HETEROCYCLES, Vol. 74, 2007, pp. 283 - 292. © The Japan Institute of Heterocyclic Chemistry
Received, 24th May, 2007, Accepted, 2nd July, 2007, Published online, 3rd July, 2007. COM-07-S(W)5

PALLADIUM(II)-CATALYZED CYCLIZATION OF URETHANES AND ITS APPLICATION TO A TOTAL SYNTHESIS OF 1-DEOXYNOJIRIMYCIN

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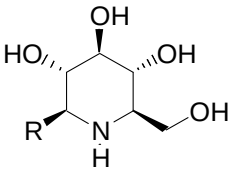
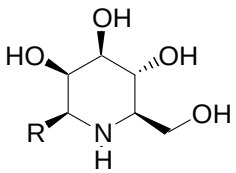
Abstract –We have employed a palladium(II)-catalyzed cyclization of allylic alcohol as a key reaction to achieve a total synthesis of the azasugar 1-deoxynojirimycin from D-mannitol. This reaction should be useful for the stereoselective construction of natural poly-substituted piperidine derivatives.

INTRODUCTION

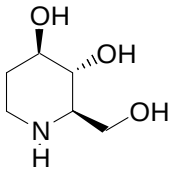
Azasugars inhibit glycosidases, and are useful for studying the action mechanisms of glycosidases, as well as being candidate drugs for treatment of a range of diseases, including cancer, diabetes, AIDS and influenza infection.[1] 1-Deoxynojirimycin (**1**) and related compounds have become synthetic targets on account of their novel structures and promising biological activities.[2-4] An efficient and flexible total synthesis of 1-deoxynojirimycin, which would also provide a ready access to other interesting members of the azasugar series, would be of great value. The C-N bond formation reaction is an important approach to the synthesis of alkaloids, and we therefore examined the synthetic utility of a novel Pd(II)-catalyzed cyclization reaction[5] for this purpose. Herein we describe a total synthesis of the azasugar 1-deoxynojirimycin by using this reaction.



nojirimycin : R=OH
1-deoxynojirimycin **1**: R=H



mannojirimycin : R=OH
1-deoxymannojirimycin **2**: R=H

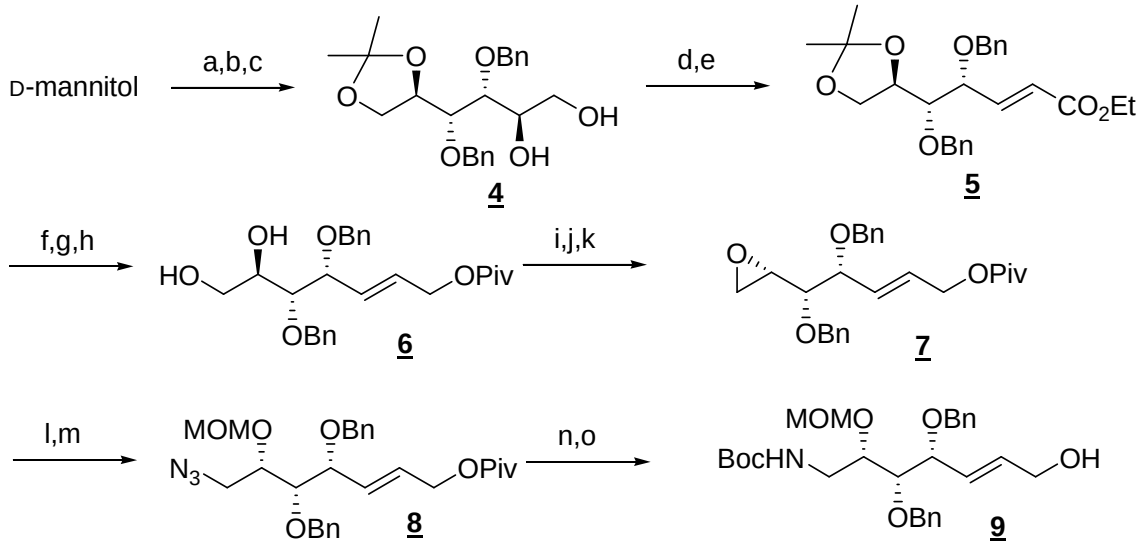


fagomine **3**

This paper is dedicated to Prof. Dr. Ekkehard Winterfeldt on the occasion of his 75th birthday.

