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Asymmetric synthesis of fagomine

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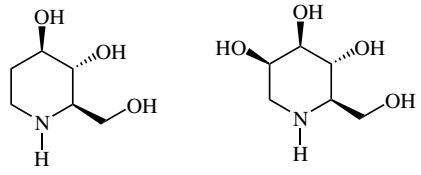
Dedicated to the memory of Professor Yoshihiko Ito

Abstract—We report an asymmetric synthesis of the alkaloid fagomine, which is an inhibitor of mammalian α-glucosidase and β-galactosidase, by means of Sharpless asymmetric dihydroxylation and Pd(II)-catalyzed cyclization, starting from 3-(*t*-butoxylcarbonylamino)propanol.

1. Introduction

Aza sugars, such as 1-deoxynojirimycin (DNJ; see Fig. 1), are potential drug candidates for the treatment of diabetes, cancer, AIDS, and viral infections, because of their glycosidase-inhibitory activity. Among them, fagomine **1** is a piperidine alkaloid isolated from buckwheat seeds (*Fagopyrum esculentum*) (Polygonaceae) and, more recently, from *Xanthocericis zambesiaca*, which is found in dry forests in southern Africa.[1–3] Fagomine has inhibitory activity towards mammalian α-glucosidase and β-galactosidase.[2]

Herein, we report an asymmetric synthesis of fagomine via Sharpless asymmetric dihydroxylation[4] and Pd(II)-catalyzed cyclization, which is a useful tool in the synthesis of alkaloids.[5]

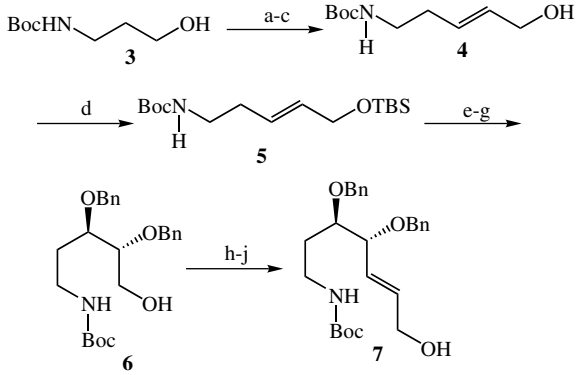


Fagomine **1** DNJ **2**

Figure 1.

2. Results and discussion

The substrate **7** for the Pd(II)-catalyzed cyclization was prepared from 3-(*t*-butoxylcarbonylamino)propanol **3** as shown in Scheme 1. The Swern oxidation of **3** and subsequent Horner–Wittig reaction gave the α,β-unsaturated ester, which was subjected to DIBAL–H reduction to afford allyl alcohol **4** in 83% yield over three steps. The alcohol group of **4** was protected with TBSCl to give **5**. Sharpless asymmetric dihydroxylation of **5** with AD-mix-β and $CH_3SO_2NH_2$ in *t*-BuOH and water at 0 °C afforded the diol. The hydroxyl moieties were protected with benzyl



Scheme 1. Reagents and conditions: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (b) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, −78 °C; (c) DIBAL, THF, −78 °C, three steps 83%; (d) TBSCl, imidazole, DMF, 89%; (e) AD-mix-β, $CH_3SO_2NH_2$, *t*-BuOH/H_2O; (f) BnBr, NaH, Bu_4NI, THF; (g) *p*-TsOH, MeOH, three steps 29%; (h) IBX, THF/DMSO; (i) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF; (j) DIBAL–H, THF, −78 °C, three steps 40%.

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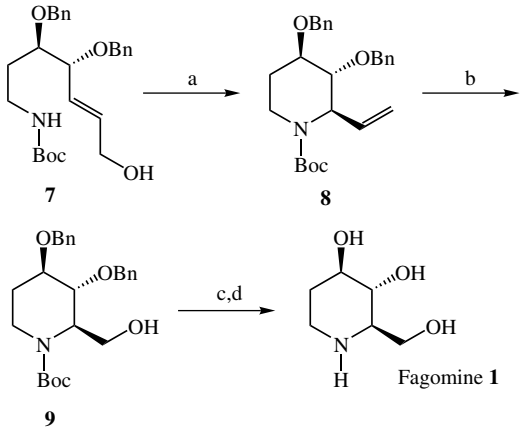

Scheme 2. Reagents and conditions: (a) $PdCl_2(MeCN)_2$, THF, rt, 90%; (b) O_3, CH_2Cl_2/MeOH (1:4), −78 °C; $NaBH_4$, −78 °C, 80%; (c) HCl aq, MeOH, 70 °C, 64%; (d) H_2, Pd–C, AcOH, 87%.

