HETEROCYCLIC COMPOUNDS FOUND IN BRYOPHYTES*

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Abstract-Bryophytes contain various heterocyclic terpenoids and aromatic compounds which show occasionally interesting biological activity and are of very valuable for the chemosystematic study of bryophytes. The distribution of the heterocyclic compounds in the bryophytes and some biological activity of heterocyclic terpenoids and aromatic compounds isolated from the bryophytes will be reviewed.

Introduction

Bryophytes are taxonomically placed between the algae and the pteridophytes (=ferns) and 25000 species are known in the world. They are divided into three classes, Musci (=mosses, 14000 species), Hepaticae (=liverworts 6000 species) and Anthocerotae (=hornworts, 300 species). Among the bryophytes, the chemical constituents of the Hepaticae have been investigated in more detail since the Hepaticae possess cellular oil bodies which are very important markers for the classification in the liverworts, while the other two classes lack such complex oil bodies. At present, only 6% of all liverworts species and less than 2% of all mosses have been studied chemically. Concerning the hornworts, only 1% of all Anthocerotae has been checked chemically.

We are continuing to study the chemical constituents of bryophytes, particularly the Hepaticae from view point of the structural determination and the biological activity of the isolated compounds and chemosystematic study of the bryophytes. The chemical constituents found in the Hepaticae and those of the bryophytes have been reviewed in Progress in the Chemistry of Organic Natural Products Vol. 42[1] and Vol. 65,[2] respectively. Here the heterocyclic compounds (except flavonoids) detected in or isolated from the bryophytes since 1983 will be reviewed. In addition, some biological activity of the isolated compounds is also described.

I. Heterocyclic terpenoids

1. Monoterpenoids

Only one heterocyclic monoterpene, 1,8-cineole (**1**) has been detected in the liverwort, *Lophocolea heterophylla.*[3]

*This paper is dedicated to the memory of the late Professor Shun-ichi Yamada.

2. Sesquiterpenoids

2.1 Acoranes

Acorane-type sesquiterpenoids are very rare in liverworts. *Jungermmania hattoriana* is one of the very interesting liverworts since it elaborates acorane diepoxide (**2**), together with diepoxycuparenes (see later).[4,5]

2.2 Africanes

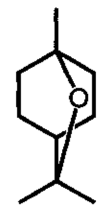
A number of heterocyclic sesqui- and diterpenoids have been isolated in bryophytes, particularly, in the Hepaticae.[1,2] The Colombian liverwort, *Porella swartziana,* contains five africane-, two secoafricane- two guaiane-, one germacrane- and nor-secoafricane-type sesquiterpenoids of which caespitenone (**3**), secoswartzianin A (**4**) and norswartzianin (**5**) are heterocyclic compounds.[6-11] The ether extract of *Porella subobtusa* yielded a new africane-type sesquiterpene acetate, named 14-acetoxycaespitenone (**6**), together with three africanes including caespitenone (**3**) and secoswartzianin A (**4**).[12]

2.3 Amorphanes

The Taiwanese liverwort, *Lepidozia fauriana* contains 5β–hydroperoxylepidozenolide (**7**) and lepidozenolide (**8**).[13-15] The former compound has been isolated from *L. vitrea.*[13] Both compounds showed antiplatelet effects and caused vasorelaxation of rat thoracic aorta in the phasic and tonic contraction induced by norepinephrine (3 μm) at 100 μg/mL level. Compound (**8**) showed antimicrobial activity against *Staphylococcus aureus*, *Candida albicans* and *Trichomonas feetus* at (100 μg/mL) and cytotoxic activity against P-388 (ED_{50} 2.10 μg/mL) and inhibited the potassium-(80 mM) and calcium-(1.9 mM) induced vasoconstriction.[13]

2.4 2,3-Secoaromadendranes

The liverworts, *Plagiochila* are widely distributed in the world and there are *ca.* 3000 species. The species belonging to the Plagiochilaceae are chemically divided into two types: one contains very pungent components and the other is tasteless. The pungent species contain 2,3-secoaromadendrane-type sesquiterpenoids such as plagiochiline A (**9**), one of the popular sesquiterpene hemiacetals distributed in *Plagiochila* species. The ether extract of *Plagiochila fruticosa* was chromatographed on silica gel and Sephadex LH-20 to afford plagiochiline A (**9**), plagiochilide (**10**) and plagiochiline C (**11a**). The absolute structure of compound (**9**) has been determined by its chemical degradation and CD spectrum.[1] The stereostructure was further confirmed by X-Ray crystallographic analysis of **9**.[16] It has been known that compound (**9**) shows persistent pungent taste. Compound (**9**) was treated with human saliva (pH 6.9) at 37°C for 24 h to give plagiochiline B (**12**) and furanoplagiochilal (**13**) which are due to the hot-taste of the pungent *Plagiochila* species. Possible mechanism of **9** into **12** and **13** by human saliva has been proposed.[16] Plagiochiline A (**9**) has been found in many South American and Asiatic *Plagiochila* species.[17,18] Compound (**9**) shows cytotoxicity (ED_{50} 2.98 μg/mL) against KB cell and piscicidal activity against killie-fish which is killed within 240 min at a concentration of 0.4 ppm.[19,20] The chemical constituents of *P. fruticosa* was reinvestigated to afford the new 2,3-secoaromadendranes, pungent plagiochiline B (**12**), and J (**14**) and K



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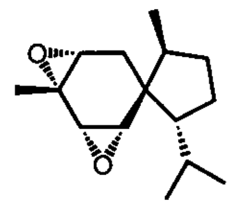

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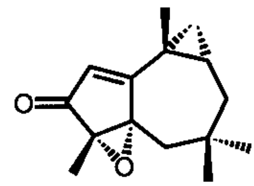

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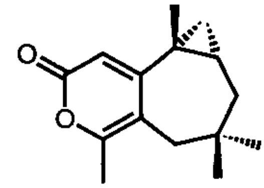

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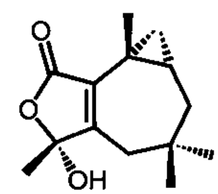

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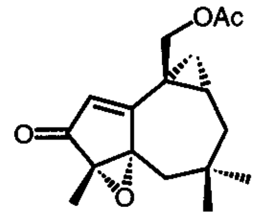

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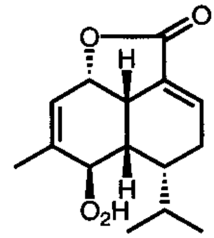

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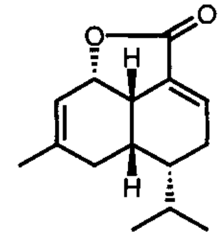

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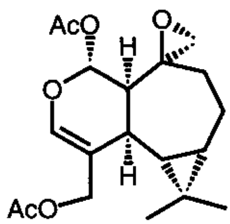

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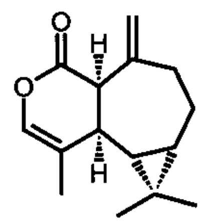

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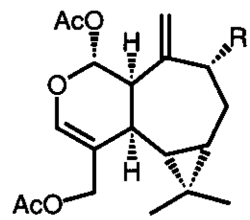

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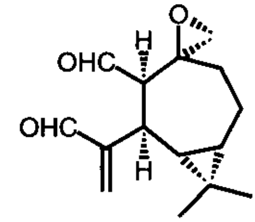
(11b) R=OAc



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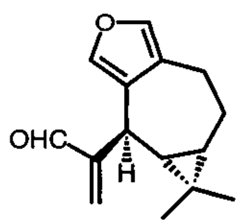

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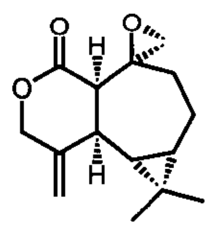

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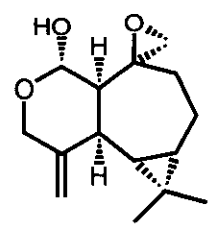

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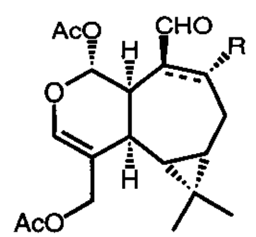
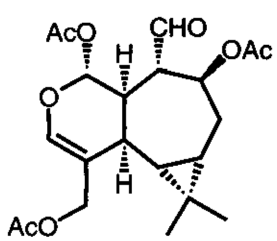


(16a) R=OAc
(16b) R=H, $\Delta^{9,10}$



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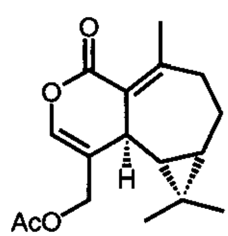

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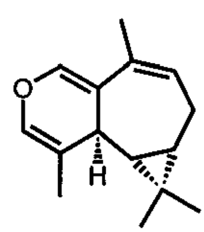

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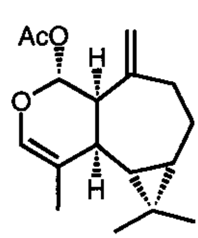

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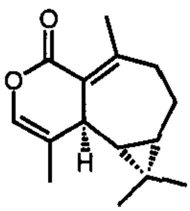

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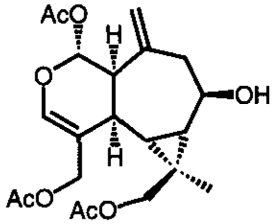

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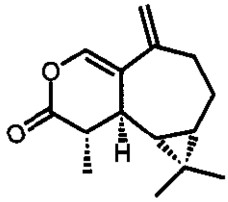

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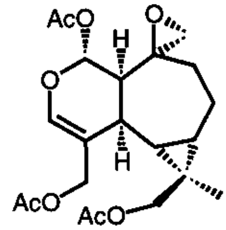

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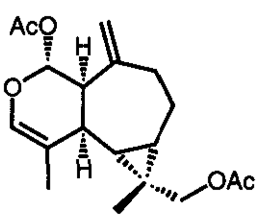

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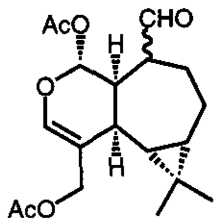

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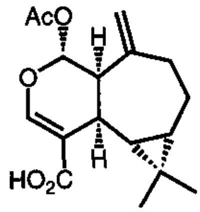

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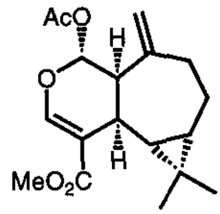

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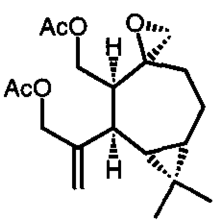

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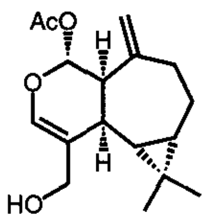

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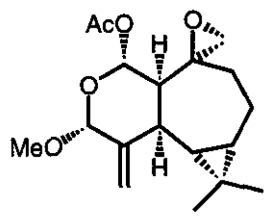

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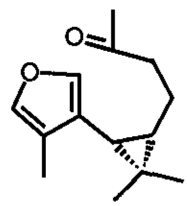

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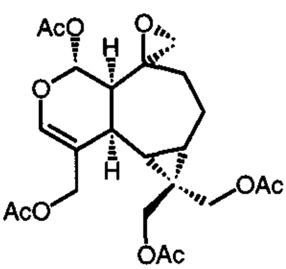

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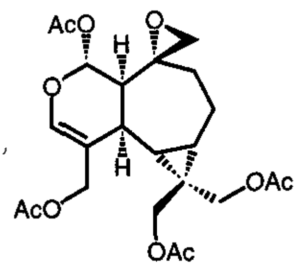

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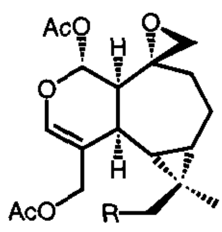


(35) R= nC_9H_{19}-
(36) R= nC_7H_{15}-

(37) n-$Me(CH_2)_4CH\overset{Z}{=}CH(CH_2)_2$-

(**15**) as well as the known compounds (**9, 10**).[21] Compound (**12**) showed not only acceleration of neurite sprouting but also enhancement of choline acetyl transferase activity in a neuronal cell culture of the fetal rat cerebral hemisphere at 10^{-5} M.[21] Plagiochilide (**10**) shows superoxide anion release inhibitory activity.[19,20] The Taiwanese *P. peculiaris* biosynthesizes two new hemiacetals, 9α-acetoxy-10β-ovalifolienal (**16a**) and 9β-acetoxy-10α-ovalifolienal (**17**).[22] It is known that the Japanese *P. ovalifolia* produces various sesquiterpene hemiacetals.[1] Further fractionation of the *n*-hexane extract of the same liverwort resulted in the isolation of two new hemiacetals, *ent*-acetoxyisoplagiohilide (**18**)[23,24] and plagiochilide N (**19**).[24,25] Plagiochiline C (**11a**) showed antiplatelet effects on arachidonate and collagen induced aggregations of washed rabbit platelets.[26]

The Taiwanese *Plagiochila elegans* produces not only plagiochilines C (**11a**) and H (**20**) but also a new 2,3-secoaromadendrane lactone, isoplagiochilide (**21**).[26] Three new 2,3-secoaromadendranes, plagiochilines O (**22**) and Q (**23**) have been isolated from *P. cristata*, together with plagiochilines C (**11a**) and H (**20**).[27] Furthermore, plagiochilines R (**24**), C (**11a**) and H (**20**) have been obtained from African-alpine *P. ericicola* and isoplagiochilide (**21**)[26] from *P. sinuosa* var. *squamulosa*, plagiochiline S (**25**), 9,10-dihydroovalifolienal (**26**) from axenic culture of *P. adianthoides*, together with the previously known plagiochilines A (**9**) and H (**20**).[27]

The Japanese *Heteroscyphus planus* which belongs to the Lophocoleaceae is chemically very interesting because it produced two new 2,3-secoaromadendrane-type sesquiterpenoids, plagiochiline L (**27**) and plagiochiline M (**28**), along with some characteristic heterocyclic diterpenoids (see later). Their stereostructures were established by chemical transformation from **27** to **28** and **27** to plagiochiline C (**11a**).[25,28,29] The methanolic extract of cultured cell of *H. planus* contained two new 2,3-secoaromadendranes, *ent*-2,3-diacetoxy-10α,15α-epoxy-2,3-secoaromadendra-4(14)-ene (**29**) and 4-*O*-deacetylplagiochiline C (**30**), along with plagiochiline A (**9**) and methoxyplagiochiline A2 (**31**).[1,30] Nabeta *et al.*[30] suggested that 2,3-dihydroxyalloaromadendranes might be intermediate precursors for 2,3-secoaromadendranes.

The European *Mylia taylorii* (Jungermanniaceae) elaborates a new nor-1,10-secoarmadendrane-type sesquiterpene (**32**), along with its related *ent*-aromadendrane-type sesquiterpenoids.[31] The known plagiochilide (**10**), plagiochilines C (**11a**), D (**33**), E (**34**) and H (**20**), 9α-acetoxyovalifoliene (**11b**) and ovalifolienal (**16b**) have been isolated from or detected in a number of South American *Plagiochila* liverworts.[17,18] The European *P. porelloides* produces not only plagiochiline D (**33**), but also a mixture of 2,3-secoaromadendrane-type sesquiterpene esters (**35, 36**) and a similar ester (**37**).[32]

2.5 Bazzananes

Bazzanane-type sesquiterpenoids are chemical markers of the Lepidoziaceae liverworts, however, the New Zealand unidentified *Frullania* species belonging to the Frullaniaceae produces bazzanenone (**38**) with three oxobazzanane-type sesquiterpenoids. This is the first report of the isolation of bazzanane-type sesquiterpenoid from the *Frullania*.[33]

2.6 Bergamotanes

The liverwort *Lepidolaena clavigera* grown in New Zealand contains a very unique bergamotane-type sesquiterpene diacetate, named clavigerin (**39**) as a major component. Compound (**39**) might prove to be one of the valuable indicators of the *Lepidolaena* species.[33]

2.7 Elemanes

Two South American liverworts *Clasmatocolea humilis* elaborates dehydrosaussurea lactone (**40**) and saussurea lactone (**41**).[34] The former compound has been detected in the South American *Plagiochila hondurensis.*[18] A new elemanolide (**42**) was isolated from the French liverwort, *Plagiochasma repestre*, along with elema-1,4(15),11-trien-3-al.[35]

2.8 Cadinanes and Caryophyllanes

Gongylantoxide (**43**) has been detected in the liverwort *Gogylanthus ericetorum.*[36] *Porella canariensis* produces 7,10-epoxycadina-5-ene (**44**).[37] (-)-β-Caryophyllene oxide (**45**) was isolated from *Marchantia paleaceae* var. *deptera* with β-caryophyllene.[38] *Ca.* 70% of the sesquiterpenoids found in the liverworts are estimated as the enantiomers of those found in higher plants. Compound (**45**) possesses the same absolute configuration as that isolated from the higher plant.

2.9 Chiloscyphanes

The liverworts *Chiloscyphus* species are biosynthetically very interesting, because they produce very characteristic chilosyphane-type sesquiterpenoids. The Taiwanese *Chiloscyphus pallescens* biosynthesizes 11ξ,12-epoxychiloscypholone (**46**) with two related chiloscyphanes, chiloscyphone and chiloscypholone.[39]

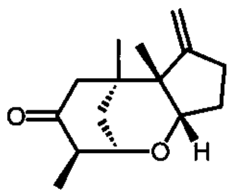
2.10 Cuparanes and Herbertanes

The cuparane-type sesquiterpenoids are very popular in the liverworts, while, the herbertane-type is limited in some liverworts, *Herbertus* and *Marchantia* species.[2] Two cuparene-type lactones, cuparenolide (**47**) and cuparenolidol (**48**) have been isolated from the European liverwort *Ricciocarpos natans*.[40,41] The former compound shows molluscicidal activity against *Biomphalaria glabtata* with LC_{100} at 32 ppm, however, the latter lactone has no activity.[42] The European *Nardia scalaris* produces 3,6-epoxycupar-1-ene (**49**), along with 2-hydroxycuparene.[43] A herbertane lactone, herbertenolide (**50**) has been isolated from the Japanese liverwort, *Herbertus aduncus* as well as various herbertane-type sesquiterpenoids.[44,45-48] *Jungermmania hattoriana* is rich source of cupanene-type sesquiterpenoids. Purification of the ether extract yielded two epoxides (**51**) and (**52**). Their absolute configurations were established by a combination of X-Ray crystallographic analysis and the modified Mosher's method.[49]

2.11 Daucanes (=Carotanes) and Drimanes

Only one daucane-type sesquiterpene lactone, hercinolactone (**53**) has been isolated from the four European liverworts, *Barbilophozia lycopodioides,*[50,51] *B. hatcheri,* [51-53] *B. floerkei* [52,53] and *B. barbata.*[54]

The American liverwort *Porella roellii* is the rich source of drimane-type sesquiterpenoids, drimeninol (**54**), isodrimeninol (**55**), 6α-hydroxydrimeninol (**56**) and dehydroconfertifolin (**57**), together with pungent sesquiterpene dial, polygodial.[25] The American *Porella cordaeana* also produces drimenin (**58**), 7-



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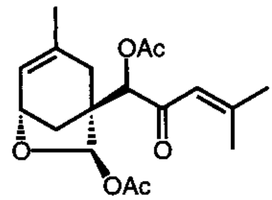

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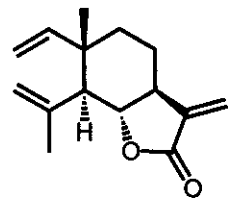

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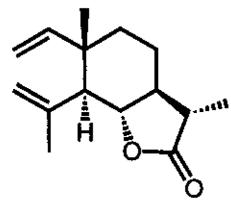

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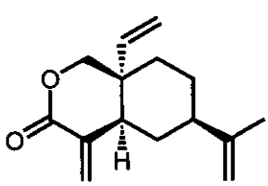

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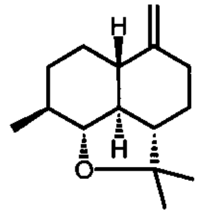

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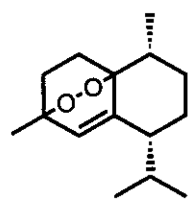

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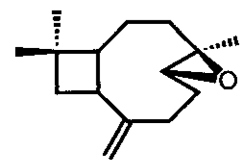

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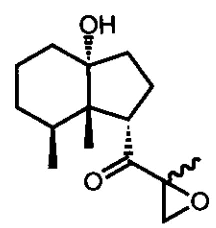

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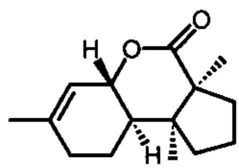

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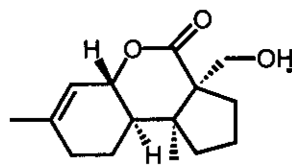

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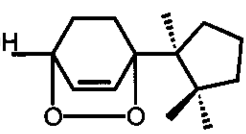

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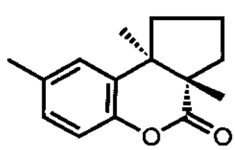

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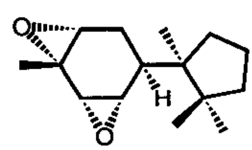

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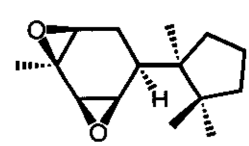

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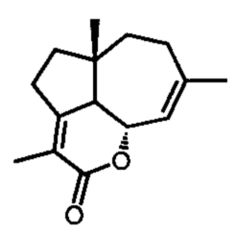

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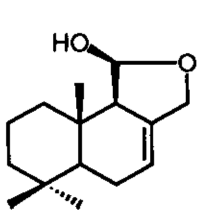

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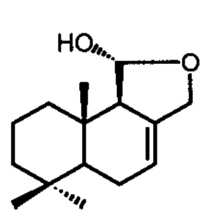

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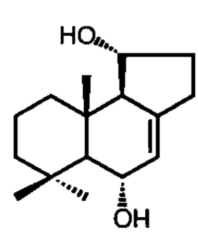

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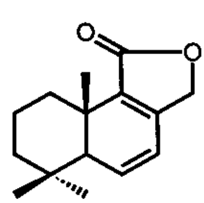

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ketoisodrimenin (**59**) and 7-ketoisodrimenin-5-ene (**60**).[55] Cinnamolide (**61**) which indicated antifeedant activity against lavae of the Japanese *Pieris* species is also found in cell suspension culture of *Porella vernicosa*, along with pungent polygodial.[56,57] The methanol extract of the European *P. canariensis* contains the previously known three drimanes, (**60**), *cis*-dihydrocinnamolide (**62**) and isodrimeninol (**55**).[37] Furthermore, the Japanese liverwort *Makinoa crispata* elaborates 7α-chloro-6β-hydroxyconfertifolin (**63**), 6β,7α-dihydroxy-confertifolin (**64**) and 6β,7β-epoxyconfertifolin (**65**).[58] This is the first record of the isolation of a chlorine-containing substance from the Hepaticae.

