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Total synthesis of deoxymannojirimycin and D-mannolactam via carbonylation of 5-vinyloxazolidin-2-ones

Julian G. Knight* and Kirill Tchabanenko

School of Natural Sciences, Newcastle University, Bedson Building, Newcastle upon Tyne NE1 7RU, UK

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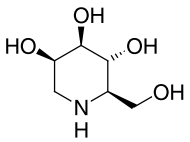
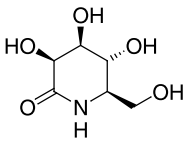
Abstract—The stereoselective synthesis of piperidine alkaloids deoxymannojirimycin and D-mannolactam from D-serine has been achieved. The key step involves palladium-catalysed decarboxylative carbonylation of a serine-derived 5-vinyloxazolidin-2-one to give 6-(*tert*-butyldimethylsilyloxymethyl)-3,6-dihydro-1*H*-pyridin-2-one which was subsequently converted into the title compounds.

1. Introduction

Polyhydroxylated piperidine alkaloids are frequently found in living systems,[1] and display a wide range of biological activities due to their ability to mimic carbohydrate substrates in a variety of enzymatic processes.[2] Selective inhibition of a number of enzymes involved in the binding and processing of glycoproteins has rendered piperidine alkaloids important tools in the study of biochemical pathways.[3] Deoxymannojirimycin **1**[4] has been shown to inhibit α-L-fucosidase, α-D-mannosidase and α-D-glucosidase activity,[5] while D-mannolactam **2** inhibits both α-D-mannosidase and α-D-glucosidase.[6] Both compounds have potential therapeutic value and a number of carbohydrate based[7–12] and de novo[13–22] total syntheses have been reported.

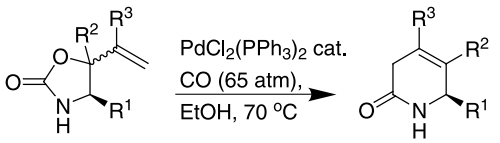


Deoxymannojirimycin **1**



D-Mannolactam **2**

Recently we reported[23,24] a novel approach to δ-lactams **4** via a palladium-catalyzed decarboxylative carbonylation of 5-vinyloxazolidin-2-ones **3** (Scheme 1). Lactams **4** are ideally functionalized for elaboration into polyhydroxylated piperidines and we now report the total synthesis of deoxymannojirimycin **1** and D-mannolactam **2** using this approach.



3 **4**

Scheme 1. Proposed route to piperidines.

2. Results and discussion

D-Serine was converted in four steps into aldehyde **5** in 79% overall yield and >98% ee via a route previously reported[25] for its enantiomer. Addition of vinyl magnesium bromide, followed by treatment of the resulting diastereoisomeric *N*-Boc amino alcohols with potassium *tert*-butoxide resulted in a mixture of *anti* and *syn* vinyloxazolidinones **6**, in a 2:1 ratio, which were subjected to carbonylation. Heating a solution of **6** in ethanol at 60°C under pressure of CO (65 atm) in the presence of $PdCl_2(PPh_3)_2$ (10 mol%) for 32 h gave the δ-lactam **7** in 81% yield. We planned to use the stereocentre at the 6-position of the lactam **7** to control the sequential introduction of hydroxyl groups around the ring. Stereoselective epoxidation, by treatment with Oxone®, proceeded in 95% yield to give a 4.1:1 ratio of the *anti* (**8a**) and *syn* (**8b**) epoxides, respectively. Although the stereochemistry of these epoxides could not be unambiguously assigned at this point, the ultimate conversion of the major epoxide into D-mannolactam and deoxymannojirimycin served to confirm our assumption that epoxidation occurs preferentially on the less hindered face of the double bond, away from the bulky CH_2OTBS group. We anticipated that base-mediated epoxide opening to the corresponding allylic alcohols would occur under mild conditions because the allylic protons in the 3-position are α to the lactam carbonyl group. In the event, the epoxides were separated by column

Keywords: deoxymannojirimycin; carbonylation; D-mannolactam.

* Corresponding author. Tel./fax: +44-191-2227068; e-mail: j.g.knight@ncl.ac.uk

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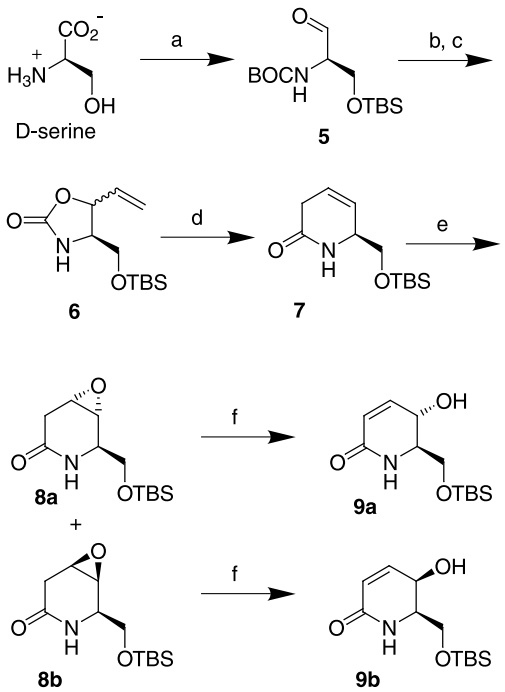
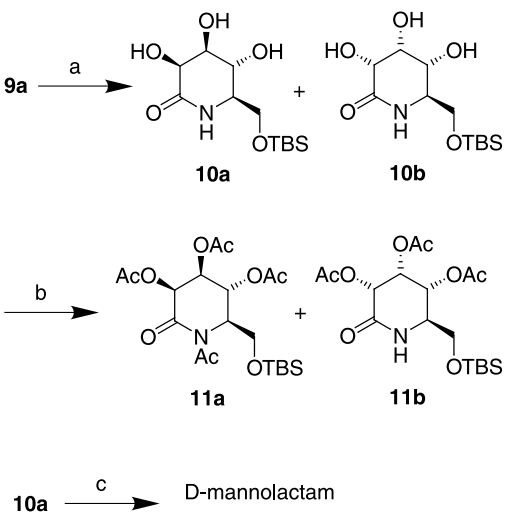


