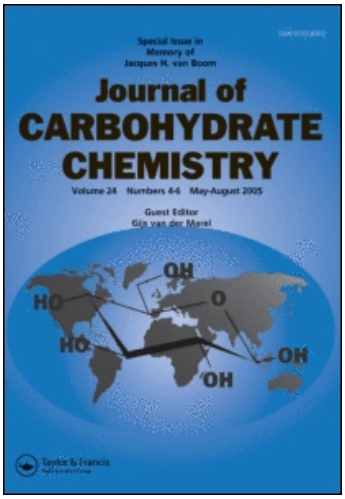

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CYANOSUGARS. IV. SYNTHESIS OF α-D-GLUCOPYRANOSYL AND α-D-GALACTOPYRANOSYL CYANIDES AND RELATED 1,2-CIS C-GLYCOSIDES

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ABSTRACT

Reaction of 1-O-acetyl-2,3,4,6-tetra-O-benzyl-D-glucopyranose (1) and the corresponding galactopyranose (2) with trimethylsilylcyanide in the presence of BF_3 afforded a mixture of the β- and α-D-glucopyranosyl cyanides, 3 and 5, and the β- and α-D-galactopyranosyl cyanides, 4 and 6, respectively, in good yields. Reduction of the cyano groups of 3 and 5 with 1 mol of $LiAlH_4$ gave the 1-amino-1-deoxy-D-glycero-D-gulo- and D-glycero-D-ido heptitols, 8 and 10, respectively. Reduction of 5 with 0.5 mol of $LiAlH_4$ afforded, after work up, the corresponding D-glycero-D-ido-heptopyranose (11).

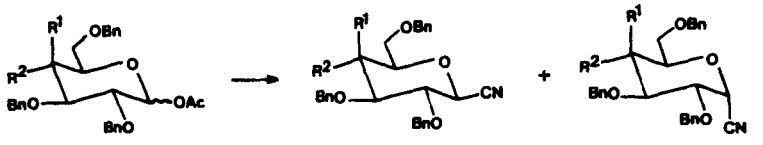
INTRODUCTION

For a project underway on the synthesis of analogues of uridine 5'-diphosphate glucose, we needed to prepare fully protected α-D-glucopyranosyl and α-D-galactopyranosyl cyanides and the 1-amino-2,6-anhydro-1-deoxyheptitols obtained by reduction of their cyano groups. Glycosyl cyanides are prepared by reaction of a peracylated glycosyl halide with silver of mercury (II) cyanide,[2,3] which only affords 1,2-trans-glycosyl cyanides, and by reaction of a 1-O-acyl sugar with trimethylsilyl cyanide in the presence of a Lewis acid.[4,5] Both methods have been used for the synthesis in high yields of a variety of fully acylated 1,2-trans-furanosyl and pyranosyl cyanides, except the corresponding per-O-acyl-β-D-glucopyranosyl cyanides.[2,4,6-8] Recently, the reaction of benzyl protected glycosyl fluorides with Me_3SiCN to give the corresponding glycosyl cyanides and isocyanides has been reported.[9] Here we describe the reaction of easily accesible 1-O-acetyl-2,3,4,6-tetra-O-benzyl-D-

gluco and D-galactopyranose with Me_3SiCN to afford the corresponding 1,2-cis and 1,2-trans glycosyl cyanides.

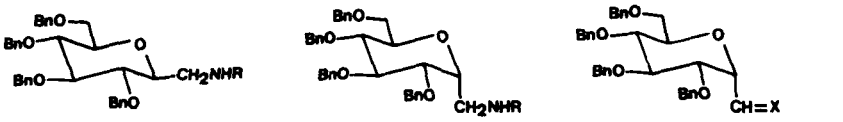
RESULTS AND DISCUSSION

Reaction of 1-O-acetyl-2,3,4,6-tetra-O-benzyl-D-glucopyranose (1) with trimethylsilyl cyanide and boron trifluoride etherate in acetonitrile afforded a mixture of the β- and α-D-glucopyranosyl cyanides 3 and 5 in 40% and 50% yields, respectively. Similarly, 1-O-acetyl-2,3,4,6-tetra-O-benzyl-D-galactopyranose (2) afforded a mixture of the β- and α-D-galactopyranosyl cyanides 4 and 6 each in 40% yield. Both anomeric mixtures were separated by chromatography. The anomeric configurations of glycosyl cyanides 3-6 were assigned based on the corresponding $J_{1,2}$ coupling constants of 10.2 and 9.85 Hz for the gluco (3) and galacto (4) β-anomers and 6.1 and 6.0 Hz for the gluco (5) and galacto (6) α-anomers, respectively.