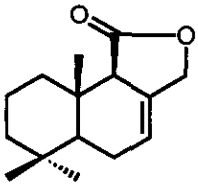
2.12 Eremophilanes

Two new *ent*-eremophilane-type sesquiterpene lactones, dilatanolides A (**66**) and B (**67**) have been isolated from the ether extract of the Bulgarian liverwort, *Frullania dilatata* var. *anomala,* together with spiroeudesmanolides (see later).[4,5] Compound (**67**) has also been isolated from the European *F. muscicola* with four eudesmanolides (see later).[59]

2.13 Eudesmanes and Trinoreudesmanes

A unique *cis*-eudesmane, named 6β-acetoxyvitranoxide (**68**) has been isolated from the Taiwanese *Lepidozia fauriana* and *L. vitrea* and its structure established by X-Ray crystallographic analysis.[13-15] Eudesmanolides are distributed not only in the Jungermanniales species, the *Frullania*, *Lophocolea*, *Plagiochila* and *Clasmatocolea* genera but also the Marchantiales species, *Conocephalum* genus. Frullanoeudesma-1,3-diene (**69**) has been detected in the essential oil of *Lophocolea heterophylla.*[3] (+)-Frullanolide (**70**) and (-)-frullanolide (**71**) which have been isolated from *Frullania dilatata* and *F. tamarsci* subsp. *tamarisci,* respectively show the potent contact allergenic property[1] and antifeedant activity against lavae of the Japanese *Pieris* species. The former lactone shows piscicidal activity against killie-fish which is killed within 240 min at a concentration of 0.4 ppm.[19,20] (-)-Frullanolide (**71**) is widely distributed in the other *Frullania* species: *F. apiculata*[60] *F. asagrayana,*[61] *F. bicornistipula,*[62] *F. brasiliensis,*[63] *F. nisquallensis,*[64] *F. ternatensis* and *F. serrata*[60] and *F. shaerocephala.*[63] Formal total synthesis of (±)-frullanolide has been reported by Banerjee *et al.*[65] Dihydrofrullanolide (**72**) has been detected in five *Frullania* species[61-63] and one *Plagiochila* species, *P. tenerrima.*[18] The New Zealand liverwort *Clasmatocolea vermicularis* elaborates two eudesmanolides, oxyfrullanolide (**73**) and dehydrooxyfrullanolide (**74**).[60] Two *ent*-eudesmanolides, (+)-β-frullanolide (**75**) and (+)-brothenolide (**76**) have been isolated from the Japanese *F. brotheri.*[66] (+)-Arbsculin B (**77**) and its enantiomer (**78**) have been distributed in three *Frullania* species[62-69] and *F. usamiensis,* respectively.[70] The latter species also biosynthesizes *ent*-β-cyclocostunolide (**79**).[70] Dihydro-β-frullanolide (**80**) has been detected in *F. bicornistipula.*[62] *Conocephalum japonicum* belonging to the Conocephalaceae produces arbusculin A (**81**) and its dihydro derivative, colartin (**82**), together with germacranolides (see later).[71] (11*S*)-Dihydro-β-cyclocostunolide (**83**) has been isolated from *F. bicornistipula.*[62] 8α-Acetoxy-β-cyclocostunolide (**84**) and rothin A acetate (**85**) have been isolated from *Wiesnerella denudata*[69] belonging to the Conocephalaceae and unidentified South American *Frullania* species.[6,72] The latter species also elaborates α-cyclocostunolide (**86**).[72]

α-Santonin (**87**) which shows antibacterial activity has been isolated from differentiated culture of the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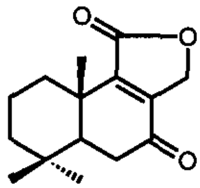
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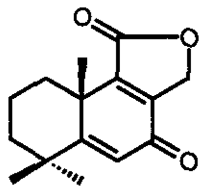
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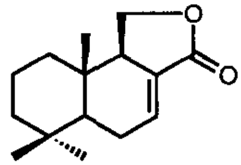
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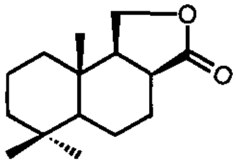
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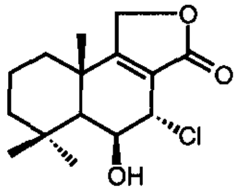
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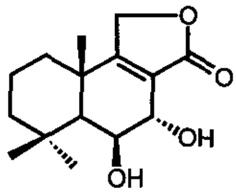
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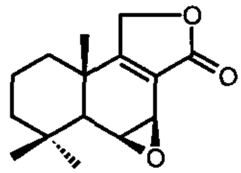
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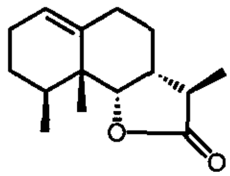
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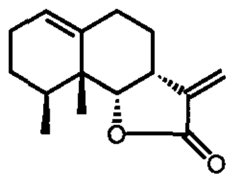
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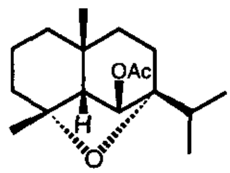
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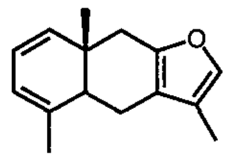
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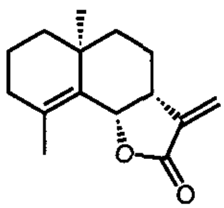
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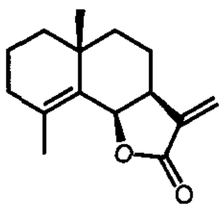
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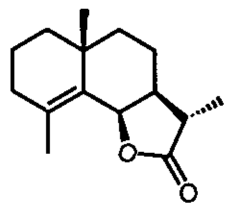
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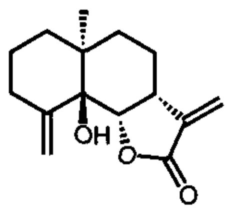
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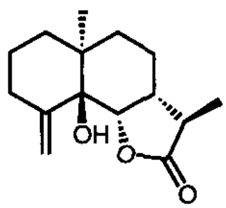
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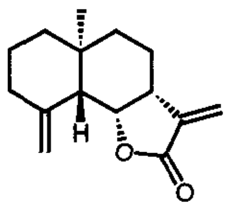
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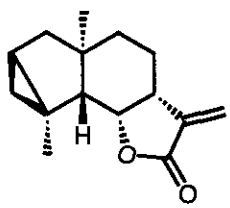
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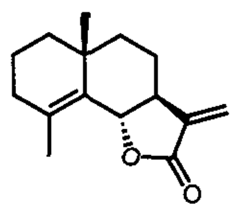
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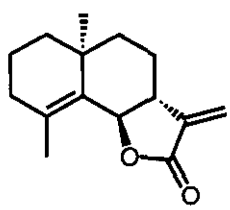
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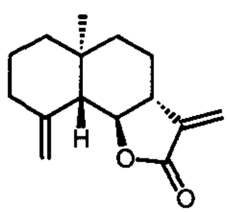
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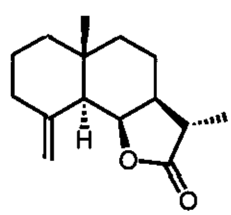
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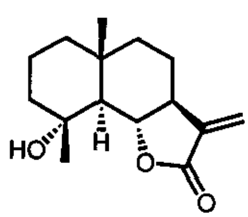
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liverwort *Fossombronia pusilla*.[73] Four new eudesmanolides, nepalensolides A-C (**88-90**) and nepalensolide D (=*ent*-critonilide) (**91**) and the previously known *ent*-β-frullanolide (**75**) have been isolated from the Taiwanese *Frullania nepalensis* [61,74,75] *F. serratta* is chemically very close to *F. nepalensis* since it produces the same lactones (**88-90**) as those found in *F. nepalensis*, along with arbsculin B (**78**).[69] The ether extract of the Bulgarian *F. dilatata* var. *anomala* was fractionated to give three rearranged *ent*-spiroeudesmane-type sesquiterpene lactones named spirodilatanolides A (**92**), B (**93**) and C (**94**), along with the known (+)-frullanolide (**70**) and critonilide (**95**).[4,5] The absolute configurations of the spirolactones were established by a combination of X-Ray crystallographic analysis of **92** and the CD spectrum of degraded product from **92** through the reduction, acetylation and ozonolysis.[4,5] The European *Frullania muscicola* produces two new *ent*-eudesmanolides, 5α,6α,7α,10α-4(15),11(13)-eudesmadiene-12,6-olide (**96**) and its dihydro derivative (**97**), together with the known (+)-arbusculin B (**77**), (+)-frullanolide (**70**) and *ent*-critonilide (=nepalensolide D) (**95**).[59]

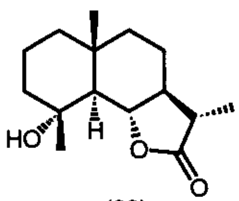
F. densiloba elaborates two new eudesmanolide, named densilobalide A (**98**) and densilobalide B (**99**), together with α-dihydrocyclocostunolide (**100**). 2D-NMR spectrum showed that the structure of **100** was identical to the dihydro derivative prepared from α-santonin (**87**), except for the sign of the optical rotation. It is the first report of the isolation of eudesmane-12,8-olides from the Frullaniaceae.[76] Chromatography of the ether extract of the New Zealand *Plagiochila conjugatus* yielded two new *ent*-eudesmanolides, 10-carbomethoxy-*ent*-eudesm-4(15),11-dien-12,8β-olide (**101**) and 10-methoxycarbonyl-5β,6β-epoxy-*ent*-eudesm-4(15),11-dien-12,8β-olide (**102**).[33]

The European *F. tamarisci* subsp. *tamarisci* contains two unique eudesmane-type sesquiterpene lactone dimers (**103,104**)[77] and methoxyfrullanolide (**105**).[25] The dimeric lactones have been found in the dried material which has been stored in the laboratory for a year. However, they have not been isolated from the fresh material.[77] Much earlier, the same lactone dimers whose structures should be revised to **103** and **104** have been isolated from the Indian *F. yunnanensis*, together with (-)-frullanolide (**71**) and (-)-dihydrofrullanolide (**84**).[78]

The similar eudesmane dimers (**106, 107**) have also been isolated from the European *F. muscicola*.[59] Possible formation of **106** and **107** from costunolide-like units has been proposed by Mues *et al.*[59]

The Japanese *Lophocolea heterophylla* belonging to the Lophocoleaceae produces two eudesmanolides (**108, 109**).[79] The European same species also produces *ent*-isoalantolactone (**110**).[80] South American *L. coadunata*[63] and *L. bidentata*[3] elaborate dihydroisoalantolactone (**111**) and diplophyllolide (**112**), respectively. The latter compound has been found in *Clasmatocolea vermicularis*,[60] *Plagiochila moritziana*[62,81,82] and *Tritomaria quinquedentata*.[52,53]

T. quinquedentata also produces *ent*-dihydrodiplophyllolide (**113**).[52,53,83] The European *Chiloscyphus polyanthos* contains very potent pungent substances. This taste is due to the presence of eudesmanolides (**112, 114-116**).[1] Compounds (**112, 116**) have antifeedant activity against lavae of the Japanese *Pieris* species. Diplophyllin (**114**) shows piscicidal activity against killie-fish which is killed within 240 min at a concentration of 6.7 ppm.[19,20] The structure of the reported pungent lactone from the same species was revised to be **116** by using NMR shift reagent.[60] *Ent*-diplophyllin (**114**) has been isolated from *Clasmatocolea vermicularis*[60] and *Plagiochila moritziana*.[62,81,82]



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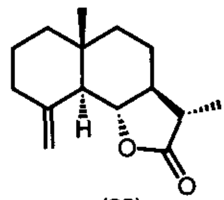

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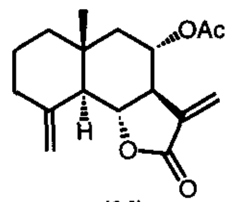

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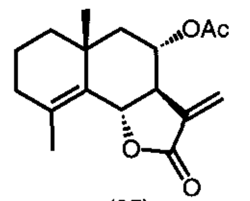

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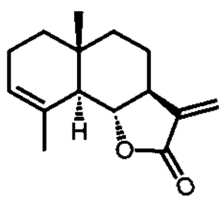

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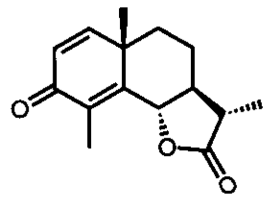

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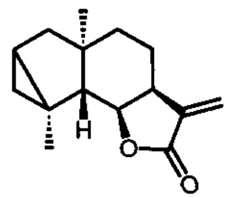

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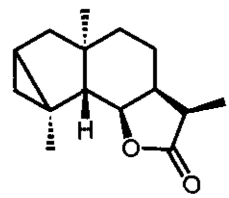

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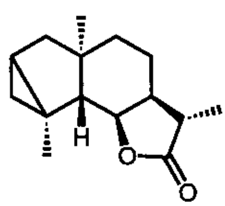

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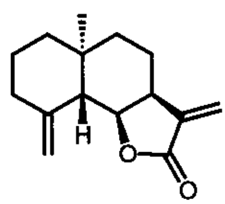

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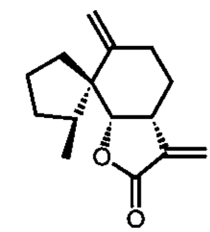

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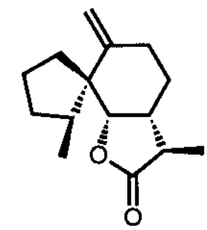

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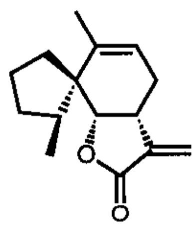

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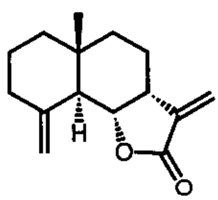

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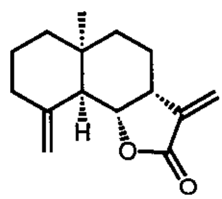

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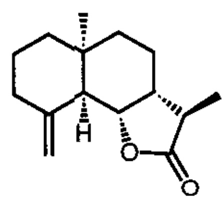

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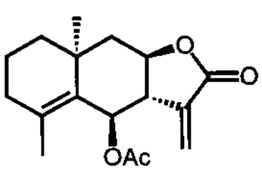

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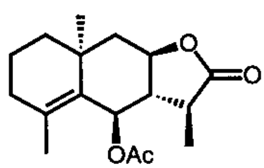

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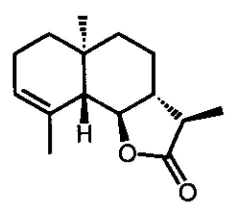

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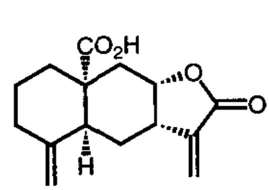

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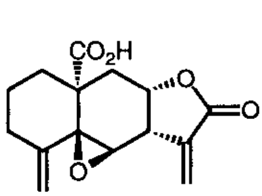

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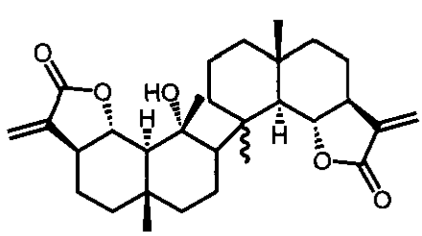

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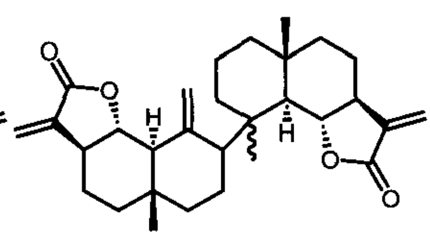

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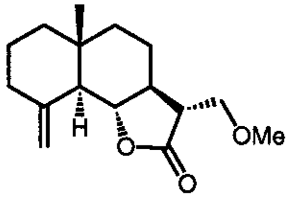

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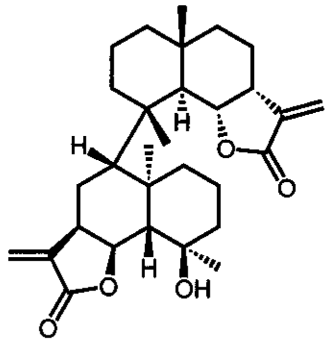

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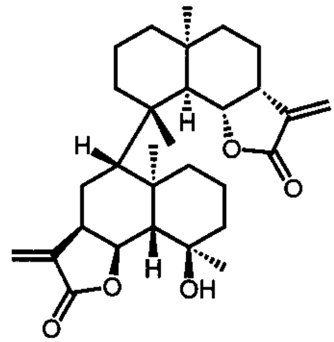

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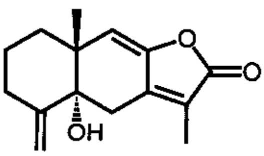

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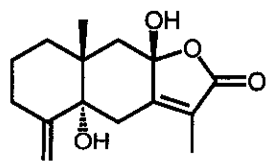

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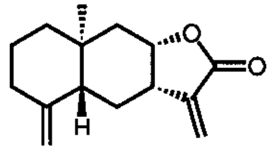

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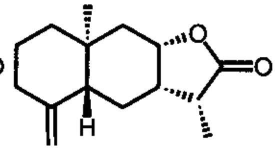

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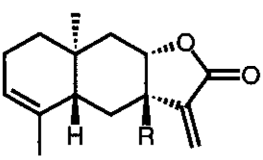

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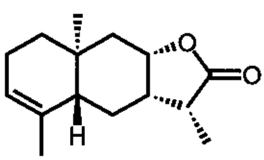
(116) R=OH



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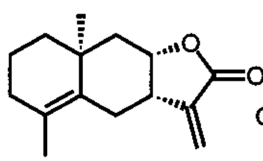

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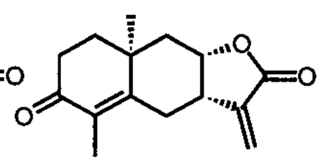

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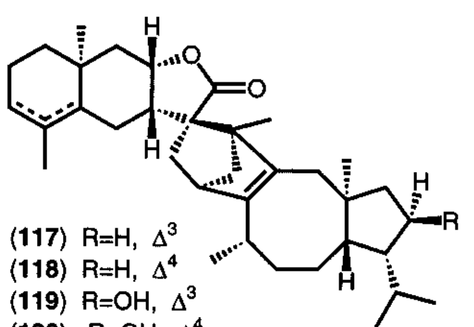
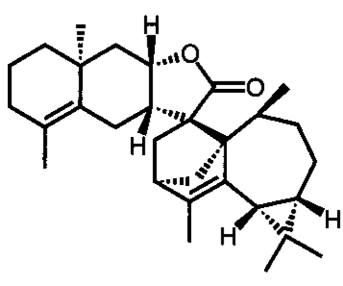


(117) R=H, Δ^3
(118) R=H, Δ^4
(119) R=OH, Δ^3
(120) R=OH, Δ^4



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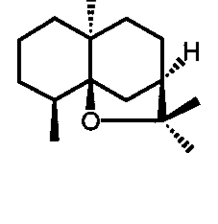

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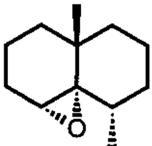

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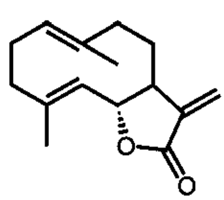

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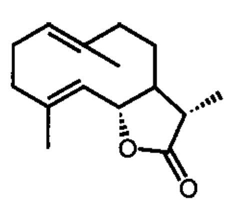

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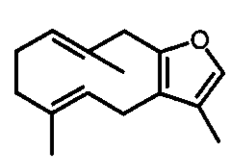


(126)

Five unique C-35 lactones, plagiospirolides A-E (**117-121**) have been isolated from the Panamanian liverwort *Plagiochila moritziana*.[62,81,82] Compounds (**117**) and (**118**) might be formed by a Diels-Alder type cycloaddition reaction between two dienophiles (**112**) and (**114**) present in the same species and the fusicocca-2,5-diene. Compounds (**117, 118**) have been synthesized by Kato *et al.*[84] Fusicocca-2(6),3-diene and fusicocca-2,5-diene were used to convert into compounds (**117, 118**), *via* a biogenetic-type Diels-Alder reaction with diplophyllolide (**112**) and diplophyllin (**114**).

