ENANTIOSPECIFIC SYNTHESIS OF 2,3,5-SUBSTITUTED PIPERIDINES AS ANALOGUES OF NOJIRIMYCIN

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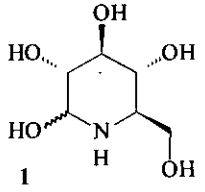
Abstract- Chiral 2,3,5-trihydroxypiperidines have been synthesised from the readily available 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose.

Naturally occurring 5-amino-5-deoxy-D-glucopyranose, nojirimycin **(1)**, was isolated in 1967.[1] At the time this was the sole example of a sugar in which the ring oxygen atom had been replaced by a nitrogen atom. Interest in nojirimycin has arisen primarily from the fact that it functions as a potent glycosidase inhibitor.[1] In subsequent years there followed the isolation of 1-deoxynojirimycin (**2**), 1-deoxymannonojirimycin (**3**), alongside the isolation of castanospermine (**4**) and swainsonine (**5**).[2] Research activity towards these molecules has been heightened due to the emergence of the human immunodeficiency virus (**HIV**) since they inhibit glycoprotein processing.[3]



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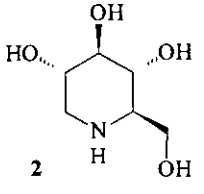

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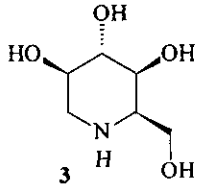

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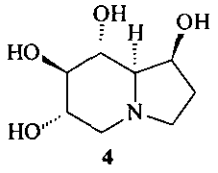

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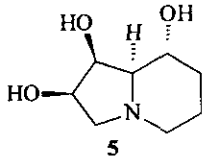

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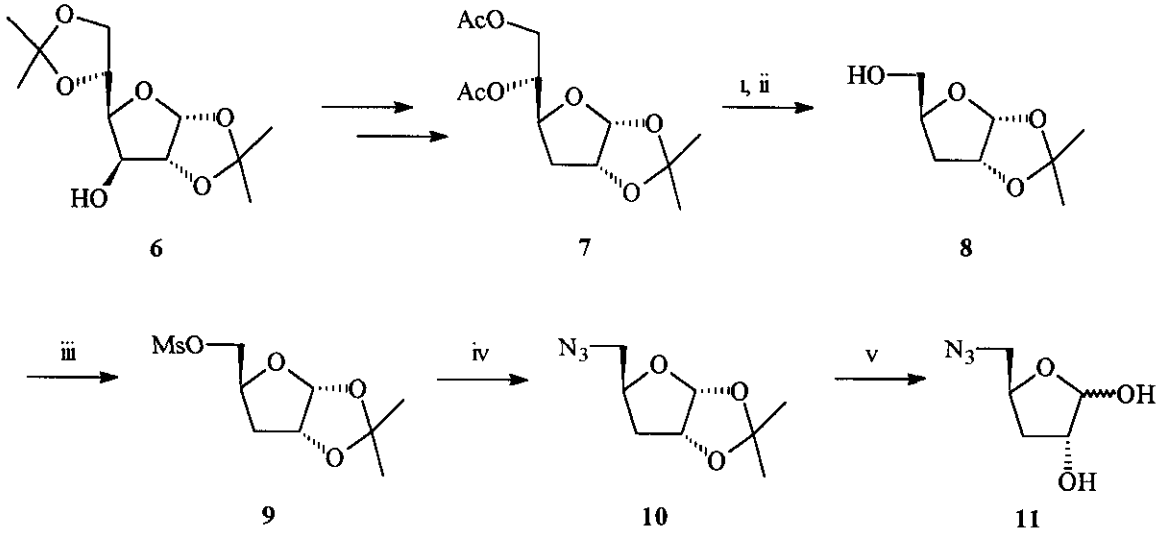
Our investigations into these molecules were initiated by our desire to understand the structural requirements that are necessary for nojirimycin (**1**) to function as a glycosidase inhibitor. In this regard we decided to investigate the synthesis of its analogues lacking both the 3-hydroxy and 5-hydroxymethyl (nojirimycin numbering) functions. The diverse chemistry of carbohydrates led us to consider these as rich sources of chirality that would provide piperidines with these structural features. Additionally this would give access to substituted piperidines that would be of use for synthesis of castanospermine and swainsonine analogues.

