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Asymmetric Routes to Azasugars from Chiral Bicyclic Lactams. Synthesis of 1,4-Dideoxy-1,4-imino-D-lyxitol; L-Deoxymannojirimycin; *rhammo*-1-Deoxynojirimycin and 1-Deoxy-6-epicastanospermine.[1]

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Summary: By employing the appropriate chiral bicyclic lactams, the asymmetric total synthesis of four enantiopure azasugars mentioned in the title were successfully achieved. A series of diastereoselective oxidations (OsO_4/NMO) followed by diastereoselective reductions (BH_3, 9-BBN) gave good yields of the trisubstituted (**16**) and tetrasubstituted (**2,3,4**) pyrrolidine and piperidines respectively.

Keywords: Hydroxylation, Aza Compounds, Anti-tumor, Antibiotics

Azasugars have generated a great deal of synthetic interest because of their ability to mimic carbohydrates in various biological processes.[2] They function as potent inhibitors of glycosidases[2] and they have been shown to have considerable activity in cancer,[3] diabetes,[2] and viral infections (anti-HIV behavior).[4]

The core structure of an azasugar may contain various heterocyclic ring sizes such as polyhydroxyl pyrrolidines **1**,[5a] polyhydroxy piperidines **2,3**[5b] and the bicyclic [4.3.0] system, indolizidines, **4**.[5c] We now wish to describe in detail our overall program which has led to the syntheses of **1-4** from non-carbohydrate precursors in high enantiomeric purity. The starting materials employed in this work were the readily available chiral bicyclic lactams (Scheme 1 and 4), some of which are now commercially available. [6] There have been a number of synthetic efforts to reach these and other azasugars both from carbohydrate[7] and non-carbohydrate[8] starting materials and many of these routes suffer from excess length and/or lack of stereoselectivity. It is to be noted that asymmetric routes to systems such as **1-4** will require incorporation of three or four stereogenic centers consisting of three or four hydroxyl substituents.

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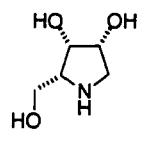
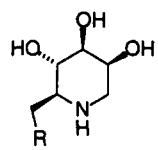
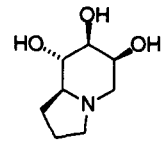


(-)-1



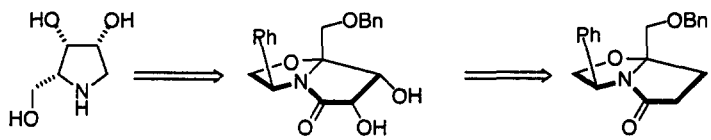
(+)-2, R = OH
(+)-3, R = H



(+)-4

We, therefore, felt that the chiral bicyclic lactams would offer a highly versatile entry into a wide assortment of azasugars with the ability to allow considerable variation in the stereochemical placement of the substituents. When carbohydrate precursors are employed, one is generally confined to the stereochemistry of the starting sugar, although many variations of these exist.[7]

Scheme 1

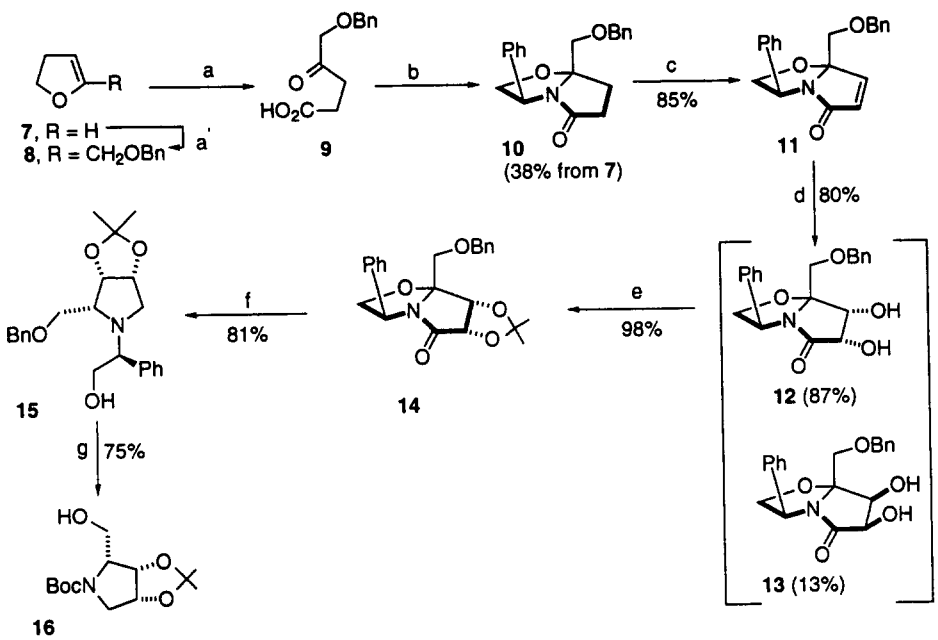


2*R*,3*S*,4*R*-(-)-1 **12** **10**

The synthetic strategy to reach pyrrolidine systems such as (-)-**1** is outlined in Scheme 1. It was envisioned that bicyclic lactam **10**, which contained a benzyloxymethyl C-2 substituent, could be elaborated to the α,β-unsaturated lactam. The olefin moiety would be subjected to dihydroxylation conditions to afford **12** with some degree of *endo-exo* selectivity to make the route viable. Reductive cleavage of **12** and debenzylation would then complete the route to (-)-**1** in a relatively efficient manner.

The preparation of pyrrolidine (-)-**1** began with the synthesis of the requisite ketoacid **9** (Scheme 2). Treatment of 2,3-dihydrofuran **7** under metallation conditions followed by quenching with BOMCl afforded **8**. Oxidation of **8** with Jones reagent afforded ketoacid **9** which was condensed with *S*-phenylglycinol under cyclodehydration conditions to afford lactam **10** in 40% overall yield from **7**. The introduction of the unsaturation to produce **11** was carried out using a method devised in our laboratory several years ago.[9] Although the published route utilized KH to generate the enolate, we have subsequently found that LiHMDS may be also employed and is more convenient. With **11** in hand, attention turned toward the introduction of the two new hydroxyl stereocenters with a high level of selectivity. Treatment of **11** with OsO_4-NMO afforded an 87:13

Scheme 2

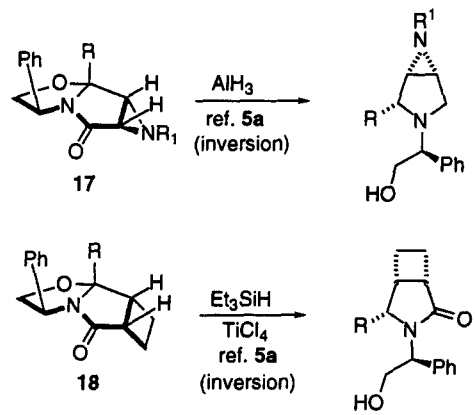


Scheme 2: a') t-Buli, THF, BOMCl, –78°C; a) Jones rgt, 25 °C; b) (*S*)-phenylglycinol, toluene, Δ; c) LiHMDS, $PhSO_2Me$, THF; Δ, toluene; d) OsO_4, NMO, aq. acetone; e) 2, 2-dimethoxypropane, *p*-TsOH, CH_2Cl_2; f) 9-BBN, 10 equiv., THF; g) H_2-$Pd(OH)_2$, Boc_2O

(NMR) mixture of **12** and **13** and the crude mixture was subjected to chromatography and recrystallization to afford **12** in 64% yield. The *endo*-facial selectivity during the dihydroxylation step was confirmed by single-crystal X-ray determination of **12**.[10] The two hydroxyl groups were protected as the acetonide under standard conditions to afford **14** and attention was directed towards the critical C-O cleavage step to afford **15** (single diastereomer, NMR). The reduction had to proceed with high stereoselectivity to prevent the formation of **15** as an epimeric mixture at C-2. In a number of instances, these reductions have proceeded with retention of configuration of the angular substituent.[11] We had also previously described reduction of the ring C-O bond in related systems (Scheme 3) wherein hydride delivery to **17** proceeded with inversion producing the all-*cis* substituted pyrrolidine. In another case, we reduced the ring C-O bond in **18** using Et_3SiH-$TiCl_4$ and also observed inversion to the all-*cis* cyclobutano-fused pyrrolidine. While in both of these cases, the angular substituent underwent inversion of configuration, it was deemed that the

acetonide in **14** would serve as a "steric control element" in the reduction step.[12] In the event, treatment of **14** with alane, used successfully in earlier studies,[11] resulted in only a 2:1 mixture of

