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Note

Selective demesylation of 2-*O*-(methylsulfonyl)-D-mannopyranoside derivatives with sodium amalgam and 2-propanol

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In this laboratory, we have been investigating methods of glycoside and oligosaccharide synthesis that can be conducted in homogeneous solution, with high stereospecificity, at reasonable rates, with near-equivalent amounts of only two reactants. A series of sulfonate leaving-groups of varied reactivity at C-1 have been applied to the synthesis of both *cis*-1,2 and *trans*-1,2 glycosides. If these are used in the D-*manno* series, a participating substituent on C-2 directs the glycosidation almost exclusively to the 1,2-*trans*-α-D-glycoside[1], whereas a non-participating, electron-withdrawing methylsulfonyl (mesyl) group at O-2 usually results in a substantial preponderance of the β-D-mannoside[2–5]. However, until recently, we had found no method to cleave the mesyl group selectively in the presence of such other protecting groups as benzyl. Treatment of the benzylated 2-*O*-mesylmannopyranoside with nickel and ethanol, or sodium–naphthalene in oxolane (THF) resulted in formation of the starting material[3]. Removal of both benzyl groups and mesyl groups was effected with sodium in liquid ammonia[3].

Reber and Reichstein reported the selective removal of a *p*-tolylsulfonyl group with sodium amalgam and methanol–water, in the presence of benzylidene and methyl groups[6]. Methyl 3,4,6-tri-*O*-benzyl-2-*O*-(methylsulfonyl)-α-D-mannopyranoside (**1**) was treated, therefore, with 80% methanol and sodium amalgam. As reaction of the sodium seemed too rapid and inefficient with aqueous methanol, pure methanol was also used. After 24 h, the amalgam was decomposed and only a small quantity of product was evident. It was considered that the amalgam would reduce compound **1** more efficiently in the presence of a less acidic, hydroxylated solvent, and so it was dissolved in ethyl ether to which abs. ethanol had been added. After 48 h, the reaction was 20% complete, and two more additions of amalgam over several days were required to complete the reaction. When 2-propanol in diethyl ether was used instead as a proton source, the reaction was complete overnight, and **3** was isolated in 98% yield. The identical reaction was performed with methyl 3,4,6-tri-*O*-benzyl-2-*O*-(methylsulfonyl)-β-D-mannopyranoside (**2**), and the demesylated product (**4**) was secured in 84% yield.

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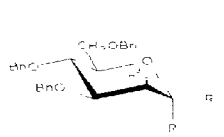

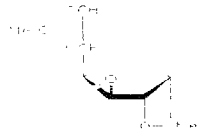

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1 R = H, R' = OMe, R'' = Ms
2 R = OMe, R' = H, R'' = Ms
3 R = H, R' = OMe, R'' = H
4 R = OMe, R' = R'' = H
5 R = H, R' = H, R'' = Ms
6 R' = H, R = [illegible], R'' = Ms
7 R = 13, R' = H, R'' = Ms
8 R' = 13, R = R'' = H
9 R' = H, R'' = 13, R = Ac or Bz
10 R' = H, R = Ts, R'' = Ac or Bz
11 R = H, R' = 13, R'' = Ac or Bz
12 R = R' = R'' = 13

As a further test of the deblocking procedure, a relatively hindered disaccharide derivative was prepared by coupling 3,4,6-tri-*O*-benzyl-2-*O*-(methylsulfonyl)-1-*O*-(2,2,2-trifluoroethylsulfonyl)-D-mannopyranose (**6**) with 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose. The reaction was slow, requiring 3 days, and the desired β-linked product (**7**) was isolated crystalline in 35% yield. Compound **7** was then treated with sodium amalgam in ether and 2-propanol to yield 66% of the demesylated disaccharide (**8**). The configuration of **8** was established by synthesis of its α anomer (**12**).

