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Note

Synthesis of bis(*C*-glycosyl)flavonoid precursors

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Abstract

Treatment of 3,5-dimethoxyphenol with one equivalent of *O*-glucosyl trichloroacetimidate **1** in the presence of TMSOTf as catalyst afforded, in a Fries-type reaction, *C*-glucosyl compound **4**. Reaction of **4** with one equivalent of **1** or with one equivalent of *O*-galactosyl trichloroacetimidate **8** gave, under similar reaction conditions, bis(*C*-glycosyl) compounds **5** and **9**, respectively. Hydrogenolytic *O*-debenzylation of **5** afforded 3,5-dimethoxy-2,6-bis(β-D-glucopyranosyl)phenol (**6**) in high yield. Due to hindered rotation around the *C*-glycosyl C-C bond, structural assignment was carried out by recording ^{1}H NMR spectra at elevated temperatures.

Keywords: *C*-Glycosyl compounds; "*C*-Glycosides"; Bis(*C*-glycosyl)phenol derivatives; *O*-Glycosyltrichloroacetimidates; Fries rearrangement

Various types of bis(*C*-glycosyl)flavonoids have been found in nature [1]; some also exhibit interesting biological properties [2]. Compounds having two glycosyl residues attached to the 6- and 8-position of the flavonoid skeleton which contain a phloroglucinol moiety occur especially frequently. Two typical examples are compounds **A** and **B** (Scheme 1) exhibiting the potential presence of identical and also of different sugar residues.

Usually, *C*-glycosyl compounds are synthesized by a Friedel-Crafts-type reaction of glycosyl donors with electron-rich aromatic compounds as glycosyl acceptors [3,4]. However, earlier attempts to obtain bis(*C*-glycosyl)flavonoids with glycosyl bromides as glycosyl donors were met with little success [1]. Recently, we have reported on a different strategy for the synthesis of phenolic *C*-glycosyl derivatives via glycosylation of partially *O*-unprotected phenol derivatives followed by Fries-type rearrangement of the *O*-glycoside intermediate [5,7]. Thus, with *O*-glycosyl trichloroacetimidates as donors, only catalytic amounts of trimethylsilyl triflate as promoter are required for reaction with phenol derivatives. A related method with relatively reactive glycosyl fluorides as glycosyl donors which are preferably activated by Lewis acids from the Group IVa metallocenes ($Cp_2ZrCl_2/AgClO_4$ or $Cp_2HfCl_2/AgClO_4$) in up to a fivefold molar excess has been also described [8].

Efforts to directly *C*-glycosylate via this approach the flavanoid moiety or phloroglucinol precursors having, for instance, electron withdrawing acyl

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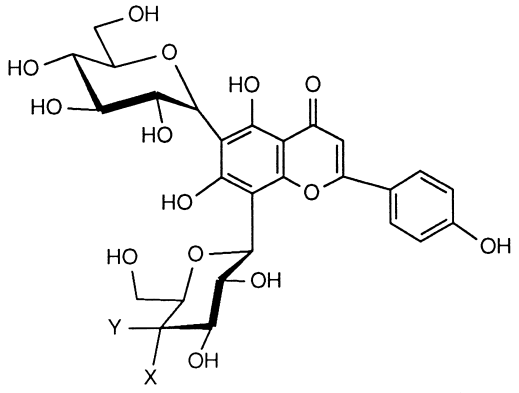


A: X = OH, Y = H (Vicenin-2)
B: X = H, Y = OH

Scheme 1.

groups were less successful [9,10]. Therefore, we undertook investigations in order to obtain a consecutive bis-*C*-glycosylation of partially O-protected phloroglucinol derivatives with *O*-glycosyl trichloroacetimidates as glycosyl donors, thus eventually leading to bis(*C*-glycosyl)flavonoids [11]. A recently reported related study using tetra-*O*-benzylglucosyl fluoride as glycosyl donor and 3,5-di-benzyloxy-phenol as acceptor [10] prompts us to report on our results with di-*O*-methylphloroglucinol as acceptor (Scheme 2).