Scheme 3

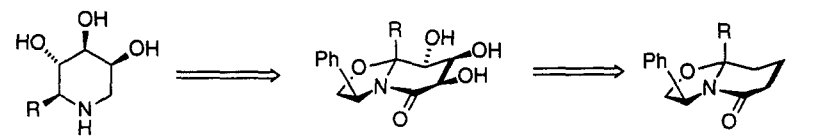


15 epimeric at C-2. Variation of solvents, temperature, and different diol protecting groups under these reaction conditions failed to improve the diastereomeric ratio. In addition, attempts to cleave the C-O bond with exposed, unprotected hydroxyl groups under reductive conditions also failed, mainly due to solubility problems. After considerable experimentation, treatment of **14** with 9-BBN (10 eq) in THF afforded **15** in 81% yield as a single diastereomer. The stereochemistry at C-2 was tentatively assigned as shown and would reveal itself in the final product. Hydrogenolyses of the *N*-benzyl and *O*-benzyl groups under standard conditions in the presence of Boc_2O afforded **16** in 75% yield. The preparation of the Boc derivative aided in the characterization and its physical data were in good agreement with those reported by Fleet.[13] The fact that the data agreed with (2*R*,3*S*,4*R*)-**16** and also gave $[\alpha]_D$ -38.9 ($CHCl_3$) (Fleet's compound[14] gave $[\alpha]_D$ -42.2) strongly supports the 9-BBN stereoselective reduction as having proceeded with the expected inversion at the benzyloxy methyl group in **14**. Thus, one may consider the acetonide in **14** as a steric control element, much the same as the aziridine in **17** and the cyclobutane group in **18**. It is also noteworthy that the carbonyl group in the latter case was simultaneously reduced to afford pyrrolidine **15**. In summary, the protected 1,4-dideoxy-1,4-imino-D-lyxitol, **16**, which has been previously transformed[14] into the hydroxy system, **1**, was prepared in eight steps in 12% overall yield from dihydrofuran **7** in high enantiomeric purity (>95% ee).

As a further extension of this work, attention was turned toward the synthesis of piperidine systems **2**, **3**, and **4** which have **four** stereogenic centers. As discussed above, **16** required the *syn*-glycol (introduced by osmylation) along with the appropriate angular substituent. In the

piperidine series, the synthetic approach would have to involve the intermediates shown in Scheme 4. The starting 5,6-lactam **22a** (R = CH_2OBn) or **22b** (R = Me) would contain the appropriate 2-substituents in the final targets **2** and **3**. However, after introduction of the double bond in **22**, the key to this strategy will be the stereospecific introduction of **three** hydroxyl groups to afford **25**, which will ultimately provide azasugars **2** and **3**. Since this approach is not based on known, readily available carbohydrates which contain the mannose configuration, the three hydroxyls will need to be installed in the proper configuration.

Scheme 4



(+)-**2**, R = CH_2OH
(+)-**3**, R = Me

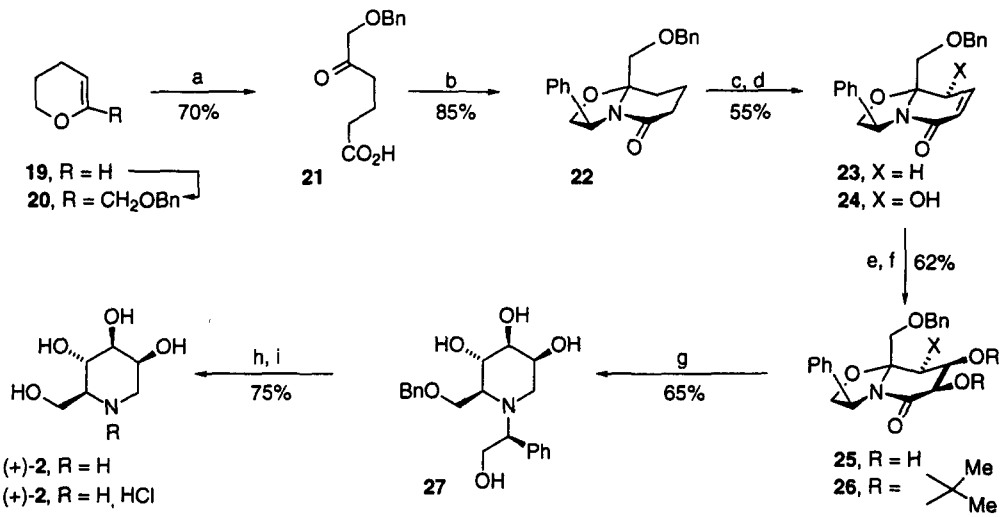
25a, R = CH_2OBn
b, R = Me

22a, R = CH_2OBn
b, R = Me

The initial task to be undertaken was to construct the bicyclic lactam **22** with the appropriate angular substituent (Scheme 5). Treatment of 2,3-dihydropyran **19** with *t*-BuLi and paraformaldehyde at -78 °C afforded the crude hydroxymethyl-2,3-dihydropyran which was converted directly to ether **20** under standard conditions in 65% overall yield (see Experimental). The requisite keto acid **21** was prepared by Jones oxidation in 70% yield from ether **20**. Cyclodehydration of ketoacid **21** in the presence of (*S*)-phenylglycinol in toluene at reflux afforded bicyclic lactam **22**. Treatment of lactam **22** under the conditions described previously (methyl phenylsulfinate and KH) afforded **23** and set the stage for an allylic oxidation to introduce the first hydroxy group. After considerable experimentation, it was found that treatment of **23** with SeO_2 in hot dioxane afforded the allylic alcohol **24** as a single diastereomer in 64% yield. At this point of the synthesis, the stereochemistry was tentatively assigned and would be determined later. The diol functionality was installed upon treatment under the dihydroxylation conditions (OsO_4, NMO) employed previously to afford **25**. Only a single diastereomer could be detected and the stereochemistry was tentatively shown as in **25**, and would have to be confirmed upon completion of the synthesis of L-deoxymannojirimycin, **2**. Triol **25** was smoothly converted to acetonide **26** with 2,2-dimethoxypropane and *p*-TsOH in quantitative yield. It should be noted that if the allylic oxidation gave the β-hydroxyl in **24**, one might expect a mixture of acetonides in the protection step since the putative *cis* diol can only give one acetonide, **26**. Acetonide **26** was then subjected to reduction conditions (BH_3-THF) to afford piperidine **27** as a 20:1 mixture of diastereomers at the

angular position. It should be noted that both the C-O and C=O linkages were reductively cleaved in the single step under the reductive conditions. Although no further comment needs be made, there were various attempts at SeO_2 oxidation and BH_3 reductions on OH-protected **24** (e.g. TBDMS, $PhCH_2$) and protected OH in the borane reductions to **27**. However, none of these

Scheme 5



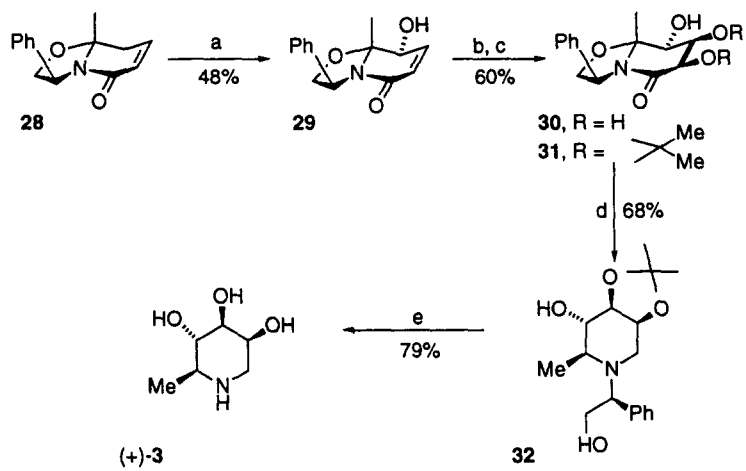
a) CrO_3, H_2SO_4, THF; **b)** (*S*)-phenylglycinol, toluene, Δ; **c)** KH, $PhSO_2Me$, THF; Δ, toluene; **d)** SeO_2, dioxane, Δ; **e)** OsO_4-NMO, aq. acetone; **f)** $(CH_3)_2C(OMe)_2$, CH_2Cl_2, *p*-TsOH; **g)** BH_3-THF, Δ; **h)** H_2-$Pd(OH)_2$, EtOH, TFA, MeOH; **I)** HCl, Et_2O

protocols were as efficient as the route described below.

