SYNTHESIS OF HOMOCHIRAL β-HYDROXY-α-AMINOACIDS [(2S,3R,4R)-3,4-DIHYDROXYPROLINE AND (2S,3R,4R)-3,4-DIHYDROXYPIPECOLIC ACID] AND OF 1,4-DIDEOXY-1,4-IMINO-D-ARABINITOL [DAB1] AND FAGOMINE [1,5-IMINO-1,2,5-TRIDEOXY-D-ARABINO-HEXITOL]

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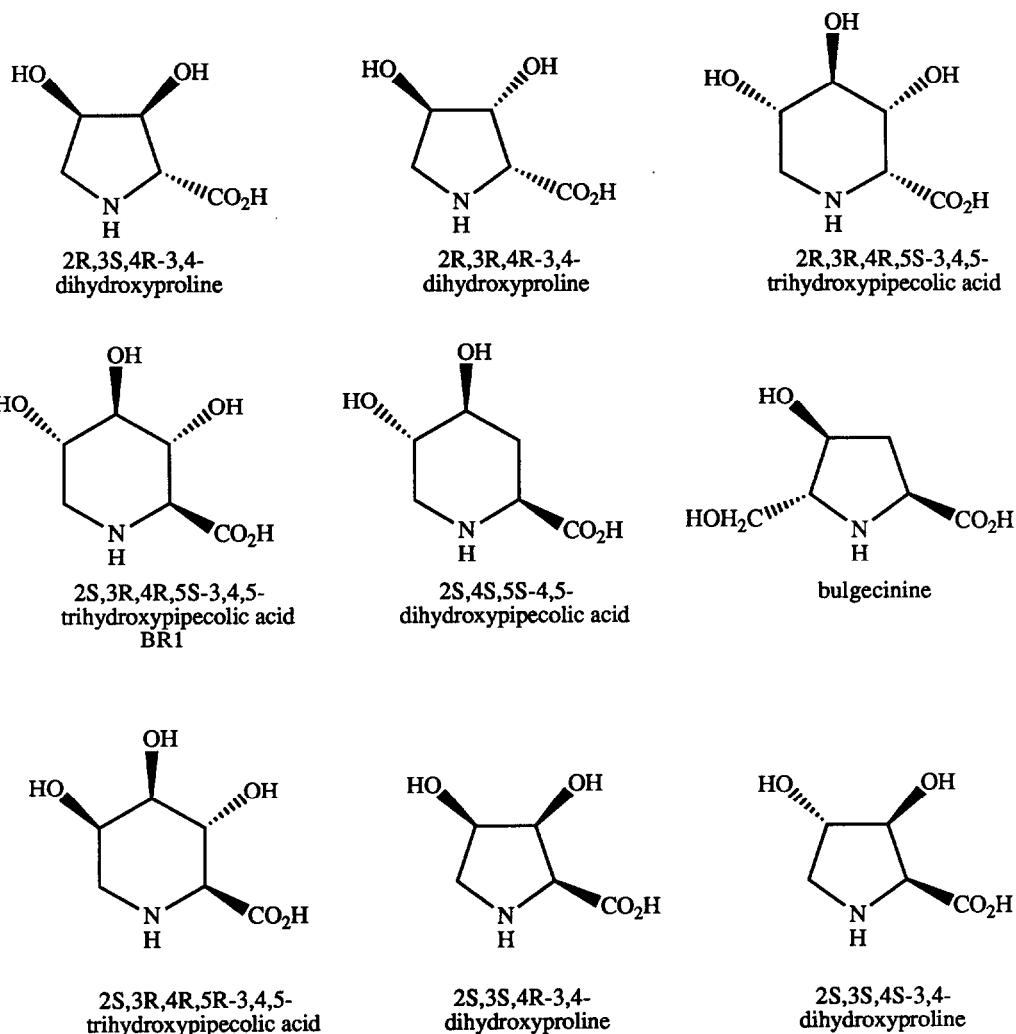Dyson Perrins Laboratory, Oxford University, South Parks Road, Oxford OX1 3QY, UK.

Abstract Efficient syntheses from diacetone glucose of 1,4-dideoxy-1,4-imino-D-arabinitol, (2S,3R,4R)-3,4-dihydroxyproline, fagomine [1,5-imino-1,2,5-trideoxy-D-*arabino*-hexitol], and (2S,3R,4R)-3,4-dihydroxypipecolic acid by intramolecular nucleophilic displacement by an amino function of 2-O-trifluoromethanesulphonates of anomeric mixtures of methyl furanosides are reported.

This paper illustrates the efficient construction of the nitrogen ring of chiral pyrrolidines and piperidines by the intramolecular ring closure of anomeric mixtures of 5-amino- and 6-amino-2-trifluoromethanesulphonates of methyl furanosides; the syntheses of 1,4-dideoxy-1,4-imino-D-arabinitol - known as DAB1 - (1), (2S,3R,4R)-3,4-dihydroxyproline (2), fagomine [1,5-imino-1,2,5-trideoxy-D-*arabino*-hexitol] (3), and (2S,3R,4R)-3,4-dihydroxypipecolic acid (4) from diacetone glucose are reported. All four compounds have been screened as potential inhibitors of HIV replication[1,2] as part of a project looking at the potential of amino sugar derivatives in dissecting glycoprotein biosynthesis;[3] 1,4-dideoxy-1,4-imino-L-arabinitol LAB1, the enantiomer of (1), is a powerful inhibitor of the cytopathic effect of HIV at concentrations which were not cytotoxic.[2,4]


(1)   (2)   (3)

(4)   LAB1   FR 900483
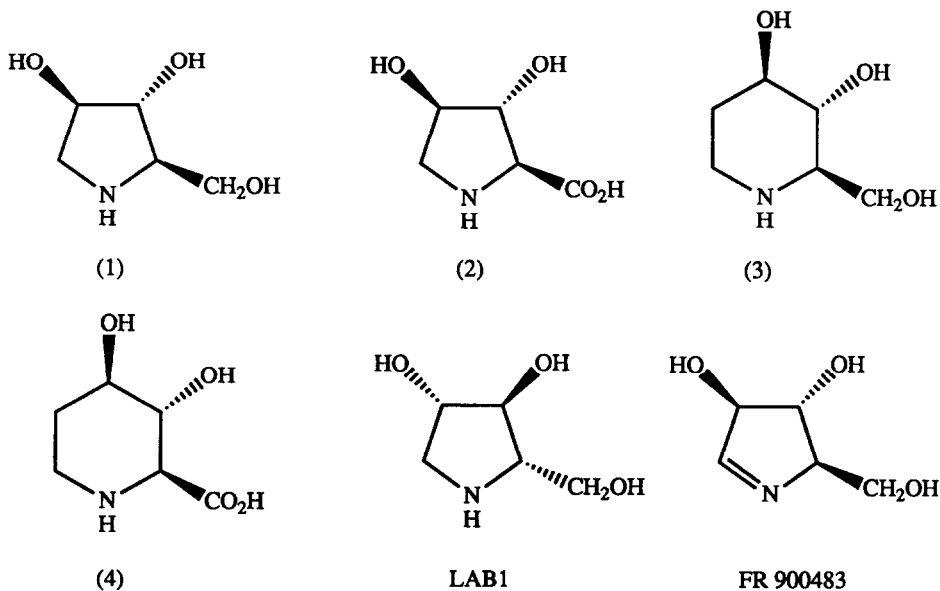
Naturally occurring[5] and synthetic[6] polyhydroxylated pyrrolidines and piperidines constitute a powerful class of glycosidase inhibitors. Both the natural product DAB1 (1), isolated from *Angylocalyx boutiqueanus* [7,8] and *Arachniodes standishii*,[9] and its enantiomer LAB1 are powerful inhibitors of a range of α-glucosidases.[10,11] DAB1 (1) has been synthesised previously from D-xylose[12] and from (S)-glutamic acid;[13] LAB1 has been prepared from D-xylose[12,14] and L-arabinose.[8] The structurally related fungal metabolite FR 900483, an anhydro form of 4-amino-4-deoxy-D-arabinose, has been shown to be an immunomodulator;[15,16] other hydroxylated pyrrolidines may have promise as immunoregulatory agents.[17] Fagomine (3), isolated from *Fagopyrum esculentum*[18,19] and as the 4-O-β-glucoside from *Xanthocercis zambesiaca*,[20] is a moderate inhibitor of isomaltase;[11] fagomine has previously been prepared from glucose.[21] Both DAB1 (1) and fagomine have also been prepared by sequences involving aldolases.[22,23]

2R,3S,4R-3,4-
dihydroxyproline

2R,3R,4R-3,4-
dihydroxyproline

2R,3R,4R,5S-3,4,5-
trihydroxypipecolic acid

2S,3R,4R,5S-3,4,5-
trihydroxypipecolic acid
BR1

2S,4S,5S-4,5-
dihydroxypipecolic acid

bulgecinine

2S,3R,4R,5R-3,4,5-
trihydroxypipecolic acid

2S,3S,4R-3,4-
dihydroxyproline

2S,3S,4S-3,4-
dihydroxyproline
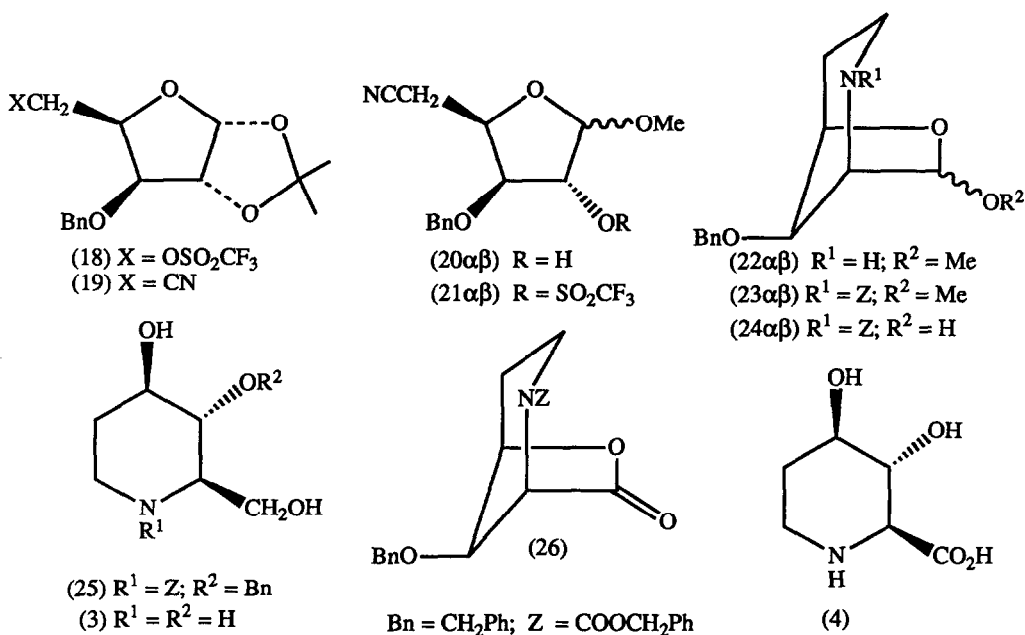
There is considerable interest in the synthesis of optically pure β- and γ-hydroxy-α-amino acids. Although a few good non-enzymic methods for their asymmetric synthesis have been devised, [24] carbohydrates have long been established as homochiral starting materials for the synthesis of non-protein amino acids.[25,26] The value of simply protected sugar lactones - in which azide is easily introduced at the carbon α to the lactone carbonyl - in short and efficient syntheses of highly functionalised amino acids such as hydroxylated prolines and pipecolic acids has been recognised. Introduction of an azide function with retention of configuration at C-2 of D-ribonolactone[27] provides a powerful intermediate for the synthesis of homochiral D-amino acids such as 2R,3S,4R-3,4-dihydroxyproline.[28] Introduction of azide α to the carbonyl group of glucuronolactone[29] allowed short syntheses of the D-amino acids 2R,3R,4R-3,4-dihydroxyproline and 2R,3R,4R,5S-3,4,5-trihydroxypipecolic acids and of the L-amino acids 2S,3R,4R,5S-3,4,5-trihydroxypipecolic acid (BR1), 2S,4S,5S-4,5-dihydroxypipecolic acid and bulgecinine.[30,31] More lengthy syntheses derived by introduction of nitrogen at C-2 of glucose have been reported for the synthesis of 2S,3R,4R,5R-3,4,5-trihydroxypipecolic acid,[21] BR1[32] and bulgecinine.[33] 2S,3S,4R-3,4-Dihydroxyproline has been prepared by initial introduction of nitrogen at C-3 of glucose;[34] a similar approach has been used for the synthesis of other β-hydroxy-α-amino acids.[35] This paper describes a new strategy for the synthesis of polyfunctionalised amino acids in which the nitrogen is first introduced in the sugar at C-5 [for a pyrrolidine - (2S,3R,4R)-3,4-dihydroxyproline (2)] and at C-6 [for a piperidine - (2S,3R,4R)-3,4-dihydroxypipecolic acid (4)]. Both racemic[36] and optically active[37] (2) have previously been synthesised from racemic and resolved 3,4-dehydroproline; homochiral (2), together with 2S,3S,4S-3,4-dihydroxyproline [the enantiomer of the dihydroxyproline obtained from glucuronolactone], has been prepared from β-hydroxyallyl glycine derivatives.[38] No synthesis of (2S,3R,4R)-3,4-Dihydroxypipecolic acid (4) has previously been reported.

