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Syntheses of the Enantiomers of 1-Deoxynojirimycin and 1-Deoxyaltronojirimycin via Chemo- and Diastereoselective Olefinic Oxidation of Unsaturated Amines

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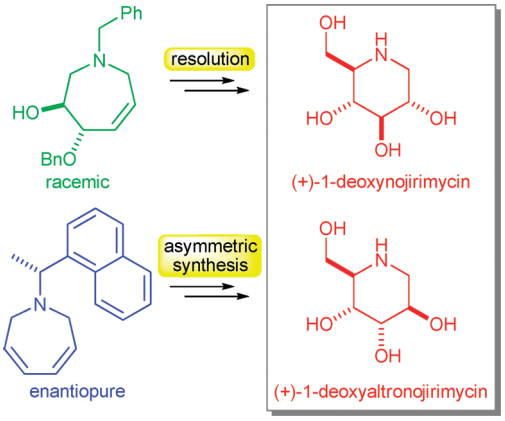

Oxidation of enantiomerically pure (*R*)-*N*(1)-1′-(1″-naphthyl)ethyl-2,7-dihydro-1*H*-azepine with *m*-CPBA in the presence of HBF_4 and BnOH gave (3*S*,4*R*,5*S*,6*S*,1′*R*)-*N*(1)-1′-(1″-naphthyl)ethyl-3-hydroxy-4-benzyloxy-5,6-epoxyazepane as the major product and as a single diastereoisomer after chromatography. Elaboration of this highly functionalized intermediate via ring contraction to (2*S*,3*R*,4*S*,5*S*,1′*R*)-*N*(1)-benzyl-2-chloromethyl-3-benzyloxy-4,5-epoxypiperidine followed by regioselective epoxide ring opening, functional group manipulation, and deprotection gave (+)-1-deoxyaltronojirimycin. Alternatively, resolution of (*RS*,*RS*)-*N*(1)-benzyl-3-hydroxy-4-benzyloxy-2,3,4,7-tetrahydro-1*H*-azepine or (3*RS*,4*SR*,5*RS*,6*RS*)-*N*(1)-benzyl-3-hydroxy-4-benzyloxy-5,6-epoxyazepane by preparative chiral HPLC and subsequent elaboration allows access to the enantiomers of 1-deoxynojirimycin and 1-deoxyaltronojirimycin, respectively.

Introduction

Polyhydroxylated piperidines are produced as secondary metabolites in a vast array of different organisms, although the majority originate in plants.[1] They are widely known as iminosugars (or azasugars) due to their inherent similarity to monosaccharides (the difference being that the endocyclic oxygen atom is replaced by a nitrogen atom) with the result that many are named with reference to their "parent" sugar, e.g., 5-amino-5-deoxy-D-glucopyranose [(+)-nojirimycin, **1**],[2] 1,5-dideoxy-1,5-imino-D-glucitol [(+)-1-deoxynojirimycin, **2**],[3] and 1,5-dideoxy-1,5-imino-D-altroitol [(+)-1-deoxyaltronojirimycin, **3**][3e,f] (Scheme 1).

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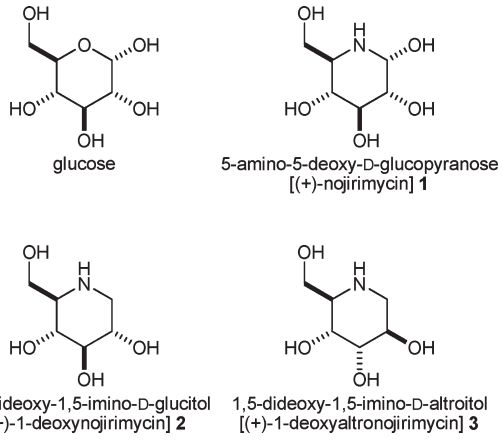
SCHEME 1



The biological activity of this class of compounds is wide and varied, although most effects are attributed to their ability to act as glycosidase inhibitors.[4] Polyhydroxylated piperidines act to inhibit these enzymes by mimicking the saccharides that would usually be targeted by the enzyme. The interaction of the mimic with the enzyme can be greater than that of the desired target as the piperidine can become protonated in the enzyme pocket, thereby mimicking the postulated oxo-carbenium ion intermediate of glycosidic bond cleavage. Due to their inherent biological activity both naturally occurring and synthetic polyhydroxylated piperidines have been targeted and extensively tested as potential therapeutics for various conditions including HIV, cancer, diabetes, and hereditary diseases such as Gaucher's (lysosomal storage) disease, all exploiting the prevalence of sugar processing enzymes in the proliferation of these conditions.[5]

As part of an ongoing research program directed toward the de novo preparation of imino and amino sugars and their derivatives, we developed an ammonium-directed oxidation protocol for a range of cyclic allylic[6] and homoallylic[6c] amines upon treatment with *m*-CPBA in the presence of Cl_3CCO_2H.[7] We recently disclosed the application of a modification of this protocol as one of the key steps to facilitate the stereoselective syntheses of (±)-1-deoxynojirimycin **2** and (±)-1-deoxyaltronojirimycin **3**.[8−10] In this synthesis, oxidation of *N*(1)-benzyl-2,7-dihydro-1*H*-azepine **4** in the presence of aqueous HBF_4 and 1.5 equiv of *m*-CPBA in a mixture of $BnOH/CH_2Cl_2$ (v/v 2:1) gave an 85:15 mixture of **5**:**8**, from which **5** was isolated in 29% yield and >99:1 dr, while use of 4 equiv of *m*-CPBA gave **8** in 50% isolated yield and >99:1 dr. Ring contraction of **8** gave piperidine epoxide **9** in 76% yield and >99:1 dr, while ring contraction of **5** followed by further oxidation of the double bond with F_3CCO_3H in the presence of F_3CCO_2H gave the diastereoisomeric epoxide **7** in 62% yield over the two steps and in 98:2 dr. Further manipulation of **7** and **9** via regioselective epoxide ring-opening, functional group manipulation, and deprotection gave (±)-1-deoxynojirimycin **2** (in 99:1 dr) and (±)-1-deoxyaltronojirimycin **3** (in >99:1 dr), which were isolated as their hydrochloride salts **2**·**HCl** and **3**·**HCl**, respectively (Scheme 2).

We wished to develop an asymmetric version of this versatile protocol. Our strategy in this area was 2-fold: development of a practical resolution protocol for one of the intermediates en route to either **2** or **3** would allow the efficient preparation of the enantiomerically pure polyhydroxylated piperidines and their derivatives or, alternatively, incorporation of a chiral *N*-protecting group on the nitrogen atom would promote diastereoselective oxidation, and we delineate herein our investigations within these areas.

Results and Discussion

Synthesis of Polyhydroxylated Piperidines Employing a Resolution Protocol: Application to the Synthesis of (+)-1-Deoxynojirimycin. We first investigated the potential for resolution of one of the synthetic intermediates in our previously reported routes to (±)-1-deoxynojirimycin **2** and (±)-1-deoxyaltronojirimycin **3**, which thus required preparation of the functionalized racemic tetrahydroazepine **5** and racemic azepane **8**. Upon scale up of our previously reported oxidation protocol for dihydroazepine **4** using 1.5 equiv of *m*-CPBA in the presence of aqueous HBF_4 in $BnOH/CH_2Cl_2$,[8] we noted (in addition to the formation of **5**)[11] the appearance of an undesired by product in the ^1H NMR spectrum of the

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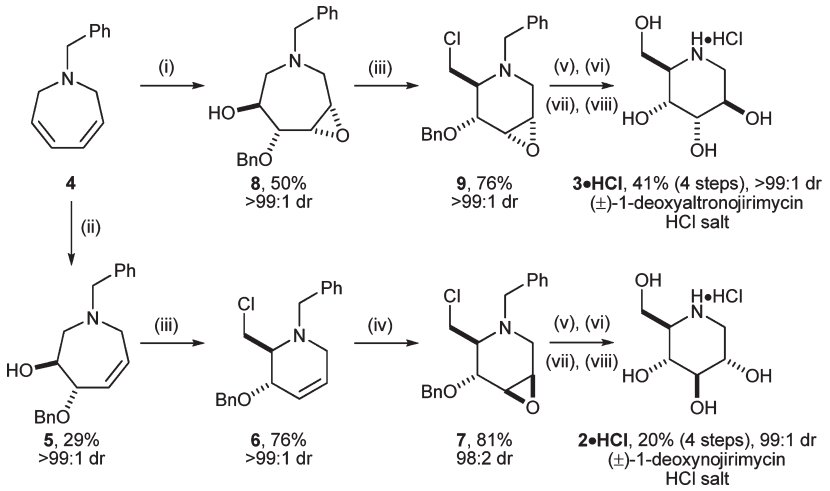
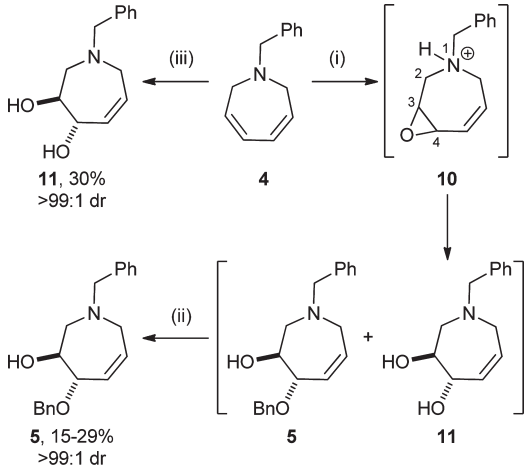
(11) Azepane **8** was also present in the crude reaction mixture (the ratio of **5**:**8** was 85:15); see ref 8.

SCHEME 2[a]



[a]Reagents and conditions: (i) HBF_4 (40% w/w in H_2O), *m*-CPBA (4 equiv), CH_2Cl_2, BnOH, rt, 24 h; (ii) HBF_4 (40% w/w in H_2O), *m*-CPBA (1.5 equiv), CH_2Cl_2, BnOH, rt, 24 h; (iii) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1.5 h; (iv) F_3CCO_2H, F_3CCO_3H, CH_2Cl_2, 0 °C to rt, 6 h; (v) Cl_3CCO_2H, CH_2Cl_2, rt, 16 h, then NaOH (2 M, aq); (vi) AgOAc, DMF, 65 °C, 24 h; (vii) K_2CO_3, MeOH, rt, 16 h; (viii) H_2, $Pd(OH)_2/C$, MeOH, rt, 72 h, then HCl (aq).

SCHEME 3[a]

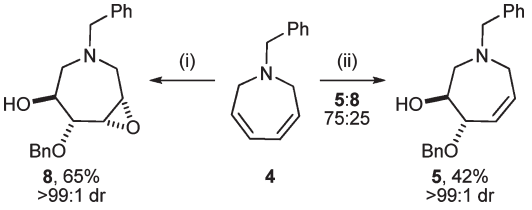


[a]Reagents and conditions: (i) HBF_4 (40% w/w in H_2O), *m*-CPBA (1.5 equiv), CH_2Cl_2, BnOH, rt, 24 h; (ii) chromatography; (iii) Cl_3CCO_2H, *m*-CPBA, CH_2Cl_2, rt, 21 h, then NaOH (2 M, aq).

crude reaction mixture. Although this compound was not isolated upon chromatography, it was assigned as diol **11**: given our previous observations concerning the production of monobenzyl-protected diol **5** from the oxidation of dihydroazepine **4** by *m*-CPBA in the presence of aqueous HBF_4 in a solvent mixture of $BnOH/CH_2Cl_2$, in which BnOH acts as the nucleophile to effect ring-opening of epoxide **10**, we postulated that competitive ring-opening of **10** by H_2O would result in the formation of the diol **11**. Indeed, oxidation of dihydroazepine **4** with *m*-CPBA in the presence of Cl_3CCO_2H and basic aqueous workup (2 M aq NaOH) gave quantitative conversion to **11** as a single diastereoisomer, which was isolated in 30% yield (Scheme 3).

In order to circumvent this problem, we modified our experimental protocol to employ $HBF_4 \cdot OEt_2$ in place of aqueous HBF_4, which was found to give improved crude mass return as well as complete suppression of the formation

SCHEME 4[a]



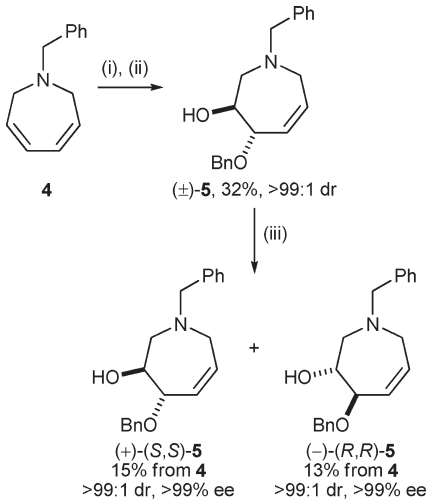
[a]Reagents and conditions: (i) $HBF_4 \cdot OEt_2$, *m*-CPBA (4 equiv), CH_2Cl_2, BnOH, rt, 24 h; (ii) $HBF_4 \cdot OEt_2$, *m*-CPBA (1.5 equiv), CH_2Cl_2, BnOH, rt, 24 h.

of diol **11**. Treatment of **4** with 5 equiv of $HBF_4 \cdot OEt_2$ followed by 1.5 equiv of *m*-CPBA resulted in oxidation to a 75:25 mixture of (±)-**5** and (±)-**8**, respectively. Purification gave (±)-**5** as a single diastereoisomer in 42% yield after chromatography on silica gel. Meanwhile, analogous oxidation of **4** employing 4 equiv of *m*-CPBA gave oxidation of both double bonds to give (±)-**8** as a single diastereoisomer, which was isolated in 65% yield and >99:1 dr after silica gel chromatography (Scheme 4).

After extensive experimentation, we subsequently found that both (±)-**5** and (±)-**8** were amenable to resolution via preparative HPLC using a Chiralpak AD-H column. Thus, oxidation of dihydroazepine **4** with 1.5 equiv of *m*-CPBA in the presence of $HBF_4 \cdot OEt_2$ followed by chromatographic purification and resolution enabled the preparation of (+)-**5** in 15% yield (out of a maximum of 50% from **4**) and >99% ee, and (−)-**5** in 13% yield (out of a maximum of 50% from **4**) and >99% ee {for (+)-**5**, $[\alpha]^{25}_D$ +82.8 (*c* 1.0 in $CHCl_3$); for (−)-**5**, $[\alpha]^{25}_D$ −81.8 (*c* 1.0 in $CHCl_3$)} (Scheme 5). Under analogous conditions but using 4 equiv of *m*-CPBA in the oxidation reaction, (+)-**8** was isolated in 11% yield (out of a maximum of 50% from **4**) and 98% ee and (−)-**8** in 12% yield (out of a maximum of 50% from **4**) and >99% ee {for (+)-**8**, $[\alpha]^{25}_D$ +52.4 (*c* 1.0 in $CHCl_3$); for (−)-**8**, $[\alpha]^{25}_D$ −56.4 (*c* 1.0 in $CHCl_3$)} (Scheme 6).

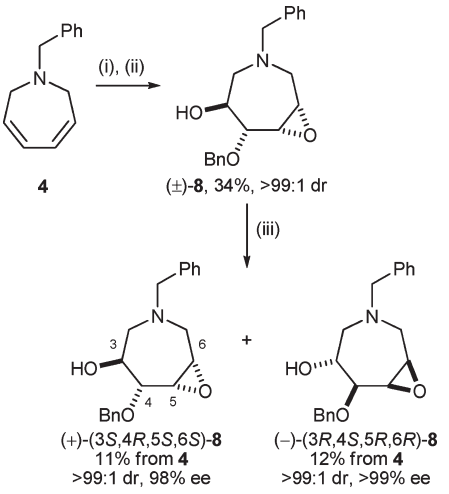
The absolute configurations within (+)-**5** and (−)-**5** could not be assigned a priori; they were established as (+)-(*S*,*S*)-**5**

SCHEME 5[a]



[a]Reagents and conditions: (i) $HBF_4 \cdot OEt_2$, *m*-CPBA (1.5 equiv), CH_2Cl_2, BnOH, rt, 24 h; (ii) chromatography; (iii) preparative chiral HPLC (Chiralpak AD-H column).

