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Note

Isolation of Compounds Including Two New Compounds from Asiasarum Root and Their Anti-glycation Activity

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Two new glycosides, named 3-methoxy-5-methylphenol-6-*O*-*β*-glucopyranosyl-(1→6)-*β*-glucopyranoside (compound 1) and 1-*O*-feruloyl-*α*-arabinofuranosyl-(1→6)-*β*-glucopyranoside (compound 2), were isolated from Asiasarum root, together with eight known compounds. Asiasarum root (crude drug name in Latin: ASIASARI RADIX) is well known for its anti-inflammation and antitussive properties and is commonly found in Kampo formula in Japan. The structures of new compounds 1 and 2 were characterized using one- and two-dimensional (1D and 2D) NMR spectroscopy and MS. In addition, the anti-glycation activity of the isolates was evaluated. Glycation is particularly advanced in patients with diabetes and is suspected to be associated with diabetic complications such as nephropathy, osteoporosis, and Alzheimer's disease. The inhibition of this reaction is thought to be linked to the prevention and treatment of these diseases. Compounds 2 (79.4%), 4 (82.4%), 5 (79.8%), 6 (86.5%), 7 (90.1%), 9 (61.4%), and 10 (82.2%) showed activities comparable to that of aminoguanidine (45.3%) used as a positive control.

Key words Asiasarum root, phenolic glycoside, phenylpropanoid glycoside, anti-glycation activity

Introduction

Asiasarum root, referred to as ASIASARI RADIX in Latin and "Saisin" in Japanese, is prepared from the roots or rhizomes of *Asiasarum heterotropoides* F. Maekawa var. *mandshuricum* F. Maekawa or *A. sieboldii* F. Maekawa (Aristolochiaceae) according to the Japanese Pharmacopoeia (JP XVIII).[1] Asiasarum root is well known for its anti-inflammation[2] and antitussive[3] properties, and it is commonly found in Kampo formulas, such as Shoseiryuto, Tokishigyakuto, and Maobushisaishinto. The secondary metabolite identified in Asiasarum roots include essential oils (safrole, eucarvone, *α*-pinene, cineole), monoterpenes, lignans ((−)-asarinin, (−)-sesamin, xanthoxyol), alkaloids (hygenamine), and phenylpropanoids (methyleugenol).[4–8] These compounds exhibit various biological activities, such as antitussive,[3] anticancer,[9] and antiallergic.[10] This paper reports on the isolation, purification, and structural analysis of two new compounds 3-methoxy-5-methylphenol-6-*O*-*β*-glucopyranosyl-(1→6)-*β*-glucopyranoside and 1-*O*-feruloyl-*α*-arabinofuranosyl-(1→6)-*β*-glucopyranoside along with eight known compounds from Asiasarum root. The anti-glycation activities of the isolated compounds were investigated using *in vitro* assays. Proteins *in vivo* react non-enzymatically with reducing sugars, such as glucose, and are transformed *via* Schiff base and Amadori products into terminal glycation products called advanced glycation end products (AGEs). This reaction, called glycation, is said to be particularly accelerated in diabetic patients and is suspected to be associated with diabetic complications such as nephropathy,[11] osteoporosis,[12] and Alzheimer's disease.[13] Inhibiting glycation is therefore thought to be a promising approach for preventing and treating these diseases.

Results and Discussion

Compounds **1**–**10** were isolated from the methanolic extract of Asiasarum roots by chromatographic purification. The structures of known compounds **3**–**10** were confirmed by comparing their spectroscopic data, including NMR and MS, with literature values. These compounds were identified as 1-*O*-feruloyl-*β*-xylopyranosyl-(1→6)-*β*-glucopyranoside (**3**),[14] 7-*O*-*β*-glucopyranosyl naringenin (**4**),[15] 5,7-di-*O*-*β*-glucopyranosyl naringenin (**5**),[14] 4-hydroxy benzoic acid (**6**),[16] (−)-sesamin (**7**),[17,18] kakuol (**8**),[19] methyl kakuol (**9**),[20] and (−)-episesamin (**10**).[21–23] The structures of the 10 isolated compounds (**1**–**10**) are shown in Fig. 1.

