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A New Route to Diverse 1-Azasugars from *N*-Boc-5-hydroxy-3-piperidene as a Common Building Block

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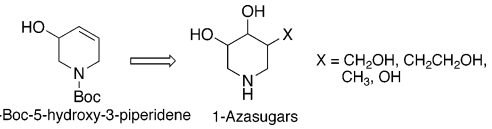

N-Boc-5-hydroxy-3-piperidene 1-Azasugars

A new general method for the synthesis of a variety of 1-azasugars with a nitrogen atom at the anomeric position is described. The readily available chiral *N*-Boc-5-hydroxy-3-piperidene **3** is transformed to isofagomine (**2**), homoisofagomine (**13**), and 5′-deoxyisofagomine (**14**) via stereoselective epoxidation and regioselective ring-cleavage in a highly stereocontrolled manner. In addition, the synthesis of all four stereoisomers of 3,4,5-trihydroxypiperidines (**18**−**21**) classified as 1-azasugar-type glycosidase inhibitors was stereoselectively achieved from the (chiral) piperidene **3**.

Introduction

Glycosciences are emerging as a key research field at the frontiers of biology, synthetic and supramolecular chemistry, and enzymology.[1] Among the carbohydrate processing enzymes, glycosidases have been identified as an important class of therapeutic targets with applications in the treatment of influenza infection,[2] cancer,[3] AIDS,[4] and diabetes.[5] As a result, numerous classes of inhibitors have been developed, some of which provide interesting insights into the mechanism of enzymatic glycoside hydrolysis. Among them, both naturally occurring and synthetic polyhydroxylated piperidines[6] have been shown to be specific and potent inhibitors of glycosidases[7] and have been demonstrated to have great potential as drugs for treating a variety of carbohydrate-mediated diseases.[8]

The transition states for enzymatic glycosidase hydrolysis have considerable oxocarbenium-ion characteristics, in that the anomeric carbon acquires sp^2 hybridization and a partial positive charge develops at the anomeric carbon and the endocyclic oxygen.[9] Iminosugars such as 1-deoxynojirimycin (**1**) and isofagomine (**2**), as transition-state analogues, are of particular interest in terms of inhibitor design (Figure 1). A new class of sugar mimic inhibitor having a nitrogen atom at the anomeric position is 1-azasugars such as **2**. These compounds are

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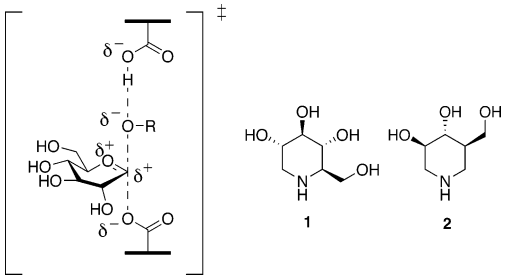


FIGURE 1. Transition state for the hydrolysis step of an inverting glycosidase and azasugars.

highly potent inhibitors of β-glycosidases, whose substrates they mimic.[10]

As a consequence, in recent years there has been a great deal of interest not only in the synthesis of the natural products themselves but also in the nature of chemically modified analogues. However, most of the methodologies described for the synthesis of these compounds, which can be regarded as azasugars (also called iminosugars), start from carbohydrates and, in general, require a large number of steps to reach a specific target. Thus, the development of new methods for the enantioselective synthesis of polyhydroxylated piperidines constitutes an area of considerable current interest.[11]

As a part of our ongoing interest in the polyhydroxy piperidines,[12] we envisioned the use of *N*-Boc-5-hydroxy-3-piperidene (**3**) as a general representative chiral building block that might permit easy access to these classes of compounds. This design was surmised keeping in mind the general substitution pattern of the 1-azasugars of **4**.

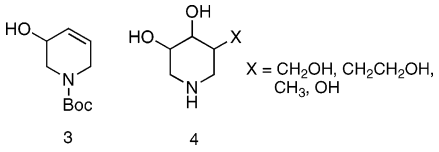
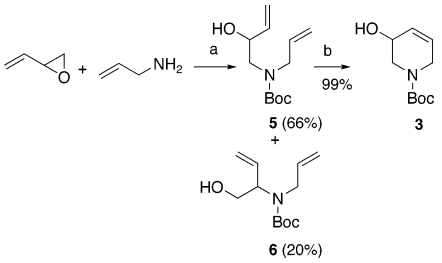


FIGURE 2. Structures of a common building block **3** and 1-azasugars **4**.

SCHEME 1 [a]



[a] Reagents and conditions: (a) (i) cat. H_2O, 100 °C, (ii) Boc_2O, NaOH; (b) Grubbs' catalyst, CH_2Cl_2, rt.

We report herein a full paper[13] describing the synthesis of both enantiomers of a variety of the 1-azasugars **4** such as isofagomine (**2**) by a general route starting from the (chiral) *N*-Boc-5-hydroxy-3-piperidene (**3**) as depicted in Figure 2.

Results and Discussion

Synthesis of racemic *N*-Boc-5-hydroxy-3-piperidene (**3**) as the starting material began with the regioselective opening of butadiene monoxide with allylamine followed by protection of the secondary amine to afford the metathesis precursor **5** (66%) together with the undesired ring-opening product **6** (20%).[14] The Grubbs' catalyst[15] could be used directly on **5** to afford the ring-closing metathesis product **3** in 99% yield (Scheme 1).

Ogasawara reported[16] on the lipase-catalyzed transesterification of *N*-Cbz-5-hydroxy-3-piperidene with vinyl acetate. We applied this method to **3** using lipase and vinyl acetate. Of the various lipases tested, resolution was best achieved with lipase PS (*Pseudomonas cepacia*), immobilized on ceramic particles, in *tert*-butyl methyl ether at 40 °C, which gave the acetate (−)-**7** in 49% yield, along with the unreacted alcohol (+)-**3**, in 48% yield. In addition, the enzymatic hydrolysis of the acetate (−)-**7** with the same lipase in 0.1 M phosphate buffer afforded the enantiometic alcohol (−)-**3** in 98% yield. The enantiomeric purities of (+)- and (−)-**3** were >99% ee, as determined by chiral HPLC analysis after replacing the *N*-protecting group with Cbz (Scheme 2).

Alcohol (+)-**3** was initially converted into the TBDPS derivative **8**, thus avoiding the possible assistance of the hydroxyl group in the favored approach of the oxidant.

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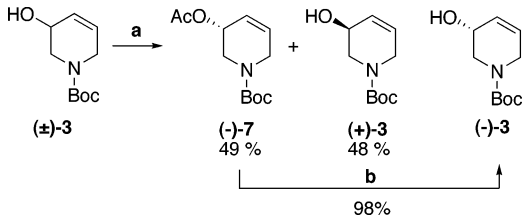
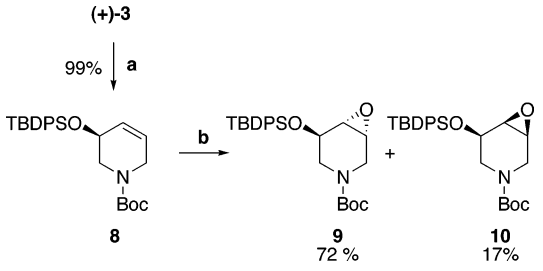
SCHEME 2 [a]



[a] Reagents and conditions: (a) vinyl acetate, lipase PS (immobilized on ceramic particles)/*t*-BuOMe, 40 °C, 18 h; (b) lipase PS (immobilized on ceramic particles)/0.1 M phosphate buffer (pH 7), acetone, 40 °C, 18 h.

SCHEME 3 [a]



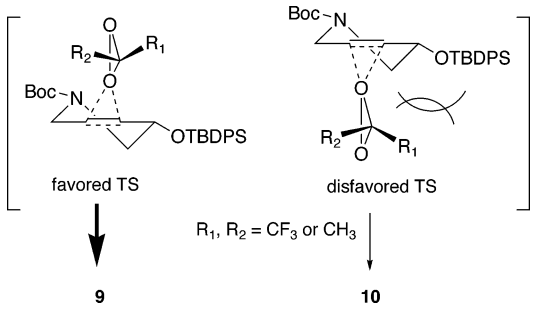
[a] Reagents and conditions: (a) TBDPSCl, imidazole, cat. DMAP/CH_2Cl_2, rt, 3 h; (b) Oxone, aq Na_2EDTA, $NaHCO_3$, CF_3COCH_3/CH_3CN, 0 °C, overnight.