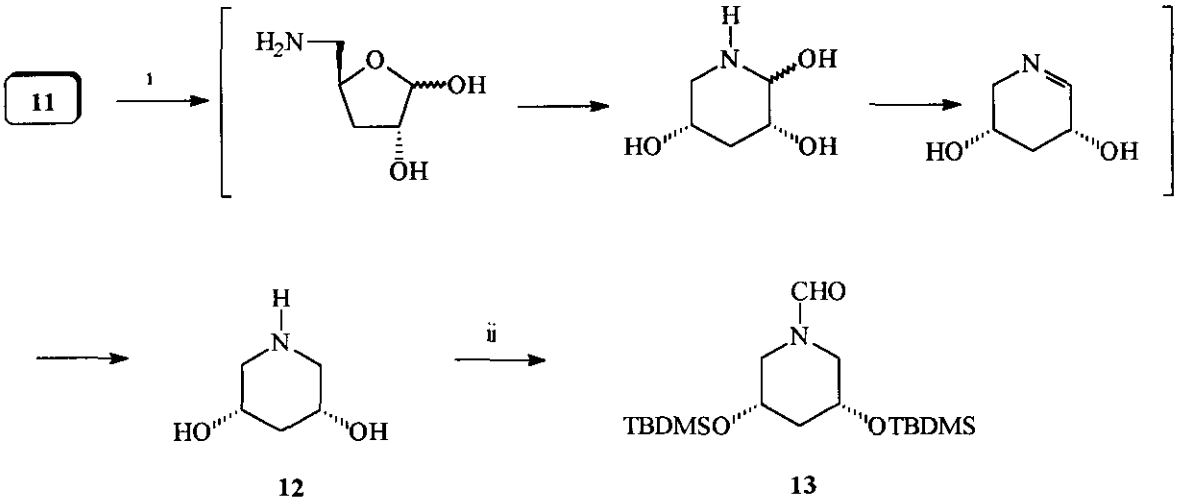
1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (**6**) was converted to the deoxy derivative (**7**) by literature procedures. Hydrolysis of **7** followed by oxidative cleavage and reduction furnished the primary alcohol (**8**) in 90% yield.[4,5] Treatment of **8** with mesyl chloride in pyridine gave the corresponding mesylate (**9**), which was converted to the azide (**10**) in 94% yield as a colourless oil. Removal of the isopropylidene protecting group was smoothly accomplished which afforded the lactol (**11**) in 92% yield



Scheme 1 i, NaOMe . MeOH, room temperature, 2 h; ii, $NaIO_4$,H_2O, room temperature, 3 h; then $NaBH_4$, room temperature, 3 h, iii, $MeSO_2Cl$, Py, -10 °C to room temperature, 2 h; iv, NaN_3 (3 eq), DMF, 100 °C, 4 h; v, 2M HCl, 1,4-dioxane, room temperature, 16 h.

With the lactol (**11**) in hand we then investigated its chemistry. Hydrogenation of the azide function in the presence of palladium catalyst led to the formation of piperidine (**12**) which was subsequently treated with

t-butyldimethylsilyl chloride in DMF to give the *N*-formylpiperidine **(13)** in a yield of 90%, $[\alpha]_D$ 0.0° (c 2.08, $CHCl_3$).



