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PRENYL BIBENZYLS FROM THE LIVERWORT *RADULA KOJANA**

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Key Word Index—*Radula kojana*; Radulaceae; Jungermanniales; Hepaticae; prenyl bibenzyls; chromenes; benzofuran; bis(bibenzyls); 5-lipoxygenase and calmodulin inhibitory activity; synthesis; chemosystematics.

Abstract—Fourteen new bibenzyl derivatives have been isolated from the liverwort *Radula kojana* together with two previously known bis(bibenzyls) and their structures characterized by spectral and chemical evidence. Seven new bibenzyls, 3,5-dihydroxy-2-(3-methyl-2-butenyl)-, 3-methoxy-5-hydroxy-2-(3-methyl-2-butenyl)-, 3-hydroxy-5-methoxy-2-(3-methyl-2-butenyl)- and 2-geranyl-3,5-dihydroxybibenzyls, 2,2-dimethyl-7-methoxy-5-(2-phenylethyl)-, 2,2-dimethyl-5-methoxy-7-(2-phenylethyl)- and 2-methyl-2-(4-methyl-3-pentenyl)-7-methoxy-5-(2-phenylethyl) chromenes have been synthesized from pinosylvin and its dimethyl ether. 3,5-Dihydroxy-2-(3-methyl-2-butenyl)- and 2-geranyl-3,5-dihydroxybibenzyls showed 5-lipoxygenase and calmodulin inhibitory activity. *Radula kojana* belonging to the subgenus *Odontoradula* is chemically different from species of the subgenera *Radula* and *Cladoradula* as it produces chromene derivatives (six-membered) and the latter two genera elaborate dihydrooxepins (seven-membered) and benzofurans with a propenyl group (five-membered). Our chemical results support the modern classification of *Radula* species.

INTRODUCTION

Radula species of liverwort are rich sources of prenyl bibenzyls [1–6]. As part of a chemosystematic study [7, 8] and search for biologically active substances [9–12], we have investigated the chemical constituents of *R. kojana* and isolated 14 new bibenzyl derivatives along with the previously known two bis(bibenzyls) [6, 7]. In this paper, we wish to report the isolation, characterization and synthesis of new bibenzyls and their biological activity, and to discuss the chemosystematics of *R. kojana*.

RESULTS AND DISCUSSION

A combination of column chromatography on silica gel and Sephadex LH-20, and preparative TLC of the methanol extract of *R. kojana* resulted in the isolation of 14 bibenzyls, viz. 3,5-dihydroxy-2-(3-methyl-2-butenyl)- (**1**), 3-methoxy-5-hydroxy-2-(3-methyl-2-butenyl)- (**2**), 3-hydroxy-5-methoxy-2-(3-methyl-2-butenyl)- (**3**), 2-geranyl-3,5-dihydroxy- (**5**), 3-methoxy-4′-hydroxy-4-(3-methyl-2-butenyl)- (**8**), 3,5-dihydroxy-2-(2,3-epoxy-3-methylbutyl)- (**9**) and 3-hydroxy-5-methoxy-2-(3-hydroxy- 3-methylbutyl) bibenzyls (**10**), 2,2-dimethyl-7-hydroxy- 5-(2-phenylethyl) chromene (**12**) and its methyl ether (**13**), 2,2-dimethyl-5-hydroxy-7-(2-phenylethyl)- (**14**), 2,2-dimethyl-5-hydroxy-6-carboxy-7-(2-phenylethyl)- (**16**), 2(*S*)-2-methyl-2-(4-methyl-3-pentenyl)-7-hydroxy-5-(2-phenylethyl)- (**18**) and 2(*S*)-2-methyl-2-(4-methyl-3-pentenyl)-6-carboxy-7-hydroxy-5-(2-phenylethyl) chromenes (**20**) and 6-hydroxy-4-(2-phenylethyl) benzofuran (**22**) together with two previously known bis(bibenzyls), perrottetins E (**24**) and F (**25**) [6, 7]. The crude extract was also directly analysed by GC-MS to detect the presence of *trans*-β-farnesene, 2-hydroxycuparene, campesterol, stigmasterol and sitosterol.

The molecular formula, $C_{19}H_{22}O_2$ ($[M]^+$ *m/z* 282.1637) of **1** was determined by high resolution mass spectrometry. The UV and IR spectra indicated the presence of a hydroxyl group (3600 cm^{-1}) and an aromatic ring (λ 230, 285 nm; 1620, 1590 cm^{-1}). Methylation of **1** with methyl iodide gave a dimethyl ether (**4**) ($C_{21}H_{26}O_2$ $[M]^+$ *m/z* 310.1913; δ 3.75, 3.79 each 3H, *s*), indicating the presence of two phenolic hydroxyl groups in **1**. The presence of a non-substituted benzyl group was confirmed by the intense fragment ion at *m/z* 91 (84%) and the ^1H NMR signals at δ 7.18 (3H, *m*) and 7.28 (2H, *m*). The ^1H NMR spectrum (Table 1) of **1** contained the signals of a 2,2-dimethylallyl group (δ 1.72, 1.79 each 3H, *s*, 3.28, 2H, *d*, $J = 6.4$, 5.09, 1H, *t*, $J = 6.4$ Hz) and two *meta*-coupled protons (δ 6.23, 6.26, each 1H, *d*, $J = 2.4$ Hz) and two benzylic methylenes (δ 2.83, 4H, *s*). The above data indicated that **1** was a bibenzyl with two phenolic hydroxyls and one 2,2-dimethylallyl group. The substitution pattern of the benzene rings and the position of each functional group were confirmed by difference NOE experiments on **1** and **4**. NOEs were observed between (i) benzylic methylene protons (H-α) and H-6, (ii) H-α and H-1′ in **1** and between (i) H-α and H-6, (ii) H-α and H-1′, (iii) H-4 and OMe-5, (iv) H-6 and OMe-5 and (v) H-4 and OMe-3 in **4**. Thus, the structure of **1** was shown to be 3,5-dihydroxy-2-(3-methyl-2-butenyl)bibenzyl. The ^{13}C NMR spectra of **1** and **4** supported this structure. All the carbon signals of **1** and **4** (Table 2) were assigned by the long range ^1H–^{13}C 2D COSY NMR spectra and it

*Part 39 in the series 'Chemosystematics of Bryophytes'. For Part 38, see ref. [25].

Table 1. ^{1}H NMR (400 MHz) spectral data for compounds **1–10** and **12–23** ($CDCl_3$–TMS)

H	1	2	3	4	5	6	7	8	9	10	12
2	—	—	—	—	—	—	—	6.63 *d* (1.3)	—	—	—
3	—	—	—	—	—	—	—	—	—	—	5.50 *d* (10.0)
4	6.23 *d* (2.4)*	6.30 *d* (2.3)	6.31 *d* (2.6)	6.35 *d* (2.4)	6.23 *d* (2.5)	6.35 *d* (2.7)	6.34 *d* (2.7)	—	6.21 *d* (2.4)	6.343 *d* (0.7)	6.44 *d* (10.0)
5	—	—	—	—	—	—	—	7.03 *d* (8.6)	—	—	—
6	6.26 *d* (2.4)	6.26 *d* (2.3)	6.34 *d* (2.6)	6.31 *d* (2.4)	6.28 *d* (2.5)	6.31 *d* (2.7)	6.30 *d* (2.7)	6.71 *dd* (8.6, 1.3)	6.33 *d* (2.4)	6.341 *d* (0.7)	6.18 *s*
7	—	—	—	—	—	—	—	—	—	—	—
8	—	—	—	—	—	—	—	—	—	—	6.19 *s*
1′	3.28 *d* (6.4)	3.29 *d* (6.4)	3.30 *d* (7.8)	3.32 *d* (6.6)	3.27 *d* (6.4)	3.32 *d* (6.3)	3.31 *d* (6.6)	3.28 *d* (7.2)	2.48 *dd* (16.5, 5.4) 2.72 *dd* (16.5, 5.4)	2.67 *t* (7.4)	1.40 *s*
2′	5.09 *t* (6.4)	5.05 *t* (6.4)	5.11 *t* (7.8)	5.08 *t* (6.6)	5.08 *t* (6.4)	5.07 *t* (6.3)	5.11 *t* (6.6)	5.29 *t* (7.2)	3.72 *t* (5.4)	1.67 *t* (7.4)	1.40 *s*
3′	—	—	—	—	—	—	—	—	—	—	—
4′	1.72 *s*	1.66 *s*	1.73 *s*	1.66 *s*	2.02 *m*	2.00 *m*	2.04 *m*	1.70 *s*	1.24 *s*[a]	1.28 *s*	—
5′	1.79 *s*	1.74 *s*	1.80 *s*	1.75 *s*	2.02 *m*	2.00 *m*	2.04 *m*	1.73 *s*	1.29 *s*[a]	1.28 *s*	—
6′	—	—	—	—	5.03 *t* (6.4)	5.05 *t* (6.3)	5.04 *t* (6.6)	—	—	—	—
7′	—	—	—	—	—	—	—	—	—	—	—
8′	—	—	—	—	1.55 *s*	1.55 *s*	1.57 *s*	—	—	—	—
9′	—	—	—	—	1.63 *s*	1.62 *s*	1.65 *s*	—	—	—	—
10′	—	—	—	—	1.74 *s*	1.74 *s*	1.78 *s*	—	—	—	—
α	2.83 *s*	2.83 *s*	2.85 *m*	2.86 *s*	2.77 *br s*	2.86 *s*	2.85 *m*	2.84 *s*	2.76 *m*	2.86 *s*	2.80 *br s*
β	2.83 *s*	2.86 *s*	2.85 *m*	2.86 *s*	2.77 *br s*	2.88 *s*	2.85 *m*	2.84 *s*	2.83 *m*	2.86 *s*	2.80 *br s*
2″6″	7.17 *m*	7.19 *m*	7.18 *m*	7.20 *m*	7.13 *m*	7.20 *m*	7.17 *m*	7.07 *d* (8.4)	7.14 *m*	7.20 *m*	7.17 *m*
3″5″	7.28 *m*	7.29 *m*	7.29 *m*	7.29 *m*	7.24 *m*	7.29 *m*	7.30 *m*	6.75 *d* (8.4)	7.26 *m*	7.29 *m*	7.28 *m*
4″	7.19 *m*	7.20 *m*	7.22 *m*	7.21 *m*	7.15 *m*	7.19 *m*	7.17 *m*		7.18 *m*	7.20 *m*	7.18 *m*
OH	4.80 *br s* 5.25 *br s*	4.69 *br s*	5.19 *s*	—	5.71 *br s* 6.12 *br s*	—	5.35 *s*	4.68 *br s*	5.20 *br s*	—	4.83 *br s*
3-OMe	—	3.78 *s*	—	3.79 *s*	—	3.79 *s*	—	3.79 *s*	—	—	—
5-OMe	—	—	3.73 *s*	3.75 *s*	—	3.75 *s*	3.71 *s*	—	3.73 *s*	3.73 *s*	—
6-OMe	—	—	—	—	—	—	—	—	—	—	—
7-OMe	—	—	—	—	—	—	—	—	—	—	—
CO_2Me	—	—	—	—	—	—	—	—	—	—	—

*Coupling constants (J in Hz) are given in parentheses.
[a]Assignments may be interchangeable in each vertical column.

Table 1. *Continued*

H	13	14	15	16	17	18	19	20	21	22	23
2	—	—	—	—	—	—	—	—	—	7.47 *d* (2.2)	7.51 *d* (2.2)
3	5.50 *d* (10.0)	5.55 *d* (10.0)	5.51 *d* (10.0)	5.52 *d* (10.0)	5.63 *d* (10.0)	5.46 *d* (10.0)	5.46 *d* (10.0)	5.51 *d* (10.0)	5.52 *d* (10.0)	6.65 *dd* (2.2, 1.0)	6.67 *dd* (2.2, 1.0)
4	6.45 *d* (10.0)	6.59 *d* (10.0)	6.62 *d* (10.0)	6.68 *d* (10.0)	6.54 *d* (10.0)	6.47 *d* (10.0)	6.48 *d* (10.0)	6.52 *d* (10.0)	6.49 *d* (10.0)	—	—
5	—	—	—	—	—	—	—	—	—	6.62 *d* (2.2)	6.70 *d* (2.2)
6	6.26 *s*	6.11 *s*	6.18 *d* (1.0)	—	—	6.16 *d* (2.4)	6.24 *d* (2.4)	—	—	—	—
7	—	—	—	—	—	—	—	—	—	6.83 *dd* (2.2, 1.0)	6.90 *br d* (2.2)
8	6.27 *s*	6.30 *s*	6.33 *d* (1.0)	6.22 *s*	6.47 *s*	6.18 *d* (2.4)	6.26 *d* (2.4)	6.30 *br d*	6.31 *s*	—	—
1′	1.41 *s*	1.42 *s*	1.41 *s*	1.43 *s*	1.43 *s*	1.66 *m*	1.67 *m*	1.66 *m*	1.67 *m*	—	—
2′	1.41 *s*	1.42 *s*	1.41 *s*	1.43 *s*	1.43 *s*	2.08 *m*	2.09 *m*	2.05 *m*	2.09 *m*	—	—
3′	—	—	—	—	—	5.10 *t* (7.0)	5.10 *t* (7.0)	5.07 *t* (7.0)	5.10 *t* (7.0)	—	—
4′	—	—	—	—	—	—	—	—	—	—	—
5′	—	—	—	—	—	1.58 *s*	1.58 *s*	1.57 *s*	1.58 *s*	—	—
6′	—	—	—	—	—	1.66 *s*	1.66 *s*	1.65 *s*	1.67 *s*	—	—
7′	—	—	—	—	—	1.36 *s*	1.37 *s*	1.33 *s*	1.38 *s*	—	—
8′	—	—	—	—	—	—	—	—	—	—	—
9′	—	—	—	—	—	—	—	—	—	—	—
10′	—	—	—	—	—	—	—	—	—	—	—
α	2.86 *br s*	2.77 *m*	2.81 *m*	3.18 *m*	2.83 *m*	2.83 *s*	2.85 *br s*	3.27 *m*	2.81 *s*	3.05 *s*	3.09 *m*
β	2.86 *br s*	2.86 *m*	2.87 *m*	2.85 *m*	2.83 *m*	2.83 *s*	2.85 *br s*	2.77 *m*	2.81 *s*	3.05 *s*	2.99 *m*
2″6″	7.18 *m*	7.17 *m*	7.18 *m*	7.17 *m*	7.18 *m*	7.17 *m*	7.18 *m*	7.13	7.20 *m*	7.20 *m*	7.20 *m*
3″5″	7.28 *m*	7.28 *m*	7.28 *m*	7.25 *m*	7.28 *m*	7.28 *m*	7.28 *m*	∼	7.29 *m*	7.28 *m*	7.29 *m*
4″	7.18 *m*	7.18 *m*	7.19 *m*	7.17 *m*	7.19 *m*	7.19 *m*	7.19 *m*	7.29 *m*	7.20 *m*	7.20 *m*	7.20 *m*
OH	—	4.82 *br s*	—	—	—	4.89 *br s*	—	—	—	7.10 *br s*	—
3-OMe	—	—	—	—	—	—	—	—	—	—	—
5-OMe	—	—	3.76 *s*	—	3.80 *s*	—	—	—	—	—	—
6-OMe	—	—	—	—	—	—	—	—	—	—	3.83 *s*
7-OMe	3.73 *s*	—	—	—	—	—	3.73 *s*	—	3.79 *s*	—	—
CO_2Me	—	—	—	—	3.90 *s*	—	—	—	3.89 *s*	—	—