Scheme 2. *Reagents and conditions*: (a) Ref. 25 four steps, 79%; (b) $H_2C{=}CHMgBr$ (2.5 equiv.), THF, −78°C to rt, 3 h; (c) KO^{t}Bu, THF, rt, 3 h, 75% from **5**; (d) $PdCl_2(PPh_3)_2$ (10 mol%), CO (65 atm), EtOH, 60°C, 32 h, 81%; (e) Oxone (5 equiv.), $NaHCO_3$ (15 equiv.), acetone/H_2O, rt, 3 h, 95% (**8a/8b**, 4.1:1); (f) DBU (2 equiv.) CH_2Cl_2, reflux, 3 h, 95%.

chromatography and each was converted in excellent yield into the corresponding α,β-unsaturated lactam (**9a** and **9b**, respectively) on treatment with DBU (Scheme 2).

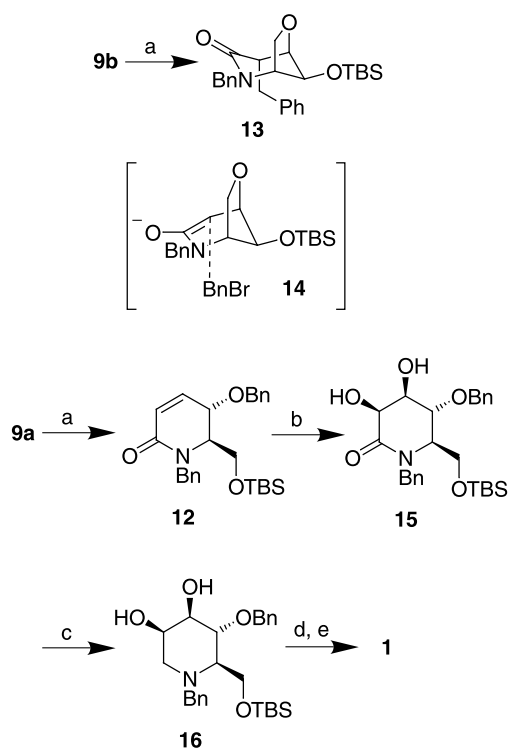
Our initial strategy centered on dihydroxylation of the lactam **9a** bearing an unprotected hydroxyl group. Dihydroxylation of **9a** gave a 3.2:1 mixture of diastereoisomeric triols **10a** and **10b**. The major isomer was expected[26] to arise from dihydroxylation *anti* to the allylic hydroxyl group **10a** (Scheme 3). In order to aid isolation of the triol lactams, they were treated with acetic anhydride. Surprisingly, peracetylation of the mixture of **10a** and **10b** resulted in



Scheme 3. *Reagents and conditions*: (a) OsO_4 (9 mol%), NMO (3 equiv.), ^{t}BuOH, rt, 3 h, 56% (**10a/10b**, 3.2:1); (b) Ac_2O, reflux, 4 h, 56% from **9a**; (c) TFA/H_2O (1:1), rt, 10 h, 70%.

tetraacetate **11a** and a triacetate **11b**, which were easily separable by chromatography. Unfortunately, we were unable to convert **11a** into **2** due to problems with isolation of the D-mannolactam from the deacetylation mixture. In fact, it proved possible to isolate the major triol **10a** from the dihydroxylation by column chromatography and this was then deprotected by treatment with TFA/water to give D-mannolactam **2**.[7] Recrystallization of **2** proved straightforward since, despite our expectations,[27] we found it to be only sparingly soluble in cold water.

Protection of the free hydroxyl of the lactam **9a** was expected to lead to a higher selectivity in the dihydroxylation and, hence, both epimers **9a** and **9b** were subjected to benzylation. Whereas **9a** gave the expected N,O-dibenzylated product **12** in 64% yield, we were surprised to find that the diastereoisomeric lactam **9b** did not behave in the same way. Attempted N,O-dibenzylation of **9b** gave rise to a C,N-dibenzylated product as a single diastereoisomer, as judged by ^{1}H NMR, which we have tentatively assigned as bicyclic lactam **13**. Compound **13** may be formed via migration of the silicon from the primary to the secondary hydroxyl group, intramolecular conjugate addition of the resulting primary alkoxide to the enamide, followed by benzylation of the intermediate enolate **14**. The stereochemistry of **13** is proposed on the assumption that benzylation will preferentially occur on the less-hindered face of the enolate **14** to form bicyclic **13** as a single diastereoisomer (Scheme 4). A related cyclization of a 5,6-*syn* 6-hydroxymethyl-5-benzoyloxypyridinone to an oxazabicyclo[3.2.1]octane under mild basic conditions has been reported.[28] Dihydroxylation of the fully protected lactam **12** gave the 4,5-*anti* diol **15** in high diastereoselectivity with only traces



Scheme 4. *Reagents and conditions*: (a) NaH (2 equiv.), DMF, BnBr, 0°C to rt, 3 h (**13**, 50%; **12** 64%); (b) OsO_4 (7 mol%), NMO (3 equiv.), ^{t}BuOH, rt, 3 h, 89%; (c) $LiAlH_4$ (5 equiv.), Et_2O, rt, 3 h, 89%; (d) Bu_4NF (1.5 equiv.), THF, rt, 1 h; (e) H_2, Pd/C, EtOH, HCl, rt, 2 h, 68% from **15**.

of the 4,5-*syn* isomer detectable by NMR. Reduction of the lactam with $LiAlH_4$ in diethyl ether produced the piperidine **16** which was converted to the hydrochloride salt of deoxymannojirimycin **1** via TBAF promoted TBS deprotection and catalytic hydrogenolytic benzyl deprotection.[13] The hydrochloride salt of **1** showed identical data to that previously reported.[29]

3. Conclusion

In summary, we have succeeded in applying our palladium catalyzed decarboxylative carbonylation of the serine-derived 5-vinyloxazolidinone **6** to the stereoselective total synthesis of polyhydroxylated piperidine alkaloids deoxymannojirimycin **1** and D-mannolactam **2**. We are currently applying this methodology to the synthesis of more complex piperidines and this work will be reported in due course.

