# A New Lignan from *Phyllanthus virgatus*

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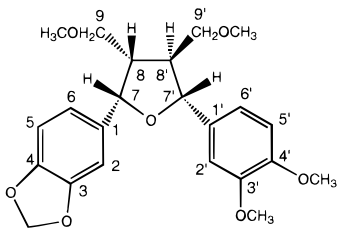
A new lignan, (−)-7,8-*cis*-8,8′-*trans*-7′,8′-*trans*-7-(3,4-(methylenedioxy)phenyl)-7′-(3′,4′-dimethoxyphenyl)-8,8′-bis(methoxymethyl)tetrahydrofuran, named virgatusin (**1**), was isolated from the EtOH extract of the whole herb of *Phyllanthus virgatus*, together with seven known lignans and indole-3-carboxylic acid.

On the basis of the reputation of *Phyllanthus amarus* Forst. f. as a herbal drug with liver−protecting qualities,[1] we initiated a series of studies to investigate the bioactive constituents of the genus *Phyllanthus* (Euphorbiaceae). Previously, we reported the isolation of a new lignan, isolintetralin, from *Phyllanthus niruri* L.[2] In the present investigation, the constituents of *Phyllanthus virgatus* Forst. f. were examined. Chromatographic separation of an EtOH extract of whole plants of *P. virgatus* resulted in the isolation of a new tetrahydrofuran lignan, virgatusin (**1**), and a further eight compounds of known structure, of which five—hinokinin, hypophyllanthin, isolintetralin, niranthin, and nirtetralin—were identified by spectral analysis and by direct comparison with authentic samples.[2] Indole-3-carboxylic acid,[3] (+)-8-(3,4-(methylenedioxy)benzyl)-8′-(3′,4′-dimethoxybenzyl)butyrolactone,[4] and phyltetralin[5] were identified by comparison of their spectral data with those in the literature. The structural establishment of compound **1** is described as follows.




**1**

Compound **1** was obtained as a viscous oil, $[\alpha]^{25}_{D}$ −12.7°. The HRMS showed a molecular ion peak at *m*/*z* 416.1835 corresponding to $C_{23}H_{28}O_7$. Analysis of its $^1$H-NMR spectral data indicated that compound **1** belongs to the tetrahydrofuran class of lignans, and it displayed two aliphatic methoxyl groups at $\delta$ 3.07 and 3.34, two aromatic methoxyl groups at $\delta$ 3.87 and 3.90, and one methylenedioxy group at $\delta$ 5.93. Additionally, a pair of multiplets at $\delta$ 2.33 and 2.58, which exhibited a HETCOR correlation with the carbon signals at $\delta$ 50.87 and 46.54, appeared as the typical resonances for the methine protons at C-8′ and C-8, respectively. The $^1$H-NMR signals at $\delta$ 2.96 and 3.50 (2H each, m) were assigned to the methylene protons at C-9 and C-9′, respectively. A pair of doublets at $\delta$ 4.70 ($J$ = 7.8 Hz) and 5.04 ($J$ = 7.1 Hz), showing a HETCOR correlation with the carbon signals at $\delta$ 82.57 and 81.42, were attributed to the oxymethine protons at C-7′ and C-7, respectively.[6,7] The remaining signals for six aromatic protons indicated the presence of both a piperonyl system [$\delta$ 6.80 (1H, d, $J$ = 8.4 Hz, H-5), 6.84 (1H, dd, $J$ = 1.5, 8.4 Hz, H-6), and 6.91 (1H, d, $J$ = 1.5 Hz, H-2)] and a veratryl system [$\delta$ 6.85 (1H, d, $J$ = 8.4 Hz, H-5′), 7.02 (1H, dd, $J$ = 1.7, 8.4 Hz, H-6′), and 7.05 (1H, d, $J$ = 1.7 Hz, H-2′)]. After irradiation of one aromatic methoxyl signal at $\delta$ 3.87 and another at $\delta$ 3.90, NOE effects were observed at the aromatic proton signals at $\delta$ 6.85 (H-5′) and 7.05 (H-2′), respectively, suggesting the placement of the aromatic methoxyl groups at C-4′ and C-3′. Consequently, the methylenedioxy group was assigned at C-3 and C-4. Furthermore, on irradiation of the oxymethine signal at $\delta$ 5.04 (H-7), the NOE effects were observed at $\delta$ 4.70 (H-7′), 2.58 (H-8), 6.84 (H-6), and 6.91 (H-2), respectively, which suggested a cis configuration between H-7 and H-7′ as well as between H-7 and H-8, and the connection of the benzene ring bearing the methylenedioxy group with C-7. In addition, on irradiation of the oxymethine signal at $\delta$ 4.70 (H-7′), the NOE effect was only observed at $\delta$ 3.50 (H-9′), indicating the trans configuration of H-7′ and H-8′. On the basis of the above evidence, compound **1** was therefore determined to be (−)-7,8-*cis*-8,8′-*trans*-7′,8′-*trans*-7-(3,4-(methylenedioxy)phenyl)-7′-(3′,4′-dimethoxyphenyl)-8,8′-bis(methoxymethyl)tetrahydrofuran and has been accorded the trivial name virgatusin.

