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Note

A simple preparation of 6-deoxy-D-gulose

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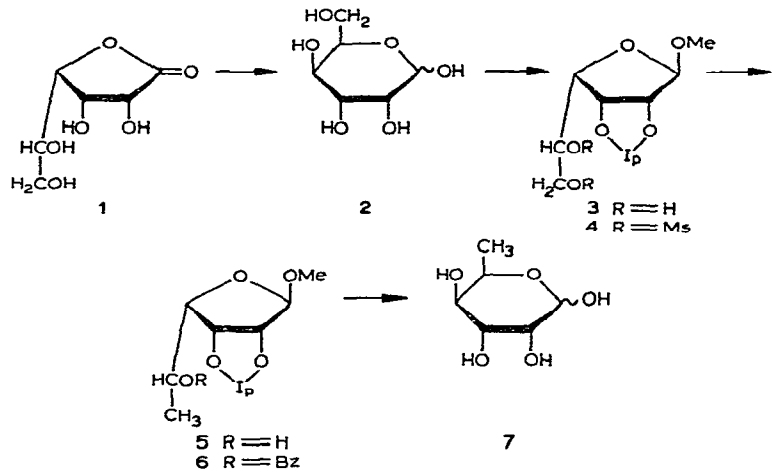
6-Deoxy-D-gulose (antiarose, **7**) is found in Nature as a component of several cardiac glycosides[1]. It was originally prepared by the cyanohydrin synthesis from 5-deoxy-D-xylose[2]. Another route consisted of the treatment of methyl 3,4-anhydro-6-deoxy-α-D-galactopyranoside with a mixture of aqueous sulfuric acid and acetone, which gave 6-deoxy-2,3-*O*-isopropylidene-β-D-gulofuranose and methyl 6-deoxy-α-D-gulopyranoside[3], both of which can yield **7** upon acid hydrolysis. Recently, a preparation of **7** from methyl 2-*O*-acetyl-3,4-anhydro-6-deoxy-α-D-galactopyranoside by hydrolysis with a strongly acidic ion-exchange resin was reported[4]. All these methods suffer from the distinct disadvantage of starting from substances which themselves are the results of multistep syntheses. Utilizing a pathway similar to that reported earlier for the preparation of D-rhamnose[5], a simple preparation of **7** starting from commercially available D-gulono-1,4-lactone (**1**) is described.

D-Gulono-1,4-lactone (**1**) was reduced to D-gulose (**2**) by the general technique with sodium borohydride under acidic conditions[6]. Syrupy D-gulose has recently[7] been converted into methyl 2,3-*O*-isopropylidene-β-D-gulofuranoside (**3**) in an overall yield of about 60%. In the present work, **3** was utilized for the preparation of methyl 2,3-*O*-isopropylidene-5,6-di-*O*-methylsulfonyl-β-D-gulofuranoside (**4**). This sequence of reactions was based upon the recent synthesis of methyl 2,3-*O*-isopropylidene-5,6-di-*O*-(methylsulfonyl)-α-D-mannofuranoside developed by Evans and Parrish[8]. However, in the present case, **4** did not crystallize and it was treated with lithium aluminum hydride in benzene–ethyl ether. The alcoholic group at the C-6 position was reduced to a terminal methyl group and the methylsulfonyl group at O-5 was cleaved off to give methyl 6-deoxy-2,3-*O*-isopropylidene-β-D-gulofuranoside (**5**) in good yield.

Compound **5** was reported to have been prepared by treatment of methyl 2,3-*O*-isopropylidene-5-*O*-tosyl-α-L-rhamnofuranoside with sodium benzoate in hot *N*,*N*-dimethylformamide[9]. Attempts to repeat this work gave poor results, with only a 4% yield being the highest amount obtainable. Brimacombe *et al.*[10] appear to have fared a little better with a yield of 15.2%, and they pointed out that, under the reaction conditions, the main products were the unsaturated derivatives, methyl 5,6-dideoxy-2,3-*O*-isopropylidene-α-L-*lyxo*-hex-5-enofuranoside and methyl 5,6-dideoxy-



2,3-*O*-isopropylidene-β-D-*erythro*-hex-4-enofuranoside. The present synthesis of **5** represents a superior and practical synthesis of this interesting intermediate.

