Natural Halogenated Diterpenoids

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Abstract

The review is dedicated to a small group of natural compounds of a new type – halogenated diterpenoids. These metabolites are synthesized mainly by marine organisms, and only a small part of them have been found in plants, including fungi. Structures of more than 100 compounds have been considered. Data on their biological activity are presented.

Contents

INTRODUCTION

Diterpenoids are a widespread class of natural compounds that includes molecules of more than 20 structural types [1, 2]. They are produced mainly by plants, microorganisms, sea algae and sea invertebrates. Halogen-containing diterpenoids are so far a not numerous group of compounds of this class. However, the peculiarity of their structure and their manifold biological activity draw progressively more attention. Especially interesting compounds have been isolated from sea algae and sea invertebrates. Marine organisms are producers of diterpenes having unique, sometimes surprising, structure.

One of the main stimuli to study marine metabolites, in particular deterpenoids, is no doubt the search for molecules that not only have a high biological activity, but also supplement databanks used for designing new structures. Halogenated natural metabolites have not so far occupied the due place in plans and programs of researchers engaging in the problems of synthesis of biologically active compounds having a medicinal and agricultural significance. In the present review which continues the series of publications concerning halogenated natural compounds [3–5], the structure and biological activity of chlorine- and bromine-containing diterpenes are discussed.

The main goal of the authors of the present review, as before, is to convince the specialists in fine organic synthesis and biologically active compounds that halogenated natural metabolites are exciting objects of study.

PLANT DITERPENOIDS

Producers of chlorine-containing diterpenes of ent-labdane series include plants of genus *Exocoecaria* (Euphorbiaceae family) widespread in tropical parts of Asia and Africa and in the north-west of Australia [6–8]. Among the 40 species of this genus, plants containing skin irritants and promotors of skin cancer are known [9].

The tree *Excoecaria agallocha* grows along the sea coast of the tropical zone of Africa and East Asia, and is sometimes cultivated along the shore for protection from winds. The leaves and latex of this plant are used in India [11], New Caledonia [11] and Malaysia [12] for preparing arrow poison for fishing. The bark and wood of the tree are used in the traditional medicine of Thailand for treatment of stomach diseases [9]. The wood, latex and leaves contain alkaloids and terpenoids among which agents with anticarcinogenic activity have been found [11–16]. Roots of the tree have served as a source of chlorine-containing diterpenes – agallochines A–C (**1**)–(**3**), and of a secoderivative of agallochine A (**4**) [17].

Multifunctional chlorine-containing lactones have been found in plants of genera *Gutierrezia* (Compositae family) and *Teucrium* (Labiatae family). Thus, from the herbaceous plant *Gutierrezia adracunculoides,* a gueurolide (**5**) [18] has been isolated, and from the plant *Teucrium africanum,* they have succeeded in isolating tafricanines A, B (**6**), (**7**). It has been established that the presence of these diterpenes accounts for the antifidant and antifungal effects of the plant extracts. It is not ruled out that the anticarcinogenic and the antimicrobial activity of the extracts is associated with the presence of tafricanines [19]. Tafricanine B has been found also in *Teucrium racemosum* collected in Australia [20].

The Portuguese plant *Teucrium subsp. vincentium* produces teuvincetin A (**8**) [21] and *Teucrium pernui* contains teuperine D (**9**) [22].

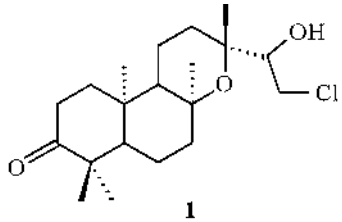
From the leaves of the plant *Ajuga nipponensis* (Labiatae family), chlorolactone (**10**) has been isolated.

The fungal metabolite coltilenine B (**11**) contains a residue of 4-deoxy-4-ketoglucose bound by an unusual fragment [24]. The plant *Silfium perfoliatum* (Compositae family) is widespread in the central and the eastern parts of North America. It is known that in traditional native medicine the leaves have been used as an antiinflammatory remedy. One of the main components of leaves turned out to be chlorosifanol A (**12**) [25, 26].

DITERPENOIDS FROM SEA ALGAE

Red sea algae belonging to the genus *Laurencia* (Rhodomelaceae ceramiales) produce halogenated metabolites [27–29]. From one of the species, *L. japonensis,* bromoditerpenes aplisiadiol (**13**) and anhydroaplisiadiol (**14**) have been isolated [30].

Derivatives of 20-ent-labdane have been isolated from algae of the genus mentioned.



