Tetrahedron 65 (2009) 9765–9771

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Asymmetric syntheses of 6-deoxyfagomin, D-deoxyrhamnojirimycin, and D-rhamnono-1,5-lactam

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ARTICLE INFO

Article history:
Received 29 July 2009
Received in revised form
13 September 2009
Accepted 18 September 2009
Available online 22 September 2009

Keywords:
Aza-sugars
Asymmetric synthesis
Building block
Samarium diiodide

ABSTRACT

N-Allyl protected 3-*O*-benzyloxglutarimide **11** was synthesized as a useful variant of the chiral building block **10**. This modification allowed a high-yielding deprotection of the allyl group from the lactam intermediate **14**. Starting from this building block, the asymmetric syntheses of aza-sugars 6-deoxyfagomine (**2**), D-rhamnono-1,5-lactam (**6**), as well as D-deoxyrhamnojirimycin (**5**) have been achieved in high regio- and/or diastereo-controlled manner.

1. Introduction

Aza-sugars (also known as iminosugars) are polyhydroxylated alkaloids with either five- or six-membered, mono- or bi-cyclic structures.[1] Being 'nitrogen-in-the-ring' analogs of pyranoses and furanoses, many aza-sugars were found to be potent inhibitors of carbohydrate-processing enzymes involved in important biological systems. Consequently, they are promising for the treatment of metabolite disorder-associated diseases such as diabetes, cancer, AIDS, and viral infections.[1] Indeed, Miglitol[2] and Zavesca[3] (Miglustat) have been launched on market as drugs for the treatment of Type II diabetes and Gaucher's disease, respectively.

Fagomine[4,5] (**1**) and 6-deoxyfagomine[4] (**2**) (Fig. 1) are two polyhydroxylated piperidine alkaloids isolated from *Lycium chinense* (Solanaceae) roots. Before that, the occurrence of fagomine[5] and its stereoisomers in the leaves of *Xanthocercis zuinbesiaca* (Leguminosae) has already been reported.[5a] Fagomine and 3-*epi*-fagomine were shown to have activities against mammalian α-glucosidase and β-galactosidase,[5a] and have a potent antihyperglycaemic effect in streptozocin-induced diabetic mice and a potentiation of glucose-induced insulin secretion.[5b] 1,6-Dideoxynojirimycin (**3**) was isolated as a new sugar-mimic alkaloid from the Pods of *Angylocalyx pynaertii*.[6] α-Homo-L-rhamnojirimycin **4** is an effective inhibitor of naringinase.[7] In addition, D-deoxyrhamnojirimycin (DRJ) (**5**),[8a,b] and its enantiomer L-deoxyrhamnojirimycin (LRJ),[8b,c] and D-rhamnono-1,5-lactam[8b] (**6**) have also been synthesized for biological test. The synthesis of aza-sugars, their stereoisomers, and analogs have attracted considerable attention, and a number of methods have been developed.[1]

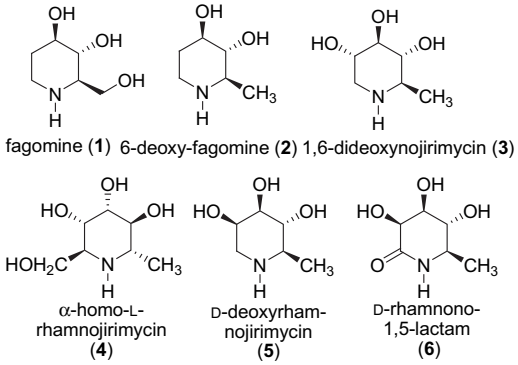

Figure 1.

In continuation of our study on the development of protected 3-hydroxyglutarimide-based synthetic methodology,[9] we wish to report *N*-allyl protected 3-*O*-benzyloxyglutarimide **11** as

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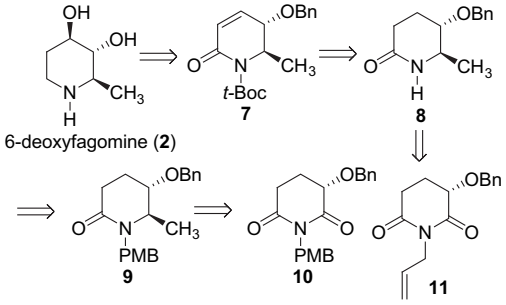
doi:10.1016/j.tet.2009.09.083

a beneficial variant of the building block **10**, and its application to the enantioselective syntheses of 6-deoxyfagomine (**2**), D-rhamnono-1,5-lactam (**6**), and D-deoxyrhamnojirimycin (**5**).

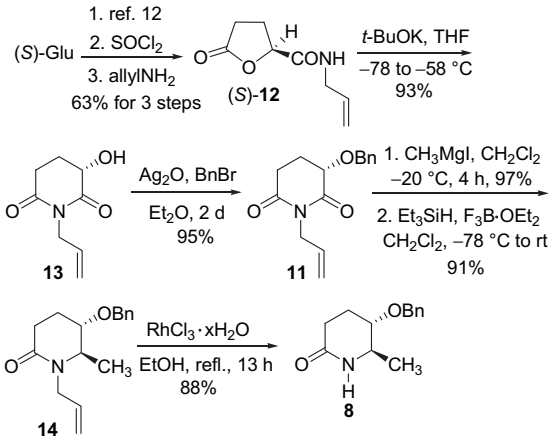
2. Results and discussion

The retrosynthetic analysis of 6-deoxyfagomine (**2**) is outlined in Scheme 1, which featured the introduction of the hydroxyl group at C-4 via the α,β-unsaturated mixed imide **7**. The latter was envisioned to be prepared from lactam **9**,[10] which is available from the known building block **10**. In practicing this plan, it was observed that the ceric ammonium nitrate (CAN)-mediated oxidative cleavage of the *p*-methoxybenzyl group (PMB) in lactam **9** produced lactam **8** in only 60% yield. We decided to develop the *N*-allyl protected[11] glutarimide derivative **11** as an improved building block for our general synthetic program.[9]



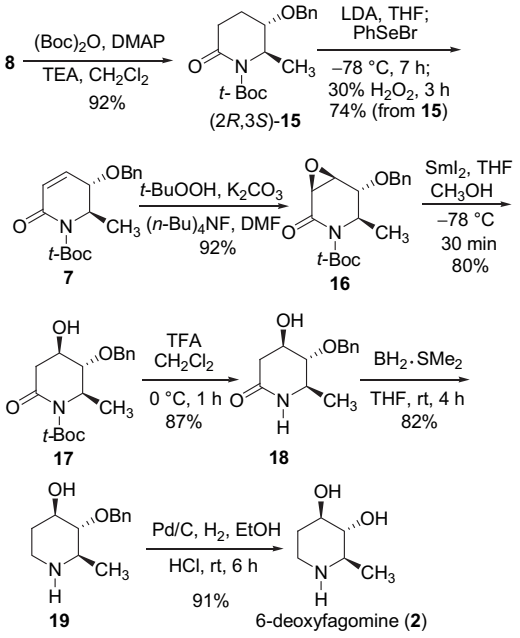
Scheme 1.

