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Note

Improved synthesis of substituted 2,6-dioxabicyclo[3.1.1]heptanes: 1,3-anhydro-2,4,6-tri-*O*-benzyl- and 1,3-anhydro-2,4,6-tri-*O*-*p*-bromobenzyl-β-D-mannopyranose

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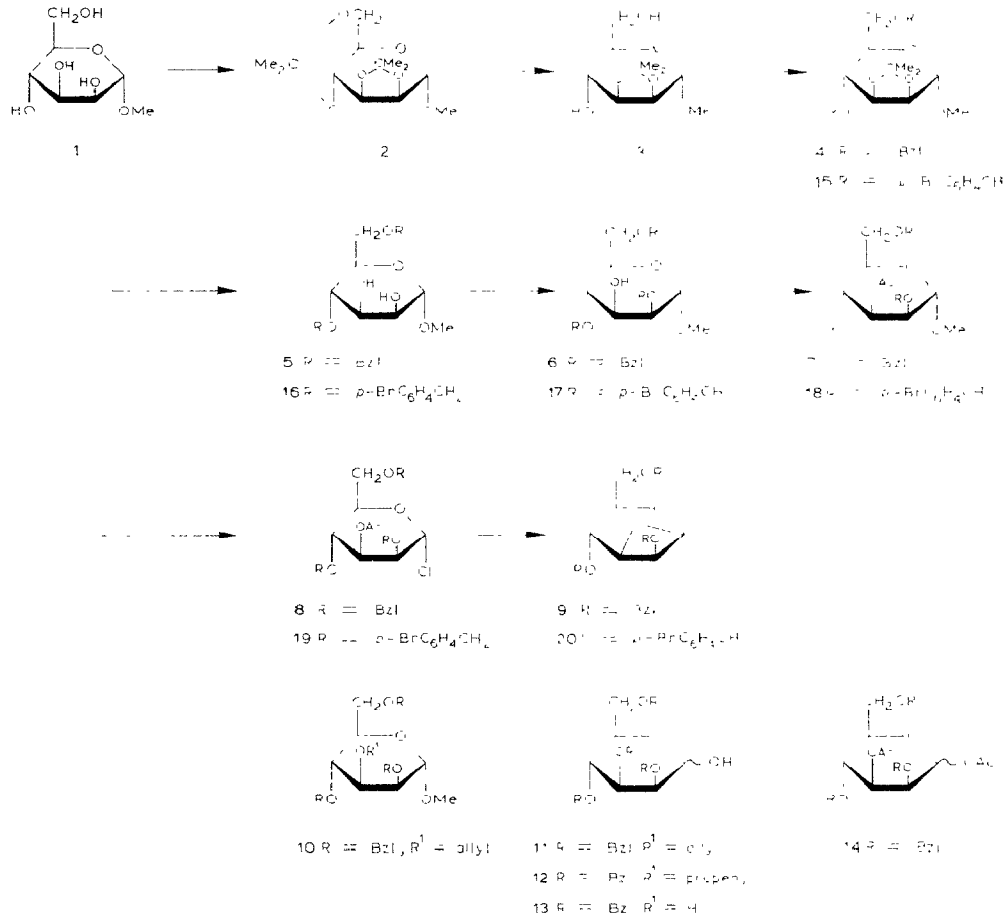
The synthesis of 1,3-anhydro-2,4,6-tri-*O*-benzyl-β-D-mannopyranose (**9**) and 1,3-anhydro-2,4,6-tri-*O*-(*p*-bromobenzyl)-β-D-mannopyranose (**20**) is of interest, since their stereospecific polymerization would give an α-(1→3)-linked mannopyranan. Terminal α-(1→3)-linked mannopyranosyl groups are important immunodeterminants of yeast mannans[1], and α-(1→3)-linked mannose residues are found at branch points of glycosyl side-chains of a number of glycoproteins[2].

In previous syntheses of the title compounds[3], the key intermediates were 2,4,6-tri-*O*-benzyl- and 2,4,6-tri-*O*-(*p*-bromobenzyl)-α-D-mannopyranosyl chloride. There were two difficulties in the syntheses. First, it was difficult to convert reproducibly large quantities of methyl 2,4,6-tri-*O*-benzyl- and methyl 2,4,6-tri-*O*-(*p*-bromobenzyl)-α-D-mannopyranosides into the corresponding mannosyl chlorides, because some disaccharides were readily formed both in the reaction and in the purification when the 3-hydroxyl group was not protected. Second, by-products formed in the ring-closure reaction prevented crystallization of the monomer. In the present paper, we have employed a new method as follows.

