Two New Stereoisomers of Neolignan and Lignan from the Flower Buds of *Magnolia fargesii*

Jun LEE,[a] Eun-Kyoung SEO,[b] Dae Sik JANG,[a] Tae Joung HA,[c] Jong-Pyung KIM,[d] Joo-Won NAM,[b] Green BAE,[b] Yun Mi LEE,[a] Min Suk YANG,*,[e] and Jin Sook KIM*,[a]

[a] *Diabetes Research Center, Division of Traditional Korean Medicine (TKM) Integrated Research, Korea Institute of Oriental Medicine (KIOM); Daejeon 305–811, Korea:* [b] *Natural Product Chemistry Laboratory, College of Pharmacy & The Center for Cell Signaling and Drug Discovery Research, Ewha Womans University; Seoul 120–750, Korea:* [c] *Yeongnam Agricultural Research Institute, National Institute of Crop Science, Rural Development Administration; Miryang 627–803, Korea:* [d] *Korea Research Institute of Bioscience and Biotechnology; Daejeon 305–333, Korea: and* [e] *Division of Applied Life Science, Gyeongsang National University; Jinju 660–701, Korea.*
Received October 13, 2008; accepted December 4, 2008; published online January 6, 2009

A new stereoisomer of 8-*O*-4′ system neolignan, (7*R*,8*S*)-1-(3,4-dimethoxyphenyl)-2-[4-(3-hydroxy-1-propenyl)-2-methoxyphenoxy]-propane-1,3-diol (1) and a new stereoisomer of tetrahydrofuranoid lignan, (7*R*,8*S*,7′*S*,8′*R*)-(3,4,5,3′,4′)-pentamethoxy-9,7′-dihydroxy-8.8′,7.*O*.9′-lignan (2) along with seven known lignans and neolignans (3—9) were isolated from the methanol extracts of the flower buds of *Magnolia fargesii*. The structures of these compounds (1—9) were elucidated by spectroscopic methods including 1D- and 2D-NMR as well as by comparison with reported values. Absolute configurations of new stereoisomers 1 and 2 were determined by circular dichroism (CD) spectra. The absolute configuration of (7*S*,8*S*,10*S*)-[tetrahydro-4-hydroxy-2-(3,4,5-trimethoxyphenyl)furan-3-yl]methyl 3,4-dimethoxy benzoate (3) was determined by Mosher's esterification method for the first time in this study. Three lignans, tanegool (4), (+)-dehydrodiconiferyl alcohol (5), and epieudesmin (6), were isolated from this plant for the first time. Superoxide radical scavenging activities of the isolates (1—9) were measured by irradiated riboflavin/ethylenediaminetetraacetic acid (EDTA)/Nitroblue tetrazolium (NBT) system, and their *in vitro* rat lens aldose reductase (RLAR) inhibitory activities were also evaluated.

Key words *Magnolia fargesii*; lignan; superoxide radical; aldose reductase; diabetic complication

Members of *Magnolia* (Magnoliaceae) have traditionally been used for medicinal purposes in China for a long period of time. Especially, Xinyi, dried flower buds of *Magnolia fargesii* Cheng, has been used in Chinese herbal medicine for the treatment of inflammatory-related disease such as nasal congestion, empyema, sinusitis, and allergic rhinitis.[1] Previous phytochemical investigations have reported that this species contains several secondary metabolites such as lignans, neolignans, sesquiterpenes, and essential oils, which show various biological activities.[2—6]

Previous studies demonstrated that over-expressed aldose reductase (AR), the key enzyme in the polyol pathway, has been implicated in the pathogenesis of various diabetic complications such as cataract formation,[7] and associated with reactive oxygen species (ROS) production including superoxide radical, which also plays significant roles in the pathogenesis of diabetic complications.[8—10] Especially, superoxide radical is a precursor to other more harmful ROS including the hydroxyl radical, which induces various diseases such as diabetes, cancer, and cardiovascular disease.[11—13] Thus AR inhibitor and superoxide radical scavenger may contribute to the prevention or treatment of diabetic complications.