The building block **11** was synthesized from (*S*)-glutamic acid and allylamine by the method established previously,[10,12] namely, diazodation, lactone-amide formation, ring expansion, and *O*-benzylation (Scheme 2). Methyl magnesium iodide addition, followed by boron trifluoride etherate-mediated reductive dehydroxylation with triethylsilane produced lactam **14** in excellent regio- and diastereo-selectivities. The stereochemistry of the major diastereomer **14** was tentatively assigned as *trans* on the basis of the observed vicinal coupling constant ($J_{5,6}$=1.4 Hz; cf. *N*-PMB protected analog: $J_{5,6}$=1.5 Hz for *trans*-diastereomer,[10a] and $J_{5,6}$=4.6 Hz for *cis*-diastereomer[10c]), that was confirmed after final conversion of **14** into the natural product 6-deoxyfagomine (**2**). Cleavage of the lactam *N*-allyl group was achieved by heating **14** with rhodium trichloride hydrate, in refluxing ethanol,[13] which afforded lactam **8** in 88% yield.



Scheme 2.

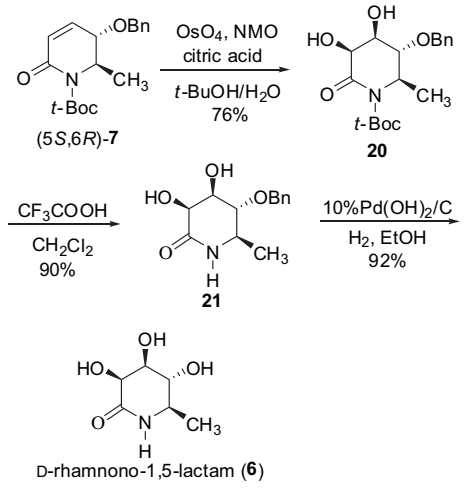
To introduce the carbon–carbon double bond, lactam **8** was converted into its activated form, namely, the mixed imide (2*R*,3*S*)-**15**, by the reaction with $(Boc)_2O$ [DMAP (cat.), TEA, CH_2Cl_2]. Successive treatment of **15** with LDA (THF, −78 °C) and PhSeBr produced an α-phenylselenide derivative,[14] which, without purification, was subjected to oxidation with H_2O_2 in wet CH_2Cl_2 at rt to give directly **7** in 74% overall yield from compound **15** (Scheme 3). For the introduction of the hydroxyl group at C-4, an epoxidation–regioselective SmI_2 reduction[15] procedure was envisioned. Thus, in the presence of tetrabutyl ammonium fluoride, and potassium carbonate, α,β-unsaturated mixed imide **7** was treated with *tert*-butyl hydroperoxide (TBHP) in DMF[15a,16] to furnish epoxide **16** as a single diastereomer in 92% yield. The stereochemistry of the product was assumed to be *trans* with respect to OBn group on the basis of the steric effect of the benzyloxyl group in the epoxidation,[17] that was confirmed after its transformation into the natural product **2**. Reductive ring-opening of the epoxide **16** with samarium diiodide[15] yielded regioselectively the 4-hydroxy-2-piperidinone derivative **17** in high yield. Compound **17** was subjected successively to *N*-deprotection with TFA, lactam reduction with borane dimethyl sulfide complex, and *O*-debenzylation under catalytic hydrogenolytic conditions to give 6-deoxyfagomine (**2**) in high overall yield. The physical {$[\alpha]_D^{20}$ −10.8 (*c* 0.4, H_2O); lit.[4] $[\alpha]_D^{20}$ −11.1 (*c* 0.1, H_2O)} and spectroscopic data of our synthetic compound were in agreement with those reported for the natural product.[4]



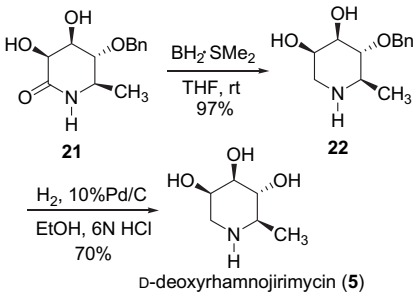
Scheme 3.

To further explore the possibility to use mixed imide **7** for the synthesis of other aza-sugars such as **4**, **5**, and **6**, the dihydroxylation of **7** was investigated. In the presence of 1.5 molar equiv of citric acid, treatment of α,β-unsaturated lactam **7** with the co-oxidant system OsO_4 (cat.)–NMO in a mixed solvent system[18] (*t*-BuOH/H_2O, 1:1) at rt for 18 h produced the dihydroxylated product **20** as a single diastereomer in 76% yield (Scheme 4). Stirring compound **20** with CF_3CO_2H in CH_2Cl_2 cleaved the Boc group to give lactam **21** in 90% yield. Hydrogenolysis of lactam **21** in the presence of 10%Pd(OH)$_2$/C led to the target molecule D-rhamnono-1,5-lactam (**6**) in 92% yield. The physical and spectroscopic data of the synthetic compound were in agreement with those of natural product {$[\alpha]_D^{20}$ −15.6 (*c* 0.4, H_2O) {lit.[8b] $[\alpha]_D^{20}$ −16.6 (*c* 0.27, H_2O)}.

On the other hand, reduction of lactam **21** with $BH_3 \cdot SMe_2$ in THF at rt for 4 h gave piperidine **22** in 97% yield (Scheme 5). Subjection of **22** to catalytic hydrogenolytic conditions (H_2, 10%Pd/C) led to D-deoxyrhamnojirimycin (**5**) in 70% yield. The physical and



Scheme 4.



Scheme 5.

spectroscopic data of synthetic D-deoxyrhamnojirimycin (**5**) were in agreement with those reported {$[\alpha]_D^{20}$ −55.2 (*c* 0.4, H_2O); lit.[19] $[\alpha]_D^{20}$ −52.7 (*c* 0.42, H_2O)}.

