Carbohydrate Research, 127 (1984) 146–148
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Note

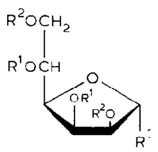
Convenient preparation of 1,4-anhydro-D-mannitol

HENRY B. SINCLAIR

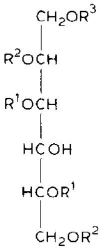
Northern Regional Research Center, Agricultural Research Service, U.S. Department of Agriculture, Peoria, Illinois 61604 (U.S.A.)*

(Received March 1st, 1983; accepted for publication, June 7th, 1983)

Preparation[1] of 1,4-anhydro-D-mannitol (**1**) by the acid-catalyzed dehydration of D-mannitol proceeds in 5–6% yield. Although simple in concept, the experimental procedure produces a wide variety of products[1,2], and it requires much processing of appreciable amounts of syrupy material to obtain crystalline **1** in low yield. Moderate amounts of **1** were needed as starting material for synthesis[3] of a derivative of 1-deoxy-D-*erythro*-2,3-hexodiulose. A convenient, high-yielding method for producing **1** using readily available reagents was developed.



1 $R^1 = R^2 = R^3 = H$
2 $R^1 + R^2 = Ip, R^3 = OH$
3 $R^1 + R^2 = Ip, R^3 = H$



$$\begin{array}{c} CH_2OR^3 \\ | \\ R^2OCH \\ | \\ R^1OCH \\ | \\ HCOH \\ | \\ HCOR^1 \\ | \\ CH_2OR^2 \end{array}$$

4 $R^1 + R^2 = Ip, R^3 = H$
5 $R^1 + R^2 = Ip, R^3 = Ts$

$Ip = CMe_2$

D-Mannose may be converted[4] into 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (**2**) in high yield. Reduction of **2** with borohydride to yield 1,2:4,5-di-*O*-isopropylidene-D-mannitol (**4**) has been reported[5] to give variable results. These results may be due to the unusual nature of **2**; although it mutarotates[6], it does not reduce[7] Fehling's solution, suggesting that the proportion of *aldehydo* form of **2** in solution must be extremely small. The *aldehydo* form of sugars is usually consid-

---

*The mention of firm names or trade products does not imply that they are endorsed or recommended by the U.S. Department of Agriculture over other firms or similar products not mentioned.

ered to be the form that borohydride attacks. In water and methanol, borohydride undergoes hydrolysis and progressively loses reducing power. Also, **2** and **3** are expected to display similar solubilities in polar organic solvents. When borohydride was added in small portions to **2** over several h, the mixture made neutral, and the solution continuously extracted, compound **4** was isolated in 85 ±2% yield. Without purification, compound **4** was treated with *p*-toluenesulfonyl (tosyl) chloride in pyridine. A syrupy product was obtained whose ^{1}H-n.m.r. spectrum surprisingly revealed no aromatic ring nor aromatic methyl protons, but did show two isopropylidene groups. When this crude syrup was hydrolyzed with 50% acetic acid, crystalline **1** was isolated. Clearly, the tosylation reaction not only produced **5**, but the subsequent conversion of **5** into **1** had also occurred in solution. The sequence of borohydride reduction, tosylation–anhydride formation, and hydrolysis gave **1** from **2** in 60 ±5% yield using readily available reagents and easily handled volumes. Progress of the reaction was conveniently monitored by t.l.c. because each step results in only one product.

EXPERIMENTAL

General methods. — See ref. 8. Additional ^{1}H-n.m.r. spectra were recorded with a Bruker WH-90 instrument. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

*2,3:5,6-Di-*O*-isopropylidene-*D*-mannofuranose* (**2**). — This compound was prepared as reported in ref. 4.

Conversion of **2** *into 1,4-anhydro-*D*-mannitol* (**1**). — Compound **2** (10 g) was dissolved in 4:1 (v/v) methanol–water (200 mL) and sodium borohydride was added in 0.2-g portions every 2–2.5 h. T.l.c. [2:1 (v/v) toluene–ethyl acetate] monitored the progress of the reduction; R_F **2**, 0.34 and R_F **4**, 0.14. About 1 g of sodium borohydride per 10 g of **2** was needed. When the reduction was complete, the bulk of the solvent was removed, the solution was diluted with water, and the pH was adjusted to 7.0 ±0.1 with M HCl. Continuous extraction with ethyl acetate (overnight) and removal of solvent left syrupy **3** (8.1–8.6 g), whose ^{1}H-n.m.r. spectrum revealed two isopropylidene groups [δ 1.51, 1.40(2), 1.35] and no anomeric proton. Syrupy **4** was dissolved in dry pyridine (8–10 mL/g), and tosyl chloride (11.0 g) was added. After storage overnight at 4–5°, the mixture was examined by t.l.c. [2:1 (v/v) toluene–ethyl acetate], R_F **1**, 0.57, to determine if tosylation–anhydride formation was complete. If **4** remained, an additional 0.5 mol of tosyl chloride/mol of **4** was added and the mixture was stored overnight. If tosylation was complete, water (1 mL/g of tosyl chloride) was added and the solvent was removed to yield a syrup. Dilution of the syrup with water, extraction with dichloromethane (4 equal vol. of 1/4 water vol.), drying of the extracts, and evaporation gave syrupy **5** (7–7.5 g), whose ^{1}H-n.m.r. spectrum revealed two isopropylidene groups [δ 1.5, 1.4(2), 1.3]. Syrupy **5** (7–7.5 g) was covered with 50% acetic acid (~30 mL/g of **5**), heated on a steam bath for 2 h, cooled, and vacuum concentrated to give crystalline **1**. Traces of acetic acid were removed by two additional concentrations from water. Recrystallization from 95% ethanol (~3 mL/g) yielded 3.5–4.1 g of **1**, m.p. 141–143°, $[\alpha]_D^{20}$ −22° (*c* 0.356, water) [lit.[1] m.p. 145–148°, $[\alpha]_D^{20}$ −24° (water)]; melting point undepressed when mixed with known **1**.

REFERENCES

1 A. B. FOSTER AND W. G. OVEREND, *J. Chem. Soc.*, (1951) 680–684; L. F. WIGGINS, *ibid.*, (1945) 4–7.
2 R. MONTGOMERY AND L. F. WIGGINS, *J. Chem. Soc.*, (1948) 2204–2208; H. G. FLETCHER, JR., AND H. W. DIEHL, JR., *J. Am. Chem. Soc.*, 74 (1952) 3175–3176.
3 B. E. FISHER, J. C. GOODWIN, AND H. B. SINCLAIR, *Carbohydr. Res.*, 116 (1983) 209–215.
4 O. TH. SCHMIDT, *Methods Carbohydr. Chem.*, 2 (1963) 318–325.
5 (a) J. W. BIRD AND J. K. N. JONES, *Can. J. Chem.*, 41 (1963) 1877–1881. (b) W. M. DOANE, B. S. SHASHA, C. R. RUSSELL, AND C. E. RIST, *J. Org. Chem.*, 32 (1967) 1080–1083.
6 J. C. IRVINE AND A. F. SKINNER, *J. Chem. Soc.*, (1926) 1089–1097.
7 K. FREUDENBERG AND R. M. HIXON, *Ber.*, 56 (1923) 2119–2127.
8 H. B. SINCLAIR, *J Org. Chem.*, 46 (1981) 2450–2455.