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SESQUITERPENE LACTONES AND ACETOGENIN LACTONES FROM THE HEPATICAE AND CHEMOSYSTEMATICS OF THE LIVERWORTS *FRULLANIA, PLAGIOCHILA* AND *PORELLA*

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Abstract - Liverworts (Hepaticae) contain various sesquiterpene lactones and acetogenin lactones which show occasionally interesting biological activity and are of very valuable for the chemosystematic study of liverworts. The distribution of the sesquiterpene lactones and acetogenin lactones in liverworts and their biological activity and chemosystematics of the *Frullania*, *Plagochila* and *Porella* are reviewed.

INTRODUCTION

The bryophytes which are the spore-forming terrestrial green plants are morphologically placed between the algae and the pteridophytes (fern) and there are *ca.* 24,000 species in the world (Table 1). Among the bryophytes almost all liverworts possess cellular oil bodies which are very important markers for the classification in the Hepaticae. On the other hand, the Musci and the Anthocerotae do not contain oil bodies. This morphological difference is reflected in the chemical difference as shown in Table 1.

It has been demonstrated that most of the Hepaticae contain mainly mono-, di- and sesquiterpenoids and lipophilic aromatic compounds (bibenzyls, bis(bibenzyls), naphthalenes, phthalides, isocoumarins, cinnamates, benzoates, benzyl and β-phenethyl acrylates and prenylindoles etc.) which constitute the oil bodies. The characteristic components of the Musci are highly unsaturated fatty acids and triterpenoids. The neolignan is the most important chemical marker of the Anthocerotae.

Some bryophytes show characteristically fragrant odors and intensely hot and bitter or saccharine-like taste. Generally, the bryophytes are not damaged by bacteria, fungi, insects, snails, slugs and other small animals. Furthermore, some liverworts cause intense allergenic contact dermatitis and allelopathy. Some bryophytes living in lake, river and pond accumulate heavy metals. Many bryophyte species have been used as medicinal plants, particularly in China as shown in Table 2. However, only tasting substances and allergens of some species have been fully investigated. We have been interested in these biologically active substances found in the bryophytes and the evolution and differentiation of the bryophytes. At

This paper is dedicated to the memory of Professor Sho Ito.

Table 1. Classification of bryophytes-Chemical characters of each classes

Bryophyta	No. of subclass	Order	Species	Chemical characters
Musci (Mosses)	7	15	14,000	Unsaturated fatty acids, triterpenoids
Hepaticae (Liverworts)	2	7	6,000	Monoterpenoids, sesquiterpenoids, diterpenoids, bibenzyls, bis(bibenzyls), naphthalenes, phthalides, isocoumarins, cinnamates, benzoates etc.
Anthocerotae (Hornworts)	3*		300	Neolignans

* Number of family

present we studied about 1000 species of the bryophytes collected in America, Africa, India, Pakistan, Nepal, Taiwan, Australia, New Zealand, Europe and Japan with respect to their chemistry, pharmacology, and application as sources of cosmetics, and medicinal or agricultural drugs. At present more than 300 new compounds have been isolated from the Hepaticae and their structures elucidated.

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 distribution of sesquiterpene lactones and acetogenin lactones in liverworts will be reviewed. In addition, some biological activity of the isolated lactones and chemosystematics of the *Frullania*, *Plagiochila* and *Porella* genera will also be discussed.

Table 2. Some medicinal bryophytes and their pharmacological activity and effects

[**Musci**] Species	
Bryum argenteum	Antidotal, antipyretic, antirhinitic activity; for bacteriosis
Cratoneuron filicinum	For malum cordis
Ditrichum pallidum	For convulsions, particularly in infants
Fissidens japonicum	Diuretic activity; for growth of hair, burns and choloplania
Funaria hygrometrica	For hemostasis, pulmonary tuberculosis, hematemesis, bruises, athlete’s foot dermatophytosis
Haplocladium catillatum	Antidotal, antipyretic activity; for adenopharyngitis, uropathy, mastitis, erysipelas, pneumonia, urocystitis and tympanitis
Leptodictyum riparium	Antipyretic; for choloplania and uropathy
Mnium cuspidatum	For hematostasis and nose bleed

Oreas martiana	For anodyne, hemostasis, external wounds, epilepsy, menorrhalgia and neurasthenia
Philonotis fontana	Antipyretic, antidotal activity; for adenopharyngitis
Plagiopus oederi	As a sedative, and for epilepsy, apoplexy and cardiopathy
Polytrichum species	Diuretic activity; for growth of hair
Polytrichum commune	Antipyretic, antidotal; for hemostasis, cuts, bleeding from gingivae, hematemesis and pulmonary tuberculosis
Rhodobryum giganteum	Antipyretic, diuretic, antihypertensive; for sedation, neurasthenia, psychosis, cuts, cardiopathy and expansion of hear blood vessels
Rhodobryum roseum	As a sedative and for neurasthenia and cardiopathy
Taxiphyllum taxirameum	Antiphlogistic; for hemostasis and external wounds
Weissia viridula	Antipyretic, antidotal; for rhinitis
[**Hepaticae**] Species	
Conocephalum conicum	Antimicrobial, antifungal, antipyretic, antidotal activity; used to cure cuts, burns, scalds, fractures, swollen tissue, poisonous snake bites and gallstones
Frullania tamarisci	Antiseptic activity
Marchantia polymorpha	Antipyretic, antihepatic, antidotal, diuretic activity; used to cure cuts, fractures, poisonous snake bites, burns, scalds and open wounds
Reboulia hemisphaerica	For blotches, hemostasis, external wounds and bruises

Table 3 shows the classification of the Hepaticae in which sesquiterpene lactones and acetogenin lactones have been found in 19 genera of the subclass Jungermanniideae and five genera of the subclass Marchantiidae. In Table 4, the names of sesquiterpene lactones isolated from each genus have been listed.

Table 3. Classification of the Hepaticae (Liverworts)

Subclass: Jungermanniideae

Order: Metzgeriales

Suborder: Metzgeriineae

Family: Metzgeriaceae: *Metzgeria, Apometzgeria*

Phyllothalliaceae: *Phillothallia*

Aneuraceae (=Riccardiaceae): ***Aneura****, *Cryptothallus*, *Riccardia*

Pelliaceae (=Dilaenaceae): ***Makinoa****, *Pellia*

Pallaviciniaceae: *Jensenia*, *Pallavicinia; Moerckia*

Blasiaceae: *Blasia*

Suborder: Codoniaceae (=Fossombroniaceae)

Family:Treubiaceae: *Treubia*

Codoniaceae: ***Fossombronia****, *Petalophyllum, Neteroclada*

Hymenophytaceae, *Verdoonia, Symphyogyna, Allisonia, Hymenophyton, Podomitrium, Xenothullus*

Order: Takakiales

Family: Takakiaceae: ***Takakia****

Order: Calobryales

Family: Haplomitriaceae: *Haplomitrium*

Order: Jungermanniales

Suborder: Jungermanniineae

Family: Jungermanniaceae

Subfamily: Lophozioideae:*Chandonanthus,* ***Barbilophozia****, *Anastrepta, Lophozia, Gymnocolea, Sphenolobopsis, Sphenobus, Anastrophyllum,* ***Tritomaria****

Jamesonielloideae: *Jamesoniella*

Myliioideae: *Mylia*

Jungermannioideae: *Jungermannia, Nardia*

Family: Gymnomitriaceae: *Marsupella, Gymnomitrion, Prasanthus*

Acrobolbaceae: *Acrobolbus, Tylimanthus*

Arnelliaceae: Arenellia, *Southbya, Gongylanthus*

Plagiochilaceae: *Pedinophyllum,* ***Plagiochila****

Lophocoleaceae: *Leptoscyphus,* ***Lophocoleae****, ***Chiloscyphus****, ***Clasmatocolea****

Geocalycaceae: *Geocalyx, Harpanthus, Saccogyna*

Scapaniaceae; *Douinia,* ***Diplophyllum****, *Scapania*

Family: Balantiopsidaceae: *Balantiopsis*

Schistochilaceae: *Schistochila*

Suborder: Lepidoziineae

Family: Adelanthaceae

Subfamily: Adelanthoideae: *Adelanthus*

Odontoschismatoideae: *Odontoschisma, Jackiella*

Family: Cephaloziellaceae: *Cephaloziella*

Cephaloziaceae: *Cephalozia, Nowellia, Cladopodiella,*

Subfamily *Cephalozia, Nowellia, Cladopodiella, Pleuroclada*

Hygrobielloideae: *Hygrobiella*

Family: Antheliaceae: *Anthelia*

Lepidoziaceae

Subfamily: Lepidozioideae: *Telaranea, Kurzia,* ***Lepidozia****

Acromastigoideae(= Bazzaioideae): *Bazzania*

Zoopsidoideae: *Zoopsis, Bonneria, Paracromastigum*

Family: Calypogeiaceae: *Calypogeia*

Suborder: Ptilidiineae

Family: Isotachidaceae: *Isotachis, Neesioscyphus, Eoisotachis*

Pseudolepicoleaceae

Subfamily: Pseudolepicoleideae: *Pseudolepicolea*

Blepharostomatoideae: *Blephasrostoma*

Family: Trichocoleaceae: *Trichocolea*, *Trichocoleopsis*, *Neotrichocleae*

Ptilidiaceae: ***Ptilidium****

Lepicoleaceae

Subfamily: Mastigophoroideae: *Mastigophora*

Family: Herbertaceae: ***Herbertus****, *Triandrophyllum*

Suborder: Radulineae

Family: *Radula*

Suborder: Pleuriziineae

Family: Pleuroziaceae: *Plerozia*

Suborder: Porellineae

Family: Porellaceae:***Porella****

Suborder: Jubulineae

Family: Frullaniaceae (=Jublaceae): ***Frullania****, *Jubula*

Lejeuneaceae

Subfamily: Ptychanthoideae: *Marchesinia, Dicranolejeunea*

Lejeuneoideae: ***Acrolejeunea****, ***Archilejeunea****, *Cheilolejeunea;*
Drepanolejeunea, Frullanoides, Harpalejeunea, ***Lejeunea*, Ptychantus*, Trocholejeunea****

Cololejeuneoideae: *Colura, Cololejeunea*

Subclass: Marchantiidae

Order: Sphaerocarpales

Family: Riellaceae: *Riella*

Sphaerocarpaceae: *Shaerocarpos*

Order: Monocleales

Family: Monocleaceae: *Monoclea*

Order: Marchantiales

Suboder: Marchantiineae

Family: Targioniaceae: ***Targionia****

Aytoniaceae (=Grimaldiaceae)

Subfamily Aytonioideae: ***Plagiochasma****

Reboulioideae: *Reboulia, Mannia, Asterella*

Family: Conocephalaceae: ***Conocephalum****, ***Wiesnerella****

Lunulariaceae: *Lunularia*

Cleveaceae: *Peltolepsis, Sauteria, Athalamia*

Marchántiaceae: *Bucegia; Prelssia, Marchantia, Dumortiera, Neohodgsonia*

Family: Exormothecaceae: *Exormotheca*

Corsiniaceae: *Cordinia*

Suboder:Ricciineae

Family: Oxymitraceae: *Oxymitria*

Ricciaceae: ***Ricciocarpos****, *Riccia*

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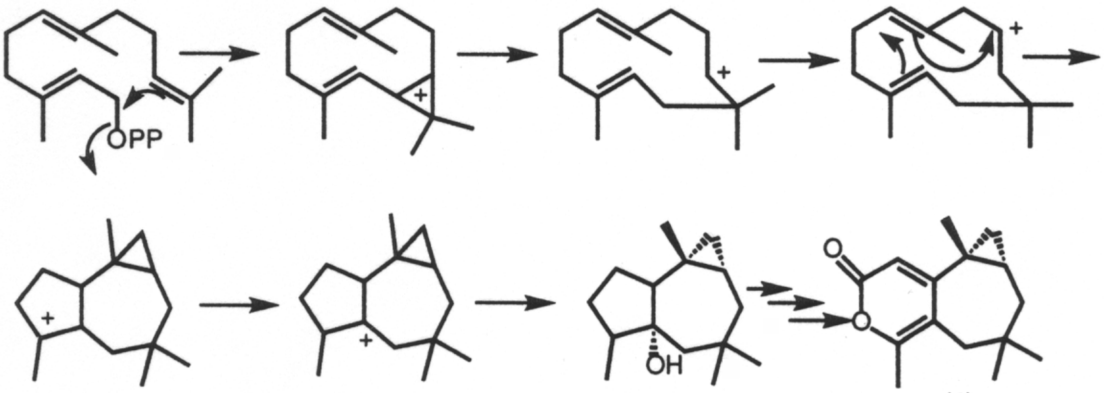
* Genus which produces sesquiterpene lactones and acetogenin lactones

1. Sesquiterpene lactones

1.1 Africanolides

The african-type sesquiterpenoids are very rare in nature. The Colombian liverwort, *Porella swartziana* (Porellaceae) contains africane-, secoafricane- and nor-secoafricane-type sesquiterpenoids of which secoswartzianin A (**1**) and norswartzianin (**2**) contain a lactone group in the molecule.[3] The ether extract of *Porella subobtusa* yielded secoswartzianin A (**1**) together with two new africanes.[4] The africane-type sesquiterpenoids might be biosynthesized from a sesquiterpene hydrocarbon, humulene as shown in Scheme 1.[2]

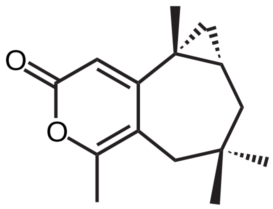


(1)

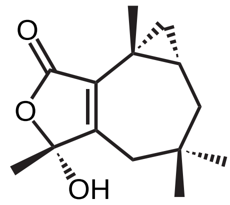
Scheme 1. Possible biogenetic pathway for africane-type sesquiterpenoids found in *Porella* species.