Bicyclic intermediates, such as (13), formed from the ring closure from a nitrogen function at C-2 of a furanoside onto a leaving group at C-5 of a sugar have been used in the synthesis of the homochiral pyrrolidines 2R,5R-dihydroxymethyl-3R,4R-dihydroxypyrrolidine,[39,40] the pyrrolizidine alkaloid alexine and some of its diastereomers,[41] and DAB1 (1).[12] The major practical problem in these syntheses is the introduction of nitrogen by nucleophilic substitution by azide ion of a triflate at C-2 of a furanoside. While 2-O-trifluoromethanesulphonates of furanosides in which the triflate leaving group is *cis* to the anomeric substituent undergo efficient nucleophilic displacement by azide, triflates which are *trans* to the anomeric substituent give low yields of S_N2 products; thus, such syntheses incur a wasteful - and often experimentally tricky - separation of the furanoside anomers. This paper demonstrates that intramolecular displacement of a triflate at C-2 of a furanoside by a 5-amino group to give such bicyclic pyrrolidines occurs easily with both α– and β–anomers.

The synthesis of DAB1 (1) and the dihydroxyproline (2) requires introduction of nitrogen at C-5 of a suitably protected derivative of xylose. Diacetone glucose was converted to the protected xylofuranose (8) by minor changes to literature procedures.[42] Thus reaction of diacetone glucose (5) with sodium hydride and benzyl bromide in tetrahydrofuran in the presence of tetrabutyl ammonium iodide gave the fully protected furanose (6) [97% yield][43] which on hydrolysis by acetic acid in aqueous methanol afforded the diol (7) [87% yield].[44] Periodate oxidation of the diol (7), followed by treatment with sodium borohydride in aqueous ethanol gave 3-O-benzyl-1,2-O-isopropylidene-α-D-xylofuranose (8)[45] in 88% yield [74% overall yield from (5)]. Esterification of the primary hydroxyl function in (8) with methanesulphonyl chloride in pyridine gave the corresponding mesylate (9) [94% yield] which with sodium azide in dimethyl formamide introduced the azide function at C-5 of the sugar to give (10) [97% yield]. Treatment of the furanose (10) with methanolic hydrogen chloride gave the methyl furanosides (11) [82% yield] as an anomeric mixture in which the β isomer was in marginal excess.
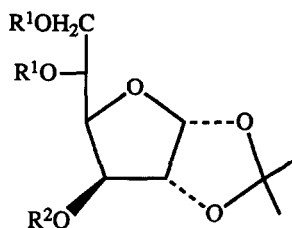
(5) $R^1 = Me_2C;$ $R^2 = H$
(6) $R^1 = Me_2C;$ $R^2 = Bn$
(7) $R^1 = H;$ $R^2 = Bn$
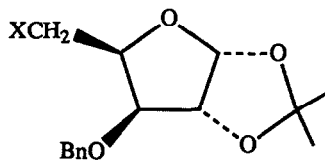
(8) X = OH
(9) X = OSO$_2$Me
(10) X = N$_3$

(11αβ) R = H
(12αβ) R = SO$_2$CF$_3$
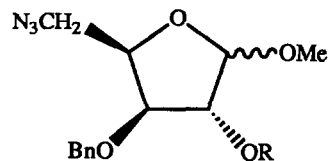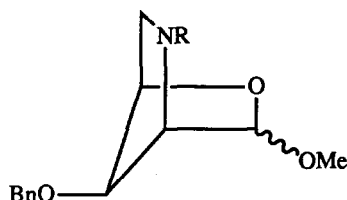
(13αβ) R = H
(14αβ) R = Z
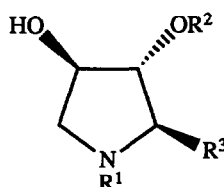
(15) $R^1 = Z;$ $R^2 = Bn;$ $R^3 = CHO$
(16) $R^1 = Z;$ $R^2 = Bn;$ $R^3 = CH_2OH$
(1) $R^1 = R^2 = H;$ $R^3 = CH_2OH$
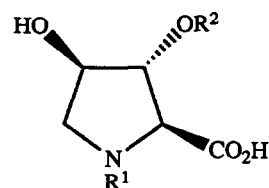
(17) $R^1 = Z;$ $R^2 = Bn$
(2) $R^1 = R^2 = H$

Although the anomers of (11) are easily separable, the subsequent reactions may be carried out on a mixture of anomers with no reduction in the yield of cyclised products obtained. The remaining free hydroxyl group at C-2 in (11) reacted with trifluoromethanesulphonic anhydride in dichloromethane in the presence of pyridine to give the corresponding triflates (12) in 92% yield for the α–anomer and in 78% yield for the β-anomer. Hydrogenation of (12α) in ethyl acetate in the presence of 5% palladium on charcoal caused reduction of the azide to the corresponding amine which underwent spontaneous cyclisation to give the iminolyxofuranoside (13α) in 95% yield; similar treatment of (12β) gave (13β) in 93% yield. The bicyclic amines (13αβ) are relatively unstable compounds and were immediately converted to the carbamates (14αβ) by reaction with benzyl chloroformate in a biphasic mixture of ether and saturated sodium bicarbonate in 76% yield for the α–anomer and in 90% yield for the β-anomer. Hydrolysis of (14α) with aqueous trifluoroacetic acid gave the protected iminolyxose (15) in 92% yield; similar hydrolysis of the β anomer gave (15) in 87% yield. Reduction of the lyxose (15) with sodium borohydride in aqueous ethanol gave the diol (16) in 98% yield. Removal of the carbamate and O-benzyl protecting groups in (16) by hydrogenolysis in acetic acid in the presence of palladium black gave DAB1 (1) in 98% yield, isolated as the easily crystallised hydrochloride. The overall yield of DAB1 (1) was 44% from the protected xylose (8) and 33% from diacetone glucose (5). Oxidation of the lyxose (15) with bromine in aqueous dioxan containing barium carbonate gave the Z-protected proline derivative (17) [75% yield] from the which the free amino acid (2) was obtained by hydrogenolytic removal of the protecting groups [palladium black, acetic acid] in 94% yield. The overall yield of (2S,3R,4R)-3,4-dihydroxy proline (2) was 24% from the protected xylose (8) and 18% from diacetone glucose (5).

(18) X = OSO$_2$CF$_3$
(19) X = CN

(20αβ) R = H
(21αβ) R = SO$_2$CF$_3$

(22αβ) R^1 = H; R^2 = Me
(23αβ) R^1 = Z; R^2 = Me
(24αβ) R^1 = Z; R^2 = H

(25) R^1 = Z; R^2 = Bn
(3) R^1 = R^2 = H

(26)

Bn = CH$_2$Ph; Z = COOCH$_2$Ph   (4)

For the synthesis of fagomine (3) and dihydroxypipecolic acid (4), the free hydroxyl group in (8) was esterified with trifluoromethanesulphonic anhydride in the presence of pyridine to give the triflate (18) [94% yield] which, with potassium cyanide in dimethyl formamide, afforded the nitrile (19) [96% yield]; this excellent yield in the displacement of the triflate ester (8) is in marked contrast to the reaction of cyanide with the corresponding mesylate (9) which gave a very low yield of displacement product. Treatment of the cyanide (19) with methanolic hydrogen chloride gave the methyl furanosides (20) in a yield of 95% as a mixture of anomers in an α:β ratio of 3:4. The mixture of anomers (20) was converted to the corresponding triflates (21) [95% yield]; reduction of the nitriles (21) with borane-dimethyl sulphide to the corresponding 6-amino sugar gave, after work up with potassium carbonate, the bicyclic piperidine (22) in 96% yield.This excellent yield for the cyclisation of a mixture of anomers confirms the value of this strategy, already exemplified in an efficient synthesis of deoxymannojirimycin,[46] for the synthesis of chiral piperidines. The bicyclic amines (22) were reacted with benzyl chloroformate and the resulting carbamates (23) hydrolysed by aqueous trifluoroacetic acid to afford the lactols (24) in an overall yield of 77%. Reduction of the lactols (24) by sodium borohydride in aqueous ethanol gave (25) in 97% yield; hydrogenolytic removal of the protecting groups gave fagomine (3), (98% yield), again isolated as the easily crystallised hydrochloride. The overall yield of fagomine (3) was 45% from the protected xylose (8) and 34% from diacetone glucose (5). Oxidation of the lactol (24) with bromine in aqueous dioxan containing barium carbonate gave the Z-protected lactone (26) [84% yield] from the which the free amino acid (4) was obtained as the monohydrate by hydrogenolytic removal of the protecting groups in 89% yield. The overall yield of (2S,3R,4R)-3,4-dihydroxy pipecolic acid (4) was 34% from the protected xylose (8) and 25% from diacetone glucose (5).

In summary, this paper indicates that intramolecular cyclisations by amines onto a triflate at C-2 of a furanoside occurs very readily for both anomers of the sugar and this provides a flexible route to a number of potential glycosidase inhibitors.The very high yield of the cyclisation of both anomers of (12) to give the pyrrolidines (13) and of both anomers of (21) to give the piperidines (22) confirm the value of this strategy.