With piperidine **27** in hand, catalytic hydrogenolysis (H_2, 3 atm, $Pd(OH)_2$) followed by treatment with TFA effected a global deprotection to afford azasugar **2**. The title compound was purified using a Dowex ion-exchange resin and the hydrochloride salt of **2** was prepared for comparison purposes. The NMR spectrum of the hydrochloride salt of **2** (R = H_2Cl) was identical to that of an authentic sample.[15] Furthermore, the sign of rotation ($[\alpha]_D$ +9.6 (c 1.2, H_2O) of the synthetic material when compared to that of L-enantiomer of **2** ($[\alpha]_D$ +10.2 (c 0.37, H_2O),[16] confirmed the absolute configuration of **2**. In addition, this data confirmed that both the SeO_2 oxidation and the OsO_4 dihydroxylation steps proceeded as shown in Scheme 5. The stereochemical outcome of both processes can be rationalized on the basis of steric effects dictated by the bicyclic lactam framework. The efficiency of this entire sequence is summarized by a 6 step sequence from **22** in 17% overall yield.

During this study, we also explored a route to the more simplified sugar, *rhammo*-1-deoxynojirimycin, **3**. We felt we could rapidly and efficiently prepare **3** from known[9] bicyclic lactam **28** using a similar approach as described above. Oxidation at the allylic position using SeO_2 afforded alcohol **29** in 48-50% yield as a single diastereomer in which stereochemistry appears to be once again dictated by the lactam framework (Scheme 6). The introduction of the two hydroxyl groups was again accomplished by using OsO_4-NMO which afforded **30** in 70% yield as a single diastereomer. Protection of the *syn*-hydroxyl group as the acetonide proceeded quantitatively and the resulting product, **31** was subjected to the reductive cleavage protocol. Once again, BH_3 proved to be the best reducing agent and **32** was obtained in 70% yield as a 20:1 mixture of diastereomers at the angular position (C-2). This example represents the second case wherein BH_3 has been the reagent of choice to efficiently cleave the bicyclic lactams containing oxygen functionality with good diastereoselection. While the stereochemistry at the angular position is rationalized by hydride entry from the *endo* face in **26** and **31**, the α-hydroxy group in the latter

Scheme 6



a) SeO_2, dioxane, Δ; b) OsO_4-NMO, aq. acetone; c) 2, 2-dimethoxypropane, CH_2Cl_2, *p*-TsOH; d) BH_3, THF, Δ; e) H_2-Pd/C, MeOH, then TFA, MeOH

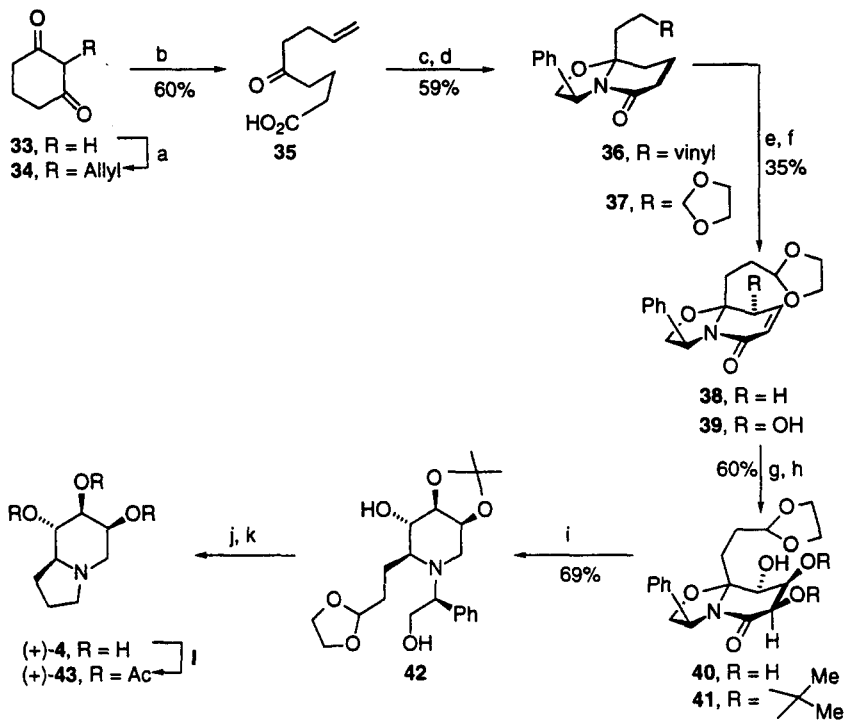
may provide a precomplexation or CIPE[17]. While such a complexation is not known with certainty, further investigations on related systems may lend insight into this rationale.

To complete the synthesis of *rhammo*-1-deoxynojirimycin (+)-**3**, the acetonide and *N*-benzyl group were both removed by treatment with H_2-Pd/C followed by TFA, in an analogous fashion to **27**, to provide (+)-**3** in 79% overall yield. Comparison of the ^{1}H-NMR of (+)-**3** with literature data for an authentic sample confirmed the identity of the azasugar and once again the sign of the $[\alpha]_D$ confirmed the absolute stereochemistry.[18]

We then undertook a more complex problem to showcase the synthetic versatility of the chiral bicyclic lactams. In Scheme 7, the synthetic route to 1-deoxy-6-epicastanospermine, (+)-**4**, is outlined. The retrosynthetic analysis was analogous to that already described for (+)-**2** in Scheme 5 in which the C-2 substituent of the piperidine ring would derive from the angular substituent in the starting bicyclic lactam. In order to implement this strategy, it was necessary to produce the ketoacid **35**, which was readily available by a two-step cleavage sequence of 2-substituted cyclohexane dione **34**. With ketoacid **35** in hand, condensation with (*S*)-phenylglycinol with azeotropic removal of water afforded allyl bicyclic lactam **36** as a 10:1 mixture of diastereomers (NMR) at the angular position. The unwanted diastereomer (9-10%) could be removed by chromatography at this point, but for the sake of expediency, the 10:1 mixture was subjected to ozonolysis and the resulting crude aldehyde was immediately converted to dioxolane **37**. Purification by flash chromatography afforded **37** in 59% overall yield from ketoacid **35** as a single diastereomer (NMR). Treatment of **37** with LiHMDS or KH followed by methyl phenylsulfinate gave lactam **38** in 80% yield according to procedures described above.[9]

Attention was turned toward the stereospecific introduction of three hydroxyl groups utilizing the methodology analogous to that outlined in Scheme 6. Oxidation of **38** with SeO_2 gave the allylic alcohol **39** as a single diastereomer. Surprisingly, the dioxolane subunit of **38** survived the acidic conditions that usually accompanies selenium oxidations.[19] In accordance with precedent for related systems (Scheme 5), the hydroxyl group of **39** was expected to be installed exclusively from the α-face to position itself as *psuedo*-axial. The high degree of facial selectivity observed in this oxidation may be explained by the presence of the angular dioxanyl group shielding the β-face of the lactam, as previously observed in related systems (Scheme 5). Treatment of **39** under dihydroxylation conditions (OsO_4-NMO) gave the vicinal diol **40** as a single diastereomer which was tentatively assigned the *manno* configuration based upon the precedent established during the synthesis of L-mannodeoxynojirimycin (+)-**2** as described above. It should be pointed out that firm stereochemical assignments for the oxidation steps would be obtained at the completion of the synthesis. The trihydroxy lactam **40** was transformed to the acetonide, **41** using 2,2-dimethoxypropane in CH_2Cl_2 and *p*-TsOH in an overall yield of 60% from **38**.

Scheme 7



a) KOH, Cu powder, allyl bromide, H_2O; b) $Ba(OH)_2$, H_2O; c) (*S*)-phenylglycinol, toluene, Δ; d) O_3, DMS, then ethylene glycol, benzene, Δ; e) LiHMDS, $PhSO_2Me$,THF, then toluene, Δ; f) SeO_2, dioxane, Δ; g) OsO_4-NMO, aq. acetone; h) 2, 2-dimethoxypropane, CH_2Cl_2, *p*-TsOH; i) BH_3, THF, Δ; j) H_2-Pd/C, MeOH, HCl; k) *p*-TsOH, acetone, H_2O; l) Ac_2O, DMAP, pyridine.

