STEREOSELECTIVE SYNTHESIS OF D-1-DEOXYNOJIRIMYCIN AND ITS STEREOISOMERS

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Abstract – A stereoselective synthesis of D-1-deoxynojirimycin (**1**), D-1-deoxymannojirimycin (**2**), and D-1-deoxyallonojirimycin (**3**) was achieved via the regioselective and diastereoselective amination of *anti*-1,2-dibenzyl ether using chlorosulfonyl isocyanate (CSI), ring-closing metathesis, diastereoselective dihydroxylation, and the regioselective stereochemical inversion of the resulting diol.

INTRODUCTION

Polyhydroxylated piperidine alkaloids and their synthetic analogs have attracted a great deal of attention because they selectively inhibit glycosidases and glycotransferases.[1] In particular, D-1-deoxyazasugars, such as, D-1-deoxynojirimycin (**1**, DNJ),[2] D-1-deoxymannojirimycin (**2**, DMJ),[3] and D-1-deoxyallonojirimycin (**3**, *allo*-DNJ),[4] have been reported to inhibit various glycosidases in a reversible or competitive manner due to their structural resemblances to the sugar moieties of natural substrates.[5] For example, D-1-deoxynojirimycin (**1**), isolated from *Morus alba* in 1976,[6] significantly inhibits all mammalian α–glycosidase types.[7] Also, D-1-deoxymannojirimycin (**2**), isolated from *Lonchocarpus sericeus* in 1979,[8] potently inhibits α–D-mannosidase, α–D-glucosidase and α–L-fucosidase.[9]

Because of their structural features and potent inhibitory effects on various glycosidases, azasugars have been extensively examined as the therapeutic agents for various metabolic disorders such as viral infection,[10] diabetes,[11] malaria,[12] and cancer.[13] Moreover, the realization that these azasugars might have the enormous biological activities, has led to the recent developments of an impressive number of synthetic routes to these compounds (Figure 1).
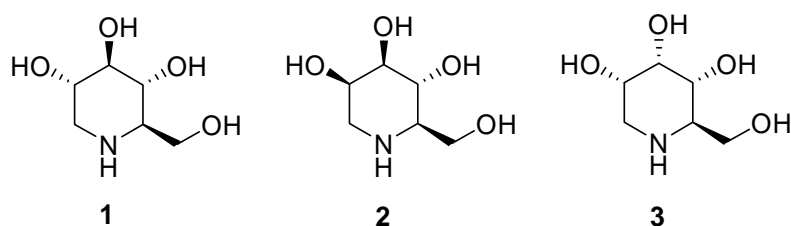

Figure 1. Structure of D-1-deoxynojirimycin and its stereoisomers.

In connection with our previous project, on the chlorosulfonyl isocyanate (CSI)-mediated stereoselective amination of various allylic ethers[14] and the application of this method to the enantioselective synthesis of polyhydroxylated alkaloids,[15] we considered that the stereoselective total synthesis of D-1-deoxynojirimycin (**1**) and of its stereoisomers **2** and **3** would be possible via the stereoselective dihydroxylation of the common intermediate **6** produced during the synthesis of (2*S*,3*S*)-3-hydroxypipecolic acid.[15a,b]

RESULTS AND DISCUSSION

The requisite common intermediate **6** for the preparation of title piperidine alkaloids **1**–**3** were synthesized from commercially available *p*-anisaldehyde, which was converted into *anti*-1,2-dibenzyl ether **4** by Brown's asymmetric aldol reaction and subsequent perbenzylation, as shown in Scheme 1.
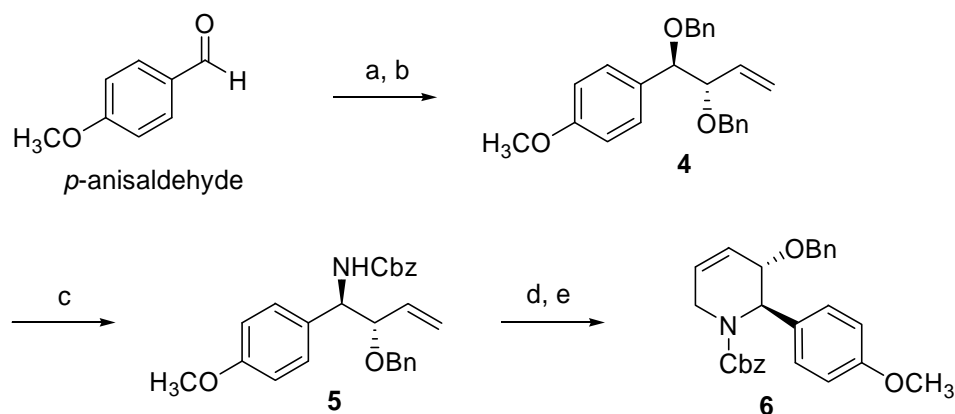
Scheme 1. *Reagents and conditions*: (a) (i) allyl(diisopropylamino)dimethylsilane, *n*-BuLi, TMEDA, (−)-*B*-methoxydiisopinocamphenylborane, BF$_3$·OEt$_2$, Et$_2$O, −78 ℃, 3 h; (ii) KF, KHCO$_3$, 30% H$_2$O$_2$, THF, MeOH, rt, 20 h, 52%; (b) NaH, BnBr, THF, DMF, rt, 11 h, 99%; (c) (i) CSI, Na$_2$CO$_3$, toluene, −78 ℃, 24 h; (ii) 25% Na$_2$SO$_3$, rt, 24 h, 90%; (d) NaH, allyl bromide, THF, DMF, rt, 2 h, 100%; (e) 1st generation Grubbs catalyst, CH$_2$Cl$_2$, rt, 4 h, 91%.

The regioselective and diastereoselective CSI reaction of **4** was carried out in anhydrous toluene at −78 ℃ for 24 h, followed by desulfonylation with an aqueous 25% sodium sulfite solution, to afford the *anti*-1,2-amino alcohol **5** with excellent diastereoselectivity (*anti*/*syn* = 49:1, 98% ds by NMR analysis) in 90% yield. Allylation of **5** followed by ring-closing metathesis afforded compound **6** in high yields.

