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THE SYNTHESIS FROM D-XYLOSE OF THE POTENT AND SPECIFIC ENANTIOMERIC GLUCOSIDASE INHIBITORS, 1,4-DIDEOXY-1,4-IMINO-D-ARABINITOL AND 1,4-DIDEOXY-1,4-IMINO-L-ARABINITOL

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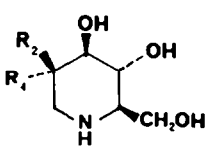
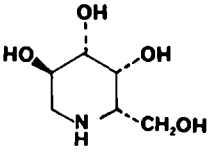
Both enantiomers of 1,4-dideoxy-1,4-iminoarabinitol are specific inhibitors of glucosidases. The synthesis of 1,4-dideoxy-1,4-imino-D-arabinitol involves connecting C2 and C5 of xylose together with nitrogen, whereas the synthesis of 1,4-dideoxy-1,4-imino-L-arabinitol requires C1 and C4 of xylose to be joined together by nitrogen. 1,4-Dideoxy-1,4-imino-D-arabinitol is a naturally occurring pyrrolidine alkaloid found in Arachniodes standishii and Angylocalyx boutiqueanus.

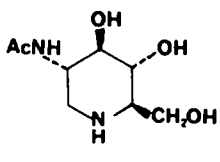
1,5-Dideoxy-1,5-iminohexitols, analogues of pyranoses in which the ring oxygen is replaced by nitrogen and the anomeric hydroxyl group replaced by hydrogen, have been found to be specific inhibitors of the hydrolysis of the corresponding glycopyranosides catalysed by the specific glycosidases.[1,2] Thus the natural products deoxynojirimycin (1), the corresponding analogue of glucose, and the manno isomer deoxymannojirimycin (2) are specific inhibitors of glucosidases[3] and mannosidases[4] respectively. Two synthetic analogues have also been shown to be powerful and specific inhibitors of glycosidase activity; 1,5-dideoxy-1,5-imino-L-fucitol (3) is a potent α-L-fucosidase inhibitor[5] and 2-acetamido-1,5-imino-1,2,5-trideoxy-D-glucitol (4), the analogue of N-acetylglucosamine, is an effective inhibitor of a number of β-N-acetylglucosaminidases.[6] More surprisingly, 1,4-dideoxy-1,4-imino-D-mannitol (5) the azafuranose analogue of mannose is a powerful inhibitor of the hydrolysis of mannopyranosides catalysed by mannosidases both in vitro[7] and in vivo.[8,9] Also some 1,4-iminopentitols have been found to be powerful glycosidase inhibitors; thus 1,4-dideoxy-1,4-imino-D-lyxitol (6) is an α-galactosidase inhibitor.[10]



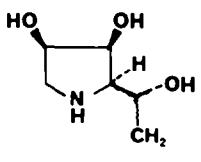
(1) R_1 = OH; R_2 = H
(2) R_1 = H; R_2 = OH



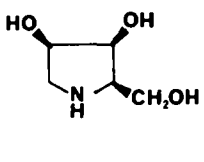
(3)



(4)



(5)

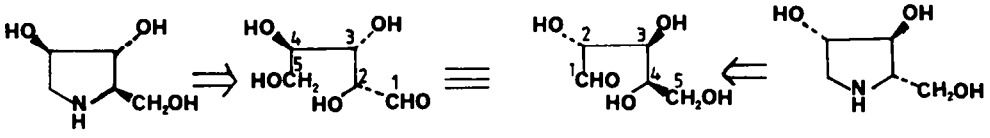


(6)

1,4-Dideoxy-1,4-imino-D-arabinitol (7) has been found both in Arachniodes standishii[11] and Angylocalyx boutiqueanus[12] and has been shown to be a potent inhibitor of the hydrolysis of 4-nitrophenyl α-D-glucopyranoside catalysed by yeast

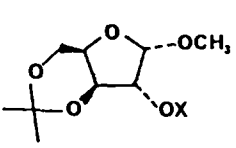
α-glucosidase (50% inhibition at 1.8 x 10^{-7}M); rather weaker inhibition of the same reaction is shown by the enantiomer (8) (50% inhibition at 1.0 x 10^{-5}M).[10] A recent study on the inhibition of a number of mouse gut disaccharidases has shown that synthetic L-isomer (8) is a more potent inhibitor than (7) of the hydrolysis of some natural substrate disaccharides; for example, the concentrations required to cause 50% inhibition of the hydrolysis of the 6-O-α-D-glucopyranosyl disaccharides isomaltose and palatinose for the synthetic L isomer were 6.6 x 10^{-8}M and 2.4 x 10^{-7}M, in comparison to concentrations of 4.0 x 10^{-6}M and 1.3 x 10^{-5}M respectively for the naturally occurring D isomer (7).[13] The synthesis of the L isomer from L-arabinose has been reported.[14] This paper describes the synthesis of both enantiomers from D-xylose; a preliminary account of this work has been published.[10]