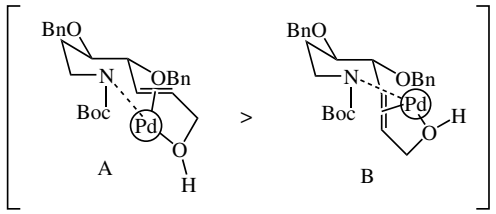

Figure 2.

groups and the TBS protecting group was removed under acidic conditions (*p*-TsOH, MeOH) to give alcohol **6**[6] in 29% yield and 74% ee from **5**. The IBX oxidation[7] of **6** and subsequent Horner–Wittig reaction gave the α,β-unsaturated ester, which was subjected to DIBAL–H reduction to afford allyl alcohol **7** in 40% overall yield.

The next task was the Pd(II)-catalyzed cyclization (Scheme 2). Allyl alcohol **7** was treated with $PdCl_2(MeCN)_2$ in THF at room temperature to give cyclic compound **8** in 90% yield.

A possible reaction mechanism is shown in Figure 2. The π-allyl–oxy palladium complex is produced by the coordination of the Pd catalyst with allyl alcohol and the amine. The stereoselective formation of **8** can be explained by assuming transition state **A**. Transition state **B** is disadvantageous, because of the non-bonding interaction between the carbamate moiety and π-allyl–oxy palladium complex (Fig. 2).

Next, we examined the transformation of **8** into fagomine **1**. Ozonolysis of **8** followed by reductive work-up with $NaBH_4$ provided the alcohol **9**. Deprotection of the Boc group of **9** under acidic conditions and removal of the benzyl groups by hydrogenation provided fagomine **1**. The spectral data of (+)-**1** were in agreement with reported data.[3d]

3. Conclusion

In conclusion, we have achieved an asymmetric synthesis of fagomine, using an approach that should be easily extended to the synthesis of various piperidine alkaloids with potential biomedical applications.

4. Experimental

4.1. 3-[*N*-(*tert*-Butoxycarbonyl)amino]-propan-1-ol 3

To a solution of 3-amino-propan-1-ol (1.0 g, 13.30 mmol) in CH_2Cl_2 (26.6 mL) was added di-*tert*-butyl dicarbonate (4.58 mL, 19.95 mmol) at room temperature under an argon atmosphere. Triethylamine (2.78 mL, 19.95 mmol) was added to the mixture at room temperature and the mixture was then stirred at the same temperature for 21 h. The reaction mixture was quenched with 10% aqueous HCl and the resulting mixture was extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent; Hex:AcOEt = 4:1) to afford 3-[*N*-(*tert*-butoxycarbonyl)-amino]-propan-1-ol (2.08 g, 89%) as colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 3.66 (t, $J = 5.9$ Hz, 2H), 3.28 (t, $J = 6.1$ Hz, 2H), 1.65 (tt, $J = 5.9$, 6.1 Hz, 2H), 1.44 (s, 9H), IR (neat) 3729–3093, 2978, 2936, 2879, 1690, 1526, 1172, 1046 cm^{-1}.

4.2. 3-[*N*-(*tert*-Butoxycarbonyl)amino]-propanal

To a stirred solution of dimethylsulfoxide (3.15 mL, 42.0 mmol) in CH_2Cl_2 (140 mL) under an argon atmosphere was added oxalyl chloride (1.94 mL, 21.0 mmol) at −78 °C. The resultant mixture was stirred for 15 min and a solution of 3-[*N*-(*tert*-butoxycarbonyl)amino]-propan-1-ol (2.60 g, 14.0 mmol) in CH_2Cl_2 was added dropwise. After stirring for 1 h at −78 °C, triethylamine (9.67 mL, 70.0 mmol) was added, and the resulting mixture was allowed to warm into room temperature. After 30 min, the reaction mixture was quenched with 10% aqueous HCl and the resulting mixture extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$. Concentration afforded the crude aldehyde (2.50 g), which was used in the next step without further purification.

