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# DISTRIBUTION OF CYCLIC AND ACYCLIC BIS-BIBENZYLS IN THE MARCHANTIOPHYTA (LIVERWORTS), FERNS AND HIGHER PLANTS AND THEIR BIOLOGICAL ACTIVITIES, BIOSYNTHESIS, AND TOTAL SYNTHESIS

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**Abstract** – The Marchantiophyta (liverworts) are rich sources of cyclic and acyclic bis-bibenzyls which are very rare natural products in the plant kingdom. At present more than 70 of bis-bibenzyls have been found in liverworts. The structurally unique cyclic and acyclic bis-bibenzyls shows various biological activities such as antimicrobial, antifungal, cytotoxicity, antiobesitic, muscle relaxation, antitripanosomal activity, among others. They are biosynthesized from dimerization of lunularic acid *via* dihydrocoumaric acid and prelunularin. The present paper deals with the distribution of bis-bibenzyls in liverworts, fern and higher plants and their biological activity, biosynthesis, and total synthesis

## INTRODUCTION

The bryophytes (mosses, liverworts and hornworts) have not been studied chemically since almost one century because they are generally very tiny, and their identification and collection of a large amount are very difficult. Among three classes, only liverworts contain beautiful oil bodies in the cells. The bryophytes are distributed everywhere in the world except in the sea. The most charming countries of the bryophytes are New Zealand, Argentina and Japan. There are so many endemic genera in Southern hemispheric countries. On contrary, in North America, Europe and Africa, the distribution of the endemic genus of bryophytes is very poor. The bryophytes have been considered to be useless for human diets, however, 24 species of the bryophytes have been used in China as medicinal plants.[1] For example, one of

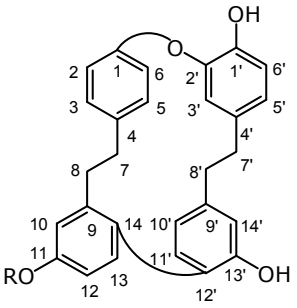
This paper is dedicated to Professor Ei-ichi Negishi for his 77 birthday

the very popular liverwort, *Marchantia polymorpha* shows antipyretic, antidotal, antihepatic and diuretic activity. *Conocephalum conicum* also demonstrates antimicrobial and antifungal activity as well as elimination of gall stone. *Frullania tamarisci* and *Reboulia hemisphaerica* contains antiseptic and hemostatic activity, respectively. Although several liverworts possess such pharmacologically important substances, their isolation was neglected for one century.

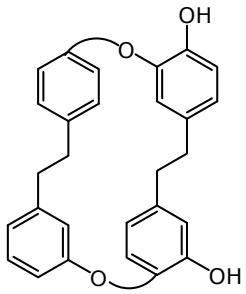
In this paper, the distribution of cyclic- and acyclic bis-bibenzyls in liverworts, their biological activity, biosynthesis, and total synthesis are reported.

## 1. DISTRIBUTION OF CYCLIC AND ACYCLIC BIS-BIBENZYLS IN THE PLANT KINGDOM

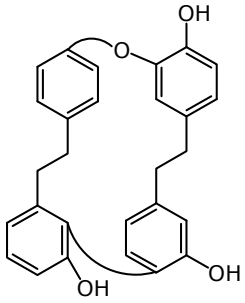
The occurrence, conformation, biosynthesis, biological activity, and synthesis of bis-bibenzyls have been reviewed by *Asakawa*'s group,[2-5] and *Keseru* and *Nogradi*.[6,7] Such macrocyclic and acyclic bis-bibenzyls are very rare plant metabolites possessing structures that occur exclusively in the Marchantiophyta. Such characteristic bis-bibenzyls are not only very significant chemical markers of several Marchantiophyta families but also important for considering the phylogeny of the bryophytes and the evolutionary processes of the lower terrestrial spore-forming plants.



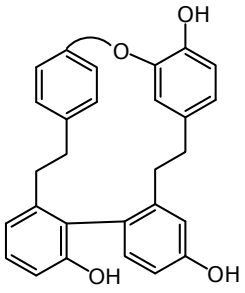

**1** riccardin A: R=Me
**3** riccardin C: R=H



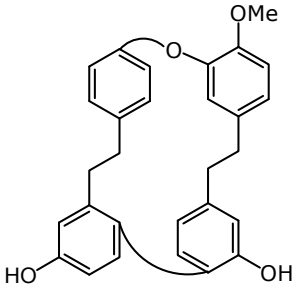

**2** riccardin B



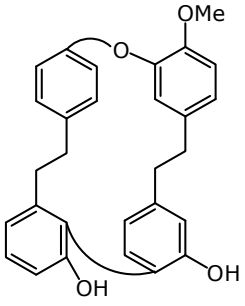

**4** riccardin D




**4a** plagiochin E:
(tentative structure)




**5** riccardin F




**6** riccardin G

In Table 1, the distribution of cyclic and acyclic bis-bibenzyls has been shown. Since two cyclic bis-bibenzyls, riccardin A (**1**) and marchantin A (**14**) were isolated from the thalloid liverworts, *Riccardia*

*multifida* and *Marchantia polymorpha*, more than 70 bis-bibenzyls have been isolated from the Jungermanniales, Metzgeriales and Marchantiales species.[5,8] The isolated bis-bibenzyls are divided into two groups, cyclic and acyclic. The cyclic bis-bibenzyls are further divided into six groups, where bibenzyls are connected with 1) one ether ($C_1$-$C_{2'}$) and one biphenyl linkage ($C_{12}$-$C_{10'}$, $C_{14}$-$C_{10'}$, $C_{14}$-$C_{12'}$); 2) one ether ($C_{14}$-$C_{11'}$) and one biphenyl ($C_6$-$C_{2'}$); 3) one ether ($C_6$-$C_{2'}$) and one biphenyl ($C_{13}$-$C_{10'}$); 4) two ethers ($C_1$-$C_{2'}$ and $C_{13}$-$C_{12'}$, $C_{14}$-$C_{11'}$, $C_{13}$-$C_{10'}$, $C_{12}$-$C_{11'}$); 5) two biphenyls ($C_6$-$C_{2'}$ and $C_{14}$-$C_{12'}$) and 6) two biphenyls ($C_6$-$C_{3'}$ and $C_{14}$-$C_{11'}$). Among these type 4 (two ether linkage between $C_1$-$C_{2'}$ and $C_{14}$-$C_{11'}$) and type 5 (two biphenyls between $C_6$-$C_{2'}$ and $C_{14}$-$C_{12'}$) are most abundant. The former type is distributed in the Marchantiales and the latter in the Jungermanniales.

**Table 1.** Bis-bibenzyls found in the Marchantiophyta

| Structure number | Name of compounds | A-C and B-D ring connection pattern | A-C and B-D ring connection position | Plant source + References |
|---|---|---|---|---|
| **1** | Riccardin A | O-C | $C_1$-$C_{2'}$/$C_{14}$-$C_{12'}$ | *Riccardia multifida*[9]<br>*Riccardia multifida* subsp. *decrescens*[10]<br>*Riccardia nagasakiensis*[11] |
| **2** | Riccardin B | O-O | $C_1$-$C_{2'}$/$C_{13}$-$C_{12'}$ | *Asterella angusta*[12]<br>*Preissia quadrata*[13]<br>*Riccardia multifida*[9] |
| **3** | Riccardin C | O-C | $C_1$-$C_{2'}$/$C_{14}$-$C_{12'}$ | *Blasia pusilla*[14]<br>*Dumortiera hirsuta*[15,16]<br>*Jungermannia infusca*[17]<br>*Mastigophora diclados*[18]<br>*Plagiochasma pterospermum*[19]<br>*Plagiochasma rupestre*[20]<br>*Plagiochasma intermedium*[21]<br>*Plagiochila* sp.[22] |
| **4** | Riccardin D (= Plagiochin E) | O-C | $C_1$-$C_{2'}$/$C_{14}$-$C_{12'}$ | *Asterella angusta*[12]<br>*Dumortiera hirsuta*[16]<br>*Marchantia polymorpha*[23]<br>*Plagiochasma japonica*[24]<br>*Plagiochila cristata*[25] |
| **5** | Riccardin F | O-C | $C_1$-$C_{2'}$/$C_{14}$-$C_{12'}$ | *Blasia pusilla*[14]<br>*Plagiochasma intermedium*[21] |
| **6** | Riccardin G | O-C | $C_1$-$C_{2'}$/$C_{14}$-$C_{12'}$ | *Marchantia chenopoda*[26] |
| **7** | Riccardin H | O-C | $C_1$-$C_{2'}$/$C_{14}$-$C_{12'}$ | *Marchantia polymorpha*[23] |
| **8** | Isoriccardin C | O-C | $C_1$-$C_{2'}$/$C_{12}$-$C_{10'}$ | *Marchantia paleacea*[27]<br>*Plagiochasma intermedium*[21]<br>*Plagiochasma rupestre*[20] |
| **9** | Isoriccardin D | O-C | $C_1$-$C_{2'}$/$C_{12}$-$C_{10'}$ | *Marchantia polymorpha*[28] |
| **10** | IsoriccardinquinoneA | O-C | $C_1$-$C_{2'}$/$C_{12}$-$C_{10'}$ | *Marchantia paleacea*[27] |
| **11** | Isoriccardinquinone B | O-C | $C_1$-$C_{2'}$/$C_{12}$-$C_{10'}$ | *Marchantia paleacea*[27] |
| **12** | 13,13′-*O*-Isopropylidenericcardin D | O-C | $C_1$-$C_{2'}$/$C_{14}$-$C_{12'}$ | *Marchantia polymorpha*[23] |
| **13** | Polymorphatin A | O-C | $C_1$-$C_{2'}$/$C_{12}$-$C_{12'}$ | *Marchantia polymorpha*[28] |
| **14** | Marchantin A | O-O | $C_1$-$C_{2'}$/$C_{14}$-$C_{11'}$ | *Marchantia emarginata* subsp. *tosana*[29] |

