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.*O*.9′-lignan (2) along with nine known lignans including tetrahydrofuranoids (3, 4) and tetrahydrofurofuranoids (5—11) were isolated from a $CHCl_3$-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_{50} 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.[1)] 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.[2—6)] 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.*O*.9′-lignan (**2**), respectively, although their stereoisomers, 3,4,3′,4′-tetramethoxy-9,7′-dihydroxy-8.8′,7.*O*.9′-lignan, has been known previously.[7—10)] Compounds **3** and **4** were identified as the known tetrahydrofuranoid lignans, magnostellin A[11)] and lariciresinol dimethyl ether,[12)] respectively, which have been found in this plant for the first time. The known compounds, **5**—**11** were identified as fargesin,[13)] kobusin,[14)] aschantin,[15)] pinoresinol,[16)] eudesmin,[13)] magnolin,[13)] and yangambin,[17)] 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[18)] and the CD data have been used.

Compound **1** was obtained as sticky oils, with the molecular formula of $C_{22}H_{28}O_7$ 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^{-1} for one or more hydroxyl(s) and aromatic group(s), respectively. The ^{1}H-NMR spectrum of **1** showed signals for four methoxyl groups attached to the aromatic systems at δ_H 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_H 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_H 3.90, 3.99, 4.05, 4.14, 4.94, and 5.09 together with two aliphatic protons at δ_H 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

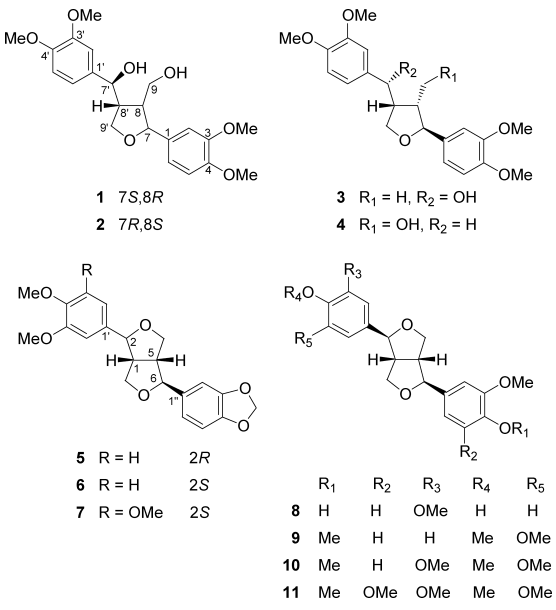

Fig. 1. Structures of Lignans **1**—**11** from the Flower Buds of *M. fargesii*

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such as COSY, HSQC, and HMBC were similar with those of 3,4,3′,4′-tetramethoxy-9,7′-dihydroxy-8.8′,7.*O*.9′-lignan[7—10] 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[18] affording (*R*)- and (*S*)-MTPA ester derivatives of **1** (**1r**, **s**), 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,[19] 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.[20,21] The CD spectrum of compound **1** ($[\alpha]_D$ +25.4°, $CHCl_3$) showed the positive absorption peaks at 230 and 280 nm, which were identical with the known compound tanegool ($[\alpha]_D$ +12.0°, $CHCl_3$). 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.*O*.9′-lignan (**1**).

Compound **2** was obtained as sticky oils, with the molecular formula $C_{22}H_{28}O_7$ derived from its HR-EI-MS at *m*/*z* 404.1831. The ^{1}H- and ^{13}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°, $CHCl_3$) 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.*O*.9′-lignan (**2**).

All the isolates (**1**—**11**) were evaluated for their antioxidant activities using a modified superoxide radical-scavenging assay.[22] Compounds **5**—**8** showed the potent superoxide radical-scavenging activities with the ED_{50} 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 tetrahydrofurofuranoids having piperonyl or vanillyl type of phenyl rings (**5**—**8**) may contribute superoxide radical scavenging activity.

