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An effective synthesis of isoorientin: the regioselective synthesis of a 6-*C*-glucosylflavone

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Abstract

Isoorientin, a 6-*C*-β-D-glucopyranosyl-3′,4′,5,7-tetrahydroxyflavone, was synthesized in a 15% overall yield, in ten steps, starting from the commercially available phloroacetophenone. The *C*-glucosyl phloroacetophenone derivative, a synthetic intermediate that contains a free hydroxyl group that is para to the glucosyl moiety, was obtained by hydrogenolysis by taking advantage of differences in the hydrogenolysis rates between a benzyl protecting group and a 2-methylbenzyl protecting group. Aldol condensation of the *C*-glucosyl phloroacetophenone derivative with 3,4-bis-benzyloxybenzaldehyde afforded the corresponding chalcone as a precursor of the 6-*C*-glucosyl flavone. Construction of the flavone system by application of I_2–DMSO, followed by deprotection, yielded isoorientin.

Keywords: Isoorientin; 6-*C*-Glycosyl flavone; *C*-Glycosyl compound; 2-Methylbenzyl group; Hydrogenolysis

1. Introduction

C-Glycosyl flavones, which are plant constituents [1], are used as natural dyestuffs and many are biologically active. This is particularly true for 6-*C*-glycosyl flavones. For instance, UV-tolerant rice cultures show increased levels of 6-*C*-glycosyl flavones when subjected to UV irradiation [2]. Some 6-*C*-glycosyl flavones show hypotensive activity [3], and derivatives that contain a *trans*-caffeoyl group show cytotoxic activity against P388 lymphocytic leukemia cells [4]. It has been reported that 6″-*O*-glucosylisovitexin serves as a deterrent for the feeding of the fourth instar larvae of a butterfly, *Pieris napi oleracea*, indigenous to North America [5]. Further, it has also been shown that maysin and its derivatives, which are 6-*C*-glycosyl luteolins, have an extremely high antibiosis activity against the corn earworm, *Helicoverpa zea* [6]. In contrast to the growth inhibitor effects described above, some 6-*C*-glycosyl flavones, isolated from the rice plant, were found to act as probing stimulants for planthoppers. [7].

Reports of these biological activities encouraged us to attempt the synthesis of 6-*C*-glycosyl flavone derivatives. Several reports related to the synthesis of 6-*C*-glycosyl flavones have already appeared. Chopin and Dellamonica reported that the reaction of 5,7-dihydroxyflavones with glycosyl bromides afforded 6-*C*-glycosyl flavones, but in low yields

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[1a]. Schmidt and co-workers reported the synthesis of isovitexin, a 6-*C*-glucosyl flavone, as well as vitexin itself, which is 8-*C*-glucosyl flavone [8]. Unfortunately, their method was not regioselective, since the reaction involved the use of the Baker–Venkataraman rearrangement. Previously we reported that the synthesis of *C*-glycosyl phloroacetophenone, in conjunction with a regio- and stereoselective O→C glycosyl rearrangement [9]. However, the C-glycosylation reaction, as well as our method, involved a Fries-type O→C glycosyl rearrangement in which the glycosyl moiety is transferred from a hydroxyl group to an ortho position in the aglycon, and not to the para position. In order to synthesize a 6-*C*-glycosyl flavonoid exclusively and regioselectively, it is necessary to obtain a *C*-glycosyl phloroacetophenone derivative as a substrate in which the sugar moiety is positioned para to a free hydroxyl group in the phloroacetophenone aglycon. Therefore, considering the protection and deprotection techniques, after C-glycosylation, the selection of favorable protection groups for the phenolic hydroxyl groups is critical. In this paper we describe the effective regioselective synthesis of isoorientin, a 6-*C*-glucosyl flavone, using selective hydrogenolysis. Whereas isoorientin has been isolated from many sources, the pathway of its biosynthesis remains unclear. In this connection, a recent report of the relation between isoorientin and maysin, mentioned above, is noteworthy [10].

2. Results and discussion

Glucosyl acceptor **5** was synthesized first (Scheme 1). Selective protection of the commercially available phloroacetophenone with methoxymethyl chloride (MOMCl) afforded the partially O-protected phloroacetophenone derivative **2**. After the protection of a chelated phenolic hydroxyl group of **2** with benzyl chloride to afford compound **3**, deprotection, which involved the removal of both methoxymethyl groups of **3**, gave the mono benzyl-protected compound **4**. The selective protection of **4** with 2-methylbenzyl chloride then afforded glucosyl acceptor **5** in an overall yield of 71%, in four steps.