1.2. Amorphanolides

The Taiwanese liverwort, *Lepidozia fauriana* (Lepidoziaceae) contains 5β-hydroperoxylepidozenolide **(3)** and lepidozenolide (**4**) which 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.[5] Compound **(4)**



(**1**)



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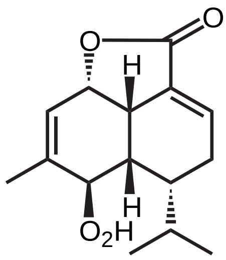
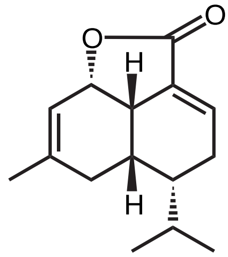
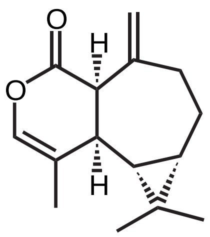


(**3**)



(**4**)



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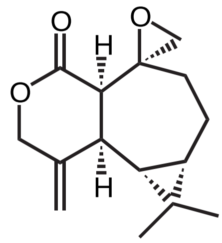

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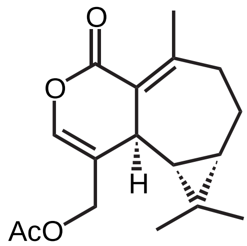
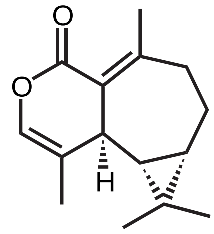
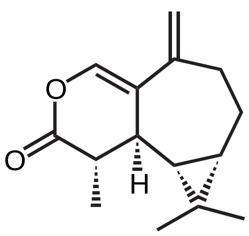


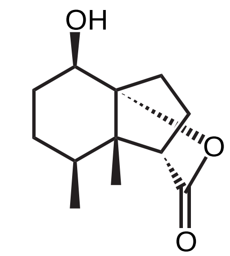
(**7**)



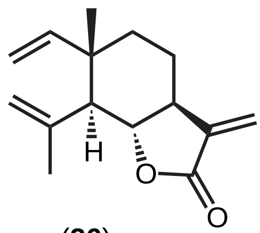
(**8**)



(**9**)



(**22**)



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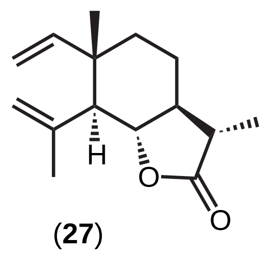
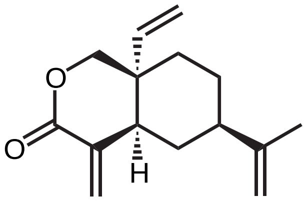


(**27**)



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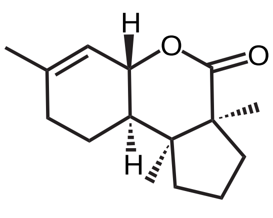

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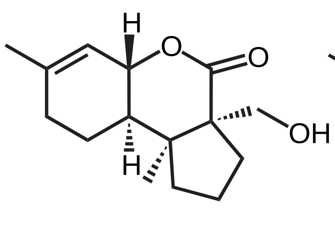

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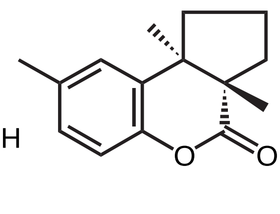

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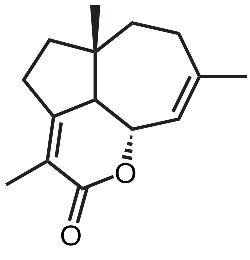
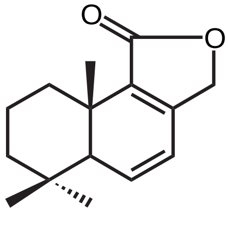


(**36**)



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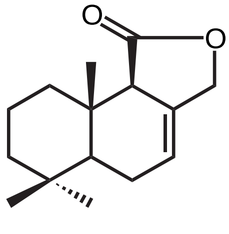
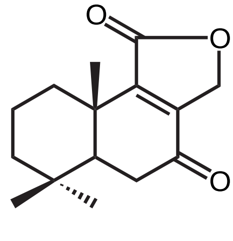


(**38**)



(**39**)

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.[5] Compound (**3**) has also been isolated from *L. vitrea*.[5]

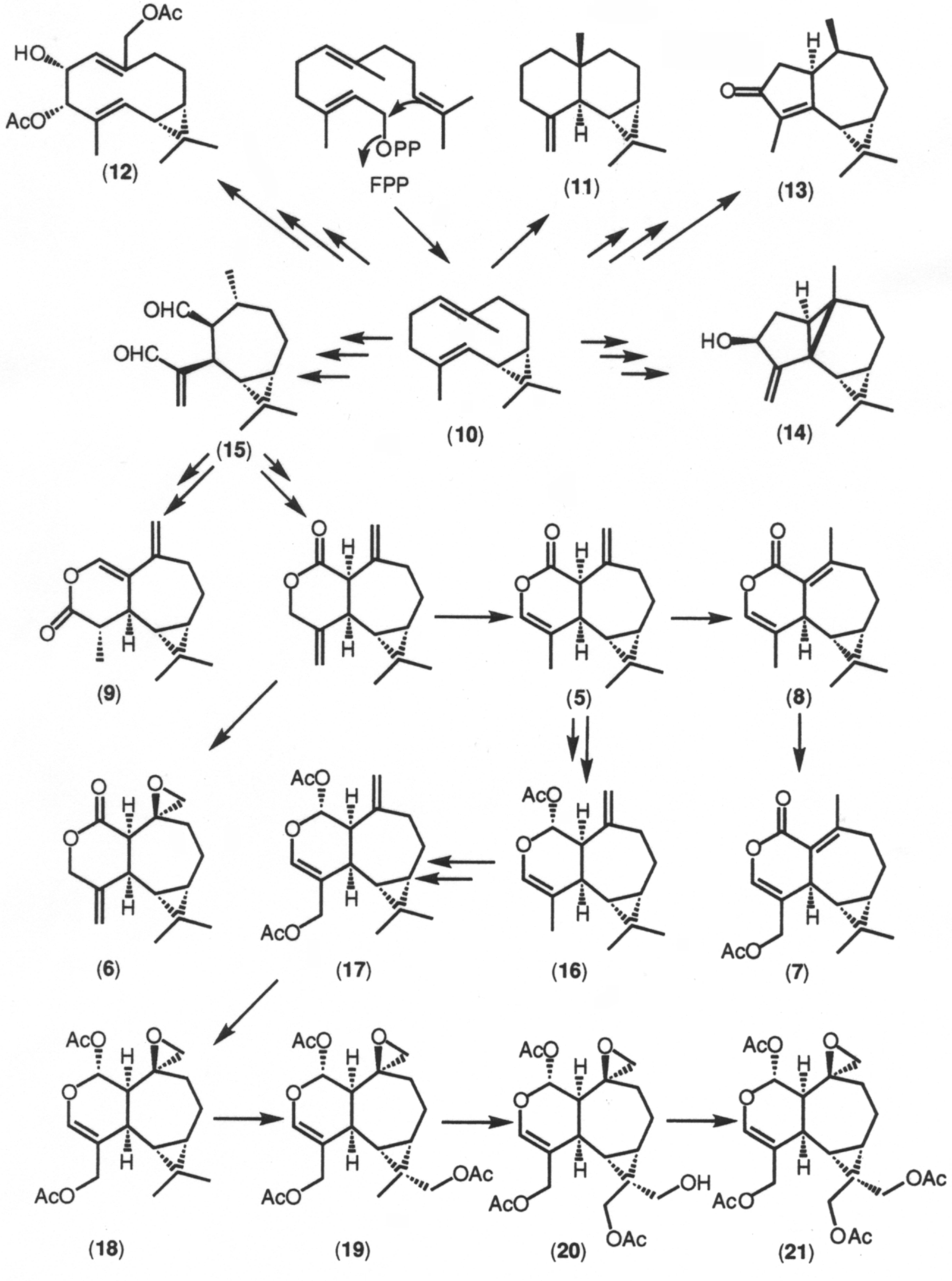
Table 4. Distribution of sesquiterpene lactones and acetogenin lactones in liverworts

Sesquitepene lactones	Liverwort genus
Africanolides	*Porella*
Amorphanolides	*Lepidozia*
2,3-Secoaromadendranolides	*Plagochila*
Chiloscyphanolides	*Chiloscypus*
Cuparanolides	*Herbertus, Ricciocarpos*
Elemanolides	*Clasmatocolea, Plagiochasma, Plagiochila*
Eremophilanolides	*Frullania*
Eudesmanolides	*Chiloscyphus, Clasmatocolea, Conocephalum, Frullania, Fossombronia, Lepicolea, Lophocolea, Makinoa, Plagiochila, Takakia, Tritomaria*
Germacranolides	*Conocephalum, Frullania, Marchantia, Plagiochila, Porella, Wiesnerella*
Guaianolides	*Frullania, Frullanoides, Porella, Targionia, Wiesnerella*
Herbertanolides	*Herbertus*
Drimanolides	*Porella, Makinoa*
Daucanolides	*Barbilophozia*
Monocyclofarnesanolides	*Ricciocarpos*
Pinguisanolides	*Aneura, Archilejeunea,* Arcolejeunea, *Brachiolejeunea, Frullanoides, Plagiochila, Porella, Ptychantus, Trocholejeunea*
Acetogenin lactones	*Cheilolejeunea, Marchantia*

1.3 2,3-Secoaromadendranolides

The liverworts, *Plagiochila* species are widely distributed in the world and there are *ca*. 3000 species and are rich sources of *ent*-aromadendrane- (**13**, **14**), *ent*-bicyclogermacrene-(**10**, **12**), maaliane- (**11**) (see Scheme 2) and *ent*-2,3-secoaromadendrane-type sesquiterpenoids (**5-9**, **15-21**). The species belonging to the Plagiochilaceae are chemically divided into two types: one contains very pungent 2,3-

secoaromadendrane-type sesquiterpenoids, such as plagiochiline A (**18**) and the other is tasteless. The latter group is further classified chemically into at least 8 groups as shown in Table 5.[7,8]



Scheme 2. Possible biogenetic pathway for aromadendrane-, 2,3-secoaromadendrane- and maaliane-type sesquiterpenoids found in *Plagiochila* species.

Plagiochila fruticosa produces plagiochilide (**5**) and plagiochiline J (**6**), together with plagiochiline C (**17**), and plagiochiline A (**18**), which 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.[9,10] Plagiochilide (5) inhibited superoxide release from guinea pig macrophage (IC_{50} 25μg/ml).[10] The Japanese *P. ovalifolia* produces various sesquiterpene hemiacetals.[1] Refractionation of the *n*-hexane extract of *P. ovalifolia* resulted in the isolation of *ent*-acetoxyisoplagiochilide (**7**) together with plagiochiline N possessing a furane ring.[11,12] The Taiwanese *Plagiochila elegans* produces a new 2,3-secoaromadendrane lactone, isoplagiochilide (**8**), together with two plagiochiline hemiacetals[13] Plagiochiline Q (**9**) has been isolated from *P. cristata*, together with the two known plagiochilines.[14] *P. squamulosa* var. *sinuosa* also contains isoplagiochilide (**8**).[14] The known plagiochilide (**10**) has been detected in the Chilean *Plagiochila* gayana.[7] The biogenesis of 2,3-secoaromadendrane-type sesquiterpenoids has been proposed in Scheme 2.

Table 5. Chemical type of *Plagiochila* (Plagiochilaceae)

Type	Species	2,3-Secoaroma-dendranes	Bibenzyls	Aroma-dendranes	Pinguisanes	Maali-anes
I	*Plagiochila sciophila*			+++*		+++
II	*P. adiantoides*	+++++				
	P. asplenioides	++++	+	+		
	P. cristata	++				
	P. cucullata	+++++				
	P. falcata	+++++				
	P. fruticosa	+++++		+		
	P. crustatissima	+++++				
	P. cipaconensis	+++++				
	P. dilatata	+++++				
	P. dula	++++				
	P. elegans	+++				
	P. goebeliana	+++++				
	P. guayarapurienesnsis	+++++				
	P. guilleminiana	++++++				
	P. huokeriana	+++++				
	P. lecheri	+++				
	P. magna	++++				
	P. orbicularis	+++		+		

	P. ovalifolia	+++++		+		+
	P. pittieri	+++++				
	P. porelloides	+++		+		
	P. pulcherrima	+++++				+
	P. scopulosa	+++++				
	P. scuamulosa var. *sinuosa*	+++				
	P. tenerrima	+++++				
	P. traveculata	++				
	P. yokogurensis	+++++		++		
III	*P. arbuscula*		+++			
	P. chacabucensis		+++			
	P. fuegiensis		+++			
	P. oresitopha		+++			
	P. parvitexta		+++			
	P. subdura		++			
IV	*P. elegantula*				++++	
	P. stephensoniana		+++		+++	
	P. rosariensis				++++	
V	*P. bispinosa* †					
VI	*P. gayana* ‡	+++				
VII	*P. conjugata* §					
	P. tenerrima §					
VIII	*P. dendorides*	0 ‖	0	0	0	0
	P. engelii	0	0	0	0	0
	P. neesiana	0	0	0	0	0
	P. mayebarae	0	0	0	0	0
	P. parvidens	0	0	0	0	0

* The symbols +, ++, +++, etc. are relative concentrations estimated by GC/MS.

† Cuparene-herbertane-type.

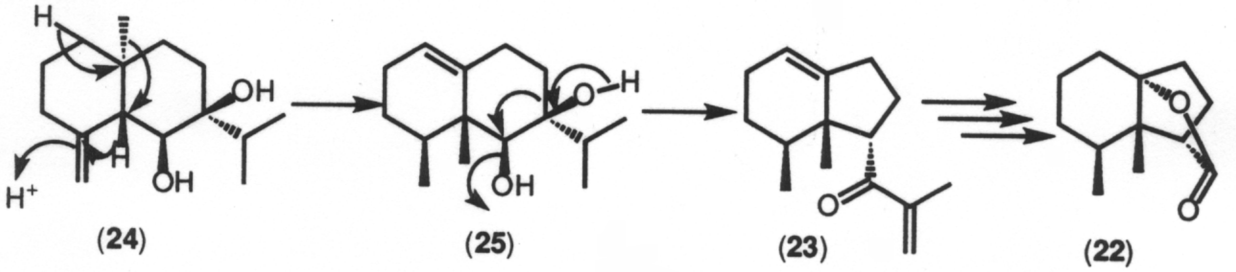
‡ :2,3-Secoaromadendrane-Eudesmanolide-type

§ Eudesmanolide-type; **** 0 ; not detected

‖ Not detected.

1.4 Chiloscyphanolide

The liverworts *Chiloscyphus* species (Lophocoleaceae) are biosynthetically very interesting, because they produce the characteristic chilosyphane-type sesquiterpenoids.[2] The American *C. rivularis* produces rivulalactone (**22**), together with chiloscyphone (**23**) which might be the precursor of this lactone.[15] Chiloscyphane-type sesquiterpenoids might originate from some eudesmane-type sesquiterpenoids (**24**) as shown in Scheme 3. [16]



Scheme 3. Possible biogenetic pathway for chiloscyphane-type sesquiterpenoids (**22, 23**) found in *Chiloscyphus* species.

