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Note

An efficient synthesis of 3,4,6-tri-*O*-benzyl-2-*C*-methyl-D-glucal

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The use of glycals as chiral starting materials is attractive due to the minimization of the often tedious selective protecting-group schemes required for fully oxygenated sugars. As an extension, we planned to utilize an alkyl-substituted glycal as a synthetic starting material, which required the development of a reliable and straightforward approach to previously unreported 3,4,6-tri-*O*-benzyl-2-*C*-methyl-D-glucal (1,5-anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-methyl-D-*arabino*-hex-1-enitol, **4**).

The most relevant method of preparing 2-alkyl-2-deoxyglucose derivatives in the literature consists of cuprate opening of epoxides derived from 1,6-anhydro-β-D-glucose. Upon diaxial opening and anhydro sugar hydrolysis, these epoxides lead to the desired retention of configuration at C-3 [1]. However, such an approach was deemed too lengthy and low-yielding for our purposes. We envisioned the desired methyl-group installation arising from a 1,2-cyclopropanated glycal, a relatively unexplored system [2–4]. The use of mercuric ion to catalyze the opening of cyclopropanes is precedented [5], and we expected the reaction with an oxacyclopropane to lead to regioselective C–C bond cleavage accompanied by nucleophilic addition α to the pyran oxygen. This approach led to the development of a unique and straightforward synthesis of the desired alkylated glucal in four steps.

The synthesis begins with 3,4,6-tri-*O*-benzyl-D-glucal [1,5-anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-D-*arabino*-hex-1-enitol, **1** (see Scheme 1)], which undergoes directed cyclopropanation under modified Simmons–Smith conditions [6] to provide cyclopropane **2** as mainly one isomer ($\sim$ 30:1) [3]. The cyclopropane is opened regioselectively with

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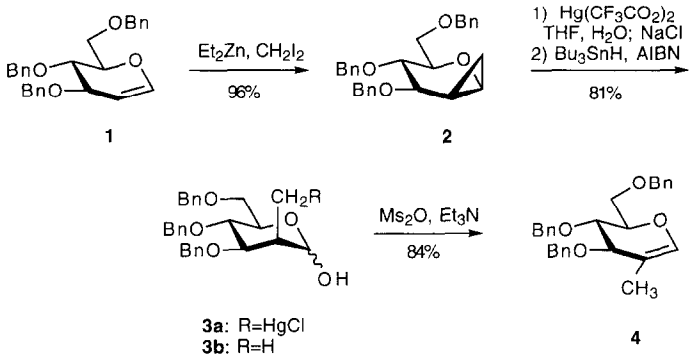

Scheme 1.

mercuric trifluoroacetate in the presence of water to provide organomercurial **3a** after NaCl workup [5]. Reductive removal of the mercury from the crude material with Bu_3SnH and catalytic AIBN provides 3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-methyl-D-mannose (**3b**) as a mixture of anomers [7]. The use of methanol as the nucleophile provides a higher selectivity at the anomeric position (> 10:1); however, the elimination requires harsh reaction conditions. Elimination of the anomeric hydroxyl of **3b** proceeds cleanly with methanesulfonic anhydride in the presence of triethylamine to provide the title compound. The four-step sequence installs the desired methyl group in 65% overall yield. The benzyl groups can be removed cleanly with Na/NH_3 to provide fully deprotected 2-*C*-methyl-D-glucal.

In summary, a straightforward four-step transformation has been developed to convert 3,4,6-tri-*O*-benzyl-D-glucal into 3,4,6-tri-*O*-benzyl-2-*C*-methyl-D-glucal in high overall yield. The synthesis has been used to provide several grams of the desired glucal in the course of a few days of laboratory time.

1. Experimental

General.—Flash chromatography was carried out using Merck Silica Gel 60 230–400 mesh as the stationary phase. Thin-layer chromatography was performed with Merck Silica Gel $60F_{254}$ glass plates (0.25 mm). Melting points are uncorrected and were measured in open capillary tubes. Unless otherwise indicated, IR spectra were of thin films on NaCl plates and NMR spectra measured in $CDCl_3$. The NMR chemical shifts are reported in ppm of the δ scale using the residual proton-containing NMR solvent as an internal reference, and the coupling constants are reported in Hz. Optical rotations were measured at room temperature. Elemental analyses were performed by the Microanalytical Laboratory operated by the UCB College of Chemistry.