Experimental

M.p.s were recorded on a Kofler block. Infra red spectra were recorded on Perkin Elmer 297 or 781 spectrophotometers; unless otherwise stated, infra red spectra of solids were obtained in $CHCl_3$ solution and those of syrups as thin films. ^{1}H NMR spectra were run at 200 MHz on a Varian Gemini 200, or at 300 MHz on a Bruker WH 300 spectrometer; ^{13}C NMR were recorded on Varian Gemini 200 (50.3 MHz) or Bruker AM 250 (62.9 MHz) spectrometers. All NMR spectra were obtained using deuteriochloroform as solvent unless otherwise stated; for ^{13}C NMR spectra in D_2O, 1,4-dioxan (δ 67.6) was used as an internal standard. Mass spectra were recorded on VG Micromass 16F or 30F spectrometers, using the desorption chemical ionisation technique (DCI NH_3) unless otherwise stated. Optical rotations were measured on a Perkin Elmer 241 polarimeter; concentrations are given in g/100 ml. Microanalyses were performed by the microanalytical service of the Dyson Perrins laboratory. TLC was performed on glass plates coated with silica gel blend 41 or on aluminium sheets pre-coated with Merck silica gel $60F_{254}$, and compounds were visualised with sprays of 5% v/v concentrated sulphuric acid in methanol, 5% w/v ninhydrin in ethanol or a solution 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, and dry column chromatography using Merck Kieselguhr 60H. The solvent system CMAW refers to a mixture of chloroform, methanol, acetic acid and water in ratio 60:30:3:5. The following ion exchange resins were utilised: Aldrich Chemical Company 50x 8-100, Sigma CG 120 (fine mesh) Na^+ form, Sigma CG 400 Cl^- form. The acid resin was used in the H^+ form, eluting with 0.5 M NH_3 solution in the cases of amino alcohols and 0.5 M pyridine solution for amino acids. The basic resin was used as the OH^- form, with water as eluent and used only for purification of amino alcohols. Solutions in organic solvents were dried with anhydrous sodium sulphate unless stated otherwise, and solvents were removed under reduced pressure.

3-O-Benzyl-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (6).

A solution of diacetone glucose (5) (Aldrich) (18.0 g, 69.1 mmol) in THF (80 ml) was added dropwise to a stirred suspension of sodium hydride, (50% dispersion in oil, 3.67 g, 76.5 mmol) and tetrabutylammonium iodide (0.2 g, 0.54mmol) in THF (50ml) at 0°C. The mixture was warmed to room temperature and benzyl bromide (9.04 ml, 13.0 g, 76.0 mmol) added, then heated to 50°C for 2 hours. Methanol (20 ml) was added and the mixture stirred for a further 2 hours before cooling, filtering through celite and concentrating. The resulting oil was dissolved in dichloromethane (100 ml), washed with water (2 x 30 ml), dried, filtered and evaporated to give 3-O-benzyl-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (23.5 g, 97%) as a pale brown oil. A small quantity was purified by flash chromatography (ethyl acetate-hexane 1:5) to give a clear oil, $[\alpha]_{20}^{D}$ -29.8° (c, 1.06 in chloroform) [lit.[43] -27.7° (c, 3.32 in ethanol)]; ^{1}H NMR δ 1.32, 1.39, 1.44, 1.51 (12H, 4 x s, 2 x acetonide); 3.99-4.11 (5H, m, H-3, H-4, H-5, H-6,6'); 4.59 (1H, d, H-2); 4.59 (1H, d, H-2); 4.65, 4.70 (2H, 2 x d, CH_2Ph, $J_{H,H'}$ 11.8 Hz); 5.90 (1H, d, H-1, $J_{1,2}$ 3.7 Hz); 7.32-7-36 (5H, m, H-Ph).

3-O-Benzyl-1,2-O-isopropylidene-*α*-D-glucofuranose (7). Crude 3-O-benzyl-1,2:5,6-di-O-isopropylidene-*α*-D-glucofuranose (6) (23.5 g, 75.6 mmol) was dissolved in a 1:1:1 mixture of methanol, acetic acid and water (200 ml) and stood at 50°C for 16 hours. The solvents were evaporated and the crude syrup purified by flash chromatography (ethyl acetate-hexane 3:2) to give 3-O-benzyl-1,2-O-isopropylidene-*α*-D-glucofuranose (18.1 g, 87%) as a clear oil, $[\alpha]_{20}^{D}$ -49.9° (c, 1.08 in chloroform) [lit.[44] -50.8° (c, 1.24 in chloroform)]; ^{1}H NMR δ 1.33, 1.49 (6H, 2 x s, acetonide); 2.17 (2H, bs, 2 x OH); 3.69, 3.81 (2H, 2 x dd, H-6,6', $J_{6,6'}$ 11.4 Hz, $J_{5,6}$ 5.5 Hz, $J_{5,6'}$ 3.4 Hz); 4.00-4.15 (3H, m, H-3, H-4, H-5); 4.56, 4.73 (2H, 2 x d, CH₂Ph, $J_{H,H'}$ 11.7 Hz); 4.63 (1H, d, H-2); 5.94 (1H, d, 1-H, $J_{1,2}$ 3.7 Hz); 7.31-7.38 (5H, m, H-Ph).

3-O-Benzyl-1,2-O-isopropylidene-*α*-D-xylofuranose (8). Sodium periodate (17.3 g, 81.1 mmol) was added portionwise to a stirred solution of 3-O-benzyl-1,2-O-isopropylidene-*α*-D-glucofuranose (7) (17.3 g, 155.8 mmol) in 10% aqueous ethanol (400 ml). After 3 hours, dichloromethane (100 ml) was added and the precipitate filtered off, washing the residue with dichloromethane. The combined organic layers were concentrated to 350 ml and cooled to 0°C. Sodium borohydride (4.09 g, 181 mmol) dissolved in 20% aqueous ethanol (150 ml) was added dropwise over 10 minutes, then the solution was stirred for 8 hours at room temperature. Excess ammonium chloride was added and the solution concentrated by evaporation. 10% sodium thiosulphate solution (200 ml) was added and the product extracted into dichloromethane (4 x 100 ml), dried, filtered and evaporated to give 3-O-benzyl-1,2-O-isopropylidene-*α*-D-xylofuranose (13.8 g, 88%) as a clear oil.[45] A small quantity was purified by flash chromatography (ether-hexane 2:1), $[\alpha]_{20}^{D}$ -69.1° (c, 1.07 in chloroform); ^{1}H NMR δ 1.33, 1.49 (6H, 2 x s, acetonide); 2.20 (1H, bs, OH); 3.86, 3.95 (2H, 2 x dd, H-5,5', $J_{5,5'}$ 12.0 Hz, $J_{4,5}$ 4.8 Hz, $J_{4,5'}$ 5.2 Hz); 4.02 (1H, d, H-3, $J_{3,4}$ 3.5 Hz); 4.29 (1H, m, H-4); 4.50, 4.72 (2H, 2 x d, CH₂Ph, $J_{H,H'}$ 12.0 Hz); 4.65 (1H, d, H-2); 5.99 (1H, d, H-1, $J_{1,2}$ 3.8 Hz); 7.31-7.38 (5H, m, H-Ph).

3-O-Benzyl-1,2-O-isopropylidene-5-O-methanesulphonyl-*α*-D-xylo-furanose (9). A solution of 3-O-benzyl-1,2-O-isopropylidene-*α*-D-xylofuranose (8) (5.00 g, 17.9 mmol) in pyridine (30 ml) was cooled to 0°C under nitrogen. Methanesulphonyl chloride, (2.76 ml, 35.7 mmol, 2.0 molar equivalents) was added with stirring and the solution allowed to warm to room temperature over two hours. The reaction mixture was poured into brine (100 ml), extracted into dichloromethane (4 x 50 ml) and the combined organic phase dried, filtered, and evaporated. Purification by flash chromatography (ether-hexane 1:1) afforded 3-O-benzyl-1,2-O-isopropylidene-5-O-methanesulphonyl-*α*-D-xylo-furanose (6.01 g, 94%), m.p. 61-62°C, $[\alpha]_{20}^{D}$ +113.5° (c, 0.96 in chloroform); ν_{max} (chloroform) 2920, 1360, 1175, 1080 and 910 cm⁻¹; ^{1}H NMR δ 1.33, 1.50 (6H, 2 x s, acetonide); 3.02 (3H, s, CH₃); 4.01 (1H, d, 3-H, $J_{3,4}$ 2.8 Hz); 4.01-4.50 (4H, m, H-4, H-5,5', CHPh); 4.65 (1H, d, H-2, $J_{1,2}$ 3.8 Hz); 4.69 (1H, d, CH'Ph, $J_{H,H'}$ 11.8 Hz); 5.97 (1H, d, H-1); 7.31-7.38 (5H, m, H-Ph). ^{13}C NMR δ 26.30, 26.86 (2 x q, CH₃-acetonide); 37.56 (q, CH₃S); 67.59 (t, C-5); 72.12 (t, CH₂Ph); 77.98, 81.61, 82.08 (3 x d, C-2,3,4); 105.35 (d, C-1); 112.19

(s, acetonide); 127.84, 128.24, 128.64 (3 x d, H$\underline{C}$-Ph); 136.91 (s, $\underline{C}$-Ph). m/z : 376 ($\underline{M}$+NH$_4^+$, 100%), 318 (32%). (Found C, 53.62; H, 6.19. C$_{16}$H$_{22}$SO$_6$ requires C, 54.03; H, 6.19).

5-Azido-3-O-benzyl-5-deoxy-1,2-O-isopropylidene-α-D-xylofuranose (10). Sodium azide (2.72 g, 41.9 mmol) was added to a stirred solution of 3-$\underline{O}$-benzyl-1,2-$\underline{O}$-isopropylidene-5-$\underline{O}$-methanesulphonyl-α-D-xylo-furanose (9) (5.00 g, 14.0 mmol) in dry DMF (100 ml) and the mixture kept at 70°C for 12 h. The solvent was removed, the resulting oil poured into brine (50 ml), and the product extracted into dichloromethane (3 x 50 ml). The combined organic phase was dried, filtered and evaporated. Purification by flash chromatography (ether-hexane 1:2) gave 5-azido-3-O-benzyl-5-deoxy-1,2-O-isopropylidene-α-D-xylofuranose (4.11 g, 97%) as a clear oil, $[\alpha]_{20}^{D}$ -27.5° (c, 1.00 in chloroform); ν_{max} (film) 2920, 2000 (N$_3$), 1455 and 1075 cm^{-1}, ^{1}H NMR δ 1.34, 1.51 (6H, 2 x s, acetonide); 3.48, 3.60 (2H, 2 x dd, H-5,5', J$_{5,5'}$ 12.5 Hz); 3.96 (1H, d, H-3); 4.32 (1H, dt, H-4, J$_{4,5}$ 6.5 Hz, J$_{4,5'}$ 6.8 Hz, J$_{3,4}$ 3.3 Hz); 4.65 (1H, d, H-2, J$_{2,3}$ 3.8 Hz); 4.53, 4.70 (2H, 2 x d, C$\underline{H}_2$, J$_{H,H'}$ 11.8 Hz); 5.95 (1H, d, H-1, J$_{1,2}$ 3.8 Hz); 7.32-7.38 (5H, m, H-Ph). ^{13}C NMR δ 26.13, 26.68 (2q, acetonide); 111.76 (s, acetonide); 49.12 (t, C-5); 71.77 (t, $\underline{C}$H$_2$Ph); 78.66, 81.45, 81.97 (3d, C-2, C-3, C-4); 104.99 (d, C-1); 127.64, 127.96, 128.42 (3d, H$\underline{C}$-Ph); 137.04 (s, C-Ph). m/z (CI NH$_3$) : 323 ($\underline{M}$+NH$_4^+$, 20%), 278 (100%), 220 (32%), 91 (40%). (Found C, 58.86; H, 6.37; N, 13.46. C$_{15}$H$_{19}$N$_3$O$_4$ requires C, 59.01; H, 6.27; N, 13.76).

Methyl 5-Azido-3-O-benzyl-5-deoxy-D-xylofuranoside (11$\alpha\beta$). 5-azido-3-O-benzyl-5-deoxy-D-1,2-O-isopropylidene-α-D-xylofuranoside (10) (3.85 g, 12.6 mmol) was added to a solution of acetyl chloride (5.89 g, 0.075 mol) in methanol (75 ml) and stood at 0°C under nitrogen for 36 hours. The solution was neutralised with excess anhydrous sodium bicarbonate and, after the addition of dichloromethane (100 ml), filtered and concentrated. Purification by flash chromatography (ether-hexane 2:1) gave the separate α and β anomers of methyl 5-azido-3-O-benzyl-5-deoxy-D-xylofuranoside as colourless oils.