We previously reported that several tetrahydrofurofuranoid lignans with specific moiety showed potent superoxide radical-scavenging activities from this plant.[14] These results led to further phytochemical investigations on this species, affording two new stereoisomers of neolignan and lignan (**1**, **2**) along with seven known lignans and neolignans (**3**—**9**), as part of our ongoing program to discover new preventive agents for diabetic complications from medicinal herbs (Fig. 1). The structures of all the isolates (**1**—**9**) were elucidated by various spectroscopic methods including 1D- and 2D-NMR as well as by comparison with reported values. Especially, the absolute configurations of **1** and **2** were determined by circular dichroism (CD) studies and that of **3** by Mosher's esterification method for the first time in this study. Six compounds, previously known structures, were identified as tanegool (**4**),[15] (+)-dehydrodiconiferyl alcohol (**5**),[16] and epieudesmin (**6**),[17] (+)-de-*O*-methylmagnolin (**7**),[1] biondinin A (**8**),[18] and magnone B (**9**).[19] Three lignans **4**—**6** were isolated from this plant for the first time. In this paper, we describe the isolation and structural elucidation of the isolates (**1**—**9**) as well as their biological activities including superoxide radical scavenging activities and AR inhibitory activities.

Compound **1** was obtained as sticky oil with small amount. The molecular formula of **1** was determined as $C_{21}H_{26}O_7$ from the HR-ESI-MS at *m/z* 413.1595 [M+Na]$^+$ (Calcd for $C_{21}H_{26}O_7Na$, 413.1570), suggesting nine degrees of unsaturation. The ^{1}H-NMR spectrum of **1** revealed six aromatic proton signals at δ_H 6.84 (1H, d, J=8.4 Hz), 6.901 (1H, dd, J=2.0, 8.4 Hz), 6.904 (1H, d, J=8.0 Hz), 6.92 (1H, dd, J=2.0, 8.0 Hz), and 6.97 (2H, overlapping), supporting the presence of two ABX system aromatic rings. Three methoxyl groups attached to the aromatic rings at δ_H 3.875 (3H, s), 3.882 (3H, s), and 3.907 (3H, s) together with signals for *trans* double bond at δ_H 6.29 (1H, dt, J=6.0, 15.6 Hz) and 6.57 (1H, d, J=15.6 Hz) were also confirmed by the ^{1}H-NMR spectrum. Two oxygenated aliphatic methines (δ_H 4.17, 4.99) and two oxygenated aliphatic methylenes (δ_H 3.68, 3.93, 4.33) were also observed. The ^{13}C-NMR and distortionless enhancement by polarization transfer (DEPT)

* To whom correspondence should be addressed. e-mail: jskim@kiom.re.kr; msyang@nongae.gsnu.ac.kr © 2009 Pharmaceutical Society of Japan

