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METHYL 2-AZIDO-3-O-BENZYL-2-DEOXY-α-D-MANNOFURANOSIDE AS A DIVERGENT INTERMEDIATE FOR THE SYNTHESIS OF POLYHYDROXYLATED PIPERIDINES AND PYRROLIDINES: SYNTHESIS OF 2,5-DIDEOXY-2,5-IMINO-D-MANNITOL [2R,5R-DIHYDROXYMETHYL-3R,4R-DIHYDROXYPYRROLIDINE]

George W. J. Fleet and Paul W. Smith
Dyson Perrins Laboratory, Oxford University, South Parks Road, Oxford, OX1 3QY, UK

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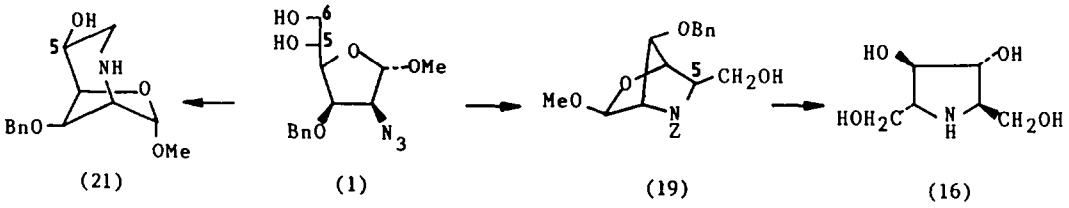
The synthesis of methyl 2-azido-3-O-benzyl-2-deoxy-α-D-mannofuranoside (1) from D-glucose is reported; the conversions of (1) into derivatives of methyl 3-O-benzyl-2,6-dideoxy-2,6-imino-α-D-mannofuranoside (as precursors for the synthesis of polyhydroxylated piperidines) and into the hydroxylated pyrrrolidine, 2,5-dideoxy-2,5-imino-D-mannitol [2R,5R-dihydroxymethyl-3R,4R-dihydroxypyrrolidine] are described.

Methyl 2-azido-3-O-benzyl-2-deoxy-α-D-mannofuranoside (1) is a divergent intermediate for the synthesis of polyhydroxylated pyrrolidines and piperidines; for example, a pyrrolidine ring arises from formation of a bond between nitrogen and C-5 with retention of configuration to give the bicyclic amine (19), whereas formation of a bond between nitrogen and C-6 of the sugar leads to a bicyclic amine (21) containing a piperidine ring (Scheme). This paper describes the synthesis of the azidomannofuranoside (1) from D-glucose, and the conversion of (1) into the hydroxylated pyrrrolidine, 2,5-dideoxy-2,5-imino-D-mannitol (16) via the intermediate bicyclic [2.2.1] amine (19). The preparation of carbamates of the bicyclic [3.2.1] amine (21) from (1) is also reported; the accompanying paper discusses the use of these bicyclic intermediates containing a piperidine ring in the synthesis of hydroxylated piperidines.[1] A preliminary account of this work has been published.[2]



(21) (1) (19) (16)

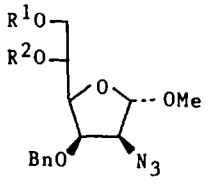
SCHEME

The preparation of methyl 2-azido-3-O-benzyl-2-deoxy-α-D-mannofuranoside (1) from D-glucose requires the formation of a glucofuranose in which only the C-2 hydroxyl is unprotected. Diacetone glucose (6) was benzylated to give (7), the side chain acetonide was removed by selective mild acid hydrolysis and the resulting diol (8) treated with dimethyl carbonate to give the carbonate (9);[3] these transformations may be carried out sequentially without the need for purification of intermediates to give the carbonate (9) in an overall yield of 80% on a 50 g scale.

The carbonate protecting group is stable to acid, and so treatment of (9) with methanol in the presence of acid ion exchange resin gave a mixture of the α- (10) and β- (12) furanosides in 92% yield in a ratio of approximately 1:2. The anomers may be separated by flash chromatography, and the β- anomer treated with acid resin and methanol to reestablish the equilibrium anomeric mixture; in this manner the α-anomer (10) may be prepared in 10 g quantities. It is worth noting that when the acetonide (9) is treated with 50% trifluoracetic acid in methanol, a more favourable

α:β ratio of 4:1 is formed;[4] however, the major product of this reaction (70%) is the corresponding lactol, 3-O-benzyl-D-glucofuranose-5,6-carbonate.

