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Note

Some 2,3,4,6-tetra-*O*-(*p*-chlorobenzyl)-α-D-hexopyranoses

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Recent studies on new glycosylation procedures using such stable precursors as 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose and relatives[1] led us to prepare crystalline 2,3,4,6-tetra-*O*-(*p*-chlorobenzyl)-α-D-mannopyranose (**2**).

Methyl α-D-mannopyranoside was converted into methyl 2,3,4,6-tetra-*O*-(*p*-chlorobenzyl)-α-D-mannopyranoside (**1**) by heating in *N*,*N*-dimethylformamide containing *p*-chlorobenzyl chloride in the presence of sodium hydride. Compound **1** was then hydrolyzed, to give **2**, whose yield from the starting material was 53%. The α configuration of the weakly levorotatory **2** was determined by methylation with methyl iodide and silver oxide in $HCONMe_2$, and measurement of[2] the $J_{C\text{-}1,H\text{-}1}$ value of the product.

Similarly, highly crystalline 2,3,4,6-tetra-*O*-(*p*-chlorobenzyl)-α-D-glucopyranose (**4**) and -galactopyranose (**6**) were prepared from methyl α-D-glucopyranoside and β-D-galactopyranoside, respectively, in good yields. The *p*-chlorobenzyl group was readily removed by hydrogenolysis in acetic acid in the presence of palladium black.

p-Chlorobenzyl chloride, a solid, is much less lachrymatory than benzyl chloride. The *O*-(*p*-chlorobenzyl)ated carbohydrates appear to be much more apt to crystallize than the *O*-benzylated ones; thus, compounds **1**, **2**, and **3** solidified, whereas the corresponding *O*-benzyl compounds are syrupy[3,4]. One recrystallization of crude **4** and **6** afforded configurationally pure compounds, whereas the corresponding *O*-benzyl derivatives contained an appreciable proportion of the β anomer, detected, after recrystallization, by ^{13}C-n.m.r. spectroscopy. In acid hydrolysis, the *p*-chlorobenzyl group is more stable than the methoxyl group of compounds **1**, **3**, and **5**, but it makes the methoxyl group more resistant to hydrolysis than does the benzyl group[3].

EXPERIMENTAL

General. — Melting points were determined in an MP-1 melting-point apparatus

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TABLE I

PHYSICAL AND ANALYTICAL DATA FOR COMPOUNDS PREPARED

Compound	*M.p. (°C)*	*Recryst. from*[a]	$[\alpha]_D^{20}$ *(degrees)*[b]	$[\alpha]_D^{20}$ *(degrees)*[c]	*Analysis (%)*	
					Found	
					C	*H*
1	45–47[d]		+13	−9	60.43	4.89[e]
1-β	81–83[f]	(Hx)	−31	−32	60.82	5.05[e]
2	81–82[f]	(Hx + ip)	−2	−19	60.08	4.74[g]
3	42–44[d]		+14	+56	60.86	5.05[e]
4	153–155[f]	(ip + EA)	+10	+41	60.17	4.91[g]
5	113–115[f]	(Hx + ip)	+15	+49	60.81	4.94[e]
6	94–95[f]	(ip)	+17	+88	60.13	4.76[g]

[a]Solvents used for recrystallization; EA = ethyl acetate, Hx = hexane, and ip = diisopropyl ether. [b](*c* 1.0, chloroform). [c](*c* 1.0, pyridine). [d]Prisms. [e]Calc. for $C_{35}H_{34}Cl_1O_6$: C, 60.71, H, 4.95%. [f]Needles. [g]Calc. for $C_{34}H_{32}Cl_4O_6$: C, 60.19, H, 4.76%.

(Yanagimoto); uncorrected values are given. Specific rotations were measured at 20° in a jacketed, 1-dm cell by means of a DIP-180 automatic polarimeter (Japan Spectroscopic). Column chromatography was conducted on silica gel (Kanto Kagaku), using solvent systems of benzene–butanone; each fraction was examined by t.l.c. on silica gel (Merck, 7731). The *p*-chlorobenzyl chloride (Tokyo Kasei), sodium hydride (Wako; 50% dispersion in oil), methyl α-D-mannopyranoside (Sigma), methyl α-D-glucopyranoside (Tokyo Kasei), and methyl β-D-galactopyranoside (Sigma) were used without any pretreatment. *N*,*N*-Dimethylformamide (Tokyo Kasei) was distilled before use. Evaporation was conducted under diminished pressure at 35–40°, unless otherwise stated. ^{13}C-N.m.r. spectra were recorded with a JEOL-PS-100 spectrometer equipped with a JEOL-EC-100 computer. Physical and analytical data for the compounds prepared are summarized in Table I.

