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Concise synthesis of flavocommelin, 7-*O*-methylapigenin 6-*C*-, 4′-*O*-bis-β-D-glucoside, a component of the blue supramolecular pigment from *Commelina communis*

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ABSTRACT

Flavocommelin, 7-*O*-methylapigenin 6-*C*-, 4′-*O*-bis-β-D-glucoside, was synthesized in 9 steps from the C-glycosylation of 6-*O*-benzy-4-*O*-methylphloroacetophenone via the introduction of a cinnamoyl residue by aldol condensation and the formation of a C-ring by regioselective and oxidative ring-closure to regio- and stereoselective O-glycosylation for an overall yield of 31%.

1. Introduction

A variety of C-glycosylflavonoids are widely distributed in plants, in which sugars are generally linked at C-6 and/or C-8 on the A-ring. C-glycosides show different various biological activities[1] from the related aglycone and O-glycoside, because they are not enzymatically hydrolyzed in vivo. We have achieved the synthesis of some naturally occurring mono- and di-C-glycosylflavonoids (flavone, isoflavone, flavanone, and chalcone) showing biological activity based on our development of two different C-glycosylation methods: C-glycosylation of phloroacetophenone 4,6-bis-ether by O–C glycoside rearrangement,[2] and a direct mono- and di-C-glycosylation of the non-protected phloroacetophenone with a non-protected sugar in an aqueous solution.[3] However, we have not attempted the synthesis of C,O-diglycosylflavonoid. More than 100 naturally occurring C,O-diglycosylflavonoids have been discovered and their structure comfirmed.[4] Among them, some compounds have shown biological activity. For example, saponarin (6-C-glucosylapigenin 7-O-glucoside) shows potent anti-inflammatory and antidiabetic activities.[5]

Flavocommelin (**1**) (Fig. 1) is one of the components of commelinin, a blue supramolecular pigment that is a metalloanthocyanin (a metal-complex anthocyanin) in *Commelina communis*, which has been elucidated by Kondo's group.[6] For the structure analysis of the supramolecular pigment, Oyama and Kondo first synthesized **1** via 12 steps in a 6.2% overall yield from (±) naringenin, using the C-glycosylation of the flavan as a key reaction. This is the only report of the synthesis of C,O-diglycosylflavonoid.[7]

Herein we describe the concise synthesis of **1** using the former of our two C-glycoside synthetic methods, with planning and examination as shown in Scheme 1: (1) C-glycosylation of 2-*O*-benzyl-4-*O*-methylphloroacetophenone by the O–C glycoside rearrangement method; (2) introduction of a cinnamoyl residue by aldol condensation; (3) regioselective deprotection of the 6-OH group on the A-ring followed by the formation of a flavone skeleton using oxidative cyclization; and, (4) regioselective deprotection of the 4′-OH group on the B-ring and its stereoselective O-glycosylation by the Koenigs–Knorr reaction according to the conditions stipulated by Oyama.[6]

2. Results and discussion

C-glycosylation of 2-*O*-benzyl-4-*O*-methylphloroacetophenone (**2**)[2e] was carried out by raising the reaction temperature from −78 °C to room temperature for 5 h, using 1.0 equiv of per-*O*-benzyl-α-D-glucosyl fluoride as a glycosyl donor to 2.0 equiv of **2** in CH_2Cl_2 in the presence of 1.5 equiv of $BF_3{\cdot}OEt_2$ and powdered molecular sieves 4A. The desired C-glycoside **3**[2e] was furnished in 85% yield. The advantage of this method is that the reaction proceeds smoothly in an excellent yield using $BF_3{\cdot}OEt_2$ with neither the use of a potent and expensive catalyst metallocene (Cp_2MCl_2: M = Ti, Zr, Hf) and Ag salt, nor scandium(III) trifluoromethanesulfonate [$Sc(OTf)_3$] to give the desired C-glycoside, owing to formation

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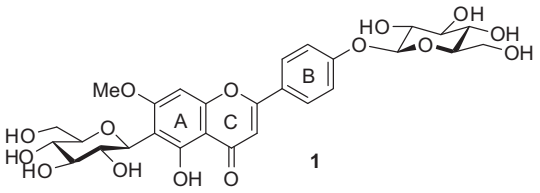
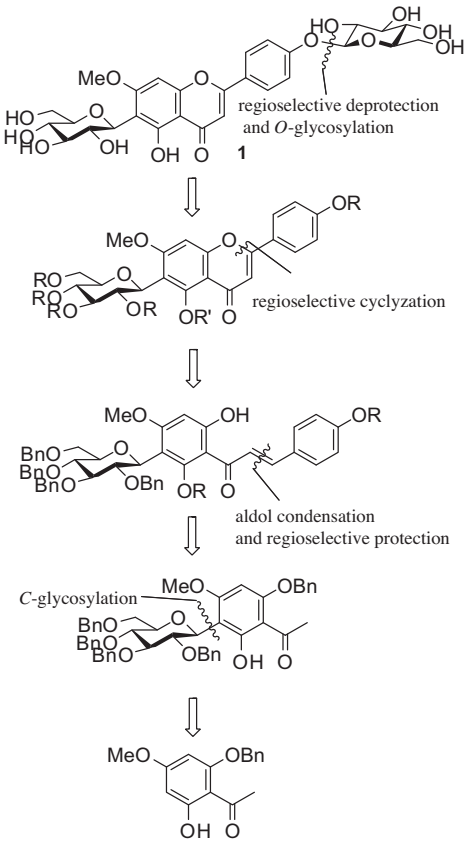


Figure 1. Structure of flavocommelin (**1**).