The previously described reaction of *O*-benzyl protected *O*-glucosyl trichloroacetimidate **1** [12] with 3,5-dimethoxyphenol (**2**) in the presence of trimethylsilyl triflate as catalyst led to *C*-glucoside **4** [6,11]. Contrary to the results with the corresponding glucosyl fluoride as donor [10], neither the α- nor the β-anomeric *O*-glucoside **3** was obtained [6]. Ensuing reaction of **4** with a second equivalent of **1** under similar reaction conditions afforded the desired bis(*C*-glycosyl) derivative **5** in very high yield (93%). The structural assignment by NMR spectroscopy was hampered by slow rotation around the C–C bond between C-1 of the sugar residues and the phenolic carbon atoms. However, at 120 °C in dimethylsulfoxide-d_6 as solvent, the C_2-symmetry in the molecule became obvious resulting in a doublet for H-1 of the two glucopyranosyl residues (δ: 4.94, d, $J_{1,2}$ 9.7 Hz), thus indicating a β-configuration and 3,5-attachment of the sugar residues. *O*-Acetylation of **5** with acetic anhydride in pyridine in the presence of dimethylaminopyridine (DMAP) gave **5a** which exhibited even higher rotational hindrance than **5**. Hydrogenolytic *O*-debenzylation of **5** with Pd/C as catalyst worked selectively, furnishing the O-unprotected compound **6**; *O*-acetylation as described above led to the per-*O*-acetyl derivative **7** which could be also obtained from **5a** via the same reaction sequence. Again, **7** exhibited at room temperature in its ^{1}H NMR spectrum (600 MHz, chloroform-*d*) two data sets indicating the presence of two conformers; at 100 °C (250 MHz, dimethylsulfoxide-d_6) only one data set was present, yet for the anomeric protons still a broad signal was observed. Detailed conformational studies based on these phenomena have been carried out [13,14].

