Tetrahedron Vol. 49, No. 42, pp. 9605-9612, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

2-Acetamido-1,2-Dideoxynojirimycin: An Improved Synthesis

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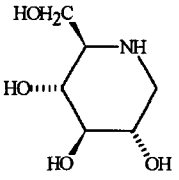
(*Received in UK* 6 *July* 1993; *accepted* 6 *August* 1993)

Abstract: The potent β-*N*-acetylglucosaminidase inhibitor, 2-acetamido-1,2-dideoxynojirimycin, was prepared in 6 steps from *N*-acetyl-D-glucosamine (overall yield 10%) *via* the double reductive amination of a keto aldehyde as the key step.

Exoglycosidases, those enzymes responsible for the removal of terminal sugar residues, are critical for the modification of glycolipids and glycoproteins in many biological processes. The aza sugars, where the ring oxygen has been replaced by nitrogen, constitute an expanding class of exoglycosidase inhibitors that has become important in the investigation and treatment of several diseases.[1-3] The structural resemblance between aza sugar and parent monosaccharide is important for inhibition of the corresponding glycosidase. Thus, for example, deoxynojirimycin **1** and deoxyfuconojirimycin **2**, the aza sugar analogues of glucose **3** and fucose **4**, are potent glucosidase and fucosidase inhibitors, respectively.[2]



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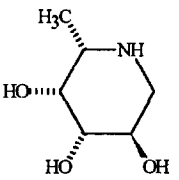

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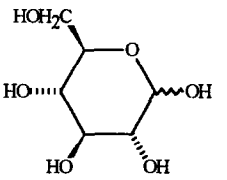

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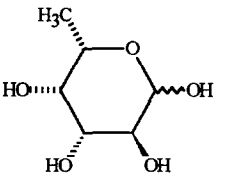

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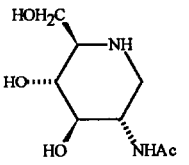
A large number of glycoconjugates contain *N*-acetyl-D-glucosamine or *N*-acetyl-D-galactosamine residues hence inhibitors of hexosaminidases are potentially desirable compounds. For example, β-*N*-acetylglucosaminidase inhibitors have been linked to the treatment of cancer.[4]

2-Acetamido-1,2-dideoxynojirimycin **5** [2-acetamido-1,2,5-trideoxy-1,5-imino-D-glucitol], the aza sugar analogue of *N*-acetyl-D-glucosamine **6**, was prepared initially by Fleet and coworkers[5,6] from D-glucose (17 steps) and subsequently by others from deoxynojirimycin (8-10 steps)[7,8] and *N*-acetyl-D-glucosamine (10 steps).[9]



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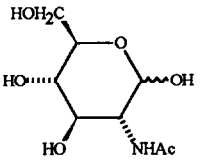

