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# MARCHANTIOPHYTA (LIVERWORTS): RICH SOURCES OF MACROCYCLIC BIS(BIBENZYLS)

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**Abstract** - The Marchantiophyta (liverworts) produce which show interesting biological activity such as antimicrobial, antifungal, antiobesity and muscle relaxing activity etc. and are of very valuable for the chemosystematic and evolutional study of the Marchantiophyta and pteridophytes. The isolation, identification, structural elucidation and total synthesis of these characteristic natural products and their biological activity are reviewed.

## INTRODCUTION

The bryophytes [Musci (mosses), Marchantiophyta (liverworts) and Anthocerotae (hornworts)], which are the spore-forming terrestrial green plants are morphologically placed between the algae and the pteridophytes (fern) and there are ca. 24,000 species in the world. They are considered to be the oldest terrestrial plants, although no strong scientific evidence for this has appeared in the literature. This hypothesis was mainly based on the resemblance of the present-day liverworts to the first land plant fossils, the spores of which date back almost 500 million years. Among the bryophytes almost all liverworts possess cellular oil bodies which are peculiar, membrane-bound cell organelles that consist of ethereal terpenoids and aromatic oils suspended in carbohydrates-or protein-rich matrix. These oil bodies are very important marker for the classification in the Marchantiophyta.

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This paper is dedicated to Professor Ryoji Noyori for his 70th birthday.

In 1905, Müller[1] predicted that oil bodies of liverworts are composed of sesquiterpenes. After 62 years later, Huneck and Klein[2] found that some liverworts actually contained *ent*-sesquiterpenoids. On the other hand, the mosses and the hornworts do not contain oil bodies. It has been demonstrated that most of the liverworts contain mainly mono-, sesqui- and diterpenoids and lipophilic aromatic compounds [bibenzyls, bis(bibenzyls), naphthalenes, phthalides, isocoumarins, benzoates, cinnamates, acrylates and prenyl indoles etc.] which constitute the oil bodies.[3-5] The characteristic components of the Musci are highly unsaturated fatty acids and alkanones, such as 5,8,11,14,17-eicosapentaenoic acid, 7,10,13,16,19-docosapentaenoic acid and 10,13,16-nonadecatrien-7-yn-2-one and triterpenoids. The neolignan is one of the most important chemical markers of the Anthocerotae.

Some liverworts show strong fragrant odor and intensely hot and bitter or saccharine-like taste. Generally, liverworts are not damaged by bacteria, fungi, insects, snails, slugs and other small animals. Furthermore, some liverworts cause intense allergenic contact dermatitis and allelopathy. Some bryophytes growing in lake, river and pond accumulate heavy metals. Many bryophyte species have been used as medicinal plants, particularly in China.[4] However, only tasting substances and allergens of some species have been fully investigated. We have been interested in these biologically active substances found in the bryophytes and the evolution and differentiation of the bryophytes. At present we studied about 1000 species of the bryophytes collected in America, Argentina, Australia, Africa, Europe, India, Madagascar, Malaysia, Nepal, New Zealand, Pakistan, Taiwan, Turkey and Japan with respect to their chemistry, pharmacology, and application as sources of cosmetics, and medicinal or agricultural drugs. More than several hundred new compounds have been isolated from liverworts so far and they have been shown to have interesting biological activities from antiviral to antiobesity. The chemical constituents found in liverworts and those of the Musci and Anthocerotae have been reviewed in Progress in the Chemistry of Organic Natural Products Vol. 42[3] and Vol. 65[4], respectively. Previously, the distribution of heterocyclic terpenoids and aromatic compounds in the bryophytes including bis(bibenzyls) and their biological activity was reviewed.[6-15] The present paper concerns with the distribution of cyclic bis(bibenzyls) in the Marchantiophyta and their biological activity and total synthesis.

## 1. Structures of cyclic bis(bibenzyls)

Among the Marchantiales, Aytoniaceae and Marchantiaceae are rich sources of macrocyclic bis(bibenzyls). The Plagiochilaceae, Lejeuneaceae, Lepidoziaceae in the Jungermanniales and the Pelliaceae, Riccardiaceae and Blasiaceae in the Metzgeriales are also bis(bibenzyl)-rich liverworts. The distribution of cyclic bis(bibenzyls) in liverworts is shown in Table. 1. The first isolation of the bis(bibenzyls) is riccardins A (**1a**) and B (**2**) from the Japanese tiny thalloid liverwort *Riccardia multifida* (Riccardiaceae)[3,16-19] and marchantin A (**8a**) from a common *Marchantia polymorpha* (Marchantiaceae).[3,16] The conclusive evidence of the stereostructure of **1a** was obtained by X-ray crystallographic analysis of the diacetate (**1b**). In the $^1$H NMR spectra of **1a** and its trimethoxy derivative (**1c**), H-3' appears at unusually high field (δ5.33, d, J=1.9 Hz). This is due to the result of the paramagnetic effect of two benzene rings A and D between which H-3' is sandwiched. Riccardin C (**3**) which was firstly isolated from *Reboulia hemisphaerica* (Aytoniaceae)[20] is widely distributed in *Marchantia* species (Marchantiaceae),[21,22] New Zealand *Monoclea forsteri* (Monocoleaceae),[23] *Blasia pusila* (Blasiaceae),[24-26] *Marchantia paleacea* var. *diptera,*[27] *Dumortiera hirsuta* (Marchanchiaceae),[28] *Plagiochasma pterospermum* (Aytoniaceae),[29] *R. rupestre,*[30] neotropical *Plagiochila* species (Plagiochilaceae)[31] and *Ricciocarpos natans* (Ricciaceae).[32] *Monoclea forsteri* also produced riccardin D (**4**) and riccardin E (**5**).[23] Furthermore, riccardin F (**6**) was isolated from *Blasia pusilla,*[24-26] *Marchantia paleacea* var. *diptera*[29] and *Marchantia tosana.*[33] The Venezuelan *Marchantia chenopoda* produces riccardin G (**7**).[34]

Table 1. The liverworts which contain cyclic bis(bibenzyls)

| Cyclic bis(bibenzyls) | Species | References |
|---|---|---|
| Riccardin A (**1a**) | *Riccardia multifida* | 4,16-19 |
| Riccardin B (**2**) | *Riccardia multifida* | 4,16-19 |
| | *Preissia quadrata* | 64 |
| | *Asterella angusta* | 80 |
| Riccaridn C (**3**) | *Blasia pusilla* | 24-26 |
| | *Dumortiera hirsuta* | 28 |
| | *Marchantia paleacea* var. *diptera* | 27 |
| | *Marchantia palmata* | 22 |

Table 1. (Continued)

| Cyclic bis(bibenzyls) | Species | References |
|---|---|---|
| | *Marchantia polymorpha* | 21-22 |
| | *Mastigophora diclados* | 15 |
| | *Monoclea forsteri* | 23 |
| | *Plagiochasma petrospermum* | 29 |
| | *Plagiochila deflexa* | 31 |
| | Plagiochasma rupestre | 32 |
| | *Reboulia hemisphaerica* | 20 |
| | *Ricciocarpos natans* | 32 |
| Riccardin D (**4a**) | *Monoclea forsteri* | 23 |
| 13,13’-*O*-isoproylidene-riccardin D (**4b**) | *Marchantia polymorpha* | 43 |
| Riccardin E (**5**) | *Monoclea forsteri* | 23 |
| Riccardin F (**6**) | *Blasia pussila* | 24-26 |
| | *Marchantia tosana* | 33 |
| Riccardin G (**7a**) | *Marchantia chenopoda* | 34 |
| Riccardin H (**7b**) | *Marchantia polymorpha* | 43 |
| Marchantin A (**8a**) | *Marchantia paleacea* var. *diptera* | 33,40 |
| | *Marchantia plicata* | 39 |
| | *Marchantia polymorpha* | 16,21,33,35-37<br>43 |
| | *Marchantia tosana* | 33 |
| | *Plagiochasma appendiculatum* | 40 |
| | *Wiesnerella denudata* | 41 |
| Marchantin B (**9a**) | *Marchantia paleacea* var. *diptera* | 33 |
| | *Marchantia palmata* | 21 |
| | *Marchantia polymorpha* | 16,21,33,35-37, 43 |
| | *Marchantia tosana* | 33 |
| | *Plagiochasma appendiculatum* | 41 |
| | *Plagiochasma rupestre* | 30 |
| | *Wiesnerella denudata* | 41 |
| Marchantin C (**10**) | *Dumortiera hirsuta* | 27, 28 |
| | *Marchantia paleacea* var. *diptera* | 33 |
| | *Marchantia polymorpha* | 16,21,33,35-37 |
| | *Monoclea forsteri* | 53 |
| | *Plagiochasma appendiculatum* | 40 |
| | *Plagiochila sciophila* | 54 |

