Practical Synthesis of a *C*-Glycosyl Flavonoid via *O*→*C* Glycoside Rearrangement

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The *C*-glycosylation of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl fluoride and 2-acetylphloroglucinol 3,5-bis(alkyl ether) in the presence of boron trifluoride etherate as an activator stereoselectively gave the β-*C*-glucoside in a good yield via *O*→*C* glycoside rearrangement. Subsequently, aldol condensation of the *C*-glucoside with benzaldehyde afforded the corresponding β-*C*-glucosyl chalcone in a good yield.

The naturally-occurring glycosyl flavonoids so far isolated have been mostly *O*-glycosides. Recently, *C*-glycosyl flavonoids with β-anomeric stereochemistry have been isolated from plants.[1a,b] Some of these show biological activities such as DNA binding activity[2] and hypotensive activity.[3] The synthesis of *C*-glycosyl flavonoids has also been achieved mainly by Friedel–Crafts-type reactions or Koenigs–Knorr glycosylations. However, yields were poor due to steric hindrance of the substrates.[1a] Especially, flavonoids possessing a phloroglucinol skeleton as the A-ring, such as hemiphloin,[4] 6-*C*-glucosyl dihydrokaempferol,[5] and nothofagin,[6] are expected to be even more hindered. An efficient and applicable synthetic method for these hindered compounds has not been developed yet.[1a,7,8]

Recently, a new simple aryl *C*-glycosylation method via *O*→*C* glycoside rearrangement was developed by Suzuki and coworkers,[9] in which excellent regio- and β-stereoselectivity and high yields are achievable.

We attempted to apply this method to the synthesis of a *C*-glucosyl flavonoid possessing a *C*-glucosyl phloroglucinol moiety, and the results are described in this paper.

Results and Discussion

For simple and practical synthesis of the *C*-glucosyl flavonoid, two methods are possible; 1) a chalcone synthesis followed by *C*-glycosylation and 2) aldol condensation of the *C*-glucoside with benzaldehyde (see Scheme 2). The problems associated with the latter synthetic plan are as follows; 1) selective protection/deprotection of the phenolic hydroxyl, 2) *C*-glycosylation conditions via *O*→*C* glycoside rearrangement, and 3) aldol condensation of the *C*-glucoside. To determine the most appropriate *C*-glycosylation conditions, we initially prepared eight phloroglucinol derivatives as glycosyl acceptors as follows; phloroglucinol derivatives; diacetate **1** by deacetylation of phloroglucinol triacetate with aqueous $NaHCO_3$ solution, bis(methyl ether) **2** by regioselective methylation with diazomethane, and 2-acetylphloroglucinol derivatives; 3,5-bis(methyl ether) **3**, 3,5-bis(benzyl ether) **4**, 3-acetate 5-methyl ether **5**, 3-benzyl 5-methyl ether **6**, and 1,3-bis(benzyl ether) **7** which were prepared by deacetylation with aqueous $NaHCO_3$ solution or regioselective methylation with diazomethane or regioselective debenzylation with boron trifluoride etherate (BF_3·OEt_2), or by their combination, respectively, in moderate yields (Fig. 1).

Among the possible Lewis acids originally proposed by Suzuki et al., we selected BF_3·OEt_2 for its ready availability and low price. First, we examined the glycosylation of two phloroglucinol derivatives (**1** and **2**) by using 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl fluoride (**8**) and 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl fluoride (**9**)[10] as glycosyl donors (see Table 1).

Glycosylation using phloroglucinol diacetate **1** as an acceptor afforded *O*-glucoside predominantly in a good yield (Entries 1 and 2).[11] The reaction using benzyl-protected glucosyl fluoride **9** as a donor afforded α-*O*-glucoside stereoselectively (Entry 2). Further, the reaction using bis(methyl ether) **2** afforded α-*O*- and β-*C*-glucosides (**12** and **13**) in a total 84% yield. Although Suzuki et al. obtained the *C*-glucoside in a good yield when using resorcinol monoacetate as an acceptor,[9e] the *C*-glucoside could not be obtained when

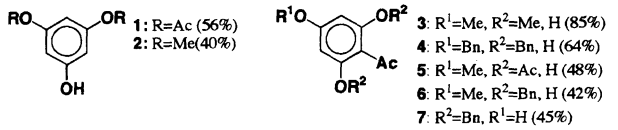
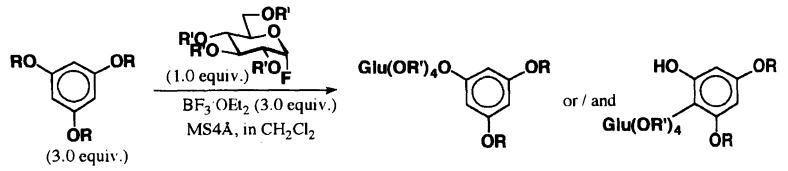


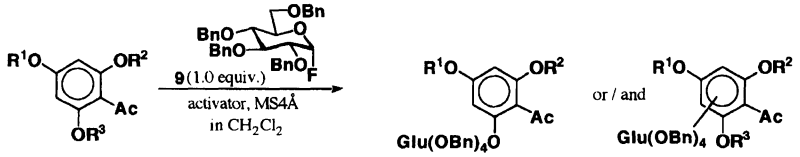
Fig. 1.

