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PRENYL BIBENZYLS FROM THE LIVERWORTS *RADULA PERROTTETII* AND *RADULA COMPLANATA**

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Key Word Index—*Radula perrottetii*, *R. complanata*; Radulaceae; Jungermannialies; Hepaticae; 2(*R*)-2-isopropenyl-6-hydroxy-4-(2-phehylethyl) dihydrobenzofuran; 2,2-dimethyl-7,8-dihydroxy-5-(2-phenylethyl) chromene; radulanin L; prenyl bibenzyls; revised structures; synthesis of prenyl bibenzyls; 5-lipoxygenase and calmodulin inhibitory activity; vasopressin antagonist activity; chemosystematics.

Abstract—A new dihydrobenzofuran and a new chromene derivatives have been isolated from the liverwort *Radula perrottetii*, together with the known 3,5-dihydroxy-2-(3-methyl-2-butenyl)bibenzyl, 2(*R*)-2-isopropenyl-6,7-dihydroxy-4-(2-phenylethyl)dihydrobenzofuran, 2,2-dimethyl-7-hydroxy-5-(2-phenylethyl)chromene, 3,5-dihydroxy-6-carbomethoxy-2-(3-methyl-2-butenyl)bibenzyl, three bis(bibenzyls) and perrottetins E, F and G. The structures of the new compounds have been characterized as 2(*R*)-2-isopropenyl-6-hydroxy-4-(2-phenylethyl)dihydrobenzofuran and 2,2-dimethyl-7,8-dihydroxy-5-(2-phenylethyl)chromene by ^{1}H and ^{13}C NMR spectral analysis and synthesis. The structures of the previously reported chalcone and three prenyl bibenzyls, perrottetins A, B and C, and the other two bibenzyls, isolated from *R. perrottetii* are revised by analysis of their ^{1}H and ^{13}C NMR data, difference NOE experiments and synthesis of their derivatives. Radulanin L, a new bibenzyl with a dihydrooxepin skeleton was isolated from *R. complanata* together with 2- and 4-(3-methyl-2-butenyl)-3,5-dihydroxybibenzyls and its structure elucidated by comparison of ^{1}H and ^{13}C NMR spectral data with those of radulanins A and H. The structures of the previously reported radulanins A and H isolated from *R. complanata* are confirmed as correct by difference NOE. Some prenyl-containing bibenzyls showed 5-lipoxygenase and calmodulin in hibitory activity and vasopressin antagonist activity. *R. perrottetii* is a chemically isolated species in the Radulaceae.

INTRODUCTION

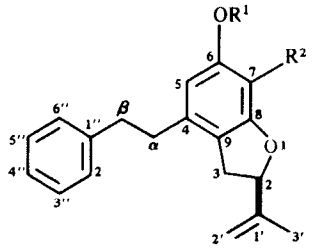
Radula species are small stem-leafy liverworts which are distributed worldwide. The Radulaceae are morphologically isolated from the other families of the Jungermanniales [1]. In previous papers [2–10], we reported that *Radula* species elaborated several characteristic prenyl bibenzyls and their related phenolic compounds and that these components could be used as chemical markers. Various bibenzyls have been isolated from *R. perrottetii* and *R. complanata* and their structures characterized by 60 and 90 MHz ^{1}H NMR spectroscopy [4, 6]. Further fractionation of the methanol extract of *R. perrottetii* gave two new bibenzyls (**1** and **8**), together with the previously known bibenzyls (**3**, **6**, **10** and **12**) [6, 9] and bis(bibenzyls), perrottetins E (**38**), F (**39**) and G (**40**) [7]. A new bibenzyl named radulanin L (**36**) was also isolated from the methanol extract of *R. complanata*, along with the known prenyl bibenzyls (**10** and **16**) [4, 6, 9]. Moreover, the structures of the previously reported six bibenzyl derivatives (**19**, **21**–**23**, **30** and **31**) were revised to **14**, **24**, **26**, **28**, **12** and **3** by 400 MHz ^{1}H and 100 MHz ^{13}C NMR analysis as well as synthesis of their derivatives. In this paper, we report the isolation, characterization and synthesis of two new bibenzyls from *R. perrottetii* and revision of the structures of the previously isolated bibenzyls from *R. perrottetii*. We also discuss the biological activity of selected prenyl bibenzyls and the chemosystematics of *Radula* sp. In addition, we report on the structure of a new and two known bibenzyls with a dihydrooxepin skeleton isolated from *R. complanata*.

*Part 40 in the series 'Chemosystematics of Bryophytes'. For Part 39, see ref. [9].

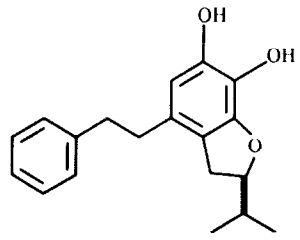
RESULTS AND DISCUSSION

The methanol extract of *R. perrottetii* was chromatographed on silica gel, followed by purification on prep. TLC to afford two new bibenzyls (**1** and **8**), along with the know bibenzyls **3**, **6**, **10** and **12** [6, 9] and the three bis(bibenzyls) perrottetins E (**38**), F (**39**) and G (**40**) [7]. The methanol extract of *R. complanata* treated in the same manner gave a new bibenzyl named radulanin L (**36**), along with three prenyl bibenzyls (**10**, **14** and **16**) [4, 6, 9] and radulanins A (**32**) and H (**34**) [3, 4, 6].

Compound **1**, $C_{19}H_{20}O_2$ ([M]$^+$ 280.1463) contained a hydroxyl group (3600 cm^{-1}) and an aromatic ring (1490, 1602 cm^{-1}). Methylation of **1** with methyl iodide gave a monomethyl ether (**2**), $C_{20}H_{22}O_2$ ([M]$^+$ 294.1635; δ3.75, 3H, *s*), indicating the presence of one phenolic hydroxyl group. The IR spectrum of **2** showed neither carbonyl nor hydroxyl absorption. This is indicative of an ether oxygen in **1**. The presence of a monosubstituted and a 1,2,3,5-tetrasubstituted benzene ring was confirmed by the ^{1}H NMR signals (δ7.14, 7.27, each 2H, *m*, 7.19, 1H, *m* and 6.19, 2H, *s*). The ^{1}H and ^{13}C NMR spectra (Table 2) of **1**



1 $R^1 = R^2 = H$
2 $R^1 = Me$, $R^2 = H$
3 $R^1 = H$, $R^2 = OH$
4 $R^1 = Me$, $R^2 = OMe$



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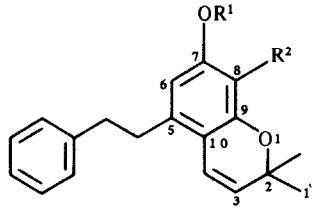
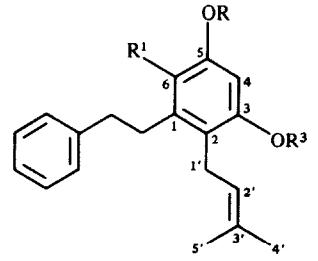
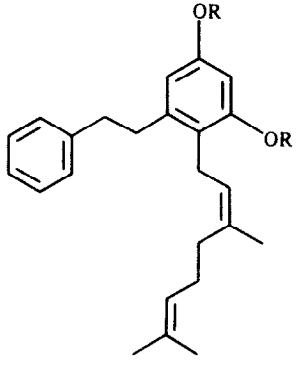


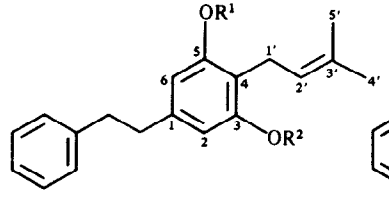
6 $R^1 = R^2 = H$
7 $R^1 = Me$, $R^2 = H$
8 $R^1 = H$, $R^2 = OH$
9 $R^1 = Me$, $R^2 = OMe$



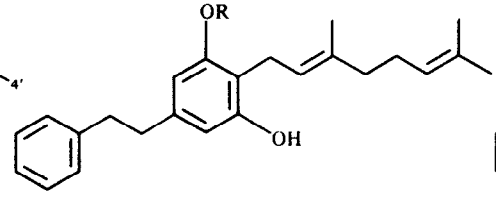
10 $R^1 = R^2 = R^3 = H$
11 $R^1 = R^3 = H$, $R^2 = Me$
12 $R^1 = CO_2Me$, $R^2 = R^3 = H$
13 $R^1 = CO_2Me$, $R^2 = R^3 = Me$



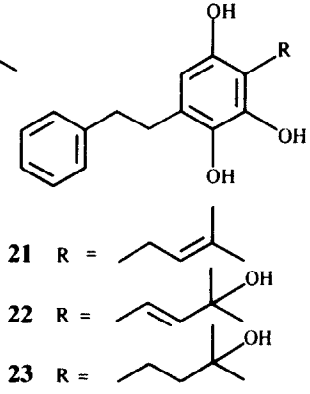
14 R = H
15 R = Me



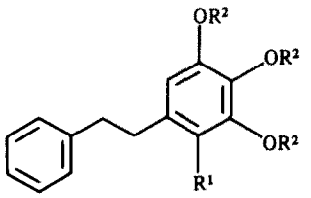
16 $R^1 = R^2 = H$
17 $R^1 = Me$, $R^2 = H$
18 $R^1 = R^2 = Me$

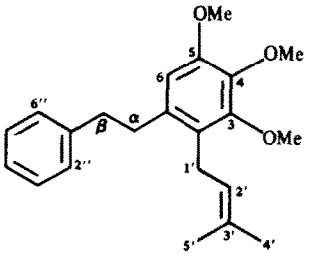


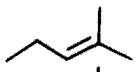
19 R = H
20 R = Me

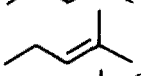


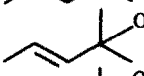
21 R =
22 R =
23 R =

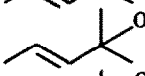


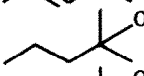


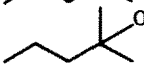
24 R^1 =  , R^2 = H

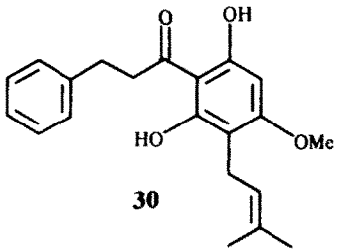
25 R^1 =  , R^2 = Me

26 R^1 =  , R^2 = H

27 R^1 =  , R^2 = Me

28 R^1 =  , R^2 = H

29 R^1 =  , R^2 = Me



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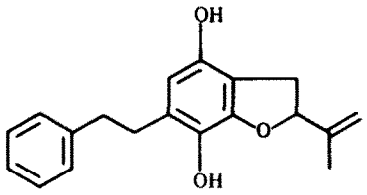

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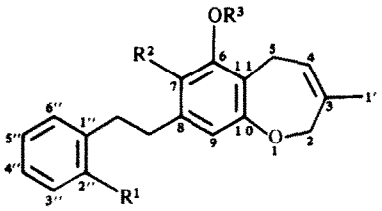
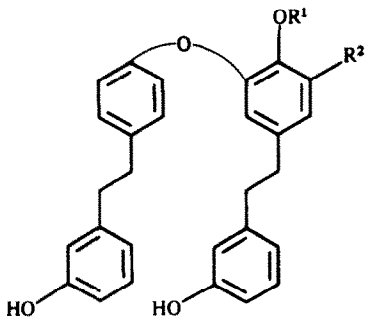


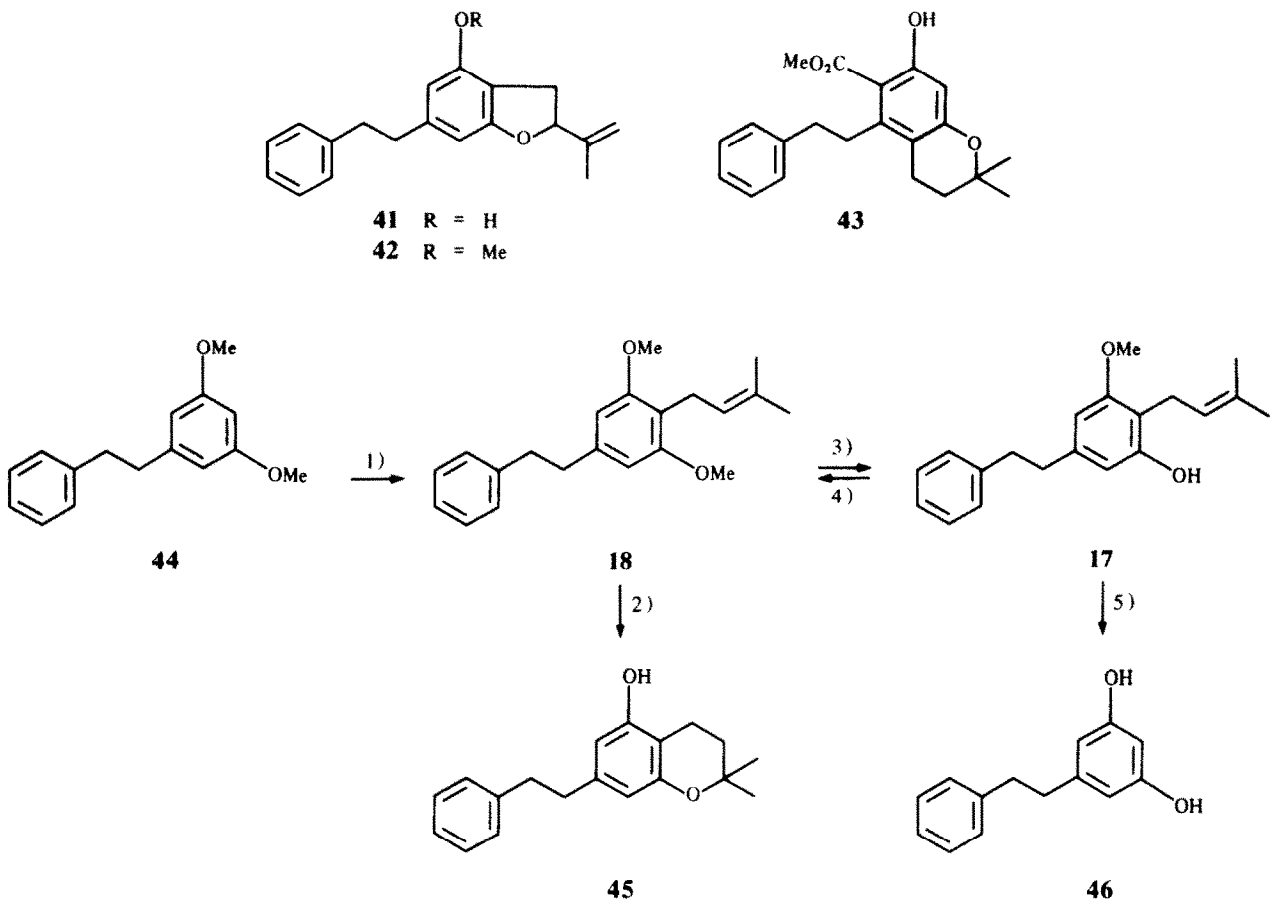
32 R^1 = R^2 = R^3 = H
33 R^1 = R^2 = H, R^3 = Me
34 R^1 = R^3 = H, R^2 = CO_2H
35 R^1 = H, R^2 = CO_2Me, R^3 = Me
36 R^1 = OH, R^2 = R^3 = H
37 R^1 = OMe, R^2 = H, R^3 = Me



