DMSO. Procedure A: same as procedure B, omitting sonication.)
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Asymmetric Synthesis of L-Deoxymannojirimycin

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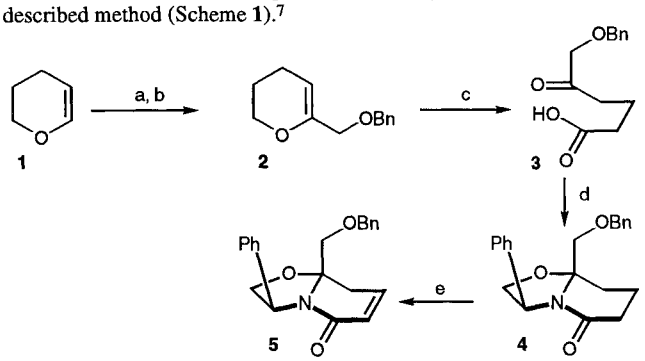
Dedicated to Professor E. J. Corey for his outstanding contributions to organic chemistry.

Abstract: Starting from dihydropyran **1**, the chiral lactam **4** was rapidly obtained. Following unsaturation, highly diastereoselective allylic oxidation and dihydroxylation furnished lactam **7** from which the azasugar, L-deoxymannojirimycin, could be prepared.

The synthesis of azasugars has stimulated a great deal of attention due to their importance as glycosidase inhibitors,[1] showing potential for the treatment of cancer[2] and viral infections.[3] As part of our continuing interest in the preparation of these compounds,[4] utilising the nonracemic lactam methodology developed in our laboratories,[5] we prepared the titled compound from noncarbohydrate precursors.

The synthetic route began with the keto-acid **3**, available from dihydropyran **1** in three steps. Metallation of dihydropyran[6] and reaction with paraformaldehyde gave a primary alcohol which was protected as its benzyl ether **2**. The latter was hydrolysed and oxidised to yield the keto-acid **3**. Cyclodehydration of this acid with *S*-phenylglycinol furnished the lactam **4** ($[\alpha]_D^{23}$ +82.5, CH_2Cl_2) in 40% overall yield from dihydropyran, without purification or separation of the intermediates. Introduction of the unsaturation to produce **5** ($[\alpha]_D^{23}$ -15.1, CH_2Cl_2) was accomplished in 85% yield by a previously described method (Scheme **1**).[7]

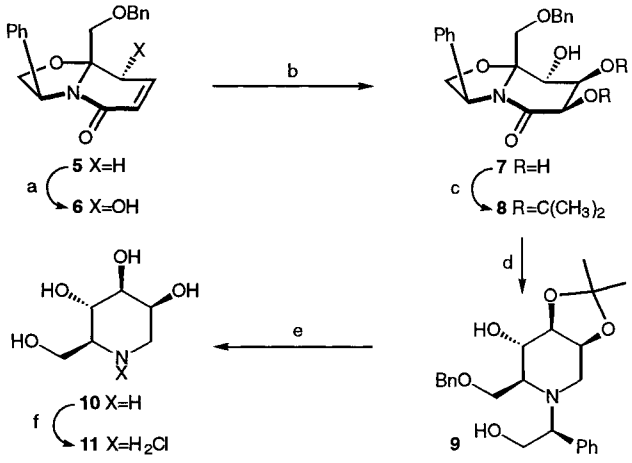


a t-BuLi, $(CH_2O)_n$, THF, -78°C, 70%; b NaH, BnBr, DMF, 92%; c CrO_3 / H_2SO_4, THF, 70%; d *S*-phenylglycinol, PhMe, Δ, 80%; e KH, $PhSO_2Me$, THF, then PhMe, Δ, 85%

Scheme **1**

Stereospecific introduction of three hydroxyl groups, present in the azasugars, was the next task to be undertaken. We found that allylic oxidation of lactam **5** with SeO_2 gave the allylic alcohol **6** ($[\alpha]_D^{23}$ -82.9, CH_2Cl_2) in 64% yield as a single diastereomer. Subsequent dihydroxylation produced the triol, again as a single diastereoisomer.

