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Note

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Chemical Constituents from the Aerial Parts of *Aster koraiensis* with Protein Glycation and Aldose Reductase Inhibitory Activities

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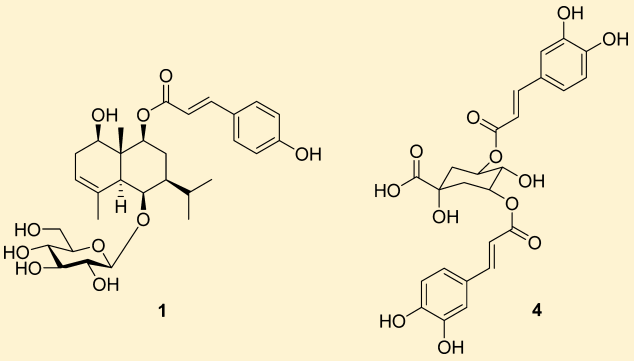
Supporting Information

ABSTRACT: Two new eudesmane-type sesquiterpene glucosides, 9β-*O*-(*E*-*p*-hydroxycinnamoyl)-1β,6β-dihydroxy-*trans*-eudesm-3-en-6-*O*-β-D-glucopyranoside (**1**) and 9α-*O*-(*E*-*p*-hydroxycinnamoyl)-1α,6α-11-trihydroxy-*trans*-eudesm-3-en-6-*O*-β-D-glucopyranoside (**2**), were isolated by the activity-guided fractionation of an EtOAc-soluble fraction from the aerial parts of *Aster koraiensis*. A new dihydrobenzofuran glucoside, (2*R*,3*S*)-6-acetyl-2-[1-*O*-(β-D-glucopyranosyl)-2-propenyl]-5-hydroxy-3-methoxy-2,3-dihydrobenzofuran (**3**), was also isolated, in addition to 15 known compounds. The structures of **1**−**3** were determined by spectroscopic data interpretation. All of the isolates were evaluated for in vitro inhibitory activity against the formation of advanced glycation end-products and rat lens aldose reductase.



Aster koraiensis (Nakai) Kitamura (syn. *Gymnaster koraiensis*, Compositae), an endemic Korean species, is distributed in the southern and central parts of the Korean peninsula and Jeju Island. It is grown widely as a decorative plant for its beautiful and long-lasting flowers, and its young leaves and stems are used as a food source in Korea. This plant has been used to remedy pertussis, chronic bronchitis, and pneumonia in traditional Korean medicine.[1−4] Previous research on this plant has reported that it contains several types of polyacetylenes,[5−7] benzofurans,[8] and sesquiterpenoids[9,10] associated with biological activities such as cytotoxicity,[5] modulation of antinuclear factor in activated T cells,[7] and hepatoprotection.[11]

As part of an ongoing project directed toward discovering new preventive agents against diabetic complications using medicinal herbs, it has been reported previously that an ethanol extract from the aerial parts of *A. koraiensis* showed a preventive effect against diabetic nephropathy.[12] No other studies on diabetes or diabetic complications by this herb have been reported. In the present investigation, three new compounds (**1**−**3**) and 15 known compounds were isolated from this plant. All of the isolates were evaluated in vitro for their inhibitory activity against the formation of advanced glycation end-products (AGEs) and rat lens aldose reductase (RLAR; alditol/NADP$^+$ oxidoreductase, E.C.1.1.1.21). Previous studies have demonstrated that AGE accumulation and AR play an important role in the pathogenesis of diabetic complications, such as cataracts, retinopathy, neuropathy, and nephropathy.[13−18] Thus, the elucidation of AGE and AR inhibitors may be a potential therapeutic strategy for the prevention and treatment of diabetic complications.[19,20]