38 R^1 = R^2 = H
39 R^1 = H, R^2 = OH
40 R^1 = Me, R^2 = OH

further indicated the presence of two benzylic methylenes, one vinylic methyl, an exomethylene, one proton (δ5.10, *dd*, J = 9.4, 8.1 Hz) on a carbon (δ86.4, *d*) bearing an ether oxygen which was coupled with one additional benzylic methylene protons (δ2.67, 1H, *dd*, J = 15.0, 8.1 Hz and 3.02, 1H, *dd*, J = 15.0, 9.4 Hz). On the basis of the above data, four alternative structures including **1** were suggested for the new compound. The structure **1** was given for the new bibenzyl by the presence of the higher field carbon signals at δ95.3 in **1** and δ93.7 in **2** [9] and the NOEs between (i) H-α and H-5, (ii) H-5 and OMe-6 and (iii) H-7 and OMe-6 in **2**. Thus, compound **1** was established to be 2-isopropenyl-6-hydroxy-4-(2-phenylethyl)-dihydrobenzofuran. The absolute configuration at C-2 was established to be *R* by the positive Cotton effect of **2** [11, 12]. Compound **1** could be biosynthesized from the coexisting prenyl bibenzyl (**10**). Conclusive evidence for the structure **1** was obtained by the synthesis of **1** and **2** and their isomers (**41** and **42**) (see later).

Compound **8**, $C_{19}H_{20}O_3$ ([M]$^+$ 296.1416), had a hydroxyl group (3570 cm^{-1}) and an aromatic ring (1602, 1510 cm^{-1}). Methylation of **8** with methyl iodide afforded a dimethyl ether (**9**), $C_{21}H_{24}O_3$ ([M]$^+$ 324.1701; δ3.78, 3.83, each 3H, *s*) indicating the presence of two phenolic hydroxyl groups. The ^{1}H and ^{13}C NMR spectra of **8** and **9** were almost identical to those of 2,2-dimethyl-



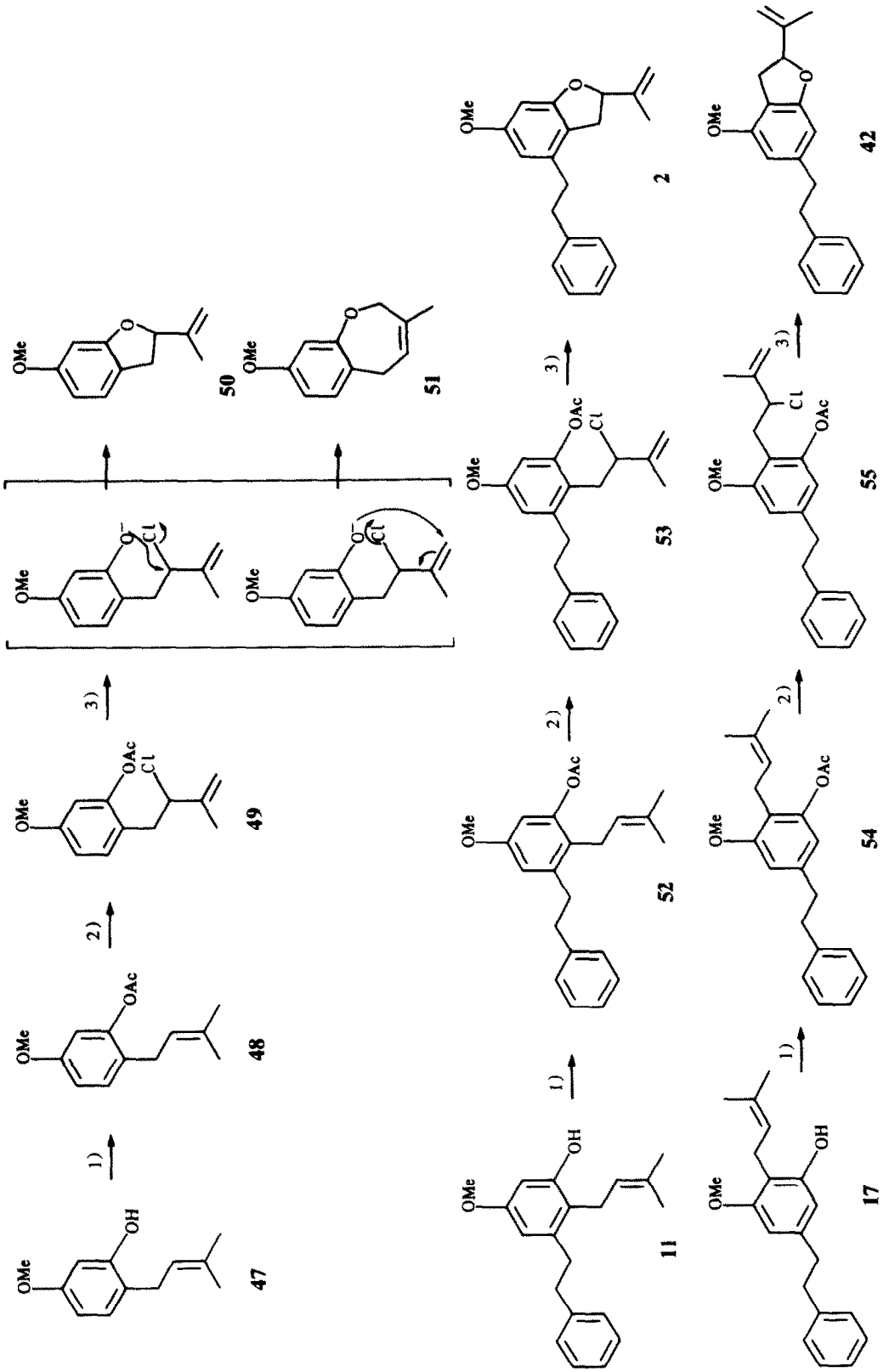
1) *n*-BuLi/$Me_2C{=}CH{-}CH_2Br$ 2) BBr_3 3) EtSNa/DMF 4) MeI 5) EtSNa/HMPA

Scheme 1.

7-hydroxy-5-(2-phenylethyl)chromene (**6**), coexisting in the same species and *R. kojana* [9] and its dimethyl ether (**7**) [9], except for the absence of one aromatic proton and the higher field carbon signal at C-8, suggesting that **8** was 2,2-dimethyl-7,8-dihydroxy-5-(2-phenylethyl) chromene. This assumption was further confirmed by the difference NOE examinations of **9**. Thus NOEs were observed between (i) H-α and H-4, (ii) H-α and H-6, and (iii) H-6 and OMe-7. Final proof of the structure of **8** came from the synthesis of the dimethyl ether (**9**) (see later). The chromenes **6** and **8** could originate from the prenyl bibenzyls **10** and **24** co-occurring in the same species.

Previously, we reported the presence of 3,5-dihydroxy-4-(3-methyl-2-butenyl)bibenzyl (**16**) and its monomethyl ether (**17**) in *R. complanata* [4]. Further fractionation of the crude extract of *R. complanata* has yielded 3,5-dihydroxy-2-(3-methyl-2-butenyl)bibenzyl (**10**) and a new bibenzyl, radulanin L (**36**) which is discussed later. The R_fs of **10** and **16** are the same and their mass spectra are almost identical, except for the relative intensity of *m/z* 225 (73% in **10** and 6% in **16**) and base peak (*m/z* 227 in **10** and *m/z* 91 in **16**). However, these two compounds are easily differentiated by TLC [R_f 0.3 (**10**) and 0.6 (**16**) in C_6H_6–EtOAc, 4:1] and the ^1H and ^{13}CNMR data (Tables 1 and 2). The chemical shifts of H-2 and H-6, C-2 and C-6, and C-3 and C-5 in **16** are the same, but the same protons and carbons in **10** show different chemical shifts [13]. The natural bibenzyls **11** and **17** have been synthesized from 3-hydroxy-5-methoxybibenzyl (**56**) by prenylation with 2,2-dimethylallylbromide in the presence of sodium methoxide [9]. Compound **10** has also been prepared from **11** by demethylation with sodium thioethoxide (EtSNa) in hexamethylphosphoric triamide (HMPA). In order to obtain the natural bibenzyl **16**, demethylation reaction of the dimethyl ether **18** was carried out (Scheme 1). Treatment of 3,5-dimethoxybibenzyl (**44**) with *n*-butyl lithium (*n*-BuLi) and 2,2-dimethylallylbromide gave regiospecifically 3,5-dimethoxy-4-(3-methyl-2-butenyl)bibenzyl (**18**) (71.2%) which was also obtained from **17** by methylation with methyl iodide. Demethylation of **18** with boron tribromide (BBr_3) gave a 2,2-dimethylchroman derivative (**45**). Treatment of **18** with EtSNa in dimethylformamide (DMF) afforded a monodemethyl bibenzyl (**17**) which on further demethylation with EtSNa in HMPA gave 3,5-dihydroxybibenzyl (**46**). In these chemical reactions, the natural prenyl bibenzyl (**16**) could not be synthesized.

The co-occurrence of **10**, **16** and **17** in *R. complanata* and the presence of **11** in *R. kojana* [9] prompted us to reanalyse the chemical constituents of *R. perrottetii* and indicated that **16** was not detected in this species and the previously reported **16** was revised to **10**, by the identity of the spectral data with those of the synthetic **10** [9].


OMe
OH
47
1)
OAc
48
2)
Cl
49
3)
50
51
2
11
52
53
54
55
17
42
1) Ac_2O/Py 2) $Ca(OCl)_2$ 3) $Ba(OH)_2$

Scheme 2.