4. Experimental

4.1. General

Melting points were determined on a Linkham TC92 hot stage and are uncorrected. Optical rotations were measured on a polAAr 2001 digital polarimeter at ambient temperature and are reported as follows $[\alpha]_D^T$ (c g/100 ml, solvent). Infrared spectra were recorded on a Nicolet 20 PCIR instrument. Mass spectra were recorded on Micromass autospec M and Kratos MS80 RF spectrometers in electron impact (EI) mode. ^{1}H NMR spectra were recorded on Bruker AC 200 (200 MHz), Bruker WM 300 (300 MHz), JEOL LA 500 (500 MHz) and Bruker AMX 500 (500 MHz) spectrometers at ambient temperature. ^{13}C NMR were recorded on Bruker AC 200 (50 MHz) and JEOL LA 500 (125 MHz) spectrometers at ambient temperature. Thin layer chromatography was performed on EM reagent 0.25 mm silica gel 60-F plates. Flash column chromatography was performed on Fluorochem LC3025 silica gel (40–63 μm). All reactions were carried out under an atmosphere of nitrogen in pre-dried glassware unless otherwise stated. Where necessary, solvents were dried prior to use. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride under nitrogen immediately prior to use. Ethanol was distilled from magnesium under nitrogen and stored over 4 Å molecular sieves. Ether and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl immediately prior to use. All chemicals were purchased from the Aldrich, Fluka, Sigma or Lancaster chemical companies and were used as supplied except where indicated.

4.1.1. (4*R*,5*RS*)-4-(*tert*-Butyldimethylsilanyloxymethyl)-5-vinyloxazolidin-2-one 6. To a stirred solution of aldehyde **5**[25] (14.19 g, 46.7 mmol) in THF (150 ml) was added vinylmagnesium bromide (117 ml, 1.0 M solution in THF, 117 mmol) at −78°C dropwise over 30 min and the resulting solution was stirred for 1 h, allowed to warm to room temperature and stirred for an additional 3 h, cooled to 0°C and saturated aqueous ammonium chloride (20 ml) was added. The resulting mixture was stirred for 10 min and concentrated on a rotary evaporator. Ethyl acetate (100 ml) and water (50 ml) were added and the phases were separated. The aqueous phase was extracted with additional ethyl acetate (2×20 ml). The combined organic extracts were washed with brine (2×50 ml), dried ($MgSO_4$) and the solvent was removed under reduced pressure to give the crude allylic alcohols as a pale yellow oil (12.37 g), to which was added THF (150 ml) and potassium *tert*-butoxide (8.35 g, 74.5 mmol) while stirring at room temperature. The resulting dark red suspension was stirred for 3 h and saturated aqueous ammonium chloride (20 ml) was added. The resulting mixture was stirred for 10 min and concentrated on a rotary evaporator. Ethyl acetate (100 ml) and water (50 ml) were added and phases were separated. The aqueous phase was extracted with additional ethyl acetate (2×20 ml). The combined organic extracts were washed with brine (2×50 ml), dried ($MgSO_4$) and the solvent was removed under reduced pressure to give the crude oxazolidinones as a dark red oil. Flash column chromatography on silica gel using petrol/ethyl acetate (2:1) as eluent afforded oxazolidinones **6** as a colorless oil (7.23 g, 75%) in a 2:1 (4*R*,5*S*)/(4*R*,5*R*) ratio. ν_{max}/cm^{-1} (film) 3293 (NH), 2954, 1760 (C=O); δ_H (500 MHz, $CDCl_3$) 6.85 (1H, br s, NH, major), 6.65 (1H, br s, NH minor), 6.00–5.75 (1H, m, C*H*=CH_2, major and minor), 5.37 (1H, d, J=18.3 Hz, CH=CH^a*H*^{b}, minor), 5.32 (1H, d, J=17.4 Hz, CH=CH^a*H*^{b}, major), 5.27 (1H, d, J=12.1 Hz, CH=C*H*^{a}H^b, minor), 5.20 (1H, d, J=10.5 Hz, CH=C*H*^{a}H^b, major), 5.05 (1H, dd, J=7.2, 7.0 Hz; H-5, minor), 4.72 (1H, dd, J=5.2, 5.1 Hz; H-5, major), 3.80 (1H, m, H-4, minor), 3.60–3.47 (3H, m, C*H*$_2$OTBS major and minor, H-4 major), 0.80 (9H, s, $(CH_3)_3$C major and minor), 0.00 (6H, s, $(CH_3)_2$Si major and minor), δ_C (125 MHz, $CDCl_3$) 160.30, 159.71, 135.46, 130.97, 120.66, 118.45, 80.97, 80.85, 64.07, 62.59, 57.62, 55.87, 21.03, 20.08, 15.06, 14.72, −5.05, −5.10; m/z (EI$^+$) 257 (M$^+$, 10%), 141 (60), 117 (80), 91 (100). Found (M$^+$) 257.1451 $C_{12}H_{23}NO_3Si$ requires 257.1447.