Both the α- (10) and β- (12) anomers form stable triflates on treatment with trifluoromethanesulphonic anhydride in dichloromethane. Treatment of the α-triflate (11) with sodium azide in dimethylformamide at 50°C gave the manno-azide (14) in 88% yield; under similar conditions, the highly crystalline β-triflate (13) reacted very slowly giving several products. Tetrabutylammonium azide[5] in dimethyl formamide at room temperature over several days effected conversion of (13) to the required azide (15) in modest yield, but substantial amounts of the triflate (13) remained and several unidentified minor products were also formed. Attempts to perform the azide displacement on mixtures of the anomeric triflates (11) and (13) gave a low yield of the α-azide (14), contaminated with impurities from the reaction of the β-triflate. For this reason the use of the pure α-anomer (10) in this sequence of



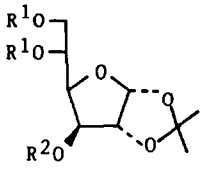
(1) $R^1 = R^2 = H$

(2) $R^1 = PhCO$; $R^2 = H$

(3) $R^1 = PhCO$; $R^2 = MeSO_2$

(4) $R^1 = H$; $R^2 = MeSO_2$

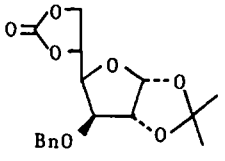
(5) $R^1 = p\text{-}Me\text{-}C_6H_4\text{-}SO_2$; $R^2 = H$



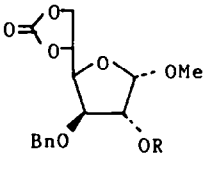
(6) $R^1 = Me_2C$; $R^2 = H$

(7) $R^1 = Me_2C$; $R^2 = Bn$

(8) $R^1 = H$; $R^2 = Bn$

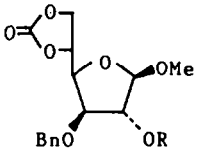


(9)



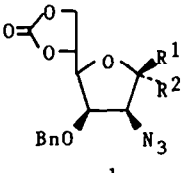
(10) R = H

(11) $R = CF_3SO_2$



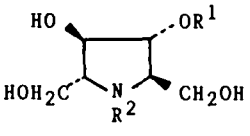
(12) R = H

(13) $R = CF_3SO_2$



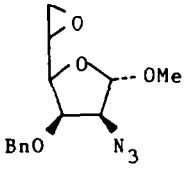
(14) $R^1 = H$; $R^2 = MeO$

(15) $R^1 = MeO$; $R^2 = H$



(16) $R^1 = R^2 = H$

(17) $R^1 = Bn$; $R^2 = Z$



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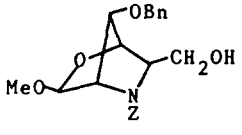
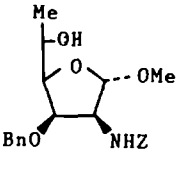
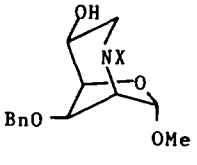


(19)



(20)



(21) X = H

(22) X = Z

(23) X = BOC

(Bn = $PhCH_2$; Z = $PhCH_2OCO$; BOC = tBuOCO)

transformations is highly desirable. Removal of the carbonate group from (14) was accomplished using a trace of methoxide in methanol at room temperature to give the key azidodiol (1). The α-anomer (10) may be converted in 3 steps to the crystalline azidodiol (1) in 75% overall yield without purification of the intermediates [overall yield from diacetone glucose (6) 53%, allowing for reequilibration of β-anomer (12)].

The hydroxylated pyrrolidine 2,5-dideoxy-2,5-imino-D-mannitol (16), isolated from Derris elliptica[6] and the closely related Lonchocarpus spp.,[7] has been shown to be a glucosidase inhibitor.[8] For the synthesis of (16) from the azidodiol (1), it is necessary to form a bond between the nitrogen function at C-2 and C-5, with overall retention of configuration at C-5. Selective esterification of the primary hydroxyl group in (1) with benzoyl chloride gave the benzoate (2) [81% yield] which reacted with excess methane sulphonyl chloride to form (3) [94% yield]. The benzoyl group was removed on treatment with sodium methoxide at 50°C to form the primary alcohol (4) which subsequently cyclised, with inversion of configuration at C-5, to the epoxide (18) [82% yield].

Hydrogenation of the azidoepoxide (18) in the presence of palladium black in ethanol led to the formation of two products which were isolated and characterised as the corresponding N-benzyloxycarbonyl derivatives. The major product (43% yield) was the carbamate (19), in which the amine produced by reduction of the azide (18) had cyclised by a 5-exo-tet process in preference to a 7-endo-tet cyclisation;[9] an analogous cyclisation to produce a carbocyclic system has been reported.[10] The minor product (20) (24% yield) arose from hydrogenolysis of the epoxide. Hydrolysis of the bicyclic carbamate (19) with aqueous trifluoroacetic acid, followed by reduction of the resulting lactol with sodium borohydride, gave the triol (17) [73% yield]. The protecting groups were removed by hydrogenolysis in acetic acid in the presence of palladium black to give, after neutralisation and purification by ion exchange chromatography, 2,5-dideoxy-2,5-imino-D-mannitol (16) which was identical (^{1}H NMR spectrum, mass spectrum and optical rotation) with an authentic sample.[11] An alternative synthesis of (16) from L-sorbose has been reported.[12]

