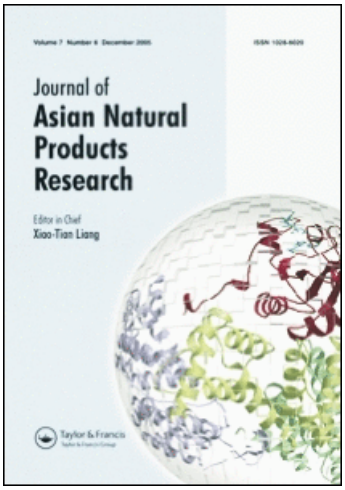

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CHEMICAL CONSTITUENTS FROM THE LEAVES OF *MAGNOLIA DENUDATA*

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20 compounds were isolated from the leaves of *Magnolia denudata* including 16 lignans, which belong to 6 structural types. Except for (7*R*, 8*S*, 1′*S*) -$\Delta^{8'}$- 1′, 4′ - dihydro - 5′- methoxy - 3, 4 - methylenedioxy - 4′ - oxo -7.O.2′, 8.1′ - neolignan (**6**), magliflonenone (**9**), 2, 5′ - diene-2′, 8′- epoxy - 5′ - methoxy - 8 - methyl - 4′- oxo - 3, 4-methylenedioxy - spiro (5, 5) - undecane (**10**), veraguensin (**16**) and β-sitosterol (**20**), the other 15 compounds were obtained from this species for the first time. The absolute configurations of 3 compounds (**1**, **4**, **10**) were determined by CD spectroscopy for the first time. The anti-inflammatory activities of compounds **1**, **2** and **16** were assessed and **2** was shown to have significant inhibition effect on mice hind-paw edema induced by carrageenan.

Keywords: *Magnolia denudata*; Lignan; Anti-inflammation activity

INTRODUCTION

Magnolia denudata is an important original plant of the traditional Chinese medicine "Xin Yi" which has been used for headache and rhinitis [1]. Terpenes and lignans have been isolated from this plant [2, 3]. As part of our systematic studies on the biologically active constituents of traditional Chinese medicine, we obtained 20 compounds from the leaves of this plant, including 16 lignans that belong to 6 structural types. With the exception of