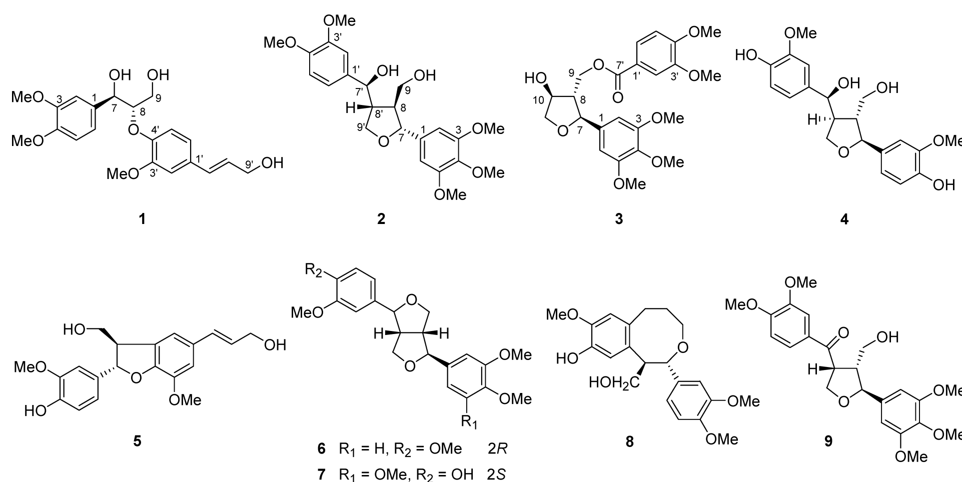

Fig. 1. Structures of Compounds **1**—**9** from the Flower Buds of *M. fargesii*

spectra presented carbon signals for 10 methines, 2 methylenes, 3 methyls, and 6 quaternary carbons. These 1D-NMR spectra suggested that nine degrees of unsaturation were presumed to be due to two aromatic rings and a double bond. The ^{1}H–^{1}H COSY spectrum showed good connectivities between both H-7/H8/H-9 and H-7′/H8′/H-9′ in the two propanyl groups. The positions of three methoxyl groups were determined by correlation peaks with C-3, C-4, and C-3′, and the connections of C-1 with C-7 and C-1′ with C-7′ in two phenylpropanoid units were determined by correlations peaks between H-7 with C-2/C-6 and H-7′ with C-2′/C-6′, in the HMBC spectrum (Fig. 2). The unassigned connection between two phenylpropanoid units was unambiguously demonstrated because the HMBC spectrum showed correlation peak of H-8 resonated at δ_H 4.17 with C-4′, which supported that compound **1** was 8-*O*-4′ system neolignan. The *erythro* configuration between two chiral centers at C-7 and C-8 positions was determined by its smaller coupling constant ($J_{7,8}$=4.8 Hz).[20,21] The "8*S*" absolute configuration was determined by its CD spectrum with both positive signs at 216 and 235 nm.[20,21] Thus the structure of **1** was determined to be a new stereoisomer of 8-*O*-4′ system neolignan, (7*R*,8*S*)-1-(3,4-dimethoxyphenyl)-2-[4-(3-hydroxy-1-propenyl)-2-methoxyphenoxy]-propane-1,3-diol (**1**). The synthesized 7*R*,8*R*-isomer of **1** has been reported with no spectral data previously.[22]

Compound **2** was obtained as sticky oil with small amount. Its molecular formula was determined as $C_{23}H_{30}O_8$ with nine degrees of unsaturation from the HR-EI-MS at *m/z*: 434.1945 $[M]^+$ (Calcd for $C_{23}H_{30}O_8$, 434.1941). The UV spectrum of **2** exhibited characteristic absorption maxima of tetrahydrofuranoid lignan at 228 and 278 nm. The presence of a veratryl group and a 3,4,5-trimethoxyphenyl group were suggested by ^{1}H-NMR spectrum, which showed five aromatic methoxyl groups at δ_H 3.83 (3H, s), 3.87 (6H, s), 3.88 (3H, s), and 3.90 (3H, s), together with five aromatic protons including ABX system signals at δ_H 6.84 (1H, d, J=8.0 Hz), 6.90 (1H, dd, J=1.8, 8.0 Hz), and 6.93 (1H, d, J=1.8 Hz), and a symmetrical singlet at δ_H 6.58 (2H, s). The ^{13}C-NMR and DEPT spectra showed two aromatic rings with carbon signals for 9 methines, 2 methylenes, 5 methyls, and 7 quaternary carbons, which supported that the extra degree of unsaturation except

