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Note

A synthesis of 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-mannopyranose

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It has been shown that stereoregular, linear α-(1→6)-linked polysaccharides can be synthesized by Lewis acid-catalyzed polymerization of 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-glycopyranoses, followed by debenzylation of the polymer produced[1]. The synthetic glucan has the same structure as the main chain of clinical dextran, but is free of branches[2], and has consequently been useful in clarifying the molecular basis of the immunogenicity of clinical dextran[3,4] and the immunological reactivity of myeloma globulins[5]. A mannan similarly prepared from the title compound (**1**) has the same backbone as mannans produced by various dermatophytes[6,7] and yeasts, and causes delayed-type skin reactions in guinea pigs. Animals immunized with the synthetic mannan show delayed-type skin reactivity with a mannan from the dermatophyte species *Trichophytum rubrum*[8].

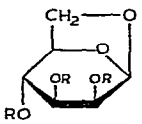
Compound **1** is usually prepared by pyrolysis of ivory-nut meal[9], isolation of the anhydro sugar as the triacetate, and subsequent benzylation[6]. Although yields up to 8% have been reported for the pyrolysis[9], the reaction is susceptible to negative catalysis by a variety of impurities. In considering possible synthetic alternatives, one of us (S.J.S.) suggested a reaction-sequence culminating in displacement of a 6-*p*-toluenesulfonate by means of a C-1 alkoxide, which proved successful. This sequence is reminiscent of the synthesis of 1,4-anhydroglycopyranoses[10,11] and various other intramolecular glycosides "glycosans"[12–15].

Methyl α-D-mannopyranoside (**2**) was tritylated in the presence of a slight excess of the glycoside, and methyl 6-*O*-trityl-α-D-mannopyranoside (**3**) was obtained as an amorphous powder or, apparently for the first time, as a solvent-free, crystalline compound (compare refs. 16, 17). Benzylation with sodium hydride and benzyl chloride in *N*,*N*-dimethylformamide provided methyl 2,3,4-tri-*O*-benzyl-6-*O*-trityl-α-D-mannopyranoside[17] (**4**). Occasionally, t.l.c. indicated that a second benzylation was required for complete reaction. Detritylation of **4** proved somewhat troublesome and incomplete, probably because of its reversibility[18,19]. As a result, methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside (**5**) was obtained often contaminated with tritylated

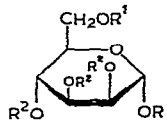
materials, and column chromatography was not uniformly successful in our hand. Conventional tosylation of **5** gave the expected 6-*p*-toluenesulfonate (**6**).

We experienced no difficulty in obtaining crystalline 1-*O*-acetyl-2,3,4-tri-*O*-benzyl-6-*O*-p-tolylsulfonyl-α-D-mannopyranose (**7**) in high yield by acetolysis[10] of **6**. (compare ref. 20). Deacetylation of **7** and ring closure was effected by reaction with 2.2 mol of sodium ethoxide in abs. ethanol. Compound **1** was obtained crystalline in 85% yield, but it was found to polymerize sluggishly. The presence of traces of a 5,6-epoxide was suspected[15]. Refluxing with ethanolic alkali did not alter the melting point or optical rotation, but the resulting material polymerized normally.

Acetolysis may also be carried out on compound **5** and the resulting diacetate (**8**) converted, by deacetylation and tosylation with 2 moles of *p*-toluenesulfonyl chloride in lutidine followed by hydrolysis of the 1-sulfonate, into 2,3,4-tri-*O*-benzyl-6-*O*-tosyl-D-mannopyranose (**9**). This sequence is more wasteful of reagent, more subject to purification problems and provides no advantages to the synthesis.



1 R = CH_2Ph



2 R = OMe, R^1 = H, R^2 = H
3 R = OMe, R^1 = Tr, R^2 = H
4 R = OMe, R^1 = Tr, R^2 = CH_2Ph
5 R = OMe, R^1 = H, R^2 = CH_2Ph
6 R = OMe, R^1 = Ts, R^2 = CH_2Ph
7 R = OAc, R^1 = Ts, R^2 = CH_2Ph
8 R = OAc, R^1 = Ac, R^2 = CH_2Ph
9 R = H, R^1 = Ts, R^2 = CH_2Ph

EXPERIMENTAL

General methods. — N.m.r. spectra were determined with a Varian A-60-A spectrometer on solutions in chloroform-*d*, with tetramethylsilane as internal standard. Optical rotations were determined with a Perkin–Elmer model 141 polarimeter. Melting points were determined on a Mel-temp apparatus. Solutions were concentrated *in vacuo*. T.l.c. was performed on Bakerflex silica gel 1B-F and column chromatography on V.W.R. silica, grade 950, 60–200 mesh.

Materials. — *N,N*-Dimethylformamide (DMF) was distilled from calcium hydride. Lutidine was distilled from potassium hydroxide. Other solvents and reagents were used without purification.

