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Review paper

PINGUISANE-TYPE SESQUITERPENOIDS, UNIQUE SECONDARY METABOLITES OF LIVERWORTS: A REVIEW

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Abstract. *This review summarizes the current knowledge on pinguisane-type sesquiterpenoids, unique secondary metabolites of Hepaticae, their isolation, structural elucidation, possible biosynthetic pathways, total synthesis, and biological/pharmacological activities. Overall, 76 compounds are presented, the majority of which are isolated from or detected in liverwort material as secondary metabolites, while 4 compounds represent artifacts of the isolation procedure. Pinguisane-type sesquiterpenes can be used as chemotaxonomic markers for different taxonomic levels of liverworts, as well as to delineate chemical as well as evolutionary relationships within the Marchantiophyta phylum.*

Key words: *liverworts, natural products, pinguisanes, sesquiterpenoids*

1. INTRODUCTION

Phylum Marchantiophyta (Hepatophyta, Hepaticae), commonly referred to as hepatics or liverworts, together with hornworts (Anthocerotophyta) and mosses (Bryophyta), are considered by the English name of bryophytes, a term having no taxonomic status (subkingdom Bryobiotina) (Glime, 2021). Depending on the author, synonyms, and taxon consistency, the division covers up to 10,000 species divided into 74 families, and over 300 genera (Veljić et al., 2018). Liverworts, considered the oldest aquatic-terrestrial plants in the world, are first mentioned in literature in 1753 by Carl Linnaeus when he determined and named *Marchantia* in his *Species Plantarum* (Linnaeus, 1753). Phylum

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Marchantiophyta is distinguished from phyla Bryophyta and Anthocerotophyta, in addition to other distinctiveness (dorsoventral orientation, unicellular rhizoids, inoperculate capsules, absence of a columella in the center of the capsule, and no stomata in the capsule), by the presence of cellular oil bodies, membrane-bound organelles, rich in aromatic compounds and lipophilic terpenoids suspended in a carbohydrate-rich or proteinaceous matrix. The first description of these intracellular organelles in liverworts was given by Hübener, in 1834 (Hübener, 1834), and a year later, by Mirbel (Mirbel, 1835). The initially introduced terms, cell bodies (Gottsche, 1843) and cell vesicles (Von Holle, 1857), were replaced by the current name, oil bodies, on the account of their fatty nature (Pfeffer, 1874). Suire and coworkers proved that the oil body is an active cell compartment representing the site of the intracellular isoprenoid synthesis, present in all mature cells of both diploid and haploid generation in Jungermanniopsida and Haplomitrales, and in the specialized idioblasts of Marchantiopsida and Treubiales (Suire et al., 2000).

Liverworts produce a number of secondary metabolites, such as mono-, sesqui-, di-, and triterpenoids, as well as steroids, lipids, carbohydrates, and sulfur-containing substances (Asakawa, 1995). Some sesquiterpenoids found in liverworts, excluding drimane-, germacrane-, and guajane-type ones, represent the enantiomers of those found in higher plants, while some terpenoid skeletons, for example, pinguisanes, are exclusively found in Hepaticae, so far (Xie and Lou, 2009). Pinguisane-type sesquiterpenes possess a unique *cis*-fused 1,2,6,7-tetra-methylbicyclo[4.3.0]nonane ring system, with two pairs of vicinal stereogenic carbons and four *cis*-methyl groups (Fig. 1). Since the first member of this class was identified, up to now, around 80 pinguisanes have been reported mainly from families of the order Jungermanniales and the representatives of the family Aneuraceae (Metzgeriales). Pinguisane-type sesquiterpenes show a remarkable degree of diversity, i.e. functional groups, alcohols, esters, ethers, dienes, ketones, aldehydes, butenolides, furan- and spiro-moieties, etc. This peculiarity may be used in resolving taxonomic problems.

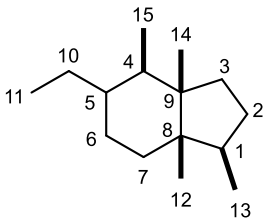


Fig. 1 The pinguisane skeleton (3-ethyl-1,2,6,7-tetramethylbicyclo[4.3.0]nonane) with the numbering of carbon atoms

This review summarizes the current knowledge on pinguisane-type sesquiterpenoids, their isolation, structural elucidation, systematic and evolutionary significance, as well as biological activities, including cytotoxic, immunomodulatory, antimicrobial, antioxidant, etc. Additionally, since their carbon skeleton appears to be inconsistent with the isoprene rule, possible biosynthetic pathways are proposed, as well as some of the developed synthetic approaches.

2. Structural Diversity of Pinguisane Metabolites of Hepaticae

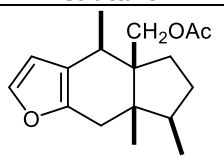
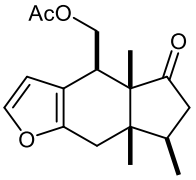
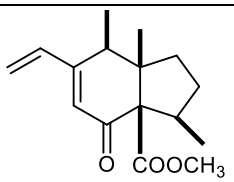
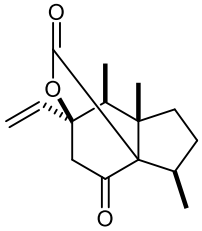
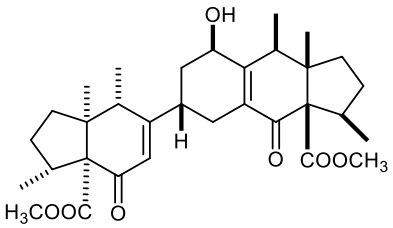
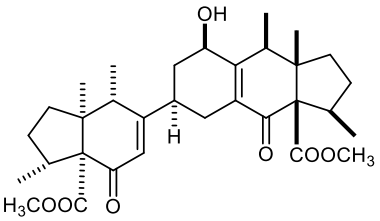
The following section deals with pinguisane-type sesquiterpene compounds from various liverwort species. More than 70 pinguisanes secondary metabolites have been identified, isolated from liverworts extracts and/or essential oil and/or synthesized (Table 1), displaying a wide spectrum of structural diversity, many of which possess interesting and significant biological/pharmacological activities.

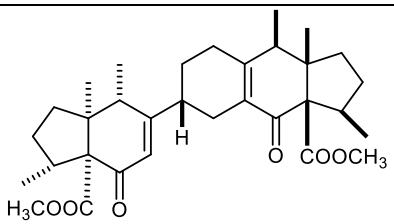
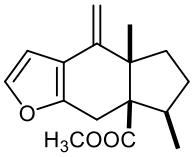
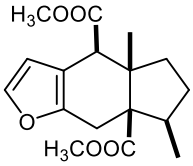
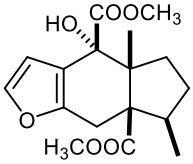
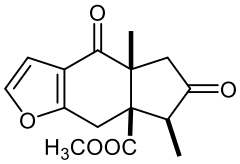
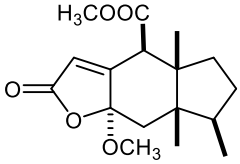
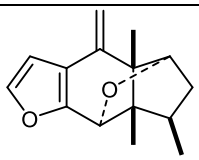
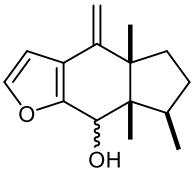
2.1. Isolation and structure elucidation of pinguisane-type terpenoids

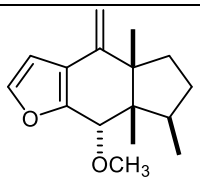
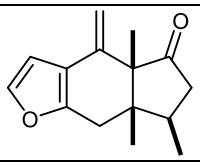
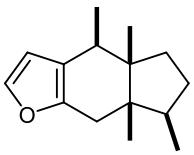
Orders Jungermaniales (families Lejeuneaceae, Lepidolaenaceae, Lepidoziaceae, Plagochilaceae, Porellaceae, Ptilidiaceae) and Metzgeriales (only the family Aneuraceae) of liverworts represent significant sources of pinguisane sesquiterpenes (Gauvin-Bialecki et al., 2010). The first member of the pinguisane-type skeleton class of compounds was isolated in 1969 by Benešová and coworkers from *Aneura pinguis* (L.) Dumort. and the structure of this furanosesquiterpene ketone, named **pinguisone** (Table 1), was deduced after extensive ^{1}H NMR decoupling experiments and derivatization reactions (Benešová et al., 1969). The second isolated pinguisane-type sesquiterpenoid was the deoxygenated compound named **deoxopinguisone** isolated from *Ptilidium ciliare* (L.) Hampe. Its structure was determined based on the correlation of its IR and ^{1}H NMR spectra with those of pinguisone and further confirmed by comparison of its spectra with those of synthetic deoxopinguisone obtained by the reduction of pinguisone isolated from *A. pinguis* (Krutov et al., 1973). After the first GC-MS detection in *Wettsteinia schusteriana* Grolle, deoxopinguisone was detected in a range of *Lejeunea* Lib. species (Asakawa et al., 1980a; 1980b; Gradistein et al., 1981), various *Porella* L. species, while it was isolated from a CH_2Cl_2 extract of *P. vernicosa* Lindb. (Asakawa et al., 1976a; 1976b; 1978; 1979a; 1979b; 1979c; 1979d; 1980d; Cullmann and Becker, 1999; Ono et al., 1996). The same sesquiterpene compound was isolated from Et_2O extracts of *Trichocolepsis sacculata* (Mitt)S.Okamura, *Ptilidium ciliare* (Asakawa et al., 1981a; Krutov et al., 1973), *Dicranolejeunea yoshinagana* (S.Hatt.) Mizut., *Trocholejeuna sandvicensis* Mizut., (Asakawa et al., 1977; 1979d; 1980c), and *Plagiochila alternans* Lindenb. & Gottsche, and acetone extract of *Ptychanthus striatus* (Lehm. & Lindenb.) Nees, therefore, representing one of the most commonly found pinguisane-type compound (Asakawa et al., 1980b; Nagashima et al., 1991; 1999; Takeda et al., 1981; Toyota et al., 1995).

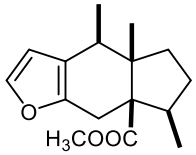
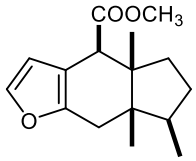
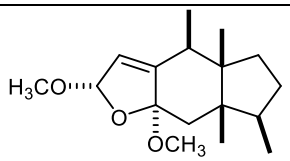
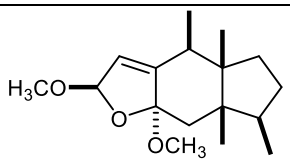
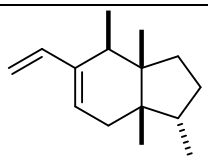
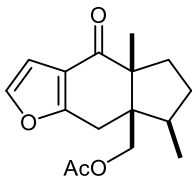
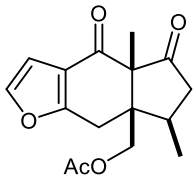
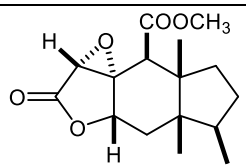
Deoxopinguisone derivatives **9-formyldeoxopinguisone** and **14-acetoxydeoxopinguisone** were isolated from the Et_2O extract of *Dicranolejeunea yoshinagana* and their structures were elucidated by ^{1}H and ^{13}C NMR, and IR analysis, as well as by $LiAlH_4$ reduction reaction that yielded the same primary alcohol in both cases (Toyota et al., 1995). **15-Acetoxypinguisone** was detected in the $CDCl_3$ extract of *Cryptothallus mirabilis* Malmb., by comparison of its spectroscopic data with the ones of pinguisone and by NOE difference experiments (Rycroft and Cole, 1998). **Methyl esters** of **deoxopinguisone-15-oic** and **deoxopinguisone-12-oic acids** were isolated from the dichlormethane extract of *Porella canariensis* (F.Weber) Underw. (Cullmann and Becker, 1999).

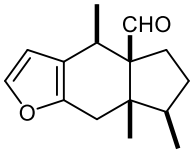
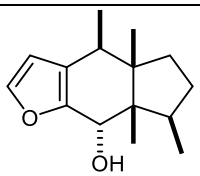
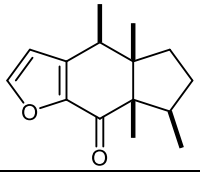
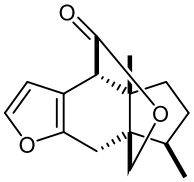
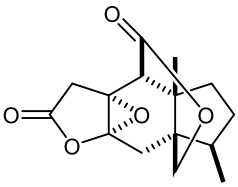
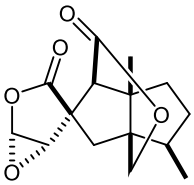
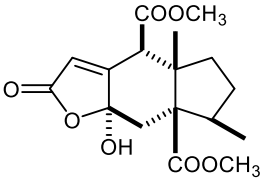
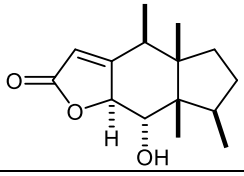
Table 1 Structures of pinguisane-type sesquiterpenoids with the representative Hepaticae species they are isolated from

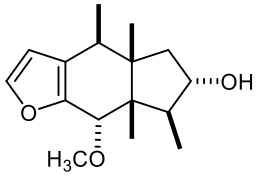
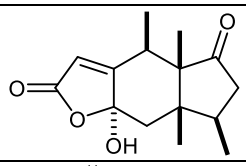
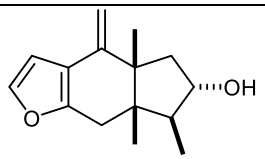
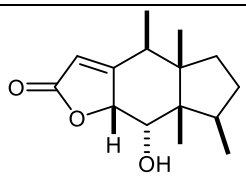
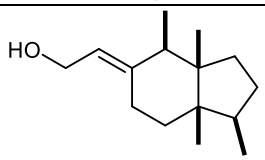
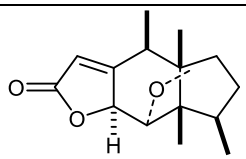
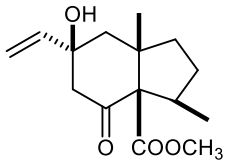
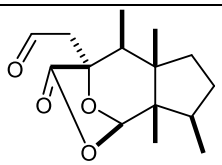
No	Structure	Name	Plant Species	Reference
1.		14-Acetoxydeoxopinguisone	*Dicranolejeunea yoshinagana* (Hatt.) Mizut. (Lejeunaceae)	Toyota et al., 1995
2.		15-Acetoxypinguisone	*Cryptothallus mirabilis* Malmb. (Aneuraceae)	Rycroft and Cole, 1998
3.		Acutifolone A	*Porella acutifolia* subsp. *tosana*.(Steph.) Hatt. (Porellaceae)	Hashimoto et al., 1998; Hashimoto et al., 2000
4.		Acutifolone B	*Porella acutifolia* subsp. *tosana* (Steph.) Hatt. (Porellaceae)	Hashimoto et al., 1998; Hashimoto et al., 2000
5.		Bisacutifolone A	*Porella acutifolia* subsp. *tosana* (Steph.) Hatt. (Porellaceae)	Hashimoto et al., 1998; Hashimoto et al., 2000
6.		Bisacutifolone B	*Porella acutifolia* subsp. *tosana* (Steph.) Hatt. (Porellaceae)	Hashimoto et al., 1998; Hashimoto et al., 2000

