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Inhibition of α-Mannosidases by Seven Carbon Sugars: Synthesis of Some Seven Carbon Analogues of Mannofuranose

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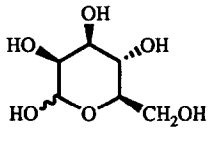
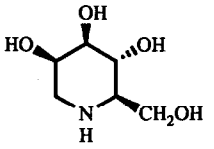
Abstract: The effects on human liver glycosidases of some seven carbon analogues of mannopyranose and mannofuranose are compared with those of deoxymannojirimycin and DIM. The syntheses of the seven carbon mannofuranose analogues, α-(aminomethyl)-1-deoxy-mannofuranose and of α-homoDIM, are described.

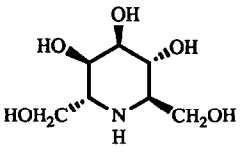
Polyhydroxylated nitrogen heterocycles constitute a major class of glycosidase inhibitors[1] and may also provide clues to the nature of many carbohydrate recognition processes;[2] glycosidase inhibition may be of value in the study of diabetes,[3] cancer,[4] and some viral diseases.[5] Because of the potential chemotherapeutic applications of such materials, there is continuing interest in the synthesis of both mono-[6] and bi-[7]cyclic analogues. In particular, the specific inhibition of individual N-linked glycoprotein processing α-mannosidases by nitrogen analogues of mannopyranose[8] and mannofuranose[9,10] may provide a useful anticancer[11] strategy. This paper compares the inhibition of human liver glycosidases by six and seven carbon mannopyranose {DMJ [deoxymannojirimycin] (1)[12] and homomannojirimycin (HMJ) (2)} and mannofuranose analogues {DIM (3),[13] homoDIM (4) and α-(aminomethyl)-1-deoxy-mannofuranose (5)}. All these seven carbon mannose analogues may be prepared from the lactones (10) and (7) derived from the Kiliani ascension of diacetone mannose (6);[14] the preparation of the seven carbon mannofuranose analogues (4) and (5) is described in this paper, and the following paper[15] reports the synthesis of HMJ (2) and some other highly functionalised piperidines.



α-D-mannopyranose



(1)



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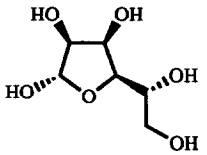
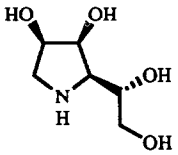


α-D-mannofuranose



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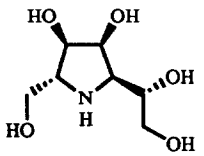

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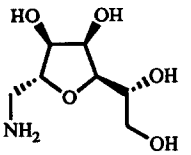
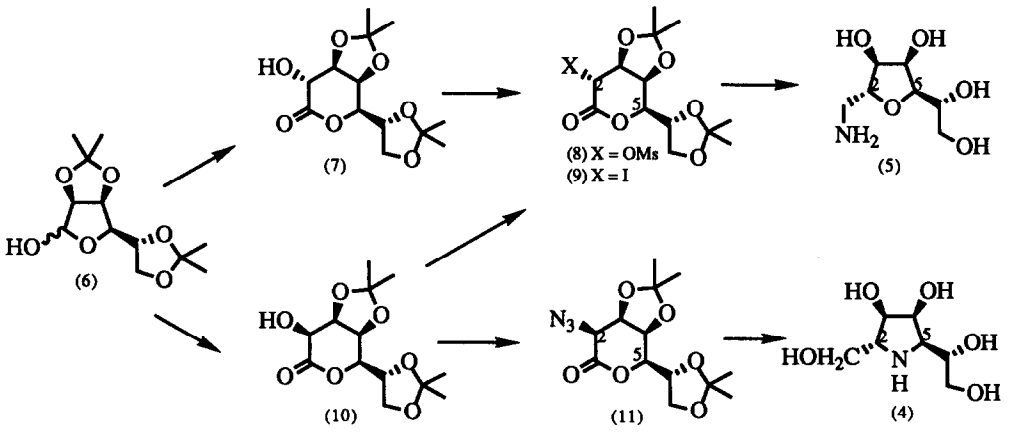


(5)

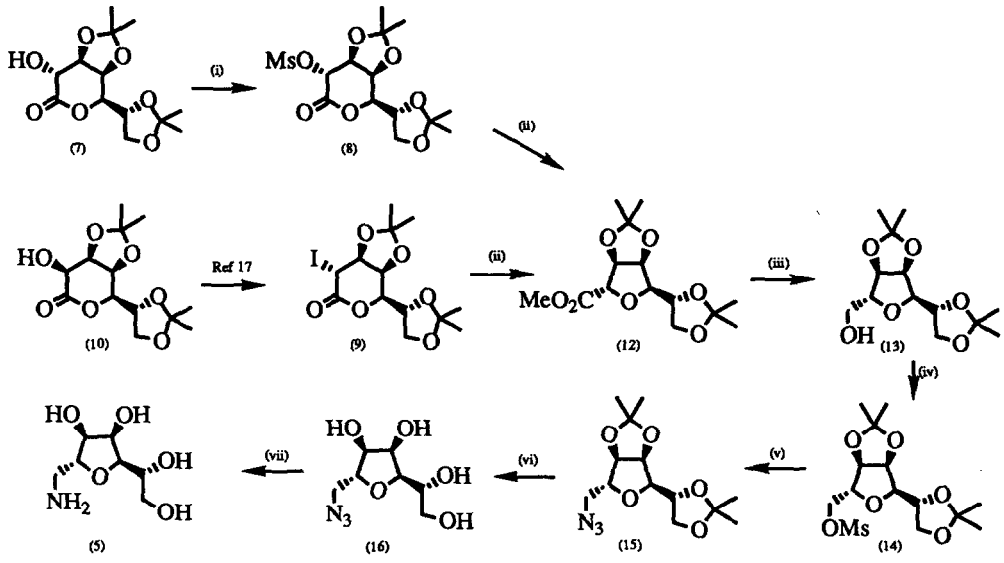
Synthesis of α-homoDIM (4) and α-(aminomethyl)-1-deoxy-mannofuranose (5)

Both materials were synthesised from the seven carbon epimeric alcohols (7) and (10), both of which are obtained from the Kiliani ascension[14] of diacetone mannose (6) [Scheme 1]. The tetrahydrofuran ring in (5) is formed by displacement of a leaving group from C-2 of the sugar by the lactone ring oxygen with inversion of configuration at C-2 and retention of configuration at C-5. The pyrrolidine ring in (4) is formed by introduction of nitrogen with retention of configuration at C-2 of the alcohol (10) [the major product of the Kiliani reaction], followed by joining the nitrogen function at C-2 to C-5 with overall retention of configuration, achieved by a double inversion of configuration at C-5; a similar strategy has been used for the construction of the pyrrolidine ring in the syntheses of DIM (3)[13] and of diastereomers of the bicyclic alkaloid, alexine.[16]



Scheme 1

For the synthesis of the tetrahydrofuran analogue (5) [Scheme 2], the *galacto*-alcohol (7) was treated with mesyl chloride in pyridine to give the mesylate (8) [83% yield], together with a small amount of the mesylate epimeric at C-2 of the lactone. The key step in the synthesis is a ring contraction reaction of the mesylate (8) induced by methoxide, in which the leaving group at C-2 is displaced by the ring oxygen function; addition of solid potassium carbonate to a methanolic solution of the mesylate (8) resulted in an efficient ring contraction to the tetrahydrofuran ester (12) [81% yield]. This transformation proceeds by nucleophilic addition of methoxide to the lactone carbonyl, ring opening and subsequent ring closure by nucleophilic displacement of the mesylate by the C-5 oxygen function; the overall stereochemical result of this sequence is inversion of configuration at C-2 of the sugar. The iodide (9) may be prepared from the major product (10) of the Kiliani ascension; conversion of the alcohol (10) to the corresponding triflate followed by treatment with tetrabutyl ammonium iodide give the iodide (9) in quantitative yield.[17] This iodide (9) on treatment with potassium carbonate in methanol underwent a similarly efficient ring contraction to give the methyl ester (12) in 80% yield. This general reaction of δ-lactones with α-leaving groups provides a powerful strategy for the synthesis of tetrahydrofurans with carbon substituents at C-2 and C-5.[18]