Based on our previous method, **5** was reacted with 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl fluoride [11] in the presence of boron trifluoride etherate to afford the *C*-glucosyl phloroacetophenone derivative **6** in 73% yield. The chelated phenolic hydroxyl group of **6** was protected with 2-methylbenzyl chloride to afford the fully protected *C*-glucoside **7**. The second 2-methylbenzyl group was chosen in order to achieve a selective deprotection at each ortho position of the aromatic acetyl group. Davis and Muchowski reported on the comparative hydrogenolysis rates of the benzyl group versus the 2-methylbenzyl group [12]. The latter group undergoes hydrogenolysis at a slower rate than the benzyl group. Because of this, the selective deprotection of the benzyl group in the aglycon of **7** by hydrogenolysis could be achieved using a catalytic amount of 10% palladium-on-charcoal under an atmosphere of H_2 to give **8**, which contains a hydroxyl group which is positioned para to the glucosyl moiety.

A hydroxyl group is important in the synthesis of the 6-*C*-glucosyl flavone. The aldol condensation of **8** and 3,4-bis-benzyloxybenzaldehyde afforded the chalcone derivative **9**, a precursor of the 6-*C*-glucosyl flavone. The individual structures of compounds **6**–**9** were confirmed by ^{1}H NMR spectra and ^{1}H–^{1}H COSY at elevated temperatures. The experiments were conducted at elevated temperature because the structural assignments by NMR spectroscopy at ambient temperature were hampered by the slow rotation around the C-1–aglycon bond. This is probably the result of the influence of both methyl groups in each of the two protecting groups around the glucose moiety. Thus, the ^{1}H NMR spectra of the compounds **7**–**9** were carried out at a temperature of 180 °C. As a result, the signals of **7** and **8** in the ^{1}H NMR spectra became clear at 180 °C, but those of chalcone derivative **9** did not. We speculate that this is due to steric hindrance between the glucosyl moiety and the 2-methylbenzyl groups at both ortho positions, as well as steric interactions between the cinnamoyl group and the 2-methylbenzyl group.

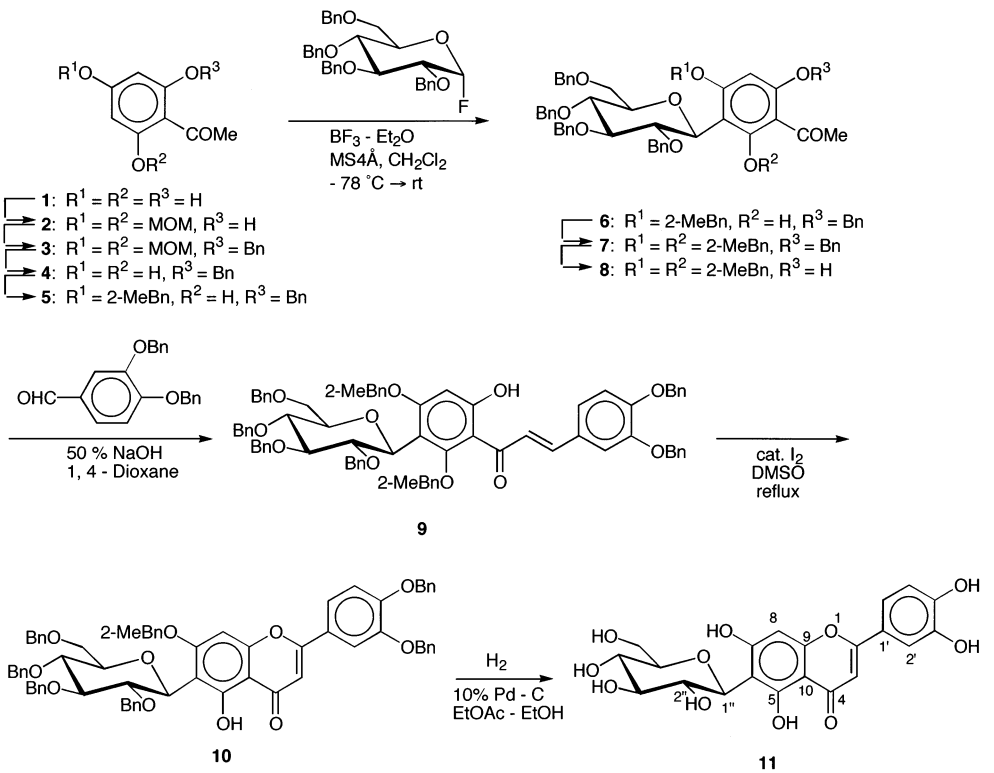
Normally, selenium dioxide is used as a reagent for the oxidative cyclization of 2′-hy-