2-*O*-Acetyl (or benzoyl) 3,4,6-tri-*O*-benzyl-1-*O*-*p*-tolylsulfonyl-α-D-mannopyranose (**10**) was coupled with 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, and the product was deacylated to afford **12**. The α anomer had the expected a higher positive specific rotation; α anomer $[\alpha]_D^{25}$ +49.8° (*c* 0.8, chloroform); β anomer $[\alpha]_D^{25}$ +31.1° (*c* 0.9, chloroform). The ^{13}C-n.m.r. spectrum showed the expected upfield shift of the respective anomeric resonances from β to α. Furthermore C-5 of the β disaccharide resonated at 75.33 p.p.m. and C-5 of the α disaccharide was shifted upfield, in agreement with the data published for a series of α- and β-D-mannopyranosides[3,4,7,8]. The ^{1}H spectra of **8** and **12** showed the H-1 signal of the β anomer at lower field than H-1′ of the α anomer, which is the reverse of that usually expected for β- and α-D-mannopyranosides.

EXPERIMENTAL

General methods. — ^{1}H-N.m.r. spectra were recorded with a Varian EM-360 spectrometer with chloroform-*d* as solvent and tetramethylsilane (Me_4Si) as the in-

ternal standard. All other general methods followed were those previously used in this laboratory[1].

Materials. — Acetonitrile was distilled from calcium hydride (CaH_2), and dried over molecular sieves. 2,6-Lutidine was dried over potassium hydroxide, boiled under reflux with CaH_2, and distilled into a flask containing 4Å molecular sieves[9]. Sodium amalgam was prepared according to Vogel[10]. 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose was purchased from Pfanstiehl Laboratories and used directly. Methyl 3,4,6-tri-*O*-benzyl-α- and β-D-mannopyranosides (**3** and **4**), prepared by Fischer glycosidation of 3,4,6-tri-*O*-benzyl-D-mannopyranose[11], were formed in the α:β ratio of 9:1. The anomers were separated by l.c. in ethyl acetate–hexanes (1:1, v/v). Physical constants agreed with those previously reported[3,12]. Compounds **1** and **2** were prepared by mesylation of methyl 3,4,6-tri-*O*-benzyl-α- and β-D-mannopyranoside (**3** and **4**) with methanesulfonyl chloride and 2,6-lutidine[2,3].

Methyl 3,4,6-tri-O-benzyl-α-D-mannopyranoside (**3**). — Compound **1** (0.1782 g, 0.328 mmol), anhydrous 2-propanol (2 mL), anhydrous ethyl ether (8 mL), and 6.75% sodium amalgam (1.18 g) were added to a round-bottomed flask equipped with a drying tube. The mixture was stirred overnight. The solution was brought to pH 7 with acetic acid, decanted from the mercury, and the solvents were evaporated. The remaining mixture was dissolved in dichloromethane (CH_2Cl_2), washed with distilled water (H_2O), and then dried with sodium sulfate (Na_2SO_4). Purification by l.c. with ethyl acetate–hexanes (1:2, v/v) resulted in 0.15 g (98.6%) of **3**: ^{13}C-n.m.r. ($CDCl_3$): 127.8–128.5 (m, 18 C, aromatic), 101.2 (C-1), 69.8 (C-2), 80.9 (C-3), 75.7 (C-4), 72.5 (C-5), 68.8 (C-6), and 55.2 (OMe).

The $[\alpha]_D^{20}$ and ^{1}H-n.m.r. data agreed with those reported in the literature[1,11].

Methyl 3,4,6-tri-O-benzyl-β-D-mannopyranoside (**4**). — Compound **2** (0.1454 g, 0.268 mmol), anhydrous 2-propanol (2 mL), anhydrous ethyl ether (8 mL), and 6.78% sodium amalgam (0.96 g) were added to a round-bottomed flask equipped with a drying tube. The mixture was stirred for 48 h. The solvent was removed under vacuum, and the remaining mixture was centrifuged in diethyl ether. The solution was decanted, and the pellet again mixed with ether and the mixture centrifuged. The combined solutions were evaporated, the residue dissolved in CH_2Cl_2, washed with H_2O, dried ($NaSO_4$), and evaporated again. The product was purified by l.c. with ethyl acetate–hexanes (1:2, v/v) resulting in 0.1048 g (84.4%) of **4**; $[\alpha]_D^{20}$ −8.77° (*c* 1.0, chloroform); lit.[12] $[\alpha]_D^{20}$ −10.2° (*c* 0.45, chloroform); ^{13}C-n.m.r. ($CDCl_3$): 127.8–128.5 (m, 18 C, aromatic), 101.04 (C-1), 69.43 (C-2), 81.76 (C-3), 75.17 (C-4), 75.47 (C-5), 68.25 (C-6), and 56.93 (OMe).