Table 1. Glycosylation of Phloroglucinol Derivatives



Entry	Acceptor R	Donor R′	Temp °C	Product (Yield; %) *O*-Glu. (α : β)	*C*-Glu. (β)
1	Ac Ac H (**1**)	Ac (**8**)	R.T.	**10**α,**10**β (37 : 51)	0
2	Ac Ac H (**1**)	Bn (**9**)	−20	**11** (95 : 0)	0
3	Me Me H (**2**)	Bn (**9**)	−20→R.T.	**12** (30 : 0)	**13** (54)

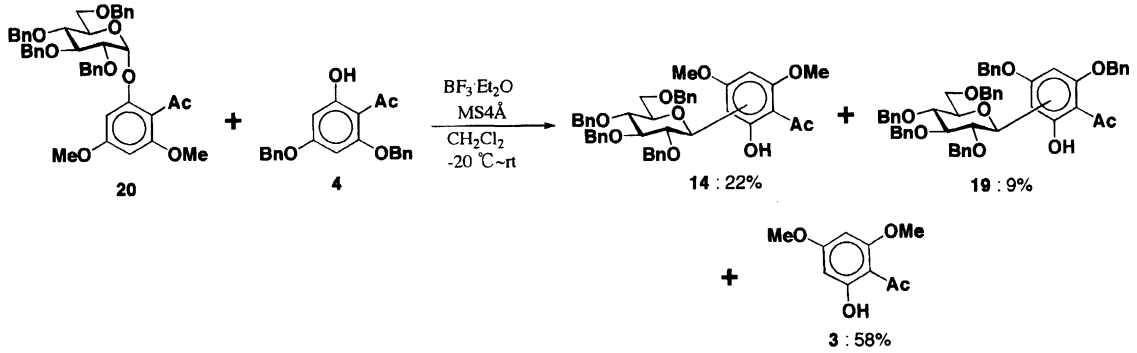
Table 2. Glycosylation of 2-Acetylphloroglucinol Derivatives



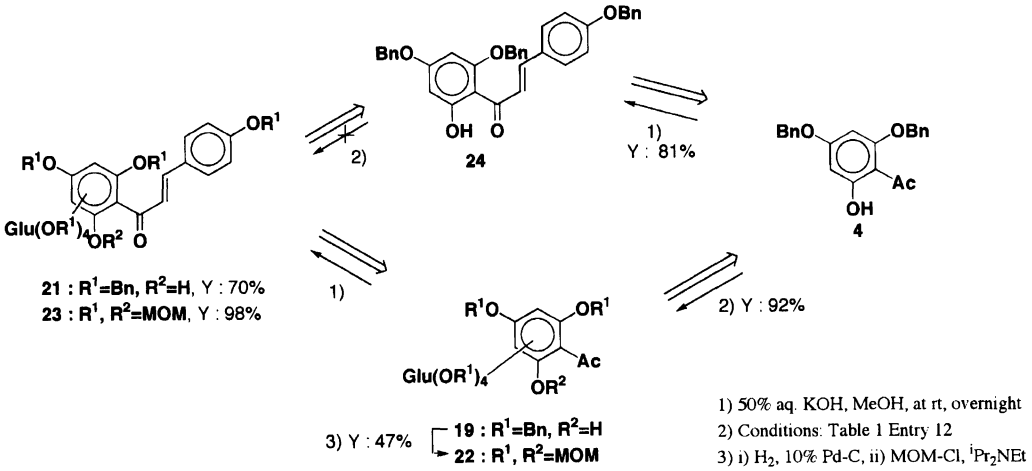
Entry	Acceptor R^1	R^2	R^3		(equiv)	Activator (equiv)		Temp °C	Product (Yield;%) *O*-Glu.(α)	*C*-Glu.(β)
1	Me	Me	H	(**3**)	(3.0)	BF_3·OEt_2	(2.0)	−20→−10	(0)	**14** (54)
2					(3.0)		(2.0)	−78→R.T.	(0)	(87)
3					(3.0)		(3.0)	−78→−10	(0)	(92)
4					(2.0)	Cp_2ZrCl_2	(3.0)	−20	(0)	(57)
						$AgClO_4$	(5.0)			
5					(3.0)		(1.0)	−78→0	(0)	(43)
							(2.0)			
6	Me	Ac	H	(**5**)	(3.0)	BF_3·OEt_2	(2.0)	−20→R.T.	**15** (52)	(0)
7	Me	Bn	H	(**6**)	(3.0)		(2.0)	−20→R.T.	**16** (15)	**17** (26)
8					(3.0)		(2.0)	−78→R.T.	(0)	(78)
9	H	Bn	Bn	(**7**)	(3.0)		(3.0)	−20→−10	**18** (42)	(0)
10					(3.0)			−78→−5	(58)	(0)
11					(3.0)	Cp_2ZrCl_2	(2.0)	−20→−10	(31)	(0)
						$AgClO_4$	(4.0)			
12	Bn	Bn	H	(**4**)	(3.0)	BF_3·OEt_2	(3.0)	−20→R.T.	(0)	**19** (92)

using phloroglucinol diacetate as an acceptor. It was found that these glycosylation conditions required both an *O*-alkyl protecting acceptor and donor for synthesizing the *C*-glucoside. Further, the resulting β-*C*-glucoside is presumed to be substituted at the position *ortho* to the hydroxyl group, since two doublet signals due to two aromatic protons were observed at 6.06 and 6.15 ppm in the ^{1}H NMR spectrum.