Compound **1** was obtained as a whiteyellow, amorphous compound. The molecular formula of **1** was determined to be $C_{20}H_{30}O_{12}$ using high-resolution (HR)-FAB-MS *m/z*: 463.1831 $[M+H]^+$ (Calcd for $C_{20}H_{31}O_{12}$: 463.1813). The ^{1}H-NMR spectrum displayed two singlet signals due to a methyl group at δ_H 2.97 (3H, s) and a methoxyl proton at δ_H 3.77 (3H, s), two anomeric protons at δ_H 4.35 (1H, d, J=7.7 Hz) and δ_H 4.90 (1H, d, J=7.5 Hz), and three aromatic protons at δ_H 6.44 (1H, brs), 6.52 (1H, dd, J=2.1 Hz), and 6.54 (1H, brs). The ^{13}C-NMR spectrum of **1** showed 20 carbon resonances classified by their chemical shift values and heteronuclear single quantum coherence (HSQC) spectra: one methoxyl carbon (δ_C 56.0), three sp^2 methine carbons (δ_C 101.5, 109.9, 111.0), three sp^2 quaternary carbons (δ_c 141.6, 160.2, 162.2), and an sp^3 methyl carbon

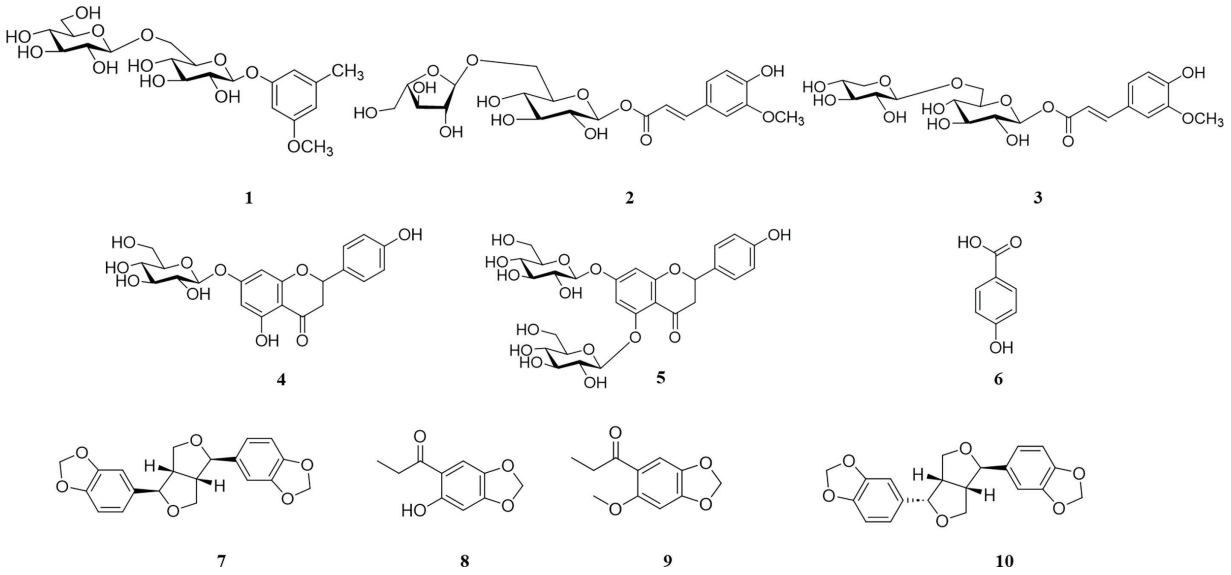

Fig. 1. Structure of Isolates (**1**–**10**) from Asiasarum Root

(δ_C 22.1). Furthermore, two sets of glucopyranosides were inferred by comparing the ^{1}H-NMR and ^{13}C-NMR data with those in the literature[24,25] (outer glucopyranoside: δ_C 62.9, 71.8, 75.1, 78.2, 78.2, and 105.1; inner glucopyranoside: δ_C 71.2, 71.6, 75.3, 77.4, 78.0, and 102.4). The NMR spectral data are presented in Table 1. The ^{13}C-NMR spectroscopic data of **1** were very similar to those of 3-methoxyl-5-methylphenol-1-*O*-*β*-D-glucopyranoside[26] except for the appearance of a resonance