The $[\alpha]_D^{20}$ and ^{1}H-n.m.r. data agreed with those reported[12].

3,4,6-Tri-O-benzyl-2-O-(methylsulfonyl-α-D-mannopyranosyl chloride (**5**). — 3,4,6-Tri-*O*-benzyl-D-mannopyranose (0.5205 g, 1.1567 mmol) was weighed into an oven-dried flask and CH_2Cl_2 (2 mL), 2.5 molar equivalents of 2,6-lutidine (0.34 mL, 2.89 mmol), and 2.5 molar equivalents of methanesulfonyl chloride (0.2238 mL, 2.89 mmol) were added in succession. The solution was heated for 72

h on a steam bath. One major and one minor slower-moving spot appeared on the t.l.c. plate. The colored solution was extracted with CH_2Cl_2, and the extract was washed with H_2O, M hydrochloric acid (HCl) and sodium hydrogencarbonate ($NaHCO_3$), and dried (Na_2SO_4). Column chromatography with silica gel removed the color. The eluant was then chromatographed in ethyl acetate–hexanes (1:2, v/v) to remove the slower-moving spot, resulting in 0.5492 g (84% yield) of the α anomer (**5**) whose $[\alpha]_D^{20}$ value was in agreement with that in the literature[3]; ^{1}H-n.m.r. ($CDCl_3$): δ 7.1–7.46 (m, 15 H, aromatic), 6.20 (d, 1 H, $J_{1,2}$ 1.8 Hz, H-1), 5.10 (t, 1 H, $J_{2,3}$ 3.0 Hz, H-2), 4.29–4.92 (m, 6 H, benzyl CH_2), 3.35–4.25 (m, 5 H, H-3,4,5,6,6″), and 2.92 (s, 3 H, Ms). The slower-moving spot (β anomer) showed ^{1}H-n.m.r. data δ 5.3 (d, 1 H, $J_{1,2}$ 1.8 Hz, H-1).

1,2:5,6-Di-O-isopropylidene-3-O-[3,4,6-tri-O-benzyl-2-O-(methylsulfonyl)-β-D-mannopyranosyl]-α-D-glucofuranose (**7**). — The chloride **5** (0.5163 g, 0.915 mmol), in a high-vacuum rack, was dissolved in acetonitrile and mixed with 1.25 molar equivalents of silver 2,2,2-trifluoroethylsulfonate (0.31 g, 1.1427 mmol) also dissolved in the minimal amount of acetonitrile. This reaction formed the sulfonyl derivative[3] (**6**) after 1 h in the dark at room temperature. The silver chloride (AgCl) was then filtered off and 1.25 molar equivalents of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (0.298 g, 1.1429 mmol) was mixed with the sulfonyl derivative. The mixture was allowed to react further for 84 h in the dark at room temperature. Dichloromethane was then added to the mixture and the organic phase was washed with sodium thiosulfate, $NaHCO_3$, and H_2O, the solution was dried (Na_2SO_4) and evaporated to afford the desired disaccharide(**7**). The compound was chromatographed twice with ethyl acetate–hexanes (1:2, v/v) and recrystallized from ether–petroleum ether to yield 0.2539 g of crystalline material, m.p. 121–124°, $[\alpha]_D^{22}$ +10.2° (*c* 1.0, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 7.1–7.45 (m, 15 H, aromatic), 5.85 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 5.33 (d, 1 H, $J_{1',2'}$ 2 Hz, H-1′), 5.03 (t, 1 H, H-2′), 4.4–4.50 (m, 6 H, benzyl CH_2), 3.44–4.40 (H-2,3,3′,4,4′,5,5′,6,6″,6′), 3.0 (s, 3 H, OMs), and 1.1–1.5 (m, 12 H, isopropylidene); ^{13}C-n.m.r. ($CDCl_3$): 126.8–129.5 (m, 18 C, aromatic), 109.7 and 112.2 (CMe_2), 105.5 (C-1), 99.2 (C-1′), 83.8 (C-3), 81.6 (C-2 and C-4), 77.3 (C-3′), 75.6 and 75.3 (C-4′ and C-5′), 74.5, 73.7, 72.9 (2 C), 72.2, 69.1 (C-6′), 67.9 (C-6), 38.9 (Ms), 24.8, 25.8, and 26.5, (4 C, CMe_2).

