

## Two New Stereoisomers of Tetrahydrofuranoid Lignans from the Flower Buds of *Magnolia fargesii*

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Two new stereoisomers of tetrahydrofuranoid lignans, 7*S*,8*R*,7'*S*,8'*R*- (**1**) and 7*R*,8*S*,7'*S*,8'*R*-3,4,3',4'-tetramethoxy-9,7'-dihydroxy-8,8',7,0.9'-lignan (**2**) along with nine known lignans including tetrahydrofuranoids (**3**, **4**) and tetrahydrofuranoids (**5**–**11**) were isolated from a CHCl<sub>3</sub>-soluble fraction of the flower buds of *Magnolia fargesii*. Two tetrahydrofuranoids, magnostellin A (**3**) and lariciresinol dimethyl ether (**4**) were isolated from this species for the first time. The structures of these compounds (**1**–**11**) were identified by spectroscopic methods as well as by comparison with published values. Absolute configurations of new stereoisomers (**1**, **2**) were determined by the Mosher's esterification method and Circular Dichroism (CD) studies. All the isolates (**1**–**11**) were evaluated for their antioxidant activities using modified superoxide radical-scavenging assay. Compounds **5**–**8** showed the potent superoxide radical-scavenging activities with the ED<sub>50</sub> values of 19.2, 19.2, 16.5, and 27.7 μM, respectively, as compared with standard antioxidants (BHA: 22.8 μM; Trolox: 940 μM).

**Key words** *Magnolia fargesii*; Magnoliaceae; Xinyi; lignan; tetrahydrofuranoid; antioxidant activity; superoxide radical

It is well-known that Xinyi, dried flower buds of *Magnolia fargesii* CHENG (Magnoliaceae), has been widely used for the treatment of empyema, nasal congestion, sinusitis, and allergic rhinitis due to its anti-inflammatory activity in Chinese herbal medicine.<sup>1)</sup> This species has been reported to contain many kinds of essential oils, lignans, neolignans, and sesquiterpenes associated with biological activities such as anti-platelet-activating factor (PAF), anti-TNFα, and calcium antagonism.<sup>2–6)</sup> During our research program to find antioxidants of plant origin, the chloroform extracts of *M. fargesii* showed significant activity, thus, the extracts were subjected to detailed laboratory investigation, affording compounds **5**–**8** as active principles along with inactive compounds, **1**–**4** and **9**–**11** (Fig. 1).

Compounds **1** and **2** were determined as the new stereoisomers, 7*S*,8*R*,7'*S*,8'*R*- (**1**) and 7*R*,8*S*,7'*S*,8'*R*-3,4,3',4'-tetramethoxy-9,7'-dihydroxy-8,8',7,0.9'-lignan (**2**), respectively, although their stereoisomers, 3,4,3',4'-tetramethoxy-9,7'-dihydroxy-8,8',7,0.9'-lignan, has been known previously.<sup>7–10)</sup> Compounds **3** and **4** were identified as the known tetrahydrofuranoid lignans, magnostellin A<sup>11)</sup> and lariciresinol dimethyl ether,<sup>12)</sup> respectively, which have been found in this plant for the first time. The known compounds, **5**–**11** were identified as fargesin,<sup>13)</sup> kobusin,<sup>14)</sup> aschantin,<sup>15)</sup> pinoresinol,<sup>16)</sup> eudesmin,<sup>13)</sup> magnolin,<sup>13)</sup> and yangambin,<sup>17)</sup> respectively, which were reported previously from this species. The structures of **1**–**11** were identified by various spectroscopic means including 1D and 2D NMR data analysis as well as by comparison with published data. To determine the absolute configurations of compounds **1** and **2**, the Mosher's esterification method<sup>18)</sup> and the CD data have been used.

Compound **1** was obtained as sticky oils, with the molecular formula of C<sub>22</sub>H<sub>28</sub>O<sub>7</sub> derived from the molecular ion peak at *m/z* 404.1828 in its HR-EI-MS. The UV spectrum of **1** showed absorption maxima at 230 and 277 nm due to the

presence of separate aromatic ring systems. Their IR spectra showed characteristic absorption bands at 3376 and 1596 cm<sup>-1</sup> for one or more hydroxyl(s) and aromatic group(s), respectively. The <sup>1</sup>H-NMR spectrum of **1** showed signals for four methoxyl groups attached to the aromatic systems at δ<sub>H</sub> 3.858 (3H, s), 3.864 (3H, s), 3.869 (3H, s), and 3.873 (3H, s). Two ABX systems of aromatic protons were resonated at δ<sub>H</sub> 6.82, 6.83, 6.87, 6.87, 6.88, and 6.89, supporting the presence of two veratryl groups. Six oxygenated aliphatic protons at δ<sub>H</sub> 3.90, 3.99, 4.05, 4.14, 4.94, and 5.09 together with two aliphatic protons at δ<sub>H</sub> 2.27 and 2.80 were evident for the presence of a tetrahydrofuranoid lignan skeleton. All the spectral data including 1D- and 2D-NMR spectra