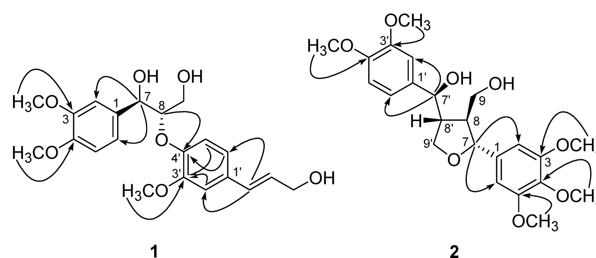

Fig. 2. Selected Correlations in the HMBC Spectra of **1** and **2**

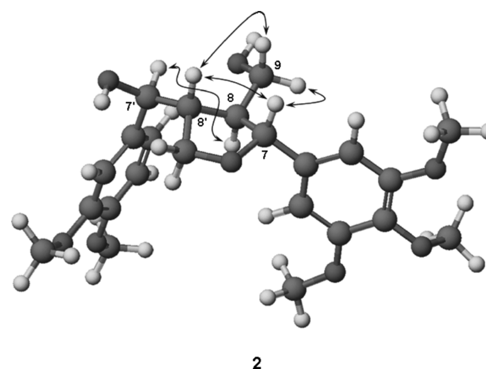

Fig. 3. Energy-Minimized 3D Structure by CAChe^{TM} 5.0 Molecular Modeling Program and Key ROESY Correlations of **2**

two phenyl rings was presumed to be due to tetrahydrofuran ring. The 8.8′-linked tetrahydrofuran skeleton between two propanyl groups was certified by good connectivities in the ^{1}H–^{1}H COSY spectrum, which showed correlations between H-8 with H-7/H-9/H-8′ and H-8′ with H-7′/H-9′/H-8. The veratryl and 3,4,5-trimethoxyphenyl groups were linked to C-7′ and C-7, respectively, since correlations between H-7′ with C-1′/C-2′/C-6′ and H-7 with C-1/C-2/C-6 were observed in the HMBC spectrum (Fig. 2). All *trans* orientation between H-7, H-8, and H-8′ of **2** was determined by the ROE cross peaks of H-7/H-9, H-7/H-8′, H-8/H-7′, and H-8′/H-9 in the ROESY spectrum (Fig. 3). The absolute configurations at the four chiral centers of **2** were determined by comparison of its CD data and $[\alpha]_D$ value with those of reference compound. The CD spectrum of **2** ($[\alpha]_D$ −33.6, $CHCl_3$) showed a negative sign at 238 nm and a positive sign at 284

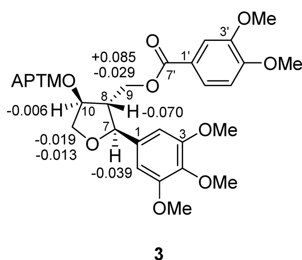

Fig. 4. The $\Delta\delta$ ($\delta_S - \delta_R$) Values of MTPA Esters of **3** by Mosher's Esterification Method

Table 1. Superoxide Radical Scavenging Activity and Inhibitory Activity on Rat Lens Aldose Reductase (RLAR) *in Vitro* of the Isolates from *M. fargesii* (n=3)

Compounds	Superoxide scavenging activity EC_{50} (μM)	RLAR inhibitory activity IC_{50} (μM)
1	18.3	>100
4	13.4	>100
5	42.2	>100
7	11.7	>100
8	54.4	36.6
9	62.8	54.6
PCs[a)]	31.7[b)]	28.7[c)]

a) Positive controls; *b*) butylated hydroxyanisole (BHA) and *c*) 3.3-tetramethyleneglutaric acid (TMG) were used as positive controls for superoxide scavenging and aldose reductase assay, respectively. Compounds **2**, **3**, and **6** were not active in both superoxide radical scavenging and RLAR assay systems.

nm, which were identical with the known analogous compound[14)] ([α]$_D$ −5.0, $CHCl_3$) having 7*R*,8*S*,7′*S*,8′*R*-configuration. Thus the structure of **2** was determined to be a new stereoisomer of tetrahydrofuranoid lignan, (7*R*,8*S*,7′*S*,8′*R*)-(3,4,5,3′,4′)-pentamethoxy-9,7′-dihydroxy-8.8′,7.*O*.9′-lignan (**2**). In our previous works, compound **3**, a structurally rare neolignan having C_6–C_5–*O*–C_7 skeleton, has been reported as a new compound[23)] with no absolute stereochemistry due to its small amounts. In this study, further investigation on this plant led to the additional isolation of **3** and successful absolute configurations, which were determined by Mosher's esterification method performed in NMR tubes (Fig. 4).[24)] Consequently, the absolute configuration of **3** was demonstrated as (7*S*,8*S*,10*S*)-[tetrahydro-4-hydroxy-2-(3,4,5-trimethoxyphenyl)furan-3-yl]methyl 3,4-dimethoxy benzoate (**3**).