Compound **1** was obtained as a white, amorphous solid with the molecular formula $C_{30}H_{42}O_{10}$, which was deduced from the HRESIMS peak at *m*/*z* 561.2708 [M − H]$^-$ (calcd for $C_{30}H_{41}O_{10}$, 561.2705). In addition to the signals for a glucopyranose unit, the ^{13}C NMR data showed signals for 28 carbons, comprising a carbonyl group (δ 168.8), four methyl groups (δ 21.9, 21.8, 21.8, 11.8), two sp^3 methylenes (δ 29.6, 29.1), three sp^3 methines (δ 52.2, 51.4, 29.1), three oxygenated methines (δ 81.3, 80.3, 75.9), five sp^2 methines (δ 146.8, 131.4, 120.2, 117.0, 116.3), and four quaternary carbons (δ 161.4, 136.2, 127.3, 42.2). The ^{1}H NMR spectrum showed signals for *trans*-α,β-unsaturated protons [δ 7.63 (1H, d, *J* = 16.0 Hz), 6.34 (1H, d, *J* = 16.0 Hz)], two aromatic protons [δ 7.48 (2H, d, *J* = 8.5 Hz), 6.81 (2H, d, *J* = 8.5 Hz)], and a *E*-*p*-hydroxycinnamoyl group. On the basis of the ^{1}H, ^{13}C, and 2D-NMR data (^{1}H−^{1}H COSY, HMQC, and HMBC) and a comparison of NMR data with eudesmane sesquiterpenes,[10] **1** was found to be similar to 1,6-dihydroxyeudesm-3-ene, except for the glucopyranosyl and *E*-*p*-hydroxycinnamoyl groups. The β-form of D-glucose was assigned using the coupling constant of the anomeric proton

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(δ 4.39, J = 8.0 Hz).[21] The HMBC correlations of H-1″ [δ 4.39 (1H, d, J = 8.0 Hz)] with C-6 (δ 75.9) and of H-9 [δ 4.98 (1H, dd, J = 10.5 and 6.0 Hz)] with C-9′ (δ 168.8) indicate that the D-glucopyranose and *E*-*p*-hydroxycinnamoyl groups are linked to C-6 and C-9, respectively. The relative configurations of the hydroxy groups at C-1, C-6, and C-9 were all β, based on the NOESY correlations for H-1 with H-5/H-9, H-7 with H-5/H-6/H-9, and H-9 with H-5 (Figure 1), whereas no NOESY

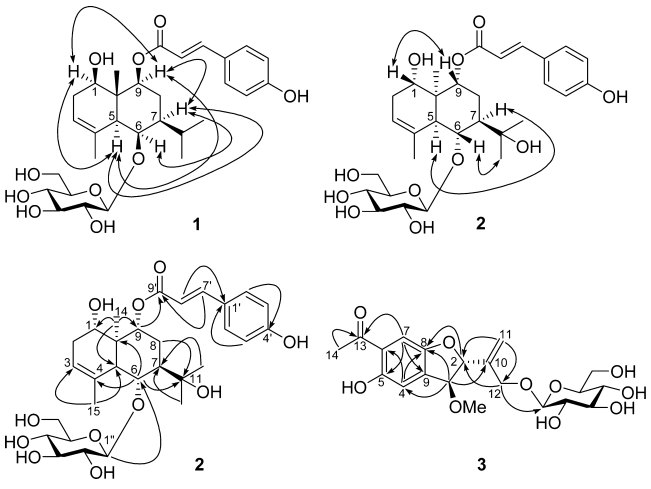

Figure 1. Key NOESY (↔, **1** and **2**) and HMBC (→, **2** and **3**) correlations.

correlation was observed with H-14. Thus, compound **1** was assigned as 9β-*O*-(*E*-*p*-hydroxycinnamoyl)-1β,6β-dihydroxy-*trans*-eudesm-3-en-6-*O*-β-D-glucopyranoside.