SCHEME 6[a]



[a]Reagents and conditions: (i) $HBF_4 \cdot OEt_2$, *m*-CPBA (4 equiv), CH_2Cl_2, BnOH, rt, 24 h; (ii) chromatography; (iii) preparative chiral HPLC (Chiralpak AD-H column).

and (−)-(*R*,*R*)-**5** via chemical correlation to the enantiomers of 1-deoxynojirimycin **2**. Thus, ring contraction of (+)-**5** was effected upon treatment with MsCl to give **6** in 75% yield and >99:1 dr.[12] Chemo- and diastereoselective oxidation of the olefin within **6** was achieved upon treatment with F_3CCO_3H in the presence of F_3CCO_2H, giving piperidine epoxide **7** in 98:2 dr, which was isolated in 62% yield. Upon treatment with Cl_3CCO_2H, epoxide ring-opening occurred at C(5) with modest levels of regioselectivity[13] [the ratio of C(4):C(5) ring opened products in the crude reaction mixture was 88:12], with saponification of the crude reaction mixture with aqueous NaOH giving **12** in 51% isolated yield and 99:1 dr. Subsequent displacement of the chloride functionality within **12** gave acetate ester **13**[12] and was followed by treatment with K_2CO_3 in MeOH to effect transesterification to give **14**, with subsequent hydrogenolysis and acidification giving (+)-1-deoxynojirimycin hydrochloride (+)-**2·HCl** in 30% yield from **12** [7% overall yield from (+)-**5** in 6 steps] and 99:1 dr. Similar elaboration of (−)-**5** gave a sample of (−)-1-deoxynojirimycin hydrochloride (−)-**2·HCl** in 8% overall yield in six steps, and 99:1 dr. The values of the specific rotations of our samples of the antipodes of **2** {for (+)-**2·HCl**, $[\alpha]^{25}_D$ +31.0 (*c* 0.45 in H_2O); lit.[3a] for sample isolated from natural source $[\alpha]^{22}_D$ +38.0 (*c* 1.0 in H_2O); lit.[9m] $[\alpha]^{23}_D$ +36.9 (*c* 1.1 in H_2O); for (−)-**2·HCl**, $[\alpha]^{25}_D$ −34.0 (*c* 0.45 in H_2O); lit.[9i] $[\alpha]^{25}_D$ −46.0 (*c* 1.3 in H_2O); lit.[9m] $[\alpha]^{24}_D$ −38.7 (*c* 1.0 in H_2O)} allowed the absolute configurations within (+)-**5** and (−)-**5** to be unambiguously assigned as (+)-(*S*,*S*)-**5** and (−)-(*R*,*R*)-**5**, and the absolute configurations within the synthetic intermediates **6**, **7**, and **12**−**14** were therefore also unambiguously established. Furthermore, given the enantiomeric purities of (+)-**5** and (−)-**5** (>99% ee in both cases), the enantiomeric purities of (+)-**2·HCl**, (−)-**2·HCl**, **6**, **7**, and **12**−**14** can be inferred as >99% ee (Scheme 7).

Having determined the absolute configurations within (+)-**5** and (−)-**5**, the absolute configurations within (+)-**8** and (−)-**8** were established via chemical correlation. Thus, oxidation of (+)-(*S*,*S*)-**5** (>99% ee) with *m*-CPBA in the presence of aqueous HBF_4[14] gave (+)-**8** in >99% ee[15] {$[\alpha]^{25}_D$ +54.1 (*c* 1.0 in $CHCl_3$)}, while oxidation of (−)-(*R*,*R*)-**5** (>99% ee) gave (−)-**8** in >99% ee[16] {$[\alpha]^{25}_D$ −54.3 (*c* 1.0 in $CHCl_3$)}, thus allowing the absolute configurations within (+)-**8** and (−)-**8** to be unambiguously assigned as (+)-(3*S*,4*R*,5*S*,6*S*)-**8** and (−)-(3*R*,4*S*,5*R*,6*R*)-**8**. We have previously demonstrated the elaboration of (±)-**8** into (±)-1-deoxyaltronojirimycin,[8] and therefore, elaboration of (+)-(3*S*,4*R*,5*S*,6*S*)-**8** via an analogous series of reactions should culminate in the preparation of (+)-1-deoxyaltronojirimycin, while similar elaboration of (−)-(3*R*,4*S*,5*R*,6*R*)-**8** should permit the synthesis of (−)-1-deoxyaltronojirimycin (Scheme 8).

Synthesis of Polyhydroxylated Piperidines Employing Diastereoselective Olefinic Oxidation of an Enantiopure Substrate: Application to the Synthesis of (+)-1-Deoxyaltronojirimycin. Having developed a route to the antipodes of 1-deoxynojirimycin **2** (and 1-deoxyaltronojirimycin **3**) relying on resolution of functionalized tetrahydroazepine **5** and azepane **8**, we turned our attention to the development of a de novo asymmetric synthesis.[17] Our strategy in this area centered on employing a chiral *N*-protecting group as it was envisaged that this would break the symmetry of the 7-membered ring, potentially allowing diastereoselective oxidation. A range of *N*-substituted dihydroazepanes **19**−**22**, all bearing a chiral *N*-protecting group based upon the α-methylbenzyl scaffold, was prepared from *cis*,*cis*-muconic acid **15**. Methylation of **15** with MeI and K_2CO_3 gave diester **16** in 91% yield. Reduction of **16** with DIBAL-H

(12) This reaction presumably proceeds via the intermediacy of the corresponding aziridinium ion; see ref 8.

(13) For a discussion concerning the regioselectivity of ring-opening, see ref 8.

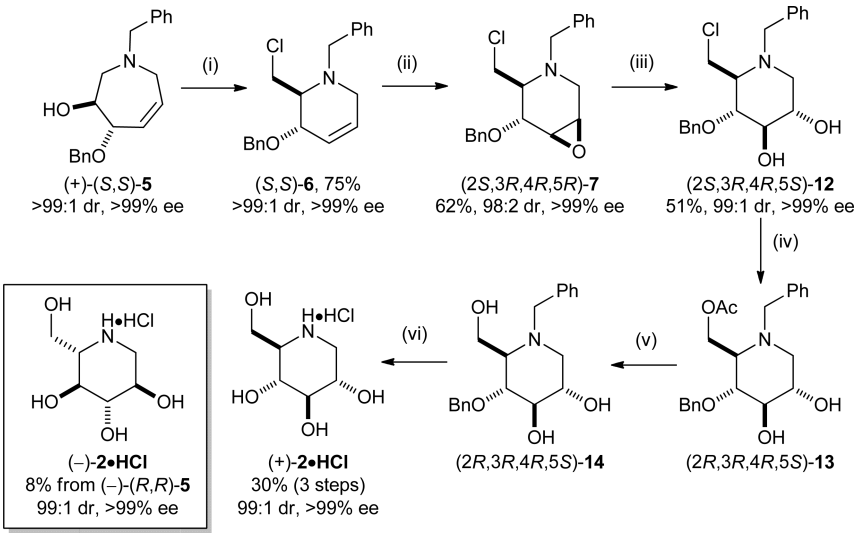
(14) Aqueous HBF_4 was used for these reactions as it was found to give cleaner crude reaction mixtures than the analogous procedures using $HBF_4 \cdot OEt_2$.

(15) The enantiomeric purity of (+)-**8** prepared in this manner was inferred from the enantiomeric purity of the starting material (+)-**5** (i.e., >99% ee).

(16) The enantiomeric purity of (−)-**8** prepared in this manner was inferred from the enantiomeric purity of the starting material (−)-**5** (i.e., >99% ee).

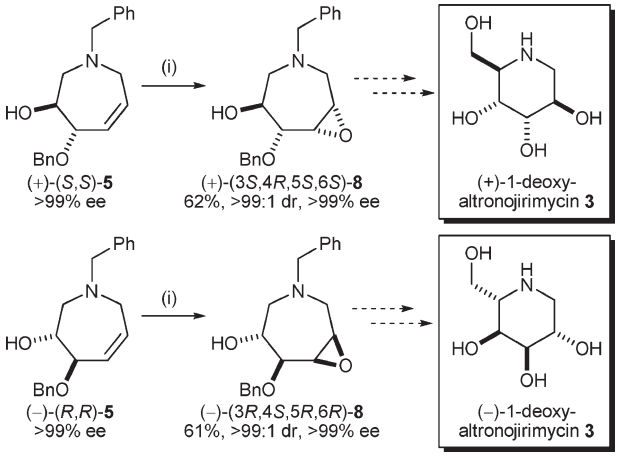
(17) Brown, J. M.; Davies, S. G. *Nature* **1989**, *342*, 631.

SCHEME 7[a]



[a]Reagents and conditions: (i) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1.5 h; (ii) F_3CCO_2H, F_3CCO_3H, CH_2Cl_2, 0 °C to rt, 6 h; (iii) Cl_3CCO_2H, CH_2Cl_2, rt, 16 h, then NaOH (2 M, aq); (iv) AgOAc, DMF, 65 °C, 24 h; (v) K_2CO_3, MeOH, rt, 16 h; (vi) H_2, $Pd(OH)_2/C$, MeOH, rt, 72 h, then HCl (aq).

SCHEME 8[a]

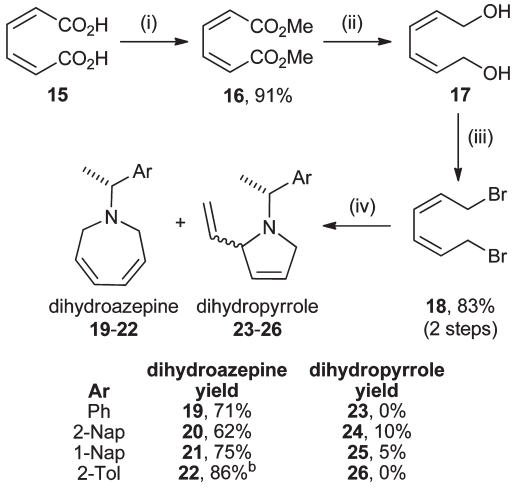


[a]Reagents and conditions: (i) HBF_4 (40% w/w in H_2O), *m*-CPBA (4 equiv), CH_2Cl_2, BnOH, rt, 24 h.

followed by treatment of the resultant diol **17** with PBr_3 gave dibromide **18** in 83% yield (two steps). Addition of a range of chiral primary amines[18] to **18** furnished, in each case, the corresponding dihydroazepanes **19**−**22** as the major products, along with the corresponding dihydropyrroles **23**−**26** as minor products.[19] Chromatography allowed isolation of **19**−**22** in good yield (Scheme 9).

The oxidation of *N*-α-methylbenzyl protected dihydroazepine **19** with *m*-CPBA (2 equiv) in the presence of

SCHEME 9[a]



Ar	dihydroazepine yield	dihydropyrrole yield
Ph	**19**, 71%	**23**, 0%
2-Nap	**20**, 62%	**24**, 10%
1-Nap	**21**, 75%	**25**, 5%
2-Tol	**22**, 86%[b]	**26**, 0%

[a]Reagents and conditions: (i) MeI, K_2CO_3, DMF, rt, 24 h; (ii) DIBAL-H, CH_2Cl_2, 0 °C to rt, 16 h; (iii) PBr_3, Et_2O, 0 °C to rt, 7 h; (iv) $ArCH(Me)NH_2$, K_2CO_3, THF, rt, 24 h. [b]Isolated as a 93:7 mixture of **22**:**26**. 2-Nap = 2-naphthyl. 1-Nap = 1-naphthyl. 2-Tol = 2-tolyl.

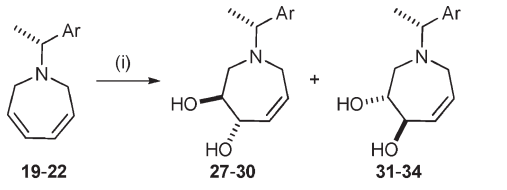
Cl_3CCO_2H (5 equiv) over 21 h[6a] proceeded to full conversion to give a chromatographically inseparable 65:35 mixture of two diastereoisomeric diols **27** and **31**, which were assigned the relative *anti*-configurations on the basis of the reaction proceeding via epoxidation followed by stereospecific S_N2-type epoxide ring-opening.[20] Under identical reaction conditions, oxidation of 2-naphthyl substrate **20** and 2-tolyl substrate **22** gave incomplete conversion to chromatographically inseparable 65:35

(18) Enantiopure (*R*)-α-methylbenzylamine (99% ee), (*R*)-1-(2′-naphthyl)-ethylamine, and (*R*)-1-(1′-naphthyl)ethylamine (98% ee) are commercially available. A racemic sample of 1-(2′-tolyl)ethylamine was prepared according to the procedure outlined by Li et al. for the preparation of (*RS*)-1-(*p*-xylyl)-ethylamine; see: Li, Y.; Selvaratnam, S.; Vittal, J. J.; Leung, P.-H. *Inorg. Chem.* **2003**, *42*, 3229.

(19) Peak overlap and the presence of unidentified impurities in the ^1H NMR spectra of the crude reaction mixtures precluded the determination of the dihydroazepine to dihydropyrrole product ratios. Dihydropyrroles **23**−**26** were formed as single diastereoisomers of unknown relative configuration.

(20) The absolute configurations within the major diastereoisomeric diols **27**−**30** resulting from these oxidation reactions were tentatively assigned as (3*S*,4*S*,1′*R*) by analogy to the stereochemical outcome observed upon oxidation of **21** with HBF_4 in the presence of BnOH, which gave the corresponding (3*S*,4*S*,1′*R*)-diastereoisomer **38** as the major product, the stereochemistry of which was unambiguously established by single-crystal X-ray analyses of derivatives and by chemical correlation to (+)-1-deoxy-altronojirimycin **3**.

SCHEME 10[a]



	Ar	dr	combined yield %
19	Ph	**27**:**31**, 65:35	35
20	2-Nap	**28**:**32**, 65:35	-
21	1-Nap	**29**:**33**, 80:20	32
22	2-Tol	**30**:**34**, 65:35	-

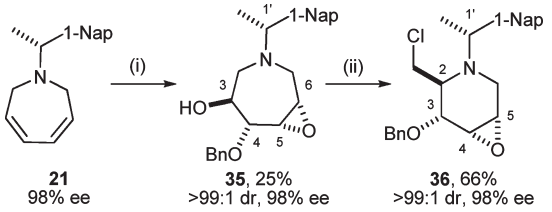
[a]Reagents and conditions: (i) Cl_3CCO_2H, *m*-CPBA, CH_2Cl_2, rt, 21 h, then NaOH (2 M, aq). 2-Nap = 2-naphthyl. 1-Nap = 1-naphthyl. 2-Tol = 2-tolyl.

mixtures of the corresponding *anti*-diols **28** and **32** and **30** and **34**, respectively. Meanwhile, oxidation of 1-naphthyl substrate **21** gave incomplete conversion to an 80:20 mixture of the diastereoisomeric *anti*-diols **29** and **33**, with chromatographic purification allowing partial separation of the diastereoisomers[20,21] (Scheme 10).

Encouraged by these initial results, the oxidation of 1-naphthyl substrate **21** was further investigated. Using our previously optimized conditions for *N*-benzyl protected dihydroazepine **4**, oxidation of **21** with 4 equiv of *m*-CPBA in the presence of 5 equiv of $HBF_4 \cdot OEt_2$ in BnOH[22] gave quantitative conversion to a mixture of products with the functionalized tetrahydroazepine **35** as the major component.[23] Purification gave a sample of **35** in 25% isolated yield and >99:1 dr. Treatment of **35** with MsCl in the presence of Et_3N effected ring contraction to give piperidine **36** as a single diastereoisomer, which was isolated in 66% yield. Single-crystal X-ray analysis of **36** unambiguously established its relative configuration, with the absolute (2*S*,3*R*,4*S*,5*S*,1′*R*)-configuration being assigned from the known (*R*)-stereocenter of the 1-(1′-naphthyl)ethyl group.[24] Therefore, the absolute (3*S*,4*R*,5*S*,6*S*,1′*R*)-configuration within **35** could also be confidently assigned. Given the known enantiomeric purity of the (*R*)-(+)-1-(1′-naphthyl)ethylamine (98% ee)[18] used in the preparation of **21**, the enantiomeric purities of **35** and **36** can be inferred as 98% ee (Scheme 11).