Scheme 1. Synthetic plan of flavocommelin (**1**).

of the C-glycoside via O-glycosylation to the chelated phenolic hydroxyl. Further, Schmidt's C-glycosylation method[8] using **2** and 1.2 equiv of per-*O*-benzyl-α-D-glucosyl trichloroacetimidate in place of the fluoride as a donor and 0.2 equiv of trimethylsilyl trifluoromethanesulfonate (TMSOTf) as a catalyst to 1.0 equiv of **2** also afforded **3** in an 81% yield. Structure analysis of the synthetic compounds was conducted mainly by means of ^{1}H NMR and ^{1}H–^{1}H COSY, and FAB-MS. A ^{1}H NMR spectrum gave a complex spectrum due to a mixture of rotamers, particularly on the A-ring bearing a C-glycoside. The ^{1}H NMR spectra measured in DMSO-d_6 at more than 120 °C were simple without a mixture of rotamers, which allowed assignment. However, C-glycosides bearing an O-glycoside could not be measured at more than 120 °C due to instability. Both the use of fluoride/BF_3·OEt_2 and imidate/TMSOTf as a combination of donor and catalyst gave **3** in good yield. Next, the aldol condensation of **3** with 1.1 equiv of *p*-benzyloxybenzaldehyde in the presence of 1.5 equiv of sodium methoxide in 1,4-dioxane at room temperature for 2 h gave chalcone **4** in a 98% yield. After a 2-OH group on the A-ring of **4** was benzoylated with benzoyl chloride and pyridine (**5** Y: 95%), selective deprotection of the 6-*O*-benzyl group on the A-ring was attempted. Under hydrogenolysis conditions using 5% or/and 10% Pd–C as a catalyst, reduction of the olefin proceeded in preference to O-debenzylation. Next, hydrogenolysis in a solution containing HCl was examined and the desired **6** was produced in a maximum yield of 38%. Further, one-pot formation of the flavanone by deprotection and cyclization by refluxing in HCl aqueous solution or in the presence of Dowex® (H^+) resin, and one-pot formation of flavones via deprotection and oxidative cyclization by heating in DMSO in the presence of a catalytic amount of I_2 were attempted. However, they yielded a mixture of many products. Since a 6-*O*-benzyl group of chalcone **5** can be more labile by comparison with other benzyl groups, 6-O-debenzylation using a Lewis acid was next examined. A treatment of **5** with 4.5 equiv of BF_3·OEt_2 in an ice-salt bath for 5 h proceeded smoothly, providing **6** in a 76% yield. In succession, regioselective oxidative cyclization by the heating of **6** in DMSO at 130 °C for 30 min in the presence of 0.1 equiv of I_2 proceeded satisfactorily, affording the desired flavone **7** in an 88% yield[2d] (Scheme 2).

Toward the next regioselective O-glycosylation, the regioselective debenzylation of the 4′-phenolic benzylether on the B-ring of **7** by the above hydrogenolysis using 5% Pd–C in AcOEt was carried out, and the desired 4′-OH-free flavone **8** was acquired in a 68% yield. Since a partial deprotection of the benzyl ether of the glucose hydroxyls proceeded well under these conditions, the yield was moderate. In order to improve the yield, first, a protecting element of the 6-OH group of **7** was changed from a benzyl to an acetyl group, then the regioselective deprotection of the 4′-*O*-acetyl group on the B-ring of acetate **10** was examined using Oyama's method [2.5 equiv of tetramethylguanidine (TMG) in CH_3CN at rt, for 2 h].[9] This regioselective deprotection reaction proceeded smoothly to give 4′-OH-free **10** (**11**) in an 89% yield.

Finally, the stereoselective O-glycosylation of **11** was carried out via a Koenigs–Knorr reaction using the procedure established by Oyama [per-*O*-acetylglucosyl bromide (3.0 equiv), Ag_2CO_3 (1.5 equiv), in quinoline, at 0 °C to rt, for 3 h],[9] providing **12** in an 80% yield. The final deprotection of acetyl and benzoyl groups was conducted via treatment with sodium methoxide in methanol followed by neutralization using Dowex® 50Wx8 (H^+) resin, then recrystallization from H_2O–CH_3CN gave **1** as a white solid in an 84% yield. The ^{1}H NMR data of **1** gave a complex spectrum due to the mixture of rotamers, but it was identical to that of a natural compound as well as that of Oyama and Kondo's synthetic one. The other physico-chemical data were also identical.[7]