Compound **2** was obtained as a white, amorphous solid with the molecular formula $C_{30}H_{42}O_{11}$ from the HRESIMS peak at m/z 601.2616 $[M + Na]^+$ (calcd for $C_{30}H_{42}O_{11}Na$, 601.2619). The NMR spectra for **2** were similar to compound **1** except for an additional quaternary oxygenated carbon signal in the ^{13}C NMR spectrum being observed. Compound **2** exhibited signals for three oxygenated methines (δ 79.9, 80.2, 80.1) and an additional quaternary oxygenated carbon (δ 72.7). The position of the quaternary oxygenated carbon at δ 72.7 was established as C-11 because the coupling pattern [δ 1.37 (3H, s) and 1.21 (3H, s)] in the ^1H NMR spectrum was different from that for **1** (Table 1). Further, the C-11 (δ 72.7) signal correlated with H-6 and H-8 in the HMBC experiment (Figure 1). The relative configuration was confirmed from the NOESY data (Figure 1), which showed correlations between H-1 and H-9, H-7 and H-5, and H-6 and H-12. Therefore, compound **2** was established as 9α-*O*-(*E*-*p*-hydroxycinnamoyl)-1α,6α-11-trihydroxy-*trans*-eudesm-3-en-6-*O*-β-D-glucopyranoside.

Compound **3** was obtained as a yellowish solid with the molecular formula $C_{20}H_{26}O_{10}$, observed from the HRESIMS at m/z 449.1418 $[M + Na]^+$ (calcd for $C_{20}H_{26}O_{10}Na$, 449.1418). The ^1H and ^{13}C NMR data showed signals for a carbonyl group, a sp^2 methylene, a sp^3 oxygenated methylene, two oxygenated methines, two aromatic methines, a methyl, a methoxy group, and five sp^2 quaternary carbons, in addition to a glucopyranose moiety. A carbonyl, four double bonds, and a glucopyranose were evident from the ^{13}C NMR data. On the basis of the ^1H, ^{13}C, and 2D-NMR (^1H–^1H COSY, HMQC, and HMBC), the two degrees of unsaturation remaining were attributed to a benzofuran ring system with a $-C(CH_2)-CH_2$-OH unit and one acetyl group. In the HMBC experiment on **3**,

Table 1. ^1H and ^{13}C NMR Data (CD_3OD) for Compounds 1 and 2

	1		**2**	
position	δ_H (J in Hz)	δ_C, mult.	δ_H (J in Hz)	δ_C, mult.
1	4.89 m[a]	81.3, CH	4.91 dd (10.0, 6.0)	79.9, CH
2α	2.25 m	29.6, CH_2	2.24 m	29.4, CH_2
2β	2.09 m			
3	5.30 brs	120.2, CH	5.33 brs	120.9, CH
4		136.2, C		135.9, C
5	2.11 brs	52.2, CH	2.12 brs	52.4, CH
6	4.47 brs	75.9, CH	4.50 brs	80.2, CH
7	1.18 m	51.4, CH	1.56 m	51.3, CH
8α	1.93 m	29.1, CH_2	2.19 m	26.0, CH_2
8β			1.90 m	
9	4.98 dd (10.5, 6.0)	80.3, CH	5.05 dd (11.5, 4.5)	80.1, CH
10		42.2, C		42.3, C
11	1.98 m	29.1, CH		72.7, C
12	1.02 d (6.5)	21.8, CH_3	1.37 s	29.1, CH_3
13	0.92 d (6.5)	21.8, CH_3	1.21 s	29.4, CH_3
14	1.37 s	11.8, CH_3	1.39 s	12.1, CH_3
15	1.87 s	21.9, CH_3	1.77 s	22.3, CH_3
1′		127.3, C		127.2, C
2′	7.48 d (8.5)	131.4, CH	7.48 d (8.5)	131.5, CH
3′	6.81 d (8.5)	117.0, CH	6.80 d (8.5)	117.1, CH
4′		161.4, C		161.8, C
5′	6.81 d (8.5)	117.0, CH	6.80 d (8.5)	117.1, CH
6′	7.48 d (8.5)	131.4, CH	7.48 d (8.5)	131.5, CH
7′	7.63 d (16.0)	146.8, CH	7.62 d (16.0)	146.8, CH
8′	6.34 d (16.0)	116.3, CH	6.33 d (16.0)	116.0, CH
9′		168.8, C		168.9, C
1″	4.39 d (8.0)	104.4, CH	4.40 d (8.0)	105.4, CH
2″	3.16 brt (8.0)	76.2, CH	3.18 dd (9.0, 7.5)	75.8, CH
3″	3.32 m	78.5, CH	3.38 m	78.2, CH
4″	3.31 m	72.0, CH	3.33 m	72.3, CH
5″	3.21 m	77.5, CH	3.23 m	77.3, CH
6″	3.83 dd (11.5, 2.5)	63.3, CH_2	3.80 dd (12.0, 3.0)	63.6, CH_2
	3.69 dd (11.5, 5.5)		3.67 dd (11.5, 5.5)	