To evaluate antioxidant activities of isolates (**1**—**9**), their superoxide radical scavenging activities were measured by irradiated riboflavin/ethylenediaminetetraacetic acid (EDTA)/Nitroblue tetrazolium (NBT) system.[25)] Additionally, the isolates were subjected to an *in vitro* bioassay system[26,27)] to evaluate their rat lens aldose reductase (RLAR) inhibitory activities. As a result, compounds **1**, **4**, **5**, and **7**—**9** showed significant superoxide radical scavenging activities compared with standard antioxidant, BHA. Especially, compounds **1**, **4**, and **7** exhibited potent scavenging activities with the EC_{50} values of 18.3, 13.4, and 11.7 μM, respectively, (BHA: 31.7 μM), whereas, compounds **8** and **9** showed both radical scavenging and AR inhibitory activities. As has been noted in our previous report,[14)] these results also supported that lignans (neolignans) having phenyl ring(s) hydroxylated at the *para* position including vanillyl groups revealed potent superoxide radical scavenging activities. Oxidative stress and AR are associated with various diabetic complications as discussed above. Thus *M. fargesii* could be considered as a good medicinal source for prevention or treatment of diabetic complications.

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) and a Varian Inova (400 MHz) FT-NMR with tetramethylsilane (TMS) as internal standard. EI-MS and HR-EI-MS were recorded on a Jeol JMS-700 instrument operated at 70 eV. ESI-MS and HR-ESI-MS were recorded on a Mariner instrument (Perseptive Biosystem, U.S.A.). TLC analysis was performed on Silica gel 60 F_{254} (Merck) and RP-18 F_{254S} (Merck) plates. Silica gel (230—400 mesh, Merck) and RP-18 YMC·GEL (ODS-A, 12 nm, S-150 μm) were 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 of *Magnolia fargesii* (1 kg) were extracted with MeOH (5l×3) at room temperature. The extract was concentrated *in vacuo* to afford a dark brown gum (304 g), which was dissolved in water and continuously partitioned with solvents, then concentrated to give sticky extracts of *n*-hexane (113 g), EtOAc (139 g), *n*-BuOH (25 g), and water (25 g) layer, respectively. The EtOAc extract (139 g) was chromatographed on a Si gel column eluted with a gradient mixture of 100% $CHCl_3$ to 100% MeOH to afford 45 fractions (F01—F45). Fraction F29 was chromatographed on a Si gel column eluted with $CHCl_3$/acetone gradient mixture (9 : 1→4 : 1) to afford 14 subfractions A01—A14. Fractions A11—A13 were chromatographed on a Sephadex LH-20 column (MeOH 100%) to give 10 subfractions AA01—AA10. Further chromatographic separations of these fractions were carried out by ODS-A reverse phase column (MeOH/water=1 : 1) to give **1** (1.6 mg), **4** (1.4 mg), and **5** (1.8 mg). Fraction F27 was chromatographed on a Si gel column eluted with $CHCl_3$/acetone gradient mixture (9 : 1→4 : 1) to produce 11 subfractions B01—B11. Compounds **2** (2.7 mg, purified by Prep. TLC), **3** (3.1 mg), **8** (22 mg), and **9** (6 mg) were obtained from fractions B06—B08 by Si gel column chromatography ($CHCl_3$/AcN=9 : 1→2 : 1). Fraction F24 was chromatographed on a Si gel column ($CHCl_3$/acetone=49 : 1→19 : 1) to afford 15 subfractions D01—D15. Fractions D08 was chromatographed on a Si gel column ($CHCl_3$/AcN=49 : 1→19 : 1) to give **7** (5.5 mg). Fraction F13 was chromatographed on a Si gel column eluted with *n*-hexane/EtOAc gradient mixture (4 : 1→2 : 1) to give 11 subfractions E01—E11. Fraction E06 was chromatographed on a Si gel column ($CHCl_3$/acetone=99 : 1→49 : 1) to give **6** (3.8 mg).