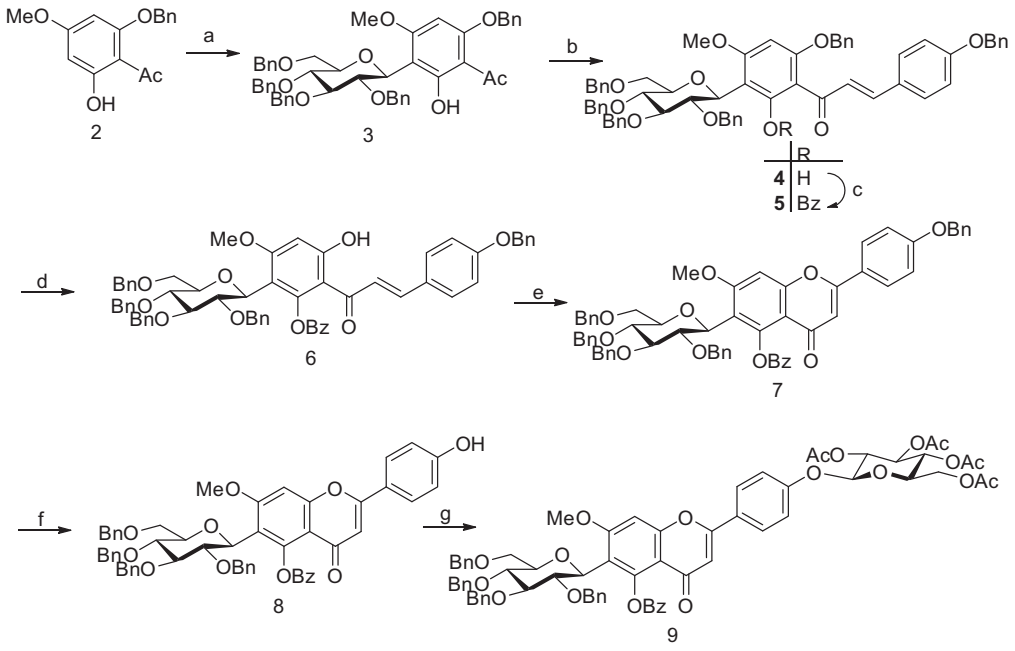
3. Conclusion

Flavocommelin (**1**) was efficiently synthesized via 9 steps from **2** in an overall 31% yield. A concise synthesis of C,O-diglycosylflavone using phloroacetophenone bis-ether as a starting material was achieved. The synthetic route proposed here was shown to be viable for the synthesis of various C,O-diglycosylflavonoids. Synthesis of the more complex 6-*C*-7-*O*-β-D-diglucosylapigenin, saponarin is in progress.

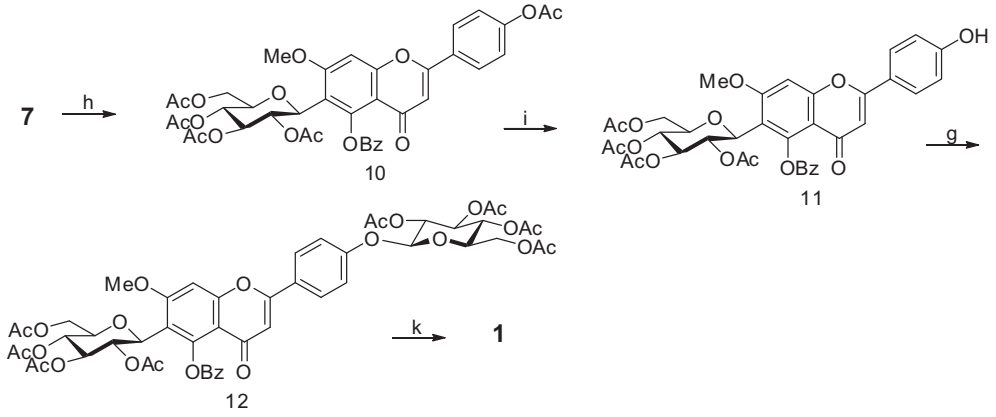
4. Experimental

4.1. General

The solvents used in these reactions were purified by distillation. 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 on a JASCO DIP-370 polarimeter. Melting points were determined using an



Reagents and conditions : a) **2** (2 equiv), per-*O*-benzylglucosyl fluoride (1 equiv), $BF_3{\cdot}OEt_2$ (2 equiv) in CH_2Cl_2, at -70 °C – rt, 5 h, Y:85% b) *p*-BnO-benzaldehyde (1.2 equiv), NaOMe (1.2 equiv), in dioxane, rt, 1.5 h, Y:98% c) BzCl (1.5 equiv), in pyridine, 0 °C – rt, 3 h, Y: 95% d) $BF_3{\cdot}OEt_2$ (3.5 equiv), in CH_2Cl_2, -20 – -10 °C, 3 h, Y:76% e) I_2 (0.1 equiv) in DMSO at 130 °C, 30 min, Y:88% f) H_2 / 5 and 10% Pd-C, in AcOEt, rt, 6 h. Y:68% g) per-*O*-acetylglucosyl bromide (3.5 equiv), Ag_2CO_3 (1.5 equiv), in quinoline, at 0 °C – rt, 3 h, Y:70%



Reagents and conditions : h) 1. H_2 / 10% $Pd(OH)_2$, AcOEt/EtOH (1:1), rt, 3 h, 2. Ac_2O/Py, rt, 3 h, Y:98%, i) TMG (2.5 equiv), in CH_3CN, rt, 3h, Y:80% g) Y:80% k) NaOMe in MeOH, rt, for 1 h, then Dowex50W (H^+), Y: 100%.

