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Asymmetric Syntheses of (−)-3-*epi*-Fagomine, (2*R*,3*S*,4*R*)-Dihydroxypipecolic Acid, and Several Polyhydroxylated Homopipecolic Acids

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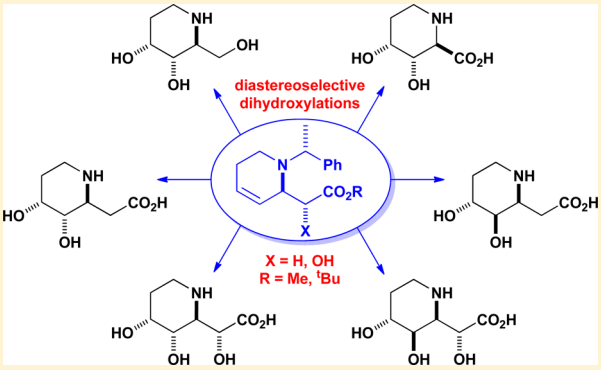
Supporting Information

ABSTRACT: A range of enantiopure polyhydroxylated piperidines, including (2*R*,3*S*,4*R*)-dihydroxypipecolic acid, (−)-3-*epi*-fagomine, (2*S*,3*S*,4*R*)-dihydroxyhomopipecolic acid, (2*S*,3*R*,4*R*)-dihydroxyhomopipecolic acid, and two trihydroxy-substituted homopipecolic acids, have been prepared using diastereoselective olefinic oxidations of a range of enantiopure tetrahydropyridines as the key step. The requisite substrates were readily prepared from *tert*-butyl sorbate using our diastereoselective hydroamination or aminohydroxylation protocols followed by ring-closing metathesis. After diastereoselective olefinic oxidation of the resultant enantiopure tetrahydropyridines and deprotection, enantiopure polyhydroxylated piperidines were isolated as single diastereoisomers (>99:1 dr) in good overall yield.



INTRODUCTION

Polyhydroxylated piperidines, which are also known as iminosugars, are produced as secondary metabolites in a vast array of different organisms, although the majority originate in plants.[1] The structures of (+)-1-deoxynojirimycin **1**, (+)-fagomine **2**, and hydroxy-substituted pipecolic acids such as **3** and **4** are representative of this class of natural products.[2,3] Their structural similarity to monosaccharides means that they can act as potent substrate mimics for a variety of glycosidases, and this often potent biological activity has spurred research into both the synthesis of polyhydroxylated piperidines and their application as therapeutic agents.[4] In addition to displaying desirable biological activity,[5] pipecolic acid and its derivatives are often substituted for proline in conformational and ligand-binding studies of biologically active peptides and foldamers.[6]

As part of our ongoing research program directed toward the de novo preparation of imino- and aminosugars and their derivatives,[7] we decided to investigate the synthesis of a range of polyhydroxylated piperidines, including fagomines **8** (Z = CH_2), dihydroxypipecolic acids **8** (Z = CO), and their corresponding homopipecolic acids **9** (Y = H, OH), via the diastereoselective dihydroxylation of enantiopure tetrahydropyridines **7** (Y = H, OH). It was envisaged that the requisite tetrahydropyridine substrates **7** (Y = H, OH) could be prepared using our lithium amide conjugate addition methodology[8] for the hydroamination or aminohydroxylation of a dienyl ester **5** followed by ring-closing metathesis of the resultant *β*-amino ester **6** (X = H) or *α*-hydroxy-*β*-amino ester **6** (X = OH), respectively. Subsequent diastereoselective *syn*-dihydroxylation (using either Upjohn[9] or Donohoe[10] protocols) or *anti*-dihydroxylation (using our chemoselective olefinic oxidation[7a,b,d,11] procedure) of these tetrahydropyridine substrates **7** would then give the target compounds after elaboration/deprotection (Figure 1).

RESULTS AND DISCUSSION

Conjugate addition of lithium (*R*)-*N*-(but-3-en-1-yl)-*N*-(*α*-methylbenzyl)amide **11** to dienyl ester **10** (which was produced in 80% yield upon esterification of commercially available sorbic acid) followed by treatment of the resultant lithium (*Z*)-*β*-amino enolate[12] with either saturated aq NH_4Cl or (−)-camphorsulfonyloxaziridine [(−)-CSO] produced the known *β*-amino ester **12**[13] in 69% yield (>99:1 dr) or *α*-hydroxy-*β*-amino ester **13** in 64% yield (>99:1 dr), respectively. The stereochemical outcomes of these reactions were initially assigned by reference to our transition-state mnemonic[14] for the conjugate addition reaction and by analogy to the well-established outcomes of these hydroamination and aminohydroxylation protocols.[8,15] Subsequent ring-closing metathesis of both **12** and **13** with Grubbs I catalyst gave tetrahydropyridines **14**[13] and **15** in 74 and 76% yield, respectively, as single diastereoisomers (>99:1 dr) in each case. Transesterification of **14** and **15** upon treatment with $SOCl_2$ and MeOH gave the

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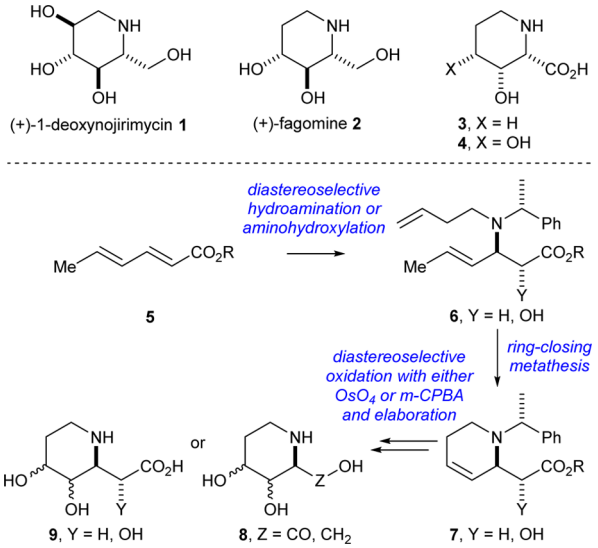
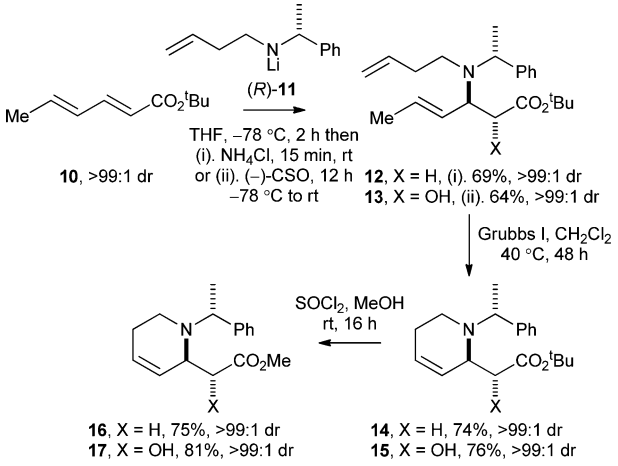


Figure 1. Synthesis of polyhydroxylated piperidines **8** and **9** via the diastereoselective dihydroxylation of enantiopure tetrahydropyridines **7**.

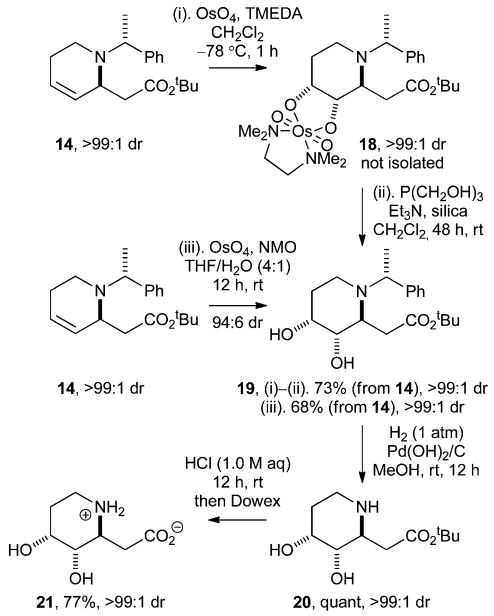
corresponding methyl esters **16**[13] and **17** in 75 and 81% yield, respectively (Scheme 1).

Scheme 1



Under Upjohn[9] conditions (i.e., OsO_4/NMO), *syn*-dihydroxylation of tetrahydropyridine **14** gave diol **19** (94:6 dr) and, after chromatographic purification, **19** was isolated in 68% yield as a single diastereoisomer (>99:1 dr). Similarly, oxidation of **14** under Donohoe[10] conditions (i.e., OsO_4/TMEDA) gave single osmate ester−TMEDA complex **18** (>99:1 dr). After treatment of **18** with $P(CH_2OH)_3$, Et_3N, and silica gel,[16] diol **19** was isolated in 73% yield (from **14**, >99:1 dr). Hydrogenolytic N-deprotection of **19** in the presence of Pearlman's catalyst [$Pd(OH)_2$/C] gave **20** in quantitative yield (>99:1 dr), and hydrolysis of the ester moiety within **20**, upon treatment with 1.0 M aq HCl, gave (2*S*,3*S*,4*R*)-dihydroxyhomopipecolic acid **21**. After purification by ion exchange chromatography on Dowex 50WX8 resin, **21** was isolated in 77% yield (>99:1 dr) (Scheme 2). The relative configuration within **21** was initially established by ^{1}H NMR ^3J coupling constant analysis ($^3J_{2',3'}$ = 8.9 Hz; $^3J_{3',4'}$ = 2.5 Hz), and this assignment was subsequently confirmed unambiguously via single crystal X-ray diffraction

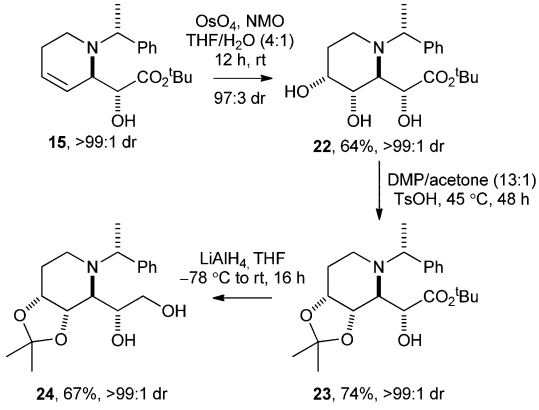
Scheme 2



analysis,[17] which also allowed the assigned configurations within **18**−**20** to be confirmed.

Under Upjohn[9] conditions, *syn*-dihydroxylation of the hydroxyl-bearing analogue **15** gave **22** in 64% yield (>99:1 dr), and protection of 1,2-diol **22** as the corresponding acetonide gave **23** in 74% yield (>99:1 dr) (Scheme 3). The

Scheme 3



relative configuration within **23** was established unambiguously via single crystal X-ray diffraction analysis,[17] and the absolute (2*R*,2′*S*,3′*S*,4′*R*,α*R*)-configuration of **23** was assigned by reference to the known (*R*)-configuration of the α-methylbenzyl fragment. Furthermore, the determination of a Flack *x* parameter[18] of 0.07(17) for the structure of **23** confirmed the assigned absolute configuration of **23**, and therefore also that of **22**. The addition of a hydroxyl group therefore has little effect on the diastereoselectivity of the dihydroxylation step. Subsequent reduction of the ester moiety within **23** upon treatment with $LiAlH_4$ gave diol **24** in 67% yield (>99:1 dr) (Scheme 3).

Oxidative cleavage of the 1,2-diol unit within **24** upon treatment with $NaIO_4$, followed by oxidation of the resultant aldehyde using a modified literature procedure,[19] gave substituted pipecolic acid **25**, which was immediately treated

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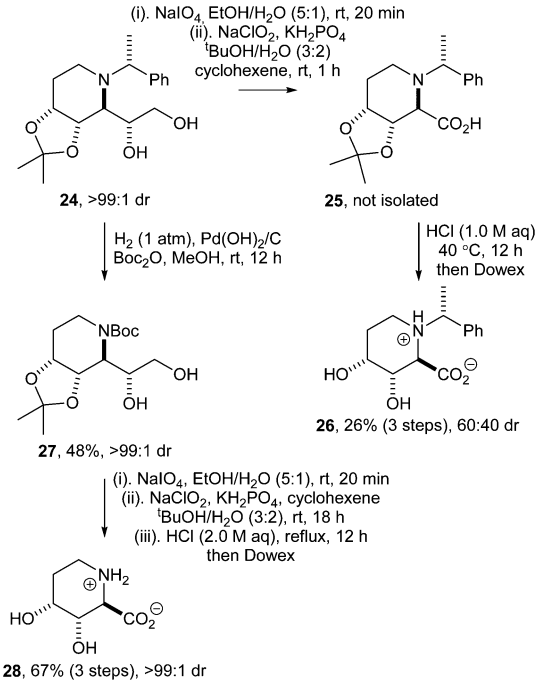
with 1.0 M aq HCl to remove the acetonide protecting group, giving **26** in 26% yield (from **24**, 60:40 dr). An alternative protecting group strategy was then employed in an effort to prevent epimerization from occurring during the oxidation process. Hydrogenolytic N-deprotection of **24** in the presence of Boc_2O gave *N*-Boc-substituted piperidine **27** in 48% yield (>99:1 dr). Subsequent oxidative cleavage of the 1,2-diol unit[19] within **27**, further oxidation of the resultant aldehyde, and acid-catalyzed deprotection of the acetonide group gave (2*R*,3*S*,4*R*)-dihydroxypipecolic acid **28** in 67% yield (>99:1 dr) (Scheme 4).

Scheme 4

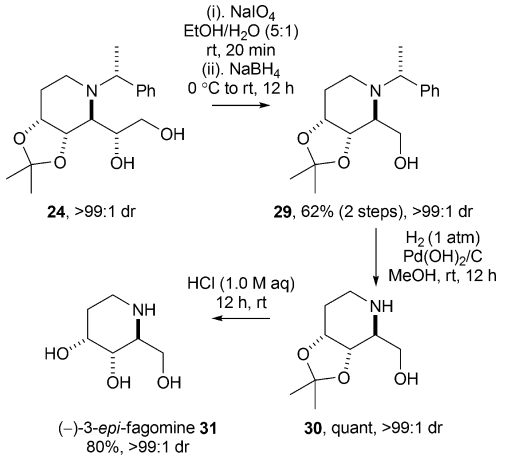


Diol **24** was also elaborated to (−)-3-*epi*-fagomine **31** via a three-step procedure: Oxidative cleavage of the 1,2-diol unit within **24** upon treatment with $NaIO_4$ and reduction of the resultant aldehyde with $NaBH_4$ gave **29** in 62% yield (>99:1 dr). Deprotection of **29** was achieved by hydrogenolysis to give **30**. Then, acid-catalyzed hydrolysis of the acetonide group within **30** gave (−)-3-*epi*-fagomine **31** as a single diastereoisomer (>99:1 dr) in 80% overall yield (Scheme 5). The spectroscopic data and specific rotation of **31** were in excellent agreement with literature values: $[\alpha]_D^{20}$ − 72.2 (*c* 1.0, H_2O); lit.[20e] for *ent*-**31**, $[\alpha]_D^{26}$ + 74.4 (*c* 0.95, H_2O); and lit.[21] for *ent*-**31**, $[\alpha]_D$ + 69 (*c* 0.5, H_2O).