Treatment of (+)-**3** with *tert*-butyldiphenylsilyl chloride under basic conditions gave the TBDPS derivative **8** in 99% yield. In an initial experiment, the oxidation of **8** with *m*-CPBA resulted in a low diastereoselectivity to give the anti epoxide **9** and the syn epoxide **10** in 41% and 23% yields, respectively. Subsequently, the use of (trifluoromethyl)methyldioxirane instead of *m*-CPBA as an oxidizing agent improved both the yield and the diastereoselectivity. Thus, the dioxirane, generated in situ[17] from Oxone with 1,1,1-trifluoroacatone, was reacted with **8** to give the anti epoxide **9** and the syn epoxide **10** in 72% and 17% yields, respectively.

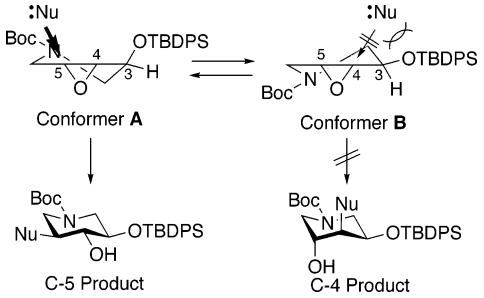
In diastereoselective epoxidation of allylically substituted six-membered cyclic alkene, dioxrane can be an oxygen atom to the olefin double bond of substrate from both faces, so there are two possible spiro transition states based on steric considerations.[18] In the favored TS leading to anti epoxide **9**, there are little interactions between the R_1 and the allylic hydrogen of substrate. On the other hand, severe steric interaction between the R_1 and the allylic large OTBDPS group is expected in the disfavored TS leading to syn epoxide **10**. Therefore, it appears that an attack on the dioxirane preferably occurred preferentially at the less hindered anti side to the large OTBDPS group (Scheme 4).

The nucleophilic opening of the anti epoxide **9** with "higher order" cuprate[19] free halide ions in the presence of boron trifluoride etherate as the activating species was carried out as follows: treatment of **9** with $(CH_2{=}CH)_2$-

SCHEME 4. Stereochemistry of the Epoxidation of 8



SCHEME 5. Regiochemistry of the Nucleophilic Opening of the Epoxide 9



$CuCNLi_2$ in the presence of $BF_3{\cdot}OEt_2$ at −78 °C for 2 h gave **11** as the sole isolable product in 74% yield. Analogously, the reaction of **9** with $Me_2CuCNLi_2$ afforded only **12** in 71% yield. An attempt to employ Grignard reagents in the presence of cuprous bromide[20] resulted in no reaction. Although the rationale for this high selectivity remains unclear, the following mechanism is consistent with the results. The regiochemistry of the nucleophilic opening of the epoxide on a six-membered ring is mainly subject to trans diaxial opening (Fürst−Plattner rule).[21] Consequently, a high regioselectivity would result if the opening proceeded through only one of the two possible half-chair conformations (**A** and **B**). Thus, the exclusive attack of the nucleophile at C-5 through conformer **A** would occur with trans diaxial opening. On the other hand, an attack of a nucleophile at C-4 of **9** through conformer **B** would be subject to steric hindrance by the pseudoequatorial OTBDPS group at C-3. Therefore, a trans diaxial opening through one of the half-chair conformers, namely conformer **A**, would occur (Scheme 5). A similar regioselectivity has been reported for ring-opening reactions of *trans*-3-(benzyloxy)-1,2-epoxycyclohexane derivatives.[22]

With the vinyl product **11** in hand, our interest was directed to its conversion to isofagomine (**2**) and homo-

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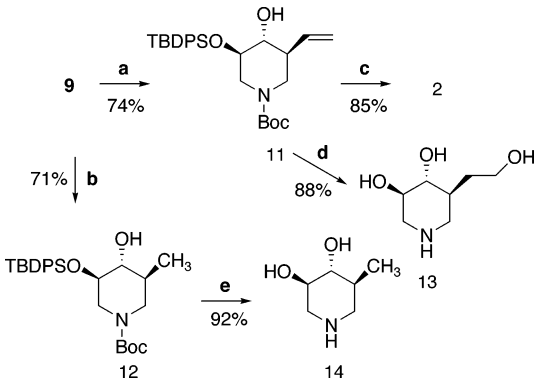
SCHEME 6 [a]



[a] Reagents and conditions: (a) $(CH_2{=}CH)_2CuCNLi_2$ (5 equiv), $BF_3{\cdot}OEt_2$ (2 equiv)/Et_2O, −78 °C, 2 h; (b) $Me_2CuCNLi_2$ (5 equiv), $BF_3{\cdot}OEt_2$ (2 equiv),/Et_2O, −78 °C; (c) (i) cat. OsO_4, $NaIO_4$/50% EtOH, rt, overnight, (ii) $NaBH_4$/50% EtOH, rt, 1 h, (iii) 10% HCl/dioxane, reflux, 1 h; (d) (i) 9-BBN/THF, rt, 6 h, (ii) H_2O_2, 3 mol/L of NaOH/THF, rt, 1 h, (iii) 10% HCl/dioxane, reflux, 1 h; (e) 10% HCl/dioxane, reflux, 1 h.

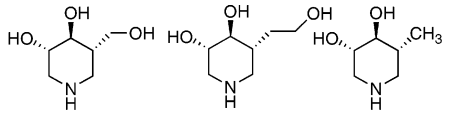


FIGURE 3. Structures of the enantiomers of **2**, **13**, and **14**,

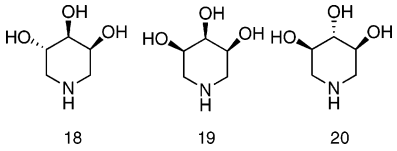


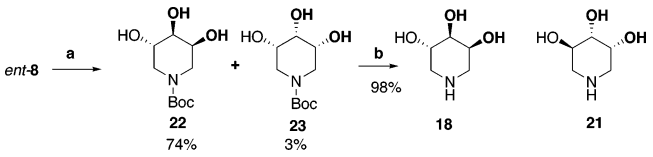
FIGURE 4. Structures of three 3,4,5-trihydroxypiperidines isolated from *Eupatorium fortunei* TURZ.

isofagomine (**13**). Oxidative cleavage of the vinyl group of **11** with OsO_4 and $NaIO_4$ afforded the aldehyde, which without purification, and after reduction with $NaBH_4$ followed by deprotection, afforded isofagomine (**2**) in 85% combined yield. The optical rotation and spectral characteristics of **2** were in good agreement with those reported in the literature.[11g] Next, the hydroboration of the vinyl group of **11** with 9-BBN followed by treatment with hydrogen peroxide gave the corresponding primary alcohol. Deprotection of the alcohol with 10% HCl in 1,4-dioxane afforded **13** in 86% combined yield. Conversion of **12** to 5′-deoxyisofagomine (**14**) was accomplished by deprotection. The complete deprotection of **12** by treatment with 10% HCl in 1,4-dioxane afforded **14** in 92% yield. Thus the first synthesis of **13** and **14** was achieved (Scheme 6).

Enantiomers of **2**, **13**, **14**, and **15**−**17** were also prepared starting from (−)-**3**, following the same procedure as above (Figure 3).

The above successes led us to consider the synthesis of some of the most important 3,4,5-piperidine triols, namely, **18**, **19**, and **20** (Figure 4). These trihydroxy piperidines are regarded as derivatives of their parent deoxynojirimycin and have been shown to possess moderate to good glycosidase inhibitory activity. A careful consideration of these structural moieties reveals that these molecules can also be classified as 1-*N*-iminosugar-type glycosidase inhibitors, although they do not resemble any of the presently known pyranose sugars.