In order to investigate the origin of selectivity in the oxidation of **21**, the reaction was repeated using only 1.5 equiv of *m*-CPBA, which gave incomplete (~50%) conversion to a chromatographically inseparable 80:20 mixture of two diastereoisomeric diols **38** and **39**, which were isolated in 32% combined yield and 80:20 dr.[25] The absolute configuration within

SCHEME 11[a]



[a]Reagents and conditions: (i) $HBF_4 \cdot OEt_2$, *m*-CPBA (4 equiv), BnOH, rt, 24 h; (ii) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1.5 h. 1-Nap = 1-naphthyl.

38 was assigned by subsequent chemical correlation with **35**, while the absolute configuration within **39** was assigned as the alternative stereochemical outcome resulting from an epoxidation step followed by an S_N2-type ring-opening process. These observations are consistent with the *N*-1-(1′-napthyl)ethyl group within **21** promoting the diastereoselective formation of the intermediate epoxide **37** (in 80:20 dr), which undergoes ring-opening via an S_N2-type process upon attack of BnOH exclusively at C(4), which is both distal to the protonated nitrogen atom[26] and an activated allylic position,[27] to give an 80:20 mixture of the monobenzyl protected diols **38** and **39**. Meanwhile, oxidation of the 80:20 mixture of **38** and **39** using aqueous HBF_4[14] and *m*-CPBA gave a crude reaction mixture containing **35** and a diastereoisomeric compound (assigned as **40**) in the ratio of 80:20, along with ~10% of other unidentifiable products. Purification gave an 80:20 mixture of **35**:**40** in 60% combined yield. This result suggests that **38** undergoes completely diastereoselective epoxidation to give **35** and that **39** undergoes completely diastereoselective epoxidation to give **40**. Given that the analogous tetrahydroazepine **5** bearing an *N*-benzyl group (which is incapable of promoting a diastereoselective reaction) undergoes highly diastereoselective epoxidation to give **8** as a single diastereoisomer, these studies imply that the configuration of the *N*-1-(1′-naphthyl)ethyl group has little or no effect in determining the facial selectivity of the epoxidation reaction of **38** and **39** (Scheme 12).

There are four potential sites for oxidation within the ammonium ions derived from dihydroazepines **19**−**22**: two olefins, each with two faces. Assuming that the chiral *N*-protecting group acts as a steric block to oxidation at one of these sites, with oxidation occurring with equal probability at the remaining three sites, then the maximum diastereoselectivity attainable in this scenario would be 67:33 (two of the three epoxides becoming equivalent on deprotonation during basic aqueous workup): essentially the same as observed experimentally for oxidation of α-methylbenzyl **19**, 2-naphthyl **20**, and 2-tolyl **22** with *m*-CPBA in the presence of Cl_3CCO_2H. In the case of 1-naphthyl **21**, however, an enhanced diastereoselectivity of 80:20 is noted for both oxidation under *m*-CPBA/Cl_3CCO_2H conditions and *m*-CPBA/HBF_4/BnOH conditions and therefore these results cannot be accounted for solely by invoking a sterically driven process. Examination of the X-ray crystal structure of 1-naphthyl **21**[28] reveals that the 7-membered ring preferentially

(21) We also investigated *N*(1)-(1′-phenyl-2′-hydroxyethyl)-2,7-dihydro-1*H*-azepine (derived from the reaction of phenylglycinol with dibromide **18**) as a potential substrate for the oxidation reaction, but all conditions investigated returned only starting material or gave rise to a complex mixture of products.

(22) Unlike *N*-benzyl-substituted dihydroazepine **4**, *N*-1-(1′-naphthyl)-ethylamine-substituted dihydroazepine **21** was freely soluble in BnOH and therefore the addition of CH_2Cl_2 to the reaction mixture to aid solubility was not necessary; this modification to the experimental conditions did not affect the reaction diastereoselectivity or efficiency.

(23) Following preparation of an authentic sample, **40** could also be identified as a constituent of the crude reaction mixture; the ratio of **35**:**40** was ~80:20.

(24) Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 788733.

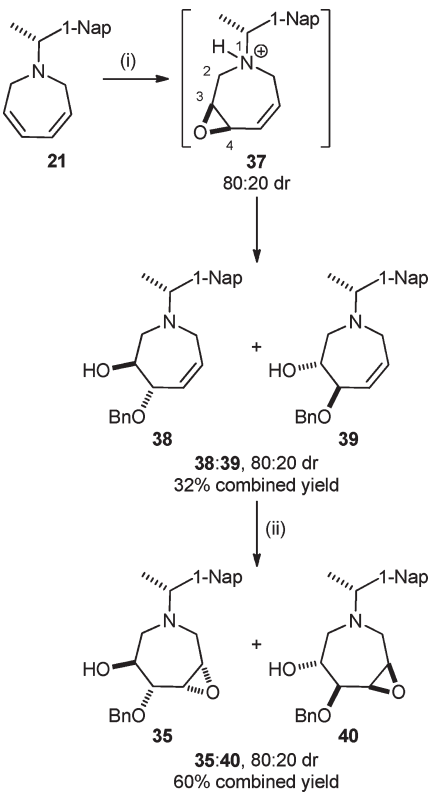
(25) Attempts to drive the reaction to full conversion of starting material resulted in overoxidation to **35** and **40**.

(26) Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, *59*, 737. Addy, J. K.; Parker, R. E. *J. Chem. Soc.* **1963**, 915.

(27) Smith, M. B.; March, J. *March's Advanced Organic Chemistry − Reactions, Mechanisms, and Structure*, 5th ed.; John Wiley & Sons, Inc.: New York, 2001; p 434.

(28) Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 788732.

SCHEME 12[a]



[a]Reagents and conditions: (i) $HBF_4 \cdot OEt_2$, *m*-CPBA (1.5 equiv), BnOH, rt, 24 h; (ii) HBF_4 (40% w/w in H_2O), *m*-CPBA (4 equiv), BnOH, rt, 24 h. 1-Nap = 1-naphthyl.

adopts an envelope-type conformation, with a near planar arrangement of the six carbon atoms and the nitrogen atom out of this plane. The chiral *N*-protecting group adopts a pseudo-axial position, with the C(1′)−H bond oriented directly over the 7-membered ring. ^{1}H NMR NOE data was supportive of an analogous solution phase conformation for ammonium ion **41** (prepared from **21** and F_3CCO_2H in $CDCl_3$). When viewed as a Newman projection along the N−C(1′) bond, the 1-naphthyl group shields the lower face of one of the olefins, presumably blocking reaction at this site. The origin of enhanced diastereoselectivity in this case is consistent with selective epoxidation occurring on the face of the olefin away from the 1-naphthyl group within ammonium ion **41**, with a rate acceleration for oxidation at this site promoted by stabilization of the partial positive charges that develop within the epoxidation transition state on the olefinic carbons by interaction with the π-system of the 1-naphthyl group, resulting in the production of epoxide **37** as the major product (Figure 1). Regioselective ring-opening of **37** by BnOH gives **38**, with further diastereoselective oxidation of **38** giving **35**. It may be assumed that after the first oxidation, the conformation of the 7-membered ring switches from envelope-like to chairlike,[29] with the *N*-1-(1′-naphthyl)ethyl group occupying a pseudoequatorial position, being somewhat remote from the reaction site and therefore playing little

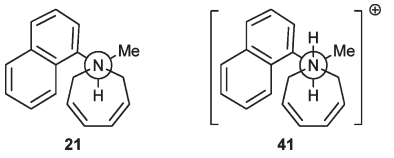
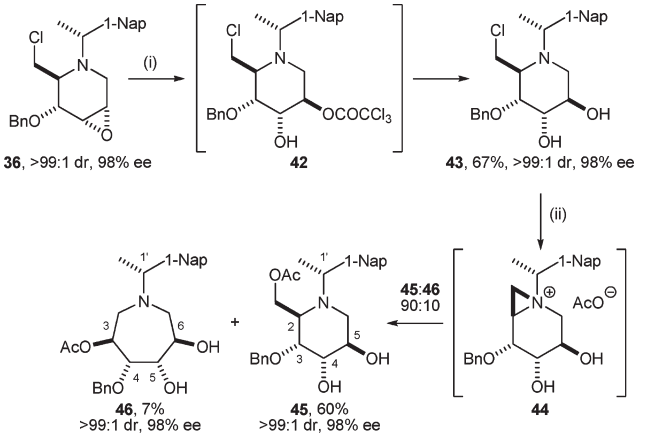


FIGURE 1. Newman projections along the N−C(1′) bond of **21** in the preferred solid-state conformation and the corresponding ammonium ion **41**.

SCHEME 13[a]



[a]Reagents and conditions: (i) Cl_3CCO_2H, CH_2Cl_2, rt, 16 h, then NaOH (2 M, aq); (ii) AgOAc, DMF, 65 °C, 24 h. 1-Nap = 1-naphthyl.

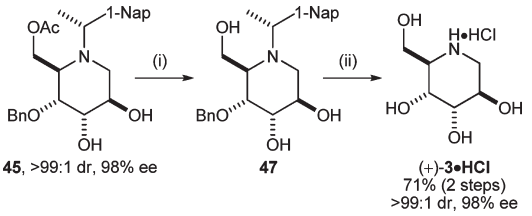
or no part in determining the facial selectivity of the ensuing epoxidation reaction. Given the known conformational lability of 7-membered rings,[29a] the origin of selectivity in the second epoxidation reaction of **5** to **8**, of **38** to **35**, and of **39** to **40** is not clear, although it may plausibly be a result of hydrogen-bonded delivery of the oxidant, or epoxidation on the sterically most accessible face, or a combination of both factors.

With a diastereo- and enantiomerically pure sample of piperidine epoxide **36** in hand, its elaboration to (+)-1-deoxy-altronojirimycin **3** was pursued. Epoxide ring-opening upon treatment of **36** with Cl_3CCO_2H proceeded exclusively at C(5) to give trichloroacetate ester **42** as a single regio- and diastereoisomer, that could be isolated as a 98:2 mixture of **42**:**43** upon workup using 0.1 M aqueous $NaHCO_3$, followed by recrystallization of the crude reaction mixture. Alternatively, workup using 2 M aqueous NaOH effected ester hydrolysis to give diol **43** directly in 67% yield, >99:1 dr and 98% ee.[30] The relative configuration within **43** was assigned on the basis of ^{1}H NMR ^3J coupling constant analysis. Subsequent treatment of **43** with AgOAc in DMF at 65 °C resulted in conversion to a 90:10 mixture of piperidine **45** and azepane **46**. Chromatography facilitated separation of this mixture, giving piperidine **45** in 60% yield, >99:1 dr and 98% ee,[30] and azepane **46** in 7% yield, >99:1 dr and 98% ee.[30] This product distribution is consistent with the reaction proceeding via the intermediacy of the aziridinium ion **44**, which may undergo ring-opening at either the least substituted site (leading to piperidine **45**) or the more substituted site (leading to azepane **46**). The relative configuration

(29) Both cycloheptene and cycloheptene oxide have been shown to favor a chairtype conformation in solution; see: (a) Leong, M. K.; Mastryukov, V. S.; Boggs, J. E. *J. Mol. Struct.* **1998**, *445*, 149. (b) Abraham, R. J.; Castellazzi, I.; Sancassan, F.; Smith, T. A. D. *J. Chem. Soc., Perkin Trans. 2* **1999**, 99.

(30) The enantiomeric purities of **43**, **45**, and **46** were inferred from the enantiomeric purity of the (*R*)-(+)-1-(1′-naphthyl)ethylamine used to prepare the original starting material **21** (i.e., 98% ee).

SCHEME 14[a]



[a]Reagents and conditions: (i) K_2CO_3, MeOH, rt, 16 h; (ii) H_2, $Pd(OH)_2/C$, MeOH, rt, 72 h, then HCl (aq). 1-Nap = 1-naphthyl.

within **45** was unambiguously established by single crystal X-ray analysis, with the absolute (2*R*,3*R*,4*S*,5*R*,1′*R*)-configuration being assigned from the known (*R*)-stereocenter of the 1-(1′-naphthyl)ethyl group.[31] This analysis also affirms the relative configurations within **42** and **43** (and thereby also confirms the regioselectivity of the ring-opening reaction). The absolute (3*R*,4*S*,5*S*,6*R*,1′*R*)-configuration within azepane **46** was assigned on the basis of an S_N2-type ring-opening of aziridinium **44** at the more substituted site (Scheme 13).

Finally, treatment of piperidine **45** with K_2CO_3 in MeOH was followed by hydrogenolysis of the resultant triol **47** to give (+)-1-deoxyaltronojirimycin (**3**), which was isolated as its hydrochloride salt (+)-**3·HCl** in 71% yield (two steps) and >99:1 dr (Scheme 14). The spectroscopic data of our sample of (+)-**3·HCl** were in excellent agreement with those previously reported in the literature {$[\alpha]^{25}_D$ +31.1 (*c* 0.5 in MeOH); lit.[9i] $[\alpha]^{23}_D$ +31.0 (*c* 2.0 in MeOH); lit.[10f] $[\alpha]^{25}_D$ +33.2 (*c* 0.5 in MeOH)}. Given the enantiomeric purity of the (*R*)-(+)-1-(1′-naphthyl)ethylamine (98% ee) used in the preparation of **21**, the enantiomeric purity of (+)-**3·HCl** prepared in this manner can be inferred as 98% ee.

Conclusion

In conclusion, oxidation of enantiomerically pure (*R*)-*N*(1)-1′-(1″-naphthyl)ethyl-2,7-dihydro-1*H*-azepine with *m*-CPBA in the presence of HBF_4 and BnOH gave (3*S*,4*R*,5*S*,6*S*,1′*R*)-*N*(1)-1′-(1″-naphthyl)ethyl-3-hydroxy-4-benzyloxy-5,6-epoxyazepane as the major product and as a single diastereoisomer after chromatography. Elaboration of this highly functionalized intermediate via ring contraction to (2*S*,3*R*,4*S*,5*S*,1′*R*)-*N*(1)-benzyl-2-chloromethyl-3-benzyloxy-4,5-epoxypiperidine followed by regioselective epoxide ring-opening, functional group manipulation, and deprotection gave (+)-1-deoxyaltronojirimycin. Alternatively, resolution of (*RS*,*RS*)-*N*(1)-benzyl-3-hydroxy-4-benzyloxy-2,3,4,7-tetrahydro-1*H*-azepine or (3*RS*,4*SR*,5*RS*,6*RS*)-*N*(1)-benzyl-3-hydroxy-4-benzyloxy-5,6-epoxyazepane by preparative chiral HPLC and subsequent elaboration allows access to the enantiomers of 1-deoxynojirimycin and 1-deoxyaltronojirimycin, respectively.

Experimental Section

General Experimental Details. *m*-CPBA was supplied as a 70−77% slurry in water and titrated according to the procedure of Swern[32] immediately before use. Water was purified by an Elix UV-10 system. Organic solvents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminum plates coated with 60 F_{254} silica. Plates were visualized using UV light (254 nm), iodine, 1% aqueous $KMnO_4$, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed either on Kieselgel 60 silica on a glass column or on an automated flash column chromatography platform.

Melting points are uncorrected. IR spectra were recorded as either a thin film on NaCl plates (film) or a KBr disk (KBr), as stated. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded in the deuterated solvent stated. The field was locked by external referencing to the relevant deuteron resonance. $^1H-^1H$ COSY and $^1H-^{13}C$ HMQC analyses were used to establish atom connectivity.