attributed to the two glucose moieties. The heteronuclear multiple bond connectivity (HMBC) spectra showed correlations between δ_H 2.97 (5-CH_3) and δ_C 109.9 (C-4), δ_C 141.6 (C-5). The resonance at δ_H 3.77 (3-OMe) also correlated with δ_C 162.2 (C-3) in the HMBC experiments. The long-range correlations of δ_H 6.44 (H-4) to δ_C 101.5 (C-2), δ_C 162.2 (C-3), δ_H 6.52 (H-2) to δ_C 162.2 (C-3), and δ_H 6.54 (H-6) to δ_C 109.9 (C-4) were observed in HMBC experiments. In addition, the long-range correlations of the two anomeric protons at δ_H 4.35 (H-1″) and δ_H 4.90 (H-1′) with δ_C 71.2 (C-6′) and δ_C 160.2 (C-1) confirmed the linkage of these sugars, as shown in Fig. 2. Consequently, compound **1** was elucidated as 3-methoxy-5-methylphenol-6-*O*-*β*-glucopyranosyl-(1→6)-*β*-glucopyranoside.

Table 1. ^{1}H- and ^{13}C-NMR Spectra of Compound **1** in MeOH-d_4

Position	δ_H (J in Hz)	δ_C
1	–	160.2 (s)
2	6.52 (1H, dd, J=2.1)	101.5 (d)
3	–	162.2 (s)
4	6.44 (1H, brs)	109.9 (d)
5	–	141.6 (s)
6	6.54 (1H, brs)	111.0 (d)
1′	4.90 (1H, d, J=7.5)	102.4 (d)
2′	3.24 (1H, m)	75.3 (d)
3′	3.46 (1H, m)	78.0 (d)
4′	3.42 (1H, m)	71.6 (d)
5′	3.70 (1H, m)	77.4 (d)
6′	3.85 (1H, dd, J=6.0, 11.5)	71.2 (t)
	4.17 (1H, dd, J=2.0, 11.5)	
1″	4.35 (1H, d, J=7.7)	105.1 (d)
2″	3.47 (1H, m)	75.1 (d)
3″	3.26 (1H, m)	78.2 (d)
4″	3.30 (1H, m)	71.8 (d)
5″	Overlapped with solvent signals	78.2 (d)
6″	3.66 (1H, dd, J=5.7, 11.9)	62.9 (t)
	3.87 (1H, dd, J=2.2, 11.9)	
5-CH_3	2.97 (3H, s)	22.1 (q)
3-OCH_3	3.77 (3H, s)	56.0 (q)

