Natural Halogenated Non-Terpenic C_{15}-Acetogenins of Sea Organisms

VALERY M. DEMBITSKY[1], ALEXANDER G. TOLSTIKOV[2] and GENRICH A. TOLSTIKOV[3]

[1]*Department of Pharmaceutical Chemistry and Natural Products, School of Pharmacy, P. O. Box 12065,The Hebrew University of Jerusalem, Jerusalem 91120 (Israel)*

E-mail: dvalery@cc.huji.ac.il

[2]*Institute of Technical Chemistry, Ural Branch of the Russian Academy of Sciences, Ul. Lenina 13a, Perm' 614000 (Russia)*

[3]*Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, Pr. Akademika Lavrentyeva 9, Novosibirsk 630090 (Russia)*

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Abstract

Halogenated non-terpenic C_{15}-acetogenins of sea organisms make up a large group of natural compounds. Structures of more than 130 compounds are considered and data on their biological activity are presented.

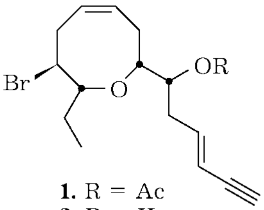
Contents

INTRODUCTION

Lately, non-terpenoid metabolites that make up a separate group of C_{15}-acetogenins have been discovered [1, 2]. These compounds are derivatives of straight-chain fatty acids and are formed in the organisms by condensation of acetate (acetyl-Co-A) [3]. The difference of C_{15}-acetogenins from C_{15}-sesquiterpenes consists in different biogenesis pathways. Sesquiterpenes, like all terpenoids, are formed by condensation of isopentylpyrophosphate [4]. Acetogenins are widespread in nature: they have been detected in plants [5], in sea red algae belonging to the genus *Laurencia* [3, 6] and in sea invertebrates [2, 7, 8]. Halogenated acetogenins considered in the present review are synthesized mainly by sea algae and only few of them have been found in invertebrates.

ACETOGENINS OF SEA ALGAE

The first halogenated acetogenin isolated in 1965 from sea red alga *Laurencia glandulifera* independently by two teams of Japanese [9] and Australian [10] scientists was called laurencin (**1**). The following investigations of these teams not only confirmed the presence of the bromine-containing metabolite, but also permitted to establish its stereochemistry [11, 12]. Biosynthesis of laurencin (**1**) has been carried out by action of lactoperoxidase, bromide and



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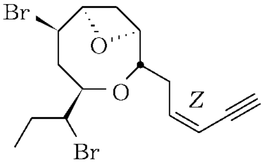

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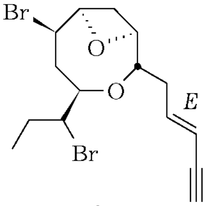

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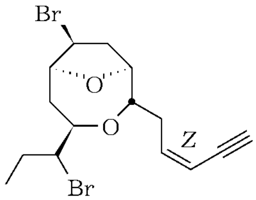

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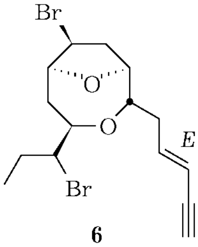

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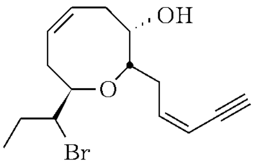

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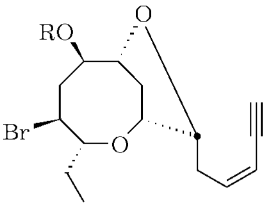

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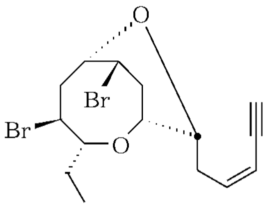

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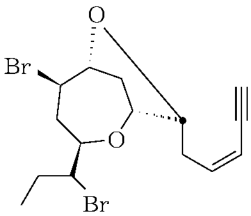

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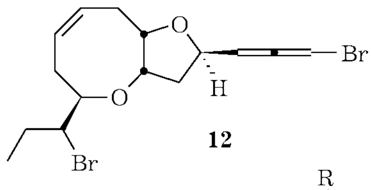
hydrogen peroxide on (*3E, 6R, 7R*)-laurediol [13, 14]. Diacetyllaurencin (**2**) which is an intermediate in laurencin (**1**) biosynthesis was later found in the alga *Laurencia nipponica* [13, 15]. Bicyclic analogs of laurencin – Z-laurentin (**3**) and E-laurentin (**4**), Z-isolaurentin (**5**) and E-isolaurentin (**6**), as well as prelaurentin (**7**), have been isolated from *L. nipponica* [16–20]. Later studies of the alga *L. nipponica* demonstrated that its extracts contained geometric isomers of (**5**) and (**6**), and also acetyllaurefucin (**8**), laurefucin (**9**), isoprelaurefucin (**10**) and metabolite (**11**) [15, 21–23]. The latter four compounds differ in the position of the oxide bridge. Compounds (**1**)–(**10**) inhibited in various degree the effect of pentobarbital in mice and displayed a high insecticide activity on gnat and mosquito larvae [24].