(+)-(*S,S*)- and (−)-(*R,R*)-*N*(1)-Benzyl-3-hydroxy-4-benzyloxy-2,3,4,7-tetrahydro-1*H*-azepine 5. $HBF_4 \cdot Et_2O$ (4.07 mL, 29.7 mmol) was added to a stirred solution of **4** (1.1 g, 5.94 mmol) in BnOH/CH_2Cl_2 (v/v 2:1, 33 mL), and the resultant solution was stirred for 5 min at rt. *m*-CPBA (75%, 2.05 g, 8.91 mmol) was then added, and the resultant solution was stirred for 24 h before the addition of solid Na_2SO_3 (~4 g) until starch−iodide paper indicated that no oxidant remained. The mixture was diluted with CH_2Cl_2 (50 mL), and the organic layer was washed with 2 M aq NaOH (2 × 100 mL). The combined aqueous washings were extracted with $CHCl_3/^iPrOH$ (v/v 3:1, 2 × 100 mL), and the combined organic extracts were dried and concentrated in vacuo. The residue was then passed through a Biotage SCX-2 scavenger column, eluting first with CH_2Cl_2/MeOH (v/v 1:1), then 2 M NH_3 in MeOH. The ammonia-containing eluent was concentrated in vacuo to give a 75:25 mixture of **5**:**8**. Purification via flash column chromatography (gradient elution, 5→50% EtOAc in 30−40 °C petroleum ether) gave (±)-**5** as a colorless oil (580 mg, 32%, >99:1 dr):[33] IR ν_{max} (film) 3450 (O−H), 3028, 2918 (C−H); NMR δ_H (400 MHz, $CDCl_3$) 2.88 (1H, dd, J = 13.4, 7.6 Hz, C(7)H_A), 3.04−3.29 (4H, m, C(2)H_2, C(7)H_B, O*H*), 3.69 (2H, AB system, NCH_2Ph), 3.85 (1H, td, J = 7.0, 3.7 Hz, C(3)*H*), 4.30−4.35 (1H, m, C(4)*H*), 4.55 (1H, d, J = 11.6 Hz, OC$H_A$$H_B$Ph), 4.73 (1H, d, J = 11.6 Hz, OC$H_A$$H_B$Ph), 5.69−5.84 (2H, m, C(5)*H*, C(6)*H*), 7.25−7.42 (10H, m, *Ph*); NMR δ_C (100 MHz, $CDCl_3$) 55.0 (*C*(7)), 59.3 (*C*(2)), 62.5 (N*C*H_2Ph), 69.6 (*C*(3)), 71.6 (O*C*H_2Ph), 80.2 (*C*(4)), 127.2, 127.8, 127.9, 128.4, 128.5, 128.9 (*o,m,p-Ph*), 130.0, 130.1 (*C*(5), *C*(6)), 138.1, 138.6 (*i-Ph*); MS m/z (ESI^+) 332 ($[M + Na]^+$, 40%), 310 ($[M + H]^+$, 100); HRMS (ESI^+) $C_{20}H_{24}NO_2^+$ ($[M + H]^+$) requires 310.1802, found 310.1798. Preparative chiral HPLC (Chiralpak AD-H [250 × 21.2 mm (i.d.)], mobile phase: MeOH/EtOH [v/v 1:1]) gave (−)-(*R,R*)-**5** as a colorless oil (240 mg, 13% from **4**, >99:1 dr, >99% ee): $[\alpha]^{25}_D$ −81.8 (*c* 1.0 in $CHCl_3$). Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.6; H, 7.5; N, 4.5. Found: C, 77.8; H, 7.7; N, 4.6. Further elution gave (+)-(*S,S*)-**5** as a colorless oil (280 mg, 15% from **4**, >99:1 dr, >99% ee): $[\alpha]^{25}_D$ +82.8 (*c* 1.0 in $CHCl_3$).

(+)-(*S,S*)-*N*(1)-Benzyl-2-chloromethyl-3-benzyloxy-1,2,3,6-tetrahydropyridine 6. Et_3N (0.35 mL, 2.49 mmol) and MsCl (0.14 mL, 1.87 mmol) in CH_2Cl_2 (12 mL) were added sequentially to a stirred solution of (+)-(*S,S*)-**5** (385 mg, 1.24 mmol) in CH_2Cl_2 (12 mL) at 0 °C, and the resultant solution was stirred for 1.5 h at 0 °C before being concentrated in vacuo. Purification via flash column chromatography (gradient elution, 2→20% EtOAc in 30−40 °C petroleum ether) gave (+)-(*S,S*)-**6** as a yellow oil (304 mg, 75% >99:1 dr, >99% ee):[33] $[\alpha]^{25}_D$ +49.6 (*c* 1.0 in $CHCl_3$); IR ν_{max} (film) 3063, 3031, 2868 (C−H); NMR δ_H (400 MHz, $CDCl_3$) 3.09−3.13 (2H, m, C(6)H_2), 3.15−3.21 (1H, m, C(2)*H*), 3.55 (1H, dd, J 11.3, 8.0, C$H_A$$H_B$Cl), 3.71 (1H, d, J = 13.1 Hz, NC$H_A$$H_B$Ph), 3.88 (1H, dd, J = 11.3, 3.5 Hz, CH$_A$$H_B$Cl), 4.01 (1H, d, J = 13.1 Hz,

(31) Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 788734.

(32) Swern, D. *Org. React.* **1953**, *VII*, 392.

(33) The synthesis of racemic **5**−**8** and **12** has previously been reported by us; see ref 8.

NCH_AH_BPh), 4.11−4.15 (2H, m, C(3)*H*), 4.56−4.63 (2H, AB system, OCH_2Ph), 5.86−5.95 (2H, m, C(4)*H*, C(5)*H*), 7.26−7.46 (10H, m, *Ph*); NMR δ_C (100 MHz, $CDCl_3$) 40.4 (*C*H_2Cl), 48.4 (*C*(2)), 57.7 (N*C*H_2Ph), 60.9 (*C*(6)), 70.9 (O*C*H_2Ph), 71.7 (*C*(3)), 123.6 (*C*(5)), 127.2, 127.6, 127.9, 128.4, 128.9 (*o*,*m*,*p*-*Ph*), 129.1 (*C*(4)), 138.3, 138.5 (*i*-*Ph*); MS *m*/*z* (ESI$^+$) 330 ([M + H]$^+$, ^{37}Cl, 79), 328 ([M + H]$^+$, ^{35}Cl, 100); HRMS (ESI$^+$) $C_{20}H_{23}{}^{35}ClNO^+$ ([M + H]$^+$) requires 328.1463, found 328.1462.

(−)-(*R*,*R*)-*N*(1)-Benzyl-2-chloromethyl-3-benzyloxy-1,2,3,6-tetrahydropyridine 6. Et_3N (0.35 mL, 2.49 mmol) and MsCl (0.14 mL, 1.87 mmol) in CH_2Cl_2 (12 mL) were added sequentially to a stirred solution of (−)-(*R*,*R*)-**5** (385 mg, 1.24 mmol) in CH_2Cl_2 (12 mL) at 0 °C, and the resultant solution was stirred for 1.5 h at 0 °C before being concentrated in vacuo. Purification via flash column chromatography (gradient elution, 2→20% EtOAc in 30−40 °C petroleum ether) gave (−)-(*R*,*R*)-**6** as a yellow oil (304 mg, 75% >99:1 dr, >99% ee):[33] $[\alpha]^{25}_D$ −49.5 (*c* 1.0 in $CHCl_3$).

(+)-(2*S*,3*R*,4*R*,5*R*)-*N*(1)-Benzyl-2-chloromethyl-3-benzyloxy-4,5-epoxypiperidine 7. $(F_3CCO)_2O$ (0.64 mL, 4.58 mmol) was added to a stirred solution of H_2O_2 (35% solution in H_2O, 0.18 mL, 1.83 mmol) and CH_2Cl_2 (2.5 mL) at 0 °C, and the resultant solution was stirred for 1.5 h at rt. A solution of (+)-(*S*,*S*)-**6** (250 mg, 0.76 mmol) and CF_3CO_2H (0.14 mL, 1.91 mmol) in CH_2Cl_2 (5 mL) was then added, and the resultant mixture was allowed to warm to rt over 6 h. Solid Na_2SO_3 (∼500 mg) was then added until starch−iodide paper indicated that no oxidant remained. CH_2Cl_2 (20 mL) was then added, and the organic layers were washed with 2 M aq NaOH (2 × 100 mL). The combined aqueous layers were extracted with $CHCl_3$/^{i}PrOH (v/v 3:1, 2 × 50 mL), and the combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (gradient elution, 5→25% EtOAc in 30−40 °C petroleum ether) gave (+)-(2*S*,3*R*,4*R*,5*R*)-**7** as a colorless oil (159 mg, 62%, 98:2 dr, >99% ee):[33] $[\alpha]^{25}_D$ +16.0 (*c* 1.0 in $CHCl_3$); IR ν_{max} (film) 3086, 3062, 3028, 3005, 2887, 2805 (C−H); NMR δ_H (400 MHz, $CDCl_3$) 2.86−2.94 (2H, m, C(2)*H*, C(6)H_A), 3.11 (1H, app d, *J* = 14.2 Hz, C(6)H_B), 3.27−3.31 (1H, m, C(3)*H*), 3.35 (1H, app d, *J* = 4.0 Hz, C(4)*H*), 3.61 (1H, d, *J* = 13.4 Hz, NCH_AH_BPh), 3.77 (1H, dd, *J* = 11.6, 4.8 Hz, CH_AH_BCl), 3.83 (1H, dd, *J* = 11.6, 6.6 Hz, CH_AH_BCl), 3.93 (1H, d, *J* = 13.4 Hz, NCH_AH_BPh), 3.98 (1H, app d, *J* = 5.1 Hz, C(5)*H*), 4.60−4.69 (2H, AB system, OCH_2Ph), 7.25−7.45 (10H, m, *Ph*); NMR δ_C (100 MHz, $CDCl_3$) 41.1 (*C*H_2Cl), 47.3 (*C*(6)), 51.4 (*C*(5)), 52.4 (*C*(4)), 56.8 (N*C*H_2Ph), 60.8 (*C*(2)), 71.3 (*C*(3)), 72.1 (O*C*H_2Ph), 127.3, 128.0, 128.1, 128.4, 128.5, 128.8 (*o*,*m*,*p*-*Ph*), 137.5, 138.1 (*i*-*Ph*); MS *m*/*z* (ESI$^+$) 368 ([M + Na]$^+$, ^{37}Cl, 18), 366 ([M + Na]$^+$, ^{35}Cl, 48), 346 ([M + H]$^+$, ^{37}Cl, 34), 344 ([M + H]$^+$, ^{35}Cl, 100); HRMS (ESI$^+$) $C_{20}H_{23}{}^{35}ClNO_2{}^+$ ([M + H]$^+$) requires 344.1412, found 344.1406. Anal. Calcd for $C_{20}H_{22}ClNO_2$: C, 69.9; H, 6.45; N, 4.1. Found C, 70.0; H, 6.6; N, 4.0.

(−)-(2*R*,3*S*,4*S*,5*S*)-*N*(1)-Benzyl-2-chloromethyl-3-benzyloxy-4,5-epoxypiperidine 7. $(F_3CCO)_2O$ (0.76 mL, 5.49 mmol) was added to a stirred solution of H_2O_2 (35% solution in H_2O, 0.21 mL, 2.20 mmol) and CH_2Cl_2 (3 mL) at 0 °C, and the resultant solution was stirred for 1.5 h at rt. A solution of (−)-(*R*,*R*)-**6** (300 mg, 0.92 mmol) and CF_3CO_2H (0.17 mL, 2.29 mmol) in CH_2Cl_2 (5 mL) was then added, and the resultant mixture was allowed to warm to rt over 6 h. Solid Na_2SO_3 (∼500 mg) was then added until starch−-iodide paper indicated that no oxidant remained. CH_2Cl_2 (20 mL) was then added, and the organic layers were washed with 2 M aq NaOH (2 × 100 mL). The combined aqueous layers were extracted with $CHCl_3$/^{i}PrOH (v/v 3:1, 2 × 50 mL), and the combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (gradient elution, 5→25% EtOAc in 30−40 °C petroleum ether) gave (−)-(2*R*,3*S*,4*S*,5*S*)-**7** as a colorless oil (174 mg, 58%, 98:2 dr, >99% ee):[33] $[\alpha]^{25}_D$ −15.5 (*c* 1.0 in $CHCl_3$).

(+)-(3*S*,4*R*,5*S*,6*S*)- and (−)-(3*R*,4*S*,5*R*,6*R*)-*N*(1)-Benzyl-3-hydroxy-4-benzyloxy-5,6-epoxyazepane 8. Method A. HBF_4·Et_2O (0.56 mL, 4.04 mmol) was added to a stirred solution of **4** (500 mg, 2.70 mmol) in BnOH/CH_2Cl_2 (v/v 2:1, 15 mL), and the resultant solution was stirred for 5 min at rt. *m*-CPBA (75%, 2.48 g, 10.8 mmol) was then added and the resultant solution was stirred for 24 h before the addition of solid Na_2SO_3 (∼4 g) until starch−iodide paper indicated that no oxidant remained. The mixture was diluted with CH_2Cl_2 (50 mL), and the organic layer was washed with 2 M aq NaOH (2 × 100 mL). The combined aqueous washings were extracted with $CHCl_3$/^{i}PrOH (v/v 3:1, 2 × 100 mL), and the combined organic extracts were dried and concentrated in vacuo. The residue was then passed through a Biotage SCX-2 scavenger column, eluting first with CH_2Cl_2/MeOH (v/v 1:1) and then 2 M NH_3 in MeOH. The ammonia-containing eluent was concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/EtOAc, 2:1) gave (±)-**8** as a beige solid (300 mg, 34%, >99:1 dr):[33] mp 51−53 °C; IR ν_{max} (KBr) 3443 (O−H), 3062, 3029, 3002, 2914 (C−H); NMR δ_H (400 MHz, $CDCl_3$) 2.42 (1H, dd, *J* = 13.6, 8.6 Hz, C(2)H_A), 2.65 (1H, br s, O*H*), 2.97 (1H, dd, *J* = 14.9, 2.0 Hz, C(7)H_A), 3.04 (1H, dd, *J* = 13.6, 2.8 Hz, C(2)H_B), 3.12 (1H, td, *J* = 4.7, 2.0 Hz, C(6)*H*), 3.24 (1H, dd, *J* = 14.9, 4.7 Hz, C(7)H_B), 3.36 (1H, dd, *J* = 4.7, 2.7 Hz, C(5)*H*), 3.82 (2H, A_2 system, NCH_2Ph), 3.83−3.84 (1H, m, C(3)*H*), 3.96 (1H, td, *J* = 8.5, 2.7 Hz, C(4)*H*), 4.7 (1H, d, *J* = 11.6 Hz, OCH_A-H_BPh), 4.87 (1H, d, *J* = 11.6 Hz, OCH_AH_BPh), 7.25−7.45 (10H, m, *Ph*); NMR δ_C (100 MHz, $CDCl_3$) 52.0 (*C*(2)), 54.2, 54.3 (*C*(5), *C*(6)), 57.2 (*C*(7)), 61.4 (N*C*H_2Ph), 67.8 (*C*(4)), 71.6 (O*C*H_2Ph), 81.2 (*C*(3)), 127.2, 127.9, 128.0, 128.4, 128.6, 128.8 (*o*,*m*,*p*-*Ph*), 137.8, 138.7 (*i*-*Ph*); MS *m*/*z* (ESI$^+$) 348 ([M + Na]$^+$, 15), 326 ([M + H]$^+$, 100); HRMS (ESI$^+$) $C_{20}H_{24}NO_3{}^+$ ([M + H]$^+$) requires 326.1751, found 326.1747. Preparative chiral HPLC (Chiralpak AD-H [250 × 21.2 mm (i.d.)], mobile phase: MeOH/EtOH [v/v 1:1]) of an aliquot (150 mg) gave (−)-(3*R*,4*S*,5*R*,6*R*)-**8** as a beige solid (51 mg, 12% from **4**, >99:1 dr, >99% ee): $[\alpha]^{25}_D$ −56.4 (*c* 1.0 in $CHCl_3$). Further elution gave (+)-(3*S*,4*R*,5*S*,6*S*)-**8** as a beige solid (47 mg, 11% from **4**, >99:1 dr, 98% ee): $[\alpha]^{25}_D$ +52.4 (*c* 1.0 in $CHCl_3$).

Method B. HBF_4 (40% w/w in H_2O, 0.13 mL, 8.56 mmol) was added to a stirred solution of (+)-(*S*,*S*)-**5** (50 mg, 0.16 mmol) in BnOH/CH_2Cl_2 (v/v 2:1, 1.5 mL), and the resultant solution was stirred for 5 min at rt. *m*-CPBA (75%, 149 mg, 0.65 mmol) was then added, and the resultant solution was stirred for 24 h before the addition of solid Na_2SO_3 (∼500 mg) until starch−iodide paper indicated that no oxidant remained. The mixture was diluted with CH_2Cl_2 (50 mL), and the organic layer was washed with 2 M aq NaOH (2 × 20 mL). The combined aqueous washings were extracted with $CHCl_3$/^{i}PrOH (v/v 3:1, 2 × 20 mL), and the combined organic extracts were dried and concentrated in vacuo. The residue was then passed through a Biotage SCX-2 scavenger column, eluting first with CH_2Cl_2/MeOH (v/v 1:1) and then 2 M NH_3 in MeOH. The ammonia-containing eluent was concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/EtOAc, 2:1) gave (+)-(3*S*,4*R*,5*S*,6*S*)-**8** as a beige solid (36 mg, 62%, >99:1 dr, >99% ee): $[\alpha]^{25}_D$ +54.1 (*c* 1.0 in $CHCl_3$).