Table 2. ^{13}C NMR (100 MHz) spectral data for **1–7**, **9**, **10** and **12–23** ($CDCl_3$–TMS)*

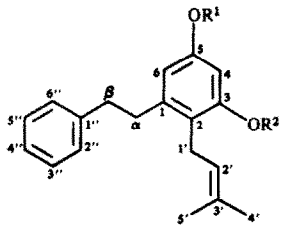
C	1	2	3	4	5	6	7	9	10	12	13	14	15	16	17	18	19	20	21	22	23
1	142.1	142.0	141.8	142.0	142.0	142.0	144.7	142.4	141.9	—	—	—	—	—	—	—	—	—	—	—	—
2	117.6	120.7	117.4	120.7	117.6	120.9	117.6	109.3	119.7	75.6	75.6	75.9	75.9	77.5	76.4	78.0	77.9	78.7	78.5	143.1	143.5
3	155.7	158.7	155.7	158.4	155.9	158.5[a]	155.7	155.4	155.3	127.9	127.9	128.5	128.1	127.6	130.1	127.0	126.9	127.8	127.7	111.5	111.5
4	101.4	97.0	99.9	96.4	101.5	96.5	100.0	102.0	100.1	118.7	118.9	116.3	116.8	116.2	116.6	119.2	119.2	119.2	118.8	135.2	135.3
5	154.4	154.3	158.6	158.4	154.4	158.4[a]	158.5	153.7	158.5	139.1	138.8	151.1	155.1	158.3	154.0	139.0	138.7	140.8	136.1	104.7	104.8
6	108.9	107.9	107.8	105.6	108.9	105.8	107.7	109.0	107.2	108.7	107.9	107.9	103.5	103.8	112.8	108.5	107.7	109.7	112.3	154.6	158.0
7	—	—	—	—	—	—	—	—	—	155.9	160.0	143.5	143.4	147.8	141.4	154.9	160.0	153.7	157.3	95.8	93.6
8	—	—	—	—	—	—	—	—	—	102.0	100.1	109.3	109.4	111.8	113.2	101.9	100.0	103.3	98.4	155.8	155.8
9	—	—	—	—	—	—	—	—	—	154.6	154.5	153.9	153.6	160.5	155.0	155.9	154.8	159.5	155.8	119.4	120.1
10	—	—	—	—	—	—	—	—	—	112.9	112.8	107.4	108.5	107.6	120.2	112.8	112.6	113.3	116.5	—	—
1′	24.9	24.4	24.9	24.4	24.8	24.4	24.9	28.4	19.4	27.7	27.7	27.8	27.8	28.3	27.9	41.0	41.0	41.4	40.1	—	—
2′	122.6	123.8	122.6	123.8	123.8	124.4	122.6	69.9	42.9	27.7	27.7	27.8	27.8	28.3	27.9	22.7	22.7	22.7	22.7	—	—
3′	134.2	130.7	134.3	130.5	138.1	134.2	137.7	76.3	71.9	—	—	—	—	—	—	124.2	124.2	123.9	124.0	—	—
4′	25.7	25.7	25.7	25.7	39.6	39.7	39.6	24.6	29.5	—	—	—	—	—	—	131.7	131.6	131.8	131.8	—	—
5′	18.0	17.9	18.0	17.9	26.4	26.7	26.4	21.9	29.5	—	—	—	—	—	—	25.7	25.7	25.6	25.7	—	—
6′	—	—	—	—	122.5	123.9	123.8	—	—	—	—	—	—	—	—	17.7	17.6	17.6	17.6	—	—
7′	—	—	—	—	132.0	131.2	131.9	—	—	—	—	—	—	—	—	26.2	26.2	26.7	26.3	—	—
8′	—	—	—	—	25.7	25.7	25.6	—	—	—	—	—	—	—	—	—	—	—	—	—	—
9′	—	—	—	—	17.7	17.7	17.7	—	—	—	—	—	—	—	—	—	—	—	—	—	—
10′	—	—	—	—	16.2	16.3	16.2	—	—	—	—	—	—	—	—	—	—	—	—	—	—
α	35.7	35.2	35.9	35.5	35.7	35.6	35.9	34.5	35.5	34.4	34.6	37.4	37.6	38.0	36.1	34.4	34.6	31.8	32.2	35.2	35.4
β	37.5	37.5	37.7	37.6	37.5	37.6	37.6	36.6	37.8	37.4	37.5	37.9	38.5	38.9	37.6	37.4	37.5	37.1	37.4	36.7	36.8
1″	141.7	142.0	141.8	141.6	141.7	141.8	141.7	141.7	141.4	141.6	141.6	141.7	141.8	142.0	141.6	141.6	141.7	142.0	141.6	141.7	141.7
2″6″	128.4	128.4	128.4	128.3	128.4	128.4	128.4	128.4	128.4	128.4	128.4	128.3	128.3	128.4	128.4	128.4	128.4	128.3	128.3	128.3	128.4
3″5″	128.4	128.4	128.4	128.3	128.4	128.4	128.4	128.5	128.5	128.4	128.4	128.4	128.5	128.4	128.4	128.4	128.4	128.4	128.5	128.3	128.4
4″	126.0	125.9	126.0	125.9	126.0	125.9	126.0	126.0	126.0	126.0	126.0	125.9	126.0	125.9	126.0	126.0	126.0	125.9	126.1	125.5	126.0
3-OMe	—	55.6	—	55.4	—	55.7	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
5-OMe	—	—	55.2	55.1	—	55.3	55.1	—	55.2	—	—	—	55.6	—	52.1	—	—	—	—	—	—
6-OMe	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	55.7
7-OMe	—	—	—	—	—	—	—	—	—	—	55.2	—	—	—	—	—	55.2	—	52.2	—	—
CO_2Me	—	—	—	—	—	—	—	—	—	—	—	—	—	—	63.1	—	—	—	55.9	—	—
CO	—	—	—	—	—	—	—	—	—	—	—	—	—	175.5	168.5	—	—	163.1	169.0	—	—

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

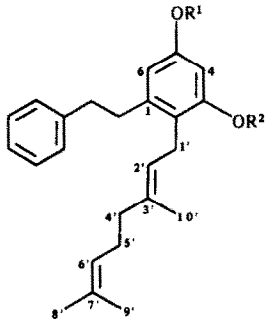
[a]Assignments may be interchangeable in each vertical column.

was confirmed that C-4 of **1** and **4** appeared at very high fields (δ 96.4 in **1** and 101.4 in **4**), which was useful for the structural determination of the other bibenzyl analogues (**2**, **3**, **5**, **9**, **10**, **18**, **20** and **22**). Conclusive evidence that the structure of **1** was correct was obtained by its synthesis (see later).

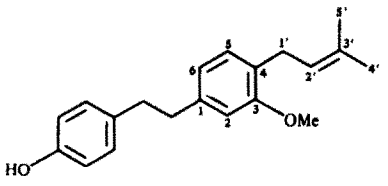
A high resolution mass spectrum established the molecular formula, $C_{20}H_{24}O_2$, for **2**. Its ^1H NMR spectral data (Table 1) were quite similar to those of **1**, except for the presence of one methoxyl group (δ 3.78, 3H, *s*) in place of a hydroxyl group in **1**, suggesting that one of the two phenolic hydroxyl groups is methylated in **2**. The



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



5 $R^1 = R^2 = H$
6 $R^1 = R^2 = Me$
7 $R^1 = Me$, $R^2 = H$



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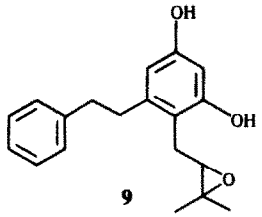

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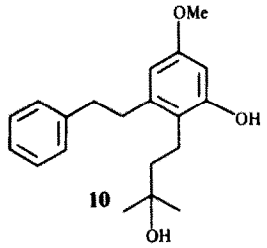

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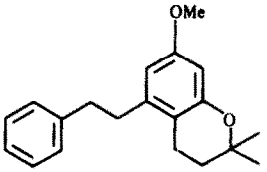

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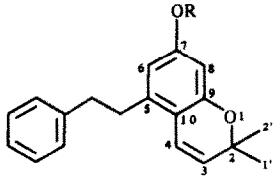
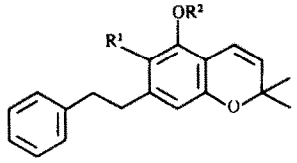
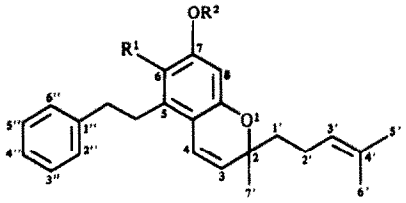


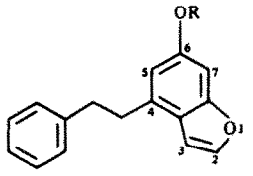
12 R = H
13 R = Me



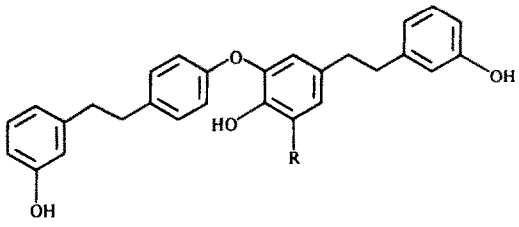
14 $R^1 = R^2 = H$
15 $R^1 = H$, $R^2 = Me$
16 $R^1 = CO_2H$, $R^2 = H$
17 $R^1 = CO_2Me$, $R^2 = Me$



18 $R^1 = R^2 = H$
19 $R^1 = H$, $R^2 = Me$
20 $R^1 = CO_2H$, $R^2 = H$
21 $R^1 = CO_2Me$ $R^2 = Me$



22 R = H
23 R = Me



24 R = H
25 R = OH

position of the methoxyl group at C-3 was established by the difference NOE examination of **2** and thereby the NOEs were observed between (i) H-α and H-6, (ii) H-α and H-1′, (iii) H-α and H-2′ and (iv) H-4 and OMe-3. Thus, the structure of **2** was determined to be 3-methoxy-5-hydroxy-2-(3-methyl-2-butenyl)bibenzyl. The structure (**2**) was conclusively confirmed by synthesis (see later).

Compound **3** possessed the same molecular formula $C_{20}H_{24}O_2$ as that of **2**, and its ^1H and ^{13}C NMR spectral patterns were almost identical to those of **2** with the difference of their chemical shifts, showing that **3** was 3-hydroxy-5-methoxy-2-(3-methyl-2-butenyl) bibenzyl. This assumption was confirmed by difference NOE experiments. NOEs were observed between (i) H-4 and OMe-5, (ii) H-6 and OMe-5, (iii) H-α and H-6 and (iv) H-α and H-2′. Furthermore, this structure was supported by the ^{13}C NMR (Table 2) and its synthesis (see later).

Compound **5**, $C_{24}H_{30}O_2$ ([M]$^+$ 350.2229) had a hydroxyl group (3600 cm^{-1}) and an aromatic ring (λ 232, 265 nm; 1620, 1598 cm^{-1}). Treatment of **5** with methyl iodide gave a dimethyl ether (**6**), $C_{26}H_{34}O_2$ ([M]$^+$ m/z 378.2554; δ 3.75, 3.79 each 3H, *s*), indicating the presence of two phenolic hydroxyl groups in **5**. The ^1H and ^{13}C NMR spectral data (Tables 1 and 2) of **5** and **6** resembled those of **1** and **4**, except for the presence of three vinylic methyls, two additional allylic methylenes and one proton on a trisubstituted double bond, suggesting that **5** might be 2-geranyl-3,5-dihydroxybibenzyl. This assumption was further confirmed by a NOE experiment on **5** and **6**. NOEs were observed between (i) H-α and H-6 and (ii) H-α and H-2′ in **5** and between (i)H-6 and OMe-5, (ii) H-4 and OMe-5 and (iii) H-4 and OMe-3 in **6**. Recently, Crombie *et al.* [13] predicted the presence of 2- and 4-geranyl-3,5-dihydroxybibenzyls (= *o*- and *p*-cannabigerols) (**5** and **43**) in plants and synthesized them by geranylation of 3,5-dihydroxybibenzyl (**41**) with geraniol in the presence of *p*-toluene sulphonic acid and at the same time, pointed out that our previously reported 3,5-dihydroxy-4-geranylbibenzyl (**43**) isolated from *R. complanata* [7], *R. javanica* (= *R. variabilis*) [2] and *R. tokiensis* [4] should be revised to 2-geranyl-3,5-dihydroxybibenzyl (**5**). We also synthesized **5** and 3,5-dimethoxy-4-geranylbibenzyl (**44**) using a different prenylation method (see later) and carefully compared their spectral data with those of natural products and their methyl ethers. In fact, the natural geranyl bibenzyl isolated from the present and previously reported species was identical to 2-geranyl-3,5-dihydroxybibenzyl (**5**). More recently, we found that some *Radula* species collected in Ecuador produced both 2- and 4-geranylbibenzyls (**5** and **43**) [Asakawa, Y. and Kondo, K., unpublished results].