An interesting group of compounds – halogenated allenes (**12**)–(**18**) – has been detected in various alga species of the genus *Laurencia*. So, laurallene (**12**) – the first compound from this group – was found in *L. nipponica* [25] growing off the coasts of Japan. Another alga species – *L. okamurai* – contained chlorohydrin (14) and its acetate (15) [26], and from the species *L. microcladia* were isolated bicyclic microcladallenes A (**16**), C (**17**) and B (**18**) [27].

A bicyclic structure related to those of metabolites (**12**)–(**15**) is characteristic of isolaurallene (**19**) and neolaurallene (**20**) produced by algae *L. nipponica* [28, 29] and *L. okamurai* [30], respectively.

Halogenated bicyclic allenes (**21**)–(**24**) found in the Mediterranean alga *L. obtusa* [31–35] contain an oxacyclododecane skeleton which is rare even in sea organisms. The structure of one of them – obtusallene I (**21**) – has been confirmed using X-ray diffraction analysis [32].

Allenes of new structural types (**25**)–(**32**) have been detected in algae of genus *Laurencia*. Thus, kumausallene (**25**) is contained in *L. nipponica* [36], an analog of kumausallene (**26**) [37, 38] okamurallene (**27**) [26, 39, 40], desoxyokamurallene (28) [41], isookamurallene (**29**) [25, 40, 41] and allene containing a chlorine atom (**30**) [26] have been found in *L. okamurai*. Gratiosallene (**31**) has been isolated from ethanol extracts of *L. obtusa* [42], and allene (**32**) is produced by the alga *L. implicata* [43, 44].



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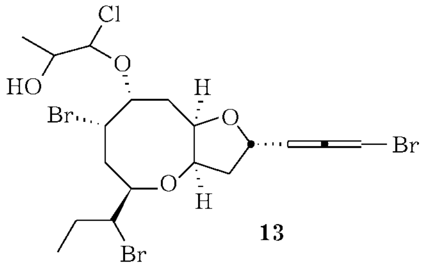

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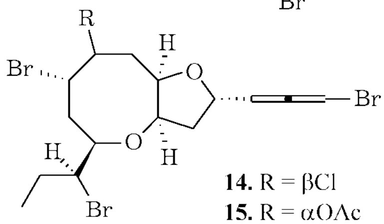

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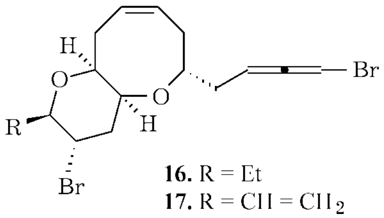
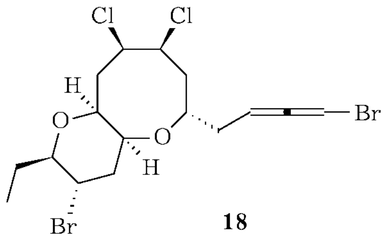


16. R = Et
17. R = CH = CH_2



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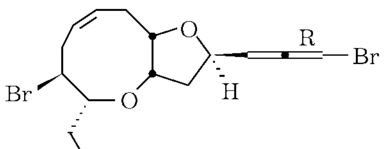

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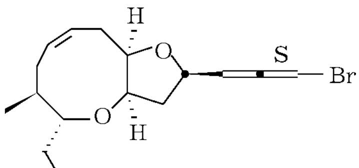

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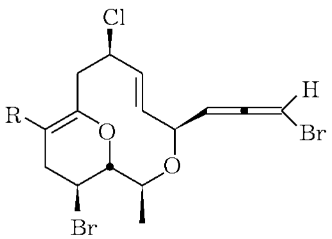

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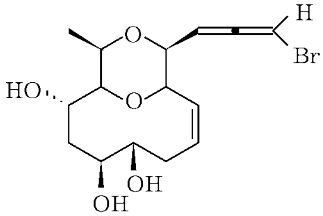

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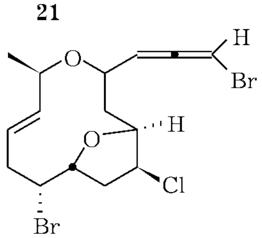

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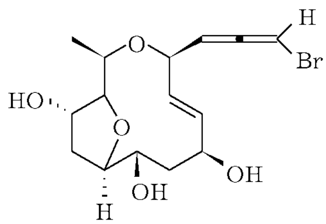

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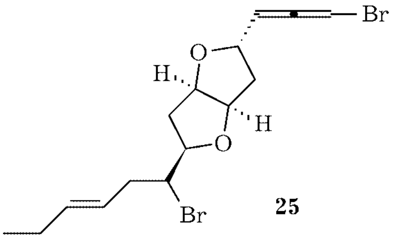

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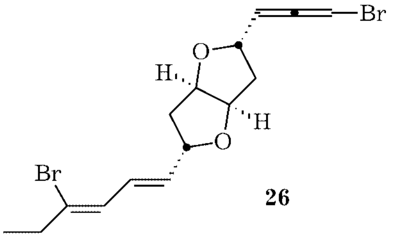