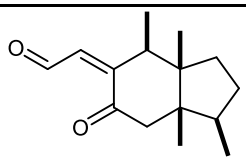
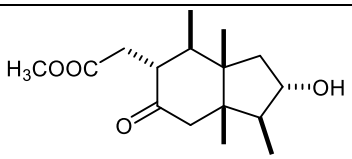
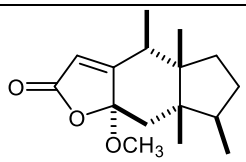
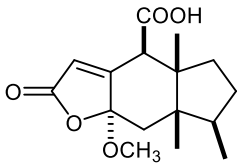
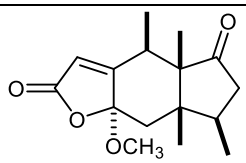
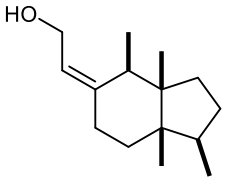
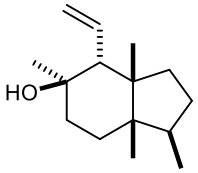
7.		Bisacutifolone C	*Porella acutifolia* subsp. *tosana* (Steph.) Hatt. (Porellaceae)	Hashimoto et al., 2000
8.		Bryopterin A	*Bryopteris filicina* (Sw.) Ness (Lejeuneaceae)	Nagashima et al., 1994
			Porella viridissima (Mitt.) Grolle (Porellaceae)	Métoyer et al., 2019
9.		Bryopterin B	*Bryopteris filicina* (Sw.) Ness (Lejeuneaceae)	Nagashima et al., 1994
			Porella grandiloba Lindb. (Porellaceae)	Tazaki et al., 1998
10.		Bryopterin C	*Bryopteris filicina* (Sw.) Ness (Lejeuneaceae)	Nagashima et al., 1994
11.		Bryopterin D	*Bryopteris filicina* (Sw.) Ness (Lejeuneaceae)	Nagashima et al., 1994
12.		4*β*-Carbometoxy-6*α*-metoxypinguis-6,11-olide	*Porella canariensis* (F. Weber) Underw. (Porellaceae) (Artifact)	Nagashima et al., 1996
13.		Dehydropinguisanin	*Trocholejeunea sanvicensis* Mizut. (Lejeuneaceae)	Asakawa et al., 1980b
14.		Dehydropinguisenol	*Trocholejeunea sanvicensis* Mizut. (Lejeuneaceae)	Asakawa et al., 1980b
			Trocholejeunea sanvicensis (Gott.) Mizut. (Lejeuneaceae)	Lahlou et al., 2000

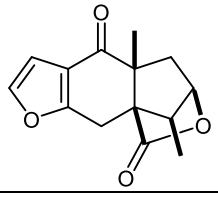
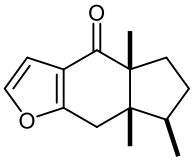
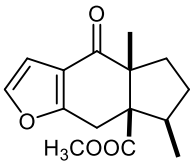
15.		Dehydropinguisenol methyl ether	*Trocholejeunea sanvicensis* Mizut. (Lejeuneaceae) (Artifact)	Tori et al., 1993
16.		Dehydropinguisone	*Plagiochilla retrospectans* (Ness) Ness (Plagiocilaceae)	Nagashima et al., 1994
17.		Deoxopinguisone	*Dicranolejeunea yoshinagana* (Hatt.) Mizut. (Lejeunaceae)	Toyota et al., 1995
			Ptychantus striatus (LEHM. et LINDENB.) Nees (Lejeunaceae)	Takeda et al., 1981
			Trocholejeunea sandvicensis Mizut. (Lejeunaceae)	Asakawa et al., 1980b
			Porella canarensis (F. Weber) Bryhn. (Porellaceae)	Cullman and Becker, 1999
			Porella platyphylla (L.) Pfeiff (Porellaceae)	Asakawa et al., 1979a
			Porella vernicosa Lindb. (Porellaceae)	Ono et al.,, 1996
			Plagiochila alterans Lindbg. and Gott. (Plagiocilaceae)	Nagashima et al., 1991
			Ptilidium ciliare (L.) Hampe. (Ptilidiaceae)	Nagashima et al., 1999
			Trichocoleopsis sacculata (Mitt.) S. Okamura (Ptilidiaceae)	Asakawa et al., 1981b

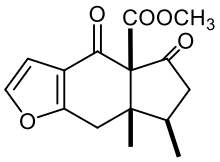
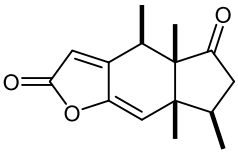
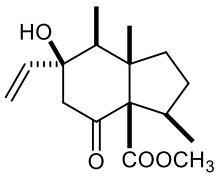
18.		Deoxopinguisone-12-oic acid methyl ester	*Porella canariensis* (F. Weber) Bryhn. (Porellaceae)	Cullmann and Becker, 1999
19.		Deoxopinguisone-15-oic acid methyl ester (Deoxopinguisone methyl ester)	*Porella canariensis* (F. Weber) Underw. (Porellaceae)	Cullmann and Becker, 1999
			Porella vernicosa Lindb (Porellaceae)	Ono et al., 1996
20.		6*α*,11*α*-Dimethoxypinguis-5(10)-ene	*Trocholejeunea sandvicensis* Mizut. (Lejeunaceae) (Artifact)	Tori et al., 1993
21.		6*α*,11*β*-Dimethoxypinguis-5(10)-ene	*Trocholejeunea sandvicensis* Mizut. (Lejeunaceae) (Artifact)	Tori et al., 1993
22.		1-*Epi*-*α*-pinguisene	*Drepanolejeunea madagascariensis* (Steph.) (Lejeuneaceae)	Gauvin-Bialecki et al., 2010
23.		6,11-Epoxy-15-nor-4-oxo-5,10-pinguisadien-12-acetate	*Porella recurva* (Taylor) Kuhnem. (Porellaceae)	Van Klink et al., 2002
24.		6,11-Epoxy-15-nor-3,4-dioxo-5,10-pinguisadien-12-acetate	*Porella recurva* (Taylor) Kuhnem. (Porellaceae)	Van Klink et al., 2002
25.		5*α*,10*α*-Epoxy-pinguisane-11,6-olide-15-carboxylic acid methyl ester	*Porella navicularis* (Lehm. et Lindenb.) Lindb. (Porellaceae)	Bungert et al., 1998

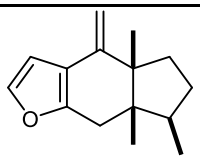
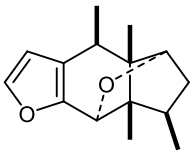
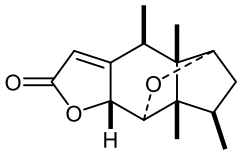
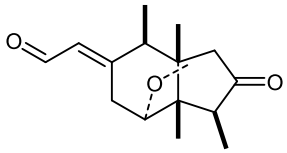
26.		9-Formyl deoxopinguisone	*Dicranolejeunea yoshinagana* (Hatt.) Mizut. (Lejeuneaceae)	Toyota et al., 1995
27.		*α*-Furanopinguisanol	*Porella coradeana* (Huebener) Moore (Porellaceae)	Radulović et al., 2016
28.		Furanopinguisanone	*Porella cordaeana* (Huebener) Moore (Porellaceae)	Radulović et al., 2016
29.		Grandilobalide A	*Porella grandiloba* Lindb. (Porellaceae)	Tazaki et al., 1998
30.		Grandilobalide B	*Porella grandiloba* Lindb. (Porellaceae)	Tazaki et al., 1998
31.		Grandilobalide C	*Porella grandiloba* Lindb. (Porellaceae)	Tazaki et al., 1998
32.		6*α*-Hydroxy-4,8-dimethoxycarbonyl-pinguis-11,6-olide	*Porella grandiloba* Lindb. (Porellaceae)	Tazaki et al., 1998
33.		Hydroxyisopinguisanolide	*Brachiolejeunea chinantlana* (Lejeuneaceae)	Gradstein et al., 1981

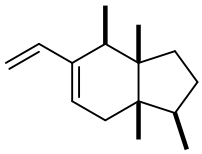
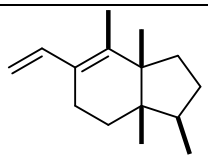
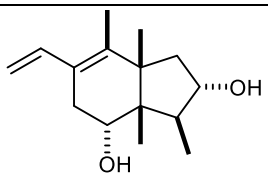
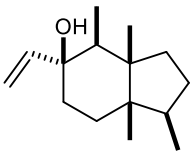
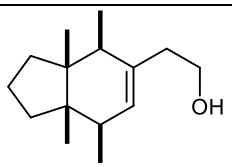
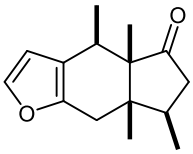
34.		2-Hydroxy-7-methoxydeoxopinguisone	*Porella platyphylla* (L.) Pfeiff. (Porellaceae)	Connoly, 1990
35.		6*α*-Hydroxy-3-oxo-pinguis-5(10)-ene-11,6-olid	Axenic culture of *Aneura pinguis* (L.) Dumort. (Aneuraceae)	Tazaki et al., 1996
36.		2-Hydroxypinguisanene	*Porella platyphylla* (L.) Pfeiff. (Porellaceae)	Connoly, 1990
37.		Hydroxypinguisanolide	*Brachiolejeunea chinantlana (Lejeuneaceae)*	Gradstein et al., 1981
38.		Isonaviculol	*Frullanoides densifolia* Radii (Lejeuneaceae)	Tori et al., 1993
39.		Isopinguisanolide	*Ptilidium pulcherrimum* (Weber) Hampe (Ptilidiaceae)	Asakawa et al., 1981a
40.		7-Keto-8-carbomethoxypinguisenol	*Porella acutifolia* subsp. *tosana* (Porellaceae)	Toyota et al., 1991
			Porella canariensis (F. Weber) Bryhn (Porellaceae)	Cullman and Becker, 1999
41.		Lejeuneapinguisanolide	*Trocholejeunea sandvicensis* (Gott.) Mizut. (Lejeuneaceae)	Lahlou et al., 2000

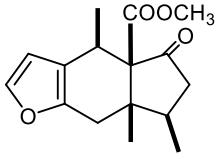
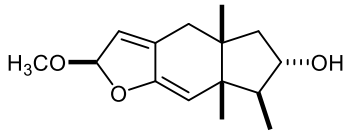
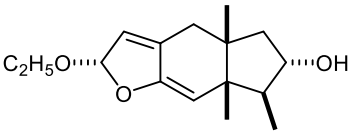
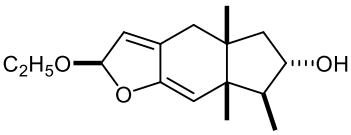
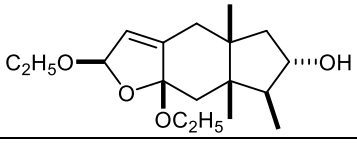
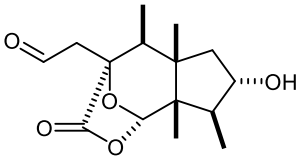
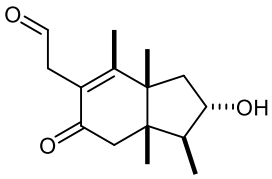
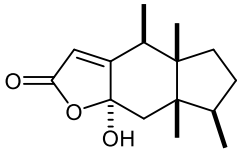
42.		Lejeuneapinguisenone	*Trocholejeunea sandvicensis* (Gott.) Mizut. (Lejeuneaceae)	Lahlou et al., 2000
43.		Methyl 2*α*-hydroxy-6-oxo-11-pinguisanoate	*Porella platyphylla* (L.) Pfeiff. (Porellaceae)	Buchanan et al., 1996
44.		6*α*-Metoxypinguis-5(10)-en-11,6-olide	*Porella navicularis* (Lehm. et Lindenb.) Lindb. (Porellaceae)	Bungert et al., 1998
45.		6*α*-Metoxypinguis-5(10)-en-11,6-olide-15-carboxylic acid	*Porella navicularis* (Lehm. et Lindenb.) Lindb. (Porellaceae)	Bungert et al., 1998
46.		6*α*-Metoxy-3-oxo-pinguis-5(10)-ene-11,6-olide	Axenic culture of *Aneura pinguis* (L.) Dumort. (Aneuraceae)	Tazaki et al., 1996
47.		Naviculol	*Porella navicularis* (Lehn. & Lindenb.) Pfeiff. (Porellaceae)	Toyota et al., 1989a; Bungert et al., 1998
			Frullanoides densifolia Radii (Lejeuneaceae)	Tori et al., 1993
			Bazzania novae-zelandiae (Mitt.) (Lepidozieaceae)	Nagashima et al., 2010
48.		Neopinguisenol	*Dicranolejeunea yoshinagana* (Hatt.) Mizut. (Lejeuneaceae)	Toyota et al., 1995

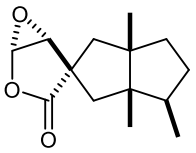
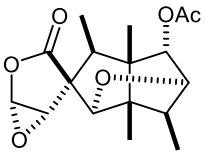
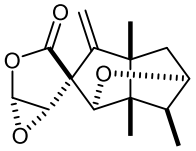
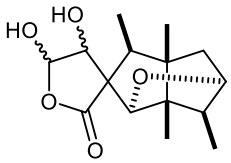
49.		Norpinguisanolide	*Porella elegantula* (Mont.) E.A.Hodgs. (Porellaceae)	Fukuyama et al., 1988
50.		Norpinguisone	*Porella elegantula* (Mont.) E.A.Hodgs. (Porellaceae)	Fukuyama et al., 1988
			Porella navicularis (Lehn. & Lindenb.) Pfeiff. (Porellaceae)	Toyota et al., 1989a
			Porella canariensis (F. Weber) Bryhn. (Porellaceae)	Cullman and Becker, 1999
			Porella vernicosa Lindb. (Porellaceae)	Ono et al., 1996
			Porella chilensis (Lehm. & Lindenb.) Trevis (Porellaceae)	Gilabert et al., 2011
			Porella recurva (Taylor) Kuhnem (Porellaceae)	Van Klink et al., 2002
			Porella densifolia (Stephani) S. Hatt. (Porellaceae)	Qang and Asakawa, 2010
51.		Norpinguisone 12- acetate (Norpinguisone methyl ester)	*Bryopteris filicina* (Sw.) Ness (Lejeuneaceae)	Nagashima et al., 1994
			Porella canariensis (F. Weber) Bryhn. (Porellaceae)	Cullman and Becker, 1999
			Porella chilensis (Lehm. & Lindenb.) Trevis (Porellaceae)	Gilabert et al., 2011
			Porella cordaeana (Huebener) Moore (Porellaceae)	Toyota et al., 1989b
			Porella densifolia (Stephani) S. Hatt.	Qang and Asakawa, 2010