Method C. HBF_4 (40% w/w in H_2O, 0.13 mL, 8.56 mmol) was added to a stirred solution of (−)-(*R*,*R*)-**5** (50 mg, 0.16 mmol) in BnOH/CH_2Cl_2 (v/v 2:1, 1.5 mL), and the resultant solution was stirred for 5 min at rt. *m*-CPBA (75%, 149 mg, 0.65 mmol) was then added, and the resultant solution was stirred for 24 h before the addition of solid Na_2SO_3 (∼500 mg) until starch−iodide paper indicated that no oxidant remained. The mixture was diluted with CH_2Cl_2 (50 mL), and the organic layer was washed with 2 M aq NaOH (2 × 20 mL). The combined aqueous washings were extracted with $CHCl_3$/^{i}PrOH (v/v 3:1, 2 × 20 mL),

and the combined organic extracts were dried and concentrated in vacuo. The residue was then passed through a Biotage SCX-2 scavenger column, eluting first with CH_2Cl_2/MeOH (v/v 1:1) and then 2 M NH_3 in MeOH. The ammonia-containing eluent was concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/EtOAc, 2:1) gave (−)-(3*R*,4*S*,5*R*,6*R*)-**8** as a beige solid (35 mg, 61%, >99:1 dr, >99% ee): $[\alpha]^{25}_D$ −54.3 (*c* 1.0 in $CHCl_3$).

(***RS*,*RS***)**-1-Benzyl-2,3,4,7-tetrahydro-1*H*-azepine-3,4-diol 11.** Cl_3CCO_2H (1.54 g, 9.45 mmol) was added to a stirred solution of **4** (350 mg, 1.89 mmol) in CH_2Cl_2 (3.5 mL), and the resultant solution was stirred for 5 min at rt. *m*-CPBA (75%, 870 mg, 3.78 mmol) was then added, and the resultant solution was stirred for 21 h before the addition of solid Na_2SO_3 (~500 mg) until starch−iodide paper indicated that no oxidant remained. The mixture was diluted with CH_2Cl_2 (50 mL), and the organic layer was washed with 2 M aq NaOH (2 × 50 mL). The combined aqueous washings were extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 40−60 °C petroleum ether/EtOAc, 1:1) gave **11** as a colorless oil (124 mg, 30%, >99:1 dr): IR ν_{max} (film) 3385 (O−H), 3079, 2985, 2971 (C−H); NMR δ_H (400 MHz, $CDCl_3$) 2.68 (1H, dd, *J* = 13.4, 7.3 Hz, C(7)H_A), 3.09−3.19 (3H, m, C(7)H_B, C(2)H_2), 3.64 (2H, A_2 system, NCH_2Ph), 3.70−4.00 (3H, m, C(3)*H*, 2 × O*H*), 4.36 (1H, ddd, *J* = 7.3, 3.7, 1.4 Hz, C(4)*H*), 5.60−5.69 (1H, m, C(6)*H*), 5.73−5.80 (1H, m, C(5)*H*), 7.23−7.36 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 55.4 (*C*(7)), 60.1 (*C*(2)), 62.1 (N*C*H_2Ph), 71.4 (*C*(3)), 73.1 (*C*(4)), 127.4, 128.5, 128.8, 129.0 (*o*,*m*,*p*-*Ph*, *C*(6)), 132.1 (*C*(5)), 138.2 (*i*-*Ph*); MS *m*/*z* (ESI$^+$) 220 ([M + H]$^+$, 100); HRMS (ESI$^+$) $C_{13}H_{18}NO_2^+$ [M + H] $^+$ requires 220.1332, found 220.1332.

(−)-(2*S*,3*R*,4*R*,5*S*)-*N*(1)-Benzyl-2-chloromethyl-3-benzyloxy-4,5-dihydroxypiperidine 12. Cl_3CCO_2H (1.05 g, 6.40 mmol) was added to a stirred solution of (+)-(2*S*,3*R*,4*R*,5*R*)-**7** (110 mg, 0.32 mmol) in CH_2Cl_2 (1.1 mL), and the resultant solution was stirred for 16 h at rt. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and then washed with 2 M aq NaOH (2 × 50 mL). The combined aqueous layers were extracted with $CHCl_3$/^{i}PrOH (v/v 3:1, 2 × 20 mL). The combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (gradient elution, 10→100% EtOAc in 30−40 °C petroleum ether) gave (−)-(2*S*,3*R*,4*R*,5*S*)-**12** as a colorless oil (59 mg, 51%, 99:1 dr, >99% ee):[33] $[\alpha]^{25}_D$ −26.7 (*c* 1.0 in $CHCl_3$); IR ν_{max} (film) 3387 (O−H) 3030, 2915 (C−H); NMR δ_H (400 MHz, $CDCl_3$) 1.98 (1H, app t, *J* = 10.5 Hz, C(6)H_A), 2.45 (1H, app d, *J* = 8.8 Hz, C(2)*H*) 2.78 (1H, br s, O*H*), 2.97−3.05 (2H, m, C(6)H_B, O*H*), 3.16 (1H, d, *J* = 12.9 Hz, NC$H_A$$H_B$Ph), 3.42−3.66 (3H, m, C(3)*H*, C(4)*H*, C(5)*H*), 4.00 (1H, dd, *J* = 12.6, 3.3 Hz, C$H_A$$H_B$Cl), 4.09 (1H, dd, *J* = 12.6, 1.8 Hz, CH$_A$$H_B$Cl), 4.14 (1H, d, *J* = 12.9 Hz, NCH$_A$$H_B$Ph), 4.82 (1H, d, *J* = 11.4 Hz, OC$H_A$$H_B$Ph), 4.90 (1H, d, *J* = 11.4 Hz, OCH$_A$$H_B$Ph), 7.25−7.43 (10H, m, *Ph*); NMR δ_C (100 MHz, $CDCl_3$) 41.8 (*C*H_2Cl), 54.7 (*C*(6)), 56.0 (N*C*H_2Ph), 64.6 (*C*(2)), 69.7 (*C*(5)), 75.3 (O*C*H_2Ph), 78.7 (*C*(4)), 79.3 (*C*(3)), 127.4, 128.0, 128.1, 128.4, 128.7, 129.2 (*o*,*m*,*p*-*Ph*), 137.7, 138.2 (*i*-*Ph*); MS *m*/*z* (ESI$^+$) 386 ([M + Na]$^+$, ^{37}Cl, 34), 384 ([M + Na]$^+$, ^{35}Cl, 100), 364 ([M+H]$^+$, ^{37}Cl, 24), 362 ([M + H]$^+$, ^{35}Cl, 64); HRMS (ESI$^+$) $C_{20}H_{25}{}^{35}ClNO_3^+$ ([M + H]$^+$) requires 362.1517, found 362.1516.

(+)-(2*R*,3*S*,4*S*,5*R*)-*N*(1)-Benzyl-2-chloromethyl-3-benzyloxy-4,5-dihydroxypiperidine 12. Cl_3CCO_2H (1.19 g, 7.27 mmol) was added to a stirred solution of (−)-(2*R*,3*S*,4*S*,5*S*)-**7** (125 mg, 0.36 mmol) in CH_2Cl_2 (1.3 mL), and the resultant solution was stirred for 16 h at rt. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and then washed with 2 M aq NaOH (2 × 50 mL). The combined aqueous layers were extracted with $CHCl_3$/^{i}PrOH (3:1, 2 × 20 mL). The combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (gradient elution, 10→100% EtOAc in 30−40 °C petroleum ether) gave (+)-(2*R*,3*S*,4*S*,5*R*)-**12** as a colorless oil (65 mg, 50%, 99:1 dr):[12] $[\alpha]^{25}_D$ +26.9 (*c* 1.0 in $CHCl_3$).

(+)-(2*R*,3*R*,4*R*,5*S*)-2-Hydroxymethyl-3,4,5-trihydroxypiperidine Hydrochloride [(+)-1-Deoxynojirimycin hydrochloride] 2·HCl. Step 1. AgOAc (21 mg, 0.12 mmol) was added to a stirred solution of (−)-(2*S*,3*R*,4*R*,5*S*)-**12** (30 mg, 0.08 mmol) in DMF (1 mL), and the resultant suspension was stirred for 24 h at 65 °C. The reaction mixture was then allowed to cool to rt before the addition of H_2O (4 mL). The mixture was extracted with Et_2O (3 × 2 mL), and the combined organic extracts were washed with H_2O (3 × 6 mL) before being dried and concentrated in vacuo to give (2*R*,3*R*,4*R*,5*S*)-**13** as a colorless oil (20 mg) that was used without purification.

Step 2. K_2CO_3 (143 mg, 1.04 mmol) was added to a stirred solution of (2*R*,3*R*,4*R*,5*S*)-**13** (20 mg, 0.05 mmol) in MeOH (1 mL), and the resultant suspension was stirred for 16 h at rt before being concentrated in vacuo. The residue was dissolved in H_2O (2 mL) and extracted with $CHCl_3$/^{i}PrOH (v/v 3:1, 2 × 2 mL). The combined organic extracts were dried and concentrated in vacuo to give (2*R*,3*R*,4*R*,5*S*)-**14** as a colorless oil (18 mg) that was used without purification.

Step 3. $Pd(OH)_2$/C (18 mg) was added to a stirred solution of (2*R*,3*R*,4*R*,5*S*)-**14** (18 mg, 0.05 mmol) in degassed MeOH (0.5 mL), and the resultant suspension was stirred for 72 h under an atmosphere of H_2 (1 atm). Concentrated aq HCl (10 μL) was then added, and the resultant suspension was stirred for a further 5 min before being filtered through Celite (eluent MeOH). The filtrate was concentrated in vacuo, and the residue was purified via flash column chromatography (eluent $CHCl_3$/MeOH, 4:1) to give (+)-(2*R*,3*R*,4*R*,5*S*)-**2**·HCl as a white semisolid (5 mg, 30% from (−)-(2*S*,3*R*,4*R*,5*S*)-**12**, 99:1 dr, >99% ee):[2] $[\alpha]^{25}_D$ +31.0 (*c* 0.45 in H_2O) [lit.[3a] for natural sample $[\alpha]^{22}_D$ +38.0 (*c* 1.0 in H_2O); lit.[9m] $[\alpha]^{23}_D$ +36.9 (*c* 1.1 in H_2O)]; NMR δ_H (500 MHz, D_2O) 3.17 (1H, dd, *J* = 13.6, 2.8 Hz, C$H_A$$H_B$OH), 3.27−3.35 (2H, m, C(4)*H*, CH$_A$$H_B$OH), 3.77 (1H, dd, *J* = 12.6, 6.9 Hz, C(6)H_A), 3.91 (1H, dd, *J* = 12.6, 3.2 Hz, C(6)H_B), 3.94−3.99 (2H, m, C(3)*H*, C(5)*H*), 4.08−4.11 (1H, br m, C(2)*H*); NMR δ_C (125 MHz, D_2O) 43.9 (*C*H_2OH), 55.8 (*C*(4)), 58.2 (*C*(6)), 63.6 (*C*(5)), 66.2 (*C*(2)), 68.5 (*C*(3)).

(−)-(2*S*,3*S*,4*S*,5*R*)-2-Hydroxymethyl-3,4,5-trihydroxypiperidine Hydrochloride [(−)-1-Deoxynojirimycin Hydrochloride] (2·HCl). Step 1. AgOAc (21 mg, 0.12 mmol) was added to a stirred solution of (+)-(2*R*,3*S*,4*S*,5*R*)-**12** (30 mg, 0.08 mmol) in DMF (1 mL), and the resultant suspension was stirred for 24 h at 65 °C. The reaction mixture was then allowed to cool to rt before the addition of H_2O (4 mL). The mixture was extracted with Et_2O (3 × 2 mL), and the combined organic extracts were washed with H_2O (3 × 6 mL) before being dried and concentrated in vacuo to give (2*S*,3*S*,4*S*,5*R*)-**13** as a colorless oil (20 mg) that was used without purification.

Step 2. K_2CO_3 (143 mg, 1.04 mmol) was added to a stirred solution of (2*S*,3*S*,4*S*,5*R*)-**13** (20 mg, 0.05 mmol) in MeOH (1 mL), and the resultant suspension was stirred for 16 h at rt before being concentrated in vacuo. The residue was dissolved in H_2O (2 mL) and extracted with $CHCl_3$/^{i}PrOH (v/v 3:1, 2 × 2 mL). The combined organic extracts were dried and concentrated in vacuo to give (2*S*,3*S*,4*S*,5*R*)-**14** as a colorless oil (18 mg) that was used without purification.

Step 3. $Pd(OH)_2$/C (18 mg) was added to a stirred solution of (2*S*,3*S*,4*S*,5*R*)-**14** (18 mg, 0.05 mmol) in degassed MeOH (0.5 mL), and the resultant suspension was stirred for 72 h under an atmosphere of H_2 (1 atm). Concentrated aq HCl (10 μL) was then added, and the resultant suspension was stirred for a further 5 min before being filtered through Celite (eluent MeOH). The filtrate was concentrated in vacuo, and the residue was purified via flash column chromatography (eluent $CHCl_3$/MeOH, 4:1) to give (−)-(2*S*,3*S*,4*S*,5*R*)-**2**·HCl as a white semisolid (6 mg, 36% from (+)-(2*R*,3*S*,4*S*,5*R*)-**12**, 99:1 dr, >99% ee):[2] $[\alpha]^{25}_D$ −34.0 (*c* 0.45 in H_2O) [lit.[9i] $[\alpha]^{25}_D$ −46.0 (*c* 1.3 in H_2O); lit.[9m] $[\alpha]^{24}_D$ −38.7 (*c* 1.0 in H_2O)].

Dimethyl (*Z*,*Z*)-Hexa-2,4-dienedioate 16. MeI (9.59 mL, 155 mmol) and K_2CO_3 (38.9 g, 281 mmol) were added sequentially to a stirred solution of **15** (10.0 g, 70.4 mmol) in DMF (200 mL), and the resultant mixture was stirred for 24 h at rt. H_2O (800 mL) was then added, and the aqueous layer was extracted with Et_2O (3 × 200 mL). The combined organic extracts were then washed with H_2O (3 × 500 mL) before being dried and concentrated in vacuo to give **16** as a white solid (11.4 g, 91%):[8,34] mp 74−75 °C (lit.[34] mp 72−73 °C); NMR δ_H (400 MHz, $CDCl_3$) 3.76 (6H, s, CO_2CH_3), 5.95−6.04 (2H, m, C(2)*H*, C(5)*H*), 7.86−7.95 (2H, m, C(3)*H*, C(4)*H*).

(*Z*,*Z*)-1,6-Dibromohexa-2,4-diene 18. Step 1. DIBAL-H (1.0 M in cyclohexane, 195 mL, 195 mmol) was added to a stirred solution of **16** (8.29 g, 48.7 mmol) in CH_2Cl_2 (290 mL) at 0 °C, and the resultant solution was stirred for 16 h at rt. The reaction mixture was cooled to 0 °C, and MeOH was added dropwise until effervescence ceased. The resultant mixture was diluted with MeOH (500 mL), which produced a paste-like suspension. The suspension was filtered through Celite (eluent MeOH). The insoluble aluminum-containing solids were collected from the column and ground using a pestle and mortar, MeOH (100 mL) was added, and the mixture was filtered though Celite (eluent MeOH). The combined filtrates were dried and concentrated in vacuo to give **17** as a yellow oil (5.55 g) that was used without purification.

Step 2. A solution of PBr_3 (3.02 mL, 32.1 mmol) in Et_2O (260 mL) was added to a stirred solution of **17** (5.55 g) in Et_2O (170 mL) at 0 °C. After 7 h, the reaction mixture was concentrated in vacuo. The residue was recrystallized from hexane to give **18** as a light red/brown solid (9.71 g, 83%):[8,34] mp 84−86 °C (lit.[34] mp 91−93 °C); NMR δ_H (400 MHz, $CDCl_3$) 4.12 (4H, d, *J* 8.2, C(1)H_2, C(6)H_2), 5.87−5.99 (2H, m, C(2)*H*, C(5)*H*), 6.41−6.50 (2H, m, C(3)*H*, C(4)*H*).

