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Nitrogen Atom Configurational Lability as a Diastereomeric Relay, A Novel Stereodynamic Strategy in Aza-Sugar Synthesis: The First Synthesis of Adenophorine[**]

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Abbreviations

Aq	Aqueous
Bn	Benzyl
DBU	1,8-Diazabicyclo-[5.4.0]-undec-7-ene
DCM	Dichloromethane
DIAD	Diisopropylazodicarboxylate
dr	Diastereomeric ratio
DMF	Dimethylformamide
Et	Ethyl
EtOAc	Ethyl acetate
Eq	Molar equivalent(s)
Me	Methyl
Ms	Methanesulphonate
NCS	*N*-Chlorosuccinimide
NMR	Nuclear magnetic resonance
PCC	Pyridinium chlorochromate
Ph	Phenyl
Py	Pyridine
TBAF	Tetrabutylammonium fluoride
TBDPS	*Tert*-Butyldiphenylsilyl
THF	Tetrahydrofuran
tlc	Thin Layer Chromatography
TMP	2,2,6,6-Tetramethylpiperidine

General Experimental

^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on Varian Gemini 200, Unity 300, VXR 400, Varian Inova 500 or Bruker AMX 500 NMR spectrometers at the frequencies indicated. Where indicated, NMR peak assignments were made using COSY, DEPT, HETCOR or NOESY experiments; all others are subjective. All chemical shifts are quoted on the δ-scale and were referenced to residual solvent as an internal standard. Combinations of the following abbreviations are used to describe NMR spectra: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad, obs; obscured; r; roofing; p, pseudo. Infra-red spectra were recorded on a Perkin-Elmer Fourier Transform spectrophotometer. The following abbreviations are used to describe infra red absortion bands: br, broad; s, strong. Mass spectra were recorded using electron impact, chemical ionisation or electrospray ionisation techniques on Micromass Autospec or LCT mass spectrometers; high resolution electrospray spectra were recorded by the UK EPSRC mass spectrometry service at Swansea, UK. Thin layer chromatography (TLC) was carried out on aluminium sheets coated with silica gel $60F_{254}$ (Merck, 1.05554). Plates were developed using an ethanolic phosphomolybdic acid or aqueous basic potassium permanganate dip. Flash column chromatography was performed using silica gel (Merck, 60A, 230-400 Mesh). Diethyl ether, tetrahydrofuran, and dichloromethane were dried immediately prior to use according to standard procedures: diethyl ether and tetrahydrofuran were distilled under N_2 over Na, and DCM was distilled under N_2 from CaH_2. Toluene was distilled from sodium and stored over 4Å sieves under nitrogen. Methanol and ethanol were distilled from magnesium/iodine, and stored over 4Å sieves under nitrogen. Other dry solvents used were commercial, and stored

and handled under dry nitrogen. All solvents were removed by evaporation under reduced pressure.

2,3,4,6-Tetra-*O*-benzyl-1,5-di-*O*-methanesulphonyl-D-glucitol:

2,3,4,6-Tetra-*O*-benzyl-D-glucitol (2.15 g, 0.003967 mol, 1 eq) was dissolved in dry pyridine (20 mL), under N_2 and cooled to 0°C. A cooled (0°C) solution of methanesulphonyl chloride (1.11 g, 2.45 eq, 0.00970 mol) in dry pyridine (10 mL) was added, with stirring. The reaction was stirred at –1°C for 72 h, when tlc analysis (50:50 EtOAc : hexane) showed complete conversion of starting material (R_f 0.3) to product (R_f 0.45). The mixture was diluted with chloroform (50 mL), and washed with HCl (aq, 1M) (1 × 20 mL), H_2O (1 × 20 mL), $NaHCO_3$ (aq, saturated) (1×20 mL), the organic layers isolated, dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography (40:50 EtOAc : hexane) to yield 2,3,4,6-tetra-*O*-benzyl-1,5-di-*O*-methanesulfonyl-D-glucitol (1.95 g) as a pale yellow oil (71%): $[\alpha]_D^{23}$ (c = 1, $CHCl_3$) + 4.8; *m/z* 721 (ES, $[M+Na]^+$, 100 %, MeOH); ν_{max} (film)/cm^{-1}: 1175, 1356 (SO_2 stretch) 2873, 2936 (aliphatic C-H stretch), 3031, 3063, 3094 (aromatic C-H stretch); δ_H ($CDCl_3$, 500 MHz, gCOSY, gHSQC) 2.83 (s, 3H, C$\underline{H}_3SO_3$), 2.95 (s, 3H, C$\underline{H}_3SO_3$), 3.72 (pt, 1H, H-3, $J_{2,3}$ 5.0 Hz, $J_{3,4}$ 5.0 Hz), 3.78 (dd, 1H, H-6, $J_{5,6}$ 7.8 Hz, $J_{6,6'}$ 11.0 Hz), 3.87 (dd, 1H, H-6' $J_{6,6'}$ 11.0 Hz, $J_{5,6}$ 2.7 Hz), 3.93 (ddd, 1H, H-2, $J_{H,H}$ 2.5 Hz $J_{H,H}$ obs. $J_{H,H}$ obs.), 4.05 (dd, 1H, H-4, $J_{3,4}$ 4.9 Hz, $J_{4,5}$ 2.9 Hz), 4.26 (dd, 1H, H-1, $J_{1,2}$ 6.9 Hz, $J_{1,1'}$ 10.7 Hz), 4.47 (s, 2H, OC$\underline{H}_2$Ph), 4.49 (dd, 1H, H-1', $J_{1',2}$ 2.3 Hz, $J_{1,1'}$ obs.) 4.56 (s, 2H, OC$\underline{H}_2$Ph), 4.53 (d, 1H, OC$\underline{H}_2$Ph, J_{HH} 11.6 Hz), 4.57 (d, 2H, OC$\underline{H}_2$Ph, J_{HH} 11.1 Hz, J_{HH} 65.78 Hz), 4.71 (d, 1H, OC$\underline{H}_2$Ph, $J_{H,H}$ 11.6 Hz), 4.83 (d, 1H, OC$\underline{H}_2$Ph, $J_{H,H}$ 11.1 Hz), 5.05 (ddd, 1H, H-5, $J_{4,5}$ 2.7 Hz, $J_{5,6}$ 7.8 Hz, $J_{5,6'}$ 2.7 Hz), 7.30 (m, 20H, aromatic CH); δ_C ($CDCl_3$, 125.7 MHz, gHSQC, DEPT) 36.9, 38.3 (q, 2 × $\underline{C}H_3SO_3$), 68.9 (t, C-6), 70.2 (t, C-1), 73.3, 73.5, 74.2, 74.6 (4 × t, 4 × Ph$\underline{C}H_2$), 76.6 (d, C-2), 77.8 (d, C-3), 79.0 (d, C4), 82.9, (d, C-5), 127.7, 127.9, 128.1, 128.2, 128.4 (6 of 15 aromatic $\underline{C}$H), 137.2, 137.3, 137.3, 137.4 (aromatic quaternary).

1-Azido-1-deoxy-2,3,4,6-tetra-*O*-benzyl-5-*O*-methanesulfonyl-D-glucitol:

2,3,4,6-tetra-*O*-benzyl-1,5-di-*O*-methanesulfonyl-D-glucitol (0.249 mmol, 174 mg) was dissolved in dry dimethyl formamide (4 mL). Sodium azide was added (1.8 eq, 0.448 mmol, 29 mg) and the reaction stirred under N_2 for 72 h. Analysis by tlc (50:50 EtOAc : hexane) showed partial conversion of starting material (R_f 0.8) to product (R_f 0.9). The reaction was stopped after 72 h by removing the solvent, and the residue dissolved in $CHCl_3$ (50 mL), washed with H_2O (2 × 30 mL). The aqueous layers were combined and back extracted with $CHCl_3$ (30 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and the solvent removed. The residue was purified by flash chromatography (25:85 EtOAc : hexane) to give recovered starting material (75 mg, 43%) and 1-azido-1-deoxy-2,3,4,6-tetra-*O*-benzyl-5-*O*-methanesulfonyl-D-glucitol (56 mg, 42%) as a colourless oil; *m/z* (MeOH, ES+) 668 ($[M+Na]^+$, 100), 1313.5 ($[2M+Na]^+$, 5); ν_{max} (film)/cm^{-1}: 2099 (azide stretch), 2854, 2922, 2952 (aliphatic C-H stretch), 3026, 3060, 3094 (aromatic C-H stretch); δ_H ($CDCl_3$, 500 MHz, gCOSY, gHSQC) 2.91 (s, 3H, C<u>H</u>$_3SO_2$), 3.31 (dd, r, 1H, H-1, $J_{1,2}$ 7.44Hz, $J_{1,1'}$ 13.1 Hz), 3.35 (dd, r, 1H, H-1', $J_{1',2}$ 3.4 Hz, $J_{1,1'}$ 13.1 Hz), 3.62 (pt, 1H, H-3, $J_{2,3}$ 5.5 Hz, $J_{3,4}$ 5.5 Hz), 3.68 (ddd, 1H, H-2, $J_{1,2}$ 3.3 Hz, $J_{2,3}$ 5.4 Hz, $J_{1',2}$ 7.3 Hz), 3.75 (dd, r, 1H, H-6, $J_{5,6}$ 7.8 Hz $J_{6,6'}$ 11.1 Hz), 3.80 (dd, r, 1H, H-6', $J_{5,6'}$ 3.0 Hz, $J_{6,6'}$ 11.1 Hz), 3.95 (dd, 1H, H-4, $J_{4,5}$ 2.6 Hz, $J_{3,4}$ 5.6 Hz), 4.40 (s, 2H, 2 × PhC<u>H</u>$_2$O), 4.51-4.62 (m, 5H, 5 × PhC<u>H</u>$_2$O), 4.72 (d, r, 1H, 1 × PhC<u>H</u>$_2$O), 5.00 (dpt, 1H, H-5, $J_{4,5}$ 2.9Hz, $J_{5,6'}$ 2.9 Hz, $J_{5,6}$ 7.8 Hz), 7.20-7.33 (m, 20H, aromatic CH); δ_C ($CDCl_3$, 125.7 MHz, DEPT, gHSQC) 38.6 (q, C<u>H</u>$_3SO_3$), 51.5 (t, C-1), 69.2 (t, C-6), 73.6, 73.7, 74.8, 74.9 (4 × t, 4 × Ph<u>C</u>H_2O), 78.5 (d, C-3), 78.6 (d, C-2), 79.8 (d, C-4), 83.4 (d, C-5), 128.00, 128.16, 128.22, 128.25, 128.30, 128.40, 128.52, 128.65, 128.71, 128.73, 128.75 (11 × d, 11 of 20 aromatic CH, others coincident), 137.69, 137.73, 137.76 (3 × s, 3 of 4 quaternary

aromatic, two coincident); HRMS found 663.2850 ($C_{35}H_{39}N_3O_7S.NH_4$ requires 663.2852).

2,3,4,6-Tetra-*O*-benzyl-1,5-dideoxy-1,5-imino-L-iditol (tetrabenzyl-INJ, 8):

Method 1: 1-azido-1-deoxy-2,3,4,6-tetra-*O*-benzyl-5-*O*-methanesulfonyl-D-glucitol (31.5 mg, 0.0487 mmol, 1.0 eq) was dissolved in dry dichloromethane (3 mL) under N_2. Triphenylphosphine was added (14.0 mg, 0.0535 mmol, 1.1 eq), and the reaction stirred. The reaction was monitored by tlc (20:80 EtOAc:hexane), showing complete consumption of starting material (R_f 0.55). After 48 h, HCl was added (3.0 M, aq, 0.5 mL), and the mixture stirred for 5 h, before addition of NaOH (3.0 M, 2.0 mL) and further stirring under nitrogen for 48 h. The reaction mixture was diluted with chloroform (50 mL) and washed with dilute NaOH (pH 11-12) (2 × 30 mL). All aqueous washings were back extracted with chloroform (20 mL), and the organic layers combined, dried (Na_2SO_4), filtered, and the solvent removed. The residue was purified by repeated flash chromatography (75:25 EtOAc:hexane) to give 2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1,5-imino-L-iditol (**8**) as a colourless oil (12.5 mg, 50%);

Method 2: 2,3,4,6-Tetra-*O*-benzyl-1,5-di-*O*-methanesulphonyl-D-glucitol (2.09 g, 2.98 mmol, 1.0 eq), and sodium azide (583 mg, 8.97 mmol, 3.0 eq) were dissolved in dry DMF under nitrogen, and the mixture stirred at 80°C. After 5 h the reaction mixture was cooled to room temperature, and triphenyl phosphine added (860 mg, 3.28 mmol, 1.1 eq), and the mixture stirred at 80°C for a further 17 h. The reaction mixture was diluted with diethyl ether (200 mL) then washed with water (100 mL) then dried (Na_2SO_4), filtered, and the solvent removed. The crude oil was passed through a column of Dowex H^+ (50X 2-200, 10 g) and washed with methanol (100 mL) then the desired product eluted with methanol : saturated ammonia (aq) (80:20), 100 mL, and the solvent removed *in vacuo*. The resultant oil was purified by flash

chromatography (75:25 EtOAc:hexane) to give 2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1,5-imino-L-iditol as a colourless oil (958 mg, 61 %); δ_H ($CDCl_3$, 500 MHz, gCOSY, gHSQC) 2.47 (s, br, 1H, NH), 2.93 (dd, r, 1H, H-1, $J_{1,2}$6.6 Hz, $J_{1,1'}$ 12.8 Hz), 3.07 (dd, 1H, H-1', $J_{1',2}$ 3.8 Hz, $J_{1,1'}$ 12.9 Hz), 3.45 (m, 1H, H-5), 3.51 (m, 1H, H-2), 3.61 (dd, H-6, $J_{5,6}$ 5.2 Hz, $J_{6,6'}$ 9.5 Hz), 3.67-3.71 (m, 2H, H-3, H-4), 3.74 (pt, 1H, H-6', $J_{5,6}$ 9.2 Hz, $J_{6,6'}$ 9.2 Hz), 4.56-4.73 (m, 8H, 8 × PhC$\underline{H}_2$O), 7.30-7.41 (m, 20H, aromatic CH); δ_C (100.6 MHz, $CDCl_3$, DEPT, gHSQC), 54.7 (t, C-1), 67.2 (d, C-5), 72.1, 72.6, 73.4, 74.1 (4 × t, 4 × $PhCH_2O$), 76.9 (d, br, C-2), 77.4, 78.0 (2 × d, br, C-4, C-4), 127.64, 127.68, 127.74, 127.82, 127.86, 127.96, 128.37, 128.41, 128.47 (9 × d, 9 of 20 aromatic CH, others coincident), 138.34, 138.46, 138.57, 138.63 (4 × s, 4 × quaternary aromatic); HRMS found 524.2801 ($C_{34}H_{38}NO_4$ requires 524.2801).