			(Porellaceae)	
			Porella elegantula (Mont.) E.A.Hodgs. (Porellaceae)	Fukuyama et al., 1988
			Porella grandiloba Lindb. (Porellaceae)	Tazaki et al., 1998
			Porella navicularis (Lehn. & Lindenb.) Pfeiff. (Porellaceae)	Toyota et al., 1989a
			Porella navicularis (Lehm. & Lindenb.) Pfeiff (Porellaceae)	Bungert et al., 1998
			Porella recurva (Taylor) Kuhnem (Porellaceae)	Van Klink et al., 2002
			Porella vernicosa Lindb (Porellaceae)	Ono et al., 1996
			Porella viridissima (Mitt.)Grolle (Porellaceae)	Métoyer et al., 2019
52.		Norpinguisonon methyl ester	*Aneura pinguis* (L.) Dumort. (Aneuraceae)	Asakawa, 1982b
53.		3-Oxo-pinguis-5(10),6-diene-11,6-olide	Axenic culture of *Aneura pinguis* (L.) Dumort. (Aneuraceae)	Tazaki et al., 1996
54.		7-Oxopinguisenol-12-methyl ester (7-Ketopinguisenol-12-oic acid methyl ester; 7-keto-8-carbometoxy-pinguisenol)	*Porella acutifolia* subsp. *tosana* (Steph.) Hatt. (Porellaceae)	Toyota et al., 1991; Hashimoto et al., 2000
			Porella canariensis (F. Weber) Bryhn (Porellaceae)	Cullmann and Becker, 1999
			Porella perrottiana (Mont.) Trevis. (Porellaceae)	Komala et al., 2011

55.		Pinguisanene (Dehydrodeoxopinguisone)	*Ptychanthus striatus* (LEHM. et LINDENB.) Nees (Lejeunaceae)	Takeda et al., 1981
56.		Pinguisanin	*Porella cordaeana* (Huebener) Moore (Porellaceae)	Toyota et al., 1989a
			Porella platyphylla (L.) Pfeiff (Porellaceae)	Asakawa et al., 1979a; Nagashima et al., 1996; Clarke et al., 2006
			Ptilidium ciliare (L.) Hampe (Ptilidiaceae)	Nagashima et al., 1999
			Ptilidium pulcherrimum (Weber) Hampe (Ptilidiaceae)	Asakawa et al., 1981a
			Trocholejeunea sandvicensis Mizut. (Lejeuneaceae)	Asakawa et al., 1980b
57.		Pinguisanolide	*Porella platyphylla* (L.) Pfeiff. (Porellaceae)	Asakawa et al., 1979a
			Trocholejeunea sandvicensis Mizut. (Lejeuneaceae)	Asakawa et al., 1980b
			Ptilidium pulcherrimum (Weber) Hampe (Ptilidiaceae)	Asakawa et al., 1981a
58.		Pinguisenal	*Trocholejeunea sandvicensis* Mizut. (Lejeuneaceae)	Asakawa et al., 1980b
			Ptilidium pulcherrimum (Weber) Hampe (Ptilidiaceae)	Asakawa et al., 1981a

59.		*α*-Pinguisene	*Porella canariensis* (F. Web.) Bryhn. (Porellaceae)	Cullman and Becker, 1999
			Porella viridissima (Mitt.) Grolle (Porellaceae)	Métoyer et al., 2019
60.		*β*-Pinguisene	*Porella viridissima* (Mitt.) Grolle (Porellaceae)	Métoyer et al., 2019
61.		*β*-Pinguisenediol	*Porella platyphylla* (L.) Pfeiff. (Porellaceae)	Asakawa et al., 1979a; Buchanan et al., 1996
62.		*α*-Pinguisenol	*Porella vernicosa* Lindb. (Porellaceae)	Ono et al., 1996
			Porella canariensis (F. Weber) Underw. (Porellaceae)	Cullmann and Becker, 1999
			Porella chilensis (Lehm. & Lindenb.) Trevis. (Porellaceae)	Gilabert et al., 2011
			Porella viridissima (Mitt.) Grolle (Porellaceae)	Métoyer et al., 2019
			Bazzania novae-zelandiae (Mitt.) (Lepidoziaceae)	Nagashima et al., 2010
63.		5-Pinguisen-11-ol	*Porella navicularis* (Lehm. et Lindenb.) Lindb. (Porellaceae)	Bungert et al., 1998
64.		Pinguisone	*Trichocoleopsis sacculata* (Mitt.) S. Okamura (Lejeuneaceae)	Asakawa et al., 1981b
			Axenic culture of *Aneura pinguis* (L.) Dumort. (Aneuraceae)	Tazaki et al., 1996

65.		Pinguisone methyl ester	*Aneura pinguis* (L.) Dumort. (Aneuraceae)	Asakawa, 1982b
66.		Porellacetal A	*Porella cordaeana* (Huebener) Moore (Porellaceae)	Tan et al., 2017
67.		Porellacetal B	*Porella cordaeana* (Huebener) Moore (Porellaceae)	Tan et al., 2017
68.		Porellacetal C	*Porella cordaeana* (Huebener) Moore (Porellaceae)	Tan et al., 2017
69.		Porellacetal D	*Porella cordaeana* (Huebener) Moore (Porellaceae)	Tan et al., 2017
70.		Porellapinguisanolide	*Porella cordaeana* (Huebener) Moore (Porellaceae)	Toyota et al., 1989b
			Porella platyphylla (L.) Pfeiff. (Porellaceae)	Buchanan et al., 1996
71.		Porellapinguisenone	*Porella cordaeana* (Huebener) Moore (Porellaceae)	Toyota et al., 1989b
72.		Ptychanolactone	*Ptychanthus striatus* (LEHM. et LINDENB.) Nees (Lejeunaceae)	Hashimoto et al., 1993
			Bryopteris filicina (Sw.) Nees (Lejeuneaceae)	Nagashima et al., 2003

73.		Ptychanolide	*Ptychanthus striatus* (LEHM. et LINDENB.) Nees (Lejeunaceae)	Takeda et al., 1981; Takeda et al., 1983
			Frullanoides densifolia Radii (Lejeunaceae)	Tori et al., 1993
			Trocholejeunea sandvicensis (Gott.) Mizut. (Lejeuneaceae)	Tori et al., 1993
			Dicranolejeunea yoshinagana (Hatt.) Mizut. (Lejeuneaceae)	Toyota et al., 1995
			Porella canarensis (F. Weber) Bryhn. (Porellaceae)	Cullmann and Becker, 1999
74.		Spirodensifolin A	*Frullanoides densifolia* Radii (Lejeuneaceae)	Tori et al., 1992; Tori et al., 1993
75.		Spirodensifolin B	*Frullanoides densifolia* Radii (Lejeuneaceae)	Tori et al., 1992; Tori et al., 1993
76.		Spiropinguisanin	*Porella cordaeana* (Huebener) Moore (Porellaceae)	Toyota et al., 1989b

Investigating the *Porella* species, *P. vernicosa* and *P. densifolia*, in 1976, Asakawa first mentioned the structures which were later established to be, ***α*-pinguisene** and ***β*-pinguisene**, during the determination of, the until then unknown, **pinguisenol** (Asakawa et al., 1976a). ***α*-Pinguisenol**, also known as just pinguisenol, was isolated from the members of the *P. vernicosa* complex (*P. macroloba* and *P. gracillima*) (Asakawa et al., 1978), as well as from the CH_2Cl_2 extract of *P. canariensis* and the Et_2O extracts of *P. chilensis*, *P. vernicosa* and *Bazzania novae-zelandiae*, while it was only detected in *P. viridissima* (Cullmann and Becker, 1999; Gilabert et al., 2011; Métoyer et al., 2019; Nagashima et al., 2010; Ono et al., 1996). This important compound is thought to be the precursor for many other pinguisanes, such as ***α*-pinguisene**, ***β*-pinguisene**, **deoxopinguisone**, **deoxopinguisone-methyl ester**, **norpinguisone**, and **norpinguisone methyl ester**. The first isolation of the readily obtained pinguisenol dehydration derivative, ***α*-pinguisene**, was from the *Drepanolejeunea*

madagascariensis (Gauvin-Bialecki, 2010). After that, ***α*-pinguisene** was isolated from the Et_2O and CH_2Cl_2 extracts of two *Porella* species, *P. elegantula* and *P. canariensis*, respectively, while it was only detected in the *P. viridissima* (Cullmann and Becker, 1999; Métoyer et al., 2019). ***β*-Pinguisene**, with the double bond between C-5 and C-4, instead of C-5 and C-6, as in *α*-pinguisene, was detected in *P. viridissima* (Métoyer et al., 2019). **Pinguisanene**, a compound with a double bond between C-4 and C-15, was isolated from the acetone extract of the *Ptychanthus striatus* (Takeda et al., 1981). **1-*Epi*-*α*-pinguisene**, differing from *α*-pinguisene only in the orientation of the C-13 methyl group, was detected in *Drepanolejeunea madagascariensis*, *Porella obtusata* and *Ptilidium ciliare* (Gauvin-Bialecki, 2010; Joulain and Köning, 1998). **Pinguisenal**, pinguisane-type sesquiterpene with a five-membered ketone moiety, ether linkage between C-3 and C-7, and an aldehyde group at C-11, was isolated from the diethyl-ether extracts of Japanese *Trocholejeuna sandvicensis* and French *Ptilidium pulcherimum* (Asakawa et al., 1980b; 1981a). **Methyl 2*α*-hydroxy-6-oxo-11-pinguisanoate**, a pinguisanoic acid sesquiterpenoid derivative, was isolated from the methanol extract of *Porella platyphylla* (Buchanan et al., 1996).

***β*-Pinguisenediol** was first isolated in 1979 from the Et_2O extract of *P. platyphylla* (Asakawa et al., 1979a) and then, in 1996, from the MeOH extract of the same liverwort (Buchanan et al., 1996). Two new natural products, ***α*-furanopinguisanol** and **furanopinguisanone,** were identified from the liverwort *P. cordaeana*, by Radulović and coworkers (Radulović et. al., 2016) who also revised a structure of a compound that was previously erroneously assigned to *α*-furanopinguisanol (Tori et al, 1993). **Naviculol**, a bicyclic sesquiterpene alcohol with the primary allylic hydroxyl group, was first isolated from the MeOH extract of *Porella navicularis* and its structure was determined by HRMS, IR, ^{1}H and ^{13}C NMR, as well as by its chemical transformation to monoacetate (Toyota et al., 1989a). Additionally, this compound was identified in the Et_2O extract of the same species (Bungert et al., 1998), as well as the Et_2O extracts of *Bazzania novae-zelandiae* (Nagashima et al., 2010) and *Frullanoides densifolia* (Tori et al., 1993). Moreover, in the Et_2O extract of *F. densifolia*, its (*E*)-geometrical isomer, **isonaviculol**, was identified (Tori et al., 1993).

Hydroxyisopinguisanolide and **hydroxypinguisanolide** were detected in the Et_2O extract of Columbian liverwort *Brachiolejeunea chinantlana*, subgenus *Plicolejeunea* (Gradistein et al., 1981). Unstable pinguisane-type sesquiterpene alcohol, **2-hydroxypinguisanene**, easily transformed into isopinguisanin in $CDCl_3$ in the NMR tube, and methoxylated alcohol **2-hydroxy-7-methoxydeoxopinguisone**, were isolated from the liverwort *Porella platyphylla* (Connoly, 1990). Neopinguisan-type alcohol, **neopinguisenol**, with the rearranged pinguisane skeleton, was isolated as a new compound from the Et_2O extract of *Dicranolejeunea yoshinagana* (Toyota et al., 1995). Moreover, **5-pinguisen-11-ol** was isolated from the Et_2O extract *Porella navicularis* depicting the variability of the hydroxyl group position for this type of skeleton (Bungert et al., 1998).

Further research on liverworts constituents resulted in the isolation of **pinguisanin**, a compound easily decomposed in air, and presence of mild acids. Up to now, pinguisanin was isolated from two *Porella* species, *P. platyphylla* (French, English and Switzerland specimens) and *P. cordaeana* (Oregon State specimens), and two *Ptilidium* species, *P. ciliare* and *P. pulcherimum* (Asakawa et al., 1979d; 1980b; 1981; Buchanan et al., 1996; Nagashima et al., 1999; Toyota et al., 1989a). Oxidation of pinguisane core in position 3 leads to **dehydropinguisone**, isolated from the Et_2O extract of *Plagiochilla retrospectans* (Nagashima et al., 1994). **Dehydropinguisanin** and **dehydropinguisenol** were isolated from the Et_2O extract of *Trocholejeuna sandvicensis* (Asakawa et al., 1980b; Lahlou et al., 2000).

Asakawa with his coworkers accomplished the first isolation of **norpinguisone** and **norpinguisone methyl ester**, compounds with a typical retro-Diels-Alder fragment ion at *m/z* 108 and a fragment ion at *m/z* 192 originating from successive *β*-cleavages followed by aromatization, in 1976, from *Porella vernicosa* (Asakawa et al., 1976a). After that, **norpinguisone** was isolated from different *Porella* species using various solvents (Et_2O, CH_2Cl_2, and MeOH) for extraction (Cullman and Becker, 1999; Fukuyama et al., 1988; Gilabert et al., 2011; Van Klink et al., 2002; Ono et al., 1996; Toyota et al., 1989a; Qang and Asakawa, 2010). **Norpinguisone methyl ester** was identified in, in total, 12 liverworts (Bungert et al., 1998; Cullman and Becker, 1999; Fukuyama et al., 1988; Gilabert et al., 2011; Van Klink et al., 2002; Métoyer et al., 2019; Nagashima et al. 1994; Ono et al., 1996; Tazaki et al., 1998; Toyota et al., 1989a; 1989b; Qang and Asakawa, 2010). The results of 2D long-range ^{13}C-^{1}H COSY experiments, obtained by Fukuyama and coworkers, implied that the assignments of the methoxycarbonyl group at C14 and the tertiary methyl group at C-12 in **norpinguisone methyl ester** must be revised, that these two groups should exchange places and the structure of the compound in question was revised to be methyl 4-oxonorpinguisan-12-oate (Fukuyama et al., 1988). Further research of *Porella* and *Aneura* species resulted in the identification of **methyl esters of pinguisone, norpinguisone**, and **norpinguisonon** (Asakawa, 1982b). **Norpinguisanolide**, pinguisane-type norsesquiterpene with a γ-lactone unit, was first isolated from the Et_2O extract of *Porella elegantula* (Fukuyama et. al., 1988). From the CH_2Cl_2 extract of *P. recurva* two new pinguisane-type norsesquiterpenoids with an acetate group at position 12 were isolated, **6,11-epoxy-15-nor-3,4-dioxo-5,10-pinguisadien-12-acetate** and **6,11-epoxy-15-nor-4-oxo-5,10-pinguisadien-12-acetate** (Van Klink et al., 2002).

Several products of the oxidation of the pinguisane ring were also reported. 2-Keto-norpinguisonmethyl ester, **bryopterin D**, was isolated from the Et_2O extract of Panaman *Bryopteris filicina* (Nagashima et al., 1994), along with **bryopterins A, B** and **C** (Nagashima et al., 1994). **7-Keto-8-carbomethoxypinguisenol (7-oxopinguisenol-12-methyl ester)** is an oxygenated pinguisane-type sesquiterpene compound found in the Et_2O extract of *Porella acutifolia* (Toyota et al., 1991), the CH_2Cl_2 extract of *P. canarensis* (Cullman and Becker, 1999) and the reextracted MeOH extracts of *P. perrottetiana* (Komala et al., 2011).