Dihydroagarofurane (**122**) has been detected in the liverworts *Fossombronia pusilla*[73] belonging to the Codoniaceae and *Symphyogyna brasiliensis* belonging to the Hymenophytaceae by GC-MS.[62]

A unique trinoreudesmane-type sesquiterpene, (+)-(4*S*,4a*S*, 5*R*,8a*S*)-*trans*-4,8a-dimethyl-4a,5-epoxydecalin (**123**) has been isolated from the essential oils of European *Lophocolea bidentata* as major component and *L. heterophylla* as minor one.[85] The structure of **123** has been confirmed by spectroscopic evidence and synthesis.[85]

2.14 Germacranes, Gorgonanes and Guaianes

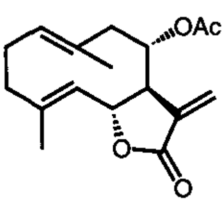
Costunolide (**124**) has been found in four *Frullania* species,[61,69,86] the South American *Clasmatocolea humilis*[34] and *Plagiochila hondurensis*.[18] Kim *et al.*[64] reported that compound (**124**) was isolated from the American *Frullania nisquallensis* and showed cytotoxic activity (IC_{50} 12μg/mL) against A-549 human lung carcinoma cell line, with inactive (-)-frullanolide (**71**). Dihydrocostunolide (**125**) has also been detected in *C. humilis*[34] and *P. hondurensis*[18] by GC-MS. Furanogermacra-1(10),4-diene (**126**) has been detected in *Lophocolea heterophylla* as a minor component.[3]

Tulipinolide (**127**) which is the major component of the Japanese liverwort, *Wiesnerella denudata* and its (11*R*)-dihydro- (**128**) and (11*S*)-dihydrotulipinolide (**129**) have been isolated from *Frullania serratta*.[69] Compound (**127**) shows antifeedant activity against the Japanese butterfly's lavae *Pieris* species.[19,20] *W. denudata* contains compound (**129**) as a minor constituent.[69] *Porella acutifolia* subsp. *tosana* is the rich source of germacra-12,8-olides (**130-134**).[87,88] Compound (**130**) has also been isolated from the Compositae and its structure determined by X-Ray crystallographic analysis.[89]

Ent-maalioxide (**135**) belonging to the gorgonane-type sesquiterpenoid which has been previously isolated from the Japanese liverworts, *Plagiochila sciophila* (= *P. acanthophylla* subsp. *japonica*) and *Jubula japonica*[1] has been found in the European *Barbilophozia floerkei*,[52] *Lophozia ventricosa*[90] and Japanese *Radula perrottetii*.[91]

Porella species produce not only drimane-type sesquiterpenoids but also guaiane- and germacrane-type sesquiterpenoids. *P. acutifolia* subsp. *tosana* elaborates two new guaianolides, isoporelladiolide (**136**) and dehydroisoporelladiolide (**137**),[88] together with the known porelladiolide (**138**) which has been isolated from *Porella japonica*.[1] The East Malaysian *Frullania serratta* produces not only eudesmane- and germacrane- (**127**) , but also guaiane-type sesquiterpenoid, such as 8α-acetoxyzaluzanin D (**139**).[69] A new guaianolide, dihydroestafiatin (**140**) has been isolated from Bolivian *Frullanoides densifolia*, along with the known estafiatin (**141**)[92-94] which was first obtained from the Compositae.[95]

2.15 Monocyclofarnesanes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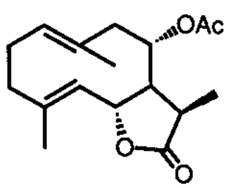
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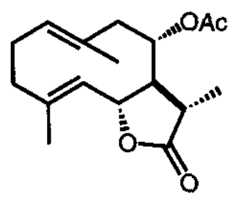
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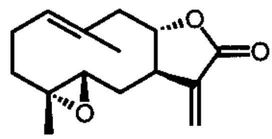
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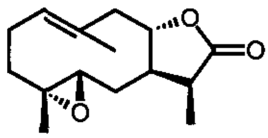
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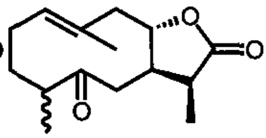
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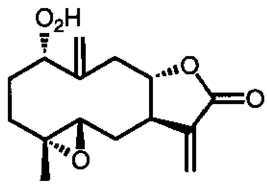
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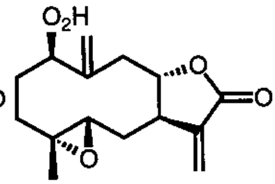
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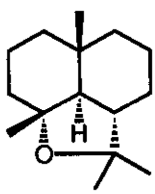
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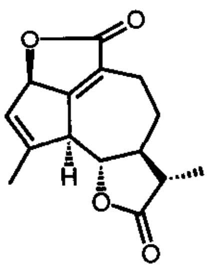
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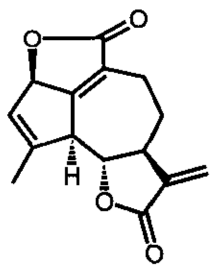
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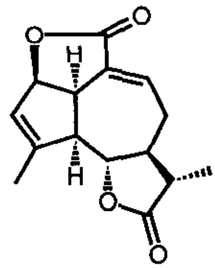
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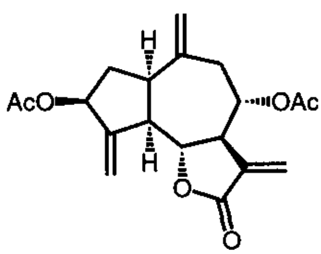
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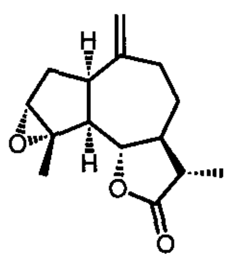
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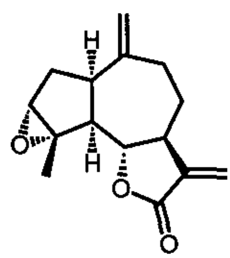
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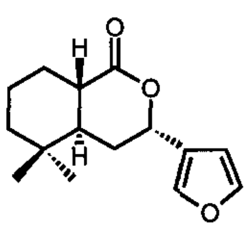
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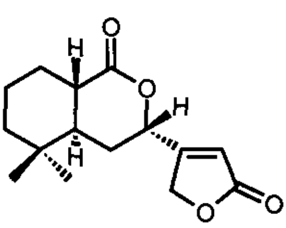
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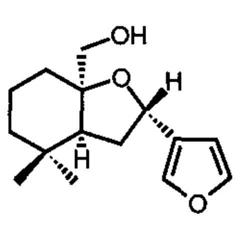

(144)

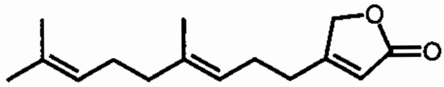
Three novel monocyclofarnesane-type sesquiterpenoids, ricciocarpins A (**142**) and B (**143**) and ricciofuranol (**144**) have been isolated from an axenic culture of the European liverwort, *Ricciocarpos natans* belonging to the Ricciaceae.[40,41] Both compounds have mollascicidal activity against *Biomphalaria glabtata* at a concentration of 11 and 43 ppm (LC_{100}).[42] The total synthesis of **142** has been accomplished by Eicher in 9 steps.[96] An additional monocyclofarnesane sesquiterpene lactone (**145**) was isolated from the Venezuelan unidentified liverwort, *Frullania* species.[72] It is the first example of the isolation of **145** as a natural product.

2.16 Pinguisanes and Norpinguisanes

The Liverworts, belonging to the Lejeuneaceae, Porellaceae, Ptilidiaceae and Trichocoleaceae (Jungermanniales) are rich sources of pinguisane- and norpinguisane-type sesquiterpenoids which have been found neither in the other terrestrial plants nor marine organisms and whose carbon skeleton does not obey the biogenetic isoprene rule. Sixteen pinguisanes and four norpinguisanes have been reported from the liverwort families mentioned earlier.[1] *Aneura pinguis* which belongs to the Metzgeriales also produces pinguisanes (**146-148**).[1] This is one of the most important facts that the liverworts belonging to the Jungermanniales and the Metzgeriales originated from the same ancestor.[1] Furthermore, three new pinguisane-type sesquiterpenes, 2α-hydroxy-3-oxopinguis-5(10)-en-11,6-olide (**149**), its methyl ether (**150**) and 3-oxo-pinguis-5(10)-6-dien-11,6-olide (**151**) have been obtained from an axenic culture of *A. pinguis*, together with pinguisone (**148**).[97] Oxidation of **148** by *m*-chloroperbenzoic acid gave compound (**149**) which was converted to **150** and **151** by methylation and dehydration, respectively.[97]

Possible biogenetic pathway of pinguisone (**148**) has been proposed by Tazaki *et al.*,[98] using [2-^{13}C]-acetate to the cultured gametophytes of *A. pinguis*. The labeling pattern showed two methyl (C_{15} and C_{13}) migration and C_9-C_{10} bond cleavage of main chain in farnesyl diphosphate in the formation of pinguisone. Deoxopinguisone (**147**) has been found in *Porella densifolia* subsp. *appendiculata*,[106] cell suspension culture of *P. vernicosa*[56] and *Plagiochila alternans*[67] and *P. rosariensis*.[18] The New Zealand *Plagiochila retrosptectans* contains dehydropinguisone (**152**) the absolute configuration of which has been established by X-Ray crystallographic analysis of *p*-bromobenzoate of the hydroxy derivative obtained from **152.**[23,24,33] Refractionation of the ether extract of the New Zealand *Plagiochila elegantula* gave a new norpinguisanolide (**153**), along with deoxopinguisone (**147**) and norpinguisone methyl ester (**154**).[33,99] *Plagiochila rosariennsis*,[18] *Ptychanthus striatus*[100] and *Thysanannthus fruticosus*[101] produce dehydrodeoxopinguisone (**155**). The Japanese small liverwort, *Tricholejeunea sandvicensis* belonging to the Lejeuneaceae produces various types of pinguisane- and norpinguisane-type sesquiterpenoids: furanopinguisanol (**156**), dehydropinguisenol (**157**), dehydropinguisenenol methyl ether (**158**), 6α,11α,-dimethoxypinguis-5(10)-ene (**159**), 6β,11β-dimethoxypinguis-5(10)-ene (**160**), pinguisanin (**161**), dehydropinguisanin (**162**) and ptychanolide (**163**).[87,92-94]

The Bolivian *Frullanoides densifolia* is also interesting liverwort because it contains many pinguisane-type sesquiterpenoids: pinguisanin (**161**), pinguisenal (**164**), ptychanolide (**163**), pinguisanolide (**165**) isopinguisanolide (**166**), spirodensifolins A (**167**) and B (**168**).[92-94] The structure previously reported for pinguisanin isolated from *Porella platyphylla*[1] has been revised to **161** by means of 2D-NMR and NOESY



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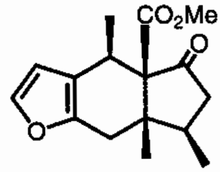

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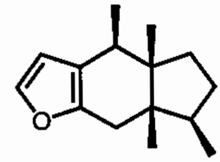

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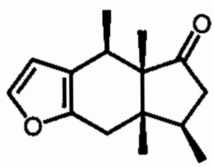

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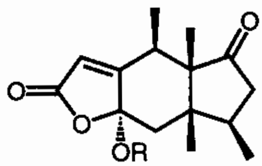
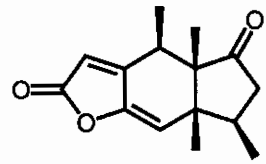


(149) R=H
(150) R=Me



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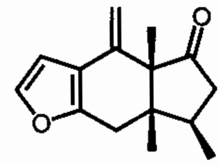

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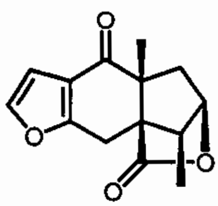

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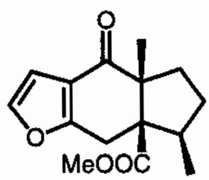

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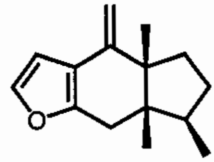

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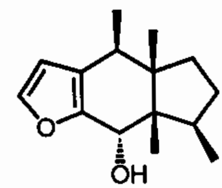

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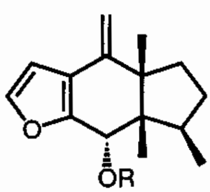
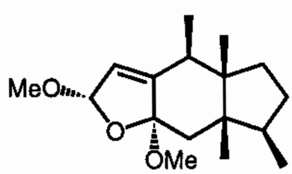


(157) R=H
(158) R=Me



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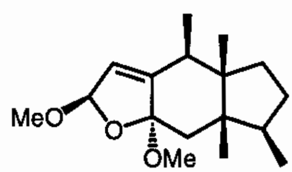

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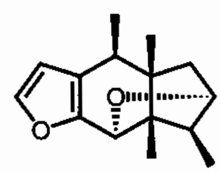

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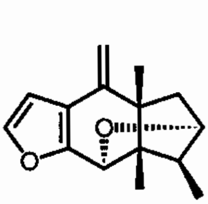

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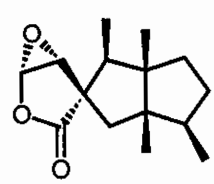

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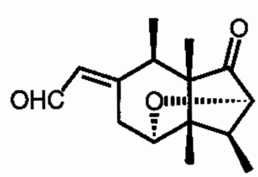

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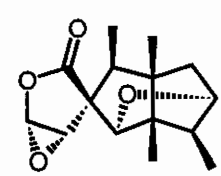


(165)

spectra.[102] Pinguisanin (**161**) has also been found in *Acrolejenuea pusilla*,[101] *A. pycnoclada*,[101] *Neotrichocolea bissetii*,[91] *Porella cordaeana*[103] and *P. platyphylla*.[54,77,102,104] The former two species also produce dehydropinguisanin (**162**), pinguisenal (**164**), pinguisanolide (**165**) and isopinguisanolide (**166**).[101] *Acrolejeunea torulosa* and *A. pusilla* contain dehydropinguisanin (**162**) and dehydropinguisenol (**157**).[101] The European *Porella platyphylla* also contains pinguisanes (**166, 169-171**)[77] and porellapinguisanolide (**172**).[105] *P. cordaeana* produces not only drimanes but also highly oxygenated pinguisanes (**172, 173**),[103] norpinguisone methyl ester (**154**)[103] and norpinguisanolide (**153**).[55] Compound (**154**) is also distributed in *Bryopteris filicina*,[54,105] *Lejeunea discreta*,[101] *Porella densifolia* subsp. *appendiculata*,[106] *P. elegantula*,[32,99] *P. navicuralis*[107] and cell suspension culture of *P. vernicosa*.[56,57] Norpinguisone (**174**) has been firstly isolated from the pungent liverwort, *Porella vernicosa*.[1] Later, this compound has been found in *P. densifolia* subsp. *appendiculata*,[106] *P. navicularis*[107] and cell suspension culture of *P. vernicosa*.[56,57] Compounds (**154, 174**) inhibit superoxide release anion from guinea pig peritoneal macrophage.[19,20,99]
Three pinguisane methyl esters, bryopterins A (**175**), B (**176**) and C (**177**) and a norpinguisane, bryopterin D (**178**) have been isolated from the ether extract of the Panamanian *Bryopteris filicina* belonging to the Lejeuneaceae.[105,108] The Japanese *Ptychanthus striatus* contains not only various labdane-type diterpenoids (see later) but also ptychanolactone (**179**),[25] ptychanolide (**163**) and pinguisanolide (**165**).[100]
The ether extract of *Declanolejeunea yoshinagana* (Lejeuneaceae) contains two new pinguisanes (**180** and **181**) together with two known pinguisanes (**147**) and (**163**).[109] These structures have been proposed by 2D-NMR spectra, however they should be revised to the structures (**182**) and (**183**) by careful analysis of 2D-NMR spectra.[110] Cell suspension culture of *Porella vernicosa* also contains deoxopinguisone methyl ether (**184**).[57] These pinguisanes and norpinguisanes are very unstable upon the exposure of the air, light and acidic condition to afford polymerized artefacts.

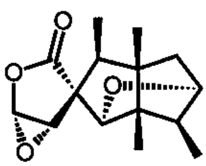
2.17 Miscellaneous sesquiterpenoids

A new arranged drimane-type sesquiterpene ether, peculiaoxide (**185**) has been isolated from the Taiwanese *Plagiochila peculiaris*.[22,111,112] The methanol extract of the Japanese liverwort *Riccardia crassa* belonging to the Riccardiaceae elaborates two unique merosesquiterpenoids, riccardiphenols A (**186**) and riccardiphenol B.[113] Recently the total synthesis of the optical active riccardiphenol A has been achieved by Tori *et al.*[114] and the absolute stereostructure of the natural product (**186**) was confirmed to be correct. Perry *et al.*[115] reported the isolation of riccardiphenol C (**187**) which showed mild cytotoxic activity against BSC-1 cells at 60 µg/disk and antimicrobial activity against *Bacillus subtilis* at 60 µg/disk, from the New Zealand *R. crassa*.

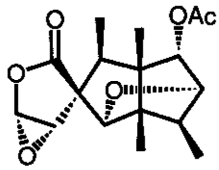
3. Diterpenoids

3.1 Cembranes

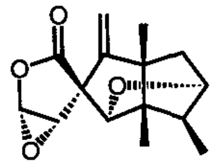
Two new cembrane-type diterpenoids have been known in the liverworts. Setiformenol (**188**) and chandonanthone (**189**) were isolated from *Chandonanthus setiformis* (=*Tetralophozia setiformis*),[52,83,116,117] and *Chandonanthus hirtellus*,[2] respectively. Both structures have been elucidated by 2D-NMR spectroscopy. This is the first record of cembrane-type diterpenoids from bryophytes.