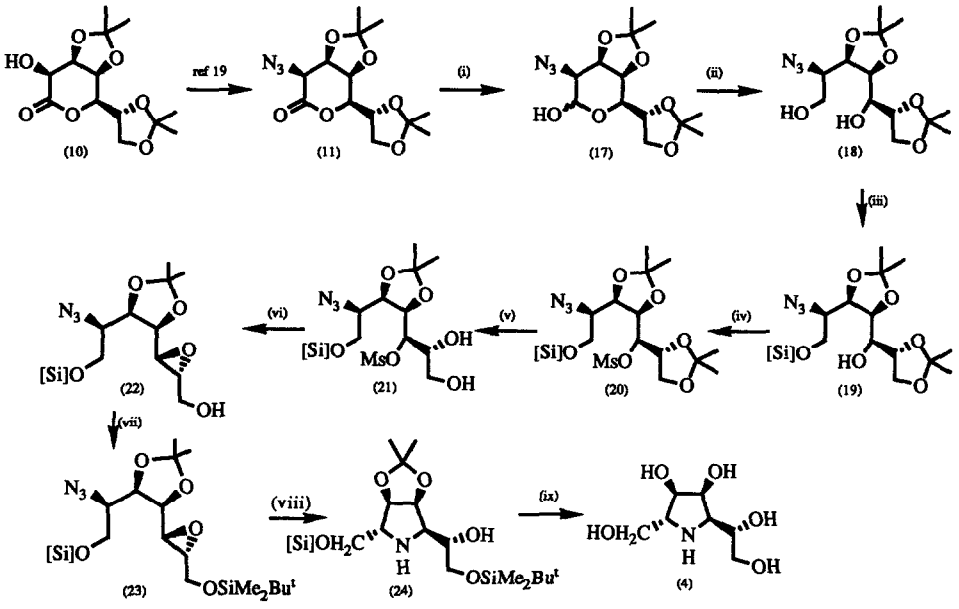
i) MsCl, pyridine, room temp, 3 h (ii) K_2CO_3, MeOH, room temp, 3 h iii) $LiAlH_4$, Et_2O iv) MsCl, py, CH_2Cl_2, 0°C
v) NaN_3, DMF, 40°C, 24 h ; vi) TFA, H_2O, room temp, 2 h vii) H_2, MeOH, 10% Pd/C, room temp, 24 h; then HCl (aq).

Scheme 2

Subsequent functional group manipulations on (12) gave the furan analogue (5). The ester (12) was reduced by lithium aluminum hydride in ether to the primary alcohol (13) [83% yield] which was esterified by mesyl chloride in pyridine to afford the mesylate (14) [95% yield]. Nucleophilic displacement of the mesylate function in (14) by sodium azide in dimethyl formamide gave the corresponding azide (15) [51% yield] from which the isopropylidene protecting groups were removed by treatment with aqueous trifluoroacetic acid to give the azidotetraol (16) [75% yield]. Subsequent hydrogenation of the azide (16) in methanol in the presence of palladium gave the required aminomethyl furanose analogue (5), isolated as the crystalline hydrochloride [88% yield - 18% overall yield for either the six steps from (7) or the seven steps from (10)].

For the synthesis of α-homoDIM (4) [Scheme 3], the alcohol (10) was converted, with overall retention at C-2, to the azide (11) as previously described.[19] Attempts at the direct reduction of the azidolactone (11) to the azidodiol (18) were unsuccessful; accordingly the lactone (11) was reduced first by di-*iso*butylaluminum hydride to the lactol (17) which, on subsequent treatment with sodium borohydride, gave the required diol (18) [78% overall yield]. The primary hydroxyl group was protected as the diphenyl-*tert*-butylsilyl ether (19) [92% yield] which on treatment with mesyl chloride in pyridine gave the azidomesylate (20) [90% yield]. Selective hydrolysis of the terminal acetonide in (20) with aqueous acetic acid gave the monoacetonide (21) [79% yield] together with a small amount of the completely deprotected tetraol [4% yield]. Treatment of the dihydroxymesylate (21) with barium methoxide gave the epoxide (22) [84% yield]. Hydrogenation of (22) gave relatively complex mixtures; accordingly, the primary hydroxyl group in (22) was protected as the *tert*-butyldimethylsilyl ether (23) [84% yield] which on hydrogenation in ethanol in the presence of palladium black gave the protected pyrrolidine (24) in 75% yield. Removal of both silyl protecting

groups and also of the isopropylidene group from (24) was achieved by aqueous trifluoroacetic acid to give α-homoDIM (4) [78% yield] as the crystalline hydrochloride salt [21% overall yield from the azidolactone (11)].



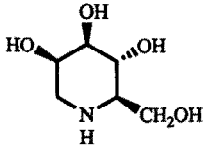
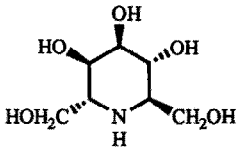
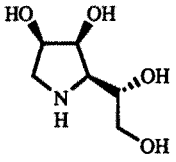
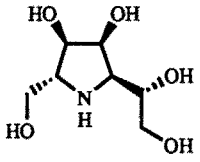
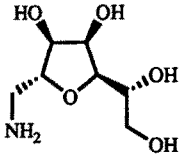
(i) *iso*-Bu_2AlH in THF (ii) $NaBH_4$ in MeOH (iii) Ph_2Bu^tSiCl, imidazole, DMF, 0°C (iv) MsCl, DMAP in pyridine (v) MeCOOH in aq. 1,4-dioxan (vi) $Ba(OMe)_2$ in MeOH, 0°C (vii) Me_2Bu^tSiCl, imidazole, DMF, 0°C (viii) H_2, Pd black, EtOH (ix) CF_3COOH/H_2O, 48h

Scheme 3

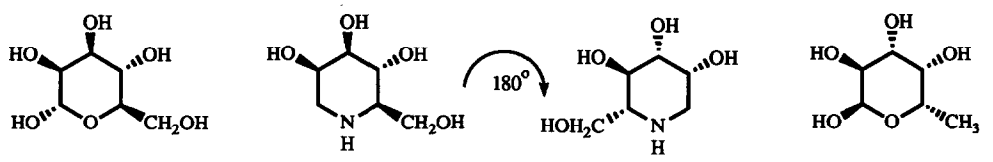
Glycosidase Inhibition

Human liver glycosidases were assayed in the absence and presence [1mM] of each of the potential inhibitors, using the appropriate buffered 4-methylumbelliferyl glycosides as substrates, as previously described. [20] The seven carbon compounds (2) and (4) can be considered as derivatives of the mannopyranose analogue, DMJ (1), and the mannofuranose analogue, DIM (3), in which an anomeric α-hydroxymethyl group has been introduced into the unsubstituted carbon atom of the ring. The addition of the anomeric substituent to DMJ does not affect appreciably the inhibition of the multiple forms of α-mannosidase, but it does abolish the moderate inhibition of β-hexosaminidase and decrease markedly the potent inhibition of α-fucosidase (Table). α-HomoDMJ (2) is thus a much more selective inhibitor of α-mannosidases than is the parent compound DMJ (1). The loss of inhibition of β-hexosaminidase can probably be attributed to the hydrophilic nature and incorrect configuration of the hydroxymethyl substituent; in general, analogues with hydrophobic groups on the anomeric carbon or the ring nitrogen bind more strongly to hexosaminidase. The decrease in inhibition of α-fucosidase can be understood by comparing the structure of α-homoDMJ with other derivatives of DMJ that inhibit α-fucosidase.[21] Both DMJ (1) and α-homoDMJ possess the minimum structural requirement for the inhibition of α-fucosidases by polyhydroxylated

% Inhibition of Glycosidase Activity at 1 mM concentration of inhibitor

Inhibitor / Enzyme	 DMJ (1)	 αHomoDMJ (2)	 DIM (3)	 α-HomoDIM (4)	 Manhepamine (5)
α-Mannosidase					
Lysosomal	58	49	97 K_i 13 μM	71	2
Neutral	30	33	89	76	2
Golgi	45	56	96	92	not determined
β-Mannosidase	0	0	0	18	3
α-Glucosidase	21	4	0	12	0
β-Glucosidase	0	0	16	23	14
α-Galactosidase	0	0	0	11	0
β-Galactosidase	0	0	76	35	0
β-Hexosaminidase	55	1	28	0	46
α-Fucosidase	92 K_i 5 μM	29	24	27	77
β-Glucuronidase	53	0	9	0	7
α-Arabinosidase	5	0	66	25	0
β-Xylosidase	3	0	45	21	6

piperidines, that is the correct absolute configuration of the three secondary hydroxyl groups is the same for both D-mannose and L-fucose.