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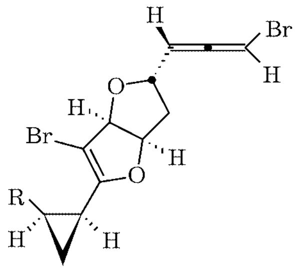

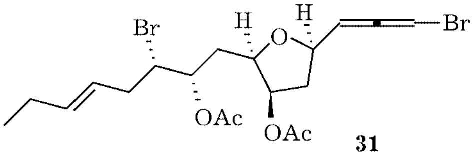

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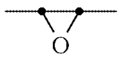
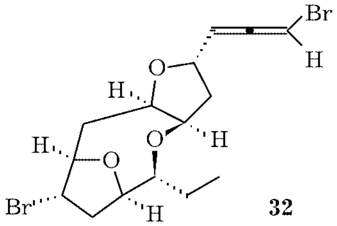
27. R = 

28. R = CHCH = $CHCH_3$
29. R = CH_2Ac
30. R = $CH(Cl)CH(OH)CH_3$



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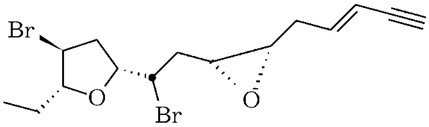
A series of new acetogenins containing a tetrahydrofuran ring (**33**)–(**41**) have been detected in various species of *Laurencia* algae. For example, compounds (**33**)–(**39**) have been found *in L. nipponica* [45–48], bisezakyne A (**40**) containing chlorine and bromine atoms has been isolated from methanol extract of *Laurencia* growing near the Okinawa Island [49], and gratiosyne (**41**) turned out to be a metabolite of alga *L. obtusa* collected near the Canary Isls [50].

Laurencia algae produce metabolites whose molecules have two successively bound tetrahydrofuran cycles. Notorin (**42**) has been isolated from the Japanese alga *L. nipponica* [51], whereas metabolite (**43**) is produced by the Hawaiian species *L. majuscula* [52]. Metabolites (**44**), (**45**) isolated from the alga *L. obtusa*



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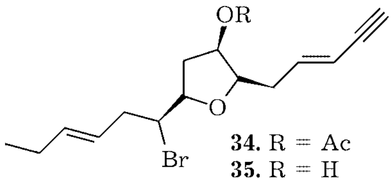
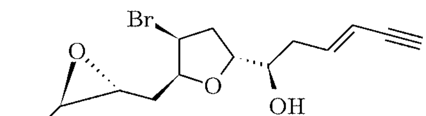


34. R = Ac
35. R = H



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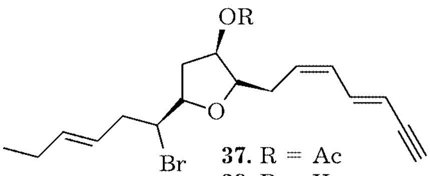
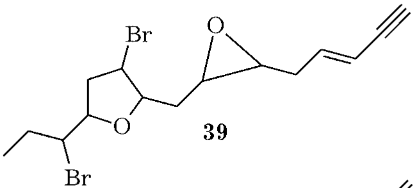


37. R = Ac
38. R = H



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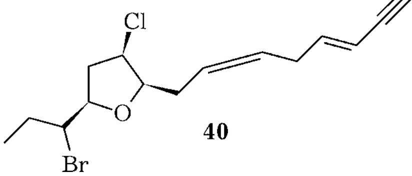

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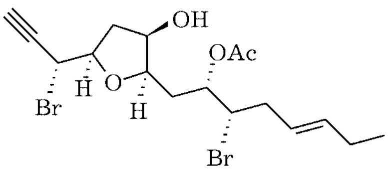

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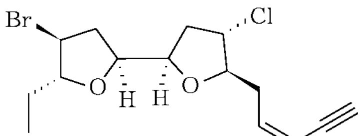

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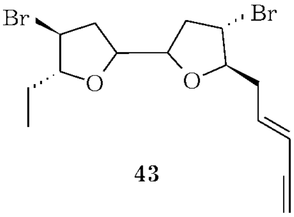

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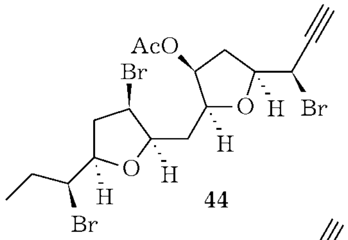

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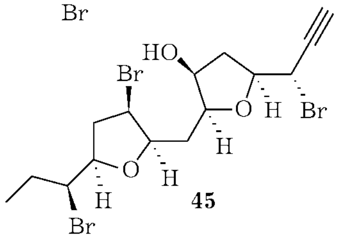

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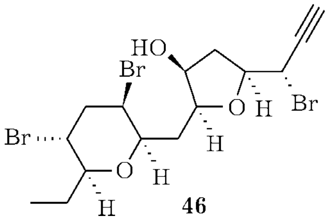

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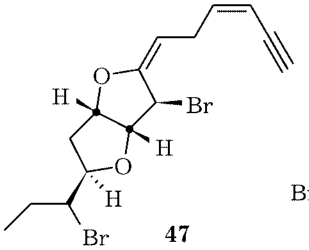
(Canary Isls) [50] differ in the character of bond of cyclic fragments. The same alga produces a metabolite (**46**) of somewhat different type [53].