The formation of a piperidine ring from the azidodiol (1) requires cyclisation from the C-2 nitrogen function onto C-6. Selective esterification of the diol with p-toluenesulphonyl chloride in pyridine at 0°C gave the p-toluenesulphonate ester (5) in 95% yield. Hydrogenation of the azide (5) in the presence of palladium black gave the corresponding amine which on treatment with sodium acetate in ethanol at 50°C cyclised to methyl 3-O-benzyl-2,6-dideoxy-2,6-imino-α-D-mannofuranoside (21). The bicyclic amine (21) could be isolated cleanly as the benzyl carbamate (22) by treatment of the crude reaction mixture with benzyl chloroformate in a two phase system of ethyl acetate and aqueous sodium bicarbonate [65% yield from (5); 62% from (1)]; alternatively, treatment of (21) with di-tert-butyldicarbonate in pyridine gave the corresponding BOC protected amine (23) [76% yield from (5); 73% from (1)]. The accompanying paper[1] describes the use of the carbamates (22) and (23) in the synthesis of polyhydroxylated piperidines.[13]

Experimental

M.p.s were recorded on a Kofler block. Infra red spectra were recorded on Perkin-Elmer 297, 310, 781 or Pye-Unicam SP3-200 spectrophotometers; unless otherwise stated, infra red spectra of solids were obtained in $CHCl_3$ solution and of syrups were obtained as thin films. ^{1}H NMR spectra were run at 300 MHz on a Bruker WH 300 spectrometer (500 MHz on a Bruker AM 500 spectrometer); ^{13}C NMR 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 ^{13}C NMR spectra in D_2O, 1,4-dioxan (δ 67.6) was used as the internal standard.

Mass spectra were recorded on VG Micromass 16F or 30F spectrometers, using the desorption chemical ionisation (DCI, NH_3) technique 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 services of the Dyson Perrins Laboratory. TLC was performed on glass plates coated with silica gel Blend 41 or on aluminum sheets pre-coated with Merck silica gel $60F_{254}$, and compounds were visualised with a spray of 5% v/v sulphuric acid in methanol or 5% dodecamolybdophosphoric acid in ethanol, or 5% w/v ninhydrin in ethanol. Flash chromatography was carried out using Merck Kieselgel 60, 230-400 mesh and dry column chromatography. 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. Organic solutions were dried with anhydrous sodium sulphate; organic solvents were removed under reduced pressure. Diacetone glucose (6) was obtained from the Aldrich Chemical Company and used without purification.

3-O-Benzyl-1,2-O-isopropylidene-α-D-glucofuranose-5,6-carbonate (9). Diacetone glucose (6) (52 g, 0.2 mol) in dry THF (480 ml) was added dropwise, with cooling and stirring, to a suspension of sodium hydride (50% dispersion in oil, washed with hexane, 10.6 g, 1.1 equivs) in THF (60 ml). Benzyl bromide (26 ml, 1.1 equivs) and tetrabutylammonium iodide (0.6 g) were added and the mixture refluxed for 45 min. The solution was cooled, filtered through celite and concentrated to a yellow syrup (79 g) which was used directly in the next step. The crude 3-O-benzyl-1,2;5,6-di-O-isopropylidene-α-D-glucofuranose (7) (79 g) was dissolved in a solution of concentrated hydrochloric acid (2.2 ml) and water (40 ml) in methanol (400 ml) and stirred at room temperature. After 20 h, t.l.c (ether : hexane, 2:1) showed no starting material (R_f 0.9) and one product (R_f 0.2). The solution was neutralised with ammonia solution (specific gravity 0.88) and concentrated to a syrup which was dissolved in ethyl acetate (400 ml) and washed with water (2 x 400 ml). Evaporation of the solvent gave a crude syrup of 3-O-benzyl-1,2-O-isopropylidene-α-D-glucofuranose (8) which was dissolved in dimethyl carbonate (400 ml) and refluxed for 3 h with sodium methoxide (10 g, 185 mmol). The reflux condenser was then replaced with a still head and the heating continued until the still head thermometer reached 90°C (this was approximately two hours). Periodically further dimethyl carbonate was added to keep the volume of the reaction mixture constant. At this stage, t.l.c. showed that the conversion to carbonate (9) was complete. The solution was cooled, washed with water (500 ml) and concentrated to a syrup which was crystallised spontaneously on addition of ether to afford 3-O-benzyl-1,2-O-isopropylidene-α-D-glucofuranose-5,6-carbonate (9), [54 g, 80% yield from (6)] as colourless crystals, m.p 119-120°C, $[\alpha]_D^{20}$ -52.2° (c, 1.15 in $CHCl_3$) [lit[3] m. p. 119-120.5°C, $[\alpha]_D^{20}$ -53.0° (c, 3.7 in $CHCl_3$)], ν_{max} 1810 cm^{-1}, ^1H NMR δ 7.5-7.3 (5H, m, ArH); 5.97 (1H, d, H-1, J_{12} 3.6 Hz); 4.88 (1H, ddd, H-5); 4.64 (1H, d, H-2); 4.57 (1H, dd, H-4); 4.58 (2H, ABq, $PhCH_2$); 4.47 (3H, m, H-3,6,6'); 1.50, 1.34 (6H, 2s, CH_3C). m/z: 354 ($M + NH_4^+$, 100%).