Methyl 6-O-trityl-α-D-mannopyranoside (**3**). — Chlorotriphenylmethane (280 g, 1.01 mol) was added to a suspension of methyl α-D-mannopyranoside (212 g, 1.09 mol) in pyridine (950 ml). Solution occurred and a pink color appeared within 30 min. A precipitate formed overnight and the mixture was poured into 3 l of ice–water with stirring. The solid was filtered off, dissolved in chloroform, and the

solution washed with water, dried (magnesium sulfate), and evaporated to a syrup. Traces of pyridine were removed by distillation of toluene from the residue, to leave a solid glass, which was crystallized from dichloromethane–hexane to give 348 g of white powder (**3A**). Upon concentration of the mother liquors, 38 g of pink, cubic crystals were obtained (**3B**); yield 90%; m.p. of **3A**, 92–95°, $[\alpha]_D$ +23.6 ±0.3° (*c* 2.7, chloroform); m.p. of **3B** 112–118°, $[\alpha]_D$ +23.7 ±0.2° (*c* 0.9, chloroform); n.m.r.: δ 2.9–3.2 (3H, m, exchanges with D_2O, OH), 3.3 (3H, s, OCH_3) 7.1–7.5 (15H, m, aromatic H).

Anal. Calc. for $C_{26}H_{18}O_6$: C, 70.74; H, 6.65. Found (for **3A**): C, 70.82; H, 6.62. Found (for **3B**): C, 70.74; H, 6.65.

Watters *et al.*[16] reported m.p. 101–102°, $[\alpha]_D$ +23.45° for methyl 6-*O*-trityl-α-D-mannopyranoside cocrystallized with one equivalent of pyridine.

*Methyl 2,3,4-tri-*O*-benzyl-6-*O*-trityl-α-*D*-mannopyranoside* (**4**). — Lindberg's[17] preparation of compound **4** was modified as follows to give the entire product crystalline. A solution of compound **3** (235 g) in DMF (400 ml) was added dropwise to a suspension of 50% sodium hydride (103 g) in 300 ml of DMF at 0°. The mixture was allowed to come to room temperature, and the addition of benzyl chloride (250 ml) was begun at a rate sufficient to maintain a reaction temperature of 40–50° (about 4 h). The suspension was stirred overnight, quenched with methanol, and poured into ice–water. The mixture was extracted with chloroform and processed conventionally to give a syrup, which was triturated with several portions of warm hexane until a gummy solid remained. Crystals appeared overnight in the hexane fraction and the gum was crystallized from ether. The product from both fractions was combined and recrystallized from dichloromethane–hexane; yield 286 g (75%); m.p. 117–118°, $[\alpha]_D$ +20° (*c* 1, chloroform); lit.[17] m.p. 116–118°, $[\alpha]_D$ +20°. Whenever t.l.c. of the mother liquors indicated significant quantities of unbenzylated material, they were rebenzylated by the same method.

*Methyl 2,3,4-tri-*O*-benzyl-α-*D*-mannopyranoside* (**5**). — Compound **4** (178.4 g) was dissolved in 700 ml of acetic acid, and 65 g of 30% hydrogen bromide in acetic acid was added. The mixture was stirred and cooled in an ice bath for 10 min, and then filtered into 3 l of ice–water. The two phases of the filtrate were extracted with chloroform. The chloroform solution was washed with saturated sodium hydrogencarbonate and water until neutral, dried (magnesium sulfate), and concentrated to a syrup. T.l.c. (in dichloromethane) of the syrup showed one main spot (R_F 0.1, **5**) and 2 faint spots (R_F 0.6, 0.7) that cochromatographed with **4** and triphenylmethanol. The crude syrup was used for the tosylation (compare ref. 16).

*Methyl 2,3,4-tri-*O*-benzyl-6-*O*-tosyl-α-*D*-mannopyranoside* (**6**). — To a solution of 130.7 g of syrupy **5** (from 178 g of **4**) in pyridine (475 ml), *p*-toluenesulfonyl chloride (170 g) was added. A precipitate appeared after 15 min. The reaction was monitored by t.l.c. with chloroform as eluent and appeared complete after 3 h. The mixture was kept one h longer, and was then cooled in an ice bath and 18 ml of water was added. After stirring overnight to ensure complete decomposition of the *p*-toluenesulfonyl chloride, the mixture was poured into ice–water and the organic constituents

were extracted into chloroform. The organic phase was washed successively with water, saturated sodium hydrogencarbonate, dilute hydrochloric acid, and water until neutral, dried (magnesium sulfate), and evaporated to give 135 g of syrup. After three recrystallizations from ether–hexane, the yield was 114 g (75%) of white prisms. When pure **5** was used, the yield was 85%; m.p. 110–111°, $[\alpha]_D$ +34.4° (*c* 1.1, chloroform); n.m.r.: δ 2.3 (3H, s tosyl CH_3), 3.25 (3H, s, OMe), 7.1–7.9 (19H, m, aromatic H).

Anal. Calc. for $C_{35}H_{38}SO_8$: C, 67.95; H, 6.19; S, 5.17. Found: C, 67.85; H, 6.23; S, 5.12.