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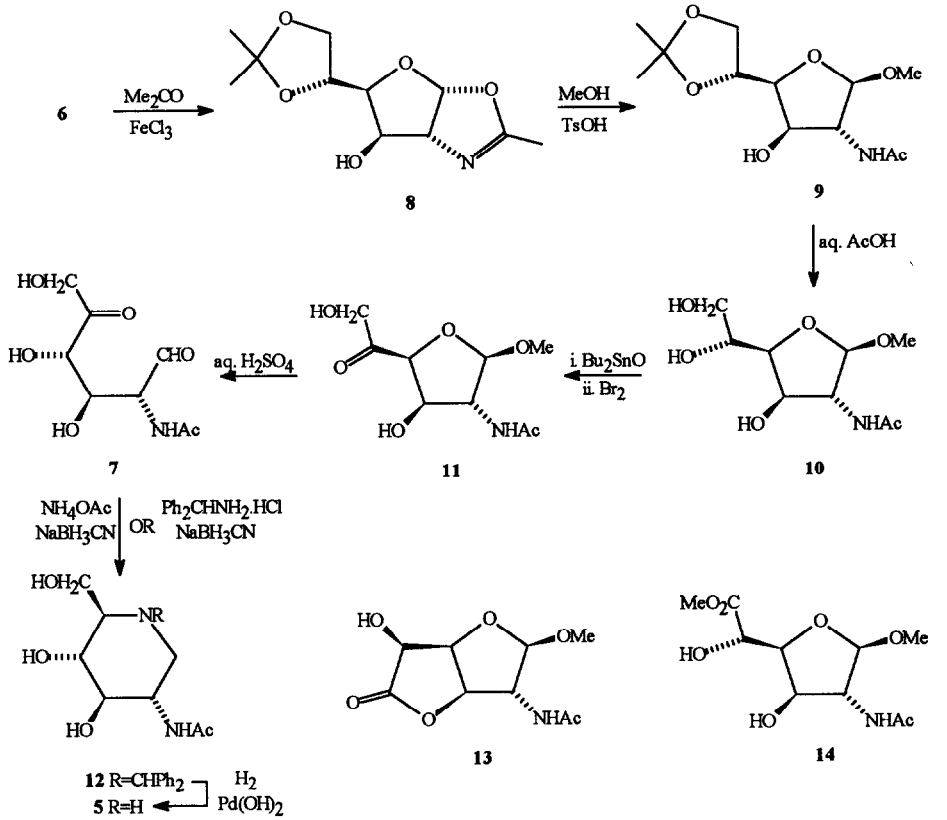
Wong and coworkers[10] have employed an aldolase in a chemoenzymatic approach for the construction of **5**. Thi analogue of deoxynojirimycin was found to be a potent inhibitor of a number of *N*-acetylglucosaminidases.[5,9,1



This report describes a new synthesis of 2-acetamido-1,2-dideoxynojirimycin **5** in just 6 steps from th readily available *N*-acetyl-D-glucosamine **6**. We envisaged that **5** could be prepared *via* a double reductiv amination of keto aldehyde **7** in a manner analogous to that reported by Baxter and Reitz[11] for the synthesis (deoxymannojirimycin.

By the method of Brossmer and coworkers,[12] *N*-acetyl-D-glucosamine **6** was treated with iron(III) chloric in acetone to give oxazoline **8** (71% yield) in > 95% purity by ^{1}H NMR which was used without furth purification in the next step. Acidic methanolysis of the oxazoline ring in **8** provided the methyl furanoside **9** (83%) which was followed by aqueous acetic acid hydrolysis of the acetonide to give triol **10**[13] (89%

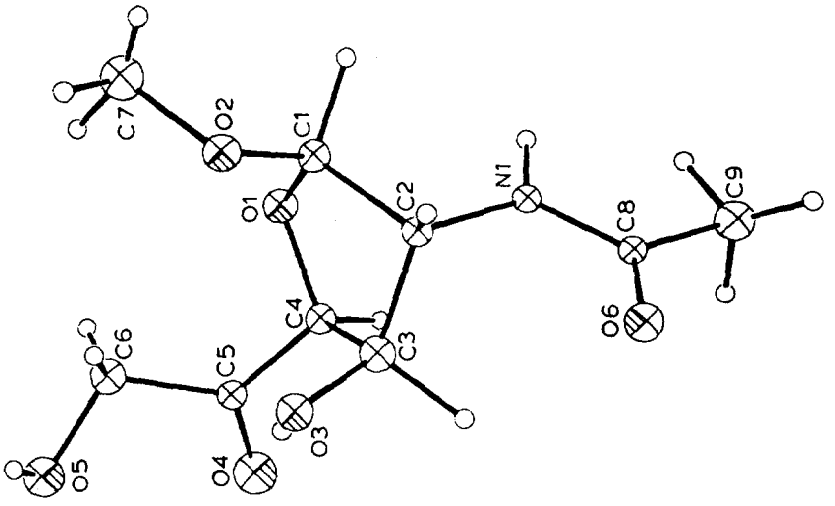


Figure 1: Thermal ellipsoid plot of ketone 11 drawn with experimental coordinates (ellipsoids drawn at the 50% probability level).