3. Conclusion

To summarize, the *N*-allyl protected 3-*O*-benzyloxglutarimide **11** is an effective variant of the building block **10**. Starting from this building block, the enantioselective syntheses of the naturally occurring aza-sugars 6-deoxyfagomin (**2**), D-rhamnono-1,5-lactam (**6**), and D-deoxyrhamnojirimycin (**5**) were achieved. Through this work we were able to demonstrate that the hydroxylation at C-4 of the building block **11** can be achieved in high regio- and diastereocontrolled manner. Application of this versatile building block to the asymmetric synthesis of more complex alkaloids is currently in progress, and will be reported in due course.

4. Experimental

4.1. General

Melting points were determined on a Yanaco MP-500 micro melting point apparatus and were uncorrected. Infrared spectra were measured with a Nicolet Avatar 360 FT-IR spectrometer using film KBr pellet techniques. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker AV 400 spectrometer with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) units downfield from TMS. Mass spectra were recorded by a Bruker Dalton ESquire 3000 plus liquid chromatography–mass spectrum (direct injection). HRMS spectra were recorded on a Shimadzu LCMS-IT-TOF apparatus. Optical rotations were measured with Perkin–Elmer 341 automatic polarimeter. Flash column chromatography was carried out with silica gel (300–400 mesh). THF was distilled over sodium benzophenone ketyl under N_2.

4.2. (*S*)-*N*-Allyl-5-oxo-tetrahydro-2-furancarboxamide (12)

A mixture of γ-lactone-carboxylic acid (1.076 g, 8.28 mmol), prepared from L-glutamic acid according to the known procedure,[12] and thionyl chloride (2.42 mL, 33.11 mmol) was refluxed for 5 h and then stirred at room temperature overnight. The excess thionyl chloride was removed under reduced pressure and the residue was dissolved in dry CH_2Cl_2 (17 mL). At −20 °C and under nitrogen atmosphere, triethylamine (1.73 mL, 12.42 mmol) and allylamine (0.93 mL, 12.42 mmol) in CH_2Cl_2 (2 mL) were added successively. After being stirred at 0 °C for 3 h, water (10 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (2×5 mL). The combined organic layers were washed with brine (4 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude was flash chromatographed (eluent: ethyl acetate/petroleum ether=3:2) to give compound **12** (880 mg, yield, 63% from L-glutamic acid) as white crystals. R_f 0.30 (ethyl acetate/petroleum ether=3:2); mp 50–51 °C (EtOAc/PE); $[\alpha]_D^{20}$ −30.2 (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3307, 3084, 2929, 1786, 1668, 1539, 1420, 1272, 1247, 1178, 1147, 1057 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33–2.24 (m, 1H, CHC*H*$_2$), 2.50 (dd, *J*=8.1, 7.6 Hz, 2H, COC*H*$_2$), 2.62–2.49 (m, 1H, CHC*H*$_2$), 3.91–3.76 (m, 2H, NHC*H*$_2$), 4.82 (dd, *J*=7.9, 6.9 Hz, 1H, OC*H*), 5.08 (ddt, *J*=10.3, 2.8, 1.3 Hz, 1H, =C*H*$_2$), 5.12 (ddt, *J*=17.2, 2.8, 1.3 Hz, 1H, =C*H*$_2$), 5.75 (ddt, *J*=17.2, 10.3, 5.7 Hz, 1H, C*H*=), 6.77 (br s, 1H, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6, 27.4, 41.3, 77.3, 116.6, 133.2, 169.1, 175.8; MS (ESI, *m*/*z*): 192 (M+Na^+, 100%). Anal. Calcd for $C_8H_{11}NO_3$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.47; H, 6.50; N, 8.47.

4.3. (*S*)-1-Allyl-3-hydroxy-2,6-piperidinedione (13)

To a THF solution (10 mL) of compound **12** (500 mg, 2.96 mmol), was added a cooled suspension of potassium *tert*-butoxide (166 mg, 1.48 mmol) in anhydrous THF (5 mL) at −78 °C and under nitrogen atmosphere. After 10 min of stirring at −78 °C, the temperature was allowed to arise to −65 °C over 25 min, and then the solution was stirred at −60 °C to −58 °C for 30 min. The reaction was quenched with saturated aqueous NH_4Cl (2.5 mL) at −65 °C. The residue was extracted with ethyl acetate (2×5 mL). The extracts were washed with brine (3 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was flash chromatographed (eluent: ethyl acetate/petroleum ether=1:1) to give compound **13** (465 mg, yield, 93%) as white crystals. R_f 0.35 (ethyl acetate/petroleum ether=1:1); mp 36–37 °C (PE/EtOAc); $[\alpha]_D^{20}$ −97.1 (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3436, 1731, 1677, 1418, 1375, 1334, 1236, 1176, 1131 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.92 (dddd, *J*=13.5, 13.0, 12.7, 4.8 Hz, 1H, CHC*H*$_2$), 2.35 (dddd, *J*=13.0, 5.5, 5.4, 2.7 Hz, 1H, CHC*H*$_2$), 2.66 (ddd, *J*=18.0, 13.5, 5.4 Hz, 1H, COC*H*$_2$), 2.91 (ddd, *J*=18.0, 4.8, 2.7 Hz, 1H, COC*H*$_2$), 3.61 (d, *J*=1.0 Hz, 1H, O*H*), 4.22 (ddd, *J*=12.7, 5.5, 1.0 Hz, 1H, C*H*OH), 4.27 (ddt, *J*=14.6, 5.9, 1.3 Hz, 1H, NC*H*$_2$), 4.34 (ddt, *J*=14.6, 5.9, 1.3 Hz, 1H, NC*H*$_2$), 5.16 (ddt, *J*=10.2, 2.6, 1.3 Hz, 1H, =C*H*$_2$), 5.18 (ddt, *J*=17.3, 2.6, 1.3 Hz, 1H, =C*H*$_2$), 5.78 (ddt, *J*=17.3, 10.2, 5.9 Hz, 1H, =C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 30.8, 42.4, 68.3, 118.0, 131.4, 170.8, 174.8; MS (ESI, *m*/*z*): 192 (M+Na^+, 100%). Anal. Calcd for $C_8H_{11}NO_3$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.63; H, 6.41; N, 8.50.