Compound **1**: Sticky oil; $[\alpha]_D^{20}$ +5.0 (c=0.1, MeOH). UV λ_{max}^{MeOH} nm (log ε): 206 (4.55), 267 (4.07). CD (MeOH, c=1.6×10^{-4} M) $\Delta\varepsilon$ (nm): +1.99 (216), +2.53 (235). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.68 (1H, br d, J=11.6 Hz, H-9), 3.875 (3H, s, 4-OMe), 3.882 (3H, s, 3-OMe), 3.907 (3H, s, 3′-OMe), 3.93 (1H, dd, J=5.6, 12.0 Hz, H-9), 4.17 (1H, m, H-8), 4.33 (2H, d, J=5.6 Hz, H-9′), 4.99 (1H, d, J=4.8 Hz, H-7), 6.29 (1H, dt, J=6.0, 15.6 Hz, H-8′), 6.57 (1H, d, J=15.6 Hz, H-7′), 6.84 (1H, d, J=8.4 Hz, H-5), 6.901 (1H, dd, J=2.0, 8.4 Hz, H-6), 6.904 (1H, d, J=8.0 Hz, H-5′), 6.92 (1H, dd, J=2.0, 8.0 Hz, H-6′), 6.97 (2H, overlapping, H-2/H-2′). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 56.0 (OMe, C-3/C-4/C-3′), 60.8 (C-9), 63.7 (C-9′), 72.8 (C-7), 87.5 (C-8), 109.2 (C-2), 109.9 (C-2′), 111.1 (C-5), 118.4 (C-6), 120.1 (C-6′), 120.9 (C-5′), 128.2 (C-8′), 130.5 (C-7′), 132.4 (C-1), 133.1 (C-1′), 146.6 (C-4′), 148.6 (C-4), 149.1 (C-3), 151.6 (C-3′). HR-ESI-MS m/z: 413.1595 [M+Na]$^+$ (Calcd for $C_{21}H_{26}O_7Na$: 413.1570). ESI-MS (positive ion mode) m/z: 413 [M+Na]$^+$.

Compound **2**: Sticky oils; $[\alpha]_D^{20}$ −33.6 (c=0.4, $CHCl_3$). UV λ_{max}^{MeOH} nm (log ε): 228 (4.06), 278 (3.40). IR ν_{max}^{KBr} cm^{-1}: 3360, 3006, 2930, 2846, 1594, 1511, 1460, 1422. CD (MeOH, c=2.0×10^{-4} M) $\Delta\varepsilon$ (nm): −2.48 (238), +0.65 (284). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.33 (1H, m, H-8), 2.62 (1H, m, H-8′), 3.61—3.71 (3H, m, H-9′/H-9), 3.82 (1H, dd, J=3.4, 6.9 Hz, H-9), 3.83 (3H, s, 4-OMe), 3.87 (6H, s, 3,5-OMe), 3.88 (3H, s, 4′-OMe), 3.90 (3H, s, 3′-OMe), 4.40 (1H, d, J=9.1 Hz, H-7), 4.51 (1H, d, J=9.7 Hz, H-7′),