12 **13**

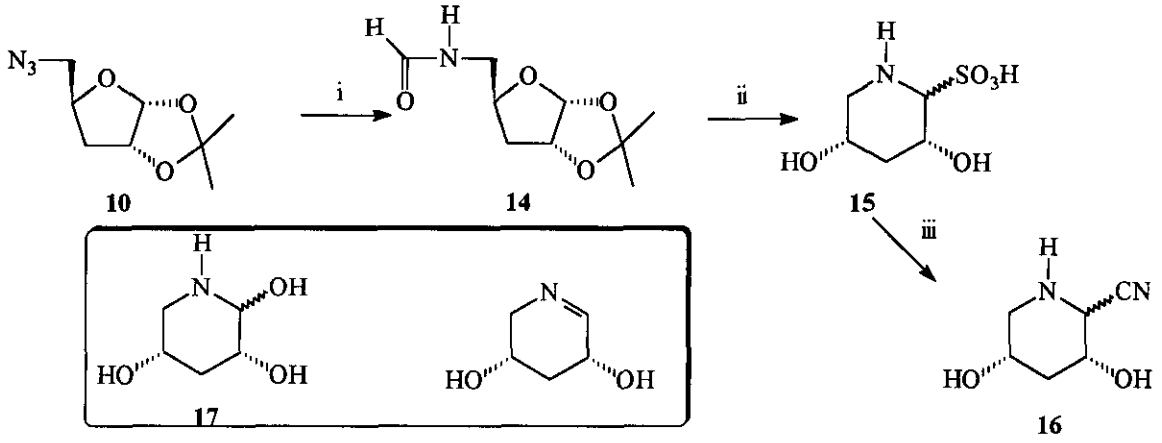
Scheme 2 i, H_2 (2 atm), 10% Pd-C, MeOH; ii, TBDMSCl (3 5 eq), Im (3 5 eq), DMF, 12 h

The piperidine **(12)** was presumably formed by over reduction of the intermediate azapyranose or that of the imine that is formed by the expulsion of a molecule of water, as illustrated in the above scheme. This over reduction of azapyranoses has also been observed in the synthesis of 1-deoxynojirimycin and its stereoisomer under exhaustive hydrogenation in acidic conditions.[6,7]

In the light of these findings we investigated alternative strategies that would provide the requisite piperidine or an appropriate derivative Hydrogenation of the azide **(10)** followed by reaction of the crude material with *t*-butyldimethylsilyl chloride in DMF afforded the *N*-formyl protected sugar **(14)** in 75% yield, $[\alpha]_D$ -12.2° (c 2.9, $CHCl_3$), mp 84 °C An interesting point of note is that this formylation reaction did not occur if the silylating agent was omitted Removal of the isopropylidene group was effected by treatment with sulphur dioxide and this gave the piperidine sulphonic acid **(15)** as a colourless crystalline compound in 80% yield, $[\alpha]_D$ +34.8° (c 0.2, H_2O) This product could also be obtained by hydrogenation of the azide **(10)** in methanol followed by immediate reaction of the resultant amine with sulphur dioxide, however the overall yield for this sequence was appreciably lower

The azasugar **(17)** was obtained by passage of the sulphonic acid **(15)** through a Dowex-50 ($^-$OH form) ion exchange resin column, however this material was of very limited stability. Displacement of the sulphonic acid function was effected by barium cyanide[8] which gave the nitrile **(16)** in 71% yield The

sulphonic acid **(15)** and intermediate compounds did not exhibit any significant activity when screened against a range of organisms.



Scheme 3 i, H_2 (2atm), 10% Pd-C, MeOH; then DMF, TMSCl (1.25 eq), Im (2.5 eq), 12 h, room temperature; ii, SO_2, H_2O, 40 h; iii, $Ba(OH)_2$, NaCN, HCl, H_2O, 3 h, room temperature.

ACKNOWLEDGEMENTS

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EXPERIMENTAL

Ir spectra were recorded on a Perkin Elmer 1600 FT spectrophotometer. Mass spectrometry was performed with an AEI MS 902 spectrometer using an ionisation energy of 70ev. Nmr spectra were recorded on Jeol EX90 and Bruker WH 400 spectrometers using deuteriochloroform as solvent unless otherwise stated. Melting points were determined using a Reichert apparatus and are uncorrected. Absorption chromatography was carried out using Kieselgel 60. Optical rotations were determined with a Bellingham Stanley P20 polarimeter. All air-sensitive reactions were performed in flame dried apparatus under an argon atmosphere.