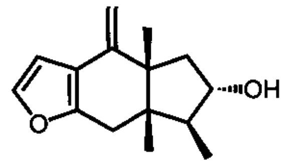
(**166**)



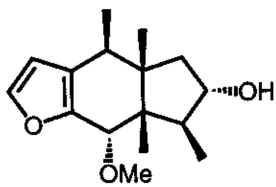
(**167**)



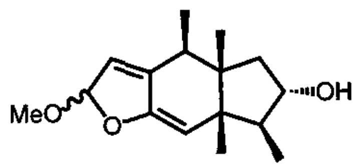
(**168**)



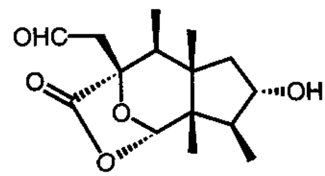
(**169**)



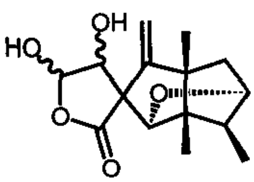
(**170**)



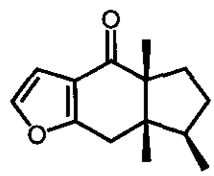
(**171**)



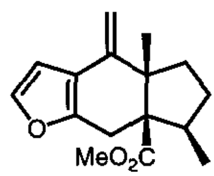
(**172**)



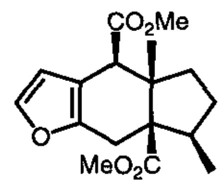
(**173**)



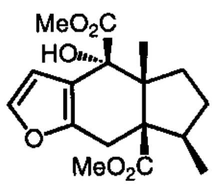
(**174**)



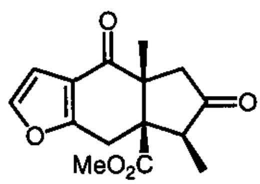
(**175**)



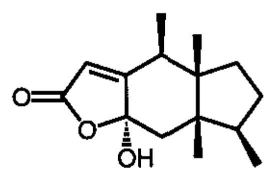
(**176**)



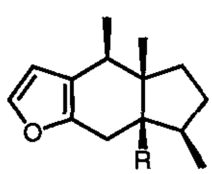
(**177**)



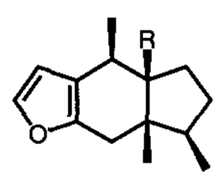
(**178**)



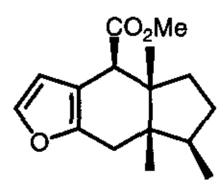
(**179**)



(**180**) R=CHO
(**181**) R=CH_2OAc



(**182**) R=CHO
(**183**) R=CH_2OAc



(**184**)

3.2 Clerodanes

A furanoclerodane, *ent*-junceic acid (**190**) has been isolated from the Japanese liverwort *Heteroscyphus coalitus* (=*H. bescherellei*).[118] The enantiomer of (**190**) has also been isolated from the Compositae.[119] The *Jungermannia* species are rich sources of clerodane-type diterpenoids. *J. paroica* produces three epoxyclerodanes (**191-193**).[120,121] The German *J. hyalina* which is morphologically very similar to *J. paroica* elaborates a new epoxyclerodane (**194**), together with **191** and **192**.[122] *Gymnocolea inflata* which is grown in Hokkaido and Europe is very bitter. One of the bitter principle, gymnocolin (**195**) was isolated and its structure was established by X-Ray crystallographic analysis.[50,123] This diterpene has antifeedant activity against lavae of the Japanese *Pieris* species.[19,20]

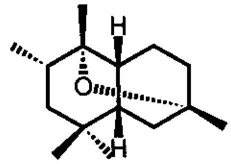
Anastrepta orcadensis is also very bitter liverwort. Two unique clerodanes, anastreptin (**196**) and orcadensin (**197**) have been isolated.[50,121] The similar furanoclerodanes, linguifolide (**198**) and its dihydro derivative (**199**) have also been isolated from the Malaysian *Demotarisia linguifolia*.[124] The liverwort *Lophozia ventricosa* contains ventricosenediolide (**200**).[52,53,83] It is well known that the Japanese and European liverwort *Jamesoniella autumnalis* contain very strong bitter principles. Three new furanoclerodanes, 17-acetylfuranolactone (**201**), jamesoniellides A (**202**), B (**203**) and C (**204**) have been isolated from the European species.[125,126] The stereostucture of the last compound has been established by X-Ray crystallographic analysis. Further fractionation of *in vitro* cultured cells of the same liverwort resulted in the isolation of nine new furanoclerodanes named jamesoniellides D-J (**205-216**), along with two new labdanes.[127] Furthermore, more complex new clerodane-diterpenoids, heteroscyphones A-D (**217-220**) have been obtained from the ether extract of the Japanese liverwort *Heteroscyphus planus*, together with new hydroxyclerodane-type diterpene. The structure of **217** was determined by a combination of 2D-NMR, chemical transformation and X-Ray crystallographic analysis.[25,29,128] Furthermore two new spiro-clerodanes, named heteroscypholides A (**221**) and B (**222**) have been isolated from cultured cells and gametophytes of *H. planus*.[129] The relative stereostructure of **221** was confirmed by X-Ray crystallographic analysis. Suspension culture of *H. planus* also produces a new clerodane with a carboxylic acid named heteroscyphic acid C (**223**) and two new carboxyclerodanes which might be intermediates in the biosynthesis of C-9 spiro-γ-lactones, e.g. **217-222**.[130]

3.3 Dolabellanes

The liverworts, *Barbilophozia* species belonging to the Lophoziaceae are rich sources of dolabellane-type diterpenoids. Barbilycopodin (**224**) has been isolated from *B. attenuata, B. floerkei*,[52,53,83,131] *B. hatcheri*,[52,53,83] *B. lycopodioides*[50,131] and *Chandonanthus setiformis*.[132] *B. barbata* and *B. floerkei* produce 10-deacetoxybarbilicopodin (**225**),[52,53,54,83,131] and the latter species also elaborates 10*R*,16-diacetoxy-3*S*,4*S*-epoxydolabella-7*E*-ene (**226**).[131] The Japanese liverwort *Odontoschisma denudatum* contains 6-acetoxy-3,4-epoxy-12-hydroxydolabella-7*E*-en-16-al (**227**), together with four new dolabellanes.[133]

3.4 Fusicoccanes

The liverwort, *Pleurozia gigantea* is one of the most unique species in the Jungermanniales since it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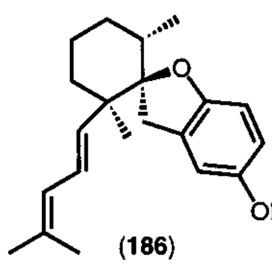
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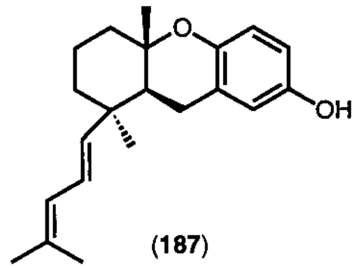
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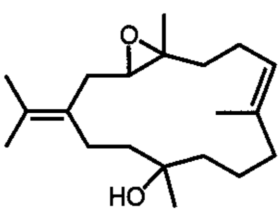
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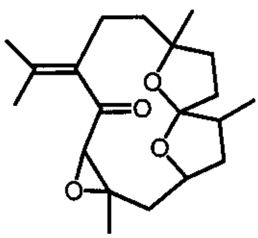
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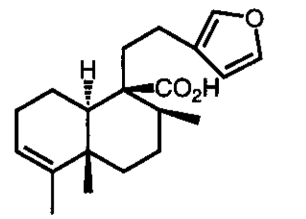
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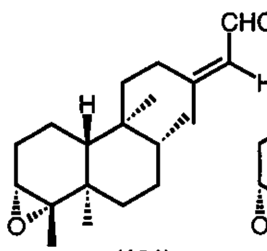
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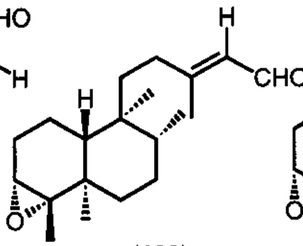
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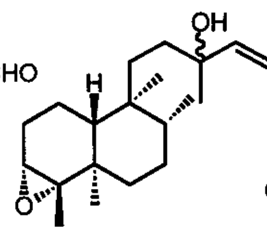
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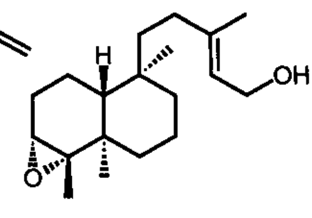
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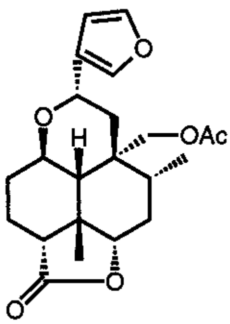
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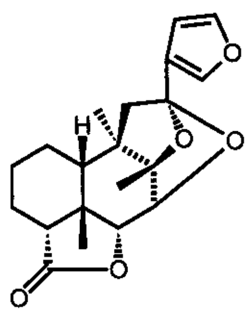
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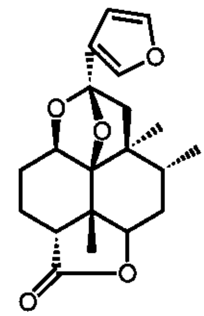
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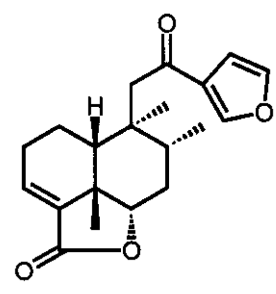
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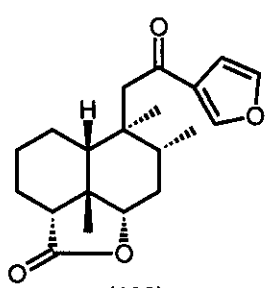
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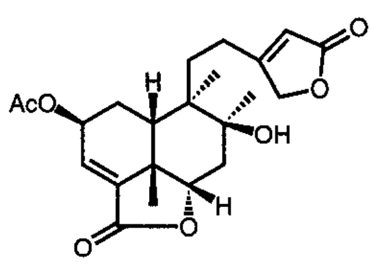
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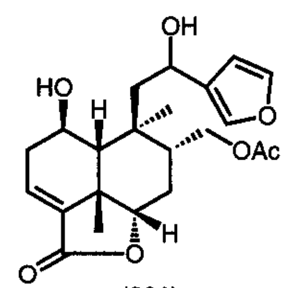
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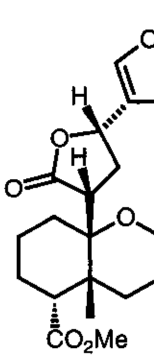

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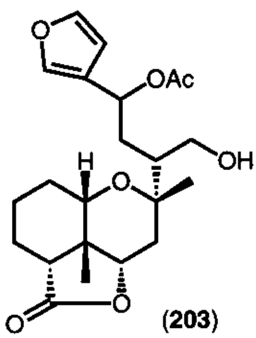

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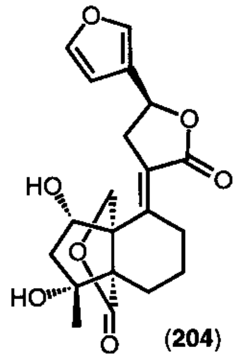

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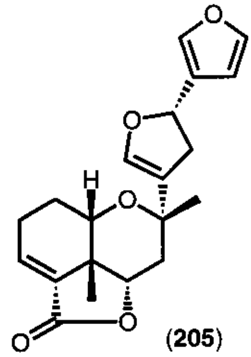

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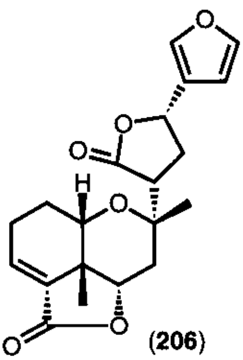

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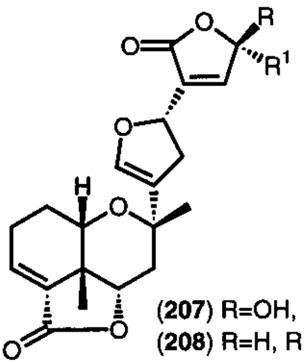
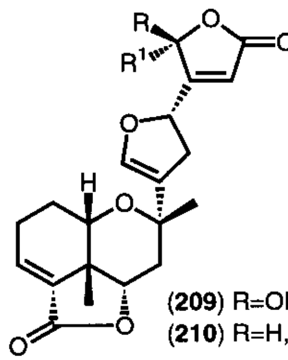
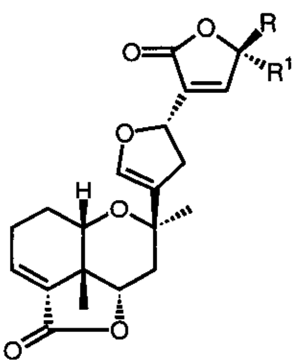


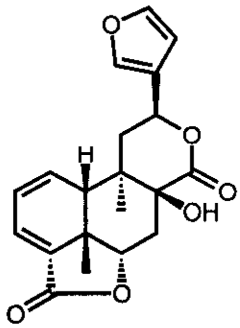
(207) R=OH, R^1=H
(208) R=H, R^1=OH



(209) R=OH, R^1=H
(210) R=H, R^1=OH



(211) R=OH, R^1=H
(212) R=H, R^1=OH



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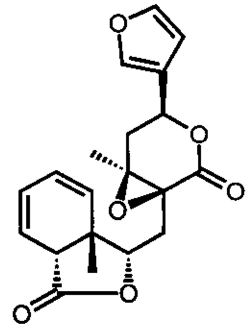

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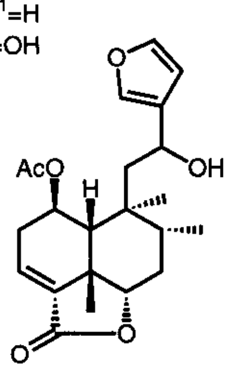

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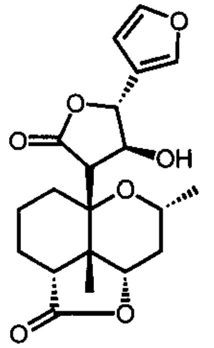


(216)

elaborates three new epoxyfusicoccanes, fusicogigantones A (**228**), B (**229**) and fusicogigantepoxide (**230**) the structure of which was determined by X-Ray crystallographic analysis.[134] *Bryopteris filicina* contains not only pinguisane-type sesquiterpenoids but also fucicoccane-type epoxide (**230**).[105] Compounds (**228**) and (**229**) have been obtained from axenic culture of *Plagiochila adianthoides*.[135] Three fusicoccanes (**228-230**) have been synthesized from fusicoccan-2(6),3-diene and fusicocca-2,5-diene.[84] A new fusicorrugatol (**231**) has been isolated from the Venezuelan *Plagiochila corrugata* along with fusicogigantone A (**228**).[136,137] The ether extract of European *Anastrophyllum auritum* contains not only sphenolobane-type diterpenoids (see later), but also a new fusicoccane named fusicoauritone (**232**) with fusicogigantones A (**228**) and B (**229**).[138] Fusicoplagin C (**233**) has been isolated from the Japanese *Plagiochila sciophila*, along with three fusicoccane-type diterpenoids.[139] The British *P. spinulosa* is characteristic liverwort because it contains two unique fusicoccane-type diterpenes, spinuloplagins A (**234**) and B (**235**).[121]

3.5 Halimanes

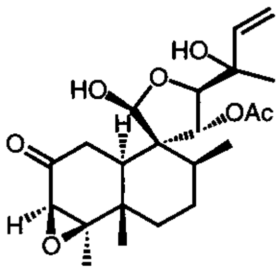
The distribution of the halimane-type diterpenoid is very rare in nature. The ether extract of *Heteroscyphus coalitus* (=*H. bescherellei*) was chromatographed on silica gel and Sephadex LH-20 to afford a new halimane- (**236**) and a new seco-halimane-type diterperne lactones (**237**).[140] Their relative configurations were determined by a combination of 2D-NMR and X-Ray crystallographic analysis.

3.6 Kauranes

The liverwort *Jungermannia exertifolia* subsp. *cordifolia* is rich source of kaurane-type diterpenoids. Fractionation of the ether extract of the French species resulted in the isolation of a new bis-*ent*-kaurene-type, exertifolin A (**238**), two new 6,7-seco-*ent*-kaurene-type, secoexertifolins A (**239**) and B (**240**), together with five new epoxykaurene-type diterpenoids, exertifolins B-F (**241-245**) and two new and seven previously known kaurene diterpernoids.[141,142] Their structures have been established mainly by X-Ray crystallographic analysis and chemical degradations. The absolute configuration have been suggested by CD spectra. This is the first example of the isolation of bis-*ent*-kaurane-type and 9,11-epoxy-*ent*-kaurane-type diterprenoids from the liverworts. The New Zealand liverwort *Lepidolaena taylorii* produces *ent*-8,9-seco-7-hydroxykaura-8,14-epoxy-16-dien-9,15-dione (**246**) with two related 8,9-kaurenes.[143] Compound (**246**) shows cytotoxicity against P-388 leukemia cell at a concentration of 0.27 μg/mL.

3.7. Labdanes

Labdane- and *ent*-labdane-type diterpenoids are widespread in the Jungermanniales liverworts. A simple labdane epoxide, (+)-manoyl oxide (**247**) has been isolated from *Mylia nuda*.[144] From the Japanese *Jungermannia infusca*, three known labdanes, gomeraldehyde (**248**) and epi-gomeraldehyde (**249**) have been isolated. More complex labdanes, haplomitrenolides A-C (**250-252**) are the major components of the Japanese *Haplomitrium mnioides* which is one of the primitive liverworts.[152] Their absolute configuration have not been determined. The European and Japanese *Scapania undulata*, a large stem-leafy liverwort, is rich source not only of *ent*-sesquiterpenoids but also of labdanes possessing an oxyrane-ring, named scapanins (**253-261**).[50,145,146] Scapanin G (**262**) and a 7,8-seco-labdanoid, pallavicinin (**263**) which have



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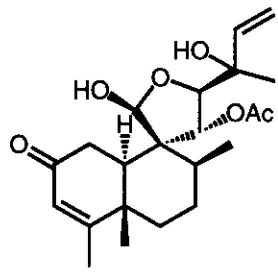

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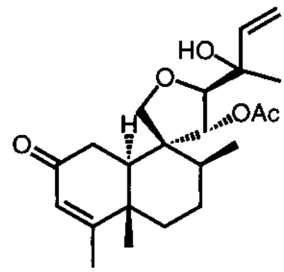

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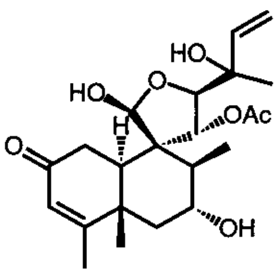

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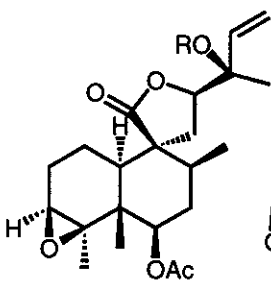
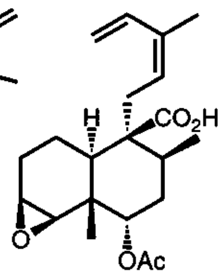
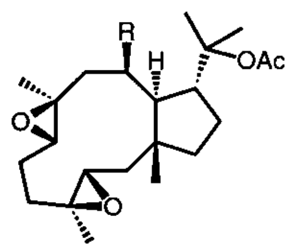


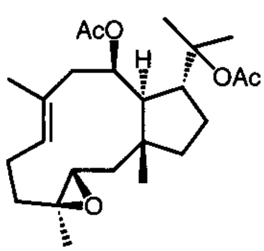
(221) R=Ac
(222) R=H



(223)



(224) R=OAc
(225) R=H



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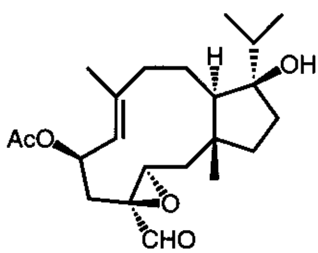
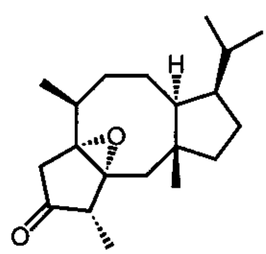


(227)



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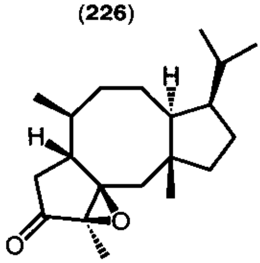

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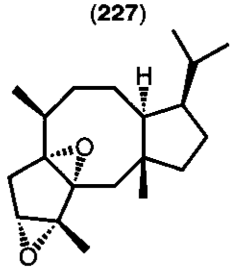

