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Total synthesis of three naturally occurring 6,8-di-*C*-glycosylflavonoids: phloretin, naringenin, and apigenin bis-*C*-β-D-glucosides

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Abstract—Three naturally occurring di-*C*-glycosylflavonoids, phloretin (dihydrochalcone), naringenin (flavanone), and apigenin (flavone) bis-6,8-*C*-β-D-glucopyranosides (**4**, **5**, and **6**), were synthesized in total yields of 52.3%, 53.5%, and 36.4%, respectively, starting from the key compound, di-*C*-β-D-glucopyranosylphloroacetophenone (**1**). Benzyl protection of the phenolic hydroxyls in **1** and a subsequent aldol condensation with benzyloxybenzaldehyde led to the production of chalcone **3**, which, after hydrogenolysis or acid hydrolysis and deprotection, gave **4** and **5**, respectively. The acetylation of **5**, followed by DDQ oxidation and deprotection, gave **6**.

Keywords: Di-*C*-β-D-glycopyranosylflavonoids; Dihydrochalcone; Flavanone; Flavone; Direct C-glycosylation; Total synthesis

1. Introduction

A variety of *C*-glycosylflavonoids are widely distributed in plants.[1] They are relatively harmless but are biologically active. They have been reported to have antioxidant and radioprotective effects,[2] to inhibit HOCl-dependent damage to erythrocytes,[3] suppress of alcohol drinking in alcohol-preferring rats, high alcohol drinking rats, and monkeys,[4] and to have strong mitogenic and colony-stimulating factor-inducing activities.[5] Among such compounds, 6,8-di-*C*-glycosylflavonoids, which are found mainly in citrus plants,[1] have been reported to have hypotensive effects,[6] to inhibit β-glucuronidase activity,[7] stimulate the ovipositional response of *Paoillo xuthus* females,[8] and affect the germination of seeds.[9]

However, only a few syntheses of the *C*-glycosyflavonoids have been reported.[1a,10] In previous studies,[11] we reported the synthesis of *C*-β-D-glycosylflavonoids using Suzuki's O→C glycoside rearrangement method,[12] in which selectively hydroxyl-protected phloroacetophenone is reacted with a benzyl-protected glycosyl fluoride in the presence of a catalytic amount of $BF_3{\cdot}OEt_2$. However, this Fries-type O→C glycoside rearrangement was not applicable for the second C-glycosylation to produce di-*C*-glycosylphloroacetophenone.[13a] Therefore, the bis-*C*-glycosylphloroacetophenone was prepared via the double C-glycosylation of the selectively benzyl-protected phloroglucinol followed by C-acetylation.[13a] Thus, the second C-glycosylation of the aryl *C*-glycoside in which electron-withdrawing groups were not present was accomplished via a Fries-type or a Friedel–Crafts-type reaction.[13a–c] Therefore, although the synthesis of aryl bis-*C*-glycosides has been developed, an efficient total synthesis of di-*C*-glycosylflavonoids has not yet been achieved.[13d–f] The focus of our research is on developing methods for the direct C-glycosylation of phloroacetophenone, a key compound in the overall synthesis of flavonoids. The method that we developed is an environmentally friendly and simple synthetic procedure in which unprotected D-glucose and

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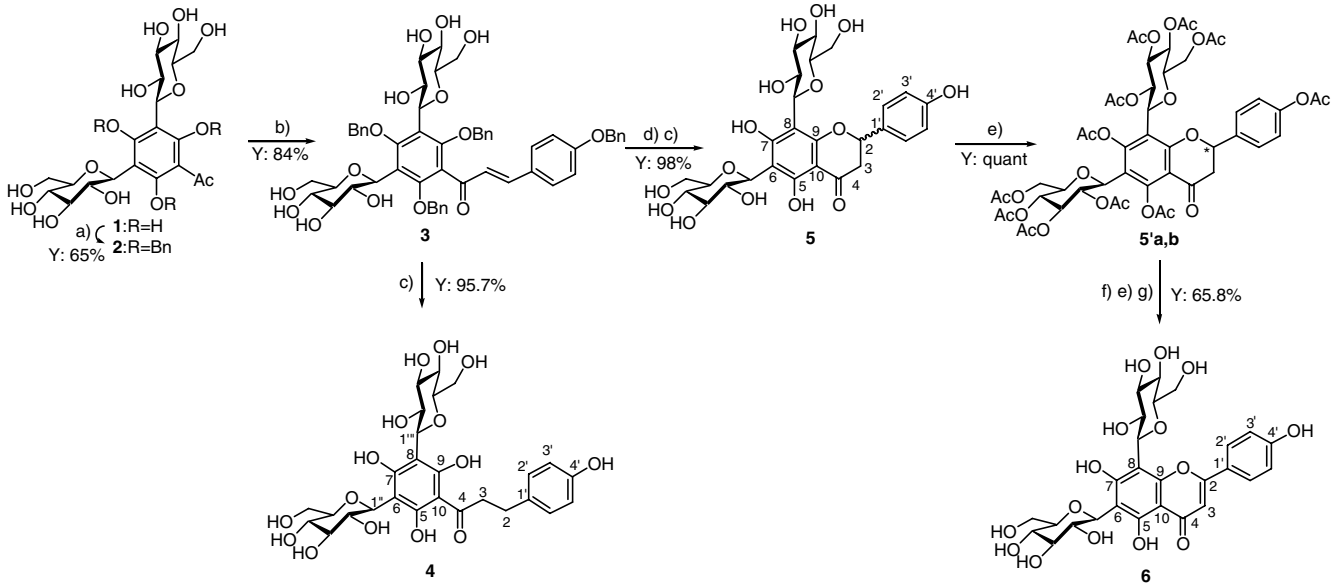
phloroacetophenone are reacted in the presence of a catalytic amount of scandium(III) trifluoromethanesulfonate [$Sc(OTf)_3$] in an aqueous solution, leading to the production of the bis-*C*-β-D-glucoside (**1**) in 40% yield, along with the mono-*C*-β-D-glucoside, in 39% yield.[14] The direct C-glycosylation method can be used to prepare di-*C*-β-D-glycosylphloroacetophenone in a one-step reaction without the need for tedious hydroxyl protection or the use of harmful reagents.