Based on these results, we next examined glycosylation using 2-acetyl phloroglucinol derivatives as glycosyl acceptors (see Table 2). Fluoride **9** was employed as a glycosyl donor and 2-acetylphloroglucinol methyl and/or benzyl ethers (**3**, **4**, **6**, and **7**) were employed as glycosyl acceptors. When there was a free hydroxyl group *ortho* to the acetyl group, the glycosylation reaction gave the *C*-glucoside predominantly (Entries 1—5). Especially, using BF_3·OEt_2 as an activator (Entries 2 and 3), the reaction afforded the *C*-glucoside in good yields (87 and 92%). Since the *C*-glucoside shows a dark brown color with $FeCl_3$ and the *O*-glucoside shows no color, we could discriminate the *O*-glucoside and *C*-glucoside on TLC. It was shown that the *O*-glucoside was initially yielded as a main product at −78 or −20 °C. When the reaction temperature was gradually warmed up to 0 °C or room temperature, the *C*-glucoside appeared.[9d] When the warming time of the reaction was short, some *O*-glucoside still remained. The reaction using Suzuki's activator, the combination of zirconocene (Cp_2ZrCl_2) and silver perchlorate ($AgClO_4$), did not give the *C*-glucoside in an excellent yield (Entries 4 and 5).[12] The glycosylation reaction using 2-acetylphloroglucinol monomethyl ether monoacetate **5** as an acceptor yielded the *O*-glucoside predominantly (Entry 6), with the same result obtained in Table 1. By using bis(benzyl ether) **4** or methyl benzyl ether **6** as an acceptor (Entries 12 and 8), the reac-



Scheme 1. Cross-over experiment of the glycoside rearrangement.



Scheme 2.

tion gave only the *C*-glucoside in good yields (92 and 78%), similar to the case of bis(methyl ether) **3**. The resulting *C*-glucoside was a mixture of *ortho*- and *para*-positioned regioisomers of the free hydroxyl group in a ratio of ca. 1 : 1, from the observation of two singlets of an aromatic proton and a hydroxyl group at 5.98 and 5.93 ppm, and at 14.41 and 14.21 ppm, respectively, in the ^{1}H NMR spectrum of **19**. When there was a free hydroxyl group *para* to the acetyl group (Entries 9, 10, and 11), surprisingly, all glycosylation reactions gave only the *O*-glucoside in a low yield. It is known that phenolic hydroxyl groups with intramolecular hydrogen bonds are less reactive in glycosylations.[11] In spite of this, even the glycosylation reactions of 2-acetylphloroglucinol derivatives having a hydroxyl group hydrogen-bonded to the acetyl-carbonyl group afforded the *C*-glucoside predominantly in an excellent yield.

It was proven that the glycosylation reaction of 2-acetylphloroglucinol derivatives gave good results in the following cases; i) the glucosyl donor is a benzyl-protected glucosyl fluoride and ii) the glucosyl acceptor is a bis(alkyl ether) derivative which has a free hydroxyl group at the *ortho*-position to the acetyl group. An *O*-glucoside *ortho*-positioned to the acetyl group seems to be easy to migrate, but this is still unclear.

However, the *C*-glucosyl-acetylphloroglucinol derivative obtained was a mixture of isomers *ortho*- and *para*-positioned to the hydroxyl group. These results suggest that this *O*→*C* glucoside rearrangement proceeds intermolecularly.[9b] To make sure that the *O*→*C* glucoside rearrangement proceeds intermolecularly, cross-over experiments were carried out (Scheme 1).

2,4-Dimethoxy-6-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyloxy)acetophenone (**20**) was allowed to react with an equimolar amount of 2-acetylphloroglucinol 3,5-bis(benzyl ether) **4** under the glycosylation conditions mentioned above to afford the corresponding intermolecular *O*→*C* glucoside-rearrangement product; a mixture of 2,4-dibenzyloxy-6-hydroxy-3- and -5-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)acetophenones (**19**) in a 9% yield, together with a 22% yield of the corresponding intramolecular *O*→*C* glucoside-rearrangement products; 2-hydroxy-4,6-dimethoxy-3- and -5-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)acetophenones (**14**). This result supports that this *O*→*C* glucoside rearrangement proceeds intermolecularly, thereby being difficult to control regioselectivity. However, the glucosylation of phloroglucinol bis(alkyl ether) proceeded only by *ortho*-migration (Table 1).