α-anomer (1.35 g, 38%), R$_f$ 0.45 (ether-hexane 3:1); $[\alpha]_{20}^{D}$ +99.6° (c, 1.14 in chloroform); ν_{max} (film) 3470 (OH), 2930, 2095 (N$_3$), 1450, 1120 and 1040 cm^{-1}; ^{1}H NMR δ 1.65 (1H, bs, OH); 3.45-3.51 (2H, m, H-5); 3.50 (3H, s, CH$_3$); 4.01 (1H, dd, H-3); 4.29 (1H, dd, H-2, J$_{2,3}$ 4.1Hz); 4.33 (1H, dd, H-4 J$_{3,4}$ 6.1Hz); 4.58, 4.79 (2H, 2 x d, C$\underline{H}_2$Ph, J$_{H,H'}$ 12 Hz); 5.00 (1H, d, H-1, J$_{1,2}$ 4.7 Hz); 7.30-7.37 (5H, m, H-Ph). ^{13}C NMR δ 50.73 (t, C-5); 55.70 (q, CH$_3$); 71.77 (t, $\underline{C}$H$_2$Ph); 76.99 (2d, C-3, C-4); 83.2 (d, C-2); 101.76 (d, C-1); 127.67, 127.81, 128.40 (3 x d, H$\underline{C}$-Ph); 137.61 (s, C-Ph). m/z : 252 (100%), 91 (53%), 220 (30%), 297 ($\underline{M}$+NH$_4^+$, 30%). (Found C, 55.66; H, 6.31; N, 14.79. C$_{13}$H$_{17}$N$_3$O$_4$ requires C, 55.91; H, 6.14; N, 15.04).

β-anomer (1.53 g, 44%), R$_f$ 0.40 (ether-hexane 3:1); $[\alpha]_{20}^{D}$ -30.5° (c, 1.11 in chloroform); ν_{max} (film) 3420 (OH), 2920, 2100 (N$_3$), 1450, 1110 and 1050 cm^{-1}; ^{1}H NMR δ 1.65 (1H, bs, OH); 3.39, 3.56 (2H, 2 x dd, H-5,5', J$_{5,5'}$ 13.0 Hz); 3.45 (3H, s, CH$_3$); 4.02 (1H, dd, H-3); 4.28 (1H, dd, H-2 J$_{2,3}$ 3.4 Hz); 4.40 (1H, ddd, H-4, J$_{3,4}$ 6.5 Hz, J$_{4,5}$ 4.4 Hz, J$_{4,5'}$ 13.02 Hz); 4.58, 4.70 (2H, 2 x d, C$\underline{H}_2$Ph, J$_{H,H'}$ 12.1 Hz); 4.83 (1H, d, H-1, J$_{1,2}$ 1.1 Hz); 7.29-7.39 (5H, m, H-Ph). ^{13}C NMR δ 51.94 (t, 5-C); 55.77 (q, CH$_3$); 72.47 (t, $\underline{C}$H$_2$Ph); 79.74, 79.59 (2d, C-3, C-4); 83.42 (d, C-2); 109.61 (d, C-1); 127.76, 127.99, 128.49, (3 x d, H$\underline{C}$-Ph); 137.42 (s, C-Ph). m/z (NH$_3$ CI) : 297 ($\underline{M}$+NH$_4^+$, 30%),

252 (100%), 220 (90%), 91 (95%). (Found C, 55.69; H, 6.28; N, 14.65. $C_{13}H_{16}N_3O_4$ requires C, 55.91; H, 6.14; N, 15.04).

Methyl 5-Azido-3-O-benzyl-5-deoxy-2-O-trifluoromethanesulphonyl-D-xylofuranoside (12αβ). A solution of methyl 5-azido-3-O-benzyl-5-deoxy-α-D-xylofuranoside (11α) (1.18 g, 4.23 mmol) in dichloromethane (50ml) was cooled, under nitrogen, to -50°C. Dry pyridine (820 μl, 10.2 mmol) and trifluoromethanesulphonic anhydride (853 μl, 5.07 mmol) were added sequentially to the stirred solution, which was allowed to warm to -30°C over 1 hour. Excess anhydride was quenched with methanol (0.5 ml) and the solution warmed to room temperature then poured into brine (50 ml). The aqueous layer was separated and extracted with dichloromethane (3 x 50 ml). The combined organic phase was dried and concentrated to give a yellow oil which on purification by flash chromatography (10% ether in hexane) afforded methyl 5-azido-3-O-benzyl-5-deoxy-2-O-trifluoromethanesulphonyl-α-D-xylofuranoside (1.60 g, 92%) as a clear oil, R_f 0.65 (ether-hexane 1:3); $[\alpha]_{20}^{D}$ +93.1° (c, 1.00 in chloroform); ν_{max} (film) 2935, 2100 (N_3), 1415, 1210, 1145, 1050 and 985 cm^{-1}; ^{1}H NMR δ 3.46 (2H, m, H-5); 3.48 (3H, s, CH_3); 4.32 (1H, dt, H-4); 4.47 (1H, dd, H-3, $J_{3,4}$ 7.0 Hz); 4.55, 4.74 (2H, 2 x d, CH_2Ph, $J_{H,H'}$ 11.7 Hz); 5.13 (1H, dd, H-2, $J_{2,3}$ 4.7 Hz); 5.14 (1H, bs, H-1); 7.27-7.41 (5H, m, H-Ph). ^{13}C NMR δ 50.55 (t, C-5); 55.91 (q, CH_3); 73.12 (t, CH$_2$Ph); 75.36,79.17 (2d, C-3, C-4); 87.67 (d, C-2); 99.67 (d, C-1); 115.66 (q, CF_3); 127.95, 128.45, 128.70 (3d, HC-Ph); 136.35 (s, C-Ph). m/z : 236 (M+H$^+$, 100%), 68 (30%), 91 (15%). The β-anomer reacted similarly; 5-azido-3-O-benzyl-5-deoxy-β-D-xylofuranoside (11β) (1.37 g, 4.89 mmol) when treated with 1.15 molar equivalent of the same reagents for the same period, afforded methyl 5-azido-3-O-benzyl-5-deoxy-2-O-trifluoromethanesulphonyl-β-D-xylofuranoside (1.57 g, 78%) as a clear oil, R_f 0.70 (ether-hexane 1:3); $[\alpha]_{20}^{D}$ -32.0 (c, 1.1 in chloroform); ν_{max} (film) 2930, 2100 (N_3), 1420, 1210, 1145, 1055 and 960 cm^{-1}; ^{1}H NMR δ 3.41, 3.57 (2H, 2 x dd, H-5,5', $J_{5,5'}$ 13.0 Hz, $J_{4,5}$ 4.8 Hz, $J_{4,5'}$ 8.1 Hz); 3.47 (3H, s, CH_3); 4.26 (1H, dd, H-3, $J_{3,4}$ 6.3 Hz, $J_{2,3}$ 1.9 Hz); 4.44 (1H, m, H-4); 4.54, 4.76 (2H, 2 x d, CH_2Ph, $J_{HH'}$ 11.9 Hz); 5.08 (1H, s, H-1); 5.22 (1H, bs, H-2); 7.30-7.43 (5H, m, H-Ph). m/z (NH$_3$ CI) : 91 (100%), 108 (45%), 412 (M+H$^+$, 35%).

Methyl 3-O-Benzyl-2,5-dideoxy-2,5-imino-D-lyxofuranoside (13αβ). Methyl 5-azido-3-O-benzyl-5-deoxy-2-O-trifluoromethanesulphonyl-α-D-xylofuranoside (12α) (1.60 g, 3.89 mmol) was dissolved in ethyl acetate (30 ml) and stirred under hydrogen at room temperature with 5% palladium on charcoal (200 mg) for four hours. The solution was filtered through celite, concentrated, and purified by flash chromatography (10% ethanol in dichloromethane) to yield methyl 3-O-Benzyl-2,5-dideoxy-2,5-imino-α-D-lyxofuranoside (870 mg, 95%) as a pale brown oil, which rapidly darkened, R_f 0.3 (10% ethanol in dichloromethane); ν_{max} (film) 3420 (NH), 2940, 1450, 1245, 1170, 1025 and 640 cm^{-1}; ^{1}H NMR δ 3.14, 3.37 (2H, 2 x d, H-5,5', $J_{5,5'}$ 15.0 Hz); 3.79 (1H, s, H-2); 4.29, 4.40 (2H, 2 x bs, H-3, H-4); 4.52, 4.70 (2H, 2 x d, CH_2Ph, $J_{H,H'}$ 12.4 Hz); 5.88 (1H, s, H-1); 6.23 (1H, bs, N H); 7.30-7.42 (5H, m, H-Ph). ^{13}C NMR δ 49.47 (t, C-5); 55.56 (q, CH_3); 59.88 (d, C-2); 72.85 (t, CH$_2$Ph); 74.03, 78.32 (2d, C-3, C-4); 103.38 (d, C-1); 128.19, 128.37, 128.67 (3d, HC-Ph); 136.64 (s, C-Ph). m/z : 236 (M+H$^+$, 100%), 68 (30%), 91 (15%).

Methyl 5-azido-3-$\underline{O}$-benzyl-5-deoxy-2-$\underline{O}$-trifluoromethanesulphonyl-β-D-xylofuranoside (12β) (1.57 g, 3.82 mmol) under the same conditions gave methyl 3-O-benzyl-2,5-dideoxy-2,5-imino-β-D-lyxofuranoside (829 mg, 92.5%) after chromatography, as a rapidly darkening oil, R$_f$ 0.4 (10% ethanol in dichloromethane); ν_{max} (film) 3400 (NH), 2910, 1450, 1255, 1115, 1030 and 640 cm^{-1}; ^{1}H NMR δ 3.46 (3H, s, CH$_3$); 3.48 (2H, m, H-5); 4.21, (1H, s, H-2); 4.28 (2H, bs, H-3, H-4); 4.55, 4.76 (2H, 2 x d, C$\underline{H}_2$Ph, $J_{H,H'}$ 12.0 Hz); 5.06 (1H, d, H-1, $J_{1,2}$ 1.9 Hz); 6.29 (1H, bs, NH); 7.33-7.38 (5H, m, H-Ph). ^{13}C NMR δ 49.94 (t, C-5); 55.92 (q, CH$_3$); 60.50 (d, C-2); 72.58 (t, C$\underline{H}_2$Ph); 76.27, 78.84 (2 x d, C-3, C-4); 100.50 (d, C-1); 128.34, 128.64, (2 x d, H$\underline{C}$-Ph); 136.37 (s, C-Ph). m/z : 236 (M+H$^+$, 100%), 68 (40%), 91 (20%).

