Medicinal Flowers. XXXVIII.¹⁾ Structures of Acylated Sucroses and Inhibitory Effects of Constituents on Aldose Reductase from the Flower Buds of *Prunus mume*

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The methanolic extract from the flower buds of *Prunus mume*, cultivated in Zhejiang province, China, showed an inhibitory effect on aldose reductase. From the methanolic extract, five new acylated sucroses, mumeoses F–J, were isolated together with 29 known compounds. The chemical structures of the new compounds were elucidated on the basis of chemical and physicochemical evidence. The inhibitory effects of the isolated compounds on aldose reductase were also investigated. Acylated quinic acid analogs, which are one of the major compounds of the flower buds of *P. mume*, were shown to substantially inhibit aldose reductase. In particular, mumeic acid-A was found to exhibit a potent inhibitory effect [$IC_{50}=0.4\mu M$].

Key words *Prunus mume*; mumeose; acylated sucrose; medicinal flower; aldose reductase; acylated quinic acid analog

In the course of our studies on bioactive constituents from medicinal flower,^{2–6)} we previously reported the isolation and structure elucidation of acylated sucroses named prunosides I (11), II (12), and III (13) with inhibitory effects on platelet aggregation and aldose reductase and radical scavenging effect from the flower buds of *Prunus* (*P.*) *mume* Sieb. et Zucc. (Rosaceae) cultivated in Wakayama prefecture, Japan.^{7,8)} In addition, the methanolic (MeOH) extract from the flower buds of *P. mume* cultivated in Zhejiang province, China, showed inhibitory effects on melanogenesis. From the MeOH extract, five new acylated sucroses, mumeoses A (6), B (7), C (8), D (9), and E (10), and three new acylated quinic acid analogs, mumeic acid-A (15) and its methyl ester (16) and 5-*O*-(*E*)-*p*-coumaroylquinic acid ethyl ester (22), were isolated and their structures as well as the inhibitory effects on melanogenesis were characterized.¹⁾

As a continuing study, five new acylated sucroses termed mumeoses F (1), G (2), H (3), I (4), and J (5) were isolated from the flower buds of Chinese *Prunus mume* together with 29 known compounds including acylated quinic acid analogs. This paper deals with the structure elucidation of new acylated sucroses (1–5) and the inhibitory effects of principle constituents on aldose reductase.

The MeOH extract (30.4% from the dried flower buds of *P. mume* cultivated in Zhejiang province, China) was found to show an inhibitory effect on aldose reductase. [$IC_{50}=3.0\mu g/mL$]. The MeOH extract was partitioned into an EtOAc–H₂O (1:1, v/v) mixture to furnish an EtOAc-soluble fraction (6.6%) and an aqueous layer. The aqueous layer was further extracted with 1-butanol to give 1-butanol- (7.5%) and H₂O- (13.0%) soluble fractions. The 1-butanol- and the EtOAc-soluble fractions were found to have significant inhibitory effects on aldose reductase [$IC_{50}=1.7, 1.5\mu g/mL$, respectively], whereas the H₂O-soluble fraction [$IC_{50}=3.5\mu g/mL$] showed weaker effects than those of the 1-butanol- and the EtOAc-soluble fractions.

The 1-butanol- and EtOAc-soluble fractions with the inhibitory activity were subjected to normal- and reversed-phase

silica-gel column chromatography and repeated HPLC. From those fractions, five new acylated sucroses called mumeose F (1, 0.00117%), mumeose G (2, 0.0017%), H (3, 0.0005%), I (4, 0.0003%), J (5, 0.0033%) was isolated together with 29 known compounds, 2',3',4',6'-tetra-*O*-acetyl-3-*O*-(*E*)-*p*-coumaroylsucrose (14, 0.0127%),⁹⁾ mumeic acid-A (15, 0.0039%),¹⁾ mumeic acid-A methyl ester (16, 0.0034%),¹⁾ 5-*O*-(*E*)-*p*-coumaroylquinic acid (17, 0.0132%),¹⁰⁾ chlorogenic acid (18, 0.0120%),¹¹⁾ 5-*O*-(*E*)-*p*-coumaroylquinic acid methyl ester (19, 0.0129%),¹²⁾ chlorogenic acid methyl ester (20, 0.0346%),¹³⁾ 5-*O*-(*E*)-feruloyl quinic acid methyl ester (21, 0.0129%),¹⁴⁾ 5-*O*-(*E*)-*p*-coumaroylquinic acid ethyl ester (22, 0.0031%),¹⁾ chlorogenic acid ethylester (23, 0.0378%),¹⁵⁾ (*E*)-*p*-coumaric acid (24, 0.0007%),¹⁶⁾ (*E*)-caffeic acid (25, 0.0016%),¹⁷⁾ (*E*)-ferulic acid (26, 0.0015%),¹⁶⁾ (*S,R*)-1-*O*-caffeoylglycerol (27, 0.0011%),¹⁸⁾ (*S,R*)-1-*O*-feruloylglycerol (28, 0.0043%),¹⁹⁾ eugenyl β -D-glucopyranoside (29, 0.0006%),²⁰⁾ 1-*O*-(3-hydroxy-4-methoxybenzoyl)- β -D-glucopyranose (30, 0.0005%),²¹⁾ mumeoses A–E (6–10),¹⁾ quercetin 3'-*O*-(2"-*O*-acetyl)- β -D-glucopyranoside,²²⁾ quercetin 3-*O*-(6"-*O*-acetyl)- β -D-glucopyranoside,²³⁾ isorhamnetin 3-*O*- β -D-glucopyranoside,²⁴⁾ quercetin 3-*O*-(6"-*O*-benzoyl)- β -D-galactopyranoside,²⁵⁾ isorhamnetin 3-*O*- β -D-galactopyranoside,²⁶⁾ D-mandelic acid,²⁷⁾ and quercetin.²⁷⁾ In this isolation procedure, acylated sucroses, prunosides I (11), II (12), and III (13), which were isolated from the flower buds of Japanese *P. mume*, could not be isolated from the flower buds of Chinese *P. mume*.