Since satisfactory *C*-glycosylations of 2-acetyl-

phloroglucinol derivatives were obtained, we applied this method to the synthesis of *C*-glucosyl chalcone. For a synthetic plan, we have the two methods as mentioned before (see Scheme 2).

We attempted both methods. Initially, the aldol condensation of *C*-glucoside **19** shown in Table 2 with *p*-benzyloxybenzaldehyde proceeded satisfactorily to afford *C*-glucosyl chalcone **21** in a 70% yield. Further, aldol condensation of **4** with *p*-benzyloxybenzaldehyde also gave chalcone **24** in a 81% yield. However, in the subsequent stereoselective *C*-glycosylation of chalcone **24** in the same manner as that established previously, neither the *O*- nor *C*-glucoside was obtained. De-*O*-benzylation of **19** followed by protection with chloromethyl methyl ether gave **22** in a 47% yield. Aldol condensation of **22** with *p*-methoxymethoxybenzaldehyde gave *C*-glucosyl chalcone methoxymethyl ether **23** in a 98% yield.

Thus, the *C*-glycosylation reaction confirmed here is applicable for the synthesis of various *C*-glycosyl flavonoids. It was found that *C*-glycosylation of 2-acetylphloroglucinol derivatives via *O*→*C* glycoside rearrangement requires a free hydroxyl group *ortho* to the acyl group. The resulting *C*-glucoside stereoselectively formed the *β*-anomer and a mixture of *ortho*- and *para*-regioisomers for the hydroxyl group. The chalcone possessing a phloroglucinol skeleton as the A-ring failed to undergo the glycosylation reaction via *O*→*C* glycoside rearrangement.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus (hot plate) and are uncorrected. Infrared spectra were recorded on a Horiba FT-200 IR spectrometer as KBr tablets, or neat on a NaCl cell. ^{1}H and ^{13}C NMR spectra were obtained on Hitachi R-600, Hitachi 90H or JEOL EX-270 FT NMR spectrometers, with tetramethylsilane as an internal standard. Mass spectra were recorded on a Hitachi RMU-6M or a JEOL JMS-AX505 HA mass spectrometer. The optical rotations were recorded on a JASCO DIP-360 digital polarimeter using a 0.5-dm cell.

General Glycosylation Procedure. To a stirred mixture of 2-acetylphloroglucinol 3,5-bis(benzyl ether) (**4**, 0.276 mmol, 96.3 mg), 2,3,4,6-tetra-*O*-benzyl-*α*-D-glucopyranosyl fluoride (**9**, 0.092 mmol, 50 mg), and powdered molecular sieves 4 Å (50 mg) in dry CH_2Cl_2 (1 ml) at −20 °C, BF_3·OEt_2 (0.184 mmol, 22.7 μl) was added and the mixture was stirred for 2 h under an argon atmosphere. After the disappearance of **9** on TLC (hexane–ethyl acetate–acetic acid=5 : 2 : 0.1), the reaction temperature was raised from −20 °C to room temperature. The resulting mixture was stirred for 45 min until the disappearance of the *O*-glucoside. After adding water, the resulting mixture was filtered through a Celite pad. The filtrate was evaporated in vacuo, and the residual syrup was column chromatographed on silica gel (hexane–ethyl acetate–acetic acid=2 : 1 : 0.1) to give the *C*-glucoside (**19**, colorless syrup, 73.7 mg, 92.1% yield).

General Procedure for Debenzylation and Acetylation of the *C*-Glucoside Benzyl Ether. For elucidation of the anomeric configuration with ^{1}H NMR, the benzyl-protecting group of the *C*-glucoside obtained was transformed into an acetyl group.

A suspension of **19** and 10% palladium–carbon (20 mg) in ethyl acetate (8 ml) and ethyl alcohol (25 ml) was stirred at room temperature for 1.5 d under a H_2 atmosphere. After filtering through a Celite pad, the filtrate was evaporated in vacuo to afford colorless crystals. Subsequently, the crystals were dissolved in acetic anhydride (15 ml) and pyridine (7 ml), and a catalytic amount of 4-dimethylaminopyridine was then added. The resulting mixture was stirred at room temperature for 16 h. The reaction mixture was quenched with ice-cold 2 M HCl solution (1 M=1 mol dm^{-3}) and extracted with ethyl acetate twice. The extracts were collected, washed with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The crude acetate was column chromatographed on silica gel (hexane–ethyl acetate–acetic acid=1 : 1 : 0.1) to afford **19′** (colorless crystals, 640 mg, 85.0% yield).

Cross-Over Experiment. To a stirred mixture of **20** (154.7 mg, 0.204 mmol), **4** (71.0 mg, 0.204 mmol), and powdered molecular sieves 4 Å (40 mg) in CH_2Cl_2 (0.6 ml), BF_3·OEt_2 (50 μl, 0.41 mmol) was added at −20 °C. After being stirred for 80 min, the reaction temperature was raised to room temperature, and the mixture was stirred for 60 min. After adding water, the resulting mixture was filtered through a Celite pad. The filtrate was extracted with ethyl acetate twice. The combined extracts were washed with water and brine, dried over anhydrous Na_2SO_4, then evaporated in vacuo. The residual syrup was separated by column chromatography on silica gel (hexane–ethyl acetate–acetic acid=5 : 1 : 0.1) to afford 2-hydroxy-4,6-dimethoxyacetophenone (**3**) (23.1 mg, 57.8%) and two *C*-glycosides, **14** (34.3 mg, 22.2%) and **19** (15.9 mg, 8.96%).