Methyl 3-O-Benzyl-α-D-glucofuranoside-5,6-carbonate (10) and Methyl 3-O-Benzyl-β-D-glucofuranoside-5,6-carbonate (12). 3-O-Benzyl-1,2-O-isopropylidene-α-D-glucofuranose-5,6-carbonate (9) (8.95 g, 26.6 mmol) was dissolved in methanol (150 ml) containing acid resin (Dowex 50W-XH, 16 g) and the suspension refluxed for 12 h. The solution was filtered and concentrated to a syrup. Purification by flash chromatography (eluant ether : hexane, 1:1) gave three fractions. The first contained pure methyl 3-O-benzyl-α-D-glucofuranoside-5,6-carbonate (10) (1.68 g), $[\alpha]_D^{20}$ +88.6° (c, 1.3 in MeOH) [lit[3] $[\alpha]_D^{20}$ +93.3° (c, 2.7 in MeOH)], ν_{max} 3500 (br), 1805, 1790 cm^{-1}. ^1H NMR δ 7.5-7.3 (5H, m, ArH); 5.06 (1H, d, H-1, J_{12} 4.5 Hz); 4.87

(1H, ddd, H-5); 4.61 (2H, ABq, $PhCH_2$); 4.58 (1H, dd, H-4); 4.43 (2H, m, H-6,6'); 4.20 (1H, dd, H-2); 4.07 (1H, dd, H-3); 3.50 (3H, s, CH_3O); 2.81 (1H, d, OH). m/z: 328 ($M + NH_4^+$, 100%).

The second fraction contained a mixture of the anomers (10) and (12) (2.18 g), and the third fraction contained pure methyl 3-O-benzyl-β-D-glucofuranoside-5,6-carbonate (12) (4.3 g), $[\alpha]_D^{20}$ -40.1° (c, 3.4 in MeOH) [lit[3] $[\alpha]_D^{20}$ -61° (c, 3.3 in MeOH)], ^1H NMR δ 7.5-7.3 (5H, m, ArH); 4.93 (1H, s, H-1); 4.82 (1H, ddd, H-5); 4.75 (1H, d, H-3); 4.69 (1H, d, H-4); 4.52 (2H, ABq, $PhCH_2$); 4.32 (2H, m, H-6,6'); 4.00 (1H, d, H-2); 3.41 (3H, s, CH_3O); 3.25 (1H, br s, OH). m/z : 328 ($M + NH_4^+$, 100%). The yield of the combined fractions of the anomers was 8.16 g (99%).

Methyl 2-Azido-3-O-benzyl-2-deoxy-α-D-mannofuranoside-5,6-carbonate (14). Trifluoromethanesulphonic anhydride (2.06 ml, 1.2 equivs) was added dropwise, with stirring, at -30°C to a solution of methyl 3-O-benzyl-α-D-glucofuranoside-5,6-carbonate (10) (3.16 g, 10.2 mmol) in dry dichloromethane (20 ml) containing pyridine (1.65 ml, 2 equivs). After 15 min, the solution was washed with water (2 x 20 ml) and saturated sodium bicarbonate solution (20 ml), and concentrated to a pale yellow syrup of methyl 3-O-benzyl-2-O-trifluoromethanesulphonyl-α-D-glucofuranoside-5,6-carbonate (11). A small quantity of (11) was purified by flash chromatography (ether : hexane, 2:1) to give a colourless syrup, $[\alpha]_D^{20}$ +70.5° (c, 0.24 in $CHCl_3$), ν_{max} 1805 cm^{-1}. ^1H NMR δ 7.4-7.2 (5H, m, ArH); 5.19 (1H, d, H-1, J_{12} 4.3 Hz); 5.02 (1H, t, H-2); 4.86 (1H, ddd, H-5); 4.56 (1H, dd, H-4); 4.57 (2H, ABq, $PhCH_2$); 4.46 (3H, m, H-3,6,6'); 3.46 (3H, s, CH_3O). m/z : 460 ($M + NH_4^+$, 100%).

The crude syrup (11) was dissolved in dry DMF (20 ml) and stirred at 50°C for 24 h with sodium azide (2.2 g, 3 equivs) when t.l.c (ether : hexane, 3:1) showed no triflate (R_f 0.5) and one product (R_f 0.4). The solvent was removed and the resulting syrup dissolved in chloroform (50 ml). The chloroform was washed with water (3 x 50 ml), dried and evaporated to give a pale yellow syrup which was purified by flash chromatography (ether : hexane, 2:1) to give methyl 2-azido-3-O-benzyl-2-deoxy-α-D-mannofuranoside-5,6-carbonate, (3.02 g, 88%), a colourless syrup, $[\alpha]_D^{20}$ +56.2° (c, 0.49 in $CHCl_3$), ν_{max} 2110, 1800 cm^{-1}, ^1H NMR δ 7.41-7.31 (5H, m, ArH); 4.97 (1H, d, H-1, J_{12} 1.5 Hz); 4.86 (1H, ddd, H-5); 4.75-4.37 (6H, m, $PhCH_2$,H-3,4,6,6'); 3.94 (1H, dd, H-2); 3.36 (3H, s, CH_3O). m/z (FD) : 336 ($M + H^+$); 307 ($M^+ - N_2$) (Found C, 53.5; H, 5.15; N, 12.2. $C_{15}H_{17}N_3O_6$ requires C, 53.7; H, 5.1; N, 12.5%).