4.4. (*S*)-1-Allyl-3-benzyloxy-2,6-piperidinedione (11)

To a mixture of compound **13** (390 mg, 2.31 mmol) and silver oxide (1.61 g, 6.92 mmol) in dry ether (13.8 mL) was added benzyl bromide (0.83 mL, 6.92 mmol). The mixture was stirred at room temperature for 2 days in dark. After filtration through silica gel, the

solvent was removed under reduced pressure. Flash chromatographic purification of the residue on silica gel (eluent: ethyl acetate/petroleum ether=1:8) provided compound **11** (566 mg, yield, 95%) as a colorless oil. R_f 0.30 (ethyl acetate: petroleum ether=1:8); $[\alpha]_D^{20}$ −72.2 (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3088, 3063, 3031, 2942, 2875, 1732, 1682, 1455, 1417, 1357, 1334, 1239, 1167, 1129, 1069, 1019 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.17–2.03 (m, 2H, CHC*H*$_2$), 2.60 (ddd, *J*=17.7, 12.4, 6.1 Hz, 1H, COC*H*$_2$), 2.94 (ddd, *J*=17.7, 7.7, 6.4 Hz, 1H, COC*H*$_2$), 4.09 (dd, *J*=6.0, 5.1 Hz, 1H, BnOC*H*), 4.37 (dt, *J*=5.7, 1.4 Hz, 2H, NC*H*$_2$), 4.68 (d, *J*=11.8 Hz, 1H, C*H*$_2$Ph), 4.88 (d, *J*=11.8 Hz, 1H, C*H*$_2$Ph), 5.15 (ddt, *J*=10.2, 2.6, 1.4 Hz, 1H, =C*H*$_2$), 5.18 (ddt, *J*=17.2, 2.6, 1.4 Hz, 1H, =C*H*$_2$), 5.82 (ddt, *J*=17.2, 10.2, 5.7 Hz, 1H, C*H*=CH$_2$), 7.39–7.27 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.1, 28.9, 41.6, 72.4, 73.6, 117.3, 127.9, 128.0, 128.4, 131.8, 137.1, 171.0, 171.3; MS (ESI, *m*/*z*): 282 (M+Na^+, 100%); Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.61; H, 6.65; N, 5.27.

4.5. (5*S*,6*R*)-1-Allyl-5-(benzyloxy)-6-methylpiperidin-2-one (14)

To a cooled (−20 °C) solution of compound **11** (385 mg, 1.54 mmol) in CH_2Cl_2 (15 mL) was added dropwise a solution of MeMgI in Et_2O (2 M, 2.3 mL, 4.6 mmol). The mixture was stirred for 4 h at −20 °C. The reaction was quenched with saturated aqueous NH_4Cl (5 mL). After extraction with ethyl acetate (2×10 mL), the combined organic layers were washed with brine (4 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: ethyl acetate/petroleum ether=2:1) to yield the *N*,*O*-acetal as a diastereomeric mixture (390 mg, yield, 97%), which is used in the next step without further separation. To a cooled (−78 °C) solution of the diastereomeric mixture of *N*,*O*-acetal (210 mg, 0.76 mmol) in CH_2Cl_2 (6 mL) were added dropwise Et_3SiH (1.2 mL, 7.6 mmol) and $BF_3{\cdot}OEt_2$ (0.3 mL, 2.3 mmol) successively. The mixture was stirred at −78 °C for 4 h, then allowed to warm up slowly, and stirred at room temperature overnight. To the resultant mixture was added a half saturated aqueous $NaHCO_3$ (6 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were washed with brine (4 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: ethyl acetate/petroleum ether=4:3) to yield compound **14** (180 mg, yield, 91%) as a colorless oil. $[\alpha]_D^{20}$ +77.3 (*c* 1.3, $CHCl_3$); IR (film) ν_{max}: 3428, 2973, 2941, 2872, 1634, 1472, 1454, 1413, 1358, 1273, 1094, 1073 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.17 (d, *J*=6.7 Hz, C*H*$_3$), 2.08–1.95 (m, 2H, C*H*$_2$CH), 2.35 (ddd, *J*=18.1, 5.6, 3.5 Hz, 1H, COC*H*$_2$), 2.63 (ddd, *J*=18.1, 10.2, 8.2 Hz, 1H, COC*H*$_2$), 3.49 (ddt, *J*=15.6, 6.6, 1.5 Hz, 1H, NC*H*$_2$), 3.56 (ddd, *J*=3.1, 2.9, 2.4 Hz, 1H, BnOC*H*), 3.65 (qd, *J*=6.7, 2.4 Hz, 1H, C*H*CH$_3$), 4.54 (ddt, *J*=15.6, 4.5, 1.5 Hz, 1H, NC*H*$_2$), 4.54 (d, *J*=11.8 Hz, 1H, C*H*$_2$Ph), 4.58 (d, *J*=11.8 Hz, 1H, C*H*$_2$Ph), 5.14 (ddt, *J*=10.3, 3.0, 1.5 Hz, 1H, C=C*H*$_2$), 5.23 (ddt, *J*=17.1, 3.0, 1.5 Hz, 1H, C=C*H*$_2$), 5.77 (dddd, *J*=17.1, 10.3, 6.6, 4.5 Hz, 1H, C*H*=), 7.36–7.24 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 21.2, 27.1, 47.2, 55.1, 70.0, 75.1, 116.7, 127.3, 127.6, 128.3, 133.3, 138.1, 169.1; MS (ESI, *m*/*z*): 282 (M+Na^+, 100%); Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.92; H, 8.42; N, 5.43.

4.6. (5*S*,6*R*)-5-(Benzyloxy)-6-methylpiperidin-2-one (8)

$RhCl_3{\cdot}xH_2O$ (217 mg, 0.4 mmol) was added to a solution of compound **14** (2.087 g, 8.09 mmol) in EtOH (16 mL). The suspension was heated to reflux for 13 h. After cooling to room temperature, the reaction mixture was concentrated and purified by column chromatography on silica gel (eluent: EtOAc/petroleum ether 4:1) to give compound **8** (1.553 g, yield: 88%) as a wax solid. $[\alpha]_D^{20}$ −49.3 (*c* 0.9, $CHCl_3$); IR (film) ν_{max}: 3206, 3063, 2924, 1668, 1496, 1454, 1410, 1094 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (d, *J*=6.5 Hz, 1H, C*H*$_3$), 1.88 (dddd, *J*=13.9, 8.0, 7.0, 6.6 Hz, 1H, C*H*$_2$CH), 2.08 (dddd, *J*=13.9, 7.0, 6.6, 3.0 Hz, 1H, C*H*$_2$CH), 2.31 (ddd, *J*=17.7, 7.0, 7.0 Hz, 1H, COC*H*$_2$), 2.54 (ddd, *J*=17.7, 6.6, 6.6 Hz, 1H, COC*H*$_2$), 3.37 (ddd, *J*=8.0, 3.0, 1.4 Hz, 1H, BnOC*H*), 3.54 (qd, *J*=6.5, 1.4 Hz, 1H, C*H*CH$_3$), 4.51 (d, *J*=11.7 Hz, 1H, OC*H*$_2$), 4.64 (d, *J*=11.7 Hz, 1H, OC*H*$_2$), 5.66 (br s, 1H, NH), 7.20–7.40 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 23.3, 28.1, 52.5, 70.8, 76.3, 127.6, 127.8, 128.5, 137.9, 171.7; MS (ESI, *m*/*z*): 220 (M+H^+, 100%). Anal. calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.01; H, 7.44; N, 6.26.

