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Note

Synthesis of 2,3,4,6-tetra-*O*-benzyl-D-glucal on the gram scale. A convenient method for its facile synthesis and subsequent stereoselective cyclopropanation

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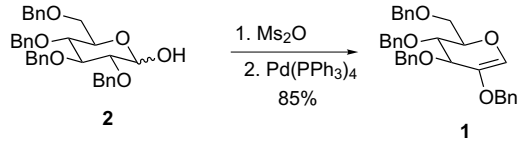
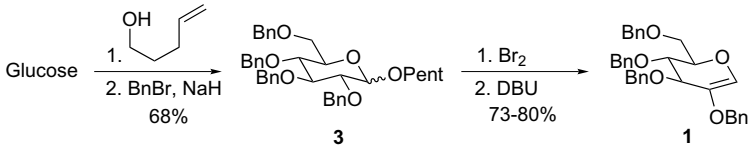
Due to their utility in a variety of processes, glycals have received considerable attention in the carbohydrate field.[1] Examples include Danishefsky's epoxidation/glycosidation methodology,[2] Ferrier-type rearrangements,[3] cyclopropanations,[4] C-glycosylations,[5] and metal-catalyzed transformations.[6] Reports on the use of 2,3,4,6-tetra-*O*-benzyl-D-glucal (**1**), however, have been limited, perhaps due to its low yielding and problematical synthesis. The most recently reported synthesis involves the mesylation then $Pd(PPh_3)_4$-catalyzed elimination of **2** (Eq. 1).[7] We have found this strategy to be difficult as the use of pristine methanesulfonic anhydride is required, purification of **1** by radial chromatography is required,[†] and the synthesis of **2**[8] is low yielding (29%). Other reports of the formation of **1** as byproducts in reactions of diazirines have also appeared, but these do not appear to be synthetically useful.[9]



(1)

Glycal **1** has been shown to be useful in epoxidation[10] and lithiation[11] chemistry and would presumably be an excellent substrate for our[12] and others' recently developed cyclopropanation chemistry.[4] We have therefore developed a more facile synthesis of **1** based on well-established procedures[13] using Fraser-Reid's *n*-pentenyl glycoside chemistry. Thus, pentenyl glycoside **3** is prepared according to literature procedure in two steps and overall 68% yield (Eq. 2).[14] Glycoside **3** is subsequently treated with bromine,[15] followed by DBU. As reported, the bromination of **3** gives exclusively α-D-glucopyranosyl bromide, thus allowing for the subsequent



(2)

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† Our attempted purification via flash chromatography resulted in an impure product.

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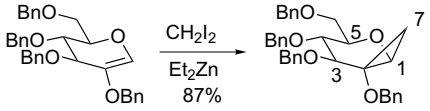
antiperiplanar elimination reaction. The overall process is highly reproducible, and we have synthesized glycal **1** on the gram scale. We prefer using Fraser-Reid's methodology for the formation of the glucopyranosyl bromide, as apposed to other methods,[16] since it is a highly robust, short, and facile procedure and allows for a multigram synthesis. It should be noted that the addition of bromine to **3**, followed by immediate treatment with DBU, is critical, as prolonged exposure to bromine leads to lower yields.

Straightforward access to **1** has enabled us to initiate a new area of chemistry of this glycal (Eq. 3). Using Furukawa cyclopropanation conditions,[17] the allylic oxygen-directed cyclopropanation[18] gave cyclopropane **4** in 87% yield and as a single diastereomer. The stereochemistry of the cyclopropane derivative **4** was determined by NOE experiments in which positive effects were observed between H-1, H-3, and H-5. This stereochemistry is in agreement with the cyclopropanation of tri-*O*-benzyl-D-glucal.[12c,19]



1 **4** (3)

In summary, we have developed new methodology suitable for the convenient and large-scale synthesis of 2,3,4,6-tetra-*O*-benzyl-D-glucal. The cyclopropanation of this glycal has been achieved in excellent yield and selectivity, and the chemistry of this new derivative will be reported in due course.

1. Experimental

1.1. General

All reactions were carried out under argon using oven-dried glassware unless otherwise stated. Purification of products via flash chromatography was conducted using E. Merck Silica Gel 60 using distilled MeOH, CH_2Cl_2, hexanes, or EtOAc. ^1H and ^{13}C NMR spectra were recorded on a Varian INOVA spectrometer at 300 and 75 MHz, respectively, in $CDCl_3$. 4-Penten-1-ol was synthesized using the published procedure.[20] The synthesis of **3** is reported as a modification of literature procedures[15,21] and was obtained as a mixture of anomers.