Furthermore, as **16** is absent in *R. perrottetii*, the structures of the previously reported prenyl bibenzyls (**19**, **21–23**, **30** and **31**) isolated from *R. perrottetii* [6] were carefully reinvestigated by 400 MHz ^{1}H and 100 MHz ^{13}C NMR spectroscopy and synthesis of some methyl ethers of the natural bibenzyls. 2- and 4-Geranyl-3,5-dihydroxybibenzyls (**14** and **19**) and their dimethyl ethers have been synthesized [9, 13]. The structure of the previously reported geranyl bibenzyl (**19**) was revised to **14** because its NMR data were identical to those of the synthetic **14**. The structure of perrottetin A (**21**) was revised to **24** on the basis of the difference NOE examination of trimethoxyperrottetin A (**25**) [6] obtained from **24** by methylation with methyl iodide. The NOEs were observed between (i) H-α and H-1′, (ii) H-α and H-2′, (iii) H-α and H-6, (iv) H-6 and OMe-5, (v) H-1′ and OMe-3, (vi) H-2′ and OMe-3, (vii) H-1′ and H-5′, (viii) H-β and H-2″ and (ix) H-β and H-6″. The structure for perrottetin A (**24**) was further evidenced by the synthesis of **25** (see later). The structures of perrottetins B (**22**) and C (**23**) were revised to **26** and **28**, as the following chemical correlation had been carried out [6]. Hydrogenation of the trimethyl ether **27** gave a dihydro derivative **29** which on dehydration afforded **25**. The structure **30** proposed by ^{1}H NMR (90 MHz) was revised to **12** by difference NOE experiments with **12** and **13** and chemical reaction of **12** as well as the NMR spectral data (Tables 1 and 2). Compound **12**, $C_{21}H_{24}O_4$ ([M]$^+$ 340.1675), showed the presence of two phenolic hydroxyl groups (3550 cm^{-1}) which was confirmed by methylation to give a dimethyl ether (**13**), $C_{23}H_{28}O_4$ ([M]$^+$ 368.1982; δ3.84, 3.85, each 3H, *s*) with one conjugated methoxycarbonyl group (δ171.9, *s*; 52.2, *q*; 1650 cm^{-1}), a 2,2-dimethylallyl group, a monosubstituted benzene ring, two benzylic methylenes and one proton on a benzene ring (Tables 1 and 2), indicating that **12** was not chalcone, but a prenyl bibenzyl with a methoxycarbonyl and two phenolic hydroxyl group. This assumption and the position of one hydroxyl and a prenyl group were confirmed by the formation of the 2,2-dimethylchroman derivative **43** from **12** by treatment with acid. The position of the remaining functional groups in **12** was further established by difference NOE experiments and the ^{13}C NMR data (Table 2) of **12** and **13**. In **12**, the NOE was observed between H-α and H-1′, but not between any other protons and the OMe group. In **13**, NOEs were observed between (i) H-α and H-1′ and H-4 and OMe-3. On the basis of the above spectral data and the presence of the higher field carbon signals (δ102.3 in **12** and 93.6 in **13**) of C-4 as well as the similarity of the ^{1}H and ^{13}C NMR spectra of **12** and **13** with those of **10** and **11**, the structure of **30** was revised to 3,5-dihydroxy-6-carbomethoxy-2-(3-methyl-2-butenyl)bibenzyl (**12**). The structure **31** has been proposed for perrottetin D on the basis of the ^{1}H NMR data [6]. The NOE data of its dimethyl ethers [6] obtained from **31** by methylation with methyl iodide showed the presence of NOEs between (i)

Table 1. ^{1}H NMR (400 MHz) spectral data for compounds **1–5**, **8–10**, **12**, **13**, **16**, **18**, **24**, **25**, **29**, **32–37**, **41** and **42** ($CDCl_3$–TMS)

H	1	2	3	4	5
2	5.10 *dd* (9.4, 8.1)*	5.11 *dd* (9.5, 8.1)	5.13 *t* (9.3)	5.15 *t* (8.8)	4.48 *dd* (15.7, 8.6)
3	2.67 *dd* (15.0, 8.1)	2.70 *dd* (15.0, 8.1)	2.68 *m*	2.71 *dd* (15.0, 8.8)	2.57 *dd* (14.9, 8.6)
	3.02 *dd* (15.0, 9.4)	3.04 *dd* (15.0, 9.5)	3.01 *dd* (14.9, 9.3)	3.06 *dd* (15.0, 8.8)	2.85 *m*
4					
5	6.19 *s*	6.26 *d* (2.2)	6.32 *s*	6.21 *s*	6.29 *s*
6					
7	6.19 *s*	6.27 *d* (2.2)			
9					
1′					1.90 *m*
2′	4.87 *s*	4.88 *s*	4.88 *s*	4.86 *s*	0.90 *d* (6.7)
	5.04 *s*	5.04 *s*	5.04 *s*	5.05 *s*	
3′	1.71 *s*	1.71 *s*	1.70 *s*	1.72 *s*	0.99 *d* (6.7)
4′					
5′					
α	2.74 *m*	2.78 *m*	2.68 *m*	2.75 *m*	2.69 *m*
β	2.87 *m*	2.86 *m*	2.83 *m*	2.85 *m*	2.85 *m*
2″	7.14 *m*	7.14 *m*	7.11 *m*	7.13 *m*	7.14 *m*
3″	7.27 *m*	7.27 *m*	7.24 *m*	7.27 *m*	7 26 *m*
4″	7.19 *m*	7.19 *m*	7.18 *m*	7.19 *m*	7.19 *m*
5″	7.27 *m*	7.27 *m*	7.24 *m*	7.27 *m*	7.26 *m*
6″	7.14 *m*	7.14 *m*	7.11 *m*	7.13 *m*	7.14 *m*
OH	4.68 *s*		5.28 *s*		4.90 *br s*
			5.45 *s*		5.22 *br s*
3-OMe					
4-OMe					
5-OMe					
6-OMe		3.75 *s*		3.81 *s*	
7-OMe				3.91 *s*	
8-OMe					
2″-OMe					
CO_2Me					

H-α and H-5 and (ii) H-5 and OMe-4. The alternative structure **3**, however, could not be excluded by this experiment. The ^{1}H NMR spectral data of **3** and **4** were almost identical to those of **1** which coexisted in the same species and its methyl ether (**2**), except for the absence of one proton on the benzene ring. The chemical shifts of the ^{13}C NMR of **3** and **4** resembled those of **1** and **2**. The above spectral data suggested the structure of perrottetin D to be **3** and not **31**. The absolute configuration at C-2 was established to be *R* by the positive Cotton effects [11, 12] of **3**, **4** and dihydroperrottetin D (**5**) obtained from **3** by hydrogenation. Further evidence for the structure of **3** was obtained by the synthesis of the dimethyl ether (**4**) (see later).

Radulanin A (**32**) has been isolated from *R. javanica* (=*R. variabilis*) [3] and *R. complanata* [4]. The latter species also produces radulanin H (**34**) [6]. The structures **32** and **34** having a dihydrooxepin skeleton have been given for each compound. To reconfirm these structures, the difference NOEs of their methyl ethers **33** [3] and **35** were measured. Compound **33** exhibited NOEs between (i) H-α and H-7 and (ii) H-α and H-9. The long range ^{1}H and ^{13}C 2D COSY NMR spectra of **33** showed a correlation ($J=10$ Hz) between C-11 (δ122.4, *s*) and H-7 [14], indicating that the prenyl group was located at C-11 *meta* to H-7. This was further supported by the ^{13}C NMR spectra of **32** and **33** in which the higher chemical shift of one aromatic carbon observed in **1**, **2**, **12** and **13** was not present [9]. The above data coupled with the ^{1}H NMR (400 MHz) data reconfirmed that the structure **32** was correct. In **35**, NOEs were also present between (i) H-α and H-9 and (ii) H-5 and OMe-6. On the basis of the above data coupled with the presence of a hydrogen bonded carboxyl group (1640 cm^{-1}) in **34** and the analyses of the NMR data (^{1}H **32–35**; ^{13}C for **32–34**) (see Tables 1 and 2), the structure **34** was also reconfirmed to be correct.

Radulanin L (**36**), a new bibenzyl isolated from *R. complanata* had the molecular formula, $C_{19}H_{20}O_3$ ([M]$^+$ 296.1446). The spectral data of **36** showed the presence of a hydroxyl group (3580 cm^{-1}) and an aromatic ring (1620, 1585, 1500 cm^{-1}; λ275, 282 nm). Methylation of **36** with methyl iodide gave a dimethyl ether (**37**) ([M]$^+$ 324.1674; δ3.76, 3.83, each 3H, *s*), indicating that **36** had two phenolic hydroxyl groups. One of the three oxygen atoms in **36** was an ether oxygen as no absorption band corresponding to a hydroxyl or a carbonyl group was observed in the IR spectrum of **37**. The ^{1}H and ^{13}C NMR spectra of **36** and **37** were very similar to those of **32** and **33**, except for the presence of a 1,2-disubstituted benzene ring (δ6.74, *dd*, $J=7.4$, 1.1 Hz, 6.84, *ddd*, $J=7.4$, 7.4, 1.1 Hz, 7.08, *ddd*, $J=7.4$, 7.4, 1.1 Hz and 7.09, *dd*, $J=7.4$, 1.1 Hz in **36**) in place of a monosubstituted benzene ring, suggested that **36** might be 2′-hydroxyradulanin A. The substitution pattern of each benzene ring was further confirmed by difference NOE experiments with **36** and **37**. Thus NOEs were observed between (i) H-α and H-7, (ii) H-α and H-9 and (iii) H-β and H-6″ in **36** and between (i) H-7 and OMe-6, (ii) H-3″ and OMe-2″, (iii) H-α and H-7, (iv) H-α and H-9

Table 1. *Continued*

H	8	9	10	12	13	16	18
2						6.26 *s*	6.35 *s*
3	5.48 *d* (10.0)	5.56 *d* (10.0)					
4	6.42 *d* (10.0)	6.47 *d* (10.0)	6.23 *d* (2.4)	6.36 *s*	6.39 *d* (6.6)		
5							
6	6.33 *s*	6.20 *s*	6.26 *d* (2.4)			6.26 *s*	6.35 *s*
7							
9							
1′	1.42 *s*	1.46 *s*	3.28 *d* (6.4)	3.38 *d* (6.6)	3.33 *d* (6.6)	3.38 *d* (7.3)	3.30 *d* (7.1)
2′	1.42 *s*	1.46 *s*	5.09 *t* (6.4)	5.07 *t* (6.6)	5.02 *t* (6.6)	5.26 *t* (7.3)	5.18 *t* (7.1)
3′							
4′			1.72 *s*	1.72 *s*	1.66 *s*	1.76 *s*	1.66 *s*
5′			1.79 *s*	1.79 *s*	1.74 *s*	1.82 *s*	1.76 *s*
α	2.80 *s*	2.83 *br s*	2.83 *s*	3.22 *m*	2.81 *s*	2.87 *m*	2.90 *m*
β	2.80 *s*	2.83 *br s*	2.83 *s*	2.82 *m*	2.81 *s*	2.77 *m*	2.90 *m*
2″	7.16 *m*	7.16 *m*	7.17 *m*	7.22 *m*	7.20 *m*	7.18 *m*	7.21 *m*
3″	7.28 *m*	7.29 *m*	7.28 *m*	7.32 *m*	7.29 *m*	7.28 *m*	7.29 *m*
4″	7.17 *m*	7.19 *m*	7.19 *m*	7.22 *m*	7.20 *m*	7.19 *m*	7.21 *m*
5″	7.28 *m*	7.29 *m*	7.28 *m*	7.32 *m*	7.29 *m*	7.28 *m*	7.29 *m*
6″	7.16 *m*	7.16 *m*	7.17 *m*	7.22 *m*	7.20 *m*	7.18 *m*	7.21 *m*
OH	5.29 *br s*		4.80 *br s*	5.54 *br s*		5.00 *br s*	
	5.38 *br s*		5.25 *br s*	11.31 *s*			
3-OMe					3.85 *s*		3.78 *s*
4-OMe							
5-OMe					3.84 *s*		3.78 *s*
6-OMe							
7-OMe		3.78 *s*					
8-OMe		3.83 *s*					
2″-OMe							
CO_2Me				3.96 *s*	3.91 *s*		

Table 1. *Continued*

H	24	25	29	32	33	34	35
2				4.40 *br s*	4.39 *br s*	4.28 *br s*	4.40 *br s*
3							
4				5.60 *t* (3.9)	5.60 *t* (3.6)	5.45 *br s*	5.61 *t* (4.2)
5				3.40 *d* (3.9)	3.43 *d* (3.6)	3.25 *br s*	3.41 *d* (4.2)
6	6.34 *s*	6.45 *s*	6.45 *s*				
7				6.35 *d* (1.6)	6.44 *d* (1.6)		
9				6.53 *d* (1.6)	6.56 *d* (1.6)	6.21 *s*	6.70 *s*
1′	3.28 *d* (6.9)	3.30 *d* (6.4)	2.63 *m*	1.53 *s*	1.53 *s*	1.49 *s*	1.53 *s*
2′	5.09 *t* (6.9)	5.07 *t* (6.4)	1.62 *m*				
3′							
4′	1.71 *s*	1.68 *s*	1.28 *s*				
5′	1.82 *s*	1.75 *s*	1.28 *s*				
α	2.77 *s*	2.85 *s*	2.86 *s*	2.86 *m*	2.88 *s*	3.00 *m*	2.83 *m*
β	2.77 *s*	2.85 *s*	2.86 *s*	2.78 *m*	2.88 *s*	2.61 *m*	2.83 *m*
2″	7.15 *m*	7.18 *m*	7.19 *m*	7.17 *m*	7.18 *m*	6.85	7.17 *m*
3″	7.27 *m*	7.29 *m*	7.29 *m*	7.27 *m*	7.28 *m*	}	7.28 *m*
4″	7.18 *m*	7.20 *m*	7.20 *m*	7.18 *m*	7.19 *m*	} (*m*)	7.19 *m*
5″	7.27 *m*	7.19 *m*	7.29 *m*	7.27 *m*	7.28 *m*	}	7.28 *m*
6″	7.18 *m*	7.18 *m*	7.19 *m*	7.17 *m*	7.18 *m*	7.00	7.17 *m*
OH	5.37 *s*		1.70 *br s*	5.06 *br s*			
	5.43 *s*						
	5.53 *s*						
3-OMe		3.85 *s*	3.85 *s*				
4-OMe		3.89 *s*	3.89 *s*				
5-OMe		3.79 *s*	3.79 *s*				
6-OMe					3.75 *s*		3.74 *s*
7-OMe							
8-OMe							
2″-OMe							
CO_2Me							3.91 *s*

and (v) H-β and H-6″ in **37**. The above spectral and chemical data led to the structure **37** for radulanin L.