2,3,4,6-Tetra-*O*-benzyl-*N*-chloro-1,5-dideoxy-1,5-imino-D-glucitol (9):

2,3,4,6-Tetra-*O*-benzyl-1,5-dideoxy-1,5-imino-D-glucitol (**7**) (1.0 eq, 300 mg, 0.573 mmol), was placed in a dry round bottomed flask with 5 mL dry DCM under nitrogen with stirring. NCS (1.1 eq, 0.632 mmol 84.4 mg) was added. The reaction was followed by tlc revealing consumption of starting material. After 22 hours the reaction mixture was diluted with DCM (20 mL), and washed with distilled water (2 × 30 mL). The organic layer was separated, dried (Na_2SO_4), filtered, and the solvent removed on a rotary evaporator to a colourless oil, which was flushed though a silica plug (50 : 50 EtOAc : hexane eluant) and the solvent removed in vacuo to give 2,3,4,6-tetra-*O*-benzyl-*N*-chloro-1,5-dideoxy-1,5-imino-D-glucitol (**9**) as a colourless oil which formed a white crystalline solid on standing (310 mg, 97%); $[\alpha]_D^{24}$ + 8.0 (c = 1, $CHCl_3$); m/z (ES, MeOH) 558 ($[M]^+$,12%), 580 ($[M+Na]^+$, 20, ^{35}Cl), 582 ($[M+Na]^+$, 7, ^{37}Cl), 524 ($[M-Cl+H]^+$, 100); ν_{max} (KBr disc)/cm^{-1}: 3027 (aromatic C–H stretch), 2930 - 2900 (aliphatic C–H stretch); δ_H ($CDCl_3$, 500 MHz, gCOSY) 2.75 (d,

br, 1H), 2.92 (t, 1H), 3.55 (t, 1H), 3.65 (m, 4H), 3.95 (dd, 1H), 4.50–5.00 (m, 9H), 7.20 (m, 2H, 2 × C<u>H</u> aromatic), 7.40-7.75 (m, 18H, 18 × C<u>H</u> aromatic); δ_C ($CDCl_3$, 125 MHz, DEPT) 64.2 (t, br, C-1), 66.7 (t, C-6), 72.6 (d, br, C-5), 73.4, 73.8, 75.8, 75.8 (4 × t, benzyl), 76.9, 77.3, 86.6 (CH, C-3, C-4, C-5), 127.6, 127.7, 127.8, 127.9, 128.0, 128.0, 128.1, 128.4, 128.4, 128.4, 128.5 (11 of 12 × <u>d</u>, aromatic <u>C</u>H), 137.8, 137.9, 138.0, 138.5 (4 × s, quarternary aromatic); HRMS found 580.2224; ($C_{34}H_{36}{}^{35}ClNO_4$.Na requires 580.2231). Found: C, 72.93; H, 6.45; N, 2.46 %; $C_{34}H_{36}ClNO_4$ requires C, 73.17; H, 6.50; N, 2.51 %.

2,3,4,6-Tetra-*O*-benzyl-*N*-chloro-1,5-dideoxy-1,5-imino-L-iditol (10):

2,3,4,6-Tetra-*O*-benzyl-1,5-dideoxy-1,5-imino-L-iditol (**8**) (1.0 eq, 1.91 mmol, 1.00 g) was placed in a round bottom flask with dry DCM (20 mL), and *N*-chlorosuccinimide added (1.2 eq, 2.30 mmol, 311 mg). The mixture was stirred under nitrogen and followed by tlc until complete conversion of starting material to a less polar product was observed. After 16h the reaction mixture was diluted with DCM (80 mL), and washed with water (2 × 50 mL), then the organic layer dried (Na_2SO_4), filtered, and the solvent removed to give a pale yellow oil which was purified by passing through a plug of silica (20:80 ethyl actetate:hexane eluant). Evaporation of the solvent gave 2,3,4,6-tetra-*O*-benzyl-*N*-chloro-1,5-dideoxy-1,5-imino-L-iditol (**10**) as a colourless oil (987 mg, 93 %); $[\alpha]_D{}^{25}$ + 9.9 (c, 1, in $CHCl_3$); *m/z* 582 ($[M+Na]^+$, ^{37}Cl, 34%), 580 (ES, $[M+Na]^+$,^{35}Cl, 100%, MeOH), 524 ($[M-Cl+2H]^+$, 90%); ν_{max} (film)/cm^{-1}: 2865 (br, aliphatic C-H stretch), 3029, 3062, 3090 (aromatic C-H stretch); δ_H ($CDCl_3$, 500 MHz, COSY) 3.35-3.45 (m, 2H, H-1, H-1'), 3.54 (dd, 1H, H-5, $J_{4,5}$ 4.8 Hz, $J_{5,6}$ 9.60 Hz), 3.75 (pt, 1H, H-3, $J_{2,3}$ 8.0 Hz, $J_{3,4}$ 8.0 Hz), 3.81 (m, 2H, H-2, H-6), 3.91 (dd, 1H, H-6', $J_{5,6'}$ 4.4 Hz, $J_{6,6'}$ 10.1 Hz), 4.0 (dd, 1H, H-4, $J_{3,4}$ 7.8 Hz, $J_{4,5}$ 5.3 Hz), 4.57 (s, 2H, 2 × PhC<u>H</u>$_2$O), 4.59-4.73 (m, 5H, 5 × PhC<u>H</u>$_2$O), 4.76 (d, r, 1H, 1 × PhC<u>H</u>$_2$O, J_{HH} 11.3

Hz), 7.27-7.37 (m, 20H, aromatic CH); δ_C (125.7 MHz, $CDCl_3$, DEPT, gHSQC) 59.4 (t, br, C-1), 67.4 (t, C-6), 68.3 (d, C-5), 73.1, 73.5, 73.6, 75.0 (4 × t, 4 × Ph<u>C</u>H_2O), 76.9 (d, C-2), 77.8 (d, C-4), 80.2 (d, br, C-3), 127.8, 127.9, 128.0, 128.0, 128.2, 128.2, 128.6, 128.6, 128.7 (9 × d, 9 of 20 aromatic <u>C</u>H, others coincident), 138.3, 138.4, 138.4, 138.8 (4 × s, 4 × quaternary aromatic); HRMS (ES, $[M+H]^+$) found 558.2416, ($C_{34}H_{37}{}^{35}ClNO_4$ requires 558.2411).

2,3,4,6-Tetra-*O*-benzyl-1,5-dideoxy-5,*N*-dehydro-1,5-imino-D-glucitol (13): 2,3,4,6-Tetra-*O*-benzyl-*N*-chloro-1,5-dideoxy-1,5-imino-D-glucitol (**9**) (1.0 eq, 0.179 mmol, 100 mg), was placed in a flask with 4 mL dry diethyl ether under N_2 with stirring. DBU (1.05 eq, 0.188 mmol, 28.5 mg, 28 μl) was added, and the reaction followed by tlc (15 : 85 EtOAc : hexane) revealing consumption of starting material and formation of a new product. A white precipitate of DBU.HCl was seen to form quickly. After 135 minutes, the reaction mixture was filtered through a glass sinter, under nitrogen and concentrated *in vacuo* to give 2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-5,*N*-dehydro-1,5-imino-D-glucitol (**13**) as a pale orange oil (96 mg, 100%);ν_{max} (film)/cm^{-1}: 1667 (C=N stretch), 2953, 2850 (aliphatic C-H stretch), 3030, 3088 (aromatic C-H stretch); δ_H ($CDCl_3$, 400 MHz, gCOSY, gHSQC) 3.60 (ddd, 1H, H-1, $J_{1,4}$ 1.4 Hz, $J_{1,2}$ 8.4 Hz, $J_{1,1'}$ 16.6 Hz,), 3.70 (ddd, 1H, H-2, $J_{1',2}$ 4.6 Hz, $J_{1,2}$ 8.4 Hz, $J_{2,3}$ 8.4 Hz), 3.90 (dd, 1H, H-3, $J_{3,4}$ 7.1 Hz, $J_{2,3}$ 8.6 Hz), 4.05 (dd, 1H, H-1', $J_{1',2}$ 4.7 Hz, $J_{1,1'}$ 16.9 Hz), 4.10 (d, 1H, H-6, $J_{6,6'}$ 13.0 Hz), 4.13 (dd, 1H, H-4, $J_{1,4}$ 1.3 Hz, $J_{3,4}$ 7.0 Hz), 4.40 (d, 1H H-6', $J_{6,6'}$ 13.3 Hz), 4.5-4.9 (m, 8H, 8 × PhC<u>H</u>$_2$O), 7.23-7.40 (m, 20H, 20 × aromatic); δ_C ($CDCl_3$, 75 MHz, DEPT, gHSQC) 53.2 (t, C-1), 71.9 (t, C-6), 72.4, 73.0, 74.3, 74.9 (4 × t, 4 × Ph<u>C</u>H_2O), 75.7 (d, C-2), 78.5 (d, C-4), 81.7 (d, C-3), 137.6, 137.8, 138.0, 138.2 (4 × s, 4 × quaternary aromatic), 127.65, 127.66, 127.68, 127.76, 127.78, 127.84, 127.87, 128.03, 128.13, 128.16, 128.24, 128.27, 128.32,

128.34, 128.45 (15 × d, 15 of 20 CH aromatic, others coincident), 168.5 (s, C-5, C=N).

2,3,4,6-Tetra-*O*-benzyl-1,5-dideoxy-1,*N*-dehydro-1,5-imino-D-glucitol (11): 2,3,4,6-Tetra-*O*-benzyl-*N*-chloro-1,5-dideoxy-1,5-imino-D-glucitol (**9**) (58 mg, 0.1038 mmol, 1.0 eq), was placed in a round bottomed flask under N_2 with 5 mL dry diethyl ether under N_2 with magnetic stirring. The resulting solution was cooled to –78° C, and lithium tetramethylpiperidide (0.96 mL of a 0.1187 M solution in diethyl ether, 1.1 eq) was added slowly over 5 minutes. The reaction was followed by t.l.c. (15:85 EtOAc:hexane). After 3 hours, distilled H_2O was added (5 mL) to the cold reaction mixture, and the mixture allowed to warm to room temperature. The reaction mixture was diluted with diethyl ether (20 mL), and washed with H_2O (2 × 20 mL). The organic layer was isolated, dried (Na_2SO_4), filtered, and the solvent removed on a rotary evaporator to yield **11** (50mg, 90%) as a pale orange oil. A small amount of **11** was purified by flash chromatography (50:50 EtOAc: hexane) and in addition to **11** yielded pyridine elimination products through loss of benzyl alcohol; ν_{max} (film)/cm^{-1}: 1654 (C=N stretch), 2940, 2860 (aliphatic C-H stretch), 3025, 3090 (aromatic C-H stretch); δ_H ($CDCl_3$, 200 MHz), 3.11–4.03 (m, 6H, H-1), 4.22–4.91 (8H, 4 × benzyl C$\underline{H}_2$), 7.00 – 7.40 (20 H, aromatic), 7.60 (br s, 1H, H-1); δ_C (50 MHz, $CDCl_3$): 66.4, 69.6, 73.6, 73.9, 75.3, 75.5, 76.5, 81.1, 82.6 ppm (C-2, C-3, C-4, C-5, C-6, 4 × benzyl $\underline{C}H_2$), 127.9–128.8 (aromatic $\underline{C}$-H), 137.0–138.0 (aromatic $\underline{C}$), 162.3 (C-1).

2,3,4,6-Tetra-*O*-benzyl-1,5-dideoxy-1,*N*-dehydro-1,5-imino-L-iditol (12):

Method 1: 2,3,4,6-Tetra-*O*-benzyl-*N*-chloro-1,5-dideoxy-1,5-imino-L-iditol (**10**) (1.0 eq, 0.0842 mmol, 47.0 mg) was dissolved in dry diethyl ether (2 mL) and DBU added (1.1 eq, 0.0926 mmol, 14.1 mg, 13.8 μL) and the mixture stirred at reflux for 7.5 h,

after which time tlc indicated complete consumption of starting material. The mixture was filtered under nitrogen, and further dry ether (1 mL) washed through the filter. The solvent was removed from the filtrate *in vacuo*, to give 2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1,*N*-dehydro-1,5-imino-L-iditol (**11**) (45 mg) as a pale yellow oil which was used directly.

