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BIBENZYL DERIVATIVES FROM THE AUSTRALIAN LIVERWORT *FRULLANIA FALCILOBA**

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Key Word Index—*Frullania falciloba*; Jungermanniales; Hepaticae; sesquiterpenoids; bibenzyls; 3,4-methylenedioxy-3'-methoxybibenzyl; 3-hydroxy-4,3'-dimethoxybibenzyl; 3-[4'-methoxybenzyl]-5,6-dimethoxyphthalide; chemosystematics.

Abstract—Three new bibenzyl derivatives were isolated from the Australian liverwort *Frullania falciloba* and their structures were established to be 3,4-methylenedioxy-3'-methoxybibenzyl, 3-hydroxy-4,3'-dimethoxybibenzyl and 3-[4'-methoxybenzyl]-5,6-dimethoxyphthalide by spectral methods and synthesis. The present species belongs to the bibenzyl-type, Chemotype III, in the Frullaniaceae.

INTRODUCTION

Frullania species belong to the Jungermanniales and are rich sources of sesquiterpene lactones, which cause intense allergenic contact dermatitis and simple bibenzyl derivatives [2–4]. In a previous paper [4] we reported the distribution of terpenoids and bibenzyl derivatives in 25 *Frullania* species. The Australian *F. falciloba* produces sesquiterpenoids [5]. Further investigation of the chemical constituents of *F. falciloba* resulted in the isolation of three new bibenzyl derivatives. In this paper, we report the chemical structures of the new bibenzyls and discuss the chemosystematics of *F. falciloba*.

RESULTS AND DISCUSSION

The ether extract of dried *F. falciloba* was examined by TLC, GC and GC/MS. α-Pinene, β-caryophyllene, β-barbatene, bicyclogermacrene [5] and 3,4'-dimethoxybibenzyl (1) [5, 6], three bibenzyl derivatives [M^+ 256, 258 and 314], and campesterol, stigmasterol and sitosterol were detected. Bicyclogermacrene and bibenzyls were the major components on the gas chromatogram. The remaining material was chromatographed on silica gel to give three new bibenzyl derivatives (2–4).

The spectral data of 2 indicated the presence of an aromatic ring (1610, 1587 cm^{-1}), a methoxy group (δ3.80, 3H, *s*), two benzylic methylenes (δ2.85, 4H, *s*) and a methylenedioxy group (δ5.91, 2H). The mass spectrum showed the intense fragments ions at *m/z* 135 and 121, indicating that the methoxyl and methylenedioxyl groups must be in different aryl residues. The 1,3,4- and 1',3'-substitution of the two benzene rings were established by analysis of 400 MHz ^1H NMR spectrum including spin decoupling examination (see Experimental). The arrangement of the functional groups on the benzene rings was confirmed by the presence of NOEs between: (i) the benzylic methylene and H-2, H-6, H-2' and H-6' and (ii) the methoxyl group at C-3' and H-2', and H-4' (Fig. 1). Thus, the structure of 2 was assigned as 3,4-methylenedioxy-3'-methoxybibenzyl. This structure was further confirmed by the synthesis of 2 (Scheme 1). 3,4-Methylenedioxybenzyl bromide (6) prepared from 3,4-methylenedioxybenzyl alcohol (5) was treated by triphenylphosphine in the presence of dimethylformamide (DMF) to give a phosphonium bromide (7). Wittig condensation of 7 with 3-methoxybenzaldehyde (8) gave a stilbene mixture (9) which was hydrogenated in the presence of PtO_2 to afford a dihydrostilbene whose physical and spectral data were identical to those of the natural bibenzyl (2).

