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Asymmetric Synthesis of the Four Possible Fagomine Isomers

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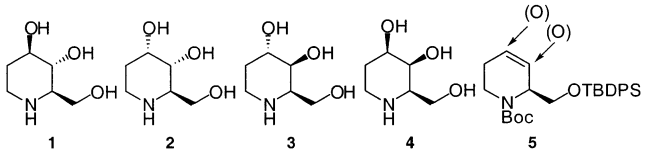
The asymmetric synthesis of fagomine and its congeners **1**−**4** has been achieved by catalytic ring-closing metathesis (RCM). The synthesis involved the construction of the piperidene-type chiral building block **5** followed by dihydroxylation, starting from the D-serine-derived Garner aldehyde **6**.

Introduction

Polyhydroxylated nitrogen heterocycles (azasugars) represent sugar analogues in which the ring oxygen has been substituted for a nitrogen atom. Many of these compounds, which are frequently inhibitors of carbohydrate-processing enzymes, have the potential for use in a wide range of potential therapeutic strategies including the treatment of viral infections, cancer, diabetes, tuberculosis, and lysosomal storage diseases, and as inhibitors of the growth of parasitic protozoa.[1−5] As a result, the synthesis of polyhydroxylated piperidines and their synthetic analogues has attracted a great deal of attention in recent years.[6] Recently the isolation of three fagomine isomers **1**−**3** from *Xanthocercis zambesiaca* occurring in a southern African dry forest has been reported.[6] Among these, fagomine **1** and 3-*epi*-fagomine **2** were found to have some activity against mammalian gut α-glucosidase and *β*-galactosidase.[7] More recently, **1** was reported to have a potent antihyperglycemic effect in streptozocin-induced diabetic mice and the potentiation for glucose-induced insulin secretion.[8] Very recently it was reported that fagomine isomer **4** (not naturally occurring) is an inhibitor of lysosomal α-galactosidase A activity in Fabry lymphoblasts.[9] Thus far, the asymmetric synthesis of **1** has been reported twice,[10] whereas no report of the synthesis of **2** and 3,4-di-*epi*-fagomine **3** has been yet appeared. On the other hand, 4-*epi*-fagomine (1,2-dideoxygalactstatin) **4** has been obtained once by transformation from **1**.[11] In a project focusing on the chiral synthesis of glycosidase inhibitors, our goal was the preparation of a new common chiral building block, hydroxymethylpiperidene **5**, which appears to be an ideal precursor for the synthesis of dihydroxypiperidinols. In this paper we report on a new synthesis of all fagomine isomers **1**−**4** *via* the preparation of **5** in a straightforward and stereoselective manner with Garner aldehyde **6** and catalytic ring-closing metathesis (RCM) of the diene system **9** for the construction of the piperidine ring.[12,13]



Results and Discussion

Our synthesis of **5** began with the Wittig reaction of the D-serine-derived Garner aldehyde **6**.[14] Treatment of **6** with methyltriphenylphosphonium iodide in the presence of sodium bis(trimethylsilyl)amide gave olefin **7** in

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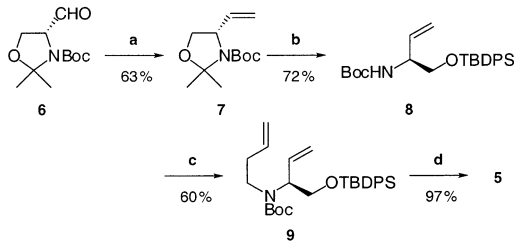
SCHEME 1[a]

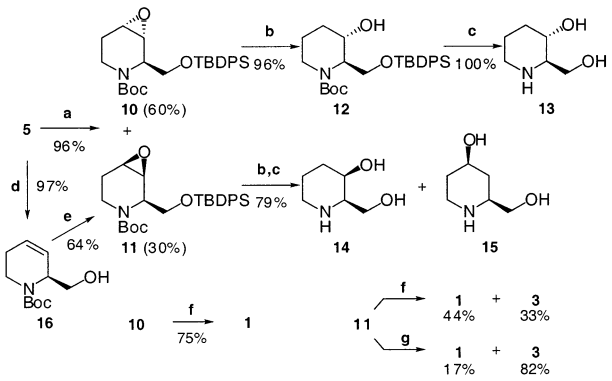


[a] Reagents and conditions: (a) $Ph_3P^+CH_3I^-$, $NaN(TMS)_2$, THF. (b) (i) *p*-TsOH·H_2O, MeOH; (ii) TBDPSCl, DMAP, imidazole, CH_2Cl_2. (c) (i) CF_3COOH, CH_2Cl_2; (ii) 4-bromo-1-butene, K_2CO_3, CH_3CN; (iii) $(Boc)_2O$, Et_3N, THF. (d) Grubbs' catalyst, CH_2Cl_2.

63% yield.[15] Hydrolysis of **7** with *p*-toluenesulfonic acid in MeOH followed by *O*-silylation afforded **8** in 72% yield. *N*-Alkylation of **8** with 4-bromo-1-butene under various conditions resulted in the recovery of the starting material **8**.[16] However, a three-step sequence [(1) deprotection of the *N*-Boc group; (2) alkylation; and (3) *N*-protection] provided the butenylated product **9** in 60% overall yield. RCM of **9** with Grubbs' catalyst, (benzylidine)bis(tricyclohexylphosphine)ruthenium(IV) dichloride, under the usual conditions gave the desired intermediate **5** {$[\alpha]^{27}_D$ −150.1° (*c* 1.04, $CHCl_3$)} in 97% yield.