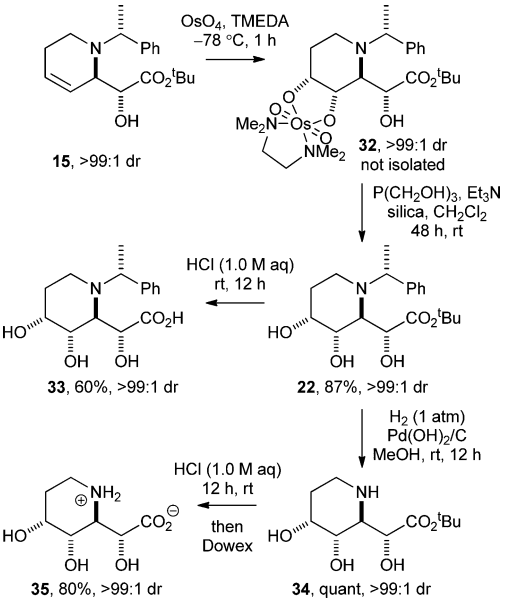
Under Donohoe[10] conditions, *syn*-dihydroxylation of **15** gave a single osmate ester−TMEDA complex **32** (>99:1 dr). After treatment of **32** with $P(CH_2OH)_3$, Et_3N, and silica gel,[16] triol **22** was isolated in 87% yield (from **15**, >99:1 dr). Hydrolysis of the ester moiety within **22** gave carboxylic acid **33** in 60% yield (>99:1 dr). However, this compound was found to be fairly insoluble, and hydrogenolytic deprotection of **33** was therefore not possible. However, hydrogenolysis of **22** proceeded efficiently to give **34** in quantitative yield (>99:1 dr). Subsequent hydrolysis of **34** gave polyhydroxy-substituted homopipecolic acid **35** in 80% yield (>99:1 dr) (Scheme 6).

Attempted *anti*-dihydroxylation of tetrahydropyridine **14** under our chemo- and diastereoselective olefinic oxidation

Scheme 5



Scheme 6



procedure[7a,b,d,11] (i.e., treatment of the unsaturated amine with CCl_3CO_2H followed by *m*-CPBA) produced a 34:56:10 mixture of **36**, **37**, and **38**, respectively. Purification of the crude reaction mixture allowed the isolation of lactone **36** [ν_{max}: 1773 cm^{-1} (C═O)] in 12% yield (>99:1 dr), diol **37** in 15% yield (>99:1 dr), and diol **38** in 7% yield (>99:1 dr) (Scheme 7). The relative configuration within **37** was established unambiguously via single crystal X-ray diffraction analysis,[17] and the absolute (2′*S*,3′*R*,4′*R*,α*R*)-configuration of **37** was assigned by reference to the known (*R*)-configuration of the α-methylbenzyl fragment. The configuration within lactone **36** was next established by chemical correlation upon treatment of diol **37** with aqueous HBF_4 in CH_2Cl_2, which promoted complete conversion to lactone **36** as a single diastereoisomer (>99:1 dr); following chromatographic purification, **36** was isolated in 41% yield (>99:1 dr). Reaction of diol **38** under the same conditions gave a 70:30 mixture of lactones **39** and **40**, which were isolated in 70 and 29% yield, respectively, as single diastereoisomers (>99:1 dr) in each case (Scheme 7). The structure of lactone **40** was established by $^1H-^{13}C$ NMR HMBC spectroscopic analysis and from the diagnostic value of the C═O absorbance in the infrared spectrum [ν_{max}: 1785

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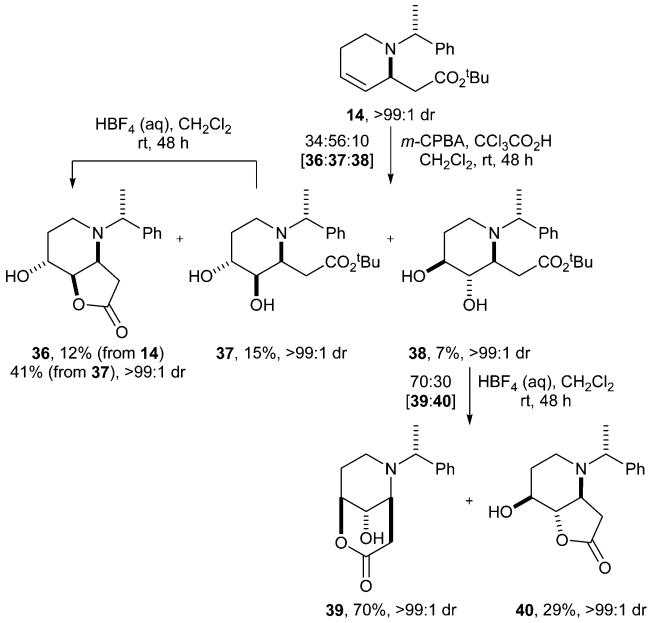
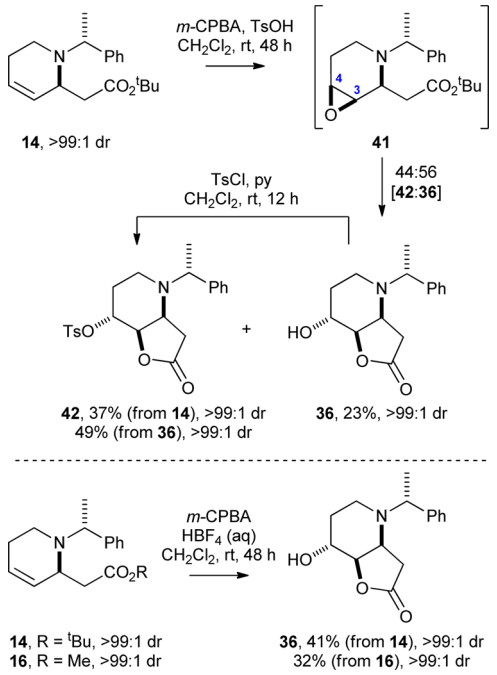
Scheme 7



Scheme 8

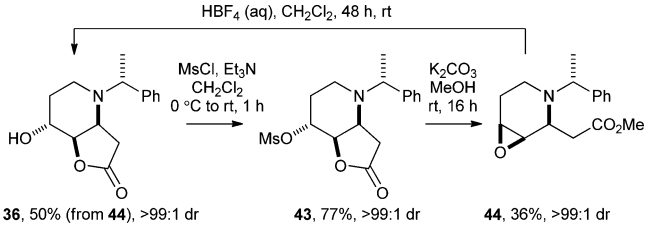


cm^{-1} (C═O)]. The relative configuration within **39** [ν_{max}: 1739 cm^{-1} (C═O)] was established unambiguously via single crystal X-ray diffraction analysis,[17] and the absolute (1*S*,5*S*,9*S*,α*R*)-configuration of **39** was assigned by reference to the known (*R*)-configuration of the α-methylbenzyl fragment. Furthermore, the determination of a Flack *x* parameter[18] of −0.09(17) for the structure of **39** confirmed its assigned absolute configuration, and therefore also those of **38** and **40**.

Repeating the oxidation reaction with TsOH as the Brønsted acid reagent produced a 56:44 mixture of lactones **36** and **42**, which were isolated in 23 and 37% yield, respectively (>99:1 dr for both). The identity of **42** was confirmed unambiguously via chemical correlation: Treatment of an authentic sample of **36** with TsCl and pyridine gave **42** as the sole reaction product, which was isolated in 49% yield (>99:1 dr) after chromatographic purification. Employing aqueous HBF_4 as the Brønsted acid reagent produced only lactone **36** upon oxidation of either tetrahydropyridine **14** (R = ^{t}Bu) or **16** (R = Me), giving **36** as a single diastereoisomer (>99:1 dr) in 41 or 32% yield, respectively (Scheme 8). The formation of tosylate **42** is consistent with a mechanism whereby epoxidation of tetrahydropyridine **14** occurs on the 3*Si*,4*Re* face[22] (i.e., the upper face as drawn) followed by regioselective ring-opening of intermediate epoxide **41** with tosylate at the C(4)-position and lactonization of the resultant alcohol to give lactone **42**; lactone **36** can be formed via a similar process in which intermediate epoxide **41** is attacked at the C(4)-position by H_2O.

In support of this mechanistic hypothesis, an authentic sample of epoxide **44** was prepared from lactone **36** and independently treated with aqueous HBF_4 under conditions analogous to those employed during the olefinic oxidation of tetrahydropyridines **14** and **16**. Initially, mesylation of the hydroxyl group within **36** gave mesylate **43** in 77% yield (>99:1 dr), and subsequent treatment of **43** with K_2CO_3 in MeOH then effected methanolysis of the lactone and base-induced epoxide formation to give **44** as a single diastereoisomer (>99:1 dr) in 36% isolated yield. Treatment of this authentic sample of epoxide **44** with aqueous HBF_4 promoted the exclusive formation of lactone **36**, which was isolated in 50% yield (>99:1 dr) after purification of the crude reaction mixture (Scheme 9). This result is therefore consistent with the intermediacy of epoxide **44** in the formation of lactone **36** upon olefinic oxidation of tetrahydropyridine **16**.

Scheme 9



Next, attempts were made to isolate the corresponding epoxides directly upon oxidation of tetrahydropyridines **14** and **16** with CF_3CO_3H [prepared in situ from UHP and $(CF_3CO)_2O$]. Oxidation of **16** gave a 63:37 mixture of lactone **36** and epoxide **44**, whereas oxidation of **14**, after workup, gave a 29:26:45 mixture of lactone **36**, epoxide **41**, and diol **37**, respectively. Unfortunately, attempts to correlate the stereochemistries between epoxides **41** and **44** upon transesterification of **41** were not successful as only decomposition of **41** was observed; the configuration of **41** was therefore assigned by analogy to that of **44**. This authentic sample of **41** was treated with aqueous HBF_4 under conditions analogous to those employed during the olefinic oxidation of tetrahydropyridine **14** and was found to give lactone **36** exclusively; after purification of the crude reaction mixture, **36** was isolated in 48% yield (>99:1 dr). This result is therefore also consistent with the intermediacy of epoxide **41** in the formation of lactone **36** upon olefinic oxidation of tetrahydropyridine **14** (Scheme 10).

Finally, removal of the *N*-α-methylbenzyl group within **36** via hydrogenolytic deprotection in the presence of $Pd(OH)_2/C$

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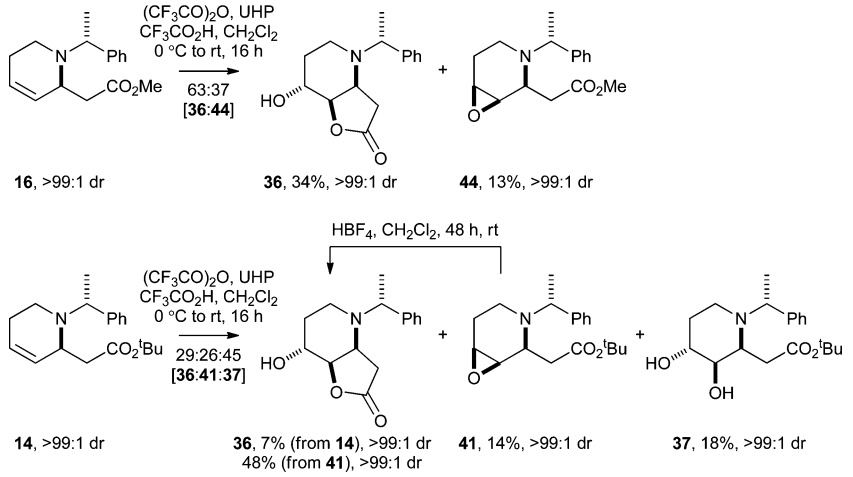
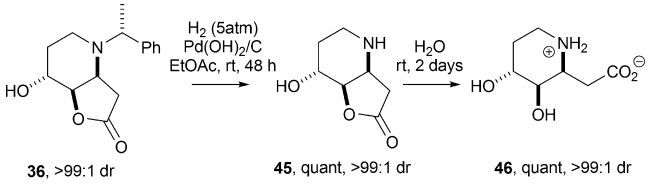
Scheme 10



gave quantitative conversion to **45**; standing a solution of **45** in H_2O for two days effected hydrolysis to give the zwitterionic β-amino acid **46**. Purification of **46** by ion exchange chromatography on Dowex 50WX8 resin gave (2*S*,3*R*,4*R*)-dihydroxyhomopipecolic acid **46** as a single diastereoisomer (>99:1 dr) in quantitative yield (Scheme 11). The relative

Scheme 11

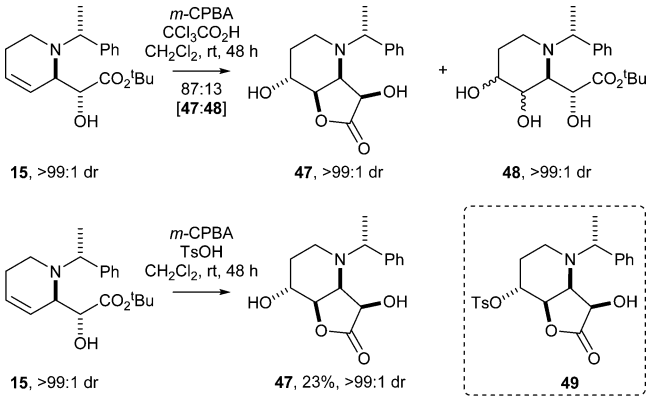


configuration within **46** was confirmed unambiguously via single crystal X-ray diffraction analysis,[17] and the determination of a Flack *x* parameter[18] of 0.1(2) for the structure of **46** confirmed the assigned absolute (2′*S*,3′*R*,4′*R*)-configuration of **46**, and therefore also those of **36** and **45**.

Olefinic oxidation of the analogous hydroxy-bearing tetrahydropyridine **15** in the presence of CCl_3CO_2H gave an inseparable 87:13 mixture of lactone **47** and triol **48** (of undetermined relative configuration), respectively. However, repetition of the reaction employing TsOH as an alternative Brønsted acid reagent gave lactone **47** exclusively; the corresponding tosylate **49** was not observed in this case. After purification of the crude reaction mixture, we isolated **47** in 23% yield (>99:1 dr) (Scheme 12). The relative configuration within **47** was then established unambiguously via single crystal X-ray diffraction analysis,[17] and the absolute (2*R*,3*S*,4*R*,5*R*,α*R*)-configuration of **47** was assigned by reference to the known (*R*)-configuration of the α-methylbenzyl fragment. The addition of a hydroxyl group does not therefore perturb the high diastereoselectivity observed in the epoxidation of these tetrahydropyridines.

Following the oxidation of tetrahydropyridine **15** in the presence of aqueous HBF_4, lactone **47** and trihydroxy β-amino acid **50** were isolated in 47 and 20% yield, respectively (>99:1 dr for each). The identity of **50** was confirmed by chemical correlation to lactone **47** upon treatment of an aliquot with CF_3CO_2H, which promoted quantitative conversion to **47**. Oxidation of tetrahydropyridine **17** under identical conditions

Scheme 12



gave lactone **47** as the only isolable product in 20% yield (>99:1 dr). Both **50** and **47** were then converted into polyhydroxy-substituted homopipecolic acid **51**. Hydrogenolytic N-deprotection of **50** in the presence of $Pd(OH)_2/C$ gave **51** in quantitative yield after purification via ion exchange chromatography on Dowex 50WX8 resin. Similarly, hydrogenolysis of **47** followed by standing a solution of **52** in H_2O at rt for two days gave **51** in quantitative yield (>99:1 dr) (Scheme 13).

■ CONCLUSION

In conclusion, the asymmetric syntheses of (2*R*,3*S*,4*R*)-dihydroxypipecolic acid, (−)-3-*epi*-fagomine, (2*S*,3*S*,4*R*)-dihydroxyhomopipecolic acid, (2*S*,3*R*,4*R*)-dihydroxyhomopipecolic acid, and two trihydroxy-substituted homopipecolic acids have been achieved in good yield and high diastereoisomeric purity. Conjugate addition of lithium (*R*)-*N*-(but-3-en-1-yl)-*N*-(α-methylbenzyl)amide to *tert*-butyl sorbate followed by treatment of the resultant lithium (*Z*)-β-amino enolate with either saturated aq NH_4Cl or (−)-camphorsulfonyloxaziridine gave the corresponding enantiopure β-amino ester or α-hydroxy-β-amino ester, respectively. Subsequent ring-closing metathesis constructed the requisite tetrahydropyridine scaffold. Olefinic oxidations of these enantiopure tetrahydropyridines proceeded with extremely high diastereoselectivity to give *syn*- or *anti*-diols (or the corresponding lactones). Following deprotection, enantiopure polyhydroxylated piperidines were all prepared as single diastereoisomers (>99:1 dr) in good overall yield.