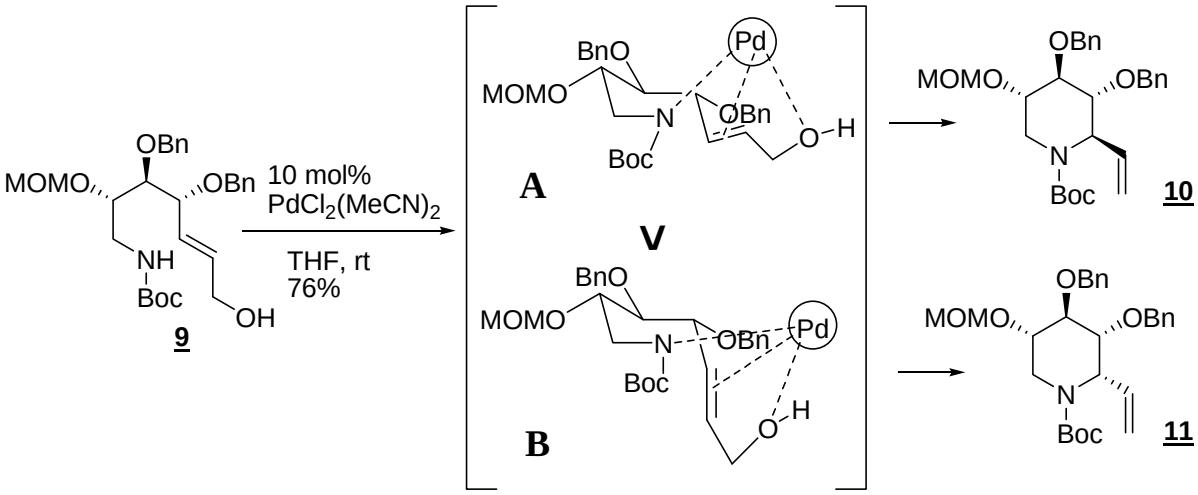
RESULTS AND DISCUSSION

1-Deoxynojirimycin was first prepared by hydrogenation of a streptomyces product, nojirimycin, isolated from mulberries, and is an inhibitor of various glucosidases.[6] The starting material for our synthesis was the diol (**4**), which was readily obtained by using a previously reported procedure.[5] Oxidative cleavage of the diol (**4**) followed by Emmons-Horner Wittig reaction of the resulting aldehyde afforded the ester (**5**). Reduction of **5** with DIBAL and protection of the resulting alcohol moiety with pivaloyl chloride gave the pivaloyl ester, the acetonide of which was removed to provide the diol (**6**) in 83% yield (3 steps). Benzoylation of the primary alcohol of **6**, followed by protection of the remaining secondary alcohol with tosyl chloride, gave the tosylate, which was treated with K_2CO_3 in MeOH to afford the epoxide (**7**). Reaction of **7** with sodium azide in DMF at 55 °C afforded an alcohol, which was transformed to the azide (**8**). The azide (**8**) was reduced with $LiAlH_4$, followed by *N*-(tert-butyloxy)carbonylation of the amino group to afford the key intermediate (**9**).



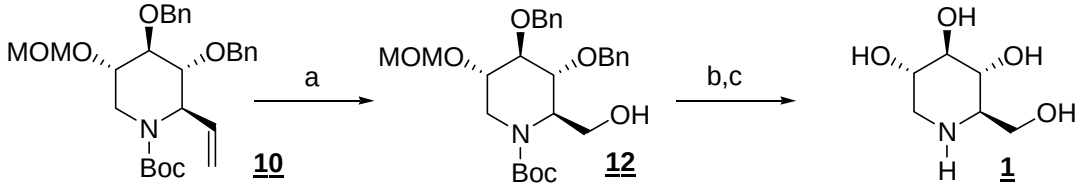
Scheme 1. *Reagents and conditions*: a) acetone, $ZnCl_2$, rt (78%); b) BnBr, NaH, THF, 0°C(84%); c) 60%-AcOH, rt (38%); d) $NaIO_4$, Et_2O-H_2O, 0°C(79%); e) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0°C(89%); f) DIBAL, THF, -78°C(94%); g) PivCl, pyridine, THF, 0°C(93%); h) 10%-HCl aq., THF, 40°C(95%); i) BzCl, pyridine, CH_2Cl_2, rt (78%); j) TsCl, pyridine, CH_2Cl_2, rt (85%); k) K_2CO_3, MeOH, rt (68%); l) NaN_3, NH_4Cl, 15-crown-5, DMF, 55°C (76%); m) MOMCl, $^iPr_2NEt$, rt (99%); n) $LiAlH_4$, Et_2O, 0°C; o) $(Boc)_2O$, Na_2CO_3, CH_2Cl_2, rt (2 steps 75%).

The palladium(II)-catalyzed cyclization of **9** was performed as follows. The key intermediate (**9**) was treated with a catalytic amount (10 mol%) of $PdCl_2(MeCN)_2$ in THF as a solvent at rt under an argon atmosphere to afford a separable mixture of piperidines (**10**) and (**11**) in the ratio of 2:1 (76% yield). It is likely that two chair-form transition state are involved.[5] The transition state **A**, leading to the major product, would be more stable than the transition state **B**, which is subject to steric repulsion between the π-allyl-oxy palladium complex and carbamate moiety.



Scheme 2.

Conversion of **10** into 1-deoxynojirimycin was performed as shown in Scheme 3. Oxidation of the major product (**10**) with ozone, followed by reductive work-up, gave the alcohol (**12**). The Boc group, methoxymethyloxy group and benzyl group of **12** were removed to give 1-deoxynojirimycin. The spectral data of the product were essentially identical with the literature data.[3]



Scheme 3. *Reagents and conditions*: a) O_3, CH_2Cl_2-MeOH, -78°C; $NaBH_4$, -78°C-rt (94%); b) 10%-HCl aq., MeOH, 70°C(90%);c) H_2, Pd/C, conc.HCl, EtOH rt (92%).

SUMMARY

In conclusion, we have achieved a total synthesis of 1-deoxynojirimycin from D-mannitol via a novel Pd(II)-catalyzed cyclization of an allylic alcohol as a key step. This Pd(II)-catalyzed cyclization is expected to be applicable to total syntheses of a variety of azasugars and related compounds.

EXPERIMENTAL

General

^{1}H-NMR spectra were measured with JEOL Model Mac-FX90M (90 MHz) or JEOL Model α-400 (400 MHz) spectrophotometer. Chemical shifts were relative to tetramethylsilane or chloroform (7.26 ppm) as an internal standard. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet) and br (broadened). Infrared spectra (IR) were recorded on a JASCO Model FT/IR-7300 spectrophotometer. List of infrared absorptions were diagnostic. Elemental analyses were performed by micro analytical laboratory of Toyama University (Yanaco CHN corder MT-5). Optical rotations ($[\alpha]_D$) were determined with a JASCO DIP-370 polarimeter.

1,2:5,6-Di-*O*-isopropylidene-D-mannitol.

