Asymmetric total synthesis of L-*allo*-1-deoxynojirimycin

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Dedicated to Dr. J. S. Yadav on the occasion of his 65th birthday

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Abstract

Asymmetric total synthesis of L-*allo*-1-deoxynojirimycin (L-*allo*-DNJ) was achieved from *cis*-butene-1,4-diol by employing Sharpless asymmetric dihydroxylation, stereoselective flash dihydroxylation and ring enlargement reactions as key steps.

Keywords: Sharpless asymmetric dihydroxylation, diastereoselective flash dihydroxylation, ring-enlargement reaction

Introduction

Polyhydroxypiperidine alkaloids (commonly called azasugars or iminosugars) have gained great deal of attention mainly due to their structural features and biological properties.[1-6] This class of compounds has ability to inhibit the carbohydrate-processing enzymes glycosidases and glycosyl transferases.[7-8] Iminosugars have tremendous potential in the treatment of prominent diseases, such as cancer,[9-11] diabetes,[12-15] AIDS[16-17] and viral infections.[18] Recently, 1-deoxynojirimycin (DNJ) **1** (Figure 1) derivatives such as miglitol **2** (Figure 1) and *N*-butyl-1-deoxynojirimycin **3** (Figure 1) have been used for the treatment of type II diabetes and type I Gaucher's diseases. Recently, L-*allo*-1-deoxynojirimycin (L-*allo*-DNJ) **4** (Figure 1) has been shown to be more potent inhibitor of α-mannosidase as compared to D-*manno*-DNJ **5**[19-20] (Figure1).

In literature, there are several protocols for the synthesis of L-*allo*-DNJ **4**[21-30] mostly based on carbohydrates or amino acids as chiral templates. " Earlier, asymmetric syntheses of L-allo-DNJ 4 have been reported which was based on Sharpless asymmetric epoxidation,[31] Sharpless asymmetric dihydroxylation[32] and chemoenzymatic approach.[33] Synthetic challenge in

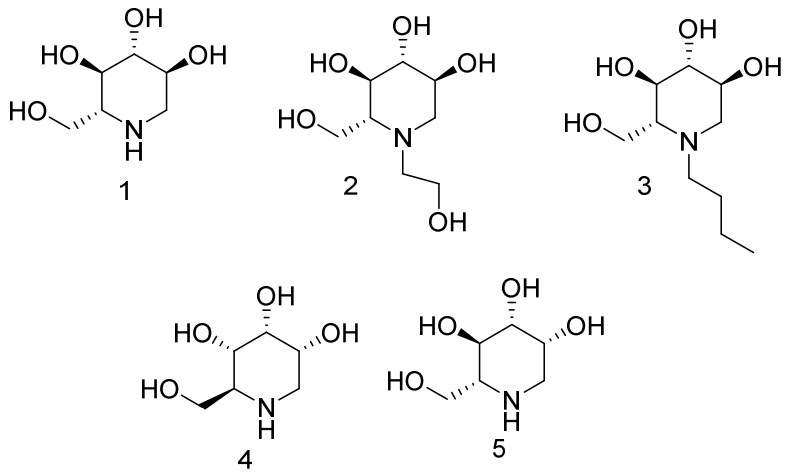
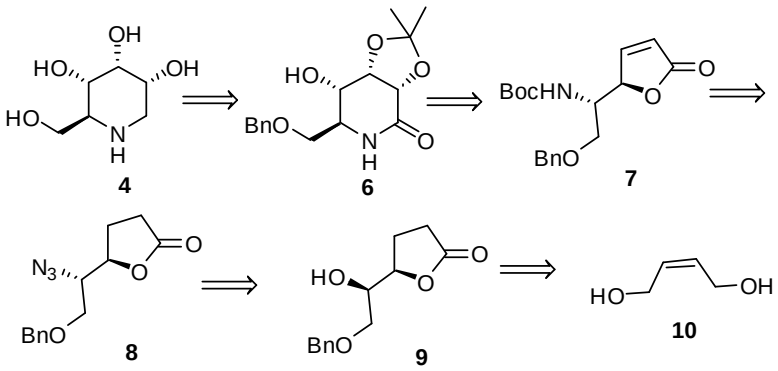


Figure 1. Azasugars and its derivatives.