Synthesis of (±)-**1**, **2**, **41** *and* **42** (*Schemes* 2 *and* 3)

Before attempting the synthesis of **1**, the model reaction was carried out using 2-hydroxy-3-methoxy-2′,2′-dimethylallylbenzene (**47**) (Scheme 2). In this reaction, the formation of the dihydrobenzofuran **50** and dihydrooxepin derivatives **51** might be expected and the monomethyl ether **2** of the natural bibenzyl **1** with a five-membered ring and a still unknown bibenzyl with a seven-membered bibenzyl would be synthesized. Acetylation of **47** with acetic anhydride in pyridine gave a mono acetate (**48**, 87.5%) which on treatment with calcium hypochloride [$Ca(OCl)_2$] [15] afforded an allyl monochloride (**49**, 46.1%). The chloride (**49**) was further treated with barium hydroxide to furnish only a five-membered compound (**50**, 41.5%). On the basis of this model reaction, the synthetic 3-hydroxy-5-methoxy-2-(3-methyl-2-butenyl)-bibenzyl (**11**) [9] was treated in the same manner as described above to give **52** (99.3%), **53** (49.7%) and finally **2** (47.7%) which was identical to the methyl ether of the natural product (**1**) isolated from *R. perrottetii*. The isomer (**42**) of **2** was also synthesized (Scheme 2). The synthetic product **17** [9] was treated with the same reagents as described above to afford **42** (21.3%), which was not identical to the methyl ether **2**, although the spectral data of both methyl ethers were similar (Tables 1 and 2). Compounds **2** and **42** were prepared from **56** by a one step reaction (Scheme 3). However, the yields were poor. The synthetic bibenzyl **56** [9] was treated with 1,4-dibromo-2-methyl-2-butene in the presence of sodium methoxide to give two cyclized products which were purified by prep. TLC to afford **2** (5.6%) and **42** (5.7%), respectively. Dihydropinosylvin (**46**) was treated in the same manner as described above to yield the natural dihydrobenzofuran **1** (17.6%) and its isomer (**41**) (4.9%), respectively.

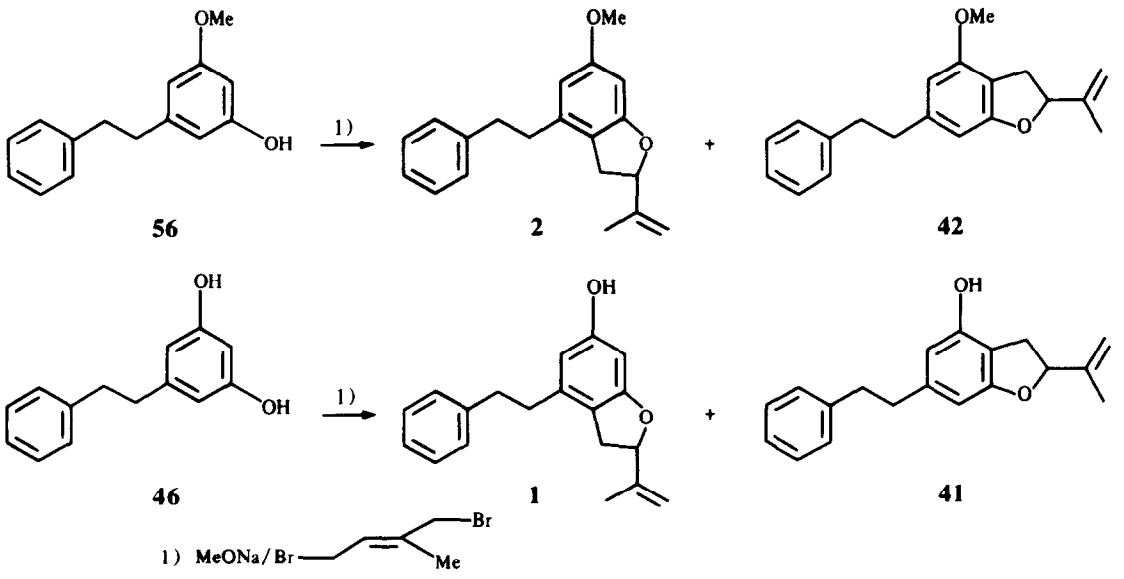
Synthesis of **4** *and* **9** (*Schemes* 4 *and* 5)

3,4,5-Trimethoxybenzaldehyde (**57**) was treated with benzylmagnesiumbromide to give a secondary alcohol (**58**) (98.6%) which was hydrogenolysed to afford 3,4,5-trimethoxybibenzyl (**59**) (86.5%) (Scheme 4). Compound **59** was demethylated with EtSNa to give the two monodemethyl ethers **65** (40.2%) and **66** (41.2%). The former product was treated with 1,4-dibromo-2-methyl-2-butene in the presence of MeONa to afford a dihydrobenzofuran (23.8%), the spectral data of which were superimposable on those of the dimethyl ether (**4**) of the natural product **3**. 3-Hydroxy-4,5-dimethoxybibenzyl (**65**) was prenylated with 2,2-dimethylallylbromide in the presence of MeONa to give 3-hydroxy-4,5-dimethoxy-2-(3-methyl-2-butenyl)-bibenzyl (**67**) (8.9%) and a prenyloxy product (**68**)

Table 1. *Continued*

H	36	37	41	42
2	4.40 *br s*	4.40 *br s*	5.19 *dd* (9.5, 7.8)	5.16 *dd* (9.6, 8.1)
3			2.93 *dd* (15.1, 7.8)	2.92 *dd* (15.5, 8.1)
			3.25 *dd* (15.1, 9.5)	3.24 *dd* (15.5, 9.6)
4	5.61 *t* (4.4)	5.60 *br t* (6.0)		
5	3.40 *d* (4.4)	3.43 *br d* (6.0)	6.13 *s*	6.18 *s*
6				
7	6.39 *d* (1.7)	6.48 *d* (1.3)	6.30 *s*	6.34 *s*
9	6.55 *d* (1.7)	6.59 *d* (1.3)		
1′	1.54 *s*	1.53 *s*		
2′			4.90 *s*	4.88 *s*
			5.08 *s*	5.07 *s*
3′			1.76 *s*	1.76 *s*
4′				
5′				
α	2.83 *m*	2.84 *m*	2.79 *m*	2.88 *m*
β	2.83 *m*	2.84 *m*	2.85 *m*	2.88 *m*
2″			7.15 *m*	7.15 *m*
3″	6.74 *dd* (7.4, 1.1)	6.86 *d* (7.8)	7.29 *m*	7.29 *m*
4″	7.08 *ddd* (7.4, 7.4, 1.1)	7.19 *ddd* (7.8, 7.8, 1.8)	7.16 *m*	7.15 *m*
5″	6.86 *ddd* (7.4, 7.4, 1.1)	6.87 *t* (7.8)	7.29 *m*	7.29 *m*
6″	7.09 *dd* (7.4, 1.1)	7.10 *dd* (7.8, 1.8)	7.16 *m*	7.15 *m*
OH	4.79 *br s*		5.16 *br s*	
	4.87 *br s*			
3-OMe				
4-OMe				3.75 *s*
5-OMe				
6-OMe		3.76 *s*		
7-OMe				
8-OMe				
2″-OMe		3.83 *s*		
CO_2Me				

*Coupling constants (J in Hz) are given in parentheses.



Scheme 3.

Table 2. ^{13}C NMR (400 MHz) spectral data for compounds **1–5**, **8–10**, **12**, **13**, **16**, **18**, **24**, **25**, **29**, **32–37**, **41** and **42** ($CDCl_3$–TMS)*

C	1	2	3	4	5	8	9	10	12	13	16
1								142.1	144.1	139.1	141.7[a]
2	86.4	86.3	87.7	86.9	90.5	76.6	75.5	117.6	119.4	121 1	108.2
3	32.9	32.9	33.7	33.3	31.8	127.6	128.6	155.7	162.7	159.3	154.8
4	138.9	138.6	129.6	131.6	129.4	119.2	119.0	101.4	102.3	93.6	111.0
5	107.1	106.0	107.7	104.7	107.2	129.4	132.3	154.4	159.8	155.8	154.8
6	156.2	160.7	143.5	152.3	144.3	108.4	105.3	108.9	106.2	116.7	108.2
7	95.3	93.7	125.7	126.0	125.6	143.9	152.7				
8	160.7	160.5	146.4	151.3	146.6	130.1	136.1				
9	117.7	117 5	117.9	119.6	118.4	140.0	146.7				
10						112.4	114.0				
11											
1′	144.1	144.2	144.5	144.0	33.2	27.8	27.6	24.9	25 1	24.5	22.3
2′	111.9	111.8	112.4	111.9	18.3	27.8	27.6	122.6	122.4	123.6	121.7
3′	17.2	17.1	17.1	17.1	17.8			134.2	134.0	131.0	135.5
4′								25 7	25.7	25.7	25.8
5′								18.0	18.1	18.0	17.9
α	35 6	35.8	35.0	35.5	35.0	33.8	34.5	35.7	33.4	33.3	37 5
β	36.5	36.6	36.7	36.8	36.9	37.9	37.7	37 5	37.3	37.3	37.5
1″	141.5	141.6	141.6	141.5	141.8	141.7	141.5	141.7	142 1	142.1	141.8[a]
2″	128.4	128.4	128.3	128.3	128.3	128.4	128 3	128.4	128.2	128.3	128.4
3″	128.4	128.5	128.5	128.5	128.5	128.4	128.4	128.4	128.5	128.5	128.4
4″	126 1	126.0	125.9	126.0	126.0	125.9	125.9	126 0	126 1	126.0	125.9
5″	128.4	128.5	128.5	128.5	128.5	128.4	128.4	128.4	128.5	128.5	128.4
6″	128.4	128.4	128.3	128.3	128.3	128.4	128.3	128.4	128.2	128 3	128.4
3-OMe										56.1	
4-OMe											
5-OMe										55 8	
6-OMe		55.2		60.6							
7-OMe				56.4			55.9				
8-OMe							60.9				
2″-OMe											
CO_2Me									171.9	169.5	
									52.2	52.2	

(23.1%). The former compound was dehydrogenated with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to furnish a chromene derivative (88.4%) whose spectral data were identical to those of the dimethyl ether (**9**) of the natural product **8**.

Synthesis of **25** (*Scheme* 4)

Compound **59** was brominated with *N*-bromosuccinimide to give a mono- (**60**) (83.7%) and a dibromide (**61**) (13.9%). Treatment of the former product with *n*-BuLi and 2,2-dimethylallylbromide gave a debrominated product (**59**) (20.1%) and a prenylated product (74.5%) whose spectral data were consistent with those of the trimethyl ether (**25**) of the natural perrottetin A (**24**). Demethylation of **25** with EtSNa gave two bisdemethyl products **62** (50.7%) and **63** (38.2%). On the other hand when **25** was treated with BBr_3 it gave a chroman derivative (**64**) (80.3%). The structures of all intermediates obtained during the course of the syntheses of the natural bibenzyls and their derivatives were established by spectral methods (UV, IR, ^{1}H and ^{13}C NMR, difference NOE, HRMS and EIMS).

It is known that bibenzyl derivatives show significant antimicrobial, antifungal [16–19], hyaluronidase [20], 5-lipoxygenase and calmodulin inhibitory activity [9]. The prenyl bibenzyls (**3**, **24**, **32** and **36**) found in *R. perrottetii* and *R. complanata* also showed 5-lipoxygenase and calmodulin inhibitory activity (Table 3). One natural bibenzyl (**17**) and two synthetic bibenzyls (**15** and **20**) [9] possessed vasopressin antagonist activity (Table 4).

The distribution of bibenzyls in several *Radula* species have been reported [6, 8]. *Radula constricta*, *R. okamurana* and *R. brunnea* (subgenus: *Radula*) and *R. companigera* and *R. chinensis* (subgenus: *Cladoradula*) have chemically been investigated and neither perrottetin A-type compounds (**24**, **26** and **28**) nor the cyclized compounds (**1**, **3** and **8**) have been detected by TLC, GC or GC-MS [8]. *R. perrottetii* (subgenus: *Cladoradula*) is chemically different from the other *Radula* species so far examined because it produces 3,4,5-trihydroxy-2-(3-methyl-2-butenyl)bibenzyl and its cyclized products as major components.

EXPERIMENTAL

Mps: uncorr. The solvents used for spectral measurements were TMS–$CDCl_3$ [^{1}H NMR (400 MHz); ^{13}C NMR (100 MHz)]; EtOH (UV); $CHCl_3$ (IR); MeOH (CD and $[\alpha]_D$) unless otherwise stated. The solvent MeOH–$CHCl_3$ (1:1) was

Table 2. *Continued*

	18	24	25	29	32	33	35	36	37	41	42
1	140.7	133.9	140.5	140.5							
2	104.2	118.2	126.1	126.5	74.3	74.1	74.3	74.3	74.2	86.4	86.3
3	157.9	142.9	151.9	151.8	133.9	133.9	134.3	134.1	134.0	31.6	32.1
4	116.0	130.2	130.8	135.5	120.7	121.0	120.1	120.7	121.1	152.0	156.1
5	157.9	141.9	151.2	151.3	21.7	21.3	22.3	21.7	21.3	107.9	102.6
6	104.2	108.8	108.8	108.7	156.1[a]	156.1[a]	154.4	152.1	156.1	143.9	143.7
7					111.6	107.2	127.8	111.6	107.3	102.3	103.4
8					146.6[b]	141.7[b]	138.9	141.6	142.0	161.6	161.2
9					113.6	113.7	118.1	113.8	113.7	109.8	111.0
10					159.6[a]	159.4[a]	160.4	159.9	159.4		
11					120.7	122.4	124.4	120.7	122.2		
1′	22.1	25.4	25.2	21.1	20.1	20.1	19.9	20.1	20.1	143.9	144.2
2′	123.2	122.8	124.1	44.8						112.1	111.7
3′	130.9	131.9	135.4	70.9						17.2	17.2
4′	25.9	25.7	25.7	29.1							
5′	17.7	17.9	18.0	29.1							
α	38.0[a]	35.0	35.2	35.2	37.4[c]	37.8[c]	35.6	35.7	36.2	37.7	38.0
β	38.5[a]	37.9	37.7	38.1	37.5[c]	37.9[c]	37.5	32.0	32.3	37.9	38.4
1″	141.9	141.9	141.9	141.8	141.4[b]	141.3[b]	141.4	127.8	130.2	141.7	141.8
2″	128.3	128.4	128.3	128.4	128.3	128.3	128.4	153.5	157.5	128.3	128.3
3″	128.5	128.4	128.5	128.5	128.4	128.5	128.4	115.4	110.3	128.4	128.4
4″	125.9	125.9	125.9	126.0	125.9	125.9	126.0	127.4	127.2	125.9	125.9
5″	128.5	128.4	128.5	128.5	128.4	128.5	128.4	120.9	120.4	128.4	128.4
6″	128.3	128.4	128.3	128.4	128.3	128.3	128.4	130.3	129.9	128.3	128.3
3-OMe	55.8		60.9	61.0							
4-OMe			60.7	60.7							55.2
5-OMe	55.8		55.9	55.9							
6-OMe						55.7	52.1		55.8		
7-OMe											
8-OMe											
2″-OMe									55.3		
CO_2Me							168.7				
							62.8				

*All assignments were confirmed by the INEPT, ^1H–^{13}C and long range ^1H-^{13}C COSYs.