4.3. Ethyl-5-[*N*-(*tert*-butoxycarbonyl)amino]-2-pentenoate

To a suspension of NaH (784 mg, 19.6 mmol) in THF (135 mL) was added diethyl triethyl phosphonoacetate (4.16 mL, 21.0 mmol) at 0 °C under an argon atmosphere and the mixture was stirred at the same temperature for 10 min. A solution of 3-[*N*-(*tert*-butoxycarbonyl)amino]-propanal (2.50 g) in THF (5 mL) was added to the Wittig mixture at −50 °C and the reaction mixture was warmed to room temperature for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and the resulting mixture was extracted with hexane (20 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent; Hex: AcOEt = 9:1) to afford ethyl-5-[*N*-(*tert*-butoxycarbonyl)-amino]-2-pentenoate (2.86 g, two steps 84%) as a yellow

oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (dt, $J = 1.5$, 15.6 Hz, 1H), 5.87 (dt, $J = 7.1$, 15.6 Hz, 1H), 4.20 (q, $J = 7.1$ Hz, 2H), 3.23–3.26 (m, 2H), 2.43–2.37 (m, 2H), 1.44 (s, 9H), 1.28 (t, $J = 7.1$ Hz, 3H), IR (neat) 3367, 1716 cm^{-1}.

4.4. 5-[*N*-(*tert*-Butoxycarbonyl)amino]-2-penten-1-ol 4

To a solution of ethyl-5-[*N*-(*tert*-butoxycarbonyl)amino]-2-pentenoate (2.37 g, 9.7 mmol) in THF (97 mL) was added diisobutylaluminum hydride (0.93 M *n*-hexane solution) (31.4 mL, 29.1 mmol) at −78 °C under an argon atmosphere. The mixture was stirred for 2 h at the same temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl and the resulting mixture extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent; Hex:AcOEt = 8:2) to afford 5-[*N*-(*tert*-butoxycarbonyl)amino]-2-penten-1-ol (1.93 g, 99%) as a yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.69 (tq, $J = 5.4$, 6.6 Hz, 2H), 4.11 (d, $J = 5.4$ Hz, 2H), 3.18 (t, $J = 6.6$ Hz, 2H), 2.24 (dt, $J = 6.6$ Hz, 2H), 1.44 (s, 9H), IR (neat) 3278–3100, 2978, 2933, 1694 cm^{-1}.

4.5. 5-[*N*-(*tert*-Butoxycarbonyl)amino]-(*tert*-butyl-dimethyl-silyloxy)-2-pentene 5

To a solution of 5-[*N*-(*tert*-butoxycarbonyl)amino]-2-penten-1-ol (1.93 g, 9.70 mmol) in DMF (5.0 mL) was added imidazole (792 mg, 11.6 mmol) and TBSCl (1.60 g, 10.7 mmol) at 0 °C under an argon atmosphere. The reaction mixture was stirred for 3 h at the room temperature. The mixture was quenched with 10% aqueous HCl and the resulting mixture extracted with diethyl ether (5 mL × 3). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent; Hex:AcOEt = 33:1) to afford 5-[*N*-(*tert*-butoxycarbonyl)amino]-(*tert*-butyl-dimethyl-silyloxy)-2-pentene (2.73 g, 89%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.59–5.55 (m, 2H), 4.07 (d, $J = 4.8$ Hz, 2H), 3.13–3.08 (br s, 2H), 2.16 (dt, $J = 6.2$ Hz, 2H), 1.48 (s, 9H), 0.84 (s, 9H), 0.00 (s, 6H), IR (neat) 3356, 2957, 2897, 2857, 1698, 1253, 837, 777 cm^{-1}.