SCHEME 7 [a]



[a] Reagents and conditions: (a) (i) cat. OsO_4, NMO, acetone, (ii) TBAF, THF, rt; (b) (i) 10% HCl, dioxane, reflux, (ii) Amberlite IRA-410.

Triols **18**, **19**, and **20** were isolated from *Eupatorium fortunei* TURZ by Kusano and co-workers[23] in 1995 and have been shown to be the active components of the extracts of this plant, which are traditionally used in Chinese and Japanese folk medicine as a diuretic, antipyretic, emmenagogue, and antidiabetic agent. Triols **18**−**20** have also been synthesized by Ganem[24] and others[25] and have been shown to be good selective inhibitors of glycosidases.

We realized that our precursors (+)-, (−)-, and (±)-**3** would be ideal candidates for the synthesis of these molecules together with the enantiomer of **18**, **21**. The synthesis of des(hydroxymethyl)deoxymannojirimycin (**18**) commenced with *ent*-**8**, which was previously synthesized from (−)-**3**. The stereoselective dihydroxylation of the double bond was also examined. Treatment of *ent*-**8** with a catalytic amount of OsO_4 (5 mol %) and 4-methylmorphorine *N*-oxide as a cooxidant[26] gave an inseparable mixture of diastereomeric diols, which was subjected to treatment with TBAF to provide the triol **22** as a major product along with minor amounts of triol **23**. This high diastereoselectivity in the dihydroxylation step can be attributed to the a steric blocking of an allylic *O*-TBDPS substituent.[25h] Deprotection of **22** with HCl in dioxane followed by treatment with an ion-exchange resin (Amberlite IRA-410 OH^- form) afforded **18** in 98% combined yield. In a similar procedure, the enantiomer **21** was prepared from (+)-**3** in 69% yield (Scheme 7). The spectral data and optical rotation for **18** and **21** were found to be in good agreement with reported values from the literature.[23,25c]Donohoe reported[27] that osmium tetroxide produces a bidendate and reactive complex with TMEDA, which can be used to achieve the directed

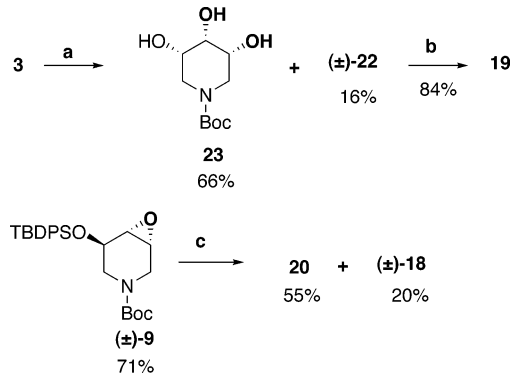
(23) Sekioka, T.; Shibano, M.; Kusano, G. *Nat. Med.* (*Tokyo*, *Jpn.*) **1995**, *49*, 332−335.

(24) Bernotas, R. C.; Papandreou, G.; Urbach, J.; Ganem, B. *Tetrahedron Lett.* **1990**, *31*, 3393−3396.

(25) (a) Tschamber, T.; Backenstrass, F.; Neuburger, M.; Zehnder, M.; Streith, J. *Tetrahedron* **1994**, *50*, 1135−1152. (b) Legler, G.; Stütz, A. E.; Immich, H. *Carbohydr. Res.* **1995**, *272*, 17−30. (c) Godskesen, M.; Lundt, I.; Madsen, R.; Winchester, B. *Bioorg. Med. Chem.* **1996**, *4*, 1857−1865. (d) Sames, D.; Polt, R. *Synlett* **1995**, 552−554. (e) Amat, M.; Llor, N.; Huguet, M.; Molins, E.; Espinosa, E.; Bosch, J. *Org. Lett.* **2001**, *3*, 3257−3260. (f) Patil, N. T.; John, S.; Sabharwal, S. G.; Dhawale, D. D. *Bioorg. Med. Chem.* **2002**, *10*, 2155−2160. (g) Pandey, G.; Kapur, M. *Org. Lett*. **2002**, *4*, 3883−3886. (h) Han, H. *Tetrahedron Lett*. **2003**, *44*, 1567−1569. In this paper, a highly stereocontrolled synthesis of **18** and **20** as hydrochloride salts from the *O*-MOM protected piperidene of **3** has been reported. (i) Pandey, G.; Kapur, M.; Khan, M. S.; Gaikwad, S. M. *Org. Biomol. Chem*. **2003**, *1*, 3321−3326.

(26) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett*. **1976**, *17*, 1973−1976.

SCHEME 8 [a]



[a] Reagents and conditions: (a) (i) OsO_4,TMEDA, CH_2Cl_2, −78 °C, (ii) conc HCl, MeOH, rt, (iii) Boc_2O, Et_3N, MeOH; (b) (i) 10% HCl, dioxane, reflux, (ii) Amberlite IRA-410; (c) (i) 10% H_2SO_4, dioxane, 95 °C, 3 h, (ii) Amberlite IRA-410.

dihydroxylation of cyclic allylic alcohols. Under this condition, hydrogen bonding control leads to the formation of the syn isomer in almost every case. Therefore, the oxidation of (±)-**3** with a combination of OsO_4 with TMEDA gave the *all-cis*-triol **23** and (±)-**22** in moderate selectivity (4:1) in 66% and 16% yields, respectively. Finally, removal of the Boc group from **23**, followed by ion-exchange chromatographic purification yielded **19** in 94% yield, the spectral data for which were in excellent agreement with data reported in the literature. Next, the anti epoxide (±)-**9** obtained from (±)-**8** according to the same procedure for the preparation of (+)-**9** was hydrolyzed with 10% H_2SO_4 in dioxane to afford the triol **20** as a major product and (±)-**18** as a minor one in 55% and 20% yields, respectively. This moderate diastereoselectivity compared with the high selectivity of nucleophilic cleavage of **9** with vinylmetal may be due to the following reason. Because partial desilylation prior to ring opening of epoxide in acidic condition can occur, the steric hindrance between nucleophile (H_2O) and allylic hydroxy substituent in analogous conformer **B** described in Scheme 5 would diminish.

Summary

An efficient synthesis of isofagomine (**2**), homoisofagomine (**13**), 5-deoxyisofagomine (**14**), and their enantiomers **15**−**17** with a nitrogen atom at the anomeric position was achieved in 44−50% overall yields from the readily obtainable chiral *N*-Boc-5-hydroxy-3-piperidene (**3**). The reaction involved the epoxidation into a double bond and a regioselective epoxide ring opening reaction with higher ordered cuprates. To our knowledge our route to isofagomine (**2**) is shorter and more efficient than the other reported syntheses.[10] In addition, the stereoselective synthesis of all four of the stereoisomers of 3,4,5-trihydroxypiperidines (**18**−**21**) was achieved from the common building block **3**. This synthetic route permits the preparation of substantial amounts of 1-azasugars having a glucose configuration and would be suitable for further studies of such compounds as glycosidase inhibitors.

Experimental Section

***tert*-Butyl *N*-Allyl-*N*-(2-hydroxy-3-butenyl)carbamate (5) and *tert*-Butyl Allyl-1-hydroxybut-3-enylcarbamate (6).** To a solution of allylamine (8.5 mL, 20 mmol) and water (530 μL) was added butadiene monoxide (3.0 mL, 37.5 mmol) at 15 °C. The mixture was warmed to 100 °C and stirred for 6 h. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in dioxane (50 mL) and water (10 mL), 1 mol/L of NaOH (40 mL, 40 mmol), and $(Boc)_2O$ (8.37 g, 40 mmol) were added. The mixture was stirred at room temperature overnight. The residue obtained after evaporation was taken up in Et_2O (200 mL), and washed with water (100 mL), 20% citric acid (100 mL), and brine (100 mL). The combined aqueous solutions were extracted with Et_2O (2 × 50 mL). The combined organic solutions were dried over $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography on silica gel (*n*-hexane:AcOEt = 4:1−1:1) to give **5** (5.62 g, 66%) as a colorless oil and **6** (1.68 g, 20%) as a colorless oil.