Two rearranged pinguisane-type sesquiterpenoids, **spirodensifolin A** and **B**, were isolated from the Et_2O extract of *Frullanoides densifolia* (Tori et al., 1992; 1993). The structure of spirodensifolin A was elucidated using extensive ^{1}H- and ^{13}C NMR experiments, as well as X-ray crystallographic analysis. The structure of spirodensifolin B was determined by the comparison of its NMR spectral data with those of spirodensifolin A. The spectral data resembled those of spirodensifolin A, except for the presence of two protons of an exomethylene group and the absence of a secondary methyl group and an acetoxy group (Tori et al., 1992).

Pinguisane-type lactones, **pinguisanolide** and **isopinguisanolide**, with an epoxide ring in their structures, have been detected in the *Porella platyphylla* (Asakawa et al., 1979a), *Trocholejeunea sandvicensis* (Asakawa et al., 1980b), as well as in the European specimens *Ptilidium pulcherrimum* (Asakawa et al., 1981a; Connoly, 1990). Another spiropinguisane, with an epoxide moiety, differing in the relative configuration of the lactone ring compared to pinguisanolide, named **ptychanolide**, was isolated from five liverwort species (Cullman and Becker, 1999; Takeda et al., 1981; Tori et al., 1992; 1993; Toyota et al., 1995). **Ptychanolactone** was present in two liverworts *Ptychanthus striatus* (Hashimoto et al., 1993) and *Bryopteris filicina* (Nagashima et al., 2003).

Spiropinguisanin, the spirolactone structurally similar to ptychanolide, was isolated from CH_2Cl_2 extract of *P. cordaeana* (Toyota et al., 1989b).

Grandilobalide A, a 15,12-olide compound with a δ-lactone ring, **grandilobalide B**, which differs from Grandilobalide A only in the presence of an epoxide at C-5 and C-6 in the α-position forming the 3,4-epoxy-γ-lactone, and the rearranged pinguisane-type compound **grandilobalide C**, with a spiro lactone moiety, were isolated from the Et_2O extract of *P. grandiloba* (Tazaki et al., 1998). HRMS, IR, UV, and NMR experiments were used to elucidate the structure of two new pinguisane-type sesquiterpenoids **acutifolone A** and **acutifolone B**, as well as three new Diels-Alder reaction-type dimeric pinguisane sesquiterpenoids **bisacutiofolones A**, **B** and **C**, as novel compounds from the Et_2O extracts of *P. acutifolia* subsp. *tosana* (Hashimoto et al., 1998; 2000).

Three pinguisane-derivatives with γ-lactone ring, **6α-methoxypinguis-5(10)-en-11,6-olide-15-carboxylic acid**, **6α-methoxypinguis-5(10)-en-11,6-olide** and **5α,10α-epoxypinguisane-11,6-olide-15-carboxylic acid methyl ester**, the later containing an additional epoxide ring, were isolated for the first time from the Et_2O extract of North American *P. navicularis* (Bungert et al., 1998). Moreover, three butenolides, **6α-hydroxy-3-oxopinguis-5(10)-en-11,6-olide**, the product of its methylatation **6α-methoxy-3-oxopinguis-5(10)-ene-11,6-olide,** and the product of its dehydration, **3-oxopinguis-5(10),6-dien-11,6-olide**, were isolated from the Et_2O extract of the axenic culture of *Aneura pinguis* gametophytes (Tazaki et al., 1996). **6α-Hydroxy-4,8-dimethoxycarbonylpinguis-11,6-olide**, a pinguisane derivative with α,β-conjugated-γ-lactone ring, two carbomethoxy groups at C-15 and C-12, and a hydroxy group at C-6, has been isolated from the liverwort *P. grandiloba* (Tazaki et al., 1998).

Porellacetales A-D were isolated from the Et_2O extract of Turkish specimens of *P. cordaeana* and their structures were determined using one- and two-dimensional NMR experiments (Tan et al., 2017). It was concluded that all porellacetals are pinguisane-type derivatives with an α-oriented hydroxyl group at C-2. Porellacetals A possesses β-oriented methoxy-, while porellacetals B and C possess α- and β- oriented ethoxy-group, respectively, at C-11, and they all contain conjugated double bonds. Porellacetal D does not contain a conjugated double bond system but contains β-oriented ethoxy groups at C-6 and C-11. Oregon State *P. cordaeana* CH_2Cl_2 extract contained two highly oxidized sesquiterpene lactones, **porellapinguisanolide** and **spiropinguisanin,** as well as a ketoaldehyde **porellapinguisenone** (Toyota et al., 1989b). Additionally, porellapinguisanolide was further detected in the MeOH extract of *P. platyphylla* (Buchanan et al., 1996).

Two novel compounds were identified from the Et_2O extract of *Trocholejeunea sandvicensis*, **lejeuneapinguisanolide**, a pinguisane-type sesquiterpene with a high degree of oxidation, and **lejeuneapinguisone** formed by the cleavage of the epoxide of the former one (Lahlou et al., 2000).

In the end, it is worth mentioning that during the identification of pinguisane-type secondary metabolites from liverworts, several artifacts, formed during the separation procedure, were identified. **Dehydropinguisenol methyl ether**, **6α,11α-dimethoxypinguis-5(10)-ene**, and **6α,11β-dimethoxypinguis-5(10)-ene,** were isolated from the *n*-hexane extract of *Trocholejeunea sandvicensis*, and can be considered as artifacts formed during the chromatographic separation of the extract when methanol and chloroform were used as eluents (Tori et al., 1993). Moreover, **4β-carbomethoxy-6α-methoxypinguis-6,11-olide**, was isolated from *Porella canariensis* MeOH extract and identified as an artifact of the isolation procedure (Nagashima et al., 1996).

2.2. Chemosystematic, chemotaxonomic and evolutionary significance of pinguisane-type terpenoids

Although the morphological classification of liverworts is difficult, due to their small gametophytes, the chemical complexity of their secondary metabolite profiles provides an insight into evolutionary relationships among genera, and the analysis of these profiles enables chemosystematics and chemotaxonomic investigations of liverworts (Asakawa 1982b; 1995; 2001; Asakawa, 2004; Gradistein et al., 1985; Rycroft, 2003). Oil bodies present in both the gametophytes and the sporophytes of liverworts, not only exhibit diverse morphological features (shape, number, size, color, distribution, etc.) but also vary in the secondary metabolite profiles.

The taxonomic significance of pinguisane-type sesquiterpenes lies in the fact that they can be used, as chemotaxonomic markers of the species or orders belonging to liverworts. Pinguisane-type sesquiterpenes are significant chemical markers of some species belonging to Lejeuneaceae, Porellaceae, Trichocoleaceae, and Aneuraceae (Riccardiaceae) families (Asakawa, 1982b). The same type of pinguisanes are produced by *Frulanoides densifolia*, *Trocholejeunea sandvicensis* and *Ptychantus striatus* (Lejeuneace family), and by *Porella* species, *P. navicularis*, *P. densifolia*, *P. platyphylla*, *P. japonica* (Porelaceae family), despite a significant morphological difference between these two families (Asakawa et al., 1980b). On the other hand, the morphological resemblance between genus *Bryopteris*, and the genus *Ptychanthus* is accompanied by the similarity in their pinguisane-type sesquiterpenoids profiles, since these secondary metabolites are produced as the major ones in both of these genera of Lejeunaceae family (Nagashima et al., 1994).

The pinguisanes profiles allow us also to distinguish clades within families; pinguisanin and deoxopinguisone are considered to be chemical markers of *Acrolejeuna* complex: *Acrolejeuna* species, *Trocholejeuna sanvicensis*, *Frullanoides densifolia*, while pinguisone, norpinguisone methyl ester, pinguisene and neopinguisenol are markers of Ptychanthinae and Brachiolejeuneinae clades, all belonging to the Lejeuneaceae family (Gradistein et al., 1988). The presence of 1-*epi*-*α*-pinguisene confirms the possible use of pinguisane-type sesquiterpenoids as characteristic chemical markers of the order Jungermanniales (Gauvin-Bialecki et al., 2010). Furthermore, pinguisane-type sesquiterpenes may be chemosystematic markers of Ptilidiaceae since deoxopinguisone found in *Ptilidium ciliare* (Krutov et al, 1973) has not been detected in *P. pulcherrimum* (Asakawa et al., 1981a). French *P. pulcherrimum* produces pinguisanin and pinguisanolide (Asakawa et al., 1981a; 1995) as the major pingusanes. Thus, the pinguisanes can be considered chemical markers of the genus *Ptilidium* (Nagashima et al., 1999).

Moreover, species can be divided into chemotypes depending on the presence of pinguisane sesquiterpenes. Genus *Porella*, widespread in humid habitats over the world, comprises two major chemotypes, a pungent (referring to taste), producing the intensely pungent drimane polygodial and related compounds, and a non-pungent one, producing large amounts of pinguisanes (Buchanan et al., 1996). Further classification of *Porella* species into chemotypes is accomplished through secondary metabolite profile screening. Based on chemical data, *Porella* species can be divided into, according to some authors (Ludwiczuk et al., 2011), six chemotypes (the drimane- (I), sacculatane- (II), pinguisane-sacculatane- (III), guaiane-germacrane- (IV), pinguisane- (V) and africane- (VI) types), or, according to others (Gilabert et al., 2011) into ten chemotypes (the drimanearomadendrane-pinguisame (I), sacculatane (II), pinguisane (III), pinguisane-sacculatane (IV), africanane (V), santalane-africanane-cyclofarnesane, guaiane (VII), germacrane-pinguisane-sacculatane

(VIII), germacrane-africanane-guaiane (IX), pinguisanes-aromadendranes- fusicoccanes (X) types). Thus, pinguisanes alone or as co-occurring metabolites can be used as chemotaxonomic markers of some chemotypes in *Porella* species. Even the species within a chemotype V described by Gilabert and coworkers (Gilabert et al., 2011) can be mutually differentiated based on the production of just norpinguisanes (*Porella recurva*) or pinguisanes (*P. cordaeana* and *P. navicularis*). The presence of the Diels-Alder reaction-type dimeric pinguisane sesquiterpenoids (bisacutifolones A-C) in the Et_2O extract of Japanese *P. acutifolia* subsp. *tosana* differentiates this *Porella* species from any other belonging to this family (Hashimoto et al., 2000). In addition, the same group of authors pointed out the existence of two chemotypes of *P. acutifolia* subsp. *tosana* in Japan, one producing bisacutifolones, and the other producing guaianolides (Hashimoto et al., 2000).

Plagiochila species are classified into twelve chemotypes among which, chemotype IX is the pinguisane-producing one (Asakawa, 1982b). Deoxopinguisone and dehydropinguisone are the main constituents of *P. alterans* and Peruvian *P. rosariensis*, both of which are very distinctive from other *Plagiochila* species and belong to pinguisane-type chemotype of the Plagiochilaceae (Asakawa, 1982b). It is also worth mentioning that it is possible, based on pinguisane sesquiterpenes, to distinguish chemotype I of the species *Trocholejeunea sandvicensis* (Lejeunaceae) containing pinguisanin, from chemotype II, which produces dehydropinguisanin, as the major compound (Asakawa et al., 2009).

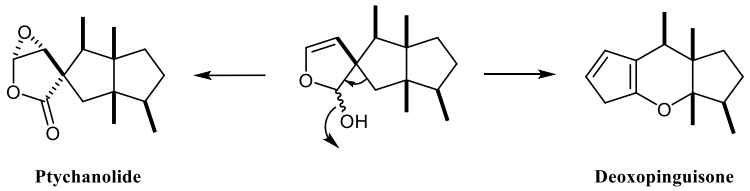
The chemical composition of liverworts may be used to delineate chemical, as well as evolutionary relationships within the Marchantiophyta at the genus or family level (Ludwiczuk et al., 2008). Identifying and relating pinguisane-type sesquiterpenes, as essential oil constituents of bryophyte taxa, may provide an insight into the evolutionary history and phylogenies trace patterns of shared ancestry between taxa. In line with this, it can be speculated that, based on the presence of the pinguisane sesquiterpenes in the essential oils of the plant species of genera Jungermaniales and Metzgeriales, these genera originate from the same ancestor (Asakawa, 1995). *Aneura pinguis* (Aneuraceae; Metzgeriales), *Ptilidium ciliare*, and *Ptilidium pulcherimum* (Ptilidiaceae; Jungermaniales) could be taxonomically and evolutionary correlated concerning the presence of pinguisane-type sesquiterpenes (Tori et al., 1993). Moreover, the chemical composition of *Aneura pinguis*, *Pellia endiviifolia* (Dicks.) Dumort., and *Makinoa crispata* (Stephani) Miyake, all belonging to the order Metzgeriales, particularly the presence of pinguisane-type sesquiterpenes and diterpene dialdehydes, similar to the chemical composition of *Porella* species and *Trichocolepsis sacculata*, confirm the close relationship between the enzymes responsible for the production of characteristic sesquiterpenes in Jungermanniales and Metzgeriales, which unites them in the subclass Jungermanniae (Schuster, 1979). Three species, *Trichocolea tomentella* (Ehrh.) Dumort., *Neotrichocolea bissetii* (Mitt.) S.Hatt., and *Trichocoleopsis sacculata*, belonging to the same family Trichocoleaceae, although morphologically similar, turned out to be chemically different. *T. sacculata* is classified into the suborder *Lepidolaenineae*, placed next to the suborders *Ptilidineae* and *Porellineae*, due to the presence of pinguisane-sesquiterpenes and sacculatane-type diterpenes that are found in *Porella* species and *T. sacculata*. This suggests that, despite the far morphological distance, these two species belong to close or even the same evolutionary line. However, chemical evidence suggests that *T. sacculata* is in a completely different evolutionary line from *N. bissethi* (Asakawa et al., 1981b).