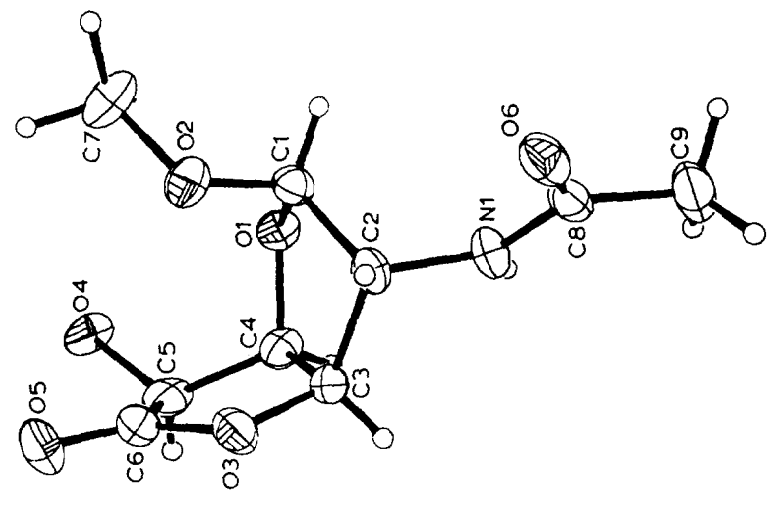


Figure 2: Thermal ellipsoid plot of lactone 13 drawn with experimental coordinates (ellipsoids drawn at the 30% probability level).

Regioselective oxidation at C5 *via* reaction with dibutyltin oxide followed by addition of tributyltin methoxide and bromine[11,14] at room temperature furnished the ketone **11** (52%) along with unreacted starting material **10** (18%). When bromine addition to the stannylene intermediate was carried out at lower temperatures oxidation at the primary site (C6) became competitive resulting in the formation of two side products which were assigned as the lactone **13** (δ_C 180.0 s) and the methyl ester **14**, the latter identified as having two non-ketonic carbonyls (δ_C 176.8 s, 177.1 s) and two methoxy groups (δ_H 3.27, 3.69; δ_C 55.6 q, 58.3 q). The reaction at 0°C gave the desired ketone **11** (50%), lactone **13** (8%), methyl ester **14** (3%) and starting material **10** (3%). At -15°C the lactone **13** became the major product (29%) followed by ketone **11** (9%) and methyl ester **14** (2%) along with recovered starting material (19%). Traces of methanol from the stannylation or from tributyltin methoxide present during the bromine oxidation account for methyl ester formation. The structures of both ketone **11** and lactone **13** were confirmed by X-ray crystallography (Figures 1 and 2). Hydrolysis of the ketone **11** in dilute sulfuric acid at 60°C provided the keto aldehyde **7** as a mixture of open chain and cyclic forms which was committed directly to reductive amination. Treatment with benzhydrylamine hydrochloride and sodium cyanoborohydride at 0°C followed by refrigeration (0-4°C) for two weeks provided the *N*-substituted aza sugar **12** (40%) after reversed phase flash chromatography. Hydrogenolysis of the benzhydryl group in acidic methanol with palladium hydroxide catalyst followed by ion exchange chromatography gave the title aza sugar **5** (49%).

An improvement to the lengthy reductive amination was achieved by replacing benzhydrylamine with ammonium acetate in the reaction thereby halving the reaction time and also eliminating the final hydrogenation step. The target aza sugar **5** was thereby obtained directly from crude keto aldehyde **7** in 37% yield. Both reductive aminations proceeded with high stereoselectivity at C5 as no product with an L-ido configuration was observed.

To summarise, we have prepared the potent β-*N*-acetylglucosaminidase inhibitor 2-acetamido-1,2-dideoxynojirimycin **5** in 6 steps from *N*-acetyl-D-glucosamine with an overall yield of 10%.

CRYSTALLOGRAPHY

Methyl 2-acetamido-2-deoxy-β-D-xylo-hexofuranosid-5-ulose 11. $C_9H_{15}NO_6$, orthorhombic, space group $P2_12_12_1$ (18),[16] a = 7.907(2), b = 14.422(3), c = 9.565(2) Å, V = 1090.7(4) Å^3. Z = 4, Dc = 1.42 gcm^{-3}, T = 193 K, MoKα radiation (λ = 0.71069 Å), μ = 1.29 cm^{-1}. Nicolet R3m diffractometer, 1386 independent reflections measured (3° < 2θ < 54°), of which 587 had $I_{net} > 2.5\sigma(I_{net})$. No absorption correction. Solved by direct methods[17] and refined to R, R_w of 0.091, 0.041.[18] All but three hydrogen atoms located; all atoms refined with isotropic thermal parameters. Final maximum shift/error 0.03 and Δρ excursions -0.55 to 0.58 e/Å^3.