5: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.44 (s, 9H), 3.26 (br s, 1H), 3.31 (br s, 1H), 3.66 (br s, 1H), 3.74−3.94 (m, 2H), 4.29−4.32 (m, 1H), 5.09−5.15 (m, 3H), 5.32 (d, *J* = 16.5 Hz, 1H), 5.66−5.84 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 51.7, 53.4, 72.7, 80.4, 115.7, 116.4, 133.8, 138.4, 157.6. IR (neat) (cm^{-1}) 3432, 1675. EI-MS (*m/z*) 228 ($M^+ + 1$). HRMS calcd for $C_{10}H_{17}NO_3$ 227.1521, found 227.1538. Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.10; H, 9.52; N, 6.28.

6: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 9H), 2.27−3.00 (br, 1H), 3.77 (br d, *J* = 7.1 Hz, 4H), 4.38 (br d, *J* = 5.6 Hz, 1H), 5.06−5.26 (m, 4H), 5.74−5.96 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.4, 48.3, 61.1, 63.6, 80.3, 117.5, 134.0, 135.3, 156.3. IR (neat) (cm^{-1}) 3436, 1694. EI-MS (*m/z*) 228 ($M^+ + 1$). HRMS calcd for $C_{12}H_{21}NO_3$ 227.1521, found 227.1546.

(±)-*N*-*tert*-Butoxycarbonyl-5-hydroxy-3-piperidene ((±)-3). To a deoxygenated solution of **5** (4.54 g, 20 mmol) in CH_2Cl_2 (340 mL) under argon atomosphere was added bis(tricyclohexylphosphine)benzylidine ruthenium(IV) dichloride (0.58 g, 0.71 mmol, 5 mol %). The solution was stirred at room temperature overnight, then concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (*n*-hexane:AcOEt = 2:1) to give (±)-**3** (3.95 g, 99%) as colorless prisms; mp 55−56 °C (*n*-hexane). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.47 (s, 9H), 1.64 (br s, 1H), 3.53 (br s, 1H), 3.58 (br s, 1H), 3.80 (dd, *J* = 18.7, 2.2 Hz, 1H), 3.97 (br s, 1H), 4.19 (br s, 1H), 5.84 (br s, 1H), 5.89−5.93 (m, 1H).^{13}C NMR (67.8 MHz, $CDCl_3$) δ 28.4, 43.3, 47.7, 63.6, 80.1, 126.9, 128.3, 155.0. IR (KBr) (cm^{-1}) 3255, 1699. EI-MS (*m/z*) 199 (M^+). HRMS calcd for $C_{10}H_{17}NO_3$ 199.1169, found 199.1208. Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.46; H, 8.50; N, 6.87.

(*S*)-*N*-*tert*-Butoxycarbonyl-5-hydroxy-3-piperidene ((+)-3) and (*R*)-*N*-*tert*-Butoxycarbonyl-5-acetoxy-3-piperidene ((−)-7). A mixture of (±)-**3** (1.99 g, 10 mmol) and vinyl acetate (4.3 g, 50 mmol) in *tert*-butyl methyl ether (100 mL) was stirred with lipase (1 g, immobilized on Ceramic particles from *Psedomonas cepacia*) at 40 °C for 18 h. After filtration, the filtrate was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel to give acetate (−)-**7** (1.18 g, 49%) as a colorless oil from the *n*-hexane/AcOEt (3:1) fraction and the alcohol (+)-**3** (0.96 g, 48%) as colorless needles from the *n*-hexane/AcOEt (1:1) fraction.

(+)-**3**: mp 70−71 °C (*n*-hexane). $[\alpha]^{32}_D$ +83.7 (*c* 1.08, $CHCl_3$).

(−)-**7**: $[\alpha]^{30}_D$ −110.4 (*c* 2.20, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.46 (s, 9H), 2.05 (s, 3H), 3.47 (dd, *J* = 13.9, 3.7 Hz, 1 H), 3.76 (d, *J* = 19.4, 1H), 3.76 (dd, *J* = 13.9, 4.0 Hz, 1H), 4.12 (m, 1H), 5.15 (br s, 1H), 5.85−5.97 (m, 2H). ^{13}C NMR (67.8

(27) (a) Donohoe, T. J.; Blades, K.; Moore, P. R.; Waring, M. J.; Winter, J. J. G.; Helliwell, M.; Newcombe, Ni. J.; Stemp, G. *J. Org. Chem.* **2002**, *67*, 7946−7956. (b) Donohoe, T. J. *Synlett* **2002**, 1223−1232.

MHz, $CDCl_3$) δ 21.1, 28.4, 42.8, 44.9, 65.7, 79.9, 123.7, 130.4, 154.5, 170.3. IR (neat) (cm^{-1}) 1740, 1700. EI-MS (*m/z*) 242 ($M^+ + 1$). HRMS calcd for $C_{12}H_{19}NO_4$ 241.1314, found 241.1321.

(*R*)-*N*-*tert*-Butoxycarbonyl-5-hydroxy-3-piperidene ((−)-3). A mixture of acetate (−)-**7** (1.1 g, 4.5 mmol) and acetone (3.14 mL) in phosphate buffer (0.1 mol/L, pH 7.0, 51 mL) was stirred with lipase (0.46 g, immobilized on Ceramic particles from *Psedomonas cepacia*) at 40 °C for 18 h. After filtration, the filtrate was extracted with AcOEt (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (*n*-hexane:AcOEt = 1:1) to give (−)-**3** (0.88 g, 98%) as colorless needles; mp 71−72 °C (*n*-hexane). $[\alpha]^{30}_D$ −83.3 (*c* 1.10, $CHCl_3$).

(*S*)-*N*-*tert*-Butoxycarbonyl-5-(*tert*-butyldiphenylsilyloxy)-3-piperidene (8). To a solution of (+)-**3** (996 mg, 5 mmol) in CH_2Cl_2 (10 mL) was added imidazole (511 mg, 7.5 mmol), DMAP (122 mg, 1 mmol), and *tert*-butylchlorodiphenylsilane (1.512 g, 5.5 mmol). The mixture was stirred at room temperature for 3 h. The reaction mixture was filtered through a Celite pad. The filtrate was washed with brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (*n*-hexane:AcOEt = 8:1) to give **8** (2.35 g, 99%) as a colorless oil; $[\alpha]^{27}_D$ +22.6 (*c* 1.80, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.40 (s, 9H), 3.21 (br s, 1H), 3.62−3.96 (m, 3H), 4.25 (br s, 1H), 5.58−5.72 (m, 2H), 7.36−7.44 (m, 6H), 7.67−7.70 (m, 4H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 19.2, 26.9, 28.4, 42.7, 47.9, 65.1, 79.5, 126.0, 127.4, 129.2, 129.5, 133.7, 135.5, 154.4. IR (neat) (cm^{-1}) 1703. EI-MS (*m/z*) 438 ($M^+ + 1$). HRMS calcd for $C_{26}H_{35}NO_3Si$ 437.2386, found 437.2448. Anal. Calcd for $C_{26}H_{35}NO_3Si$: C, 71.35; H, 8.06; N, 3.20. Found: C, 71.16; H, 7.96; N, 3.23.

(3*R*,4*R*,5*R*)-*N*-*tert*-Butoxycarbonyl-3-(*tert*-butyldiphenylsilyloxy)-4,5-epoxypiperidine (9) and (3*R*,4*S*,5*S*)-*N*-*tert*-Butoxycarbonyl-3-(*tert*-butyldiphenylsilyloxy)-4,5-epoxypiperidine (10). To a cooled (0 °C) solution of **8** (945 mg, 2.16 mmol) in CH_3CN (20 mL) was added 4 mmol/L of aq Na_2EDTA (10 mL, 0.04 mmol) and 1,1,1-trifluoroacetone (2 mL). The mixture of $NaHCO_3$ (1.26 g, 15 mmol) and Oxone (6.13 g, 10 mmol) as a solid was added slowly over a period of 1 h at 0 °C. After being stirred at 0 °C overnight, the solution was quenched by adding water (60 mL) and extracted with $CHCl_3$ (3 × 60 mL). The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (*n*-hexane:AcOEt = 8:1) to give **9** (706 mg, 72%) as colorless prisms and **10** (170 mg, 17%) as colorless needles.