*3-Deoxy-1,2-*O*-isopropylidene-5-*O*-methanesulphonyl-α-D-ribofuranose* **(9)**.

Methanesulphonyl chloride (20 ml, 29.48 g, 127 6 mmol) was added dropwise, during 30 min, to a cold (-10 °C) solution of *3-deoxy-1,2-*O*-isopropylidene-α-D-ribofuranose* **(8)** (9.75 g, 56.03 mmol) in pyridine (150 ml). After addition the mixture was warmed to room temperature and stirring continued for 2 h. The

solvent was removed *in vacuo* and the residue was passed down a small plug of silica gel eluting with ether The resulting solution was concentrated and the residue chromatographed using ether as eluent. This afforded the title compound, (9 11 g, 79%), as colourless crystals ($CHCl_3$), mp 69 °C, $[\alpha]_D$ = -13 0° (c = 2.9, $CHCl_3$), ir (KBr) 2995, 2950, 1360, 1280 cm^{-1}; ^1H nmr (90 MHz) 1.32 (3H, s), 1.50 (3H, s), 1.80 (2H, m, H_2-3), 3.06 (3H, s), 4.40 (3H, m, H-4, H_2-5), 4.78 (1H, dd, *J* 3.7, 5.7 Hz, H-2), 5.85 (1H, d, *J* 3.7 Hz, H-1); ^{13}C nmr (22.5 MHz) 26.2, 26.8, 34.6 (C-3), 37.7(OMs), 69.7 (C-5), 75.5 (C-4), 80.3 (C-2), 105.7 (C-1), 111.7; m/z 237 (M^+-CH_3), 143 , 141. Anal. Calcd for $C_9H_{16}O_6S$; C 42.85, H 6.39. Found C 42.58, H 6.41

5-Azido-3,5-dideoxy-1,2-O-isopropylidene-α-D-ribofuranose **(10)**.

3-Deoxy-1,2-O-isopropylidene-5-*O*-methanesulphonyl-α-D-ribofuranose **(9)** (9.5 g, 40.25 mmol) was added to a stirred suspension of sodium azide (8.0 g, 126.98 mmol) in dimethylformamide (250 ml). The resulting suspension was heated at 100 °C for 4 h, after which DMF was removed *in vacuo*. The residue was partitioned between aqueous ammonium chloride (100 ml) and ether (2 x 200 ml). The combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. Chromatography ($CHCl_3$) gave 7.4 g (94%) of the title compound Kugelrohr distillation (130 °C / 3 mmHg) afforded analytically pure material, $[\alpha]_D$= +3.7° (c= 12.2 $CHCl_3$), ir (neat film) 2995 , 2970, 2100, 1380, 1375 cm^{-1}; ^1H nmr (400 MHz) 1.31 (3H, s) 1.50 (3H, s), 1.76 (1H, ddd, *J* 4.7, 10.7, 13 4 Hz, H_a-3), 2.05 (1H, dd, *J* 4.5, 13 4 Hz, H_b-3), 3.25 (1H, dd, *J* 4.7, 13.4 Hz, H_a-5), 3.57 (1H, dd, *J* 4.7, 13.4 Hz, H_b-5), 4.39 (1H, m, H-4), 4.76 (1H, dd, *J* 3.7, 4 7 Hz, H-2), 5 83 (1H, d, *J* 3.7 Hz, H-1); ^{13}C nmr (22.5 MHz) 26 2, 26.8, 35.6 (C-3), 52.9 (C-5), 76 7 (C-4), 80.6 (C-2), 105.6 (C-1), 111 5 Anal. Calcd for $C_8H_{15}N_3O_3$; C 48.23, H 6 58, N 21 09. Found C 47.98, H 6.60, N 20 85.

5-Azido-3,5-dideoxy-α,β-D-ribofuranose **(11)**.

