominated and chlorinated at C-2 and C-3, often with a 2,3-*trans*-halide arrangement. It is worth noting that the structure of caespitol (**337**), originally assigned as that of a chamigrane sesquiterpene on the basis of analysis of its spectroscopic data [375], was later revised to that of a bisabolane based on the results of the X-ray crystallographic analysis of isocaespitol (**346**), a sesquiterpene co-occurring in the same sample of *Laurencia caespitosa*, as well as by chemical correlation between the two isomers [376]. In 2003 and 2006, de Carvalho and co-workers reported the isolation of aldingenins A–D from specimens of *Laurencia aldingensis* collected at Castelhanos, Brazil [373, 378], attributing to them bisabolane structures containing multiple oxacyclic rings. The synthesis of the proposed structure of aldingenin B revealed that it was incorrect due to discrepancies observed between the spectroscopic data of the natural and synthetic products [385, 386]. Subsequently, the synthesis of the proposed structure of aldingenin C by Takahashi et al. in 2014 proved that it also merited revision, while re-examination

of the ^{13}C NMR data of the natural product suggested that the correct structure should be that of caespitol (**337**) [374]. In a similar manner, it was suggested that the correct structure of aldingenin D is that of (5*S*)-5-acetoxy-caespitol (**342**) [374], isolated in the interim from a Brazilian *Laurencia catarinensis* collected in Ilha do Arvoredo [370]. In 2015, Mukhina et al. presented computational evidence based primarily on the computed proton spin-spin coupling constants that the correct structures of aldigenins A and B should be those depicted in structures **340** and **350**, respectively [379]. Compounds **351–357** are bromochlorinated C_{12} terpenoids, regarded as degraded bisabolanes [387]. In 1992, de Nys and co-workers reported the isolation of metabolites **358–360** from *Laurencia majuscula* collected from Geoffrey Bay, Magnetic Island, Australia [153]. These compounds feature a bicyclic framework that could result from a further cyclization between C-7 and C-12 of the bisabolane skeleton. Similarly, metabolites **361–371**, isolated from several *Laurencia* species, possess a bicyclic system that could arise from a further cyclization between C-11 and C-14 of the bisabolane skeleton. The structure of **361**, including absolute stereochemistry, was established on the basis of X-ray crystallographic analysis [389]. With the exception of **361** and **364–366**, all of these compounds were obtained as inseparable diastereomeric mixtures. Specimens of *L. caespitosa* collected at Punta del Hidalgo, Tenerife, and near the Island of La Graciosa in the Canary islands, yielded the irregular rearranged bisabolane-related sesquiterpenes, laucapyranoids A-C (**372–374**) [369]. Aplysiadactydiol (**375**), a rearranged bisabolane originally reported as aplysiadiol, but later renamed, since this particular trivial name was already used for a previously published diterpene, was obtained from *A. dactylomela* collected from La Palma Island, Spain [368, 392].

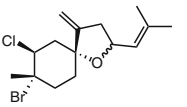




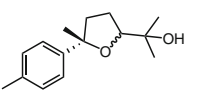
321 (9*R**)
322 (9*S**)



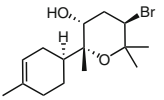
323 (9*R**)
324 (9*S**)



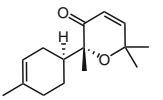
325, **326** (epimers at C-9)



327 (10*R**)
328 (10*S**)



329



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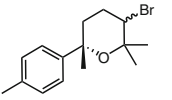
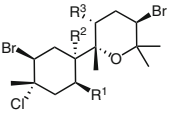
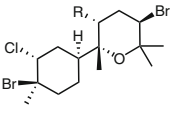


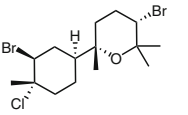
331 (10*S**)
332 (10*R**)



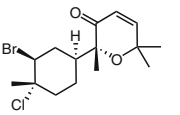
333 $R^1 = R^2 = R^3 = H$
334 $R^1 = OH$, $R^2 = R^3 = H$
335 $R^1 = OAc$, $R^2 = R^3 = H$
336 $R^1 = R^3 = H$, $R^2 = OH$
337 $R^1 = R^2 = H$, $R^3 = OH$
338 $R^1 = R^2 = H$, $R^3 = OAc$
339 $R^1 = H$, $R^2 = R^3 = OH$
340 $R^1 = OH$, $R^2 = H$, $R^3 = OH$
341 $R^1 = OH$, $R^2 = H$, $R^3 = OAc$
342 $R^1 = OAc$, $R^2 = H$, $R^3 = OH$
343 $R^1 = R^3 = OAc$, $R^2 = H$
344 $R^1 = R^2 = OH$, $R^3 = OAc$



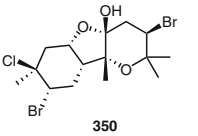
345 R = H
346 R = OH
347 R = OAc



348



349



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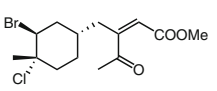

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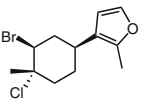

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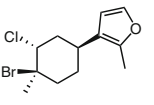

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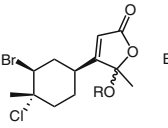
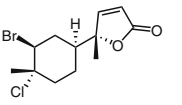


354 (10*S**), R =H
355 (10*R**), R = Me
356 (10*S**), R = Me



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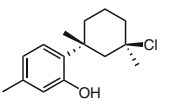

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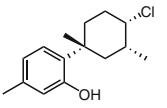

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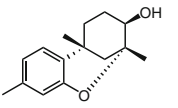

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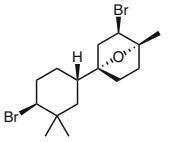

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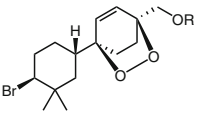
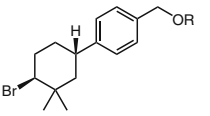
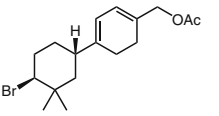


362 R = H
363 R = Ac



364 R = H
365 R = Ac



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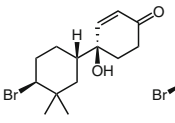

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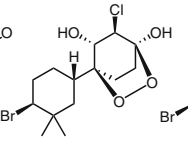

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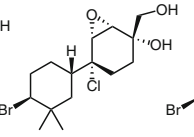

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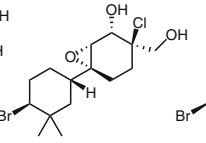

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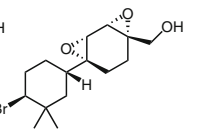

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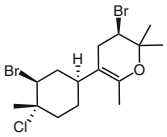

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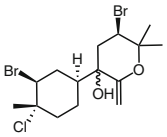
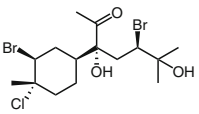


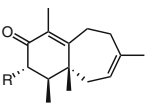
373 (8*R*)
374 (8*S*)



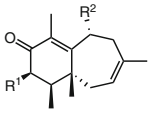
375

3.1.5 Perforanes, Cycloperforanes, and Related Sesquiterpenes

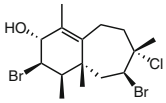
Perforanes, cycloperforanes, and related metabolites comprise a relatively small group of sesquiterpenes isolated from species of *Laurencia* and mollusks feeding on them, encompassing 22 members (**376**–**397**). Perforanes (**376**–**385**) possess a bicyclo[5.4.0]undecane skeleton, while a further cyclization between C-1 and C-9 of the seven-membered ring gives rise to the cycloperforanes (**387**–**395**) featuring a 4,5,6-fused tricyclic carbocycle. Both carbocycles are postulated to originate biosynthetically from chamigranes [474]. Perforene (**386**), obtained from a *Laurencia perforata* population collected off Corralejos, Fuerteventura, Canary Islands, displayed a perforane-related skeleton resulting from a 1,3-methyl migration [401]. Compounds **396** and **397**, possessing a rearranged cycloperforane carbocycle, were isolated from *Laurencia tenera* [402] and *L. perforata* [399], respectively, both collected near Magnetic Island in Australia.



376 R = H
377 R = OH
378 R = Cl



379 R^1 = OH, R^2 = H
380 R^1 = OMe, R^2 = H
381 R^1 = R^2 = OH



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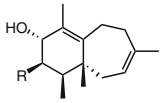
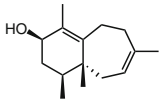


383 R = H
384 R = Br



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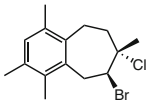

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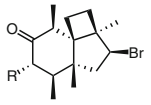
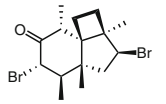


387 R = H
388 R = Br



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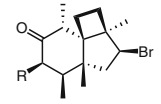
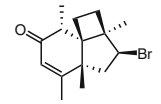
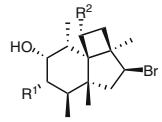


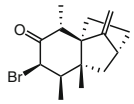
390 R = H
391 R = Br
392 R = OMe



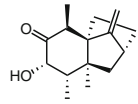
393



394 R^1 = R^2 = H
395 R^1 = Br, R^2 = OAc



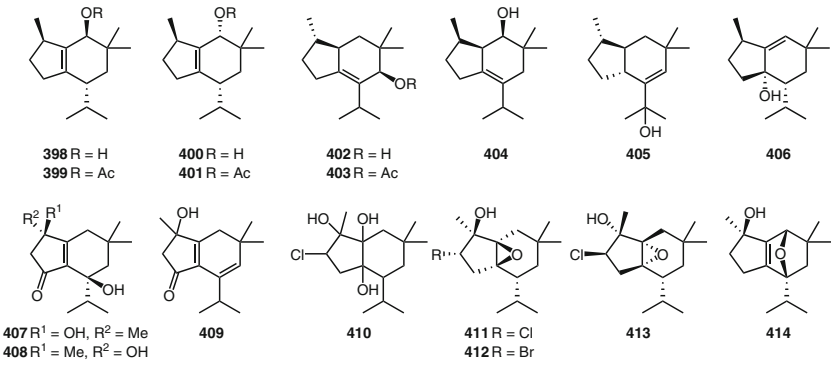
396



397

3.1.6 Brasilanes

To date, 17 sesquiterpenes featuring the brasilane skeleton (**398**–**414**) have been isolated from species of *Laurencia* and the sea hares consuming them. Brasilanes possess a rearranged bicyclo[4.3.0]nonane carbocycle with a *gem*-dimethyl group at C-3, an isopropyl group at C-5, and a fifth methyl group at C-9. The presence of a tetrasubstituted double bond between C-1 and C-6 is rather common, while in three metabolites (**411**–**413**), isolated from *L. obtusa* collected in Milos Island, Greece [405], a 1,6-epoxy moiety can be observed. A number of these derivatives bear an OH substitution at C-9, whereas in four brasilanes C-8 is halogenated. Brasilenol (**398**) and epibrasilenol (**400**) were isolated isolated from *Aplysia brasiliana* collected in Padre Island, southern Texas in 1978 [406]. However, their dietary origin was later confirmed when Howard and Fenical reported their isolation from a Mediterranean *L. obtusa* population [320]. Subsequently, two total syntheses of brasilenol (**398**) were published by Greene et al., determining its absolute stereochemistry [408, 409].



398 R = H
399 R = Ac

400 R = H
401 R = Ac

402 R = H
403 R = Ac

404

405

406

407 R^1 = OH, R^2 = Me
408 R^1 = Me, R^2 = OH

409

410

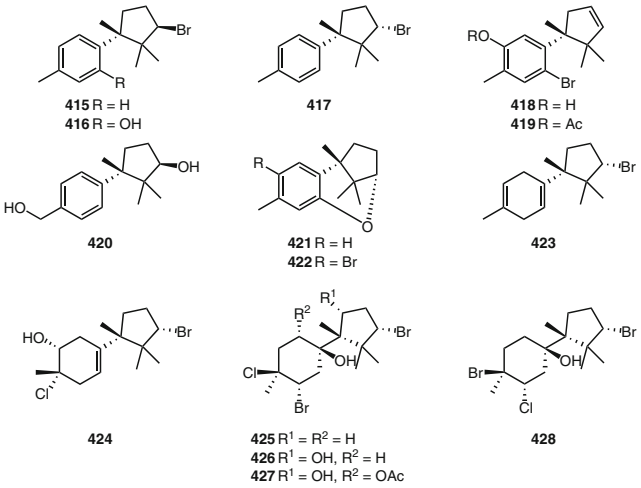
411 R = Cl
412 R = Br

413

414

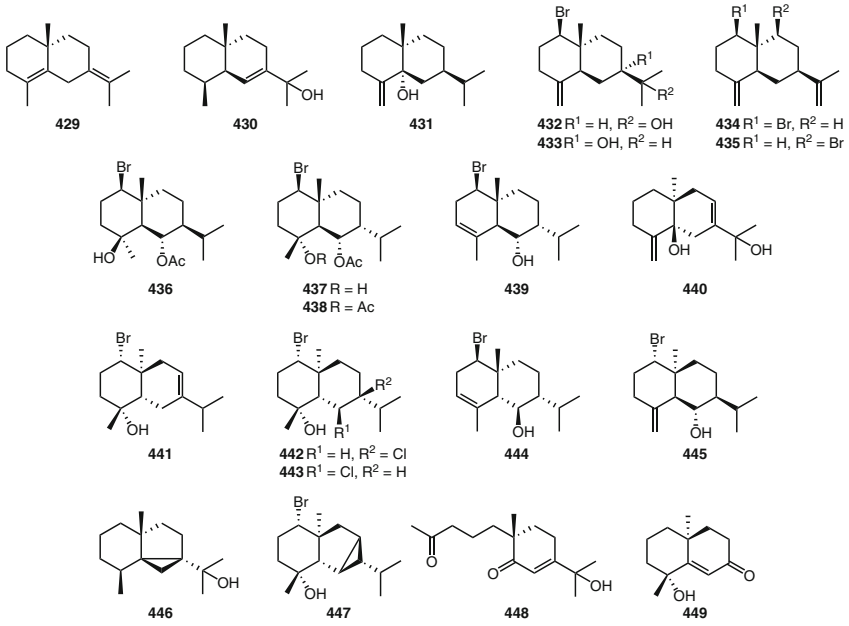
3.1.7 Cuparanes

Cuparanes are found in higher plants and liverworts and occasionally in marine organisms. Up to the present, 14 members of this class of sesquiterpenes (**415**–**428**) have been discovered from the genus *Laurencia* and mollusks feeding on these red algae. Cuparanes arise by a further cyclization between carbons C-7 and C-11 of the bisabolane skeleton forming a five-membered ring. In several cases, C-10 is brominated. α-Bromocuparene (**415**) and its epimer at C-10, α-isobromocuparene (**417**), isolated initially from *Laurencia glandulifera* in 1975, were the first cuparanes to be reported from macroalgae [414].



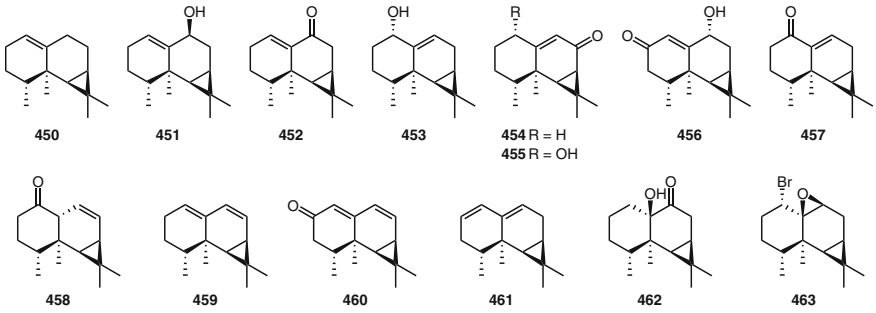
3.1.8 Eudesmanes, Cycloeudesmanes, and Related Sesquiterpenes

Even though eudesmanes, also referred to as selinanes, and cycloeudesmanes are commonly encountered in higher plants, to date only 21 related metabolites (**429**–**449**) have been reported as constituents of *Laurencia* spp. or their grazers. Among them, 17 eudesmanes (**429**–**445**), one 5,7-cycloeudesmane (**446**), and one 6,8-cycloeudesmane (**447**) can be distinguished. Chabrolidione B (**448**) and teuhetenone A (**449**), isolated from *L. obtusa*, are a *seco*-eudesmane and a eudesmane-related C_{12} terpene, respectively [423]. Several of these metabolites feature bromine substitution at C-1.



3.1.9 Aristolanes

Aristolanes, sesquiterpenes arising from cyclization of eremophilanes between carbons C-6 and C-11, which in turn are derived from eudesmanes after migration of the methyl group at C-10 to C-5, are rarely detected in red algae of the genus *Laurencia* or in gastropods feeding on them. Nonetheless, up to now 14 aristolanes (**450–463**) have been reported from such sources. Aristolan-1α-bromo-9β,10β-epoxide (**463**), isolated from *Laurencia similis* collected in Hainan Island, People's Republic of China, is the only halogenated derivative characterized so far [431].

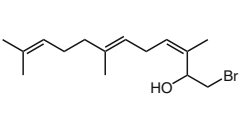


450 **451** **452** **453** **454** R = H, **455** R = OH **456** **457** **458** **459** **460** **461** **462** **463**

3.1.10 Miscellaneous Sesquiterpenes

In addition to the sesquiterpenes belonging to the classes discussed above, there are 49 more sesquiterpenes (**464–512**) possessing skeletons that are rarely encountered either in the genus *Laurencia* or from natural sources in general. Among these, derivatives of known skeletons, such as the germacrane **466**, the humulanes **467** and **468**, the cadinanes **475** and **476**, the oplopane **477**, the guaiane **480**, the triquinanes **490–492**, the cedrane **494**, the africanane **495**, and the aromadendranes **496–498**, have been isolated, and are all non-halogenated with the exception of **494**. The linear bromohydrin **464** and the tetrahydropyran-containing sesquiterpene obtusenol (**465**) were isolated from *Laurencia luzonensis* collected in Kudaka Island, Okinawa [323] and *Laurencia obtusa* collected in Gökçeada Island, Aegean Sea [435], respectively. *Laurencia okamurai* collected near Nanji Island in the East China Sea afforded *seco*-laurokamurone (**469**) featuring a monocarbocyclic framework, possibly formed by oxidative cleavage of the rearranged laurane skeleton [275]. *L. nipponica* from Hokkaido, Japan, yielded the *seco*-chamigranes lauracetals A (**470**), B (**471**), C (**474**), D (**472**), and E (**473**), possessing a carbocycle that could arise from a 10-bromo-chamigrene derivative by oxidative cleavage of the bond between C-1 and C-2, followed by acetal formation [75, 199, 438–440]. Dactylol (**478**) and poitediol (**479**) were reported as constituents of *Aplysia dactylomela* [442] and *L. poitei* [441], respectively, almost simultaneously in 1978 by two different research groups. They feature an uncommon rearranged bicyclo[6.3.0]undecane

skeleton, designated as poitane or precapnellane. The total synthesis of racemic poitediol (**479**) was accomplished in 1984 [447] and one year later the conversion of **479** to dactylol (**478**) was achieved by the same group [443]. In 1977, Wratten and Faulkner reported the isolation of oppositol (**481**) and the related epimeric diols **482** and **483**, possessing an 8(7 → 6)-*abeo*-eudesmane skeleton named oppositane, from *Laurencia subopposita* collected at La Jolla, California [248, 448]. The bromoketone **484**, isolated from *Laurencia mariannensis* collected from Geoffrey Bay, Magnetic Island, Australia [198], is the sole representative of this carbocycle containing a bicyclo[4.3.0]nonane core, different, however, from the oplopane skeleton. Pacifigorgiol (**485**) is a highly rearranged sesquiterpene representing the pacifigorgiane skeleton and has been reported as a constituent of several *Laurencia* species [118, 149, 323, 335, 451]. Laurencial (**486**), containing a *spiro*[4.5]decane core, was obtained from *Laurencia nipponica* collected off the Pacific Coast of Hokkaido [452] and its synthesis was achieved utilizing the stereospecific bromination-cyclization of spirocyclic cyclohexanones [453]. Another Japanese *L. nipponica* population afforded spirolaurenone (**487**) [78, 199, 454, 455], which also features a *spiro*[4.5]decane system. Its total synthesis has been accomplished based on the cyclization of geranonitrile [456]. Laurenones A (**488**) and B (**489**), isolated from a different *L. nipponica* population from Japan, were considered as biogenetic transformation products of **487** [457]. The isolation of viridianol (**493**), a sesquiterpene with a 3,6-cyclo-precapnellane skeleton, was reported from *Laurencia viridis* in 1994 by Norte and co-workers [459]. *Laurencia obtusa* from Cayo Coco, Cuba, afforded bromocyclococanol (**499**), possessing the tricyclic skeleton cyclococane, postulated to be biosynthetically related to the bisabolanes [461]. Calenzanol (**500**) and debromoisocalenzanol (**501**), obtained from *Laurencia microcladia* collected from Calenzana Bay, Italy, represent a 3,6,5-fused tricyclic carbocycle named calenzanane [462, 463]. A tricyclic humulane-related sesquiterpene named laurobtusol (**502**) was isolated from a Mediterranean *L. obtusa* [464]. Synthesis of several stereoisomers of **502** provided evidence that the structure was not correctly assigned but failed to propose another structure for laurobtusol [465]. Güimarediol (**503**) and dactylomelatriol (**504**), are the first tricyclic sesquiterpenes featuring the omphalane skeleton to be isolated from the marine environment [132, 135, 466]. Chromatographic separations of a *L. majuscula* extract from La Gomera in the Canary islands resulted in the isolation of gomerones A (**505**), B (**506**), and C (**507**), possessing the tricyclic skeleton designated as gomerane [467]. The total synthesis of racemic gomerone C (**507**) led to the revision of the relative configurations of the asymmetric centers for **506** and **507** [468]. Compounds **508**–**511**, bearing the uncommon tricyclic skeleton rhodolaurane, have been reported from a number of *Laurencia* species [74, 132, 158, 469], whereas aplydactone (**512**) is a highly strained metabolite featuring a related tetracyclic carbon framework that has been isolated from *A. dactylomela* collected in the northern part of Magadascar [471]. Its structure, including absolute stereochemistry, was determined by single crystal X-ray diffraction analysis [471].



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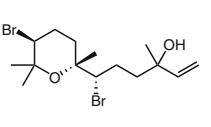

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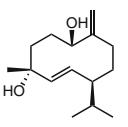

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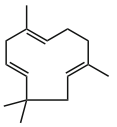

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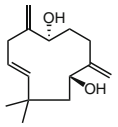

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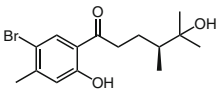

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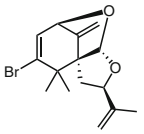

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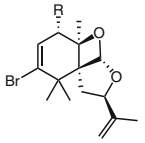
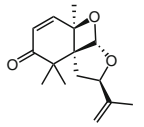


471 R=OH
472 R=Br
473 R=Cl



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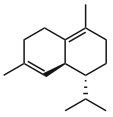

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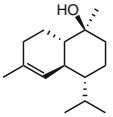

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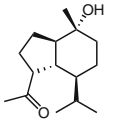

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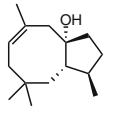

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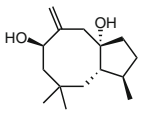

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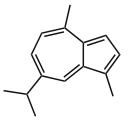

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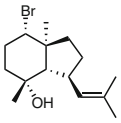

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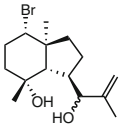
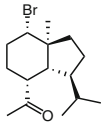


482 8*S**
483 8*R**



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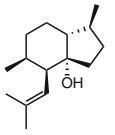

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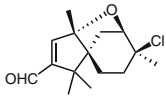

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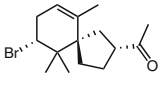

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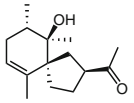

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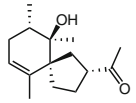

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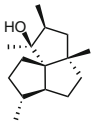

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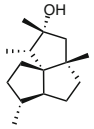

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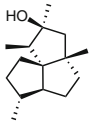

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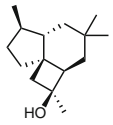

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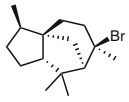

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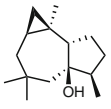

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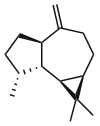

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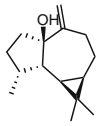

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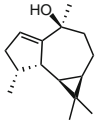

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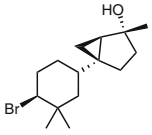

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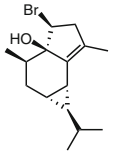

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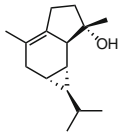

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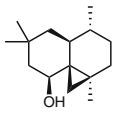

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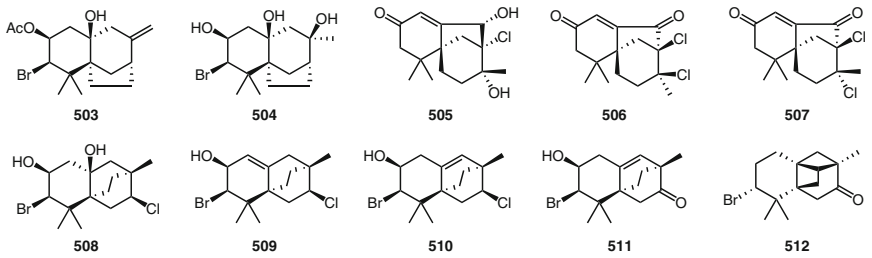


3.2 *Diterpenes*

Diterpenes are C_{20} compounds consisting of four isoprene units that are derived from geranylgeranyl pyrophosphate. In contrast to the high number and variety of sesquiterpenes from species of the genus *Laurencia*, as well as mollusks grazing on them, diterpenes constitute a small group and up to now 133 diterpenes and related metabolites (**513**–**645**, Table 2), featuring 25 different skeletons (see Figs. 6 and 7), have been reported.

3.2.1 Pargueranes, Isopargueranes, and Related Diterpenes

Pargueranes, isopargueranes, and related metabolites (**513**–**545**), featuring a modified pimarane skeleton, comprise the major group of diterpenes isolated from *Laurencia* and sea hares feeding on these red algae, encompassing 33 derivatives. Pargueranes (**513**–**538**) contain a cyclopropane ring between C-3 and C-4 of the pimarane skeleton, while the rearranged tetracyclic skeleton of isopargueranes (**539**–**543**) contains a cyclobutane ring incorporating C-19. The first representatives of this group of metabolites, namely, parguerol (**514**) and its 16-acetate (**517**), deoxyparguerol (**525**), isoparguerol (**540**), and its 16-acetate (**541**), were reported in 1982 by Schmitz et al. from *A. dactylomela* collected in Puerto Rico [156, 270]. The algal biosynthetic origin of these compounds was confirmed when deoxyparguerol 16-acetate (**527**) was isolated from *L. obtusa* collected at Kimmeridge Bay, Dorset, United Kingdom [482]. Two *seco*-analogues of pargueranes and isopargueranes featuring tricyclic carbocycles containing either a seven- (**544**) or an eight-membered (**545**) ring A, respectively, have been isolated. It is worth noting that both rare skeletons were named neopargueranes [249, 483]. In the majority of these diterpenes C-15 is brominated, while C-16 is oxygenated. Frequently, C-2, C-7 and C-19 are also oxygenated. Furthermore, most of these derivatives, with the exception of **533** and **538**, possess a $\Delta^{9,11}$ double bond.

Table 2 Diterpenes from *Laurencia* spp.