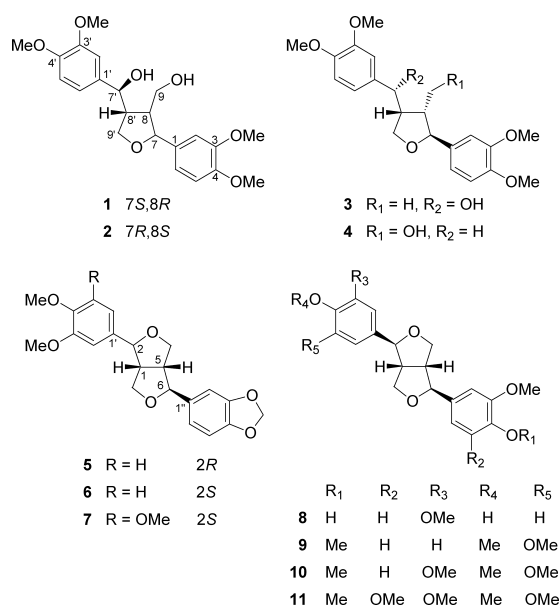


Fig. 1. Structures of Lignans **1**–**11** from the Flower Buds of *M. fargesii*

such as COSY, HSQC, and HMBC were similar with those of 3,4,3',4'-tetramethoxy-9,7'-dihydroxy-8,8',7,7'-lignan<sup>7-10</sup>) except for the stereochemistry at four chiral centers. The relative stereochemistry in the tetrahydrofuran ring was determined by its ROESY spectrum (Fig. 2). A ROESY correlation between H-7 and H-9 indicated that the two protons, H-7 and H-8, were oriented as *trans* each other. The ROE cross peak was observed between H-7' and H-9, whereas any ROE was not observed between H-8' and H-9. Thus, the relative configuration between H-8 and H-8' of **1** was determined to be *cis*. To solve the absolute configuration at C-7' of **1**, compound **1** was treated with (*S*)- and (*R*)-MTPA-Cl using the Mosher's esterification method<sup>18</sup>) affording (*R*)- and (*S*)-MTPA ester derivatives of **1** (**1r**, **1s**), respectively. The absolute configuration at C-7' of **1** was determined as *S* according to the values of  $\Delta\delta$  ( $\delta_S - \delta_R$ ), which were represented in Fig. 3. According to the published paper by Fukuyama's group,<sup>19</sup>) the Mosher's derivatization was performed after acetylation for the primary hydroxyl to determine the absolute configuration at C-7 of fargesol which is a stereoisomer of compound **1**. In the present study, the both hydroxyls were esterified by the MTPA reagents without acetylation. The  $\Delta\delta$  ( $\delta_S - \delta_R$ ) value patterns for the H-2' and H-8' in compound **1** treated with MTPA reagents, were similar with those of 7*S*,8*R*,7'*S*,8'*S*-(-)fargesol in the reference. Thus, it was assumed that the Mosher's esterification without acetylation in this study showed regular  $\Delta\delta$  ( $\delta_S - \delta_R$ ) values. On the other hand, to solve the absolute configurations at C-8', C-8, and C-7 in **1**, the Circular Dichroism spectrum of **1** was compared with that of tanegool.<sup>20,21</sup>) The CD spectrum of compound **1** ( $[\alpha]_D +25.4^\circ$ , CHCl<sub>3</sub>) showed the positive absorption peaks at 230 and 280 nm, which were identical with the known compound tanegool ( $[\alpha]_D +12.0^\circ$ , CHCl<sub>3</sub>). Thus, the structure of compound **1** was determined to be the new isomer, 7*S*,8*R*,7'*S*,8'*R*-3,4,3',4'-tetramethoxy-9,7'-dihydroxy-8,8',7,7'-lignan (**1**).