The synthesis of the D enantiomer (7) required the introduction of nitrogen function with inversion of configuration at C-2, followed by intramolecular cyclisation onto C-5 of the sugar. The synthesis of the L enantiomer (8) required the formation of a xylitol derivative in which only the hydroxyl groups from C-1 and C-4 of xylose were unprotected, allowing the formation of the pyrrolidine ring by nucleophilic nitrogen displacements of leaving groups at these positions (Scheme). Methyl 3,5-O-isopropylidene-α-D-xylofuranoside (9), a suitable starting material for both syntheses, may be conveniently prepared as the pure anomer from D-xylose on a large scale.[15]



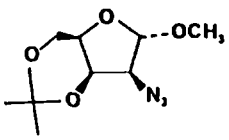
(7) D-XYLOSE (8)

For the synthesis of 1,4-dideoxy-1,4-imino-D-arabinitol (7), the protected xylofuranose (9) was esterified with trifluoromethanesulphonic anhydride to give the corresponding triflate (10) which underwent smooth nucleophilic displacement with azide ion to form the required azide with the lyxo configuration (11) [76% yield from (7)]; it was necessary to use the triflate ester, since the corresponding mesylate does not react with azide ion even in refluxing dimethyl formamide. Mild acid hydrolysis of (11) selectively removed the acetonide to give the diol (12) [99% yield], the primary hydroxyl group of which reacted with p-toluenesulphonyl chloride to form the tosylate (13) [74% yield]. Reduction of the azide (13) by palladium catalysed hydrogenation gave an amine which underwent intramolecular cyclisation to give, after treatment with benzyl chloroformate, the protected bicyclic carbamate (14) [63% yield]. Aqueous acid hydrolysis of the acetal group in (14), followed by reduction of the resulting lactol with sodium borohydride, gave the crystalline N-benzyloxycarbonyl pyrrolidine (15) [81% yield]. The proton NMR spectra of (14) and (15) are not informative because the presence of rotamers results in extensive broadening of the signals. Removal of the N-protecting group by palladium catalysed hydrogenolysis gave 1,4-dideoxy-1,4-imino-D-arabinitol (7), readily crystallised as the hydrochloride salt [80% yield; 23% overall yield from (9)]. The synthetic material was identical with a sample of the alkaloid isolated from Angylocalyx boutiqueanus[16] both spectroscopically (^{13}C and ^{1}H NMR spectra and mass spectra) and in its ability to inhibit the activity of a range of glycosidases.[10]

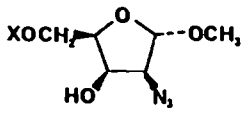


(9) X = H

(10) X = SO_2CF_3

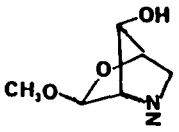


(11)

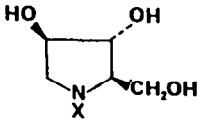


(12) X = H

(13) X = Ts

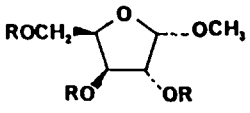


(14)



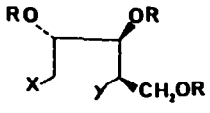
(15) X = Z

(7) X = H



(16) R = H

(17) R = Bzl

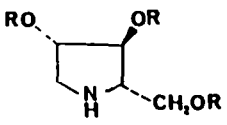


R = Bzl

(18) X = Y = OH

(19) X = Y = OMs

(20) X = N_3; Y = OMs



(21) R = Bzl

(8) R = H

(Ts = p Me-$C_6H_4SO_2$; Ms = $MeSO_2$; Z = $PhCH_2OCO$; Bzl = $PhCH_2$.)

For the synthesis of the L-isomer (8), the isopropylidene protecting group in (9) was removed by selective acid hydrolysis to give methyl α-D-xylofuranoside (16) [85% yield].[17] Treatment of (16) with benzyl bromide in the presence of silver oxide gave protection of the free hydroxyl groups to form the tribenzyl ether (17) [63% yield]. Aqueous acid hydrolysis of (17) followed by reduction of the resulting lactol with sodium borohydride gave the xylitol (18) [76% yield] in which only the hydroxyl groups at C-1 and C-4 of the sugar were unprotected. Esterification of both hydroxyl groups with methanesulphonyl chloride gave the dimesylate (19) [96% yield] which with azide ion underwent selective nucleophilic attack at the primary mesylate to give the primary azide (20) [78% yield]. Hydrogenation of the azide (20) gave an amine which spontaneously cyclised to give the tribenzyl protected amine (21) which on further hydrogenation gave 1,4-dideoxy-1,4-imino-L-arabinitol (8), readily crystallised as the hydrochloride salt [97% yield from (20); 30% overall yield from (9)]. The L isomer (8) had the same physical properties as the D enantiomer (7), and the mass and NMR spectra of the two compounds were superimposable; however, (7) and (8) had opposite specific rotations and their biological properties in regard to their ability to inhibit glycosidase activity was markedly different.[10,13]

