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Note

Efficient preparation of benzyl glycosides of lactose and cellobiose using stannic chloride

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We describe herein an efficient method for the preparation of benzyl lactoside (**5**) and benzyl cellobioside (**6**). The method is based on a one-step glycosidation of the corresponding peracetylated disaccharides with benzyl alcohol in dry acetonitrile in the presence of stannic chloride. This method has practical advantages; however, it is not stereospecific (see Table I).

TABLE I

YIELDS AND OPTICAL ROTATIONS FOR THE BENZYL GLYCOSIDES OBTAINED BY TWO DIFFERENT METHODS

Compound	*Method*				*Lit.*[5] $[\alpha]_D^{20}$ *for β-glycoside*
	A ($SnCl_4$)		*B [$(Hg(CN)_2$]*		
	Yield (%)[a]	$[\alpha]_D^{25}$ *(degrees)*	*Yield (%)*[a]	$[\alpha]_D^{25}$ *(degrees)*	
Benzyl hepta-*O*-acetylcellobioside (**4**)	66	−20.4	52	−36.4	−37.4
Benzyl lactoside (**5**)	72	−16.8	30	−28.3	n.a.[b]
Benzyl cellobioside (**6**)	68	−14.6	53	−17.2	n.a.

[a]Yields related to peracetylated disaccharides. [b]n.a., not available.

Benzyl glycosides are useful and belong to a group of the most important derivatives in synthetic carbohydrate chemistry. The benzyl functionality effectively protects the anomeric carbon atom in a wide variety of carbohydrate transformations and, when necessary, the benzyl group may be efficiently cleaved[1].

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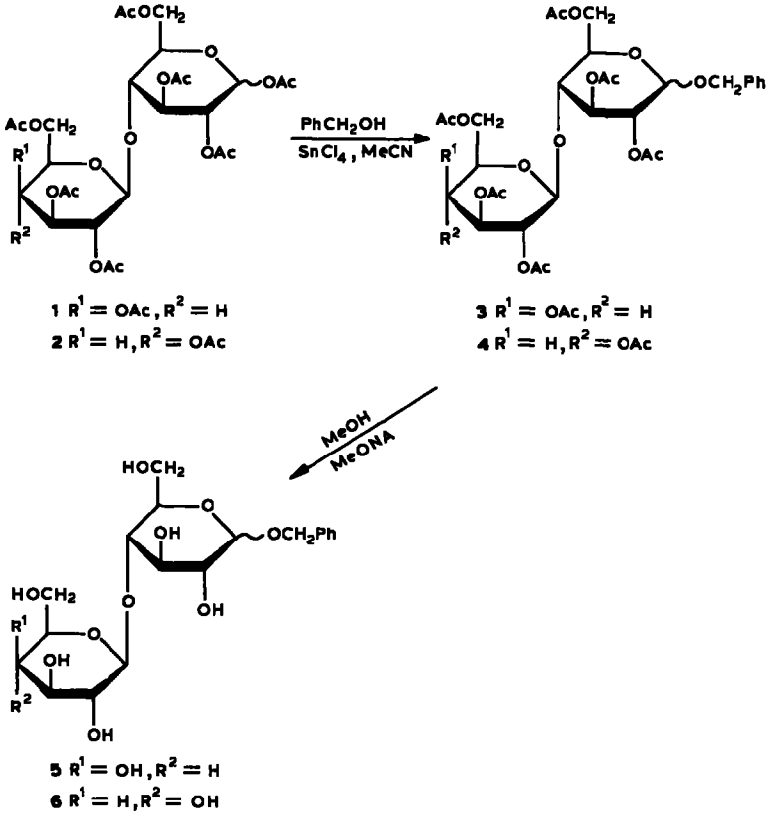