L-*allo*-DNJ **4** is the construction of piperidine moiety and installation of hydroxyl groups in a stereoselective manner. Due to its interesting biological activity and structural features, L-*allo*-DNJ **4** has attracted many organic chemists towards its synthesis. Herein, we describe an enantioselective synthesis of L-*allo*-DNJ **4** from commercially inexpensive and easily available starting material *viz. cis*-butene-1,4- diol.

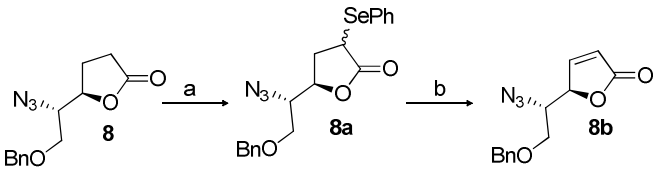
Results and Discussion

According to the retrosynthetic plan (Scheme 1), lactam **6** can be generated from butenolide **7** *via* dihydroxylation, protection and deprotection sequence. Azidolactone **8** could be easily accessed from *cis*-butene-1,4-diol by employing OsO_4 as the catalyst in presence of chiral ligand $(DHQD)_2PHAL$ by following the procedure reported by us.[34]



Scheme 1. Retrosynthetic analysis of L-*allo*-1-deoxynojirimycin.

We have recently disclosed the synthesis of *trans*-3-hydroxy pipecolic acid,[34-38] L-*altro*-DNJ, *cis*-3-hydroxy- pipecolic acid (*R*)-piperidinol and other related non- natural piperidine alkaloids[36] from chiral hydroxy lactone which was in turn derived from *cis*-2-butene-1,4-diol employing the protocol described by us.[34-38] This group has also reported total synthesis D-*allo*-DNJ, L-*talo*-DNJ by chiron approach from L-tartaric acid.[35] In continuation of our interest in synthesis of piperidine alkaloids, we then turned our attention towards the asymmetric synthesis of L-*allo*-DNJ **4** from *cis*-butene-1,4-diol (Scheme 3) employing isomerisation,[39] Claisen orthoester rearrangement,[40] Sharpless asymmetric dihydroxylation,[41-43]



Scheme 2. Reagents and conditions: a) LDA, PhSeSePh, THF, -78 ^{o}C; b) Acetic acid, THF, H_2O_2, 10-20% yield.