In summary, this paper reports the syntheses from methyl 3,5-O-isopropylidene-α-D-xylofuranoside of 1,4-dideoxy-1,4-imino-D-arabinitol (7) and 1,4-dideoxy-1,4-imino-L-arabinitol (8) in overall yield of 23% and 30% respectively. It is noteworthy that both these enantiomers are powerful and specific inhibitors of a number of α-glucosidases; in contrast, no significant glucosidase inhibition was caused by the diastereoisomers, 1,4-dideoxy-1,4-imino-D-lyxitol[10] and 1,4-dideoxy-1,4-imino-L-ribitol.[18] Further studies on 1,4-dideoxy-1,4-iminopentitols as potential glycosidase inhibitors are in progress.[19]

Experimental

M.p.s were recorded on a Kofler block. Infra red spectra were recorded on a Perkin-Elmer 297 spectrophotometer. ^1H NMR spectra were run at 300 MHz on a Bruker WH 300 spectrometer (500 MHz on a Bruker AM 500 spectrometer); ^{13}C NMR spectra were recorded on a Bruker AM 250 (62.9 MHz) or a Bruker AM 500 (125.0 MHz) spectrometer. All NMR spectra were obtained using deuteriochloroform as solvent unless otherwise stated; for NMR spectra in D_2O, 1,4-dioxan (δ 67.6) was used as the internal

standard. Mass spectra were recorded on VG Micromass ZAB 1F or MM 30F spectrometers; in order to obtain satisfactory mass spectra for these highly polar compounds, it was necessary to use DCI or FAB techniques. Microanalyses were performed by the microanalytical services of the Dyson Perrins Laboratory. TLC was performed on glass plates coated with silica gel Blend 41, and compounds were visualised with a spray of 5% v/v sulphuric acid in ethanol or a solution of 5% dodecamolybdophosphoric acid in ethanol. Flash chromatography was carried out using Merck Kieselgel 60, 230-400 mesh. THF was distilled from a solution dried with sodium in the presence of benzophenone under dry nitrogen. p-Toluenesulphonyl chloride was recrystallised from benzene/30-40 petroleum ether. Methyl 3,5-O-isopropylidene-α-D-xylofuranoside was prepared in 33% yield from D-xylose by the method described by Baker.[15]

Methyl 2-azido-2-deoxy-3,5-O-isopropylidene-α-D-lyxofuranoside (11). Methyl 3,5-O-isopropylidene-α-D-xylofuranoside (9) (6.57 g, 32.2 mmol) was dissolved in dichloromethane (100 ml) containing pyridine (5.17 ml, 2 equivalents) and the solution cooled to -30°C under nitrogen. Trifluoromethanesulphonic anhydride (10 g, 1.1 equivalents) was added with stirring, and the reaction mixture was stirred at -30°C for 30 min. The solution was then allowed to warm to room temperature, washed with water (100 ml) and saturated aqueous sodium bicarbonate solution (100 ml); the organic layer was then dried (sodium sulphate) and concentrated *in vacuo* to afford a pale yellow syrup, a small amount of which was purified by flash chromatography (25% ethyl acetate in hexane) to give methyl 3,5-O-isopropylidene-2-O-trifluoromethanesulphonyl-α-D-xylofuranoside (10), an oil, $[\alpha]_D^{20}$ +98.8° (c, 1.38 in MeOH). ^{1}H NMR δ 5.25 (1H, d, H-1, $J_{1,2}$ 4.3 Hz), 5.02 (1H, dd, H-2), 4.45 (1H, dd, H-3, $J_{2,3}$ 1.8 Hz), 4.15 (1H, q, H-4, $J_{3,4}$ 3.8 Hz), 4.05 (1H, dd, H-5', $J_{4,5'}$ 3.8 Hz), 3.90 (1H, dd, H-5, $J_{5,5'}$ 12.8 Hz, $J_{4,5}$ 3.8 Hz), 3.51 (3H, s, MeO), 1.42 (3H, s, Me) and 1.39 (3H, s, Me); ^{13}C NMR δ 20.51 (q, MeC), 27.54 (q, MeC), 56.39 (q, MeO), 59.86 (t, C-5), 70.90, 73.36 (2d, C-3, C-4), 88.23 (d, C-2), 98.96 (s, Me_2C), 101.08 (d, C-1), and 118.50 (q, CF_3, not proton decoupled); m/z (in beam EI) 321 (20%, M-Me$^+$).