4.6. (2*R*,3*R*)-5-[*N*-(*tert*-Butoxycarbonyl)amino]-(*tert*-butyl-dimethyl-silyloxy)-2-penten-2,3-diol

To a solution of AD-mix-β (6.65 g) in *t*-BuOH (18.0 mL) and water (18.0 mL) was added methanesulfonamide (451 mg, 4.75 mmol) at room temperature and reaction mixture was stirred at 0 °C. 5-[*N*-(*tert*-Butoxycarbonyl)amino]-(*tert*-butyl-dimethyl-silyloxy)-2-pentene (1.5 g, 4.75 mmol) was added to the mixture at 0 °C. The resulting mixture was stirred at the same temperature for 20 h, then quenched with sodium sulfite (7.13 g). After being stirred for 1 h at room temperature, the resulting mixture was extracted with ethyl acetate and the aqueous layer was extracted with AcOEt (5 mL × 3). The combined organic layers were washed with 2 M KOH (5 mL × 1), dried over $MgSO_4$ and concentrated in vacuo. The crude diol was used without further purification for the next step.

4.7. (2*R*,3*R*)-5-[*N*-(*tert*-butoxycarbonyl)amino]-2,3-dibenzyloxy-(*tert*-butyl-dimethyl-silyloxy)-pentane

To a suspension of NaH (309 mg, 7.71 mmol) in THF (12.8 mL) was added (2*R*,3*R*)-5-[*N*-(*tert*-butoxycarbonyl)amino]-(*tert*-butyl-dimethyl-silyloxy)-pentan-2,3-diol (900 mg, 2.57 mmol) at 0 °C under an argon atmosphere and the reaction mixture was stirred for 1.5 h at the same temperature. Benzyl bromide (0.67 mL, 5.65 mmol) and tetrabutylammonium iodide (9.4 mg, 0.02 mmol) were added to the mixture at 0 °C. The resulting mixture was stirred at room temperature for 4 h and then quenched with ice water. The resulting mixture was extracted with ethyl acetate (5 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude dibenzylether was used without further purification for the next step.

4.8. (2*R*,3*R*)-5-[*N*-(*tert*-Butoxycarbonyl)amino]-2,3-dibenzyloxypentan-1-ol 6

To a solution of (2*R*,3*R*)-5-[*N*-(*tert*-butoxycarbonyl)-amino]-2,3-dibenzyloxy-(*tert*-butyl-dimethyl-silyloxy)-pentane (804 mg) in MeOH (15 mL) was added *p*-TsOH (26 mg, 0.01 mmol) at 0 °C under an argon atmosphere and the reaction mixture was stirred for 3 h at room temperature. The mixture was quenched with saturated aqueous $NaHCO_3$ and the resulting mixture extracted with ethyl acetate (5 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent; Hex:AcOEt = 8:2) to afford (2*R*,3*R*)-5-[*N*-(*tert*-butoxycarbonyl)amino]-2,3-dibenzyloxypentan-1-ol (368 mg, two steps 29%, 74% ee) as colorless oil. $[\alpha]_D^{24} = +16.8$ (*c* 0.25, $CHCl_3$), ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35–7.27 (m, 10 H), 4.62–4.59 (m, 3H), 4.50 (d, $J = 11.6$ Hz, 1H), 3.77 (dd, $J = 3.3$, 13.7 Hz, 1H), 3.66–3.61 (m, 3H), 3.15–3.10 (br, 2H), 1.82 (ddt, $J = 3.3$, 6.6, 18.1 Hz, 1H), 1.60 (ddt, $J = 6.0$, 6.6, 18.1 Hz, 1H), 1.40 (s, 9H), IR (neat) 3699–3137, 2976, 2931, 2877, 1694, 1170, 1092, 1059 cm^{-1}.

4.9. (2*R*,3*R*)-5-[*N*-(*tert*-Butoxycarbonyl)amino]-2,3-dibenzyloxypentanal

To a solution of (2*R*,3*R*)-5-[*N*-(*tert*-butoxycarbonyl)-amino]-2,3-dibenzyloxypentan-1-ol (237 mg, 0.57 mmol) in THF–DMSO (4.5 mL:4.5 mL) was added 1-hydroxy-1,2-benziodoxol-3(1*H*)-one-1-oxide (319 mg, 1.14 mmol) at 0 °C under an argon atmosphere and the reaction mixture stirred for 4 h at room temperature. The mixture was quenched with ice and the resulting mixture extracted with ethyl acetate (5 mL × 3). The organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$. Concentration afforded the crude aldehyde (187 mg), which was used in the next step without further purification.