To a suspension of $ZnCl_2$ (47.0 g, 0.34 mol) in acetone (300 mL) was added D-mannitol (30.0 g, 0.16 mol) at 0 °C under an argon atmosphere and the reaction mixture was stirred at rt for 24 h. After quenching with a solution of K_2CO_3 (47.7 g, 0.35 mol) in water (60 mL) at 0 °C, the resulting mixture was stirred at rt for 1 h. The acetone layer was collected by decantation and the precipitates were extracted with AcOEt (50 mL x 3). The conc. NH_4OH (1.0 mL) was added to acetone layer, and the resulting mixture was concentrated in vacuo. The residue was diluted with water and extracted with AcOEt. The combined AcOEt extracts were washed with water, dried over K_2CO_3 and concentrated in vacuo. The resulting precipitates were recrystallized from AcOEt to afford 1,2:5,6-di-*O*-isopropylidene-D-mannitol (33.7 g, 78%) as colorless needles (mp 119.5 – 121 °C; Lit. mp 119 - 121°C). $[\alpha]^{25}_D$ 2.4 ° (c 1.00, EtOH); Lit$[\alpha]^{23}_D$ 1.8 ° (c 1.5, MeOH); ^{1}H NMR (400MHz, $CDCl_3$) δ : 4.24-4.15 (m, 2H), 4.12 (dd, *J* = 6.4, 8.5 Hz, 2H), 3.98 (dd, *J* = 5.6, 8.5 Hz, 2H), 3.78-3.73 (brt, 2H), 2.57 (d, *J* = 6.6 Hz, 2H), 1.42 (s, 6H), 1.36 (s, 6H); IR (neat) 3314 cm^{-1}; Anal. Calcd for $C_{12}H_{22}O_6$: C, 54.95; H, 8.45. Found: C, 54.79; H, 8.51.

3,4-Di-*O*-benzyl-1,2:5,6-di-*O*-isopropylidene-D-mannitol.

To a suspension of NaH (4.12 g, 60% in mineral oil, 0.10 mol) in THF (170 mL) was added 1,2:5,6-di-*O*-isopropylidene-D-mannitol (8.89 g, 33.9 mmol) at 0 °C under an argon atmosphere and the reaction mixture was stirred for 2 h at same temperature. The benzyl bromide (9.5 mL, 79.7 mmol) and tetrabutylammonium iodide (4.0 mg, 0.01 mmol) were added to the mixture at 0 °C. The resulting mixture was stirred at rt for 6 h, then quenched with ice and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography to afford 3,4-di-*O*-benzyl-1,2:5,6-di-*O*-isopropylidene-D-mannitol (12.6 g, 84%) as an yellow oil. $[\alpha]^{27}_D$ 37.7 ° (c 1.08, $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$) δ : 7.33-7.30 (m, 10H), 4.70 (s, 4H), 4.24 (brq, 2H), 4.00 (dd, *J* = 6.3, 8.5 Hz, 2H), 3.85 (dd, *J* = 6.3, 8.5 Hz, 2H), 3.79 (d, *J* = 5.4 Hz, 2H), 1.41 (s, 6H), 1.33 (s, 6H); IR (neat) 1072 cm^{-1}; Anal. Calcd for $C_{26}H_{34}O_6$: C, 70.56; H, 7.74. Found: C, 70.30; H, 7.89.

3,4-Di-*O*-benzyl-5,6-*O*-isopropylidene-D-mannitol. (4)

A solution of 3,4-di-*O*-benzyl-1,2:5,6-di-*O*-isopropylidene-D-mannitol (2.22 g, 5.0 mmol) in 60% acetic acid was stirred at rt for 3.5 h. The reaction mixture was diluted with AcOEt and neutralized with $NaHCO_3$. The sluggish mixture was filtered and the filtrate was extracted with AcOEt (200 mL x 3). The combined organic layers were washed with $NaHCO_3$, 5% NaOH aq. and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed by silica gel column to give 3,4-di-*O*-benzyl-5,6-*O*-isopropylidene-D-mannitol (761 mg, 38%)(eluent; hexane : AcOEt = 4 : 1) as a colorless oil and starting material (400 mg). $[\alpha]^{31}_D$ 24.3 ° (c 1.06, CH_2Cl_2); Lit$[\alpha]^{25}_D$ 24.8 ° (c 1.0, $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$) δ : 7.36-7.25 (m, 10H), 4.75 (d, *J* = 11.5 Hz, 1H), 4.70 (d, *J* = 11.5 Hz, 1H), 4.65 (d, *J* = 11.2 Hz, 1H), 4.60 (d, *J* = 11.2 Hz, 1H), 4.30 (dt, *J* = 5.9, 6.3 Hz, 1H), 4.05 (dd, *J* = 6.3, 8.3 Hz, 1H), 3.96-3.92 (m, 2H), 3.80 (ddd, *J* = 3.4, 4.6, 7.8 Hz, 1H), 3.72 (dd, *J* = 3.4, 11.5 Hz, 1H), 3.66-3.61 (m, 2H), 1.44 (s, 3H), 1.34 (s, 3H); IR (neat) 3445 cm^{-1}.

(2*S*,3*R*,4*R*)-2,3-Dibenzyloxy-4,5-isopropylidenedioxypentanal.

To a solution of $NaIO_4$ (4.79g, 22.4 mmol) in water (45 mL) was added a solution of 3,4-di-*O*-benzyl-5,6-*O*-isopropylidene-D-mannitol (6.17 g, 15.3 mmol) in Et_2O (3 mL) at 0 °C and the reaction mixture was stirred at rt for 2.5 h. The reaction mixture was extracted with AcOEt (10 mL x 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; hexane : AcOEt = 4 : 1) to afford (2*S*,3*R*,4*R*)-2,3-dibenzyloxy-4,5-isopropylidenedioxypentanal (4.51 g, 79%) as a colorless oil. $[\alpha]^{26}_D$ 7.96 ° (c 1.06,

CH_2Cl_2); ^{1}H NMR (400MHz, acetone-d_6) δ : 9.81 (d, *J* = 1.0 Hz, 1H), 7.45-7.27 (m, 10H), 4.82 (d, *J* = 11.7 Hz, 1H), 4.66 (d, *J* = 11.2 Hz, 1H), 4.61 (d, *J* = 11.7 Hz, 1H), 4.55 (d, *J* = 11.2 Hz, 1H), 4.31 (brq, 1H), 4.20 (dd, *J* = 1.0, 3.2 Hz, 1H), 4.13 (dd, *J* = 3.2, 5.9 Hz, 1H), 4.05 (dd, *J* = 6.3, 8.3 Hz, 1H), 3.99 (dd, *J* = 6.3, 8.3 Hz, 1H), 1.37 (s, 3H), 1.29 (s, 3H); IR (neat) 1732 cm^{-1}; Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.07. Found: C, 71.05; H, 7.33.