Scheme 2. Total synthesis of flavocommelin (**1**).

ASONE micro-melting point apparatus and uncorrected values were reported. IR spectra were recorded on a Horiba FT-720 IR spectrometer using a KBr disk. NMR spectra were recorded on a JEOL ECX-500 spectrometer using Me_4Si as the internal standard. Mass spectral data were obtained by fast-atom bombardment (FAB) using 3-nitrobenzyl alcohol (NBA) as a matrix on a JEOL JMS-AX505HA instrument. High-resolution mass spectra (HRMS) were obtained under electron spray ionization (ESI) conditions on a JEOL JMS-T100LP. Elemental analyses were performed on a Perkin–Elmer PE 2400 II instrument. After drying at 70 °C under reduced pressure for more than 2 h, each product was subjected to elemental analysis.

4.1.1. 4′,6-Dibenzyloxy-3-*C*-(2″,3″,4″,6″-tetra-*O*-benzyl-β-D-glucopyranosyl)-4-methoxychalcone (4)

To a solution of **3** (1.24 g, 1.56 mmol) and *p*-benzyloxybenzaldehyde (0.330 g, 1.56 mmol) in 1,4-dioxane (10 mL), a 28% NaOMe–MeOH solution (8.0 mL) was added and the mixture was stirred at room temperature for 1.5 h. To the reaction mixture, ice-cold 2 N-HCl solution (20 mL) was added, then the mixture 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.

$[\alpha]_D^{22}$ −6.6 (*c* 0.550, $CHCl_3$). IR (KBr): 3425, 3030, 2920, 2856, 1624, 1558, 1508, 1454, 1423, 1230, 1066, 735, 696 cm^{-1}. ^1H NMR (DMSO-d_6, at 120 °C) δ 3.50 (1H, m, H5″), 3.59 (1H, t, *J* = 9.1 Hz, H4″), 3.67 (2H, m, H6″a,b), 3.68 (1H, m, H3″), 3.86 (3H, s, OCH_3), 4.20 (1H, d, *J* = 12.1 Hz, CH_2Ph), 4.31 (1H, t, *J* = 9.1 Hz, H2″), 4.46 and 4.49 (each 1H, d, *J* = 12.1 Hz, CH_2Ph), 4.56 (1H, d, *J* = 12.1 Hz, CH_2Ph), 4.62 (1H, d, *J* = 11.3 Hz, CH_2Ph), 4.76–4.85 (3H, m, CH_2Ph), 4.81 (1H, d, *J* = 9.1 Hz, H1″), 5.15 (2H, s, ArOCH_2Ph), 5.26 (2H, s, ArOCH_2Ph), 6.38 (1H, s, 8-ArH), 7.59 and 7.64 (each 1H, d, *J* = 15.9 Hz, *trans*-vinyl H), 6.90–7.51 (34H, m, ArH), 14.0 (1H, br s, 5-OH); FAB-MS (*m*/*z*) 989 $(M+H)^+$. Anal. Calcd for $C_{64}H_{60}O_{10}\cdot 0.5H_2O$: C, 77.01; H, 6.16. Found: C, 76.96; H, 6.12.

4.1.2. 2-Benzoyl-4′,6-dibenzyloxy-3-*C*-(2″,3″,4″,6″-tetra-*O*-benzyl-β-D-glucopyranosyl)-4-methoxychalcone (5)

To a solution of **4** (1.21 g, 1.22 mmol) in pyridine (2.5 mL), benzyl chloride (556 μL, 6.71 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 4 h. To the resultant mixture ice-cold water and 2 N HCl (15 mL) were added, then the mixture 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 = 3:1–2:1) to afford **5** (1.27 g, Y:95%) as a pale-yellow amorphous powder.

$[\alpha]_D^{22}$ −40 (*c* 1.88, $CHCl_3$). IR (KBr): 3446, 3031, 2904, 2864, 1743, 1602, 1508, 1452, 1250, 1099, 1070, 737, 698 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.95 (2H, t, *J* = 9.1 Hz, H4″), 2.95 (1H, m, H6″a), 3.36 (1H, br d, *J* = 10.6 Hz, H6″b), 3.43 (1H, br t, *J* = 6.8 Hz, 8.4, H5″), 3.67 (1H, t, *J* = 9.1 Hz, H3″), 3.77 (3H, s, OCH_3), 4.09 (1H, t, *J* = 9.1 Hz, H2″), 4.16 (1H, d, *J* = 10.6 Hz, CH_2Ph), 4.22 and 4.26 (each 1H, d, *J* = 9.9 Hz, CH_2Ph), 4.32 (each 1H, d, *J* = 12.1 Hz, CH_2Ph), 4.60 (2H, t, *J* = 12.1 and 11.3 Hz, CH_2Ph), 4.80 (1H, d, *J* = 10.6 Hz, CH_2Ph), 4.91 (1H, d, *J* = 10.6 Hz, CH_2Ph), 4.95 (1H, d, *J* = 9.9 Hz, H1″), 5.08 (2H, s, ArOCH_2Ph), 5.15 (2H, s, ArOCH_2Ph), 6.46 (1H, s, 8-ArH), 6.86–8.04 (36H, m, ArH × 34, vinyl H × 2); FAB-MS (*m*/*z*) 1093 $(M+H)^+$. Anal. Calcd for $C_{71}H_{64}O_{11}$: C, 78.00; H, 5.90. Found: C, 78.34; H, 5.90.

