Stereoselective synthesis of 1-deoxynojirimycin, D-glucono-δ-lactam and D-altrono-δ-lactam from a common chiral intermediate derived from D-mannitol

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Abstract

A stereoselective synthesis of 1-deoxynojirimycin, D-glucono-δ-lactam and D-altrono-δ-lactam were accomplished from a common chiral intermediate derived from D-mannitol. The key transformations in the synthesis include Miyashita C-2 selective endo-mode azide opening of epoxy alcohol and Sharpless asymmetric dihydroxylation.

Keywords: Epoxidation, dihydroxylation, diastereoselectivity, cyclization, azasugars

Introduction

Polyhydroxylated piperidines and their derivatives commonly known as azasugars or iminosugars are of great interest in synthetic organic chemistry, bio-chemistry, and pharmacology due to their extraordinary biological properties. A large number of azasugars have been extracted from natural sources, mainly from plants, microorganisms and more recently from insects and sea sponges. Among the azasugars, naturally occurring 1-deoxy-azasugars and their analogues such as deoxynojirimycin 1 (DNJ), deoxymannojirimycin 2 (DMJ), adenophorine 3, fagomine 4 and D-glucono-δ-lactam 5 (Figure 1) are the structural analogues of pyranose carbohydrates in which the ring oxygen atom is replaced by a nitrogen atom have been found to act as potent glycosidase and glycosyl transferase inhibitors. Moreover these 1-deoxy-azasugars are used as therapeutic agents for the treatment of various conditions such as cancer, HIV infection, hepatitis C virus infection, diabetes, influenza viral infection, and other carbohydrate related metabolic disorders. Synthetic 1-deoxynojirimycin derivatives such as N-hydroxyethyl-
DNJ 7 (Miglitol or Glyset) and N-butyl-DNJ 8 (Zavesca) have been already approved for the treatment of non-insulin-dependent diabetes and Gaucher’s disease respectively.\(^5\)

![Polyhydroxypiperidines](image)

**Figure 1.** Some polyhydroxypiperidines.

At present there are about 35 natural azasugars that act as glycosidase inhibitors; however, their isolation in the pure form from natural sources is a laborious and expensive exercise. Although a number of synthetic routes to azasugars are published to date, development of new synthetic strategy for the synthesis of natural as well as unnatural azasugars from easily available starting materials with high level of stereocontrol is always in demand in organic chemistry.\(^6\) In continuation of our research on the synthesis of N-heterocyclic compounds\(^7\) and natural products,\(^8\) herein we describe an efficient synthetic approach to the stereoselective synthesis of 1-deoxynojirimycin (1), as well as its analogues D-glucono-\(\delta\)-lactam (5) and D-altrono-\(\delta\)-lactam (6) in good yield from a common chiral intermediate derived from the inexpensive starting material D-mannitol.

**Results and Discussion**

A retrosynthetic analysis for the synthesis of targeted azasugars is shown in Scheme 1. The target molecules 1, 5 and 6 were envisioned to be obtained from the common chiral intermediate 10 that could be derived from 9 through regioselective epoxide opening with azide nucleophile and Wittig olefination as key steps. The epoxy alcohol 9 could be obtained from D-mannitol via cyclohexylidene D-glyceraldehyde.
Scheme 1. Retrosynthetic plan for the synthesis of the title compounds 1, 5 and 6.

Reagents and conditions: (a) ref. 9; (b) diethyl L-tartrate, Ti(O\text{Pr})_4, cumene hydroperoxide, 4Å MS, DCM, -20 °C, 72 h, 93%, 94% de; (c) (MeO)_3B, NaN_3, DMF, 50 °C, 6 h, then NaIO_4, 95%; (d) benzyl bromide, NaH, THF, n-Bu_4NI, 0 °C-rt, 16 h, 94%; (e) 10% HCl, CH_3CN, rt, 4 h, 95%; (f) (i) NaIO_4, aq.CH_3CN (60%), rt, 30 min, quantitative; (ii) (EtO)_2P(O)CH_2CO_2Et, LiCl, (\text{Pr})_2NEt, CH_3CN, rt, 24 h, 93% (98:2, E:Z).