[a–c]Values in any vertical column may be interchanged.

used for Sephadex LH-20 CC. TLC, GC and GC-MS were carried out as previously reported [21].

Plant materials. *R. perrottetii* Gott. and *R. complanata* (L.) Dum. were collected in Momizigawa, Aioi-cho, Tokushima Japan in Nov. 1983 and Dordogne, France 1979, respectively and identified by Drs S. Hattori, M. Mizutani and K. Yamada. The voucher specimens are deposited in the Herbarium of the Institute of Pharmacognosy, Tokushima Bunri University.

Extraction and isolation. Air-dried and powdered *R. perrottetii* (347 g) was extracted with MeOH for 5 months. The resultant MeOH extract was evapd *in vacuo* to give a green oil (25.90 g). This was chromatographed on silica gel using a *n*-hexane–EtOAc gradient which was collected as 3 fractions. Fr. 1 (*n*-hexane 100%, 1.52 g) contained mixts of mono- and sesquiterpene hydrocarbons and *n*-paraffins in which the presence of α-pinene, β-barbatene [22], cuparene [6, 22] and squalence were confirmed by GC-MS. Fr. 2 (*n*-hexane–EtOAc, 10–30%, 6.25 g) was rechromatographed on Sephadex LH-20 to give Fr. 2-A and 2-B. A part of Fr. 2A was purified by prep. TLC (C_6H_6–EtOAc 4:1) to give **8** (22 mg) as an oil. The remainder of Fr. 2-A was purified by CC on silica gel impregnated with 10% $AgNO_3$ (*n*-hexane–EtOAc gradient) to give **1** (14 mg), **6** (9 mg) [9] and **12** (22 mg). Fr. 2-B was rechromatographed on silica gel using $CHCl_3$–MeOH (49:1) to give **10** (300 mg) [9] and perrottetin D (**3**) (520 mg). Fr. 3 (*n*-hexane–EtOAc, 50–75%, 3.98 g) was rechromatographed on Sephadex LH-20 to give **10** (25 mg), perrottetins E (**38**) (290 mg), F (**39**) (300 mg) and G (**40**) (16 mg) [7].

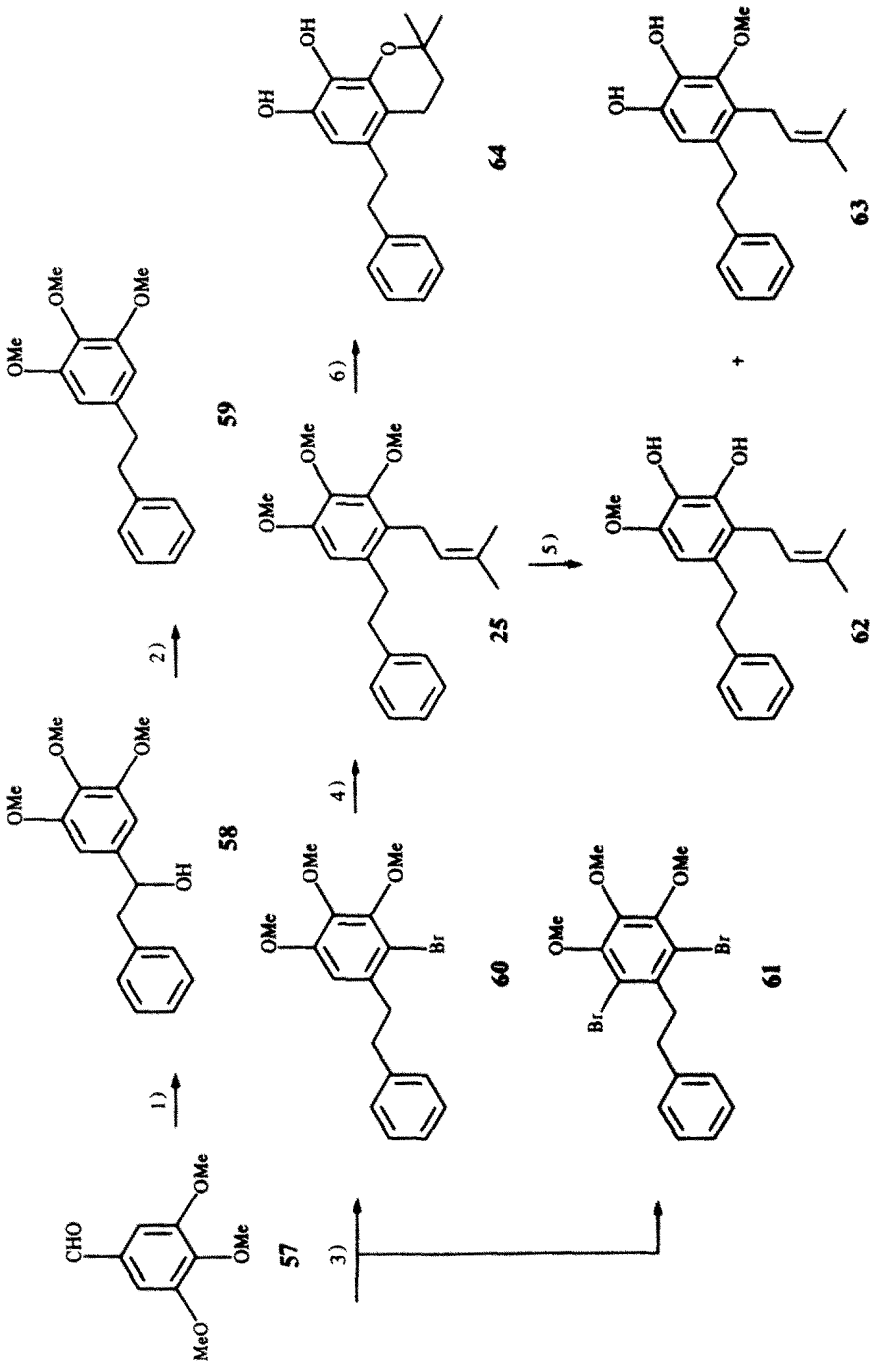
Compound **8**. UV λ_{max} nm (log ε): 211 (4.23), 280 (3.67), 335 (3.64); IR ν_{max} cm^{-1}: 3570, 1620, 1510, 1375, 1180, 1130, 690; ^1H and ^{13}C NMR: Tables 1 and 2; HRMS: found: 296.1416, $C_{19}H_{20}O_3$ requires 296.1413; EIMS *m/z* (rel. int.): 296 $[M]^+$ (30), 281 (100), 205 (15), 190 (33), 91 (25).

Compound **1**. Mp 109–115.5° (from *n*-hexane); $[\alpha]_D$ −13.6° (*c* 0.09); UV λ_{max} nm (log ε): 211 (4.08), 235 (3.49), 288 (3.21); IR ν_{max} cm^{-1}: 3600, 1602, 1490, 1450, 1443, 1119, 1112, 972, 900, 830, 690; ^1H and ^{13}C NMR: Tables 1 and 2; HRMS: found: 280.1459, $C_{19}H_{20}O_2$ requires 280.1463; EIMS *m/z* (rel. int.): 280 $[M]^+$ (100), 265 (28), 225 (17), 189 (51), 175 (32), 174 (22), 105 (13), 91 (24).

Compound **12**. Mp 95–98° (from Et_2O); ^1H and ^{13}C NMR Tables 1 and 2; HRMS: found: 340.1677, $C_{21}H_{24}O_4$ requires 340.1675. This compound was previously reported as **30** [6].

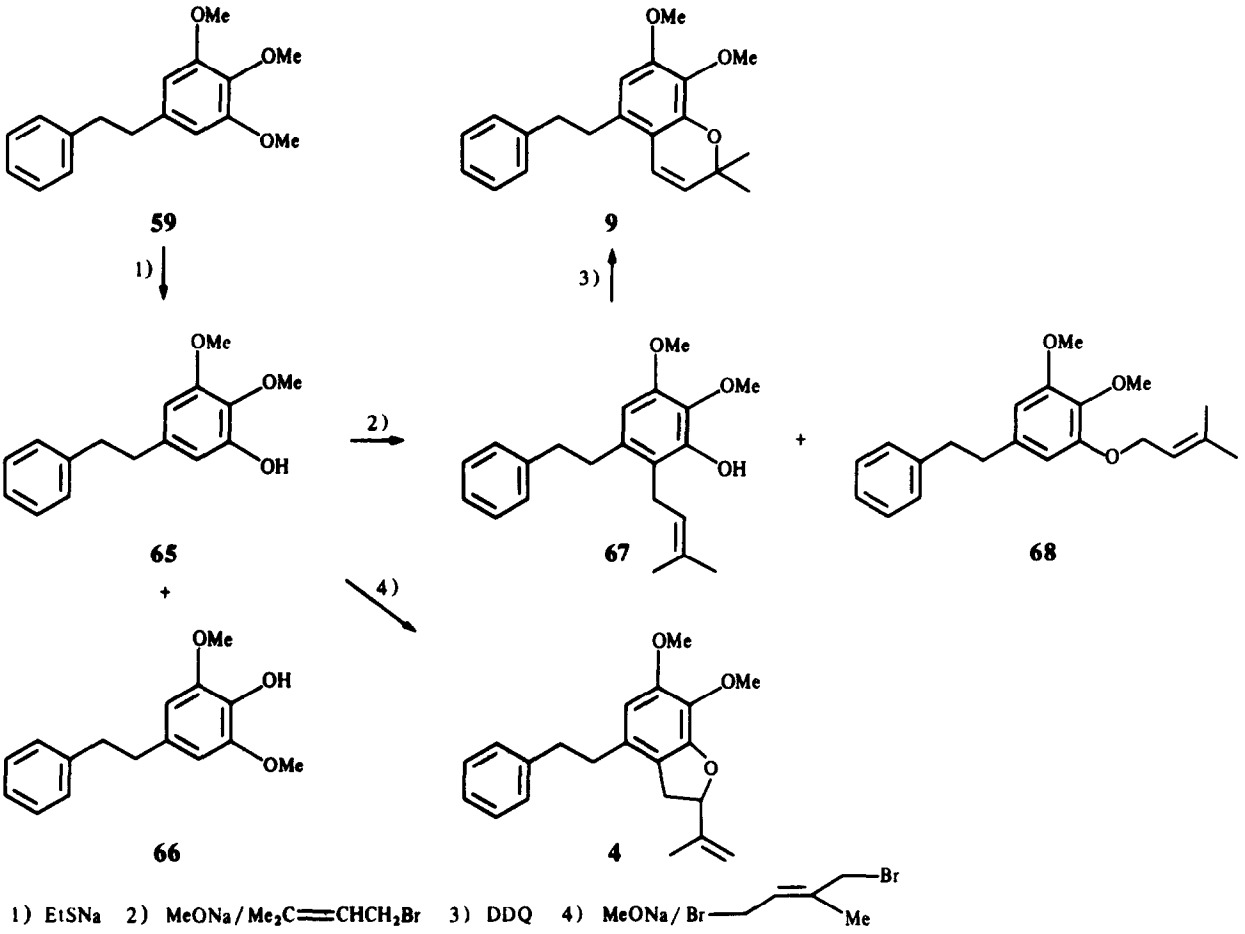
Compound **3**. Mp 82–83° (from cyclohexane); $[\alpha]_D$ −9.0° (*c* 0.1); ^1H and ^{13}C NMR: Tables 1 and 2; HRMS: found: 296.1425, $C_{19}H_{20}O_3$ requires 296.1413; CD: $\Delta\varepsilon_{207\,nm}$ +0.29, $\Delta\varepsilon_{235\,nm}$ −0.02, $\Delta\varepsilon_{265\,nm}$ +0.06 (c 3.4×10^{-3} mol l^{-1}). This compound was previously reported as **31** [6].

A part (35.028 g) of the crude extract (55.587 g) obtained from



1) $C_6H_5CH_2MgBr$ 2) 20% Pd-C/H_2 3) NBS 4) *n*-BuLi/Me_2C═══CH——CH_2Br 5) EtSNa 6) BBr_3

Scheme 4.



Scheme 5.