Hydrolysis of **5** with hot, aqueous acid afforded 6-deoxy-D-gulose (**7**), which was obtained in crystalline form and characterized further as the phenylosazone. Benzoylation of **5** gave methyl 5-*O*-benzoyl-6-deoxy-2,3-*O*-isopropylidene-β-D-gulofuranoside (**6**) which is an important intermediate to be used in this laboratory for the preparation of nucleosides.

A word of caution must be mentioned here concerning the melting points and optical rotations of the D-gulofuranose derivatives. As shown in Table I, compounds **3**, **5**, **6**, and methyl 2,3:5,6-di-*O*-isopropylidene-β-D-gulofuranoside[7] (**8**) have virtually the same melting point, and **3** and **5** have very close optical rotations. Therefore, mixed melting points, i.r. spectra, and n.m.r. spectra must be obtained to verify their identities. N.m.r. spectrometry is particularly useful in differentiating **5** from **3**, because the terminal methyl group of **5** appears as a doublet centered at δ 1.28.

TABLE I

PHYSICAL CONSTANTS OF METHYL D-GULOFURANOSIDE DERIVATIVES

Compound	*m.p.* (°)	$[\alpha]_D$ (°)	*Solvent*
8	78.5-79	−44.9	chloroform
3	77.5-79.5	−83.5	methanol
5	78.5-79.5	−90.7 (−85.3 ± 3.4)[a]	methanol
6	78.5-79.5	−118	methanol

[a]From Ref. 9.

EXPERIMENTAL

General. — Melting points were determined with a Kofler hot-stage and correspond to corrected values. The n.m.r. spectra were recorded with a Varian T-60A

spectrometer on solutions in chloroform-*d* and with tetramethylsilane as the internal reference. I.r. spectra were recorded with a Perkin–Elmer Model 21 spectrophotometer and optical rotations were obtained with a Rudolph polarimeter. Evaporations were performed under reduced pressure in a rotary evaporator, usually at a bath temperature of 40°. Elemental analyses were performed by the Spang Microanalytical Laboratory, Ann Arbor, Michigan, or the Baron Consulting Co., Orange, Connecticut.

D-*Gulose* (**2**). — D-Gulono-1,4-lactone (**1**) was purchased from Pfanstiehl Labs, Inc. (Waukegan, Ill. 60085). It was conveniently reduced in 30-g lots by the standard sodium borohydride method[6]. In this procedure, Amberlite IR-45 (OH^-) resin was substituted for the anion-exchange resin used in the reference. Residual boric acid, which crystallized in the syrupy product, was removed by addition and evaporation of methanol. The yield of **2** was generally about 23 g of a thick, colorless syrup.

*Methyl 2,3-*O*-isopropylidene-5,6-di-*O*-methylsulfonyl-β-*D*-gulofuranoside* (**4**). — Methyl 2,3-*O*-isopropylidene-β-D-gulofuranoside (**3**) was prepared from D-gulose as previously described[7] and was utilized without recrystallization. From **2** (20 g) was obtained **3** (14.4 g) which was dissolved in dry pyridine (100 ml). The solution was chilled in an ice-bath, methanesulfonyl chloride (28 ml) was added, dropwise, and the mixture was stirred for 2 h at room temperature. The mixture was chilled again and treated very slowly with water (50 ml) and, after 0.5 h, the contents of the flask were poured into water (1000 ml). The product was extracted with chloroform (3 × 75 ml) and the chloroform layer was washed with saturated sodium hydrogencarbonate solution (200 ml), water (200 ml), and dried (magnesium sulfate). The solvent was evaporated and traces of pyridine were removed by addition and evaporation three times of toluene to give a tan syrup (23.7 g); n.m.r. data: δ 1.25, 1.40 (both s, 6, *gem*-dimethyl), 3.02, 3.07 (both s, 6, methylsulfonyl), 3.25 (s, 3, methoxy), 4.08–5.13 (series of complex unresolved multiplets, 7, sugar protons); these data were almost identical with those obtained for methyl 2,3-*O*-isopropylidene-5,6-di-*O*-methylsulfonyl-δ-D-mannofuranoside[7,8]; i.r. data: ν_{max}^{film} 1358 (very broad, *gem*-dimethyl and sulfonyl) and 1174 cm^{-1} (sulfonyl); there was no hydroxyl peak.