droxylchalcone to the corresponding flavone. Because chalcone **9** contains two 2-methylbenzyl groups, the method using a catalytic amount of iodide in dimethyl sulfoxide [13] was chosen for this cyclization in order to avoid oxidation of the methyl groups in the protection groups. Chalcone **9** was oxidized, followed by cleavage of a 2-methybenzyl protection group positioned ortho to the cinnamoyl group, to subsequently afford flavone **10**. This oxidative cyclization was accomplished in a short time. Finally, all protection groups on **10** were removed by hydrogenolysis with a catalytic amount of 10% palladium-on-charcoal under an atmosphere of H_2 to afford the desired **11** [14] (Scheme 1).

3. Experimental

General methods.—All nonaqueous reactions were carried out under an atmosphere of anhyd argon using freshly distilled solvents, unless otherwise noted. All reactions were monitored by thin-layer chromatography (TLC), which was carried out on 0.25 mm E. Merck Silica Gel 60 F_{254} plates using either UV light for visualization, a 5% ethanolic solution of ferric chloride, or a 5% ethanolic solution of phosphomolybdic acid, followed by heating, as developing agents. Wakogel C-300® (particle size 0.045–0.075 mm) was used for column chromatography. Melting points are uncorrected. Optical rotations were recorded using $CHCl_3$ or EtOH as solvents on a JASCO DIP-370 digital polarimeter. IR spectra were recorded on a Horiba FT-200 IR spectrometer as KBr pellets or films on a NaCl plate. Mass spectra were recorded on a JEOL JMS-AX-505-HA mass spectrometer under electron ionization (EI) conditions or under fast-atom bombardment (FAB) conditions using 3-nitrobenzyl alcohol as the matrix. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian INOVA 500 instrument using Me_4Si as the internal reference.

2 - Hydroxy - 4,6 - bis(methoxymethyloxy)-acetophenone (**2**).—To a suspended soln of phloroacetophenone (13.0 g, 77.3 mmol) in CH_2Cl_2 (130 mL) at 0 °C, *N*,*N*-diisopropylethylamine (28.2 mL, 164 mmol, 2.1 equiv) was added, and the mixture was stirred for 15 min. Methoxymethyl chloride (15.4 mL,



Scheme 1.

162 mmol, 2.1 equiv) was then added dropwise at 0 °C, and the mixture was stirred for 15 min, after which time the temperature was increased to rt with stirring over a 45-min period. The reaction mixture was then poured into water and extracted with $CHCl_3$. The organic layer was washed with water and brine, followed by drying over anhyd $MgSO_4$. The solvent was evaporated under reduced pressure, and the resulting syrup was chromatographed on a silica gel column (10:1 hexane–EtOAc) to give colorless prismatic crystals **2** (16.7 g, 84%). Compound **2** was recrystallized from hexane–Et_2O: mp 42 °C; R_f 0.27 (10:1 hexane–EtOAc); IR (KBr): 1618, 1593, 1269, 1151, 1065 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.66 (s, 3 H, ArAc), 3.47 (s, 3 H, –OMe), 3.52 (s, 3 H, –OMe), 5.17 (s, 2 H, methylene), 5.26 (s, 2 H, methylene), 6.24 (d, 1 H, *J* 2.4 Hz, ArH), 6.27 (d, 1 H, *J* 2.4 Hz, ArH), 13.72 (s, 1 H, ArOH); EIMS: *m*/*z* 256 $[M]^+$. Anal. Calcd for $C_{12}H_{16}O_6$: C, 56.25; H, 6.29. Found: C, 56.34; H, 6.39.