Method 2: 5-Azido-2,3,4,6-tetra-*O*-benzyl-5-deoxy-D-idose (1.0 eq, 0.0725 mmol, 41.0 mg) was dissolved in dry diethyl ether (1.5 mL) with triphenylphosphine (3.0 eq, 0.217 mmol, 57.0 mg), and the mixture stirred under nitrogen at room temperature for 90 minutes when tlc indicated complete consumption of starting material. The solvent was removed *in vacuo* to give crude 2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1,*N*-dehydro-1,5-imino-L-iditol (**11**) as a waxy white solid which was used directly: $[\alpha]_D^{25}$ – 14.7 (c = 2, $CHCl_3$); ν_{max} (film)/cm^{-1}: 1647 (C=N stretch), 2863, 2921 (aliphatic C-H stretch), 3029, 3062, 3086 (aromatic C-H stretch); δ_H ($CDCl_3$, 400 MHz, gCOSY) 3.77-3.87 (m, 4H, H-2), 3.98 (dd, 1H, J_{HH} 4.0 Hz, J_{HH} 8.7 Hz), 4.00 (pt, 1H, J_{HH} 5.3 Hz), 4.47-4.57 (m, 3H, 3 × PhC$\underline{H}_2$O), 4.60 (d, r, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.5 Hz), 4.62 (d, r, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.8 Hz), 4.63 (d, r, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.4 Hz), 4.68 (d, r, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.8 Hz), 4.70 (d, r, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.5 Hz), 7.24-7.37 (aromatic C-H), 7.80 (s, 1H, H-1); δ_C ($CDCl_3$, 100.6 MHz, DEPT) 60.2 (d, C-5), 69.6 (t, C-6), 74.4, 72.5, 72.8, 73.4 (4 × t, 4 × Ph$\underline{C}H_2$O), 75.0, 77.8, 78.6 (3 × d, C-2, C-3, C-4), 127.8-128.8 (aromatic CH), 137.8, 138.2, 138.4 (3 × s, 3 of 4 quaternary aromatic, 2 coincident), 164.0 (d, C-1); *m/z* 554 (ES, $[M+MeOH+H]^+$)

4,5,6,8-Tetra-*O*-benzyl-1,2,3,7-tetra-deoxy-3,7-imino-L-glycero-L-ido-octitol or 2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1α-ethyl-1,5-imino-L-iditol (16):

2,3,4,6-Tetra-*O*-benzyl-*N*-chloro-1,5-dideoxy-1,5-imino-L-iditol (**10**) (1.0 eq, 0.111 mmol, 62 mg) was placed in a round bottom flask with dry diethyl ether (2.0 mL) and

DBU added (1.1 eq, 0.122 mmol, 18.6 mg). The mixture was immediately heated to reflux under nitrogen for 7 h when tlc showed complete consumption of starting material. The mixture was then filtered under nitrogen to remove the white precipitate of DBU.HCl, and the flask and precipitate washed with dry ether (1 mL) under nitrogen. The combined colourless filtrate was used immediately and was added drop-wise to a freshly prepared, cooled (-78ºC) solution of Et_2Mg [Preparation of Et_2Mg reagent: Diethyl ether (dry, 5.0 mL) was placed in a dry round bottom flask, under nitrogen, and ethyl magnesium bromide added (5.4 eq, based on 100% conversion of **10** to **12**), 0.60 mmol, 0.2 mL of a 3 M solution in diethyl ether (Aldrich)). The mixture was stirred under nitrogen as dry dioxan was added (5.4 eq, 53 mg, 51 μL). A white precipitate formed immediately, and the mixture was stirred under nitrogen for 15 minutes at room temperature, before cooling to –78ºC]. The mixture was stirred at –78ºC for 2h then allowed to warm to room temperature for 30 minutes before quenching with 3.0 M HCl (1 mL). The mixture was diluted with DCM (30 mL) and basified with NaOH (pH 13). The organic layer was washed with aqueous NaOH (0.1 M, 2 × 15 mL), and the organic layer dried (Na_2SO_4), filtered, and the solvent removed to give a colourless oil. Flash chromatography (25:75, EtOAc:hexane) gave recovered tetrabenzyl INJ (7) (16 mg, 27 %) and **16** as a colourless oil (21 mg, 34%, 47% based on recovered material): $[\alpha]_D^{25}$ + 9.9 (c, 0.67, in $CHCl_3$); *m/z* 552 (ES, $[M+H]^+$, 100 %, MeOH), 574 ($[M+Na]^+$, 15 %); ν_{max} (film)/cm^{-1}: 2866, 2922, 2958 (aliphatic C-H stretch), 3028, 3062, 3086 (aromatic C-H stretch); δ_H ($CDCl_3$, 500 MHz, gCOSY, gHSQC), 0.78 (t, 3H, C<u>H</u>$_3$CH$_2$, $J_{1,2}$ 7.5 Hz), 1.49-1.56 (m, 2H, CH$_3$C<u>H</u>$_2$), 1.90 (s, br, 2H, NH), 2.78 (pt, br, 1H, H-3, $J_{2,3}$ 7.0 Hz, $J_{3,4}$ 7.0 Hz), 3.26 (pt, br, 1H, H-7, $J_{6,7}$ 6.5 Hz, $J_{7,8}$ 6.5 Hz), 3.28 (s, br, 1H, H-4), 3.48 (pt, 1H, H-8, $J_{7,8}$ 8.7, $J_{8,8'}$ 8.7 Hz), 3.50 (s, br, 1H, H-6), 3.60 (dd, 1H, H-8', $J_{7,8}$ 7.3 Hz, $J_{8,8'}$ 8.6 Hz), 3.74 (pt, 1H, H-5, $J_{4,5}$ 2.5 Hz, $J_{5,6}$ 2.5 Hz), 4.32 (d, r, 1H, 1 × PhC<u>H</u>$_2$O,

J_{HH} 12.0 Hz), 4.36 (d, r, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 12.2 Hz), 4.42 (d, r, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 12.3 Hz), 4.45 (d, r, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 12.3 Hz), 4.47 (d, r, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.8 Hz), 4.50-4.54 (m, 2H, 2 × PhC$\underline{H}_2$O), 4.56 (d, r, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 12.0 Hz), 7.21-7.37 (m, 20H, 20 × aromatic C-H); δ_C ($CDCl_3$ 125.7 Hz, DEPT, gHSQC) 10.7 (q, C-1), 24.7 (t, C-2), 55.5 (d, C-7), 57.3 (d, C-3), 70.8 (t, br, C-8), 70.9 (d, C-5), 72.0, 72.1, 72.5, 73.4 (4 × t, 4 × Ph$\underline{C}H_2$O), 72.9 (d, C-6), 74.0 (d, br, C-4), 127.66, 127.73, 127.8, 127.9, 128.0, 128.35, 128.37, 128.5, 128.6 (9 × d, 9 of 20 aromatic CH, others coincident), 138.3, 138.55, 138.60, 138.7 (4 × s, 4 × quaternary aromatic); HRMS found 552.3192 ($C_{36}H_{42}NO_4$ requires 552.3114).

1,2,3,7-Tetradeoxy-3,7-imino-L-glycero-L-ido-octitol or 1,5-dideoxy-1α-ethyl-1,5-imino-L-iditol (1-*epi*-adenophorine) (4):

4,5,6,8-Tetra-*O*-benzyl-1,2,3,7-tetra-deoxy-3,7-imino-L-glycero-L-ido-octitol (**16**) (1.0 eq, 0.0254 mmol, 14.0 mg) was dissolved in ethanol (2 mL), and $PdCl_2$ added (2.2 eq, 0.0564 mmol, 10.0 mg). The flask was evacuated, degassed and back-filled with hydrogen for four cycles before stirring under hydrogen at atmospheric pressure for 1.5 h, when all starting material had been consumed and a single product was visible by tlc (EtOAc/hexane). The mixture was filtered through celite and the solvent removed *in vacuo*, the residue was purified by ion exchange chromatography (Dowex 50WX, washing with methanol, eluting with methanol : saturated ammonia (aq), 90:10) to give 1,2,3,7-tetradeoxy-3,7-imino-L-glycero-L-ido-octitol (**4**) as a colourless oil (4.2 mg, 86 %); δ_H (D_2O, 500 MHz, nOesy) 0.83 (t, 3H, C$\underline{H}_3$CH$_2$, $J_{1,2}$ 7.5 Hz) 1.38-1.49 (m, 2H, CH$_3$C$\underline{H}_2$), 2.72 (dpt, 1H, H-3, $J_{3,4}$ 1.42 Hz, $J_{2,3}$ 7.3 Hz), 2.95 (dpt, 1H, H-7, $J_{6,7}$ 1.6 Hz, $J_{7,8}$ 6.6 Hz), 3.54 (dd, 1H, H-8, $J_{7,8}$ 6.6 Hz, $J_{8,8'}$ 11.1), 3.60 (dd, 1H, H-8', $J_{7,8}$ 6.7 Hz, $J_{8,8'}$ 11.1 Hz), 3.63 (m, 1H, H-4), 3.68 (m, 1H, H-6), 3.94 (t,

1H, H-5, $J_{4,5}$ 3.1Hz, $J_{5,6}$ 3.1 Hz); δ_C (D_2O, 125.7 MHz) 9.83 (C-1), 23.8 (C-2), 55.4, 55.5, 62.2, 68.6, 69.0, 69.4 (C-3, C-4, C-5, C-6, C-7, C-8).

2,3,4,6-Tetra-*O*-benzyl-5-benzyl-1,5-dideoxy-1,5-imino-L-iditol (21):

To a cooled (-78 ºC) freshly prepared solution of tetra-*O*-benzyl-6,*N*-dehydro-2-deoxynojirimycin (**13**) (3.33 mL of a 0.034 M solution in dry diethyl ether, 0.112 mmol, 1.0 eq) under N_2, was added benzyl magnesium chloride (0.336 mL of a 1M solution in diethyl ether, 0.336 mmol, 3.0 eq) with stirring. After 2 hours at –78 ºC the mixture was warmed to room temperature and stirred for a further 12 hours. The reaction was quenched by the addition of water (5 mL). The solution was diluted with diethyl ether (10 mL), and washed with water (2 × 20 mL). The organic layer was isolated, dried (Na_2SO_4), filtered, and the solvent removed. The resultant oil was separated by flash column chromatography (20:80, EtOAc : hexane) to yield tetra-*O*-benzyl-2-deoxy-6-benzyl idonojirimycin (**21**) (13.2 mg, 19 %); $[\alpha]_D^{20}$ + 14.6 (c = 1, $CHCl_3$); *m/z* 614 (ES, $[M+H]^+$,100 %, MeOH), 636 ($[M+Na]^+$, 10 %); ν_{max} (film)/cm^{-1} 3348 (N–H stretch), 3090, 3062, 3029 (aromatic C–H stretch), 2916 (aliphatic C–H stretch), 1603 (aromatic C=C stretch); δ_H ($CDCl_3$, 500 MHz, gCOSY, NOESY) 2.74 (dd, 1H, H-1, $J_{1,2}$ 11.1 Hz, $J_{1,1'}$ 12.0 Hz), 2.90 (d, 1H, H-7, $J_{7,7'}$ 13.6 Hz), 3.10 (d, 1H, H-7', $J_{7,7'}$ 13.6 Hz), 3.12 (dd, 1H, H-1', $J_{1,2}$ 5.4 Hz, $J_{1,1'}$ 11.9 Hz), 3.37 (d, 1H, H-4, $J_{3,4}$ 8.9 Hz), 3.43 (ddd, 1H, H-2, $J_{2,3}$ 5.3 Hz, $J_{1,2}$ 10.1 Hz), 3.61 (d, 1H, H-6, $J_{6,7}$ 9.8 Hz), 3.83 (pt, 1H, H-3, $J_{2,3}$ 9.1 Hz, $J_{3,4}$ 9.1 Hz), 3.96 (d, 1H, H-6', $J_{6,6'}$ 9.6 Hz), 4.53 (d, r, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.9 Hz), 4.56 (d, r, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.9 Hz), 4.63 (s, 2H, PhC$\underline{H}_2$O), 4.66 (d, r, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.9 Hz), 4.69 (d, r, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 10.2 Hz), 4.95 (d, r, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 10.2 Hz), 5.02 (d, r, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.9 Hz), 7.20-7.35 (m, 25H, 25 × C$\underline{H}$ aromatic); δ_C ($CDCl_3$, 125.7 MHz, DEPT, ^{1}H-^{13}C HETCOR) 42.1 (t, C-7, Ph$\underline{C}H_2$C), 43.4 (t, C-1), 60.6 (s, C-5), 69.4 (t, C-6), 72.5,

73.5, 74.8, 75.4 (4 × t, 4 × Ph<u>C</u>H_2O), 81.0 (d, C-2), 82.0 (d, C-4), 84.8 (d, C-3), 126.3, 126.8, 127.3, 127.6, 128.0, 128.3, 130.8 (7 × d, 7 of 20 aromatic CH, others coincident), 137.2, 138.4, 138.5, 138.6, 139.3 (5 × s, 5 × quaternary aromatic); HRMS found 614.3269 ($C_{41}H_{44}NO_4$ requires 614.3270).

2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1,5-imino-5-methyl-D-glucitol (23) and 2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1,5-imino-5-methyl-L-iditol (22):

To a cooled (-78 ºC) freshly prepared solution of tetra-*O*-benzyl-6,*N*-dehydro-2-deoxynojirimycin (**13**) (3.33 mL of a 0.034 M solution in dry diethyl ether, 0.112 mmol, 1.0 eq) under N_2, was added methyl magnesium bromide (0.112 mL of a 3.0 M solution in diethyl ether, 0.112 mmol, 3.0 eq) with stirring. After 2 hours at –78 ºC the mixture was warmed to room temperature and stirred for a further 12 hours. The reaction was quenched by the addition of water (5 mL). The solution was diluted with diethyl ether (10 mL), and washed with water (2 × 20 mL). The organic layer was isolated, dried (Na_2SO_4), filtered, and the solvent removed. The resultant oil was purified by flash column chromatography (20:80 EtOAc:hexane) to yield **22** : **23**, (10.2 mg, 17%, dr 1:8). Further flash chromatography (20:80 EtOAc:hexane) yielded pure **23** (6.0 mg, 10 %): $[\alpha]_D^{21.5}$ +22.2 (c = 0.65, $CHCl_3$); *m/z* 192 (ES, $[M+H]^+$, 100 %, MeOH), 538 ($[M+H]^+$, 100 %, MeOH), 560 ($[M+Na]^+$, 80%), 1097 ($[2M+Na]^+$, 10%); ν_{max} (film)/cm^{-1}: 2854, 2918 (aliphatic C-H stretch), 3030, 3062 (aromatic C-H stretch); δ_H ($CDCl_3$, 500 MHz, gCOSY, gHSQC nOesy) 1.09 (s, 3H, CH_3), 1.96 (s, br, 1H, NH), 2.72 (1H, dd, H-1, $J_{1,2}$ 11.0 Hz, $J_{1,1'}$ 13.6 Hz), 3.09 (dd, 1H, H-1', $J_{1,2}$ 5.6 Hz, $J_{1,1'}$ 13.6 Hz), 3.18 (d, 1H, H-6, $J_{6,6'}$ 8.8 Hz), 3.44 (ddd, 1H, H-2, $J_{1',2}$ 5.5 H, $J_{2,3}$ 9.1 Hz, $J_{1,2}$ 10.8 Hz), 3.53 (d, 1H, H-6', $J_{6,6'}$ 8.7 Hz), 3.62 (d, 1H, H-4, $J_{3,4}$ 9.6 Hz), 3.72 (t, 1H, H-3, $J_{2,3}$ 9.2 Hz, $J_{3,4}$ 9.2 Hz), 4.37 (d, r, 1H, 1 × PhC<u>H_2</u>O, J_{HH} 11.8 Hz), 4.44 (d, r, 1H, 1 × PhC<u>H_2</u>O, J_{HH} 11.8 Hz), 4.51 (d, r, 1H, 1 × PhC<u>H_2</u>O, J_{HH} 11.2 Hz),

4.61 (d, r, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.6 Hz), 4.72 (d, r, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.6 Hz), 4.81 (d, r, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 10.6 Hz), 4.90 (d, r, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.3 Hz), 4.93 (d, r, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 10.7 Hz), 7.21-7.37 (m, 20H, aromatic); δ_C ($CDCl_3$, 125.7 MHz, DEPT, gHSQC) 15.4 (q, CH_3), 43.3 (t, C-1), 57.7 (s, C-5), 73.1, 73.3, 75.4, 75.9 (4 × t, 4 × Ph$\underline{C}H_2$O), 75.0 (t, C-6), 81.2 (d, C-4), 82.0 (d, C-2), 84.2 (d, C-3), 127.5, 127.7, 127.8, 127.86, 127.92, 127.94, 128.1, 128.4, 128.50, 128.52, 128.57 (11 × d, 11 × aromatic CH, others coincident), 138.1, 138.7, 139.1, 139.2 (4 × s, 4 × quaternary aromatic); HRMS found 538.2959 ($C_{36}H_{39}NO_4$ requires 538.2957).