4.7. *tert*-Butyl (2*R*,3*S*)-3-(Benzyloxy)-2-methyl-6-oxopiperidine-1-carboxylate (15)

To a cooled (0 °C) solution of compound **8** (158 mg, 0.72 mmol) and DMAP (cat.) in CH_2Cl_2 (2.5 mL) was added Et_3N (0.30 mL, 2.2 mmol) under nitrogen atmosphere. After stirred for 10 min at the same temperature, Boc_2O (0.33 mL, 1.5 mmol) was added dropwise. The mixture was allowed to warm to room temperature over 15 min and stirred overnight. The resultant mixture was quenched with saturated aqueous NH_4Cl (0.5 mL), diluted with CH_2Cl_2 (2 mL) and brine (1 mL). The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3 mL×3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (EtOAc/PE) to give compound **15** (210 mg, yield: 92%) as a white solid. Mp 43–45 °C (PE/CH_2Cl_2); $[\alpha]_D^{20}$ −6.3 (*c* 0.98, $CHCl_3$); IR (film) ν_{max}: 2934, 2836, 1673, 1621, 1462, 1095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (d, *J*=6.7 Hz, 3H, CH$_3$), 1.52 (s, 9H, *t*-Bu-H), 2.02–1.99 (m, 2H, BnOCHC*H*$_2$), 2.42 (dd, *J*=17.6, 4.8, 4.8 Hz, 1H, COCH$_2$), 2.73 (ddd, *J*=17.6, 8.8, 8.7 Hz, 1H, COC*H*$_2$), 3.59–3.61 (m, 1H, BnOC*H*), 4.51–4.46 (m, 1H, CH$_3$C*H*), 4.57 (s, 2H, OC*H*$_2$Ph), 7.36–7.26 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 28.0, 29.8, 54.7, 70.1, 74.3, 82.8, 127.5, 127.8, 128.5, 137.5, 152.3, 170.9; MS (ESI, *m*/*z*): 320 (M+H^+, 100%); Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.61; H, 8.24; N, 4.41.

4.8. *tert*-Butyl (5*S*,6*R*)-5-(benzyloxy)-6-methyl-2-oxo-5,6-dihydropyridine-1(2*H*)-carboxylate (7)

To a solution of **15** (200 mg, 0.63 mmol) in THF (1.5 mL) was added slowly a solution of freshly prepared 2 mL of a THF solution of LDA (0.45 M, 0.90 mmol) at −78 °C, and the mixture was stirred at this temperature for 1.5 h. To the resultant mixture was added slowly a solution of PhSeBr (190 mg, 0.82 mmol) in THF (1.5 mL), and the solution was stirred at −78 °C for 7 h. The reaction mixture was poured into 20 mL of saturated aqueous $NaHCO_3$ and extracted with EtOAc (10 mL×3). The combined organic layers were washed successively with water (5 mL×2) and brine (5 mL×2), dried over Na_2SO_4, filtered, and concentrated in vacuum. To the residue was added successively CH_2Cl_2 (5 mL), water (0.1 mL), and a solution of 30% aqueous H_2O_2 (0.05 mmol). After being stirred for 1 h, the mixture was treated with another portion of 30% aqueous H_2O_2 (0.05 mmol) and stirred for 2 h. The reaction was quenched with water. The organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2 (5 mL×3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by column chromatography on silica gel (EtOAc/PE) to give compound **7** as a colorless oil. $[\alpha]_D^{20}$ +143.5 (*c* 1.1, $CHCl_3$); IR (film) ν_{max}: 2969, 1766, 1715, 1400, 1365, 1299, 1248, 1159, 1062 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (d, *J*=6.9 Hz, 3H, C*H*$_3$), 1.55 (s, 9H, *t*-Bu), 3.79 (dd, *J*=5.8, 1.6 Hz, 1H, BnOC*H*), 4.57 (d, *J*=11.9 Hz, 1H, PhC*H*$_2$), 4.64 (d, *J*=11.9 Hz, 1H, PhC*H*$_2$), 4.71 (qt, *J*=6.9, 1.6 Hz, 1H, BocNC*H*), 6.11 (d, *J*=9.7 Hz, 1H, COC*H*=), 6.62 (ddd, *J*=9.7, 5.8, 1.6 Hz, 1H, COCH=C*H*), 7.28–7.41 (m, 5H, Ph-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6, 28.0, 53.3, 70.8,

71.8, 83.1, 127.8, 128.0, 128.6, 128.9, 137.1, 137.5, 152.3, 162.0; MS (ESI, *m*/*z*): 340.1 (M+Na^+, 100%); HRMS calcd for $C_{18}H_{23}NO_4Na$ [M+Na^+]: 340.1525; found: 340.1533.