With the promising educt **5** in hand, our interest was then directed to the synthesis of all isomers **1**−**4** of fagomine. We first introduced the epoxy-functionality into the double bond to obtain both **1** and **3** containing trans diols at the 3 and 4 positions. The dioxirane, generated in situ from Oxone with 1,1,1-trifluoroacetone according to a recent procedure,[17] was reacted with **5** to give a mixture of stereoisomeric epoxy compounds **10** and **11** which were separated by medium-pressure chromatography in a high yield of 90% though the diastereoselectivity was low (ds: 33%).[18,19] The stereochemistry of the epoxy products was determined by the stereoselective cleavage of the epoxy ring with Super-Hydride. Treatment of **10** with Super-Hydride in THF led to the hydroxylated product **12** (96%). Complete deprotection of **12** with hydrochloric acid in 1,4-dioxane followed by treatment of the resulting salt with an ion-exchange resin (Dowex 1×2 OH^- form) afforded the known (2*R*,3*S*)-3-hydroxy-2-hydroxymethylpiperidine **13**[20] in quantitative yield. An analogous procedure, using **11**, provided (2*R*,3*R*)-3-hydroxy-2-hydroxymethylpiperidine **14**[21] and (2*S*,4*R*)-4-hydroxy-2-hydroxymethylpiperidine **15**[22] as a 1:5 ratio in 79% combined yield. The *syn* epoxide **11** was stereoselectively obtained by an alternative method. Desilylation of **5** with TBAF was carried out to afford **16** (97% yield). Starting with **16**, hydroxy-directed epoxidation

SCHEME 2[a]



[a] Reagents and conditions: (a) Oxone, CF_3COCH_3, $NaHCO_3$, aq Na_2·EDTA, CH_3CN. (b) Super-Hydride, THF. (c) (i) 35% HCl, 1,4-dioxane; (ii) Dowex 1× 2 (OH^- form). (d) TBAF, THF. (e) (i) *m*-CPBA, $NaHCO_3$, CH_2Cl_2; (ii) TBDPSCl, DMAP, imidazole, CH_2Cl_2. (f) H_2SO_4, 1,4-dioxane, H_2O. (g) KOH, 1,4-dioxane, H_2O.

with *m*-CPBA followed by silylation afforded **11** in 64% overall yield. The acid hydrolysis of the epoxy ring of **10** was accomplished by using a mixture of H_2SO_4/1,4-dioxane/H_2O in a milliliter ratio of 0.2/3/2,[23] and further treatment with an ion-exchange resin (Amberlite IRA-410) gave only fagomine **1** in 75% yield. Although a rationale of this high selectivity remains unclear, we consider the following explanation: an attack of H_2O, as a nucleophile with backside displacement of the leaving oxygen in the epoxy-substituted ring, occurs at the more remote site (4 position) because a nucleophilic attack at the 3 position has a *syn* orientation with respect to the adjacent hydroxymethyl substiuent at the 2 position. In addition, opening of cyclohexene oxide generally proceeds in such a fashion that the diaxial reaction product is obtained. On the other hand, similar treatment of **11** afforded a mixture of **1** and 3,4-di-*epi*-fagomine **3** in 77% combined yield and a ratio of 1.3:1, which were separated by ion-exchange resin (Dowex 1×2 OH^- form) chromatography. In this case, due to the *anti* relation between the hydroxymethyl substiuent at the 2 position and the attack orientation, a backside attack of H_2O on the epoxy ring would occur at both the 3 and 4 positions with a nearly equal probability. In contrast, the basic cleavage of epoxide **11** with use of a mixture of KOH/1,4-dioxane/H_2O gave **3** preferentially, in a ratio of 5:1 (**3** to **1**) in 99% combined yield.

The stereoselective dihydroxylation of the double bond was next examined. Under modified Upjohn conditions,[24] the treatment of **5** with a catalytic amount of K_2OsO_4·$2H_2O$ (5 mol %) and 4-methylmorpholine *N*-oxide (1.5 equiv) as a cooxidant gave the diol **17** as a single diastereoisomer in a high yield of 92%.[18] Deprotection of **17** with 10% hydrochloric acid in 1,4-dioxane followed by treatment with ion-exchange resin (Dowex 1×2 OH^- form) afforded 3-*epi*-fagomine **2** in 91% yield. Surprisingly, both AD-mix-α- and β-mediated dihydroxylation provided **17** with no diastereomer detected, in 94% and 96% yields, respectively. Dihydroxylation exclusively

(15) This is a two-step yield from the Garner alcohol.[14]

(16) Several conditions: (1) NaH, *N*,*N*-dimethylformamide, 60 °C; (2) pulverized KOH, cat. *n*-Bu_4NI, THF, reflux; (3) pulverized KOH, cat. 18-crown-6-ether, THF, reflux.

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(19) *m*-CPBA epoxidation resulted in very low yield (6%).