Ethyl (4*R*,5*R*,6*R*)-4,5-dibenzyloxy-6,7-isopropylidenedioxy-2-heptenoate. (5)

To a suspension of NaH (0.12 g, 60% in mineral oil, 3.0 mmol) in THF (20 mL) was added diethyl ethoxycarbonylmethylphosphonate (0.7 mL, 3.5 mmol) at 0 °C under an argon atmosphere and the mixture was stirred at same temperature for 45 min. A solution of (2*S*,3*R*,4*R*)-2,3-dibenzyloxy-4,5-isopropylidenedioxypentanal (1.0 g, 2.7 mmol) in THF (7.0 mL) was added to the mixture at -78 °C and the reaction mixture was warmed to -20 °C over 3 h. The reaction mixture was quenched with water and extracted with AcOEt (20 mL x 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; hexane : AcOEt = 9 : 1) to afford ethyl (4*R*,5*R*,6*R*)-4,5-dibenzyloxy-6,7-isopropylidenedioxy-2-heptenoate (1.06 g, 89%) as a colorless oil. $[\alpha]^{31}_D$ -2.33 ° (c 1.03, CH_2Cl_2); ^{1}H NMR (400MHz, acetone-d_6) δ : 7.40-7.25 (m, 10H), 7.00 (dd, *J* = 5.9, 15.9 Hz, 1H), 6.13 (dd, *J* = 1.5, 15.9 Hz, 1H), 4.74 (d, *J* = 11.2 Hz, 1H), 4.67 (d, *J* = 11.2 Hz, 1H), 4.62 (d, *J* = 11.7 Hz, 1H), 4.50 (d, *J* = 11.7 Hz, 1H), 4.34 (ddd, *J* = 1.5, 4.2, 5.9 Hz, 1H), 4.29 (dt, *J* = 4.2, 6.6 Hz, 1H), 4.18 (dq, *J* = 11.0, 7.3 Hz, 1H), 4.17 (dq, *J* = 11.0, 7.3 Hz, 1H), 3.94 (dd, *J* = 1.5, 6.6 Hz, 2H), 3.90 (t, *J* = 4.2 Hz, 1H), 1.37 (s, 3H), 1.28 (s, 3H), 1.26 (t, *J* = 7.3 Hz, 3H); IR (neat) 1715, 1658 cm^{-1}; Anal. Calcd for $C_{26}H_{32}O_6$: C, 70.89; H, 7.32. Found: C, 71.09; H, 7.57.

(4*R*,5*R*,6*R*)-4,5-Dibenzyloxy-6,7-isopropylidenedioxy-2-hepten-1-ol.

To a solution of ethyl (4*R*,5*R*,6*R*)-4,5-dibenzyloxy-6,7-isopropylidenedioxy-2-heptenoate (1.02 g, 2.3 mmol) in THF (20 mL) was added diisobutylaluminum hydride (0.95M n-Hexane solution) (7.3 mL, 6.9 mmol) at -78 °C under an argon atmosphere. The reaction mixture was warmed to -20 °C for 4 h. The reaction mixture was diluted with Et_2O and quenched with saturated aqueous Na_2SO_4 at 0 °C and stirred at rt for 20 min. The mixture was dried over Na_2SO_4 and filtered through Celite. The filtrate was concentrated in vacuo and the residue was purified by silica gel column chromatography (eluent; hexane : AcOEt = 4 : 1) to afford (4*R*,5*R*,6*R*)-4,5-dibenzyloxy-6,7-isopropylidenedioxy-2-hepten-1-ol (0.87 g, 94%) as a colorless oil. $[\alpha]^{31}_D$ -5.86 ° (c 0.99, CH_2Cl_2); ^{1}H NMR (400MHz, $CDCl_3$) δ : 7.35-7.25 (m, 10H), 5.83 (dt, *J* = 5.1, 15.6 Hz, 1H), 5.67 (dd, *J* = 7.6, 15.6 Hz, 1H), 4.77 (d, *J* = 11.5 Hz, 1H), 4.66 (d, *J* = 11.5 Hz, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 4.36 (d, *J* = 12.0 Hz, 1H), 4.23 (dt, *J* = 3.9, 7.1 Hz, 1H), 4.10 (d, *J* = 5.1 Hz, 2H), 3.98 (d, *J* = 7.1 Hz, 2H), 3.90 (dd, *J* = 3.9, 7.6 Hz, 1H), 3.74 (t, *J* = 3.9 Hz, 1H), 1.41 (s, 3H), 1.34 (s, 3H); IR (neat) 3442cm^{-1}; Anal. Calcd for $C_{24}H_{30}O_5$: C, 72.34; H, 7.59. Found: C, 72.08; H, 7.74.

(4*R*,5*R*,6*R*)-4,5-Dibenzyloxy-6,7-isopropylidenedioxy-1-pivaloyloxy-2-heptene.

To a solution of (4*R*,5*R*,6*R*)-4,5-dibenzyloxy-6,7-isopropylidenedioxy-2-hepten-1-ol (1.44 g, 3.6 mmol) in pyridine (3.6 mL) and THF (3.6 mL) was added pivaloyl chloride (0.6 mL, 0.59 g, 4.9 mmol) at 0 °C under an argon atmosphere and the mixture was stirred at rt for 2.5 h. The reaction mixture was diluted with AcOEt and quenched with ice. The organic layer was washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent; hexane : AcOEt = 9 : 1) to afford (4*R*,5*R*,6*R*)-4,5-dibenzyloxy-6,7-isopropylidenedioxy -1-pivaloyloxy-2-heptene (1.63 g, 93 %) as a colorless oil. $[\alpha]^{29}_D$ -2.26 ° (c 0.93, CH_2Cl_2); ^{1}H NMR (400MHz, $CDCl_3$) δ : 7.36-7.24 (m, 10H), 5.81 (dt, *J* = 4.4, 15.6 Hz, 1H), 5.76 (dd, *J*

= 5.6, 15.6 Hz, 1H), 4.74 (d, *J* = 11.5 Hz, 1H), 4.67 (d, *J* = 11.5 Hz, 1H), 4.61-4.54 (m, 3H), 4.36 (d, *J* = 12.0 Hz, 1H), 4.23 (dt, *J* = 3.9, 7.0 Hz, 1H), 3.98-3.90 (m, 3H), 3.74 (t, *J* = 3.9 Hz, 1H), 1.43 (s, 3H), 1.37 (s, 3H), 1.21 (s, 9H); IR (neat) 1731 cm^{-1}; Anal. Calcd for $C_{29}H_{38}O_6$: C, 72.17; H, 7.94. Found: C, 71.94; H, 8.17.

