Pergamon

Tetrahedron 55 (1999) 4501–4520

TETRAHEDRON

Tetrazoles of Manno- and Rhamno- Furanoses

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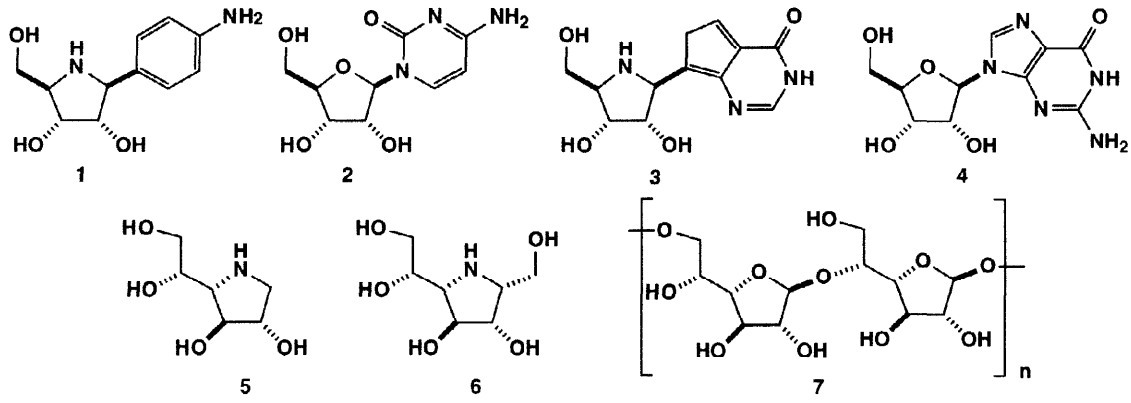
Received 9 December 1998; revised 14 January 1999; accepted 4 February 1999

Abstract: The synthesis of [3.3.0] bicyclic tetrazoles derived from D-manno and D-rhamnofuranose starting from D-mannose, and of L-rhamnofuranose starting from L-rhamnose is described. The key step in the formation of all three examples of this novel class of sugar mimics is an intramolecular [1,3]-dipolar cycloaddition of azide and nitrile moieties. © 1999 Elsevier Science Ltd. All rights reserved.

Introduction

Polyhydroxylated pyrrolidines are potent inhibitors of enzymes that process furanosides; a property which may attributed to their close resemblance to the five membered heterocyclic substrates in the transition state of the reactions that these enzymes catalyze.[1-4] For example, **1**[1], amongst others,[2] is a potent inhibitor of nucleoside hydrolases, and **3**[3] is potent inhibitor of nucleoside phosphorylase; enzymes that process **2** and **4**, respectively.

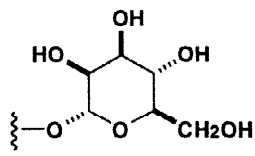


The galactofuranose analogues **5** and **6** are the first known inhibitors of UDP-Gal mutase and mycobacterial galactan biosynthesis.[4] The inhibitory activities of these compounds are highly specific and may represent a novel therapeutic strategy for the treatment of mycobacterial infections such as tuberculosis and leprosy that contain integral galactofuranosyl structures such as **7**.

It is also often the case that pyrrolidines are more powerful inhibitors of glycosidases that process six membered pyranoside substrates than their piperidine, 6-membered equivalents.[5,6] This potency has been rationalized by the greater resemblance of the envelope conformation of 5-membered ring pyrrolidines to the half-chair conformation adopted by the glycan in the transition state of the mechanism of glycosidases.[7] For example, despite its resemblance to D-mannopyranose, deoxymannojirimycin (DMJ) **9** is only a moderate inhibitor of α-mannosidases which process pyranoside substrates such as **8**;[8,9] indeed, DMJ is generally a

PII: S0040-4020(99)00138-6

more potent inhibitor of α-L-fucosidases than of mannosidases.[10] However, nitrogen containing analogues of D-mannofuranoses, such as D-(-)-swainsonine **10**[6,9] and 6-deoxy-DIM **11**,[11] typically show much more powerful inhibitory activities.



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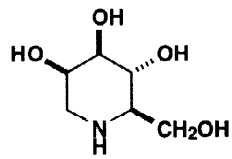

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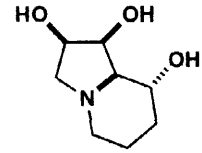

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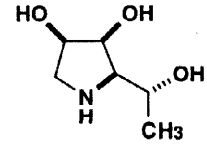

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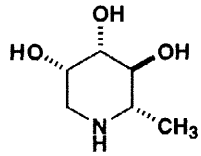

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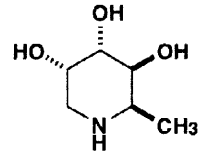

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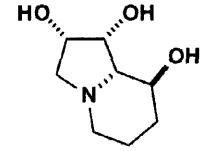

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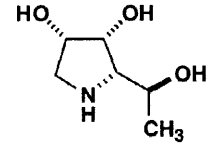

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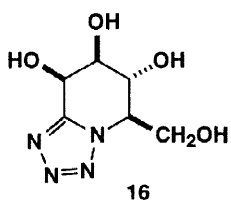
The inhibition of rhamnosidases shows a similar pattern of activity: whilst LRJ **12** shows little or no inhibition of naringinase[12] (an α-L-rhamnosidase from *Penicillium decumbens*), although the epimeric compound **13** is a potent rhamnosidase inhibitor,[13] the furanose analogues L-(+)-swainsonine **14** and DRAM **15** completely inhibit enzyme activity at ~1mM concentrations and display submicromolar values of K_i.[14]

Tetrazoles of pyranoses, such as D-mannotetrazole **16**,[15] an analogue of DMJ **9**, are transition state analogue inhibitors of glycosidases and other sugar-processing enzymes.[16] Given the often-greater inhibitory potency of pyrrolidine analogues towards these enzymes, it was therefore of interest to us to prepare furanotetrazole equivalents. This paper describes the synthesis of the D-manno **17** and D-rhamno **18** tetrazoles from D-mannose and of the L-rhamnotetrazole **19** from L-rhamnose; some aspects of this work have been published in preliminary form.[17]



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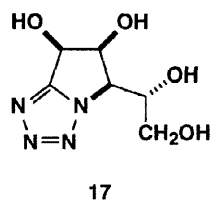

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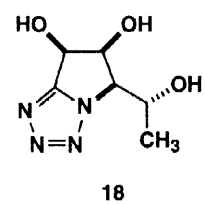

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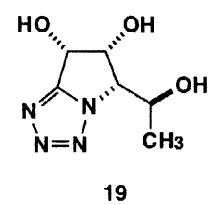

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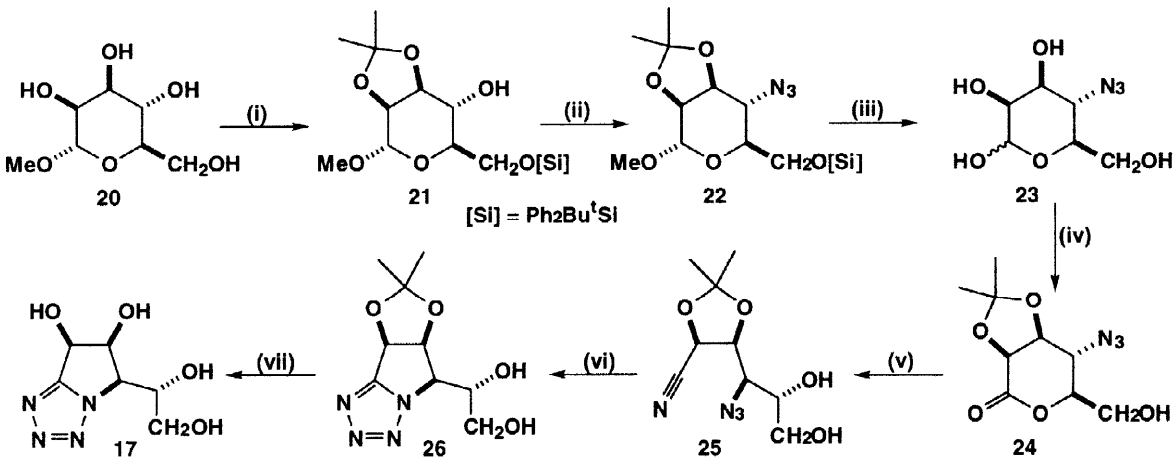
Synthesis

The synthesis of furanotetrazoles **17**, **18** and **19** followed a similar general strategy to that described in the preceding paper[18] for the corresponding pyranotetrazoles and accordingly required the formation of 4-azidonitriles as substrates for cyclization. For the synthesis of the [3.3.0] bicyclic D-mannotetrazole **17** from D-mannose, it was initially necessary to introduce an azide group at C-4 with overall retention of configuration. The cheap and readily available methyl pyranoside **20** was chosen as a starting material and was protected to allow access to the hydroxyl group of C-4 only. Thus, treatment of **20** with *tert*-butyldiphenylsilyl chloride in DMF and then dimethoxypropane in acidic acetone gave **21**[19] in 90% yield [Scheme 1]. Oxidation of **21** to the corresponding ketone with pyridinium chlorochromate, followed by stereoselective reduction with sodium borohydride inverted the configuration at C-4. Esterification of the inverted alcohol using trifluoromethanesulphonic anhydride in the presence of excess pyridine and reaction of the resulting triflate

with sodium azide in DMF gave azide **22** in which the nitrogen function had been introduced with overall retention of configuration, in 56% yield from **21**. Global deprotection of **22** was achieved sequentially; cleavage of the silyl ether using fluoride ion, and then hydrolysis of the O-2, O-3-ketal and O-1, O-5-acetal protecting groups using aqueous trifluoroacetic acid at room temperature and at 100°C, respectively, gave 4-azido-4-deoxy-D-mannose **23** in 80% yield [40% yield from **20**].

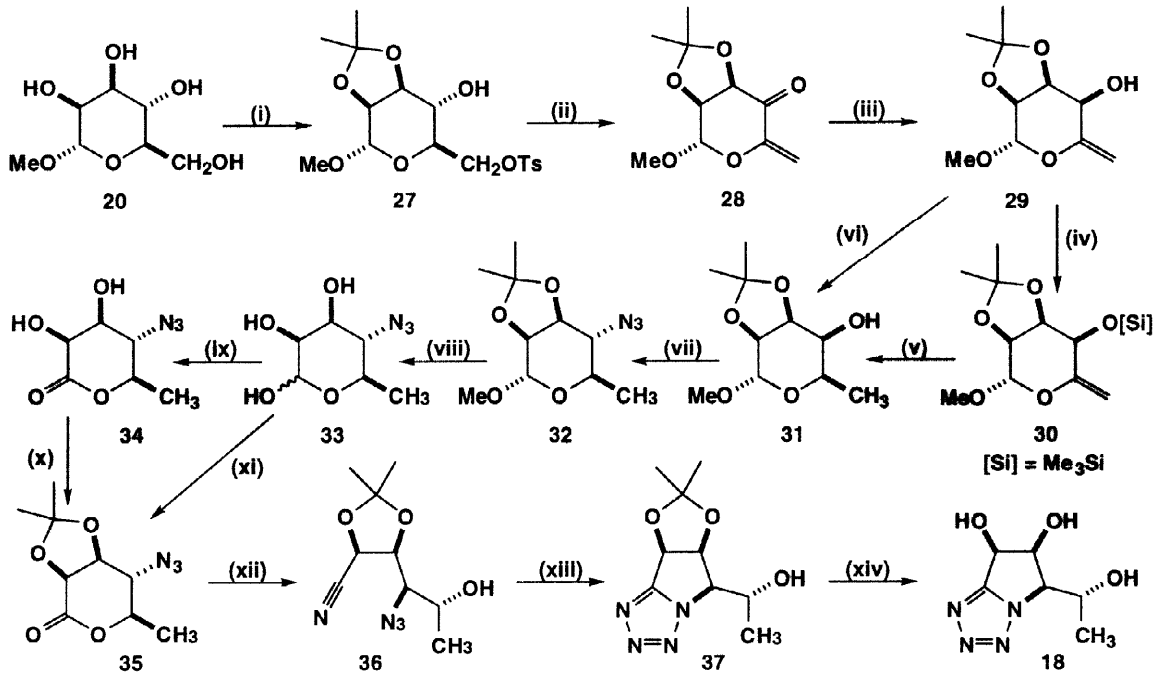


Scheme 1:(i) Ph_2Bu^tSiCl/imidazole/DMF; then $Me_2C(OMe)_2$/CSA/Me_2CO, 90% (ii) PCC/sieve/CH_2Cl_2 then $NaBH_4$/EtOH/H_2O; then Tf_2O/pyridine/CH_2Cl_2/-20°C then NaN_3/DMF, 64% (iii) Bu_4NF/THF then CF_3COOH:H_2O(1:1)/dioxan/100°C, 80% (iv) $Me_2C(OMe)_2$/TsOH/DMF/80°C then Br_2/$BaCO_3$/dioxan/H_2O, 43% (v) NH_3/MeOH then $(CF_3CO)_2O$/pyridine/-30°C, 80% (vi) Δ/DMSO, 92% (vii) CF_3COOH:H_2O (1:1), 75%

Difficulties encountered with the direct oxidation of **23** to the corresponding δ-lactone meant that the preparation of protected lactone **24** was more conveniently achieved *via* the 2,3-isopropylidene ketal of **23**. This ketal was prepared in accord with the method of Hasegawa and Fletcher[20] and oxidised to **24** using buffered bromine water. Protected lactone **24** was opened with ammonia and afforded the corresponding primary amide [37% yield from **23**] which was dehydrated using trifluoroacetic anhydride to give stable nitrile **25** [94% yield]. When a solution of nitrile **25** in dimethylsulphoxide was heated at 110°C, efficient intramolecular cycloaddition of azide and nitrile groups resulted in the formation of [3.3.0] bicyclic tetrazole **26** in 92% yield, although at a slower rate as compared with corresponding [4.3.0] bicyclic tetrazoles.[18] Deprotection of **26** with aqueous acid afforded mannotetrazole **17** in 75% yield [10% overall yield from **20**].