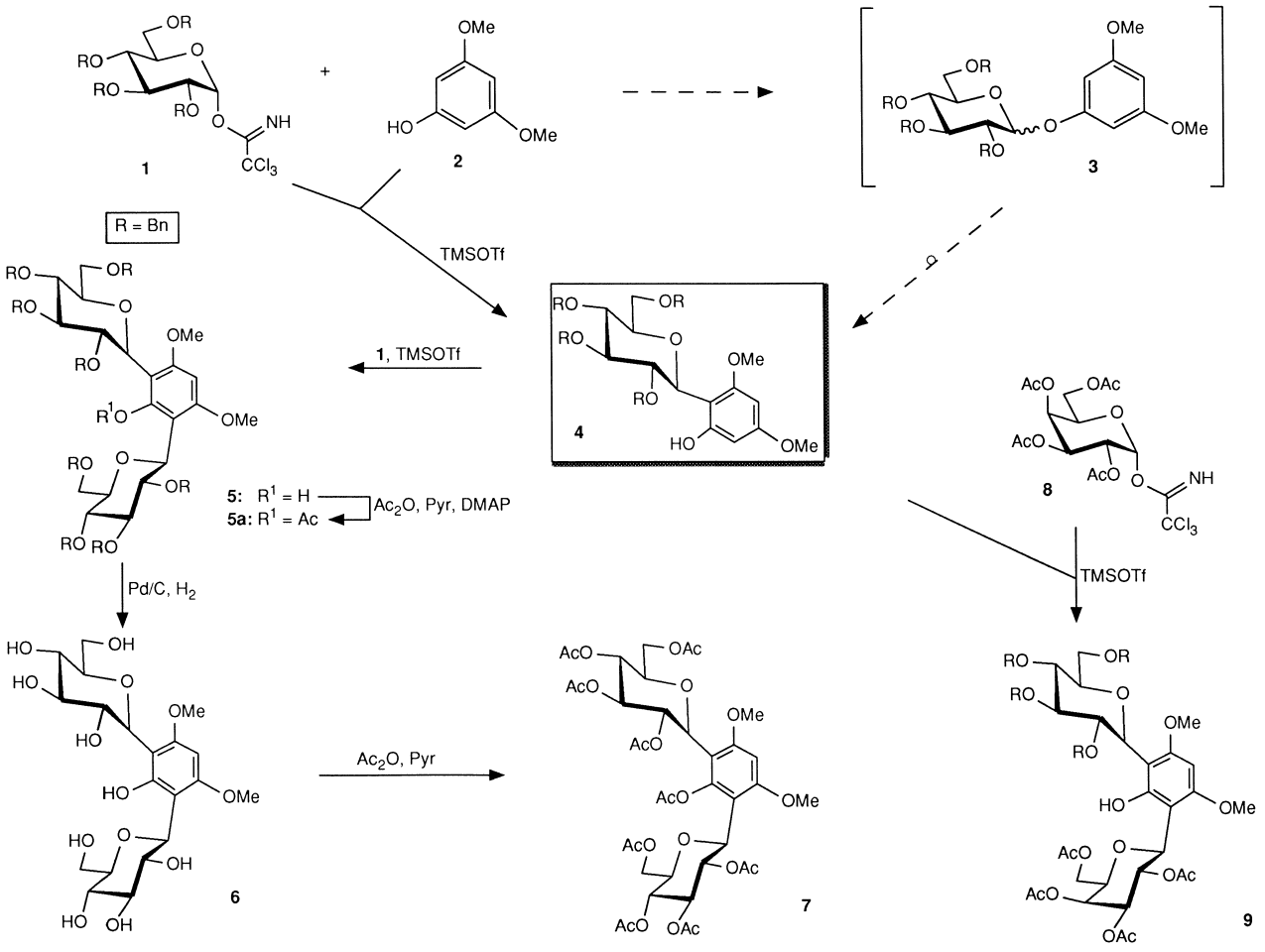
Obviously, intermediate **4** is also useful for the attachment of an other sugar residue. To this aim, we selected the *O*-galactosyl trichloroacetimidate **8** [12,15]; reaction with **4** in the presence of catalytic amounts of trimethylsilyl triflate gave the desired bis-*C*-glycosylated compound **9** in good yield. At 100 °C the structural assignment could be based on the ^{1}H NMR data (250 MHz, dimethylsulfoxide-d_6: δ: 4.93, d, $J_{1',2'}$ 9.7 Hz; 5.10, d, $J_{1',2'}$ 9.8 Hz). Thus, based on the readily available bis(*C*-glycosyl)phloroglucinols, access to various types of bis(*C*-glycosyl) flavonoids should be feasible.

1. Experimental

General methods.—Solvents were purified and dried by standard procedures before use; petroleum ether of boiling range 35–70 °C was used. Melting points are uncorrected. ^{1}H NMR spectra: Avance DRX_{600}, Bruker AC 250, internal standard tetramethylsilane (Me_4Si): *J*-values in Hz. Elemental analysis: Heraeus CHN-O-Rapid. Mass spectra: Varian MAT 312/AMD 5000 FAB.

Flash chromatography: Silica Gel 60 (Baker 0.03–0.06 mm) at a pressure of 0.3 bar. Thin layer chromatography (TLC): plastic foil plates, Kiesel Gel 60 F_{254} (E. Merck; layer thickness 0.2 mm); detection by treatment with a soln of 20 g of ammonium molybdate and 0.4 g of cerium (IV) sulfate in 400 mL of 10% H_2SO_4 and heating at 150 °C. Optical rotations: Perkin–Elmer polarimeter 241/MS, 1 dm cell.

