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ASYMMETRIC SYNTHESIS OF ALL STEREOISOMERS OF ISOFAGOMINE USING [2,3]-WITTIG REARRANGEMENT

Yukiko Mihara,[a] Hidetomo Ojima,[a] Tatsushi Imahori,[a] Yuichi Yoshimura,[a] Hidekazu Ouchi,[b] and Hiroki Takahata[a]*

[a]Faculty of Pharmaceutical Sciences, Tohoku Pharmaceutical University, Sendai 981-8558, Japan:takahata@tohoku-pharm.ac.jp

[b]Faculty of Pharmaceutical Sciences, Aomori University, Aomori, 030-0943, Japan

Abstract – The asymmetric synthesis of all stereoisomers of isofagomine from 5-hydroxymethyl-3-piperidene **6**, which was prepared by [2,3]-Wittig rearrangement of *O*-alkylstannylmethyl compound **5** derived from readily available chiral 3-hydroxypiperidene **4**, is described.

INTRODUCTION

Azasugars (or iminosugars), such as 1-deoxynojirimycin (**1**), are an important class of glycosidase inhibitors and are currently attracting great interest as potential therapeutic agents such as antidiabetics, antiobesities, antivirals, and therapeutic agents for certain types of genetic disorders.[1-5] Miglitol (Glyset)[6] has been approved as a second-generation α-glucosidase inhibitor for the treatment of type 2 diabetes, and *N*-butyl-1-deoxynojirimycin (Zavesca)[7-9] has also been approved for use in patients with type 1 Gaucher disease in the European Union in 2002 and in the U.S. in 2003. The promising therapeutic potential of iminosugars has led to an increased interest and demand. In the process of the design and development of anomer-selective β-glycosidase inhibitors based on transition state mimics for hydrolysis by a glycosidase, Bols and co-workers noticed a subtle change in glycosidase inhibitory activity when the nitrogen atom of fagomine **2** was moved to the anomeric C_1 position.[10] This led to the development of isofagomine **3** which showed stronger and more selective β-glucosidase inhibitory activity than previously developed compounds. A number of isofagomine derivatives have been synthesized during the last few years.[11] Most of the syntheses start from carbohydrates and, in general, require numerous steps to reach a specific target. The development of efficient and general procedures for their synthesis is still an

area of great interest, not only for the synthesis of natural products, but also for chemically modified analogues.

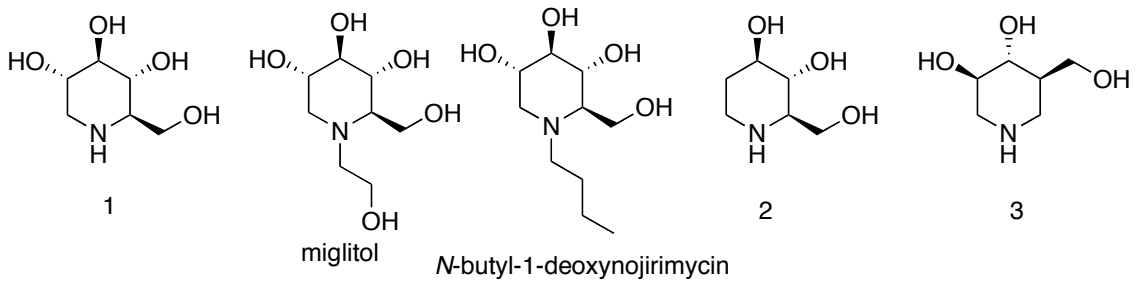
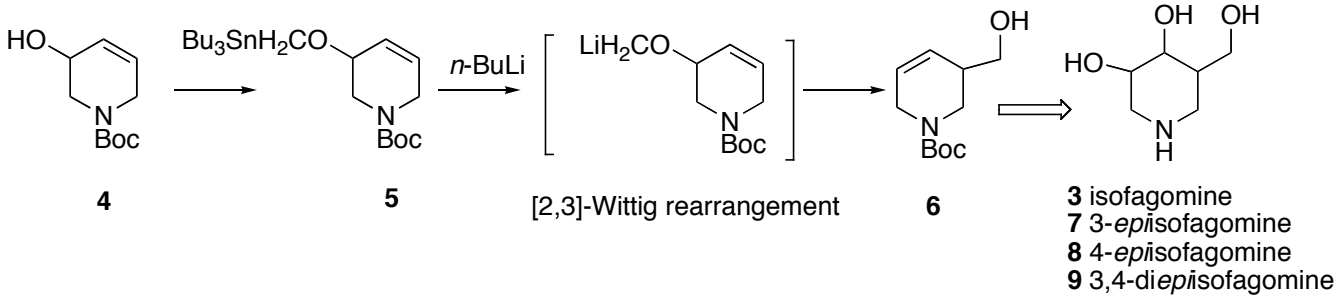


Figure 1

As a part of our ongoing interest in polyhydroxy piperidines,[12] we envisioned the use of *N*-Boc-5-hydroxy-3-piperidene (**4**) as a general representative chiral building block that might permit easy access to these classes of compounds.[13] We report herein on the asymmetric synthesis of all stereoisomers of the 1-azasugars such as isofagomine (**3**), using the [2,3]-Wittig rearrangement[14] as a key step starting from the chiral *N*-Boc-5-hydroxy-3-piperidene (**4**) as depicted in Scheme 1.