2-Benzyloxy-4,6-bis(methoxymethyloxy)acetophenone (**3**).—A mixture of **2** (16.6 g, 65.0 mmol), benzyl chloride (9.00 mL, 78.0 mmol, 1.2 equiv), and anhyd K_2CO_3 (13.5 g, 97.5 mmol, 1.5 equiv) in DMF (100 mL) was stirred for 3 h at 80 °C. The reaction mixture was poured into water (500 mL) and extracted with $CHCl_3$. The extract was washed with water and brine, followed by drying over anhyd $MgSO_4$. The solvent was evaporated under reduced pressure, and the resulting syrup was chromatographed on a silica gel column (5:1 hexane–EtOAc) to give **3** (18.3 g, quant). Recrystallization from hexane–Et_2O afforded colorless prismatic crystals: mp 64–65 °C; R_f 0.22 (5:1 hexane–EtOAc); IR (KBr): 1689, 1605, 1589, 1232, 1147, 1118, 1074, 1061, 1024 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.48 (s, 3 H, ArAc), 3.461 (s, 3 H, –OMe), 3.463 (s, 3 H, –OMe), 5.06 (s, 2 H, benzylic CH_2), 5.13 (s, 2 H, methylene), 5.14 (s, 2 H, methylene), 6.38 (d, 1 H, *J* 2.0 Hz, ArH), 6.47 (d, 1 H, *J* 2.0 Hz), 7.26–7.39 (m, 5 H, ArH); EIMS: *m*/*z* 346 $[M]^+$. Anal. Calcd for $C_{19}H_{22}O_6$: C, 65.88; H, 6.40. Found: C, 66.11; H, 6.54.

2-Benzyloxy-4,6-dihydroxyacetophenone (**4**).—To **3** (22.6 g, 65.3 mmol), suspended in MeOH (420 mL), 2 M HCl (60 mL) was added. The soln was refluxed for 1 h, whereupon it gradually became clear, after which **4** precipitated as crystals. After refluxing, the reaction mixture was cooled. Compound **4** was isolated on a filter and washed with water (16.9 g, quant): mp 245–246 °C; R_f 0.50 (2:1 hexane–EtOAc); IR (KBr): 3140, 1626, 1560, 1288, 1165, 1105 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.53 (s, 3 H, ArAc), 5.07 (s, 2 H, benzylic CH_2), 6.01 (d, 1 H, *J* 2.2 Hz, ArH), 6.05 (d, 1 H, *J* 2.2 Hz, ArH), 7.34–7.44 (m, 5 H, ArH), 9.80 (s, 1H, ArOH), 13.96 (s, 1 H, ArOH); EIMS: *m*/*z* 258 $[M]^+$. Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.70; H, 5.39.

2-Benzyloxy-6-hydroxy-4-(2-methylbenzyloxy)acetophenone (**5**).—To a stirred soln of **4** (5.00 g, 19.4 mmol) and anhyd K_2CO_3 (2.81 g, 20.3 mmol, 1.05 equiv) in DMF (50 mL) at 0 °C, 2-methylbenzyl chloride (2.86 g, 20.3 mmol, 1.05 equiv) was added. After 10 min, the mixture was allowed to warm to rt, and it was stirred for 12 h. The reaction mixture was poured into 1 M HCl (500 mL) and extracted with EtOAc. The organic layer was washed with water and brine, and then dried over anhyd $MgSO_4$. The solvent was evaporated under reduced pressure. The residue was chromotographed on a silica gel column (10:1 hexane–EtOAc), and then recrystallized from hexane–EtOAc to afford colorless prismatic crystals **5** (5.86 g, 84%): mp 95 °C; R_f 0.28 (10:1 hexane–EtOAc); IR (KBr): 1618, 1591, 1365, 1267, 1225, 1161, 1115 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.36 (s, 3 H, ArMe), 2.56 (s, 3 H, ArAc), 5.04 (s, 2 H, benzylic CH_2), 5.06 (s, 2 H, benzylic CH_2), 6.09 (d, 1 H, *J* 2.3 Hz, ArH), 6.20 (d, 1 H, *J* 2.3 Hz, ArH), 7.21–7.42 (m, 9 H, ArH), 14.05 (s, 1 H, ArOH); EIMS: *m*/*z* 362 $[M]^+$. Anal. Calcd for $C_{23}H_{22}O_4$: C, 76.22; H, 6.12. Found: C, 76.22; H, 6.12.

