A Facile Synthesis of 1,2; 5,6-Di-*O*-cyclohexylidene-α-D-allose[*1]

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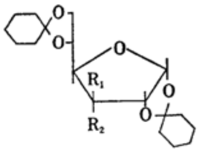
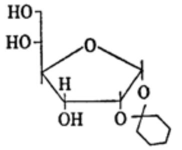
1,2; 5,6-Di-*O*-cyclohexylidene-α-D-allose (III) is required for a study of asymmetric synthesis with sugar derivatives. It has been shown that 1,2; 5,6-di-*O*-cyclohexylidene-α-D-glucose (I) is more effective for some asymmetric reactions than the corresponding isopropylidene derivative.[1]

Sowa and Thomas[2] reported that 1,2; 5,6-di-*O*-isopropylidene-α-D-allose was prepared in a 62% yield from the corresponding glucose by oxidation with dimethyl sulfoxide - acetic anhydride (DMSO-Ac_2O), followed by reduction with sodium borohydride. This synthetic procedure, however, involves complicated manipulations, such as the removal of the excess DMSO-Ac_2O *in vacuo* at 35—40°C and the purification of the product by column chromatography.

The authors have found that the use of I,[3] which is more readily available than the corresponding isopropylidene derivative,[4] afforded a convenient method for preparing III and related compounds without the cumbersome treatment described above. The method, because of its simplicity, seems to be suitable for studies of allose chemistry.



I: R_1=OH, R_2=H
II: R_1, R_2=OH
III: R_1=H, R_2=OH



IV

The oxidation of I with DMSO-Ac_2O was carried out in the usual manner, and the reaction mixture was treated with aqueous potassium carbonate and ammonium hydroxide to give gummy materials, which were then reduced with sodium borohydride in a mixture of ether and methanol. The removal of the solvents provided crystalline products, which then gave pure III in a 50% yield after recrystallization. The relatively low yield of III was attributed to the formation of by-products, which presumably consist mainly of methylthiomethylene and acetyl derivatives of I formed in the oxidation step,[5] judging from the results of thin-layer chromatography. The *allo* configuration of III was confirmed by the conversion of the product into D-allose.

The selective cleavage of the 5,6-cyclohexylidene group of III was performed with aqueous acetic acid, affording 1,2-*O*-cyclohexylidene-α-D-allose (IV) in a 88% yield.

1,2; 5,6-Di-*O*-cyclohexylidene-α-D-*ribo*-hexofuranos-3-ulose could also be easily obtained from the gummy

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[*1] In a journal which came to hand after this manuscript had been contributed to this Bulletin, K. James, A. R. Tatchell and P. K. Ray (*J. Chem. Soc.*, (*C*), **1967**, 2681) describe the synthesis of the title compound, but their techniques differ in some details.

1) M. Kawana and S. Emoto, This Bulletin, **41**, 259 (1968).

2) W. Sowa and G. H. S. Thomas, *Can. J. Chem.*, **44**, 836 (1966).

3) R. C. Hockett, R. E. Miller and A. Scattergood, *J. Am. Chem. Soc.*, **71**, 3072 (1949).

4) W. L. Glen, G. S. Myers and G. A. Grant, *J. Chem. Soc.*, **1951**, 2568.

5) J. D. Albright and L. Goldman, *J. Am. Chem. Soc.*, **89**, 2416 (1967); W. W. Epstein and F. W. Sweat, *Chem. Revs.*, **67**, 247 (1967).

materials as a crystalline mono hydrate (II), although in a low yield. The infrared spectrum of II in potassium bromide showed the presence of the hydroxyl group but no carbonyl group; however, the absorption band of the latter appeared in carbon tetrachloride, as in the case of the corresponding isopropylidene derivative.[6] The reduction of II with sodium borohydride yielded III stereospecifically under conditions similar to those of the reduction of the gummy materials.