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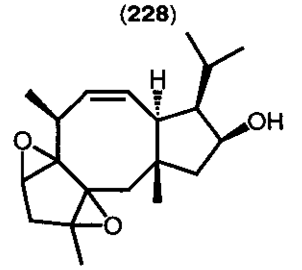
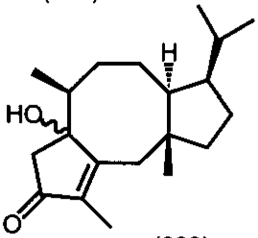


(231)



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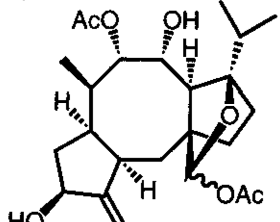

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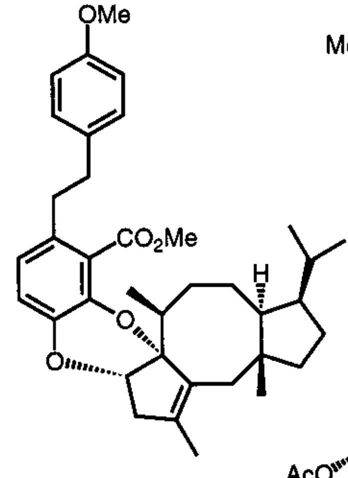
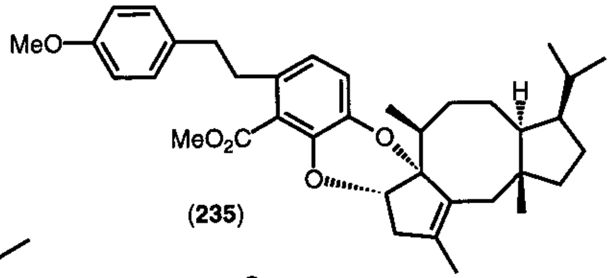


(**234**)



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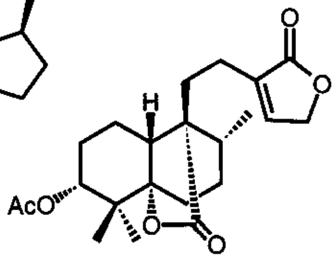
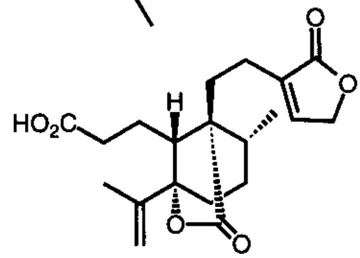
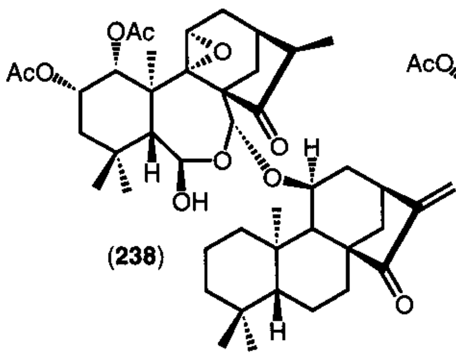


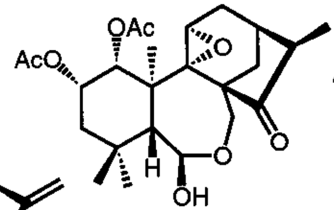
(**236**)



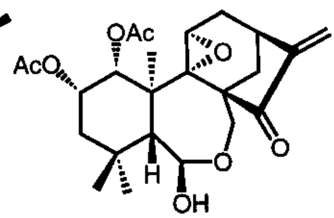
(**237**)



(**238**)



(**239**)



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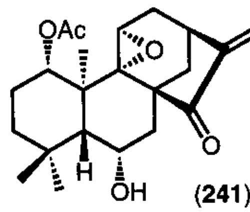

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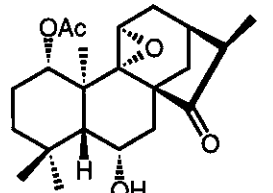
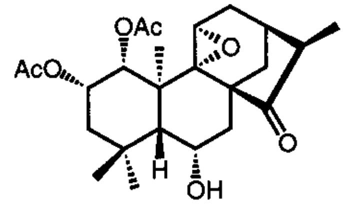


(**242**)



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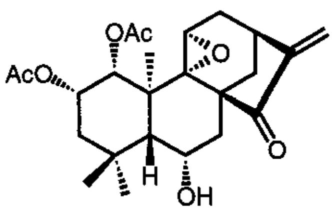

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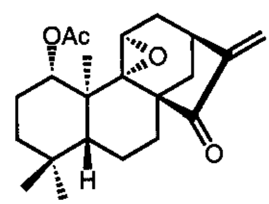
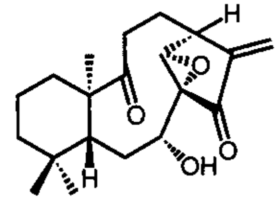
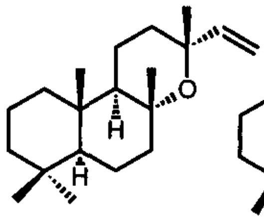


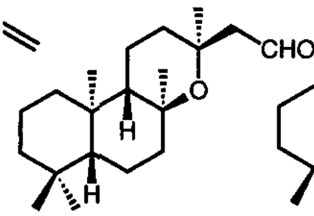
(**245**)



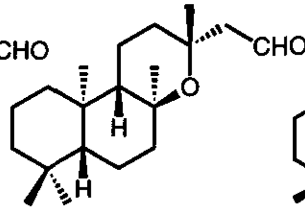
(**246**)



(**247**)



(**248**)



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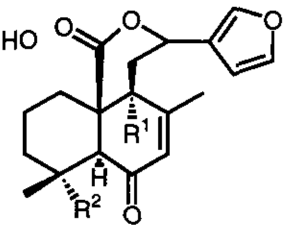
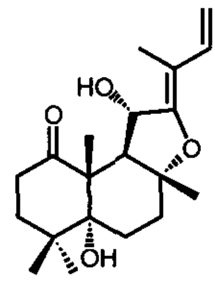
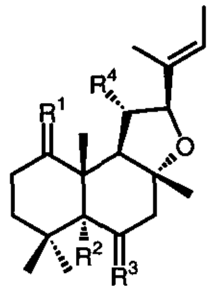


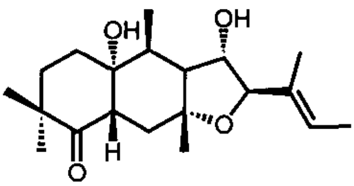
(**250**) R^1=H, R^2=Me
(**251**) R^1=OH, R^2=Me
(**252**) R^1=H, R^2=COOMe



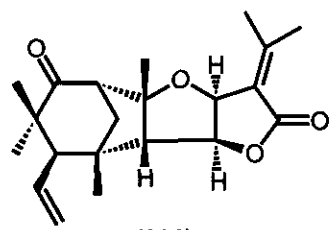
(**253**)



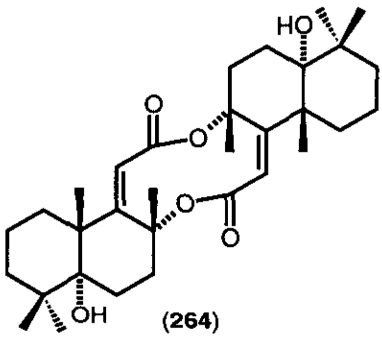
(**254**) Scapanin B ; R^1=O, R^2=R^4=OH, R^3=H_2
(**255**) R^1=H_2, R^2=R^4=H, R^3=H, β-OH
(**256**) R^1=R^3=H, β-OH, R^2=R^4=H
(**257**) R^1=R^3=H, β-OH, R^2=H, R^4=OH,
(**258**) R^1=O, R^2=H, R^3=H, β-OH, R^4=OH
(**259**) R^1=H, β-OH, R^2=R^4=H, R^3=H_2
(**260**) R^1=O, R^2=H, R^3=H_2, R^4=OH
(**261**) R^1=H, β-OH, R^2=H, R^3=H_2, R^4=OH



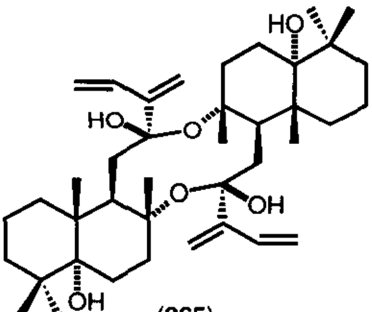
(**262**)



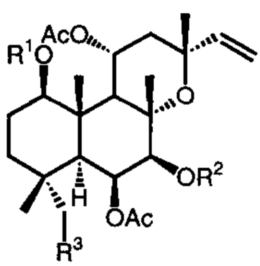
(**263**)



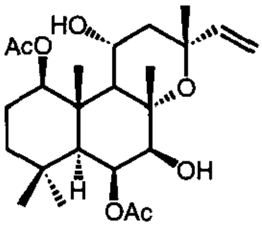
(**264**)



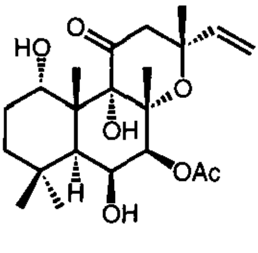
(**265**)



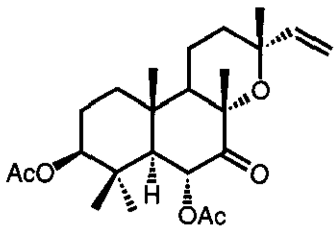
(**266**) R^1=R^2=Ac, R^3=H
(**267**) R^1=Ac, R^2=R^3=H
(**268**) R^1=R^2=R^3=H
(**269**) R^1=Ac, R^2=H, R^3=OH



(**270**)



(**271**)



(**272**)

been isolated from *S. undulata*[50,,146] and *Pallavicinia subcilliata*[15,147], respectively are the rearranged labdane-type diterpenoids. The stereostructure of the latter compound has been confimed by X-Ray crystallography. Further purification of the Japanese *Scapania undulata* gave two new labdane dimers named scapaundulins A (**264**) and B (**265**) whose structures were determined by HRFAB mass spectrometry and 2D-NMR spectra.[148]

The ether extract of the Japanese liverwort *Ptychanthus striatus* contains five highly oxygenated novel labdanes, ptychanthins A-E (**266-270**),[1,149,150] closely related to folskolin (**271**) isolated from the higher plant *Coleus forskohlii*, indicating a number of interesting biological activity such as positive inotropic and antihypertensive activity, together with four new labdanes.[151] The absolute structure of **267** was established by a combination of X-Ray crystallographic analysis and CD spectrum of a dibenzoate. Hamatilobenes A-E (**272-275**) are the predominant components of the Japanese *Frullania hamatiloba.*[68] Their absolute configuration are based on the negative Cotton effect of the benzoate derived from **272.** Symphyogynolide (**276**) has been isolated from the Venezuelan liverwort *Symphyogyna brasiliensis* and its structure determined by 2D-NMR, however, the absolute configurtion was not determined.[72]

3.8. Phytanes and Pimaranes

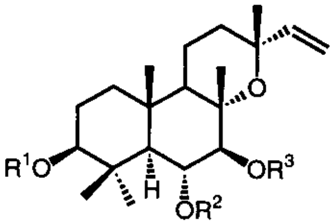
Naviculide (**277**) and haplomitrenone (**278**) have been isolated from two liverworts, *Porella navicularis*[107] and *Haplomitrium mnioides*,[152] respectively. *Jamesoniella tasmanica* produces not only epi-verrucosane diterpenoids (see later) but also a phytane-type epoxide (**279**).[33] Lower terpenoids are very rare in mosses. Two pimarane-type diterpenoids, momilactones A (**280**) and B (**281**) which have been isolated from seed of rice in husk have been found in the moss, *Hypnum plumaeforme.*[153]

3.9 Sacculatanes

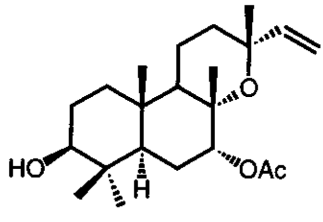
The thalloid liverwort, *Pellia endiviifolia* is a rich source of sacculatane-type diterpenoids. n-Hexane extract of *P. endiviifolia* contains sacculatanolide (**282**), 1β-hydroxysacculatanolide (**283**), 11α-hydroxysacculatanolide (**284**), 1β,11β-dihydroxysacculatanolide (**285**), 12-deoxo-1β,11α-dihydroxysacculatanolide (**286**) and 1β,11α-dihydroxysacculatenolide (**287**), along with the related compounds, such as a very pungent sacculatal and its epimer.[154,155] All these stereostuctures have been determined by a combination of chemical reactions, NOEs, X-Ray crystallographic analysis and CD spectra.[155] Two sacculatane-hemiacetals, sacculaplagin (**288**) and sacculaporellin (**289a**) have been isolated from the Japanese liverwort *Plagiochila sciophila* (=*P. acanthophylla* subsp. *japonica*)[156] and *Porella perrottetiana*,[118] respectively. The configuration at C-13 in sacculaporellin (**289a**) has been revised from 13*R* to 13*S* (**289b**).[104] Furthermore a new sacculatane hemiacetal, (5*S*,9*S*,10*R*,13*S*)-epoxy-8(12),17-sacculatadiene-13β,15ξ-diol [=(13*S*)-15ξ-hydroxysacculaporellin)] (**290**) has been obtained from the English *Porella platyphylla.*[104]

3.10 Sphenolobanes

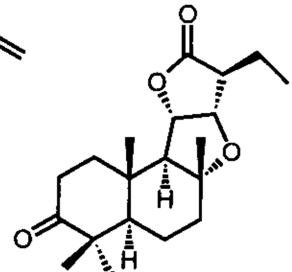
The European liverwort *Anastrophyllum minutum* is chemically interesting liverwort since it elaborates unique sphenolobane-type diterpenoids (**291-296**).[157,158] Compound (**291**) possesses inhibitory activity



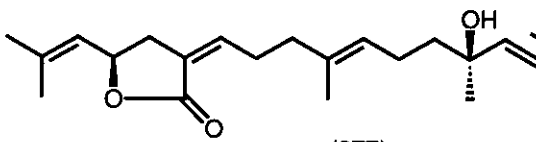
(**273**) R^1=R^2=Ac, R^3=H
(**274**) R^1=R^3=Ac, R^2=H



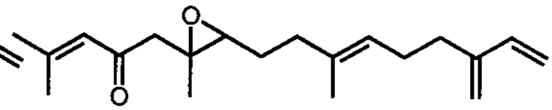
(**275**)



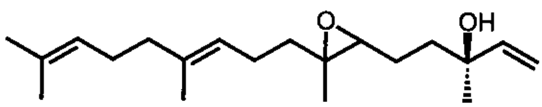
(**276**)



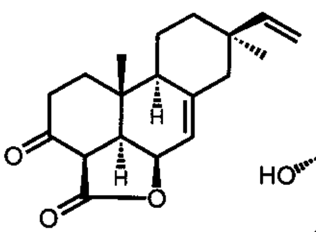
(**277**)



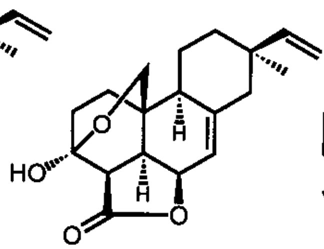
(**278**)



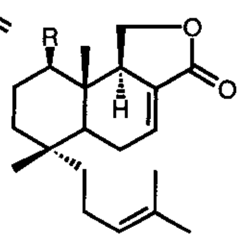
(**279**)



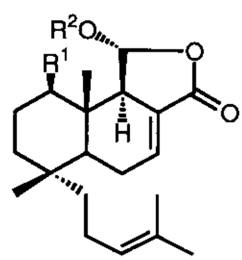
(**280**)



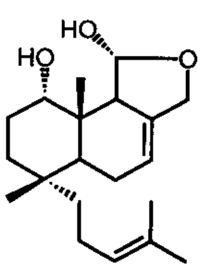
(**281**)



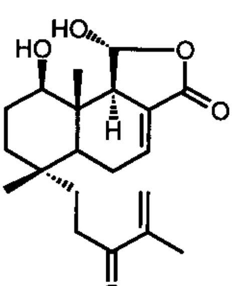
(**282**) R=H
(**283**) R=OH



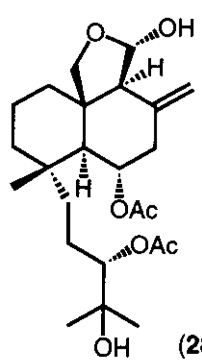
(**284**) R^1=R^2=H
(**285**) R^1=OH, R^2=H



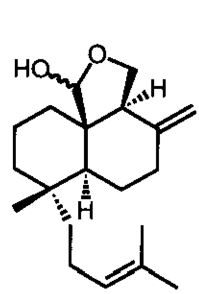
(**286**)



(**287**)



(**288**)



(**289a**) 13*R*
(**289b**) 13*S*

against shoot and root elongation of rice in husk at a concentration between 10 and 500 ppm. The ether extract of *A. auritum* produces six new sphenolobanes (**297-302**), together with 3α,4α-epoxy-5α,18-dihydroxysphenoloba-13*E*(15),16*E*-diene (**292**).[138] It is noteworthy that the similar compound (**303**) has been found in the Japanese sponge, *Halichondria panicea.*[159] Further study of the secondary metabolites of *A. donnianum* resulted in the isolation of four new sphenolobanes (**304-307**), along with 3α,4α-epoxysphenoloba-13*E*,16*E*-dien-18-ol (**297**) and 3α,4α-epoxysphenoloba-13*E*,17-diene (**302**).[160]

3.11 Cyathanes (=Verrucosanes)

The Jungermanniales liverworts, *Gyrothyra underwiidiana,*[161] *Heteroscyphus planus,*[128] *Mylia taylorii,*[162] *M. verrucosa,*[163] *Plagiochila stephensoniana,*[164] *Scapania bolanderi,*[165] *Schistochila nobilis*[166] and *S. acuminata*[167] produce verrucosane and homoverrucosane-type diterpenoids. *M. taylorii* elaborates a unique-verrucosane hemiacetal, (15*S*,16*S*)-2β,16-epoxyverrucosane-16-ol (**308**).[162] The ether extract of the New Zealand *Jamesoniella tasmanica* contains 10 diterpenoids of which three are 20-acetoxy-4β,5β-epoxy-13-epi-neohomoverrucos-15(17)-en-16,12β-olides (**309-311**).[168]

II. Heterocyclic acetogenins

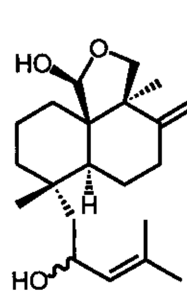
The ether extract of the liverwort *Cheilolejeunea imbricata* was purified by HPLC to give two milky-smelling lactones, (*R*)-dodec-2-en-1,5-olide (**312**) and (*R*)-tetradec-2-en-1,5-olide (**313**).[169] Neither terpenoids nor lipophilic aromatic compounds were detected in this liverwort.