Methyl 3-O-benzyl-N-benzyloxycarbonyl-2,5-dideoxy-2,5-imino-D-lyxofuranoside (14$\alpha\beta$). Methyl 3-O-benzyl-2,5-dideoxy-2,5-imino-α-D-lyxofuranoside (13α) (870 mg, 3.70 mmol) was stirred with a 3:2 mixture of ether and saturated aqueous sodium bicarbonate (60 ml). Benzyl chloroformate (1.57 ml, 11.1 mmol) was added to the mixture which was stirred at room temperature for 12 hours. The ether layer was separated and the aqueous phase further extracted with ether (4 x 25 ml). The combined extracts were dried, filtered and the solvent removed. Purification by flash chromatography (ether-hexane 1:10 - 1:3) afforded methyl 3-O-benzyl-N-benzyloxycarbonyl-2,5-dideoxy-2,5-imino-α-D-lyxofuranoside (1.04 g, 76%) as a white crystalline solid, m.p. 74-75°C, R$_f$ 0.2 (ether-hexane 1:3); [α]$_{20}^D$ +12.0° (c, 0.98 in chloroform); ν_{max} (chloroform) 2940, 1695 (C=O), 1420, 1260, 1230, 1090 and 750 cm^{-1}; ^{1}H NMR δ 3.38, 3.41 (3H, 2 x s, CH$_3$); 3.3-3.7 (2H, m, 5,5'-H); 4.05-4.90 (5H, m, H-3, H-2, H-4, C$\underline{H}_2$Ph); 5.12-5.20 (3H, m, H-1, C$\underline{H}_2$-Z). 7.2-7.4 (10H, m, 2 x H-Ph). ^{13}C NMR δ 50.71 (t, C-5); 55.15, 55.33 (2 x q, Me); 59.63, 60.17 (2 x d, C-2); 66.95, 67.08 (2 x t, C$\underline{H}_2$-Z); 72.28 (t, C$\underline{H}_2$Ph); 75.09, 75.49, 77.93, 78.48 (4 x d, C-3, C-4); 105.67, 105.90 (d, C-1); 127.83, 127.92, 128.15, 128.64 (4 x d, H$\underline{C}$-Ph); 136.68, 137.46 (2 x s, C-Ph); 155.68, 155.81 (2 x s, C=O). m/z : 91 (100%), 108 (25%), 158 (20%), 370 (M+H$^+$, 10%). (Found C, 67.98; H, 6.39; N, 3.60. C$_{21}$H$_{23}$NO$_5$ requires C, 68.28; H, 6.28; N, 3.79). Methyl 3-O-benzyl-2,5-dideoxy-2,5-imino-β-D-lyxofuranoside (13β) (829 mg, 3.53 mmol) was treated likewise giving methyl 3-O-benzyl-N-benzyloxycarbonyl-2,5-dideoxy-2,5-imino-β-D-lyxofuranoside (1.18 g, 90%) as a clear oil, R$_f$ 0.35 (ether-hexane 1:3); [α]$_{20}^D$ -75.2° (c, 0.83 in chloroform); ν_{max} (film) 2930, 1705 (C=O), 1425, 1275, 1255, 1105 and 750 cm^{-1}; ^{1}H NMR δ 3.36, 3.42 (3H, 2 x s, CH$_3$); 3.50 (1H, 2 x d 5-H); 3.67 (1H, 2 x d, H-5'); 4.02-4.06 (1H, m, H-3); 4.29 (1H, bs, H-2); 4.49, 4.54 (1H, bs and dd, H-4); 4.52-4.65 (2H, m, C$\underline{H}_2$Ph); 5.0-5.2 (2H, 2 x dd, CH$_2$Ph); 5.21 (1H, s, H-1); 7.28-7.38 (10H, m, H-Ph). ^{13}C NMR δ 50.02 (t, C-5); 55.70, 55.89 (2 x q, Me); 60.17, 59.52 (2 x d, C-2); 66.79 (t, C$\underline{H}_2$-Z); 72.00, 72.10 (t, C$\underline{H}_2$Ph); 77.56, 78.08, 78.52, 79.18 (4 x d, C-3, C-4); 104.71, 105.11 (2 x d, C-1); 128.79, 127.96, 128.33, 128.61, 128.78 (5 x d, H$\underline{C}$-Ph); 137.09, 137.22 (2 x s, C-Ph); 156.20, 156.45 (2 x s, C=O). m/z : 91 (100%), 370 (M+H$^+$, 60%), 202 (30%). (Found C, 68.08; H, 6.39; N, 3.40. C$_{21}$H$_{23}$NO$_5$ requires C, 68.28; H, 6.28; N, 3.79).

3-O-Benzyl-N-benzyloxycarbonyl-2,5-dideoxy-2,5-imino-D-lyxose (15). Methyl 3-$\underline{O}$-benzyl-N-benzyloxycarbonyl-2,5-dideoxy-2,5-imino-α-D-lyxofuranoside (14α) (1.015 g, 2.77 mmol) was

stirred in a 1:1 mixture of trifluoroacetic acid and water (20 ml). Once all the starting material had dissolved, the solvents were evaporated (without heat) and purification by flash chromatography (ethyl acetate-hexane 1:2) gave 3-O-benzyl-N-benzyloxycarbonyl-2,5-dideoxy-2,5-imino-D-lyxose (901 mg, 92%) as a clear oil, $[\alpha]_{20}^{D}$ -24.2° ($\underline{c}$, 1.39 in chloroform); ν_{max} (film) 3400 (OH), 1700 (2 x CO), 1425, 1360, 1195 and 700 cm^{-1}; δ_{H} (rotamers cause double peaks) 2.5 (1H, bs, OH); 3.65 (1H, 2 x d, H-5); 3.79 (1H, 2 x dd, H-5'); 4.03 , 4.31 (2H, 2 x bs, H-2, H-3); 4.44, 4.55 (1H, bs and dd, H-4); 4.51-4.71 (2H, m, C$\underline{H}_2$Ph); 5.09-5.20 (2H, m, C$\underline{H}_2$-Z); 7.29-7.40 (10H, m, H-Ph); 9.49, 4.59 (1H, s and d, H-1, $J_{1,2}$ 0.7 Hz). $\underline{m/z}$: 91 (100%), 108 (68%), 230 (50%), 356 ($\underline{M}$+H^{+}, 20%). (Found C, 67.76; H, 6.48; N, 3.77. C$_{20}$H$_{21}$NO$_5$ requires C, 67.59; H, 5.96; N, 3.94). Methyl 3-$\underline{O}$-benzyl-$\underline{N}$-benzyloxycarbonyl-2,5-dideoxy-2,5-imino-β-D-lyxofuranoside (14β) (976 mg, 2.64 mmol) reacted similarly: it afforded the title compound (15) (820 mg, 87%), spectroscopically identical to that prepared above, under the same reaction conditions.

2-O-Benzyl-N-benzyloxycarbonyl-1,4-deoxy-1,4-imino-D-arabinitol (16).

A solution of 3-$\underline{O}$-benzyl-$\underline{N}$-benzyloxycarbonyl-2,5-dideoxy-2,5-imino-D-lyxose (15) (506 mg, 143 mmol) in ethanol was treated with a suspension of sodium borohydride (38.9 mg, 0.75 meq) in ethanol-water 1:1 (2 ml). After 15 minutes, excess ammonium chloride was added and the solution concentrated by evaporation, then partitioned between water (10 ml) and dichloromethane (10 ml). The aqueous layer was further extracted with dichloromethane (4 x 10 ml), and the combined organic layers dried, filtered and evaporated to give 2-O-benzyl-N-benzyloxycarbonyl-1,4-deoxy-1,4-imino-D-arabinitol, (501 mg, 98%) as a colourless oil, $[\alpha]_{20}^{D}$ -16.4° ($\underline{c}$, 1.26 in chloroform); ν_{max} (film) 3360 (OH), 2930, 1670 (CO), 1430, 1355, 1090 and 700 cm^{-1}; ^{1}H NMR δ (poorly resolved due to rotameric exchange) 1.9 (1H, bs, OH); 3.50-4.25 (7H, m, H-1,1',2,3,4,5, 5'); 4.60 (2H, s, C$\underline{H}_2$Ph); 5.09, 5.17 (2H, 2 x d, C$\underline{H}_2$-Z, $J_{H,H'}$ 12.5 Hz); 7.29-7.41 (10H, m, H-Ph). $\underline{m/z}$: 358 ($\underline{M}$+H^{+}, 100%), 250 ($\underline{M}$-PhCH$_2$O^{+}, 80%), 91 (80%), 314 (35%). ^{13}C NMR δ 54.63 (t, C-1); 62.36 (t, C-5); 65.12 (d, C-4); 67.12 (t, $\underline{C}$H$_2$-Z); 71.55 (t, $\underline{C}$H$_2$Ph); 72.64 (d, C-2); 86.49 (d, C-3); 127.07, 127.83, 128.01, 128.13, 128.45, 128.70 (6 x d, H$\underline{C}$-Ph); 136.49, 137.54 (2 x s, C-Ph); 156.19 (s, C=O). (Found C, 66.90; H, 6.23; N, 3.61. C$_{20}$H$_{23}$NO$_5$ requires C, 67.21; H, 6.47; N, 3.92).

1,4-Dideoxy-1,4-imino-D-arabinitol (1).

2-$\underline{O}$-Benzyl-$\underline{N}$-benzyloxycarbonyl-1,4-deoxy-1,4-imino-D-arabinitol (16) (483 mg, 1.35) was dissolved in acetic acid (8 ml) and stirred under hydrogen at atmospheric pressure with palladium black (150 mg). After 18 hours, the catalyst was removed by filtration and the solvent removed. Purification by flash chromatography (CMAW) and ion exchange chromatography afforded 1,4-dideoxy-1,4-imino-D-arabinitol, (224 mg, 97.6%) as its hydrochloride salt, a white crystalline solid, m.p. 111-113°C, [lit.[12] 113-115°C], $[\alpha]_{20}^{D}$ +36.7° ($\underline{c}$, 1.255 in water) [lit.[12] 37.9° ($\underline{c}$, 0.53 in water)]; ν_{max} (KBr disc) 3350, 1575, 1405, 1265, 1080, 1019, 1045 & 970 cm^{-1}; ^{1}H NMR (D$_2$O) δ 3.20, 3.42 (1H, 2 x dd, H-1,1', $J_{1,1'}$ 12.5 Hz, $J_{1,2}$ 2.4 Hz, $J_{1',2}$ 4.6 Hz); 3.47 (1H, dd, H-4, $J_{4,5}$ 8.4 Hz, $J_{4,5'}$ 4.3 Hz); 3.67, 3.80 (2H, 2 x dd, H-5,5'); 3.93 (1H, t, H-3, $J_{2,3}$ 3.4 Hz); 4.17 (1H, m, H-2). ^{13}C NMR (D$_2$O) δ 50.80 (t, C-1); 59.64 (t, C-5); 67.30 (t, C-4); 75.03, 76.50 (2 x d, C-3, C-2). $\underline{m/z}$: 102 ($\underline{M}$-CHO^{+}, 100%), 55 (30%), 134 ($\underline{M}$+H^{+}, 17%).

(2S, 3R, 4R)-3-O-Benzyl-N-benzyloxycarbonyl-3,4-dihydroxyproline (17).   A solution of 3-O-benzyl-N-benzyloxycarbonyl-2,5-dideoxy-2,5-imino-D-lyxose (15) (900 mg, 2.54 mmol), in a 1:1 mixture of water and 1,4-dioxan (15 ml) containing barium carbonate (1.46 g, 7.62 mmol), was cooled to 0°C and treated with bromine (298 μl, 5.33 mmol). After stirring for 24 hours excess bromine was destroyed by the dropwise addition of 10% sodium thiosulphate solution and the suspension acidified with 2M HCl (20 ml). The product was extracted into dichloromethane (4 x 50 ml), dried, filtered and evaporated. Purification by flash chromatography (ethyl acetate-hexane 1:1 to ethyl acetate) afforded (2S, 3R, 4R)-3-O-benzyl-N-benzyloxycarbonyl-3,4-dihydroxyproline (738 mg, 75%) as a clear oil, $[\alpha]_{20}^{D}$ -3.7° (c, 0.88 in chloroform); ν_{max} (film) 3400 (OH), 2950, 1680 (2 x CO), 1425, 1360 and 1195 cm^{-1}; ^{1}H NMR δ 3.62-3.78 (2H, 2 x dd, H-5); 4.21, 4.26 (2H, s and bs, H-3, H-2); 4.49-4.69 (3H, m, C$\underline{H}_2$Ph); 5.06-5.18 (2H, 2 x dd, C$\underline{H}_2$-Z); 5.6 (2H, bs, 2 x OH); 7.27-7.38 (10H, m, 2 x H-Ph). m/z : 91 (100%), 310 (45%), 372 (M+H$^+$, 30%).