No.	Name	Source of isolation/synthesis
513	Deacetylparguerol	*L. saitoi* [475[a]], *A. pulmonica* [476], *A. punctata* [249]
514	Parguerol	*L. saitoi* [477], *A. dactylomela* [156[a], 178, 270], *A. kurodai* [478], *A. pulmonica* [476], *A. punctata* [249]
515	Parguerol 19-acetate	*L. saitoi* [477[a], 480]
516	Parguerol 7-acetate	*L. saitoi* [477]
517	Parguerol 16-acetate	*L. saitoi* [477], *A. dactylomela* [156[a], 178]
518	Parguerol 7,19-diacetate	*L. saitoi* [480]
519	Parguerol 16,19-diacetate	*L. saitoi* [475[a], 477, 480]
520	Parguerol 7,16-diacetate	*L. filiformis* [421[a]], *L. saitoi* [477]
521	Parguerol triacetate	*L. filiformis* [421], *L. saitoi* [475, 477, 479[a], 480]
522	15-Bromo-parguer-9(11)-en-16-ol	*L. nipponica* [97[a]], *L. saitoi* [480]
523	2-Deacetoxy-deoxyparguerol	*L. saitoi* [475[a], 477]
524	15-Bromo-2,7,16-trihydroxy-parguer-9(11)-ene	*L. saitoi* [475, 479[a,c,d]], *A. pulmonica* [476]
525	Deoxyparguerol	*L. saitoi* [475, 477], *A. dactylomela* [156[a,d], 178, 270]
526	Deoxyparguerol 7-acetate	*L. filiformis* [421[a,d]]
527	Deoxyparguerol 16-acetate	*L. filiformis* [421], *L. lageniformis* [481], *L. obtusa* [482[a,d]], *L. saitoi* [477, 480], *A. fasciata* [326]
528	Deoxyparguerol 7,16-deacetate	*L. filiformis* [421[a], 479[d]], *A. kurodai* [478]
529	–	*L. filiformis* [421]
530	15-Bromoparguer-9(11)-ene-2,16-diol 2-acetate	*L. filiformis* [421]
531	16-Acetoxy-15-bromo-7-hydroxy-parguer-9(11)-ene	*A. fasciata* [326]
532	–	*L. saitoi* [475]
533	15-Bromo-parguer-7-en-16-ol	*L. nipponica* [97[a]], *L. saitoi* [480]
534	15-Bromo-isoparguer-9(11)-en-16-ol	*L. filiformis* [421]
535	–	*L. saitoi* [477]
536	–	*L. saitoi* [477]
537	–	*L. saitoi* [477]
538	Preparguerene	*L. filiformis* [421[a]], *L. saitoi* [477]
539	Deacetylisoparguerol	*L. saitoi* [475[a]], *A. pulmonica* [476]
540	Isoparguerol	*L. saitoi* [477], *A. dactylomela* [156[a], 270], *A. kurodai* [478], *A. pulmonica* [476]
541	Isoparguerol 16-acetate	*A. dactylomela* [156[a], 270]
542	Isoparguerol 7,16-diacetate	*L. saitoi* [475[a], 477]
543	–	*L. saitoi* [477]
544	–	*L. saitoi* [475, 483[a]]

(continued)

Table 2 (continued)

No.	Name	Source of isolation/synthesis
545	Neopargueroldione	*A. punctata* [249]
546	Aplysin-20	*L. venusta* [484], *A. kurodai* [485, 486[a,c,d]]; Synthesis [487[f], 488[f]]
547	*epi*-Aplysin-20	*A. kurodai* [489[d]]
548	Venustanol	*L. venusta* [484]
549	Concinndiol	*L. concinna* [490[c,d]], *L. snyderae* [354]
550	Isoconcinndiol	*L. snyderae* var. *guadalupensis* [491[a]], *A. dactylomela* [492[b,c,d]], *A. punctata* [249]; Synthesis [488[b,f], 493[b,f]]
***ent*-550**	*ent*-Isoconcinndiol	*A. kurodai* [489[d]]
551	Pinnatol A	*L. pinnata* [494[d]]
552	Pinnatol B	*L. pinnata* [494[d]]
553	Isopinnatol B	*A. dactylomela* [50]
554	Pinnatol C	*L. pinnata* [494[d]]
555	Pinnatol D	*L. pinnata* [494]; Synthesis [493[f]]
556	–	*Laurencia* sp. [105]
557	Isoaplysin-20	*L. perforata* [495], *L. snyderae* var. *guadalupensis* [491], *A. kurodai* [496[a]]; Synthesis [497[b,e], 498[b,c,f], 499[b,c,f]]
558	–	*L. perforata* [495[d]]
559	Paniculatol	*L. paniculata* [500[c,d]]
560	–	*Laurencia* sp. [106[c,d]]
561	–	*Laurencia* sp. [106]
562	–	*L. obtusa* [501]
563	–	*L. obtusa* [501]
564	3-Bromobarekoxide	*L. luzonensis* [502[c,d]]
565	Laukarlaol	*L. karlae* [333]; Synthesis [503[b,f]]
566	Neoconcinndiol hydroperoxide	*L. snyderae* [354[c]]
567	3,15-Dibromo-7,16-dihydroxy-isopimar-9(11)-ene	*L. perforata* [495]
568	3,15-Dibromo-7,12,16-trihydroxy-isopimar-9(11)-ene	*L. perforata* [495]
569	Irieol	*Laurencia* cf. *irieii* [504[a]], *L. pinnata* [505]
570	Iriediol	*Laurencia* cf. *irieii* [504[b,d], 506[a,c]]
571	Irieol A	*Laurencia* cf. *irieii* [504[d], 506[a,c]]
572	Irieol C	*Laurencia* cf. *irieii* [504[a,d], 507], *L. mariannensis* [74]
573	Pinnaterpene A	*L. pinnata* [508[c,d]]
574	Irieol E	*Laurencia* cf. *irieii* [504[a], 507]
575	Irieol B	*Laurencia* cf. *irieii* [504]
576	Pinnaterpene B	*L. pinnata* [508[d]]
577	Irieol F	*Laurencia* cf. *irieii* [504]

(continued)

Table 2 (continued)

No.	Name	Source of isolation/synthesis
578	Irieol G	*Laurencia* cf. *irieii* [504]
579	Irieol D	*Laurencia* cf. *irieii* [504[a], 507]
580	11-Deacetylpinnaterpene C	*L. decumbens* [160[a], 509[a]], *L. nangii* [94]
581	Pinnaterpene C	*L. decumbens* [160], *L. mariannensis* [74], *L. pinnata* [494, 508[a,d]]
582	Pinnaterpene D	*L. pinnata* [494[a], 508[d]]
583	Angasiol	*L. nangii* [94], *A. angasi* [510[a,c,d]]
584	Angasiol acetate	*A. juliana* [511[c,d]]
585	10-Acetoxy-angasiol	*Laurencia* sp. [187]
586	Prepinnaterpene	*L. pinnata* [505[a]]; Synthesis [449[f]]
587	Neoirieone	*Laurencia* cf. *irieii* [507[a,c,d]], *L. nangii* [94]
588	Neoirietriol	*L. yonaguniensis* [512[c,d]]
589	Neoirietetraol	*L. nangii* [94], *L. yonaguniensis* [513[a], 514[c,d]]
590	Luzodiol	*L. luzonensis* [324[a,d]], *A. fasciata* [326], *A. depilans* [515]
591	Laurendecumtriol	*L. decumbens* [160[a], 509[a]]
592	–	*A. depilans* [515]
593	–	*A. depilans* [515]
594	–	*A. depilans* [515]
595	–	*A. depilans* [515]
596	–	*A. depilans* [515]
597	–	*A. depilans* [515]
598	–	*A. depilans* [515]
599	–	*A. depilans* [515]
600	Dactylomelol	*Laurencia* sp. [516], *A. dactylomela* [50, 517[a,c,d]]
601	Punctatene	*Laurencia* sp. [516[d]]
602	Punctatene acetate	*A. punctata* [249]
603	(*E*)-Dactylohydroperoxide A	*Laurencia* sp. [516]
604	(*Z*)-Dactylohydroperoxide A	*Laurencia* sp. [516]
605	Dactylo-3,14-diol	*Laurencia* sp. [516]
606	Dactylohydroperoxide B	*Laurencia* sp. [516]
607	Dactylohydroperoxide C	*Laurencia* sp. [516]
608	Obtusadiol	*L. microcladia* [518], *L. obtusa* [320[a]]
609	14-Bromo-obtus-1-ene-3,11-diol	*A. dactylomela* [519[c,d]]
610	Rogioldiol A	*L. microcladia* [518[d]]
611	Rogioldiol B	*L. microcladia* [520]
612	Rogioldiol C	*L. microcladia* [520]
613	Laurenditerpenol	*L. intricata* [521]; Synthesis [522[f], 523[f], 524[d,g], 525[e], 526[g]]
614	Rogiolal	*L. microcladia* [518[c,d]]
615	Isorogiolal	*L. microcladia* [518[d]]
616	Prevezol A	*L. obtusa* [527]

(continued)

Table 2 (continued)

No.	Name	Source of isolation/synthesis
617	Prevezol B	*L. obtusa* [527, 528[b]]; Synthesis [529[b,g]]
618	Prevezol C	*L. obtusa* [528]; Synthesis [530[b,g], 531[e]]
619	Prevezol D	*L. obtusa* [528]
620	Prevezol E	*L. obtusa* [528]
621	Neorogioldiol	*L. microcladia* [532[a,d]], *L. obtusa* [528]
622	Neorogioldiol B	*L. obtusa* [528]
623	Neorogioltriol	*L. glandulifera* [533]
624	Viridiol A	*L. viridis* [534]
625	Viridiol B	*L. viridis* [534]
626	Laurencianol	*L. obtusa* [535[c,d]]
627	Punctatol	*A. punctata* [249]
628	Glandulaurencianol A	*L. glandulifera* [536]
629	Glandulaurencianol B	*L. glandulifera* [536[a]], *A. punctata* [536[a]]
630	Glandulaurencianol C	*A. punctata* [536]
631	Dactylopyranoid	*A. dactylomela* [50]
632	Kahukuene B	*L. majuscula* [537]
633	10-Hydroxy-kahukuene B	*L. mariannensis* [74[a]], *L. nangii* [94], *L. obtusa* [271]
634	Kahukuene A	*L. majuscula* [537]
635	Dactyloditerpenol acetate	*A. dactylomela* [178[d]]
636	Rogioldiol D	*L. microcladia* [532]
637	*O*-11,15-Cyclo-14-bromo-14,15-dihydrorogiol-3,11-diol	*L. glandulifera* [538], *L. microcladia* [532[a]], *L. obtusa* [528]
638	Aplysiadiol	*L. caduciramulosa* [195], *L. japonensis* [93], *L. nangii* [310], *Laurencia* sp. [187], *A. kurodai* [539[a]]; Synthesis [540]
639	Aplysiadiol methyl ether	*A. kurodai* [539]
640	Anhydroaplysiadiol	*L. japonensis* [93]
641	(*E*)-Phytol	*L. implicata* [91], *L. nipponica* [96, 97], *L. tristicha* [290, 541], *C. papillosus* [342]
642	(*E*)-Phytol acetate	*L. nipponica* [96]
643	–	*L. pinnatifida* [219]
644	2,3-Epoxy-phytyl acetate	*L. composita* [214]
645	(–)-Geranyl-linalool	*L. microcladia* [532]

[a]The isolation and structure elucidation of this compound was reported for the first time
[b]The structure of this compound has been revised
[c]The structure of this compound or of a derivative has been confirmed by X-ray crystallographic analysis
[d]The absolute stereochemistry of this compound has been established
[e]Partial synthesis
[f]Stereoselective total synthesis
[g]Enantioselective total synthesis
[h]Formal synthesis

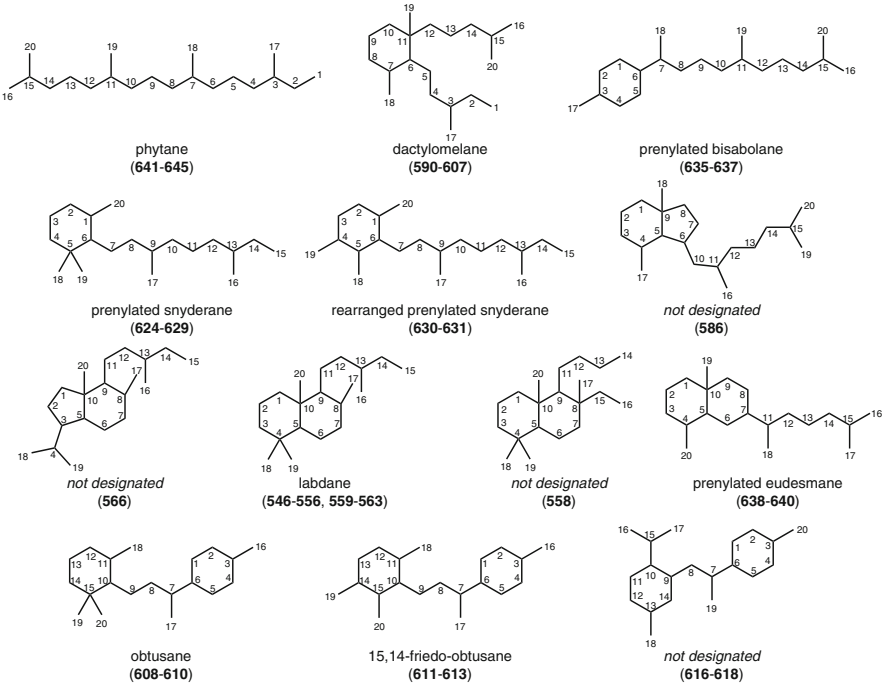


Fig. 6 Acyclic, monocyclic, and bicyclic carbon skeletons of diterpenes isolated from *Laurencia* species

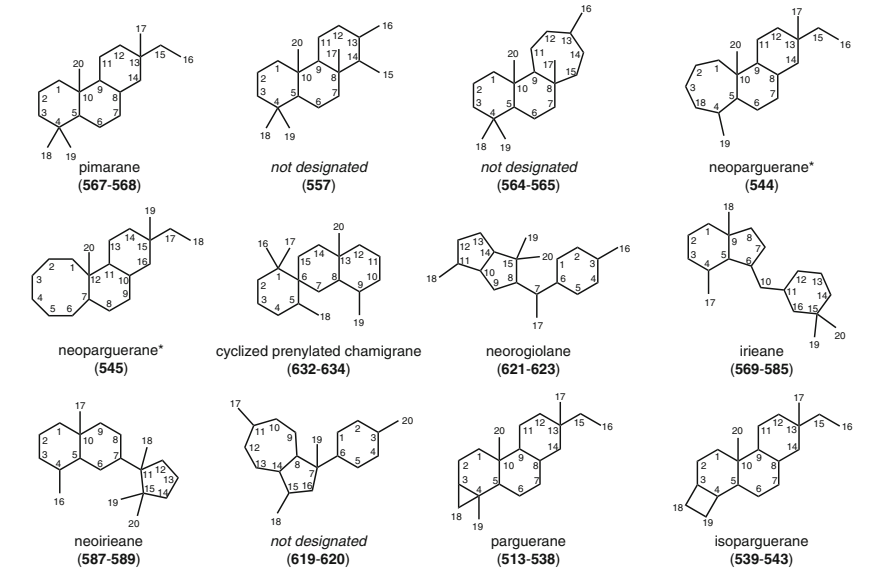
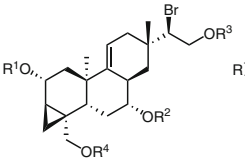
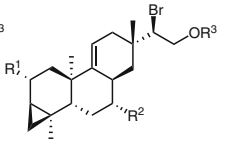


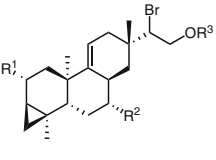
Fig. 7 Tricyclic and tetracyclic carbon skeletons of diterpenes isolated from *Laurencia* species



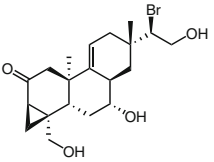
513 $R^1 = R^2 = R^3 = R^4 = H$
514 $R^1 = Ac$, $R^2 = R^3 = R^4 = H$
515 $R^1 = R^4 = Ac$, $R^2 = R^3 = H$
516 $R^1 = R^2 = Ac$, $R^3 = R^4 = H$
517 $R^1 = R^3 = Ac$, $R^2 = R^4 = H$
518 $R^1 = R^2 = R^4 = Ac$, $R^3 = H$
519 $R^1 = R^3 = R^4 = Ac$, $R^2 = H$
520 $R^1 = R^2 = R^3 = Ac$, $R^4 = H$
521 $R^1 = R^2 = R^3 = R^4 = Ac$



522 $R^1 = R^2 = R^3 = H$
523 $R^1 = R^3 = H$, $R^2 = OH$
524 $R^1 = R^2 = OH$, $R^3 = H$
525 $R^1 = OAc$, $R^2 = OH$, $R^3 = H$
526 $R^1 = R^2 = OAc$, $R^3 = H$
527 $R^1 = OAc$, $R^2 = OH$, $R^3 = Ac$
528 $R^1 = R^2 = OAc$, $R^3 = Ac$



529 $R^1 = R^2 = R^3 = H$
530 $R^1 = OAc$, $R^2 = R^3 = H$
531 $R^1 = H$, $R^2 = OH$, $R^3 = Ac$



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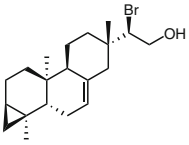

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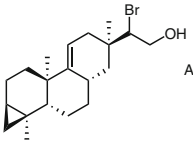

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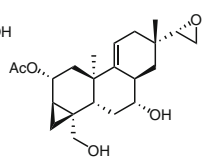

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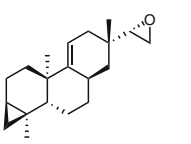

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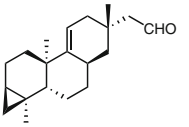

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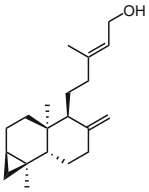

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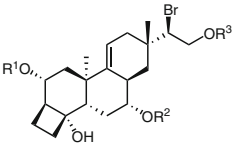
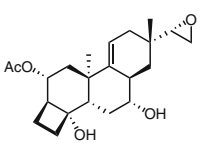


539 $R^1 = R^2 = R^3 = H$
540 $R^1 = Ac$, $R^2 = R^3 = H$
541 $R^1 = R^3 = Ac$, $R^2 = H$
542 $R^1 = R^2 = R^3 = Ac$



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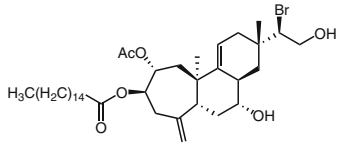

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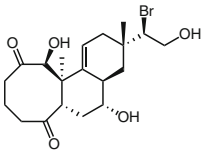
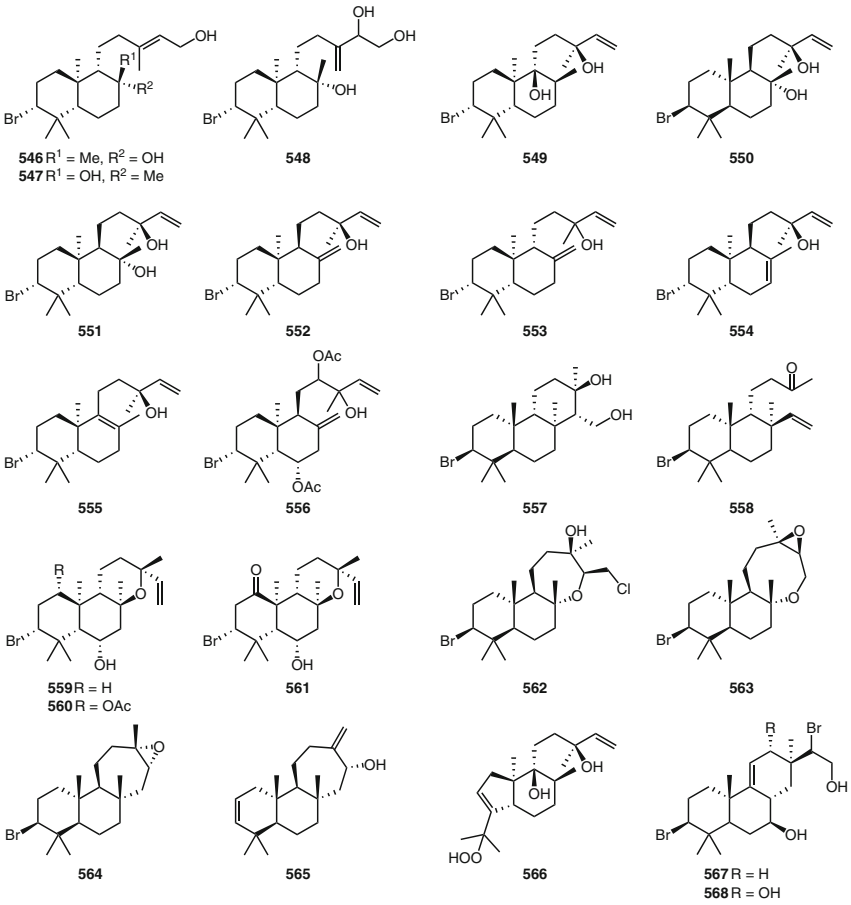


545

3.2.2 Labdanes, Pimaranes, and Related Diterpenes

Labdanes, pimaranes, and related metabolites (**546**–**568**) constitute the second largest group of diterpenes isolated from species of the genus *Laurencia* and their grazers, including 23 compounds so far. Each of them is brominated at C-3, with the exception of laukarlaol (**565**) and neoconcinndiol hydroperoxide (**566**). Furthermore, many of them have OH substitutions at C-8, C-9, or C-13. Aplysin-20 (**546**) and isoaplysin-20 (**557**) were the first members of this group to be isolated from the

sea hare *Aplysia kurodai* in 1971 by Yamamura and Hirata [485, 486] and in 1977 by Yamamura and Terada [496], respectively.

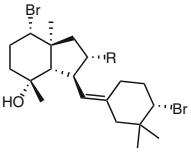


The initially proposed structures were revised after the total syntheses of the natural products [488, 497–499]. The rearranged labdane **558** was obtained from *Laurencia perforata*, along with the pimarane derivatives **567** and **568** [495]. Paniculatol (**559**) and the related metabolites **560** and **561** possess a tetrahydropyran ring [106, 500], while metabolites **562** and **563**, isolated from *Laurencia obtusa* collected from Mitikas Bay in the Ionian Sea, contain oxepane and oxocane moieties, respectively [501]. *Laurencia snyderiae* from Santa Catalina Island afforded neoconcinndiol hydroperoxide (**566**), featuring a modified ring A,

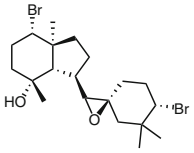
the structure of which was established on the basis of single-crystal X-ray diffraction analysis [354].

3.2.3 Irieanes and Neoirieanes

Taken together, irieanes and neoirieanes consist the third most often encountered group of diterpenes characterized from *Laurencia* spp. and gastropods consuming them, amounting to 21 compounds in total (**569**–**589**). The irieane and neoirieane skeletons are unique in Nature and so far have only been found in *Laurencia* species and sea hares feeding on them. In 1975 and 1978, Fenical and co-workers reported irieol (**569**) and iriediol (**570**), as well as irieols A (**571**), B (**575**), C (**572**), D (**579**), E (**574**), F (**577**), and G (**578**), from *Laurencia* cf. *irieii* collected near Puerto Peñasco, Mexico [504, 506]. These compounds possess a regular tricarbocyclic framework that closely resembles the sesquiterpene skeleton oppositane. The structure of irieol A (**571**) was determined on the basis of X-ray crystallographic analysis [506]. In 1982, reinvestigation of *L.* cf. *irieii* by the same group led to the isolation of neoirieone (**587**), a diterpene possessing a different but closely related to irieane skeleton [507]. The structure of neoirieone (**587**) was elucidated by X-ray crystallographic analysis of the reduction product of **587** [507]. All irieane and neoirieane derivatives are dibrominated at C-1 and C-14, with the exception of prepinnaterpene (**586**) that bears only one bromine atom at C-1. Furthermore, apart from compounds **580**–**585**, all others possess an α-oriented OH substitution at C-4.



569 R = H
570 R = OH



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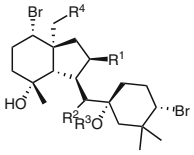
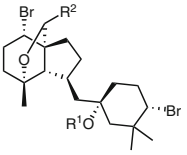
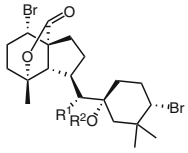


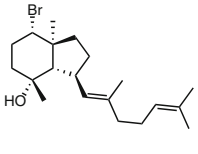
572 $R^1 = R^2 = R^3 = R^4 = H$
573 $R^1 = R^2 = R^4 = H$, R^3 = Ac
574 $R^1 = R^3 = R^4 = H$, R^2 = OH
575 R^1 = OH, $R^2 = R^3 = R^4 = H$
576 $R^1 = R^2 = H$, R^3 = Ac, R^4 = OH
577 $R^1 = R^2$ = OH, $R^3 = R^4 = H$
578 R^1 = OH, R^2 = OAc, $R^3 = R^4 = H$
579 R^1 = OAc, R^2 = OH, $R^3 = R^4 = H$



580 $R^1 = H$, R^2 = OH
581 R^1 = Ac, R^2 = OH
582 R^1 = Ac, $R^2 = H$



583 $R^1 = R^2 = H$
584 $R^1 = H$, R^2 = Ac
585 R^1 = OAc, $R^2 = H$



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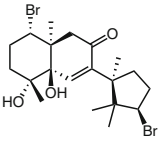

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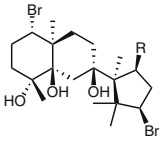
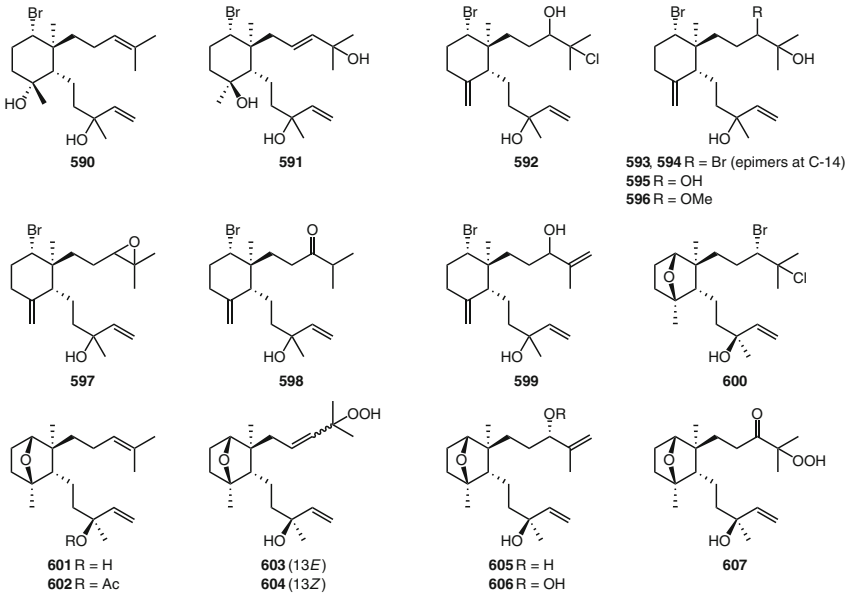


588 R = H
589 R = OH

3.2.4 Dactylomelanes

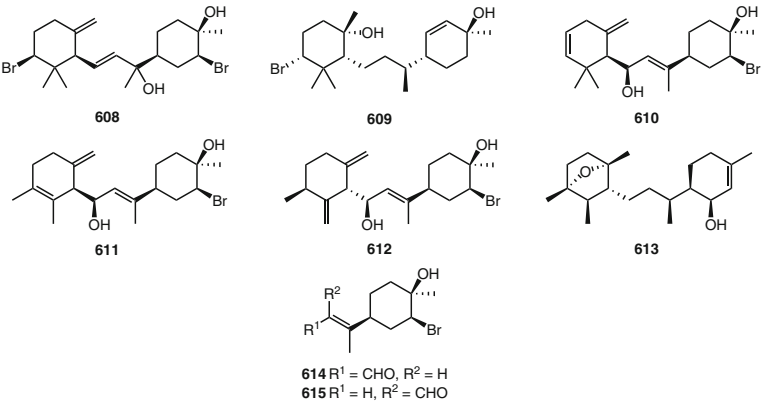
To date, 18 diterpenes featuring the dactylomelane skeleton (**590–607**) have been isolated from species of *Laurencia* and the sea hares consuming them. Dactylomelanes possess a monocarbocyclic framework arising by cyclization between carbons C-6 and C-11 of the phytane skeleton. Dactylomelol (**600**), the first representative of this class, was reported initially as a constituent of *A. dactylomela* collected from Tenerife, Canary islands, and its structure, including the absolute stereochemistry, was determined by single-crystal X-ray diffraction analysis [517]. Compounds **590–599** bear an α-oriented Br substitution at C-10, whereas the remaining substances (**600–607**) possess a 7,10-epoxy ring. In all cases, the side chain attached to C-6 is the same, with the exception of **602**, in which the hydroxy group at C-3 is acetylated.



3.2.5 Obtusanes, 15,14-Friedoobtusanes, and Related Diterpenes

Obtusanes, 15,14-friedoobtusanes, and related metabolites comprise a small group of diterpenes isolated from species of *Laurencia* and their grazers, encompassing eight members (**608–615**). Three diterpenes featuring the bicyclic obtusane skeleton (**608–610**) and three 15,14-friedoobtusanes (**611–613**), resulting from a 1,2-methyl migration to C-14, have been reported so far. Obtusadiol (**608**), the first diterpene featuring the bicyclic obtusane skeleton, was originally isolated from

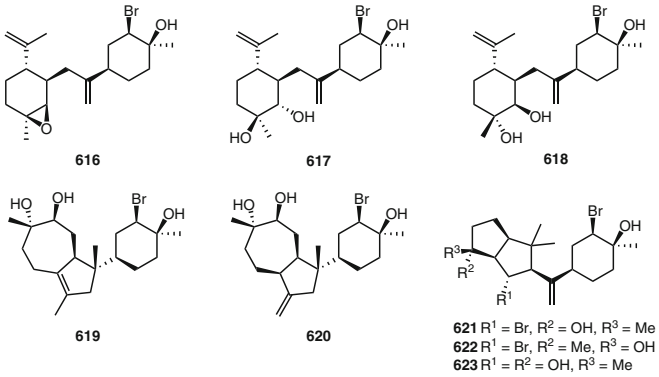
L. obtusa collected from the Greek shores near Athens [320] and later from *L. microcladia* from Il Rogiolo, Italy [518]. The latter population afforded also two related degraded C_{11} derivatives, namely, rogiolal (**614**) and isorogiolal (**615**) [518]. Most of the metabolites belonging to this group are characterized by a *cis*-1,2-bromohydrin functionality, with the exception of compound **609** and laurenditerpenol (**613**).



3.2.6 Prevezanes and Neorogiolanes

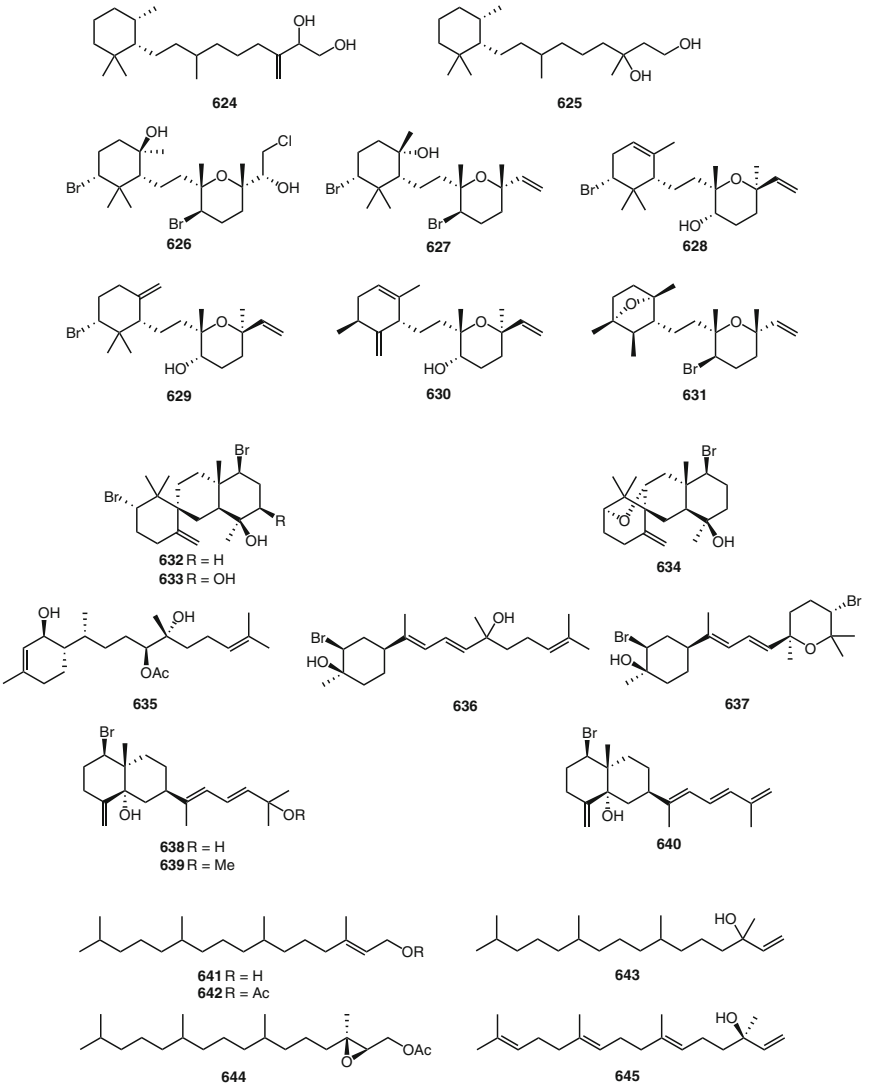
Diterpenes belonging to the group of the prevezanes and neorogiolanes (**616–623**) feature three rare carbon frameworks that so far are found exclusively in species of *Laurencia*. To date, eight diterpenes featuring these skeletons have been reported. In 2001, Mihopoulos et al. reported the isolation of prevezols A (**616**) and B (**617**) from a *L. obtusa* population collected from Preveza, Greece [527]. In 2003, the same group published the structures of prevezols C (**618**), D (**619**), and E (**620**), obtained from another population of *L. obtusa* collected again from Preveza, while prevezol B (**617**) was re-isolated and its structure revised [528]. Prevezols A (**616**), B (**617**) and C (**618**) incorporate a 1,2-dicyclohexylethane core into their structure, while prevezols D (**619**) and E (**620**) contain a 1-cyclohexyldecahydroazulene ring system. Comparison of the spectroscopic data of the natural products **617** and **618** with those of the products obtained through total syntheses of the proposed structures for prevezols B [529] and C [530], respectively, exhibited slight discrepancies, albeit without suggesting alternative structures for the natural products. *L. microcladia* collected from Il Rogiolo, Italy, yielded neorogioldiol (**621**) [532], whereas its epimer at C-11, neorogioldiol B (**622**), was isolated from *L. obtusa* collected from Preveza [528]. The related metabolite neorogioltriol (**623**) was isolated from *L. glandulifera* collected in Kefalonia Island, Greece [533]. Compounds **621–623** possess a 2-(cyclohexylmethyl)octahydropentalene

system. Without exception, all of these metabolites feature a *cis*-1,2-bromohydrin functionality.



