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Note

Hydroxymethylation of 2,3:5,6-di-*O*-isopropylidene-D-mannono-1,4-lactone. A synthesis of D-*manno*-heptulose

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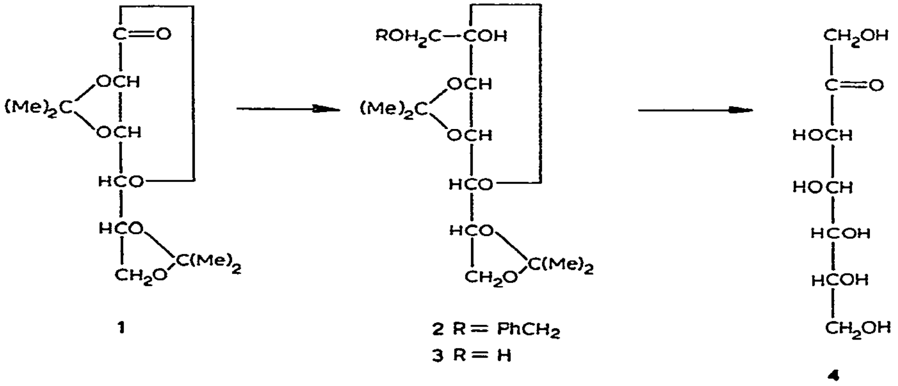
The "diazomethane synthesis" seems to be the reaction of choice for the synthesis of 2-keto sugars (uloses) by the extension of the carbon atom chain of a fully acylated aldonyl chloride by one carbon atom[1]. The 2-ketose synthesis from aldoses and 2-nitroethanol[1], with extension of the carbon atom chain with two units, yields a pair of epimers which have to be separated.

We report the synthesis of a 2-keto sugar, by the carbon chain extension of a protected aldonolactone, through its reaction with benzyloxymethylmagnesium chloride. Grignard reaction of 2,3:5,6-di-*O*-isopropylidene-D-mannono-1,4-lactone[2] (**1**) with benzyl chloromethyl ether[3] afforded 1-*O*-benzyl-3,4:6,7-di-*O*-isopropylidene-D-*manno*-heptulofuranose (**2**). Palladium-catalyzed hydrogenolysis of **2** yielded 3,4:6,7-di-*O*-isopropylidene-D-*manno*-heptulofuranose (**3**), which was hydrolyzed to give D-*manno*-heptulose (**4**).



EXPERIMENTAL

General. — Benzyl chloromethyl ether[3] was redistilled before use. Thin-layer chromatography was performed at room temperature on silica gel (Kiesel gel D-5, Camag, Muttenz, Switzerland) activated at 110°, with 1:1 cyclohexane–ethyl acetate as developer. Compounds were visualized by spraying with sulfuric acid (5% in ethanol) and charing. Palladium-on-carbon (10%) was purchased from Engelhard, Italy. Melting points were determined with a Büchi melting-point apparatus (Tottoli), and are not corrected. Optical rotations were measured, in a 1-dm cell, with a Perkin–Elmer Model 141 polarimeter. N.m.r. spectra were taken with a Varian T-60 n.m.r. spectrometer on solutions, in chloroform-*d* (tetramethylsilane being the internal reference). The microanalysis was done at the Weizman Institute, Rehovot, Israel.

*1-O-Benzyl-3,4:6,7-di-O-isopropylidene-*D-manno-*heptulofuranose* (**2**). — A soluton of benzyloxymethyl magnesium chloride, prepared[3] at 0° from benzyl chloromethyl ether (15.7 g, 0.1 mole) in tetrahydrofuran (50 ml) and magnesium (2.4 g, 0.1 g-atom), was added dropwise to a stirred solution of lactone **1** (21.0 g, 81.5 mmoles) in benzene (250 ml) at 4°. The reaction was continued for 4 h at 4° and for 2 h at room temperature. The reaction mixture was treated with a saturated ammonium chloride solution (250 ml), the organic phase separated, washed with water, and dried. The solvents were evaporated and the residue dissolved in benzene. Unreacted lactone **1** (8.0 g, 38.0%) crystallized on addition of petroleum ether (60–80°). The filrate was concentrated to a syrup and the residue dissolved in ethanol (100 ml). An aqueous solution (30 ml) of sodium hydroxide (2.0 g) was added, and the solution brought to the boiling point. The cooled solution was neutralized with carbon dioxide and concentrated. Water (50 ml) was added and the aqueous solution extracted with chloroform (3 × 70 ml). The oil obtained on evaporation of the chloroform was distilled at 180–200°/0.1 mm (9.4 g, 49.1% of reacted **1**) as a chromatographycally homogenous product, R_F 0.60; n.m.r. data: τ 2.74 (singlet, 5 aromatic protons), 5.44 (singlet, 2 benzyl methylene protons), 6.17 (singlet, exchangeable with D, 1 proton, OH), 8.58 (singlet, 6-protons, 2-CH_3), 8.65 (singlet, 3 protons, CH_3), and 8.72 (singlet, 3 protons, CH_3).

*3,4:6,7-Di-O-isopropylidene-*D-manno-*heptulofuranose* (**3**). — A solution of **2** (8.6 g, 22.6 mmoles) in ethanol (100 ml) was hydrogenolyzed with palladium-on-carbon (2.0 g) in a Parr hydrogenation apparatus at room temperature and 35×10^3 kg m^{-2}. After 48 h, more catalyst (4.0 g) was added and reduction continued for 70 h. The solvent was evaporated and the residue crystallized from benzene–petroleum ether (40–60°), m.p. 75–77° (4.64 g, 70.5%). Three recrystallizations from the same solvent raised the m.p. to 88–89°; R_F 0.30; $[\alpha]_D^{20}$ +20.4° (*c* 1.0, chloroform); n.m.r. data: τ 6.25 [singlet, 2 protons, (C-1)–CH_2–], 6.50 and 7.16 (two singlets, 2 protons exchangeable with D, 2 OH), 8.57 (singlet, 6 protons, 2 CH_3), 8.63 (singlet, 3 protons, CH_3), and 8.66 (singlet, 3 protons CH_3).

Anal. Calc. for $C_{13}H_{22}O_7$: C, 53.78; H, 7.64. Found: C, 53.60; H, 7.45.

D-manno-*Heptulose* (**4**). — A solution of **3** (2.0 g, 6.9 mmoles) in 25mM sulfuric acid (50 ml) was maintained overnight at 60°, neutralized with barium carbonate, filtered, and concentrated to dryness. The product crystallized from methanol (1.17 g, 80.6%), and the m.p., 151°, was unchanged when **4** was mixed with authentic D-*manno*-heptulose; $[\alpha]_D^{20}$ +29.1° (*c* 1.0, water); lit.[4]: m.p. 152°;

$[\alpha]_D$ +29.0°. The synthetic product yielded a 1-(1-benzyl-1-phenyl)-2-(1-phenyl) osazone, m.p. 200–204° [lit.[5]: 193–4° (corr)] showing no depression on admixture with an authentic sample; $[\alpha]_D^{25}$ +106.8° → +102.7° (*c* 1.5, pyridine, 24 h).

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