(2S, 3R, 4R)-3,4-Dihydroxyproline (2).   (2S, 3R, 4R)-3-O-benzyl-N-benzyloxycarbonyl-3,4-dihydroxyproline (17) (523 mg, 1.95 mmol) was dissolved in glacial acetic acid (12 ml) containing palladium black (100 mg) and stirred under hydrogen at atmospheric pressure for 48 hours. The solution was filtered and the solvent removed. Purification by flash chromatography (CMAW) and ion exchange resin gave (2S, 3R, 4R)-3,4-dihydroxyproline (220 mg, 93.5%) as a white crystalline solid, m.p. 220-245°C decomposed without melting (lit.[37] 250° dec.), $[\alpha]_{20}^{D}$ -12.2° (c, 0.83 in water) [lit.[37] $[\alpha]_{D}^{25}$ -19° (c, 0.4 in water)]; ν_{max} (KBr disc) 3260, 1615 (CO), 1370, 1270, 1075, 1050 and 760 cm^{-1}; ^{1}H NMR δ (D$_2$O) 3.35 (1H, d, H-5, $J_{5,5'}$ 12.5 Hz); 3.44 (1H, dd, H-5', $J_{4,5'}$ 3.7 Hz); 3.90 (1H, s, H-2); 4.14 (1H, dt, H-4, $J_{3,4}$ 1.2 Hz); 4.36 (1H, bs, H-3). ^{13}C NMR (D$_2$O) δ 51.71 (t, C-5); 66.33 (d, C-2); 74.75 (d, C-4); 79.14 (d, C-3); 171.86 (s, C-1). m/z : 124 (100%), 104 (77%), 148 (M+H$^+$, 75%), 84 (67%).

3-O-Benzyl-1,2-O-isopropylidene-5-O-trifluoromethanesulphonyl-α-D-xylofuranose (18). A solution of 3-O-benzyl-1,2-O-isopropylidene-α-D-xylofuranose (8) (2.00 g, 7.14 mmol) in dry dichloromethane (25 ml) was treated with dry pyridine (1.15 ml, 14.3 mmol) and cooled to -50°C under nitrogen. Trifluoromethanesulphonyl chloride (1.45 ml, 8.57 mmol) was added and the stirred solution allowed to warm to -30°C over 1 hour. Methanol (0.5 ml) was added, the solution warmed to room temperature and the solvents removed to give a waxy yellow solid. Ice cold ether (10 ml) was added and the mixture filtered, washing the solid with further ether (3 x 5 ml). The ether was evaporated yielding a yellow oil. This was purified by flash chromatography (eluting with ether-hexane 1:5) to give 3-O-benzyl-1,2-O-isopropylidene-5-O-trifluoromethanesulphonyl-α-D-xylofuranose (2.76 g, 94%) an unstable colourless oil used immediately in the next step, ν_{max} (film) 2920, 1415, 955 and 700 cm^{-1}; ^{1}H NMR δ 1.26, 1.42 (6H, 2 x s, acetonide); 3.99 (1H, dd, H-3, $J_{2,3}$ 1.2 Hz, $J_{3,4}$ 3.3 Hz, 4.00-4.65 (6H, m, H-2, H-4, H-5,5', C$\underline{H}_2$Ph); 5.96 (1H, d, H-1, $J_{1,2}$ 4.8 Hz); 7.25-7.40 (5H, m, H-Ph). m/z : 430 (M+NH$_4^+$, 100%) 372 (M-(CH$_3$)$_2$CO+NH$_4^+$, 25%), 91 (50%).

3-O-Benzyl-5-cyano-5-deoxy-1,2-O-isopropylidene-α-D-xylofuranose (19). Finely ground, dry potassium cyanide (4.39 g, 67.6 mmol) was added to a stirred solution of 3-O-benzyl-1,2-O-isopropylidene-5-O-trifluoromethanesulphonyl-α-D-xylofuranose (18) (9.28 g, 22.5 mmol) in dry DMF (100 ml) and stirred vigorousley at 30°C for 6 hours. Most of the solvent was removed by evaporation and the resulting oil partitioned between dichloromethane (100 ml) and water (100 ml). The aqueous phase was extracted with dichloromethane (3 x 100 ml) and the combined organic layers washed with brine (50 ml), dried, filtered and concentrated to a viscous oil. Purification using flash chromatography (25% ether in hexane) gave 3-O-benzyl-5-cyano-5-deoxy-1,2-O-isopropylidene-α-D-xylofuranose (6.28 g, 96 %) as a white crystalline solid, m.p. 86-87°C, $[\alpha]_{20}^{D}$ -85.2° (c, 0.41 in chloroform); ν_{max} (chloroform) 2980, 2245 (CN), 1450 and 1165 cm^{-1}, ^{1}H NMR δ 1.34, 1.51 (6H, 2 x s, acetonide); 2.74 (2H, d, H-5,5'); 4.01 (1H, d, H-3); 4.50 (1H, dd, H-4, $J_{3,4}$ 3.3 Hz, $J_{4,5}$ 7.1 Hz); 4.58, 4.73 (1H, d, CH$_2$Ph, $J_{H,H'}$ 11.5 Hz); 4.65 (1H, d, H-2); 5.92 (1H, d, H-1, $J_{1,2}$ 3.7 Hz); 7.30-7.41 (5H, m, H-Ph). ^{13}C NMR δ 26.28, 26.87 (2 x q, CH$_3$-acetonide); 72.64 (t, CH$_2$Ph); 72.64, 81.76, 82.17 (3 x d, C-2,3,4); 105.37 (d, C-1); 112.18 (s, acetonide); 116.83 (s, CN); 127.96, 128.28, 128.66 (3 x d, HC-Ph); 136.97 (s, C-Ph). m/z : 91 (100%), 290 (M+H$^+$, 65%), 307 (M+NH$_4^+$, 70%). (Found C, 66.13; H, 6.90; N, 4.58. C$_{16}$H$_{19}$NO$_4$ requires C, 66.42; H, 6.62; 4.84).

Methyl 3-O-Benzyl-5-cyano-5-deoxy-D-xylofuranoside (20$\alpha\beta$). A solution of 3-O-benzyl-5-cyano-5-deoxy-1,2-O-isopropylidene-α-D-xylofuranose (19) (6.01 g, 20.8 mmol) was dissolved in dry methanol (150 ml) containing acetyl chloride (11.8 g, 0.15 mol) and stood at -5°C for 12 hours. The solution was basified (Na$_2$CO$_3$), concentrated and partitioned between water (150 ml) and dichloromethane (150 ml). The light brown aqueous phase was extracted further with dichloromethane (3 x 150 ml) and the combined extracts washed with brine (30 ml), dried (Na$_2$SO$_4$), filtered and evaporated to give an oil. Flash chromatography (ether-hexane 3:1 to 1:1), gave methyl 3-O-benzyl-5-cyano-5-deoxy-D-xylofuranoside (4.44 g, 81%) as a partially separated 4:3 mixture of the β and α anomers.

α-anomer, m.p. 59-60°C, R$_f$ 0.2 (ether-hexane 1:1); $[\alpha]_{20}^{D}$ +67.2° (c, 0.81 in chloroform); ν_{max} 3450, 2940, 2230 (CN), 1455, 1110 and 1045 cm^{-1}; ^{1}H NMR δ 2.66 (1H, d, OH, $J_{OH,2}$ 5.1 Hz); 2.66, 2.72 (2H, 2 x d, H-5,5', $J_{4,5}$ 7.6 Hz); 3.50 (3H, s, CH$_3$); 4.02 (1H, dd, H-3, $J_{2,3}$ 4.0 Hz, $J_{3,4}$ 6.0 Hz); 4.30 (1H, m, H-2); 4.46 (1H, dt, H-4); 4.60, 4.81 (1H, d, CH$_2$Ph, $J_{H,H'}$ 11.75 Hz); 4.99 (1H, d, H-1, $J_{1,2}$ 4.5 Hz); 7.31-7.38 (5H, m, H-Ph). ^{13}C NMR δ 18.99 (t, C-5); 55.88 (q, CH$_3$); 71.66 (t, CH$_2$Ph); 73.83, 76.64, 82.59, (3 x d, C-2, C-3, C-4); 101.79 (d, C-1); 117.49 (s, CN); 127.70, 127.87, 128.40 (3 x d, HC-Ph); 137.25 (s, C-Ph). m/z : 91 (100%), 281 (M+NH$_4^+$, 65%), 264 (M+H$^+$, 25%). (Found C, 64.13; H, 6.70; N, 5.51. C$_{14}$H$_{17}$NO$_4$ requires C, 63.87; H, 6.51; N, 5.32).

β-anomer, colourless oil, R$_f$ 0.18 (ether-hexane 1:1); $[\alpha]_{20}^{D}$ -64.5° (c, 0.895 in chloroform); ν_{max} (film) 3440 (OH), 2920, 2250 (CN), 1450, 1100 and 1040 cm^{-1}; ^{1}H NMR δ 2.62, 2.77 (2H, 2 x dd, H-5,5', $J_{5,5'}$ 15.7 Hz, $J_{4,5}$ 4.7 Hz, $J_{4,5'}$ 7.5 Hz); 2.71 (1H, s, OH); 3.42 (3H, s, CH$_3$); 4.00 (1H, dd, H-3, $J_{2,3}$ 2.8 Hz, $J_{3,4}$ 6.3 Hz); 4.23 (1H, bs, H-2); 4.55 (1H, m, H-4); 4.57, 4.71 (2H, 2 x d, CH$_2$Ph, $J_{H,H'}$ 11.9 Hz); 4.81 (1H, d, H-1, $J_{1,2}$ 1.3 Hz); 7.27-7.41 (5H, m, H-Ph). ^{13}C NMR δ 20.24 (t, C-5); 55.80 (q, Me); 72.76 (t, CH$_2$Ph); 76.66, 79.38 (2 x d, C-3, C-4); 83.49 (d, C-2); 110.11 (d, C-1); 118.19 (s, CN); 128.15, 128.38, 128.81 (3 x d, HC-Ph); 137.41 (s, C-Ph). (Found C, 63.63; H, 6.77; N, 5.14.

$C_{14}H_{17}NO_4$ requires C, 63.87; H, 6.51; N, 5.32).

Methyl 3-O-Benzyl-5-cyano-5-deoxy-2-O-trifluoromethanesulphonyl-D-xylofuranoside

(21$\alpha\beta$). A 4:3 mixture of the β and α anomers of methyl 3-O-benzyl-5-cyano-5-deoxy-D-xylofuranoside (20$\alpha\beta$) (4.23 g, 16.1mmol) was dissolved in dry dichloromethane and cooled to -50°C under nitrogen. Dry pyridine (3.11 ml, 3.06 g, 38.6 mmol) and trifluoromethanesulphonic anhydride (3.25 ml, 5.45 g, 19.3 mmol) were added and the stirred solution allowed to warm to 0°C over 90 minutes. Methanol (1 ml) was added and the solvents removed. The residue was dissolved in ether (50 ml), filtered, and evaporated to give a yellow oil. Purification by flash chromatography (ether-hexane 1:10 to 1:3) gave the partially separated title compounds (β:α 4:3) (6.04 g, 95%).