Laurenenynes A (**47**) and B (**48**) were contained in extracts from two alga species – *L. tristicha* [54] and *L. japonensis* [55]. The two compounds turned out to be unstable, and even when stored at −18 °C, they slowly converted into respective furan derivatives [54]. The algae *L. obtusa* [56] living in shores of Spain and Sicily turned out to be a producer of obtusin (**49**) and neoobtusin (**50**) [57].

Recently, it was proved that algae of *Laurencia* genus contained both mono- and bicyclic acetogenins of tetrahydropyrane type. Thus, ketometabolite scanlonenin (**51**) was isolated from the alga *Laurencia obtusa* growing near the coasts of Ireland [59]. Bicyclic compounds (**52**)–(**55**) which may be considered as ketone (**51**) derivatives were found in *L. japonensis* [55].

Bisezakyne B (**56**), dactylyne (**57**) and srilankinyne (**58**) containing bromine and chlorine atoms are synthesized by an alga belonging to the genus *Laurencia* whose specific denomination has not been established [49].

The structures discussed above contain cyclic fragments formed by means of dehydration processes with participation of hydroxyl groups; therefore it is rather easy to detach a unitary linear C_{15}-skeleton. More complicated transformations have taken place in the carbon chain of metabolites (**59**)–(**66**). As one can see from the formulae presented herein below, the formation of these metabolites requires a single, double or triple reclosures of the chain. Therein, formation of oxygen-containing cyclic fragments also takes place.



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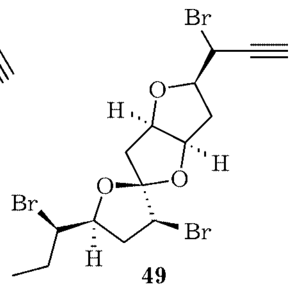

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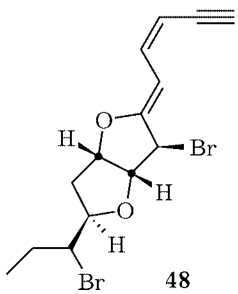

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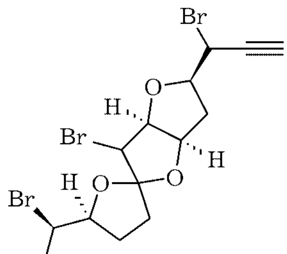

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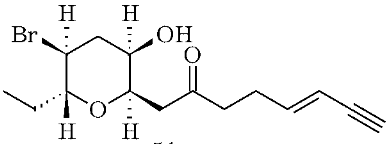

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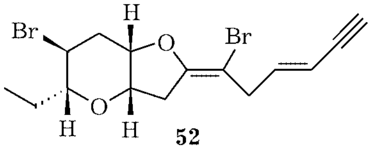

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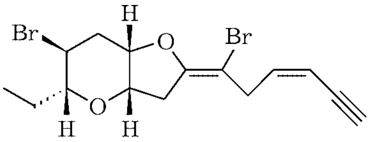

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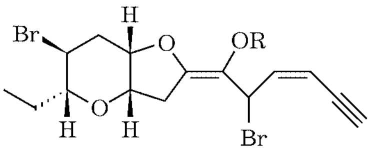
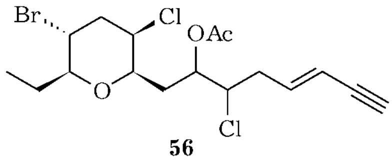


54. R = CH_3
55. R = H



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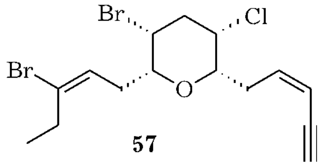

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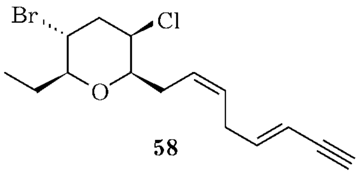
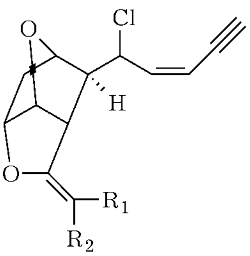


58

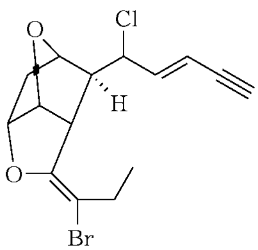
Going to the question of sources of these unique metabolites, let us note that the alga *Laurencia nidifica* growing near the Hawaii coasts produces *cis*-maneonene A (**59**), *cis*-maneonene B (**60**) and *trans*-maneonene B (**61**) [59–61]. *Cis*-maneonene C (**62**) has been isolated from *L. nidifica* [61] and from an unidentified alga from genus *Laurencia* collected near the coasts of Malaysia [62]. Isomaneonene A (**63**), isomaneonene B (**64**) are produced by the alga *L. nidifica* [59–61], and lembyne B (**65**) and its E-isomer (**66**) have been isolated from the Malaysian algae *Laurencia* sp. [62]. Compounds (**62**)–(**66**) have demonstrated a high antibacterial activity [62].