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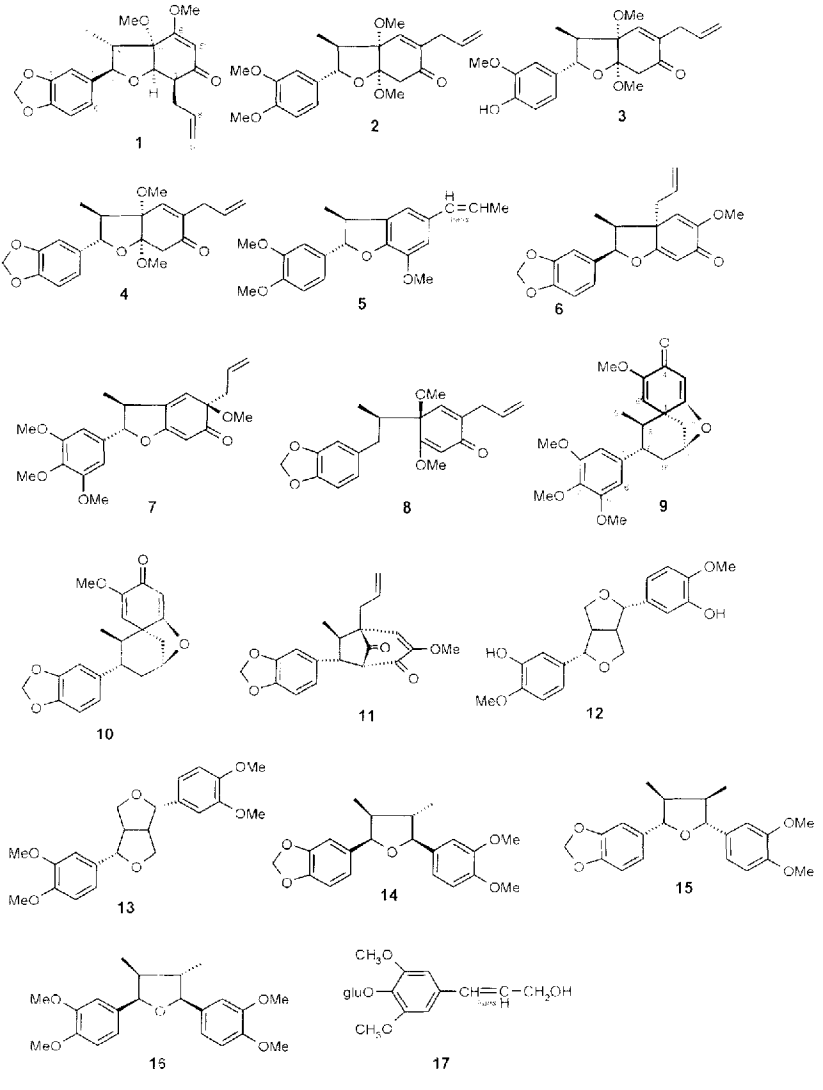
(7*R*, 8*S*, 1′*S*) -$\Delta^{8'}$ - 1′, 4′ - dihydro - 5′- methoxy - 3, 4 - methylenedioxy -4′ - oxo -7.O.2′, 8.1′ - neolignan (**6**), magliflonenone (**9**), 2, 5′ - diene-2′, 8′- epoxy - 5′ - methoxy - 8 - methyl - 4′- oxo - 3, 4 -methylenedioxy - spiro (5, 5) - undecane (**10**), veraguensin (**16**) and β-sitosterol (**20**), the other 15 compounds were isolated from this species for the first time. The absolute configurations of 3 compounds (**1**, **4** and **10**) were determined by CD spectroscopy for the first time. The anti-inflammatory activities of



compounds **1**, **2** and **16** were assessed and **2** showed significant inhibition effect on mice hind-paw edema induced by carrageenan.

RESULTS AND DISCUSSION

Fargesone A (**1**) was obtained as yellow oil. $[\alpha]_D^{21}$ −115 (*c* 0.15, $CHCl_3$). The presence of carboxyl groups (1666 cm^{-1}) and double bonds (3074, 1610 cm^{-1}) was indicated by the IR spectrum. The ^{1}H-NMR spectrum of compound **1** showed two methoxyls (δ 3.76, 3.21 ppm), a methyl doublet (δ 1.07, d, J=6.9 Hz), a methylene (δ 5.94 ppm) and two coupled protons (δ 6.77, d, J=7.8 Hz; δ 6.79, d, J=7.8 Hz). It has the skeleton of benzofuran lignan deduced by its ^{1}H and ^{13}C NMR spectra. The methyl at C-8 and the piperonyl should be *trans* and 1′-OCH_3 and 8-Me should be *cis* [4], this was confirmed by the chemical shift of H-9 (δ 1.07 ppm), H-8 (δ 2.21 ppm) and C-9 (δ 8.7 ppm) in ^{1}H and ^{13}C spectra, respectively. The relative configuration of **1** was the same as that of fargesone A [5]. In order to determine its absolute configuration, CD spectrum was measured. It exhibited a negative Cotton effect at 216–326 nm. Therefore the absolute configuration of fargesone A should be 7*R*, 8*S*, 1′*S*, 2′*R*, 3′*S*−$\Delta^{8'}$-1′, 6′-dimethoxy-3, 4-methylenedioxy-1′, 2′, 3′, 4′-tetrahydro-4′-oxo-7.O.2′, 8.1′-neolignan.