(2*R*,3*R*,4*R*)-3,4-Dibenzyloxy-7-pivaloyloxy-5-heptene-1,2-diol. (6)

To a solution of (4*R*,5*R*,6*R*)-4,5-dibenzyloxy-6,7-isopropylidenedioxy-1-pivaloyloxy-2-heptene (0.55 g, 1.1 mmol) in THF (10 mL) was added 10% aqueous HCl (2 mL). The solution was stirred at 40 °C for 5 h. The reaction mixture was diluted with water and extracted with AcOEt (10 mL x 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; hexane : AcOEt = 3 : 2) to afford (2*R*,3*R*,4*R*)-3,4-dibenzyloxy-7- pivaloyloxy-5-heptene-1,2-diol (0.48 g, 95%) as a colorless oil. $[\alpha]^{29}_D$ -7.61 ° (c 1.03, $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$) δ : 7.38-7.26 (m, 10H), 5.92-5.80 (m, 2H), 4.66-4.59 (m, 5H), 4.38 (d, *J* = 11.7 Hz, 1H), 4.13 (t, *J* = 4.6 Hz, 1H), 3.80 (ddd, *J* = 3.7, 4.4, 7.3 Hz, 1H), 3.70 (dd, *J* = 3.7, 11.5 Hz, 1H), 3.65 (dd, *J* = 4.4, 11.5 Hz, 1H), 3.63 (dd, *J* = 4.6, 7.3 Hz, 1H), 2.60-2.20 (brs, 2H), 1.22 (s, 9H); IR (neat) 3445, 1729 cm^{-1}.

(2*R*,3*R*,4*R*)-3,4-Dibenzyloxy-7-pivaloyloxy-1-benzoyloxy-5-hepten-2-ol.

To a solution of (2*R*,3*R*,4*R*)-3,4-dibenzyloxy-7-pivaloyloxy-5-heptene-1,2-diol (1.75 g, 3.95 mmol) in pyridine (0.6 mL) and CH_2Cl_2 (20 mL) was added benzoyl chloride (0.5 mL, 4.34 mmol) at 0 °C under an argon atmosphere and the mixture was stirred at rt for 1.5 h. The reaction mixture was diluted with $CHCl_3$ and quenched with 10% aqueous HCl. The aqueous layer was extracted with $CHCl_3$ (5 mL x 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 chromatographed by silica gel column to give (2*R*,3*R*,4*R*)-3,4-dibenzyloxy-7-pivaloyloxy-1-benzoyloxy-5-hepten-2-ol (1.68 g, 78%) (eluent; hexane : AcOEt = 4 : 1) as a colorless oil. $[\alpha]^{28}_D$ 4.07 ° (c 2.15, $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$) δ : 8.01 (dd, *J* = 1.3, 7.3 Hz, 2H), 7.56 (dt, *J* = 1.3, 7.3 Hz, 1H), 7.43 (t, *J* = 7.3 Hz, 2H), 7.39-7.19 (m, 10H), 5.97-5.83 (m, 2H), 4.67 (d, *J* = 11.8 Hz, 1H), 4.66 (d, *J* = 11.3 Hz, 1H), 4.62 (d, *J* = 2.4 Hz, 2H), 4.58 (d, *J* = 11.3 Hz, 1H), 4.52 (dd, *J* = 2.8, 11.7 Hz, 1H), 4.40 (d, *J* = 11.8 Hz, 1H), 4.39 (dd, *J* = 5.5, 11.7 Hz, 1H), 4.21 (dd, *J* = 4.1, 6.1 Hz, 1H), 4.12 (ddd, *J* = 2.8, 5.5, 7.1 Hz, 1H), 3.65 (dd, *J* = 4.1, 7.1 Hz, 1H), 1.21 (s, 9H); IR (neat) 3503, 1723 cm^{-1}; Anal. Calcd for $C_{33}H_{38}O_7$: C, 72.51; H, 7.01. Found: C, 72.40; H, 7.09.

(4*R*,5*R*,6*R*)-6-Tosyloxy-7-benzoyloxy-4,5-dibenzyloxy-1-pivaloyloxy-2-heptene.

To a solution of (2*R*,3*R*,4*R*)-3,4-dibenzyloxy-7-pivaloyloxy-1-benzoyloxy-5-hepten-2-ol (8.15 g, 14.9 mmol) in pyridine (3.0 mL) and CH_2Cl_2 (15 mL) was added p-toluenesulfonyl chloride (3.41 g, 17.9 mmol) and 4-dimethylaminopyridine (0.18 g, 1.49 mmol) at 0 °C under an argon atmosphere and the reaction mixture was stirred at rt for 3 day. The mixture was quenched with ice and extracted with $CHCl_3$. The combined organic layers were washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent; hexane : AcOEt = 9 : 1) to afford (4*R*,5*R*,6*R*)-6-Tosyloxy-7-benzoyloxy-4,5-dibenzyloxy-1-pivaloyloxy-2-heptene (8.85 g, 85%) as a white crystal. $[\alpha]^{27}_D$ 14.6 ° (c 2.20, $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$) δ : 7.80 (d, *J* = 7.5 Hz, 2H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.35-7.21 (m, 10H), 7.02 (d, *J* = 8.3 Hz, 2H), 5.89 (dt, *J* = 5.1, 15.8 Hz, 1H), 5.76 (dd, *J* = 6.8, 15.8 Hz, 1H), 4.92 (m, 1H), 4.78 (d, *J* = 11.5 Hz, 1H), 4.72 (d, *J* = 11.5 Hz, 1H), 4.67 (dd, *J* = 1.4, 12.8 Hz, 1H), 4.60 (d, *J* = 5.1 Hz, 1H), 4.59 (d, *J* = 12.0 Hz, 2H), 4.46 (dd, *J* = 8.4, 12.8 Hz, 1H), 4.40 (dd, *J* = 12.0 Hz, 1H), 4.05-3.92 (m, 2H), 2.22 (s, 3H), 1.21 (s, 9H); IR(neat): 1715 cm^{-1}; Anal. Calcd for $C_{40}H_{44}O_9S$: C, 68.55; H, 6.33. Found: C, 68.16; H, 6.43.