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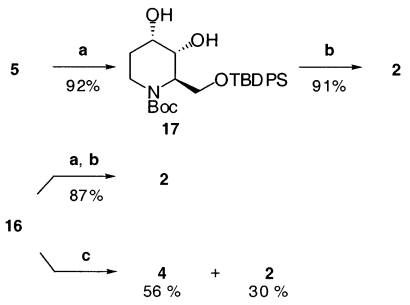
SCHEME 3[a]



[a] Reagents and conditions: (a) cat. $K_2OsO_4 \cdot 2H_2O$, NMO, H_2O, acetone. (b) 10% HCl, 1,4-dioxane. (c) (i) OsO_4, TMEDA, CH_2Cl_2; (ii) 35% HCl, MeOH.

occurred from the less hindered *anti* side of the siloxymethyl substituent, which adopts an axial position due to 1,3-allylic strain. The dihydroxylation of **16** under the above modified Upjohn conditions also took place from the *anti* side of the hydroxymethyl group followed by deprotection to give **2** as a single diastereomer in 87% combined yield. Very recently, Donohoe reported[25] that osminum tetroxide produces a bidendate and reactive complex with TMEDA, which accomplishes the directed dihydroxylation of homoallyic alcohols. Therefore, the oxidation of **16** with use of a combination of OsO_4 with TMEDA followed by deprotection gave **4** and **2** in moderate selectivity (2:1) in 56% and 30% yields, respectively.

In conclusion, a rapid and straightforward route to the stereoselective asymmetric synthesis of all fagomine isomers **1**−**4** (the first total synthesis for **2** and **3**) with use of a common chiral piperidene **5** is described. Piperidene **5** should be useful as a chiral building block for the synthesis of the piperidine-related alkaloids.[26]

Experimental Section

General Procedures. Melting points were determined with a Yanaco micro melting point apparatus and are uncorrected. Microanalyses were performed by Microanalysis Center of Toyama Medical & Pharmaceutical University with a Perkin-Elmer 2400 Series II Analyzer. IR spectra were measured with a Perkin-Elmer 1600 series FTIR spectrophotometer. ^{1}H NMR spectra were recorded either at 300 MHz on a Varian Gemini-300, at 400 MHz on a JEOL GSX 400, or at 500 MHz on a Varian Unity-500 with $CHCl_3$ (7.26 ppm) as internal standard. ^{13}C NMR spectra were recorded at 75 or 100 or 125 MHz with $CHCl_3$ (77.2 ppm) as an internal standard unless otherwise specified. MS and HRMS were measured on a JEOL JMS D-200 spectrometer. Optical rotations were measured on a JASCO DIP-140 instrument. Column chromatography was performed on silica gel (Fuji-Division BW-200 or Merck 60 (No. 9385)) with a medium-pressure apparatus and a mixture of ethyl acetate/hexane or acetone/hexane was used as eluent unless otherwise specified. Purification of products via ion-exchange resin chromatography was performed with Dowex 1×2 OH^- form, using water as eluent. The extracts were dried over Na_2SO_4 unless otherwise specified. Copies of ^{1}H and ^{13}C NMR spectra are supplied in the Supporting Information.

(*R*)-2,2-Dimethyl-4-vinyloxazolidine-3-carboxylic Acid *tert*-Butyl Ester (7). NaHMDS (1 N, 27.4 mL, 27.4 mmol) in THF was added dropwise to a suspension of methyltriphenylphosphonium iodide (11.1 g, 27.4 mmol) in THF (32.9 mL) at −20 °C and the mixture was stirred for 15 min. A solution of the Garner aldehyde (**6**, 4.74 g, 20.7 mmol) in THF (20.7 mL) was added dropwise to the mixture and then the reaction mixture was stirred at −20 °C overnight. Saturated NH_4Cl was added to the mixture and extracted with ether. The extract was washed with brine, dried, and evaporated. The residue was purified by chromatography (5−6% AcOEt in hexane) to yield **7** (2.61 g, 63%) as an oil; $[\alpha]^{26}_D$ −18.9° (*c* 1.32, $CHCl_3$); [lit.[27] $[\alpha]^{20}_D$ −17.1° (*c* 1.20, $CHCl_3$)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.38 (s, 6H), 1.44 (s, 3H), 1.46 (s, 3H), 1.56 (s, 3H), 3.70 (dd, J = 8.7, 2.5 Hz, 1H), 4.00 (dd, J = 8.9, 6.4 Hz, 1H), 4.22 (br s, 0.5H), 4.35 (br s, 0.5H), 5.09 (m, 1H), 5.19 (br s, J = 17 Hz, 1H), 5.77 (br d, J = 6.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.7, 24.9, 26.6, 27.3, 28.5, 59.7, 68.2, 79.6, 94.0, 115.8, 137.5, 152.0; IR (neat) 2979.1, 1697.6, 1382.5 cm^{-1}; HRMS calcd for $C_{12}H_{21}NO_3$ (M^+) 227.1617, found 227.1493.

***(S)*-[1-(*tert*-Butyldiphenylsilanyloxymethyl)allyl]-carbamic Acid *tert*-Butyl Ester (8).** A mixture of **7** (3.96 g, 17.4 mmol) and *p*-TsOH·H_2O (910 mg, 4.79 mmol) in MeOH (163.1 mL) was stirred at room temperature overnight. After evaporation, saturated $NaHCO_3$ was added to the residue. The mixture was extracted with AcOEt. The extract was dried and evaporated to leave a yellow oil. A mixture of the residue (2.96 g), imidazole (1.58 g, 23.2 mmol), DMAP (379 mg, 3.10 mmol), and TBDPSCl (4.44 mL, 17.1 mmol) in CH_2Cl_2 (21.7 mL) was stirred at room temperature overnight. The mixture was filtered off and the filtrate was washed with brine, dried, and evaporated. The residue was purified by chromatography (5−10% AcOEt in hexane) to yield **8** (5.30 g, 72%) as an oil; $[\alpha]^{25}_D$ −27.7° (*c* 1.02, $CHCl_3$); IR (neat) 2932.5, 1495.6, 1110.5 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.47 (s, 9H), 3.64−3.66 (m, 1H), 3.75−3.76 (m, 1H), 4.27 (br s, 1H), 4.87 (br s, 1H), 5.18 (dd, J = 10.2, 1.2 Hz, 1H), 5.24 (dd, J = 17.5, 1.2 Hz, 1H), 5.85 (ddd, J = 12.5, 10.4, 5.3 Hz, 1H), 7.35−7.46 (m, 6H), 7.65−7.75 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.5, 27.0, 28.6, 54.4, 66.1, 79.6, 115.7, 127.7, 129.8, 133.1, 133.2, 135.5, 135.6, 136.4, 155.4; HRMS calcd for $C_{25}H_{35}NO_3Si$ (M^+) 425.2403, found 425.2373.