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|---|---|---|---|---|
| | | | | *Marchantia paleacea* var. *diptera*[30]<br>*Marchantia polymorpha*[23]<br>*Plagiochasma appendiculatum*[31] |
| **15** | Marchantin B | O-O | $C_1$-$C_{2'}$/$C_{14}$-$C_{11'}$ | *Marchantia paleacea* var. *diptera*[27,32]<br>*Marchantia polymorpha*[23]<br>*Plagiochasma appendiculatum*[31]<br>*Plagiochasma rupestre*[20] |
| **16** | Marchantin C | O-O | $C_1$-$C_{2'}$/$C_{14}$-$C_{11'}$ | *Dumortiera hirsuta*[15,16,33]<br>*Jungermannia infusca*[17]<br>*Marchantia foliacea*[29,34]<br>*Marchantia paleacea* var. *diptera*[27,32]<br>*Plagiochasma appendiculatum*[31]<br>*Plagiochila barteri*[35,36]<br>*Schistochila glaucescens*[37]<br>*Reboulia hemisphaerica*[38,39]<br>*Riccardia nagasakiensis*[11] |
| **17** | Marchantin D | O-O | $C_1$-$C_{2'}$/$C_{14}$-$C_{11'}$ | *Marchantia polymorpha*[32] |
| **18** | Marchantin E | O-O | $C_1$-$C_{2'}$/$C_{14}$-$C_{11'}$ | *Marchantia paleacea* var. *diptera*[30]<br>*Marchantia polymorpha*[23] |
| **19** | Marchantin G | O-O | $C_1$-$C_{2'}$/$C_{14}$-$C_{11'}$ | *Marchantia polymorpha*[32] |
| **20** | Marchantin H | O-O | $C_1$-$C_{2'}$/$C_{14}$-$C_{11'}$ | *Asterella angusta*[12]<br>*Plagiochasma intermedium*[21]<br>*Plagiochila barteri*[35] |
| **21** | Marchantin I | O-O | $C_1$-$C_{2'}$/$C_{14}$-$C_{11'}$ | *Riccardia multifida* subsp. *decrescens*[10] |
| **22** | Marchantin J | O-O | $C_1$-$C_{2'}$/$C_{14}$-$C_{11'}$ | *Marchantia polymorpha*[28] |
| **23** | Marchantin K | O-O | $C_1$-$C_{2'}$/$C_{14}$-$C_{11'}$ | *Plagiochasma rupestre*[20] |
| **24** | Marchantin M | O-O | $C_1$-$C_{2'}$/$C_{14}$-$C_{11'}$ | *Asterella angusta*[12]<br>*Reboulia hemisphaerica*[38] |
| **25** | Marchantin N | O-O | $C_1$-$C_{2'}$/$C_{14}$-$C_{11'}$ | *Reboulia hemisphaerica*[38] |
| **26** | Marchantiaquinone | O-O | $C_1$-$C_{2'}$/$C_{14}$-$C_{11'}$ | *Reboulia hemisphaerica*[38]<br>*Mannia subpilosa*[32,34] |
| **27** | Marchantin O | O-O | $C_1$-$C_{2'}$/$C_{14}$-$C_{11'}$ | *Reboulia hemisphaerica*[38,40] |
| **20** | Marchantin P | O-O | $C_1$-$C_{2'}$/$C_{14}$-$C_{11'}$ | *Asterella angusta*[12]<br>*Marchantia chenopoda*[26]<br>*Marchantia foliacea*[29] |
| **29** | Isomarchantin C | O-O | $C_1$-$C_{2'}$/$C_{13}$-$C_{10'}$ | *Bryopteris filicina*[36]<br>*Dumortiera hirsuta*[15]<br>*Marchantia paleacea* var. *diptera*[32]<br>*Marchantia foliacea*[29] |
| **30** | Isomarchantin C 1'-methyl ether | O-O | $C_1$-$C_{2'}$/$C_{13}$-$C_{10'}$ | *Marchantia foliacea*[29] |
| **31** | Neoisomarchantin C | O-O | $C_1$-$C_{2'}$/$C_{13}$-$C_{11'}$ | *Marchantia foliacea*[29] |
| **32** | Neomarchantin A | O-O | $C_1$-$C_{2'}$/$C_{12}$-$C_{11'}$ | *Marchantia polymorpha*[23]<br>*Plagiochasma intermedium*[21]<br>*Preissia quadrata*[13]<br>*Schistochila glaucescens*[34,37,41] |
| **33** | Neomarchantin B | O-O | $C_1$-$C_{2'}$/$C_{12}$-$C_{11'}$ | *Schistochila glaucescens*[34,37] |
| **34** | Asterellin A | O-C-O | $C_1$-$C_{2'}$/$C_{14}$-$C_{12'}$/<br>$C_{13}$-$C_{13'}$ | *Asterella angusta*[12] |

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| **35** | Asterellin B | O-C-O | $C_1$-$C_{2'}$/$C_{14}$-$C_{12'}$/ $C_{13}$-$C_{13'}$ | *Asterella angusta*[12] |
| **36** | 11-*O*-Demethylmarchantin I | O-O | $C_1$-$C_{2'}$/$C_{14}$-$C_{11'}$ | *Asterella angusta*[12] |
| **37** | Dihydroptychantol A | O-O | $C_1$-$C_{2'}$/$C_{13}$-$C_{10'}$ | *Asterella angusta*[12] |
| **38** | Pakyonol | O-O | $C_1$-$C_{2'}$/$C_{12}$-$C_{11'}$ | *Plagiochasma intermedium*[21,42] *Plagiochasma pterospermum*[19] |
| **39** | Planusin A | O-C | $C_6$-$C_{2'}$/$C_{13}$-$C_{11'}$ | *Heteroscyphus planus*[43] |
| **40** | Plagiochin D | O-C | $C_1$-$C_{2'}$/$C_{14}$-$C_{10'}$ | *Plagiochila ovalifolia*[44] |
| **41** | Plagiochin A | O-C | $C_1$-$C_{2'}$/$C_{14}$-$C_{10'}$ | *Plagiochila ovalifolia*[44] |
| **42** | Plagiochin C | O-C | $C_1$-$C_{2'}$/$C_{14}$-$C_{10'}$ | *Plagiochila ovalifolia*[44] |
| **43** | Plagiochin B | O-C | $C_1$-$C_{2'}$/$C_{14}$-$C_{10'}$ | *Plagiochila ovalifolia*[44] |
| **44** | Isoplagiochin A | C-O | $C_6$-$C_{2'}$/$C_{14}$-$C_{11'}$ | *Heteroscyphus planus*[43] *Plagiochila diversifolia*[45] *Plagiochila fruticosa*[46,47] *Plagiochila permista* var. *integerrima*[48] |
| **45** | Isoplagiochin B | C-O | $C_6$-$C_{2'}$/$C_{14}$-$C_{11'}$ | *Plagiochila fruticosa*[47] |
| **46** | Isoplagiochin C | C-C | $C_6$-$C_{2'}$/$C_{14}$-$C_{12'}$ | *Herbertus sakuraii*[49-51] *Lepidozia incurvata*[52] *Plagiochila fruticosa*[47] *Plagiochila* sp.[22] |
| **47** | Isoplagiochin D | C-C | $C_6$-$C_{2'}$/$C_{14}$-$C_{12'}$ | *Bazzania trilobata*[53] *Herbertus sakuraii*[49-51] *Lepidozia fauriana*[54] *Plagiochila fruticosa*[47] *Plagiochila* sp.[22] |
| **48** | Isoplagiochin E | C-O | $C_6$-$C_{2'}$/$C_{14}$-$C_{11'}$ | *Plagiochila permista* var. *integerrima*[48] |
| **49** | Isoplagiochin F | C-O | $C_6$-$C_{2'}$/$C_{14}$-$C_{11'}$ | *Plagiochila permista* var. *integerrima*[48] *Plagiochila* sp.[22] |
| **50** | Isoplagiochin G | C-O | $C_6$-$C_{2'}$/$C_{14}$-$C_{11'}$ | *Plagiochila* sp.[22] |
| **51** | 2′,10,10′,12,14′-Pentachloro-7′,8′-dehydroisoplagiochin D | C-O | $C_6$-$C_{2'}$/$C_{14}$-$C_{12'}$ | *Bazzania tricrenata*[55] |
| **52** | 12-Chloroisoplagiochin D | C-C | $C_6$-$C_{2'}$/$C_{14}$-$C_{12'}$ | *Mastigophora diclados*[49] *Plagiochila permista* var. *integerrima*[48] |
| **53** | 2,12-Dichloroisoplagiochin D | C-C | $C_6$-$C_{2'}$/$C_{14}$-$C_{12'}$ | *Herbertus sakuraii*[49-51] *Mastigophora diclados*[49] |
| **54** | 12,7′-Dichloroisoplagiochin D | C-C | $C_6$-$C_{2'}$/$C_{14}$-$C_{12'}$ | *Herbertus sakuraii*[49-51] |
| **55** | 12,10′-Dichloroisoplagiochin C | C-C | $C_6$-$C_{2'}$/$C_{14}$-$C_{12'}$ | *Herbertus sakuraii*[49-51] |
| **56** | Bazzanin A | C-C | $C_6$-$C_{2'}$/$C_{14}$-$C_{12'}$ | *Bazzania trilobata*[56] |
| **57** | Bazzanin B | C-C | $C_6$-$C_{2'}$/$C_{14}$-$C_{12'}$ | *Bazzania trilobata*[56] |
| **58** | Bazzanin C | C-C | $C_6$-$C_{2'}$/$C_{14}$-$C_{12'}$ | *Bazzania trilobata*[56] |
| **59** | Bazzanin D | C-C | $C_6$-$C_{2'}$/$C_{14}$-$C_{12'}$ | *Bazzania trilobata*[56] |
| **60** | Bazzanin E | C-C | $C_6$-$C_{2'}$/$C_{14}$-$C_{12'}$ | *Bazzania trilobata*[56] |
| **61** | Bazzanin F | C-C | $C_6$-$C_{2'}$/$C_{14}$-$C_{12'}$ | *Bazzania trilobata*[56] |
| **62** | Bazzanin G | C-C | $C_6$-$C_{2'}$/$C_{14}$-$C_{12'}$ | *Bazzania trilobata*[56] |
| **63** | Bazzanin H | C-C | $C_6$-$C_{2'}$/$C_{14}$-$C_{12'}$ | *Bazzania trilobata*[56] |
| **64** | Bazzanin I | C-C | $C_6$-$C_{2'}$/$C_{14}$-$C_{12'}$ | *Bazzania trilobata*[56] |
| **65** | Bazzanin J | C-C | $C_6$-$C_{2'}$/$C_{14}$-$C_{12'}$ | *Bazzania trilobata*[56] |
| **66** | Bazzanin K | C-C | $C_6$-$C_{2'}$/$C_{14}$-$C_{12'}$ | *Bazzania trilobata*[56] |
| **67** | Bazzanin L | C-C | $C_6$-$C_{2'}$/$C_{14}$-$C_{12'}$ | *Lepidozia incurvata*[52] |
| **67a** | Cavicularin | O-C | $C_1$-$C_{2'}$/$C_{14}$-$C_{12'}$ | *Cavicularia densa*[101] |
| **68** | Bazzanin M | C-C | $C_6$-$C_{2'}$/$C_{14}$-$C_{12'}$ | *Lepidozia incurvata*[52] |
| **69** | Bazzanin N | C-C | $C_6$-$C_{2'}$/$C_{14}$-$C_{12'}$ | *Lepidozia incurvata*[52] |
| **70** | Bazzanin O | C-C | $C_6$-$C_{2'}$/$C_{14}$-$C_{12'}$ | *Lepidozia incurvata*[52] |