Table 1. (Continued)

| Cyclic bis(bibenzyls) | Species | References |
|---|---|---|
| | *Reboulia hemisphaerica* | 47,58 |
| | *Riccardia nagasakiensis* | 18 |
| | *Schistochila glaucescens* | 61 |
| Marchantin C dimethyl ether (**11**) | *Reboulia hemisphaerica* | 47 |
| Marchantin D (**12**) | *Marchantia paleacea* var. *diptera* | 33 |
| | *Marchantia polymorpha* | 16,21,33,35-37 |
| Marchantin E (**13**) | *Marchantia paleacea* var. *diptera* | 33 |
| | *Marchantia polymorpha* | 16,21,33,35-37,43 |
| Marchantin F (**14**) | *Marchantia paleacea* var. *diptera* | 33 |
| | *Marchantia polymorpha* | 16,21,33,35-37 |
| Marchantin G (**15**) | *Marchantia paleacea* var. *diptera* | 33 |
| | *Marchantia palmata* | 21 |
| | *Marchantia polymorpha* | 16,21,33,35-37 |
| Marchantin H (**16**) | *Marchantia diptera* | 57 |
| | *Marchantia polymorpha* | 22 |
| | *Plagiochasma repestre* | 44 |
| | *Plagiochila sciophila* | 54 |
| | *Asterella angusta* | 22 |
| Marchantin I (**17a**) | *Riccardia multifida* | 44 |
| 11-*O*-demethylmarchantin I (**17b**) | *Asterella angusta* | 80 |
| Marchantin J (**18a**) | *Marchantia polymorpha* | 36 |
| Marchantin K (**18b**) | *Marchantia polymorpha* | 36 |
| | *Plagiochasma rupestre* | 30 |
| Marchantin L (**19**) | *Marchantia polymorpha* | 36 |
| Marchantin M (**20**) | *Reboulia hemisphaerica* | 55 |
| | *Asterella angusta* | 80 |
| Marchantin N (**21**) | *Reboulia hemisphaerica* | 55 |
| Isomarchantin C (**22a**) | *Dumortiera hirsuta* | 27 |
| Dihydroptychantol (**22b**) | *Asterella angusta* | 80 |
| | *Mylia nuda* | 51,52 |
| Isoriccardin C (**23**) | *Bryopteris filicina* | 50 |
| | *Dumortiera hirsuta* | 27 |

Table 1. (Continued)

| Cyclic bis(bibenzyls) | Species | References |
|---|---|---|
| | *Monoclea forsteri* | 53 |
| | *Plagiochasma rupestre* | 28,56 |
| | *Plagiochila sciophila* | 54 |
| | *Reboulia hemisphaerica* | 55 |
| Marchantin O (**24**) | *Reboulia hemisphaerica* | 55,57,58 |
| Marchantin P (**25**) | *Marchantia chenopoda* | 34 |
| | *Asterella angusta* | 80 |
| Marchantiaquinone (**26**) | *Mannia subpilosa* | 47 |
| | *Reboulia hemisphaerica* | 55, 58 |
| Ptychantol A (**27**) | *Ptychantus striatus* | 59 |
| Ptychantol B (**28**) | *Ptychantus striatus* | 59 |
| Ptychantol C (**29**) | *Ptychantus striatus* | 59 |
| Pakyonol (**30**) | *Mannia fragrans* | 59 |
| | *Plagiochasma petrospermum* | 30 |
| Neomarchantin A (**31**) | *Marchantia polymorpha* | 43 |
| | *Schistochila glaucescens* | 61 |
| | *Monoclea forsteri* | 53 |
| | *Preissia quadrata* | 64 |
| Neomarchantin B (**32a**) | *Schistochila glaucescens* | 61 |
| Glaucescens Bis Bibenzy (GBB)A (**32b**) | *Schistochila glaucescens* | 62, 63 |
| Glaucescens Bis Bibenzyl(GBB)B (**32c**) | *Schistochila glaucescens* | 62, 63 |
| Plagiochin A (**33**) | *Plagiochila fruticosa* | 54 |
| Plagiochin B (**34**) | *Plagiochila fruticosa* | 54 |
| Plagiochin C (**35**) | *Plagiochila fruticosa* | 54 |
| Plagiochin D (**36a**) | *Plagiochila fruticosa* | 54 |
| Plagiochin E (**36b**) | *Marchantia polymorpha* | 43 |
| | *Asterella angusta* | 80 |
| Isoplagiochin A (**37**) | *Plagiochila fruticosa* | 24,65-68 |
| | *Plagiochila deflexa* | 71 |
| | *Heteroscyphus planus* | 70 |
| | *Plagiochila diversifolia* | 69 |
| Isoplagiochin B (**38**) | *Plagiochila fruticosa* | 24,65-68 |
| Isoplagiochin C (**39**) | *Plagiochila fruticosa* | 24,65-68 |
| | *Herbertus sakuraii* | 75 |
| | *Plagiochila deflexa* | 31 |
| | *Lepidozia incurvata* | 73 |

Table 1. (Continued)

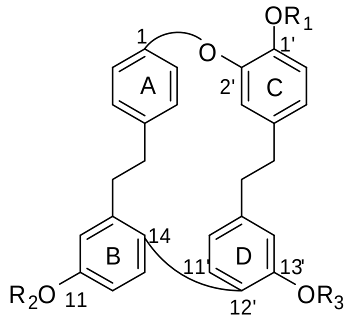
| Cyclic bis(bibenzyls) | Species | References |
|---|---|---|
| Isoplagiochin D (**40a**) | *Plagiochila fruticosa* | 24,65-68 |
| | *Plagiochila deflexa* | 31 |
| | *Herbertus sakuraii* | 75 |
| Bazzanin S (**40b**) | *Bazzania trilobata* | 74 |
| Plunusin ( **41** ) | *Heteroscyphus planus* | 70 |
| Isoplagiochin E (**42**) | *Plagiochila deflexa* | 71 |
| Isoplagiochin F (**43a**) | *Plagiochila deflexa* | 31 |
| Isoplagiochin G **(43b**) | *Plagiochila deflexa* | 31,71 |
| 12-Chloroiso-plagiochin D (**44**) | *Plagiochila deflexa*<br>*Mastigophora diclados* | 31<br>75 |
| Bazzanin A (**45**) | *Bazzania trilobata* | 72 |
| Bazzanin B (**46**) | *Bazzania trilobata* | 72 |
| Bazzanin C (**47**) | *Bazzania trilobata* | 72 |
| Bazzanin D (**48**) | *Bazzania trilobata* | 72 |
| Bazzanin E (**49**) | *Bazzania trilobata* | 72 |
| Bazzanin F **(50**) | *Bazzania trilobata* | 72 |
| Bazzanin G **(51**) | *Bazzania trilobata* | 72 |
| Bazzanin H (**52**) | *Bazzania trilobata* | 72 |
| Bazzanin I (**53**) | *Bazzania trilobata* | 72 |
| Bazzanin J (**54**) | *Bazzania trilobata* | 74 |
| Bazzanin K **(55**) | *Bazzania trilobata* | 72 |
| 12,10’-Dichloroiso-plagiochin C (**56**) | *Herbertus sakuraii* | 75 |
| 2,12-Dichloroiso-plagiochin D **(57**) | *Herbertus sakuraii*<br>*Mastigophora diclados* | 75<br>75 |
| 12,7’-Dichloroiso-plagiochin D(**58**) | *Herbertus sakuraii* | 75 |
| Bazzanin L (**59**) | *Lepidoiza incurvata* | 73 |
| Bazzanin M (**60**) | *Lepidoiza incurvata* | 73 |
| Bazzanin N (**61**) | *Lepidoiza incurvata* | 73 |
| Bazzanin O (**62**) | *Lepidoiza incurvata* | 73 |
| Bazzanin P (**63**) | *Lepidoiza incurvata* | 73 |
| Bazzanin Q (**64**) | *Lepidoiza incurvata* | 73 |
| Bazzanin R (**65**) | *Lepidoiza incurvata* | 73 |
| Bazzanin S (**40b**) | *Bazzania trilobata* | 74 |