Methyl 2-acetamido-2-deoxy-β-D-glucofuranosidurono-6,3-lactone 13. $C_9H_{13}NO_6.H_2O$, monoclinic, space group C2 (5),[15] a = 16.846(3), b = 9.0101(12), c = 7.6408(10) Å, β = 94.84(1), V = 1155.6(3) Å^3, Z = 4, Dc = 1.43 gcm^{-3}, T = 293 K, MoKα radiation (λ = 0.71069 Å), μ = 1.34 cm^{-1}. Nonius CAD-4 diffractometer, 1063 unique reflections collected (2° < 2θ < 50°) of which 1017 had $I_{net} > 2.5\sigma(I_{net})$. No absorption correction. Solved by direct methods[17] and refined to final R, R_w of 0.052, 0.069.[18] Hydrogen atoms located, but not all stable to refinement; non-hydrogen atoms refined with anisotropic thermal parameters. Secondary extinction coefficient 6.7(6). Final maximum shift/error was 0.06 and Δρ excursions -0.19 to 0.30 e/Å^3.

The independent molecules (Figures 1 and 2) are hydrogen bonded in both crystals utilising the amino proton

either to the carbonyl oxygen O5 (in **11**, N1-H···O5 1.96 Å) or oxygen of the included water molecule (in **13**, N1-H···OW, 1.90 Å). In the latter structure a further hydrogen bond exists between a water proton and oxygen O5. An envelope conformation with flap atom C3 is adopted in **11**. The lactone ring in **13** can be described as a flattened envelope with C4 as the flap atom; the constrained geometry of this ring does not prevent the furanoside ring from retaining an envelope conformation with C1 as the flap atom. The major difference between the conformations of the two structures involves a different twist in the acetamide with the dihedral angle C8-N1-C2-C3 -74.6 and -144.0, in **11** and **13**, respectively. There are no abnormal bonding distances or angles.[19,20]

EXPERIMENTAL

Melting points were recorded on a Reichert hot stage microscope and are uncorrected. Optical rotations were measured using a Perkin-Elmer 241 polarimeter. NMR spectra were recorded on a Bruker AC300 operating at 300 MHz for ^{1}H NMR (δ_H) and 75 MHz for ^{13}C NMR (δ_C). Assignments were made with the assistance of DEPT and COSY experiments. Mass spectra were recorded on a VG70-250S double-focusing mass spectrometer under positive EI or NH_3 CI conditions. Elemental analyses were performed by the Campbell Microanalytical Laboratory, University of Otago, Dunedin. Thin layer chromatography was carried out on silica gel coated aluminium sheets. Flash chromatography was performed on Sorbsil C60-H (40-60) unless otherwise stated. Solvents were dried and purified before use according to standard procedures.

2-Methyl-(1,2-dideoxy-5,6-O-isopropylidene-α-D-glucofurano)-[2,1-d]-2-oxazoline ***8***