Close biochemical relationship within the families Porellaceae and Lejeunace can be deduced from the presence of pinguisane-type sesquiterpenes in some *Porella*, *Lejeunea* and *Ptilidium* species (Asakawa, 1995; Asakawa et al., 1981a). Lejeuneaceae is the largest family of the Hepaticae, with mostly epiphytic species widespread in tropical rainforests. Subfamily Ptychanthoideae has been divided, on the bases of the presence or absence of striatene-, deoxopinguisone-, and pinguisane-type sesquiterpenoids, into a *Ptychanthus* complex (*Mastigolejeunea*, *Thysananthus*, *Ptychanthus* and *Tuzibeanthus*), an *Acrolejeunea* complex (*Acrolejeunea*, *Trocholejeunea* and *Frullanoides*), an *Archilejeunea* complex (*Spruceanthus* and *Archilejeunea*) and a *Lopholejeunea* complex (*Lopholejeunea* and *Marchesinia*) (Asakawa, 1982a). The close chemical relationship between *Frullanoides densifolia* (Lejeuneaceae) and *Porella japonica* (Porellaceae), is proven by the fact that both species produce pinguisanes and guaianolides (Arbiyanti, 1991). *P. cordaeana* and *P. navicularis* also produce closely related pinguisanes, rearranged pinguisanes, and monocyclofarnesanes like those found in *Frullanoides densifolia* (Toyota et al., 1989a; 1989b). *P. platyphylla* is considered more primitive than the other *Porella* species since its major constituents are only pinguisanes (Asakawa, 1988). Pinguisane- and the same norpinguisane-type sesquiterpenoids found in *Porella* species have been isolated from *Bryopteris filicina* belonging to the subfamily Bryopteridoideae (Lejeuneaceae) (Asakawa, 1988). The close relationship between *B. filicina* and *Ptychanthus striatus*, both in Ptychanthinae clade, besides their morphological resemblance, is additionally supported by the production of pinguisane-type sesquiterpenes. These results further support the conclusion that Lejeuneaceae and Porellaceae originate from a common ancestor (Asakawa, 1982b). Pinguisane-type sesquiterpenes could be the good chemical markers of the order Ptilidiales, *i.e.* pinguisanes produced by *Neotricholea bissetii*, pinguisanin, pinguisanolide, and *T. sacculata*, pinguisone, deoxopinguisone, placed Neotricholaceae family in the order Ptilidiales in a new classification of Marchantiophyta (Crandall-Stroller et al., 2009). Pinguisanes are chemical markers of the genus *Ptilidium*, as they are the major constituents of *Ptilidium* species (Nagashima et al., 1999) but have not been found in the species belonging to the genus *Mastigophora* (Ptilidiaceae) that could indicate that these two families do not have a common ancestor.

2.3. Biosynthesis of pinguisane-type terpenoids – unique, non-isoprenoid liverwort secondary metabolites

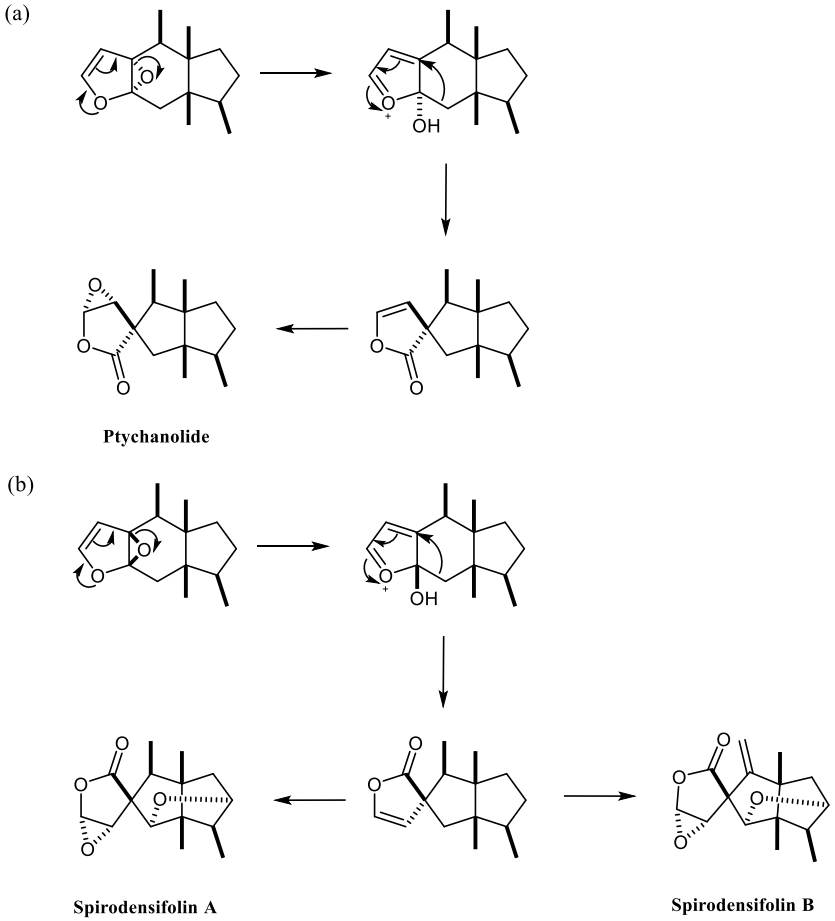
The biosynthesis of sesquiterpenes occurs following the principle of the biogenetic isoprene rule, also known as Ružička rule, according to which sesquiterpenes are made up of three isoprene units and their biosynthesis involves farnesyl pyrophosphate unit, derived from acetyl coenzyme A (Ružička, 1953). Fossil evidence and phylogenetic studies suggest that the first land plants were liverwort-like, thus metabolic pathways of liverworts, their adaptive strategies and evolutionary mechanisms may help us understand the vegetative and reproductive changes that favored the successful adaptation of land plants.

The biogenesis of pinguisanes, secondary metabolites exclusively found in liverworts, cannot be explained simply by the isoprene rule. After the isolation of ptychanolide, together with deoxopinguisone and pinguisone, from the acetone extract of the liverwort *Ptychanthus striatus*, Takeda and coworkers (Takeda et al., 1983) proposed that these pinguisanes are derived from the same biosynthetic intermediate, that undergoes, until then still unclear biosynthetic pathways (Scheme 1).



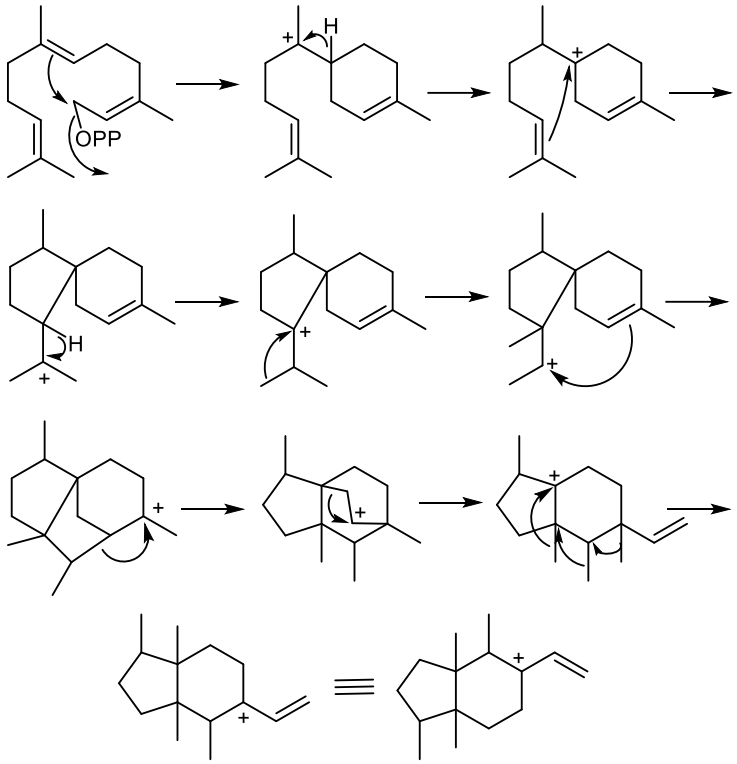
Scheme 1 Possible biosynthetic pathway of ptychanolide and deoxopinguisone (Takeda et al., 1983)

In 1990, the biogenesis of ptychantolide, along with spiropinguisanes, was further elaborated by Connoly, who proposed that the formation of the ptychantolide and spirodensifolins A and B occurs *via* the 5*β*,6*β*- and 5*α*,6*α*-epoxides of pinguisanes, respectively (Scheme 2) (Connoly, 1990).



Scheme 2 a) Plausible biosynthetic pathway of ptychanolide; b) Plausible biosynthetic pathway to spirodensifolins A and B (Connoly, 1990)

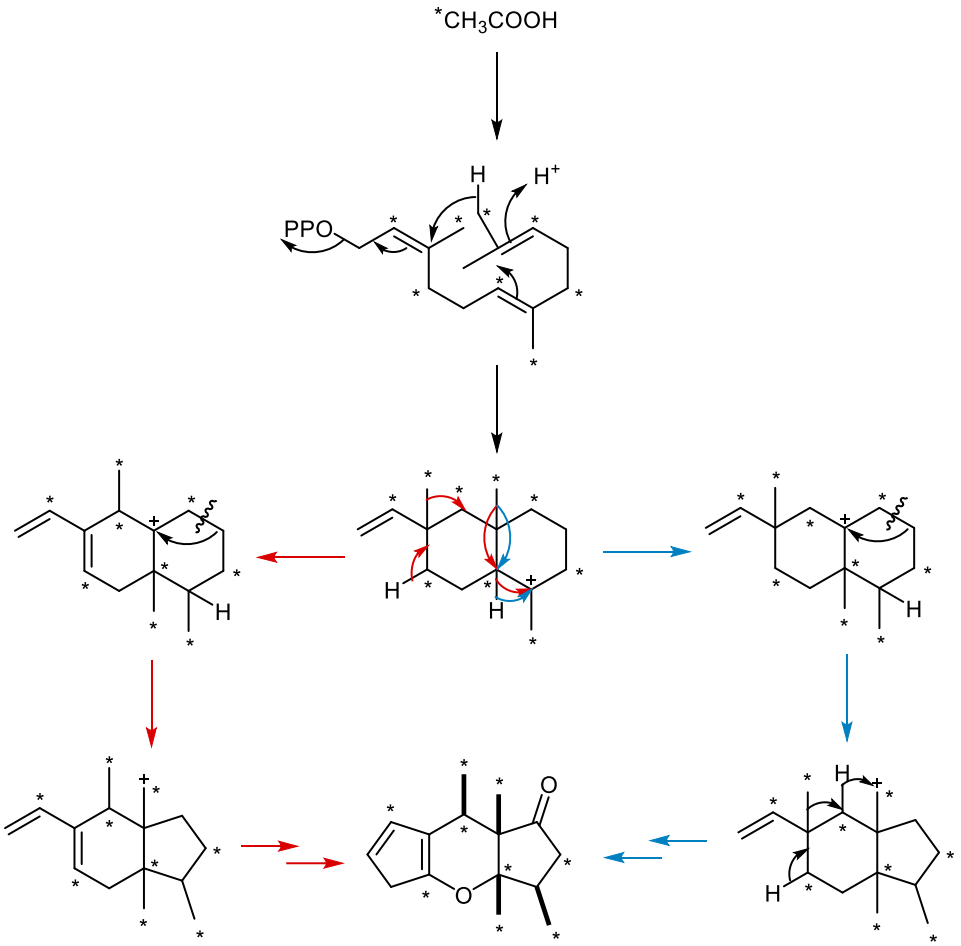
In 1993, a biosynthetic pathway of pinguisane formation from farnesyl pyrophosphate *via* bisabolanyl and the acoranyl ions, followed by a series of 1,2-migrations, was proposed by Tori and coworkers (Scheme 3) (Tori et al., 1993).



Scheme 3 Plausible biosynthetic pathway of the pinguisane-type sesquterpenoides from farnesyl pyrophosphate (Tori et al., 1993)

In 1995, Tazaki and co-workers performed a biosynthetic study on the formation of pinguisone by feeding [2-^{13}C]-acetate to the cultured gametophytes of *Aneura pinguis* who accumulated high amounts of this ^{13}C-labeled compound (Tazaki et al., 1995). Pinguisone was labeled at an adequate level that enabled the determination of the labeling positions by ^{13}C NMR analysis that revealed the specific distribution of the ^{13}C-enriched carbons (at C-2, C-4, C-6, C-8, C-10, C-12, C-13, C-14, and C-15 positions). Based on ^{13}C–^{13}C couplings between C-4 and C-15, and between C-8 and C-12 it was concluded that two (Me-13 and Me-15) of four methyl groups migrate in the formation of pinguisone. The incorporation pattern indicated the formation of decaline cation *via* the formation of C-3–C-12 (or C-13) and C-6–C-11 bonds in farnesyl diphosphate, with the elimination of diphosphate. Further conversions of decaline cation included two 1,2-methyl and a 1,2-hydride shifts (from the C-6–C-7 position, confirmed by the deuterium incorporation/retention in the C-1). The rupture of the C-9–C-10 bond in decaline cation and recyclization to form a cyclopentane ring gave indane cation that further gave

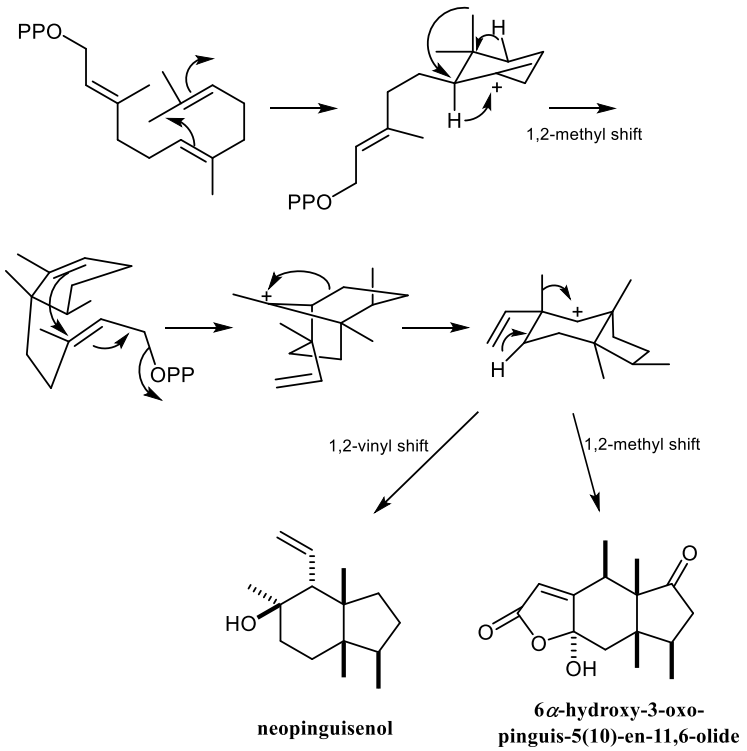
pinguisone. Scheme 4 illustrates the proposed biosynthetic pathway for the formation of pinguisone (Scheme 4, red arrows), and an alternative route to form the indane cation *via* the decalin cation (Scheme 4, blue arrows). These findings excluded the biosynthetic pathway previously proposed by Tori and coworkers (Tori et al, 1993).



Scheme 4 Incorporation pattern of [2-^{13}C]-labeled acetate into pinguisone; Biosynthetic pathway for pinguisane-type sesquterpenoids (Tazaki et al., 1995)

In further experiments, axenic cultures of the *A. pinguis* were fed with ^{2}H- and ^{13}C-labelled mevalonates (MVA), [4,5-$^{13}C_2$]-, [5-^{13}C]-, [2-$^{2}H_2$]- and [6-$^{2}H_3$]-MVA, producing the labeled 6*α*-hydroxy-3-oxopinguis-5(10)-ene-11,6-olide, as the main sesquiterpene. ^{2}H- and ^{13}C NMR analysis of the latter compound, isolated from the cultured gametophytes, clarified the biosynthesis of pinguisane-type sesquiterpenes from farnesyl pyrophosphate (FPP) *via* a 1,2-hydride shift, two 1,2-methyl shifts, cleavage of the main

FPP chain and then recyclization (Scheme 5) (Tazaki et al., 1999). The cyclized cation is formed *via* the formation of a C-6–C-11 bond from FPP without the elimination of diphosphate. 1,2-Methyl and 1,2-hydride shift resulted in C-3–C-10 bond formation that was followed by the diphosphate elimination giving the cation with the bicyclo[3.3.1]nonane skeleton. The isomerization of this cation to the cation with bicyclo[4.3.0]nonane skeleton, followed by 1,2-methyl or 1,2-vinyl shift, led to the formation of pinguisane and neopinguisane skeleton, respectively. This biosynthetic pathway seems to be widely occurring in liverworts which produce not only pinguisane-type sesquiterpene but also three other skeletal sesquiterpenes represented by *β*-monocyclonerolidol, striatene, and trifarienol A.