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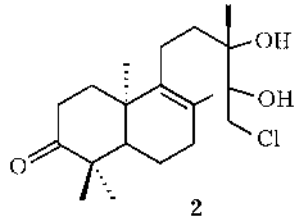

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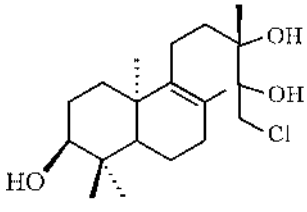

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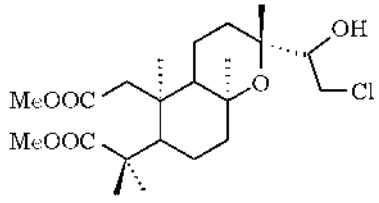

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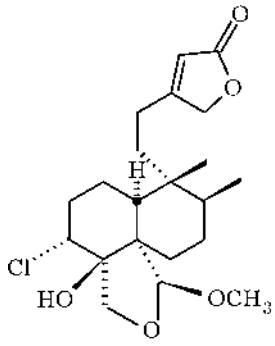

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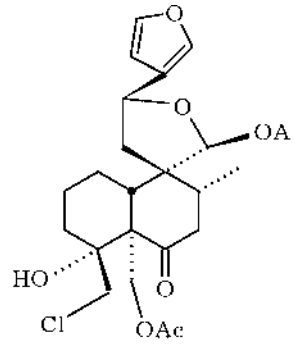

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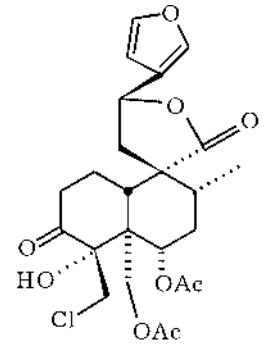

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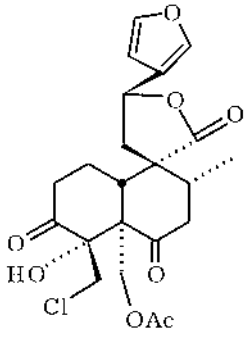

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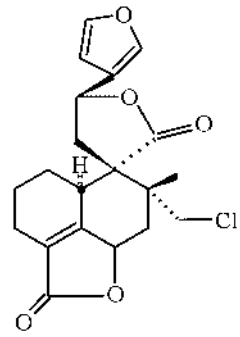

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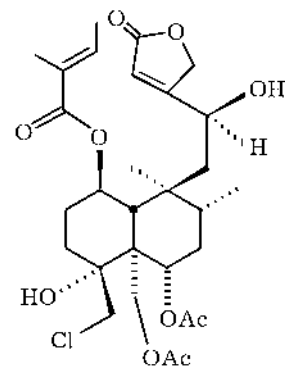

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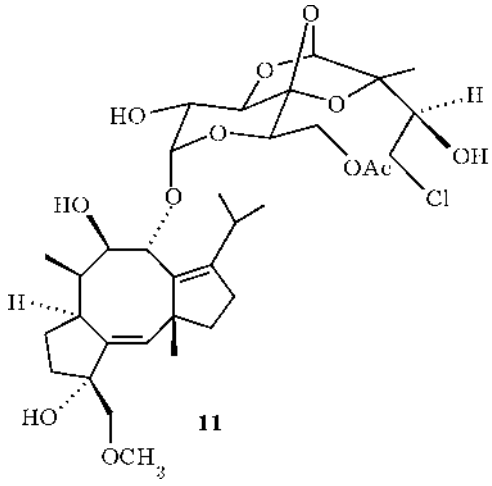

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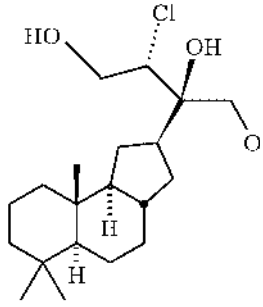

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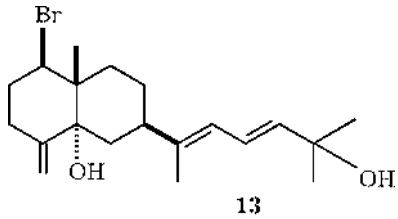

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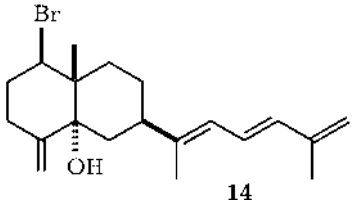

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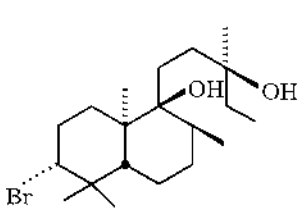
So, kotzindiol (**15**) is produced by algae *Laurencia concinna* [31] and *L. snyderi* [32]. Pinatols A–D (**16**)–(**19**) are contained in *L. pinnata* [33], and bromotriol vencetanol (**20**) has been detected in *L. venusta* [34]. Diterpenes (**21**)–(**23**) isolated from *L. perforata* have unusual carbon skeletons [35].

Diterpenoids of new structural types have been found in algae *Laurencia irieii* [36, 37] and *L. pinnata* [38, 39]. These compounds have been given the following names: irieol (**24**), iriediol (**25**), prenols A–G (**26**) – (**32**), pinaterpenes A–C (**33**)–(**35**) and priepinnaterpene (**36**).



