# Phenolic Constituents from the Stem Bark of *Magnolia officinalis*

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Three new compounds, magnolianone (**1**), *erythro*-honokitriol (**2**), and *threo*-honokitriol (**3**), together with 14 known compounds, magnaldehyde (**4**), magnatriol B (**5**), randaiol (**6**), obovatol (**7**), magnolignan B (**8a** and **8b**), magnolol, honokiol (**9**), *p*-hydroxylbenzaldehyde, coniferaldehyde, coniferol alcohol, syringaldehyde, syringaresinol, and acteoside, were isolated from the MeOH-soluble part of a water extract of the stem bark of *Magnolia officinalis*. Among these compounds, **2**−**8b** were studied for anti-inflammatory and antioxidative activities. Compound **7** displayed more potent antioxidative potential than **9**. Compounds **4**−**7** effectively inhibited LPS-induced NO production, whereas **5** and **6** were more potent than **9**.

The stem bark of *Magnolia officinalis* L. (Magnoliae Cortex; Magnoliaceae) is a Chinese crude drug used for relieving asthma and treatment of abdominal distention and pain, dyspepsia, and asthmatic cough.[1,2] Magnolol and honokiol are the major phenolic constituents of *M. officinalis*.[3] The pharmacological effects of magnolol and honokiol have been studied, and they are reported to show antiplatelet,[4] antioxidative,[5,6] antibacterial,[7] and cytotoxic[8] activities. Since most Chinese drug decoctions are obtained by extraction with boiling water, polar and bioactive compounds might occur in the water extract. In this paper, we report the constituents of the water extract of stem bark of *M. officinalis* and the antioxidative and anti-inflammatory activities of some constituents.

The water extract of the bark of *M. officinalis* was concentrated in vacuo and then lyophilized to give a dark brown solid, which was then divided into MeOH-soluble and -insoluble parts. The MeOH-soluble portion was repeatedly chromatographed to afford three new compounds, magnolianone (**1**), *erythro*-honokitriol (**2**), and *threo*-honokitriol (**3**), together with 14 known substances, magnaldehyde (**4**),[9] magnatriol B (**5**),[9] randaiol (**6**),[9] obovatol (**7**),[10] magnolignan B (**8a** and **8b**),[9] magnolol,[9] honokiol (**9**),[9] *p*-hydrox-ylbenzaldehyde,[11] coniferaldehyde,[12] coniferol alcohol,[13] syringal-dehyde,[11] syringaresinol,[9] and acteoside.[14]

Compound **1** was isolated as a brown gum. The molecular formula, $C_{19}H_{22}O_6$, was deduced from HREIMS and NMR analysis. The IR spectrum of **1** showed the presence of hydroxyl (3345 $cm^{-1}$) and conjugated carbonyl (1655 $cm^{-1}$) groups. The $^{13}C$ and DEPT NMR spectra exhibited 19 carbon signals comprising one carbonyl at $\delta$ 186.4, five quaternary $sp^2$ carbons, one quaternary $sp^3$ carbon linked to an oxygen atom, seven tertiary $sp^2$ carbons, one aliphatic secondary $sp^3$ carbon, and four methoxy carbons. The $^1H$ NMR spectrum displayed signals of an ABX type for aromatic protons [$\delta$ 6.69 (1H, d, 8.0 Hz), 6.73 (1H, dd, 1.5 and 8.0 Hz), and 6.85 (1H, d, 1.5 Hz)], two *trans*-olefinic protons [$\delta$ 5.67 (1H, m) and 6.29 (1H, d, 15.5 Hz)], two overlapping olefinic protons [$\delta$ 5.54 (2H, s)], two aliphatic protons [$\delta$ 2.78 (2H, d, 7.5 Hz)], and four methoxy groups [$\delta$ 3.03 (3H, s), 3.78 (3H, s), and 3.80 (6H, s)]. In the HMBC spectrum, correlations of H-7/C-2, C-6 and H-8/C-1 indicated that the *trans* double bond was attached to a benzene ring. In addition, correlations of H-7/C-9, H-8/C-10, and H-12 (H-14)/C-10 were observed, which suggested that a three-carbon chain with a *trans* double bond was linked to a cyclohexadienone ring. The HMBC correlations of OCH3-10/C-10 and OCH3-11 (OCH3-15)/C-11 (C-15) revealed that three methoxy groups were located at C-10, C-11, and C-15. Moreover, the correlations between H-9 and C-11 and C-15 confirmed that two of these methoxy groups