1,3-Diacetoxy-5-(2,3,4,6-tetra-*O*-acetyl-*α*-D-glucopyranosyloxy)benzene (10*α*). MS (20 eV, *m/z*) 540 (M^+); $[\alpha]_D^{23}$ +112° (*c* 1.22, $CHCl_3$); IR (neat) 3023, 2962, 1749, 1616, and 1456 cm^{-1}; ^{1}H NMR ($CDCl_3$) *δ*=6.77 (2H, s, ArH×2), 6.65 (1H, s, ArH), 5.68 (1H, d, *J*=3.5 Hz, H-1), 5.64 (1H, t, *J*=9.9 Hz, H-3), 5.15 (1H, t, *J*=9.9 Hz, H-4), 5.05 (1H, dd, *J*=3.5 and 9.9 Hz, H-2), 4.27 (1H, dd, *J*=4.7 and 12.4 Hz, H-6a), 4.08 (2H, m, H-5 and H-6b), 2.28 (6H, s, ArOAc×2), 2.07, 2.06, 2.05, and 2.04 (12H, s×4, OAc×4); ^{13}C NMR ($CDCl_3$) *δ*=94.41 (C-1).

1,3-Diacetoxy-5-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyloxy)benzene (10*β*). Colorless needles; mp 156—157 °C; FAB-MS (glycerol, *m/z*) 541 (M^++H); $[\alpha]_D^{23}$ −24.0° (*c* 1.06, $CHCl_3$); IR (KBr) 3477, 2964, 1751, 1616, 1452, and 1225 cm^{-1}; ^{1}H NMR ($CDCl_3$) *δ*=6.65—6.60 (2H, m, ArH×2), 5.32—5.06 (4H, m, H-1—4), 4.27 (1H, dd, *J*=5.6 and 12.2 Hz, H-6a), 4.17 (1H, dd, *J*=3.0 and 12.2 Hz, H-6b), 3.88 (1H, ddd, *J*=9.8, 5.6, and 3.0 Hz, H-5), 2.27 (3H, s, Ar<u>Ac</u>), 2.08, 2.06, 2.05, and 2.03 (12H, s, OAc×4); ^{13}C NMR ($CDCl_3$) *δ*=98.76 (C-1). Found: C, 53.21; H, 5.09%. Calcd for $C_{24}H_{28}O_{14}$: C, 53.33; H, 5.22%.

1,3-Diacetoxy-5-(2,3,4,6-tetra-*O*-benzyl-*α*-D-glucopyranosyloxy)benzene (11). MS (25 eV, *m/z*) 732 (M^+); $[\alpha]_D^{23}$ +74.2° (*c* 0.585, $CHCl_3$); IR (KBr) 3915, 3031, 2916, 2868, 1770, 1614, and 1454 cm^{-1}; ^{1}H NMR ($CDCl_3$) *δ*=7.4—7.2 (20H, m, CH_2<u>Ph</u>×4), 6.77—6.61 (3H, m, ArH×3), 5.40 (1H, d, *J*=3.7 Hz, H-1), and 2.25 (6H, s, OAc×2). Found: C, 71.97; H, 6.06%. Calcd for $C_{44}H_{44}O_{10}$:

C, 72.11; H, 6.05%.

1,3-Dimethoxy-5-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyloxy)benzene (12). MS (20 eV, *m/z*) 676 (M^+); $[\alpha]_D^{24}$ +48.9° (*c* 1.04, $CHCl_3$); IR (neat) 3029, 2931, 2866, 1604, and 1454 cm^{-1}; ^1H NMR ($CDCl_3$) δ=6.30 and 6.15 (3H, m, ArH), 5.46 (1H, d, *J*=3.3 Hz, H-1), and 3.73 (6H, s, OMe). Found: C, 74.28; H, 6.60%. Calcd for $C_{42}H_{44}O_8$: C, 74.53; H, 6.55%.

3,5-Dimethoxy-2-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)phenol (13). Colorless needles; mp 112—113 °C; $FeCl_3$: dark brown; MS (20 eV, *m/z*) 676 (M^+); $[\alpha]_D^{25}$ +31.6° (*c* 0.995, $CHCl_3$); IR (KBr) 3315, 3029, 2910, 1626, 1591, and 1454 cm^{-1}; ^1H NMR ($CDCl_3$) δ=8.04 (1H, br. s, OH), 6.15 and 6.06 (2H, each d, *J*=3.8 Hz, ArH), 5.00 (1H, t, *J*=10.5 Hz, H-2), 4.85 (1H, d, *J*=10.5 Hz, H-1), 4.55 (1H, t, *J*=10.5 Hz, H-3), 3.77 and 3.67 (6H, s, OMe×2). Found: C, 74.83; H, 6.61%. Calcd for $C_{42}H_{44}O_8$: C, 74.53; H, 6.55%.