9: mp 70−72 °C (*n*-pentane); $[\alpha]^{30}_D$ +29.2 (*c* 1.11, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.10 (s, 9H), 1.37 and 1.46 (2 s, 9H), 3.07−3.41 (m, 4H), 3.07−3.88 (m, 2H), 4.09−4.15 (m, 1H), 7.36−7.45 (m, 6H), 7.63−7.69 (m, 4H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 19.3, 27.0, 28.4, 41.4, 45.3, 50.6, 53.7, 65.2, 79.8, 127.7, 129.8, 133.1, 135.5, 154.9. IR (KBr) (cm^{-1}) 1701. EI-MS (*m/z*) 453 (M^+). HRMS calcd for $C_{26}H_{35}NO_4Si$ 453.2336, found 453.2343. Anal. Calcd for $C_{26}H_{35}NO_4Si$: C, 68.84; H, 7.78; N, 3.09. Found: C, 69.03; H, 7.64; N, 2.93.

10: mp 110−111 °C (*n*-pentane); $[\alpha]^{26}_D$ −6.2 (*c* 0.80, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.35 (s, 9H), 2.87 (br t, *J* = 10.7 Hz, 1H), 3.09 (br s, 1H), 3.20−3.40 (m, 2H), 3.75 (br s, 1H), 3.99−4.03 (m, 2H), 7.37−7.46 (m, 6H), 7.67−7.74 (m, 4H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 19.3, 27.0, 28.3, 40.6, 43.1, 53.3, 54.6, 67.5, 79.9, 127.7, 129.8, 133.1, 135.6, 154.0. IR (KBr) (cm^{-1}) 1698. EI-MS (*m/z*) 454 ($M^+ + 1$). HRMS calcd for $C_{26}H_{35}NO_4Si$ 453.2336, found 453.2351. Anal. Calcd for $C_{26}H_{35}NO_4Si$: C, 68.84; H, 7.78; N, 3.09. Found: C, 68.96; H, 7.88; N, 3.12.

(3*R*,4*R*,5*S*)-*N*-*tert*-Butoxycarbonyl-3-(*tert*-butyldiphenylsilyloxy)-4-hydroxy-5-vinylpiperidine (11). A solution of *n*-BuLi (3.125 mL, 1.6 M in *n*-hexane, 5 mmol) was added to a solution of tetravinyltin (1.14 g, 5 mmol) in Et_2O (7 mL) at room temperature and the mixture was stirred for 1 h at the same temperature. The solution was added to a suspension of CuCN (224 mg, 2.5 mmol) in dry Et_2O (20 mL) at −78 °C and the mixture was stirred under argon atmosphere at −78 °C for 10 min. The resulting solution was warmed to −10 °C and stirred for 30 min. The reaction mixture was cooled to −78 °C and a solution of **9** (454 mg, 1 mmol) in dry Et_2O (20 mL) was added to the reaction mixture dropwise via syringe at −78 °C. The mixture was stirred at −78 °C for 10 min. $BF_3{\cdot}OEt_2$ (4 mol/L in Et_2O, 5 mL, 2 mmol) was added to the reaction mixture at −78 °C and the solution was stirred for 2 h. The reaction mixture was quenched with 28% NH_4OH/sat. NH_4Cl (1:9) solution (50 mL) and stirred overnight at room temperature. The organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (*n*-hexane:AcOEt = 8:1) to give **11** (357 mg, 74%) as a colorless oil; $[\alpha]^{24}_D$ −10.5 (*c* 1.16, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.31 (s, 9H), 2.12 (br s, 1H), 2.23 (br s, 1H), 2.50 (br s, 1H), 2.65 (dd, *J* = 11.0, 12.5 Hz, 1H), 3.42 (t, *J* = 9.0 Hz, 1H), 3.51−3.55 (m, 1H), 3.82−4.23 (m, 2H), 5.16−5.20 (m, 2H), 5.66−5.72 (m, 1H), 7.38−7.45 (m, 6H), 7.68−7.71 (m, 4H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 19.4, 27.0, 28.3, 45.8, 46.5, 48.7, 73.6, 77.7, 79.8, 117.7, 127.7, 129.8, 133.3, 135.7, 135.9, 154.0. IR (neat) (cm^{-1}) 3472, 1698. EI-MS (*m/z*) 482 ($M^+ + 1$). HRMS calcd for $C_{28}H_{39}NO_4Si$ 481.2649, found 481.2686. Anal. Calcd for $C_{28}H_{39}NO_4Si$: C, 69.82; H, 8.16; N, 2.91. Found: C, 70.10; H, 8.07; N, 2.77.

(3*R*,4*R*,5*R*)-3,4-Dihydroxy-5-(hydroxymethyl)piperidine (2, isofagomine). To a solution of **11** (193 mg, 0.4 mmol) in EtOH (4 mL) and H_2O (4 mL) was added an aqueous solution of 4% OsO_4 (131 μL, 0.02 mmol) and the solution was stirred at room temperature for 10 min. $NaIO_4$ (190 mg, 0.88 mmol) as a powder was added slowly over a period of 30 min, and the mixture was stirred at room temperature for 24 h. $NaBH_4$ (76 mg, 2 mmol) as a powder was added, and the reaction mixture was stirred at room temperature for 1 h. The solvent was removed in vacuo. The residue was diluted with $CHCl_3$ (80 mL) and successively washed with 10% $Na_2S_2O_3$ (20 mL), sat. $NaHCO_3$ (20 mL), and brine (10 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (*n*-hexane:AcOEt = 1:1) to give (3*R*,4*R*,5*R*)-*N*-*tert*-butoxycarbonyl-3-(*tert*-butyldiphenylsilyloxy)-4-hydroxy-5-(hydroxymethyl)piperidine (167 mg, 86%) as a colorless oil; $[\alpha]^{25}_D$ −15.9 (*c* 1.35, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.31 (s, 9H), 1.66 (br s, 1H), 2.48 (br s, 3H), 2.63 (t, *J* = 11.0 Hz, 1H), 3.48−3.56 (m, 2H), 3.67 (s, 2H), 3.85−4.16 (m, 2H), 7.39−7.46 (m, 6H), 7.67−7.69 (m, 4H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 19.4, 27.0, 28.3, 42.8, 43.9, 48.5, 63.2, 73.6, 77.7, 79.9, 127.8, 129.9, 133.3, 135.5, 154.2. IR (neat) (cm^{-1}) 3420, 1696, 1674. EI-MS (*m/z*) 486 ($M + H^+$). HRMS calcd for $C_{27}H_{39}NO_5Si$ 485.2598, found 485.2585. To a solution of the prepared diol (160 mg, 0.33 mmol) in dioxane (2.5 mL) was added a solution of 10% HCl (10 mL), and the solution was refluxed for 1 h. After the reaction mixture was cooled to room temperature and diluted with H_2O (50 mL), the resulting dilute solution was washed with Et_2O (2 × 20 mL). The aqueous layer was concentrated under reduced pressure. The residue was dissolved in 28% NH_4OH and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (28% NH_4OH:EtOH = 1:10) to give **2** (48.5 mg, 99%) as a white powder; $[\alpha]^{25}_D$ +25.4 (*c* 1.30, EtOH). ^1H NMR (600 MHz, D_2O) δ 1.61−1.68 (m, 1H), 2.33−2.38 (m, 2H), 3.05 (dd, *J* = 13.0, 3.5 Hz, 1H), 3.10 (dd, *J* = 12.1, 4.8 Hz, 1H), 3.27 (t, *J* = 9.9 Hz, 1H), 3.43−3.48 (m, 1H), 3.59 (dd, *J* = 11.4, 7.0 Hz, 1H), 3.78 (dd, *J* = 11.4, 3.3 Hz, 1H). ^{13}C NMR (67.8 MHz, D_2O) δ 43.9, 45.7, 48.8, 59.8, 71.4,