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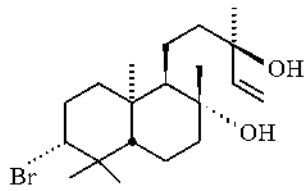

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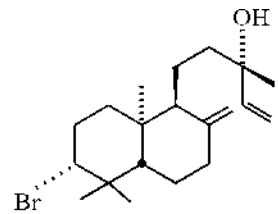

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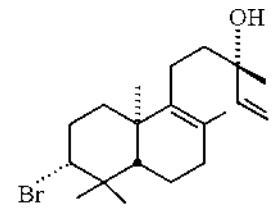

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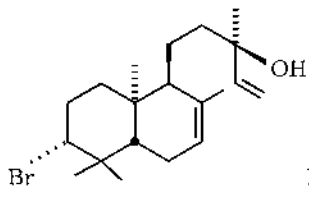

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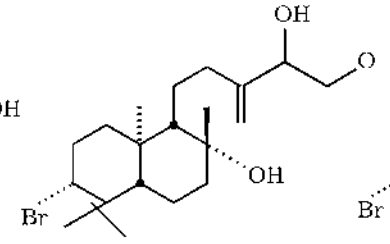

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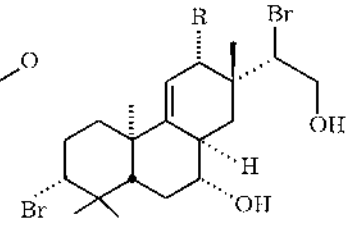
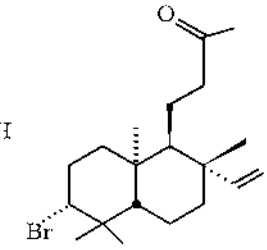


21. R = H; **22**. R = OH



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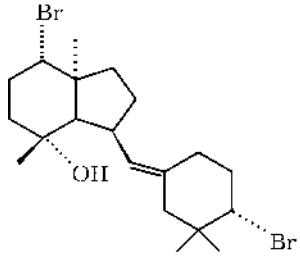
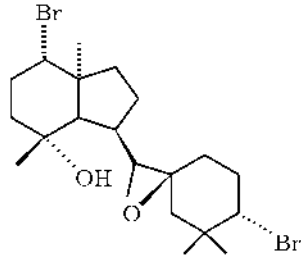


24. R = H
25. R = OH



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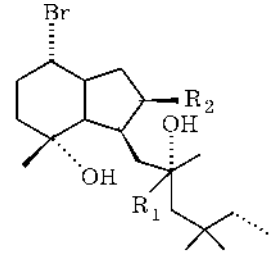
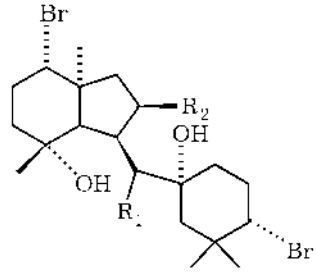
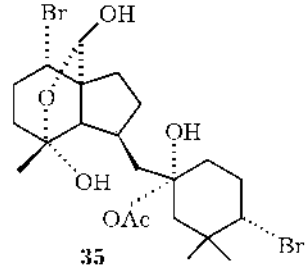


27. R_1 – H; R_2 – OH
28. R_1 – R_2 – H
29. R_1 = OH; R_2 = OAc
30. R_1 – OH; R_2 – H
31. R_1 = R_2 = OH
32. R_1 = OAc; R_2 = OH



33. R_1 = R_2 = H
34. R_1 – Ac; R_2 – OH



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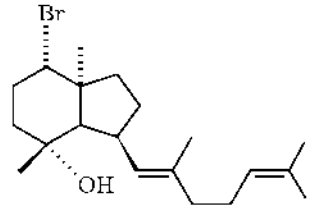

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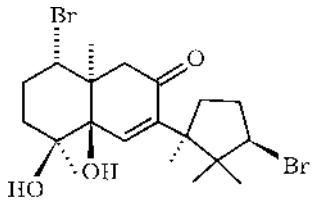
The alga *Laurencia irieii* contains a dibromoketol of a unique structure – neoprienone (**37**) [40]. Laurencianol (**38**) that has shown a high antibacterial activity with respect to *Bacillus subtilis* and *Escherichia coli* has been isolated from the alga *L. obtusa* growing on the western coast of Sicilia [41]. Dibromodiol obtusadiol (**39**) is contained in the mentioned alga [42].

Diterpenoids of parguerane and isoparguerane type containing a cyclopropane fragment are produced by the alga *Laurencia obtusa*. A distinctive feature of terpenoid (**40**) from compounds (**41**)–(**46**) is its belonging to the pimarane series [43, 44]. According to [43, 45], parguerol triacetate (**41**) has a high cytostatic activity, while compounds (**42**), (**43**), (**45**) and (**46**) are less active.

The alga *Laurencia saitoi* is widespread off shore Japan. In particular, it covers with a continuous carpet the littoral stones of the Sutsu coast of the Hokkaido iseland. This alga con-



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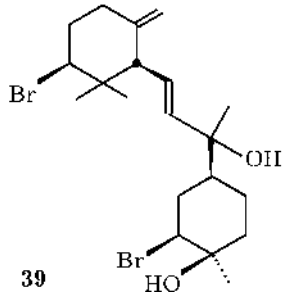

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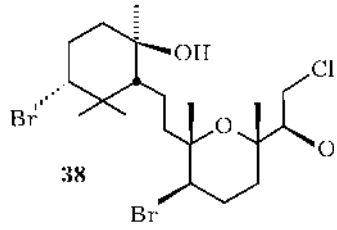

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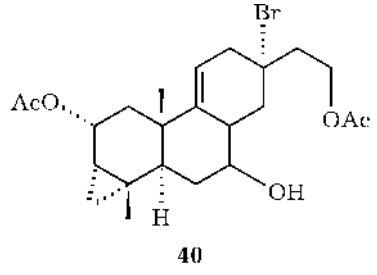
tains a complicated mixture of diterpenoids possessing an inhibitory effect with respect to development of larvae of sea urchins *Strongylocentrotus nudus* and *S. intermedius*, as well as of larvae of mollusk *Haltis discus Hannai* [46].