With acetonide **41** in hand, treatment with BH_3-THF (10 eq), as described previously, afforded piperidine **42** in 69% yield as a 20:1 mixture of diastereomers at the angular position. It was again noteworthy to observe the excellent ratio of diastereomers in piperidine **42** and the simultaneous reduction of the carbonyl group under the reaction conditions. The stereochemistry of the ring cleavage was expected to proceed with retention at C-2, indicating that the hydride from BH_3 was delivered from the *endo*-face of **41**. The *exo*-face, with its excessive substitution, should disfavor this approach although this would be resolved by completion of the synthesis. Furthermore, treatment of **42** with acid liberated the aldehyde as well as removed the acetonide. The final step in this sequence simply involved hydrogenation of **42** with Pd/C in methanolic HCl to effect, in a single operation, *N*-benzyl removal and reductive amination to afford (+)-**4**. The title compound was purified using an ion-exchange resin (Dowex 50 WX2) which gave 1-deoxy-6-

epicastanospermine, (+)-**4** as a colorless oil in 74% yield. Conversion to the known triacetate **43**[20] and comparison to spectral data (IR, NMR) in the literature confirmed the structural assignment. In addition, comparison of the rotation of synthetic (+)-**43** with the literature value confirmed the absolute stereochemistry.[20] Thus, oxidation of **38** proceeded, as expected, from the *exo*-face whereas reduction of **41** proceeded, as expected from the *endo*-face (with retention) at C-2 in the piperidine, **42**.

In summary, we have described asymmetric routes to four azasugars, **1-4**, in high enantiomeric purity and with considerable synthetic efficiency. This use of chiral bicyclic lactams should open routes to other variants of the azasugar family of compounds.

Experimental Section

General Methods: All ^{1}H NMR spectra were recorded on a Bruker AC 300 MHz spectrometer. ^{13}C NMR spectra were recorded at 75 MHz and were also obtained on a Bruker AC 300 MHz instrument. Fourier transform infrared absorption spectra were recorded on a Perkin-Elmer model PE 1600 spectrophotometer. Optical rotations were determined with a Rudolph Research Autopol III instrument and are referenced to the D-line of sodium. Melting points were measured in open pyrex capillary tubes on a Mel-Temp melting point apparatus and are uncorrected. Elemental analyses were obtained from Atlantic Microlabs of Norcross, Ga. Thin layer chromatography and flash chromatography were performed with E. Merck or Amicon Matrix silica gel (230-400 mesh). All non-aqueous reactions were conducted under an argon atmosphere in a flame-dried apparatus. Dichloromethane and toluene were dried via distillation from calcium hydride prior to use. HMPA was dried via distillation from calcium hydride under reduced pressure. Tetrahydrofuran was dried via distillation from sodium-benzophenone ketyl. Concentrations were performed under reduced pressure with a Buchi rotary evaporator.

Saturated Bicyclic Lactam 10: To a solution of 2,3-dihydrofuran **7** (8.0 mL, 105.8 mmol) in THF (200 mL) at –78 °C was added *t*-BuLi (76.0 mL, 1.67 M in pentane). The solution was stirred at –78 °C for 15 min, warmed to 0 °C for 20 min, and recooled to –78 °C. Benzylchloromethyl ether (17.6 mL, 127.0 mmol) was added dropwise and the reaction mixture was allowed to warm to room temperature and stirred for an additional 1h. The mixture was cooled to 0 °C, and 10% NH_4Cl (140 mL) was added. The mixture was extracted with 1:1 ether:pentane (3 x 150 mL), and the combined organic extracts were washed with brine (1 x 100 mL), dried

($MgSO_4$), filtered, and concentrated under reduced pressure to give the crude benzyloxymethyl (BOM) furan **8**.

To a solution of crude **8** in THF (250 mL) at 0 °C was added Jones reagent (117.5 mL, 2.7 M, 317.4 mmol) which was added dropwise *via* addition funnel over 90 min. The reaction mixture was warmed to rt and stirred overnight. The mixture was diluted with CH_2Cl_2 (400 mL) and water (200 mL), stirred for 30 min, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (4 x 150 mL) and the organic layers were combined. The organic layer was washed with water (2 x 150 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford 21.9 g of the crude ketoacid **9** as a yellow oil.

A mixture of the crude ketoacid **9** (12.5 g, 56.3 mmol) and (*S*)-phenylglycinol (11.8 g, 68.0 mmol) in benzene (500 mL) was heated at reflux in an apparatus fitted with a Dean-Stark trap for 6 h. The reaction mixture was cooled, diluted with ethyl acetate (200 mL) and washed with 1 M HCl (200 mL) followed by sat. $NaHCO_3$ (200 mL). The organic solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography eluting with hexanes/EtOAc (4:1) to give 7.4 g (38%) of **10** as a yellow solid: mp 72-73 °C; $[\alpha]_D^{23}$ +131.4 (c 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.14 (m, 1H), 2.54 (m, 2H), 2.92 (m, 1H), 3.41 (AB_Q, J_{AB} = 9.7 Hz, $\Delta\nu_{AB}$ = 25.9 Hz, 2H), 4.41 (dd, J = 8.6, 6.5 Hz, 1H), 4.47 (s, 2H), 4.60 (t, J = 8.4 Hz, 1H), 5.24 (app t, J = 7.3 Hz, 1H), 7.23-7.35 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 30.6, 33.7, 57.2, 71.3, 73.5, 74.2, 100.9, 125.4, 127.4, 127.6, 127.8, 128.4, 128.7, 137.6, 140.1, 179.2; IR (neat) 1713 cm^{-1}.

Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55. Found: C, 74.13; H, 6.61.

Unsaturated Bicyclic Lactam 11: To a suspension of potassium hydride (254 mg, 6.34 mmol) or lithium hexamethyldisilazide (1.0 equiv.) in THF (5 mL) was added a solution of the lactam **10** (820 mg, 2.54 mmol) in THF (2.5 mL) at rt. After 30 min, a solution of methyl phenylsulfinate (475 mg, 3.04 mmol) in THF (2.5 mL) was added dropwise and the mixture was stirred at room temperature for 3 h. The mixture reaction was quenched with water (1 mL) and concentrated under reduced pressure. The residue was partitioned between 0.5 M H_3PO_4 (25 mL) and CH_2Cl_2 (50 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL) and the organic layers were combined. The organic layer was dried (Na_2SO_4), filtered,

and concentrated under reduced pressure. The residue was dissolved in toluene (20 mL) and solid Na_2CO_3 (2.5 g) was added and the resulting mixture was heated at reflux for 6 h. The mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with hexanes/EtOAc (4:1) afforded 693 mg (85%) of **11** as a yellow solid: mp 57 °C; $[\alpha]_D^{23}$ +142.8 (c 0.75, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.20 (AB_Q, J_{AB} = 10.3 Hz, $\Delta\nu_{AB}$ = 61.6 Hz, 2H), 4.32 (dd, J = 8.9, 6.2 Hz, 1H), 4.50 (AB_Q, J_{AB} = 12.1 Hz, $\Delta\nu_{AB}$ = 23.0 Hz, 2H), 4.67 (app t, J = 8.3 Hz, 1H), 5.09 (app t, J = 7.0 Hz, 1H), 6.15 (d, J = 5.8 Hz, 1H), 7.20-7.35 (m, 11H); ^{13}C NMR ($CDCl_3$) δ 58.6, 70.8, 74.0, 76.4, 102.3, 126.1, 127.9, 128.0, 128.2, 128.8, 129.0, 129.5, 137.7, 139.9, 149.8, 178.5; IR (neat) 2868, 1719, 1494, 1317, 1096 cm^1.

Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96. Found: C, 74.66; H, 5.98.