3.2.7 Miscellaneous Diterpenes

In addition to the diterpenes belonging to the classes discussed above, there are 22 more diterpenes (**624–645**) that are either linear or possess prenylated sesquiterpene skeletons reported so far from species of the genus *Laurencia* or mollusks feeding on them. Compounds **624–629** feature a prenylated snyderane (or 10,15-cyclophytane) framework, whereas metabolites **630** and **631** possess a prenylated rearranged snyderane carbocycle. Among these, derivatives **626–631** represent an etherification between carbons C-9 and C-13. Laurencianol (**626**) and punctatol (**627**) are dibrominated, bearing bromine atoms at both C-4 and C-10, glandulaurencianols A (**628**) and B (**629**) have only one Br substitution at C-4, whereas dactylopyranoid (**631**) has a Br substitution at C-10. Kahukuenes A (**634**) and B (**632**), isolated from a Hawaiian *L. majuscula* [537] collection, as well as compound **633** are the only examples of diterpenes possessing a prenylated chamigrane backbone that has been further cyclized to yield a tricarbocyclic skeleton. Dactyloditerpenol acetate (**635**), obtained from *A. dactylomela* collected off Mona Island, Puerto Rico [178], as well as rogioldiol D (**636**) and *O*-11,15-cyclo-14-bromo-14,15-dihydrorogiol-3,11-diol (**637**), isolated from *L. microcladia* from Il Rogiolo [532], feature a prenylated bisabolane skeleton. The latter compound exhibits an etherification between carbons C-11 and C-15, while both **636** and **637** display a *cis*-1,2-bromohydrin moiety in their structures. In 1990, Yamada and co-workers reported the isolation of aplysiadiol (**638**) and its methyl ether derivative **639**, diterpenes possessing a prenylated eudesmane skeleton, from *A. kurodai* [539], whereas anhydroaplysiadiol (**640**) was later isolated together with **638** from *Laurencia japonensis* [93]. Furthermore, five linear diterpenes (**641–645**) have been isolated from a number of *Laurencia* species.



3.3 Triterpenes

Triterpenes isolated from species of the genus *Laurencia*, as well as mollusks grazing on them, encompass to date 59 non-carbocyclic polyethers and related metabolites (**646–704**, Table 3) that display a diversity of ring sizes and functionalization. From a biogenetic point of view, triterpenes may arise from a common precursor,

Table 3 Triterpenes from *Laurencia* spp.

No.	Name	Source of Isolation/Synthesis
646	Thyrsiferol	*L. catarinensis* [542], *L. mariannensis* [543], *L. saitoi* [480, 544], *L. tryrsifera* [545[a,c], 546], *L. venusta* [547], *L. viridis* [548], *A. dactylomela* [549]; Synthesis [550[e], 551[e], 552[d,g], 553[f]]
647	Thyrsiferyl 23-acetate	*L. saitoi* [480, 544[a], 546], *L. venusta* [547]; Synthesis [552[d,g], 553[f]]
648	Aplysiol A (21α-Hydroxy-thyrsiferol)	*L. mariannensis* [543], *A. dactylomela* [549[a,d]]
649	15(28)-Anhydrothyrsiferol (Dehydrothyrsiferol)	*L. pinnatifida* [272[a,d]], *L. viridis* [554, 555]
650	Dehydrothyrsiferyl 23-acetate	*L. obtusa* [556]
651	15(28)-Anhydrothyrsiferyl diacetate	*L. saitoi* [557[d]]
652	16-Hydroxy-dehydrothyrsiferol	*L. viridis* [554]
653	16-*epi*-Hydroxy-dehydrothyrsiferol	*L. viridis* [558]
654	3-*epi*-Dehydrothyrsiferol	*L. viridis* [559]
655	10-*epi*-Dehydrothyrsiferol	*L. viridis* [560]
656	15,16-Anhydrothyrsiferol	*L. omaezakiana* [561[d]]
657	15-Anhydrothyrsiferyl diacetate	*L. saitoi* [557[d]]
658	10-*epi*-15,16-Dehydrothyrsiferol	*L. viridis* [554]
659	Venustatriol	*L. venusta* [547[c,d]], *A. dactylomela* [549]; Synthesis [552[g], 562[g]]
660	Dehydrovenustatriol	*L. viridis* [554]
661	22-Hydroxy-15(28)-dehydro-venustatriol	*L. viridis* [563]
662	15,16-Dehydrovenustatriol	*L. viridis* [554]
663	15,16-Epoxy-thyrsiferol A	*L. viridis* [564]
664	15,16-Epoxy-thyrsiferol B	*L. viridis* [564]
665	Magireol A	*L. saitoi* [557[d]]
666	Magireol B	*L. saitoi* [557]
667	Magireol C	*L. saitoi* [557]
668	Aplysiol B (Laurenmariannol)	*L. mariannensis* [543], *A. dactylomela* [549[a,d], 565[b]]
669	Saiyacenol A	*L. viridis* [555]
670	Saiyacenol B	*L. viridis* [555]
671	28-Hydroxy-saiyacenol B	*L. viridis* [564]
672	Callicladol	*L. calliclada* [566]
673	Isodehydrothyrsiferol	*L. viridis* [560]
674	Iubol	*L. viridis* [563]
675	Aplysqualenol A	*A. dactylomela* [567]
676	Aplysqualenol B	*A. dactylomela* [567]
677	Thyrsenol A	*L. viridis* [568]

(continued)

Table 3 (continued)

No.	Name	Source of Isolation/Synthesis
678	Thyrsenol B	*L. viridis* [568]
679	15-Dehydroxythyrsenol A	*L. viridis* [569]
680	Spirodehydrovenustatriol	*L. viridis* [570]
681	Martiriol	*L. viridis* [558]
682	1,2-Dehydropseudodehydro-thyrsiferol	*L. viridis* [563]
683	–	*L. viridis* [559]
684	–	*L. viridis* [559]
685	Pseudodehydrothyrsiferol	*L. viridis* [558]; Synthesis [571[d,g]]
686	Lactodehydrothyrsiferol	*L. viridis* [559]; Synthesis [572]
687	14-Keto-dehydrothyrsiferol	*L. viridis* [570]
688	Clavidol	*L. viridis* [559]
689	Prethyrsenol A	*L. viridis* [569]
690	13-Hydroxy-prethyrsenol A	*L. viridis* [569]
691	Saiyacenol C	*L. viridis* [564]
692	Predehydrovenustatriol acetate	*L. viridis* [554]
693	Secodehydrothyrsiferol	*L. viridis* [563]
694	Adejen A	*L. viridis* [570]
695	Adejen B	*L. viridis* [570]
696	Aurilol	*D. auricularia* [573]; Synthesis [574[d,g]]
697	Enshuol	*L. omaezakiana* [575]; Synthesis [576[d,g]]
698	Dioxepandehydrothyrsiferol	*L. viridis* [558]
699	Teurilene	*L. saitoi* [544[a,c]]; Synthesis [577–582]
700	Intricatetraol	*L. intricata* [583[a]], *L. nangii* [94], *Laurencia* sp. [584]; Synthesis [585[d,g]]
701	Squalene	*Laurencia* spp. [586]
702	(+)-(10*R*,11*R*)-Squalene-10,11-epoxide	*L. okamurai* [587[a,d,g], 588]
703	Auriculol	*D. auricularia* [589[d,g]]
704	Omaezakianol	*L. omaezakiana* [561]; Synthesis [590[d,g]]

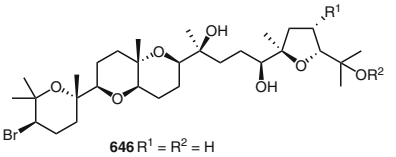
[a]The isolation and structure elucidation of this compound was reported for the first time
[b]The structure of this compound has been revised
[c]The structure of this compound or of a derivative has been confirmed by X-ray crystallographic analysis
[d]The absolute stereochemistry of this compound has been established
[e]Partial synthesis
[f]Stereoselective total synthesis
[g]Enantioselective total synthesis

(+)-(10*R*,11*R*)-squalene-10,11-epoxide (**702**), which could evolve to the hypothetical common intermediate (6*S*,7*S*,10*R*,11*R*,14*R*,15*R*,18*S*,19*S*)-squalene tetraepoxide [591]. From this intermediate, three main routes can be proposed and as such three different subgroups can be distinguished, namely: (1) those possessing a

2,7-dioxabicyclo[4.4.0]decane ring system, such as thyrsiferol (**646**), venustatriol (**659**) and their congeners; (2) those possessing a 2,8-dioxabicyclo[5.4.0]undecane ring system, such as enshuol (**697**); and (3) those possessing a symmetry element, such as teurilene (**699**). A fourth group would include miscellaneous triterpenes, including linear analogues.

3.3.1 Triterpenes Possessing a 2,7-Dioxabicyclo[4.4.0]decane Ring System and Related Metabolites

Since the isolation of thyrsiferol (**646**) from *Laurencia thyrsifera* collected in Seal Reef-Kaikoura, New Zealand by Blunt et al. in 1978 [545], a number of related compounds have been reported. In particular, 50 triterpenes and related metabolites possessing a 2,7-dioxabicyclo[4.4.0]decane moiety (**646**–**695**) have been isolated from *Laurencia* species and the sea hares consuming them so far. In most cases (**646**–**679** and **681**), the 2,7-dioxabicyclo[4.4.0]decane core is connected through a single bond to a tetrahydropyran ring in the left side, whereas in the right side it is connected to a side chain. The latter differs from C-15 to C-23 presenting variations in the number, size and position of the cyclic ether rings, varying degrees of oxidation, and different configurations of the chiral centers. In the case of spirodehydrovenustatriol (**680**), the 2,7-dioxabicyclo[4.4.0]decane core has been modified to a 1,6-dioxaspiro[4.5]decane ring system. With the exception of 3-epidehydrothyrsiferol (**654**) that bears an α-oriented Br substitution at C-3, and martiriol (**681**), with a β-oriented OH substitution at C-3, all the other derivatives (**646**–**653** and **655**–**679**) feature a β-oriented Br substitution at C-3. In compounds **682**–**686**, the 2,7-dioxabicyclo[4.4.0]decane core is instead connected through a single bond to a tetrahydrofuran ring on the left side, while in metabolites **692** and **693** the basic ring system is connected to a linear side chain on the left side. Furthermore, triterpenes **687**–**691** lack the 10,14-ether ring, but also bear a β-oriented Br substitution at C-3. Adejens A (**694**) and B (**695**) are two unusual C_{17} terpenoids obtained from *L. viridis* and their biogenetic origin has been proposed on the basis of an oxidative degradation of the squalene skeleton [570]. It is worth noting that the spectroscopic data of 21α-hydroxy-thyrsiferol and laurenmariannol, reported from a Chinese *L. mariannensis* sample in 2008 as new natural products [543], were found to be the same as those of aplysiols A (**648**) and B (**668**), respectively, isolated by Manzo et al. in 2007 from the mantle of the sea hare *A. dactylomela*, collected from the South China Sea [549]. The relative configurations of the asymmetric centers of aplysiol B (**668**) were later revised [555, 565].



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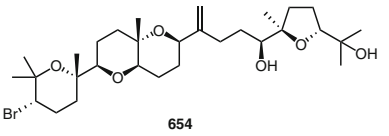
647 $R^1 = H$, $R^2 = Ac$
648 $R^1 = OH$, $R^2 = H$



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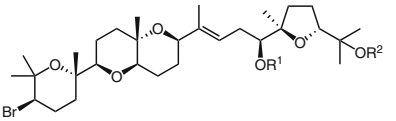
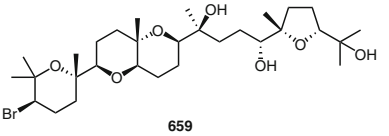


656 $R^1 = R^2 = H$
657 $R^1 = R^2 = Ac$



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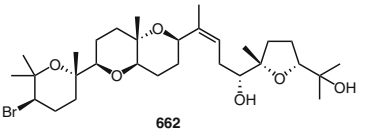

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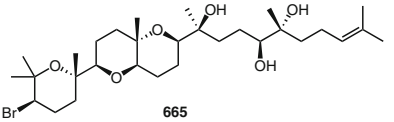

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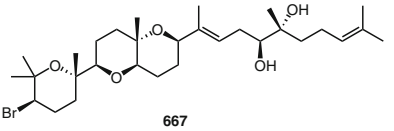

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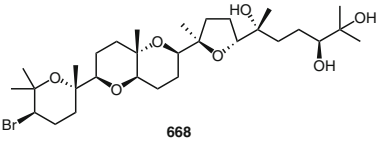

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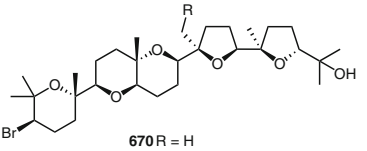
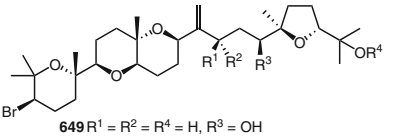
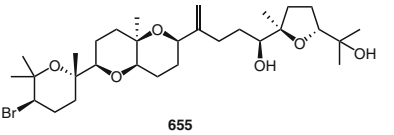


670 R = H
671 R = OH



649 $R^1 = R^2 = R^4 = H$, $R^3 = OH$
650 $R^1 = R^2 = H$, $R^3 = OH$, $R^4 = Ac$
651 $R^1 = R^2 = H$, $R^3 = OAc$, $R^4 = Ac$
652 $R^1 = R^4 = H$, $R^2 = R^3 = OH$
653 $R^1 = R^3 = OH$, $R^2 = R^4 = H$



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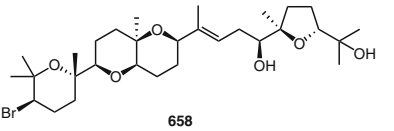

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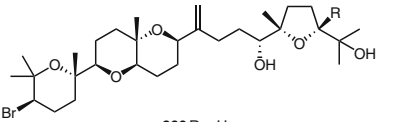
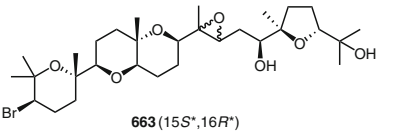
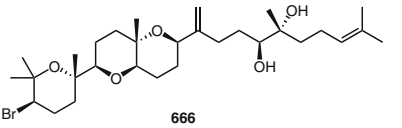


660 R = H
661 R = OH



663 (15*S**,16*R**)
664 (15*R**,16*S**)



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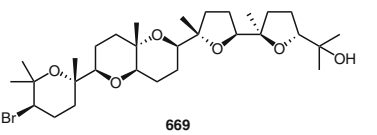
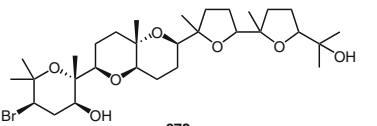


669



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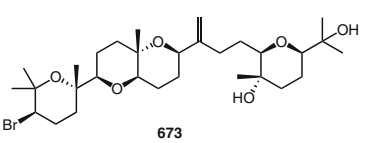

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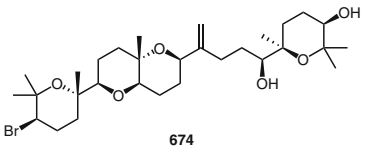
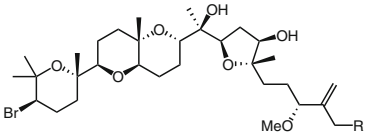
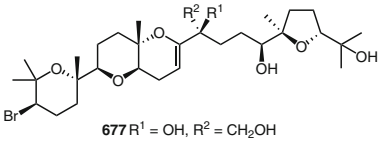


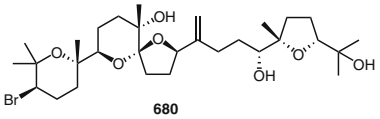
674



675 R = H
676 R = OH



677 R^1 = OH, R^2 = CH_2OH
678 R^1 = CH_2OH, R^2 = OH
679 R^1 = H, R^2 = CH_2OH



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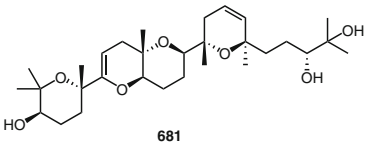

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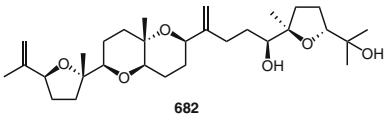

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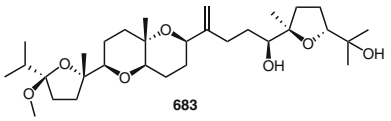

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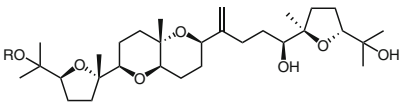
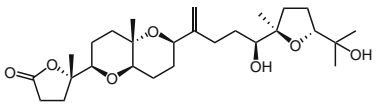
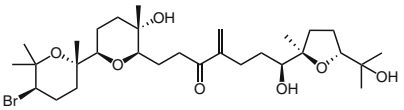


684 R = Me
685 R = H



686



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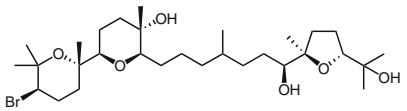
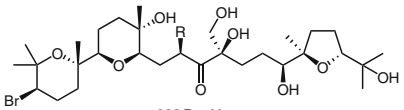
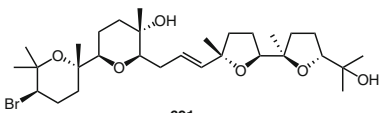


688



689 R = H
690 R = OH



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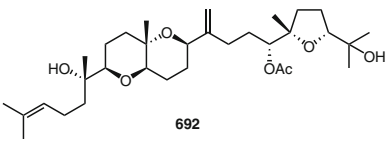

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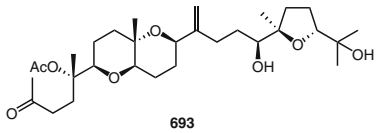

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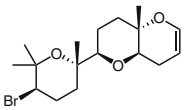

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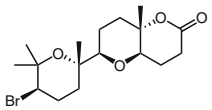
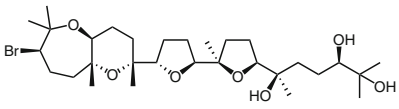


695

3.3.2 Triterpenes Possessing a 2,8-Dioxabicyclo[5.4.0]undecane Ring System

Up to the present, only three triterpenes possessing a 2,8-dioxabicyclo[5.4.0]undecane unit (**696**–**698**) have been identified in red algae of the genus *Laurencia* or in gastropods feeding on them. In aurilol (**696**), isolated from the sea hare *Dolabella auricularia* [574], and enshuol (**697**), obtained from *Laurencia omaezakiana* [575], the 2,8-dioxabicyclo[5.4.0]undecane unit is connected through a single bond to two and three isolated tetrahydrofuran rings, respectively. The absolute stereochemistry of **697** was established by total synthesis [575, 576]. Dioxepandehydrothyrsiferol (**698**), isolated from *L. viridis* collected in Macaronesia, Canary islands [558], features a second oxepane ring that is fused to the 2,8-dioxabicyclo[5.4.0]undecane core to yield a 7,7,6-fused ring system, which further connects to a tetrahydropyran ring through single bonds. All three triterpenes share a β-oriented bromine substitution at C-3 and a hydroxy group at C-23.



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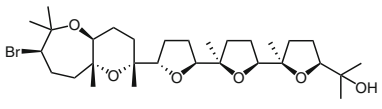

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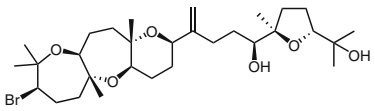
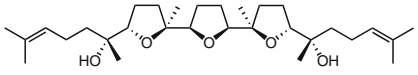


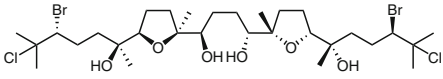
698

3.3.3 Triterpenes Possessing Symmetry Elements

Only two triterpenes possessing symmetric elements (**699** and **700**) have been isolated so far from *Laurencia* species or their grazers. In particular, the non-halogenated teurilene (**699**), isolated from *Laurencia saitoi* collected from Teuri Island, Hokkaido, Japan, in spite of having eight stereogenic centers and three tetrahydrofuran rings in its structure, has a mirror symmetry (C_s) (*meso* form), thus making it achiral [544]. The bromochlorinated intricatetraol (**700**), initially obtained from *Laurencia intricata* collected at different sites near Hokkaido, Japan, is the only example of a triterpene with a C_2 symmetrical structure [583].



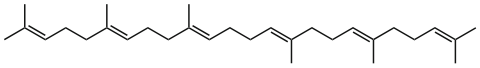
699

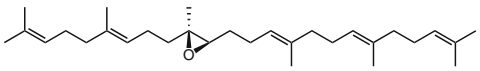


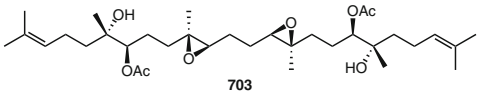
700

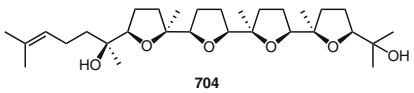
3.3.4 Miscellaneous Triterpenes

There are four triterpenes (**701**–**704**) reported so far from *Laurencia* species or mollusks feeding on them that cannot be classified into the three subgroups discussed above. Squalene (**701**) and (+)-(10*R*,11*R*)-squalene-10,11-epoxide (**702**) are considered precursors in the biogenesis of all other triterpenes. The structure of auriculol (**703**), a linear non-halogenated triterpene isolated from a Japanese *D. auricularia* specimen, was established by analysis of its spectroscopic data and from organic synthesis [589]. *L. omaezakiana* collected from Omaezaki, Shizuoka Prefecture, Japan, yielded omaezakianol (**704**) consisting of four tetrahydrofuran rings and its total synthesis was achieved from squalene via a biomimetic epoxide-opening cascade reaction in six steps [561, 590].









3.4 C_{15} Acetogenins

Red algae of the genus *Laurencia* are a unique source of non-terpenoid C_{15} acetogenins, polyketides arising in all probability from a C_{16} fatty acid. Up to now chemical investigations on species of the genus *Laurencia*, as well as mollusks grazing on them have afforded 244 acetogenins and related metabolites (**705**–**948**, Table 4). In general, these are brominated, quite frequently bromochlorinated or dibrominated, while it is not uncommon to contain three or more halogen atoms, and only seldom do they lack halogen atoms. These acetogenins are usually characterized by a conjugated (*E*)- or (*Z*)-enyne or bromoallene terminus, and, with the exception of a few linear acetogenins, most of them contain at least one cyclic ether of variable ring size. The latter can be further classified into groups according to the size of the largest ether ring present, namely, acetogenins containing five-, six-, seven-, eight-, nine-, ten-, or twelve-membered rings.

Table 4 C_{15} Acetogenins from *Laurencia* spp.

No.	Name	Source of Isolation/Synthesis
705	Graciosallene	*L. obtusa* [592[a,d], 593]
706	Graciosin	*L. obtusa* [318[a], 592[b,c,d], 593]
707	Itomanallene B	*L. intricata* [422[a]], *L. nangii* [94, 594]
708	Dihydroitomanallene B	*L. nangii* [594]
709	Omaezallene	*Laurencia* sp. [584[d,g]]
710	–	*Laurencia* sp. [584[d,g]]
711	–	*Laurencia* sp. [584]
712	(*E*)-Deacetylkumausyne	*L. nipponica* [595[d]]; Synthesis [596[g]]
713	(*Z*)-Deacetylkumausyne	*L. nipponica* [595[d]]
714	(*E*)-Kamausyne	*L. nipponica* [111, 595[a]]; Synthesis [597[f], 598[d,g], 599[e], 600[g], 601[h], 602[h], 603[h], 604[f]]
715	(*Z*)-Kamausyne	*L. nipponica* [595[d]]
716	12-Acetoxy-marilzafurenyne	*L. marilzae* [605]
717	Marilzafurollene A	*L. marilzae* [605]
718	Marilzafurollene B	*L. marilzae* [605]
719	Marilzafurollene C	*L. marilzae* [605]
720	Marilzafurollene D	*L. marilzae* [605]
721	Laureoxolane	*L. nipponica* [606]
722	–	*L. glandulifera* [607]
723	–	*L. glandulifera* [607]
724	–	*L. glandulifera* [607]
725	–	*L. glandulifera* [607]
726	–	*L. glandulifera* [607]
727	Bisezakyne A	*Laurencia* sp. [608]
728	Laureepoxide	*L. nipponica* [418, 606, 609[a,d]]
729	Hurgadenyne	*L. obtusa* [145]
730	–	*L. obtusa* [593[d]]
731	–	*L. obtusa* [610]
732	Notoryne	*L. nipponica* [138[d]]
733	Laurendecumbenyne B	*L. decumbens* [611[a], 612[b]]; Synthesis [613[g]]
734	(3*E*)-Elatenyne	*L. majuscula* [614]; Synthesis [613[g]]
735	Elatenyne	*L. decumbens* [611], *L. elata* [196[a], 221, 615, 617, 618[b]]; Synthesis [613[g], 616[b]]
736	Laurefurenyne B	*Laurencia* sp. [619]; Synthesis [620, 621[b]]
737	Laurefurenyne A	*Laurencia* sp. [619]; Synthesis [620, 621[b,d,g]]
738	–	*L. majuscula* [416, 615]; Synthesis [616[b]]
739	Kumausallene	*L. nipponica* [111, 622[a,c,d]]; Synthesis [623[f], 624[g,h], 625[g], 626[g], 627[g,h]]
740	Aplysiallene	*L. okamurai* [192[a]], *Laurencia* sp. [105, 584], *A. kurodai* [308, 628]; Synthesis [629[b,d]]
741	Laurenmariallene	*L. mariannensis* [74]
742	Okamurallene	*L. okamurai* [69, 630[a], 631[b], 632[d]]
743	Deoxyokamurallene	*L. okamurai* [631[b], 633[a]]
744	Isookamurallene	*L. okamurai* [631[b], 633[a]]

(continued)

Table 4 (continued)

No.	Name	Source of Isolation/Synthesis
745	–	*L. okamurai* [631[d]]
746	Panacene	*A. brasiliana* [634]; Synthesis [635[f], 636[b,f], 637[f]]
747	Obtusin	*L. obtusa* [318, 389, 593, 638[a,c,d]]
748	Neoobtusin	*L. obtusa* [639]
749	Chinzallene	*Laurencia* sp. [105]
750	Laurenenyne A	*L. caduciramulosa* [195], *L. japonensis* [92[a,d], 93]; Synthesis [640[e]]
751	Laurenenyne B	*L. caduciramulosa* [195], *L. japonensis* [92[a,d], 93]; Synthesis [640[e]]
752	Laurenidificin	*L. nidifica* [641]
753	(*E*)-Ocellenyne	*A. oculifera* [642]
754	(*Z*)-Ocellenyne	*A. oculifera* [642]
755	–	*L. majuscula* [416]
756	–	*L. majuscula* [416]
757	–	*L. majuscula* [416]
758	(*Z*)-Maneonene A	*L. nidifica* [643[a], 644], *L. obtusa* [645]; Synthesis [646[b,f]]
759	(12*E*)-Lembyne A	*L. mariannensis* [62[a]], *Laurencia* sp. [118], *A. dactylomela* [118]
760	(*Z*)-Maneonene C	*L. nidifica* [644, 647[a]], *A. dactylomela* [182]
761	(*Z*)-Maneonene E	*L. obtusa* [645[a]], *L. papillosa* [101]
762	(*Z*)-Maneonene B	*L. nidifica* [643[a], 644]; Synthesis [646[b,f]]
763	Lembyne A	*Laurencia* sp. [118, 165[a]], *A. dactylomela* [118]
764	(*Z*)-Maneonene D	*L. obtusa* [645]
765	(*E*)-Maneonene B	*L. nidifica* [643[a], 644], *L. papillosa* [101]; Synthesis [648[b,f]]
766	(*E*)-Maneonene C	*L. obtusa* [645]
767	Isomaneonene A	*L. nidifica* [644, 647[a]]
768	Isomaneonene B	*L. nidifica* [644, 647[a]]
769	Lembyne B	*Laurencia* sp. [165]
770	Isodactylyne	*A. dactylomela* [649]; Synthesis [650[d,g], 651[g]]
771	Dactylyne	*L. lageniformis* [310], *Laurencia* sp. [270, 608], *A. dactylomela* [652[a,c,d]]; Synthesis [650[g], 651[g]]
772	Scanlonenyne	*L. obtusa* [349]; Synthesis [653[d,g]]
773	Srilankenyne	*A. oculifera* [654]
774	Bisezakyne B	*Laurencia* sp. [608]
775	–	*L. obtusa* [593[d]]
776	–	*L. obtusa* [411], *L. paniculata* [610[c,d]]
777	–	*L. paniculata* [610]
778	Japonenyne A	*L. japonensis* [655]
779	Japonenyne B	*L. japonensis* [655]
780	Japonenyne C	*L. japonensis* [655]
781	Laurobtusin	*L. obtusa* [656]
782	(3*E*)-Dactylomelyne	*L. obtusa* [413], *A. dactylomela* [372[a]]; Synthesis [657[e], 658[f], 659[f]]

(continued)

Table 4 (continued)