## Experimental Section

**General Experimental Procedures.** Optical rotations were measured on a JASCO DIP-140 digital polarimeter. UV spectra were recorded on a JASCO Model 7800 UV/vis spectrometer. IR spectra were taken on a Bio-Rad FTS-7 spectrometer. EIMS were obtained using a JEOL JMS-D100 spectrometer. $^1$H- and $^{13}$C-NMR spectra were measured with a Varian Gemini-200 spectrometer.

**Plant Material.** The whole plants of *P. virgatus* Forst. f. were collected at Pintoung, Taiwan, in July 1993. A voucher specimen was deposited in the herbarium of the National Research Institute of Chinese Medicine.

**Extraction and Isolation.** The air-dried whole plants of *P. virgatus* (3.0 kg) were extracted with 95% EtOH. After evaporation of the solvent, the residue was chromatographed on a Si gel column (7 × 40 cm, 70−230 mesh) and eluted with a gradient solvent of *n*-hex-

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ane−EtOAc (10:1 → 0:1) and $CH_2Cl_2$−MeOH (10:1 → 0:1) to yield 38 fractions. Fractions 8−26 were eluted with *n*-hexane−EtOAc (5:1). Of these fractions 14−22 were found to contain isolintetralin (22 mg), hinokinin (56 mg), nirtetralin (67 mg), niranthin (37 mg), and hypophyllanthin (63 mg) on the basis of direct comparison with authentic samples isolated from *P. niruri*.[2] Fraction 24 was rechromatographed on a Si gel column (5.5 × 50 cm, 230−400 mesh) and preparative TLC ($CH_2Cl_2$−*n*-hexane−$Me_2CO$, 18:6:1) to obtain phyltetralin (58 mg), virgatusin (**1**) (23 mg), and (+)-8-(3,4-methylenedioxy)benzyl)-8′-(3′,4′-dimethoxybenzyl)butyrolactone (37 mg). Fraction 27, eluted with EtOAc, was further purified through a Si gel column (5.5 × 50 cm, 230−400 mesh, $CH_2Cl_2$:MeOH, 15:1) and Sephadex LH-20 (3 × 45 cm, MeOH) to afford indole-3-carboxylic acid (17 mg).

**Virgatusin (1):** viscous oil; $[\alpha]^{25}_D$ −12.7° (*c* 0.5, $CH_2Cl_2$); UV ($CH_2Cl_2$) $\lambda_{max}$ (log $\epsilon$) 239 (4.99), 241 (5.00), 283 (5.07) nm; IR (dry film) $\nu_{max}$ 2923, 2875, 1607, 1491, 1443, 1257, 1237, 1134, 1033, 934, 810 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.33 (1H, m, H-8′), 2.58 (1H, m, H-8), 2.96 (2H, m, $H_2$-9), 3.07 (3H, s, OMe-9′), 3.34 (3H, s, OMe-9), 3.50 (2H, m, $H_2$-9′), 3.87 (3H, s, OMe-4′), 3.90 (3H, s, OMe-3′), 4.70 (1H, d, $J$ = 7.8 Hz, H-7′), 5.04 (1H, d, $J$ = 7.1 Hz, H-7), 5.93 (2H, s, O−$CH_2$−O), 6.80 (1H, d, $J$ = 8.4 Hz, H-5), 6.84 (1H, dd, $J$ = 1.5, 8.4 Hz, H-6), 6.85 (1H, d, $J$ = 8.4 Hz, H-5′), 6.91 (1H, d, $J$ = 1.5 Hz, H-2), 7.02 (1H, dd, $J$ = 1.7, 8.4 Hz, H-6′), 7.05 (1H, d, $J$ = 1.7 Hz, H-2′); $^{13}C$ NMR ($CDCl_3$) $\delta$ 46.54 (C-8), 50.87 (C-8′), 55.84, 55.89 (OMe-3′, OMe-4′), 58.63 (OMe-9), 59.03 (OMe-9′), 73.03 (C-9, C-9′), 81.42 (C-7), 82.57 (C-7′), 100.86 (O-$CH_2$-O), 107.04 (C-5′), 107.82 (C-5), 109.92 (C-2′), 110.94 (C-2), 118.74 (C-6′), 119.59 (C-6), 132.77, 134.06 (C-1, and C-1′), 146.52, 147.34, 148.49, and 148.91 (C-3, C-4, C-3′, and C-4′); EIMS (70 eV) $m/z$ $[M]^+$ 416 (100), 224 (31), 208 (53), 189 (90), 173 (56), 149 (25), 135 (15), 115 (35); HRMS $m/z$ $[M]^+$ 416.1835 (calcd for $C_{23}H_{28}O_7$, 416.1827).

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## References and Notes

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