4.1.3. 2-Benzoyl-4′-benzyloxy-3-*C*-(2″,3″,4″,6″-tetra-*O*-benzyl-β-D-glucopyranosyl)-6-hydroxy-4-methoxychalcone (6)

To a solution of **5** (730 mg, 0.668 mmol) in CH_2Cl_2 (5.0 mL) $BF_3\cdot OEt_2$ (371 μL, 3.01 mmol) was dropwise added at −15 °C, and the mixture was stirred at −15 to −10 °C for 5 h. To the reaction mixture, ice-cold water was added, then the mixture 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** (509 mg, Y: 76%) as a yellow amorphous powder.

$[\alpha]_D^{23}$ −34 (*c* 1.95, $CHCl_3$). IR (KBr): 3435, 3031, 2922, 2860, 1751, 1628, 1554, 1508, 1452, 1350, 1219, 737, 698 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.87 (1H, dd, *J* = 10.6 and 5.3 Hz, H6″a), 3.06 (1H, t, *J* = 9.0 and 9.1 Hz, H4″), 3.27 (1H, d, *J* = 9.8 Hz, H6″b), 3.39 (1H, m, H5″), 3.75 (1H, t, *J* = 9.1 Hz, H3″), 3.87 (3H, s, OCH_3), 4.26 (1H, t, *J* = 9.1 Hz, H2″), 4.06 and 4.12 (each 1H, d, *J* = 12.1 Hz, CH_2Ph), 4.20 and 4.62 (each 1H, d, *J* = 11.3 Hz, CH_2Ph), 4.50 and 4.72 (each 1H, d, *J* = 11.4 Hz, CH_2Ph), 4.92 and 4.99 (each 1H, d, *J* = 11.3 Hz, CH_2Ph), 4.89 (1H, d, *J* = 9.8 Hz, H1″), 5.02 (2H, s, ArOCH_2Ph), 6.46 (1H, s, 8-ArH), 6.86–7.99 (36H, m, ArH × 34, vinyl H × 2); FAB-MS (*m*/*z*) 1003 $(M+H)^+$. Anal. Calcd for $C_{76}H_{60}O_{11}$: C, 76.63; H, 5.83. Found: C, 76.89; H, 6.06.

4.1.4. 5-Benzoyl-4′-benzyloxy-6-*C*-(2″,3″,4″,6″-tetra-*O*-benzyl-β-D-glucopyranosyl)-7-methoxyflavone (7)

A solution of **6** (422 mg, 0.421 mmol) and iodide (10.6 mg, 0.0421 mmol) in DMSO (1.4 mL) was stirred at 130 °C (oil bath) for 0.5 h. 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 (*n*-Hexane–AcOEt = 3:1–2:1) to afford **7** (371 mg, Y: 88%) as a colorless amorphous powder.

$[\alpha]_D^{23}$ −5.3 (*c* 1.77, $CHCl_3$). IR (KBr): 3483, 3062, 3030, 2912, 2866, 1751, 1643, 1608, 1510, 1452, 1352, 1257, 1097, 833, 737, 698 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.00 (1H, dd, *J* = 10.9 and 5.7 Hz, H6″a), 3.13 (1H, t, *J* = 9.5 Hz, H4″), 3.41 (1H, dd, *J* = 1.5 and 10.6 Hz, H6″b), 3.46 (1H, ddd, *J* = 1.5, 6.1 and 7.2 Hz, H5″), 3.74 (1H, t, *J* = 9.5 Hz, H3″), 4.21-4.29 (4H, m, H2″ and CH_2Ph), 3.91 and 3.72 (3H, s, OCH_3), 4.67 (1H, d, *J* = 10.6 Hz, H1″), 4.66 (1H, d, *J* = 11.4 Hz, CH_2Ph), 4.68 (1H, d, *J* = 10.6 Hz, CH_2Ph), 4.87 and 4.94 (each 1H, d, *J* = 11.3 Hz, CH_2Ph), 4.99 (1H, d, *J* = 9.8 Hz, H1″), 5.14 (2H, s, ArOCH_2Ph), 6.47 (3H, s, ArOCH_2Ph), 6.47 (1H, s, H3), 6.83 (1H, s, 8-ArH), 6.96–8.17 (34H, m, ArH); FAB-MS (*m*/*z*) 1001 $(M+H)^+$. Anal. Calcd for $C_{64}H_{56}O_{11}$: C, 76.78; H, 5.64. Found: C, 76.64; H, 5.46.