Table 1. (Continued)

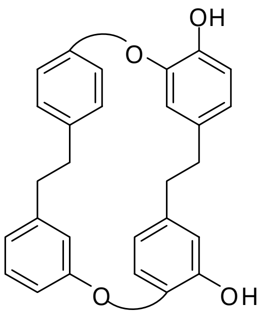
| Cyclic bis(bibenzyls) | Species | References |
|---|---|---|
| 10,12,2’,10’,14’-chloroisoplagiochin C (**66**) | *Bazzania tricrenata* | 14 |
| Asterelin A (**67**) | *Asterella angusta* | 80 |
| Asterelin B (**68**) | *Asterella angusta* | 80 |
| Pusilatin A (**69a**) | *Blasia pussilla* | 25,26,66,67,81 |
| Pusilatin B (**70**) | *Blasia pussilla* | 25,26,66,67,81 |
| Pusilatin C (**71**) | *Blasia pussilla* | 25,26,66,67,81 |
| Pusilatin D (**72**) | *Blasia pussilla* | 25,26,66,67,81 |
| Pusilatin E (**73**) | *Riccardia multifida* | 82 |
| Cavicularin (**76**) | *Cavicularia densa* | 83 |
| $C_{28}H_{16}O_4Cl_6$ | *Bazzania tricrenata* | 14 |
| $C_{28}H_{16}O_4Cl_6$ | *Bazzania tricrenata* | 14 |
| $C_{28}H_{18}O_4Cl_4$ | *Bazzania tricrenata* | 14 |

*Marchantia polymorpha* is a common thalloid liverwort, which is widely distributed in Europe, Asia and America. The crude extract shows antihepatic, antimicrobial, diuretic and allergenic contact dermatitis.[4,7-15] The fractionation of the methanol extract of the Japanese *M. polymorpha* resulted in the isolation of marchantin A (**8a**) as a major component, along with marchantin B (**9**), C (**10**), D (**12**), E (**13**), F (**14**) and G (**15**) [16,21,32,35-37.] The structure of **8a** was suggested by a combination of the chemical degradation and NMR spectrometry. Marchantin series are very viscous gum, however, only the trimethyl ether (**8b**), furnished crystals suitable for X-ray crystallographic analysis. Marchantin A (**8a**) has also been isolated from the other two Japanese *Marchantia*, *M. paleacea* var. *diptera*,[33,38] *M. tosana*[33] and Ecuadorian *M. plicata*,[39] the Pakistan *Plagiochasma appendiculatum* belonging to the Aytoniaceae[40] and *Wiesnerella denudata* to the Concephalaceae.[41]

The structures of the other marchantins B, D-G (**9-15**) were determined by comparison of their spectral data with those of marchantin A (**8a**) and chemical correlation. The stereochemistry of marchantin G (**15**) was confirmed by its X-ray crystallographic analysis.[42] The yield of marchantin A (**8a**) depends on the *Marchantia* species. For example 120 g of pure marchantin A has been obtained from 2 kg of the dried Japanese *M. polymorpha*.



**1a** $R_1 = R_3 =$ H, $R_2 =$ Me
**1b** $R_1 = R_3 =$ Ac, $R_2 =$ Me
**1c** $R_1 = R_2 = R_3 =$ Me
**3** $R_1 = R_2 = R_3 =$ H
**6** $R_1 =$ Me, $R_2 = R_3 =$ H



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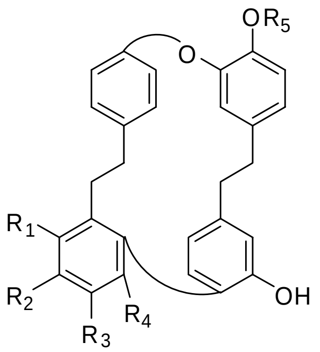
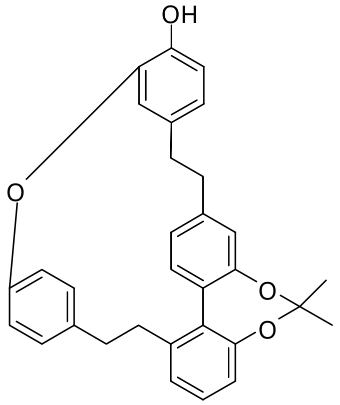
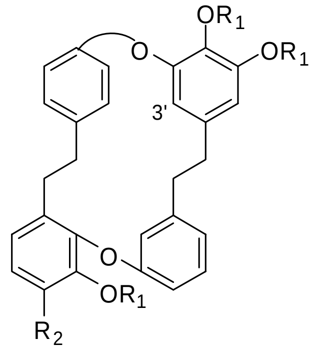


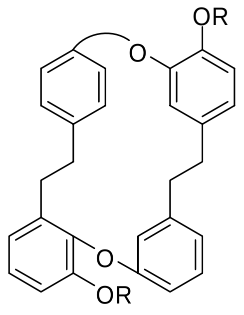
**4a** $R_1 = R_2 = R_3 = R_5 =$ H, $R_4 =$ OH
**5** $R_1 = R_2 = R_3 = R_5 =$ H, $R_4 =$ OMe
**7a** $R_1 = R_2 = R_3 =$ H, $R_4 =$ OH, $R_5 =$ Me
**7b** $R_1 = R_2 = R_3 =$ OH, $R_4 = R_5 =$ H



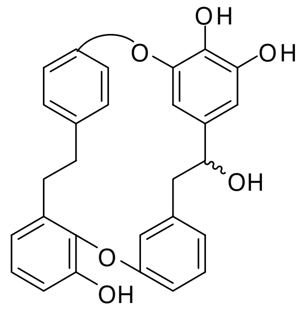
**4b**



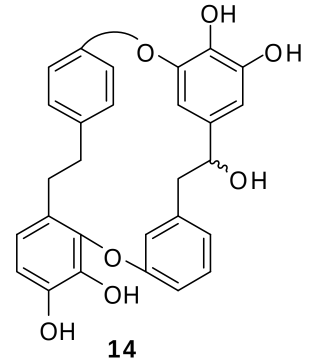
**8a** $R_1 = R_2 =$ H
**8b** $R_1 =$ Me, $R_2 =$ H
**8C** $R_1 =$ Ac, $R_2 =$ H
**9** $R_1 =$ H, $R_2 =$ OH



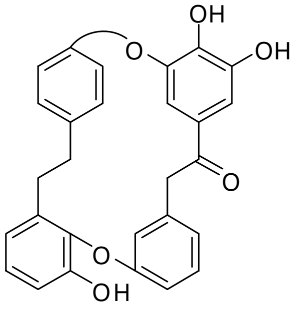
**10** R = H
**11** R = Me



**12** R = H
**13** R = Me

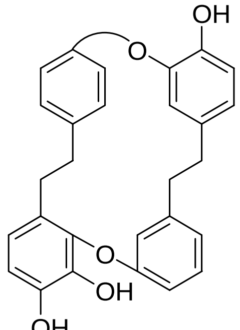


**14**

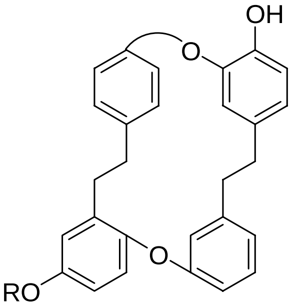


**15**

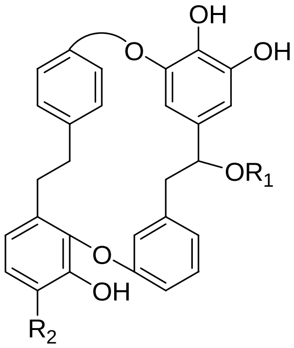
Bioactivity-guided fractionation of the crude ether extract of the Chinese *M. polymorpha* using TLC bioautography assay gave three new bis(bibenzyls), 13, 13'-O-isopropylidenericcardin D (**4b**), riccardin H (**7b**) and plagiochin E (**36b**),