were at C-11 and C-15. The location of the methoxy group on the benzene ring was established at C-3 by a NOESY experiment, which showed a cross-peak between the methoxy group and H-2. Accordingly, the structure of compound **1** was determined to be (*E*)-3,4,5-trimethoxy-4-[3-(3-methoxy-4-hydroxyphenyl)-2-prope-nyl]cyclohexa-2,5-dienone, and it has been given the trivial name magnolianone.

Compound **2** was obtained as a colorless solid, for which the molecular formula $C_{18}H_{20}O_5$ was deduced by HREIMS. The $^{13}C$ NMR and DEPT spectra showed 18 carbon signals attributed to one methylene ($\delta$ 35.0), one oxymethylene ($\delta$ 64.5), two oxyme-thine ($\delta$ 76.0 and 76.2), and 14 $sp^2$ carbons. The $^1H$, COSY, and HMQC NMR spectra revealed the presence of one methylene [$\delta$ 3.40 (2H, d, 6.5 Hz)], one oxygenated methylene [$\delta$ 3.63 (2H, m)], two oxygenated methines [$\delta$ 3.72 (1H, m) and 4.59 (1H, d, 6.0 Hz)], one terminal double bond ($\delta$ 4.97, 5.09, and 6.03), and six aromatic protons ($\delta$ 6.86−7.32). Analysis of the COSY, HMQC, and HMBC NMR spectra indicated that compound **2** is an oxidized derivative of honokiol (**9**), which contains a 1,2,3-trihydroxypropyl group instead of an allyl group at the *para* position of a phenolic hydroxyl group. The locations of the 1,2,3-trihydroxypropyl and allyl groups were confirmed by HMBC correlations of H-7/C-1, C-2, C-6, C-9 and H-7′/C-1′, C-2′, C-6′, C-9′ as well as NOESY correlations of H-7/H-2, H-6, H-8 and H-7′/H-2′, H-8′. Thus, the structure of **2** was established as 1-(3′-allyl-6,4′-dihydroxybiphenyl-3-yl)propane-1,2,3-triol, and it was given the trivial name honokitriol.

Compound **3** was obtained as a colorless solid with the same molecular formula as **2**. Its $^{13}C$ NMR spectrum was very similar to that of **2** except that the signals of C-7, C-8, and C-9 shifted from $\delta$ 76.0, 76.2, and 64.5 to $\delta$ 74.6, 77.8, and 63.9, respectively. Moreover, the $^1H$ NMR signals of H-8 and H-9 shifted from $\delta$ 3.72 and 3.63 to $\delta$ 3.65 and 3.41, 3.51. Detailed analysis of 2D NMR spectra revealed that the structure of compound **3** was also 1-(3′-allyl-6,4′-dihydroxybiphenyl-3-yl)propane-1,2,3-triol. The simi-larity of the NMR spectra of **2** and **3** suggested that these two compounds could be *erythro* and *threo* isomers. The OH configura-tions of two stereogenic centers in compounds **2** and **3** were deduced by comparison with the $^{13}C$ NMR spectra of similar compounds, *erythro*- and *threo*-1-C-syringylglycerol, for which the structures were confirmed by synthesis.[15] The $^{13}C$ NMR signals of C-7 and C-8 in *erythro*-1-C-syringylglycerol ($\delta$ 74.1 and 75.3) were closer together than those in the *threo* isomer ($\delta$ 72.9 and 75.8).[15] In compound **2**, C-7 and C-8 showed signals at $\delta$ 76.0 and 76.2, respectively, which were closer than those of compound **3** ($\delta$ 74.6 and 77.8). Thus, the structures of compounds **2** and **3** were determined with *erythro* and *threo* configurations, respectively. In the literature, four stereoisomers of 1-phenylglycidol with (1*R*,2*R*), (1*R*,2*S*), (1*S*,2*S*), and (1*R*,2*R*) configurations were synthesized by

