First Synthesis of Saponarin, 6-*C*- and 7-*O*-Di-*β*-D-glucosylapigenin

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Saponarin, apigenin 6-*C*- and 7-*O*-bis-*β*-D-glucoside, was synthesized in an overall yield of 37% *via* 11 steps, which included the *C*-glycosylation of 2,4-*O*-dibenzylphloroacetophenone, the introduction of a cinnamoyl residue by aldol condensation, the formation of a flavone by regioselective deprotection, and oxidative ring-closure to the final regioselective deprotection and stereoselective *O*-glycosylation.

Key words *C*,*O*-diglycosylflavone; regioselective deprotection; glycosylation; phloroacetophenone; hypoglycemic activity

By the year 2004, there had been 188 *C*,*O*-diglycosylflavonoides isolated from plants, and their structures had been elucidated.[1)] Now, a new one has been found. *C*,*O*-Diglycosylflavonoides have almost a flavon-skeleton with a *C*-glycoside at the 6- or 8-position of the A-ring and an *O*-glycoside at either the 7-position of the A-ring or at the 4-position of the B-ring. *C*,*O*-Diglycosylflavonoides also show various bioactivities. Among them, saponarin, 6-*C*- and 7-*O*-di-*β*-D-glucopyranosyl-4′,5,7-trihydroxyflavone has shown potent antioxidant,[2,3)] hematoprotective,[4)] and hypoglycemic[5)] activities.

In the synthesis of *C*,*O*-diglycosylflavonoides, that of flavocommelin, 6-*C*- and 4′-*O*-di-*β*-D-glucopyranosyl-7-*O*-methyl-4′,5,7-trihydroxyflavone has been reported only by Oyama and Kondo.[6)] Those researchers synthesized one in 12-steps for an overall yield of 6.2% *via C*-glycosylation to the flavan prepared by the reduction of the 4-carbonyl group of an available naringenin, followed by oxidation to the flavone and *O*-glycosylation.

Herein, we disclose the first synthesis of saponarin, 6-*C*- and 7-*O*-di-*β*-D-glucopyranosyl-4′,5,7-trihydroxyflavone (**1**), which is more complex than the afore-mentioned compounds due to the adjacent 6-*C*- and 7-*O*-bis glucosides. We achieved the synthesis of flavone and isoflavone *C*-glycosides by using phloroacetophenone *C*-glycoside as the key-compound.[7–9)] Herein, we include our proposal for a synthetic plan for the total synthesis of **1** employing phloroacetophenone *C*-glycoside as the key-compound (Chart 1). We used a benzyl group as the protecting group for the glucose- and phenol-hydroxyls. The benzyl group was easy to deprotect under the neutral conditions of hydrogenolysis. For the regioselective deprotection of the flavone-ring formation, we employed a 2-ethylbenzyl group that is less deprotectable than a benzyl group.[7)] Kan and co-workers employed a *tert*-butyldiphenylsilyl group so it could be distinguished from a benzyl group.[10)] Although Schmidt and co-workers first used a methyl group for phenol protection, because of the difficulty of deprotection, they later selected a *tert*-butyldimethylsilyl group.[11)] Both of these silyl-protecting reagents are expensive. In the present study, we applied the deprotectability of the phenol-hydroxyls at the 2′,6′-positions of the A-ring of the chalcone due to the acidity of the intramolecular hydrogen-bonding between the phenol-hydroxyl and acyl-carbonyl groups, using 2,4-*O*-dibenzylphloroacetophenone as a starting material. Therefore, the need for the tedious regioselective introduction of a different protecting group for phenol-hydroxyls was avoided. The synthesis of **1** was examined according to the synthetic plan shown in Chart 1, as follows: 1) regio- and stereoselective *C*-glycosylation to 2,4-*O*-dibenzylphloroacetophenone; 2) introduction of a cinnamoyl group by aldol condensation with *p*-methoxymethoxybenzaldehyde; 3) regioselective 6′-*O*-debenzylation of *C*-glycosylchalcone with $BF_3 \cdot OEt_2$; 4) formation of 6-*C*-glycosylflavone *via* an oxidative cyclization with I_2; 5) conversion of the hydroxyl-protecting group to an acetyl group from a benzyl group followed by regioselective 7-*O*-deacetylation with tetramethylguanidine (TMG); and, 6)