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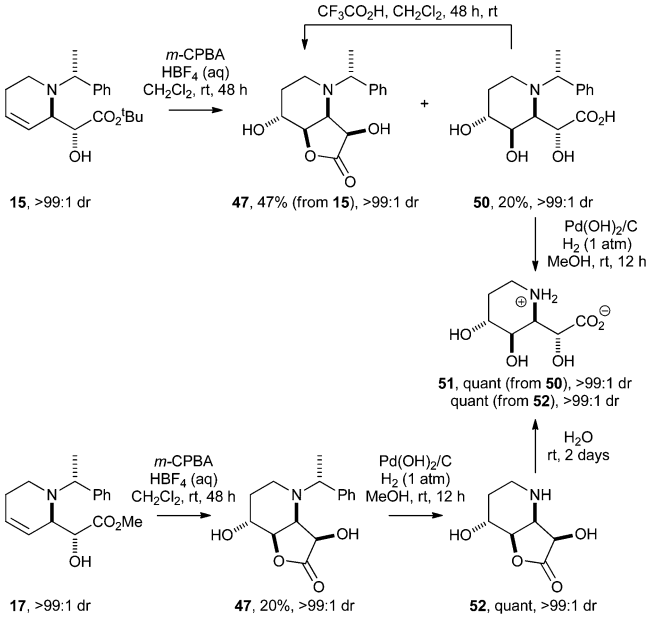
Scheme 13



EXPERIMENTAL SECTION

General Experimental Details. All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen atmosphere using standard vacuum line techniques and glassware that was flame-dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[23] BuLi was purchased as a solution in hexanes and titrated against diphenylacetic acid before use. All other reagents were used as supplied without prior purification. Organic layers were dried over Na_2SO_4. Thin layer chromatography was performed on aluminum plates coated with 60 F_{254} silica. Plates were visualized using UV light (254 nm), 1% aq $KMnO_4$, or Dragendorff's reagent. Flash column chromatography was performed on Kieselgel 60 silica. Melting points are uncorrected. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded using an ATR module. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded in the stated deuterated solvent. Spectra were recorded at rt unless otherwise stated. The field was locked by external referencing to the relevant deuteron resonance. When the diastereotopic methyl groups of acetonide functionalities could not be unambiguously assigned, the descriptor *Me*CMe was employed. $^1H-^1H$ COSY, $^1H-^{13}C$ HMQC, and $^1H-^{13}C$ HMBC analyses were used to establish atom connectivity. Accurate mass measurements were run on a TOF spectrometer internally calibrated with polyalanine.

X-ray Crystal Structure Determination.[17] Data were collected using either graphite-monochromated Mo Kα (for **37**) or Cu Kα (for **21**·H_2O, **23**, **39**, **46**, and **47**) 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 the CRYSTALS program.[24]

***(R)*-*N*-(But-3-en-1-yl)-*N*-(α-methylbenzyl)amine.** 4-Bromobut-1-ene (75.0 g, 555 mmol) was added to a stirred mixture of (*R*)-α-methylbenzylamine (177 mL, 1.39 mol, >99% ee) and K_2CO_3 (92.1 g, 666 mmol) at rt, and the resultant mixture was heated at 50 °C for 12 h. The reaction mixture was allowed to cool to rt. H_2O (1.5 L) and Et_2O (1.5 L) were added, and the aqueous layer was extracted with Et_2O (2 × 750 mL). The combined organic extracts were then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O/NEt_3, 30:70:1) gave (*R*)-*N*-(but-3-en-1-yl)-*N*-(α-methylbenzyl)amine as a yellow oil (65.8 g, 68%, >99:1 dr):[25] $[\alpha]_D^{20}$ + 42.1 (*c* 1.0, $CHCl_3$), lit.[25] $[\alpha]_D^{25}$ + 41.6 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.36 (3H, d, *J* = 6.6 Hz, C(α)*Me*), 2.24–2.34 (2H, m, C(2)H_2), 2.54–2.70 (2H, m, C(1)H_2), 3.77 (1H, q, *J* = 6.6 Hz, C(α)*H*), 5.06–5.19 (2H, m, C(4)H_2), 5.75–5.91 (1H, m, C(3)*H*), 7.22–7.36 (5H, m, *Ph*).

***tert*-Butyl (*E,E*)-Hexa-2,4-dienoate [*tert*-Butyl Sorbate] 10.** Condensed isobutene (60 mL) at −78 °C was added to a stirred solution of sorbic acid (10.0 g, 89.2 mmol) and concd aq H_2SO_4 (1.0 mL) in CH_2Cl_2 (200 mL) at 0 °C, and the resultant mixture was stirred at 0 °C for 1 h. The reaction mixture was then allowed to warm to rt and stirred for 48 h. The reaction mixture was then washed with saturated aq $NaHCO_3$ (5 × 100 mL), and the combined aqueous washings were extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried, and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 50:1) gave **10** as a colorless oil (12.0 g, 80%, >99:1 dr):[7c] δ_H (400 MHz, $CDCl_3$) 1.49 (9H, s, CMe_3), 1.85 (3H, d, *J* = 6.2 Hz, C(6)H_3), 5.71 (1H, d, *J* = 15.4 Hz, C(2)*H*), 6.07–6.21 (2H, m, C(4)*H*, C(5)*H*), 7.14 (1H, dd, *J* = 15.4, 10.0 Hz, C(3)*H*).

***tert*-Butyl (3*S*,α*R*,4*E*)-3-[*N*-But-3′-enyl-*N*-(α-methylbenzyl)-amino]hex-4-enoate 12.** BuLi (2.40 M in hexanes, 11.5 mL, 27.6 mmol) was added dropwise to a stirred solution of (*R*)-*N*-(but-3-en-1-yl)-*N*-(α-methylbenzyl)amine (5.00 g, 28.6 mmol, >99:1 er) in THF (20 mL) at −78 °C. After this mixture was stirred for 30 min, a solution of **10** (3.00 g, 17.8 mmol, >99:1 dr) in THF (5 mL) at −78 °C was added dropwise via a cannula. The reaction mixture was left to stir at −78 °C for 2 h, and then saturated aq NH_4Cl (10 mL) was added. The resultant mixture was allowed to warm to rt and stirred for 15 min, and then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (200 mL) and H_2O (100 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL). The combined organic extracts were washed sequentially with 10% aq citric acid (200 mL) and saturated aq $NaHCO_3$ (200 mL), and then dried and concentrated in vacuo. Purification via flash column chromatography (eluent isohexane/EtOAc, 8:1) gave **12** as a pale yellow oil (4.23 g, 69%, >99:1 dr):[13] $[\alpha]_D^{20}$ − 14.6 (*c* 1.0, $CHCl_3$), lit.[13] $[\alpha]_D^{24}$ − 11.3 (*c* 2.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.37 (3H, d, *J* = 6.8 Hz, C(α)*Me*), 1.41 (9H, s, CMe_3), 1.71 (3H, d, *J* = 5.4 Hz, C(6)H_3), 1.99–2.09 (2H, m, C(2′)H_2), 2.29 (1H, dd, *J* = 14.1, 8.4 Hz, C(2)H_A), 2.42 (1H, dd, *J* = 14.1, 6.6 Hz, C(2)H_B), 2.48–2.58 (2H, m, C(1′)H_2), 3.77–3.81 (1H, m, C(3)*H*), 3.94 (1H, q, *J* = 6.8 Hz, C(α)*H*), 4.88–4.94 (2H, m, C(4′)H_2), 5.50–5.53 (2H, m, C(4)*H*, C(5)*H*), 5.65 (1H, ddt, *J* = 17.1, 10.3, 6.9 Hz, C(3′)*H*), 7.19–7.39 (5H, m, *Ph*).

***tert*-Butyl (*R,R,R,E*)-2-Hydroxy-3-[*N*-but-3′-enyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 13.** BuLi (2.40 M in hexanes, 11.5 mL, 27.6 mmol) was added dropwise to a stirred solution of (*R*)-*N*-(but-3-en-1-yl)-*N*-(α-methylbenzyl)amine (5.00 g, 28.6 mmol, >99:1 er) in THF (20 mL) at −78 °C. After the mixture was stirred for 30 min, a solution of **10** (3.00 g, 17.8 mmol, >99:1 dr) in THF (5 mL) at −78 °C was added dropwise via a cannula. The reaction mixture was left to stir at −78 °C for 2 h, and then (−)-CSO (6.95 g, 30.3 mmol) was added. The resultant mixture was allowed to warm to rt over 12 h and then concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (150 mL), and the resultant solution was washed sequentially with 10% aq citric acid (200 mL) and saturated aq $NaHCO_3$ (200 mL), and then dried and concentrated in vacuo. Purification via flash column chromatography (eluent isohexane/EtOAc, 6:1) gave **13** as a pale yellow oil (4.12 g, 64%, >99:1 dr): $[\alpha]_D^{23}$ − 82.7 (*c* 1.0, $CHCl_3$); ν_{max} (ATR) 3500 (O—H), 1724 (C═O), 1640 (C═C); δ_H (400 MHz, $CDCl_3$) 1.35 (3H, d, *J* = 6.8 Hz, C(α)*Me*), 1.49 (9H, s, CMe_3), 1.70 (3H, d, *J* = 6.1 Hz, C(6)H_3), 2.00–2.15 (2H, m, C(2′)H_2), 2.59–2.64 (1H, m, C(1′)H_A), 2.77 (1H, ddd, *J* = 13.9, 9.5, 6.6 Hz, C(1′)H_B), 3.49 (1H, dd, *J* = 9.0, 3.5 Hz, C(3)*H*), 4.08 (1H, d, *J* = 3.5 Hz, C(2)*H*), 4.19 (1H, q, *J* = 6.8 Hz, C(α)*H*), 4.92–4.97 (2H, m, C(4′)H_2), 5.50–5.69 (3H, m, C(4)*H*, C(5)*H*, C(3′)*H*), 7.22–7.42 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.6 (C(α)*Me*), 18.0 (C(6)), 28.0 (CMe_3), 34.9 (C(2′)), 46.7 (C(1′)), 57.2 (C(α)), 64.6 (C(3)), 73.4 (C(2)), 81.7 (CMe_3), 115.6 (C(3′)), 126.7 (C(4)), 127.7, 128.0, 128.7 (*o,m,p*-*Ph*), 129.8 (C(5)), 136.9 (C(4′)), 144.3 (*i*-*Ph*), 172.2 (C(1)); *m/z* (ESI$^+$) 360 ([M + H]$^+$, 100%);

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HRMS (ESI$^+$) $C_{22}H_{33}NNaO_3^+$ ([M + Na]$^+$) requires 382.2353, found 382.2346.

***tert*-Butyl (2′*S*,α*R*)-2-[*N*(1′)-(α-Methylbenzyl)-1′,2′,5′,6′-tetrahydropyridin-2′-yl]ethanoate 14.** Grubbs I catalyst (638 mg, 1.02 mmol) was added to a stirred solution of **12** (3.50 g, 10.2 mmol, >99:1 dr) in anhydrous, degassed CH_2Cl_2 (400 mL) at rt. The resultant mixture was stirred at 40 °C for 48 h and then concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (150 mL). The resultant solution was stirred at rt, and $P(CH_2OH)_3$[26] (12.6 g, 102 mmol) and Et_3N (2.84 mL, 20.4 mmol) were added sequentially. The resultant mixture was stirred at rt for 5 min. Then, excess silica gel (~8 g) was added, and stirring was continued for 12 h. The reaction mixture was then concentrated in vacuo. Purification via flash column chromatography (eluent isohexane/EtOAc, 8:1) gave **14** as a pale yellow oil (2.28 g, 74%, >99:1 dr):[13] $[\alpha]_D^{20}$ + 38.1 (*c* 1.0, $CHCl_3$), lit.[13] $[\alpha]_D^{25}$ + 41.8 (*c* 1.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.39 (3H, d, *J* = 6.6 Hz, C(α)*Me*), 1.49 (9H, s, C*Me*$_3$), 1.68−1.75 (1H, m, C(5′)H_A), 2.07−2.11 (1H, m, C(5′)H_B), 2.38 (1H, dd, *J* = 14.2, 6.3 Hz, C(2)H_A), 2.45−2.51 (1H, m, C(6′)H_A), 2.61 (1H, dd, *J* = 14.2, 7.2 Hz, C(2)H_B), 2.82−2.89 (1H, m, C(6′)H_B), 3.73−3.76 (1H, m, C(2′)*H*), 3.91 (1H, q, *J* = 6.6 Hz, C(α)*H*), 5.66 (1H, dt, *J* = 10.1, 3.8 Hz, C(3′)*H*), 5.80−5.84 (1H, m, C(4′)*H*), 7.21−7.33 (5H, m, *Ph*).

***tert*-Butyl (*R*,*R*,*R*)-2-Hydroxy-2-[*N*(1′)-(α-methylbenzyl)-1′,2′,5′,6′-tetrahydropyridin-2′-yl]ethanoate 15.** Grubbs I catalyst (714 mg, 1.14 mmol) was added to a stirred solution of **13** (4.10 g, 11.4 mmol, >99:1 dr) in anhydrous, degassed CH_2Cl_2 (500 mL) at rt. The resultant mixture was stirred at 40 °C for 48 h and then concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (180 mL). The resultant mixture was stirred at rt, and $P(CH_2OH)_3$[26] (14.2 g, 114 mmol) and Et_3N (3.18 mL, 22.8 mmol) were added sequentially. The resultant mixture was stirred at rt for 5 min. Then, excess silica gel (~10 g) was added, and stirring was continued for 12 h. The reaction mixture was then concentrated in vacuo. Purification via flash column chromatography (eluent isohexane/EtOAc, 4:1) gave **15** as a pale yellow oil (2.74 g, 76%, >99:1 dr): $[\alpha]_D^{23}$ + 48.7 (*c* 1.0, $CHCl_3$); ν_{max} (film) 3500 (O—H), 2977 (C—H), 1727 (C═O), 1654 (C═C); δ_H (400 MHz, $CDCl_3$) 1.47 (3H, obsc d, C(α)*Me*), 1.49 (9H, s, C*Me*$_3$), 1.93−2.09 (2H, m, C(5′)H_2), 2.36−2.42 (1H, m, C(6′)H_A), 3.06 (1H, ddd, *J* = 12.0, 6.7, 5.0 Hz, C(6′)H_B), 3.62 (1H, app d, *J* = 2.2 Hz, C(2′)*H*), 4.08 (1H, q, *J* = 6.8 Hz, C(α)*H*), 4.43 (1H, d, *J* = 3.9 Hz, C(2)*H*), 5.41 (1H, ddt, *J* = 10.0, 3.4, 2.2 Hz, C(3′)*H*), 5.98 (1H, dtd, *J* = 10.0, 3.9, 2.0 Hz, C(4′)*H*), 7.21−7.33 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.5 (C(α)*Me*), 23.9 (*C*(5′)), 28.0 (C*Me*$_3$), 41.1 (*C*(6′)), 58.0 (*C*(α)), 58.6 (*C*(2′)), 71.0 (*C*(2)), 81.8 (*C*Me$_3$), 124.0 (*C*(3′)), 127.2, 128.0, 128.2 (*o*,*m*,*p*-*Ph*), 129.4 (*C*(4′)), 141.5 (*i*-*Ph*), 172.4 (*C*(1)); *m*/*z* (ESI$^+$) 318 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{27}NNaO_3^+$ ([M + Na]$^+$) requires 340.1883, found 340.1869.

Methyl (2′*S*,α*R*)-2-[*N*(1′)-(α-Methylbenzyl)-1′,2′,5′,6′-tetrahydropyridin-2′-yl]ethanoate 16. $SOCl_2$ (1.35 mL, 18.6 mmol) was added to MeOH (3.0 mL) at 0 °C, and the resultant mixture was stirred at rt for 1 min. A solution of **14** (800 mg, 2.65 mmol, >99:1 dr) in MeOH (3.0 mL) was then added, and the reaction mixture was stirred at rt for 16 h and then concentrated in vacuo. The residue was partitioned between saturated aq $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were then dried and concentrated in vacuo. Purification via flash column chromatography (eluent isohexane/EtOAc, 4:1) gave **16** as yellow oil (520 mg, 75%, >99:1 dr):[13] $[\alpha]_D^{20}$ + 99.0 (*c* 1.0, $CHCl_3$), lit.[13] $[\alpha]_D^{16}$ + 42.1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.36 (3H, d, *J* = 6.6 Hz, C(α)*Me*), 1.65−1.72 (1H, m, C(5′)H_A), 2.08−2.18 (1H, m, C(5′)H_B), 2.49 (1H, dd, *J* = 14.4, 6.3 Hz, C(2)H_A), 2.49−2.55 (1H, m, C(6′)H_A), 2.69 (1H, dd, *J* = 14.4, 7.8 Hz, C(2)H_B), 2.84 (1H, ddd, *J* = 13.6, 10.1, 4.5 Hz, C(6′)H_B), 3.65 (3H, s, O*Me*), 3.83−3.87 (1H, m, C(2′)*H*), 3.88 (1H, q, *J* = 6.6 Hz, C(α)*H*), 5.65−5.69 (1H, m, C(3′)*H*), 5.84−5.88 (1H, m, C(4′)*H*), 7.21−7.33 (5H, m, *Ph*).