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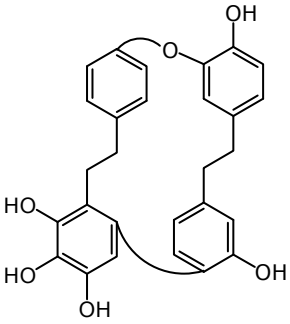
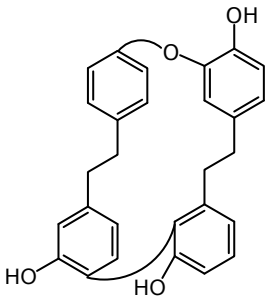
|---|---|---|---|---|
| **71** | Bazzanin P | C-C | $C_6$-$C_{2'}$/$C_{14}$-$C_{12'}$ | *Lepidozia incurvata*[52] |
| **72** | Bazzanin Q | C-C | $C_6$-$C_{2'}$/$C_{14}$-$C_{12'}$ | *Lepidozia incurvata*[52] |
| **73** | Bazzanin R | C-C | $C_6$-$C_{2'}$/$C_{14}$-$C_{12'}$ | *Lepidozia incurvata*[52] |
| **74** | Bazzanin S | C-C | $C_6$-$C_{2'}$/$C_{14}$-$C_{12'}$ | *Bazzania trilobata*[53] |
| **75** | Ptychantol A | O-O | $C_1$-$C_{2'}$/$C_{13}$-$C_{10'}$ | *Ptychanthus striatus*[57] |
| **76** | Ptychantol B | O-O | $C_1$-$C_{2'}$/$C_{13}$-$C_{10'}$ | *Ptychanthus striatus*[57] |
| **77** | Ptychantol C | O-O | $C_1$-$C_{2'}$/$C_{13}$-$C_{10'}$ | *Ptychanthus striatus*[57] |
| **78** | Pusilatin A | O-C/O-C | $C_1$-$C_{2'}$/$C_{14}$-$C_{12'}$ / $C_{1''}$-$C_{2'''}$/$C_{14''}$-$C_{12'''}$ /$C_{12}$-$C_{12''}$ | *Blasia pusilla*[14] |
| **79** | Pusilatin B (= 6′,6‴-Bisriccardin C) | O-C/O-C | $C_1$-$C_{2'}$/$C_{14}$-$C_{12'}$/ $C_{1''}$-$C_{2'''}$/$C_{14''}$-$C_{12'''}$/ $C_{6'}$-$C_{6'''}$ | *Blasia pusilla*[14] *Ricciocarpos natans*[58] |
| **80** | Pusilatin C | O-C/C-O | $C_1$-$C_{2'}$/$C_{14}$-$C_{12'}$ /$C_{1''}$-$C_{2'''}$/ $C_{14''}$-$C_{12'''}$/ $C_{12}$-$C_{6''}$ | *Blasia pusilla*[14] |
| **81** | Pusilatin D | O-C/C-O | $C_1$-$C_{2'}$/$C_{14}$-$C_{12'}$ / $C_{1''}$-$C_{2'''}$/$C_{14''}$-$C_{12'''}$ /$C_{14'}$-$C_{11''}$ | *Blasia pusilla*[14] |
| **82** | Pusilatin E | O-C/O-C | $C_1$-$C_{2'}$/$C_{14}$-$C_{12'}$/ $C_{1''}$-$C_{2'''}$/$C_{14''}$-$C_{12'''}$/ $C_{6'}$-$C_{6'''}$ | *Riccardia multifida* subsp. *decrescens*[10] |
| **85** | 12′,12‴-Bis(10′-hydroxyperrottetin E) | O-C-O | $C_1$-$C_{2'}$/ $C_{1''}$-$C_{2'''}$/ $C_{12'}$-$C_{12'''}$ | *Pellia epiphylla*[59] |
| **83** | GBB A (Glaucescens Bis-Bibenzyl A) | O-O | $C_1$-$C_{2'}$/ $C_{12}$-$C_{11'}$ | *Schistochila glaucescens*[37,41] |
| **84** | GBB B (Glaucescens Bis-bibenzyls B) | O-O | $C_1$-$C_{2'}$/ $C_{12}$-$C_{11'}$ | *Schistochila glaucescens*[37,41] |
| **86** | Glossophyllin | C-C-C | $C_{6-(7)}$-$C_{2'}$ | *Lethocolea glossophylla*[60] |
| **87** | Plagilin | C-C | $C_5$-$C_{5'}$ | *Plagiochila* sp.[22] |
| **88** | Isoplagilin | C-C | $C_5$-$C_{6'}$ | *Plagiochila* sp.[22] |
| **89** | Plagiolin | C-C | $C_5$-$C_{7'}$ | *Plagiochila* sp.[22] |
| **90** | Perrottetin E | O | $C_1$-$C_{2'}$ | *Asterella angusta*[12] *Frullania convoluta*[61] *Jungermannia commata*[9] *Jungermannia infusca*[62] *Marchantia polymorpha*[28] *Monoclea forsteri*[63] *Nardia subclavata*[55] *Pellia epiphylla*[59,64] *Radula laxiramea*[65] |
| **91** | Perrottetin F | O | $C_1$-$C_{2'}$ | *Frullania convoluta*[61] |
| **92** | Perrottetin G | O | $C_1$-$C_{2'}$ | *Frullania convoluta*[61] |
| **93** | 7',8'-Dehydroperrottetin F | O | $C_1$-$C_{2'}$ | *Frullania convoluta*[61] |
| **94** | Perrottetin E 11'-methyl ether | O | $C_1$-$C_{2'}$ | *Pellia epiphylla*[55] |
| **95** | Paleatin B | O | $C_{14}$-$C_{11'}$ | *Nardia cubclavata*[55] |
| **96** | 6,6′,10,10′,12,12′-Hexachloro-isoperrottetin A | O | $C_6$-$C_{6'}$ | *Jamesoniella colorata*[66] |
| **97** | Perrottetin E-11-methyl ether | O | $C_6$-$C_{6'}$ | *Pellia epiphylla*[59] |
| **98** | 14′-Hydroxyperrottetin E | O | $C_6$-$C_{6'}$ | *Pellia epiphylla*[59] |
| **99** | 10′-Hydroxyperrottetin E | O | $C_6$-$C_{6'}$ | *Pellia epiphylla*[59,64] |
| **100** | 10′-Hydroxyperrottetin E-11-methyl ether | O | $C_6$-$C_{6'}$ | *Pellia epiphylla*[59,64] |
| **101** | 10,10′-Dihydroxyperrottetin E | O | $C_6$-$C_{6'}$ | *Pellia epiphylla*[59] |
| **102** | Isoperrottetin A | C | $C_6$-$C_{6'}$ | *Radula perrottetii*[3] |
| **103** | Curciatin | O | $C_1$-$C_{2'}$/ $C_{1''}$-$C_{2'''}$ | *Lunularia curciata*[3] |

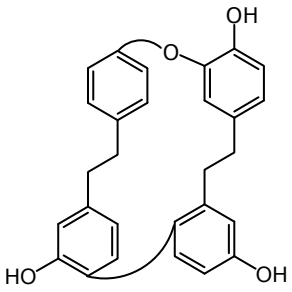
Among riccardin type bis-bibenzyls (type 1), riccardin C (**3**) have been distributed in the Marchantiaceae and *Plagiochasma* species belonging to the Aytoniaceae. The type five, where one biphenyl connected between $C_6$-$C_{2'}$ and second between $C_{14}$-$C_{12'}$ is distributed in the stem-leafy liverwort, *Plagiochila fruticosa* collected in the southern Shikoku, Japan.



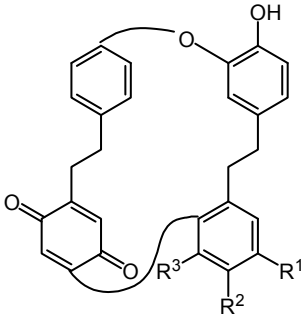
**7** riccardin H



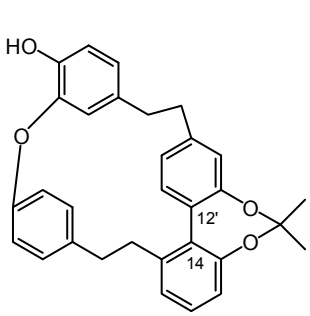
**8** isoriccardin C



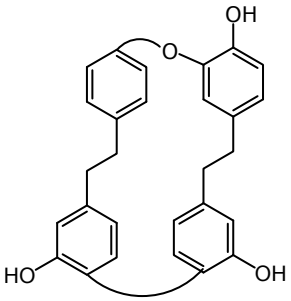
**9** isoriccardin D



**10** isoriccardinquinone A: $R^1$=OH, $R^2$=H, $R^3$=OMe
**11** isoriccardinquinone B: $R^1$=$R^3$=H, $R^2$=OMe



**12** 13,13'-*O*-isopropylidenericcardin D



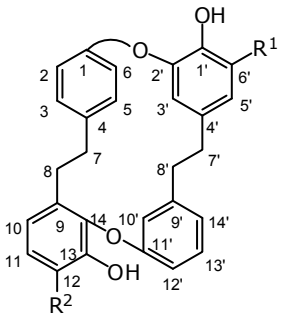
**13** polymorphatin A

Plagiochin- and isoplagiochin types (type 1 and 2) of bis-bibenzyls have been distributed in the *Plagiochila*, *Heteroscyphus* and *Herbertus* species belonging to the Jungermanniales. Cyclic bis-bibenzyls are restricted to Aneuraceae, Blasiaceae which belong to the Metzgeriales, and the Aytoniaceae, Marchantiaceae, Monocleaceae and Ricciaceae belonging to the Marchantiales.

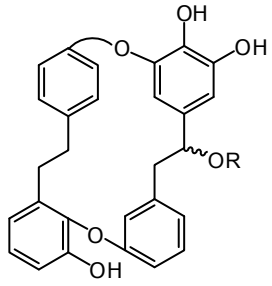
Since 1995, 14 acyclic bis-bibenzyls (**87-102**) have been isolated from the Marchantiophyta and their structures elucidated. These are mainly distributed in the *Radula, Plagiochila, Nardia* and *Jungermannia* belonging to the Jungermanniales, *Pellia* to the Metzgeriales, and *Marchantia* and *Lunularia* to the Marchantiales.

The crude extract of the higher plant, *Primula macrocalyx* (Primulaceae), which has been used in folk medicine to treat paralysis, scurvy, tuberculosis, and fever was fractionated by column chromatography using a reversed-phase resin to give bis-bibenzyl identified as riccardin C (**3**).[67] This is the first record of the isolation of the macrocyclic bis-bibenzyl from a higher plant. On the other hand, the acyclic bis-bibenzyl, perrottetin H (**92a**), has been isolated from the Japanese fern, *Hymenophyllum barbatum*.[68]

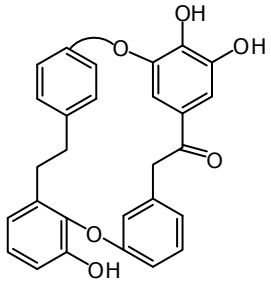
Such characteristic bis-bibenzyls are not only very significant chemical markers of several Marchantiophyta families but also important for considering the phylogeny of the bryophytes and the evolutionary processes of the lower terrestrial spore-forming plants.