The remainder of the crude triflate (10) was dissolved in DMF (80 ml) and stirred with sodium azide (6 g, 92.2 mmol) at 100°C for 18 h to give a clean conversion to the azide (11) as judged by TLC (R_f 0.4, 30% ethyl acetate in hexane). The DMF was then removed from the reaction mixture by evaporation and the residue was partitioned between chloroform (100 ml) and water (100 ml). The organic layer was dried (sodium sulphate), and the solvent removed to give, after purification by flash chromatography (25% ethyl acetate in hexane), methyl 2-azido-2-deoxy-3,5-O-isopropylidene-α-D-lyxofuranoside (11), (5.62 g, 76%), as an oil, $[\alpha]_D^{20}$ +128.0°, (c, 0.97 in $CHCl_3$); ν_{max} ($CHCl_3$) 2905, 2100 (N_3) and 1370 cm^{-1}; ^{1}H NMR δ 1.47 (6H, s, isopropylidene CH_3), 3.49 (3H, s, MeO), 3.64 (1H, t, H-2), 3.96 - 4.10 (3H, m, H-4, H-5, H-5'), 4.45 (1H, dd, H-3), and 5.23 (1H, d, H-1, $J_{1,2}$ 4.8 Hz); ^{13}C NMR δ 19.01 (q, MeC), 28.34 (q, MeC), 56.33 (q, MeO), 60.41 (t, C-5), 67.65 (d, C-2), 70.76, 71.93 (2d, C-3, C-4), 97.90 (s, Me_2C), and 106.66 (d, C-1); m/z (DCI, NH_3) 247 (15%, M+NH_4^+), 230 (55%, M+H$^+$), 202 (100%) (Found C, 47.4; H, 6.6; N, 18.3. $C_9H_{15}N_3O_4$ requires C, 47.4; H, 6.6; N, 18.4%).

Methyl 2-azido-2-deoxy-α-D-lyxofuranoside (12). Methyl 2-azido-2-deoxy-3,5-O-isopropylidene-α-D-lyxofuranoside (11) (1.74 g, 7.6 mmol) was dissolved in a mixture of water (3 ml) and acetic acid (7 ml), and the solution was warmed to 50°C for 1 h. Evaporation of the solvent and purification by flash chromatography (20% hexane in ethyl acetate) gave methyl 2-azido-2-deoxy-α-D-lyxofuranoside (12), (1.42 g, 99%), as a colourless oil, $[\alpha]_D^{20}$ +131.9°,(c, 0.39 in $CHCl_3$); ν_{max} ($CHCl_3$) 3400 (br), 2110 (N_3), 1270, 1100 and 1040 cm^{-1}; ^{1}H NMR δ 2.37 (1H, br s, OH), 3.39 (3H, s, MeO), 3.42 (1H, d, OH), 3.95 (3H, m, H-3, H-5, H-5'), 4.17 (1H, m, H-2), 4.69 (1H,

m, H-4) and 4.93 (1H, d, H-1, $J_{1,2}$ 1.6 Hz); ^{13}C NMR δ 55.44 (q, MeO), 61.15 (t, C-5), 67.60 (d, C-2), 73.06, 78.47 (2d, C-3, C-4), and 105.71 (d, C-1); m/z (DCI, NH_3) 207 (100%, $M+NH_4^+$), 190 (20%) (Found C, 38.07; H, 6.04; N, 22.15. $C_6H_{11}N_3O_4$ requires C, 38.09; H, 5.82; N, 22.22%).