III. Heterocyclic aromatic compounds (except Flavonoids)

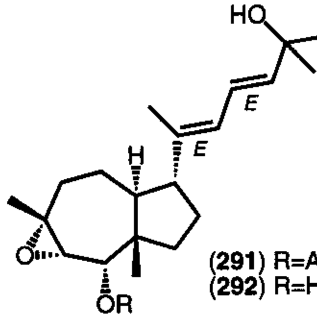
1. Bibenzyls

Liverworts contains various bibenzyl derivatives, but these simple compounds have not been detected in or isolated from mosses and hornworts. The liverworts, *Frullania* (Frullaniaceae), *Radula* (Radulaceae) are the most popular liverworts which produce bibenzyl derivatives. 3-Hydroxy-4,5-methylenedioxybibenzyl (**314**) has been isolated from *Radula javanica* (=*R. variabilis*).[170,171] *Frullania ericoides,*[70] *F. falciloba,*[172] *F. incumbens*[33] and *Tricholejeunea sandvicensis*[87] and the unidentified Venezuelan *Frullania* species[33,72] produce 3,4-methylenedioxy-3'-methoxybibenzyl (**315**), having weak calmodulin inhibitory activity (ID_{50} 100 μg/mL). [19,20]

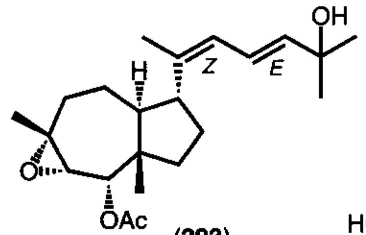
F. bonincola and *F. ericoides* also produce 3,3'-dimethoxy-4,5-methylenedioxy-4'-hydroxybibenzyl (**316**) and 3,3'-dimethoxy-4,5-methylenedioxybibenzyl (**317**), respectively.[55] *F. parvistipula* biosynthesizes 3,4:3'4'-dimethylenedioxybibenzyl (**318**) which shows weak inhibitory activity against calmodulin (ID_{50} 100 μg/mL)[19,20] and 3,3'-dihydroxy-4,5;4'5'-dimethylenedioxybibenzyl (**319**).[70] 3-Methoxy-4,5methylenedioxy-4'-hydroxybibenzyl (**320**) is the secondary metabolite of South American *Plagiochila chacabucensis.*[17] Brittonin B (**321**) which has been isolated from *Frullania brittoniae* subsp. *truncatifolia* (=*F. muscicola*)[1] has been obtained from *F. serratta.*[69] *Radula complanata* collected in France contains 3,5-dihydroxy-4-(2,3-epoxy-3-methylbutyl)bibenzyl (**322**).[171] The similar epoxide, 3,5-dihydroxy-2-(3-methylbutyl)bibenzyl (**323**) has been isolated from the Japanese *R. kojana* with many chromenes, 2,2-dimethyl-7-hydroxy-5-(2-phenylethyl)chromene (**324**), 2,2-dimethyl-7-methoxy-



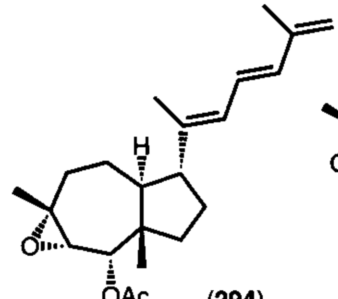
(**290**)



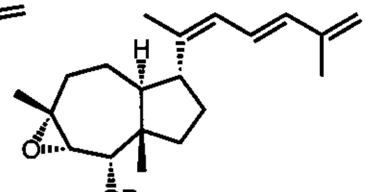
(**291**) R=Ac
(**292**) R=H



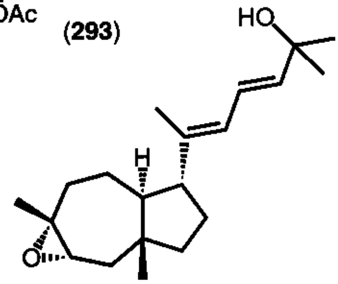
(**293**)



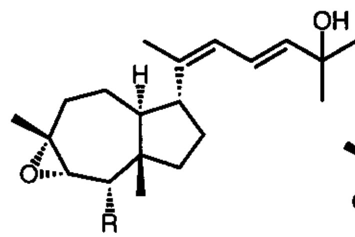
(**294**)



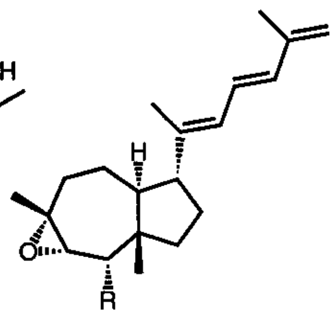
(**295**) R=Ac
(**296**) R=H



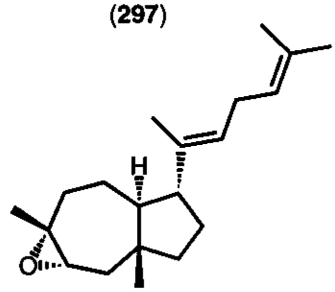
(**297**)



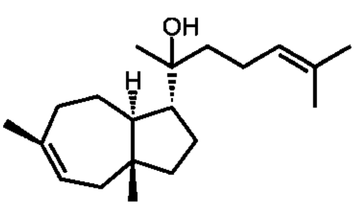
(**298**) R=H
(**299**) R=OH



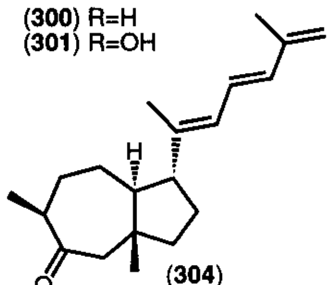
(**300**) R=H
(**301**) R=OH



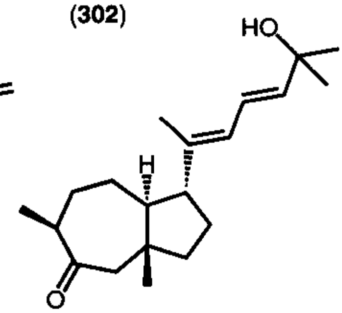
(**302**)



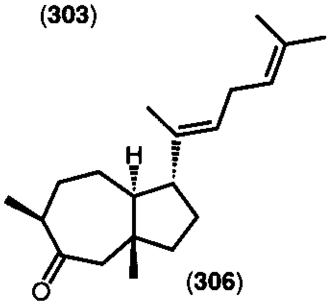
(**303**)



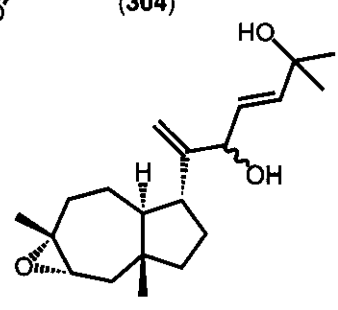
(**304**)



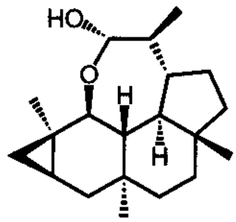
(**305**)



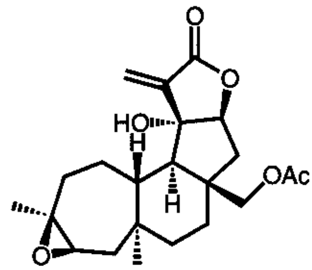
(**306**)



(**307**)



(308)



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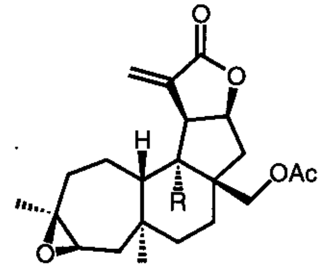
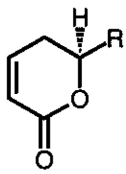
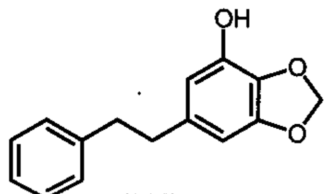


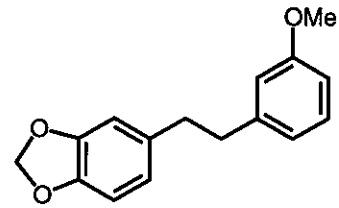
(310) R=H
(311) R=OH



(312) R= $-(CH_2)_6Me$
(313) R= $-(CH_2)_8Me$



(314)



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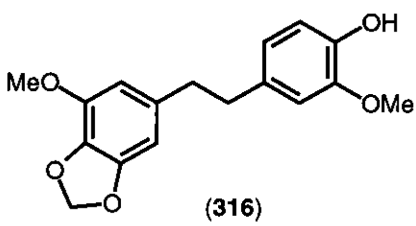

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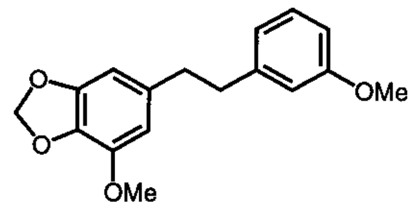

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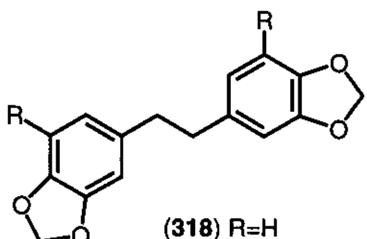
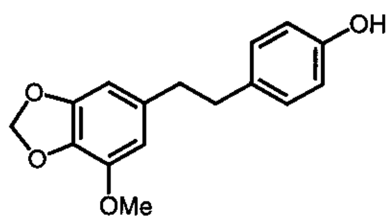


(318) R=H
(319) R=OH



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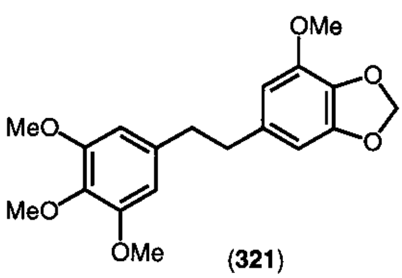

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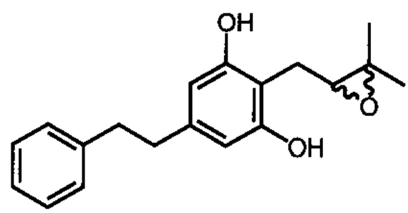


(322)

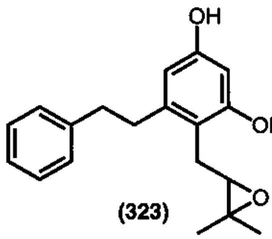
5-(2phenylethyl)chromene (**325**), 2,2-dimethyl-7,8-dihydroxy-5-(2-phenylethyl)chromene (**326**) and their isomers (**327-329**) as well as 2(*S*)-methyl-2-(4-methyl-3-pentenyl)-7-hydroxy-5-(2-phenylethyl)chromene (**330**) and its derivative (**331**).[173] The same chromenes (**324, 325**) have been isolated from *Radula perrottetii*.[33,174] This liverwort also produces 2(*R*)-isopropenyl-6-hydroxy-4-(2-phenylethyl)dihydrobenzofuran (**332**) and perrottetin D (**333**)[174] which possesses calmodulin and 5-lipoxygenase inhibitory activity.[19,20,175] Compound (**333**) is also effective against cyclooxgenase and lipid-peoxidation assay.[175] Compounds (**324, 325**) have also been isolated from the New Zealand *Tylimanthus saccatus*.[33] Very similar benzofurans (**334-336**) named tylimanthins have been detected in Chilean *Tylimanthus urvilleanus*[34] while *T. saccatus* does not contain these dihydrobenzofurans.[33] *R. kojana*[173] and *R. buccinifera*[33] also elaborate a simple benzofuran (**337**).

Radula species are rich sources of bibenzyls possessing a dihydrooxepin structure. Radulanin A (**338**) possessing calmodulin inhibitory activity[19,20] has been found in *R. buccinifera*,[33,171] *R. complanata*[174] and *R. voluta*.[33,63] *R. buccinifera* also contains radulanin C (**339**)[171] and **330**, **332** and **335**.[33] Radulanin C showed 5-lipoxygenase inhibitory activity.[19,20] *R. complanata* also produces radulanin H (**340**),[171] radulanin L (**341**) and 4'-hydroxyradulanin H (**342**)[174] which shows calmodulin inhibitory activity.[19,20] *R. javanica* (=*R. variabilis*) produces not only dihydrooxepins (**338, 340**), but also three unique bibenzyls, named radulanins I-K (**343-345**).[170] *R. grandis* also produces radulanin A (**338**) as the predominant component and radulanin I (**343**) and J (**344**) as the minor components.[33] This is the first isolation of cyclopropanochroman from natural sources. *R. perrottetii* contains a unique bibenzyl, perrottetinene (**346**), its structure and relative configuration are determined by 600 MHz NMR spectrometry.[91]

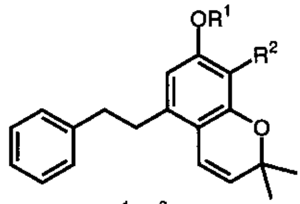
A novel optically active cyclic bibenzyl-dihydrophenanthrene derivative named (+)-cavicularin (**347**) has been isolated from the liverwort *Cavicularia densa*.[176] The structure was determined by 600 MHz NMR spectrum and X-Ray crystallographic analysis. Compound (**347**) possesses both planar and axial chirality. This is the first example of the isolation of such a compound from nature.

2. Bis-bibenzyls

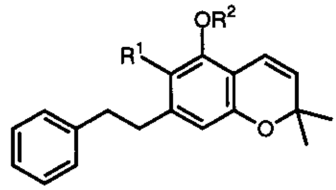
Liverworts are also very rich sources of bis-bibenzyl derivatives which have not been found in any other organisms. Riccardin A (**348**) and riccardin B (**349**) which show cytotoxicity against KB cells at a concentration of 10 and 12 µg/mL have been found in the thalloid liverwort, *Riccardia multifida* belonging to the Metzgeriales.[1,177-179] The former compound shows 5-lipoxygenase (4 x 10^{-6} mol) and calmodulin inhibitory activity (ID_{50} 20.0 µg/mL).[19,20] This liverwort also produces marchantin I (**350**) as a minor component.[179-181] This is the first isolation of cyclic bis-bibenzyls from the bryophytes. Riccardin B (**349**) has been isolated from European *Preissia quadorata* which belongs to the Marchantiales.[182] Riccardin C (**351**) is one of the most popular cyclic bis-bibenzyls in liverworts and found in *Blasia pusilla*[25] belonging to the Blaciaceae (Metzgeriales), *Dumortiera hirsuta* (Wiesnerellaceae),[183] *Marchantia palmata*,[184] *M. polymorpha*,[184,185] *Monoclea forsteri* (Monocleales),[186] *Reboulia hemisphaerica* (Aytoniaceae, Marchantiales)[187] and *Ricciocarpos natans* (Ricciaceae, Marchantiales).[188] *Monoclea forsteri* also elaborates two cyclic bis-bibenzyls, riccardin D (**352**) and E (**353**).[186] The former compound was isolated from *Plagiochila crispata*.[27] *Marchantia chenopoda* collected in Venezuera produces riccardin G (**354**).[189]



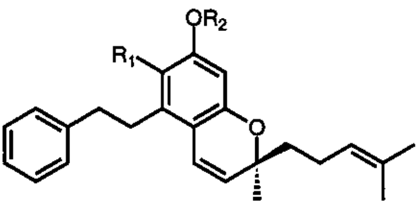
(323)



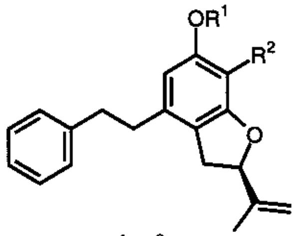
(324) $R^1=R^2=H$
(325) $R^1=Me$, $R^2=H$
(326) $R^1=H$, $R^2=OH$



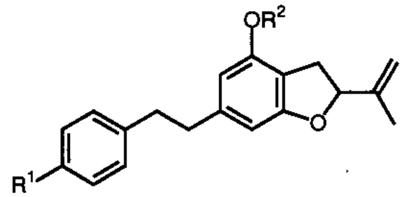
(327) $R^1=R^2=H$
(328) $R^1=H$, $R^2=Me$
(329) $R^1=CO_2H$, $R^2=H$



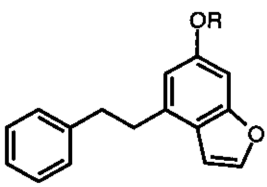
(330) $R^1=R^2=H$
(331) $R^1=CO_2H$, $R^2=H$



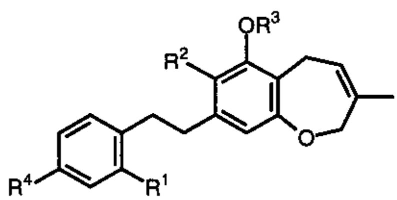
(332) $R^1=R^2=H$
(333) $R^1=H$, $R^2=OH$



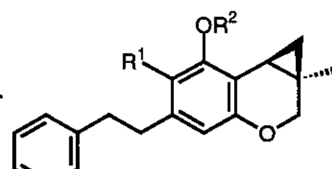
(334) $R^1=H$, $R^2=Me$
(335) $R^1=R^2=H$
(336) $R^1=OMe$, $R^2=Me$



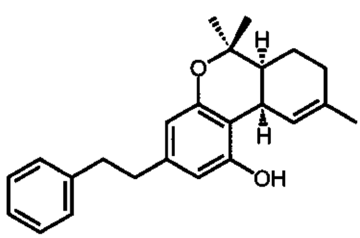
(337) R=H



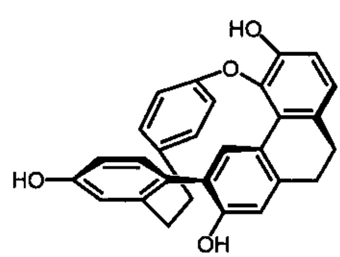
(338) $R^1=R^2=R^3=R^4=H$
(339) $R^1=R^2=R^3=H$, $R^4=OH$
(340) $R^1=R^3=R^4=H$, $R^2=CO_2H$
(341) $R^1=OH$, $R^2=R^3=R^4=H$
(342) $R^1=R^3=H$, $R^2=CO_2H$, $R^4=OH$



(343) $R^1=R^2=H$
(344) $R^1=H$, $R^2=Me$
(345) $R^1=CO_2H$, $R^2=H$



(346)



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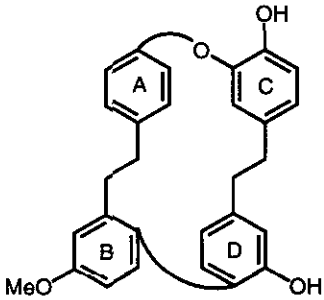

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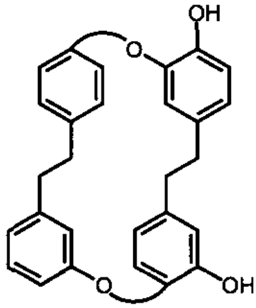

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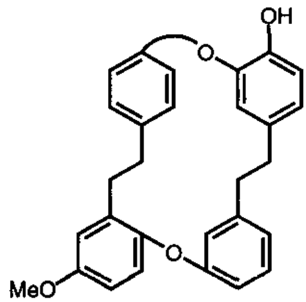

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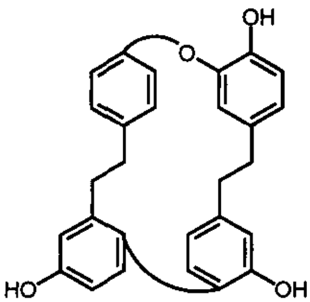

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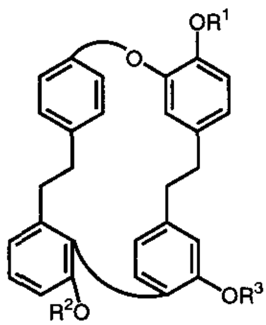
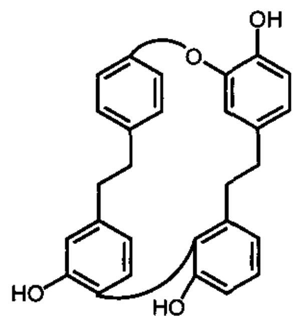
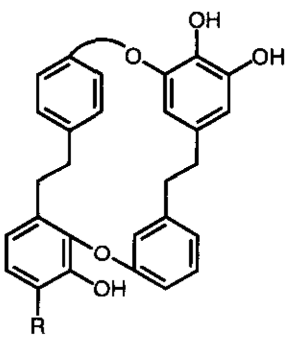


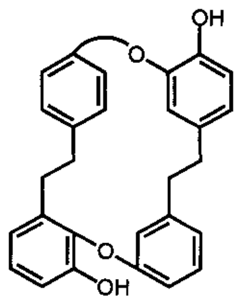
(352) $R^1=R^2=R^3=H$
(353) $R^1=R^3=H$ $R^2=Me$
(354) $R^1=Me$ $R^2=R^3=H$



(355) R=H



(356) R=H
(357) R=OH



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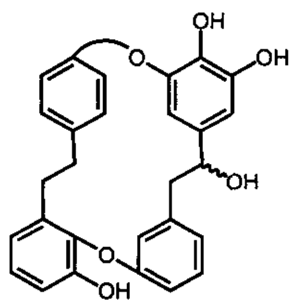

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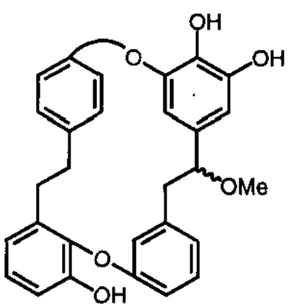

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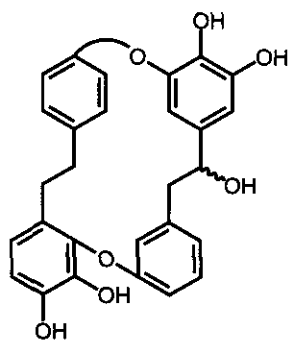

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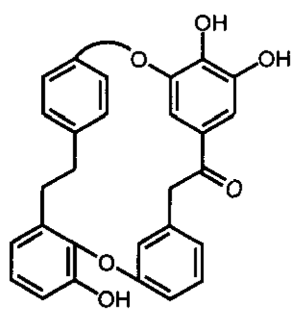


