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SYNTHESIS FROM A HEPTONOLACTONE AND EFFECT ON GLYCOSIDASES OF (1S,2R,6R,7S)-1,2,6,7-TETRAHYDROXYPYRROLIZIDINE

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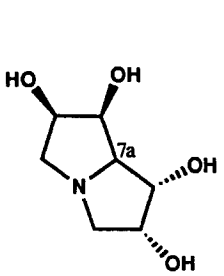
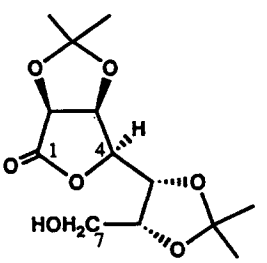
A five step synthesis of the pseudo C_2 symmetric (1S,2R,6R,7S)-1,2,6,7-tetrahydroxypyrrolizidine from 2,3:5,6-di-*O*-isopropylidene-D-*glycero*-D-*talo*-heptono-1,4-lactone is reported. The effects of structure of some polyhydroxylated pyrrolizidines and pyrrolidines on inhibition of mannosidases are compared.

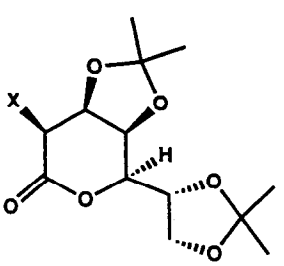
This paper describes the the synthesis of (1S,2R,6R,7S)-1,2,6,7-tetrahydroxypyrrolizidine (1) from the diacetonide of the γ-lactone of D-*glycero*-D-*talo*-heptonolactone (2),[1] in which nitrogen is initially introduced at C-7 of the lactone; the effect of (1) on human liver glycosidases is reported. Diacetonides of heptonolactones, with seven adjacent functional groups and five adjacent chiral centres, have a single hydroxyl group unprotected.[1] Such compounds are highly convenient starting materials for, among other targets, the synthesis of polyhydroxlyated nitrogen heterocycles; thus the protected δ-lactone of D-*glycero*-D-*talo*-heptonolactone (3) has only the C-2 hydroxyl group free and allows easy access to the corresponding azide (4).[2] Subsequent closure of the nitrogen function in (2) onto C-6 of the lactone allows the preparation of piperidines, such as homomannojirimycin (5),[3] whereas closure onto C-5 of the lactone leads to functionalised pyrrolidines such as (6).[4]



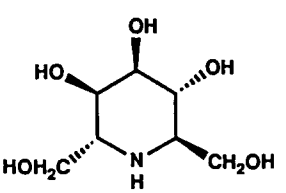
(1)



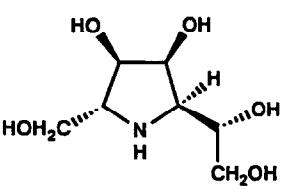
(2)



(3) R=OH (4) R=N_3

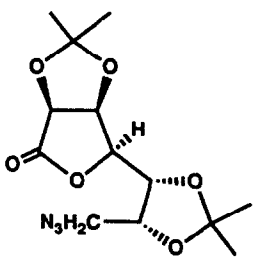


(5)

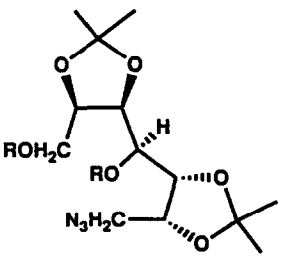


(6)

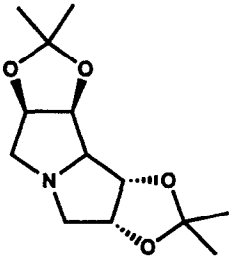
The synthesis of the homochiral pyrrolizidine (1) requires the joining by nitrogen of C-1, C-4 and C-7 of the diacetonide (2). A stereochemical feature of the pyrrolizidine (1), is that it possesses a chirotopic, non-stereogenic centre at C-7a and is pseudo C_2 symmetric (i.e. the molecule would possess C_2 symmetry other than for the centre at C-7a). C-7a in (1) is derived from C-4 of the sugar lactone, so that the introduction of nitrogen at this carbon with inversion or retention of configuration will still result in the synthesis of (1). Esterification of the primary alcohol in (2) with trifluoromethanesulphonic anhydride in the presence of pyridine, followed by displacement of the triflate with sodium azide in dimethylformamide, gave the fully protected azide (7) [89% yield]. Reduction of the lactone (7) with sodium borohydride in ethanol afforded the diol (8) [84% yield] which, on treatment with methanesulphonyl chloride in pyridine, was converted to the dimesylate (9) [82% yield]. Hydrogenation of the azide (9) in the presence of palladium black in ethanol gave the corresponding amine which, with sodium acetate, cyclised to the diisopropylidene pyrrolizidine (10) [81% yield]. Removal of the acetonides from (10) with aqueous trifluoroacetic acid gave the target pyrrolizidine (1) in 84% yield [42% overall yield from lactone (2)].



