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RETENTION AND APPARENT INVERSION DURING AZIDE DISPLACEMENT OF α-TRIFLATES OF 1,5-LACTONES

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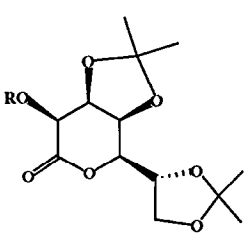
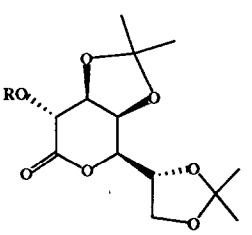
Reactions of azide ion with 2-O-trifluoromethanesulphonates of both 3,4:6,7-di-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone and of 3,4:6,7-di-O-isopropylidene-D-glycero-D-galacto-heptono-1,5-lactone give predominantly 2-azido-2-deoxy-3,4:6,7-di-O-isopropylidene-D-glycero-D-galacto-heptono-1,5-lactone initially which then isomerises under the reaction conditions to 2-azido-2-deoxy-3,4:6,7-di-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone. X-ray crystal structure analyses of 3,4:6,7-di-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone and 2-azido-2-deoxy-3,4:6,7-di-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone are reported.

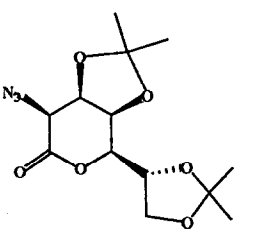
Sugar lactones have been used as intermediates for the synthesis of highly functionalised nitrogen heterocycles.[1] The readily available acetonide of glucuronolactone, in which only the C-5 hydroxyl group α- to the carbonyl group is unprotected, has been used in the synthesis of a number of D- and L-amino acids.[2] Suitably protected heptonolactones with seven adjacent functional groups and five adjacent chiral centres may provide powerful intermediates for the synthesis of complex and highly functionalised targets. The epimeric lactones (1) and (3) may be obtained as a mixture in 39% yield, in which the lactone (1) predominates, from the treatment of diacetone mannose (7) with sodium cyanide.[3] The stereoselectivity in this reaction is in marked contrast to that observed in the reaction of cyanide with mannose.[4] This paper describes the nucleophilic azide ion displacement of both of the protected heptonolactone 2-O-trifluoromethanesulphonates (2) and (4), derived from (1) and (3) respectively, to give initially the galacto-azide (6) which is subsequently epimerised to talo-azide (5) under the reaction conditions.



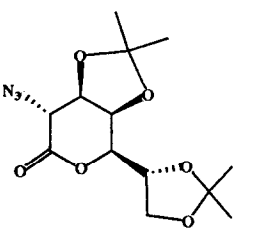
(1) R=H
(2) R=SO_2CF_3



(3) R=H
(4) R=SO_2CF_3



(5)



(6)

The talo-hydroxylactone (1) was esterified with triflic anhydride to give the stable talo-triflate (2) in 93% yield. Reaction of the triflate (2) with excess sodium azide in dimethyl formamide at room temperature for 4 h gave the talo-azide (5) in 81% yield in which the configuration at C-2 of the lactone had been retained. It was found, by monitoring the progress of the azide displacement reaction by TLC, that nearly all the triflate (2) first gives the inverted galacto-azide (6) which equilibrates under the reaction conditions to the more stable talo-azide. Thus the galacto-azide (6) may be isolated in 54% yield [based on unrecovered triflate (2)] under kinetic conditions; this yield for the preparation of (6) has not been optimised. The isolated galacto-azide (6) was shown to equilibrate to the talo-azide (5) both under the reaction conditions for the displacement and also on treatment with sodium acetate in dimethyl formamide. When the triflate (2) was treated with sodium azide in dimethyl formamide in the presence of deuterium oxide and the reaction mixture worked up after 4 min,, the starting talo-triflate (2) was recovered in 46% yield with 60% deuterium incorporated at C-2 and the galacto-azide (6) was isolated in 37% yield with 50% deuterium incorporated at C-2; a small amount (about 2%) of the talo-azide (5) was isolated with 90% deuterium incorporated at C-2. No galacto-triflate (4) was isolated from the reaction mixture. When the azide displacement in the presence of deuterium oxide was run for 90 min, no triflates were isolated but both the talo-azide (37% yield) and the galacto-azide (38% yield), each with greater than 90% deuterium incorporation at C-2, were formed.

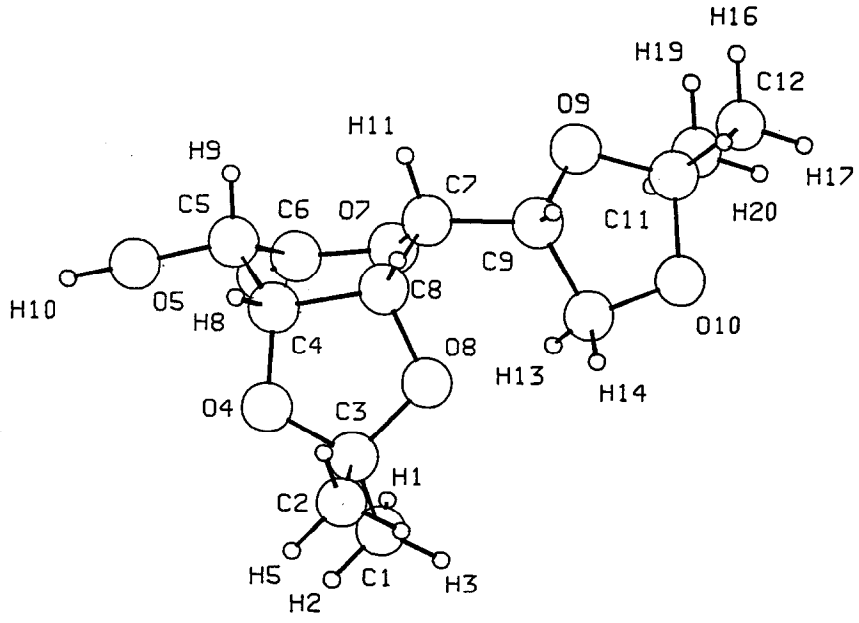


FIGURE. X-Ray molecular structure of 3,4:6,7-di-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone (1) showing crystallographic numbering scheme

