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Note

Synthesis of 1,2-anhydro-3,4,6-tri-*O*-benzyl-α-D-glucopyranose

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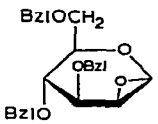
Sugar derivatives having an epoxide ring linked to C-1 have as synthetic intermediates, although few examples have been rep We have recently summarized the available information in the fiel that these derivatives can best be prepared by SN2 reaction of a fre bearing a leaving group[1]. The successful synthesis of 1,2-anhydro-3, β-D-mannopyranose (**1**) demonstrated the validity of this approa specific polymerization of **1** with inversion at C-1 to form a low-r (1→2)-α-D-mannopyranan[2] suggested that 1,2-anhydro-3,4,6-tri-*O*-b pyranose (**2**) should be an appropriate monomer for the formatio glucopyranans, a current objective of our research.

Initial attempts to form **2** involved treatment of 3,4,6-tri-*O*-b pyranosyl chloride or bromide with base. 3,4,6-Tri-*O*-benzyl-D-gluc was treated with hydrogen chloride in ether and chloroform to f benzyl-α-D-glucopyranosyl chloride (**4**). This compound is stable and can be readily isolated, in contrast to its D-mannopyranosyl e highly reactive and labile. (The greater reactivity of the latter co doubtedly due to the *trans*-diaxial relationship of substituents at Compound **4** failed to react with ammonia in the presence or absen ammonium bromide and could be isolated largely unchanged fro mixtures.

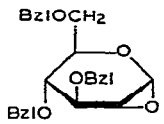
When the more reactive 3,4,6-tri-*O*-benzyl-α-D-glucopyranos was prepared under similar conditions and allowed to react with tetrab bromide and ammonia, no anhydro sugar was found, but a mixture formed. Analysis of the product mixture by h.p.l.c. on polyvinyl ac suggested the presence of two main fractions, one of which prob hydroxyl groups[1,5]. Gel permeation chromatography suggested that probably were dimeric. This reaction course was not changed in a mo system. Presumably, formation of the disaccharide and cyclic dime

the sequence of bromide anomerization, conformational change to $^1C_4$(D) with diaxial groups at C-1 and C-2, and intramolecular reaction.

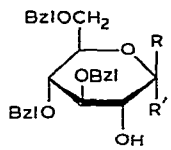
In contrast, a modification of the method of Micheel and Kreutzer[6,7] for the formation of 1,4-anhydro-2,3,6-tri-*O*-benzyl-α-D-glucopyranose proved successful. The D-glucosyl chloride derivative **4** was allowed to react with silver fluoride to form stable, crystalline 3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl fluoride (**6**). Ring closure did not occur on treatment with ammonia but was effected with potassium *tert*-butoxide in benzene. The desired product was separated from residual inorganic material, *tert*-butanol, and dimers by passage through a Styragel permeation column and further purified by h.p.l.c. Prior washing appeared to decrease the yield. The resulting syrup crystallized spontaneously, and careful recrystallization[1] gave 1,2-anhydro-3,4,6-tri-*O*-benzyl-α-D-glucopyranose (**2**) of correct analysis. The yield of **2** was better when it was prepared from **3** without isolation of intermediates.



1



2



3 R, R′ = H, OH
4 R = H, R′ = Cl
5 R = H, R′ = Br
6 R = F, R′ = H

The ^{1}H-n.m.r. spectrum of **2** is consistent with the assigned structure and specifically with the presence of an oxirane ring involving C-1 and C-2. No peak was observed between δ 5 and 6, where the signal for the anomeric proton of glucopyranoside derivatives is expected. A doublet at δ 3.04 and a doublet of doublets at 4.98 were assigned to H-2 and H-1 by decoupling experiments. In the case of the corresponding anhydro-D-mannose derivative **1**, the signal for H-2 appears as a doublet of doublets, since the dihedral angles between the bonds C-1–H-1, C-2–H-2, and C-3–H-3 are from 0 to <60°, whereas in **2**, the dihedral angle between C-2–H-2 and C-3–H-3 is nearer 90°. In **1**, H-1 is visibly coupled only to H-2, whereas in **2**, H-1 is also engaged in long-range coupling.

The ^{13}C-n.m.r. spectrum of **2** is also similar to that of **1**. A characteristic C-2 peak at 52.7 was observed, as compared to 54.3 p.p.m. for C-2 of **1**.

EXPERIMENTAL

Methods and materials. — Instrumental characterization and synthetic operations were carried out as described previously[1]. H.p.l.c. was carried out by use of a Valvco septumless injector (1.0 mL), a Glenco pump (Model HPLPS-1), a Waters differential refractometer R-401, with stainless-steel columns (60 × 1.9 cm o.d.) containing Styragel (100 Å, Waters Assoc., Milford, MA 01757) for gel permeation

separation, or polyvinyl acetate (Fractogel PVA 6000, EM Laboratories Inc., Elmsford, NY 10523) for partition chromatography; the flow rate of toluene was 3.0 mL/min. To separate the glycosyl chloride and fluoride derivatives **4** and **6**, a silica gel column (Whatman, Partisil M9 10/25) and ethyl acetate–hexane as eluent at a flow rate of 8.0 mL/min were used with the same instrumentation.