The synthesis of D-rhamnotetrazole **18** from D-mannose required the removal of the C-6 hydroxyl functionality in addition to the introduction of azide at C-4 with retention of configuration [Scheme 2]. Selective tosylation of the primary hydroxyl group in **20** and subsequent acetonation gave **27**.[21] Oxidation of the remaining free hydroxyl group in **27** gave a ketone, which upon treatment with triethylamine, readily eliminated tosylic acid to give α,β-unsaturated ketone **28**. Highly stereoselective reduction of **28** using sodium borohydride in aqueous ethanol gave the unstable allylic alcohol **29** [62% yield from **20**]. Hydrogenation of the exocyclic double bond in **29**, under a range of conditions and in the presence of a number of different catalysts, gave only complex reaction mixtures from which the saturated alcohol **31**[21] could only be isolated in moderate yield; optimal conditions using pre-reduced palladium on carbon in methanol gave **31** in only 62% yield. These problems were overcome by the protection of **29** as the corresponding trimethylsilyl ether **30**. Stereoselective hydrogenation of **30** in the presence of palladium black and subsequent removal of the silyl protecting group by fluoride ion afforded the required alcohol **31**. This temporary protection of the C-4 hydroxyl group allowed the formation of **31** with greater preparative ease and

efficiency [77% yield from **29**]. Triflation of the free alcohol in **31** followed by treatment with sodium azide in DMF gave azide **32** in 67% yield. This use of a triflate ester allowed this step to be achieved efficiently and is in contrast to the lack of success or selectivity reported for less powerful nucleofuges.[21,22] After 42h, a solution of **32** in aqueous trifluoroacetic acid heated under reflux afforded 4-azido-4-deoxy-D-rhamnose **33**[22] in 67% yield.

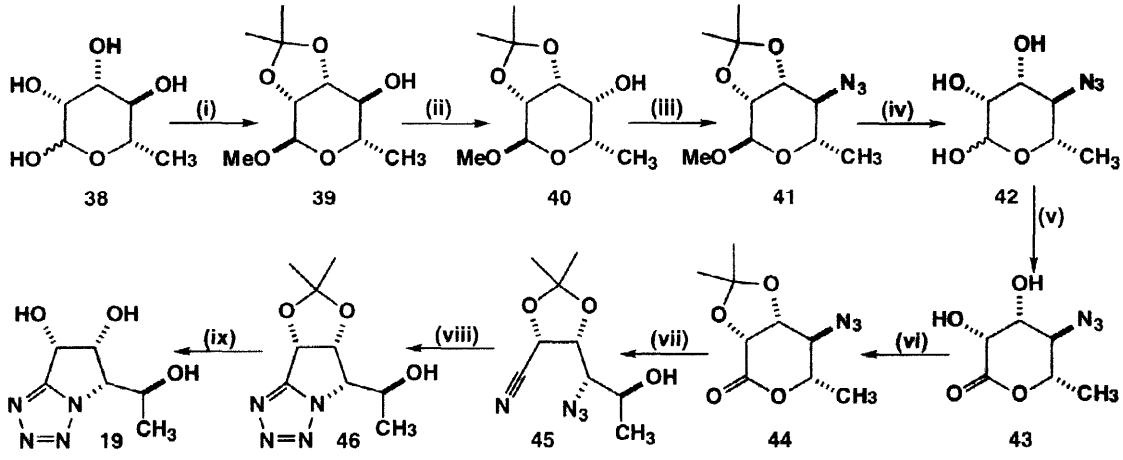


Scheme 2: (i) TsCl/pyridine/-10°C then $Me_2C(OMe)_2$/CSA/Me_2CO (ii) PCC/mol. sieve/CH_2Cl_2 then Et_3N/EtOH (iii) $NaBH_4$/EtOH/H_2O, 62% from **20** (iv) Me_3SiCl/pyridine/THF, 94% (v) H_2/Pd-black/EtOAc then Bu_4NF/THF, 82% (vi) H_2/10%Pd-C/MeOH, 62% (vii) Tf_2O/pyridine/CH_2Cl_2/-20°C then NaN_3/DMF, 67% (viii) CF_3COOH:H_2O (1:1)/dioxan/Δ, 67% (ix) Br_2/$BaCO_3$/dioxan /H_2O, 75% (x) c.H_2SO_4/acetone, 76% (xi) $Me_2C(OMe)_2$/TsOH/DMF/80°C then Br_2/$BaCO_3$/dioxan /H_2O, 52% (xii) NH_3/MeOH then $(CF_3CO)_2O$/py/-30°C, 86% (xiii) Δ/DMSO, 87% (xiv) CF_3COOH:H_2O (1:1), 85%

In contrast to the behaviour shown by 4-azido-4-deoxy-D-mannose **23**, buffered bromine oxidation of lactol **33** to its δ-lactone **34** proceeded smoothly [75% yield]. Lactone **34** was protected as its acetonide **35** using acidified acetone [76% yield]. Protected lactone **35** was also prepared, for the sake of comparison, *via* the 2,3-acetonide of lactol **33** in similar overall yield [52% from **33**]. When treated with methanolic ammonia **35** afforded the corresponding primary amide which, with trifluoroacetic anhydride in pyridine, yielded the nitrile **36** [86% yield from **35**]. Upon heating, the nitrile **36** underwent an intramolecular [1,3]-dipolar cycloaddition to give protected tetrazole **37** [87% yield] which was hydrolysed using aqueous acid to the target D-rhamnotetrazole **18** [85% yield, 8% overall yield from **20**].

As Scheme 3 shows, L-rhamnotetrazole **19** was prepared from L-rhamnose **38**. As for **17**,**18** it was necessary to introduce an azide function at C-4 with overall retention of configuration; accordingly rhamnose was protected to provide selective access to the C-4 hydroxyl group. Thus, reaction with methanolic hydrochloride, prepared using acetyl chloride in anhydrous methanol, followed by treatment with dimethoxypropane in acidic acetone gave **39**[23] [89% yield]. Oxidation of **39** with pyridinium chlorochromate in dichloromethane in the presence of molecular sieve gave a ketone which upon stereoselective reduction with sodium borohydride afforded the inverted alcohol **40** [92% yield from **39**]. An essentially identical sequence of reactions [Scheme 3] was performed on **40** to produce the required L-tetrazole **19** as had been conducted

on the enantiomer **31** to produce D-rhamnotetrazole **18**; final deprotection of tetrazole **46** using aqueous trifluoroacetic acid gave the [3.3.0] bicyclic L-rhamnotetrazole **19** [74% yield, 15% overall yield from **38**].



Scheme 3: (i) MeOH/HCl then $Me_2C(OMe)_2$/CSA/Me_2CO, 89% (ii) PCC/sieve/CH_2Cl_2 then $NaBH_4$/EtOH/H_2O, 92% (iii) Tf_2O/pyridine/CH_2Cl_2/-20°C then NaN_3/DMF, 69% (iv) CF_3COOH:H_2O (1:1)/dioxan/Δ, 67% (v) Br_2/$BaCO_3$/dioxan/H_2O, 74% (vi) c.H_2SO_4/Me_2CO, 78% (vii) NH_3/MeOH then $(CF_3CO)_2O$/pyridine/-30°C, 82% (viii) Δ/DMSO, 90% (ix) CF_3COOH:H_2O (1:1), 82%

The preceding paper[18] reports the biological evaluation of compounds **17**, **18**, and **19** and compares their ability to inhibit D-mannosidases and L-rhamnosidases with those of the corresponding pyranotetrazoles and other nitrogen analogues of mannose and rhamnose.[24]

Experimental

Melting points were recorded on a Kofler hot block and are uncorrected. Proton nuclear magnetic resonance (δ_H) spectra were recorded, unless otherwise stated on a Varian Gemini 200 (200MHz), Bruker AC 200 (200MHz) or Bruker AM 500 (500MHz) spectrometer. Carbon-13 nuclear magnetic resonance (δ_C) spectra were recorded, unless otherwise stated on a Varian Gemini 200 (50.3MHz), Bruker AC 200 (50.3MHz) or Bruker AM 500 (125MHz) spectrometer and multiplicities were assigned using DEPT sequence. All chemical shifts are quoted on the δ-scale using residual solvent as an internal standard; for samples carbon-13 nuclear magnetic resonance spectra run in D_2O, 1,4-dioxan (δ_C 67.3ppm) or methanol (δ_C 49.6ppm) were used. The following abbreviations were used to explain multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; p, pseudo. Infra-red spectra were recorded on a Perkin Elmer 1750 IR Fourier Transform or Perkin Elmer Paragon 1000 spectrophotometer. Mass spectra (*m/z*) were recorded on a VG Micromass 20-250, ZAB1F, VG Platform, or VG Autospec spectrometers using desorption chemical ionization (NH_3, DCI), chemical ionization (NH_3, CI), electrospray (ES) as stated. Optical rotations were measured on a Perkin-Elmer 241 polarimeter with a path length of 1 dm; concentrations are given in g/100ml. Hydrogenations were executed at atmospheric pressure under an atmosphere of hydrogen gas maintained by an inflated balloon. The removal of water, aqueous acetic acid or aqueous trifluoroacetic acid as solvents was aided by co-evaporation with toluene. Microanalyses were performed by the microanalysis service of the Dyson-Perrins Laboratory. Thin layer chromatography (t.l.c.) was carried out on aluminium or plastic sheets coated with $60F_{254}$ silica. Plates were developed using a spray of 0.2% w/v cerium (IV) sulphate and 5% ammonium molybdate in 2M sulphuric acid. Flash chromatography was carried out using Sorbsil C60 40/60 silica. Aqueous orthophosphate solution buffering to pH ~7 (pH 7 buffer) was prepared through the dissolution of 85g KH_2PO_4 and 14.5g NaOH in 950ml distilled water. Solvents and commercially available reagents were

dried and purified before use according to standard procedures; hexane was distilled at 68°C before use to remove involatile fractions. All solvents were removed *in vacuo*.

Methyl 6-O-tert-butyldiphenylsilyl-α-D-mannopyranoside: *Tert*-butylchlorodiphenylsilane (10.43 g, 37.9 mmol, 1.31 equiv.) was added dropwise to a stirred solution of methyl α-D-mannopyranoside **20** (6.70 g, 34.5 mmol) and recrystallized imidazole (5.17 g, 75.9 mmol, 2.2 equiv.) in DMF (100 ml) under nitrogen at room temperature. After 4h, t.l.c. (methanol : ethyl acetate, 1:9) showed the loss of starting material (R_f 0.1) and the formation of a major product (R_f 0.7). The reaction solvent was removed, the residue dissolved in chloroform (100 ml), and washed with hydrochloric acid (0.1M, 100 ml) and water (100 ml). The aqueous fractions were re-extracted with chloroform (30 ml x 2). The organic fractions were combined, dried (magnesium sulphate), filtered and the solvent removed. The residue was purified by flash chromatography (ethyl acetate : hexane, 3:1) to give methyl 6-*O*-*tert*-butyldiphenylsilyl-α-D-mannopyranoside (14.69 g, 98%) as a colourless oil; $[\alpha]_D^{21}$ +29.0 (*c*, 1.16 in $CHCl_3$) {lit.,[19] $[\alpha]_D^{27}$ +23 (*c*, 1.5 in $CHCl_3$)}; δ_H ($CDCl_3$, 500 MHz) 1.09 (s, 9H, $SiC(CH_3)_3$), 2.42, 2.81, 3.06 (s br x 3, 1H x 3, OH x 3), 3.33 (s, 3H, OCH_3), 3.63 (m, 1H, H-5), 3.82 (m, 2H, H-6, H-6'), 3.93 (m, 3H, H-2, H-3, H-4), 4.69 (d, 1H, H-1, $J_{1,2}$ 1.5Hz), 7.39-7.47 (m, 6H, Ar), 7.69-7.72 (m, 4H, Ar). δ_C ($CDCl_3$) 19.2 (s, $Si\underline{C}(CH_3)_3$), 26.8 (q, $SiC(\underline{C}H_3)_3$, 54.7 (q, OCH_3), 64.9 (t, C-6), 69.4, 70.4, 71.7, 71.8 (d x 4, C-2, C-3, C-4, C-5), 100.7 (d, C-1), 127.8, 129.8, 135.6 (d x 3, Ar), 133.2 (s, Ar).

Methyl 6-O-tert-butyldiphenylsilyl-2,3-O-isopropylidene-α-D-mannopyranoside ***21****:* Methyl 6-*O*-*tert*-butyldiphenylsilyl-α-D-mannopyranoside (14.57 g, 33.7 mmol) was dissolved in a solution of 2,2-dimethoxypropane in acetone (1 : 9 v/v, 150 ml) and the resulting solution adjusted to pH 4 using camphorsulphonic acid (CSA). The reaction solution was stirred under nitrogen at room temperature for 4h at which point t.l.c. (ethanol : chloroform, 1:19) showed the complete conversion of starting material (R_f 0.2) to a single product (R_f 0.8). The solution was neutralised using aqueous ammonia solution (d 0.880) and the solvent removed. The residue was dissolved in chloroform (100 ml), washed with distilled water (100 ml x 2) and the aqueous layers re-extracted with chloroform (40 ml x 2). The resultant organic fractions were combined, dried (magnesium sulphate), filtered and the solvent removed. The residue was purified by flash chromatography (ethyl acetate : hexane, 1:3) to give methyl 6-*O*-*tert*-butyldiphenylsilyl-2,3-*O*-isopropylidene-α-D-mannopyranoside **21** (14.57 g, 92%) as a colourless oil, $[\alpha]_D^{23}$ +2.2 (*c*, 1.14 in $CHCl_3$) {lit.,[19] $[\alpha]_D^{20}$ +2 (*c*, 1.8 in $CHCl_3$)}. δ_H ($CDCl_3$, 500 MHz) 1.08 (s, 9H, $SiC(CH_3)_3$), 1.36, 1.51 (s x 2, 3H x 2, $C(CH_3)_2$), 2.78 (d, 1H, OH, $J_{4,OH}$ 3.8Hz), 3.35 (s, 3H, OCH_3), 3.64 (ddd, 1H, H-5, $J_{4,5}$ 9.4Hz, $J_{5,6}$ 4.7Hz, $J_{5,6'}$ 4.9Hz), 3.81 (ddd, 1H, H-4, $J_{3,4}$ 6.6Hz, $J_{4,5}$ 9.3Hz, $J_{4,OH}$ 3.8Hz), 3.91 (dd, 1H, H-6', $J_{5,6'}$ 5.0Hz, $J_{6,6'}$ 10.8Hz), 3.94 (dd, 1H, H-6, $J_{5,6}$ 4.9Hz, $J_{6,6'}$ 10.8Hz), 4.14 (m, 2H, H-2, H-3), 4.89 (s, 1H, H-1), 7.42 (m, 6H, Ar), 7.72 (m, 4H, Ar). δ_C ($CDCl_3$) 19.2 (s, $Si\underline{C}(CH_3)_3$), 26.1, 27.9 (q x 2, $C(\underline{C}H_3)_2$), 26.8 (q, $SiC(\underline{C}H_3)_3$, 54.9 (q, OCH_3), 64.6 (t, C-6), 69.4, 70.6, 75.3, 78.2 (d x 4, C-2, C-3, C-4, C-5), 98.2 (d, C-1), 109.5 (s, $\underline{C}(CH_3)$, 127.8, 129.8, 135.6, 135.7 (d x 4, Ar), 132.9 (s, Ar).