6.58 (2H, s, H-2/H-6), 6.84 (1H, d, $J=8.0$ Hz, H-5′), 6.90 (1H, dd, $J=1.8$, 8.0 Hz, H-6′), 6.93 (1H, d, $J=1.8$ Hz, H-2′). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 53.7 (C-8′), 56.1 (C-8), 56.4, 56.6 (OMe, C-3′/C-4′/C-3/C-4), 61.2 (OMe), 63.9 (C-9), 70.9 (C-9′), 77.7 (C-7′), 85.0 (C-7), 103.8 (C-2/C-6), 109.8 (C-2′), 111.5 (C-5′), 119.5 (C-6′), 135.6 (C-1′), 136.9 (C-1), 138.3 (C-4), 149.6 (C-4′), 149.8 (C-3′), 153.8 (C-3/C-5). HR-EI-MS *m/z*: 434.1945 [M^+] (Calcd for $C_{23}H_{30}O_8$: 434.1941). EI-MS *m/z* (70 eV, rel. int.): 434 (M^+, 78), 268 (24), 237 (31), 224 (68), 195 (35), 177 (58), 167 (100), 165 (61), 151 (52), 139 (69).

Compound **3**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.57 (1H, m, H-8), 3.83 (3H, s, 4-OMe), 3.84 (6H, s, 3, 5-OMe), 3.91 (3H, s, 3′-OMe), 3.94 (3H, s, 4′-OMe), 4.08 (2H, d, $J=4.4$ Hz, H-11), 4.47 (3H, m, H-9/H-10), 4.63 (1H, d $J=8.0$ Hz, H-7), 6.66 (2H, s, H-2/H-6), 6.88 (1H, d, $J=8.4$ Hz, H-5′), 7.50 (1H, d, $J=2.0$ Hz, H-2′), 7.58 (1H, dd, $J=2.0$, 8.4 Hz, H-6′).

Preparation of (*S*)- and (*R*)-MTPA Ester Derivatives of 3 by Mosher's Esterification Method (*S*)- and (*R*)-MTPA esters of **3** were prepared using Mosher's esterification method performed in NMR tubes in the same manner as described previously.[24]

(*S*)-MTPA Ester of **3**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.666 (1H, m, H-8), 4.082 (1H, dd, $J=5.6$, 10.0 Hz, H-11), 4.350 (1H, br d, $J=11.2$ Hz, H-9), 4.485 (1H, dd, $J=5.8$, 12.0 Hz, H-11), 4.536 (1H, dd, $J=5.6$, 11.2 Hz, H-9), 4.588 (1H, d, $J=7.6$ Hz, H-7), 5.589 (1H, dd, $J=2.0$, 3.2 Hz, H-10).

(*R*)-MTPA Ester of **3**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.736 (1H, m, H-8), 4.101 (1H, dd, $J=4.4$, 11.2 Hz, H-11), 4.265 (1H, br d, $J=10.8$ Hz, H-9), 4.498 (1H, dd, $J=6.4$, 11.6 Hz, H-11), 4.565 (1H, dd, $J=5.6$, 11.2 Hz, H-9), 4.627 (1H, d, $J=6.8$ Hz, H-7), 5.595 (1H, dd, $J=2.8$, 4.0 Hz, H-10).

Superoxide Radical Scavenging Activity Superoxide radical scavenging activities of compounds **1**—**9** were measured by modified irradiated riboflavin/ethylenediaminetetraacetic acid (EDTA)/Nitroblue tetrazolium (NBT) system described previously.[25]

Rat Lens Aldose Reductase (RLAR) Inhibitory Activity Rat lens aldose reductase acquired from the eyes of 8 weeks old Sprague-Dawley rats was used for assay according to methods described previously.[26,27]

Acknowledgments This research was supported by a grant [L08010] from Korea Institute of Oriental Medicine. NMR and MS experiments were performed by the Korea Basic Science Institute (KBSI).