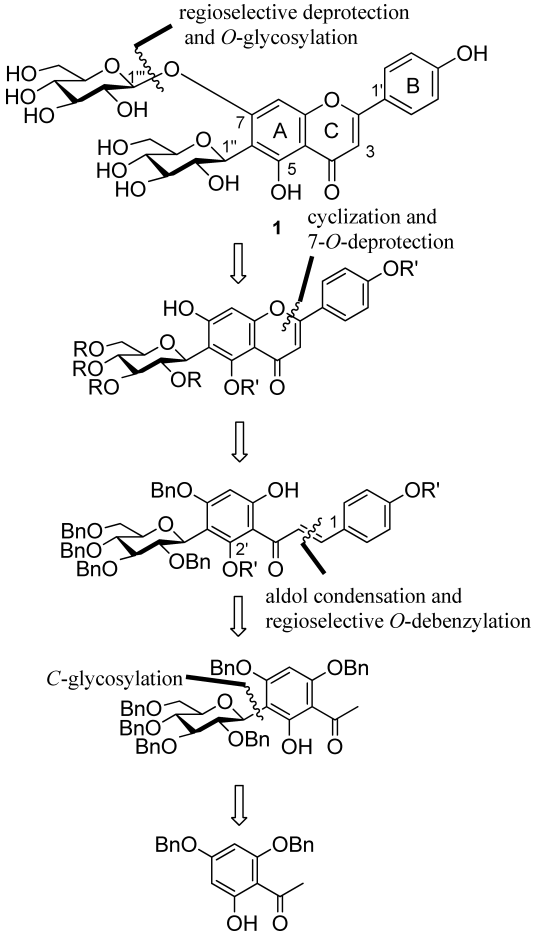

Chart 1. Synthetic Plan of Saponarin **1**

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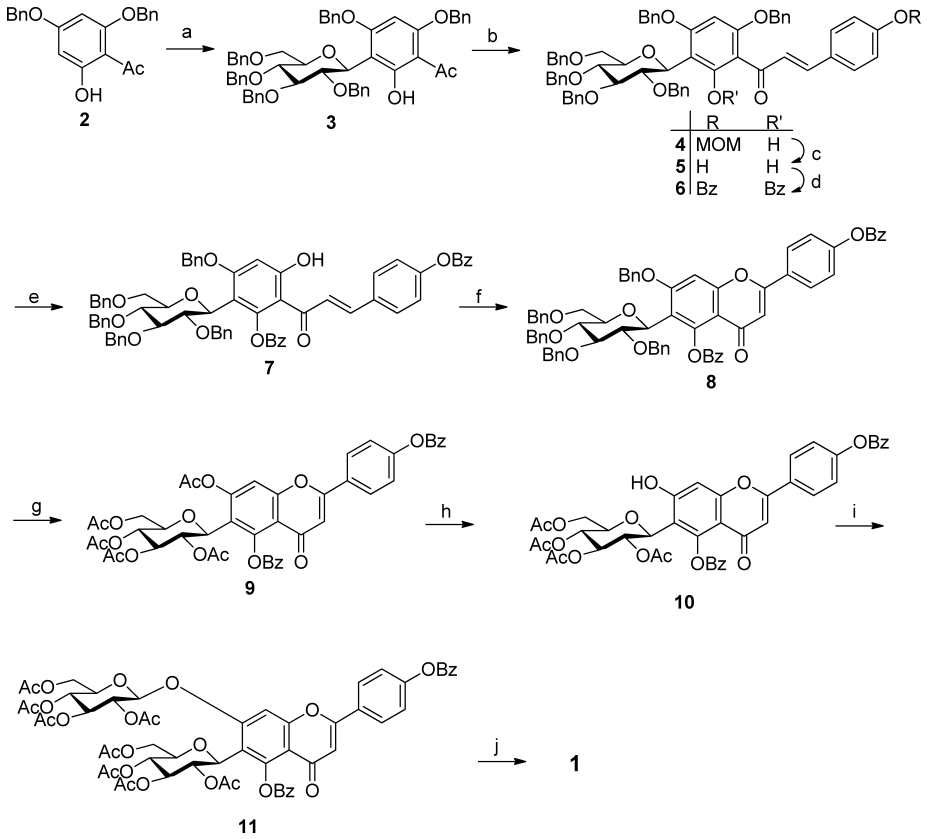

Reagents and conditions: a) **2** (3 eq), per-*O*-benzylglucosyl α-fluoride (1 eq), $BF_3 \cdot OEt_2$ (2 eq), MS4A in CH_2Cl_2, at −70°C–rt, 3 h, Y: 96% or per-*O*-benzylglucosyl α-trichloroimidate (1.2 eq), TMS OTf (0.2 eq) in CH_2Cl_2, at −10°C–rt, 5 h, Y: 79%; b) *p*-MOMO-benzaldehyde (1.5 eq), NaOMe (1.2 eq), in dioxane, rt, 1.5 h,Y: 98%; c) 2 N HCl–MeOH (1 : 10), reflux, 2 h, Y: 95%; d) BzCl in pyridine, rt, 1.5 h, Y: 100%; e) BF_3OEt_2 (4.5 eq), in CH_2Cl_2, –10–0°C, 4 h, Y: 81%; f) I_2 (0.1 eq) in DMSO at 130°C, 20 min, Y: 84%; g) 1. H_2–10% Pd–C, in AcOEt, rt, 4 h, 2. Ac_2O–pyridine (1 : 1), rt, 2 h, Y: 98% (2 steps); h) TMG (2.5 eq) in CH_3CN, rt, 3 h, Y: 83%; i) per-*O*-acetylglucosyl α-bromide (2 eq), Ag_2CO_3 (2 eq), in quinoline, at 0°C–rt, 3 h, Y: 86%; j) NaOMe in MeOH, rt, for 1 h, then Dowex 50W (H^+), recrystallization from H_2O–CH_3CN, Y: 87%.