Compound **2** was obtained as sticky oils, with the molecular formula C<sub>22</sub>H<sub>28</sub>O<sub>7</sub> derived from its HR-EI-MS at *m/z* 404.1831. The <sup>1</sup>H- and <sup>13</sup>C-NMR spectra of **2** were similar with those of compound **1**. The COSY, HSQC, and HMBC of **2** showed similar peaks with those of **1**. There were apparent differences in the ROESY data of **1** and **2**. The relative configurations between H-7, H-8, and H-8' in the structure of **2** were determined as *trans* each other by the cross peaks of H-7/H-9, H-7/H-8', H-8/H-7', and H-8'/H-9 in the ROESY spectrum of **2** (Fig. 2). The absolute configuration at C-7' in **2** was determined as *S* by the Mosher's esterification method as shown in **1** (Fig. 3). The CD spectrum of compound **2** ( $[\alpha]_D -5.0^\circ$ , CHCl<sub>3</sub>) exhibited a negative absorption peak at 230 nm and a positive peak at 280 nm, which are different with those of compound **1** and tanegool. Thus, the structure of compound **2** was determined to be the new isomer, 7*R*,8*S*,7'*S*,8'*R*-3,4,3',4'-tetramethoxy-9,7'-dihydroxy-8,8',7,7'-lignan (**2**).

All the isolates (**1**–**11**) were evaluated for their antioxidant activities using a modified superoxide radical-scavenging assay.<sup>22</sup>) Compounds **5**–**8** showed the potent superoxide radical-scavenging activities with the ED<sub>50</sub> values of 19.2, 19.2, 16.5, and 27.7 μM, respectively, as compared with standard antioxidants (BHA: 22.8 μM; Trolox: 940 μM). These results supported that tetrahydrofuranoids having piperonyl

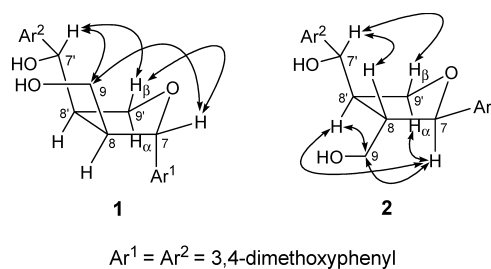


Fig. 2. Selected Correlations in the ROESY Spectra of Compounds **1** and **2**

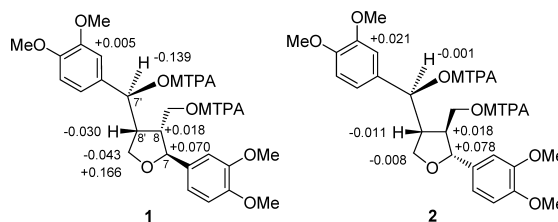


Fig. 3. The  $\Delta\delta$  ( $\delta_S - \delta_R$ ) Values of MTPA Esters of **1** and **2** by the Mosher's Esterification Method

or vanillyl type of phenyl rings (**5**–**8**) may contribute superoxide radical scavenging activity.

#### Experimental

**General Experimental Procedures** Optical rotations were obtained using a Perkin-Elmer polarimeter. IR spectra were recorded on a Bruker IFS66 infrared Fourier transform spectrophotometer (KBr) and UV spectra were measured on a Beckman DU650 spectrophotometer. CD spectra were obtained with a JASCO 715 spectropolarimeter. NMR experiments were conducted either on a Bruker (AM 500 MHz) FT-NMR or a Varian Inova (400 MHz) with tetramethylsilane (TMS) as internal standard. EI-MS and HR-EI-MS were recorded on a Jeol JMS-700 instrument operated at 70 eV. TLC analysis were performed on Kieselgel 60 F<sub>254</sub> (Merck) plates and silica gel (230–400 mesh) was used for column chromatography.

**Plant Material** The flower buds of *M. fargesii* were purchased from Daechang Oriental Herb Store in Jinju, South Korea. A voucher specimen (Lee, J. & M. S. Yang 021) was deposited at the Herbarium of Gyeongang National University (GNUC).