Herein, we describe the total synthesis of three naturally occurring di-*C*-β-D-glycosylflavonoids: phloretin (dihydrochalcone), naringenin (flavanone), and apigenin (flavone) 6,8-bis-*C*-β-D-glucopyranosides (**4**,[15] **5**,[16] and **6**[17]), using di-*C*-β-D-glucopyranosylphloroacetophenone (**1**) synthesized by this direct C-glycosylation method as a starting material (Scheme 1). The simple synthetic method, which proceeded in short steps without protection of the hydroxyl groups in the sugar moiety, was explored in an attempt to take advantage of this direct C-glycosylation reaction.

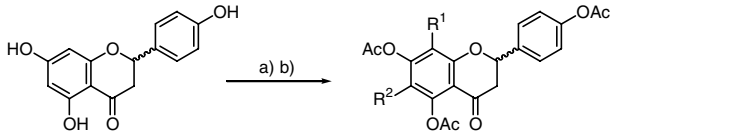
2. Results and discussion

We first examined the one-stage synthesis by the direct C-glycosylation of (±)-naringenin in an attempt to synthesize di-*C*-glycosylflavonoids utilizing reaction conditions that had been developed in a previous study (Scheme 2).[14] The desired 6,8-di-*C*-glucosylnaringenin (**5′**) was produced in a low yield of 17.3%, along with 6- or 8-*C*-glucosylnaringenin (**7**) in 19.0% yield as the acetate derivatives. Since the direct bis-C-glycosylation of (±)-naringenin resulted in low yield, we directed our attention to the stepwise synthesis of di-*C*-β-D-glucosylflavonoids using di-*C*-β-D-glucosylphloroacetophenone (**1**) as the starting material (Scheme 1).

The phenolic hydroxyls of **1** were selectively protected by reaction with benzyl bromide (4.5 equiv) in the presence of potassium carbonate (4.5 equiv) in 65% yield. The resulting benzyl ether **2** was next subjected to an aldol condensation with benzyloxybenzaldehyde (2 equiv) in the presence of potassium hydroxide (2 equiv) at



Scheme 1. Total synthesis of three naturally occurring 6,8-di-*C*-glucosylflavonoids (**4**–**6**). Reagents and conditions: (a) BnBr (4.5 equiv), K_2CO_3 (4.5 equiv) in DMF, rt; (b) benzyloxybenzaldehyde (2 equiv), KOH (2 equiv) in MeOH, rt; (c) H_2/10% Pd–C, in MeOH; (d) 1:2 concd HCl–MeOH, reflux, 30 min; (e) Ac_2O/Py; (f) (i) DDQ (4 equiv) in PhCl, 160 °C, overnight, (ii) for the recovery: DDQ (5 equiv) in *o*-dichlorobenzene, 180 °C, 7 h; (g) (i) NaOMe in MeOH, (ii) Dowex 50 (H^+) in MeOH.



Scheme 2. Direct C-glycosylation of (±)-naringenin. Reagents and conditions: (a) D-glucose (3.0 equiv), $Sc(OTf)_3$ (0.4 equiv) in 2:1 CH_3CN–H_2O, reflux, 2 days; (b) Ac_2O, Pyridine, DMAP.