Compound **2** was obtained as a whiteyellow, amorphous compound. The molecular formula of **2** was determined to be $C_{21}H_{28}O_{13}$ by HR-FAB-MS *m/z*: 487.1465 $[M-H]^-$ (Calcd for $C_{21}H_{27}O_{13}$: 487.1448). The ^{1}H-NMR spectrum of **2** showed the signals for *trans* olefinic proton at δ_H 6.40 (1H, d, J=15.9 Hz) and δ_H 7.48 (1H, d, J=15.9 Hz), and ABX-type signals at δ_H 6.83 (1H, d, J=8.2 Hz), δ_H 7.11 (1H, dd, J=1.9, 8.2 Hz), and δ_H 7.22 (1H, d, J=1.9 Hz) due to the 1,3,4-trisubstituted benzene ring. Furthermore, one methoxyl group signal at δ_H 3.91 (3H, s) and two anomeric protons at δ_H 4.94 (1H, d, J=1.3 Hz) and δ_H 5.57 (1H, d, J=7.8 Hz) were observed. The ^{13}C-NMR spectrum of **2** showed 21 carbon resonances that were classified by their chemical shift values and HSQC spectra as one methoxyl carbon (δ_C 56.6), five sp^2 methine carbons (δ_C 112.0, 114.7, 116.8, 124.7, and 148.6), and four sp^2 quaternary carbons (δ_C 127.6, 149.7, 151.6, and 167.8). In addition, an arabinofuranoside and a glucopyranoside were inferred by comparisons of the ^{1}H-NMR and ^{13}C-NMR data with that in the literature[15,27–30] (arabinofuranoside: δ_C 63.2, 79.0, 83.4, 85.9, and 110.2 and glucopyranoside: δ_C 68.1, 71.8, 74.2, 77.8, 78.2, and 95.9). The NMR spectral data are presented in Table 2. The ^{13}C-NMR spectroscopic data of **2** were very similar to those of **3** except for the chemical shifts of the glucose moiety. The HMBC spectrum exhibited a correlation between the anomeric proton of arabinofuranoside at between δ_H 4.94 (H-1‴) and δ_C 68.1 (C-6″). In addition, the linkage of δ_H 5.57 (H-1″) attributed to the anomeric proton of glucopyranoside and δ_C 167.8 (C-1) was confirmed by the HMBC spectrum, as shown in Fig. 3. Furthermore, the positions of mthoxyl group were confirmed by analysis of HMBC and nuclear Overhauser

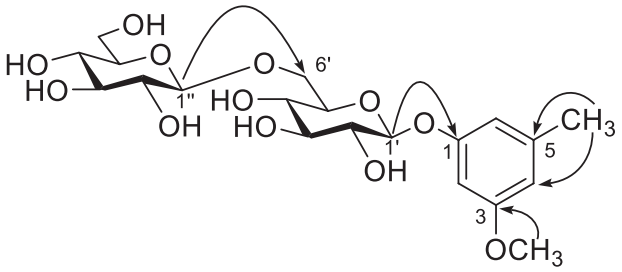

Fig. 2. Diagnostically Significant Long-Range (HMBC) Correlations of **1**

Table 2. ^{1}H- and ^{13}C-NMR Spectra of Compound **2** in MeOH-d_4

Position	δ_H (J in Hz)	δ_C
1		167.8 (s)
2	6.40 (1H, d, J=15.9)	114.7 (d)
3	7.75 (1H, d, J=15.9)	148.6 (d)
1′		127.6 (s)
2′	7.22 (1H, d, J=1.9)	112.0 (d)
3′		151.6 (s)
4′		149.7 (s)
5′	6.83 (1H, d, J=8.2)	116.8 (d)
6′	7.11 (1H, dd, J=1.9, 8.2)	124.7 (d)
1″	5.57 (1H, d, J=7.8)	95.9 (d)
2″	3.44 (1H, m)	74.2 (d)
3″	3.46 (1H, m)	78.2 (d)
4″	3.38 (1H, m)	71.8 (d)
5″	3.61 (1H, m)	77.8 (d)
6″	3.63 (1H, m)	68.1 (t)
	4.22 (1H, dd, J=1.9, 10.8)	
1‴	4.94 (1H, d, J=1.4)	110.2 (d)
2‴	4.02 (1H, dd, J=1.4, 3.4)	83.4 (d)
3‴	3.83 (1H, dd, J=3.4, 6.0)	79.0 (d)
4‴	3.98 (1H, m)	85.9 (d)
5‴	3.69 (2H, m)	63.2 (t)
3′-OCH_3	3.91 (3H, s)	56.6 (q)

effect spectroscopy (NOESY) spectra. Consequently, compound **2** was elucidated as 1-*O*-feruloy-*α*-arabinofuranosyl-(1→6)-*β*-glucopyranoside.