Methyl 2-azido-2-deoxy-5-O-p-toluenesulphonyl-α-D-lyxofuranoside (13). Methyl 2-azido-2-deoxy-α-D-lyxofuranoside (12) (3.8 g, 20.1 mmol) was dissolved in pyridine (70 ml) and stirred at 0°C with p-toluenesulphonyl chloride (4.03 g, 1.05 equivalents) for 12 h. The bulk of the pyridine was removed in vacuo, and the residue dissolved in chloroform (100 ml). The resulting solution was washed successively with dilute aqueous hydrochloric acid (2M, 100 ml), water (100 ml) and saturated aqueous sodium bicarbonate (100 ml), dried (sodium sulphate) and then concentrated to a syrup which was purified by flash chromatography (30% ethyl acetate in hexane) to give methyl 2-azido-2-deoxy-5-O-p-toluenesulphonyl-α-D-lyxofuranoside (13), (5.09 g, 74%), as a colourless syrup, $[\alpha]_D^{20}$ +67.2°, (c, 1.14 in $CHCl_3$); ν_{max} ($CHCl_3$) 3500 (br), 2110 (N_3), 1350 and 1170 cm^{-1}; ^{1}H NMR δ 2.41 (1H, d, OH), 2.46 (3H, s, MeAr), 3.38 (3H, s, MeO), 3.89 (1H, dd, H-2, $J_{1,2}$ 3.1 Hz, $J_{2,3}$ 5.0 Hz), 4.12 - 4.47 (4H, m, H-3, H-4, H-5, H-5'), 4.93 (1H, d, H-1), 7.35 (2H, d, ArH) and 7.81 (2H, d, ArH); ^{13}C NMR δ 21.61 (q, MeAr), 55.95 (q, MeO), 67.79 (t, C-5), 68.09 (d, C-2), 71.47, 77.48 (2d, C-3, C-4), 106.43 (d, C-1), 128.02 (d), 129.85 (d), 132.72 (s) and 145.00 (s); m/z (DCI, NH_3) 361 (100%, $M+NH_4^+$), 329 (40%), 316 (40%) (Found C, 45.72; H, 5.10; N, 12.15. $C_{13}H_{17}N_3O_6S$ requires C, 45.48; H, 4.96; N, 12.24%).

Methyl N-benzyloxycarbonyl-2,5-dideoxy-2,5-imino-α-D-lyxofuranoside (14). Methyl 2-azido-2-deoxy-5-O-p-toluenesulphonyl-α-D-lyxofuranoside (13) (1.0 g, 2.9 mmol) was dissolved in ethanol (10 ml) and stirred at room temperature in a hydrogen atmosphere in the presence of palladium black (0.1 g) for 24 h. The reaction mixture was filtered to remove the catalyst and concentrated in vacuo to a brown syrup which was partitioned between ethyl acetate (10 ml) and aqueous sodium bicarbonate solution (4 ml). The two layers were cooled to 0° and benzyl chloroformate was added to the biphasic system, which was vigorously stirred for 1 h. The organic layer was then separated, dried (sodium sulphate) and the solvent removed in vacuo; the residue was purified by flash chromatography (30% ethyl acetate in hexane) to give methyl N-benzyloxycarbonyl-2,5-dideoxy-2,5-imino-α-D-lyxofuranoside (14), (0.51g, 63%), as an oil, ν_{max} ($CHCl_3$) 3400 (br), 1690 (CO), 1420, 1355, 1320, 1255, 1195 and 1090 cm^{-1}; m/z (DCI, NH_3) 280 (100%, $M+H^+$), 236, 158, 91. The ^{1}H NMR spectrum of (14) is complex due to the existence of rotamers; (14)is unstable and should be used in the next step immediately.

N-Benzyloxycarbonyl-1,4-dideoxy-1,4-imino-D-arabinitol (15). Freshly prepared methyl N-benzyloxycarbonyl-2,5-dideoxy-2,5-imino-α-D-lyxofuranoside (14) (1.99 g, 7.1 mmol) was dissolved in a mixture of trifluoroacetic acid (16 ml) and water (4 ml). After a clear solution had been obtained, the solvent was immediately evaporated and the residue dissolved in ethyl acetate (25 ml). The ethyl acetate solution was carefully washed with saturated aqueous sodium bicarbonate solution (25 ml), dried (sodium sulphate) and the solvent removed. The residue was dissolved in ethanol (20 ml) and a solution of sodium borohydride (0.2 g, 0.75 molar equivalents) in water (2 ml) was added at room temperature. After 15 min, saturated aqueous ammonium chloride (0.5 ml) was added; when the effervescence ceased, the ethanol was removed and the residue partitioned between water (30 ml) and ethyl acetate (30 ml). The aqueous layer was then extracted with further ethyl acetate (4 x 30 ml) and the organic extracts combined, dried (sodium sulphate) and the solvent removed to give a residue

