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Synthesis of Disaccharides Containing β-D-Mannopyranosyl Groups

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An efficient synthesis of β-D-mannopyranosides is described. D-Mannose is converted by acetalization under kinetic control into crystalline 2,3:4,6-di-*O*-cyclohexylidene-α-D-mannopyranose. Reaction of the acetal with methanesulfonyl chloride in the presence of triethylamine affords crystalline 2,3:4,6-di-*O*-cyclohexylidene-α-D-mannopyranosyl chloride which is used in Koenigs-Knorr syntheses using silver carbonate as promotor and dichloromethane as solvent. Yields in disaccharide syntheses, including the β-D-mannosylation of unreactive secondary hydroxyl groups are in the range of 22–84 %. The influences of solvent and of promotor upon the reaction product are examined.

Although significant progress has been made in the synthesis of 1,2-*cis*-glycopyranosides with the D-*gluco*- or D-*galacto*-configuration using a non-participating group in the 2-position,[1-4] the corresponding syntheses of 1,2-*cis*-mannosides (β-D-mannopyranosides) have until now required multistep procedures of significantly lower overall yields. Thus 4,6-di-*O*-acetyl-2,3-*O*-carbonyl-α-D-mannopyranosyl bromide,[5,6] 2,3,4-tri-*O*-benzyl-6-*O*-acetyl-α-D-mannopyranosyl bromide[7] and 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl bromide[8] have been used in Koenigs-Knorr syntheses of β-D-mannopyranosides. The latter method, in which silver salicylate is used as a promotor, appears to be limited to aglycones with good steric accessibility.[8] Another approach to this problem is to start from a 3,4,6-tri-*O*-benzyl-D-glucopyranose-1,2-orthoester, make a β-D-glucopyranoside and then, after deacylation in the 2-position, invert the configuration at this position by means of oxidation and reduction to obtain β-D-mannopyranosides.[9,10]

We have previously given a preliminary account of a convenient route to β-D-mannopyranosides,[11] taking advantage of the fact that acetalization of D-mannose under kinetic control gives rise to 2,3:4,6-acetals rather than the thermodynamically preferred 2,3:5,6-acetals.[12] 2,3:4,6-Di-*O*-cyclohexylidene-α-D-mannopyranosyl chloride, obtained from the corresponding 2,3:4,6-acetal was used in Koenigs-Knorr reactions.[11] The scope of this β-D-mannopyranoside synthesis has now been explored; the influence of solvent and promotor upon the product distribution has been examined and we now present a more detailed account of this work.

In order to obtain optimum conditions, promotor and solvent were varied in the mannosylation of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose with 2,3:4,6-di-*O*-cyclohexylidene-α-D-mannopyranosyl chloride. The results are shown in Table 1. Silver carbonate as promotor and dichloromethane as solvent gave the highest yield of β-1,6-linked disaccharide (74 %) and they were then used throughout this work. The disaccharides thus made and the yields of the α- and β-D-anomers obtained are shown in Scheme 1. High yields of β-D-mannopyranosyl disaccharides are obtained for the sterically readily accessible hydroxyl groups in the first three examples. The yield for 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose is moderate and that for the singularly unreactive *p*-nitrophenyl 3,4,6-tri-*O*-acetyl-β-D-galactopyranoside is, as expected, low. Previous α-D-glucosylation of the latter, using 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide in a halide-assisted reaction, gave a yield of α-1,2-linked disaccharide of only 27 %,[13] which is similar to the yield of β-D-mannopyranoside *9*.

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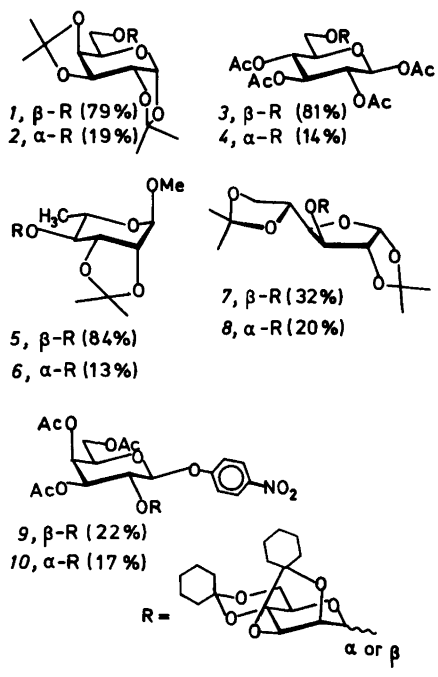
Table 1. Mannosylation of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose with 2,3:4,6-di-*O*-cyclohexylidene-α-D-mannopyranosyl chloride. Effect of varying promotor and solvent.