Methyl α-D-mannopyranoside (**1**) was converted into methyl 2,3:4,6-di-*O*-isopropylidene-α-D-mannopyranoside (**2**) and the crude product was partially hydrolyzed to methyl 2,3-*O*-isopropylidene-α-D-mannopyranoside[4] (**3**). Benzylation or *p*-bromobenzylation of **3** followed by hydrolysis of the isopropylidene group afforded methyl 4,6-di-*O*-benzyl- (**5**) and 4,6-di-*O*-(*p*-bromobenzyl)-α-D-mannopyranoside (**16**). The 2-OH groups of **5** and **16** were selectively etherified to give, respectively, methyl 2,4,6-tri-*O*-benzyl- (**6**) and methyl 2,4,6-tri-*O*-(*p*-bromobenzyl)-α-D-mannopyranoside[5] (**17**). Compounds **6** and **17** were acetylated[6] to give methyl 3-*O*-acetyl-2,4,6-tri-*O*-benzyl- (**7**) and 3-*O*-acetyl-2,4,6-tri-*O*-(*p*-bromobenzyl)-α-D-mannopyranoside (**18**). Treatment with anhydrous hydrogen chloride converted **7** and **18** into 3-*O*-acetyl-2,4,6-tri-*O*-benzyl- and 3-*O*-acetyl-2,4,6-tri-*O*-(*p*-bromobenzyl)-α-D-mannopyranosyl chloride (**8** and **19**), respectively. A satisfactory yield



was obtained and the mannosyl chlorides thus obtained were quite stable. Ring-closure of **8** and **19** was achieved with potassium *tert*-butoxide to give nearly quantitative yields of **9** and **20**.

Compared with the previous procedure[3], the improved method has nine steps instead of eleven and the intermediates, mostly obtained in high yield, are readily purified.

We have also obtained satisfactory results with 2,4,6-tri-*O*-benzyl-D-mannopyranose (**13**) although its preparation by hydrolysis of **6** was difficult because of substantial decomposition. However, its 3-allyl ether (**10**) could be hydrolyzed by a previously reported method[7] to give 3-*O*-allyl-2,4,6-tri-*O*-benzyl-D-mannopyranose (**11**), and the allyl group could then be removed by treatment with chlorotris(triphenylphosphine)rhodium[8] to provide **13**. Acetylation of **13** to give the 1,3-diacetate **14** and the conversion of **14** into **8** were quantitative.

The 1,3-anhydro sugars obtained by the present methods were characterized by

^{1}H-n.m.r. spectroscopy and optical rotation. The values were the same as those reported before[3]. However, one monomer was obtained crystalline instead of as a syrup.

EXPERIMENTAL

General methods. — These are as described in ref. 3. Organic solutions were dried with anhydrous sodium sulfate.

Methyl 2,3-O-isopropylidene-α-D-mannopyranoside (**3**). — Methyl α-D-mannopyranoside (145 g, 0.747 mol), 2,2-dimethoxypropane (591 g, 5.67 mol) and *p*-toluenesulfonic acid (29.2 g, 0.15 mol) were added to acetone (2.6 L) and the mixture was stirred vigorously for 5 h at room temperature. A colorless solution containing methyl 2,3:4,6-di-*O*-isopropylidene-α-D-mannopyranoside (**2**) was obtained. Water (20 mL) was added to the solution at room temperature with vigorous stirring and after 0.5 h another 20 mL of water was added. When about one-half of compound **2** had been hydrolyzed to **3** [as indicated by t.l.c. (pure ethyl acetate)], the reaction was stopped by passing gaseous ammonia through the solution until it became weakly basic. A small amount of precipitate (starting material) was filtered off and the filtrate evaporated to a syrup. Water (70 mL) was added to the syrup and the mixture extracted with hexanes several times to remove compound **2** (95 g), which could be reused. The aqueous layer was extracted with ethyl acetate in a continuous extractor for 24 h and the organic phase evaporated to a syrup. The syrup was dissolved in dichloromethane (100 mL), hexane (~50 mL) was added, and white crystals were obtained. The crude crystals of **3** were purified by recrystallization from dichloromethane–hexanes and 82 g of **3** was obtained; m.p. 103–104°, $[\alpha]_D^{25}$ +30.2° (c 0.94, chloroform); lit.[4,9], m.p. 104–105°, $[\alpha]_D^{25}$ +28.3° (*c* 1, methanol).