(4*R*,5*R*,6*S*)-6,7-Epoxy-4,5-dibenzyloxy-1-pivaloyloxy-2-heptene. (7)

To a solution of (4*R*,5*R*,6*R*)-6-tosyloxy-7-benzoyloxy-4,5-dibenzyloxy-1-pivaloyloxy-2-heptene (8.85 g, 12.6 mmol) in MeOH (120 mL) was added K_2CO_3 (2.10 g, 15.2 mmol) at 0 ^oC under an argon atmosphere, and the reaction mixture was stirred at rt for 2.5 h. The mixture was diluted with ether, and filtered through Celite. The filtrate was concentrated in vacuo. The residue was purified by silica gel chromatography (eluent; hexane : AcOEt = 85 : 15) to afford (4*R*,5*R*,6*S*)-6,7-epoxy-4,5-dibenzyloxy-1-pivaloyloxy -2-heptene (3.63 g, 68%) as a colorless oil. $[\alpha]^{27}_D$ -34.2 ° (c 1.00, $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$) δ : 7.38-7.21 (m, 10H), 5.89-5.77 (m, 2H), 4.83 (d, *J* = 11.9 Hz, 1H), 4.66 (d, *J* = 11.9 Hz, 1H), 4.64 (d, *J* = 12.2 Hz, 1H), 4.60 (d, *J* = 3.2 Hz, 2H), 4.39 (d, *J* = 12.2 Hz, 1H), 3.98 (m, 1H), 3.21-3.07 (m, 2H), 2.69 (t, *J* = 4.5 Hz, 1H), 2.51 (dd, *J* = 1.9, 4.5 Hz, 1H), 1.22 (s, 9H); IR (neat) 1731 cm^{-1}; Anal. Calcd for $C_{26}H_{32}O_5$: C, 73.56; H, 7.60. Found: C, 73.52; H, 7.85.

(2*S*,3*R*,4*R*)-1-Azido-3,4-dibenzyloxy-7-pivaloyloxy-5-heptene-2-ol.

To a solution of (4*S*,5*R*,6*S*)-6,7-epoxy-4,5-dibenzyloxy-1-pivaloyloxy-2-heptene (0.50 g, 1.18 mmol) in DMF (6.0 mL) was added NaN_3 (0.23 g, 3.54 mmol), NH_4Cl (0.19 g, 3.54 mmol) and 15-crown-5 (0.025 mL, 0.12 mmol) at rt under an argon atmosphere, and the mixture was stirred at 55 °C for 9 h. The suspension was diluted with ether and washed with water. The aqueous layer was extracted with ether and 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; hexane : AcOEt = 4 : 1) to afford (2*S*,3*R*,4*R*)-1-azido-3,4-dibenzyloxy-7-pivaloyloxy-5-heptene-2-ol (0.42 g, 76 %) as a colorless oil. $[\alpha]^{29}_D$ -9.04 ° (c 1.35, $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$) δ : 7.40-7.24 (m, 10H), 5.89 (dt, *J* = 5.3, 15.6 Hz, 1H), 5.77 (ddt, *J* = 1.3, 7.3, 15.6 Hz, 1H), 4.85 (d, *J* = 11.3 Hz, 1H), 4.63 (d, *J* = 11.6 Hz, 1H), 4.61 (d, *J* = 5.3 Hz, 2H), 4.59 (d, *J* = 11.3, Hz, 1H), 4.39 (d, *J* = 11.6 Hz, 1H), 4.11 (dd, *J* = 5.9, 7.3 Hz, 1H), 3.82 (dddd, *J* = 3.4, 5.4, 5.9, 6.6, 6.7 Hz, 1H), 3.49 (dd, *J* = 3.4, 5.9 Hz, 1H), 3.29 (dd, *J* = 6.7, 12.5 Hz, 1H), 3.18 (dd, *J* = 5.4, 12.5 Hz, 1H), 2.50 (d, *J* = 6.6 Hz, 1H), 1.22 (s, 9H); IR (neat): 3477, 2102, 1728 cm^{-1}; Anal. Calcd for $C_{26}H_{33}N_3O_5$: C, 66.79; H, 7.11; N, 8.99. Found: C, 66.53; H, 7.23; N, 8.69.

(4*R*,5*R*,6*S*)-7-Azido-4,5-dibenzyloxy-6-methoxymethyloxy-1-pivaloyloxy-2-heptene. (8)