Scheme 5 Biosynthetic pathway for pinguisane-type sesquterpenoids (Tazaki et al., 1997)

2.4. Total synthesis of pinguisane-type terpenoids

Structurally, pinguisanes are bicyclic sesquiterpenes with a *cis*-1,2,6,7-tetramethylbicyclo[4.3.0]nonane carbon skeleton with *cis*-junction between five- and six-membered ring and for adjacent *cis*-methyl groups (Fig. 1). Unique structural features, demanding stereochemistry of stereogenic centers that may be responsible for potential biological activities, and lack of the starting compounds obtained from nature, make this class of natural products an attention-grabbing synthetic targets. After the first isolation of **pinguisone** from the liverwort *Aneura pinguis*, by Benešová and coworkers in 1969,

and **deoxopinguisone** from the liverwort *Ptilidium ciliare* in 1973, by Herout and coworkers (Krutov et al., 1973), the synthesis of pinguisanes became a huge challenge for organic chemists around the world.

The first successful synthesis of these two furanopinguisanes was performed in 1985 by Uyehara and coworkers (Uyehara et al., 1985). The synthetic approach to *cis*-bicyclo[4.3.0]non-4-en-7-one, as a precursor of **(±)- pinguisone** and **(±)-deoxopinguisone,** was based on the photochemical [1,3] acyl migration of the bicyclo[3.2.2]non-6-en-2-ones to yield the appropriate [5-6] fused ring system, as a key step (Scheme 6) (Uyehara et al., 1985; 1986). Another successful synthesis of **(+)-pinguisone** was accomplished by Gambacorta and coworkers by synthetic elaboration of 3*β*,3a*β*,7,7a*β*-tetramethylbibyclo[4.3.0]non-6-en-1-one obtained by acid-catalyzed skeletal rearrangement of 1,4*β*,5,9-tetramethylbibyclo[3.3.1]nonan-9-hydroxy-2-one (Scheme 6) (Gambacorta et al., 1988). Tori and coworkers synthesized a homochiral bicyclic ketone having a pinguisane skeleton, a precursor of deoxopinguisone, starting from homochiral methyl 3-[(1'*S*,6'*R*)-1',6'-dimethyl-2'-oxo-1-yl]propionate prepared from pulegone using phenylethylamine as a chiral auxiliary pulegone (Scheme 6) (Tori et al., 2001).

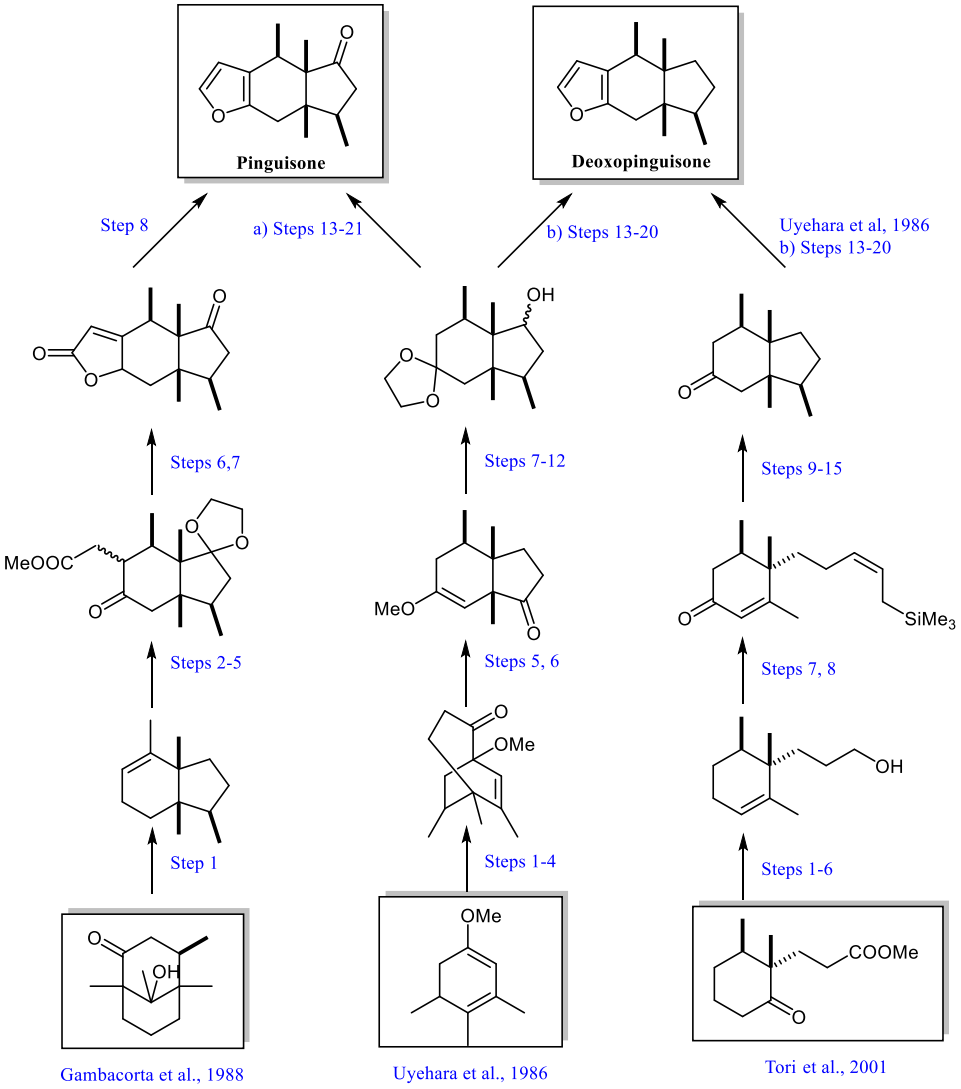
Total, 11-step, synthesis of **(±)-*α*-pinguisene** was achieved in 1995, by Schinzer and coworkers who demonstrated that a propargylsilane-terminated cyclization initiated by acidic resin Amberlyst 15 (A 15) is a powerful method of constructing highly hindered hydrindanone skeletons that contains three neighboring *β*-methyl groups, two of which are quaternary centers (Schinzer et al., 1995). An important intermediate in this synthesis is so-called Schinzer's ketone which was transformed to the final product *via* palladium-mediated cross-coupling of an enol triflate with a vinylstannane. Please take note that, Srikrishna and Vijaykumar noted that Schinzer and coworkers referred to *α*-pinguisene as *β*-pinguisene (Srikrishna and Vijaykumar, 1997).

A year later, Schinzer and Ringe performed the total syntheses of **(±)-*α*-pinguisene** and **(±)-pinguisenol** following the same procedure (Schinzer et al., 1995) to obtain Schinzer's ketone (Scheme 7) (Schinzer and Ringe, 1996). Various total syntheses of pinguisenol are given in Scheme 7. Deprotonation of Schinzer's ketone with LDA at low temperature and *in situ* trapping with *N*-phenyl-*bis*(trifluoromethanesulfoneimide) gave a single enol triflate, which was coupled with vinylstannane in the presence of *tetrakis*(triphenylphosphine)palladium(0) to yield a single isomer of ***α*-pinguisene**, while an addition of vinylmagnesium bromide to Schinzer's ketone in an equatorial position provided **(±)-pinguisenol**, as a single diastereomer.

Furthermore, total syntheses of racemic **(±)-pinguisenol** and **(±)-*α*-pinguisene** was accomplished by employing an orthoester Claisen rearrangement and an intramolecular diazo ketone cyclopropanation reaction for the stereospecific construction of vicinal quaternary carbon atoms, using Hagemann's ester as the starting material (Scheme 7) (Srikrishna and Vijaykumar, 1997).

The first enantiospecific total synthesis of **(+)-pinguisenol**, the optical antipode of naturaly occurring (-)-pinguisenol, starting from (*R*)-carvone, was described by Srikrishna and Vijaykumar (Srikrishna and Vijaykumar, 1998). This synthesis enabled the determination of the absolute stereochemistry of the natural compound as 1*S*,2*S*,3*R*,6*S*,7*R*. During this synthesis, four more pinguisane analogs were obtained (Fig. 2). An important intermediate in the synthesis of **(+)-pinguisenol** was **10-methylenepinguisen-8-one** (**1**) that was transformed into deoxygenated analog, **10-methylenepinguisene** (**2**) by Huang-Minlon modified Wolff-Kishner reduction. Further ozonolysis of (**2**) followed by reductive workup transformed it into

(-)-pinguisen-10-one (**3**), while ozonolysis of compound (**1**) gave **(+)-pinguisen-8,10-dione** (**4**) (Fig. 2).



Scheme 6 Total syntheses of pinguisone and deoxopinguisone, reagents and conditions:
Gambacorta et al., 1988: 1. H^+, multiple rearrangements, 2. protection; 3. allylic oxidation; 4. Britch reduction; 5. quenching with $BrCH_2COOCH_3$; 6. basic hydrolysis; 7. heating at 110 °C; 8. DIBAL-H, -20 °C.
Uyehara et al., 1986: 1. $ClCH_2CN$, hydroquinone, PhMe, 90 °C, over night; 2. Na_2S, KOH, H_2O, reflux, 8 h; 3. Collins oxidation; 4. $BF_3{\cdot}OEt_2$, CH_2Cl_2, -78 °C, $TMSCHN_2$, 1.5 h; 5. Irradiation of THF solution with 100-W high-pressure Hg lamp, 4 h; 6. 2-ethyl-2-methyl-1,3-dioxolane, PhH, TsOH, r.t., 2 days; 7. LDA, $PhSSO_2Ph$, THF; 8. $NaIO_4$,

MeOH-H_2O; 9. $CaCO_3$, PhMe, 90 °C; 10. MeLi, ether; 11. PCC, NaOAc, CH_2Cl_2; 12. Li, NH_3, *t*-BuOH, THF; (a) **pinguisone**: 13. NaH, TBAI, DME, BnBr; 14. HCl, H_2O-acetone; 15. LDA, ICH_2COOEt, THF-HMPA; 16. K_2CO_3, MeOH-H_2O; 17. TsOH, PhH, reflux; 18. BBr_3, CH_2Cl_2, 0 °C; 19. DIBAL-H, THF; 20. 1M H_2SO_4; 21. $(Ac)_2O$, DMSO. b) **deoxopinguisone**: 13. NaH, imidazole, CS_2, THF, reflux; 14. $(n\text{-}Bu)_3SnH$, PhMe, reflux; 15. HCl, H_2O-acetone; 16. LDA, ICH_2COOEt, THF-HMPA; 17. K_2CO_3, MeOH-H_2O; 18. TsOH, PhH, reflux; 19. DIBAL-H, THF; 20. 1M H_2SO_4.

Tori et al., 2001: 1. LAH; 2. TBDPSCl, Et_3N; 3. Swern oxidation; 4. MeMgBr, $CeCl_3$; 5. $POCl_3$, py; 6. TBAF, THF; 7. Swern oxidation; 8. Ph_3PMeBr, ICH_2SiMe_3, *n*-BuLi; 9. PDC, *t*BuOOH; 10. TBAF, 4 Å, molecular sieves; 11. O_3, CH_2Cl_2; then Me_2S; 12. $NaBH_4$; 13. TsCl, Py; 14. LAH; 15. Jones oxidation; Steps 16-23 for deoxopinguisone Uyehara et al., 1986.

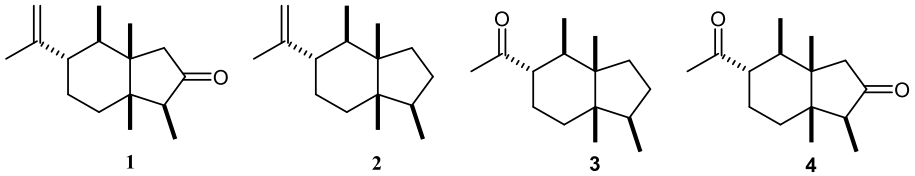
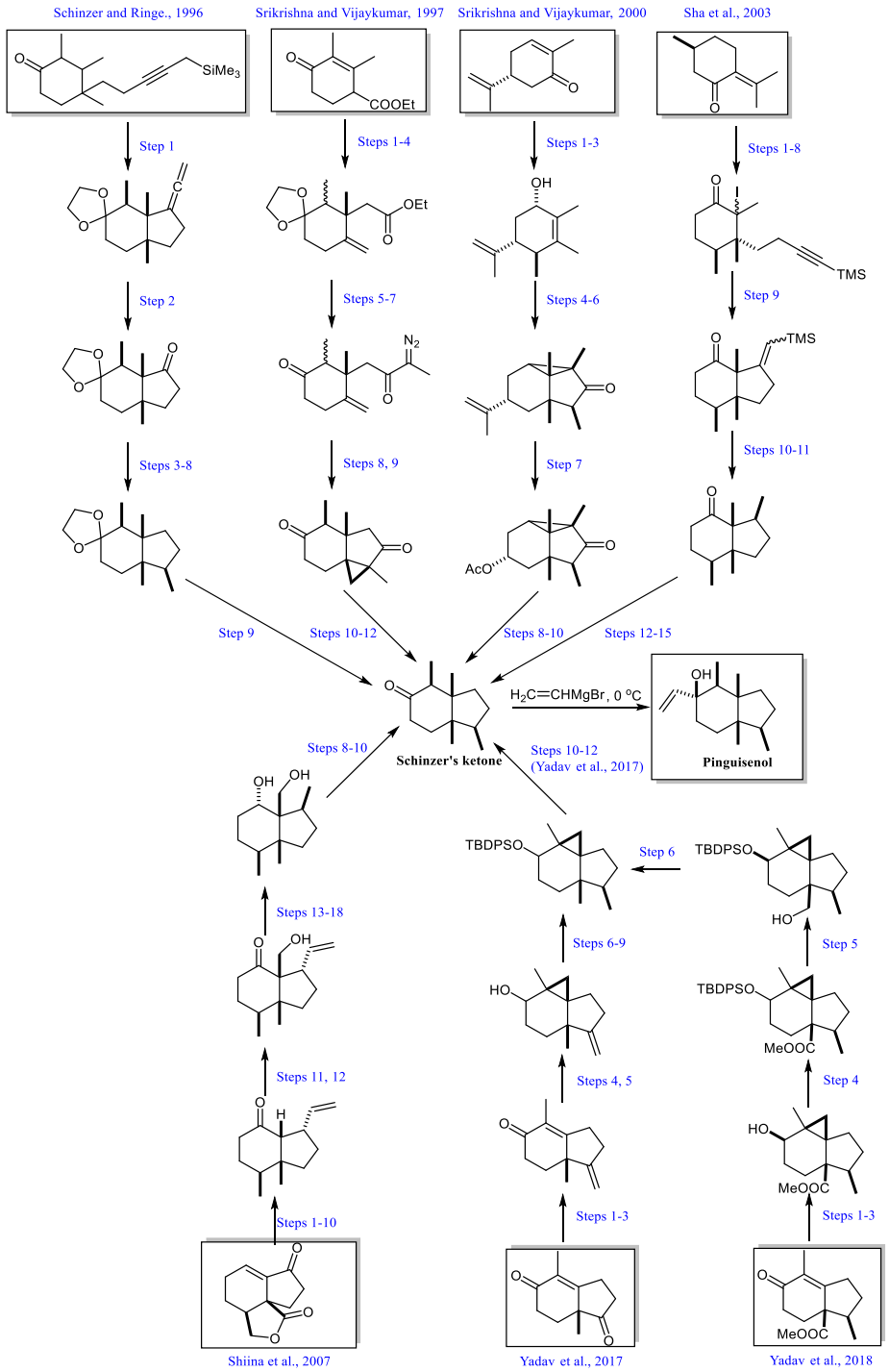


Fig. 2 Synthesized pinguisane-type sesquiterpenes: 10-methylenepinguisen-8-one (**1**), 10-methylenepinguisene (**2**), pinguisen-10-one (**3**), pinguisen-8,10-dione (**4**) (Srikrishna and Vijaykumar, 1998)

In 2000, the same authors (Srikrishna and Vijaykumar, 2000) reported an enantiospecific approach to pinguisanes starting from (*R*)-carvone by employing an orthoester Claisen rearrangement of the allyl alcohol, intramolecular diazo ketone cyclopropanation and a regioselective reductive cyclopropane ring-cleavage sequence (Scheme 7). The synthesis of (+)-pinguisenol was accomplished in 13 steps, starting from *trans*-6-methylcarvone, obtained from carvone, which established the absolute stereochemistry of the natural pinguisenol.