4.1.2. 6*S*-6-(*tert*-Butyldimethylsilanyloxymethyl)-3,6-dihydro-1*H*-pyridin-2-one 7. The mixture of vinyl oxazolidinones **6** (3.380 g, 13.1 mmol) and $PdCl_2(PPh_3)_2$ (911 mg, 1.3 mmol) in EtOH (50 ml) was transferred to a 300 ml autoclave. The autoclave was pressurized with CO (60 atm) and heated to 60°C (the pressure increased to 65 atm) with stirring for 32 h. After cooling and depressurization the crude reaction mixture was filtered through a short pad of Celite and the solvent was evaporated under reduced pressure. Purification of the crude material by column chromatography (eluted with EtOAc/petrol, 1:2) afforded the δ-lactam **7** as a pale yellow oil (2.57 g, 81%); $[\alpha]_D^{20}$=−10.4 (c=1.5, $CHCl_3$); ν_{max}/cm^{-1} (film) 3226 (br), 1656 (s), 1089 (br), 1022 (br), 800 (s); δ_H (500 MHz, $CDCl_3$) 6.51 (1H, br s, NH), 5.76 (1H, m, CH=C*H*), 5.56 (1H, m, C*H*=CH), 4.02 (1H, m, H-6), 3.63 (1H, dd, J=9.4, 4.0 Hz, one of CH_2OTBS), 3.37 (1H, dd, J=9.4, 8.6 Hz, one of CH_2OTBS), 2.86 (2H, m, 2H-3), 0.83 (9H, s, ^{t}Bu), 0.00 (6H, s, Si$(CH_3)_2$); δ_C (125 MHz, $CDCl_3$) −5.45, 18.44, 25.79, 31.53, 56.0, 66.91, 121.52, 128.00, 169.03; m/z (EI$^+$) 241 (M$^+$, 20%), 132 (80), 116 (40), 91 (100). Found (M$^+$) 241.1501, $C_{12}H_{23}NO_2Si$ requires 241.1498.

4.1.3. (1*R*,2*R*,6*S*) 2-(*tert*-Butyldimethylsilanyloxymethyl)-7-oxa-3-aza-bicyclo[4.1.0]heptan-4-one 8a and (1*S*,2*R*,6*R*) 2-(*tert*-butyldimethylsilanyloxymethyl)-7-oxa-3-aza-bicyclo[4.1.0]heptan-4-one 8b. To a stirred

suspension of the δ-lactam **7** (562 mg, 2.33 mmol) and sodium hydrogen carbonate (3 g, 35 mmol) in acetone (50 ml) and water (25 ml) was added Oxone (7.2 g, 11.66 mmol) over 5 min and the suspension was stirred for 3 h at room temperature when TLC indicated complete consumption of the stating material. The organic phase was extracted into ethyl acetate (3×50 ml), and the combined organic extracts were washed with 10% aqueous sodium bisulfite (50 ml) and water (2×50 ml), dried ($MgSO_4$) and the solvent was removed under reduced pressure to give the mixture of epoxides **8a** and **8b** as a yellow oil. Purification by column chromatography (eluted with EtOAc/petrol, 1:1) gave **8a** (457 mg, 76%) as a colorless oil; $[\alpha]_D^{20}=+32.5$ ($c=1.0$, $CHCl_3$); ν_{max}/cm^{-1} (film) 3140 (NH), 1645 (C=O), 1030; δ_H (500 MHz, $CDCl_3$) 7.30 (1H, br s, NH), 3.80 (1H, m, H-2), 3.73 (1H, dd, $J=10.4$, 3.3 Hz, one of CH_2OTBS), 3.68 (1H, dd, $J=10.4$, 4.6 Hz, one of CH_2-OTBS), 3.31 (1H, dd, $J=4.1$, 2.1 Hz; H-1), 3.25 (1H, br d, $J=4.1$ Hz, H-6), 2.77 (1H, br d, $J=18.3$ Hz, one of H-5), 2.67 (1H, br d, $J=18.3$ Hz, one of H-5) 0.81 (9H, s, ^{t}Bu), 0.00 (3H, s, one of $(CH_3)_2Si$), −0.02 (3H, s, one of $(CH_3)_2Si$); δ_C (125 MHz, $CDCl_3$) 175.6, 68.2, 61.7, 52.8, 50.4, 40.1, 21.3, 14.5, −5.5; *m/z* (EI^+) 257 (M^+, 20%), 141 (80), 116 (40), 91 (100). Found (M^+) 257.1460, $C_{12}H_{23}NO_3Si$ requires 257.1447; and **8b** as a colorless oil (109 mg, 19%); $[\alpha]_D^{20}=-9.6$ ($c=0.2$, $CHCl_3$); ν_{max}/cm^{-1} (film) 3140 (NH), 1645 (C=O), 1030; δ_H (500 MHz, $CDCl_3$) 5.93 (1H, br s, NH), 3.78 (1H, d, $J=10.6$ Hz, one of CH_2OTBS), 3.76 (1H, d, $J=10.6$ Hz, one of CH_2OTBS), 3.58 (1H, t, $J=10.6$ Hz, H-2), 3.33 (1H, ddd, $J=4.3$, 2.1, 1.8 Hz; H-6), 3.19 (1H, d, $J=4.3$ Hz, H-1), 2.84 (1H, dd, $J=18.6$, 1.8 Hz, one of H-5), 2.64 (1H, dd, $J=18.6$, 2.1 Hz, one of H-5), 0.81 (9H, s, ^{t}Bu), 0.00 (6H, $Si(CH_3)_2$); δ_C (125 MHz, $CDCl_3$) 179.0, 67.5, 62.8, 51.9, 50.6, 38.1, 25.1, 13.8, −4.8; *m/z* (EI^+) 257 (M^+, 20%), 141 (80), 116 (40), 91 (100). Found (M^+) 257.1460, $C_{12}H_{23}NO_3Si$ requires 257.1447.