No.	Name	Source of Isolation/Synthesis
783	(3*Z*)-Dactylomelyne	*A. dactylomela* [372]; Synthesis [657[e], 658[f], 659[f]]
784	Isolaurepinnacin	*L. pinnata* [660]; Synthesis [661[e], 662[d,g], 663[g], 664[g,h], 665[g,h], 666[g,h]]
785	Rogioloxepane A	*L. microcladia* [667]; Synthesis [666[g,h], 668[d,g], 669[g]]
786	Rogioloxepane B	*L. microcladia* [667[d]]
787	Rogioloxepane C	*L. microcladia* [667[d]]
788	Neonipponallene	*L. nipponica* [670[d]]
789	Rogiolenyne D	*L. microcladia* [671[d]]
790	Rogiolenyne A	*L. microcladia* [671[d], 672]
791	Rogiolenyne B	*L. microcladia* [671[d], 672], *L. obtusa* [413]
792	Rogiolenyne C	*S. zimocca* in the vicinity of *L. microcladia* [163]
793	(3*E*)-Isoprelaurefucin	*L. nipponica* [673[a], 674[d]], *L. subopposita* [248]; Synthesis [675[g]]
794	(3*Z*)-Isoprelaurefucin	*L. subopposita* [248[a]], *L. nipponica* [199, 674[d]]
795	(3*E*)-Neoisoprelaurefucin	*L. obtusa* [413[a]], *L. okamurai* [100, 109]
796	Neoisoprelaurefucin	*L. nipponica* [676]; Synthesis [677[d,g]]
797	Laurenyne	*L. chondrioides* [73], *L. obtusa* [678[a,c], 679], *A. fasciata* [326], *A. punctata* [249]; Synthesis [680[b,d,g], 681[g], 682[e]]
798	(3*Z*)-Laurenyne	*L. nangii* [94, 310], *L. yonaguinensis* [513[a]], *A. dactylomela* [407]
799	(3*Z*)-Venustinene	*L. venusta* [683[a]], *A. fasciata* [326]
800	(*E*)-Rhodophytin	*Laurencia* sp. [684]
801	(*Z*)-Rhodophytin	*Laurencia* sp. [30, 684[b], 685[a]]
802	(*E*)-Chondriol	*Laurencia* sp. [684[d]]
803	(*Z*)-Chondriol	*Laurencia* sp. [30, 684[d], 685, 686[a], 687[b,c]]
804	(3*E*)-Venustin (Venustin B)	*L. venusta* [688]
805	(3*Z*)-Venustin	*L. venusta* [683]
806	Epoxy-rhodophytin	*Laurencia* sp. [684[c,d]]
807	(3*E*)-Epoxy-venustin (Venustin A)	*L. venusta* [683[d], 688]
808	(3*Z*)-Epoxy-venustin	*L. venusta* [683[c,d]]
809	(*E*)-Dihydrorhodophytin	*L. pinnatifida* [689, 690[a,d]]
810	(*Z*)-Dihydrorhodophytin	*L. filiformis* [420], *L. nangii* [94, 691], *L. pinnatifida* [689, 690[d]], *A. brasiliana* [692[a,c,d]]
811	Prelaureatin	*L. nipponica* [693[a]]; Synthesis [694–698[d,g], 699[g], 700[h], 701[e]]
812	(3*E*,12*R*,13*R*)-Pinnatifidenyne	*L. obtusa* [407[b,c,d], 702[a]]
***ent*-812**	(3*E*,6*R*,7*R*)-Pinnatifidenyne	*A. dactylomela* [407[c,d]]
813	(*Z*)-*epi*-Dihydrorhodophytin	*L. filiformis* [420]
814	(3*E*)-Pinnatifidenyne	*L. chondrioides* [73], *L. obtusa* [593], *L. pinnatifida* [689[b,c,d], 703[a,c]], *A. dactylomela* [407]; Synthesis [704[g], 705[f,h]]
815	(3*Z*)-Pinnatifidenyne	*L. pinnatifida* [272, 689[b,c,d], 703[a,c]]; Synthesis [704[g], 705[f,h]]

(continued)

Table 4 (continued)

No.	Name	Source of Isolation/Synthesis
***ent*-815**	–	*L. nangii* [94, 118, 310[a,d]], *A. dactylomela* [118]
816	(3*Z*)-13-*epi*-Pinnatifidenyne	*L. claviformis* [107[a]], *A. fasciata* [326]
817	(*Z*)-Isodihydrorhodophytin	*L. obtusa* [435], *A. brasiliana* [692[a]]
818	(*E*)-Epoxy-isodihydrorhodophytin	*L. obtusa* [706[c,d]]
819	Laurencienyne	*L. obtusa* [321, 404, 411, 413, 707[a,c,d], 708]
820	Laurencienyne B	*L. obtusa* [411]
821	(3*E*)-13-Epilaurencienyne	*L. obtusa* [321[a], 702]
822	(3*Z*)-13-Epilaurencienyne	*L. obtusa* [702]
823	–	*L. obtusa* [709]
824	–	*L. obtusa* [702]
825	–	*L. obtusa* [702]
826	–	*Laurencia* sp. cf. *L. gracilis* [103]
827	–	*Laurencia* sp. cf. *L. gracilis* [103]
828	–	*Laurencia* sp. cf. *L. gracilis* [103]
829	Doliculol A	*D. auricularia* [710]
830	Doliculol B	*D. auricularia* [710]
831	Marilzallene	*L. marilzae* [711[d]]
832	(+)-4-Acetoxy-marilzallene	*L. marilzae* [711[c,d]]
833	Marilzallene B	*L. chondrioides* [73]
834	(–)-4-Acetoxy-marilzallene	*L. marilzae* [711]
835	Deacetyllaurencin	*L. nipponica* [609[a,d]], *Laurencia* sp. cf. *L. gracilis* [103]; Synthesis [694]
836	Laurencin	*L. glandulifera* [712[a], 713, 714[c,d]], *L. nipponica* [418, 606]; Synthesis [664[g], 696, 701[e], 715[g], 716[g], 717[g], 718[g], 719[g], 720[g], 721[g], 722[g,h], 723[g,h]]
837	Intricenyne	*L. intricata* [724[a]], *L. tryrsifera* [725[d]]
838	Laurepinnacin	*L. pinnata* [660]; Synthesis [661[e]]
839	Bermudenynol	*L. intricata* [726[c]]; Synthesis [727[d,g]]
840	Bermudenynol acetate	*L. intricata* [726[c]]; Synthesis [727[d,g]]
841	–	*L. tryrsifera* [725]
842	–	*L. glandulifera* [728]
843	–	*L. tryrsifera* [729]
844	–	*L. tryrsifera* [729[a]], *L. glandulifera* [728]
845	–	*L. glandulifera* [728]
846	–	*L. glandulifera* [728]
847	–	*L. glandulifera* [728]
848	–	*L. glandulifera* [728]
849	Poiteol	*L. poitei* [730[c,d]]
850	–	*L. tryrsifera* [725]
851	–	*L. tryrsifera* [725]
852	Laurallene	*L. nipponica* [77[b], 731[a]]; Synthesis [698[d,g], 700[g,h], 732, 733[g], 734[g]]
853	Pannosallene	*L. nangii* [94, 594], *L. pannosa* [735[a]]; Synthesis [734[b,d,g]]

(continued)

Table 4 (continued)

No.	Name	Source of Isolation/Synthesis
854	Nipponallene	*L. nipponica* [670[d]]
***ent*-854**	Epilaurallene	*L. nipponica* [77[a], 735[b], 736], *L. okamurai* [152]
855	–	*L. intricata* [631[a]], *Laurencia* sp. [105, 193]
856	–	*L. implicata* [91[b], 415[a]]
857	Laurendecumallene B	*L. decumbens* [611]; Synthesis [737[e]]
858	–	*L. implicata* [91]
859	–	*L. obtusa* [593[d]]
860	–	*L. obtusa* [318[a], 593[b,d]]
861	Aplyparvunin	*A. parvula* [291[c,d]]
862	Desepilaurallene	*L. okamurai* [152]
863	(*E*)-Laureatin	*L. nipponica* [736, 738[a]]
864	Laureatin	*L. nipponica* [77, 200, 739[a], 740[b], 741[b,d]], *L. okamurai* [109]; Synthesis [695, 742[g], 743[g], 744[e]]
865	(*E*)-Isolaureatin	*L. nipponica* [77, 736, 738[a]]
866	Isolaureatin	*L. nipponica* [77, 200, 740[b], 741[b,c,d], 745[a]]; Synthesis [743[g]]
867	(*Z*)-Chondrin	*Laurencia* sp. [684[d]]
868	(*Z*)-Chondrin	*Laurencia* sp. [684[d]]
869	Okamuragenin	*L. okamurai* [109]
870	(3*E*)-Laurefucin	*L. nipponica* [609, 746[a], 747[b,c,d]], *L. subopposita* [248], *Laurencia* sp. cf. *L. gracilis* [103]; Synthesis [705[f,h]]
871	(3*Z*)-Laurefucin	*L. nipponica* [138], *L. subopposita* [248[a]]
872	(3*E*)-Acetyllaurefucin	*L. nipponica* [609, 746[a], 747[b,d]], *L. subopposita* [248]
873	(3*Z*)-Acetyllaurefucin	*L. nipponica* [138], *L. subopposita* [248[a]]
874	Chlorofucin	*L. pannosa* [735], *L. snyderae* [730[a,c]], *Laurencia* sp. [193]
875	(3*Z*)-Chlorofucin	*L. elata* [221], *L. pannosa* [238[a]]
876	Bromofucin	*L. implicata* [415[a]], *L. pannosa* [735]
877	(3*Z*)-Bromofucin	*A. parvula* [748]
878	Laurefurenyne D	*Laurencia* sp. [619]
879	Laurefurenyne C	*Laurencia* sp. [619]
880	Laurefurenyne F	*Laurencia* sp. [619]
881	Laurefurenyne E	*Laurencia* sp. [619]
882	(3*E*)-Dehydrobromolaurefucin	*L. subopposita* [248[a]], *Laurencia* sp. cf. *L. gracilis* [103[b]]; Synthesis [705[e]]
883	(3*Z*)-Dehydrobromolaurefucin	*L. subopposita* [248]
884	(3*E*)-5-Hydroxy-dehydrobromolaurefucin	*Laurencia* sp. cf. *L. gracilis* [103]
885	Laurendecumenyne A	*L. decumbens* [611]
886	Laureoxanyne	*L. nipponica* [749]
887	Microcladallene A	*L. obtusa* [750[a]], *Laurencia* sp. [106]

(continued)

Table 4 (continued)

No.	Name	Source of Isolation/Synthesis
888	Microcladallene C	*L. obtusa* [750[a]], *L. majuscula* [122]
889	Microcladallene B	*L. obtusa* [750]; Synthesis [751[b,d]]
890	–	*L. implicata* [415]
891	Brasilenyne	*A. brasiliana* [692[c,d]]; Synthesis [752[g], 753[g]]
892	Obtusenyne	*L. nangii* [310], *L. obtusa* [730, 754[a,c,d]]; Synthesis [755[e], 756[e], 757[g], 758[g], 759[g], 760[g]]
893	(+)-(3*E*)-12-Epiobtusenyne	*A. dactylomela* [372[c,d]]
894	(+)-(3*Z*)-12-Epiobtusenyne	*L. lageniformis* [310], *A. dactylomela* [372[a,d]]
895	(–)-(3*E*,12*R*,13*R*)-Obtusenyne	*L. chondrioides* [73], *L. pinnatifida* [689]; Synthesis [761[b,d]]
***ent*-895**	(+)-(3*E*,6*R*,7*R*)-Obtusenyne	*A. dactylomela* [407[c,d]]
896	(–)-(3*Z*,12*R*,13*R*)-Obtusenyne	*L. pinnatifida* [689]; Synthesis [761[b,d]]
***ent*-896**	(+)-(3*Z*,6*R*,7*R*)-Obtusenyne	*L. nangii* [94], *A. dactylomela* [407[a,d]]
897	–	*L. implicata* [415]
898	Isolaurallene	*L. nipponica* [762[a,c,d], 763]; Synthesis [734[g], 764[g], 765[g]]
899	Neolaurallene	*L. implicata* [91, 415], *L. intricata* [631, 763, 766[a,c,d]], *L. nangii* [94], *L. okamurai* [109], *L. saitoi* [480]; Synthesis [734[g]]
900	Itomanallene A	*L. intricata* [422]; Synthesis [734[b,g], 767[b,d,g]]
901	Laurendecumallene A	*L. decumbens* [611]
902	–	*L. implicata* [91]
903	Obtusallene II	*L. chondrioides* [73], *L. obtusa* [679[a,c,d], 769]; Synthesis [768[e]]
904	Obtusallene VIII	*L. obtusa* [770]
905	Obtusallene IX	*L. obtusa* [770]
906	Obtusallene IV (Dactylallene)	*L. marilzae* [711], *L. obtusa* [769[a]], *A. dactylomela* [771[a,c,d]]; Synthesis [768[e]]
907	12-Epoxy-obtusallene IV	*L. marilzae* [711]
908	–	*L. marilzae* [711]
909	Obtusallene X	*L. marilzae* [711]
910	ObtusalleneVII	*L. obtusa* [770, 772[b]]
911	Obtusallene III	*L. chondrioides* [73], *L. obtusa* [679[a,c], 769]
912	Kasallene	*L. obtusa* [773]
913	Chondrioallene	*L. chondrioides* [73]
914	Obtusallene I	*L. obtusa* [679, 769, 774[a], 775[c,d], 776]
915	10-Bromo-obtusallene I	*L. obtusa* [769, 776[a]]
916	ObtusalleneVI	*L. chondrioides* [73], *L. obtusa* [770[a], 772[b]]
917	Obtusallene V	*L. chondrioides* [73], *L. obtusa* [770[a], 772[b,c]]
918	Marilzabicycloallene A	*L. marilzae* [777]
919	Marilzabicycloallene C	*L. marilzae* [777]
920	Marilzabicycloallene D	*L. marilzae* [777]
921	Marilzabicycloallene B	*L. marilzae* [777]
922	Poitediene	*L. poitei* [778]

(continued)

Table 4 (continued)

No.	Name	Source of Isolation/Synthesis
923	(*Z*)-Neolaurencenyne	*L. okamurai* [779[a]]; Synthesis [780[f]]
924	Neolaurencenyne	*L. composita* [31], *L. okamurai* [192, 204[a,f], 780]
925	(*Z*)-Laurencenyne	*L. composita* [31, 88], *L. nipponica* [138], *L. okamurai* [779[a]]; Synthesis [780[f], 781[f]]
926	Laurencenyne	*L. okamurai* [192, 204[a,f], 780], *L. composita* [31, 88], *A. punctata* [249]; Synthesis [781[f]]
927	(3*E*,6*Z*,9*Z*,12*E*)-Pentadeca-3,6,9,12-tetraen-1-yne	*L. majuscula* [416]
928	(3*E*,6*Z*,9*Z*,12*E*)-Pentadeca-3,6,9,12,14-pentaen-1-yne	*L. majuscula* [416]
929	(*E*)-12,13-Dihydrolaurediol	*L. nipponica* [782]
930	(*Z*)-12,13-Dihydrolaurediol	*L. nipponica* [782]
931	–	*L. pinnatifida* [689]
932	–	*L. pinnatifida* [689]
933	–	*L. pinnatifida* [689]
934	–	*L. pinnatifida* [689]
935	(3*Z*,9*Z*)-7-Chloro-6-hydroxy-12-oxo-pentadeca-3,9-dien-1-yne	*A. fasciata* [326]
936	(*Z*)-Adrienyne	*L. marilzae* [711]
937	(*E*)-Adrienyne	*L. marilzae* [711]
938	(*E*)-(12*Z*)-Laurediol	*L. nipponica* [782[a]], *L. okamurai* [109]
939	(*Z*)-(12*Z*)-Laurediol	*L. nipponica* [782]
940	–	*L. pinnatifida* [689]
941	(3*Z*,6*R*,7*R*,9*Z*,12*Z*)-6-Acetoxy-7-chloro-pentadeca-3,9,12-trien-1-yne	*L. pinnatifida* [689, 703[a,d]], *A. fasciata* [326]; Synthesis [783[b,g]]
942	(3*E*)-Laurediol	*L. nipponica* [738[a]], *L. obtusa* [593], *A. dactylomela* [178]; Synthesis [602[g], 784[g], 785[g], 786[g], 787[g]]
943	(3*Z*)-Laurediol	*L. nipponica* [738[a]], *L. obtusa* [593]; Synthesis [785[g]]
944	(3*Z*)-Acetyllaurediol	*L. nipponica* [138]
945	(3*E*)-Laurediol diacetate	*L. nipponica* [97, 670, 738[a]]; Synthesis [785[g]]
946	(3*Z*)-Laurediol diacetate	*L. nipponica* [138, 738[a]]; Synthesis [785[g]]
947	Prerogioloxepane	*L. microcladia* [667[d]]
948	(3*Z*,9*Z*,12*E*)-7-Acetoxy-6-chloro-pentadeca-3,9,12-trien-1-yne	*L. glandulifera* [607]

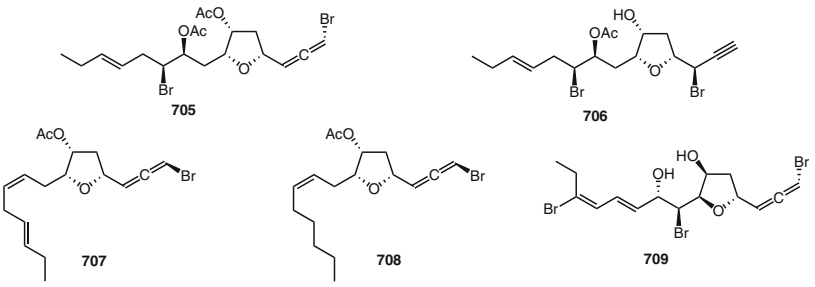
[a]The isolation and structure elucidation of this compound was reported for the first time
[b]The structure of this compound has been revised
[c]The structure of this compound or of a derivative has been confirmed by X-ray crystallographic analysis
[d]The absolute stereochemistry of this compound has been established
[e]Partial synthesis
[f]Stereoselective total synthesis
[g]Enantioselective total synthesis
[h]Formal synthesis

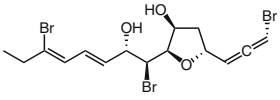
3.4.1 Acetogenins Containing a Five-Membered Cyclic Ether (Tetrahydrofuran) Ring

To date, the group of acetogenins containing five-membered cyclic ethers includes a total of 65 compounds (**705**–**769**) that have been isolated from *Laurencia* species or sea hares feeding on them. These can be roughly divided into four subgroups, namely: (1) those containing one tetrahydrofuran ring (**705**–**729**); (2) those containing two isolated tetrahydrofuran rings (**730**–**738**); (3) those containing two fused tetrahydrofuran rings (**739**–**757**); and (4) maneonenes and isomaneonenes containing three tetrahydrofuran rings (**758**–**769**).

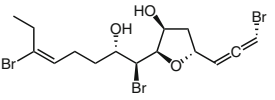
Acetogenins containing one tetrahydrofuran ring can feature either a 4,7-epoxy (**705**–**711**), a 6,9-epoxy (**712**–**720**), a 7,10-epoxy (**721**–**726**), a 9,12-epoxy (**727**), or a 10,13-epoxy (**728** and **729**) ring. The 4,7-epoxy acetogenins are characterized by either a bromoallene functionality (**705** and **707**–**711**) or a bromopropargylic unit (**706**), the 6,9-epoxy acetogenins possess either a (*E*)- or (*Z*)-enyne moiety (**712**–**716**) or a bromoallene functionality (**717**–**720**), whereas the 7,10-epoxy, the 9,12-epoxy and the 10,13-epoxy acetogenins exhibit a (*E*)- or (*Z*)-enyne moiety (**721**–**729**). Acetogenins containing two isolated tetrahydrofuran rings can either possess a bis(tetrahydrofuran-2-yl)methane (**730** and **731**) or a 2,2′-bis-tetrahydrofuran (**732**–**738**) core. The 2,2′-bis-tetrahydrofuran acetogenins (**732**–**738**) display a (*E*)- or (*Z*)-enyne terminus, while the bis(tetrahydrofuran-2-yl)methane acetogenins possess either a bromopropargylic (**730**) or a bromoallenic (**731**) unit. It is worth noting that the structures of elatenyne (**735**), isolated from *Laurencia elata* and *Laurencia decumbens* [196, 611], laurendecumbenyne B (**733**), isolated from *L. decumbens* [611], and compound **738**, obtained from *Laurencia majuscula* [416], were originally determined to contain a 2,7-dioxabicyclo[4.4.0]decane core. The structure of elatenyne (**735**) attracted the attention of many research groups, who, utilizing chemical and computational methods, finally succeeded in synthesizing the molecule corresponding to the spectroscopic data of the natural product, and revising the proposed structure to that of a 2,2′-bis-tetrahydrofuran derivative. However, the absolute stereochemistry is still unknown [221, 613, 615–618]. A similar revision was made to the structure of laurendecumbenyne B (**733**), which was established only on the basis of comparison of NMR data with those originally assigned for **735** [612]. Based on the same rationale, the proposed structure for **738** was also revised, albeit not yet confirmed by total synthesis [615]. Acetogenins containing two fused tetrahydrofuran rings can be differentiated into those with either a 2,6-dioxabicyclo[3.3.0]octane (**739**–**752**) or a 2,5-dioxabicyclo[2.2.1]heptane (**753**–**757**) substructure. The former can be further classified into 4,7:6,9-bisepoxy acetogenins featuring either a bromoallene functionality (**739**–**746** and **749**) or a bromopropargylic terminus (**747** and **748**) and to 7,10:9,12-bisepoxy acetogenins possessing a (*E*)- or (*Z*)-enyne moiety (**750**–**752**). All five 2,5-dioxabicyclo[2.2.1]heptane acetogenins exhibit a (*E*)- or (*Z*)-enyne terminus (**753**–**757**). Compounds **747**–**749** contain an additional

tetrahydrofuran ring derived from etherification between C-9 and C-12, thus forming a bicyclic ketal motif. Maneonenes (**758–766**) and isomaneonenes (**767–769**) contain three tetrahydrofuran rings and all feature a (*E*)- or (*Z*)-enyne terminus. However, their structures are unique among all reported C_{15} acetogenins in that the carbon chain has cyclized back on itself to create a monocarbocyclic (through the formation of bond between C-6 and C-11) and a bicarbocyclic (through the formation of bonds between C-5 and C-13, as well as between C-6 and C-11) framework, respectively. Maneonenes bear a chlorine atom at C-5 and a bromine atom at C-13, whereas isomaneonenes bear two bromine atoms at C-12 and C-13. The first members of these series, namely, (*Z*)-maneonenes A (**758**), B (**762**) and C (**760**), (*E*)-maneonene B (**765**), and isomaneonenes A (**767**) and B (**768**), were originally reported from a Hawaiian *Laurencia nidifica* population by the group of Erickson in 1976 [643, 644, 647]. The total synthesis of racemic **758**, **762** and **765** by Holmes et al. contributed to the structure elucidation of the series [646, 648]. In 2011, (12*E*)-(*Z*)-maneonene E (**761**) was reported twice by the same group from *L. papillosa* [101] and *L. obtusa* [645], both collected off the Saudi Arabia Red Sea coast at Jeddah, depicting though a different configuration at C-6 in the two reports. Moreover, in their second report, the authors also describe the isolation of (12*Z*)-*cis*-maneonene D (**764**) and (12*Z*)-(*Z*)-maneonene C (**766**), along with that of the known (*Z*)-maneonene A, for which, however, they incorrectly depicted the structure of the 6-*endo* isomer that is actually (*Z*)-maneonene C [645]. In agreement with the comment by Blunt and colleagues in 2013 [9] concerning the proposed structures, one has to admit that they are not very credible. Specifically, (12*Z*)-(*Z*)-maneonene D should have the same structure as either lembyne A (**763**) or (12*Z*)-(*Z*)-maneonene C, the semisynthetic product obtained after treatment of (*Z*)-maneonene C (**760**) with *p*-toluenesulfonic acid, which are thought to be C-5 epimers. Nonetheless, the NMR data of (12*Z*)-(*Z*)-maneonene D do not match either. In a similar manner, the structure depicted for (12*E*)-(*Z*)-maneonene E was, in fact, that of the known *cis*-maneonene A (**758**). Should (12*E*)-(*Z*)-maneonene E be the 6-*endo* isomer, then its NMR data do not match those reported for the C-5 epimers (12*E*)-lembyne (**759**) or *cis*-maneonene C (**760**).

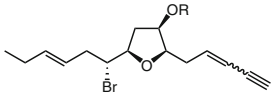




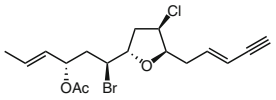
710



711



712 (3*E*), R = H
713 (3*Z*), R = H
714 (3*E*), R = Ac
715 (3*Z*), R = Ac



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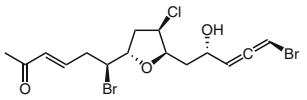

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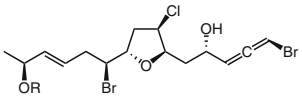
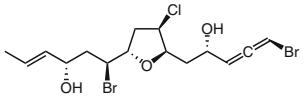


718 R = H
719 R = Me



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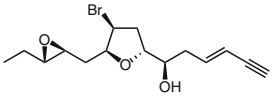

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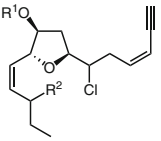
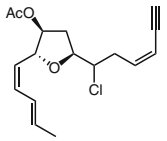


722 R^1 = Ac, R^2 = Cl
723 R^1 = H, R^2 = OH



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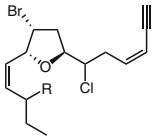
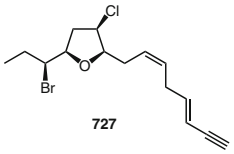


725 R = Br
726 R = OMe



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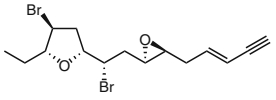

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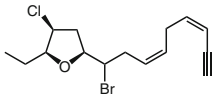

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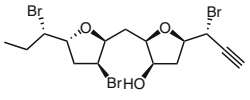

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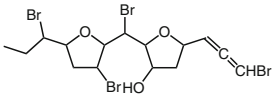

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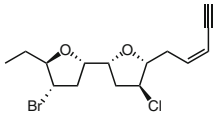

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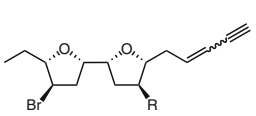
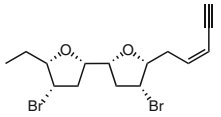


733 (3*Z*), R = Cl
734 (3*E*), R = Br



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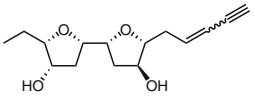
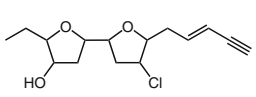


736 (3*E*)
737 (3*Z*)



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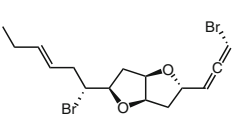

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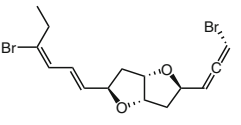

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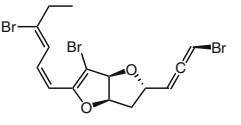

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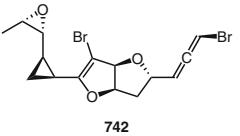

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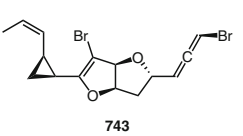

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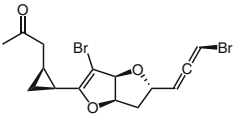

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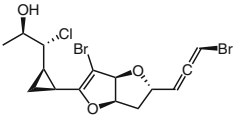

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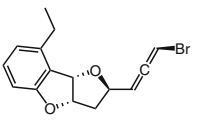

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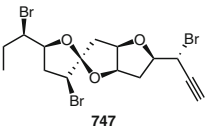

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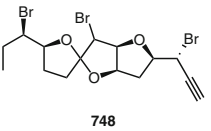

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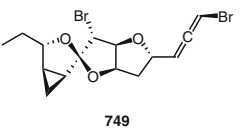

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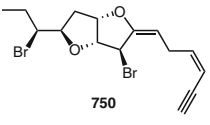

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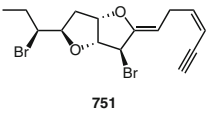

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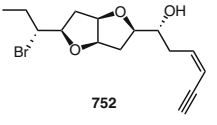

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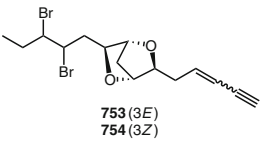
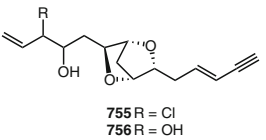
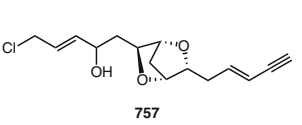


753 (3*E*)
754 (3*Z*)



755 R = Cl
756 R = OH



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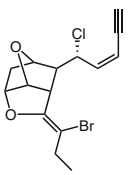

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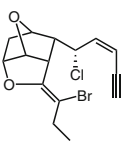

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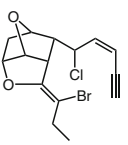

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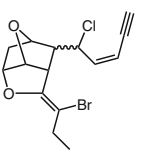

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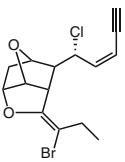

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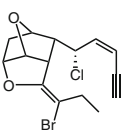

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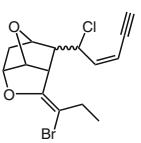

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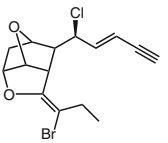

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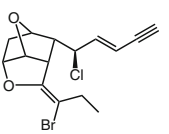

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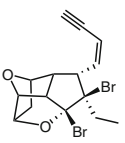

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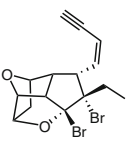

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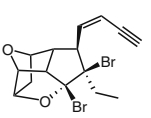
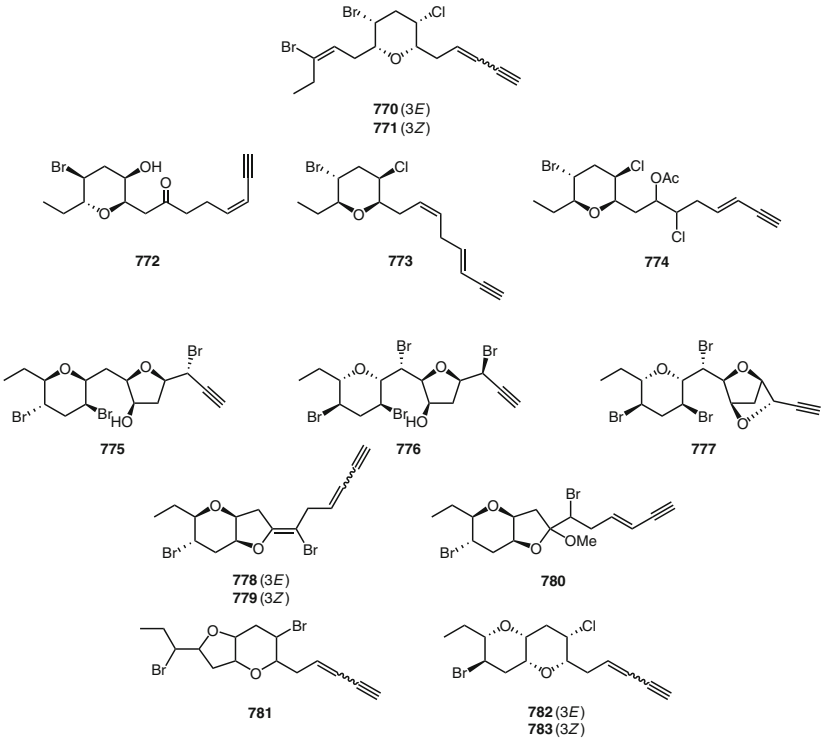


769

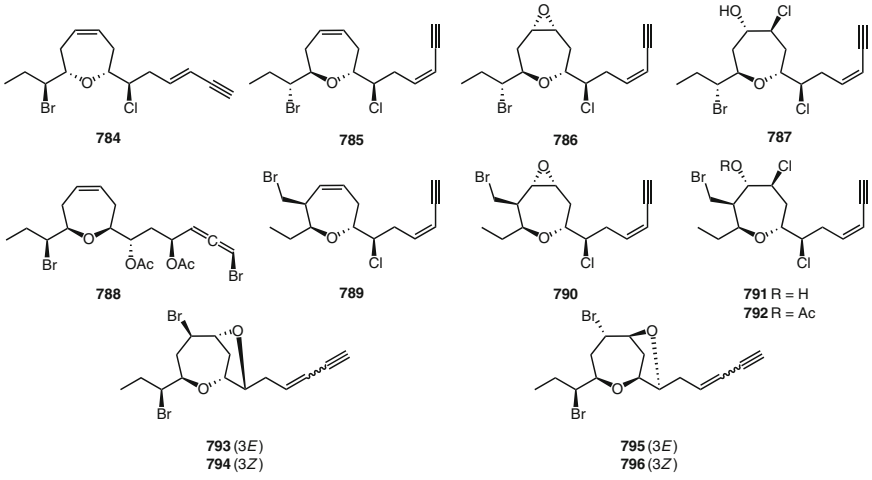
3.4.2 Acetogenins Containing a Six-Membered Cyclic Ether (Tetrahydropyran) Ring

The group of acetogenins containing six-membered cyclic ethers so far is rather small, including only 14 compounds (**770**–**783**) that have been reported from the genus *Laurencia* or mollusks feeding on these algae. These can be roughly divided into four subgroups, namely: (1) those containing one tetrahydropyran ring (**770**–**774**); (2) those containing isolated tetrahydrofuran and tetrahydropyran rings (**775**–**777**); (3) those containing fused tetrahydrofuran and tetrahydropyran rings (**778**–**781**); and (4) those containing two fused tetrahydropyran rings (**782** and **783**). Acetogenins containing one tetrahydropyran ring can feature either a 6,10-epoxy (**770** and **771**) or a 9,13-epoxy (**772**–**774**) ring. Nonetheless, all five display a (*E*)- or (*Z*)-enyne terminus. Acetogenins containing isolated tetrahydrofuran and tetrahydropyran rings present either a bromopropargylic functionality (**775** and **776**) or a terminal acetylene (**777**), but in all three cases isolated thus far C-6 was oxygenated and C-10 and C-12 were brominated. Acetogenins containing fused tetrahydrofuran and tetrahydropyran rings incorporate the 2,7-dioxabicyclo[4.3.0]nonane system in their structures through formation of either a 7,10:9,13-bisepoxy (**778**–**780**) or a 6,10:9,12-bisepoxy (**781**) core. Nonetheless, all four compounds are characterized by a (*E*)- or (*Z*)-enyne moiety. (3*E*)-Dactylomelyne (**782**) and its geometrical isomer **783**, isolated from the digestive glands of the sea hare *A. dactylomela* [372], are the only two metabolites featuring a 2,7-dioxabicyclo[4.4.0]decane substructure with a (*E*)- and (*Z*)-enyne terminus, respectively. Their structures have been secured by means of chemical synthesis [658, 659].