Chart 2. Total Synthesis of Saponarin **1**

stereoselective 7-*O*-glycosylation by Koenigs–Knorr glycosylation and de-*O*-acylation with NaOMe.

Results and Discussion

Results are shown in Chart 2. *C*-Glycosylation to 2,4-*O*-dibenzylphloroacetophenone (**2**) was examined using both *O*→*C* glycoside rearrangement methods with per-*O*-benzylglucosyl α-fluoride/$BF_3 \cdot OEt_2$ and per-*O*-benzylglucosyl α-trichloroimidate/trimethylsilyl trifluoromethanesulfonate (TMSOTf) as the combination of a glycosyl donor and a Lewis acid promoter. Both methods gave the desired *C*-glucoside **3** in good yields (96, 79%, respectively). When 1.5 eq of α-fluoride was used for **2**, the yield was 84%, but, when 3 eq of **2** was used for α-fluoride, the yield was increased to 96%.[7] Next, an aldol condensation of **3** with methoxymethoxy (MOM) benzaldehyde (1.5 eq) was conducted by stirring at room temperature for 2 h in the presence of 28% NaOMe in 1,4-dioxane to synthesize **4** in an excellent yield (98%). The *O*-demethoxymethylation of **4** was achieved by 2 h of refluxing in 2 N HCl–MeOH (1 : 10), furnishing **5** in a 95% yield. Subsequently, a free 4-hydroxyl group of **5** was benzoylated with benzoyl chloride (1.5 eq) in pyridine to give **6** quantitatively. Next, the regioselective 6′-*O*-debenzylation of chalcone **6** was examined, which is an important step in the total synthesis. The use of $BF_3 \cdot OEt_2$ as a Lewis acid appeared to afford easy control of this reaction, though some Lewis acids have been known to enable regioselective debenzylation. Finally, when 4.5 eq of $BF_3 \cdot OEt_2$ was added to **6** in CH_2Cl_2 at −15°C, and the reaction temperature was gradually raised to 0°C for 4 h, and 6′-hydroxylchalcone **7** was afforded in an 81% yield without deprotection of the other benzyl groups. The oxidative cyclization of **7** proceeded smoothly in the presence of 0.1 equiv of iodine following heating in dimethyl sulfoxide (DMSO) at 130°C for 20 min to give 6-*C*-glucosylflavone **8** in a good yield (84%).[7,12] Since selective debenzylation of the 7-*O*-benzyl group of **8** is difficult under these same conditions, we changed all the benzyl groups into acetyl groups for a yield of 98% (2 steps). Next, the selective 7-*O*-deacetylation of 7-*O*-acetyl-4′,5-*O*-dibenzoyl-6-(2″,3″,4″,6″-tetra-*O*-acetyl-β-D-glucosyl)apigenin (**9**) was achieved by employing a method established by Oyama,[13] which uses TMG (2.5 eq) and produced 7-hydroxyflavone **10** in a good yield (83%). *O*-β-Glycosylation of **10** with per-*O*-acetylglucosyl bromide (2.5 eq) in the presence of $AgCO_3$ (2 eq) in quinoline proceeded β-selectively and furnished **11** in a good yield (86%).[14] Finally, the deacylation of **11** was conducted using NaOMe, followed by neutralization with Dowex® 50W×8 (H^+) resin and recrystallization from MeOH, providing saponarin **1** in an 87% yield as a white crystal. The spectra for ^{1}H- and ^{13}C-NMR were measured at room temperature and in a mixture of rotamers along with those of the above intermediates. This compound, however, enabled the measurement of NMR (in DMSO-d_6+D_2O) at 90°C overnight with no cleavage, and gave the ^{1}H- and ^{13}C-NMR spectra without a mixture of rotamers. The ^{13}C-NMR spectrum of synthetic **1** agreed with that of the natural sample,[2] as shown in Table 1. Its melting point

Table 1. ^{13}C-NMR Spectra of Saponarin **1**

Carbon No.	Natural[1-a] DMSO-d_6	Synthetic DMSO-d_6+D_2O
2	164.4	164.4
3	103.3	103.4
4	182.1	182.1
5	159.9	159.5
6	110.9	110.7
7	162.3	162.6
8	94.1	94.2
9	156.5	156.5
10	105.4	105.3
1′	121.2	121.3
2′	128.5	128.5
3′	116.1	116.1
4′	161.3	161.2
5′	116.1	116.1
6′	128.5	128.5
1′	73.8	73.6
1‴	101.7	101.6
2″	71.0	70.8
2‴	73.0	72.9
3″	79.2	78.9
3‴	76.2	76.0
4″, 4‴	70.5, 70.1	70.8, 69.9
5″	81.0	81.0
5‴	77.3	77.3
6″, 6‴	61.1, 61.1	60.9, 60.9

and specific rotation also approximated those of the natural samples.[2)]

Conclusion

Saponarin **1** was efficiently synthesized *via* 11 steps from **2** for an overall yield of 37%. A concise synthesis of the *C*,*O*-diglycosylflavone was achieved using phloroacetophenone bis-benzylether as a starting material. The synthetic route proposed here was a practical one, and it proved to be applicable to the synthesis of various *C*,*O*-diglycosylflavonoids.