1.5 Elemanolides

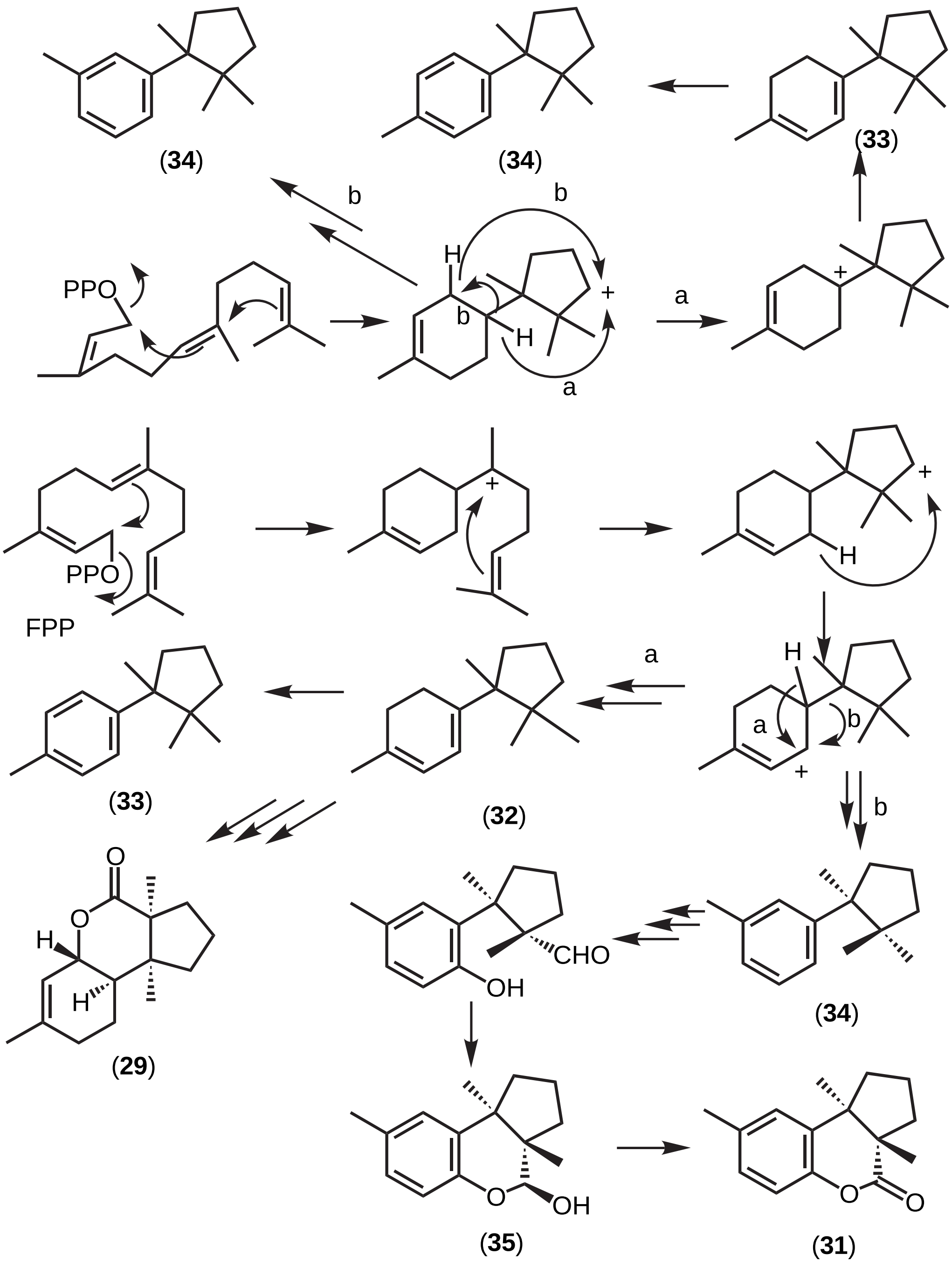
The South American liverworts *Clasmatocolea humilis* (Lophocoleaceae) elaborates dehydrosaussurea lactone (**26**) and saussurea lactone (**27**).[17] The former compound has been detected in the South American *Plagiochila hondurensis*.[8] A new elemanolide (**28**) was isolated from the French liverwort, *Plagiochasma repestre* (Aytoniaceae).[18]

1.6 Cuparanolides and Herbertanolides

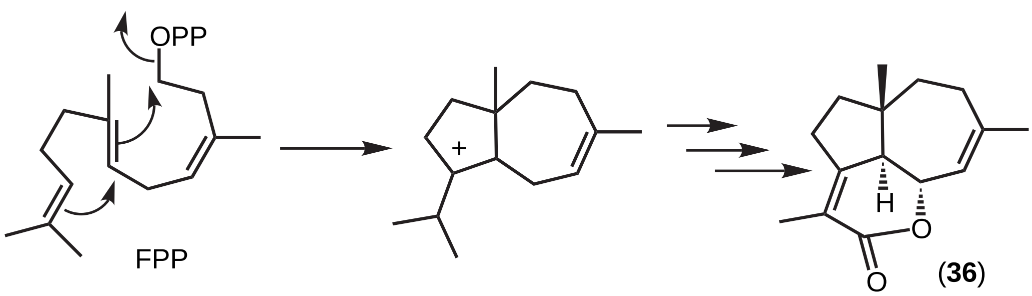
The cuparane-type sesquiterpenoids, for example, cuparene (**32**) and α-cuprenene (**33**), are very popular in the liverworts, while, the herbertane-type sesquiterpenoids like herbertene (**34**) is limited in some liverworts, *Herbertus* (Herbertaceae), *Mastigophora* (Mastigophoroideae) and *Marchantia* species (Marchantiaceae).[2] Two cuparane-type lactones, cuparenolide (**29**) and cuparenolidol (**30**) have been isolated from the European liverwort *Ricciocarpos natans* (Ricciaceae).[19,20] The former compound shows molluscicidal activity against *Biomphalaria glabtata* with LC_{100} at 32 ppm, however, the latter lactone has no activity.[19,20] A herbertane lactone, herbertenolide (**31**) has been isolated from the Japanese liverwort, *Herbertus aduncus* as well as various herbertane-type sesquiterpenoids.[21-25] Compound (**31**) has also been isolated from *H. sakuraii* and Canadian and Japanese *H. aduncus*.[26] Both cuparane and herbertane-type sesquiterpenoids might be formed from farnesyl pyrophosphate (FPP) as shown in Scheme 4.

1.7 Daucanolides (=Carotanolides)

Only one daucane-type sesquiterpene lactone, hercinolactone (**36**) has been isolated from the four European liverworts, *Barbilophozia lycopodioides*,[27,28] *B. hatcheri*, [27-31] *B. floerkei*[29,30] and *B. barbata*.[32] Hercinolactone might be biosynthesized from FPP as shown in Scheme. 5.[2]



Scheme 4. Possible biogenetic pathway for cuparane- and herbertane-type sesquiterpenoids found in *Ricciocarpos* and *Herbertus* species.



Scheme 5. Possible biogenetic pathway for daucane (=carotane)-type sesquiterpenoids found in *Barbilophozia* species.

1.8 Drimanolides

The *Porella* species are rich sources of drimane-type sesquiterpenoids (**36-48**). They are divided into at least six chemical type as shown in Table 6. The most characteristic group contains the potent hot tasting substances. This taste is responsible for the drimane-type sesquiterpene dialdehyde, polygodial (**47**).[1] The *Porella* species belonging to Type I produce not only polygodial but also its related drimane-type sesquiterpene lactones as well as pinguisane-type sesquiterpenoids (see later).

Table 6. Chemical type of Porellacea

Type	Species	Drimanes	Pinguisanes	Aroma-dendranes	Germacra-nolides & Guaianolides	Sacculatanes
I	*Porella arboris-vitae*	+++++	++	++		
	P. canariensis	++++	++			
	P. cordaeana	+	+++			
	P. fauriei	+++++				
	P. gracillima	+++++	++	++		
	P. obtusata	+++++	++	++		
	P. roelii	+++++				
	P. vernicosa	+++++	++	+++++		
II	*P. campylo-phylla*					+++++
	P. stephaniana					++
	P. perrottetiana					+++++
III	*P. densifolia*		+++++			
	P. navicularis		+++++			
IV	*P. grandiloba*		++			+++++
	P. platyphylla		+++++			+++
V	*P. japonica*		++		+++++	+++
	P. acutifolia subp. *tosana*		+++		+++	
VI	*P. caespitans*†					+
	P. subobtusa†					
	P. swartziana†					

Macvicaria ulophylla	+++++

* The symbols +, ++, +++, etc. are relative concentrations estimated by GC/MS.
† This species belongs to africane-type.

The American liverwort *Porella roellii* is the rich source of drimane-type sesquiterpenoids, dehydroconfertifolin (**37**), together with pungent sesquiterpene dial, polygodial (**47**) as well as two drimane-type sesquiterpene hemiacetals.[12] The American *Porella cordaeana* also produces drimenin (**38**), 7-ketoisodrimenin (**39**) and 7-ketoisodrimenin-5-ene (**40**).[33] Cinnamolide (**41**) 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.[34] The European *P. canariensis* contains the previously known three drimanes, 7-ketoisodrimanin-5-ene (**40**) along with *cis*-dihydrocinnamolide (**42**) and isodrimeninol (**48**).[35] Furthermore, the Japanese liverwort *Makinoa crispata* (Riccardiaceae) elaborates 7α-chloro-6β-hydroxyconfertifolin (**43**), 6β,7α-dihydroxyconfertifolin (**44**) and 6β,7β-epoxyconfertifolin (**45**).[36] This is the first record of the isolation of a chlorine-containing substance from the Hepaticae. Plausible biogenetic pathway for drimane-type sesquiterpenoids found in the liverworts is shown in Scheme 6.

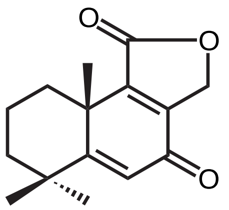
1.9 Eremophilanolides

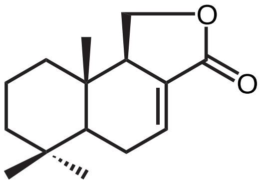
Two eremophilanolides, eremofrullanolide (**49**) and dihydroeremofrullanolide (**50**) have been isolated from European *Frullania dilatata*, together with several eudesmane-type sesquiterpene lactones (see later).[37] The former lactone showed the strong allergenic contact dermatitis (Table 7). This is the first isolation of both eremophiranolides and eudesmanolides from the same plant. Two new *ent*-eremophilane-type sesquiterpene lactones, dilatanolides A (**51**) and B (**52**) have been isolated from the ether extract of the Bulgarian *Frullania dilatata* var. *anomala*, together with spiroeudesmanolides (see later).[38,39] Compound (**52**) has also been isolated from the European *F. muscicola* with four eudesmanolides (see later).[40]

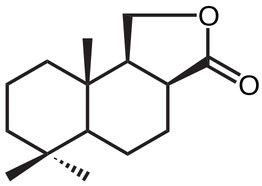
Table 7. Allergenic test of sesquiterpene lactones isolated from the liverwort *Frullania dilatata* (Patch-test, 1‰)[37]

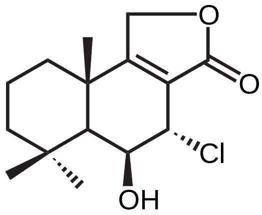
Compounds	Patients								
	1-5	6-14	15	16	17	18,19	20,21	22	23
(+)-Eremofrullanolide (**49**)	+	x	+	x	0	+	+	+	0
(+)-Frullanolide (**53**)	+	+	+	+	+	0	0	0	0
(+)-Oxyfrullanolide (**56**)	+	+	0	+	+	+	+	0	0
(+)-*cis*-β-Cyclo-constunolide (**79a**)	+	+	0	0	0	+	0	0	+

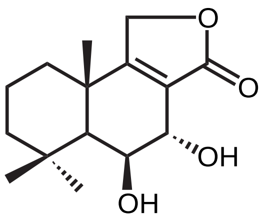
+: positive; 0: inactive; x: not tested

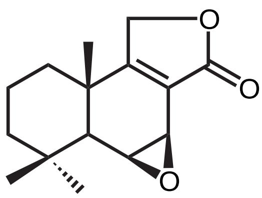

(**40**)

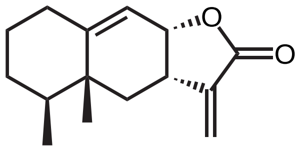

(**41**)

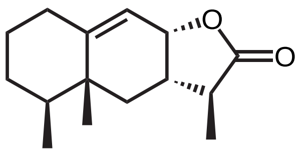

(**42**)

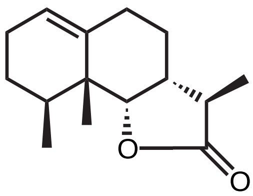

(**43**)

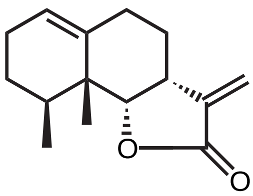

(**44**)

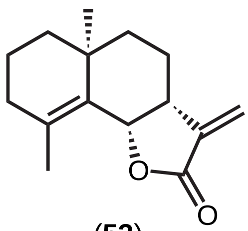

(**45**)

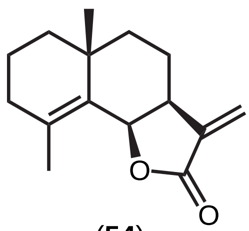

(**49**)

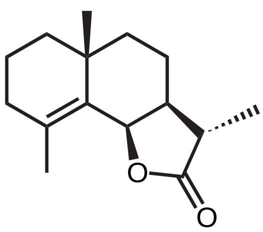

(**50**)

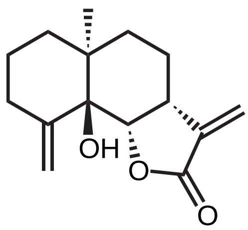

(**51**)

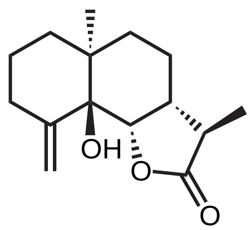

(**52**)

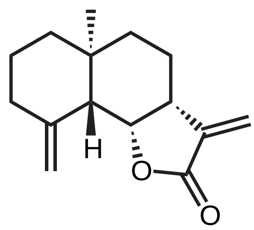

(**53**)