Methyl 4,6-di-O-benzyl-α-D-mannopyranoside (**5**). — To a solution of compound **3** (60 g, 0.256 mol) in toluene (270 mL) was added finely powdered potassium hydroxide (120 g). Benzyl chloride (150 mL, 1.30 mol) was then slowly added during 2 h under reflux and with vigorous agitation. The mixture was boiled for 0.5 h more under reflux. T.l.c. (pure ethyl acetate) indicated the reaction to be complete. The mixture was extracted with water and the excess of benzyl chloride removed by steam distillation. The mixture was extracted repeatedly with dichloromethane and the organic layer dried. Dichloromethane was removed and syrupy methyl 4,6-di-*O*-benzyl-2,3-*O*-isopropylidene-α-D-mannopyranoside (**4**) was obtained. To a solution of **4** in methanol (450 mL) was added hydrochloric acid (100 mL, 0.5M) and the mixture was boiled under reflux for 1 h. T.l.c. (pure ethyl acetate) indicated the reaction to be complete. The mixture was made neutral with sodium hydrogencarbonate and the solvent evaporated to give a wet solid. The crude product was extracted repeatedly with dichloromethane and the organic layer dried. Hexanes (200 mL) were added to the solution (100 mL) and white crystals of **5** obtained; these were purified by recrystallization from dichloromethane–hexanes; yield (from **3**) 97%; m.p. 101–102°, $[\alpha]_D^{25}$ +74.7° (*c* 1.11, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 7.33–7.29

(10 H, m, aromatic H), 4.90–3.75 [11 H, m, H-1, 2 CH_2Ph, (2) H-6, H-2,3,4,5], 3.33 (3 H, s, OCH_3), and 2.85–2.60 [2 H, s, (2) OH].

*Methyl 2,4,6-tri-*O*-benzyl-α-*D*-mannopyranoside* (**6**). — To a solution of **5** (40 g, 0.107 mol), tetrabutylammonium hydrogensulfate (8 g), and benzyl bromide (32 mL, 0.269 mol) in dichloromethane (1.2 L) was added aqueous sodium hydroxide (100 mL, 5%) and the mixture was boiled for 7 days under reflux. The mixture was washed with water twice and the organic layer evaporated to a syrup. The excess of benzyl bromide was removed by steam distillation. The mixture was extracted repeatedly with dichloromethane, the organic layer dried, and the solvent removed. The syrup thus obtained was separated by preparative l.c. with 1:3 ethyl acetate–hexanes and pure **6** (31.5 g) obtained; yield 81.9% (because 9 g of crystalline starting-material **5** was recovered and could be reused); $[\alpha]_D^{25}$ +17.2° (*c* 1.0, chloroform); lit.[3] $[\alpha]_D^{23}$ +16.9° (*c* 1.5, chloroform).

*Methyl 3-*O*-acetyl-2,4,6-tri-*O*-benzyl-α-*D*-mannopyranoside* (**7**). — Compound **6** (3.1 g, 7.1 mmol) was acetylated by a standard method[6] and syrupy compound **7** (3.3 g) was obtained; yield 98%; $[\alpha]_D^{25}$ +8.3° (*c* 0.97, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 5.24 (1 H, m, $J_{3,4}$ 9, $J_{2,3}$ 3 Hz, H-3), and 1.9 (3 H, equatorial OAc); lit.[5] $[\alpha]_D^{24}$ +9.1° (*c* 1, chloroform).

