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Total synthesis of D-fagomine and 6-deoxyfagomine

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ABSTRACT

Total synthesis of D-fagomine and 6-deoxyfagomine from readily available D-lyxose is described. The key steps included regioselective and diastereoselective amination, hydroboration–oxidation, and Appel reaction. The reaction of 3,4-*anti*-tribenzyl ether with chlorosulfonyl isocyanate in toluene at 0 °C afforded 3,4-*anti*-amino alcohol, an essential compound for the preparation of D-fagomine and 6-deoxyfagomine, with a high diastereoselectivity (dr=26:1) in 74% yield. The origin of diastereoselectivity can be explained by the neighboring group effect, which leads to retention of the stereochemistry.

1. Introduction

Discovery of polyhydroxylated piperidines (azasugars) is one of the most notable achievements in the field of natural products. They bind specifically to the active sites of glycosidases by mimicking the corresponding natural sugars. Since glycosidases are involved in numerous biological processes, polyhydroxylated piperidines have remarkable therapeutic potential for the treatment of a wide range of diseases including viral infections, cancer, AIDS, and diabetes.[1] For this reason, a variety of natural and non-natural polyhydroxylated piperidines have been prepared and evaluated for their clinical applications.[2] Indeed, miglitol (Glyset™) and *N*-butyldeoxynojirimycin (Zavesca™) are currently used as drugs for the treatment of type II diabetes and Gaucher's disease, respectively.[3]

1,2-Dideoxy azasugars are a representative example of naturally occurring polyhydroxylated piperidines and represent an important class of glycosidase inhibitors (Fig. 1).[4] D-Fagomine (**1**), a member of this family, was first isolated from Japanese buckwheat seeds of *Fagopyrum esculentum* Moench in 1974,[5] and was found in the seeds of *Castanospermum australe* (Leguminosae).[6] Later, D-fagomine (**1**) and 6-deoxyfagomine (**5**) were also isolated from the roots of *Lycium chinense* (Solanaceae).[7] D-Fagomine (**1**) was found to be a potent inhibitor against mammalian α-glucosidase and β-galactosidase,[8] and was also reported to display a strong antihyperglycemic activity in streptozocin-induced diabetic mice and in potentiation of glucose-induced insulin secretion.[9] In addition, non-naturally occurring 4-*epi*-fagomine (**4**) was found to be a potent lysosomal α-galactosidase A inhibitor in Fabry lymphoblasts.[10]

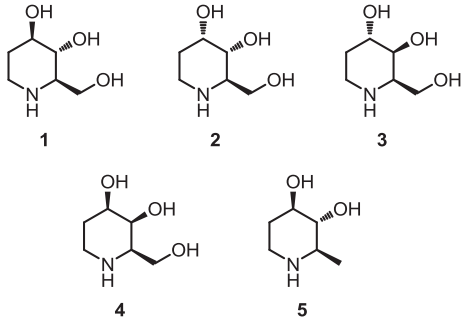

Fig. 1. Structures of fagomine family.

To date, a number of synthetic methods for the preparation of **1** and **5** have been reported.[11–13] A majority of synthetic approaches have involved asymmetric synthesis for the construction of stereogenic centers,[11] chemical and enzymatic resolution,[12] and synthetic strategy from a readily available chiral pool.[13] In a recent example for asymmetric synthesis, Ham reported a total synthesis of **1** via palladium-catalyzed stereoselective intramolecular oxazine formation followed by catalytic hydrogenation of oxazine intermediate.[11a] Wong described a one-pot chemoenzymatic aldol reaction for the synthesis of a variety of iminocyclitols including **1** and **5** from readily available non-phosphorylated donor substrates.[12d] Takahata demonstrated the total synthesis of fagomine

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and its congeners **1**–**4**, starting from Garner aldehyde derived from D-serine, via ring-closing metathesis and dihydroxylation as the key steps.[13d]

As part of an ongoing research program aimed at developing asymmetric total synthesis of biologically active compounds,[14] we recently described a facile strategy for the preparation of (−)-lentiginosine and its analogues via diastereoselective amination of chiral allylic ethers using chlorosulfonyl isocyanate (CSI).[15] In connection with previous works, we herein describe an asymmetric total synthesis of D-fagomine (**1**) and 6-deoxyfagomine (**5**) starting from commercially available D-lyxose via highly stereoselective amination of chiral allylic ether using chlorosulfonyl isocyanate as the key step.