(7)

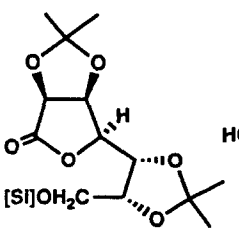


(8)R=H (9)R=SO_2Me



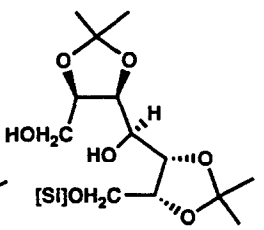
(10)

An alternative approach to the syntheis of the pyrrolizidine (1) might involve initial introduction of azide at C-4 of the sugar, followed by subsequent cyclisation of the nitrogen onto leaving groups at C-1 and C-7. Reduction of the silyl ether (11)[1] with sodium borohydride in ethanol gave the diol (12) [86% yield] which with *tert*-butylchlorodiphenylsilane gave the secondary alcohol (13) [77% yield]. Reaction of (13) with methanesulphonyl chloride in pyridine in the presence of DMAP gave the mesylate (14) [78% yield], suitable for introduction of nitrogen at C-4. Strong confirmatory evidence for the structure of the alcohol (13) was obtained by pyridinium chlorochromate oxidation to the corresponding ketone (15). Both the alcohol (13) and mesylate (14) are pseudo C_2 symmetric and have complex ^1H and ^{13}C NMR spectra; in contrast, the ketone (15) is C_2 symmetric with very much simpler NMR spectra.

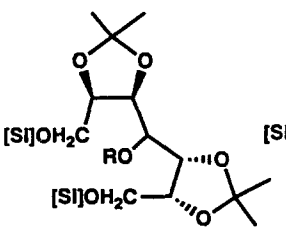


(11)

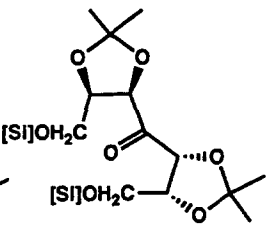
[Si]=Ph_2Bu^tSi



(12)

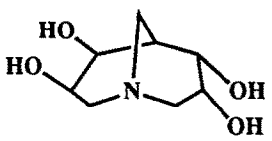


(13)R=H (14)R=SO_2Me

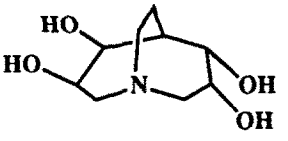


(15)

The symmetry features of compounds such as (13), (14) and (15) may be exploited in two methods of elaboration of the basic carbon skeleton. For acyclic molecules of this symmetry type, the method of two directional chain synthesis has been pioneered by Schreiber[5] in the synthesis of precursors of biologically active compounds. However in this case, an alternative strategy of one and two carbon chain extension reactions at the non-stereogenic centre would allow the synthesis of analogues of the pyrrolizidine structure, such as (16) and (17), which retain the C_2 pseudo symmetry. Furthermore a three carbon chain extension at C-4, coupled with the diastereoselective incorporation of two hydroxyl groups, may provide a synthetic route to (18), an extremely highly functionalised chiral tertiary amine possessing a C_3 axis of symmetry. At present there is considerable interest in, and some differing views about the mechanism of, the asymmetric dihydroxylation of olefins by osmium tetroxide in the presence of chiral amines;[6] such bicyclic amines as (1), (16), (17), and (18) may provide interesting probes on the course of this reaction.



(16)



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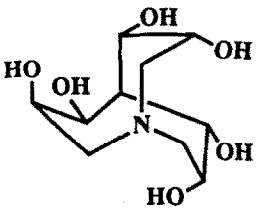
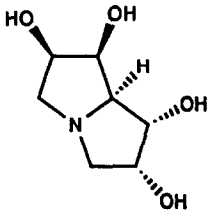


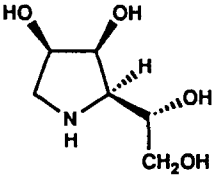
(18)