The mentioned alga contains all the earlier described diterpenes (**40**)–(**46**) and isopaguerane (**47**). The latter terpenoid and the ester (**48**) showing a high cytostatic activity have been isolated from the alga *L. obtusa* [45, 47].

Two terpenoids of new structural types – kahukuenes A, B (**49**), (**50**) – have been found in acetone extract from alga *Laurencia majuscula* [48]. The Okinawa red alga *L. luzonensis Masuda* produces mainly brominated sesquiterpenes. However, one of metabolites – 3-bromobarecoxide (**51**) – belongs to the diterpene series [49].

Another red alga species – *Sphaerococcus coronopifolium* – produces diterpenoids (**52**)–(**58**). Thus, sphaerococenol A (**58**) has been isolated from an alga growing off shores of Spain [50] and Italy [51]. Bromosphaerol (**55**), 12-hydroxybromosphaerols (**56**), (**58**)**4**, bromosphaerodiols (**53**), (**54**) and dibromosphaerodiol (**52**) are contained in an alga growing in various parts of Mediterranean [52–55].

Bromine-containing diterpenoids (**59**)–(**67**) are metabolites of the mentioned alga species growing in the Adriatic Sea [56–61]. One of these terpenoids – 13-epiconcindinol (**65**) – has been isolated from the red alga *Chondria tenuissima* growing on the shelf off the shores of Turkey [62].



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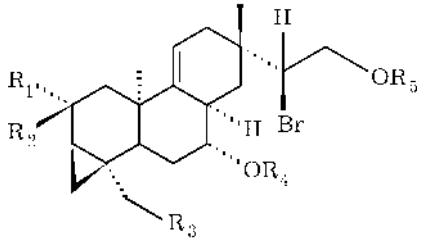
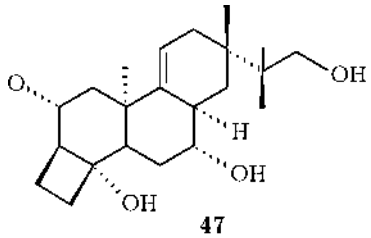


	R_1	R_2	R_3	R_4	R_5
41.	OAc	H	OAc	Ac	Ac
42.	OH	H	H	H	H
43.	OH	H	OH	H	H
44.	OAc	H	H	H	Ac
45.	=O	=O	OH	H	H
46.	H	H	H	H	H

DITERPENOIDS FROM SEA INVERTEBRATES

Sea sponges belong to producers of terpenoids of various types. By today, isolation of more than ten halogenated terpenoids has been described. Compound (**68**) that has a classical pimarane skeleton is contained in the sponge *Spongia zimocca* [63]. In sea sponges *Acanthella* sp. [64] and *Acanthella klethra* [65] inhabiting the waters of Fiji and Guam islands, and in sponges *Chelon aplysilla* sp. and *Dendrilla* sp. inhabiting the coasts of Cambodia [66, 67],



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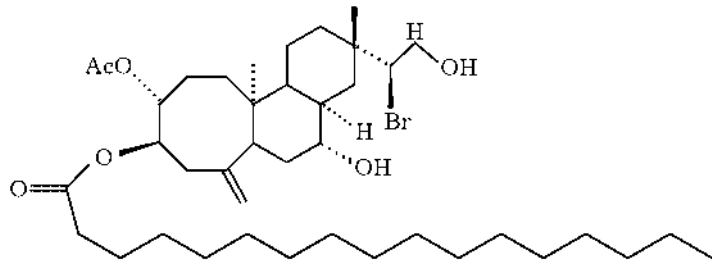

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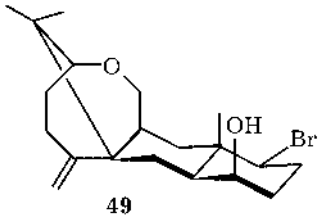

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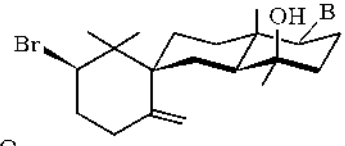

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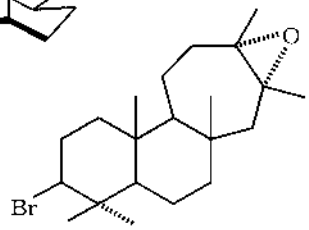

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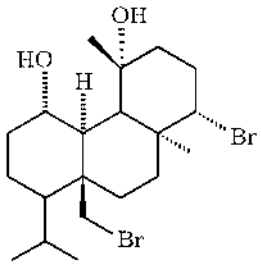