Experimental

General The solvents used in these reactions were purified by distillation. The reactions were monitored by TLC on 0.25-mm silica gel F254 plates (E. Merck) using UV light, and a 7% ethanolic solution of phosphomolybdic acid with heat as the coloration agent. Flash column chromatography was performed on silica-gel (40–50 μm, Kanto Reagents Co., Ltd., silica-gel 60) to separate and purify the reaction products. Optical rotations were recorded using a JASCO DIP-370 polarimeter. Melting points were determined using an ASONE micro-melting point apparatus, and uncorrected values were reported. The IR spectra were recorded on a Horiba FT-720 IR spectrometer using a KBr disk. The NMR spectra were recorded on a JEOL ECX-500 spectrometer using Me_4Si as the internal standard. A chemical shift in the parenthesis showed another of the rotamers, since the NMR spectra of the *C*-glucosides were observed as a mixture of rotamers. The mass spectral data were obtained by fast-atom bombardment (FAB) using 3-nitrobenzyl alcohol (NBA) as a matrix on a JEOL JMS-AX505HA instrument. Elemental analyses were performed with a Perkin-Elmer PE 2400 II instrument. After drying at 100°C under reduced pressure for more than 2 h, each product was subjected to elemental analysis.

4′,6′-Dibenzyloxy-4-methoxymethoxy-2′-hydroxy-3′-*C*-(2″,3″,4″,6″-tetra-*O*-benzyl-*β*-D-glucopyranosyl)chalcone (4) To a solution of **3** (1.65 g, 1.89 mmol) and *p*-methoxymethoxybenzaldehyde (0.472 g, 2.84 mmol) in 1,4-dioxane (10 mL), a 28% NaOMe–MeOH solution (3.0 mL) was added, and the mixture was stirred under an Ar atmosphere at room temperature for 2 h. Ice-cold 2 N HCl solution (2 mL) was added to the reaction mixture, which then was extracted three times with AcOEt. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and evaporated to dryness. The residual solid was purified by silica-gel column chromatography (*n*-hexane–AcOEt=4 : 1–3 : 1) to afford **4** (1.51 g, Y: 98%) as a yellow amorphous powder. $[\alpha]_D^{22}$ −4.75 (*c*=0.505, $CHCl_3$). Silica-gel TLC: *Rf*=0.47 (*n*-hexane–AcOEt=2 : 1). IR (KBr) cm^{-1}: 3448, 2925, 2856, 1623, 1560, 1508, 1454, 1232, 1151, 1068, 831, 736, and 698. ^{1}H-NMR ($CDCl_3$) *δ*: 2.46 (2H, s, 4-MOM), 3.493 (3.485) (3H, s, 4-MOM), 3.61 (1H, m H5″), 3.68 (1H, t, *J*=9.8, 9.1 Hz, H4″), 3.77 (1H, d, *J*=10.6 Hz, H6″a), 3.81 (1H, dd, *J*=2.3, 10.6 Hz, H6″b), 3.81 (1H, t, *J*=9.2, 9.1 Hz, H3″), 4.26 (1H, t, *J*=9.1, 9.8 Hz, H2″), 4.29 (1H, d, *J*=11.4 Hz, C$\underline{H_2}$Ph), 4.34 (1H, d, *J*=11.3 Hz, C$\underline{H_2}$Ph), 4.50 (1H, d, *J*=12.1 Hz, C$\underline{H_2}$Ph), 4.54 (1H, d, *J*=11.4 Hz, C$\underline{H_2}$Ph), 4.56 (1H, d, *J*=11.3 Hz, C$\underline{H_2}$Ph), 4.60 (1H, d, *J*=8.3 Hz, C$\underline{H_2}$Ph), 4.65 (1H, m, C$\underline{H_2}$Ph), 4.71 (1H, d, *J*=12.1 Hz, C$\underline{H_2}$Ph), 4.83–5.06 (4H, m, C$\underline{H_2}$Ph×2), 5.09 (1H, d, *J*=10.6 Hz, H1″), 6.07 (6.01) (1H, s, H5′), 6.85–7.75 (36H, m, ArH×36H), and 14.9 (14.6) (1H, s, 2-OH). FAB-MS *m*/*z*: 1020 $(M+H)^+$. *Anal.* Calcd for $C_{65}H_{62}O_{11}$: C, 76.60; H, 6.13. Found: C, 76.52; H, 6.12.