A minor compound **8**, $C_{20}H_{24}O_2$ ([M]$^+$ *m/z* 296) showed the presence of one methoxyl group (δ 3.79, 3H, *s*), a *p*-hydroxybenzyl group [*m/z* 107 (79%); 6.75, 7.07 (each 2H, *d*, *J* = 8.4 Hz)], a 1,3,4-trisubstituted benzene ring (δ 6.63, 1H, *d*, *J* = 1.3 Hz, 6.71, 7.03, each 1H, *dd*, *J* = 8.6, 1.3 and *d*, *J* = 8.6 Hz) with a 2,2-dimethylallyl group and two benzyl methylenes (Table 1). The position of the methoxyl and prenyl groups were determined by difference NOE measurement. NOEs were observed between (i) H-α and H-2, (ii) H-α and H-6, (iii) H-β and H-2″, (iv) H-β and H-6″ and (v) H-2 and OMe-3. The above data established that **8** was 3-methoxy-4′-hydroxy-4-(3-methyl-2-butenyl)bibenzyl. The presence of **8** in *R. oyamensis* has been suggested by GC-MS [5]. The identity of the mass spectrum of **8** with that obtained from the GC-MS of the crude extract of *R. oyamensis* further supported the existence of **8** in *R. oyamensis*.

The ^1H NMR signal pattern of compound **9**, $C_{19}H_{22}O_3$ ([M]$^+$ *m/z* 298.1550), was similar to that of **1**, except for the presence of a 2-methyl-2,3-epoxybutyl group (δ 1.24, 1.29, each 3H, *s*, 2.48, 2.72, each 1H, *dd*, *J* = 16.5, 5.4 Hz; δ 28.4 *t*, 69.9 *d*, 76.3 *s*), in place of a 2,2-dimethylallyl group, suggesting that **9** was 3,5-dihydroxy-2-(2,3-epoxy-3-methylbutyl)bibenzyl. Oxidation of **1** with *m*-chloroperbenzoic acid afforded an epoxide, the spectral data of which were identical to those of the natural epoxide **9**.

The ^1H and ^{13}C NMR spectra of compound **10**, $C_{20}H_{26}O_3$ ([M]$^+$ *m/z* 314.1914) showed the same bibenzyl substitution pattern as that of **1**–**3**. The presence of a methoxyl and a 2-hydroxy-2-methylbutyl groups was confirmed by the ^1H and ^{13}C NMR signals (δ 1.28, 6H, *s*, 1.67, 2.67 each *t*, *J* = 7.4 Hz; δ 19.4, *t*, 42.9, *t*, 29.5, *q*, 71.9, *s*). A difference NOE experiment indicated the presence of NOEs between (i) H-α and H-1′, (ii) H-α and H-2′, (iii) H-4 and OMe-5 and (iv) H-6 and OMe-5. The above data suggested that **10** was 3-hydroxy-5-methoxy-2-(3-hydroxy-3-methylbutyl)bibenzyl. This assumption was further confirmed by the following chemical reaction. Treatment of **10** with *p*-toluenesulphonic acid gave a chroman (**11**), $C_{20}H_{24}O_2$ ([M]$^+$ *m/z* 296.1795; δ 1.30, 6H, *s*) and a dehydrated product whose spectral data were identical to those of **3**.

The high resolution mass spectrometry established the molecular formula, $C_{19}H_{20}O_2$ ([M]$^+$ *m/z* 280.1459), for **12**. That compound **12** was a bibenzyl derivative with a non-substituted benzyl group and 1,2,4-trisubstituted benzyl group was confirmed by the ^1H NMR (δ 7.17, 3H, *m*; 7.28, 2H, *m*; 6.18, 6.19, 1H, *br s*, 2.80, 4H, *br s*) and by the ^{13}C NMR spectrum (Table 2). Methylation of **12** with methyl iodide afforded a monomethyl ether (**13**), $C_{20}H_{22}O_2$ ([M]$^+$ *m/z* 294.1610), which was also isolated from the same species. The UV and ^1H NMR spectra further showed the presence of a 2,2-dimethyl chromene moiety in **12** since absorption bands were observed at λ 305 and 312 nm in UV and chemical shifts at δ 5.50, 6.44 (each 1H, *d*, *J* = 10.0 Hz) and 1.40 (6H, *s*) [14, 15], together with the higher field carbon signal (δ 102.0 *d*, C-8). On the basis of the above data, **12** and **13** are suggested to be 2,2-dimethyl-5-(2-phenylethyl)-7-hydroxychromene and its 7-methyl ether, respectively. This presumption was further proved by the measurement of the difference NOE of **13** and thereby NOEs were observed between (i) H-α and H-4, (ii) H-α and H-6, (iii) H-6 and OMe-7 and (iv) H-8 and OMe-7. The chromene (**13**) was further synthesized to establish the structure (**12**) (see later).

The molecular formula, $C_{19}H_{20}O_2$ ([M]$^+$ *m/z* 280.1443), of **14** was identical to that of **12** and its spectral data indicated the presence of a 2,2-dimethylchromene group [14, 15], a 2-phenylethyl group and a 1,2,3,5-tetrasubstituted benzene ring (Tables 1 and 2). Methylation of **14** with methyl iodide gave a monomethyl ether (**15**), $C_{20}H_{22}O_2$ ([M]$^+$ *m/z* 294.2609; δ 3.76, 3H, *s*), indicating the presence of one phenolic hydroxyl group. The similarity of the ^1H and ^{13}C NMR spectra of **14** and **15** with those of **12** and **13** suggested that **14** and **15** were 2,2-dimethyl-5-hydroxy-7-(2-phenylethyl)chromene and its methyl ether. This was further supported by the measurement of the difference NOE of **15** and thereby NOEs were observed between (i) H-6 and OMe-5, (ii) H-α and H-6

and (iii) H-α and H-8. Conclusive evidence for structure **14** was obtained by the synthesis of **15** (see later).

Compound **16**, $C_{20}H_{20}O_4$ ([M]$^+$ *m/z* 324.1357) obtained from the polar fraction had a hydrogen bonded carboxylic group (3600–3400, 1640 cm^{-1}; δ175.5, *s*). Methylation of **16** with methyl iodide gave a methyl ester (**17**), ($C_{22}H_{24}O_4$ ([M]$^+$ *m/z* 352.1656); δ3.80, 3H, *s*, OMe, 3.90, 3H, *s*, CO_2Me). The NMR signal pattern (Tables 1 and 2) of **16** and **17** resembled those of the chromenes **14** and **15**, suggesting that **16** contained the carboxylic group at C-6 of **14**. This hypothesis was further proved by the presence of difference NOEs between (i) H-α and H-8 in **16** and between (i) H-α and H-8 and (ii) H-4 and OMe-5 in **17**. On the basis of the above data, **16** is established to be 2,2-dimethyl-5-hydroxy-6-carboxy-7-(2-phenylethyl)chromene.

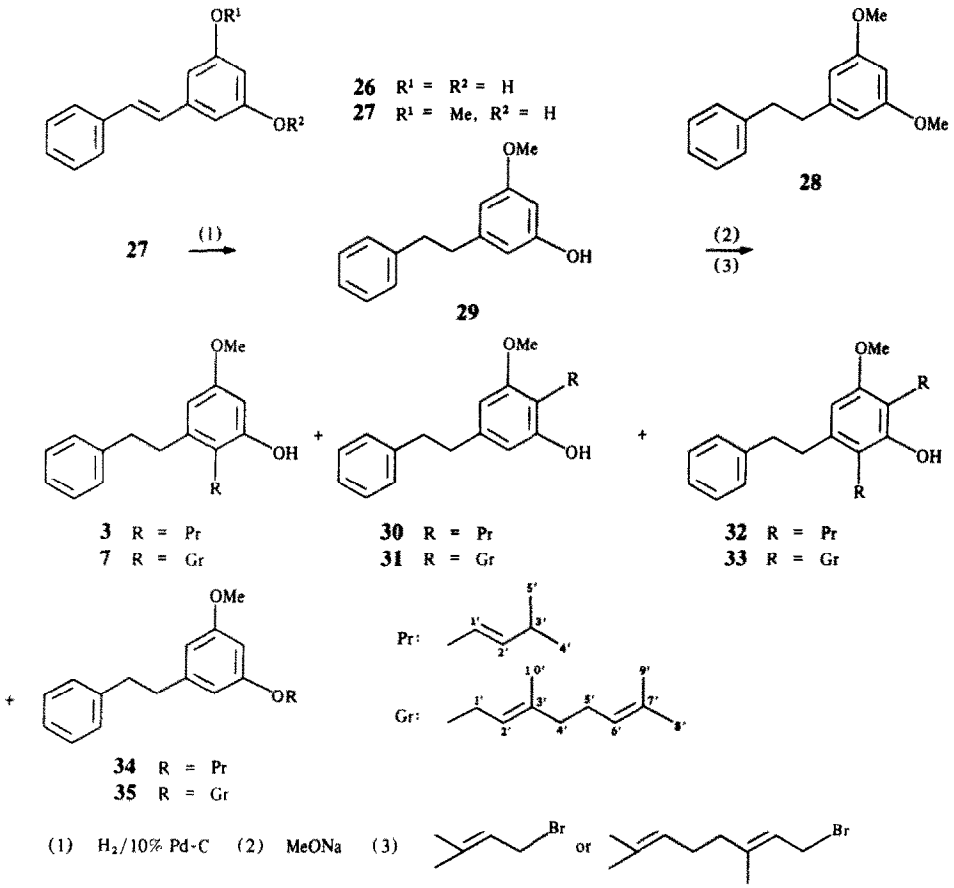
Compound **18**, $C_{22}H_{28}O_2$ ([M]$^+$ *m/z* 348.2115), was an unstable liquid which gradually polymerized to become a brown oil at room temperature. Methylation of **18** with methyl iodide afforded a monomethyl ether (**19**), $C_{25}H_{30}O_2$ ([M]$^+$ *m/z* 362.2256; δ3.73, 3H, *s*), indicating the presence of one phenolic hydroxyl group in **18**. The ^{1}H NMR signal pattern of **18** was similar to that of **12**, except for the presence of two sp^3 methylenes, two vinyl methyls and one proton on a trisubstituted double bond, in place of one of two tertiary methyl groups, suggesting that **18** was a chromene derivative formed by cyclization between the hydroxyl group at C-3 and C-3′ of 2-geranyl-3,5-dihydroxybibenzyl (**5**). This assumption was further confirmed by the presence of a base peak at *m/z* 265 corresponding to [M−C_6H_{11}]$^+$ [16, 17] and by the ^{13}C NMR spectrum (Table 2). The substitution pattern and the position of the phenolic hydroxyl group at C-7 and the 2-phenylethyl group at C-5 were established by the presence of difference NOEs between (i) H-α and H-4, (ii) H-α and H-6, (iii) H-6 and OMe-7 and (iv) H-8 and OMe-7 in **19**. The absolute configuration of C-2′ in **18** and **19** was established to be *S* by the presence of positive Cotton effects at 262 nm in **18** and 271 nm in **19**, in their CD spectra [15]. Consequently, **18** was 2(*S*)-2-methyl-2-(4-methyl-3-pentenyl)-7-hydroxy-5-(2-phenylethyl) chromene. The methyl ether (**19**) was synthesized from **6** by dehydrogenation with DDQ (see later). Crombie *et al.* [13] have synthesized (±)-*o*-cannabichromene (**18**) and its *p*-isomer by base catalysed chromenylation of 3,5-dihydroxybibenzyl (**41**) with citral by heating. The spectral data of the natural product (**18**) were identical to those of synthetic *o*-cannabichromene.

Compound **20**, $C_{25}H_{28}O_4$ ([M]$^+$ *m/z* 392.1977), was obtained as a liquid from the polar fraction. It was very unstable and again gradually decomposed to give a brown oil. The IR spectrum of **20** indicated the presence of a hydrogen bonded carboxyl group (3500–3100; 1635 cm^{-1}; δ163.1, *s*). Compound **20** when treated with methyl iodide gave a carbomethoxy derivative (**21**), $C_{27}H_{32}O_4$ ([M]$^+$ *m/z* 420.2302; δ3.89, 3H, *s*; δ169.0, 55.9 each *s*) with a methoxyl group (δ3.79, 3H; δ52.2, *s*). The above data showed that the carboxyl and phenolic hydroxyl groups were placed at an *ortho* position. The ^{1}H and ^{13}C NMR spectra of **20** and **21** were similar to those of the chromenes (**18** and **19**), except for the absence of one aromatic proton signal. The above spectral and chemical evidence indicated that compound **20** was a chromene carboxylated at C-6 of **18**. Conclusive evidence for this assumption was obtained by the presence of the NOEs between (i) H-α and H-4 and (ii) H-8 and OMe-7 in **21**. The absolute configuration at C-2′ was also determined as *S* since the CD spectra of **20** and **21** showed positive Cotton effects at 250.5 nm in **20** and 275 nm in **21** [15]. Thus, 2(*S*)-2-methyl-2-(4-methyl-3-pentenyl)-6-carboxy-7-hydroxy-5-(2-phenylethyl)chromene is given as **20**.