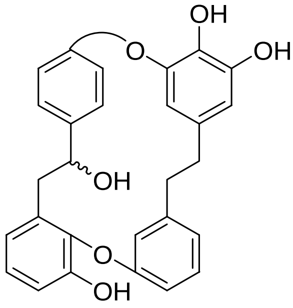
**16**



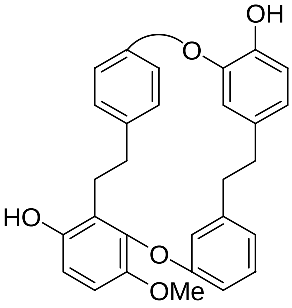
**17a** R = Me
**17b** R = H



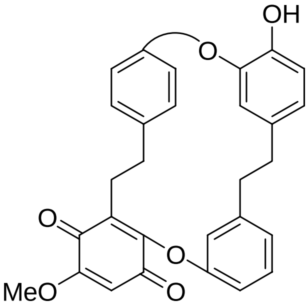
**18a** $R_1$ = Me, $R_2$ = H
**18b** $R_1$ = Et, $R_2$ = OH



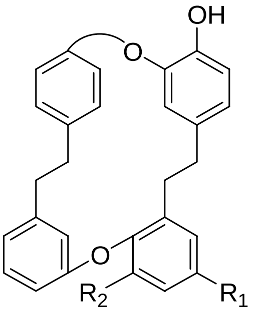
**19**



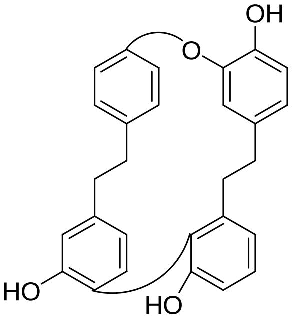
**20**



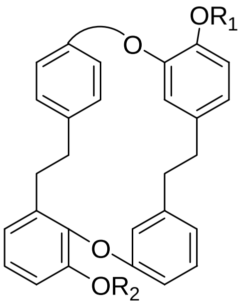
**21**



**22a** $R_1$ =H, $R_2$= OH
**22b** $R_1$ = OH, $R_2$ =H



**23**



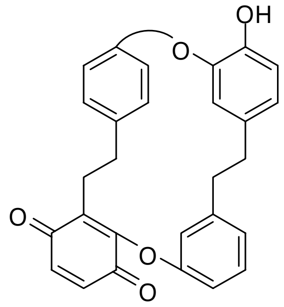
**24** $R_1$ = H, $R_2$ = Me
**25** $R_1$ = Me, $R_2$ = H

together with four known bis(benzyls), marchantin A (**8a**), marchantin B (**9b**), marchantin E (**13**) and neomarchantin A (**31**).[43]

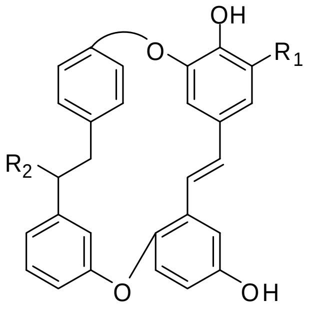
Marchantin A (**8a**) is not stable in the chloroform solution. The chloroform solution of **8a** was stocked for a few days in day light at room temperature, gave an unknown dimer ($M^+$ 878). When marchantin D (**12**) was dissolved in methanol and allowed to stand for one day, the spot of 12 gradually disappeared on TLC and marchantin E (**13**) was then obtained.

The methanol solution of **12** was chromatographed on CN Lobar ® column using 30%

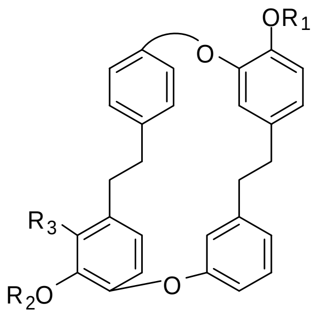
n-hexane/methylene chloride to give marchantin E (**13**) in 50% yield. Thus it is clear that marchantin E (**13**) which has been reported as natural product is artifact.[14]



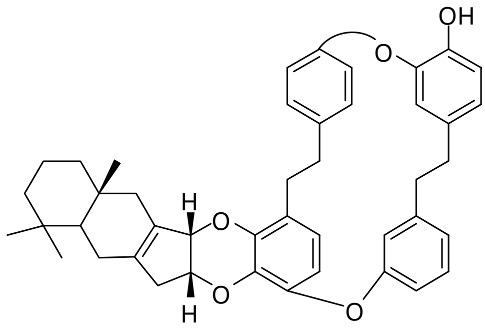
**26**



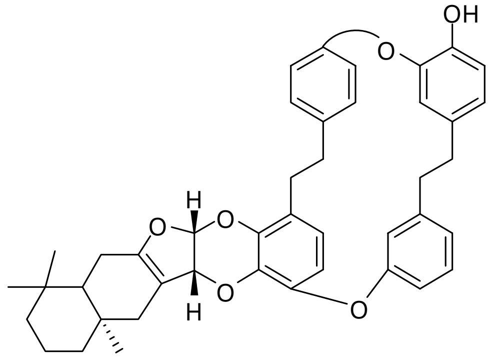
**27** $R_1 = R_2 = H$
**28** $R_1 = OH, R_2 = H$
**29** $R_1 = H, R_2 = OH$



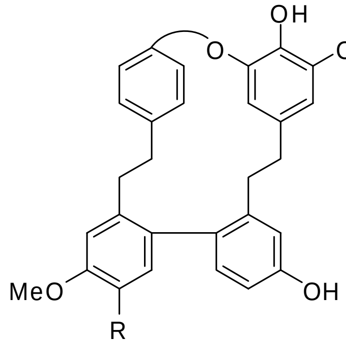
**30** $R_1 = Me, R_2 = R_3 = H$
**31** $R_1 = R_2 = R_3 = H$
**32a** $R_1 = R_2 = H, R_3 = OH$



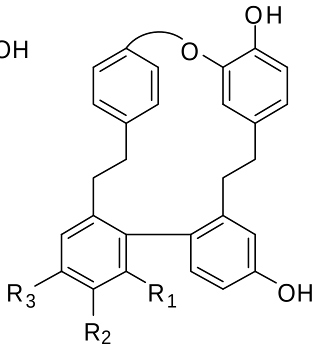
**32b**



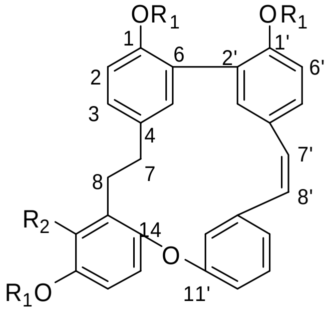
**32c**



**33** R = OH
**34** R = H



**35** $R_1 = H, R_2 = OH, R_3 = OMe$
**36a** $R_1 = R_2 = H, R_3 = OMe$
**36b** $R_1 = OH, R_2 = R_3 = H$



**37** $R_1 = R_2 = H$
**38** $R_1 = H, R_2 = OH$

The similar marchantin series, marchantin H (**16**) and marchantin I (**17a**) were isolated from *Plagiochasma rupestre* and *Riccardia multifida*, respectively.[44] Biosynthetic study of marchantin A (**8a**) was carried out by Zenk and his coworkers and established that marchantin A has been formed from lunularic acid (**74**) by shikimate-malonate pathway.[45,46]

Marchantin C dimethyl ether (**11**)[47], marchantin J-N (**18-21**), isomarchantin C (**22a**) and isoriccardin C (**23**) have been isolated from the different *Marchantia* species,[21,22,32,33, 39-41,48,49] *Dumortiera hirsuta*,[27] *Bryopteris filicina* (Lejeuneaceae),[50] *Mylia nuda* (Jungermanniaceae),[51,52] *Wiesnerella denudata*,[52] *Monoclea forsteri*,[53] *Plagiochila sciophila*,[54] *Reboulia hemisphaerica*[55] and *Plagiochasma rupestre*.[56] as shown in Table 1.