4′,6′-Dibenzyloxy-2′,4-dihydroxy-3′-*C*-(2″,3″,4″,6″-tetra-*O*-benzyl-*β*-D-glucopyranosyl)chalcone (5) To a solution of **4** (1.21 g, 1.22 mmol) in MeOH (100 mL), 2 N HCl (10 mL) was added, and the mixture was refluxed for 2 h. The reaction mixture was concentrated *in vacuo*, and the residue was extracted three times with AcOEt. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and then evaporated to dryness. The residual solid was purified by silica-gel column chromatography (*n*-hexane–AcOEt=3 : 1–2 : 1) and recrystallized from MeOH to afford **5** (1.80 g, Y: 95%) as yellow needles. mp=166°C. $[\alpha]_D^{22}$ +7.31 (*c*=0.520, $CHCl_3$). Silica-gel TLC: *Rf*=0.24 (*n*-hexane–AcOEt=2 : 1). IR (KBr) cm^{-1}: 3421, 2916, 2871, 1618, 1608, 1560, 1508, 1458, 1147, 737, and 698. ^{1}H-NMR ($CDCl_3$) *δ*: 3.45 (1H, t, *J*=9.8 Hz, H4″), 3.65 (1H, dd, *J*=6.8, 11.4 Hz, H6″a), 3.76 (1H, m, H5″), 3.78 (1H, brd, *J*=9.1 Hz, H6″b), 3.83 (1H, t, *J*=9.1 Hz, H3″), 4.28–5.08 (10H, m, C$\underline{H_2}$Ph×5), 4.30 (1H, t, *J*=9.1, 9.9 Hz, H2″), 5.16 (1H, d, *J*=10.6 Hz, H1″), 5.714 (5.710) (1H, s, H5), 6.40, 6.35 (each 1H, d, *J*=9.0 Hz, H3″,5″), 6.59, 6.67 (each 1H, d, *J*=8.4 Hz, H2′,6′), 6.95–7.52 (30H, m, ArH), 7.41, 7.46 (each 0.5H, d, *J*=15.1 Hz, *trans*-vinyl H), 7.61, 7.68 (each 0.5H, d, *J*=15.1 Hz, *trans*-vinyl H), and 15.31 (15.21) (1H, s, 2-OH). FAB-MS *m*/*z*: 976 $(M+H)^+$. *Anal.* Calcd for $C_{63}H_{58}O_{10}$: C, 77.60; H,6.00. Found: C, 77.58; H, 6.22.

2′,4-Dibenzoyloxy-4′,6′-dibenzyloxy-3′-*C*-(2″,3″,4″,6″-tetra-*O*-benzyl-*β*-D-glucopyranosyl)chalcone (6) To a solution of **5** (1.80 g, 1.85 mmol) in pyridine (6 mL), benzoyl chloride (1.5 mL) was dropwise added at 0°C. The reaction mixture was stirred at room temperature for 1.5 h under an Ar atmosphere. Ice-cold 2 N HCl (40 mL) was added to the

mixture, which then was extracted three times with AcOEt. The organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4, and then evaporated to dryness. The residual solid was purified by silica-gel column chromatography (*n*-hexane–AcOEt=4 : 1–2 : 1) to afford **5** (2.22 g, Y: 100%) as a pale-yellow amorphous powder. $[\alpha]_D^{23}$ −32.8 (*c*=0.525, $CHCl_3$). Silica-gel TLC: *Rf*=0.46 (*n*-hexane–AcOEt=2 : 1). IR (KBr) cm^{-1}: 3062, 3029, 2860, 1743, 1647, 1612, 1452, 1346, 1261, 1170, 1061, 735, and 696. ^{1}H-NMR ($CDCl_3$) *δ*: 3.02 (1H, t, *J*=9.1, 9.8 Hz, H4″), 3.10 (1H, dd, *J*=5.3, 9.8 Hz, H6″a), 3.37 (1H, 1H, br d, *J*=9.8 Hz, H6″b), 3.44 (1H, m, H5″), 3.68 (1H, t, *J*=9.1, 9.2 Hz, H3″), 4.11 (1H, t, *J*=9.1, 9.8 Hz, H2″), 4.19, 4.60 (each 1H, d, *J*=10.6 Hz, C$\underline{H_2}$Ph), 4.24, 4.66 (each 1H, d, *J*=11.4 Hz, C$\underline{H_2}$Ph), 4.29, 4.32 (each 1H, d, *J*=10.6 Hz, C$\underline{H_2}$Ph), 4.81, 4.89 (each 1H, d, *J*=11.3 Hz, C$\underline{H_2}$Ph), 4.94, 5.01 (each 1H, d, *J*=12.9 Hz, C$\underline{H_2}$Ph), 5.02, 5.05 (each 1H, d, *J*=12.1 Hz, C$\underline{H_2}$Ph), 5.02 (1H, d, *J*=11.4 Hz, H1″), 6.45 (1H, s, H5), and 6.94–8.21 (46H, m, ArH). FAB-MS *m/z*: 1184 $(M+H)^+$. *Anal.* Calcd for $C_{77}H_{66}O_{12}$: C, 78.15; H, 5.62. Found: C, 78.47; H, 5.58.