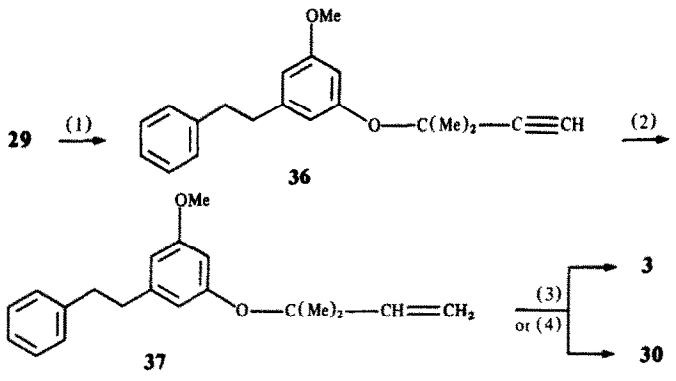
The final compound **22**, $C_{16}H_{14}O_2$ ([M]$^+$ *m/z* 238.1015), possessed a hydroxyl group (3580 cm^{-1}), an aromatic ring (1620, 1600 cm^{-1}), a non-substituted benzyl group (*m/z* 91 (base); δ7.20, 3H, *m*, 7.28, 2H, *m*), two benzylic methylenes (δ3.05, 4H, *s*) and *meta*-coupled protons (δ6.62, 1H, *d*, *J* = 2.2, 6.83, 1H, *dd*, *J* = 2.2, 1.0 Hz), one of which showed long range coupling (*J* = 1.0 Hz). Methylation of **22** with methyl iodide gave a monomethyl ether (**23**), $C_{17}H_{16}O_2$ ([M]$^+$ *m/z* 252.1137; δ3.83, 3H, *s*; δ55.7, *s*), showing the presence of one phenolic hydroxyl group in **22**. One of the two oxygens of **22** was suggested to be the ether oxygen atom since neither a carbonyl nor a hydroxyl absorption band was observed in the IR spectrum of **23**. The ^{1}H NMR spectral data of **22** and **23** and decoupling experiments of **22** showed the presence of a 4,6-disubstituted benzofuran; irradiation of the doublet and δ7.47 (*J* = 2.2, H-2) caused the double doublet at δ6.65 (*J* = 2.2, 1.0 Hz, H-3) to collapse to a doublet (*J* = 1.0 Hz). Irradiation of the double doublet at δ6.83 (*J* = 2.2, 1.0 Hz, H-7) caused the doublet at δ6.62 (*J* = 2.2, H-5) and the double doublet at δ6.65 (*J* = 2.2, 1.0, H-3) to collapse to a singlet and a doublet (*J* = 1.0 Hz), respectively, indicating long range coupling between H-3 and H-7. Conclusive evidence of the substitution pattern of each benzene ring and the position of each functional group on the benzofuran ring were provided by the presence of NOEs between (i) H-5 and OMe-6, (ii) H-7 and OMe-6 and (iii) H-α and H-5. Thus, the structure of **22** is elucidated as 6-hydroxy-4-(2-phenylethyl)benzofuran.

Syntheses of prenyl bibenzyls 1–3

We focused on pinosylvin (**26**) and pinosylvin monomethyl ether (**27**) obtained from the higher plant, *Alnus sieboldiana* (Betulaceae) [18] to synthesize **1–3** and **5**. Stilbene derivatives (**26** and **27**) are obtained from male buds of *A. sieboldiana* in high yield. The stilbene (**27**) was hydrogenated in the presence of 10% Pd-C to give 3-hydroxy-5-methoxybibenzyl (**29**). The methanol solution of **29** was treated with 28% sodium methoxide in methanol and the reaction mixture was prenylated with 2,2-dimethylallylbromide to give prenylated products which were purified by column chromatography on silica gel to afford 3-hydroxy-5-methoxy-2-(3-methyl-2-butenyl) bibenzyl (**3**) (34.9%), 3-hydroxy-5-methoxy-4-(3-methyl-2-butenyl)bibenzyl (**30**) (27.2%), 3-hydroxy-2,4-di (3-methyl-2-butenyl)bibenzyl (**32**) (2.2%) and 3-(2,2-dimethylallyloxy)-5-methoxybibenzyl (**34**) (6.8%), respectively (Scheme 1). Compound **3** was also prepared from **29** by the following method (Scheme 2). The dihydrostilbene (**29**) was treated with 3-chloro-3-methyl-1-butyne in the presence of potassium carbonate to give the etherated product (**36**), which was hydrogenated in the presence of Pd–$BaSO_4$ to afford a dihydro product (**37**), followed by heating at 140° in xylene to furnish **3** (10.4%) and **30** (11.7%). Treatment of **37** with silica gel at room temperature also gave **3** (13.5%) and **30** (17.8%). These two synthetic routes for **3** produced byproducts and the yield of **3** was low. To improve the above synthetic methods, the regioselective introduction of a prenyl group to C-2

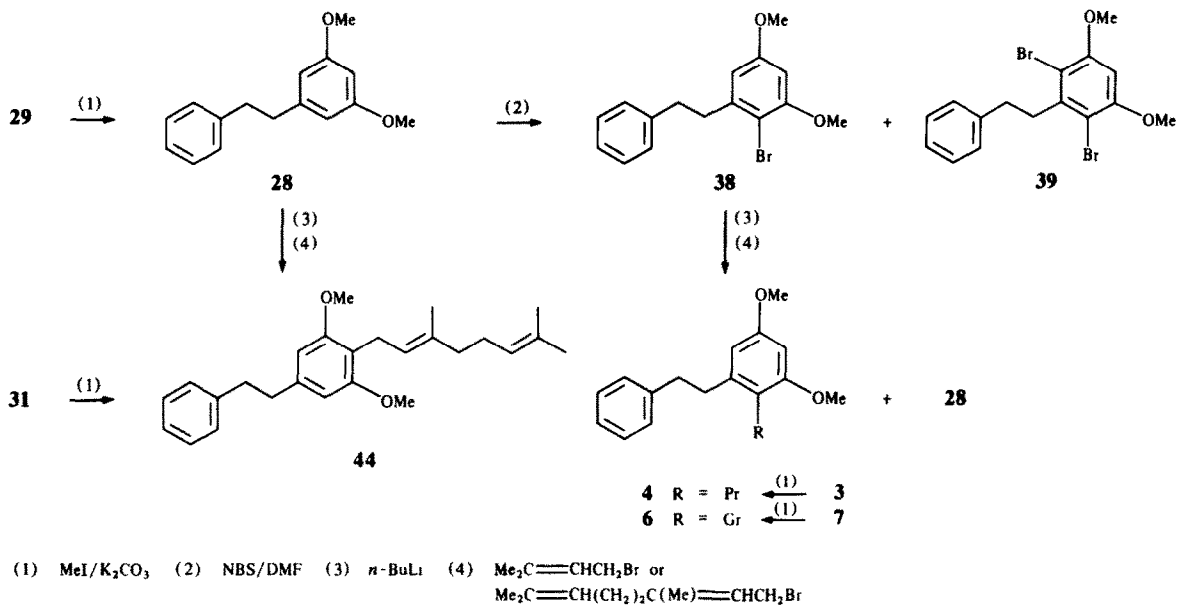


Scheme 1. Synthesis of prenyl bibenzyls from stilbene derivative **27**.



Scheme 2. Synthesis of prenyl bibenzyls from stilbene derivative **29**.

for **27** was carried out as follows (Scheme 3). The 3,5-dimethoxybibenzyl (**28**) obtained from **29** by methylation with methyl iodide was brominated with *N*-bromosuccinimide (NBS) to give a monobromide (**38**) (79.5%) and a dibromide (**39**) (6.4%). The former bromide (**38**) was treated with *n*-butyl lithium (*n*-BuLi) and then prenylated with 2,2-dimethylallyl bromide to afford 3,5-dimethoxy-2-methyl-2-butenyl)- (**4**) (58%) which was also prepared from **3** by methylation with methyl iodide, and 3,5-dimethoxybibenzyl (**28**) (38%). Treatment of **4** with BBr_3



Scheme 3. Synthesis of prenyl bibenzyls from stilbene derivative **28**.

gave a demethyl product (**1**) (19.8%) and a chroman derivative (**40**) (67%) which was formed from **1** (Schemes 3 and 4). On the other hand, **4** was treated with NaH in the presence of ethanethiol (EtSH) to yield two mono demethyl products (**2**) (28.0%) and **3** (34.4%). Furthermore, the reaction of **3** with NaH in EtSH and hexamethylphosphoric triamide (HMPA) gave **1** (52.5%) and the deprenylated product, **41** (17.8%) (Scheme 4). Compound **1** was also prepared from **26**. Hydrogenation of **26** gave a dihydro derivative (**41**) which was treated with sodium methoxide and 2,2-dimethylallylbromide to afford **1** (21.6%), and two 2,2-dimethylchromans (**40**) (17.9%) and **42** (17.2%), respectively (Scheme 5).

Synthesis of **5** *and* **44**

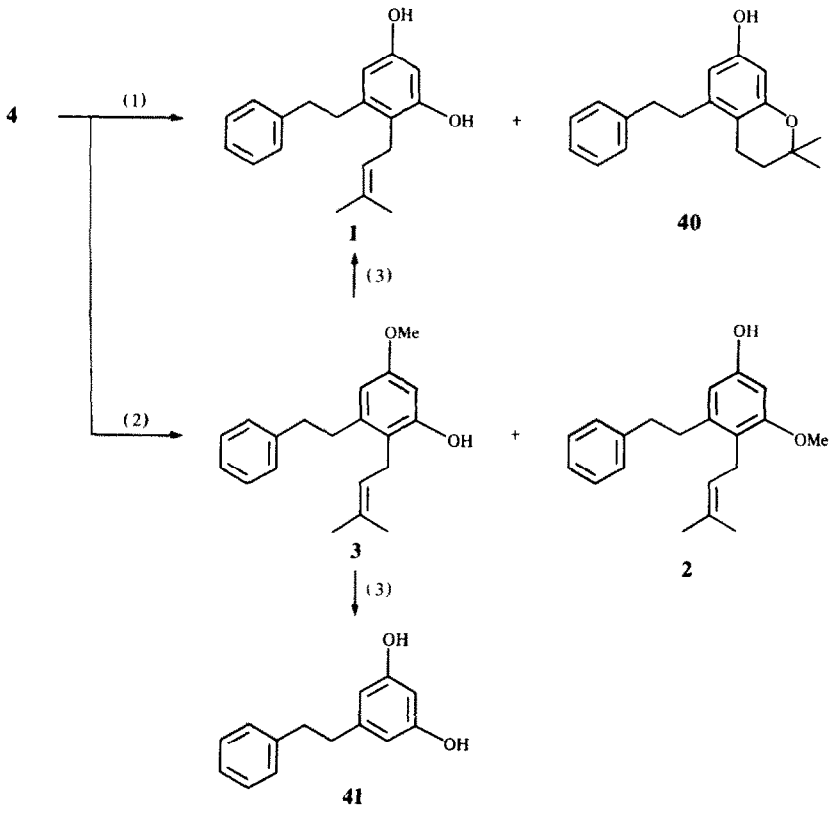
Compound **29** was treated with geranylbromide in the presence of sodium methoxide to give 2-geranyl-3-hydroxy-5-methoxybibenzyl (**7**) (29.7%), 3-hydroxy-5-methoxy-4-geranylbibenzyl (**31**) (21.8%), 3-hydroxy-5-methoxy-2,4-digeranylbibenzyl (**33**) (6.1%) and 3-geranyloxy-5-methoxybibenzyl (**35**) (6.7%), respectively (Scheme 1). In order to obtain 2-geranyl-3,5-dimethoxybibenzyl (**6**), **28** was treated with NBS, followed by prenylation with geranylbromide in *n*-BuLi to furnish **6** (58.5%) which was also obtained from **7** by methylation with methyl iodide (Scheme 3). Compound **7** was then treated with EtSNa in HMPA to yield 2-geranyl-3,5-dihydroxybibenzyl (**5**) (61.2%) and a dealkyl product (**41**) (14.8%) (Scheme 5). Compound **28** was treated with *n*-BuLi and geranylbromide to give 4-geranyl-3,5-dimethoxybibenzyl (**44**) which was also prepared from **31** by methylation (Scheme 3).

Synthesis of **13**, **15** *and* **19**

3-Hydroxy-5-methoxy-2-(3-methyl-2-butenyl)bibenzyl (**3**) was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in benzene to give 2,2-dimethyl-7-methoxy-5-(2-phenylethyl)chromene (**13**) (36.3%) (Scheme 6). The same treatment of 3-hydroxy-5-methoxy-4-(3-methyl-2-butenyl)bibenzyl (**30**) and 2-geranyl-3-hydroxy-5-methoxybibenzyl (**7**) as described above gave 2,2-dimethyl-5-methoxy-7-(2-phenylethyl)chromene (**15**) (62.3%) and 2-methyl-2-(4-methyl-3-pentenyl)-7-methoxy-5-(2-phenylethyl)chromene (**19**) (72.9%) (Scheme 6). The spectral data of the synthetic bibenzyls (**1**–**3**, **5**, **13**, **16** and **19**) were identical to those of the natural products. The structures of all intermediates and byproducts during the course of the syntheses of the natural bibenzyls were established by analyses of their spectral data (UV, IR, ^1H and ^{13}C NMR, ^1H–^1H, ^1H–^{13}C and long range ^1H–^{13}C NMR and difference NOE, mass spectrometry) and elemental analyses.