Methyl 6-O-tert-butyldiphenylsilyl-2,3-O-isopropylidene-α-D-talopyranoside: Methyl 6-*O*-*tert*-butyldiphenylsilyl-2,3-*O*-isopropylidene-α-D-mannopyranoside **21** (14.32 g, 30.3 mmol), powdered dried molecular sieve (17.29 g) and pyridinium chlorochromate (20.0 g, 92.9 mmol, 3.06 equiv.) were stirred in dry dichloromethane (100 ml) under nitrogen at room temperature for 3h. At this point t.l.c. (ether : hexane, 1:2) showed complete conversion of starting material (R_f 0.3) to a single product (R_f 0.5). The reaction mixture was triturated with ether (100 ml), and filtered through a silica plug topped with celite (ether eluant). The solvent was removed and the residue dissolved in ethanol : water (100 ml, 9:1) and cooled to 0°C. Sodium borohydride (2.07 g) was added and the solution allowed to warm slowly to room temperature. After 2h t.l.c. (ethyl acetate : hexane, 1:3) showed the formation of a single product (R_f 0.4) and the complete consumption of starting material (R_f 0.5). The reaction was quenched by addition of an excess of ammonium

chloride with stirring until effervescence ceased. The solvent was removed and the residue dissolved in chloroform (100 ml), and washed with distilled water (2 x 100 ml). The organic fraction was dried (magnesium sulphate), filtered and the solvent removed. The residue was purified by flash chromatography (ethyl acetate : hexane, 1:3) to yield methyl 6-*O*-*tert*-butyldiphenylsilyl-2,3-*O*-isopropylidene-α-D-talopyranoside (12.46 g, 87%) as a clear, colourless oil. $[\alpha]_D^{22}$ +24.2 (*c*, 1.44 in $CHCl_3$). ν_{max} ($CHCl_3$) 3500cm^{-1} (O-H, br). *m/z* (NH_3, DCI): 490 (M + NH_4^+, 40), 457 (10), 216 (70%). δ_H ($CDCl_3$, 500 MHz) 1.07 (s, 9H, $SiC(CH_3)_3$), 1.40, 1.59 (s x 2, 3H x 2, $C(CH_3)_2$), 2.27 (d, 1H, OH, $J_{4,OH}$ 6.2Hz), 3.40 (s, 3H, OCH_3), 3.81 (pt, 1H, H-5, $J_{5,6}$ 6.3Hz, $J_{5,6'}$ 6.3Hz), 3.86 (pt, 1H, H-4, *J* 5.6Hz), 3.89 (dd, 1H, H-6', $J_{5,6'}$ 6.3Hz, $J_{6,6'}$ 10.3Hz), 3.93 (dd, 1H, H-6, $J_{5,6}$ 6.3Hz, $J_{6,6'}$ 10.3Hz), 4.07 (d, 1H, H-2, $J_{2,3}$ 6.4Hz), 4.23 (dd, 1H, H-3, $J_{2,3}$ 6.3Hz, $J_{3,4}$ 5.1Hz), 4.98 (s, 1H, H-1), 7.41 (m, 6H, Ar), 7.70 (m, 4H, Ar). δ_C ($CDCl_3$) 19.2 (s, $SiC(CH_3)_3$), 25.2, 25.8 (q x 2, $C(CH_3)_2$), 26.8 (q, $SiC(CH_3)_3$, 55.1 (q, OCH_3), 63.2 (t, C-6), 69.4, 70.6, 75.3, 78.2 (d x 4, C-2, C-3, C-4, C-5), 98.2 (d, C-1), 109.5 (s, $C(CH_3)_2$), 127.8, 129.8, 135.6, 135.7 (d x 4, Ar), 132.9 (s, Ar).

Methyl 4-azido-4-deoxy-6-O-tert-butyldiphenylsilyl-2,3-O-isopropylidene-α-D-mannopyranoside **22***:* Methyl 6-*O*-*tert*-butyldiphenylsilyl-2,3-*O*-isopropylidene-α-D-talopyranoside (3.98 g, 8.43 mmol) was dissolved in dry dichloromethane (80 ml) under nitrogen. Pyridine (0.95 ml, 1.4 equiv.) was added and the stirred at -35°C. Trifluoromethanesulphonic anhydride (1.64 ml, 1.16 equiv.) was added dropwise with stirring and the mixture allowed to warm to -10°C After 2h t.l.c. (ethyl acetate : hexane, 1:3) showed only partial conversion of starting material (R_f 0.4) to a major product (R_f 0.5). Therefore the solution was again cooled to -35°C, pyridine (0.47 ml, 0.7 equiv.) and trifluoromethanesulphonic anhydride (0.82 ml, 0.58 equiv.) added, and the solution warmed to -5°C. After 4h t.l.c. showed almost complete conversion of starting material to product. Methanol (1 ml) was added to quench the reaction and the resulting solution warmed to room temperature. The solution was washed with water (100 ml), pH 7 buffer solution (100 ml) and the aqueous layers re-extracted with chloroform (30 ml x 2). The organic fractions were combined, dried (magnesium sulphate), filtered and the solvent removed. The residue was dissolved in DMF (35 ml) under nitrogen and sodium azide (650 mg) added to the solution. The resulting mixture was sonicated for 20 minutes and then stirred vigorously for 4h, at which point t.l.c. (ethyl acetate : hexane, 1:3) showed the consumption of starting material (R_f 0.5) and the formation of a major product (R_f 0.6). The reaction solvent was removed, the residue dissolved in chloroform (100 ml), washed with distilled water (100 ml x 2) and the aqueous layers re-extracted with chloroform (50 ml x 2). The organic fractions were combined, dried (magnesium sulphate), filtered and the solvent removed. The residue was purified by repeated flash chromatography (ether : hexane, 1:9) to give methyl 4-azido-4-deoxy-6-*O*-*tert*-butyldiphenylsilyl-2,3-*O*-isopropylidene-α-D-mannopyranoside **22** (2.68 g, 64%) as a colourless oil. (Found: C, 62.78; H, 7.37; N, 8.28%; $C_{26}H_{35}N_3O_5Si$ requires C, 62.75; H, 7.09; N, 8.44%). $[\alpha]_D^{26}$ -7.4 (*c*, 0.87 in $CHCl_3$). ν_{max} (KBr) 2120cm^{-1} (N_3). *m/z* (NH_3, DCI): 515 (M + NH_4^+, 8), 466 (20), 412 (15), 115 (25%).δ_H ($CDCl_3$, 500 MHz) 1.10 (s, 9H, $SiC(CH_3)_3$), 1.41, 1.57 (s x 2, 3H x 2, $C(CH_3)_2$), 3.36 (s, 3H, OCH_3), 3.49 (dt, 1H, H-5, $J_{4,5}$ 10.6Hz, $J_{5,6}$ 3.0Hz, $J_{5,6'}$ 3.0Hz), 3.76 (dd, 1H, H-4, $J_{3,4}$ 8.2Hz, $J_{4,5}$ 10.6Hz), 3.90 (d, 1H, H-6, H-6', $J_{5,6}$ 3.1Hz, $J_{5,6'}$ 3.1Hz), 4.12 (d, 1H, H-2, $J_{2,3}$ 5.5Hz), 4.23 (dd, 1H, H-3, $J_{2,3}$ 5.4Hz, $J_{3,4}$ 8.2Hz), 5.00 (s, 1H, H-1), 7.39-7.47 (m, 6H, Ar), 7.74-7.78 (m, 4H, Ar). δ_C ($CDCl_3$) 19.2 (s, $SiC(CH_3)_3$), 26.2, 28.1 (q x 2, $C(CH_3)_2$), 26.7 (q, $SiC(CH_3)_3$, 54.8 (q, OCH_3), 60.6, 68.9, 74.9, 77.0 (d x 4, C-2, C-3, C-4, C-5), 63.2 (t, C-6), 98.2 (d, C-1), 110.1 (s, $C(CH_3)_2$), 127.8, 127.9, 129.9, 135.6, 136.1 (d x 5, Ar), 133.3, 133.6 (s x 2, Ar).

Methyl 4-azido-4-deoxy-2,3-O-isopropylidene-α-D-mannopyranoside: A solution of tetra-*n*-butylammonium fluoride (1.1M in THF, 6.75 ml, 1.81 equiv.) was added to a solution of methyl 4-azido-4-deoxy-6-*O*-*tert*-butyldiphenylsilyl-2,3-*O*-isopropylidene-α-D-mannopyranoside **22** (2.04 g, 4.1 mmol) in dry THF (23 ml) under nitrogen at room temperature. The resulting solution was stirred for 5h at which point t.l.c. (ethyl acetate

: hexane, 1:3) showed the complete consumption of starting material (R_f 0.55) and the formation of a major product (R_f 0.15). The reaction solvent was removed, the residue dissolved in chloroform (40 ml) and washed with distilled water (40 ml x 2). Each aqueous fraction was re-extracted with chloroform (40 ml x 2) and the organic fractions combined, dried (magnesium sulphate), filtered and the solvent removed. The residue was the purified by flash chromatography (ether : hexane, 3:1) to give methyl 4-azido-4-deoxy-2,3-*O*-isopropylidene-α-D-mannopyranoside (952 mg, 90%) as a white solid, m.p. 62-64°C (hexane). (Found: C, 46.53; H, 6.61; N, 16.30%; $C_{10}H_{17}N_3O_5$ requires C, 46.33; H, 6.56; N, 16.21%). $[\alpha]_D^{22}$ +54.3 (*c*, 1.12 in $CHCl_3$). ν_{max} (KBr) 3350cm^{-1} (br, OH), 2116cm^{-1} (N_3). *m/z* (EI): 244 (M^+ - Me, 30), 228(M^+ - OMe, 8), 43 (80%). δ_H ($CDCl_3$, 500 MHz) 1.37, 1.56 (s x 2, 3H x 2, $C(CH_3)_2$), 2.07 (dd, 1H, OH, $J_{6,OH}$ 7.8Hz, $J_{6',OH}$ 5.4Hz), 3.38 (s, 3H, OCH_3), 3.47 (ddd, 1H, H-5, $J_{4,5}$ 10.7Hz, $J_{5,6}$ 4.3Hz, $J_{5,6'}$ 2.7Hz), 3.57 (dd, 1H, H-4, $J_{3,4}$ 8.0Hz, $J_{4,5}$ 10.6Hz), 3.76 (ddd, 1H, H-6, $J_{6,OH}$ 7.8Hz, $J_{5,6}$ 4.3Hz, $J_{6,6'}$ 12.1Hz), 3.85 (ddd, 1H, H-6', $J_{6',O-H}$ 5.2Hz, $J_{5,6'}$ 2.6Hz, $J_{6,6'}$ 12.1Hz), 4.10 (d, 1H, H-2, $J_{2,3}$ 5.4Hz), 4.23 (dd, 1H, H-3, $J_{2,3}$ 5.4Hz, $J_{3,4}$ 8.1Hz), 4.96 (s, 1H, H-1). δ_C ($CDCl_3$) 26.2, 28.1 (q x 2, $C(\underline{C}H_3)_2$), 55.1 (q, OCH_3), 60.4, 68.1, 74.8, 76.8 (d x 4, C-2, C-3, C-4, C-5), 62.0 (t, C-6), 98.2 (d, C-1), 110.1 (s, $\underline{C}(CH_3)$).

Methyl 4-azido-4-deoxy-α-D-mannopyranoside: Aqueous trifluoroacetic acid (1:1, 3 ml) was added to a solution of methyl 4-azido-4-deoxy-2,3-*O*-isopropylidene-α-D-mannopyranoside (65 mg, 0.25 mmol) in 1,4-dioxan (5 drops) at room temperature. After 2h, t.l.c. showed complete conversion of starting material (R_f 0.5 in ether : hexane, 3:1) to a major product (R_f 0.0 in ether : hexane, 3:1; R_f 0.6 in methanol : ethyl acetate, 1:9). The solvent was removed, the residue co-evaporated with toluene (2 ml x 3) and purified by flash chromatography (ethyl acetate) to give methyl 4-azido-4-deoxy-α-D-mannopyranoside (51.4 mg, 93%) as a colourless, highly crystalline solid, m.p. 150-152°C (ethyl acetate). (Found: C, 38.53; H, 6.11; N, 18.92%; $C_7H_{13}N_3O_5$ requires C, 38.36; H, 5.98; N, 19.17%). $[\alpha]_D^{22}$ +159.2 (*c*, 0.86 in $(CH_3)_2CO$). ν_{max} (KBr) 3370cm^{-1} (O-H, br), 2119cm^{-1} (N_3). *m/z* (NH_3, DCI): 237 (M + NH_4^+, 100), 220 (M + H^+, 5), 205 (M + NH_4^+ - MeOH, 6), 194 (45), 192 (M + H^+ - N_2, 58%). δ_H ($(CD_3)_2CO/D_2O$, 500 MHz) 3.30 (s, 3H, OCH_3), 3.33 (dq, 1H, *J* 10.0Hz, *J* 2.2Hz), 3.68 (dd, 1H, *J* 4.4Hz, *J* 12.1Hz), 3.73 (m, 4H), 4.66 (d, 1H, H-1, $J_{1,2}$ 1.1Hz). δ_C ($(CD_3)_2CO$, 125MHz) 54.9 (q, OCH_3), 60.6, 71.0, 71.6, 72.1 (d x 4, C-2, C-3, C-4, C-5), 62.5 (t, C-6), 102.1 (d, C-1).