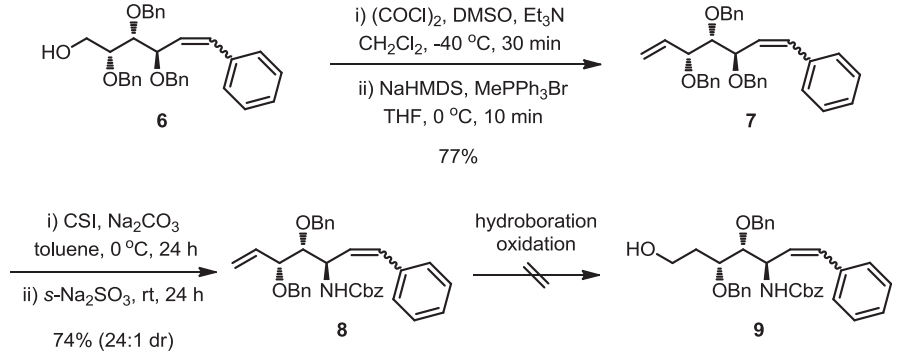
2. Results and discussion

Our initial investigations focused on the efficient construction of aminoalcohol **9**, which can provide piperidine core by Appel reaction of primary alcohol followed by intramolecular cyclization under basic condition, based on the reported literature (Scheme 1).[14g] The synthesis of **9** began with the alcohol **6** prepared from commercially available D-lyxose. Swern oxidation of **6** and subsequent Wittig reaction furnished the dienic compound **7**. Treatment of **7** with CSI in toluene at 0 °C followed by desulfonylation using a saturated sodium sulfite solution afforded the cinnamylic amine **8** in 74% yield with a high diastereoselectivity (*anti*/*syn*=24:1). A range of hydroboration and oxidation conditions, such as BH_3–THF, 9-BBN, and catecholborane, were conducted for the chemoselective oxidation of terminal olefin of **8**, but with limited/no success.

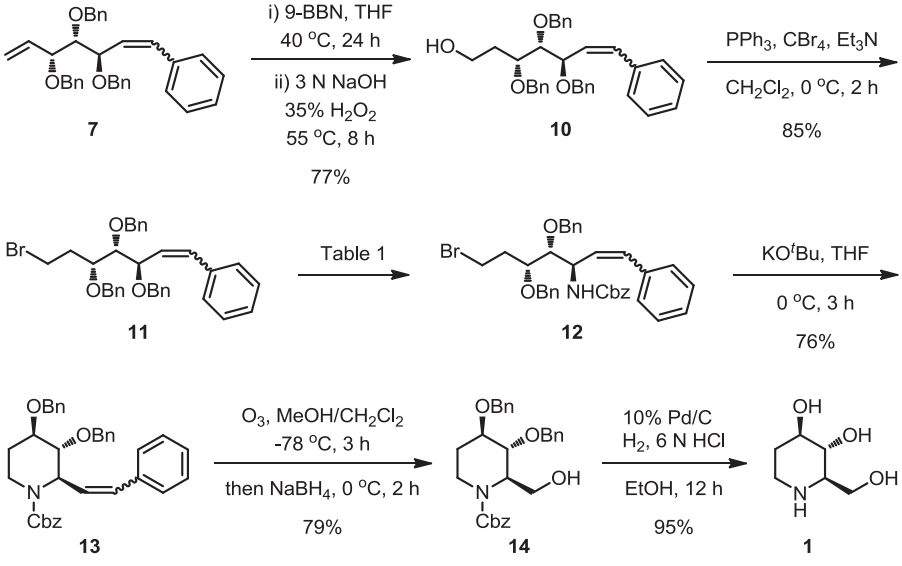
In view of these unsuccessful results, we exchanged our synthetic plan to prepare the piperidine framework, as shown in Scheme 2. To our delight, a terminal olefin of the diene **7** under standard hydroboration and oxidation conditions (9-BBN, $NaOH/H_2O_2$) was converted into the primary alcohol **10**, which was subjected to the Appel reaction (PPh_3, CBr_4, and Et_3N) to furnish compound **11** in 85% yield.

Next, the diastereoselective amination reaction of **11** using chlorosulfonyl isocyanate was examined under various reaction conditions, and the selected results are summarized in Table 1. As shown in entry 1, the reaction in methylene chloride at 0 °C gave the desired product **12** with 17:1 of a diastereomeric ratio. After screening of solvents under otherwise identical conditions, toluene was found to be most effective solvent in this reaction, affording exclusively the compound **12** in 74% yield with an excellent diastereoselectivity of 26:1 (Table 1, entry 5). The diastereoselectivity of compound **12** can be explained by the neighboring group effect, whereby the orientation of the NHCbz group retains its original configuration through double inversion of configuration.[15b]

Treatment of **12** with potassium *tert*-butoxide afforded the piperidine **13**. Ozonolysis of **13** and subsequent reduction using $NaBH_4$ gave the alcohol **14**, which was hydrogenated to provide D-fagomine (**1**) in 95% yield. The spectroscopic data (^1H NMR and ^{13}C NMR) and specific rotation of the compound **1** were in full agreement with the reported literature values.[11a]



Scheme 1.



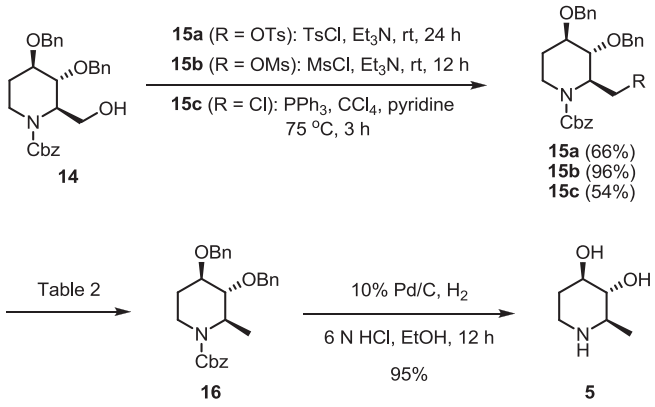
Scheme 2.