In order to introduce the 4,5-*trans*-dihydroxyl group into the olefin moiety of **6**, we first planned the epoxidation of olefin and regioselective ring-opening using an acetoxy reagent to afford the *trans*-diol **8**, which could be easily converted to D-1-deoxynojirimycin (**1**). However, several attempts at epoxidation (*m*-CPBA,[16] Oxone®,[3b,17] CF$_3$CO$_3$H/Na$_2$HPO$_4$,[18] ^{t}BuOOH/VO(acac)$_2$,[19] CH$_3$ReO$_3$/H$_2$O$_2$,[20] and others) failed to afford the corresponding epoxy compound **7**.
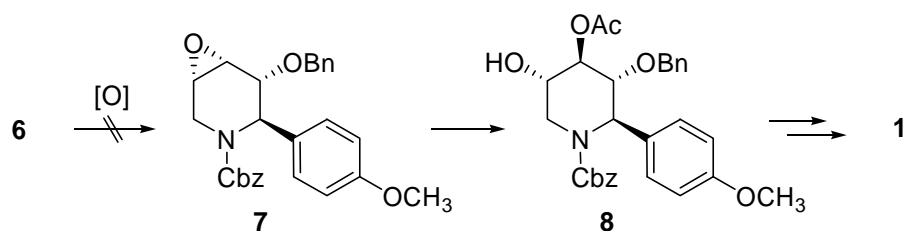
Scheme 2

Since epoxidation route proved troublesome, we next focused on diastereoselective dihydroxylation of olefin **6** and subsequent regioselective stereochemical inversion of the resulting diol **10** to accomplish the total synthesis of D-1-deoxynojirimycin series **1–3**, as described in Scheme 3.
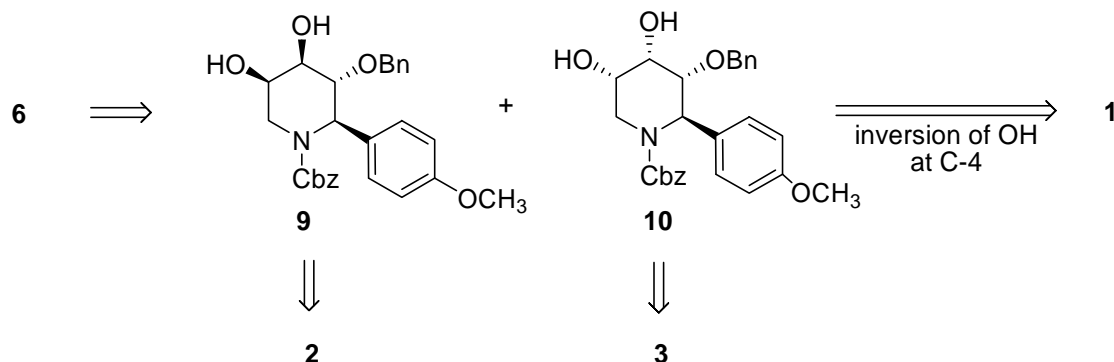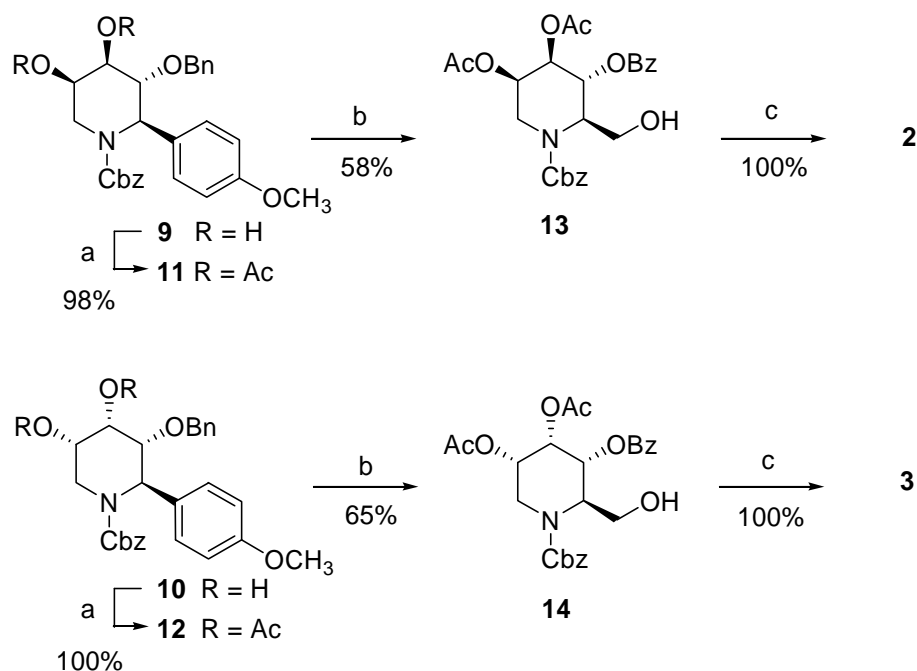

Scheme 3

Initially, It was observed that the standard dihydroxylation of **6** using Upjohn's method[21] (cat. OsO_4, NMO, 80% acetone) afforded a separable mixture of the diols **9** and **10** with a diastereoselectivity of 1:6.0 and in a combined yield of 75%. Similarly, the dihydroxylation in *tert*-butyl alcohol took favored **10** at the same level of diastereoselectivity (1:5.3). However, Donohoe's condition[22] (1 equiv. of OsO_4 and 1 equiv. of TMEDA) did not afford the dihydroxylated compounds, probably because the internal alkene was less accessible to the bulky OsO_4/TMEDA complex due to the presence of the *pseudo*-axial groups (OBn and *p*-MeOPh). Because the stereochemical assignments of **9** and **10** proved to be difficult by ^{1}H NMR and nOe analysis, we attempted to determine the relative configurations of peracetylated compounds **11** and **12** using nOe experimental study, as shown in Figure 2.
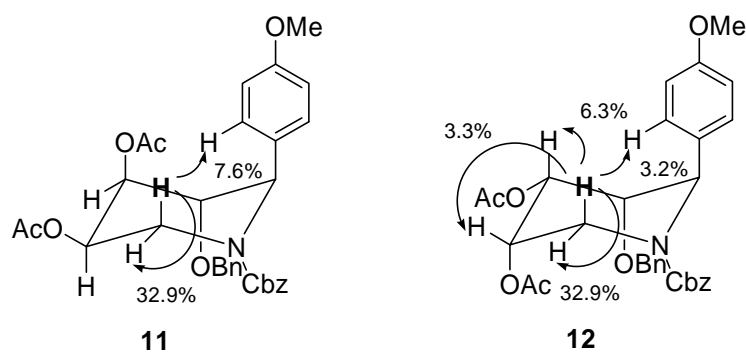
Figure 2. nOe experimental study of **11** and **12**.