4-Azido-4-deoxy-α,β-D-mannopyranose 23: Method 1: Methyl 4-azido-4-deoxy-α-D-mannopyranoside (45 mg, 0.22 mmol) was partially dissolved in 1,4-dioxan (4 drops). To this mixture aqueous trifluoroacetic acid was added (3 ml, 1:1 by volume) and the resulting solution warmed to 100°C. After 49h, t.l.c. (methanol : ethyl acetate, 1:9) showed conversion of the starting material (R_f 0.6) to a mixture of products (R_f 0.4). The reaction mixture was cooled and the solvent removed. The residue was co-evaporated with toluene (5 ml x 3) and purified by flash chromatography (methanol : ethyl acetate, 3:97) to yield 4-azido-4-deoxy-α,β-D-mannopyranose **23** (33 mg, 79%) as a white foam.

Method 2: Methyl 4-azido-4-deoxy-2,3-*O*-isopropylidene-α-D-mannopyranoside (950 mg, 3.67 mmol) was dissolved in 1,4-dioxan (40 drops). To this solution aqueous trifluoroacetic acid (44 ml, 1:1 by volume) was slowly added and the resulting solution warmed to 100°C. After 48h, t.l.c. showed conversion of starting material (R_f 0.5 in ether : hexane, 3:1) to a mixture of products (R_f 0.0 in ether : hexane, 3:1; R_f 0.4 in methanol : ethyl acetate, 1:9). The reaction mixture was cooled and the solvent removed. The residue was co-evaporated with toluene (30 ml x 3) and purified by flash chromatography (methanol : ethyl acetate, 3:97) to yield 4-azido-4-deoxy-α,β-D-mannopyranose **23** (666 mg, 89%) as a white foam. $[\alpha]_D^{25}$ + 23.5 (5 min), + 25.0 (eqlbm.) (*c*, 0.69 in H_2O). ν_{max} (KBr) 3370cm^{-1} (O-H, br), 2119cm^{-1} (N_3). *m/z* (NH_3, DCI): 223 (M + NH_4^+, 100), 205 (M + NH_4^+ - H_2O, 48), 162 (23%). δ_H (CD_3CN/D_2O, 500 MHz, 3:1 mixture of anomers, * indicates minor anomer) 3.11 (ddd, 0.25H, H-5*, *J* 2.3Hz, *J* 4.4Hz, *J* 10.1Hz), 3.51-3.67 (m, 3.75H), 3.69-3.74 (m, 0.25H), 3.72 (dd, 0.75H, H-2, $J_{1,2}$ 1.8Hz, $J_{2,3}$ 3.4Hz), 3.78 (dd, 0.25H, H-2*, $J_{1*,2*}$

1.1Hz, $J_{2*,3*}$ 3.2Hz), 3.81 (dd, 0.75H, H-3, $J_{2,3}$ 3.3Hz, $J_{3,4}$ 9.2Hz), 4.68 (d, 0.25H, H-1*, $J_{1*,2*}$ 1.1Hz), 5.07 (d, 0.75H, H-1, $J_{1,2}$ 1.1Hz). δ_C (CD_3CN, 125MHz) 58.9, 59.5, 70.0, 70.5, 70.7, 71.3, 72.8, 74.4 (d x 8 C-2, C-3, C-4, C-5), 61.2, 61.5 (t x 2, C-6), 93.7, 94.0 (d x 2, C-1).

4-Azido-4-deoxy-2,3-O-isopropylidene-α,β-D-mannose: 4-Azido-4-deoxy-α,β-D-mannopyranose **23** (475 mg, 2.32 mmol) was dissolved in DMF (20 ml) under nitrogen and the solution was heated to 80°C. A solution of toluenesulphonic acid (36 mg) in 2,2-dimethoxypropane (0.95 ml) was added and the resulting solution stirred for 3h at which point t.l.c. (methanol : ethyl acetate, 1:9) showed the formation of a major product (R_f 0.7). The solution was cooled, neutralised by stirring with excess sodium hydrogencarbonate, filtered and the solvent removed. The residue was purified by flash chromatography (ethyl acetate : hexane, 1:1) to give 4-azido-4-deoxy-2,3-*O*-isopropylidene-α-D-mannose (318 mg, 56%) as a colourless oil which was pure enough for further reactions. For analytical purposes a small sample was purified by further flash chromatography (ethyl acetate : hexane, 1:1) and recrystallization (ethyl acetate/hexane) to give a white solid; m.p. 102-106°C (ethyl acetate / hexane). (Found C, 43.95; H, 5.97; N, 17.43%; $C_9H_{15}N_3O_5$ requires C, 44.08; H, 6.17; N, 17.13%). $[\alpha]_D^{26}$ +17.1 (5 min), +10.4 (eqlbm.) (*c*, 1.17 in $CHCl_3$). ν_{max} (KBr) 3380cm^{-1} (OH), 2114cm^{-1} (N_3). *m/z* (NH_3, DCI): 263 (M + NH_4^+, 100), 246 (M + H^+, 11), 228 (M + H^+ - H_2O, 23), 158 (35%). δ_H ($CDCl_3$, 500MHz, 4:1 mixture of anomers, * indicates minor anomer) 1.39, 1.57 (s x 2, 2.4H x 2, $C(CH_3)_2$), 1.42, 1.60 (s x 2, 0.6H x 2, $C(CH_3)_2$*), 2.78 (br s, 0.8H, OH*), 3.28 (ddd, 0.2H, H-5*, *J* 2.6Hz, *J* 4.5Hz, *J* 10.2Hz), 3.50 (dd, 0.8H, H-4, $J_{3,4}$ 8.2Hz, $J_{4,5}$ 10.4Hz), 3.68-3.78 (m, 2.4H), 3.86-3.88 (m, 1H), 4.00 (br s, 0.8H, OH-1*), 4.15 (d, 0.8H, H-2, $J_{2,3}$ 5.4Hz), 4.25-4.27 (m, 0.4H, H-2*, H-3*), 4.30 (dd, 0.8H, H-3, $J_{2,3}$ 5.4Hz, $J_{3,4}$ 8.1Hz), 5.06 (d, 0.2H, H-1*, $J_{1*,2*}$ 7.2Hz), 5.49 (s, 0.8H, H-1). δ_C ($CDCl_3$, 125MHz) 26.1, 26.2, 27.8, 28.1 (q x 4 , $C(\underline{C}H_3)_2$) 60.0, 60.8, 68.5, 74.1, 75.2, 76.6, 78.1 (d x 7, C-2, C-3, C-4, C-5), 61.9, 62.2 (t x 2, C-6), 91.8, 92.6 (d x 2, C-1) 110.2, 111.1 (s x 2, $\underline{C}(CH_3)_2$).

4-Azido-4-deoxy-2,3-O-isopropylidene-D-mannono-1,5-lactone ***24****:* 4-Azido-4-deoxy-2,3-*O*-isopropylidene-α,β-D-mannose (270 mg, 1.10 mmol) was dissolved in aqueous 1,4-dioxan (18 ml, 1:3 dioxan : water) and barium carbonate (650 mg, 3.0 equiv.) added. Bromine (0.2 ml, 3.53 equiv.) was then slowly added to the mixture with vigorous stirring. After 3h t.l.c. (ethyl acetate : hexane, 3:1) showed complete conversion of starting material (R_f 0.4) to a single product (R_f 0.55). The reaction mixture was filtered and air passed through the resulting filtrate until decolourized and the solvent removed. The residue was extracted with boiling ethyl acetate. The extracts were combined, filtered and the solvent removed to give 4-azido-4-deoxy-2,3-*O*-isopropylidene-D-mannono-1,5-lactone **24** as a colourless oil (206 mg, 77%) which was pure enough for further reactions. For analytical purposes a small sample was purified by repeated flash chromatography (ethyl acetate : hexane, 3:2) to give a colourless oil. (Found: C, 44.45; H, 5.33; N, 17.22%; $C_9H_{13}N_3O_5$ requires C, 44.45; H, 5.39; N, 17.28%). $[\alpha]_D^{26}$ +129.0 (*c*, 0.67 in $CHCl_3$). ν_{max} (film) 3450cm^{-1} (O-H, br), 2115cm^{-1} (N_3), 1758cm^{-1} (C=O). *m/z* (NH_3, DCI): 261 (M + NH_4^+, 100), 244 (M + H^+, 12), 218 (33%). δ_H ($CDCl_3$, 500MHz) 1.45, 1.55 (s x 2, 3H x 2, $C(CH_3)_2$), 3.88 (dd, 1H, H-4, $J_{3,4}$ 7.5Hz, $J_{4,5}$ 10.5Hz), 3.89 (dd, 1H, H-6', $J_{5,6'}$ 3.0Hz, $J_{6,6'}$ 12.9Hz), 4.03 (dd, 1H, H-6, $J_{5,6}$ 2.2Hz, $J_{6,6'}$ 13.0Hz), 4.10 (ddd, 1H, H-5, $J_{4,5}$ 10.5Hz, $J_{5,6}$ 2.5Hz, $J_{5,6'}$ 2.8Hz), 4.57 (dd, 1H, H-3, $J_{2,3}$ 8.2Hz, $J_{3,4}$ 8.2Hz), 4.74 (d, 1H, H-2, $J_{2,3}$ 8.2Hz). δ_C ($CDCl_3$) 25.0, 26.6 (q x 2, $C(\underline{C}H_3)_2$), 60.1, 71.9, 77.2, 77.3 (d x 4, C-2, C-3, C-4, C-5), 60.4 (t, C-6), 112.8 (s, $\underline{C}(CH_3)$, 169.3 (s, C-1).

4-Azido-4-deoxy-2,3-O-isopropylidene-D-mannonoamide: A solution of 4-azido-4-deoxy-2,3-*O*-isopropylidene-D-mannono-1,5-lactone **24** (206 mg) in methanol (1 ml, anhydrous) was added to a freshly prepared saturated solution of ammonia in methanol (5 ml, anhydrous) and stirred under nitrogen at room temperature. After 1h, t.l.c. (ethyl acetate) showed complete conversion of starting material (R_f 0.65) to a single product (R_f 0.1). The solvent was removed and the residue crystallized from ethyl acetate to yield 4-

azido-4-deoxy-2,3-*O*-isopropylidene-D-mannonoamide (187 mg, 85%) as a white solid, m.p. 150-152°C (ethyl acetate). (Found: C, 41.61; H, 6.25; N, 21.53%; $C_9H_{16}N_4O_5$ requires C, 41.54; H, 6.20; N, 21.53%). $[\alpha]_D^{26}$ -42.1 (*c*, 0.56 in MeOH). ν_{max} (film) 3350cm^{-1} (O-H, br), 2114cm^{-1} (N_3), 1675cm^{-1} (C=O, amide I), 1589cm^{-1} (C=O, amide II). *m/z* (NH_3, DCI): 278 (M + NH_4^+, 5), 261 (M + H^+, 100), 233 (M + H^+ - N_2, 26), 173 (53%). δ_H (CD_3OD, 500MHz) 1.34, 1.59 (s x 2, 3H x 2, $C(CH_3)_2$), 3.57 (dd, 1H, H-4, $J_{3,4}$ 2.3Hz, $J_{4,5}$ 8.9Hz), 3.62 (m, 1H, H-6), 3.74-3.79 (m, 2H, H-5, H-6), 4.63 (d, 1H, H-2, $J_{2,3}$ 8.3Hz), 4.87 (dd, 1H, H-3, $J_{2,3}$ 8.3Hz, $J_{3,4}$ 2.3Hz). δ_C (CD_3OD) 24.4, 26.4 (q x 2, $C(\underline{C}H_3)_2$), 61.7, 72.4, 76.8, 78.0 (d x 4, C-2, C-3, C-4, C-5), 64.7 (t, C-6), 111.1 (s, $\underline{C}(CH_3)$, 175.4 (s, C-1).

4-Azido-4-deoxy-2,3-O-isopropylidene-D-mannononitrile 25: Trifluoroacetic anhydride (0.35 ml) was added to a solution of 4-azido-4-deoxy-2,3-*O*-isopropylidene-D-mannonoamide (125 mg, 0.48 mmol) in dry pyridine (10 ml) under nitrogen at -30°C. After 2h t.l.c. (ethyl acetate) showed the consumption of starting material (R_f 0.1) and the formation of a major product (R_f 0.7). Excess anhydride was quenched by the addition of methanol (0.5 ml) and the reaction solvent removed. The residue was purified by flash chromatography (ethyl acetate : hexane, 3:2) to give 4-azido-4-deoxy-2,3-*O*-isopropylidene-D-mannononitrile **25** (109 mg, 94%) as a yellow oil. $[\alpha]_D^{25}$ +39.1 (*c*, 0.82 in $CHCl_3$). ν_{max} (film) 3450cm^{-1} (s br, OH); 2218cm^{-1} (w, CN), 2117cm^{-1} (N_3). *m/z* (NH_3, DCI): 260 (M + NH_4^+, 24), 243 (M + H^+, 100), 215 (M + H^+ - N_2, 17%). δ_H ($CDCl_3$, 500 MHz) 1.44, 1.62 (s x 2, 3H x 2, $C(CH_3)_2$), 3.48 (p dt, 1H, H-5, $J_{4,5}$ 9.5Hz, *J* 3.8Hz), 3.83 (dd, 1H, H-6, $J_{5,6}$ 4.3Hz, $J_{6,6'}$ 11.2Hz), 3.87 (dd, 1H, H-6', $J_{5,6'}$ 3.3Hz, $J_{6,6'}$ 11.1Hz), 3.93 (pt, 1H, H-4, *J* 9.3Hz), 4.27 (dd, 1H, H-3, $J_{2,3}$ 5.1Hz, $J_{3,4}$ 9.0Hz), 5.01 (d, 1H, H-2, $J_{2,3}$ 5.1Hz). δ_C ($CDCl_3$) 25.8, 26.8(q x 2, $C(\underline{C}H_3)_2$), 62.6, 67.4, 71.3, 79.5 (d x 4, C-2, C-3, C-4, C-5), 63.0 (t, C-6), 111.7 (s, $\underline{C}(CH_3)_2$), 117.8 (s, C-1).