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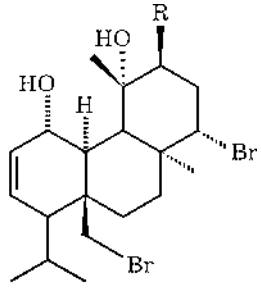
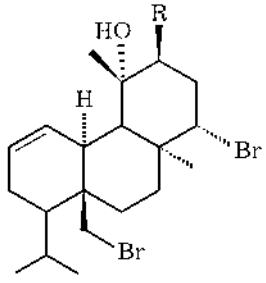
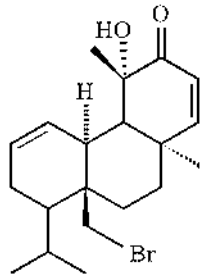


53. R = H; **54**. R = OH





55. R = H; **56**. R = β-OH; **57**. R = α-OH

58

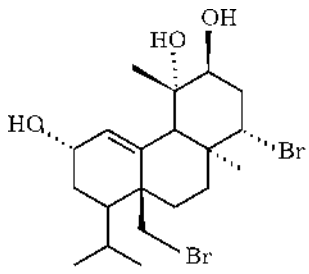
and in the Mediterranean sponge *Mycoli rotalis* [68], diterpenoids (**69**)–(**79**) have been detected whose molecules include a tetrahydrofurane or tetrahydropirane fragments.

The sponge *Acanthella cavernosae* widespread off shores of Japan and Thailand produces the mentioned diterpenoids (**68**), (**72**) and (**73**), and a ten-membered cyclic ester (**80**) and a derivative of α-bromofuran (**81**) [69, 70]. It has been established that compounds (**72**), (**73**) and (**77**) possess the capacity for blocking the development of the parasite *Nipponstrongylus brasiliensis* [71].

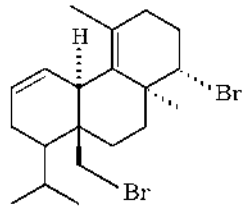
Corneous corals, or Gorgoniae, belonging to Gorgonaria family (type Coelenterata) are widespread in tropical regions of the Pacific, Indian and Atlantic oceans. These invertebrates are producers of unique diterpenes of a rare bicyclo[8,4,0]-tetradecane type. It has been proposed to use these diterpenes as a chemotaxonomic sign of corneous corals [72].

Corals *Minabea* sp. which surround the East Caroline islands of Pacific in a compact ring contain minabeines (**82**)–(**86**) [73]. Solenolides A–E (**86**)–(**90**) having an antiviral and antimicrobial effect have been isolated from octocoral *Solenopodium* sp. [74]. Diterpene (**91**) turned out to be a component of coral *Plexanureides praelonga* collected in the South Chinese Sea [75].

Chlorine-containing diterpenes (**92**)–(**104**) have been isolated from corals *Junceella*. So, coral *Junceella squamata* inhabiting the South Chinese Sea produces gemmacolides A–E (**92**)–(**96**) [76]. Coral *Junceella juncea* is a source of jancines (**97**)–(**99**), whereas coral *Junceella gemmacea* from the Caribbean Sea contains, apart



59



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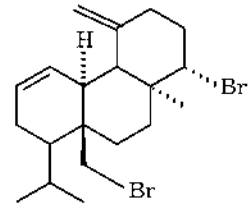

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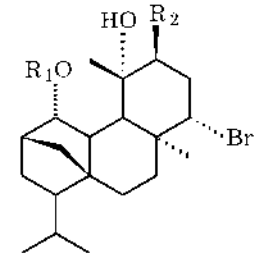
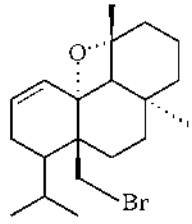
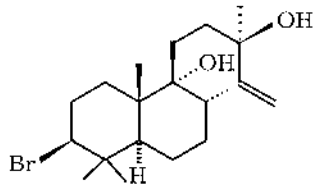


62. $R_1 = R_2 = H$
63. $R_1 = CH_3$, $R_2 = O$



64



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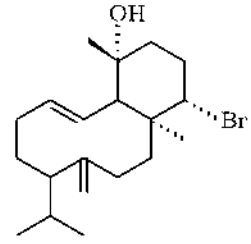
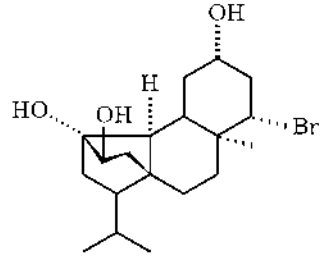


66



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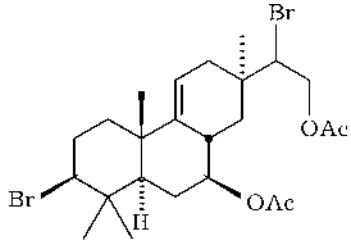
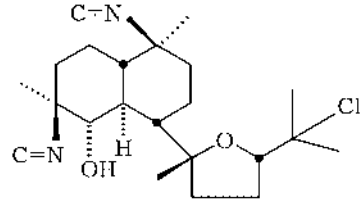
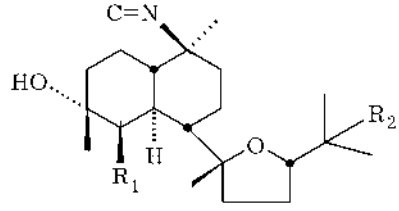