α-D-mannopyranose DMJ (1) α-L-fucopyranose

Although α-L-fucosidase is inhibited strongly by some compounds which have either a different substituent to the methyl group of fucose or a substituent with the incorrect configuration at the anomeric position, incorrect substituents at both positions lead to a significant loss of inhibition even though the configuration of the secondary hydroxyl groups is correct.

The mannofuranose analogue DIM (3) is a much more potent inhibitor than the piperidine analogues (1) and (2) of all the mannosidases investigated. The introduction of the anomeric hydroxymethyl group to give α-HomoDIM (4) decreases the inhibition of the lysosomal and neutral enzymes, but not of the Golgi α-mannosidase. These results confirm that the binding of aminosugars to α-mannosidases does not require an anomeric substituent; the introduction of the substituent changes the relative specificity of the inhibitor while still retaining significant inhibitory properties towards α-mannosidases. Thus the homologues (2) and (4) may allow the further development of substituents in the anomeric position which are specific inhibitors for individual processing α-mannosidases. None of nitrogen heterocycles (1) - (5) inhibit β-mannosidase, suggesting this enzyme has a strict requirement for a β-anomeric substituent in order to bind strongly.

The tetrahydrofuran derivative (5), which is related to α-HomoDIM (4) by interchanging the ring nitrogen and the exocyclic oxygen, did not inhibit any of the α-mannosidases, indicating the need of the ring nitrogen to be protonated rather than an exocyclic amine. The structural basis for the moderate inhibition of α-fucosidase by (5) is not obvious but is interesting in view of the recent report[22] of the inhibition of a mammalian α-fucosidase by the furanose analogue of deoxyfuconojirimycin. The amino group on the anomeric substituent of (5) is probably responsible for the weak inhibitory properties towards β-N-acetylhexosaminidase. The specificities of inhibition of glycosidases by these seven carbon sugars are consistent with our previous deductions about the structural requirements for the inhibition of mammalian α-fucosidase and the multiple forms of α-mannosidase.

Experimental Melting points were recorded on a Kofler hot block and are uncorrected. Proton nucl magnetic resonance (δ_H) spectra were recorded on Varian Gemini 200 (200 MHz) or Bruker WH 300 MHz) spectrometers. ^{13}C Nuclear magnetic resonance (δ_C) spectra were recorded on a Varian Gem (50 MHz) spectrometer and multiplicities were assigned using DEPT sequence. ^{13}C spectra run in D referenced to methanol (δ_C 49.6 ppm) as an internal standard. All chemical shifts are quoted on Infra-red spectra were recorded on a Perkin-Elmer 781 or on a Perkin-Elmer 1750 FT spectr Mass spectra were recorded on VG Micromass ZAB 1F, Masslab 20-250 or Trio-1 GCMS spectrometers using desorption chemical ionisation (NH_3, DCI) or chemical ionisation (NH Optical rotations were measured on a Perkin-Elmer 241 polarimeter with a path

Concentrations are given in g/100 ml. Microanalyses were performed by the microanalysis service of the Dyson-Perrins Laboratory. Thin layer chromatography (t.l.c.) was carried out on aluminium sheets coated with $60F_{254}$ silica or glass plates coated with silica Blend 41. Plates were developed using a spray of 0.2% w/v cerium (IV) sulphate and 5% ammonium molybdate in 2M sulphuric acid or 0.5% ninhydrin in methanol (for amines). Flash chromatography was carried out using Sorbsil C60 40/60 silica. Ion exchange columns were packed with 'Dowex' 50W-X8 resin in the H^+ form. Solvents and commercially available reagents were dried and purified before use according to standard procedures; dichloromethane was refluxed over and distilled from calcium hydride, methanol was distilled from magnesium methoxide, pyridine was distilled from, and stored over, potassium hydroxide; tetrahydrofuran was distilled, under nitrogen, from a solution dried with sodium in the presence of benzophenone. Hexane was distilled at 68 °C before use to remove involatile fractions. The epimeric alcohols (7) and (10) were obtained from diacetone mannose;[14] the azide (11)[19] and the iodide (9)[17] were prepared from (10). Deoxymannojirimycin (1)[12] and DIM (3)[13] were synthesised as previously described.

Synthesis of α-(Aminomethyl)-1-deoxy-mannofuranose (5)

3,4:6,7-Di-O-isopropylidene-2-O-methanesulphonyl-D-glycero-D-galacto-heptono-1,5-lactone (8). Methanesulphonyl chloride (2.6 ml, 26 mmol) was added dropwise over 2 min to a stirred solution of the *galacto* -lactone (7) (3.0 g, 10 mmol) in dry pyridine (5 ml) at 0 °C under nitrogen. After a further 3 h, ^1H NMR of the crude reaction mixture indicated that no starting material remained. The solvent was removed *in vacuo* , and the residue dissolved in chloroform (50 ml), washed with dilute hydrochloric acid (3 x 30 ml), water (2 x 30 ml), brine (2 x 20 ml) and dried (magnesium sulphate). The solvent was removed *in vacuo* and the residue purified by flash chromatography (ether : hexane, 1 : 1) to give *3,4:6,7-di-O-isopropylidene-2-O-methanesulphonyl-D-glycero-D-galacto-heptono-1,5-lactone (8)* (2.49 g, 83 %) m.p. 136-137 °C. (Found: C, 45.72; H, 6.16. $C_{14}H_{22}O_9S$ requires C, 45.89; H, 6.05%); $[\alpha]_D^{20}$ +67.4 ° (*c* 1.0 in $CHCl_3$); δ_H ($CDCl_3$) 1.40, 1.44, 1.48 (12H, 3 x s, 4 x Me), 3.15 (3H, s, $-SO_2Me$), 4.11 (1H, dd, H-7, $J_{6,7}$ 3.9 Hz, $J_{7,7'}$ 9.3 Hz), 4.17 (1H, dd, H-7', $J_{6,7'}$ 5.6 Hz), 4.41 (1H, ddd, H-6, $J_{5,6}$ 8.3 Hz), 4.48 (1H, dd, H-5, $J_{4,5}$ 1.5 Hz), 4.70 (1H, dd, H-4, $J_{3,4}$ 7.4 Hz), 4.78 (1H, dd, H-3, $J_{2,3}$ 2.3 Hz), 5.02 (1H, d, H-2); δ_C ($CDCl_3$) 23.9, 24.8, 25.6, 26.8 (4 x q, 4 x Me), 38.6 (q, $-SO_2Me$), 66.4 (t, C-7), 70.5, 72.7, 73.4, 74.2, 76.8 (5 x d, C-2, C-3, C-4, C-5, C-6), 110.1, 111.2 (2 x s, 2 x $\underline{C}Me_2$), 163.6 (s, C-1); *m/z* (NH_3, DCI) 384 ($M+NH_4^+$, 100%), 367 ($M+H^+$, 80%). A small amount of the mesylate epimeric at C-2 (0.19 g, 5%) was also formed.