(5R,6S,7R)-5,6,7-Trihydro-5-(1R-1,2-dihydroxyethyl)-6,7-O-isopropylidenepyrrolo[1,2-d]tetrazole-6,7-diol 26: 4-Azido-4-deoxy-2,3-*O*-isopropylidene-D-mannononitrile **25** (109 mg, 0.45mmol) was dissolved in anhydrous DMSO (0.55 ml) and heated to 110°C. The reaction was followed by t.l.c. (ethyl acetate) and after 160h showed the complete conversion of starting material (R_f 0.7) to a single product (R_f 0.25). The reaction solution was cooled and the solvent removed. The residue was purified by flash chromatography (ethyl acetate) to give (5*R*,6*S*,7*R*)-5,6,7-trihydro-5-(1*R*-1,2-dihydroxyethyl)-6,7-*O*-isopropylidene-pyrrolo[1,2-d]tetrazole-6,7-diol **26** (100 mg, 92%) as a white solid, m.p. 153-155°C (ethyl acetate). (Found: C, 44.47; H, 5.62; N, 23.18%; $C_9H_{14}N_4O_4$ requires C, 44.63; H, 5.83; N, 23.13%). $[\alpha]_D^{22}$ -2.3 (*c*, 1.42 in CH_3OH). ν_{max} (KBr) 3400cm^{-1} (OH). *m/z* (NH_3, DCI): 260 (M + NH_4^+, 4), 243 (M + H^+, 100%). δ_H (CD_3OD, 500 MHz) 1.26, 1.46 (s x 2, 3H x 2, $C(CH_3)_2$), 4.08-4.14 (m, 2H, $CH(OH)C\underline{H}_2OH$), 4.18 (pdt, 1H, $C\underline{H}(OH)CH_2OH$, *J* 8.8Hz, *J* 3.8Hz), 4.77 (dd, 1H, H-7, $J_{6,7}$ 4.6Hz, *J* 8.8Hz), 5.60 (dd, 1H, H-6, $J_{6,7}$ 5.3Hz, $J_{5,6}$ 4.7Hz), 5.67 (d, 1H, H-4, $J_{4,5}$ 5.5Hz). δ_C (CD_3OD) 25.8, 27.2 (q x 2, $C(\underline{C}H_3)_2$), 62.5, 70.2, 71.5, 87.0 (d x 4, C-5, C-6, C-7, $\underline{C}H(OH)CH_2OH$), 64.6 (t, $CH(OH)\underline{C}H_2OH$), 115.2 (s, $\underline{C}(CH_3)_2$), 162.4 (s, C-7a).

(5R,6S,7R)-5,6,7-Trihydro-5-(1R-1,2-dihydroxyethyl)pyrrolo[1,2-d]tetrazole-6,7-diol 17: (5*R*,6*S*,7*R*)-5,6,7-Trihydro-5-(1*R*-1,2-dihydroxyethyl)-6,7-*O*-isopropylidene-pyrrolo[1,2-d]tetrazole-6,7-diol **26** (45 mg, 0.186 mmol) was dissolved in aqueous trifluoroacetic acid (50% v/v, 3.5 ml) and stirred at room temperature. After 28h t.l.c. (methanol : ethyl acetate, 1:9) showed the conversion of starting material (R_f 0.5) to a major product (R_f 0.3). The reaction solvent was removed and the residue purified by flash chromatography (methanol : ethyl acetate, 1:9) to give (5*R*,6*S*,7*R*)-5,6,7-trihydro-5-(1*R*-1,2-dihydroxyethyl)pyrrolo[1,2-d]tetrazole-6,7-diol **17** (28 mg, 75%) as a glassy solid. (HRMS *m/z* (CI+): Found 203.078408 (M + H^+); $C_6H_{11}N_4O_4$ requires 203.078030). $[\alpha]_D^{22}$ -19.7 (*c*, 0.89 in CH_3OH). ν_{max} (KBr) 3450cm^{-1} (OH). *m/z* (NH_3, DCI): 220 (M + NH_4^+, 10), 203 (M + H^+, 92), 150 (100%). δ_H (D_2O, 500 MHz) 3.96 (dd, 1H, $CHC\underline{H}H'OH$, *J* 5.9Hz, *J* 12.2Hz), 4.02 (dd, 1H, $CH(OH)CH\underline{H}'OH$, *J* 3.4Hz, *J* 12.2Hz), 4.32 (ddd, 1H,

CHCH$_2$OH, *J* 3.4Hz, *J* 6.0Hz, *J* 6.7Hz), 4.80 (dd, 1H, H-5, *J* 5.2Hz, *J* 6.8Hz), 5.19 (t, 1H, H-6, *J* 5.3Hz), 5.32 (d, 1H, H-7, $J_{6,7}$ 5.3Hz). δ_C (CD_3OD) 61.5, 63.6, 70.2, 77.2 (d x 4, C-5, C-6, C-7, CH(OH)CH$_2$OH), 62.8 (t, CH(OH)CH$_2$OH), 161.8 (s, C-7a).

Methyl 6-deoxy-5-ene-2,3-O-isopropylidene-β-L-ribohexopyranoside ***29****:* A solution of *p*-toluenesulphonyl chloride (11.43 g, 1.13 equiv.) in dry pyridine (40 ml) was added to a solution of methyl α-D-mannopyranoside **20** (10.29 g, 53 mmol) in dry pyridine (180 ml) at -10°C. This solution was left for at 100h at -13°C at which point t.l.c. (ethyl acetate : hexane, 1:1) showed the consumption of starting material (R_f 0.0), and the formation of a major product (R_f 0.2). Ice-water (1 l) was added and the mixture evaporated to an oil which was partitioned between chloroform (500 ml) and water (500 ml). The aqueous layer was further extracted with chloroform (300 ml). The organic fractions were combined, dried (magnesium sulphate), filtered and the solvent removed to give methyl 6-*O*-*p*-toluenesulphonyl-α-D-mannopyranoside (16.35 g) as a yellow syrup. 2,2-Dimethoxypropane (30 ml, 245 mmol) and camphorsulphonic acid (1.5 g) were added to a solution of this crude mixture in dry acetone (400 ml) under nitrogen. After 17h, t.l.c. (ethyl acetate : hexane, 1:1) showed the conversion of starting material (R_f 0.2) to a major product (R_f 0.5). The solution was neutralised with aqueous ammonia solution (d 0.880) and the solvent removed. The residue was dissolved in chloroform (500 ml) and then washed with water (500 ml). The aqueous layer was further extracted with chloroform (300 ml). The organic fractions were combined, dried (magnesium sulphate), filtered and the solvent removed to give methyl 2,3-*O*-isopropylidene-6-*O*-*p*-toluenesulphonyl-α-D-mannopyranoside **27** (14.91 g) as a yellow oil. A small sample was purified by flash chromatography (ethyl acetate : hexane, 1:3) to give a colourless oil. $[\alpha]_D^{24}$ +16.0 (*c*, 2.1 in $CHCl_3$) {lit.,[21] $[\alpha]_D$ +12.3 (*c*, 2.75 in CH_2Cl_2)}. δ_H ($CDCl_3$) 1.33, 1.48 (s x 2, 3H x 2, C(CH$_3$)$_2$), 2.45 (s, 3H ArCH$_3$), 3.35 (s, 3H, OCH$_3$), 3.59 (m, 1H, H-4), 3.73 (m, 1H, H-5), 4.10 (s, 1H, H-3), 4.11 (s, 1H, H-2), 4.28, 4.30 (1H x 2, s x 2, H-6, H-6'), 4.84 (s, 1H, H-1), 7.35 (d, 2H, ArH, $J_{ArH,ArH'}$ 8Hz), 7.81 (d, 2H, ArH', $J_{ArH,ArH'}$ 8Hz). δ_C ($CDCl_3$) 21.5 (q, ArCH$_3$), 25.9, 27.7 (s x 2, C(CH$_3$)$_2$), 55.2 (q, OCH$_3$), 68.1, 68.5, 75.4, 78.2 (d x 3, C-2, C-3, C-4, C-5), 69.2 (t, C-6), 98.3 (d, C-1), 109.9 (s, C(CH$_3$)$_2$), 128.2, 129.6 (d x 2, Ar), 130.0, 145.2 (s x 2, Ar). Pyridinium chlorochromate (25.8 g, 120 mmol) and powdered molecular sieve (25 g) were added to a solution of crude **27** in freshly distilled dichloromethane (270 ml) under nitrogen. After 17h, t.l.c. (ethyl acetate : hexane, 1:1) showed the conversion of starting material (R_f 0.5) to a major product (R_f 0.6). Ether (400 ml) and a small amount of magnesium sulphate were added, the mixture triturated and filtered through a celite-topped silica plug which was eluted with ether (2 l). The solvent was removed to give methyl 2,3-*O*-isopropylidene-6-*O*-toluenesulphonyl-α-D-lyxohexopyran-4-uloside as a yellow oil, which was used directly in the next step. Triethylamine (6 ml) was added to a stirred solution of crude ketone in ethanol (150 ml) under nitrogen. After 1.5h, t.l.c. (ethyl acetate : hexane, 1:1) showed conversion to a major product (R_f 0.7). The reaction solution was used immediately in the next step. Distilled water (15 ml) was added to this solution and the solution cooled to 0°C. Sodium borohydride (3.15 g, 83 mmol) was then added to form a white mixture which was stirred for 6h. Excess ammonium chloride was added and the solvent removed. The residue was partitioned between chloroform (400 ml) and water (400 ml). The aqueous layer was further extracted with chloroform (200 ml). The organic fractions were combined, dried (magnesium sulphate), filtered and the solvent removed. The residue was purified by flash chromatography (ethyl acetate : hexane, 1:3) to give methyl 6-deoxy-5-ene-2,3-*O*-isopropylidene-β-L-ribohexopyranoside **29** (7.19 g, 62% over 5 steps) as an unstable white solid, m.p. 57-61°C (ethyl acetate/hexane). $[\alpha]_D^{21}$ -28.4 (*c*, 0.81 in $CHCl_3$). δ_H ($CDCl_3$, 500MHz) 1.32, 1.43 (s x 2, 3H x 2, C(CH$_3$)$_2$), 2.58 (d, 1H, OH, $J_{4,OH}$ 7.5Hz), 3.40 (s, 3H, OCH$_3$), 4.30 (dd, 1H, H-2, $J_{1,2}$ 1.7Hz, $J_{2,3}$ 7.7Hz), 4.43 (1H, s, H-6), 4.48 (dd, 1H, H-3, $J_{2,3}$ 7.7Hz, $J_{3,4}$ 4.0Hz), 4.52 (1H, s, H-6'), 4.54 (1H, m, H-4), 4.81 (d, 1H, H-1, $J_{1,2}$ 1.6Hz). δ_C ($CDCl_3$, 125MHz) 24.6, 25.9 (s x 2, C(CH$_3$)$_2$), 55.8 (q, OCH$_3$), 65.5, 73.5, 74.6 (d x 3, C-2, C-3, C-4), 88.4 (t, C-6), 98.2 (d, C-1), 110.6 (s, C(CH$_3$)$_2$), 155.8 (s, C-5).

Methyl 6-deoxy-5-ene-2,3-O-isopropylidene-4-O-trimethylsilyl-β-L-ribohexopyranoside ***30****:* Methyl 6-deoxy-5-ene-2,3-*O*-isopropylidene-β-L-ribohexopyranoside **29** (1.47 g, 6.81 mmol) was dissolved in freshly distilled THF (60 ml) under nitrogen. Dry pyridine (1.1 ml, 2 equiv.) and then trimethylsilylchloride (1.15 ml, 1.33 equiv.) were added and the resulting mixture stirred under nitrogen. After 5h t.l.c. (ethyl acetate : hexane, 1:3) showed the formation of a major product (R_f 0.5) from starting material (R_f 0.2). The volume of solvent in the reaction mixture was reduced (to 5 ml) and purified by flash chromatography (ethyl acetate : hexane, 1:3) to give methyl 6-deoxy-5-ene-2,3-*O*-isopropylidene-4-*O*-trimethylsilyl-β-L-ribohexopyranoside **30** (1.88 g, 94%) as a white solid, m.p. 31-34°C (hexane). (Found: C, 54.17; H, 8.67%; $C_{13}H_{24}O_5Si$ requires C, 54.14; H, 8.39%). $[\alpha]_D^{24}$ +21.1 (*c*, 0.9 in $CHCl_3$). ν_{max} (film) 1650cm^{-1} (w br, C=C). *m/z* (NH_3, DCI): 289 ($M+H^+$, 33), 202 (27), 90 (100%). δ_H ($CDCl_3$) 0.20 (s, 9H, $SiMe_3$), 1.34, 1.49 (s x 2, 3H x 2, $C(CH_3)_2$), 3.44 (s, 3H, OMe), 4.26 (dd, 1H, H-2, $J_{1,2}$ 1Hz, $J_{2,3}$ 8Hz), 4.40 (m, 2H), 4.52 (s br, 1H), 4.74 (m, 1H), 4.77 (d, 1H, H-1, $J_{1,2}$ 1Hz). δ_C ($CDCl_3$) -0.05 (q, $SiMe_3$), 24.8, 26.3 (s x 2, $C(\underline{C}H_3)_2$), 55.9 (q, $O\underline{C}H_3$), 66.3, 74.9, 75.5 (d x 3, C-2, C-3, C-4,), 88.6 (t, C-6), 99.6 (d, C-1), 111.0 (s, $\underline{C}(CH_3)_2$), 155.0 (s, C-5).