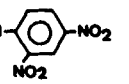


1, $R^1 = H$; $R^2 = OBn$ 3, $R^1 = H$; $R^2 = OBn$ 5, $R^1 = H$; $R^2 = OBn$

2, $R^1 = OBn$; $R^2 = H$ 4, $R^1 = OBn$; $R^2 = H$ 6, $R^1 = OBn$; $R^2 = H$



7, R = H 9, R = H 11, X = O

8, R = $COCH_3$ 10, R = $COCH_3$ 12, X = N–HN– 

Reduction of glucopyranosyl cyanides 3 and 5 with 1 mol of $LiAlH_4$ per mol of cyanide in tetrahydrofuran at reflux afforded the corresponding aminomethyl derivatives, 1-amino-2,6-anhydro-3,4,5,7-tetra-O-benzyl-1-deoxy-D-glycero-D-gulo (7) and D-glycero-D-ido (9) heptitols. These compounds decomposed on standing and were identified as the corresponding 1-acetamido-1-deoxy heptitols 8 and 10, after acetylation with acetic

anhydride and pyridine. Reduction of the α-glucopyranosyl cyanide 5 with 0.5 mol of $LiAlH_4$ per mol of cyanide in tetrahydrofuran at 0°C, followed by hydrolysis of the intermediate aldimine, afforded 2,6-anhydro-3,4,5,7-tetra-O-benzyl-D-glycero-D-ido-heptopyranose (11) in 95% yield. The formation of an aldehyde was demonstrated by the presence of a strong band at 1700 cm^{-1} in the IR spectrum and the presence of a doublet at δ 9.20 ppm corresponding to the aldehyde H-1 proton. The value of the coupling constant ($J_{2,3}$ = 3 Hz) indicates the equatorial disposition of H-2 and, thus, the D-glycero-D-ido configuration of 11. In other preparations of aldehydes from nitriles, the reduction step is carried out in the presence of different reagents which trap the aldehyde to avoid further transformation.[10-14] However, subsequent liberation of the aldehyde from these intermediates is in some cases troublesome. Aldoheptose 11 is rather stable, but decomposes when stored for long times. It was fully characterised as the 2,4-dinitrophenylhydrazone derivative 12.

EXPERIMENTAL

are uncorrected. ^1H NMR spectra were recorded with a Varian EM-390 or a Varian XL-300 spectrometer operating at 90 or 300 MHz, respectively, with Me_4Si as an internal standard. IR spectra were recorded with a Perkin-Elmer 257 spectrophotometer. Optical rotations were determined with a Perkin-Elmer 141 polarimeter. Analytical TLC was performed on aluminium sheets coated with a 0.2 mm layer of silica gel 60 F_{254} (Merck), and preparative thin layer chromatography was performed on 20 x 20 cm glass plates coated with a 2 mm layer of silica gel PF_{254} (Merck).

2,3,4,6-Tetra-O-benzyl-β-D-glucopyranosyl Cyanide (3) and 2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl Cyanide (5). A solution of 1 (1 g, 1.7 mmol), trimethylsilyl cyanide (1 mL, 7.3 mmol) and boron trifluoride etherate (3 drops) in acetonitrile (20 mL) was stirred at room temperature for 15 min. The solvent was evaporated under reduced pressure and the residue chromatographed on preparative TLC plates using a mixture of hexane-EtOAc (6:1) as the eluent. Under UV light, two major bands were visible. The faster running band (Rf = 0.42) gave a solid which crystallized from EtOAc to give 3 (0.38 g, 40%); mp 76-78°C; $[\alpha]_D$ + 29° (c 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 3.42 (ddd, 1H, $J_{4,5}$ 9.5 Hz, H-5), 3.60, 3.66 (2t, 2H, $J_{3,4} = J_{4,5}$ = 8.9 Hz, H-3, H-4), 3.69 (m, 2H, H-6),

Anal. Calcd for $C_{35}H_{35}NO_5$: C, 76.50; H, 6.37; N, 2.55. Found: C, 76.16; H, 6.72; N, 2.61.