Experimental

All melting points are uncorrected. The infrared spectra were measured with a Perkin-Elmer Model 521 grating infrared spectrophotometer. The optical rotations were determined with a Perkin-Elmer Model 141 photoelectric polarimeter in a 1-dm tube. The elemental analyses were performed by the Organic Analysis Laboratory of this Institute.

The thin-layer chromatography was performed by the ascending technique on a 250μ-layer of silica gel G (E. Merck, Darmstadt, Germany), activated for 2 hr at 120°C. The spray reagent was a mixture of methanol, sulfuric acid, and *p*-methoxybenzaldehyde (85: 10: 5, v/v).

1,2;5,6-Di-*O*-cyclohexylidene-*α*-D-allose (III). A mixture of 1,2;5,6-di-*O*-cyclohexylidene-*α*-D-glucose[3] (I; 3.4 g, 0.01 mol), dimethyl sulfoxide (15 m*l*), and acetic anhydride (10 m*l*) was allowed to stand at room temperature for 24 hr. A thin-layer chromatogram of the solution showed three main spots (one at R_f 0.43 due to the hydrate (II) of D-*ribo*-hexos-3-ulose, and those at 0.56 and 0.73 due to by-products) with benzene-ether (85 : 15, v/v). The reaction mixture was then stirred into an ice-water mixture (100 m*l*) containing potassium carbonate (15 g). After 30 min, 38% ammonium hydroxide (10 m*l*) was added, and the stirring was continued for 20 more min. The resulting gummy materials were washed with aqueous potassium carbonate and dissolved in ether (40 m*l*). The ethereal solution was washed with 10% aqueous potassium carbonate (10 m*l*) and then water (4 × 10 m*l*), and diluted with ether (5 m*l*) and methanol (10 m*l*).

To this solution there was added solid sodium borohydride (420 mg, 0.011 mol) under cooling in an ice-water bath; the mixture was stirred for 30 min, and then water (5 m*l*) was added. After the stirring had been continued for 5 min, the reaction mixture, now diluted with ether (20 m*l*), was washed with water (4 × 10 m*l*), and then the solution was dried over sodium sulfate. A thin-layer chromatogram of the solution showed four spots with benzene-ether (85 : 15, v/v) (R_f 0.25 due to III, 0.44 (faint) due to an unknown substance which was distinguishable from II by color, and 0.56 and 0.71 presumably due to by-products produced in the oxidative reaction). The evaporation of the solvents gave a crystalline product, which in turn provided III (1.7 g, 50%) after recrystallization from ligroin - ethyl acetate (9 : 1, v/v): mp 125—126°C; $[\alpha]_D^{25}$ +41.4° (*c* 0.65, ethanol); IR (KBr), 3495 cm^{-1}.

Found: C, 63.64; H, 8.02%. Calcd for $C_{18}H_{28}O_6$: C, 63.51; H, 8.29%.

A thin-layer chromatogram of III showed one spot (R_f 0.71) which could be distinguished from a spot (R_f 0.59) of I with chloroform-methanol (97 : 3, v/v).

A mixture of III (681 mg, 2.0 mmol) and Dowx 50W-X8 (H$^+$; 3 g (wet)) in dioxane (4 m*l*) and water (4 m*l*) was stirred as 80 °C for 45 min. The spots of the starting material and of 1,2-*O*-cyclohexylidene-*α*-D-allose (IV) on the thin-layer chromatograms almost completely disappeared; as solvent systems, chloroform-methanol (97: 3, v/v) and (85: 15, v/v) were employed respectively. The resin was filtered and washed with water, and the filtrate was extracted with chloroform (3 × 10 m*l*). The water layer was concentrated to dryness at 60°C in a rotary evaporator with the aid of a water aspirator, and the residue was crystallized from ethanol-water, affording analytically-pure D-allose (175 mg, 48.6%) (Found: C, 39.78; H, 6.61%): mp 127—131°C; $[\alpha]_D^{20}$ +2.1° (4 min) → +13.5° (20 hr) (*c* 1.46, water) (lit.[7] mp 128—128.5°C, $[\alpha]_D^{20.1}$ +2.10° (4 min) → +14.41° (20 hr)). The X-ray powder diffraction patterns of the product were identical with those of an authentic sample.