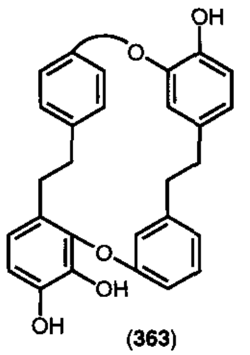
(362)

Isoriccardin C (**355**), the isomer of riccardin C (**351**) has been isolated from Indian *M. palmata* and *M. polymorpha.*[184] Marchantin A (**356**) has been isolated from *Marchantia paleaceae* var. *diptera,*[38] *M. plicata,*[67] *M. polymorpha,*[38,177,184,190-192] *M. tosana,*[38] *Wiesnerella denudata* (Conocephalaceae, Marchantiales).[69] The yield of marchantin A depends on the species. For example, pure marchantin A has been isolated in 100-120 g quantity from the Japanese *M. paleacea* var. *diptera* (from 2 kg of dried material) whereas the total extract of *M. polymorpha* collected in Duisburg, Germany contains 20% of marchantin A.[191] The stereostructure of **356** has been established by a combination of spectroscopy and X-Ray crystallographic analysis of trimethyl ether of (**356**).[190,192] Marchantin A (**356**) shows various biological activity: antimicrobial and antifungal, cytotoxic, 5-lipoxygenase and calmodulin inhibitory activity[19,20] and muscle reluxing.[193] Marchantin A also increases coronary blood flow (2.5 mL/min at 0.1 mg).[19,20]

The Indian *M. palmata,*[184] *M. polymorpha,*[38,177,190-192] *M. tosana*[69] and *W. denudata*[69] contain marchantin B (**357**) as a minor component. Marchantin B with two catechol moieties exerted an enhanced inhibitory effect in cyclooxygenase and 5-lipoxygenase.[175,194] Further purification of the methanol extract of the Japanese, French, German and Indian *M. polymorpha* resulted in the isolation of marchantins C-H (**358-363**), J-L (**364-366**), isomarchantin C (**367**),[38,177,184,185,189-192,195] together with perrottetin E (**368**) which might be a precursor of cyclic bis-bibenzyls found in the Hepaticae. Marchantins D (**359**) and E (**360**) indicate calmodulin and 5-lipoxygenase inhibitory activity.[19,20]

Marchantin C (**358**) has also been isolated from *Dumortiera hirsuta,*[90,182] *Marchantia chenopoda,*[188] *M. paleacea* var. *diptera, M. palmata,*[184] *M. tosana,*[38] the New Zealand *M. foliacea,*[33] *Monoclea forsteri,*[62] *M. gottschei* subsp. *neotropica,*[196] and the Japanese *Plagiochila sciophila,*[197] *Reboulia hemisphaerica,*[198] *Riccardia nagasakiensis*[199] and the New Zealand *Schitochilla glaucescens.*[200] *R. nagasakiensis* also contains riccardin A (**348**).[199] *R. hemisphaerica* which was previously reported as *Mannia subpilosa*[201] also contains marchantin C dimethyl ether (**369**)[25] and marchanin C monomethyl ether (=marchantin O) (**370**),[15,25,198] marchantiaquinone (**371**), and marchantins M (**372**) and N (**373**).[198] Compound (**371**) showed prominent antiplatelet activity.[198] The Venezuelan *M. chenopoda* elaborates not only new chenopodane sesquiterpenoids but also macrocyclic bisbibenzyl, marchantin P (**374**) as a minor component.[189] The major component of the Japanese *M. paleacea* var. *diptera* is marchantin A. This liverwort also produces marchantins D-G (**359-362**)[38] and H (**363**).[22] Marchantin H is the secondary metabolite of *Bryopteris filicina*[108] and *Mylia nuda*[144,202] which are classified into the Lejeuneaceae and the Jungermanniaceae. The Indian *M. palmata* elaborates marchantin G (**362**) and isomachantin C (**367**).[184] The latter compound has also been isolated from *Bryopteris filicina*[105] and *Dumortiera hirsuta.*[183] The structure of compound (**367**) was characterized by X-Ray crystallographic analysis.[183] *Plagiochasma intermedium*[180,181] and *Plagiochila sciophila*[197] biosynthesize marchantin H (**363**) as a minor constituent. *Mannia fragrans* produces patyonol (**375**). Neomarchantins A and B (**376-377**) are the major components of the New Zealand *Schistochila glaucescens.*[200] The former compound has been isolated from *Monoclea forsteri*[63] and *M. gottschei* subsp. *neotropica*[196] and *Preissia quadorata.*[182]

Four unique cyclic bis-bibenzyls, named plagiochins A-D (**378-381**) have been isolated from *Plagiochila sciophila*, together with perrottetin E.[197] The similar cyclic bibenzyl-dehydrobibenzyls, named isoplagiochins



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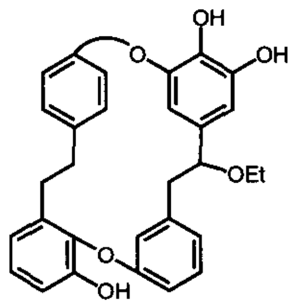

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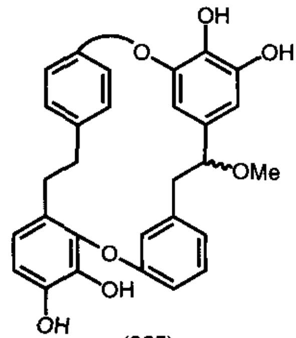

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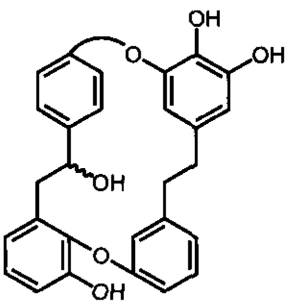

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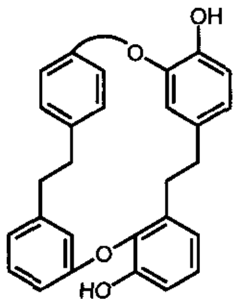

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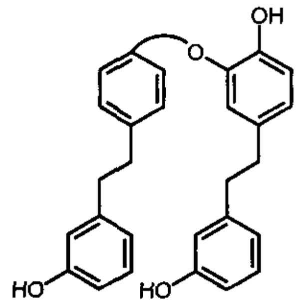

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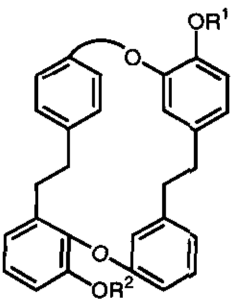
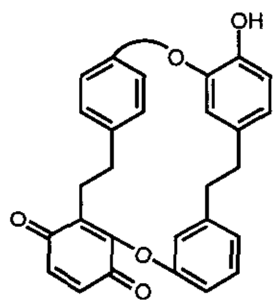


(369) $R^1=R^2=Me$
(370) $R^1=H$, $R^2=Me$
(374) $R^1=Me$, $R^2=H$



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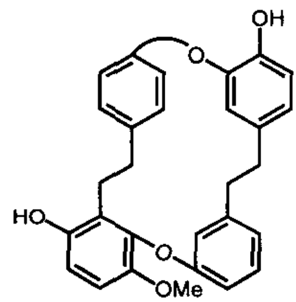

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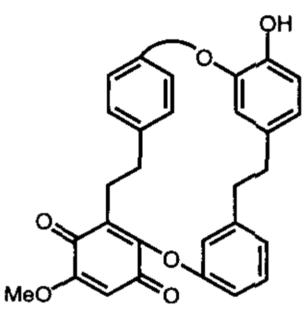

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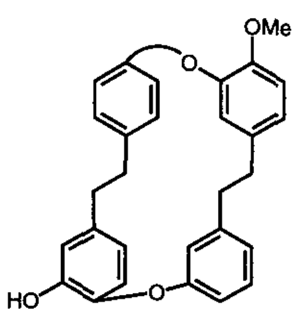

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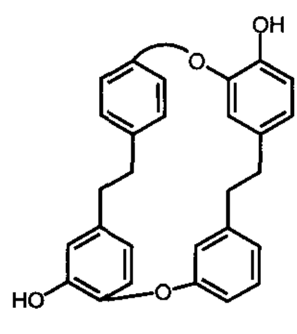

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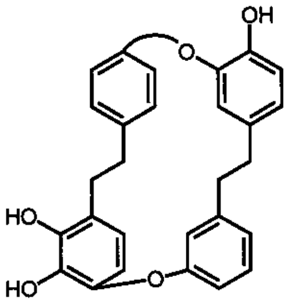

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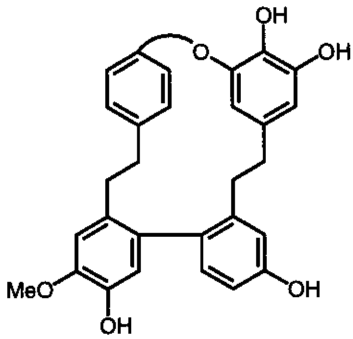

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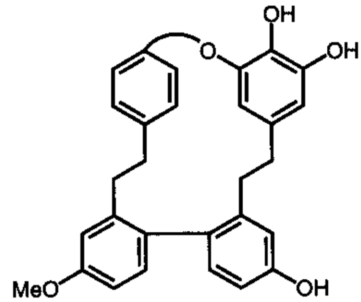

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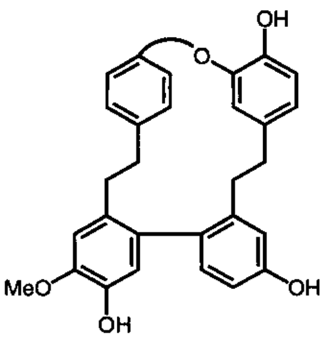

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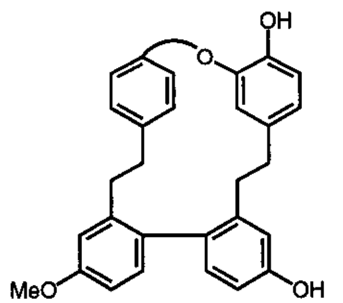

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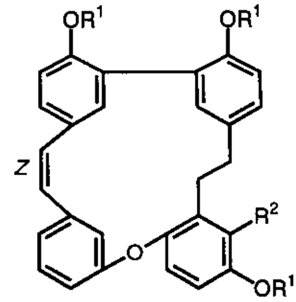
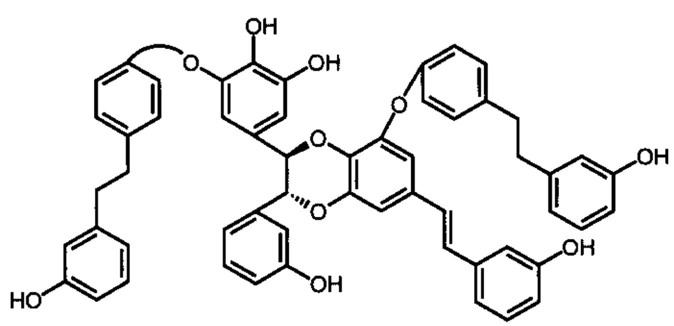


(382) R^1=R^2=H
(383) R^1=H, R^2=OH



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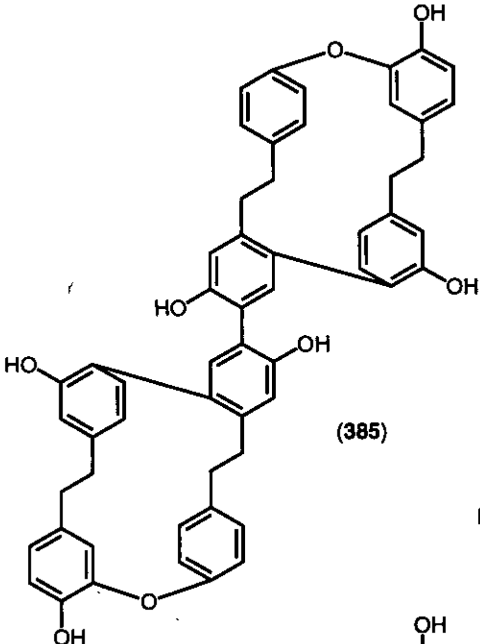

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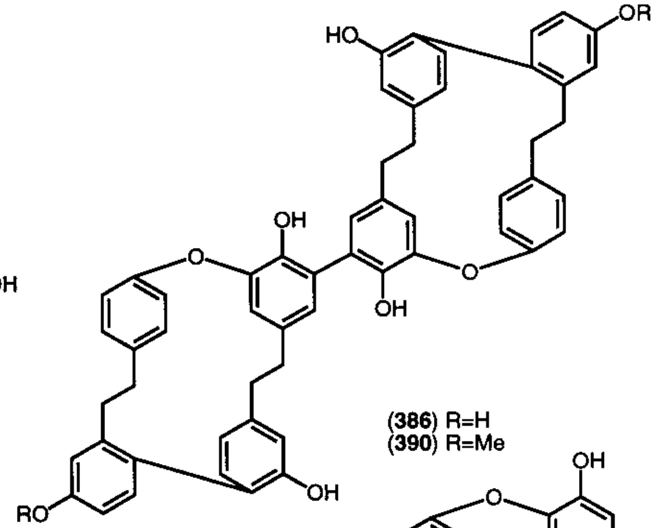
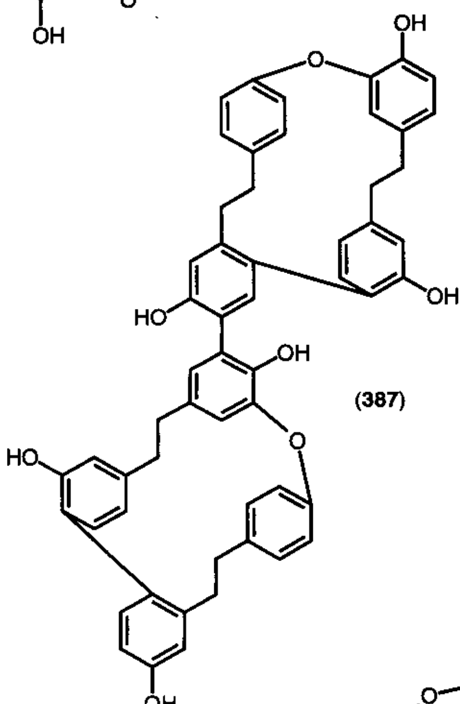


(386) R=H
(390) R=Me



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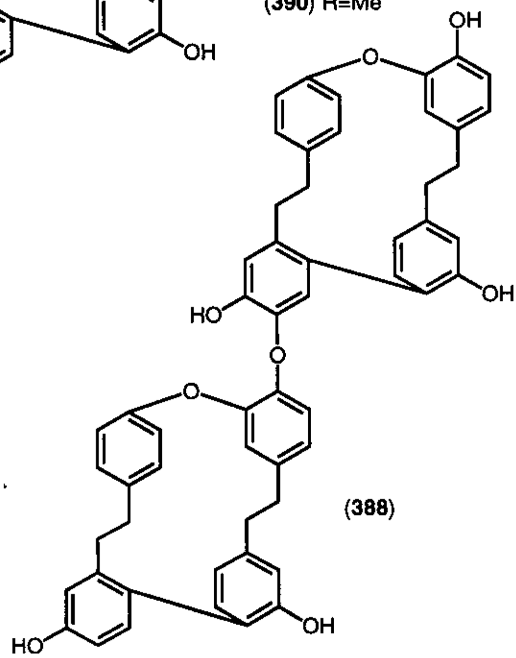

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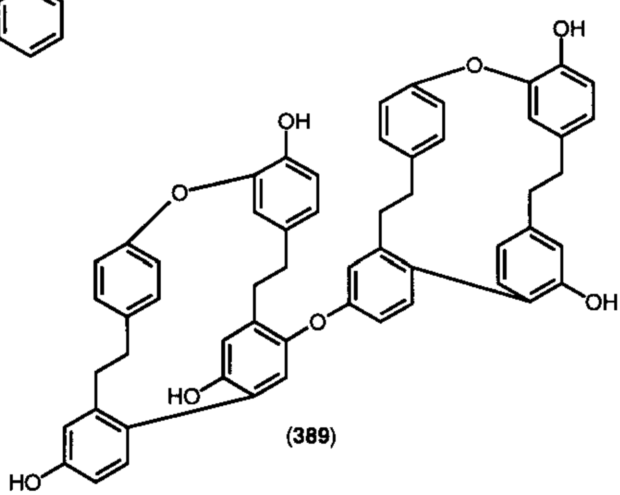


(389)

A (**382**) and B (**383**) have been isolated from Japanese *P. fruticosa* together with two cyclic bis-bibenzyls possessing two biphenyl linkages.[25,203-206] The structure of **382** was determined by chemical degradation and X-Ray crystallographic analysis of its acetate. Plagiochins A and B possess a C14-C11' ether and C6-C2' biphenyl bond. This is the first report of the isolation of macrocyclic bis-bibenzyl possessing a *cis*-stilbene and the biphenyl linkage between rings A and C.

Lunularia cruciata, one of the most popular liverworts in the world contains not only sesquiterpenoids but also a unique bis-bibenzyls, named cruciatin (**384**) whose structure has been deduced from chemical degradation.[33]

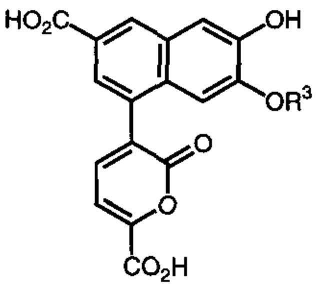
Four novel cyclic bis-bibenzyl dimers named pusilatins A-D (**385-388**) have been isolated from the methanol extract of *Blasia pussila* (Blasiaceae) and their structures elucidated by a combination of spectral data, chemical modification and X-Ray crystallographic analysis of its hexaacetate derivative.[204,205,207,208] However, the previously assigned structure of pusilatin D has been revised to **389** by careful analysis of HOHAHA, HSQC and HMBC spectra.[208] Pusilatis B (**386**) and C (**387**) showed selective DNA polymerase β inhibitory activity (IC_{50} 13.0 and 5.11 μM).[208] An axenic culture of *Ricciocarpos natans* (Ricciaceae) also contains pusilatin B (=6,6'''-bis-riccardin C).[209]

Riccardia multifida subsp. *decrescens* biosynthesizes not only monomeric bis-bibenzyls, riccardin A (**348**), marchantin I (**350**), and non-heterocyclic bis-bibenzyl ether, perrottetin E (**368**) but also dimeric bis-bibenzyl named psilatin E (**390**).[179] The structure was established by 2D-NMR and by the chemical correlation. Treatment of **348** with $Mn(OAc)_3$ gave pusilatin E (**390**) which was converted into pusilatin B (**386**).[179]

3. Naphthalenes, Isocoumarins, Lignanes, Neolignans and α-Pyrones

Naphthalene, isocoumarin, lignan and neolignan derivatives are rare in bryophytes. *Scapania undulata* produces not only a number of sesquiterpenoids but also a new naphthalene derivative, scapaniapyrone A (**391**).[210] The similar new compounds (**392-395**) have been isolated from the methanol extract of an aseptic culture of *Jamesoniella autumnalis*, with a new non-heterocyclic naphthalene derivative.[211] One more complex lignan, pelliatin (**396**) has been obtained from the ethyl acetate extract of the European liverwort, *Pellia epiphylla*[212]. Possible biogenetic pathway of C-8 aliphatic moiety of **396** has been proposed.[212] The New Zealand liverwort, *Wettsteinia schusterana* is a unique liverwort, because it elaborates 1,2,3,4-tetrasubstituted napthalene derivatives, wettsteins A (**397**) and B (**398**),[213] along with a new naphthalene derivatives and two dihydroisocoumarins, dihydroinversin (**399**) and wettsteinolide (**400**)[214] while the Taiwanese *W. inversa* contains two new isocoumarins, 8-hydroxy-6,7-dimethoxy-3-methylisocoumarin (**401**), inversin (**402**), together with dihydroinversin (**399**).[15,215] Compound (**402**) displayed potent antiplatelet activity.[215] An axenic culture of *Plagiochila adianthoides* gave (+)-enantiomer (**403**) of the previously known racemic hydrangenol monomethyl ether, together with new 2,3-secoaromadendrane-type sesquiterpene hemiacetals as mentioned earlier.[27] 3-(3,4-Dihydroxyphenyl)-8-hydroxyisocoumarin (**404**) was isolated from *in vitro* culture of *Marchantia polymorpha*, along with flavonoids and two new phenanthrenes.[216]

The aqueous methanolic extract of the gametophyte of the mosses, *Atrichum undulatum* and *Polytrichum*