3,5-Dimethoxy-2,6-bis(2,3,4,6-tetra-O-*benzyl*-β-D-*glucopyranosyl)phenol* (**5**).—To a soln of **4** [6] (500 mg, 0.73 mmol) and **1** [12] (505 mg, 0.73 mmol) in anhyd CH_2Cl_2 (5 mL) at −65 °C was added trimethylsilyl triflate (16 μL, 0.1 equiv); the mixture was stirred for 30 min. The temperature was raised to room temperature within 3 h. The reaction was



Scheme 2.

quenched by addition of satd $NaHCO_3$ soln (2 mL); stirring was continued for 15 min and then water (5 mL) was added. Extraction with CH_2Cl_2 (4×5 mL), drying of the organic extracts over anhyd $MgSO_4$, and evaporation of the solvent under reduced pressure gave a syrup. Flash silica gel chromatography with light petroleum-EtOAc (10:3) as eluent gave **5** (816 mg, 93%) as a colourless foam; mp 49–50 °C; TLC (10:3 light petroleum–EtOAc): R_f 0.37; $[\alpha]_D^{20}$ +5.42 (*c* 1, $CHCl_3$); ^{1}H NMR (250 MHz, Me_2SO-d_6 at 120 °C): δ 8.28 (s, 1 H, Ar-OH), 6.89–7.36 (m, 40 H, 8 C_6H_5), 6.25 (s, 1 H, Ar-H), 4.94 (d, 2 H, $J_{1,2}$ 9.7 Hz, H-1′,1″), 4.54–4.83 (m, 14 H, 7 CH_2-benzylic), 4.26 (m, 2 H, CH_2-benzylic), 3.95–4.08 (m, 4 H, H-2′,2″,3′,3″), 3.61–3.78 (m, 14 H, H-5,5″,6′a,6″a,6′b,6″b,4′,4″, 2 CH_3O). FABMS: *m*/*z* 1222 $[\overline{M+Na}]^+$. Anal. Calcd for $C_{76}H_{78}O_{13}$ (1199.44): C, 76.10; H, 6.55. Found: C, 75.80; H, 6.38.

1-Acetoxy-3,5-dimethoxy-2,6-bis(2,3,4,6-tetra-O-*benzyl*-β-D-*glucopyranosyl)benzene* (**5a**).—To a stirred mixture of 5 (1 g, 0.83 mmol), Ac_2O (10 mL), and pyridine (5 mL), a catalytic amount of DMAP (5 mg) was added. The reaction mixture was stirred at room temperature for 12 h. The solvent was evaporated under reduced pressure. Flash chromatography on silica gel of the residual brown syrup with a mixture of light petroleum–EtOAc (5:2) gave **5a** (900 mg, 87%) as colourless crystals; mp 46–47 °C, TLC (5:2 light petroleum–EtOAc): R_f 0.29; $[\alpha]_D^{20}$ +2.27 (*c* 1, $CHCl_3$); ^{1}H NMR (250 MHz, Me_2SO-d_6, at 120 °C); δ 6.87–7.36 (m, 40 H, 8 C_6H_5), 6.63 (s, 1 H, Ar-H), 4.44–4.81 (m, 16 H, 7 CH_2-benzylic, H-1′,1″), 4.50 (m, 2 H, CH_2-benzylic), 4.0–4.20 (m, 4 H, H-2′,2″,3′,3″), 3.80 (s, 6 H, 2 CH_3O), 3.55–3.65 (m, 6 H, H-4′,4″,6′a, 6″a,6′b,6″b), 3.44–3.54 (m, 2 H, H-5′,5″), 2.16 (s, 3 H, OAc). FABMS: *m*/*z* 1264 $[\overline{M+Na}]^+$. Anal. Calcd for $C_{78}H_{80}O_{14}$ (1241.48): C, 75.46; H, 6.49. Found: C, 75.04; H, 6.32.

*3,5-Dimethoxy-2,6-bis(*β-D-*glucopyranosyl)phenol* (**6**).—To a soln of **5** (500 mg, 0.41 mmol) in a mixture of dioxane–EtOH–AcOH (1550.5 mL), 10% palladium on charcoal (50 mg) was added, and the