4.9. *tert*-Butyl (1*S*,4*R*,5*R*,6*S*)-5-(benzyloxy)-4-methyl-2-oxo-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (16)

To a solution of compound **7** (80 mg, 0.252 mmol) in DMF (2.5 mL) under nitrogen atmosphere were added K_2CO_3 (34.8 mg, 0.252 mmol) and *t*-BuOOH (5.5 M solution in nonane, 0.10 mL, 0.56 mmol). After stirring at ambient temperature for 30 min, a 1.0 M THF solution of Bu_4NF was added in small portions until the reaction was completed (as indicated by TLC monitoring). The reaction was quenched with a saturated ammonium chloride solution and diluted with Et_2O (8 mL) and water (25 mL). The layers were separated and the water layer extracted with Et_2O (10×3 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: EtOAc/petroleum ether=1:5) to give compound **16** (77 mg, 92%) as a white solid. Mp 63–64 °C (PE/EtOAc); $[\alpha]_D^{20}$ +35.3 (*c* 1.2, $CHCl_3$); IR (film) ν_{max}: 2969, 2922, 1766, 1723, 1373, 1287, 1248, 1147 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (d, *J*=7.1 Hz, 3H, C*H*$_3$), 1.52 (s, 9H, *t*-Bu), 3.57–3.61 (m, 2H, BnOCHC*H*, BnOC*H*), 3.97–4.01 (m, 1H, COC*H*), 4.48–4.54 (m, 1H, BocNC*H*), 4.56 (d, *J*=12.1 Hz, 1H, PhC*H*$_2$), 4.72 (d, *J*=12.1 Hz, 1H, PhC*H*$_2$), 7.28–7.43 (m, 5H, Ph-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 27.9, 51.9, 52.8, 54.7, 71.8, 74.4, 83.6, 127.7, 128.2, 128.6, 137.1, 152.1, 167.5; MS (ESI, *m*/*z*): 355.9 (M+Na^+, 100%); Anal. Calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.91; H, 6.98; N, 4.15.

4.10. *tert*-Butyl (2*R*,3*R*,4*R*)-3-(benzyloxy)-4-hydroxy-2-methyl-6-oxopiperidine-1-carboxylate (17)

Epoxide **16** (91 mg, 0.273 mmol) in a mixed solvent of THF (0.6 mL) and MeOH (0.3 mL) was added dropwise under argon to a stirring solution of SmI_2 (0.1 M in THF, 6.8 mL, 0.683 mmol) at −78 °C. After being stirred about 0.5 h at −78 °C, a saturated aqueous solution of K_2CO_3 was added. The mixture was allowed to reach room temperature and was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: EtOAc/petroleum ether=1:1) to give compounds **17** (73 mg, 80%) as a colorless oil. $[\alpha]_D^{20}$ −63.6 (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3447, 2976, 2918, 1766, 1727, 1459, 1369, 1291, 1248, 1147 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.38 (d, *J*=7.0 Hz, 3H, C*H*$_3$), 1.52 (s, 9H, *t*-Bu), 2.39 (d, *J*=3.4 Hz, OH, D_2O exchangeable), 2.51 (dd, *J*=16.9, 9.1 Hz, 1H, COC*H*$_2$), 2.87 (dd, *J*=16.9, 5.2 Hz, 1H, COC*H*$_2$), 3.47 (dd, *J*=6.0, 3.1 Hz, 1H, BnOC*H*), 4.05–4.14 (m, 1H, HOC*H*), 4.35 (qd, *J*=7.0, 3.1 Hz, 1H, BocNC*H*), 4.63 (d, *J*=11.7 Hz, 1H, PhC*H*$_2$), 4.72 (d, *J*=11.7 Hz, 1H, PhC*H*$_2$), 7.27–7.42 (m, 5H, Ph-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 27.9, 39.7, 54.8, 68.4, 72.4, 82.5, 83.4, 127.8, 128.1, 128.6, 137.5, 152.2, 169.2; MS (ESI, *m*/*z*): 358.2 (M+Na^+, 100%); HRMS calcd for $C_{18}H_{25}NO_5Na$ [M+Na^+]: 358.1630; found: 358.1633.

4.11. (4*R*,5*R*,6*R*)-5-(Benzyloxy)-4-hydroxy-6-methylpiperidin-2-one (18)

Trifluoroacetic acid (0.83 mL) was added dropwise to a solution of compound **17** (72 mg, 0.215 mmol) in CH_2Cl_2 (7.2 mL) at 0 °C. The mixture was stirred for 10 min and then warmed to room temperature. After 1 h, the reaction mixture was concentrated under reduced pressure. The product was purified by flash column chromatography on silica gel (eluent: EtOAc) to afford compound **18** (44 mg, yield: 87%) as a white solid. Mp 125–127 °C (EtOAc); $[\alpha]_D^{20}$ +4.1 (*c* 0.9, $CHCl_3$); IR (film) ν_{max}: 3381, 3202, 2875, 1676, 1400, 1104, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (d, *J*=6.2 Hz, 1H, C*H*$_3$), 2.43 (dd, *J*=17.3, 9.6 Hz, 1H, COC*H*$_2$), 2.78 (dd, *J*=17.3, 6.0 Hz, 1H, COC*H*$_2$), 3.21 (t, *J*=8.3 Hz, 1H, BnOC*H*), 3.26 (s, OH, D_2O exchangeable), 3.30–3.39 (m, 1H, NHC*H*), 3.92–4.02 (m, 1H, HOC*H*), 4.75 (d, *J*=11.2 Hz, 1H, PhC*H*$_2$), 4.82 (d, *J*=11.2 Hz, 1H, PhC*H*$_2$), 6.68 (s, N*H*, D_2O exchangeable), 7.28–7.48 (m, 5H, Ph-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 37.9, 50.5, 68.7, 74.9, 84.0, 128.0, 128.1, 128.6, 137.6, 170.7; MS (ESI, *m*/*z*): 258.1 (M+Na^+, 100%); Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.72; H, 7.03; N, 5.74.

4.12. (2*R*,3*R*,4*R*)-3-(Benzyloxy)-2-methylpiperidin-4-ol (19)

To a solution of **18** (47 mg, 0.2 mol) in dry THF (2 mL) $BH_3 \cdot SMe_2$ (0.076 mL, 0.8 mmol) was added at 0 °C and the mixture was stirred under nitrogen for 4 h at room temperature. The reaction was quenched by cautiously adding methanol until gas evolution stopped. Additional methanol was added and the solvents were evaporated. The residue was dissolved in methanol and 6 M HCl was added to the solution, the mixture was refluxed for 5 min to destroy the borane–amine complex. After cooling, the solution was evaporated and the pH was adjusted to 11–12 with $NH_3 \cdot H_2O$. The solution was evaporated and residue purified by flash column chromatograph on silica gel (eluent: CH_2Cl_2/CH_3OH=10:1) to afford compound **19** (26 mg, 82%) as a wax solid. $[\alpha]_D^{20}$ +24.6 (*c* 1.0, CH_3OH); IR (film) ν_{max}: 3346, 2918, 1595, 1381, 1093, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (d, *J*=6.3 Hz, 3H, C*H*$_3$), 1.52 (ddt, *J*=12.6, 11.8, 4.6 Hz, 1H, NHCH$_2$C*H*$_2$), 1.92 (2H, OH, NH, D_2O exchangeable), 1.97 (ddt, *J*=12.6, 4.8, 2.4 Hz, 1H, NHCH$_2$C*H*$_2$), 2.59 (m, 1H, NHC*H*), 2.64 (ddd, *J*=12.2, 4.6, 2.4 Hz, 1H, NHC*H*$_2$), 2.87 (t, *J*=8.8 Hz, 1H, BnOC*H*), 2.99 (ddd, *J*=12.2, 4.6, 2.4 Hz, 1H, NHC*H*$_2$), 3.56 (ddd, *J*=11.8, 8.8, 4.8 Hz, 1H, HOC*H*), 4.70 (d, *J*=11.3 Hz, 1H, PhC*H*$_2$), 4.79 (d, *J*=11.3 Hz, 1H, PhC*H*$_2$), 7.20–7.40 (m, 5H, Ph-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 33.9, 44.0, 55.9, 73.6, 75.2, 88.4, 127.9 (2C), 128.6, 138.4; MS (ESI, *m*/*z*): 222.1 (M+H^+, 100%); HRMS calcd for $C_{13}H_{20}NO_2$ [M+H^+]: 222.1494; found: 222.1499.