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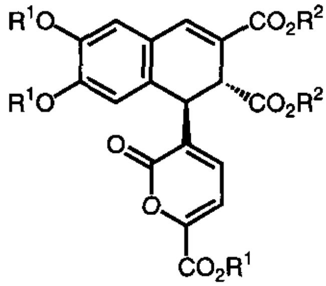
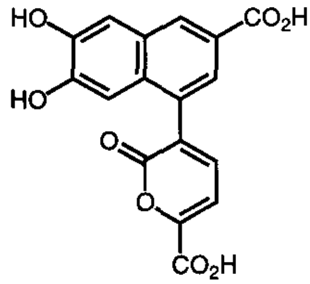


(392) $R^1=R^2=R^3=H$
(393) $R^1=R^3=H$, $R^2=Me$
(394) $R^1=R^2=H$, $R^3=Me$



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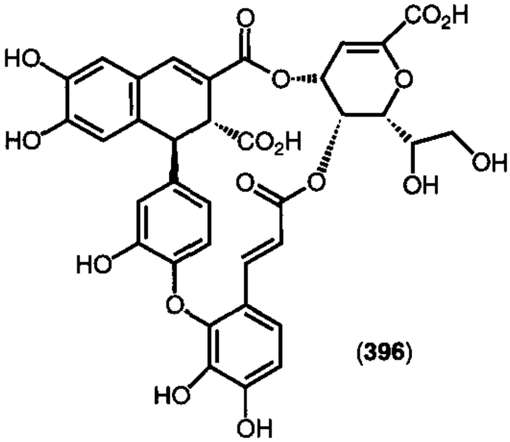

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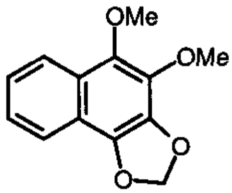

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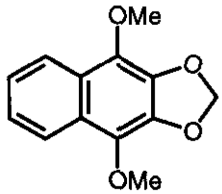

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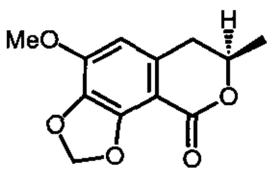

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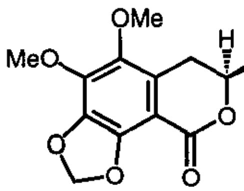

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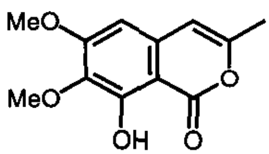

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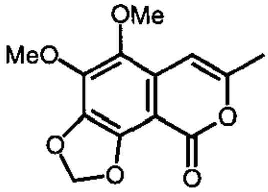

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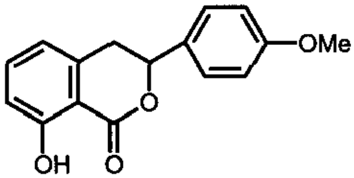

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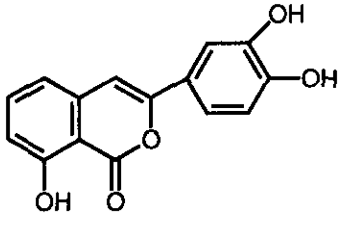

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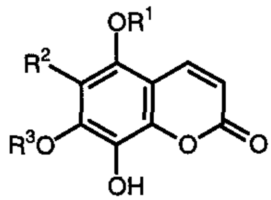
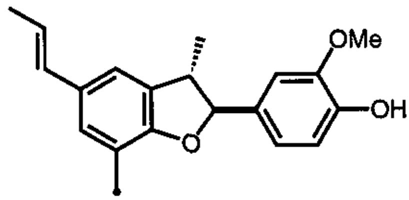
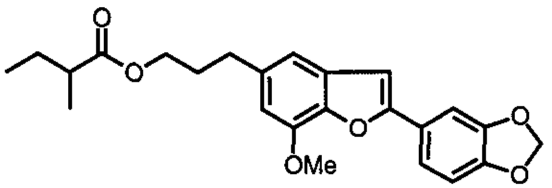


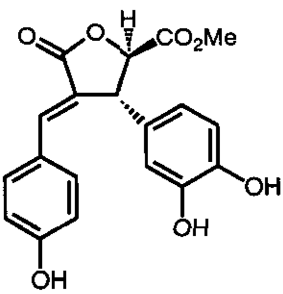
(**405**) R^1=Glc, R^2=OH, R^3=H
(**406**) R^1=malGlc, R^2=OH, R^3=H
(**407**) R^1=Glc, R^2=R^3=H
(**408**) R^1=Gentiob, R^2=R^3=H
(**409**) R^1=Glc, R^2=H, R^3=Me
(**410**) R^1=Glc, R^2=OH, R^3=Me
(**411**) R^1=malGlc, R^2=R^3=H
(**412**) R^1=Me, R^2=H, R^3=Soph



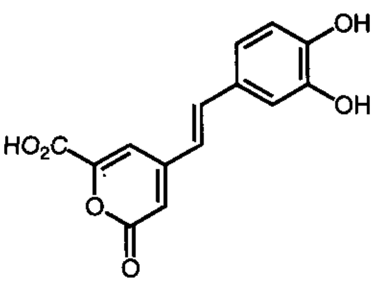
(**413**)



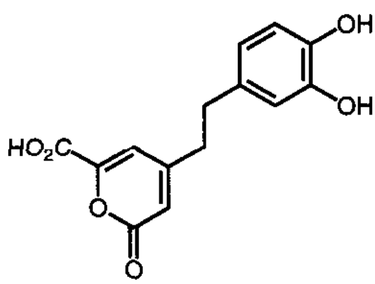
(**414**)



(**415**)



(**416**)



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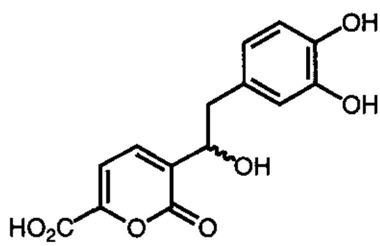


(**418**)

formosum contain tri- and tetrahydroxycoumarins (**405-409**).[217] The moss *Tetraphis pellucida* (Tetraphidaceae) contins the same coumarin glycosides (**405-409**) as mentioned above and three new 7-methoxy-5,6,8-trihydroxycoumarin-5-β-glucopyranoside (**410**), 5,7,8-trihydroxycoumarin-5-β-(6-O-malonylglucopyranoside) (**411**) and 7,8-dihydroxy-5-methoxycoumarin-7-β-sophoroside (**412**) as the new natural products.[218]

A neolignan, (-)-licarin (**413**) has been obtained from the liverwort, *Jackiella javanica.*[219] This is the first isolation of the neolignan from the Hepaticae. *Riccardia multifida* subsp. *decrescens* produces the known neolignan, egonol 2-methylbutanoate (**414**).[179] Megacerotonic acid (**415**) is the first neolignan from the hornwort, *Anthoceros laevis (=Phaeoceros laevis), Dendroceros japonicus, Megaceros flagellaris* and *Notothylas punctatus* (Anthocerotae).[220,,221]

Three new carboxylated α-pyrone derivatives, dumortins A-C (**416-418**) with a new flavone and three known flavonoid glycosides have been isolated from the European *Dumortiera hirsuta.*[222] The structures of compounds (**416**) and (**417**) were confirmed by their synthesis.

4. Phthalides

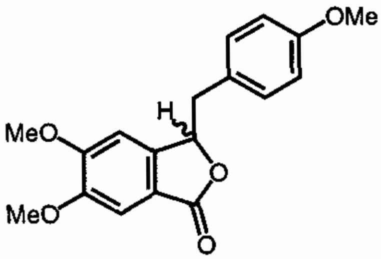
Five phthalides have been isolated from the Jungermanniales liverworts. 3-(4'-Methoxybenzyl)-5,6-dimethoxyphthalide (**419**) is one of the aromatic components of *Frullania falciloba.*[172] The New Zealand *Balantiopsis rosea* produces three thioacrylates as well as 3-(3',4'-dimethoxybenzyl)-7-hydroxy-5-methoxyphthalide (**420**)[223] which has also been isolated from the European *Frullania muscicola.*[59] *F. muscicola* also produces two new phthalides, 3-(3',4'-dimethoxybenzyl)-5,7-dimethoxyphthalide (**421**) and its mono demethyl compound (**422**).[59] The Japanese *Trocholejeunea sandvicensis* elaborates two phthalides (**423, 424**).[87] Radulanolide (**425**) possessing a dihydrooxepin moiety has been isolated from the European *Radula complanata.*[171]

5. Benzonaphthoxanthenones

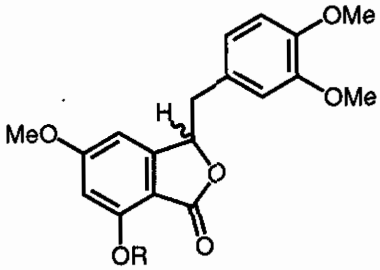
The mosses belonging to the Polytrichaceae contain highly unsaturated fatty acids. Fractionation of 95% ethanol extract of the American *Polytrichum ohioense* resulted in the isolation of five benzonaphthoxanthenones, named ohioensins A-E (**426-430**).[224,225] Their structures have been established by a combination of spectroscopy and X-Ray crystallography. Ohioensin A-E show cytotoxic activity not only against 9KB, but also murine P-388 leukemia and human lung carcinoma, human breast adenocarcinoma at a concentration of 1-10 μg/mL (ED_{50}).

6. Miscellaneous heterocyclic aromatic compounds

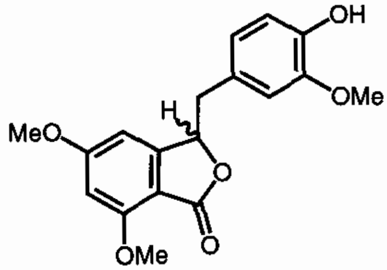
A unique alkaloid named anthocerodiazonin (**431**) was isolated from *in vitro* culture of the hornwort *Anthoceros agrestis* along with six glutamic acid amides.[2276] This is the first nitrogen-containing compound from the Anthocerotae. Two Jungermanniales liverworts, *Plagiochila asplenioides* and *Lophocolea bidentata* contains ellagic acid (**432**).[227] The prenyl indole derivatives, 6-(3-methyl-2-butenyl)indole (**433**) and its isomer (**434**) have been isolated from the European *Riccardia chamedryfolia*[1,228] and the Japanese *R. multifida.*[177] Indoleacetic acid (**435**) which is the endogenous plant hormone, is the minor component of



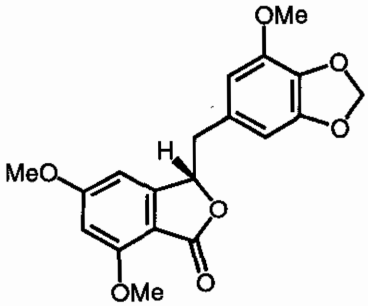
(**419**)



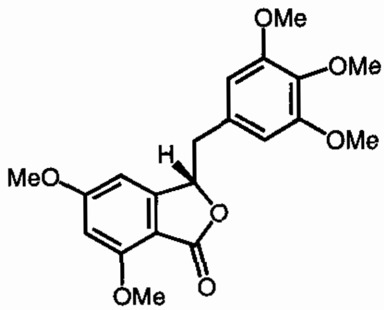
(**420**) R=H
(**421**) R=Me



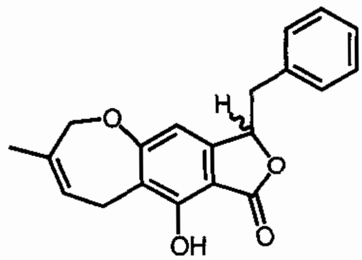
(**422**)



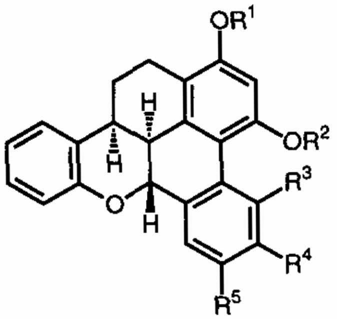
(**423**)



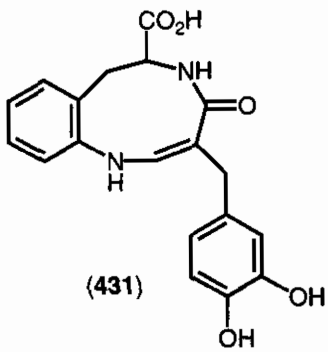
(**424**)



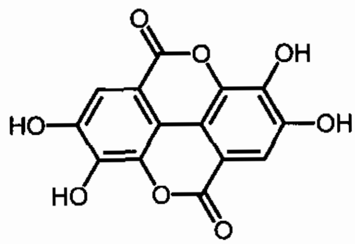
(**425**)



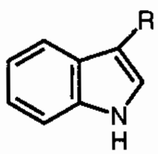
(**426**) $R^1=R^2=R^3=R^4=H$, $R^5=OH$
(**427**) $R^1=R^4=R^5=H$, $R^2=Me$, $R^3=OH$
(**428**) $R^1=R^2=R^4=R^5=H$, $R^3=OH$
(**429**) $R^1=R^5=H$, $R^2=Me$, $R^3=R^4=OH$
(**430**) $R^1=R^5=H$, $R^2=Me$, $R^3=OH$, $R^4=OMe$



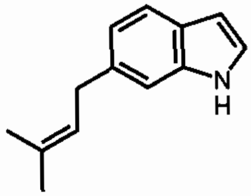
(**431**)



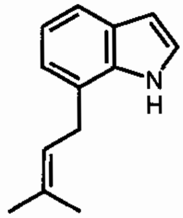
(**432**)



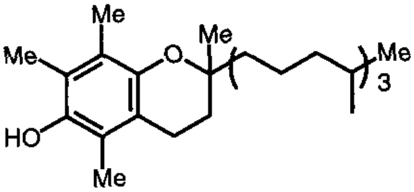
(**435**) $R=CH_2CO_2H$
(**436**) R=Me



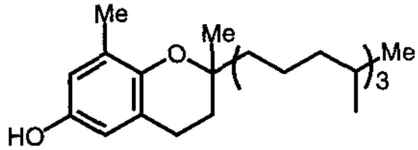
(**433**)



(**434**)



(437)



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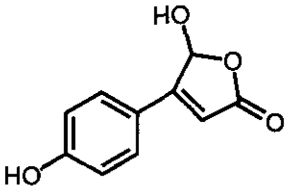
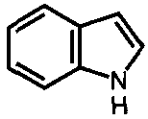
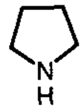


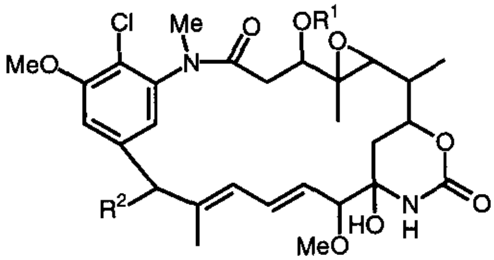
(439)

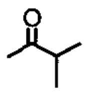


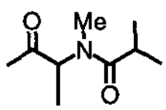
(440)

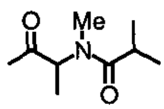


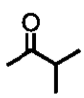
(441)

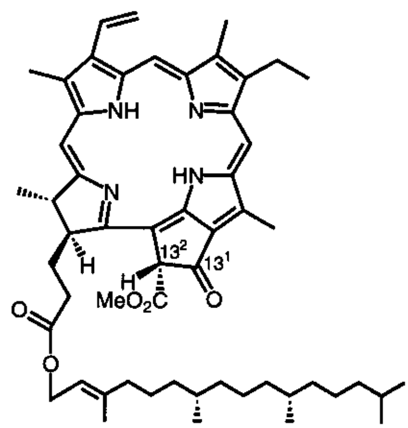


(442) R^1=  , R^2=H

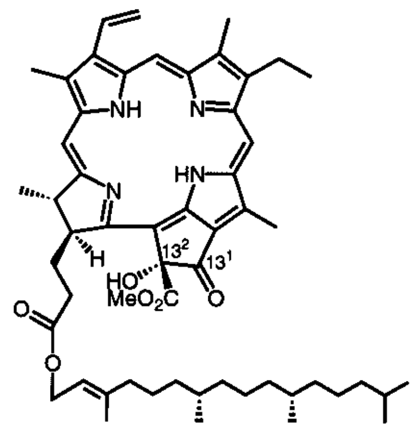
(443) R^1=  , R^2=H

(444) R^1=  , R^2=OMe

(445) R^1=  , R^2=OMe



(446)



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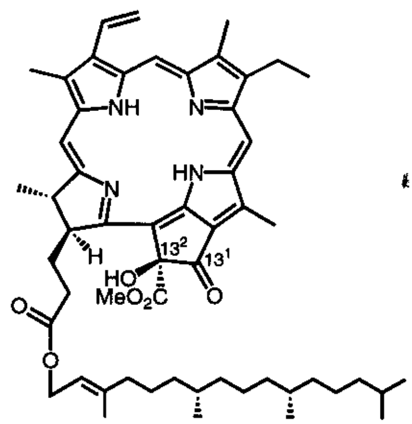
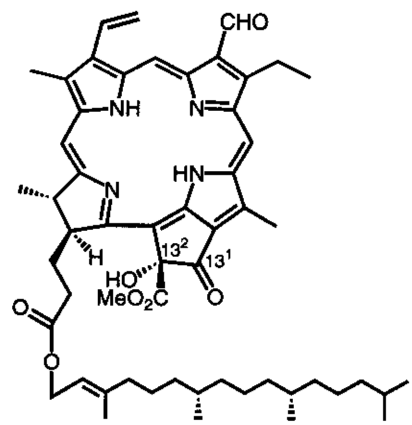
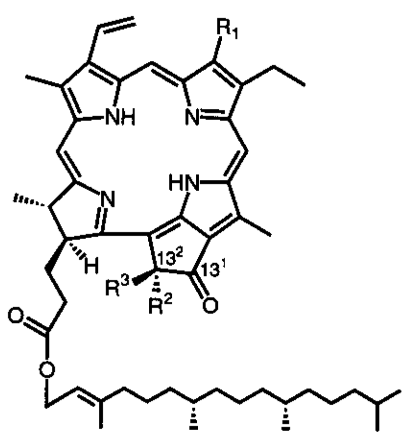


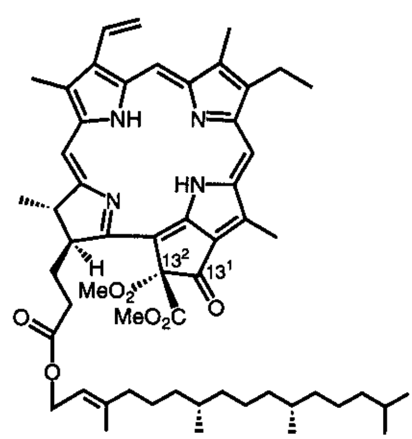
(448)



(449)



(450) R^1=CHO, R^2=CO_2Me, R^3=OH
(452) R^1=CHO, R^2=CO_2Me, R^3=H
(453) R^1=Me, R^2=R^3=H



(451)

Marchantia polymorpha and *Conocephalum conicum.*[229] The Malaysian liverwort, *Asterella* species contains skatole (**436**) which is responsible for very strong unpleasant odor of this tiny liverwort.[230] α-Tocopherol (**437**) has been obtained from *Marchantia polymorpha, Pellia epiphylla* (liverworts), *Atrichum undulatum* and *Mnium hornum* (mosses).[19,20] δ-Tocopherol (**438**) has been isolated from *Radula perrottetii.*[92] 2,5-Dihydro-5-hydroxy-4-(4'-hydroxyphenyl)-2-furanone (**439**) has been found in the mosses *Sphagnum magellanicum.*[231] *S. rubrum* contains indole (**440**) and pyrrolidine (**441**).[232]

Three known maytansinoids (**442-444**) and a new 15-methoxyansamitocin P-3 (**445**) have been isolated from two mosses, *Isothecium subdiversiforme* and *Thamnobryum sandei.*[233] These compounds originated from leaf mold which consisted the decayed mosses. The moss *Entodon rubicundus* produces phaeophytins (**446-450**) and a new phaeophytin (**451**) with a methyl ether of hydroperoxide on the C-13^2.[153] The same compounds (**446-450**) and phaeophytin b (**452**) and pyrophaeophytin a (**453**) have been obtained from the hornwort *Megaceros flagellaris.*[234]A suspension culture of the liverwort *Plagiochila ovalifolia* gave the same phaeophytins (**446-449**, **451**).[235] Compounds (**447**) and (**448**) have *in vitro* cytotoxicity against hepatoma tissue culture (HTC) cells.[236]

Since 1982, 78 flavonoids have been detected in or isolated from liverworts.[2] Flavonoids have also been found in mosses. They include flavones, isoflavones and biflavones.[2,237]

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