**Extraction and Isolation** The air-dried flower buds (1 kg) of *Magnolia fargesii* were extracted with MeOH (51×3) at room temperature. The combined extract was concentrated *in vacuo* to afford a brown gum (67 g), which was partitioned with chloroform and water. The chloroform layer was washed brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and then concentrated to give a thickish residue (34 g). The residue was chromatographed on a silica gel (650 g) column eluting with a gradient of 100% of chloroform to 100% MeOH to afford 40 fractions (F01–F40). Fraction F27 (0.66 g) were carried out silica gel chromatography with gradient mixture of CHCl<sub>3</sub> and acetone (19:1→4:1) to give 14 subfractions A01–A14. Fractions A09–A11 were chromatographed over silica gel, with CHCl<sub>3</sub>-acetonitrile gradient (from 19:1 to 2:1 v/v) to produce subfractions B01–B09. Further chromatographic separation of these fractions were carried out by preparative TLC to afford **1** (3.3 mg) and **2** (3.6 mg) (*R<sub>f</sub>*=0.59 and 0.62, respectively, CHCl<sub>3</sub>-acetone=3:2). Fraction F24 (0.78 g) was chromatographed over silica gel, with CHCl<sub>3</sub>-acetone gradient (from 99:1 to 1:3 v/v) to afford 17 fractions (C01–C17). From these, fractions C06–C08 were chromatographed over silica gel, with CHCl<sub>3</sub>-acetonitrile gradient (from 49:1 to 9:1 v/v) to produce subfractions D01–D13. Further chromatographic purification of these fractions were carried out by preparative TLC to give **3** (5.5 mg), **4** (6.3 mg), and **8** (7.5 mg) (*R<sub>f</sub>*=0.45, 0.42, and 0.48, respectively, CHCl<sub>3</sub>-acetone=3:1). Fraction F13 (0.92 g) was chromatographed over silica gel as stationary phase using a *n*-hexane-EtOAc gradient (from 4:1 to 1:1 v/v) as mobile phase to afford 11 fractions (G01–G11). Of these, fraction G03 (0.8 g) was chromatographed over silica gel, with CHCl<sub>3</sub>-acetone gradient (from 99:1 to 12:1 v/v) to produce subfractions H01–H06. Further chromatographic purification of these fractions were carried out by preparative TLC to give **5** (7.4 mg), **6** (8.8 mg), and **7** (9.6 mg) (*R<sub>f</sub>*=0.74,

0.63, and 0.57, respectively,  $\text{CHCl}_3$ -acetone=9:1). Fraction G09 (1.1 g) was chromatographed over silica gel, with  $\text{CHCl}_3$ -acetone gradient (from 99:1 to 12:1 v/v) to produce subfractions J01–J08. Further chromatographic purification of these fractions were carried out by preparative TLC to give **9** (21 mg), **10** (23 mg), and **11** (12 mg) ( $R_f$ =0.57, 0.50, and 0.44, respectively,  $\text{CHCl}_3$ -acetone=9:1).

