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Inversion at C-2 of 3,4,6-Tri-*O*-benzyl-α-D-mannopyranosides by Oxidation and Reduction

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Inversion of the configuration at C-2 of four disaccharides containing 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl units linked (1→2), (1→3), (1→4) and (1→6) to protected glucosyl and galactosyl units, as examples of a method for the synthesis of α-D-glucopyranosides is described. After deacetylation and oxidation in the 2-position with chromium(III) oxide–pyridine–acetic anhydride, the hexosiduloses are reduced to the corresponding α-D-glucopyranosides. Various reduction agents are evaluated for this purpose. Stereoselectivity up to 90 % is obtained using diborane.

Several solutions to the classical problem in carbohydrate chemistry of the synthesis of 1,2-*cis*-glycopyranosides with the *galacto*- and *gluco*-configuration have been proposed.[1–5] One route to β-D-mannopyranosides [6,7] and α-D-glucopyranosides [7] developed in this laboratory involves initially the synthesis of β-D-glucopyranosides and α-D-mannopyranosides with an acetyl group in the 2-position and benzyl groups in the 3,4,6-positions. Inversion at C-2 by means of deacetylation, followed by oxidation and stereoselective reduction affords β-D-mannopyranosides and α-D-glucopyranosides, respectively. Good yields of 2-*O*-acetyl-3,4,6-tri-*O*-benzyl α-D-mannopyranosides are obtainable by condensing 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl chloride [8] with suitable alcohols in the presence of mercury(II) cyanide or silver triflate.[8] This paper describes attempts to obtain high yields in the oxidation and reduction of four such mannosides at C-2 to give the corresponding α-D-glucopyranosides.

Four disaccharide derivatives (Scheme 1, *1*, *5*, *9* and *13*) were deacetylated with methanolic ammonia and then oxidized at C-2 with chromium(III) oxide–pyridine–acetic anhydride in dichloromethane.[9] The yields of the products, containing 3,4,6-tri-*O*-benzyl-α-D-*arabino*-2-hexulopyranosyl units (*3*, *7*, *11* and *15*) were 75–90 %. The efficiency of the various reducing agents, for carrying out the next step was assessed by using *3*, and the results are summarized in Table 1. Of the nucleophilic reagents used, sodium borohydride gave the highest yield of glycosides, the ratio of *gluco*/*manno* obtained was, however, only 60:40. Two electrophilic reducing agents were used; diborane in tetrahydrofuran clearly is the reagent of choice. The transformation of the disaccharides *5*, *9* and *13* into the disaccharide derivatives *8*, *12* and *16* in the same deacetylation-oxidation-reduction sequence using diborane effected conversions of the mannosides to the corresponding glucosides in overall yields of 73, 59, 56 and 38 % for the (1→6), (1→4), (1→3) and (1→2)-linked disaccharides *13*, *14*, *15* and *16* respectively. A significant amount of the *manno*-isomer was obtained in the reduction of the (1→2)-linked hexosidulose *15*.

The starting material for these α-D-glucopyranoside syntheses is 3,4,6-tri-*O*-benzyl-1,2-*O*-(methoxyethylidene)-β-D-mannopyranose,[8,10] from which the chloro sugar is made and used without purification. The orthoester is easily made on a large scale and can be stored. Although the glycosylation and subsequent C-2 inversion proceed in lower yields than those reported for other α-D-glucopyranoside syntheses,[1–5] the method described here may have some merit in terms of total economy, partic-

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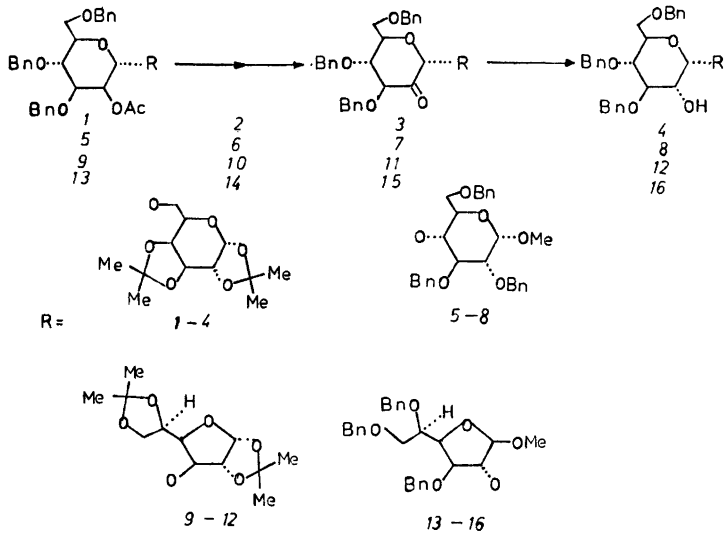

Scheme 1.

ularly if further synthetic transformation in the 2-position is desired.