Methyl 2,5-anhydro-3,4:6,7-di-O-isopropylidene-D-glycero-D-talo-heptonate (12) (i) From mesylate (8): Potassium carbonate (1.10 g, 7.93 mmol) was added to a solution of the mesylate (8) (2.90 g, 7.93 mmol) in dry methanol (25 ml) and the reaction mixture stirred at room temperature. After 4 h, t.l.c. (hexane : ethyl acetate, 1 : 1) indicated complete conversion of the starting material (R_f 0.7) to a single product (R_f 0.8). The solution was filtered and the solvent removed *in vacuo*. The residue was purified by flash chromatography (hexane : ethyl acetate, 4 : 1) to give *methyl 2,5-anhydro-3,4:6,7-di-O-isopropylidene-D-glycero-D-talo-heptonate (12)* (1.94 g, 81%), m.p. 79-80 °C. (Found: C, 55.91; H, 7.45. $C_{14}H_{22}O_7$ requires C, 55.64; H, 7.34%); $[\alpha]_D^{20}$ -11.4 ° (*c* 1.0 in $CHCl_3$); δ_H ($CDCl_3$) 1.36, 1.39, 1.46, 1.52 (12H, 4 x s, 4 x Me), 3.77 (3H, s, $-CO_2Me$), 4.01 (1H, dd, H-5, $J_{4,5}$ 3.7 Hz, $J_{5,6}$ 7.9 Hz), 4.11 (1H, dd, H-7, $J_{6,7}$ 5.0 Hz, $J_{7,7'}$ 8.7 Hz), 4.14 (1H, dd, H-7', $J_{6,7'}$ 5.8 Hz), 4.41 (1H, dt, H-6), 4.56 (1H, br s, H-2), 4.81 (1H, dd, H-4, $J_{3,4}$

6.0 Hz), 4.97 (1H, dd, H-3, $J_{2,3}$ 0.7 Hz); δ_C ($CDCl_3$) 24.5, 24.9, 25.8, 26.6 (4 x q, 4 x Me), 52.1 (q, -CO_2Me), 66.9 (t, C-7), 72.9, 80.4, 82.8, 84.1 (5 x d, C-2, C-3, C-4, C-5, C-6) 109.3, 113.3 (2 x s, 2 x $\underline{C}Me_2$), 170.7 (s, C-1); *m/z* (NH_3, CI) 320 ($M+NH_4^+$, 10%), 303 ($M+H^+$, 100%).

(ii) From iodide (9): Potassium carbonate (56 mg, 0.40 mmol) was stirred with a solution of the iodide (9) (0.16 g, 0.40 mmol) in methanol (20 ml) at room temperature. After 4 h, t.l.c. (hexane : ethyl acetate, 1 : 1) indicated complete conversion of the starting material (R_f 0.8) to a single product (R_f 0.7). The solution was filtered and the solvent removed *in vacuo*. The residue was purified by flash chromatography (hexane : ethyl acetate, 4 : 1) to give *methyl 2,5-anhydro-3,4:6,7-di-O-isopropylidene-D-glycero-D-talo-heptonate (12)* as a colourless crystalline solid (97 mg, 80%), m.p. 79-80 °C, identical by ^1H NMR to that obtained above from the mesylate (8).

2,5-Anhydro-3,4:6,7-di-O-isopropylidene-D-glycero-D-talo-heptitol (13). Lithium aluminium hydride (95.0 mg, 2.49 mmol) was added in small portions to a solution of the ester (12) (0.50 g, 1.66 mmol) in dry ether (5 ml) and the reaction mixture stirred at 0 °C under nitrogen. After 20 min, t.l.c. (hexane : ethyl acetate, 1 : 1) indicated complete conversion of the starting material (R_f 0.8) to a single product (R_f 0.3). The reaction was quenched by the addition of sodium fluoride (0.10 g, 1.66 mmol) and a few drops of water. The reaction mixture was filtered, the solvent removed *in vacuo*, and the residue purified by flash chromatography (hexane : ethyl acetate, 3 : 1) to give *2,5-anhydro-3,4:6,7-di-O-isopropylidene-D-glycero-D-talo-heptitol (13)* (0.38 g, 83%) a colourless crystalline solid, m.p. 82-83 °C. (Found: C, 57.02; H, 8.37. $C_{13}H_{22}O_6$ requires C, 56.92; H, 8.08%); $[\alpha]_D^{20}$ -6.9 ° (*c* 1.0 in $CHCl_3$); δ_H ($CDCl_3$) 1.36, 1.39, 1.46, 1.52 (12H, 4 x s, 4 x Me), 1.83 (1H, br s, OH), 3.63 (2H, br d, H-1, H-1', J 5.0 Hz), 3.99 (1H, dd, H-5, $J_{4,5}$ 3.9 Hz, $J_{5,6}$ 7.1 Hz), 4.07 (1H, dd, H-7, $H_{6,7}$ 5.0 Hz, $J_{7,7'}$ 8.8 Hz), 4.11 (1H, dd, H-7', $J_{6,7'}$ 6.3 Hz), 4.17 (1H, br t, H-2), 4.40 (1H, m, H-6), 4.68 (1H, dd, H-3, $J_{2,3}$ 1.3 Hz, $J_{3,4}$ 6.1 Hz), 4.81 (1H, dd, H-4); δ_C ($CDCl_3$) 24.4, 24.9, 25.9, 26.6 (4 x q, 4 x Me), 62.0, 66.4 (2 x t, C-1, C-7), 73.7, 81.0, 81.3, 82.5, 84.8 (5 x d, C-2, C-3, C-4, C-5, C-6), 109.0, 112.8 (2 x s, 2 x $\underline{C}Me_2$); *m/z* (NH_3, CI) 292 ($M+NH_4^+$, 5%), 275 ($M+H^+$, 80%), 217 (100%).

2,5-Anhydro-3,4:6,7-di-O-isopropylidene-1-O-methanesulphonyl-D-glycero-D-talo-heptitol (14). Methanesulphonyl chloride (1.18 ml, 11.8 mmol) was added dropwise over 2 min to a stirred solution of the *talo*-heptitol (13) (1.40 g, 4.0 mmol) in dry pyridine (5 ml) and dichloromethane (5 ml) at 0 °C under nitrogen. After a further 30 min, t.l.c. (hexane : ethyl acetate, 1 : 1) indicated complete conversion of the starting material (R_f 0.3) to a single product (R_f 0.6). The solvent was removed *in vacuo*, the residue dissolved in chloroform (50 ml), washed with dilute hydrochloric acid (3 x 30 ml), water (2 x 30 ml), brine (2 x 20 ml) and dried (magnesium sulphate). The solvent was removed *in vacuo* and the residue purified by flash chromatography (ether : hexane 1, : 1) to give *2,5-anhydro-3,4:6,7-di-O-isopropylidene-1-O-methanesulphonyl-D-glycero-D-talo-heptitol (14)* (1.70 g, 95%), a colourless crystalline solid, m.p. 102 °C. (Found: C, 47.89; H, 7.04. $C_{14}H_{24}O_8S$ requires C, 47.72; H, 6.87%); $[\alpha]_D^{20}$ -5.9 ° (*c* 1.0 in $CHCl_3$); δ_H ($CDCl_3$) 1.33, 1.39, 1.45, 1.48 (12H, 4 x s, 4 x Me), 3.06 (3H, s, -SO_2Me), 3.59 (1H, dd, H-5, $J_{4,5}$ 3.3 Hz, $J_{5,6}$ 7.3 Hz), 3.88 (1H, m, H-2), 4.04 (1H, dd, H-7, $J_{6,7}$ 4.7 Hz, $J_{7,7'}$ 8.7 Hz), 4.10 (1H, dd, H-7', $J_{6,7'}$ 6.0 Hz), 4.40 (1H, dd, H-1, $J_{1,1'}$ 11.2 Hz, $J_{1,2}$ 7.1 Hz), 4.41 (1H, m, H-6), 4.50 (1H, dd, H-1', $J_{1',2}$ 4.5 Hz), 4.76 (1H, dd, H-3, $J_{2,3}$ 3.5 Hz, $J_{3,4}$ 6.1 Hz), 4.80 (1H, dd, H-4); δ_C ($CDCl_3$) 24.2, 25.0, 25.5,

26.7 (4 x q, 4 x Me), 37.3 (q, -SO_2Me), 66.6, 67.8 (2 x t, C-1, C-7), 72.8, 79.0, 80.4, 80.5, 82.0 (5 x d, C-2, C-3, C-4, C-5, C-6), 109.2, 113.1 (2 x s, 2 x $\underline{C}Me_2$); *m/z* (NH_3, DCI) 370 ($M+NH_4^+$, 15%), 353 ($M+H^+$, 100%).