The inhibitory activities of the 10 compounds were evaluated using AGE-specific enzyme-linked immunosorbent assay (ELISA) as previously reported methods.[31,32] Compounds **1–10** at 1 mM showed inhibitory activities of −5.0% (**1**), 79.4% (**2**), 32.6% (**3**), 82.4% (**4**), 79.8% (**5**), 86.5% (**6**), 90.1% (**7**), −3.1% (**8**), 61.4% (**9**), and 82.2% (**10**), respectively (Table 3). In comparison, the inhibitory activity of aminoguanidine, used as a positive control, was 45.3% at 1 mM. Based on the glycation inhibitory activity of the isolated compounds, the strongest inhibitory activity was observed at **7**, which had not been previously reported for its anti-glycation activity. Compounds **4**, **6**, and **10** showed >80% inhibition, supporting previously reported glycation inhibitory activity.[33,34] The anti-glycation activity of compound **10** has even been reported as a patent.[35] Although **2** and **3** have the same aglycon, the types of bound sugars are different. Furthermore, their anti-glycation activities differed (the inhibitory activity of **2** was stronger than that of **3**). These results indicate that the type of bound sugar influences the inhibition of glycation. With regard to **8** and **9**, methylation of **8** strongly increased the inhibitory activity. According to the literature review, there have been no direct reports on the inhibitory activity of Asiasarum roots against glycation. Recently, glycation has also been implicated in the development of non-alcoholic steatohepatitis (NASH)[36,37] and osteoarthritis.[38] Here, we present the various biological activities of Asiasarum root by its constituent research.

Conclusion

In this study, we aimed to explore the constituents of Asiasarum root and to evaluate their anti-glycation activities. Two new glycosides, named 3-methoxy-5-methylphenol-6-*O*-*β*-glucopyranosyl-(1→6)-*β*-glucopyranoside (compound **1**) and 1-*O*-feruloyl-*α*-arabinofuranosyl-(1→6)-*β*-glucopyranoside (compound **2**), were isolated from Asiasarum root, together with eight known compounds. Compounds **2**, **4**–**7**, **9**, and **10** showed anti-glycation activities comparable to that of aminoguanidine, which was used as a positive control.

Experimental

General Experimental Procedures FAB-MS and HR-FAB-MS data were recorded using a JMS-700 instrument (JEOL, Tokyo, Japan) with glycerol as a matrix. ^{1}H-, ^{13}C-, and 2D-NMR spectra were recorded at 400 MHz on an AVANCE NEO 400 (Bruker Corporation, Billerica, MA, U.S.A.) instrument (400 MHz for ^{1}H and 100 MHz for ^{13}C) at room temperature. NMR chemical shifts were recorded in ppm with solvent signals as internal references (δ_H 3.31, δ_C 49.2 for MeOH-d_4). Methanol-d_4 (CD_3OD) was purchased from Kanto Chemical Co., Inc. (Tokyo, Japan). Optical rotation was measured using a P-2200 instrument (Jasco, Tokyo, Japan). HPLC purification was performed using the following equipment: SSC-3414 (Senshu Scientific Co., Ltd., Tokyo, Japan), PU-4086 (Jasco), UV-4070 (Jasco), and RI-4030 (Jasco); column oven: CO631C (GL Sciences Inc., Tokyo, Japan).

Plant Material Roots of *Asiasarum heterotropoides* F. Maekawa var. *mandshuricum* F. Maekawa (Lot. No. K6W0202) were purchased from Uchida Wakan-yaku Co., Ltd. (Tokyo, Japan). Specimens (JUTNK210720) were maintained at the Laboratory of Natural Products and Phytochemistry, Department of Pharmaceutical Sciences, Faculty of Pharmacy and Pharmaceutical Sciences, Josai University, Japan.