Compound **4** was obtained as yellow oil. Comparison of the ^{1}H and ^{13}C-NMR data of **4** with those of compound **2** revealed that compound **4** was very similar to **2**, except for the presence of a piperonyl in **4** instead of a veratryl in **2** [9]. The relative configuration of **4** was readily identified by comparison of their spectral data with those of the literature values [6]. CD spectrum was employed to determine its absolute configuration. It exhibited a negative Cotton effect due to the $n \rightarrow \pi^*$ transition and a positive Cotton effect in the $\pi \rightarrow \pi^*$ region. Therefore the absolute configuration of **4** was identified as 7*S*, 8*R*, 1′*S*, 2′*R*-$\Delta^{8'}$-1′, 2′-dimethoxy-3, 4-methylenedioxy-1′, 2′, 3′, 4′-tetrahydro-4′-oxo-7.O.2′, 8.1′-neolignan.

Compound **10** was obtained as white amorphous powder. It has a spiro (5, 5)-undecane neoligan skeleton, which can be determined by its ^{1}H and ^{13}C-NMR spectra [7]. 8-CH_3 and piperonyl should be *trans* orientated since there was a NOE correlation between H-9 and H-7. But in its ^{1}H NMR spectrum the H-9 signal appeared at 0.59 ppm, which indicated that the methyl at C-8 should be shielded by the benzene ring. Compound **10** was obtained from the same species before [3], but its absolute configuration has not been resolved. CD analysis of this compound showed a negative Cotton

effect at 250–320 nm. Based on Octant Rule the absolute configuration at C-1′ should be *S*. Furthermore, ring B should have a twist-chair conformation to satisfy the shielding effect of the benzene ring to the methyl group at C-8, while the CD spectrum showed negative Cotton effect due to the n-π^* transition and a positive Cotton effect in the π-π^* region. So the absolute configuration of compound **10** was (7*S*, 8*R*, 1′*S*, 8′*S*)-2, 5′-diene-2′, 8′-epoxy-5′-methoxy-8-methyl-4′-oxo-3, 4-methylenedioxy-spiro (5, 5)-undecane. The spectral data ($[\alpha]_D$, ^{1}H-NMR) of compound **9** was very similar to that of compound **10** except for the presence of a 3, 4, 5-trimethoxybenzyl in **9** instead of a piperonyl in **10**. Compound **9** should have the same absolute configuration as compound **10**.

The other compounds including pipernone (**2**) [8], (7*S*, 8*R*, 1′*S*, 2′*R*) -$\Delta^{8'}$ -4-hydroxy-3, 1′, 2′-trimethoxy-1′, 2′, 3′, 4′-tetrahydro-4′-oxo-7.O.2′, 8.1′-neolignan (**3**) [9], (7*S*, 8*R*)-$\Delta^{7'}$-3,4,3′-trimethoxy-7.O.2′,8.1′-neolignan (**5**) [10], (7*R*,8*S*,1′*S*)-$\Delta^{8'}$-1′, 4′-dihydro- 4′-oxo-7.O.2′,8.1′-neolignan (**6**) [11, 12], (7*S*, 8*R*, 5′*R*)-$\Delta^{8'}$ -3, 4, 5, 5′-trimethoxy-4′, 5′-hydro-4′-oxo-7.O.2′,8.1′-neolignan (**7**) [13, 14], isodihydrofutoquinol B (**8**) [6], magliflonenone (**9**) [3], (7*R*, 8*R*, 1′*R*, 3′*R*)-$\Delta^{5',8'}$-5′-methoxy-3, 4-methylenedioxy-2′, 4′-dioxo-8.1′, 7.3′-neolignan (**11**) [15], pinoresinol (**12**) [16], pinoresinol dimethyl ether (**13**) [17], zoionin A (**14**) [6], calopiptin (**15**) [18], veraguensin (**16**) [3], syringin (**17**) [5], 4-hydroxy-3-methoxybenzoic acid (**18**), shikimic acid (**19**) [19] and β-sitosterol (**20**) [20] were also isolated from this species. Their structures were readily identified by comparison of their spectral data ($[\alpha]_D$, ^{1}H-NMR, ^{13}C-NMR and EIMS) with those of the literature values.