73.1. EI-MS (*m/z*) 147 (M^+). HRMS calcd for $C_6H_{13}NO_3$ 147.0895, found 147.0845.

(3*R*,4*R*,5*S*)-3,4-Dihydroxy-5-(hydroxyethyl)piperidine (13, homoisofagomine). To a cooled (0 °C) solution of **11** (96 mg, 0.2 mmol) in THF (3 mL) was added a solution of 9-BBN (0.5 mol/L in THF, 2 mL, 1 mmol). The mixture was warmed to room temperature and stirred for 6 h. The reaction mixture was then cooled to 0 °C. To this solution was added 3 mol/L of NaOH solution (1 mL) and 30% H_2O_2 solution (1 mL). The mixture was stirred at room temperature for 1 h. A sat. NH_4Cl solution (3 mL) was added, and the mixture was extracted with AcOEt (3 × 20 mL). The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (*n*-hexane:AcOEt = 1:1) to give (3*R*,4*R*,5*S*)-*N*-*tert*-butoxycarbonyl-3-(*tert*-butyldiphenylsilyloxy)-4-hydroxy-5-(hydroxyethyl)piperidine (93 mg, 93%) as a colorless oil; $[\alpha]^{25}_D$ −4.97 (*c* 1.30, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.29 (br s, 9H), 1.47−1.75 (m, 4H), 2.37 (br s, 1H), 2.61 (t, J = 11.7 Hz, 1H), 2.94 (br s, 1H), 3.33 (t, J = 9.0 Hz, 1H), 3.47−3.51 (m, 1H), 3.59−3.63 (m, 1H), 3.69−3.73 (m, 1H), 3.84−4.20 (m, 2H), 7.38−7.51 (m, 6H), 7.66−7.69 (m, 4H). IR (neat) (cm^{-1}) 3323, 1697, 1673. EI-MS (*m/z*) 499 (M^+). HRMS calcd for $C_{28}H_{41}NO_5Si$ 499.2754, found 499.2740. To a solution of the above diol (180 mg, 0.36 mmol) in dioxane (2.5 mL) was added a solution of 10% HCl (10 mL), and the solution was heated at reflux for 1 h. After the reaction mixture was cooled to room temperature and diluted with H_2O (50 mL), the resulting dilute solution was washed with Et_2O (2 × 20 mL). The aqueous layer was concentrated under reduced pressure. The residue was dissolved in MeOH and made alkaline with Na_2CO_3. The mixture was filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (10% NH_4OH:MeOH = 1:50) to give **13** (55 mg, 95%) as a white powder; $[\alpha]^{20}_D$ +17.70 (*c* 1.10, EtOH). ^{1}H NMR (600 MHz, D_2O) δ 1.22−1.28 (m, 1H), 1.36−1.43 (m, 1H), 1.76−1.82 (m, 1H), 2.11 (dd, J = 12.8, 11.7 Hz, 1H), 2.23 (dd, J = 12.3, 10.8 Hz, 1H), 2.87 (ddd, J = 13.0, 4.2, 1.5 Hz, 1H), 2.94−3.01 (m, 2H), 3.27−3.32 (m, 1H), 3.46−3.55 (m, 2H). ^{13}C NMR (67.8 MHz, D_2O) δ 76.5, 71.3, 58.8, 48.8, 47.6, 39.1, 30.7. IR (neat) (cm^{-1}) 3324, 1697, 1674. EI-MS (*m/z*) 161 (M^+). HRMS calcd for $C_7H_{15}NO_3$ 161.1052, found 161.1088.

(3*R*,4*R*,5*S*)-*N*-*tert*-Butoxycarbonyl-3-(*tert*-butyldiphenylsilyloxy)-4-hydroxy-5-methylpiperidine (12). To a suspension of CuCN (135 mg, 1.5 mmol) in dry Et_2O (15 mL) at −78 °C was added a solution of MeLi (2.9 mL, 1.04 mol/L in Et_2O, 3 mmol) at −78 °C and the mixture was stirred under argon atmosphere at −78 °C for 10 min. The resulting solution was warmed to −10 °C then stirred for 30 min. The reaction mixture was cooled to −78 °C, and a solution of **9** (273 mg, 0.6 mmol) in dry Et_2O (15 mL) was added to the reaction mixture dropwise via syringe at −78 °C. The mixture was stirred at −78 °C for 10 min. $BF_3{\cdot}OEt_2$ (4 mol/L in Et_2O, 3 mL, 1.2 mmol) was added to the reaction mixture at −78 °C and the solution was stirred for 2 h. The reaction mixture was quenched with 28% NH_4OH/sat. NH_4Cl (1:9) solution (30 mL) and stirred overnight at room temperature. The organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 30 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (*n*-hexane:AcOEt = 8:1) to give **12** (200 mg, 71%) as a colorless oil; $[\alpha]^{23}_D$ −16.7 (*c* 1.25, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.97 (d, J = 6.6 Hz, 3H), 1.09 (s, 9H), 1.30 (s, 9H), 1.43 (br, 1H), 2.15−2.36 (m, 2H), 2.62 (dd, J = 12.5, 11.0 Hz, 1H), 3.18 (t, J = 9.0 Hz, 1H), 3.46−3.51 (m, 1H), 3.97 (br, 2H), 7.37−7.46 (m, 6H), 7.65−7.73 (m, 4H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.6, 19.3, 26.9, 28.2, 35.9, 48.7, 74.0, 79.6, 80.2, 127.9, 129.9, 133.3, 135.6, 154.2. IR (neat) (cm^{-1}) 3476, 1699. EI-MS (*m/z*) 470 ($M^+ + 1$). HRMS calcd for $C_{27}H_{39}NO_4Si$ 469.2649, found 469.2657.

(3*R*,4*R*,5*S*)-3,4-Dihydroxy-5-methylpiperidine (14, 5′-deoxyisofagomine). To a solution of **12** (141 mg, 0.30 mmol) in dioxane (2.5 mL) was added a solution of 10% HCl (10 mL), and the solution was heated at reflux for 1 h. After the reaction mixture was cooled to room temperature and diluted with H_2O (50 mL), the resultant dilute solution was washed with Et_2O (2 × 20 mL). The aqueous layer was concentrated under reduced pressure. The residue was dissolved in MeOH and made alkaline with Na_2CO_3. The mixture was filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (10% NH_4OH:MeOH = 1:50) to give **14** (37 mg, 92%) as a white powder; $[\alpha]^{25}_D$ +6.5 (*c* 0.5, EtOH). ^{1}H NMR (600 MHz, D_2O) δ 0.81 (d, J = 6.6 Hz, 3H), 1.36−1.44 (m, 1H), 2.09 (dd, J = 12.8, 11.7 Hz, 1H), 2.25 (dd, J = 12.1, 11.0 Hz, 1H), 2.76 (ddd, J = 13.1, 4.4, 1.5 Hz, 1H), 2.91 (t, J = 9.5 Hz, 1H), 2.97 (ddd, J = 12.3, 5.1, 1.6 Hz, 1H), 3.27−3.32 (m, 1H). ^{13}C NMR (67.8 MHz, D_2O) δ 78.1, 71.2, 49.7, 49.0, 36.8, 13.1. EI-MS (*m/z*) 131 (M^+). HRMS calcd for $C_6H_{13}NO_2$ 131.0946, found 131.0984.

(*R*)-*N*-*tert*-Butoxycarbonyl-5-(*tert*-butyldiphenylsilyloxy)-3-piperidene (*ent*-8). This compound was prepared from (−)-**3** (897 mg, 4.5 mmol), imidazole (511 mg, 7.5 mmol), DMAP (122 mg, 1 mmol), and *tert*-butylchlorodiphenylsilane (1.374 g, 5 mmol) according to the procedure described for the preparation of **8** to give *ent*-**8** (1.96 g, 99%); $[\alpha]^{29}_D$ −22.3 (*c* 1.40, $CHCl_3$).