The structure of isomarchantin C (**22a**) isolated from the Indian *Marchantia polymorpha* and *M. palmata*[21] and *Dumortiera hirsuta*[28] was confirmed by X-ray crystallographic analysis. *R. hemisphaerica* and *Mannia subpilosa* (Aytoniaceae) produce marchantiaquinone (**26**).[47] Marchantin O (**24**), the monomethyl ether of marchantin C (**10**), and marchantin P (**25**) were obtained from *R. hemisphaerica*[56-58]and the Venezuelan *Marchantia chenopoda*, respectively.[34]

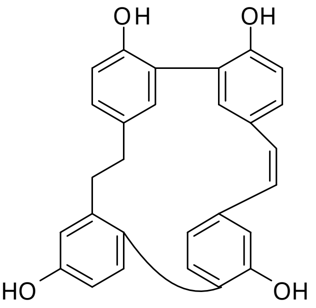
Three novel macrocyclic bis(bibenzyls) named ptychantols A-C (**27-29**), which possess a *trans*-stilbene moiety were isolated from the Japanese liverwort *Ptychantus striatus* (Lejeuneaceae) possessing potent mossy odor and bitter taste.[59] The conclusive evidence for the structure of **27** was established by X-ray crystallographic analysis. Compound **29** was isolated as optically active form with a specific rotation ($[\alpha]_D$ –14.8$^o$) and Cotton effect [289 nm ($\Delta\varepsilon$ +10.6), 270 nm ($\Delta\varepsilon$ –3.0), 233 nm ($\Delta\varepsilon$ +21.2) and 235 nm ($\Delta\varepsilon$ –30.8) in CD spectrum. However, the absolute configuration of **29** remained to be identified. *Mannia fragrans* which contains characteristic fragrant scent elaborates a new bis(bibenzyl) named pakyonol (**30**).[60] The New Zealand liverwort *Schitochila glaucescens* (Schistochilaceae) elaborates neomarchantin A (**31**) and B (**32a**).[61] Further fractionation of the extract of the same species resulted in the isolation of two new bis(bibenzyls) coupled to a sesquiterpene, named Glaucescens Bis Bibenzyl (GBB)A (**32b**) and (GBB) B (**32c**).[62,63] Compound **31** was also isolated from the German *Preissia quadrata* (Marchantiaceae).[64] *Plagiochila sciophila* produces not only marchantin C (**10**) and an acyclic bis(bibenzyl), perrottetin E (**59**), the latter member of the perrottetin class, which contains single *o*,p-ether linkage between two bis(bibenzyl) groups, but also four unique cyclic bis(bibenzyls), plagiochin A-D (**33-36**) which possess two *ortho* biphenyl linkage between the two benzyl groups.[54,65-68] The stereochemistry of compound (**33**) was established by an X-ray crystallographic analysis of its tetramethyl ether.

Further fractionation of the methanol extract of the Japanese *Plagiochila fruticosa* resulted in the isolation of isoplagiochin A-D (**37-40a**).[30] The stereostructure of **37** was established by X-ray crystallographic analysis. Isoplagiochin A (**37**) was identified in *Plagiochila diversifolia*.[69] Pulunasin (**41**) was obtained from culture cell of *Hetroscyphus planus* (Lophocoleaceae) together with isoplagiochin A (**37**).[70] Anton *et al.*[71] reported the isolation and structure elucidation of a new chlorinated bis(bibenzyl), 12-chloroisoplagiochin D (**44**), as well as isoplagiochin respectively. The molecular formula, $C_{28}H_{23}O_4Cl$, of **44** was confirmed by CIMS, which indicated two peaks at m/z 458 and 460 with a ratio of ca 100:35. This indicated that **44** was suggested to be isoplagiochin D monochlorinated compound. The whole structure was determined by comparison of the $^1H$ and $^{13}C$ NMR data with those of isoplagiochin D (**40a**).[68]

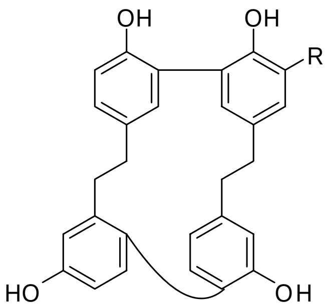
A neotropical *Plagiochila* species which is closely related morphologically to *P. orestitropha* or *P. permista e*laborated a new bis(bibenzyl), named isoplagiochin G (**43b**), along with isoplagiochin C (**39**), D (**40a**), F (**43a**) and a few acyclic bis(bibenzyls).[31]

The *Bazzania* and *Lepidozia* species (Lepidoziaceae) produce a number of peculiar sesquiterpenoids.[4,12] Martin *et al.*[72] reported the isolation of 10 chlorinated bis(bibenzyls), bazzanin A-J (**45-54**) from *Bazzania trilobata* along with bazzanin K (**55**) which possesses a very rare bibenzyl-phenanthrene skeleton. The structure elucidation of these halogen-containing compounds was carried out by high-resolution mass spectrometry as well as 2D-NMR spectra. *Lepidozia incurvata* collected in Costa Rica elaborated bazzanins L-R (**59-65**), together with isoplagiochin C (**39**).[73] Further fractionation of the crude methylene chloride

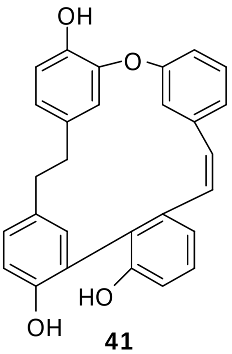
E (**42**) and F (**43a**), isolated from *Plagiochila deflexa*, together with the know isoplagiochin A (**37**). Isoplagiochin E (**43**) and F (**43a**) were C7’-C8’ dihydroisoplagiochin A and 10-hydroxy C7’-C8’ dihydroisoplagiochin A, extract of *Bazzania trilobata* resulted in the isolation of two optical active chlorinated bis(bibenzyls), bazzanin S (**40b**), bazzanin J (**54**). together with isoplagiochin C (**39**) which was detected in the genus *Bazzania* for the first time.[74] In Japan approximately 20 *Bazzania* species are known. *Bazzania tricrenata* also elaborated three chlorinated bis(bibenzyls), among which the structure of **66** was elucidated as 10,12,2’,10’,14’-pentachloroisoplagiochin C.[14] Thus *Lepidozia* is closely related chemically to the *Bazzania.*



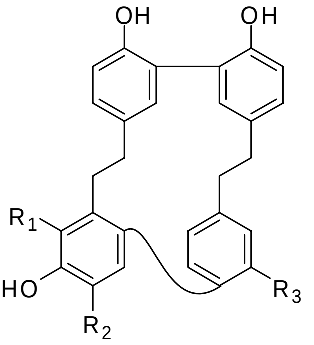
**39**



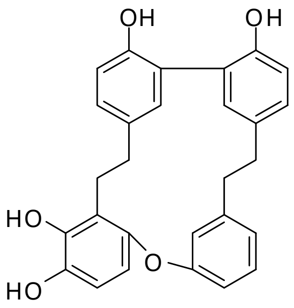
**40a** R =H
**40b** R = Cl



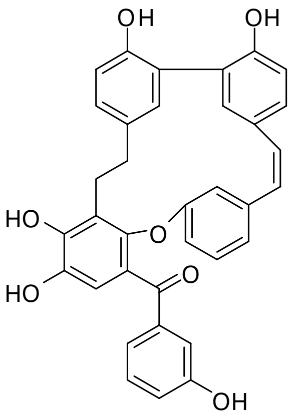
**41**



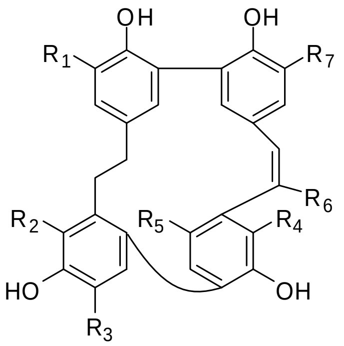
**42** $R_1 = R_2 = R_3 = H$
**44** $R_1 = H, R_2 = Cl, R_3 = OH$



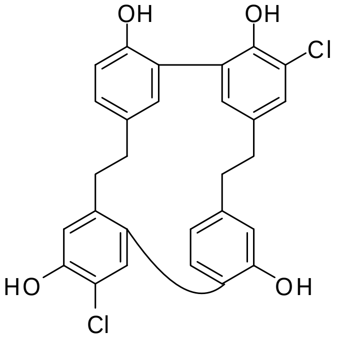
**43a**



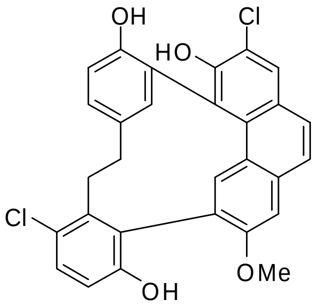
**43b**



**45** $R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = H, R_7 = Cl$
**46** $R_1 = R_2 = R_3 = R_4 = R_5 = H, R_6 = R_7 = Cl$
**47** $R_1 = R_2 = R_4 = R_5 = H, R_3 = R_6 = R_7 = Cl$
**48** $R_1 = R_2 = R_3 = R_5 = H, R_4 = R_6 = R_7 = Cl$
**49** $R_1 = R_2 = R_5 = H, R_3 = R_4 = R_6 = R_7 = Cl$
**50** $R_1 = R_3 = R_4 = H, R_2 = R_5 = R_6 = R_7 = Cl$
**51** $R_1 = R_2 = R_4 = R_6 = R_7 = Cl, R_3 = R_5 = H$
**52** $R_1 = R_3 = H, R_2 = R_4 = R_5 = R_6 = R_7 = Cl$
**53** $R_1 = R_3 = R_4 = R_5 = R_6 = R_7 = Cl, R_2 = H$