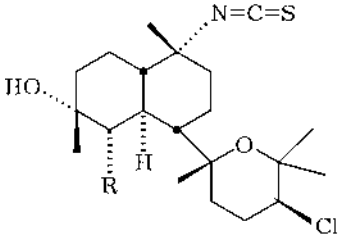
68



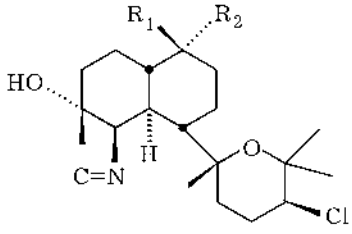
69



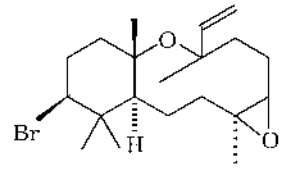
70. R_1 = N≡C, R_2 = Cl
71. R_1 = Cl, R_2 = N≡C



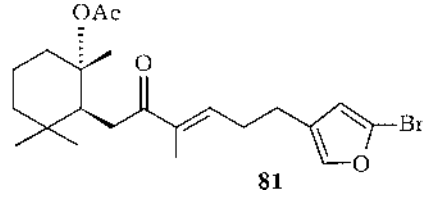
72. R = N=C=S
73. R = NHCHO



74. R_1 = N≡C, R_2 = CH_3
75. R_1 = N≡C, R_2 = CH_3
76. R_1 = CH_3, R_2 = N=C=S
77. $R_1 = R_2 = CH_2$
78. R_1 = CH_3, R_2 = N≡C
79. R_1 = CH_3, R_2 = NHCHO



80

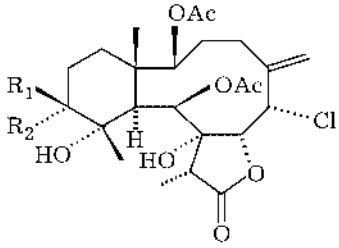


81

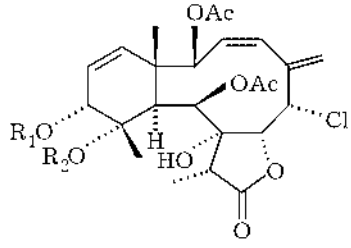
from gemmacolides, jancelines (**100**), (**101**) and jancillolides A–C (**102**), (**103**) [78–80].

The octaradial coral *Erythropodium caribaeorum* synthesizes erythrollides (**105**)–(**110**) one of which has a peculiar structure of the A ring [81, 82]. *Ptilosarcus gurneyi* is a source of ptilosarcone (**111**) and ptilosarcol (**112**) [83, 84), while ketoester (**113**) has been found in coral *Tochuina tetraguetra* [85].

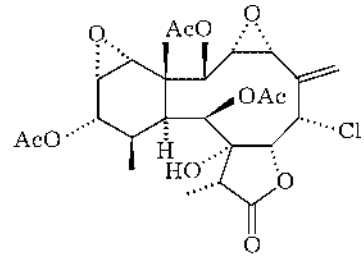
Gorgonia *Briareum asbestinum* synthesizes briaraeine A (**114**) [86], whereas brianteines (**115**)–(**118**) have been isolated from other coral species belonging to this genus. In particular, there have been reports of isolation of



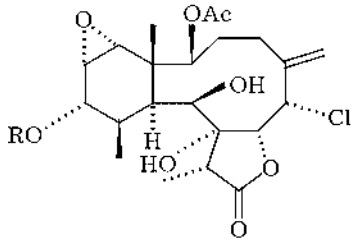
82. $R_1 = R_2 = O$
83. $R_1 = H$, $R_2 = OAc$



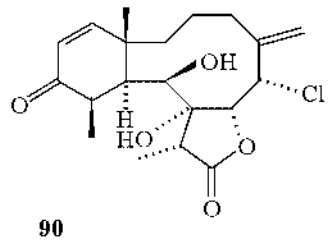
84. $R_1 = Ac$, $R_2 = H$
85. $R_1 = R_2 = H$