2,5-Anhydro-1-azido-1-deoxy-3,4:6,7-di-O-isopropylidene-D-glycero-D-talo-heptitol (15). Sodium azide (0.98 g, 15 mmol) was added to a solution of the mesylate (14) (1.70 g, 4.8 mmol) in dry DMF (10 ml) and the reaction mixture stirred at 40 °C. After 24 h, t.l.c. (ethyl acetate : hexane, 3 : 1) indicated partial conversion of the starting material into a single product. The solvent was removed *in vacuo* and the residue dissolved in dichloromethane, washed with water (3 x 20 ml) and dried over magnesium sulphate. The product was separated from the remaining starting material by flash chromatography (ether : hexane, 1 : 1) to give *2,5-anhydro-1-azido-1-deoxy-3,4:6,7-di-O-isopropylidene-D-glycero-D-talo-heptitol (15)*, (0.66 g, 44%, 51% based on recovered starting material), a colourless crystalline solid , m.p. 69 °C. (Found: C, 52.35; H, 7.35; N, 13.97. $C_{13}H_{21}O_5N_3$ requires C, 52.17; H, 7.07; N, 14.07%); $[\alpha]_D^{20}$ -7.1 ° (*c* 1.0 in $CHCl_3$); ν_{max} (KBr disc) 2093 (N_3) cm^{-1}; δ_H ($CDCl_3$) 1.36, 1.39, 1.46, 1.52 (12H, 4 x s, 4 x Me), 3.25 (1H, dd, H-1, $J_{1,1'}$ 12.9 Hz, $J_{1,2}$ 4.7 Hz), 3.45 (1H, dd, H-1', $J_{1',2}$ 6.6 Hz), 3.95 (1H, dd, H-5, $J_{4,5}$ 3.8 Hz, $J_{5,6}$ 7.5 Hz), 4.06 (1H, dd, H-7, $J_{6,7}$ 4.7 Hz, $J_{7,7'}$ 8.8 Hz), 4.11 (1H, dd, H-7', $J_{6,7'}$ 6.0 Hz), 4.24 (1H, br t, H-2), 4.40 (1H, ddd, H-6), 4.65 (1H, dd, H-3, $J_{2,3}$ 1.3 Hz, $J_{3,4}$ 6.1 Hz), 4.82 (1H, dd, H-4); δ_C ($CDCl_3$) 24.5, 24.9, 26.0, 26.7 (4 x q, 4 x Me), 51.3, 66.7 (2 x t, C-1, C-7), 73.3, 81.0, 81.6, 83.2, 83.6 (5 x d, C-2, C-3, C-4, C-5, C-6), 109.3, 113.1 (2 x s, 2 x $\underline{C}Me_2$); *m/z* (NH_3, DCI) 317 ($M+NH_4^+$, 5%), 300 ($M+H^+$, 100%).

2,5-Anhydro-1-azido-1-deoxy-D-glycero-D-talo-heptitol (16). The azide (15) (0.52 g, 1.72 mmol) was stirred in trifluoroacetic acid : water, 1 : 1 (5 ml) at room temperature. After 2 h, t.l.c. (5% methanol in ethyl acetate) indicated complete conversion of the starting material (R_f 1.0) to a single product (R_f 0.3). The solvent was removed *in vacuo*, and the co-evaporated with toluene (3 x 10 ml) to remove the last traces of acid. The residue was taken up in methanol and preabsorbed on to silica before purification by flash chromatography (1% methanol in ethyl acetate) to give *2,5-anhydro-1-azido-1-deoxy-D-glycero-D-talo-heptitol (16)* (0.28 g, 75%), m.p. 86 °C. (Found: C, 38.18; H, 6.09; N, 18.89. $C_7H_{13}O_5N_3$ requires C, 38.36; H, 5.98; N, 19.17%); $[\alpha]_D^{20}$ +71.5 ° (*c* 1.0 in $CHCl_3$); ν_{max} (KBr disc) 2108 (N_3) cm^{-1} ; δ_H (CD_3OD) 3.25 (1H, dd, H-1, $J_{1,1'}$ 13.2 Hz, $J_{1,2}$ 5.2 Hz), 3.51 (1H, dd, H-1', $J_{1',2}$ 2.7 Hz), 3.55 (1H, dd, H-7, $J_{6,7}$ 6.0 Hz, $J_{7,7}$ 11.5 Hz), 3.77 (1H, dd, H-7', $J_{6,7'}$ 3.0 Hz), 3.86 (1H, dd, H-5, $J_{4,5}$ 3.0 Hz, $J_{5,6}$ 8.5 Hz), 3.90-3.93 (2H, m, H-2, H-6), 4.08 (1H, dd, H-3, $J_{2,3}$ 8.4 Hz, $J_{3,4}$ 4.1 Hz), 4.20 (1H, dd, H-4); δ_C (CD_3OD) 52.9, 64.5 (2 x t, C-1, C-7), 70.9, 72.7, 74.3, 81.1, 81.5 (5 x d, C-2, C-3, C-4, C-5, C-6); *m/z* (NH_3, DCI) 237 ($M+NH_4^+$, 100%), 220 ($M+H^+$, 20%).

α-(Aminomethyl)-1-deoxy-mannofuranose [1-Amino-2,5-anhydro-1-deoxy-D-glycero-D-talo-heptitol hydrochloride] (5). The azide (16) (0.12 g, 0.63 mmol) was stirred in methanol (5 ml) at room temperature under hydrogen in the presence of 10% palladium on carbon (10 mg). After 24 h, t.l.c. (5% methanol in ethyl acetate) indicated conversion of the starting material (R_f 0.3) to a single product (R_f 0.0). The reaction mixture was filtered through celite, the solvent removed *in vacuo*, and the resulting solid purified by ion exchange chromatography with Dowex '50W-X8' using 0.5 M ammonia as eluant. After freeze drying, 1-amino-2,5-

anhydro-1-deoxy-**D**-*glycero*-**D**-*talo*-heptitol (5) (95 mg, 88%) was obtained as a yellowish solid. The solid was taken up in water, and the solution neutralised with dilute aqueous hydrochloric acid. Freeze drying, followed by recrystallisation from methanol / chloroform, gave *1-amino-2,5-anhydro-1-deoxy-D-glycero-D-talo-heptitol hydrochloride (5)* as a colourless crystalline solid, m.p. 189 °C (dec.). (Found: C, 36.61; H, 7.27; N, 5.42. $C_7H_{16}O_5NCl$ requires C, 36.61; H, 7.02; N, 6.10%); $[\alpha]_D^{20}$ +38.6 ° (*c* 1.0 in $CHCl_3$); δ_H (D_2O) 3.00 (1H, dd, H-1, $J_{1,1'}$ 13.4 Hz, $J_{1,2}$ 8.8 Hz), 3.18 (1H, dd, H-1', $J_{1',2}$ 2.9 Hz), 3.52 (1H, dd, H-7, $J_{6,7}$ 5.0 Hz, $J_{7,7'}$ 12.1 Hz), 3.66 (1H, dd, H-7', $J_{6,7'}$ 2.7 Hz), 3.80 (1H, ddd, H-6, $J_{5,6}$ 9.0 Hz), 3.87 (1H, dd, H-5, $J_{4,5}$ 2.6 Hz), 3.91 (1H, dt, H-2, $J_{2,3}$ 8.4 Hz), 4.05 (1H, dd, H-3, $J_{3,4}$ 4.1 Hz), 4.17 (1H, dd, H-4); δ_C (D_2O) 41.8, 63.1 (2 x t, C-1, C-7), 69.0, 71.6, 74.3, 77.2, 79.6 (5 x d, C-2, C-3, C-4, C-5, C-6); *m/z* (NH_3, DCI) 194 ($M+H^+$, 100%).