Methyl (*R*,*R*,*R*)-2-Hydroxy-2-[*N*(1′)-(α-methylbenzyl)-1′,2′,5′,6′-tetrahydropyridin-2′-yl]ethanoate 17. $SOCl_2$ (1.28 mL, 17.6 mmol) was added to MeOH (3.0 mL) at 0 °C, and the resultant mixture was stirred at rt for 1 min. A solution of **15** (800 mg, 2.52 mmol, >99:1 dr) in MeOH (3.0 mL) was added, and the reaction mixture was stirred at rt for 16 h and then concentrated in vacuo. The residue was partitioned between saturated aq $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were then dried and concentrated in vacuo. Purification via flash column chromatography (eluent isohexane/EtOAc, 4:1) gave **17** as yellow oil (560 mg, 81%, >99:1 dr): $[\alpha]_D^{20}$ + 59.4 (*c* 1.0, $CHCl_3$); ν_{max} (ATR) 3505 (O—H), 1739 (C═O), 1655 (C═C); δ_H (400 MHz, $CDCl_3$) 1.47 (3H, d, *J* = 6.6 Hz, C(α)*Me*), 1.92−1.96 (1H, m, C(5′)H_A), 2.01−2.07 (1H, m, C(5′)H_B), 2.36−2.42 (1H, m, C(6′)H_A), 2.99 (1H, dt, *J* = 11.9, 5.8 Hz, C(6′)H_B), 3.69−3.70 (1H, m, C(2′)*H*), 3.77 (3H, s, O*Me*), 4.04 (1H, q, *J* = 6.6 Hz, C(α)*H*), 4.54 (1H, d, *J* = 4.8 Hz, C(2)*H*), 5.41 (1H, dd, *J* = 10.1, 1.5 Hz, C(3′)*H*), 5.98−6.00 (1H, m, C(4′)*H*), 7.26−7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.5 (C(α)*Me*), 23.5 (*C*(5′)), 41.2 (*C*(6′)), 58.0 (*C*(α)), 58.3 (*C*(2′)), 71.1 (*C*(2)), 123.9 (*C*(3′)), 127.3, 128.0, 128.3 (*o*,*m*,*p*-*Ph*), 129.7 (*C*(4′)), 141.5 (*i*-*Ph*), 173.5 (*C*(1)); *m*/*z* (ESI$^+$) 276 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{21}NNaO_3^+$ ([M + Na]$^+$) requires 298.1414, found 298.1410.

***tert*-Butyl (2′*S*,3′*S*,4′*R*,α*R*)-2-[*N*(1′)-(α-Methylbenzyl)-3′,4′-dihydroxypiperidin-2′-yl]ethanoate 19.** *Method A − Upjohn Oxidation.* OsO_4 (13 mg, 49 μmol) was added to a stirred solution of **14** (150 mg, 0.49 mmol, >99:1 dr) in THF/H_2O (4:1, 1.2 mL) followed by a solution of NMO (233 mg, 1.99 mmol) in H_2O (0.1 mL), and the resultant mixture was stirred at rt for 12 h. Saturated aq Na_2SO_3 (1 mL) was then added, and the resultant mixture was left to stir at rt for 1 h. The reaction mixture was then extracted with EtOAc (3 × 3 mL), and the combined organic extracts were dried and concentrated in vacuo to give **19** (94:6 dr). Purification via flash column chromatography (eluent 30−40 °C petrol/EtOAc, 4:1) gave **19** as a yellow oil (114 mg, 68%, >99:1 dr): $[\alpha]_D^{20}$ + 11.2 (*c* 0.5, $CHCl_3$); ν_{max} (film) 3418 (O—H), 1726 (C═O); δ_H (400 MHz, $CDCl_3$) 1.37 (9H, s, C*Me*$_3$), 1.39 (3H, d, *J* = 6.6 Hz, C(α)*Me*), 1.62−1.73 (1H, m, C(5′)H_A), 1.83−1.88 (1H, m, C(5′)H_B), 2.25 (1H, dd, *J* = 14.4, 9.7 Hz, C(2)H_A), 2.37−2.50 (2H, m, C(2)H_B, C(6′)H_A), 2.79 (1H, d, *J* = 9.6 Hz, O*H*), 2.93 (1H, dt, *J* = 12.4, 2.1 Hz, C(6′)H_B), 3.31−3.35 (1H, m, C(2′)*H*), 3.61−3.66 (1H, m, C(3′)*H*), 3.70−3.79 (2H, m, C(4′)*H*, C(α)*H*), 7.22−7.38 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.4 (C(α)*Me*), 28.0 (C*Me*$_3$), 29.7 (*C*(5′)), 30.3 (*C*(2)), 40.4 (*C*(6′)), 58.1 (*C*(2′)), 59.6 (*C*(α)), 66.1 (*C*(4′)), 70.4 (*C*(3′)), 80.9 (*C*Me$_3$), 127.0, 127.3, 128.3 (*o*,*m*,*p*-*Ph*), 144.2 (*i*-*Ph*), 170.9 (*C*(1)); *m*/*z* (ESI$^+$) 336 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{30}NO_4^+$ ([M + H]$^+$) requires 336.2169, found 336.2156.

Method B − Donohoe Oxidation. OsO_4 (186 mg, 0.73 mmol) was added to a stirred solution of **14** (200 mg, 0.66 mmol, >99:1 dr) and TMEDA (140 μL, 0.93 mmol) in CH_2Cl_2 (5 mL) at −78 °C. The resultant mixture was stirred at −78 °C for 1 h, and then allowed to warm to rt over 15 min before being concentrated in vacuo to give **18** (>99:1 dr). The residue of **18** was dissolved in CH_2Cl_2 (6 mL); the resultant solution was stirred at rt, and $P(CH_2OH)_3$[26] (7.56 g, 59.5 mmol) and Et_3N (1.67 mL, 11.9 mmol) were added sequentially. After the mixture had been stirred at rt for 5 min, excess silica gel (~5 g) was added, and stirring of the reaction mixture was continued at rt for 48 h. The resultant suspension was then concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/EtOAc, 1:1) gave **19** as a colorless oil (162 mg, 73% from **14**, >99:1 dr), which displayed characterization data consistent with those described above.

***tert*-Butyl (2′*S*,3′*S*,4′*R*)-(3′,4′-Dihydroxypiperidin-2′-yl)-ethanoate 20.** $Pd(OH)_2/C$ (50% w/w of substrate, 52 mg) was added to a stirred solution of **19** (104 mg, 0.31 mmol, >99:1 dr) in degassed MeOH (3 mL) at rt. The resultant suspension was placed under H_2 (1 atm) and stirred vigorously at rt for 12 h. The reaction mixture was then filtered through a short plug of Celite (eluent MeOH) and concentrated in vacuo to give **20** as a yellow oil (72 mg, quant, >99:1 dr): $[\alpha]_D^{20}$ − 4.0 (*c* 0.5, $CHCl_3$); ν_{max} (film) 3316 (O—H), 1718 (C═O); δ_H (400 MHz, $CDCl_3$) 1.46 (9H, s, C*Me*$_3$), 1.70−1.79 (1H, m, C(5′)H_A), 1.85−1.91 (1H, m, C(5′)H_B), 2.35 (1H, dd, *J* = 16.4, 8.1 Hz, C(2)H_A), 2.71−2.79 (2H, m, C(2)H_B, C(6′)H_A),

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2.99 (1H, td, J = 12.1, 3.0 Hz, C(6′)H_B), 3.14 (1H, app dt, J = 8.1, 4.5 Hz, C(2′)H), 3.35 (1H, dd, J = 9.2, 3.9 Hz, C(3′)H), 4.04 (1H, app q, J = 3.9 Hz, C(4′)H); δ_C (100 MHz, $CDCl_3$) 28.1 (CMe_3), 31.9 (C(2)), 38.8 (C(5′)), 39.5 (C(6′)), 53.3 (C(2′)), 68.0 (C(4′)), 73.2 (C(3′)), 81.2 (CMe_3), 172.7 (C(1)); m/z (ESI$^+$) 232 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{11}H_{22}NO_4^+$ ([M + H]$^+$) requires 232.1543, found 232.1551.

(2′*S*,3′*S*,4′*R*)-(3′,4′-Dihydroxypiperidin-2′-yl)ethanoic Acid 21. A solution of **20** (40 mg, 0.17 mmol, >99:1 dr) in 1.0 M aq HCl (2 mL) was stirred at rt for 12 h and then concentrated in vacuo. Purification via ion exchange chromatography (Dowex 50WX8−200, eluent 1.0 M aq NH_4OH) gave **21** as a white solid (23 mg, 77%, >99:1 dr): mp 137−138 °C; $[\alpha]_D^{20}$ − 72.6 (c 0.5, MeOH); ν_{max} (film) 3284 (O—H), 1577 (zwitterionic β-amino acid); δ_H (500 MHz, D_2O) 1.88−1.95 (1H, m, C(5′)H_A), 2.00−2.05 (1H, m, C(5′)H_B), 2.49 (1H, dd, J = 17.5, 8.9 Hz, C(2)H_A), 2.73 (1H, dd, J = 17.5, 3.8 Hz, C(2)H_B), 3.22 (2H, app dd, J = 8.7, 3.8 Hz, C(6′)H_2), 3.55 (1H, td, J = 8.9, 3.8 Hz, C(2′)H), 3.72 (1H, dd, J = 8.9, 2.5 Hz, C(3′)H), 4.1 (1H, app td, J = 5.1, 2.5 Hz, C(4′)H); δ_C (125 MHz, D_2O) 27.0 (C(5′)), 34.7 (C(2)), 38.1 (C(6′)), 52.9 (C(2′)), 65.3 (C(4′)), 68.7 (C(3′)), 177.5 (C(1)); m/z (FI$^+$) 175 ([M]$^+$, 100%); HRMS (FI$^+$) $C_7H_{13}NO_4^+$ ([M]$^+$) requires 175.0839, found 175.0849.

***tert*-Butyl (2*R*,2′*R*,3′*S*,4′*R*,α*R*)-2-Hydroxy-2-[*N*(1′)-(α-methylbenzyl)-3′,4′-dihydroxypiperidin-2′-yl]ethanoate 22.** *Method A − Upjohn Oxidation.* OsO_4 (48 mg, 0.19 mmol) was added to a stirred solution of **15** (600 mg, 1.89 mmol, >99:1 dr) in THF/H_2O (4:1, 7.2 mL) followed by a solution of NMO (886 mg, 7.56 mmol) in H_2O (0.3 mL), and the resultant mixture was stirred at rt for 12 h. Saturated aq Na_2SO_3 (5 mL) was then added, and the resultant mixture was left to stir at rt for 1 h. The reaction mixture was then extracted with EtOAc (3 × 10 mL), and the combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent PhMe/^{i}PrOH, 4:1) gave **22** as a yellow oil (425 mg, 64%, >99:1 dr): $[\alpha]_D^{20}$ + 22.6 (c 1.0, $CHCl_3$); ν_{max} (film) 3307 (O—H), 1732 (C═O); δ_H (400 MHz, $CDCl_3$) 1.37 (9H, s, CMe_3), 1.47 (3H, d, J = 6.6 Hz, C(α)Me), 1.71−1.78 (1H, m, C(5′)H_A), 1.80−1.86 (1H, m, C(5′)H_B), 2.82−2.87 (1H, m, C(6′)H_A), 2.97−3.04 (1H, m, C(6′)H_B), 3.28 (1H, t, J = 2.8 Hz, C(2′)H), 3.63 (1H, br s, C(3′)H), 4.04−4.12 (2H, m, C(4′)H, C(α)H), 4.56 (1H, d, J = 2.8 Hz, C(2)H), 7.22−7.37 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 21.4 (C(α)Me), 28.0 (CMe_3), 29.3 (C(5′)), 41.5 (C(6′)), 58.9 (C(4′)), 62.9 (C(2′)), 67.5 (C(α)), 69.1 (C(3′)), 69.3 (C(2)), 83.1 (CMe_3), 127.1, 127.2, 128.5 (*o*,*m*,*p*-Ph), 143.8 (*i*-Ph), 173.6 (C(1)); m/z (ESI$^+$) 352 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{30}NO_5^+$ ([M + H]$^+$) requires 352.2118, found 352.2120.

Method B − Donohoe Oxidation. OsO_4 (132 mg, 0.52 mmol) was added to a stirred solution of **15** (150 mg, 0.47 mmol, >99:1 dr) and TMEDA (100 μL, 0.66 mmol) in CH_2Cl_2 (5 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h, then allowed to warm to rt over 15 min, and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (6 mL). $P(CH_2OH)_3$[26] (3.94 g, 29.1 mmol) and Et_3N (0.81 mL, 5.81 mmol) were added sequentially, and the resultant solution was stirred at rt for 5 min. Excess silica gel (∼5 g) was then added, and stirring of the mixture was continued at rt for 48 h. The resultant suspension was then concentrated in vacuo. Purification via flash column chromatography (eluent PhMe/^{i}PrOH, 4:1) gave **22** as a colorless oil (89 mg, 87%, >99:1 dr), which displayed characterization data consistent with those described above: $[\alpha]_D^{20}$ + 23.0 (c 1.0, $CHCl_3$).

***tert*-Butyl (2*R*,2′*S*,3′*S*,4′*R*,α*R*)-2-Hydroxy-2-[*N*(1′)-(α-methylbenzyl)-3′,4′-dihydroxy-3′,4′-*O*-isopropylidenepiperidin-2′-yl]ethanoate 23.** TsOH·H_2O (162 mg, 0.85 mmol) was added to a stirred solution of **22** (600 mg, 1.70 mmol) in DMP/acetone (13:1, 8 mL), and the resultant mixture was stirred at 45 °C for 48 h. Saturated aq $NaHCO_3$ (10 mL) was then added, and the reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried, and concentrated in vacuo. Purification via flash column chromatography (eluent $CHCl_3$/^{i}PrOH, 95:5) gave **23** as a yellow solid (493 mg, 74%, >99:1 dr): mp 82−83 °C; $[\alpha]_D^{20}$ + 13.0 (c 1.0, $CHCl_3$); ν_{max} (film) 3445 (O—H), 1731 (C═O); δ_H (400 MHz, $CDCl_3$) 1.27 (3H, s, MeCMe), 1.42 (3H, s, MeCMe), 1.47 (3H, d, J = 6.8 Hz, C(α)Me), 1.49 (9H, s, CMe_3), 1.71−1.78 (1H, m, C(5′)H_A), 1.81−1.89 (1H, m, C(5′)H_B), 2.56 (1H, ddd, J = 12.1, 9.2, 3.0 Hz, C(6′)H_A), 2.75 (1H, ddd, J = 12.1, 6.6, 3.6 Hz, C(6′)H_B), 3.50 (1H, m, C(2)H), 4.10 (1H, dd, J = 6.0, 3.0 Hz, C(2′)H), 4.16 (1H, q, J = 6.8 Hz, C(α)H), 4.21 (1H, m, C(3′)H), 4.27 (1H, app q, J = 5.0 Hz, C(4′)H), 7.21−7.37 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 19.6 (C(α)Me), 25.5, 27.4 (CMe_2), 27.7 (C(5′)), 28.0 (CMe_3), 40.4 (C(6′)), 59.7 (C(2′)), 59.8 (C(α)), 71.7 (C(4′)), 72.4 (C(2)), 72.7 (C(3′)), 82.7 (CMe_3), 107.4 (CMe_2), 126.9, 127.9, 128.2 (*o*,*m*,*p*-Ph), 143.0 (*i*-Ph), 173.1 (C(1)); m/z (ESI$^+$) 392 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{33}NNaO_5^+$ ([M + Na]$^+$) requires 414.2251, found 414.2247.