Catalyst	Solvent	Total yield of α-1,6- and β-1,6-linked disaccharides (%)	Yield of β-1,6-linked disaccharide (%)
Ag_2CO_3	CH_2Cl_2	89	74
Ag_2O	CH_2Cl_2	75	62
$Hg(CN)_2$	CH_2Cl_2	41	26
$AgCF_3SO_3$ + $[(CH_3)_2N]_2CO$	CH_2Cl_2	78	22
Silver disym. collidine perchlorate	CH_2Cl_2	94	20
Ag_2CO_3	$(CH_3CH_2)_2O$	70	46
Ag_2CO_3	toluene	34	19
Ag_2CO_3	CH_3NO_2	48	26

Although the yields are low and the stereoselectivity is lost for particularly unreactive aglycons, the short route still makes the method a convenient alternative to those previously described.[3-10]



Scheme 1.

EXPERIMENTAL

General methods were the same as those described before.[14,15] NMR spectra, recorded on a JEOL JNM FX 100 instrument for all new substances, were invariably in agreement with postulated structures; only especially significant NMR data are presented. Chemical shifts (δ) for solutions in $CDCl_3$ are given in ppm downfield from internal tetramethylsilane, those in D_2O in ppm downfield from external tetramethylsilane for ^{13}C NMR, and in ppm downfield from internal 1,1,2,2,3,3-hexadeuterio-4,4-dimethyl-4-silapentane-1-sulfonate for ^1H NMR.

2,3:4,6-Di-O-cyclohexylidene-α-D-mannopyranosyl chloride. Methanesulfonyl chloride (4.8 g) in dry dichloromethane (10 ml) was added dropwise to a stirred solution of 2,3:4,6-di-*O*-cyclohexylidene-α-D-mannopyranose (3.4 g) in dry dichloromethane (100 ml) and triethylamine (10 ml). After stirring for 2 h at 40 °C, the solution was cooled to room temperature, washed with water, dried (silica gel) and concentrated. The product was filtered through a short silica gel column (toluene–dichloromethane 1:1) and concentrated to yield the title compound (3.0 g, 83 %), $[\alpha]_D$ +47° (*c* 4.5, $CHCl_3$). Crystallization from propan-2-ol gave material m.p. 87–88 °C, $[\alpha]_D$ +47° (*c* 3.0, $CHCl_3$).

6-O-(2,3:4,6-Di-O-cyclohexylidene-β-D-mannopyranosyl) 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (1). A mixture of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose[16] (145 mg, 0.56 mmol), 2,3:4,6-di-*O*-cyclohexylidene-α-D-mannopyranosyl chloride[11] (780 mg, 2.2 mmol) and silver carbonate (875 mg, 3.2 mmol) in dry dichloromethane (25 ml) containing 4 Å molecular sieve was stirred in the

dark at room temperature for 3 days and then filtered. The residue was washed with dichloromethane and the combined filtrates were concentrated. Silica gel column chromatography (toluene – ethyl acetate 4:1) gave the title compound *1* (256 mg, 79 %) $[\alpha]_D$ −80° (*c* 1.2 $CHCl_3$) (Lit.[11] $[\alpha]_D$ −82° ($CHCl_3$)) as well as the corresponding α-1,6-linked disaccharide *2* (61 mg, 19 %) $[\alpha]_D$ −30° (*c* 3.0, $CHCl_3$). ^{1}H NMR for *1* ($CDCl_3$): δ 5.51 (1H, $J_{1,2}$ 4.9 Hz, H-1 galactose residue), 4.90 (1H, $J_{1,2}$ 2.4 Hz, H-1, mannosyl group). ^{1}H NMR for *2* ($CDCl_3$): δ 5.49 (1H, $J_{1,2}$ 5.1 Hz, H-1 galactose residue), 5.04 (1H, $J_{1,2}$ 0 Hz, H-1 mannosyl group).

1,2,3,4-Tetra-O-acetyl-6-O-(2,3:4,6-di-O-cyclohexylidene-β-D-mannopyranosyl)-β-D-glucopyranose (3). A mixture of 1,2:3,4-tetra-*O*-acetyl-β-D-glucopyranose[17] (200 mg 0.6 mmol), 2,3:4,6-di-*O*-cyclohexylidene-α-D-mannopyranosyl chloride[11] (861 mg, 2.4 mmol) and silver carbonate (458 mg, 1.7 mmol) in dry dichloromethane containing 4 Å molecular sieve was stirred in the dark at room temperature for 3 days and then worked up as described above. Silica gel column chromatography (toluene – ethyl acetate 3:1) gave the title compound *3* (312 mg, 81 %) $[\alpha]_D$ −32° (*c* 6.0, $CHCl_3$) as well as the corresponding α-1,6-linked disaccharide *4* (54 mg, 14 %) $[\alpha]_D$ +155°. ^{1}H NMR for *3* ($CDCl_3$) δ 5.69 (1H, $J_{1,2}$ 8.1 Hz, H-1 glucose residue), 4.81 (1H, $J_{1,2}$ 2.4 Hz, H-1 mannosyl group), ^{1}H NMR for *4* ($CDCl_3$): δ 5.66 (1H, $J_{1,2}$ 7.7 Hz, H-1 glucose residue).