Structures of Mumeoses F–J (1–5) Mumeose F (1) was isolated as a white amorphous powder with positive optical rotation (1: [α]_D²⁵ +40.8°, in MeOH). Its IR spectrum showed absorption bands at 3400, 1730, 1716, 1604, 1515, and 1031 cm^{–1} due to hydroxyl, ester, α,β -unsaturated ester, aromatic ring, and ether functions. The positive-ion mode FAB-MS of 1 revealed a quasimolecular ion peak ([M+Na]⁺) at *m/z* 637 from which the molecular formula C₂₇H₃₄O₁₆ was determined by high-resolution (HR) MS measurement. Treatment of 1 with a 10% aqueous KOH–1,4-dioxane (1:1, v/v) mixture yielded sucrose, which was identified by HPLC analysis. Acid hydrolysis of 1 with 5% aqueous H₂SO₄–1,4-dioxane yielded D-glucose

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Fig. 1. Structure of Constituents Isolated from the Flower Buds of *P. mume*

Fig. 2. Important 2D-NMR Correlations of 1–5

and fructose together with (*E*)-*p*-coumaric acid. D-Glucose was identified by HPLC of the tolylthiocarbamoyl thiazolidine derivative.²⁸⁾ (*E*)-*p*-Coumaric acid was also identified by HPLC. The ¹H-NMR (methanol-*d*₄) and ¹³C-NMR (Table 1) spectra of 1, which were assigned by various NMR experiments,²⁹⁾ showed signals assignable to three acetyl groups [δ 1.78, 1.98, and 2.06 (all s, CH₃CO- $\times$ 3)] and a (*E*)-*p*-coumaroyl group [δ 6.42 (d, *J*=15.9 Hz, H-8''), 6.80 (d, *J*=8.2 Hz, H-3'', 5''), 7.74 (d, *J*=15.9 Hz, H-7''), 7.54 (d, *J*=8.2 Hz, H-2'', 6'')] and a sucrose moiety [δ 3.59 (d, *J*=12.2 Hz, H-1a), 3.68 (d, *J*=12.2 Hz, H-1b), 3.71 (dd, *J*=3.7, 9.0 Hz, H-2'), 3.80 (m, H₂-6), 3.98 (m, H-5), 4.15 (m, H₂-6'), 4.32 (m, H-4), 4.32 (m, H-5'), 4.88 (m, H-4'), 5.22 (dd, *J*=9.0, 9.0 Hz, H-3'), 5.45 (d, *J*=7.1 Hz, H-3), 5.62 (d, *J*=3.7 Hz, H-1')]. The positions

of three acetyl groups and a (*E*)-*p*-coumaroyl moiety were confirmed based on heteronuclear multiple bond connectivity (HMBC) spectroscopy analysis. Namely, long-range correlations were observed between the following proton and carbon pairs: H-3 and C-9'', H-3', 4', 6' and three acetyl carbonyl carbon, H-2'', 6'' and C-1'', 7'', H-3'', 5'' and C-4'', H-7'' and C-9'', H-8'' and C-9'', three acetyl proton and three acetyl carbonyl carbon. On the basis of all this evidence, the chemical structure of mumeose F (1) was determined to be 3',4',6'-tri-*O*-acetyl-3-*O*-(*E*)-*p*-coumaroylsucrose.

Mumeoses G (2) and H (3), which were obtained as a white amorphous powder with positive optical rotations (2: [α]_D¹⁵ +47.3°; 3: [α]_D¹⁵ +29.0°, in MeOH), showed absorption bands due to hydroxyl, ester, α,β -unsaturated ester, aromatic

Table 1. ^{13}C -NMR (125 MHz) Spectroscopic Data for Compounds **1–5** in CD_3OD

Position	1	2	3	4	5
1	65.4	64.6	63.5	65.3	63.4
2	105.6	105.6	106.5	105.8	105.0
3	79.3	77.3	76.8	79.3	78.1
4	74.6	76.4	76.8	74.8	76.7
5	84.2	82.5	82.5	81.9	83.6
6	63.5	64.9	63.8	65.3	63.4
1'	92.8	93.3	91.4	92.7	91.3
2'	70.9	71.2	72.3	70.9	71.5
3'	74.4	76.7	73.8	74.4	71.1
4'	70.3	69.8	69.2	70.4	69.9
5'	69.7	72.3	74.1	69.7	69.8
6'	63.8	64.6	61.7	64.0	65.4
1''	127.3	127.2	127.1	127.2	127.1
2'', 6''	131.5	131.6	131.6	131.5	131.7
3'', 5''	116.8	116.7	116.8	116.8	116.8
4''	161.4	161.4	161.5	161.5	161.6
7''	147.7	147.9	148.0	147.7	148.3
8''	114.6	114.3	114.1	114.5	113.9
9''	168.1	168.1	168.1	167.9	167.5
CH ₃ COO–	171.5	172.0	172.0	171.5	171.3
	172.1	172.7	172.2	172.2	171.5
	172.5	172.8	172.3	172.5	171.8
				172.6	171.8
					171.9
					172.5
CH ₃ COO–	20.5	20.7	20.7	20.4	20.3
	20.7	20.7	20.9	20.7	20.5
	20.8	21.1	20.9	20.7	20.6
				20.8	20.7
					20.7
					20.8