room temperature to afford the desired chalcone **3** in 84% yield.[18] Chalcone **3**, in which the phenolic hydroxyls were protected with benzyl groups, readily afforded dihydrochalcone **4** via both debenzylation and the reduction of the alkene bond of the cinnamoyl group by hydrogenation (10% Pd–C in MeOH, overnight) in 95.7% yield. Chalcone **3** was converted to ring-closed **5** by refluxing in 1:2 HCl–MeOH for 30 min, followed by hydrogenolysis (10% Pd–C in MeOH, 1 h), in a total yield of 98% as a mixture of diastereomers. After the acetyl protection of **5** with acetic anhydride (Ac_2O) and pyridine, flavanone acetate **5′** was oxidized with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone, 4 equiv) in chlorobenzene at 160 °C for 16 h to afford the flavone acetate **6′**.[10d,19] Since the resulting **6′** was a mixture including the C-5 O-deacetylated derivative, after acetylation, the acetate was purified by column chromatography to afford **6′** in 56% yield, with a 30% yield of recovered **5′**. The recovered intact flavanone was largely one of two possible diastereomers (**5′a**: the stereochemistry at C-2 is R[16]), deduced from the ^{1}H NMR chemical shifts of H-3b (δ **5′a**: 3.01 ppm, **5′b**: 3.11 ppm). This intact flavanone acetate **5′** was again oxidized by heating with 5 equiv of DDQ in 1,2-dichlorobenzene at 180 °C for 7 h, followed by acetylation to afford **6′** in 55% yield with a recovery of 22.5%. As a result, two DDQ oxidations of flavanone acetate **5′ab**, followed by acetylation, gave **6′** in a total yield of 72.5%. Compound **6′** was deacetylated with NaOMe to afford flavone **6** in 90.7% yield. Furthermore, the mixture diastereomers of flavanone acetates **5′ab** were separated by silica-gel column chromatography ($CHCl_3$–AcOEt), giving diastereomers **5′a** and **5′b**, the specific rotations of which were identical to those of authentic samples.[16]

In conclusion, phloretin di-*C*-glucoside (**4**) was synthesized from **1** in three steps, in a total yield of 52.3%; naringenin di-*C*-glucoside (**5**) via four steps in a total yield of 53.5%; and apigenin di-*C*-glucoside (**6**) via eight steps in a total yield of 35.2%. The ^{13}C NMR spectra of the compounds were identical to those of natural product specimens, although the assignment was difficult due to the appearance of duplicate signals derived from rotamers, except for **4**, as shown in Table 1. We thus conclude that this direct C-glycosylation method can be effectively used in the synthesis of 6,8-di-*C*-glycosylflavonoids. However the synthesis of di-*C*-β-glycosylflavonoids that contain different sugars will require further investigation.

3. Experimental

3.1. General

The solvents used in this study were purified by distillation. Reactions were monitored by TLC on 0.25-mm Silica Gel F254 plates (E. Merck) using UV light, and either a 5% ethanolic solution of iron(III) chloride or a 7% ethanolic solution of phosphomolybdic acid with heat, as coloration agents. For separation and purification, flash column chromatography was performed on silica gel (230–400 mesh, Fuji-Silysia Co., Ltd., BW-300) and column chromatography used Sephadex

Table 1. ^{13}C NMR spectral data[a] for the three di-*C*-glycosylflavonoids

Compound number	**4** (in CD_3OD)		**5** (in C_5D_5N)		**6** (in DMSO-d_6)	
	Natural[15]	Synthetic	Natural[16]	Synthetic	Natural[17]	Synthetic
2	31.0	30.9	78.6	80.1	164.1	164.6
3	47.8	47.7	43.2/43.5	43.1/44.1	102.6	102.9
4	207.2	207.3	196.6/196.9	198.9/199.0	182.3	182.2
5	162.2	162.1	162.4/162.5	163.2	158.5	158.9
6	104.4	104.3	106.3	106.7 (br)	107.5	107.7
7	163.1	163.1	165.1	165.5	161.2	161.6
8	104.4	104.3	105.1	105.7 (br)	105.3	105.5
9	162.2	162.1	160.8	162.7	155.1	155.5
10	106.2	106.2	102.5/102.7	103.3/103.4	103.8	104.3
1′	133.9	133.9	129.2/129.6	130.7/131.0	121.5	121.8
2′	130.4	130.4	127.7/128.2	128.8/129.1	129.0	129.4
3′	116.1	116.1	116.0	116.4	115.8	116.3
4′	156.4	156.2	158.5/158.7	158.6/158.7	160.7	161.1
Sugar moiety						
G1	76.7	76.6	79.7[b]	79.7[b]	74.0/73.3	74.4/73.7
G2	74.2	74.0	75.2[b]	75.4[b]	71.9/70.8	72.3/71.4
G3	79.1	78.9	80.0[b]	80.0[b]	78.8/77.8	79.0/78.0
G4	71.1	70.9	72.9/71.2[b]	73.0/71.3[b]	70.5/69.1	70.9/69.4
G5	82.7	82.5	82.6[b]	82.8/82.6[b]	81.8/80.8	82.1/81.2
G6	61.9	61.7	62.1[b]	62.2[b]	61.5/61.3	61.6/60.2

[a] The measurement of each synthetic compound was carried out under the same conditions as those for authentic samples.
[b] Sugar moiety was not assigned.

LH-20 gel (Amersham Pharmacia Biotech AB). HPLC analysis was performed using an Inertsil ODS-3 column (GL Science; 5 μm, 4.6 × 250 mm, mobile phase: MeOH–H_2O). Melting points were determined on a Shibayama micro-melting point apparatus and are uncorrected. Optical rotations were recorded on a JASCO DIP-370 polarimeter. FTIR spectra were recorded on a Horiba FT-720 FTIR spectrometer using a KBr disk. NMR spectra were recorded on a Varian Inova 500 spectrometer using Me_4Si as the internal standard. Mass spectral data were obtained by fast-atom bombardment (FAB) using 3-nitrobenzyl alcohol (NBA) or glycerol as a matrix on a JEOL JMS-AX505HA instrument. Elemental analyses were performed on a Perkin–Elmer PE 2400 II instrument.