1.1.1. Pent-4-enyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (3). A mixture of D-glucose (5.00 g, 27.8 mmol), 4-penten-1-ol (40 mL), and camphorsulfonic acid (100 mg, 0.43 mmol) was refluxed for 48 h with vigorous stirring. The solution was quenched with Et_3N (~0.25 mL), and the bulk of the pentenol alcohol was distilled for reuse under vacuum using a liquid nitrogen condenser. The residue was poured into water, washed with CH_2Cl_2, and the aqueous layer was concentrated under vacuum to give a brown crystalline substance. Flash chromatography using a gradient mixture of 20:1–10:1 CH_2Cl_2–MeOH gave 5.70 g (85% yield) of pent-4-enyl D-glucopyranoside as an oil. R_f 0.15 (9:1 CH_2Cl_2–MeOH). A 2.00-g (8.10 mmol) sample of this oil was dissolved in DMF (20 mL), then added dropwise to a suspension of NaH (1.35 g, 56.5 mmol) in DMF (20 mL) at 0 °C. After hydrogen evolution subsided, benzyl bromide (6.07 g, 35.5 mmol) was slowly added and then stirred overnight, while warming to room temperature. The reaction was quenched with MeOH, diluted with Et_2O (250 mL), and washed with water (100 mL), satd aq $NaHCO_3$ (100 mL), and brine (100 mL), and the Et_2O extract was then dried with Na_2SO_4. After filtration and concentration, the crude residue was purified by flash chromatography (10:1 hexanes–EtOAc) to give 4.00 g (82% yield) of **3** as a mixture of α and β anomers that existed as a white crystalline solid (β anomer) in a colorless oil (α anomer): R_f 0.58 (5:1 hexanes–EtOAc). Comparison of the NMR spectrum to that reported was identical in all respects.[21]

1.1.2. 1,5-Anhydro-2,3,4,6-tetra-*O*-benzyl-D-*arabino*-hex-1-enitol (1). Bromine (1.83 mL of a 1.98 M soln in CH_2Cl_2, 3.33 mmol) was added dropwise to a solution of **3** (2.0 g, 3.30 mmol) in CH_2Cl_2 (20 mL) at 0 °C until the solution maintained an orange color. The solvent was immediately removed in vacuo at 20 °C, leaving an orange oil characterized by a one-proton doublet at 6.45 (J 3.7 Hz) in the ^1H NMR spectrum. The resulting oil was redissolved in CH_2Cl_2 (20 mL), cooled to −20 °C, and 1,5-diazabicyclo[5,4,0]-undec-5-ene (DBU) (1.01 g, 6.60 mmol) was added dropwise over 10 min. The solution was stirred for 30 min in the dark, with warming to room temperature. The mixture was diluted with CH_2Cl_2 (50 mL), washed successively with 5% HCl, water, and satd aq $NaHCO_3$, and the extract was dried with $MgSO_4$, filtered, and concentrated. The crude residue was purified by flash chromatography (10:1 hexane–EtOAc) to give **1** as a colorless oil that solidified on standing (1.25 g, 73% yield). Recrystallization from MeOH can be performed but is generally not required: R_f 0.54 (5:1 hexanes–EtOAc). IR: 1098, 1070, 1027 cm^{-1}; ^1H NMR: δ 3.70–3.82 (m, 2H, H-6), 3.92 (dd, J 5 Hz, J 2 Hz, 1H, H-4), 4.11–4.16 (m, 1H, H-5), 4.29 (d, J 5 Hz, 1H, H-3), 4.55–4.80 (m, 8H, CH_2Ph), 6.34 (s, 1H, H-1), 7.26–7.37 (m, 20H, Ar); ^{13}C NMR: δ 139.1, 138.6, 138.3, 138.1, 137.4, 128.7–127.8 (aromatic), 76.4, 75.9, 75.8, 74.4, 73.7, 73.1, 72.5, 71.2, 68.5. Anal. Calcd for $C_{34}H_{34}O_5$: C, 78.14; H, 6.56. Found: C, 78.56; H, 6.76.

1.1.3. 1,5-Anhydro-2,3,4,6-tetra-*O*-benzyl-2-deoxy-1,2-*C*-(methylene)-D-*glycero*-D-hexitol (4). To a solution of **1** (380 mg, 0.727 mmol) in CH_2Cl_2 (4.0 mL) at 0 °C was added Et_2Zn (4.4 mL, 1 M in hexane, 4.36 mmol), fol-

lowed by CH_2I_2 (351 μL, 4.36 mmol). The reaction was stirred at 0 °C for 1 h, then 9 h at room temperature. The solution was poured into satd aq NH_4Cl (50 mL) and extracted with Et_2O (2×20 mL). The ether layers were washed with brine (50 mL), dried with $MgSO_4$, filtered, and concentrated. Flash chromatography with 10:1 hexanes–EtOAc gave **4** (340 mg, 87%) as a colorless oil. IR: 1163, 1078 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.20 (m, 1H, H-7b), 1.31–1.38 (m, 1H, H-7a), 3.93 (dd, *J* 3.9 Hz, 1H, H-1), 4.46 (d, *J* 10.9 Hz, 1H, H-3), 3.25 (m, 1H, H-4), 3.56 (m, 1H, H-5), 3.73 (d, *J* 8.5 Hz, 2H, H-6), 4.49–5.01 (m, 8H, CH_2Ph), 7.17–7.41 (m, 24H, CH_2Ph); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.8 (C-7), 60.1 (C-1), 66.3 (C-2), 69.5 (C-6), 77.5 (C-5), 79.5 (C-4), 80.4 (C-3); HRMS: Calcd for $C_{35}H_{36}O_5Na$ [M+Na], *m*/*z* 559.2455; found, *m*/*z* 559.2539.

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