The galacto-hydroxylactone (3) was also esterified with triflic anhydride to give the galacto-triflate (4) in high yield; however, in contrast to the kinetic stability of the talo-triflate (2), (4) is more labile and decomposes on standing at room temperature. Nonetheless, (4) undergoes an efficient displacement of triflate by azide with inversion of configuration to give the talo-azide (5) in 82% yield. It was initially assumed that the inverted azide (5) was formed by a direct displacement reaction; however, investigation of the reaction by TLC showed that the triflate (4) was consumed rapidly to give a mixture containing the epimeric triflate (3), the galacto-azide (6) and a minor amount of the talo-azide (5). The galacto-triflate (4) was rapidly epimerised to the talo-triflate by treatment with sodium acetate in dimethyl formamide. Thus the major pathway for the formation of the talo-azide (5) from galacto-triflate (4) involves initial epimerisation of (4) to the talo-triflate (2), direct displacement to give the galacto-azide (6), followed by a second epimerisation to give the thermodynamically more stable azide (5). Further evidence for the double epimerisation pathway was provided by deuterium incorporation experiments. Thus treatment of (4) with sodium azide in dimethyl formamide in the presence of deuterium oxide for 10 min at room temperature gave talo-triflate (33% isolated yield with greater than 90% deuterium incorporated at C-2), galacto-azide (6) (30% isolated yield with greater than 90% deuterium incorporated at C-2), and talo-azide (5) (16% isolated yield with 20% deuterium incorporated at C-2); no galacto-triflate was recovered from the reaction mixture. These results indicate that the predominant pathway for the formation of the talo-azide involves a double epimeristaion and that direct displacement of triflate by azide constitutes a minor competing pathway.

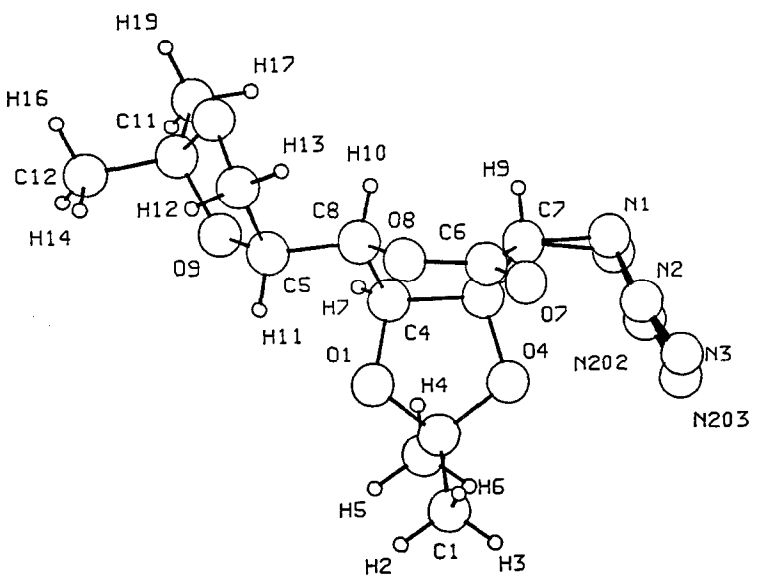
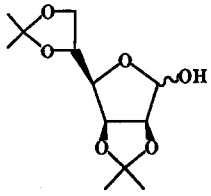
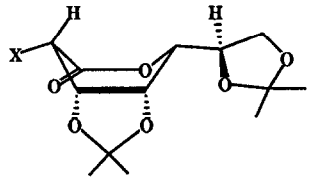


FIGURE. X-Ray molecular structure of 2-azido-2-deoxy-3,4:6,7-di-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone (5) showing crystallographic numbering scheme

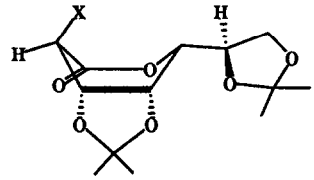


(7)



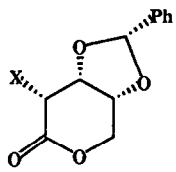
talo

(1) X=OH (2) X=SO_2CF_3
(5) X=N_3

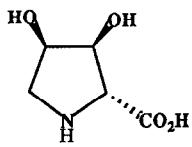


galacto

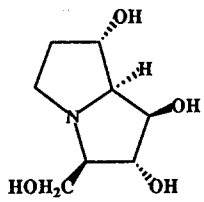
(3) X=OH (4) X=SO_2CF_3
(6) X=N_3



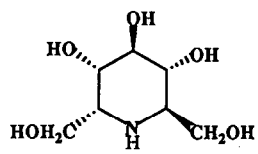
(8) X=OSO_2CF_3
(9) X=N_3



(10)



(11)



(12)

Although the coupling constants ($J_{H-2,H-3}$) between the talo-compounds (1) (3.5 Hz), triflate (2) (3.3 Hz) and azide (5) (3.3 Hz) were consistently higher than those for for the galacto-compounds (3) (2.5 Hz) and azide (6) (2.1 Hz), such small differences could not reasonably be used with confidence to establish the stereochemistry of the substituent at C-2. The structures of the talo-hydroxylactone (1) and the talo-azidolactone (5) were firmly established by single crystal X-ray analysis (see FIGURES). The high carbonyl stretching frequencies (up to 1793 cm^{-1}) of all the 1,5-lactones in this paper are consistent with boat conformations for all the compounds reported.[5]

All the results in this paper are consistent with the hypothesis that the galacto-compounds (3), (4) and (6) are thermodynamically less stable than the corresponding talo-isomers (1), (2) and (5) because in the boat form of the galacto-isomers the 2-substituent is in a flag-pole position whereas in the talo-compounds the substituents are in less sterically hindered bowsprit positions. Thus, the equilibrations of the galacto-triflate and the galacto-azide to the corresponding talo-isomers may take place via the anion derived by removal of the the proton at C-2. Also, the direct displacement of triflate from the galacto-triflate (4) by azide is slower than equilibration of (4) to the more stable talo-epimer (2); thus the apparent inversion by azide in the displacement of triflate from C-2 of the galactono-lactone (4) occurs by epimerisation of (4) to the more stable triflate (2) followed by displacement with inversion to give the less stable azide (6) which subsequently isomerises to the more stable azide (5).