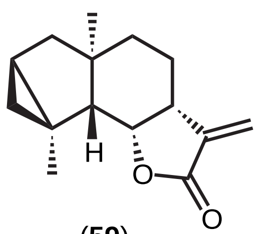

(**54**)

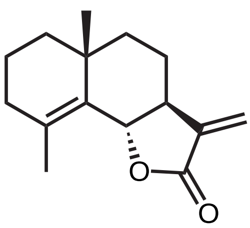

(**55**)

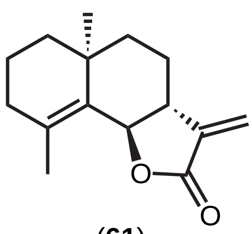

(**56**)

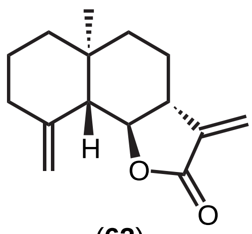

(**57**)

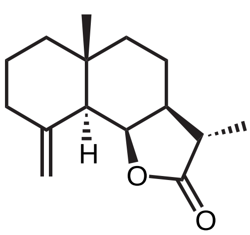

(**58**)

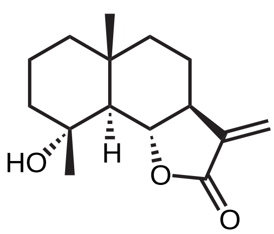

(**59**)

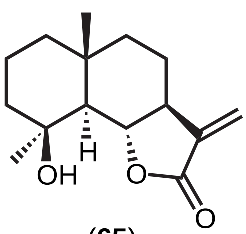

(**60**)

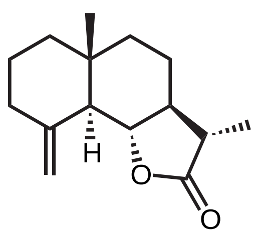

(**61**)

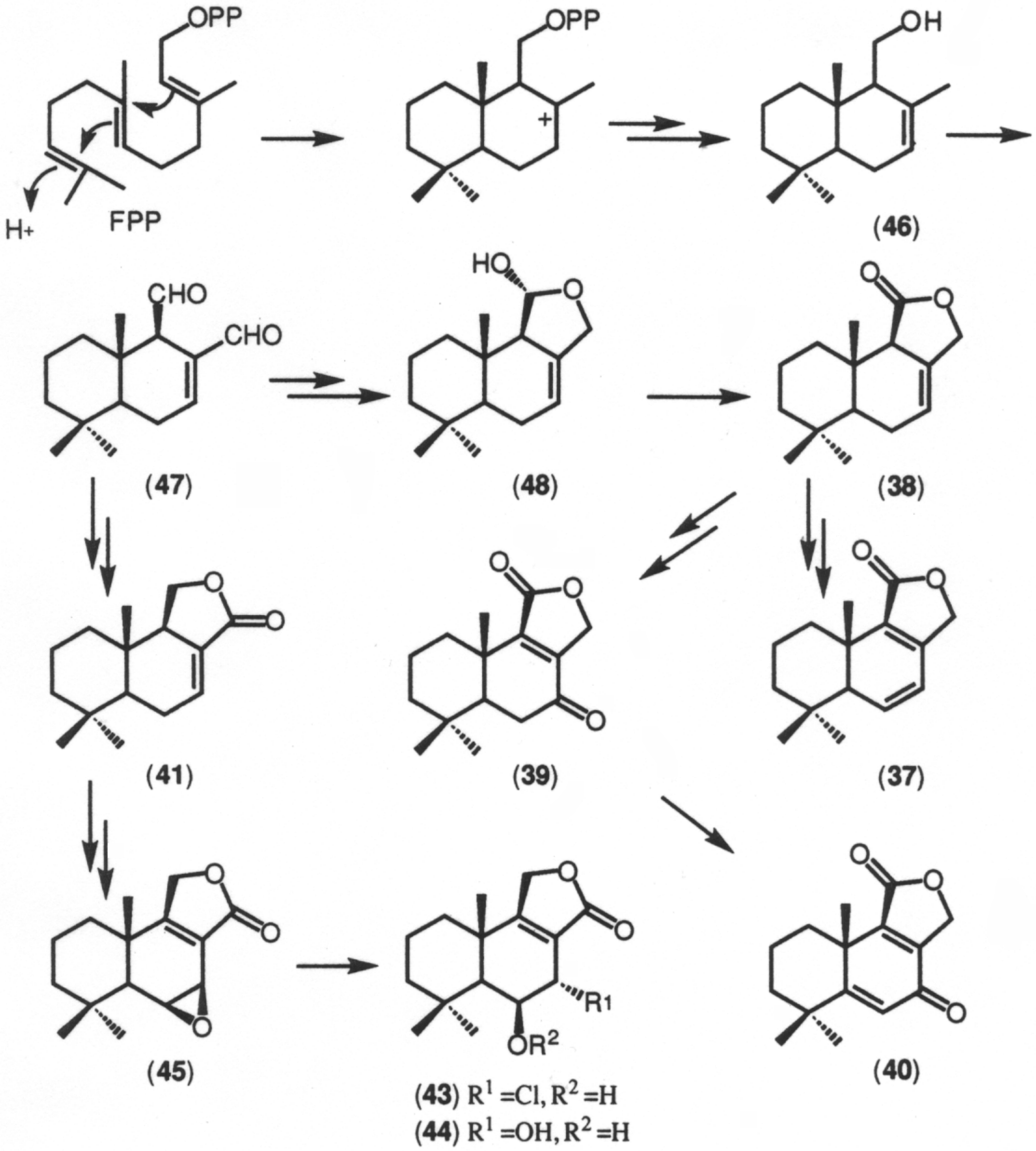

(**62**)


(**63**)


(**64**)


(**65**)


(**66**)



Scheme 6. Possible biogenetic pathway for drimanes found in *Porella* species.

1.10 Eudesmanolides

The eudesmanolides are distributed not only in the *Frullania*, *Lophocolea* and *Plagiochila* (Jungermanniales) but also *Conocephalum* (Marchantiales) and *Makino*a (Metzgeriales) species among which the *Frullania* are the most important sources of eudesmane-type sesquiterpenoids. There are *ca*. 300 species of *Frullania* (Frullaniaceae) which are the epiphytic liverworts. The *Frullania* species are chemically divided into at least 5 types as shown in Table 8.

(+)-Frullanolide (**53**) and (-)-frullanolide (**54**) which have been isolated from *Frullania dilatata* and *F. tamarisci* subsp. *tamarisci*, respectively show the potent contact allergenic property (Table 7) 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.[9,10] (-)-Frullanolide (**54**) is widely distributed in the other *Frullania* species: *F. apiculata,*[41] *F. asagrayana*,[42] *F bicornistipula*,[43] *F. brasiliensis*,[44] *F. nisquallensis*,[45] *F. ternatensis* and *F. serrata*[41] and *F. shaerocephala*.[43] Dihydrofrullanolide (**55**) has been detected in five *Frullania*[42-44] and one *Plagiochila* species, *P. tenerrima.*[8] The New Zealand liverwort *Clasmatocolea vermicularis* contains two eudesmanolides, oxyfrullanolide (**56**) and dehydrooxyfrullanolide (**57**).[41] Two *ent*-eudesmanolides, (+)-β-frullanolide (**58**) and (+)-brothenolide (**59**) have been isolated from the Japanese *F. brotheri.*[45] (+)-Arbsculin B (**60**) and its enantiomer (**61**) have been distributed in three *Frullania* species[43-49] and *F. usamiensis*[50], respectively. The latter species also biosynthesizes *ent*-β-cyclocostunolide (**62**).[50] Dihydro-β-frullanolide (**63**) has been detected in *F. bicornistipula*.[43] *Conocephalum japonicum* (Conocephalaceae) produces arbusculin A (**64**) and its dihydro derivative, colartin, together with germacranolides (see later).[51] The C-4 epimer (**65**) of **64** has been isolated from the Japanese *Frullania tamarisci* subsp. *obscura*.[1] (11*S*)-Dihydro-β-cyclocostunolide (**66**) has been isolated from *F. bicornistipula.*[43] 8α-Acetoxy-β-cyclocostunolide (**67**) and rothin A acetate (**68**) have been isolated from *Wiesnerella denudata* (Conocephalaceae)[49] and unidentified South American *Frullania* species.[52] The latter species also elaborates α-cyclocostunolide (**69**).[52]

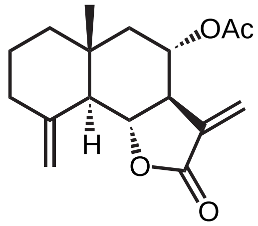
Table 8. Chemical type of *Frullania* (Frullaniaceae)

Type	Species	Mono-terpenes	Sesquiterpene-lactones	Diterpenes	Bibenzyls
I	*F. apiculata*		+++*		
	F. tamarisci subsp. *asagrayana*		+++++		
	F. biconistipula		+++		
	F. brasiliensis		+++		
	F. brotheri		++++		
	F. convoluta		++++		
	F. hamatiloba	+++	+++	+++	
	F. inflata	+	++		
	F. motoyana		++	+++	
	F. nepalensis		+++++		
	F. tamarisci subsp. *nisquallensis*		+++		
	F. ramuligera		+++++		
	F. serrata		+++	++	
	F. sphaerosephara		+++		
	F. ternatensis		+++		

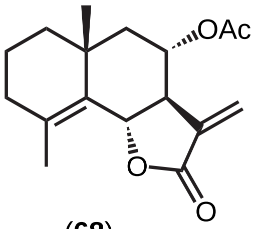
	F. vethii		+++++				
II	*F. densiloba*	+	++++		++		+
	F. dilatata	+	++		++		+
	F. dilatata var . *anomala*	+	++++				+
	F. muscicola		+++				+++++
	F. osumiensis		++++				+
	F. paravistipula		++++				+++
	F. tamarisci subsp. *tamarsci*	+	++++				+
	F. tamarisci subp. *obscura*	+	++++				+
	F. usamiensis	+	+++++				+
	F. yunnanesis	+	+++++				+
III	*F. amplicrania*			++		++++	
	F. bonincola						+++
	F. davurica						+++++
	F. monocera						+++++
IV	*F. pedicellata*				++++		++
	F. taradakensis				+++++		+++++
V	*F. fragilifera*	+++++					
VI	*F. diversitexta*				++		
	F. kagoshimensis				+++++		

* The symbols +, ++, +++, etc. are relative concentrations estimated by GC/MS.

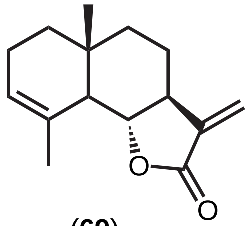
α-Santonin (**70**) which shows antibacterial activity has been isolated from differentiated culture of the liverwort *Fossombronia pusilla* (Codoniaceae).[53] Four new eudesmanolides, nepalensolides A-C (**71-73**) and nepalensolide D (=*ent*-critonilide) (**74**) and the known *ent*-β-frullanolide (**58**) have been isolated from the Taiwanese *Frullania nepalensis* [42,54,55] *F. serratta* is chemically very close to *F. nepalensis* since it produces the same lactones (**71-74**) as those found in *F. nepalensis*, along with arbsculin B (**61**).[49] The ether extract of the Bulgarian *F. dilatata* var. *anomala* was fractionated to give three rearranged *ent*-spiroeudesmane-type sesquiterpene lactones named spirodilatanolides A (**75**), B (**76**) and C (**77**), along with the known (+)-frullanolide (**53**) and critonilide (**78**).[38,39] The absolute configurations of the spirolactones were established by a combination of X-Ray crystallographic analysis of **75** and the CD spectrum of degraded product from **75** through the reduction, acetylation and ozonolysis.[38,39] The European *Frullania*



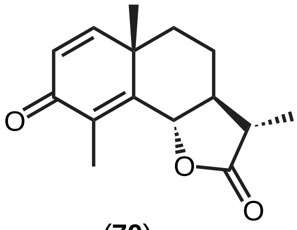
(**67**)



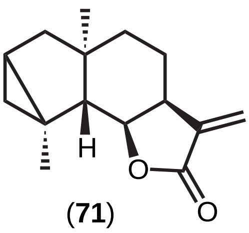
(**68**)



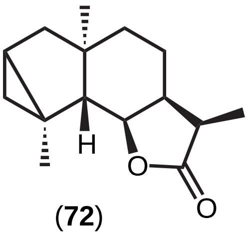
(**69**)



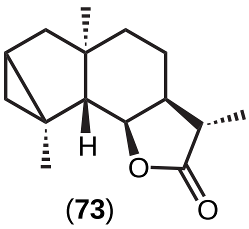
(**70**)



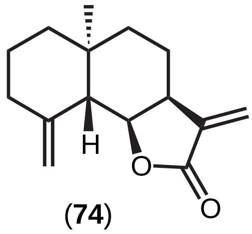
(**71**)



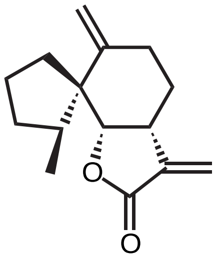
(**72**)



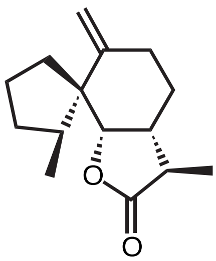
(**73**)



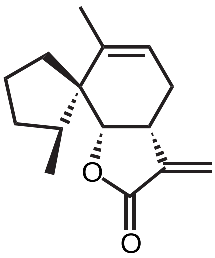
(**74**)



(**75**)



(**76**)



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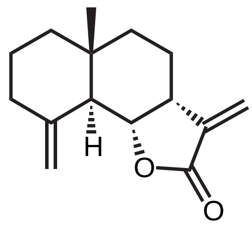

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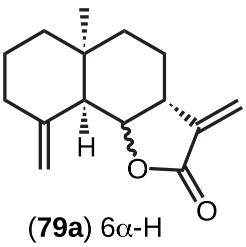
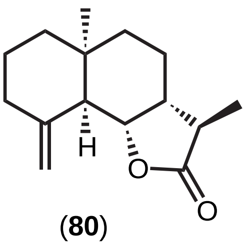


(**79a**) 6α-H
(**79b**) 6β-H



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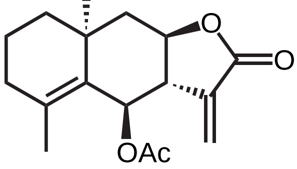

