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Synthesis of 1,4-anhydro-2,3,6-tri-*O*-benzyl-*α*-D-glucopyranose by *cis*-ring-closure of a glycosyl chloride

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ABSTRACT

A synthetic approach to 1,4-anhydro-2,3,6-tri-*O*-benzyl-*α*-D-glucopyranose by *cis*-ring closure of a glycosyl chloride has been studied to furnish a starting sugar for the synthesis of a linear (1→4)-linked polysaccharide. Cyclomaltoheptaose was benzylated and the product hydrolyzed to afford 2,3,6-tri-*O*-benzyl-*α*-D-glucopyranose, which was converted by HCl–Et_2O into the corresponding glycosyl chloride. Treatment of the latter with NaH in Me_2SO gave mainly 2-benzyloxy-3,6-di-*O*-benzyl-D-glucal, with 1,4-anhydro-2,3,6-tri-*O*-benzyl-*α*-D-glucopyranose as a byproduct. However, the 1,4-anhydro sugar could be prepared in good yield by *cis* ring-closure of 2,3,6-tri-*O*-benzyl-*α*-D-glucopyranosyl chloride in a mixture of tetrahydrofuran and sodium hydride.

INTRODUCTION

Many synthetic polysaccharides have been obtained by stepwise coupling, polycondensation, ring-opening polymerization, and the orthoester method. As the ring-opening polymerization of an anhydro sugar could give polysaccharides with a high degree of polymerization, some preparations of 1,4-anhydro sugars by ring closure of trisubstituted glucopyranosyl derivatives have been examined. The *cis* closure of a 1,4-anhydro ring has been demonstrated in heterogeneous reactions of trimethylated glucopyranose derivatives[1-3]. Micheel and Kreutzer[4] reported the synthesis of 1,4-anhydro-2,3,6-tri-*O*-benzyl-*α*-D-glucopyranose by *trans*-closure of the *β*-glycosyl fluoride.

In this work, we report the preparation of 1,4-anhydro-2,3,6-tri-*O*-benzyl-*α*-D-glucopyranose by *cis* ring-closure of a glycosyl chloride, and the reaction mechanism is discussed.

RESULTS AND DISCUSSION

Although many cyclomaltoheptaose (*β*-CD) derivatives have been prepared, the benzylation of *β*-CD has not been reported. Accordingly, benzylation of *β*-CD was

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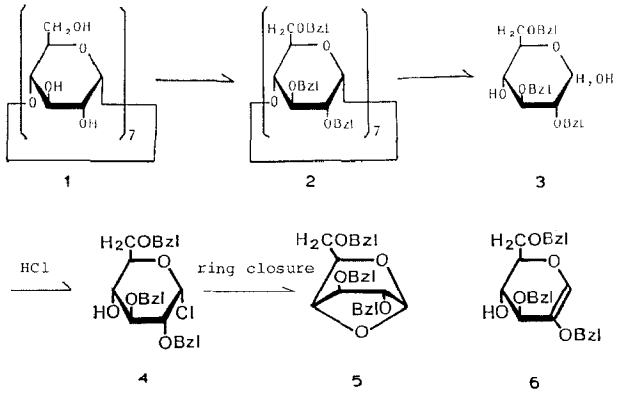
attempted by reaction with benzyl chloride in dimethyl sulfoxide sodium hydride.

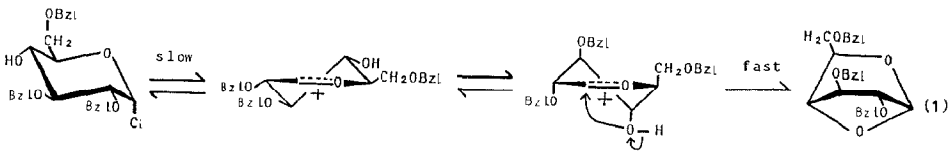
The preparation of 2,3,6-tri-*O*-benzyl-β-CD (**2**) was carried out with stirring for 6 h at 21° and the product identified by its i.r. spectrum, ^{1}H-n.m.r. data, and elemental analysis. Acid hydrolysis of **2** with 75% aqueous sulfuric acid, with chromatographic purification gave pure, crystalline 2,3,6-tri-*O*-benzyl-α-D-glucopyranose (**3**) in 43% yield, which is higher than that obtained by hydrolysis of corresponding cellulose[5], maltose[4], and amylose[6,7] derivatives.

The tribenzylated glucopyranose **3** was treated with hydrogen chloride in diethyl ether to afford the corresponding glycosyl chloride **4**.