***(S)*-But-3-enyl[1-(*tert*-butyldiphenylsilanyloxymethyl)allyl]carbamic Acid *tert*-Butyl Ester (9).** A mixture of **8** (11.6 g, 27.3 mmol) and TFA (131.1 mL) in CH_2Cl_2 (131.1 mL) was stirred at room temperature for 1 h and evaporated. To the mixture was added saturated $NaHCO_3$. The mixture was extracted with CH_2Cl_2, dried with K_2CO_3, and evaporated to leave an yellow oil (8.35 g). K_2CO_3 (2.206 mg, 15.96 mmol) was added to a solution of the residue (5.19 g, 15.96 mmol) in CH_3CN (64.4 mL) and the mixture was stirred for 1 h. 4-Bromo-1-butene (1.62 mL, 15.96 mmol) was added to the mixture and then the reaction mixture was heated at 90 °C overnight. The insoluble materials were filtered off and the filtrate was evaporated. To the residue was added CH_2Cl_2 and saturated $NaHCO_3$. After being stirred for 30 min, the mixture was separated in organic and aqueous layers. The aqueous layer was extracted with CH_2Cl_2. The combined organic solvents were dried with K_2CO_3 and evaporated. Et_3N (5.48 mL, 39.3 mmol) was added to a solution of the residue (5.61 g, 14.8 mmol) in THF (56.7 mL) at 0 °C and then a solution of $(Boc)_2O$ (4.2 mL, 18.3 mmol) in THF (28.6 mL) was added to the mixture over 1 h at the same temperature. After being stirred at room temperature overnight, the mixture was evaporated. HCl (1 N) was added to a solution of residue in ether with ice cooling. The mixture was separated in organic and aqueous layers. The aqueous layer was extracted with ether. The combined organic solvents were washed with saturated $NaHCO_3$, dried, and evaporated. The residue was

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purified by chromatography (3−4% AcOEt in hexane) to yield **9** (4.88 g, 60%) as an oil; $[\alpha]^{25}_D$ −0.36° (*c* 1.02, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (s, 9H), 1.38−1.59 (m, 9H), 2.30 (q, J = 7.6 Hz, 1H), 3.14−3.22 (m, 2H), 3.65−3.80 (m, 2H), 4.23 (br s, 0.5H), 4.59 (br s, 0.5H), 4.92−5.21 (m, 4H), 5.68−5.89 (m, 2H), 7.35−7.45 (m, 6H), 7.64−7.67 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5, 27.0, 28.7, 33.6, 45.7, 50.9, 65.2, 79.5, 115.2, 116.1, 127.6, 127.7, 129.6, 129.7, 133.4, 135.6, 135.7, 135.8, 137.1, 155.4; IR (neat) 2933.0, 2859.7, 1693.3; HRMS calcd for $C_{29}H_{41}NO_3Si$ (M^+) 479.2863, found 479.2849.

(*S*)-6-(*tert*-Butyldiphenylsilanyloxymethyl)-3,6-dihydro-2*H*-pyridine-1-carboxylic Acid *tert*-Butyl Ester (5). A solution of Grubbs' catalyst (223 mg, 0.271 mmol) in CH_2Cl_2 (103 mL) was added to a solution of **9** (2.60 g, 5.42 mmol) in CH_2Cl_2 (103 mL) under Ar and the reaction mixture was stirred at room temperature overnight. After evaporation, the residue was purified by chromatography (4% AcOEt in hexane) to yield **5** (2.371 g, 97%) as an oil; $[\alpha]^{27}_D$ −150.0° (*c* 1.04, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.39−1.49 (m, 9H), 1.96 (m, 1H), 2. 22 (m, 1H), 2.93 (m, 1H), 3.71−3.72 (m, 2H), 4.45 (m, 0.5H), 4.64 (m, 0.5H), 5.82 (m, 1H), 5.97 (m, 1H), 7.38−7.45 (m, 6H), 7.68−7.71 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.3, 24.9, 26.9, 28.5, 37.4, 39.5, 53.8, 65.3, 79.6, 126.2, 126.8, 127.7, 129.7, 133.4, 135.6, 135.7, 154.7; IR (neat) 2931.5, 1419.4, 1110.1 cm^{-1}; HRMS calcd for $C_{27}H_{37}NO_3Si$ (M^+) 451.2534, found 451.2550.