4.1.5. 5-Benzoyl-6-*C*-(2″,3″,4″,6″-tetra-*O*-benzyl-β-D-glucopyranosyl)-4′-hydroxy-7-methoxyflavone (8)

To a solution of **7** (100 mg, 0.0999 mmol) in AcOEt, 5% Pd–C (50 mg) was added, and the mixture was stirred vigorously under hydrogen atmosphere at room temperature for 4 h. To the reaction mixture 10% Pd–C (10 mg) was added, and the mixture was again vigorously stirred under hydrogen atmosphere at room temperature for 1 h. After monitoring the disappearance of **7** by silica-gel TLC (*n*-Hexane:AcOEt = 2:1), the resultant mixture was filtered with a celite pad, followed by washing with AcOEt, and then it was allowed to evaporate to dryness. The residual solid was purified by silica-gel column chromatography (*n*-Hexane:AcOEt = 3:1–2:1) to afford **8** (61.9 mg, Y:68%) as a colorless solid.

$[\alpha]_D^{23}$ 9.0 (*c* 0.840, $CHCl_3$). IR (KBr): 3435, 3030, 2923, 2860, 1751, 1629, 1608, 1512, 1452, 1354, 1255, 1095, 837, 737, 698 cm^{-1}. ^1H NMR ($CDCl_3$) was observed with rotamers, δ 2.88 (1H, dd, *J* = 7.6 and 10.6 Hz, H6″a), 2.94 (1H, t, *J* = 9.8 Hz, H4″), 3.36 (1H, d, *J* = 9.8 Hz, H6″b), 3.51 (1H, m, H5″), 3.73 (1H, t, *J* = 8.3 and 9.1 Hz, H3″), 3.73 and 3.82 [3H (2.6:1), each s, OCH_3], 4.18 (1H, d, *J* = 11.3 Hz, CH_2Ph), 4.24 (1H, t, *J* = 9.1 and 9.8 Hz, H2″), 4.27 (1H, d, *J* = 11.3 Hz, CH_2Ph), 4.32 and 4.33 (each 1H, d, *J* = 12.1 Hz, CH_2Ph), 4.63 (1H, d, *J* = 10.6 Hz, CH_2Ph), 4.66 (1H, d, *J* = 11.3 Hz, CH_2Ph), 4.86 (1H, d, *J* = 10.6 Hz, CH_2Ph), 4.94 (1H, d, *J* = 11.3 Hz, CH_2Ph), 4.95 (1H, d, *J* = 9.8 Hz, H1″), 6.35 (1H, s, H3), 6.53 (1H, s, H8), 6.70–8.40 (30H, m, ArH × 29 and 4′-OH); FAB-MS (*m*/*z*) 911 $(M+H)^+$. Anal. Calcd for $C_{57}H_{50}O_{11}\cdot 0.25H_2O$: C, 74.78; H, 5.56. Found: C, 74.51; H, 5.41.

4.1.6. 5-Benzoyl-6-*C*-(2″,3″,4″,6″-tetra-*O*-benzyl-β-D-glucopyranosyl)-4′-*O*-(2‴,3‴,4‴,6‴-tetra-*O*-acetyl-β-D-glucopyranosyl)-7-methoxyflavone (9)

To a solution of **8** (20.0 mg, 0.0220 mmol) in quinoline (0.3 mL), Ag_2CO_3 (9.1 mg, 0.0330 mmol) and acetobromoglucose per-*O*-acetylglucosyl bromide (27.1 mg, 0.0660 mmol) were added at 0 °C and the mixture was stirred at room temperature under a shielded light 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 (0.5 mL) was added, then the mixture was extracted three times with AcOEt. The organic layer was washed with water and brine, then dried over anhydrous Na_2SO_4. After evaporation, the residual solid was purified by silica-gel column chromatography (*n*-Hexane:AcOEt = 2:1–1:1) to afford **12** (19.1 mg, Y: 70%) as a white solid.

$[\alpha]_D^{24}$ −17 (*c* 1.14, $CHCl_3$). IR (KBr): 3030, 2929, 2866, 1751, 1647, 1610, 1508, 1452, 1232, 1068, 698 cm^{-1}. ^1H NMR (DMSO-d_6) was observed with a mixture of rotamers, δ 1.972, 2.010, 2.015, 2.024 (each 3H × 4, s × 4, OAc × 4), 2.65 (1H, dd, *J* = 6.9 and 10.6 Hz, H6″a), 2.78 (1H, t, *J* = 9.1 Hz, H4″), 3.18 (1H, br d, *J* = 10.6 Hz, H6″b), 3.39 (1H, m, H5″), 3.68 (1H, t, *J* = 9.1 Hz, H3″), 3.97 (3H, s, OCH_3), 4.08 (1H, dd, *J* = 2.2 and 12.1 Hz, H6‴a), 4.14 (1H, t, *J* = 9.1 and 9.9 Hz, H2″), 4.21 (1H, dd, *J* = 5.3 and 12.1 Hz, H6‴b), 4.31 (1H, m, H5‴), 4.87 (1H, d, *J* = 9.9 Hz, H1″), 5.03 (1H, t, *J* = 9.8 Hz, H4‴), 5.11 (1H, dd, *J* = 8.3 and 9.8 Hz, H2‴), 5.43 (1H, t, *J* = 9.8 Hz, H3‴), 5.76 (1H, d, *J* = 7.6 Hz, H1‴), 6.71 (1H, s, H3), 6.94–8.21 (30H, m, ArH × 30); FAB-MS (*m*/*z*) 1241 $(M+H)^+$. Anal. Calcd for $C_{71}H_{68}O_{20}$: C, 68.70; H, 5.52. Found: C, 68.60; H, 5.35.