The triflate of a protected ribono-1,5-lactone (8) has been shown to undergo nucleophilic displacement by azide in high yield to give the ribo-azide (9) in which the configuration at C-2 is retained; (9) has been used for the synthesis of D-amino acids such as (2R,3S,4R)-dihydroxyproline (10).[6] The talo-azide (5), with 5 adjacent chiral centres, is an intermediate which may allow the synthesis of α-amino acids with seven adjacent functional groups and five adjacent chiral centres, and may also provide strategies for the synthesis of such highly functionalised alkaloids as alexine (11)[7] and homonojirimycin (12).[8]

Experimental

M.p.s were recorded on a Kofler block. Infra red spectra were recorded in solution on a Perkin-Elmer 781 spectrophotometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter; concentrations are given in g/100ml. ^{1}H NMR spectra were run at 200 MHz on a Varian Gemini 200 spectrometer, or at 300 MHz on a Bruker WH 300 spectrometer. ^{13}C NMR spectra were recorded at 50 MHz on a Varian Gemini 200 spectrometer. Mass spectra were recorded on VG Micromass ZAB 1F spectrometer. Microanalyses were performed by the microanalytical services of the Dyson Perrins Laboratory. TLC was performed on glass plates coated with silica gel Blend 41, and compounds were visualised with a spray of 0.2% w/v ceric sulphate and 5% ammonium molybdate in 2M sulphuric acid. Flash chromatography was carried out using Merck Kieselgel 60, 230-400 mesh. Dimethyl formamide and dichloromethane were distilled from calcium hydride immediately prior to use. D-Mannose was obtained from Sigma Chemical Company and was converted into 2,3:5,6-di-O-isopropylidene-D-mannofuranose in 80%-90% yield as previously described.[9]

3,4:6,7-Di-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone (1) and 3,4:6,7-Di-O-isopropylidene-D-glycero-D-galacto-heptono-1,5-lactone (3). A mixture of 2,3:5,6-di-O-isopropylidene-D-mannofuranose (7) (10.8 g, 41.0 mmol), sodium cyanide (1.84 g, 38.0 mmol) and sodium hydrogen carbonate (3 g) in water (200 ml) was stirred at room temperature for 4 days after which time a clear solution was obtained which was free of cyanide. The reaction mixture was then heated at 90°C for 1.5 h, cooled to room temperature and extracted with dichloromethane (2 x 20 ml); the dichloromethane layer was dried (sodium sulphate) and the solvent removed to give unreacted starting material (7) (1.84 g, 17%). The aqueous layer was adjusted to pH 3 by dropwise addition of concentrated sulphuric acid and then extracted with ethyl acetate (3 x 150 ml). The combined ethyl acetate extracts were dried (sodium sulphate) and the solvent removed to give a residue which, after purification by flash chromatography [ethyl acetate:hexane, 1:2], gave:

3,4:6,7-di-O-isopropylidene-D-glycero-D-galacto-heptono-1,5-lactone (3), R_f 0.7 (ethyl acetate:hexane, 2:1) and R_f 0.6 (ethyl acetate:hexane, 1:1), (0.78 g, 6.6% yield, 8% based on unrecovered starting material), m.p. 140°-141°C

(ether:hexane), $[\alpha]_D^{20}$ +93.4° (c, 1.2 in $CHCl_3$), ν_{max} ($CHCl_3$): 3350 (OH), 1755 (C=O) cm^{-1}; δ_H ($CDCl_3$): 1.39 (3H, s, Me), 1.40 (3H, s, Me), 1.42 (3H, s, Me), 1.47 (3H, s, Me), 3.06 (1H, br d, HO, J 3.9 Hz), 4.11 (1H, dd, H-7, $J_{6,7}$ 4.3 Hz, $J_{7,7'}$ 9.2 Hz), 4.16 (1H, dd, H-7', $J_{6,7'}$ 5.7 Hz), 4.40 (1H, ddd, H-6, $J_{5,6}$ 8.6 Hz), 4.42 (1H, H-2), 4.61 (1H, dd, H-3, $J_{2,3}$ 2.5 Hz, $J_{3,4}$ 7.4 Hz), 4.67 (1H, dd, H-4, $J_{4,5}$ 1.7), 4.72 (1H, dd, H-5). δ_C ($CDCl_3$): 23.88, 24.94, 25.70, 26.72 (4 x q, 4 x MeC), 66.54 (t, C-7) 69.17 (d, C-2), 71.07, 72.89, 75.22, 76.25 (4 x d, 4 x CHO), 109.93, 110.46 (2 x s, 2 x Me_2C), 170.13 (s, C-1). m/z (NH_3, DCI): 306 ($M+NH_4^+$, 90%), 289 ($M+H^+$, 100%). (Found: C, 54.17; H, 7.25. $C_{13}H_{20}O_7$ requires: C, 54.16; H, 7.01%), and

3,4:6,7-di-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone (1), R_f 0.5 (ethyl acetate:hexane, 2:1) and R_f 0.3 (ethyl acetate:hexane, 1:1), (3.08 g, 26% yield, 31% based on unrecovered starting material), m.p. 157°-159°C (ethyl acetate:hexane), $[\alpha]_D^{20}$ +63.8° (c, 1.3 in $CHCl_3$), ν_{max} ($CHCl_3$): 3540 (OH), 1767 (C=O) cm^{-1}; δ_H ($CDCl_3$): 1.39 (6H, s, 2 x Me), 1.45 (3H, s, Me), 1.46 (3H, s, Me), 3.25 (1H, d, HO, J 6.0 Hz), 4.03 (1H, dd, H-5, $J_{4,5}$ 1.7 Hz, $J_{5,6}$ 8.3 Hz), 4.08 (1H, dd, H-7, $J_{6,7}$ 3.8 Hz, $J_{7,7'}$ 9.3 Hz), 4.16 (1H, dd, H-7', $J_{6,7'}$ 6.0 Hz), 4.36 (1H, dd, H-2, $J_{2,3}$ 3.5 Hz), 4.43 (1H, ddd, H-6), 4.70 (1H, dd, H-4, $J_{3,4}$ 7.8), 4.84 (1H, dd, H-3). δ_C ($CDCl_3$): 24.16, 24.79, 25.62, 26.83 (4 x q, 4 x MeC), 66.39 (t, C-7) 68.61 (d, C-2), 72.28, 72.50, 74.72, 76.32 (4 x d, 4 x CHO), 110.03, 111.01 (2 x s, 2 x Me_2C), 171.47 (s, C-1). m/z (NH_3, DCI): 306 ($M+NH_4^+$, 90%), 289 ($M+H^+$, 100%). (Found: C, 54.12; H, 7.09. $C_{13}H_{20}O_7$ requires: C, 54.16; H, 7.01%).