[1S-(1α,3α,4β,5α,6α)]-4,5-bis(phenylmethoxy)-3-[(phenylmethoxy)methyl]-2-oxabicyclo[4.1.0]heptane (**2**).—(Note: this compound is reported in ref. [3]; however, characterization data are not presented). To a solution of **1** (30.00 g, 0.0720 mol) in ether (200 mL) was added Et_2Zn (~ 200 mL, 15% soln in hexane) followed by CH_2I_2

(23 mL, 0.2855 mol). After 50 min at rt, an additional portion of CH_2I_2 (5 mL, 0.0620 mol) was added. After 3.5 h at rt, the solution was added to 1 M HCl (500 mL). The phases were separated and the organic phase was extracted once with 1 M HCl (300 mL) and satd NaCl (150 mL). The organic layer was dried (K_2CO_3), filtered, concentrated, and purified by flash chromatography (1:4 EtOAc–hexanes) to provide 29.67 g (96%) of the cyclopropane as an oil which slowly solidified over several days: mp 37–39 °C; $[\alpha]_D$ −59° (*c* 1.0, CH_2Cl_2); IR: ν 3086, 3062, 3029 (Ar C–H), 1496, 1453 (Ar C–C) cm^{-1}; ^1H NMR (400 MHz): δ 7.42–7.17 (m, 15 H, 3 Ph), 4.83 and 4.59 (2 d, 2 H, J_{gem} 11.7 Hz, PhCH_2), 4.81 and 4.52 (2 d, 2 H, J_{gem} 11.1 Hz, PhCH_2), 4.57 and 4.54 (2 d, 2 H, J_{gem} 12.2 Hz, PhCH_2), 4.18 (dd, 1 H, $J_{2,3} = J_{3,4} = 7.0$ Hz, H-3), 3.84 (ddd, 1 H, $J_{1,7a}$ 2.9, $J_{1,7b}$ 5.6, $J_{1,2}$ 6.7 Hz, H1), 3.70 (dd, 1 H, $J_{5,6a}$ 1.9, $J_{6a,6b}$ 10.5 Hz, H-6a), 3.55 (dd, 1 H, $J_{5,6b}$ 5.4 Hz, H-6b), 3.45 (ddd, 1 H, $J_{4,5}$ 9.9 Hz, H-5), 3.35 (dd, 1 H, H-4), 1.39 (dddd, 1 H, $J_{2,7a}$ 6.2, $J_{2,7b}$ 9.8 Hz, H-2), 0.83 and 0.77 (2 ddd, 2 H, $J_{7a,7b}$ 5.9 Hz, H-7a,7b). ^{13}C NMR (100 MHz): δ 11.91, 15.46, 54.94, 69.31, 69.71, 73.43, 74.06, 77.31, 78.33, 78.59, 127.42, 127.45, 127.49, 127.72, 127.76, 128.19, 128.28, 138.05, 138.36, 138.39. Anal. Calcd for $C_{28}H_{30}O_4$: C, 78.11; H, 7.02. Found: C, 78.16; H, 6.97.