From observations of vicinal coupling constants and nOe correlations, the dihydroxylation of **6** was concluded to have occurred preferentially due to the steric effect of the *p*-methoxyphenyl group to provide the diol **10** as a major isomer. Furthermore, structure of the peracetylated piperidines **11** and **12** allowed a remarkably undistorted chair-like conformation in the presence of axially-oriented bulky substituents, such as, *p*-methoxyphenyl and benzyloxy groups.[15a]

For the syntheses of D-1-deoxymannojirimycin (**2**) and D-1-deoxyallonojirimycin (**3**), the diols **9** and **10**, respectively, were converted into the peracetylated compounds **11** and **12** using acetic anhydride, 4-*N,N'*-(dimethylamino)pyridine and triethylamine in quantitative yields (Scheme 4). The oxidation of the *p*-methoxyphenyl groups of **11** and **12** using RuCl$_3$ (0.15 equiv.), NaIO$_4$ (17 equiv.), and H$_2$O/MeCN/EtOAC (2/1/1)[23] produced carboxylic acid intermediates in which the benzyl groups were also oxidized to benzoates, followed by reduction with borane-tetrahydrofuran to provide the primary alcohols **13** and **14** in 58% and 65% yields, respectively. Finally, exposure of **13** or **14** to 6 N HCl in methanol followed by treatment with ion-exchange resin furnished D-1-deoxymannojirimycin (**2**) and D-1-deoxyallonojirimycin (**3**) in quantitative yields. Spectroscopic data and the specific rotation of **2**[2f,3f,24] and **3**[2f,4c,24] were consistent with literature values.

Finally, the synthesis of D-1-deoxynojirimycin (**1**) was accomplished by converting the *cis*-diol **10** into the *trans*-diol **18**. Thus, treatment of **10** with *p*-toluenesulfonyl chloride gave a separate mixture of the tosylates **15** and **16** with a regioselectivity of 2.1:1 in favor of **15** in a combined yield of 99% (Scheme 5).

Scheme 4. *Reagents and conditions*: (a) Ac$_2$O, DMAP, Et$_3$N, CH$_2$Cl$_2$, rt, 3 h; (b) (i) cat. RuCl$_3$, NaIO$_4$, H$_2$O/MeCN/EtOAc (2:1:1), rt, 4 h; (ii) BH$_3$− THF, THF, 0 ℃, 24 h; (c) (i) 6 N HCl. MeOH, reflux, 14 h; (ii) DOWEX-50WX8 (H$^+$ form, 0.5 M NH$_4$OH as eluent).

In this case, tosylation of **10** took place mainly at the C-4 equatorial OH, since the approach to the C-5 axial OH by TsCl was slightly shielded by the C-3 benzyloxy group due to 1,3-diaxial interaction.
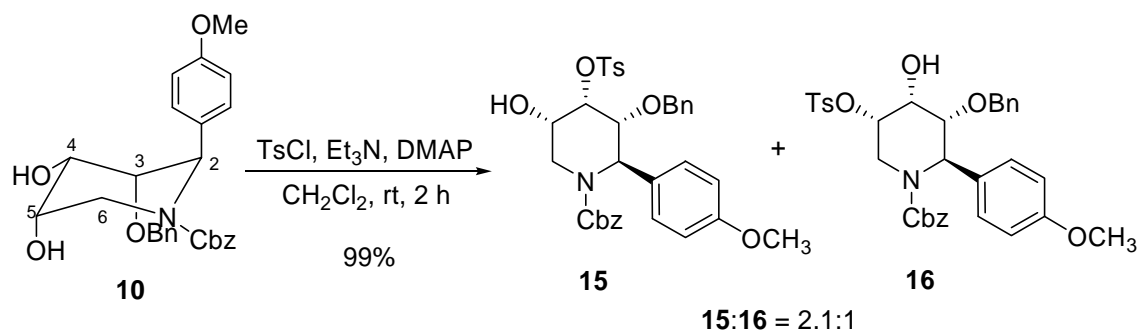
Scheme 5

As shown in Scheme 6, acetylation of the alcohol **15** produced the acetate **17** in 99% yield. To afford the required *trans*-diol, the stereo-inversion of the tosylate **17** was attempted using cesium acetate in the presence of DMF to give the peracetate **18**. Displacement of the C-4 equatorial tosylate by axial acetate was smoothly achieved because this nucleophilic substitution occurred in an axial fashion with respect to the six-membered chair conformation. To complete the synthesis of D-1-deoxynojirimycin (**1**), the peracetate **18** was converted into the alcohol **19** via Sharpless' oxidation of the *p*-methoxyphenyl group and subsequent reduction of the resulting carboxylic acid intermediate. Acid hydrolysis of **19** in refluxing methanol furnished D-1-deoxynojirimycin (**1**) with specific rotation and spectral data (^{1}H and ^{13}C NMR) identical to those reported in the literature.[2f,24]
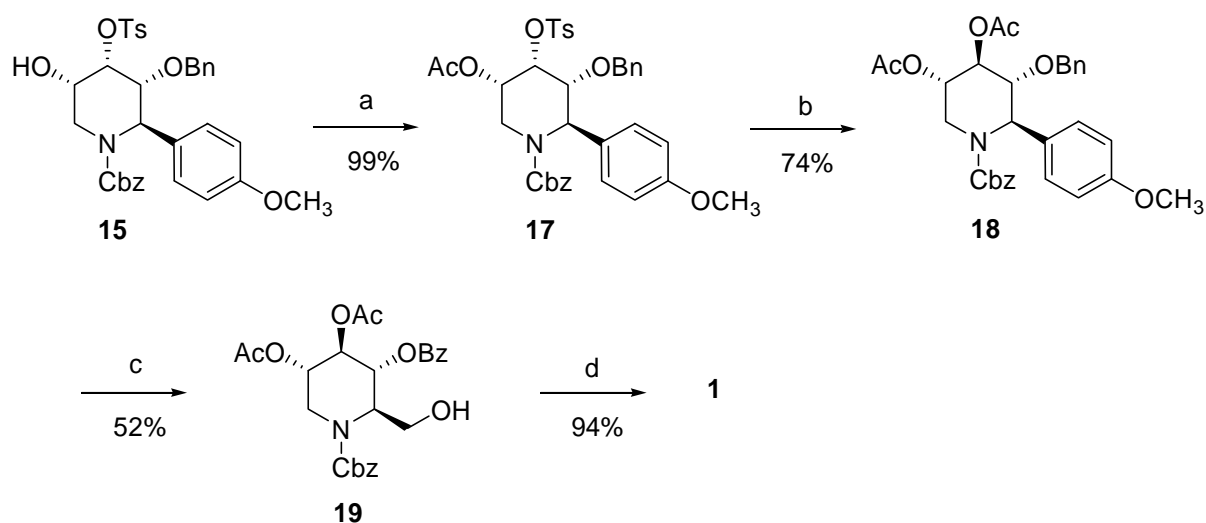
Scheme 6. *Reagents and conditions*: (a) Ac_2O, DMAP, Et_3N, CH_2Cl_2, rt, 2 h; (b) CsOAc, DMF, 60 ℃, 4 h; (c) (i) cat. $RuCl_3$, $NaIO_4$, $H_2O/MeCN/EtOAc$ (2:1:1), rt, 4 h; (ii) BH_3– THF, THF, 0 ℃, 24 h; (d) (i) 6 N HCl. MeOH, reflux, 12 h; (ii) DOWEX-50WX8 (H^+ form, 0.5 M NH_4OH as eluent).