3.2. 2,4,6-Tri-*O*-benzyl-3,5-di-*C*-β-D-glucopyranosylphloroacetophenone (2)

To a solution of **1** (100 mg, 0.203 mmol) in dry DMF (0.5 mL), $PhCH_2Br$ (108 μL, 0.915 mmol) and K_2CO_3 (126 mg, 0.915 mmol) were added, and the resulting solution was stirred at room temperature for overnight. After confirming the disappearance of **1** by TLC, the reaction mixture was poured into H_2O (10 mL). The resulting precipitate was filtered and washed with H_2O and Et_2O, and purified by column chromatography on silica gel (5:1 $CHCl_3$–MeOH) to give **2** (100 mg, 65%) as colorless prisms ($CHCl_3$–EtOH): mp 143.5–144.5 °C; $[\alpha]_D^{21}$ −11.2 (*c* 1.00, MeOH); FTIR *ν* (KBr) 3400, 2881, 1697, 1577, 1498, 1456, 1352, 1176, 1082 cm^{-1}; ^1H NMR (DMSO-d_6 at 160 °C): *δ* 2.44 (s, 3H, $COCH_3$), 3.21 (m, 2H, H-4″,4″), 3.22 (m, 2H, H-5′,5″), 3.24 (t, 2H, *J* 8.5 Hz, H-3′,3″), 3.51 (dd, 2H, *J* 4.5, 11.1 Hz, H-6′a,3″a), 3.72 (d, 2H, *J* 11.1 Hz, H-6′b,6″b), 3.80, 4.05, 4.17, 4.19 (each br s, 2H, OH × 8), 4.26 (t, 2H, *J* 8.7 Hz, H-2′,2″), 4.70 (d, 2H, *J* 9.8 Hz, H-1′,1″), 4.90 and 5.25 (d and br d, each 2H, *J* 11.1 Hz, CH_2 × 2), 4.91 and 5.34 (d and br d, each 1H, *J* 11.1 Hz, CH_2), 7.23–7.55 (m, 15H, CH_2Ph × 3); ^{13}C NMR (DMSO-d_6 at 160 °C): *δ* (aglycon moiety) 201.47 (C=O), 160.72 (C4), 156.22 (C2,6), 137.98 (C1), 137.45 (C3,5), 127.2–128.9 (C2,4,6-CH_2*Ph*), 71.22 (C4–*CH_2*Ph), 71.15 (C2- and 6-*CH_2*Ph), 32.71 and 32.57 (CO*CH_3*), (glucose moiety) 81.89, 79.84, 78.31, 75.36, 71.43, 62.30 (C6′,6″); FABMS (NBA, *m*/*z*) 763 $(M+H)^+$. Anal. Calcd for $C_{41}H_{46}O_{14}\cdot H_2O$: C, 63.07; H, 6.20. Found: C, 62.86; H, 6.25.

3.3. 1-(*p*-Benzyloxy)cinnamoyl-2,4,6-tribenzyloxy-3,5-di-*C*-β-D-glucopyranosylbenzene (3)

KOH (22 mg, 0.393 mmol) was added to a solution of **2** (100 mg, 0.131 mmol) and *p*-benzyloxybenzaldehyde (83 mg, 0.393 mmol) in MeOH (0.5 mL). The resulting solution was stirred at room temperature for 1 day. After confirming the disappearance of **2** by TLC, the reaction mixture was poured into 0.2 M aq HCl (20 mL). The resulting precipitate was isolated on a filter, washed with water, and then purified by column chromatography on silica gel (20:1 and 10:1 $CHCl_3$–MeOH) to give **3** (105.5 mg, 84%) as yellow prisms (2-propanol): mp 140–141 °C; $[\alpha]_D^{21}$ −11.4 (*c* 1.00, MeOH); FTIR *ν* (KBr) 3400, 2925, 2877, 1624, 1577, 1508, 1454, 1082 cm^{-1}; ^1H NMR (DMSO-d_6 at 160 °C): *δ* 3.20 (t, 2H, *J* 8.5 Hz, H-4″,4‴), 3.23 (m, 2H, H-5″,5‴), 3.26 (t, 2H, *J* 8.5 Hz, H-3″,3‴), 3.54 (dd, 2H, *J* 5.6, 11.6 Hz, H-6″a,6‴a), 3.74 (dd, 2H, *J* 2.4, 11.6 Hz, H-6″b,6‴b), 4.28 (t, 2H, *J* 8.5 Hz, H-2″,2‴), 4.74 (d, 2H, *J* 9.8 Hz, H-1″,1‴), (aglycon moiety) 4.80 and 5.23 (each d, 2H, *J* 11.1 Hz, 5- and 9-*CH_2*Ph), 4.94 and 5.37 (each d, 1H, *J* 11.5 Hz, 7-*CH_2*Ph), 5.14 (s, 2H, 4′-*CH_2*Ph), 7.02 and 7.50 (each d, 1H, *J* 8.9 Hz, *p*-substituted ArH × 2), 7.42 and 7.57 (each d, 1H, *J* 7.9 Hz, *p*-substituted ArH × 2), 6.91 and 7.41 (each d, 1H, *J* 16.2 Hz, *trans*-vinyl H × 2); ^{13}C NMR (DMSO-d_6 at 160 °C): *δ* (aglycon moiety) 192.73 (C=O), 160.47, 160.19, 156.55 (C5,7,9), 144.08 (C4′), 137.45, 136.97, 136.60 (C6,8,10), 129.87 (C2), 129.72 (C1′), 127.2 (C2′,6′), 126–128 (CH_2*Ph* × 4), 123.00 (C3), 115.50 (C3′,5′), 70.64 (5,9-*CH_2*Ph), 70.73 (7-*CH_2*Ph), (glucose moiety) 81.33, 79.29, 77.42, 74.92, 70.92, 61.80 (C-6″,6‴); FABMS (NBA, *m*/*z*) 957 $(M+H)^+$. Anal. Calcd for $C_{55}H_{56}O_{15}\cdot 1.5H_2O$: C, 67.13; H, 6.04. Found: C, 67.22; H, 5.98.