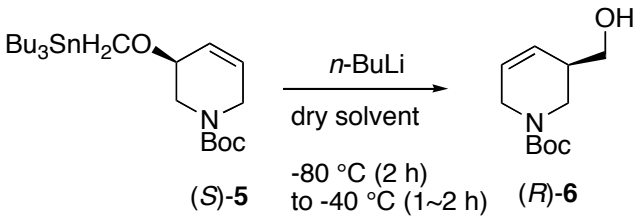


Scheme 1

RESULTS AND DISCUSSION

We began with the synthesis of a precursor **5** for the [2,3]-Wittig rearrangement from **4**. *O*-Alkylation of (*S*)-**4**[12] with tributyl(iodomethyl)stannane[15] in the presence of KH and *n*-Bu_4NI gave the stannane product (*S*)-**5** in 98% yield. With (*S*)-**5** in hand, the [2,3]-Wittig rearrangement of (*S*)-**5** by transmetallation using *n*-BuLi to obtain the requisite hydroxymethyl substituent (*R*)-**6** was examined.[16] After screening various reaction conditions, we were very pleased to find that the desired [2,3]-Wittig rearrangement of (*S*)-**5** proceeded smoothly to afford (*R*)-**6** with no racemization.[17] The results are shown in Table 1. The use of less polar solvents such as *n*-pentane and *n*-hexane gave good results.

Table 1. [2,3]-Wittig rearrangement of (*S*)-**5**

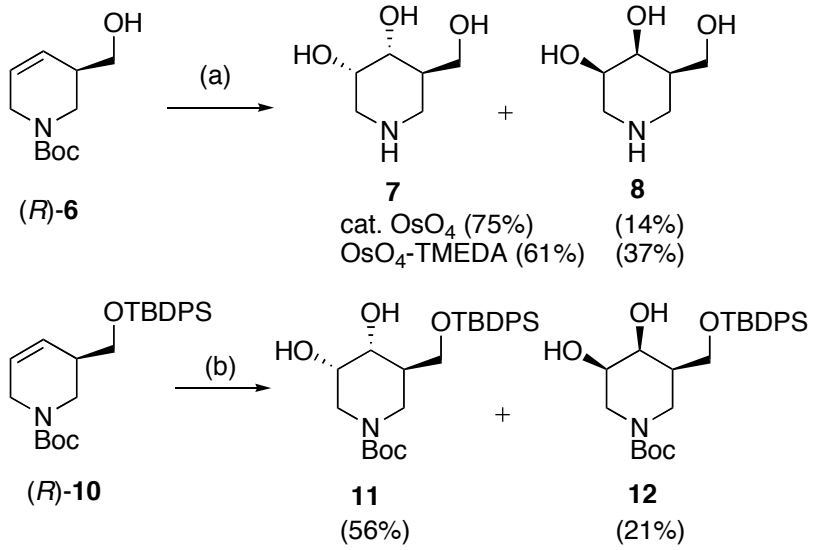


Entry	Solvent	(*R*)-**6a**, Yield[%]
1	*n*-pentane	65
2	*n*-hexane	53
3	Et_2O	50
4	THF	33
5	DME	16

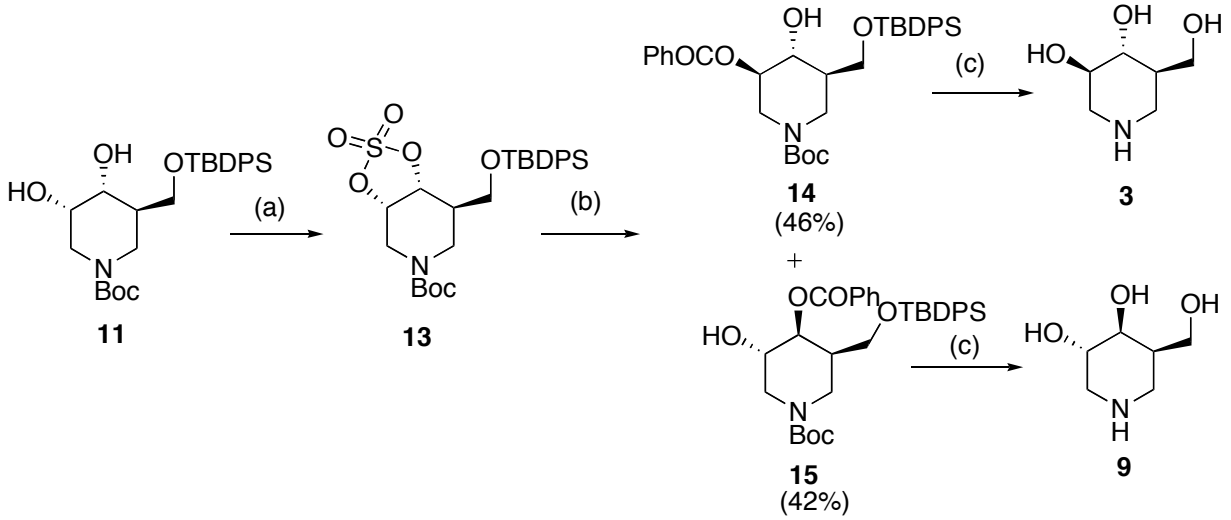
Having the key intermediate (*R*)-**6** in hand, the stereoselective dihydroxylation of the double bond was examined. Treatment of (*R*)-**6** with a catalytic amount of OsO_4 (5 mol %) and 4-methylmorphorine *N*-oxide as a cooxidant gave an inseparable mixture of diastereomeric diols, which, after deprotection with 10% HCl in dioxane followed by silica gel column chromatography using a mixture eluent (methanol:10% NH_4OH), gave 3-*epi*isofagomine (**7**) (75%) and 4-*epi*isofagomine (**8**) (14%). The *O*-TBDPS protected piperidene **10** was next dihydroxylated under similar conditions to give **11** (56%) and **12** (21%). Unfortunately, diastereoselectivity was not improved. The spectral data for **7** and **8** were found to be in good agreement with reported values from the literature.[11a,c] Donohoe reported that osmium tetroxide produces a bidentate and reactive complex with TMEDA, which can be used in the directed dihydroxylation of cyclic homoallylic alcohols.[18] Under the condition, hydrogen bonding control preferentially led to the formation of the syn isomer in almost every case. However, the oxidation of (*R*)-**6** with a combination of OsO_4 with TMEDA gave **7** and **8** in 61% and 37% yields, respectively. Although the yield of **8** was increased, inversion of the ratio did not occur.