4.10. (4*R*,5*R*)-Ethyl-7-[*N*-(*tert*-butoxycarbonyl)amino]-4,5-dibenzyloxy-2-heptenate

To a suspension of NaH (32 mg, 0.79 mmol) in THF (6 mL) was added diethyl triethyl phosphonoacetate (0.17 mL, 0.86 mmol) at 0 °C under an argon atmosphere and the mixture was stirred at the same temperature for 10 min. A solution of (2*R*,3*R*)-5-[*N*-(*tert*-butoxycarbonyl)-amino]-2,3-dibenzyloxypentanal (187 mg, 0.57 mmol) was added to the Wittig mixture at the same temperature and the reaction mixture was refluxed for 30 min. The reaction mixture was quenched with saturated aqueous NH_4Cl and the resulting mixture extracted with ethyl acetate (5 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent; Hex:AcOEt = 6:1) to afford (4*R*,5*R*)-ethyl-7-[*N*-(*tert*-butoxycarbonyl)amino]-4,5-dibenzyloxy-2-heptenate (173 mg, 63%) as a yellow oil. $[\alpha]_D^{24} = +7.9$ (*c* 1.00, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.28 (m, 10H), 6.93 (dd, $J = 5.9$, 15.9 Hz, 1H), 6.07 (dd, $J = 1.5$, 15.9 Hz, 1H), 4.66 (dd, $J = 11.4$, 12.0 Hz, 2H), 4.50 (d, $J = 11.4$ Hz, 1H), 4.40 (d, $J = 12.0$ Hz, 1H), 4.20 (q, $J = 7.1$ Hz, 2H), 4.14 (dt, $J = 1.5$, 5.4 Hz, 1H), 3.58 (ddd, $J = 1.5$, 3.2, 5.4 Hz, 1H), 3.19–3.11(m, 2H), 1.78–1.70 (m, 1H), 1.41 (s, 9H), 1.31 (t, $J = 7.1$ Hz, 3H), IR (neat) 3429, 3375, 2978, 2931, 2871, 1715, 1657 cm^{-1}.

4.11. (4*R*,5*R*)-Ethyl-7-[*N*-(*tert*-butoxycarbonyl)amino]-4,5-dibenzyloxy-2-hepten-1-ol 7

To a solution of (4*R*,5*R*)-ethyl-7-[*N*-(*tert*-butoxycarbonyl)-amino]-4,5-dibenzyloxy-2-heptenoate (173 mg, 0.36 mmol) in THF (3.5 mL) was added diisobutylaluminum hydride (0.93M *n*-hexane solution) (1.15 mL, 1.07 mmol) at −78 °C under an argon atmosphere. The mixture was warmed up to room temperature and stirred for 5 h at the same temperature. The reaction mixture was quenched with 10% aqueous HCl at 0 °C and the resulting mixture extracted with ethyl acetate (5 mL × 3). The combined organic layers were washed with $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent; Hex:AcOEt = 8:2) to afford (4*R*,5*R*)-ethyl-7-[*N*-(*tert*-butoxycarbonyl)amino]-4,5-dibenzyloxy-2-hepten-1-ol (101 mg, 64%) as a yellow oil. $[\alpha]_D^{24} = +14.0$ (*c* 0.27, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.30 (m, 10H), 5.93 (dt, $J = 15.6$, 5.1 Hz, 1H), 5.65 (dd, $J = 15.6$, 7.3 Hz, 1H), 4.72 (d, $J = 11.3$ Hz, 1H), 4.63 (d, $J = 11.8$ Hz, 1H), 4.55 (d, $J = 11.3$ Hz, 1H), 4.42 (d, $J = 11.8$ Hz, 1H), 4.19 (br t, $J = 5.1$ Hz, 2H), 3.97 (t, $J = 6.8$ Hz, 1H), 3.58–3.53 (m, 1H), 3.18–3.12 (m, 2H), 1.79–1.76 (m, 2H), 1.41 (s, 9H), IR (neat) 3695–3128, 2977, 2931, 2869, 1694 cm^{-1}.