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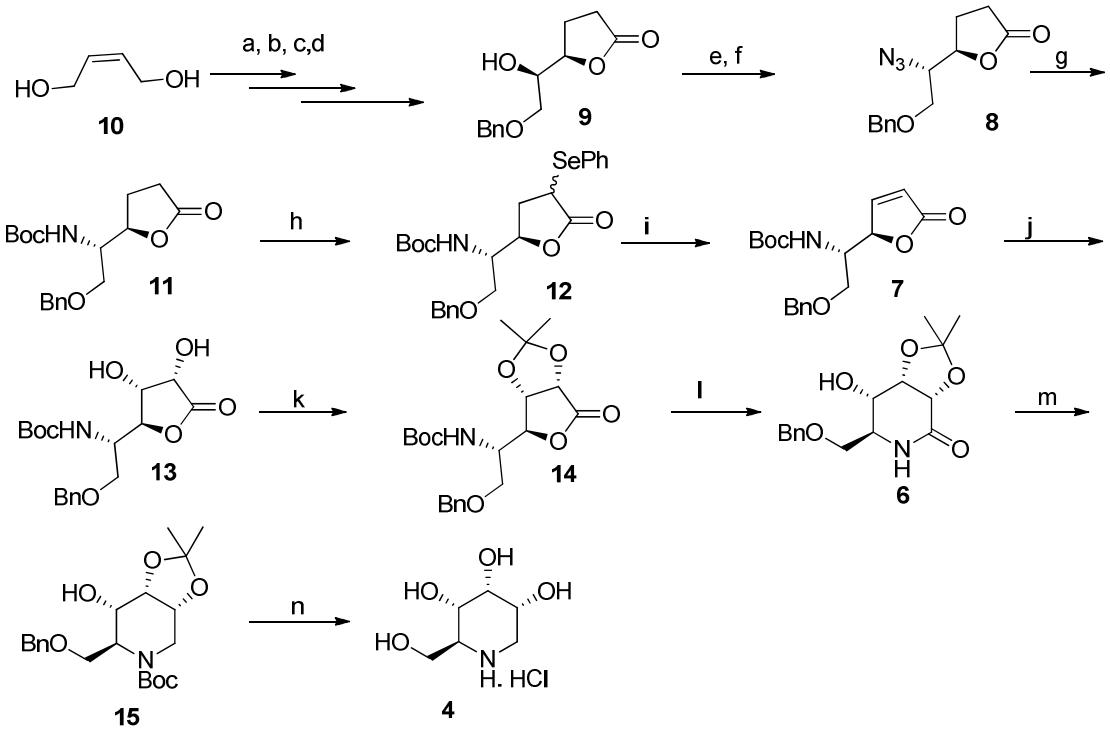
stereoselective flash dihydroxylation and intra- molecular lactone ring opening reaction as the key steps. Azidolactone **8** is a versatile intermediate reported and exploited by our group. It was decided to utilise this azido lactone for the synthesis of L-*allo*-DNJ. So with this idea in mind, azidolactone was treated with LDA and diphenyl diselenide at -78 ^{o}C, furnished the phenyl *α*-selenolacone **8a** which on subsequent treatment with H_2O_2 (Scheme 2) furnished the azido butenolide compound **8b** in low yields Attempts to improve the yield of this conversion using varying amounts of LDA were unsuccessful. So an alternate reaction sequence strategy was employed wherein one pot azide reduction of **8** and *in situ* protection of amine was carried out using $Pd(OH)_2$ under hydrogen atmosphere in the presence of $(Boc)_2O$, TEA to provide urethane **11** in 88% yield (Scheme 3). Carbamate **11** was treated with LDA (4 eq.) in THF at -78 ^{o}C followed by addition of diphenyldiselenide to furnish diastereomeric mixture of *α*- phenylseleno lactone **12** in 57% yield. We did not establish the stereochemistry of its diastereomers at this stage, as it was to be eliminated in the next step. The *α*-phenylseleno lactone **12** was subjected to elimination by using hydrogen peroxide in the presence of acetic acid in THF to afford butenolide **7** in 78% yield. Butenolide **7** was subjected to flash dihydroxylation[44] to provide diol **13** in 71% yield. We followed the same reaction sequence for the synthesis of racemic diol **13** and established the enantiomeric excess (*ee*>97%) and diastereomeric ratio (*dr* 95:5) by chiral HPLC. Literature survey for similar butenolide revealed that α-stereogenic centre directs the dihydroxylation reaction mediated by osmium tetraoxide[45] or $KMnO_4$[46] or $RuCl_3$/ $NaIO_4$.[47] To carry out other functional group transformations, diol **13** was protected as its acetonide by using DMP and cat. CSA in DCM to furnish acetonide **14** in 91% yield. Ring expansion of acetonide compound **14** was carried out out using TFA in DCM to provide the desired six membered