***Endo*-diol-substituted Lactam 12**: To a solution of lactam **11** (1.82 g, 5.66 mmol) in acetone (5 mL) at rt was added a solution of NMO (1.40 g, 12.0 mmol) in water (3.4 mL). Osmium tetroxide (0.5 mL of a 2.5 % w/w *t*-BuOH solution) was added dropwise and the mixture was stirred at rt for 2 days. The crude mixture was loaded directly on a flash chromatography column and eluted with hexanes/EtOAc (3:1 to 1:1). The purified *endo* diol diastereomer was recrystallized three times from toluene to provide 1.29 g (64%) of **12** as colorless crystals: mp 131-132 °C; $[\alpha]_D^{23}$ +74.0 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.82 (s, 1H), 3.01 (d, J = 8.1 Hz, 1H), 3.37 (d, J = 9.8 Hz, 1H), 3.56 (d, J = 9.8 Hz, 1H), 4.44 (dd, J = 8.3, 4.8 Hz, 1H), 4.48 (m, 4H), 4.91 (dd, J = 8.1, 4.0 Hz, 1H), 5.35 (dd, J = 7.2, 4.8 Hz, 1H), 7.20-7.40 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 30.0, 57.5, 74.1, 74.2, 74.6, 97.3, 126.8, 128.1, 128.4, 128.9, 129.1, 137.3, 139.1, 178.0; IR (neat) 3422, 1714 cm^{-1}.

Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96. Found: C, 67.50; H, 6.00.

Lactam Acetonide 14: To a solution of the diol lactam **12** (477 mg, 1.34 mmol) in CH_2Cl_2 (10 mL) was added 2,2-dimethoxypropane (0.82 mL, 6.70 mmol) followed by *p*-TsOH (10 mg). The solution was stirred at rt for 30 min and was concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (4:1) to afford 522 mg (98%) of **14** as a colorless foam: $[\alpha]_D^{23}$ +81.3 (c 1.1, C_6H_6); ^1H NMR (C_6D_6) δ 1.28 (s, 3H), 1.52 (s, 3H), 3.19 (AB_Q, J_{AB} = 9.4 Hz, $\Delta\nu_{AB}$ = 69.6 Hz, 2H), 3.98-4.12 (m, 4H), 4.54 (d, J = 4.1 Hz, 1H), 5.16 (d, J = 4.0 Hz, 1H), 5.30 (dd, J = 5.9, 3.2 Hz, 1H), 6.95-7.23 (m, 10 H); ^{13}C NMR (C_6D_6) δ 26.5, 27.6,

57.9, 72.3, 73.0, 73.5, 80.7, 81.8, 96.4, 112.6, 126.3, 127.7, 128.4, 128.5, 128.6, 137.5, 139.7, 175.1; IR (neat) 1728 cm^{-1}.

Anal. Calcd for $C_{23}H_{25}NO_5$: C, 69.86; H, 6.37. Found: C, 69.63; H, 6.31.

Pyrrolidine 15: To a solution of the acetonide **14** (228 mg, 0.577 mmol) in THF (1 mL) at rt was added 9-BBN (11.5 mL, 0.5 M in THF). The mixture was heated at reflux for 24 h, cooled to 0 °C, and was quenched by careful addition of 3 M NaOH (1.1 mL) and 30% H_2O_2 (1.7 mL). The mixture was stirred for 30 min, diluted with H_2O (10 mL), and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with saturated $Na_2S_2O_3$ (1 x 20 mL) and brine (1 x 20 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography eluting with hexanes/EtOAc (1:1) to afford 179 mg (81%) of **15** as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.28 (s, 3H), 1.47 (s, 3H), 2.55 (br s, 1H), 2.70 (dd, J = 11.0, 4.6 Hz, 1H), 2.85 (dd, J = 9.8, 5.3 Hz, 1H), 3.08 (d, J = 11.0 Hz, 1H), 3.54 (dd, J = 9.8, 6.1 Hz, 1H), 3.75 (m, 2H), 3.98 (dd, J = 12.0, 8.9 Hz, 1H), 3.99 (s, 1H), 4.39-4.56 (m, 4H), 7.20-7.36 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 25.1, 26.3, 56.3, 62.7, 63.8, 64.4, 68.9, 73.3, 77.3, 80.8, 111.3, 127.5, 127.6, 127.7, 128.3, 128.5, 138.0; IR (neat) 3461 cm^{-1}.

***N*-Boc-pyrrolidine 16**: To a pressure tube charged with pyrrolidine **15** (110 mg, 0.287 mmol) in EtOH (2 mL) was added $Pd(OH)_2$ (85 mg) and Boc_2O (125 mg, 0.574 mmol). The mixture was fitted with a pressure regulator and was stirred vigorously under H_2 (3 atm) for 36 h. The mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with hexanes/EtOAc (2:1) to afford 59 mg (75%) of **16** as a colorless oil: $[\alpha]_D^{23}$ -38.3 (c 0.23, $CHCl_3$) (lit. $[\alpha]_D^{23}$ -42.2 (c 0.23, $CHCl_3$)[13]); ^1H NMR (C_6D_6) δ 1.02 (s, 3H), 1.27 (s, 3H), 1.36 (s, 9H), 3.10 (br s, 1H), 3.51 (dd, J = 12.4, 2.1 Hz, 1H), 3.62 (br, 1H), 3.96 (dt, J = 6.2, 2.4 Hz, 1H), 4.09 (app t, J = 6.2 Hz, 1H), 4.17 (br s, 1H), 5.15 (br s, 1H); ^{13}C NMR (C_6D_6) δ 24.5, 26.2, 28.1, 52.3, 62.7, 77.4, 80.1, 80.6, 99.9, 111.7, (C=O not observed due to excessive line broadening); IR (neat) 3407, 1684 cm^{-1}.

6-Benzyloxymethyl-3,4-dihydro-2H-pyran 20: To a solution of 3,4-dihydro-2H-pyran (7.6 mL, 80.9 mmol) in the THF (800 mL) at –78 °C was added *t*-BuLi (55.0 mL, 1.6 M in pentane) dropwise. The mixture was stirred –78 °C for 15 min, warmed to 0 °C and stirred for 40 min, and recooled to –78 °C. Trioxane (3.0 g, 33.3 mmol) was added in one portion and the mixture was

warmed to rt and stirred for 15 min. Water (75 mL) was carefully added to the mixture and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 100 mL) and the organic layers were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford the crude alcohol as an oil.

To a solution of NaH (2.48 g, 103 mmol) in DMF (10 mL) at 0 °C was added a solution of alcohol (6.5 g, 57.0 mmol) in DMF (100 mL) dropwise. The mixture was warmed to rt and stirred for 1 h whereupon the mixture was recooled to 0 °C. Benzyl chloride (6.5 mL, 56.4 mmol) was added dropwise to the mixture which was warmed to rt and stirred for 16h. Water (1 L) was added to the mixture and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 500 mL) and the organic layers were combined, washed with brine (2 X 200 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford 10.7 g (92%) of **20** as an oil. This material was carried onto the next transformation without further purification.

Benzyloxymethylene Ketoacid 21: To a solution of crude ether **20** (10.7 g, 52.4 mmol) in THF (250 mL) at 0 °C was added Jones reagent (90 mL, 2.7 M) dropwise by addition funnel. Upon completion of the addition, the mixture was warmed to rt and stirred overnight (12 h). The mixture was diluted with CH_2Cl_2 (150 mL) and the mixture was stirred for an additional 30 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The organic layers were combined, washed with water (2 x 100 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford 13.8 g (70%) of **21** as an oil. This material was carried onto the next transformation without further purification.

5,6-Benzyloxymethylene Lactam 22: A solution of crude benzyloxymethylene ketoacid **21** (13.8 g, 58.5 mmol) and (*S*)-phenylglycinol (5.6 g, 40.9 mmol) in toluene (250 mL) was heated at reflux in an apparatus fitted with a Dean-Stark trap and condenser for 18 h. The mixture was cooled to rt and concentrated under reduced pressure. The crude material was purified by flash chromatography eluting with toluene/EtOAc/$CHCl_3$ (1:1:10) to afford 8.0 g (58% based on phenylglycinol) of **22** as an oil: $[\alpha]_D^{23}$ +82.5 (c 1.9, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.63 (m, 1H), 1.87 (m, 2H), 2.39-2.67 (m, 4H), 3.47 (m, 2H), 3.94 (dd, *J* = 7.3, 9.0 Hz, 1H), 4.43 (d, *J* = 11.9 Hz, 1H), 4.51-4.62 (m, 2H), 5.43 (app t, *J* = 7.4 Hz, 1H), 7.17-7.39 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 16.3, 30.0, 30.6, 58.3, 68.8, 69.6, 73.1, 76.5, 76.9, 77.4, 94.3, 125.1, 127.0, 127.4, 127.6, 128.2, 128.4, 137.4,

139.7, 170.4; IR (neat) 1655 cm^{-1}; HRMS (FAB, M+H) Calcd for $C_{21}H_{24}NO_3$: 338.1756. Found: 338.1759.

