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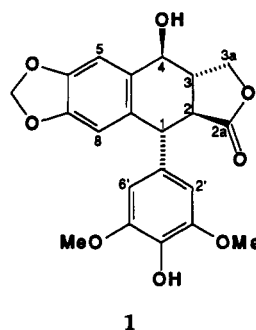
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A NEW PODOPHYLLOTOXIN-TYPE LIGNAN FROM
DYSOSMA VERSIPELLIS VAR. *TOMENTOSA*PEI-ZHONG YU,¹ LI-PING WANG,* and ZE-NAI CHEN

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ABSTRACT.—A new 1-aryltetralin lignan, 4'-demethylisopodophyllotoxin (**1**), and four known lignans were isolated from *Dysosma versipellis* var. *tomentosa*. Uv, ir, ms, cd, ¹H-nmr, ¹³C-nmr, and optical rotation evidence established its structure as (1*R*,2*S*,3*S*,4*S*)-6,7-methylenedioxy-1-(4'-hydroxy-3',5'-dimethoxyphenyl)-3-hydroxymethyl-tetrahydronaphthalene-2-carboxylic acid lactone. This lignan has not been encountered before in nature or prepared synthetically.

Many podophyllotoxin-type lignans have been isolated from podophyllin-bearing plants, including those in the *Podophyllum*, *Dysosma*, and *Diphyllia* genera. These lignans have aroused considerable interest because of their anti-tumor, antimetabolic, antiviral, and other bioactivities (1). *Dysosma* (*Podophyllum*) *versipellis* (Hance) M. Cheng var. *tomentosa* (Berberidaceae) is a traditional Chinese herb distributed in the Anhui Province of China; it has a satisfactory effect on the treatment of encephalitis B (2) and parotitis (3). Four known lignans, podophyllotoxone, isopicropodophyllone, dehydropodophyllotoxin, and podophyllotoxin, and a new lignan, 4'-demethylisopodophyllotoxin (**1**), which has a (2β,3α)-γ-lactone, have now been isolated from the root of the plant. Some lignans with (2α,3β)-, (2β,3β)-, and (2α,3α)-γ-lactones in the podophyllotoxin group (such as podophyllotoxin, picropodophyllotoxin, and isopicropodophyllone) have been isolated from the podophyllin-bearing plants, but a podophyllotoxin-type lignan with a (2β,3α)-γ-lactone has not been isolated before from nature. In this paper, we provide evidence for the structure of the new lignan **1**, which we named 4'-demethyl isopodophyllotoxin according to the suggestion of Schreier (4).



RESULTS AND DISCUSSION

The molecular formula of the lignan **1**, C₂₁H₂₀O₈, was determined by hirms. Compound **1** exhibited uv absorption maxima at λ 205, 240 sh, 284 nm (log ε 4.62, 3.95, 3.59) and major ir absorption bands at ν 3423 (OH), 1758 (γ-lactone), 1612, 1557, 1521, 1497 (aromatic ring), 932 (methylenedioxy), and 845 cm⁻¹ (1,2,3-trisubstituted aromatic ring), which were similar to those of 4'-demethylpodophyllotoxin (5), λ max 206, 240, 290 nm (log ε, 4.47, 3.80, 3.32); ν max 3480, 1763, 1620, 1490, 930 cm⁻¹. The ¹H-nmr spectrum of **1** displayed a signal for two methoxyls (3'-, 5'-OMe) at δ 3.82 (s, 6H). Its eims showed the presence of a 4'-hydroxy-3',5'-dimethoxyphenyl (*m/z* 154). Thus, **1** was indicated to be an isomer of 4'-demethylpodophyllotoxin; the four chiral carbons were assigned their stereochemistry according to the following spectral analysis.

The configuration of C-1 was established by the cd spectrum. Swan, Klyne

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and co-workers (6–8) studied the ORD and CD curves of 1-aryltetralin lignans. The general conclusion was that all 1- β -aryl compounds gave negative Cotton effects and all 1- α -aryl compounds gave positive Cotton effects between 290 and 280 nm. The CD curve of **1** gave positive Cotton effects at 287 nm, so the 1-aryl group was indicated as being in the α position.