3,4:6,7-Di-O-isopropylidene-2-O-trifluoromethanesulphonyl-D-glycero-D-talo-heptono-1,5-lactone (2). Dry pyridine (4 ml, 50 mmol) and trifluoromethanesulphonic anhydride (5.0 g, 18 mmol) were added over 5 min to a stirred solution of the talo-lactone (1) (3.72 g, 13 mmol) in dichloromethane (75 ml) at -30°C under nitrogen; after a further 5 min, no starting material remained and the reaction was quenched by addition of dilute aqueous hydrochloric acid (60 ml). The organic layer was washed with brine (2 x 60 ml) and dried (sodium sulphate); the solvent was removed to give the stable crude triflate (2), a cream solid, (5.1 g, 93%), which was used directly directly for the conversion to azide without further purification. A sample of the crude triflate was recrystallised to give 3,4:6,7-di-O-isopropylidene-2-O-trifluoromethanesulphonyl-D-glycero-D-talo-heptono-1,5-lactone (2), m.p. 118°-119°C (dec.) (ether:hexane), $[\alpha]_D^{20}$ +37.0° (c, 1.02 in $CHCl_3$), ν_{max} ($CHCl_3$): 1793 (C=O) cm^{-1}; δ_H ($CDCl_3$): 1.39 (3H, s, Me), 1.42 (3H, s, Me), 1.48 (3H, s, Me), 1.50 (3H, s, Me), 4.07 (1H, dd, H-5, $J_{4,5}$ 1.7 Hz, $J_{5,6}$ 8.3 Hz), 4.10 (1H, dd, H-7, $J_{6,7}$ 3.6 Hz, $J_{7,7'}$ 9.5 Hz), 4.16 (1H, dd, H-7', $J_{6,7'}$ 5.9 Hz), 4.42 (1H, ddd, H-6), 4.82 (1H, dd, H-4, $J_{3,4}$ 7.8), 4.94 (1H, dd, H-3, $J_{2,3}$ 3.3 Hz), 5.24 (1H, d, H-2). δ_C ($CDCl_3$): 24.13, 24.72, 25.51, 26.80 (4 x q, 4 x MeC), 66.31 (t, C-7) 72.29, 72.69, 73.53, 76.61 (4 x d, 4 x CHO), 78.93 (d, C-2), 110.32, 112.40 (2 x s, 2 x Me_2C), 118.45 (q, CF_3, not proton decoupled), 162.85

(s, C-1). m/z (NH_3, DCI): 438 ($M+NH_4^+$, 100%), 421 ($M+H^+$, 20%). (Found: C, 40.05; H, 4.59. $C_{14}H_{19}F_3O_9S$ requires: C, 40.00; H, 4.56%).

3,4:6,7-Di-O-isopropylidene-2-O-trifluoromethanesulphonyl-D-glycero-D-galacto-heptono-1,5-lactone (4). Dry pyridine (0.5 ml, 6 mmol) and trifluoromethanesulphonic anhydride (670 mg, 2.4 mmol) were added to a stirred solution of the galacto-lactone (3) (465 mg, 1.6 mmol) in dichloromethane (20 ml) at -30°C under nitrogen; after stirring for a further 2 h at -20°C, only a little starting material remained and the reaction was quenched by addition of dilute aqueous hydrochloric acid (10 ml). The organic layer was washed with brine (10 ml) and dried (sodium sulphate); the solvent was removed and the residue purified by flash chromatography [ethyl acetate:hexane, 1:4] to give 3,4:6,7-di-O-isopropylidene-2-O-trifluoromethanesulphonyl-D-glycero-D-galacto-heptono-1,5-lactone (4), (564 mg, 84%), δ_H ($CDCl_3$): 1.40 (3H, s, Me), 1.41 (3H, s, Me), 1.44 (3H, s, Me), 1.48 (3H, s, Me), 4.15 (2H, m), 4.42 (2H, m), 4.76 (2H, br s), 5.16 (1H, br s). δ_C ($CDCl_3$): 23.92, 24.75, 25.60, 26.79 (4 x q, 4 x MeC), 66.54 (t, C-7) 70.55, 72.60, 74.14, 76.81 (4 x d, 4 x CHO), 77.24 (d, C-2), 110.25, 111.82 (2 x s, 2 x Me_2C), 118.38 (q, CF_3, not proton decoupled), 161.06 (s, C-1). (Found: C, 39.5; H, 4.9. $C_{14}H_{19}F_3O_9S$ requires: C, 40.00; H, 4.56%). In contrast to the talo-triflate (2), this galacto-triflate (4) decomposed and darkened at room temperature rapidly and needed to be used immediately in the next step; it was advantageous to purify this triflate by flash chromatography to obtain good yields in the subsequent displacement step.