In before mentioned syntheses, as the key intermediate, the racemic form of Schinzer's ketone (Scheme 7) was used yielding the racemic (±)-pinguisenol and (±)-*α*-pinguisene (Schinzer et al., 1995; Schinzer and Ringe, 1996; Srikrishna and Vijaykumar, 1997; 1998; 2000). The first enantiospecific synthesis of Schinzer's ketone, from (*R*)-(+)-pulegone, *via* *α*-carbonyl radical cyclization, was accomplished by Sha and coworkers (Sha et al., 2003) and further led to the enantiospecific formal syntheses of (-)-pinguisenol and (-)-*α*-pinguisene.

Yadav and coworkers reported a short and efficient enantioselective approach to pinguisane-type sesquiterpenes, and among others to the natural (-)-pinguisenol, from a Hajos–Parrish-type ketone (Scheme 7). The key reactions were regioselective thioketal protection, stereoselective cyclopropanation using Furukawa's protocol, diastereoselective hydrogenation of an olefin using a Thalesnano H-Cube Pro flow reactor, and Li/liquid NH_3 mediated cyclopropane reduction (Yadav et al., 2017). A year later, the same group of authors reported the stereoselective total syntheses of pinguisane-type of sesquiterpenoids using a chiral building block derived from (*R*)-pulegone (Yadav et al., 2018). The key reactions employed in the synthesis were Luche reduction, Furukawa's modified Simmons−Smith cyclopropanation, and cyclopropane ring opening with Li/liquid NH_3.



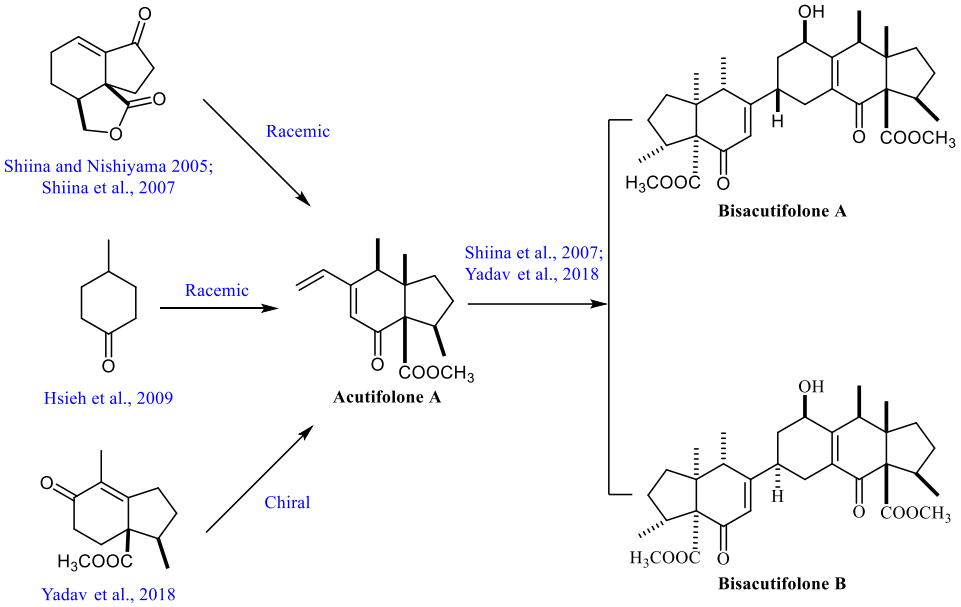
Scheme 7 Total synthesis of pinguisenol, reagents and conditions:

Schinzer and Ringe, 1996: 1. A 15, methoxy-dioxolane; 2. O_3, Sudan red, Zn/CH_3COOH; 3. LDA, -78 °C, PhSeBr; 4. H_2O_2, 5. CH_3MgBr, CuI; 6. LAH; 7. NaH, CS_2, MeI; 8. AIBN, Bu_3SnH; 9. A 15.
Srikrishna and Vijaykumar, 1997: 1. NaH, MeI, -50 °C; 2. $(CH_2OH)_2$, PTSA, PhH, 48 h; 3. LAH, Et_2O, -70 °C; 4. $MeC(OEt)_3$, $EtCO_2H$ (cat.), 180 °C, 48 h; 5. 3 M HCl, THF, 2 h; 6. 10% NaOH, MeOH, reflux, 4 h; 7. $(COCl)_2$, PhH, r.t., 2 h; $MeCHN_2$, Et_2O, 0 °C, 2 h; 8. Cu, $CuSO_4$, cyclohexane, reflux, 1.5 h; 9. K_2CO_3, MeOH, rt, 48 h; 10. Li, liq. NH_3, THF; 11. NH_2NH_2, $(CH_2OH)_2$, 180 °C, 2h; Na, 4 h; 12. PCC, CH_2Cl_2, 2 h.
Srikrishna and Vijaykumar, 2000: 1. i, LDA, MeI; ii, DBU, iii, recrystallization; 2. i, MeMgI; ii, PCC–silica gel; 3. i, LAH; 4. $CH_3C(OEt)_3$, $EtCO_2H$, reflux; ii, NaOH; 5. i, $(COCl)_2$; ii, CH_3CHN_2; 6. $CuSO_4$, 7. O_3/O_2; Ac_2O, Et_3N; 8. Li, liq. NH_3; 9. Wolff–Kishner reduction; 10. PCC, silica gel.
Sha et al., 2003: 1. lithium cyclohexylisopropylamide, BuLi; 2. MeI; 3.CH_3Li, THF, -78 °C; 4. O_3, CH_2Cl_2; 5. DMS; 6. PTSA, PhH; 7. 4-(trimethylsilyl)-3-butynylmagnesium chloride, THF, -78 °C, CuI, HMPA, TMSCl, Et_3N; 8. *m*CPBA, NaI, CH_2Cl_2; 9. Bu_3SnH, AIBN, PhH, 65 °C; 10. TFA, CH_2Cl_2; 11. Pd/C, H_2, MeOH; 12. H_2NNHTs, MeOH, reflux; 13. *n*-BuLi, TMEDA, hexane; 14. CrO_3, DMP, CH_2Cl_2; 15. Pd/C, H_2, MeOH.
Shiina et al., 2007: 1. $NaBH_4$, $CeCl_3{\cdot}7H_2O$/MeOH, –70 °C; 2. TIPSOTf, 2,6-lutidine/CH_2Cl_2, 0 °C; 3. DIBAL-H/CH_2Cl_2, 0 °C; 4. MsCl, py, 0 °C, 5. Na_2S/ DMF, r.t.; 6. Raney Ni W-4/THF, r.t.; 7. $BH_3{\cdot}$THF/THF, 0 °C, then H_2O_2, NaOH, r.t.; 8. TFAA, DMSO, Et_3N/CH_2Cl_2, –65 °C; 9. DBU/PhMe, 0 °C; 10. CH_2=CHMgBr, CuI/THF, –78 °C; 11. TESCl, Et_3N, LiI/CH_2Cl_2, 40 °C; 12. HCHO (aq.) $Sc(OTf)_3$/THF, 65 °C; 13. $LiAlH(OtBu)_3$/THF, 0 °C; 14. TBSOTf, 2,6-lutidine/CH_2Cl_2, 0 °C; 15. OsO_4, Me_3NO/acetone, H_2O, 0 °C, then $NaIO_4$, r.t.; 16. DBU/PhH, 50 °C; 17. $HS(CH_2)_3SH$, $BF_3{\cdot}OEt_2/CH_2Cl_2$, 0 °C; 18. Raney Ni W-4/THF, reflux; 19. PDC/DMF, r.t.; 20. $HS(CH_2)_3SH$, $BF_3{\cdot}OEt_2/CH_2Cl_2$, –78 °C; 21. Raney Ni W-4/ THF, reflux.
Yadav et al., 2017: 1. $HS(CH_2)_2SH$, $BF_3{\cdot}Et_2O$, MeOH, 0 °C, r.t., 24 h; 2. PPh_3CH_3Br, *t*BuOK, PhMe, 60 °C; 3. $TI(NO_3)_3{\cdot}3H_2O$, THF/MeOH/H_2O, r.t., 1 h; 4. $CeCl_3{\cdot}7H_2O$, MeOH, $NaBH_4$, -20 °C, 30 min; 5. Et_2Zn, CH_2I_2, PhH, *n*BuLi, Et_2O, -20 °C to r.t., 24 h.t., 24 h; 6. imidazole, CH_2Cl_2, TBDPSCl, 0 °C to r.t., 12 h; 7. Thalenano H-Cube Pro Flow reactor, 10% Pd/C, EtOAc, 5 bar H_2, 0.3 mL/min flow rate; 8. TBAF, THF, 24 h; 9. DMP, CH_2Cl_2, 0 °C to r.t., 1 h; 10. Li/liq. NH_3, THF, -33 °C, 15 min, K_2CO_3, MeOH.
Yadav et al., 2018: 1. $CeCl_3{\cdot}7H_2O$, MeOH, $NaBH_4$, -20 °C, 1 h; 2. Et_2Zn, CH_2I_2, CH_2Cl_2, 0 °C, 24 h; 3. DMP, CH_2Cl_2, 0 °C, 2 h; 4. imidazole, CH_2Cl_2, TBDPSCl, 0 °C to -25 °C, 24 h; 5. DIBAL-H, 0 °C, CH_2Cl_2 2h; 5. TsCl, Et_3N, CH_2Cl_2, DMAP, 0 °C to -25 °C, 24 h; LAH, THF, 50 °C, 12 h.

Another stereoselective total synthesis of pinguisenol and some other pinguisane-type sesquiterpenoids has been achieved by using the Mukaiyama aldol reaction as the key step (Scheme 7) (Shiina et al., 2007).

Shiina and Nishiyama, in 2005, reported the first total synthesis of **acutifolone A** (Scheme 8) (Shiina and Nishiyama, 2005). The starting compound with the bicyclo[4.3.0]nonane system was obtained by using the intramolecular Diels–Alder reaction of (*E*)-3-(3-hydroxyhepta-4,6-dien-1-yl)furan-2(5*H*)-one. This protocol enabled the stereocontrolled synthesis of not only the bicyclo[4.3.0]nonane framework but also the introduction of a variety of functional groups to desired positions. The key step in acutifolone A synthesis was the successful introduction of the oxygenated function at the C-8 position by the Mukaiyama aldol reaction. The slightly modified synthesis of acutifolone A starting from the same starting material with bicyclo[4.3.0]nonane system was performed by Shiina and coworkers, who also performed the first synthesis of acutifolone A dimeric derivatives, **bisacutifolone A** and **bisacutifolone B** (Scheme 8), by biomimetic dimerization of acutifolone A by Diels–Alder reaction (Shiina et al., 2007). The less complex starting material, 4-methylcyclohexanone, was used in the 14-steps total synthesis of acutifolone A, in racemic form (Hsieh et al., 2009). The key step in this synthesis was cyclopentene annulation of keto ester, obtained from 4-methylcyclohexanone. The first enantioselective synthesis of acutifolone A and bisacutifolones A and B in a concise manner with a good overall yield was performed by Yadav and coworkers, starting from a common chiral building block derived from (*R*)-pulegone. The key steps in this synthesis were Luche reduction, Furukawa's modified Simmons−Smith cyclopropanation, cyclopropane ring opening with Li/liquid NH_3, Saegusa−Ito oxidation, PCC-mediated 1,3-oxidative transposition reaction, and Diels−Alder dimerization reaction (Yadav et al., 2018).

A Brønsted acid-promoted transannular cyclization of an enol onto an unactivated alkene represented a conceptually novel asymmetric approach for the formation of bicyclo[4.3.0]nonane ring system of the pinguisane-type sesquiterpenoids and enabled an enantioselective route to this class of molecules (Clarke et al., 2006). Further studies on the transannulation reactions across a nine-membered ring were accomplished by Iqbal and coworkers (Iqbal et al., 2011). Transannular cyclizations through oxygen functionality generated a number of bicyclo[5.3.1]systems containing bridged cyclic ethers and bicyclo[5.2.2]lactones, as well as a tetrahydrofuran-containing bridged analog of hexacyclic acid. An unprecedented Brønsted acid-mediated transannular cyclization between proximal carbons generated bicyclo[4.3.0]nonanes that is characteristic of the pinguisane-type sesquiterpenoids. On the other hand, Horak and coworkers developed a one-pot, three-step domino sequence synthesis of furo[2,3-*f*]-isoindoles, the aza-analogs of pinguisane-type sesquiterpenes, using inexpensive and readily available starting compounds, maleic anhydride and (3-furyl)allylamines, followed by a domino sequence involving acylation/cycloaddition/proton shift steps. The key step was the intramolecular Diels–Alder vinylfuran reaction that proceeds under mild conditions, with high levels of diastereoselectivity and acceptable yields (Horak et al., 2015).