3.4. 3′,5′-Di-*C*-β-D-glucopyranosylphloretin (4)

To a solution of **3** (100 mg, 0.105 mmol) in MeOH (5 mL), 10% Pd–C (70 mg) was added, and the suspension mixture was stirred vigorously under an H_2 atmosphere at room temperature for 1 day. [Caution! Pd–C can cause MeOH to catch fire either before hydrogenation or after.] After the disappearance of **3**, as evidenced by TLC, the reaction mixture was filtered through a Celite pad, and the pad was washed with MeOH. The filtrate was purified by column chromatography on Sephadex LH-20 gel (MeOH) to give **4** (60.1 mg, 95.7%) as a pale-yellow solid: $[\alpha]_D^{25}$ +90.0 (*c* 1.05, MeOH); natural product, $[\alpha]_D^{20}$ +83.6 (*c* 1.0, MeOH);[14] FTIR *ν* (KBr) 3367, 2922, 1622, 1516, 1456, 1244, 1080 cm^{-1}; ^1H NMR (CD_3OD): *δ* (aglycon moiety) 2.86 (m, 2H, H-2), 3.34 (m, 2H, H-3), 6.70 (d, 2H, *J* 8.5 Hz, H-3′,5′), 7.04 (d, 2H, *J* 8.5 Hz, H-2′,6′), (glucose moiety) 3.4 (m, 2H, H-5″,5‴), 3.54 (t, 2H, *J* 9.4 Hz, H-3″,3‴), 3.57 (t, 2H, *J* 9.4 Hz, H-4″,4‴), 3.63 (t, 2H, *J* 9.4 Hz, H-2″,2‴), 3.82 (dd, 2H, *J* 12.5, 4.0 Hz, H-6″a,6‴a), 3.86 (dd, 2H, *J* 12.5, 2 Hz, H-6″b,6‴b), 4.95 (d, 1H, *J* 9.5 Hz, H-1″,1‴); ^{13}C NMR (Table 1); FABMS (NBA, *m*/*z*) 599 $(M+H)^+$. Anal. Calcd for $C_{27}H_{34}O_{15}\cdot 2H_2O$: C, 51.10; H, 6.04. Found: C, 50.75; H, 5.98.

3.5. 6,8-Di-*C*-β-D-glucopyranosylnaringenin (5)

Concd HCl (0.5 mL) was added to a solution of **3** (100 mg, 0.105 mmol) in 1 mL of MeOH. The solution was refluxed for 15 min. After the disappearance of **3** by TLC, the reaction mixture was evaporated in vacuo, EtOH was added to the residue and the solution was again evaporated in vacuo to remove HCl. The residual solid was dissolved in MeOH (5 mL) and 10% Pd–C (20 mg) was added to the solution. [Caution! Pd–C can cause MeOH to catch fire either before hydrogenation or after.] The suspension was vigorously stirred under an H_2 atmosphere at room temperature for 1 h. The reaction mixture was filtered through a Celite pad, which was then washed with MeOH. The filtrate was evaporated in vacuo to give **5** (61.3 mg, 98%) as a pale-yellow solid: FTIR *v* (KBr) 3370, 2927, 2893, 1618, 1520, 1458, 1346, 1209, 1080 cm^{-1}; ^1H NMR (CD_3OD): δ (aglycon moiety) 2.80 (dd, 1H, *J* 3.0, 16.5 Hz, CH_2), 3.11 (dd, 1H, *J* 13.0, 16.5 Hz, CH_2), 5.40 (dd, 1H, *J* 3.0, 13.0 Hz, H-2), 6.84 (d, 2H, *J* 8.5 Hz, *p*-substituted ArH × 2), 7.34 and 7.37 (each d, 1H, *J* 8.5 Hz, *p*-substituted ArH × 2), 9.25 (br s, 1H, ArOH), 12.74 and 12.77 (each s, 1H, ArOH), (glucose moiety at 60 °C) 3.32–3.53 (m, 6H), 3.71–3.97 (m, 6H), 4.82–4.91 (m, 2H); ^{13}C NMR (Table 1); FABMS (glycerol, *m*/*z*) 597 $(M+H)^+$. Anal. Calcd for $C_{27}H_{30}O_{15}\cdot 2.5H_2O$: C, 50.54; H, 5.81. Found: C, 50.69; H, 5.51.