This preparation follows the method of Brossmer and coworkers.[12] Anhydrous iron(III) chloride (22.5 g, 0.14 mol) was added to a suspension of 2-acetamido-2-deoxy-D-glucopyranose (**6**) (15.0 g, 0.068 mol) in dry acetone (300 ml) and the mixture was stirred and heated under reflux for 20 min with exclusion of moisture. The solution was cooled to 0°C and diethylamine (38.5 g) and acetone (200 ml) were added with stirring followed by the dropwise addition of a solution of sodium carbonate (32 g) in water (200 ml). Acetone, diethylamine and some water were removed *in vacuo* at < 30°C. The mixture was then extracted with ether (10 x 100 ml) and the combined extracts were dried (magnesium sulfate) and concentrated at room temperature to give the oxazoline **8** as a brownish syrup (11.7 g, 71%). δ_H ($CDCl_3$)[12] 1.35, 1.42 (2 x 3H, s, CMe_2), 2.03 (3H, d, $J_{2,Me}$ 1.5 Hz, N=CMe), 2.63 (1H, s, OH), 3.74 (1H, dd, $J_{4,5}$ 7.7 Hz, $J_{4,3}$ 2.6 Hz, H4), 4.01 (1H, dd, $J_{6,6}$ 8.6 Hz, $J_{6,5}$ 5.0 Hz, H6), 4.13 (1H, dd, $J_{6,6}$ 8.7 Hz, $J_{6,5}$ 6.0 Hz, H6), 4.32 (1H, m, H5), 4.36 (1H, d, $J_{3,4}$ 2.9 Hz, H3), 4.43 (1H, qd, $J_{2,1}$ 5.0 Hz, $J_{2,Me}$ 1.3 Hz, H2), 6.16 (1H, d, $J_{1,2}$ 5.0 Hz, H1). δ_C ($CDCl_3$) 14.1 (N=C*Me*), 25.2 and 26.8 (C*Me*$_2$), 67.3 (C6), 72.8 (C2), 74.3 (C5), 78.3 (C3), 81.9 (C4), 107.2 (C1), 109.3 (*C*Me$_2$), 167.2 (N=C). The crude product was > 95% pure and was used without further purification in the next step.

Methyl 2-acetamido-2-deoxy-5,6-O-isopropylidene-β-D-glucofuranoside ***9***

The oxazoline **8** (11.64 g, 47.8 mmol), was dissolved in dry methanol (520 ml) and sufficient *p*-toluenesulfonic acid was added to adjust the stirred solution to pH 3-4. The reaction was monitored by t.l.c. and after 3 h the reaction was quenched by the addition of sufficient triethylamine to adjust the pH to > 7. The methanol was removed *in vacuo* and, although the crude product could be used directly in the next step, flash chromatography

(2% methanol/chloroform) gave the methyl furanoside **9** (10.93 g, 83%) as an oil, $[\alpha]_D$ -37° (c 1.2, MeOH), lit.[13] $[\alpha]_D$ -39.5° (c 1, MeOH). δ_H ($CDCl_3$) 1.36, 1.43 (2 x 3H, s, CMe_2), 2.01 (3H, s, Ac), 3.37 (3H, s, OMe), 3.45 (1H, br s, OH), 4.02 (1H, dd, $J_{6,6}$ 8.4 Hz, $J_{6,5}$ 5.6 Hz, H6), 4.13 (1H, dd, $J_{6,6}$ 8.5 Hz, $J_{6,5}$ 6.3 Hz, H6), 4.17-4.21 (2H, m, H3,4), 4.26 (1H, d, J 6.8 Hz, H2), 4.38 (1H, q, J 6.1 Hz, H5), 4.86 (1H, s, H1), 6.96 (1H, d, J 6.7 Hz, NH). δ_C ($CDCl_3$) 22.8 (NCO*Me*), 25.1 and 26.6 (CMe_2), 55.4 (OMe), 62.2 (C2), 66.8 (C6), 74.0 (C5), 74.9 (C3), 83.2 (C4), 107.7 (C1), 109.1 (CMe_2), 170.7 (C=O). *m/z* calculated for $C_{12}H_{22}NO_6$ (MH^+) 276.1447, found 276.1462.

Methyl 2-acetamido-2-deoxy-β-D-glucofuranoside ***10***

The furanoside **9** (9.33 g, 33.9 mmol) was dissolved in aqueous acetic acid (60% v/v, 220 ml) and stirred at room temperature. The hydrolysis was monitored by t.l.c. and the reaction stopped when the pyranoside byproduct began to appear (5 h). The solvent was removed *in vacuo* at < 25°C. Flash chromatography (10-15% methanol/chloroform) afforded unreacted starting material **9** (0.80 g) followed by the triol **10** (7.05 g, 89%) as an oil, $[\alpha]_D$ -60° (c 1, MeOH), lit.[13] $[\alpha]_D$ -56° (c 1, MeOH). δ_H (D_2O) 2.16 (3H, s, Ac), 3.53 (3H, s, OMe), 3.86 (1H, dd, $J_{6,6}$ 12.0 Hz, $J_{6,5}$ 5.8 Hz, H6), 4.02 (1H, dd, $J_{6,6}$ 11.9 Hz, $J_{6,5}$ 2.8 Hz, H6), 4.17 (1H, m, H5), 4.29 (1H, t, J 4.6 Hz, H4), 4.32 (1H, s, H2), 4.46 (1H, d, $J_{3,4}$ 4.7 Hz, H3), 5.06 (1H, s, H1). δ_C (D_2O) 24.4 (NCO*Me*), 57.9 (OMe), 61.9 (C2), 66.1 (C6), 72.3 (C5), 76.4 (C3), 83.6 (C4), 110.3 (C1), 176.7 (C=O). *m/z* calculated for $C_9H_{18}NO_6$ (MH+) 236.1134, found 236.1138.