We next set out to synthesize **3** and **9** from this advanced intermediate **11**. Thus, the *cis*-diol **11** was converted into the cyclic sulfate ester **13** in 76% yield in a two-step sequence, including cyclic sulfite formation with $SOCl_2$ and triethylamine followed by oxidation with $RuCl_3/NaIO_4$ (Scheme 8).[19] Treatment of 1**3** with benzoic acid in the presence of cesium carbonate (DMF, 60 °C) resulted in the non-regioselective substitution at the C_3 and C_4 positions to produce benzoates **14** and **15** in 46% and 42% yields, respectively, after acid hydrolysis of the resultant sulfate esters. Finally, the deprotection of **14** and **15** by treatment with 6N hydrochloric acid at 120 °C gave **3** and **9** in 98% and 96% yields, respectively,

the spectral data for which were found to be in good agreement with reported values from the literature.[11f]

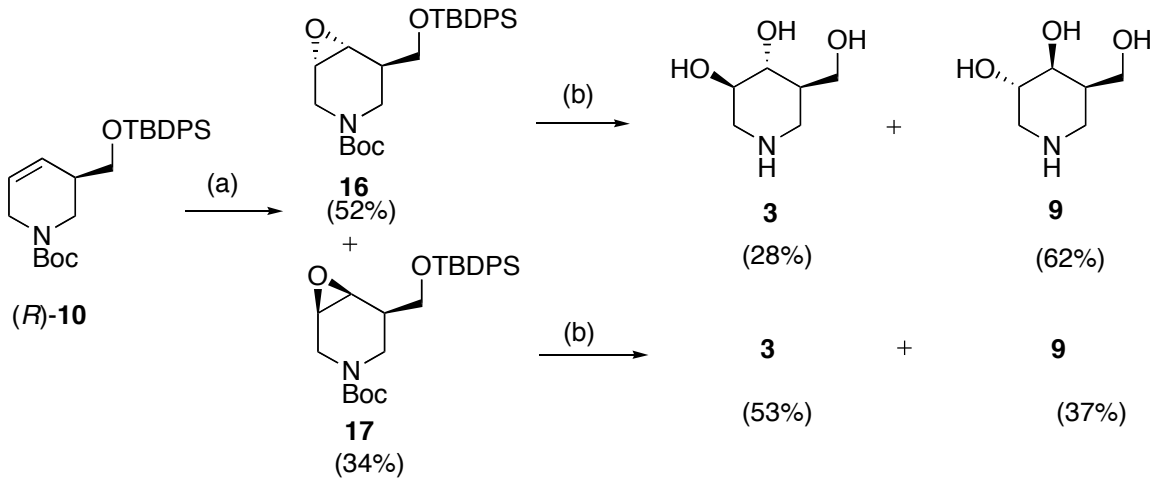


Scheme 2. (a) 1) cat. OsO_4, NMO, acetone; 2) 10% HCl, dioxane, reflux; 3) NH_4OH; or 1) OsO_4-TMEDA, CH_2Cl_2; 2) conc HCl, MeOH; 3) NH_4OH; (b) cat. OsO_4, NMO, acetone



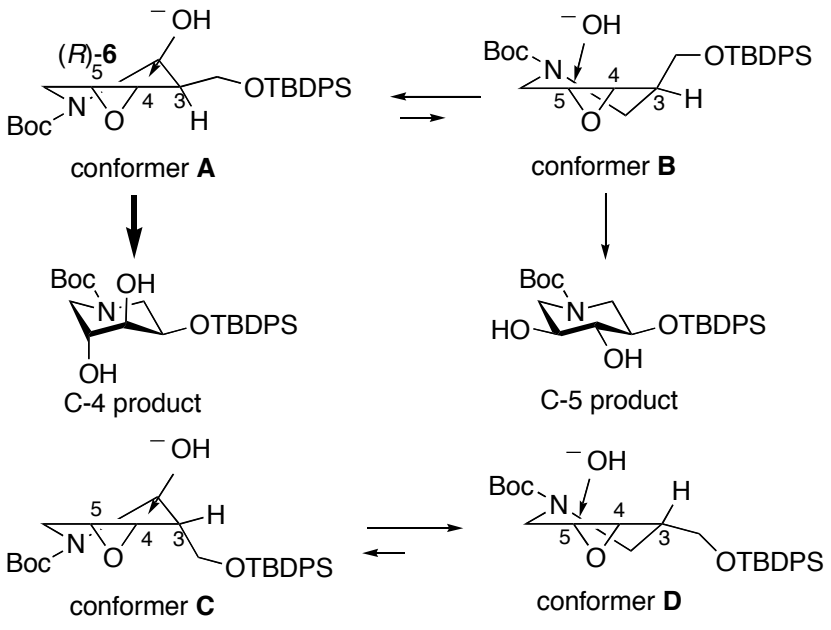
Scheme 3. (a) 1) $SOCl_2$, Et_3N, CH_2Cl_2; 2) cat. $RuCl_3$-$3H_2O$, $NaIO_4$, CCl_4-MeCN-H_2O; (b) 1) PhCOOH, $CsCO_3$, DMF; 2) conc H_2SO_4, H_2O, THF; (c) 1) 6N HCl; 2) NH_4OH