1-Acetoxy-3,5-dimethoxy-2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)benzene (13′). MS (25 eV, *m/z*) 526 (M^+); $[\alpha]_D^{23}$ −31.4° (*c* 1.03, $CHCl_3$); IR (KBr) 3469, 2945, 1751, 1620, 1369, and 1225 cm^{-1}; ^1H NMR ($CDCl_3$) δ=6.31 (1H, br. s, ArH), 6.20 (1H, br. s, ArH), 5.65—3.8 (7H, br. m, sugar moiety), 3.77 (6H, s, OMe×2), 2.37 (3H, br. s, ArOAc), 2.06, 2.04, 2.02, and 1.76 (12H, s, OMe×4). In the ^1H NMR spectra, the per-*O*-acetate of the *C*-aryl glucosides gave broad signals. Even after increasing the temperature or adding DMSO-d_6, the spectra were scarcely improved. Found: C, 54.46; H, 5.77%. Calcd for $C_{24}H_{30}O_{13}$: C, 54.75; H, 5.74%.

2-Hydroxy-4,6-dimethoxy-3- and -5-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)acetophenones (14). $FeCl_3$: dark brown; MS (20 eV, *m/z*) 718 (M^+); IR (neat) 3030, 2860, 1622, 1597, and 1454 cm^{-1}; ^1H NMR ($CDCl_3$) δ=15.74 and 15.55 (1H, s, OH, ratio; 1:1), 8.68—8.29 (20H, m, CH_2Ph×4), 7.28 and 7.15 (1H, s, ArH, 1:1), 3.98 (3H, s, OMe), 3.94 (3H, s, OMe), and 2.91 (3H, s, Ac).

2-Acetoxy-4,6-dimethoxy-3- and -5-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)acetophenones (14′). Colorless prisms; mp 126—127 °C; MS (20 eV, *m/z*) 568 (M^+); IR (KBr) 2947, 1751 (ester), and 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ=6.35 (1H, br., ArH), 5.89 (1H, br. d, *J*=9.9 Hz, H-1), 3.95 (2H, br., H-6a, b), 3.88 (6H, s, OMe×2), 3.72 (1H, ddd, *J*=9.9, 2.3, and 4.6 Hz, H-5), 2.44 (3H, s, Ac), 2.30 (3H, br. s, ArOAc), 2.07, 2.05, 2.02, and 1.84 (12H, s, OAc×4). Found: C, 54.70; H, 5.63%. Calcd for $C_{26}H_{32}O_{16}$: C, 54.93; H, 5.67%.

2-Acetoxy-4-methoxy-6-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyloxy)acetophenone (15). $FeCl_3$: dark brown; MS (25 eV, *m/z*) 704 (M^+); IR (KBr) 3031, 2927, 2866, 1749, 1622, and 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ=13.98 (1H, s, OH), 7.32—7.16 (20H, m, CH_2Ph×4), 6.30 and 6.13 (2H, d, *J*=2.5 Hz, ArH×2), 5.47 (1H, d, *J*=3.6 Hz, H-1), 5.0—3.6 (14H, m, sugar moiety and CH_2Ph×4), 3.76 (3H, s, Me), and 2.75 (3H, s, Ac).

2-Acetoxy-4-methoxy-6-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyloxy)acetophenone (15′). MS (20 eV, *m/z*) 554 (M^+); $[\alpha]_D^{23}$ +120° (*c* 0.565, $CHCl_3$); IR (KBr) 3438, 1754, 1249, 1226, and 1058 cm^{-1}; ^1H NMR ($CDCl_3$) δ=6.72 and 6.36 (2H, s, *J*=2.3 Hz, ArH×2), 5.69 (1H, d, *J*=3.6 Hz, H-1), 5.59 (1H, dd, *J*=9.9 and 10.2 Hz, H-3), 5.17 (1H, t, *J*=9.9 Hz, H-4), 5.06 (1H, dd, *J*=3.6 and 10.2 Hz, H-2), 4.12 (1H, ddd, *J*=2.3, 3.6, and 9.9 Hz, H-5), 4.08—4.07 (2H, m, H-6), 3.80 (3H, s, OMe), 2.60 (3H, s, ArAc), 2.26 (3H, s, ArOAc), 2.08, 2.05, 2.04, and 2.02 (12H, s, OAc×4). Found: C, 54.22; H, 5.56%. Calcd for $C_{25}H_{30}O_{14}$: C, 54.15; H, 5.45%.

2-Benzyloxy-4-methoxy-6-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyloxy)acetophenone (16). MS (20 eV, *m/z*) 794 (M^+); $[\alpha]_D^{23}$ +76.9° (*c* 0.775, $CHCl_3$); IR (KBr) 3030, 2920, 1699, and 1606 cm^{-1}; ^1H NMR ($CDCl_3$) δ=6.37 (1H, d, *J*=2.0 Hz, ArH), 6.21 (1H, d, *J*=2.0 Hz, ArH), 5.43 (1H, d, *J*=3.5 Hz, H-1), 5.06 (2H, s, ArOCH_2Ph), 3.66 (3H, s, OMe), and 2.51 (3H, s, Ac). Found: C, 75.24; H, 6.38%. Calcd for $C_{50}H_{50}O_9$: C, 75.54; H, 6.34%.