(2*S*,3*R*,4*R*)-1-azido-3,4-dibenzyloxy-7-pivaloyloxy-5-heptene-2-ol (0.40 g. 0.86 mmol) in ethyldiisopropylamine (0.23 mL, 1.30 mmol) was added chloromethyl methyl ether (0.10 mL, 1.30 mmol) at 0 °C under an argon atmosphere, and the mixture was stirred at rt for 18.5 h. The reaction mixture was diluted with AcOEt and quenched with ice. The aqueous layer was extracted with AcOEt (5 mL x 3). The combined organic layers were washed with 10 % aqueous HCl, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent; hexane : AcOEt = 9 :1) to afford (4*R*,5*R*,6*S*)-7-Azido-4,5-dibenzyloxy-6-methoxymethyloxy-1-pivaloyloxy-2-heptene (0.44 g, 99%) as a colorless oil. $[\alpha]^{29}_D$ -47.4 ° (c 1.05, $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$) δ : 7.38-7.22 (m, 10H), 5.84 (dt, *J* = 5.0, 15.7 Hz, 1H), 5.77 (dd, *J* = 6.6, 15.7 Hz, 1H), 4.73 (d, *J* = 11.5 Hz, 1H), 4.70 (d, *J* = 6.9 Hz, 1H), 4.67 (d, *J* = 11.5 Hz, 1H), 4.66 (d, *J* = 6.9 Hz, 1H), 4.60 (d, *J* = 11.7 Hz, 1H), 4.57 (d, *J* = 5.0 Hz, 2H), 4.35 (d, *J* = 11.7 Hz, 1H), 4.03 (dd, *J* = 5.1, 6.6 Hz, 1H), 3.78 (br q, *J* = 5.2 Hz, 1H), 3.58 (t, *J* = 5.1 Hz, 1H), 3.45 (dd, *J* = 4.8, 12.9 Hz, 1H), 3.35 (s, 3H), 3.28 (dd, *J* = 5.6, 12.9 Hz, 1H), 1.22 (s, 9H); IR (neat) 2101, 1731 cm^{-1}.

(4*R*,5*R*,6*S*)-4,5-Dibenzyloxy-7-[*N*-(tert-butoxycarbonyl)amino]-6-methoxymethyloxy-2-heptene-1-ol. (9)

To a solution of (4*R*,5*R*,6*S*)-7-azido-4,5-dibenzyloxy-6-methoxymethyloxy-1-pivaloyloxy-2-heptene (2.02 g, 3.84 mmol) in Et_2O was added lithium aluminum hydride (0.44 g, 11.5 mmol) at 0 °C under an argon atmosphere and the mixture was stirred at the same temperature for 4 h. The reaction mixture was

quenched with saturated aqueous Na_2SO_4 at 0 °C, and dried over Na_2SO_4 for 1 h at rt. The suspension was filtered through Celite. The filtrate was concentrated in vacuo. Then to a solution of the residue (1.43 g, 3.55 mmol) in CH_2Cl_2 (20 mL) was added di-tert-butyl dicarbonate (1.3 mL, 5.33 mmol) and Na_2CO_3 (0.57 g, 5.33 mmol) at rt under an argon atmosphere, and the mixture was stirred at the same temperature for 1.5 h. The reaction mixture was quenched with 10 % aqueous HCl at 0 °C and extracted with Et_2O (20 mL x 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; hexane : AcOEt = 55 : 45) to afford (4*R*,5*R*,6*S*)-4,5-dibenzyloxy-7-[*N*-(tert-butoxycarbonyl)-amino]-6-methoxymethyloxy-2-heptene-1-ol (1.60 g, 2 steps 75%) as a colorless oil. $[\alpha]^{25}_D$ -23.2 ° (c 1.35, $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$) δ : 7.39-7.29 (m, 10H), 5.92 (dt, *J* = 5.1, 15.6 Hz, 1H), 5.69 (dd, *J* = 7.3, 15.6 Hz, 1H), 4.82 (m, 1H), 4.77-4.64 (m, 4H), 4.61 (d, *J* = 11.7 Hz, 1H), 4.41 (d, *J* = 11.7 Hz, 1H), 4.17-4.07 (m, 3H), 3.74 (q, *J* = 5.3 Hz, 1H), 3.47 (t, *J* = 5.3 Hz, 1H), 3.41-3.25 (m, 1H), 3.36 (s, 3H), 3.13 (dt, *J* = 5.9, 13.9 Hz, 1H), 1.95 (s, 1H), 1.41 (s, 9H); IR (neat) 3429, 3361, 1713 cm^{-1}; Anal. Calcd for $C_{28}H_{39}NO_7$: C, 67.04; H, 7.84; N, 2.79. Found: C, 66.65; H, 8.16; N, 2.90.

(2*R*,3*R*,4*R*,5*S*)-3,4-Dibenzyloxy-*N*-tert-butoxycarbonyl-5-methoxymethyloxy-2-vinylpiperidine.
To a solution of (4*R*,5*R*,6*S*)-4,5-dibenzyloxy-7-[*N*-(tert-butoxycarbonyl)amino]-6-methoxymethyloxy-2-heptene-1-ol (0.93 g, 1.86 mmol) in THF(37 mL) was added $PdCl_2(CH_3CN)_2$ (0.04g, 0.186mmol) at 0 °C under an argon atmosphere, and the mixture was stirred at rt for 10.5 h. The reaction mixture was diluted with Et_2O. The mixture was filtered through Celite. The filtrate was 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; hexane : AcOEt = 85 : 15) to afford (2*R*,3*R*,4*R*,5S)-3,4-Dibenzyloxy-*N*-tert-butoxycarbonyl-5-methoxymethyloxy-2-vinylpiperidine (0.47g, 51%) as a colorless oil and (*2S*)-diastereomer (0.23 g, 25%) as a colorless oil.

(2*R*,3*R*,4*R*,5*S*)-3,4-Dibenzyloxy-*N*-tert-butoxycarbonyl-5-methoxymethyloxy-2-vinylpiperidine. (10) $[\alpha]^{28}_D$ 13.0 ° (c 1.30, $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$) δ : 7.39-7.21 (m, 10H), 5.95-5.80(m, 1H), 5.20-5.10(m, 2H), 4.80-4.60(m, 7H), 3.87 (ddd, *J* = 3.9, 5.3, 5.4 Hz, 1H), 3.77 (dd, *J* = 5.4, 13.7 Hz, 1H), 3.65 (brdt, *J* = 5.0 Hz, 1H), 3.55 (brdt, *J* = 4.5 Hz, 1H), 3.40 (dd, *J* = 3.9, 13.7 Hz, 1H), 3.37 (s, 3H), 1.44 (s, 9H); IR (neat)1694cm^{-1}; Anal. Calcd for $C_{28}H_{37}NO_6$: C, 69.54; H, 7.71; N, 2.90. Found: C, 69.36; H, 7.94; N, 2.97.