As part of a programme to study the effect of polyhydroxylated pyrrolizidines and related compounds as inhibitors of glycosidases,[7] the effect of the tetrahydroxylated pyrrolizidine (1) on the activity of 15 human liver glycosidases[8] was investigated. Although (1) is a moderrate inhibitor of α-L-fucosidase (76%) and β-D-galactosidase (53%) at a concentration of 1 mM, it is only a very weak inhibitor of the different forms of α-D-mannoisdase. This behaviour is in marked contrast to the very potent inhibition of these activities by DIM, 1,4-dideoxy-1,4-imino-D-mannitol, (19), a nitrogen analogue of the aza-furanose form of mannose. A comparison of the relative inhibitory properties of a series of analogues of (19) and of the pyrrolizidine (1) provides some insight into structural features affecting the relative potency of such structures as mannosidase inhibitors (Figure). N-Methylation of DIM, to give (20),[9] virtually abolishes inhibition of lysosomal α-D-mannosidase at the enzyme's pH optimum and also greatly decreases the inhibition of other α-mannosidases. The pyrrolizidine (1) is related to DIM (19) by an additional methylene bridge between the ring nitrogen and the carbon bearing the primary hydroxyl function, and is related to N-methyl DIM by elimination of hydrogen between the N-methyl and primary alcohol methylene groups. In contrast, 6-deoxy DIM (20),[10] a potent inhibitor of Jack bean α-mannosidase,[11] is an even more potent inhibitor of the human liver α-D-mannosidases than is DIM itself; accordingly, it is probable that the loss of freedom in regard to the side chain hydroxyl groups in (1) is an unimportant feature in its lack of glycosidase inhibition. The trihydroxypyrrolizidine (22),[12] a cyclised analogue of 6-deoxy DIM (20) and a ring contracted form of swainsonine (24), is a better inhibitor of the α-mannosidases than the tetrahydroxylated pyrrolizidine (1); in contrast, the trihydroxypyrrolizidine (23), the C-7 epimer of (22) is inactive towards the enzymes. This behaviour parallels the behaviour observed in the stereoisomers of swainsonine itself.[13]

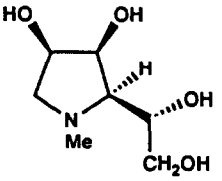
Acknowledgment: This work has been supported by the Science & Engineering Research Council and by G. D. Searle Monsanto.



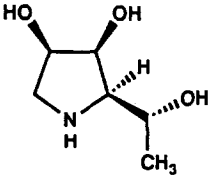
(1) [20,8,32]



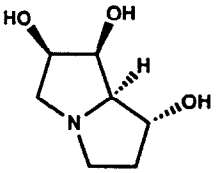
(19) [89,84,96]



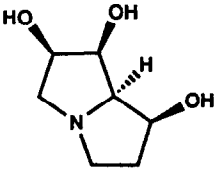
(20) [14,45,42]



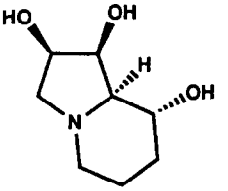
(21) [100,91,91]



(22) [50,35,44]



(23) [10,8,7]



(24) [100,89,98]

Figure: Numbers in [brackets] indicate the percentage inhibition at 1 mM concentration of inhibitor of respectively lysosomal, neutral and Golgi human liver α-D-mannosidases

Experimental

Melting points were recorded on a Kofler hot block and are corrected. Proton nuclear magnetic resonance (δ_H) spectra were recorded on Varian Gemini 200 (at 200 MHz), Bruker WH 300 (300 MHz), or Bruker WH 500 (500 MHz) spectrometers. ^{13}C Nuclear magnetic resonance (δ_C) spectra were recorded on a Varian Gemini 200 (50 MHz) spectrometer and multiplicities were assigned using DEPT sequence. ^{13}C Spectra run in D_2O were referenced to methanol (δ_C 49.6 ppm) as an internal standard. All chemical shifts are quoted on the δ-scale. Infra-red spectra were recorded on a Perkin-Elmer 781, or on a Perkin-Elmer 1750 FT spectrophotometer. Mass spectra were recorded on VG Micromass 30F, ZAB 1F, Masslab 20-250 or Trio-1 GCMS (DB-5 column) spectrometers using desorption chemical ionisation (NH_3, DCI) or fast atom bombardment (FAB), as stated. Optical rotations were measured on a Perkin-Elmer 241 polarimeter with a path length of 1 dm. 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 chromatography was carried out with Dowex 50x, 8-100 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. 2,3:5,6-Di-*O*-isopropylidene-D-*glycero*-D-*talo*-heptono-1,4-lactone (2) and 7-*O*-*tert*-butyldiphenylsilyl-2,3:5,6-di-*O*-isopropylidene-D-*glycero*-D-*talo*-heptono-1,4-lactone (11) were prepared from diacetone mannose.[1]