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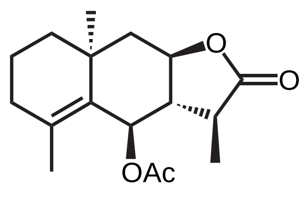

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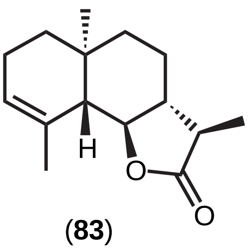

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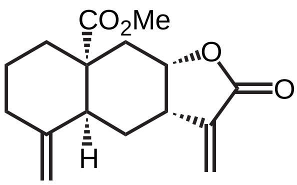

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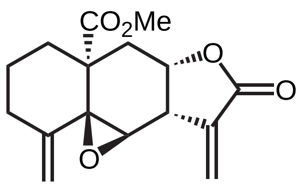

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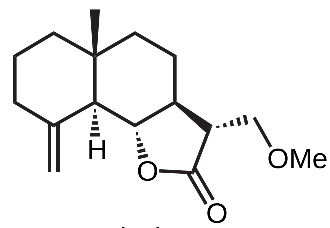

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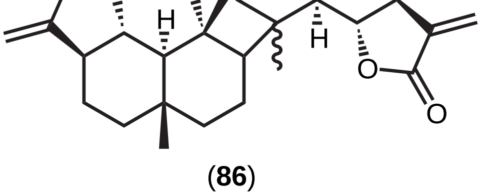

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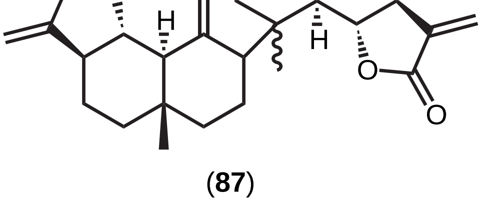
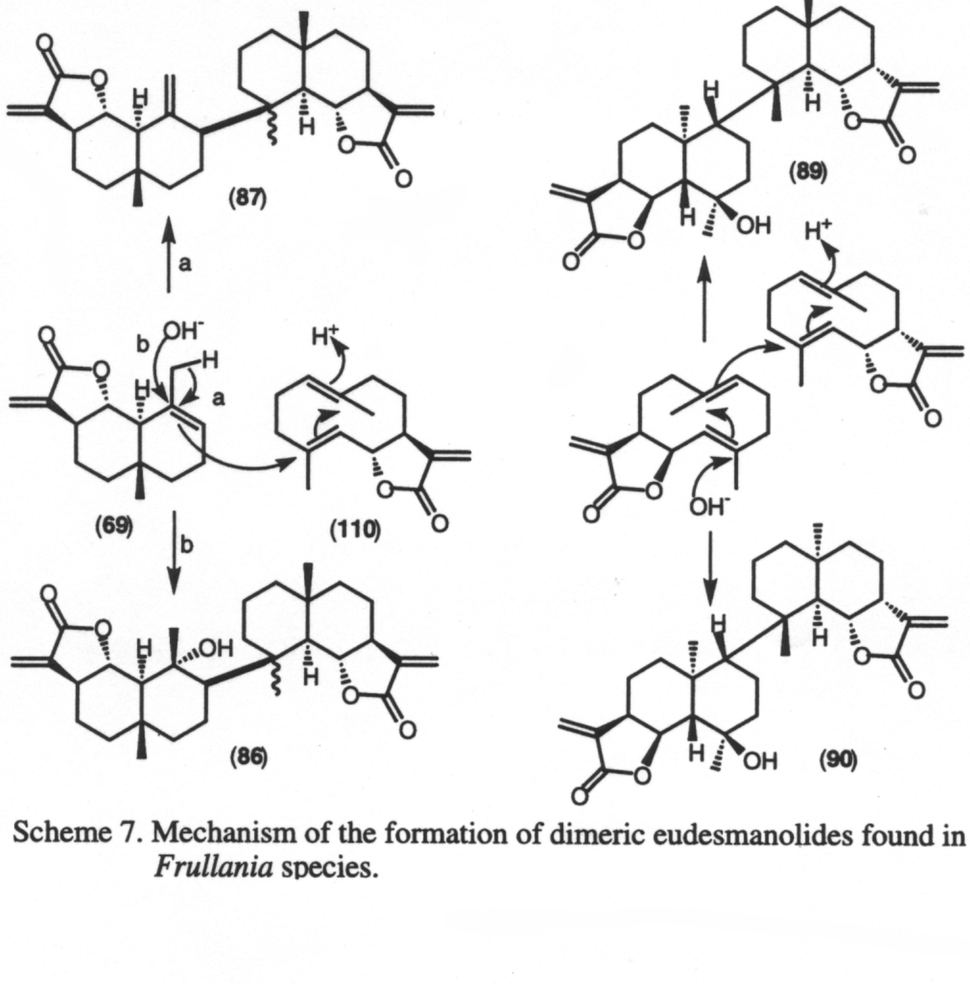


(**87**)

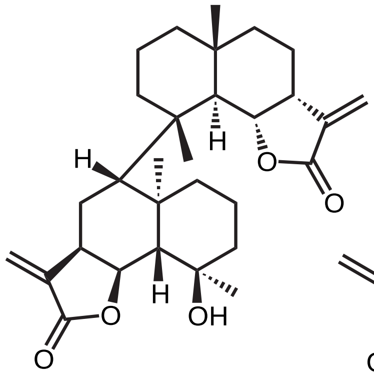
muscicola produces two new *ent*-eudesmanolides, 5α,6α,7α,10α-4(15),11(13)-eudesmadiene-12,6-olide (**79b**) and its dihydro derivative (**80**), together with the known (+)-arbusculin B (**60**), (+)-frullanolide (**53**) and nepalensolide D (=*ent*-critonilide) (**78**).[40] *F. densiloba* elaborates two new eudesmanolide, named densilobalide A (**81**) and densilobalide B (**82**), together with α-dihydrocyclocostunolide (**83**). 2D-NMR spectrum showed that the structure of **83** was identical to the dihydro derivative prepared from α-santonin **70**), except for the sign of the optical rotation. It is the first report of the isolation of eudesmane-12,8-olides from the Frullaniaceae.[56] The New Zealand *Plagiochila conjugatus* yielded two new *ent*-eudesmanolides, 10-methoxycarbonyl-*ent*-eudesm-4(15),11-dien-12,8β-olide (**84**) and 10-methoxycarbonyl-5β,6β-epoxy-*ent*-eudesm-4(15),11-dien-12,8β-olide (**85**).[57]

F. convoluta contains (-)-α-cyclocostunolide (**69**), (-)-ent-α-dihydrocylocostunolide (**83**), (+)-brothenolide (**59**), (+)-nepalensolide A (**71**) and (+)-nepalensolide B (**72**), along with a new germacranolide, epi-isocostunolide (**124**) (see later).[58]

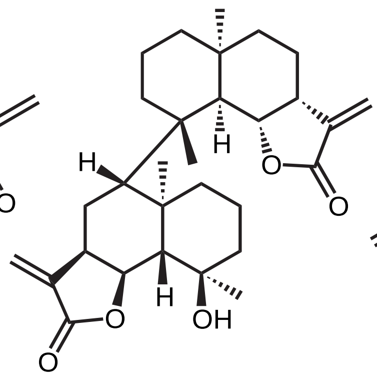
The European *F. tamarisci* subsp. *tamarisci* contains two unique eudesmane-type sesquiterpene lactone dimers (**86,87**)[59] and methoxyfrullanolide (**88**).[12] The dimeric lactones have been found in the dried material which has been stored in the laboratory for a year. However, they have not been isolated from the fresh material.[59] The similar eudesmane dimers (**89,90**) have also been isolated from the European *F. muscicola.*[40] Possible formation of **89** and **90** from costunolide-like units has been proposed by Connolly *et al.* [59] and Kraut *et al.*[40] as shown in Scheme 7.



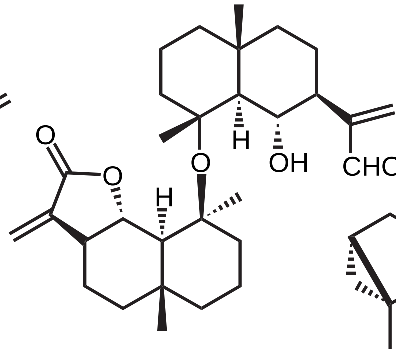
Scheme 7. Mechanism of the formation of dimeric eudesmanolides found in *Frullania* species.



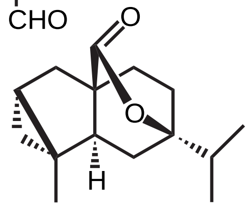
(**89**)



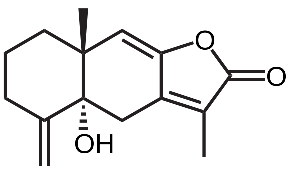
(**90**)



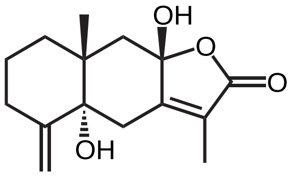
(**91**)



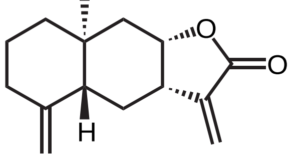
(**92**)



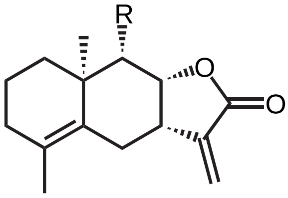
(**93**)



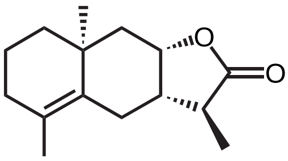
(**94**)



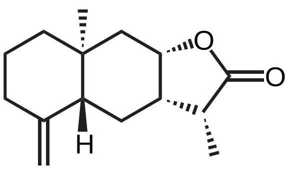
(**95**)



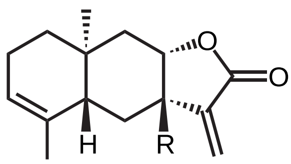
(**96**) R=H
(**98**) R=OH
(**99**) R=OAc



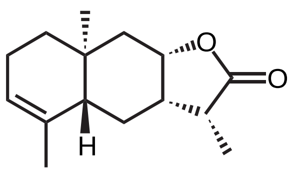
(**97**)



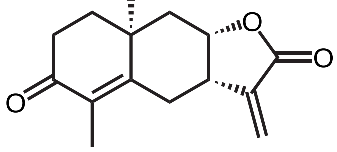
(**100**)



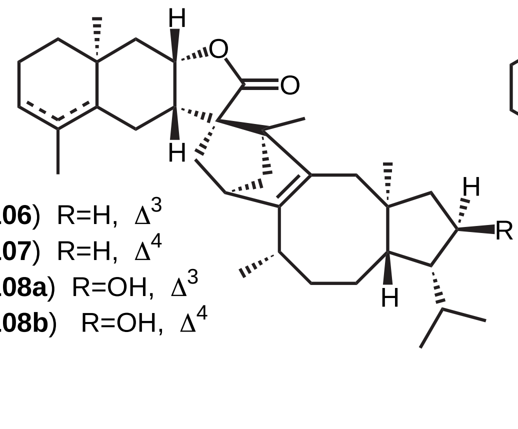
(**101**) R=H
(**102**) R=OH



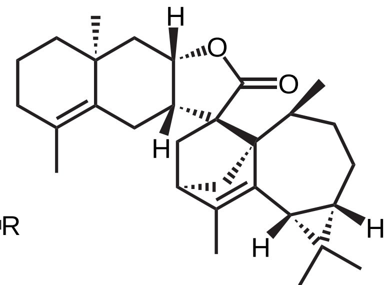
(**103**)



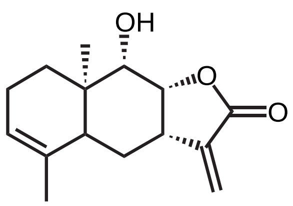
(**104**)



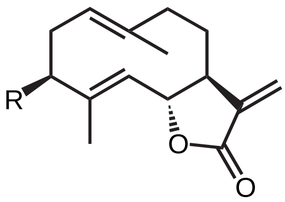
(**106**) R=H, Δ^3
(**107**) R=H, Δ^4
(**108a**) R=OH, Δ^3
(**108b**) R=OH, Δ^4



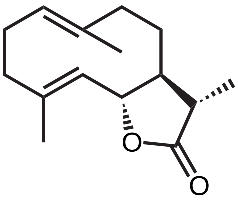
(**109**)



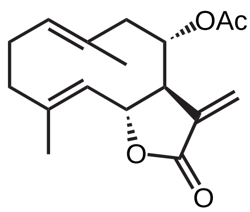
(**105**)



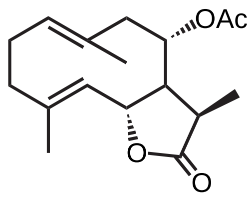
(**110**) R=H
(**111**) R=OAc



(**112**)

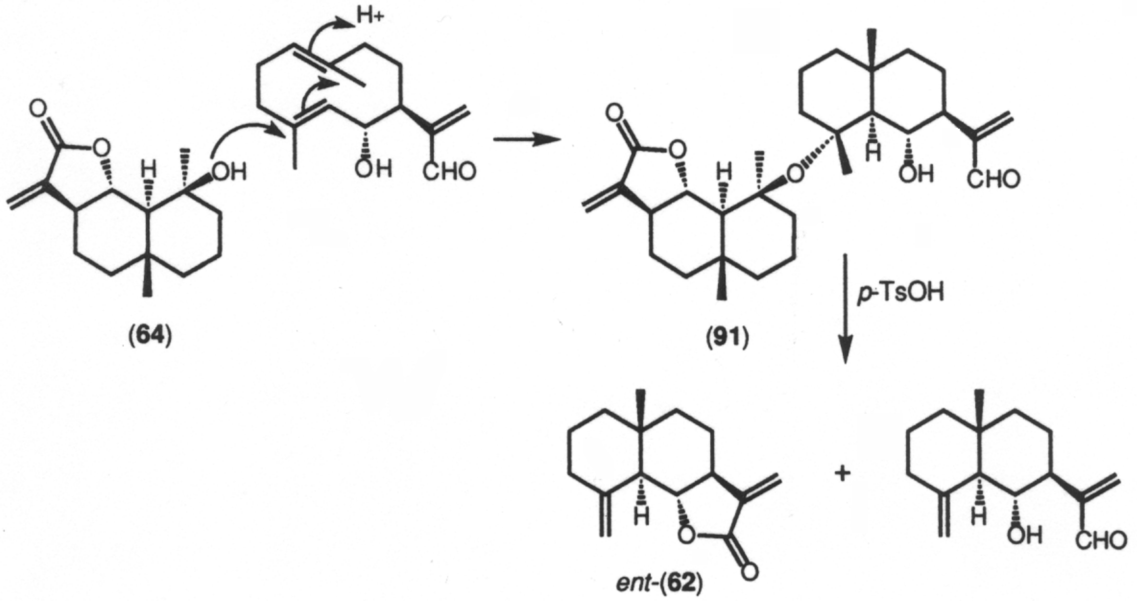


(**113**)



(**114**)

One unique sesquiterpene dimer (**91**) has been isolated form the Japanese *F. tamarisci* subsp. *obscura.*[60] The structure of **91** has been determined by chemical degradation as shown in Scheme 8.