1-O-Acetyl-2,3,4-tri-O-benzyl-6-O-tosyl-β-D-mannopyranose (**7**). — A cold solution of sulfuric acid (0.5 ml) in acetic anhydride (20 ml) was added to **6** (28.0 g) in acetic anhydride (80 ml). The mixture was stirred for 75 min at room temperature, and then poured into ice–water, stirred overnight, and the resulting white solid was removed by filtration. All operations thereafter were carried out at room temperature as the product appeared heat-sensitive. The product was dissolved in dichloromethane, washed with saturated sodium hydrogencarbonate and water until neutral, dried, treated with activated charcoal, and evaporated to a syrup that crystallized on dissolving in ether, adding ethanol, and concentrating; yield 27.4 g (93%); m.p. 108–109°, $[\alpha]_D$ +31.1° (*c* 1.3, chloroform); n.m.r.: δ 1.98 (3H, s, OAc); 2.35 (3H, s, tosyl CH_3); 6.0–6.05 (1H, d, $J_{1,2}$ 1.5 Hz, H-1α); 7.15–7.85 (19H, m, aromatic H).

Anal. Calc. for $C_{36}H_{38}SO_9$: C, 66.87; H, 5.88; S, 4.95. Found C, 66.50; H, 6.13; S, 4.93.

1,6-Anhydro-2,3,4-tri-O-benzyl-α-D-mannopyranose (**1**). — Compound **7** (90 g, 0.14 mol) was suspended in ethanol (3 l). A solution of sodium (7.2 g, 0.31 mol) in ethanol (700 ml) was added in portions during 30 min. Sodium *p*-toluenesulfonate precipitated as the sugar dissolved. After 1 h, 2 ml of water was added and carbon dioxide bubbled into the mixture. The precipitate obtained was filtered off and washed with benzene. The combined filtrates were evaporated and the solid residue was partitioned between chloroform and water. The organic phase was washed with water until neutral, dried (sodium sulfate), evaporated to a syrup, and crystallized from ether–hexane; yield 49.4 g (84%); m.p. 60–61°, $[\alpha]_D$ −31.4° (*c* 0.9, chloroform); lit.[6] m.p. 60–61°, $[\alpha]_D$ −31.2°, −32°.

This product was refluxed for 3 h in 0.75M sodium hydroxide in ethanol (500 ml), kept overnight, concentrated, and partitioned between chloroform and water. The chloroform phase was dried, treated with activated charcoal, and the product recrystallized to give 46 g of **1**, with identical physical constants, and which polymerized normally.

1,6-Di-O-acetyl-2,3,4-tri-O-benzyl-D-mannopyranose (**8**). — A cold solution of sulfuric acid (0.5 ml) in acetic anhydride (50 ml) was added to a solution of **5** (33 g) in acetic anhydride (100 ml). This was stirred for 90 min at room temperature, poured into ice–water and extracted with chloroform. The organic phase was washed with water and aqueous sodium hydrogencarbonate until neutral, dried, and concentrated to give 40 g of syrup. Crystallization from ethanol gave 25 g (52%) of

white needles; m.p. 98–100°, $[\alpha]_D$ +30.8° (*c*, 2.4, chloroform); n.m.r.: δ 2.1 (6H, acetyl H), 6.2 (1H, anomeric H) 7.2–7.5 (15H, aromatic H).

Anal. Calc. C, 69.65; H, 6.41. Found: C, 69.11; H 6.35.

2,3,4-Tri-O-benzyl-6-O-tosyl-D-mannopyranose (**9**). — A solution of sodium methoxide in methanol was added to a suspension of **8** (22 g) in methanol (500 ml). This mixture was stirred until solution occurred and then concentrated to a syrup, which was partitioned between benzene and water. The benzene fraction was dried and evaporated to give 17 g of 2,3,4-tri-*O*-benzyl-D-mannopyranose as a syrup, which was dissolved in lutidine (150 ml) and *p*-toluenesulfonyl chloride (33 g, 4 eq.) was added. After 48 h at room temperature, water (3 ml) was added to decompose the excess of tosyl chloride. The mixture was stirred for 4 h and poured into ice–water. After extraction with chloroform and washing until neutral, the organic phase was dried and purified on a column to give 17 g (70%) of a syrup (R_F 0.2 in chloroform); n.m.r. δ 2.3 (3H, s, tosyl CH_3) 7.15–7.75 (19H, m, aromatic H).

1,6-Anhydro-2,3,4-tri-O-benzyl-β-D-mannopyranose (**1**). — To a solution of **9** (17 g) in 2-propanol (1 l), sodium (770 mg) in 2-propanol (250 ml) was added. After stirring overnight, 1 ml water was added. The mixture was concentrated and partitioned between water and chloroform. The chloroform fraction was washed, dried, and evaporated to give 12 g of a syrup. On gradient-elution column chromatography, a fraction from dichloromethane (5.6 g) was obtained, which crystallized from ethanol to give 4.3 g of **1**, m.p. 60–61°.

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