The second bibenzyl (3) possessed a hydroxyl group (3450 cm^{-1}), two methoxyl group (δ3.79, 3.86, each 3H, *s*) and two benzylic methylenes (δ2.84, 4H, *s*). The presence of a hydroxymethoxybenzyl and a methoxybenzyl groups in different aryl residues was supported by the strong MS fragment ions at *m/z* 137 and 121. The 1,3,4- and 1',3'-substitution of the two benzene rings were confirmed by analysis of the 400 MHz ^1H NMR spectrum (see Experimental). The arrangement of two methoxyl and one hydroxyl groups was established by NOE difference spectra of 3. Compound 3 showed NOEs between: (i) the benzyl methylenes and H-2, H-6, H-2', and H-6', (ii) the methoxyl group at C-4 and H-5, and (iii) the methoxyl group at C-3' and H-2', and H-4'. On the basis of the above spectral data, the structure of 3 was established to be 3-hydroxy-4,3'-dimethoxybibenzyl.

The ^1H NMR spectrum of the third compound (4) showed the presence of three methoxyl groups (δ3.57, 3.72, 3.80, each 3H, *s*), four protons on the *para* substituted benzene ring (δ6.71, 7.03, each 2H, *d*, J = 8.6 Hz), two isolated protons (δ6.11, 6.29 each 1H, *s*) on the benzene ring and a benzyl methylene (δ2.97, 3.04, each, 1H, *dd*, J = 14.3, 6.2 Hz) coupled with a proton (δ5.35, 1H, *t*, J = 6.2 Hz) on a carbon bearing an ether oxygen. The MS spectrum indicated strong fragment ions at *m/z* 193 $[M-121]^+$ and 121 indicating the presence of a methoxybenzyl group. The presence of a phthalide moiety was

*Part 22 in the series "Chemosystematics of Bryophytes". For Part 21, see ref. [1].

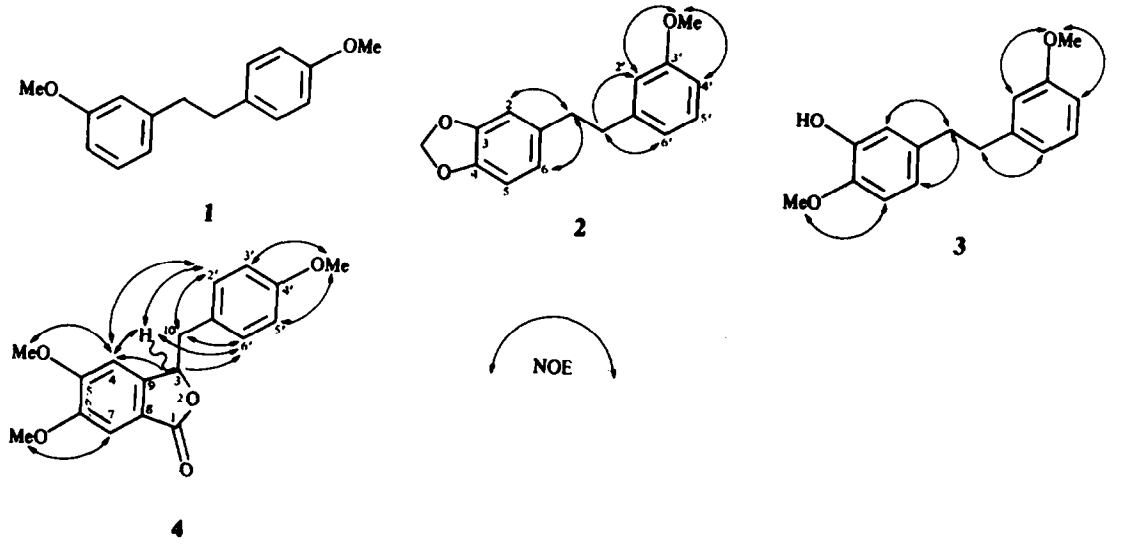
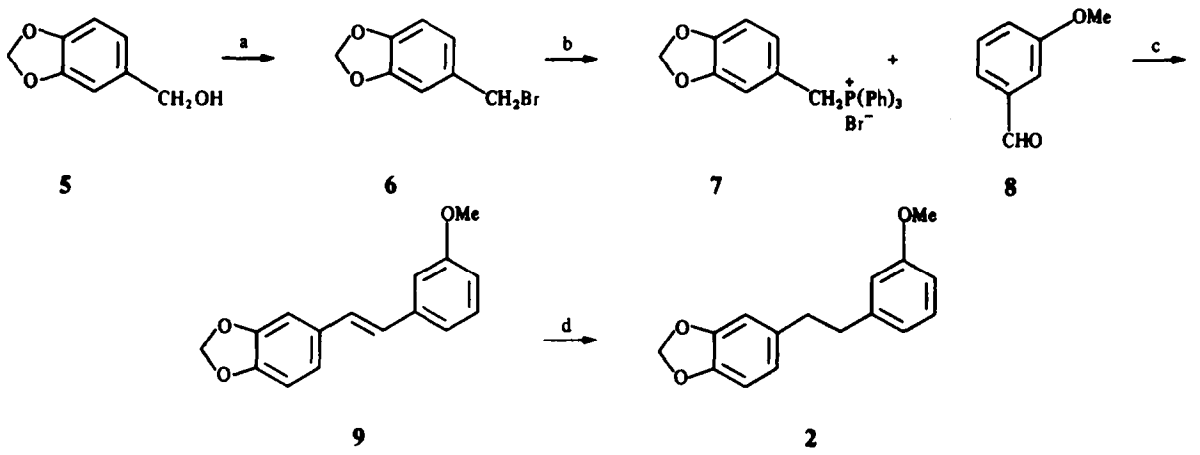