4.12. (2*R*,3*R*,4*R*)-*N*-*tert*-Butoxycarbonyl-3,4-dibenzyloxy-2-vinylpiperidine 8

To a solution of (4*R*,5*R*)-ethyl-7-[*N*-(*tert*-butoxycarbonyl)-amino]-4,5-dibenzyloxy-2-hepten-1-ol (130 mg, 0.3 mmol) in THF (3.0 mL) was added a catalytic amount of $PdCl_2$ $(CH_3CN)_2$ (7.63 mg, 0.03 mmol) at 0 °C under an argon atmosphere and the mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with diethyl ether and filtered through a silica gel pad and followed by Florisil sequentially with diethyl ether and the eluent was concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent; Hex:AcOEt = 93:7) to afford (2*R*,3*R*,4*R*)-*N*-*tert*-butoxycarbonyl-3,4-dibenzyloxy-2-vinylpiperidine (112 mg, 90%) as a colorless oil. $[\alpha]_D^{24} = -18.6$ (*c* 0.85, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.26 (m, 10H), 6.07–5.99 (m, $J = 1.7$ Hz, 1H), 5.12–5.11 (m, $J = 1.7$ Hz, 1H), 5.09–5.08 (br, 1H), 4.69 (d, $J = 11.9$ Hz, 1H), 4.50–4.47 (m, $J = 11.9$ Hz, 3H), 3.88–3.85 (br d, $J = 12.9$ Hz, 1H), 3.70 (dt, $J = 2.7$, 3.2 Hz, 1H), 3.58 (br, 1H), 3.21 (dt, $J = 2.7$, 13.2 Hz, 1H), 1.98 (ddt, $J = 3.7$, 2.7, 13.2 Hz, 1H), 1.66 (dd, $J = 2.7$, 13.2 Hz, 1H), 1.44 (s, 9H), IR (neat) 3065, 3030, 2975, 2930, 2882, 1692 cm^{-1}; EI-Mass (*m*/*z*) 423.

4.13. (2*R*,3*R*,4*R*)-(*N*-*tert*-Butoxycarbonyl-3,4-dibenzyloxy-2-piperidinyl)-methanol 9

O_3 gas was bubbled into a solution of (2*R*,3*R*,4*R*)-*N*-*tert*-butoxycarbonyl-3,4-dibenzyloxy-2-vinylpiperidine (10 mg, 0.02 mmol) in CH_2Cl_2–MeOH (4:1, 1.3 mL) at −78 °C until the solution turned to blue. Then an argon gas bubbled through the solution until its color became clear. To the reaction mixture was added $NaBH_4$ (9.1 mg, 0.24 mmol) at −78 °C. The mixture was warmed slowly to the room temperature, and stirred for 2 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$. The resulting mixture was extracted with ethyl acetate (3 mL × 3). The combined organic layers were washed with brine and dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent; Hex:AcOEt = 4:1) to afford (2*R*,3*R*,4*R*)-(*N*-*tert*-butoxycarbonyl-3,4-dibenzyloxy-2-piperidinyl)-methanol (8.0 mg, 80%) as a colorless oil. $[\alpha]_D^{25} = -45.6$ (*c* 1.00, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.28 (m, 10H), 4.65 (d, $J = 11.7$ Hz, 1H), 4.60 (d, $J = 11.7$ Hz, 1H), 4.48 (dd, $J = 11.7$, 11.9 Hz, 3H), 3.94 (ddd, $J = 4.9$, 7.3, 11.7 Hz, 1H), 3.90–3.80 (br, 1H), 3.79–3.74 (ddd, $J = 2.2$, 7.3, 11.7 Hz, 1H), 3.74–3.70 (br d, $J = 3.2$ Hz, 1H), 3.29–3.22 (br t, $J = 12.4$ Hz, 1H), 1.98 (ddt, $J = 3.2$, 4.9, 12.4 Hz, 1H), 1.71 (dd, $J = 2.2$, 11.7 Hz, 1H), 1.45 (s, 9H), IR (neat) 3721–3139, 2975, 2930, 2886, 1687, 1423, 1171, 1069 cm^{-1}.