Synthesis of α-HomoDIM (4)

2-Azido-2-deoxy-3,4:6,7-di-O-isopropylidene-D-glycero-D-talo-heptose (17). Di-*iso*butylaluminium hydride (1.0 M in heptane, 15 ml, 15 mmol) was added, under nitrogen, to a stirred solution of the azidolactone (11) (3.99 g, 12.75 mmol) in dry THF (20 ml) at -70 °C. After an additional 1 h at -70 °C, the solution was allowed to stand for 6 h at -20 °C when ^1H NMR indicated complete lactol formation. Sodium fluoride (0.5 g, 12 mmol), saturated aqueous ammonium sulphate (2 ml), and ether (40 ml) were added sequentially whereupon a white gelatinous precipitate formed. The mixture was filtered and the precipitate washed with ether (2 x 20 ml). The filtrate and washings were combined, dried (magnesium sulphate) and the solvent removed to afford *2-azido-2-deoxy-3,4:6,7-di-O-isopropylidene-D-glycero-D-talo-heptose (17).* A small amount of material was recrystallized (ether), to give a white crystalline solid, m.p.114-115 °C. (Found: C, 49.82; H, 6.99; N, 12.99. $C_{13}H_{21}O_6N_3$ requires: C, 49.52; H, 6.71; N, 13.32%); $[\alpha]_D^{20}$ +0.41 ° (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 3400 (br, OH), 2120 (N_3) cm^{-1}; δ_H ($CDCl_3$) 1.38 (6H, s, 2 x Me), 1.43, 1.48 (6H, 2 x s, 2 x Me), 3.16 (1H, d, OH, D_2O exch., $J_{1,OH}$ 3.1 Hz), 3.54 (1H, dd, H-2, $J_{1,2}$ 6.8 Hz, $J_{2,3}$ 2.6 Hz), 3.62 (1H, dd, H-5, $J_{4,5}$ 1.6 Hz, $J_{5,6}$ 7.9 Hz), 4.00 (1H, dd, H-7, $J_{6,7}$ 4.3 Hz, $J_{7,7'}$ 8.7 Hz), 4.01 (1H, dd, H-7', $J_{6,7'}$ 6.0 Hz), 4.22 (1H, ddd, H-6), 4.45 (1H, dd, H-4, $J_{3,4}$ 7.8 Hz), 4.60 (1H, dd, H-3), 5.26 (1H, dd, H-1); δ_C ($CDCl_3$) 24.8, 25.6, 26.7 (3 x q, 4 x Me), 60.9 (d, C-2), 66.6 (t, C-7), 70.8, 72.8, 73.4, 73.6 (4 x d, C-3, C-4, C-5, C-6), 92.7 (d, C-1), 109.7, 110.8 (2 x s, 2 x $\underline{C}Me_2$); *m/z* (NH_3, DCI) 333 ($M+NH_4^+$, 35%), 316 ($M+H^+$, 25%), 288 ($M+H^+-N_2$, 100%).

2-Azido-2-deoxy-3,4:6,7-di-O-isopropylidene-D-glycero-D-talo-heptitol (18). The remainder of the crude lactol (17) was dissolved in methanol (20 ml) and sodium borohydride (530 mg, 14 mmol) was added over 30 min at 0 °C. After an additional 1 h at 0 °C the reaction was allowed to warm to room temperature and stirred for a further 1 h. at which point t.l.c. (hexane : ethyl acetate, 1 : 1) indicated complete consumption of the lactol (17) (R_f 0.6) to give a single product (R_f 0.5). The reaction was quenched by addition of saturated aqueous ammonium sulphate (2 ml). Flash chromatography (hexane : ethyl acetate, 3 : 1) gave *2-azido-2-deoxy-3,4:6,7-di-O-isopropylidene-D-glycero-D-talo-heptitol (18)* (3.16 g, 78% over two steps from (11)), a white crystaline solid, m.p. 74-75 °C (ether / hexane). (Found: C, 49.14; H, 7.41; N, 13.03. $C_{13}H_{23}N_3O_6$ requires: C, 49.20; H, 7.31; N, 13.24%); $[\alpha]_D^{20}$ -45.0 ° (*c* 1.1 in $CHCl_3$); ν_{max} ($CHCl_3$): 3550 (OH), 2110 (N_3) cm^{-1}; δ_H ($CDCl_3$) 1.37, 1.38, 1.44, 1.50 (12H, 4 x s, 4 x Me), 2.01 (1H, dd, HO-1, $J_{OH,1}$ 5.1 Hz, $J_{OH,1'}$ 7.0 Hz), 2.18 (1H, d, HO-5, $J_{OH,5}$ 9.5 Hz), 3.8-4.1 (7H, m), 4.15 (1H, dd, J 6.9 Hz, J 9.6 Hz)

4.45 (1H, d, J 6.9 Hz);δ_C($CDCl_3$) 24.3, 25.1, 26.3, 26.6 (4 x q, 4 x Me), 61.3 (d, C-2), 63.5, 66.7 (2 x t, C-1, C-7), 69.5, 74.9, 75.2, 73.3 (4 x d, C-3, C-4, C-5, C-6), 108.9, 109.4 (2 x s, 2 x $\underline{C}Me_2$); *m/z* (NH_3, DCI) 335 ($M+NH_4^+$, 10%), 318 ($M+H^+$, 20%), 290 ($M+H^+-N_2$, 100%).

2-Azido-1-O-tert-butyldiphenylsilyl-2-deoxy-3,4:6,7-di-O-isopropylidene-D-glycero-D-talo-heptitol (19). *tert*-Butyldiphenylsilylchloride (0.55 ml, 2.12 mmol) was added, under nitrogen, to a stirred solution of the diol (18) (612 mg, 1.93 mmol) and imidazole (263 mg, 3.8 mmol) in dry DMF at 0 °C. The solution was then warmed to room temperature and stirred for 5 h, when t.l.c. (hexane : ethyl acetate, 3 : 1) showed only a trace of starting material (R_f 0.3) and one major product (R_f 0.7). The solvent was removed, the residue shaken with dichloromethane (30 ml) and then filtered. Evaporation and purification by flash chromatography (hexane : ethyl acetate, 4 : 1) gave *2-azido-1-O-tert-butyldiphenylsilyl-2-deoxy-3,4:6,7-di-O-isopropylidene-D-glycero-D-talo-heptitol (19)* (983 mg, 92%), a viscous oil, $[\alpha]_D^{20}$ -35.0 ° (*c* 1.05 in $CHCl_3$); ν_{max} (film) 3500 (br, OH), 2125 (N_3) cm^{-1}; δ_H ($CDCl_3$) 1.09 (9H, s, Me_3C), 1.34, 1.38, 1.41, 1.45 (12H, 4 x s, 4 x Me), 2.13 (1H, d, OH, $J_{OH,5}$ 9.1 Hz, D_2O exch.), 3.91 (3H, m), 4.05 (4H, m), 4.23 (1H, dd, J 6.9 Hz, J 9.6 Hz), 4.44 (1H, d, J 6.9 Hz), 7.43 (6H, m), 7.73 (4H, m); δ_C ($CDCl_3$) 19.0 (s, $\underline{C}Me_3$), 24.3, 25.3, 26.4 (3 x q, 3 x Me), 26.5 (q, $C\underline{Me}_3$), 26.7 (q, Me), 61.2 (d, C-2), 64.9, 66.9 (2 x t, C-1, C-7), 69.6, 74.0, 75.3, 76.4 (4 x d, C-3, C-4, C-5, C-6), 108.7, 109.4 (2 x s, 2 x $\underline{C}Me_2$), 127.9, 129.9 (2 x d, 2 x Ar-C), 133.0 (s, Ar-C), 135.8 (d, Ar-C); *m/z* (NH_3, DCI) 528 ($M+H^+-N_2$, 20%), 510 ($M+H^+-N_2-OH_2$, 100%).