(2*R*,6*S*,7*R*)-2-(*tert*-Butyldiphenylsilanyloxymethyl)-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylic Acid *tert*-Butyl Ester (11) and (2*R*,6*R*,7*S*)-2-(*tert*-Butyldiphenylsilanyloxymethyl)-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylic Acid *tert*-Butyl Ester (10). To a solution of **9** (290 mg, 0.64 mmol) in CH_3CN (4.9 mL) was successively added 4×10^{-4} M Na_2·EDTA (3.2 mL) and CF_3COCH_3 (0.6 mL) at 0 °C. A mixture of $NaHCO_3$ (419 mg) and Oxone (1.97 g) was added to the reaction mixture over 1 h at 0 °C and the whole mixture was stirred at the same temperature for 30 min. H_2O (5 mL) was added to the reaction mixture and the mixture was extracted with CH_2Cl_2. The extract was dried and evaporated. The residue was purified by chromatography (hexane:AcOEt 5:1) to yield **10** and **11** (298 mg) as a diastereomeric mixture. The mixture was repurified by medium-pressure chromatography (hexane:AcOEt 15:1) to yield **11** (91 mg, 30%) and **10** (181 mg, 60%) as oils. **11**: $[\alpha]^{24}_D$ −71.2° (*c* 1.27, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.07 (s, 9H), 1.38 (s, 6H), 1.44 (s, 3H), 1.86−2.01 (m, 2H), 2.63−2.67 (m, 1H), 3.34−3.71 (m, 3H), 3.79−3.83 (m, 2H), 4.44−4.45 (m, 0.75H), 4.75 (br s, 0.25H), 7.36−7.41 (m, 6H), 7.69−7.73 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.4, 25.3, 26.9, 28.4, 33.6, 51.5, 51.6, 51.9, 61.6, 80.4, 127.8, 129.8, 133.6, 135.6, 135.7, 135.8, 154.3; IR (neat) 2931.7, 1696.0, 1416.1, 1110.8, 1003.5 cm^{-1}; HRMS calcd for $C_{27}H_{37}NO_4Si$ (M^+) 467.2422, found 467.2398. **10**: $[\alpha]^{26}_D$ −50.3° (*c* 1.42,$CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.06 (s, 9H), 1.40 (s, 9H), 1.88−1.93 (m, 1H), 1.99 (br s, 1H), 3.00 (br s, 1H), 3.28 (br s, 1H), 3.31 (br s, 1H), 3.40−3.88 (m, 3H), 4.50 (br s, 1H), 7.36−7.45 (m, 6H), 7.63−7.67 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.3, 22.8, 26.9, 28.5, 50.5, 51.8, 63.8, 80.3, 127.95, 127.96, 129.9, 130.0, 133.109, 135.6, 135.7, 155.3; IR (neat) 2932.3, 1695.4, 1421.5, 1172.1, 1109.9 cm^{-1}; HRMS calcd for $C_{27}H_{37}NO_4Si$ (M^+) 467.2422, found 467.2552.

(2*R*,3*S*)-2-(*tert*-Butyldiphenylsilanyloxymethyl)-3-hydroxypiperidine-1-carboxylic Acid *tert*-Butyl Ester (12). Super-Hydride (0.77 mL, 0.77 mmol) was added to a solution of **10** (181.1 mg, 0.39 mmol) in THF (1.5 mL) and the mixture was stirred at 0 °C for 3 h. Several pieces of ice were added to the mixture. After the mixture was stirred for 15 min, H_2O (1.29 mL) was added to the mixture. The mixture was extracted with CH_2Cl_2 (10.4 mL) three times. The extracts were dried and evaporated. The residue was purified by chromatography (hexane:AcOEt 3:1) to yield **12** (175 mg, 96%) as a pale yellow oil; $[\alpha]^{23}_D$ −32.9° (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.43 (s, 9H), 1.50−1.89 (m, 5H), 2.67 (td, J = 13.2, 3.1 Hz, 1H), 3.69 (d, J = 6.6 Hz, 2H), 3.96 (br d, J = 12.2 Hz, 1H), 4.11 (br s, 1H), 4.34 (br s, 1H), 7.37−7.46 (m, 6H), 7.64−7.66 (m, 4H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 19.1, 19.5, 26.6, 27.1, 28.7, 39.8, 59.0, 61.9, 65.4, 79.9, 127.9, 129.9, 133.1, 133.3, 135.6, 156.0; IR (neat) 3440.4, 2932.3, 2858.6, 1688.4 cm^{-1}; HRMS calcd for $C_{27}H_{39}NO_4Si$ 467.2422, found 467.2552.

(2*R*,3*S*)-2-Hydroxymethylpiperidin-3-ol (13). A solution of **12** (148.6 mg, 0.31 mmol) and 35% HCl (1.2 mL) in 1,4-dioxane (1.2 mL) was refluxed for 1 h. The mixture was evaporated, diluted with H_2O, washed with ether, and evaporated. Two drops of 30% NaOH was added to the residue. The mixture was dissolved with a mixture of $CHCl_3$:IPA (4:1) (15 mL), dried with K_2CO_3, and evaporated. The residue was purified by ion-exchange resin chromatography to yield **13** (45 mg, 100%) as a solid; mp 154−155 °C; $[\alpha]^{23}_D$ +58.3° (*c* 1.06, MeOH); ^1H NMR (500 MHz, D_2O) δ 1.27 (br d, J = 10.2 Hz, 1H), 1.40 (br d, J = 10.2 Hz, 1H), 1.65 (br s, 1H), 1.93 (br s, 1H), 2.46 (br s, 2H), 2.91 (br d, J = 9.4 Hz, 1H), 3.34 (br s, 1H), 3.51 (br s,1H), 3.74 (br s, 1H); ^{13}C NMR (125 MHz, D_2O/free) δ 24.1, 32.9, 45.0, 61.9, 63.1, 68.1; ^{13}C NMR (125 MHz, D_2O/HCl salt) δ 21.0, 31.1, 44.1, 58.6, 62.2, 65.2. Anal. Calcd for $C_6H_{13}NO_2$: C, 54.94; N, 10.68; H, 9.99. Found: C, 54.66; N, 10.55; H, 9.71.