1,2-Anhydro-3,4,6-tri-O-benzyl-α-D-glucopyranose (**2**). — 3,4,6-Tri-*O*-benzyl-D-glucopyranose[3,4] (**3**; 0.8 g, m.p. 89–90°) was dissolved in pure chloroform (5 mL) in the reaction vessel previously described[1], and anhydrous ether (50 mL) was added, with a syringe, under nitrogen. The solution was saturated with hydrogen chloride while being cooled in an ice bath. The reaction vessel was closed and stored for 2 days at 0°. It was then allowed to return to room temperature (with release of pressure), and benzene (50 mL) was added. Hydrogen chloride was removed by passing a stream of nitrogen for 1 h. Powdered Linde 4 Å molecular sieve (5 mL) was added, and the nitrogen flow continued for an additional hour. The solution was neutralized with ammonia gas and filtered under vacuum into another round-bottomed flask containing a Teflon-coated, magnetic stirring-bar. The first flask and sieves were washed with benzene (30 mL), and the wash liquors added to the second flask by vacuum filtration. Benzene (50 mL) and acetonitrile (10 mL) were added directly to the second flask. Silver fluoride (0.40 g) was added to the solution, the reaction vessel was wrapped in aluminum foil, and the reaction solution was stirred vigorously overnight. A white precipitate formed after addition of silver fluoride. The solution was transferred by vacuum filtration into another round-bottomed flask containing toluene (50 mL) and concentrated to ~50 mL. Potassium *tert*-butoxide was prepared from *tert*-butyl alcohol and 1.3 equiv. of potassium (based on **3**), dried *in vacuo*, and added to the residue. After addition of the base, the solution turned yellow and then dark maroon. The solution was kept for 5 h at room temperature, and then evaporated under vacuum to a syrup. The syrup was dissolved in toluene (~10 mL), and the solution fractionated by h.p.l.c. in Styragel and polyvinyl acetate. Appropriate fractions were combined and evaporated to a syrup that crystallized spontaneously. (It is probable that toluene could be used throughout instead of benzene. This change would help in the removal of acetonitrile and simplify the procedure.) The solid, crystalline residue was transferred to the crystallization apparatus[1], recrystallized from benzene–hexane, and stored as previously described for **1** (yield ~0.27 g), m.p. 77–78°, $[\alpha]_D^{25}$ +31.1° (*c* 0.5, chloroform); ^{1}H-n.m.r.: δ 7.36–7.20 (m, 15 H, aromatic H), 5.00–4.95 (dd, 1 H, $J_{1,2}$ ~2.4, $J_{1,3?}$ ~1.0 Hz, H-1), 4.88–4.60 (m, 6 H, C*H*C$_6$H$_5$), 3.72–3.68 (bs, 2 H, H-6), 4.02–3.92 (d or bm, 1 H, H-4?), 3.75–3.55 (bm, 2 H, H-3 and -5?), and 3.07–3.03 (d, 1 H, $J_{1,2}$ ~2.4 Hz, H-2); ^{13}C-n.m.r.: 138.3, 128.8, 128.6, 128.0, 127.9 (aromatic); 79.2, 77.6, 74.5, 69.7, 52.7 (=CH-); and 74.6, 73.7, 72.5, 68.5 (-CH$_2$-).

Anal. Calc. for $C_{27}H_{28}O_5$: C, 74.98; H, 6.53. Found: C, 75.61; H, 6.53.

3,4,6-Tri-O-benzyl-α-D-glucopyranosyl chloride (**4**). — The ammonia-neutralized solution, described for the preparation of **2**, was evaporated to a syrup and the residue fractionated by silica gel chromatography in 1:2 (v/v) ethyl acetate–hexane (~5 mL),

as described earlier. The eluate was evaporated, and crystals were obtained spontaneously from the appropriate fractions. The product was recrystallized from carbon tetrachloride–hexane (yield 73%); m.p. 85–85.5°; $[\alpha]_D^{25}$ +128.3° (*c* 1.27, chloroform); the configuration at C-1 was established by anomeric-proton coupling in the n.m.r. spectrum.

Anal. Calc. for $C_{27}H_{29}ClO_5$: C, 69.14; H, 6.23; Cl, 7.56. Found: C, 69.61; H, 6.44; Cl, 7.20.

*3,4,6-Tri-*O*-benzyl-β-*D*-glucopyranosyl fluoride* (**6**). — After silver fluoride treatment for the preparation of **2**, the solution was separated from solids, evaporated to a syrup, and fractionated by silica gel chromatography in 1:2 (v/v) ethyl acetate–hexane (~5 mL). The eluate was crystallized from carbon tetrachloride–hexane (yield 40%); m.p. 81°, $[\alpha]_D^{25}$ +37.3° (*c* 0.85, chloroform); the configuration at C-1 was established by anomeric-proton coupling in the n.m.r. spectrum.

Anal. Calc. for $C_{27}H_{29}FO_5$: C, 71.7; H, 6.5; F, 4.2. Found: C, 71.2; H, 6.2; F, 4.7.

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