reaction mixture stirred at room temperature for 1 d under H_2 atmosphere. The catalyst was filtered off over Celite and the filtrate was concentrated; flash chromatography (2:1 $CHCl_3$–MeOH) of the residue yielded **6** (160 mg, 81%) as a colourless powder; mp 185–186 °C, TLC (1:1 $CHCl_3$–MeOH): R_f 0.46; $[\alpha]_D^{20}$ +30.67 (*c* 1, MeOH); ^{1}H NMR (600 MHz, MeOH-d_4, at 47 °C): δ 6.23 (s, 1 H, Ar-H), 4.84 (d, 2 H, $J_{1,2}$ 9.9 Hz, H-1′,1″), 3.96 (m, 2 H, H-2′,2″), 3.78–3.83 (m, 8 H, H-6″a,6″b, 2 CH_3O–), 3.71–3.74 (m, 2 H, H-6′a,6′b), 3.43–3.5 (m, 4 H, H-3′,3″,4′,4″), 3.36–3.38 (m, 2 H, H-5′,5″). ^{13}C NMR (at 47 °C): δ 161.04 (Ar-), 157.826, 107.29, 90.17 (C-4), 82.27 (C-5′,5″), 79.88 (C-3′,3″), 76.15 (C-1′,1″), 72.97 (C-2′,2″), 71.64 (C-4′,4″), 62.58 (C-6′,6″), 56.53 (-OCH_3), FABMS: *m*/*z* 479 $[\overline{M+H}]^+$.

1-Acetoxy-3,5-dimethoxy-2,6-bis(2,3,4,6-tetra-O-*acetyl*-β-D-*glucopyranosyl)benzene* (**7**).—(a) From **5a**: To a soln of **5a** (400 mg, 0.32 mmol) in a mixture of dioxane–EtOH–AcOH (15:50.5 mL), 10% palladium–charcoal (40 mg) was added, and the reaction mixture stirred at room temperature for 1 day under H_2 atmosphere. The catalyst was filtered over Celite, and the filtrate evaporated under reduced pressure. The residue subsequently was dissolved in Ac_2O (10 mL) and pyridine (5 mL) in the presence of DMAP (5 mg). The mixture was stirred at room temperature for 1 day. The solvent was evaporated under reduced pressure, flash chromatography (2:1 EtOAc–light petroleum) of the residue yielded **7** (200 mg, 81%) as colourless solid; mp 116–117 °C; TLC (2:1 EtOAc–light petroleum): R_f 0.43, $[\alpha]_D^{20}$ −28.97 (*c* 1, $CHCl_3$). (b) From **6**: **6** (100 mg, 0.20 mmol) was dissolved in Ac_2O(5 mL) and pyridine (2 mL) in the presence of a catalytic amount of DMAP (5 mg) following the same procedure as described above yielding **7** (60 mg, 70%); ^{1}H NMR (600 MHz, $CDC1_3$), shows the presence of two conformers in slow exchange. δ 6.30 (s, 1 H, Ar-H), 5.94 (dd, 1 H, $J_{1',2'}$ 9.1, $J_{2',3'}$ 9.3 Hz, H-2′), 5.53 (dd, 1 H, $J_{1'',2''}$ 9.7, $J_{2'',3''}$ 8.5 Hz, H-2″), 5.22–5.23 (m, 2 H, H-3′,3″), 5.12 (m, 2 H, H-4′,4″), 4.96 (d, 1 H, $J_{1'',2''}$ 9.7 Hz, H-1″), 4.23 (br, 1 H, H-1′), 3.92, 4.38 (m, 2 H, H-6′b,6″b), 4.07–4.16 (m, 2 H, H-6′a,6″a), 3.87 (s, 3 H, CH_3O), 3.79 (s, 3 H, CH_3O), 3.70 (m, 1 H, H-5″), 3.59 (m, 1 H, H-5′), 2.36 (s, 3 H, -OAc), 1.66–2.02 (m, 24 H, 8 OAc). ^{13}C NMR: δ 76.44 (C-5″), 76.28 (C-5′), 74.69 (C-3″), 74.99 (C-3′), 71.98 (C-1″), 73.37 (C-1′), 70.30 (C-2″), 69.09 (C-2′), 68.68 (C-4″), 68.68 (C-4′), 62.5 (C-6′), 62.09 (C-6″). ^{1}H NMR (250 MHz, Me_2SO-d_6 at 100 °C): δ 6.09 (s, 1 H, Ar-H), 5.65 (m, 2 H, H-2′,2″), 5.25 (dd, 2 H, $J_{2',3'} = J_{2'',3''} = J_{3',4'} = J_{3'',4''}$ 9.4 Hz, H-3′,3″), 4.92 (dd, 2 H, $J_{3',4'} = J_{3'',4''} = J_{4',5'} = J_{4'',5''}$ 9.4 Hz, H-4′,4″), 4.70 (m, 2 H, H-1′,1″), 3.87–4.15 (m, 6 H, H-5′,5″,6′a,6″a,6′b,6″b), 3.85 (s, 6 H, 2 OMe), 2.3 (s, 3 H, OAc), 1.9–2.02 (sss, 18 H, 6 OAc), 1.7 (s, 6 H, 2 -OAc). FABMS: *m*/*z* 879 $[\overline{M+Na}]^+$. Anal. Calcd for $C_{38}H_{48}O_{22}$ (856.78): C, 53.27; H, 5.64. Found: C, 53.38; H, 5.18.