(2*R*,3*R*)-2-Hydroxymethylpiperidin-3-ol (14) and (2*S*,4*R*)-2-Hydroxymethylpiperidin-4-ol (15). Super-Hydride (0.77 mL, 0.77 mmol) was added to a solution of **11** (90.9 mg, 0.19 mmol) in THF (0.8 mL) and the mixture was stirred at 0 °C for 3 h. Several pieces of ice were added to the mixture. After the mixture was stirred for 15 min, H_2O (1.29 mL) was added to the mixture. The mixture was extracted with CH_2Cl_2 (10 mL) three times. The extracts were dried and evaporated. The residue was purified by chromatography (hexane:AcOEt 3:1) to yield piperidinols (77.7 mg) as an inseparable mixture. A solution of the mixture (59.4 mg) and 35% HCl (0.5 mL) in 1,4-dioxane (0.5 mL) was refluxed for 1 h. The mixture was evaporated, diluted with H_2O, washed with ether, and evaporated. Two drops of 30% NaOH was added to the residue. The mixture was dissolved with a mixture of $CHCl_3$:IPA (4:1) (25 mL), dried with K_2CO_3, and evaporated. The residue was purified by ion-exchange resin chromatography to yield **14** and **15**. **14**: oil; $[\alpha]^{21}_D$ −12.4° (*c* 2.51, H_2O); ^1H NMR (400 MHz, D_2O) δ 1.32−1.38 (m, 1H), 1.46−1.72 (m, 3H), 2.50 (td, J = 12.3, 3.2 Hz, 1H), 2.68 (ddd, J = 7.3, 6.0, 1.6 Hz, 1H), 2.90 (d, J = 12.7 Hz, 1H), 3.41−3.51 (2H, m), 3.80−3.81 (m, 1H); ^{13}C NMR (75 MHz, D_2O/free) δ 20.6, 31.0, 45.2, 60.0, 62.7, 65.7; ^{13}C NMR (75 MHz, D_2O/HCl salt) δ 17.2, 29.2, 44.9, 60.5, 61.1, 63.3; ^{13}C NMR (75 MHz, D_2O/*p*-TsOH salt) δ 18.5, 21.9, 31.0, 46.0, 61.9, 62.7, 64.1, 127.2, 130.2, 142.2, 143.6; HRMS calcd for $C_6H_{13}NO_2$ (M^+) 131.0879, found 131.0956. **15**: oil; $[\alpha]^{21}_D$ +11.2° (*c* 1.10, H_2O); ^1H NMR (500 MHz, D_2O) δ 0.87 (dd, J = 23.5, 11.8 Hz, 1H), 1.14 (ddd, J = 24.1, 12.8, 4.5 Hz, 1H), 1.74−1.79 (m, 2H), 2.42 (td, J = 12.7, 2.4 Hz, 1H), 2.52−2.57 (m, 1H), 2.90 (ddd, J = 12.6, 4.3, 2.4 Hz, 1H), 3.30 (dd, J = 11.2, 7.1 Hz, 1H), 3.38 (dd, J = 11.3, 4.8 Hz, 1H), 3.53−3.61 (m, 1H); ^{13}C NMR (75 MHz, D_2O/free) δ 34.4, 36.9, 43.8, 58.4, 65.7, 68.8; ^{13}C NMR (75 MHz, D_2O/HCl salt) δ 31.1, 33.7, 43.1, 57.5, 62.1, 65.8; HRMS calcd for $C_6H_{13}NO_2$ (M^+) 131.0879, found 131.0881.

(*S*)-6-Hydroxymethyl-3,6-dihydro-2*H*-pyridine-1-carboxylic Acid *tert*-Butyl Ester (16). TBAF (1.04 mL, 1.04 mmol) was added to a solution of **5** (390 mg, 0.86 mmol) in THF (10 mL) with ice cooling and the mixture was stirred at room temperature for 2.5 h. After being diluted with H_2O, the mixture was extracted with AcOEt three times. The extracts were washed with brine, dried, and evaporated. The residue was purified by chromatography (hexane:AcOEt 3:1) to yield **16** (179.2 mg, 97%) as an oil; $[\alpha]^{24}_D$ −227.5° (*c* 1.02, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 9H), 1.91−1.99 (m, 1H), 2.12−2.21 (m, 1H), 2.52 (br s, 0.5H), 2.83−2.90 (m, 1H), 3.17 (br s, 0.5H), 3.57−3.63 (m, 2H), 4.05 (br s, 1H), 4.49 (br s, 1H), 5.57−5.63 (m, 1H), 5.88−5.93 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0, 26.7, 28.6, 39.3, 54.2, 64.8, 80.2, 124.7, 127.5,

134.7; IR (neat) 3440.0, 2975.8, 2930.1, 1693.0, 1674.3, 1423.6 cm^{-1}; HRMS calcd for $C_{11}H_{19}NO_3$ (M^+) 213.1652, found 213.1287.