7-Azido-7-deoxy-2,3:5,6-di-O-isopropylidene-D-glycero-D-talo-heptono-1,4-lactone (7). 2,3:5,6-Di-*O*-isopropylidene-D-*glycero*-D-*talo*-heptono-1,4-lactone (2) (0.21 g , 0.73 mmol) was dissolved in dry dichloromethane (10 ml). Dry pyridine (0.12 ml, 2 equiv), was added and the solution stirred at -30°C, under nitrogen. Trifluoromethanesulphonic anhydride (0.183 ml, 1.5 equiv) was added slowly and the mixture allowed to warm up to room temperature at which point t.l.c.(ethyl acetate: hexane, 1:3) indicated complete product formation (R_f 0.4). The reaction mixture was worked up as quickly as possible. Ice cold brine (10 ml), a drop of dilute hydrochloric acid and a further 10ml of dichloromethane were added. The layers were separated and the aqueous layer was further extacted with dichloromethane (2 x 10 ml). The combined organic extracts were then dried with magnesium sulphate, filtered, and the solvent removed to produce an orange residue. Without further purification, this residue was dissolved in dry dimethylformamide (10 ml) and sodium azide (94 mg, 2 equiv based on quantitative triflation) added. The reaction mixture was stirred under nitrogen at room temperature for 12h when t.l.c. (ethyl acetate: hexane, 1:1) indicated the formation of a single product (R_f 0.8). The solvent was removed, dichloromethane (10 ml) was added, and the resulting solution filtered. The solvent was then removed and the residue purified by flash chromatography (ethyl acetate: hexane, 1:2) to yield *7-azido-7-deoxy-2,3:5,6-Di-O-isopropylidene-D-glycero-D-talo-heptono-1,4-lactone (7)* (0.20 g, 89% over 2 steps) as a colourless oil, $[\alpha]_D^{20}$ -38.7 (c, 1.00 in $CHCl_3$), ν_{max} (thin film): 2104 (N_3), 1790 (C=O) cm^{-1}; δ_H ($CDCl_3$): 1.35 (3H, s, Me), 1.39 (3H, s, Me), 1.41 (3H, s, Me), 1.48 (3H, s, Me), 3.54 (1H, dd, H-7, $J_{6,7}$ 6.1 Hz, $J_{7,7'}$ 12.5 Hz), 3.83 (1H, dd, H-7', $J_{6,7'}$ 7.4 Hz), 4.29 (1H, d, H-5, $J_{5,6}$ 7.4), 4.4-4.5 (1H, m, H-6), 4.66 (1H, s, H-4), 4.70 (1H, d, H-3, $J_{2,3}$ 5.5 Hz), 4.77 (1H, d, H-2). δ_C ($CDCl_3$): 24.34, 25.31, 25.83, 26.53 (4 x q, 4 x MeC), 50.70 (t, C-7), 75.04, 75.27, 75.96, 78.91, 79.45 (5 x d, C-2, C-3, C-4, C-5, C-6), 110.17, 113.34 (2 x s, 2 x CMe_2), 174.17 (s, C-1). m/z (NH_3 DCI): 331 ($M+NH_4^+$, 100%) , 286(MH^+-N_2, 90%), 288 ($M^+NH_4^+-HN_3$, 90%). (Found: C, 49.97 H, 6.40 N, 13.78. $C_{13}H_{19}O_6N_3$ requires: C, 49.84; H, 6.11; N, 13.41%).

7-Azido-7-deoxy-2,3:5,6-di-O-isopropylidene-D-glycero-D-talo-heptitol (8). 7-Azido-7-deoxy-2,3:5,6-di-*O*-isopropylidene-D-*glycero*-D-*talo*-heptono-1,4-lactone (7) (0.29 g, 0.94 mmol) was dissolved in ethanol (20 ml). Sodium borohydride (0.073 g, 2 equiv) was added and the solution stirred at room temperature under nitrogen. After 12 h t.l.c. (ethyl acetate:hexane, 1:1) indicated complete conversion to product (R_f 0.5). The reaction was quenched by addition of an excess of ammonium chloride with effervescence, filtered and the solvent removed to produce a residue which was purified by flash chromatography (ethyl acetate: hexane, 2:3) yielding *7-azido-7-deoxy-2,3:5,6-di-O-isopropylidene-D-glycero-D-talo-heptitol (8)* (0.25 g, 84%) as a colourless viscous oil; $[\alpha]_D^{20}$ +3.5 (c, 1.00 in $CHCl_3$), ν_{max} (thin film): 3450 (broad OH), 2100 (N_3) cm^{-1}; δ_H ($CDCl_3$): 1.37 (3H, s, Me), 1.41(6H, s, 2 x Me), 1.42 (3H, s, Me), 3.51 (1H, dd, H-7, $J_{6,7}$ 4.2 Hz, $J_{7,7'}$ 12.6 Hz), 3.67 (1H, dd, H-7', $J_{6,7'}$ 7.4 Hz), 3.78-3.9 (3H, m), 4.14 (1H, dd, J 6.1, 9.6 Hz), 4.34-4.45 (3H, m). δ_C ($CDCl_3$): 24.67, 25.85, 26.91, 27.48 (4 x q, 4 x MeC), 51.45 (t, C-7), 60.47 (t, C-1), 66.92, 75.75, 76.04, 76.72, 77.29 (5 x d, C-2, C-3, C-4, C-5, C-6), 108.69, 108.94 (2 x s, 2 x CMe_2). m/z (NH_3 DCI): 290 (MH^+-N_2, 100%). (Found: C, 49.50; H, 7.60; N, 13.15%. $C_{13}H_{23}N_3O_6$ requires: C, 49.20; H, 7.30; N, 13.26%).