*6-Benzyloxy-2-hydroxy-4-(2-methylbenzyloxy)-3-(2,3,4,6-tetra-*O*-benzyl-β-*D*-glucopyranosyl)acetophenone* (**6**).—To a stirred mixture of **5** (8.01 g, 22.1 mmol, 3 equiv), 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl fluoride (4.00 g, 7.4 mmol), and powdered 4 Å molecular sieves (8 g) in CH_2Cl_2 (200 mL) at −78 °C, $BF_3{\cdot}Et_2O$ (1.90 mL, 15.5 mmol, 2.1 equiv) was added dropwise, and the mixture was stirred for 30 min. The temperature was allowed to

gradually increase to −42 °C, and the stirring was continued for 30 min, then to −20 °C for 1 h, and finally to rt for 1 h. After adding water, the resulting mixture was filtered through a Celite® pad. The filtrate was extracted with $CHCl_3$, and the organic layer was dried over anhyd $MgSO_4$. The solvent was evaporated under reduced pressure, and the resulting syrup was chromatographed on a silica gel column (5:1 hexane–EtOAc) to give **6** (4.88 g, 75%) as a colorless highly viscous oil: $[\alpha]_D^{22}$ −16° (*c* 1.00, $CHCl_3$); R_f 0.30 (5:1 hexane–EtOAc); IR (NaCl): 3030, 2864, 1621, 1593, 1430, 1360, 1273, 1165, 1097, 1066 cm^{-1}; ^1H NMR (Me_2SO-d_6 at 140 °C): δ 2.31 (s, 3 H, ArMe), 2.53 (s, 3 H, ArAc), 3.41–3.46 (m, 2 H, H-4′, 5′) 3.57 (dd, 1 H, *J* 4.5, 10.4 Hz, H-6′a), 3.62 (dd, 1 H, *J* 8.4, 8.8 Hz, H-3′), 3.65 (d, 1 H, *J* 10.4 Hz, H-6′b), 4.15 (d, 1 H, *J* 11.4 Hz, benzylic CH_2), 4.29 (dd, 1 H, *J* 8.8, 9.8 Hz, H-2′), 4.41 (d, 1 H, *J* 11.4 Hz, benzylic CH_2), 4.42 (d, 1 H, *J* 12.4 Hz, benzylic CH_2), 4.47 (d, 1 H, *J* 12.4 Hz, benzylic CH_2), 4.55 (d, 1 H, *J* 11.3 Hz, benzylic CH_2), 4.70 (d, 1 H, *J* 11.3 Hz, benzylic CH_2), 4.73 (d, 1 H, *J* 11.7 Hz, benzylic CH_2), 4.77 (d, 1 H, *J* 11.7 Hz, benzylic CH_2), 4.82 (d, 1 H, *J* 9.8 Hz, H-1′), 5.12 (d, 1 H, *J* 12.5 Hz, benzylic CH_2), 5.14 (d, 1 H, *J* 12.5 Hz, benzylic CH_2), 5.26 (d, 1 H, *J* 12.5 Hz, benzylic CH_2), 5.28 (d, 1 H, *J* 12.5 Hz, benzylic CH_2), 6.42 (s, 1 H, ArH), 6.87–7.47 (m, 29 H, ArH), 13.70 (br. s, 1 H, ArOH); FABMS (negative ion): *m*/*z* 883 $[M-H]^-$. Anal. Calcd for $C_{57}H_{56}O_9 \cdot 2.5H_2O$: C, 73.60; H, 6.38. Found: C, 73.41; H, 6.18.