3.6. 5,7,4′-Tri-*O*-acetyl-6,8-di-*C*-(octa-*O*-acetyl-β-D-glucopyranosyl)naringenin (5′a,b)

A solution of **5** (50 mg, 0.084 mmol) in Ac_2O (1 mL) and pyridine (1 mL) was stirred overnight at room temperature. The reaction mixture was poured into water (50 mL), the solution stirred for 0.5 h and then extracted twice with AcOEt. The combined extracts were washed with H_2O, dried over anhydrous Na_2SO_4, and then evaporated in vacuo. The residue was purified by column chromatography on silica gel (2:1 and 1:1 $CHCl_3$–AcOEt) to give **5′a** (39 mg, 44%), a mixture of **5′a** and **5′b** (17 mg, 19%), and **5′b** (32 mg, 36%), as pale-yellow amorphous solids.

3.6.1. Data for 5′a. $[\alpha]_D^{21}$ −38.0 (*c* 1.11, $CHCl_3$); natural product,[16] $[\alpha]_D^{21}$ −40.8 (*c* 2.05, $CHCl_3$); FTIR *v* (KBr) 3446, 2943, 1780, 1755, 1697, 1604, 1369, 1230 cm^{-1}; ^1H NMR ($CDCl_3$): δ (glucose moiety) 1.78, 1.90, 1.96, 2.02, 2.03, 2.04, 2.05, 2.06 (each s, 3H, OAc × 8), 3.65 (ddd, 1H, *J* 2.1, 4.9, 9.8 Hz, H-5‴), 3.77 (ddd, 1H, *J* 1.7, 4.9, 9.8 Hz, H-5″), 3.94 (dd, 1H, *J* 1.7, 12.8 Hz, H-6″a), 4.15 (dd, 1H, *J* 2.1, 12.4 Hz, H-6‴a), 4.24 (dd, 1H, *J* 4.9, 12.4 Hz, H-6‴b), 4.30 (dd, 1H, *J* 4.9, 12.8 Hz, H-6″b), 4.35 (d, 1H, *J* 9.8 Hz, H-1‴), 4.70 (br d, 1H, *J* 9.8 Hz, H-1″), 5.02 (t, *J* 9.8 Hz, H-4‴), 5.12 (t, 1H, *J* 9.8 Hz, H-4″), 5.27 (t, 1H, *J* 9.8 Hz, H-3″), 5.29 (t, 1H, *J* 9.8 Hz, H-3‴), 5.63 (t, 1H, *J* 9.8 Hz, H-2″), 5.93 (t, 1H, *J* 9.8 Hz, H-2‴), (aglycone moiety) 2.32, 2.44, 2.49 (each s, 3H, ArOAc × 3), 2.84 (dd, 1H, *J* 2.8, 16.8 Hz, H-3a), 3.01 (dd, 1H, *J* 14.1, 16.8 Hz, H-3b), 5.78 (dd, 1H, *J* 2.8, 14.1 Hz, H-2), 7.22 (d, 2H, *J* 8.8 Hz, H-2′ and 6′), 7.60 (d, 2H, *J* 8.8 Hz, H-3′ and 5′); FABMS (NBA, *m*/*z*) 1059 $(M+H)^+$. Anal. Calcd for $C_{49}H_{54}O_{26}\cdot 0.5H_2O$: C, 55.11; H, 5.19. Found: C, 54.99; H, 5.28.

3.6.2. Data for 5′b. $[\alpha]_D^{20}$ −45.9 (*c* 1.19, $CHCl_3$); natural product,[16] $[\alpha]_D^{21}$ −43.1 (*c* 1.48, $CHCl_3$); FTIR *v* (KBr) 3446, 2941, 1780, 1755, 1699, 1602, 1373, 1228 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.71, 1.78, 1.81, 1.93, 2.04, 2.06 (each s, 3H, OAc × 6), 2.02 (s, 6H, OAc × 2), 3.61 (m, 1H, H-5‴), 3.76 (m, 1H, H-5″), 3.94 (d, 1H, *J* 12.0 Hz, H-6″a), 4.02 (dd, 1H, *J* 1.7, 12.4 Hz, H-6‴a), 4.14 (dd, 1H, *J* 5.0, 12.4 Hz, H-6‴b), 4.35 (d, 1H, *J* 9.8 Hz, H-1‴), 4.41 (dd, 1H, *J* 5.0, 12.0 Hz, H-6″b), 4.64 (d, 1H, *J* 9.8 Hz, H-1″), 4.93 (t, 1H, *J* 9.8 Hz, H-4‴), 5.12 (t, 1H, *J* 9.8 Hz, H-4″), 5.26 (t, 1H, *J* 9.8 Hz, H-3″), 5.28 (t, 1H, *J* 9.8 Hz, H-3‴), 5.66 (t, 1H, *J* 9.8 Hz, H-2″), 5.99 (t, 1H, *J* 9.8 Hz, H-2‴), (aglycone moiety) 2.32, 2.43, 2.49 (each s, 3H, ArOAc × 3), 2.85 (dd, 1H, *J* 2.6, 16.2 Hz, H-3a), 3.11 (dd, 1H, *J* 14.5, 16.2 Hz, H-3b), 5.57 (m, 1H, H-2); FABMS (NBA, *m*/*z*) 1059 $(M+H)^+$. Anal. Calcd for $C_{49}H_{54}O_{26}\cdot 0.5H_2O$: C, 55.11; H, 5.19. Found: C, 55.00; H, 5.24.