(*R*)-*N*(1)-α-Methylbenzyl-2,7-dihydro-1*H*-azepine 19. (*R*)-α-Methylbenzylamine (3.26 g, 26.9 mmol, 99% ee)[18] and K_2CO_3 (7.44 g, 53.8 mmol) were added sequentially to a stirred solution of **18** (3.23 g, 13.5 mmol) in THF (160 mL) at rt. After 24 h, the reaction mixture was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (50 mL) and filtered through Celite (eluent CH_2Cl_2), and the filtrate was concentrated in vacuo. Purification via flash column chromatography (gradient elution, 0→10% EtOAc in 30−40 °C petroleum ether) gave **19** as a pale yellow oil (1.92 g, 71%, 99% ee): $[\alpha]^{25}_D$ +45.0 (*c* 1.0 in $CHCl_3$); IR ν_{max} (film) 3059, 3013, 2972, 2934 (C−H); NMR δ_H (400 MHz, $CDCl_3$) 1.37 (3H, d, *J* = 6.6 Hz, C(α)*Me*), 3.38−3.46 (2H, m, C(2)H_A, C(7)H_A), 3.58−3.67 (2H, m, C(2)H_B, C(7)H_B), 3.87 (1H, q, *J* = 6.6 Hz, C(α)*H*), 5.61 (2H, ddd, *J* = 12.6, 3.8, 3.6 Hz, C(3)*H*, C(6)*H*), 5.91−5.98 (2H, m, C(4)*H*, C(5)*H*), 7.22−7.38 (5H, m, *Ph*); NMR δ_C (100 MHz, $CDCl_3$) 21.3 (C(α)*Me*), 53.5 (*C*(2), *C*(7)), 58.2 (*C*(α)), 126.5 (*C*(4), *C*(5)), 126.9, 127.6, 128.2 (*o*,*m*,*p*-*Ph*), 132.6 (*C*(3), *C*(6)), 145.1 (*i*-*Ph*); MS *m*/*z* (ESI^+) 200 ([M + H]$^+$,100); HRMS (ESI^+) $C_{14}H_{18}N^+$ ([M + H]$^+$) requires 200.1434, found 200.1433.

(*R*)-*N*(1)-1′-(2″-Naphthyl)ethyl-2,7-dihydro-1*H*-azepine 20. (*R*)-1-(2′-Naphthyl)ethylamine (1.00 g, 5.83 mmol)[18] and K_2CO_3 (1.61 g, 11.7 mmol) were added sequentially to a stirred solution of **18** (700 mg, 2.92 mmol) in THF (35 mL) at rt. After 24 h, the reaction mixture was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (25 mL) and filtered through Celite (eluent CH_2Cl_2), and the filtrate was concentrated in vacuo. Purification via flash column chromatography (gradient elution, 0→5% EtOAc in 30−40 °C petroleum ether) gave **24** as a colorless oil (70 mg, 10%): $[\alpha]^{25}_D$ +152 (*c* 1.0 in $CHCl_3$); IR ν_{max} (film) 3056, 2974, 2931, 2873, 2789 (C−H) 1724 (C═C); NMR δ_H (400 MHz, $CDCl_3$) 1.51 (3H, d, *J* 6.6, C(1′)*Me*), 3.44−3.52 (1H, m, C(5)H_A), 3.61−3.69 (1H, m, C(5)H_B), 4.04 (1H, q, *J* = 6.6 Hz, C(1′)*H*), 4.25−4.32 (1H, m, C(2)*H*), 5.08 (1H, app d *J* = 10.1 Hz, CH═C$H_A$$H_B$), 5.18 (1H, app d, *J* = 17.3 Hz, (CH═CH$_A$$H_B$), 5.66 (1H, dq, *J* = 6.4, 2.0 Hz, C(4)*H*), 5.77 (1H, dq, *J* = 6.4, 2.0 Hz, C(3)*H*), 5.93 (1H, ddd, *J* = 17.3, 10.1, 7.8 Hz, C*H*═CH$_2$), 7.42−7.52 (2H, m, *Ar*), 7.56 (1H, dd, *J* = 8.3, 2.0 Hz, *Ar*), 7.76 (1H, s, *Ar*), 7.82−7,87 (3H, m, *Ar*); NMR δ_C (100 MHz, $CDCl_3$) 23.6 (*C*(1′)*Me*), 58.2 (*C*(5)), 62.4 (*C*(1′)), 70.9 (*C*(2)), 114.6 (CH═*C*H$_2$), 125.4, 125.8, 126.1, 127.2, 127.6, 127.8, 128.0 (*C*(3), *Ar*), 131.2 (*C*(4)), 132.7, 133.4 (*Ar*), 141.4 (*C*H═CH$_2$), 142.6 (*Ar*); MS *m*/*z* (ESI^+) 250 ([M + H]$^+$, 100); HRMS (ESI^+) $C_{18}H_{20}N^+$ ([M + H]$^+$) requires 250.1590, found 250.1587. Further elution gave **20** as a white solid (450 mg, 62%): mp 59−61 °C; $[\alpha]^{25}_D$ +48.1 (*c* 1.0 in $CHCl_3$); IR ν_{max} (film) 3053, 3010, 2971, 2933 (C−H), 1601 (C═C); NMR δ_H (400 MHz, $CDCl_3$) 1.54 (3H, d, *J* = 6.6 Hz, C(1′)*Me*), 3.55 (2H, dd, *J* = 16.7, 3.5 Hz, C(2)H_A, C(7)H_A), 3.76 (2H, dd, *J* = 16.7, 3.5 Hz, C(2)H_B, C(7)H_B), 4.14 (1H, q, *J* = 6.6 Hz, C(1′)*H*), 5.75 (2H, app dt, *J* = 12.6, 3.5 Hz, C(3)*H*, C(6)*H*), 6.02−6.12 (2H, m, C(4)*H*, C(5)*H*), 7.48−7.56 (2H, m, *Ar*), 7.67−7.73 (1H, m, *Ar*), 7.81−7.95 (4H, m, *Ar*); NMR δ_C (100 MHz, $CDCl_3$) 21.3 (C(1′)*Me*), 53.6 (*C*(2), *C*(7)), 58.3 (*C*(1′)), 125.5, 125.7, 125.8, 126.2, 126.6, 127.6, 127.9, 128.0 (*C*(4), *C*(5), *Ar*), 132.9 (*C*(3), *C*(6)), 132.8, 133.4, 147.8 (*Ar*); MS *m*/*z* (ESI^+) 250 ([M + H]$^+$, 100); HRMS (ESI^+) $C_{18}H_{20}N^+$ ([M + H]$^+$) requires 250.1590, found 250.1588.

X-ray Crystal Structure Determination for 20. Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite-monochromated Mo Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealized positions. The structure was refined using CRYSTALS.[35]

X-ray crystal structure data for **20** [$C_{18}H_{19}N$]: M = 249.36, orthorhombic, space group $P2_12_12_1$, a = 5.60290(10) Å, b = 8.2626(2) Å, c = 30.1557(8) Å, V = 1396.04(6) Å^3, Z = 4, μ = 0.068 mm^{-1}, colorless plate, crystal dimensions = 0.11 × 0.17 × 0.19 mm^3. A total of 1816 unique reflections were measured for $5 < \theta < 27$, and 1815 reflections were used in the refinement. The final parameters were wR_2 = 0.089 and R_1 = 0.047 [$I > -3.0\sigma(I)$].

Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 788731. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

(*R*)-*N*(1)-1′-(1″-Naphthyl)ethyl-2,7-dihydro-1*H*-azepine 21. (*R*)-1-(1′-Naphthyl)ethylamine (8.03 mL, 50.0 mmol, 98% ee)[18] and K_2CO_3 (13.8 g, 100 mmol) were added sequentially to a stirred solution of **18** (6.00 g, 25.0 mmol) in THF (300 mL) at rt. After 24 h, the reaction mixture was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (150 mL) and filtered through Celite (eluent CH_2Cl_2), and the filtrate was concentrated in vacuo. Purification via flash column chromatography (gradient elution, 0→5% EtOAc in 30−40 °C petroleum ether) gave **25** as a green oil (312 mg, 5%, 98% ee): $[\alpha]^{25}_D$ +96.6 (*c* 1.0 in $CHCl_3$); IR ν_{max} (film) 3010, 2971 (C−H); NMR δ_H (400 MHz, $CDCl_3$) 1.55 (3H, d, *J* = 6.8 Hz, C(1′)*Me*), 3.39−3.47 (1H, m, C(5)H_A), 3.62−3.75 (1H, m, C(5)H_B) 4.35−4.42 (1H, m, C(2)*H*), 4.65 (1H, q, *J* = 6.8 Hz, C(1′)*H*), 4.99−5.03 (1H, m, CH═C$H_A$$H_B$), 5.08−5.15 (1H, m, CH═CH$_A$$H_B$), 5.59−5.63 (1H, m, C(4)*H*), 5.74−5.79 (1H, m, C(3)*H*), 5.89−6.00 (1H, m, C*H*═CH$_2$), 7.45−7.55 (3H, m, *Ar*), 7.67−7.79 (2H, m, *Ar*), 7.85−7.91 (1H, m, *Ar*), 8.45 (1H, d, *J* 7.4, *Ar*); NMR δ_C (100 MHz, $CDCl_3$) 23.0 (C(1′)*Me*), 59.3 (*C*(5)), 59.8 (C(1′)), 71.3 (*C*(2)),

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114.1 (CH=CH_2), 123.8, 124.8, 125.2, 125.5, 125.6, 127.0, 127.1, 128.8 (*C*(3), *C*H=CH_2, *Ar*), 131.2, 134.0, 141.3, 141.9 (*C*(4), *Ar*); MS *m*/*z* (ESI$^+$) 250 ([M + H]$^+$, 100); HRMS (ESI$^+$) $C_{18}H_{20}N^+$ ([M + H]$^+$) requires 250.1590, found 250.1594. Further elution gave **21** as a white solid (4.67 g, 75%, 98% ee): mp 55−57 °C; $[\alpha]^{25}_D$ +76.4 (*c* 1.0 in $CHCl_3$); IR ν_{max} (film) 3008, 2974, 2934, 2874, 2791 (C−H); NMR δ_H (400 MHz, $CDCl_3$) 1.72 (3H, d, *J* = 6.8 Hz, C(1′)*Me*), 3.54 (2H, dd, *J* = 16.7, 3.5 Hz, C(2)H_A, C(7)H_A), 3.74 (2H, dd, *J* = 16.7, 3.5 Hz, C(2)H_B, C(7)H_B), 4.72 (1H, m, C(1′)*H*), 5.70 (2H, dt, *J* = 8.8, 3.5 Hz, C(3)*H*, C(6)*H*), 5.97−6.06 (2H, m, C(4)*H*, C(5)*H*), 7.42−7.55 (3H, m, *Ar*), 7.66−7.73 (1H, m, *Ar*), 7.74−7.81 (1H, m, *Ar*), 7.84−7.94 (1H, m, *Ar*), 8.51 (1H, d, *J* = 4.3 Hz, *Ar*); NMR δ_C (100 MHz, $CDCl_3$) 21.0 (*C*(1′)*Me*), 53.6 (*C*(2), *C*(7)), 55.2 (*C*(1′)), 124.2, 125.2, 125.4, 125.6, 126.5, 127.2, 128.7 (*Ar*, *C*(4), *C*(5)), 131.7 (*C*(3), *C*(6)), 133.2, 134.0, 141.4 (*Ar*); MS *m*/*z* (ESI$^+$) 250 ([M + H]$^+$, 100); HRMS (ESI$^+$) $C_{18}H_{20}N^+$ ([M + H]$^+$) requires 250.1590, found 250.1593. Anla. Calcd for C, 86.7; H, 7.7; N, 5.6. Found: C, 86.8; H, 7.6; N, 5.5.

X-ray Crystal Structure Determination for 21. Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite-monochromated Mo Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealized positions. The structure was refined using CRYSTALS.[35]

X-ray crystal structure data for **21** [$C_{18}H_{19}N$]: *M* = 249.36, orthorhombic, space group $P2_12_12_1$, *a* = 7.1891(2) Å, *b* = 7.2120(2) Å, *c* = 27.0900(9) Å, *V* = 1404.56(7) Å^3, *Z* = 4, μ = 0.068 mm^{-1}, colorless plate, crystal dimensions = 0.12 × 0.14 × 0.19 mm^3. A total of 1860 unique reflections were measured for 5 < θ < 27 and 1860 reflections were used in the refinement. The final parameters were wR_2 = 0.118 and R_1 = 0.084 [$I > -3.0\sigma(I)$].

Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 788732. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

(*RS*)-*N*(1)-1′-(2′′-Tolyl)ethyl-2,7-dihydro-1*H*-azepine 22. (*RS*)-1-(2′-Tolyl)ethylamine (600 mg, 4.44 mmol)[18] and K_2CO_3 (1.23 g, 8.87 mmol) were added sequentially to a stirred solution of **18** (532 mg, 2.22 mmol) in THF (30 mL) at rt. After 24 h, the reaction mixture was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (30 mL) and filtered through Celite (eluent CH_2Cl_2), and the filtrate was concentrated in vacuo. Purification via flash column chromatography (gradient elution, 0→10% EtOAc in 30−40 °C petroleum ether) gave a 93:7 mixture of **22**:**26** as a pale yellow oil (405 mg, 86%): IR ν_{max} (film) 2970 (C−H), 1605 (C=C); MS *m*/*z* (ESI$^+$) 214 ([M + H]$^+$, 100); HRMS (ESI$^+$) $C_{15}H_{20}N^+$ ([M + H$^+$]) requires 214.1590, found 214.1589. Data for **22**: NMR δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, *J* = 6.6 Hz, C(1′)*Me*), 2.33 (3H, s, Ar*Me*), 3.48 (2H, dd, *J* = 17.2, 3.1 Hz, C(2)H_A, C(7)H_A), 3.64 (2H, dd, *J* = 17.2, 3.1 Hz, C(2)H_B, C(7)H_B), 4.19 (3H, q, *J* = 6.6 Hz, C(1′)*H*), 5.68 (2H, app dt, *J* 12.4, 3.1, C(3)*H*, C(6)*H*), 5.90−6.00 (2H, m, C(4)*H*, C(5)*H*), 7.08−7.15 (2H, m, *Ar*), 7.20 (1H, app t, *J* = 7.1 Hz, *Ar*), 7.56 (1H, d, *J* = 7.6 Hz, *Ar*); NMR δ_C (100 MHz, $CDCl_3$) 19.5 (Ar*Me*), 20.8 (C(1′)*Me*), 53.4 (*C*(1′), *C*(2), *C*(7)), 126.2 (*C*(4), *C*(5)), 126.1, 126.2, 126.5, 126.9, 130.3, 133.1 (*C*(3), *C*(6), *Ar*), 135.6, 143.6 (*Ar*).