Methyl 6-deoxy-2,3-O-isopropylidene-4-O-trimethylsilyl-α–D-talopyranoside: Palladium black (313 mg) was added to a solution of methyl 6-deoxy-5-ene-2,3-*O*-isopropylidene-4-*O*-trimethylsilyl-β-L-ribohexopyranoside **30** (1.88 g, 6.53 mmol) in ethyl acetate (190 ml). The solution was thoroughly degassed and stirred under hydrogen. After 24h, t.l.c. (ethyl acetate : hexane, 1:3) indicated the formation of a major product (R_f 0.5). The reaction mixture was filtered through celite and the solvent removed. The residue was purified by flash chromatography (ethyl acetate : hexane, 1:9) to give methyl 6-deoxy-2,3-*O*-isopropylidene-4-*O*-trimethylsilyl-α-D-talopyranoside (1.56 g, 82%) as a colourless oil. (Found: C, 53.38; H, 9.02; $C_{13}H_{26}O_5Si$ requires C, 53.76; H, 9.02%). $[\alpha]_D^{24}$ +42.0 (*c*, 1.1 in $CHCl_3$). *m/z* (NH_3, DCI): 308 ($M+NH_4^+$, 3), 276 ($M+NH_4^+$-MeOH, 20), 259 ($M+H^+$-MeOH, 43), 100 (45), 90 (100%). δ_H ($CDCl_3$, 500MHz) 0.17 (s, 9H, $SiMe_3$), 1.29 (d, 3H, H-6, $J_{5,6}$ 6.3Hz), 1.35, 1.56 (s x 2, 3H x 2, $C(CH_3)_2$), 3.43 (s, 3H, OMe), 3.88 (m, 2H, H-4, H-5), 4.02 (dd, 1H, H-2, $J_{1,2}$ 2.5Hz, $J_{2,3}$ 7.0Hz), 4.24 (dd, 1H, H-3, $J_{2,3}$ 7.0Hz, $J_{3,4}$ 4.2Hz), 4.82 (d, 1H, H-1, $J_{1,2}$ 2.5Hz). δ_C ($CDCl_3$, 125MHz) 0.40 (q, $SiMe_3$), 17.1 (q, C-6), 25.1, 25.7 (s x 2, $C(\underline{C}H_3)_2$), 55.6 (q, $O\underline{C}H_3$), 67.1, 67.4, 74.2, 74.7 (d x 4, C-2, C-3, C-4, C-5), 99.0 (d, C-1), 109.8 (s, $\underline{C}(CH_3)_2$).

Methyl 6-deoxy-2,3-O-isopropylidene-α–D-talopyranoside ***31****:* Method 1: A solution of methyl 6-deoxy-5-ene-2,3-*O*-isopropylidene-β-L-ribohexopyranoside **29** (1.035 g, 4.79 mmol) in anhydrous methanol (50 ml) was added to a pre-reduced suspension of palladium on carbon (10%, 1.01 g, pre-reduced under hydrogen for 3h) in anhydrous methanol (110 ml). The resulting mixture was thoroughly degassed and stirred under hydrogen. After 3h, t.l.c. (ethyl acetate : hexane, 1:3) showed the consumption of starting material (R_f 0.3) and the formation of a major product (R_f 0.15). The reaction mixture was filtered through celite (eluant methanol) and the solvent removed. The residue was purified by repeated flash chromatography (ethyl acetate : hexane, 1:3) to give methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-talopyranoside **31** (636 mg, 62%) as a yellow oil.

Method 2: A solution of tetra-*n*-butylammonium fluoride in THF (1.1M, 2.15 ml, 3.47 equiv.) was added to a solution of methyl 6-deoxy-2,3-*O*-isopropylidene-4-*O*-trimethylsilyl-α-D-talopyranoside (620 mg, 2.14 mmol) in freshly distilled THF (17 ml) under nitrogen. After 20 minutes, t.l.c. (ethyl acetate : hexane, 1:3) showed the conversion of starting material (R_f 0.5) to one product (R_f 0.15). The reaction solvent was removed and the residue purified by flash chromatography (ethyl acetate : hexane, 1:3) to give methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-talopyranoside **31** (477 mg, 100%) as a yellow oil. $[\alpha]_D^{25}$ +47.9 (*c*, 1.3 in $CHCl_3$) {lit.,[21] $[\alpha]_D$ +48.9 (*c*, 1.3 in MeOH)}. δ_H ($CDCl_3$, 500MHz) 1.31 (d, 3H, H-6, $J_{5,6}$ 6.6Hz), 1.35, 1.56 (s x 2, 3H x 2, $C(CH_3)_2$), 2.20 (s br, 1H, OH), 3.38 (s, 3H, OMe), 3.53 (d, 1H, H-4, $J_{3,4}$ 4.7Hz), 3.80 (q, 1H, H-5, $J_{5,6}$ 6.6Hz), 4.00 (d, 1H, H-2, $J_{2,3}$ 6.4Hz), 4.18 (dd, 1H, H-3, $J_{2,3}$ 6.2Hz, $J_{3,4}$ 5.2Hz),

4.90 (s, 1H, H-1). δ_C ($CDCl_3$) 16.7 (q, C-6), 25.2, 25.8 (s x 2, $C(\underline{C}H_3)_2$), 55.1 (q, $O\underline{C}H_3$), 64.3, 66.8, 72.9, 73.2 (d x 4, C-2, C-3, C-4, C-5), 98.4 (d, C-1), 109.2 (s, $\underline{C}(CH_3)_2$).

Methyl 4-azido-4-deoxy-2,3-O-isopropylidene-α-D-rhamnopyranoside **32**: Trifluoromethanesulphonic anhydride (0.64 ml, 1.5 equiv.) was added dropwise to a solution of pyridine (0.7ml, 3.5 equiv.) and methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-talopyranoside **31** (550 mg, 2.52 mmol) in freshly distilled dichloromethane (25 ml) under nitrogen at -20°C. After 4h, t.l.c. (ethyl acetate : hexane, 1:3) showed complete conversion of starting material (R_f 0.15) to a single product (R_f 0.3). The reaction mixture was diluted with dichloromethane (70 ml) and washed with dilute hydrochloric acid (2M, 15 ml), saturated aqueous sodium hydrogencarbonate (15 ml) and brine (15 ml). The organic fraction was dried (magnesium sulphate), filtered and the solvent removed. The residue was dissolved in dry DMF (20 ml) under nitrogen and sodium azide (360 mg) added. The reaction mixture was placed in a sonic bath for 15 minutes and was then stirred at room temperature for 22h at which point t.l.c. (ethyl acetate : hexane, 1:3) showed the formation of a single product (R_f 0.55). The solvent was removed and the residue partitioned between dichloromethane (75 ml) and distilled water (20 ml). The aqueous layer was further extracted with dichloromethane (15 ml x 2). The organic extracts were combined, washed with brine (15 ml x 2), dried (magnesium sulphate), filtered and the solvent removed. The residue was purified by flash chromatography (ethyl acetate : hexane, 1:19) to yield methyl 4-azido-4-deoxy-2,3-*O*-isopropylidene-α-D-rhamnopyranoside **32** (411 mg, 67%) as a colourless oil. (Found C, 49.72; H, 7.37; N, 17.10%; $C_{10}H_{17}O_4N_3$ requires C, 49.37; H, 7.04; N, 17.27%). $[\alpha]_D^{21}$ +7.8 (*c*, 0.6 in $CHCl_3$). ν_{max} (film) 2113cm^{-1} (N_3). *m/z* (NH_3, DCI): 244 ($M + H^+$, 15), 229 ($M + NH_4^+$ - MeOH, 13), 216 ($M + H^+$ - N_2, 100), 186 (77), 172 (90%). δ_H ($CDCl_3$) 1.28 (d, 3H, H-6, $J_{5,6}$ 6.3Hz), 1.35, 1.54 (s x 2, 3H x 2, $C(CH_3)_2$), 3.15 (dd, 1H, H-4, $J_{3,4}$ 8.2Hz, $J_{4,5}$ 10.3Hz), 3.35 (s, 3H, OMe), 3.52 (dq, 1H, H-5, $J_{4,5}$ 10.4Hz, $J_{5,6}$ 6.3Hz), 4.06 (d, 1H, H-2, $J_{2,3}$ 5.5Hz), 4.12 (dd, 1H, H-3, $J_{2,3}$ 5.4Hz, $J_{3,4}$ 8.1Hz), 4.86 (s, 1H, H-1). δ_C ($CDCl_3$) 17.8 (q, C-6), 26.1, 28.0 (q x 2, $C(\underline{C}H_3)_2$), 54.9 (q, $O\underline{C}H_3$), 64.1, 66.7, 75.0, 76.6 (d x 4, C-2, C-3, C-4, C-5), 98.0 (d, C-1), 110.0 (s, $\underline{C}(CH_3)_2$).

4-Azido-4-deoxy-α,β-D-rhamnopyranose **33**: Aqueous trifluoroacetic acid (1:1 v/v, 20 ml) was added dropwise to a solution of methyl 4-azido-4-deoxy-2,3-*O*-isopropylidene-α-D-rhamnopyranoside **32** (400 mg, 1.65 mmol) in 1,4-dioxan (1 ml). The resulting solution was heated under reflux. After 42h, t.l.c. (ethyl acetate) showed the formation from starting material (R_f 0.9), via an intermediate (R_f 0.65), of a mixture of products (R_f 0.5). The reaction mixture was cooled and the solvent removed. The residue was co-evaporated with toluene (1 ml x 4) and purified by flash chromatography (ethyl acetate : hexane, 1:1) to yield 4-azido-4-deoxy-α,β-D-rhamnopyranose **33** (209 mg, 67%) as a white crystalline solid, m.p. 117-120°C (ethyl acetate/hexane) {lit.,[22] m.p. 118-118.5°C (ethanol/n-pentane)}. $[\alpha]_D^{23}$ +13.9, (initial) +25.4 (30min), +54.8 (equilibrium) (*c*, 0.64 in MeOH) {lit.,[22] $[\alpha]_D^{27}$ +21.6 (initial), +57.4 (30min) (*c*, 1.0 in MeOH)}. δ_H (CD_3CN, 500MHz) [a 3:2 mixture of anomers, ' indicating the minor anomer] 1.22 (d, 1.8H, H-6, $J_{5,6}$ 6.2Hz), 1.25 (d, 1.2H, H-6', $J_{5',6'}$ 5.8Hz), 3.17 (m, 0.8H, H-4', H-5'), 3.25 (pt, 0.6H, H-4, $J_{3,4}$ 10.0Hz, $J_{4,5}$ 10.0Hz), 3.53 (dd, 0.4H, H-3', $J_{2',3'}$ 3.3Hz, $J_{3',4'}$ 9.3Hz), 3.65 (dq, 0.6H, H-5, $J_{4,5}$ 10.1Hz, $J_{5,6}$ 6.2Hz), 3.69 (dd, 0.6H, H-2, $J_{1,2}$ 1.7Hz, $J_{2,3}$ 3.3Hz), 3.72 (dd, 0.4H, H-2', $J_{1',2'}$ 0.7Hz, $J_{2',3'}$ 3.3Hz), 3.74 (dd, 0.6H, H-3, $J_{2,3}$ 3.3Hz, $J_{3,4}$ 9.9Hz), 4.59 (s, 0.4H, H-1'), 4.97 (d, 0.6H, H-1, $J_{1,2}$ 1.5Hz). δ_C (CD_3CN, 125MHz) 18.7 (q x 2, C-6), 66.0, 66.6, 67.0, 70.6, 71.0, 71.5, 71.9, 73.7 (d x 8, C-2, C-3, C-4, C-5), 94.5, 94.8 (d x 2, C-1).

4-Azido-4-deoxy-D-rhamnono-1,5-lactone **34**: 4-Azido-4-deoxy-α,β-D-rhamnopyranose **33** (96 mg, 0.51 mmol) was dissolved in aqueous 1,4-dioxan (1:3 dioxan : water, 12 ml) and barium carbonate (323 mg, 3.09 equiv.) added. Bromine (0.1 ml, 3.66 equiv.) was then slowly added to the mixture with vigorous stirring. After 2h t.l.c. (ethyl acetate) showed complete conversion of starting material (R_f 0.35) to a single product (R_f 0.5). The reaction mixture was filtered, air passed through the resulting filtrate until decolourized, and the

solvent removed. The residue was extracted with boiling ethyl acetate (20 ml x 2). The extracts were combined, filtered and the solvent removed to yield 4-azido-4-deoxy-D-rhamnono-1,5-lactone **34** (71 mg, 75%) as a white crystalline solid, m.p. 112-114°C (ethyl acetate/hexane). (Found: C, 38.66; H, 4.47; N 22.08%; $C_9H_{13}O_4N_3$ requires C, 38.51; H, 4.85; N, 22.45%). $[\alpha]_D^{25}$ +128.8 (*c*, 0.82 in EtOAc). ν_{max} (film) 3349cm^{-1} (O-H), 2111cm^{-1} (N_3), 1751cm^{-1} (C=O). *m/z* (NH_3, DCI) 205 ($M+NH_4^+$, 100), 160 ($M+H^+-H_2O$, 41%). δ_H (CD_3CN, 500MHz) 1.43 (d, 3H, H-6, $J_{5,6}$ 6.2Hz), 3.56 (dd, 1H, H-4, $J_{3,4}$ 2.2Hz, $J_{4,5}$ 9.6Hz), 4.19 (dq, 1H, H-5, $J_{4,5}$ 9.6Hz, $J_{5,6}$ 6.3Hz), 4.20 (dd, 1H, H-3, $J_{2,3}$ 4.4Hz, $J_{3,4}$ 2.4Hz), 4.45 (d, 1H, H-2, $J_{2,3}$ 4.3Hz). δ_C (CD_3CN, 125MHz) 19.3 (q, C-6), 68.1, 69.1, 73.0, 74.3 (d x 4, C-2, C-3, C-4, C-5), 172.9 (s, C-1).

4-Azido-4-deoxy-2,3-O-isopropylidene-D-rhamnono-1,5-lactone 35: Method 1: A solution of *p*-toluenesulphonic acid (10 mg) in 2,2-dimethoxypropane (0.51 ml) was added to a solution of 4-azido-4-deoxy-α,β-D-rhamnopyranose **33** (370 mg, 1.96 mmol) in DMF (10.5 ml) under nitrogen at 80°C. After 2h, t.l.c. (ethyl acetate) showed the consumption of starting material and the formation of a mixture of products (R_f 0.6). The reaction solution was cooled, stirred with excess sodium hydrogencarbonate, filtered and the solvent removed. The residue was purified by flash chromatography and then dissolved in aqueous 1,4-dioxan (30 ml, 1:3, dioxan : water) and barium carbonate (986 mg) added. Bromine (0.3 ml) was then slowly added to the mixture with vigorous stirring. After 2h, t.l.c. (ethyl acetate : hexane, 1:1) showed the consumption of starting material (R_f 0.35) and the formation of a single product (R_f 0.4). The reaction mixture was filtered and air passed through the resulting filtrate, until decolourized, and the solvent removed. The residue was extracted with boiling ethyl acetate (20 ml x 2). The extracts were combined, filtered and the solvent removed. The residue was purified by flash chromatography (ethyl acetate : toluene, 1:3) to give 4-azido-4-deoxy-2,3-*O*-isopropylidene-D-rhamnono-1,5-lactone **35** (232 mg, 52% over 2 steps) as a white solid.