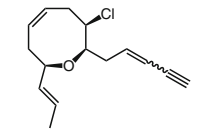
3.4.3 Acetogenins Containing a Seven-Membered Cyclic Ether (Oxepane) Ring

To date, only 13 acetogenins containing seven-membered cyclic ethers (**784**–**796**) have been obtained from *Laurencia* species or their grazers. Their oxepane ring is formed in all cases by etherification between C-7 and C-12. Among them, three subgroups can be discerned, namely: (1) monocyclic acetogenins with a 1-bromopropanyl side chain attached to C-12 (**784**–**788**); (2) branched monocyclic acetogenins with bromomethyl and ethyl side chains attached to C-11 and C-12, respectively (**789**–**792**); and (3) acetogenins with a 1-bromopropanyl side chain attached to C-12 featuring a second ether ring formed between C-6 and C-9 (**793**–**796**). All these compounds display a (*E*)- or (*Z*)-enyne terminus, with the exception of **788** that bears a bromoallene moiety. While metabolites **784**–**788** and **793**–**796** bear a bromine atom at C-13, the branched acetogenins **789**–**792** have a Br substitution at C-15. Furthermore, compounds **784**–**787** and **789**–**792** have a chlorine atom at C-6, whereas the 6,9:7,12-bisepoxy acetogenins **793**–**796** display a second Br substitution at C-10. Rogiolenynes A (**790**), B (**791**), C (**792**), and D (**789**) can be singled out from all the other C_{15} acetogenins isolated to date in that they are branched instead of having a straight C_{15} chain. These were reported from *L. microcladia* and the sponge *Spongia zimocca*, co-occurring in the same small area of the Mediterranean Sea off the area Il Rogiolo, south of Livorno [163, 671, 672]. Guella and Pietra suggested that rogiolenyne A (**790**) could be transferred from the red alga to *S. zimocca* where it undergoes epoxide opening by Cl^- to give rogiolenyne B (**791**), followed by acetylation to give rogiolenyne C (**792**) [672].

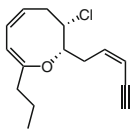


3.4.4 Acetogenins Containing an Eight-Membered Cyclic Ether (Oxocane) Ring

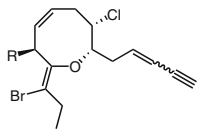
The group of acetogenins containing eight-membered cyclic ethers is by far the largest group among all acetogenins isolated from red algae of the genus *Laurencia* or sea hares consuming them, encompassing a total of 93 derivatives (**797**–**889**). These can be roughly divided into six subgroups, namely: (1) those with a 6,12-epoxy, also known as laurenan-type acetogenins (**797**–**834**); (2) those with a 7,13-epoxy, also known as lauthisan-type acetogenins (**835**–**851**); (3) those with a 4,7:6,12-bisepoxy (**852**–**862**); (4) those with a 6,12-epoxy and a second epoxy system between C-7 and either C-9, C-10 or C-11 (**863**–**869**); (5) those with a 7,13-epoxy and a second epoxy system between C-6 and either C-9 or C-10 (**870**–**886**); and (6) those with a 4,10:9,13-bisepoxy (**887**–**889**) functionality. All laurenan-type acetogenins display a (*E*)- or (*Z*)-enyne terminus, with the exception of **831**–**834** that bear a bromoallene moiety. The majority of these compounds have a chlorine atom at C-7 and frequently they have a bromine atom at C-13. Similarly, all lauthisan-type acetogenins feature a (*E*)- or (*Z*)-enyne terminus. However, they often have a Cl substitution at C-6 and a Br substitution at C-12. All acetogenins possessing a 4,7:6,12-bisepoxy core bear a bromoallene functionality as terminus, with the exception of **859** and **860** having a bromopropargylic moiety and desepilaurallene (**862**) that is a C_{12} derivative. In all cases, they exhibit a Br substitution at C-13. Among them, aplyparvunin (**861**), obtained from a Japanese *A. parvula* sample, possesses a cyclopropane ring fused with the eight-membered ether [291]. Its structure was determined by single-crystal X-ray diffraction analysis. Both acetogenins with a 6,12-epoxy and a second epoxy system between C-7 and either C-9, C-10, or C-11, as well as those with a 7,13-epoxy and a second epoxy system between C-6 and either C-9 or C-10 possess a (*E*)- or (*Z*)-enyne terminus, apart from the C_{12} derivative okamuragenin (**869**).



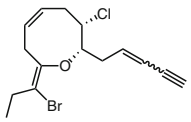
797 (3*E*)
798 (3*Z*)



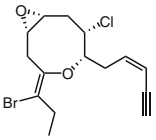
799



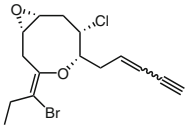
800 (3*E*), R = H
801 (3*Z*), R = H
802 (3*E*), R = OH
803 (3*Z*), R = OH



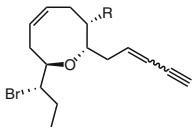
804 (3*E*)
805 (3*Z*)



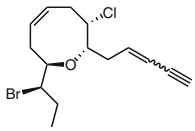
806



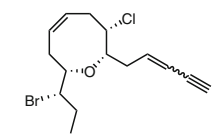
807 (3*E*)
808 (3*Z*)



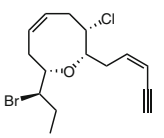
809 (3*E*), R = Cl
810 (3*Z*), R = Cl
811 (3*Z*), R = OH



812 (3*E*)
813 (3*Z*)



814 (3*E*)
815 (3*Z*)



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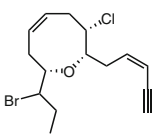

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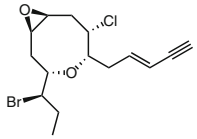
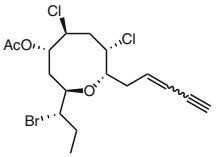
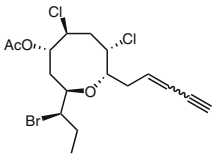


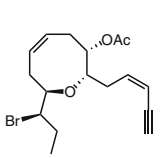
818



819 (3*E*)
820 (3*Z*)



821 (3*E*)
822 (3*Z*)



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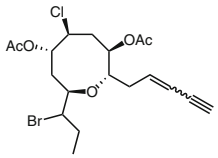
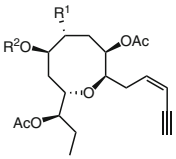
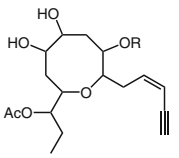


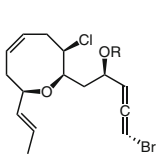
824 (3*E*)
825 (3*Z*)



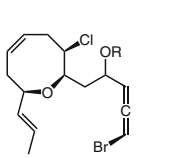
826 R^1 = Cl, R^2 = Ac
827 R^1 = OAc, R^2 = H
828 R^1 = OH, R^2 = Ac



829 R = H
830 R = Ac

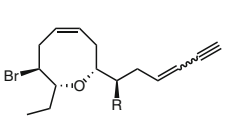


831 R = H
832 R = Ac

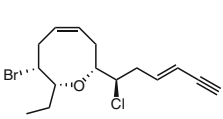


833 R = H
834 R = Ac

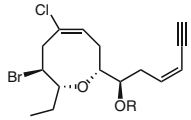
All members of the former subgroup, including **869**, have a Br substitution at C-13, whereas most members of the latter subgroup bear a Br substitution at C-12. The efficient isomerization of (*Z*)-enyne systems to (*E*)-enyne was exemplified by the chemical conversion of laureatin (**864**) to (*E*)-isolaureatin (**865**) [788]. Microcladallenes A (**887**), B (**889**), and C (**888**), initially isolated from *L. microcladia* collected off the French coast at Cape Ferrat [750], are the only examples of acetogenins incorporating a 4,10:9,13-bisepoxy core in their structures. All three bear a bromoallene moiety as the terminus and a bromine atom at C-12.



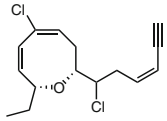
835 (3*E*), R = OH
836 (3*E*), R = OAc
837 (3*Z*), R = Cl



838



839 R = H
840 R = Ac



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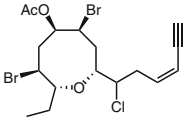

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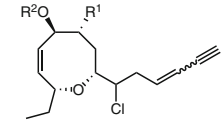
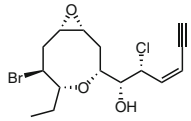


843 (3*E*), R^1 = OH, R^2 = H
844 (3*Z*), R^1 = OH, R^2 = H
845 (3*Z*), R^1 = OH, R^2 = Ac
846 (3*Z*), R^1 = OAc, R^2 = H
847 (3*Z*), R^1 = OAc, R^2 = Ac
848 (3*Z*), R^1 = Br, R^2 = Ac



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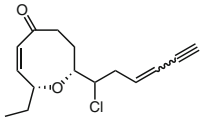
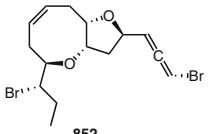


850 (3*E*)
851 (3*Z*)



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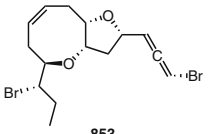

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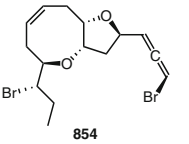

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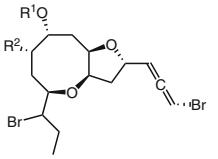
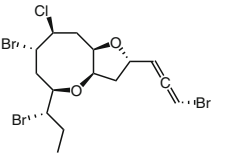


855 R^1 = H, R^2 = Br
856 R^1 = Ac, R^2 = Br
857 R^1 = H, R^2 = OH



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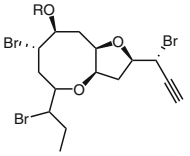
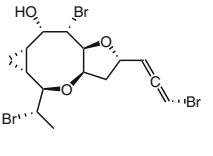
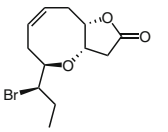


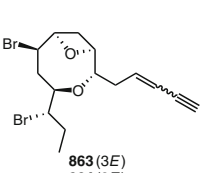
859 R = H
860 R = Ac



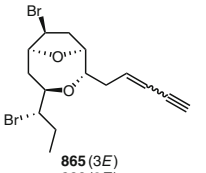
861



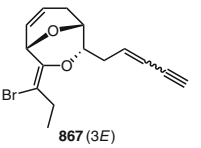
862



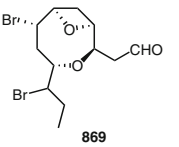
863 (3*E*)
864 (3*Z*)



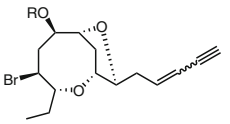
865 (3*E*)
866 (3*Z*)



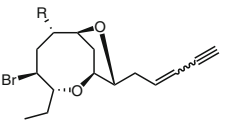
867 (3*E*)
868 (3*Z*)



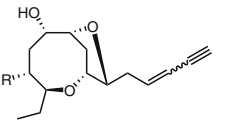
869



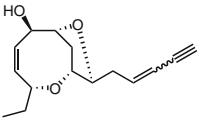
870 (3*E*), R = H
871 (3*Z*), R = H
872 (3*E*), R = Ac
873 (3*Z*), R = Ac



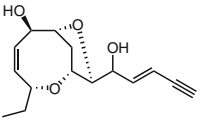
874 (3*E*), R = Cl
875 (3*Z*), R = Cl
876 (3*E*), R = Br
877 (3*Z*), R = Br



878 (3*E*), R = OH
879 (3*Z*), R = OH
880 (3*E*), R = Br
881 (3*Z*), R = Br



882 (3*E*)
883 (3*Z*)



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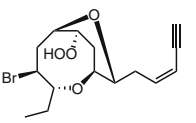

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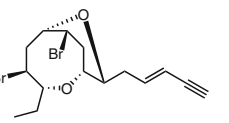

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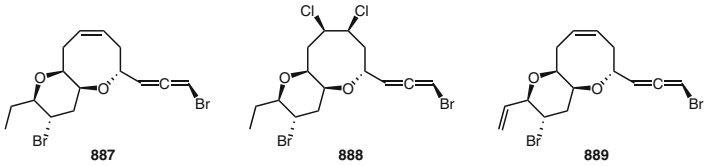
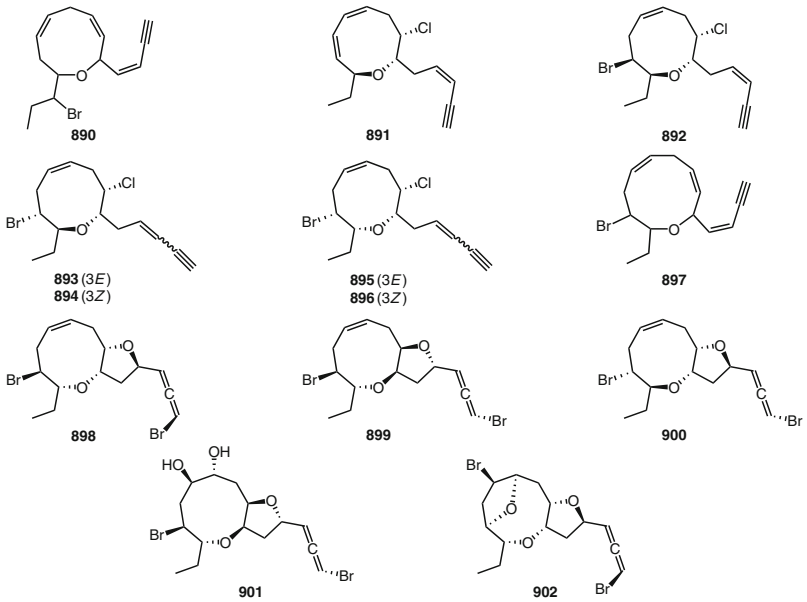


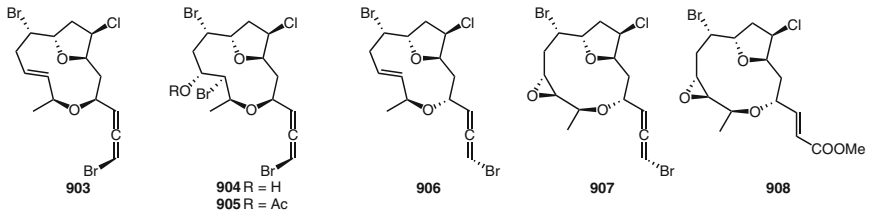
3.4.5 Acetogenins Containing a Nine- or Ten-Membered Cyclic Ether Ring

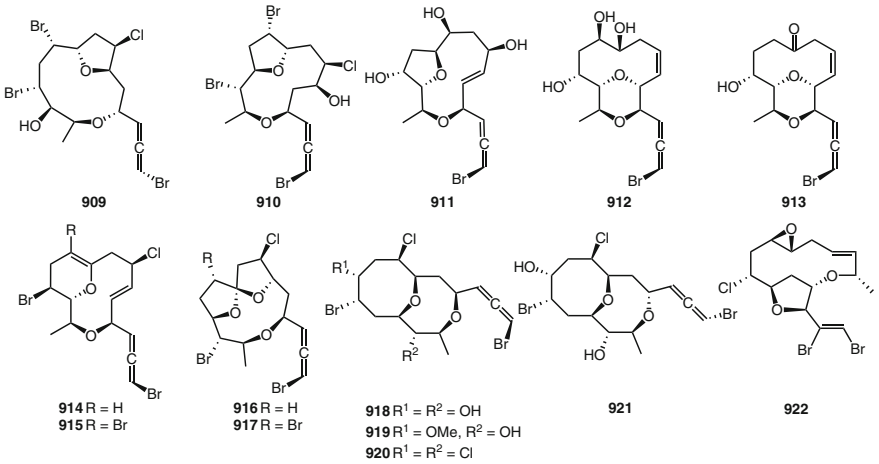
So far, twelve acetogenins containing a nine-membered cyclic ether unit (**890–896** and **898–902**) and only one containing a ten-membered cyclic ether (**897**) have been reported from *Laurencia* species and/or gastropods feeding on them. Among the nine-membered acetogenins, three subgroups can be discriminated, namely: (1) those containing a 5,12-epoxy ring (**890**); (2) those containing a 6,13-epoxy ring (**891–896**); and (3) those containing a 4,7:6,13-bisepoxy system (**898–902**). The first two subgroups feature a (*E*)- or (*Z*)-enyne terminus, while the third subgroup is characterized by a bromoallene functionality. With the exception of **890**, **891**, and **902**, all derivatives have a bromine atom at C-12, whereas compounds **891–896** possess a chlorine atom at C-7 as well. Noteworthy is obtusenyne (**892**), the first nine-membered acetogenin to be isolated, which was obtained from two Mediterranean samples of *Laurencia obtusa* almost simultaneously by two different research groups [730, 754]. Its first total synthesis was achieved in 1999 by the group of Murai [757], while three more synthetic protocols have also been reported [758–760]. Metabolite **897**, for which the relative configurations of its asymmetric centers have not been assigned yet, was isolated from *Laurencia implicata* collected in Florence Bay, Magnetic Island, and is the sole representative of the ten-membered acetogenins [415].



3.4.6 Acetogenins Containing a Twelve-Membered Cyclic Ether Ring

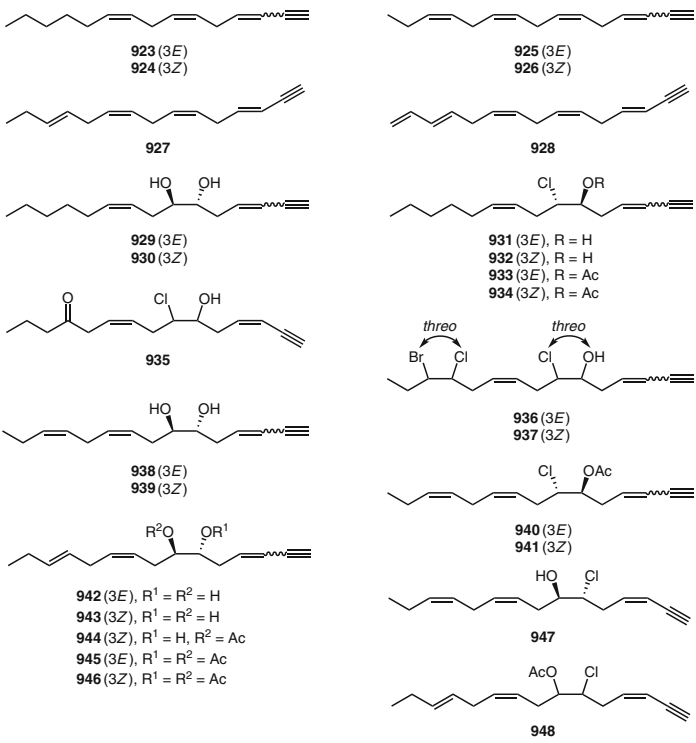
The group of acetogenins containing 12-membered cyclic ethers includes 20 compounds (**903–922**) that have been reported to date from the genus *Laurencia* or mollusks feeding on these algae. Metabolites **903–917**, known as obtusallenes, are characterized by a 4,14-epoxy core, a bromoallene functionality as one terminus at C-4 (with the exception of **908**) and a methyl group as the second terminus at C-14, and all of them incorporate one or two more ether rings into their structures. Among these, **903–909** feature a 6,9-epoxy ring, **910** presents a 9,12-epoxy ring, **911** contains a 10,13-epoxy ring, **912** and **913** have a 5,13-epoxy ring, and **914** and **915** display a 9,13-epoxy ring. Obtusallenes VI (**916**) and V (**917**) have two tetrahydrofuran rings as a result of etherification between C-6 and C-9, as well as between C-9 and C-12, thus leading to the formation of a *spiro*-ketal motif. The first member of this class, obtusallene I (**914**), was reported from a *Laurencia obtusa* population collected in Gökçeada Island, Aegean Sea, and its structure was determined by means of single crystal X-ray diffraction analysis [774, 775]. Obtusallene IV (**906**), also known as dactylallene, was isolated simultaneously from *A. dactylomela* from the Canary Islands and *L. obtusa* from Turkey [769, 771]. In the original report on the isolation of obtusallenes V (**917**), VI (**916**), and VII (**910**) from *L. obtusa*, the bromine and chlorine atoms were placed at C-7 and C-13, respectively, on the basis of analysis of the NMR spectroscopic data [770]. Several extensive investigations concerning the biosynthesis of these natural products were undertaken by Braddock and co-workers [768, 789, 790] that finally led to the reassignment of the position of the halogens at C-7 and C-13 on the basis of a ^{13}C NMR chlorine induced isotopic shift, which was further confirmed by X-ray crystallographic analysis [772]. The latter study also predicted the existence of compounds with a 4,13-dioxabicyclo[5.5.1]tridecane ring system [772]. Subsequently, metabolites with this framework were isolated from *Laurencia marilzae* in 2011 and designated as marilzabicycloallenes A (**918**), B (**921**), C (**919**), and D (**920**) [777]. Poitediene (**922**), obtained from *Laurencia poitei* collected at Boca Grande Key, Florida [778], is a unique tricyclic acetogenin featuring a *cis*-dibromo-olefin functionality as terminus. Its structure, including absolute stereochemistry, was established on the basis of X-ray diffraction analysis.





3.4.7 Linear Acetogenins

Besides the cyclic ether-containing acetogenins, which constitute the majority of acetogenins isolated so far from *Laurencia* species and their grazers, 26 linear acetogenins (**923–948**) have been reported to date. All of them feature a (*E*)- or (*Z*)-enyne terminus, while most are characterized by multiple double bonds, but in all cases by a Δ^9 functionality with (*Z*) configuration. Apart from compounds **923–928**, which do not have any heteroatoms in their structures, all the others bear oxygen and/or chlorine substitutions at C-6 and C-7. In particular, compounds **929**, **930**, **938**, **939**, and **942–946** are oxygenated at both C-6 and C-7, while **931–937**, **940**, and **941** are oxygenated at C-6 and chlorinated at C-7. Less frequently, chlorination at C-6 and oxygenation at C-7 is observed, as in the case of **947** and **948**. Metabolites **923–926**, found in Japanese populations of *L. okamurai* [192, 204, 779, 780], are considered to be biosynthetic precursors of various C_{15} non-terpenoid metabolites found in *Laurencia* species. Their synthesis was reported by the Yamada group in 1981 and 1986 [204, 780], while another synthesis of laurencenyne (**926**) and its (*E*)-isomer **925** was later achieved by Holmeide et al. starting from eicosapentaenoic acid [781]. A Japanese *L. nipponica* population afforded a mixture of optical isomers ((6*R*,7*R*) and (6*S*,7*S*)) of (*E*)- (**942**) and (*Z*)-laurediol (**943**), along with their diacetates **945** and **946**, respectively [738].



Biosynthesis studies were undertaken to understand the role of these compounds in the production of medium-sized ring ethers. The enzymatic syntheses of laurencin (**836**) (a lauthisan-type eight-membered acetogenin) from (3*E*,6*R*,7*R*)-laurediol and of prelaureatin (**811**) and laureatin (**864**) (laurenan-type eight-membered acetogenins) from (3*Z*,6*S*,7*S*)-laurediol, have been accomplished [694–697]. (*E*)-Adrienyne (**936**) and its (*Z*)-isomer **937** were found in *L. marilzae* from the Canary Islands. The relative configurations of the stereocenters C-6, C-7, C-12, and C-13 were determined using a configurational analysis based on coupling constants [711].

3.5 Indoles

To date, 35 indoles (**949**–**983**, Table 5) have been reported from *Laurencia* species and/or gastropods feeding on them.

All of these compounds contain at least two bromine atoms, with the exception of **972**, which is not brominated, and **973**, which is monobrominated. Indoles can be divided into three subclasses, namely: (1) monoindoles (**949**–**973**); (2) bisindoles

Table 5 Indoles from *Laurencia* spp.

No.	Name	Source of isolation/synthesis
949	*N*-Methyl-3,5-dibromo-indole	*L. similis* [791]
950	3,5,6-Tribromo-indole	*L. similis* [118, 176[a], 431, 792], *C. papillosus* [342], *A. dactylomela* [118]
951	2.3.6-Tribromo-indole	*L. similis* [176[a]]
952	2,3,5,6-Tetrabromo-indole	*L. brongniartii* [793[a]], *L. complanata* [433], *L. saitoi* [794], *L. similis* [118, 176, 431, 432, 792, 795, 796], *C. papillosus* [342], *A. dactylomela* [118, 277]; Synthesis [797]
953	2,4,6-Tribromo-indole	*L. brongniartii* [798]
954	2,3,4,6-Tetrabromo-indole	*L. brongniartii* [798]
955	3-Methylthio-2,4,6-tribromo-indole	*L. brongniartii* [798, 799]
956	3-Methylsulfinyl-2,4,6-tribromo-indole	*L. brongniartii* [799]
957	4,6-Dibromo-2-methylthio-indole	*L. brongniartii* [798[a], 799]
958	4,6-Dibromo-2,3-di(methylthio)indole	*L. brongniartii* [798, 799]
959	Itomanindole B	*L. brongniartii* [798, 800[a]]
960	Itomanindole A	*L. brongniartii* [798–800[a]]
961	4,6-Dibromo-2,3-di(methylsulfinyl)-indole	*L. brongniartii* [799]
962	3-Methylthio-2,4,5,6-tetrabromo-indole	*L. brongniartii* [798, 799]
963	2,3-Di(methylthio)-4,5,6-tribromo-indole	*L. brongniartii* [798, 799]
964	4,5,6-Tribromo-2-methyl-sulfinylindole	*L. brongniartii* [801]
965	2-Methylsulfinyl-3-methylthio-4,5,6-tribromo-indole	*L. brongniartii* [799]
966	*N*-Methyl-2,3,6-tribromo-indole	*L. brongniartii* [793[a]]; Synthesis [797, 802]
967	*N*-Methyl-2,3,4,6-tetrabromo-indole	*L. decumbens* [160]
968	*N*-Methyl-2,5-dibromo-indole	*L. similis* [431]
969	*N*-Methyl-2,3,5-tribromo-indole	*L. brongniartii* [793[a]], *L. complanata* [433], *L. decumbens* [160], *L. similis* [176, 431, 432, 792], *Laurencia* sp. [187], *A. dactylomela* [156, 270, 277]; Synthesis [797]
970	*N*-Methyl-3,5,6-tribromo-indole	*L. similis* [176[a]]
971	*N*-Methyl-2,3,5,6-tetrabromo-indole	*L. brongniartii* [793[a]], *L. complanata* [433], *L. decumbens* [160], *L. similis* [432, 792, 795, 796], *C. papillosus* [342], *A. dactylomela* [118, 277]; Synthesis [797, 802]
972	Indolyl-3-carbaldehyde	*L. tristicha* [290]
973	*N*-Methyl-5-bromo-1,3-dihydro-indole-2-one	*L. similis* [792]
974	3,3′-bis-(2,5,6-Tribromo)indole	*L. similis* [791[a], 792]
975	3,3′-bis-(4,6-Dibromo-2-methylthio)indole	*L. brongniartii* [798[a], 799]
976	3,3′-bis-(2′-Methylsulfinyl-2-methylthio-4,6,4′,6′-tetrabromo)indole	*L. brongniartii* [799]
977	3,3′-bis-(4,6-Dibromo-2-methylsulfinyl) indole	*L. brongniartii* [799]
978	2,4,4′,6,6′-Pentabromo-2′-(methylsulfanyl)-1*H*,1′*H*-3,3′-bisindole	*L. brongniartii* [803]

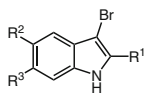
(continued)

Table 5 (continued)

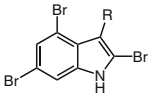
No.	Name	Source of isolation/synthesis
979	2,4,4′,6,6′-Pentabromo-2′,3-bis (methylsulfanyl)-1′*H*-1,3′-bisindole	*L. brongniartii* [803]
980	2,4,4′,5′,6,6′-Hexabromo-2′,3-bis (methylsulfanyl)-1′*H*-1,3′-bisindole	*L. brongniartii* [803]
981	2,4,4′,5,6,6′-Hexabromo-2′,3-bis (methylsulfanyl)-1′*H*-1,3′-bisindole	*L. brongniartii* [803]
982	2,4,4′,5,5′,6,6′-Heptabromo-2′,3-bis (methylsulfanyl)-1′*H*-1,3′-bisindole	*L. brongniartii* [803]
983	Similisine A	*L. similis* [792[b]]
***ent*-983**	Similisine B	*L. similis* [792[b]]

[a]The isolation and structure elucidation of this compound was reported for the first time
[b]The absolute stereochemistry of this compound has been established

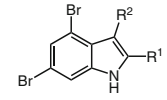
(**974–982**); and (3) *spiro*-trisindoles (**983**). Among these, monoindoles **955–965** and bisindoles **975–982** contain sulfur in their structures. Similisines A (**983**) and B (***ent*-983**), for which the structures and absolute configurations were determined by comprehensive analysis of their spectroscopic data, computer modeling and comparison of their experimental and theoretically calculated electronic circular dichroism (ECD) spectra, are a pair of enantiomeric polybrominated *spiro*-trisindoles isolated in 2013 from *L. similis* collected in the South China Sea [792].