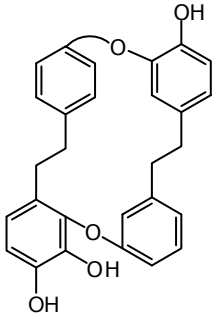
**14** marchantin A: $R^1$=OH; $R^2$=H
**15** marchantin B: $R^1$=$R^2$=OH
**16** marchantin C: $R^1$=$R^2$=H



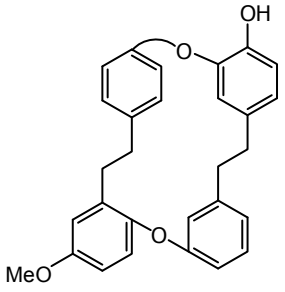
**17** marchantin D :R=H
**18** marchantin E: R=Me



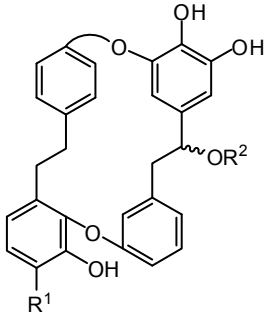
**19** marchantin G



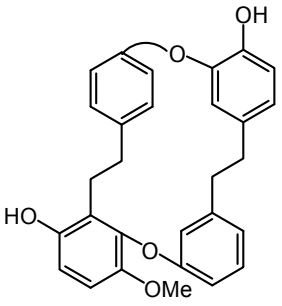
**20** marchantin H



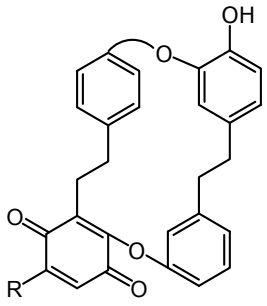
**21** marchantin I



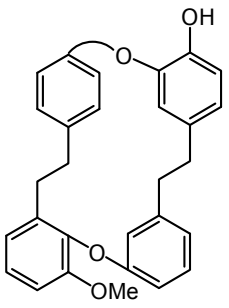
**22** marchantin J: $R^1$=H; $R^2$=Et
**23** marchantin K: $R^1$=OH, $R^2$=Me



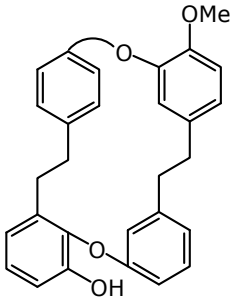
**24** marchantin M



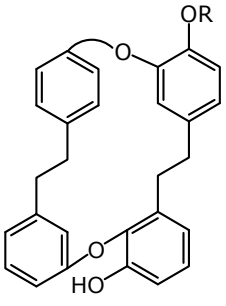
**25** marchantin N: R=OMe
**26** marchantiaquinone: R=H



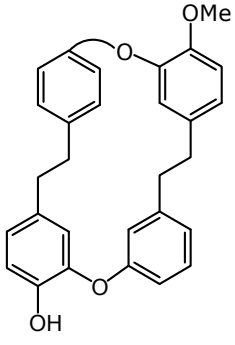
**27** marchantin O



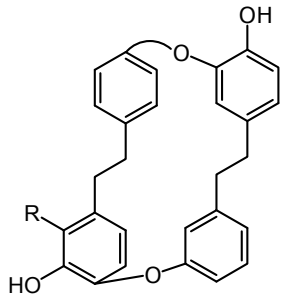
**28** marchantin P



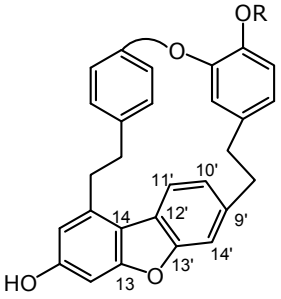
**29** isomarchantin C: R=H
**30** isomarchantin C1'-methyl ether: R=Me



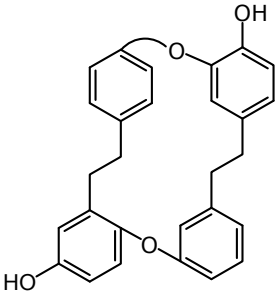
**31** neoisomarchantin C



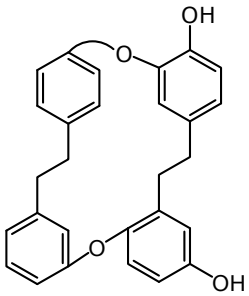
**32** neomarchantin A: R=H
**33** neomarchantin B: R=OH



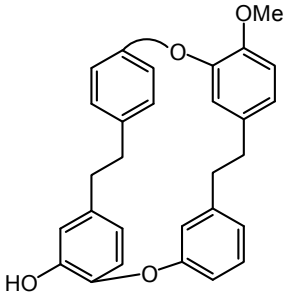
**34** asterelin A: R=H
**35** asterelin B: R=Me



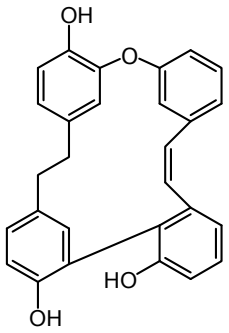
**36** 11-*O*-demethylmarchantin I



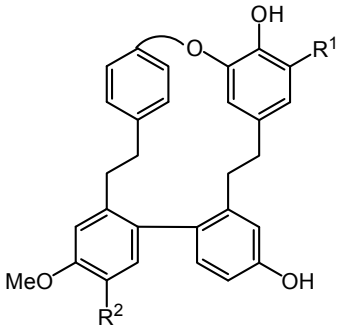
**37** dihydroptychantol A



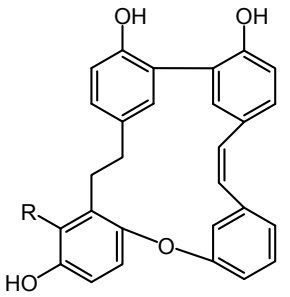
**38** pakyonol



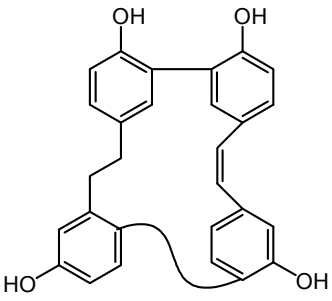
**39** planusin A



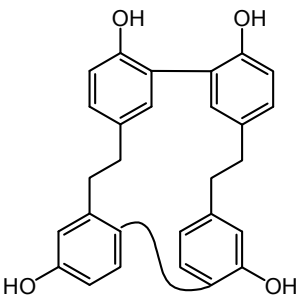
**40** plagiochin D: $R^1$=$R^2$=H
**41** plagiochin A: $R^1$=$R^2$=OH
**42** plagiochin C: $R^1$=H, $R^2$=OH
**43** plagiochin B: $R^1$=OH, $R^2$=H



**44** isoplagiochin A: R=H
**45** isoplagiochin B: R=OH



**46** isoplagiochin C



**47** isoplagiochin D

## 2. BIOLOGICAL ACTIVITY OF BIS-BIBENZYLS

In earlier reviews,[2,3] chemical constituents isolated from liverworts (Marchantiophyta) were discussed,

possessing characteristic fragrances, bitterness, pungency, and sweetness as well as allergenic contact dermatitis, cytotoxic, antimicrobial, antifungal, calmodulin inhibitory, cardiotonic, insect antifeedant, 5-lipoxygenase inhibitory, molluscicidal, muscle relaxant, neurotrophic, plant growth regulatory, superoxide release inhibitory, thromboxane synthase inhibitory, and vasopressin antagonist activities. Several reviews dealing with biologically active compounds from liverworts have been published more recently.[69-79]

### 2.1. Antibacterial, Antifungal and Antiviral Activity

Six bis(bibenzyls), riccardin C (**3**), riccardin F (**5**), isoriccardin C (**8**), marchantin H (**20**), neomarchantin A (**32**), and pakyonol (**38**) isolated from *Plagiochasma intermedium* possessed weak *in vitro* antifungal activity against the fluconazole-sensitive and resistant strains of *Candida albicans* at *MIC*'s ranging from 32 to >512μg/cm$^3$. When riccardin C (**3**) was combined to fluconazole, the synergistic or additive activity of **3** caused the *MIC*s of fluconazole to be reduced from 256 to <8μg/cm$^3$ against three resistant strains of *C. albicans*.[21]

*Guo* and associates[80] reported that riccardin D (**4**) indicated antifungal activity against the fluconazole-resistant *Candida albicans* strains, QL-14, QL-28, SDEY-24R and SDEY-09R at *MIC* 16, 32, 16 and 16μg/cm$^3$, respectively. This activity is more potent than fluconazole itself. When riccardin D (**4**) was mixed with fluconazole, the antifungal activity dramatically increased to 0.3125-0.375μg/cm$^3$.

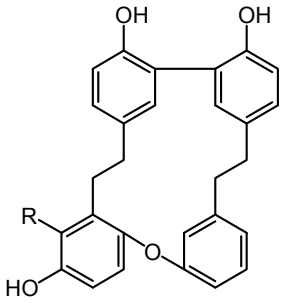
*Wu* and colleagues[81] demonstrated that the antifungal activity of riccardin D (**4**) (= plagiochin E) might be attributed to its inhibitory effect on cell wall chitin synthesis in *Candida albicans*.

Riccardin D (**4**) exerts its antifungal activity through mitochondrial dysfunction-induced reactive oxygen species accumulation in *Candida albicans*.[82] Riccardin D (**4)** also induced apoptosis in *Candida albicans* through activating the metacaspase.[83]

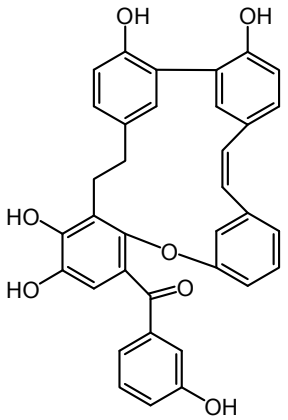
The known bis-bibenzyls, isoplagiochin D (**47**), 6',8'-dichloroisoplagiochin C (= bazzanin B) (**57**), and 6'-chloroisoplagiochuin D (= bazzanin S) (**66**), isolated from *Bazzania trilobata*, showed discernible antifungal activity in a micro titer plate test against *Pyricularia oryzae* and *Septoria tritici.* Compound **47** also demonstrated inhibitory activity against *Botrytis cinerea.* Free hydroxyl groups on the benzene rings of bis-bibenzyls play an important role in mediating inhibitory activity against fungi such as *Cladosporium cucumerinum*.[53]

Marchantin C (**16**), neomarchantins A (**32**) and B (**33**) isolated from *Schistochila glaucescens* showed antimicrobial activity against the *Gram*-positive bacterium, *Bacillus subtilis*, with *MIC* 2, 1.5, and 2μg/cm$^3$, and were also active against the dermatophytic fungus *Trichophyton mentagrophytes*, with *MIC* values of 0.5, 0.5, and 1μg/cm$^3$. [37]

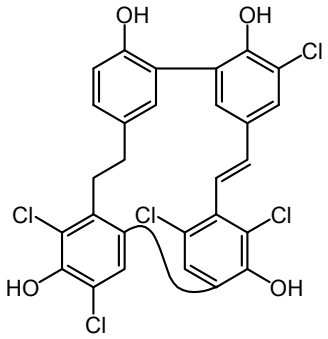
The H1N1 and H5N1 influenza A virus caused pandemics throughout the world in 2009. Influenza A possesses an endonuclease within its RNA polymerase which comprises PA, PB1, and PB2 subunits. In order to obtain potential new anti-influenza compounds, 33 different types of phytochemicals using a PA endonuclease inhibition assay *in vitro* and an antiinfluenza virus assay were investigated.[84] Among them, marchantins A (**14**), B (**15**), and E (**18**), plagiochin A (**41**), and perrottetin F (**91**) inhibited influenza PA endonuclease activity at a concentration of 10μM. This is the first evidence that the phytochemicals derived from liverworts can inhibit the influenza A endonuclease.