*Methyl 6-deoxy-2,3-*O*-isopropylidene-β-*D*-gulofuranoside* (**5**). *Method A.* — Compound **4** (14.2 g) was dissolved in a mixture of benzene (165 ml) and ethyl ether (330 ml). Lithium aluminum hydride (9.8 g) was added and the mixture was heated at reflux for 7 days. The flask was chilled in an ice-bath and water (10 ml), a 15% aqueous sodium hydroxide solution (30 ml), and again water (10 ml) were cautiously added in succession. The precipitate was removed by filtration and washed thoroughly with ethyl ether. Removal of the solvents by evaporation afforded a white solid which was recrystallized from hexane to give 5.90 g (74%) of **5** in three crops. In a separate preparation, which was boiled for 4 days, a 68% yield was obtained; m.p. 78.5–79.5°, $[\alpha]_D^{25}$ −90.7° (*c* 1.26, methanol); the i.r. spectrum was identical to that of the product described in method B and no lowering of the m.p. was observed on admixture, 78.5–79.5°; lit.[9]: m.p. 78–78.5°, $[\alpha]_D^{23}$ −85.3 ±3.4° (methanol).

Anal. Calc. for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found: C, 55.01; H, 8.29.

Method B. — The procedure of Arzoumanian *et al.*[9] was used. Methyl 2,3-*O*-isopropylidene-5-*O*-tosyl-α-L-rhamnofuranoside[5] (6 g) was treated with sodium benzoate in *N*,*N*-dimethylformamide. After work-up and treatment of the product with methanolic sodium methoxide, **5** was obtained as crystals from hexane (140 mg, 4%), m.p. 72–75°. One recrystallization raised the melting point to 79–80°.

Methyl 5-O-benzoyl-6-deoxy-2,3-O-isopropylidene-β-D-gulofuranoside (**6**). — A solution of **5** (2 g) in dry pyridine (17 ml) was treated with benzoyl chloride (1.7 ml) in the usual manner. After 17 h at room temperature, the mixture was poured as a fine stream into a vigorously stirred mixture of saturated sodium hydrogencarbonate and ice (200 ml). The product crystallized immediately and was filtered off and washed thoroughly with water (yield, 2.88 g, 98%), m.p. 76–78°. A sample (400 mg) was recrystallized from methanol–water to afford 272 mg of white needles, m.p. 78.5–79°, $[\alpha]_D^{22}$ −118° (*c* 1.30, methanol); i.r. data: ν_{max}^{KBr} 1720 (carbonyl), 1380 (*gem*-dimethyl), and 714 cm^{-1} (monosubstituted phenyl).

Anal. Calc. for $C_{17}H_{22}O_6$: C, 63.33; H, 6.88. Found: C, 63.39; H, 6.76.

6-Deoxy-D-gulose (**7**). — A mixture of **5** (1.6 g) and 0.5M sulfuric acid solution (60 ml) was heated at reflux for 2 h. The solution was neutralized with barium carbonate, heated on a steam bath for several min, cooled, and filtered through a pad of Celite. The filtrate was concentrated to a small volume and passed through a small column (1.8 × 11 cm) of Amberlite MB-3 resin. Evaporation of the eluate afforded a colorless syrup which crystallized after several weeks by rubbing it with a glass rod while it was under acetone. The first crop of crystals weighed 0.902 g (75%), m.p. 130–132°, $[\alpha]_D^{23}$ −40.0° (*c* 2.02, water, 3 h); a second crop was obtained from the mother liquor (73 mg; total yield: 81%), m.p. 128–130°; lit.[2]: m.p. 130–131°, $[\alpha]_D^{20}$ −38.03° (*c* 3.444, water, 30 min); lit.[11]:m.p. 130–134°, $[\alpha]_D$ −39.3 ±2° (*c* 0.97, water).

The phenylosazone of **7** was obtained by heating a mixture of the sugar (30 mg), phenylhydrazine hydrochloride (60 mg), anhydrous sodium acetate (90 mg), and water (2 ml) for 0.5 h in a boiling water bath. The product was recrystallized from aqueous methanol, m.p. 180–182° (dec.); lit.[2]: m.p. 182–183°.

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