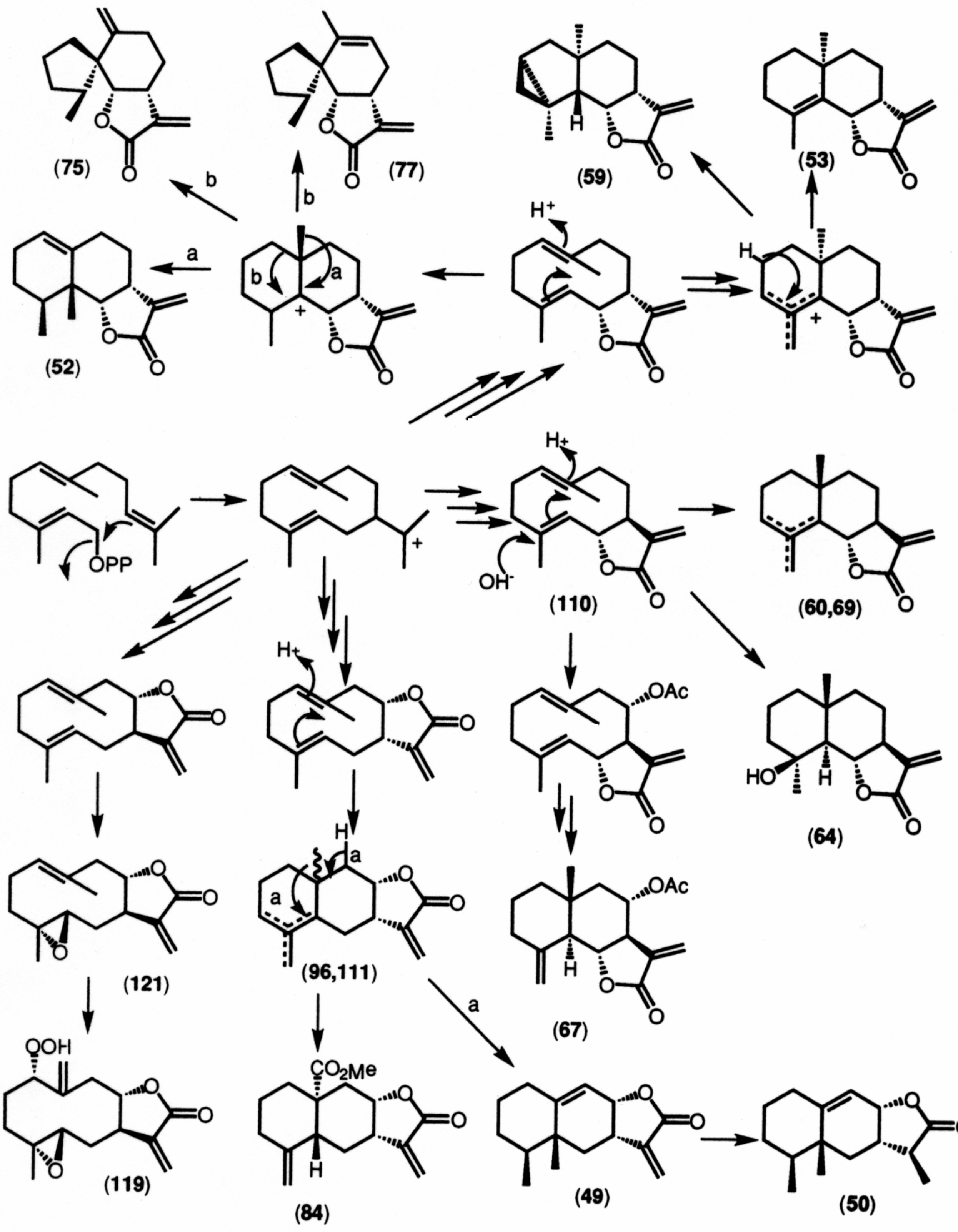


Scheme 8. Mechanism of the formation of dimeric eudesmanolide (**91**) found in *Frullania tamarisci* subp.*obscura* and degradation of **91** by acid.

The thalloid liverwort *Makinoa crispata* elaborates not only drimane-type sesquiterpenoids as mentioned earlier but also a unique eudesmanolide, crispatanolide (**92**).[60]The Japanese *Lophocolea heterophylla* (Lophocoleaceae) produces two eudesmanolides (**93,94**).[62] The European same species also produces *ent*-isoalantolactone (**95**).[63] *Diplophyllum albicans* is a rich source of eudesma-12,8-olides, such as diplophyllin (**96**), dihydrodiplophyllin (**97**), 9α-hydroxydiplophyllin (**98**) and 9α-acetoxydiplophyllin (**99**).[1] South American *L. coadunata*[44] and *L. bidentata*[2] elaborate dihydroisoalantolactone (**100**) and diplophyllolide (**101**), respectively. The latter compound has been found in *Clasmatocolea vermicularis*,[41] *Plagiochila moritziana*[43,64,65] and *Tritomaria quinquedentata.*[29,30]

T. quinquedentata also produces *ent*-dihydrodiplophyllolide (**103**).[29,30,66,67] The European *Chiloscyphus polyanthos* contains very potent pungent substances. This taste is due to the presence of eudesmanolides (**96, 101, 102, 104**)[1] Compounds (**101,102**) have antifeedant activity against lavae of the Japanese *Pieris* species.[9,10] *C. polyanthos* also produces 9α-hydroxydiplophyllolide (**105**).[1] Diplophyllin (**96**) shows piscicidal activity against killie-fish which is killed within 240 min at a concentration of 6.7 ppm.[9,10] The structure of the reported pungent lactone from the same species was revised to be **102** by using NMR shift reagent.[41] *Ent*-diplophyllin (**96**) has been isolated from *Clasmatocolea vermicularis*[60] and *Plagiochila moritziana.*[43,64,65]

Five unique C-35 lactones, plagiospirolides A-E (**106-109**) have been isolated from the Panamanian liverwort *Plagiochila moritziana.*[43,64,65] Compounds (**106**) and (**107**) might be formed by a Diels-Alder type cycloaddition reaction between two dienophiles (**96**) and (**101**) present in the same species and fusicocca-2,5-diene, a fusicoccane-type diterpene hydrocarbon [64,65] which is widely distributed in liverworts.



Scheme 9. Possible biogenetic pathways for eudesmanolides and eremophilanolides found in *Frullania*, *Lophocolea*, *Chiloscyphus* and *Plagiochila* species.

1.11 Germacranolides

The *Conocephalum* (Conocephalaceae) and some *Porella* species are rich sources of germacranolides. *C.*

japonicum produces costunolide (**110**) as a major component.[68] The same compound has been found in four *Frullania* species,[42,49,69] the South American *Clasmatocolea humilis*[15] and *Plagiochila hondurensis*.[8] Kim *et al*.[45] reported that **110** was isolated from the American *Frullania nisquallensis* and showed cytotoxic activity (IC_{50} 12μg/mL) against A-549 human lung carcinoma cell line, together with (-)-frullanolide (**54**). Dihydrocostunolide (**112**) has also been isolated from *C. japonicum*,[67] and detected in *C. humilis*[15] and *P. hondurensis*[8] by GC-MS.

Wiesnerella denudata produces the characteristic pungent substance. This hot-tasting is responsible for tulipinolide (=7α-acetoxycostunolide) (**113**).[70] (11*R*)-Dihydrotulipinolide (**114**) and (11*S*)-dihydrotulipinolide (**115**) have been isolated from *Frullania serratta*.[49] Compound (**113**) shows antifeedant activity against the Japanese butterfly's lavae *Pieris* species.[9,10] *W. denudata* contains compound (**115**) as a minor constituent.[49]

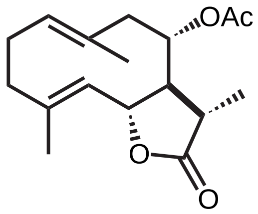
W. denudata and *C. japonicum* belong to the same Conocephalaceae family. The former species produces not only germacranolides (**110, 113**) but also several guaianolides (see later). However, only costunolide (**110**) and dihydrocostunolide (**112**) have been isolated from the latter species. These results indicate that *W. denudata* is more advanced chemically than *C. japonicum*. Two known germacranolides (**116,117**) have been obtained from *Targionia lorbeeriana* (Targioniaceae) belonging to the Marchantiales collected in Portugal.[71] The latter lactones shows antifungal activity against *Candida albicans Cladosporium cucumerinum.*[71]

The Indian *Frullania inflata* elaborates (11*S*)-11,13-dihydrolipiferolide (=8β-acetoxydihydroparthenolide) (**118**).[72] The ether extract of *Porella japonica* showed cathepsin L and B inhibitory activity. It contains costunolide (**110**) and 3β-acetoxycostunolide (**111**), together with some guaianolides (see later).[72] *P. acutifolia* subsp. *tosana* is a pungent stem-leafy liverwort. It elaborates two hydroperoxygermacra-12,8-olides (**119,120**) which showed hot taste, along with their related 12,8-olides (`**121-123**).[74,75]

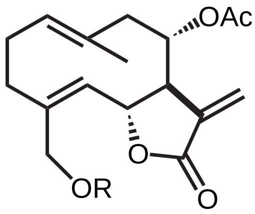
A new germacranolide, epi-isocostunmolide (**124**) has also been isolated from *Frullania convoluta*, together with several eudesmanolides.[58] In Scheme 9, possible biogenetic pathways of germacranolides, eremophilanolides and eudesmanolides found in liverworts are summarized.

1.12 Guaianolides

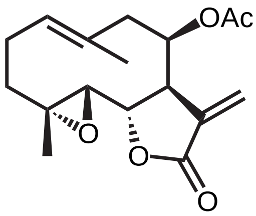
Some *Porella* species are rich sources of guaianolides. *P. japonica* elaborates not only germacranolides but also five guaianolides, porelladiolide (**125**), 3α,4α-epoxyporelladiolide (**126**), eregoyadizin (**127**), isoeremanthin (**128**) and dihydroisoeremanthin (**129**).[73] Further fractionation of the crude extract of *P. japonica* resulted in the isolation of three new guaianolides, 11-epiporelladiolide (**130**), 11,13-dehydroporelladiolide (**131**) and porellaolide (=2β-hydroxy-4,9,11-guaiene-12,6-olide) (**132**) whose structures were elucidated by X-Ray crystallographic analysis.[76] Compound 131 possessed a weak inhibitory activity against cathepsin B (13.4% at 10^{-5}M) and cathepsin L (24% at 10^{-5} M).[76] *P. acutifolia* subsp. *tosana* elaborates two new guaianolides, isoporelladiolide (**133**) and dehydroisoporelladiolide (**134**),[75] together with the known porelladiolide (**125**) which has been isolated from *Porella japonica*.[1] Thus, *P.*



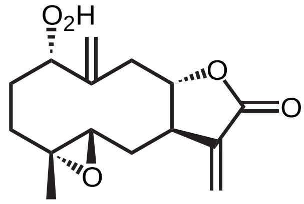
(**115**)



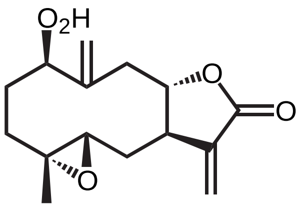
(**116**) R=Ac
(**117**) R=H



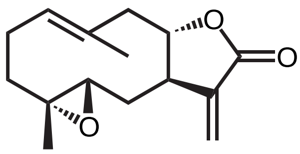
(**118**)



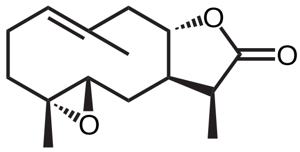
(**119**)



(**120**)



(**121**)



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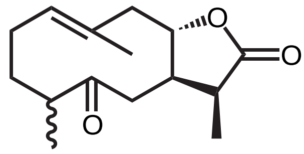
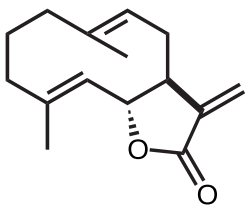
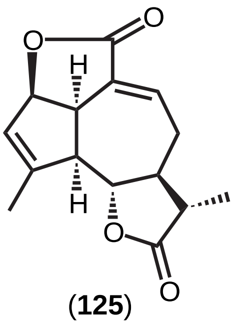


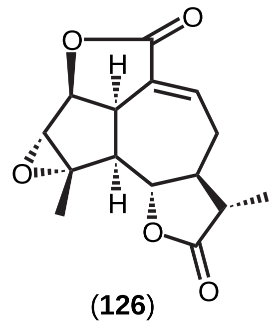
(**123**)



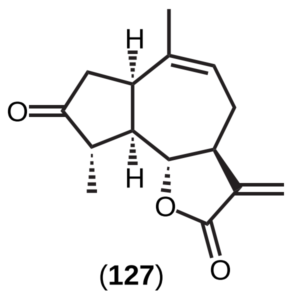
(**124**)



(**125**)



(**126**)



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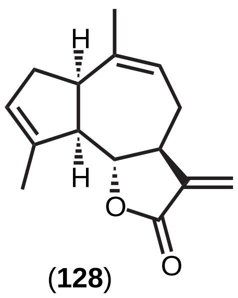
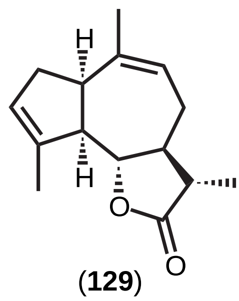
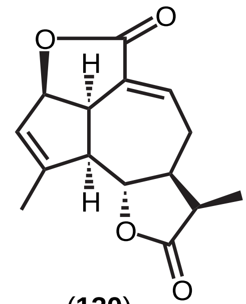


(**128**)



(**129**)