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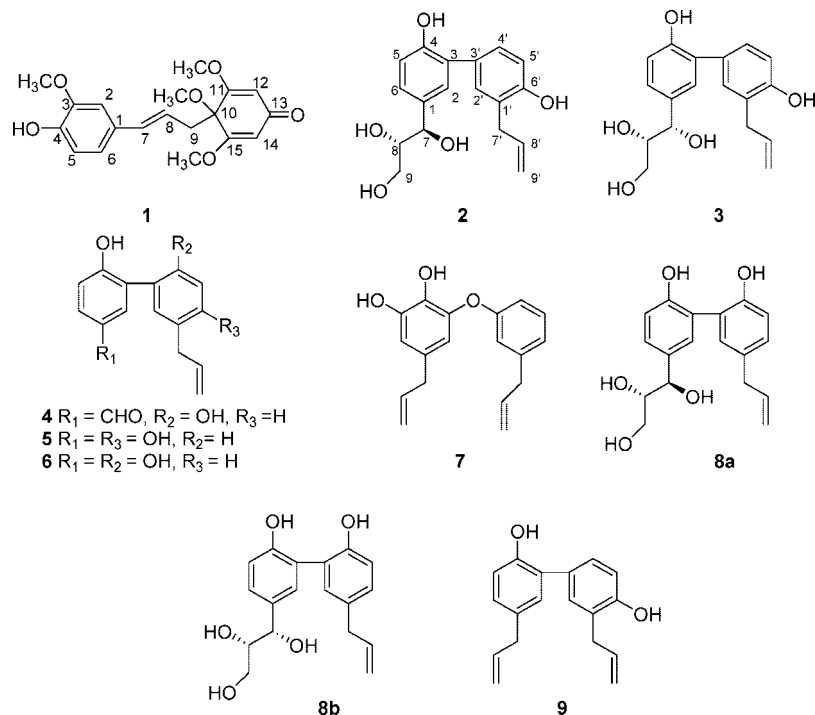
an asymmetric method.[16] By comparison of their signs of $[\alpha]_D$ with those of *erythro*- and *threo*-honokitriol, it was deduced that the stereostructures of compounds **2** and **3** were (1*R*,2*S*)-*erythro*-honokitriol and (1*S*,2*S*)-*threo*-honokitriol, respectively.

The HREIMS of compounds **8a** and **8b** gave the same molecular formula, $C_{18}H_{20}O_5$, and they exhibited very similar $^1H$ and $^{13}C$ NMR spectra. 2D NMR spectroscopic analysis of **8a** and **8b** indicated that both compounds have the structure of magnolignan B, which was obtained as an oxidized derivative of magnolol with a 1,2,3-trihydroxypropyl group.[9] Similar to **2** and **3**, compounds **8a** and **8b** were suspected as *erythro* and *threo* isomers. In compound **8a**, C-7 and C-8 showed signals at $\delta$ 75.9 and 76.2, respectively, which were closer than those of compound **8b** ($\delta$ 74.5 and 77.2). Thus, the structures of compounds **8a** and **8b** were determined with *erythro* and *threo* configurations, respectively. Since the magnitude of $[\alpha]_D$ for **8a** and **8b** was too small at 589 nm, the measurement of their optical rotatory dispersion spectra over a range of wavelengths was attempted. However, the values were near zero and no distinct ORD curves were obtained. Therefore, their absolute configurations were not determined.