Scheme 3. *Reagents and conditions:* (a) $HgSO_4$, H_2SO_4 (cat), H_2O, 100 ^oC, 3 h, 65%; (b) KOH, BnCl, benzene, reflux, 65%; (c) Triethyl orthoacetate, propanoic acid, 140 ^oC, 3 h, 85%; (d) $K_3Fe(CN)_6$, K_2CO_3, $(DHQD)_2PHAL$, OsO_4, $MeSO_2NH_2$, *t*-BuOH:H_2O (1:1) 0 ^oC, 24 h, 94%; (e) MsCl, Et_3N, DMAP (cat.), DCM, 5 h, 91%; (f) NaN_3, DMF, 80 ^oC, 18 h, 87%; (g) $Pd(OH)_2$, H_2, TEA, $(Boc)_2O$, ethyl acetate, 3 h, 88%; (h) LDA, diphenyl diselenide, THF, -78 ^oC, 55% (bsmr); (i) H_2O_2, CH_3COOH, THF, 30 min, 0 ^oC, 78%; (j) $RuCl_3$, $NaIO_4$, EtOAc:MeCN:H_2O (1:1:0.5), 0 ^oC, 71%; (k) DMP, CSA, DCM, rt, 91%; (l) TFA, DCM, 0 ^oC to rt, 3 h, 53%; (m) i) BH_3.DMS, THF, 0 ^oC-rt, 24 h, ii) TEA, $(Boc)_2O$, DMAP (cat.), THF, rt, overnight, 58% (over two steps); (n) i) $Pd(OH)_2$, H_2, MeOH, rt; ii) MeOH, conc. HCl, rt, 3 h, 80% (over two steps).

lactam **6** in 53% yield. Lactam **6** was reduced by using BH_3.DMS in THF to give corresponding amine, which without purification was protected using TEA, $(Boc)_2O$ and DMAP (cat.) in THF to afford urethane **15** in 58% (over two steps). The *O*-debenzylation of urethane compound **15** was carried out using $Pd(OH)_2$ as the catalyst under hydrogen atmosphere followed by acid treatment to provide hydrochloride salt of L-*allo*-DNJ **4**.[48] In principle, one can easily synthesize D-isomer of L-*allo*-DNJ by switching catalyst from $(DHQD)_2PHAL$ to $(DHQ)_2PHAL$ and by following same protocol.

Conclusions

We have been able to develop a protocol for asymmetric total synthesis of L-*allo*-DNJ **4** (14 steps, 1.6% overall yield) from *cis*-butene-1,4-diol by employing Sharpless asymmetric dihydroxylation, stereoselective dihydroxylation and ring expansion as the key steps.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AV200 MHz, AV400 MHz, and AV500 digital NMR spectrometer in $CDCl_3$ or D_2O. The solvents were purified and dried by standard procedures prior to use; petroleum ether of boiling range 60–80 ^{o}C was used for column chromatography. Optical rotations were measured using a sodium D line on a JASCO-P-1020-polarimeter. Infrared spectra were recorded on a Perkin–Elmer FT-IR spectrometer. An enantiomeric excesses of the products were determined by HPLC (Agilent) employing chiralcel OJ-H column (250 × 4.6 mm) or comparing the specific rotation of the known compounds. All evaporations were performed under reduced pressure. For column chromatography, flash silica gel (230-240 mesh) was employed.

***tert*-Butyl ((S)-2-(benzyloxy)-1-((R)-5-oxotetrahydrofuran-2-yl)ethyl)carbamate (11).** To a solution of azide **8** (2 gm, 7.6 mmol) in EtOAc (30 mL) were added Et_3N (1.6 mL, 11.4 mmol), $(Boc)_2O$ (1.8 mL, 8.36 mmol) and $Pd(OH)_2$ (10 mg). After stirring under an atmosphere of hydrogen for 3 h at normal temperature and pressure, the reaction mixture was filtered through celite and celite was washed thoroughly with methanol (3 × 50 mL) and the filtrate was concentrated under reduced pressure and residue thus obtained was purified by silica gel column chromatography using light petroleum ether: EtOAc (7:3) as an eluent to afford pure urethane **11** (2.3 gm, 88% yield) as a colorless syrup. $[\alpha]_D^{25}$ = - 1.97 (c 1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 3119, 1776, 1605, 1445, 758; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.45 (s, 9H), 2.19-2.31 (m, 2H), 2.48-2.61 (m, 2H), 3.59 (dd, J 9 Hz, 3 Hz, 1H), 3.82 (bd, 2H), 4.53 (s, 2H), 4.57-4.64 (m, 1H), 5.06 (bs, 1H), 7.28-7.37 (m, 5H); ^{13}C (50 MHz, $CDCl_3$ + CCl_4): δ 24.6, 28.0, 28.3, 52.9, 68.9, 73.5, 78.5, 79.9, 127.7, 127.9, 128.4, 137.6, 155.5, 176.7.