1,5-dideoxy-1,5-imino-5-methyl-D-glucitol (5):

Methanol (1.0 mL), was added to a mixture of 2,3,4,6-tetra-O-benzyl-1,5-dideoxy-1,5-imino-5-methyl-D-glucitol (**23**) (1.0 eq, 0.0260 mmol, 14.0 mg) and $PdCl_2$ (1.5 eq, 0.039 mmol, 7.0 mg,) with stirring. The flask was purged with hydrogen by successive evacuation then refilling. The mixture was stirred under an atmosphere of hydrogen at room temperature for 1h, after which time tlc (20:80:1, MeOH : DCM : Et_3N) indicated full consumption of starting material. The reaction mixture was filtered through celite, and the solvent removed. The residue was purified by ion exchange chromatography (Dowex 50WX, washing with methanol, eluting with methanol : saturated ammonia (aq), 90:10) to give 1,5-dideoxy-1,5-imino-5-methyl-D-glucitol (**5**) as a colourless oil (4.3 mg, 93 %): $[\alpha]_D^{24}$ + 4.3 (c = 0.52, MeOH); *m/z* 178 (ES, $[M+H]^+$, 100 %, MeOH), 200 ($[M+Na]^+$, 10 %); δ_H (D_2O, 400 MHz, gCOSY, gHSQC) 1.25 (s, 3H, CH_3) 3.05 (dd, 1H, H-1, $J_{1,2}$ 11.5 Hz, $J_{1,1'}$ 12.7 Hz), 3.35 (dd, 1H, H-1', $J_{1,1'}$ 12.9 Hz, $J_{1',2}$ 5.5 Hz), 3.55-3.59 (m, 2H, H-4, H-6), 3.64 (pt, 1H, H-3, $J_{2,3}$ 9.3 Hz, $J_{3,4}$ 9.3 Hz), 3.73 (ddd, 1H, H-2, $J_{1',2}$ 5.4 Hz, $J_{2,3}$ 9.3 Hz, $J_{1,2}$ 11.4 Hz), 12.6 (d, r, 1H, H-6', $J_{6,6'}$ 12.6 Hz); δ_C (D_2O, 100.6 MHz, DEPT, gHSQC) 11.7 (q, CH_3), 41.8 (t,

C-1), 62.4 (s, C-5), 63.3 (t, C-6), 67.4 (d, C-2), 69.2 (d, C-3), 72.8 (d, C-4); HRMS found 178.1078 ($C_7H_{16}NO_4$ requires 178.1079).

2,3,4,6-Tetra-*O*-benzyl-1,5-dideoxy-1,5-imino-D-glucitol (7):

DBU (4.2 eq, 0.375 mmol, 57.1 mg) was added to a solution 2,3,4,6-tetra-*O*-benzyl-*N*-chloro-1,5-dideoxy-1,5-imino-D-glucitol (**9**) (1.0 eq, 0.0896 mmol, 50 mg) in dry diethyl ether (2 mL) under N_2. After 2 h, the reaction mixture was filtered through a glass sinter, under nitrogen and concentrated *in vacuo* to give crude 2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-5,*N*-dehydro-1,5-imino-D-glucitol (**13**) as a pale orange oil (98 mg) which was identified by NMR and IR. The residue was dissolved in dry ether (2 mL), and $LiAlH_4$ added (5.0 eq, 0.448 mmol, 0.448 mL of a 1.0 M solution in THF). The reaction was quenched after 10 minutes by addition of NH_4Cl (saturated, 1 mL). The resulting mixture was diluted with ether (30 mL), washed with water (20 mL), the organic layer dried (Na_2SO_4), filtered and the solvent removed *in vacuo* to give a colourless oil. Flash chromatography of the crude product (30 : 70 ethyl acetate : hexane) gave 2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1,5-imino-D-glucitol (**7**) as a colourless oil (41 mg, 87 %) which formed a white solid on standing; δ_H ($CDCl_3$, 400 MHz, gCOSY) 1.86 (br, 1H, NH), 2.51 (dd, 1H, H-1, $J_{1,2}$ 10.2 Hz, $J_{1,1'}$ 12.2 Hz), 2.73 (ddd, 1H, H-5, $J_{5,6'}$ 2.7 Hz, $J_{5,6}$ 6.3 Hz, $J_{4,5}$ 9.4 Hz), 3.25 (dd, 1H, H-1', $J_{1',2}$ 4.88 Hz, $J_{1,1'}$ 12.0 Hz), 3.36 (dd, 1H, H-4, $J_{3,4}$ 8.8 Hz, $J_{4,5}$ 9.5 Hz), 3.47-3.55 (m, 2H, H-2, H-6), 3.56 (pt, 1H, H-3, $J_{2,3}$ 9.0 Hz, $J_{3,4}$ 9.0 Hz), 3.68 (dd, 1H, H-6', $J_{5,6'}$ 2.5 Hz, $J_{6,6'}$ 8.9 Hz), 4.43 (d, r, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.8 Hz), 4.47 (d, r, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.8 Hz), 4.50 (d, r, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.1 Hz), 4.67 (d, r, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.6 Hz), 4.71 (d, r, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.6 Hz), 4.86 (pt, 2H, 2 × PhC$\underline{H}_2$O, J_{HH} 10.5 Hz), 4.99 (d, r, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 10.9 Hz), 7.19-7.22 (m, 2H, 2 × aromatic), 7.27-7.38 (m, 18H, 18 × aromatic); δ_C ($CDCl_3$, 125.7 MHz, DEPT) 48.1 (t, C-1), 59.7 (d, C-5),

70.2 (t, C-6), 72.8, 73.3, 75.2, 75.7 (4 × t, 4 × Ph<u>C</u>H_2O), 80.0, 80.6, 87.3 (3 × d, C-2, C-3, C-4), 127.5, 127.63, 127.65, 127.72, 127.74, 127.82, 127.91, 127.99, 128.33, 128.35, 128.37, 128.38 (12 × d, 12 of 20 aromatic CH, others coincident), 137.9, 18.3, 138.4, 138.8 (4 × s, 4 × quaternary aromatic).

2,3,4,6-Tetra-*O*-benzyl-5-dehydro-5-deutero-1,5-dideoxy-1,5-imino-D-glucitol ([5-D]-7)

2,3,4,6-Tetra-*O*-benzyl-*N*-chloro-1,5-dideoxy-1,5-imino-D-glucitol (54.5 mg, 0.098 mmol) was dissolved in ether (2 ml). On addition of DBU (61.4 μl, 0.41 mmol) a white precipitate was formed. The reaction mixture was stirred at room temperature under argon. After 3h, t.l.c. (1:1, petrol:ethyl acetate) indicated complete consumption of starting material (R_f 0.7) to give a single intermediate (R_f 0.5). The white precipitate was removed by filtration under argon. Lithium aluminium deuteride (0.49 ml, 0.49 mmol of a 1M solution in ether) was added. The reaction mixture was stirred at room temperature under argon. After 20 min, t.l.c. (1:1 petrol:ethyl acetate) indicated the absence of the intermediate and the presence of a single product (R_f 0.2). Ammonium chloride (ca. 2 ml of a saturated aqueous solution) was added. The reaction mixture was diluted with ether (40 ml) and washed with water (30 ml). The aqueous layer was extracted with ether (30 ml). The organic extracts were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:1, petrol:ethyl acetate) to afford 2,3,4,6-tetra-*O*-benzyl-5-dehydro-5-deutero-1,5-dideoxy-1,5-imino-D-glucitol (**[5-D]-7**) (47.8 mg, 93%) as a pale yellow oil, $[\alpha]_D^{23}$ +24.3 (c, 0.5 in $CHCl_3$); ν_{max} (thin film) 3030 (s, NH), 2919 (s, CH)cm^{-1}; δ_H (400MHz, $CDCl_3$) 2.54 (1H, dd, $J_{1,1'}$ 12.3 Hz, $J1_{,2}$ 10.2 Hz, H-1), 3.27 (1H, dd, $J_{1',2}$ 4.8 Hz, H-1'), 3.38 (1H, d, $J_{3,4}$ 8.7 Hz, H-4), 3.49-3.61 (3H, m, H-2, H-3, H-6), 3.69 (1H, d, $J_{6,6'}$ 9.1 Hz, H-6'), 4.44-5.03 (8H,

m, 4 × C<u>H</u>$_2$Ph), 7.22-7.40 (20H, m, Ar-H); δ_C (100.6MHz, $CDCl_3$) 48.1 (t, C-1), 59.2 (equal intensity triplet, C-5), 70.2 (t, C-6), 72.8, 73.4, 75.2, 75.6 (4 × t, 4 × <u>C</u>H$_2$Ph), 80.0 (d, C-4), 80.7 (d, C-2), 87.3 (d, C-3), 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.3, 128.4 (8 × d, 8 of 15 Ar-CH), 138.0, 138.4, 138.5, 138.9 (4 × s, 4 x Ar-C); *m/z* (ESI) 525 ($M+H^+$, 100%); HRMS (CI) Calcd. for $C_{34}H_{37}NO_4D$ (MH^+) 525.2864. Found 525.2842.

2,3,4,6-Tetra-*O*-benzyl-D-glucitol:

2,3,4,6-Tetra-*O*-benzyl-D-glucose (**17**) (0.00924 mol, 5 g) was dissolved in THF (70 mL). Distilled water (35 mL) was added, and N_2 bubbled through the solution for 30 seconds. Sodium borohydride was added (10 eq, 0.0924 mol, 3.50 g) in one portion, and the reaction stirred under N_2 for 24, after which tlc analysis (5:4, EtOAc : hexane) revealed complete conversion of starting material (R_f 0.6 (two spots)) to product (R_f 0.3). The reaction was quenched after 24h by addition of NH_4Cl (aq, saturated) until effervescence ceased. The THF was removed *in vacuo*, then diethyl ether added (150 mL), and the organic layer washed with H_2O (3 × 50 mL). The organic layers were isolated, dried ($MgSO_4$), filtered, and the solvent removed to give a colourless oil which was purified by flash chromatography to yield 2,3,4,6-tetra-*O*-benzyl-D-glucitol (4.98 g, 100%) as a colourless oil: $[\alpha]_D^{26}$ + 11.8 (c = 1, $CHCl_3$) {lit[1] $[\alpha]_D^{19}$ + 10.3 (c = 4.5, $CHCl_3$)}; *m/z* 565 (ES, $[M+Na]^+$, 100 %, MeOH), 1107 ($[2M+Na]^+$, 40 %); ν_{max} (film)/cm^{-1}: 2867, 2923 (aliphatic C-H stretch), 3028, 3061 (aromatic C-H stretch), 3447 (br, O-H stretch); δ_H ($CDCl_3$, 500 MHz, gCOSY, gHSQC) 2.13 (pt, 1H, CH_2O<u>H</u>, J_{HH} 4.8 Hz), 2.97 (d, 1H, CHO<u>H</u>, J_{HH} 5.5 Hz), 3.57 (pdt, 1H, J_{HH} 5.0 Hz, $J_{1,1'}$ 11.4 Hz), 3.65 (m, 2H, H-6, H-6') 3.71-3.83 (m, 3H, H-1, H-2, H-4), 3.90 (dd, 1H, H-3, J_{HH} 3.70 Hz, J_{HH} 6.4 Hz), 4.04 (m, 1H, H-5), 4.52 (d, r, 1H, one of PhC<u>H</u>$_2$O, J_{HH} 11.8 Hz), 4.55 (d, r, 1H, one of PhC<u>H</u>$_2$O, J_{HH} 11.6 Hz), 4.56 (d, r, 1H, one of PhC<u>H</u>$_2$O,

J_{HH} 11.8 Hz), 4.60 (d, r, 1H, one of PhC$\underline{H}_2$O, J_{HH} 11.6 Hz), 4.64 (d, r, 1H, one of PhC$\underline{H}_2$O, J_{HH} 11.6 Hz), 4.67 (d, r, 1H, one of PhC$\underline{H}_2$O, J_{HH} 11.3 Hz), 4.68 (d, r, 1H, one of PhC$\underline{H}_2$O, J_{HH} 11.6 Hz), 4.73 (d, r, 1H, one of PhC$\underline{H}_2$O, J_{HH} 11.3 Hz), 7.21-7.39 (m, 20H, aromatic CH); δ_C ($CDCl_3$, 125.7 MHz, DEPT, gHSQC) 62.0 (t, C-1), 70.8, (d, C-5), 71.2 (t, C-6), 73.2, 73.4, 73.6, 74.6 (4 × t, 4 × Ph$\underline{C}H_2$O), 77.4, 79.2 (2 × d, C-2, C-4), 79.6 (d, C-3), 127.92, 127.98, 128.04, 128.07, 128.12, 128.28, 128.55, 128.57, 128.59, 128.60, 128.61 (d, 11 of 15 aromatic $\underline{C}$H, others coincident), 137.93, 137.97, 138.10, 138.27 (s, 4 × quaternary aromatic).