Methyl 2-Azido-3-O-benzyl-2-deoxy-α-D-mannofuranoside (1). Methyl 2-azido-3-O-benzyl-2-deoxy-α-D-mannofuranoside-5,6-carbonate (14) (3 g, 9.0 mmol) was dissolved in methanol (15 ml) containing a trace of sodium methoxide and the solution left at room temperature for 6 h. The solvent was removed and the resulting crude syrup partitioned between chloroform (50 ml) and water (50 ml). The chloroform layer was dried and evaporated to a crude solid which was purified by flash chromatography (ether : hexane, 4:1) to afford methyl 2-azido-3-O-benzyl-2-deoxy-α-D-mannofuranoside, (2.23 g, 80%), colourless crystals, m.p 88-90°C (from ethyl acetate / hexane), $[\alpha]_D^{20}$ +69.6° (c, 0.79 in MeOH), ν_{max} 2100 cm^{-1}, ^1H NMR δ 7.43-7.35 (5H, m, ArH); 4.94 (1H, d, H-1, J_{12} 1.6 Hz); 4.70 (2H, ABq, $PhCH_2$); 4.55 (1H, t, H-3); 4.07 (2H, m, H-4,5); 3.84 (1H, dd, H-2); 3.76 (2H, m, H-6,6'); 3.36 (3H, s, CH_3O); 3.00 (1H, br d, OH); 2.17 (1H, br s, OH). m/z (FD) : 310 ($M + H^+$) (Found C, 53.9; H, 5.9; N, 13.1. $C_{14}H_{19}N_3O_5$ requires C, 54.4; H, 6.15; N, 13.6%).

Methyl 2-Azido-6-O-benzoyl-3-O-benzyl-2-deoxy-α-D-mannofuranoside (2). Benzoyl chloride (0.31 ml, 1.1 equivs) was added dropwise, with stirring, to a solution of methyl 2-azido-3-O-benzyl-2-deoxy-α-D-mannofuranoside (1) (0.76 g, 2.43 mmol) in

pyridine (7 ml) at 0°C. The solution was slowly allowed to warm to room temperature and stirred for 4 h. The mixture was then diluted with dichloromethane (50 ml) and washed successively with hydrochloric acid (2M aq, 2 x 25 ml), water (50 ml) and saturated sodium bicarbonate solution (50 ml). The solution was dried, the solvent evaporated and the residue purified by flash chromatography (ether : hexane, 1:1) to give methyl 2-azido-6-O-benzoyl-3-O-benzyl-2-deoxy-α-D-mannofuranoside, (0.82 g, 81%), a colourless syrup which crystallised, m.p 73-74°C, $[\alpha]_D^{20}$ +20.7° (c, 0.45 in $CHCl_3$); ν_{max} 2110, 1725, 1360, 1270, 1180 cm^{-1}, ^1H NMR δ 8.1-7.3 (10H, m, ArH); 4.98 (1H, s, H-1, J_{12} 1.8 Hz); 4.73 (2H, ABq, $PhCH_2$); 4.63 (1H, dd, H-6, $J_{66'}$ 11.6 Hz); 4.58 (1H, t, H-3); 4.44 (1H, dd, H-6'); 4.33 (1H, m, H-5); 4.16 (1H, dd, H-4); 3.85 (1H, dd, H-2); 3.35 (3H, s, CH_3O); 3.00 (1H, br s, OH). m/z (FD) : 414 ($M + H^+$) (Found C, 61.5; H, 5.8; N, 9.5. $C_{21}H_{23}N_3O_6$ requires C, 61.0; H, 5.6; N, 10.1%).