A family of halogenated acetogenins (**67**)–(**74**) has been discovered lately mainly in sea algae. So, isolaurepinnacin (**67**) was found in the extract of the algae *Laurencia pinnata* [63]. The isomer (**68**) of the already known isoprelaurefucin (**11**) was found in the alga *L. nipponica* [48]. Rogiolenyne A (**69**), rogiolenyne B (70), rogiolenin D (**71**), rogioloxepane A (**72**), rogioxepan B (**73**) and rogioxepan C (**74**) were isolated from methanol extracts of *L. microcladia* [64–66].

A surprising diversity is characteristic of metabolites having an oxacyclooctane element. In addition to the above described metabolites of this type (structures (**1**)–(**10**)), let us present



59. R_1 = Br, R_2 = Et
60. R_1 = Et, R_2 = Br



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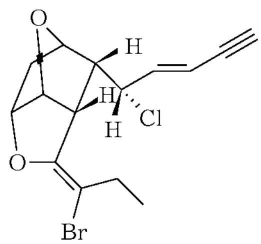

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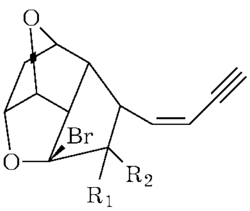
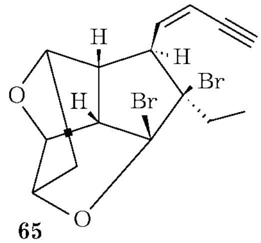


63. R_1 = Et, R_2 = Br
64. R_1 = Br, R_2 = Et



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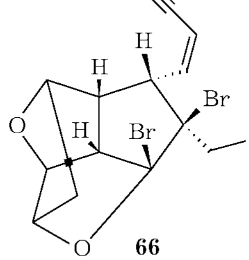

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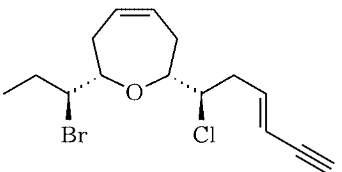
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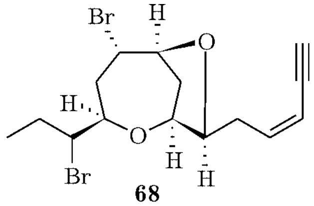
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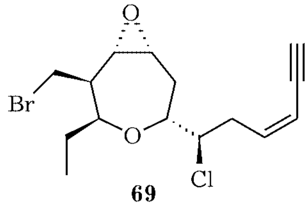
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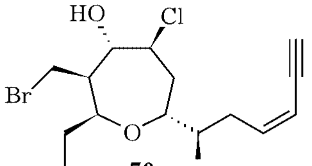
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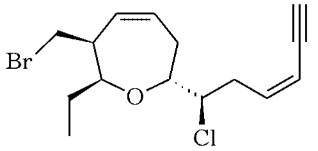
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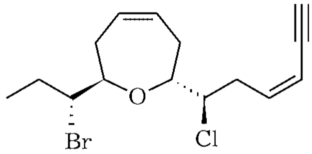
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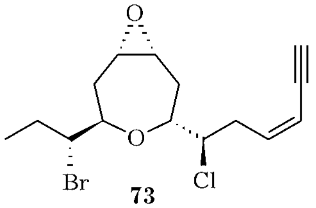
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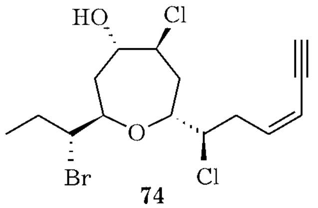
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the information about 22 acetogenins produced by algae.

Bromo-, chloro- and mixed eight-membered acetogenins are produced by various alga species belonging to the genus *Laurencia*. Thus, intricenin (**75**), bermudeninol (**81**) and its acetate (**82**) have been isolated from *L. intricata* [67, 68]. Laurentienin (**76**) [69–71], laurenin (**77**) [72], epoxy-*trans*-dihydrorhodophytin (**78**) [73], *trans*-rhodophytin (**79**) [74] and *trans*-chondriol (**80**) [74] were detected in methanol extracts of algae *L. obtusa*. Poiteol (**83**) was found in *L. poitei* [75], and epoxy-rhodophytin (**84**), *cis*-rhodophytin (**85**), *trans*-(86) and *cis*-chondrin (**87**) are contained in the alga *Laurencia* sp. [74, 76].

The alga *Laurencia pinnata* inhabiting in the littoral waters of the Japan Archipelago produces laurepinnacin (**88**) [63], and the alga *L. pinnatifida* synthesizes *cis*-(**89**) and *trans*-pinnatifidienin (**90**) [77, 78].

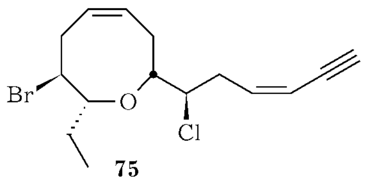
A series of chlorine-containing metabolites (**91**)–(**95**) has been found in extracts of the alga *Laurencia venusta*: *trans*-venustin A (**91**) [79], 3-*cis*-epoxyvenustin (**92**) [80], *trans*-venustin B (**93**) [79], 3-*cis*-venustin (**94**) [80] and venustinene (**95**) [80]. All the compounds isolated possess an antibacterial activity [79, 80].