(2*R*,2′*S*,3′*S*,4′*R*,α*R*)-2-[*N*(1′)-(α-Methylbenzyl)-3′,4′-dihydroxy-3′,4′-*O*-isopropylidenepiperidin-2′-yl]ethane-1,2-diol 24. $LiAlH_4$ (1.0 M in THF, 2.6 mL, 2.55 mmol) was added dropwise to a stirred solution of **23** (400 mg, 1.02 mmol, >99:1 dr) in THF (8 mL) at −78 °C; the resultant mixture was allowed to warm to rt over 16 h. Aq NaOH (1.0 M, 1 mL) was then added, and the resultant suspension was heated at reflux for 1 h. The reaction mixture was then filtered through a short plug of Celite (eluent EtOAc) and concentrated in vacuo. Purification via flash column chromatography (eluent PhMe/acetone, 3:1) gave **24** as a colorless oil (220 mg, 67%, >99:1 dr): $[\alpha]_D^{20}$ + 39.5 (c 1.0, $CHCl_3$); ν_{max} (film) 3395 (O—H), 2932 (C—H); δ_H (500 MHz, $CDCl_3$) 1.33 (3H, s, MeCMe), 1.45 (3H, s, MeCMe), 1.50 (3H, d, J = 6.9 Hz, C(α)Me), 1.66−1.74 (1H, m, C(5′)H_A), 1.78−1.81 (1H, m, C(5′)H_B), 2.49−2.54 (1H, m, C(6′)H_A), 2.58−2.61 (1H, m, C(6′)H_B), 3.28 (1H, dd, J = 7.1, 3.3 Hz, C(2′)H), 3.76−3.78 (2H, m, C(1)H_2), 3.88−3.92 (1H, m, C(2)H), 4.24 (1H, q, J = 6.9 Hz, C(α)H), 4.29 (1H, app q, J = 5.3 Hz, C(4′)H), 4.44 (1H, dd, J = 6.1, 3.3 Hz, C(3′)H), 7.24−7.35 (5H, m, Ph); δ_C (125 MHz, $CDCl_3$) 20.5 (C(α)Me), 25.4 (C(5′)), 25.8, 27.7 (CMe_2), 40.7 (C(6′)), 59.6 (C(2′)), 60.1 (C(α)), 65.7 (C(1)), 69.7 (C(2)), 71.0 (C(4′)), 72.7 (C(3′)), 107.8 (CMe_2), 127.3 (*p*-Ph), 127.6, 128.5 (*o*,*m*-Ph), 142.5 (*i*-Ph); m/z (ESI$^+$) 322 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{27}NNaO_4^+$ ([M + Na]$^+$) requires 344.1832, found 344.1834.

(2*R*,3*S*,4*R*,α*R*)-*N*(1)-(α-Methylbenzyl)-3,4-dihydroxypiperidine-2-carboxylic Acid 26. $NaIO_4$ (166 mg, 0.77 mmol) was added to a solution of **24** (100 mg, 0.31 mmol, >99:1 dr) in EtOH/H_2O (5:1, 4.4 mL) at rt, and the resultant suspension was stirred at rt for 20 min. The reaction mixture was then filtered through a short plug of Celite (eluent EtOH) and concentrated in vacuo. The residue was dissolved in Et_2O (10 mL), and the resultant solution was filtered through a short plug of Celite (eluent Et_2O) and concentrated in vacuo. Cyclohexene (0.32 mL) was added to a solution of the residue in ^{t}BuOH (4.8 mL) at rt. A solution of $NaClO_2$ (31 mg, 0.34 mmol) and KH_2PO_4 (47 mg, 0.34 mmol) in H_2O (0.8 mL) was then added dropwise at rt. The resultant mixture was stirred at rt for 1 h and then concentrated in vacuo. The residue was partitioned between EtOAc (2 mL) and H_2O (2 mL), and the aqueous layer was extracted with EtOAc (2 × 2 mL). The combined organic extracts were then dried and concentrated in vacuo to give **25**. A solution of residue **25** in 1.0 M aq HCl (0.5 mL) was stirred at 40 °C for 12 h. The reaction mixture was then allowed to cool to rt and concentrated in vacuo. Purification via ion exchange chromatography (Dowex 50WX8−200, eluent 1.0 M aq NH_4OH) gave **26** as an orange oil (21 mg, 26% from **24**, 60:40 dr). Data for mixture: ν_{max} (ATR) 3345 (O—H), 1457 (zwitterionic α-amino acid); m/z (ESI$^+$) 266 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{19}NNaO_4^+$ ([M + Na]$^+$) requires 288.1206, found 288.1219. Data for major diastereoisomer: δ_H (500 MHz, D_2O) 1.62 (3H, d, J = 6.6 Hz, C(α)Me), 1.79−1.87 (2H, m, C(5)H_2), 2.82−2.87 (1H, m, C(6)H_A), 3.05−3.10 (1H, m, C(6)H_B), 3.31−3.39 (1H, m, C(2)H), 3.87−3.90 (2H, m, C(3)H, C(4)H), 4.32 (1H, q, J = 6.6 Hz, C(α)H), 7.40−7.48 (5H, m, Ph); δ_C (125 MHz, D_2O) 18.3 (C(α)Me), 27.0 (C(5)), 43.0 (C(6)), 58.3 (C(α)), 65.6 (C(3)), 70.1 (C(2)), 70.4 (C(4)), 127.5, 129.3, 129.5 (*o*,*m*,*p*-Ph), 136.1 (*i*-Ph), 177.9 (CO_2H). Data for minor diastereoisomer: δ_H (500 MHz, D_2O) 1.61 (3H, d, J = 6.9 Hz, C(α)Me), 1.93−2.02 (2H, m, C(5)H_2), 2.88−2.93 (1H, m, C(6)H_A), 2.98−3.03 (1H, m, C(6)H_B), 3.15 (1H, d, J =

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7.6 Hz, C(2)*H*), 3.96−3.99 (1H, m, C(3)*H*), 4.02 (1H, app d, *J* = 3.5 Hz, C(4)*H*), 4.47 (1H, q, *J* = 6.9 Hz, C(*α*)*H*), 7.40−7.48 (5H, m, *Ph*); δ_C (125 MHz, D_2O) 17.2 (C(*α*)*Me*), 30.3 (*C*(5)), 42.8 (*C*(6)), 58.2 (*C*(*α*)), 65.0 (*C*(2)), 70.2 (*C*(3)), 75.3 (*C*(4)), 128.3, 129.2, 129.3 (*o*,*m*,*p*-*Ph*), 136.1 (*i*-*Ph*), 179.9 (CO_2H).

(2*R*,2′*S*,3′*S*,4′*R*)-2-[*N*(1′)-*tert*-Butoxycarbonyl-3′,4′-dihydroxy-3′,4′-*O*-isopropylidenepiperidin-2′-yl]ethane-1,2-diol 27. $Pd(OH)_2$/C (50% w/w of substrate, 40 mg) was added to a stirred solution of **24** (80 mg, 0.25 mmol, >99:1 dr) and Boc_2O (59 mg, 0.27 mmol) in degassed MeOH (2 mL) at rt. The resultant suspension was placed under H_2 (1 atm) and stirred vigorously at rt for 12 h. The reaction mixture was then filtered through a short plug of Celite (eluent MeOH) and concentrated in vacuo to give **27** as a colorless oil (37 mg, 48%, >99:1 dr): $[\alpha]_D^{20}$ + 25.2 (*c* 1.0, $CHCl_3$); ν_{max} (ATR) 3416 (O—H), 2979 (C—H), 1665 (C═O); δ_H (500 MHz, $CDCl_3$) 1.33 (3H, s, *Me*CMe), 1.45 (3H, s, MeC*Me*), 1.46 (9H, s, C*Me*$_3$), 1.72−1.75 (1H, m, C(5′)H_A), 1.81−1.86 (1H, m, C(5′)H_B), 3.07 (1H, br s, O*H*), 3.21−3.23 (1H, m, C(6′)H_A), 3.36−3.42 (2H, m, C(2)*H*, C(6′)H_B), 3.57−3.61 (2H, m, C(1)H_2), 4.04 (1H, dd, *J* = 10.5, 1.8 Hz, C(2′)*H*), 4.29 (1H, br s, O*H*), 4.41−4.43 (1H, m, C(4′)*H*), 4.81−4.82 (1H, m, C(3′)*H*); δ_C (125 MHz, $CDCl_3$) 24.2, 26.4 (*C*Me_2), 28.3 (*C*Me_3), 36.8 (*C*(5′)), 53.9 (*C*(6′)), 62.0 (*C*(1)), 68.8 (*C*(2′)), 71.7 (*C*(4′)), 72.6 (*C*(2)), 77.2 (*C*(3′)), 80.9 (*C*Me$_3$), 107.6 (*C*Me$_2$), 157.9 (NCO); *m*/*z* (ESI$^+$) 340 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{15}H_{27}NNaO_6^+$ ([M + Na]$^+$) requires 340.1731, found 340.1738.

(2*R*,3*S*,4*R*)-3,4-Dihydroxypiperidine-2-carboxylic Acid [(−)-3,4-Dihydroxypipecolic Acid] 28. $NaIO_4$ (55 mg, 0.23 mmol) was added to a solution of **27** (30 mg, 91 *μ*mol, >99:1 dr) in EtOH/H_2O (5:1, 1.3 mL) at rt, and the resultant suspension was stirred at rt for 20 min. The reaction mixture was then filtered through a short plug of Celite (eluent EtOH) and concentrated in vacuo. The residue was dissolved in Et_2O (10 mL), and the resultant solution was filtered through a short plug of Celite (eluent Et_2O) and concentrated in vacuo. Cyclohexene (0.10 mL) was added to a solution of the residue in ^{t}BuOH (1.4 mL) at rt. A solution of $NaClO_2$ (85 mg, 0.95 mmol) and KH_2PO_4 (128 mg, 0.95 mmol) in H_2O (0.9 mL) was then added dropwise at rt. The resultant mixture was stirred at rt for 18 h and then concentrated in vacuo. The residue was partitioned between EtOAc (2 mL) and H_2O (2 mL), and the aqueous layer was extracted with EtOAc (2 × 2 mL). The combined organic extracts were then dried and concentrated in vacuo. A solution of the residue in 2.0 M aq HCl (0.5 mL) was heated at reflux for 12 h. The reaction mixture was then allowed to cool to rt and concentrated in vacuo. Purification via ion exchange chromatography (Dowex 50WX8−200, eluent 1.0 M aq NH_4OH) gave **28** as an orange solid (13 mg, 67%, >99:1 dr): mp 233−238 °C (dec); $[\alpha]_D^{20}$ − 6.1 (*c* 1.0, H_2O); ν_{max} (ATR) 3345 (O—H), 2948 (C—H), 1452 (zwitterionic *α*-amino acid); δ_H (700 MHz, D_2O) 1.83−1.87 (1H, m, C(5)H_A), 1.99 (1H, dtd, *J* = 14.5, 7.4, 4.5 Hz, C(5)H_B), 3.17−3.24 (2H, m, C(6)H_2), 3.81 (1H, d, *J* = 7.0 Hz, C(2)*H*), 3.95−3.97 (1H, m, C(4)*H*), 4.09 (1H, dd, *J* = 7.0, 2.4 Hz, C(3)*H*); δ_C (175 MHz, D_2O) 25.8 (*C*(5)), 38.9 (*C*(6)), 59.2 (*C*(2)), 65.4 (*C*(4)), 68.4 *C*(3)), 172.4 (CO_2H); *m*/*z* (ESI$^+$) 162 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_6H_{11}NNaO_4^+$ ([M + Na]$^+$) requires 184.0580, found 184.0583.

(2*S*,3*S*,4*R*,*αR*)-*N*(1)-(*α*-Methylbenzyl)-2-hydroxymethyl-3,4-dihydroxy-3,4-*O*-isopropylidenepiperidine 29. $NaIO_4$ (219 mg, 1.03 mmol) was added to a stirred solution of **24** (110 mg, 0.34 mmol, >99:1 dr) in EtOH/H_2O (5:1, 3.9 mL) at rt, and the resultant suspension was stirred at rt for 20 min. The reaction mixture was then filtered through a short plug of Celite (eluent EtOH), and the filtrate was concentrated in vacuo to half of its original volume. The residue was cooled to 0 °C, and $NaBH_4$ (30 mg, 0.79 mmol) was added. The resultant mixture was allowed to warm to rt and stirred at rt for 12 h before saturated aq NH_4Cl (0.5 mL) was added. The reaction mixture was then filtered through Celite (eluent $CHCl_3$/MeOH, 3:1) and concentrated in vacuo. Purification via flash column chromatography (eluent PhMe/acetone, 2:3) gave **29** as a yellow oil (62 mg, 62%, >99:1 dr): $[\alpha]_D^{20}$ + 48.3 (*c* 1.0, $CHCl_3$); ν_{max} (film) 3442 (O—H), 2982 (C—H); δ_H (400 MHz, $CDCl_3$) 1.29 (3H, s, *Me*CMe), 1.42 (3H, d, *J* = 6.6 Hz, C(*α*)*Me*), 1.44 (3H, s, MeC*Me*), 1.55−1.63 (1H, m, C(5)H_A), 1.77 (1H, dddd, *J* = 14.2, 8.2, 6.0, 3.4 Hz, C(5)H_B), 2.43−2.49 (1H, m, C(6)H_A), 2.52−2.58 (1H, m, C(6)H_B), 3.34−3.41 (2H, m, C(2)C$H_A$$H_B$, C(2)*H*), 3.62−3.68 (1H, m, C(2)C$H_A$$H_B$), 3.95−3.97 (1H, m, C(3)*H*), 4.14−4.21 (2H, m, C(*α*)*H*, C(4)*H*), 7.20−7.32 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.7 (C(*α*)*Me*), 25.5 (*C*(5)), 25.6, 27.9 (*C*Me_2), 39.7 (*C*(6)), 56.3 (*C*(2)), 59.2 (*C*(*α*)), 59.9 (C(2)CH_2), 71.3 (*C*(4)), 73.7 (*C*(3)), 107.8 (*C*Me_2), 127.1 (*p*-*Ph*), 127.4, 128.3 (*o*,*m*-*Ph*), 143.4 (*i*-*Ph*); *m*/*z* (ESI$^+$) 292 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{17}H_{26}NO_3^+$ ([M + H]$^+$) requires 292.1907, found 292.1897.

(2*S*,3*S*,4*R*)-2-Hydroxymethyl-3,4-dihydroxypiperidine [(−)-3-*epi*-Fagomine] 31. *Step 1.* $Pd(OH)_2$/C (50% w/w of substrate, 21 mg) was added to a stirred solution of **29** (42 mg, 0.15 mmol, >99:1 dr) in MeOH (0.5 mL). The resultant suspension was placed under H_2 (1 atm) and stirred vigorously at rt for 12 h. The reaction mixture was then filtered through a short plug of Celite (eluent MeOH) and concentrated in vacuo to give **30** as a yellow oil (28 mg, quant, >99:1 dr): δ_H (400 MHz, $CDCl_3$) 1.33 (3H, s, *Me*CMe), 1.47 (3H, s, MeC*Me*), 1.97−2.02 (1H, m, C(5)H_A), 2.08−2.12 (1H, m, C(5)H_B), 2.71−2.74 (1H, m, C(2)*H*), 2.84 (1H, td, *J* = 12.3, 3.3 Hz, C(6)H_A), 2.93−2.98 (1H, m, C(6)H_B), 3.56 (1H, dd, *J* = 11.1, 7.2 Hz, C(2)C$H_A$$H_B$), 3.81 (1H, dd, *J* = 9.0, 4.9 Hz, C(3)*H*), 3.87 (1H, dd, *J* = 11.1, 3.3 Hz, C(2)C$H_A$$H_B$), 4.11 (2H, br s, N*H*, O*H*), 4.28−4.31 (1H, m, C(4)*H*); δ_C (100 MHz, $CDCl_3$) 26.2 (*Me*CMe), 26.9 (*C*(5)), 28.3 (MeC*Me*), 40.2 (*C*(6)), 59.5 (*C*(2)), 62.4 (C(2)CH_2), 71.7 (*C*(4)), 72.7 (*C*(3)), 108.7 (*C*Me_2).