2-Azido-1-O-tert-butyldiphenylsilyl-2-deoxy-3,4:6,7-di-O-isopropylidene-5-O-methanesulphonyl-D-glycero-D-talo-heptitol (20). Methanesulphonyl chloride (0.20 ml, 2.0 mmol) was added, under nitrogen, to a stirred solution of the alcohol (19) (447 mg, 0.81 mmol) and 4-*N,N'*-dimethylaminopyridine (20 mg, 0.16 mmol) in dry pyridine (5 ml) at room temperature. After 12 h, t.l.c. (hexane : ethyl acetate, 3 : 1) indicated complete consumption of starting material (R_f 0.6) to give a single product (R_f 0.5). The solvent was removed and the residue dissolved in chloroform (50 ml), washed with water (2 x 30 ml) and dried (magnesium sulphate). Removal of the solvent followed by flash chromatography (hexane : ethyl acetate, 6 : 1) gave *2-azido-1-O-tert-butyldiphenylsilyl-2-deoxy-3,4:6,7-di-O-isopropylidene-5-O-methanesulphonyl-D-glycero-D-talo-heptitol (20)* (458 mg, 90%), a white crystalline solid, m.p. 90-91 °C. (Found C, 56.70; H, 6.85; N, 6.86. $C_{30}H_{43}N_3O_8SSi$ requires C, 56.85; H, 6.84; N, 6.63%); $[\alpha]_D^{20}$ -45.3 ° (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2108 (N_3) cm^{-1}; δ_H ($CDCl_3$) 1.09 (9H, s, Me_3C), 1.39, 1.44, 1.48, 1.57 (12H, 4 x s, 4 x Me), 3.06 (3H, s, $MeSO_3$), 3.9-4.1 (4H, m), 4.13 (1H, dd, J 6.2 Hz, J 8.8 Hz), 4.3 (2H, m), 4.38 (1H, dd, J 1.9 Hz, J 6.2 Hz), 5.15 (1H, dd, H-5, J 1.8 Hz, J 4.9 Hz), 7.43 (6H, m), 7.71 (4H, m); δ_C ($CDCl_3$) 19.00 (s, $\underline{C}Me_3$), 25.0, 25.4, 26.0, 26.2 (4 x q, 4 x Me), 26.5 (q, $C\underline{Me}_3$), 39.8 (q, $-SO_2Me$), 59.5 (d, C-2), 64.6, 65.8 (2 x t, C-1, C-7), 74.0, 75.5, 76.0, 77.7 (4 x d, C-3, C-4, C-5, C-6), 109.4, 110.2 (2 x s, 2 x $\underline{C}Me_2$), 128.0, 130.2 (2 x d, 2 x Ar-C), 133.0 (s, Ar-C), 136.0 (d, Ar-C); *m/z* (NH_3, DCI) 651 ($M+NH_4^+$, 30%), 606 ($M+H^+-N_2$, 100%).

2-Azido-1-O-tert-butyldiphenylsilyl-2-deoxy-3,4-O-isopropylidene-5-O-methanesulphonyl-D-glycero-D-talo-heptitol (21). The diacetonide (20) (463 mg, 0.73 mmol) was dissolved in 1,4-dioxan (3 ml) and 80% aqueous acetic acid (6 ml) was then added. The reaction was stirred at 50 °C for 1.5 h when t.l.c. (hexane : ethyl acetate, 2 : 1) showed only a trace of starting material (R_f 0.8), a major product (R_f 0.3) and a minor

product (R_f 0.1). The solvent was removed at 20 °C and the residue co-evaporated with toluene (3 x 5 ml). Purification by flash chromatography (hexane : ethyl acetate, 1 : 1) gave three products; the first to be eluted was unreacted starting material (20) (14 mg, 3%); the second fraction was the diol, *2-azido-1-O-tert-butyldiphenylsilyl-2-deoxy-3,4-O-isopropylidene-5-O-methanesulphonyl-D-glycero-D-talo-heptitol (21)* (344 mg, 79%), a viscous oil. (Found: C, 54.71; H, 6.94; N, 6.91. $C_{27}H_{39}N_3O_8SSi$ requires C, 54.61; H, 6.62; N, 7.08%); $[\alpha]_D^{20}$ - 40.5 ° (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3450 (br, OH), 2110 (N_3) cm^{-1}; δ_H ($CDCl_3$) 1.09 (9H, s, Me_3C), 1.33, 1.35 (6H, 2 x s, 2 x Me), 2.7 (1H, br. s, OH), 3.13 (3H, s, -SO_2Me) , 3.65 (1H, br s, OH), 3.8 (5H, m), 4.10 (1H, m), 4.21 (1H, dd, J 5.6 Hz, J 10.0 Hz), 4.46 (1H, t, J 5.5 Hz), 5.16 (1H, t, H-5, J 5.5 Hz), 7.43 (6H, m), 7.70 (4H, m); δ_C ($CDCl_3$) 19.0 (s, $\underline{C}Me_3$), 25.4 (q, $C\underline{Me}_3$), 26.7 (q, $C\underline{Me}_2$), 39.3 (q, -SO_2Me), 60.1 (d, C-2), 62.1, 64.9 (2 x t, C-1, C-7), 72.9, 74.7, 76.6, 78.4 (4 x d, C-3, C-4, C-5, C-6), 109.5 (s, $\underline{C}Me_2$), 127.9, 130.0 (2 x d, 2 x Ar-C), 132.8 (s, Ar-C), 136.0 (d, Ar-C). Continued elution yielded the tetrol, *2-azido-1-O-tert-butyldiphenylsilyl-2-deoxy-5-O-methanesulphonyl-D-glycero-D-talo-heptitol* (16 mg, 4%), a viscous oil which rapidly decomposed, δ_H: 1.09 (9H, s, Me_3C), 3.13 (3H, s, $MeSO_3$), 3.5-3.9 (8H, m), 4.04 (4H, m), 4.98 (1H, d, H-5, J 6.2 Hz), 7.44 (6H, m), 7.69 (4H, m); δ_C 18.9 (s, $\underline{C}Me_3$) , 26.6 (q, $C\underline{Me}_3$), 38.2 (q, $MeSO_3$), 62.3, 63.9 (2 x t, C-1, C-7), 64.9 (d, C-2), 70.2, 70.6, 71.4 , 79.2 (4 x d, C-3, C-4, C-5, C-6), 128.1, 130.2 (2 x d, 2 x Ar-C), 132.6 (s, Ar-C), 135.7 (d, ArC).

5,6-Anhydro-2-azido-1-O-tert-butyldiphenylsilyl-2-deoxy-3,4-O-isopropylidene-D-glycero-L-allo-heptitol (22). Saturated methanolic barium methoxide solution (0.5 ml) was added to a stirred solution of the diol (21) (457 mg, 0.77 mmol) in dry methanol (5 ml) at 0 °C. After 30 min at room temperature, t.l.c. (hexane : ethyl acetate, 1 : 1) indicated no starting material (R_f 0.25) and a single product (R_f 0.5). The solution was filtered, a small amount of solid carbon dioxide added to the filtrate and the solvent removed. Flash chromatography (hexane : ethyl acetate, 4 : 1) gave *5,6-anhydro-2-azido-1-O-tert-butyldiphenylsilyl-2-deoxy-3,4-O-isopropylidene-D-glycero-L-allo-heptitol (22)* (354 mg, 92%), a colourless oil. (Found: C, 62.74; H, 7.27; N, 8.14. $C_{27}H_{39}N_3O_8SiS$ requires C, 62.75; H, 7.09; N, 8.44%); $[\alpha]_D^{20}$ -12.3 ° (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3450 (br, OH) cm^{-1}; δ_H ($CDCl_3$) 1.10 (9H, s, Me_3C), 1.30, 1.36 (6H, 2 x s, 2 x Me), 1.70 (1H, br s, OH), 3.20 (2H, m, H-5, H-6), 3.63 (1H, ddd, H-2, $J_{1,2}$ 2.8 Hz, $J_{1',2}$ 6.8 Hz, $J_{2,3}$ 9.7 Hz), 3.74 (1H, m, H-7), 3.90 (1H, dd, H-1', $J_{1,1'}$ 10.8 Hz), 4.00 (1H, br d, H-7'), 4.02 (1H, t, H-4), 4.06 (1H, dd, H-1), 4.15 (1H, dd, H-3, $J_{3,4}$ 5.7 Hz), 7.46 (6H, m), 7.73 (4H, m); δ_C ($CDCl_3$) 19.0 (s, $\underline{C}Me_3$), 25.0 (q, Me), 26.5 (q, $C\underline{Me}_3$), 27.5 (q, Me), 52.2, 56.5 (2 x d, C-5, C-6), 61.0, 64.9 (2 x t, C-1, C-7), 61.6 (d, C-2), 75.2, 77.0 (2 x d, C-3, C-4), 109.5 (s, $\underline{C}Me_2$), 127.9, 130.0 (2 x d, 2 x Ar-C), 133.0 (s, Ar-C), 135.8 (d, Ar-C); *m/z* (NH_3, DCI) 470 ($M+H^+-N_2$, 100%).