Among the compounds isolated, **2**−**8** were studied for their anti-inflammatory potential on NADPH-induced reactive oxygen species (ROS) production by NADPH oxidase (NOX) in microglia cell lysates and lipopolysaccharide (LPS)-induced nitric oxide (NO) production in microglial cells. Compounds **5** and **7** displayed antioxidative effects against NOX-dependent ROS production with $IC_{50}$ values of 20.6 and 4.8 $\mu$g/mL, respectively. Compound **7** was more potent than **9** ($IC_{50}$, 14.9 $\mu$g/mL). The antioxidative effects of these compounds were partially due to their direct free-radical scavenging capacities with DPPH free-radical scavenging ($IC_{50}$) values of 27.6, 21.6, 33.0, and 38.5 $\mu$g/mL for **5**, **6**, **7**, and **9**, respectively. Compounds **4**−**7** also effectively inhibited LPS-induced NO production with $IC_{50}$ values of 9.2, 0.5, 1.2, and 9.0 $\mu$g/mL, respectively. Among them, compounds **5** and **6** were more potent than **9** ($IC_{50}$, 5.0 $\mu$g/mL) in the inhibition of NO production. The present results suggest that bioactive components **4**−**7**, isolated from *M. officinalis* bark, exhibited anti-inflammatory activities that could be partially explained by their different potential for the inhibition of NOX-dependent ROS and iNOS-dependent NO production in activated microglial cells as well as their direct free-radical scavenging capacities.

## Experimental Section

**General Experimental Procedures.** Melting points were determined on a Yanaco MP-I3 micro melting point apparatus and were uncorrected. Optical rotations were taken with a JASCO DIP-370 digital polarimeter. UV spectra were measured on a Hitachi U-3310 spectrophotometer. IR spectra were recorded on a Nicolet Avatar 320 FT-IR spectrometer. $^1H$, $^{13}C$, and 2D NMR spectra were taken on a Varian Unity INOVA 500 MHz or Bruker Avance 400 MHz spectrometer. EIMS and HRMS were obtained on Finnigan MAT GCQ and JEOL JMS-700 spectrometers, respectively. HPLC was conducted on a HP model 1100 system equipped with a HP G1311A QuatPump, a HP G1322A degasser, and a HP G1315B photodiode array detector set at 254 nm. Semipreparative HPLC was performed using a reversed-phase column (Cosmosil 5$C_{18}$ MS-II, 5 $\mu$m, 10 mm i.d. × 250 mm) at a flow rate of 2.0 mL/min.

**Plant Material.** The stem bark of *Magnolia officinalis* was purchased from a market in Taipei, Taiwan, in August 2006, and identified by Dr. I-Jung Lee, Assistant Research Fellow of the National Research Institute of Chinese Medicine. A voucher specimen (no. NHT 00038) is deposited at the Herbarium of National Research Institute of Chinese Medicine, Taipei.