Step 2. A solution of **30** (20 mg, 0.11 mmol, >99:1 dr) in 1.0 M aq HCl (0.5 mL) was stirred at rt for 12 h and then concentrated in vacuo. Purification via ion exchange chromatography (Dowex 50WX8−200, eluent 1.0 M aq NH_4OH) gave **31** as a white solid (13 mg, 80%, >99:1 dr):[20e,21] mp 141−145 °C, lit.[20e] mp 220−222 °C; $[\alpha]_D^{20}$ − 72.2 (*c* 1.0, H_2O), lit.[20e] for *ent*-**31** $[\alpha]_D^{26}$ + 74.4 (*c* 0.95, H_2O), lit.[21] for *ent*-**31** $[\alpha]_D$ + 69 (*c* 0.5, H_2O); δ_H (500 MHz, D_2O) 1.65−1.71 (1H, m, C(5)H_A), 1.77−1.82 (1H, m, C(5)H_B), 2.73−2.83 (2H, m, C(6)H_2), 2.85 (1H, ddd, *J* = 10.1, 6.6, 3.2 Hz, C(2)*H*), 3.44 (1H, dd, *J* = 10.1, 2.8 Hz, C(3)*H*), 3.58 (1H, dd, *J* = 11.7, 6.6 Hz, C(2)C$H_A$$H_B$), 3.77 (1H, dd, *J* = 11.7, 3.2 Hz, C(2)$H_A$$H_B$), 4.03 (1H, q, *J* = 2.8 Hz, C(4)*H*).

(2*R*,2′*R*,3′*S*,4′*R*,*αR*)-2-Hydroxy-2-[*N*(1′)-(*α*-methylbenzyl)-3′,4′-dihydroxypiperidin-2′-yl]ethanoic Acid 33. A solution of **22** (60 mg, 0.17 mmol, >99:1 dr) in 1.0 M aq HCl (1.5 mL) was stirred at rt for 12 h and then concentrated in vacuo. Purification via ion exchange chromatography (Dowex 50WX8−200, eluent 1.0 M aq NH_4OH) gave **33** as a colorless oil (30 mg, 60%, >99:1 dr): $[\alpha]_D^{20}$ − 5.8 (*c* 0.5, H_2O); ν_{max} (ATR) 3351 (O—H), 1611 (C═O); δ_H (500 MHz, D_2O), 1.65 (3H, d, *J* = 6.6 Hz, C(*α*)*Me*), 1.76−1.78 (1H, m, C(5′)H_A), 2.06 (1H, app dtd, *J* = 14.0, 10.4, 3.8 Hz, C(5′)H_B), 2.93−2.95 (1H, m, C(6′)H_A), 3.30−3.31 (1H, m, C(6′)H_B), 3.76−3.77 (1H, m, C(2′)*H*), 4.08−4.19 (2H, m, C(3′)*H*, C(4′)*H*), 4.48 (1H, d, *J* = 6.9 Hz, C(2)*H*), 4.92−4.93 (1H, m, C(*α*)*H*), 7.43−7.50 (5H, m, *Ph*); δ_C (125 MHz, D_2O) 18.4 (C(*α*)*Me*), 23.3 (C(5′)), 42.9 (C(6′)), 61.8 (C(*α*)), 63.0 (*C*(2′)), 64.7 (*C*(4′)), 66.9 (*C*(3′)), 67.0 (*C*(2)), 127.9, 129.5, 129.9 (*o*,*m*,*p*-*Ph*), 136.7 (*i*-*Ph*), 177.6 (*C*(1)); *m*/*z* (ESI$^+$) 296 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{15}H_{21}NNaO_5^+$ ([M + Na]$^+$) requires 318.1312, found 318.1307.

***tert*-Butyl (2*R*,2′*R*,3′*S*,4′*R*)-2-Hydroxy-2-(3′,4′-dihydroxypiperidin-2′-yl)ethanoate 34.** $Pd(OH)_2$/C (50% w/w of substrate, 35 mg) was added to a stirred solution of **22** (70 mg, 0.20 mmol, >99:1 dr) in degassed MeOH (1.5 mL). The resultant suspension was placed under H_2 (1 atm) and stirred vigorously at rt for 12 h. The reaction mixture was then filtered through a short plug of Celite (eluent MeOH) and concentrated in vacuo to give **34** as a colorless oil (49 mg, quant, >99:1 dr): $[\alpha]_D^{20}$ − 18.2 (*c* 0.5, MeOH); ν_{max} (ATR) 3346 (O—H, N—H), 2978 (C—H), 1728 (C═O); δ_H (500 MHz, MeOH-d_4) 1.59 (9H, s, C*Me*$_3$), 1.83−1.89 (1H, m, C(5′)H_A), 1.94−1.97 (1H, m, C(5′)H_B), 3.02−3.09 (1H, m, C(6′)H_A), 3.25 (1H, app td, *J* = 12.8, 3.2 Hz, C(6′)H_B), 3.70 (1H, dd, *J* = 10.2, 1.1 Hz, C(2′)*H*), 3.85 (1H, dd, *J* = 10.2, 2.5 Hz, C(3′)*H*), 4.02−4.04 (1H, m, C(4′)*H*), 4.26−4.27 (1H, m, C(2)*H*); δ_C (125 MHz, MeOH-d_4) 28.4

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(CMe_3), 29.9 (C(5′)), 40.2 (C(6′)), 58.4 (C(2′)), 67.6 (C(3′)), 67.9 (C(4′)), 70.4 (C(2)), 83.6 (CMe_3), 171.8 (C(1)); *m*/*z* (ESI^+) 248 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{11}H_{22}NO_5^+$ ($[M + H]^+$) requires 248.1492, found 248.1496.

(2*R*,2′*R*,3′*S*,4′*R*)-2-Hydroxy-2-(3′,4′-dihydroxypiperidin-2′-yl)ethanoic Acid 35. A solution of **34** (30 mg, 0.12 mmol, >99:1 dr) in 1.0 M aq HCl (1.5 mL) was stirred at rt for 12 h and then concentrated in vacuo. Purification via ion exchange chromatography (Dowex 50WX8−200, eluent 1.0 M aq NH_4OH) gave **35** as a white solid (19 mg, 80%, >99:1 dr): mp 150−145 °C; $[\alpha]_D^{20}$ − 46.4 (*c* 0.5, H_2O); ν_{max} (ATR) 3317 (O—H), 2944 (C—H), 1415 (zwitterionic *β*-amino acid); δ_H (500 MHz, D_2O) 1.87−1.94 (1H, m, C(5′)H_A), 1.96−2.02 (1H, m, C(5′)H_B), 3.21−3.24 (2H, m, C(6′)H_2), 3.67 (1H, dd, *J* = 10.1, 2.8 Hz, C(2′)*H*), 3.95 (1H, dd, *J* = 10.1, 2.8 Hz, C(3′)*H*), 4.09−4.11 (1H, m, C(4′)*H*), 4.19 (1H, d, *J* = 2.8 Hz, C(2)*H*); δ_C (125 MHz, D_2O) 26.9 (C(5′)), 38.6 (C(6′)), 57.2 (C(2′)), 65.9 (C(4′)), 66.0 (C(3′)), 69.6 (C(2)), 176.4 (C(1)); *m*/*z* (ESI^+) 192 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_7H_{14}NO_5^+$ ($[M + H]^+$) requires 192.0866, found 192.0869.

(3*S*,4*R*,5*R*,*αR*)-5-Hydroxy-3,7-*N*-(α-methylbenzyl)imino-4-heptanolactone 36. *Method A (from **14**).* HBF_4 (48% aq, 217 μL, 1.66 mmol) was added to a stirred solution of **14** (100 mg, 0.33 mmol, >99:1 dr) in CH_2Cl_2 (1 mL) at rt, and the resultant mixture was stirred at rt for 5 min. *m*-CPBA (75%, 305 mg, 1.33 mmol) was then added, and the resultant mixture was stirred at rt for 48 h. A mixture of $CHCl_3$/^{i}PrOH (3:1, 10 mL) was then added, and the organic layer was washed with saturated aq Na_2SO_3 (5 mL) until starch iodide paper indicated no remaining oxidant. The organic layer was then washed with saturated aq $NaHCO_3$ (5 mL), and the combined aqueous washings were extracted with $CHCl_3$/^{i}PrOH (3:1, 3 × 10 mL). The combined organic extracts were then dried and concentrated in vacuo. Purification via flash column chromatography (eluent $CHCl_3$/^{i}PrOH, 95:5) gave **36** as a yellow oil (36 mg, 41%, >99:1 dr): $[\alpha]_D^{20}$ + 39.9 (*c* 1.0, $CHCl_3$); ν_{max} (ATR) 3407 (O—H), 1773 (C═O); δ_H (400 MHz, $CDCl_3$) 1.41 (3H, d, *J* = 6.7 Hz, C(α)*Me*), 1.69 (1H, app dtd, *J* = 13.6, 9.7, 4.8 Hz, C(6)H_A), 1.99 (1H, app ddd, *J* = 13.6, 8.3, 5.0 Hz, C(6)H_B), 2.25 (1H, dd, *J* = 17.0, 7.4 Hz, C(2)H_A), 2.47−2.53 (1H, m, C(7)H_A), 2.58 (1H, dd, *J* = 17.0, 9.6 Hz, C(2)H_B), 2.96 (1H, app dd, *J* = 12.1, 4.8 Hz, C(7)H_B), 3.61 (1H, q, *J* = 6.7 Hz, C(α)*H*), 3.69 (1H, app dt, *J* = 9.6, 7.4 Hz, C(3)*H*), 3.77 (1H, ddd, *J* = 9.7, 7.0, 4.8 Hz, C(5)*H*), 4.25 (1H, app t, *J* = 7.0 Hz, C(4)*H*), 7.16−7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.8 (C(α)*Me*), 27.7 (C(2)), 29.6 (C(6)), 39.7 (C(7)), 56.0 (C(3)), 61.2 (C(α)), 69.4 (C(5)), 82.0 (C(4)), 127.1, 127.5, 128.7 (*o*,*m*,*p*-*Ph*), 142.7 (*i*-*Ph*), 175.3 (C(1)); *m*/*z* (ESI^+) 262 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{15}H_{19}NNaO_3^+$ ($[M + Na]^+$) requires 284.1257, found 284.1249.

*Method B (from **16**).* HBF_4 (48% aq, 251 μL, 1.93 mmol) was added to a stirred solution of **16** (100 mg, 0.39 mmol, >99:1 dr) in CH_2Cl_2 (1 mL) at rt, and the resultant solution was stirred at rt for 5 min. *m*-CPBA (75%, 355 mg, 1.54 mmol) was then added, and the resultant mixture was stirred at rt for 48 h. A mixture of $CHCl_3$/^{i}PrOH (3:1, 5 mL) was then added, and the organic layer was washed with saturated aq Na_2SO_3 (5 mL) until starch iodide paper indicated no remaining oxidant. The organic layer was then washed with saturated aq $NaHCO_3$ (5 mL), and the combined aqueous layers were extracted with $CHCl_3$/^{i}PrOH (3:1, 3 × 10 mL). The combined organic extracts were then dried and concentrated in vacuo. Purification via flash column chromatography (eluent $CHCl_3$/^{i}PrOH, 95:5) gave lactone **36** as a yellow oil (32 mg, 32%, >99:1 dr), which displayed characterization data consistent with those described above.

*Method C (from **37**).* HBF_4 (48% aq, 68 μL, 0.52 mmol) was added to a stirred solution of **37** (35 mg, 0.10 mmol, >99:1 dr) in CH_2Cl_2 (0.5 mL) at rt, and the resultant mixture was stirred at rt for 48 h. A mixture of $CHCl_3$/^{i}PrOH (3:1, 5 mL) was then added, and the organic layer was washed with saturated aq $NaHCO_3$ (1 mL), dried, and concentrated in vacuo. Purification via flash column chromatography (eluent $CHCl_3$/^{i}PrOH, 95:5) gave **36** as a yellow oil (11 mg, 41%, >99:1 dr), which displayed characterization data consistent with those described above.

*Method D (from **41**).* HBF_4 (48% aq, 72 μL, 0.52 mmol) was added to a stirred solution of **41** (35 mg, 0.11 mmol, >99:1 dr) in CH_2Cl_2 (0.5 mL) at rt, and the resultant mixture was stirred at rt for 48 h. A mixture of $CHCl_3$/^{i}PrOH (3:1, 2 mL) was then added, and the organic layer was washed with saturated aq $NaHCO_3$ (1 mL), dried, and concentrated in vacuo. Purification via flash column chromatography (eluent $CHCl_3$/^{i}PrOH, 95:5) gave **36** as a yellow oil (14 mg, 48%, >99:1 dr), which displayed characterization data consistent with those described above.

*Method E (from **44**).* HBF_4 (48% aq, 47 μL, 0.36 mmol) was added to a stirred solution of **44** (20 mg, 0.07 mmol, >99:1 dr) in CH_2Cl_2 (0.2 mL) at rt, and the resultant solution was stirred at rt for 48 h. A mixture of $CHCl_3$/^{i}PrOH (3:1, 2 mL) was then added, and the organic layer was washed with saturated aq $NaHCO_3$ (1 mL), dried, and concentrated in vacuo. Purification via flash column chromatography (eluent $CHCl_3$/^{i}PrOH, 95:5) gave **36** as a yellow oil (9 mg, 50%, >99:1 dr), which displayed characterization data consistent with those described above.

***tert*-Butyl (2′*S*,3′*R*,4′*R*,*αR*)-2-[*N*(1′)-(α-Methylbenzyl)-3′,4′-dihydroxypiperidin-2′-yl]ethanoate 37 and *tert*-Butyl (2′*S*,3′*S*,4′*S*,*αR*)-2-[*N*(1′)-(α-Methylbenzyl)-3′,4′-dihydroxypiperidin-2′-yl]ethanoate 38.** CCl_3CO_2H (542 mg, 3.32 mmol) was added to a stirred solution of **14** (200 mg, 0.66 mmol, >99:1 dr) in CH_2Cl_2 (2 mL) at rt, and the resultant mixture was stirred at rt for 5 min. *m*-CPBA (75%, 611 mg, 2.65 mmol) was then added, and the resultant mixture was stirred at rt for 48 h. A mixture of $CHCl_3$/^{i}PrOH (3:1, 5 mL) was then added, and the organic layer was washed with saturated aq Na_2SO_3 (5 mL) until starch iodide paper indicated no remaining oxidant. The organic layer was washed with saturated aq $NaHCO_3$ (5 mL), and the combined aqueous layers were extracted with $CHCl_3$/^{i}PrOH (3:1, 3 × 10 mL). The combined organic extracts were then dried and concentrated in vacuo to give a 34:56:10 mixture of **36**, **37**, and **38**, respectively. Purification via flash column chromatography (eluent $CHCl_3$/^{i}PrOH, 95:5) gave **36** as a colorless oil (21 mg, 12%, >99:1 dr). Further elution gave **37** as a yellow solid (33 mg, 15%, >99:1 dr): mp 96−97 °C; $[\alpha]_D^{20}$ − 15.3 (*c* 1.0, $CHCl_3$); ν_{max} (ATR) 3397 (O—H), 1726 (C═O); δ_H (400 MHz, $CDCl_3$) 1.35 (3H, d, *J* = 6.6 Hz, C(α)*Me*), 1.41 (9H, s, CMe_3), 1.57−1.68 (1H, m, C(5′)H_A), 1.84−1.89 (1H, m, C(5′)H_B), 2.42−2.53 (3H, m, C(2)H_2, C(6′)H_A), 2.83−2.88 (1H, m, C(6′)H_B), 3.54−3.68 (3H, m, C(2′)*H*, C(3′)*H*, C(4′)*H*), 3.97 (1H, q, *J* = 6.6 Hz, C(α)*H*), 7.20−7.30 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 22.1 (C(α)*Me*), 28.0 (CMe_3), 30.2 (C(2)), 31.1 (C(5′)), 41.0 (C(6′)), 56.2 (C(2′)), 59.4 (C(α)), 70.2 (C(4′)), 74.2 (C(3′)), 80.9 (CMe_3), 127.0, 127.9, 128.4 (*o*,*m*,*p*-*Ph*), 145.4 (*i*-*Ph*), 173.4 (C(1)); *m*/*z* (ESI^+) 336 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{19}H_{30}NO_4^+$ ($[M + H]^+$) requires 336.2169, found 336.2167. Further elution gave **38** as a colorless oil (16 mg, 7%, >99:1 dr): $[\alpha]_D^{20}$ + 13.7 (*c* 0.5, $CHCl_3$); ν_{max} (ATR) 3345 (O—H), 1725 (C═O); δ_H (500 MHz, $CDCl_3$) 1.45 (9H, s, CMe_3), 1.57 (3H, d, *J* = 6.9 Hz, C(α)*Me*), 1.67−1.74 (1H, m, C(5′)H_A), 2.02−2.06 (1H, m, C(5′)H_B), 2.21−2.26 (1H, m, C(6′)H_A), 2.86−2.88 (1H, m, C(2′)*H*), 2.95 (2H, app d, *J* = 5.7 Hz, C(2)H_2), 3.04−3.08 (1H, m, C(6′)H_B), 3.44−3.48 (1H, m, C(4′)*H*), 3.65 (1H, t, *J* = 7.1 Hz, C(3′)*H*), 4.38 (1H, q, *J* = 6.9 Hz, C(α)*H*), 4.80 (2H, br s, 2 × O*H*), 7.22−7.38 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 19.6 (C(α)*Me*), 28.1 (CMe_3), 30.4 (C(5′)), 34.2 (C(2)), 41.8 (C(6′)), 56.8 (C(α)), 59.9 (C(2′)), 72.0 (C(4′)), 74.9 (C(3′)), 81.1 (CMe_3), 127.1, 127.9, 128.9 (*o*,*m*,*p*-*Ph*), 140.5 (*i*-*Ph*), 172.3 (C(1)); *m*/*z* (ESI^+) 336 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{19}H_{30}NO_4^+$ ($[M + H]^+$) requires 336.2169, found 336.2169.