For our research, we needed large quantities of benzyl hepta-*O*-acetyllactoside (**3**) and benzyl hepta-*O*-acetylcellobioside (**4**). These derivatives are usually prepared from the peracetylated disaccharides (**1** and **2**) in two steps[2], namely, (*a*) bromination of **1** and **2**, to afford hepta-*O*-acetyl-4-*O*-β-D-galactopyranosyl-α-D-glucopyranosyl bromide and hepta-*O*-acetyl-4-*O*-β-D-glucopyranosyl-α-D-glucopyranosyl bromide, and (*b*) glycosidation of the bromide with benzyl alcohol in the presence of mercury salts [*e.g.*, $Hg(CN)_2$, method B in Table I]. We found that this two-step method is very laborious when applied to large-scale synthesis of these glycosides, particularly that of benzyl hepta-*O*-acetyllactoside (**3**).

Although stannic chloride has been used[3] in the preparation of some glycosides in the D-ribofuranose and D-glucopyranose series, examples of this glycosidation method for disaccharides are not available. It might be expected that the lower reactivity of the glycosidic carbon atoms in disaccharides, as compared to monosaccharides, combined with a limited stability of the products towards Lewis acids, could have a detrimental effect on the glycosidation of lactose and cellobiose derivatives with the aid of stannic chloride. Indeed, reactions of both octa-*O*-acetyllactose (**1**) and octa-*O*-acetylcellobiose (**2**) with benzyl alcohol and stannic chloride

in dry dichloromethane (conditions described for monosaccharides[3]) proceed at a very low rate and produce large proportions of by-products. However, when dichloromethane was replaced with dry acetonitrile, and the molar ratios of disaccharide acetates to stannic chloride and benzyl alcohol adjusted to 1:3:3, the benzyl glycosides **3** and **4** were obtained in good yields, even though the reactions were still relatively slow (24 h at ambient temperature).

Table I compares the yields (%) and specific optical rotations, $[\alpha]_D$, of the products from the two methods: using stannic chloride (Method A) and mercuric cyanide (Method B). In one case, we could not use the yields of benzyl hepta-*O*-acetyllactoside (**3**) to judge the efficiency of the $SnCl_4$ reaction, because of difficulties with crystallization of the product after work-up. This purification problem might result from a large proportion of benzyl α-lactoside formed in the $SnCl_4$ reaction. Consequently, we compared only the yields of benzyl lactoside (**5**) after *O*-deacetylation of crude **3** from both methods. The values for $[\alpha]_D$ indicate that the stannic chloride method is not stereospecific, and gives mixtures of α- and β-glycosides. Our attempts to calculate accurately the α to β ratios in crude and pure materials using ^{1}H-n.m.r. spectroscopy were not successful, due to insufficient resolution of peaks corresponding to the anomeric protons.

The method described has a practical advantage over the traditional two-step synthesis involving bromides: it is more efficient and uses cheap, less toxic materials.

EXPERIMENTAL

Disaccharide peracetates should be free from residual acetic acid and acetic anhydride (which can be readily detected by their characteristic odor). If these impurities are present, they should be removed prior to glycosidation, *e.g.*, by extracting toluene solutions of the acetylated disaccharides with sodium hydrogencarbonate. Stannic chloride, purchased from Aldrich, was used directly from "sure/seal" bottles. Acetonitrile was refluxed with calcium hydride for 30 min, and distilled. T.l.c. was performed on silica gel GF (Analtech) with 9:11 hexane–ethyl acetate. ^{1}H-N.m.r. spectra were recorded with a General Electric GN 500-MHz spectrometer and ^{13}C-n.m.r. spectra were recorded with a JEOL 270-MHz spectrometer.

General procedure for glycosidation. — In a typical reaction, the disaccharide (lactose or cellobiose) octaacetate (80 g, 118 mmol) was dissolved in a solution of benzyl alcohol (36.6 mL, 354 mmol) in dry acetonitrile (400 mL). Stannic chloride (41.4 mL, 354 mmol) was gradually added at 0° and the clear solution was stirred at room temperature until t.l.c. showed complete disappearance of the peracetate (~24 h); the acid was then neutralized with a saturated solution of sodium hydrogencarbonate. The resulting mixture was vigorously stirred with dichloromethane (500 mL), a pasty precipitate was filtered off in a Büchner funnel layered with a pad (24 cm × 3 cm) of Celite and the filter cake was washed with fresh

dichloromethane (250 mL). The two-phase filtrate was separated, and the organic phase was dried (anhydrous sodium sulfate), and evaporated. The residue was processed as described for the specific products.