Fig. 1.



a: 47% HBr–C_6H_6 b: Ph_3P–DMF c: NaOEt–EtOH d: H_2–PtO_2–EtOAc

Scheme 1.

supported by the strong IR band at 1750 cm^{-1} [6] and ^{13}C NMR signals at δ_C 168.2 (*s*) and 80.1 (*d*). From the above evidence coupled with the molecular formula, the structure of **4** might be represented by 3-[4′-methoxybenzyl]-dimethoxyphthalide. The arrangement of the functional groups on the two benzene rings were established by the presence of NOEs between: (i) the methoxyl group at C-5 and H-4, (ii) the methoxyl group at C-6 and H-7, (iii) H-3 and H-4, (iv) H-3 and H-2′,6′, (v) H-10 and H-2′,6′ (vi) H-4 and H-2′,6′,10′ and (vii) the methoxyl group at C-4′ and H-3′,5′. Thus, the structure of the new phthalide was established as 3-[4′-methoxybenzyl]-5,6-dimethoxyphthalide (**4**). Similar 3-substituted phthalides have been isolated from the liverworts *Radula complanata* [6] and *Balantiopsis rosea* [7].

Frullania species can be divided into five chemotypes: (I) the sesquiterpene–bibenzyl type, (II) the sesquiterpene lactone type, (III) the bibenzyl type, (IV) the monoterpene type and (V) the cyclocolorenone type [4]. In the present species bibenzyl derivatives were produced as major components and no sesquiterpene lactones were detected. Thus, *F. falciloba* belongs to chemotype III.

EXPERIMENTAL

TLC, GC and GC/MS were carried out as previously reported [8]. The solvents used for spectral determination were: TMS–$CDCl_3$ [^1H NMR (400 MHz) and ^{13}C NMR (100 MHz)]; EtOH (UV); $CHCl_3$ (IR).

Plant material. Frullania falciloba (Hook. & Tayl.) Lehm. identified by Professor W. B. Schofield and Dr. S. Hattori was deposited at the Herbarium of the Institute of Pharmacognosy, Tokushima Bunri University.