The azide **(10)** (1 00 g, 5.03 mmol) in dioxane (20 ml) was treated with 2 *M* hydrochloric acid (12 ml) and the mixture was stirred at room temperature for 16 h The solvents were removed *in vacuo*, and the residue chromatographed (chloroform methanol, 99·1) to give the title compound (0.757 g, 92%) as a mixture of anomers, $[\alpha]_D$= + 44.4° (c 2.82, Et_2O); ir (neat film) 3940, 2940, 2100 , 1440 cm^{-1}; ^1H nmr (90 MHz) 2 01 (2H, m), 2.55 (2H, br s), 3.38(2H, m), 4.41(2H, m), 5.29 (0.5H, s, H-1β), 5 40 (0.5H, s, H-

1α); ^{13}C nmr (22.5 MHz) 34.6, 35.1, 54.5, 55.8, 71.70, 75 70, 76.51, 78.3, 97.3, 103.1; m/z HRms (FAB) cacld for $C_5H_9N_3O_3$ (MH^+) 160.0724; found 160.0722. Anal Calcd for $C_5H_9N_3O_3$; C 37.74, H 5.70, N 26.40. Found C 37 45, H 5 79, N 26.38.

3,5-Di-t-butyldimethylsilyloxy-1-formyl-piperidine **(13)**.

The azidofuranose **(11)** (0.12 g, 0 78 mmol), in methanol (30 ml), was hydrogenated, using 10% palladium on carbon (10 mg), at 30 psi for 4 h. Filtration through Celite followed by removal of the solvent *in vacuo* gave the crude material which was dissolved in DMF (5 ml) and treated with imidazole (0.32 g, 4.7 mmol) and *t*-butyldimethylsilyl chloride (0.48 g, 3.2 mmol) and the mixture stirred at room temperature for 16 h. Removal of the solvent *in vacuo* followed by chromatography ($CHCl_3$) gave the title compound as a colourless oil, (0 26 g, 90%), $[\alpha]_D$ = 0° (c 2.1, $CHCl_3$), ir (neat film) 1680 cm^{-1}; ^{1}H nmr (400 MHz) 0.06 (12H, s, x2 $SiMe_2$), 0 86(9H, s), 0.87(9H, s), 1 45(1H, m, H_a-4), 2.18 (1H, m, H_b-4), 3 29(1H, dd, *J* 10 4, 12 4 Hz, H-5), 3.51 (3H, m), 3 75 (1H, dd, *J* 9.8, 12 0 Hz, H-3), 4.38 (1H, dd, *J* 5.1, 12.4 Hz), 7.99 (1H, s, NCHO); ^{13}C nmr (22.5 MHz) -4.7 (3C), -4 5, 18.1(2C), 25 8 (2C), 45.0, 46.3, 52.4, 65.4, 66.8, 161.3; m/z HRms (CI, NH_3), calcd for $C_{18}H_{40}NO_3Si_2$ (MH^+) 374 2547 found 374.2547 Anal. Calcd for $C_{18}H_{39}NO_3Si_2$, C 57.86; H 10.52, N 3 75 Found C 57.85, H 10 55, N 3.75.

*3,5-Dideoxy-5-*N*-formyl-1,2-*O*-isopropylidene-α-D-ribofuranose* **(14)**.

The azide **(10)** (0.25g, 1.26 mmol) in methanol (10 ml) was hydrogenated at 30 psi with 10% palladium on carbon (10 mg) for 12 h Filtration through celite and removal of the solvent afforded the crude amine This material was dissolved in DMF (10 ml) and treated with imidazole (0.21 g, 3 1 mmol) and trimethylsilyl chloride (0.2 ml, 3.1 mmol). The mixture was stirred at room temperature for 12 h and the solvent removed *in vacuo*. The residual material was taken up in chloroform (50 ml) and washed with brine (2 x 10 ml), dried over anhydrous sodium sulphate and concentrated *in vacuo*. Chromatography ($CHCl_3$), afforded the title compound as colourless crystals, (0.19 g, 75%). $[\alpha]_D$ -12.2° (c 2.87, $CHCl_3$); mp 84 °C (from $CHCl_3$), ir (KBr)1660 cm^{-1}; ^{1}H nmr (400 MHz) 1.31 (3H, s), 1.49 (3H, s), 1.56 (1H, ddd, *J* 4.8, 10.9, 13 5 Hz, H_a-3), 2.08 (1H, dd, *J* 4.3, 13 5 Hz, H_b-3), 3.35(1H, dt, *J* 14.2, 6.1 Hz, H_a- 5) 3.68 (1H, ddd, *J* 3 2, 6 2, 14.2 Hz, H_b-5), 4.31 (1H, m, H-2), 4 74 (1H, t, *J* 4 2 Hz, H-4), 5.79 (1H, d, *J* 3.7 Hz, H-1), 5 88 (1H, br s, NH), 8 21(1H, d, *J* 1 1 Hz, NCHO); ^{13}C nmr (22.5 MHz) 26 1, 26.6, 35.7, 40.0, 76.6, 80.5, 105.4, 111 3, 161.4. Anal Calcd for $C_9H_{15}NO_4$; C 53.72, H 7.51, N 6.96. Found C53.46, H 7.54, N 6 78.