2-Azido-2-deoxy-3,4:6,7-di-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone (5). (i) From talo-triflate (2). The crude triflate (2) (5.1 g, 12 mmol), prepared above, in dimethyl formamide (25 ml) was stirred with sodium azide (1.0 g, 15 mmol) at room temperature for 4 h. The solvent was then removed and the residue partitioned between dichloromethane (60 ml) and brine (60 ml). The organic layer was dried (sodium sulphate) and the solvent removed to give, after purification by flash chromatography [ethyl acetate:hexane, 1:3], 2-azido-2-deoxy-3,4:6,7-di-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone (5), [3.05 g, 81%, 76% from alcohol (1)], as a colourless syrup which crystallised on standing, m.p. 103°-104°C (ether:hexane), $[\alpha]_D^{20}$ +96.7° (c, 1.13 in $CHCl_3$), ν_{max} ($CHCl_3$): 2125 (N_3), 1773 (C=O) cm^{-1}; δ_H ($CDCl_3$): 1.38 (3H, s, Me), 1.40 (3H, s, Me), 1.45 (3H, s, Me), 1.48 (3H, s, Me), 3.90 (1H, d, H-2, $J_{2,3}$ 3.3 Hz), 4.01 (1H, dd, H-5, $J_{4,5}$ 1.6 Hz, $J_{5,6}$ 8.3 Hz), 4.04 (1H, dd, H-7, $J_{6,7}$ 3.9 Hz, $J_{7,7'}$ 9.3 Hz), 4.13 (1H, dd, H-7', $J_{6,7'}$ 5.8 Hz), 4.38 (1H, ddd, H-6), 4.69 (1H, dd, H-4, $J_{3,4}$ 7.8), 4.85 (1H, dd, H-3). δ_C ($CDCl_3$): 24.10, 24.75, 25.56, 26.74 (4 x q, 4 x MeC), 59.14 (d, C-2), 66.34 (t, C-7) 72.22, 72.42, 75.34, 76.62 (4 x d, 4 x CHO), 110.01, 111.19 (2 x s, 2 x Me_2C), 166.68 (s, C-1). m/z (NH_3, DCI): 331 ($M+NH_4^+$, 100%), 314 ($M+H^+$, 25%). (Found: C, 49.81; H, 6.19; N, 13.70. $C_{13}H_{19}N_3O_6$ requires: C, 49.84; H, 6.11; N, 13.41%).

(ii) From galacto-triflate (4). The purified galacto-triflate (4) (472 mg, 1.1 mmol), prepared above, in dimethyl formamide (5 ml) was stirred with sodium azide (292 mg, 4.5 mmol) at room temperature for 4 h. The solvent was then removed and the residue was extracted with dichloromethane (30 ml); the organic extract was then washed with brine (3 x 20 ml), dried (sodium sulphate) and the solvent removed. The residue was purified by flash chromatography [ethyl acetate:hexane, 1:3] to give the talo-azide (5), (288 mg, 82%), identical in all respects to the material made in (i) above.

2-Azido-2-deoxy-3,4:6,7-di-O-isopropylidene-D-glycero-D-galacto-heptono-1,5-lactone (6). (i) From talo-triflate (2). The crude triflate (2) (200 mg, 0.48 mmol) in dimethyl formamide (5 ml) was stirred with sodium azide (20 mg, 0.30 mmol) at room temperature for 3 h. The solvent was then removed and the residue partitioned between dichloromethane (20 ml) and brine (30 ml). The organic layer was dried (sodium sulphate) and the solvent was removed. Purification by flash chromatography [ethyl acetate:hexane, 1:4] gave three compounds. The first compound eluted was 2-azido-2-deoxy-3,4:6,7-di-O-isopropylidene-D-glycero-D-galacto-heptono-1,5-lactone (6), (60 mg, 40 %, 54% based on unrecovered starting material), m.p. 89°-90°C (ether:hexane), $[\alpha]_D^{20}$ +164.1° (c, 1.05 in $CHCl_3$), ν_{max} ($CHCl_3$): 2120 (N_3), 1760 (C=O) cm^{-1}; δ_H ($CDCl_3$): 1.38 (3H, s, Me), 1.40 (3H, s, Me), 1.43 (3H, s, Me), 1.48 (3H, s, Me), 4.12 (1H, dd, H-7, $J_{6,7}$ 4.1 Hz, $J_{7,7'}$ 9.2 Hz), 4.16 (1H, dd, H-7', $J_{6,7'}$ 5.5 Hz), 4.34 (1H, d, H-2, $J_{2,3}$ 2.2 Hz), 4.38 (1H, ddd, H-6, $J_{5,6}$ 8.5 Hz), 4.48 (1H, dd, H-5, $J_{4,5}$ 1.6 Hz), 4.53 (1H, dd, H-3, $J_{3,4}$ 7.4 Hz), 4.60 (1H, dd, H-4). δ_C ($CDCl_3$): 23.95, 24.86, 25.68, 26.89 (4 x q, 4 x MeC), 60.42 (d, C-2), 66.57 (t, C-7) 70.57, 72.70, 74.10, 76.53 (4 x d, 4 x CHO), 110.04, 110.75 (2 x s, 2 x Me_2C), 165.32 (s, C-1). m/z (NH_3, DCI): 331 ($M+NH_4^+$, 100%), 314 ($M+H^+$, 20%). (Found: C, 49.55; H, 6.26; N, 13.47. $C_{13}H_{19}N_3O_6$ requires: C, 49.84; H, 6.11; N, 13.41%).

The second compound to be eluted was unreacted talo-triflate (2), (52 mg, 26%), while the third compound was the talo-azide (5), (3 mg, 2%).

(ii) From galacto-triflate (4). The galacto-triflate (4), prepared as described above immediately prior to use from the galacto-lactone (3), 2.9 g, 10 mmol), was stirred with sodium azide (2.3 g, 35 mmol) in dimethylformamide (7 ml) at room temperature for 2 h, after which time dichloromethane (20 ml) was added. The reaction mixture was filtered and the solvent removed; the residue was purified by flash chromatography [ethyl acetate:hexane, 1:3] to give the galacto-azide (6), [1.10 g, 35% from galacto-lactone (3)], and the talo-azide (5), [0.91 g, 29% from galacto-lactone (3)]. TLC [ethyl acetate:hexane, 1:2] of the reaction mixture indicated that the galacto-triflate (4) (R_f 0.7) was consumed within a few minutes of the start of the reaction, while the intermediate talo-triflate (2) (R_f 0.6) was consumed in 2 h to give circa 1:1 mixture of galacto-azide (6) (R_f 0.65) and talo-azide (5) (R_f 0.45).

Conversion of galacto-azide (6) to the talo-azide (5). The galacto-azide (6) (68 mg, 0.22 mmol) in dimethyl formamide (1 ml) was stirred with anhydrous sodium acetate (53 mg, 0.65 mmol) at room temperature for 3 h. After addition of dichloromethane (10 ml) and filtration, the solvent was removed to give a residue which on purification by flash chromatography [ethyl acetate:hexane, 1:5] gave the talo-azide (5) (46 mg, 68%) and galacto-azide (6) (8 mg, 11%). A similar conversion was observed when sodium azide was used instead of sodium acetate.