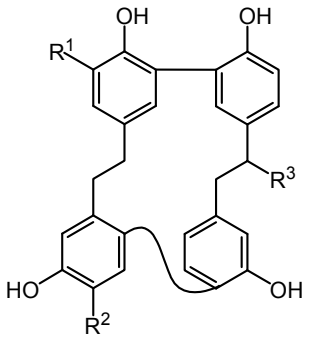
**48** isoplagiochin E: R=H
**49** isoplagiochin F: R=OH



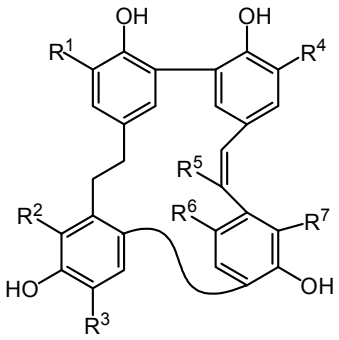
**50** isoplagiochin G



**51** 2',10,10',12,14'-pentachloro-7',8'-dehydroisoplagiochin D



**52** 12-chloroisoplagiochin D: $R^1$=$R^3$=H, $R^2$=Cl
**53** 2,12-dichloroisoplagiochin D: $R^1$=$R^2$=Cl, $R^3$=H
**54** 12,7'-dichloroisoplagiochin D: $R^1$=H,$R^2$=$R^3$=Cl

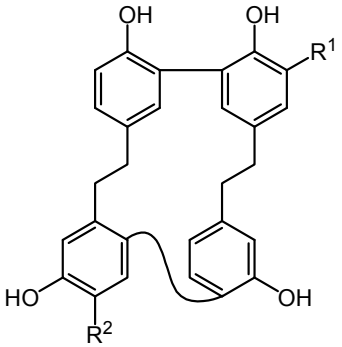


**55** 12,10'-dichloroisoplagiochin C: $R^1$=$R^2$=$R^4$=$R^5$=$R^7$=H, $R^3$=$R^6$=Cl
**56** bazzanin A: $R^1$=$R^2$=$R^3$=$R^5$=$R^6$=$R^7$=H, $R^4$=Cl
**57** bazzanin B: $R^1$=$R^2$=$R^3$=$R^6$=$R^7$=H, $R^4$=$R^5$=Cl
**58** bazzanin C: $R^1$=$R^2$=$R^6$=$R^7$=H, $R^3$=$R^4$=$R^5$=Cl
**59** bazzanin D: $R^1$=$R^2$=$R^3$=$R^7$=H, $R^4$=$R^5$=$R^6$=Cl
**60** bazzanin E: $R^1$=$R^2$=$R^7$=H, $R^3$=$R^4$=$R^5$=$R^6$=Cl
**61** bazzanin F: $R^1$=$R^3$=$R^6$=H, $R^2$=$R^4$=$R^5$=$R^7$=Cl
**62** bazzanin G: $R^3$=$R^7$=H, $R^1$=$R^2$=$R^4$=$R^5$=$R^6$=Cl
**63** bazzanin H: $R^1$=$R^3$=H, $R^2$=$R^4$=$R^5$=$R^6$=$R^7$=Cl
**64** bazzanin I: $R^2$=H, $R^1$=$R^3$=$R^4$=$R^5$=$R^6$=$R^7$=Cl

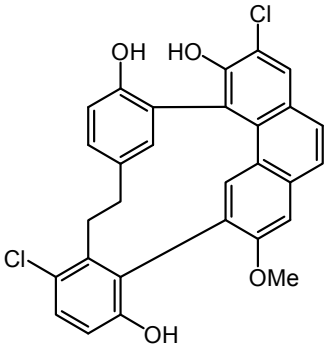
## 2.2. Antioxidant Activity

Marchantin A (**14**) also showed free radical scavenging activity at $EC_{50}$ 20μg/cm$^3$.[85] Marchantin H (**20**) showed non-enzymatic iron-induced lipid peroxidation in rat brain homogenates at $IC_{50}$ 0.51μM.[86] It is

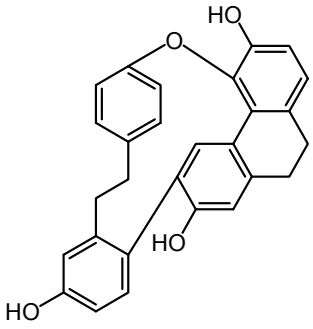
stronger than desferrioxamine or other classical antioxidants. Compound (**20**) suppressed NADPH-dependent microsomal lipid peroxidation at $IC_{50}$ 0.32μM without affecting microsomal electron transport of NADPH-cytochrome P450 reductase. It also inhibited copper-catalyzed oxidation of human low-density lipoprotein. *Hsiao* and colleagues concluded that marchantin H (**20**) is a potentially effective and versatile antioxidant, and can be used as a chaperone protecting the biomacrocyclic molecule against peroxidative damage.[86]



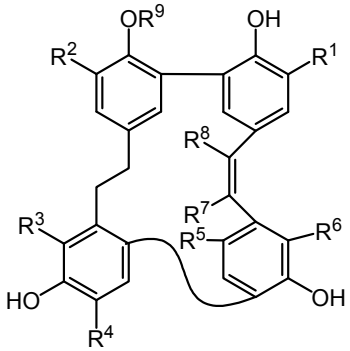

**65** bazzanin J: $R^1$=$R^2$=Cl
**66** bazzanin S: $R^1$=Cl, $R^2$=H



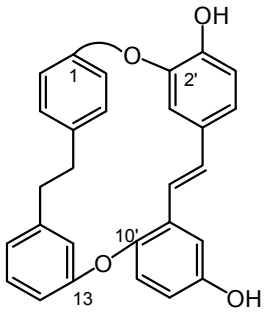

**67** bazzanin K



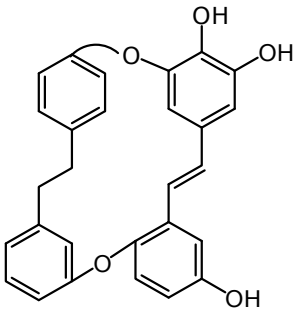

**67a** cavicularin



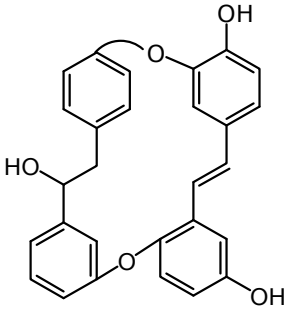

**68** bazzanin L: $R^1$=$R^2$=$R^6$=$R^7$=$R^8$=H, $R^3$=$R^4$=$R^5$=Cl, $R^9$=Me
**69** bazzanin M: $R^1$=$R^2$=$R^6$=$R^7$=$R^8$=$R^9$=H, $R^3$=$R^4$=$R^5$=Cl
**70** bazzanin N: $R^1$=$R^6$=$R^7$=$R^8$=$R^9$=H, $R^2$=$R^3$=$R^4$=$R^5$=Cl
**71** bazzanin O: $R^2$=$R^7$=$R^8$=H, $R^1$=$R^3$=$R^4$=$R^5$=$R^6$=Cl, $R^9$=Me
**72** bazzanin P: $R^1$=$R^2$=$R^3$=$R^4$=$R^5$=Cl, $R^6$=$R^7$=$R^8$=$R^9$=H
**73** bazzanin Q: $R^1$=$R^2$=$R^3$=$R^4$=$R^5$=$R^6$=Cl, $R^7$=$R^8$=$R^9$=H
**74** bazzanin R: $R^1$=$R^2$=$R^3$=$R^4$=$R^5$=$R^6$=$R^7$=$R^8$=Cl, $R^9$=H




**75** ptychantol A




**76** ptychantol B




**77** ptychantol C

## 2.3. Antiplatelet Activity

Marchantiaquinone (**26**), obtained from *Reboulia hemisphaerica*, showed antiplatelet activity at a concentration level of 100μg/cm$^3$.[38]

### 2.4. Antithrombin Activity

Perrottetin E (**90**) showed inhibitory activity against thrombin ($IC_{50}$ 18μ*M*), which is associated with blood coagulation.[9]

### 2.5. Cytotoxic and Apoptotic Activity

Riccardin D (= plagiochin E) (**4**) indicated proliferation inhibitory activity on human glioma A172 cell and induction of apoptosis at 16μ*M*. Compound **4** also possesses strong effects in reversing P-glycoprotein-mediated multidrug resistance. Thus, compound **4** is a potential candidate for reversing drug resistance in cancer chemotherapy.[87]

The antitumor activity of riccardin F (**5**) and pakyonol (**38**) were evaluated *in vitro* by employing K562 and K562/1702 cells, the well-known Adriamycin-induced multidrug resistance tumor cell lines over-expressing P-glycoprotein. In the presence of riccardin F (**5**) or pakyonol (**38**) $ID_{50}$ of ADR against K562/1702 cells decreased by 2.51- and 4.78-fold, respectively.[88]

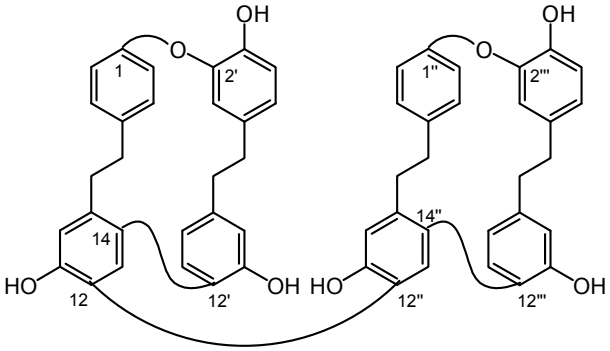
Marchantin C (**16**), neomarchantins A (**32**) and B (**33**), and a mixture of sesquiterpene/bis-bibenzyl dimers, GBB A (**83**) and GBB B (**84**) from *Schistochila glaucescens* showed growth inhibitory effects for the P-388 cell line, with $IC_{50}$ values of 8.5, 18, 7.6, and 10.3μg/cm$^3$, respectively.[37]