*3,4,6-Tri-*O*-benzyl-2-deoxy-2-*C*-methyl-*D*-mannose* (**3b**).—To a solution of cyclopropane **2** (11.86 g, 0.0275 mol) in THF (155 mL) and H_2O (28 mL) was added mercuric trifluoroacetate (20.86 g, 0.0489 mol). After 10 min at rt, a solution of satd NaCl was added (100 mL) and the mixture stirred vigorously. After 15 min, the solution was added to CH_2Cl_2 (400 mL) and the layers were separated. The organic phase was extracted with 2.5 M NaOH (100 mL) to remove trifluoroacetic acid and the layers were separated. The organic phase was shaken well with 2 M HCl (200 mL), and separated. The organic layer was dried (Na_2SO_4), filtered, and concentrated. To a solution of the organomercurial in THF (200 mL) was added Bu_3SnH (20.0 mL, 0.0744 mol) followed by AIBN (73 mg, 0.44 mmol). After stirring at rt for 35 min, 15% aq KF (200 mL) was added. The mixture was added to ether (400 mL) and the phases separated. The organic layer was extracted with satd NaCl soln twice. The organic solution was dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography (30–40% EtOAc–hexanes) to provide 10.06 g (81%) of the methylated deoxygenated sugar as a colorless oil. This material is obtained as an ~4:1 mixture of anomers; NMR data are given for the major isomer, other values are for the mixture: $[\alpha]_D$ +24° (*c* 1.0, CH_2Cl_2); IR: ν 3408 (O–H), 3086, 3062, 3030 (Ar C–H), 1496, 1455 (Ar C–C) cm^{-1}; ^1H NMR (400 MHz, acetone-d_6): δ 7.42–7.22 (m, 15 H, 3 Ph), 5.34 (d, 1 H, *J* 3.6 Hz, OH), 5.08 (dd, 1 H, $J_{1,2}$ 1.7 Hz, H-1), 4.90 and 4.58 (2 d, 2 H, J_{gem} 11.2 Hz, PhCH_2), 4.67 and 4.55 (2 d, 2 H, J_{gem} 11.7 Hz, PhCH_2), 4.59 and 4.50 (2 d, 2 H, J_{gem} 12.0 Hz, PhCH_2), 4.08 (dd, 1 H, *J* 5.2, 9.0 Hz, H-3), 4.00 (ddd, 1 H, *J* 1.7, 4.6, 9.8 Hz, H-5), 3.78–3.61 (m, 3 H, H-4,6a,6b), 2.42 (m, 1 H, H-2), 1.04 (d, 3 H, $J_{Me,2}$ 7.3 Hz, CH_3). ^{13}C NMR (100 MHz, acetone-d_6): δ 11.64, 37.93, 70.59, 71.16, 72.04, 73.59, 75.08, 75.35, 80.07, 96.77, 127.98, 128.02, 128.28, 128.30, 128.44, 128.85, 128.95, 139.76, 140.02, 140.07. Anal. Calcd for $C_{28}H_{32}O_5$: C, 74.97; H, 7.19. Found: C, 74.85; H, 7.20.

*3,4,6-Tri-*O*-benzyl-2-*C*-methyl-*D*-glucal (1,5-anhydro-2,4,6-tri-*O*-benzyl-2-*C*-methyl-*D*-arabino-hex-1-enitol)* (**4**).—To a solution of **3b** (4.81 g, 10.7 mmol) in CH_2Cl_2 (160 mL) was added 4-dimethylaminopyridine (DMAP, 152 mg, 1.24 mmol) followed by

Et_3N (20 mL, 143 mmol). The solution was cooled in an ice–water bath followed by the addition of mesyl anhydride (4.70 g, 27.0 mmol). After 10 min, the ice bath was removed. After stirring for 14 h at rt, the solution was added to 1 M NaOH (200 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried (K_2CO_3), filtered, concentrated, and purified by flash chromatography (15% EtOAc–hexanes) to provide 3.89 g (84%) of the glycal as a colorless oil: $[\alpha]_D$ +9° (*c* 1.0, CH_2Cl_2); IR: ν 3086, 3063, 3030 (Ar C–H), 1673 (C=C), 1496, 1453 (Ar C–C) cm^{-1}; ^1H NMR (400 MHz): δ 7.39–7.28 (m, 15 H, 3 Ph), 5.27 (br s, 1 H, H-1), 4.72 and 4.67 (2 d, 2 H, J_{gem} 11.6 Hz, PhCH_2), 4.62 and 4.54 (2 d, 2 H, J_{gem} 11.4 Hz, PhCH_2), 4.58 (s, 2 H, PhCH_2), 4.17–4.12 (m, 1 H, H-5), 4.01 (br d, 1 H, $J_{3,4}$ 5.0 Hz, H-3), 3.95 (dd, 1 H, $J_{4,5}$ 6.9 Hz, H-4), 3.82 and 3.74 (2 dd, 2 H, $J_{5,6a}$ 5.5, $J_{5,6b}$ 3.5, $J_{6a,6b}$ 10.5 Hz, H-6a,6b), 1.64 (br s, 3 H, CH_3). ^{13}C NMR (100 MHz): δ 14.60, 68.22, 71.46, 72.87, 73.29, 73.68, 75.87, 77.60, 108.07, 127.50, 127.55, 127.61, 127.68, 127.79, 128.24, 128.26, 128.33, 137.95, 138.25, 139.82. Anal. Calcd for $C_{28}H_{30}O_4$: C, 78.11; H, 7.02. Found: C, 77.90; H, 7.04.

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