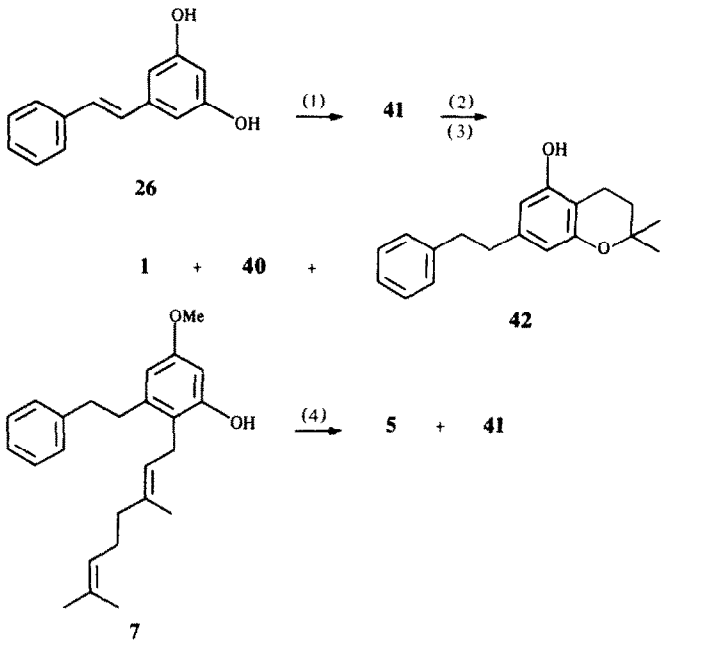
The Radulaceae are taxonomically divided into three subgenera: *Radula*, *Cladoradula* and *Odontoradula* [19]. Previously, we studied the chemical constituents of species belonging to the *Radula* and *Cladoradula* and reported that the former produced characteristic bibenzyls with a dihydrooxepin skeleton (seven-membered ring) and the latter elaborated bibenzyls with a five-membered ring, together with 2-prenyl-3,4,5-trihydroxybibenzyls [1–5, 7]. The present species belonging to the *Odontoradula* biosynthesized the bibenzyls with a 2,2-dimethylchromene skeleton (six-membered ring), along with 2-prenyl-3,5-dihydroxybibenzyls. These chemical differences among the three genera support the modern classification of the Radulaceae [19]. Almost all the compounds isolated from *Radula* species are bibenzyl derivatives and the presence of terpenoids is extremely rare. These data also support that the Radulaceae is a very isolated family in the Jungermanniales [19].

Prenyl bibenzyl derivatives possess antimicrobial and antifungal properties [20–23]. Compounds **1** and **5** showed 5-lipoxygenase (50% at 10^{-6} mol in **1** and 11% at 10^{-6} mol in **5**) and calmodulin inhibitory activity (ID_{50} 4.9 $\mu g\,ml^{-1}$ in **1** and 4.0 $\mu g\,ml^{-1}$ in **5**).



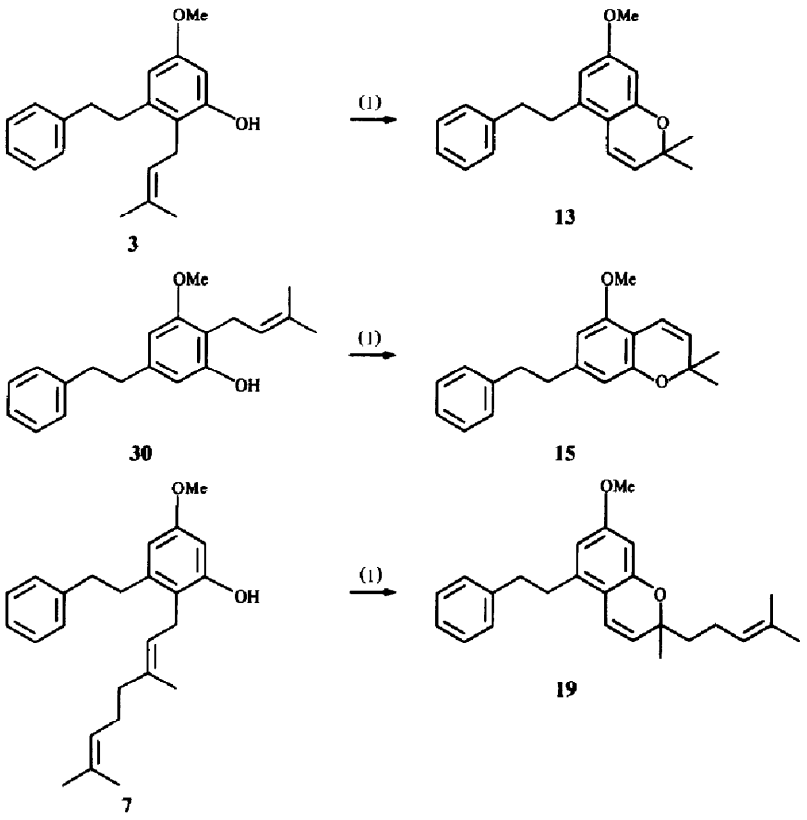
(1) BBr_3, −78° to −40° (2) EtSNa/DMF, 170° (3) EtSNa/HMPA, 180°

Scheme 4. Synthesis of prenyl bibenzyls from compound **4**.

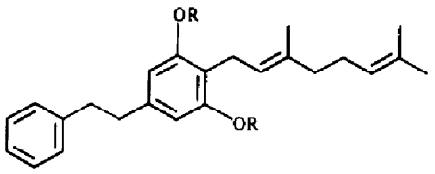


(1) H_2/10% Pd-C (2) MeONa (3) (4) EtSNa/HMPA

Scheme 5. Synthesis of prenyl bibenzyls from compound **26**.



Scheme 6. Synthesis of compounds **13**, **15**, and **19**.



43 R = H
44 R = Me

EXPERIMENTAL

Mps: uncorr. Solvents used for spectral measurements were TMS–$CDCl_3$ [^{1}H NMR (400 MHz); ^{13}C NMR (100 MHz)]; EtOH (UV); MeOH (CD and $[\alpha]_D$); $CHCl_3$ (IR), unless otherwise stated. $CHCl_3$–MeOH (1:1) was used for Sephadex LH-20 CC. TLC, GC and GC-MS were carried out as previously reported [24].

Plant material. R. kojana Steph. was collected in Kainan-cho, Todoroki, Tokushima in April 1985 and identified by Dr M. Mizutani and Y.A. A voucher specimen is deposited in The Institute of Pharmacognosy, Tokushima Bunri University.

Extraction and isolation. Air-dried *R. kojana* (237 g) was extracted with MeOH for 1 month. The resultant MeOH extract evapd *in vacuo* gave a green oil (15.1 g). A small amount of the crude extract was analysed by TLC, GC and GC-MS to detect the presence of *trans*-β-farnesene, 2-hydroxycuparene, campe-, stigma- and sitosterol. The remaining material (15.05 g) was chromatographed on silica gel using a C_6H_6–EtOAc gradient to give 5 frs. Fr. 1 (C_6H_6 100%, 1.289 g) was further chromatographed on silica gel using a *n*-hexane–C_6H_6 gradient to give chromene (**13**) (55.8 mg). Fr. 2 (2% EtOAc, 705 mg) was rechromatographed on Sephadex LH-20 and then silica gel using C_6H_6 and purified by prep. TLC (*n*-hexane–EtOAc, 4:1) to afford bibenzyls (**2**) (5.3 mg), **3** (6.5 mg), **8** (1.9 mg), **9** (16 mg), **14** (7.3 mg) and **18** (17.8 mg). Fr. 3 (5–10% EtOAc, 8.818 g) was further chromatographed on Sephadex LH-20 and then on silica gel using a C_6H_6–EtOAc gradient to afford bibenzyls **1** (4.600 g), **5** (400 mg) and **22** (12 mg). Fr. 4 (20–50% EtOAc, 2.063 g) was rechromatographed on Sephadex LH-20 and then on silica gel using the same solvent system as described above and further purified by prep. TLC (C_6H_6–EtOAc, 4:1 or 9:1) to afford **1** (16.0 mg), **9** (39 mg), **10** (14 mg), **16** (22 mg), **20** (6 mg), **24** (16 mg) [5, 7] and **25** (8 mg) [5, 7]. Fr. 5 (EtOAc 100%, 4.3148 g) was also chromatographed on Sephadex LH-20, but no bibenzyls were isolated.

Compound **1**. Mp 91.5–92.5° (from cyclohexane). UV λ_{max} nm (log ε): 215 (4.37), 230sh (4.03), 285 (3.44). IR ν_{max} cm^{-1}: 3600, 1620, 1595, 1495, 1450, 1370, 1130, 1040, 840, 690. ^{1}H and ^{13}C NMR (Tables 1 and 2). HRMS: found: 282.1637, $C_{19}H_{22}O_2$ requires 282.1620; EIMS *m/z* (rel. int.): 282 $[M]^+$ (99), 227 (100), 225 (73), 191 (39), 177 (33), 149 (40), 91 (84).

Compound **2**. Mp 63–64° (from *n*-hexane). UV λ_{max} nm (log ε): 218 (4.36), 230sh (4.20), 282.5 (3.60). IR ν_{max} cm^{-1}: 3600, 2940, 1602, 1595, 1462, 1080, 690. ^{1}H and ^{13}C NMR (Tables 1 and 2). HRMS: found: 296.1774, $C_{20}H_{24}O_2$ requires 296.1776; EIMS *m/z* (rel. int.): 296 $[M]^+$ (74), 281 (8), 240 (29), 239 (100), 205 (12), 191 (33), 163 (22), 137 (10), 105 (13), 91 (38).

Compound **3**. Mp 40–41° (from *n*-hexane). UV λ_{max} nm (log ε): 215 (4.40), 230sh (4.06), 280 (3.47), 287.5 (3.75). IR ν_{max} cm^{-1}: 3600, 2950, 1618, 1585, 1495, 1450, 1140, 690. ^1H and ^{13}C NMR (Tables 1 and 2). HRMS: found: 296.1772, $C_{20}H_{24}O_2$ requires 296.1776; EIMS *m/z* (rel. int.): 296 $[M]^+$ (100), 281 (8), 265 (17), 241 (77), 240 (29), 239 (71), 238 (9), 205 (26), 191 (37), 163 (25), 147 (29), 137 (29), 105 (16), 91 (62).

Compound **5**. Mp 57–58° (from *n*-hexane). UV λ_{max} nm (log ε): 216 (4.40), 232sh (4.04), 285 (3.58). IR ν_{max} cm^{-1}: 3600, 1620, 1598, 1492, 1450, 1130, 835, 822, 690. ^1H and ^{13}C NMR (Tables 1 and 2). HRMS: found: 350.2229 $C_{24}H_{30}O_2$ requires 350.2246; EIMS *m/z* (rel. int.): 350 $[M]^+$ (15), 265 (69), 227 (100), 225 (32), 189 (26), 105 (35), 91 (82), 69 (26). The ^1H and ^{13}C NMR spectral data of **5** were identical to those of synthetic *o*-cannabigerol [13].

Compound **8**. ^1H NMR (Table 1). EIMS *m/z* (rel. int.): 296 $[M]^+$ (82), 241 (12), 239 (28), 180 (100), 107 (79).

Compound **9**. Mp 90–91° (from Et_2O–cyclohexane). UV λ_{max} nm (log ε): 214 (4.32), 229sh (4.00), 280 (3.42), 287 (3.43). IR ν_{max} cm^{-1}: 3600, 2980, 1620, 1598, 1495, 1488, 1450, 1130, 1060, 1025, 1005, 690. ^1H and ^{13}C NMR (Tables 1 and 2). HRMS: found: 298.1550 $C_{19}H_{22}O_3$ requires 298.1569; EIMS *m/z* (rel. int.): 298 $[M]^+$ (74), 265 (7), 227 (100), 225 (7), 207 (14), 91 (43).

Compound **10**. Mp 97–98° (from *n*-hexane). UV λ_{max} nm (log ε): 214 (4.38), 230 (4.06), 280 (3.50), 287 (3.52). IR ν_{max} cm^{-1}: 3600, 2960, 1610, 1585, 1495, 1330, 1190, 1140, 1048, 960, 900, 830, 690. ^1H and ^{13}C NMR (Tables 1 and 2). HRMS: found: 314.1914, $C_{20}H_{26}O_3$ requires 314.1882; EIMS *m/z* (rel. int.): 314 $[M]^+$ (12), 296 (37), 241 (100), 205 (36), 91 (43).

Compound **12**. UV λ_{max} nm (log ε): 217 (4.29), 235 (4.11), 280 (3.73), 287 (3.74), 305 (3.56), 317 (3.52). IR ν_{max} cm^{-1}: 3550, 1610, 1580, 1490, 1448, 1135, 1125, 690. ^1H and ^{13}C NMR (Tables 1 and 2). HRMS: found: 280.1466, $C_{19}H_{20}O_2$ requires 280.1463; EIMS *m/z* (rel. int.): 280 $[M]^+$ (21), 265 (100), 189 (7), 174 (31), 91 (10).

Compound **13**. UV λ_{max} nm (log ε): 218 (4.30), 233 (4.21), 243 (4.04), 277 (3.77), 287 (3.78), 306 (3.57), 316 (3.53). IR ν_{max} cm^{-1}: 3000, 2980, 2850, 1608, 1490, 1140, 1120, 690. ^1H and ^{13}C NMR (Tables 1 and 2). HRMS: found: 294.1610, $C_{20}H_{22}O_2$ requires 294.1620; EIMS *m/z* (rel. int.): 294 $[M]^+$ (21), 279 (100), 203 (7), 188 (29), 91 (9).

Compound **14**. UV λ_{max} nm (log ε): 230 (4.31), 280 (3.94), 290 (3.91). IR ν_{max} cm^{-1}: 3590, 2950, 2900, 1620, 1575, 1570, 1240, 1109, 1050, 690. ^1H and ^{13}C NMR (Tables 1 and 2). HRMS: found: 280.1443, $C_{19}H_{20}O_2$ requires 280.1463; EIMS *m/z* (rel. int.): 280 $[M]^+$ (16), 265 (100), 189 (9), 174 (41), 91 (11).