4.1.7. 4′-Acetoxy-5-benzoyl-6-*C*-(2″,3″,4″,6″-tetra-*O*-acetyl-β-D-glucopyranosyl)-7-methoxyflavone (10)

To a solution of **9** (322 mg, 0.260 mmol) in AcOEt (2.0 mL) and EtOH (2.0 mL), 10% Pd–C (120 mg) was added and the mixture was vigorously stirred at room temperature under H_2 atmosphere for 3 h. The resultant mixture was filtered with a celite pad followed by washing with EtOH and the filtrate was evaporated to dryness. The residual white powder was dissolved in Ac_2O (1.5 mL) and pyridine (1.5 mL), and stirred at room temperature for 3 h. To the reaction mixture ice-cold water was added then the mixture was extracted three times with AcOEt. The organic layer was washed with water, brine, and dried over anhydrous Na_2SO_4, and the organic solvent was evaporated together with toluene to dryness. The residual solid was purified by silica-gel column chromatography (*n*-Hexane:AcOEt = 2:1–1:1) to afford **10** (194 mg, Y: 98%, 2 steps) as a white solid.

$[\alpha]_D^{22}$ −21 (*c* 0.910, $CHCl_3$). IR (KBr): 3068, 2943, 1764, 1737, 1656, 1612, 1508, 1452, 1369, 912, 847, 706 cm^{-1}. ^1H NMR ($CDCl_3$) was observed with a mixture of rotamers, δ 1.82, 1.87, 1.95, 1.99, 2.02, 2.03, 2.06, 2.09 (12H, OAc × 4), 2.34 (3H, s, ArOAc), 3.64, 3.70, 3.77 (1H, m, H5″), 3.98, 4.05, 4.08 [3H (1.8:1.0:3.3), s, OCH_3], 3.76 and 4.17 [1H (1:2.3), br d, *J* = 12.1 Hz, H6″a], 3.89 and 4.26 [1H (1;2.3), dd, *J* = 12.1 and 4.5 Hz, H6″b], 4.77 and 5.17 [1H (1:2.3), m, H4″], 4.86 and 5.15 [1H (1:2.3), d, *J* = 9.9 Hz, H1″], 5.19 and 5.28 [1H (1:2.3), m, H3″], 5.78 and 5.93 [1H (1:2.3), t, H2″] 6.51 [1H, s, H3], 6.88 and 6.94 [1H (1:2.4), s, H8], 7.24 and 7.85 (each 2H, d, *J* = 8.3 and 9.1 Hz, *p*-substituted ArH), 7.57 (2H, m, Ph), 7.64–7.70 (1H, m, Ph), 8.23 and 8.31 [1H (2.3:1), d, *J* = 7.6 Hz, Ph]; FAB-MS (*m*/*z*) 761 $(M+H)^+$. Anal. Calcd for $C_{39}H_{36}O_{16}$: C, 61.58; H, 4.77. Found: C, 61.18; H, 4.64.

4.1.8. 5-Benzoyl-4′-hydroxy-6-*C*-(2″,3″,4″,6″-tetra-*O*-acetyl-β-D-glucopyranosyl)-7-methoxyflavone (11)

To a solution of **5** (55.6 mg, 0.0730 mmol) in CH_3CN (1.0 mL), TMG (23.0 mL, 0.183 mmol) was added dropwise at room temperature and the mixture was stirred for 3 h. To the reaction mixture, a saturated NH_4Cl aqueous solution (2.0 mL) was added, then the solution 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 **11** (42.0 mg, Y: 80%) as a pale-yellow solid.

$[\alpha]_D^{23}$ −21 (*c* 0.585, $CHCl_3$). IR (KBr): 3442, 2941, 1751, 1631, 1608, 1452, 1352, 1244, 1047, 837, 704 cm^{-1}. ^1H NMR ($CDCl_3$) was observed with a mixture of rotamers, δ 1.941, 1.958, 2.010, 2.036, 2.077, 2.087, 2.094 (12H, each s, OAc × 4), 3.73 and 3.79 [1H (1:2.4), m, H5″], 3.78 and 4.19 [1H (1:2.4), br d, *J* = 10.6 Hz, H6″a], 3.99, 4.03, and 4.09 [3H (1.8:1.0:3.3), s, OCH_3], 4.00 and 4.25 [1H (1:2.4), dd, *J* = 4.6 and 12.1 Hz, H6″b], 4.74 and 5.18 [1H (1:2.4), t, *J* = 9.8 Hz, H4″], 4.86 and 5.16 [1H (2.4:1), d, *J* = 9.9 Hz, H1″], 5.20 and 5.21 [1H (2.4:1), t, *J* = 9.9 Hz, H3″], 5.78 and 5.96 [1H (1:2.4), t, *J* = 9.8 Hz, H2″], 7.41 (1H, br s, 4′-OH), 6.27 and 6.34 [1H (1:2.4), s, H3], 6.78 (1H, s, H8), 7.58 (2H, m, Ph), 7.69 (1H, m, Ph), 8.25 and 8.33 [2H (1:2.4), d, *J* = 7.6 Hz, Ph]; FAB-MS (*m*/*z*) 719 $(M+H)^+$. Anal. Calcd for $C_{37}H_{34}O_{15}\cdot 1.5H_2O$: C, 59.59; H, 5.00. Found: C, 59.70; H, 4.60.