which was purified by flash chromatography (2% ethanol in ethyl acetate) to give N-benzyloxycarbonyl-1,4-dideoxy-1,4-imino-D-arabinitol (15), a colourless syrup which slowly crystallised, (1.54 g, 81%), m.p. 128-129°C, $[\alpha]_D^{20}$ -29.7°,(c, 0.30 in MeOH); ν_{max} 3350 (br), 1680 (CO), 1465, 1435, 1360, 1210 and 1140 cm^{-1}; ^1H NMR (D_2O) δ 3.1 (1H, m, CHN), 3.7 (2H, m, CH_2N), 4.0 (1H, m), 4.8 (4H, m), and 5.0 (1H, m) and 7.2 (5H, ArH) [substantial broadening of these resonance is due to the existence of rotamers]; ^{13}C NMR (D_2O) (rotamers) δ 54.35, 54.79 (t, CH_2N), 61.64, 61.82 (t, CH_2OH),68.08 (t, $ArCH_2$), 68.27, 68.55 (d, CHN), 75.61, 76.15 (d, CHOH), 78.72, 79.39 (d, CHOH), 128.85, 128.98 (d), 129.09, 129.53 (d) 137.95 (s) and 157.18 (s) [Two signals are observed for most carbons due to the existence of rotamers]. m/z (DCI, NH_3) 268 (100%, $M+H^+$) (Found C, 58.15; H, 6.50; N, 5.09. $C_{13}H_{17}NO_5$ requires C, 58.43; H, 6.37; N, 5.24%).

1,4-Dideoxy-1,4-imino-D-arabinitol (7) and 1,4-Dideoxy-1,4-imino-D-arabinitol Hydrochloride. N-Benzyloxycarbonyl-1,4-dideoxy-1,4-imino-D-arabinitol (15) (1.54 g, 5.77 mmol) was dissolved in glacial acetic acid (20 ml) and stirred in a hydrogen atmosphere in the presence of palladium black (0.1 g) for 30 min. The catalyst was removed by filtration and the reaction mixture was concentrated to a brown syrup which was purified first by flash chromatography (10% water in methanol) and then by ion exchange chromatography (CG 400, OH^- form, eluted with water, then Dowex 50x 8-100, H^+ form, eluted with 0.5M aqueous ammonia) to give the free base, 1,4-dideoxy-1,4-imino-D-arabinitol (7), a colourless oil, $[\alpha]_D^{20}$ +7.8°,(c, 0.46 in H_2O); ^1H NMR (D_2O) δ 2.79 (1H, dd, H-1, $J_{1,1'}$ 12.3 Hz, $J_{1,2}$ 3.7 Hz), 2.97 (1H, dt, H-4), 3.06 (1H, dd, H-1', $J_{1',2}$ 5.6 Hz), 3.55 (1H, dd, H-5, $J_{5,5'}$ 11.8 Hz, $J_{4,5}$ 6.8 Hz), 3.63 (1H, dd, H-5', $J_{4,5'}$ 5.6 Hz), 3.73 (1H, t, H-3) and 4.03 (1H, dt, H-2); m/z (DCI, NH_3) 134 (100%, $M+H^+$), 102 ($M-CH_2OH^+$). The ^1H and ^{13}C NMR spectra of synthetic (7) were identical to those of an authentic sample.[16] The free base (7) was dissolved in water (5 ml) and acidified to pH 4 with dilute aqueous hydrochloric acid. The solution was then freeze dried to give, after crystallisation from aqueous acetone, 1,4-dideoxy-1,4-imino-D-arabinitol hydrochloride, (0.78 g, 80%), m.p. 113-115°C (lit.[11] 115°C), $[\alpha]_D^{20}$ +37.9°,(c, 0.53 in H_2O); ^1H NMR (D_2O) δ 3.21 (1H, dd, H-1, $J_{1,1'}$ 12.5 Hz, $J_{1,2}$ 2.6 Hz), 3.46 (2H, m, H-1'and H-4), 3.69 (1H, dd, H-5, $J_{5,5'}$ 12.2 Hz, $J_{4,5}$ 8.1 Hz), 3.81 (1H, dd, H-5', $J_{4,5'}$ 4.7 Hz), 3.95 (1H, m, H-3) and 4.19 (1H, m, H-2); ^{13}C NMR (D_2O) δ 51.03 (t, CH_2N), 59.93 (t, CH_2OH), 67.59 (d, CHN), 75.25 (d, CHOH), and 76.67 (d, CHOH); m/z (in beam EI) 134 (100%, $M+H^+$), 102 ($M-CH_2OH^+$), 84, 73, 55, and 41.

Methyl α-D-xylofuranoside (16). Methyl 3,5-O-isopropylidene-α-D-xylofuranoside (9) (2 g, 9.8 mmol) was dissolved in acetic acid - water (2:1, 30 ml) and left at room temperature for 12 h. The solvent was removed and the resulting syrup purified by flash chromatography (5% ethanol in ethyl acetate) to give methyl α-D-xylofuranoside (16), (1.36 g, 85%), m.p. 82-83°C (lit.[17] 85°C); ^1H NMR (D_2O) δ 3.29 (3H, s, MeO), 3.56 (1H, dd, H-5', $J_{4,5'}$ 5.7Hz), 3.62 (1H, dd, H-5, $J_{4,5}$ 3.7Hz, $J_{5,5'}$ 12.2Hz), 4.00 (1H, dd, H-2, $J_{2,3}$ 5.2Hz), 4.09 (2H, m, H-3, H-4) and 4.85 (1H, d, H-1, $J_{1,2}$ 4.5Hz); ^{13}C NMR (D_2O) δ 56.62 (q, MeO), 61.45 (t, CH_2OH), 75.95 (d, CHOH), 77.69 (d, CHOH), 79.27 (d, CHOH) and 103.06 (d, C-1).