ring, and ether functions in their IR spectra. In the FAB-MS spectra of **2** and **3**, the common quasimolecular ion peak was observed at m/z 637 ($[\text{M}+\text{Na}]^+$) and the molecular formula $\text{C}_{27}\text{H}_{34}\text{O}_{16}$ was determined by HR-MS measurement. The alkaline hydrolysis of **2** and **3** yielded sucrose, whereas the acid hydrolysis of **2** and **3** yielded D-glucose and fructose together with (*E*)-*p*-coumaric acid.²⁸⁾ The ^1H -NMR (methanol- d_4) and ^{13}C -NMR (Table 1) spectra²⁹⁾ of **2** showed signals assignable to three acetyl groups [δ 2.06, 2.06, and 2.10 (all s, $\text{CH}_3\text{CO}-\times 3$)], a (*E*)-*p*-coumaroyl group [δ 6.38 (d, $J=16.1$ Hz, H-8''), 6.79 (d, $J=8.3$ Hz, H-3'', 5''), 7.53 (d, $J=8.3$ Hz, H-2'', 6''), 7.65 (d, $J=16.1$ Hz, H-7'')] and a sucrose moiety [δ 3.48 (dd, $J=9.4$, 9.4 Hz, H-4'), 3.60 (m, H₂-1), 3.64 (m, H-2'), 3.77 (m, H-6a), 3.89 (m, H-6b), 4.13 (m, H-5), 4.20 (m, H-5'), 4.20 (m, H-6'a), 4.48 (m, H-6'b), 5.23 (dd, $J=9.4$, 9.4 Hz, H-3'), 5.51 (d, $J=3.4$ Hz, H-1'), 5.53 (m, H-4), 5.70 (d, $J=7.5$ Hz, H-3)]. The positions of three acetyl groups and a (*E*)-*p*-coumaroyl moiety were confirmed by HMBC spectroscopy analysis. Namely, long-range correlations were observed between the following proton and carbon pairs: H-3 and C-9'', H-4, 3', 6' and three acetyl carbonyl carbons. The ^1H -NMR (methanol- d_4) and ^{13}C -NMR (Table 1) spectra of **3** showed signals assignable to three acetyl groups [δ 2.03, 2.05, and 2.05 (all s, $\text{CH}_3\text{CO}-\times 3$)], a (*E*)-*p*-coumaroyl group [δ 6.39 (d, $J=16.0$ Hz, H-8''), 6.79 (d, $J=8.6$ Hz, H-3'', 5''), 7.52 (d, $J=8.6$ Hz, H-2'', 6''), 7.65 (d, $J=16.0$ Hz, H-7'')] and a sucrose moiety. The proton and carbon signals in the ^1H - and ^{13}C -NMR (Table 1) spectra of **3** were superimposable on those of **2**, except for the signals

around the glucose part of **3**. The positions of acetyl groups of **3** were confirmed based on HMBC spectroscopy. Namely, long-range correlations were observed between the following proton and carbon pairs: H-4, 2', 3' and three acetyl carbonyl carbons. On the basis of all this evidence, the chemical structures of mumeose G (**2**) and mumeose H (**3**) were determined to be 4,3',6'-tri-*O*-acetyl-3-*O*-(*E*)-*p*-coumaroylsucralose and 4,2',3'-tri-*O*-acetyl-3-*O*-(*E*)-*p*-coumaroylsucrose, respectively.

Mumeoses I (**4**) and J (**5**), obtained as a white amorphous powder with positive optical rotations (**4**: $[\alpha]_D^{15} +38.9^\circ$, **5**: $[\alpha]_D^{15} +28.9^\circ$, in MeOH), showed absorption bands due to hydroxyl, ester, α,β -unsaturated ester, aromatic ring and ether functions in their IR spectra. Their molecular formulas ($\text{C}_{29}\text{H}_{36}\text{O}_{17}$ of **4**, $\text{C}_{33}\text{H}_{40}\text{O}_{19}$ of **5**) were determined from the quasimolecular ion peaks (m/z 679 $[\text{M}+\text{Na}]^+$ for **4**, 763 $[\text{M}+\text{Na}]^+$ for **5**) in the positive-ion FAB-MS and by HR-MS measurement. The alkaline hydrolysis of **4** and **5** yielded sucrose and the acid hydrolysis of **4** and **5** yielded D-glucose, fructose, and (*E*)-*p*-coumaric acid, respectively.²⁸⁾ The ^1H -NMR (methanol- d_4) and ^{13}C -NMR (Table 1) spectra²⁹⁾ of **4** and **5** showed signals assignable to four acetyl groups [δ 1.76, 1.99, 2.06, and 2.08 (all s, $\text{CH}_3\text{CO}-\times 4$) for **4**] and six acetyl groups [δ 1.78, 1.94, 2.04, 2.07, 2.09, and 2.09 (all s, $\text{CH}_3\text{CO}-\times 6$) for **5**], respectively, together with a (*E*)-*p*-coumaroyl group and a sucrose moiety. The positions of acetyl groups of **4** and **5** were confirmed based on HMBC spectroscopy. Namely, long-range correlations were observed between the following proton and carbon pairs [H-6, 3', 4', 6' and four acetyl carbonyl carbons

for **4**, H-1, 4, 2', 3', 4', 6' and six acetyl carbonyl carbons for **5**]. Consequently, the chemical structures of mumeoses I (**4**) and J (**5**) were characterized to be 6,3',4',6'-tetra-*O*-acetyl-3-*O*-(*E*)-*p*-coumaroylsucrose and 1,4,2',3',4',6'-hexa-*O*-acetyl-3-*O*-(*E*)-*p*-coumaroylsucrose, respectively.