Benzyl hepta-O-*acetyl*-α,β-*lactoside* (**3**). — An accurate yield could not be determined because of difficulties in crystallization; however, a small sample was repeatedly recrystallized from ethanol until no further change in optical rotation was detected; R_F 0.33; m.p. 143–144° (lit.[4] m.p. 145–146°), $[\alpha]_D^{25}$ −32° (*c* 2.08, $CHCl_3$) (lit.[4] −34.4°). The rotation, as well as the n.m.r. data, indicated that recrystallization did not completely separate the anomers; ^{1}H-n.m.r. data ($CDCl_3$): δ 7.32–7.20 (m, 5 H, Ph), 5.30 (dd, 1 H, $J_{3',4'}$ 3.3, $J_{4',5'}$ 0.9 Hz, H-4′), 5.11 (t, 1 H, $J_{2,3} = J_{3,4}$ = 9.4 Hz), 5.05 (dd, 1 H, $J_{2',3'}$ 10.5, $J_{1'2'}$ 7.9 Hz, H-2′), 4.92 (dd, 1 H, $J_{2,3}$ 9.4, $J_{1,2}$ 7.9 Hz, H-2), 4.81 (d, 1 H, $J_{PhCHa, PhCHb}$ 12.3 Hz, $PhCH_b$), 4.55 (d, 1 $J_{PhCHa, PhCHb}$ 12.3 Hz, $PhCH_a$), 4.43–4.50 (m, 3 H, H-1, H-6_b, H-1′), 4.00–4.11 (m, 3 H, H-6_a,$6'_a$,$6'_b$), 3.83 (m, 1 H, $J_{5',6'}$ 13.6, $J_{4',5'}$ 0.9 Hz, H-5′), 3.78 (t, 1 H, $J_{4,5}$ 9.5, $J_{3,4}$ 9.4 Hz, H-4), and 3.54 (ddd, 1 H, $J_{4,5}$ 9.5, $J_{5,6a}$ 6.2, $J_{5,6b}$ 2.1 Hz, H-5); ^{13}C ($CDCl_3$): δ 169.95, 169.86, 169.72, 169.57, 169.34, 169,11, 168.85 (>C=O acetyls), 136.29, 128.02, 127.56, 127.47, 127.33 (phenyl ring), 100.47, 98.60 (C-1,1′), 75.99, 75.82, 72.39, 72.25, 71.21, 70.55, 70.23 (C-2,3,4,5,2′,3′,5′, CH_2–Ph), 68.74 (C-4′), and 61.71 and 60.53 (C-6,6′).

Benzyl hepta-O-*acetyl*-α,β-*cellobioside* (**4**) crystallized, and was recrystallized, from ethanol; yield 57.0 g (66%); R_F 0.31; m.p. 186–188° (lit.[5] m.p. 187°), $[\alpha]_D^{25}$ −20.4° (*c* 2.53, $CHCl_3$); ^{13}C-n.m.r. data ($CDCl_3$): δ 170.24, 170.09, 169.98, 169.57, 169.98, 168.80 (>C=O acetyls), 136.46, 128.25, 127.82, 127.56 (phenyl ring), 100.52, 98.88 (C-1,1′), 76.51, 76.25, 72.74, 72.51, 71.70, 71.38, 70.52 (C-2,3,4,5,2′,3′,5′, CH_2–Ph), 67.58 (C-4′), 61.71, 61.36 (C-6,6′), 20.65, 20.42, 20.33 (CH_3 acetyls).