Extraction and Isolation Dried Asiasarum roots (4 kg) were subjected to extraction with MeOH (2.0 L) for 3 h under reflux. This extraction was repeated three times. The organic solvent was removed by vacuum evaporation to obtain an MeOH extract (354.7 g). The residue was dried and extracted with *n*-hexane under reflux, and the organic solvent was removed under vacuum to obtain the *n*-hexane extract (5.6 g). Part of the MeOH (15.0 g) extract was separated using MCI GEL (Mitsubishi Chemical Corporation, Tokyo, Japan) and eluted with 30% MeOH, 50% MeOH, 70% MeOH, MeOH, and acetone, in that order. The yields of the fractions were 30% MeOH (2.7 g), 50% MeOH (1.9 g), 70% MeOH (2.8 g), MeOH (6.0 g), and acetone (2.0 g). The 30% MeOH fraction was subjected to chromatography using a TOYOPEARL HW-40F column (TOSOH, Tokyo, Japan) (H_2O:MeOH=1:1) to obtain Fr. m1–Fr. m25. Fr. m4 (797.9 mg) was fractionated using a column packed with silica gel (silica gel 60; Kanto Chemical Co., Inc.) ($CHCl_3$: MeOH: H_2O=65:35:10) to obtain fractions Fr. m4-1–Fr. m4-25. Compound **1** (7.9 mg) was obtained from Fr. m4-6 (101.6 mg) by

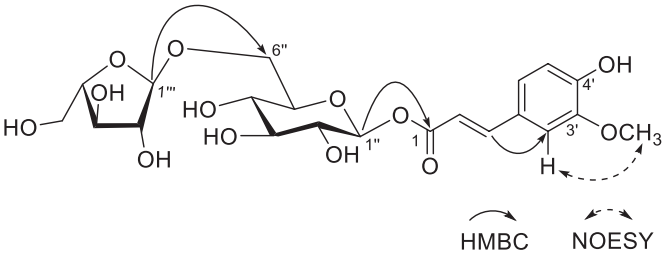

Fig. 3. Diagnostically Significant Long-Range (HMBC) and NOESY Correlations of **2**

Table 3. Anti-glycation Activity of Isolated Compounds

Compound	Inhibition (%)
1	−5.0±4.8
2	79.4±0.9
3	32.6±0.6
4	82.4±1.4
5	79.8±4.4
6	86.5±1.0
7	90.1±2.2
8	−3.1±7.5
9	61.4±2.9
10	82.2±3.4
AG	45.3±4.0

Data are presented as the mean value±S.D. (n=3). AG: aminoguanidine.

HPLC preparation using an ODS column (column; PEGASIL ODS SP100 (Senshu Scientific Co., Ltd.), φ10×150 mm, solvent; H_2O: MeOH=2:5, flow rate; 3 mL/min, Column temperature; 25 °C, Detector; refractive index detector (RI), retention time; 12.4 min). Compounds **2** (2.6 mg) and **3** (35.0 mg) were obtained from Fr. m4-7 (86.4 mg) by HPLC purification (PEGASIL ODS SP100 φ10×150 mm, H_2O:MeOH=2:5, 3 mL/min, 25°C, RI, 8.7 min for compound **2**, 10.3 min for compound **3**). Fr. m5 (195.3 mg) was purified using a column packed with silica gel ($CHCl_3$:MeOH:H_2O=65:35:10) to obtain fractions Fr. m5-1–Fr. m5-20. Compound **4** (4.5 mg) was obtained from Fr. m5-2 (27.4 mg) using HPLC (PEGASIL ODS SP100, φ10×150 mm, H_2O:MeCN=3:1, 3 mL/min, 40°C, RI, 7.1 min). Compound **5** (2.0 mg) was obtained from Fr. m5-8 (12.7 mg) by HPLC purification (PEGASIL ODS SP100, φ10×150 mm, H_2O:MeCN=3:1, 3 mL/min, 40°C, RI, 7.1 min). Fr. m9 (21.4 mg) was fractionated using a column packed with silica gel ($CHCl_3$:MeOH:H_2O=65:35:10) to obtain fractions Fr. m9-1–Fr. m9-25. Fr. m9-2 was a pure compound and was designated as compound **6** (2.1 mg). The precipitate (60.8 mg) from acetone elution was purified by HPLC (AQUASIL SP100 φ10×250 mm (Senshu Scientific Co., Ltd.), $CHCl_3$, 3 mL/min, 30°C, RI, 6.0 min) to obtain pure compound and this was designated compound **7** (3.4 mg). n-Hexane extract (3.6 g) was fractionated on a column packed with silica gel (n-hexane:EtOAc=3:1) to obtain Fr. he1 to Fr. he47. HPLC purification (PEGASIL ODS SP100 φ10×150 mm, H_2O:MeOH= 2:5, 3 mL/min, 45°C, RI, 7.2 min) was performed on Fr. he5 (68.8 mg) to yield compound **8** (2.6 mg). Fr. he7 (31.8 mg) was also subjected to HPLC purification (PEGASIL ODS SP100 φ10×150 mm, H_2O:MeCN=1:2, 3 mL/min, 20°C, RI, 5.5 min) to obtain compound **9** (17.4 mg). Fr. he8 (32.1 mg) was purified by HPLC (PEGASIL ODS SP100 φ10×150 mm, H_2O:MeOH=1:3, 3 mL/min, 45°C, RI, 9.6 min) to yield compound **10** (15.6 mg).