7-Azido-7-deoxy-2,3:5,6-di-O-isopropylidene-1,4-di-O-methanesulphonyl-D-glycero-D-talo-heptitol (9). 7-Azido-7-deoxy-2,3:5,6-di-*O*-isopropylidene-D-*glycero*-D-*talo*-heptitol (8) (0.182 g, 5.7 mmol),and DMAP (1mg, cat) were dissolved in dry pyridine (8 ml) and stirred at 0°C under nitrogen. Methanesulphonyl chloride

(0.28 ml, 6 equiv), was added slowly and after 4h the reaction was allowed to warm up to room temperature. After a further 12h t.l.c (ethyl acetate: hexane, 2:3) indicated the formation of a major product (R_f 0.4) and also a small amount of a side product (R_f 0.8). The solvent was removed to produce a brown oil which was dissolved in ethyl acetate (15 ml) and washed with water (10 ml). After drying (magnesium sulphate), the solvent was removed to produce a residue which was purified by flash chromatography (ethyl acetate: hexane, 1:2) to afford *7-azido-7-deoxy-2,3:5,6-di-O-isopropylidene-1,4-di-O-methanesulphonyl-D-glycero-D-talo-heptitol (9)* (0.22 g, 82%) as a colourless viscous oil ; ν_{max} (thin film): 2105 (N_3) cm^{-1}; δ_H ($CDCl_3$): 1.37 (3H, s, Me), 1.42 (3H, s, Me), 1.52 (3H, s, Me), 1.59 (3H, s, Me), 3.11 (3H, s, MeSO$_2$), 3.22 (3H, s, MeSO$_2$), 3.51 (2H, d, H-7, H-7', J 4.6 Hz), 4.32 (1H, dd, J 5.8, 8.4 Hz), 4.36-4.42 (2H, m), 4.46-4.56 (3H, m), 5.21 (1H, t, J 8.4 Hz). δ_C ($CDCl_3$): 24.93, 25.31, 26.39, 27.23 (4 x q, 4 x MeC), 37.21, 39.31 (2 x q, 2 x MeSO$_2$), 51.24 (t, C-7), 68.88 (t, C-1), 74.69, 75.99, 76.30, 76.66, 77.17 (5 x d, C-2, C-3, C-4, C-5, C-6), 109.34, 110.18 (2 x s, 2 x CMe$_2$). m/z (NH_3 DCI): 446 (MH^+-N_2, 100%), 491 ($M+NH_4^+$, 75%).

1S,2R,6R,7S-1,2:6,7-Di-O-isopropylidene-1,2,6,7-tetrahydroxypyrrolizidine (10). 7-Azido-7-deoxy-2,3:5,6-di-*O*-isopropylidene-1,4-di-*O*-methanesulphonyl-D-*glycero*-D-*talo*-heptitol (9) (0.16 g, 3.38 mmol) was dissolved in ethanol (10 ml) and palladium black (10 mg) was added. After degassing the solution, the reaction mixture was stirred vigorously under hydrogen for 15h when t.l.c. (ethyl acetate: hexane, 1:1) indicated complete formation of a product at the baseline. The reaction mixture was filtered through celite to remove the catalyst, sodium acetate (83 mg, 3 equiv) was added and the mixture stirred at 50°C under nitrogen. After 24h t.l.c. (ethyl acetate: methanol, 9:1) indicated complete product formation (R_f 0.4). The solvent was removed and the residue purified by flash chromatography (eluant ethyl acetate, increasing polarity to ethyl acetate: methanol, 9:1) yielding *1S,2R,6R,7S-1,2:6,7-di-O-isopropylidene-1,2,6,7-tetrahydroxy pyrrolizidine (10)* (70 mg, 81%) as a pale yellow solid, m.p. 68-70°C; $[\alpha]_D^{20}$ -10.0 (c, 1.00 in $CHCl_3$), δ_H ($CDCl_3$): 1.29 (3H, s, Me), 1.34 (3H, s, Me), 1.45 (3H, s, Me), 1.54 (3H, s, Me), 3.0 (1H, dd, H-3, $J_{2,3}$ 4.7 Hz, $J_{3,3'}$ 14.4 Hz), 3.17 (1H, d, H-3'), 3.26 (1H, d, H-5, $J_{5,5'}$ 10.9 Hz), 3.42-3.50 (2H, m, H-5', H-7a), 4.66-4.70 (1H, m, H-2), 4.76-4.81 (2H, m, H-1, H-6), 4.94 (1H, d, H-7, $J_{6,7}$ 6.2 Hz) . δ_C ($CDCl_3$): 22.68, 23.81, 25.77, 26.06 (4 x q, 4 x MeC), 54.93, 59.22 (2 x t, C-3, C-5), 73.8 (d, C-7a), 79.7, 81.6, 81.8, 83.4 (4 x d, C-1, C-2, C-6, C-7), 110.72, 111.77 (2 x s, 2 x CMe$_2$). m/z (NH_3 DCI): 256 ($M+H^+$,100%). (Found: C, 60.96; H, 8.42; N, 5.24%. $C_{13}H_{21}NO_4$ requires: C, 61.16; H, 8.29; N, 5.49%).