Methyl 2-Azido-6-O-benzoyl-3-O-benzyl-2-deoxy-5-O-methanesulphonyl-α-D-mannofuranoside (3). Methyl 2-azido-6-O-benzoyl-3-O-benzyl-2-deoxy-α-D-mannofuranoside (2) (0.815 g, 1.97 mmol) was dissolved in pyridine (5 ml) and stirred at room temperature with methanesulphonyl chloride (0.19 ml, 1.5 equivs). After 4 h, the solution was diluted with dichloromethane (50 ml) and washed with hydrochloric acid (2M aq, 50 ml), water (50 ml) and saturated sodium bicarbonate solution. The organic layer was dried and evaporated to a syrup which was purified by flash chromatography (ether : hexane, 1:1) to give methyl 2-azido-6-O-benzoyl-3-O-benzyl-2-deoxy-5-O-methanesulphonyl-α-D-mannofuranoside, (0.92 g, 94%), a clear syrup, $[\alpha]_D^{20}$ +43.2° (c, 0.75 in $CHCl_3$), ν_{max} 2110, 1720, 1360, 1270 cm^{-1}, ^1H NMR δ 8.1-7.3 (10H, m, ArH); 5.37 (1H, m, H-5); 5.00 (1H, d, H-1, J_{12} 2.4 Hz); 4.87 (1H, dd, H-6, $J_{66'}$ 12.7 Hz); 4.75 (2H, ABq, $PhCH_2$); 4.62 (1H, dd, H-6'); 4.47 (2H, m, H-3,4); 3.87 (1H, dd, H-2); 3.37 (3H, s, CH_3O); 2.98 (3H, s, CH_3S). m/z (FD) : 492 ($M + H^+$), 477 ($M + H^+$-Me) (Found C,53.3; H, 5.1; N, 8.5. $C_{22}H_{25}N_3O_8S$ requires C, 53.77; H, 5.09; N, 8.55%).

Methyl 5,6-Anhydro-2-azido-3-O-benzyl-2-deoxy-β-L-gulofuranoside (18). Methyl 2-azido-6-O-benzoyl-3-O-benzyl-2-deoxy-5-O-methanesulphonyl-α-D-mannofuranoside (3) (0.5 g, 1.01 mmol) was dissolved in dry DMF (7 ml) and heated at 50°C with sodium methoxide (0.11 g, 2 equiv). After 5 min t.l.c (ether : hexane, 1:1) showed complete loss of starting material (R_f 0.5) and one product (R_f 0.1), methyl 2-azido-3-O-benzyl-2-deoxy-5-O-methanesulphonyl-α-D-mannofuranoside (4), [^1H NMR δ 7.5-7.3 (5H, m, ArH); 5.02 (1H, m, H-5); 4.96 (1H, d, H-1, J_{12} 2.4 Hz); 4.70 (2H, ABq, $PhCH_2$); 4.42 (2H, m, H-3,4); 4.12 (1H, dd, H-6, $J_{66'}$ 12.8 Hz); 3.94 (1H, dd, H-6'); 3.86 (1H, dd, H-2); 3.37 (3H, s, CH_3O); 3.03 (3H, s, CH_3S); 2.17 (1H, br s, OH).]. When the reaction mixture was heated for a further 3 h, a second product (R_f 0.7) was formed with concurrent loss of (4). The solvent was removed and the residue partitioned between water (20 ml) and chloroform (20 ml). The organic layer was dried and evaporated to a syrup which was purified by flash chromatography (ether : hexane, 1:2) to give methyl 5,6-anhydro-2-azido-3-O-benzyl-2-deoxy-β-L-gulofuranoside, (0.25 g, 82%), a colourless syrup, $[\alpha]_D^{20}$ +19.5° (c, 0.58 in $CHCl_3$); ν_{max} 2110 cm^{-1}; ^1H NMR δ 7.5-7.3 (5H, m, ArH); 4.98 (1H, d, H-1, J_{12} 1.2 Hz); 4.65 (2H, ABq, $PhCH_2$); 4.47 (1H, dd, H-3); 3.88 (1H, dd, H-2); 3.69 (1H, t, H-4); 3.36 (3H, s, CH_3O); 3.33 (1H, m, H-5); 2.84 (1H, t, H-6); 2.51 (1H, dd, H-6'). m/z (FD) : 292 ($M + H^+$), 263 ($M + H^+-N_2$).

Methyl N-Benzyloxycarbonyl-3-O-benzyl-2,5-dideoxy-2,5-imino-α-D-mannofuranoside (19). Methyl 5,6-anhydro-2-azido-3-O-benzyl-2-deoxy-β-L-gulofuranoside (18) (0.25 g, 0.87 mmol) was dissolved in ethanol (10 ml) and hydrogenated at atmospheric pressure in the presence of palladium black (30 mg). After 1 h, all the azide had been