[a]Signal partially overlapped with the solvent signal.

the following long-range correlations were observed: C-13 (δ 206.1) with H-7 (δ 7.35) and H-14 (δ 2.62) as well as C-12 (δ 70.3) with H-2 (δ 5.21) (Figure 1). These results suggested that the acetyl group and the $-C(CH_2)-CH_2$-OH are attached to the C-6 and C-2 positions, respectively. The β-form of D-glucose was assigned from the coupling constant of the anomeric proton (δ 4.26, J = 7.5 Hz).[22] The HMBC correlation of C-12 (δ 70.3) with H-1′ (δ 4.26) demonstrated that the D-glucopyranose group is attached to C-12. The H-2 and H-3 protons were determined as *trans* positioned by the $J_{2,3}$ coupling constant of 2.5 Hz. The absolute configuration of the C-2 position was determined to be *R* on the basis of the negative sign for optical rotation.[23] Consequently, compound **3** was identified as (2*R*,3*S*)-6-acetyl-2-[1-*O*-(-β-D-glucopyranosyl)-2-propenyl]-5-hydroxy-3-methoxy-2,3-dihydrobenzofuran.

The 15 known compounds were identified as 3,5-di-*O*-caffeoylquinic acid (**4**),[24] 4,5-di-*O*-caffeoylquinic acid (**5**),[25] 5-*O*-caffeoylquinic acid (**6**),[26] isorhamnetin-3-*O*-β-D-glucopyranoside (**7**),[27] isoquercitrin (**8**),[28] quercetin-3-*O*-α-L-arabinopyranoside (**9**),[29] isorhamnetin-3-*O*-β-D-rutinoside (**10**),[30] laricitrin-3-*O*-α-L-rhamnopyranoside (**11**),[31] kaempferol-3-*O*-β-D-rutinoside (**12**),[32] gymnasterkoreayne E,[5] gymnasterkoreaside A,[6] 8*E*-decaene-4,6-diyn-1-*O*-β-D-glucopyranoside,[33] daucosterol,[34]

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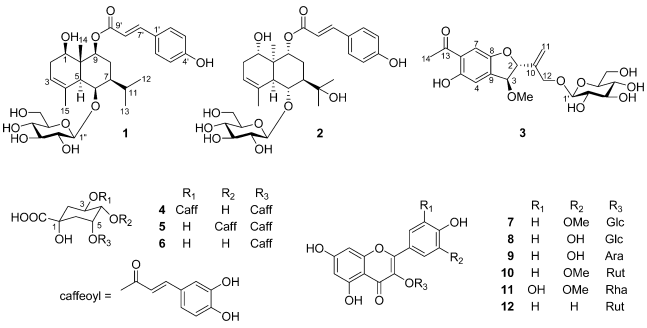
α-spinasterol,[35] and eugenyl-4-*O*-β-D-glucopyranoside.[36] Compounds **4**–**12** were isolated from this plant for the first time.



All isolates were evaluated in vitro for inhibitory activity against the formation of AGEs and RLAR (Table 2). In the AGE assay, compounds **4**, **5**, and **8**–**10** showed inhibitory activities with IC_{50} values 6.6, 6.4, 9.2, 9.0, and 8.2 μM, respectively. In the RLAR assay, compound **4** showed the most potent inhibitory activity, with an IC_{50} value of 0.30 μM, which was followed by compounds **9** (IC_{50} = 0.32 μM) and **6** (IC_{50} = 0.95 μM) (Table 2). These results indicated that the above two major groups, the quinic acids and flavonoids, are the main contributors to the activities of this edible herb. Further biological studies on this plant and its constituents are necessary to develop the potential use in the prevention and treatment of diabetic complications and other related diseases.