***tert*-Butyl ((*S*)-2-(benzyloxy)-1-((*R*)-5-oxo-2,5-dihydrofuran-2-yl)ethyl)carbamate (7).** Saturated lactone **11** (2.1 gm, 6.26 mmol) in dry THF (20 mL) was added to the solution of LDA (prepared from diisopropyl amine (3.5 mL, 25 mmol), n-butyl lithium (15.7 mL, 25 mmol, 1.6 M in hexane) in dry THF (20 mL) at 0 ^{o}C under the nitrogen atmosphere at -78 ^{o}C. After 30 min, diphenyldiselenide (1.9 gm, 6.26 mmol) was added and the reaction mixture was stirred at -78 ^{o}C for 60 minutes. The reaction mixture was quenched with saturated solution of NH_4Cl (50 mL) and extracted with ethyl acetate (3 × 30 mL). Drying over anhydrous sodium sulphate, filtering and evaporation of solvent furnished a residue which was purified by flash column

chromatography (SiO_2) using 20 % ethyl acetate in pet. ether as an eluent to obtain α-phenylseleno lactone **12** as white semisolid compound (1.2 gm, 55% bsmr).

To a solution of α-phenylseleno lactone **12** (75 mg, 0.15 mmol) in THF (5 mL) containing CH_3COOH (0.025 mL) cooled to 0 ^oC, was added 30% H_2O_2 (0.035 mL). The reaction mixture was stirred for 30 minutes at 0 ^oC, then poured into cold saturated solution of sodium carbonate solution and extracted with ethyl acetate (2 × 20 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish a residue which was purified by column chromatography over flash silica gel, eluting with 20% ethyl acetate in pet. ether as the eluent to afford butenolide **7** (40 mg, 78%) as a white semisolid. $[\alpha]_D^{25}$ = +51.4 (c 2.1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 1757, 1699, 1683; ^1H NMR (200 MHz, $CDCl_3$): δ 1.45 (s, 9H), 3.57 (dd, *J* 8.5, 3.0 Hz, 1H), 3.77-3.88 (m, 2H), 4.53 (s, 2H), 5.05-5.18 (m, 2H), 6.10-6.14 (m, 1H), 7.25-7.40 (m, 5H), 7.49 (d, *J* 5.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 28.1, 52.4, 68.6, 73.3, 79.8, 81.8, 121.2, 127.6, 127.7, 128.3, 137.2, 154.9, 155.0, 172.1; MS (EI): *m/z* : 356.37 $(M+Na)^+$; HRMS calculated for $[C_{18}H_{23}NO_5+Na]^+$ 356.1468; found: 356.1477.

***tert*-Butyl ((I)-2-(benzyloxy)-1-((2*S*,3*R*,4*S*)-3,4-dihydroxy-5-oxotetrahydrofuran-2-yl)ethyl)carbamate (13).** To a vigorously stirred solution of butenolide **7** (0.320 gm, 0.96 mmol) in acetonitrile: ethyl acetate (1:1, 12 mL) at 0 ºC was added a solution of $RuCl_3.3H_2O$ (0.014 gm) and $NaIO_4$ (0.3 gm, 1.44 mmol) in distilled water (6 mL). The reaction mixture was stirred for 2 minutes after which a saturated solution of $Na_2S_2O_3$ (30 mL) was added and extracted with ethyl acetate (3 × 20 mL). Organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish a residue which was purified by column chromatography over silica gel, eluting with 50% ethyl acetate in pet ether as the eluent to afford dihydroxylated lactone **13** (0.250 gm, 71%) in analytically pure form. $[\alpha]_D^{25}$ = -8.42 (c 0.95, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 3425, 1791, 1772, 1701, 1683, 1166; ^1H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 1.43 (s, 9H), 3.42-3.55 (m, 2H), 3.66-3.79 (m, 2H), 4.34-4.40 (m, 1H), 4.52 (s, 2H), 4.65 (d, *J* 4 Hz, 1H), 5.30 (bd, *J* 8 Hz, 1H), 7.24-7.37 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 28.3, 50.4, 68.4, 68.5, 69.1, 73.6, 80.5, 83.1, 127.7, 127.9, 128.5, 137.4, 155.8, 175.9; MS (EI): *m/z* 390.09 $(M+Na)^+$; HRMS calculated for $[C_{18}H_{25}NO_7+Na]^+$ 390.1523; found: 390.1538.