Compound **16**. Mp 122–123° (from *n*-hexane–$CHCl_3$). UV λ_{max} nm (log ε): 207 (4.16), 248 (4.25), 290 (3.56), 330 (3.39). IR ν_{max} cm^{-1}: 3600–3400, 2980, 2930, 1640, 1618, 1565, 1495, 1465, 1452, 1372, 1265, 1122, 690. ^1H and ^{13}C NMR (Tables 1 and 2). HRMS: found: 324.1357, $C_{20}H_{20}O_4$ requires 324.1361; EIMS *m/z* (rel. int.): 324 $[M]^+$ (2), 309 (20), 291 (17), 265 (8), 150 (38), 122 (29), 105 (45), 104 (41), 91 (100), 77 (31), 51 (16).

Compound **18**. UV λ_{max} nm (log ε): 220 (4.34), 237 (4.26), 245 (4.10), 280 (3.79), 288 (3.80), 307.5 (3.66), 318 (3.62). IR ν_{max} cm^{-1}: 3600, 2930, 1612, 1585, 1451, 1140, 1130, 692. ^1H and ^{13}C NMR (Tables 1 and 2). HRMS: found: 348.2115, $C_{24}H_{28}O_2$ requires 348.2090; EIMS *m/z* (rel. int.): 348 $[M]^+$ (7), 333 (4), 265 (100), 174 (21), 91 (13): $[\alpha]_D$ + 21.4° (*c* 0.14); CD: $\Delta\varepsilon_{262\,nm}$ + 0.6, $\Delta\varepsilon_{295\,nm}$ + 0.3 (*c* 1.98×10^{-3} mol l^{-1}).

Comound **20**. UV λ_{max} nm (log ε): 213 (4.39), 247 (4.11), 290 (3.64), 325 (3.34). IR ν_{max} cm^{-1}: 3600, 3500–3100, 2920, 1635, 1600, 1492, 1450, 1370, 1250, 1150, 1140, 690. ^1H and ^{13}C NMR (Tables 1 and 2). HRMS: found: 392.1977, $C_{25}H_{28}O_4$ requires 392.1988; EIMS *m/z* (rel. int.): 392 $[M]^+$ (1), 333 (8), 265 (100), 174 (41), 149 (13), 91 (11), 69 (6), 57 (6), 44 (6), 41 (8). $[\alpha]_D$ + 26.8° (*c* 0.047). CD: $\Delta\varepsilon_{206\,nm}$ − 2.0, $\Delta\varepsilon_{250\,5\,nm}$ + 1.3, $\Delta\varepsilon_{280\,nm}$ + 1.1.

Compound **22**. Mp 217–218° (from MeOH–Et_2O, 1:1). UV λ_{max} nm (log ε): 219 (4.36), 249 (4.09), 262 (4.05), 289 (3.89), 295 (3.72). IR ν_{max} cm^{-1}: 3580, 2910, 1620, 1600, 1490, 1132, 1105, 690. ^1H and ^{13}C NMR (Tables 1 and 2). HRMS: found: 238.1015, $C_{16}H_{14}O_2$ requires 238.0993; EIMS *m/z* (rel. int.): 238 $[M]^+$ (35), 147 (100), 91 (23), 65 (10).

Methylation of **1**. To compound **1** (20 mg) in Me_2CO (10 ml) was added MeI (0.1 ml) in the presence of K_2CO_3 (50 mg). Work-up gave a diMe ether (**4**) (19 mg). UV λ_{max} nm (log ε): 214 (4.42), 232sh (4.06), 282 (3.47). IR ν_{max} cm^{-1}: 1609, 1590, 1463, 1455, 1310, 1200, 1148, 1082, 1055, 695. ^1H and ^{13}C NMR (Tables 1 and 2). HRMS: found: 310.1913, $C_{21}H_{26}O_2$ requires 310.1933; EIMS *m/z* (rel. int.): 310 $[M]^+$ (69), 295 (13), 255 (13), 254 (32), 253 (100), 242 (15), 219 (18), 205 (51), 151 (20), 105 (18), 91 (23).

Methylation of **5**. Compound **5** (57 mg) was treated in the same manner described above to afford a diMe ether (**6**) (43 mg). UV λ_{max} nm (log ε): 216 (4.44), 230sh (4.12), 279 (3.49), 285 (3.48). IR ν_{max} cm^{-1}: 2940, 1609, 1590, 1490, 1462, 1455, 1421, 1342, 1282, 1200, 1148, 1085, 1070, 1055, 820, 695. ^1H and ^{13}C NMR (Tables 1 and 2). HRMS: found: 378.2554, $C_{26}H_{34}O_2$ requires 378.2559; EIMS *m/z* (rel. int.): 378 $[M]^+$ (36), 309 (20), 255 (100), 254 (25), 253 (46), 151 (28), 121 (12), 105 (40), 91 (25), 69 (19), 57 (6).

Dehydration of **10**. To compound **10** (10 mg) in C_6H_6 (3 ml) was added *p*-TsOH (1 ml) and the soln refluxed for 40 min. Work-up gave a residue which was purified by prep. TLC (*n*-hexane–EtOAc, 4:1) to afford the starting material **10** (1 mg), **3** (1 mg) and **11** (4 mg). Compound **11**. UV λ_{max} nm (log ε): 212.5 (4.27), 230sh (3.81), 280 (3.12), 287.5 (3.13). IR ν_{max} cm^{-1}. 2930, 1610, 1580, 1480, 1378, 1315, 1138, 1114, 1045, 690. ^1H NMR (90 MHz): δ 1.30 (6H, *s*), 1.76 (2H, *t*, *J* = 6.8 Hz), 2.55 (2H, *t*, *J* = 6.8), 2.84 (4H, *s*), 3.74 (3H, *s*, OMe), 6.26 (1H, *d*, *J* = 2.6), 6.38 (1H, *d*, *J* = 2.6), 7.24 (5H, *m*). HRMS: found: 296.1795, $C_{20}H_{24}O_2$ requires 296.1776; EIMS *m/z* (rel. int.): 296 (69), 241 (100), 239 (17), 205 (20), 191 (11), 163 (10), 137 (16), 105 (7), 91 (27).

Methylation of **12**. Compound **12** (5 mg) was treated with MeI as described above to give a monoMe ether (2 mg) whose spectral data were identical to those of the natural chromene (**13**).

Methylation of **14**. Compound **14** (3 mg) was also methylated with MeI as described above to give a monoMe ether (**15**) (3 mg). Mp 31–32° (from *n*-hexane). UV λ_{max} nm (log ε): 230 (4.30), 281 (3.97), 290 (3.95). IR ν_{max} cm^{-1}: 2940, 1615, 1570, 1461, 1450, 1423, 1370, 1120, 1100, 690. ^1H and ^{13}C NMR (Tables 1 and 2). HRMS: found: 294.1609, $C_{20}H_{22}O_2$ requires 294.1620; EIMS *m/z* (rel. int.): 294 $[M]^+$ (13), 279 (100), 203 (3), 188 (28), 91 (7).

Methylation of **16**. Compound **16** (4 mg) was treated in the same manner as described above to give a Me ester (**17**) (5 mg). UV λ_{max} nm (log ε): 214 (4.29), 237 (3.84), 273 (3.84), 283 (3.82), 307 (3.44), 313 (3.33). IR ν_{max} cm^{-1}: 2940, 1720, 1609, 1560, 1450, 1320, 1280, 1235, 1149, 1111, 1055, 970, 690. ^1H and ^{13}C NMR (Tables 1 and 2). HRMS: found: 352.1656, $C_{22}H_{24}O_4$ requires 352.1675; EIMS *m/z* (rel. int.): 352 $[M]^+$ (13), 337 (100), 321 (4), 261 (5), 231 (13), 91 (3).

Methylation of **18**. Treatment of **18** (3 mg) with MeI as described above gave a monoMe ether (19) (2 mg). UV λ_{max} nm (log ε): 219 (4.28), 227 (4.26), 235 (4.23), 277 (3.76), 287 (3.75), 307 (3 63), 317 (3.57). IR ν_{max} cm^{-1}: 2930, 1610, 1570, 1490, 1450, 1141, 690. ^1H and ^{13}C NMR (Tables 1 and 2). HRMS: found: 362.2251, $C_{25}H_{30}O_2$ requires 362.2246; EIMS *m/z* (rel. int.): 362 $[M]^+$ (6), 347 (5), 279 (100), 188 (18), 91 (3). $[\alpha]_D$ + 828° (*c* 0.005). CD: $\Delta\varepsilon_{271\,nm}$ + 9.8, $\Delta\varepsilon_{300\,nm}$ + 8.0 (*c* 1.38×10^{-4} mol l^{-1}).

Methylation of **20**. Compound **20** (2.7 mg) was methylated with MeI as described above to afford a monoMe ether (**21**) (2.3 mg). UV λ_{max} nm (log ε): 212.5 (4.29), 219 (4.33), 227 (4.32), 234 (4.31), 242 (4.21), 292 (3.63), 307 (3.61), 320 (3.53). IR ν_{max} cm^{-1}: 2824, 1724, 1600, 1434, 1375, 1365, 1275, 1190,

1144, 995, 690. ^{1}H and ^{13}C NMR (Tables 1 and 2). HRMS: found: 420.2302, $C_{27}H_{32}O_4$ requires 420.2301; EIMS *m/z* (rel. int.): 420 (6), 389 (3), 337 (100), 305 (5), 231 (12), 188 (4), 91 (9), 69 (5). $[\alpha]_D$ +125.8° (*c* 0.024). CD: $\Delta\varepsilon_{201\,nm}$ −2.0, $\Delta\varepsilon_{219.5\,nm}$ +0.3, $\Delta\varepsilon_{275\,nm}$ +1.2 (*c* 5.7×10^{-4} mol l^{-1}).

Methylation of **22**. Treatment of **22** (7.2 mg) with MeI as described above yielded a monoMe ether (**23**) (3.6 mg). UV λ_{max} nm (log ε): 218 (4.34), 249 (4.04), 261 (4.02), 286 (3.64), 294 (3.61). IR ν_{max} cm^{-1}: 2920, 1618, 1600, 1490, 1450, 1420, 1298, 1140, 1118, 1038, 690. ^{1}H and ^{13}C NMR (Tables 1 and 2). HRMS: found: 252.1137, $C_{17}H_{16}O_2$ requires 252.1150; EIMS *m/z* (rel. int.): 252 [M]$^+$ (36), 161 (100), 118 (18), 91 (14).

Oxidation of **1**. Compound **1** (15 mg) was dissolved in $CHCl_3$ (3 ml) and then *m*-chloroperbenzoic acid (MCPBA) (15 mg) was added. The reaction mixt. was stirred at room temp. for 2 hr, the resulting product filtered to remove excess MCPBA and *m*-chlorobenzoic acid, and the filtrate treated in the usual manner to give a residue which was purified by prep. TLC to give an epoxide (5 mg) whose spectral data were identical to those of the natural epoxybibenzyl (**9**).

Isolation of pinosylvin (**26**) *and pinosylvin mono*Me *ether* (**27**). Fresh male buds of *Alnus sieboldiana* Matsum. (11.7 kg) collected at Naruto, Tokushima in February 1986 were extd with MeOH (20 l × 2). The MeOH ext (248 g) was chromatographed on silica gel (800 g) and eluted with a *n*-hexane–EtOAc gradient. The 30% EtOAc–*n*-hexane eluant gave a residue (36 g) which was subjected to Sephadex LH-20 CC to yield pinosylvin monoMe ether (**27**) (18.92 g) as white crystals [18]. The 50% EtOAc–*n*-hexane eluant gave a residue (11.2 g) which was chromatographed on Sephadex LH-20 to give pinosylvin (**26**) (7.85 g) as lemon yellow crystals [18].

Catalytic reduction of **27**. Compound **27** (9.2 g) was hydrogenated over 10% Pd-C (2 g) in EtOAc (50 ml) at room temp. for 2 hr with stirring. After removal of catalyst, the filtrate was concd *in vacuo*. The residue (9.25 g) was chromatographed on Sephadex LH-20 to afford dihydropinosylvin monoMe ether (**29**) (8.95 g, 96.4%) as an oil. IR ν_{max} cm^{-1}: 3400, 1615, 1600, 1495, 1455, 1340, 1190, 1150, 1055. ^{1}H NMR: δ 2.76, 2.83 (each 2H, *m*, H-α and H-β), 3.64 (3H, *s*, OMe), 6.27, 6.28, 6.30, (each 1H, *dd*, *J* = 2.2, 2.2 Hz, H-2, H-4 and H-6), 7.08–7.24 (5H, *m*). HRMS: found: 228.1166, $C_{15}H_{16}O_2$ requires 228.1150; EIMS *m/z* (rel. int.): 228 [M]$^+$ (100), 138 (11), 137 (100), 91 (55).

Reaction of **29** *with* NaOMe *and 2,2-dimethylallylbromide*. To a soln of **29** (1.432 g) in dry MeOH (10 ml) was added 28% NaOMe–MeOH soln (1.4 ml). The resultant soln was stirred at room temp. for 30 min and evapd to dryness *in vacuo*. The residual brown crystals were suspended in dry C_6H_6 (10 ml) and evapd again to remove traces of H_2O. The residue was again suspended in dry C_6H_6 (15 ml), to which was added 2,2-dimethylallylbromide (860 mg). The mixt. was vigorously stirred at 50–55° for 30 min and then poured into ice-H_2O and extracted with EtOAc. The EtOAc layer was successively washed with 1 M HCl, H_2O, dried over $MgSO_4$ and evapd to give an oil (2.25 g) which was chromatographed on silica gel using a *n*-hexane–EtOAc gradient. The eluant with 2% EtOAc–*n*-hexane was evapd to give an oil (305 mg) which was further chromatographed on silica gel (C_6H_6–*n*-hexane, 1:1) to yield **32** (51 mg; 2.2%) and **34** (126 mg; 6.8%). The eluant with 5% EtOAc–*n*-hexane was evapd to yield **30** (515 mg; 27.2%). The eluant with 6% EtOAc–*n*-hexane gave **3** (660 mg; 34.9%) as white crystals. Evapn of the eluant with 10% EtOAc–*n*-hexane gave **29** (289 mg; 20.2%).