The slower running band (Rf = 0.34) afforded 5 (0.47 g, 50%) as an homogeneous syrup; $[\alpha]_D$ + 37° (c 1, $CHCl_3$) [Lit.[9] + 31.5° (c 0.75, $CHCl_3$); Lit[15] + 36.3° (c 5.3, $CHCl_3$)]; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.61-3.93 (m, 6H, H-2, H-3, H-4, H-5, H-6), 4.60 (d, 1H, $J_{1,2}$ 6.1 Hz, H-1). [Lit.[9] ^1H NMR ($CDCl_3$, 200 MHz): δ 3.31-4.06 (m, 6H, H-2, H-3, H-4, H-5, H-6), 4.46-4.93 (m, 9H, H-1 and $PhCH_2$ x 4)].

2,3,4,6-Tetra-O-benzyl-β-D-galactopyranosyl Cyanide (4) and 2,3,4,6-Tetra-O-benzyl-α-D-galactopyranosyl Cyanide (6). A solution of 2 (1 g, 1.7 mmol), trimethylsilyl cyanide (1 mL, 7.3 mmol) and boron trifluoride etherate (3 drops) in acetonitrile (20 mL) was stirred at room temperature for 15 min. The reaction mixture was concentrated and the residue chromatographed by preparative TLC using hexane-EtOAc (3:1) as the eluent. The faster running band (Rf = 0.52) afforded a solid which crystallized from EtOAc to give 6 (0.37 g, 40%), mp 84-85°C; $[\alpha]_D$ + 29.6° (c 1, $CDCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 3.50 (m, 2H, H-6), 3.81 (dd, 1H, $J_{2,3}$ 9.8, $J_{3,4}$ 2.8 Hz, H-3), 3.95-4.16 (m, 2H, H-4, H-5), 4.1 (dd, 1H, $J_{1,2}$ 6.0 Hz, H-2), 4.68 (d, 1H, H-1).

Anal. Calcd for $C_{35}H_{35}NO_5$: C, 76.50; H, 6.37; N, 2.55. Found: C, 76.32; H, 6.35; N, 2.46.

The slower running band (Rf = 0.36) afforded 4 (0.37 g, 40%); mp 85-86°C; $[\alpha]_D$ + 12.71° (c 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 3.47-3.55 (m, 4H, H-3, H-5, H-6), 3.93 (dd, 1H, $J_{3,4}$ 2.8, $J_{4,5}$ < 1 Hz, H-4), 4.02 (d, 1H, $J_{1,2}$ 9.8 Hz, H-1), 4.18 (t, 1H, $J_{2,3}$ 9.6 Hz, H-2).

Anal. Calcd for $C_{35}H_{35}NO_5$: C, 76.50; H, 6.37; N, 2.55. Found: C, 76.24; H, 6.39; N, 2.40.

1-Acetamido-2,6-anhydro-3,4,5,7-tetra-O-benzyl-1-deoxy-D-glycero-D-gulo-heptitol (8). A mixture of the cyanide 3 (1 g, 1.82 mmol), $LiAlH_4$ (0.5 g) and tetrahydrofuran (20 mL) was heated under reflux for 1 h. A solution of ammonium hydroxide was added dropwise. The mixture was filtered and the filtrate was treated again with ammonium hydroxide and filtered. The filtrate was extracted with chloroform and dried over Na_2SO_4. Evaporation of the chloroform phase gave 1-amino-2,6-anhydro-3,4,5,7-tetra-O-benzyl-1-deoxy-D-glycero-D-gulo-heptitol (7) (0.81 g, 80%) as an unstable syrup. This syrup was treated with a mixture of pyridine (10 mL) and acetic anhydride (1.2 mL) and the resulting solution was stirred at room temperature overnight. The mixture was evaporated under reduced pressure and the residue, dissolved in chloroform, was washed with diluted sulfuric acid (4 mL, 2 N), a saturated aqueous

solution of sodium bicarbonate (10 mL) and water (10 mL). The organic layer was dried over sodium sulfate, filtered and evaporated to dryness to give 8 as an amorphous solid (0.54 g, 63%); $[\alpha]_D$ + 17° (c 1, $CHCl_3$); IR (Nujol) ν: 3300, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.87 (s, 3H, NAc), 3.4-3.8 (m, 8H, H-1, H-3, H-4, H-5, H-6, H-7), 4.08 (m, 1H, $J_{1,2}$ 10.2 Hz, H-2), 4.45-4.92 (4 AB systems, 8H, CH_2-C_6H_5), 5.81 (t, 1H, NH).