Table 2. Inhibitory Effects of Compounds 4–12 from the Aerial Parts of *A. koraiensis* against AGE Formation and RLAR

	inhibitory effect (IC_{50} value; μM)[a]	
compound	AGE formation[b]	RLAR
4	6.6 ± 0.04	0.30 ± 0.05
5	6.4 ± 0.12	2.3 ± 0.47
6	>50	0.95 ± 0.28
7	44.4 ± 0.61	9.3 ± 1.96
8	9.2 ± 0.27	4.4 ± 0.28
9	9.0 ± 0.21	0.32 ± 0.04
10	>50	12.1 ± 2.37
11	8.2 ± 0.08	7.4 ± 0.93
12	>50	11.3 ± 2.05
AG[c]	965.9 ± 26.9	
EP[c]		0.067 ± 0.009

[a]The inhibitory effect is presented as the mean ± SD from triplicate experiments. The IC_{50} values were calculated from the dose inhibition curve. [b]After incubating for 14 days, the fluorescent reaction products were assayed on a spectrofluorometric detector. [c]Aminoguanidine (AG) and epalrestat (EP) were used as positive controls. Compounds **1**–**3**, gymnasterkoreayne E, gymnasterkoreasides A, 8*E*-decaene-4,6-diyn-1-*O*-β-D-glucopyranoside, daucosterol, α-spinasterol, and eugenyl-4-*O*-β-D-glucopyranoside were inactive in both the AGE (IC_{50} > 50 μM) and RLAR (IC_{50} > 30 μM) assays.

EXPERIMENTAL SECTION

General Experimental Procedures. The optical rotations were obtained using a JASCO P-2000 digital polarimeter. The UV spectra were measured on a Varian Cary 300 spectrophotometer, and the IR spectra were recorded on a JASCO FTIR-4100 spectrophotometer. The LRESIMS and HRESIMS results were measured on a hybrid ion-trap time-of-flight mass spectrometer (Shimadzu LCMS-IT-TOF) that was equipped with an ESI source (ESI-IT-TOFMS). The NMR experiments were conducted on either a Bruker DRX-300 or a Bruker Advance 500 FT-NMR, with tetramethylsilane (TMS) as the internal standard. TLC analysis was performed on silica gel 60 F_{254} (Merck) and RP-18 F_{254S} (Merck) plates. Silica gel (230–400 mesh, Merck), reversed-phase silica gel (YMC, ODS-A, 12 nm, S-150 μm), Sephadex LH-20 (Amersham Pharmacia Biotech), and Diaion HP-20 (Supelco) were used for column chromatography (CC). The preparative MPLC system (Yamazen YFLC AI-580, Osaka, Japan) was equipped with a solvent delivery pump (pump 580), a variable UV wavelength detector (prep UV-10V), and a fraction collector (FR360). Ultra Pack glass columns (C-18 ODS prepacked; size C: 37 × 300 mm, size B: 26 × 300 mm; 50 μm, 120 Å, Yamazen) and Hi-Flash 2 L disposable columns (silica gel prepacked; 26 × 150 mm; 40 μm, 45 g, Yamazen) were used for separation. Prep AI software was used for data collection.

Plant Material. The aerial parts of *Aster koraiensis* were collected in Euidang-myun, Gongju city, Chungchengnam-do, Republic of Korea, in August 2007, and identified by one of the authors (J.-H.K.). A voucher specimen (no. KIOM-ASKO2) was deposited at the Herbarium of the Diabetic Complications Research Center, Division of Traditional Korean Medicine (TKM) Integrated Research, Korea Institute of Oriental Medicine, Republic of Korea.