The $^1\text{H-NMR}$ spectra of **1** and 4'-demethylpodophyllotoxin showed differences in the chemical shifts of H-8 and H-2', -6'. The signals of H-2', -6' (s, 2H) and H-8 of **1** were at δ 6.63 and δ 6.17, respectively, contrary to those of 4'-demethylpodophyllotoxin, which were at δ 6.44 (H-8) and 6.31 (H-2', -6') (5). The reported $^1\text{H-NMR}$ spectra of some 1-aryltetralin compounds (5, 9–12) showed that the chemical shift of H-2', -6' was more upfield than that of H-8 when H-1 and H-2 were in the *cis* position; conversely, the chemical shift of H-2', -6' was shown at lower field than that of H-8 when H-1 and H-2 were in the *trans* position. Thus, the H-2 of **1** was concluded to be in the α position, and the 2-carbonyl group was in the β position. The coupling constant of H-1 and H-2 (about 7.0 Hz) also established its configuration.

Chen *et al.* (10) have studied the MS of some epimers of podophyllotoxin and its derivatives and discovered that lignans with a 2,3-*cis*- γ -lactone gave a low abundance molecular ion peak and a high abundance peak corresponding to the ion losing H_2O and the γ -lactone ring ($[\text{M} - \text{H}_2\text{O} - \text{C}_4\text{H}_4\text{O}_2]^+$) through the retro-Diels-Alder fragmentation pattern; on the contrary, the lignans with a 2,3-*trans*- γ -lactone gave a high abundance molecular ion and other peaks were in low abundance. Because the molecular ion peak was a base peak, other peaks including the peak at m/z 298 corresponding to $[\text{M} - \text{H}_2\text{O} - \text{C}_4\text{H}_4\text{O}_2]^+$ were in low abundances in **1**. Thus, the H-3 was presumed to be in the β position. The CD curve of **1** gave a negative

Cotton effect at 219 nm and was different from that of podophyllotoxin, which gave a positive Cotton effect at 216 nm. The $^1\text{H-NMR}$ spectrum of **1** showed that the coupling constant of H-2 and H-3 was 9.4 Hz. These results indicated that **1** has a (2 β ,3 α)- γ -lactone.

The configuration of C-4 was determined by optical rotation and the $^1\text{H-NMR}$ spectrum. Podophyllotoxin and 4'-demethylpodophyllotoxin have approximate optical rotations of -132° and -130° , respectively, in CHCl_3 (13). However, the optical rotations of **1** and epi-isopodophyllotoxin were -6.58° and -37.5° (11), respectively, in pyridine, and both have the same configurations at C-1, C-2, and C-3. Thus, the 4-OH of **1** was assigned in the β position contrary to epi-isopodophyllotoxin which has a 4 α -OH. The $^1\text{H-NMR}$ spectrum of **1** gave the coupling constant of H-3 and H-4 (10.5 Hz), also indicating the configuration of C-4.

Further evidence in favor of the configuration of C-2 and C-4 was obtained from the $^{13}\text{C-NMR}$ data. The $^{13}\text{C-NMR}$ spectrum of **1** showed that the chemical shifts of C-2a (C=O, 177.2 ppm) and C-4 (67.1 ppm) were, respectively, similar to the chemical shift of C-2a (C=O, 178.0 ppm, β -position) of picropodophyllotoxin and C-4 (4 β -OH, 66.5 ppm) of epipodophyllotoxin and not similar to podophyllotoxin, which has a 2 α carbonyl (C-2a, 174.6 ppm) and 4 α hydroxy (C-4, 72.1 ppm) (14).

The structures of the other four lignans isolated were elucidated as the known compounds podophyllotoxone, isopicropodophyllone, dehydropodophyllotoxin, and podophyllotoxin on the basis of analysis of their UV, IR, MS, and $^1\text{H-NMR}$ spectra.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Mp's are uncorrected. The UV spectra were recorded on a Shimadzu 2100, and the IR spectra were recorded on a Perkin-Elmer 983G instrument; EIMS were recorded on Finnigan Mat 4510 and HREIMS on Varian Mat-212 spectrometers.

The ^1H nmr and ^{13}C nmr were recorded on Varian EM-360L, JEOL, FX-90 and Brüker AM-400 instruments. The cd was recorded on a JASCO J-500A, and optical rotation was observed on a JASCO DIP-181 instrument.