References

1) Miyazawa M., Kasahara H., Kameoka H., *Phytochemistry*, **31**, 3666—3668 (1992).
2) Pan J. X., Hensens O. D., Zink D. L., Chang M. N., Hwang S. B., *Phytochemistry*, **26**, 1377—1379 (1987).
3) Chen C. C., Huang Y. L., Chen H. T., Chen Y. P., Hsu H. Y., *Planta Med.*, **54**, 438—440 (1988).
4) Jung K. Y., Kim D. S., Oh S. R., Park S. H., Lee I. S., Lee J. J., Shin D. H., Lee H. K., *J. Nat. Prod.*, **61**, 808—811 (1998).
5) Chae S. H., Kim P. S., Cho J. Y., Park J. S., Lee J. H., Yoo E. S., Baik K. U., Lee J. S., Park M. H., *Arch. Pharm. Res.*, **21**, 67—69 (1998).
6) Cho J. Y., Yoo E. S., Baik K. U., Park M. H., *Arch. Pharm. Res.*, **22**, 348—353 (1999).
7) Beyer-Mears A., Cruz E., *Diabetes*, **34**, 15—21 (1985).
8) Maritim A. C., Sanders R. A., Watkins J. B., *J. Biochem. Mol. Toxicol.*, **17**, 24—38 (2003).
9) Rahimi R., Nikfar S., Larijani B., Abdollahi M., *Biomed. Pharmacother.*, **59**, 365—373 (2005).
10) Niedowicz D. M., Daleke D. L., *Cell Biochem. Biophys.*, **43**, 289—330 (2005).
11) Hemnani T., Parihar M. S., *Indian J. Physiol. Pharmacol.*, **42**, 440—452 (1998).
12) Nabasree D., Bratati D., *Food Chem.*, **88**, 219—224 (2004).
13) Wu S. J., Ng L. T., Lin C. C., *Phytother. Res.*, **18**, 1008—1012 (2004).
14) Lee J., Lee D., Jang D. S., Nam J. W., Kim J. P., Park K. H., Yang M. S., Seo E. K., *Chem. Pharm. Bull.*, **55**, 137—139 (2007).
15) Francisco A. M., Adriana L., Rosa M. V., Ascension T., Jose M. G. M., *J. Agric. Food Chem.*, **52**, 6443—6447 (2004).
16) Hirai N., Okamoto M., Udagawa H., Yamamuro M., Kato M., Koshimizu K., *Biosci. Biotechnol. Biochem.*, **58**, 1679—1684 (1994).
17) Iida T., Nakano M., Ito K., *Phytochemistry*, **21**, 673—675 (1982).
18) Ma Y. L., Huang Q., Han G. Q., *Phytochemistry*, **41**, 287—288 (1996).
19) Jung K. Y., Kim D. S., Oh S. R., Park S. H., Lee I. S., Lee J. J., Shin D. H., Lee H. K., *J. Nat. Prod.*, **61**, 808—811 (1998).
20) Fang J. M., Lee C. K., Cheng Y. S., *Phytochemistry*, **31**, 3659—3661 (1992).
21) Marina D. G., Antonio M., Pietro M., Lucio P., *Phytochemistry*, **35**, 777—779 (1994).
22) Tezuka Y., Kasimu R., Li J. X., Basnet P., Tanaka K., Namba T., Kadota S., *Chem. Pharm. Bull.*, **46**, 107—112 (1998).
23) Lee J., Yang M. S., Nam S. H., Shon M. Y., Hwang S. W., Park K. H., *Bull. Korean Chem. Soc.*, **26**, 913—915 (2005).
24) Su B. N., Park E. J., Mbwambo Z. H., Santarsiero B. D., Mesecar A. D., Fong H. H. S., Pezzuto J. M., Kinghorn A. D., *J. Nat. Prod.*, **65**, 1278—1282 (2002).
25) Lertvorachon J., Kim J. P., Soldatov D. V., Boyd J., Roman G., Cho S. J., Popek T., Jung Y. S., Lau P. C., Konishi Y., *Bioorg. Med. Chem.*, **13**, 4627—4637 (2005).
26) Kim H. Y., Oh J. H., *Biosci. Biotechnol. Biochem.*, **63**, 184—188 (1999).
27) Matsuda H., Morikawa T., Toguchida I., Yoshikawa M., *Chem. Pharm. Bull.*, **50**, 788—795 (2002).