Extraction and isolation. Dried and ground *F. falciloba* (28.8 g) which was collected in Blue Mountain, Australia in August 1981, was extracted with Et_2O. Removal of the solvent gave a green oil

(1.22 g). A small amount of the extract was checked by TLC, GC and GC/MS equipped with a computer. The components obtained by GC/MS were identified by direct comparison of the MS spectra with those of authentic samples. The presence of α-pinene, β-caryophyllene, β-barbatene, bicyclogermacrene, 3,4'-dimethoxybibenzyl (1), three bibenzyls [M^+ 256 (135), 258 (137) and 314 (193)] corresponding to the compounds (2–4), campesterol, stigmasterol and sitosterol were detected [5]. The GC/MS also showed the presence of unidentified sesquiterpenoids [M^+ 204 (69), 204 (121), 204 (93), and 204 (69)] and diterpenoids [M^+ 272 (133), 272 (135), 272 (135), 274 (137), 274 (124), 272 (121), 304 (95), 304 (147) and 304 (137)]. The major components appeared on GC were bicyclogermacrene and three bibenzyls (2–4). The remaining extract was chromatographed on silica gel using an *n*-hexane–EtOAc gradient to give 8 fractions. From fraction 3 (15% EtOAc) 3,4-methylenedioxy-3'-methoxybibenzyl (2) (70 mg) was obtained. Mp 49–50°; $C_{16}H_{16}O_3$; UV λ_{max} nm (log ε): 208 (4.15), 272 (3.65), 278 (3.72); IR ν_{max} cm^{-1}: 3020, 1610, 1601, 1587, 1503, 1490, 1440, 1240, 1150, 1040, 937, 690; ^{1}H NMR: δ2.85 (4H, *s*), 3.80 (3H, *s*), 5.91 (2H, *s*), 6.62 (1H, *dd*, *J* = 7.8, 2.0 Hz, H-6), 6.68 (1H, *d*, *J* = 2.0, H-2), 6.72 (1H, *t*, *J* = 2.0 Hz, H-2'), 6.72 (1H, *d*, *J* = 7.8 Hz, H-5), 6.74 (1H, *dd*, *J* = 7.5, 2.0 Hz, H-4'), 6.77 (1H, *dd*, *J* = 7.5, 2.0 Hz, H-6'), 7.19 (1H, *t*, *J* = 7.5 Hz, H-5'); MS *m/z* (rel. int.): 256 [M]$^+$ (29), 135 (100), 121 (37), whose physical and spectral data were identical to those of the synthetic 3,4-methylenedioxy-3'-methoxybibenzyl. Fraction 5 (20% EtOAc) was recrystallized from *n*-hexane to give 3-hydroxy-4,3'-dimethoxybibenzyl (6 mg) (3): mp 81–82°; $C_{16}H_{18}O_3$; UV λ_{max} nm (log ε): 207.5 (4.35), 218 (4.31), 270 (3.81), 276.5 (3.87); IR ν_{max} cm^{-1}: 3540, 1610, 1594, 1586, 1512, 1490, 1466, 1453, 1440, 1272, 1150, 1125, 1030, 952, 870, 690; ^{1}H NMR: δ2.84 (4H, *s*), 3.79, 3.86 (each, 3H, *s*), 5.56 (1H, *s*, OH disappeared on addition of D_2O), 6.65 (1H, *dd*, *J* = 8.2, 2.1, H-6), 6.73 (1H, *br t*, *J* = 1.0, H-2'), 6.74 (1H, *ddd*, *J* = 7.5, 1.0, 1.0 Hz, H-4'), 6.76 (1H, *d*, *J* = 8.2 Hz, H-5), 6.78 (1H, *ddd*, *J* = 7.5, 1.0, 1.0 Hz, H-6'), 6.80 (1H, *d*, *J* = 2.1 Hz, H-2), 7.19 (1H, *d*, *J* = 7.5, 1.5 Hz, H-4'). The signals of 6.74 and 6.78 were overlapped with those of H-2, H-5 and H-2'. MS *m/z* (rel. int.): 258 [M]$^+$ (17), 137 (100), 122 (6), 121 (4). From fraction 6 (30% EtOAc) (119 mg) was rechromatographed on silica gel using C_6H_6–EtOAc (98:2) to give 3-[4'-methoxybenzyl]-5,6-dimethoxyphthalide (4) (57 mg): mp 78–80°; $C_{18}H_{18}O_5$; UV λ_{max} nm (log ε): 221 (4.40), 253 (4.11), 280 (3.71), 287 (3.67); IR ν_{max} cm^{-1}: 2950, 1750 (γ-lactone), 1612, 1602, 1515, 1245, 1157, 1034, 838, 818, 685; ^{1}H NMR: δ2.97, 3.04 (each 1H, *dd*, *J* = 14.3, 6.2 Hz, H-10), 3.67 (3H, *s*, OMe-C_4), 3.72 (3H, *s*, OMe-C_5), 3.80 (3H, *s*, OMe-C_6), 5.35 (1H, *t*, *J* = 6.2 Hz, H-3), 6.11 (1H, *s*, H-4), 6.29 (1H, *s*, H-7), 6.71 (2H, *d*, *J* = 8.6 Hz, H-3',5'), 7.03 (2H, *d*, *J* = 8.6 Hz, H-2', H-6'); ^{13}C NMR: 40.0 (CH_2, *t*, C-10), 55.2 (OMe-C_4, *q*), 55.9 (OMe-C_5,C_6, *q*), 80.1 (CH, *d*, C-3), 98.2, 98.9 (Ph-CH, *d*, C_4, C_7), 107.0, 127.2, 154.3, 158.3, 159.6, 166.5 (each Ph-C, *s*), 113.8 (Ph-CH × 2, *d*, C_3', C_5'), 130.8 (Ph-CH × 2, *d*, C_2', C_6'), 168.2 (C=O, *s*); MS *m/z* (rel. int.): 314 [M]$^+$ (9), 193 [M − 121]$^+$ (100), 121 (90).