2,3,4,6-Tetra-*O*-benzyl-1-*O*-tert-butyldiphenylsilyl-D-glucitol (18):

2,3,4,6-Tetra-*O*-benzyl-D-glucitol (1.0 eq, 2.04 mmol, 1.11 g) was dissolved in dry DMF (3 mL), and imidazole (2.2 eq, 4.50 mmol, 306 mg) added with stirring under N_2. *Tert*-butyldiphenylsilyl chloride (1.3 eq, 2.66 mmol, 0.689 mL) was added dropwise with stirring. The reaction was stirred under N_2 for 24 h when tlc analysis (50:50, EtOAc : hexane) revealed complete conversion of starting material to product. The reaction was stopped after 24 h removal of the solvent and the residue purified by flash chromatography (15 : 85 EtOAc : hexane) to yield 2,3,4,6-tetra-*O*-benzyl-1-*O*-tert-butyldiphenylsilyl-D-glucitol (**18**) as a colourless oil (1.58 g, 99%): $[\alpha]_D^{20}$ +19.5 (c = 1, $CHCl_3$); ν_{max} (film)/cm^{-1}: 3490 (br, O-H stretch), 3806, 3065, 3029 (aromatic C-H stretch), 2929, 2857 (aliphatic C-H stretch); δ_H ($CDCl_3$, 400 MHz, gCOSY, gHSQC) 1.06 (s, 9H, 2 × ($C\underline{H}_3$)$_3$CSiPh$_2$), 2.94 (d, 1H, OH, $J_{H,H}$ 4.8 Hz), 3.60-3.63 (m, 2H, H-6, H-6'), 3.76-3.82 (m, 2H, H-1, H-2), 3.85 (dd, 1H, J 4.9 Hz, J 9.6 Hz), 3.91 (dd, 1H, H-1, $J_{1,2}$ 4.6 Hz, $J_{1,1'}$ 10.1 Hz), 3.96 (dpt, 1H, H-5, J_{HH} 4.4 Hz, J_{HH} 10.7 Hz), 4.00 (pt, 1H, J_{HH} 4.4 Hz), 4.47-4.56 (m, 5H, 5 × PhC$\underline{H}_2$O), 4.64-4.67 (m, 3H, 3 × PhCH_2O), 7.10-7.42 (m, 26H, aromatic CH), 7.63-7.66 (4H, aromatic CH); δ_C ($CDCl_3$, 100.6 MHz, DEPT, gHSQC) 19.2 (s, (CH_3)$_3\underline{C}$SiPh$_2$), 27.0 (q, ($\underline{C}H_3$)$_3$CSiPh$_2$),

63.2 (t, C-1), 71.1 (d, C-5), 71.3 (t, C-6), 73.1, 73.4, 73.5, 74.3 (4 × t, 4 × Ph<u>C</u>H_2O), 77.5 (d, C-2), 78.0, 79.7 (2 × d, C-3, C-4), 127.66, 127.76, 127.81, 127.83, 127.93, 128.07, 128.37, 128.40, 128.42, 128.49, 128.56, 129.80, 129.82, 135.75 (14 × d, 14 of 25 aromatic CH, others coincident), 133.40, 133.48 (2 × s, 2 × quaternary aromatic <u>C</u>Si), 138.20, 138.24, 138.29, 138.49 (4 × s, 4 × quaternary aromatic).

2,3,4,6-Tetra-*O*-benzyl-1-*O*-tert-butyldiphenylsilyl-5-*O*-methanesulphonyl-D-glucitol:

2,3,4,6-tetra-*O*-benzyl-1-*O-tert*-butyldiphenylsilyl-D-glucitol (**18**) (1.0 eq, 1.28 mmol, 1.00 g) was dissolved in dry pyridine (20 mL) under N_2. Methanesulfonyl chloride (1.5 eq, 0.149 mL, 1.92 mmol,) was added, and the mixture stirred under N_2 for 72 h; no change in R_f (EtOAc/hexane) was observed. The reaction mixture was diluted with $CHCl_3$ (500 mL) and washed with H_2O (2 × 250 mL) and the aqueous washings extracted with $CHCl_3$ (100 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and the solvent removed. The resultant oil was purified by flash chromatography (15:85 EtOAc : hexane) to yield 2,3,4,6-tetra-*O*-benzyl-1-*O-tert*-butyldiphenylsilyl-5-methanesulphonyl-D-glucitol as a colourless oil (1.08 g, 97%): $[\alpha]_D^{25}$ + 15.7 (c, 1, in $CHCl_3$); *m/z* 881 (ES, $[M+Na]^+$, 100%, MeOH); ν_{max} (film)/cm^{-1}: 2857, 2929, 2953 (aliphatic C-H stretch), 3030, 3066 (aromatic C-H stretch); δ_H ($CDCl_3$, 500 MHz, gCOSY, gHSQC) 2.87 (s, 3H, CH_3SO_2), 3.75-3.81 (m, 3H, H-1, H-1, H-6), 3.83 (pt, 1H, J_{HH} 5.2 Hz), 3.86 (dd, 1H, H-6', $J_{5,6'}$ 2.5 Hz, $J_{6,6'}$ 11.2 Hz), 3.89-3.94 (m, 1H, H-1'), 4.04 (dd, 1H, J_{HH} 2.7 Hz, J_{HH} 5.7 Hz), 4.41 (d, r, 1H, PhC<u>H</u>$_2$O, J_{HH} 11.7 Hz), 4.44 (d, r, 1H, PhC<u>H</u>$_2$O, J_{HH} 11.7 Hz), 4.50 (d, r, 1H, PhC<u>H</u>$_2$O, J_{HH} 11.2 Hz), 4.57 (d, r, 1H, PhC<u>H</u>$_2$O, J_{HH} 11.6 Hz), 4.60 (s, 2H, PhC<u>H</u>$_2$O), 4.68 (d, r, 1H, PhC<u>H</u>$_2$O, J_{HH} 11.2 Hz), 4.98 (dpt, 1H, H-5, $J_{5,6'}$ 2.6 Hz, $J_{4,5}$ 7.9 Hz, $J_{5,6}$ 7.9 Hz), 7.14-7.43 (m, 26H, aromatic CH), 7.65 (pt, 4H, aromatic CH, J_{obs} 8.2 Hz); δ_C

($CDCl_3$, 125.7 MHz, DEPT, gHSQC) 19.3 (s, $(CH_3)_3\underline{C}Si$), 27.0 (q, $(\underline{C}H_3)_3CSi$), 38.5 (q, CH_3SO_2), 63.3 (t, C-1), 69.2 (t, C-6), 73.3, 73.4, 74.7, 74.8 (4 × t, 4 × $Ph\underline{C}H_2O$), 78.7, 80.0, 80.1 (3 × d, C-2, C-3, C-4), 83.6 (d, C-5), 127.7, 127.79, 127.83, 127.89, 127.95, 128.1, 128.2, 128.41, 128.44, 128.45, 128.5, 128.6, 129.80, 129.85, 135.78, 135.82 (16 × d, 16 of 30 aromatic CH, others coincident), 133.41, 133.45 (2 × s, 2 × quaternary aromatic CSi), 137.8, 137.9, 138.1, 138.5 (4 × s, 4 × quaternary aromatic).

5-azido-2,3,4,6-tetra-*O*-benzyl-1-*O*-tert-butyldiphenylsilyl-5-deoxy-L-iditol:

Method 1: 2,3,4,6-Tetra-*O*-benzyl-1-*O-tert*-butyldiphenylsilyl-5-methanesulphonyl-D-glucitol (1.0 eq, 0.0439 mmol, 37.7 mg) was placed in dry flask under nitrogen and a solution of tetrabutylammonium azide (TBAAZ) (10 eq, 0.439 mmol, 124.6 mg) in dry toluene (1 mL) was added and the mixture stirred briefly at room temperature to dissolve all reactants. The mixture was then refluxed at reflux for 90 minutes until tlc indicated full consumption of starting material. The solution was cooled to room temperature, diluted with dichloromethane (40 mL), and washed with water (2 × 20 mL), and the organic phase dried ($MgSO_4$), filtered, and the solvent removed to give a pale yellow oil. Repeated flash column chromatography of the crude mixture (5 : 95 EtOAc : hexane and 10 : 90 diethyl ether : hexane) gave 5-Azido-2,3,4,6-tetra-*O*-benzyl-1-*O*-tert-butyldiphenylsilyl-5-deoxy-L-iditol (8.1 mg, 23 %).

Method 2: 1-*O-tert*-butyldiphenylsilyl-2,3,4,6-tetra-*O*-benzyl-D-glucitol (**18**) (1.0 eq, 1.28 mmol, 1.00 g) was placed in a round bottom flask with dry toluene (20 mL), and freshly prepared HN_3 solution added (2.5 eq, 3.21 mmol, 1.79 mL of a 1.79 M solution in toluene) and the solution stirred under nitrogen for 10 minutes. In a separate flask triphenylphosphine (2.5 eq, 3.20 mmol, 840 mg) was dissolved in dry toluene (20 mL), and DIAD added slowly (2.5 eq, 3.20 mmol, 647 mg, 630 μl), and the resultant mixture stirred under nitrogen for 15 minutes. The prepared solution of

HN_3 and 1-*O*-*tert*-butyldiphenylsilyl-2,3,4,6-*O*-benzyl-D-glucitol (**18**) was added over 5 minutes, and the formation of a white precipitate was observed. The resultant mixture was stirred under nitrogen for 3 h after which time tlc indicated complete consumption of starting material. The reaction was stopped by addition of NaOH (aq, 3M, 4 mL), then the mixture was diluted with diethyl ether (250 mL) and washed with NaOH (aq) (0.5 M, 2 × 150 mL), and the organic layer dried ($MgSO_4$), filtered, and the solvent removed to give a colourless oil which was purified by flash chromatography (5 : 95 diethyl ether : hexane) to give 5-azido-2,3,4,6-tetra-*O*-benzyl-1-*O*-tert-butyldiphenylsilyl-5-deoxy-L-iditol as a colourless oil (894 mg) (87%): $[\alpha]_D^{24}$ + 23.9 (c = 1, $CHCl_3$); *m/z* 828 (ES, $[M+Na]^+$, 100%, MeOH), 785 ($[M-HN_3+Na]^+$, 15%); ν_{max} (film)/cm^{-1}: 2097 (azide stretch), 2857, 2929, 2955 (aliphatic C-H stretch), 3030, 3066, 3088 (aromatic C-H stretch); δ_H ($CDCl_3$, 500 MHz, gCOSY, gHSQC) 1.06 (s, 9H, $(C\underline{H}_3)_3CsiO$), 3.21 (ddd, 1H, H-5, $J_{5,6'}$ 3.0 Hz $J_{5,6}$ 4.6 Hz, $J_{4,5}$ 7.7 Hz), 3.31 (dd, (1H, 1H, H-6, $J_{5,6}$ 4.7 Hz, $J_{6,6'}$ 9.5 Hz), 3.50-3.56 (m, 2H, H-2, H-6'), 3.79, dd, 1H, H-4, $J_{3,4}$ 3.0 Hz, $J_{4,5}$ 7.7 Hz), 3.84 (dd, r, 1H, H-1, $J_{1,2}$ 5.6 Hz, $J_{1,1'}$ 10.5 Hz), 3.91 (dd, r, 1H, H-1', $J_{1',2}$ 6.5 Hz, $J_{1,1'}$ 10.6 Hz), 4.28 (d, r, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 12.0 Hz), 4.36 (d, r, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.8 Hz), 4.39 (d, r, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.8 Hz), 4.51 (d, r, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.5 Hz), 4.59 (d, r, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.8 Hz), 4.63 (d, r, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.1 Hz), 4.74 (pt, 2H, 2 × $PhC\underline{H}_2O$, J_{HH} 11.8 Hz), 7.15-7.24 (m, 26H, aromatic), 7.63-7.70 (m, 4H, aromatic); δ_C ($CDCl_3$, 125.7 MHz, DEPT, gHSQC) 19.3 (s, $(CH_3)_3\underline{C}siO$), 27.0 (q, $(\underline{C}H_3)_3CsiO$), 61.4 (d, C-5), 62.4 (t, C-1), 70.0 (t, C-6), 72.5, 73.3, 75.0, 75.4 (4 × t, 4 × $Ph\underline{C}H_2O$), 77.9 (d, C-2), 78.5 (d, C-4), 79.1 (d, C-3), 127.7, 128.0, 128.1, 128.5, 129.9, 130.0, 135.7, 135.9 (8 × d, 8 of 30 aromatic CH, others coincident), 133.4 (s, aromatic CSi), 137.9, 138.0, 138.3, 138.4 (4 × s, 4 × quaternary aromatic); HRMS found 828.3877 ($C_{50}H_{55}N_3O_5SiNa$ requires 828.3809).

5-azido-2,3,4,6-tetra-*O*-benzyl-5-deoxy-L-iditol:

5-Azido-2,3,4,6-*O*-benzyl-1-*O*-tert-butyldiphenyl-silyl-5-deoxy-L-iditol (1.0 eq, 0.689 mmol, 555 mg) was dissolved in THF (14 mL), and TBAF was added (1.5 eq, 1.03 mmol, 1.03 mL of a 1 M solution in THF), and the resultant solution stirred under nitrogen for 3 h, after which time tlc showed complete consumption of starting material. The reaction mixture was concentrated. The residue was dissolved in DCM (150 mL) and washed with water (2 × 50 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to give a colourless oil which was purified by flash chromatography (20 : 80 EtOAc : hexane) to give 5-azido-2,3,4,6-*O*-benzyl-5-deoxy-L-iditol, as a colourless oil (390 mg, 100 %); $[\alpha]_D^{20}$ +18.3 (c, 1, $CHCl_3$); *m/z* 590 (ES, $[M+Na]^+$, 100%, MeOH), 1157.5 ($[2M+Na]^+$, 4%); ν_{max}/cm^{-1} (film): 3440 (br, OH), 3088, 3062, 3030 (aromatic C-H stretch), 2926, 2866 (aliphatic C-H stretch), 2098 (azide stretch); δ_H ($CDCl_3$, 500 MHz, gCOSY, gHSQC) 1.91 (s, br, 1H, OH), 3.46 (dd, 1H, H-6, $J_{5,6}$ 5.0 Hz, $J_{6,6'}$ 9.3 Hz), 3.54 (dd, 1H, H-6', $J_{5,6'}$ 7.2 Hz, $J_{6,6'}$ 9.3 Hz), 3.56-3.59 (m, 2H, H-2, H-5), 3.64 (m, 1H, H-1), 3.75 (m, 1H, H-1'), 3.88 (dd, r, 1H, H-3 or H-4, J_{HH} 3.0 Hz, J_{HH} 7.0 Hz), 3.86 (dd, r, 1H, H-3 or H-4, J_{HH} 4.2, J_{HH} 7.0 Hz), 4.38 (d, r, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.9 Hz), 4.42 (d, r, 1H, 1 × $PhCH_2O$, J_{HH} 11.9 Hz), 4.54-4.60 (m, 3H, 3 × $PhCH_2O$), 4.62 (d, r, 1H, 1 × $PhCH_2O$, J_{HH} 11.3 Hz), 4.67 (d, r, 1H, 1 × $PhCH_2O$, J_{HH} 11.3 Hz), 4.47 (d, r, 1H, 1 × $PhCH_2O$, J_{HH} 11.6 Hz), 7.22-7.33 (m, 20H, aromatic CH); δ_C ($CDCl_3$, 125.7 MHz, DEPT, gHSQC) 61.1 (d, C-5), 61.5 (t, C-1), 69.6 (t, C-6), 72.5, 73.4, 74.8, 74.9 (4 × t, 4 × $Ph\underline{C}H_2O$), 78.0 (d, C-2), 78.1, 79.1 (2 × d, C-3, C-4), 127.8, 127.92, 127.93, 128.1, 128.4, 128.55, 128.57, 128.63, 128.64 (9 × d, 9 of 20 aromatic CH, others coincident), 137.8, 137.88, 137.90, 138.0 (4 × s, 4 × quaternary aromatic); HRMS found 568.2813 ($C_{34}H_{38}O_5$ requires 568.2811).