Extraction and Isolation. The dried and ground plant material (2.5 kg) was extracted with EtOH (3 × 20 L) by maceration at room temperature for 3 days. The extracts were combined and concentrated in vacuo at 40 °C to produce a dried extract (303 g). This EtOH extract was suspended in water and partitioned with solvents of increasing polarity, to generate *n*-hexane- (37.5 g), EtOAc- (34.4 g), *n*-BuOH- (81.3 g), and water-soluble extracts (149 g). The active EtOAc extract (34.4 g) was separated by chromatography using a silica gel column ($CHCl_3$–EtOAc, 20:1 to 2:1, $CHCl_3$–MeOH, 3:1 to 1:1, $CHCl_3$–MeOH–water, 7:4:1), to generate 10 fractions (F01–F10). α-Spinasterol (white needle, 50 mg) and daucosterol (white needle, 128 mg) were recrystallized from F03 (878 mg) and F07 (2.26 g), respectively. Fraction F04 (364 mg) was separated by chromatography using a silica gel column ($CHCl_3$–EtOAc, 20:1 to 1:1), and an ODS-A reversed-phase column (water–MeOH, 2:8 to 0:10) was used to generate gymnasterkoreayne E (brown oil, 20 mg). Fraction F08 (11.5 g) was separated by chromatography, using a silica gel column eluted with a CH_2Cl_2–MeOH gradient mixture (20:1 to 1:1) to generate seven subfractions (F0801–F0807). Further separation of F0806 (793 mg) was performed by MPLC using an Ultra Pack C column [MeOH–water, 3:7 (60 min), 4:6 (30 min), 5:5 (200 min), 10:0 (60 min); flow rate: 12 mL/min] to generate gymnasterkoreaside A (brown oil, 50 mg) and **7** (yellow powder, 20 mg). Subfraction F0804 (2.23 g) was subjected to Sephadex LH-20 column chromatography (MeOH 100%) and MPLC [MeOH–water, 3:7 (60 min), 4:6 (100 min), 5:5 (150 min); Ultra Pack B column; flow rate: 5 mL/min] to generate 8*E*-decaene-4,6-diyn-1-*O*-β-D-glucopyranoside (amorphous solid, 19 mg), eugenyl-4-*O*-β-D-glucopyranoside (light yellow powder, 18 mg), and **3** (yellow powder, 3 mg). Chromatographic separation of fraction F09 (8.56 g) was performed using MPLC [MeOH–water, 1:9 (60 min), 2:8 (90 min), 3:7 (60 min), 4:6 (70 min), 10:0 (80 min); Ultra Pack C column; flow rate: 12 mL/min] to produce 16 subfractions (F0901–F0916). Compound **4** (white powder, 170 mg) was purified by precipitation in MeOH from subfraction F0904. Compounds **8** (yellow powder, 29 mg), **9** (yellow powder, 9 mg), **10** (yellow powder, 15 mg), **11** (yellow powder, 8 mg), **5** (white powder, 18 mg), and **12** (yellow powder, 7 mg) were separated from subfractions F0908 (276 mg) and F0909 (348 mg), respectively, by MPLC [$CHCl_3$–MeOH–water, 8:2:0.2 (100 min), 7:3:0.5 (100 min), MeOH 100% (100 min); Hi-Flash 2 L column; flow rate: 3 mL/min]. Subfractions F0911 (220 mg) and F0913 (258 mg) were subjected to MPLC [$CHCl_3$–MeOH–water, 8:2:0.2 (150 min), 7:3:0.5 (150 min); Hi-Flash 2 L column; flow rate: 3 mL/min] to generate **1** (white, amorphous solid, 32 mg) and **2** (white, amorphous solid, 10 mg), respectively. Fraction F10 (1.40 g) was fractionated by MPLC using an Ultra Pack C column [MeOH–water, 1:9 (70 min), 2.5:7.5 (30 min), 4:6 (60 min), 10:0 (80 min); flow rate: 10 mL/min], which yielded seven subfractions (F1001–F1007). Further chromatographic separation of subfraction F1002 (85 mg) was also performed by MPLC [MeOH–water, 0.5:9.5 (250 min); Ultra Pack B column; flow rate: 3 mL/min], and

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the subfraction was then purified by Sephadex LH-20 column chromatography to generate **6** (white powder, 10 mg).

