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Note

A simple, one-flask, two-step synthesis of 1,6-anhydro-β-D-mannopyranose (D-mannosan) from D-mannose

MICHAEL GEORGES*
Guelph-Waterloo Centre for Graduate Work in Chemistry, University of Waterloo, Waterloo, Ontario N2L 3G1 (Canada)

AND BERT FRASER-REID**
Paul M. Gross Chemical Laboratory, Duke University, Durham, North Carolina 27705 (U.S.A.)

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1,6-Anhydro-β-D-mannopyranose (D-mannosan, **3**) was needed in fairly large quantities for synthesis of sibirosamine[1], and, according to the literature, the readiest preparation thereof is by pyrolysis of ivory-nut meal[2]. In our hands, the yields from this operation were only 3–6%, and we did not find that washing the D-mannan with hydrochloric acid had the advantages reported[3].

Two chemical syntheses are outlined in the literature; that by Sondheimer *et al.*[4] requires seven steps from methyl α-D-mannopyranoside. The second, by Angyal and Beveridge[5], involves only one step from D-mannose, and the use of *p*-toluenesulfonic acid to induce formation of the 1,6-anhydro ring. Unfortunately, 1,6-anhydro-α-D-mannofuranose is also produced in substantial proportions; moreover, the high dilution needed in order to prevent competing polymerization reactions makes the procedure impractical for large-scale preparations.

In seeking an alternative route, we noted that, in one synthesis[4], the key reaction is the displacement of a 6-sulfonyloxy group by the anomeric hydroxyl group, the 2-, 3-, and 4-hydroxyl groups being protected as benzyl ethers. We reasoned that, if the 6-hydroxyl group of D-mannose (**1**) could be selectively sulfonylated, to give **2**, the large number of steps involving protection and deprotection could be avoided.

We assumed that selective sulfonylation could best be achieved by dropwise addition of a solution of *p*-toluenesulfonyl chloride to D-mannose at low temperature. However, at −15°, several side-products were formed, and lower temperatures, or slower addition, or both, were of no advantage.

We eventually found it best to add a solution of 1.1 equivalents of *p*-toluenesulfonyl chloride in one lot to D-mannose at room temperature. After 1

*Holder of a NSERC Postgraduate Scholarship, 1982–1983.
**To whom correspondence should be addressed

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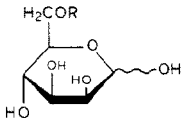
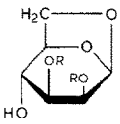
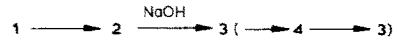




1 R = H
2 R = Ts

3 R = H
4 R,R = CMe_2



h, water was added, and the pH was brought to 9 by addition of sodium hydroxide solution. Formation of the 1,6-anhydro ring was then allowed to proceed during 1 h, and conventional processing afforded a syrup from which **3** was obtained by extraction with ethyl acetate.

The overall yield of **3** from D-mannose (**1**) in this two-step, one-flask operation requiring 3–4 h of working time is 77%. However, for preparations on a larger scale, it was found advantageous to isolate the product as the 2,3-isopropylidene acetal **4**, and to regenerate **3** therefrom under the published conditions[2].

EXPERIMENTAL

1,6-Anhydro-2,3-O-isopropylidene-β-D-mannose (**4**). — To a solution of D-mannose (**1**; 1.0 g, 5.5 mmol) in dry pyridine (15 mL) at 0° under argon was added a solution of *p*-toluenesulfonyl chloride (1.1 g, 6.0 mmol) in pyridine (5 mL). The mixture was stirred for 1 h, and then the reaction was quenched with water (10 mL), the main product in solution at this point being assumed to be **2**. A solution of M NaOH was added dropwise until pH 9 was attained, the mixture was stirred for 1 h, the pH adjusted to 7 with M HCl, and the solution was evaporated *in vacuo*. Traces of water were removed as the azeotrope with toluene, and the resulting solid was extracted with hot ethyl acetate (3 × 25 mL). The extracts were combined, and evaporated *in vacuo*, to afford **3** as an oil (0.75 g, 77%). To a solution of the oil in dry acetone (20 mL) was added a catalytic amount of *p*-toluenesulfonic acid and 2,2-dimethoxypropane (0.7 mL, 6.0 mmol). The mixture was stirred for 15 min, the reaction quenched with triethylamine (0.2 mL), and the solution evaporated *in vacuo*. The crystalline residue was dissolved in dichloromethane (50 mL), and the solution was washed with saturated, aqueous sodium chloride solution, dried (sodium sulfate), and evaporated *in vacuo*, to give **4** (670 mg; 60% from **1**). Recrystallization from dichloromethane–hexane afforded crystals having the following characteristics: R_F 0.45 (1:19 methanol–dichloromethane); m.p. 159–169° (lit.[2] m.p. 161–162°); $\nu_{max}^{CHCl_3}$ 3540 (free OH), 3420, 2880, 1352, 1310, 1122, 1080, and 970 cm^{-1}; ^{1}H-n.m.r. (80 MHz, $CDCl_3$): δ 1.32 (s, 3 H, CH_3), 1.53 (s, 3 H, CH_3), 2.45 (bs, 1 H, OH), 3.64–4.65 (m, 6 H, H-2,3,4,5,6,6′), and 5.37 (bs, 1 H, H-1).

Anal. Calc. for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.15; H, 7.14.

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