The alga *L. thyrsifera* growing along the coasts of the southers island of New Zealand produces *cis*-(**96**) and *trans*-(**97**) diols, *cis*-(**98**) and *trans*- (**99**)chloroketones, and metabolite (**100**) [81, 82]. The alga *Laurencia filiformis* growing along the western coast of Australia in the aquatory of Pert city has turned out to be a producer of *cis*-dihydrorhodophytin (**101**) and *cis*-epi-dihydrorhodophytin (**102**) [83]. A red alga *Chondria oppositiclada* living along the Pacific coast of the USA contains chondriol (**103**) [84, 85].

Chlorofucin (**104**) and its dibromo-containing analog (**105**) similar in their structures to the already known metabolites (**8**)–(**10**) have been found in algae *L. snyderae* [75] and *L. implicata* [43, 44], respectively. Three new metabolites (**106**)–(**108**) one of which contained a chlorine atom (**106**) were isolated from the alga *L. gracilis* collected near the shores of New Zeland [86].

Metabolites (**109**)–(**112**) belong to a rare type of oxygen heterocycles. *Trans*-(**109**) and *cis*-(**110**) oxacanes and metabolite (**111**), partially hydrated oxanin derivatives – a nine-membered oxygen-containing heterocycle, have been detected in algae *L. venusta* [78] and *L. implicata* [43, 44].

A bromine-containing acetogenin 1-oxacyclodecane (**112**) has been isolated from the alga *L. implicata* [43, 44].



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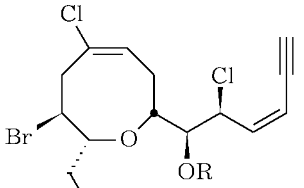
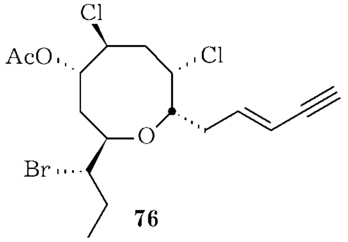


81. R = H
82. R = Ac



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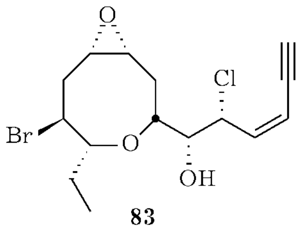

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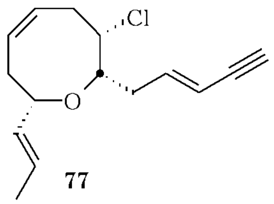

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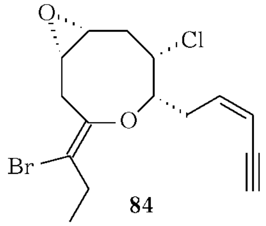

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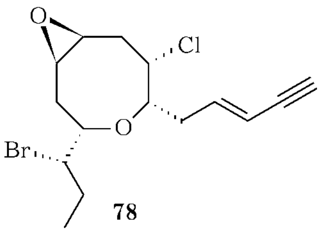

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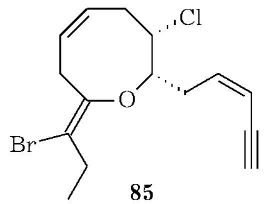

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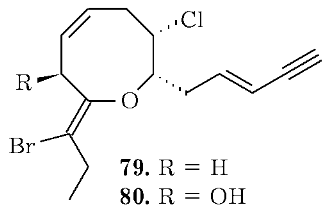
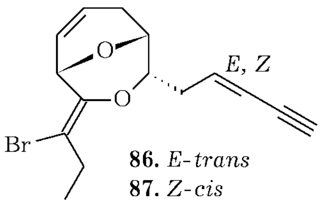


79. R = H
80. R = OH



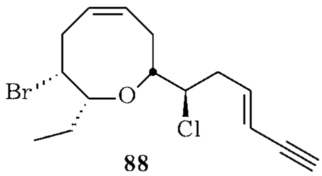
86. *E-trans*
87. *Z-cis*

ACETOGENINS OF SEA INVERTEBRATES

From sea invertebrates, so far a comparatively small number of halogenated acetogenins have been isolated. These compounds have been found in invertebrates that consume algae as food. As many authors [1–3, 6–8] believe, they are ingested with food and can be modified by the enzymes of the invertebrates.

Cis-(**113**) and *trans*- (**114**) analogs of metabolites (**109**) and (**110**) that have been found in algae *L. venusta* [78] and *L. implicata* [43, 44] were isolated from extracts of the mollusk sea hare *Aplysia dactylomela* [87] inhabiting the Caribbean Sea and feeding exclusively on sea algae. Brasilenin (**115**) discovered in another mollusk species *Aplysia brasiliana*, as the authors suppose [88], is also produced by algae. In the same mollusk species, metabolites (**117**) [88, 89] and *cis*-dihydrorhodophytin (**101**) found earlier in the alga *L. implicata* [43, 44] have been detected.