2-Benzyloxy-6-hydroxy-4-methoxy-3- and -5-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)acetophenones (17). $FeCl_3$: dark brown; MS (20 eV, *m/z*) 794 (M^+); IR (KBr) 3029, 2861, 1616, and 1592 cm^{-1}; ^1H NMR ($CDCl_3$) δ=14.40 and 14.21 (1H, s, OH, ca. 1:1), 7.50—6.90 (25H, m, CH_2Ph×5), 6.00 and 5.88 (1H, s, ArH, ca. 1:1), 3.79 and 3.64 (3H, s, OMe), 2.58 and 2.55 (3H, s, Ac, ca. 1:1).

2,6-Diacetoxy-4-methoxy-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)acetophenone (17′). MS (20 eV, *m/z*) 596 (M^+); $[\alpha]_D^{23}$ +3.38° (*c* 1.01, $CHCl_3$); IR (KBr) 1753 (ester) and 1614 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6, at 50 °C) δ=6.63 (1H, s, ArH), 5.71 (1H, br., H-2), 5.27 (1H, t, *J*=10 Hz, H-3), 5.13 (1H, t, *J*=10 Hz, H-4′), 4.89 (1H, br., H-1), 4.28 (1H, br., H-6a), 4.04 (1H, br. d, *J*=12 Hz, H-6b), 3.87 (3H, s, OMe), 3.76 (1H, ddd, *J*=2.3, 6.6, and 9.7 Hz, H-5), 2.38 (3H, s, ArAc), 2.31 and 2.27 (6H, s, ArOAc×2), 2.05, 2.03, 2.00, and 1.77 (12H, s, OAc×4); ^{13}C NMR (acetone-d_6) δ=72.35 (C-1). Found: C, 54.15; H, 5.39%. Calcd for $C_{27}H_{32}O_9$: C, 54.36; H, 5.41%.

2,6-Dibenzyloxy-4-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyloxy)acetophenone (18). MS (25 eV, *m/z*) 870 (M^+); $[\alpha]_D^{23}$ +60.4° (*c* 0.990, $CHCl_3$); IR (KBr) 3031, 2916, 2868, 1699, and 1603 cm^{-1}; ^1H NMR ($CDCl_3$) δ=6.39 (2H, s, ArH), 5.39 (1H, d, *J*=3.3 Hz, H-1), 5.00 (4H, s, ArOCH_2Ph×2), and 2.47 (3H, s, Ac). Found: C, 77.03; H, 6.25%. Calcd for $C_{56}H_{54}O_9$: C, 77.22; H, 6.25%.

2,4-Dibenzyloxy-6-hydroxy-3- and -5-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)acetophenones (19). $FeCl_3$: dark brown; MS (20 eV, *m/z*) 870 (M^+); IR (neat) 3031, 2868, 1629, and 1597 cm^{-1}; ^1H NMR ($CDCl_3$) δ=14.41 and 14.21 (1H, s, OH, 1.8:1), 7.64—6.87 (30H, m, CH_2Ph×6), 5.98 and 5.93 (1H, s, ArH, 1.6:1), and 2.58 and 2.53 (3H, s, Ac, 1:1.7). Found: C, 77.68; H, 6.23%. Calcd for $C_{56}H_{54}O_9$: C, 77.22; H, 6.25%.

2,4,6-Triacetoxy-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)acetophenone (19′). Colorless prisms; mp 191—193 °C (lit,[13] 193—194 °C); MS (20 eV, *m/z*) 624 (M^+); $[\alpha]_D^{23}$ −22.1° (*c* 1.02, $CHCl_3$); IR (KBr) 3440, 1755, 1369, 1226, 1182, and 1033 cm^{-1}; ^{13}C NMR (acetone-d_6) δ=197.09 (s), 170.35 (s), 170.07 (s), 169.34 (s), 168.73 (s)×2, 151.72 (s), 148.67 (s), 120.59 (s), 117.14 (d), 76.80 (d), 74.88 (d), 72.99 (d, C-1), 70.77 (d), 69.12 (d), 62.69 (t), 20.88 (q), 20.64 (q), 20.58 (q), 20.45 (q), and 20.18 (q); ^1H NMR ($CDCl_3$) δ=7.02 (1H, s, ArH), 5.62 (1H, br. t, *J*=10.0 Hz, H-2), 5.26 (1H, t, *J*=10.0 Hz, H-3), 5.15 (1H, t, *J*=10.0 Hz, H-4), 4.74 (1H, d, *J*=10.0 Hz, H-1), 4.40 (1H, br. m, H-6a), 3.99 (1H, dd, *J*=12.4 and 2.1 Hz, H-6b), 3.76 (1H, ddd, *J*=10.0, 4.3, and 2.1 Hz, H-5), 2.43, 2.36, and

2.27 (9H, s, ArOAc×3), 2.07, 2.04, 2.02, and 1.80 (12H, s, OAc×4). Found: C, 53.62; H, 5.16%. Calcd for $C_{28}H_{32}O_{16}$: C, 53.85; H, 5.16%.