As an alternative synthesis of **3** and **9**, we attempted an epoxidation of (*R*)-**10** followed by cleavage. Thus, the dioxirane, generated *in situ*[20] from Oxone® by treatment with 1,1,1-trifluoroacetone was reacted with (*R*)-**10** to give the *anti* epoxide **16** and the *syn* epoxide **17** in 52% and 34% yields, respectively, which were tentatively assigned based on steric considerations between the allylic substitutent of the six membered cyclic alkene and a substituent of dioxirane.[21] Subsequently, basic cleavage of the epoxy ring of **16** was accomplished using a mixture of KOH/1,4-dioxane/H_2O at reflux followed by a sequence of deprotection with 6N hydrochloric acid and desalting to give **3** and **9**, 28% and 62% yields, respectively.



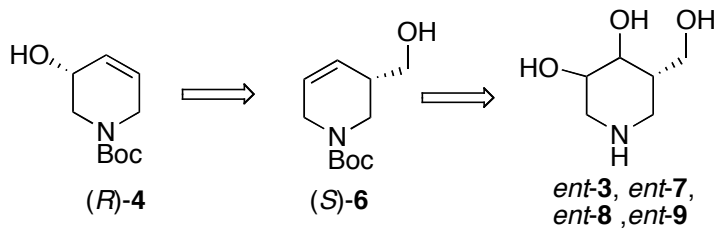
Scheme 4. (a) Oxone®, CF_3COCH_3, Na_2EDTA(aq.), $NaHCO_3$, MeCN;
(b) 1) 0.3M KOH, 1,4-dioxane; 2) 6N HCl; 3) NH_4OH

The regiochemistry of the nucleophilic opening of the epoxide on a six-membered ring is mainly subject to *trans* diaxial opening (Fürst-Plattner rule).[22] Consequently, this regioselectivity would result, if the opening proceeded through the two possible half chair conformations (**A** and **B**) in the following explanation. A substituent at C-3 would preferentially occupy a pseudoequatrial orientation compared with a pseudoaxial one. Thus, the somewhat preferential attack of the hydroxide anion at C-4 through conformer **A** would occur with *trans* diaxial opening. On the other hand, a similar reaction using **17** somewhat preferentially gave **3** (53%) together with **9** (37%). On the basis of the above reasoning, the existence of conformer **D** would be major species and conformer **C**, the minor species.



Scheme 5

In addition, four enantiomers of **3**, **7**, **8**, and **9** were prepared from (*R*)-**4** according to the above described procedure (Scheme 6).



Scheme 6

In summary, the asymmetric synthesis of all stereoisomers **3**, **7**, **8**, and **9** of isofagomine is described using the [2,3]-Wittig rearrangement as a key step starting from the chiral *N*-Boc-5-hydroxy-3-piperidene (**4**). This rearrangement of **5** by transmetallation using *n*-BuLi proceeded smoothly in nonpolar solvents such as *n*-pentane with no racemization. Thus, the prepared hydoxymethylpiperidene **6** was transformed by dihydroxylation, cyclic sulfenylation, and epoxidation into stereoisomers of isofagomine, although their diastereoselectivities were not always high.

EXPERIMENTAL

Infrared (IR) spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrometer. Mass spectra (MS) were recorded on a JEOL JMN-DX 303/JMA-DA 5000 spectrometer. Microanalyses were performed on a Perkin-Elmer CHN 2400 Elemental Analyzer. Optical rotations were measured with a JASCO DIP-360 or JASCO P-1020 digital polarimeter. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on JEOL JNM-EX 270 (270 MHz) or JEOL JNM-AL 400 (400 MHz) or JNM-LA (600 MHz) spectrometer, using tetramethylsilane as an internal standard. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Column chromatography was carried out on Merck Silica gel 60 (230-400 mesh) or KANTO Silica Gel 60N (40-50 mm) for flash chromatography.