6-O-β-D-Mannopyranosyl-D-glucose. 1,2,3,4-Tetra-*O*-acetyl-6-*O*-(2,3:4,6-di-*O*-cyclohexylidene-β-D-mannopyranosyl)-β-D-glucopyranose (*3*) (160 mg, 0.24 mmol) was dissolved in trifluoroacetic acid (0.85 ml). The solution was cooled to 0 °C, water (0.15 ml) was added and the solution was allowed to stand until the hydrolysis was complete (~15 min, TLC). After concentration and three co-distillations with acetone, the product was deacetylated with a catalytic amount of sodium methoxide in methanol, neutralized with Dowex 50 (H^+ form) to give the title compound (55 mg, 67 %) m.p. 188 – 190 °C (ethanol), $[\alpha]_D$ −5° (*c* 2.0, H_2O) (Lit.[5] m.p. 209 – 210 °C $[\alpha]_D$ 0→ −5° (*c* 1)). ^{13}C NMR (D_2O): δ 101.7 (C-1, mannosyl group), 97.1 and 93.2 (β-D- and α-D-C-1, respectively, glucose residue).

Methyl 4-O-(2,3:4,6-di-O-cyclohexylidene-β-D-mannopyranosyl)-2,3-O-isopropylidene-α-L-rhamnopyranoside (5). A mixture of methyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside[18] (119 mg, 0.55 mmol), 2,3:4,6-di-*O*-cyclohexylidene-α-D-mannopyranosyl chloride[11] (755 mg, 2.10 mmol) and silver carbonate (700 mg, 2.5 mmol) in dry dichloromethane (25 ml) containing 4 Å molecular sieve was stirred in the dark at room temperature for 3 days and then worked up as described above. Silica gel column chromatography (toluene – ethyl acetate 7:1) gave the title compound *5* (247 mg, 84 %) m.p. 163 – 164 °C (propan-2-ol), $[\alpha]_D$ −73° (*c* 6.2, $CHCl_3$) as well as the corresponding α-1,4-linked disaccharide *6* (38 mg, 13 %), m.p. 136 – 139 °C (propan-2-ol), $[\alpha]_D$ −3° (*c*, 3.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$) for *5*: δ 5.28 (1H, $J_{1,2}$ 2.4 Hz, H-1 mannosyl group), 4.83 (1H, $J_{1,2}$ 0 Hz rhamnosyl residue). ^{1}H NMR ($CDCl_3$) for *6*: δ 5.08 (1H, $J_{1,2}$ 0 Hz, H-1 mannosyl group), 4.82 (1H, $J_{1,2}$ 0 Hz rhamnosyl residue).

Methyl 4-O-β-D-mannopyranosyl-α-L-rhamnopyranoside. Methyl 4-*O*-(2,3:4,6-di-*O*-cyclohexylidene-β-D-mannopyranosyl)-2,3-*O*-isopropylidene-α-L-rhamnopyranoside (5) (83 mg) in trifluoroacetic acid (0.85 ml) and water (0.15 ml) was hydrolyzed as described above to give the title compound (45 mg, 86 %). The compound crystallized after two concentrations from propan-2-ol. After recrystallization from propan-2-ol the material had m.p. 107 – 109 °C, $[\alpha]_D$ −65° (*c* 1.2 H_2O). Lit.[6] m.p. 108.5 – 110 °C, $[\alpha]_D$ −72° (H_2O)). ^{13}C NMR (D_2O): δ 101.9 and 101.7 (C-1, mannosyl group and rhamnosyl residue).

3-O-(2,3:4,6-Di-O-cyclohexylidene-β-D-mannopyranosyl)-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (7). A mixture of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose[16] (102 mg, 0.39 mmol), 2,3:4,6-di-*O*-cyclohexylidene-α-D-mannopyranosyl chloride[11] (540 mg, 1.50 mmol) and silver carbonate (294 mg, 1.07 mmol) in dry dichloromethane (10 ml) containing 4 Å molecular sieve was stirred in the dark at room temperature for 5 days and then worked up as described above. Silica gel column chromatography (toluene – ethyl acetate 4:1) gave the title compound *7* (73 mg, 32 %), $[\alpha]_D$ −68° (*c* 3.6 $CHCl_3$) as well as the corresponding α-1,3-linked disaccharide *8* (46 mg, 20 %), $[\alpha]_D$ +3° (*c* 2, $CHCl_3$). ^{1}H NMR for *7* ($CDCl_3$): δ 5.77 (1H, $J_{1,2}$ 3.7 Hz, H-1 glucosyl residue), 4.93 (1H, $J_{1,2}$ ~0 Hz, H-1, mannosyl group). ^{1}H NMR for *8* ($CDCl_3$): δ 5.86 (1H, $J_{1,2}$ 3.4 Hz, H-1 glucosyl residue), 5.31 (1H, $J_{1,2}$ 0 Hz, H-1, mannosyl group).