Methyl 2,3,5-tri-O-benzyl-α-D-xylofuranoside (17). Methyl α-D-xylofuranoside (1.36 g, 8.29 mmol) was dissolved in dimethyl formamide (15 ml) containing benzyl bromide (6.7 ml, 56 mmol) and silver (I) oxide (9.2g, 39.7 mmol). The reaction mixture was stirred vigorously at room temperature in the dark for 24 h. Addition of ether (10 ml) caused precipitation of the silver salts; the reaction mixture was then filtered through celite and concentrated to a syrup which was purified by flash

chromatography (20% ether in hexane) to give methyl 2,3,5-tri-O-benzyl-α-D-xylofuranoside (17), (2.26 g, 63%), as a colourless syrup, $[\alpha]_D^{20}$ +59°, (c, 0.63 in $CHCl_3$); ^{1}H NMR δ 3.41 (3H, s,MeO), 3.59 (1H, dd, H-5', $J_{4,5'}$ 6.1 Hz), 3.72 (1H, dd, H-5, $J_{4,5}$ 3.9 Hz, $J_{5,5'}$ 10.6 Hz), 4.02 (1H, dd, H-2), 4.32 (1H, dd, H-3, $J_{2,3}$ 5.9 Hz, $J_{3,4}$ 7.1 Hz), 4.40 (1H, m, H-4), 4.58 (6H, m, $PhCH_2$), 4.81 (1H, d, H-1, $J_{1,2}$ 4.3 Hz) and 7.2 - 7.4 (15H, m, ArH); m/z (DCI, NH_3) 452 (20%, $M+NH_4^+$) (Found C, 74.83; H, 7.00. $C_{27}H_{30}O_5$ requires C, 74.65; H, 6.91%).

2,3,5-Tri-O-benzyl-D-xylitol (18). Methyl 2,3,5-tri-O-benzyl-α-D-xylofuranoside (17) (2.0 g, 4.6 mmol) was dissolved in 50% aqueous trifluoroacetic acid (10 ml) and left at 50°C for 1 h. The solvent was removed in vacuo and the residue dissolved in chloroform (10 ml) and washed with saturated aqueous sodium bicarbonate to remove the last traces of trifluoroacetic acid. The chloroform was removed; the resulting syrup was dissolved in ethanol (10 ml) and treated with sodium borohydride (0.19 g, 5.1 mmol) at 0°C for 15 min after which time the reaction was quenched with excess ammonium chloride. The ethanol was removed and the residue partitioned between water (20 ml) and chloroform (20 ml). The organic layer was dried (sodium sulphate) and the solvent evaporated to give a colourless syrup which was purified by flash chromatography (66% ether in hexane) to yield 2,3,5-tri-O-benzyl-D-xylitol (18), (1.48 g, 76%), an oil, $[\alpha]_D^{20}$ -11°3°, (c, 0.91 in $CHCl_3$); ν_{max} 3550-3300 (OH) cm^{-1}; ^{1}H NMR δ 2.85 (2H, br s, OH), 3.44 (1H, dd, H-5', $J_{4,5'}$ 6.3 Hz), 3.53 (1H, dd, H-5, $J_{4,5}$ 6.4 Hz, $J_{5,5'}$ 9.4 Hz), 3.72 (2H, m, H-2, H-3), 3.81 (2H, m, H-1, H-1'), 4.07 (1H, dt, H-4), 4.57 (6H, m, $PhCH_2$) and 7.2 - 7.4 (15H, m, ArH); m/z (DCI, NH_3) 440 (35%, $M+NH_4^+$), 423 (76%, $M+H^+$), and 91 (100%. $PhCH_2$) (Found C, 73.97; H, 7.32. $C_{26}H_{30}O_5$ requires C, 73.93; H, 7.11%).