Conversion of galacto-triflate (4) to the talo-triflate (2). Anhydrous sodium acetate (45 mg, 0.55 mmol) was added in one portion to a stirred solution of purified galacto-triflate (4) (77 mg, 0.18 mmol) in dimethyl formamide (1 ml). TLC (ethyl acetate:hexane, 1:2) after 2 min indicated that starting material (4) (R_f 0.7) had been completely converted to the talo-triflate (2) (R_f 0.6). The reaction mixture was diluted with dichloromethane (5 ml), filtered and the solvents removed to give, after flash chromatography [ethyl acetate:hexane, 1:4], the talo-triflate (2) (59 mg, 77%).

General procedure for deuterium exchange experiments. The triflate or azide (0.2 to 0.7 mmol) was stirred with a relevant amount of sodium azide in dimethyl formamide (1 to 2 ml) containing 5-10% v/v deuterium oxide at room temperature. After an appropriate time interval, dichloromethane (10 ml) was added, and the reaction mixture filtered and the solvent removed to give a residue which was purified by flash chromatography. The amount of deuterium incorporated at C-2 by the procedure was determined from the relative reduction in intensity of the H-2 doublet in the 200 MHz ^{1}H NMR spectra.

X-Ray Crystal Structure Analyses. The structures of 3,4:6,7-di-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone (1) (crystallised from ethyl acetate:hexane) and of 2-azido-2-deoxy-3,4:6,7-di-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone (5) (crystallised from ether:hexane) were established by single crystal X-ray analyses.

For both compounds: Cell dimensions and intensity data were measured with an Enraf-Nonius CAD4-F diffractometer up to θ = 75° (Cu-Kα radiation). The data were corrected for absorption, Lorentz and polarisation effects.[10] All calculations were carried out on a VAX 11/750 computer using SHELXS-86[11] for direct methods and CRYSTALS[12] for all other calculations. Atomic scattering factors were taken from International Tables.[13] Atomic coordinates for both compounds have been deposited at the Cambridge Crystallographic Data Centre.

For the hydroxy-lactone (1): The coordinates of all non-hydrogen atoms were given by SHELXS-86. The hydrogen atoms were placed geometrically. The structure was refined by full-matrix least-squares with isotropic temperature factors for the hydrogen atoms and anisotropic temperature factors for all other atoms using data with merged Friedel pairs. A correction for secondary extinction[14] was applied and the model refined almost to convergence. The Flack enantiopole parameter[15] was refined for the data with unmerged Friedel pairs. Consideration of its final value, 0.69 (e.s.d. 0.3), together with a listing of the largest Bijvoet differences, indicated that the absolute configuration needed to be inverted, in agreement with the absolute configuration arising from the chemical synthesis. The merged data were refined using a Chebyshev weighting scheme[16] to give a final value of R = 0.0375.

Crystal data for 3,4:6,7-di-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone (1): Molecular Formula $C_{13}H_{20}O_7$ Formula Weight 288.2968

Crystal data:-

Crystal system	monoclinic primitive		
a/A	6.70(0.002)	$\alpha/^{\circ}$	90
b/A	8.63(0.001)	$\beta/^{\circ}$	102.66(0.02)
c/A	12.496(0.002)	$\gamma/^{\circ}$	90
U/A^3	706.26		
space group	$P2_1$	Z =	2
$D_c/g\ cm^{-3}$	1.3562	F(000)	308
Linear absorp. coeff./cm^{-1}	8.9464	Crystal size / mm	0.3x0.3x0.9

Data Collection:

X-Radiation λ = 1.5418A Cu-Kα

θ min., max./$^{\circ}$ 0, 75 $(\sin\theta/\lambda)_{max}$ 0.6265

ω-scan parameters: A,B($^{\circ}$) (A+Btanθ) A = 1 B = 0.15

Horizontal aperture parameters: A,B(mm) (A+Btanθ) A = 4 B = 0

Scan speed/$^{\circ}$ min^{-1} 1.5(min) to 6.7(max)

Total data 2205 Total unique data 2199

Observed data 1552 for [I>nσ(I)] where n = 3

Absorption correction: min 1.16, max 1.30 Merging R 2.61%

Refinement:

Solved by SHELXS-86

Weighting scheme type	Chebyshev 14 3	Weights	3.85, 2.25, 1.58
Extinction parameter		90.35(2)	
Final (shift/error)		0.101	
Maximum residual electron density/ eA^{-3}		0.8	
Final R	3.75%	Rw	3.99%

TABLE 1. Fractional atomic coordinates and equivalent isotropic temperature factors* with e.s.d.'s in parentheses for hydroxylactone (1) (atomic labelling as in FIGURE)

Atom	x/a	y/b	z/c	U(eq)
C(1)	0.0393(8)	0.0280(8)	0.7295(5)	0.0756
C(2)	-0.2970(5)	-0.0638(5)	0.7572(3)	0.0469
C(3)	-0.0684(5)	-0.0913(5)	0.7818(3)	0.0392
C(4)	0.0200(5)	-0.2509(4)	0.9331(2)	0.0323
C(5)	0.2195(5)	-0.2812(4)	1.0158(2)	0.0327
C(6)	0.3955(5)	-0.2595(5)	0.9598(3)	0.0367
C(7)	0.2062(5)	-0.4342(4)	0.8290(2)	0.0295
C(8)	0.0087(5)	-0.3484(4)	0.8296(2)	0.0328
C(9)	0.2130(5)	-0.4964(4)	0.7163(2)	0.0309
C(10)	0.2345(6)	-0.3844(5)	0.6270(3)	0.0405
C(11)	0.4175(4)	-0.6076(5)	0.6131(2)	0.0336
C(12)	0.3113(7)	-0.7485(6)	0.5586(3)	0.0547
C(13)	0.6437(5)	-0.6075(7)	0.6166(3)	0.0497
O(4)	0.0173(3)	-0.0952(3)	0.8964(2)	0.0425