PLANT MATERIAL.—Dried roots of *D. versipellis* var. *tomentosa* were obtained commercially from the Anhui Province of China and authenticated by Prof. Mao-Bing Deng, Jiangsu Institute of Botany. A voucher specimen is deposited in the Department of Chemistry, Shanghai Second Medical University, Shanghai, China.

ISOLATION OF LIGNANS.—The roots (3 kg) were powdered and percolated with 85% EtOH. The percolate was concentrated, diluted with 1 liter of H_2O , and extracted with 2 liters of EtOAc. The extract was evaporated, and the residue was extracted with 500 ml of CH_2Cl_2 . After removal of solvent, 58 g of residue was obtained of which 10 g was chromatographed on a Si gel column using CHCl_3 -EtOAc (90:10) and (80:20). The fractions A and B were rechromatographed on a Si gel column with CHCl_3 /EtOAc to give the four known lignans. The fraction C (2.2 g) was subjected to a Si gel column with CHCl_3 -MeOH (98:2) to yield **1** (42 mg).

4'-DEMETHYLISOPODOPHYLLOTOXIN [1].—White needle-like crystals: hrms found *m/z* 400.1177, calcd for $\text{C}_{21}\text{H}_{20}\text{O}_8$, *m/z* $[\text{M}]^+$ 400.1160; mp 256.5–258.5°; $[\alpha]^{22\text{D}} -6.58^\circ$ (pyridine, $c=0.0073$); ^1H nmr (400 MHz, $\text{Me}_2\text{CO}-d_6$) δ 7.15 (s, 1H, H-5), 6.63 (s, 2H, H-2', -6'), 6.17 (s, 1H, H-8), 5.92 (m, 2H, O- CH_2 -O), 4.60 (dd, $J=1.3, 9.4$ Hz, 1H, H-3a β), 4.48 (d, $J=10.5$ Hz, 1H, H-4), 4.44 (dd, $J=6.3, 9.4$ Hz, 1H, H-3a α), 3.91 (d, $J=7.0$ Hz, 1H, H-1), 3.82 (s, 6H, 3', -5'-OMe), 3.38 (dd, $J=7.0, 9.4$ Hz, 1H, H-2), 2.65 (m, 1H, H-3); ^{13}C nmr (90 MHz, $\text{DMSO}-d_6/\text{CDCl}_3$) δ 177.2 (C-2a), 147.7 (C-3', -5'), 145.6, (C-6, -7), 134.5 (C-4'), 134.0 (C-1'), 133.1 (C-10), 131.0 (C-9), 107.3 (C-8), 106.7 (C-2', -6'), 104.4 (C-5), 100.3 (O- CH_2 -O), 68.9 (C-3a), 67.1 (C-4), 56.0 (3', -5'-OMe), 44.2 (C-2), 43.1 (C-1), 42.6 (C-3); eims (70 eV) *m/z* (rel. int.) $[\text{M}]^+$ 400 (100), 382 (5), 340 (4), 324 (3), 315 (4), 283 (5), 201 (2), 169 (2), 167 (2), 154 (2), 139 (2), 115 (3), 91 (2), 77 (3); uv λ max (MeOH) 205 nm ($\log \epsilon$ 4.62), 240 (sh, 3.95), 284 (3.59); ir ν (KBr) 3423, 2922, 2847, 1758, 1612, 1557, 1521, 1497, 1478, 1429, 1333, 1256, 1218, 1175, 1117, 1081, 1037, 995, 932, 845 cm^{-1} ; cd (MeCN) $\Delta\epsilon_{287} +2.85$, $\Delta\epsilon_{271} -1.30$, $\Delta\epsilon_{245} -0.6$, $\Delta\epsilon_{219} -4.0$, $\Delta\epsilon_{204} +16.5$. The assignments of ^1H and ^{13}C signals were assigned on the basis of decoupling ($^1\text{H}-^1\text{H}$), and DEPT experiments, respectively.

IDENTIFICATION OF KNOWN COMPOUNDS.
—The four known lignans podophyllotoxone,

isopropodophyllone, dehydropodophyllotoxin, and podophyllotoxin were identified by spectral analysis of eims, uv, ir, and ^1H -nmr spectra, compared with the data published previously (15–18).

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