Table 3. 5-Lipoxygenase and calmodulin inhibitory activity of some prenyl bibenzyls isolated from *Radula* species

Compounds	5-Lipoxygenase inhibition (at 10^{-6} mol)	Calmodulin inhibition ID_{50} ($\mu g\,ml^{-1}$)
3	40%	2
24	76	4
32	Not tested	95
34	15	17
36	not tested	18

Table 4. Vasopressin (VP) antagonist activity of some prenyl bibenzyls

Compounds	ID_{50} ($\mu g\,ml^{-1}$)
14	no activity
15	57
17	27
19	no activity
20	17
25	no activity

the dried *R. complanata* (610 g) was fractionated by silica gel CC using a *n*-hexane–EtOAc gradient which was collected as 6 fractions: Fr.1 (*n*-hexane 100%, 1.20 g), Fr. 2 (95–90% *n*-hexane, 7.74 g), Fr. 3 (85–70% *n*-hexane, 7.24 g), Fr. 4 (60–40% *n*-hexane, 11.29 g), Fr. 5 (30–10% *n*-hexane, 3.47 g) and Fr. 6 (EtOAc 100%, 3.45 g). Fr. 1–4 were further fractionated by CC on silica gel and several bibenzyls obtained [6]. A part of Fr. 3 (957 mg) was chromatographed on silica gel using the same solvent as described above to give radulanin A (**32**) (20 mg) [3, 4]. ^1H and ^{13}C NMR: Tables 1 and 2. A part of Fr. 4 (4.593 g) was rechromatographed on Sephadex LH-20 to afford 3,5-dihydroxy-2-(3-methyl-2-butenyl)bibenzyl (**10**) (39 mg) [9], 3,5-dihydroxy-4-(3-methyl-2-butenyl)bibenzyl (**16**) (12 mg) [4], 2-geranyl-3,5-dihydroxybibenzyl (**14**) (14 mg), radulanin H (**34**) (120 mg) [6] and radulanin L (**36**) (900 mg).

Compounds **10** *and* **16**. ^1H and ^{13}C NMR: Tables 1 and 2.

Compound **36**. Mp 125–126° (from Et_2O); UV λ_{max} nm (log ε): 214 (4.29), 275 (3.75), 282 (3.66); IR ν_{max} cm^{-1}: 3580, 2900, 1620, 1585, 1500, 1480, 1450, 1420, 1245, 1060; ^1H and ^{13}C NMR: Tables 1 and 2; HRMS: found: 296.1446, $C_{19}H_{20}O_3$ 296.1412; EIMS *m/z* (rel. int.): 296 $[M]^+$ (100), 281 (27), 189 (91), 187 (58), 174 (26), 160 (23), 107 (36), 91 (11), 77 (30).

Methylation of **1**. Compound **1** (2.3 mg) in dry Me_2O (3 ml) was methylated with MeI (0.1 ml) in the presence of K_2CO_3 (100 mg) for 4 hr under reflux. Work-up as usual gave an oil which was purified by prep. TLC (*n*-hexane–EtOAc, 4:1) to afford a monomethyl ether (**2**) (2.2 mg). mp 30.5–32.0°; $[\alpha]_D$

$-25.5°$ (*c* 0.08); UV λ_{max} nm (logε): 215 (4.12), 231sh (3.74), 288 (3.37); IR ν_{max} cm^{-1}: 1620, 1600, 1492, 1440, 1130, 690; ^{1}H and ^{13}C NMR: Tables 1 and 2; HRMS: found: 294.1635, $C_{20}H_{22}O_2$ requires 294.1620; CD: $\Delta\varepsilon_{208\,nm}$ +0.57, $\Delta\varepsilon_{220\,nm}$ −0.27, $\Delta\varepsilon_{270\,nm}$ +0.39 (*c* 2.7×10^{-3} mol l); EIMS *m/z* (rel. int.): 294 [M]$^+$ (100), 279 (23), 239 (15), 203 (61), 189 (35), 105 (13), 91 (28).

Methylation of **8**. Compound **8** (16 mg) was treated with MeI as described above to give a dimethyl ether (**9**): UV λ_{max} nm (logε): 220 (4.36), 275 (4.01), 280 (4.02), 350 (3.40); IR ν_{max}cm^{-1}: 1600, 1500, 1460, 1450, 1418, 1130, 1060, 690; ^{1}H and ^{13}C NMR: Tables 1 and 2; HRMS: found: 324.1701, $C_{21}H_{24}O_3$ requires 324.1725; EIMS *m/z* (rel. int.): 324 [M]$^+$ (18), 309 (100), 233 (10), 218 (5), 203 (18), 91 (11).

Methylation of **12**. Treatment of **12** (5 mg) with MeI as described above afforded a dimethyl ether (**13**) (5 mg). Mp 82–85°; UV λ_{max} nm (logε): 218 (4.42), 287 (3.60); IR ν_{max} cm^{-1}: 1722, 1595, 1433, 1320, 1270, 1150, 1140, 1080, 945, 690; ^{1}H and ^{13}C NMR: Tables 1 and 2; HRMS: found: 368.1982, $C_{23}H_{28}O_4$ requires 368.1987; EIMS *m/z* (rel. int.): 368 [M]$^+$ (100), 337 (50), 321 (18), 311 (42), 280 (27), 279 (94), 263 (29), 245 (57), 203 (55).

Methylation of **34**. Compound **34** (60 mg) was methylated as described above to give a methyl ester (**35**) (26 mg): UV λ_{max} nm (logε): 212 (4.32), 266 (3.85), 310 (2.85); IR ν_{max} cm^{-1}: 2940, 1730, 1600, 1570, 1445, 1298, 1260, 1140, 1060, 1018, 980, 690; ^{1}H and ^{13}C NMR: Tables 1 and 2; HRMS: found: 352.1653, $C_{22}H_{24}O_4$ requires 352.1675; EIMS *m/z* (rel. int.): 352 [M]$^+$ (79), 337 (35), 321 (12), 289 (42), 261 (95), 231 (26), 91 (100).

Methylation of **36**. Compound **36** (33 mg) was methylated with MeI as described above to give a dimethyl ether (**37**) (20 mg): UV λ_{max} nm (logε): 212.5 (4.28), 270.5 (3.67), 277.5 (3.67); IR ν_{max}cm^{-1}: 2950, 1615, 1600, 1585, 1465, 1452, 1420, 1240, 1100, 1048, 1030; ^{1}H and ^{13}C NMR: Tables 1 and 2; HRMS: found: 324.1674, $C_{21}H_{24}O_3$ requires 324.1725; EIMS *m/z* (rel. int.): 324 [M]$^+$ (98), 309 (89), 293 (8), 203 (74), 121 (100), 91 (92).

Methylation of **3**. Compound **3** (20 mg) was methylated with MeI as described above to afford a dimethyl ether (**4**) (16 mg): $[\alpha]_D$ −13.8° (*c* 0.25); UV λ_{max} nm (logε): 217 (4.44), 277.5 (3.27); IR ν_{max}^{neat} cm^{-1}: 3025, 2925, 1650, 1600, 1500, 1430, 1360, 1230, 1105, 1070, 1020, 970, 900, 810, 750, 700; ^{1}H and ^{13}C NMR: Tables 1 and 2; CD: $\Delta\varepsilon_{210\,nm}$ +0.65, $\Delta\varepsilon_{234\,nm}$ −0.08, $\Delta\varepsilon_{265\,nm}$ +0.15 (*c* 3.6×10^{-3} mol l^{-1}); EIMS *m/z* (rel. int.): 324 [M]$^+$ (44), 263 (17), 234 (17), 233 (100), 167 (15), 91 (39).

Catalytic hydrogenation of **3**. Compound **3** (15 mg) in EtOH (2 ml) was hydrogenated in the presence of 10% Pd-C (40 mg) for 30 min. The product (14.8 mg), after filtration and removal of the solvent was purified by prep. TLC (C_6H_6–EtOAc, 4:1) to afford a dihydro deriative (**5**) (6 mg): mp 72–73°; $[\alpha]_D$ −27.9° (*c* 0.11); UV λ_{max} nm (logε): 215 (4.38), 235sh (4.02), 275 (3.11); IR ν_{max}cm^{-1}: 3550, 2950, 1610, 1520, 1455, 1280, 1175, 1032, 998, 690; ^{1}H and ^{13}C NMR: Tables 1 and 2; HRMS: found: 298.1596, $C_{19}H_{22}O_3$ requires 298.1569; CD: $\Delta\varepsilon_{215\,nm}$ +1.68, $\Delta\varepsilon_{240\,nm}$ −0.25, $\Delta\varepsilon_{266\,nm}$ +0.13 (*c* 3.6×10^{-3} mol l^{-1}); EIMS *m/z* (rel. int.): 298 [M]$^+$ (51), 207 (100), 165 (22), 151 (32), 123 (18), 105 (11), 91 (82).

Prenylation of 3,5-*dimethoxybibenzyl* (**44**). To a soln of **42** (736 mg) [9] in dry Et_2O (20 ml) was added 1.6 M *n*-BuLi soln (1.9 ml). The resultant soln was refluxed under Ar for 8 hr and then 2,2-dimethylallylbromide (550 mg) in dry Et_2O was added dropwise over 10 min. After stirring for 1 hr at 40°, the reaction mixt. was poured into ice-H_2O and extracted with EtOAc. The organic layer was washed with H_2O, dried over $MgSO_4$ and concd to an oil (993 mg), which was chromatographed on silica gel using an *n*-hexane–EtOAc gradient to afford 3,5-dimethoxy-4-(3-methyl-2-butenyl)bibenzyl (**18**) (671 mg, 71.2%) as an oil and the starting material (**42**) (102 mg, 13.9%).

Compound **18**. IR ν_{max}^{neat} cm^{-1}: 2925, 1605, 1585, 1450, 1415, 1220, 1160, 1110; ^{1}H and ^{13}C NMR: Tables 1 and 2; HRMS: found: 310.1942, $C_{21}H_{26}O_2$ requires 310.1933; EIMS *m/z* (rel. int.): 310 [M]$^+$ (100), 295 (65), 255 (22), 242 (25), 219 (57), 151 (12), 105 (16), 91 (15).

Reaction of **18** *with* BBr_3. To a soln of **18** (175 mg) in dry CH_2Cl_2 (10 ml) was added BBr_3 (0.2 ml) at −78° with stirring. After stirring for 2 hr at −10–0° Et_3N (1 ml) was added. The reaction mixt. was poured into ice-H_2O and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried over $MgSO_4$ and concd to an oil (178 mg) which was chromatographed on silica gel using 10% EtOAc–*n*-hexane to afford 2,2-dimethyl-5-hydroxy-7-(2-phenylethyl)chroman (**45**) (118 mg, 74.2%): IR ν_{max}^{neat} cm^{-1}: 3400, 2975, 2925, 1625, 1580, 1450, 1360, 1345, 1225, 1150, 1110, 1045, 1020, 985; ^{1}H NMR: δ1.30 (6H, *s*), 1.75 (2H, *t*, *J* = 6.8 Hz), 2.61 (2H, *t*, *J* = 6.8 Hz), 2.70–2.83 (4H, *m*), 5.54 (1H, *br s*, OH), 6.12, 6.33 (each 1H, *br s*), 7.12–7.25 (5H, *m*); ^{13}C NMR: δ16.7 (*t*), 26.6 (*q*), 32.2, 37.4, 37.5 (each *t*), 74.0 (*s*), 106.2 (*s*), 106.5, 109.4, 125.8, 128.3 (each *d*), 141.3, 141.8, 153.7, 154.7 (each *s*); HRMS: found: 282.1632; $C_{19}H_{22}O_2$ requires 282.1620; EIMS *m/z* (rel. int.): 282 [M]$^+$ (63), 227 (100), 191 (40), 91 (46).

Methylation of **17**. To a soln of **17** (42 mg) in dry Me_2CO (10 ml) was added K_2CO_3 (350 mg) and MeI (1.0 ml). The mixt. was stirred at 70–80° for 6 hr. Work-up as usual gave an oil which was purified by prep. TLC (*n*-hexane–EtOAc, 4:1) to afford **18** (37.5 mg, 85.2%) as an oil.

Demethylation of **18** *with* EtSNa *in* DMF. To a soln of 60% NaH (77 mg) in dry DMF (2 ml) was added a soln of EtSH (120 mg) in dry DMF (2 ml) under Ar at room temp. After stirring for 5 min, a soln of **18** (100 mg) in dry DMF (1 ml) was added and refluxed for 3 hr at 170–180°. The reaction mixt. was poured into ice-H_2O and extracted with Et_2O. The organic layer was successively washed with 1 M HCl, H_2O, dried over $MgSO_4$ and concd *in vacuo* to give a residue (125 mg) which was purified by prep. TLC (*n*-hexane–EtOAc, 4:1) to yield a bibenzyl (66 mg, 69.0%) whose spectral data were identical to those of the natural 3-hydroxy-5-methoxy-4-(3-methyl-2-butenyl)bibenzyl (**17**) [4, 9].

Treatment of **17** *with* EtSNa *in* HMPA. To a soln of 60% NaH (164 mg) in dry hexamethylphosphoramide (HMPA) (2 ml) was added a soln of EtSH (0.43 ml) in HMPA (2 ml) under Ar at room temp. After stirring for 10 min, a soln of **17** (101 mg) in dry HMPA (2 ml) was added and the mixt. refluxed for 5 hr at 170–180°. The reaction mixt. was treated in the same manner as described above to afford 3,5-dihydroxybibenzyl (**46**) (55 mg, 57.2%) [9].