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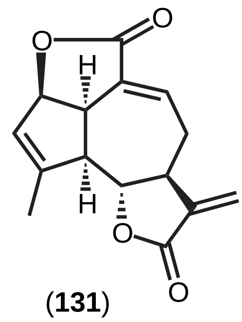
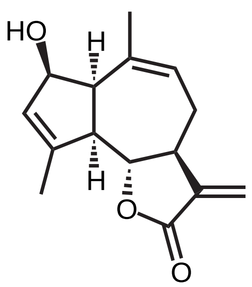
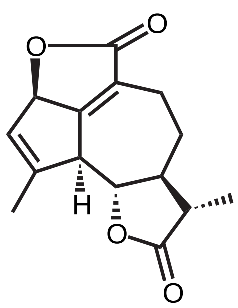


(**131**)



(**132**)



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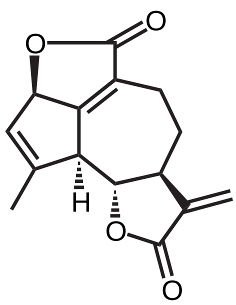
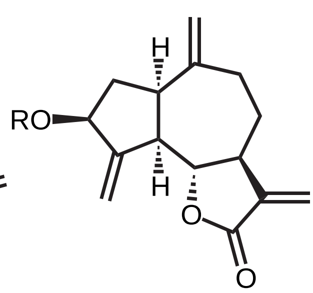


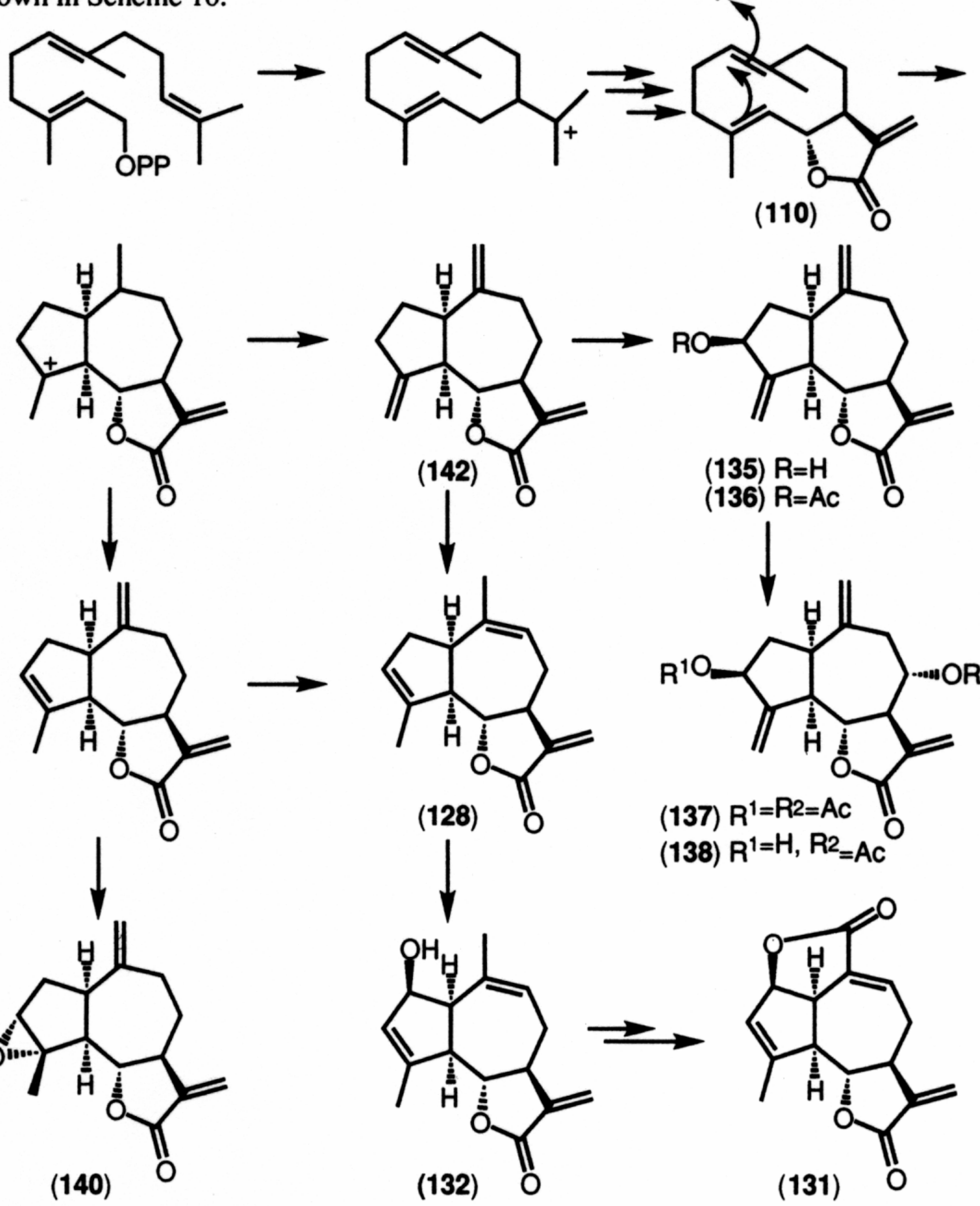
(**134**)



(**135**) R= H
(**136**) R=Ac

acutifolia subsp. *tosana* is chemically closely related to *P. japonica*. *Wiesnerella denudata* biosynthesized germacranolides as well as guaianolides (**135-138**).[70] The East Malaysian *Frullania serratta* produces not only eudesmane- and germacrane-type sesquiterpene lactones (**113**), but also guaiane-type sesquiterpenoid, such as 8α-acetoxyzaluzanin D (**137**).[49] A new guaianolide, dihydroestafiatin (**139**) has been isolated from the Bolivian *Frullanoides densifolia*, along with the known estafiatin (**140**)[77-79]

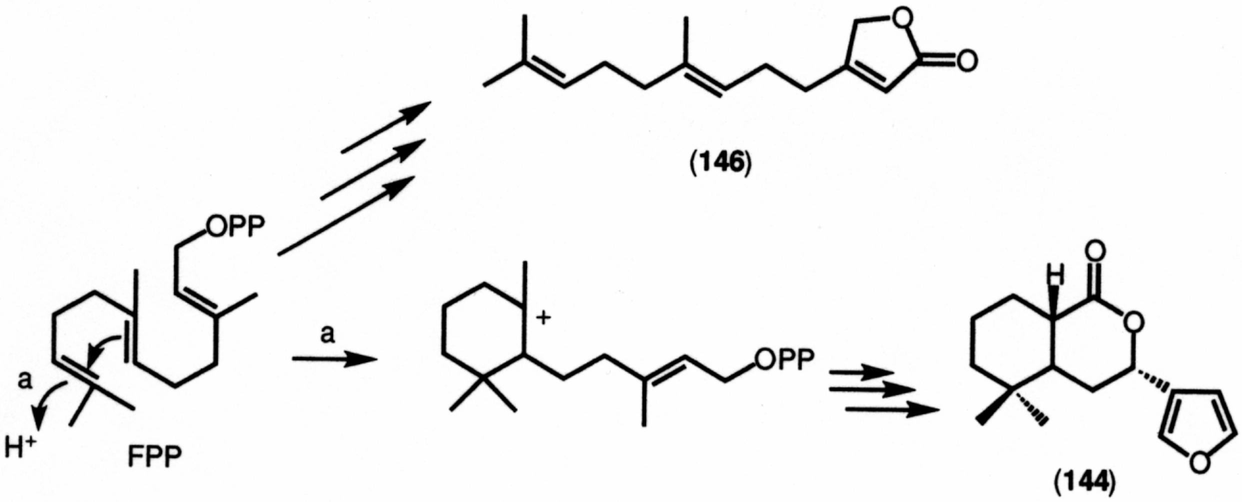
Portuguese liverwort, *Targionia lorbeeriana* produces a new guaianolide (**141**) whose structure was determined by X-Ray crystallographic analysis, together with the known dehydrocostuslactone (**142**) and its dihydro derivative (**143**), as well as two germacranolides (**116,117**), as discussed earlier. Compound (**142**) showed the strongest antifungal activity against *Cladosporium cucumerinum* and larvicidal activity against *Aedes aegypti*.[71] The guaianolides found in the liverworts might be formed by the biogenetic pathways as shown in Scheme 10.



Scheme 10. Possible biogenetic pathway for guaianolides found in *Porella* and *Wiesnerella* species.

1.13 Monocyclofarnesanolides

Two novel monocyclofarnesane-type sesquiterpene lactones ricciocarpins A (**144**) and B (**145**) have been isolated from an axenic culture of the European liverwort, *Ricciocarpos natans* (Ricciaceae).[17,20] Both compounds have molluscicidal activity against *Biomphalaria glabtata* at a concentration of 11 and 43 ppm (LC_{100}).[80] An additional monocyclofarnesane sesquiterpene lactone (**146**) was isolated from the Venezuelan unidentified liverwort, *Frullania* species.[52] It is the first example of the isolation of **146** as a natural product. Compounds (**144-146**) might be formed from FPP as shown in Scheme 11.



Scheme 11. Possible biogenetic pathway for monocyclofarnesenes fround in *Frullania* and *Ricciocarpos* species.

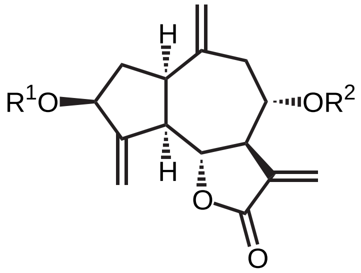
1.14 Pinguisanolides

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]

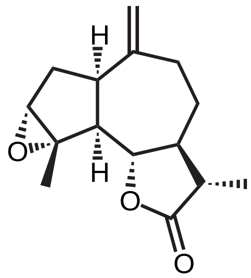
Three new pinguisane-type sesquiterpene lactones , 2α-hydroxy-3-oxopinguis-5(10)-en-11,6-olide (**147**), its methyl ether (**148**) and 3-oxo-pinguis-5(10)-6-dien-11,6-olide (**149**) have been obtained from an axenic culture of *Aneura pinguis* (Riccardiaceae).[81]

Two possible biogenetic pathways of pinguisane-type sesquiterpenoids have been proposed by Tazaki *et al.*, [82] using [2-^{13}C]-acetate to the cultured gametophytes of *A. pinguis* as shown in Scheme 12.[82] 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 (**150**). The New Zealand *Plagiochila elegantula* gave a new norpinguisanolide (**151**), along with deoxopinguisone and norpinguisone methyl ester.[57,83] The Japanese small liverwort *Trocholejeunea sandvicensis* (Lejeuneaceae) produces various types of pinguisane- and norpinguisane-type sesquiterpenoids one of which is ptychanolide (**152**).[74,77-79]

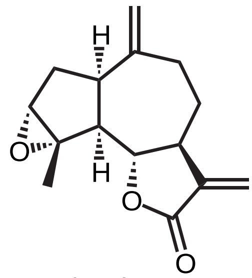
The Bolivian *Frullanoides densifolia* is also interesting liverwort because it contains many pinguisane-type



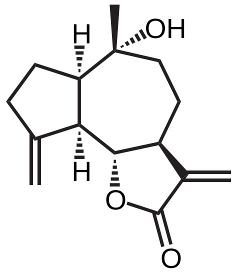
(**137**) R^1=R^2=Ac
(**138**) R^1=H, R^2=Ac



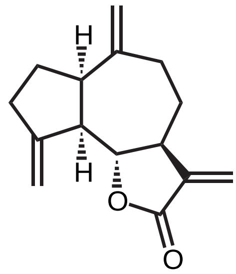
(**139**)



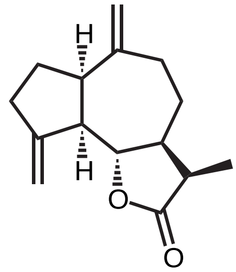
(**140**)



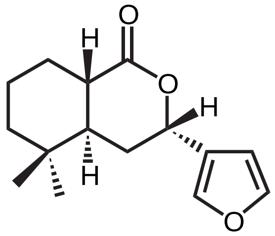
(**141**)



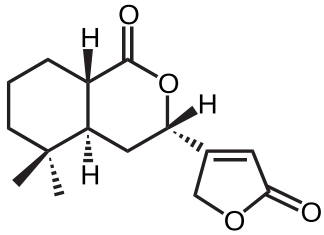
(**142**)



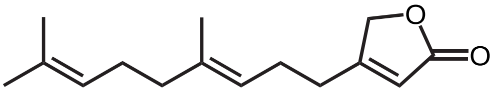
(**143**)



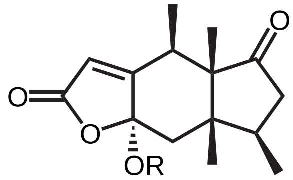
(**144**)



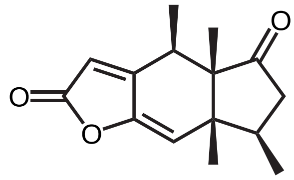
(**145**)



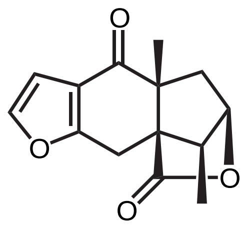
(**146**)



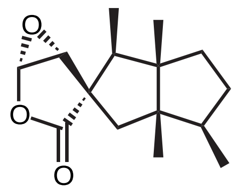
(**147**) R=H
(**148**) R=Me



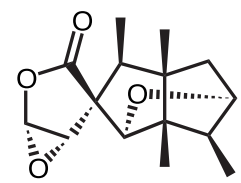
(**149**)



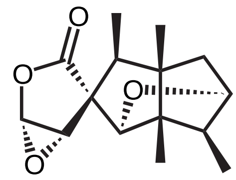
(**151**)



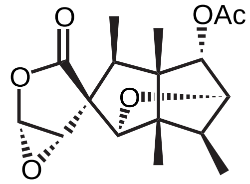
(**152**)



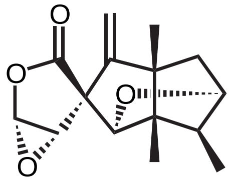
(**153**)



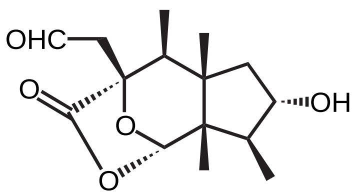
(**154**)



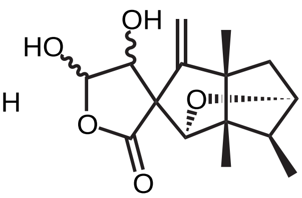
(**155**)



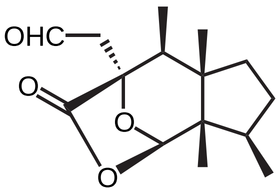
(**156**)