Marchantins A (**14**), B (**33**), D (**15**), perrottetin F (**91**), and paleatin B (**95**) showed DNA polymerase β□ inhibitory ($IC_{50}$ range 14.4-97.5μ*M*), cytotoxicity against KB cells ($IC_{50}$ range 3.7-20μ*M*), and anti-HIV-1 activity ($IC_{50}$ range 5.3-23.7μg/cm$^3$).[5,55] Marchantin A (**14**) induced cell growth inhibition in human MCF-7 breast cancer cells at $IC_{50}$ 4.0μg/cm$^3$. Fluorescence microscopic and a Western blot analysis indicated that compound **14** actively induced apoptosis of MCF cells through a caspase dependent pathway. The phenolic hydroxyl groups at $C_{1'}$ and $C_{6'}$ are responsible for inducing cytotoxic and antioxidant activity. Thus, marchantin A (**14**) is also a potential candidate drug for chemotherapy.[85]

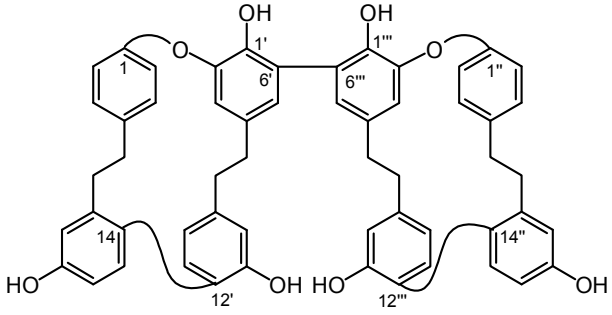
Marchantin C (**16**) influences the migration and invasion of brain cancer cells and is capable to inhibit angiogenesis at low concentrations. The same compound appears to affect matrix metalloproteinase (MMP)-2 activity *via* the MAPK pathway.[89]

### 2.6. Farnesoid X-receptor (FXR) activation

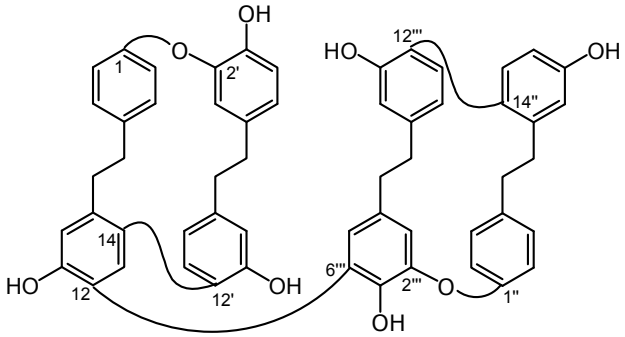
The farnesoid X-receptor (FXR), a member of the nuclear-receptor super-family, controls the expression of critical genes in bile acid and cholesterol homeostasis. Marchantins A (**14**) and E (**18**) activated FXR in this receptors assay at a high potency level, comparable to that of the most potent endogenous bile acid, chenodeoxycholic acid.[30]



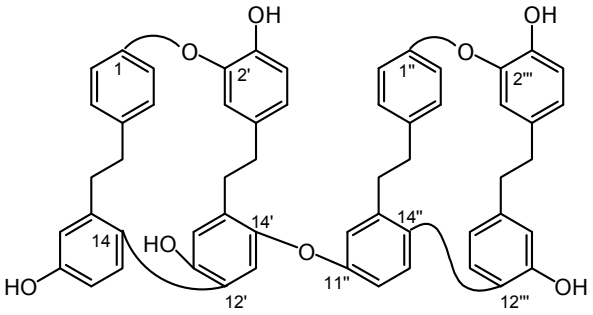
**78** pusilatin A



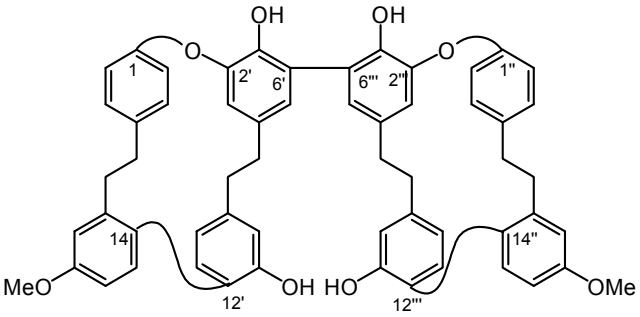
**79** pusilatin B



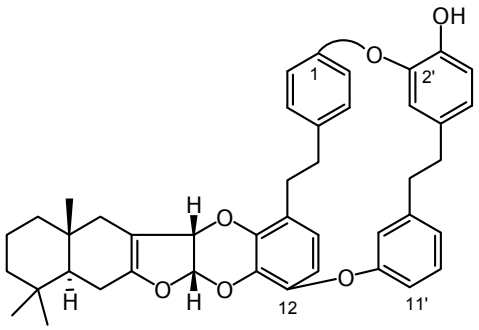
**80** pusilatin C



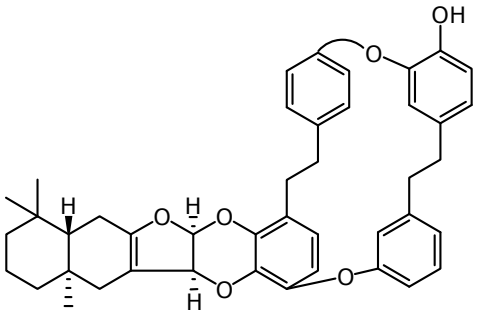
**81** pusilatin D



**82** pusilatin E



**83** GBB A

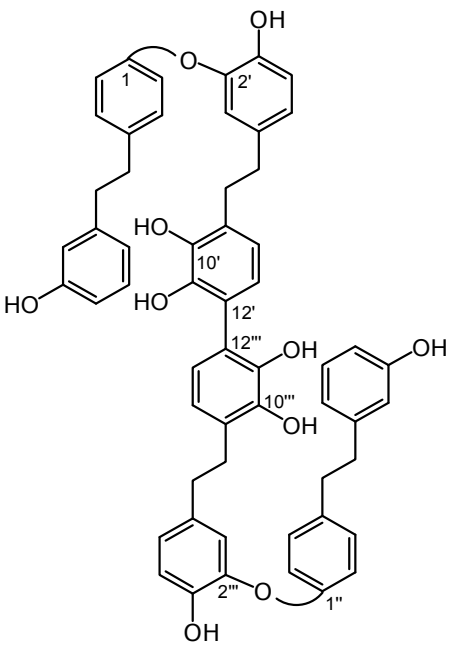


**84** GBB B

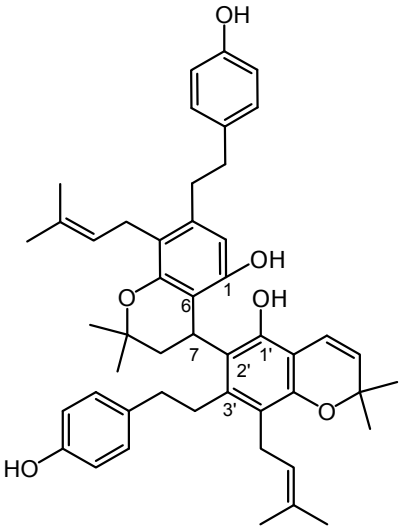
## 2.7. α-Glucosidase Inhibitory Activity

Inhibitory activity of α-glucosidase is associated with anti-obesity and anti-diabetes. Among bis-bibenzyls found in liverworts, only marchantin C (**16**) thus far has shown inhibitory activity against α-glucosidase (52.2% at 1m*M*). This activity is lower than that of the 1-deoxynojirimycin (100% at

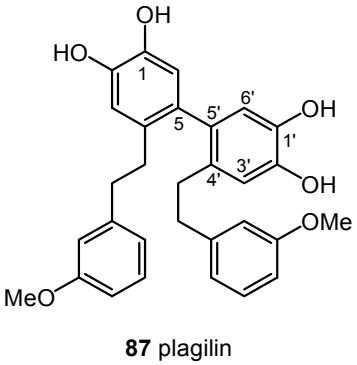
0.4m*M*). This is the first report on the α-glucosidase inhibitory activity of macrocyclic bis-bibenzyls.[35]



**85** 12',12'''-bis(10'-hydroxyperrottetin E)



**86** glossophyllin



**87** plagilin

## 2.8. Liver X Receptor Alpha (LXRα) Agonist Activity

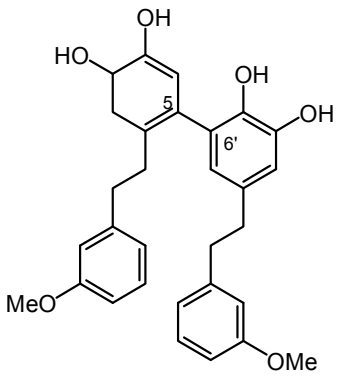
Riccardin C (**3**) isolated from *Blasia pusila* possesses a nuclear receptor LXRα selective agonist activity. Thus, riccardin C (**3**) and its seven *O*-methyl derivatives, including riccardins A (**1**) and F (**5**), were synthesized. According to a preliminary structure-activity relationship study of these seven *O*-methylated riccardins, the three phenolic hydroxyl groups of riccardin C were determined as being indispensable for binding to the LXRα receptor.[90]

## 2.9. Tubulin Polymerization Inhibition

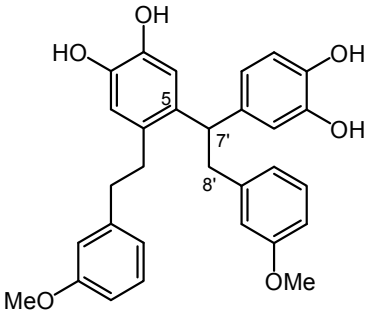
Marchantin C (**16**) strongly inhibited the growth of human cervical tumor engrafts in nude mouse and decreased the quantity of microtubules in a time- and dose-dependent mannterin G2/M phase in human glioma tumor cells and HeLa (human cervical adenocarcinoma cell line) cells at 8-16μ*M*. Marchantin C (**16**) decreased the polymerization rate of gross tubulin, similar to microtubule depolymerizer vincristine at 8-24μ*M*. These results indicated that marchantin C (**16**) plays the same role in microtubule depolymerization and apoptotic effects and subsequent anti-tumoral activity *in vivo.* Marchantin C (**16**) is a novel microtubule inhibitor that induces mitotic arrest of tumor cells and suppresses tumor cell growth. The structure of marchantin C is distinct from classical microtubule inhibitors like colchicine, vinblastine, and vincristine, and paclitaxel. However, this macrocyclic bis bibenzyl is a potential antitumor agent by inhibiting microtubule polymerization.[91,92]

Marchantin C (**16**) and its dimethyl ether, 7,8-dehydro-marchantin C and its dimethyl ether were synthesized and their possible modulatory effect on *p*-glycoprotein in VCR-resistant KB/VCR cells was investigated[93]. The results indicated that **16** was the most potent inhibitor of cell proliferation in both KB and KB/VCR ells among these four synthetic compounds, while the three derivatives of **16** have little anti-proliferative activity. Potent apoptosis in KB/VCR cells was induced by treatment with 16μ*M* of dimethyl ether of marchantin C (**16**) and 0.2μ*M* VCR for 48h.[93]