4.1.4. (5*S*,6*R*)-6-(*tert*-Butyldimethylsilanyloxymethyl)-5-hydroxy-5,6-dihydro-1*H*-pyridin-2-one 9a. A solution of epoxide **8a** (157 mg, 0.61 mmol) and DBU (185 mg, 1.22 mmol) in CH_2Cl_2 (10 ml) was heated at reflux for 3 h at which time tlc indicated complete consumption of the starting material. Saturated aqueous ammonium chloride (10 ml) was added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2×10 ml), the combined organic extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure to give a yellow oil. Purification by column chromatography (eluted with EtOAc/petrol, 1:1) gave the dihydropyridinone **9a** as a pale yellow oil (149 mg, 95%); $[\alpha]_D^{20}=-23.5$ ($c=1.1$, $CHCl_3$); ν_{max}/cm^{-1} (film) 3210 (br NH, OH), 1608 (C=O), 1022; δ_H (500 MHz, $CDCl_3$) 6.50 (1H, dd, $J=-10.1$, 3.1 Hz; H-4), 6.31 (1H, br s, NH), 5.77 (1H, dd, $J=10.1$, 1.8 Hz; H-3), 4.23 (1H, m, H-5), 3.75–3.66 (2H, m, H-6 and OH), 3.58 (1H, dd, $J=15.2$, 1.2 Hz, one of CH_2OTBS), 3.55 (1H, dd, $J=15.2$, 1.0 Hz, one of CH_2OTBS), 0.81 (9H, s, ^{t}Bu), 0.00 (3H, s, one of $Si(CH_3)_2$), −0.02 (3H, s, one of $Si(CH_3)_2$); δ_C (125 MHz, $CDCl_3$) 165.2, 143.6, 123.9, 65.3, 64.5, 58.8, 25.8, 18.2, −5.5; *m/z* (EI^+) 257 (M^+, 10%), 125 (60), 132 (50), 91 (100). Found (M^+) 257.1455, $C_{12}H_{23}NO_3Si$ requires 257.1447.

4.1.5. (5*R*,6*R*)-6-(*tert*-Butyldimethylsilanyloxymethyl)-5-hydroxy-5,6-dihydro-1*H*-pyridin-2-one 9b. Following the procedure for the synthesis of **9a**, epoxide **8b** (35 mg, 0.14 mmol) afforded the dihydropyridinone **9b** (33 mg, 95%) as a pale yellow oil: $[\alpha]_D^{20}=-19.2$ ($c=0.4$, $CHCl_3$); ν_{max}/cm^{-1} (film) 3210 (br NH, OH), 1608 (C=O), 1022; δ_H (500 MHz, $CDCl_3$) 6.62 (1H, dd, $J=10.5$, 4.9 Hz, H-4), 5.85 (1H, d, $J=10.5$ Hz, H-3), 5.82 (1H, br s, NH), 4.17 (1H, m, H-5), 3.79 (1H, m, H-6), 3.45 (1H, dd, $J=10.8$, 2.5 Hz, one of CH_2OTBS), 3.39 (1H, dd, $J=10.8$, 3.4 Hz, one of CH_2OTBS), 2.85 (1H, br s, OH), 0.8 (9H, s, ^{t}Bu), 0.00 (6H, s, $Si(CH_3)_2$); δ_C (125 MHz, $CDCl_3$) 165.5, 143.8, 122.0, 70.9, 65.8, 55.8, 20.8, 14.5, −6.0; *m/z* (EI^+) 257 (M^+, 10%), 125 (60), 132 (50), 91 (100). Found (M^+) 257.1455, $C_{12}H_{23}NO_3Si$ requires 257.1447.

4.1.6. (3*S*,4*S*,5*R*,6*R*)-6-(*tert*-Butyldimethylsilanyloxymethyl)-3,4,5-trihydroxy-piperidin-2-one 10a. To a stirred solution of the dihydropyridinone **9a** (204 mg, 0.79 mmol) and NMO (321 mg, 2.4 mmol) in ^{t}BuOH (10 ml) was added a drop of water and osmium tetroxide (1.5 ml, 0.05 M solution in ^{t}BuOH, 75 μmol) and the resulting solution was stirred at room temperature for 3 h. The reaction was quenched by addition of aqueous saturated sodium metabisulfite (5 ml) and concentrated on a rotary evaporator. To the resulting mixture was added ethyl acetate (30 ml) and water (10 ml), the layers were separated, and the organic layer was washed with 1 M HCl (5 ml) and water (10 ml), dried ($MgSO_4$) and the solvent was removed under reduced pressure to give the crude product mixture. NMR analysis indicated the presence of two diastereomeric dihydroxylation products in a 3.2:1 ratio. Column chromatography (elution with 20:1 DCM/MeOH) afforded the major diastereoisomer, triol **10a**, a white prisms (98 mg, 43%): mp 125–127°C; $[\alpha]_D^{20}=4.5$ ($c=0.8$, $CHCl_3$); ν_{max}/cm^{-1} (KBr) 3324 (br, OH), 1741 (C=O), 1116, 838; δ_H (500 MHz, d_6-DMSO) 7.04 (1H, br s, NH), 5.05 (1H, d, $J=3.7$ Hz, H-3), 4.87 (1H, d, $J=7.4$ Hz, H-5), 4.63 (1H, d, $J=4.2$ Hz, H-6), 3.88 (1H, m, H-4), 3.71–3.58 (2H, m, CH_2OTBS), 3.30 (3H, br s, OH), 0.82 (9H, s, ^{t}Bu), 0.01 (3H, s, one of $Si(CH_3)_2$), −0.01 (3H, s, one of $Si(CH_3)_2$); δ_C (125 MHz, d_6-DMSO) 172.1, 71.6, 68.7, 65.4, 62.0, 56.3, 25.8, 17.9, −5.3. *m/z* (CI^+) 292 (MH^+, 37%), 234 (100), 216 (15), 116 (15), 75 (30). Found (MH^+) 292.1593, $C_{12}H_{26}NO_5Si$ requires 292.1580. The minor diastereoisomer **10b** was not isolated.