(2*R*,6*S*,7*R*)-2-(*tert*-Butyldiphenylsilanyloxymethyl)-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylic Acid *tert*-Butyl Ester (11). Alternate method: NaH_2PO_4 (185.7 mg, 1.55 mmol) and *m*-CPBA (267 mg, 1.55 mmol) were added to a solution of **16** (47.9 mg, 0.224 mmol) in CH_2Cl_2 (4 mL). After being stirred at room temperature overnight, the mixture was diluted with AcOEt. The mixture was successively washed with 10% Na_2SO_3, H_2O, 5% Na_2CO_3, and brine and dried. Evaporation yielded (2*R*,6*S*,7*R*)-2-hydroxymethyl-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylic acid *tert*-butyl ester (42.3 mg, 82%) as a yellow oil; $[\alpha]^{21}_D$ −106.8° (*c* 0.59, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.88−2.00 (m, 2H), 2.24 (br s, 0.5H), 2.78−2.94 (m, 1.5H), 3.36 (br s, 2H), 3.69−3.81 (m, 3H), 4.37 (br s, 0.5H), 4.53 (br s, 0.5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.3, 28.6, 33.9, 35.0, 51.2, 51.9, 61.8, 62.4, 80.4; IR (neat) 3439.0, 2977.3, 2933.4, 1684.8 cm^{-1}; HRMS calcd for $C_{11}H_{19}NO_4$ (M^+) 229.1333, found 229.1309.

Imidazole (18.9 mg, 2.78 mmol), DMAP (1 mg), and TBDPSCl (53 μL, 0.203 mmol) were added to a solution of the prepared epoxide (42.3 mg, 0.185 mmol) in CH_2Cl_2 (0.26 mL) with ice cooling and the mixture was stirred at room temperature overnight. The insoluble materials were filtered off. The filtrate was washed with brine, dried, and evaporated. The residue was purified by chromatography (hexane:AcOEt 5:1) to yield **11** (67.3 mg, 78%) as an oil.

D-Fagomine [(2*R*,3*R*,4*R*)-2-Hydroxymethylpiperidine-3,4-diol] (1). A mixture of **10** (170 mg, 0.356 mmol), 1,4-dioxane (2.2 mL), H_2O (1.46 mL), and H_2SO_4 (0.15 mL) was heated at 95 °C for 3 h. After evaporation of the reaction mixture, the residue was treated with ion-exchange resin (Amberlite IRA-410) to yield D-fagomine (**1**) (40 mg, 75%) as a solid; mp 185 °C; $[\alpha]^{25}_D$ +18.0° (*c* 0.92, H_2O) [lit.[7] $[\alpha]_D$ +19.5° (*c* 1.0, H_2O)]; ^{1}H NMR (500 MHz, D_2O) δ 1.31 (ddd, J = 20.0, 12.8, 4.2 Hz, 1H), 1.83−1.87 (m, 1H), 2.36−2.40 (m, 1H), 2.46 (td, J = 12.8, 2.56 Hz, 1H), 2.84−2.88 (m, 1H), 3.02 (t, J = 9.4 Hz, 1H), 3.47−3.43 (m, 1H), 3.50 (dd, J = 11.5, 6.4 Hz, 1H), 3.72 (dd, J = 11.5, 2.9 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 33.5, 43.4, 61.7, 62.5, 74.0, 74.0.

D-3,4-Di-*epi*-fagomine [(2*R*,3*S*,4*S*)-2-Hydroxymethylpiperidine-3,4-diol] (3). Acidic Condition. A mixture of **11** (90 mg, 0.192 mmol), 1,4-dioxane (1.2 mL), H_2O (0.77 mL), and H_2SO_4 (0.08 mL) was heated at 95 °C for 3 h. After evaporation of the reaction mixture, the residue was treated with an ion-exchange resin (Amberlite IRA-410) to yield a yellow oil, which was separated by ion-exchange resin chromatography to give D-fagomine (**1**) (12.5 mg, 44%) and 3,4-di-*epi*-fagomine (**3**) (9.4 mg, 33%) as a yellow oil. **3**: $[\alpha]^{25}_D$ +13.4° (*c* 0.32, H_2O) [lit.[7] $[\alpha]_D$ −8.7° (*c* 0.3, H_2O)]; ^{1}H NMR (500 MHz, D_2O) δ 1.43−1.50 (m, 1H), 1.86 (m, 1H), 2.78 (m, 2H), 3.02−3.06 (m, 1H), 3.56−3.57 (m, 2H), 3.61 (br s, 1H), 3.80 (br s, 1H); ^{13}C NMR (125 MHz, D_2O) δ 28.2, 39.3, 56.0, 61.3, 68.2, 69.1.

Basic Condition. A mixture of **11** (95 mg, 0.20 mmol), 1,4-dioxane (5.1 mL), and 0.3 M KOH (10.2 mL) was refluxed overnight. After evaporation, MeOH (1.9 mL) and 6 N HCl (5.6 mL) were added to the residue. The mixture was heated at 60 °C for 1 h and then evaporated to give an oil. The residue was separated by ion-exchange resin chromatography to give D-fagomine (**1**) (4,9 mg, 17%) and D-3,4-di-*epi*-fagomine (**3**) (24,6 mg, 82%).