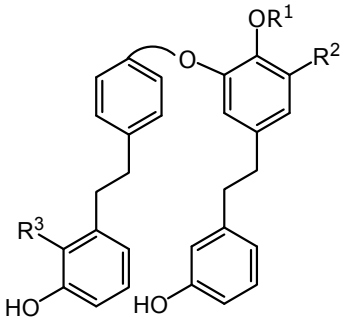
Isoplagiochins A (**44**) and B (**45**) isolated from *Plagiochila fruticosa* inhibited the polymerization of tubulin with $IC_{50}$ values of 50 and 25μ*M*. The dihydro derivatives of both **44** and **45** were found to be inactive ($IC_{50}$ >100μ*M*), and, when compared with the parent compounds, indicated that a restricted biaryl ring system is favorable for tubulin binding. A Monte Carlo search showed that the presence of two aromatic rings connected by a two-carbon bridge with a double bond may serve to maintain the backbone conformation.[46]



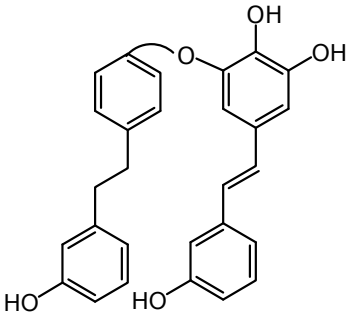

**88** isoplagilin



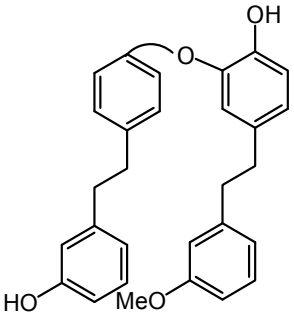

**89** plagiolin



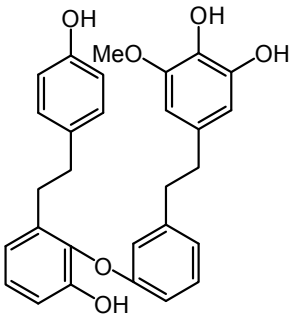

**90** perrottetin E: $R^1$=$R^2$=$R^3$=H
**91** perrottetin F: $R^1$=$R^3$=H, $R^2$=OH
**92** perrottetin G: $R^1$=Me, $R^2$=OH, $R^3$=H
**92a** perrottetin H: $R^1$=H, $R^2$=$R^3$=OH




**93** 7',8-dehydroperrottetin F




**94** perrottetin E 11'-methyl ether

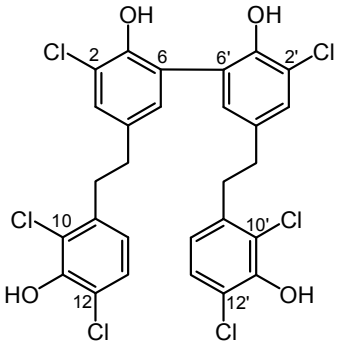



**95** paleatin B

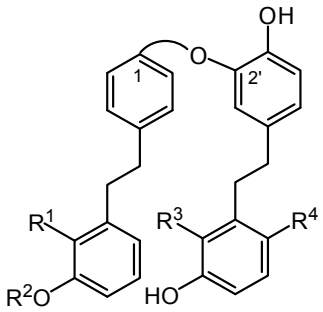
## 2.10. Calcium inhibitory activity

Conformational analysis of riccardin A (**1**) and marchantin A (**14**) was carried out by systematic unbounded multiple minimum search (SUMM). Mobility of the macrocyclic rings of both compounds

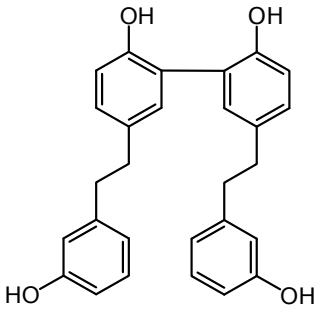
was analyzed by a variable temperature (20-100 °C) $^1$H NMR study. The results indicated the restricted mobility of the macrocyclic ring of riccardin A (**1**) and gave further evidence for its more rigid nature in comparison to marchantin A (**14**). Comparing the calcium inhibitory activity of **1** and **14** ($ID_{50}$: 20 and 1.85μg/cm$^3$) implied the reduced affinity of **1** to calcium ions, which is identical to the calculated differences in steric and electrostatic properties of **1** and **14**. Thus introduction of the biphenyl linkage to the macrocyclic ring decreased its mobility and this fact might be responsible for the reduction of biological activity.[94]



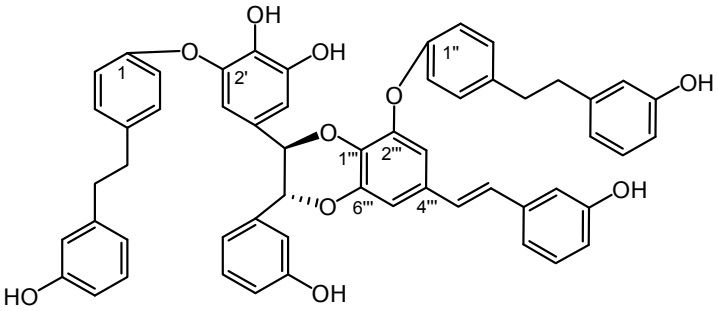
**96** 2,2',10,10',12,12'-hexachloro-isoperrottetin A



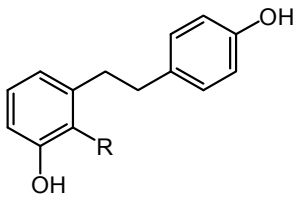
**97** perrottetin E-11-methyl ether: $R^2$=Me, $R^1$=$R^3$=$R^4$=H
**98** 14'-hydroxyperrottetin E: $R^1$=$R^2$=$R^3$=H, $R^4$=OH
**99** 10'-hydroxyperrottetin E: $R^1$=$R^2$=$R^4$=H, $R^3$=OH
**100** 10'-hydroxyperrottetin 11-methyl ether: $R^1$=$R^4$=H, $R^2$=Me, $R^4$=OH
**101** 10,10'-dihydroxyperrottetin E: $R^1$=$R^3$=OH, $R^2$=$R^4$=H



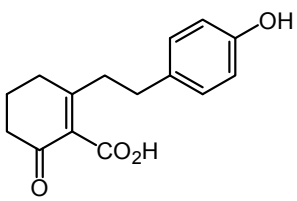
**102** isoperrottetin A



**103** cruciatin



**104** lunularin R=H
**106** lunularic acid R=$CO_2$H

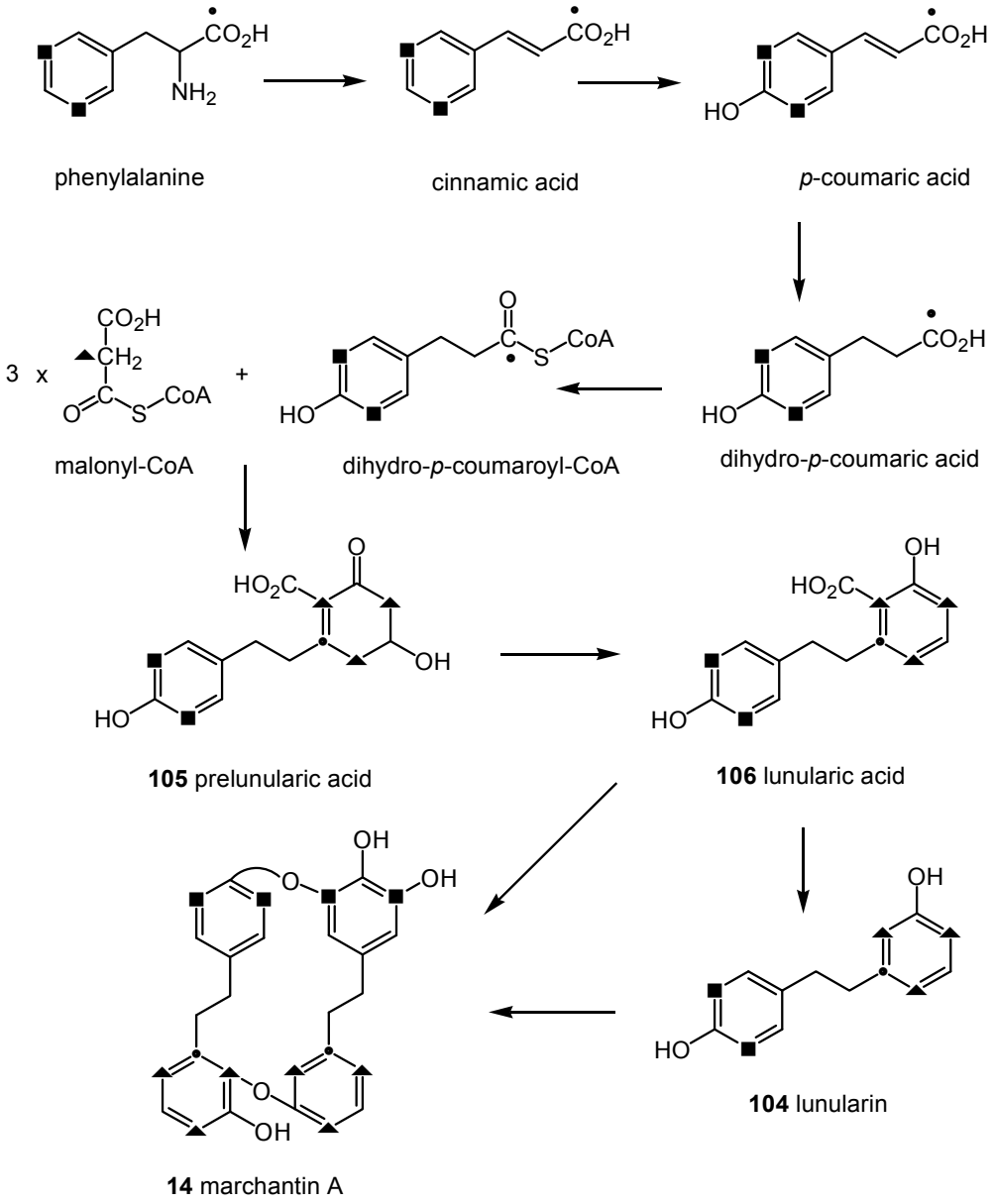


**105** prelunularin

## 3. BIOSYNTHESIS OF BIS-BIBENZYLS

The naturally occurring bis-bibenzyls are categorized into four structure types, which are made up of

macrocyclic rings linked *via* one biphenyl ether C-O bond, two biphenyl ether C-O bonds, one biaryl C-C bond, and two biphenyl bonds.