α-anomer, a colourless oil, R_f 0.1 (ether-hexane 1:4); $[\alpha]_{20}^{D}$ +87.8 (c, 1.15 in chloroform); ν_{max} (film) 2940, 2250 (CN), 1410, 1245, 1150, 1040 and 990 cm^{-1}; ^{1}H NMR δ 2.66 (2H, s, H-5,5'); 3.48 (3H, s, CH$_3$); 4.46-4.48 (2H, m, H-3, H-4); 4.57, 4.76 (2H, 2 x d, CH$_2$Ph, $J_{H,H'}$ 11.6 Hz); 5.11 (1H, dd, H-2, $J_{1,2}$ 0.8 Hz, $J_{2,3}$ 1.2 Hz); 5.12 (1H, bs, H-1); 7.34-7.39 (5H, m, H-Ph). ^{13}C NMR δ 19.00 (t, C-5); 56.05 (q, Me); 72.54, 78.95 (2 x d, C-3, C-4); 72.54 (t, CH$_2$Ph); 87.39 (d, C-2); 99.95 (d, C-1); 116.92 (s, CN); 118.56 (q, CF$_3$); 128.24, 128.74, 128.92 (3 x d, HC-Ph); 136.10 (s, C-Ph). (Found C, 45.58; H, 4.08; N, 3.54. $C_{15}H_{16}NO_6SF_3$ requires C, 45.63; H, 4.01; N, 3.69).

β-anomer, m.p. 59-60°C, R_f 0.18 (ether-hexane 1:4); $[\alpha]_{20}^{D}$ -59.4° (c, 1.085 in chloroform); ν_{max} (chloroform) 2930, 2250 (CN), 1420, 1245, 1155, 1045 and 955 cm^{-1}; ^{1}H NMR δ 2.70, 2.79 (2H, 2 x dd, H-5,5', $J_{5,5'}$ 16.7 Hz, $J_{4,5}$ 6.5 Hz, $J_{4,5'}$ 7.9 Hz); 3.47 (3H, s, CH$_3$); 4.29 (1H, dd, H-3, $J_{2,3}$ 1.6 Hz, $J_{3,4}$ 6.3 Hz); 4.58, 4.78 (2H, 2 x d, CH$_2$Ph, $J_{H,H'}$ 11.8 Hz); 4.63 (1H, m, H-4); 5.08 (1H, s, H-1); 5.20 (1H, bs, H-2); 7.34-7.41 (5H, m, H-Ph). ^{13}C NMR δ 20.16 (t, C-5); 56.03 (q, Me); 73.41 (t, CH$_2$Ph); 77.16, 80.85 (2 x d, C-3, C-4); 90.65 (d, C-2); 106.70 (d, C-1); 116.8 (s, CN); 117.64 (q, CF$_3$); 128.20, 128.67, 128.79 (3 x d, HC-Ph); 135.85 (s, C-Ph). m/z : 413 (M+NH$_4^+$, 100%), 174 (35%), 91 (40%). (Found C, 45.42; H, 4.17; N, 3.18. $C_{15}H_{16}NO_6SF_3$ requires C, 45.63; H, 4.01; N, 3.69).

Methyl 3-O-Benzyl-2,6-imino-2,5,6-trideoxy-D-lyxo-hexofuranoside (22$\alpha\beta$).

A 1:2 mixture of the α and β anomers of methyl 3-O-benzyl-5-cyano-5-deoxy-2-O-trifluoromethanesulphonyl-D-xylofuranoside (21$\alpha\beta$) (2.51 g, 6.36 mmol) dissolved in cyclohexane (200 ml) at 40°C was treated with borane-dimethyl sulphide complex (10M in THF, 955µl, 9.55 mmol) then stirred at room temperature overnight. Methanol (1 ml) was added, and the solvents evaporated then replaced with a 1:1 mixture of methanol and pyridine (50 ml). This was stirred with potassium carbonate (5 g) at room temperature for 48 hours. The solvents were removed and the residue dissolved in dichloromethane (20 ml), filtered and concentrated by evaporation. Purification using flash chromatography produced methyl 3-O-benzyl-2,6-imino-2,5,6-trideoxy-D-lyxo-hexofuranoside (α:β 1:2) (1.52 g, 96%) as a partially separated mixture of colourless oils which rapidly turn brown on storage.

α-anomer, R_f 0.30 (10% ethanol in dichloromethane); $[\alpha]_{20}^{D}$ +20.7° (c, 1.35 in chloroform); ν_{max} (film) 2920, 1440, 1250, 1160, 1030 and 640 cm^{-1}; ^{1}H NMR δ 1.55-1.65 (1H, m, H-5); 2.05-2.20 (1H,

m, H-5); 3.11, 3.43 (2H, 2 x dd, H-6,6', $J_{6,6'}$ 9.0 Hz); 3.41 (1H, s, CH_3); 3.73 (1H, d, H-2, $J_{2,3}$ 9.2 Hz); 3.75 (1H, bs, NH); 4.26 (1H, dd, H-3, $J_{3,4}$ 6.0 Hz); 4.38-4.42 (1H, m, H-4); 4.58, 4.72 (2H, 2 x d, CH_2Ph, $J_{H,H'}$ 12 Hz); 5.19 (1H, s, H-1); 7.30-7.40 (5H, m, H-Ph). ^{13}C NMR δ 25.89 (t, C-5); 38.86 (t, C-6); 55.29 (q, Me); 58.81 (d, C-2); 72.12 (t, $\underline{C}H_2$Ph); 74.30, 75.36 (2 x d, C-3, C-4); 104.91 (d, C-1); 127.73, 128.04, 128.54 (3 x d, H$\underline{C}$-Ph); 137.83 (s, C-Ph). m/z : 91 (100%), 108 (55%), 250 (M+H$^+$, 30%).

β-anomer; R_f 0.25 (10% ethanol in dichloromethane); $[α]_{20}^{D}$ -63.2° (c, 1.25 in chloroform); $ν_{max}$ (film) 3040, 1455, 1255, 1085, 1030 and 640 cm^{-1}; ^{1}H NMR δ 1.71-1.80 (1H, m, H-5); 2.16-2.63 (1H, m, H-5'); 3.43, 3.71 (2H, 2 x dd, H-6,6', $J_{6,6'}$ 8,0 Hz); 3.53 (1H, s, CH_3); 3.99, 4.01 (2H, 2 x s, H-2, H-3); 4.28-4.31 (1H, m, H-4); 4.60, 4.87 (2H, 2 x d, $C_2\underline{H}$Ph, $J_{H,H'}$ 12 Hz); 5.15 (1H, d, H-1, $J_{1,2}$ 2.8 Hz); 6.2 (1H, bs, NH); 7.30-7.40 (5H, m, H-Ph). ^{13}C NMR δ 24.71 (t, C-5); 38.49 (t, C-6); 55.21 (q, Me); 56.71 (d, C-2); 71.80 (t, $\underline{C}H_2$Ph); 74.79, 75.00 (2 x d, C-3, C-4); 103.25 (d, C-1); 127.70, 127.92, 128.55 (3 x d, H$\underline{C}$-Ph); 137.45 (s, C-Ph). m/z : 250 (M+H$^+$, 100%), 98 (40%).

<u>Methyl 3-O-Benzyl-N-benzyloxycarbonyl-2,6-imino-2,5,6-trideoxy-D-lyxo-hexofuranoside (23αβ).</u> Benzyl chloroformate (1.30 ml, 9.17 mmol) was added to a solution of methyl 3-O-benzyl-2,6-imino-2,5,6-trideoxy-D-<u>lyxo</u>-hexofuranoside epimers (22αβ) (α:β 1:2) (1.52 g, 6.11 mmol), in a stirred 3:2 mixture of ether and saturated sodium bicarbonate (60 ml). After 18 hours the ether layer was removed and the aqueous phase extracted further with ether (3 x 50 ml). The combined ether extracts were dried, filtered and evaporated. Purification by flash chromatography afforded both the <u>methyl 3-O-Benzyl-N-benzyloxycarbonyl-2,6-imino-2,5,6-trideoxy-D-lyxo-hexofuranoside</u> anomers as clear oils.

<u>α-anomer</u> (612 mg, 26%), R_f 0.65 (ether-hexane 1:1); $[α]_{20}^{D}$ -12° (c, 0.7 in chloroform); $ν_{max}$ (film) 1695, 1430, 1260, 1105 and 1040 cm^{-1}; ^{1}H NMR δ 1.55-1.68 (1H, m, H-5); 2.08-2.22 (1H, m, H-5'); 3.16-3.22 (1H, m, H-6); 3.40, 3.41 (3H, 2 x s, CH_3); 4.04-4.21 (2H, m, H-6', H-3); 4.40-4.59 (2H, m, H-2, H-4); 4.70, 4.72 (2H, 2 x s, CH_2Ph); 5.01, 5.08 (2H, dd, CH_2-Z, $J_{H,H'}$ 3.4 Hz); 5.13, 5.15, (1H, 2 x s, H-1); 7.20-7.39 (10H, m, 2 x H-Ph). ^{13}C NMR δ 24.54 (t, C-5); 38.33 (t, C-6); 55.27 (q, Me); 56.83, 57.33 (2 x d, C-2); 67.51 (t, $\underline{C}H_2$-Z); 72.13, 72.40 (2 x t, $\underline{C}H_2$Ph); 74.51 (d, C-3, C-4); 104.75, 105.24 (2 x d, C-1); 127.20, 127.70, 128.05, 128.52 (4 x d, H$\underline{C}$-Ph); 136.48 (s, C-Ph). m/z : 91 (100%), 108 (47%), 250 (20%), 384 (M+H$^+$, 15%). (Found C, 68.60; H, 6.72; N, 3.69. $C_{22}H_{25}NO_5$ requires C, 68.91; H. 6.57; N, 3.65).

β-anomer (1.25 g, 53%), R_f 0.35 (ether-hexane 1:1); $[α]_{20}^{D}$ -63.0° (c, 1.25 in chloroform); $ν_{max}$ (film) 1695, 1430, 1220, 1110 and 1030 cm^{-1}; ^{1}H NMR δ 1.54-1.64 (1H, m, H-5); 2.03-2.14 (1H, m, H-5'); 3.47 ,3.48 (3H, 2 x s, CH_3); 3.50-3.61 (1H, m, H-6); 3.83-4.09 (2H, m, H-6', H-3); 4.33-4.92 (4H, m, H-2, H-4, CH_2Ph); 5.02-5.23 (3H, m, H-1, CH_2-Z); 7.21-7.39 (10H, m, 2 x H-Ph). m/z : 91 (100%), 108 (45%), 188 (17%), 384 (M+$^+$, 12%). ^{13}C NMR δ 23.96 (t, C-5); 38.63 (t, C-6); 53.88, 54.41 (2 x q, Me); 56.46 (d, C-2); 67.03 (t, $\underline{C}H_2$-Z); 71.65 (t, $\underline{C}H_2$Ph); 73.39, 75.36 (2 x d, C-3, C-4); 102.82, 103.30 (2 x d, C-1); 127.40; 127.58, 127.73, 127.80, 127.96, 128.43 (6 x d, H$\underline{C}$-Ph); 136.00 (s, C-Ph); 155.35 (s, C=O). (Found C, 68.75; H, 7.14; N, 3.43. $C_{22}H_{25}NO_5$ requires C, 68.91; H, 6.57; N, 3.65).