Scheme 8 Total syntheses of acutifolone A, and bisacutifolones A and B; reagents and conditions:

Shiina and Nishiyama, 2005: 1. $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, -70 °C; 2. TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; 3. DIBAL-H, CH_2Cl_2, -40 °C; 4. MsCl, py, 0 °C; 5. Na_2S, DMF, r.t.; 6. Raney Ni W-4, THF, reflux; 7. $BH_3{\cdot}$THF, THF, 0 °C, then H_2O_2, NaOH, r.t.; 8. TFAA, DMSO, Et_3N/CH_2Cl_2, -60 °C; 9. DBU/PhMe, 0 °C; 10. CH_2=CHMgCl, CuI, THF, -78 °C; 11. TESCl, Et_3N, LiI, CH_2Cl_2, 40 °C; 12. HCHO (aq.), $Sc(OTf)_3$, THF, 65 °C; 13. $LiAlH(OtBu)_3$, THF, 0 °C; 14. TBSOTf, 2,6-lutidine/CH_2Cl_2, 0 °C; 15. OsO_4, Me_3NO, acetone, H_2O, 0 °C, than $NaIO_4$, r.t.; 16. DBU/PhH, 50 °C; 17. $HS(CH_2)_3SH$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C; 18. Raney Ni W-4, THF, reflux; 19. PDC/DMF, r.t.; 20. $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*BuOH–H_2O, 0 °C; 21. $TMSCHN_2$, MeOH, 0 °C; 22. TIPSOTf, 2,6-lutidine, CH_2Cl_2, r.t.; 23. TBHP, 20% $Pd(OH)_2$–C, Cs_2CO_3, CH_2Cl_2, O_2, 0 °C; 24. CH_2=CHMgCl, $CeCl_3$, THF, 0 °C; 25. CSA, MeOH, r.t.

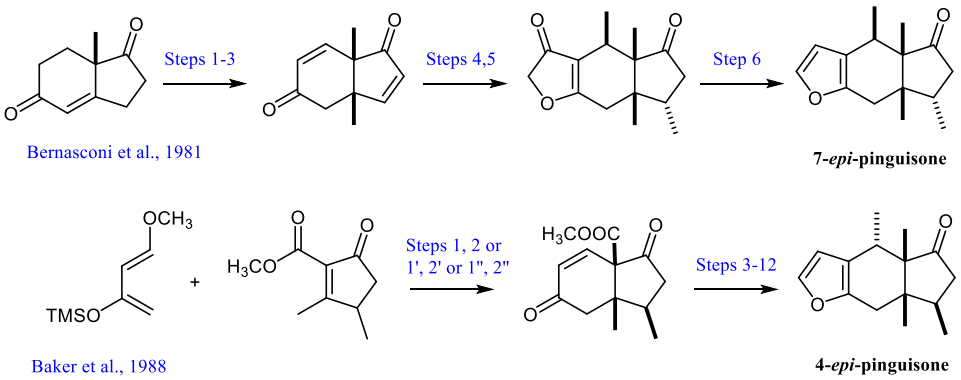
Shiina et al., 2007, Synthesis of acutifolone A: Steps 1-21 the same as in Shiina and Nishiyama, 2005; 22. IBX, DMSO, THF, 80 °C; 23. CH_2=CHMgCl, CuI/THF, -78 °C; 24. IBX or TMSOTf, Et_3N, then $Pd(OAc)_2$; Synthesis of bisacutifolones A and B: BHT, PhMe, 120 °C in a sealed tube.

Hsieh et al., 2009:1. NaH, $CO(OMe)_2$, THF, reflux, 2 h; 2. PhSeCl, py, CH_2Cl_2, 0 °C, 1h then 30% H_2O_2, 0 °C, 8 min; 3. MeLi, CuI, THF, -78 °C, 30 min; 4. PhSeCl, py, CH_2Cl_2, r.t., 3 h then 30% H_2O_2, 0 °C, 10 min; 5. 3-butenylmagnesium bromide, CuI, THF/Me_2S (20:1), -78 °C, 30 min; 6. $Pd(OAc)_2$ (1.4 eq.), THF, r.t., 16 h; 7. H_2, 10% Pd/C, MeOH, r.t.; 8. LHMDS, THF, -78 °C, 15 min, then TMSCl, 3 h; 9. $Pd(OAc)_2$, CH_3CN, reflux, 50 h; 10. vinylmagnesium bromide, CuI, THF/Me_2S (20:1), -78 °C to 0 °C, 2 h; 11. LHMDS, THF, -78 °C, 15 min, then TMSCl, 3 h; 12. $Pd(OAc)_2$, CH_3CN, reflux, 52 h.

Yadav et al., 2018, Synthesis of acutifolone A: 1. $CeCl_3{\cdot}7H_2O$, MeOH, $NaBH_4$, -20 °C, 1 h; 2. Et_2Zn, CH_2I_2, CH_2Cl_2, 0 °C, 24 h; 3. DMP, CH_2Cl_2, 0 °C, 2 h; 4. Li/liq. NH_3, THF, -

33 °C, 15 min; 5. LDA, -78 °C, MeI, 0 °C, 12 h; 6. TMS-acetylene, BuLi, -78 °C, -10 °C, 12 h; 7. PCC, celite, CH_2Cl_2, 25 °C, 24 h; 8. K_2CO_3, MeOH, 0 °C, 1 h; 9. Lindlar's catalyst, Quinoline, H_2 gas, EtOAc, 25 °C, 1h; Synthesis of bisacutifolones A and B: BHT, 24 h, 125 °C.

The syntheses of *epi*-pinguisanes, differing from pinguisanes only in the orientation of a methyl group, were also reported. Bernasconi and coworkers performed the synthesis of **7-*epi*-pinguisone** from a chiral synthon (*S*)-7a-methyl-2,3,7,7a-tetrahydro-1*H*-indene-1,5(6*H*)-dione obtained by asymmetric aldol cyclization of Hajos-Parrish-triketone, 2-methyl-2-(3-oxobutyl)cyclopentane-1,3-dione, in the presence of the catalytic amounts of (*S*)-(-)-proline (Scheme 9) (Bernasconi et al., 1981). Introduction of the third and fourth methyl group at C-1 and C-4, respectively, and the formation of the *β*-furanone ring in one step, allowed the synthesis of optically active 7-*epi*-pinguisone with very high stereoselectivity in only a few steps. The quenching of an enolate with chloroacetyl chloride was a new synthetic approach to the *β*-furanones. Diels-Alder cycloaddition of 1-methoxy-3-(trimethylsiloxy)buta-1,3-diene (Danishefsky's diene) onto the doubly-activated dienophile methyl 2,3-dimethyl-5-oxocyclopent-1-ene-carboxylate, at very high pressure, followed by hydrolysis gave an indene intermediate in a good yield, that was further transformed, in 9 steps, into **4-*epi*-pinguisone** (Scheme 9) (Baker et. al., 1988).



Scheme 9 Synthetic approaches to 4-*epi*-pinguisone and 7-*epi*-pinguisone, reagents and conditions:

Bernasconi et al., 1981: 1. $(CH_3)_2CuLi$, anhyd. Et_2O, -25 °C, 1 h; 2. Br_2, CH_3COOH, 5 °C, then 10% NaOH; 3. $CaCO_3$, DMAc, reflux, 2h; 4. $(CH_3)_2CuLi$, anhyd. Et_2O, -35 °C, 1h; 5. $(CH_3)_2CuLi$, anhyd. Et_2O, 1h, -25 °C 6. 9-BBN, N_2, anhyd. THF, 0 °C, 2h.

Baker et al., 1988: 1. 155 °C, 24 h; 2. H_3O^+; or 1'. 13 kBar, 35 °C; 2'. CSA; or 1''. 13 kBar, 35 °C; 2''. Bu_4NF; 3. $NaBH_4$, $CeCl_3$, MeOH, r.t.; 4. SEMCl, *i*PrNEt$_2$, CH_2Cl_2; 5. LAH, THF, r.t.; 6. TsCl, py, DMAP (1 eq.), r.t.; 7. NaI, Zn, HMPA, 110 °C; 8. TBAF, HMPA, 85 °C; 9. PCC, CH_2CI_2; 10. Me_2CuLi; 11. $ClCH_2COCI$; 12. 9-BBN, 0 °C.

2.5. Biological activities of pinguisane-type terpenoids

Medicinal plants and natural products isolated from them have been used to alleviate and cure illnesses since antiquity (Verpoorte et al., 2006). In particular, higher plants have been considered a fruitful source of biologically/pharmacologically active compounds, and

the inspiration for their scientific evaluation is frequently found in traditional medicine. On contrary, lower plants have not been exhaustively studied in this sense, although some of them, for example, bryophytes, have been used in traditional medicine to cure cuts, burns, external wounds, bacteriosis, pulmonary tuberculosis, neurasthenia, fractures, convulsions, scalds, uropathy, inflammation, fever and pneumonia (Glime, 2021). Liverworts, the second largest group of bryophytes, synthesize numerous secondary metabolites some of which display interesting biological activities, including antimicrobial, antifungal, antiviral, cytotoxic, anticancer, insecticidal, enzyme inhibitory, vasorelaxant, etc. (Asakawa et al., 2013b). Many of these compounds are characterized by inimitable structures, and some of them, like the pinguisane-type sesquiterpenoids, have not been found in any other existing land or marine organism (Asakawa, 1982b; 1995; 2013; Ludwiczuk et al., 2011).

Crude extracts and essential oils isolated from liverworts contain a number of bioactive molecules (Asakawa, 1982b; 1995; Asakawa et al., 2013a). For example, a crude extract of *Bazzania nova-zelandiae* was found to contain cytotoxic active substances against P-388 leukemia in the NCI's panel of human tumor cell lines (Asakawa, 1995). Furthermore, crude extracts of some *Porella* species displayed antimicrobial activity against gram-positive bacteria, and ornithine decarboxylase activity (Pavletić and Stlinović, 1963; Toyota et al., 1991). In a research performed by Gilabert and coworkers (Gilabert et al., 2011), pinguisanes isolated from the diethyl-ether extract of *Porella chilensis* (pinguisenol, norpinguisone, norpinguisone acetate, norpinguisone methyl ester) slightly enhanced growth of *Pseudomonas aeruginosa*, in concentrations of 5 and 50 μg/mL. For pinguisenol and norpinguisone a good correlation between bacterial growth and biofilm and autoinducer production was observed. Norpinguisone acetate inhibited 20 and 27% of biofilm production at 5 and 50 μg/mL, respectively, while norpinguisone methyl ester produced increments in bacterial growth and autoinducer formation that did not result in an enhancement of the biofilm percentage (Gilabert et al., 2011). Moreover, norpinguisone exhibited an antifungal activity (Asakawa and Aratani, 1976).

Furthermore, norpinguisone from *Porella vernicosa* and norpinguisone methyl ester from *P. elegantula* inhibited the release of superoxide from the guinea pig peritoneal macrophage (Asakawa, 2007). Moreover, norpinguisone and norpinguisone methyl ester, isolated from the ether extract of *P. densifolia*, exhibited the inhibitory activity of nitric oxide (NO) production in RAW 264.7 cells stimulated by lipopolysaccharide, with IC_{50} values of 45.5 and 1.68 μM, respectively (Quang and Asakawa, 2010). Radulović and coworkers, recently identified two new pinguisane derivatives, *α*-furanopinguisanol and furanopinguisanone, in *P. cordaeana*, and evaluated their immunomodulatory effects (Radulović et al., 2016). *α*-Furanopinguisanol, in higher concentration (100 μM) induced a blast-like transformation of rat splenocytes while it was cytotoxic in lower concentrations (10 nM to 1 μM). On contrary, furanopinguisanone exerted prominent cytotoxicity in all concentrations (10 nM to 100 μM). Dehydropinguisenol showed cytotoxic activity against KB cells with ED_{50} 12.5 μg/mL (Tori et al., 1993). Moreover, **7**-oxopinguisenol-12-methyl ester isolated from Japanese *P. perrottetiana* exhibited significant cytotoxic activity against human promyelocytic leukemia cell line, HL-60 (IC_{50} 8.53 μM) and human pharyngeal squamous carcinoma, KB cells (IC_{50} 52.64 μM) (Komala et al., 2011). Two products obtained by its chemical transformation, 7α-hydroxypinguisenol-12-methyl ester and acutifolone A were also tested for cytotoxic activity. The former significantly decreased inhibitory activity against HL-60 cells (IC_{50} 83.10 μM) and lost activity against KB cells (IC_{50} > 177 μM), while acutifolone A had increased cytotoxic activity against HL-60 (IC_{50} 2.65 μM) and KB

cells (IC_{50} 46.58 μM) (Komala et al., 2011). Moreover, pinguisone, isolated from *Aneura pinguis*, exhibited insect feeding inhibitory activity against 10-13 days larvae of polyphagous insect *Spodoptera littoralis* Boisd. suggesting the possibility of protecting plants against insect pests by treating the leaves of plants with this compound (Wada and Munakata, 1971).

ABBREVIATIONS

A-15	Amberlyst 15
AIBN	Azobisisobutyronitrile
anhyd.	Anhydrous
aq.	Aqueous
9-BBN	9-Borabicyclo[3.3.1]nonane
BnBr	Benzyl bromide
CSA	Camphorsulfonic acid
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIBAL-H	Diisobutylaluminum hydride
DMAc	Dimethylacetamide
DMAP	4-(Dimethylamino)pyridine
DME	Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMP	Dess–Martin periodinane
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide
eq.	Equivalent
FFP	Farnesyl pyrophosphate
HMPA	Hexamethylphosphoramide
IBX	2-Iodoxybenzoic acid
LAH	Lithium aluminium hydride
LDA	Lithium diisopropylamide
LHMDS	Lithium *bis*(trimethylsilyl)amide
liq.	Liquidus
MsCl	Methanesulfonyl chloride (Mesyl chloride)
MVA	Mevalonate
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
PhH	Benzene
PhMe	Toluene
PTSA	*p*-Toluenesulfonic acid
py	Pyridine
r.t.	Room temperature
SEMCl	2-(Trimethylsilyl)ethoxymethyl chloride
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBDPSCl	*tert*-Butyl(chloro)diphenylsilane
TBHP	*tert*-Butyl hydroperoxide
TBSOTf	*tert*-Butyldimethylsilyl trifluoromethanesulfonate
TESCl	Triethylchlorosilane
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TIPSOTf	Triisopropylsilyl trifluoromethanesulfonate
TMEDA	*N,N,N′,N′*-Tetramethylethylenediamine

$TMSCHN_2$	Trimethylsilyldiazomethane
TMSCl	Trimethylsilyl chloride
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
TsOH	4-Toluenesulfonic acid
TsCl	4-Toluenesulfonyl chloride (Tosyl chloride)

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PINGVIZANSKI SESKVITERPENOIDI, JEDINSTVENI SEKUNDARNI METABOLITI JETRENJAČA

U ovom radu dat je pregled rezultata dosadašnjih istraživanja na temu pingvizanskih seskviterpenoida koji predstavljaju jedinstveno obeležje jetrenjača: izolovanje, određivanje strukture, mogući biosintetski putevi, totalna sinteza pingvizana i njihova biološka/farmakološka aktivnost. Ukupno je predstavljeno 76 jedinjenja, među kojima su pobrojana, kako ona koja su izolovana ili detektovana u biljnom materijalu, tako i 4 pingvizana koji predstavljaju artefakte procesa izolovanja. Pored toga, u radu je razmatran i hemotaksonomski i evolutivni značaj pingvizana, mogućnost njihovog korišćenja kao hemotaksonomskih markera na nivou vrste ili reda jetrenjača, kao i i utvrđivanja hemijskih i evolucionih veza u okviru razdela Marchantiophyta.

Ključne reči: *jetrenjače, prirodni proizvodi, pingvizani, seskviterpenoidi*