O(5)	0.2392(3)	-0.1851(4)	1.1074(2)	0.0416
O(6)	0.5413(4)	-0.1789(4)	0.9959(2)	0.0525
O(7)	0.3819(3)	-0.3345(3)	0.8644(2)	0.0349
O(8)	-0.0297(5)	-0.2402(4)	0.7423(2)	0.0460
O(9)	0.3891(3)	-0.5928(3)	0.7233(2)	0.0342
O(10)	0.3274(5)	-0.4736(4)	0.5556(2)	0.0460

*$U_{eq} = (U_1 x U_2 x U_3)^{1/3}$ where the mean square displacements (A^2) are along the principle axes of the thermal ellipsoid

TABLE 2. Bond lengths (A) for the non-hydrogen atoms with e.s.d.'s in parentheses for hydroxylactone (1) (atomic labelling as in FIGURE)

C(1)	C(3)	1.489(6)	C(2)	C(3)	1.514(5)
C(3)	O(4)	1.423(4)	C(3)	O(8)	1.422(5)
C(4)	C(5)	1.524(4)	C(4)	C(8)	1.531(4)
C(4)	O(4)	1.418(5)	C(5)	C(6)	1.510(4)
C(5)	O(5)	1.397(4)	C(6)	O(6)	1.204(4)
C(6)	O(8)	1.342(4)	C(7)	C(8)	1.519(4)
C(7)	C(9)	1.517(4)	C(7)	O(7)	1.448(4)
C(8)	O(8)	1.417(4)	C(9)	C(10)	1.509(5)
C(9)	O(9)	1.431(4)	C(10)	O(10)	1.422(4)
C(11)	C(12)	1.496(6)	C(11)	C(13)	1.508(4)
C(11)	O(9)	1.438(3)	C(11)	O(10)	1.424(5)

TABLE 3. Bond angles (°) for the non-hydrogen atoms with e.s.d.'s in parentheses for hydroxylactone (1) (atomic labelling as in FIGURE)

C(2)	C(3)	C(1)	111.7(4)	O(4)	C(3)	C(1)	109.3(4)
O(4)	C(3)	C(2)	112.1(3)	O(8)	C(3)	C(1)	109.3(4)
O(8)	C(3)	C(2)	109.0(4)	O(8)	C(3)	O(4)	105.3(3)
C(8)	C(4)	C(5)	110.6(3)	O(4)	C(4)	C(5)	109.2(3)
O(4)	C(4)	C(8)	104.7(3)	C(6)	C(5)	C(4)	108.9(2)
O(5)	C(5)	C(4)	111.4(3)	O(5)	C(5)	C(6)	111.3(3)
O(6)	C(6)	C(5)	123.4(3)	O(7)	C(6)	C(5)	116.4(3)
O(7)	C(6)	O(6)	120.2(3)	C(9)	C(7)	C(8)	112.4(2)
O(7)	C(7)	C(8)	111.2(3)	O(7)	C(7)	C(9)	107.8(2)
C(7)	C(8)	C(4)	113.0(3)	O(8)	C(8)	C(4)	104.8(3)
O(8)	C(8)	C(7)	109.2(3)	C(10)	C(9)	C(7)	119.2(3)
O(9)	C(9)	C(7)	110.0(2)	O(9)	C(9)	C(10)	101.9(3)
O(10)	C(10)	C(9)	104.1(3)	C(13)	C(11)	C(12)	112.9(4)
O(9)	C(11)	C(12)	111.0(3)	O(9)	C(11)	C(13)	108.4(2)
O(10)	C(11)	C(12)	108.9(3)	O(10)	C(11)	C(13)	109.1(3)
O(10)	C(11)	O(9)	106.3(3)				

For the azidolactone (5): Although the crystals of the azide (5) were normally stable in air, they decomposed rapidly in the X-ray beam. Data were collected from four different crystals and approximately scaled together using three standard reflections measured every hour. The coordinates of all non-hydrogen atoms were given by SHELXS-86. The hydrogen atoms were placed geometrically. The structure was refined by full-matrix least-squares with isotropic temperature factors for the hydrogen and nitrogen atoms and anisotropic temperature factors for all other atoms. Individual scale factors (0.951, 0.970, 0.975, 0.889, e.s.d. 0.005) were refined for each crystal. A correction for secondary extinction was applied.[14] A difference map for the partially refined structure showed the azide group to be disordered. The occupation parameters for two separate orientations (with bond lengths and bond angles restrained to conventional values and with common isotropic temperature factors for each azide group) were refined to 0.44 and 0.56. Because four crystals were used, consistent indexing of the data was not possible and so the absolute configuration was assigned by the chemical synthesis.[16] The data were refined using a Chebyshev weighting scheme to give a final value of R = 0.0701.

Crystal data for 2-azido-2-deoxy-3,4:6,7-di-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone (5): Molecular Formula $C_{13}H_{20}N_3O_6$ Formula Weight 314.3175

Crystal data:- Crystal system orthorhombic primitive

a/A	10.517(0.004)	$\alpha/^{\circ}$	90
b/A	10.704(0.004)	$\beta/^{\circ}$	90
c/A	14.081(0.004)	$\gamma/^{\circ}$	90

U/A^3 1585.1

space group $P2_12_12_1$ Z = 4

$D_c/g\ cm^{-3}$ 1.325 F(000) 668

Linear absorp. coeff./cm^{-1} 8.5152 Crystal size /mm (approx) 0.6x0.6x0.8

Data Collection: X-Radiation λ = 1.5418A Cu-Kα

θmin., max./$^{\circ}$ 0, 75 $(\sin\theta/\lambda)_{max}$ 0.6265

ω-scan parameters: A,B($^{\circ}$) (A+Btanθ) A = 1.10 B = 0.15

Horizontal aperture parameters: A,B(mm) (A+Btanθ) A = 3.50 B = 0.00

Scan speed/$^{\circ}$ min^{-1} 1.7(min) to 6.7(max)