**54**



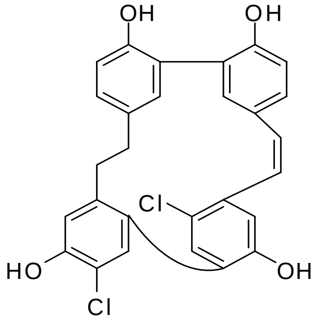
**55**

The Japanese primitive stem-leafy liverwort *Herbertus sakuraii* (Herbertaceae) produces two optically active chlorinated compounds, (-)-12,10'-dichloroisoplagiochin C (**56**) ($[\alpha]_D^{21}$ -19.1 ° and CD : $\lambda_{nm}$ ($\Delta\varepsilon$) : 322 (+7.80), 282 (-7.47), 244 (+48.08), 214 (-157.72) and (-)-12,7'-dichloroisoplagiochin D (**58**)

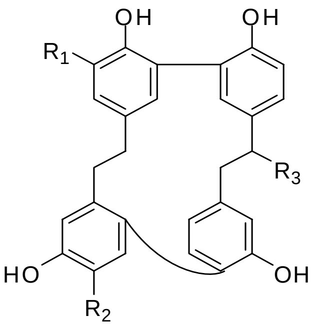
($[\alpha]_D^{20}$ -2.7 ° and CD : $\lambda$nm ($\Delta\varepsilon$) : 300(+0.74), 281(-0.39), 234 (+5.34) and an optically inactive compound, 2,12-dichloroisoplagiochin D (**57**), together with two known optically active isoplagiochin C (**39**) and isoplagiochin D (**40a**).[75] The stereochemistry of **57** was established by X-ray crystallographic analysis.

Their absolute configuration remained to be clarified. The optically inactive isoplagiochin C (**39**) and D (**40a**) have already been isolated from *Plagiochila fruticosa*.[55] However, the present same compounds showed positive optical rotation ($[\alpha]_D$ +74.8° for **39**; +47.5° for **40a**) and Cotton effects [$\lambda_{nm}$ ($\Delta\varepsilon$) : 231 (+24.4), 213 (-63.2) for **39**; 252 (+2.4), 225 (+22.5) for **40a**).

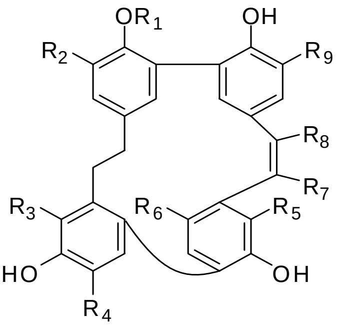
The separation of the enatiomers of isoplagiochin C (**39**) and isoplagiochin D (**40a**) on a chiral phase HPLC was succeeded and this method resolved enantiomes of almost all bis(bibenzyls) isolated from *B. trilobata*.[74] A direct stereochemical online analysis of the peaks by LC-CD coupling showed opposite CD curves clearly revealing that the separated products are enantiomers but not enantio pure in nature. The assignment of these two peaks to the respective enantiomers was achieved by quantum chemical CD calculation using a molecular



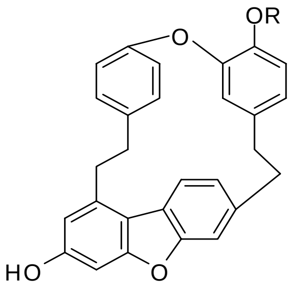
**56**



**57** $R_1 = R_2 = Cl, R_3 = H$
**58** $R_1 = H, R_2 = R_3 = Cl$

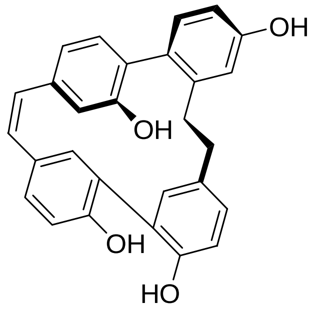


**59** $R_1 = Me, R_2 = R_6 = R_7 = R_8 = R_9 = H, R_3 = R_4 = R_5 = Cl$
**60** $R_1 = R_2 = R_6 = R_7 = R_8 = R_9 = H, R_3 = R_4 = R_5 = Cl$
**61** $R_1 = R_3 = R_7 = R_8 = R_9 = H, R_2 = R_4 = R_5 = R_6 = Cl$
**62** $R_1 = Me, R_2 = R_7 = R_8 = H, R_3 = R_4 = R_5 = R_6 = R_9 = Cl$
**63** $R_1 = R_6 = R_7 = R_8 = H, R_2 = R_3 = R_4 = R_5 = R_9 = Cl$
**64** $R_1 = R_7 = R_8 = H, R_2 = R_3 = R_4 = R_5 = R_6 = R_9 = Cl$
**65** $R_1 = H, R_2 = R_3 = R_4 = R_5 = R_6 = R_7 = R_8 = R_9 = Cl$
**66** $R_1 = R_2 = R_7 = R_8 = H, R_3 = R_4 = R_5 = R_6 = R_9 = Cl$



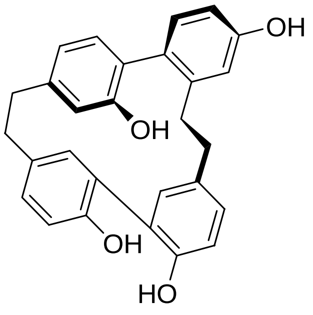
**67** R=H
**68** R=Me

dynamics (MD) based approach.[76] Isoplagiochin C (**39**) and isoplagiochin D (**40a**) are not enatiomerically pure, but composes of 85:15 and 48:52 ratio, respectively in favor of the enantiomer possessing the P-configuration (**39-P** and **40a-P**) at the stereochemically stable axis.[74,77]



isoplagiochin C (P-configuration)

**39-P**



isoplagiochin D (P-configuration)