(*S*)-*N*-*tert*-Butoxycarbonyl-5-(tributylstannyl)methoxy-3-piperidene [(*S*)-5]

A solution of (*S*)-**4** (995 mg, 5 mmol) in THF (5 mL) was added to a suspension of KH (860 mg, 35 wt% in oil, 7.5 mmol) in THF (20 mL) and DMF (5 mL) at 0 °C and the whole was stirred for 1 h. A solution of Bu_3SnCH_2I (3.235 g, 7.5 mmol) in THF (5 mL) was added to the reaction mixture at 0 °C and the whole was stirred overnight. Ice water was added to the reaction mixture and the whole was extracted with Et_2O (50 mL) three times. The extracts were washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by flash column chromatography on silica gel (*n*-hexane : AcOEt = 15 : 1) to give **(*S*)-5** (2.46 g, 98 %) as an oil; $[\alpha]_D^{25}$ +45.7° (*c* 5.10, $CHCl_3$). ^{1}H NMR (600 MHz,$CDCl_3$) d 0.86–0.94

(m, 15H), 1.25–1.35 (m, 6H), 1.46–1.56 (m, 15H), 3.11 (br s, 0.5H), 3.31 (br s, 0.5H), 3.63–4.00 (m, 6H), 5.71–5.92 (m, 2H). ^{13}C NMR (67.8 MHz, $CDCl_3$) d 9.0, 13.7, 27.2, 28.4, 29.1, 43.6, 44.5, 59.4, 74.6, 79.5, 125.8, 126.9, 154.5. IR (neat) cm^{-1}: 1703, 758. EI-MS (*m*/*z*): 502 (M^+–1). HRMS calcd for $C_{23}H_{45}NO_3Sn$: 503.2422, found: 503.2367.

(*R*)-5 : (99%) $[\alpha]_D^{26}$ –43.9° (*c* 1.08, $CHCl_3$)

(*R*)-*N*-*tert*-Butoxycarbonyl-5-(hydroxymethyl)-3-piperidene [(*R*)-6]

n-BuLi (4.5 mL, 1.6M in *n*-hexane, 6.98 mmol) was dropwise added to a solution of (*S*)-**5** (2.12 g, 4.23 mmol) in dry pentane (85 mL) at –80 °C and stirred for 1 h at the same temperature, and subsequently stirred at –40 °C for 2 h. *sat*. aqueous NH_4Cl (20 mL) was added the reaction mixture and the whole was separated. The organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash column chromatography on silica gel (*n*-hexane : AcOEt = 15 : 1~ 2 : 1) to give (*R*)-**6** (582 mg, 65%) as an oil; $[\alpha]_D^{24}$ –92.1° (*c* 1.10, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.46 (s, 9H), 2.11 (br s, 0.5H), 2.38 (br s, 1H), 2.96 (br s, 0.5H), 3.21–3.83 (m, 5H), 4.03 (d, *J* = 18.3Hz, 1H), 5.73 (br s, 2H). ^{13}C NMR (67.8 MHz, $CDCl_3$) d 28.4, 38.1, 41.3, 44.2, 63.1, 79.9, 125.8, 126.2, 154.9. IR (neat) cm^{-1}: 3435, 1698. EI-MS (*m*/*z*): 213 (M^+). HRMS calcd for $C_{11}H_{19}NO_3$: 213.1365, found: 213.1361.

(*S*)-6 (65%); $[\alpha]_D^{22}$ +89.1° (*c* 1.50, $CHCl_3$).

(3*S*,4*R*,5*R*)-3,4-Dihydroxy-5-(hydroxymethyl)piperidine [(+)-3-*epi*isofagomine (7)] and (3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(hydroxymethyl)piperidine ((-)-4-*epi*isofagomine (8))

To a solution of (*R*)-**6** (200 mg, 0.94 mmol) in acetone (6 mL) was added an aqueous 4% OsO_4 solution (130 mL, 0.02 mmol). After 10 min, an aqueous 50% NMO solution (352 mg, 1.5 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 ($CHCl_3$: MeOH = 10 : 1) to give a diastereoisomeric mixture of *tert*-butyl 3,4-dihydroxy-5-(hydroxymethyl)piperidine-1-carboxylates (210 mg, 90 %). To a solution of the above diol in 1,4-dioxane (6 mL) was added 10% HCl (15 mL). The reaction mixture was refluxed for 1 h and evaporated. 28% NH_4OH was added to the residue and evaporated. The residue was chromatographed on silica gel (MeOH : 10% NH_4OH = 10 : 1) to give **7** (104 mg, 83%) and **8** (20 mg, 16%) as oils;

7; $[\alpha]_D^{24}$ +85.2° (*c* 1.04, EtOH). ^{1}H NMR (270 MHz, D_2O) δ 1.72–1.88 (m, 1H), 2.22 (t, *J* = 12.1 Hz, 1H), 2.54 (d, *J* = 14.2 Hz, 1 H), 2.80–2.98 (m, 2H), 3,42–3.54 (m, 2H), 3.61 (dd, *J* = 11.4, 3.8 Hz, 1H), 3.73 (s, 1H). ^{13}C NMR (67.8 MHz, D_2O) δ 39.0, 44.9, 48.1, 60.3, 66.8, 69.2. EI-MS (*m*/*z*): 147 (M^+). HRMS calcd for $C_6H_{13}NO_3$: 147.0895, found: 147.0894.

8; $[\alpha]_D^{25}$ –5.1° (*c* 0.98, EtOH). ^{1}H NMR (270 MHz, D_2O) δ 1.64–1.78 (m, 1H), 2.33 (t, *J* = 12.3 Hz, 1H), 2.53 (t, *J* = 11.6 Hz, 1 H), 2.63 (dd, *J* = 12.9, 4.5 Hz, 1H), 2.72 (dd, *J* = 12.1, 4.9 Hz, 1H), 3.36–3.57 (m, 3H), 4.61 (s, 1H). ^{13}C NMR (67.8 MHz, D_2O) δ 39.9, 41.5, 43.5, 60.1, 67.1, 68.1. EI-MS (*m*/*z*): 147 (M^+).

HRMS calcd for $C_6H_{13}NO_3$: 147.0895, found: 147.0887.