***tert*-Butyl ((*R*)-2-(benzyloxy)-1-((3a*R*,4*R*,6a*R*)-2,2-dimethyl-6-oxotetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)ethyl)carbamate (14).** To a solution of dihyroxy lactone **13** (0.2 gm, 0.54 mmol) in DCM was added *p*-TSA (cat) and 2,2-dimethoxypropane (0.28 mL, 2.7 mmol). After stirring under an atmosphere of nitrogen for 18 h at room temperature, the reaction mixture was concentrated under reduced pressure. Saturated solution of sodium carbonate was poured on residue and extracted with DCM (3 × 20 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish a residue which was purified by column chromatography over silica gel, eluting with 20% ethyl acetate in pet. ether as an eluent to afford compound **14** (0.2 gm, 91%) as a colorless syrup. $[\alpha]_D^{25}$ = +25.7

(c 0.7, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 3340, 1794, 1711, 1500, 1369, 1157, 1091; ^1H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 1.34 (s, 3H), 1.45 (s, 9H), 1.46 (s, 3H), 3.50 (dd, *J* 9.0, 4.8 Hz, 1 H), 3.72 (dd, *J* 9, 2.8 Hz, 1H), 3.78-3.88 (m, 1H), 4.51 (s, 2H), 4.60 (d, *J* 7.3 Hz, 1H), 4.70 (d, *J* 5.8 Hz, 1H), 4.80 (d, *J* 5.8 Hz, 1H), 5.11 (d, *J* 9 Hz, 1H), 7.22-7.42 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 25.3, 26.6, 28.3, 51.4, 68.1, 73.7, 74.7, 77.4, 80.4, 82.5, 113.5, 127.8, 128.1, 128.5, 137.0, 155.3, 173.5; MS (EI): m/z 430.11 $(M+Na)^+$; HRMS calculated for $[C_{21}H_{29}NO_7+Na]^+$ 430.1836; found: 430.1849.

(3a*S*,6*S*,7*S*,7a*S*)-6-((benzyloxy)methyl)-7-hydroxy-2,2-dimethyltetrahydro-[1,3] dioxolo[4,5-*c*]pyridin-4(3a*H*)-one (6). To a solution of lactone **14** (0.2 gm, 0.49 mmol) in anhydrous DCM (5 mL) was added TFA (0.2 mL, 2.45 mmol) at 0 ^oC under nitrogen atmosphere. The mixture was stirred for 30 minutes at room temperature. After completion of reaction, solvent and excess TFA were removed under reduced pressure. The reaction mixture was neutralized and basified by using triethyl amine and extracted with DCM (3 × 30 mL). Organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel chromatography using petroleum ether/ethyl acetate (2:8) as an eluent to afford white semisolid lactam **6** (79.5 mg, 53%). $[\alpha]_D^{25}$ = -18.3 (c 1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 3395, 1676, 1196; ^1H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 1.40 (s, 3H), 1.50 (s, 3H), 2.50 (bs, 1H), 3.48-3.56 (m, 1H), 3.70-3.82 (bs, 3H), 4.46 (d, *J* 6.5 Hz, 1H), 4.58-4.59 (m, 3H), 6.21 (bs, 1H), 7.28-7.38 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 24.8, 26.5, 52.3, 67.7, 69.9, 73.7, 73.9, 74.9, 110.9, 127.8, 128.1, 128.6, 137.2, 168.2; MS (EI): m/z 330.22 $(M+Na)^+$; HRMS calculated for $[C_{16}H_{21}NO_5+Na]^+$ 330.1312; found: 330.1322.