(3*S*,4*S*,5*S*,*αR*)-4-Hydroxy-3,7-*N*-(α-methylbenzyl)imino-5-heptanolactone 39 and (3*S*,4*S*,5*S*,*αR*)-5-Hydroxy-3,7-*N*-(α-methylbenzyl)imino-4-heptanolactone 40. HBF_4 (48% aq, 48 μL, 0.45 mmol) was added to a stirred solution of **38** (30 mg, 0.09 mmol, >99:1 dr) in CH_2Cl_2 (0.4 mL) at rt, and the resultant mixture was stirred at rt for 48 h. $CHCl_3$/^{i}PrOH (3:1, 1 mL) was then added, and the organic layer was washed with saturated aq $NaHCO_3$ (1 mL), dried, and concentrated in vacuo to give a 70:30 mixture of **39** and **40**, respectively. Purification via flash column chromatography (eluent $CHCl_3$/^{i}PrOH, 95:5) gave **39** as a white solid (16 mg, 70%, >99:1 dr):

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mp 97–98 °C; $[\alpha]_D^{20}$ + 59.3 (*c* 1.0, $CHCl_3$); ν_{max} (ATR) 3505 (O—H), 1739 (C═O); δ_H (500 MHz, $CDCl_3$) 1.34 (3H, d, *J* = 6.6 Hz, C(*α*)*Me*), 1.99 (1H, app d, *J* = 14.8 Hz, C(6)H_A), 2.25–2.34 (2H, m, C(6)H_B, C(7)H_A), 2.52 (1H, app td, *J* = 12.8, 3.2 Hz, C(2)H_A), 2.84 (1H, d, *J* = 19.2 Hz, C(7)H_B), 3.08–3.13 (2H, m, C(2)H_B, C(4)*H*), 3.26 (1H, d, *J* = 9.8 Hz, O*H*), 3.63 (1H, q, *J* = 6.6 Hz, C(*α*)*H*), 3.81–3.86 (1H, m, C(3)*H*), 4.50 (1H, d, *J* = 2.2 Hz, C(5)*H*), 7.24–7.51 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 21.4 (C(*α*)*Me*), 26.4 (*C*(6)), 27.6 (*C*(7)), 38.7 (*C*(2)), 52.0 (*C*(4)), 61.1 (*C*(*α*)), 63.6 (*C*(3)), 74.7 (*C*(5)), 127.0, 127.8, 129.0 (*o,m,p-Ph*), 143.2 (*i-Ph*), 169.6 (*C*(1)); *m*/*z* (ESI^+) 262 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{15}H_{20}NO_3^+$ ($[M + H]^+$) requires 262.1438, found 262.1440. Further elution gave **40** as a colorless oil (6 mg, 29%, >99:1 dr): $[\alpha]_D^{20}$ + 79.8 (*c* 0.5, $CHCl_3$); ν_{max} (ATR) 3407 (O—H), 1785 (C═O); δ_H (500 MHz, $CDCl_3$) 1.48 (3H, d, *J* = 6.6 Hz, C(*α*)*Me*), 1.64–1.71 (1H, m, C(6)H_A), 2.06–2.21 (3H, m, C(6)H_B, C(7)H_A, O*H*), 2.34–2.39 (1H, m, C(3)*H*), 2.45–2.51 (1H, m, C(2)H_A), 2.75 (1H, dd, *J* = 15.4, 5.7 Hz, C(2)H_B), 3.06 (1H, app d, *J* = 10.1 Hz, C(7)H_B), 3.66–3.71 (1H, m, C(5)*H*), 3.80–3.87 (2H, m, C(4)*H*, C(*α*)*H*), 7.21–7.40 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 17.0 (C(*α*)*Me*), 31.9 (*C*(6)), 36.2 (*C*(2)), 46.2 (*C*(7)), 60.1 (*C*(*α*)), 61.3 (*C*(3)), 70.1 (*C*(5)), 87.2 (*C*(4)), 127.6, 128.0, 128.2 (*o,m,p-Ph*), 138.6 (*i-Ph*), 173.7 (*C*(1)); *m*/*z* (ESI^+) 262 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{15}H_{19}NNaO_3^+$ ($[M + Na]^+$) requires 284.1257, found 284.1260.

***tert*-Butyl (2′*S*,3′*R*,4′*S*,*αR*)-2-[*N*(1′)-(*α*-Methylbenzyl)-3′,4′-epoxypiperidin-2′-yl]ethanoate 41.** $(CF_3CO)_2O$ (0.18 mL, 1.33 mmol) was added to a stirred solution of UHP (468 mg, 4.97 mmol) and CH_2Cl_2 (1.5 mL) at 0 °C, and the resultant mixture was stirred at 0 °C for 30 min. A solution of **14** (100 mg, 0.33 mmol, >99:1 dr) and CF_3CO_2H (62 μL, 0.83 mmol) in CH_2Cl_2 (1.5 mL) was added, and the resultant mixture was stirred at rt for 16 h. Saturated aq Na_2SO_3 (2 mL) was then added until starch iodide paper indicated no remaining oxidant. CH_2Cl_2 (5 mL) was then added, and the organic layer was washed with 2.0 M aq NaOH (2 × 5 mL). The combined aqueous layers were extracted with CH_2Cl_2 (2 × 10 mL); then, the combined organic extracts were dried and concentrated in vacuo to give a 29:26:45 mixture of **36**, **41**, and **37**, respectively. Purification via flash column chromatography (eluent $CHCl_3$/^{i}PrOH, 95:5) gave **37** as a yellow oil (20 mg, 18%, >99:1 dr). Further elution gave **36** as a yellow oil (6 mg, 7%, >99:1 dr). Then, further elution gave **41** as a colorless oil (15 mg, 14%, >99:1 dr): $[\alpha]_D^{20}$ + 2.8 (*c* 0.5, $CHCl_3$); ν_{max} (ATR) 2979 (C—H), 1718 (C═O); δ_H (500 MHz, $CDCl_3$) 1.36 (3H, d, *J* = 6.5 Hz, C(*α*)*Me*), 1.48 (9H, s, CMe_3), 1.55–1.58 (1H, m, C(5′)H_A), 1.87–1.94 (1H, m, C(5′)H_B), 2.30–2.34 (1H, m, C(6′)H_A), 2.51–2.65 (3H, m, C(2)H_2, C(6′)H_B), 3.26 (1H, app t, *J* = 4.4 Hz, C(3′)*H*), 3.33–3.34 (1H, m, C(4′)*H*), 3.77–3.84 (2H, m, C(2′)*H*, C(*α*)*H*), 7.21–7.27 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 20.8 (*C*(5′)), 22.5 (C(*α*)*Me*), 28.1 (CMe_3), 35.5 (*C*(6′)), 36.3 (*C*(2)), 49.6 (*C*(2′)), 51.9 (*C*(4′)), 52.5 (*C*(3′)), 58.2 (*C*(*α*)), 80.2 (CMe_3), 126.9 (*p-Ph*), 127.1, 128.3 (*o,m-Ph*), 144.8 (*i-Ph*), 171.5 (*C*(1)); *m*/*z* (ESI^+) 318 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{19}H_{28}NO_3^+$ ($[M + H]^+$) requires 318.2064, found 318.2063.

(3*S*,4*R*,5*R*,*αR*)-5-(*p*-Toluenesulfonyloxy)-3,7-*N*-(*α*-methylbenzyl)imino-4-heptanolactone 42. *Method A (from **14**).* $TsOH·H_2O$ (315 mg, 1.66 mmol) was added to a stirred solution of **14** (100 mg, 0.33 mmol) in CH_2Cl_2 (1 mL) at rt, and the resultant mixture was stirred at rt for 5 min. *m*-CPBA (75%, 305 mg, 1.33 mmol) was then added, and the reaction mixture was stirred at rt for 48 h. A mixture of $CHCl_3$/^{i}PrOH (3:1, 2 mL) was then added, and the organic layer was washed with saturated aq Na_2SO_3 (5 mL) until starch iodide paper indicated no remaining oxidant. The organic layer was washed with saturated aq $NaHCO_3$ (5 mL), and the combined aqueous layers were extracted with $CHCl_3$/^{i}PrOH (3:1, 3 × 10 mL). The combined organic extracts were then dried and concentrated in vacuo to give a 56:44 mixture of **36** and **42**, respectively. Purification via flash column chromatography (eluent $CHCl_3$/^{i}PrOH, 95:5) gave **42** as a yellow oil (51 mg, 37%, >99:1 dr): $[\alpha]_D^{20}$ + 8.3 (*c* 1.0, $CHCl_3$); ν_{max} (ATR) 1785 (C═O); δ_H (400 MHz, $CDCl_3$) 1.39 (3H, d, *J* = 6.8 Hz, C(*α*)*Me*), 1.76–1.85 (1H, m, C(6)H_A), 2.11–2.19 (1H, m, C(6)H_B), 2.30 (1H, dd, *J* = 16.9, 6.4 Hz, C(2)H_A), 2.45 (3H, s, Ar*Me*), 2.55–2.64 (2H, m, C(2)H_B, C(7)H_A), 2.68–2.72 (1H, m, C(7)H_B), 3.52 (1H, app q, *J* = 6.4 Hz, C(3)*H*), 3.70 (1H, q, *J* = 6.8 Hz, C(*α*)*H*), 4.24 (1H, app t, *J* = 6.0 Hz, C(4)*H*), 4.51 (1H, ddd, *J* = 8.2, 6.0, 4.4 Hz, C(5)*H*), 7.20–7.77 (9H, m, *Ph*, *Ar*); δ_C (100 MHz, $CDCl_3$) 20.1 (C(*α*)*Me*), 21.7 (Ar*Me*), 28.8 (*C*(6)), 30.0 (*C*(2)), 38.8 (*C*(7)), 56.1 (*C*(3)), 60.0 (*C*(*α*)), 77.5 (*C*(5)), 77.8 (*C*(4)), 127.4, 127.7, 127.9, 128.6, 129.8 (*Ar*, *o,m,p-Ph*), 133.2, 140.9 (*Ar*, *i-Ph*), 145.1 (*C*Me), 174.0 (*C*(1)); *m*/*z* (ESI^+) 438 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{22}H_{25}NNaO_5S^+$ ($[M + Na]^+$) requires 438.1346, found 438.1344. Further elution gave **36** as yellow oil (20 mg, 23%, >99:1 dr).

*Method B (from **36**).* TsCl (82 mg, 0.43 mmol) was added to a stirred solution of **36** (70 mg, 0.27 mmol, >99:1 dr) and pyridine (43 μL, 0.54 mmol) in CH_2Cl_2 (5 mL) at rt, and the resultant mixture was stirred at rt for 12 h. The reaction mixture was then washed with saturated aq $CuSO_4$ (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic extracts were washed with saturated aq $NaHCO_3$ (15 mL), dried, and concentrated in vacuo. Purification via flash column chromatography (eluent $CHCl_3$/^{i}PrOH, 95:5) gave **42** as a yellow oil (54 mg, 49%, >99:1 dr), which displayed characterization data consistent with those described above.

(3*S*,4*R*,5*R*,*αR*)-5-(Methanesulfonyloxy)-3,7-*N*-(*α*-methylbenzyl)imino-4-heptanolactone 43. MsCl (47 μL, 61 mmol) was added dropwise to a stirred solution of **36** (100 mg, 0.38 mmol, >99:1 dr) and Et_3N (107 μL, 0.77 mmol) in CH_2Cl_2 (1.6 mL) at 0 °C. The resultant mixture was stirred at rt for 1 h, and then washed with saturated aq $CuSO_4$ (3 × 2 mL), dried, and concentrated in vacuo. Purification via flash column chromatography (eluent CH_2Cl_2) gave **43** as a yellow oil (99 mg, 77%, >99:1 dr): $[\alpha]_D^{20}$ + 55.2 (*c* 0.5, $CHCl_3$); ν_{max} (ATR) 1784 (C═O); δ_H (500 MHz, $CDCl_3$) 1.41 (3H, d, *J* = 6.6 Hz, C(*α*)*Me*), 1.87–1.94 (1H, m, C(6)H_A), 2.24 (1H, app dtd, *J* = 13.0, 5.1, 2.5 Hz, C(6)H_B), 2.30 (1H, dd, *J* = 16.9, 7.1 Hz, C(2)H_A), 2.54–2.64 (2H, m, C(2)H_B, C(7)H_A), 2.97 (1H, app dt, *J* = 12.3, 4.2 Hz, C(7)H_B), 3.08 (3H, s, SO_2Me), 3.64 (1H, q, *J* = 6.6 Hz, C(*α*)*H*), 3.72–3.77 (1H, m, C(3)*H*), 4.39 (1H, app t, *J* = 7.1 Hz, C(4)*H*), 4.59 (1H, ddd, *J* = 10.7, 7.1, 5.1 Hz, C(5)*H*), 7.27–7.41 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 20.8 (C(*α*)*Me*), 27.4 (*C*(2)), 29.9 (*C*(6)), 38.6 (SO_2Me), 39.5 (*C*(7)), 56.6 (*C*(3)), 61.1 (*C*(*α*)), 78.2 (*C*(4)), 80.1 (*C*(5)), 127.0, 128.8, 129.7 (*o,m,p-Ph*), 142.2 (*i-Ph*), 174.0 (*C*(1)); *m*/*z* (ESI^+) 340 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{16}H_{21}NNaO_5S^+$ ($[M + Na]^+$) requires 362.1033, found 362.1041.