2′,4-Dibenzoyloxy-4′-benzyloxy-6′-hydroxy-3′-*C*-(2″,3″,4″,6″-tetra-*O*-benzyl-*β*-D-glucopyranosyl)chalcone (7) To a solution of **5** (1.10 g, 0.930 mmol) in CH_2Cl_2 (2.5 mL) $BF_3 \cdot OEt_2$ (525 *μ*L, 4.18 mmol) was dropwise added at −10°C, and the mixture was stirred for 4 h under an Ar atmosphere with the temperature being raised gradually to 0°C over a priod of 4 h. Ice-cold water was added to the mixture, which then was extracted three times with AcOEt. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and evaporated to dryness. The residual solid was purified by silica-gel column chromatography (*n*-hexane–AcOEt=4 : 1–3 : 1) to afford **6** (824 mg, Y: 81%) as a yellow amorphous powder. $[\alpha]_D^{23}$ −34.8 (*c*=0.535, $CHCl_3$). Silica-gel TLC: *Rf*=0.55 (*n*-hexane–AcOEt=2 : 1). IR (KBr) cm^{-1}: 3483, 3062, 3030, 2917, 2856, 1743, 1635, 1560, 1508, 1452, 1213, 1061, 737, and 698. ^{1}H-NMR ($CDCl_3$) *δ*: 2.90 (1H, dd, *J*=5.3, 10.6 Hz, H6″a), 3.12 (1H, t, *J*=9.1, 9.8 Hz, H4″), 3.28 (1H, br d, *J*=10.6 Hz, H6″b), 3.39 (1H, m, H5″), 3.76 (1H, t, *J*=9.0, 9.1 Hz, H3″), 4.03, 4.12 (each 1H, d, *J*=12.2 Hz, C$\underline{H_2}$Ph), 4.21, 4.99 (each 1H, d, *J*=10.6 Hz, C$\underline{H_2}$Ph), 4.25 (1H, t, *J*=9.0, 9.1 Hz, H2″), 4.55, 4.74 (each 1H, d, *J*=11.3 Hz, C$\underline{H_2}$Ph), 4.75 (1H, d, *J*=11.4 Hz, H1″), 4.93, 4.97 (each 1H, d, *J*=10.6 Hz, C$\underline{H_2}$Ph), 5.09, 5.15 (each 1H, d, *J*=12.1 Hz, C$\underline{H_2}$Ph), 6.48 (1H, s, H8′), 6.94–8.20 (41H, m, ArH), and 13.50 (1H, s, 6′-OH). FAB-MS *m/z*: 1094 $(M+H)^+$. *Anal.* Calcd for $C_{70}H_{60}O_{12}$: C, 76.90; H,5.53. Found: C, 77.29; H, 5.45.

4′,5-Dibenzoyloxy-7-benzyloxy-6-*C*-(2″,3″,4″,6″-tetra-*O*-benzyl-*β*-D-glucopyranosyl)flavone (8) A solution of **7** (750 mg, 0.686 mmol) and iodine (18.8 mg, 0.0686 mmol) in DMSO (1.5 mL) was stirred at 130°C (oil bath) for 0.5 h under an Ar atmosphere. After cooling at room temperature, ice-cold water was added to the resultant mixture, which then was extracted three times with AcOEt. The organic layer was washed with a saturated $Na_2S_2O_3$ solution and brine, and dried over anhydrous Na_2SO_4, and then evaporated to dryness. The residual solid was purified by silica-gel column chromatography (1st, *n*-hexane–AcOEt=3 : 1–2 : 1. 2nd, toluene–AcOEt–AcOH=10 : 1 : 0.1) to afford **8** (629 mg, Y: 84%) as a colorless amorphous powder. $[\alpha]_D^{23}$ +8.71 (*c*=0.505, $CHCl_3$). Silica-gel TLC: *Rf*=0.19 (*n*-hexane–AcOEt=3 : 1). IR (KBr) cm^{-1}: 3062, 3029, 2864, 1743, 1647, 1612, 1452, 1346, 1261, 1209, 1170, 1061, 735, and 696. ^{1}H-NMR ($CDCl_3$) *δ*: 3.04 (1H, dd, *J*=6.0, 11.3 Hz, H6″a), 3.19 (1H, t, *J*=9.1, 9.9 Hz, H4″), 3.41 (1H, dd, *J*=2.2, 11.3 Hz, H6″b), 3.47 (1H, m, H5″), 3.74 (1H, t, *J*=9.1 Hz, H3″), 4.20, 4.27 (each 1H, d, *J*=12.9 Hz, C$\underline{H_2}$Ph), 4.25 (1H, t, *J*=9.0, 9.9 Hz, H2″), 4.27, 4.68 (each 1H, d, *J*=10.6 Hz, C$\underline{H_2}$Ph), 4.31, 4.72 (each 1H, d, *J*=12.1 Hz, C$\underline{H_2}$Ph), 4.87, 4.93 (each 1H, d, *J*=10.6 Hz, C$\underline{H_2}$Ph), 5.07 (1H, d, *J*=9.9 Hz, H1″), 5.10, 5.18 (each 1H, d, *J*=11.4 Hz, C$\underline{H_2}$Ph), 6.56 (1H, s, H3), 6.88 (1H, s, H8), and 7.00–8.24 (35H, m, ArH). FAB-MS *m/z*: 1092 $(M+H)^+$. *Anal.* Calcd for $C_{70}H_{58}O_{12}$: C, 77.05; H, 5.36. Found: C, 77.04; H, 5.26.