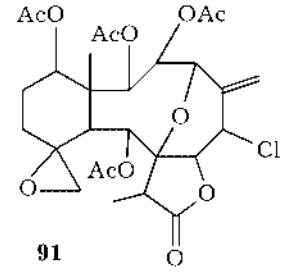
86. R = H
87. R = Ac



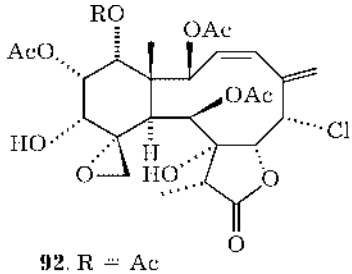
88. R = $CO(CH_2)_4CH_3$
89. R = Ac



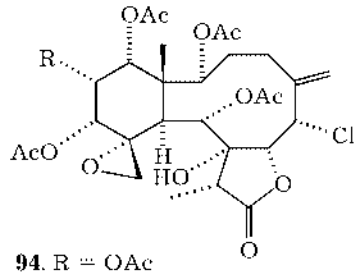
90



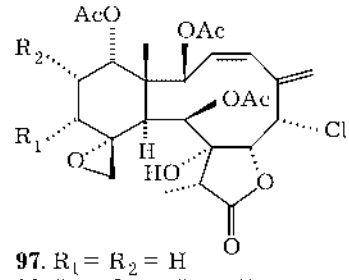
91



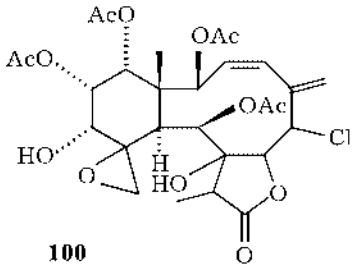
92. R = Ac
93. R = H



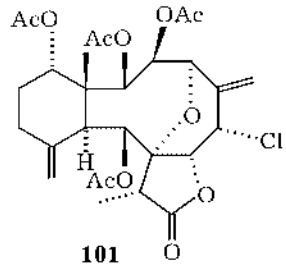
94. R = OAc
95. R = H
96. R = $OCOCH_2(CH_3)_2$



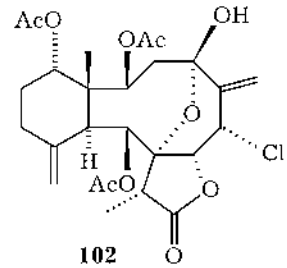
97. $R_1 = R_2 = H$
98. $R_1 = OAc$, $R_2 = H$
99. $R_1 = R_2 = OAc$



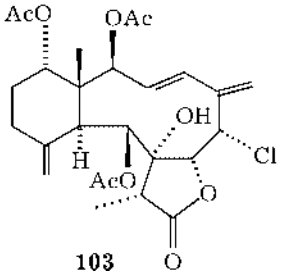
100



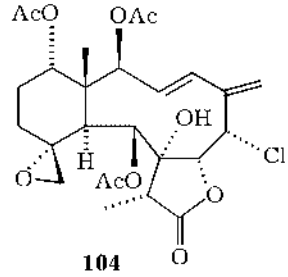
101



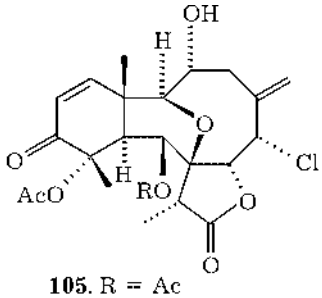
102



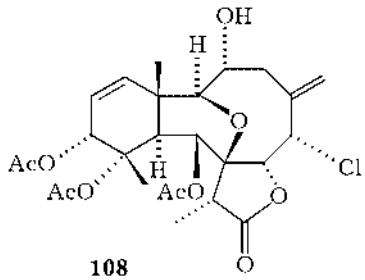
103



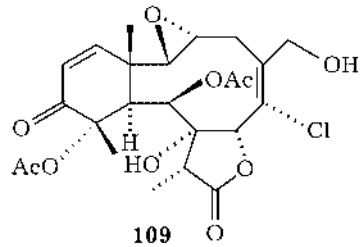
104



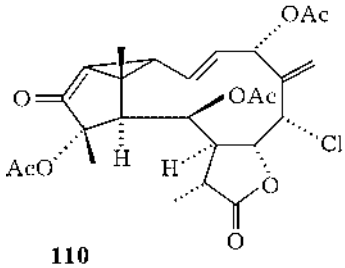
105. R = Ac
106. R = $COCH_2OAc$
107. R = $COCH_2OH$



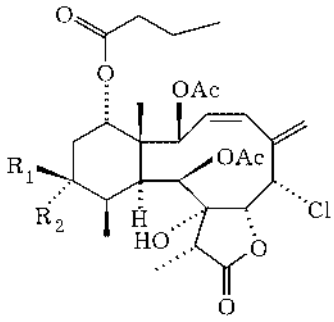
108



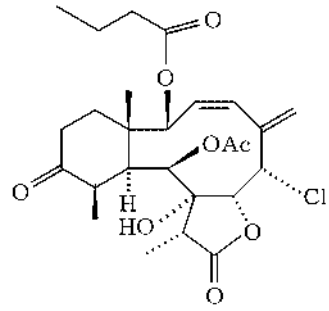
109



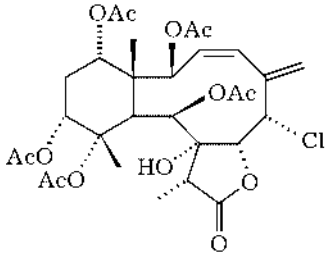
110



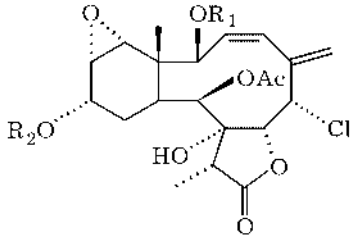
111. R_1 = R_2 = O
112. R_1 = H, R_2 = OH