(2*S*)-Diastereomer. (11) ^{1}H NMR (400MHz, $CDCl_3$) δ : 7.41-7.31 (m, 10H), 6.15-6.05(m, 1H), 5.41-5.28(m, 1H), 5.27-5.08(m, 1H), 4.95-4.56(m, 6H), 4.31-4.02(m, 1H), 3.63-3.46(m, 3H), 3.36 (s, 3H), 2.95-2.70(m, 1H), 1.54-1.34 (m, 9H).

(2*R*,3*R*,4*R*,5*S*)-(3,4-Dibenzyloxy-*N*-tert-butoxycarbonyl-5-methoxymethyloxy-2-piperidinyl)methanol. (12)
A gas of O_3 in O_2 was bubbled into a solution of (2*R*,3*R*,4*R*,5*S*)-3,4-dibenzyloxy-*N*-tert-butoxycarbonyl-5-methoxymethyloxy-2-vinylpiperidine (0.37 g. 0.77 mmol) in CH_2Cl_2-MeOH (4 : 1, 10 mL) at -78 °C until the solution was turned to blue. Then an argon gas was bubbled through the solution until its color was cleared. To the reaction was added $NaBH_4$ (0.23 mg, 6.13 mmol) at -78 °C and mixture was warmed slowly to the rt, and stirred for additional 5.5 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$. 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; hexane : AcOEt = 7 : 3) to afford (2*R*,3*R*,4*R*,5*S*)-(3,4-Dibenzyloxy-*N*-tert-butoxycarbonyl-5-methoxymethyloxy-2-piperidinyl)methanol (0.35 g, 94 %) as a colorless oil.

$[\alpha]^{25}_{D}$ -26.0 ° (c 0.95, $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$) δ : 7.37-7.24 (m, 10H), 4.78-4.64 (m, 6H), 3.87 (d, *J* = 4.1 Hz, 2H), 3.78-3.59 (m, 5H), 3.40-3.24 (m, 4H), 1.46 (s, 9H); IR (neat) 3446, 1694cm^{-1}; Anal. Calcd for $C_{27}H_{37}NO_7$: C, 66.51; H, 7.65; N, 2.87. Found: C, 66.22; H, 7.74; N, 2.92.

(2*R*,3*R*,4*R*,5*S*)-(3,4-Dibenzyloxy-*N*-tert-butoxycarbonyl-5-hydroxy-2-piperidinyl)methanol.
To a solution of (2*R*,3*R*,4*R*,5*S*)-(3,4-Dibenzyloxy-*N*-tert-butoxycarbonyl-5-methoxymethyloxy-2-piperidinyl)methanol (0.25 g. 0.508 mmol) in MeOH (5.0 mL) was added 10% aqueous HCl (5.0 mL) at rt, and the reaction mixture was stirred at 70 °C for 20 h. The mixture was concentrated in vacuo. The resulting precipitates were recrystallized from acetone to afford (2*R*,3*R*,4*R*,5*S*)-(3,4-Dibenzyloxy-*N*-tert-butoxycarbonyl-5-hydroxy-2-piperidinyl)methanol (0.16 g, 90%) as a white needles (mp 171-174 °C). $[\alpha]^{26}_{D}$ 6.32 ° (c 0.25, H_2O); ^{1}H NMR (400 MHz, D_2O) δ : 7.35-7.19 (m, 10H), 4.82 (d, *J* = 11.1 Hz, 1H), 4.71 (d, *J* = 11.1 Hz, 1H), 4.66 (d, *J* = 10.5 Hz, 1H), 4.57 (d, *J* = 10.5 Hz, 1H), 3.90-3.70 (m, 3H), 3.70-3.50 (m, 2H), 3.39 (dd, *J* = 5.1, 12.2 Hz, 1H), 3.16 (ddd, *J* = 3.0, 5.3, 9.3 Hz, 1H), 2.87 (t, *J* = 12.2 Hz, 1H); IR (KBr) 3490, 3397 cm^{-1}.

1-Deoxynojirimycin(1,5-dideoxy-1,5-imino-D-glucitol).(1)
To a solution of the (2*R*,3*R*,4*R*,5*S*)-(3,4-Dibenzyloxy-*N*-tert-butoxycarbonyl-5-hydroxy-2-piperidinyl)-methanol (0.054 g, 0.155 mmol) in EtOH (1.5 mL) was added conc. HCl (1.5 mL) and 10% Palladium on actived carbon (0.155 g) at rt, and the mixture was stirred under H_2 gas atmosphere at same temperature for 2 days. The reaction mixture was filtered through Celite and the filtrate was concentrated in vacuo. The residue was dissolved in water, and stirred with Dowex 50w-X8 (H+ form) ion-exchange for 5 h. The suspension was eluted with water then 1N NH_4OH, so gave 1-deoxynojirimycin(1,5-dideoxy-1,5-imino-D-glucitol) (23 mg, 92%) as a white crystal. ^{1}H NMR (400MHz, D_2O) δ : 3.70 (dd, *J* = 2.9, 11.7 Hz, 1H), 3.50 (dd, *J* = 6.2, 11.7 Hz, 1H), 3.36 (ddd, *J* = 5.1, 9.0, 10.9 Hz, 1H), 3.19 (t, *J* = 9.2 Hz, 1H), 3.10 (t, *J* = 9.4 Hz, 1H), 2.99 (dd, *J* = 5.1, 12.2 Hz, 1H), 2.42 (ddd, *J* = 2.9, 6.2, 9.8 Hz, 1H), 2.35(dd, *J* = 10.9, 12.2 Hz, 1H).

ACKNOWLEDGEMENTS

We are grateful to Prof. C. Kibayashi, Tokyo University of Pharmacy and life Science, for kindly providing us with NMR data of the 1-deoxynojirimycin. This work was supported by Grant-in Aid for Scientific Research on Priority Areas (18032032) from The Ministry of Education, Culture, Sports, Science and Technology (MEXT).

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