**Scheme 1.** Biosynthetic pathway for marchantin A (**14**)[96]

*Asakawa* and *Matsuda*[95] proposed that cyclic bis-bibenzyls, such as riccardin C (**3**) and marchantin A (**14**), might be biosynthesized from bibenzyls that correspond chemically to dihydrostilbenes. This assumption was proved by feeding experiments of radioactive and $^{13}$C-labelled precursors, like L-[*U*-$^{14}$C] phenylalanine, [U-$^{14}$C] dihydro-*p*-coumaric acid, [2-$^{13}$C] acetate, and L-[$^{13}$COOH] phenylalanine, as shown in Scheme 1.[96] The aqueous precursor solutions were applied to 0.5 cm$^2$ samples of aseptic thallus tissue of *Marchantia polymorpha* and incubated for 24 h. The A- and B-rings of the marchantin molecule

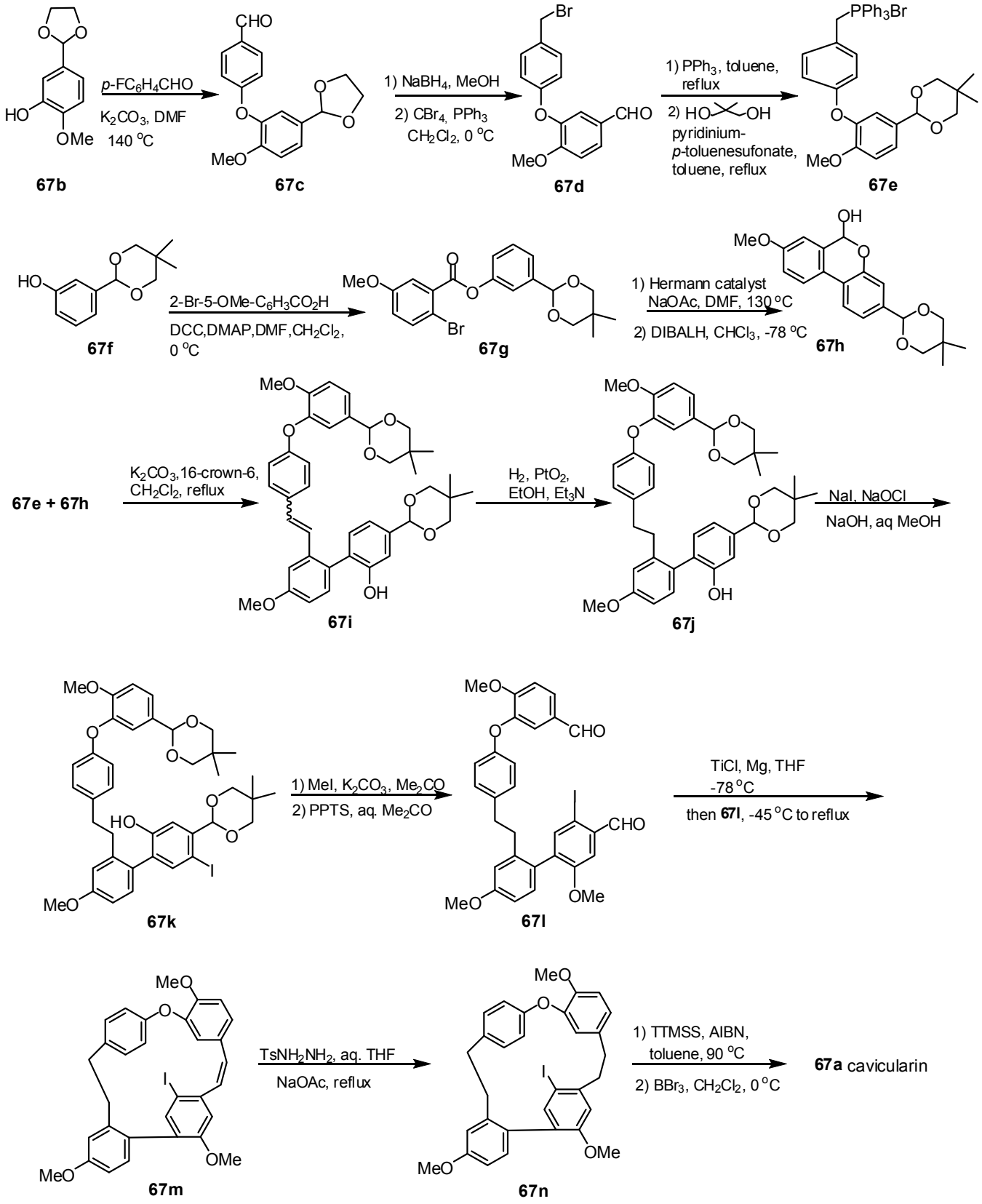
are derived from the benzene ring of L-phenylalanine *via trans*-cinnamic acid and *p*-coumaric acid. Application of the $^{13}$C-labelled precursor with subsequent $^{13}$C NMR spectroscopy established that dihydrocoumaric acid is an intermediate in marchantin biosynthesis. Enzymatically hydrogenated dihydrocoumaric acid from coumaric acid condenses with three molecules of malonyl-Co A to form prelunularic acid (**105**). The latter is aromatized to yield lunularic acid (**106**) and possibly lunularin (**104**), which is followed by condensation of lunularin or lunularic acid to afford marchantin A (**14**). The mechanism of this final coupling step is still unknown.

## 4. TOTAL SYNTHESIS OF BIS-BIBENZYLS

Since cyclic bis-bibenzyls found in liverworts possess unusual structures and various interesting biological activities, several organic chemists have focused on their total synthesis. *Gottsegen* and colleagues[97] synthesized riccardins A-C (**1-3**) using a combination of *Ullmann*, *Wittig*, and *Wurtz* reactions and Ni (0)-assisted intermolecular coupling reaction. The total synthesis of riccardin C (**3**) was also accomplished by *Harrowven* and associates[98-100] using is vanillin as the starting material in the course of the total synthesis of cavicularin (**67a**) as shown in Scheme 2. Cavicularin (**67a**) isolated from the liverwort, *Cavicularia densa* is a structurally interesting phenanthrene-bibenzyl derivative which has a highly strained structure and the benzene ring A was twisted. Although the structure has no chiral centre, it shows positive specific optical rotation, $[\alpha]_D$ +168.2 and CD Cotton effects [312 nm ($\Delta\varepsilon$ +4.6), 280 (+2.6), 255 (-2.6) and 208 (+24.6). This phenomenon implicated that **67a** possessed both planar and axial chirality.[101]

The total synthesis of riccardin C (**3**), and its seven *O*-methylated derivatives were achieved by *Hioki* and coworkers[90] *via* intramolecular *Suzuki-Miyaura* coupling to construct the necessary 18-membered biaryl linkage. Riccardin C (**3**) has been also synthesized by *Takiguchi* and coworkers[102] using an intramolecular $S_N$ reaction of $\alpha$-sulfinylfluorobenzene (A-ring) by internal phenolate (C-ring), providing the key 18-membered ring closure in high yield.

Plagiochin E (**4a**) was isolated from the Chinese *Marchantia polymorpha*[23] and *Asterella angusta*[12] through bioassay-guided fractionation of the antifungal constituents. A short and efficient total synthesis of plagiochin E (**4a**) was accomplished by *Speicher* and associates.[103] However, its spectroscopic data were not the same as those of the natural product **4a**, but identical with those of riccardin D (**4**) which was isolated from *Plagiochila fruticosa*.[3] Thus, the structure of **4a** should be revised as riccardin D (**4**). Riccardin G (**6**), the methyl ether of **4**, has been found in *Marchantia chenopoda*.[3]




DMF= *N*,*N*-dimethylformamide, DCC=dicyclohexylcarbodiimide, DMAP= 4-dimethylaminopyridine, DIBALH= diisobutylaluminium hydride, TS= *p*-toluenesufonyl, TTMSS= tris(trimethylsilyl)silane, AIBN= azo-bis(isobutyronitrile)

**Scheme 2.** Total synthesis of cavicularin (**67a**)[98]

*Xi* and associates[93] accomplished the total synthesis of marchantin C (**16**) by 12 steps from 2-hydroxy-3-methoxybenzaldehyde with the sufficient yield (23%). Total synthesis of marchantiaquinone (**26**) was accomplished by *López* and associates[104] by macro-cyclization from a dichloride precursor using an active nickel complex under high dilution conditions, giving marchantin M (**24**) trimethyl ether, followed by demethylation with boron tribromide and oxidation using silver oxide.

*Nogradi* and associates accomplished the total synthesis of pakyonol (**38**) by *Ullmann* coupling of 3-benzoyloxy-4-(3-formylphenoxy)benzoic acid benzyl ester with *Wittig* and modified *Wittig* reactions.[105]

*Fukuyama* and associates[106] accomplished the total synthesis of plagiochin D (**40**) using *m*-anisaldehyde as the starting material, followed by a *Wardworth-Emmons* condensation reaction, hydrogenation, and a *Stille-Kelly* reaction using hexamethylditin and tetrakis(triphenylphosphine)palladium, to yield plagiochin D (**40**), after removal of the MOM group by HBr in methanol.

The total synthesis of isoplagiochin A (**44**) was achieved by *Gerencsér* and colleagues[107] in 23 steps by coupling methyl 3-(2-methoxy-5-formylphenyl)-4-methoxybenzoate with methyl (2-(hydroxymethyl)-4-methoxyphenoxy)benzoate, in an overall yield of 15%.

*Eicher* and associates established the total synthesis of isoplagiochin C (**46**).[108] The total synthesis of isoplagiochin D (**47**), a highly strained macrocyclic bis-bibenzyl with two biaryl units isolated from *Plagiochila fruticosa*, was achieved by *Sumy* and colleagues in 1.6% overall yield and in 11 steps, by construction of tetramethoxyisoplagiochin D by a palladium(0)-catalyzed *Suzuki-Miyaura* cross-coupling reaction, followed by demethylation with boron tribromide in methylene chloride.[109] The tetramethyl ether of isoplagiochin D (**47**) as well as related compounds possessing the (*Z*)- and (*E*)-alkenes with more rigid two-carbon biaryl bridges, were synthesized using *Sonogashira* and *McMurry* protocols.[103]

*Speicher* and coworkers accomplished the total synthesis of 12-chloroisopalgiochin D (**52**) isolated from *Plagiochila* species, and 6'-chloroisopalgiochin C (= bazzanin A) (**56**) and 6,12'-dichloroisoplagiochin D (= bazzanin J) (**65**) from *Bazzania trilobata*, by construction of the biaryl moiety using regioselective *Suzuki* protocols and coupling to acyclic bibenzyl and cyclic bibenzyls by *Wittig* and *MacMurry* procedures, followed by hydrogenation and deprotection.[110]

## CONCLUSIONS

In conclusion, the Marchantiophyta (liverworts) are rich sources of cyclic and acyclic bis-bibenzyls among which marchantin A (**14**) shows interesting biological activity, such as antioxidant, antifungal and antimicrobial activity, cytotoxicity, antiinfluenza, farnesoid X-receptor (FXR) activation, calcium and NO production inhibitory activity. Riccardin C (**3**), and isoplagiochins A (**44**) and B (**45**) are therapeutically interesting compounds since they show antiobesity and inhibition of the polymerization of tubulin, respectively. Some cyclic bis-bibenzyls have optical activity and the structures of two conformers have

been established by CD spectral analysis. An acyclic bis-bibenzyl, perrottetin H (**92a**) and a cyclic bis-bibenzyl, riccardin C (**3**) have been isolated from the fern, *Hymenophyllum barbata*[68] and the higher plant, *Primula* species, respectively.[67] The presence of such bis-bibenzyls in different plants from the Marchantiophyta is quite interesting phenomenon to consider the plant phylogeny.[3,111]

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