*3-*O*-Acetyl-2,4,6-tri-*O*-benzyl-α-*D*-mannopyranosyl chloride* (**8**) — Compound **7** (2.0 g, 3.9 mmol) was dissolved in a dry, 1:1 mixture (150 mL) of dichloromethane and acetic acid. Hydrogen chloride gas was bubbled in to saturation (under nitrogen and in an ice-bath). After 4 days at room temperature, the reaction was ~90% complete (n.m.r.). The solvents were evaporated and the product purified by analytical l.c. (1:2 ethyl acetate–hexanes on a column of silica gel). Pure, syrupy **8** (1.5 g, 2.9 mmol) was obtained. Compound **8** was stable and could be stored under refrigeration for 5 months; yield 74.4%; $[\alpha]_D^{24}$ +51.2° (*c* 0.93, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 7.30–7.22 (15 H, m, aromatic H), 6.07 (1 H, d, *J* 2.4 Hz, H-1), 5.45 (1 H, m, $J_{3,4}$ 9, $J_{2,3}$ 3 Hz, H-3), 4.80–4.39 (6 H, m, 3 CH_2Ph), 4.18–3.73 [5 H, m, (2) H-6,2,4,5), and 1.92 (3 H equatorial OAc); ^{13}C-n.m.r. ($CDCl_3$), 170.24 (C=O), 138.30, 137.64 (aromatic C-1), 128.68, 128.58, 128.26, 128.04, 127.91 (aromatic C), 90.93 (C-1), 78.89 (C-2), 74.90, 74.49, 73.63, 73.33, 72.86, 72.45 (C-3,4,5, 3 OCH_2), 68.32 (C-6), and 20.89 (CH_3C=O).

Anal. Calc. for $C_{29}H_{31}ClO_6$: C, 68.17; H, 6.07. Found: C, 67.59; H, 6.19.

*1,3-Anhydro-2,4,6-tri-*O*-benzyl-β-*D*-mannopyranose* (**9**). — Compound **8** (450 mg, 0.88 mmol) was dissolved in dry oxolane (10 mL), and potassium *tert*-butoxide (197 mg, 1.8 mmol) was added. The ring-closure reaction was conducted for 2 h at room temperature, after which time most of the solvent was evaporated and the excess of *tert*-butoxide decomposed by adding ice–water. The product was extracted with dichloromethane, the solution dried, and evaporated to a syrup that was purified by analytical l.c. (1:3 ethyl acetate–hexanes on a column of silica gel). The reaction was quantitative and a syrupy product was obtained; $[\alpha]_D^{25}$ +53.3° (*c* 1.1, chloroform); lit.[3] $[\alpha]_D^{23}$ +53.0° (*c* 1.8, chloroform). Compound **9** gave spectra the same as recorded in the literature[3].

Methyl 4,6-di-O-(p-*bromobenzyl*)-α-D-*mannopyranoside* (**16**). — To a solution of **3** (20 g, 85 mmol) in toluene (60 mL) was added finely powdered potassium hydroxide (40 g). *p*-Bromobenzyl bromide (99 g, 0.4 mol) was dissolved in toluene (60 mL), and the solution was then slowly added to the solution of **3** during 2 h with boiling under reflux and with vigorous agitation by a mechanical stirrer. The reaction was processed and the product purified by the same procedure as used for converting **3** into **5**. Crystalline **16** (43.5 g) was obtained; yield (for two steps) 89%; m.p. 122.0–122.2°, $[\alpha]_D^{25}$ +70.3° (*c* 1.0, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 7.52–7.02 (8 H, m, aromatic H), 4.87–3.56 (11 H, m, H-1, 2 $CH_2C_6H_4Br$, (2) H-6, H-2, 3,4,5), 3.33 (3 H, s, OCH_3), and 2.67–2.47 (2 H, s, 2 OH); ^{13}C-n.m.r. ($CDCl_3$): δ 137.61, 137.18 (aromatic C-1), 131.76, 129.72, 129.44, 121.85 (aromatic C), 100.90 (C-1), 75.99, 73.81, 72.87, 72.06, 71.21, 70.64 (C-2, C-3, C-4, C-5, -OCH_2), 69.14 (C-6), and 55.04 (-OCH_3).

Anal. Calc. for $C_{21}H_{24}Br_2O_6$: C, 47.37; H, 4.51. Found: C, 47.40; H, 4.52.

Methyl 2,4,6-tri-O-(p-*bromobenzyl*)-α-D-*mannopyranoside* (**17**). — To a solution of compound **16** (36 g, 68 mmol), tetrabutylammonium hydrogensulfate (7.2 g), and *p*-bromobenzyl bromide (27.7 g, 0.11 mol) in dichloromethane (1.2 L) was added aqueous sodium hydroxide (110 mL, 5%), and the mixture was boiled for 4 days under reflux. The reaction was processed and the product purified by the same procedure as used for converting **5** into **6**. Crystalline **17** (39 g) was obtained; yield, 82.2%; m.p. 71–71.5°, $[\alpha]_D^{25}$ +14.2° (*c* 1.1, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 7.56–7.03 (12 H, m, aromatic H), 4.94–3.56 [13 H, m, H-1, 3 CH_2Ph, (2) H-6, H-2,3,4,5], 3.37 (3 H, s, OCH_3), and 2.08 (1 H, s, OH); ^{13}C-n.m.r. ($CDCl_3$): δ 137.72, 137.54, 136.99 (aromatic C-1), 131.82, 131.62, 129.49, 122.05, 121.63 (aromatic C), 98.09 (C-1), 78.67 (C-2), 76.64, 73.85, 72.76, 72.16, 71.81, 70.98 (C-3, C-4, C-5, OCH_2Ph), 69.34 (C-6), and 54.95 (OCH_3).