3R,5S-Dihydroxypiperidine-2RS-sulphonic acid **(15)**.

The *N*-formylribose derivative **(14)** (0.12 g, 0.59 mmol) in water (5 ml) was saturated with gaseous sulphur dioxide After 40 h methanol (50 ml) was added and the solution resaturated. Filtration of the suspension gave directly the title compound (92 mg, 70%) as colourless crystals. $[\alpha]_D$ +34 8° (c 0.2, H_2O); mp 142-144 °C; ir (KBr) 3420, 1620 cm^{-1}; ^1H nmr (400 MHz, D_2O) 1.65(0.65H, ddd, *J* 2.0, 10.4, 12.6 Hz, H_a-4), 1.95 (0 35H, dt, *J* 3.3, 15.5 Hz, H_a-4), 2.23 (0.35H, ddd, *J* 3.0, 5.6, 15.5 Hz, H_b-4), 2.47 (0.65H, ddd, *J* 4.3, 8 6, 12.6 Hz, H_b-4), 2.89 (0.65H, dd, *J* 10.4, 12.3 Hz, H_a-6), 3.35 (0.35H, dd, *J* 2.4, 13.6 Hz, H_a-6), 3 48 (1H, m, H_b-6), 4.03 (2x0.65H, m, H-2, H-3), 4.14 (0.65H, m,H-5), 4.24(0.35H, m H-3), 4 31 (0.35H, d, *J* 1 6 Hz, H-2), 4.60 (0 35H, m, H-5); ^{13}C nmr (22.5 MHz) 40.4, 41.0, 47 0, 50.7, 66.2, 68 1, 67.2, 70.1, 73.7, 87 2; Anal. Calcd for $C_5H_{13}NO_6S\ H_2O$, C 27.90, H 6.09, N 6.51, S 14.90. Found, C 28.09, H 6.13, N 6.25 S 14.60.

2RS-Cyano-3R,5S-Dihydroxypiperidine **(16)**.

To a suspension of barium hydroxide octahydrate (0 16 g, 0 5 mmol) in water (1 ml), was added the sulphonic acid **(15)** (0.1 g, 0.46 mmol), followed by sodium cyanide (0.33 g, 0.75 mmol) and 6M hydrochloric acid (2 drops) The stirring was continued at room temperature for 3 h Filtration followed by removal of the solvent *in vacuo* afforded the crude product Crystallisation from methanol / acetonitrile (1 1) gave the title compound (0.055 g, 83%), $[\alpha]_D$ -3 6° (c 0 41, H_2O); ir (KBr) 3419 cm^{-1}; ^1H nmr (90 MHz, CD_3OD) 1 98 (2H, m, H-4), 3 25(2H, m, H-6), 4 10 (2H, m, H-3, H-5), 4.67 (1H, m, H-2), ^{13}C nmr (22.5 MHz, CD_3OD) 37.5, 40 3 (both, C-4), 50.0 (C-6), 51 9 (C-2), 64.24 (C-5), 66 3, 67.4 (both C-3), 116 4, 116 7 (CN); m/z HRms (CI, NH_3), Calcd for $C_6H_{11}N_2O_2$ (M^+ + H) 143.0821, found 143.0820.

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