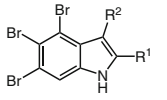
949 $R^1 = R^3 = H$, $R^2 = Br$
950 $R^1 = H$, $R^2 = R^3 = Br$
951 $R^1 = R^3 = Br$, $R^2 = H$
952 $R^1 = R^2 = R^3 = Br$



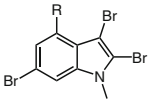
953 R = H
954 R = Br
955 R = SMe
956 R = SOMe



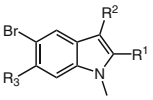
957 R^1 = SMe, R^2 = H
958 $R^1 = R^2$ = SMe
959 R^1 = SMe, R^2 = SOMe
960 R^1 = SOMe, R^2 = SMe
961 $R^1 = R^2$ = SOMe



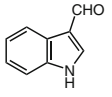
962 R^1 = Br, R^2 = SMe
963 $R^1 = R^2$ = SMe
964 R^1 = SOMe, R^2 = H
965 R^1 = SOMe, R^2 = SMe



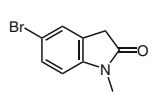
966 R = H
967 R = Br



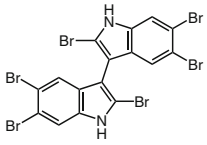
968 R^1 = Br, $R^2 = R^3 = H$
969 $R^1 = R^2$ = Br, $R^3 = H$
970 $R^1 = H$, $R^2 = R^3$ = Br
971 $R^1 = R^2 = R^3$ = Br



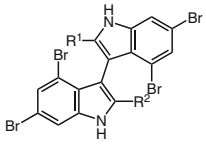
972



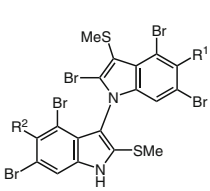
973



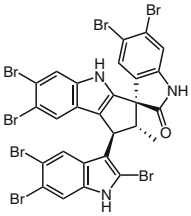
974



975 $R^1 = R^2$ = SMe
976 R^1 = SOMe, R^2 = SMe
977 $R^1 = R^2$ = SOMe
978 R^1 = Br, R^2 = SMe



979 $R^1 = R^2 = H$
980 $R^1 = H$, R^2 = Br
981 R^1 = Br, $R^2 = H$
982 $R^1 = R^2$ = Br



983

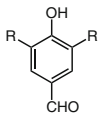
3.6 Aromatic Compounds

Only nine aromatic compounds (**984–992**, Table 6) have been isolated so far from red algae of the genus *Laurencia*.

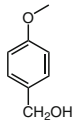
These include four simple monoaryl derivatives (**984–987**), two diaryl derivatives (**988** and **989**), and three naphthalene derivatives (**990–992**). With the exception of **984**, **986**, and **987**, all other compounds are brominated. According to Blunt et al. the structures of **990–992** should be re-examined due to inconsistencies in the published NMR data [9].

Table 6 Aromatic compounds from *Laurencia* spp.

No.	Name	Source of isolation/synthesis
984	4-Hydroxy-benzaldehyde	*L. papillosa* [804], *L. tristicha* [290], *A. dactylomela* [277]
985	–	*L. nipponica* [805]
986	4-Methoxy-benzyl alcohol	*L. papillosa* [804]
987	3-Hydroxy-4-methyl-acetophenone	*L. chilensis* [806]
988	3′,5′,6′,6-Tetrabromo-2,4-dimethyldiphenyl ether	*L. similis* [807]
989	2′,5′,6′,5,6-Pentabromo-3′,4′,3,4-tetramethoxybenzophenone	*L. similis* [807]
990	2,5,6-Tribromo-3-bromoamino-7-bromomethylnaphthalene	*L. similis* [807]
991	2,5,8-Tribromo-3-bromoamino-7-bromomethylnaphthalene	*L. similis* [807]
992	1,2,5-Tribromo-3-bromoamino-7-bromomethylnaphthalene	*L. similis* [807]



984 R = H
985 R = Br



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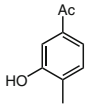

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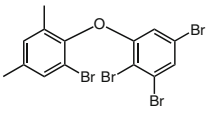

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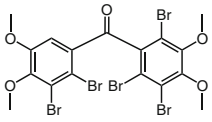

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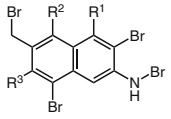


990 $R^1 = R^2 = H$, $R^3 = Br$
991 $R^1 = R^3 = H$, $R^2 = Br$
992 $R^1 = Br$, $R^2 = R^3 = H$

3.7 Steroids

A total of 17 steroids (**993**–**1009**, Table 7) have been identified to date from species of the genus *Laurencia*.

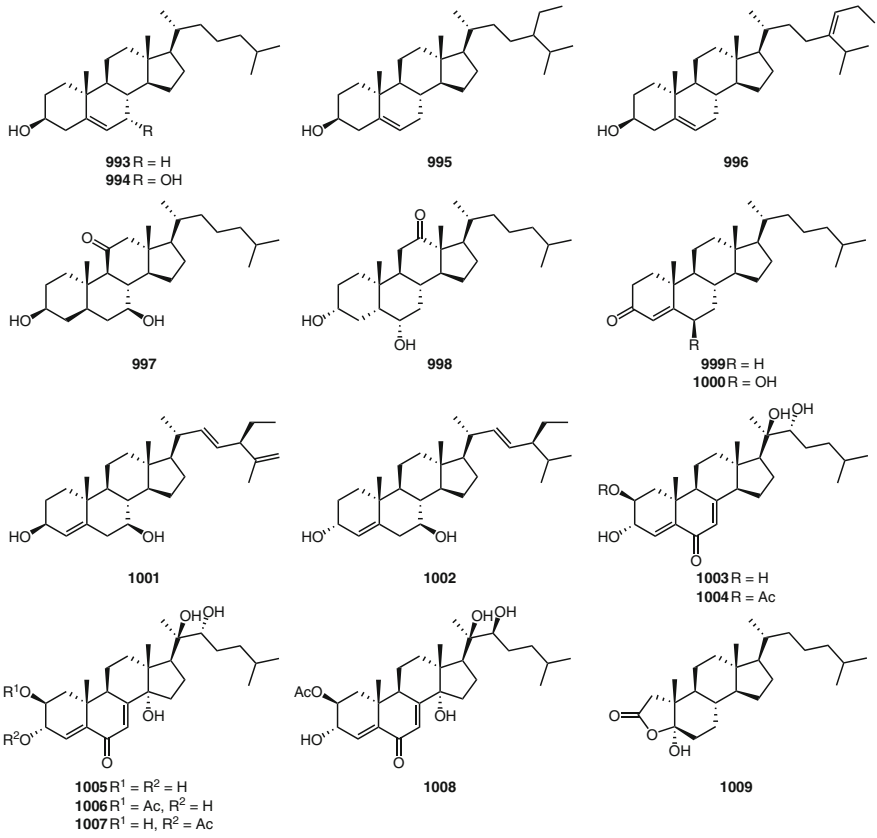
Without exception, all steroids isolated thus far from *Laurencia* species are non-halogenated. Among them, 2a-oxa-2-oxo-5*α*-hydroxy-3,4-dinorcholestane (**1009**), obtained from *L. obtusa* collected in the Lakshadweep Islands in India, represents the first example of a ring A bisnorsteroid isolated from a natural source [816].

Table 7 Steroids from *Laurencia* spp.

No.	Name	Source of isolation/synthesis
993	Cholesterol	*L. aldingensis* [373], *L. distichophylla* [264], *L. elata* [196], *L. karlae* [808], *L. majuscula* [809], *L. obtusa* [145], *L. okamurai* [60, 100], *L. tristicha* [290], *C. papillosus* [342]
994	Cholest-5-en-3*β*,7*α*-diol	*L. okamurai* [100], *L. tristicha* [290]
995	β-Sitosterol	*L. tristicha* [290]
996	24-Propylidene-cholest-5-en-3-ol	*L. papillosa* [810]
997	3*β*,7*β*-Dihydroxy-5*α*-cholestan-11-one	*L. papillosa* [811]
998	3*α*,6*α*-Dihydroxy-5*β*-cholestan-12-one	*L. papillosa* [812]
999	Cholest-4-en-3-one	*L. obtusa* [98]
1000	6*β*-Hydroxy-cholest-4-en-3-one	*L. papillosa* [812]
1001	(24*S*)-Stigmasta-4,25-diene-3*β*,6*β*-diol	*L. majuscula* [813]
1002	Stigmast-4-en-3*α*,6*β*-diol	*L. saitoi* [794]
1003	Pinnasterol	*L. pinnata* [814[b]]
1004	Acetylpinnasterol	*L. pinnata* [814[a,b]]
1005	–	*L. pinnata* [815]
1006	–	*L. pinnata* [815]
1007	–	*L. pinnata* [815]
1008	–	*L. pinnata* [815]
1009	2a-Oxa-2-oxo-5*α*-hydroxy-3,4-dinorcholestane	*L. obtusa* [816]

[a]The structure of this compound or of a derivative has been confirmed by X-ray crystallographic analysis

[b]The absolute stereochemistry of this compound has been established



3.8 Miscellaneous Metabolites

In addition to the *Laurencia* metabolites discussed above that can be assigned to distinct classes, such as sesquiterpenes, diterpenes, triterpenes, and acetogenins, 38 compounds isolated from *Laurencia* species feature atypical structures and cannot be classified into specific groups (**1010**–**1047**, Table 8).

Among them, the carotenoid zeaxanthin (**1010**) was isolated from *L. tristicha* [290]. Chilenones A (**1011**) and B (**1012**), a dimer and a trimer of 2-methyl-3(2*H*)-furanone, and the tetracyclic polyketal **1013** were isolated as naturally occurring racemates from *Laurencia chilensis* and their structures were elucidated on the basis of X-ray crystallographic analysis [817–819]. *Spiro*-bis-pinnaketal (**1014**) was isolated as a natural product from *Laurencia pinnatifida* [821], but was later proven to be an artifact derived from laurencione (**1015**), which was subsequently obtained as a labile mixture of tautomers from an extract of *Laurencia spectabilis* [822]. The related compounds **1016** and **1017** were isolated from *L. chilensis* [827]

Table 8 Miscellaneous metabolites from *Laurencia* spp.

No.	Name	Source of isolation/synthesis
1010	Zeaxanthin	*L. tristicha* [290]
1011	Chilenone A	*L. chilensis* [817[c]]
1012	Chilenone B	*L. chilensis* [818[c]]
1013	–	*L. chilensis* [819[c]]; Synthesis [820[e]]
1014	*spiro*-bis-Pinnaketal	*L. pinnatifida* [821[c], 822]
1015	Laurencione	*L. spectabilis* [822]; Synthesis [820[f], 823[f], 824[f,h], 825[f], 826[f,h]]
1016	2-Methyl-3(2*H*)-dihydrofuranone	*L. chilensis* [827]
1017	4-Hydroxy-2,3-dimethylnon-2-eno-4-lactone	*L. composita* [214]
1018	5-Hydroxy-methylfurfural	*L. undulata* [828]
1019	*cis*-1-Methylcyclohexane-1,4-diol	*L. composita* [214]
1020	*trans*-1-Methylcyclohexane-1,4-diol	*L. composita* [214]
1021	Benkarlaol	*L. karlae* [829]
1022	3*β*-Hydroxy-5*α*,6*α*-epoxy-β-ionone	*L. tristicha* [290]
1023	3*β*-Hydroxy-5*β*,6*β*-epoxy-β-ionone	*L. tristicha* [290]
1024	2-Bromo-γ-ionone	*L. saitoi* [335]
1025	–	*L. mariannensis* [74]
1026	Hexadecyl-1-*O*-*α*-L-arabinopyranoside	*L. majuscula* [830]
1027	*n*-Hexadecyl-*β*-D-pyranoside	*L. karlae* [808]
1028	Floridoside	*L. undulata* [831], *Laurencia* spp. [32]
1029	D-Isofloridoside	*L. pinnatifida* [832[a]], *L. undulata* [831]
1030	1-*O*-Hexadecanoyl-3-*O*-*β*-D-galactopyranosylglycerol	*L. tristicha* [290]
1031	1-*O*-Hexadecanoyl-3-*O*-*β*-D-galactopyranosylglycerol	*L. tristicha* [290]
1032	–	*L. pedicularioides* [833]
1033	–	*L. majuscula* [809]
1034	(2*Z*)-Chloro-pentadec-2-enal	*L. flexilis* [149]; Synthesis [834]
1035	(*E*)-2-((*E*)-Tridec-2-en-2-yl) heptadec-2-enal	*L. papillosa* [812]
1036	(*E*)-2-Tridecyl-2-heptadecanal	*L. filiformis* [89], *L. microcladia* [255], *L. obtusa* [145], *L. papillosa* [61[a]], *L. scoparia* [134], *L. undulata* [61[a]]; Synthesis [835]
1037	–	*L. nidifica* [836]
1038	Hybridalactone	*L. hybrida* [837[a], 838[c,d]]; Synthesis [839[g], 840[g], 841[g]]
1039	Papillamide	*L. papillosa* [842]
1040	–	*L. hybrida* [843]
1041	Pentadecanal	*L. filiformis* [89]
1042	(12*S*)-HEPE	*L. hybrida* [843, 844[b]], *L. spectabilis* [822]
1043	–	*L. okamurai* [845]
1044	–	*L. okamurai* [845]

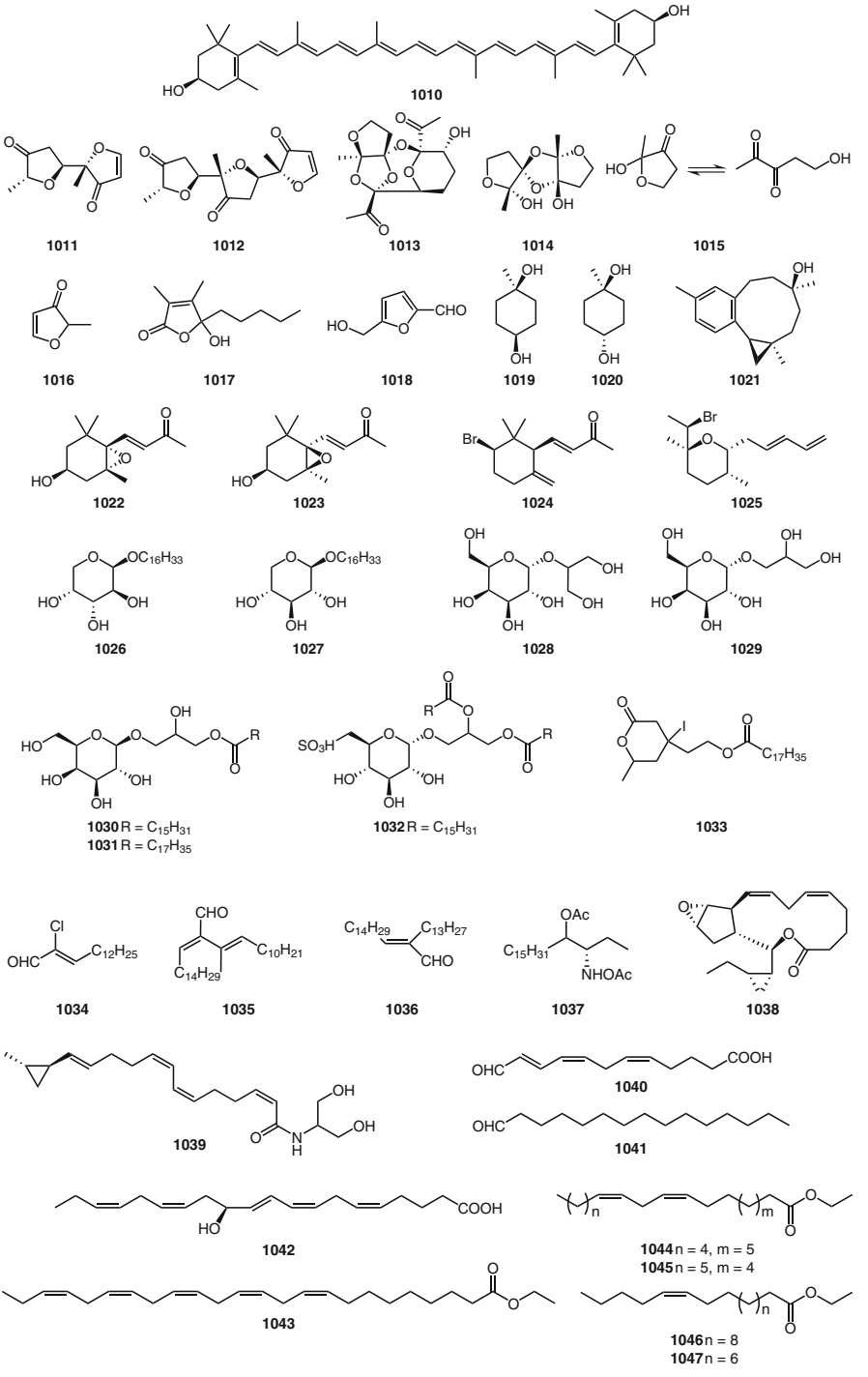
(continued)

Table 8 (continued)

No.	Name	Source of isolation/synthesis
1045	–	*L. okamurai* [845]
1046	–	*L. okamurai* [845]
1047	–	*L. okamurai* [845]

[a]The isolation and structure elucidation of this compound was reported for the first time
[b]The structure of this compound has been revised
[c]The structure of this compound or of a derivative has been confirmed by X-ray crystallographic analysis
[d]The absolute stereochemistry of this compound has been established
[e]Partial synthesis
[f]Stereoselective total synthesis
[g]Enantioselective total synthesis
[h]Formal synthesis

and *Laurencia composita* [214], respectively, while 5-hydroxy-methylfurfural (**1018**) was recognized as a component of the edible alga *Laurencia undulata* [828]. The epimeric *cis*- (**1019**) and *trans*-1-methylcyclohexane-1,4-diol (**1020**) were also obtained from *L. composita* [214]. Benkarlaol (**1021**) was isolated from *Laurencia karlae* collected from the Nansha Islands in the South China Sea [829], the ionone derivatives **1022** and **1023** were obtained from *Laurencia tristicha* [290], 2-bromo-γ-ionone (**1024**) was found in *L. saitoi* [335], and the tetrahydropyran **1025** was extracted from *Laurencia mariannensis* collected from Hainan and Weizhou Islands of the People's Republic of China [74]. The glycolipids **1026** and **1027**, floridoside (**1028**) and D-isofloridoside (**1029**) and the related metabolites **1030–1032** were isolated from various species of *Laurencia*, all collected from mainland China, South Korea or India [290, 808, 830–833]. The iodolactone **1033** was isolated from *Laurencia majuscula* [809], and (*Z*)-2-chloropentadec-2-enal (**1034**) containing an unusual chloroenal functionality was obtained from *Laurencia flexilis* [149], and its synthesis was achieved in one step from commercial tridecanal [834], whereas the α,β-unsaturated aldehydes **1035** and **1036** have been isolated from a number of *Laurencia* species [61, 134, 145, 255, 812]. The latter metabolite is considered the aldol product of pentadecanal (**1041**), with which it was also isolated from *Laurencia filiformis* [89]. The sphingosine derivative **1037** was obtained from a Hawaiian *Laurencia nidifica* specimen [836], while the fatty acid amide **1039**, designated as papillamide, was isolated from a Japanese *Laurencia papillosa* [842]. Hybridalactone (**1038**), an unusual C_{20} fatty acid-derived metabolite containing a cyclopropane and a macrolactone ring, was isolated from *Laurencia hybrida* and its structure, including the absolute stereochemistry, was established on the basis of analysis of its spectroscopic data, X-ray diffraction analysis, molecular mechanics calculations, chemical derivatizations, and total synthesis [837–841]. A number of fatty acid derivatives (**1040** and **1042–1047**) have been isolated from species of *Laurencia* [822, 843, 844]. Finally, common fatty acids, such as palmitic acid, eicosanoic acid, arachidonic acid and eicosapentaenoic acid, have been registered as constituents of the genus *Laurencia* [145, 373, 809, 846].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1029
1030 R = C15H31
1031 R = C17H35
1032 R = C15H31
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1042
1043
1044 n = 4, m = 5
1045 n = 5, m = 4
1046 n = 8
1047 n = 6

4 Biological Activity

The identification of natural products that can become lead molecules towards the development of new drugs requires investigation of the highest possible number of chemical entities in as many pharmacological activity screening assays as possible. In prescreening bioassays, large numbers of initial samples are tested so it can be determined whether or not some of them possess the desired type of activity. The detection of biological activity can be performed by either general screening bioassays or specialized screening bioassays. Depending on the strategy adopted, either a general screening, which can pick up many different effects, or a specific assay focused on finding effects against a specific disease, is selected. Specialized screening bioassays can be subdivided according to the target organisms that are used. These can be lower organisms e.g. microorganisms, insects, mollusks, protozoa, helminthes, and isolated subcellular systems, such as enzymes, receptors, organelles, isolated intact cells of human or animal origin, isolated organs or vertebrates, or whole animals [847]. Although the chemistry of *Laurencia* species has been investigated thoroughly, the biological activity evaluation of the isolated secondary metabolites has not been studied in a systematic way. The activity of *Laurencia* metabolites is organized below according to the biological target, regardless of the bioassays used for the evaluation.

4.1 Cytotoxic Activity

Cancer remains a most serious health threat to mankind and is considered as one of the leading causes of death worldwide. Natural products frequently possess highly selective and specific biological activities and are recognized as a promising reservoir of bioactive compounds for modern medicine, particularly for the treatment of cancer. In vitro cell proliferation assays are the most widely used assays for evaluating preliminary anticancer activity of both natural products and synthetic derivatives. These assays give an indication of whole cell cytotoxicity, but in order to determine the exact molecular target specialized assays are needed. Although these screens have assisted in the bioguided isolation of many active compounds, they are considered non-specific for the discovery of the next generation of drugs. Fortunately, a large number of specific biochemical and genetics-based screens are now available routinely [848–850].

The chamigrane ma'iliohydrin (**36**) displayed cytotoxicity in the NCI 60-cell line human tumor screen at a mean panel GI_{50} concentration of 10^{-5} M, with the greatest activity observed for the NCI/ADR-RES breast cancer cell line ($GI_{50} = 10^{-8}$ M) [148]. A dechloro-hydroxy analogue of hurgadol (**32**) was found to be weakly cytotoxic against HL-60 and THP-1 leukemia cells with IC_{50} values of 102 and 152 μM, respectively [144]. Dactylone (**39**) was proven effective at

non-toxic doses as a cancer preventive agent, initiating early apoptosis in HL-60 and THP-1 cells [144, 851].

The chamigranes cartilagineol (**31**), **44**, **46**, elatol (**59**), isoobtusadiene (**64**) and mailione (**131**) exhibited remarkable cytotoxicity against P-388, A-549, HT-29 and MEL-28 cancer cell lines, but especially against HT-29 cells [142]. The cytotoxic properties of **44**, its geometric isomer (**46**), and isoobtusadiene (**64**) were evaluated against the NCI 60-cell line panel and were proven cytotoxic to specific cell lines of the colon cancer subpanel at concentrations 10–100-fold lower than the mean cytotoxic concentration observed for the other tumor subpanels [154].

The chamigrane sesquiterpenes elatol (**59**), allolaurinterol acetate (**152**), isoobtusol acetate (**50**), **44**, **46**, and the indole derivative **969** were tested for cytotoxicity against P-388 cells, but their potency was rather weak [156]. It is worth noting that the activity of compounds **44**, **46**, and **59** on the P-388 cancer cell line was inconsistent with previously published values.

Obtusadiene (**63**) and isoobtusadiene (**64**) were devoid of any discernible cytotoxic activity against the KB cancer cell line [131]. The chamigranes deschlorelatol (**56**), its acetate **57**, elatol (**59**), its acetate **60**, as well as the bisabolanes caespitol (**337**), and 8-acetylcaespitol (**338**) were evaluated against HeLa, HEP-2 and non-tumor Vero cells and **59** proved to be the most active of the tested compounds, while **337** was slightly active and **56** and **57** were inactive [86].

Pacifenol (**105**), cycloelatanenes A (**119**) and B (**118**), and the acetogenin (3*Z*)-chlorofucin (**875**) displayed negligible cytotoxic activity when tested [221]. The inhibition of cytokinesis in the embryos of the sea urchin *Tetrapygus niger*, used as a preliminary test for an indication of antineoplastic activity, revealed that 4,10-dibromo-3-chloro-α-chamigrene (**5**), prepacifenol (**88**), deoxyprepacifenol (**87**), and claviol (**124**) had no effect on the cytokinesis, while **6** and pacifenol (**105**) displayed only weak inhibition [87]. Chemical transformation of pacifenol (**105**) afforded a number of derivatives that were also evaluated for their cytotoxicity [852].

Among the sesquiterpenes johnstonol (**113**), **163**–**165**, aplysin (**195**), 10-hydroxy-aplysin (**196**), 10-hydroxy-bromo-*epi*-aplysin (**198**), 10-hydroxy-*epi*-aplysin (**199**), laurentristich-4-ol (**246**), debromoaplysinol (**202**), aplysinol (**204**), debromo-*epi*-aplysinol (**210**), aplysin-9-ene (**201**), *epi*-aplysinol (**211**), **222**, cyclolauren-2-ol (**228**), laurebiphenyl (**239**), gossonorol (**319**), **320**, **327**, **328**, and the linear diterpene (*E*)-phytol (**641**), only laurebiphenyl (**239**) showed moderate cytotoxicity against the tested cancer cell lines (A-549, BGC-823, BEL-7402, HCT-8, and HeLa), while **202** and **210** were selectively cytotoxic against the HeLa cell line [232, 290, 295].

Laurepoxyene (**185**), 10-hydroxy-aplysin (**196**), 3β-hydroperoxy-aplysin (**197**), 10-hydroxy-*epi*-aplysin (**199**), 3α-hydroperoxy-3-*epi*-aplysin (**200**), aplysinol (**204**), 10-bromoisoaplysin (**207**), 8,10-dibromoisoaplysin (**208**), laurokamurene A (**242**), (5*S*)-5-acetoxy-β-bisabolene (**307**), and *seco*-laurokamurone (**469**) were evaluated for their cytotoxicity against the HL-60 and A-549 human cancer cell lines, but only **196** and **197** showed moderate levels of inhibitory activity against A-549 cells [275].

Aplysin (**195**), isolaurinterol (**161**), aplysinal (**209**), and laurinterol (**231**) were found to be cytotoxic against the A-549, SK-OV-3, SK-MEL-2, XF-498, and HT-15 cancer cell lines [268]. Noteworthy were the inconsistent results for aplysin (**195**) on the A-549 cell line in comparison to earlier published data. Aplysin (**195**) was reported to act as a sensitizer for TRAIL (TNF-related apoptosis-inducing ligand) using several TRAIL-resistant cancer cell lines and to potentiate TRAIL-induced apoptosis in A-549 and MCF-7 cells [853].

Debromoallolaurinterol (**149**), *iso*-laurenisol (**174**), bromolaurenisol (**175**), **184**, laurinterol (**231**), perforenone A (**377**), 3-*epi*-perforenone A (**379**), perforenol B (**384**), **393**, **421**, and (*E*)-2-tridecyl-2-heptadecenal (**1036**) were evaluated against five human cancer cell lines (K-562, MCF-7, PC-3, HeLa, A-431) and Chinese hamster ovary (CHO) cells [255]. Moreover, the cytotoxicity of bromolaurenisol (**175**), laurinterol (**231**), **240**, and **421** was evaluated against the NSCLC-N6 and A-549 cancer cell lines [255]. A *L. okamurai* extract containing laurinterol (**231**) was reported to induce apoptosis in melanoma cells [854]. Debromolaurinterol (**226**), laurinterol (**231**) and its acetate **232** were moderately cytotoxic against HeLa cells, while debromolaurinterol acetate (**227**) was inactive [309]. Allolaurinterol (**151**) and its acetate **152**, isolaurenisol (**176**) and its acetate **177** were tested for cytotoxicity against the P-388 and BSC-1 cancer cell lines, and showed that the moderate levels of activity exhibited by **151** and **176** were even lower for their acetates **152** and **177** [260].

The laurane sesquiterpene **217**, bromolaurinterol (**235**), 8-iodolaurinterol (**236**), the dimer **238**, *ent*-α-bromocuparene (***ent*-415**), and α-isobromocuparene (**417**) were devoid of any significant activity against five human cancer cell lines (HT-29, MCF-7, PC-3, HeLa, and A-431) [262]. 10-Hydroxy-isolaurene (**181**), and the rearranged metabolites **242** and **422** were cytotoxic towards the NSCLC-N6 and A-549 lung cancer cell lines, with **181** and **242** exhibiting the highest levels of activity [274].

The cytotoxic activity against KB, HEP-G2 and MCF-7 cancer cell lines of the compounds laur-2-ene-3,12-diol (**167**), **245**, **420**, and kahukuen-10-ol B (**633**) was evaluated. Kahukuen-10-ol B (**633**) was active against all cell lines, while the cuparane **420** exhibited moderate activity against KB cells, laur-2-ene-3,12-diol (**167**) exhibited moderate activity towards KB and MCF-7 cells, and **245** was inactive [271]. Isolauraldehyde (**183**) and 8,11-dihydro-12-hydroxy-isolaurene (**191**) showed very promising activity in an in vitro model of Ehrlich ascites carcinoma [98]. *epi*-Obtusane (**51**) and oculiferane (**428**) exhibited high levels of cytotoxic activity against the PC-3, A-549, MCF-7, HEP-G2, and HCT-116 cell lines [167].

The snyderanes α-snyderol (**247**) and its acetate (**248**), and **256**, **258**, **264**, and **265** did not exhibit cytotoxic activity against a panel of cell lines (KB, LU1, Col 2, LNCaP) [319]. Aplysistatin (**276**) and its 6β-hydroxy derivative **277** were cytotoxic the against KB cell line [343, 855] and the former was also active against P-388 cells [343]. Luzonensol (**252**), **254**, isopalisol (**261**), palisadin B (**266**), 5β-acetoxy-palisadin B (**268**), 4-hydroxy-palisadin C (**272**), aplysistatin (**276**), palisadin A (**278**), and the aristolanes **451**, **452**, **454**, **457**–**459**, **461**, and **462** were

proven inactive against BEL-7402 cells [325]. Aplysistatin (**276**), **454**, and **460** were inactive against K-562, SGC-7901, and SMMC-7721 cells, the aristolane derivative **451** was found cytotoxic, whereas (*E*)-phytol (**641**) showed only weak activity against SGC-7901 cells [342]. The aristolanes ***ent*-451** and **453** displayed cytotoxic effects against selected cancer cell lines, while compounds **454** and **455** were inactive [432]. The bisabolane-related sesquiterpene majapolene A (**362**) displayed modest activity in the NCI 60-cell line cytotoxicity screen [390].