Anal. Calc. for $C_{28}H_{29}Br_3O_6$: C, 47.93; H, 4.14. Found: C, 48.00; H, 4.08.

Methyl 3-O-*acetyl-2,4,6-tri*-O-(p-*bromobenzyl*)-α-D-*mannopyranoside* (**18**). — Compound **17** (34.5 g, 48.5 mmol) was acetylated by a standard method[6]. The reaction was quantitative, and crystalline **18** (37 g) was obtained; m.p. 64–64.5°, $[\alpha]_D^{25}$ +4.6° (*c* 1.04, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 7.5–6.93 (12 H, m, aromatic H), 5.24 (1 H, m, $J_{3,4}$ 9, $J_{2,3}$ 3 Hz, H-3), 4.79–3.50 (12 H, m, H-1,2,4,5, (2) H-6, 3 CH_2Ph), 3.35 (3 H, s, OCH_3), and 1.95 (3 H, equatorial OAc); ^{13}C-n.m.r. ($CDCl_3$): δ 170.09 (C=O), 137.49, 137.26 (aromatic C-1), 131.55, 129.41, 129.27, 121.70, 121.54 (aromatic C), 98.85 (C-1), 76.46 (C-2), 73.77, 73.61, 72.71, 72.24, 71.53 (C-3, C-4, C-5, -OCH_2), 69.08 (C-6), 54.90 (O-CH_3), and 20.93 (CH_3C=O).

Anal. Calc. for $C_{30}H_{31}Br_3O_7$: C, 48.45; H, 4.17. Found: C, 48.37; H, 4.28.

3-O-*Acetyl-2,4,6-tri*-O-(p-*bromobenzyl*)-α-D-*mannopyranosyl chloride* (**19**). — Compound **18** (750 mg, 1 mmol) was converted into **19** by the procedure used for converting **7** into **8**. Pure, syrupy **19** was obtained; yield 630 mg (84%), $[\alpha]_D^{25}$ +31.3° (*c* 1.08, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 7.57–6.96 (12 H, m, aromatic H), 6.07 (1 H, d, $J_{1,2}$ 2 Hz, H-1), 5.47 (1 H, m, $J_{3,4}$ 10, $J_{2,3}$ 4 Hz, H-3), 4.78–3.56 [11 H, m, 3 CH_2Ph, (2) H-6, H-2,4,5], and 1.93 (3 H, equatorial OAc); ^{13}C-n.m.r. ($CDCl_3$):

δ 169.90 (C=O), 137.15, 136.55 (aromatic C-1), 131.72, 131.60, 129.46, 122.08, 121.67 (aromatic C), 90.61 (C-1), 79.10 (C-2), 74.33, 73.86, 72.64, 72.49, 72.19 (C-3,4,5, -OCH_2), 68.21, (C-6), and 20.81 (CH_3C=O).

Anal. Calc. for $C_{29}H_{28}Br_2ClO_6$: C, 46.56; H, 3.75. Found C, 46.79; H, 3.87.

1,3-Anhydro-2,4,6-tri-O-(p-*bromobenzyl*)-β-D-*mannopyranose* (**20**). – Compound **19** (470 mg, 0.63 mmol) was dissolved in dry oxolane (6 mL) and potassium *tert*-butoxide (141 mg, 1.25 mmol) was added. After 2 h at room temperature, compound **19** (470 mg, 0.63 mmol) was converted into target compound **20** by the procedure used for converting **8** into **9**. Crystalline **20** (360 mg) was obtained from ether–hexanes: yield 85.6%; m.p. 91–92°, $[\alpha]_D^{25}$ +31.7° (*c* 1.0, chloroform); lit.[3] $[\alpha]_D^{25}$ +31.2° (syrup) (*c* 0.52, chloroform). Compound **20** gave spectra the same as in the literature[3].