(3aR,6S,7S,7aS)-tert-butyl 6-((benzyloxy)methyl)-7-hydroxy-2,2dimethyltetrahydro-[1,3]dioxolo[4,5-c]pyridine-5(6H)-carboxylate (15). To a solution of lactam **6** (0.1 gm, 0.32 mmol) in anhydrous THF (5 mL) was added BH_3.DMS (0.15 mL, 1.6 mmol) dropwise at 0 ^oC under the nitrogen atmosphere. The reaction mixture was allowed to stir at room temperature for 18 h, cooled to 0 ^oC and quenched by addition of ethanol (5 mL). Solvent was removed under reduced pressure and the crude semisolid residue was treated with additional ethanol (5 mL) and refluxed for 6 h. Solvent was removed under reduced pressure to furnish crude amine. To the solution of crude amine in THF was added TEA (0.07 mL) followed by addition of $(Boc)_2O$ (0.089 mL) and DMAP (cat.) and was stirred at room temperature for 24 h. The reaction mixture was extracted with ethyl acetate (3 × 20 mL), washed with water, brine and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography using petroleum ether/ethyl acetate (7:3) as an eluent to afford colorless oily carbamate **15** (74 mg, 58% (over two steps)). $[\alpha]_D^{25}$ = +70.6 (c 0.53, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 3445, 1698, 1682, 1455, 1416, 1161; ^1H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 1.34 (s, 3H), 1.42 (s, 9H), 1.46 (s, 3H), 2.62-2.82 (m, 1H), 3.56-3.74 (m, 1H), 3.78-4.18 (m, 4H), 4.00-4.29 (m, 1H), 4.44-4.63 (m, 3H), 7.21-7.37 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 24.4, 26.2, 28.4, 41.9, 43.3, 53.3, 53.8, 67.3, 67.8, 69.7, 70.2, 73.4,

73.7, 74.2, 79.7, 109.4, 127.4, 127.7, 128.4, 138.2, 154.9; MS (EI): m/z 416.51 $(M+Na)^+$; HRMS calculated for $[C_{21}H_{31}NO_6+Na]^+$ 416.2044; found: 416.2060.

(2*S*,3*S*,4*R*,5*R*)-2-(hydroxymethyl)piperidine-3,4,5-triol hydrochloride (4). To a solution of urethane **15** (30 mg, 0.076 mmol) in MeOH (5 mL) was added $Pd(OH)_2$ under an atmosphere of hydrogen. The reaction mixture was allowed to stir for 6 h. After completion of reaction (monitored by TLC), the reaction mixture was filtered through a celite bed and was thoroughly washed with methanol (20 mL) for 3 times. Concentration of the reaction mixture under reduced pressure provided the diol. To the solution of diol in methanol (3 mL) was added conc. HCl (0.1 mL) at 0 ^oC. The reaction mixture was stirred for 3 h at room temperature. After completion of reaction, the volatiles were concentrated under reduced pressure. The semisolid mass was dried under high vacuum for 3 h (17.6 mg, 80% over two steps). $[\alpha]_D^{25}$ = -32.7 (c 1, MeOH); lit for L-*allo*-1-DNJ.HCl **4**[49] $[\alpha]_D^{25}$= -37.5 (c 1, MeOH), lit.[48] for *ent*-**4** $[\alpha]_D^{25}$= +33.4 (c 1, MeOH), ^1H NMR 400 MHz, D_2O): δ 4.19 (s, 1H), 4.02 (ddd, *J* 11.7, 5.0, 2.5 Hz, 1H), 3.96 (dd, *J* 12.8, 3.1 Hz,1H), 3.91-3.82 (m, 2H), 3.36 (ddd, *J* = 10.7, 5.1, 3.2 Hz, 1H), 3.29 (dd, *J* 12.1, 5.0 Hz, 1H), 3.15 (t, *J* 11.9 Hz, 1H); ^{13}C NMR (125 MHz, D_2O): δ 41.4, 54.6, 57.5, 64.4, 65.2, 69.8.

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Supplementary Data

Supplementary data associated with this article can be found in the online version at doi: http://www.arkat-usa.org/get-file/54990/ .

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