(3*S*,4*S*,5*S*)-*N*-*tert*-Butoxycarbonyl-3-(*tert*-butyldiphenylsilyloxy)-4,5-epoxypiperidine (*ent*-9) and (3*S*,4*R*,5*R*)-*N*-*tert*-Butoxycarbonyl-3-(*tert*-butyldiphenylsilyloxy)-4,5-epoxypiperidine (*ent*-10). These compounds were prepared from *ent*-**8** (1.40 g, 3.2 mmol), 4 mmol/L of aq Na_2-EDTA (17.5 mL, 0.07 mmol), 1,1,1-trifluoroacetone (3.5 mL), $NaHCO_3$ (2.21 g, 26.25 mmol), and Oxone (10.73 g, 17.5 mmol) according to the procedure described for the preparation of **9** and **10** to give *ent*-**9** (1.04 g, 72%) and *ent*-**10** (272 mg, 19%).

***ent*-9**: $[\alpha]^{31}_D$ −29.7 (*c* 1.82, $CHCl_3$).

***ent*-10**: $[\alpha]^{30}_D$ +6.9 (*c* 1.10, $CHCl_3$).

(3*S*,4*S*,5*R*)-*N*-*tert*-Butoxycarbonyl-3-(*tert*-butyldiphenylsilyloxy)-4-hydroxy-5-vinylpiperidine (*ent*-11). This compound was prepared from *ent*-**9** (454 mg, 1 mmol), *n*-BuLi (3.125 mL, 1.6 M in *n*-hexane, 5 mmol), tetravinyltin (1.14 g, 5 mmol), CuCN (224 mg, 2.5 mmol), and $BF_3{\cdot}OEt_2$ (4 mol/L in Et_2O, 5 mL, 2 mmol) according to the procedure described for the preparation of **11** to give *ent*-**11** (383 mg, 80%); $[\alpha]^{30}_D$ +10.6 (*c* 1.00, $CHCl_3$).

(3*S*,4*S*,5*S*)-3,4-Dihydroxy-5-(hydroxymethyl)piperidine (15). This compound was prepared from *ent*-**11** (241 mg, 0.5 mmol), 4% OsO_4 (164 μL, 0.025 mmol), $NaIO_4$ (238 mg, 1.1 mmol), and $NaBH_4$ (95 mg, 2.5 mmol) according to the procedure described for the preparation of **2** to give (3*S*,4*S*,5*S*)-*N*-*tert*-butoxycarbonyl-3-(*tert*-butyldiphenylsilyloxy)-4-hydroxy-5-(hydroxymethyl)piperidine (216 mg, 89%); $[\alpha]^{30}_D$ +15.5 (*c* 1.16, $CHCl_3$). This compound was prepared from *ent*-**8** (131 mg, 0.27 mmol) according to the procedure described for the preparation of **2** to give **15** (38 mg, 96%); $[\alpha]^{24}_D$ −23.8 (*c* 1.10, EtOH).

(3*S*,4*S*,5*R*)-3,4-Dihydroxy-5-(hydroxyethyl)piperidine (16). This compound was prepared from *ent*-**11** (121 mg, 0.5 mmol), 9-BBN (0.5 mol/L in THF, 2.5 mL, 1.25 mmol), 3 mol/L of aq NaOH (1 mL), and 30% aq H_2O_2 (1 mL) according to the procedure described for the preparation of **13** to give (3*S*,4*S*,5*R*)-*N*-*tert*-butoxycarbonyl-3-(*tert*-butyldiphenylsilyloxy)-4-hydroxy-5-(hydroxyethyl)piperidine (113 mg, 91%); $[\alpha]^{23}_D$ +5.3 (*c* 1.35, $CHCl_3$). This compound was prepared from the diol (90 mg, 0.18 mmol) according to the procedure described for the preparation of **13** to give **16** (28 mg, 97%); $[\alpha]^{25}_D$ −17.8 (*c* 1.13, EtOH).

(3*S*,4*S*,5*R*)-*N*-*tert*-Butoxycarbonyl-3-(*tert*-butyldiphenylsilyloxy)-4-hydroxy-5-methylpiperidine (*ent*-12). This compound was prepared from *ent*-**9** (182 mg, 0.4 mmol), MeLi (2.4 mL, 1.04 mol/L in Et_2O, 2.5 mmol), CuCN (112 mg, 1.25 mmol), and $BF_3{\cdot}OEt_2$ (4 mol/L in Et_2O, 2.5 mL, 1 mmol)

according to the procedure described for the preparation of **12** to give *ent*-**12** (133 mg, 71%); $[\alpha]^{25}_D$ +17.2 (*c* 1.03, $CHCl_3$).

(3*S*,4*S*,5*R*)-3,4-Dihydroxy-5-methylpiperidine (17). This compound was prepared from *ent*-**12** (127 mg, 0.27 mmol) according to the procedure described for the preparation of **3** to give **17** (34 mg, 96%); $[\alpha]^{25}_D$ −7.4 (*c* 0.90, EtOH).

(3*S*,5*S*)-*tert*-Butyl 3,4,5-Trihydroxypiperidine-1-carboxylate (22) and (3*R*,4*s*,5*S*)-*tert*-Butyl 3,4,5-trihydroxypiperidine-1-carboxylate (23). To a solution of *ent*-**8** (219 mg, 0.5 mmol) in acetone (2 mL) was added an aqueous 4% OsO_4 solution (65 μL, 0.01 mmol). After 10 min, an aqueous 50% NMO solution (176 mL, 0.75 mmol) was added and the mixture was stirred overnight. To the solution were added Na_2SO_3 and Na_2SO_4. The mixture was filtered through a Celite pad and the filtrate was evaporated. The residue was chromatographed on silica gel (*n*-hexane:AcOEt = 1:1) to give a diastereoisomeric mixture of *N*-*tert*-butoxycarbonyl-5-*tert*-butyldiphenylsilyloxy-3,4-dihydroxypiperidine (236 mg, 99%). To a solution of the above diol (513.8 mg, 1.09 mmol) in THF (10 mL) was added 1 M TBAF (2,2 mL, 2.2 mmol) in THF at room temperature. After being stirred overnight, sat. K_2CO_3 (5 mL) was added and the reaction mixure was extracted with $CHCl_3$. The aqueous layer was extracted with $CHCl_3$. The combined organic solvents were dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel ($CHCl_3$:MeOH = 1:1) to give **23** (7.4 mg, 3%) and **22** (189 mg, 74%). **22**: $[\alpha]^{22}_D$ +24.5 (*c* 1.74, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (9H, s), 2.57 (1H, br s), 2.73 (1H, br s), 3.01 (1H, d, J = 12.4 Hz), 3.50 (1H, d, J = 7.1 Hz), 3.83 (1H, br s), 3.98−4.05 (3H, m), 4.21−4.43 (1H, m). ^{1}H NMR (400 MHz, CD_3OD) δ 1.45 (9H, s), 2.97, 3.12 (1H, br s), 3.30 (2H, dd, J = 3.2, 1.7 Hz), 3.52−3.86 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.4, 29.7, 47.7, 67.5, 67.9, 74.9, 80.5, 156.0. IR (KBr) (cm^{-1}) 3371 (−OH), 2966, 2932, 2876, 1682 (C=O), 1462, 1428, 1366, 1246, 1168, 1073. EI-MS (*m/z*) 233 (M^+). HRMS calcd for $C_{10}H_{19}NO_5$ 233.1263, found 233.1242.

23: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (9H, s), 3.28 (2H, d, J = 13.2 Hz), 3.74−4.28 (7H, m). ^{1}H NMR (400 MHz, CD_3OD) δ 1.45 (9H, s), 3.16 (1H, br s), 3.29−3.65 (5H, m), 3.85−3.86 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 46.0, 68.8, 70.3, 80.5, 155.9. IR (KBr) (cm^{-1}) 3416 (−OH), 2929, 1693 (C=O), 1540, 1464, 1416, 1367, 1325, 1264, 1232, 1168, 1076, 1017. EI-MS (*m/z*) 233 (M^+). HRMS calcd for $C_{10}H_{19}NO_5$ 233.1263, found 233.1286.