**Extraction and Isolation.** The dried bark of *M. officinalis* (3 kg) was extracted with boiling water. The water extract was concentrated in vacuo and then lyophilized to give a dark brown solid (282 g), which was divided into MeOH-soluble and -insoluble parts. The MeOH-soluble portion was subjected to silica gel column (66 × 11.5 cm) chromatography, eluting with *n*-hexane−EtOAc (3:1, 3 L), *n*-hexane−EtOAc (1:1, 11 L), EtOAc (7 L), and EtOAc−MeOH (10:1, 6 L). Fractions (500 mL each) were collected and combined on the basis of TLC into four pools ($F_1$−$F_4$). Fraction $F_1$ (*n*-hexane−EtOAc, 3:1) was rechromatographed on Sephadex LH-20 (MeOH) and then further purified by preparative TLC (*n*-hexane−CHCl₃, 2:1) to afford three compounds, magnolol, honokiol (**9**), and *p*-hydroxylbenzaldehyde (9.3 mg). Fraction $F_2$ (*n*-hexane−EtOAc, 1:1) was chromatographed on Sephadex LH-20 (MeOH) to furnish two subfractions, $F_2$-1 and $F_2$-2. Subfraction $F_2$-1 was repeatedly chromatographed on Sephadex LH-20 (MeOH) and silica gel (CHCl₃−MeOH, 30:1) columns to give three compounds, magnaldehyde (**4**, 20.5 mg), magnatriol (**5**, 53.4 mg), and randaiol (**6**, 102 mg). Subfraction $F_2$-2 was repeatedly chromatographed using silica gel (*n*-hexane−EtOAc, 1:1) and Sephadex LH-20 (MeOH) columns to afford five compounds, magnolianone (**1**, 4.0 mg), obovatol (**7**, 73.4 mg), coniferaldehyde (2.2 mg), coniferol alcohol (1.6 mg), and syringaldehyde (8.4 mg). Fraction $F_3$ (EtOAc) was repeatedly chromatographed on Sephadex LH-20 (MeOH) and silica gel (CHCl₃−MeOH, 8:1) columns to afford syringaresinol (29.5 mg) and

**Table 1.** $^{13}$C and $^1$H NMR Spectroscopic Data for *erythro*-Honokitriol (**2**), *threo*-Honokitriol (**3**), *erythro*-Magnolignan B (**8a**), and *threo*-Magnolignan B (**8b**)

| position | 2$^a$ δC | 2$^a$ δH | 3$^a$ δC | 3$^a$ δH | 8a$^b$ δC | 8a$^b$ δH | 8b$^b$ δC | 8b$^b$ δH |
|---|---|---|---|---|---|---|---|---|
| 1 | 135.0 | | 134.7 | | 135.7 | | 135.5 | |
| 2 | 129.0$^c$ | 7.27 m | 129.0$^c$ | 7.26 m | 131.2 | 7.31 d (2.0) | 131.0 | 7.31 d (2.0) |
| 3 | 128.6 | | 128.8 | | 127.4 | | 127.2 | |
| 4 | 154.0 | | 154.1 | | 153.9 | | 154.0 | |
| 5 | 116.3$^d$ | 6.86 d (8.4) | 116.4$^d$ | 6.88 d (8.4) | 116.9 | 6.93 d (8.5) | 117.0 | 6.94 d (8.0) |
| 6 | 127.2 | 7.14 dd (2.0, 8.4) | 127.0 | 7.13 dd (2.4, 8.4) | 128.3 | 7.27 dd (2.0, 8.5) | 128.1 | 7.26 dd (2.0, 8.0) |
| 7 | 76.0 | 4.59 d (6.0) | 74.6 | 4.59 d (6.0) | 75.9 | 4.61 d (6.0) | 74.5 | 4.64 d (5.5) |
| 8 | 76.2 | 3.72 m | 77.8 | 3.65 m | 76.2 | 3.73 m | 77.2 | 3.66 m |
| 9 | 64.5 | 3.63 m | 63.9 | 3.41 m 3.51 dd (4.0, 11.2) | 64.5 | 3.63 dd (5.0, 11.0) 3.67 dd (4.5, 11.0) | 63.9 | 3.43 dd (6.0, 11.0) 3.54 dd (4.5, 11.0) |
| 1′ | 126.7 | | 126.7 | | 132.7 | | 132.7 | |
| 2′ | 131.7 | 7.32 d (2.0) | 131.7 | 7.32 d (2.4) | 132.5 | 7.12 d (2.0) | 132.5 | 7.11 d (2.0) |
| 3′ | 131.1 | | 131.0 | | 126.4 | | 126.6 | |
| 4′ | 129.9$^c$ | 7.27 m | 129.7$^c$ | 7.26 m | 153.1 | | 153.1 | |
| 5′ | 115.4$^d$ | 6.87 d (8.4) | 115.4$^d$ | 6.86 d (8.4) | 117.4 | 6.91 d (8.0) | 117.4 | 6.92 d (8.0) |
| 6′ | 154.7 | | 154.7 | | 129.6 | 7.06 dd (2.0, 8.0) | 129.6 | 7.06 dd (2.0, 8.0) |
| 7′ | 35.0 | 3.40 d (6.5) | 35.0 | 3.40 d (6.8) | 40.0 | 3.35 d (6.5) | 40.0 | 3.35 d (6.5) |
| 8′ | 138.2 | 6.3 m | 138.1 | 6.03 m | 139.1 | 5.97 tdd (6.5, 10.0, 17.0) | 139.1 | 5.97 tdd (6.5, 10.0, 17.0) |
| 9′ | 115.3 | 4.97 d (10.0) 5.09 dd (1.5, 17.0) | 115.3 | 4.98 d (10.0) 5.10 dd (1.6, 17.2) | 115.5 | 4.99 tdd (1.0, 2.0, 10.0) 5.07 tdd (1.5, 2.0, 17.0) | 115.5 | 4.99 tdd (1.0, 2.0, 10.0) 5.07 tdd (1.5, 2.0, 17.5) |