Compound **30**. UV λ_{max}^{MeOH} nm (log ε): 219 (4.35), 272.5 (3.13). IR ν_{max}^{neat} cm^{-1}: 3450, 2925, 2850, 1615, 1590, 1510, 1495, 1420, 1340, 1220, 1155, 1080. ^{1}H NMR: δ 1.73, 1.80 (each 3H, *s*), 2.83, 2.90 (4H, *m*), 3.37 (2H, *d*, *J* = 6.8 Hz), 3.76 (3H, *s*), 5.23 (1H, *t*, *J* = 6.8 Hz), 6.28 (1H, *br s*), 6.35 (1H, *br s*), 7.17–7.30 (5H, *m*). ^{13}C NMR: δ 17.8, 25.8 (each *q*, C-4′ and C-5′), 22.2 (*t*, C-1′), 37.7, 38.0 (*t*, C-α and C-β), 55.7 (*q*, OMe), 103.7 (*d*, C-2), 108.8 (*d*, C-6), 113.0 (*s*, C-4), 122.4 (*d*, C-2′), 125.9 (*d*, C-4″) 128.3, 128.4 (*d*, C-2″, C-3″, C-5″ and C-6″), 133.6 (*s*, C-3′), 141.2, 141.8 (*s*, C-1 and C-1″), 155.0 (*s*, C-5), 157.9 (*s*, C-3). HRMS: found: 296.1792, $C_{20}H_{24}O_2$ requires 296.1776; EIMS *m/z* (rel. int.): 296 [M]$^+$ (100), 281 (31), 241 (98), 209 (10), 205 (62), 163 (10), 137 (12), 105 (16), 91 (30).

Compound **32**. IR ν_{max}^{neat} cm^{-1}: 3475, 2925, 1615, 1585, 1495, 1455, 1420, 1210, 1165, 1105. ^{1}H NMR: δ 1.17, 1.72, 1.79, 1.80 (each 3H, *s*), 2.86 (4H, *m*), 3.33 (2H, *d*, *J* = 6.6 Hz), 3.37 (2H, *d*, *J* = 7.1 Hz), 3.74 (3H, *s*), 5.12 (1H, *t*, *J* = 6.6 Hz), 5.22 (1H, *t*, *J* = 7.1 Hz), 5.43 (1H, *br s*, OH), 6.28 (1H, *s*), 7.19–7.30 (5H, *m*). ^{13}C NMR: δ 17.8, 18.0, 25.7, 25.8 (each *q*), 22.5, 25.2, 35.9, 37.9 (each *t*), 104.4 (*d*), 113.6, 118.5, (each *s*), 122.5, 123.3, 125.9, 128.3, 128.4 (each *d*), 132.9, 133.5, 138.6, 142.0, 153.8, 155.8 (each *s*). HRMS: found: 364.2393, $C_{25}H_{32}O_2$ requires 364.2403; EIMS *m/z* (rel. int.): 364 [M]$^+$ (100), 309 (27), 308 (36), 307 (21), 293 (60), 273 (10), 265 (22), 259 (11), 253 (33), 241 (10), 217 (62), 203 (31), 175 (20), 91 (67), 69 (18).

Compound **34**. IR ν_{max}^{neat} cm^{-1}: 2925, 1595, 1460, 1450, 1375, 1340, 1285, 1190, 1145, 1055, 1035, 820, 690. ^{1}H NMR: δ 1.72, 1.78, (each 3H, *s*), 2.87 (4H, *m*), 3.72 (3H, *s*), 4.43 (2H, *d*, *J* = 6.8 Hz), 5.47 (1H, *t*, *J* = 6.8 Hz), 6.33, 6.35 (3H, *m*), 7.17–7.29 (5H, *m*). ^{13}C NMR: δ 18.1, 25.8 (each *q*), 37.6, 38.2 (each *t*), 55.1 (*q*), 64.6 (*t*), 98.5 (*d*), 106.5, 107.1 (each *d*), 119.7, 125.8, 128.3, 128.4 (each *d*), 137.9, 141.6, 144.0, 159.9, 160.6 (each *s*). HRMS: found: 296.1800, $C_{20}H_{24}O_2$ requires 296.1776; EIMS *m/z* (rel. int.) 296 [M]$^+$ (5), 229 (14), 228 (100), 165 (25), 137 (79), 91 (36), 69 (18).

Reaction of **29** *with* NaOMe *and geranylbromide*. To a soln of **29** (2.30 g) in dry MeOH (20 ml) was added 28% NaOMe–MeOH (2.14 ml). The reaction mixt. was stirred at room temp. for 30 min. The resultant mixt. was treated in the same manner as described in the reaction of **29** with 2,2-dimethylallylbromide to give a residue to which was added geranylbromide (2 g). The mixt. was then vigorously stirred at 50–55° for 30 min and then poured into ice-H_2O and extd with C_6H_6. The C_6H_6 layer was treated in the same manner as described above to afford an oil (2.95 g) which was chromatographed on silica gel using a *n*-hexane–EtOAc gradient to furnish **33** (306 mg, 6.1%), **35** (247 mg, 6.7%), **31** (7.99 mg; 21.8%), **7** (1.089 g; 29.7%) and starting material (**29**) (735 mg; 31.9%), respectively.

Compound **7**. UV λ_{max} nm (log ε): 210 (4.75), 283.5 (4.00). IR ν_{max}^{neat} cm^{-1}: 3450, 2925, 1615, 1590, 1495, 1440, 1435, 1195, 1135, 1050, 825. ^{1}H and ^{13}C NMR (Tables 1 and 2). HRMS: found: 364.2413, $C_{25}H_{32}O_2$ requires 364.2423; EIMS *m/z* (rel. int.): 364 [M]$^+$ (31), 279 (48), 241 (100), 239 (28), 137 (16), 105 (23), 91 (20).

Compound **31**. UV λ_{max} nm (log ε): 211.5 (4.71), 271 (3.81). IR ν_{max}^{KBr} cm^{-1}: 3450, 2920, 1615, 1590, 1450, 1420, 1205, 1160, 1090, 1070. ^{1}H NMR: δ 1.58 (3H, *s*), 1.66, 1.79 (each 3H, *s*), 2.06 (4H, *m*), 2.84 (4H, *m*), 3.38 (2H, *d*, *J* = 7.3 Hz), 3.74 (3H, *s*), 5.05, 5.23 (each 1H, *t*, *J* = 7.3 Hz), 5.32 (1H, *br s*, OH), 6.26, 6.35 (each 1H, *d*, *J* = 1.5 Hz), 7.16–7.29 (5H, *m*). ^{13}C NMR: δ 16.1, 15.7 (each *q*), 22.1 (*t*), 25.6 (*q*), 26.5, 37.4, 37.7, 39.7 (each *t*), 55.7 (*q*), 103.6, 108.9 (each *d*), 112.8 (*s*), 122.1, 124.0, 125.9, 128.3, 128.4 (each *d*), 131.8, 137.8, 141.2, 141.8, 155.4, 157.8 (each *s*). HRMS: found: 364.2389, $C_{25}H_{32}O_2$ requires 364.2375; EIMS *m/z* (rel. int.): 364 [M]$^+$ (15), 295 (20), 279 (15), 242 (23), 241 (100), 123 (5), 105 (17), 91 (16).

Compound **33**. UV λ_{max} nm (log ε): 212.5 (4.78), 283 (3.79). IR ν_{max}^{KBr} cm^{-1}: 3450, 1900, 1615, 1580, 1492, 1450, 1370, 1315, 1205, 1105, 810, 740, 690. ^{1}H NMR: 1.57, 1.58 (each 3H, *s*), 1.64, 1.67, 1.78, 1.80 (each 3H, *s*), 2.06 (8H, *m*), 2.86 (4H, *m*), 3.34 (2H, *d*, *J* = 5.9 Hz), 3.40 (2H, *d*, *J* = 6.6 Hz), 3.74 (3H, *s*), 5.05, 5.97 (each

1H, *t*, $J = 6.2$ Hz), 5.14, 5.23 (each 1H, *t*, $J = 6.6$ Hz), 5.44 (1H, *br s*, OH), 6.29 (1H, *s*), 7.17 7.30 (5H, *m*). ^{13}C NMR: 16.1, 16.3, 17.7, 18.0 (each *q*), 22.4, 25.0 (each *t*), 25.7 (*q*), 26.5, 35.9, 37.8, 39.7, 39.8 (each *t*), 55.7 (*q*), 104.3 (*d*), 113.7, 118.7 (each *s*), 122.4, 123.3, 124.1, 125.9, 128.4, 131.6 (each *d*), 136.4, 137.2, 138.6, 142.0, 154.0, 155.8 (each *s*). HRMS: found: 500.3642, $C_{35}H_{48}O_2$ requires 500.3648; EIMS *m/z* (rel. int.): 500 $[M]^+$ (2), 405 (11), 307 (6), 203 (10), 91 (88), 69 (100).

Compound **35**. UV λ_{max} nm (log ε): 210 (4.70), 276 (3.81). IR ν_{max}^{neat} cm^{-1}: 2920, 1595, 1450, 1430, 1342, 1190, 1145, 1055, 1035, 820, 690. ^{1}H NMR: δ 1.61, 1.68, 1.73 (each 3H, *s*), 2.11, 2.88 (4H, *m*), 3.74 (3H, *s*), 4.47 (2H, *d*, $J = 6.6$ Hz), 5.10, 5.48 (each 1H, *t*, $J = 6.6$ Hz), 6.34, 6.36 (1H, *d*, $J = 2.2$ Hz), 6.71–7.29 (5H, *m*). ^{13}C NMR: δ 16.7, 17.7, 25.7 (each *q*), 26.3, 37.7, 38.2, 39.6 (*t*), 55.2 (*q*), 64.8 (*t*), 98.6 (*d*), 106.5, 107.2, 119.5, 123.8, 125.9, 128.3, 128.4 (each *d*), 131.8, 141.1, 141.7, 144.0, 160.0, 160.7 (each *s*). HRMS: found: 364.2407, $C_{25}H_{32}O_2$, 364.2402; EIMS *m/z* (rel. int.): 364 $[M]^+$ (1), 229 (16), 228 (76), 167 (16), 148 (29), 137 (96), 105 (23), 99 (21), 91 (100).

Treatment of **29** *with 2-chloro-2-methyl-1-butyne.* To **29** (1.067 g) in Me_2CO (30 ml) was added KI (0.15 g) K_2CO_3 (1.57 g) and 2-chloro-2-methyl-1-butyne (1.52 g) and the reaction mixt. refluxed at 80° with stirring for 43 hr. After filtration, evapn of solvent, the product was extracted with Et_2O, washed with H_2O, 10% NaOH and evapd to give a residue (1.06 g) which was chromatographed on silica gel (*n*-hexane–EtOAc gradient) to afford **36** (919.1 mg). ^{1}H NMR (90 MHz): δ 1.62 (6H, *s*), 2.54 (4H, *s*), 3.74 (3H, *s*). EIMS *m/z* (rel. int.): $[M]^+$ 294 (5), 279 (100), 137 (32), 91 (13).

Hydrogenation of **36**. Compound **36** (102.0 mg) in EtOAc (10 ml) was hydrogenated in the presence of Pd–$BaSO_4$ (41.5 mg) and quinoline (0.3 ml) until 1 mol H_2 was absorbed. After removal of catalyst, the filtrate was dried over $MgSO_4$ and the solvent evapd to give a residue (95.3 mg) which was chromatographed on silica gel (*n*-hexane–EtOAc gradient) to afford **37** (86.8 mg, 84.5%). IR ν_{max} cm^{-1}: 2925, 1600, 1450, 1250, 1090, 1000. ^{1}H NMR (90 MHz): δ 1.35 (6H, *s*), 2.78 (4H, *s*), 5.50 (1H, *dd*, $J = 9.0$, 2.0 Hz). EIMS *m/z* (rel. int.): 296 $[M]^+$ (45), 294 (11), 280 (16), 279 (100), 229 (25), 228 (27), 188 (35), 137 (38), 91 (27).

Claisen rearrangement reaction of **37**. Compound **37** (72 mg) in xylene (0.5 ml) was sealed in a tube which was heated at 130° for 16 hr. The reaction mixt. was chromatographed on silica gel (*n*-hexane–EtOAc gradient) to give Claisen rearrangement products which were purified by prep. TLC (*n*-hexane–EtOAc, 4:1) to furnish **3** (5.5 mg, 10.4%) and **30** (6.2 mg, 11.7%).

Treatment of **37** *with silica gel.* To **37** (292 mg) in 10% *n*-hexane–C_6H_6 (15 ml) was added silica gel (50 g) and the mixt. allowed to stand for 12 hr. After removal of silica gel and solvent evapd, the residue was chromatographed on silica gel (*n*-hexane–EtOAc gradient) to afford **3** (29.8 mg, 13.5%) and **30** (39.3 mg, 17.8%), respectively.

Methylation of **29**. To a soln of **29** (3.1 g) in dry Me_2CO (40 ml) was added MeI (8.5 ml) and K_2CO_3 (18.8 g). Work-up as usual gave 3,5-dimethoxybibenzyl (**28**) (2.90 g). IR ν_{max}^{neat} cm^{-1}: 2925, 2825, 1600, 1460, 1425, 1195, 1145, 1055, 820, 690. ^{1}H NMR (90 MHz): δ 2.83 (4H, *m*), 3.50 (6H, *s*), 6.27 (3H, *s*), 7.13 (5H, *m*), ^{13}C NMR (22.5 MHz): 37.6, 38.2 (each *t*), 55.2 (*q*), 98.0, 106.6, 125.9, 128.3, 128.4 (each *d*), 141.7, 144.1, 160.8 (each *s*). HRMS: found: 242.1307, $C_{16}H_{18}O_2$ requires 242.1307; EIMS *m/z* (rel. int.): 242 (100), 227 (5), 165 (9), 152 (25), 151 (67), 91 (43).