Methyl 2-acetamido-2-deoxy-β-D-xylo-hexofuranosid-5-ulose ***11***

Dibutyltin oxide (10.49 g, 42.1 mmol) was added to a solution of the triol **10** (3.96 g, 16.9 mmol) in dry methanol (200 ml) and the mixture heated under reflux for 3 h. The solvent was removed *in vacuo* and the residue suspended in dry dichloromethane (250 ml) with tributyltin methoxide (7.03 g, 21.9 mmol). Bromine (3.24 g, 20.3 mmol) in dichloromethane (30 ml) was added dropwise to the vigorously stirred suspension. The suspension gradually dissolved and during the later stages of bromine addition the product began to crystallise from solution. Upon complete addition of bromine, cyclohexene (1 ml) then petroleum ether (500 ml) were added. After standing for 10 h the liquor was decanted from an oily residue. The residue was purified by flash chromatography (10% methanol/chloroform) to afford unreacted starting material (0.70 g) and a white solid which was recrystallised from ethanol to give *methyl 2-acetamido-2-deoxy-β-D-xylo-hexofuranosid-5-ulose* **11** (2.06 g, 52%), mp. 180-185° (dec.), $[\alpha]_D$ -137° (c 1, H_2O). (Found: C, 46.63; H, 6.48; N, 5.95%. $C_9H_{15}NO_6$ requires C, 46.35; H, 6.48; N, 6.01%). δ_H (D_2O) 2.14 (3H, s, Ac), 3.64 (3H, s, OMe), 4.32 (1H, s, H2), 4.65 (2H, AB, J 19.2 Hz, H6), 4.71 (1H, d, $J_{3,4}$ 5.4 Hz, H3), 5.14 (1H, d, $J_{4,3}$ 5.3 Hz, H4), 5.22 (1H, s, H1). δ_C (D_2O) 24.2 (NCO*Me*), 58.4 (OMe), 64.6 (C2), 69.3 (C6), 77.5 (C3), 88.9 (C4), 111.2 (C1), 176.7 (N*C*OMe), 212.5 (C=O). *m/z* calculated for $C_9H_{16}NO_6$ (MH^+) 234.0978, found 234.0970.

Methyl 2-acetamido-2-deoxy-β-D-glucofuranosidurono-6,3-lactone ***13*** *and methyl (methyl 2-acetamido-2-deoxy-β-D-glucofuranosid)uronate* ***14***

When the above reaction was carried out at 0°C, the crude product was isolated and purified by flash chromatography to give starting material **10** (3%), the ketone **11** (50%) along with:

i. *methyl 2-acetamido-2-deoxy-β-D-glucofuranosidurono-6,3-lactone* **13** (8%) which was recrystallised from ethanol, mp. 111°C. (Found: C, 43.38; H, 5.88; N, 5.53%. $C_9H_{13}NO_6.H_2O$ requires C, 43.37; H, 6.07; N, 5.62%). δ_H (D_2O) 2.22 (3H, s, Ac), 3.57 (3H, s, OMe), 4.62 (1H, s, H2), 4.94 (1H, d, $J_{3,4}$ 6.4 Hz, H3), 5.26 (1H, dd, $J_{4,3}$ 6.4 Hz, $J_{4,5}$ 4.7 Hz, H4), 5.30 (1H, d, $J_{5,4}$ 4.5 Hz, H5), 5.33 (1H, s, H1). δ_C (D_2O) 24.4 (NCO*Me*), 58.2 (OMe), 61.9 (C2), 71.7 (C3), 80.6 (C4), 85.3 (C5), 110.8 (C1), 176.9 (NCOMe), 180.0 (C6). *m/z* calculated for $C_9H_{14}NO_6$ (MH^+) 232.0821, found 232.0819.