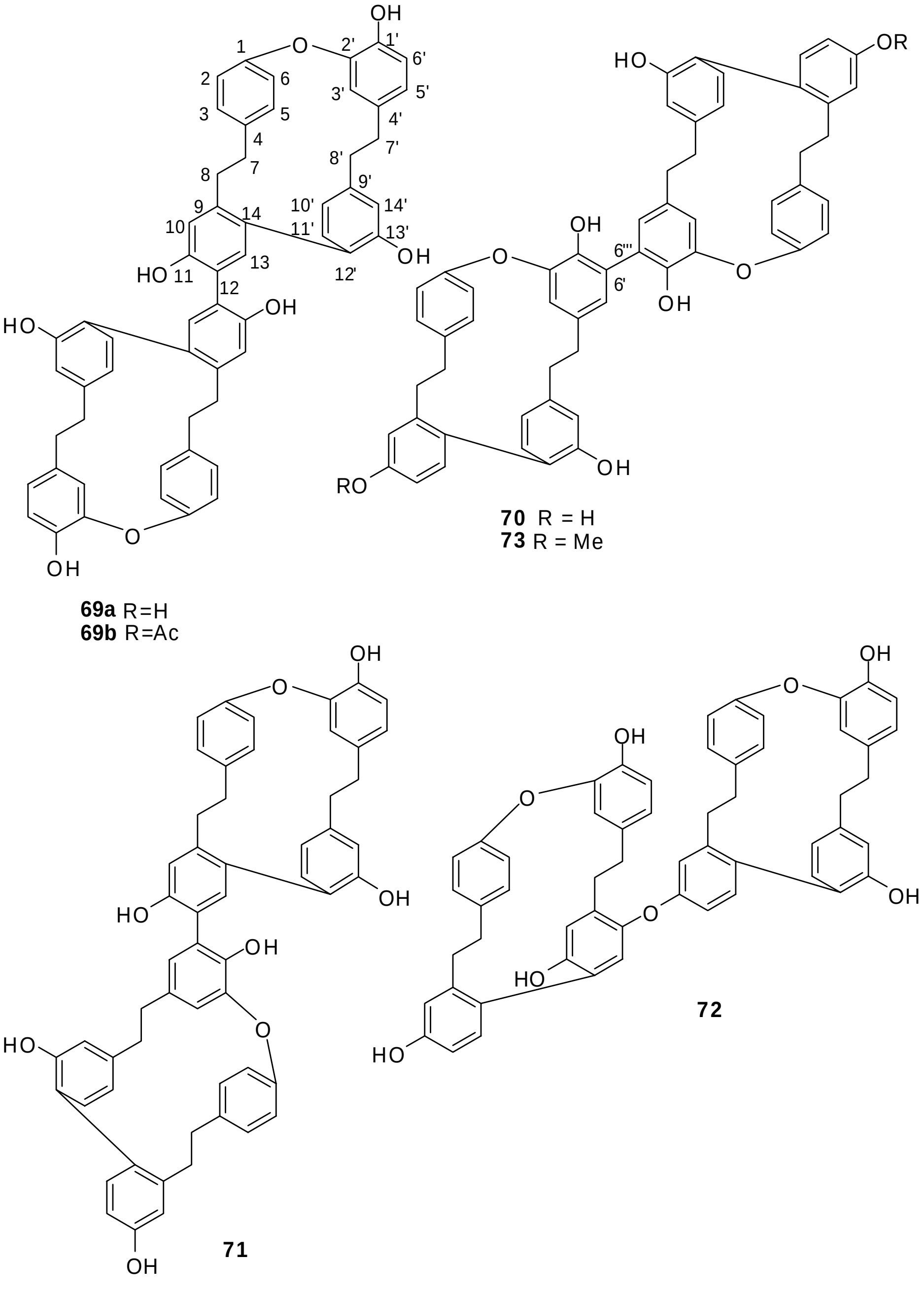
**40a-P**

Two optically inactive chlorinated bis(bibenzyls), 12-chloroisoplagochin D (**44**) and 2,12-dichloroisoplagiochin D (**57**) have also been isolated from *Mastigophora diclados* (Mastigophoroideae).[75] The former compound has been obtained from *Plagiochila deflexa*[31] as mentioned earlier.

The chlorinated bis(bibenzyls) found in the liverworts are not artifact since any chlorinated isoplagiochin C (**39**) and isoplagiochin D (**40a**) were not formed from isoplagiochins during chromatography using chlorinated solvents.

Matrix-assisted laser desorption/ionization time-of flight (MALDI-TOF) mass measurement further confirmed that the chlorinated compounds are not artifacts.[78] Spreicher *et al.*[78] succeeded in the *in vitro* chlorination of isoplagiochin C with chloroperoxydase and were able to detect an enzyme of this type in *B. trilobata.*

Guo *et al.*[79] reported the rapid identification of bis(bibenzyls) using electron ionization (EI)-TOF mass and electron spray ionization triple-quadrupole (ESI-TQ) mass spectrometry. Xing *et al.*[80] developed a simple and rapid LC-DAD/MS/MS method using full scan MS, MS/MS precursor ion scan and MS/MS product ion scan modes for the identification of bis(bibenzyls) including in the crude ether extract of liverworts. The genus *Asterella* belongs to the Aytoniaceae and there are about 80 species in the world.



**69a** R=H
**69b** R=Ac

**70** R = H
**73** R = Me

**71**

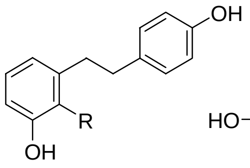
**72**

Some species emits strong bad odor. The Chinese *A. angusta* elaborates two new bibenzofurane bis(bibenzyls), asterelin A (**67**) and asterelin (**68**), 11-*O*-demethyl marchantin I (**17b**) and dihydroptychantol A (**22b**), together with known riccardin B (**2**), marchantin H (**16**), marchantin M (**20**), marchantin P (**25**), plagiochin E (**36b**) and an acyclic bis(bibenzyls), perrottetin E (**59**).[81] The structure of asterelin B was established by X-ray crystallographic analysis.

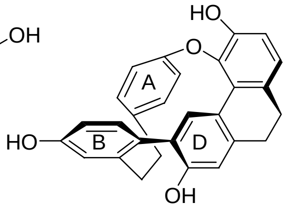
Previously, we reported that the methanol extract of Japanese liverwort, *Blasia pusilla* (Blasiaceae) produced four unique dimeric cyclic bis(bibenzyls) named pusilatin A-D (**69a, 70-72**), together with riccardin C (**3**) and riccardin F (**6**), shikimic acid, and two bibenzyls, lunularic acid (**74**) and lunularin (**75**) which ubiquitously found in liverworts[25,26,66,67,82] and the conclusive evidence for the structure of pusilatin A was obtained by X-ray crystallographic analysis of its hexaacetate (**69b**).

The similar dimeric bis(bibenzyl), pusilatin E (**73**) was isolated from *Riccardia mulitifida* and elucidated its structure as the monomethyl ether of pusilatin B (**70**).[83] Further careful fractionation of the methanol extract of both liverworts collected in the different locations in Japan resulted in the absence of any different pusilatin-type bis(bibenzyl) dimers.

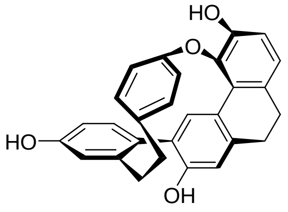
The Japanese rare liverwort *Cavicularia densa*, which belongs to the same Blasiaceae family as *B. pusilla* produces an interesting phenathrene-bibenzyl derivative, named cavicularin (**76**).[84] The absolute structure of **76** was restricted to **76a** or **76b** by X-ray crystallographic analysis. The phenthrene-bibenzyl skeleton possesses a highly strain structure and the benzene ring A was twisted. Although the structure of **76** has no chiral center, its specific optical rotation showed $[\alpha]_D$ +168.2° and the CD Cotton effect due to the $\pi-\pi^*$ transition of the asymmetric aryls [$\lambda_{nm}$ 312 ($\Delta\varepsilon$ +4.6), 280 (+2.6), 255 (-2.6), 208 (+24.6).



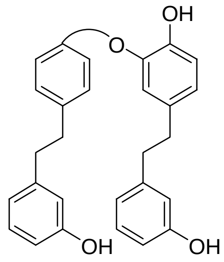
**74** R=$CO_2H$
**75** R=H



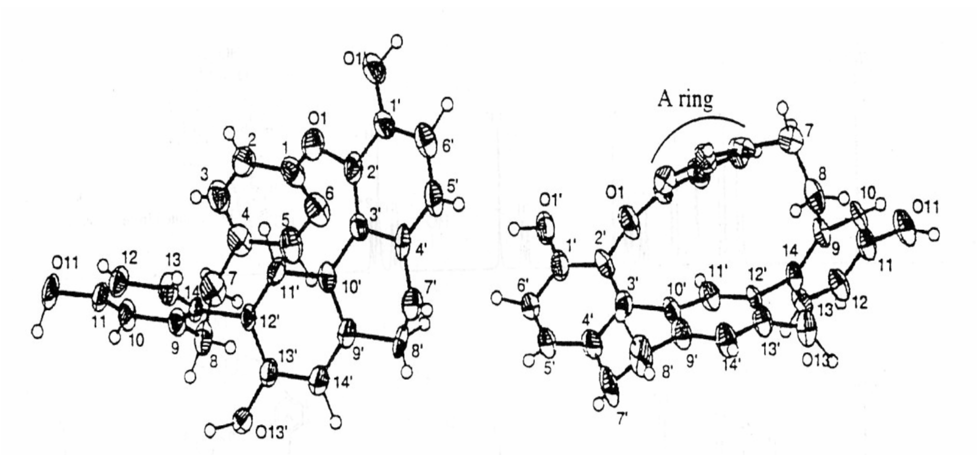
**76a**



**76b**



**77**



This phenomenon suggested that **76** possessed both planar and axial chirality. Such rare cavicularin type bis(bibenzyls) have not been found in any other liverworts so far.

## 2. Biological activity of cyclic bis(bibenzyls) [7-15]

Cyclic bis(bibenzyls) show various biological activities. Riccardin A (**1a**) and (**2**) showed cytotoxic activity against KB cell at a concentration of 10 and 12 μg/mL, respectively. Marchantin A (**8a**), B (**9a**), and C (**10**) also showed the same activity as mentioned above at a concentration of $ED_{50}$ 3.7-20μM and anti-HIV-1 at 5.30-23.7 μg/mL. The dimeric cyclic bis(bibenzyls), pusilatin B (**70**) and C (**72**) showed DNA polymerase β inhibitory activity at a concentration of $IC_{50}$ 13.0 and 5.16μM and cytotoxic activity against KB cell at 13.1 and 13.0 μg/mL, respectively.