EXPERIMENTAL

General

Commercially available reagents were used without additional purification, unless otherwise stated. All anhydrous solvents were distilled over CaH_2 or P_2O_5 or Na/benzophenone prior to reaction. All reactions were performed under an inert atmosphere of nitrogen or argon. Nuclear magnetic resonance spectra (^1H and ^{13}C NMR) were recorded on a Varian Unity Inova 500 and 300 MHz spectrometer and chemical shifts are reported as parts per million (ppm). 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 a Nicolet 205 Infrared spectrophotometer or Bruker Vector 22 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). Flash column chromatography was performed using Kieselgel 60 (230-400 mesh, E. Merck). High-resolution mass spectra (HRMS) were recorded on a JEOL, JMS-505 or JMS-600 spectrometer.

(2*R*,3*R*,4*R*,5*R*)-3-Benzyloxy-1-benzyloxycarbonyl-4,5-dihydroxy-2-(*p*-methoxyphenyl)piperidine (9) and (2*R*,3*R*,4*S*,5*S*)-3-benzyloxy-1-benzyloxycarbonyl-4,5-dihydroxy-2-(*p*-methoxyphenyl)piperidine (10).

To a stirred solution of **6** (3.5 g, 8.11 mmol) in a mixture of acetone (40 mL) and H_2O (8 mL) was added *N*-methylmorpholine *N*-oxide (5.0 mL, 24.33 mmol, 50% in H_2O) and OsO_4 (1 crystal, ~5 mol %) under N_2. The reaction mixture was stirred for 8 h at rt and quenched with a saturated aqueous Na_2SO_3 (10 mL). The aqueous layer was extracted with EtOAc (20 mL×2) and the organic layer was washed with H_2O and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 1:1) to afford a separable mixture (2.85 g, 75%, **9**:**10** = 1:6.0) of the diols **9** and **10** as colorless syrups. **9**: syrup; R_f = 0.27 (hexane/EtOAc 1:1); $[\alpha]_D^{28}$ −51.2 (*c* 0.5, CHCl$_3$); IR (CH$_2$Cl$_2$) 3459, 2918, 2876, 1683, 1589, 1247, 1069, 1034 cm^{-1}; ^1H NMR (500 MHz, CDCl$_3$) δ 1.88-2.08 (br, 2H), 3.12 (dd, 1H, J = 13.0, 10.5 Hz), 3.79 (s, 3H), 4.05 (t, 1H, J = 4.0 Hz), 4.14 (ddd, 1H, J = 10.5, 6.0, 3.0 Hz), 4.26 (dd, 1H, J = 4.0, 3.0 Hz), 4.29 (dd, 1H, J = 13.0, 6.0 Hz), 4.57 (d, 1H, J = 12.0 Hz), 4.69 (d, 1H, J = 12.0 Hz), 5.15 (d, 1H, J = 12.5 Hz), 5.18 (d, 1H, J = 12.5 Hz), 5.50-5.52 (br, 1H), 6.87 (dd, 2H, J = 9.0, 2.5 Hz), 7.15 (dd, 2H, J = 9.0, 2.5 Hz), 7.27-7.38 (m, 10H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 41.38, 55.42, 55.48, 64.92, 67.80, 70.59, 72.13, 78.14, 114.31, 127.34, 128.01, 128.20, 128.22, 128.69, 128.79, 129.83, 136.74, 137.83, 156.73, 158.80; HRMS (FAB) Calcd for $C_{27}H_{30}NO_6$ [M+H$^+$] 464.2073, found 464.2068. **10**: syrup; R_f = 0.29 (hexane/EtOAc 1:1); $[\alpha]_D^{28}$ −60.8 (*c* 0.2, CHCl$_3$); IR (CH$_2$Cl$_2$) 3458, 2920, 2856, 1739, 1695, 1455, 1374, 1245, 1124, 1027 cm^{-1}; ^1H NMR (500 MHz, CDCl$_3$) δ 3.03 (dd, 1H, J = 14.5, 1.5 Hz),

3.59-3.61 (br, 1H), 3.73 (br s, 1H), 3.81 (s, 3H), 4.43 (br s, 1H), 4.48 (br d, 1H, J = 14.5 Hz), 4.57 (d, 1H, J = 12.0 Hz), 4.84-4.86 (br, 1H), 5.26 (s, 2H), 5.94-5.95 (br, 1H), 6.89 (dd, 2H, J = 8.5, 2.5 Hz), 7.09 (dd, 2H, J = 8.5, 2.5 Hz), 7.32-7.38 (m, 10H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 46.11, 55.54, 55.55, 66.56, 68.00, 69.90, 73.06, 79.77, 114.73, 127.39, 127.64, 128.09, 128.35, 128.54, 128.78, 128.92, 136.73, 136.94, 157.53, 159.19; HRMS (FAB) Calcd for C$_{27}$H$_{30}$NO$_6$ [M+H$^+$] 464.2073, found 464.2069.

(2R,3R,4R,5R)-3-Benzyloxy-1-benzyloxycarbonyl-4,5-diacetoxy-2-(p-methoxyphenyl)piperidine (11).