The overall yield was 35%.

Anal. Calc. for $C_{40}H_{50}O_{13}S$ (*m/z* 770.87): C, 62.32; H, 6.54; S, 4.16. Found: C, 62.60; H, 7.10; S, 4.10.

1,2:5,6-Di-O-isopropylidene-3-O-(3,4,6-tri-O-benzyl-β-D-mannopyranosyl)-α-D-glucofuranose (**8**). — The mesylated disaccharide (**7**, 0.1781 g, 0.2312 mmol), anhydrous ethyl ether (8.0 mL), anhydrous 2-propanol (2.0 mL), and 6.88% sodium amalgam (0.803 g) were mixed together overnight at room temperature. To remove the solid efficiently, the mixture was diluted with diethyl ether and divided into 4 centrifuge tubes that were spun for 5 min at 4000 r.p.m. The solution was decanted, more solvent was added to the remaining material in the centrifuge tube, and the mixture was centrifuged again. The combined solutions were evaporated,

the residue dissolved in CH_2Cl_2, the solution dried ($NaSO_4$), and evaporated. The product was chromatographed to afford 0.1061 g (66%) of **8**; $[\alpha]_D^{20}$ +31.1° (*c* 1.0, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 7.1–7.47 (m, 15 H, aromatic), 5.83 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 5.13 (d, 1 H, $J_{1,2}$ 2 Hz, H-1'), 4.20–4.97 (m, 6 H, benzyl CH_2), 3.30–4.20 (m, 12 H, H-2,2',3,3',4,4',5,5',6,6'',6',6'''), 2.94 (s, 1 H, exchangeable with D_2O, OH), 1.20–1.35, 1.42, and 1.49 (4 singlets, 12 H, CMe_2); ^{13}C-n.m.r. ($CDCl_3$): 127.79–128.77 (m, 18 C, aromatic), 112.10 and 109.43 (CMe_2), 105.54 (C-1), 100.95 (C-1'), 83.68 (C-3), 81.70 (C-2), 81.44 (C-4), 79.98 (C-3'), 75.33 (C-5'), 74.61, 73.73, 72.70, 72.36 (2 C), 69.43 (C-2'), 68.48 (C-6'), 67.82 (C-6), 25.45, 26.16, and 26.88 (4 C, CM_2).

Anal. Calc. for $C_{39}H_{48}O_{11}$ (*m/z* 692.77): C, 67.61; H, 6.98. Found: C, 66.0; H, 7.01. Calc. with 1 mole H_2O, $C_{39}H_{50}O_{12}$: C, 65.89; H, 7.09.