The Hydrate of 1,2;5,6-Di-*O*-cyclohexylidene-*α*-D-*ribo*-hexofuranos-3-ulose (II). The oxidation of 1,2;5,6-di-*O*-cyclohexylidene-*α*-D-glucose (I; 3.4 g, 0.01 mol) was carried out in the same manner as has been described for the synthesis of the allose derivative (III). The ethereal solution of gummy materials was washed successively with aqueous potassium carbonate (10 m*l*) and water (40 m*l*), and then most of the ether was distilled out at 60°C under ordinary pressure and then at room temperature with the aid of a water aspirator. The oily residue gave, after the addition of *n*-hexane (15 m*l*), a crystalline product (1.3 g). Recrystallization from *n*-hexane - ethyl acetate (2 : 1, v/v) afforded II, which was then dried over phosphorus pentoxide at room temperature under reduced pressure (3 mmHg) for 2 hr. The yield of II was 0.9 g (25%): mp 119—121°C under rapid heating); $[\alpha]_D^{20}$ +40.0° (3 min) → +40.7° (5 min) → 41.8° (10 min) → +44.3° (30 min) → +44.3° (3 hr; constant) (*c* 0.28, 80% aqueous dioxane); IR, 3400 cm^{-1} (KBr), 1773 cm^{-1} (CCl_4, 40 min after solution).

Found: C, 60.87; H, 7.96%. Calcd for $C_{18}H_{28}O_7$: C, 60.66; H, 7.92%.

Solid sodium borohydride (57 mg, 1.5 mmol) was added to a solution of II (535 mg, 1.5 mmol) in a mixture of ether (16 m*l*) and methanol (4 m*l*) under cooling in an ice-water bath, and then the mixture was stirred for 30 min. Water (1 m*l*) was then added, after which the stirring was continued for 5 min. The resulting mixture, now diluted with ether (20 m*l*), was washed with water (4 × 5 m*l*), and the solution was dried over sodium sulfate. A thin-layer chromatogram of the solution showed only one spot due to III with chloroform-methanol (97: 3, v/v). The removal of the solvents gave analytically-pure III (483 mg, 94.5%) (Found: C, 63.60; H, 8.17%). Its melting point, specific rotation and infrared spectrum were identical with those of a sample prepared from the gummy materials.

1,2-*O*-Cyclohexylidene-*α*-D-allose (IV). The method reported by Gramera *et al.*,[8] but slightly modified,

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6) O. Theander, *Acta Chem. Scand.*, **18**, 2209 (1964).

7) F. P. Phelps and F. Bates, *J. Am. Chem. Soc.*, **56**, 1250 (1934).

8) R. E. Gramera, A. Park and R. L. Whistler, *J. Org. Chem.*, **28**, 3230 (1963).

was used for this preparation. A solution of 1,2;5,6-di-*O*-cyclohexylidene-α-D-allose (III; 20 g, 0.059 mol) in acetic acid (210 m*l*) was diluted with water (90 m*l*). This solution was kept at 75°C for 35 min, and then poured into a shallow evaporating dish and allowed to evaporate to dryness in a hood at room temperature. The resulting crystalline mass was thoroughly dried by the repeated evaporation of its benzene solution (3× 100 m*l*) under reduced pressure at 60°C. The crude crystals (*ca.* 20 g) were recrystallized from ligroin - ethyl acetate (2: 1, v/v), yielding IV (13.5 g, 88%): mp 111—112°C; $[\alpha]_D^{25}$ +46.1° (*c* 0.56, ethanol); Fehling test, negative; IR (KBr), 3430 (shoulder), 3300, 3160 (shoulder) cm^{-1}.

Found: C, 55.60; H, 7.49%. Calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.75%.

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