Anal. Calcd for $C_{37}H_{41}NO_6$: C, 74.62; H, 6.89; N, 2.35. Found: C, 74.94; H, 7.18; N, 2.36.

1-Acetamido-2,6-anhydro-3,4,5,7-tetra-O-benzyl-1-deoxy-D-glycero-D-ido-heptitol (10). To a solution of the cyanide 5 (1 g, 1.82 mmol), in tetrahydrofuran (5 mL), a suspension of $LiAlH_4$ (0.5 g) in tetrahydrofuran (15 mL) was slowly added. The mixture was heated under reflux for 1 h. A solution of ammonium hydroxide (6 mL, 12 N) was added dropwise and the resulting precipitate was filtered. The filtrate was treated again with ammonium hydroxide (1mL, 12 N) and filtered. The filtrate was concentrated and the residue extracted with chloroform and dried (Na_2SO_4). Evaporation of the chloroform phase gave 1-amino-2,6-anhydro-3,4,5,7-tetra-O-benzyl-1-deoxy-D-glycero-D-ido-heptitol (9) (0.95 g, 94%) as an unstable syrup. This syrup was treated with a mixture of pyridine (10 mL) and acetic anhydride (1.2 mL) and the resulting solution was stirred at room temperature for 24 h. Then, the mixture was poured into water (100 mL) and extracted with chloroform (4 x 30 mL). The organic extract was washed with sulfuric acid (4 mL, 2N), a saturated aqueous solution of sodium bicarbonate (10 mL) and water (10 mL), and then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on preparative TLC with $CHCl_3$- MeOH (80:1) as the eluent to give 10 (0.6 g, 69%) as a solid; mp 148-149°C (from EtOAc); $[\alpha]_D$ + 34° (c 1, $CDCl_3$); IR (Nujol) ν : 3300, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ : 1.95 (s, 3H, CH_3CON), 3.37 (m, 2H, H-7), 3.45 (m, 1H, H-6), 3.56-3.77 (m, 6H, H-1, H-2, H-3, H-4, H-5), 4.50-4.92 (4 AB systems, 8H, CH_2-C_6H_5), 5.99 (t, 1H, NH).

Anal. Calcd for $C_{37}H_{41}NO_6$: C, 74.62; H, 6.89; N, 2.35. Found: C, 74.41; H, 7.12; N, 2.31.

2,6-Anhydro-3,4,5,7-tetra-O-benzyl-D-glycero-D-ido-heptopyranose (11). To a cooled (-5 to 0°C) solution of 5 (0.6 g, 1.09 mmol) in tetrahydrofuran (20 mL), $LiAlH_4$ (0.1 g) was slowly added. The resulting solution was stirred at 0°C until the starting material disappeared. Then, a solution of ammonium hydroxide (1.5 mL) was added dropwise up to the formation of a white precipitate. The resulting mixture was filtered

and the filtrate was washed again with ammonium hydroxide (0.3 mL, 12 N) and filtered. The filtrate was concentrated at reduced pressure and the residue extracted with chloroform (4 x 20 mL) and dried over Na_2SO_4. Evaporation to dryness of the organic phase afforded 11 (0.45 g, 75%) as a syrup. IR (film) ν : 1700 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ : 3.57-4.80 (m, 14H, H-3, H-4, H-5, H-6, H-7, CH_2-C_6H_5), 5.80 (d, 1H, $J_{2,3}$ 3 Hz, H-2), 9.20 (s, 1H, H-1). Compound 11 was fully characterised as the 2,4-dinitrophenylhydrazone derivative as indicated as follows.

A hot solution of 2,4-dinitrophenylhydrazine (0.2 g, 1 mmol), water (1 mL), concentrated H_2SO_4 (1 mL) and ethanol (5 mL), was added to a solution of 11 (0.5 g, 0.9 mmol) in methanol (10 mL). The solid which precipitated was filtered and crystallized from ethanol to give 12 (0.44 g, 67%), mp 130°C; $[\alpha]_D$ + 45° (c 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 90 MHz) δ: 3.35-3.9 (m, 7H, H-2, H-3, H-4, H-5, H-6, H-7), 9.10 (d, 1H, H-1, $J_{1,2}$ 3 Hz).

Anal. Calcd for $C_{41}H_{40}N_4O_9$: C, 67.21; H, 5.46; N, 7.65. Found: C, 67.21; H, 5.26; N, 8.01.

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