Inhibitory Effect on Rat Lens Aldose Reductase Aldose reductase, a key enzyme in the polyol pathway, has been reported to catalyze the reduction of glucose to sorbitol. Sorbitol does not readily diffuse across cell membranes, and the intracellular accumulation of sorbitol has been implicated in the chronic complications of diabetes such as cataract. Previously, we have reported that various constituents such as flavonoids and terpenoids from natural medicines and medicinal foods inhibited aldose reductase inhibitory effect.^{30–35} In addition, we reported that acylated sucrose, prunose I (**11**), exhibited moderate inhibitory effect [$IC_{50}=58\mu M$]⁷⁾ and chlorogenic acid methyl ester (**20**) showed strong inhibitory effect [$IC_{50}=1.3\mu M$].³²⁾ In the present study, the inhibitory effects on aldose reductase of the principal isolated constituents from the flower buds of *P. mume* cultivated in China were examined for structure–activity relationship study (Table 2). Among these principal constituents, acylated quinic acid analogs were shown to substantially inhibit aldose reductase. In particular, mumeic acid-A (**15**) and mumeic acid-A methyl ester (**16**), which are quinic acids with benzoyl and cafferoyl groups, were found to exhibit a potent inhibitory effects [$IC_{50}=0.4\mu M$ for **15**, $0.6\mu M$ for **16**]. The biological effects were equal to or stronger than that of a reference compound, chlorogenic acid [**18**, $IC_{50}=0.7\mu M$], which is reported to have inhibitory effect.³⁶⁾ On the other hand, **20** showed the similar value compared with the previous reported data.³²⁾ With regard to structural requirements of acylated quinic acid analogs **15–23** for the effect, quinic acid analogs (**15**, **16**, **18**, **20**, **23**) with a cafferoyl group showed stronger inhibitory effect than quinic acid analogs (**17**, **19**, **21**, **22**) with a coumaroyl or a feruloyl group, (*E*)-*p*-coumaric acid (**24**), (*E*)-caffeic acid (**25**), and (*E*)-*p*-coumaric acid (**26**). These findings suggest that the cafferoyl group is essential for the effect, and the quinic acid part is important for the enhancement of the effect. On the other hand, acylated sucrose **1**, **2**, **3**, and **5** exhibited moderate inhibitory effect [$IC_{50}=23–51\mu M$].

In conclusion, five new acylated sucrose, mumeose F (**1**), G (**2**), H (**3**), I (**4**), and J (**5**), were isolated from the flower buds of *P. mume* cultivated in Zhejiang province, China. In addition, acylated quinic acid analogs, which are one of the major compounds of the flower buds of *P. mume*, substantially exhibited the inhibitory effects on aldose reductase. Further study for the development of acylated quinic acid analogs as potent anti-cataract agents are expected.

Experimental

General Experimental Procedures The following instruments were used to obtain physical data: specific rotations, Horiba SEPA-300 digital polarimeter ($l=5\text{ cm}$); IR spectra, a Thermo Electron Nexus 470; electron ionization (EI)-MS and HR-EI-MS, JEOL JMS-GCMATE mass spectrometer; FAB-MS and HR-FAB-MS, a JEOL JMS-SX 102A mass spectrometer; ^1H -NMR spectra, JEOL JNM-LA 500 (500 MHz) spectrometer; ^{13}C -NMR spectra, JEOL JNM-LA (125 MHz) spectrometer with tetramethylsilane as an internal standard; HPLC detector, Shimadzu SPD-10AVP UV/VIS

detector; and HPLC column, Inertsil ODS-3 (150×3.0 mm i.d.), COSMOSIL 5C18-MS-II (250×4.6 mm i.d., 250×10 mm i.d. and 250×20 mm i.d.), 5C18-PAQ (250×20 mm i.d.) and 5C18-AR-II (250×4.6 mm i.d.) columns were used for analytical and preparative purposes. The following experimental materials were used for chromatography: normal-phase silica gel column chromatography, Silica gel BW-200 (Fuji Silysia Chemical, Ltd., 150–350 mesh); reversed-phase silica gel column chromatography, Chromatorex ODS DM1020T (Fuji Silysia Chemical, Ltd., 100–200 mesh); TLC, precoated TLC plates with Silica gel 60F₂₅₄ (Merck, 0.25 mm) (ordinary phase) and Silica gel RP-18 F_{254S} (Merck, 0.25 mm) (reversed phase); reversed-phase HPTLC, precoated TLC plates with Silica gel RP-18 WF_{254S} (Merck, 0.25 mm); and detection was achieved by spraying with 1% $\text{Ce}(\text{SO}_4)_2$ –10% aqueous H_2SO_4 followed by heating.

Plant Material The dried flower buds of *P. mume* cultivated in Zhejiang province, China, were the commercial products purchased from Tochimoto Tenkaido Co., Ltd. (Osaka, Japan) in April 2011.

Extraction and Isolation The dried flower buds (2.0 kg) were extracted three times with methanol under reflux for 3 h. Evaporation of the solvent under reduced pressure provided a MeOH extract (608.0 g, 30.4%). A part of the MeOH extract (486.4 g) was partitioned into an EtOAc– H_2O (1:1, v/v) mixture to furnish an EtOAc-soluble fraction (106.0 g, 6.6%) and an aqueous phase. The aqueous phase was further extracted with 1-butanol to give a 1-butanol-soluble fraction (119.3 g, 7.5%) and an H_2O -soluble fraction (256.0 g, 16.0%). A part of the 1-butanol-soluble fraction (80.0 g) was subjected to normal phase silica gel column chromatography [2.4 kg, *n*-hexane→ CHCl_3 –MeOH (50:1→20:1→10:1→5:1→10:3, v/v)→MeOH] to give seven fractions [Fr. B1 (450 mg), Fr. B2 (960 mg), Fr. B3 (850 mg), Fr. B4 (1.37 g), Fr. B5 (4.70 g), Fr. B6 (7.24 g), Fr. B7 (41.4 g)] as reported previously.¹⁾