4.1.7. (3*S*,4*S*,5*R*,6*R*)-3,4,5-Triacetoxy-1-acetyl-2-(*tert*-butyldimethylsilanyloxymethyl)-6-oxo-piperidine 11a and (3*R*,4*R*,5*R*,6*R*)-3,4,5-triacetoxy-2-(*tert*-butyldimethylsilanyloxymethyl)-6-oxo-piperidine 11b. To the crude dihydroxylation product of dihydropyridinone **9a** (210 mg, 0.81 mmol) was added acetic anhydride (20 ml) and the resulting mixture was refluxed for 4 h, cooled to room temperature and concentrated on a rotary evaporator. Column chromatography (eluting with ethyl acetate/petrol 1:2) afforded the tetraacetate **11a** as a pale yellow oil (171 mg, 44% from **9a**) $[\alpha]_D^{20}=+24.5$ ($c=1.2$, $CHCl_3$); ν_{max}/cm^{-1} (film) 1760, 1748, 1680, 1656, 1646, 1115, 920; δ_H (500 MHz, $CDCl_3$) 5.71 (1H, d, $J=2.4$ Hz, H-3), 5.66 (1H, dd, $J=4.3$, 2.4 Hz, H-4), 5.43 (1H, dd, $J=4.3$, 3.9 Hz, H-5), 4.55 (1H, m, H-6), 3.78 (1H, dd, $J=10.7$, 1.8 Hz, one of CH_2OTBS), 3.70 (1H, dd, $J=10.7$, 2.8 Hz, one of

CH_2OTBS), 2.46 (3H, s, Ac), 2.47 (3H, s, Ac), 2.10 (3H, s, Ac), 1.95 (3H, s, Ac), 0.81 (9H, s, ^{t}Bu), δ_C (125 MHz, $CDCl_3$) 172.3, 169.7, 169.2, 168.8, 167.8, 68.5, 67.9, 67.3, 64.1, 57.6, 27.6, 25.8, 25.7, 25.5, 20.6, 18.4, −5.6; *m/z* (EI^+) 459 (M^+, 5%), 417 (10), 375 (30), 333 (37), 44 (100). Found (M^+) 459.1937, $C_{20}H_{33}NO_9Si$ requires 459.1925 and the triacetate **11b** (41 mg, 12% from **9a**) as a colorless oil $[\alpha]_D^{20}=-9.7$ (*c*=0.6, $CHCl_3$); ν_{max}/cm^{-1} (film) 3120 (NH), 1751 (C=O), 1675 (C=O), 1655 (C=O), 1640 (C=O), 1115, 881; δ_H (500 MHz, $CDCl_3$) 5.98 (1H, br s, NH), 5.75 (1H, d, *J*=5.9 Hz, H-3), 5.39 (1H, d, *J*=5.9 Hz, H-4), 4.37 (1H, d, *J*=9.4 Hz, H-5), 4.00 (1H, m, H-6), 3.78 (1H, dd, *J*=10.7, 2.1 Hz, one of CH_2OTBS), 3.57 (1H, dd, *J*=10.7, 3.4 Hz, one of CH_2OTBS), 2.05 (3H, s, Ac), 2.04 (3H, s, Ac), 1.96 (3H, s, Ac), 0.82 (9H, s, ^{t}Bu), 0.00 (6H, s, $SiMe_2$); δ_C (125 MHz, $CDCl_3$) 170.9, 170.3, 169.7, 168.7, 80.8, 69.6, 66.1, 61.0, 50.1, 25.8, 23.2, 20.5, 20.2, 18.3, −5.5; *m/z* (EI^+) 417 (M^+, 13%), 375 (25), 333 (50), 291 (17), 44 (100). Found (M^+) 417.1823, $C_{18}H_{31}NO_8Si$ requires 417.1819.

4.1.8. D-Mannolactam (2). A solution of piperidinone **10a** (65 mg, 0.22 mmol) in TFA/water (1:1, 5 ml) was stirred for 10 h and the solvents were removed under reduced pressure to give the crude product, which was recrystallized from water to give **2** as white solid (27.3 mg, 70%) δ_H (300 MHz, D_2O) 3.20 (1H, m), 3.54 (2H, m), 3.76 (1H, dd, *J*=12.0, 5.2 Hz), 4.02 (2H, m); δ_C (75 MHz, D_2O) 57.3, 61.1, 67.1, 68.2, 71.8, 174.0; mp 164–167°C, $[\alpha]_D^{20}=+1.2$ (*c*=0.2, water) (lit.[27] mp 168–170°C, $[\alpha]_D^{20}=+1.6$ (*c*=1.0, water)).