Obtusol (**28**), elatol (**59**), and compound **92** were cytotoxic against the HM02, HEP-G2 and MCF-7 cancer cell lines, while isoobtusol acetate (**50**), puertitol B acetate (**312**), caespitane (**333**), caespitol (**337**), 8-acetylcaespitol (**338**), caespitenone (**349**), furocaespitane (**352**), laucapyranoid A (**372**), 3-*epi*-perforenone A (**379**), **381**, 4-hydroxy-1,8-*epi*-isotenerone (**397**), isopinnatol B (**553**), dactylomelol (**600**), and dactylopyranoid (**631**) were inactive in this regard [50, 399]. Elatol (**59**) was also active against L-6 muscle myoblast cells with a *MIC* value of 3.3 μg/cm^3 [50]. Obtusol (**28**), isoobtusol (**49**), and its acetate **50** and the bisabolane derivatives caespitol (**337**), isocaespitol (**346**), and its acetate **347** displayed low cytotoxicity against the HeLa-229 cancer cell line, with isoobtusol acetate (**50**) being the most active ($LD_{50} = 4.5$ μg/cm^3) [384]. Semisynthetic derivatives of **49** were prepared and tested for their cytotoxicity against the A-549 and RD cancer cell lines but without evidence of improved cytotoxicy in comparison to the natural compound [856].

Caespitane (**333**), caespitol (**337**), 8-acetylcaespitol (**338**), **342**, and caespitenone (**349**) were found to be moderately active against the HT-29, MCF-7 and A-431 cell lines, exhibiting activity with IC_{50} values lower than 20 μ*M*, whereas metabolites **335**, **341** and **356** displayed weak activity and **343**, 8-desoxyisocaespitol (**345**), isocaespitol (**346**), **348**, the lactol **354**, and **355** were inactive [370]. Deodactol (**334**) showed moderate cytotoxic activity against L-1210 cells [371].

In vivo and in vitro studies were undertaken to clarify the mechanism of action of elatol (**59**). It seems that it promotes a delay in the cell cycle, probably in the G1/S transition, activating the apoptotic process, but further studies are needed to confirm this [857]. Another study has reported potent cytotoxic properties for isoobtusol (**49**), (+)-elatol (**59**), and palisadin A (**278**) [166].

The eudesmane-related C_{12} terpene teuhetenone A (**449**) and the *seco*-eudesmane chabrolidione B (**448**) were found inactive against the HEP-G2, HEP-3B, MCF-7, MDA-MB-231, and A-549 cancer cell lines [858]. In another study, teuhetenone A (**449**) exhibited higher cytotoxic activity against the MCF-7 cancer cell line in comparison to the eudesmane **440** and chabrolidione B (**448**) [423].

The diterpenes parguerol (**514**) and its 16-acetate (**517**), deoxyparguerol (**525**), isoparguerol (**540**), and its 16-acetate (**541**) exhibited cytotoxic activity against the P-388 cancer cell line [156]. The cytotoxicity of deacetylparguerol (**513**), parguerol 16,19-diacetate (**519**), parguerol triacetate (**521**), 2-deacetoxy-deoxyparguerol (**523**), **524**, deoxyparguerol (**525**), **532**, **539**, isoparguerol 7,16-diacetate (**542**), and the A-*seco*-parguerane **544** was evaluated against the HeLa and P-388 cancer cell lines and only **519**, **521**, **525**, **542**, and **544** exhibited activity, while **544** was

found cytotoxic against the B-16 cancer cell line ($IC_{50} = 0.78$ μg/cm^3) [475, 479, 483]. Parguerol 7,16-diacetate (**520**) and parguerol triacetate (**521**) were found to inhibit P-glycoprotein in multidrug resistant human cancer cells [859].

The cytotoxicity against Ehrlich carcinoma tumor cells of parguerol 16-acetate (**517**), parguerol 7,16-diacetate (**520**), deoxyparguerol (**525**) and its 7-acetate (**526**), isoparguerol (**540**), its 16-acetate (**541**) and 7,16-diacetate (**542**) were evaluated. The cytotoxicity of the isoparguerol derivatives was determined as being more potent than that of the parguerol derivatives, while the deoxyparguerol derivatives showed the lowest activity [860]. Virtual screening of the SeaWeed Metabolite Database (SWMD) resulted in the identification of four potential lead compounds with the parguerane skeleton that showed good binding with β-tubulin [861].

Luzodiol (**590**) and the dactylomelanes **592–599** were found inactive when tested against five human tumor cell lines (HeLa, MCF-7, A-431, HEP-G2, and A-549) [515]. The obtusane diterpene **609** exhibited cytotoxicity against the KB ($ED_{50} = 4.5$ μg/cm^3) and PS ($ED_{50} = 10$ μg/cm^3) cell lines in NCI in vitro bioassays [519]. The rearranged obtusane laurenditerpenol (**613**) exhibited potent inhibition of HIF-1-mediated hypoxic signaling in breast tumor cells [521]. Two analogues featuring the 7-oxabicyclo[2.2.1]heptane ring system present in the natural product were prepared and their weak inhibition of HIF-1 activation indicated the importance of the cyclohexenol part of laurenditerpenol (**613**) [862]. The diterpenes prevezols B-E (**617–620**) were tested for their cytotoxicity against five human tumor cell lines (MCF-7, PC-3, HeLa, A-431, and K-562) and prevezols B (**617**) and C (**618**) were found to be the most potent, while prevezol E (**620**) was inactive [528]. Dactyloditerpenol acetate (**635**) was tested for cytotoxicity against the A-2058 and DU-145 cancer cell lines, but displayed weak activity as the observed reductions of cell viability were only 67% and 77%, respectively [178]. Viridiols A (**624**) and B (**625**) showed significant cytotoxicity against the P-388, A-549, HT-29, and MEL-28 cancer cell lines, while only the former exhibited slight activity on RNA synthesis and neither compound had any inhibitory effect on protein and DNA synthesis [534].

The triterpenes thyrsiferol (**646**), its 23-acetate (**647**), 15(28)-anhydrothyrsiferyl diacetate (**651**), 15-anhydrothyrsiferyl diacetate (**657**), and magireols A (**665**), B (**666**), and C (**667**) displayed cytotoxicity against the P-388 cancer cell line, with compound **647** being the most active [544, 557]. Thyrsiferol (**646**) also showed cytotoxicity against the A-549, HT-29 and MEL-28 cancer cell lines [548]. Thyrsiferyl 23-acetate (**647**) was found to potently and specifically inhibit serine/threonine protein phosphatase 2A (PP2A) without affecting other phosphatases (PP1, PP2B, PP2C, PTP) and to induce apoptosis in various T- and B-leukemia cells [863, 864]. Thyrsiferol (**646**) and 15(28)-anhydrothyrsiferyl 23-acetate (**650**) also induced apoptosis, but they did not inhibit PP2A [864]. Furthermore, compound **646** inhibited mitochondrial respiration and HIF-1 activation [542]. Teurilene (**699**) did not show any cytotoxicity against P-388 cells [544], but was found to be cytotoxic against KB cells ($IC_{50} = 7.0$ μg/cm^3) [865].

The mechanisms of growth inhibition by the cytotoxic compound dehydrothyrsiferol (**649**) have been studied extensively [548, 563, 568, 569]. In

particular, **649** was shown to circumvent multidrug resistance mediated by P-glycoprotein [866] and to cause growth inhibition in KB cancer cells without inducing apoptosis [867], but did not modulate multidrug resistance-associated protein 1 (MRP1) resistance [868]. Its effects on estrogen-dependent and -independent breast cancer cells were evaluated [869] and its observed inhibition activity on VLA integrins was considered as a potent tool in controlling metastasis in breast cancer cells [870]. Furthermore, **649** showed inhibition of PP2A [871]. The antimitotic activities of a synthetic analogue, 7,11-*epi*-thyrsiferol, were evaluated and a structure-activity relationship (SAR) model was developed for such compounds [872].

16-Hydroxy-dehydrothyrsiferol (**652**), 10-*epi*-dehydrothyrsiferol (**655**), 10-*epi*-15,16-dehydrothyrsiferol (**658**), dehydrovenustatriol (**660**), 15,16-dehydrovenustatriol (**662**), isodehydrothyrsiferol (**673**), thyrsenols A (**677**) and B (**678**), and predehydrovenustatriol acetate (**692**) were proven to possess significant cytotoxicity against P-388, A-549, HT-29, and MEL-28 cancer cells [548, 560, 568]. 16-*epi*-Hydroxy-dehydrothyrsiferol (**653**), martiriol (**681**), pseudodehydrothyrsiferol (**685**), and dioxepan-dehydrothyrsiferol (**698**) exhibited moderate cytotoxic activities against the same panel of cancer cell lines [558].

The PP2A inhibition activity of the triterpenes **652**, **653**, **655**, **658**, **660**, **662**, **673**, **677**, **678**, **683**-**686**, **688**, and **698** was evaluated and the most potent metabolites were found to be 16-hydroxy-dehydrothyrsiferol (**652**) and thyrsenol B (**678**) [871].

22-Hydroxy-15(28)-dehydrovenustatriol (**661**), iubol (**674**), 15-dehydroxythyrsenol A (**679**), 1,2-dehydropseudodehydrothyrsiferol (**682**), prethyrsenol A (**689**) 13-hydroxy-prethyrsenol A (**690**), and secodehydrothyrsiferol (**693**) had significant cytotoxicity against the Jurkat, MM-144, HeLa and CADO-ES-1 cell lines [563, 569]. Since metabolites **679**, **689**, and **690** have limited water solubility, four semisynthetic analogues modulating the solubility of the lead compound, dehydrothyrsiferol (**649**), were prepared and found to maintain the same levels of activity [569].

Callicladol (**672**) showed cytotoxicity against P-388 murine leukemia cells [566]. Aplysiols A (**648**) and B (**668**) displayed significant cytotoxic activity against P-388 tumor cells with IC_{50} values of 0.6 and 6.6 mg/cm^3, respectively [543]. Metabolites **680**, **694**, and **695** did not show any discernible cytotoxicity against the HS-578-T and T-47D cell lines [570]. The triterpenes saiyacenols A (**669**) and B (**670**) exhibited cytotoxicity against Jurkat, MM-144, HeLa, and CADO-ES-1 cells [555]. Aplysqualenol A (**675**) exhibited potent cytotoxic properties against the MCF-7, NCI-H460 and SF-268 cancer cell lines [567, 873]. The triterpenes aurilol (**696**) and auriculol (**703**) exhibited cytotoxicity against HeLa S_3 cells [573, 589].

The acetogenins **722**, **723**, **726**, and **948** were evaluated for their cytotoxicity against the HT-29, MCF-7, PC-3, HeLa, and A-431 human tumor cell lines, but were devoid of any significant activity [607]. The need for the development of a computational (in silico) prescreening method for activity prediction led Brogi and co-workers to the creation of a ligand-based pharmacophore for MCF-7 cells,

which was able to predict with accuracy the cytotoxicity levels for an array of compounds against this cell line [874].

When tested, the laurenan-type acetogenin (3*Z*)-dihydro-rhodophytin (**810**) was found to be devoid of cytotoxicity against a a panel of normal and tumor cell lines [691]. Elatenyne (**735**), laurendecumbenynes A (**885**) and B (**733**), and laurendecumallenes A (**901**) and B (**857**) were not active against the A-549 cancer cell line [611, 612]. Laurefurenynes A (**737**), B (**736**), C (**879**), D (**878**), E (**881**), and F (**880**) were tested for cytotoxicity against the murine L-1210, Colon 38, CFU-GM, H-116, H-125, and human CFU-GM cell lines and only laurefurenynes C (**879**) and F (**880**) were moderately cytotoxic, but without showing any selectivity [619].

Marilzallene (**831**), (+)-4-acetoxy-marilzallene (**832**), obtusallene IV (**906**), 12-epoxy-obtusallene IV (**907**), **908**, marilzabicycloallenes A (**918**), and B (**921**) and (*E*)-adrienyne (**936**) were inactive against the A-2780, HBL-100, HeLa, SW-1573, T-47D, and WiDr solid tumor cell lines [711, 777].

Only 2,3,5,6-tetrabromoindole (**952**), among the simple bromoindoles **952**, **966**, **969**, and **971**, showed cytotoxic activity against the L-1210 tumor cell line [793]. Metabolites **952** and **971** exhibited significant cytotoxicity against the K-562, SGC-7901 and SMMC-7721 tumor cell lines, while compound **950** displayed strong cytotoxic activity only for the K-562 cell line, whereas cholesterol (**993**) was found to be inactive [342]. The monoindoles **952**, **969**, and **971**, the bisindole **974**, and the *spiro*-trisindoles similisines A (**983**) and B (***ent*-983**) did not exhibit cytotoxicity against eight human cancer cell lines (MCF-7, BGC-823, HeLa, A-549, HCT-8, HEP-G2, HL-60, Jurkat) at a concentration of 10 μg/cm^3, while metabolite **973** showed very weak cytotoxic activity only against the HL-60 ($IC_{50} = 35.1$ μM) and Jurkat ($IC_{50} = 53.3$ μM) cell lines [792]. Metabolite **969** was not active against P-388 cell line [156]. When compounds **952**, **969**, and **971** were evaluated for their cytotoxic effects against selected cancer cell lines, only **952** was found active [432]. Tetrabromoindole **952** and the sterol stigmast-4-en-3α,6β-diol (**1002**) were devoid of cytotoxic properties [794]. When the indoles **955–958**, **960–963**, **965**, and **975–977** were evaluated against the HT-29 and P-388 cancer cell lines, compound **976** exhibited cytotoxicity against both cancer cell lines, while **977** was active only against the P-388 cell line [799]. The cytotoxic activity of 4,5,6-tribromo-2-methylsulfinylindole (**964**), along with other known related compounds was evaluated [801].

4-Hydroxy-benzaldehyde (**984**) and 4-methoxy-benzyl alcohol (**986**) were found inactive when tested against the KB cancer cell line [804]. Indolyl-3-carbaldehyde (**972**), 4-hydroxy-benzaldehyde (**984**), cholesterol (**993**), β-sitosterol (**995**), zeaxanthin (**1010**), the ionone derivatives **1022** and **1023**, and the glycosides **1030** and **1031** did not display cytotoxicity, when evaluated against several human tumor cell lines (A-549, BGC-823, BEL-7402, HCT-8, and HeLa), whereas cholest-5-en-3β,7α-diol (**994**) was cytotoxic against all these cell lines [290].

(24*S*)-Stigmasta-4,25-diene-3β,6β-diol (**1001**) when tested was found to be cytotoxic against P-388 cell line ($IC_{50} = 1.2$ μg/cm^3) [813]. The arabinoside **1026** exhibited significant antitumor activity in the LOVO and BEL-7402 cell lines

and additional studies were performed to clarify the mechanism of this action [830]. (*E*)-2-((*E*)-Tridec-2-en-2-yl)-heptadec-2-enal (**1035**) demonstrated moderate cytotoxic activity against several cell lines in which it was tested (CHO, K-562, MCF-7, PC-3, HeLa, A-431) [255], whereas papillamide (**1039**) did not exhibit cytotoxic properties against the P-388 and B-16 cancer cell lines [842].

4.2 Antibacterial and Antifungal Activity

The already emerged and increasing resistance to antibiotics is becoming a global threat to public health. Only 80 years after their introduction, humans are now facing the possibility of a future without effective antibiotics. Methicillin-resistant *Staphylococcus aureus* alone infects more than 94,000 people and kills yearly 19,000 in the U.S., more deaths than those caused by HIV/AIDS, Parkinson's disease, emphysema, and homicides combined [875].

A large number of *Laurencia* metabolites have been evaluated against different bacterial and fungal strains exhibiting various levels of activity. Many of these metabolites, isolated from independent sources, were submitted to antimicrobial activity evaluation assays utilizing different methods and/or different strains of microorganisms.

Among the *Laurencia* sesquiterpenes, elatol (**59**) can be singled out as the metabolite tested for its antimicrobial activity in the highest number of investigations, but the reported results are frequently contradictory, as even against the same strains variable levels of activity have been reported over the years [50, 81, 135, 157, 165, 166, 855, 876, 877].

Isoobtusol (**49**), isoobtusol acetate (**50**), and obtusol (**175**) are also found as common constituents in several *Laurencia* species and their antibacterial and antifungal activities have been reported in a number of articles [50, 135, 155, 384, 876]. Evaluation of the related sesquiterpenes allolaurinterol (**151**) [166, 248, 259, 260, 855, 877], allolaurinterol acetate (**152**) [152, 260], debromoallolaurinterol (**149**) [248], debromoallolaurinterol acetate (**150**) [152], isolaurinterol (**161**) [62, 201, 267, 279, 877], laurinterol (**231**) [62, 105, 137, 309, 877], debromolaurinterol (**226**) [309, 855, 878], and isodebromolaurinterol (**229**) [201, 267, 279] has been performed in several, albeit fragmented, studies, which do not allow direct comparison of the structural features with the reported antimicrobial activities.

The bisabolane sesquiterpenes caespitane (**333**) [50, 135], caespitol (**337**) [50, 384], 8-acetylcaespitol (**338**) [50], isocaespitol (**346**) [384], caespitenone (**349**) [50, 135], and furocaespitane (**352**) [50] have been evaluated for their antibacterial and/or antifungal activities in a number of investigations.

Furthermore, a significant number of *Laurencia* sesquiterpenes including (–)-(10*R*)-bromo-α-chamigrene (**1**) [81], laurecomin C (**2**) [84], **7** [84], laurokamin C (**12**) [79], 10-bromo-9-hydroxy-α-chamigrene (**14**) [81], dendroidiol (**34**) [146], laurecomin B (**37**) [84], 10-bromo-β-chamigren-8-ol (**41**) [152, 275], **44** [62, 155]

and its geometric isomer **46** [62, 155], obtusane (***ent*-47**) [146], rogiolol (**48**) [162], rigidol (**53**) [81], (+)-(10*S*)-10-bromo-β-chamigrene (**55**) [81], ***ent*-56** [62], obtusadiene (**63**) [131], isoobtusadiene (**64**) [131], **76** [62], chamigrane **81** [187], **82** [152, 275], deoxyprepacifenol (**87**) [84, 201, 267, 279], prepacifenol (**88**) [878], **92** [50], laurecomin D (**94**) [84], yicterterpene A (**111**) [229], yicterterpene B (**112**) [229], laurokamin B (**120**) [79], pannosane (**137**) [238], laurokamin A (**139**) [79], laurecomin A (**140**), pannosanol (**142**) [84], laurene (**148**) [152], isolaurenisol (**176**) [260], **177** [260], **181** [201, 267, 279], 12-hydroxy-isolaurene (**182**) [275], isolauraldehyde (**183**) [275], laurepoxyene (**185**) [275], 8,11-dihydro-12-hydroxy-isolaurene (**191**) [275], 10-hydroxy-aplysin (**196**) [201, 267, 279], **197** [152, 275], **200** [152, 275], debromoaplysinol (**202**) [201, 267, 279], aplysinol acetate (**205**) [201, 267, 279], laureperoxide (**206**) [201, 267, 279], 10-bromo-isoaplysin (**207**) [201, 267, 275, 279], **208** [275], filiformin (**214**) [201, 267, 279], filiforminol (**218**) [166, 257], **227** [309], isodebromolaurinterol (**229**) [201, 267, 279], **232** [309], cyclolaurenol (**233**) [305], cyclolaurenol acetate **234** [305], laurokamurene A (**242**) [201, 267, 275, 279], laurokamurene B (**241**) [201, 267, 279], laurokamurene C (**243**) [275], aplysistatin (**276**) [339, 342, 855], **277** [855], palisadin A (**278**) [166, 337, 339], palisadin B (**266**) [337, 339], 5*β*-acetoxy-palisadin B (**268**) [337, 339], 12-hydroxy-palisadin B (**269**) [337, 339], isodactyloxene A (**302**) [74], 3-acetoxy-(*E*)-γ-bisabolene (**305**) [81], puertitol B acetate (**312**) [50], isocaespitol acetate (**347**) [384], majapolene A (**362**) [193], majapolene B (**364**) [193], majapolene A acetate (**363**) [193], majapolene B acetate (**365**) [193], tiomanene (**366**) [193], laucapyranoid A (**372**) [50], 3-*epi*-perforenone A (**379**) [399], **381** [399], 4-hydroxy-1,8-*epi*-isotenerone (**397**) [399], α-isobromocuparene (**417**) [201, 267, 279], cupalaurenol (**418**) [187, 305, 877], cupalaurenol acetate (**419**) [305], the cuparene-type ether **421** [201, 267, 279], **424** [152], **434** [84], **435** [84], cycloeudesmol (**446**) [878], **451** [342], **454** [342], **460** [342], **490** [81, 146, 458], **492** [458], and dactylomelatriol (**504**) [135] were evaluated for their antibacterial and/or antifungal properties, exhibiting variable activity levels.

The aristolanes ***ent*-451** and **453** displayed good antibacterial activity against antibiotic-resistant bacteria, while compounds **454** and **455** when tested in the same assay were inactive [432]. The eudesmane **440** and the *seco*-eudesmane chabrolidione B (**448**) exhibited significant antifungal activity, while teuhetenone A (**449**) was less active in this regard [423].

The diterpenes deacetylparguerol (**513**), parguerol (**514**), **524**, deacetylisoparguerol (**539**), and isoparguerol (**540**) were tested for their antibacterial activity against seven pathogenic bacterial strains (*Escherichia coli*, *Staphylococcus aureus*, *S. albus*, *Bacillus cereus*, *Vibrio parahemolyticus*, *Vibrio anguillarum*, and *Pseudomonas putida*). None of these compounds showed evident antibacterial activity [476]. The labdanes **560** and **561** were proven inactive against several pathogenic bacteria (*E. coli*, *Staphylococcus epidermis*, *S. aureus*, *Salmonella* sp., and *Pseudomonas* sp.) [106].

Moreover, the diterpenes isopinnatol B (**553**) [50], **556** [105], 10-acetoxy-angasiol (**585**) [187], dactylomelol (**600**) [50], dactylopyranoid (**631**) [50],

10-hydroxy-kahukuene B (**633**) [74], aplysiadiol (**638**) [187], and (*E*)-phytol (**641**) [342] have been evaluated for their antibacterial and antifungal properties.

Neoirietetraol (**589**), when tested against six bacterial strains (*Alcaligenes aquamarinus*, *Alteromonas* sp., *Azomonas agilis*, *Erwinia amylovora*, *E. coli*, and *Halococcus* sp.), exhibited weak activities only against *A. aquamarinus* and *E. coli* [513]. Dactyloditerpenol acetate (**635**) exhibited marginal antibacterial activity against *Mycobacterium tuberculosis* [178]. Laurencianol (**626**) displayed antibacterial activity against *Bacillus subtilis* and *E. coli* [535].

The triterpene thyrsiferol (**646**) and its 23-acetate (**647**), when tested, did not show any antimicrobial activity [545]. Aplysqualenol A (**675**) did not exhibit any inhibitory activity against *M. tuberculosis* [567].

The C_{15} acetogenins **842** and **844–848** were examined for their antistaphylococcal activity against a panel of multidrug- and methicillin-resistant *S. aureus* strains, displaying variable levels of activity [728]. (3*Z*)-Dihydrorhodophytin (**810**) exhibited better antibacterial activity than that of cefuroxime against six foodborne pathogens [691].

The antibacterial and/or antifungal activities of the acetogenins laurenmariallene (**741**) [74], chinzallene (**749**) [105], (12*E*)-lembyne A (**759**) [62], lembyne A (**763**) [165], (3*Z*)-laurenyne (**798**) [513], (*Z*)-chondriol (**803**) [878], ***ent*-854** [152], desepilaurallene (**862**) [152], and (3*Z*)-chlorofucin (**875**) [238] have also been evaluated in a number of studies.

Among the simple bromoindoles **952**, **966**, **969**, and **971**, only 2,3,5,6-tetrabromoindole (**952**) showed activity against *B. subtilis* and *Saccharomyces cerevisiae* [793]. Metabolites **950**, **952**, **971**, and cholesterol (**993**) did not show activity against *S. aureus* and MRSA strains [342], although **952** was previously reported as displaying a wide spectrum of activity against Gram-positive antibiotic-resistant bacteria [877]. When the indoles **952**, **969**, and **971** were tested against antibiotic-resistant clinical bacteria, only **952** was proven active [432]. The antimicrobial activity of a *Laurencia complanata* extract containing the bromoindoles **952**, **969**, and **971** and the aristolane debilone (**456**) could be, at least to some extent, attributed to the presence of compound **952** [433]. The antibacterial activity of 4,5,6-tribromo-2-methylsulfinylindole (**964**), along with a series of other previously reported related compounds has been examined [801].

3-Hydroxy-4-methyl-acetophenone (**987**) has shown moderate antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli*, *Flavobacterium* sp., *Alcaligenes* sp., and *Candida albicans* [806].

6*β*-Hydroxycholest-4-en-3-one (**1000**) showed poor antifungal activity against *C. albicans* ($MIC = 2$ mg/cm^3), but was not active against *Aspergillus fumigatus* and *Aspergillus flavus* [812]. (*E*)-2-((*E*)-Tridec-2-en-2-yl)-heptadec-2-enal (**1035**) showed antifungal activity against *A. fumigatus* and *A. flavus*, with *MIC* values of 0.2 and 1 mg/cm^3, respectively [812].

The unstable metabolites **1040** and 12-*S*-HEPE (**1042**) were reported to possess antimicrobial activity [843]. The antifungal activity of the fatty acid ethyl esters **1043–1047** was evaluated and proven to be only moderate [845].

4.3 Antiviral Activity

There is an increasing need for molecules with antiviral activity since the treatment of viral infections with the drugs now available often leads to viral resistance. Therefore, the evaluation of antiviral activities and the potential therapeutic value of marine metabolites are receiving intense interest among virologists.

The chamigranes nidificene (**29**) and nidifidienol (**73**) have exhibited significant antiviral activity against the HSV-1 virus (*Herpes simplex* virus type 1) with IC_{50} values of 1.5 and 2.4 μg/cm^3, respectively. Pacifenediol (**102**), dehydroxyprepacifenol epoxide (**85**), and pacifenol (**105**) were found moderately active, while **5**, **6**, **18**, **79**, prepacifenol epoxide (**86**), deoxyprepacifenol (**87**), prepacifenol (**88**), and jonhstonol (**113**) did not show any discernible activity [95].

The sesquiterpenes perforenone (**376**), perforenone D (**380**), perforenol (**382**), debromoperforatone (**387**), perforatone (**388**), and the related **390–392** were found to be inactive against a wide variety of different RNA and DNA viruses [393]. 3-*epi*-Perforenone A (**379**), **381** and the rearranged cycloperforane 4-hydroxy-1,8-*epi*-isotenerone (**397**) were tested for their ability to inhibit the reverse transcriptase enzyme of the HIV-1 virus (human immunodeficiency virus type 1), but were found to be devoid of activity [399].

The chamigranes obtusol (**28**), cartilagineol (**31**), isoobtusol (**49**) and its acetate **50**, elatol (**59**), **92**, the bisabolanes puertitol B acetate (**312**), caespitane (**333**), caespitol (**337**), 8-acetylcaespitol (**338**), caespitenone (**349**), furocaespitane (**352**), laucapyranoid A (**372**) and the diterpenes isopinnatol B (**553**), dactylomelol (**600**), and dactylopyranoid (**631**) were proven inactive when evaluated for the inhibition of HIV-1 reverse transcriptase [50].

The triterpenes thyrsiferol (**646**), its 23-acetate (**647**), and venustatriol (**659**) exhibited antiviral properties against the VSV (vesicular stomatitis virus) and HSV-1 viruses [547]. Aplysqualenol A (**675**) exhibited significant activity against the HSV-1, HSV-2 (*Herpes simplex* virus type 2), HCMV (human cytomegalovirus), EBV (Epstein-Barr virus), and VZV (varicella zoster virus) viruses [567].

4.4 Activity Against Parasites and Their Vectors

Many natural products with diverse molecular structures have revealed potency against parasitic tropical diseases and/or their vectors and represent interesting lead structures for the development of new and urgently needed therapeutic interventions for the control of parasitic infections [879].

The snyderanes α-snyderol (**247**) and its acetate (**248**), **256**, **258**, **264**, and **265** were evaluated for antimalarial activity in vitro, but only **258** was weakly active against the D6 and W2 clones of *Plasmodium falciparum* [319].

The chamigrane deoxyprepacifenol (**87**) and the acetogenins laureatin (**864**) and isolaureatin (**866**) showed insecticidal activity against *Culex pipiens pallens* mosquito larvae, while pacifenol (**105**) was inactive [200].

Obtusol (**28**), cartilagineol (**31**), isoobtusol (**49**) and its acetate (**50**), elatol (**59**), **92**, puertitol B acetate (**312**), caespitane (**333**), caespitol (**337**), 8-acetylcaespitol (**338**), caespitenone (**349**), furocaespitane (**352**), laucapyranoid A (**362**), isopinnatol B (**553**), dactylomelol (**600**), dactylopyranoid (**631**), as well as 3-*epi*-perforenone A (**379**), **381**, and 4-hydroxy-1,8-*epi*-isotenerone (**397**) were tested for nematicidal activity against *Caenorrhabditis elegans*, antiplasmodial activity against *P. falciparum*, and antitrypanosomal activities against *Trypanosoma brucei rhodesiense* and *Trypanosoma cruzi* [50, 399]. Obtusol (**28**), elatol (**59**), **92** and caespitol (**337**) showed nematicidal activity and only elatol (**59**) exhibited antitrypanosomal activity to *T. cruzi* ($IC_{50} = 0.92$ μg/cm^3, $MIC = 3.3$ μg/cm^3). None of the tested compounds exhibited any antiplasmodial activity [50, 399].

Elatol (**59**) showed activity against the promastigote and intracellular amastigote forms of *Leishmania amazonensis* ($IC_{50} = 4.0$ and 0.45 μ*M*, respectively, after 72 h), while it was not toxic to macrophages [172]. Its enantiomer ***ent*-59** was found to be effective as an antitrypanosomal agent without cytotoxicity to mammalian cells [880–882]. Elatol (**59**) has also displayed larvicidal activity against the dengue mosquito (*Aedes aegypti*) [883]. Furthermore, **59**, while moderately toxic, showed a high degree of repellent activity against the spider mite *Tetranychus urticae* in laboratory experiments [173].

Obtusol (**28**) and ***ent*-59** displayed in vitro and in vivo leishmanicidal activity against both the promastigote and the amastigote forms of *L. amazonensis*, while the triquinane **490** had moderate activity. None of them promoted enhanced nitric oxide production by macrophages and they had very low toxicity against two different populations of mammalian cells [126].

Obtusane (***ent*-47**), isorigidol (**35**), **42**, **44** and its geometric isomer **46**, majusculone (**130**), mailione (**131**), and (*E*)-2-tridecyl-2-heptadecenal (**1036**) demonstrated moderate in vitro anthelmintic activity against the parasitic stage of *Nippostrongylus brasiliensis*, while obtusol (**28**), (+)-(3*Z*)-bromomethylidiene-10-*β*-bromo-β-chamigrane (**43**) and its geometric isomer **45** and scopariol (**136**) were found inactive [134]. Among the β-bisabolanes **313**, **315**, and **316** and the triquinanes **490** and **491**, only **313** showed weak anthelmintic activity against the parasitic stage of *N. brasiliensis* ($EC_{50} = 0.11$ m*M*) [366].

The anthelmintic activities against earthworms (*Allolobophora caliginosa*) of parguerol 16-acetate (**517**), parguerol 7,16-diacetate (**520**), deoxyparguerol (**525**), its 7-acetate (**526**), isoparguerol (**540**), its 16-acetate (**541**), and its 7,16-diacetate (**542**) were evaluated [860]. The parguerane and isoparguerane derivatives were found to be more effective than the deoxyparguerane derivatives and displayed higher levels of anthelminthic activity in comparison to mebendazole, which was used as a reference compound.