Fraction B5 (4.70 g) was further separated by reversed phase silica gel column chromatography [132 g, MeOH– H_2O

Table 2. Inhibitory Effects on Aldose Reductase of Compounds from the Flower Buds of *P. mume*

Sample	IC_{50} (μM)
Mumeose F (1)	44.7
Mumeose G (2)	51.0
Mumeose H (3)	41.7
Mumeose J (5)	22.9
Mumeic acid-A (15)	0.4
Mumeic acid-A methyl ester (16)	0.6
5- <i>O</i> -(<i>E</i>)- <i>p</i> -Coumaroylquinic acid (17)	7.5
5- <i>O</i> -(<i>E</i>)- <i>p</i> -Coumaroylquinic acid methyl ester (19)	8.9
Chlorogenic acid methyl ester (20)	2.4
5- <i>O</i> -(<i>E</i>)-Feruloylquinic acid methyl ester (21)	72.2
5- <i>O</i> -(<i>E</i>)- <i>p</i> -Coumaroylquinic acid ethyl ester (22)	7.0
Chlorogenic acid ethyl ester (23)	1.5
(<i>E</i>)- <i>p</i> -Coumaric acid (24)	>100
(<i>E</i>)-Caffeic acid (25)	30.9
(<i>E</i>)-Ferulic acid (26)	>100
(<i>S,R</i>)-1- <i>O</i> -Feruloylglycerol (28)	36.9
Eugenyl β -D-glucopyranoside (29)	>100
30	9.7
Chlorogenic acid (18) (positive control)	0.7

Each value represents the mean of 2–4 experiments.

(20:80→30:70→40:60→50:50→60:40, v/v)→MeOH] to give ten fractions [Fr. B5-1 (0.29 g), Fr. B5-2 (0.73 g), Fr. B5-3 (0.15 g), Fr. B5-4 (0.26 g), Fr. B5-5 (0.32 g), Fr. B5-6 (0.28 g), Fr. B5-7 (0.22 g), Fr. B5-8 (0.10 g), Fr. B5-9 (0.17 g), Fr. B5-10 (0.46 g)]. Fraction B5-4 (260 mg) was purified by HPLC [H₂O–MeOH–AcOH (700:300:3, v/v/v), COSMOSIL 5C18-MS-II] to give **25** (17 mg) and **27** (12 mg). Fraction B5-9 (170 mg) was purified by HPLC [H₂O–MeOH–AcOH (650:350:3, v/v/v), COSMOSIL 5C18-MS-II] to give two fractions [Fr. B5-9-1 (61 mg), Fr. B5-9-2 (39 mg)]. Fraction B5-9-2 (39 mg) was purified by HPLC [H₂O–MeCN–AcOH (800:200:3, v/v/v), COSMOSIL 5C18-MS-II] to give **1** (13 mg) and **29** (6.1 mg). Fraction B6 (7.24 g) was further separated by silica gel column chromatography [230 g, CHCl₃–EtOAc (1:1, v/v)→CHCl₃–EtOAc–2-propanol–MeOH (20:20:1:1→15:15:1:1→10:10:1:1→5:5:1:1→1:1:1:1, v/v)→MeOH] to give five fractions [Fr. B6-1 (70 mg), Fr. B6-2 (1.56 g), Fr. B6-3 (3.83 g), Fr. B6-4 (0.92 g), Fr. B6-5 (0.49 g)]. Fraction B6-3 (3.83 g) was purified by reversed phase silica gel column chromatography [132 g, MeOH–H₂O (20:80→30:70→40:60→50:50→60:40, v/v)→MeOH] to give nine fractions [Fr. B6-3-1 (186 mg), Fr. B6-3-2 (2.47 g), Fr. B6-3-3, Fr. B6-3-4 (520 mg), Fr. B6-3-5 (158 mg), Fr. B6-3-6, Fr. B6-3-7, Fr. B6-3-8 (51 mg), Fr. B6-3-9]. Fraction B6-3-1 (186 mg) was purified by HPLC [H₂O–MeOH–AcOH (800:200:3, v/v/v)] to give **30** (5.4 mg). A part of the EtOAc-soluble fraction (80.0 g) was subjected to normal phase silica gel column chromatography [2.4 kg, *n*-hexane→*n*-hexane–EtOAc (5:1→3:1, v/v)→CHCl₃–MeOH (100:1→50:1→20:1→10:1→4:1→2:1, v/v)→MeOH] to give six fractions [Fr. E1 (15.89 g), Fr. E2 (4.13 g), Fr. E3 (9.73 g), Fr. E4 (6.39 g), Fr. E5 (20.57 g), Fr. E6 (13.33 g)]. Fraction E4 (6.39 g) was further separated by reversed phase silica gel column chromatography [200 g, MeOH–H₂O (30:70→40:60→50:50→60:40, v/v)→MeOH] to give six fractions [Fr. E4-1 (0.40 g), Fr. E4-2 (0.20 g), Fr. E4-3 (0.46 g), Fr. E4-4 (0.60 g), Fr. E4-5 (0.25 g), Fr. E4-6 (1.50 g)]. Fraction E4-3 (0.46 g) was further separated by normal phase silica gel column chromatography [15 g, *n*-hexane→*n*-hexane–EtOAc (10:1→5:1→2:1→1:1, v/v)→EtOAc→MeOH] to give five fractions [Fr. E4-3-1 (69 mg), Fr. E4-3-2 (70 mg), Fr. E4-3-3 (27 mg), Fr. E4-3-4 (122 mg), Fr. E4-3-5 (63 mg)]. Fraction E4-3-2 (70 mg) was purified by HPLC [H₂O–MeCN–AcOH (770:230:3, v/v/v), COSMOSIL 5C18-MS-II] to give **24** (7.7 mg) and **26** (17 mg). Fraction E4-3-4 (122 mg) was purified by HPLC [H₂O–MeCN–AcOH (650:350:3, v/v/v), COSMOSIL 5C18-MS-II] to two fractions [Fr. E4-3-4-1 (37 mg), Fr. E4-3-4-2 (27 mg)]. Fraction E4-3-4-1 (37 mg) was purified by HPLC [H₂O–MeCN–MeOH–AcOH (600:150:250:3, v/v/v/v), COSMOSIL 5C18-MS-II] to give **4** (3.6 mg). Fraction E4-5 (0.25 g) was further separated by normal phase silica gel column chromatography [7.5 g, *n*-hexane→*n*-hexane–EtOAc (10:1→5:1→2:1→1:1→1:1→1:2, v/v)→EtOAc→MeOH] to give three fractions [Fr. E4-5-1 (33 mg), Fr. E4-5-2 (113 mg), Fr. E4-5-3 (35 mg)]. Fraction E4-5-2 (113 mg) was purified by HPLC [H₂O–MeCN–AcOH (620:380:3, v/v/v), COSMOSIL 5C18-MS-II] to give **5** (42 mg). Fraction E5 (20.57 g) was separated by normal phase silica gel column chromatography [720 g, CHCl₃→CHCl₃–MeOH (50:1→20:1→15:1→10:1→5:1, v/v)→MeOH] to give seven fractions [Fr. E5-1 (40 mg), Fr. E5-2 (580 mg), Fr. E5-3 (950 mg), Fr. E5-4 (7.18 g), Fr. E5-5 (3.56 g), Fr. E5-6 (3.80 g), Fr. E5-7 (1.29 g)].

