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Preparation of 2,3,4,6-Tetra-*O*-benzyl-D-mannose

Shinkiti KOTO, Naohiko MORISHIMA, Yoko MIYATA, and Shonosuke ZEN
School of Pharmaceutical Sciences, Kitasato University, Shirokane, Minato-ku, Tokyo 108

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Synopsis. 2,3,4,6-Tetra-*O*-benzyl-D-mannopyranose was prepared from methyl α-D-mannopyranoside. Improved preparations of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose and -galactopyranose are described.

Since Schmidt, *et al.*[1] announced the preparation of a useful synthetic intermediate, 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose, many compounds of this type have been synthesized on various occasions.[2-4] In relation to our search for a systematic synthesis of oligosaccharide,[5,6] this note describes a preparation of 2,3,4,6-tetra-*O*-benzyl-D-mannopyranose (II) from methyl α-D-mannopyranoside. The syrupy compound II is, to the authors' knowledge, a new derivative of D-mannose and was characterized as a crystalline *p*-nitrobenzoate (α-anomer, III).

The following points are worthy of notice. The entire process of preparing the tetra-*O*-benzyl derivative of common hexoses from their corresponding methyl glycosides was significantly improved, in comparison with previous procedures.[1,3,4,7,8]

The use of a large excess of benzyl chloride, the ratio to methyl glycoside being as large as 25: 1 (v/w), in the presence of sodium hydride prevents the reaction from a sudden, violent initiation.[9] Examination of the reaction mixture indicated that the benzylation was essentially finished when the mixture recovered its fluidity with the change of color. The benzylation with use of powdered potassium hydroxide with[2] or without[1] a diluent such as *p*-dioxane was not so practical, because even after much longer heating with occasional additions of fresh potassium hydroxide the reaction was not always complete. It should also be noted that even short unnecessary heating in the hydrolysis step brought about a considerable loss of the desired products.[10]

Experimental

General. Melting points were determined by a Yanagimoto Micro Melting Point apparatus. Optical rotations were measured by a DIP-180 (Japan Spectroscopic) in a jacketed 1-dm cell. PMR was recorded by a Varian S-60-T Spectrometer. TLC was carried out over silica gel No. 7731 (Merck) with coloration by charring with sprayed aqueous sulfuric acid (10%). The column chromatography was done over silica gel (Kanto Kagaku) with irrigation of a mixed solvent system of benzene and 2-butanone.

Methyl α-D-mannopyranoside (Sigma), methyl α-D-glucopyranoside (Tokyo Kasei), and methyl β-D-galactopyranoside (Sigma) were well powdered and stored over phosphorus pentoxide. Sodium hydride (*ca.* 50% in oil, Wako) and benzyl chloride (Koso) were used without any purification.

2,3,4,6-Tetra-O-benzyl-D-mannopyranose (II). A mixture of methyl α-D-mannopyranoside (5 g), sodium hydride (8.5 g, with the oil), and benzyl chloride (125 ml) in a 500-ml round bottomed flask was heated at 125—130 °C (bath temperature) with vigorous stirring (preferably by a magnetic mixer) for 70—90 min under anhydrous conditions. During the course of the reaction, as mentioned earlier,[7] a gray reaction mixture first stiffened with evolution of hydrogen gas and much heat,[11] and then it turned into a yellow thin slurry. After removal of the insoluble material, the solution was concentrated by a water-pump over a boiling water bath to give a yellow syrup (21—25 g), which contained the dispersion oil.

A portion of this syrup (1.0 g) was purified over a column of silica gel to give pure methyl 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranoside (I), 0.55 g (95%), $bp_{0.01}$ 240—245 °C, $[\alpha]_D^{20}$ +27° (*c* 1, $CHCl_3$), $\delta_H^{CDCl_3}$ (ppm, TMS): 3.31 (3H, singlet, O–C$\underline{H}_3$), 7.30 (15H, singlet, $C_6\underline{H}_5$–), 7.20 (5H, singlet, $C_6\underline{H}_5$–).

Found: C, 75.89; H, 6.92%. Calcd for $C_{35}H_{38}O_6$: C, 75.79; H, 6.91%.

Hydrogenolysis of I (25 mg) over palladium black in methanol at room temperature under 50 psi for 8 h gave crystals (3.7 mg), mp 186—188 °C, which did not depress the melting point of the authentic specimen and showed an IR spectrum (KBr) identical with that of the authentic sample of methyl α-D-mannopyranoside.