To a stirred solution of **9** (0.25 g, 0.539 mmol) in anhydrous CH$_2$Cl$_2$ (2.7 mL) was added Ac$_2$O (0.15 mL, 2.156 mmol), Et$_3$N (0.3 mL, 2.156 mmol) and DMAP (13 mg, 0.108 mmol) under N$_2$. The reaction mixture was stirred for 3 h at rt and quenched with a saturated aqueous NH$_4$Cl (2 mL). The aqueous layer was extracted with EtOAc (10 mL) and the organic layer was washed with H$_2$O and brine, dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 3:1) to afford 0.29 g (98%) of **11** as colorless syrup. R_f = 0.27 (hexane/EtOAc 3:1); [α]$_D^{29}$ −2.0 (c 1.0, CHCl$_3$); IR (CH$_2$Cl$_2$) 2943, 2360, 1743, 1702, 1511, 1420, 1368, 1232, 1180, 1115, 1060 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.42 (s, 3H), 2.02 (s, 3H), 3.38 (dd, 1H, J = 13.0, 11.0 Hz), 3.79 (s, 3H), 4.33 (dd, 1H, J = 4.0, 2.0 Hz), 4.42 (dd, 1H, J = 13.0, 5.0 Hz), 4.73 (s, 2H), 5.14 (d, 1H, J = 12.5 Hz), 5.24 (d, 1H, J = 12.5 Hz), 5.25 (dd, 1H, J = 4.0, 2.5 Hz), 5.36 (ddd, 1H, J = 11.0, 5.0, 2.5 Hz), 5.58 (br s, 1H), 6.84 (dd, 2H, J = 8.5, 2.0 Hz), 6.97 (dd, 2H, J = 8.5, 2.0 Hz), 7.30-7.38 (m, 10H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 20.34, 21.05, 39.10, 55.58, 55.59, 65.49, 67.91, 68.87, 72.11, 75.69, 114.22, 126.42, 127.96, 128.15, 128.21, 128.24, 128.70, 128.78, 130.01, 136.70, 137.47, 156.71, 158.47, 169.83, 170.28; HRMS (FAB) Calcd for C$_{31}$H$_{34}$NO$_8$ [M+H$^+$] 548.2284, found 548.2291.

(2R,3R,4S,5S)-3-Benzyloxy-1-benzyloxycarbonyl-4,5-diacetoxy-2-(p-methoxyphenyl)piperidine (12).

To a stirred solution of **10** (1.5 g, 3.24 mmol) in anhydrous CH$_2$Cl$_2$ (16 mL) was added Ac$_2$O (0.92 mL, 9.72 mmol), Et$_3$N (1.8 mL, 12.96 mmol) and DMAP (80 mg, 0.65 mmol) under N$_2$. The reaction mixture was stirred for 3 h at rt and quenched with a saturated aqueous NH$_4$Cl (5 mL). The aqueous layer was extracted with EtOAc (20 mL) and the organic layer was washed with H$_2$O and brine, dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 3:1) to afford 1.77 g (100%) of **12** as colorless syrup. R_f = 0.24 (hexane/EtOAc 3:1); [α]$_D^{29}$ −32.1 (c 1.0, CHCl$_3$); IR (CH$_2$Cl$_2$) 2930, 1738, 1701, 1610, 1511, 1426, 1368, 1242, 1125, 1057 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.97 (s, 3H), 2.06 (s, 3H), 3.07 (dd, 1H, J = 15.0, 2.5 Hz), 3.82 (s, 3H), 4.40 (dd, 1H, J = 3.0, 2.0 Hz), 4.43 (dd, 1H, J = 15.0, 2.0 Hz), 4.61 (d, 1H, J = 12.0 Hz), 4.79 (d, 1H, J = 12.0 Hz), 5.01 (t, 1H, J = 3.0 Hz), 5.08 (br d, 1H, J = 3.0 Hz), 5.12 (d, 1H, J = 12.0 Hz), 5.27 (d, 1H, J = 12.0 Hz), 5.87 (br s, 1H), 6.90 (dd, 2H, J = 9.5, 2.5 Hz), 7.20 (dd, 2H, J = 9.5, 2.5 Hz), 7.27-7.40 (m, 10H); ^{13}C NMR (125

MHz, CDCl$_3$) δ 42.93 (two carbons), 42.93, 55.55, 56.77, 67.54, 67.76, 68.70, 72.12, 74.97, 114.75, 127.45, 127.65, 127.70, 127.94, 128.18, 128.47, 128.67, 136.80, 138.68, 157.13, 159.27, 170.65, 171.10; HRMS (FAB) Calcd for C$_{31}$H$_{34}$NO$_8$ [M+H$^+$] 548.2284, found 548.2274.

(2R,3R,4R,5R)-3-Benzoyloxy-1-benzyloxycarbonyl-4,5-diacetoxy-2-(hydroxymethyl)piperidine (13).

To a stirred solution of **11** (0.15 g, 0.274 mmol) in a mixture of H$_2$O/EtOAc/MeCN (2:1:1 v/v/v, 16 mL) was added NaIO$_4$ (1.0 g, 4.658 mmol) and RuCl$_3$ (6.8 mg, 0.033 mmol). The reaction mixture was stirred for 4 h at rt, quenched with propan-2-ol, and filtered through a Celite pad. The filtrate was concentrated in vacuo. The residual viscous oil was used without purification in the next step. To a stirred solution of crude carboxylic acid (0.12 g) from the previous step in THF (1.0 mL) was slowly added to BH$_3$–THF complex (0.55 mL, 0.548 mol, 1.0 M in THF) at 0 ℃. The reaction mixture was stirred for 24 h at 0 ℃ and quenched with H$_2$O (1 mL). The aqueous layer was extracted with EtOAc (5 mL). The organic layer was washed with H$_2$O and brine, dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 1:1.5) to afford 78 mg (58%) of **13** as colorless syrup. R_f = 0.30 (hexane/EtOAc 1:1.5); [α]$_D^{22}$ −15.2 (c 0.2, CHCl$_3$); IR (neat) 3766, 3701, 1733, 1728, 1533, 1377, 1128 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 2.03 (s, 3H), 2.14 (s, 3H), 3.32-3.46 (br, 1H), 3.93 (dd, 1H, J = 11.5, 6.0 Hz), 4.04 (dd, 1H, J = 11.5, 8.5 Hz), 4.18-4.26 (br, 1H), 4.52-4.63 (br, 1H), 5.05 (br s, 2H), 5.24-5.28 (m, 1H), 5.34 (br s, 1H), 5.45 (br s, 1H), 7.17-7.36 (m, 5H), 7.43 (t, 2H, J = 8.0, 7.0 Hz), 7.58 (t, 1H, J = 8.0, 7.0 Hz), 7.97 (d, 2H, J = 7.0 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ 20.92, 20.98, 53.64, 59.86, 60.91, 67.67, 68.09, 68.76, 71.02, 127.89, 128.25, 128.40, 128.68, 128.75, 129.26, 130.09, 133.81, 136.18, 156.48, 165.23, 169.37, 169.80; HRMS (FAB) Calcd for C$_{25}$H$_{27}$NO$_9$ [M+H$^+$] 486.1764, found 486.1771.