Synthesis of 2. To 3,4-methylenedioxybenzyl alcohol (5) (3.0 g) in C_6H_6 was added 47% HBr (2.8 ml) and stirred at room temp. for 2 hr. The organic layer was separated and the solvent removed to give 3,4-methylenedioxybenzyl bromide (6) (4.0 g): ^{1}H NMR: δ4.40 (2H, *s*), 5.90 (2H, *s*), 6.50–6.96 (3H, *m*). 6 (3.2 g) in DMF plus triphenylphosphine (5.8 g) was refluxed at 155° for 3 hr. Removal of excess DMF gave a phosphonium salt (7) (2.5 g): ^{1}H NMR: δ5.18 (2H, *d*, *J* = 14 Hz, CH_2-P), 5.76 (2H, *s*), 6.46 (3H, *br s*), 7.50–7.75 (15H, complex *m*). A mixture of the phosphonium salt (7) (2.5 g) and *m*-methoxybenzaldehyde (8) (1.0 g) was refluxed with NaOEt in EtOH (40 ml) at 93° for 9 hr to give a stilbene mixture (1.5 g), a small amount of which was purified by prep. TLC (C_6H_6–EtOAc 4:1) to give *trans*-stilbene derivative (9) (80 mg): mp 82–83°; UV λ_{max} nm (log ε): 215 (4.42), 243 (4.06), 290 (4.20), 299 (4.31), 329 (4.49); IR ν_{max} cm^{-1}: 3025, 2950, 2900, 2850, 2780, 1610, 1600, 1580, 1510, 1500, 1470, 1450, 965, 930; ^{1}H NMR: δ3.80 (3H, *s*), 5.86 (2H, *s*), 6.56–7.03 (9H, *m*); MS *m/z* (rel. int.): 255 [M + 1]$^+$ (16), 254 [M]$^+$ (100), 165 (10), 153 (14), 152 (18). Compound 9 (60 mg) in EtOAc (5 ml) was hydrogenated in the presence of PtO_2 (30 mg). The usual work up gave 3,4-methylenedioxy-3'-methoxybibenzyl (2) (27 mg) whose spectral and physical data were in good agreement with those of the natural bibenzyl (2).

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