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

0.1 mL of 6 N HCl was added to a mixture of compound **19** (26 mg), 10% Pd/C (78 mg), and EtOH (9.8 mL). The suspension was stirred under a hydrogen atmosphere for 6 h. The resultant mixture was filtered through a short pad of Celite. The filter cake was washed several times with EtOH and then concentrated under reduced pressure. The residue was dissolved in water and passed through a column of ion-exchange resin (Dowex-8×100, OH form) and eluted with water. The eluent was concentrated under reduced pressure to give 6-deoxyfagomine (**2**) (14 mg, 91%) as a wax solid. $[\alpha]_D^{20}$ −10.8 (*c* 0.4, H_2O) {lit. $[\alpha]_D^{20}$–11.1 (*c* 0.1, H_2O);[4] $[\alpha]_D^{20}$ +9.6 (*c* 0.41, H_2O)[19]}; IR (film) ν_{max}: 3346, 2918 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 1.12 (d, *J*=6.4 Hz, 1H, C*H*$_3$), 1.42 (ddt, *J*=12.8, 11.5, 4.5 Hz, 1H, NHCH$_2$C*H*$_2$), 1.94 (ddt, *J*=12.8, 5.0, 2.5 Hz, 1H, NHCH$_2$C*H*$_2$), 2.44 (m, 1H, NHC*H*), 2.55 (td, *J*=12.8, 2.5 Hz, 1H, NHC*H*$_2$), 2.89 (ddd, *J*=12.8, 4.5, 2.5 Hz, 1H, NHC*H*$_2$), 2.92 (dd, *J*=9.4, 9.0 Hz, 1H, NHCHC*H*OH), 3.46 (ddd, *J*=11.5, 9.0, 5.0 Hz, 1H, NHCH$_2$CH$_2$C*H*OH); ^{13}C NMR (100 MHz, D_2O) δ 19.9, 35.6, 45.2, 58.0, 75.6, 80.8; MS (ESI, *m*/*z*): 132.1 (M+H^+, 100%); HRMS calcd for $C_6H_{14}NO_2$ [M+H^+]: 132.1025; found: 132.1025.

4.14. *tert*-Butyl (2*R*,3*R*,4*R*,5*S*)-3-(benzyloxy)-4,5-dihydroxy-2-methyl-6-oxopiperidine-1-carboxylate (20)

A solution of OsO_4 (0.03 M, 0.8 mL) in water was added to a solution of compound **7** (78 mg, 0.25 mmol) and NMO (86 mg, 0.74 mmol) in *t*-BuOH (2.5 mL) at room temperature. After stirred for 20 h, the reaction was quenched by adding an excess of solid

Na_2SO_3. The solvents were removed under reduced pressure until the reaction color began to turn gray. The resultant mixture was diluted with MeOH and filtered. The solid was washed successively with CH_2Cl_2 and MeOH for three times. The residue was purified by chromatography on silica gel (EtOAc/PE) to give compound **20** as a colorless oil. $[\alpha]_D^{20}$ −33.8 (*c* 0.8, $CHCl_3$); IR (film) $\nu_{max:}$ 3416, 2944, 2837, 1666, 1630, 1465, 1361, 1255, 1105 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.26 (br, 1H, OH), 1.28 (d, *J*=7.0 Hz, 3H, C*H*$_3$), 1.54 (s, 9H, *t*-Bu), 1.70–1.65 (br, 1H, OH), 2.94–2.88 (m, 1H, BnOC*H*), 3.88 (d, *J*=4.9 Hz, 1H, BnOCHC*H*OH), 4.19 (dq, *J*=13.8, 7.0 Hz, 1H, NC*H*), 4.42–4.41 (m, 1H, BocNCOC*H*), 4.71 (s, 2H, C*H*$_2$Ph), 7.37–7.27 (m, 5H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.3, 28.0, 55.9, 71.2, 72.2, 77.7, 83.5, 127.3 (2C), 128.6, 137.0, 149.7, 171.9; MS (ESI, *m*/*z*): 352 ($M+H^+$, 100%); HRMS calcd for $C_{18}H_{26}NO_6$ [$M+H^+$]: 352.1760; found: 352.1765. HRMS calcd for $C_{13}H_{17}NNaO_4$ [$M+Na^+$]: 274.1055; found: 274.1043.

4.15. (3*S*,4*R*,5*R*,6*R*)-5-(Benzyloxy)-3,4-dihydroxy-6-methylpiperidin-2-one (21)

Trifluoroacetic acid (1.1 mL) was added dropwise to a solution of compound **20** (387 mg, 1.1 mmol) in CH_2Cl_2 (11 mL) at 0 °C. After stirring at 0 °C for 30 min, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatograph on silica gel (eluent: CH_2Cl_2/CH_3OH=20:1) to afford lactam **21** (250 mg, 90%) as a white solid. Mp 131–133 °C (CH_2Cl_2/CH_3OH); $[\alpha]_D^{20}$ +103.2 (*c* 0.92, $CHCl_3$); IR (film) ν_{max}: 3280, 2884, 1680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (d, *J*=6.1 Hz, 1H, CH_3), 3.37–3.47 (m, 3H, OH, D_2O exchangeable, H-5, H-6), 4.28–4.35 (m, 2H, H-3, H-4), 4.40 (br s, 1H, OH, D_2O exchangeable), 4.55 (d, *J*=11.5 Hz, 1H, PhC*H*$_2$), 4.75 (d, *J*=11.5 Hz, 1H, PhC*H*$_2$), 6.65 (br s, 1H, CON*H*, D_2O exchangeable), 7.27–7.42 (m, 5H, Ph-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0, 49.4, 68.5, 71.6, 71.9, 82.7, 128.0 (2C), 128.5, 137.3, 172.5; MS (ESI, *m*/*z*): 274 ($M+Na^+$, 100%). HRMS calcd for $C_{13}H_{17}NNaO_4$ [$M+Na^+$]: 274.1055; found: 274.1043.