5,6-Anhydro-2-azido-7-O-tert-butyldimethylsilyl-1-O-tert-butyldiphenylsilyl-2-deoxy-3,4-O-isopropylidene-D-glycero-L-allo-heptitol (23). *tert*-Butyldimethylsilyl chloride (122 mg, 0.81 mmol) was added, under nitrogen, to a stirred solution of the epoxyalcohol (22) (270 mg, 0.54 mmol) and imidazole (120 mg, 1.76 mmol) in dry DMF (5 ml) at 0 °C. The solution was allowed to warm to room temperature. After 2 h, t.l.c. (hexane : ethyl acetate, 1 : 1) showed only a trace of starting material (R_f 0.35) and one major product (R_f 0.8). The solvent was then removed and the residue dissolved in ether (10 ml), washed with water (5 ml) and brine (2 x 5 ml), and dried (magnesium sulphate). Removal of the solvent and purification by flash

chromatography (hexane : ethyl acetate, 6 : 1) gave *5,6-anhydro-2-azido-7-O-tert-butyldimethylsilyl-1-O-tert-butyldiphenylsilyl-2-deoxy-3,4-O-isopropylidene-D-glycero-L-allo-heptitol (23)* (280 mg, 84%), a viscous oil. $[\alpha]_D^{20}$ -3.3 ° (*c* 0.55 in $CHCl_3$); ν_{max} (film) 2110 (N_3) cm^{-1} ; δ_H ($CDCl_3$) 0.09 (6H, s, $SiMe_2$), 0.91, 1.09 (18H, 2 x s, 2 x Me_3C), 1.29, 1.36 (6H, 2 x s, 2 x Me), 3.11 (2H, br m, H-5, H-6), 3.66 (1H, ddd, H-2, $J_{1,2}$ 2.8 Hz, $J_{1',2}$ 6.7 Hz, $J_{2,3}$ 9.6 Hz), 3.75 (1H, dd, H-7', $J_{6,7'}$ 4.5 Hz, $J_{7,7'}$ 12.0 Hz), 3.88 (1H, dd, H-1', $J_{1',1}$ 10.8 Hz), 3.93 (1H, dd, H-7, $J_{7,6}$ 2.8 Hz), 4.01 (1H, t, H-4, J 6.0 Hz), 4.05 (1H, dd, H-1), 4.14 (1H, dd, H-3, $J_{3,4}$ 5.7Hz); δ_C ($CDCl_3$) -5.50 (q, $Si\underline{C}H_3$), 18.5, 19.0 (2 x s, 2 x $\underline{C}Me_3$), 25.1 (q, Me), 25.7, 26.6 (2 x q, 2 x $C\underline{H}_3$), 27.6 (q, Me), 52.3, 56.7 (2 x d, C-5, C-6), 61.6 (d, C-2), 62.5, 65.1 (2 x t, C-1, C-7), 73.5, 77.1 (2 x d, C-3, C-4), 109.4 (s, $\underline{C}Me_2$), 127.9, 130.0 (2 x d, 2 x Ar-C), 133.0 (s, Ar-C), 135.9 (d, Ar-C); *m/z* (NH_3, DCI) 584 ($M+H^+-N_2$, 50%).

7-O-tert-Butyldimethylsilyl-1-O-tert-butyldiphenylsilyl-2,5-dideoxy-2,5-imino-3,4-O-isopropylidene-D-glycero-D-talo-heptitol (24). The silyl protected azidoepoxyalcohol (23) (150 mg, 0.409 mmol) and palladium black (7 mg) were stirred in ethanol (4 ml) at room temperature under hydrogen. After 24 h, t.l.c (hexane : ethyl acetate, 2 : 1) indicated complete consumption of starting material (R_f 0.8) to give a single product (R_f 0.35), the cyclised amine. The reaction mixture was filtered through a small celite pad, washing with ethanol, and the solvent removed to give a colourless oil. Purification by flash column chromatography (hexane : ethyl acetate, 1 : 8) gave *7-O-tert-butyldimethylsilyl-1-O-tert-butyldiphenylsilyl-2,5-dideoxy-2,5-imino-3,4-O-isopropylidene-D-glycero-D-talo-heptitol (24)* (107 mg, 75%), a colourless oil. $[\alpha]_D^{20}$ -11.0 ° (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3200 (br OH & NH) cm^1; δ_H ($CDCl_3$) 0.08 (6H, s, $SiMe_2$), 0.89, 1.07 (18H, 2 x s, 2 x Me_3C), 1.33, 1.50 (6H, 2 x s, 2 x Me), 2.02 (br OH, NH), 3.14 (1H, dd, H-5, $J_{4,5}$ 4.3 Hz, $J_{5,6}$ 6.1 Hz), 3.34 (1H, t, H-2, J 6.2 Hz), 3.60 (4H, br m, H-1, H-1', H-7, H-7'), 3.86 (1H, br m, H-6), 4.68 (1H, d, H-3, $J_{3,4}$ 5.7 Hz), 4.75 (1H, dd, H-4), 7.39 (6H, m), 7.65 (4H, m); δ_C ($CDCl_3$) -5.6 (q, $Si\underline{C}H_3$), 18.1, 19.0 (2 x s, 2 x $\underline{C}Me_3$), 23.7, 25.7 (2 x q, 2 x Me), 25.9, 26.8 (2 x q, 2 x $C\underline{H}_3$), 62.2, 65.0 (2 x d, C-2, C-5), 64.4, 65.8 (2 x t, C-1, C-7), 71.6, 82.6, 83.6 (3 x d, C-3, C-4, C-6), 111.2 (s, $\underline{C}Me_2$), 127.9, 129.8 (2 x d, 2 x Ar-C), 133.2 (s, Ar-C), 135.7 (d, Ar-C); *m/z* (NH_3, DCI) 586 ($M+H^+$, 100%).

α-HomoDIM [2,5-Dideoxy-2,5-imino-D-glycero-D-talo-heptitol] (4). The cyclised amine (24) (52 mg, 0.09 mmol)was stirred in trifluoroacetic acid : water, 1 : 1 (2 ml) for 48 h. Removal of the solvent and purification by ion exchange chromatography with 'Dowex' 50W-X8 (H^+) then gave, after freeze drying, the free base as a gum. Addition of dilute hydrochloric acid and freeze drying gave the hydrochloride salt of *2,5-dideoxy-2,5-imino-D-glycero-D-talo-heptitol (4)* (16 mg, 78%), m.p. 148-149 °C (methanol / chloroform).(Found C, 36.30; H, 7.25; N, 5.83. $C_7H_{16}NO_5Cl$ requires C, 36.60; H, 7.02; N, 6.09%); $[\alpha]_D^{20}$ +26.9 ° (*c* 1.0 in H_2O); ν_{max} (KBr disc) 3350 (broad OH & NH), 2950 cm^{-1}; δ_H (D_2O) 3.59 (3H, m, H-2, H-5, H-7), 3.67 (1H, dd, H-7', $J_{7,7'}$ 12.1 Hz, $J_{7'6}$ 4.2 Hz), 3.76 (1H, dd, H-1, $J_{1,1'}$ 12.6, $J_{1,2}$ 5.8 Hz), 3.88 (1H, dd, H-1', $J_{1'2}$ 3.3 Hz), 4.02 (1H, m, H-6), 4.17 (1H, dd, H-4, $J_{3,4}$ 3.7 Hz, $J_{4,5}$ 9.3 Hz), 4.33 (1H, br t, H-3); δ_C (D_2O) 59.2, 62.1 (2 x d, C-2, C-5), 63.3, 63.7 (2 x t, C-1, C-7), 68.4, 71.5, 72.2 (3 x d, C-3, C-4, C-6); *m/z* (NH_3, DCI) 194 ($M+H^+$, 100%).

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