1S,2R,6R,7S-1,2,6,7-Tetrahydroxypyrrolizidine (1) 1S,2R,6R,7S-1,2:6,7-Di-*O*-isopropylidene-1,2,6,7-tetrahydroxypyrrolizidine (10) (61 mg, 0.24 mmol) was dissolved in 40% aqueous trifluoroacetic acid and stirred at room temperature for 12 h when t.l.c (ethyl acetate: methanol, 9:1) indicated complete formation of a single product (R_f 0.1). The solvent was evaporated , the residue dissolved in water and purified by ion exchange chromatography (H^+ form), eluting with 0.5 M aqueous ammonia. Freeze drying yielded *1S,2R,6R,7S-1,2,6,7-tetrahydroxy pyrrolizidine (1)* (34 mg, 84%) as a white solid m.p. 170-175°C (decomp), $[\alpha]_D^{20}$ -27.2 (c, 0.965 in H_2O), ν_{max} (KBr) 3500 (br, OH); δ_H (D_2O): 2.51(1H, m, H-3, $J_{3,3'}$ 10 Hz), 2.77 (1H, dd, H-5', $J_{5,5'}$ 12 Hz, $J_{5,6}$ 4 Hz), 3.05-3.13 (2H, m, H-5, H-3) 3.39 (1H, t, H-7a, J 6 Hz), 4.08-4.13 (2H, m, H-1, H-2), 4.19 (1H, m, H-6), 4.34 (1H, dd, H-7, $J_{6,7}$ 4 Hz) . δ_C ($CDCl_3$): 56.2, 59.6 (2 x t, C-3, C-5), 70.1, 70.2, 71.3, 73.4, 73.5 (5 x d, C-1, C-2, C-6, C-7,C-7a), . m/z (NH_3 DCI): 176 (M^+H^+,100%). A small portion was then dissolved in water, dilute hydrochloric acid (1 ml) was added, the

solvent removed and the residue recrystalised from methanol/chloroform to yield the *hydrochloride salt of (1)*, m.p. 127-129°C δ_C ($CDCl_3$): 55.5, 60.8 (2 x t, C-3, C-5), 69.4, 70.6, 72.5, 72.6, 72.7 (5 x d, C-1, C-2, C-6, C-7, C-7a) (Found: C, 34.84, H, 6.64; N, 6.12%. $C_{13}H_{21}NO_4(H_2O)_{1.5}$ requires: C, 35.23 ; H, 6.76 ; N, 5.87 %).