The entire syrup mentioned above was immediately heated with a mixture of acetic acid (250 ml) and aqueous sulfuric acid (3M, 30 ml) at 80—85 °C (inside temperature) with good stirring for 30 min. The mixture was diluted with cold water (300 ml) and benzene (300 ml). After washing the organic layer by aqueous sodium hydrogencarbonate and then by water, it was concentrated to give a syrup, which was chromatographed to afford a homogeneous syrup of II, 8.5—10 g (60—72%). Washing this material with cold hexane gave an analytical sample, $[\alpha]_D^{20}$ +11° (*c* 0.9, $CHCl_3$).

Found: C, 75.12; H, 6.67%. Calcd for $C_{34}H_{36}O_6$: C, 75.53; H, 6.71%.

Refluxing II (33 mg) in methanol (0.8 ml) containing methanesulfonic acid (3 μl) for 26 h, followed by chromatography, afforded a homogeneous syrup (21 mg, 61%), which showed an identical PMR spectrum in $CDCl_3$ with that of the above-mentioned I.

2,3,4,6-Tetra-O-benzyl-1-O-p-nitrobenzoyl-α-D-mannopyranose (III). II (0.2 g) was treated with *p*-nitrobenzoyl chloride (0.1 g) in pyridine (1 ml) overnight. The mixture was processed as usual and was chromatographed to give a homogeneous syrup of III as a faster-moving product which was crystallized by diisopropyl ether. Recrystallization from this solvent furnished an analytical sample, 0.12 g (50%), mp 106.5—107 °C, $[\alpha]_D^{20}$ +59° (*c* 0.8, $CHCl_3$), ν_{max}^{KBr} (cm^{-1}): 1730 (carbonyl), 1535, 1355 (nitro), $\delta_H^{CDCl_3}$ (ppm, TMS): 6.46 (1H, a doublet, J=2 Hz), H-1 (equatorial); 7.2—7.4 (20H), $C_6\underline{H}_5$–; a multiplet centered at 8.13 (4H), –$C_6\underline{H}_4$–.

Found: C, 71.58; H, 5.85; N, 1.87%. Calcd for $C_{41}H_{39}NO_9$: C, 71.39; H, 5.70; N, 2.03%.

The β-anomer of III was obtained as a slower-moving syrupy product, which was further washed with cold hexane, $[\alpha]_D^{20}$ −11° (*c* 0.5, $CHCl_3$), $\delta_H^{CDCl_3}$ (ppm TMS): 5.57 (1H, a doublet, J=2 Hz), H-1 (axial); 7.2—7.4 (20 H), $C_6\underline{H}_5$–; a quasi-singlet at 8.15, –$C_6\underline{H}_4$–.

Found: C, 71.07; H, 5.81; N, 1.97%. Calcd for $C_{41}H_{39}NO_9$: C, 71.39; H, 5.70; N, 2.03%.

2,3,4,6-Tetra-O-benzyl-α-D-glucopyranose. The hydrol-

ysis step was carried out at 80—85 °C for 30 min by employing a mixture of acetic acid (250 ml) and aqueous hydrochloric acid (6M, 35 ml) for a syrupy benzylation product (*ca.* 25 g) obtained from 5 g of methyl α-D-glucopyranoside. The hydrolyzate was diluted with cold water (300 ml) and hexane (50 ml) with stirring. Crude crystals (7.5—8 g) were recrystallized from hot ethyl acetate (100 ml) to give a pure material, 4.5—5 g (32—36%), mp 149—149.5 °C, $[\alpha]_D^{20}$ +48° (*c* 1, dioxane). [Lit,[1] mp 148 °C, $[\alpha]_D^{25}$ +48.3° (*c* 3, dioxane)]. (Found: C, 75.59; H, 6.78%).

2,3,4,6-Tetra-O-*benzyl*-α-D-*galactopyranose.* The crude oily benzylation product (*ca.* 25 g) obtained from 5 g of methyl β-D-galactopyranoside gave methyl 2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranoside as crystals, 11.4 g (80%), mp 82—83 °C. [Lit,[4] 80—81 °C].

This galactoside (10 g) was hydrolyzed by heating at 80—85 °C for 20 min with a mixture of acetic acid (100 ml) and aqueous sulfuric acid (3M, 12 ml). The mixture was processed in the same manner as II and chromatographed to give a syrup. This was crystallized from cyclohexane containing little diisopropyl ether to give a practically pure product, 5.4 g (54%), mp 63—66 °C, $[\alpha]_D^{20}$ +74° (*c* 0.8, benzene). [Lit,[5] mp 66—68 °C, $[\alpha]_D^{20}$ +77° (*c* 2.3, benzene)]. (Found: C, 75.02; H, 6.62%).

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9) Diminution of the ratio even to 20: 1 often allowed the reaction to run out of control.

10) For example, the yield of tetra-*O*-benzylglucose was less than 7% after heating at 80—85 °C for 50 min.

11) This violent reaction usually continued for about 10 min.