An improved, simplified synthesis of 1,2:5,6-di-0-isopropylidene-D-mannitol

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1,2:5,6-Di-O-isopropylidene-D-mannitol (1) is an important source of chiral glycerol and glyceraldehyde derivatives^{1,2}, and has been used as an intermediate in the synthesis of chiral macrocyclic ethers^{3,4}. The several syntheses of 1 are time-consuming, use large quantities of solvents and reagents, or involve tedious neutralisation steps^{1,5-7}. An improved, but low-yielding synthesis based on acetal exchange has been described⁸. Acetal exchange is frequently used^{9,10} in carbohydrate chemistry for introducing cyclic acetal groups. The reactions are considered to be under kinetic control and have led to products not always available from direct methods. The most commonly used reagent is 2,2-dimethoxypropane in N,N-dimethylformamide with toluene-p-sulphonic acid as catalyst¹⁰. A novel tetra-acetal of lactose has been prepared recently¹¹ by use of 2,2-dimethoxypropane in the absence of N,N-dimethylformamide.

As part of studies¹² of the reactions of tin(II) chloride with carbohydrate derivatives, D-mannitol was treated with 2,2-dimethoxypropane in 1,2-dimethoxyethane containing a trace of tin(II) chloride, which led to a simplified synthesis of 1. The method is rapid, involves an easy work-up procedure, and is a distinct improvement over those described previously.

D-Mannitol was treated at reflux temperature with 2,2-dimethoxypropane and 1,2-dimethoxyethane containing a trace of tin(II) chloride; a clear solution was obtained within ~35 min. The reaction was terminated by the addition of the theoretical amount of pyridine required to complex the tin(II) chloride. T.l.c. (1,2-dimethoxyethane-cyclohexane, 3:2) then indicated the presence of two main components, R_F 0.49 and 0.75, in the ratio ~ 2:1, corresponding to 1 and the 1,2:3,4:5,6-tri-O-isopropylidene derivative¹ 2. Recrystallisation of the crystalline residue obtained by evaporation of solvents from the reaction mixture gave pure 1 in 54-58% yield. Column chromatography of the mother liquor on silica gel gave a further amount of 1 (11%) and 2 (23%). The reaction was successfully performed up to a 100-g scale. Tin(II) chloride, which seems to be essential for the reaction, is apparently not acting as an ordinary Lewis-acid catalyst or as a source of hydrochloric acid

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NOTE

from reaction with hydroxyl groups. The use of zinc chloride as the catalyst was unsuccessful; the reaction mixture was not homogeneous after 48 h at reflux temperature and still contained a considerable proportion of unreacted mannitol. Fairly rapid dissolution was achieved with toluene-p-sulphonic acid as the catalyst, but the resulting mixture of 1 and 2 was difficult to separate. Lead(II) chloride and iron(III) chloride were ineffective as catalysts.



Acetone, N,N-dimethylformamide, or dibutyl ether could be substituted for 1,2-dimethoxyethane as diluents for the reaction, but all gave lower yields (40-48%) of 1, which was also more difficult to purify.

The foregoing acetalating system is being applied to other carbohydrate molecules.

EXPERIMENTAL

Kieselgel 60 (Merck) was used for column chromatography, and silica gel plates (Merck DC Fertigplatten) were used for analytical t.l.c.; compounds were detected by charring with sulphuric acid. Solvents and reagents were commercial products and were not purified. Tin(II) chloride was purchased from Ventron, Alfa Division, Danvers, MA, U.S.A.

1,2:5,6-Di-O-isopropylidene-D-mannitol (1). — D-Mannitol (25 g) was suspended with vigorous stirring in 1,2-dimethoxyethane (60 ml) containing tin(II) chloride (25 mg). 2,2-Dimethoxypropane (40 ml) was added and the mixture heated under reflux with continuous stirring until a clear solution was obtained (~35 min). The solution was cooled, treated with pyridine (25 μ l), and concentrated *in vacuo*. The crystalline residue was recrystallised from dibutyl either (95 ml) to give 1 (19.4-20.9 g, 54-58%), m.p. 118-120°; lit.⁵ m.p. 122°.

The recrystallisation mother-liquor was evaporated and a solution of the residue in cyclohexane was chromatographed on silica gel (110 g). Elution with 1,2-dimethoxyethane-cyclohexane (1:1) gave 1,2:3,4:5,6-tri-O-isopropylidene-D-mannitol (2; 9.55 g, 23%), m.p. 66-68° [from light petroleum (b.p. 60-80°)], $[\alpha]_D^{23} + 11.3°$ (c 3.6, ethanol); lit.¹ m.p. 70°, $[\alpha]_D + 12.5°$ (ethanol). Continued elution with the same solvent-mixture gave 1 (3.95 g, 11%), m.p. 117-119°.

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REFERENCES

- 1 E. BAER AND H. O. L. FISCHER, J. Biol. Chem., 128 (1939) 463-500.
- 2 B. T. GOLDING AND V. P. IOANNOU, Synthesis, (1977) 423-424.
- 3 W. D. CURTIS, D. A. LAIDLER, J. F. STODDART, AND G. J. JONES, J. Chem. Soc., Perkin Trans. 1, (1977) 1756–1769.
- 4 A. H. HAINES AND P. KARNTIANG, J. Chem. Soc., Perkin Trans. 1, (1979) 2577-2587.
- 5 E. BAER, J. Am. Chem. Soc., 67 (1945) 338-339.
- 6 A. CARAYON-GENTIL, Bull. Soc. Chim. Biol., 34 (1952) 617-618.
- 7 R. S. TIPSON AND A. COHEN, Carbohydr. Res., 7 (1968) 232-243.
- 8 G. KOHAN AND G. JUST, Synthesis, (1974) 192.
- 9 A. N. DE BELDER, Adv. Carbohydr. Chem. Biochem., 34 (1977) 179-241.
- 10 M. E. EVANS, F. W. PARRISH, AND L. LONG, JR., Carbohydr. Res., 3 (1967) 453-462; A. HASEGAWA AND M. KISO, *ibid.*, 63 (1968) 91-98, and earlier papers.
- 11 L. HOUGH, A. C. RICHARDSON, AND L. A. W. THELWALL, Carbohydr. Res., 75 (1979) c11-c12.
- 12 G. J. F. CHITTENDEN, Carbohydr. Res., 74 (1979) 333-336.