7-O-tert-Butyldiphenylsilyl-2,3:5,6-di-O-isopropylidene-D-glycero-D-talo-heptitol (12). 7-*O*-*tert*-Butyldiphenylsilyl-2,3:5,6-di-*O*-isopropylidene-D-*glycero*-D-*talo*-heptono-1,4-lactone (11)[1] (0.39 g, 0.74 mmol), was dissolved in ethanol (20 ml), sodium borohydride (73 mg, 2 equiv) was added and the mixture was stirred at room temperature for 16h. At this point t.l.c. (ethyl acetate: hexane, 1:3) indicated complete product formation (R_f 0.2). The reaction was quenched by addition of excess solid ammonium chloride with effervescence. Filtration of the mixture followed by evaporation of the solvent gave a residue which was purified by flash chromatography (eluant ethyl acetate: hexane, 1:5) to yield *7-O-tert-butyldiphenylsilyl-2,3:5,6-di-O-isopropylidene-D-glycero-D-talo-heptitol (12)* (0.34 g, 86%), as a colourless viscous oil; $[\alpha]_D^{20}$ -23.6 (c, 1.02 in $CHCl_3$), ν_{max} (film): 3500 (br, OH) cm^{-1}; δ_H ($CDCl_3$): 1.08 (9H, s, Bu^t), 1.39 (3H, s, Me), 1.40 (3H, s, Me), 1.41 (3H, s, Me), 1.52 (3H, s, Me), 3.80-3.92 (3H, m), 4.05-4.12 (2H, m), 4.23-4.32 (2H, m), 4.40-4.46 (1H, m), 4.49 (1H, d, J 7 Hz), 7.37-7.50 (6H, m, ArH), 7.66-7.75 (4H, m, ArH). δ_C ($CDCl_3$): 19.0 ($SiCMe_3$), 24.7, 25.11, 26.47, 27.74 (4 x q, 4 x MeC), 26.63 (q, ^tBu), 60.7 (t, C-1), 62.1 (t, C-7), 67.5, 75.8, 76.5, 77.6, 77.7 (5 x d, C-2, C-3, C-4, C-5, C-6), 108.5 (s, 2 x CMe_2), 128.0, 130.2, 135.7 (3 x d, ArC), 132.7 (s, ArC). m/z (NH_3, DCI): 395 ($M+H^+$-[^tBu+Ph], 100%), 531 (MH^+). (Found: C, 65.13; H, 8.43. $C_{29}H_{42}O_7Si$ requires: C, 65.63; H, 7.98%).

1,7-Di-O-tert-butyldiphenylsilyl-2,3:5,6-di-O-isopropylidene-D-glycero-D-talo-heptitol (13) 7-*O*-*tert*-Butyldiphenylsilyl-2,3:5,6-di-*O*-isopropylidene-D-*glycero*-D-*talo*-heptitol (12) (0.28 g, 0.52 mmol) and imidazole (77 mg, 2.2 equiv) were dissolved in dry dimethylformamide (8ml) and stirred at 0°C under nitrogen. *tert*-Butylchlorodiphenylsilane (0.16 ml, 1.2 equiv) was added dropwise and the reaction mixture allowed to warm up to room temperature. After 4 h t.l.c. (ethyl acetate: hexane, 1:3) indicated complete product formation (R_f 0.7). The solvent was removed and the crude reaction mixture partitioned between water (20 ml) and ether (15 ml). The layers were seperated and the aqueous layer further extracted with ether (2 x 15 ml). The combined organic extracts were washed with brine (3 x 10 ml), dried (magnesium sulphate) and filtered. Evaporation of the solvent followed by flash chromatography (dichloromethane: hexane, 3:1 increasing polarity to neat dichloromethane) yielded *1,7-di-O-tert-butyldiphenylsilyl-2,3:5,6-di-O-isopropylidene-D-glycero-D-talo-heptitol (13)* (0.305g, 77%) as a colourless viscous oil; $[\alpha]_D^{20}$ -10.9 (c, 1.01 in $CHCl_3$), ν_{max} (film): 3500 (br, OH) cm^{-1}; δ_H ($CDCl_3$): 1.01, 1.02 (18H, 2 x s, 2 x ^tBu), 1.34 (3H, s, Me), 1.35 (3H, s, Me), 1.37 (3H, s, Me), 1.50 (3H, s, Me), 3.37 (1H, d, OH, J 5.2 Hz), 3.75 (1H, dd, J 11 Hz, 6 Hz), 3.90-4.09 (4H, m), 4.19-4.45 (4H, m), 7.29-7.43 (12H, m, ArH), 7.64-7.68 (8H, m, ArH). δ_C ($CDCl_3$): 19.0 ($SiCMe_3$), 25.0, 25.4, 27.9 (q, 4 x MeC), 26.7 (q, 2 x ^tBu), 62.9 (t, C-1, C-7), 67.1, 76.2, 76.7 (d, C-2, C-3, C-4, C-5, C-6), 108.5 (s, 2 x CMe_2), 127.8, 129.9, 135.7 (3 x d, ArC), 133.2, 133.3 (2 x s, ArC). m/z (NH_3, DCI): 691 (M^+-^tBu), 711 (M^+-Ph), 769 ($M+H^+$), 786 ($M+NH_4^+$) . (Found: C, 70.35; H, 7.74 . $C_{45}H_{60}O_7Si_2$ requires: C, 70.27; H, 7.86%).