Total data 2143 Total unique data 2112

Observed data 1867 for [I>nσ(I)] where n = 3

Absorption correction: min 1.51, max 1.56 Merging R 3.58%

Refinement: Solved by SHELXS-86

Weighting scheme type Chebyshev 14 3 Weights 11.42, 2.49, 9.34

Extinction parameter 79.9 Final (shift/error) 0.056

Maximum residual electron density/ eA^{-3} 0.5

Final R 7.01% Rw 7.10%

TABLE 4 (a). Fractional atomic coordinates and equivalent isotropic temperature factors* with e.s.d.'s in parentheses for azidolactone (5) (atomic labelling as in FIGURE)

Atom	x/a	y/b	z/c	U(eq)
C(1)	-0.0815(4)	0.3869(4)	0.6859(3)	0.0698
C(2)	0.0470(4)	0.5693(4)	0.7430(3)	0.0685
C(3)	0.0476(3)	0.4411(3)	0.6984(2)	0.0489
C(4)	0.2521(3)	0.3768(3)	0.7273(2)	0.0442
C(5)	0.3169(3)	0.1892(3)	0.8274(2)	0.0458
C(6)	0.2469(4)	0.2062(3)	0.5751(2)	0.0537
C(7)	0.2965(3)	0.3384(3)	0.5527(2)	0.0544
C(8)	0.3228(3)	0.2542(3)	0.7310(2)	0.0442
C(9)	0.2444(3)	0.4301(3)	0.6258(2)	0.0484
C(10)	0.3994(4)	0.0740(3)	0.8320(3)	0.0607
C(11)	0.4914(4)	0.2192(4)	0.9267(2)	0.0601
C(12)	0.4765(6)	0.1669(5)	1.0245(3)	0.0847
C(13)	0.5930(6)	0.3167(6)	0.9190(5)	0.1088
O(1)	0.1241(2)	0.3574(2)	0.7534(1)	0.0499
O(4)	0.1108(2)	0.4434(2)	0.6097(1)	0.0527
O(7)	0.1954(3)	0.1414(3)	0.5180(2)	0.0759
O(8)	0.2663(2)	0.1677(2)	0.6640(1)	0.0501
O(9)	0.3724(3)	0.2699(2)	0.8957(1)	0.0578
O(10)	0.5181(3)	0.1222(3)	0.8608(2)	0.0636

*$U_{eq} = (U_1 x U_2 x U_3)^{1/3}$ where the mean square displacements (A^2) are along the principle axes of the thermal ellipsoid

TABLE 4 (b). Fractional atomic coordinates and isotropic temperature factors U(iso) with e.s.d.'s in parentheses for azidolactone (5) (atomic labelling as in FIGURE)

Atom	x/a	y/b	z/c	U(iso)
N(1)	0.2858(7)	0.3530(10)	0.4529(4)	0.0539(10)
N(2)	0.1788(8)	0.3466(10)	0.4222(5)	0.0575(11)
N(3)	0.0865(10)	0.3421(12)	0.3813(7)	0.0821(16)
N(201)	0.2705(6)	0.3923(8)	0.4575(4)	0.0539(10)
N(202)	0.1581(7)	0.3828(8)	0.4277(4)	0.0574(11)
N(203)	0.0604(8)	0.3840(10)	0.3937(6)	0.0821(16)

TABLE 5. Bond lengths (A) for the non-hydrogen atoms with e.s.d.'s in parentheses for azidolactone (5) (atomic labelling as in FIGURE)

C(1)	C(3)	1.484(6)	C(2)	C(3)	1.508(5)
C(3)	O(1)	1.430(4)	C(3)	O(4)	1.413(4)
C(4)	C(8)	1.507(5)	C(4)	C(9)	1.541(4)
C(4)	O(1)	1.408(4)	C(5)	C(8)	1.526(4)
C(5)	C(10)	1.507(5)	C(5)	O(9)	1.417(4)
C(6)	C(7)	1.538(5)	C(6)	O(7)	1.191(4)
C(6)	O(8)	1.334(4)	C(7)	C(9)	1.523(5)
C(7)	N(1)	1.419(6)	C(7)	N(201)	1.485(5)
C(8)	O(8)	1.449(3)	C(9)	O(4)	1.427(4)
C(10)	O(10)	1.408(5)	C(11)	C(12)	1.494(6)
C(11)	C(13)	1.494(7)	C(11)	O(9)	1.429(4)
C(11)	O(10)	1.420(5)	N(1)	N(2)	1.205(7)
N(2)	N(3)	1.128(8)	N(201)	N(202)	1.255(6)
N(202)	N(203)	1.132(7)			

TABLE 6. Bond angles (°) for the non-hydrogen atoms with e.s.d.'s in parentheses for azidolactone (5) (atomic labelling as in FIGURE)

C(2)	C(3)	C(1)	113.6(3)	O(1)	C(3)	C(1)	109.4(3)
O(1)	C(3)	C(2)	110.2(2)	O(4)	C(3)	C(1)	109.3(3)
O(4)	C(3)	C(2)	110.8(3)	O(4)	C(3)	O(1)	103.1(3)
C(9)	C(4)	C(8)	112.3(2)	O(1)	C(4)	C(8)	109.4(2)
O(1)	C(4)	C(9)	104.3(2)	C(10)	C(5)	C(8)	112.8(3)
O(9)	C(5)	C(8)	108.0(2)	O(9)	C(5)	C(10)	103.4(2)
O(7)	C(6)	C(7)	123.4(3)	O(8)	C(6)	C(7)	115.1(3)
O(8)	C(6)	O(7)	121.5(3)	C(9)	C(7)	C(6)	109.4(2)
N(1)	C(7)	C(6)	106.1(5)	N(1)	C(7)	C(9)	124.7(5)
N(201)	C(7)	C(6)	118.6(4)	N(201)	C(7)	C(9)	107.1(4)
C(5)	C(8)	C(4)	114.0(2)	O(8)	C(8)	C(4)	109.3(2)
O(8)	C(8)	C(5)	105.8(2)	C(7)	C(9)	C(4)	111.7(3)
O(4)	C(9)	C(4)	103.6(2)	O(4)	C(9)	C(7)	108.1(2)
O(10)	C(10)	C(5)	102.8(3)	C(13)	C(11)	C(12)	113.8(4)
O(9)	C(11)	C(12)	109.4(4)	O(9)	C(11)	C(13)	109.6(4)
O(10)	C(11)	C(12)	110.5(3)	O(10)	C(11)	C(13)	108.7(4)

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