1,4-Di-O-methanesulphonyl-2,3,5-tri-O-benzyl-D-xylitol (19). Methanesulphonyl chloride (0.64 ml, 2.5 equivalents) was added, with stirring to a solution of 2,3,5-tri-O-benzyl-D-xylitol (18) (1.4 g, 3.3 mmol) in pyridine (10 ml) at 0°C. After 3 h, the reaction mixture was diluted with dichloromethane (100 ml) and washed successively with dilute aqueous hydrochloric acid (2M, 100 ml), water (100 ml) and saturated aqueous sodium bicarbonate solution (100 ml). The dichloromethane solution was dried (sodium sulphate), the solvent removed and the residue purified by flash chromatography (66% ether in hexane) to afford 1,4-di-O-methanesulphonyl-2,3,5-tri-O-benzyl-D-xylitol (19), (1.84 g, 96%), an oil, $[\alpha]_D^{20}$ +16.0°, (c, 1.33 in $CHCl_3$); ^{1}H NMR δ 2.92 (3H, s, $MeSO_2$), 3.00 (3H, s, $MeSO_2$), 3.62 (2H, m, H-5, H-5'), 3.87 (2H, m, H-2,H-3), 4.5 (8H, m, H-1, H-1', $PhCH_2$), 4.96 (1H, m, H-4) and 7.2 - 7.4 (15H, m, ArH); ^{13}C NMR δ 37.32 (q, $MeSO_2$), 38.59 (q, $MeSO_2$), 68.36, 68.86, 73.34, 74.76, 76.49 (5t, C-1, C-5, $PhCH_2$), 75.94 (d, C-2, C-3), 80.15 (d, C-4), 127.90, 127.99, 128.10, 128.21, 128.52, 137.08, 137.17 (aromatic C) m/z (DCI, NH_3) 596 (20%, $M+NH_4^+$), and 91 (100%. $PhCH_2$) (Found C, 58.33; H, 6.07. $C_{28}H_{34}O_9S_2$ requires C, 58.13; H, 5.88%).

1-Azido-1-deoxy-4-O-methanesulphonyl-2,3,5-tri-O-benzyl-D-xylitol (20). 1,4-Di-O-methanesulphonyl-2,3,5-tri-O-benzyl-D-xylitol (19) (1.64 g, 2.83 mmol) was dissolved in dry dimethyl formamide (10 ml) and stirred at 50°C with sodium azide (0.2 g, 1.1 equivalents) for 12 h. The solvent was removed in vacuo and the residue partitioned between water (25 ml) and chloroform (25 ml). The chloroform layer was dried (sodium sulphate) and the solvent removed; the residue was purified by flash chromatography (40% ether in hexane) to yield 1-azido-1-deoxy-4-O-methanesulphonyl-2,3,5-tri-O-benzyl-D-xylitol (20), (1.16 g, 78%) an oil, $[\alpha]_D^{20}$ +13.8°, (c, 0.5 in $CHCl_3$); ν_{max} ($CHCl_3$) 2100 (N_3) cm^{-1}; ^{1}H NMR δ 2.88 (3H, s, $MeSO_2$), 3.47 (2H, m, H-1, H-1'), 3.61 (2H, m, H-5, H-5'), 3.72 (1H, q, H-2), 3.84 (1H, t, H-3), 4.5 (6H, m, $PhCH_2$),

4.87 (1H, dt, H-4) and 7.2 - 7.4 (15H, m, ArH); m/z (DCI, NH_3) 543 (100%, $M+NH_4^+$) (Found C, 61.43; H, 6.17; N, 7.78. $C_{27}H_{31}N_3O_6S$ requires C, 61.71; H, 5.90; N, 8.00%).

1,4-Dideoxy-1,4-imino-L-arabinitol hydrochloride (8). 1-Azido-1-deoxy-4-O-methanesulphonyl-2,3,5-tri-O-benzyl-D-xylitol (20) (0.96 g, 1.83 mmol) in ethanol (15 ml) was stirred under an atmosphere of hydrogen in the presence of a catalyst of palladium black (50 mg) at room temperature until all the starting material had disappeared (about 90 min). The solvent was then changed to acetic acid (15 ml) and fresh catalyst added and the hydrogenation continued until all the benzyl groups had been removed (about 4 days). The catalyst was then removed by filtration and the solvent evaporated. The residue was purified first by flash chromatography (10% water in methanol) and then by ion exchange chromatography (CG 400, OH^- form, eluted with water, then Dowex 50x 8-100, H^+ form, eluted with 0.5M aqueous ammonia) to give a colourless syrup of the free base (8), which was dissolved in water (5 ml) and acidified to pH 4 with dilute aqueous hydrochloric acid. The solution was then freeze dried to give 1,4-dideoxy-1,4-imino-L-arabinitol hydrochloride (8), (0.3 g, 97%), m.p. 109-111°C (from aqueous acetone), $[\alpha]_D^{20}$ -34.6°, (c, 0.37 in H_2O). The NMR and mass spectra of (8) are superimposable with those of (7).

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