(2*R*,3*R*,4*S*)-2-(*tert*-Butyldiphenylsilanyloxymethyl)-3,4-dihydroxypiperidine-1-carboxylic Acid *tert*-Butyl Ester (17). A solution of 50% NMO (0.79 mL, 3.40 mmol) in water and a solution of $K_2OsO_4 \cdot 2H_2O$ (20.9 mg, 56.7 μmol) in water (0.9 mL) were successively added to a solution of **5** (512 mg, 1.13 mmol) in acetone (9.1 mL) and the mixture was stirred at room temperature overnight. Na_2SO_3 was added to the mixture and the mixture was stirred. The insoluble materials were filtered off and the filtrate was evaporated. Cooled 1 N HCl and CH_2Cl_2 were added to the residue and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic solvents were washed with brine, dried, and evaporated. The residue was purified by chromatography (hexane:AcOEt 4:1) to yield **17** (505 mg, 92%) as a white solid; $[\alpha]^{25}_D$ −37.4° (*c* 1.03, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (s, 9H), 1.27 (s, 9H), 1.42−1.54 (m, 1H), 1.54−1.72 (m, 1H), 2.57−2.73 (m, 3H), 3.51−3.55 (m, 2H), 3.55−3.67 (m, 1H), 3.90 (m, 2H), 4.36 (br s, 1H), 7.21−7.28 (m, 6H), 7.48−7.50 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.3, 27.0, 28.0, 28.5, 39.4, 58.8, 62.0, 67.5, 68.5, 80.1, 127.8, 129.8, 132.8, 132.9, 135.5, 135.6, 155.7; IR (KBr) 3425.8, 2933.0, 1691.3, 1112.0 cm^{-1}; HRMS calcd for $C_{27}H_{39}NO_5Si$ (M^+) 485.2582, found 485.2611.

D-3-*epi*-Fagomine [(2*R*,3*R*,4*S*)-2-Hydroxymethylpiperidine-3,4-diol] (2). A mixture of **17** (490 mg, 1.01 mmol) in 1,4-dioxane (6.09 mL) and 10% HCl (27.7 mL) was heated at 100 °C for 30 min. After evaporation, the residue was washed with ether and then purified by ion-exchange resin chromatography to give D-3-*epi*-fagomine (**2**) (134.6 mg, 91%) as a white solid; mp 220−222 °C; $[\alpha]^{26}_D$ +74.4° (*c* 0.95, H_2O) [lit.[7] $[\alpha]^{26}_D$ +69° (*c* 0.5, H_2O)]; ^{1}H NMR (500 MHz, D_2O) δ 1.56−1.63 (m, 1H), 1.69−1.73 (m, 1H), 2.61−2.68 (m, 2H), 2.70−2.75 (m, 1H), 3.33 (dd, J = 10.2, 2.9 Hz, 1H), 3.49 (dd, J = 11.63, 6.5 Hz, 1H), 3.69 (dd, J = 11.5, 2.9 Hz, 1H), 3.95 (q, J = 2.9 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 31.8, 39.1, 56.5, 62.9, 68.7, 70.3. Anal. Calcd for $C_6H_{13}NO_3$: C, 48.97; N, 9.52; H, 8.90. Found: C, 48.94; N, 9.49; H, 8.98.

Alternete Method. A solution of NMO (504 mg, 2.15 mmol) and a solution of $K_2OsO_4 \cdot 2H_2O$ (13.2 mg, 35.8 μmol) in water (0.6 mL) were successively added to a solution of **16** (153 mg, 0.72 mmol) in acetone (6 mL) and the mixture was stirred at room temperature overnight. Na_2SO_3 was added to the mixture and the mixture was stirred. The insoluble materials were filtered off and the filtrate was evaporated. The residue was dissolved in 1,4-dioxane (4.3 mL), 10% HCl (12.5 mL) was added, and the mixture was heated at 60 °C for 1 h, and then evaporated. The residue was washed with ether and then purified by ion-exchange resin chromatography to give D-3-*epi*-fagomine (**2**) (91.4 mg, 87%) as a white solid.

D-4-*epi*-Fagomine [(2*R*,3*S*,4*R*)-2-Hydroxymethylpiperidine-3,4-diol] (4). A solution of OsO_4 (100 mg, 0.393 mmol) in CH_2Cl_2 (1 mL) was added to a solution of **16** (82.1 mg, 0.384 mmol) and TMEDA (48.8 mg, 0.42 mmol) in CH_2Cl_2 (10 mL) at −78 °C. The mixture was stirred at the same temperature for 2 h, warmed to room temperature, and stirred for 1 h. The reaction mixture was evaporated. The residue was dissolved in MeOH (10 mL), 35% HCl (3 drops) was added, and the mixture was stirred at room temperature for 2 h, and then evaporated. The residue was treated with ion-exchange resin (Amberlite IRA-410) and then separated by ion-exchange resin chromatography to give D-4-*epi*-fagomine (**4**) (31.4 mg, 56%) and D-3-*epi*-fagomine (**2**) (16.8 mg, 30%) as solids. **4**: mp 220−222 °C; $[\alpha]^{22}_D$ +10.2° (*c* 1.42, H_2O); ^{1}H NMR (300 MHz, D_2O) δ 1.49−1.56 (m, 2H), 2.39−2.49 (m, 1H), 2.57 (td, J = 6.9, 5.2 Hz, 1H), 2.91 (td, J = 12.9, 3.3 Hz, 1H), 3.47 (dd, J = 6.7, 3.4 Hz, 2H), 3.50−3.60 (m, 1H), 3.74 (br s, 1H); ^{13}C NMR (75 MHz, D_2O) δ 28.4, 43.6, 59.7, 62.5, 68.5, 70.7. Anal. Calcd for $C_6H_{13}NO_3$: C, 48.97; N, 9.52; H, 8.90. Found: C, 48.90; N, 9.53; H, 8.97.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all new compounds prepared in this study and HMBC for product **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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