*6-Benzyloxy-2,4-bis(2-methylbenzyloxy)-3-(2,3,4,6-tetra-*O*-benzyl-β-*D*-glucopyranosyl)-acetophenone* (**7**).—A mixture of **6** (4.53 g, 5.11 mmol), anhyd K_2CO_3 (1.06 g, 7.66 mmol, 1.5 equiv), and 2-methylbenzyl chloride (862 mg, 6.13 mmol, 1.2 equiv) in DMF (120 mL) was stirred for 3 h at 80 °C. The reaction mixture was poured into 1 M HCl (500 mL) and extracted with EtOAc. The organic layer was washed with water and brine, and then dried over anhyd $MgSO_4$. The solvent was evaporated under reduced pressure, and the resulting syrup was chromatographed on a silica gel column (8:1 hexane–EtOAc) to afford **7** (5.11 g, quant) as a colorless highly viscous oil: $[\alpha]_D^{22}$ −18° (*c* 1.00, $CHCl_3$); R_f 0.35 (5:1 hexane–EtOAc); IR (NaCl): 3030, 2866, 1701, 1597, 1454, 1350, 1257, 1159, 1099 cm^{-1}; ^1H NMR (Me_2SO-d_6 at 180 °C): δ 2.20 (s, 3 H, ArMe), 2.29 (s, 3 H, ArMe), 2.33 (s, 3 H, ArAc), 3.30–3.62 (m, 2 H, H-4′, 5′) 3.49 (dd, 1 H, *J* 5.0, 11.2 Hz, H-6′a), 3.53 (dd, 1 H, *J* 8.3, 8.5 Hz, H-3′), 3.63 (dd, 1 H, *J* 2.0, 11.2 Hz, H-6′b), 4.14 (d, 1 H, *J* 11.1 Hz, benzylic CH_2), 4.35 (dd, 1 H, *J* 8.5, 9.7 Hz, H-2′), 4.40 (s, 2 H, benzylic CH_2), 4.41 (d, 1 H, *J* 11.1 Hz, benzylic CH_2), 4.48 (d, 1 H, *J* 11.5 Hz, benzylic CH_2), 4.64 (d, 1 H, *J* 11.5 Hz, benzylic CH_2), 4.69 (d, 1 H, *J* 11.7 Hz, benzylic CH_2), 4.72 (d, 1 H, *J* 9.7 Hz, H-1′), 4.73 (d, 1 H, *J* 11.7 Hz, benzylic CH_2), 4.79 (d, 1 H, *J* 11.5 Hz, benzylic CH_2), 5.02 (d, 1 H, *J* 11.5 Hz, benzylic CH_2), 5.07 (d, 1 H, *J* 12.0 Hz, benzylic CH_2), 5.10 (d, 1 H, *J* 12.0 Hz, benzylic CH_2), 5.15 (d, 1 H, *J* 12.8 Hz, benzylic CH_2), 5.17 (d, 1 H, *J* 12.8 Hz, benzylic CH_2), 6.71 (s, 1 H, ArH), 6.88–7.44 (m, 33 H, ArH); FABMS (negative ion): *m*/*z* 988 $[M-H]^-$. Anal. Calcd for $C_{65}H_{64}O_9 \cdot 0.5H_2O$: C, 78.21; H, 6.56. Found: C, 78.00; H, 6.52.

*6-Hydroxy-2,4-bis(2-methylbenzyloxy)-3-(2,3,4,6-tetra-*O*-benzyl-β-*D*-glucopyranosyl)-acetophenone* (**8**).—A soln of **7** (1.041 g 1.05 mmol) and 10% palladium-on-charcoal (52 mg) in EtOAc (50 mL) was stirred at rt for a total of 2 h under an atmosphere of H_2, and the progress of the reaction was monitored by TLC. After filtering, the filtrate was concentrated under reduced pressure, and the residue was chromatographed on a silica gel column (8:1 hexane–EtOAc) to give **8** (380 mg, 40%) as a colorless highly viscous oil: $[\alpha]_D^{22}$ +10° (*c* 1.00, $CHCl_3$); R_f 0.48 (5:1 hexane–EtOAc); IR (NaCl): 3030, 2862, 1614, 1581, 1454, 1362, 1267, 1176, 1095, 1063 cm^{-1}; ^1H NMR (Me_2SO-d_6 at 180 °C): δ 2.17 (s, 3 H, ArMe), 2.34 (s, 3 H, ArMe), 2.39 (s, 3 H, ArAc), 3.27–3.34 (m, 2 H, H-4′, 5′) 3.46 (dd, 1 H, *J* 4.7, 11.0 Hz, H-6′a), 3.52 (dd, 1 H, *J* 8.3, 9.0 Hz, H-3′), 3.61 (d, 1 H, *J* 11.0 Hz, H-6′b), 4.18 (d, 1 H, *J* 11.4 Hz, benzylic CH_2), 4.34 (dd, 1 H, *J* 8.3, 9.0 Hz, H-2′), 4.39 (s, 2 H, benzylic CH_2), 4.44 (d, 1 H, *J* 11.4 Hz, benzylic CH_2), 4.47 (d, 1 H, *J* 11.7 Hz, benzylic CH_2), 4.63 (d, 1 H, *J* 11.7 Hz, benzylic CH_2), 4.68 (d, 1 H, *J* 11.7 Hz, benzylic CH_2), 4.72 (d, 1 H, *J* 9.0 Hz, H-1′), 4.73 (d, 1 H, *J* 11.7 Hz, benzylic