Bromination of **28** *with N-bromosuccinimide (NBS).* To a soln of **28** (2.514 g) in dry DMF (10 ml) was added NBS (1.85 g). The resultant soln was stirred for 12 hr and poured into ice-cold H_2O and extd with CH_2Cl_2. The ext. was dried over $MgSO_4$ and evapd *in vacuo* to give an oil (2.85 g), which was chromatographed on silica gel (*n*-hexane–EtOAc gradient) to afford 2-bromo-3,5-dimethoxybibenzyl (**38**) (2.651 g, 79.5%) and 2,6-dibromo-3,5-dimethoxybibenzyl (**39**) (250 mg, 6.0%).

Compound **38**. UV λ_{max}^{MeOH} nm (log ε): 210 (4.49), 282.5 (3.27). IR ν_{max}^{KBr} cm^{-1}: 3025, 2925, 2825, 1590, 1450, 1320, 1195, 1160, 1085, 1065, 1020, 820, 690. ^{1}H NMR: δ 2.88, 3.00 (4H, *m*), 3.71 (each 3H, *s*), 6.31, 6.34 (each 1H, *d*, $J = 2.7$ Hz), 7.18–7.29 (5H, *m*). ^{13}C NMR: δ 35.9, 38.8 (each *t*), 55.2, 56.1 (*q*), 97.6 (*d*), 104.6 (*s*), 106.8, 125.8, 128.2, 128.4 (each *d*), 141.3, 142.7, 156.7, 159.4 (each *s*); EIMS *m/z* (rel. int.): 322 ($[M]^+ + 2$) (33), 320 $[M]^+$ (33), 242 (17), 241 (100), 231 (31), 229 (34), 135 (22), 91 (43). Anal. Calcd for $C_{16}H_{17}O_2Br$; C, 59.82; H, 5.33; found: C, 55.66; H, 5.28.

Compound **39**. UV λ_{max}^{MeOH} nm (log ε): 212.5 (4.50), 272.5 (3.59), 292.5 (3.61). IR ν_{max}^{KBr} cm^{-1}: 2925, 1572, 1450, 1425, 1325, 1205, 1075, 1040, 940, 790, 740, 685. ^{1}H NMR: 2.82 (2H, *m*), 3.33 (2H, *m*), 3.90 (3H, *s*), 6.43 (1H, *s*), 7.22–7.36 (5H, *m*). ^{13}C NMR: 34.1, 39.7 (*t*), 56.6 (*q*), 95.4 (*d*), 105.5 (*s*), 126.1, 128.4 (each *d*), 141.5, 142.0, 156.0 (*s*). EIMS *m/z* (rel. int.): 402 ($[M]^+ + 4$) (17), 400 ($[M]^+ + 2$) (32), 398 $[M]^+$ (17), 318 (22), 316 (19), 311 (10), 309 (21), 307 (11), 241 (17), 240 (100), 239 (14), 222 (11), 215 (13), 213 (12), 91 (37). Anal. Calcd for $C_{16}H_{16}O_2Br_2$; C, 48.03; H, 4.03; found: C, 48.44, H, 4.21.

Reaction of **38** *with* n-*butyl lithium and 2,2-dimethylallylbromide.* To a soln of **38** (300 mg) in dry Et_2O (10 ml) was added 1.6 M BuLi soln (0.8 ml). The resultant soln was refluxed under Ar for 1 hr, and then 2,2-dimethylallylbromide (150 mg) in dry Et_2O (2 ml) added dropwise for 10 min. After stirring for 1 hr at 40°, the reaction mixt. was poured into ice-cold H_2O and extracted with EtOAc. The extract was washed with H_2O, dried over $MgSO_4$. Evapn of solvent gave an oil which was chromatographed on silica gel (C_6H_6–EtOAc, 3:7) to afford **4** (168 mg, 58.1%) and **28** (78 mg, 38%).

Reaction of **38** *with* BuLi *and geranylbromide.* To a soln of **38** (350 mg) in dry Et_2O (10 ml) was added 1.6 ml BuLi (1 ml). The resulting mixt. was stirred under Ar for 1 hr at room temp. and then geranylbromide (300 mg) in dry Et_2O (5 ml) was added dropwise for 10 min. The reaction mixt. was refluxed for 1 hr with stirring. Treatment of the mixt. in the same manner described above gave a crude oil which was chromatographed on silica gel (C_6H_6–EtOAc, 3:7) to afford **6** (241 mg, 58.5%) and **28** (74 mg, 28.1%).

Reaction of **28** *with* BuLi *and geranylbromide.* To a soln of **28** (200 mg) in dry Et_2O (20 ml) was added 1.6 M BuLi soln (0.5 ml). The mixt. was refluxed under Ar for 5 hr and a soln of geranylbromide (215 mg) in dry Et_2O (2 ml) was added dropwise for 3 min. The crude oil after treatment of the mixt. in the same manner as described above, was purified by prep. TLC (C_6H_6–*n*-hexane, 1:1) to give 3,5-dimethoxy-4-geranyl bibenzyl (**44**) 135 mg, 43.3%) and starting material (**28**) (85 mg, 42.5%).

Compound **44**. UV λ_{max}^{MeOH} nm (log ε): 217.5 (4.49), 271 (3.14). IR ν_{max}^{neat} cm^{-1}: 2920, 1602, 1585, 1450, 1415, 1160, 1110. ^{1}H NMR: δ 1.57, 1.64, 1.75 (each 3H, *s*), 1.94, 2.04 (each 2H, *m*), 2.89 (2H, *m*), 3.32 (2H, *d*), 3.76 (6H, *s*), 5.07 (1H, *t*, $J = 5.6$ Hz), 5.19 (1H, *t*, $J = 7.1$ Hz), 6.35 (2H, *s*), 7.17–7.30 (5H, *m*). ^{13}C NMR: δ 16.0, 17.6 (*q*), 22.0 (*t*), 25.7 (*q*), 26.8, 38.0, 38.5, 39.9 (each *t*), 55.9 (*q*), 104.3 (*t*), 116.1 (*s*), 123.1, 124.6, 125.9, 128.3, 128.5 (each *d*), 131.0, 134.3, 140.6, 141.9, 158.0 (each *s*). HRMS: found: 378.2553, $C_{26}H_{34}O_2$ requires 378.2559; EIMS *m/z* (rel. int.): 378 $[M]^+$ (11), 309 (26), 256 (19), 255 (100), 105 (18), 91 (12).

Methylation of synthetic **3**. Compound **3** (40 mg) was methylated with MeI (1 ml) to give **4** (37 mg, 88.3%).

Methylation of synthetic **7**. Compound **7** (38 mg) was methylated with MeI (0.8 ml) to give **6** (31 mg, 78.5%).

Methylation of **31**. Compound **31** (60 mg) was treated in the same manner as described above to afford **44** (58 mg, 93.1%).

Reaction of 3,5-*dimethoxy*-2-(3-*methyl*-2-*butenyl*)*bibenzyl* (**4**) *with* BBr_3. To a soln of **4** (250 mg) in dry CH_2Cl_2 (10 ml) was

added BBr_3 (0.25 ml) at $-78°$ with stirring. After stirring for 2 hr at $-10°$ to 0°, Et_3N (1 ml) was added to the reaction mixt. The resultant soln was poured into ice-cold H_2O and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried over $MgSO_4$, and concd *in vacuo* to give an oil (298 mg) which was chromatographed on silica gel (EtOAc–*n*-hexane, 1:9) to furnish 3,5-dihydroxy-2-(3-methyl-2-butenyl)bibenzyl (**1**) (45 mg, 19.8%) and 2,2-dimethyl-7-hydroxy-5-(2-phenylethyl) chroman (**40**) (152 mg, 67.0%).

Compound **40**. IR ν_{max}^{neat} cm^{-1}: 3375, 2975, 2925, 1620, 1610, 1595, 1490, 1450, 1340, 1320, 1265, 1150, 1130, 1110, 1035, 1020, 1000. ^1H NMR: δ 1.25 (6H, *s*), 1.70, 2.47 (each 2H, *t*, $J = 6.8$ Hz), 2.75 (4H, *m*), 6.10 (1H, *br s*, OH), 6.23, 6.31 (each 1H, *d*, $J = 2.4$ Hz), 7.12–7.26 (5H, *m*). ^{13}C NMR: δ 19.2 (*t*), 26.5 (*q*), 32.9 (*t*), 34.5, 36.4 (each *t*), 73.8 (*s*), 102.0, 108.1 (each *d*), 111.5 (*s*), 128.2, 128.3 (each *d*), 141.7, 141.8 (each *s*). HRMS: found: 282.1613, $C_{19}H_{22}O_2$ 282.1607; EIMS *m/z* (rel. int.): 282 $[M]^+$ (85), 227 (100), 225 (30), 191 (23), 149 (16), 123 (13), 91 (43).

Reaction of **4** *with sodium thioethoxide* (EtSNa). To a suspension of 60% NaH (52 mg) in dry DMF (1 ml) was added a soln of EtSH (92 mg) in dry DMF (2 ml) under Ar at room temp. with stirring. After stirring for 5 min, a soln of **4** (77 mg) in dry DMF (1 ml) was added and the mixt. refluxed for 3 hr at 170–180°. The reaction mixt. was poured into ice-H_2O and extd with Et_2O. The Et_2O layer was successively washed with 1 M HCl, H_2O and dried over $MgSO_4$ and concd *in vacuo* to give a residue (87 mg), which was subjected to prep. TLC (*n*-hexane–EtOAc, 4:1) to give two natural bibenzyls (**2**) (18 mg, 28.1%) and (**3**) (22 mg, 34.4%), respectively.

Reaction of **3** *with* EtSNa. To a suspension of 60% NaH (165 mg) in dry hexamethylphosphoramide (HMPA) (2 ml) was added a soln of EtSH (0.4 ml) in HMPA (2 ml) under Ar at room temp. After stirring for 10 min, a soln of **3** (98 mg) in 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 give a residue (238 mg) which was chromatographed on silica gel (*n*-hexane–EtOAc gradient) to afford **1** (37 mg, 52.8%) and 3,5-dihydroxybibenzyl (**41**) (12 mg, 17.7%).

Compound **41**. IR ν_{max}^{neat} cm^{-1}: 3350, 1295, 1600, 1450, 1320, 1300, 1140, 965. ^1H NMR: δ 2.71 (4H, *m*), 6.16 (1H, *br s*), 6.22 (2H, *br s*), 7.06–7.22 (5H, *m*). ^{13}C NMR: δ 37.1, 37.5 (each *t*), 100.7, 108.4, 125.9, 128.3, 128.4 (each *d*), 141.5, 145.1, 156.2 (each *s*). EIMS *m/z* (rel. int.): 214 $[M]^+$ (75), 123 (52), 91 (100).

Reaction of 3,5-*dihydroxybibenzyl* (**41**) *with* NaOMe *and* 2,2-*dimethylallylbromide*. To a soln of **41** (1.6 g), which was obtained from **26** (1.75 g) by hydrogenation, in dry MeOH (15 ml) was added 28% NaOMe–MeOH soln (1.5 ml). The resultant soln was stirred for 30 min at room temp. and evapd to dryness *in vacuo* to give brown crystals which were suspended in dry C_6H_6 (20 ml) and evapd again to remove traces of H_2O. The residue was again suspended in dry C_6H_6 (30 ml) to which was added 2,2-dimethylallylbromide (1.23 g). The mixt. was vigorously stirred at 50–55° for 30 min and then poured into ice-H_2O and extd with EtOAc. The EtOAc layer was washed successively with 1 M HCl, H_2O, dried over $MgSO_4$ and evapd *in vacuo* to give an oil (1.75 g) which was chromatographed on silica gel (*n*-hexane–EtOAc gradient) to afford 2,2-dimethyl-5-hydroxy-7-(2-phenylethyl)chroman (**42**) (363 mg, 17.2%), its isomer (**40**) (377 mg, 17.9%), the natural bibenzyl (**1**) (456 mg, 21.6%) and starting bibenzyl (**41**) (486 mg, 30.4%), respectively.

Reaction of **7** *with* EtSNa. To a suspension of 60% NaH (61 mg) in dry HMPA (3 ml) was added a solution of EtSH (0.08 ml) in HMPA (1 ml) under Ar at room temp. with stirring. After stirring for 10 min, a soln of **7** (63.8 mg) in HMPA (3 ml) was added. The reaction mixt. was treated in the same manner as described above to give a residue (278 mg) which was chromatographed on silica gel (*n*-hexane–EtOAc gradient) to yield the natural 2-geranyl-3,5-dihydroxybibenzyl (**5**) (15.1 mg, 24.6%) and **41** (7.1 mg, 18.9%).

Synthesis of **13**. To compound **3** (44.6 mg) in dry C_6H_6 (25 ml) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (50 mg) and the mixt. refluxed for 45 min. Excess DDQ was filtered off and the filtrate evapd *in vacuo* to give an oil which was purified by prep. TLC (*n*-hexane–EtOAc, 10:1) to afford the natural chromene (**13**) (16.1 mg, 36.3%).

Synthesis of **15**. Compound **30** (52.5 mg) was treated in the same manner as described above to afford a residue (38.0 mg) which was purified by prep. TLC to yield the monoMe ether (**15**) (32.5 mg, 62.3%) of the natural chromene (**14**).

Synthesis of **19**. Compound **7** (91 mg) was treated in the same manner as described above to give a residue (152 mg) which was purified by prep. TLC (*n*-hexane–EtOAc, 4:1) to yield the monoMe ether (**19**) (66 mg, 72.9%) of the natural chromene (**18**). Synthetic **19**. $[\alpha]_D \pm 0°$ ($CHCl_3$; *c* 2.07). All mps, UV, IR, ^1H and ^{13}C NMR, HRMS and EIMS of the synthetic natural products and their derivatives were identical to those of the natural bibenzyls and their derivatives. All the structures of the intermediates and byproducts during the course of the synthesis of the natural bibenzyls and their derivatives were established by analysis of their spectral data and elemental analyses.

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