2,3,4,6-Tetra-O-(p-*chlorobenzyl*)-α-D-*mannopyranose* (**2**). — A mixture of methyl α-D-mannopyranoside (2.5 g, 13 mmol), *p*-chlorobenzyl chloride (17 g, 105 mmol), and sodium hydride dispersion (5.0 g, ~103 mmol) in $HCONMe_2$ (25 mL) was heated under efficient stirring for 40 min at 85–90°, cooled, filtered through a bed of Kieselguhr G (Merck), and the solid washed with benzene. The filtrate and washings were combined, and evaporated on a boiling-water bath, and the product chromatographed on silica gel (300 g). Elution with the solvent system (100:1, and then 30:1) gave crude, syrupy **1** (9 g), which was heated in a mixture of acetic acid (90 mL) and 3M sulfuric acid (11 mL) under good stirring for 100 min at 80–85°. To the mixture were added cold water (150 mL) and benzene (150 mL) under stirring. The organic layer was successively washed with 5% sodium hydrogencarbonate solution and water, and evaporated, and the residue was chromatographed on silica gel (150 g). After the appearance of unchanged **1** by use of the solvent system (gradient, 60:1 → 40:1), elution with the solvent system (gradient, 20:1 →

10:1), followed by crystallization from hexane containing diisopropyl ether, gave **2** (4.6 g, 53% from the starting material). ^{13}C-N.m.r. spectroscopy of **2** in $CDCl_3$ containing Me_4Si showed that the crystals were practically pure (δ 92.4, C-1, $J_{C\text{-}1,H\text{-}1}$ 170 Hz).

Compound **2** (300 mg, 0.43 mmol) was refluxed in methanol containing methanesulfonic acid (30 μL) for 18 h. After neutralization of the acid with sodium hydrogencarbonate, and evaporation, chromatography with the solvent system (gradient, 100:1 → 40:1) gave **1** (210 mg, 69%); δ 98.8, C-1, $J_{C\text{-}1,H\text{-}1}$ 168 Hz, and then the β anomer **1**-β (72 mg, 24%); δ 102.6, $J_{C\text{-}1,H\text{-}1}$ 155 Hz.

On the other hand, methylation of **2** (42.0 mg, 62 μmol) with methyl iodide (0.1 mL) and silver oxide (30 mg) in $HCONMe_2$ (0.1 mL) for 16 h at 15° afforded **1** (37.6 mg, 88%) and **1**-β (1.1 mg, 2.6%).

Compound **1** (50 mg, 72 μmol) was hydrogenated at 50 lb. in.$^{-2}$ in acetic acid (5 mL) in the presence of palladium black (20 mg) for 16 h at 20°, to give methyl α-D-mannopyranoside (13 mg, 92%), identified by comparison with an authentic specimen.

2,3,4,6-Tetra-O-(p-*chlorobenzyl*)-α-D-*glucopyranose* (**4**). — Methyl α-D-glucopyranoside (0.97 g, 5.0 mmol) was similarly converted into methyl 2,3,4,6-tetra-*O*-(*p*-chlorobenzyl)-α-D-glucopyranoside (**3**) (3.6 g) which was heated in acetic acid (37 mL) and 6M hydrochloric acid (5.5 mL) under stirring for 1 h at 93–97°, to furnish **4** (2.5 g; 74% from the starting material).

2,3,4,6-Tetra-O-(p-*chlorobenzyl*)-α-D-*galactopyranose* (**6**). — Methyl β-D-galactopyranoside (1.79 g, 9.2 mmol) was converted into methyl 2,3,4,6-tetra-*O*-(*p*-chlorobenzyl)-β-D-galactopyranoside (**5**; 6.32 g), which spontaneously crystallized without chromatographic purification. Compound **5** was then hydrolyzed by heating it in acetic acid (63 mL) and 3M sulfuric acid (7.6 mL) for 100 min at 80–85° under stirring, to afford **6** (4.0 g; 64% from the starting material).

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