An unusual metabolite having a unique bicyclic skeleton (**116**) whose analogs are not known among algae metabolites has been discovered in the mollusk *Aplysia punctata* [90]



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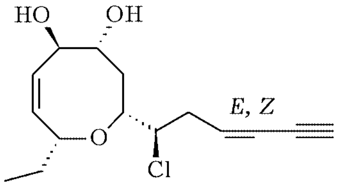
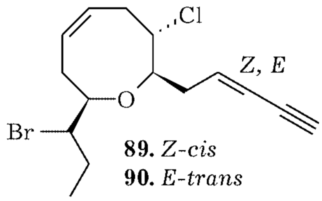
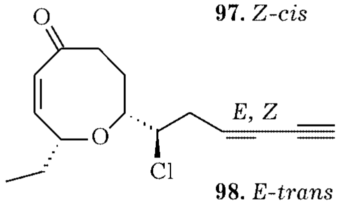


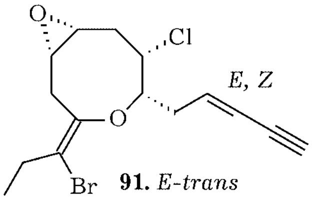
96. *E-trans*
97. *Z-cis*



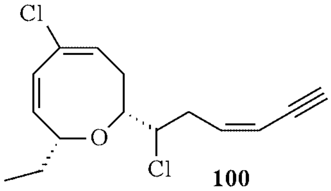
89. *Z-cis*
90. *E-trans*



98. *E-trans*
99. *Z-cis*



91. *E-trans*
92. *Z-cis*



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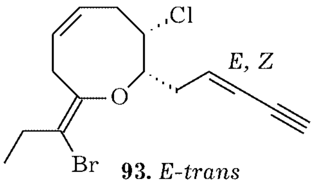
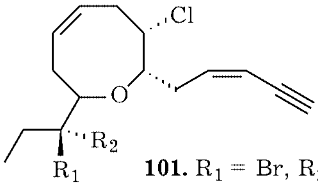
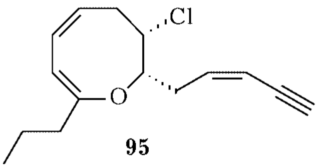


93. *E-trans*
94. *Z-cis*



101. R_1 = Br, R_2 = H
102. R_1 = H, R_2 = Br



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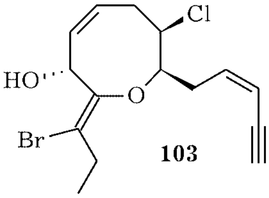
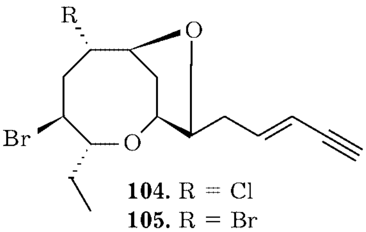
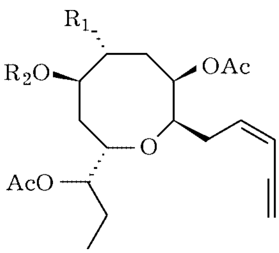


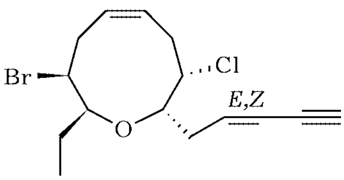
103



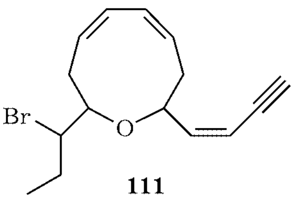
104. R = Cl
105. R = Br



106. R_1 = Cl, R_2 =Ac
107. R_1 = OAc, R_2 = H
108. R_1 = OH, R_2 =Ac



109. *E-trans*
110. *Z-cis*



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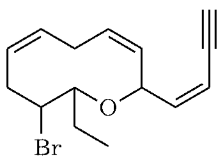

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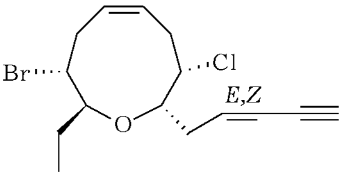
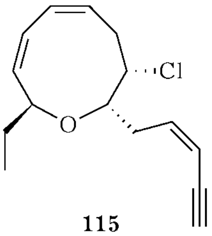


113. *Z-cis*
114. *E-trans*



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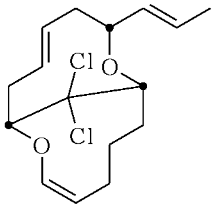

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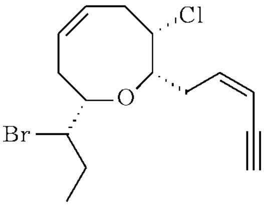

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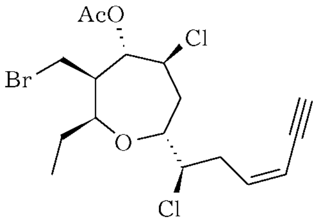

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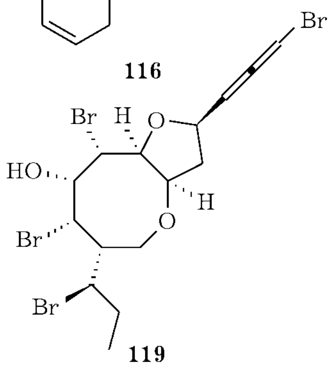


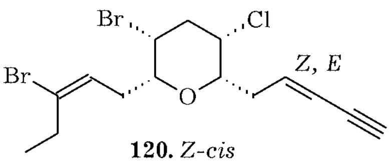
119

living in the littoral zone along the coasts of Italy.