(2R,3R,4S,5S)-3-Benzoyloxy-1-benzyloxycarbonyl-4,5-diacetoxy-2-(hydroxymethyl)piperidine (14).

To a stirred solution of **12** (0.3 g, 0.548 mmol) in a mixture of H$_2$O/EtOAc/MeCN (2:1:1 v/v/v, 33 mL) was added NaIO$_4$ (2.0 g, 9.316 mmol) and RuCl$_3$ (14 mg, 0.066 mmol). The reaction mixture was stirred for 5 h at rt, quenched with propan-2-ol, and filtered through a Celite pad. The filtrate was concentrated in vacuo. The residual viscous oil was used without purification in the next step. To a stirred solution of crude carboxylic acid (0.2 g) from the previous step in THF (1.5 mL) was slowly added to BH$_3$–THF complex (1.1 mL, 1.096 mol, 1.0 M in THF) at 0 ℃. The reaction mixture was stirred for 24 h at 0 ℃ and quenched with H$_2$O (1 mL). The aqueous layer was extracted with EtOAc (5 mL). The organic layer was washed with H$_2$O and brine, dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 1:1.5) to afford 0.172 g (65%) of **14** as colorless syrup. R_f = 0.28 (hexane/EtOAc 1:1.5); [α]$_D^{29}$ −44.6 (c 0.1, CHCl$_3$); IR (CH$_2$Cl$_2$) 3780, 3700, 2922, 2855, 2358, 1735, 1598, 1457, 1375, 1272, 1127 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.81-2.00 (br s, 6H), 2.33-2.35 (br, 1H),

3.48 (dd, 1H, J = 13.5, 11.0 Hz), 3.93 (d, 2H, J = 6.0 Hz), 4.52 (dd, 1H, J = 13.5, 3.5 Hz), 4.77 (br t, 1H, J = 6.0 Hz), 5.03 (d, 1H, J = 12.0 Hz), 5.21-5.25 (br s, 2H), 5.37 (t, 1H, J = 3.5 Hz), 5.57 (br s, 1H), 7.18-7.40 (m, 5H), 7.44 (t, 2H, J = 7.5 Hz), 7.60 (t, 1H, J = 7.5 Hz), 8.06 (d, 2H, J = 7.5 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ 20.92, 21.10, 43.57, 57.78, 61.43, 67.01, 67.41, 67.88, 68.16, 128.10, 128.35, 128.59, 128.73, 130.10, 130.14, 133.50, 136.50, 156.71, 165.92, 170.37, 170.63; HRMS (FAB) Calcd for C$_{25}$H$_{27}$NO$_9$ [M+H$^+$] 486.1764, found 486.1771.

D-1-Deoxymannojirimycin (2).

A solution of **13** (40 mg, 0.082 mmol) in a mixture of 6 N HCl (1.7 mL) and MeOH (1.7 mL) was refluxed for 14 h and concentrated in vacuo. The residue was purified by ion-exchange resin DOWEX-50WX8 (H$^+$ form) using 0.5 M aqueous NH$_4$OH as eluent to afford 14 mg (100%) of D-1-deoxymannojirimycin (**2**) as white semisolid. R_f = 0.18 (CHCl$_3$/MeOH/30%NH$_4$OH 1:1:0.2); mp 179~180 ℃ (decomp) [lit.,[3f] mp 182~184 ℃ (decomp)]; $[\alpha]_D^{25}$ −39.0 (c 0.1, H$_2$O) [lit.,[24b] $[\alpha]_D$ −40.2 (c 0.33, H$_2$O)]; ^{1}H NMR (500 MHz, D$_2$O) δ 2.52 (br t, 1H, J = 4.5 Hz), 2.77 (d, 1H, J = 14.0 Hz), 3.01 (d, 1H, J = 14.0 Hz), 3.51 (dd, 1H, J = 10.0, 3.0 Hz), 3.58 (t, 1H, J = 10.0 Hz), 3.70-3.74 (m, 2H), 3.97 (br s, 1H); ^{13}C NMR (125 MHz, D$_2$O) δ 48.30, 60.48, 60.67, 68.09, 68.81, 74.39; HRMS (CI) Calcd for C$_6$H$_{14}$NO$_4$ [M+H$^+$] 164.0923, found 164.0922.

D-1-Deoxyallonojirimycin (3).

A solution of **14** (56 mg, 0.115 mmol) in 6 M HCl (2.4 mL) and MeOH (2.4 mL) was refluxed for 14 h and concentrated in vacuo. The residue was purified by ion-exchange resin DOWEX-50WX8 (H$^+$ form) using 0.5 M aqueous NH$_4$OH as eluent to afford 20 mg (100%) of D-1-deoxyallonojirimycin (**3**) as white semisolid. R_f = 0.14 (CHCl$_3$/MeOH/30%NH$_4$OH 1:1:0.2); mp 164~165 ℃ (decomp) [lit.,[2f] mp 165 ℃]; $[\alpha]_D^{25}$ +34.0 (c 0.1, MeOH) [lit.,[24b] $[\alpha]_D$ +36.2 (c 0.83, H$_2$O)]; ^{1}H NMR (500 MHz, D$_2$O) δ 2.69 (t, 1H, J = 12.0 Hz), 2.75-2.80 (m, 1H), 2.85 (dd, 1H, J = 12.0, 5.0 Hz), 3.46 (dd, 1H, J = 10.0, 2.0 Hz), 3.61 (dd, 1H, J = 12.0, 5.0 Hz), 3.65-3.69 (m, 1H), 3.75 (dd, 1H, J = 12.0, 3.0 Hz), 4.03 (br s, 1H); ^{13}C NMR (125 MHz, D$_2$O) δ 43.51, 54.77, 60.96, 67.80, 68.36, 71.45; HRMS (CI) Calcd for C$_6$H$_{14}$NO$_4$ [M+H$^+$] 164.0923, found 164.0919.

(2R,3R,4S,5S)-3-Benzyloxy-1-benzyloxycarbonyl-5-hydroxy-2-(p-methoxyphenyl)-4-(tosyloxy)piperidine (15) and (2R,3R,4S,5S)-3-benzyloxy-1-benzyloxycarbonyl-4-hydroxy-2-(p-methoxyphenyl)-5-(tosyloxy)piperidine (16).