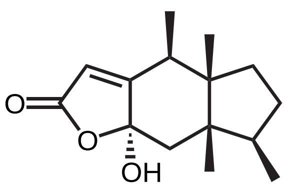
(**157**)



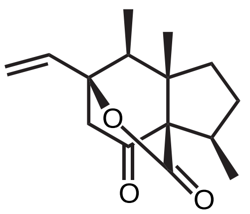
(**158**)



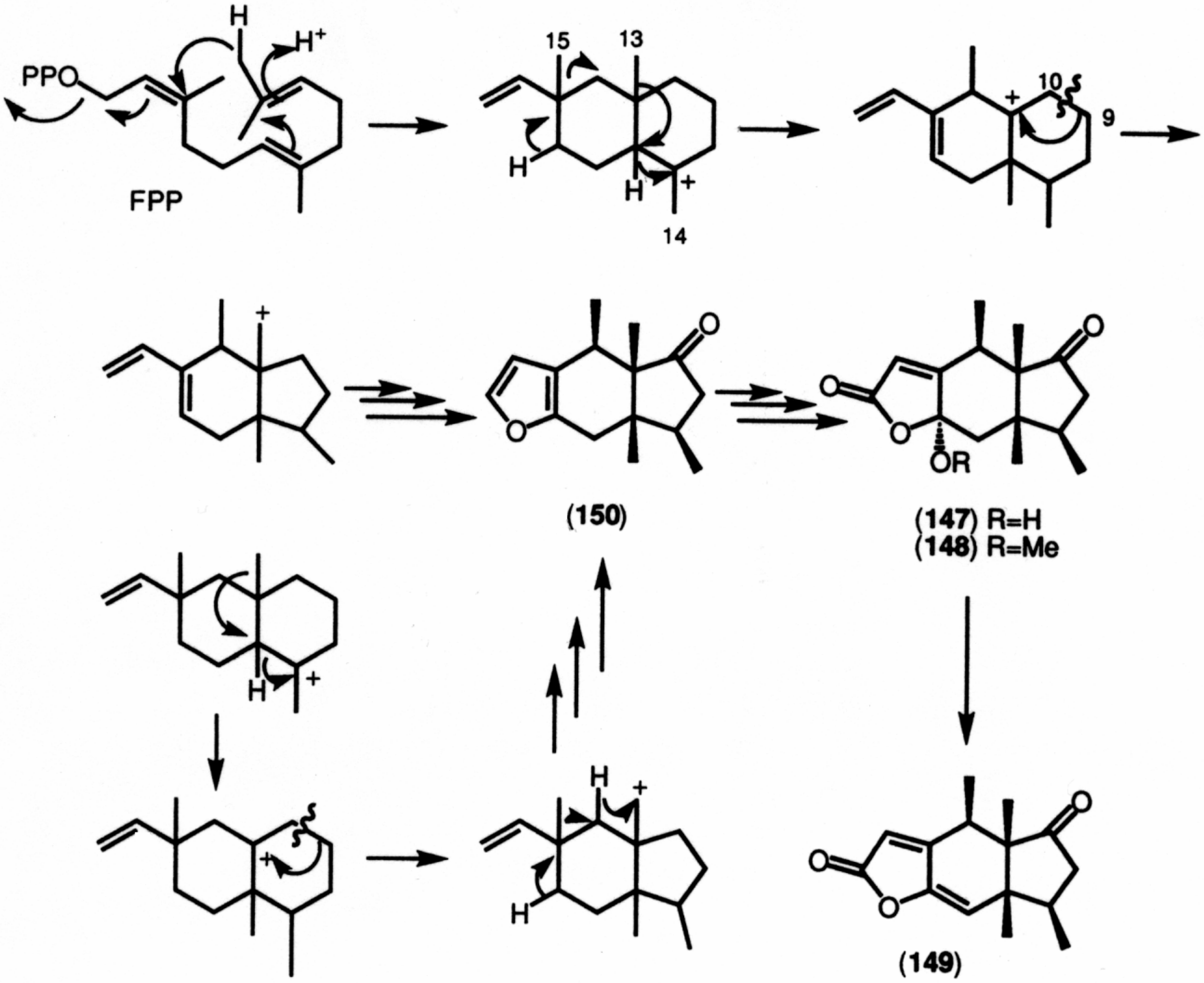
(**159**)



(**160**)



(**161**)



Scheme12. Possible biogenetic pathway for pinguisane-type sesquiterpenoids found in liverworts.

sesquiterpenoids: ptychanolide (**152**), pinguisanolide (**153**) isopinguisanolide (**154**), spirodensifolins A (**155**) and B (**156**).[76-78] *Acrolejeunea pusilla* and *A. pycnoclada* elaborate pinguisanolide (**152**) and isopinguisanolide (**154**).[83] The European *Porella platyphylla* also contains pinguisanolide (**153**), together with a few pinsuisanes.[59] *P. cordaeana* produces not only drimanes but also highly oxygenated pinguisanes (**157,158**), together with norpinguisone methyl ester[85] and norpinguisanolide (**151**).[33] It is noteworthy that *Trocholejeunea sandvicensis* produces the similar lactone (**159**) as **157**, however the absolute configuration of formyl group and lactone ring of **159** was opposite to that of **157**.[86] The Japanese *Ptychanthus striatus* contains not only various labdane-type diterpenoids but also ptychanolactone (**160**),[12] ptychanolide (**152**) and pinguisanolide (**153**).[87]

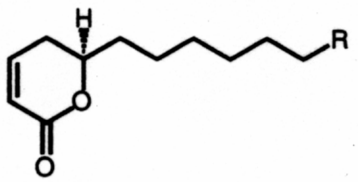
Further fractionation of the ether extract of *Porella acutifolia* subsp. *tosana* resulted in the isolation of the unique dimeric pinguisane-type sesquiterpenoids with monomeric pinguisanes of which acutifolone B (**160**) was obtained as a pinguisane-type sesquiterpene lactone. [88]

These pinguisanes and norpinguisanes are very valuable for the consideration of chemosystematics of Riccardiaceae belonging to the Metzgeriales and the Porellaceae, Lejeuneaceae, Ptilidiaceae and

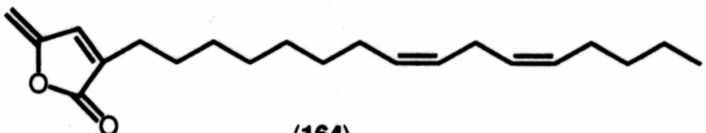
Trichocoleaceae belonging to the Jungermanniales (see later), although they are very unstable upon the exposure of the air, light and acidic condition to afford polymerized artifacts.

2. Acetogenin lactones

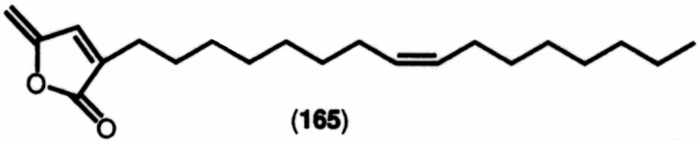
The ether extract of the liverwort *Cheilolejeunea imbricata* was purified by HPLC to give two milky-smelling lactones, (*R*)-dodec-2-en-1,5-olide (**1621**) and (*R*)-tetradec-2-en-1,5-olide (**163**).[89] Neither terpenoids nor lipophilic aromatic compounds were detected in this liverwort. *Marchantia paleacea* subsp. *diptera* produces two acetogenin lactones (**164**) and (**165**) whose structures are very similar to those (**166, 167**) isolated from the marine organisms. [90]



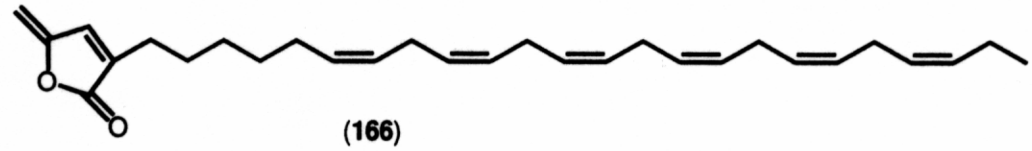
(**162**) R= Me
(**163**) R=(CH_2)Me



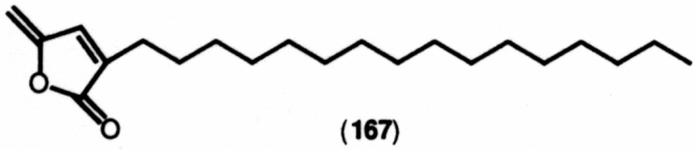
(**164**)



(**165**)



(**166**)



(**167**)

3. Chemosystematic Study of *Plagiochila* (Dum.) Dum., *Frullania* Raddi and *Porella* L.

The secondary metabolites, such as terpenoids, bibenzyl and bis(bibenzyls) found in liverworts are very valuable tools for investigation of chemosystematics.[91,92] Some liverworts biosynthesize a number of complex terpenoids and phenolic compounds whereas some other species produce one or two structurally simple compounds. We are continuing to study evolutionary relationship within Hepaticae at genus and/or family level.[1,2] Here the chemosystematics of three stem-leafy *Plagiochila*, *Porella* and *Frullania* species which are morphologically very complex are surveyed. [1,2,91-93]

3.1 Chemosystematics of *Plagiochila*

There are *ca.*3000 species of *Plagiochila* and their morphological identification is quite difficult. Among them, Two European, two New Zealand, 13 Chilean, 30 Peruvian and 12 Japanese Plagiochila species have been investigated chemically in our laboratory.[1,2] As mentioned earlier, *Plagiochila* species are divided into two types; pungent and non-pungent species. The former group mainly produces 2,3-secoaromadendrane-type sesquiterpenoids including a highly oxygenated hemiacetal, plagiochiline A (**18**) which is one of the hot-tasting substances. 2,3-Secoaromadendrane-type sesquiterpenoids is rare naturally occurring compounds and they are the most important chemical makers of *Plagiochila* genus. Non-pungent group also contains the same, but not highly oxygenated 2,3-secoaromadendrane-type sesquiterpenoids. The species producing 2,3-secoaromadendranes are classified into Type II (Table 5). The non-pungent species which does not contain secoaromadendrane are further divided into at least 7 types. Type I : aromadendranes-maalianes-humulanes, Type III: bibenzyl, Type IV: pinguisanes, Type V: cuparane-herbertane, Type VI: secoaromadendrane-eudesmane which is classified into sub-type of Type II since it elaborates 2,3-secoaromadendrane and Type VII: eudesmanolides. Many different chemical types will be found in the other *Plagiochila* species because we studied only a few percentages of the total *Plagiochila* species.

3.2 Chemosystematics of *Porella*

In Japan there are 18 species of *Porella* belonging to Porellaceae. As described earlier, Porella species are divided by tasting. One is pungent and the other is non-pungent. The former group is very hot when one chews the fresh specimens. The pungent group (Type I) constantly contains drimane-type sesquiterpenoids including a hot-tasting drimane sesquiterpedial, polygodial (**47**). The species belonging to the Type I also produce pinguisane and/or aromadendrane type sesquiterpenoids. Type II produces the characteristic sacculatane-type diterpenoids which have not yet been found in any other plant groups. Type III includes the species which produce mainly pinguisane-type sesquiterpenoids. Type IV elaborates both sacculatanes and pinguisanes. *P. japonica* and *P. acutifolia* subsp. *tosana* have been classified into Type IV, because they produce the characteristic germacranolides and guaianolides as well as pinguisanes as the major components. Type V is also specific since this group produces rare naturally occurring africane-type sesquiterpenoids as the major components The different genus, *Macvicaria ulophylla* belongs to the same Porellaceae is very closely related to Type II of *Porella* species because it elaborates sacculatal as the main component.

3.3 Chemosystematics of *Frullania*

The *Frullania* species are the small epiphytic liverworts and there are *ca*. 500 species in the world. The most important chemical markers of this species are eremophilanolides and eudesmanolides. Wood-cutters in Europe and America cause the miserable allergenic contact dermatitis when they contact with *Frullania* species possessing sesquiterpene with an α-methylene-γ-lactone. Consequently, people having some allergenic properties should not touch the host plants on which allergen-containing *Frullania* species grow. The *Frullania* species are mainly divided into six groups. Type I: produces sesquiterpene lactone, Type II: sesquiterpene lactone-bibenzyl, Type III: bibenzyl, Type IV: diterpene-bibenzyl, Type V: monoterpene, Type VI: diterpene. Among them, the species including sesquiterpene lactones are the most popular. Occasionally, the same liverwort species produce the totally different secondary metabolites in the different locations. *F. tamarisci* subsp. *obscura* growing in Asia which belongs to Type II, is further divided into two subtypes, Type-T and Type-O.[94] Type-T elaborates the unusual pacifigorgiane-type sesquiterpene alcohol, tamariscol and 5α,7β(H)-eudesm-4α,6α-diol as the major components, whereas Type-O lacks these two components while eudesmanolides such as 4-epiarbusculin A (**65**) are predominant. Representatives of Type-T have been found in high mountain at 1500-3000 meter altitude and in the northern part of Japan (42-44°N), while Type-O occurs more frequently at lower altitudes between 32-40°N. Type T is chemically resembles the American *F. tamarisci* subsp. *asagrayana* and European *F. tamarisci* subsp. *tamarisci* which produce tamariscol, although the sesquiterpene lactones present are different. The American *F. tamarisci* subsp. *nisquallensis* is chemically different from *F. tamarisci* subsp. *asagrayana* and *F. tamarisci* subsp. *tamarisci*, except for the presence of (-)- frullanolide (**54**). The Taiwanese *F. nepalensis* contains tamariscol as a minor component, but its sesquiterpene lactones differ from those in the *F. tamarisci* complex containing tamariscol. The *Frullania* are close morphologically to the *Porella*. However, the secondary metabolites found in *Frullania* species are totally different from those of *Porella* species, except for the presence of germacranolides, the precursors of eudesmanolides, eremophilanolides and guaianolides in both genera. The ancestor of the *Frullania* might be quite different from that of the *Porella.*

In conclusion, liverworts are very small plant group, however, the content of the secondary metabolites are extremely high since they contain a high amount of oil in each cell. Many compounds isolated from liverworts have not yet been found in the other organisms. Chemically, mosses and hornworts which are included in bryophytes are quite different. Thus these classes might originate from quite different ancestors. Briefly speaking, the secondary metabolites of the Hepaticae are similar to those found in brown algae. On the other hand, the Musci and the Anthocerotae have no chemical affinity with algae, except for the presence of highly unsaturated fatty acids in three different groups.

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