An alternative synthesis of 7 and 8 using OsO_4-TMEDA complex.

A solution of OsO_4 (245.2 mg, 0.95 mmol) in CH_2Cl_2 (2 mL) was added to a solution of (*R*)-**6** (186 mg, 0.87 mmol) and TMEDA (111.6 mg, 0.95 mmol) in CH_2Cl_2 (15 mL) at –78 °C. The mixture was stirred at the same temperature for 2 h, warmed to rt, and stirred for 1 h. The reaction mixture was evaporated. The residue was dissolved in MeOH (10 mL), 35% HCl (1 mL) was added, and the mixture was stirred at rt for 2 h, and then evaporated. The residue was treated with 28% NH_4OH and evaporated. The residue was chromatographed on silica gel (MeOH : 10% NH_4OH = 10 : 1) to give **7** (78 mg, 61%) and **8** (47 mg, 37%) as oils;

ent-**7** (71%); $[\alpha]_D^{25}$ –83.7° (*c* 1.06, EtOH). and *ent*-**8** (20%); $[\alpha]_D^{25}$ +3.5° (*c* 1.02, EtOH).

(*R*)-*N*-*tert*-Butoxycarbonyl-5-((*tert*-butyldiphenylsilyloxy)methyl)-3-piperidene [(*R*)-10]

To a solution of (*R*)-**6** (507 mg, 2.38 mmol) in CH_2Cl_2 (15 mL) was added imidazole (243 mg, 3.57 mmol), DMAP (5.8 mg, 0.05 mmol), and *tert*-butylchlorodiphenylsilane (720 mg, 2.62 mmol). The mixture was stirred at rt 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 = 15 : 1) to give **(*R*)-10** (1.06 g, 98 %) as a colorless oil; $[\alpha]_D^{21}$ –82.9° (*c* 1.20, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.08 (s, 9H), 1.49 (s, 9H), 2.44-2.54 (m, 1H), 3.30– 3.59 (m, 3H), 3.70–3.89 (m, 2H), 3.94 (dd, *J*= 18.7, 2.0 Hz, 1H), 5.61 (br s, 1H), 5.71 (br s, 1H), 7.38-7.45 (m, 6H), 7.67-7.70 (m, 4H). ^{13}C NMR (150 MHz, $CDCl_3$) δ19.2, 26.8, 28.4, 38.4, 43.3, 64.9, 79.4, 126.0, 127.6, 129.6, 133.6, 134.8, 135.5, 155.1. IR (KBr) cm^{-1}: 1699. EI-MS (*m*/*z*): 452 (M+1). HRMS calcd for $C_{27}H_{37}NO_3Si$: 451.2543, Found: 451.2578.

(*S*)-10 (99%); $[\alpha]_D^{21}$ +85.4° (*c* 1.30, $CHCl_3$).

(3*R*,4*R*,5*S*)-*N*-*tert*-Butoxycarbonyl-3-(*tert*-butyldiphenylsilyloxymethyl)-4,5-dihydroxypiperidine (11) and (3*R*,4*S*,5*R*)-*N*-*tert*-Butoxycarbonyl-3-(*tert*-butyldiphenylsilyloxymethyl)-4,5-dihydroxy-piperidine (12)

To a solution of (*R*)-**10** (1.05 g, 2.3 mmol) in acetone(18 mL) was added an aqueous 4% OsO_4 solution (335 mL, 0.05 mmol). After 10 min, an aqueous 50% NMO solution (905 mL mg, 3.8 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 ~ 1 : 2) to give a diastereoisomeric mixture of **11** (637 mg, 57 %) and **12** (208 mg, 19%) as oils;

11: $[\alpha]_D^{21}$ –8.9° (*c* 2.5, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.43 (s, 9H), 2.05 – 2.18 (m, 1H), 2.57 (br s, 1H), 2.86 (d, *J*= 13.7 Hz, 1H), 3.39 – 3.97 (m, 4H), 3.97 – 4.06 (m, 1H), 4.14 (d, *J*= 16.0 Hz, 1H), 7.30 – 7.48 (m, 6H), 7.60 – 7.81 (m, 4H). ^{13}C NMR(100 MHz, $CDCl_3$) δ 19.1, 26.8, 28.4,

39.4, 44.5, 47.5, 65.3, 67.6, 74.1, 79.9, 128.0, 129.9, 132.6, 135.6, 155.9. IR (KBr) cm^{-1}: 3438, 1697, 1669. EI-MS (*m*/*z*): 486 (M^++1). HRMS calcd for $C_{27}H_{39}NO_5Si$: 485.2598, Found: 485.2524.

12: $[\alpha]_D^{20}$ –32.0° (*c* 1.1, $CHCl_3$). ^1H NMR (270 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.43 (s, 9H), 1.70 – 1.83 (m, 1H), 2.78 – 3.00 (m, 2H), 3.21 – 3.64 (m, 3H), 3.67 – 3.88 (m, 2H), 3.91 – 4.05 (br, 1H), 7.26 – 7.50 (m, 6H), 7.59 – 7.84 (m, 4H). ^{13}C NMR(100 MHz, $CDCl_3$) δ 19.1, 26.7, 28.4, 40.8, 42.5, 43.6, 63.8, 66.2, 68.8, 79.9, 127.7, 129.9, 133.1, 135.5, 154.8. IR (KBr) cm^{-1}: 3436, 1697, 1674. EI-MS (*m*/*z*): 486 (M^++1). HRMS calcd for $C_{27}H_{39}NO_5Si$: 485.2598, Found: 485.2590.

ent-**11** (56%); $[\alpha]_D^{25}$ +9.7° (*c* 1.1, $CHCl_3$). *ent*-**12** (21%); $[\alpha]_D^{24}$ +32.2° (*c* 1.0, $CHCl_3$).