The 1,4-anhydro sugar derivative **5** was obtained by ring closure of **4** under various conditions. When ring closure of **4** was performed by stirring at room temperature in a mixture of Me_2SO and sodium hydride, two fractions were obtained that were separated by chromatography. The first (minor) fraction was found to be 1,4-anhydro-2,3,6-tri-*O*-benzyl-α-D-glucopyranose (**5**); (yield, 8%), identified by ^{1}H-n.m.r. The second (major) fraction was identified as 2-benzyloxy-3,6,-di-*O*-benzyl-D-glucal (**6**); (yield, 62%), identified by ^{13}C-n.m.r. In order to improve the yield of the 1,4-anhydro sugar **5** and avoid the co-product **6**, ring closure was examined with sodium hydride in tetrahydrofuran for 6 h at room temperature, under which conditions the 1,4-anhydro sugar **5** was the main product.

Micheel[4] reported earlier that the 1,4-anhydro sugar can be synthesized from 2,3,6-tri-*O*-benzyl-β-D-glucopyranosyl fluoride by an SN2 type of ring closure involving the hydroxyl and leaving groups *trans*-disposed on two different carbon atoms. In this work, the chloride **4** was converted into the 1,4-anhydro sugar **5** by an SN1 type of ring closure, as shown (Eq. *1*).



EXPERIMENTAL

General methods. — N.m.r. spectra were recorded with a JEOL FX-200 spectrometer, in the Fourier-transform mode, for solutions in chloroform-*d*, with tetramethylsilane (Me_4Si) as the internal standard. Chemical shifts are expressed in p.p.m. downfield from internal Me_4Si. Optical rotations were determined with a JASCO ORD/UV-5 model for solutions in 1-dm, jacketed cells. Melting points were determined with a micro melting-point apparatus. T.l.c. was performed on silica gel (Merck, Kieselgel, 60G, Art. 7731) plates (1.5 × 7.5 cm).

High-pressure, liquid chromatography (l.c.) was performed with a injector (0.5 mL), a U-1 column (2.5 × 50 cm) containing silica gel (Wako-Gel, C-300), at a flow rate of 1.5 mL·min^{-1}.

Chromatography-grade active charcoal, silicic acid, and Celite, were used.

2,3,6-Tri-O-benzyl-β-cyclomaltoheptaose (**2**). — Cyclomaltoheptaose (β-CD, **1**) (5.0 g, 92.5 mmol) was dissolved in Me_2SO (250 mL), to which a suspension of sodium hydride (3 g, 126 mmol) in Me_2SO (50 mL) was added. The mixture was kept at 21° with stirring, and benzyl chloride (14 mL, 122 mmol) was added dropwise during 1 h, and the reaction was monitored by i.r. spectroscopy. After stirring for 6 h, the hydroxyl absorption of β-CD had completely disappeared. The mixture was poured into water, the isolated product was dissolved in acetone, and the filtrate was evaporated. The crude benzylated β-CD was purified by reprecipitation several times with a Me_2CO–MeOH system.

The residue was dissolved in Et_2O and the solution evaporated to give **2** as a pure powder (yield, 10.2 g); ^{1}H-n.m.r. ($CDCl_3$): 7.20 (m, 5 H, aromatic) and 5.04–4.35 (m, 2 H, OCH_2).

Anal. Calc. for $C_{27}H_{28}O_5$: C, 74.99; H, 6.53. Found: C, 74.96; H, 6.52.

Preparation of 2,3,6-tri-O-benzyl-α-D-glucopyranose (**3**). — The tribenzylated-β-CD **2** (5.0 g, 3.5 mmol) was dissolved in 1,4-dioxane (250 mL), to which 75% aq. H_2SO_4 (20 mL) had been added, and the mixture was stirred at 100°.

The reaction was stopped after 3 h, even though t.l.c. [1:3:5 (v/v/v) Me_2CO–$CHCl_3$–petroleum ether] still showed a little residual **2**. The cooled mixture was extracted with $CHCl_3$ and the extract was washed 3 times with aq. $NaHCO_3$, and then 3 times with water, and dried (Na_2SO_4). Evaporation of the organic layer gave a crude syrup that was dissolved in benzene and the solution passed through a column containing 3 layers of activated charcoal, silicic acid, and Celite, respectively, and then purified by chromatography on a column of silica gel [1:5(v/v) Me_2CO–petroleum ether]. The isolated fraction (R_F 0.09) was evaporated and the residue dissolved in Me_2CO–petroleum ether. Subsequently, the benzylated glucopyranose derivative **3** was obtained by very slow crystallization from Me_2CO–petroleum ether at room temperature; fine needles (yield, 43%), m.p. 107.5–108°, $[\alpha]_D$ +6.0° (*c* 1, $CDCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 7.30 (m, 5 H, aromatic), 5.00–4.30 (m, 2 H, OCH_2), and 2.53, 2.13 (broad, 1 H, 1,4-OH); ^{13}C-n.m.r. ($CDCl_3$): δ 138.50, 137.74, 137.35 (aromatic C-1), 128.54. 128.38, 127.09, 127.99, 127.68 (aromatic), 93.35 (C-1), 80.60, 79.44, 75.45, 73.60, 73.23, 72.68, 69.57

(C-2, C-3, C-4, C-5, OCH_2), and 68.60 (C-6).