(3*S*,4*S*,α*R*)- and (*R*,*R*,*R*)-*N*(1)-α-Methylbenzyl-3,4-dihydroxy-2,3,4,7-tetrahydro-1*H*-azepine (3*S*,4*S*,α*R*)-27 and (*R*,*R*,*R*)-31. Cl_3CCO_2H (1.23 g, 7.5 mmol) was added to a stirred solution of **19** (300 mg, 1.5 mmol, >99% ee) in CH_2Cl_2 (3.0 mL), and the resultant solution was stirred for 5 min at rt. *m*-CPBA (75%, 693 mg, 3.01 mmol) was then added, and the resultant solution was stirred for 21 h before the addition of solid Na_2SO_3 (∼500 mg) until starch−iodide paper indicated that no oxidant remained. The mixture was diluted with CH_2Cl_2 (50 mL), and the organic layer was washed with 2 M aq NaOH (2 × 50 mL). The combined aqueous washings were extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic extracts were dried and concentrated in vacuo. The residue was then passed through a Biotage SCX-2 scavenger column, eluting first with CH_2Cl_2/MeOH (v/v 1:1) and then 2 M NH_3 in MeOH. The ammonia-containing eluent was concentrated in vacuo to give a 65:35 mixture of **27**:**31**. Purification via flash column chromatography (eluent 40−60 °C petroleum ether/EtOAc, 2:1) gave a 65:35 mixture of **27**:**31** as a yellow oil (122 mg, 35%): IR ν_{max} (film) 3381 (O−H), 3084, 3061, 3027, 2981, 2971 (C−H); NMR δ_C (100 MHz, $CDCl_3$) 17.8, 18.1 (2 × C(α)-*Me*), 53.4, 54.1 (2 × *C*(7)), 56.3, 56.6 (2 × *C*(2)), 62.8, 63.0 (2 × *C*(α)), 71.9, 72.1 (2 × *C*(3)), 72.8, 73.0 (2 × *C*(4)), 127.3, 127.5, 128.5, 129.8, 130.0, 130.8 (2 × *C*(5), 2 × *C*(6), 2 × *o*-,*m*-,*p*-*Ph*,), 142.8, 143.1 (2 × *i*-*Ph*); MS *m*/*z* (ESI$^+$) 234 ([M + H]$^+$, 100); HRMS (ESI$^+$) $C_{14}H_{19}NNaO_2^+$ ([M + Na]$^+$) requires 256.1308, found 256.1304. Data for **27**: NMR δ_H (400 MHz, $CDCl_3$) 1.40 (3H, d, *J* = 6.6 Hz, C(1′)*Me*), 2.69 (1H, dd, *J* = 13.8, 6.7 Hz, C(2)H_A), 3.08 (1H, m, C(2)H_B), 3.19−3.24 (2H, m, C(7)H_2), 3.73−3.88 (2H, m, C(3)*H*, C(1′)*H*), 4.34−4.39 (1H, m, C(4)*H*), 5.61−5.71 (1H, m, C(6)*H*), 5.74−5.85 (1H, m, C(5)*H*), 7.24−7.40 (5H, m, *Ph*). Data for **31**: δ_H (400 MHz, $CDCl_3$) (selected peaks) 2.63 (1H, dd, *J* = 13.6, 7.1 Hz, C(2)H_A), 3.11−3.17 (1H, m, C(2)H_B), 3.25−3.28 (1H, m, C(7)H_A), 4.26−4.34 (1H, m, C(7)H_B).

(3*S*,4*S*,α*R*)- and (*R*,*R*,*R*)-*N*(1)-1′-(1′′-Naphthyl)ethyl-3,4-dihydroxy-2,3,4,7-tetrahydro-1*H*-azepine (3*S*,4*S*,α*R*)-29 and (*R*,*R*,*R*)-33. Cl_3CCO_2H (1.64 g, 10.0 mmol) was added to a stirred solution of **21** (500 mg, 2.01 mmol, 98% ee) in CH_2Cl_2 (5.0 mL), and the resultant solution was stirred for 5 min at rt. *m*-CPBA (75%, 923 mg, 4.02 mmol) was then added, and the resultant solution was stirred for 21 h before the addition of solid Na_2SO_3 (∼500 mg) until starch−iodide paper indicated that no oxidant remained. The mixture was diluted with CH_2Cl_2 (100 mL), and the organic layer was washed with 2 M aq NaOH (2 × 100 mL). The combined aqueous washings were extracted with $CHCl_3$/^{i}PrOH (v/v 3:1, 2 × 100 mL), and the combined organic extracts were dried and concentrated in vacuo. The residue was then passed through a Biotage SCX-2 scavenger column, eluting first with CH_2Cl_2/MeOH (v/v 1:1), then 2 M NH_3 in MeOH. The ammonia-containing eluent was concentrated in vacuo to give an 80:20 mixture of **29**:**33** (50% conversion from **21**). Purification via flash column chromatography (eluent 40−60 °C petroleum ether/EtOAc, 2:1) gave **29** as a yellow oil (51 mg, 9%, >99:1 dr, 98% ee): $[\alpha]^{25}_D$ +27.4 (*c* 1.0 in $CHCl_3$); IR ν_{max} (film) 3385 (O−H), 3048, 2972 (C−H), 1658 (C=C); NMR δ_H (400 MHz, $CDCl_3$) 1.52 (3H, d, *J* 6.6, C(1′)*Me*), 2.77 (1H, dd, *J* = 13.9, 6.0 Hz, C(2)H_A), 3.20 (1H, dd, *J* = 13.9, 5.0 Hz, C(2)H_B), 3.32−3.35 (2H, m, C(7)H_2), 3.63 (1H, app q, *J* = 6.0 Hz, C(3)*H*), 4.31−4.36 (1H, m, C(4)*H*), 4.59 (1H, q, *J* = 6.6 Hz, C(1′)*H*), 5.61−5.71 (2H, m, C(5)*H*, C(6)*H*), 7.43−7.56 (4H, m, *Ar*), 7.77−7.78 (1H, m, *Ar*), 7.85−7.89 (1H, m, *Ar*), 8.32 (1H, d, *J* = 8.5 Hz, *Ar*); NMR δ_C (100 MHz, $CDCl_3$) 15.0 (C(1′)*Me*), 53.1 (*C*(7)), 56.8 (*C*(2)), 59.4 (*C*(1′)), 72.6, 72.7 (*C*(3), *C*(4)), 123.9, 124.4, 125.1, 125.6, 126.1, 128.1, 128.9 (*Ar*), 128.7, 130.5 (*C*(5), *C*(6)), 131.7, 134.1, 139.0 (*Ar*); MS *m*/*z* (ESI$^+$) 306 ([M + Na]$^+$, 100), 284 ([M + H]$^+$, 85); HRMS (ESI$^+$) $C_{18}H_{22}NO_2^+$ ([M+H]$^+$) requires 284.1645, found 284.1648. Further elution gave a 70:30 mixture of **29**:**33** as a yellow oil (116 mg, 29%). Further elution gave a 24:76 mixture of **29**:**33** as a yellow oil (15 mg, 3%). Data for **33**: NMR δ_H (400 MHz, $CDCl_3$) 1.52 (3H, d, *J* = 6.6 Hz, C(1′)*Me*), 2.80 (1H, dd, *J* = 13.9, 5.7 Hz, C(2)H_A), 3.11 (1H, dd, *J* = 13.9, 4.7 Hz, C(2)H_B), 3.38−3.42 (2H, m, C(7)H_2), 3.63−3.68 (1H, m, C(3)*H*), 4.26−4.32 (1H, m, C(4)*H*), 4.61 (1H, q, *J* = 6.6 Hz, C(1′)*H*), 5.58−5.75 (2H, m, C(5)*H*, C(6)*H*), 7.40−7.60 (4H, m, *Ar*), 7.79 (1H, d, *J* = 7.9 Hz, *Ar*), 7.87 (1H, d, *J* = 7.9 Hz, *Ar*), 8.26 (1H, d, *J* = 8.2 Hz, *Ar*); NMR δ_C (100 MHz, $CDCl_3$) (selected peaks) 14.6 (C(1′)*Me*), 53.1 (*C*(1′)), 54.5 (*C*(2)), 54.7 (*C*(7)), 72.9 (*C*(4)), 73.2 (*C*(3)).

(3*S*,4*R*,5*S*,6*S*,1′*R*)-*N*(1)-1′-(1′′-Naphthyl)ethyl-3-hydroxy-4-benzyloxy-5,6-epoxyazepane 35. From 21. $HBF_4 \cdot Et_2O$ (1.93 mL,

14.0 mmol) was added to a stirred solution of **21** (500 mg, 2.01 mmol, 98% ee) in BnOH (10 mL), and the resultant solution was stirred for 5 min at rt. *m*-CPBA (73%, 1.90 g, 8.02 mmol) was then added, and the resultant solution was stirred for 24 h before the addition of solid Na_2SO_3 (~1 g) until starch−iodide paper indicated that no oxidant remained. The mixture was diluted with CH_2Cl_2 (25 mL), and the organic layer was washed with 2 M aq NaOH (2 × 200 mL). The combined aqueous washings were extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic extracts were dried and concentrated in vacuo. The residue was then passed through a Biotage SCX-2 scavenger column, eluting first with CH_2Cl_2/MeOH (v/v 1:1) and then 2 M NH_3 in MeOH. The ammonia-containing eluent was concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/EtOAc, 10:1) gave **35** as a colorless oil (190 mg, 25%, >99:1 dr, 98% ee): $[\alpha]^{25}_D$ +21.0 (*c* 1.0 in $CHCl_3$); IR ν_{max} (film) 3443 (O−H), 2972 (C−H); NMR δ_H (400 MHz, $CDCl_3$) 1.52 (3H, d, *J* = 6.8 Hz, C(1′)*Me*), 2.66 (1H, dd, *J* = 13.4, 6.8 Hz, C(2)H_A), 2.77 (1H, d, *J* = 3.0 Hz, O*H*), 2.85 (1H, dd, *J* = 8.6, 4.3 Hz, C(7)H_A), 3.10−3.15 (2H, m, C(5)*H*, C(7)H_B), 3.16−3.20 (2H, m, C(2)H_B, C(6)*H*), 3.76−3.89 (1H, m, C(3)*H*), 3.95 (1H, dd, *J* = 7.8, 1.8 Hz, C(4)*H*), 4.57 (1H, d, *J* = 11.6 Hz, OCH_AH$_B$Ph), 4.69 (1H, q, *J* = 6.8 Hz, C(1′)*H*), 4.81 (1H, d, *J* = 11.6 Hz, OCH$_A$$H_B$Ph), 7.30−7.41 (5H, m, *Ph*), 7.43−7.57 (4H, m, *Ar*), 7.80 (1H, d, *J* = 7.8 Hz, *Ar*), 7.88 (1H, d, *J* = 7.8 Hz, *Ar*), 8.38 (1H, d, *J* = 8.3 Hz, *Ar*); NMR δ_C (100 MHz, $CDCl_3$) 14.2 (C(1′)*Me*), 49.0 (*C*(6)), 54.2 (*C*(7)), 54.5 (*C*(5)), 55.8 (*C*(2)), 59.5 (*C*(1′)), 69.4 (*C*(3)), 71.8 (O*C*H$_2$Ph), 79.7 (*C*(4)), 124.2, 124.7, 125.0, 125.5, 125.9, 127.9, 128.0, 128.7 (*o*-,*m*-,*p*-*Ph*, *Ar*), 132.1, 134.1, 138.0, 139.1 (*i*-*Ph*, *Ar*); MS *m*/*z* (ESI$^+$) 412 ([M + Na]$^+$, 96), 390 ([M + H]$^+$, 100); HRMS (ESI$^+$) $C_{25}H_{28}NO_3^+$ ([M + H]$^+$) requires 390.2064, found 390.2064.

From 38. $HBF_4 \cdot Et_2O$ (0.09 mL, 0.63 mmol) was added to a stirred solution of an 80:20 mixture of **38**:**39** (47 mg, 0.13 mmol) in BnOH (1.0 mL), and the resultant solution was stirred for 5 min at rt. *m*-CPBA (75%, 115 mg, 0.50 mmol) was then added, and the resultant solution was stirred for 24 h before the addition of solid Na_2SO_3 (~500 mg) until starch−iodide paper indicated that no oxidant remained. The mixture was diluted with CH_2Cl_2 (10 mL), and the organic layer was washed with 2 M aq NaOH (2 × 50 mL). The combined aqueous washings were extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic extracts were dried and concentrated in vacuo. The residue was then passed through a Biotage SCX-2 scavenger column, eluting first with CH_2Cl_2/MeOH (v/v 1:1) and then 2 M NH_3 in MeOH. The ammonia-containing eluent was concentrated in vacuo. Purification via flash column chromatography (gradient elution, 10→100% EtOAc in 30−40 °C petroleum ether) gave an 80:20 mixture of **35**:**40** as a colorless oil (30 mg, 60%, 80:20 dr).

(2*S*,3*R*,4*S*,5*S*,1′*R*)-*N*(1)-1′-(1″-Naphthyl)ethyl-2-chloromethyl-3-benzyloxy-4,5-epoxypiperidine 36. Et_3N (0.04 mL, 0.31 mmol) and MsCl (0.02 mL, 0.23 mmol) in CH_2Cl_2 (3 mL) were added sequentially to a stirred solution of **35** (60 mg, 0.15 mmol) in CH_2Cl_2 (6 mL) at 0 °C, and the resultant solution was stirred for 1.5 h at 0 °C before being concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/EtOAc, 20:1) gave **36** as a white solid (40 mg, 66%, >99:1 dr, 98% ee): mp 101−103 °C; $[\alpha]^{25}_D$ +76.6 (*c* 1.0 in $CHCl_3$); IR ν_{max} (KBr) 3039, 3050, 3033, 2979, 2943, 2885, 2521, 2749 (C−H); NMR δ_H (400 MHz, $CDCl_3$) 1.48 (3H, d, *J* = 6.6 Hz, C(1′)*Me*), 2.50 (1H, dd, *J* = 14.2, 4.0 Hz, C(6)H_A), 2.95 (1H, app d, *J* = 14.2 Hz, C(6)H_B), 3.07−3.15 (1H, m, C(2)*H*), 3.15 (1H, app t, *J* = 4.2 Hz, C(5)*H*), 3.35−3.41 (1H, m, C(4)*H*), 4.00 (1H, dd, *J* = 12.1, 4.0 Hz, CH_AH$_B$Cl), 4.13−4.23 (2H, m, C(3)*H*, CH$_A$$H_B$Cl), 4.76 (1H, d, *J* = 11.6 Hz, OCH_AH$_B$Ph), 4.83 (1H, d, *J* = 11.6 Hz, OCH$_A$$H_B$Ph), 5.03 (1H, q, *J* = 6.6 Hz, C(1′)*H*), 7.30−7.55 (9H, m, *Ph*, *Ar*), 7.79 (1H, d, *J* = 8.1 Hz, *Ar*), 7.84−7.89 (1H, m, *Ar*), 8.79−8.85 (1H, m, *Ar*); NMR δ_C (100 MHz, $CDCl_3$) 12.5 (C(1′)*Me*), 42.2 (*C*(6)), 42.6 (*C*H$_2$Cl), 51.3 (*C*(4)), 52.7 (*C*(5)), 53.2 (*C*(1′)), 57.0 (*C*(2)), 71.7 (O*C*H$_2$Ph), 74.1 (*C*(3)), 125.0, 125.5, 125.6, 127.8, 128.0, 128.3, 128.5 (*o*-,*m*-,*p*-*Ph*, *Ar*), 132.2, 133.9, 138.2, 134.4 (*i*-*Ph*, *Ar*); MS *m*/*z* (ESI$^+$) 432 ([M + Na]$^+$, ^{37}Cl, 28), 430 ([M + Na]$^+$, ^{35}Cl, 90), 410 ([M + H]$^+$, ^{37}Cl, 35), 408 ([M + H]$^+$, ^{35}Cl, 100); HRMS (ESI$^+$) $C_{25}H_{26}{}^{35}ClNNaO_2^+$ ([M + Na]$^+$) requires 430.1544, found 430.1543.

X-ray Crystal Structure Determination for 36. Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite-monochromated Mo Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealized positions. The structure was refined using CRYSTALS.[35]

X-ray crystal structure data for **36** [$C_{25}H_{26.5}ClNO_2$]: *M* = 816.89, triclinic, space group *P*1, *a* = 9.7315(3) Å, *b* = 10.5112(3) Å, *c* = 11.3814(4) Å, α = 64.3905(14)°, β = 87.8962(14)°, γ = 85.5140(15)°, *V* = 1046.61(6) Å^3, *Z* = 2, μ = 0.204 mm^{-1}, colorless plate, crystal dimensions = 0.11 × 0.13 × 0.22 mm^3. A total of 8261 unique reflections were measured for 5 < θ < 27 and 6624 reflections were used in the refinement. The final parameters were wR_2 = 0.084 and R_1 = 0.095 [*I* > 3.0σ(*I*)].

Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 788733. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

(3*S*,4*S*,1′*R*)- and (*R*,*R*,*R*)-*N*(1)-1′-(1″-Naphthyl)ethyl-3-hydroxy-4-benzyloxy-2,3,4,7-tetrahydro-1*H*-azepine (3*S*,4*S*,1′*R*)-38 and (*R*,*R*,*R*)-39. $HBF_4 \cdot Et_2O$ (3.58 mL, 26.1 mmol) was added to a stirred solution of **21** (968 mg, 5.20 mmol, 98% ee) in BnOH (18.5 mL), and the resultant solution was stirred for 5 min at rt. *m*-CPBA (75%, 4.81 g, 20.9 mmol) was then added, and the resultant solution was stirred for 24 h before the addition of solid Na_2SO_3 (~1 g) until starch−iodide paper indicated that no oxidant remained. The mixture was diluted with CH_2Cl_2 (50 mL), and the organic layer was washed with 2 M aq NaOH (2 × 100 mL). The combined aqueous washings were extracted with $CHCl_3$/^{i}PrOH (v/v 3:1, 2 × 100 mL), and the combined organic extracts were dried and concentrated in vacuo. The residue was then passed through a Biotage SCX-2 scavenger column, eluting first with CH_2Cl_2/MeOH (v/v 1:1) and then 2 M NH_3 in MeOH. The ammonia-containing eluent was concentrated in vacuo to give an 80:20 mixture of **38**:**39** (~50% conversion from **21**). Purification via flash column chromatography (gradient elution, 5→50% EtOAc in 30−40 °C petroleum ether) gave an 80:20 mixture of 38:39 as a colorless oil (211 mg, 32%): IR ν_{max} (film) 3453 (O−H), 3030, 2971, 2878 (C−H), 1598 (C=C); MS *m*/*z* (ESI$^+$) 374 ([M + H]$^+$, 100); HRMS (ESI$^+$) $C_{25}H_{28}NO_2^+$ ([M + H]$^+$) requires 374.2115, found 374.2117. Data for **38**: NMR δ_H (400 MHz, $CDCl_3$) 1.53 (3H, d, *J* = 6.8 Hz, C(1′)*Me*), 2.90−3.25 (5H, m, C(2)H_2, C(7)-H_2, O*H*), 3.87 (1H, ddd, *J* = 7.8, 4.3, 4.0 Hz, C(3)*H*), 4.36−4.42 (1H, m, C(4)*H*), 4.45 (1H, d, *J* = 11.6 Hz, OCH_AH$_B$Ph), 4.64−4.70 (2H, m, C(1′)*H*, OCH$_A$$H_B$Ph), 5.51−5.65 (2H, m, C(5)*H*, C(6)*H*), 7.29−7.40 (5H, m, *Ph*), 7.41−7.53 (4H, m, *Ar*), 7.79 (1H, d, *J* = 7.8 Hz, *Ar*), 7.84−7.90 (1H, m, *Ar*), 8.40−8.48 (1H, m, *Ar*); NMR δ_C (100 MHz, $CDCl_3$) 13.7 (C(1′)*Me*), 50.3 (*C*(2)), 57.9 (*C*(7)), 59.9 (*C*(1′)), 71.6 (*C*(3), O*C*H$_2$Ph), 80.1 (*C*(4)), 124.4, 124.9, 125.5, 125.8, 127.8, 127.9, 128.5, 128.6, 129.1, 130.1 (*C*(5), *C*(6), *Ar*, *o*-,*m*-,*p*-*Ph*), 132.1, 134.1, 138.3, 139.0 (*Ar*, *i*-*Ph*). Data for **39**: NMR δ_H (400 MHz, $CDCl_3$) (selected peaks) 3.69−3.78 (1H, m, C(3)*H*), 4.19 (1H, dd, *J* = 7.3, 2.1 Hz, C(4)*H*), 5.64−5.74 (2H, m, C(5)*H*, C(6)*H*); NMR δ_C (100 MHz, $CDCl_3$) (selected peaks) 15.4 (C(1′)*Me*), 54.9 (*C*(7)), 70.3 (*C*(3)), 80.3 (*C*(4)).

(2*S*,3*R*,4*S*,5*R*,1′*R*)-*N*(1)-1′-(1″-Naphthyl)ethyl-2-chloromethyl-3-benzyloxy-4,5-dihydroxypiperidine 43. Cl_3CCO_2H (241 mg, 1.47 mmol) was added to a stirred solution of **36** (30 mg,

0.07 mmol) in CH_2Cl_2 (0.3 mL), and the resultant solution was stirred for 16 h at rt. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and then washed with 2 M aq NaOH (2 × 10 mL). The combined aqueous layers were extracted with $CHCl_3$/^{i}PrOH (v/v 3:1, 3 × 5 mL). The combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (gradient elution, 10→100% EtOAc in 30−40 °C petroleum ether) gave **43** as a colorless oil (20 mg, 67%, >99:1 dr, 98% ee): $[\alpha]^{25}_D$ −12.8 (*c* 1.0 in $CHCl_3$); IR ν_{max} (film) 3443 (O−H), 3089, 3051, 3034, 2924, 2973 (C−H); NMR δ_H (400 MHz, $CDCl_3$) 1.52 (3H, d, *J* = 6.8 Hz, C(1′)*Me*), 2.17 (1H, br s, O*H*), 2.23 (1H, dd, *J* = 12.2, 4.3 Hz, C(6)H_A), 2.42 (1H, br, s, O*H*), 2.79 (1H, app d, *J* = 12.2 Hz, C(6)H_B), 3.21 (1H, app d, *J* = 7.8 Hz, C(2)*H*), 3.50−3.60 (1H, m, C(5)*H*), 3.92−4.00 (1H, m, C(4)*H*), 4.11−4.19 (2H, m, C(3)*H*, CH_AH$_B$Cl), 4.22−4.29 (1H, m, CH$_A$$H_B$Cl), 4.62−4.72 (2H, m, OCH_2Ph), 5.04 (1H, q, *J* = 6.8 Hz, C(1′)*H*), 7.31−7.58 (9H, m, *Ar*, *Ph*), 7.80 (1H, d, *J* = 7.6 Hz, *Ar*), 7.86 (1H, d, *J* = 8.1 Hz, *Ar*), 8.91 (1H, d, *J* = 8.3 Hz, *Ar*); NMR δ_C (100 MHz, $CDCl_3$) 12.0 (C(1′)*Me*), 41.8 (*C*H$_2$Cl), 45.3 (*C*(6)), 53.5 (*C*(1′)), 58.9 (*C*(2)), 67.1 (*C*(5)), 72.3 (*C*(4)), 75.3 (O*C*H$_2$Ph), 77.3 (*C*(3)), 124.7, 124.9, 125.3, 125.7, 126.1, 128.1, 128.2, 128.5, 128.7, 128.8 (*o*,*m*,*p*-*Ph*, *Ar*), 131.8, 134.2, 137.6, 137.7 (*i*-*Ph*, *Ar*); MS *m*/*z* (ESI$^+$) 450 ([M + Na]$^+$, ^{37}Cl, 6), 448 ([M + Na]$^+$, ^{35}Cl, 18), 428 ([M + H]$^+$, ^{37}Cl, 29), 426 ([M + H]$^+$, ^{35}Cl, 100); HRMS (ESI$^+$) $C_{25}H_{28}{}^{35}ClNNaO_3{}^+$ ([M + Na]$^+$) requires 448.1650, found 448.1654.

(2*R*,3*R*,4*S*,5*R*,1′*R*)-*N*(1)-1′-(1″-Naphthyl)ethyl-2-acetoxymethyl-3-benzyloxy-4,5-dihydroxypiperidine 45 and (3*R*,4*S*,5*S*,6*R*,1′*R*)-*N*(1)-1′-(1″-Naphthyl)ethyl-3-acetoxy-4-benzyloxy-5,6-dihydroxyazepane 46. AgOAc (89 mg, 0.54 mmol) was added to a stirred solution of **43** (65 mg, 0.15 mmol) in DMF (1 mL), and the resultant suspension was stirred for 24 h at 65 °C. The reaction mixture was then allowed to cool to rt before the addition of H_2O (8 mL). The mixture was extracted with Et_2O (3 × 10 mL), and the combined organic extracts were washed with H_2O (3 × 30 mL) before being dried and concentrated in vacuo. Purification via flash column chromatography (gradient elution, 10→100% EtOAc in 30−40 °C petroleum ether) gave **46** as a colorless oil (5 mg, 7%, >99:1 dr, 98% ee): $[\alpha]^{25}_D$ +44.8 (*c* 1.0 in $CHCl_3$); IR ν_{max} (film) 3444 (O−H), 3088, 3050, 3034, 3006, 2917, 2887 (C−H), 1734 (C═O); NMR δ_H (400 MHz, $CDCl_3$) 1.48 (3H, d, *J* 6.6, C(1′)*Me*), 2.15 (3H, s, CO*Me*), 2.21 (1H, br s, O*H*), 2.69 (1H, m, C(7)H_A), 2.80 (1H, dd, *J* = 14.0, 2.7 Hz, C(7)H_B), 3.17−3.22 (1H, m, C(2)H_A), 3.27 (1H, dd, *J* = 14.8, 4.1 Hz, C(2)H_B), 3.41−3.46 (1H, m, C(6)*H*), 3.87 (1H, app d, *J* = 6.3 Hz, C(4)*H*), 3.93−3.97 (1H, m, C(5)*H*), 4.49 (1H, d, *J* = 14.5 Hz, OCH_AH$_B$Ph), 4.55−4.64 (2H, m, C(1′)*H*, OCH$_A$CH_BPh), 5.11−5.15 (1H, m, C(3)*H*), 7.25−7.50 (9H, m, *Ar*, *Ph*), 7.80 (1H, d, *J* = 7.6 Hz, *Ar*), 7.88 (1H, d, *J* = 7.9 Hz, *Ar*), 8.47 (1H, d, *J* = 8.5 Hz, *Ar*); NMR δ_C (100 MHz, $CDCl_3$) 11.5 (C(1′)*Me*), 21.4 (CO*Me*), 52.3 (*C*(7)), 59.0 (*C*(2)), 60.6 (*C*(1′)), 70.5 (*C*(6)), 72.5 (O*C*H$_2$Ph), 74.1 (*C*(5)), 74.4 (*C*(3)), 79.6 (*C*(4)), 124.5, 124.7, 125.1, 125.7, 126.0, 127.7, 127.9, 128.4, 128.6, 129.0, 131.4, 134.2, 138.1, 138.3 (*Ar*, *Ph*), 170.3 (*C*OMe); MS *m*/*z* (ESI$^+$) 472 ([M + Na]$^+$, 41), 450 ([M + H]$^+$, 100); HRMS (ESI$^+$) $C_{27}H_{32}NO_5{}^+$ ([M + H]$^+$) requires 450.2275, found 450.2273. Further elution gave **45** as a white solid (40 mg, 60%, >99:1 dr, 98% ee): mp 129−131 °C; $[\alpha]^{25}_D$ +48.3 (*c* 1.0 in $CHCl_3$); IR ν_{max} (film) 3484 (O−H), 3088, 3050, 3035, 2924, 2881, 2850 (C−H), 1741 (C═O); NMR δ_H (400 MHz, $CDCl_3$) 3.01 (3H, d, *J* = 6.6 Hz, C(1′)*Me*), 1.60 (1H, br s, O*H*), 2.19 (3H, s, CO*Me*), 2.27 (1H, dd, *J* = 12.3, 4.1 Hz, C(6)H_A), 2.45 (1H, br s, O*H*), 2.81 (1H, dd, *J* = 12.3, 1.3 Hz, C(6)H_B), 3.06−3.15 (1H, m, C(2)*H*), 3.53−3.61 (1H, m, C(5)*H*), 3.90 (1H, dd, *J* = 9.1, 3.4 Hz, C(3)*H*), 4.01−4.07 (1H, m, C(4)*H*), 4.51 (1H, d, *J* = 11.3 Hz, OCH_AH$_B$Ph), 4.56 (1H, dd, *J* = 12.3, 2.5 Hz, CH_AH$_B$OAc), 4.62 (1H, d, *J* = 11.3 Hz, OCH$_A$$H_B$Ph), 4.72 (1H, d, *J* = 12.3, 2.2 hz, CH$_A$$H_B$OAc), 4.92 (1H, q, *J* = 6.6 hz, C(1′)*H*), 7.32−7.50 (9H, m, *Ar*, *Ph*), 7.76−7.82 (1H, m, *Ar*), 7.84−7.89 (1H, m, *Ar*), 8.67−8.74 (1H, m, *Ar*); NMR δ_C (100 MHz, $CDCl_3$) 11.4 (C(1′)*Me*), 21.1 (CO*Me*), 45.1 (*C*(6)), 52.4 (*C*(1′)), 57.4 (*C*(2)), 59.8 (*C*H$_2$OAc) 67.0 (*C*(5)) 67.5 (*C*(4)), 71.4 (O*C*H$_2$Ph), 73.7 (*C*(3)), 124.0, 125.0, 125.3, 125.5, 125.9, 128.0, 128.2, 128.4, 128.5, 128.7, 129.1, 131.9, 134.3, 137.2 (*Ar*, *Ph*), 170.7 (*C*OMe); MS *m*/*z* (ESI$^+$) 472 ([M + Na]$^+$, 100), 450 ([M + H]$^+$, 98); HRMS (ESI$^+$) $C_{27}H_{32}NO_5{}^+$ ([M + H]$^+$) requires 450.2275, found 450.2273.

X-ray Crystal Structure Determination for 45. Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite-monochromated Mo Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealized positions. The structure was refined using CRYSTALS.[35]

X-ray crystal structure data for **45** [$C_{27}H_{31}NO_5$]: M = 449.55, monoclinic, space group $P2_1$, a = 9.3063(2) Å, b = 9.0446(2) Å, c = 14.3162(3) Å, β = 103.4925(10)°, V = 1171.76(4) Å^3, Z = 2, μ = 0.087 mm^{-1}, colorless plate, crystal dimensions = 0.08 × 0.13 × 0.17 mm^3. A total of 2818 unique reflections were measured for 5 < θ < 27 and 2818 reflections were used in the refinement. The final parameters were wR_2 = 0.100 and R_1 = 0.048 [I > −3.0σ(I)].

Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 788734. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(0)-1223−336033 or e-mail: deposit@ccdc.cam.ac.uk).

(+)-(2*R*,3*R*,4*S*,5*R*)-2-Hydroxymethyl-3,4,5-trihydroxypiperidine Hydrochloride [(+)-1-Deoxyaltronojirimycin Hydrochloride] 3·HCl. Step1. K_2CO_3 (154 mg, 1.10 mmol) was added to a stirred solution of **45** (25 mg, 0.06 mmol) in MeOH (1 mL) and the resultant suspension was stirred for 16 h at rt before being concentrated in vacuo. The residue was dissolved in H_2O (5 mL) and extracted with $CHCl_3$/^{i}PrOH (v/v 3:1, 3 × 10 mL). The combined organic extracts were dried and concentrated in vacuo to give **47** as a colorless oil (17 mg) that was used without purification.

Step 2. Pd(OH)$_2$/C (17 mg) was added to a stirred solution of **47** (17 mg, 0.05 mmol) in degassed MeOH (0.5 mL) and the resultant suspension was stirred for 72 h under an atmosphere of H_2 (1 atm). Concentrated aq HCl (10 μL) was then added, and the resultant suspension was stirred for a further 5 min before being filtered through Celite (eluent MeOH). The filtrate was concentrated in vacuo, and the residue was purified via flash column chromatography (eluent $CHCl_3$/MeOH, 4:1) to give (+)-(2*R*,3*R*,4*S*,5*R*)-**3**·HCl as a white semisolid (8 mg, 71% from **45**, >99:1 dr, 98% ee):[3] $[\alpha]^{25}_D$ +31.1 (*c* 0.5 in MeOH) [lit.[9i] $[\alpha]^{23}_D$ +31.0 (*c* 2.0 in MeOH); lit.[10f] $[\alpha]^{25}_D$ +33.2 (*c* 0.5 in MeOH)]; NMR δ_H (500 MHz, D_2O) 3.17 (1H, dd, *J* 13.6, 2.8, CH_AH$_B$OH), 3.27−3.35 (2H, m, C(4)*H*, CH$_A$$H_B$OH), 3.77 (1H, dd, *J* 12.6, 6.9, C(6)H_A), 3.91 (1H, dd, *J* 12.6, 3.2, C(6)H_B), 3.94−3.99 (2H, m, C(3)*H*, C(5)*H*), 4.08−4.11 (1H, m, C(2)*H*); NMR δ_C (125 MHz, D_2O) 43.9 (*C*H$_2$OH), 55.8 (*C*(4)), 58.2 (*C*(6)), 63.6 (*C*(5)), 66.2 (*C*(2)), 68.5 (*C*(3)).

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra and CIF (for structures CCDC 788731−788734). This material is available free of charge via the Internet at http://pubs.acs.org.