5-Azido-2,3,4,6-tetra-*O*-benzyl-5-deoxy-D-idose (19):

5-Azido-2,3,4,6-*O*-benzyl-5-deoxy-L-iditol (1.0 eq, 0.074 mmol, 42 mg) was placed in a round bottom flask with dried powdered molecular sieves (4Å, 100 mg) and PCC (4.0 eq, 0.297 mmol, 62 mg), and dry DCM added (3.0 mL). The mixture was stirred under nitrogen for 1.5 h, when tlc indicated complete consumption of starting material. The reaction was stopped by addition of diethyl ether (10 mL), and the mixture filtered through a celite plug, then concentrated, and the resultant brown/orange oil purified by flash chromatography (10 : 90 EtOAc : hexane) to give 5-azido-2,3,4,6-*O*-benzyl-5-deoxy-L-idose (**19**) as a colourless oil (36 mg, 87%); $[\alpha]_D^{23}$ + 20.7 (c, 1, in $CHCl_3$); *m/z* 588 (ES, $[M+Na]^+$, 100%, MeOH); ν_{max} (film)/cm^{-1}: 1729 (C=O stretch), 2098 (azide stretch), 2863, 2922 (aliphatic C-H stretch), 3031, 3063, 3088 (aromatic C-H stretch); δ_H ($CDCl_3$ 400 MHz, gCOSY, gHSQC) 3.44 – 3.57 (m, 3H, H-5, H-6, H-6'), 3.87 (pt, 1H, H-4, $J_{3,4}$ 5.0 Hz, $J_{4,5}$ 5.0 Hz), 3.93 (d, r, 1H, H-2, $J_{2,3}$ 4.7 Hz), 3.97 (pt, r, 1H, H-3, $J_{2,3}$ 4.8 Hz, $J_{3,4}$ 4.8 Hz), 4.42 (pd, 2H, 2 of PhC$\underline{H}_2$O, J_{HH} 1.87 Hz), 4.50 (d, r, 1H, 1 of PhC$\underline{H}_2$O, J_{HH} 11.9 Hz), 4.55 (m, 3H, 3 of PhC$\underline{H}_2$O), 4.64 (d, r, 1H, 1 of PhC$\underline{H}_2$O, J_{HH} 11.2 Hz), 4.83 (d, r, PhC$\underline{H}_2$O, J_{HH} 11.9 Hz), 7.18 (m, 2H, 2 of aromatic C$\underline{H}$), 7.25-7.37 (m, 18H, 18 of aromatic C$\underline{H}$), 9.67 (s, 1H, H-1); δ_C (100.6 MHz, $CDCl_3$, DEPT, gHSQC), 61.6 (d, C-5), 69.3 (t, C-6), 73.2, 73.4, 74.2, 74.6 (4 × d, 4 × Ph$\underline{C}H_2$O), 77.4 (d, C-4), 79.3 (d, C-3), 80.9 (d, C-2), 127.8, 127.95, 127.99, 128.29, 128.38, 128.46, 128.48, 128.52, 128.58, 12864, 128.75 (12 × d, 12 × aromatic $\underline{C}$H, others coincident), 136.9, 137.2, 137.6, 137.7 (4 × s, 4 × quaternary aromatic), 200.9 (d, C-1).

7-azido-4,5,6,8-tetra-*O*-benzyl-1,2,7-trideoxy-L-glycero-L-ido-octitol and 7-azido-4,5,6,8-tetra-*O*-benzyl-1,2,7-trideoxy-L-glycero-L-lyxo-octitol (mixture of isomers):

5-Azido-2,3,4,6-*O*-benzyl-5-deoxy-L-idose (**19**) (1.0 eq, 0.437 mmol, 247 mg) was dissolved in dry diethyl ether (10 mL), and EtMgBr added (1.5 eq, 0.655 mmol, 218 μL, of a 3.0 M solution in diethyl ether (Aldrich)). The reaction was quenched after 90 minutes by addition of NH_4Cl (saturated, aq, 1 mL). The mixture was diluted with diethyl ether (50 mL), washed with water (30 mL) then brine (30 mL) and the organic layer dried ($MgSO_4$), filtered and concentrated. The resultant colourless oil was purified by flash chromatography (10:90, EtOAc : hexane) to give as an intractable mixture of isomers 7-azido-4,5,6,8-tetra-*O*-benzyl-1,2,7-trideoxy-L-glycero-L-ido-octitol and 7-azido-4,5,6,8-tetra-*O*-benzyl-1,2,7-trideoxy-L-glycero-L-lyxo-octitol (dr 1:3, 183 mg, 70 %); $[\alpha]_D^{26}$ +9.3 (c, 0.7 in $CHCl_3$); ν_{max} (film)/cm^{-1}: 2098 (azide stretch), 2869, 2925, 2959 (aliphatic C-H stretch), 3030, 3063, 3090 (aromatic C-H stretch), 3436 (br, O-H stretch); δ_H (400MHz, $CDCl_3$) 0.86 (3H, t, ^3J 7.5 Hz, CH_3a), 0.96 (3H, t, ^3J 7.5 Hz, CH_3b), 1.36-1.55 (3H, m, C<u>H</u>$_2$CH$_3$a, C<u>H</u>H'CH$_3$b), 1.60-1.68 (1H, m, CH<u>H</u>'CH$_3$b), 1.88-2.13 (1H, br, OH), 2.89-3.09 (1H, br, OH), 3.40 (1H, dd, ^3J 3.0 Hz, ^3J' 6.5 Hz, H-4b), 3.45 (1H, dd, ^3J 2.7 Hz, ^3J' 5.5 Hz, H-4a), 3.49-3.6 (4H, m, H-8a, H-8'a, H-8b, H-8'b), 3.62-3.66 (2H, m, H-3a, H-7), 3.75-3.80 (1H, m, H-3b), 3.82-3.89 (2H, m, H-6, H-7), 3.96-4.03 (3H, m, H-5a, H-5b, H-6), 4.30-4.80 (16H, m, 8 x C<u>H</u>$_2$Ph), 7.27-7.37 (40H, m, 40 x Ar-H); δ_C (100.6MHz, $CDCl_3$) 9.9 (q, C-1b), 10.2 (q, C-1a), 26.7, 27.7 (2 × t, 2 × C-2), 61.2, 61.3 (2 × d, 2 × C-7), 69.5, 69.9, (2 × t, 2 × C-8), 71.7, 71.9 (2 × d, 2 × C-3), 72.4, 73.2, 74.0, 74.4, 74.5, 74.5, 74.6, 74.9 (8 × t, <u>C</u>H$_2$Ph), 78.0, 78.1, 78.2, 78.4, 78.8 (5 × d, C-4b, C-5a, C-5b, C-6a, C-6b), 79.9 (d, C-4a), 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5 (11 × d,

Ar-CH), 137.4, 137.6, 137.7, 137.7, 137.8, 137.9, 138.1 (7 × s, Ar-C); *m/z* 618 (ES, $[M+Na]^+$, 100%, MeOH); HRMS found 596.3122 ($C_{36}H_{42}N_3O_5$ requires 596.3124).

7-azido-4,5,6,8-tetra-*O*-benzyl-1,2,7-trideoxy-L-glycero-L-ido-oct-3-ulo-itol (20): 7-Azido-4,5,6,8-tetra-*O*-benzyl-1,2,7-trideoxy-L-glycero-L-ido-octitol and 7-azido-4,5,6,8-tetra-*O*-benzyl-1,2,7-trideoxy-L-glycero-L-lyxo-octitol (mixture of isomers) (1.0 eq, 0.307 mmol, 183 mg), PCC (2.5 eq, 0.766 mmol, 165.2 mg), and molecular sieves (4 Å, powdered, 200 mg), were stirred in dry DCM (6 mL) under nitrogen. The reaction was stopped after 2 h by triturating with diethyl ether (30 mL), and filtering through celite. The mixture was concentrated and the resultant brown oil purified by flash chromatography (7.5 : 93.5 EtOAc:hexane) to give 7-azido-4,5,6,8-tetra-*O*-benzyl-1,2,7-trideoxy-L-glycero-L-ido-oct-3-ulo-itol (**20**) (132 mg, 72 %); $[\alpha]_D^{22}$ + 33.8 (c, 1, in $CHCl_3$); ν_{max}/cm^{-1}(film), 1713 (C=O stretch), 2098 (azide stretch), 2852, 2920 (aliphatic C-H stretch), 3030, 3064, 3088 (aromatic C-H stretch); *m/z* 616 (ES $[M+Na]^+$, 100 %, MeOH), 1209.5 ($[2M+Na]^+$, 40 %); δ_H ($CDCl_3$, 500 MHz, gCOSY, gHSQC), 0.85 (pt, 3H, $CH_2C\underline{H}_3$, J_{HH} 7.2 Hz), 2.40 (dq, r, 1H, H-2, $^3J_{HH}$ 7.2 Hz, $^2J_{HH}$ 18.8 Hz), 2.47 (dq, r, 1H, H-2', $^3J_{HH}$ 7.2 Hz, $^2J_{HH}$ 18.8 Hz), 3.23 (ddd, 1H, H-7, $J_{6,7}$ 3.6 Hz, $J_{7,8}$ 5.1 Hz, $J_{7,8'}$ 7.4 Hz), 3.38 (dd, r, 1H, H-8, $J_{7,8}$ 5.1 Hz, $J_{8,8'}$ 9.7 Hz), 3.47 (dd, r, 1H, H-8', $J_{7,8'}$ 7.3 Hz, $J_{8,8'}$ 9.6 Hz), 3.78 (dd, 1H, H-6, $J_{5,6}$ 3.6 Hz, $J_{6,7}$ 3.6 Hz), 3.89 (d, 1H, H-4, $J_{4,5}$ 3.5 Hz), 3.97 (dd, 1H, H-5, $J_{4,5}$ 3.5 Hz, $J_{5,6}$ 7.2 Hz), 4.26 (d, r, 1 × $PhC\underline{H}_2O$, J_{HH} 11.8 Hz), 4.31 (d, r, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.9 Hz), 4.35 (d, r, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.9 Hz), 4.38 (d, r, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.2 Hz), 4.47 (d, r, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.5 Hz), 4.58 (d, r, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.2 Hz), 4.64 (m, 2H, 2 × $PhC\underline{H}_2O$, J_{HH} 11.8 Hz), 7.10-7.28 (m, 20H, aromatic CH); δ_C ($CDCl_3$, 125.7 MHz, DEPT, gHSQC), 7.16 (q, C-1), 33.6 (t, C-2), 61.1 (d, C-7), 69.5 (t, C-8), 73.3, 73.4, 75.0, 75.1 (4 × t, 4 × $Ph\underline{C}H_2O$), 78.1 (d, C-6), 80.7 (d, C-5), 82.9 (d, C-4), 127.76,

127.87, 128.00, 128.10, 128.40, 128.45, 128.49, 128.52, 128.56, 128.59, 128.73 (11 × d, 11 of 20 aromatic CH, others coincident), 136.8, 137.7, 137.8, 138.0 (4 × s, 4 × quaternary aromatic), 211.5 (s, C-3); HRMS found 611.3237 ($C_{36}H_{39}N_3O_5NH_4$ requires 611.3233).

4,5,6,8-Tetra-*O*-benzyl-1,2,3,7-tetra-deoxy-3,7-imino-L-glycero-L-lyxo-octitol or 2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1β-ethyl-1,5-imino-L-iditol (15) and 4,5,6,8-tetra-*O*-benzyl-1,2,3,7-tetra-deoxy-3,7-imino-L-glycero-L-ido-octitol or 2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1α-ethyl-1,5-imino-L-iditol (16):

7-Azido-4,5,6,8-tetra-*O*-benzyl-1,2,7-trideoxy-L-glycero-L-ido-oct-3-ulo-itol (1.0 eq, .0337 mmol, 20.0 mg) and triphenylphosphine (1.5 eq, 0.0507 mmol, 13.3 mg) were dissolved in dry diethyl ether (1 mL) and stirred under nitrogen. The reaction was followed by tlc, and after six hours indicated complete consumption of starting material. The mixture was concentrated *in vacuo* and the residue dissolved in methanol (2.5 mL), and sodium borohydride added (5.0 eq, 0.167 mmol, 6.3 mg) and the mixture stirred. After a further 16 h, the reaction mixture was concentrated, then the residue dissolved in DCM (30 mL), and washed with water/NaOH (aq, 3 M), (pH 11-13) (2 × 20 mL), then brine (satd, 20 mL). The organic phase was isolated, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography to give 4,5,6,8-tetra-*O*-benzyl-1,2,3,7-tetra-deoxy-3,7-imino-L-glycero-L-lyxo-octitol (**15**) (tetra-*O*-benzyl adenophorine) (3.1 mg, 17 %) and 4,5,6,8-tetra-*O*-benzyl-1,2,3,7-tetra-deoxy-3,7-imino-L-glycero-L-ido-octitol (**16**) (tetra-*O*-benzyl-6-epi-adenophorine) (5.9 mg, 32 %).

4,5,6,8-Tetra-*O*-benzyl-1,2,3,7-tetra-deoxy-3,7-imino-L-glycero-L-lyxo-octitol or 2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1β-ethyl-1,5-imino-L-iditol (15):

Method 1: A solution of 2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1α-ethyl-1,5-imino-L-iditol (**16**) (37 mg, 0.067 mmol) and *N*-chlorosuccinimide (11 mg, 1.2 eq) in DCM (1 mL) was stirred under nitrogen. After 14h tlc showed the conversion to a less polar product and the reaction solution was diluted with DCM (10 mL), washed with water (2 × 5 mL), dried (Na_2SO_4), filtered and the solvent removed. The crude *N*-chloramine was purified by passing through a plug (15% EtOAc:hexane) and dissolved in Et_2O (3 mL) under nitrogen. The resulting solution was cooled to –78˚C and lithium tetramethylpiperidide (0.62 mL of a ~ 0.13 M solution, 1.2 eq based on complete conversion of **16**) added dropwise. After 2 h the reaction mixture was warmed to room temperature, diluted with Et_2O (10 mL), washed with water (2 × 10 mL), dried (Na_2SO_4), filtered and the solvent removed. T.l.c and NMR of the crude product mixture indicated two major products, consistent with the poor regioselectivity in this elimination step. The crude mixture was dissolved in Et_2O (3 mL), $LiAlH_4$ (0.27mL of a 1M solution in THF, 4.0 eq based on complete conversion of **16**) was added to the resulting solution and stirred under nitrogen for 30 min. The reaction mixture was quenched with NH_4Cl (aq, saturated, 1 mL), diluted with Et_2O (20 mL) and washed with water (2 × 10 mL). The organic layer was separated, dried (Na_2SO_4), filtered and the solvent removed. The crude product mixture NMR indicated more than one diastereomer, consistent with the poor regioselectivity observed in the elimination step. From this mixture 4,5,6,8-tetra-*O*-benzyl-1,2,3,7-tetra-deoxy-3,7-imino-L-glycero-L-lyxo-octitol (**15**) (9 mg, 24% from **16**) was was purified by flash column chromatography (15 : 85 EtOAc : hexane).