Table 1
Selected optimization for the diastereoselective amination of **11**[a]

Entry	Solvent	Time (h)	Yield[b] (%)	*anti*/*syn*[c]
1	CH_2Cl_2	12	50	17:1
2	Et_2O	12	60	15:1
3	CCl_4	19	58	19:1
4	*n*-Hexanes	24	65	16:1
5	Toluene	24	74	26:1

[a] Reaction conditions: (i) **11** (1 equiv), chlorosulfonyl isocyanate (4.5 equiv), Na_2CO_3 (6.8 equiv), solvent (0.2 M), 0 °C; (ii) *s*-Na_2SO_3, rt, 24 h.
[b] Isolated yield by flash column chromatography.
[c] Diastereomeric ratio was determined by ^{1}H NMR analysis of a crude reaction mixture.

Based on the above results, we focused on the synthesis of 6-deoxyfagomine (**5**) from the piperidine **14** via a three-step synthesis, as illustrated in Scheme 3. To obtain compound **16**, we initially attempted conversion of the alcohol moiety of **14** into OTs and OMs groups, which can be easily removed by the use of potent reducing reagents such as $LiAlH_4$ and $LiEt_3BH$.[16] However, these attempts were unsuccessful and led to the decomposition of the starting material (Table 2).



Scheme 3.

Table 2
Selected optimization for the reduction of **15a**–**15c**

Entry	Substrate	Reaction conditions	Yield[a] (%)
1	**15a**	$LiAlH_4$ (3 equiv), THF (0.3 M), 70 °C, 8 h	0
2	**15b**	$LiAlH_4$ (3 equiv), THF (0.3 M), 70 °C, 8 h	0
4	**15b**	$LiEt_3BH$ (3 equiv), THF (0.3 M), 100 °C, 14 h	0
3	**15c**	*n*-Bu_3SnH (2 equiv), AIBN (0.2 equiv), toluene (0.1 M), reflux, 12 h	81

[a] Isolated yield by flash column chromatography.

Consequently, our strategy was changed to conversion of primary alcohol to halogen group followed by dehalogenation using radical reaction. Thus, the alcohol **14** was subjected to Appel conditions to afford compound **15c**, which was readily hydrogenated using *n*-Bu_3SnH and AIBN to give compound **16** in 81% yield.[17] Finally, benzyl and Cbz protection groups were removed via Pd-catalyzed hydrogenation to afford 6-deoxyfagomine (**5**). The spectroscopic data and the specific rotation of **5** were found to be in full agreement with the reported literature value.[13a]

3. Conclusions

In conclusion, we have described a concise total synthesis of D-fagomine and 6-deoxyfagomine starting from readily available D-lyxose via a stereoselective amination reaction into chiral allylic ethers using chlorosulfonyl isocyanate. It is believed that this synthetic strategy can be applied to the preparation of a broad range of biologically active compounds containing polyhydroxylated alkaloids or other natural products containing a nitrogen atom in the ring.

4. Experimental

4.1. General method

Commercially available reagents were used without additional purification, unless otherwise stated. All reactions were performed under an inert atmosphere of nitrogen or argon. Nuclear magnetic resonance spectra (^{1}H and ^{13}C NMR) were recorded on Varian Unit 500 and 300 MHz spectrometers for $CDCl_3$ solutions and chemical shifts are reported as parts per million (ppm) relative to, respectively, residual $CHCl_3$ δ_H (7.26 ppm) and $CDCl_3$ δ_C (77.0 ppm) as internal standards. Resonance patterns are reported with the notations s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). In addition, the notation br is used to indicate a broad signal. Coupling constants (*J*) are reported in hertz (Hz). IR spectra were recorded on Bruker Infrared spectrophotometer and are reported as cm^{-1}. Optical rotations were measured with a Jasco P1020 polarimeter. Thin layer chromatography was carried out using plates coated with Kieselgel $60F_{254}$ (Merck). For flash column chromatography, E. Merck Kieselgel 60 (230–400 mesh) was used. LC/mass spectra (LC/MS) were recorded on a Waters 2767 LCMS system. High-resolution mass spectra (HRMS) were recorded on a JEOL JMS-600 spectrometer.

4.2. ((3*R*,4*S*,5*R*)-1-Phenylhepta-1,6-diene-3,4,5-triyl)tris(oxy) tris(methylene)tribenzene (7)