Fraction E5-4 (7.18 g) was further separated by reversed phase silica gel column chromatography [200 g, MeOH–H₂O (20:80→30:70→40:60→50:50→60:40→80:20→90:10, v/v)→MeOH] to give nine fractions [Fr. E5-4-1, Fr. E5-4-2 (959 mg), Fr. E5-4-3, Fr. E5-4-4 (220 mg), Fr. E5-4-5 (162 mg), Fr. E5-4-6 (560 mg), Fr. E5-4-7, Fr. E5-4-8 (538 mg), Fr. E5-4-9 (170 mg)]. Fraction E5-4-2 (959 mg) was purified by HPLC [H₂O–MeCN–AcOH (830:170:3, v/v/v), COSMOSIL 5C18-MS-II] to give **25** (168 mg). Fraction E5-4-4 (220 mg) was purified by HPLC [H₂O–MeCN–AcOH (800:200:3, v/v/v), COSMOSIL 5C18-MS-II] to give **28** (8.4 mg). A part of fraction E5-4-6 (200 mg) was purified by HPLC [H₂O–MeCN–MeOH–AcOH (650:200:150:3, v/v/v/v), COSMOSIL 5C18-PAQ] to give **14** (37 mg). Fraction E5-5 (3.56 g) was further separated by reversed phase silica gel column chromatography [120 g, MeOH–H₂O (20:80→30:70→40:60→50:50→60:40→80:20→90:10, v/v)→MeOH] to give nine fractions [Fr. E5-5-1 (147 mg), Fr. E5-5-2 (207 mg), Fr. E5-5-3 (326 mg), Fr. E5-5-4 (594 mg), Fr. E5-5-5 (313 mg), Fr. E5-5-6 (152 mg), Fr. E5-5-7 (261 mg), Fr. E5-5-8 (114 mg), Fr. E5-5-9 (614 mg)]. Fraction E5-5-5 (313 mg) was further separated by HPLC [H₂O–MeCN–AcOH (750:250:3, v/v/v), COSMOSIL 5C18-MS-II] to give three fractions [Fr. E5-5-5-1 (65 mg), Fr. E5-5-5-2 (16 mg), Fr. E5-5-5-3 (13 mg)]. Fraction E5-5-5-1 (65 mg) was purified by HPLC [H₂O–MeCN–MeOH–AcOH (700:150:150:3, v/v/v/v), COSMOSIL 5C18-MS-II] to give **2** (20 mg) and **3** (5.7 mg). Fraction E5-5-6 (152 mg) was purified by HPLC [H₂O–MeCN–AcOH (700:300:3, v/v/v/v), COSMOSIL 5C18-MS-II] to give **14** (47 mg). The isolation methods of several known compounds were not shown in “Extraction and Isolation.” Those isolation methods were showed in ref. 1.

Mumeose F (**1**): A white amorphous powder; $[\alpha]_D^{15} +40.8^\circ$ ($c=0.73$, MeOH); IR (attenuated total reflection (ATR)): $\nu_{\max}$ 3400, 1730, 1716, 1604, 1515, 1441, 1367, 1228, 1164, 1031, 833 cm⁻¹; ¹H-NMR (methanol-*d*₄, 500 MHz) δ : 1.78, 1.98, 2.06 (all s, CH₃CO– ×3), 3.59 (d, $J=12.2$ Hz, H-1a), 3.68 (d, $J=12.2$ Hz, H-1b), 3.71 (dd, $J=3.7$, 9.0 Hz, H-2'), 3.80 (m, H₂-6), 3.98 (m, H-5), 4.15 (m, H₂-6'), 4.32 (m, H-4), 4.32 (m, H-5'), 4.88 (m, H-4'), 5.22 (dd, $J=9.0$, 9.0 Hz, H-3'), 5.45 (d, $J=7.1$ Hz, H-3), 5.62 (d, $J=3.7$ Hz, H-1'), 6.42 (d, $J=15.9$ Hz, H-8''), 6.80 (d, $J=8.2$ Hz, H-3'', 5''), 7.54 (d, $J=8.2$ Hz, H-2'', 6''), 7.74 (d, $J=15.9$ Hz, H-7''); ¹³C-NMR: given in Table 1; positive-ion FAB-MS: m/z 637 [M+Na]⁺; high-resolution positive-ion FAB-MS: m/z 637.1747 (Calcd for C₂₇H₃₄O₁₆Na [M+Na]⁺: m/z 637.1745).