4.1.9. 5-Benzoyl-6-*C*-(2″,3″,4″,6″-tetra-*O*-acetyl-β-D-glucopyranosyl)-4′-*O*-(2‴,3‴,4‴,6‴-tetra-*O*-acetyl-β-D-glucopyranosyl)-7-methoxyflavone (12)

To a solution of **11** (47.3 mg, 0.0658 mmol) in quinoline (0.6 mL), Ag_2CO_3 (27.2 mg, 0.0987 mmol) and acetobromoglucose per-*O*-acetylglucosyl bromide (81.2 mg, 0.197 mmol) were added at 0 °C and the mixture was stirred at room temperature under a shielded light 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 (1 mL) was added, then the 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 residual solid was purified by silica-gel column chromatography (*n*-Hexane:AcOEt = 1:1–1:2) to afford **12** (55.2 mg, Y: 80%) as a white solid.

$[\alpha]_D^{23}$ −23 (*c* 0.515, $CHCl_3$). IR (KBr): 2941, 1755, 1647, 1612, 1508, 1454, 1367, 1232, 1045, 839, 706 cm^{-1}. ^1H NMR ($CDCl_3$) was observed with a mixture of rotamers, δ 1.822, 1.862, 1.954, 1.993, 2.029, 2.050, 2.061, 2.073, 2.077, 2.093 (24H, OAc × 8), 3.71, 3.77, and 3.91 (1H, m, H5″, H5‴), 3.99, 4.05, and 4.08 [3H (3.3:1.0:1.8), s, OCH_3], 5.20 and 5.31 (6H, m, H1‴, H2‴, H3″,3‴, H4″,4‴), 4.17–4.20 (2H, dd, *J* = 12.3 and 2.3 Hz, H6″a), 4.24–4.33 (2H, dd, *J* = 12.1 and 5.3 Hz, H6″b), 4.85 and 5.32 (1H, d, *J* = 9.9 Hz, H1″), 5.78 and 5.93 [1H (1:2.4), t, *J* = 9.1 Hz, H2″], 6.47 (1H, s, H3), 6.88 and 6.93 [1H (1:2.4), s, H8], 7.58 (2H, m, Ph), 7.68 (1H, m, Ph), 7.09 and 7.79 (each 2H, d, *J* = 9.1 Hz, *p*-substituted ArH), 8.23 and 8.30 [2H (2.4:1), d, *J* = 7.6 Hz, Ph]; FAB-MS (*m*/*z*) 1049 $(M+H)^+$. Anal. Calcd for $C_{51}H_{52}O_{24}$: C, 58.40; H, 5.00. Found: C, 58.54; H, 5.01.

4.1.10. Flavocommelin (1)

To a solution of **12** (24.0 mg, 0.0229 mmol) in MeOH, 28% NaOMe methanolic solution (ca. 50 mg) was added and the mixture was stirred at room temperature for 1 h. The reaction mixture was neutralized with Dowex® 50Wx8 (H^+), filtered and washed with MeOH, and evaporated to dryness. The residual solid was recrystallized from H_2O and CH_3CN to afford **1** (11.7 mg, Y: 84%) as a white solid.

Mp 209–210 °C (natural: 209–210 °C);[7] $[\alpha]_D^{21}$ −69 (*c* 0.33, H_2O) [natural: $[\alpha]_D^{24}$ −57.7 (*c* 0.3, H_2O)];[7] IR (KBr): 3400, 2923, 2889, 1655, 1608, 1508, 1491, 1448, 1350, 1244, 1203, 1074, 841, 659 cm^{-1}. ^1H NMR (DMSO-d_6) was observed with a mixture of rotamers, δ 3.15–3.12 (1H, m), 3.13–3.22 (3H, m), 3.27–3.34 (2H, m), 3.35–3.52 (3H, m), 3.68–3.72 (2H, m), 3.88 and 3.91 (3H, s, OCH_3), 4.00 and 4.18 (each 0.5H, m), 4.48 (1H, m), 4.60 (1H, t, *J* = 9.8 and 10.6 Hz), 4.63–4.68 (2H, m), 4.87 (1H, d, *J* = 4.5 Hz, OH), 4.90 (1H, m), 5.04 (1H, d, *J* = 6.8 Hz, H1‴), 5.11 (1H, d, *J* = 4.6 Hz, OH), 5.16 (1H, d, *J* = 4.6 Hz, OH), 5.43 (1H, d, *J* = 4.5 Hz, OH), 3.88 and 6.90 (each 0.5H, s, H3), 6.97 and 6.99 (each 0.5H, H8), 7.21 and 8.10 (each 2H, d, *J* = 9.1 and 8.3 Hz, *p*-substituted ArH), 13.41 and 13.43 (each 0.5H, s, OH); FAB-MS (*m*/*z*) 609 $(M+H)^+$. HRMS (ESI^+) calcd for $C_{28}H_{32}NaO_{15}$ 631.16389, found 631.16364.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.carres.2013.03.016.

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