To a stirred solution of oxalic chloride (15.1 mL, 30.18 mmol, 2.0 M in CH_2Cl_2) in anhydrous CH_2Cl_2 (91 mL) was carefully added DMSO (4.3 mL, 60.35 mmol) at −78 °C and stirred for 1 h at same temperature. The alcohol **6** (9.95 g, 20.12 mmol) and Et_3N (14.0 mL, 23.86 mmol) were added to the reaction mixture, which was stirred for 1 h at −78 °C and then stirred for 0.5 h at −40 °C. The resulting mixture was carefully quenched with H_2O and the aqueous layer was extracted with CH_2Cl_2 (100 mL). The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residual oil (about 9.9 g) was subjected to the next step without purification. To a stirred solution of $MePPh_3Br$ (10.77 g, 30.15 mmol) in THF (61.1 mL) was added NaHMDS (30.2 mL, 1.0 M in THF) at 0 °C under N_2. The reaction mixture was stirred for 1 h at 0 °C. The crude aldehyde was suspended in THF (40 mL), and then was slowly added to the reaction mixture at 0 °C. The reaction mixture was stirred for 10 min at 0 °C. The reaction mixture was quenched with H_2O and the aqueous layer was extracted with EtOAc (100 mL). The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexanes/EtOAc=20:1) to afford 7.59 g (77%, cis/trans=3.2:1) of **7** as a colorless syrup. R_f=0.29 (*n*-hexanes/EtOAc=20:1); cis-isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.57–3.61 (m, 1H), 3.90 (d, *J*=11.0 Hz, 1H), 4.07–4.15 (m, 1H), 4.24 (d, *J*=11.0 Hz, 1H), 4.41 (d, *J*=11.0 Hz, 1H), 4.61 (d, *J*=11.0 Hz, 1H), 4.70 (d, *J*=11.0 Hz, 1H), 4.81 (d, *J*=11.0 Hz, 1H), 4.83–4.86 (m, 1H), 5.22–5.37 (m, 2H), 5.78 (dd, *J*=11.5, 10.0 Hz, 1H), 5.85–5.98 (m, 1H), 6.92 (d, *J*=11.5 Hz, 1H), 7.10–7.50 (m, 20H); trans-isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.64–3.68 (m, 1H), 4.07–4.13 (m, 2H), 4.26 (d, *J*=11.0 Hz, 1H), 4.45–4.48 (m, 1H), 4.63 (d, *J*=11.0 Hz, 1H), 4.68 (d, *J*=11.0 Hz, 1H), 4.71 (d, *J*=11.0 Hz, 1H), 4.76 (d, *J*=11.0 Hz, 1H), 5.22–5.37 (m, 2H), 5.76 (dd, *J*=16.0, 7.5 Hz, 1H), 5.86–5.97 (m, 1H), 6.69 (d, *J*=16.0 Hz, 1H), 7.10–7.50 (m, 20H); ^{13}C NMR

(125 MHz, $CDCl_3$) δ 70.2, 70.5, 70.9, 73.6, 75.3, 75.5, 80.3, 80.4, 81.0, 83.7, 84.3, 118.3, 118.8, 126.9, 127.3, 127.4, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 128.8, 128.9, 129.4, 130.0, 130.5, 134.5, 134.9, 136.3, 136.5, 136.9, 137.0, 138.5, 138.6, 138.7, 138.8, 138.9; HRMS (FAB) calcd for $C_{34}H_{34}O_3$ $[M+H]^+$ 490.2508, found 490.2514.

4.3. (3*R*,4*S*,5*R*)-3,4,5-Tris(benzyloxy)-7-phenylhept-6-en-1-ol (10)

To a stirred solution of the diene **7** (7.59 g, 15.47 mmol) in anhydrous THF (8.0 mL) was added 9-BBN (62.1 mL, 0.5 M in THF) at room temperature. After stirring for 24 h at 40 °C, the reaction mixture was added to 3 N NaOH (22 mL) and 35% H_2O_2 (22 mL) at 0 °C. The reaction mixture was stirred for 8 h at 55 °C and quenched with H_2O. The aqueous layer was extracted with EtOAc (200 mL). The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexanes/EtOAc=3:1) to afford 6.06 g (77%, cis/trans=3.6:1) of **10** as a colorless syrup. R_f=0.26 (*n*-hexanes/EtOAc=3:1); IR (neat) 3445, 3061, 1716, 1495, 1453 cm^{-1}; cis-isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 1.55–1.86 (m, 3H), 3.45–3.56 (m, 2H), 3.59–3.68 (m, 1H), 3.79–3.92 (m, 1H), 4.04 (d, *J*=11.4 Hz, 1H), 4.46 (s, 2H), 4.51 (d, *J*=11.4 Hz, 1H), 4.62 (d, *J*=11.4 Hz, 1H), 4.71–4.80 (m, 1H), 4.83 (d, *J*=11.4 Hz, 1H), 5.85 (dd, *J*=12.0, 9.9 Hz, 1H), 6.91 (d, *J*=12.0 Hz, 1H), 7.09–7.43 (m, 20H); trans-isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 1.58–1.83 (m, 3H), 3.44–3.52 (m, 2H), 3.60–3.64 (m, 1H), 3.80–3.93 (m, 1H), 4.17–4.20 (m, 1H), 4.38 (d, *J*=11.4 Hz, 1H), 4.42–4.58 (m, 3H), 4.69 (d, *J*=11.4 Hz, 1H), 4.78 (d, *J*=11.4 Hz, 1H), 6.35 (dd, *J*=16.5, 7.5 Hz, 1H), 6.64 (d, *J*=16.5 Hz, 1H), 7.12–7.40 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.1, 34.3, 60.6, 60.7, 70.0, 70.3, 73.4, 73.5, 73.8, 74.7, 75.0, 77.5, 78.3, 80.7, 82.6, 83.3, 126.9, 127.2, 127.5, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 128.8, 128.9, 129.3, 130.4, 134.8, 135.0, 136.8, 138.4, 138.5, 138.6; HRMS (CI) calcd for $C_{34}H_{37}O_4$ $[M+H]^+$ 509.2692, found 509.2686.