The stereochemistry of **7** ($[\alpha]_D^{23}$ +130.2, CH_2Cl_2) was assigned subsequently upon completion of the synthesis of L-deoxymannojirimycin, however, at this point the stereochemistry was still unknown. Protection of the *cis*-diol as the acetonide **8** ($[\alpha]_D^{23}$ +11.8, CH_2Cl_2) gave the requisite intermediate for the lactam reduction and key opening of the oxazolidine ring to unmask the desired piperidine ring system. It was crucial that cleavage of the oxazolidine C-O bond in **8** proceeded with high stereoselectivity to prevent the formation of **9** as an epimeric mixture at C-2 of the piperidine ring.



a SeO_2, dioxane, Δ, 64%; b OsO_4 / NMO, acetone / water, 83%; c $(CH_3)_2C(OMe)_2$,CH_2Cl_2, pTSA, 75%; d BH_3. THF, THF, Δ, 65%; e H_2 / $Pd(OH)_2$, EtOH then TFA, MeOH, 75%; f HCl, Et_2O, 100%.

Scheme **2**

After a variety of reducing agents were screened, BH_3•THF, in refluxing THF, was found to produce the piperidine **9** in 65% yield as a 20:1 ratio of epimers at C-2, (Scheme **2**).

The acetonide, O-benzyl, and N-benzyl groups were all removed in a single step and the resulting azasugar **10** was purified using Dowex WX2 (Fluka) ion exchange resin. Comparison of the ^{1}H-nmr of the hydrochloride salt of our sample with that of an authentic sample[1] confirmed the identity of the azasugar and the optical rotation of **11** ($[\alpha]_D^{23}$ +9.6 (c 1.2, H_2O)), lit.[8] $[\alpha]_D^{20}$ +10.2 (H_2O)) enabled the assignment of the *L* configuration to be made.

With the completion of the synthesis, and a knowledge of the absolute stereochemistry of L-deoxymannojirimycin we could now deduce the outcome of the stereochemical issues in the synthesis. The initial oxidation of **5** must have occurred from the α-face of the lactam and installed the hydroxyl in a pseudo-axial position. Approach of the SeO_2 from the α-face may be due to the benzyloxymethyl group shielding the β-face. Dihydroxylation of **6** furnished the β-diol, anti to the hydroxyl group, and this has been observed previously in an analogous, racemic system.[9] After diol protection the pivotal borane reduction of the carbonyl moiety and opening of the oxazolidine ring in **8** occurred from the least sterically hindered α-face of the lactam. By forming the acetonide in **8**, we had, in effect added another "steric control element" which directed the reduction.[10] The stereoselective opening of the oxazolidine may also involve complexation of the reducing agent to the free hydroxyl group.

In conclusion, the rapid synthesis of L-deoxymannojirimycin was accomplished in only 6 steps and 17% overall yield from the readily available lactam **4**.[11] All manipulations to introduce the hydroxyl funtionalities occurred with excellent diastereoselctivities demonstrating the high stereocontrol available from non-racemic lactams.