(3a*S*,7*R*,7a*R*)-Hexahydro-*N*-*tert*-butoxycarbonyl-7-(*tert*-butyldiphenyl-silyloxymethyl)-1,3-dioxa-2-thia-5-azaindene 2,2-dioxide (13)

To a solution of diol **11** (437 mg, 0.9 mmol) in CH_2Cl_2 (11.0 mL) at –15 °C were added Et_3N (0.45 mL, 3.24 mmol) and thionyl chloride (99 μL, 1.35 mmol). The resultant mixture was stirred at –15 °C for 30 min and then poured into ice-water (20 mL). The mixture was extracted with $CHCl_3$ (3 x 20 mL), and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a cyclic sulfite (500 mg) as an oil. To a solution of the above cyclic sulfite in MeCN/CCl_4/H_2O (2:2:3, v/v, 21.0 mL) at rt were added $NaIO_4$ (339 mg, 1.6 mmol) and $RuCl_3$ (12 mg, 45 μmol) followed by water (4.0 mL). The resultant mixture was stirred at rt for 1 h and then extracted with Et_2O (60 mL). The combined organic layers were washed with brine (10 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 = 2 : 1) to give **13** (417 mg,76 %) as a colorless oil; $[\alpha]_D^{26}$ +12.7° (*c* 1.3, $CHCl_3$). ^1H NMR (270 MHz, $CDCl_3$) δ 1.07 (s, 9H), 1.45 (s, 9H), 2.32 – 2.48 (m, 1H), 2.97 (dd, *J* = 13.4, 11.2 Hz, 1H), 3.36 (d, *J* = 15.7 Hz, 1H), 3.72 (dd, *J*= 10.8, 3.4 Hz, 1H), 3.84 (br s, 1H), 4.07 (br s, 1H), 4.45 (br d, *J* = 15.2 Hz, 1H), 4.97 (br s, 1H), 5.16 (br s, 1H), 7.37 – 7.47 (m, 6H), 7.59 – 7.63 (m, 4H). ^{13}C NMR(100 MHz, $CDCl_3$) δ 19.1, 26.8, 28.1, 39.3, 42.6, 43.9, 60.9, 78.2, 81.0, 81.4, 127.8, 130.0, 132.4, 135.4, 154.3. IR (KBr) cm^{-1}: 1703. EI-MS (*m*/*z*): 546 (M^+-1). HRMS calcd for $C_{27}H_{37}NO_7SSi$: 547.2060, Found: 547.2103.

(3*R*,4*R*,5*R*)-3,4-Dihydroxy-5-hydroxymethylpiperidine [(+)-isofagomine (3)] and (3*S*,4*S*,5*R*)-3,4-Dihydroxy-5-hydroxymethylpiperidine [(+)-3,4-di-*epi*isofagomin (9)]

To a solution of cyclic sulfate **13** (164 mg, 0.3 mmol) in DMF (3.0 mL) at rt were added cesium carbonate (150 mg, 0.465 mmol) and PhCOOH (63 mg, 0.54 mmol). The resultant suspension was stirred at 60 °C for 4 h and then concentrated under reduced pressure to give an benzoxy sulfate as a pale yellow solid. To a stirred suspension of the above benzoxy sulfate in THF (6.0 mL) at rt were added concentrated H_2SO_4 (4 drops) and H_2O (6 drops). The mixture was stirred at rt for 22 h and then partitioned between

$CHCl_3$ (30 mL) and sat. aq. $NaHCO_3$ (10 mL). The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was chromatographed on silica gel (*n*-hexane : AcOEt = 1 : 1) to give (3*R*,4*R*,5*R*)-*N*-*tert*-butoxycarbonyl-3-benzoyloxy-5-(*tert*-butyldiphenylsilyloxymethyl)-4-hydroxypiperidine **14** (82 mg, 46 %) and (3*R*,4*S*,5*S*)-*N*-*tert*-butoxycarbonyl-4-benzoyloxy-5-(*tert*-butyldiphenylsilyloxymethyl)-3-hydroxypiperidine **15** (75.0 mg, 42 %) as oils. A solution of **14** (49.5 mg. 0.084 mmol) was dissolved in 6N HCl (10 mL) was heated at 120 °C for 12 h. and then washed with $CHCl_3$. The aqueous layer was evaporated and the residue was treated with 28% NH_4OH and evaporated. The residue was chromatographed on silica gel (MeOH : 10% NH_4OH = 10 : 1) to give **3** (12 mg, 98%). According to the procedure described for **3**, **15** (41 mg. 0.0695 mmol) gave (+)-3,4-di-*epi*-isofagomine, **9** (9.8 mg, 96 %).

3: $[\alpha]_D^{25}$ +25.4° (*c* 1.30, EtOH). ^{1}H NMR (600 MHz, D_2O) δ 1.61–1.68 (m, 1H), 2.33–2.38 (m, 2 H), 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.