4.4. ((3*R*,4*S*,5*R*)-7-Bromo-1-phenylhept-1-ene-3,4,5-triyl) tris(oxy)tris(methylene)tribenzene (11)

To a stirred solution of the alcohol **10** (6.06 g, 11.91 mmol) in anhydrous CH_2Cl_2 (24.4 mL) were added PPh_3 (9.37 g, 35.73 mmol), CBr_4 (5.93 g, 17.87 mmol), and Et_3N (12.2 mL) at 0 °C under N_2. The reaction mixture was stirred for 2 h at 0 °C and quenched with H_2O (15 mL). The aqueous layer was extracted with CH_2Cl_2 (30 mL×2). The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexanes/EtOAc=30:1) to afford 5.79 g (85%, cis/trans=3.3:1) of **11** as a colorless syrup. R_f=0.22 (*n*-hexanes/EtOAc=30:1); IR (neat) 3062, 3029, 1723, 1495, 1453, 1090, 1068 cm^{-1}; cis-isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 2.01–2.23 (m, 2H), 3.28 (t, *J*=6.6 Hz, 2H), 3.59–3.61 (m, 1H), 3.82–3.90 (m, 1H), 3.93 (d, *J*=11.4 Hz, 1H), 4.42 (s, 2H), 4.47 (d, *J*=11.4 Hz, 1H), 4.71 (d, *J*=11.4 Hz, 1H), 4.78–4.81 (m, 1H), 4.84 (d, *J*=11.4 Hz, 1H), 5.84 (dd, *J*=12.0, 9.9 Hz, 1H), 6.94 (d, *J*=12.0 Hz, 1H), 7.09–7.47 (m, 20H); trans-isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 1.87–1.98 (m, 2H), 3.67 (t, *J*=6.6 Hz, 2H), 3.72 (t, *J*=4.8 Hz, 1H), 3.85–3.99 (m, 3H), 4.17–4.22 (m, 1H), 4.42 (d, *J*=11.4 Hz, 1H), 4.47 (d, *J*=11.4 Hz, 1H), 4.78 (d, *J*=11.4 Hz, 1H), 4.83 (d, *J*=11.4 Hz, 1H), 6.34 (dd, *J*=16.2, 8.4 Hz, 1H), 6.66 (d, *J*=16.2 Hz, 1H), 7.10–7.44 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.9, 35.0, 69.9, 70.3, 73.6, 73.7, 73.8, 74.6, 74.8, 77.1, 80.6, 81.8, 82.8, 126.6, 126.9, 127.1, 127.3, 127.5, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 128.8, 128.9, 129.0, 129.3, 129.5, 130.4, 134.8, 135.2, 136.7, 136.8, 138.3, 138.4, 138.6, 138.7; HRMS (EI) calcd for $C_{34}H_{35}BrO_3$ $[M]^+$ 570.1770, found 570.1771.

4.5. Benzyl (3*R*,4*R*,5*R*)-4,5-bis(benzyloxy)-7-bromo-1-phenylhept-1-en-3-ylcarbamate (12)

To a stirred solution of **11** (5.79 g, 10.13 mmol) in anhydrous toluene (50.7 mL) were added Na_2CO_3 (7.25 g, 68.40 mmol) and chlorosulfonyl isocyanate (3.97 mL, 45.60 mmol) at 0 °C under N_2. The reaction mixture was stirred for 24 h at 0 °C and quenched with H_2O (15 mL). The aqueous layer was extracted with EtOAc (30 mL×2). The organic layer was added to a saturated solution of Na_2SO_3 (100 mL), and the reaction mixture was stirred for 24 h at room temperature. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexanes/EtOAc=13:1) to afford 4.61 g (74%, cis/trans=4.3:1, *anti*/*syn*=26:1) of **12** as a pale yellow syrup. R_f=0.11 (*n*-hexanes/EtOAc=13:1); IR (neat) 3417, 3062, 3030, 1710, 1498, 1454, 1217, 1070 cm^{-1}; cis-isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 1.77–1.96 (m, 2H), 2.91–3.02 (m, 1H), 3.18–3.21 (m, 1H), 3.42 (t, *J*=4.8 Hz, 1H), 3.76 (dd, *J*=5.7, 4.8 Hz, 1H), 4.41–4.74 (m, 4H), 4.97–5.18 (m, 3H), 5.54 (t, *J*=9.9 Hz, 1H), 5.56–5.61 (br, 1H), 6.60 (d, *J*=9.9 Hz, 1H), 7.13–7.32 (m, 20H); trans-isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 2.12–2.20 (m, 2H), 3.13–3.18 (m, 1H), 3.22–3.38 (m, 1H), 3.57 (t, *J*=4.8 Hz, 1H), 3.85–3.89 (m, 1H), 4.44–4.75 (m, 5H), 4.99–5.20 (m, 2H), 5.62–5.65 (br, 1H), 6.05 (dd, *J*=15.6, 7.2 Hz, 1H), 6.51 (d, *J*=15.6 Hz, 1H), 7.14–7.30 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.8, 29.9, 30.7, 33.4, 33.5, 33.7, 49.3, 53.8, 66.7, 73.1, 74.3, 74.7, 79.4, 125.9, 126.7, 126.8, 127.7, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 128.8, 128.9, 130.9, 132.9, 136.5, 136.8, 136.9, 137.8, 137.9, 156.0; HRMS (CI) calcd for $C_{34}H_{37}O_4$ $[M+H]^+$ 614.1906, found 614.1929.