$^a$ δ (ppm); 400 MHz for $^1$H and 100 MHz for $^{13}$C; acetone-$d_6$; *J* values (Hz) in parentheses. $^b$ δ (ppm); 500 MHz for $^1$H and 125 MHz for $^{13}$; acetone-$d_6$; *J* values (Hz) in parentheses. $^c$ Assignments are interchangeable. $^d$ Assignments are interchangeable.

two mixtures, MO-N and MO-S. The mixture MO-N was further purified by semipreparative reversed-phase HPLC eluting with $H_2O-CH_3CN$ (77:23) to give two compounds, *erythro*-magnolignan B (**8a**, 6.4 mg, $t_R$ = 35.09 min) and *threo*-magnolignan B (**8b**, 8.8 mg, $t_R$ = 37.73 min). The mixture MO-S was also purified by semipreparative reversed-phase HPLC using a linear gradient of 100:0 → 50:50 $H_2O-CH_3CN$ over a period of 30 min to afford two compounds, *erythro*-honokitriol (**2**, 2.4 mg, $t_R$ = 25.87 min) and *threo*-honokitriol (**3**, 5.7 mg, $t_R$ = 27.01 min). Fraction $F_4$ (EtOAc−MeOH, 10:1) was sequentially chromatographed on Sephadex LH-20 ($H_2O-MeOH$, 3:7) and silica gel (CHCl$_3$−MeOH, 3:1) columns to give acteoside (4.9 mg).

**Magnolianone (1):** brown gum; [α]$_D$ 122 (*c* 1.0, MeOH); UV (MeOH) λ$_{max}$ (log ε) 269 (4.03), 247 (4.23), 211 (4.35) nm; IR (KBr) ν$_{max}$ 3345 (OH), 1655 (C=O), 1592, 1512, 1370, 1271, 1235, 1203 cm$^{-1}$; $^1$H NMR (acetone-$d_6$, 500 MHz) δ 2.78 (2H, d, *J* = 7.5 Hz, H$_2$-9), 3.03 (3H, s, OCH$_3$-10), 3.78 (3H, s, OCH$_3$-3), 3.80 (6H, s, 11, OCH$_3$-15) 5.54 (2H, s, H-12, 14), 5.67 (1H, m, H-8), 6.29 (1H, d, *J* = 15.5 Hz, H-7), 6.69 (1H, d, *J* = 8.0 Hz, H-5), 6.73 (1H, dd, *J* = 1.5, 8.0 Hz, H-6), 6.85 (1H, d, *J* = 1.5 Hz, H-2); $^{13}$C NMR (acetone-$d_6$, 125 MHz) δ 40.7 (C-9), 52.3 (OCH$_3$-10), 56.2 (OCH$_3$-3), 56.5 (11, OCH$_3$-15), 80.0 (C-10), 105.1 (C-12, 14), 110.4 (C-2), 115.7 (C-5), 120.1 (C-8), 120.2 (C-6), 130.3 (C-1), 134.7 (C-7), 147.2 (C-4), 148.3 (C-3), 169.6 (C-11, 15), 186.4 (C-13); EIMS *m/z* 346 [M]$^+$ (10), 184 (100), 169 (50), 131 (15); HREIMS *m/z* [M]$^+$ 346.1418 (calcd for C$_{19}$H$_{22}$O$_6$, 346.1416).