9: $[\alpha]_D^{19}$ +18.4° (*c* 0.96, EtOH). ^{1}H NMR (270 MHz, D_2O) δ 1.90–2.02 (m, 1H), 2.47–2.65 (m, 3H), 2.84 (dd, *J* = 13.8, 2.9 Hz, 1H), 3.42 (dd, *J* = 11.1, 8.0 Hz, 1H), 3.48–3.68 (m, 2H), 3.69 (dd, *J* = 5.6, 3.6 Hz, 1H). ^{13}C NMR (67.8 MHz, D_2O) δ 38.2, 41.4, 45.7, 59.3, 66.8, 68.7. EI-MS (*m*/*z*): 147 (M^+). HRMS calcd for $C_6H_{13}NO_3$: 147.0895, found: 147.0926.

(3*S*,4*R*,5*S*)-*N*-*tert*-Butoxycarbonyl-3-(*tert*-butyldiphenylsilyloxymethyl)-4,5-epoxypiperidine (16) and (3*S*,4*S*,5*R*)-*N*-*tert*-Butoxycarbonyl-3-(*tert*-butyldiphenylsilyloxymethyl)-4,5-epoxypiperidine (17)

To a cooled (0 °C) solution of (*R*)-**10** (433 mg, 0.96 mmol) in MeCN (10 mL) was added 4 mmol/L aq. Na_2EDTA (5 mL, 0.02 mmol) and 1,1,1-trifluoroacetone (1 mL). The mixture of $NaHCO_3$ (630 mg, 7.5 mmol) and Oxone® (3.07 g, 5.0 mmol) as a solid were 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 (30 mL), and extracted with $CHCl_3$ (30 mL x 3). The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (*n*-hexane : AcOEt = 11 : 1) to give **16** (231 mg, 52 %) and **17** (152 mg, 34 %) as colorless oils. **16**: $[\alpha]_D^{22}$ -41.7 ° (*c* 1.23, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.06 (s, 9H), 1.41 (br d, *J* = 28.9Hz, 9H), 2.33 (br d, *J* = 25.0 Hz, 1H), 3.06-3.28 (m, 3H), 3.37-3.77 (m, 4H), 3.93 (dd, *J* = 52.4, 14.5 Hz, 1H), 7.30-7.45 (m, 6H), 7.65 (d, *J* = 7.7 Hz, 4H). ^{1}H NMR (400 MHz, C_6D_6, 60 °C) δ 1.17 (s, 9H), 1.45 (s, 9H), 2.31 (t, *J* = 5.9 Hz, 1H), 2.68 (t, *J* = 3.2 Hz, 1H), 2.96 (s, 1H), 3.10 (dd, *J* = 13.4, 6.8 Hz, 1H), 3.35 (br s, 1H), 3.57-

3.67 (m, 3H), 3.89 (d, *J* = 15.1 Hz, 1H), 7.26-7.30 (m, 6H), 7.72-7.75 (m, 4H). ^{13}C NMR (100 MHz,C_6D_6,60 °C) δ 19.5, 27.1, 28.5, 37.1, 40.9, 42.9, 49.8, 52.3, 63.9, 79.2, 127.8, 128.1, 128.3, 128.5, 130.1, 133.9, 133.9, 135.9, 136.0, 155.1. IR (neat) cm^{-1}: 2962, 2931, 2859, 1696, 1473, 1461, 1428, 1392, 1366, 1248, 1174, 1113. EI-MS (*m/z*): 468 (M^++1). HRMS calcd for $C_{27}H_{37}NO_4Si$: 467.2492, found: 467.2465.

17: $[\alpha]_D^{22}$ -32.7 ° (*c* 1.10, $CHCl_3$).^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (s, 9H), 1.44 (s, 9H), 2.27-2.32 (m, 1H), 2.70-2.72 (m, 1H), 3.25 (br s, 1H), 3.25-3.30 (m, 2H), 3.43-3.51 (m, 1H), 3.64-3.80 (m, 3H), 3.92-4.06 (m, 1H), 7.38-7.45 (m, 6H), 7.66-7.69 (m, 4H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.2, 26.8, 28.4, 38.2, 40.1, 40.7, 41.7, 50.7, 51.9, 63.7, 79.8, 127.7, 129.7, 133.4, 133.4, 135.5, 135.6, 154.7. IR (neat) cm^{-1}:2962, 2932, 2859, 1695, 1473, 1462, 1428, 1392, 1366, 1247, 1174, 1152, 1113, 1083. EI-MS (*m/z*): 468 (M^++1). HRMS calcd for $C_{27}H_{37}NO_4Si$: 467.2492, found: 467.2580.

ent-**16** (40%); $[\alpha]_D^{22}$ +41.3 ° (*c* 1.26, $CHCl_3$). *ent*-**17** (21%); $[\alpha]_D^{22}$ +30.5 ° (*c* 1.33, $CHCl_3$).

An Alternative synthesis of 3 and 9 from 16 and 17.

A mixture of **16** (103 mg, 0.22 mmol), 1,4-dioxane (5.6 mL), and 3 M KOH (11.2 mL) was refluxed overnight. After evaporation, MeOH (2 mL) and 6 N HCl (6.2mL) were added to the residue. The mixture was heated at 60 °C for 1 h and evaporated. The residue was treated with 28% NH_4OH and evaporated. The residue was chromatographed on silica gel (MeOH : 10% NH_4OH = 10 : 1) to give **3** (9 mg, 28%) and **9** (20 mg, 62%). By similar procedure described the above, **17** (104 mg, 0.22 mmol) gave **3** (17 mg, 53%) and **9** (12 mg, 37%).

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