7-Acethoxy-4′,5-dibenzoyloxy-6-*C*-(2″,3″,4″,6″-tetra-*O*-acetyl-*β*-D-glucopyranosyl)flavone (9) To a solution of **8** (300 mg, 0.275 mmol) in AcOEt (1.5 mL) and EtOH (1.5 mL), 10% Pd–C (100 mg) was added, and the mixture was vigorously stirred at room temperature under a H_2 atmosphere for 3 h. The resultant mixture was filtered with a celite pad followed by washing with EtOH, and the filtrate was then evaporated to dryness. The residual white powder was dissolved in Ac_2O (1.0 mL) and pyridine (1.0 mL), and stirred at room temperature for 2 h. Ice-cold water was added to the reaction mixture, which then was stirred for 2 h. The resultant white powder was filtered to afford **9** (229 mg, Y: 98%, 2 steps) as a colorless amorphous powder. $[\alpha]_D^{23}$ +8.14 (*c*=0.565, $CHCl_3$). Silica-gel TLC: *Rf*=0.14 (*n*-hexane–AcOEt=1 : 1). IR (KBr) cm^{-1}: 3066, 2943, 1751, 1655, 1452, 1367, 1246, 1165, 1061, and 706. ^{1}H-NMR ($CDCl_3$) *δ*: 1.90, 2.00, 2.02, 2.09 (each 3H, s, OAc ×4), 2.52 (3H, s, ArOAc), 3.79 (1H, m, H5″), 4.01 (1H, br d, *J*=11.3, 12.1 Hz, H6″a), 4.44 (1H, dd, *J*=3.8, 12.1 Hz, H6″b), 4.93 (1H, d, *J*=9.8 Hz, H1″), 5.17 (2H, m, H3″,4″), 5.78 (1H, t, *J*=9.8 Hz, H2″), 6.60 (1H, s, H3), 7.38 (1H, s, H8), 7.39 (2H, d, *J*=8.4 Hz, *p*-substituted ArH), 7.91 (2H, d, *J*=8.4 Hz, *p*-substituted ArH), 7.54, 7.60 (each 2H, t, *J*=7.5 Hz, benzoyl ArH), 7.69 (2H, q, *J*=7.5 Hz, benzoyl ArH), and 8.23 (4H, m, benzoyl ArH). FAB-MS *m/z*: 851 $(M+H)^+$. *Anal.* Calcd for $C_{45}H_{38}O_{17}$: C, 63.53; H, 4.50. Found: C, 63.23; H, 4.25.

4′,5-Dibenzoyloxy-7-hydroxy-6-*C*-(2″,3″,4″,6″-tetra-*O*-acetyl-*β*-D-glucopyranosyl)flavone (10) To a solution of **9** (290 mg, 0.341 mmol) in CH_3CN (3.5 mL), TMG (107 *μ*L, 0.183 mmol) was dropwise added at room temperature, and the mixture was stirred for 3 h. A saturated NH_4Cl aqueous solution (10 mL) was added to the reaction mixture, which then was extracted three times with AcOEt. The organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4, and evaporated to dryness. The residual solid was purified by silica-gel column chromatography ($CHCl_3$–MeOH=30 : 1) to afford **10** (229 mg, Y: 83%) as a pale-yellow amorphous powder. $[\alpha]_D^{23}$ +35.8 (*c*=0.520, $CHCl_3$). Silica-gel TLC: *Rf*=0.42 (*n*-hexane–AcOEt=2 : 3). IR (KBr) cm^{-1}: 3448, 2943, 1751, 1647, 1637, 1363, 1246, 1170, 1061, and 706. ^{1}H-NMR ($CDCl_3$) *δ*: 1.97, 2.01, 2.03, 2.04, 2.16 (12H, OAc×4), 3.89 (3.93) (1H, m, H5″), 4.17 (4.21) (1H, dd, *J*=10.6, 12.1 Hz, H6″a), 4.37 (4.35) (1H, dd, *J*=3.0, 12.1 Hz, H6″b), 4.99 (5.15) (1H, dd, *J*=9.8 Hz, H1″), 6.53 (1H, s, H3), 7.03 (1H, s, H8), 7.38 (2H, d, *J*=8.3 Hz, *p*-substituted ArH), 7.91 (2H, d, *J*=8.3 Hz, *p*-substituted ArH), 7.52–7.59 (4H, m, benzoyl ArH), 7.65–7.71 (2H, m, benzoyl ArH), and 8.21–8.25 (4H, m, benzoyl ArH). FAB-MS *m/z*: 810 $(M+H)^+$. *Anal.* Calcd for $C_{43}H_{36}O_{16}$: C, 63.86; H, 4.49. Found: C, 63.94; H, 4.64.