5,6-Benzyloxymethylene Unsaturated Lactam 23: Prepared as described above for **11** from lactam **22** (1.7 g, 5.0 mmol), methyl phenylsulfinate (0.95 g, 6.1 mmol), and KH (0.50 g, 12.6 mmol) to afford 1.4 g (86%) of lactam **23** as a clear oil after flash chromatography (hexanes/EtOAc 4:1): $[\alpha]_D^{23}$ -8.3 (c 1.4, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 2.48 (d, *J* = 17.7 Hz, 1H), 3.14 (dd, *J* = 17.7, 7.3 Hz, 1H), 3.45 (dd, *J* = 10.4, 1.2 Hz, 1H), 3.59 (d, *J* = 10.4 Hz, 1H), 4.02 (dd, *J* = 8.9, 6.5 Hz, 1H), 4.42-4.49 (m, 2H), 4.60 (d, *J* = 12.1 Hz, 1H), 5.31 (dd, *J* = 7.0, 7.0 Hz, 1H), 5.99 (dd, *J* = 10.1, 3.0 Hz, 1H), 6.46 (ddd, *J* = 10.1, 6.4, 2.1 Hz, 1H), 7.20-7.38 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 31.3, 58.5, 69.9, 70.8, 73.3, 94.2, 124.5, 125.7, 127.3, 127.5, 127.7, 128.3, 128.5, 136.3, 137.5, 139.1, 162.4; IR (neat) 1670 cm^{-1}; HRMS (FAB, M+H) Calcd for $C_{21}H_{22}NO_3$: 336.1600, Found: 336.1603.

Hydroxy Lactam 24: To a solution of SeO_2 (239 mg, 2.16 mmol) in dioxane (10 mL) at rt was added unsaturated lactam **38**. The mixture was heated at reflux for 10 h, cooled to rt, and filtered through a pad of Celite. The filtrate was diluted with EtOAc (40 mL) and the organic layer was washed with water (15 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with hexanes/EtOAc (1:3) to yield 405 mg (54%) of **24** as a pale yellow oil: $[\alpha]_D^{23}$ -82.9 (c 1.7, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 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, 6.1 Hz, 1H), 4.45 (d, *J* = 11.9 Hz, 1H), 4.60 (m, 3H), 5.33 (dd, *J* = 7.4, 5.8 Hz, 1H), 6.10 (d, *J* = 9.7 Hz, 1H), 6.64 (dd, *J* = 9.7, 6.1 Hz, 1H), 7.30 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 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; IR (neat) 3365, 1663 cm^{-1}; HRMS (EI) Calcd for $C_{21}H_{21}NO_4$: 351.1471. Found 351.1472.

Triol 25: Prepared as described above for **12** from lactam **24** (485 mg, 1.38 mmol), NMO (323 mg, 2.76 mmol), and OsO_4 (0.4 mL of a 2.5% w/w solution in *t*-BuOH) to afford 0.44 g (83%) of triol **25** as a white foam after flash chromatography (hexanes/EtOAc 4:1): $[\alpha]_D^{23}$ +130.2 (c 1.13, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 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, 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), 7.30 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 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, 171.0; IR (neat) 3410, 1654 cm^{-1}.

Acetonide 26: Prepared as described above for **14** using triol **25** (430 mg, 1.12 mmol), dimethoxypropane (0.69 mL, 5.6 mmol) and *p*-TsOH (20 mg) to afford 35 mg (75%) of **26** as a white foam after flash chromatography (hexanes/EtOAc 3:1): ^1H NMR ($CDCl_3$) δ 1.36 (s, 3H), 1.48 (s, 3H), 2.91 (br s, 1H), 3.68 (d, *J* = 10.7 Hz, 1H), 3.88 (d, *J* = 10.7 Hz, 1H), 3.99 (app t, *J* =8.6 Hz, 1H), 4.53 (m, 3H), 4.63 (m, 3H), 5.28 (app t, *J* = 8.6 Hz, 1H), 7.30 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 22.6, 25.3, 59.4, 65.7, 69.4, 70.1, 73.4, 73.8, 74.5, 95.6, 110.3, 125.4, 127.4, 127.7, 128.3, 128.6, 137.4, 138.3, 166.5; IR (neat) 3439, 1675 cm^{-1}.

Piperidine 27: To a solution of lactam **26** (0.20 g, 0.47 mmol) in THF (10 mL) at rt was added BH_3-THF (4.72 mL, 4.72 mmol, 1.0 M solution in THF) dropwise. The mixture was heated to reflux and stirred for 30 min and then cooled to 0 °C, 2 M NaOH (1mL) and 30% H_2O_2 (1 mL) were then cautiously added and the mixture was stirred for 30 min. The mixture was diluted with water (20 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography eluting with hexanes/EtOAc (1:1) to afford 126 mg (65%) of **27** as a clear oil: ^1H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.48 (s, 3H), 2.74 (dd, *J* = 14.3, 3.1 Hz, 1H), 2.94 (m, 3H), 3.68 (dd, *J* = 11.0, 4.9 Hz, 1H), 3.81 (d, *J* = 4.9 Hz, 2H), 3.98 (m, 4H), 4.12 (dd, *J* = 11.0, 4.9 Hz, 1H), 4.60 (s, 2H), 7.30 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 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, 137.7.

L-*Manno*-1-deoxynojirimycin (+)-2: To a thick-walled pressure tube charged with piperidine **27** (60 mg, 0.15 mmol) in EtOH (3 mL) was added $Pd(OH)_2$ (42 mg) in one portion. The mixture was fitted with a pressure regulator and stirred vigorously under H_2 (3 atm) for 12 h. The mixture was filtered through a pad of Celite and concentrated under reduced pressure. The residue was taken up in CD_3OD (0.5 mL) and TFA (0.5 mL) was added and the mixture was stirred at rt for 15 min. ^1H NMR analysis showed the reaction to be complete so the mixture was concentrated under reduced pressure. The resulting oil was loaded onto a Dowex 50 WX2 ion exchange resin and eluted with 5% NH_3 in water to afford 18 mg (75%) of (+)-**2** (R = H) as an oil: ^1H

NMR (D_2O) δ 2.49 (m, 1H), 2.77 (d, J = 14.3 Hz, 1H), 3.01 (dd, J = 14.3, 2.6 Hz, 1H), 3.59 (m, 2H), 3.78 (d, J = 3.7 Hz, 2H), 4.01 (m, 1H); ^{13}C NMR (D_2O) δ 49.0, 61.3, 61.5, 69.1, 70.0, 75.4.

***Manno*-1-deoxynojirimycin (+)-2** (R=H_2Cl): To a solution of **(+)-2** (18 mg, 0.11 mmol) in CH_3OH (5 mL) at rt was added HCl (1.00 mL of a 1.00 M solution in Et_2O, 1.00 mmol) dropwise with vigorous stirring. After 10 min, the mixture was concentrated under reduced pressure to afford 22 mg (100%) of (+)-**2** hydrochloride salt as a white solid: mp 182-184°C (dec.), (lit[16] 184-186°C (dec)); $[\alpha]_D^{23}$ +9.6 (c 1.20, H_2O); ^1H NMR (D_2O) δ 3.21 (m, 1H), 3.30 (d, J = 13.6 Hz, 1H), 3.47 (dd, J = 13.6, 2.2 Hz, 1H), 3.74 (dd, J = 9.5, 2.5 Hz, 1H), 3.89 (d, J = 12.5 Hz, 1H), 3.92 (app t, J = 8.8 Hz, 1H), 4.02 (dd, J = 12.5, 3.0 Hz, 1H), 4.28 (s, 1H); ^{13}C NMR (D_2O) δ 48.3, 58.9, 61.2, 66.5, 66.7, 73.2.