**Compound 1:** Sticky oils;  $[\alpha]_D^{20} +25.4^\circ$  ( $c=0.5$ ,  $\text{CHCl}_3$ ). UV  $\lambda_{\text{max}}^{\text{MeOH}}$  nm (log  $\epsilon$ ): 230 (3.84), 277 (3.37). IR  $\nu_{\text{max}}^{\text{KBr}}$   $\text{cm}^{-1}$ : 3376, 3012, 2931, 2851, 1596, 1518, 1466, 1420. CD (MeOH,  $c=2.0 \times 10^{-4}$  M)  $\Delta\epsilon$  (nm): +1.0 (232), +0.53 (284).  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.27 (1H, m, H-8), 2.80 (1H, m, H-8'), 3.858 (3H, s, OMe), 3.864 (3H, s, OMe), 3.869 (3H, s, OMe), 3.873 (3H, s, OMe), 3.90 (1H, m, H-9), 3.99 (1H, dd,  $J=3.7$ , 11.3 Hz, H-9), 4.05 (1H, t,  $J=8.3$  Hz, H-9' $\alpha$ ), 4.14 (1H, t,  $J=8.6$  Hz, H-9' $\beta$ ), 4.94 (1H, d,  $J=7.0$  Hz, H-7), 5.09 (1H, d,  $J=3.7$  Hz, H-7'), 6.82 (1H, d,  $J=8.0$  Hz, H-5'), 6.83 (1H, d,  $J=7.8$  Hz, H-5), 6.87 (1H, m, H-6'), 6.87 (1H, m, H-6), 6.88 (1H, s, H-2), 6.89 (1H, s, H-2').  $^{13}\text{C-NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 46.1 (C-8'), 49.0 (C-8), 54.13, 54.16 (OMe, C-3'/C-4'/C-3/C-4), 58.5 (C-9), 66.5 (C-9'), 70.0 (C-7'), 80.6 (C-7), 107.2 (C-2'), 107.3 (C-2), 109.3 (C-5'), 109.4 (C-5), 116.0 (C-6'), 116.3 (C-6), 133.1 (C-1), 134.2 (C-1'), 146.65, 146.68 (C-4/C-4'), 147.32, 147.34 (C-3/C-3'). HMBC correlations: H-7/C-1, C-2, C-6, C-8, C-9, C-8', C-9'; H-8/C-7, C-9, C-7', C-8', C-9'; H-9/C-7, C-8, C-8'; H-7'/C-1', C-2', C-6', C-8, C-8', C-9'; H-8'/C-7, C-8, C-9, C-7', C-9'; H-9'/C-7, C-8, C-7', C-8'; H-2/C-1, C-3, C-4, C-6, C-7; H-5/C-1, C-3, C-4, C-6, C-7; H-6/C-1, C-2, C-4, C-5, C-7; H-2/C-1', C-3', C-4', C-6', C-7'; H-5/C-1', C-3', C-4', C-6', C-7'; H-6/C-1', C-2', C-4', C-5', C-7'; 3-OCH<sub>3</sub>/C-3; 4-OCH<sub>3</sub>/C-4; 3'-OCH<sub>3</sub>/C-3'; 4'-OCH<sub>3</sub>/C-4'. HR-EI-MS  $m/z$ : 404.1828 [ $\text{M}^+$ ] (Calcd for  $\text{C}_{22}\text{H}_{28}\text{O}_7$ , 404.1835). EI-MS  $m/z$  (70 eV, rel. int.): 404 ( $\text{M}^+$ , 23), 386 (34), 238 (20), 207 (29), 189 (31), 177 (84), 167 (95), 165 (100), 151 (65), 139 (62), 124 (14).

**Compound 2:** Sticky oils;  $[\alpha]_D^{20} -5.0^\circ$  ( $c=0.5$ ,  $\text{CHCl}_3$ ). UV  $\lambda_{\text{max}}^{\text{MeOH}}$  nm (log  $\epsilon$ ): 231 (4.06), 278 (3.59). IR  $\nu_{\text{max}}^{\text{KBr}}$   $\text{cm}^{-1}$ : 3355, 3006, 2928, 2847, 1598, 1513, 1459, 1428. CD (MeOH,  $c=2.0 \times 10^{-4}$  M)  $\Delta\epsilon$  (nm): -0.79 (230), +0.74 (299).  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.32 (1H, m, H-8), 2.61 (1H, m, H-8'), 3.61 (1H, t,  $J=7.0$  Hz, H-9' $\alpha$ ), 3.66 (2H, m, H-9/H-9' $\beta$ ), 3.76 (1H, dd,  $J=3.6$ , 10.5 Hz, H-9), 3.878 (3H, s, OMe), 3.888 (3H, s, OMe), 3.900 (3H, s, OMe), 3.902 (3H, s, OMe), 4.41 (1H, d,  $J=9.3$  Hz, H-7), 4.51 (1H, d,  $J=9.7$  Hz, H-7'), 6.83 (1H, d,  $J=8.2$  Hz, H-5'), 6.84 (1H, d,  $J=8.2$  Hz, H-5), 6.87 (1H, dd,  $J=1.9$ , 8.4 Hz, H-6), 6.89 (1H, dd,  $J=1.9$ , 8.2 Hz, H-6'), 6.91 (1H, d,  $J=1.7$  Hz, H-2), 6.92 (1H, d,  $J=1.8$  Hz, H-2').  $^{13}\text{C-NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 54.8 (C-8'), 57.1 (C-8), 57.36, 57.39 (OMe, C-3'/C-4'/C-3/C-4), 64.8 (C-9), 71.8 (C-9'), 79.0 (C-7'), 85.9 (C-7), 110.9 (C-2'), 111.0 (C-2), 112.49 (C-5), 112.54 (C-5'), 120.41 (C-6), 120.55 (C-6'), 134.7 (C-1), 136.7 (C-1'), 150.41, 150.55 (C-4/C-4'), 150.68, 150.76 (C-3/C-3'). HMBC correlations: H-7/C-1, C-2, C-6, C-8, C-9, C-8', C-9'; H-8/C-7, C-9, C-7', C-8', C-9'; H-9/C-7, C-8, C-8'; H-7'/C-1', C-2', C-6', C-8, C-8', C-9'; H-8'/C-7, C-8, C-9, C-7', C-9'; H-9'/C-7, C-8, C-7', C-8'; H-2/C-1, C-3, C-4, C-6, C-7; H-5/C-1, C-3, C-4, C-6, C-7; H-6/C-1, C-2, C-4, C-5, C-7; H-2/C-1', C-3', C-4', C-6', C-7'; H-5/C-1', C-3', C-4', C-6', C-7'; H-6/C-1', C-2', C-4', C-5', C-7'; 3-OCH<sub>3</sub>/C-3; 4-OCH<sub>3</sub>/C-4; 3'-OCH<sub>3</sub>/C-3'; 4'-OCH<sub>3</sub>/C-4'. HR-EI-MS  $m/z$ : 404.1831 [ $\text{M}^+$ ] (Calcd for  $\text{C}_{22}\text{H}_{28}\text{O}_7$ , 404.1835). EI-MS  $m/z$  (70 eV, rel. int.): 404 ( $\text{M}^+$ , 42), 238 (21), 207 (28), 189 (28), 177 (37), 167 (100), 165 (58), 151 (56), 139 (61).