Synthesis of **50**. The prenyl phenol (**47**) (154.5 mg) was acetylated with Ac_2O–pyridine (each 1 ml). Work-up as usual gave an acetate (**48**) (165.2 mg, 87.5%); 1.68 (6H, *s*), 2.28 (3H, *s*), 3.12 (2H, *d*, *J* = 7.7 Hz), 3.72 (3H, *s*), 5.16 (1H, *t*, *J* = 7.2 Hz). To the acetate (**48**) (63 mg) in CH_2Cl_2 (6 ml) was added H_2O (2 ml) and $Ca(OCl)_2$ (87 mg) in an ice bath. A small piece of solid CO_2 was added to the above resultant mixt. which was then stirred for 45 min. After filtration, the CH_2Cl_2 layer was washed with H_2O, dried over $MgSO_4$ to give a residue (68 mg), which was purified by prep. TLC (*n*-hexane–EtOAc, 5:1) to afford **49** (33 mg, 46.1%) [15] ^{1}H NMR: δ1.88 (3H, *s*), 2.32 (3H, *s*), 2.96 (2H, *d*, *J* = 7.2 Hz), 3.72 (3H, *s*), 4.56 (1H, *t*, *J* = 7.2 Hz), 4.88 (2H, *d*, *J* = 7.2 Hz). To compound **49** (14.3 mg) in Me_2CO was added 0.6 M $Ba(OH)_2$ (1 ml) and the mixt. was stirred for 2 hr at room temp. and then Amberlite-IR-120-B (2 g) was added and stirred for 10 min. Filtration and evapn of the solvent gave a residue which was extracted with Et_2O, washed with H_2O, dried over $MgSO_4$ to give a residue which was purified by prep. TLC as described above to furnish **50** (4.2 mg, 41.5%) ^{1}H NMR: δ1.76 (3H, *s*), 3.04 (2H, *dd*, *J* = 14.4, 7.2 Hz), 3.72 (3H, *s*), 4.89 (1H, *s*), 5.04 (1H, *s*), 5.14 (1H, *t*, *J* = 9.0 Hz).

Synthesis of **2**. Compound **11** (99.5 mg) was acetylated with Ac_2O–pyridine as described above to give an acetate (**52**) (112.8 mg, 99.3%): IR $\nu_{max}cm^{-1}$: 1770, 1615, 1580, 1360, 1200, 1120, 1040; ^1H NMR: δ1.64, 1.68 (each 3H, *s*), 2.26 (3H, *s*), 2.88 (4H, *s*), 3.16 (2H, *d*, J=7.2 Hz), 3.70 (3H, *s*), 5.00 (1H, *t*, J=7.2 Hz), 6.48 (1H, *d*, J=3.6 Hz), 6.64 (1H, *d*, J=3.6 Hz); ^{13}C NMR: δ18.0 (*q*), 25.3 (*t*), 25.6 (*q*), 35.5, 37.4 (each *t*), 55.3 (*q*), 106.4, 111.3 (each *d*), 123.8 (*s*), 126.0, 128.4 (each *d*), 131.1, 141.7, 142.6, 149.9, 158.0, 169.5 (each *s*); EIMS *m/z* (rel. int.): 338 $[M]^+$ (5), 296 (26), 295 (100), 279 (12), 241 (66), 205 (21), 161 (25), 105 (11), 91 (27), 43 (10). Compound **52** (85.7 mg) in CH_2Cl_2 (4 ml) was treated with H_2O (2 ml) and $Ca(OCl)_2$ (82.4 mg) in the presence of solid CO_2 as described above [15]. The usual work-up gave a chloride (**53**) (22.1 mg, 49.7%) and the starting material (**52**) (26 mg): compound **53**: UV λ_{max}^{MeOH} nm (log ε): 217.5 (4.12), 282.5 (3.14); IR $\nu_{max}cm^{-1}$: 1775, 1120, 1040; ^1H NMR: δ1.89, 2.30 (each 3H, *s*), 2.92 (6H, *s*), 3.75 (3H, *s*), 4.57 (1H, *t*, J=6.0 Hz), 4.90 (2H, *s*), 6.52 (1H, *d*, J=2.4 Hz), 6.66 (1H, J=2.6 Hz); ^{13}C NMR: δ17.3 (*q*), 33.7, 37.4 (each *t*), 55.3 (*q*), 66.5, 106.1, 113.1 (each *d*), 113.9 (*t*), 120.3, 124.2 (each *s*), 126.1, 128.4 (each *d*), 143.1, 144.4, 150.4, 158.0, 169.5 (each *s*); EIMS *m/z* (rel. int.): 372 $[M]^+$ (1), 283 (16), 242 (15), 241 (100), 137 (11), 105 (7), 91 (23), 43 (16). To the chloride (**53**) (16.2 mg) in Me_2CO (4 ml) was added 0.6 M $Ba(OH)_2$ (2 ml) at room temp. with stirring for 3 hr. The reaction mixt. was treated in the same manner described in the preparation of **50** to give a cyclized product (6.1 mg, 47.7%) whose spectral data were in good agreement with those of **2** prepared from **1** by methylation with MeI.

Synthesis of **42**. The bibenzyl (**17**) (111.8 mg) was treated with Ac_2O–pyridine to give an acetate (**54**) (125.7 mg, 98.5%): UV λ_{max}^{MeOH} nm (log ε): 219.5 (4,22), 281.5 (3.38); IR $\nu_{max}cm^{-1}$: 1770, 1615, 1580, 1450, 1360, 1200, 1075; ^1H NMR: δ1.65, 1.66 (each 3H, *s*), 2.23 (3H, *s*), 2.87 (4H, *s*), 3.22 (2H, *d*, J=7.0 Hz), 3.72 (3H, *s*), 5.12 (1H, *t*, J=7.2 Hz), 6.51 (2H, *s*); ^{13}C NMR: δ17.6 (*q*), 22.8 (*t*), 25.5 (*q*), 37.4, 37.7 (each *t*), 55.9 (*q*), 108.5, 114.4 (*d*), 119.9, 122.1, 125.8, 128.3 (each *d*), 131.0, 140.7, 141.4, 149.3, 158.0, 169.2 (each *s*); EIMS *m/z* (rel. int.): 338 $[M]^+$ (20), 296 (26), 295 (100), 279 (29), 241 (62), 205 (43), 161 (13), 105 (21), 91 (30), 43 (18). The acetate **54** (116.8 mg) in CH_2Cl_2 (6 ml) was treated in the same manner as described in the preparation of **53** to afford **55** (143.7 mg) which was treated with 0.6 $Ba(OH)_2$ (1 ml), without further purification. The reaction mixt. was treated in the same manner as described in the preparation of **2** to yield **42** (24.2 mg, 21.3%). $[\alpha]_D$ ±0° ($CHCl_3$; *c* 1.5); UV λ_{max}^{MeOH} nm (log ε): 218 (4.28), 275 (3.03); IR $\nu_{max}cm^{-1}$: 1600, 1490, 1450, 1325, 1090; ^1H and ^{13}C NMR: Tables 1 and 2; HRMS: found: 294.1604, $C_{20}H_{22}O_2$ requires 294.1620; EIMS *m/z* (rel. int.): 294 $[M]^+$ (100), 280 (15), 279 (80), 203 (75), 188 (21), 105 (17), 91 (25).

Preparation of **2** *and* **42** *from* 3-*hydroxy*-5-*methoxybibenzyl* (**56**). To isoprene (27.7 ml) in CCl_4 (20 ml) Br_2 (10 ml) was added dropwise under non-aq. condition with stirring at 10±5° for 16 hr. To the reaction mixt. was added H_2O (100 ml) and the organic layer was distilled *in vacuo* to give *cis* and *trans*-1,4-dibromo-2-methyl-2-butene (13.17 g, *cis*:*trans*, 4:1). To the bibenzyl **56** (1.20 g) in dry MeOH (20 ml) was added 28% MeONa soln (1.4 ml). After stirring for 30 min, the reaction mixt. was evapd to dryness *in vacuo*. The residual brown crystals were suspended in dry C_6H_6 (20 ml) and evapd again to remove all traces of H_2O. The residue was again suspended in dry C_6H_6 (20 ml), to which was added dropwise 1,4-dibromo-2-methyl-2-butene (1.97 g), and the mixt. refluxed for 2 hr. The reaction mixt. was poured into ice-H_2O, extracted with Et_2O, washed with brine and dried over $MgSO_4$. Evapn of the solvent gave an oil (1.95 g), which was chromatographed on Sephadex LH-20 to yield the starting material (**56**) (412 mg; 34.3%) and a mixt. of **2** and **42**. The mixt. was further chromatographed on silica gel using an *n*-hexane–EtOAc gradient to give **2** (314 mg, 19.9%) and **42** (251 mg, 15.9%).

Preparation of **1** *and* **41** *from* 3,5-*dihydroxybibenzyl* (**46**). To a soln of **46** (1.00 g) in dry MeOH (20 ml) was added 28% MeONa soln (2.0 ml). The resultant mixt. was treated with 1,4-dibromo-2-methyl-2-butene (1.70 g) as described above to give an oil (1.85 g) which was chromatographed on silica gel using the same solvent system as described above to afford **1** (235 mg, 17.6%): $[\alpha]_D$ ±0° ($CHCl_3$; *c* 1.5) and **41** (65 mg, 4.8%): $[\alpha]_D$ ±0° ($CHCl_3$; *c* 0.8); UV λ_{max} nm (log ε): 213.5 (4.32), 275 (3.31), IR $\nu_{max}^{neat}cm^{-1}$: 3450, 1640, 1600, 1490, 1240, 1130, 1020; EIMS *m/z* (rel. int.): 280 $[M]^+$ (100), 265 (22), 225 (21), 189 (65), 175 (35), 174 (26), 161 (19), 147 (21), 105 (16), 91 (68); ^1H and ^{13}C NMR: Tables 2 and 3.

Preparation of 3,4,5-*trimethoxybibenzyl* (**59**). To a soln of benzyl magnesium bromide [prepared from $C_6H_5CH_2Br$ (6.54 g) and Mg (1.10 g)] in dry Et_2O (10 ml) was added a soln of 3,4,5-trimethoxybenzaldehyde (**57**) (5.50 g) in dry THF (10 ml) over 20 min under Ar at room temp. After stirring at 35–40° for 30 min, the reaction mixt. was poured into 1 M HCl (50 ml)-crushed ice and extracted with EtOAc. The EtOAc layer was washed with brine, dried over $MgSO_4$ and concd to give an oil (9.59 g) which was chromatographed on silica gel using 10%-EtOAc–CH_2Cl_2 to yield α-hydroxy-3,4,5-trimethoxybibenzyl (**58**) (7.97 g, 98.6%) as needles, mp 83–84.5°; UV λ_{max} nm (log ε): 215 (4.33), 267.5 (3.10); IR $\nu_{max}^{KBr}cm^{-1}$: 3500, 1595, 1510, 1465, 1420, 1320, 1230, 1125, 1005, 750; ^1H NMR: δ2.97 (2H, *d*, J=7.1 Hz), 3.80 (6H, *s*), 3.82 (3H, *s*), 4.79 (1H, *t*, J=7.1 Hz), 6.52 (2H, *s*), 7.16–7.30 (5H, *m*); ^{13}C NMR: δ45.9 (*t*), 55.9, 60.6 (each *q*), 75.2, 102.9, 126.3, 128.1, 129.3 (each *d*) 137.1, 137.9, 139.5, 152.8 (each *s*); HRMS: found: 288.1383, $C_{17}H_{20}O_4$ requires 288.1362; EIMS *m/z* (rel. int.): 280 $[M]^+$ (5), 198 (12), 197 (100), 169 (51), 154 (17), 138 (24), 91 (15); (found: C, 70.6; H, 6.92; $C_{17}H_{20}O_4$ requires: C, 70.81; H, 6.99). Compound **58** (3.261 g) in EtOAc (50 ml) and HOAc (5 ml) was hydrogenated in the presence of 20% Pd-C (0.80 g) for 48 hr at 40°. The catalyst was removed by filtration, washed with EtOAc and the solvent was evapd to afford **59** (2.661 g, 86.5%) as an oil. UV λ_{max}^{MeOH} nm (log ε): 211.5 (4.15), 270.5 (3.23); IR $\nu_{max}^{neat}cm^{-1}$: 2925, 1590, 1505, 1450, 1420, 1320, 1230, 1120, 1000; ^1H NMR: δ2.83–2.90 (4H, *m*), 3.79 (6H, *s*), 3.82 (3H, *s*), 6.35 (2H, *s*), 7.16–7.29 (5H, *m*); ^{13}C NMR: δ37.6 (*t*), 37.9 (*d*), 55.6, 60.4 (each *q*), 105.3, 125.5, 127.9, 128.2 (each *d*), 136.1, 137.0, 141.2, 152.7 (each *s*); HRMS: found: 272.1388, $C_{17}H_{20}O_3$ requires: 272.1412; EIMS *m/z* (rel. int.): 272 $[M]^+$ (69), 182 (28), 181 (100), 148 (16), 91 (61).