3,5-Dimethoxy-6-(2,3,4,6-tetra-O-*acetyl*-β-D-*galactopyranosyl)-2-(2,3,4,6-tetra*-O-*benzyl*-β-D-*glucopyranosyl)phenol* (**9**).—To a soln of **4** [6] (400 mg, 0.73 mmol) and **8** [12,15] (316 mg, 0.73 mmol), in anhyd CH_2Cl_2 (5 mL) at −70 °C, was added TMSOTF (16 μL, 0.1 equiv); the reaction mixture was stirred for 30 min. The temperature was raised to room temperature within 3 h. The reaction was quenched by addition of satd $NaHCO_3$ soln (2 mL); stirring was continued for 15 min and then water (5 mL) was added. Extraction with CH_2Cl_2 (4×5 mL), drying of the organic extracts over anhyd $MgSO_4$, and evaporation of the solvent under reduced pressure gave a syrup which was subjected to silica gel flash chromatography with light petroleum–EtOAc (5:3) as eluent to give **9** (500 mg, 72%) as colourless crystals; mp 79–80 °C; TLC (5:3 light petroleum–EtOAc): R_f 0.22; $[\alpha]_D^{20}$ +12.7 (*c* 1, $CHCl_3$); ^{1}H NMR (250 MHz, Me_2SO-d_6, at 120 °C): δ 8.06 (br, 1 H, Ar-OH), 6.96–7.33 (m, 20 H, 4 C_6H_5), 6.22 (s, 1 H, Ar-H), 5.87 (dd, 1 H, $J_{1'',2''} = J_{2'',3''}$ 9.8 Hz, H-2″ Gal), 5.41 (dd, 1 H, $J_{3'',4''}$ 3.4, $J_{4'',5''} < 1$ Hz, H-4″ Gal), 5.20 (dd, 1 H, $J_{3'',4''}$ 3.4, $J_{2'',3''}$ 9.8 Hz, H-3″ Gal), 5.10 (d, 1 H, $J_{1'',2''}$ 9.8 Hz, H-1″ Gal), 4.93 (d, 1 H, $J_{1',2'}$ 9.7 Hz, H-1′ glc), 4.30–4.88 (m, 8 H, 4 CH_2-benzylic), 4.19 (m, 1 H, H-5″ Gal), 3.91–4.11 (m, 3 H, H-2′ Glc,6′b,6″b Gal), 3.84 (s, 3 H, CH_3O), 3.63–3.75 (m, 8 H, H-3′ Glc,4′ Glc, 5′ Glc,6′a,6″a Glc, CH_3O), 2.10 (s, 3 H, OAc), 1.92–1.94 (ss, 6 H, 2-OAc), 1.66 (s, 3 H, OAc). FABMS: *m*/*z* 1029 $[\overline{M+Na}]^+$. Anal. Calcd for $C_{56}H_{62}O_{17}$ (1007.09): C, 66.78; H, 6. 22. Found: C, 66.53; H, 6.42.

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