4.6. (2*R*,3*R*,4*R*)-Benzyl 3,4-bis(benzyloxy)-2-styrylpiperidine-1-carboxylate (13)

To a stirred solution of **12** (3.98 g, 6.48 mmol) in anhydrous THF (32.4 mL) was slowly added potassium *tert*-butoxide (1.67 g, 14.90 mmol) at 0 °C under N_2. The reaction mixture was stirred for 3 h at 0 °C and quenched with aqueous solution of saturated NH_4Cl (15 mL). The aqueous layer was extracted with EtOAc (30 mL). The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexanes/acetone=15:1) to afford 2.63 g (76%) of **13** as a colorless syrup. R_f=0.10 (*n*-hexanes/acetone=15:1); IR (neat) 3030, 1698, 1496, 1454, 1426, 1092, 1029 cm^{-1}; cis-isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 1.71 (br d, *J*=11.4 Hz, 1H), 1.94–2.12 (m, 1H), 3.40 (dt, *J*=13.2, 2.7 Hz, 1H), 3.51 (br s, 1H), 3.66–3.68 (m, 1H), 4.01 (d, *J*=12.0 Hz, 1H), 4.08 (d, *J*=12.0 Hz, 1H), 4.47 (d, *J*=12.0 Hz, 1H), 4.54 (d, *J*=12.0 Hz, 1H), 4.74 (d, *J*=12.0 Hz, 1H), 5.11 (s, 2H), 5.61 (br d, *J*=11.7 Hz, 1H), 6.12 (dd, *J*=9.3, 8.7 Hz, 1H), 6.50 (d, *J*=9.3 Hz, 1H), 7.02–7.37 (m, 20H); trans-isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 1.96–2.11 (m, 2H), 3.25–3.74 (m, 2H), 3.96–4.06 (m, 1H), 4.18–4.57 (m, 2H), 4.64 (d, *J*=12.0 Hz, 1H), 4.77 (d, *J*=12.0 Hz, 1H), 5.22–5.28 (m, 2H), 5.46–5.62 (m, 1H), 6.22 (dd, *J*=15.6, 8.8 Hz, 1H), 6.42 (d, *J*=15.6 Hz, 1H), 6.92–7.36 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.7, 34.9, 51.3, 67.4, 71.0, 71.1, 73.7, 75.0, 126.7, 127.3, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.5, 128.6, 130.1, 137.0, 137.1, 138.2, 138.5, 156.2; HRMS (CI) calcd for $C_{35}H_{35}O_4$ $[M+H]^+$ 534.2644, found 534.2639.

4.7. (2*R*,3*R*,4*R*)-Benzyl 3,4-bis(benzyloxy)-2-(hydroxymethyl) piperidine-1-carboxylate (14)

A stirred solution of **13** (2.63 g, 4.93 mmol) in anhydrous CH_2Cl_2 (19.3 mL) and MeOH (19.3 mL) was allowed to react with ozone (40 mL/min) for 3 h at −78 °C. After removal of an excess ozone by flushing argon, $NaBH_4$ (1.70 g, 44.97 mmol) was slowly added at

−78 °C and the reaction mixture was stirred for 2 h at 0 °C. The resulting mixture was quenched with aqueous solution of saturated NH_4Cl (20 mL) and extracted with CH_2Cl_2 (35 mL×2). The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexanes/EtOAc=3:1) to afford 1.80 g (79%) of **14** as a colorless syrup. R_f=0.22 (*n*-hexanes/EtOAc=3:1); $[\alpha]_D^{29}$ −53.3 (*c* 1.2, $CHCl_3$); IR (neat) 3445, 3031, 3029, 1696, 1454, 1430, 1093, 1069 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.69 (br d, *J*=13.5 Hz, 1H), 1.94–2.04 (m, 1H), 3.32 (br d, *J*=12.6 Hz, 1H), 3.68 (s, 1H), 3.72 (br d, *J*=3.3 Hz, 1H), 3.79 (br s, 1H), 3.91 (dd, *J*=11.4, 6.9 Hz, 2H), 4.43–4.67 (m, 5H), 5.14 (s, 2H), 7.25–7.42 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.0, 35.8, 56.0, 61.9, 67.5, 71.6, 73.8, 127.8, 127.9, 128.0, 128.2, 128.6, 128.7, 128.8, 129.9, 137.0, 138.0, 138.2, 158.9; HRMS (CI) calcd for $C_{28}H_{31}NO_5$ $[M+H]^+$ 462.2280, found 462.2274.