EXPERIMENTAL

General methods were the same as those described before.[8] The following solvent systems were used in TLC and column chromatography: A (toluene – ethyl acetate, 3:1 v/v), B (toluene – ethyl acetate, 2:1 v/v), C (toluene – ethyl acetate, 4:1 v/v). Optical rotations were recorded in chloroform at room temperature (20 – 23 °C) at *c* 0.5 – 1.0 using a Perkin-Elmer 241 instrument. NMR spectra were recorded on a JEOL JMN-FX 100 instrument, in deuteriochloroform, using tetramethylsilane as internal standard. IR spectra were recorded on a Perkin-Elmer 257 instrument. For GLC a Perkin-Elmer 990 instrument was used and separations were performed on an OV-225 column (3 % on Gas Chrom Q) at 200 °C.

Materials. Compounds *1*, *5* and *9* were available from previous work,[8] and *13* was obtained as previously devised by the condensation of 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-mannosyl-chloride [8,11] with methyl 3,5,6-tri-*O*-benzyl-β-D-glucofuranoside.[14]

6-O-(3,4,6-Tri-O-benzyl-α-D-arabino-2-hexosulopyranosyl)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (3). 6-*O*-(2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (*1*) [8] (1.45 g) in methanol (50 ml) was deacetylated by the

Table 1. Reduction of compound *3*.

Method	Reducing agent	Tot. yield %	Ratio *gluco/manno* [a] %
A	B_2H_6 in tetrahydrofuran	90	90:10
B	$NaBH_4$ in aqueous ethanol	87	60:40
C	$LiBH_4$ in aqueous ethanol	89	50:50
D	Li triethylborohydride in tetrahydrofuran	92	40:60
E	Li tri-*sec.*-butylborohydride in tetrahydrofuran	90	55:45
F	9-Borabicyclo[3.3.1]nonane in tetrahydrofuran	85	45:55

[a] The protected disaccharides were hydrogenated and hydrolyzed;[7] the deprotected disaccharides were subjected to carbohydrate analysis.[15,16]

addition of ammonia-saturated methanol (50 ml) for 20 h at room temperature. After concentration, the resulting syrup *2* (1.29 g, 95 %), $[\alpha]_D$ +9°, R_F 0.3 (solvent system A), in dichloromethane (5 ml) was oxidized by a solution of chromium trioxide (0.6 g), pyridine (0.95 g) and acetic anhydride (6.2 g) in dichloromethane (15 ml).[9] After stirring for 1 h the solution was passed through a short column of silica gel with ethyl acetate as eluent and concentrated to yield syrupy *3* (1.22 g, 95 %), $[\alpha]_D$ +1°, ν_{max}^{KBr} 1740–1755 cm^{-1}, R_F 0.72 (solvent system A).

6-O-(3,4,6-Tri-O-benzyl-α-D-glucopyranosyl)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (4). Method A. *3* (640 mg) in tetrahydrofuran (50 ml), under nitrogen, was reduced by a 1 M solution of diborane in tetrahydrofuran (5 ml). The solution was stirred at room temperature for 3 h. Ethanol–water, 1:1, (v/v, 10 ml) was added and the solution was concentrated. The product was concentrated three times from methanol and the remaining oil was purified by chromatography on a silica gel column (solvent system B) to yield a syrup, *4* (518 mg, 81 %), $[\alpha]_D$ +30° (lit.[7] $[\alpha]_D$ +31°) R_F 0.49 (solvent system B).

Method B. *3* (320 mg) was dissolved in ethanol (10 ml) and water (2 ml). The solution was stirred and cooled to 5 °C. Sodium borohydride (100 mg) was added in small portions. The solution was stirred at room temperature for 3 h. The solution was diluted with acetone (10 ml) and evaporated. After repeated concentrations from methanol the resulting syrup was dissolved in ethyl acetate and the solution washed with 0.1 M tartaric acid solution. TLC showed the presence of two spots, R_F 0.49 (*gluco*) and R_F 0.42 (*manno*), (solvent system B), ratios are shown in Table 1. After concentrating the solution, the resulting syrup was purified by chromatography on a silica gel column (solvent system B) to yield *4* (167 mg, 52 %).

Method C. The reduction of *3* (320 mg) with lithium borohydride (90 mg) under the same conditions as those described under method B, yielded *4* (142 mg, 44 %).

Method D. *3* (320 mg) in tetrahydrofuran (10 ml) was added, under nitrogen, to a stirred 1 M solution of lithium triethylborohydride in tetrahydrofuran (4 ml) at −75 °C. The solution was kept for 3 h at −75 °C. Excess reagent was decomposed by the addition of methanol and the alkylboranes were oxidized with 35 % aqueous hydrogen peroxide (0.1 ml).[12,13] The salts were removed by filtration and the solution was concentrated. The syrup was purified by chromatography on a silica gel column (solvent system B) to yield *4* (118 mg, 37 %).

Method E. The reduction of *3* (320 mg) by a 1 M solution of lithium tri-*sec*-butylborohydride in tetrahydrofuran (4 ml) under the same conditions as those described under method D, yielded *4* (158 mg, 49 %).