4.1.9. (5*S*,6*R*)-1-Benzyl-5-benzyloxy-6-(*tert*-butyldimethylsilanyloxymethyl)-5,6-dihydro-1*H*-pyridin-2-one 12. To a stirred solution of dihydropyridinone **9a** (233 mg, 0.91 mmol) in dry DMF (20 ml) was added sodium hydride (73 mg, 60% dispersion in mineral oil, 1.8 mmol) at 0°C, the resulting mixture was stirred for 30 min and benzyl bromide (311 mg, 1.82 mmol) was added. The suspension was allowed to warm to room temperature and stirred for an additional 3 h. Saturated aqueous ammonium chloride (5 ml) was added followed by water (20 ml) and ethyl acetate (50 ml). The layers were separated and the aqueous layer was extracted with ethyl acetate (2×20 ml). the combined organic extracts were washed with brine (2×30 ml), dried ($MgSO_4$) and concentrated to give a crude oil which was purified by column chromatography (eluted with EtOAc/petrol, 1:3) to give the lactam **12** as a colorless oil (245.8 mg, 64%) $[\alpha]_D^{20}=97.0$ (*c*=1.5, $CHCl_3$); ν_{max}/cm^{-1} (film) 1668 (C=O), 1455, 1092; δ_H (500 MHz, $CDCl_3$) 7.36–7.14 (10H, m, Ar), 6.50 (1H, dd, *J*=9.7, 5.0 Hz; H-4), 6.17 (1H, d, *J*=9.7 Hz, H-3), 5.34 (1H, d, *J*=14.9 Hz, one of $PhCH_2N$), 4.38 (1H, d, *J*=11.6 Hz, one of $PhCH_2O$), 4.31 (1H, d, *J*=11.6 Hz, one of $PhCH_2O$), 4.11 (1H, dd, *J*=5.0, 1.5 Hz, H-5), 4.10 (1H, d, *J*=14.9 Hz, one of $PhCH_2N$), 3.72 (1H, ddd, *J*=9.2, 4.9, 1.5 Hz; H-6), 3.62 (1H, dd, *J*=10.1, 4.9 Hz, one of CH_2OTBS), 3.41 (1H, dd, *J*=10.1, 9.2 Hz, one of CH_2-OTBS), 0.86 (9H, s, ^{t}Bu), 0.02 (3H, s, one of $Si(CH_3)_2$), 0.00 (3H, s, one of $Si(CH_3)_2$); δ_C (125 MHz, $CDCl_3$) 162.2, 137.0, 134.4, 128.5, 128.2, 127.9, 127.8, 127.6, 127.4, 127.3, 126.8, 69.9, 68.2, 61.1, 59.5, 48.2, 25.6, 18.0, −5.6; *m/z* (EI^+) 437 (M^+, 20%), 345 (20), 228 (40), 117 (50), 92 (100). Found (M^+) 437.2390 $C_{26}H_{35}NO_3Si$ requires 437.2386.

4.1.10. (1*R*,4*R*,5*R*,8*S*)-2,4-Dibenzyl-8-(*tert*-butyldimethylsilanyloxy)-6-oxa-2-aza-bicyclo[3.2.1]octan-3-one 13. In a similar benzylation procedure, dihydropyridinone **9b** (132 mg, 0.75 mmol) gave bicycle **13** (66 mg, 50%) as a colorless oil: $[\alpha]_D^{20}=-12.9$ (*c*=0.5, $CHCl_3$); ν_{max}/cm^{-1} (film) 1675 (C=O), 1455, 1092; δ_H (500 MHz, $CDCl_3$) 7.34–7.20 (10H, m, Ar), 6.36 (1H, d, *J*=15.3 Hz, one of $PhCH_2N$), 4.82 (1H, dd, *J*=5.5, 2.5 Hz; H-8), 4.11 (1H, d, *J*=15.3 Hz, one of $PhCH_2N$), 3.80 (1H, dd, *J*=11.6, 2.5 Hz, H-5), 3.73 (2H, m, H-1 and H-4), 3.16 (1H, dd, *J*=20.4, 2.4 Hz, one of H-7), 3.01 (1H, dd, *J*=20.4, 5.1 Hz, one of H-7), 2.73 (1H, br d, *J*=11.6 Hz, one of $PhCH_2$), 2.67 (1H, br d, *J*=11.6 Hz, one of $PhCH_2$), 0.86 (9H, s, ^{t}Bu), 0.00 (6H, s, $Si(CH_3)_2$); δ_C (125 MHz, $CDCl_3$) 169.7, 137.1, 136.3, 128.6, 128.5, 128.1, 127.8, 127.5, 127.3, 91.8, 69.5, 61.9, 60.3, 56.7, 47.4, 31.2, 25.8, 18.2, −5.5; *m/z* (EI^+) 437 (M^+, 20%), 345 (20), 228 (40), 117 (50), 92 (100). Found (M^+) 437.2390 $C_{26}H_{35}NO_3Si$ requires 437.2386.