The inhibition effects of compounds **1**, **2**, **16** on carrageenan-induced paw edema were undertaken. Results showed that compound **2** has an inhibitory rate of 20.6% on mouse hind-paw edema induced by carrgeenan. The inhibition effects of the other two compounds have not been observed (Tab. I).

TABLE I Inhibition effect of compound **1**, **2** and **16** on carrageenan-induced paw edema in mouse (n = 8, mean ± SD)

Group	*Dose (mg/kg, PO)*	*Paw edma (mg) mean ± SD*	*Inhibition (%)*
Control		70.8 ± 11.1	
Compound 1	50	65.4 ± 16.8	7.0
Compound 2	50	54.8 ± 10.1*	20.6
Compound 16	100	64.1 ± 14.4	8.6

*$P < 0.01$, *vs.* control (physiological saline).

EXPERIMENTAL SECTION

General Experimental Procedures

Melting points were determined on a Reichert Nr-229 micromelting point apparatus and are uncorrected. The optical rotations were measured on a Perkin-Elmer 241 digital polarimeter in $CHCl_3$. IR spectra were taken on a Perkin-Elmer 683 (KBr) spectrometer. EI-mass spectra were recorded on a ZAB-2F spectrometer. HR-mass spectra were performed on VG-Autospec-3000 spectrometer. ^{1}H-NMR, ^{13}C-NMR and ^{1}H-^{1}H COSY, HMQC, HMBC spectra were run on Mercury 300 spectrometer with TMS as internal standard.

Plant Material

The roots of *Magnolia denudata* leaves were collected in September 1998 from Jiujiang, Jiangxi Province, People's Republic of China. The plant material was identified by Professor Ce-Ming Tang, Jiujiang Institute of Forestry, Jiangxi Province, People's Republic of China. A voucher specimen (no. 75) has been deposited in the herbarium of the Department of Medicinal Plants, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, P. R. China.

Extraction and Isolation

Dried leaves of *Magnolia denudata* (12.7 kg) were extracted with ethanol under reflux. The combined EtOH extract was concentrated *in vacuo* to give a residue (1.2 kg), which was suspended in water and the suspension was extracted with EtOAc. The EtOAc extract was evaporated *in vacuo* to give a residue (860 g), which was chromatographed over silica gel column (160–200 mesh, 2.0 kg). The column was eluted with petroleum ether: acetone (50 : 1 to 2 : 1). All components were purified by CC, TLC, MPLC and HPLC to yield compounds **1** (68 mg), **2** (56 mg), **3** (8 mg), **4** (11 mg), **5** (14 mg), **6** (7 mg), **7** (8 mg), **8** (8 mg), **9** (15 mg), **10** (32 mg), **11** (8 mg), **12** (8 mg), **13** (5 mg), **14** (8 mg), **15** (8 mg), **16** (40 mg), **17** (5 mg), **18** (20 mg), **19** (10.8 g) and **20** (75 mg).

Fargesone A (**1**), yellowish oil, $[\alpha]_D^{21}$ - 115 (*c* 0.15, $CHCl_3$). EIMS *m/z* (rel. int.): 372 (M^+, 42), 206 (14), 191 (48), 162 (35), 149 (100), UV (MeOH) λ max (log ε): 204 (4.43), 242 (4.12), 285 (3.67). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (3H, d, $J = 6.9$ Hz, H-9), 2.21 (1H, m, H-8), 2.56 (1H, m, H-3′),