***erythro*-Honokitriol (2):** colorless solid; [α]$_D$ −16.7 (*c* 1.0, MeOH); UV (MeOH) λ$_{max}$ (log ε) 291 (3.67), 256 (3.87), 213 (4.77) nm; IR (film) ν$_{max}$ 3375 (OH), 1600, 1485, 1267, 1081 cm$^{-1}$; $^1$H and $^{13}$C NMR, see Table 1; EIMS *m/z* 316 [M]$^+$ (4), 298 (74), 240 (100), 212 (26); HREIMS *m/z* [M]$^+$ 316.1313 (calcd for C$_{18}$H$_{20}$O$_5$, 316.1311).

***threo*-Honokitriol (3):** colorless solid; [α]$_D$ 9.3 (*c* 0.3, MeOH); UV (MeOH) λ$_{max}$ (log ε) 291 (3.87), 256 (4.06), 213 (4.45) nm; IR (film) ν$_{max}$ 3375 (OH), 1603, 1497, 1263, 1097 cm$^{-1}$; $^1$H and $^{13}$C NMR, see Table 1; EIMS *m/z* 316 [M]$^+$ (3), 298 (88), 240 (100), 212 (26); HREIMS *m/z* [M]$^+$ 316.1313 (calcd for C$_{18}$H$_{20}$O$_5$, 316.1311).

***erythro*-Magnolignan B (8a):** light brown gum; [α]$_D$ 1.3 (*c* 1.0, MeOH); UV (MeOH) λ$_{max}$ (log ε) 289 (3.97), 250 (sh), 220 (4.57) nm; $^1$H and $^{13}$C NMR, see Table 1; EIMS *m/z* 316 [M]$^+$ (2), 298 (34), 255 (90), 239 (100), 227 (13).

***threo*-Magnolignan B (8b):** light brown gum; [α]$_D$ 1.2 (*c* 0.5, MeOH); UV (MeOH) λ$_{max}$ (log ε) 290 (3.86), 250 (sh), 214 (4.59) nm;

$^1$H and $^{13}$C NMR, see Table 1; EIMS *m/z* 316 [M]$^+$ (2), 298 (30), 269 (41), 255 (58), 239 (100), 227 (10).

**Microglial Cell Culture and Measurement of Nitric Oxide (NO).**[17] A murine microglial cell line (BV2) was cultured in Dulbecco's modified Eagle medium with 5% fetal bovine serum. NO was determined by measuring the accumulation of nitrite 24 h after stimulation with LPS (0.5 μg/mL) by the Griess reagent.

**Measurement of ROS Production.**[5] BV2 cells were preloaded with 2′,7′-dichlorofluorescin diacetate and treated with test compounds for 20 min followed by stimulation with LPS. $H_2O_2$ was determined 30 min later by flow cytometry. Data are expressed as mean channel fluorescence (MCF).

**NOX Activity.**[17] O$_2^·$ in BV2 cell lysate was stimulated with NADPH in the presence of lucigenin. The chemiluminescence was monitored to determine the NOX activity.

**DPPH Radical-Scavenging Capacity Assay.**[17] The DPPH solution was added to a microplate containing the diluted drugs, and the absorbance was measured at 517 nm. The 50% inhibitory concentration (IC$_{50}$) values were calculated by the concentration−response curves for each drug.

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