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(11) **Selected Experimental and Physical Data**
Lactam **6**; SeO_2 (239 mg, 2.16 mmol) was added to a solution of lactam **5** (722 mg, 2.16 mmol) in anhydrous dioxane (10 ml) at room temperature, under argon. The reaction was heated under reflux for 12 hr, allowed to cool to room temperature and filtered through a pad of Celite to remove selenium residues. The yellow solution was taken up in EtOAc (40 ml), washed with water (15 ml), dried ($MgSO_4$), and evaporated under reduced pressure. The resulting yellow oil was purified by flash column chromatography on silica gel (70% EtOAc:hexanes) to yield **6** as a pale yellow oil (485 mg, 64%), δ_H (300 MHz, $CDCl_3$) 2.65 (br s, 1H), 3.51 (d, *J* 10.7 Hz, 1H), 3.55 (d, *J* 10.7 Hz, 1H), 4.21 (dd, *J* 8.9 and 6.1 Hz, 1H), 4.45 (d, *J* 11.9 Hz, 1H), 4.60 (m, 3H), 5.33 (dd, *J* 7.4 and 5.8 Hz, 1H), 6.10 (d, *J* 9.7 Hz, 1H), 6.64 (dd, *J* 9.7 and 6.1 Hz, 1H) and 7.30 (m, 10H); δ_C (75 MHz, $CDCl_3$) 58.6, 62.7, 70.8, 72.3, 73.4, 94.7, 126.0, 127.0, 127.4, 127.6, 127.7, 128.3, 128.5, 136.9, 137.2, 138.7, 161.9, $[\alpha]_D^{74}$ -82.9 (c 1.7, CH_2Cl_2).
Triol **7**; A solution of NMO (323 mg, 2.76 mmol) in water (1 ml) was added in one portion, at room temperature to a solution of lactam **6** (485 mg, 1.38 mmol) in acetone (3 ml). OsO_4 (0.4 ml of a 2.5% w/w solution in ^{t}BuOH) was added and the reaction stirred for 3 hr, the black mixture was then loaded directly onto a silica column and eluted with neat EtOAc to yield the triol **7** as a white foam (438 mg, 83%), δ_H (300 MHz, $CDCl_3$) 3.31 (br s, 1H), 3.48 (d, *J* 10.7 Hz, 1H), 3.80 (br s, 1H), 3.96 (d, *J* 10.7 Hz, 1H), 4.05 (dd, *J* 8.5 and 7.0 Hz, 1H), 4.43 (d, *J* 11.6 Hz, 1H), 4.50 (m, 3H), 4.64 (app t, *J* 8.9 Hz, 1H), 4.74 (s, 1H), 5.41 (app t, *J* 7.0 Hz, 1H) and 7.30 (m, 10H); δ_C (75 MHz, $CDCl_3$) 58.9, 66.1, 67.4, 68.5, 69.5, 70.2, 73.3, 94.4, 125.1, 127.3, 127.6, 127.8, 128.2, 128.5, 137.3, 139.3 and 171.1, $[\alpha]_D$ 130.2 (c 1.13, CH_2Cl_2).
Piperidine **9**; BH_3•THF complex (4.72 ml of a 1.00 M solution in THF, 4.72 mmol) was added dropwise to a stirred solution of the lactam **8** (200 mg, 0.47 mmol) in THF (10 ml) at room temperature, under argon. The reaction was heated under reflux for 30 min and then cooled to 0°C, 2 M NaOH (1 ml) and 30% H_2O_2 (1 ml) were then cautiously added and stirred at 0°C for 30 min. The reaction mixture was poured onto water (20 ml) and the aqueous extracted with EtOAc (3 x 20 ml), the combined organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure. Purification of the resulting yellow oil by column chromatography on silica (30% EtOAc:hexanes) gave the piperidine **9** as a clear oil (126 mg, 65%), δ_H (300 MHz, $CDCl_3$) 1.30 (s, 3H), 1.48 (s, 3H), 2.74 (dd, *J* 14.3 and 3.1 Hz, 1H), 2.94 (m, 3H), 3.68 (dd, *J* 11.0 and 4.9 Hz, 1H), 3.81 (d, *J* 4.9 Hz, 2H), 3.98 (m, 4H), 4.12 (dd, *J* 11.0 and 4.9 Hz, 1H), 4.60 (s, 2H) and 7.30 (m, 10H); δ_C (75 MHz, $CDCl_3$) 25.0, 27.1, 43.6, 60.6, 61.1, 63.8, 69.0, 70.3, 71.9, 73.4, 77.7, 109.2, 127.8, 127.8, 128.1, 128.4, 128.5, 137.6 and 137.7.