Mumeose G (**2**): A white amorphous powder; $[\alpha]_D^{15} +47.3^\circ$ ($c=0.65$, MeOH) IR (ATR): $\nu_{\max}$ 3400, 1733, 1716, 1604, 1516, 1457, 1364, 1227, 1155, 1032, 832 cm⁻¹; ¹H-NMR (methanol-*d*₄, 500 MHz) δ : 2.06, 2.06, 2.10 (all s, CH₃CO– ×3), 3.48 (dd, $J=9.4$, 9.4 Hz, H-4'), 3.60 (m, H₂-1), 3.64 (m, H-2'), 3.77 (m, H-6a), 3.89 (m, H-6b), 4.13 (m, H-5), 4.20 (m, H-5'), 4.20 (m, H-6'a), 4.48 (m, H-6'b), 5.23 (dd, $J=9.4$, 9.4 Hz, H-3'), 5.51 (d, $J=3.4$ Hz, H-1'), 5.53 (m, H-4), 5.70 (d, $J=7.5$ Hz, H-3), 6.38 (d, $J=16.1$ Hz, H-8''), 6.79 (d, $J=8.3$ Hz, H-3'', 5''), 7.53 (d, $J=8.3$ Hz, H-2'', 6''), 7.65 (d, $J=16.1$ Hz, H-7''); ¹³C-NMR: given in Table 1; positive-ion FAB-MS: m/z 637 [M+Na]⁺; high-resolution positive-ion FAB-MS: m/z 637.1738 (Calcd for C₂₇H₃₄O₁₆Na [M+Na]⁺: m/z 637.1745).

Mumeose H (**3**): A white amorphous powder; $[\alpha]_D^{15} +29.0^\circ$ ($c=0.24$, MeOH); IR (ATR): $\nu_{\max}$ 3400, 1733, 1717, 1603, 1516,

1436, 1373, 1228, 1150, 1014, 833 cm^{-1} ; ^1H -NMR (methanol- d_4 , 500 MHz) δ : 2.03, 2.05, 2.05 (all s, $\text{CH}_3\text{CO}-\times 3$), 3.56 (d, $J=12.2\text{ Hz}$, H-1a), 3.63 (d, $J=12.2\text{ Hz}$, H-1b), 3.66 (dd, $J=9.0, 9.0\text{ Hz}$, H-4'), 3.83 (m, H-2-6'), 3.79 (m, H-2-6), 4.00 (m, H-5'), 4.10 (m, H-5), 4.76 (dd, $J=3.9, 9.0\text{ Hz}$, H-2'), 5.40 (dd, $J=9.0, 9.0\text{ Hz}$, H-3'), 5.56 (dd, $J=7.8, 7.8\text{ Hz}$, H-4), 5.73 (d, $J=7.8\text{ Hz}$, H-3), 5.74 (d, $J=3.9\text{ Hz}$, H-1'), 6.39 (d, $J=16.0\text{ Hz}$, H-8"), 6.79 (d, $J=8.6\text{ Hz}$, H-3", 5"), 7.52 (d, $J=8.6\text{ Hz}$, H-2", 6"), 7.65 (d, $J=16.0\text{ Hz}$, H-7"); ^{13}C -NMR: given in Table 1; positive-ion FAB-MS: m/z 637 $[\text{M}+\text{Na}]^+$; high-resolution positive-ion FAB-MS: m/z 637.1744 (Calcd for $\text{C}_{27}\text{H}_{34}\text{O}_{16}\text{Na}$ $[\text{M}+\text{Na}]^+$: m/z 637.1745).

Mumeose I (4): A white amorphous powder; $[\alpha]_D^{15} +38.9^\circ$ ($c=0.16$, MeOH); IR (ATR): ν_{max} 3400, 1730, 1716, 1604, 1515, 1446, 1368, 1228, 1157, 1034, 833 cm^{-1} ; ^1H -NMR (methanol- d_4 , 500 MHz) δ : 1.76, 1.99, 2.06, 2.08 (all s, $\text{CH}_3\text{CO}-\times 4$), 3.60 (m, H-1a), 3.69 (m, H-1b), 3.70 (m, H-2'), 4.15 (m, H-2-6'), 4.13 (m, H-5), 4.36 (m, H-2-6), 4.36 (m, H-4), 4.37 (m, H-5'), 4.82 (m, H-4'), 5.20 (dd, $J=9.6, 9.6\text{ Hz}$, H-3'), 5.46 (d, $J=7.0\text{ Hz}$, H-3), 5.49 (d, $J=3.6\text{ Hz}$, H-1'), 6.42 (d, $J=16.0\text{ Hz}$, H-8"), 6.80 (d, $J=8.3\text{ Hz}$, H-3", 5"), 7.54 (d, $J=8.3\text{ Hz}$, H-2", 6"), 7.74 (d, $J=16.0\text{ Hz}$, H-7"); ^{13}C -NMR: given in Table 1; positive-ion FAB-MS: m/z 679 $[\text{M}+\text{Na}]^+$; high-resolution positive-ion FAB-MS: m/z 679.1855 (Calcd for $\text{C}_{29}\text{H}_{36}\text{O}_{17}\text{Na}$ $[\text{M}+\text{Na}]^+$: m/z 679.1850).