Method 2: 7-Azido-4,5,6,8-tetra-*O*-benzyl-1,2,7-trideoxy-L-glycero-L-ido-octitol (**20**) (1.0 eq, 0.0185 mmol, 11.0 mg), was dissolved in dry diethyl ether (1.5 mL) and

triphenylphosphine added (3.5 eq, 0.0656 mmol, 17.2 mg). The mixture was stirred under nitrogen for 3 h when tlc showed consumption of starting material. After 3 h lithiumaluminium hydride was added (4.0 eq, 74 μL of a 1.0 M solution in THF). The mixture was stirred for thirty minutes before quenching with NH_4Cl (aq, saturated, 1 mL). The mixture was diluted with diethyl ether (30 mL), and washed with water (2 × 10 mL). The organic layer was dried (Na_2SO_4), filtered, and the solvent removed. The resultant colourless oil was purified by flash column chromatography (15 : 85 EtOAc : hexane) to yield 4,5,6,8-tetra-*O*-benzyl-1,2,3,7-tetra-deoxy-3,7-imino-L-glycero-L-lyxo-octitol (**15**) as the only diastereoisomer (7.0 mg, 69 %); $[\alpha]_D^{25}$ –34.1 (c, 1, in $CHCl_3$); *m/z* 552 (ES, $[M+H]^+$, 100 %, MeOH), 574 ($[M+Na]^+$, 20 %); ν_{max}/cm^{-1}(film), 2856, 2919, 2959 (aliphatic C-H stretch), 3030, 3063, 3088 (aromatic C-H stretch); δ_H ($CDCl_3$, 500 MHz, gCOSY, gHSQC) 0.85 (t, 3H, C<u>H</u>$_3$), 1.18-1.29 (m, 1H, H-2), 1.79-1.88 (m, 1H, H-2'), 2.60 (dpt, 1H, H-3, $J_{2,3}$ 2.6 Hz, $J_{3,4}$ 9.1 Hz), 3.07 (t, 1H, H-4, $J_{3,4}$ 9.1 Hz, $J_{4,5}$ 9.1 Hz), 3.46-3.59 (m, 3H, H-5, H-7, H-8), 3.69 (pt, 1H, H-6, $J_{5,6}$ 10.0 Hz, $J_{6,7}$ 10.0 Hz), 3.72 (dd, 1H, H-8', $J_{7,8'}$ 5.8 Hz, $J_{8,8'}$ 9.6 Hz); δ_C ($CDCl_3$, 125.7 MHz, DEPT, gHSQC), 10.3 (q, C-1), 29.8 (t, C-2), 54.0, 54.2 (2 × d, C-3, C-7), 65.4 (t, C-8), 72.8, 73.7, 75.6, 75.7 (4 × t, 4 × PhC<u>H</u>$_2$O), 80.8, 83.9 (2 × d, C-5, C-6), 83.5 (d, C-4), 127.7, 127.9, 128.49, 128.54, 128.57, 128.63 (6 × d, 6 of 20 aromatic C-H, others coincident), 138.3, 138.4, 138.6, 139.0 (4 × s, 4 × quaternary aromatic); HRMS found 552.3151 ($C_{36}H_{42}NO_4$ requires 552.3114).

1,2,3,7-tetra-deoxy-3,7-imino-L-glycero-L-lyxo-octitol or 1,5-dideoxy-1β-ethyl-1,5-imino-L-iditol (adenophorine, 3):

4,5,6,8-Tetra-*O*-benzyl-1,2,3,7-tetra-deoxy-3,7-imino-L-glycero-L-lyxo-octitol (**15**) (1.0 eq, 0.014 mmol, 7.9 mg) was dissolved in absolute ethanol (2 mL) which had been degassed by boiling under reduced pressure, $PdCl_2$ (2 eq, 0.028 mmol, 5 mg) and

HCl (0.25 mL of a 3.0 M solution in water) were added. The resulting mixture was stirred under an atmosphere of hydrogen at atmospheric pressure for 1.5 h before filtering through celite. The filtrate was passed through a plug of Dowex OH^-, and eluted with methanol. The eluant was purified by ion exchange chromatography (Dowex 50W(H^+), eluant methanol (25 mL), then 20:80, methanol:ethyl acetate (10 mL)) to give **3** as a colourless oil (2.7 mg, 100 %). $[\alpha]_D^{22}$ – 52.3 (c = 0.2, H_2O) {lit. for enantiomer:[2] $[\alpha]_D^{19}$ + 59.7 (c = 1, H_2O)}; *m/z* 192 (ES, $[M+H]^+$, 100 %, MeOH), 214 ($[M+Na]^+$, 55 %); δ_H (D_2O, 500 MHz, gCOSY) 0.94 (t, 3H, H-1), 1.30-1.39 (m, 1H, H-2), 1.80-1.89 (m, 1H, H-2'), 2.64 (dpt, 1H, H-3, $J_{2,3}$ 3.0 Hz, $J_{2',3}$ 8.9 Hz, $J_{3,4}$ 8.9 Hz), 3.11 (pt, 1H, H-4, $J_{3,4}$ 9.5 Hz, $J_{4,5}$ 9.5 Hz), 3.23-3.28 (m, 1H, H-7), 3.45 (pt, 1H, H-5, $J_{4,5}$ 9.4 Hz, $J_{5,6}$ 9.4 Hz), 3.75 (dd, 1H, H-6, $J_{6,7}$ 6.0 Hz, $J_{5,6}$ 10.0 Hz), 3.77-3.84 (m, 2H, H-8, H-8'); δ_C (D_2O, 125.7 MHz, DEPT) 11.7 (C-1), 26.8 (C-2), 56.2 (C-3), 59.1 (C-8), 59.7 (C-7), 74.4 (C-6), 77.2 (C-5), 77.6 (C-4).

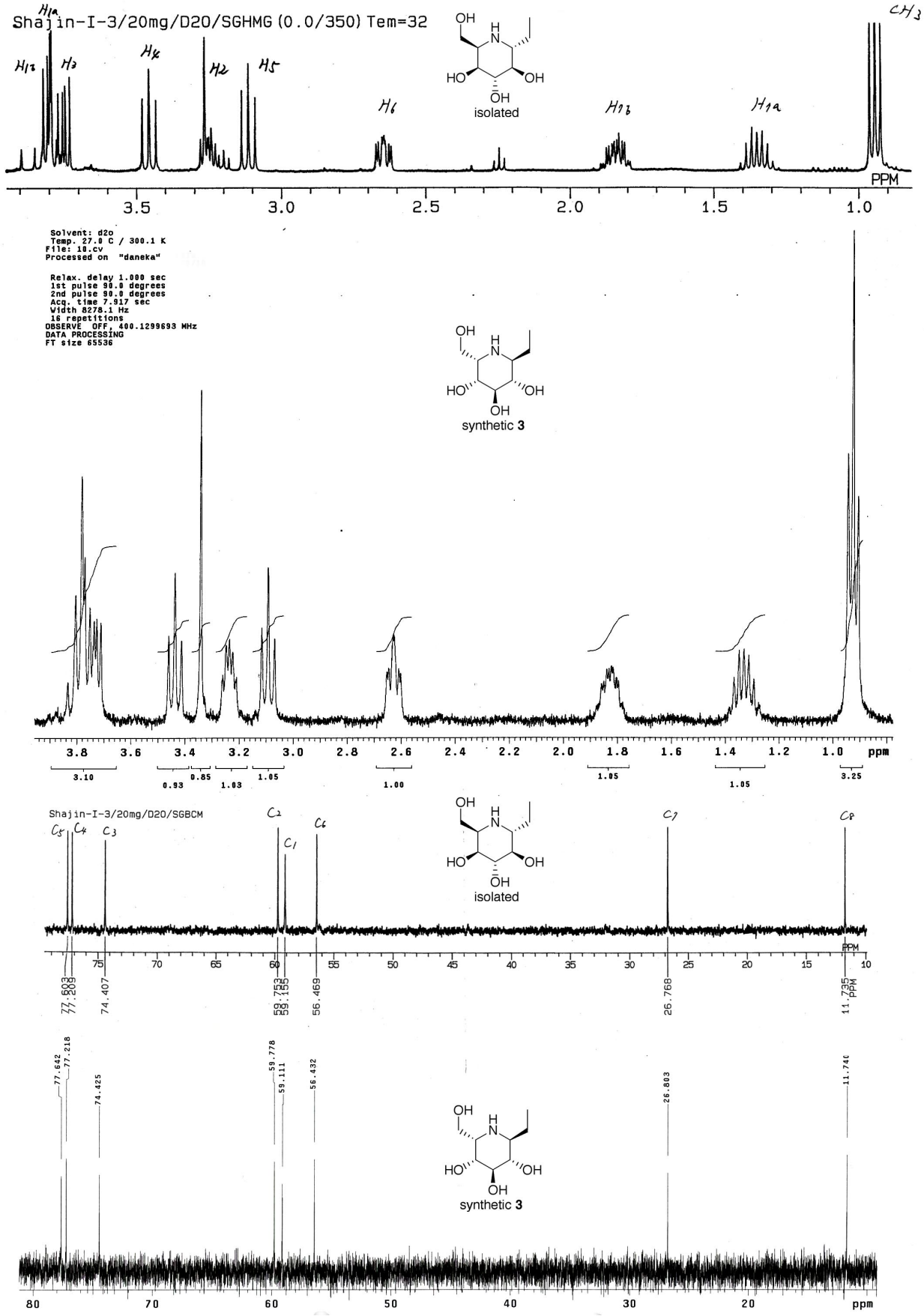
Human Lysosomal Glycosidase Inhibition Assays: Enzymes were extracted from an MCF7 cell-line harvest: cells were harvested from ~100mL of standard culture, washed in phosphate buffered saline solution (PBS) and sonicated (3 × 10s) in water (1 mL). Extract (5 μL) and inhibitor solution (0.04, 0.4 or 4 mM diluted using water from 100mM stock in DMSO, 5 μL) were diluted with the appropriate enzyme assay solution (*vide infra*, 10 μL) and incubated for the appropriate length of time (*vide infra*). The course of the assay was stopped by addition of glycine-carbonate buffer solution (0.17M, pH9.8, 150μL) and absorbance (405 nm) or fluorescence (excitation 460 nm, emission 355 nm) recorded as appropriate. Assay solutions and incubation times: α-D-glucosidase [1.25mM *para*-nitrophenyl α-D-glucopyranoside in 0.2M citrate/phosphate buffer, pH 4.4, 37° C, 16h]; β-D-glucosidase [5mM 4-methylumbelliferyl β-D-glucopyranoside in 0.2M citrate/phosphate buffer, pH 5.8,

37˚ C, 3h]; α-D-galactosidase [20mM *para*-nitrophenyl α-D-galactopyranoside, 180mM *N*-acetyl-D-glucosamine in 0.2mM citrate/phosphate buffer, pH 4.4, 37˚ C, 4h]; β-D-galactosidase [5mM *para*-nitrophenyl β-D-galactopyranoside in 0.2M citrate/phosphate buffer, pH 4.3, 37˚ C, 2h]. IC_{50} values were determined from × 2 serial dilutions as appropriate of inhibitor concentrations from 40mM. All assays were recorded in duplicate.

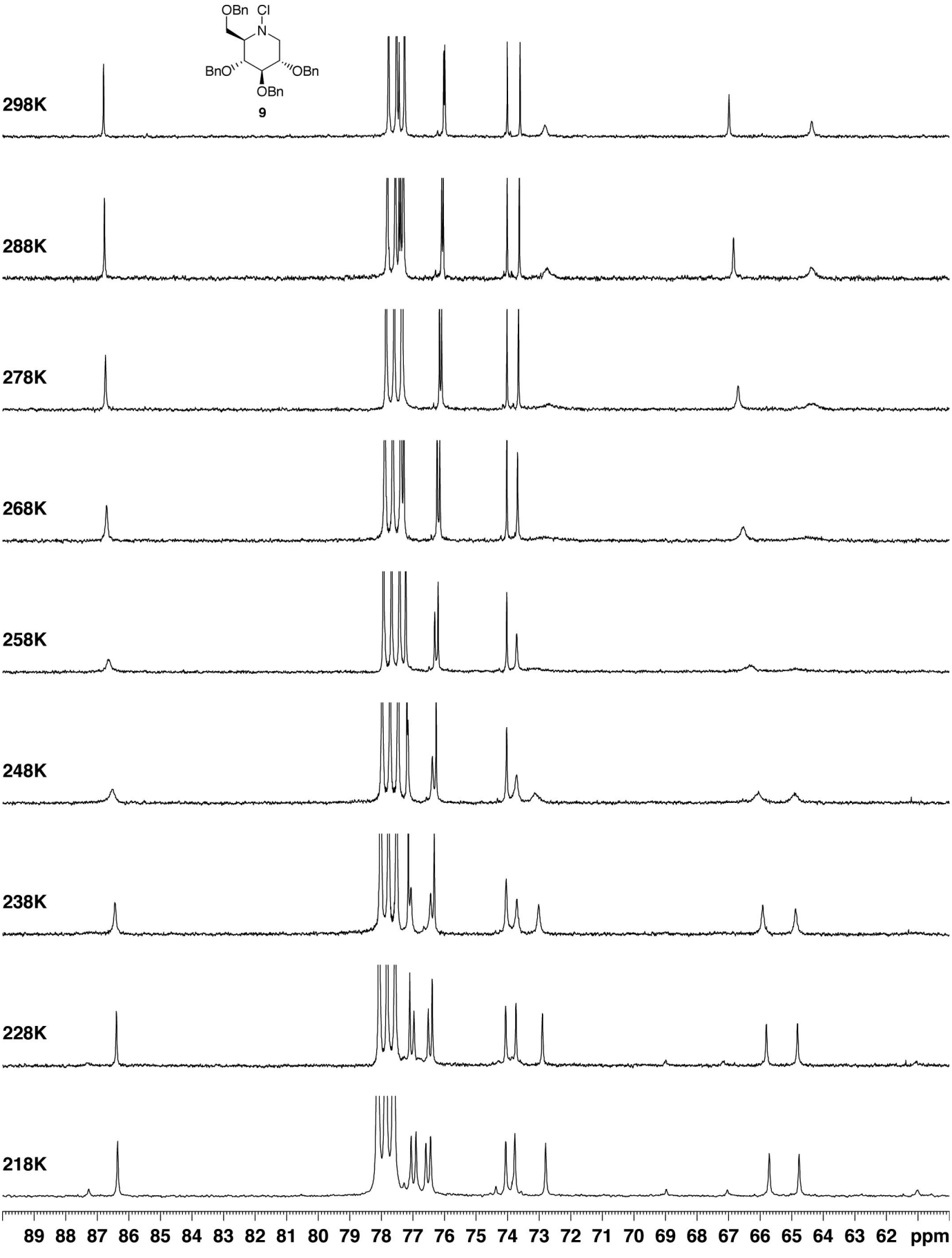
Non-Lysosomal β-Glucosidase Inhibition Assay: Conducted as for human lysosomal β-glucosidase inhibition assays except prior to assay, MCF7 extract (450 μL) was incubated for 30 min with the irreversible lysosomal β-glucosidase inhibitor conduritol β-epoxide (25mM diluted from a 250mM stock in DMSO, 4.5μL).