reduced and the catalyst was removed by filtration. The solvent was evaporated and the crude product dissolved in ether : saturated aqueous sodium bicarbonate solution (5:2, 15 ml) and stirred vigorously with benzyl chloroformate (0.25 ml, 2 equiv) at room temperature for 2 h. The two layers were separated and the aqueous phase washed with ether (2 x 10 ml). The organic extracts were combined, dried and evaporated to a syrup which was purified by flash chromatography (ether : hexane, 1:1) affording two products. The first product to be eluted was methyl 2-benzyloxycarbonylamino-3-O-benzyl-2,6-dideoxy-β-L-gulofuranoside (20), (84 mg, 24%), a syrup, ^{1}H NMR δ 7.4-7.3 (10H, m, ArH); 6.0 (1H, br d, NH); 5.1 (2H, ABq, $PhCH_2$); 4.9 (1H, s, H-1); 4.5 (2H, ABq, $PhCH_2$); 4.6 (1H, m, H-3); 4.4 (1H, m, H-4); 4.1 (1H, br m, H-5); 3.95 (1H, dd, H-2); 3.3 (3H, s, CH_3O); 2.6 (1H, br s, OH); 1.2 (3H, d, CH_3). m/z :419 ($M + NH_4^+$), 402 ($M + H^+$), 370 ($M + H^+$-OMe). The second product eluted was methyl N-benzyloxycarbonyl-3-O-benzyl-2,5-dideoxy-2,5-imino-α-D-mannofuranoside (19), (0.15 g, 43%), a syrup, $[\alpha]_D^{20}$ +10.6° (c, 0.52 in $CHCl_3$); ν_{max} 3450 (br), 1680 cm^{-1}, ^{1}H NMR δ 7.5-7.3 (10H, m, ArH); 5.1 (2H, s, $PhCH_2$); 4.8-4.2 (6H, m); 4.1 (1H, dd, H-3); 3.9 (2H, m, H-6,6'); 3.3 (3H, s, CH_3O); 1.8 (1H, br s, OH). m/z : 400 ($M + H^+$, 100%), 356, 306. (Found C, 66.1; H, 6.6; N, 4.0. $C_{22}H_{25}NO_6$ requires C, 66.2; H, 6.3; N, 3.5).

N-Benzyloxycarbonyl-3-O-benzyl-2,5-dideoxy-2,5-imino-D-mannitol (17). Methyl N-benzyloxycarbonyl-3-O-benzyl-2,5-dideoxy-2,5-imino-α-D-mannofuranoside (19) (24 mg, 0.06 mmol) was dissolved in 50% aqueous trifluoroacetic acid (1 ml) and stirred at room temperature for 15 min. The solvent was evaporated and the resulting syrup dissolved in ethanol (2 ml). Sodium borohydride (10 mg, excess) in water (1 ml) was added, and the solution stirred at room temperature for 10 min. The reaction was quenched by the addition of an excess of ammonium chloride, the solvent was removed and the residue partitioned between chloroform (10 ml) and water (10 ml). The chloroform layer was dried and evaporated to a syrup, which was purified by flash chromatography (ethyl acetate : hexane, 2:1), to give methyl N-benzyloxycarbonyl-3-O-benzyl-2,5-dideoxy-2,5-imino-D-mannitol, (17 mg, 73%), a syrup, ν_{max} 3500-3300, 1680 cm^{-1}. ^{1}H NMR δ 7.35-7.3 (10H, m, ArH); 4.65 (2H, ABq, $PhCH_2$); 5.1-4.0 (10H, m); 3.9-3.7 (2H, m, H-2,5); 2.1 (1H, br s, OH).

2,5-Dideoxy-2,5-imino-D-mannitol (16). Methyl N-benzyloxycarbonyl-3-O-benzyl-2,5-dideoxy-2,5-imino-D-mannitol (17) (30 mg, 0.076 mmol) was dissolved in glacial acetic acid (5 ml) and stirred under hydrogen with palladium black (5 mg). After 13 h, the catalyst was removed by filtration and the solvent evaporated to give the acetate salt of 2,5-dideoxy-2,5-imino-D-mannitol, [^{1}H NMR (D_2O) δ 3.9 (2H, dt, H-3,4); 3.8, 3.7 (4H, 2dd, H-1,1',6,6'); 3.4 (2H, m, H-2,5); 1.9 (3H, s, CH_3COO).]. Purification by ion exchange chromatography (CG 120, H^+ form, then elute with aqueous ammonia) gave 2,5-dideoxy-2,5-imino-D-mannitol (16), (9 mg, 70%) as a hygroscopic gum, $[\alpha]_D^{20}$ +53.8° (c, 0.32 in H_2O) [lit[6] +56.4° (c, 7 in H_2O). ^{1}H NMR (D_2O) δ 3.9 (2H, dt, H-3,4); 3.6, 3.5 (4H, 2dd, H-1,1',6,6'); 3.0 (2H, m, H-2,5). m/z : 164 ($M + H^+$, 100%), 132. This synthetic material was identical to an authentic sample.[11]

Methyl 2-Azido-3-O-benzyl-2-deoxy-6-O-p-toluenesulphonyl-α-D-mannofuranoside (5). Methyl 2-azido-3-O-benzyl-2-deoxy-α-D-mannofuranoside (1) (4.2 g, 13.6 mmol) was dissolved in dry pyridine (50 ml) and stirred at 0°C with freshly recrystallised p-toluenesulphonyl chloride (2.84 g, 1.1 equivs) for 12 h. The solution was concentrated, diluted with dichloromethane (100 ml) and washed successively with hydrochloric acid (2M aq, 100 ml), water (100 ml) and saturated sodium bicarbonate solution (100 ml). The dichloromethane was then dried and evaporated to give a