4.16. (3*S*,4*S*,5*R*,6*R*)-3,4,5-Trihydroxy-6-methylpiperidin-2-one (6)

To a suspension of 10% $Pd(OH)_2$/C (14 mg) in EtOH (1 mL) was added a solution of compound **21** (22 mg, 0.09 mmol) in EtOH (2 mL). The resultant suspension was stirred under a hydrogen atmosphere for 12 h. The resultant mixture was filtered, washed several times with EtOH, and then concentrated under reduced pressure to give D-rhamnono-1,5-lactam (**6**) (12.9 mg, 92%) as a white solid. Mp 165–166 °C; {lit.[8b] 164–166 °C}; $[\alpha]_D^{20}$ −15.6 (*c* 0.4, H_2O) {lit.[8b] $[\alpha]_D^{20}$ −16.6 (*c* 0.27, H_2O)}; IR (film) ν_{max}: 3299, 2915, 1665 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 1.35 (d, *J*=6.6 Hz, 1H, CH_3), 3.36 (qd, *J*=6.6, 7.7 Hz, 1H, H-6), 3.61 (dd, *J*=7.7, 5.7 Hz, 1H, H-5), 4.04 (dd, *J*=5.7, 4.2 Hz, 1H, H-4), 4.37 (d, *J*=4.2 Hz, 1H, H-3); ^{13}C NMR (100 MHz, D_2O) δ 19.0, 52.1, 69.6, 73.8, 74.4, 174.1; MS (ESI, *m*/*z*): 184 ($M+Na^+$, 100%). HRMS calcd for $C_6H_{11}NNaO_4$ [$M+Na^+$]: 184.0586; found: 184.0574.

4.17. (3*R*,4*R*,5*R*,6*R*)-5-(Benzyloxy)-6-methylpiperidine-3,4-diol (22)

To a solution of lactam **21** (65.2 mg, 0.26 mol) in dry THF (2.6 mL) was added $BH_3{\cdot}SMe_2$ (0.2 mL, 1.04 mmol) at 0 °C. After stirring under nitrogen and at room temperature for 4 h, the reaction was quenched by cautiously adding methanol until gas evolution ceased. Additional methanol was added and the solvents were evaporated. The residue was dissolved in methanol and 6 N HCl was added to the solution. The mixture was refluxed for 5 min to destroy the borane–amine complex. After cooling, the solution was evaporated and the pH was adjusted to 11–12 with $NH_3{\cdot}H_2O$. The solution was evaporated and the residue purified by flash column chromatograph on silica gel (eluent: CH_2Cl_2/CH_3OH=20:3) to afford piperidine derivative **22** (59.8 mg, 97%) as a wax solid. $[\alpha]_D^{20}$ +2.3 (*c* 1.1, CH_3OH); IR (film) ν_{max}: 3323, 2920 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 1.33 (d, *J*=6.5 Hz, 3H, CH_3), 2.99 (dq, *J*=9.4, 6.5 Hz, 1H, H-6), 3.07 (dd, *J*=13.3, 1.0 Hz, 1H, H-2), 3.21 (dd, *J*=13.3, 3.3 Hz, 1H, H-2), 3.57 (t, *J*=9.4 Hz, 1H, H-5), 3.72 (dd, *J*=9.4, 3.0 Hz, 1H, H-4), 4.05–4.11 (m, 1H, H-3), 4.67 (d, *J*=11.2 Hz, 1H, PhC*H*$_2$), 4.95 (d, *J*=11.2 Hz, 1H, PhC*H*$_2$), 7.25–7.42 (m, 5H, Ph-*H*); ^{13}C NMR (100 MHz, CD_3OD) δ 16.2, 49.9, 56.0, 68.6, 74.9, 76.1, 80.4, 128.8, 129.3 (2C), 139.6; MS (ESI, *m*/*z*): 238 ($M+H^+$, 100%). HRMS calcd for $C_{13}H_{20}NO_3$ [$M+H^+$]: 238.1443; found: 238.1435.

4.18. (2*R*,3*R*,4*R*,5*R*)-2-Methylpiperidine-3,4,5-triol (5)

0.2 mL of 6 N HCl was added to a mixture of compound **22** (52.5 mg, 0.22 mmol), 10% Pd/C (45 mg), and EtOH (4 mL). The suspension was stirred under a hydrogen atmosphere for 15 h. The resultant mixture was filtered through a short pad of Celite. The filter cake was washed with EtOH for several times and the filtrate was concentrated under reduced pressure. The residue was dissolved in water and passed through a column of ion-exchange resin (Dowex-8×100, OH form) eluting with water. The eluent was concentrated under reduced pressure to give D-deoxyrhamnojirimycin (**5**) (22.8 mg, 70%) as a wax solid. $[\alpha]_D^{20}$ −55.2 (*c* 0.4, H_2O) {lit.[19] $[\alpha]_D^{20}$ −52.7 (*c* 0.42, H_2O)}; IR (film) ν_{max}: 3354, 2926 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 1.19 (d, *J*=6.4 Hz, 3H, CH_3), 2.38 (dq, *J*=9.4, 6.4 Hz, 1H, H-2), 2.69 (dd, *J*=14.0, 1.5 Hz, 1H, H-6), 2.92 (dd, *J*=14.0, 2.7 Hz, 1H, H-6), 3.23 (dd, *J*=9.4, 9.4 Hz, 1H, H-3), 3.35 (dd, *J*=9.4, 3.2 Hz, 1H, H-4), 3.84–3.87 (m, 1H, H-5); ^{13}C NMR (100 MHz, CD_3OD) δ 18.3, 50.6, 57.3, 70.9, 75.8, 76.4; MS (ESI, *m*/*z*): 148 ($M+H^+$, 100%). HRMS calcd for $C_6H_{13}NNaO_3$ [$M+Na^+$]: 170.0793; found: 170.0785.

Acknowledgements

The authors are grateful to the NSFC (20832005) and NFFTBS (No. J0630429) for financial support.

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