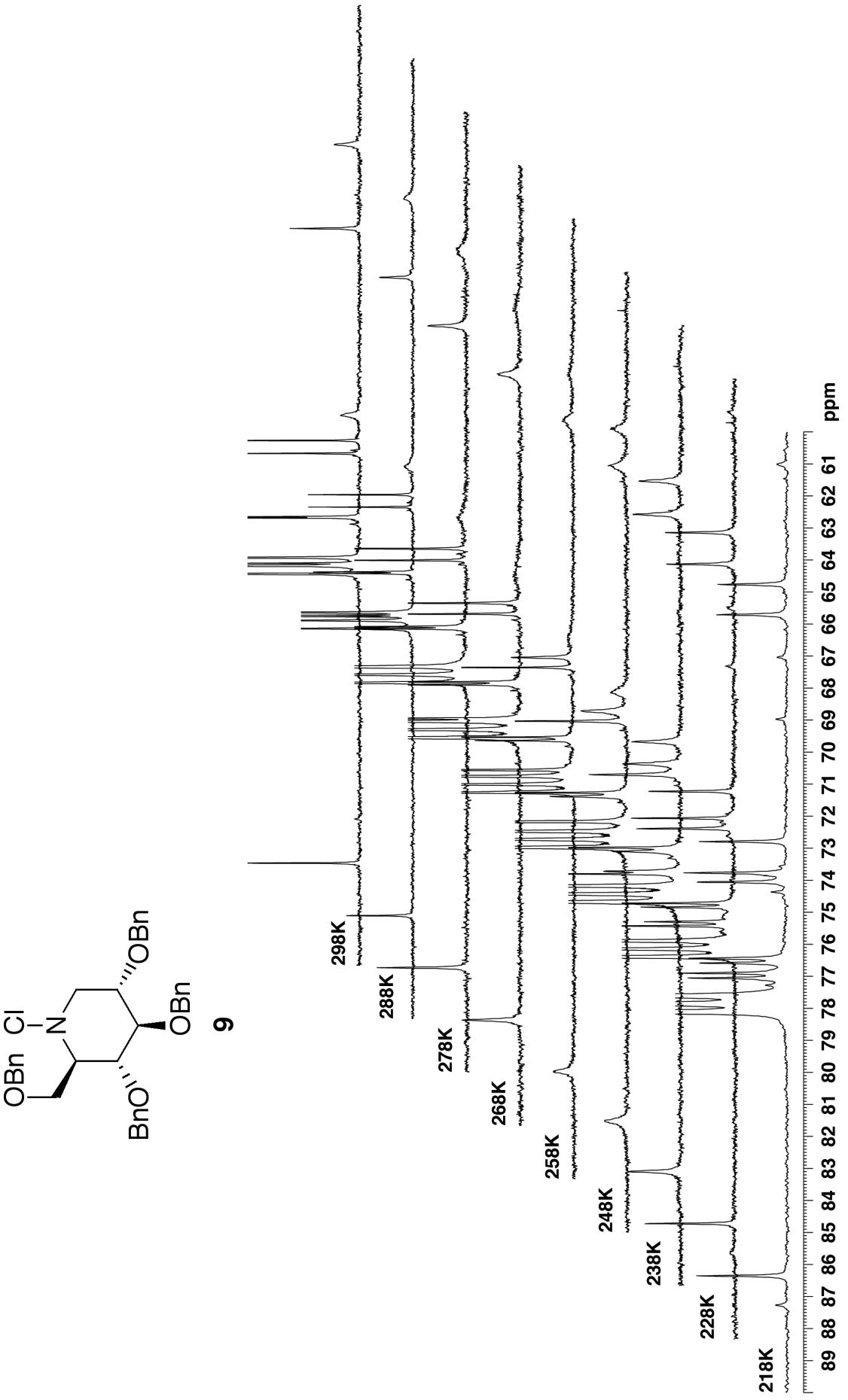
Glucosylceramide synthase (GCS) assay: GCS [UDP-glucose *N*-acylsphingosine glucosyltransferase (EC 2.4.1.80)] assay was conducted using HL-60 cell microsomes as described in reference 3.

NMR of 3 (Isolated and Synthetic):



VT-^{13}C NMR of 9 ($CDCl_3$, 125MHz):

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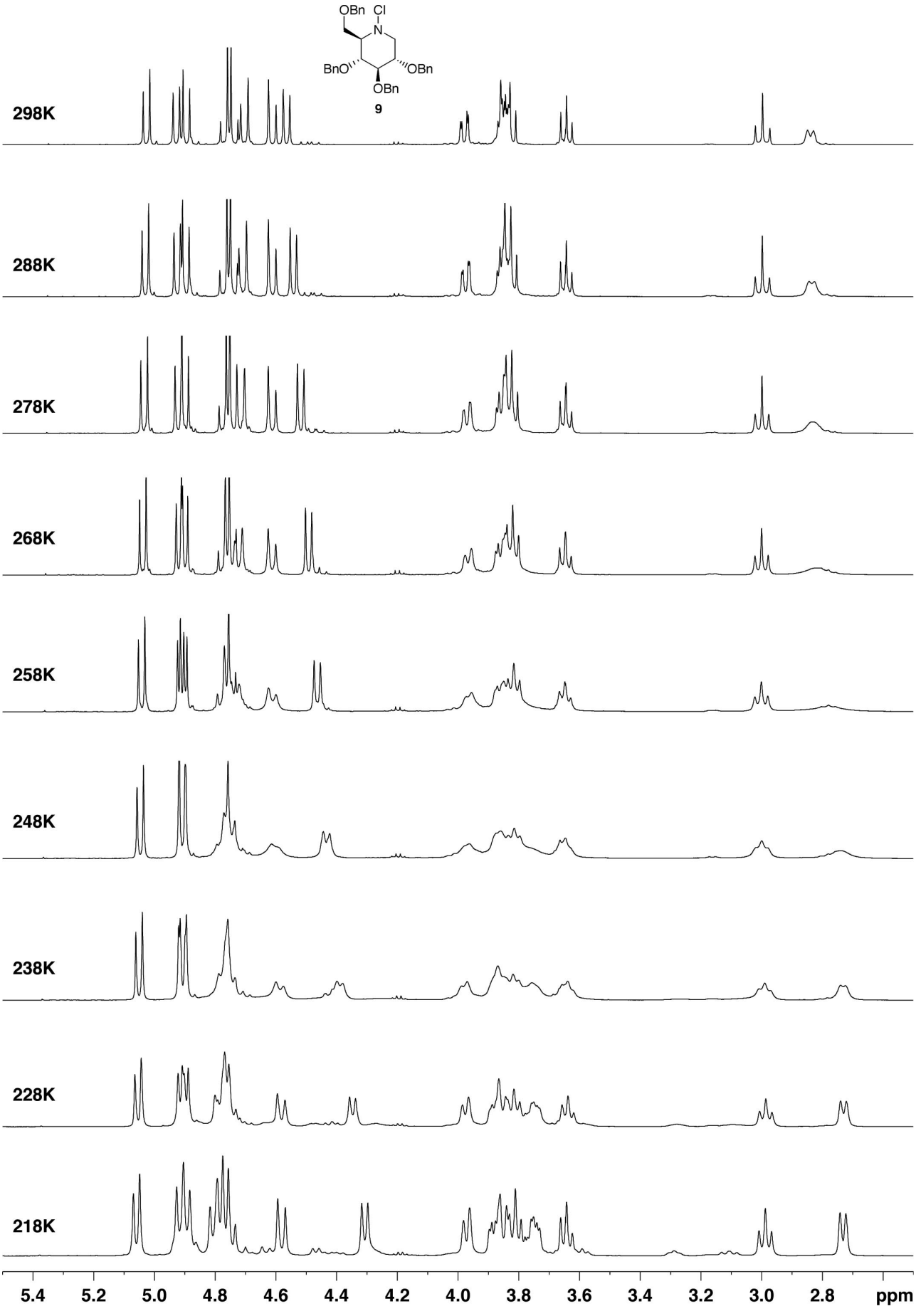
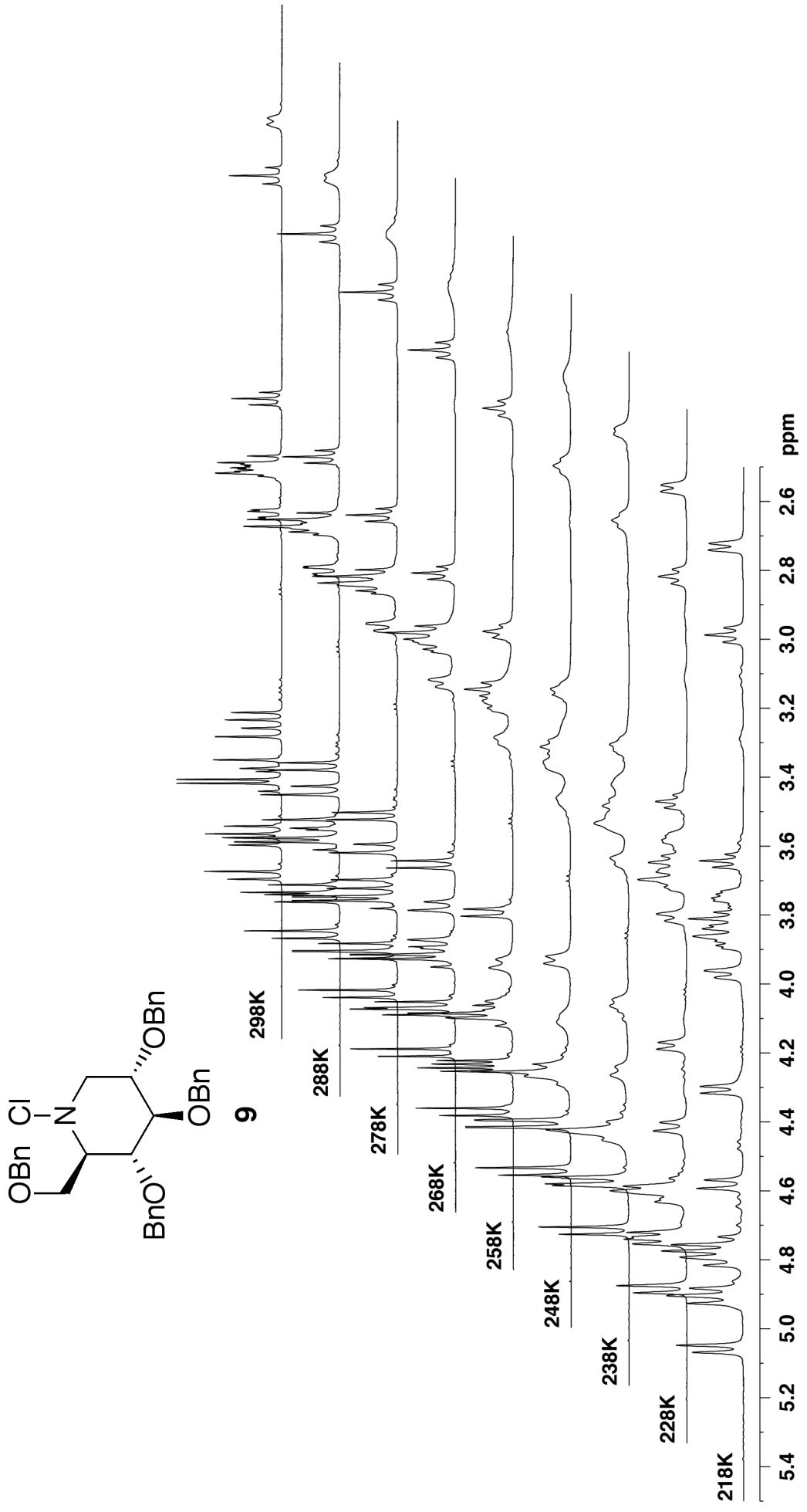
ppm

VT-^{1}H NMR of 9 ($CDCl_3$, 500MHz):

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Speculative Discussion of the Factors Influencing Sterecontrol in the Addition to Polyhydroxylated Imines

Competing modes of attack from pseudoequatorial (mode **a**) and from pseudoaxial (mode **b**) directions on polyhydroxylated imines are modulated by nucleophile size. Although organometallic additions to polyhydroxylated, piperidine imines are rare, information from reductive aminations,[4] presumed to proceed through such intermediates, reveals mixed senses of induction not entirely consistent with steric approach control.[5] We speculate that the two opposing modes may be influenced by two opposing factors: steric approach control[5] (mode **a**, H→S thereby developing strain, Figure 2) and stereoelectronic control coupled with strain relief[4b],[6] (mode **b**, H→C Figure 2). Thus, in **13**, bulkier nucleophiles (Bn) attack pseudoequatorially to avoid 1,3-diaxial interactions but *via* a **S**-like transition state with increasing strain that would subsequently relax into a chair conformer, whereas smaller nucleophiles (H,D) attack pseudoaxially via a less-strained **C**-like transition state. In **12**,**14** only mode **b** attack is observed even for an Et nucleophile. In this model and others[4b,6] the immediate skew boat products of attack will readily relax back into more stable chair conformations and are not proposed as ultimate ground state conformations but only the immediate products of the rate-limiting step. This is supported by NMR analysis of the products of this study which in all cases suggest a $^4C_1$ ground state conformation. Other size-dependent factors that might control the mode of addition, such as electronic factors or chelation control[7] cannot be excluded. Further studies with additional nucleophiles are ongoing and details will be published in due course.

References for Supporting Information

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