To a stirred solution of **10** (1.1 g, 2.37 mmol) in anhydrous CH$_2$Cl$_2$ (12 mL) was added p-toluenesulfonyl chloride (0.54 g, 2.85 mmol), Et$_3$N (0.5 mL, 3.56 mmol) and DMAP (58 mg, 0.47 mmol) under N$_2$. The reaction mixture was stirred for 2 h at rt and quenched with a saturated aqueous NH$_4$Cl (3 mL). The

aqueous layer was extracted with CH_2Cl_2 (15 mL×2) and the organic layer was washed with H_2O and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 2:1) to afford a separable mixture (1.45 g, 99%, **15**:**16** = 2.1:1) of the tosylates **15** and **16** as colorless syrups. **15**: R_f = 0.22 (hexane/EtOAc 2:1); $[\alpha]_D^{29}$ −61.1 (*c* 0.1, CHCl$_3$); IR (CH$_2$Cl$_2$) 3717, 3488, 2921, 2857, 2724, 2356, 1699, 1599, 1455, 1374, 1295, 1245, 1174, 1132, 1016 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 2.46 (s, 3H), 2.88 (d, 1H, *J* = 13.0 Hz), 3.67 (br s, 1H), 3.82 (s,3H), 4.38 (dd, 1H, *J* = 13.0, 3.0 Hz), 4.42 (t, 1H, *J* = 3.0 Hz), 4.55 (dd, 1H, *J* = 4.0, 3.0 Hz), 4.64 (d, 1H, *J* = 11.5 Hz), 4.80-4.83 (br, 1H), 5.24 (s, 2H), 5.86-5.88 (br, 1H), 6.86 (dd, 2H, *J* = 8.0, 2.0 Hz), 6.93 (dd, 2H, *J* = 8.0, 2.0 Hz), 7.26-7.35 (m, 12H), 7.72 (dd, 2H, *J* = 6.5, 2.0 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ 21.90, 46.56, 55.57, 56.41, 68.08, 68.48, 73.37, 75.72, 77.33, 114.84, 126.94, 127.25, 128.06, 128.34, 128.44, 128.51, 128.76, 128.85, 130.15, 133.94, 136.63, 136.67, 145.29, 157.32, 159.33; HRMS (FAB) Calcd for $C_{34}H_{35}NO_8S$ [M+H$^+$] 618.2162, found 618.2156. **16**: R_f = 0.19 (hexane/EtOAc 2:1); $[\alpha]_D^{28}$ −40.7 (*c* 0.1, CHCl$_3$); IR (CH$_2$Cl$_2$) 3343, 2922, 2855, 1698, 1604, 1509, 1452, 1356, 1249, 1176, 1119, 1028 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 2.42 (s, 3H), 2.98 (dd, 1H, *J* = 15.0, 1.5 Hz), 3.71 (dd, 1H, *J* = 4.0, 3.0 Hz), 3.80 (s, 3H), 4.31 (t, 1H, *J* = 3.0 Hz), 4.48 (d, 1H, *J* = 12.0 Hz), 4.54 (d, 1H, *J* = 15.0 Hz), 4.74 (br d, 1H, *J* = 1.5 Hz), 4.88 (d, 1H, *J* = 12.0 Hz), 5.07 (d, 1H, *J* = 12.5 Hz), 5.18 (d, 1H, *J* = 12.5 Hz), 5.93 (br s, 1H), 6.88 (dd, 2H, *J* = 7.0, 2.0 Hz), 7.11 (dd, 2H, *J* = 7.0, 2.0 Hz), 7.19 (d, 2H, *J* = 8.0 Hz), 7.27-7.31 (m, 10H), 7.74 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ 21.86, 43.18, 54.54, 55.56, 65.67, 67.96, 71.94, 76.85, 76.92, 114.75, 127.53, 127.56, 127.68, 127.78, 127.98, 128.04, 128.16, 128.62, 128.68, 129.83, 134.18, 136.60, 137.95, 144.69, 156.93, 159.26; HRMS (FAB) Calcd for $C_{34}H_{35}NO_8S$ [M+H$^+$] 618.2162, found 618.2167.

(2*R*,3*R*,4*S*,5*S*)-5-Acetoxy-3-benzyloxy-1-benzyloxycarbonyl-2-(*p*-methoxyphenyl)-4-(tosyloxy)piperidine (17).

To a stirred solution of **15** (0.5 g, 0.81 mmol) in anhydrous CH_2Cl_2 (4 mL) was added Ac_2O (0.12 mL, 1.22 mmol), Et$_3$N (0.17 mL, 1.22 mmol) and DMAP (20 mg, 0.16 mmol) under N_2. The reaction mixture was stirred for 2 h at rt and quenched with a saturated aqueous NH$_4$Cl (2 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL) and the organic layer was washed with H_2O and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 2:1) to afford 0.53 g (99%) of **17** as colorless syrup. R_f = 0.25 (hexane/EtOAc 2:1); $[\alpha]_D^{28}$ −30.0 (*c* 0.1, CHCl$_3$); IR (CH$_2$Cl$_2$) 2923, 2853, 1739, 1702, 1609, 1512, 1454, 1423, 1364, 1245, 1176, 1129, 1017 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.88 (s, 3H), 2.45 (s, 3H), 2.88 (dd, 1H, *J* = 15.0, 1.5 Hz), 3.83 (s, 3H), 4.39-4.43 (m, 2H), 4.55 (t, 1H, *J* = 3.5 Hz), 4.61 (d, 1H, *J* = 12.0 Hz), 4.77 (dd, 1H, *J* = 12.0 Hz), 4.86 (br d, 1H, *J* = 2.5 Hz), 5.06 (d, 1H, *J* = 12.5 Hz), 5.24 (d, 1H, *J* = 12.5 Hz), 5.80 (br s, 1H), 6.87 (dd, 2H, *J* = 7.0, 2.5 Hz),

7.02 (dd, 2H, J = 7.0, 2.5 Hz), 7.24-7.39 (m, 10H), 7.71 (dd, 2H, J = 7.0, 2.0 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ 21.00, 21.90, 42.68, 55.57, 57.06, 67.78, 67.86, 72.35, 75.18, 75.28, 114.80, 127.43, 127.46, 127.64, 127.94, 128.07, 128.21, 128.44, 128.67, 130.16, 133.76, 136.60, 138.46, 145.34, 157.08, 159.32, 170.80; HRMS (FAB) Calcd for C$_{36}$H$_{37}$NO$_9$S [M+H$^+$] 660.2267, found 660.2263.