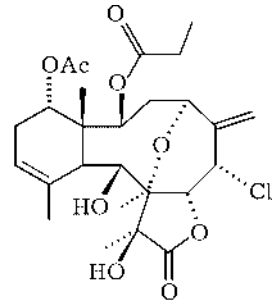
113



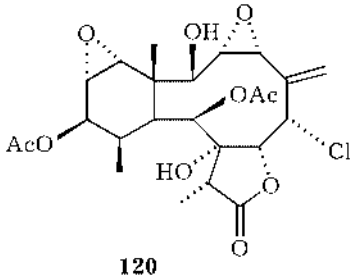
114



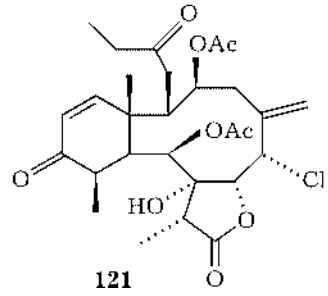
115. R_1 = R_2 = Ac
116. R_1 = H, R_2 = OAc
117. R_1 = $COCH_2CH_2CH_3$, R_2 = Ac
118. R_1 = R_2 = $COCH_2CH_2CH_3$



119



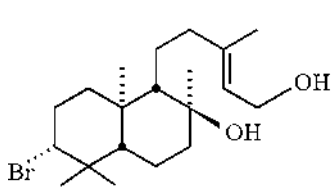
120



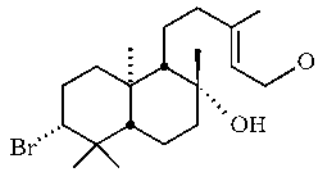
121

brianteines X, Z, Y, V (**115**)–(**118**) [87–91]. Brianteine X has been found also in the coral *Briareum polyanthes* [90], and the presence of brianteine Z has been established among the components of Australian corals. Diterpenoids (**119**), (**121**) are produced by corals of genus Briarenum collected off shores of Australia [92], while brianolide (**120**) has been isolated from a coral widespread near the Okinawa island [93].

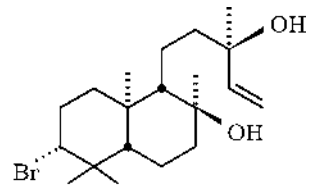
Four ent-labdane derivatives containing a bromine atom at C3 have been found in the mollusk *Aplysia kurodai* [94, 95]. These include aplysine (**122**), epiaplysine (**123**) and isoconcitediols (**124**), (**125**) [96]. It is noteworthy that diterpenoid (**126**) was isolated from algae *Laurencia* sp., and then found in extract of mollusk *Aplysia dactylomela* feeding on the mentioned alga [97].



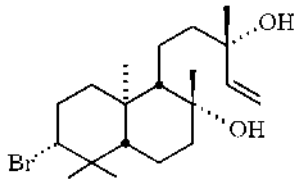
122



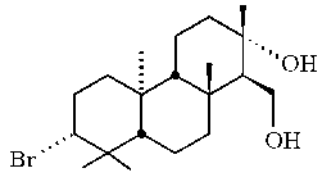
123



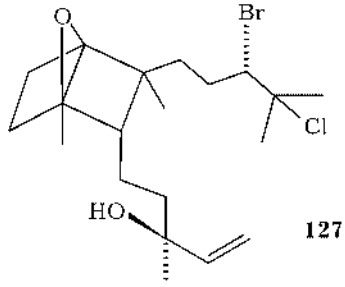
124



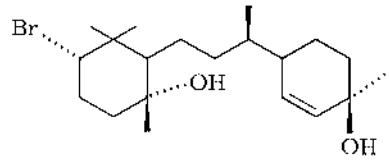
125



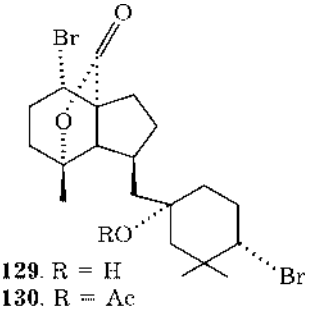
126



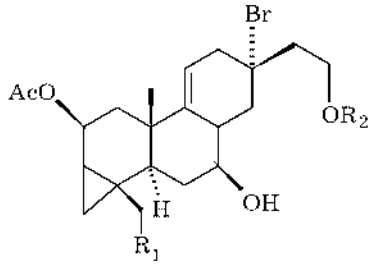
127



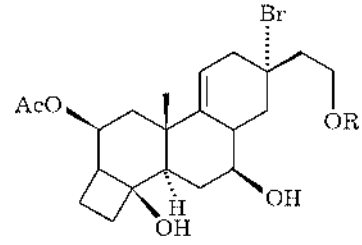
128



129. R = H
130. R = Ac



131. R_1 = OH, R_2 = H
132. R_1 = OH, R_2 = Ac
133. R_1 = R_2 = H



134. R = H
135. R = Ac

Diterpenoid dactylomelol (**127**) of a surprising structural type has been isolated from the mollusk *Aplysia dactylomela* which produces also bromediol (**128**) of an unusual structure [98, 99]. The mollusk *Aplysia angari* living in the Persian Gulph is a source of angasiol (**129**) and its acetate (**130**) [100 – 102]. Parguerol (**131**) and its derivatives (**132**), (**133**), as well as isoparguerol (**134**) and acetate (**135**) are synthesized in the organism of the mollusk *Aplysia dactylomela* [100].

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