A small sample of *pure benzyl hepta*-O-*acetyl*-β-*cellobioside* (**4**) was obtained by repeated recrystallization from ethanol; $[\alpha]_D^{25}$ −38° (*c* 4.08, $CHCl_3$); ^{1}H-n.m.r. data ($CDCl_3$): δ 7.29–7.19 (m, 5 H, Ph), 5.10–5.06 (m, 2 H, H-3,3′), 4.99 (t, 1 H, $J_{4',5'}$ 10, $J_{3',4'}$ 9.6 Hz, H-4′), 4.91 (dd, 1 H, $J_{2',3'}$ 9.6, $J_{1',2'}$ 7.9 Hz, H-2′), 4.85 (dd, 1 H, $J_{2,3}$ 9.3, $J_{1,2}$ 8 Hz, H-2), 4.79 (d, 1 H, $J_{PhCHa, PhCHb}$ 12.3 Hz, $PhCH_b$), 4.53 (d, 1 H, $J_{PhCHa, PhCHb}$ 12.3 Hz, $PhCH_a$), 4.49–4.44 (m, 3 H, H-1,6b,1′, 4.30 (dd, 1 H, $J_{6b,6'b}$ 12.5, $J_{5',6'a}$ 5 Hz, H-6a′), 4.05 (dd, 1 H, $J_{6a,6b}$ 12, $J_{5,6}$ 5 Hz, H-6a), 3.98 (dd, 1 H, $J_{6'a,6'b}$ 12.5, $J_{5',6'b}$ 2.2 Hz, H-6′b), 3.74 (t, 1 H, $J_{4,5}$ 10, $J_{3,4}$ 9.3 Hz, H-4), 3.60 (ddd, 1 H, $J_{4',5'}$ 10, $J_{5',6'a}$ 5, $J_{5',6b'}$ 2.2 Hz, H-5′a), 3.51 (ddd, 1 H, $J_{4,5}$ 10, $J_{5,6a}$ 5, $J_{5,6b}$ 2 Hz, H-5a), 2.08 (s, 3 H), 2.01 (s, 3 H), 1.97 (s, 3 H), 1.94 (s, 3 H), 1.93 (s, 3 H), and 1.91 (s, 3 H, acetyl protons).

Benzyl α,β-*lactoside* (**5**). — The crude residue containing **3**, after being dried overnight over P_2O_5 under vacuum, was deacetylated with 0.05M MeONa–MeOH (880 mL), using a standard procedure[6]. The product crystallized from absolute ethanol; yield 36.7 g (72%); m.p. 178–179°, $[\alpha]_D^{25}$ −16.8° (*c* 4.92, $CHCl_3$); ^{13}C-n.m.r. data (D_2O): δ 136.94, 129.14 (phenyl ring), 103.30, 101.43 (C-1,1′), 78.86, 75.77, 75.17, 74.73, 74.83, 72.80, 71.85, 71.34 (C-2,3,4,5,2′,3′,5′, CH_2–Ph), 68.92 (C-4′), 61.41, and 60.50 (C-6,6′).

Anal. Calc. for $C_{19}H_{28}O_{11}$: C, 52.76; H, 6.52. Found: C, 52.37; H, 6.42.

Benzyl α,β-cellobioside (**6**). — The crude residue containing **4** was converted into **6** exactly as for **5**, yield 34.5 g (68%); m.p. 196–197°, $[\alpha]_D^{25}$ −14.6° (*c* 3.87, H_2O); ^{13}C-n.m.r. data ($CDCl_3$): δ 137.01, 129.22 (phenyl ring), 103.03 (C-1β, 1′), 101.52 (C-1,1′), 79.17, 76.47, 76.00, 75.27, 74.83, 73.65, 73.40, 72.01 (C-2,3,4,5,2′,3′,5′, CH_2Ph), 69.94 (C-4′), 61.05, and 60.57 (C-6,6′).

Anal. Calc. for $C_{19}H_{28}O_{11}$: C, 52.76; H, 6.52. Found: C, 52.43; H, 6.44.

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