4.8. (2*R*,3*R*,4*R*)-2-(Hydroxymethyl)piperidine-3,4-diol (D-fagomine, 1)

To a stirred solution of **14** (0.80 g, 1.73 mmol) in EtOH (86.5 mL) were added aqueous solution of 6 N HCl (15.3 mL) and 10% Pd/C (0.40 g, 0.40 mmol). The reaction mixture was shaken on a Parr apparatus under hydrogen (60 ψ) for 12 h. The resulting mixture was filtered through a Celite pad and concentrated in vacuo. The residue was purified by ion-exchange resin DOWEX-50W×8 (H^+ form) using aqueous 0.5 M NH_4OH as eluent to afford 0.24 g (95%) of D-fagomine (**1**) as a white solid. R_f=0.36 (CH_2Cl_2/MeOH/EtOH/30%NH_4Cl=5:2:2:1); mp 184–185 °C; $[\alpha]_D^{29}$ +14.9 (*c* 0.5, CH_3OH); ^1H NMR (300 MHz, D_2O) δ 1.41 (ddt, *J*=12.9, 11.4, 4.2 Hz, 1H), 1.98 (ddd, *J*=12.9, 4.8, 2.1 Hz, 1H), 2.51 (ddd, *J*=13.5, 6.9, 3.3 Hz, 1H), 2.62 (dd, *J*=12.9, 2.4 Hz, 1H), 3.00 (ddd, *J*=12.9, 4.5, 2.1 Hz, 1H), 3.16 (t, *J*=9.3 Hz, 1H), 3.53 (ddd, *J*=14.1, 8.7, 4.8 Hz, 1H), 3.86 (dd, *J*=11.7, 6.6 Hz, 1H), 3.83 (dd, *J*=11.1, 2.7 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 34.8, 44.7, 63.3, 63.4, 75.1, 75.3; HRMS (CI) calcd for $C_6H_{13}NO_3$ $[M+H]^+$ 148.0974, found 148.0976.

4.9. (2*R*,3*R*,4*R*)-2-Benzenesulfonyloxymethyl-3,4-bis-benzyloxy-piperidine-1-carboxylic acid benzyl ester (15a)

To a stirred solution of the alcohol **14** (0.2 g, 0.433 mmol) in anhydrous CH_2Cl_2 (0.7 mL) were added Et_3N (0.18 mL, 1.299 mmol) and *p*-toluenesulfonyl chloride (0.12 g, 0.650 mmol) at 0 °C under N_2. The reaction mixture was stirred for 24 h at room temperature and quenched with H_2O (3 mL). The aqueous layer was extracted with CH_2Cl_2 (5 mL×2). The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexanes/EtOAc=2:1) to afford 0.176 g (66%) of **15a** as colorless syrup. R_f=0.42 (*n*-hexanes/EtOAc=2:1); ^1H NMR (300 MHz, $CDCl_3$) δ 1.60–1.72 (m, 1H), 1.88–1.97 (m, 1H), 2.39 (s, 3H), 2.81 (br s, 1H), 3.49 (br s, 1H), 3.65 (d, *J*=2.4 Hz, 1H), 3.88 (br s, 1H), 4.09–4.17 (m, 1H), 4.34–4.59 (m, 5H), 4.77 (br s, 1H), 5.12–5.14 (m, 2H), 7.22–7.39 (m, 17H), 7.64–7.66 (br m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9, 67.0, 67.5, 71.4, 71.5, 82.0, 127.7, 128.0, 128.1, 128.2, 128.6, 128.7, 128.9, 130.0, 133.1, 136.9, 137.9, 138.1, 144.9, 156.0; LC/MS (ESI) *m*/*z* 616.10 $[M+H]^+$.

4.10. (2*R*,3*R*,4*R*)-3,4-Bis-benzyloxy-2-methanesulfonyloxymethyl-piperidine-1-carboxylic acid benzyl ester (15b)

To a stirred solution of the alcohol **14** (0.2 g, 0.433 mmol) in anhydrous CH_2Cl_2 (0.7 mL) were added Et_3N (0.18 mL, 1.299 mmol) and methanesulfonyl chloride (67 μL, 0.866 mmol) at 0 °C under N_2. The reaction mixture was stirred for 12 h at room temperature and quenched with saturated $NaHCO_3$ (2 mL). The aqueous layer was extracted with CH_2Cl_2 (5 mL×2). The organic layer was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexanes/EtOAc=2:1) to afford 0.221 g (95%) of **15b** as colorless syrup. R_f=0.32 (*n*-hexanes/EtOAc=2:1); ^1H NMR (300 MHz, $CDCl_3$) δ 1.73 (br d, *J*=13.5 Hz, 1H), 1.97–2.05 (br m, 1H), 2.78 (br s, 3H), 3.10–3.30 (m, 1H), 3.56 (s, 1H), 3.74 (d, *J*=2.7 Hz, 1H), 4.08–4.17 (m, 1H), 4.34–4.36 (m, 1H), 4.43–4.76 (m, 5H), 4.86 (br s, 1H), 5.11–5.19 (m, 2H), 7.26–7.51 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.6, 31.8, 34.7, 37.6, 66.6, 67.6, 71.5, 71.6, 72.3, 73.3, 127.9, 128.0, 128.1, 128.2, 128.3, 128.7, 128.8, 128.9, 129.1, 129.8, 129.9, 136.9, 137.9, 138.0, 156.2; LC/MS (ESI) *m*/*z* 540.01 $[M+H]^+$.