2.24, 2.78 (each 1H, m, H-7′), 3.21 (3H, s, CH_3O-1′), 3.76 (3H, s, CH_3O-6′), 4.44 (1H, d, $J=9.0$ Hz, H-2′), 4.70 (1H, d, $J=10.2$ Hz, H-7), 5.10 (1H, dd, $J=1.5$, 13.0 Hz, H-*cis* 9′), 5.17 (1H, dd, $J=1.8$, 19.1 Hz, H-*trans* 9′), 5.56 (1H, s, H-5′), 6.78 (1H, s, H-2), 6.79 (1H, d, $J=7.8$ Hz, H-5), 6.77 (1H, d, $J=7.8$ Hz, H-6), 5.87 (1H, m, H-8′), 5.94 (2H, s, -OCH_2O). ^{13}C NMR (75 MHz, $CDCl_3$): 134.1 (C-1), 106.6 (C-2), 147.8 (C-3), 147.3 (C-4), 108.1 (C-5), 120.3 (C-6), 87.1 (C-7), 51.2 (C-8), 8.7 (C-9), 84.5 (C-1′), 79.8 (C-2′), 54.0 (C-3′), 196.2 (C-4′), 105.5 (C-5′), 172.2 (C-6′), 31.1 (C-7′), 135.2 (C-8′), 117.7 (C-9′), 51.4 (1′ - OCH_3), 56.2 (6′ - OCH_3). [θ] (MeOH): 326 (0), 252 (−14400), 216 (0).

Compound **4**, yellowish oil, $[\alpha]_D^{21}+41$ (*c* 0.10, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (3H, d, $J=7.2$ Hz, H-9), 2.61 (1H, d, $J=16.5$ Hz, H-3′), 2.82 (1H, m, H-8), 3.13 (2H, m, $J=0.9$, 6.6 Hz, H-7′), 3.27 (1H, d, $J=16.5$ Hz, H-3′), 3.39 (3H, s, OCH_3-1′), 3.51 (3H, s, OCH_3-2′), 4.07 (1H, d, $J=11.1$ Hz, 7-H), 5.11 ~ 5.17 (2H, m, H-9′), 5.86 (1H, m, 8′-H), 5.95 (2H, s, -O-CH_2-O), 6.43 (1H, s, H-6′), 6.72 (1H, bs, H-6), 6.73 (1H, s, H-2), 6.83 (1H, bs, H-5). ^{13}C NMR (75 MHz, $CDCl_3$): 133.8 (C-1), 107.3 (C-2), 147.6 (C-3), 148.0 (C-4), 107.9 (C-5), 121.2 (C-6), 85.4 (C-7), 48.9 (C-8), 9.2 (C-9), 81.8 (C-1′), 102.0 (C-2′), 43.2 (C-3′), 194.3 (C-4′), 143.2 (C-5′), 138.7 (C-6′), 33.5 (C-7′), 134.7 (C-8′), 117.6 (C-9′), 48.9 (2′-OCH_3), 52.5 (1′-OCH_3), 101.1 (OCH_2O). [θ] (MeOH): 247.6 (−14323), 232.4 (0), 219.4 (+13806), 210.8 (0).

Compound **10**, white crystal, 32 mg, mp.188 ~ 190°C; $[\alpha]_D^{21}-62$ (*c* 0.25, $CHCl_3$), IR (KBr) ν_{max}: 3072, 2929, 1664, 1610, 1591, 1512, 1458, 1254, 1132, 1007 cm^{-1}; EIMS *m/z* (rel. int.): 340 (M^+, 70), 177 (42), 163 (100), 147 (32), 135 (80); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.59 (3H, d, $J=6.3$ Hz, H-9), 1.74 (1H, dd, $J=12.0$, 13.8 Hz, H-9′), 2.03 (1H, m, H-8), 2.17 (1H, d, $J=11.4$ Hz, H-7′), 2.25 ~ 2.40 (2H, m, H-9′, 7′), 2.57 (1H, m, H-7), 3.66 (3H, s, 5′-OCH_3), 5.02 (1H, brt, H-8′), 5.43 (1H, s, H-6′), 5.79 (1H, s, H-3′), 5.89 (2H,-OCH_2O), 6.62 ~ 6.74 (3H, m, Ar-H), [θ] (MeOH): 297 (−15208), 268 (0), 256 (+13213), 244 (0), 222 (−14366).

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