Anal. Calc. for $C_{27}H_{30}O_6$: C, 71.98; H, 6.71. Found: C, 71.92; H, 6.86.

Preparation of 2,3,6-tri-O-benzyl-α-D-glucopyranosyl chloride (**4**). — Compound **4** was prepared by a modification of the method of Micheel and Kreutzer[4]. The tribenzylated glucopyranose **3** (3.8 g, 2.7 mmol) was dissolved in abs. Et_2O (50 mL), and under a nitrogen atmosphere, the solution was saturated with HCl for 20 min at 0°. After being kept at room temperature, the solution was stirred for 24 h, and nitrogen gas was bubbled into the solution to remove HCl. Addition and evaporation (at < 20°) of the solvent was repeated several times to remove the remaining HCl. The resultant syrup was dissolved in CH_2Cl_2 (300 mL) and the solution was washed with aq. $NaHCO_3$, water, and then dried ($MgSO_4$). Evaporation of the organic layer gave a crude syrup, which was dissolved in benzene and the solution passed through a column containing 3 layers of active charcoal, silicic acid, and Celite, respectively. The resultant syrup was then purified by chromatography on a column of silica gel (1:1:2, v/v/v, isopropyl ether–cyclohexane–benzene) and the solution was evaporated to give a pale-yellow syrup of **4** (yield, 76%), R_F 0.30 (1:5 v/v, acetone–petroleum ether), $[\alpha]_D$ +62.0° (*c* 1, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 6.08 (d, 1 H, J_{vic} 6.4 Hz, anomeric) and 2.14 (s, 1 H, 4-OH); ^{13}C-n.m.r. ($CDCl_3$): δ 138.50, 137.95, 137.35 (aromatic C-1), 128.54, 128.38, 128.09, 127.99, 127.68 (aromatic), 93.35 (C-1), 80.60, 79.44, 75.45, 43.60, 73.23, 72.68, 69.57 (C-2, C-3, C-4, C-5, OCH_2), and 68.6 (C-6).

Anal. Calc. for $C_{27}H_{29}ClO_5$: C, 69.15; H, 6.23; Cl, 7.56. Found: C, 68.41, H, 6.22; Cl, 8.57.

Preparation of 1,4-anhydro-2,3,6-tri-O-benzyl-α-D-glucopyranose (**5**). — *Method* A. The chloride **4** (1.0 g, 0.7 mmol) was dissolved in tetrahydrofuran (500 mL), to which sodium hydride (0.27 g, 11.3 mmol) was added. The mixture was stirred for 6 h at room temperature, and the filtrate was extracted with $CHCl_3$ and washed with water. The organic layer was dried ($MgSO_4$) and evaporated to give the 1,4-anhydro sugar **5** as a clear, colorless syrup (yield, 93%), R_F 0.30 (1:5 v/v, acetone–petroleum ether); $[\alpha]_D$ −10.5° (*c* 1, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 5.44 (s, 1 H, anomeric); ^{13}C-n.m.r. ($CDCl_3$): δ 138.07, 137.55, 137.37 (aromatic C-1), 128.46, 128.30, 127.88, 127.74, 127.60 (aromatic), 103.12 (C-1), 78.33 (C-4), 86.44, 84.85, 76.05, 73.21, 73.17, 71.73 (C-2, C-3, C-5, OCH_2), and 69.32 (C-6).

Anal. Calc. for $C_{27}H_{28}O_5$: C, 74.98; H, 6.53. Found: C, 74.80; H, 6.62.

Method B. The chloride **4** (2.0 g, 1.4 mmol) was dissolved in Me_2SO (50 mL), to which NaH (0.14 g) had been added.

After stirring for 24 h at room temperature, the solution was poured into water and dialyzed with running water for 1 week.

The solution was extracted with $CHCl_3$, and the extract was evaporated to dryness. The crude product was separated into two fractions by chromatography on a column of silica gel (1:5 v/v, Me_2CO–petroleum ether). The first fraction (R_F 0.36) was the 1,4-anhydro sugar **5** (yield, 8%). The second fraction (R_F 0.22) was 2-benzyloxy-3,6-di-*O*-benzyl-D-glucal (**6**).

The major product **6** was crystallized from Me_2CO–petroleum ether (yield, 62%), $[\alpha]_D$ −22° (*c* 1, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 6.26 (s, 1 H, anomeric) and 2.42 (s, 1

H, 4-OH); ^{13}C-n.m.r. ($CDCl_3$): δ 138.77 (C-2), 138.48, 137.86, 137.06 (aromatic C-1), 128.40, 127.89, 127.76, 127.66, 127.50 (aromatic), 116.10 (C-1), 77.14, 76.87, 73.54, 42.53, 71.15, 68.68 (C-3, C-4, C-5, OCH_2), and 68.64 (C-6).

Anal. Calc. for $C_{27}H_{28}O_5$: C, 75.98; H, 6.53. Found: C, 74.60; H, 6.58.

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