4′,5-Dibenzoyloxy-7-hydroxy-6-*C*-(2″,3″,4″,6″-tetra-*O*-acetyl-*β*-D-glucopyranosyl)-7-*O*-(2‴,3‴,4‴,6‴-tetra-*O*-

acetyl-β-D-glucopyranosyl)flavone (11) To a solution of **10** (100 mg, 0.123 mmol) in quinoline (0.3 mL), Ag_2CO_3 (67.8 mg, 0.246 mmol) and per-*O*-acetylglucosyl bromide (101 mg, 0.246 mmol) were added at 0°C, and the resultant mixture was stirred at room temperature in the dark under an Ar atmosphere for 3 h. The reaction was quenched with MeOH, and the mixture was eluted through a short silica-gel column with AcOEt. The eluate was evaporated to dryness. To the residue, 1 N HCl (8 mL) was added, and the resultant mixture was extracted three times with AcOEt. The organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4. After evaporation, the residue was purified by silica-gel column chromatography ($CHCl_3$–MeOH=30 : 1) to afford **11** (12 mg, Y: 86%) as colorless prisms. mp >300°C. $[\alpha]_D^{23}$ −47.5 (*c*=0.510, $CHCl_3$). Silica-gel TLC: *Rf*=0.32 (*n*-hexane–AcOEt=2 : 3). IR (KBr) cm^{-1}: 2945, 1751, 1653, 1508, 1458, 1375, 1226, 1063, and 707. ^{1}H-NMR ($CDCl_3$) *δ*: 1.80, 1.97, 2.02, 2.06, 2.09, 2.23 (each 3H, s, OAc×6), 2.10 (6H, s, OAc×2), 3.72–3.74 (1H, m, H5‴), 3.76 (1H, dd, *J*=1.5, 12.2 Hz, H6‴a), 3.90 (1H, dd, *J*=5.3, 12.2 Hz, H6‴b), 4.09 (1H, m, H5″), 4.26 (1H, dd, *J*=2.3, 12.1 Hz, H6″a), 4.32 (1H, dd, *J*=6.8, 12.1 Hz, H6″b), 4.78 (1H, t, *J*=9.8 Hz, H4‴), 5.08 (1H, d, *J*=10.6 Hz, H1‴), 5.19 (1H, t, *J*=9.8 Hz, H4″), 5.24 (1H, d, *J*=7.6 Hz, H1″), 5.28 (1H, t, *J*=9.1, 9.9 Hz, H3‴), 5.43 (1H, m, H3″), 5.45 (1H, m, H2″), 5.79 (1H, t, *J*=9.8, 9.9 Hz, H2‴), 6.53 (1H, s, H3), 7.03 (1H, s, H8), 7.55, 7.59 (each 2H, t, *J*=7.6 Hz, benzoyl ArH), 7.66 (2H, q, *J*=7.5 Hz, benzoyl ArH), 8.22, and 8.30 (each 2H, d, *J*=6.8 Hz, benzoyl ArH). FAB-MS *m/z*: 1140 $(M+H)^+$. *Anal.* Calcd for $C_{57}H_{54}O_{25}$: C, 60.10; H, 4.78. Found: C, 60.08; H, 4.66.

Saponarin 1 To a solution of **11** (50.0 mg, 0.0439 mmol) in tetrahydrofuran (THF)–MeOH (1.0 mL, 0.5 mL), 28% NaOMe methanolic solution (*ca.* 70 mg) was added and the mixture was stirred at room temperature for 3 h. The reaction mixture was neutralized with Dowex® 50W×8 (H^+), filtered and washed with MeOH, and evaporated to dryness. The residual solid was recrystallized from MeOH to afford **1** (22.7 mg, Y: 87%) as white crystals. mp 237–238°C (natural[2-a]: 229–231°C); $[\alpha]_D^{23}$ −36.8 (*c*=0.505, DMSO) [natural[2-a]: $[\alpha]_D^{25}$ −33 (*c*=0.50, DMSO)]; Silica-gel TLC: *Rf*=0.39 (acetone–AcOEt–H_2O–AcOH=30 : 15 : 5 : 1). IR (KBr) cm^{-1}: 3400, 2927, 1655, 1617, 1508, 1489, 1458, 1354, 1188, 1091, and 1076. ^{1}H-NMR [DMSO-d_6+D_2O (2 drops), at 90°C] *δ*: 3.2–3.29 (5H, m), 3.36 (1H, t, *J*=9.1 Hz), 3.38 (1H, t, *J*=9.0 Hz), 3.48 (1H, m), 3.55 (1H, dd, *J*=5.3, 11.4 Hz, H6″ or 6‴), 3.66 (1H, brd, *J*=9.8 Hz, H6″ or 6‴), 3.78 (1H, d, *J*=11.3 Hz, H6″ or 6‴), 4.72 (1H, d, *J*=8.4 Hz, H1″), 4.97 (1H, d, *J*=6.8 Hz, H1‴), 6.74 (1H, s, H3), 6.89 (1H, s, H8), 6.95, 7.89 (each 2H, d, *J*=8.5, 8.3 Hz, H3′,5′ and H2′,6′), 10.4 (1H, s, 4′-OH), and 13.4 (1H, brs, 6-OH). FAB-MS *m/z*: 593 $(M-H)^-$. *Anal.* Calcd for $C_{27}H_{30}O_{15}\cdot 2H_2O$, C, 51.43, H, 5.44. Found: C, 51.16, H, 5.48.

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