Mumeose J (5): A white amorphous powder; $[\alpha]_D^{15} +28.9^\circ$ ($c=0.21$, MeOH); IR (ATR): ν_{max} 3400, 1741, 1715, 1604, 1515, 1437, 1367, 1220, 1149, 1033, 834 cm^{-1} ; ^1H -NMR (methanol- d_4 , 500 MHz) δ : 1.78, 1.94–2.04, 2.07, 2.09, 2.09 (all s, $\text{CH}_3\text{CO}-\times 6$), 3.78 (m, H-2-6), 4.11 (m, H-5), 4.16 (m, H-2-1), 4.21 (m, H-2-6'), 4.33 (m, H-5'), 4.89 (m, H-2'), 4.99 (dd, $J=9.2, 9.2\text{ Hz}$, H-4'), 5.41 (m, H-3'), 5.46 (m, H-4), 5.56 (m, H-3), 5.70 (d, $J=3.6\text{ Hz}$, H-1'), 6.40 (d, $J=15.9\text{ Hz}$, H-8"), 6.81 (d, $J=7.7\text{ Hz}$, H-3", 5"), 7.53 (d, $J=7.7\text{ Hz}$, H-2", 6"), 7.71 (d, $J=15.9\text{ Hz}$, H-7"); ^{13}C -NMR: given in Table 1; positive-ion FAB-MS: m/z 763 $[\text{M}+\text{Na}]^+$; high-resolution positive-ion FAB-MS: m/z 763.2055 (Calcd for $\text{C}_{33}\text{H}_{40}\text{O}_{19}\text{Na}$ $[\text{M}+\text{Na}]^+$: m/z 763.2061).

Acid Hydrolysis of 1–5 Compounds 1–5 (1.5 mg) were dissolved in 5% aqueous H_2SO_4 –1,4-dioxane (1:1, v/v, 1.0 mL), and each solution was heated at 90°C for 3 h, and neutralized with Amberlite IRA-400 (OH^- form). After drying *in vacuo*, a small part of the residue was dissolved in H_2O –MeOH (1:1, v/v) and analyzed by reversed-phase HPLC [column: COSMOSIL 5C18-MS-II, $250\times 4.6\text{ mm}$ i.d.; mobile phase A: H_2O –AcOH (1000:3, v/v), B: MeCN–AcOH (1000:3, v/v), Linear gradient: mobile phase A–B (90:10→72:28, v/v, in 24 min); detection: UV (300 nm); flow rate: 1.0 mL/min; column temperature: ambient] to identify (*E*)-*p*-coumaric acid by comparison of the retention time with that of authentic sample [$t_R=17.1\text{ min}$]. In addition, the remaining parts of the residue from 1–5, from which glucose and fructose were identified by TLC (ordinary phase) [CHCl_3 –MeOH– H_2O (30:15:3, v/v/v)], were dissolved in pyridine (0.1 mL) containing L-cysteine methyl ester hydrochloride (0.5 mg) and each solution was heated at 60°C for 1 h. *o*-Torylisothiocyanate (0.5 mg) in pyridine (0.1 mL) was added to the mixture and heated at 60°C for 1 h. The reaction mixture was analyzed by reversed-phase HPLC [column: COSMOSIL 5C18-AR-II, $250\times 4.6\text{ mm}$ i.d.; mobile phase: MeCN–0.05 M H_3PO_4 (23:77, v/v); detection: UV (250 nm); flow rate: 0.8 mL/min; column temperature: 35°C] to identify the derivative of D-glucose by comparison of

the retention time with that of authentic sample (t_R : 19.8 min).

Alkaline Hydrolysis of 1–5 Compounds 1–5 (1.5 mg) were treated with 10% aqueous KOH–1,4-dioxane (1:1, v/v, 1.0 mL) and stirred at 37°C for 24 h. Each reaction mixture was neutralized with Dowex HCR W2 (H^+ form) and the resin was removed by filtration. Evaporation of the solvent from the filtrate under reduced pressure yielded a crude product. The crude product was dissolved in water and applied to normal-phase HPLC {column: YMC-Pack Polyamine II, $250\times 4.6\text{ mm}$ i.d.; mobile phase: MeCN– H_2O (3:1, v/v); detection: optical rotation [Shodex OR-2 (Showa Denko Co., Ltd., Tokyo, Japan)]; flow rate: 1.0 mL/min; column temperature: ambient} to identify D-(+)-sucrose by comparison of the retention time and optical rotation with that of authentic sample ($t_R=19.8\text{ min}$ with positive rotation).

Effects on Rat Lens Aldose Reductase The experiments were performed as described in our previous reports.³⁰⁾ The supernatant fluid of rat lens homogenate was used as a crude enzyme. The enzyme suspension was diluted to produce *ca.* 10 nmol/tube of nicotinamide adenine dinucleotide phosphate (NADP) in the following reaction. The incubation mixture contained phosphate buffer 135 mM (pH 7.0), Li_2SO_4 100 mM, reduced nicotinamide adenine dinucleotide phosphate (NADPH) 0.03 mM, DL-glyceraldehyde 1 mM as a substrate, and 100 μL of enzyme fraction, with 25 μL of sample solution, in a total volume of 0.5 mL. The reaction was initiated by the addition of NADPH at 30°C . After 30 min, the reaction was stopped by the addition of 150 μL of HCl 0.5 M. Then, 0.5 mL of NaOH 6 M containing imidazole 10 mM was added, and the solution was heated at 60°C for 20 min to convert NADP into a fluorescent product. Fluorescence was measured using a fluorescence microplate reader (FLUOstar OPTIMA, BMG Labtechnologies) at an excitation wavelength of 360 nm and an emission wavelength of 460 nm. Each test sample was dissolved in DMSO. Measurements were performed in duplicate, and IC_{50} values were determined graphically.

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