Methyl (2′*S*,3′*R*,4′*S*,*αR*)-2-[*N*(1′)-(*α*-Methylbenzyl)-3′,4′-epoxypiperidin-2′-yl]ethanoate 44. *Method A (from **16**).* $(CF_3CO)_2O$ (0.21 mL, 1.54 mmol) was added to a stirred solution of UHP (543 mg, 5.78 mmol) and CH_2Cl_2 (1.5 mL) at 0 °C, and the resultant mixture was stirred at 0 °C for 30 min. A solution of **16** (100 mg, 0.39 mmol, >99:1 dr) and CF_3CO_2H (72 μL, 0.96 mmol) in CH_2Cl_2 (1.5 mL) was then added, and the resultant mixture was stirred at rt for 16 h. Saturated aq Na_2SO_3 (2 mL) was then added until starch iodide paper indicated no remaining oxidant. CH_2Cl_2 (5 mL) was added, and the organic layer was washed with 2.0 M aq NaOH (2 × 5 mL). The combined aqueous layers were then extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic extracts were dried and concentrated in vacuo to give a 63:37 mixture of **36** and **44**, respectively. Purification via flash column chromatography (eluent $CHCl_3$/^{i}PrOH, 95:5) gave **36** as a yellow oil (30 mg, 34%, >99:1 dr). Further elution gave **44** as a yellow oil (14 mg, 13%, >99:1 dr): $[\alpha]_D^{20}$ + 6.5 (*c* 1.0, $CHCl_3$); ν_{max} (ATR) 2976 (C—H), 1734 (C═O); δ_H (400 MHz, $CDCl_3$) 1.34 (3H, d, *J* = 6.6 Hz, C(*α*)*Me*), 1.56 (1H, dt, *J* = 15.0, 1.7 Hz, C(5′)H_A), 1.88–1.96 (1H, m, C(5′)H_B), 2.31–2.56 (1H, m, C(6′)H_A), 2.52–2.56 (1H, m, C(6′)H_B), 2.70 (2H, app d, *J* = 7.3 Hz, C(2)H_2), 3.26–3.28 (1H, m, C(3′)*H*), 3.33–3.36 (1H, m, C(4′)*H*), 3.71 (3H, s, O*Me*), 3.79 (1H, q, *J* = 6.6 Hz, C(*α*)*H*), 3.88 (1H, app q, *J* = 6.1 Hz, C(2′)*H*), 7.21–7.50 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.6 (*C*(5′)), 22.4 (C(*α*)*Me*), 34.3 (*C*(2)), 36.3 (*C*(6′)), 49.4 (*C*(2′)), 51.5 (O*Me*), 52.0 (*C*(3′)), 52.3 (*C*(4′)), 58.4 (*C*(*α*)), 127.0, 127.1, 128.4 (*o,m,p-Ph*), 144.9 (*i-Ph*), 172.7 (*C*(1)); *m*/*z* (ESI^+) 276 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{16}H_{22}NO_3^+$ ($[M + H]^+$) requires 276.1594, found 276.1592.

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*Method B (from **43**).* K_2CO_3 (200 mg, 1.47 mmol) was added to a stirred solution of **43** (90 mg, 0.29 mmol, >99:1 dr) in MeOH (1 mL). The resultant mixture was stirred at rt for 16 h and then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (2 mL) and H_2O (2 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic extracts were then dried and concentrated in vacuo. Purification via flash column chromatography (eluent $CHCl_3$/^{i}PrOH, 95:5) gave **44** as a yellow oil (26 mg, 36%, >99:1 dr), which displayed characterization data consistent with those described above.

(2′*S*,3′*R*,4′*R*)-2-(3′,4′-Dihydroxypiperidin-2′-yl)ethanoic Acid 46. $Pd(OH)_2$/C (50% w/w of substrate, 8 mg) was added to a stirred solution of **36** (15 mg, 54 μmol, >99:1 dr) in degassed EtOAc (0.2 mL). The resultant suspension was placed under H_2 (5 atm) and stirred vigorously at rt for 48 h. The reaction mixture was then filtered through a short plug of Celite (eluent EtOAc) and concentrated in vacuo to give **45** as a yellow oil (9 mg, quant, >99:1 dr). The residue was dissolved in H_2O (0.5 mL), and the resultant solution was allowed to stand at rt for two days before being concentrated in vacuo to give **46** as a white solid (9 mg, quant, >99:1 dr): mp 219−224 °C dec; $[\alpha]_D^{20}$ + 3.8 (*c* 0.5, H_2O); ν_{max} (ATR) 3313 (O—H), 2943 (C—H), 1583 (zwitterionic *β*-amino acid); δ_H (500 MHz, D_2O) 1.78 (1H, app dd, *J* = 15.3, 3.2 Hz, C(5′)H_A), 2.13 (1H, dddd, *J* = 15.3, 12.7, 5.7, 3.0 Hz, C(5′)H_B), 2.48−2.59 (2H, m, C(2)H_2), 3.20−3.33 (2H, m, C(6′)H_2), 3.71−3.73 (1H, m, C(2′)*H*), 3.80 (1H, app d, *J* = 3.9 Hz, C(3′)*H*), 4.00 (1H, app q, *J* = 3.0 Hz, C(4′)*H*); δ_C (125 MHz, D_2O) 23.5 (*C*(5′)), 38.4 (*C*(2)), 39.0 (*C*(6′)), 52.6 (*C*(2′)), 65.1 (*C*(4′)), 67.4 (*C*(3′)), 177.4 (*C*(1)); *m*/*z* (ESI$^+$) 176 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_7H_{13}NNaO_4^+$ ([M + Na]$^+$) requires 198.0737, found 198.0740.

(2*R*,3*S*,4*R*,5*R*,α*R*)-2,5-Dihydroxy-3,7-*N*-(α-methylbenzyl)-imino-4-heptanolactone 47 and (*R*,*R*,*R*,*R*)-2-Hydroxy-2-[*N*(1′)-(α-methylbenzyl)-3′,4′-dihydroxypiperidin-2′-yl]-ethanoic Acid 50. *Method A (from **15**).* HBF_4 (48% aq, 0.32 mL, 2.45 mmol) was added to a stirred solution of **15** (136 mg, 0.49 mmol, >99:1 dr) in CH_2Cl_2 (1.4 mL) at rt, and the resultant mixture was stirred at rt for 5 min. *m*-CPBA (75%, 451 mg, 1.96 mmol) was then added, and the resultant mixture was stirred at rt for 48 h. A mixture of $CHCl_3$/^{i}PrOH (3:1, 5 mL) was then added, and the organic layer was washed with saturated aq Na_2SO_3 (5 mL) until starch iodide paper indicated no remaining oxidant. The organic layer was then washed with saturated aq $NaHCO_3$ (5 mL), and the combined aqueous washings were extracted with $CHCl_3$/^{i}PrOH (3:1, 3 × 10 mL). The combined organic extracts were then dried and concentrated in vacuo. Purification via flash column chromatography (eluent $CHCl_3$/^{i}PrOH, 95:5) gave **47** as a white solid (56 mg, 47%, >99:1 dr): mp 235−241 °C dec; $[\alpha]_D^{20}$ + 42.0 (*c* 1.0, $CHCl_3$); ν_{max} (ATR) 3505 (O—H), 1763 (C═O); δ_H (400 MHz, $CDCl_3$) 1.42 (3H, d, *J* = 6.6 Hz, C(α)*Me*), 1.58 (1H, app dtd, *J* = 13.2, 9.4, 3.6 Hz, C(6)H_A), 1.88−1.93 (1H, m, C(6)H_B), 2.73 (1H, ddd, *J* = 11.1, 6.7, 3.6 Hz, C(7)H_A), 3.06 (1H, ddd, *J* = 11.1, 9.4, 2.8 Hz, C(7)H_B), 3.36 (1H, app t, *J* = 5.5 Hz, C(3)*H*), 3.96 (1H, ddd, *J* = 9.4, 6.7, 4.3 Hz, C(5)*H*), 4.15 (1H, app t, *J* = 6.7 Hz, C(4)*H*), 4.27 (1H, d, *J* = 5.5 Hz, C(2)*H*), 4.40 (1H, q, *J* = 6.6 Hz, C(α)*H*), 7.16−7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.2 (C(α)*Me*), 31.6 (*C*(6)), 42.6 (*C*(7)), 59.4 (*C*(3)), 61.1 (*C*(α)), 69.8 (*C*(5)), 72.2 (*C*(2)), 82.8 (*C*(4)), 128.4, 129.0, 129.5 (*o*,*m*,*p*-*Ph*), 144.3 (*i*-*Ph*), 178.2 (*C*(1)); *m*/*z* (ESI$^+$) 278 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{15}H_{19}NNaO_4^+$ ([M + Na]$^+$) requires 300.1206, found 300.1198. Further elution gave **50** as colorless oil (25 mg, 20%, >99:1 dr): $[\alpha]_D^{20}$ − 18.9 (*c* 1.0, $CHCl_3$); ν_{max} (ATR) 3351 (O—H), 1611 (C═O); δ_H (400 MHz, MeOH-d_4) 1.65 (1H, app dd, *J* = 14.5, 3.1 Hz, C(5′)H_A), 1.80 (3H, d, *J* = 6.5 Hz, C(α)*Me*), 2.31−2.39 (1H, m, C(5′)H_B), 2.82 (1H, app td, *J* = 12.4, 3.1 Hz, C(6′)H_A), 3.38 (1H, app dt, *J* = 12.4, 3.7 Hz, C(6′)H_B), 3.67 (1H, dd, *J* = 3.8, 2.2 Hz, C(2′)*H*), 3.73 (1H, app q, *J* = 3.7 Hz, C(4′)*H*), 3.97−3.99 (1H, m, C(3′)*H*), 4.84 (1H, d, *J* = 3.8 Hz, C(2)*H*), 5.14 (1H, q, *J* = 6.5 Hz, C(α)*H*), 7.46−7.67 (5H, m, *Ph*); δ_C (100 MHz, MeOH-d_4) 17.6 (C(α)*Me*), 26.0 (*C*(5′)), 43.2 (*C*(6′)), 61.8 (*C*(α)), 62.1 (*C*(2′)), 66.3 (*C*(4′)), 71.9 (*C*(3′)), 72.2 (*C*(2)), 130.4, 130.9, 131.4 (*o*,*m*,*p*-*Ph*), 134.5 (*i*-*Ph*), 176.8 (*C*(1)); *m*/*z* (ESI$^+$) 296 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{15}H_{21}NNaO_5^+$ ([M + Na]$^+$) requires 318.1312, found 318.1317.

*Method B (from **15**).* TsOH·H_2O (267 mg, 1.57 mmol) was added to a stirred solution of **15** (100 mg, 0.32 mmol, >99:1 dr) in CH_2Cl_2 (1 mL) at rt, and the resultant mixture was stirred at rt for 5 min. *m*-CPBA (75%, 290 mg, 1.26 mmol) was then added, and the resultant mixture was stirred at rt for 48 h. A mixture of $CHCl_3$/^{i}PrOH (3:1, 3 mL) was then added, and the organic layer was washed with saturated aq Na_2SO_3 (5 mL) until starch iodide paper indicated no remaining oxidant. The organic layer was washed with saturated aq $NaHCO_3$ (5 mL), and the combined aqueous layers were extracted with $CHCl_3$/^{i}PrOH (3:1, 3 × 10 mL). The combined organic extracts were then dried and concentrated in vacuo. Purification via flash column chromatography (eluent $CHCl_3$/^{i}PrOH, 95:5) gave **47** as a white solid (20 mg, 23%, >99:1 dr), which displayed characterization data consistent with those described above.

*Method C (from **17**).* HBF_4 (48% aq, 240 μL, 1.81 mmol) was added to a stirred solution of **17** (100 mg, 0.36 mmol, >99:1 dr) in CH_2Cl_2 (1 mL) at rt, and the resultant mixture was stirred at rt for 5 min. *m*-CPBA (75%, 334 mg, 1.45 mmol) was then added, and the resultant mixture was stirred at rt for 48 h. A mixture of $CHCl_3$/^{i}PrOH (3:1, 2 mL) was then added, and the organic layer was washed with saturated aq Na_2SO_3 (5 mL) until starch iodide paper indicated no remaining oxidant. The organic layer was washed with saturated aq $NaHCO_3$ (5 mL), and the combined aqueous layers were extracted with $CHCl_3$/^{i}PrOH (3:1, 3 × 10 mL). The combined organic extracts were then dried and concentrated in vacuo. Purification via flash column chromatography (eluent $CHCl_3$/^{i}PrOH, 95:5) gave **47** as a white solid (20 mg, 20%, >99:1 dr), which displayed characterization data consistent with those described above.

*Method D (from **15**).* CCl_3CO_2H (129 mg, 0.79 mmol) was added to a stirred solution of **15** (50 mg, 0.16 mmol, >99:1 dr) in CH_2Cl_2 (0.5 mL) at rt, and the resultant mixture was stirred at rt for 5 min. *m*-CPBA (75%, 145 mg, 0.63 mmol) was then added, and the reaction mixture was stirred at rt for 48 h. $CHCl_3$/^{i}PrOH (3:1, 5 mL) was then added, and the organic layer was washed with saturated aq Na_2SO_3 (5 mL) until starch iodide paper indicated no remaining oxidant. The organic layer was then washed with saturated aq $NaHCO_3$ (5 mL), and the combined aqueous washings were extracted with $CHCl_3$/^{i}PrOH (3:1, 3 × 10 mL). The combined organic extracts were then dried and concentrated in vacuo. Purification via flash column chromatography (eluent $CHCl_3$/^{i}PrOH, 95:5) gave an 87:13 mixture of **47** and **48**, respectively, as a colorless oil (13 mg). Data for **48**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.39 (9H, s, CMe_3), 1.52 (3H, m, C(α)*Me*), 1.88−1.91 (1H, m, C(5′)H_A), 2.32−2.38 (2H, m, C(6′)H_2), 2.91−2.94 (1H, m, C(5′)H_B), 3.58−3.66 (2H, m, C(2′)*H*, C(3′)*H*), 4.53 (1H, d, *J* = 4.1 Hz, C(2)*H*), 4.60−4.66 (1H, m, C(4′)*H*), 7.17−7.37 (5H, m, *Ph*); the characterization data for **47** were consistent with those described above.

(*R*,*R*,*R*,*R*)-2-Hydroxy-2-(3′,4′-dihydroxypiperidin-2′-yl)-ethanoic Acid 51. *Method A (from **50**).* $Pd(OH)_2$/C (50% w/w of substrate, 10 mg) was added to a stirred solution of **50** (20 mg, 0.14 mmol, >99:1 dr) in degassed MeOH (0.5 mL). The resultant suspension was placed under H_2 (1 atm) and stirred vigorously at rt for 12 h. The reaction mixture was then filtered through a short plug of Celite (eluent MeOH) and concentrated in vacuo to give **51** as a colorless oil (13 mg, quant, >99:1 dr): $[\alpha]_D^{20}$ − 19.3 (*c* 0.4, H_2O); ν_{max} (ATR) 3320 (O—H), 2944 (C—H), 1448 (zwitterionic *β*-amino acid); δ_H (500 MHz, D_2O) 1.77 (1H, dd, *J* = 15.3, 2.7 Hz, C(5′)H_A), 2.14−2.22 (1H, m, C(5′)H_B), 3.27−3.29 (2H, m, C(6′)H_2), 3.60 (1H, dd, *J* = 6.8, 1.4 Hz, C(2′)*H*), 3.98 (1H, app q, *J* = 3.4 Hz, C(4′)*H*), 4.04 (1H, app d, *J* = 3.4 Hz, C(3′)*H*), 4.19 (1H, d, *J* = 6.8 Hz, C(2)*H*); δ_C (125 MHz, D_2O) 23.3 (*C*(5′)), 39.5 (*C*(6′)), 55.3 (*C*(2′)), 64.9 (*C*(4′)), 66.2 (*C*(3′)), 69.7 (*C*(2)), 176.8 (*C*(1)); *m*/*z* (ESI$^+$) 192 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_7H_{14}NO_5^+$ ([M + H]$^+$) requires 192.0866, found 192.0869.

*Method B (from **47**).* $Pd(OH)_2$/C (50% w/w of substrate, 25 mg) was added to a stirred solution of **47** (50 mg, 0.18 mmol, >99:1 dr) in degassed MeOH (1 mL). The resultant suspension was placed under H_2 (1 atm) and stirred vigorously at rt for 12 h. The reaction mixture

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was then filtered through a short plug of Celite (eluent MeOH) and concentrated in vacuo to give **52** as a colorless oil (31 mg, quant, >99:1 dr). The residue was dissolved in H_2O (0.5 mL), and the resultant solution was allowed to stand at rt for two days before being concentrated in vacuo to give **51** as a colorless oil (31 mg, quant, >99:1 dr): $[\alpha]_D^{20}$ − 14.2 (*c* 0.5, H_2O).

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^1H and ^{13}C NMR spectra and crystallographic information files (structures CCDC 1001521−1001526). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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