3-O-β-D-Mannopyranosyl-D-glucose. 1,2:5,6-Di-*O*-isopropylidene-3-*O*-(2,3:4,6-di-*O*-cyclohexylidene-β-D-mannopyranosyl)-α-D-glucofuranose (120 mg, 0.21 mmol) was hydrolyzed in trifluoroacetic acid (0.85 ml) and water (0.15 ml) as described above. After concentration and three co-distillations with acetone, the title compound (64 mg, 89 %), $[\alpha]_D$ +6° (*c* 4.8, H_2O) was obtained in a pure state following chromatography on Biogel P2. ^{13}C NMR (D_2O): δ 101.7 (C-1, mannosyl group), 96.8 and 93.2 (β-D- and α-D-C-1, respectively, glucose residue). An aliquot of the disaccharide was reduced with sodium borodeuteride. The product was permethylated, hydrolyzed, reduced with sodium borohydride, acetylated and analyzed by GLC-MS.[19] The

products were 3-*O*-acetyl-1-deuterio-1,2,4,5,6-penta-*O*-methylglucitol and 1,5-di-*O*-acetyl-2,3,4,6-tetra-*O*-methylmannitol.

p-*Nitrophenyl 3,4,6-tri*-O-*acetyl-2*-O-*(2,3:4,6-di*-O-*cyclohexylidene-β*-D-*mannopyranosyl)-β*-D-*galactopyranoside (9).* A mixture of *p*-nitrophenyl 3,4,6-tri-*O*-acetyl-β-D-galactopyranoside [13] (223 mg, 0.52 mmol), 2,3:4,6-di-*O*-cyclohexylidene-α-D-mannopyranosyl chloride [11] (774 mg, 2.2 mmol) and silver carbonate (1.06 g, 3.8 mmol) in dry dichloromethane (25 ml) containing 4 Å molecular sieve was stirred in the dark at room temperature for 5 days and then worked up as described above. Silica gel column chromatography (toluene – ethyl acetate 2:1) gave the title compound *9* (86 mg, 22 %), $[\alpha]_D$ −46° (*c* 2.0, $CHCl_3$) as well as the corresponding α-1,2-linked compound *10* (67 mg, 17 %), $[\alpha]_D$ −3° (*c* 4.0, $CHCl_3$).

p-*Nitrophenyl 2*-O-*β*-D-*mannopyranosyl-β*-D-*galactopyranoside. p*-Nitrophenyl 3,4,6-tri-*O*-acetyl-2-*O*-(2,3:4,6-di-*O*-cyclohexylidene-β-D-mannopyranosyl)-β-D-galactopyranoside (*9*) (41 mg, 0.055 mmol) was hydrolyzed and deacetylated as described above. Purification by chromatography on Biogel P2 gave the title compound (21 mg, 83 %), $[\alpha]_D$ −39° (*c* 3·5, H_2O) ^1H NMR (D_2O): δ 5.39 (1H, $J_{1,2}$ 7.2 Hz galactosyl residue), 5.01 (1H, $J_{1,2} \sim 0$ Hz, H-1 mannosyl group. ^{13}C NMR (D_2O): δ 101.7 (C-1, mannosyl group), 99.7 (C-1, galactosyl residue). An aliquot of the disaccharide was permethylated, hydrolyzed, reduced with sodium borohydride, acetylated and analyzed by GLC-MS.[19] The products were 1,2,5-tri-*O*-acetyl-3,4,6-tri-*O*-methylgalactitol and 1,5-di-*O*-acetyl-2,3,4,6-tetra-*O*-methylmannitol.

Solvent and catalyst dependence. A mixture of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (0.26 g 1.0 mmol), 2,3:4,6-di-*O*-cyclohexylidene-α-D-mannopyranosyl chloride and promotor (1.5 mmol) in dry solvent (5 ml) containing 4 Å molecular sieve was stirred in the dark at room temperature for 3 – 5 days and processed as described above to yield 6-*O*-(2,3:4,6-di-*O*-cyclohexylidene-α-D- and β-D-mannopyranosyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose. The yields and product compositions are shown in Table 1.

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