CH_2), 4.85 (d, 1 H, *J* 12.1 Hz, benzylic CH_2), 5.08 (d, 1 H, *J* 12.1 Hz, benzylic CH_2), 5.10 (d, 1 H, *J* 12.8 Hz, benzylic CH_2), 5.13 (d, 1 H, *J* 12.8 Hz, benzylic CH_2), 6.50 (s, 1 H, ArH), 6.90–7.46 (m, 28 H, ArH), 11.34 (br. s, 1 H, ArOH); FABMS (negative ion): *m/z* 897 $[M-H]^-$. Anal. Calcd for $C_{58}H_{58}O_9 \cdot H_2O$: C, 75.96; H, 6.59. Found: C, 75.72; H, 6.39.

*3,4-Dibenzyloxy-6′-hydroxy-2′,4′-bis(2-methybenzyloxy)-3′-(2,3,4,6-tetra-*O*-benzyl-β-*D*-glucopyranosyl)chalcone* (**9**).—A soln of **8** (380 mg 0.42 mmol) and 3,4-dibenzyloxybenzaldehyde (148 mg, 0.47 mmol) in 1,4-dioxane (10 mL), and a 50 wt.% aq soln of NaOH (10 mL) was added. The mixture was then stirred vigorously at rt for 24 h. The mixture was poured into 1 M HCl and extracted with EtOAc, and then washed with water and brine. The organic layer was dried over anhyd $MgSO_4$ and then evaporated under reduced pressure. The residual orange syrup was chromatographed on a silica gel column (6:1 hexane–EtOAc) to afford **9** (463 mg, 91%) as a highly viscous, orange oil: $[\alpha]_D^{22}$ +65° (*c* 1.00, $CHCl_3$); R_f 0.53 (3:1 hexane–EtOAc); IR (NaCl): 3030, 2866, 1738, 1622, 1556, 1504, 1454, 1257, 1167, 1138, 1095, 1066 cm^{-1}; ^1H NMR (Me_2SO-d_6 at 160 °C): δ 2.02, 2.06 (each s, 3 H, ArMe, ratio 1:3), 2.31, 2.34 (each s, 3 H, ArMe), 6.61, 6.65 (each s, 1 H, ArH), 11.60, 11.93 (each s, 1 H, ArOH); ^1H NMR (Me_2SO-d_6 at 180 °C): δ 2.07 (s, 3 H, ArMe), 2.35 (s, 3 H, ArMe), 6.57 (s, 1 H, ArH), 11.55 (br. s, 1 H, ArOH); FABMS (negative ion): *m/z* 1198 $[M-H]^-$. Anal. Calcd for $C_{79}H_{74}O_{11} \cdot H_2O$: C, 77.93; H, 6.29. Found: C, 77.88; H, 6.20.

*2-(3,4-Bisbenzyloxyphenyl)-5-hydroxy-7-(2-methybenzyloxy)-6-(2,3,4,6-tetra-*O*-benzyl-β-*D*-glucopyranosyl)-4*H*-1-benzopyran-4-one* (**10**).—A soln of **9** (447 mg 0.37 mmol) and iodine (4.7 mg, 0.02 mmol, 0.05 equiv) in Me_2SO (4.5 mL) was stirred at 200 °C for 15 min. The mixture was poured into water, and the resulting soln extracted with EtOAc. The organic phase was then washed with sodium thiosulfate soln, water and brine. The organic layer was dried over anhyd $MgSO_4$, and the solvent was then evaporated under reduced pressure. The residual syrup was chromatographed on a silica gel column (3:1 hexane–EtOAc) to afford **10** (306 mg, 76%) as a yellow oil. Recrystallization from hexane–ether afforded pale yellow crystals: mp 95–96 °C; $[\alpha]_D^{22}$ −10° (*c* 0.10, $CHCl_3$); R_f 0.28 (3:1 hexane–EtOAc); IR (KBr): 3030, 2862, 1653, 1614, 1495, 1454, 1350, 1265, 1178, 1140, 1103, 1068 cm^{-1}; ^1H NMR (Me_2SO-d_6 at 160 °C): δ 2.36 (s, 3 H, ArMe), 3.41–3.70 (m, 5 H, H-3″, 4″, 5″, 6‴a, 6‴b), 4.19 (d, 1 H, *J* 11.7 Hz, benzylic CH_2), 4.37 (dd, 1 H, *J* 9.4, 9.8 Hz, H-2‴), 4.43 (d, 1 H, *J* 12.4 Hz, benzylic CH_2), 4.46 (d, 1 H, *J* 11.7 Hz, benzylic CH_2), 4.48 (d, 1 H, *J* 12.4 Hz, benzylic CH_2), 4.57 (d, 1 H, *J* 11.4 Hz, benzylic CH_2), 4.72 (d, 1 H, *J* 11.4 Hz, benzylic CH_2), 4.75 (d, 1 H, *J* 11.7 Hz, benzylic CH_2), 4.78 (d, 1 H, *J* 11.7 Hz, benzylic CH_2), 4.90 (d, 1 H, *J* 9.8 Hz, H-1‴), 5.22 (s, 2 H, benzylic CH_2), 5.24 (s, 2 H, benzylic CH_2), 5.25 (s, 2 H, benzylic CH_2), 6.75–7.68 (m, 34 H, vinyl proton and ArH), 13.29 (br. s, 1 H, ArOH); FABMS (positive ion): *m/z* 1094 $[M+H]^+$. Anal. Calcd for $C_{71}H_{64}O_{11}$: C, 78.00; H, 5.90. Found: C, 77.90; H, 5.85.