Generally, macrocyclic bis(bibenzyls) indicate antimicrobial activity. Marchantin A (**8a**) shows antimicrobial and antifungal activity against various bacteria and fungous, particularly, it inhibited the fungi *Tricophyton mentagraphytes* at MIC 3.13μg/mL. Marchantin A (**8a**) increased coronary blood flow (2.5mL/min at 100μg).

Asterelin A (**67**), B (**68**), 11-*O*-demethylmarchantin I (**17b**), dihydroptychantol A (**22b**), marchantin H (**16**), M (**20**), P (**25**) and plagiochin E (**36b**) isolated from *Asterella angusta* showed moderate antifungal activity against clinical pathogenic fungus *Candida albicans* with MIC values ranging from 16μg/mL to 512μg/mL.[81]

Significant antifungal activity against *C. albicans* was also found for plagiochin E (**36b**), neomarchantin A (**31**), 13,13'-*O*-isopropylydenericcardin D (**4b**), with relative MID values of 0.2, 0.25 and 0.4 μg, respectively compared to that of 0.01μg for positive control miconasole. Marchantin E (**13**), marchantin A (**8a**), B (**9a**) and riccardin H (**7b**) showed the moderate activity against the same fungous at the concentration of 2.5, 2.5, 4.0 and 4.0μg, respectively.[43]

Riccardin A (**1a**) and marchantin A (**8a**), marchantin D (**12**) and E (**13**) indicated inhibitory activity against 5-lipoxigenase and calmodulin. On the other hand, compounds **8a, 9a, 13**, riccardin C (**3**) and isoriccardin C (**23**) and showed weak cyclooxygenase inhibitory activity ($IC_{50}$ 45.2-58.0μM). Isomarchantin C (**22a**) showed 95 and 93% inhibition of cathepcin L and B at 10μM, respectively. Plagiochin A (**33**) showed neurotrophic activity at 1μM.

Marchantin A (**8a**) and related macrocyclic bis(bibenzyls) are structurally similar to bis(bibenzyl)isoquinoline alkaloids such as tubocurarine which are pharmacologically important muscle relaxing active drugs. Astonishingly, marchantin A (**8a**) and its trimethyl ether (**8b**) also showed muscle relaxing activity.[85] Nicotine in frog Ringer solution effects maximum contraction of rectus abdominus frog (RAF) at a concentration of $10^{-6}$ M. After preincubation of marchantin A trimethyl ether (**8b**) at a concentration of 2 x $10^{-7}$～2 x $10^{-4}$M) in Ringer solution, nicotine ($10^{-8}$～$10^{-4}$M) was added. At a concentration of $10^{-6}$M, the contraction of RAF decreased by about 30%. D-Tubocurarine showed the similar effects does marchantin A trimethyl ether (**8b**) using acetyl choline and the same results as described above obtained. MM2 calculations demonstrated that the conformation of **8a** and **8b** and the presence of *ortho* hydroxyl group in **8a** and an *ortho* methoxy group in **8b** contribute to the muscle relaxing. It is noteworthy that marchantin A and its methyl ether possessing no nitrogen atom cause concentration dependent decrease of contraction of RAF. However, marchantin triacetate (**8c**) and inhibition of iNOS is very important to control inflammatory disease. The inhibition of nitric oxide production in lipopolysaccharide (LPS)-stimulated RAW 264.7 cells by several bis(bibenzyls)

Table 2. Inhibitory activity of NO production by bis-bibenzyls isolated from liverworts

| Compound | NO inhibition $IC_{50}$ (μM) |
|---|---|
| Riccardin A (**1a**) | 2.50 |
| Riccardin C (**3**) | > 100 |
| Riccardin F (**6**) | 5.0 |
| Marchantin A (**8a**) | 1.44 |
| Marchantin B (**9a**) | 4.10 |
| Marchantin C (**10**) | 13.28 |
| Marchantin D (**12**) | 10.18 |
| Marchantin E (**13**) | 62.16 |
| Marchantin H (**16**) | 15.34 |
| Isomarchantin C (**22a**) | >100 |
| Ptychantol A (**2**7) | >100 |
| Plagiochin A (**33**) | 9.07 |
| Isoplagiochin B (**38)** | >100 |
| Isoplagiochin D (**40a**) | 14.32 |
| Marchantin A trimethyl ether (**8b**)* | 42.50 |
| Marchantin B tetramethyl ether (**9b**)* | 42.45 |

*Derivatives from marchantin A (**8a**) and marchantin B (**9a**) was investigated and the $IC_{50}$ values of each compound are shown in Table 2. The presence of 1-2' and 14-11' diaryl ether bond is important for strong inhibition of NO production. The presence of phenolic hydroxyl group also plays an important role in the inhibitory activity.

Compounds with 7,8-unsaturation dramatically decreased the inhibition of NO, while the introduction of a hydroxyl group at C-7' resulted in significantly decreased activity.

The methyl ethers (**8b, 9b**) of marchantin A (**8a**) and marchantin B (**9a**) showed weaker activity than the original compounds.[15,86]

Farnesoid X receptor (FXR) controls the expression of critical genes in bile acid and cholesterol homeostasis. FXR is an attractive pharmacological target for the treatment of hyperlipidemia. Marchantin A (**8a**) and marchantin E (**13**) was identified as a FXR agonist.[87]

Plasma high density lipoprotein (HDL) level is inversely related to the risk of atherosclerotic cardiovascular disease. In the research for agents that increases HDL-production, we found that riccardin C (**3**) functions as a liver X-receptor (LXR)$\alpha$ agonist and an (LXR)$\beta$ antagonist. Riccardin C increases plasma HDL level without elevating triglyceride level in mice. This compound also enhances cholesterol efflux from THP-1 cells.[88] From 1.25kg of the dried liverwort *Blasia pusila*, 1 g of riccardin C (**3**) was obtained as a pure state.

## 3. Total synthesis of cyclic bis(bibenzyls)

Since cyclic bis(bibenzyls) found in liverworts possess unique structures and various biological activities, organic chemists focus on their total synthesis. Gottsegen *et al.*[89] synthesized riccardin A-C (**1a,2,3**) by using a combination of Ullmann, Wittig and Wurtz reactions and Ni(0)-assisted intermolecular coupling reaction. Kodama's group[90-92] accomplished the total synthesis of riccardin B (**2**) and marchantin A (**8a**) in twelve steps using the intramolecular Wadsworth-Emmons olefination and Wittig reaction. The total synthesis of riccardin B (**2**) using nickel-catalyzed intramolecular coupling of the acyclic precursors possessing two chlorine atom was reported by Iyoda *et al.*[93] The same compound was also synthesized by Norgadi *et al.*[94] by using a combination of Ullmann, Wittig and Wurtz reactions. Marchantin B (**9a**) and H (**16**) have also been synthesized by Ha *et al.*[95] applying the same methods as described above. By using Ullmann, Wittig and modified Wurtz reaction, Dienes *et* *al*.[96] accomplished the total synthesis of marchantin I (**17**). Keserü *et al.*[97] reported the total synthesis of plagiochin C (**34**) and D (**35**) by the same methodology as that of the total synthesis of marchantin and riccardin series. Fukuyama *et al*.[98,99] accomplished the total synthesis of plagiochins A (**33**), B (**34**) and D (**35**) by a combination of Ullmann, Wadsworth-Emmons, Still-Kelly reactions. Keseru *et al*.[100] reviewed the total synthesis of these types of compounds.

The first elegant total synthesis of cavicularin (**76**) was reported by Harrowven *et al*.[101] The same group also accomplished the shortest total synthesis of riccardin C (**3**).[101]

The bryophytes, in particular, liverworts are charming plants as the sources of natural product chemistry since they grow everywhere in the world except for the sea. Liverworts are tiny and thin leafy or thalloid plants, however, these primitive terrestrial green plants produce various bis(bibenzyls) and terpenoids which show pharmacologically interesting activity. Since the last century, only 5% of the total bryophytes have chemically been studied. Further chemical study on these plant groups will promise us to isolate different type of bioactive compounds from those found previously.

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