3-Methoxy-5-methylphenol-6-*O*-*β*-glucopyranosyl-(1→6)-*β*-glucopyranoside (1) ^{1}H- and ^{13}C-NMR data are listed in Table 1; HR-FAB-MS: m/z 463.1831 $[M+H]^+$ (Calcd for $C_{20}H_{31}O_{12}$: 463.1813), $[\alpha]_D^{27}$−53.5 (c=0.6, MeOH).

1-*O*-Feruloyl-*α*-arabinofuranosyl-(1→6)-*β*-glucopyranoside (2) ^{1}H- and ^{13}C-NMR data are listed in Table 2; HR-FAB-MS m/z: 487.1465 $[M-H]^-$ (Calcd for $C_{21}H_{27}O_{13}$: 487.1448), $[\alpha]_D^{27}$−21.5 (c=0.2, MeOH).

***In Vitro* Anti-glycation Assay** Bovine serum albumin (4 mg/mL) was incubated with 200 mM glucose in the presence or absence of a test sample (1 mM) in 0.1 M phosphate buffer (pH 7.4) for 7 d at 37°C. After incubation, the level of the generated glycated bovine serum albumin (BSA) (carboxymethyl lysine) was measured using a glycated BSA-specific ELISA.[31,32] Briefly, each well of a 96-well microtiter plate was coated with 100 μL of the indicated sample, followed by incubation for 1 h. The wells were washed three times with phosphate buffered saline (PBS) containing 0.05% Tween 20 (washing buffer). The wells were then blocked with 0.05% gelatin in PBS for 1 h. After triplicate washing with washing buffer, the wells were incubated for 1 h with 100 μL of the specific antibodies for glycated BSA (anti AGEs monoclonal antibody, Clone No. 6D12) (Trans Genic Inc., Fukuoka, Japan). After three washes with washing buffer, the wells were incubated with a horseradish peroxidase (HRP)-conjugated anti-mouse immunoglobulin G (IgG) antibody (Funakoshi Co., Ltd., Tokyo, Japan), followed by incubation with 1,2-phenylenediamine dihydrochloride. The reaction was terminated with 100 μL of 1.0 M sulfuric acid, and the absorbance was read at 492 nm with a micro-ELISA plate reader. Inhibition was calculated as follows:

$$\text{Inhibition (\%)} = [1-(\text{As}-\text{Ab})/(\text{Ac}-\text{Ab})]\times 100,$$

where: As is the level of glycated BSA of the incubated mixture with sample, Ab is the level of glycated BSA of the incubated mixture without sample and glucose as the blank control, and Ac is the level of glycated BSA of the incubated mixture without sample as a control.

Aminoguanidine, a well-known synthetic inhibitor, was used as the positive control at a concentration of 1 mM. Data are shown as the mean±standard deviation (S.D.) of n=3 independent experiments.

Conflict of Interest The authors declare no conflict of interest.

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