(2R,3R,4R,5S)-3-Benzyloxy-1-benzyloxycarbonyl-4,5-diacetoxy-2-(p-methoxyphenyl)piperidine (18).
To a stirred solution of **17** (0.8 g, 1.21 mmol) in anhydrous DMF (12 mL) was added CsOAc (0.7 g, 3.64 mmol) under N$_2$. The reaction mixture was stirred for 4 h at 60 ℃ and quenched with a saturated aqueous NH$_4$Cl (5 mL). The aqueous layer was extracted with EtOAc (20 mL) and the organic layer was washed with H$_2$O and brine, dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 2:1) to afford 0.47 g (71%) of **18** as colorless syrup. R_f = 0.25 (hexane/EtOAc 2:1); $[\alpha]_D^{28}$ +13.3 (c 0.5, CHCl$_3$); IR (CH$_2$Cl$_2$) 2922, 2856, 2230, 1741, 1700, 1609, 1510, 1451, 1367, 1233, 1118, 1040 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.77 (s, 3H), 1.95 (s, 3H), 3.63 (dd, 1H, J = 14.5, 3.0 Hz), 3.81 (s, 3H), 4.04 (t, 1H, J = 5.5 Hz), 4.29 (dd, 1H, J = 14.5, 3.0 Hz), 4.49 (d, 1H, J = 11.5 Hz), 4.54 (d, 1H, J = 11.5 Hz), 4.93 (br d, 1H, J = 3.5 Hz), 5.08 (d, 1H, J = 12.5 Hz), 5.16-5.20 (m, 2H), 5.27 (d, 1H, J = 5.5 Hz), 6.85 (d, 2H, J = 8.5 Hz), 7.12 (d, 2H, J = 8.5 Hz), 7.20-7.34 (m, 10H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 20.90, 21.07, 42.04, 55.56, 58.30, 64.52, 67.64, 70.85, 71.90, 73.19, 114.23, 127.44, 127.88, 127.97, 128.13, 128.58, 128.61, 131.22, 136.69, 137.83, 156.42, 159.02, 169.82, 170.55; HRMS (FAB) Calcd for C$_{31}$H$_{34}$NO$_8$ [M+H$^+$] 548.2284, found 548.2280.

(2R,3R,4R,5S)-3-Benzoyloxy-1-benzyloxycarbonyl-4,5-diacetoxy-2-(hydroxymethyl)piperidine (19).
To a stirred solution of **18** (0.60 g, 1.096 mmol) in a mixture of H$_2$O/EtOAc/MeCN (2:1:1 v/v/v, 64 mL) was added NaIO$_4$ (4.0 g, 18.63 mmol) and RuCl$_3$ (20 mg, 0.132 mmol). The reaction mixture was stirred for 4 h at rt, quenched with propan-2-ol, and filtered through a Celite pad. The filtrate was concentrated in vacuo. The residual viscous oil was used without purification in the next step. To a stirred solution of crude carboxylic acid (0.48 g) from the previous step in THF (4.0 mL) was slowly added to BH$_3$–THF complex (2.2 mL, 2.192 mol, 1.0 M in THF) at 0 ℃. The reaction mixture was stirred for 24 h at 0 ℃ and quenched with H$_2$O (4 mL). The aqueous layer was extracted with EtOAc (20 mL). The organic layer was washed with H$_2$O and brine, dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 1:1.5) to afford 0.28 g (52%) of **19** as colorless syrup. R_f = 0.28 (hexane/EtOAc 1:1.5); $[\alpha]_D^{22}$ +31.2 (c 0.1, CHCl$_3$); IR (CH$_2$Cl$_2$) 3778, 3705, 2918, 2855, 1736, 1593, 1455, 1378, 1277 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.94 (s, 3H), 2.06 (s, 3H), 3.40 (br t, 1H, J = 14.0 Hz), 4.33 (dt, 2H, J = 7.0, 4.0 Hz), 4.67 (br d, 1H, J = 14.0 Hz), 4.76-4.83 (br, 1H), 5.02-5.21 (m, 3H), 5.30-5.40 (m, 2H), 7.25-7.32 (m, 5H), 7.36-7.43 (br, 2H), 7.55 (t, 1H, J = 7.5 Hz), 7.92-8.03 (br, 2H); ^{13}C

NMR (125 MHz, CDCl$_3$) δ 20.92, 21.04, 42.51, 54.47, 59.98, 65.92, 68.03 (two carbons), 72.26, 128.00, 128.39, 128.72, 128.74, 129.92, 133.44, 136.36, 156.14, 166.78, 170.32, 170.97; HRMS (FAB) Calcd for C$_{25}$H$_{27}$NO$_9$ [M+H$^+$] 486.1764, found 486.1768.

D-1-Deoxynojirimycin (1).

A solution of **19** (0.12 g, 0.246 mmol) in a mixture of 6 N HCl (5 mL) and MeOH (5 mL) was refluxed for 12 h and concentrated in vacuo. The residue was purified by ion-exchange resin DOWEX-50WX8 (H$^+$ form) using 0.5 M aqueous NH$_4$OH as eluent to afford 38 mg (94%) of D-1-deoxynojirimycin (**1**) as white semisolid. R_f = 0.16 (CHCl$_3$/MeOH/30%NH$_4$OH 1:1:0.2); mp 199~201 ℃ (decomp) [lit.,[2f] mp 199~199.5 ℃]; [α]$_D^{25}$ +42.0 (c 0.1, H$_2$O) [lit.,[2f] [α]$_D^{23}$ +40.3 (c 1.47, H$_2$O)]; ^{1}H NMR (500 MHz, D$_2$O) δ 2.61 (t, 1H, J = 12.5 Hz), 2.73 (dt, 1H, J = 8.0, 4.0 Hz), 3.24 (d, 1H, J = 12.5, 5.0 Hz), 3.35 (t, 1H, J = 10.0 Hz), 3.41 (dt, 1H, J = 10.0, 1.5 Hz), 3.57-3.63 (m, 1H), 3.73 (dd, 1H, J = 12.0, 6.0 Hz), 3.90 (dd, 1H, J = 11.5, 3.0 Hz); ^{13}C NMR (125 MHz, D$_2$O) δ 48.33, 60.59, 60.89, 70.34, 71.02, 78.18; HRMS (CI) Calcd for C$_6$H$_{14}$NO$_4$ [M+H$^+$] 164.0923, found 164.0922.

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