Method F. *3* (320 mg) was dissolved in tetrahydrofuran (20 ml), the stirred solution was cooled to 5 °C and 9-borabicyclo[3.3.1]nonane (90 mg) was added in small portions. The solution was stirred for 3 h at room temperature and diluted with methanol (10 ml). After repeated concentrations from methanol the resulting syrup was purified by chromatography on a silica gel column (solvent system B) to yield *4* (122 mg, 38 %). All physical data were in agreement with those of an authentic sample of *4*.[7]

Methyl 4-O-(3,4,6-tri-O-benzyl-α-D-arabino-2-hexosulopyranosyl)-2,3,6-tri-O-benzyl-α-D-glucopyranoside (7). The deacetylation of methyl 4-*O*-(2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (*5*)[8] (470 mg) in methanolic ammonia under the same conditions as those described for *1*, yielded *6* (390 mg, 87 %), $[\alpha]_D$ +33°, R_F 0.59 (solvent system B). The oxidation of *6* under the same conditions as those described for *3*, gave a syrup, *7* (351 mg, 90 %), $[\alpha]_D$ +71°, R_F 0.70 (solvent system B).

Methyl 4-O-(3,4,6-tri-O-benzyl-α-D-glucopyranosyl)-2,3,6-tri-O-benzyl-α-D-glucopyranoside (8). The reduction of *7* under the same conditions as those described for *3*, method A, gave crystalline *8* (266 mg, 76 %), m.p. 70–72 °C $[\alpha]_D$ +92°, R_F 0.62 (solvent system B). Anal. $C_{55}H_{60}O_{11}$: C, H.

3-O-(3,4,6-Tri-O-benzyl-α-D-arabino-2-hexosulopyranosyl)-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (11). The deacetylation of 3-*O*-(2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (*9*) (680 mg) in methanol (40 ml) by ammonia-saturated methanol (40 ml) under the same conditions as those described for *1*, gave a syrup *10* (562 mg, 88 %), $[\alpha]_D$ +35°, R_F 0.51 (solvent system B). The oxidation of the above compound, under the same conditions as those described for *2*, yielded a syrup *11* (478 mg, 85 %), $[\alpha]_D$ +25°, R_F 0.68 (solvent system B).

3-O-(3,4,6-Tri-O-benzyl-α-D-glucopyranosyl)-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (12). The reduction of *11* under the same conditions as those described for *3*, method A, yielded crystalline *12* (358 mg, 75 %), m.p. 118–120 °C $[\alpha]_D$ +44°, R_F 0.42 (solvent system A). Anal. $C_{39}H_{48}O_{11}$:C, H.

Methyl 3,5,6-tri-O-benzyl-α- and -β-D-glucofuranoside. 1,2-*O*-Isopropylidene-α-D-glucofuranose was benzylated[8] in an 87 % yield. The crude compound was glycosidated by 0.5 % hydrogen chloride in methanol by boiling for 4 h. The crude yield was 90 %. Ratio: α-anomer 60 %, $[\alpha]_D$ +20° (lit.[14] $[\alpha]_D$ +26°), m.p. 55 °C, R_F 0.46 (solvent system A): β anomer 40 % $[\alpha]_D$ −50° (lit. $[\alpha]_D$ −55°),[12] R_F 0.3 (solvent system A).

Methyl 2-O-(2-O-acetyl-3,4,6-tri-O-benzyl-α-D-mannopyranosyl)-3,5,6-tri-O-benzyl-β-D-glucopyranoside (13). 2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-α-D-mannosyl chloride was glycosidated with

methyl 3,5,6-tri-*O*-benzyl-β-D-glucofuranoside [14] to afford *13* in a 61 % yield, $[\alpha]_D$ +10°, R_F 0.51 (solvent system C), ^{1}H NMR: δ 2.18 (s, 3H, $OCOCH_3$), 3.40 (s, 3H, OCH_3), 7.10–7.40 (m, 15 H, aromatic H). ^{13}C NMR: δ 21.0 ppm (CH_3CO), 55.8 (CH_3O), 97.2 (C-1, *manno*), 108.0 (C-1, *gluco*), 170.2 (C=O).

Methyl 2-O-(3,4,6-O-tri-O-benzyl-α-D-arabino-2-hexosulopyranosyl)-3,5,6-tri-O-benzyl-β-D-glucofuranoside (15). The deacetylation of *13* under the same conditions as those described for *1*, gave a syrup, *14* in 89 % yield. $[\alpha]_D$ +19°, R_F 0.33 (solvent system B), ^{13}C NMR: δ 55.8 ppm (CH_3O), 98.5 (C-1, *manno*), 108.1 (C-1 *gluco*). The oxidation of the above compound, under the same conditions as those described for *2*, yielded syrup *15* in 88 % yield, $[\alpha]_D$ +17°, R_F 0.69 (solvent system B).

Methyl 2-O-(3,4,6-tri-O-benzyl-α-D-glucopyranosyl)-3,5,6-tri-O-benzyl-β-D-glucofuranoside (16). The reduction of *15* under the same conditions as those described for *3*, method A, gave a syrup *16*, in 49 % yield. $[\alpha]_D$ +38°, R_F 0.33 (solvent system A), ^{13}C NMR: δ 55.8 ppm (CH_3O), 98.4 (C-1, glucopyranosyl), 108.2 (C-1, glucofuranosyl).

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