3.7. 5,7,4′-Tri-*O*-acetyl-6,8-di-*C*-(octa-*O*-acetyl-β-D-glucopyranosyl)apigenin (6′)

A solution of flavanone acetate **5′ab** (100 mg, 0.0945 mmol) and DDQ (86 mg, 0.38 mmol) in chlorobenzene (1.5 mL) was refluxed for 1 day. The reaction mixture was evaporated in vacuo to afford a residue, which was acetylated with Ac_2O (2 mL) and pyridine (2 mL) at room temperature overnight. The reaction mixture was poured into ice-cold water (20 mL), and the resulting mixture was stirred for 0.5 h and extracted twice with AcOEt. The combined extracts were washed with H_2O and satd aq NaCl, dried over anhyd Na_2SO_4, and then evaporated in vacuo. The residue was purified by column chromatography on silica gel (1:2 hexane–AcOEt) to give **6′** (55.9 mg, 56%) as a white powder, and the recovery of **5′ab** (30.0 mg, 30%) as a pale-yellow powder. The recovered **5′ab** was then reoxidized using the same procedure as described above.

3.7.1. Data for 6′. White solid; $[\alpha]_D^{21}$ +18.5 (*c* 0.79, $CHCl_3$); FTIR *v* (KBr) 3435, 2939, 1780, 1755, 1652, 1604, 1369, 1230, 1037 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.75, 1.88, 1.92, 1.99, 2.02, 2.05, 2.06, 2.10 (each s, 3H, OAc × 8), 2.35, 2.49, 2.55 (each s, 3H, ArOAc × 3), 3.75 (ddd, 1H, *J* 1.7, 4.7, 9.8 Hz, H-5″), 3.81 (ddd, 1H, *J* 1.3, 4.0, 9.8 Hz, H-5‴), 3.95 (dd, 1H, *J* 1.7, 12.8 Hz,

H-6″a), 4.21 (dd, 1H, *J* 1.3, 12.5 Hz, H-6‴a), 4.28 (dd, 1H, *J* 4.0, 12.5 Hz, H-6‴b), 4.45 (dd, 1H, *J* 4.7, 12.8 Hz, H-6″b), 4.58 (d, 1H, *J* 9.4 Hz, H-1″), 4.81 (br d, 1H, *J* 10.3 Hz, H-1‴), 5.15 (t, 1H, *J* 9.8 Hz, H-4″), 5.30 (t, 1H, *J* 9.8 Hz, H-3″), 5.43 (t, 1H, *J* 9.8 Hz, H-4‴), 5.48 (t, 1H, *J* 9.8 Hz, H-3‴), 5.70 (dd, 1H, *J* 10.3, 9.8 Hz, H-2‴), 5.93 (t, 1H, *J* 9.8 Hz, H-2″), 6.66 (s, 1H, H-3), 7.39 (d, 2H, *J* 8.7 Hz, H-2′,6′), 8.07 (d, 2H, *J* 8.7 Hz, H-3′,5′); FABMS (NBA, *m*/*z*) 1057 $(M+H)^+$. Anal. Calcd for $C_{49}H_{52}O_{26}\cdot 0.5H_2O$: C, 55.21; H, 5.01. Found: C, 55.16, H, 5.05.

3.8. 6,8-Di-*C*-β-D-glucopyranosylapigenin (vicenin-2) (6)

To a stirred solution of **6′** (50.0 mg, 0.473 mmol) in dry MeOH (2 mL), a 28% methanolic solution of NaOMe (0.2 mL) was added dropwise. The resulting solution was stirred at room temperature for 3 h. Dowex 50W × 8 (H^+) was added to the stirred reaction mixture until the solution became neutral. The resulting mixture was filtered and washed with MeOH. The filtrate was evaporated in vacuo to afford **6** (25.5 mg, 90.7%) as a yellow powder.

$[\alpha]_D^{21}$ +56.9 (*c* 0.745, MeOH); FTIR *v* (KBr) 3350, 2925, 2854, 1653, 1628, 1612, 1577, 1508, 1446, 1361, 1219, 1180, 1117, 1080 cm^{-1}; ^1H NMR (DMSO-d_6, at 90 °C): δ 6.67 (s, 1H, H-3), 6.97 and 7.92 (each d, 2H, *J* 8.9 Hz, *p*-substituted ArH × 4), 9.3 (br s, 1H, ArOH), 13.7 and 13.6 (each br s, 1H, ArOH), glucose moiety: 3.69 (dd, 1H, *J* 1.9, 11.7 Hz, H-6″b), 3.75 (br d, 1H, *J* 10.3 Hz, H-6‴b), 4.79 and 4.87 (d and br s, each 1H, *J* 9.8 Hz, H-1″,1‴); FABMS (NBA, *m*/*z*) 595 $(M+H)^+$. Anal. Calcd for $C_{27}H_{30}O_{15}\cdot 2H_2O$: C, 51.43; H, 5.44. Found: C, 51.71; H, 5.30.