3-O-Benzyl-N-benzyloxycarbonyl-2,6-imino-2,5,6-trideoxy-D-lyxo-hexose (24). A solution of methyl 3-O-benzyl-2,6-imino-2,5,6-trideoxy-β-D-lyxo-hexofuranoside (23β) (762 mg, 2.06 mmol) in a 1:1 mixture of trifluoroacetic acid and water (20 ml) was stirred at room temperature for 20 minutes. The solvents were removed in vacuo and the crude material purified by flash chromatography (ethyl acetate-hexane 1:2) to give 3-O-benzyl-N-benzyloxycarbonyl-2,6-imino-2,5,6-trideoxy-D-lyxo-hexose (640 mg, 87%) as a clear oil, $[\alpha]_{20}^{D}$ -17.2° (c, 0.73 in chloroform); ν_{max} (film) 3400 (OH), 2920, 1690 (C=O), 1410, 1345 and 1060 cm^{-1}; ^{1}H NMR δ 1.50-1.71 (1H, m, H-5); 1.80 (1H, bs, OH); 2.02-2.20 (1H, m, H-5'); 3.08-3.27 (1H, m, H-6); 3.94-4.20 (2H, m, 6-H, H-3); 4.25-4.85 (4H, m, H-2, H-4, CH$_2$-Ph); 5.05-5.18 (2H, m, CH$_2$-Z); 5.50, 5.53 (0.75H, 2 x s, H-1-hemiacetal); 7.20-7.40 (10H, m, 2 x H-Ph); 9.68 (0.25H, s, H-1-aldehyde). ^{13}C NMR δ 24.17 (t, C-5); 38.10 (t, C-6); 57.26, 57.77 (2 x d, C-2); 67.30, 67.48, 67.58 (3 x t, CH$_2$-Z); 71.38, 71.84, 72.12 (3 x t, CH$_2$Ph); 74.00, 74.63, 74.76 (3 x d, C-3, C-4); 98.72, 98.88, 198.17 (3 x d, C-1); 127.35, 127.58, 127.85, 128.01, 128.23, 128.63 (6 x d, HC-Ph); 136.51, 136.62, 136.73, 137.46, 155.60 (s, C=O-Z); 137.74, 137.88 (6 x s, C-Ph). m/z : 91 (100%), 262 (20%), 370 (M+H$^+$, 15%). (Found C, 68.68; H, 6.40; N, 3.71. C$_{21}$H$_{23}$NO$_5$ requires C, 68.28; H, 6.28; N, 3.79).

Methyl 3-O-benzyl-2,6-imino-2,5,6-trideoxy-α-D-lyxo-hexofuranoside (23α) (606 mg, 164 mmol) afforded the title compound (513 mg, 83%), spectroscopically identical to that produced above, under the same conditions.

4-O-Benzyl-N-benzyloxycarbonyl-1,5-imino-1,2,5-trideoxy-D-arabino-hexitol (25). 3-O-Benzyl-N-benzyloxycarbonyl-2,6-imino-2,5,6-trideoxy-D-lyxo-hexose (24) (364 mg, 0.986 mmol) was dissolved in ethanol (5 ml) and treated with a solution of sodium borohydride (30.0 mg, 0.784 mmol) in a 1:1 mixture of EtOH and H$_2$O (2 ml). After 20 minutes excess ammonium chloride was added, the solution concentrated, poured into brine (15 ml) and extracted with dichloromethane (4 x 20 ml). The organic layers were combined, dried, filtered and evaporated to give 4-O-benzyl-N-benzyloxycarbonyl-1,5-imino-1,2,5-trideoxy-D-arabino-hexitol (355 mg, 97%) as a clear oil, $[\alpha]_{20}^{D}$ -36.7° (c, 0.22 in chloroform); ν_{max} (film) 3380 (OH), 2910, 1665 (2 x CO), 1430, 1210 and 1075 cm^{-1}; ^{1}H NMR δ 1.55-1.68 (1H, m, H-2); 2.04-2.17 (1H, m, H-2'); 2.85 (2H, bs, 2 x OH); 3.40-3.57 (2H, m, H-5, H-1); 3.83-4.03 (4H, m, 6,6'-H, H-4, H-1'); 4.34 (1H, bs, H-3); 4.55, 4.72 (2H, 2 x d, CH$_2$Ph, $J_{H,H}$ 12.0 Hz); 5.15 (2H, s, CH$_2$-Z); 7.28-7.38 (10, m, 2 x H-Ph). m/z : 264 (M-benzyloxy$^+$, 100%), 91 (10%), 172 (10%),372 (M+H$^+$, 5%).

Fagomine, [1,5-Imino-1,2,5-trideoxy-D-arabino hexitol] (3). 4-O-Benzyl-N-benzyloxycarbonyl-1,5-imino-1,2,5-trideoxy-D-arabino-hexitol (25) (325 mg, 0.877 mmol) was dissolved in acetic acid (8 ml) and stirred under hydrogen at atmospheric pressure with palladium black (100 mg). After 18 hours, the solution was filtered and evaporated. Subsequent purification by flash chromatography (CMAW) and ion exchange gave 1,5-imino-1,2,5-trideoxy-D-arabino-hexitol as the hydrochloride salt (158 mg, 98%) a white crystalline solid, m.p. (methanol-ether) 173-175°C, $[\alpha]_{20}^{D}$ +17.9° (c, 0.78 in water); ν_{max} (KBr disc) 3370, 1615, 1390, 1055, 935 and 660 cm^{-1}; ^{1}H NMR (D$_2$O) δ 1.58 (1H, dddd, H-2, $J_{2,2'}$ 14.2 Hz, $J_{2,3}$ 11.4 Hz, $J_{2,1}$ 13.6 Hz, $J_{2,1'}$ 4.6 Hz); 2.06 (1H, dddd, $J_{2',1'}$ 2.4 Hz, $J_{2',3}$ 4.8 Hz, $J_{2',1}$ 3.2 Hz); 2.90-3.01 (2H, m, H-5, H-1); 3.30 (1H, ddd, H-1', $J_{1,1'}$ 13.2 Hz); 3.38 (1H, dd, H-4, $J_{3,4}$ 9.2 Hz, $J_{4,5}$ 10.5 Hz); 3.57 (1H, ddd, H-3); 3.73, 3.79

(2H, 2 x dd, H-6,6', $J_{6,6'}$ 12.7 Hz, $J_{5,6}$ 5.2 Hz, $J_{5,6'}$ 3.4 Hz). ^{13}C NMR δ 29.33 (t, C-2); 42.66 (t, C-1); 58.53 (t, C-6); 60.68 (d, C-5); 70.39, 71.24 (2 x d, C-3, C-4). m/z : 148 (M+H$^+$, 100%), 116 (10%), 72 (8%). Also characterized as free base, m.p. (acetone-water) 178-180°C, [lit.[20] 180-184°C], $[\alpha]_{20}^{D}$ +21.0° (c 0.3 in water) [lit.[20] +24.7 (c 0.4 in water)]; ^1H NMR δ 1.28 (1H, dddd, H-2), 1.81 (1H, dddd, H-2'), 2.40 (1H, ddd, H-1), 2.83 (1H, ddd, H-1'), 2.99 (1H, dd, H-4), 3.37 (1H, m, H-3), 3.46 (1H, dd, H-6), 3.68 (1H, dd, H-6'); ^{13}C NMR δ 33.45 (t, C-2), 43.30 (t, C-1), 61.59 (d, C-5), 62.45 (t, C-6), 73.98 (2 x d, C-3,4).

3-O-Benzyl-N-benzyloxycarbonyl-2,6-imino-2,5,6-trideoxy-D-lyxo-hexono-1,4-lactone (26).

A solution of 1,5-imino-1,2,5-trideoxy-D-arabino-hexitol (24) (407 mg, 1.10 mmol) in a 1:3 mixture of water and 1,4-dioxan containing barium carbonate (653 mg, 3.31 mmol), was cooled to 0°C and treated with bromine (70 μl, 221 mg, 1.37 mmol), then stirred at room temperature for 24 hours. Sodium thiosulphate solution (1M, aqueous) was added until the bromine was removed then the solution acidified with hydrochloric acid (2M, aq, 30 ml) and centrifuged. The supernatent was removed and extracted with ethyl acetate (4 x 20 ml). The combined organic phase was dried, filtered and evaporated. Purification by flash chromatography gave 3-O-benzyl-N-benzyloxycarbonyl-2,6-imino-2,5,6-trideoxy-D-lyxo-hexono-1,4-lactone (342 mg, 84%) as a clear oil, $[\alpha]_{20}^{D}$ -13.7° (c, 1.42 in chloroform); ν_{max} (film) 3030, 2880, 1790 (lactone CO), 1700 (Z CO), 1425, 1260, 1170, 1060, and 700 cm^{-1}; ^1H NMR δ 1.80-1.93 (1H, m, H-5); 2.28-2.35 (1H, m, H-5'); 3.15-3.20 (1H, m, H-6); 3.93-4.07 (1H, m, H-6'); 4.15, 4.28 (1H, 2 x dd, H-3); 4.39-4.61 (2H, m, H-2, H-4); 4.74-4.83 (2H, m, CH$_2$Ph; 5.04-5.20 (3H, m, H-1, CH$_2$-Z), 7.17-7.35 (10H, m, 2 x H-Ph). ^{13}C NMR δ 26.25 (t, C-5); 35.27, 35.49 (2 x t, C-6); 65.92, 66.17 (2 x d, C-4); 67.38 (t, CH$_2$-Z); 71.45 (t, CH$_2$Ph); 75.86 (d, C-3); 127.87, 127.98, 128.08, 128.57 (4 x d, HC-Ph); 136.78, 137.73 (2 x s, C-Ph); 155.15 (s, C=O-Z); 170.34 (s, C-1). m/z (CI NH$_3$) : 91 (100%), 324 (M-CO$_2$+H$^+$, 60%), 385 (M+NH$_4$$^+$, 25%). (Found C, 68.56; H, 5.96; N, 3.51. C$_{21}$H$_{21}$NO$_5$ requires C, 68.68; H, 5.76; N, 3.81).

(2S, 3R, 4R) 3,4-Dihydroxypipecolic acid (4).

3-O-Benzyl-N-benzyloxycarbonyl-2,6-imino-2,5,6-trideoxy-D-lyxo-hexono-1,4-lactone (26) (321 mg, 0.875 mmol) was dissolved in a 2:1 mixture of acetic acid and water (10 ml) and stirred under hydrogen with palladium black (70 mg) for 48 hours. The reaction mixture was filtered through celite, the solvent removed and the product purified by flash chromatography (CMAW) and ion exchange chromatography. Freeze drying afforded (2S, 3R, 4R) 3,4-dihydroxypipecolic acid, monohydrate (140 mg, 89%) as a white crystalline solid, m.p. 253-260°C with decomposition, $[\alpha]_{20}^{D}$ -1.3° (c, 0.54 in water); ν_{max} (KBr disc) 3390, 1595 (CO), 1400, 1080, 1060 and 890 cm^{-1}; ^1H NMR (D$_2$O) δ 1.48-1.61 (1H, m, 5-H); 1.99 (1H, ddt, H-5', $J_{5,5'}$ 14.4 Hz, $J_{5',6;5',6';5',4}$ 3.7 Hz); 2.88 (1H, ddd, 6-H, $J_{6,6'}$ 13.0 Hz, $J_{5,6}$ 11.9 Hz); 3.26 (1H, dt, H-6', $J_{5,6'}$ 3.7 Hz); 3.30 (1H, d, 2-H, $J_{2,3}$ 9.2 Hz); 3.52-3.61 (2H, m, H-3, H-4); ^{13}C NMR (D$_2$O) δ 28.33 (t, C-2); 41.13 (t, C-1); 61.51 (d, H-5); 70.24, 71.85 (2 x d, C-3,4); 172.43 (s, C-1). m/z : 124 (M-2 x H$_2$O-H$^+$, 100%), 98 (M-H$_2$O-CO$_2$H$^+$, 95%), 116 (M-CO$_2$H$^+$, 75%), 162 (M+H$^+$, 67%). (Found C, 40.16; H, 7.10; N, 7.56. C$_6$H$_{11}$NO$_4$.H$_2$O requires C, 40.22; H, 7.31; N, 7.82).

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