*9β-O-(E-p-Hydroxycinnamoyl)-1β,6β-dihydroxy-trans-eudesm-3-en-6-O-β-D-glucopyranoside (**1**):* amorphous powder; $[\alpha]^{20}_{D}$ +42.0 (*c* 0.05, MeOH); UV (MeOH) λ_{max} (log ε) 313 (4.68) nm; ^{1}H (CD_3OD, 500 MHz) and ^{13}C (CD_3OD, 75 MHz) NMR data, see Table 1; HRESIMS *m*/*z* 561.2708 $[M - H]^-$ (calcd for $C_{30}H_{41}O_{10}$, 561.2705).

*9α-O-(E-p-Hydroxycinnamoyl)-1α,6α-11-trihydroxy-trans-eudesm-3-en-6-O-β-D-glucopyranoside (**2**):* amorphous powder; $[\alpha]^{20}_{D}$ +78.0 (*c* 0.05, MeOH); UV (MeOH) λ_{max} (log ε) 312 (4.49) nm; ^{1}H (CD_3OD, 500 MHz) and ^{13}C (CD_3OD, 150 MHz) NMR data, see Table 1; HRESIMS *m*/*z* 601.2616 $[M + Na]^+$ (calcd for $C_{30}H_{42}O_{11}Na$, 601.2619).

*(2R,3S)-6-Acetyl-2-[1-O-(-β-D-glucopyranosyl)-2-propenyl]-5-hydroxy-3-methoxy-2,3,-dihydrobenzofuran (**3**):* yellow powder; $[\alpha]^{20}_{D}$ −49.0 (*c* 0.05, MeOH); UV (MeOH) λ_{max} (log ε) 259 (4.36), 368 (4.08) nm; ^{1}H NMR (CD_3OD, 500 MHz) δ 7.35 (1H, s, H-7), 7.01 (1H, s, H-4), 5.28 (1H, s, H-11), 5.22 (1H, s, H-11), 5.21 (1H, overlapped, H-2), 5.05 (1H, d, *J* = 2.5 Hz, H-3), 4.47 (1H, d, *J* = 12.5 Hz, H-12), 4.26 (1H, d, *J* = 7.5 Hz, H-1′), 4.22 (1H, d, *J* = 12.5 Hz, H-12), 3.87 (1H, dd, *J* = 2.0, 12.0 Hz, H-6′), 3.66 (1H, dd, *J* = 5.5, 12.0 Hz, H-6′), 3.47 (3H, s, 3-OMe), 3.33 (1H, m, H-3′), 3.27 (1H, m, H-4′), 3.25 (1H, m, H-5′), 3.20 (1H, dd, *J* = 8.0, 9.0 Hz, H-2′), 2.62 (3H, s, H-14); ^{13}C NMR (CD_3OD, 150 MHz) δ 206.1 (C, C-13), 158.4 (C, C-5), 144.1 (C, C-10), 136.4 (C, C-9), 121.7 (C, C-6), 116.9 (CH, C-4), 115.3 (CH_2, C-11), 111.0 (CH, C-7), 103.9 (CH, C-1′), 89.3 (CH, C-2), 85.6 (CH, C-3), 78.3 (CH, C-3′), 78.2 (CH, C-5′), 75.2 (CH, C-2′), 71.9 (CH, C-4′), 70.3 (CH_2, C-12), 63.0 (CH_2, C-6′), 56.7 (3-OCH_3), 27.4 (CH_3, C-14); HRESIMS *m*/*z* 449.1418 $[M + Na]^+$ (calcd for $C_{20}H_{26}O_{10}Na$, 449.1418).

Determination of AGE Formation. Inhibitory activity against the formation of advanced glycation end-products for the isolates was evaluated according to an established method.[37]

RLAR Inhibition Assay. All of the experiments were performed in accordance with the U.S. National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals. The crude RLAR was prepared from the eyes of 8-week-old male Sprague−Dawley rats (Orient Co., Seongnam, Korea).[38,39] The isolates were assayed according to a method described previously with slight modifications.[40]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for the new compounds **1**−**3** are available free of charge via the Internet at http://pubs.acs.org.

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