3.9. Direct C-glycosylation of (±)-naringenin with D-glucose

To a refluxed solution of (±)-naringenin (100 mg, 0.37 mmol) and D-glucose (200 mg, 1.11 mmol) was added $Sc(OTf)_3$ (36.0 mg, 0.074 mmol) and the refluxing was continued. After 12 h formation of the mono-*C*-glycoside was observed on TLC (15:30:2:1 acetone–AcOEt–H_2O–AcOH), but no bis-*C*-glycoside was evident. $Sc(OTf)_3$ (36.0 mg, 0.074 mmol) was added to the reaction mixture, and refluxing was continued for 36 h. Since the bis-*C*-glycoside was observed on TLC while the mono-*C*-glycoside decreased, the reaction was terminated. The reaction mixture was evaporated in vacuo to afford brown solids that were dissolved in pyridine (3 mL) and Ac_2O (4 mL), and to the solution was added 4-(dimethylamino)pyridine (DMAP, 20 mg). After stirring for 12 h at room temperature, the reaction mixture was poured into ice-cold water (50 mL) with stirring and extracted twice with AcOEt. The combined extracts were washed with H_2O and satd aq NaCl, dried over anhyd Na_2SO_4, and evaporated in vacuo. The residue was separated by flash column chromatography (1:1 and 1:2 hexane–AcOEt) to afford **7** (50.9 mg, 19.0%) and **5′** (67.3 mg, 17.3%) as pale-yellow solids. Both products **7** and **5′** were a 1:1 mixture of diastereomers that were analyzed by HPLC (60:40 MeOH–H_2O, t_R (min): 20.00 (**7a**), 21.70 (**7b**), 23.87 (**5′a**), 26.76 (**5′b**)). ^1H NMR of **7** gave a very complex spectrum as a diastereomeric mixture complicated with rotamers.

3.10. 4′,5,7-Tri-*O*-acetyl-6- or 8-*C*-(tetra-*O*-acetyl-β-D-glucopyranosyl)naringenin (7)

Pale-yellow amorphous solid; FTIR *v* (KBr) 3446, 2943, 1780, 1755, 1695, 1618, 1369, 1225, 1041 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.80–1.86 (m, 3H, OAc), 2.01–2.10 (m, 9H, OAc), 2.30–2.50 (m, 9H, OAc), 2.71–2.82 (m, 1H, H-6″a), 2.96–3.09 (m, 1H, H-6″b), 3.77 (m, 1H, H-5″), 3.98 (br d, 1H, *J* 11.7 Hz, H-6″a), 4.40 (dd, 1H, *J* 12.8, 4.3 Hz, H-6″b), 4.68–4.76 (m, 1H, H-1″), 5.14 (t, 1H, *J* 9.7 Hz, H-4″), 5.28 (t, 1H, *J* 9.5 Hz, H-2″), 5.44–5.54 (m, 1H, H-2), 5.58–5.69 (m, 1H, H-3″), 6.71–6.80 (m, 1H, ArH), 7.15 (d, 2H, *J* 8.5 Hz, *p*-substituted ArH × 2), 7.44 (d, 2H, *J* 8.5 Hz, *p*-substituted ArH × 2); (DMSO-d_6, at 160 °C) δ 1.725, 1.736 (each s, 3H, OAc), 1.890 (s, 3H, OAc), 1.915 (s, 3H, OAc), 1.963, 1.965 (each s, 3H, OAc), 1.981 (s, 3H, OAc), 2.229, 2.231 (each s, 3H, OAc), 2.258, 2.274 (each s, 3H, OAc), 2.73, 2.80 (each dd, 1H, *J* 3.2, 16.2 Hz, H-3a), 2.93, 2.97 (each dd, 1H, *J* 12.0, 16.2 Hz, H-3b), 3.91 (ddd, *J* 9.4, 3.0, 5.1 Hz, H-5″), 4.05 (dd, 1H, *J* 3.0, 12.3 Hz, H-6″a), 4.10 (dd, 1H, *J* 5.1, 12.3 Hz, H-6″b), 4.89, 4.90 (each d, 1H, *J* 9.8 Hz, H-1″), 4.99 (t, 1H, *J* 9.4, 9.4 Hz, H-4″), 5.22 (t, 1H, *J* 9.4 Hz, H-2″), 5.51 (m, 1H, H-2), 5.60 (t, *J* 9.4 Hz, H-3″), 6.38 (s, 1H, ArH), 7.13, 7.14 (each d, 2H, *J* 8.5 Hz, *p*-substituted ArH × 2), 7.48, 7.49 (each d, 2H, *J* 8.5 Hz, *p*-substituted ArH × 2); FABMS (NBA, *m*/*z*) 729 $(M+H)^+$. Anal. Calcd for $C_{35}H_{36}O_{17}\cdot H_2O$: C, 56.30; H, 5.13. Found: C, 56.41; H, 5.22.

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