**Preparation of (S)- and (R)-MTPA Ester Derivatives of 1 and 2 by a Mosher's Esterification Method** (S)- and (R)-MTPA esters of new stereoisomers (**1**, **2**) were prepared using a Mosher's esterification method previously described.<sup>18</sup> Dissolved compounds (**1**, **2**, each 2 mg), well-dried under vacuum condition, in pyridine-*d*<sub>5</sub> (1 ml) and divided equally into a NMR tubes, respectively. (S)-(+)- $\alpha$ - and (R)-(-)- $\alpha$ -methoxy- $\alpha$ -trifluoromethyl-phenylacetic acid chloride (MTPA-Cl) (10  $\mu\text{l}$ ), and catalyzer, 4-dimethylaminopyridine (4-DMAP) were added into the each NMR tubes immediately under a N<sub>2</sub> gas stream. The NMR tubes were shaken carefully to mix the compounds, MTPA-Cl, catalyzer evenly, and then the NMR tubes reacted in water bath for 4 h (40 °C). After the chemical reaction has finished, the unwanted products were removed by a mini silica gel column chromatography eluting with a 100%  $\text{CHCl}_3$  to afford pure (R)- and (S)-

MTPA ester derivatives of **1** and **2**, respectively.

(S)-MTPA Ester of **1**:  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.198 (1H, m, H-8), 3.088 (1H, m, H-8'), 4.253 (1H, dd,  $J=7.6$ , 11.2 Hz, H-9'), 4.398 (1H, dd,  $J=4.4$ , 11.2 Hz, H-9'), 4.780 (1H, d,  $J=4.0$  Hz, H-7), 5.834 (1H, d,  $J=10.4$  Hz, H-7'), 6.689 (1H, s, H-2').

(R)-MTPA Ester of **1**:  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.180 (1H, m, H-8), 3.118 (1H, m, H-8'), 4.087 (1H, dd,  $J=7.2$ , 11.2 Hz, H-9'), 4.441 (1H, dd,  $J=4.4$ , 11.2 Hz, H-9'), 4.710 (1H, d,  $J=4.4$  Hz, H-7), 5.973 (1H, d,  $J=10.0$  Hz, H-7'), 6.684 (1H, s, H-2').

(S)-MTPA Ester of **2**:  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.024 (1H, m, H-8), 2.741 (1H, m, H-8'), 3.491 (2H, m, H-9'), 4.462 (1H, d,  $J=9.2$  Hz, H-7), 5.848 (1H, d,  $J=9.6$  Hz, H-7'), 6.859 (1H, s, H-2').

(R)-MTPA Ester of **2**:  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.006 (1H, m, H-8), 2.752 (1H, m, H-8'), 3.499 (2H, m, H-9'), 4.384 (1H, d,  $J=8.4$  Hz, H-7), 5.849 (1H, d,  $J=10.4$  Hz, H-7'), 6.838 (1H, s, H-2').

**Superoxide Radical-Scavenging Activity** Superoxide radical-scavenging activities of compounds **1**–**11** were assayed by the modified irradiated riboflavin/EDTA/Nitroblue tetrazolium (NBT) system.<sup>22</sup>

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