Isoorientin (**11**).—A soln of **10** (50 mg) and 10% palladium-on-charcoal (10 mg) in EtOAc (2 mL) and EtOH (2 mL) was stirred at rt for 4.5 h under an atmosphere of H_2. After filtering, the filtrate was concentrated under reduced pressure to give **11** (21 mg quant) as a pale yellow–green powder: mp 237–239 °C; $[\alpha]_D^{22}$ +30° (*c* 0.50, EtOH) [15]; R_f 0.55 (25:35:5:1 Me_2CO–EtOAc–H_2O–AcOH); IR (KBr): 3390, 1650, 1619, 1578, 1491, 1450, 1356, 1302, 1267, 1119, 1082 cm^{-1}; ^1H NMR (Me_2SO-d_6) [14]: δ 3.12 (dd, 1 H, *J* 8.5, 8.9 Hz, H-4″), 3.17 (ddd, 1 H, *J* 1.8, 6.1, 8.9 Hz, H-5″), 3.19 (dd, 1 H, *J* 8.5, 10.2 Hz, H-3″), 3.40 (dd, 1 H, *J* 6.1, 11.3 Hz, H-6″a), 3.68 (dd, 1 H, *J* 1.8, 11.3 Hz, H-6″b), 4.07 (dd, 1 H, *J* 9.8, 10.2 Hz, H-2″), 4.48 (br. s, 1 H, OH), 4.58 (d, 1 H, *J* 9.8 Hz, H-1‴), 4.62 (br. s, 1 H, OH), 4.86 (br. s, 2 H, OH), 6.48 (s, 1 H, ArH), 6.67 (s, 1 H, H-3), 6.89 (d, 1 H, *J* 8.2 Hz, H-5′), 7.40 (d, 1 H, *J* 2.3 Hz, H-2′), 7.42 (dd, 1 H, *J* 2.3, 8.2 Hz, H-6′), 9.42 (br. s, 1 H, ArOH), 9.87 (br. s, 1 H, ArOH), 10.57 (br. s, 1 H, ArOH), 13.57 (s, 1 H, ArOH); ^{13}C NMR (Me_2SO-d_6) [14]: δ 61.4 (C-6″), 70.2 (C-4″), 70.5 (C-2″), 73.0 (C-1″), 78.9 (C-3″), 81.4 (C-5″), 93.4 (C-8), 102.7 (C-3), 103.3 (C-10),

108.8 (C-6), 113.2, (C-2′) 116.0 (C-5′), 118.8 (C-6′), 121.4 (C-1′), 145.7 (C-3′), 149.6 (C-4′), 156.1 (C-9), 160.6 (C-5), 163.2 (C-7), 163.6 (C-2), 181.7 (C-4); FABMS (positive ion): m/z 449 $[M+H]^+$. Anal. Calcd for $C_{21}H_{20}O_{11}\cdot 1.5\ H_2O$: C, 53.06; H, 4.74. Found: C, 52.79; H, 4.74.

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