Methyl 3-O-*allyl-2,4,6-tri*-O-*benzyl*-α-D-*mannopyranoside* (**10**). – Methyl 2,4,6-tri-*O*-benzyl-α-D-mannopyranoside (**6**, 31 g, 66.8 mmol) was allylated conventionally and **10** was obtained as a syrup: yield 100%, $[\alpha]_D^{25}$ +34.1° (*c* 0.9, chloroform), lit.[3] $[\alpha]_D^{23}$ +33.3° (*c* 0.4, chloroform). Compound **10** gave spectra the same as in the literature[3].

3-O-*Allyl-2,4,6-tri*-O-*benzyl*-D-*mannopyranose* (**11**). – Compound **10** (33 g, 65 mmol) was heated on a steam bath with a mixture of 80% acetic acid (625 mL) and M hydrochloric acid (200 mL) for 5 h. The mixture was evaporated to a syrup *in vacuo*, cooled, and extracted with chloroform. After drying and evaporation of the solvent, the remaining syrup was separated by preparative l.c. with 1:2 ethyl acetate–hexanes and syrupy **11** was obtained; yield 28 g (88%); $[\alpha]_D^{25}$ +24.9° (*c* 1.0, chloroform). Compound **11** was an α,β mixture: ^{1}H-n.m.r. ($CDCl_3$): δ 7.33–7.25 (15 H, m, aromatic H), 6.20–5.66 (1 H, m, CH_2=$CH$$CH_2O$), 5.41 (1 H, m, H-1), and 5.25–3.30 [17 H, m, CH_2=$CHCH_2O$, 3 CH_2Ph, H-2,3,4,5, (2) H-6, OCH_2CH=CH_2, OH]; ^{13}C-n.m.r. ($CDCl_3$): δ 138.83, 138.60, 138.25 (aromatic C-1), 135.26 (H_2C=$CHCH_2O$), 128.49, 128.18, 127.95, 127.75 (aromatic C), 117.03, 116.71 (H_2C=$CHCH_2O$), 94.21 (C-1β), 92.81 (C-1α), 79.67 (C-3), 75.38, 75.08, 74.66, 73.58, 73.34, 72.75, 71.44, 71.11 (C-2, C-4, C-5, OCH_2, H_2C=$CHCH_2O$), 69.92, and 69.42 (C-6).

2,4,6-Tri-O-*benzyl*-D-*mannopyranose* (**13**). – Compound **11** (38 g, 78 mmol) was dissolved in 90% ethanol (800 mL) and the solution boiled under reflux. To this solution was added tris(triphenylphosphine)chlororhodium (1.6 g, 1.7 mmol) and refluxing was continued for 6 h. As indicated by t.l.c. (1:1 ethyl acetate–hexanes), all of the starting material had been converted into 2,4,6-tri-*O*-benzyl-3-*O*-(1-propenyl)-D-mannopyranose (**12**), of which about one-half had been converted into target product **13**. To complete the reaction, M hydrochloric acid (80 mL) was added to the mixture and the mixture refluxed for one more h. Most of the solvents were evaporated off, the product was taken up in dichloromethane, the solution washed with brine, dried, and evaporated. After purification by preparative l.c., the syrup crystallized from ether–hexanes and white, crystalline **13** (24 g) was obtained: yield 68.3%;

m.p. 74–75°, $[\alpha]_D^{25}$ +3.2° (*c* 1.0, chloroform); lit.[10] m.p. 72–73°, $[\alpha]_D^{24}$ +2.6° (*c* 1, chloroform).

3-O-Acetyl-2,4,6-tri-O-benzyl-α-D-mannopyranosyl chloride (**8**) *from 1,3-di-O-acetyl-2,4,6-tri-O-benzyl-D-mannopyranose* (**14**). — Compound **13** (6.6 g, 14.8 mmol) was acetylated quantitatively and syrupy **14** (7.9 g) was obtained as an α,β mixture[10]. Compound **14** was converted into **8** by treatment with hydrogen chloride-saturated ether at room temperature for 2 h under conditions devised by Micheel and Kreutzer[11] for displacing hydroxyl groups by chloride. The reaction was quantitative, and the product obtained by this method had the same physical constants as those obtained for material prepared by another route as reported already in this paper.

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