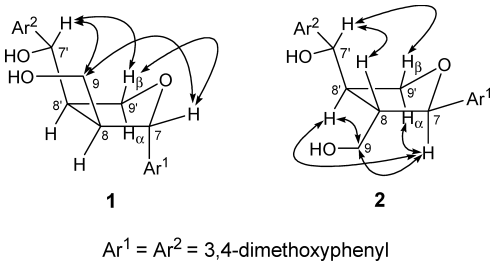

Fig. 2. Selected Correlations in the ROESY Spectra of Compounds **1** and **2**

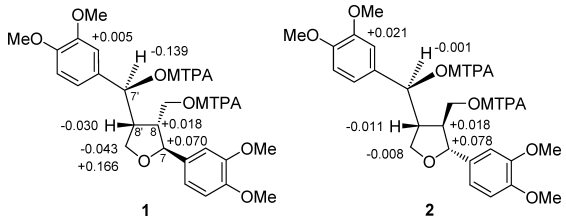

Fig. 3. The $\Delta\delta$ ($\delta_S-\delta_R$) Values of MTPA Esters of **1** and **2** by the Mosher's Esterification Method

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_{254} (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 Gyeongsang National University (GNUC).

Extraction and Isolation The air-dried flower buds (1 kg) of *Magnolia fargesii* were extracted with MeOH (5 l×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_2SO_4, 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 $CHCl_3$ and acetone (19 : 1→4 : 1) to give 14 subfractions A01—A14. Fractions A09—A11 were chromatographed over silica gel, with $CHCl_3$–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) (*Rf*=0.59 and 0.62, respectively, $CHCl_3$–acetone=3 : 2). Fraction F24 (0.78 g) was chromatographed over silica gel, with $CHCl_3$–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 $CHCl_3$–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) (*Rf*=0.45, 0.42, and 0.48, respectively, $CHCl_3$–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 $CHCl_3$–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) (*Rf*=0.74,

0.63, and 0.57, respectively, $CHCl_3$–acetone=9 : 1). Fraction G09 (1.1 g) was chromatographed over silica gel, with $CHCl_3$–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) (Rf=0.57, 0.50, and 0.44, respectively, $CHCl_3$–acetone=9 : 1).

Compound **1**: Sticky oils; $[\alpha]_D^{20}$ +25.4° (c=0.5, $CHCl_3$). UV λ_{max}^{MeOH} nm (log ε): 230 (3.84), 277 (3.37). IR ν_{max}^{KBr} cm^{-1}; 3376, 3012, 2931, 2851, 1596, 1518, 1466, 1420. CD (MeOH, $c=2.0\times10^{-4}$ M) $\Delta\varepsilon$ (nm): +1.0 (232), +0.53 (284). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 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′α), 4.14 (1H, t, J=8.6 Hz, H-9′β), 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}C-NMR (125 MHz, $CDCl_3$) δ: 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_3/C-3; 4-OCH_3/C-4; 3′-OCH_3/C-3′; 4′-OCH_3/C-4′. HR-EI-MS m/z: 404.1828 [M^+] (Calcd for $C_{22}H_{28}O_7$, 404.1835). EI-MS m/z (70 eV, rel. int.): 404 (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° (c=0.5, $CHCl_3$). UV λ_{max}^{MeOH} nm (log ε): 231 (4.06), 278 (3.59). IR ν_{max}^{KBr} cm^{-1}: 3355, 3006, 2928, 2847, 1598, 1513, 1459, 1428. CD (MeOH, $c=2.0\times10^{-4}$ M) $\Delta\varepsilon$ (nm): −0.79 (230), +0.74 (299). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.32 (1H, m, H-8), 2.61 (1H, m, H-8′), 3.61 (1H, t, J=7.0 Hz, H-9′α), 3.66 (2H, m, H-9/H-9′β), 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}C-NMR (125 MHz, $CDCl_3$) δ: 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_3/C-3; 4-OCH_3/C-4; 3′-OCH_3/C-3′; 4′-OCH_3/C-4′. HR-EI-MS m/z: 404.1831 [M^+] (Calcd for $C_{22}H_{28}O_7$, 404.1835). EI-MS m/z (70 eV, rel. int.): 404 (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.[18] Dissolved compounds (**1**, **2**, each 2 mg), well-dried under vacuum condition, in pyridine-d_5 (1 ml) and divided equally into a NMR tubes, respectively. (*S*)-(+)-α- and (*R*)-(−)-α-methoxy-α-trifluoromethyl-phenylacetic acid chloride (MTPA-Cl) (10 µl), and catalyzer, 4-dimethylaminopyridine (4-DMAP) were added into the each NMR tubes immediately under a N_2 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% $CHCl_3$ to afford pure (*R*)- and (*S*)-MTPA ester derivatives of **1** and **2**, respectively.

(*S*)-MTPA Ester of **1**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 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}H-NMR (400 MHz, $CDCl_3$) δ: 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}H-NMR (400 MHz, $CDCl_3$) δ: 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}H-NMR (400 MHz, $CDCl_3$) δ: 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.[22]

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