Method 2: 4-Azido-4-deoxy-D-rhamnono-1,5-lactone **34** (65 mg, 0.27 mmol) was dissolved in acetone (5 ml, AR grade) that had been previously acidified with concentrated sulphuric acid (5 drops), and stirred under nitrogen at room temperature. After 2h, t.l.c. (ethyl acetate : hexane, 1:1) showed the formation from starting material (R_f 0.1) of a single product (R_f 0.4). The reaction solution was neutralised using dry triethylamine and the solvent removed giving a brown oil. This residue was purified by flash chromatography (ethyl acetate : hexane, 1:3) to give 4-azido-4-deoxy-2,3-*O*-isopropylidene-D-rhamnono-1,5-lactone **26** (60 mg, 76%) as a white crystalline solid, m.p. 93-94°C (ethyl acetate/hexane). (Found: C, 47.55; H, 5.42; N 18.82%; $C_9H_{13}O_4N_3$ requires C, 47.57; H, 5.77; N, 18.49%). $[\alpha]_D^{25}$ +101.6 (*c*, 0.73 in $CHCl_3$). ν_{max} (film) 2114cm^{-1} (N_3), 1763cm^{-1} (C=O). *m/z* (NH_3, DCI): 245 ($M+NH_4^+$, 82), 228 ($M+H^+$, 24), 200 ($M+NH_4^+-N_2$, 100%). δ_H ($CDCl_3$, 500MHz) 1.45, 1.51 (s x 2, 3H x 2, $C(CH_3)_2$), 1.51 (d, 3H, H-6, $J_{5,6}$ 6.2Hz), 3.46 (dd, 1H, H-4, $J_{3,4}$ 6.9Hz, $J_{4,5}$ 10.3Hz), 4.19 (dq, 1H, H-5, $J_{4,5}$ 10.3Hz, $J_{5,6}$ 6.2Hz), 4.51 (dd, 1H, H-3, $J_{2,3}$ 8.1Hz, $J_{3,4}$ 7.0Hz), 4.70 (d, 1H, H-2, $J_{2,3}$ 8.2Hz). δ_C ($CDCl_3$ 125MHz) 18.0 (q, C-6), 25.2, 26.7 (q x 2, $C(\underline{C}H_3)_2$), 65.6, 71.8, 73.6, 77.2 (d x 4, C-2, C-3, C-4, C-5), 112.7 (s, $\underline{C}(CH_3)_2$), 168.2 (s, C-1).

4-Azido-4-deoxy-2,3-O-isopropylidene-D-rhamnonoamide: A solution of 4-azido-4-deoxy-2,3-*O*-isopropylidene-D-rhamnono-1,5-lactone **35** (140 mg, 0.62 mmol) in methanol (1.5 ml, anhydrous) was added to a freshly prepared saturated solution of ammonia in methanol (6 ml, anhydrous) and stirred under nitrogen at room temperature. After 1h, t.l.c. (ethyl acetate : hexane, 1:1) showed complete conversion of starting material (R_f 0.4) to a single product (R_f 0.1). The solvent was removed and the residue purified by flash chromatography (ethyl acetate : hexane, 3:1) to give 4-azido-4-deoxy-2,3-*O*-isopropylidene-D-rhamnonoamide (150 mg, 100%) as a hygroscopic yellow oil. $[\alpha]_D^{25}$ -14.8 (*c*, 0.66 in $CHCl_3$). ν_{max} (film) 3349cm^{-1} (br, OH, NH), 2110cm^{-1} (N_3), 1675cm^{-1} (amide I), 1585cm^{-1} (amide II). *m/z* (NH_3, DCI): 245 (M + H^+, 100), 217 (M + H^+ - N_2, 38), 173 (25%). δ_H (CD_3CN, 500MHz) 1.27 (d, 3H, H-6, $J_{5,6}$ 6.2Hz), 1.37, 1.56 (s x 2, 3H x 2, $C(CH_3)_2$), 3.31 (dd, 1H, H-4, $J_{3,4}$ 3.4Hz, $J_{4,5}$ 8.2Hz), 3.78 (dq, 1H, H-5, $J_{4,5}$

8.2Hz, $J_{5,6}$ 6.3Hz), 4.58 (d, 1H, H-2, $J_{2,3}$ 8.1Hz), 4.74 (dd, 1H, H-3, $J_{2,3}$ 8.2Hz, $J_{3,4}$ 3.4Hz), 6.23 (s br, 1H, NH), 6.80 (s br, 1H, NH). δ_C (CD_3CN, 125MHz) 21.3 (q, C-6), 24.4, 26.4 (q x 2, $C(\underline{C}H_3)_2$), 66.3, 68.0, 76.5, 77.5 (d x 4, C-2, C-3, C-4, C-5), 110.4 (s, $\underline{C}(CH_3)_2$), 173.7 (s, C-1).

4-Azido-4-deoxy-2,3-O-isopropylidene-D-rhamnononitrile ***36***: Trifluoroacetic anhydride (0.37 ml, 4.3 equiv.) was added to a solution of 4-azido-4-deoxy-2,3-*O*-isopropylidene-D-rhamnonoamide (150 mg, 0.615 mmol) in dry pyridine (4 ml) under nitrogen at -30°C. After 1.5h, t.l.c. (ethyl acetate : hexane, 1:1) showed the formation from starting material (R_f 0.1) of a major product (R_f 0.5). Excess anhydride was quenched by the addition of methanol (1 ml) and the reaction solvent removed. The residue was purified by flash chromatography (ethyl acetate : hexane, 1:3) to give 4-azido-4-deoxy-2,3-*O*-isopropylidene-D-rhamnononitrile **36** (110 mg, 86%) as a colourless oil, $[\alpha]_D^{23}$ +24.8 (*c*, 0.84 in $CHCl_3$). (Found C, 47.70; H, 6.45; N, 24.89%; $C_9H_{14}N_4O_3$ requires C, 47.78; H, 6.24; N, 24.76%). ν_{max} (film) 3491cm^{-1} (br, OH, NH), 2218cm^{-1} (w, CN), 2115cm^{-1} (N_3). *m/z* (NH_3, DCI): 244 (M + NH_4^+, 44), 227 (M + H^+, 53), 201 (42), 199 (M + H^+, 32), 155 (100%). δ_H ($CDCl_3$, 500MHz) 1.42 (d, 3H, H-6, $J_{5,6}$ 5.8Hz), 1.43, 1.62 (s x 2, 6H, $C(CH_3)_2$), 3.64 (m, 2H, H-4, H-5), 4.21 (dd, 1H, H-3, $J_{2,3}$ 5.1Hz, $J_{3,4}$ 8.7Hz), 4.95 (d, 1H, H-2, $J_{2,3}$ 5.2Hz). δ_C ($CDCl_3$) 21.3 (q, C-6), 26.0, 26.9 (q x 2, $C(\underline{C}H_3)_2$), 67.2, 67.8, 68.1 (d x 3, C-3, C-4, C-5), 79.4 (d, C-2), 111.5 (s, $\underline{C}(CH_3)_2$), 117.3 (s, C-1).

(5R,6S,7R)-5,6,7-Trihydro-5-(1R-1-hydroxyethyl)-6,7-O-isopropylidenepyrrolo[1,2-d]tetrazole-6,7-diol ***37***: 4-Azido-4-deoxy-2,3-*O*-isopropylidene-D-rhamnononitrile **36** (52 mg, 0.23 mmol) was dissolved in DMSO (anhydrous, 1.65 ml) and heated at 110-120°C. After 115h, t.l.c. (ethyl acetate) showed the formation of a single product (R_f 0.5) from starting material (R_f 0.7). The reaction solution was cooled, and the solvent removed. The residue was purified by flash chromatography (ethyl acetate : hexane, 1:1) to give (5*R*,6*S*,7*R*)-5,6,7-trihydro-5-(1*R*-1-hydroxyethyl)-6,7-*O*-isopropylidenepyrrolo[1,2-d]tetrazole-6,7-diol **37** (45 mg, 87%) as a colourless crystalline solid, m.p. 147-152°C (ethyl acetate/hexane). (Found C, 48.03; H, 6.00, N, 24.79%; $C_9O_3N_4H_{14}$ requires C, 47.78; H, 6.24; N, 24.76%). $[\alpha]_D^{22}$ +9.4 (c, 0.69 in MeOH). ν_{max} (film) 3400cm^{-1} (br, OH). m/z (NH_3,DCI): 227 (M+H+, 100). δ_H (CD_3CN, 500MHz) 1.29, 1.44 (s x 2, 3H x 2, $C(CH_3)_2$), 1.57 (d, 3H, $CH(OH)C\underline{H}_3$, *J* 6.3Hz), 3.33 (d, 1H, OH, *J* 6.3Hz), 4.30 (dqu, 1H, $C\underline{H}(OH)CH_3$, *J* 6.3Hz, $J_{CH,5}$ 7.0Hz), 4.46 (dd, 1H, H-5, $J_{5,6}$ 4.2Hz, $J_{CH,5}$ 7.2Hz), 5.61 (m, 2H, H-6, H-7). δ_C (CD_3CN, 125MHz) 21.0 (q, $CH(OH)\underline{C}H_3$), 25.4,26.7 (q x 2, $C(CH_3)_2$), 65.9, 66.3, 70.9, 86.4 (d x 4, C-5, C-6, C-7, $\underline{C}H(OH)CH_3$), 114.9 (s, $\underline{C}(CH_3)_2$), 161.4 (s, C-7a).

(5R,6S,7R)-5,6,7-Trihydro-5-(1R-1-hydroxyethyl)pyrrolo[1,2-d]tetrazole-6,7-diol ***18***: (5*R*,6*S*,7*R*)-5,6,7-Trihydro-5-(1*R*-1-hydroxyethyl)-6,7-*O*-isopropylidenepyrrolo[1,2-d]tetrazole-6,7-diol **37** (41 mg, 0.18 mmol) was dissolved in aqueous trifluoroacetic acid (50% v/v, 3 ml). After 23h, t.l.c. (ethyl acetate) showed complete conversion of starting material (R_f 0.5) to a single product (R_f 0.1). The solvent was removed and the residue was purified by flash chromatography (ethyl acetate) to give (5*R*,6*S*,7*R*)-5,6,7-trihydro-5-(1*R*-1-hydroxyethyl)pyrrolo[1,2-d]tetrazole-6,7-diol **18** (29 mg, 85%) as a white crystalline compound, m.p. 161-163.5°C (ethanol/ethyl acetate). (HRMS *m/z* (CI+): Found 187.082915 (M+H$^+$); $C_6H_{11}N_4O_3$ requires 187.083115). $[\alpha]_D^{21}$ +39.4 (*c*, 0.93 in H_2O). ν_{max} (film) 3400 cm^{-1} (br, O-H). *m/z* (NH_3, DCI): 187 (M+H$^+$, 12), 159 (M+H$^+$-N_2, 100), 141 (M+H$^+$-H_2O-N_2, 24%). δ_H (CD_3CN, 500MHz) 1.47 (d, 3H, -$CH(OH)C\underline{H}_3$, *J* 6.6Hz), 3.86 (s br, 1H, OH, exchanges in D_2O), 4.32 (qd, 1H, $C\underline{H}(OH)CH_3$, $J_{CH,5}$ 5.4Hz, *J* 6.5Hz), 4.41 (s br, 2H, OH x 2), 4.52 (t, 1H, H-5, *J* 5.3Hz), 5.06 (t, 1H, H-6, *J* 5.5Hz), 5.08 (d, 1H, H-7, $J_{6,7}$ 5.6Hz). δ_C (CD_3CN, 125MHz) 20.3 (q, $CH(OH)\underline{C}H_3$), 63.8, 65.4, 67.0, 77.7 (d x 4, C-5, C-6, C-7, -$\underline{C}H(OH)CH_3$), 161.9 (s, C-7a).

Methyl 2,3-O-isopropylidene-α-L-rhamnopyranoside ***39***: Acetyl chloride (3.5 ml, 4.5 equiv.) was added to a solution of α-L-rhamnose monohydrate **38** (11.31 g, 62 mmol) in methanol (anhydrous, 150 ml) and refluxed

under nitrogen. After 21h, t.l.c. (ethyl acetate) showed the formation of a major product (R_f 0.2). The reaction solution was cooled, neutralised with sodium hydrogencarbonate and the solvent removed. The residue was dissolved in ethyl acetate, passed through a silica plug (eluant ethyl acetate), the solvent removed and the residue dissolved in acetone (250 ml) under nitrogen. To the resulting solution, camphorsulphonic acid (0.2 g) and then 2,2-dimethoxypropane (40 ml) were added. After 18h, t.l.c. (ethyl acetate : hexane, 1:1) showed the formation of a major product (R_f 0.4) from starting material (Rf 0). The reaction solution was neutralised with aqueous ammonia solution (d 0.880) and the solvent removed. The residue was dissolved in chloroform (200 ml) and washed with distilled water (50 ml). The aqueous layer was re-extracted (50 ml x 5), the organic fractions combined, dried (magnesium sulphate), filtered and the solvent removed. The residue was purified by flash chromatography (ethyl acetate : hexane, 1:3) to give methyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside **39** (12.08 g, 89%) as a yellow oil. $[\alpha]_D^{23}$ -12.0 (*c*, 2.3 in H_2O) {lit.,[23] $[\alpha]_D^{21}$ -10.65 (*c*, 1.88 in H_2O)}. δ_H ($CDCl_3$) 1.31 (d, 3H, H-6, $J_{5,6}$ 6.3Hz), 1.35, 1.53 (s x 2, 3H x 2, $C(CH_3)_2$), 2.67 (s br, 1H, OH), 3.63 (1H, dq, H-5, $J_{4,5}$ 9.3Hz), 3.36-3.39 (m, 1H), 4.05-4.14 (m, 2H), 4.85 (s, 1H, H-1). δ_C ($CDCl_3$) 17.2 (q, C-6), 25.9, 27.8 (q x 2, $C(\underline{C}H_3)_2$), 54.7 (q, OMe), 65.5, 74.3, 75.7, 78.5 (d x 4, C-2, C-3, C-4, C-5), 98.1 (d, C-1), 109.5 (s, $\underline{C}(CH_3)_2$).

