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Note

Facile syntheses of methyl α-D-altropyranoside and its 3,4- and 4,6-*O*-isopropylidene derivatives

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Methyl α-D-altropyranoside (**2**) is usually prepared from methyl α-D-glucopyranoside by successive benzylidenation, *p*-toluenesulfonylation, epoxide formation, alkaline hydrolysis, and acid hydrolysis. The procedure is time-consuming, requiring 8–20 days, and the yield is 40–50%, depending on the exact method used[1]. The synthesis may be greatly improved by employing monomolar methanesulfonylation of methyl 4,6-*O*-isopropylidene-α-D-glucopyranoside[2], followed by generation, *in situ*, of an epoxide, and its hydrolysis to methyl 4,6-*O*-isopropylidene-α-D-altropyranoside (**1**). Compound **1** is obtained in ~55% yield, based on methyl α-D-glucoside, and only 2–3 days are required for the preparation. Compound **1** may be hydrolyzed to methyl α-D-altropyranoside (**2**), or isomerized to methyl 3,4-*O*-isopropylidene-α-D-altropyranoside (**3**), each obtained in almost quantitative yield.

EXPERIMENTAL

General. — Solutions were evaporated under diminished pressure at <40°. G.l.c. was performed with a Perkin–Elmer 801 chromatograph, by using a column (2 mm × 100 cm) of 3% of ECNSS on Embacel at 175°, with nitrogen as the carrier gas. Sample composition was estimated by weighing the peaks. T.l.c. was conducted with 0.25-mm (thick) layers of Silica Gel G (E. Merck) with the irrigant shown in parentheses. Pyridine was stored over potassium hydroxide for >24 h before use.

Methyl 4,6-O-isopropylidene-α-D-altropyranoside (**1**). — Methyl α-D-glucopyranoside (4.0 g), *p*-toluenesulfonic acid hydrate (0.04 g), 2,2-dimethoxypropane (16 ml), and *N*,*N*-dimethylformamide (16 ml) were stirred together for 16 h at 23°. Sodium hydrogen carbonate (1.2M; 10 ml) and water (30 ml) were added successively, and the solution was extracted for 6 h with chloroform. The extract was dried ($MgSO_4$), and evaporated under diminished pressure, the bath temperature being raised to 70° to remove the *N*,*N*-dimethylformamide. Xylene (6 × 4 ml) was added to and evaporated from the residue until this formed a brittle gel which was then dried for 5 min at 70°/0.01 torr.

A solution of the product in pyridine (12 ml) was stirred at $< 10°$ while methanesulfonyl chloride (1.45 ml) was added; after 10 min, the mixture was examined by t.l.c. (2:1 ethyl acetate–hexane) and found to give almost solely one spot, having R_F 0.6. [The volume of methanesulfonyl chloride required varies from preparation to preparation; if necessary, more acid chloride is added (in 0.1 ml portions) until examination by t.l.c. shows that methyl 4,6-*O*-isopropylidene-α-D-glucoside (R_F 0.1–0.2) is absent from the solution.] Water (40 ml) and chloroform (40 ml) were added, and the mixture was stirred for 10 min. The aqueous layer was separated, and extracted with chloroform (2 × 20 ml). The chloroform layers were combined, dried ($MgSO_4$), and evaporated. Toluene (30 ml) was added to and evaporated from the residue, which was then dried for 30 min at 30°/0.01 torr. Sodium hydroxide (M; 60 ml) was added, and the mixture was boiled for 16 h under reflux, cooled, and extracted for 6 h with chloroform. The extract was dried ($MgSO_4$), and evaporated. The residue was dissolved in hot ethyl acetate (50 ml) and the hot solution was passed through a mixture of charcoal (5 g) and Celite (5 g), and then through silicic acid (6 g) packed in the same column (2 cm diam.). The product was eluted from the column with ethyl acetate (100 ml), pressure being used to drive the solution and the first 20 ml of the washing through the column; without application of pressure, compound **1** tends to crystallize and block the column. The eluate was evaporated, and the product was dissolved in butyl acetate (5 ml), and the solution cooled slowly to 3°. The crystalline product was filtered off, washed with 1:1 ethyl acetate–hexane, and dried at 40°, to give **1** (2.57 g, 57%), m.p. 167–169° (sublimes from 160°), $[\alpha]_D$ +125° (*c* 0.61, water); lit. m.p. 161–163° (ref. 3), 168–169° (ref. 4), $[\alpha]_D$ +113° (*c* 1.8, water) (ref. 3), $[\alpha]_D$ +129° (*c* 0.7, water) (ref. 4). Examination by t.l.c. (ethyl acetate) showed a single spot, R_F 0.5 (the *gluco* analog has R_F 0.4 in this solvent).

Acetylation of **1** with acetic anhydride–pyridine gave the 2,3-diacetate of **1**, m.p. 134–135°, $[\alpha]_D$ +62° (*c* 1.25, chloroform) after crystallization from ethanol (3 ml.g^{-1}).

Anal. Calc. for $C_{14}H_{22}O_8$: C, 52.8; H, 6.9. Found: C, 52.8; H, 7.0.

Methyl α-D-altropyranoside (**2**). — A solution of **1** (1.5 g) in 0.1M hydrochloric acid (10 ml) was kept for 2 h at 23°, Dowex 1 X-8 ion-exchange resin (HCO_3^-, 2 ml) was added, and the solution was aerated for 10 min. The resin was filtered off and washed with water (4 × 5 ml). The filtrate and washings were combined and evaporated to a syrup which crystallized rapidly on being kept at 50°. The product was dried for 1 h at 23°/0.01 torr to give **2** (1.2 g, 97%), m.p. 106–107°. Recrystallization from propyl alcohol (1.2 ml) gave pure **2** (1.11 g, 90%), m.p. 107–108° alone or in admixture with authentic[1] **2**; $[\alpha]_D$ +125° (*c* 3.0, water); lit.[1] m.p. 107–108°, $[\alpha]_D$ +126° (*c* 3, water).

Methyl 4,6-O-isopropylidene-α-D-altropyranoside (**3**). — Compound **1** (0.50 g) was stirred for 10 min with acetone (5 ml) containing sulfuric acid (5 μl); 15M ammonium hydroxide (20 μl) was added, and the mixture was evaporated to dryness. The residue was suspended in ethyl acetate (2 ml) and the suspension passed through a column of silicic acid (5 ml); the column was eluted with ethyl acetate, and fractions

(5 ml) were collected. Fractions 1–6 yielded **3** (0.49 g, 98%) which crystallized slowly on nucleation with authentic[3] **3**, to give material having m.p. 57–60°. A sample was acetylated, and the acetate examined by g.l.c. and found to contain ~98% of **3**, ~1% of **2**, and ~1% of an unidentified compound. Although **3** forms large crystals, crystallization seems to be inhibited by even small proportions of impurities, and no conditions were found for satisfactory recrystallization. The product was dissolved in ethyl acetate (1 ml), hexane (1.3 ml) was added, and the solution was nucleated, and kept for 4 days at 3°; this gave pure **3** (0.22 g), m.p. 61–62°, alone or mixed with authentic[3] **3**; $[\alpha]_D$ +103° (*c* 1.66, water); lit.[3] m.p. 61–62°, $[\alpha]_D$ +102° (*c* 1.7, water).

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