1,7-Di-O-tert-butyldiphenylsilyl-2,3:5,6-di-O-isopropylidene-4-O-methanesulphonyl-D-glycero-D-talo-heptitol (14). 1,7-Di-*O*-*tert*-butyldiphenylsilyl-2,3:5,6-di-*O*-isopropylidene-D-*glycero*-D-*talo*-heptitol (13) (90

mg, 0.12 mmol) was dissolved in dry pyridine (5 ml) and stirred at 0°C under nitrogen. Methanesulphonyl chloride (0.06 ml, 6 equiv) and 4-(N,N-dimethylamino)-pyridine (1 mg) were added and the mixture allowed to warm up to room temperature. After 24 h, t.l.c. (ethyl acetate: hexane, 1:3) indicated the formation of a single product (R_f 0.6). The solvent was removed and the residue shaken with water (10 ml) and ether (10 ml). The layers were seperated and the aqueous layer further extracted with ether(2 x 10 ml). The combined organic extracts were then dried (magnesium sulphate), filtered and the solvent removed. The residue was then purified by flash chromatography (eluant ethyl acetate: hexane, 1:5) to yield *1,7-di-O-tert-butyldiphenylsilyl-2,3:5,6-di-O-isopropylidene-4-O-methanesulphonyl-D-glycero-D-talo-heptitol (14)* (77 mg, 78%) as a yellow white solid m.p. 32-35°C; δ_H ($CDCl_3$): 1.07, 1.11 (18H, 2 x s, 2 x ^{t}Bu), 1.28 (3H, s, Me), 1.29 (3H, s, Me), 1.36 (3H, s, Me), 1.42 (3H, s, Me), 2.97 (3H, s, $MeSO_2$), 3.69-3.98 (3H, m), 4.17-4.26 (2H, m), 4.37-4.56 (3H, m), 5.27 (1H, dd, H-4, J 3.2, 7.5 Hz), 7.38-7.42 (12H, m, ArH), 7.69-7.76 (8H, m, ArH). δ_C ($CDCl_3$): 19.0, 19.1 (2 x s, 2 x Si<u>C</u>Me_3), 25.22, 25.51, 27.13 (q, 4 x <u>Me</u>C), 26.72 (q, 2 x ^{t}Bu), 39.16 (q, <u>Me</u>SO_2), 62.44, 63.36 (2 x t, C-1, C-7), 75.77, 77.62, 78.27, 78.27, 78.46 (5 x d, C-2, C-3, C-4, C-5, C-6), 108.33, 108.87 (2 x s, 2 x <u>C</u>Me_2), 127.87, 129.87, 135.8 (3 x d, 3 x ArC), 129.86 (s, ArC). <u>m/z</u> (FAB, NaOAc): 847 (MH^+), 869 ($M+Na^+$, 100%).

1,7-Di-O-tert-butyldiphenylsilyl-2,3:5,6-di-O-isopropylidene-D-manno-hept-4-ulose (15). 1,7-Di-*O*-*tert*-butyldiphenylsilyl-2,3:5,6-di-*O*-isopropylidene-D-*glycero*-D-*talo*-heptitol (13) (200 mg, 0.26 mmol), powdered molecular sieve (300 mg) and pyridinium chlorochromate (168 mg, 3 equiv) were stirred at room temperature in dry dichloromethane (8 ml) under nitrogen for 24 h. Ether (15 ml) was then added and the mixture filtered through a silica plug (ether eluant) topped with celite. The solvent was then removed to leave a crude product which was purified by flash chromatography (ethyl acetate: hexane, 1:9) to yield *1,7-di-O-tert-butyldiphenylsilyl-2,3:5,6-di-O-isopropylidene-D-manno-hept-4-ulose (15)*, (159 mg, 80%) as a colourless viscous oil; ν_{max} (film): 1744 (C=O) cm^{-1}; δ_H ($CDCl_3$): 1.10 (18H, s, 2 x Bu^t), 1.27 (6H, s, 2 x Me), 1.55 (6H, s, 2 x Me), 3.76 (4H, d, J 6.2 Hz, H-1, H-1', H-7, H-7'), 4.44-4.54 (2H, m, H-2, H-6), 5.15 (2H, d, J 7 Hz, H-3, H-5), 7.36-7.44 (12H, m, ArH), 7.69-7.73 (8H, m, ArH). δ_C ($CDCl_3$): 19.0 (Si<u>C</u>Me_3), 25.4, 26.5 (q, 4 x <u>Me</u>C), 26.8 (q, 2 x <u>C</u>Me_3), 62.6 (t, C-1, C-7),78.4, 80.2 (2 x d, C-2, C-3, C-5, C-6), 110.4 (s, 2 x <u>C</u>Me_2), 127.9, 130.0, 135.8 (3 x d, ArC), 133.0 (s, ArC). <u>m/z</u> (NH_3, DCI): 784 ($M+NH_4^+$).

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