Triol 30: Prepared as described above for **12** from lactam **29** (0.26 g, 1.1 mmol), NMO (0.25 g, 2.1 mmol), and OsO_4 (0.25 mL of a 2.5% w/w solution in *t*-BuOH) to afford 210 mg (77%) of triol **30** as a white foam after flash chromatography (hexanes/EtOAc 1:1 to EtOAc): $[\alpha]_D^{23}$ +165.8 (c 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.54 (s, 3H), 3.23 (br s, 1H), 3.49 (br s, 1H), 4.08 (t, J = 8.1 Hz, 1H), 4.23 (d, J = 4.5 Hz, 1H), 4.40 (d, J = 4.5 Hz, 1H), 4.46 (t, J = 4.2 Hz, 1H), 4.61 (t, J = 8.7 Hz, 1H), 5.34 (t, J = 8.1 Hz, 1H), 7.18-7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 23.9, 58.7, 67.1, 68.3, 70.0, 70.8, 93.8, 125.3, 127.3, 128.6, 139.5, 170.1; IR (neat) 3399, 1645 cm^{-1}; HRMS (EI) Calcd for $C_{14}H_{17}NO_5$: 279.1094. Found: 279.1107.

Acetonide 31: Prepared as described above for **14** from triol **30** (0.13 g, 0.47 mmol), dimethoxypropane (0.50 mL, 4.0 mmol) and *p*-TsOH (5 mg) to afford 125 mg (85%) of **31** as a colorless solid after flash chromatography (hexanes/EtOAc 1:2.5): mp 196-198 °C; $[\alpha]_D^{23}$ + 43.8 (c 0.87, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.36 (s, 3H), 1.57 (s, 3H), 1.59 (s, 3H), 3.11 (s, 1H), 3.92 (t, J = 8.4 Hz, 1H), 4.15 (s, 1H), 4.48 (t, J = 8.4 Hz, 1H), 4.61 (m, 2H), 5.24 (t, J = 8.4 Hz, 1H), 7.18-7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 22.8, 22.9, 25.4, 59.3, 69.5, 70.3, 73.9, 74.7, 94.5, 110.4, 125.3, 127.4, 128.7, 138.6, 165.5; IR (neat) 3408, 1667 cm^{-1}.

Anal. Calcd for $C_{17}H_{21}O_5N$: C, 63.95; H, 6.58. Found: C, 63.76; H, 6.57.

Piperidine 32: Prepared as described above for **27** using **31** (70 mg, 0.22 mmol) and BH_3-THF (2.19 mL, 2.19 mmol, 1.0 M in THF) to afford 46 mg (68%) of **32** as a white solid after flash chromatography (hexanes/EtOAc 1:4): mp 102-104 °C; $[\alpha]_D^{23}$ +67.1 (c 1.00, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.33 (s, 3H), 1.48 (s, 3H), 2.46 (dd, J = 3.0, 13.5 Hz, 1H), 2.54 (t, J = 6.9 Hz, 1H), 2.82 (br s, 1H), 3.10 (dd, J = 3.5, 13.5 Hz, 1H), 3.47 (t, J = 6.9 Hz, 1H), 3.63 (dd, J = 5.1, 10.8 Hz, 1H), 3.81-3.96 (m, 2H), 4.09-4.16 (m, 1H), 4.19 (dd, J = 5.1, 10.2 Hz, 1H), 7.14-7.33 (m, 5H); ^{13}C

NMR ($CDCl_3$) δ 15.4, 25.9, 27.8, 44.8, 57.0, 60.2, 61.3, 72.6, 75.7, 79.1, 109.5, 127.7, 128.0, 128.5, 137.0; IR (neat) 3421, 2984, 2934 cm^{-1}.

Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.45; H, 8.14. Found: C, 66.18 H, 8.25.

***rhammo*-1-Deoxynojinomycin (+)-3:** To a thick-walled pressure tube charged with **32** (100 mg, 0.33 mmol) in MeOH (5 mL) was added $Pd(OH)_2$ (100 mg) in one portion. The mixture was fitted with a pressure regulator and was stirred vigorously under H_2 (3 atm) for 12 h. The mixture was filtered through a thin pad of Celite and concentrated under reduced pressure. The crude residue was dissolved in MeOH (3 mL) and TFA (3 mL) was added. The mixture was stirred for 2 h at rt and was concentrated under reduced pressure. The crude residue was purified on Dowex 50 WX2 using 5% NH_3 in H_2O as eluent to afford 38 mg (79%) of (+)-**3** as a colorless solid: mp 164-165 °C (lit.[18] 163-164 °C); $[\alpha]_D^{23}$ +54.8 (c 0.9, MeOH); ^1H NMR (CD_3OD) δ 1.15 (d, J = 6.3 Hz, 3H), 2.43-2.48 (m, 1H), 2.82 (AB_Q, J_{AB} = 14.1 Hz, $\Delta\nu_{AB}$ = 0.04 Hz, 2H), 3.30 (dd, J = 10.2, 10.2 Hz, 1H), 3.50 (dd, J = 3.0, 9.6 Hz, 1H), 3.97 (s, 1H).

Butenyl Lactam 36: Prepared as described above for **22** using 4-(4-pentenoyl) butanoic acid **35** (5.0 g, 29.4 mmol) and (*S*)-phenylglycinol (6.04 g, 44.0 mmol) to afford 7.1 g (89%) of **36** as a clear oil. The crude product was carried onto the next step without further purification.

Acetal 37: To a solution of olefin **36** (1.0 g, 3.7 mmol) in CH_2Cl_2/MeOH (1:1; 20 mL total) at –78 °C was bubbled O_3 until a blue endpoint persisted. A stream of Ar was bubbled through the solution to drive off excess O_3 and the mixture was treated with Me_2S (0.40 mL, 5.5 mmol). The solution was allowed to warm to rt and was concentrated under reduced pressure and the crude material was dissolved in EtOAc (30 mL) whereupon *p*-TsOH (200 mg) and ethylene glycol (0.30 mL, 5.4 mmol) were added. The mixture was heated to reflux and stirred for 1h with azeotropic removal of water (Dean-Stark trap). The mixture was cooled to rt and concentrated under reduced pressure to afford an oil. The oil was dissolved in EtOAc (30 mL) and the organic layer was washed with saturated $NaHCO_3$ (1 x 10 mL), water (1 x 10 mL), and brine (1 x 10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with hexanes/EtOAc (1:3) to afford 630 mg (54%) of **37** as an oil: $[\alpha]_D^{23}$ + 85.5 (c 1.06, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.50-2.00 (m, 7H), 2.34 (ddd, J = 13.2, 3.8, 3.8 Hz, 1H), 2.46 (dd, J = 18.1, 8.9 Hz, 1H), 2.62 (ddd, J = 18.1, 7.0, 2.4 Hz, 1H), 3.76-3.95 (m, 5H), 4.51 (dd, J = 8.5, 8.5 Hz, 1H), 4.81-4.86 (m, 1H), 5.37 (dd, J = 8.5, 8.5 Hz, 1H), 7.18-7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 16.6, 28.2, 28.4, 30.6, 30.9, 58.6, 64.8, 64.9, 69.2, 95.6, 103.5, 125.4, 127.1, 128.5, 139.7, 169.8; IR (neat) 1652 cm^{-1}.

Unsaturated Lactam 38: To a solution of lithium hexamethyldisilazide (0.62 mL, 2.9 mmoles) in THF (10 mL) at -78 °C was added a solution of the lactam **37** (600 mg, 1.89 mmol) in THF (30 mL) dropwise *via* cannula. After 30 min, $PhSO_2Me$ (457 mg, 2.93 mmol) was added in one portion and the mixture was stirred for 15 min at –78 °C and warmed to 0 °C. After 1 h, the mixture was poured into water (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting oil was dissolved in toluene (25 mL), Na_2CO_3 (1.6 g) was added, and the mixture was heated at reflux for 6 h. Upon cooling to room temperature, the solution was filtered through Celite and rinsed with EtOAc (20 mL). The filtrate was concentrated under reduced pressure and the crude residue was purified by flash chromatography eluting with hexanes/EtOAc (1:4) to afford 478 mg (80%) of **38** as a light yellow oil: $[\alpha]_D^{23}$ +7.45 (c 1.10, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.67-1.98 (m, 3H), 2.00-2.07 (m, 1H), 2.54 (d, *J* = 17.7, 1H), 2.79 (dd, *J* = 17.7, 6.4 Hz, 1H), 3.78-3.99 (m, 4H), 3.96 (dd, *J* = 8.7, 7.4 Hz, 1H), 4.44 (dd, *J* = 8.7, 8.7 Hz, 1H), 4.64 (t, *J* = 4.2 Hz, 1H), 5.30 (dd, *J* = 7.4, 7.4 Hz, 1H), 6.03 (dd, *J* = 9.5, 3.1, 1H), 6.49 (ddd, *J* = 9.5, 6.4, 2.5 Hz, 1H), 7.25-7.37 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 28.5, 30.5, 33.3, 58.6, 64.5, 64.8, 70.2, 95.0, 103.5, 124.8, 125.7, 127.1, 128.4, 135.8, 139.2, 162.1; IR (neat) 1663 cm^{-1}.