colourless syrup which was purified by flash chromatography (ether : hexane, 1:1) to give methyl 2-azido-3-O-benzyl-2-deoxy-6-O-p-toluenesulphonyl-α-D-mannofuranoside, (5.95 g, 95%), a colourless syrup, $[\alpha]_D^{20}$ +21.6° (c, 0.76 in $CHCl_3$), ν_{max} 3550 (br), 2110, 1360 cm^{-1}. ^1H NMR δ 7.8-7.3 (9H, m, ArH); 4.90 (1H, d, H-1, J_{12} 1.8 Hz); 4.67 (2H, ABq, $PhCH_2$); 4.51 (1H, t, H-3); 4.27 (1H, m, H-5); 4.16 (2H, m, H-6,6'); 4.06 (1H, dd, H-4); 3.80 (1H, dd, H-2); 3.32 (3H, s, CH_3O); 2.88 (1H, br d, OH); 2.44 (3H, s, CH_3Ar). m/z (FD) : 464 ($M + H^+$).

Methyl N-Benzyloxycarbonyl-3-O-benzyl-2,6-dideoxy-2,6-imino-α-D-mannofuranoside (22). Methyl 2-azido-3-O-benzyl-2-deoxy-6-O-p-toluenesulphonyl-α-D-mannofuranoside (5) (3.5 g, 7.6 mmol) was dissolved in ethanol (25 ml) and stirred under hydrogen with palladium black (0.2 g) at atmospheric pressure and room temperature. After 12 h, the solution was filtered and sodium acetate (0.1 g) added. The mixture was then heated at 50°C under nitrogen for a further 12 h to accomplish the cyclisation. Evaporation of the solvent and extraction of the residue into chloroform gave the crude amine (21) which was not purified. [^1H NMR δ 7.8-7.3 (5H, m, ArH); 4.99 (1H, s, H-1); 4.60 (2H, s, $PhCH_2$); 4.35-4.22 (4H, m, H-3,5,NH,OH); 3.91 (1H, dd, H-4); 3.41 (3H, s, CH_3O); 3.18 (2H, m, H-2,6); 2.58 (1H, dd, H-6').]. The crude amine (21) was dissolved in ether : saturated aqueous sodium bicarbonate solution (5 : 2, 35 ml) and treated with benzyl chloroformate (1.6 ml, 1.5 equivs) and vigorously stirred at room temperature for 2 h to ensure mixing of the two phases. The layers were then separated and the aqueous layer washed with ether (2 x 20 ml). The organic extracts were combined, dried and evaporated to a syrup. Purification by flash chromatography (ethyl acetate : hexane, 1:3) afforded methyl N-benzyloxycarbonyl-3-O-benzyl-2,6-dideoxy-2,6-imino-α-D-mannofuranoside, (1.95 g, 65%), a colourless syrup, $[\alpha]_D^{20}$ +22.6° (c, 0.46in $CHCl_3$). ν_{max} 3450 (br), 1685 cm^{-1}. ^1H NMR δ 7.4-7.2 (10H, m, ArH); 5.11 (2H, d,$PhCH_2$); 4.98 (1H, s, H-1); 4.77-4.08 (7H, m); 3.41 (3H, d, CH_3O); 2.85 (1H, m, H-6); 2.00 (1H, br s, OH). m/z : 400 ($M + H^+$), 356, 204, 91 (100%) (Found C, 65.9; H, 6.6; N, 3.6. $C_{22}H_{25}NO_6$ requires C, 66.2; H, 6.3; N, 3.5%).

Methyl N-t-Butyloxycarbonyl-3-O-benzyl-2,6-dideoxy-2,6-imino-α-D-mannofuranoside (23). Methyl 2-azido-3-O-benzyl-2-deoxy-6-O-p-toluenesulphonyl-α-D-mannofuranoside (5) (3 g, 6.5 mmol) was reduced and cyclised to the amine (21) exactly as described above. The crude amine (21) was dissolved in pyridine (15 ml) and treated with di-tert-butyl dicarbonate (1.6 g, 1.1 equivs) at room temperature. After 30 min, the pyridine was removed and the resulting syrup was purified by flash chromatography (ethyl acetate : hexane, 1:2) to yield methyl N-t-butyloxycarbonyl-3-O-benzyl-2,6-dideoxy-2,6-imino-α-D-mannofuranoside, (1.81 g, 76%), a colourless syrup which crystallised, m.p 103°C, $[\alpha]_D^{20}$ +17.7° (c, 0.38 in $CHCl_3$). ν_{max} 3430 (br), 1685, 1420, 1365 cm^{-1}. ^1H NMR δ 7.5-7.3 (5H, m, ArH); 5.0 (1H, d, H-1); 4.8-4.0 (7H, m); 3.4 (3H, s, CH_3O); 2.9 (1H, m, H-6); 2.0 (1H, br s, OH); 1.4, 1.35 (9H, d, tBu). m/z: 383 ($M + NH_4^+$), 366 ($M + H^+$), 327 ($M + NH_4^+$-butene, 100%). (Found C, 62.7; H, 7.7; N, 3.6. $C_{19}H_{27}NO_6$ requires C, 62.5; H, 7.4; N, 3.8%).

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