(3*S*,5*S*)-Piperidine-3,4,5-triol (18). A solution of **22** (179.5 mg, 0.38 mmol) in dioxane (1 mL) and 10% HCl (4 mL) was refluxed for 1 h. Et_2O (10 mL) was added to the solution and the mixture was separated. The organic layer was extracted with water and the combined aqueous layers were concentrated to yield the hydrochloride of **18** as a solid. The solid was purified by ion-exchange resin (Amberlite IRA-410, OH^-) to give the free amine **18** (49.6 mg, 98%).

18-HCl: mp 198−199 °C [lit.[25c] mp 195.5−196 °C]. $[\alpha]^{25}_D$ +20.8 (*c* 1.4, CH_3OH), [lit.[25c] $[\alpha]^{20}_D$ +22.7 (*c* 0.8, CH_3OH)]. ^{1}H NMR (400 MHz, D_2O) δ 2.93 (1H, dd, J = 12.7, 8.5 Hz), 3.18 (1H, dd, J = 12.9, 1.7 Hz), 3.27 (1H, dd, J = 12.9, 5.9 Hz), 3.31 (1H, dd, J = 12.7, 3.9 Hz), 3.75 (1H, dt, J = 7.7, 1.3 Hz), 4.04−4.09 (1H, m), 4.21 (1H, ddd, J = 5.9, 2.7, 1.7 Hz). ^{13}C NMR (67.8 MHz, D_2O, reference acetone δ 30.3) δ 45.5, 46.1, 64.7, 65.0, 70.8. IR (KBr) (cm^{-1}) 3343 (−OH), 3088, 2904, 2852, 1610, 1475, 1441, 1408, 1368, 1339, 1306, 1271, 1227, 1208, 1099, 1079, 1056. EI-MS (*m/z*) 133 (M^+). HRMS calcd for $C_5H_{11}NO_3$ 133.0739, found 133.0730.

18: $[\alpha]^{20}_D$ +65.8 (*c* 0.9, CH_3OH) [lit.[23] $[\alpha]_D$ +66.7 (*c* 0.3, CH_3OH)]. ^{1}H NMR (400 MHz, D_2O) δ 2.31 (1H, dd, J = 12.9, 9.5 Hz), 2.62 (1H, dd, J = 14.1, 2.0 Hz), 2.82 (1H, dd, J = 13.9, 3.4 Hz), 2.96 (1H, dd, J = 13.7, 4.4 Hz), 3.45 (1H, dd, J = 8.5, 3.2 Hz), 3.67 (1H, dt, J = 9.0, 4.6 Hz), 3.87 (1H, m). ^{13}C NMR (100 MHz, D_2O, reference acetone δ 30.3) δ 47.4, 47.5, 67.2, 67.3, 72.8. IR (neat) (cm^{-1}) 3388 (−OH), 2928, 2364, 2344, 1736, 1720, 1656, 1640, 1561, 1545, 1452, 1345, 1274, 1072. EI-MS (*m/z*) 133 (M^+). HRMS calcd for $C_5H_{11}NO_3$ 133.0739, found 133.0739.

(3*R*,5*R*)-Piperidine-3,4,5-triol (21). The piperidinetriol **21** was prepared from **8** according to the same procedure described for **18**, via *ent*-**22**.

ent-**22**: (79%); $[\alpha]^{28}_D$ −25.0 (*c* 1.33, $CHCl_3$).

21-HCl: $[\alpha]^{25}_D$ −20.7 (*c* 1.1, CH_3OH) [lit. [25c] $[\alpha]^{20}_D$ −22 (*c* 0.8, CH_3OH)].

21: (98%); $[\alpha]^{20}_D$ −66.0 (*c* 1.2, CH_3OH).

(3*R*,4*s*,5*S*)-*tert*-Butyl 3,4,5-trihydroxypiperidine-1-carboxylate (23) and (±)-22. A solution of OsO_4 (254.2 mg, 1 mmol) in CH_2Cl_2 (1 mL) was added to a solution of (±)-**3** (199 mg, 1 mmol) and TMEDA (116 mg, 1 mmol) in CH_2Cl_2 (22 mL) at −78 °C. The mixture was stirred at the same temperature for 2 h, warmed to room temperature, and stirred for 2 h. The reaction mixture was evaporated. The resulting residue was dissolved in MeOH (10 mL). Hydrochloric acid (conc 7 drops) was then added and the solution was stirred for 2 h at room temperature. The reaction mixture was concentrated under reduced pressure. The residue was redissolved in MeOH (15 mL) and Et_3N (202 mg, 2 mmol) and Boc_2O (262 mg, 1.2 mmol) were added to the resulting mixture. The reaction mixture was stirred at room temperature overnight and then evaporated. The residue was purified by chromatography on silica gel ($CHCl_3$:MeOH = 10:1) to give **23** (153 mg, 66%) and (±)-**22** (38 mg, 16%).

(3*R*,4*s*,5*S*)-Piperidine-3,4,5-triol (19). A solution of **23** (179.5 mg, 0.38 mmol) in dioxane (1 mL) and 10% HCl (4 mL) was refluxed for 1 h. Et_2O (10 mL) was added to the solution and the mixture was separated. The organic layer was extracted with water and the combined aqueous layers were concentrated to yield the hydrochloride of **19** as a solid. The solid was purified by ion-exchange resin (Amberlite IRA-410, OH^-) to give the free amine **19** (42.5 mg, 84%).

19-HCl: mp 182−184 °C [lit.[25c] mp 185−187 °C]. ^{1}H NMR (400 MHz, D_2O) δ 3.10−3.15 (4H, m), 3.92−3.97 (3H, m). ^{13}C NMR (100 MHz, D_2O, reference acetone δ 30.3) δ 44.1, 65.5, 68.3. IR (KBr) (cm^{-1}) 3435 (−OH), 2944, 2824, 2674, 2568, 1582, 1465, 1439, 1415, 1339, 1320, 1255, 1190, 1117, 1094. EI-MS (*m/z*) 133 (M^+). HRMS calcd for $C_5H_{11}NO_3$ 133.0739, found 133.0764.

19: mp 163−165 °C. ^{1}H NMR (400 MHz, D_2O) δ 2.57 (2H, d, J = 9.0 Hz), 2.64 (2H, dd, J = 12.7, 4.4 Hz), 3.58−3.62 (2H, m), 3.86 (1H, s). ^{13}C NMR (100 MHz, D_2O, reference acetone δ 30.3) δ 44.9, 68.6, 70.6. IR (KBr) (cm^{-1}) 3390 (−OH), 3285, 2930, 1866, 1842, 1790, 1456, 1041. EI-MS (*m/z*) 133 (M^+). HRMS calcd for $C_5H_{11}NO_3$ 133.0739, found 133.0715.

(3*S*,5*S*)-Piperidine-3,4,5-triol (20). A mixture of (±)-**9** (436 mg, 0.96 mmol) in dioxane (6 mL), H_2O (4 mL), and concentrated H_2SO_4 (0.64 mL) was heated at 95 °C for 3 h. The reaction mixture was concentrated and the residue was purified by ion-exchange resin (Amberlite IRA-410, OH^-) to give the free amines **20** (69.7 mg, 55%) and (±)-**18** (26.0 mg, 20%).

20: mp 160−162 °C. ^{1}H NMR (400 MHz, D_2O) δ 2.23 (2H, dd, J = 12.7, 0.7 Hz), 2.93 (2H, dd, J = 12.4, 4.9 Hz), 3.12 (2H, dt, J = 16.1, 2.2 Hz), 3.29−3.36 (1H, m). ^{13}C NMR (270 MHz, D_2O, reference acetone δ 30.3) δ 49.3, 71.0, 78.4. IR (KBr) (cm^{-1}) 3405 (−OH), 3308, 2976, 2909, 2860, 2690, 1654, 1457, 1365, 1337, 1286. EI-MS (*m/z*) 133 (M^+). HRMS calcd for $C_5H_{11}NO_3$ 133.0739, found 133.0728.

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Supporting Information Available: Copies of ^{1}H NMR and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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