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Note

A facile synthesis of 6-deoxy-D-glucose. Reduction of a primary sulfonate with lithium triethylborohydride

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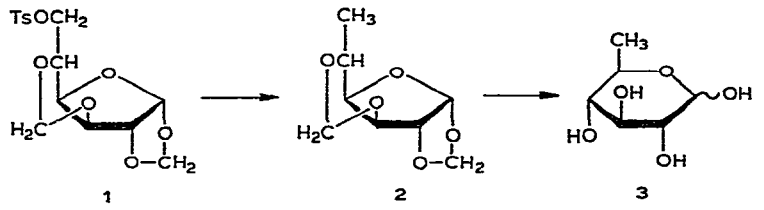
6-Deoxy-D-glucose (D-quinovose) has generally been prepared by rather lengthy, multistep syntheses requiring the selective blocking and deblocking of D-glucose, formation of terminal iodo compounds, and catalytic hydrogenolysis[1]. One of the shorter, more direct routes to 6-deoxy-D-glucose involves the formation of methyl 6-chloro-6-deoxy-α-D-glucopyranoside in one step from methyl α-D-glucopyranoside by reaction with methanesulfonyl chloride in *N,N*-dimethylformamide and reduction with lithium aluminum hydride[2]. The disadvantages of this route are the sluggishness of the reduction and the required chromatographic separation of the products at each step. Previously, another synthesis of 6-deoxy-D-glucose was achieved from D-mannose[3]. This route consisted of the formation of methyl 5-*O*-benzoyl-6-deoxy-2,3-*O*-isopropylidene-α-D-mannofuranoside and inversion of configuration at C-2 by acetolysis to obtain 1,2,3-tri-*O*-acetyl-5-*O*-benzoyl-6-deoxy-D-glucofuranose which was de-esterified to the free sugar. One advantage of this route is the formation of a hexofuranose derivative that can be utilized for the synthesis of furanose glycosides and nucleosides. Indeed, a similar route starting from 6-deoxy-L-mannose has been utilized for the preparation of 9-(6-deoxy-β-L-glucofuranosyl)adenine[4]. A previous synthesis of 6-deoxy-D-glucose had also utilized D-glucose in the furanose form[5]. Reduction of the terminal carbon of 3,5-*O*-benzylidene-1,2-*O*-isopropylidene-6-*O*-*p*-tolylsulfonyl-α-D-glucofuranose with lithium aluminum hydride resulted in the formation of 3,5-*O*-benzylidene-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose. This was also a multistep procedure which required chromatographic isolation of the desired product from a major by-product and gave only moderate yields. We wish to report a new synthesis, accomplished in only a few steps and affording high yields, of 6-deoxy-D-glucose from D-glucose that alleviates the problems of previous preparations and gives a blocked intermediate in the furanose form.

D-Glucose was converted in three steps to 1,2:3,5-di-*O*-methylidene-6-*O*-*p*-tolylsulfonyl-α-D-glucofuranose[6,7] (**1**). One advantage of the methylidene groups is their potential selective removal in order to maintain the furanose ring[6,8]. The key



to the reduction of the *p*-tolylsulfonyloxy group at C-6 was the new reagent lithium triethylborohydride. Treatment of a solution of **1** in *p*-dioxane with a solution of lithium triethylborohydride in tetrahydrofuran for only 4 h at room temperature gave an 88% yield of 6-deoxy-1,2:3,5-di-*O*-methylidene-α-D-glucofuranose (**2**). When the reaction was carried out in tetrahydrofuran alone, the yield was identical, but required 8 h for completion. Removal of the methylidene groups in hot acid solution afforded 6-deoxy-D-glucose in 92% yield.

The selection of lithium triethylborohydride for the reduction of *p*-toluenesulfonate **1** was suggested by a recent communication[9] in which the reagent was reported to reduce secondary and hindered *p*-toluenesulfonate groups effectively in addition to primary ones. Hoping to reduce secondary *p*-toluenesulfonate groups of carbohydrates directly to deoxy sugars, we treated either methyl 6-deoxy-2,3-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-L-mannofuranoside or methyl 6-deoxy-2,3-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-allofuranoside, but failed to obtain the desired 5,6-dideoxy derivatives.

EXPERIMENTAL

General methods. — Melting points were determined with a Kofler hot-stage and correspond to corrected values. The n.m.r. spectrum was recorded on a Varian T-60A spectrometer in chloroform-*d* with tetramethylsilane as the internal reference. Thin-layer chromatography was performed on Silica-Gel G plates of 0.25-mm thickness with 1:1 (v/v) ethyl acetate–hexane as the solvent. Lithium triethylborohydride (Super Hydride) was purchased from the Aldrich Chemical Co., Milwaukee, WI 53233, as a M solution in tetrahydrofuran. The elemental analysis was performed by Spang Microanalytical Laboratory, Ann Arbor, MI.

6-Deoxy-1,2:3,5-di-O-methylidene-α-D-glucofuranose (**2**). — An oven-dried flask was cooled to room temperature under nitrogen, *p*-dioxane (6 ml) was introduced, followed by 1,2:3,5-di-*O*-methylidene-6-*O*-*p*-tolylsulfonyl-α-D-glucofuranose[6] (**1**, 1.5 g). A M solution of lithium triethylborohydride in tetrahydrofuran (6 ml) was added, and the mixture was kept at room temperature for 4 h, at which time t.l.c. showed that no starting material remained. The excess hydride was decomposed with water and the organoborane was oxidized with 30% hydrogen peroxide (6 ml) and 3 M sodium hydroxide (6 ml). Chloroform was added, the organic layer was removed, and the aqueous layer was extracted further with chloroform (2 × 20 ml). The combined extracts were washed with water (2 × 60 ml), dried (sodium sulfate), and the solvents evaporated under reduced pressure to give a syrup that crystallized from

ethanol[10] to afford **2** (0.69 g, 88%), m.p. 75–76°, $[\alpha]_D^{23}$ +52.8° (*c* 0.92, chloroform); n.m.r.: δ 6.01 (d, 1, H-1), 5.04 (d, 2, 1,2-methylidene), 4.80 (m, 2, H-3, H-4), 4.33 (broad d, 2, 3,5-methylidene), 3.80 (m, 1, H-5), and 1.40 (d, 3, CH_3).

Anal. Calc. for $C_8H_{12}O_5$: C, 51.06; H, 6.43. Found: C, 51.01; H, 6.39.

*6-Deoxy-*D*-glucose* (**3**). — A solution of **2** (0.4 g) in 0.5M hydrochloric acid (10 ml) was heated for 4 h at 75–80°. The pH of the mixture was adjusted to neutral with Amberlite IR-45 (OH^-) anion-exchange resin. The resin was removed by filtration and the water evaporated under reduced pressure to afford a syrup (0.32 g, 92%) that crystallized. Recrystallization from ethyl acetate gave **3** (0.24 g, 69%), m.p. 141–142°, $[\alpha]_D^{23}$ +31.6° (*c* 0.92, water, equil.); lit.[3] m.p. 142–144°, $[\alpha]_D^{27}$ +31.0° (*c* 1.67, water, equil.).

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