Allylic Alcohol 39: Prepared as described above for **24** using **38** (0.24 g, 0.76 mmol) and SeO_2 (85 mg, 0.76 mmol) to afford 110 mg (44%) of **39** as a clear oil after flash chromatography (EtOAc): $[\alpha]_D^{23}$ -43.8 (c 1.05, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.53-1.86 (m, 4H), 3.45 (br s, 1H), 3.70-3.85 (m, 4H), 4.05 (dd, *J* = 8.5, 6.1 Hz, 1H), 4.17 (d, *J* = 6.1 Hz, 1H),), 4.46 (dd, *J* = 7.9, 7.9 Hz, 1H), 4.71 (t, *J* = 4.2 Hz, 1H), 5.24 (dd, *J* = 6.7, 6.7 Hz, 1H), 6.02 (d, *J* = 9.8 Hz, 1H), 6.61 (dd, *J* = 9.8, 6.1 Hz, 1H), 7.14-7.28 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 28.5, 29.8, 59.0, 64.4, 64.8, 64.9, 71.8, 95.6, 103.4, 125.4, 126.1, 127.4, 128.5, 136.8, 138.7, 161.6; IR (neat) 3374, 1664, cm^{-1}; HRMS (EI) Calcd for $C_{18}H_{21}NO_5$; 331.1420. Found: 331.1400.

Triol 40: Prepared as described above for **25** from **39** (104 mg, 0.32 mmol), NMO (74 mg, 0.64 mmol), and 0.10 mL of 2.5% OsO_4 in *t*-BuOH to afford 104 mg (89%) of **40** as an oil after flash chromatography (MeOH/EtOAc 1:20): $[\alpha]_D^{23}$ +137.3 (c 1.00, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.55-1.82 (m, 3H), 2.30-2.45 (m, 1H), 3.20 (br s, 1H), 3.58-3.85 (m, 5H), 3.97 (dd, *J* = 7.9, 7.9 Hz, 1H), 4.30-4.45 (m, 3H), 4.59 (dd, *J* = 8.5, 8.5 Hz, 1H), 4.61-4.80 (m, 2H), 5.31 (dd, *J* = 8.3, 8.3 Hz, 1H), 7.11-7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 28.1, 28.9, 58.8, 64.8, 64.9, 66.7, 67.2, 68.4, 69.7, 95.5, 103.6, 125.3, 127.2, 128.5, 139.4, 170.3; IR (neat) 3417, 1644 cm^{-1}; HRMS (EI) Calcd for $C_{18}H_{23}NO_7$, 365.1475. Found: 365.1437.

Acetonide 41: Prepared as described above for **26** from **40** (104 mg, 0.284 mmol), 2,2-dimethoxypropane (0.50 mL, 4.0 mmol) and *p*-TsOH (5 mg) to afford 70 mg (54%) of **41** as a colorless foam after flash chromatography (hexanes/EtOAc 1:1): $[\alpha]_D^{23}$ +36.7 (c 0.90, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.40 (s, 3H), 1.65 (s, 3H), 1.71-1.89 (m, 2H), 1.95-2.05 (m, 1H), 2.32-2.42 (m, 1H), 3.11 (br s, 1H), 3.81-3.94 (m, 4H), 4.33 (d, *J* = 2.4 Hz, 1H), 4.52 (dd, *J* = 8.2 Hz, 2H), 4.60 (dd, *J* = 7.6, 2.4 Hz, 1H), 4.66 (d, *J* = 7.6 Hz, 1H), 4.86 (t, *J* = 4.5 Hz, 1H), 5.24 (dd, *J* = 8.2 Hz, 1H), 7.25-7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 22.6, 24.8, 28.2, 28.9, 59.5, 64.7, 66.4, 69.6, 73.9, 74.8, 96.5, 103.6, 110.4, 125.3, 127.3, 128.6, 138.3, 165.7; IR (neat) 3412, 1660 cm^{-1}; HRMS (EI) Calcd for $C_{21}H_{27}NO_7$: 405.1787. Found: 405.1782.

Piperidine Diacetal 42: Prepared as described above for **27** using **41** (70 mg, 0.17 mmol) and BH_3-THF (1.71 mL, 1.71 mmol, 1.0 M in THF) to afford 48 mg (74%) of **42** as clear oil after flash chromatography (EtOAc): $[\alpha]_D^{23}$ +55.1 (c 1.07, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.29 (s, 3H), 1.48 (s, 3H), 1.67-2.08 (m, 4H), 2.61-2.73 (m, 2H), 2.95 (dd, *J* = 13.4, 5.2 Hz, 1H), 3.15-3.40 (m, 2H), 3.66 (dd, *J* = 10.7, 4.6 Hz, 1H), 3.75-4.15 (m, 9H), 4.88 (dd, *J* = 4.2, 4.2 Hz, 1H), 7.18-7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 21.5, 25.2, 27.3, 28.1, 44.4, 60.1, 60.8, 62.8, 64.7, 64.8, 69.9, 71.7, 77.7, 104.2, 109.0, 127.8, 128.4, 137.2; HRMS (EI) Calcd for $C_{21}H_{31}NO_6$: 393.2151. Found: 393.2136.

1-Deoxy-6-epicastanospermine (+)-4: To a solution of **42** (0.24 g, 0.62 mmol) acetone (4 mL) was added *p*-TsOH (23 mg) and water (1 mL). The resulting mixture was heated 6h whereupon an additional portion of *p*-TsOH (20 mg) was added. The mixture was heated at reflux for an additional 12 h, cooled to rt, and concentrated under reduced pressure. Isolation of the crude triol aldehyde was performed using Dowex 50 WX2 ion exchange resin as described above for (+)-**2**. To a thick-walled pressure tube charged with the crude aldehyde (0.18 mg, 0.57 mmol) in MeOH (10 mL) was added 10% Pd/C (54 mg) followed by HCl (0.10 mL, 1.0 M in Et_2O). The mixture was fitted with a pressure regulator and stirred under H_2 (42 psi) for 15 h. The mixture was filtered through a thin pad of Celite and concentrated under reduced pressure. The crude residue was purified by chromatography on a Dowex resin (50 WX2) using 5% NH_3 in water as eluant to afford 73 mg (74%) of (+)-**4** as an oily solid: $[\alpha]_D^{23}$ +28.5 (c 1.00, MeOH), ^1H NMR (D_2O) δ 1.48-1.63 (m, 1H), 1.72-1.87 (m, 2H), 1.93-2.10 (m, 2H), 2.15-2.35 (m, 2H), 2.92-3.03 (m, 1H), 3.08 (d, *J* = 11.4 Hz, 1H), 3.45-3.60 (m, 2H), 4.00 (br s, 1H).

Triacetate (+)-43: To a solution of (+)-**4** (70 mg. 0.40 mmol) in pyridine (3 mL) at rt was added Ac_2O (0.38 mL, 4.0 mmol) and DMAP (5 mg). The mixture was stirred for 10 min at rt and was concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with hexanes/EtOAc (1:4) to afford 65 mg (55%) of (+)-**43** as a white solid:

$[\alpha]_D^{23}$ +43.0 (c 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.96 (s, 3H), 2.00 (s, 3H), 2.12 (s, 3H), 1.60-2.21 (m, 6H), 2.37 (dd, *J* = 13.1, 1.8 Hz, 1H), 3.05-3.18 (m, 2H), 4.86 (dd, *J* = 10, 3.7 Hz, 1H), 5.15 (dd, *J* = 9.7 Hz, 1H), 5.37 (br s, 1H); ^{13}C NMR (C_6D_6) δ 20.8, 21.0, 22.3, 28.8, 53.3, 53.6, 66.6, 69.4, 72.9, 74.1, 169.8, 170.3, 170.5; IR (neat) 1742, 1672 cm^{-1}; HRMS (FAB, M+H) Calcd for $C_{14}H_{21}NO_6$. Calculated: 299.1369. Found: 299.1352.

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