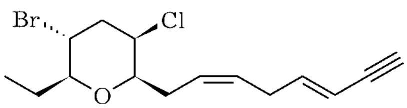
Rogiolenyne C (**118**) found in the sea sponge *Spongia zimocca*, as the authors [64, 91] believe, is a derivative of rogiolenyne A (**69**) and rogiolenyne B (**70**) which were detected in the red alga *Laurencia microcladia* [64]. The latter seem to have been modified by the enzyme system of the sponge [91].

The bromine-containing allene (**119**) that is similar in its structure to chlorohydrin (**14**) and its acetate (**15**) from the alga *L. okamurai* [26] is produced by the sponge *Mycale rotalis* [92, 93].

A series of new halogenated derivatives of tetrahydropyrane (**120**)–(**124**) and (**128**)–(**132**) have been discovered in sea mollusks and sponges. So, *cis*-dactylyne (**120**) and *trans*-isodactylyne (**121**) are produced by the sea hare



120. *Z-cis*
121. *E-trans*



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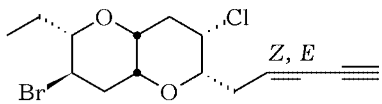
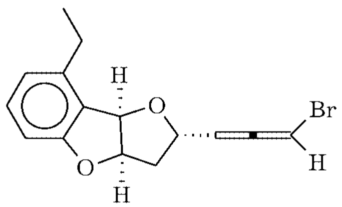


123. *Z-cis*
124. *E-trans*



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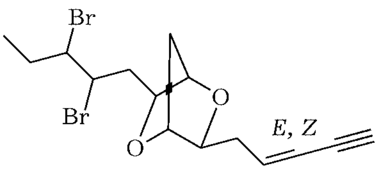
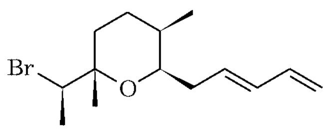


126. *E-trans*
127. *Z-cis*



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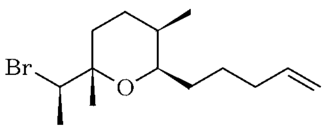

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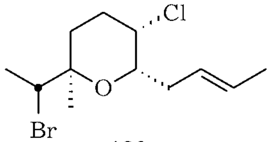

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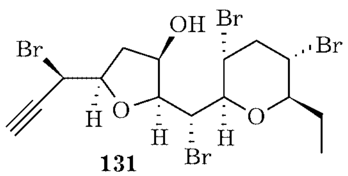

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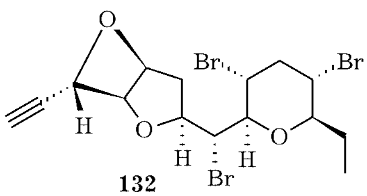

132

Aplysia dactylomela [94, 95]. An analog of these compounds – dactylyne (**57**) – has been detected in the alga *Laurencia* sp. [49]. Srilankenyne (**122**) is produced by another mollusk species – *A. aculifera* living in the vicinities of the island Sri Lanka [96]. Two bromine-containing tetrahydropyranes (**128**) and (**129**) have been isolated from the extract of the sponge *Haliclona* sp. living near the coasts of Australia [97], and the sponge *Haminoea cymbalum* living near the island Guam (the USA) produces kumepaloxane (**130**) [98]. Metabolites (**131**), (**132**) found in the sponge *Mycale rotalis*, as the authors have established [92, 93], have a common biogenesis. It is noteworthy that (**131**) is easily transformed into (**132**). Compound (**131**) is conspicuous by the presence of four bromine atoms.

Cis-isomer (**123**) and *trans*-isomer (**124**) are produced by the mollusk *Aplysia dactylomela* [87], and panacene (**125**) is produced by another mollusk – *A. brasiliana* [99]. Panacene (**125**) possesses powerful antifeedant properties, its strongly diluted solutions scare sharks away [99].

The sea hare *Aplysia oculifera* widespread in Hawaii produces new bicyclic metabolites *trans*-(**126**) and *cis*- (**127**) ocellenynes [100].

CONCLUSION

In this way, C_{15}-acetogenins that form a special class of natural metabolites are especially interesting by their diversity of variants of O-heterocyclization. Many of them have extremely valuable biological activities. Lately, interest in development of complete synthesis of metabolites containing fragments of O-heterocycles of various size has increased [101]. A series of works on the synthesis of oxygen-containing middle-size heterocycles have been carried out. There is no doubt that halogenated C_{15}-acetogenins are going more and more often to become objects of complete synthesis and models for construction of biologically active molecules.

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