*1,2:5,6-Di-*O*-isopropylidene-3-*O*-(3,4,6-tri-*O*-benzyl-α-*D*-mannopyranosyl)-α-*D*-glucofuranose* (**12**). — The chloride[1] **9** (1.0 mmol), in a high-vacuum rack, was dissolved in acetonitrile and mixed with silver *p*-toluenesulfonate (0.2792 g, 1.0 mmol) also dissolved in the minimal amount of acetonitrile. This reaction formed the sulfonyl derivative[1] (**10**) and a white precipitate (AgCl) after 1 h in the dark at room temperature. The 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (0.2792 g, 1.0 mmol) was mixed with the sulfonyl derivative and allowed to react overnight in the dark at room temperature. The isolation followed was identical to that of the previous coupling procedure. The ratio of β:α anomer of the product (**11**) was 3:2 by ^{13}C-n.m.r. spectroscopy. This is the only case in our experience in which neighboring-group participation failed to direct nearly exclusively to the α product with the acetyl or benzoyl derivative **9**. The product was then deacylated. Methanol (30 mL) was added to the disaccharide, as was a solution of sodium methoxide (20 mg of Na in 3 mL of methanol). After the reaction had reached completion (t.l.c.), the solution was made neutral with a drop of acetic acid to result in a 59% yield of deacylated disaccharide. The two anomers were separated by l.c. in 1:1 ethyl acetate–hexanes. The α anomer (**12**) was used as evidence for structure proof for the β anomer; $[\alpha]_D^{20}$ +49.8° (*c* 0.8, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 7.1–7.47 (m, 15 H, aromatic), 5.95 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 4.9 (d, 1 H, $J_{1,2}$ 2 Hz, H-1'), 4.50–4.90 (m, 6 H, benzyl), 3.60–4.50 (m, 12 H, H-2,2',3,3',4,4',5,5',6,6'',6',6'''), 3.25–3.50 (s, 1 H, OH), and 1.14–1.6 (4 s, 12 H, CMe_2); ^{13}C-n.m.r. ($CDCl_3$): 127.75–128.73 (m, 18 C, aromatic), 112.40 and 101.07 (CMe_2), 106.59 (C-1), 99.29 (C-1'), 84.23 (C-3), 80.14 (C-2), 79.45 (C-4), 75.11 (C-3' and C-4'), 74.51, 73.54 (C-5), 72.18 (C-5'), 71.34, 71.22, 69.16 (C-2'), 68.58 (C-6'), 67.47 (C-6), 27.28, 26.65, and 24.08 (4C, CMe_2).

Anal. Calc. for $C_{39}H_{48}O_{11}$ (*m/z* 692.77): C, 67.61; H, 6.98. Found: C, 65.78; H, 6.92. Calc. with 1 mole H_2O, $C_{39}H_{50}O_{12}$: C, 65.89; H, 7.09.

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REFERENCES

1 E. S. RACHAMAN, R. EBY, AND C. SCHUERCH, *Carbohydr. Res.*, 67 (1978) 147–161
2 V. K. SRIVASTAVA AND C. SCHUERCH, *Carbohydr. Res.*, 79 (1980) c13–c16.
3 V. K. SRIVASTAVA AND C. SCHUERCH, *J. Org. Chem.*, 46 (1981) 1121–1126.
4 E. S. H. EL ASHRY AND C. SCHUERCH, *Carbohydr. Res.*, 105 (1982) 33–43
5 V. K. SRIVASTAVA AND C. SCHUERCH, *Carbohydr. Res.*, 100 (1982) 411–417
6 F. REBER AND T. REICHSTEIN, *Helv. Chim. Acta*, 28 (1945) 1164–1176
7 R. KASAI, M. OKIHARA, J. ASAKAWA, K. MIZUTANI AND O. TANAKA, *Tetrahedron*, 35 (1979) 1427–1432.
8 J. B. STOTHERS, *Org. Chem. Ser. Monogr.*, 24 (1972) 270
9 D. PERRIN, *Purification of Laboratory Chemicals*, Pergamon, New York, 1966, p. 195.
10 A. VOGEL, *Textbook of Practical Organic Chemistry*, Longmans, New York, 1978, pp. 314–315
11 N. E. FRANKS AND R. MONTGOMERY, *Carbohydr. Res.*, 6 (1968) 286–298.
12 V. K. SRIVASTAVA AND C. SCHUERCH, *Tetrahedron Lett.*, (1979) 3269–3272