Methyl-6-deoxy-2,3-O-isopropylidene-α–L-talopyranoside ***40***: Methyl-2,3-*O*-isopropylidene-α–L-rhamnopyranoside **39** (12.08 g, 0.055 mol), dried powdered molecular sieve (47.8 g) and pyridinium chlorochromate (48 g, 4.02 equiv.) were stirred in dry dichloromethane (500 ml) under nitrogen at room temperature for 12h. At this point t.l.c. (ethyl acetate : hexane, 1:3) showed complete conversion of starting material (R_f 0.15) to product (R_f 0.3). The reaction mixture was triturated with ether (500 ml), and filtered through a silica plug topped with celite (ether eluant). The solvent was then removed to leave crude methyl-6-deoxy-2,3-*O*-isopropylidene-α–L-lyxohexopyran-4-uloside. ν_{max} (film) 1743 cm^{-1} (C=O). *m/z* (NH_3,DCI): 234 ($M+NH_4^+$,68), 219 ($M+H^+$,100), 204 ($M+NH_4^+$-MeOH, 34), 187 ($M+H^+$-MeOH, 50%). δ_H ($CDCl_3$, 500MHz) 1.36, 1.48 (s x 2, 3H x 2, $C(CH_3)_2$), 1.39 (d, 3H, H-6, $J_{5,6}$ 6.8Hz), 3.45 (3H, s, OMe), 4.23 (d, 1H, H-5, $J_{5,6}$ 6.8Hz), 4.40 (d, 1H, H-3, $J_{2,3}$ 6.9Hz), 4.42 (dd, 1H, H-2, $J_{1,2}$ 0.7Hz, $J_{2,3}$ 6.5Hz), 4.83 (s, 1H, H-1). δ_C ($CDCl_3$) 15.7 (q, C-6), 25.4,26.6 (q x 2, $C(\underline{C}H_3)_2$), 55.8 (q, OCH_3), 69.7, 75.9, 78.7 (d, C-2, C-3, C-5), 98.2 (d x 3, C-1), 111.5 (s, $\underline{C}Me_2$), 205.2 (s, C-4). This was immediately dissolved in ethanol : water (600 ml, 9:1) and cooled to 0°C. Sodium borohydride (4 g) was added and the solution stirred at 0°C. After 2h, t.l.c. (ethyl acetate : hexane, 1:3) indicated the formation of a single product (R_f 0.15). The reaction was quenched by addition of an excess of ammonium chloride with stirring until effervescence ceased. The solvent was removed and the residue dissolved in chloroform (500 ml), washed with distilled water (100 ml x 2), brine (100 ml), dried (magnesium sulphate), filtered and the solvent removed to yield methyl-6-deoxy-2,3-*O*-isopropylidene-α–L-talopyranoside **40** (11.1 g, 92% over two steps) as a viscous pale yellow oil. $[\alpha]_D^{23}$ -43.8 (*c*, 1.62 in $CHCl_3$), identical in all other respects to enantiomer **31** described above.

Methyl-4-azido-4-deoxy-2,3-O-isopropylidene-α-L-rhamnopyranoside ***41***: Methyl-6-deoxy-2,3-*O*-isopropylidene-α–L-talopyranoside **40** (11.1 g, 0.051 mol) was dissolved in dry dichloromethane (400 ml). Pyridine (12.5 ml, 3.17 equiv.) was added and the solution stirred at -20°C under nitrogen. Trifluoromethanesulphonic anhydride (12.1 ml, 1.41 equiv.) was added slowly. After 5h, t.l.c. (ethyl acetate : hexane, 1:3) indicated complete conversion of starting material (R_f 0.15) to product (R_f 0.3). The reaction mixture was diluted with dichloromethane (1 l), washed with dilute hydrochloric acid (2M, 200 ml), saturated aqueous sodium hydrogencarbonate (200 ml), brine (200 ml), dried (magnesium sulphate), filtered and the solvent removed. The residue was immediately dissolved in dry DMF (300 ml) and sodium azide (5.94 g) added. The reaction mixture was placed in a sonic bath for 15 minutes and was then stirred under nitrogen at room temperature for 21h when t.l.c. (ethyl acetate : hexane, 1:3) indicated the formation of a single product (R_f 0.55). The solvent was removed and the residue partitioned between dichloromethane (1 l) and distilled

water (200 ml). The organic extract was washed with brine (2 x 200 ml), dried (magnesium sulphate), filtered and the solvent removed. The residue was purified by flash chromatography (ethyl acetate : hexane, 1:19) to yield methyl-4-azido-4-deoxy-2,3-*O*-isopropylidene-α-L-rhamnopyranoside **41** (8.5 g, 69% over 2 steps) as a colourless oil. $[\alpha]_D^{22}$ -8.2 (*c*, 0.97 in $CHCl_3$), identical in all other respects to enantiomer **32** described above.

4-Azido-4-deoxy-α,β-L-rhamnopyranose ***42:*** Methyl-4-azido-4-deoxy-2,3-*O*-isopropylidene-α-L-rhamnopyranoside **41** (4.2 g, 0.017 mol) was dissolved in 1,4-dioxan (12 ml), aqueous trifluoroacetic acid (220 ml, 1:1 by volume) slowly added and the resulting solution was then heated under reflux. After 32h, t.l.c. (ethyl acetate) showed complete conversion of the starting material to a single product (R_f 0.5) via the intermediate methyl 4-azido-4-deoxy-α-L-rhamnopyranoside (R_f 0.65), a small sample of which was purified by flash chromatography (ethyl acetate : hexane, 1:1) white crystalline solid, m.p. 79-83°C (ether/hexane). (Found: C, 41.70; H, 6.34; N, 20.51%; $C_7H_{13}O_4N_3$ requires C, 41.38; H, 6.45; N, 20.68%). $[\alpha]_D^{24}$ -124.0 (*c*, 0.68 in MeOH). ν_{max} (film) 3400 cm^{-1} (OH), 2113 cm^{-1} (N_3). *m/z* (NH_3,DCI): ($M+NH_4^+$, 100), 189 ($M+NH_4^+$-MeOH, 51%). δ_H ($CDCl_3/D_2O$, 500MHz) 1.36 (d, 3H, H-6, $J_{5,6}$ 6.3Hz), 3.28 (pt, 1H, H-4, *J* 9.9Hz), 3.36 (s, 3H, OMe), 3.58 (dq, 1H, H-5, $J_{4,5}$ 10.0Hz, $J_{5,6}$ 6.3Hz), 3.82 (dd, 1H, H-3, $J_{2,3}$ 3.4Hz, $J_{3,4}$ 9.8Hz), 3.90 (dd, 1H, H-2, $J_{1,2}$ 1.6Hz, $J_{2,3}$ 3.4Hz), 4.69 (d, 1H, H-1, $J_{1,2}$ 1.6Hz). δ_C ($CDCl_3$) 18.2 (q, C-6), 55.0 (q, O<u>C</u>H_3), 65.9, 66.5, 70.1, 70.4 (d x 4, C-2, C-3, C-4, C-5), 100.6 (d, C-1). The reaction mixture was cooled and the solvent removed. The residue was co-evaporated with toluene (3 x 15 ml) and purified by flash chromatography (ethyl acetate : hexane, 1:1) to yield 4-azido-4-deoxy-α,β-L-rhamnopyranose **42** (2.19 g, 67% over 2 steps) as a white crystalline solid, m.p. 119-120°C (ethyl acetate/hexane). (Found: C, 38.39; H, 5.79; N, 21.95%; $C_6H_{11}O_4N_3$ requires C, 38.10; H, 5.86; N, 22.21%). $[\alpha]_D^{24}$ -17.5 (initial), -23.1 (40min), -57.6 (equilibrium) (*c*, 1.07 in MeOH), identical in all other respects to enantiomer **33** described above.

4-Azido-4-deoxy-L-rhamnono-1,5-lactone ***43:*** 4-Azido-4-deoxy-α,β-L-rhamnopyranose **42** (523 mg, 2.77 mmol) was dissolved in aqueous 1,4-dioxan (40 ml, 1:3, dioxan : water) and barium carbonate (1.75 g, 3.05 equiv.) added. Bromine (0.5ml, 3.5 equiv.) was then slowly added to the mixture with vigorous stirring. After 3h t.l.c. (ethyl acetate) showed complete conversion of starting material (R_f 0.35) to a single product (R_f 0.5). The reaction mixture was filtered and air passed through the resulting filtrate, until decolourized, and the solvent removed. The residue was extracted with boiling ethyl acetate. The extracts were combined, filtered and the solvent removed to yield 4-azido-4-deoxy-L-rhamnono-1,5-lactone **43** (385 mg, 74%) as a white crystalline solid, m.p. 114-115°C (ethyl acetate/hexane). $[\alpha]_D^{21}$ -134.0 (*c*, 1.17 in EtOAc), identical in all other respects to enantiomer **34** described above.

4-Azido-4-deoxy-2,3-O-isopropylidene-L-rhamnono-1,5-lactone ***44:*** 4-Azido-4-deoxy-L-rhamnono-1,5-lactone **43** (128 mg, 0.27 mmol) was dissolved in acetone (25 ml, AR grade) that had been previously acidified with concentrated sulphuric acid (25 drops), and stirred under nitrogen at room temperature. After 21h t.l.c. (ethyl acetate : hexane, 1:1) indicated the formation of a single product (R_f 0.4). The reaction mixture was neutralised with dry triethylamine and the solvent removed giving a brown oil. This residue was purified by flash chromatography (ethyl acetate : hexane, 1:3) to yield 4-azido-4-deoxy-2,3-*O*-isopropylidene-L-rhamnono-1,5 lactone **44** (122 mg, 78%) as a white crystalline solid, m.p. 93-95°C (ethyl acetate/hexane). $[\alpha]_D^{23}$ -104.8 (*c*, 1.27 in $CHCl_3$), identical in all other respects to enantiomer **35** described above.

4-Azido-4-deoxy-2,3-O-isopropylidene-L-rhamnonamide: A solution of 4-azido-4-deoxy-2,3-*O*-isopropylidene-L-rhamnono-1,5-lactone (128 mg, 0.56 mmol) in methanol (1 ml, anhydrous) was added to a freshly prepared saturated solution of ammonia in methanol (5 ml, anhydrous) and stirred under nitrogen at room temperature. After 10 minutes, t.l.c. (ethyl acetate : hexane, 1:1) showed complete conversion of starting

material (R_f 0.4) to one product (R_f 0.1). The solvent was removed to yield 4-azido-4-deoxy-2,3-*O*-isopropylidene-L-rhamnonamide (137 mg, 100%) as a colourless oil. $[\alpha]_D^{22}$ +16.3 (*c*, 0.73 in $CHCl_3$), identical in all other respects to enantiomer described above.

4-Azido-4-deoxy-2,3-O-isopropylidene-L-rhamnononitrile ***45****:* 4-Azido-4-deoxy-2,3-*O*-isopropylidene-L-rhamnonamide (133 mg, 0.545 mmol) was dissolved in distilled pyridine (3.5 ml) and cooled to -30°C. Trifluoroacetic anhydride (0.35 ml) was added. After 5h, t.l.c. (ethyl acetate : hexane, 1:3) indicated the formation of a major product (R_f 0.5). Remaining anhydride was quenched by the addition of methanol (2 ml) and the reaction solvent removed. The residue was purified by flash chromatography (ethyl acetate : hexane, 1:3) to give 4-azido-4-deoxy-2,3-*O*-isopropylidene-L-rhamnononitrile **45** (101 mg, 82%) as a colourless oil. $[\alpha]_D^{23}$ -27.1 (*c*, 0.83 in $CHCl_3$), identical in all other respects to enantiomer **36** described above.

(5S,6R,7S)-5,6,7-trihydro-5-(1S-1-hydroxyethyl)-6,7-O-isopropylidenepyrrolo[1,2-d]tetrazole-6,7-diol ***46****:* 4-Azido-4-deoxy-2,3-*O*-isopropylidene-L-rhamnononitrile **45** (70 mg, 0.31 mmol) was dissolved in anhydrous DMSO (3 ml) and heated at 110-120°C. After 186h, t.l.c. (ethyl acetate : hexane, 1:1) showed the conversion of starting material (R_f 0.5) to a single product (R_f 0.1). The reaction solution was cooled, the solvent removed and the residue purified by flash chromatography (ethyl acetate : hexane, 1:1) to give (5*S*,6*R*,7*S*)-5,6,7-trihydro-5-(1*S*-1-hydroxyethyl)-6,7-*O*-isopropylidenepyrrolo[1,2-d]tetrazole-6,7-diol **46** (63 mg, 90%) as a white crystalline solid, m.p. 150.5-152°C (ethyl acetate/hexane). $[\alpha]_D^{22}$ -11.9 (*c*, 0.43 in MeOH), identical in all other respects to enantiomer **37** described above.

(5S,6R,7S)-5,6,7-Trihydro-5-(1S-1-hydroxyethyl)pyrrolo[1,2-d]tetrazole-6,7-diol ***19****:* (5*S*,6*R*,7*S*)-5,6,7-Trihydro-5-(1*S*-1-hydroxyethyl)-6,7-*O*-isopropylidenepyrrolo[1,2-d]tetrazole-6,7-diol **46** (63 mg, 0.279 mmol) were dissolved in aqueous trifluoroacetic acid (4.5 ml, 50% by volume) and the resulting solution stirred. After 22h t.l.c. (ethyl acetate) showed complete conversion of starting material (R_f 0.5) to a single product (R_f 0.1). The solvent was removed and the residue was purified by flash chromatography (ethyl acetate) to give (5*S*,6*R*,7*S*)-5,6,7-trihydro-5-(1*S*-1-hydroxyethyl)pyrrolo[1,2-d]tetrazole-6,7-diol **19** (42 mg, 82%) as a white crystalline compound, m.p. 162.5-164°C (ethanol/ethyl acetate). $[\alpha]_D^{24}$ -36.3 (*c*, 0.71 in H_2O), identical in all other respects to enantiomer **18** described above.

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24. This work was supported by a BBSRC CASE studentship.