ii. *methyl (methyl 2-acetamido-2-deoxy-β-D-glucofuranosid)uronate* **14** (3%). δ_H (D_2O) 1.88 (3H, s, Ac), 3.27 (3H, s, CO_2Me), 3.69 (3H, s, OMe), 4.09 (1H, s, H2), 4.26 (1H, m, H4), 4.30 (1H, d, $J_{3,4}$ 5.4 Hz, H3), 4.41 (1H, d, $J_{5,4}$ 7.4 Hz, H5), 4.79 (1H, s, H1). δ_C (D_2O) 24.6 (NCO*Me*), 55.6 (OMe), 58.3 (CO_2Me), 64.5 (C2), 72.3 (C5), 76.4 (C3), 84.2 (C4), 112.8 (C1), 176.8 (C=O), 177.1 (C=O). *m/z* 264 (MH^+).

The same reaction carried out at -15°C yielded ketone **11** (9%), lactone **13** (29%), methyl ester **14** (2%) and starting material (19%).

2-Acetamido-1,5-(N-benzhydrylimino)-1,2,5-trideoxy-D-glucitol ***12***

The ketone **11** (1.66 g, 7.1 mmol) was dissolved in dilute sulfuric acid (0.26 ml conc. H_2SO_4 in 50 ml H_2O) and warmed at 60°C for 3.25 h. Sufficient barium carbonate was added to neutralise the acid. The suspension was filtered and the filtrate lyophilised. The crude residue **7** (1.69 g), containing unreacted ketone (15%) and an unknown impurity (5%), was commited directly to reductive amination. Thus, the residue was dissolved in dry methanol (40 ml) and cooled to 0°C. Benzhydrylamine hydrochloride (1.28 g, 5.8 mmol) was added followed by a solution of sodium cyanoborohydride (1.38 g, 22.0 mmol) in cold methanol (5 ml). The mixture was refrigerated for 2 weeks with occasional swirling of the flask during which time a precipitate began forming. The methanol was removed *in vacuo* and the residue was dissolved in water, basified with dilute aqueous sodium hydroxide and extracted with 10% 2-propanol/chloroform (6 x 20 ml). The extracts were combined and the solvent evaporated. Reversed phase flash chromatography (RPC-18 silica, 50% methanol/water) afforded *2-acetamido-1,5-(N-benzhydrylimino)-1,2,5-trideoxy-D-glucitol* **12** (1.05 g, 40%) which slowly crystallised from chloroform, mp. 99-113°, $[\alpha]_D$ +54° (c 1, MeOH). δ_H (CD_3OD) 1.81 (1H, dd, $J_{1,1}$ 11.3 Hz, $J_{1,2}$ 10.1 Hz, H1), 1.90 (3H, s, Ac), 2.39 (1H, dt, $J_{5,4}$ 8.4 Hz, $J_{5,6}$ 3.0 Hz, H5), 2.96 (1H, dd, $J_{1,1}$ 11.5 Hz, $J_{1,2}$ 4.1 Hz, H1), 3.13 (1H, dd, $J_{3,2}$ 9.3 Hz, $J_{3,4}$ 8.4 Hz, H3), 3.54 (1H, t, $J_{4,3}$ $J_{4,5}$ 8.3 Hz, H4), 3.87 (1H, td, $J_{2,1}$ $J_{2,3}$ 9.6 Hz, $J_{2,1}$ 4.1 Hz, H2), 3.94 (1H, dd, $J_{6,6}$ 12.1 Hz, $J_{6,5}$ 3.2 Hz, H6), 4.21 (1H, dd, $J_{6,6}$ 12.0 Hz, $J_{6,5}$ 2.9 Hz, H6), 5.64 (1H, s, C*H*Ph2), 7.17-7.38 (10H, m, Ar). δ_C ($CDCl_3$) 23.1 (NCO*Me*), 49.5 (C1), 51.0 (C2), 58.8 (C6), 63.4 (C5), 64.6 (C*H*Ph_2), 71.7 (C4), 76.0 (C3), 126.7, 126.8, 127.4, 127.8, 128.2, 128.7, 130.0, 130.2, 137.7 and 141.5 (Ar), 171.5 (NCOMe). *m/z* calculated for $C_{21}H_{26}N_2O_4$ (M^+) 370.1892, found 370.1887.