4.14. (2*R*,3*R*,4*R*)-3,4-Dibenzyloxy-1,5-imino-1,2,5-trideoxy-D-arabino hexitol

A mixture of (2*R*,3*R*,4*R*)-(*N*-*tert*-butoxycarbonyl-3,4-dibenzyloxy-2-piperidinyl)-methanol (31 mg, 0.07 mmol) and 10% aqueous HCl (2 mL) in MeOH (2 mL) was stirred at 70 °C for 5 h. The reaction mixture was alkalified with 2 M NaOH at 0 °C. The resulting mixture was extracted with CH_2Cl_2 (3 mL × 3). The combined organic layers were dried over K_2CO_3 and concentrated in vacuo. The residue was purified by silica gel chromatography (eluent; $CHCl_3$: ^{i}PrOH = 73:27) to afford (2*R*,3*R*,4*R*)-3,4-dibenzyloxy-1,5-imino-1,2,5-trideoxy-D-arabino hexitol (15 mg, 64%) as a colorless oil. $[\alpha]_D^{26} = +11.6$ (*c* 0.80, $CHCl_3$), ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37–7.27 (m, 10H), 4.98 (d,

$J = 11.0$ Hz, 1H), 4.65 (dd, $J = 11.0$, 11.6 Hz, 3H), 3.77 (dd, $J = 3.3$, 11.0 Hz, 1H), 3.65 (dd, $J = 5.5$, 11.0 Hz, 1H), 3.54 (ddd, $J = 2.2$, 3.8, 8.8 Hz, 1H), 3.30 (t, $J = 8.8$ Hz, 1H), 3.00 (ddd, $J = 3.8$, 11.5, 12.6 Hz, 1H), 2.62–2.56 (m, 2H), 2.13 (ddt, $J = 2.2$, 4.4, 12.6 Hz, 1H), 1.45 (ddd, $J = 4.4$, 11.5, 12.6 Hz, 1H), IR (neat) 3713–3128, 2927, 2867, 1454, 1098 cm^{-1}.

4.15. Fagomine, [1,5-imino-1,2,5-trideoxy-D-arabino hexitol] 1

To a solution of (2*R*,3*R*,4*R*)-3,4-dibenzyloxy-1,5-imino-1,2,5-trideoxy-D-arabino hexitol (175 mg, 0.53 mmol) in AcOH (5.4 mL) was added 10% palladium on active carbon (17.5 mg) at room temperature, and the mixture stirred under H_2 gas atmosphere at the same temperature for 2 days. The reaction mixture was filtered through a pad of Florisil sequentially with MeOH and the filtrate was concentrated in vacuo. The residue was dissolved in water, and the solution was stirred with Dowex 50w-X8 (H^+ form) ion-exchange for 5 h. The suspension was eluted with water and then 0.5 M NH_4Cl, so gave 1,5-imino-1,2,5-trideoxy-D-arabino hexitol (68 mg, 87%). $[\alpha]_D^{27} = +13.4$ (*c* 0.86, H_2O), ^1H NMR (600 MHz, D_2O) δ 3.84 (dd, $J = 2.9$, 11.6 Hz, 1H), 3.62 (dd, $J = 7.0$, 11.6 Hz, 1H), 3.53 (ddd, $J = 5.1$, 9.1, 11.4 Hz, 1H), 3.15 (t, $J = 9.6$ Hz, 1H), 3.00 (ddd, $J = 4.4$, 11.7, 12.7 Hz, 1H), 2.60 (dt, $J = 2.6$, 5.1, 12.9 Hz, 1H), 2.52 (ddd, $J = 2.9$, 7.0, 9.9 Hz, 1H), 1.90 (ddt, $J = 2.6$, 12.5, 4.4 Hz, 1H), 1.39 (ddd, $J = 2.6$, 11.7, 12.8 Hz, 1H), IR (neat) 3792–2955, 2951, 1601, 1455, 1069 cm^{-1}, EI-Mass (*m*/*z*) 147.

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6. The enantiomeric ratio was determined by ^1H NMR analysis of (*S*)-(+)-α-methoxyphenyl acetic acid derivatives of **6**.
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