Squalene (**701**) has shown activity against *P. falciparum* and *T. brucei rhodesiense*, but not against *T. cruzi* and *Leishmania donovani*, while it displayed

low cytotoxicity to mammalian cells [884]. The triterpenes aplysqualenols A (**675**) and B (**676**) showed moderate antiplasmodial activity against *P. falciparum* [567].

The seven-membered acetogenin isolaurepinnacin (**784**) and the lauthisan-type eight-membered acetogenin laurepinnacin (**838**) exhibited insecticidal activity [660]. Moreover, the laurenan-type eight-membered acetogenins, (3*E*,12*R*,13*R*)-pinnatifidenyne (**812**), (3*E*)-13-epilaurencienyne (**821**) and its (3*Z*)-isomer (**822**), and **824** and its (3*Z*)-isomer (**825**) were assayed for their toxicity to *Pheidole pallidula* ants. The (*Z*)-isomers **822** and **825** exerted strong toxicity with a noticeable knockdown effect on the first day of application, while the (*E*) isomers **812**, **821**, and **824** showed toxicity that escalated gradually [702]. (12*E*)-(*Z*)-Maneonene E (**761**) showed larvicidal activity against the larvae of both the confused flour beetle (*Tribolium confusum*) and the mosquito (*C. pipiens*) [101].

The simple aromatic compounds 4-hydroxy-benzaldehyde (**984**) and 4-methoxybenzyl alcohol (**986**) were isolated from the CH_2Cl_2 extract of *L. papillosa*, which demonstrated significant and selective in vitro antimalarial activity. 4-Hydroxy-benzaldehyde (**984**) showed, albeit weak, selective in vitro antimalarial activity against *P. falciparum*, while **986** was inactive. Inspection by NMR spectroscopy of the other active fractions resulting from the initial chromatographic separation of the extract showed the presence of typical *Laurencia* compounds, suggesting that additional metabolites might also possess antimalarial activity [804].

(*E*)-2-((*E*)-Tridec-2-en-2-yl)-heptadec-2-enal (**1035**) demonstrated moderate in vitro anthelmintic activity against the parasitic stage of *N. brasiliensis* ($ED_{50} < 100\ \mu M$) [134].

4.5 Anti-inflammatory Activity

Many of the inflammatory diseases are becoming common in aging societies throughout the world. Several clinically used anti-inflammatory drugs suffer from the disadvantages of both side effects and often a high cost. Natural products, as the largest chemical library of diverse structures, offer great hope for the identification of bioactive lead compounds for the development of new drugs for the treatment of inflammatory diseases [885, 886].

The chamigranes dendroidiol (**34**), obtusane (***ent*-47**) and debromoelatol (**72**), and the triquinane **490** were evaluated for their potential anti-inflammatory activity, with ***ent*-47**, **72**, and **490** showing inhibitory effects on NO release from lipopolysaccharide (LPS)-activated RAW 264.7 macrophages, while **72** moderately affected TNF-α production [146].

Palisol (**260**), palisadins A (**278**) and B (**266**), 5*β*-hydroxy-palisadin B (**267**), 5*β*-acetoxy-palisadin B (**268**), and pacifigorgiol (**485**) exhibited anti-inflammatory activity using LPS-stimulated RAW 264.7 cells [330, 451]. Aplysistatin (**276**) and 5*β*-hydroxy-palisadin B (**267**) inhibited NO and PGE2 production via inhibition of iNOS and COX-2 [330, 451]. The latter reduced the release of the pro-inflammatory

cytokines TNF-α, IL-1β, and IL-6 [451], and was effective in vivo in the LPS-induced zebra fish embryo model [887]. The cell viability of some of these compounds was tested with a lactate dehydrogenase (LDH) cytotoxicity assay [146, 330, 451].

The snyderanes palisadins A (**278**) and B (**266**), 5*β*-acetoxy-palisadin B (**268**) and the aristolanes **451** and **453** when tested did not inhibit bee venom-derived phospholipase A2 [888].

Pacifenol (**105**) displayed anti-inflammatory properties and was shown to be an effective inhibitor of the degranulation process in human neutrophils, inhibiting in vitro eicosanoid release [889].

The effects of (*Z*)-maneonenes D (**764**) and E (**761**) in the apoptosis on blood neutrophils were studied and it was suggested that they may be involved in the regulation of programmed cell death in the initiation and propagation of inflammatory responses [645].

The tricyclic brominated diterpenoid neorogioltriol (**623**) showed anti-inflammatory activity in vivo using the carrageenan-induced rat paw edema model and in vitro effects on LPS-treated RAW 264.7 macrophages by inhibition of LPS-induced NF-κB activation and TNF-α production [890]. Moreover, a 1 mg/kg dose of neorogioltriol (**623**) proved to be as effective as a 300 mg/kg dose of aspirin in reducing inflammation. The exact mechanism of action of neorogioltriol (**623**) needs to be clarified and the target(s) in the cell identified.

Dactyloditerpenol acetate (**635**) exhibited significant in vitro anti-neuroinflammatory activity through inhibition of thromboxane B_2 and superoxide anion generation from *E. coli* LPS-activated rat brain microglia, with concomitant low short-term toxicity [178].

4,5,6-Tribromo-2-methylsulfinylindole (**964**) and other related compounds isolated from *L. brogniartii* were evaluated for their anti-inflammatory activity [801].

(12*S*)-HEPE (**1042**), which is produced from the oxidation of EPA (eicosapentaenoic acid), is recognized as a potent inhibitor of platelet aggregation and mediator of inflammation, stimulates degranulation by neutrophils and inhibits the activity of ATPases [844]. Floridoside (**1028**) was found to exhibit anti-inflammatory properties in neurons [891].

4.6 Miscellaneous Biological Activities

Obtusol (**28**), cartilagineol (**31**), isoobtusol (**49**) and its acetate **50**, elatol (**59**), **92**, puertitol B acetate (**312**), caespitane (**333**), caespitol (**337**), 8-acetylcaespitol (**338**), caespitenone (**349**), furocaespitane (**352**), laucapyranoid A (**372**), 3-*epi*-perforenone A (**379**), **381**, 4-hydroxy-1,8-*epi*-isotenerone (**397**), isopinnatol B (**553**), dactylomelol (**600**), as well as dactylopyranoid (**631**) were evaluated for the inhibition of tyrosine kinase p56lck, but were proven inactive [50, 399].

The metabolites **4**, deschloroelatol (**56**), elatol (**59**), and their acetates **57** and **60**, caespitol (**337**), and 8-acetylcaespitol (**338**) were evaluated for their

acetylcholinesterase inhibition potential using computational techniques. Among them, acetylelatol (**60**) was found to be the most promising [892].

The lauranes debromolaurinterol (**226**) and laurinterol (**231**) and the acetogenin aplysiallene (**740**) exhibited inhibitory activity against Na^+/K^+-ATPase [308]. Aplysin (**195**) has shown a protective effect on hepatic injury induced by ethanol in rats [893]. The triquinanes **490** and **492** exhibited weak antioxidant activity when evaluated in the DPPH radical-scavenging assay [458]. The diterpenes parguerol (**514**) and isoparguerol (**540**) induced neurite outgrowth in rat pheochromocytoma (PC-12) cells at concentrations of 25 and 50 μ*M*, respectively, while deoxyparguerol 7,16-acetate (**651**) was proven inactive even at a 100 μ*M* concentration [478].

The acetogenins dactylyne (**771**), laurencin (**836**), laureatin (**864**) and isolaureatin (**866**) but not (3*E*)-laurefucin (**870**) exhibited a prolongation of pentobarbital-induced hypnosis in rats without having any other apparent effects [894, 895]. Due to the non-toxic nature of dactylyne (**771**), a theoretical study of this metabolite and its stereoisomers has been conducted, so that details of its action could be understood [897]. Dactylyne (**771**) was also proven to be an inhibitor of cytochrome P450 [896].

The tricyclic brominated diterpenoid neorogioltriol (**623**) was evaluated for its analgesic activity using a writhing test in mice and a formalin test in rats. A dose-dependent antinociceptive response was observed in the writhing test at 0.5 and 1 mg/kg with an IC_{50} value of 12.5 mg/kg. The potent analgesic activity of **623** was estimated to be 400 times higher than that of aspirin, which was used as a standard [533]. Furthermore, significant analgesic properties were demonstrated for the related prenylated bisabolane, *O*-11,15-cyclo-14-bromo-14,15-dihydrorogiol-3,11-diol (**637**), which was able to signal directly to primary afferents, through a mechanism dependent on the activation of opioid receptors [538].

An acetone extract of *L. nipponica* yielded the bromophenol **985**, which showed weak inhibition ($IC_{50} = 76.6$ μ*M*) of glucose 6-phosphate dehydrogenase (G6PD). G6PD inhibitors are considered as a potential therapy for obesity [805].

The highly brominated aromatic compounds **988** and **989** were identified as inhibitors of the protein tyrosine phosphatase 1B (PTP1B) with IC_{50} values of 3.0 and 2.7 μg/cm^3, respectively. Moreover, the brominated naphthalene derivatives **990–992** were identified in the same extract, but showed weak inhibition of PTP1B [807]. Pinnasterol (**1003**), acetylpinnasterol (**1004**) and the related steroids **1005–1008** have shown activity as molting hormones [814, 815]. 5-Hydroxymethylfurfural (**1018**), floridoside (**1028**) and D-isofloridoside (**1029**) have exhibited antioxidant activity [828, 831].

5 Ecological Functions

Irrespective of their taxon of origin, the chemicals that play a prominent role in interspecific interactions are rarely the same substances used by an organism to meet the daily challenges of living, such as respiration, digestion, excretion, or, in

the case of plants, photosynthesis. Despite their name, secondary metabolites are by no means of secondary importance to the life of the organisms and in most cases are restricted to certain organisms where they fulfill specific roles, thus being essential to their survival. The functions of marine and terrestrial natural products have obvious analogies as they primarily act as toxins, antipredator defense substances, and pheromones. Furthermore, chemical ecology studies have also highlighted their importance in the prevention of fouling, competition for space and nutrients, and mediation of larval settling and metamorphosis.

5.1 Antifeedant Activity and Toxicity to Marine Organisms

The ecological significance of marine metabolites in the chemical defense systems of the producing organisms are frequently proposed on the basis of repellence, feeding inhibition, and/or toxicity exerted on various marine animals, especially those connected to their food chain.

The chamigrane elatol (**59**) and the laurane isolaurinterol (**161**) showed potent antifeedant activities in feeding assays conducted on coral reefs and in the laboratory, while aplysin (**195**), which is a 2,7-epoxy analogue of isolaurinterol (**161**), was inactive [898]. In a more recent study, besides elatol (**59**), the sesquiterpenes isoobtusol (**49**) and palisadin A (**278**) showed equally potent antifeedant properties [166]. Additionally, elatol (**59**) reduced the feeding activity of the crab *Pachygraphus transversus* and the sea urchin *Lytechinus variegatus* [899], but surprisingly was found palatable to the black sea urchin *Echinometra lucunter* [175].

The chamigrane **84** and the rearranged chamigrane **143** were toxic to the reef damselfish *Pomacentrus coeruleus* at concentrations of 15 μg/cm^3 [188]. Cyclolaurenol (**233**), cupalaurenol (**418**) and their respective acetates (**234** and **419**) showed ichthyotoxic activity against guppies at concentrations of 5–10 ppm [305].

Parguerol (**514**), parguerol 19-acetate (**515**), parguerol 7-acetate (**516**), **517**, **519**–**521**, **523**, **525**, **527**, **535**–**538**, **540**, **542**, and **543** exhibited weak to moderate antifeedant activity against young abalone (*Haliotis discus hannai*) and young sea urchins (*Stronglyocentrotus nudus* and *Stronglyocentrotus intermedius*), with the exception of parguerol triacetate (**521**), 2-deacetoxy-deoxyparguerol (**523**), and deoxyparguerol 16-acetate (**527**), which showed potent activity against *H. discus hannai*. Furthermore, **521** and **527** were active against *S. nudus* and *S. intermedius* [477].

The triterpenes aplysiols A (**648**) and B (**668**), in a toxicity assay, were lethal to *Gambusia affinis* at a concentration of 10 ppm and active against the goldfish *Carassius auratus*, in a feeding-deterrence test, at a concentration of 50 μg/cm^2 [549].

The acetogenins (3*Z*)-laurenyne (**798**) and (−)-(3*E*,6*R*,7*R*)-pinnatifidenyne (***ent*-812**) showed antifeedant activity against *C. auratus* at 50 μg/cm^2 concentrations, while brasilenol (**398**), (*E*)-pinnatifidenyne (**814**), (+)-(3*E*, 6*R*,7*R*)-obtusenyne (***ent*-895**), and (+)-(3*Z*,6*R*,7*R*)-obtusenyne (***ent*-896**) were inactive [407].

Aplyparvunin (**861**) showed potent ichthyotoxicity against the mosquito fish with a lethal concentration of 3 ppm within 24 h [291].

The acetogenins panacene (**746**) [78], brasilenyne (**891**), (*Z*)-dihydrorhodophytin (**810**) and (*Z*)-isodihydrorhodophytin (**817**) [221], as well as the sesquiterpenes brasudol (**432**) and isobrasudol (**433**) [419] exhibited variable levels of inhibition of fish feeding activity. Pacifigorgiol (**485**), a highly rearranged sesquiterpene, exhibited toxicity towards the reef-dwelling fish *Eupomacentrus leucostictus* [900].

Dactylallene (**906**) exhibited significant toxicity against the mosquito fish (*G. affinis*) at 10 ppm and deterred the goldfish (*C. auratus*) at a concentration of 100 μg/cm^2 of food pellets [771].

5.2 Brine Shrimp Toxicity

The toxicity of marine metabolites and subsequently the ability to offer chemical protection against predators has been estimated frequently by lethality exerted on the brine shrimp *Artemia salina*. Further to this type of preliminary indication, documentation of ecological functions then requires field assays with specialized predators. The brine shrimp lethality assay was also for many years considered as a useful tool for the preliminary assessment of cytotoxicity to cancer cells. Since its introduction in 1982 by McLaughlin and co-workers [901], this test has been used for the bioguided isolation of in vivo-active natural products.

Elatol (**59**) and the chamigrane **92** exerted 100% mortality to brine shrimp after 24 h of incubation (0.5 mg/cm^3), whereas isopinnatol B (**553**) made the animals hyperactive. Obtusol (**28**), caespitane (**333**), and caespitol (**337**) showed low levels of toxicity, while isoobtusol acetate (**50**), puertitol B acetate (**312**), 8-acetylcaespitol (**338**), caespitenone (**349**), furocaespitane (**352**), laucapyranoid A (**372**), dactylomelol (**600**), and dactylopyranoid (**631**) were found to be inactive [50].

The epoxy derivative **82** of okamurene E debromoallolaurinterol acetate (**150**), and allolaurinterol acetate (**152**) exhibited potent activity in the brine shrimp assay, **41**, **424**, and epilaurallene (***ent*-854**) showed weak activity, whereas laurene (**148**) and desepilaurallene (**862**) were found inactive [152].

Laurecomins A (**140**) and B (**37**), **434**, and **435** displayed potent brine shrimp toxicity, but laurecomins C (**2**), D (**94**), and **7** displayed moderate or weak activity [84].

Pacifenol (**105**) displayed 90% toxicity to brine shrimp (23 μg/cm^3), while 2,10-dibromo-3-chloro-α-chamigrene (**5**), deoxyprepacifenol (**87**), and prepacifenol acetate (**89**) showed moderate activity [84, 89, 109]. A number of semisynthetic derivatives of pacifenol (**105**) were also assayed in a similar manner [852].

Yicterterpene A (**111**), with a chlorination at C-9, exhibited higher levels of inhibitory activity against the marine zooplankton *A. salina* than yicterterpene B (**112**), featuring a bromine at the same site [229].

In a comparative study, β-snyderol (**249**) was found as the most active metabolite, among laurencienyne (**819**) and (3*E*)-13-epilaurencienyne (**821**), which exhibited the lowest toxicity to *A. salina* [321].

Debromoallolaurinterol (**149**) exhibited potent toxicity to *A. salina* ($LD_{50} = 1.8\ \mu M$), while the sesquiterpenes **6**, **122**, laurene (**148**), debromofiliformin (**213**), filiformin (**214**), 12-bromo-filiformin (**216**), okamurenes A (**331**), B (**332**), C (**322**), D (**321**), and E (**10**) and α-isobromocuparene (**417**) and the C_{15} acetogenins **795**, laureatin (**864**), okamuragenin (**869**), neolaurallene (**899**), and (*E*)-(12*Z*)-laurediol (**938**) showed moderate or weak toxicity [109].

Deacetylparguerol (**513**), parguerol (**514**), **524**, deacetylisoparguerol (**539**), and isoparguerol (**540**) were also evaluated for their toxicity to *A. salina*, but only parguerol (**514**) and isoparguerol (**540**) showed marginal toxicity at a concentration of 0.5 μ*M* [476].

Prevezols A (**616**) and B (**617**) were proven toxic to *A. salina* ($LC_{50} = 6.35$ ppm) [527] and so was neoirietetraol (**589**) ($LC_{50} = 40.1\ \mu M$), while (3*Z*)-laurenyne (**798**) showed a weaker effect ($LC_{50} = 467.0\ \mu M$) [513].

5.3 Antifouling Activity

Biofouling represents one of the most serious problems in the modern maritime industries and its control is one of the biggest challenges of marine biotechnology. When a surface is submerged in seawater, a biofilm forms composed of microorganisms rapidly covering the surface that is subsequently colonized by algae and invertebrates, culminating in its corrosion. Settlement of marine invertebrates on the hulls of ships results in reduction of speed, increased fuel consumption, and increased air pollution. Marine natural products have attracted significant interest as candidate molecules towards the development of new efficient and biodegradable antifouling marine paints [902, 903].

The sesquiterpenes 10-bromo-9-hydroxy-α-chamigrene (**14**), deschlorelatol (**56**), allolaurinterol (**151**), 3-acetoxy-(*E*)-γ-bisabolene (**305**), and the aristolane **490** exhibited moderate antialgal activity against the unicellular alga *Chlorella fusca*, while (–)-(10*R*)-10-bromo-α-chamigrene (**1**), rigidol (**53**), (+)-(10*S*)-10-bromo-β-chamigrene (**55**), and elatol (**59**) were inactive [81, 259]. Elatol (**59**) and deschloroelatol (**56**) strongly inhibited the settlement of the barnacle *Balanus amphitrite* cyprids and the bryozoan *Bugula neritina* larvae. However, their strong toxicity restricts their commercial development as they severely affect the survival rate of *B. amphitrite* nauplii [81, 904]. In another study from the same group, obtusol (**28**), caespitane (**333**), and caespitol (**337**) showed low levels of antialgal activity (*C. fusca*), while isoobtusol acetate (**49**), elatol (**59**), **135**, puertitol B acetate (**312**), 8-acetylcaespitol (**338**), caespitenone (**349**), furocaespitane (**352**), laucapyranoid A (**372**), isopinnatol B (**553**) and dactylomelol (**600**), and dactylopyranoid (**631**) were inactive [50]. 3-*epi*-Perforenone A (**379**), **381** and 4-hydroxy-1,8-*epi*-isotenerone (**397**) were devoid of any activity against the alga

C. fusca [399]. Yicterterpene A (**111**), chlorinated at C-9, exhibited higher levels of inhibitory activity against a marine phytoplankton (*Heterosigma akashiwo*) than its brominated analogue yicterterpene B (**112**) [229].

The triterpenes dehydrothyrsiferol (**649**), saiyacenols A (**669**), B (**670**) and C (**691**), and 28-hydroxy-saiyacenol B (**671**) showed antifouling activity against benthic diatoms (*Phaeodactylum tricornutum*, *Cylindrotheca* sp., *Navicula* cf. *salinicola*) and a macroalgal zoospore (*Gayralia oxysperma*). Comparison of their chemical structures in relation to the levels of activity indicated that the hydroxy group at C-28 is an important structural element for exhibition of activity [564].

The antifouling activity of omaezallene (**709**) and its congeners **710** and **711** was evaluated against the barnacle *B. amphitrite*. Omaezallene (**709**) and **710** showed potent settlement inhibition against *B. amphitrite* cyprids with ED_{50} values of 0.22 and 0.30 μg/cm^3, respectively, while the activity of **711** was moderate ($ED_{50} = 1.5$ μg/cm^3). Intricatetraol (**700**) and aplysiallene (**740**) exhibited much weaker activity. The ecotoxicity of omaezallene (**709**) against the marine crustacean *Tigriopus japonicus* was quite low ($LC_{50} = 2.5$ μg/cm^3 in 48 h), especially when compared to that of commercial antifoulants [584].

6 Concluding Remarks

Algae, ranging in size from microscopic forms to gigantic representatives, form the basis of a complex food web involving all organisms living within the marine ecosystem. Through the years, humans have used them as food, as colorants, as fertilizers, as ingredients in folk medicinal recipes, as producers of polysaccharides, and, in the last few decades, as a source of unique metabolites with pharmacological potential.

In its current status, the genus *Laurencia*, one of the most diverse genera of marine algae, is comprised of 146 taxonomically accepted species and along with the genera *Chondrophycus*, *Osmundea*, *Palisada*, *Yuzurua*, and *Laurenciella* is included in the so called "*Laurencia* complex". The genus *Laurencia* seems to be actively evolving within the "*Laurencia* complex", considering the number of species and infrageneric categories that have been established and are constantly added on the basis of their morphological features with phylogenetic significance [22].

Even though species of *Laurencia* have been among the most well-known seaweeds in local communities for many centuries and various edible species, such as *L. undulata* and *L. nidifica* (known as "mane'one'o" in Hawaii) [828, 905], were consumed throughout the Pacific Ocean, the genus owes its reputation to the amazing treasure trove of the structurally diverse and unique metabolites that have been constantly isolated from representatives of this genus over the last few decades. The continuous interest of marine chemists, ecologists, and biologists in this genus is reflected upon by the increasing number of scientific articles reporting the isolation and evaluation of biological properties of *Laurencia* metabolites. The frequently unique structures and the significant levels of

bioactivity that they often exhibit render them challenging targets for synthetic chemists that through their efforts for enantioselective syntheses have discovered new synthetic methodologies and have confirmed or revised the proposed structures for the natural products (see Fig. 8).

The observed extraordinary chemical variation of *Laurencia*, even within morphologically homogeneous species and populations, has been the subject of numerous studies that have provided frequently contradictory explanations. Nevertheless, this chemical variation could not be ascribed only to environmental conditions or genetic variables.

The co-evolution of the algae with marine grazing invertebrates has enhanced the biosynthesis of complex secondary metabolites that act as chemical defenses to protect the algae from predators. These metabolites, in such cases, are sequestered through the food chain in the mollusks feeding on *Laurencia*, supplementing their chemical armory. For this reason, in the present chapter, metabolites isolated from *Aplysia* sea hares (invertebrates feeding on *Laurencia* most frequently) with postulated origin from *Laurencia* have been included.

Altogether, 1047 secondary metabolites, often featuring new carbocycles, have been isolated from *Laurencia* and *Aplysia* species, and have been organized in the present contribution according to their chemical class, covering the literature up to August 2015 (see Fig. 9).

The metabolites included were classified into sesquiterpenes, diterpenes, triterpenes, acetogenins, indoles, aromatic compounds, steroids, and miscellaneous compounds. Among the isolated metabolites, sesquiterpenes comprise the most abundant class with 512 representatives, followed by cyclic ether-containing and linear C_{15} acetogenins encompassing 244 chemical structures. Diterpenes and triterpenes include 133 and 59 compounds, representing the third and fourth chemical classes in abundance (see Fig. 10).

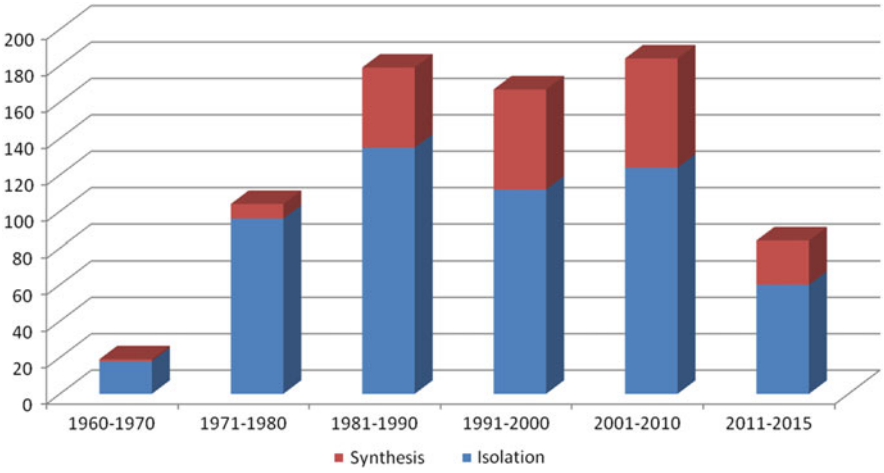

Fig. 8 Number of publications on the isolation and synthesis of *Laurencia* metabolites per decade

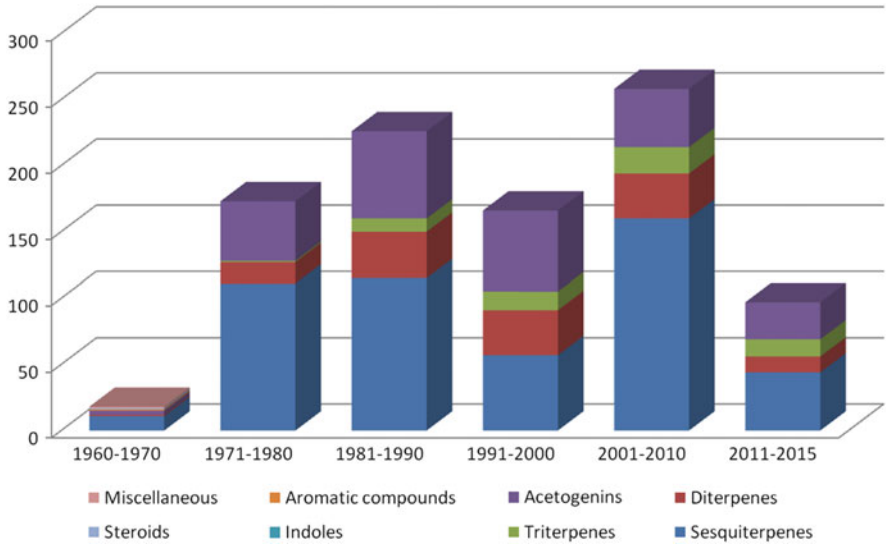

Fig. 9 Number of metabolites isolated per decade from *Laurencia* species according to their chemical class

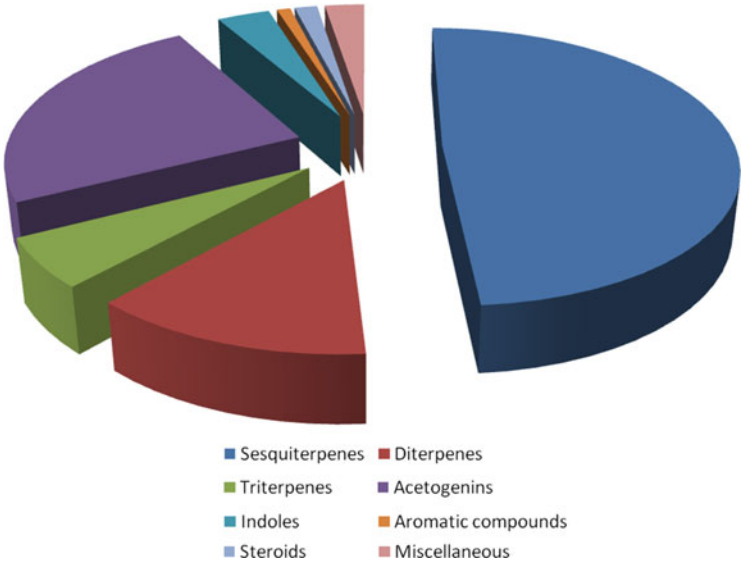

Fig. 10 Contribution of the different chemical classes to the total number of metabolites isolated from *Laurencia* species

The majority of metabolites are halogenated, with brominated compounds being more abundant than chlorinated ones, regardless of the relative concentration of bromide and chloride ions in the sea water.

Despite the fact that there are now available sophisticated chromatographic and spectroscopic techniques allowing the isolation and structure elucidation of minor metabolites in sub-milligram amounts, the astonishing number of already isolated *Laurencia* metabolites renders efforts towards the discovery of new metabolites constantly more copious. This difficulty highlights the necessity for integrated platforms, including analytical techniques, software and databases for the accelerated dereplication of known metabolites in the extracts and the detection of potentially new natural products at the early stages of phytochemical analysis.

Even though a relatively high number of *Laurencia* metabolites have been evaluated for a wide spectrum of bioactivities and many of them displayed notable levels of activity, the chemical wealth of the genus has not been systematically assessed. The unparalleled chemical ensemble of *Laurencia* metabolites represents a rich database with unique structures for in silico structure-activity studies for the design of new drugs. This represents a treasure trove of compounds available to the pharmaceutical industry, which through currently existing automated high-throughput in vitro screens can examine thousands of compounds or extracts in very short periods of time.

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Maria Harizani acquired a B.Sc. degree in Pharmacy from the National and Kapodistrian University of Athens, where she went on to obtain her M.Sc. degree in Pharmacognosy and the Chemistry of Natural Products. Her thesis focused on the isolation of secondary metabolites from species of red algae in the genus *Laurencia.* In further pursuing her research interests on bioactive natural products from marine organisms, she is currently a Ph.D. student at the Faculty of Pharmacy under the joint mentorship of Prof. Vassilios Roussis and Assistant Prof. Efstathia Ioannou.

Efstathia Ioannou received her B.Sc. degree from the Agricultural University of Athens in 2003 and her M.Sc. and Ph.D. degrees from the National and Kapodistrian University of Athens in 2005 and 2009, respectively, where she studied the isolation and structure elucidation of bioactive natural products from marine algae under the supervision of Prof. Vassilios Roussis. She carried out postdoctoral research on the chemistry of marine actinobacteria with Prof. William Fenical at Scripps Institution of Oceanography, before returning to Greece in 2010 to take up a lectureship at the Faculty of Pharmacy at the National and Kapodistrian University of Athens, where she is currently an Assistant Professor. Her research interests are on bioactive natural products from marine macro- and microorganisms.

Vassilios Roussis obtained his B.Sc. degree from the National and Kapodistrian University of Athens and his Ph.D. degree from the University of Iowa under the supervision of Prof. David F. Wiemer. Subsequently, he undertook postdoctoral research at Scripps Institution of Oceanography, La Jolla, California, with Prof. William Fenical and at the National Center for Scientific Research "Demokritos", Greece, with Dr. Basilis Mazomenos. In 1995, he joined the Faculty of Pharmacy at the National and Kapodistrian University of Athens, where in 2006 he was promoted to full professor. Since 2008, he has served as the Director of the Laboratory of Pharmacognosy at the Department of Pharmacognosy and Chemistry of Natural Products. His research interests focus on the chemical investigation of marine organisms from the eastern Mediterranean Sea.