2,4-Dimethoxy-6-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyloxy)acetophenone (20). FAB-MS (glycerol, *m/z*) 719 (M^++H); $[\alpha]_D^{23}$ +74.9° (*c* 1.25, $CHCl_3$); IR (neat) 3030, 2935, 1697, 1606, 1587, and 1454 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=7.33—7.14 (20H, m, CH_2Ph×4), 6.36 (1H, d, *J*=2.0 Hz, ArH), 6.17 (1H, d, *J*=2.0 Hz, ArH), 5.42 (1H, d, *J*=3.6 Hz, H-1), 4.04 (1H, t, *J*=9.2 Hz, H-4), 3.87 (1H, m, H-5), 3.78 and 3.70 (each 3H, s, OMe×2), 3.67 (1H, dd, *J*=3.6 and 13.6 Hz, H-6a), 3.60 (1H, dd, *J*=1.8 and 13.6 Hz, H-6b), and 2.52 (3H, s, Ac); ^{13}C NMR ($CDCl_3$) δ=96.69 (C-1).

4,2′,4′-Tris(benzyloxy)-6′-hydroxy-3′- and -5′-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)chalcones (21). FAB-MS (glycerol, *m/z*) 1065 (M^++H); IR (KBr) 3030, 2864, 1622, and 1558 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ= 14.99 (1H, s, OH), 7.75—7.67 (2H, m, vinyl H), 7.50—7.12 (35H, m, CH_2Ph×7), 7.05—6.77 (4H, m, *p*-substituted ArH), and 6.06—6.01 (1H, s, ArH). Found: C, 78.69; H, 6.08%. Calcd for $C_{70}H_{64}O_{10}$: C, 78.92; H, 6.06%.

2,4,6-Tris(methoxymethoxy)-3-(2,3,4,6-tetra-*O*-methoxymethyl-β-D-glucopyranosyl)acetophenone (22). To a solution of **19** (828 mg) in ethyl acetate (1 ml) and ethanol (10 ml), 10% Pd–C (160 mg) was added and the mixture was stirred vigorously at room temperature under a H_2 atmosphere overnight. The resulting mixture was filtered through a Celite pad. The filtrate was evaporated in vacuo to give a colorless oil (314 mg, 0.952 mmol) quantitatively. The oil was dissolved in dry CH_2Cl_2 (5 ml) and *N*-ethyl-*N*-diisopropylamine (18.3 mmol, 3.11 ml) was added with stirring. The mixture was cooled in an ice bath, chloromethyl methyl ether (16.0 mmol, 1.38 ml) was added, and the mixture was stirred at room temperature overnight. The reaction mixture was then added to ice-cold water and extracted with chloroform. The extracts were washed with brine and dried over anhydrous Na_2SO_4, then evaporated in vacuo to give **22** (287 mg, 47%). Colorless oil; FAB-MS (glycerol, *m/z*) 639 (M^++H); $[\alpha]_D^{23}$ −32.0° (*c* 0.925, $CHCl_3$). Found: C, 51.54; H, 7.10%. Calcd for $C_{28}H_{46}O_{16}\cdot H_2O$: C, 51.21; H, 7.37%.

4,2′,4′,6′-Tetrakis(methoxymethoxy)-3′-(2,3,4,6-tetra-*O*-methoxymethyl-β-D-glucopyranosyl)chalcone (23). To a solution of **22** (0.428 mmol, 273 mg) and 4-methoxymethoxybenzaldehyde (1.18 mmol, 196 mg) in ethanol (3 ml), 1 ml of 50% aqueous KOH solution was added and the mixture was stirred for 3 h. After TLC monitoring, the reaction mixture was added to ice-cold water and neutralized with 1 M HCl solution. The mixture was then extracted with ethyl acetate. The extracts were washed with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was column chromatographed on silica gel (toluene–ethyl acetate–acetic acid=6:1:0.2) to afford **23** (329 mg, 98%). Pale-yellow oil; FAB-MS (glycerol, *m/z*) 787 (M^++H); $[\alpha]_D^{23}$ −13.6° (*c* 0.925, $CHCl_3$). Found: C, 56.01; H, 6.83%. Calcd for $C_{37}H_{54}O_{18}\cdot 1/2H_2O$: C, 55.84; H, 6.93%.

4,2′,4′-Tris(benzyloxy)-6′-hydroxychalcone (24). Yellow needles; mp 140 °C; MS (70 eV, *m/z*) 542 (M^+); IR (KBr) 3033, 2937, 2877, 1603, and 1558 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=14.59 (1H, s, OH), 7.01 and 6.77 (2H, each d, *J*=8.5 Hz, *p*-substituted ArH), 6.14 (2H, s, ArH×2), 5.15, 5.07, and 5.04 (6H, s, $ArO\underline{CH_2}Ph$×3). Found: C, 79.30; H, 5.58%. Calcd for $C_{36}H_{30}O_5$: C, 79.68; H, 5.57%.

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