2-Acetamido-1,2,5-trideoxy-1,5-imino-D-glucitol ***5*** *via deprotection of* ***12***

Palladium hydroxide on carbon (0.15 g, 20%) was added to a solution of **12** (1.04 g, 2.8 mmol) in acidic methanol (0.3 ml conc. HCl in 30 ml MeOH) and stirred under hydrogen at atmospheric pressure. After 5 h the catalyst was removed by filtration and the solvent evaporated *in vacuo*. Since the crude hydrochloride salt did not crystallise it was eluted through an ion exchange column (Amberlyst A-26, HO^-) with water to afford the free amine. Crystallisation from ethanol gave 2-acetamido-1,2,5-trideoxy-1,5-imino-D-glucitol **5** (0.28 g, 49%), mp. 221°, lit.[7] 227-228°, $[\alpha]_D$ +13.3° (c 1, H2O), lit.[7] $[\alpha]_D$ +16.4 (c 1, H_2O). δ_H (D_2O)[6,7] 1.92 (3H, s, Ac),

2.34 (1H, dd, $J_{1,1}$ 12.3 Hz, $J_{1,2}$ 11.7 Hz, H1), 2.45 (1H, ddd, $J_{5,4}$ 9.3 Hz, $J_{5,6}$ 6.0 Hz, $J_{5,6}$ 3.0 Hz, H5), 2.97 (1H, dd, $J_{1,1}$ 12.7 Hz, $J_{1,2}$ 4.9 Hz, H1), 3.21 (1H, dd, $J_{4,5}$ 9.5 Hz, $J_{4,3}$ 9.0 Hz, H4), 3.31 (1H, dd, $J_{3,2}$ 9.6 Hz, $J_{3,4}$ 9.2 Hz, H3), 3.58 (1H, dd, $J_{6,6}$ 11.7 Hz, $J_{5,6}$ 6.0 Hz, H6), 3.65 (1H, td, $J_{2,1}$ $J_{2,3}$ 10.5 Hz, $J_{2,1}$ 4.7 Hz, H2), 3.74 (1H, dd, $J_{6,6}$ 11.7 Hz, $J_{6,5}$ 2.9 Hz, H6). δ_C (D_2O)[7] 24.7 (NCO*Me*), 49.6 (C1), 54.8 (C2), 63.1 (C5), 63.9 (C6), 74.7 (C4), 78.5 (C3), 177.0 (N*C*OMe). *m/z* calculated for $C_8H_{17}N_2O_4$ (MH^+) 205.1188, found 205.1187.

2-Acetamido-1,2,5-trideoxy-1,5-imino-D-glucitol **5** *directly from* **7**

The crude residue **7** (0.050 g, 0.21 mmol), generated from ketone **11** as described above, was dissolved in dry methanol (2 ml) and cooled to -10°C. To this, a solution of dry ammonium acetate (0.018 g, 0.23 mmol) and sodium cyanoborohydride (0.020 g, 0.32 mmol) in dry methanol (3 ml), cooled to -10°C, was then added and the mixture refrigerated at 0-4°C for 7 days followed by 1 day at room temperature. The methanol was removed *in vacuo* and the residue dissolved in 30% chloroform/methanol then flash chromatographed on silica gel (12:8:1 chloroform/methanol/aq. ammonia) to afford 2-acetamido-1,2,5-trideoxy-1,5-imino-D-glucitol **5** (0.016 g, 37%), $[\alpha]_D$ +16° (c 1.5, H_2O), lit.[7] $[\alpha]_D$ +16.4° (c 1, H_2O). Identical ^1H NMR to above.

ACKNOWLEDGEMENTS

We thank Herbert Wong for NMR measurements. We are grateful for financial support from the New Zealand Foundation for Research, Science and Technology.

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