4.1.11. (3*S*,4*R*,5*R*,6*R*)-1-Benzyl-5-benzyloxy-6-(*tert*-butyldimethylsilanyloxymethyl)-3,4-dihydroxy-piperidin-2-one 15. To a stirred solution of dihydropyridinone **12** (303 mg, 0.7 mmol) and NMO (284 mg, 2.1 mmol) in ^{t}BuOH was added a drop of water and osmium tetroxide (1 ml, 0.05 M solution in ^{t}BuOH, 0.05 mmol), the reaction mixture was stirred for further 3 h at room temperature, quenched by addition of aqueous saturated sodium metabisulfite (5 ml) and concentrated on a rotary evaporator. To the resulting mixture was added ethyl acetate (50 ml) and water (20 ml). The layers were separated and the organic layer was washed with 1 M HCl (10 ml) and water (2×10 ml), dried ($MgSO_4$) and the solvent was removed under reduced pressure. Purification of the crude product by column chromatography (eluted with ethyl acetate) gave the piperidinone **15** (293 mg, 89%) as white solid: mp 87–89°C; $[\alpha]_D^{20}=23.6$ (*c*=1.1, $CHCl_3$); ν_{max}/cm^{-1} (KBr) 3409 (OH), 1645 (C=O), 1250, 1074; δ_H (300 MHz, $CDCl_3$) 7.39–7.11 (10H, m, Ar), 5.27 (1H, d, *J*=15.6 Hz, one of $PhCH_2$), 4.50 (1H, d, *J*=12.0 Hz, one of $PhCH_2$), 4.44 (1H, d, *J*=12.0 Hz, one of $PhCH_2$), 4.42 (1H, m, H-3), 4.37 (1H, td, *J*=3.6, 2.1 Hz, H-6), 4.32 (1H, d, *J*=15.6 Hz, one of $PhCH_2$), 3.97 (1H, dd, *J*=2.1, 1.8 Hz, H-4), 3.61–3.78 (3H, m, CH_2OTBS and H-5), 3.39 (1H, br s, OH), 3.21 (1H, br s, OH), 0.80 (9H, s, ^{t}Bu), 0.01 (3H, s, one of $SiMe_2$), −0.01 (3H, s, one of $SiMe_2$); δ_C (75 MHz, $CDCl_3$) 171.2, 137.4, 128.5, 128.4, 128.2, 127.8, 127.7, 127.5, 127.4, 75.2, 71.4, 69.6, 68.9, 68.1, 58.9, 47.6, 20.8, 15.6, −5.6. Found (M^+) 471.2462 $C_{26}H_{37}NO_5Si$ requires 471.2441.

4.1.12. (3*R*,4*R*,5*R*,6*R*)-1-Benzyl-5-benzyloxy-6-(*tert*-butyldimethylsilanyloxymethyl)piperidin-3,4-diol 16. To a stirred solution of piperidinone **15** (183 mg, 0.39 mmol) in diethyl ether (20 ml) was added $LiAlH_4$ (76 mg, 2.0 mmol), the resulting suspension was stirred for 3 h at room temperature and quenched at 0°C via slow addition of 10% aqueous NaOH until all visible $LiAlH_4$ had been consumed. The reaction mixture was filtered, dried and concentrated to give a crude oil, which was purified by column chromatography (eluted with EtOAc) to give

piperidine **16** (160 mg, 89%) as a pale yellow oil: $[\alpha]_D^{20}=-18.6$ ($c=1.0$, $CHCl_3$); ν_{max}/cm^{-1} (film) 3070 (OH), 1495, 1098; δ_H (300 MHz, $CDCl_3$) 7.40–7.20 (10H, m, Ar), 4.90 (1H, d, $J=11.1$ Hz, one of PhCH_2), 4.56 (1H, d, $J=11.1$ Hz, one of PhCH_2), 4.16 (1H, d, $J=13.2$ Hz, one of PhCH_2), 3.83 (1H, dd, $J=10.4$, 2.6 Hz, H-5), 3.76 (1H, dd, $J=10.4$, 2.6 Hz, H-5), 3.73 (1H, m, H-3), 3.64 (1H, m, H-6), 3.55 (1H, dd, $J=8.4$, 3.3 Hz, one of CH_2OTBS), 3.27 (1H, d, $J=12.9$ Hz, one of PhCH_2), 2.91 (1H, dd, $J=12.2$, 4.4 Hz, one of H-2), 2.82 (2H, br s, OH), 2.38 (1H, dd, $J=8.4$, 2.6 Hz, one of CH_2OTBS), 2.21 (1H, dd, $J=12.2$, 1.5 Hz, one of H-2), 0.09 (9H, ^{t}Bu), 0.08 (6H, $SiMe_2$); δ_C (75 MHz, $CDCl_3$) 138.6, 138.5, 128.9, 128.4, 127.9, 127.7, 127.6, 127.2, 78.4, 74.6, 73.3, 68.1, 66.9, 64.7, 56.7, 54.7, 21.0, 15.4, −5.5; *m/z* (EI^+) 457 (M^+, 37%), 367 (60), 253 (18), 117 (50), 91 (100). Found (M^+) 457.2450 $C_{26}H_{39}NO_4Si$ requires 457.2648.

4.1.13. Deoxymannojirimycin hydrochloride salt 1. To a stirred solution of piperidine **16** (158 mg, 0.34 mmol) in THF (10 ml) was added TBAF (0.5 ml, 1 M solution in THF, 0.5 mmol) and the resulting solution was stirred for 1 h and then concentrated. The resulting mixture was taken up in ethyl acetate (30 ml) and washed with water (2×10 ml), dried ($MgSO_4$) and the solvent was removed under reduced pressure to give a crude solid, ^{1}H NMR of which showed complete TBS deprotection. To the crude solid was added EtOH (5 ml), 10% Pd on carbon (0.36 g) and conc. HCl (3 ml), and the mixture was placed under an atmosphere of H_2 and stirred at rt for 2 h. The reaction mixture was then filtered and the solvent removed under reduced pressure to give the crude product which was recrystallized (MeOH) to give pure deoxymannojirimycin hydrochloride **1** (45 mg, 68%) as a white solid: mp 192–195°C; δ_H (500 MHz, D_2O) 3.00 (1H, ddd, $J=10.0$, 6.5, 3.0 Hz), 3.10 (1H, d, $J=14.0$ Hz), 3.28 (1H, dd, $J=14.0$, 3.0 Hz), 3.56 (1H, dd, $J=9.6$, 3.0 Hz), 3.70 (1H, dd, $J=12.5$, 6.0 Hz), 3.75 (1H, t, $J=6.8$ Hz), 6.85 (1H, dd, $J=12.5$, 3.5 Hz), 4.10 (1H, m); δ_C (125 MHz, D_2O) 48.25, 58.80, 61.10, 66.40, 66.60, 73.14; $[\alpha]_D^{20}=-13.2$ ($c=0.8$, water) (lit.[29] $[\alpha]_D^{20}=-13.8$ ($c=1.1$, water)).

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