Synthesis of **4**. To a soln of 60% NAH (0.60 g) in dry DMF (20 ml) was added EtSH (2.2 ml) under Ar at room temp. After stirring for 10 min, a soln of **59** (5.23 g) in dry DMF (10 ml) was added dropwise over 20 min. The usual work-up gave a crude oil (6.96 g), which was chromatographed on silica gel (*n*-hexane–EtOAc gradient) to afford starting material (**59**) (551 mg, 10.5%), 3,4-dimethoxy-5-hydroxybibenzyl (**65**) (1.994 g, 40.2%) and 3,5-dimethoxy-4-hydroxybibenzyl (**66**) (2.043 g, 41.1%) as oils, respectively. Compound **65**: UV λ_{max} nm (log ε): 214.5 (4.46), 262 (3.03); IR $\nu_{max}^{neat}cm^{-1}$: 3420, 3020, 2925, 1595, 1510, 1450, 1350, 1230, 1195, 1160, 1130, 1100, 995; ^1H NMR: δ2.85 (4H, *br s*), 3.79, 3.85 (6H, *s*), 5.80 (1H, *br s*, OH), 6.23, 6.44 (each *d*, J=1.8 Hz), 7.22 (5H, *m*); ^{13}C NMR: δ37.7, 37.9 (each *t*), 55.8, 60.9 (each *q*), 104.6, 107.9, 125.9, 128.3, 128.4 (each *d*), 133.8, 138.0, 141.6, 149.1, 152.1 (*s*); EIMS *m/z* (rel. int.): 258 $[M]^+$ (31), 168 (15), 167 (100), 91 (14). Compound **66**: UV λ_{max}nm (log ε): 213 (4.13), 235 (3.77), 270 (3.02); ^1H NMR: δ2.87 (4H, *br s*), 3.82 (6H, *s*), 6.34 (2H, *s*), 7.10–7.30 (5H, *m*); ^{13}C NMR: δ37.6, 37.8 (each *t*), 55.8 (*s*), 105.0, 125.4, 127.8, 128.2 (each *d*), 132.3, 132.8, 141.2, 146.6 (each *s*); EIMS *m/z* (rel. int.): 258 $[M]^+$ (20), 168 (12), 167 (100), 91 (11). To a soln of **65** (646 mg) in dry MeOH (10 ml) was added 28% MeONa–MeOH soln (0.4 ml) at room temp. under

Ar. The reaction mixt. was treated with 1,4-dibromo-2-methyl-2-butene (560 mg) as described in the preparation of **1**, **2**, **41** and **42** (Scheme 2) to give an oil (1.705 g) which was chromatographed on silica gel (*n*-hexane–EtOAc gradient) to afford **4** (193 mg, 23.8%) as an oil, $[\alpha]_D \pm 0°$ ($CHCl_3$; *c* 2.1), whose spectral data were identical to those of the dimethyl ether of perrottetin D (**3**).

Synthesis of **9**. To a soln of **65** (1.00 g) in dry MeOH (15 ml) was added 28% MeONa–MeOH soln (1.0 ml) at room temp. under Ar. After stirring for 30 min, the reaction mixt. was evapd to dryness to give yellow crystals which were suspended in dry C_6H_6 (20 ml). The soln was evapd again to remove all traces of H_2O. The residue was again suspended in dry C_6H_6 (20 ml), to which was added dropwise 2,2-dimethylallylbromide (0.87 g). The reaction mixt. was stirred for 30 min at 50–55° under Ar, poured into ice-H_2O, and extracted with Et_2O. The Et_2O layer was washed with 1 M HCl and H_2O, dried over $MgSO_4$, and concd to give an oil (1.75 g), which was chromatographed on silica gel (*n*-hexane–EtOAc gradient) to give the starting material **65** (395 mg, 39.5%), **67** (125 mg, 8.9%) and **68** (320 mg, 23.1%), as oils, respectively. Compound **67**: UV λ_{max}nm (log ε): 216 (4.42), 272.5 (3.12); IR ν_{max}^{neat} cm^{-1}: 3500, 3025, 2920, 1605, 1590, 1500, 1450, 1420, 1340, 1240, 1120, 1060, 1030; ^{1}H NMR: δ1.68, 1.76 (each 3H, *s*), 2.84 (4H, *br s*), 3.33 (2H, *d*, *J* = 6.6 Hz), 3.77 (3H, *s*), 3.87 (3H, *s*), 5.14 (1H, *t*, *J* = 6.6 Hz), 5.89 (1H, *br s*, OH), 6.22 (1H, *s*), 7.17–7.30 (5H, *m*); ^{13}C NMR: δ17.9, 25.6 (each *q*), 24.9, 35.1, 37.7 (each *t*), 55.7, 60.8 (each *q*), 104.9 (*d*), 119.0 (*s*), 123.5, 125.8, 128.3, 128.4 (each *d*), 130.9, 133.8, 135.6, 141.9, 147.3, 149.8 (each *s*); EIMS *m/z* (rel. int.): 326 $[M]^+$ (47), 271 (11), 236 (15), 235 (100), 193 (15), 178 (22), 91 (73). Compound **68**: UV λ_{max}nm (log ε): 213.5 (4.53), 267.5 (3.01); IR ν_{max}^{neat} cm^{-1}: 3025, 2925, 1590, 1500, 1450, 1420, 1230, 1110, 1010; ^{1}H NMR: δ1.72, 1.76 (each 3H, *s*), 2.87 (4H, *br s*), 3.81, 3.82 (each 3H, *s*), 4.50 (2H, *d*, *J* = 6.6 Hz), 5.49 (1H, *t*, *J* = 6.6 Hz), 6.36 (2H, *s*), 7.20–7.28 (5H, *m*); ^{13}C NMR: δ17.8, 25.4 (each *q*), 37.6, 37.8 (each *t*), 55.7, 60.4 (each *q*), 65.7 (*t*), 105.5, 107.4, 120.0, 125.6, 128.0, 128.2 (each *d*), 136.8, 141.3, 152.0, 152.8 (each *s*); EIMS *m/z* (rel. int.): 326 $[M]^+$ (6), 259 (12), 258 (66), 168 (23), 167 (100), 91 (49), 69 (36). To a soln of **67** (90 mg) in dry C_6H_6 (20 ml) was added 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) (110 mg). The reaction mixt. was refluxed for 30 min, and filtered. The filtrate was evapd to afford an oil (138 mg) which was purified by prep. TLC (*n*-hexane–EtOAc, 4:1) to yield a chromene (79 mg, 88.4%) as an oil, whose spectral data were identical to those of the dimethyl ether (**9**) of the natural chromene (**8**).

Synthesis of **25**. To a soln of **59** (1.90 g) in dry DMF (20 ml) was added *N*-bromosuccinimide (1.36 g). After stirring for 1 hr, the reaction mixt. was poured into H_2O and extracted with Et_2O. The Et_2O layer was washed with brine, dried over $MgSO_4$ and concd to give an oil (2.15 g), which was chromatographed on silica gel (10% EtOAc–*n*-hexane) to yield 2-bromo-3,4,5-trimethoxybibenzyl (**60**) (2.057 g, 83.7%) and 2,6-dibromo-3,4,5-trimethoxybibenzyl (**61**) (420 mg, 13.9%) as needles. Compound **60**: mp 28.0–30.0° (from *n*-hexane–Et_2O); UV λ_{max} nm (log ε): 217.5 (4.51), 267.5 (3.17); IR ν_{max}^{KBr} cm^{-1}: 2950, 1605, 1570, 1485, 1390, 1330, 1235, 1195, 1160, 1100, 1040, 1005, 920, 795, 695; ^{1}H NMR: δ2.86, 2.97 (each 2H, *m*), 3.72, 3.84, 3.87 (each 3H, *s*), 6.43 (1H, *s*), 7.17–7.28 (5H, *m*); ^{13}C NMR: δ36.1, 38.3 (each *t*), 56.0, 60.7, 60.9 (each *q*), 109.4 (*d*), 110.4 (*s*), 125.9, 128.2, 128.4, 141.2, 141.4, 150.8, 152.3 (each *s*); EIMS *m/z* (rel. int.): 350 $[M+2]^+$ (28), 320 $[M]^+$ (22), 261 (80), 259 (100), 91 (13). (Found: C, 57.87; H, 5.39; $C_{17}H_{19}O_3Br$: C, 58.13; H, 5.45). Compound **61**: mp 80.0–81.5° (from *n*-hexane–Et_2O); UV λ_{max}nm (log ε): 216 (4.41), 282.5 (3.22); IR ν_{max}^{KBr} cm^{-1}: 2925, 1595, 1465, 1405, 1385, 1320, 1135, 1045, 995, 950, 740, 730, 690; ^{1}H NMR: δ2.82, 3.28 (each 2H, *m*), 3.91 (6H, *s*), 3.93 (3H, *s*), 7.22–7.34 (5H, *m*); ^{13}C NMR: δ34.3, 39.6 (each *t*), 60.9, 61.2 (each *q*), 115.0 (*s*), 126.1, 128.4, 136.2, 141.4, 145.9, 150.7 (each *s*); EIMS *m/z* (rel. int.): 432 $[M+4]^+$ (12), 341 (44), 339 (100), 337 (44), 91 (13); (found: C, 47.27; H, 4.19, $C_{17}H_{18}O_3Br_2$ requires: C, 47.47; H, 4.22). To compound **60** (1.20 g) in dry Et_2O (20 ml) was added 1.6 M *n*-BuLi soln (2.6 ml) at room temp. After stirring for 1 hr, 2,2-dimethylallyl bromide (609 mg) was added dropwise over 10 min to the stirred soln. The mixt. was treated in the same manner as described in the preparation of **17** (Scheme 1) to afford 3,4,5-trimethoxybibenzyl (**59**) (186 mg, 20.1%) and 2-prenyl bibenzyl (858 mg, 74.5%) as an oil, whose spectral data were identical to those of the trimethyl ether (**25**) of perrottetin A (**24**).

Reaction of **25** *with* BBr_3. To a soln of **25** (250 mg) in dry CH_2Cl_2 (5 ml) was added BBr_3 (0.3 ml) at −60°. The mixt. was treated in the same manner as described in the preparation of **45** from **18** (Scheme 1) to give a chroman (**64**) (176 mg) as needles, mp 124–125.5° (from *n*-hexane); UV λ_{max}nm (log ε): 216 (4.30), 272.5 (3.05); IR ν_{max}^{KBr} cm^{-1}: 3550, 3350, 1615, 1500, 1460, 1160, 1120, 1080, 1020, 960; ^{1}H NMR: δ1.29 (6H, *s*), 1.73, 2.48 (each 2H, *t*, *J* = 6.8 Hz), 2.72, 2.81 (each 2H, *m*), 5.52 (2H, *br s*, 2 × OH), 6.43 (1H, *s*), 7.13–7.27 (5H, *m*); ^{13}C NMR: δ19.2 (*t*), 26.6 (*q*), 32.9, 34.1, 37.0 (each *t*), 74.7 (*s*), 107.6 (*d*), 111.3 (*s*), 125.8, 128.2, 128.4 (each *d*), 130.1, 131.0, 141.1, 141.6, 141.9 (each *s*); EIMS *m/z* (rel. int.); 298 $[M]^+$ (52), 243 (14), 209 (14), 207 (100), 165 (19), 151 (15), 91 (38).

Reaction of **25** *with EtSNa in DMF*. To a suspension of 60% NaH (1.18 g) in dry DMF (8 ml) was added a soln of EtSH (2.20 ml) in dry DMF (3 ml) for 10 min under Ar at room temp. with stirring. After stirring for 20 min, a soln of **25** (1.00 g) in dry DMF (3 ml) was added, and the mixt. stirred for 30 min at 150–160°. The reaction mixt. was treated in the same manner as described in the preparation of **17** from **18** (Scheme 1) to give 3,4-dihydroxy-5-methoxy-2-(3-methyl-2-butenyl)bibenzyl (**62**) (465 mg, 50.7%) and 4,5-dihydroxy-3-methoxy-2-(3-methyl-2-butenyl)bibenzyl (**63**) (351 mg, 38.2%), as needles, respectively. Compound **62**: mp 82–83° (from *n*-hexane–Et_2O); UV λ_{max}nm (log ε): 215 (4.61), 267 (3.18), 282 (3.00); IR ν_{max}^{KBr} cm^{-1}: 3400, 2925, 1620, 1590, 1500, 1450, 1300, 1220, 1100, 1090, 1040; ^{1}H NMR: δ1.68, 1.77 (each, 3H, *s*), 2.83 (4H, *br s*), 3.34 (2H, *d*, *J* = 6.6 Hz), 3.76 (3H, *s*), 5.14 (1H, *d*, *J* = 6.6 Hz), 5.44, 5.53 (each 1H, *br s*, OH), 6.22 (1H, *s*), 7.16–7.27 (5H, *m*); HRMS: found: 312.1719, $C_{20}H_{24}O_3$ requires 312. 1725; EIMS *m/z* (rel. int.): 312 $[M]^+$ (54), 257 (14), 221 (100), 189 (14), 179 (20), 165 (15), 164 (18), 147 (21), 91 (32). Compound **63**: 74.0–74.5° (from *n*-hexane–Et_2O); UV λ_{max}nm (log ε): 214 (4.40), 282.5 (3.42); IR ν_{max}^{KBr} cm^{-1}: 3400, 3320, 3000, 1600, 1500, 1430, 1370, 1290, 1180, 1050; ^{1}H NMR: δ1.67, 1.73 (each 3H, *s*), 2.78 (4H, *m*), 3.25 (2H, *d*, *J* = 6.6 Hz), 3.77 (3H, *s*), 5.05 (1H, *t*, *J* = 6.6 Hz), 5.30, 5.49 (each 1H, *br s*, OH), 6.60 (1H, *s*), 7.16–7.30 (5H, *m*); HRMS: found: 312.1723, $C_{20}H_{24}O_3$ requires 312.1725; EIMS *m/z* (rel. int.): 312 $[M]^+$ (56), 256 (19), 221 (100), 189 (14), 179 (30), 164 (26), 147 (23), 91 (42).

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