4.11. (2*S*,3*R*,4*R*)-Benzyl 3,4-bis(benzyloxy)-2-(chloromethyl) piperidine-1-carboxylate (15c)

To a stirred solution of the alcohol **14** (1.0 g, 2.17 mmol) in anhydrous CCl_4 (10.8 mL) were added PPh_3 (1.21 g, 4.60 mmol) and pyridine (4.34 mL) at room temperature under N_2. The reaction mixture was stirred for 3 h at 75 °C and quenched with H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (15 mL×2). The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexanes/EtOAc=8:1) to afford 0.56 g (54%) of **15c** as colorless syrup. R_f=0.20 (*n*-hexanes/EtOAc=8:1); $[\alpha]_D^{29}$ −47.0 (*c* 2.0, $CHCl_3$); IR (neat) 3031, 1701, 1454, 1424, 1213, 1092, 1069 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.67 (br d, *J*=13.8 Hz, 1H), 1.95 (br m, 1H), 3.09–3.17 (br, 1H), 3.71–3.90 (m, 4H), 4.02 (br s, 1H), 4.41 (d, *J*=11.7 Hz, 1H), 4.49 (d, *J*=11.7 Hz, 2H), 4.65 (br s, 2H), 5.15 (s, 2H), 7.24–7.34 (m 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0, 29.9, 34.8, 42.2, 67.6, 67.8, 71.5, 71.6, 72.1, 73.9, 127.7, 127.9, 128.0, 128.2, 128.6, 128.7, 128.8, 128.9, 129.7, 137.0, 138.1, 138.2, 156.2; HRMS (EI) calcd for $C_{28}H_{30}ClNO_4$ $[M]^+$ 479.1863, found 479.1856.

4.12. (2*R*,3*R*,4*R*)-Benzyl 3,4-bis(benzyloxy)-2-methylpiperidine-1-carboxylate (16)

To a stirred solution of **15c** (0.56 g, 1.17 mmol) in anhydrous toluene (11.7 mL) were added AIBN (0.04 g, 0.23 mmol) and *n*-Bu_3SnH (0.63 mL, 2.34 mmol) at room temperature under N_2. The reaction mixture was refluxed for 12 h and quenched with H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (15 mL×2). The organic layer was washed with 10% KF and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexanes/EtOAc=8:1) to afford 0.44 g (81%) of **16** as colorless syrup. R_f=0.40 (*n*-hexanes/EtOAc=8:1); $[\alpha]_D^{29}$ −54.2 (*c* 1.2, $CHCl_3$); IR (neat) 3031, 1697, 1454, 1426, 1212, 1072 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (d, *J*=7.2 Hz, 3H), 1.69 (dd, *J*=13.8, 2.4 Hz, 1H), 1.93–2.04 (m, 1H), 3.20 (dt, *J*=13.2, 2.7 Hz, 1H), 3.43 (s, 1H), 3.71 (d, *J*=3.0 Hz, 1H), 3.91 (br d, *J*=11.7 Hz, 1H), 4.41 (dd, *J*=12.0, 2.7 Hz, 1H), 4.50 (d, *J*=3.9 Hz, 2H), 4.55–4.63 (br m, 2H), 5.13 (s, 2H), 7.25–7.40 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.7, 25.5, 34.2, 49.3, 67.1, 71.2, 71.3, 74.4, 76.0, 127.5, 127.7, 127.8, 127.9, 128.0, 128.5, 128.6, 128.7, 137.3, 138.5, 138.6, 156.1; HRMS (EI) calcd for $C_{28}H_{31}NO_4$ $[M]^+$ 445.2253, found 445.2251.

4.13. (2*R*,3*R*,4*R*)-2-Methylpiperidine-3,4-diol (6-deoxyfagomine, 5)

To a stirred solution of **16** (0.44 g, 0.99 mmol) in EtOH (49.5 mL) were added aqueous solution of 6 N HCl (8.76 mL) and 10% Pd/C (0.22 g, 0.22 mmol). The reaction mixture was shaken on a Parr apparatus under hydrogen (60 ψ) for 12 h. The resulting mixture was filtered through a Celite pad and concentrated in vacuo. The

residue was purified by ion-exchange resin DOWEX-50W×8 (H^+ form) using aqueous 0.5 M NH_4OH as eluent to afford 0.12 g (95%) of 6-deoxyfagomine (**5**) as a waxy solid. R_f=0.40 (CH_2Cl_2/MeOH/EtOH/30%NH_4Cl=5:2:2:1); $[\alpha]_D^{29}$ −11.5 (*c* 1.5, CH_3OH); ^1H NMR (300 MHz, D_2O) δ 1.20 (d, *J*=6.6 Hz, 3H), 1.44 (ddt, *J*=12.6, 12.0, 4.5 Hz, 1H), 2.00–2.05 (m, 1H), 2.54–2.61 (m, 1H), 2.62 (dt, *J*=12.6, 2.4 Hz, 1H), 3.01 (t, *J*=9.0 Hz, 2H), 3.50–3.58 (m, 1H); ^{13}C NMR (125 MHz, D_2O) δ 17.0, 32.5, 42.7, 55.5, 72.7, 77.8; HRMS (EI) Calcd for $C_6H_{13}NO_2$ $[M]^+$ 131.0946, found 131.0945.

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Supplementary data

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