Scheme 2. Synthesis of key intermediate 10.

Accordingly, the starting material (E)-allylic alcohol 11 was synthesized according to the reported procedure from D-mannitol.\textsuperscript{9} Thus synthesized E-allyl alcohol 11 was subjected to Sharpless catalytic asymmetric epoxidation\textsuperscript{10} by using diethyl L-tartrate, Ti(O\text{Pr})_4 and cumene hydroperoxide.
hydroperoxide to afford epoxy alcohol 9 in 93% yield with 94% de, determined by GC-MS analysis (see Experimental part). Our next task was to introduce an azido group at C-2 position of 2,3-epoxy alcohol 9 in a highly regioselective manner. Towards that objective, the highly C-2 regioselective azido epoxide opening of 9 was accomplished by using NaN3-(CH3O)3B system developed by Miyashita et al. Under Miyashita conditions, in our substance the azide nucleophile selectively attacks at the favorable C-2 position rather than at C-3 which is blocked by the hydrogens of the C-5 methylene group as well as the cyclohexylidene group, affording the single compound 12 in 95% yield.

The hydroxyl groups of the obtained azido-diol compound 12 were protected as benzyl ethers using benzyl bromide, followed by selective deprotection of cyclohexylidene group with 1N HCl in CH3CN, afforded the 4-azido-1,2-diol 14 in good yield. The obtained azido-diol compound 14 was subjected to oxidative cleavage with NaIO4 to achieve the corresponding aldehyde. This obtained aldehyde was almost pure and without column purification it was subjected to HWE olefination with triethyl phosphonoacetate under Masamune-Roush conditions to afford the desired, highly E- selective α,β-unsaturated ethyl ester 10 in 93% yield (E:Z, 98:2 based on 1H NMR analysis).

With compound 10 in hand, the next step was its selective dihydroxylation (Scheme 3). For our study we required both the dihydroxylated compounds, and towards that objective we investigated the stereoselective dihydroxylation of the α,β-unsaturated ethyl ester 10 under various reaction conditions; the results are summarized in Table 1.

Scheme 3. Dihydroxylation of azido ester 10.

Initially, compound 10 was treated with the recommended amount of AD-mix α (1.4 g/1mmol) along with methanesulfonamide at 0 °C (entry 1). But we observed that the reaction was very slow and even not completed after 5 days. Furthermore the ratio of the vicinal diols was poor in terms of stereoselectivity. In search of the better conditions, it was found that treatment of compound 10 under modified SAD conditions (entry 2) at 0 °C for 3 days gave the desired diol 15a in 73% yield after purification (dr = 15a:15b, 94:6). After successful synthesis of compound 15a, we then treated the α,β-unsaturated ethyl ester 10 with AD-mix β (1.4 g/1mmol), but we did not get a good yield (entry 3). Then we applied the modified SAD conditions on ester 10 (entry 4) and the reaction was completed in 3 days and compound 15b was obtained in good yield with improved diastereoselectivity (dr = 15a:15b, 3:97). However, better results were obtained under Upjohn conditions, on treatment of the compound 10 with 5 mol % of OsO4 and N-methylmorpholine oxide (NMO) as re-oxidant at 0 °C (entry 5). The reaction was
completed within 7 h and resulted in the formation of diol 15b in 91% yield with good diastereoselectivity (dr = 15a:15b, 1:99). It was eventually concluded that the slow rate of reaction using the AD-mix reagent (either α or β) is due to steric congestion about the double bond of the ester owing to the OBn group which hinders the approach of the bulky oxidation catalyst to the double bond and also the electron-withdrawing nature of the ester group.\textsuperscript{14,17} This type of interaction between the catalyst and the bulkiness of the substrate in stereoselective dihydroxylation has been reported earlier.\textsuperscript{18}

Table 1. Dihydroxylation of olefinic ester 10 under various reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Solvent\textsuperscript{b}</th>
<th>Time</th>
<th>15a:15b\textsuperscript{c}</th>
<th>Yield (%)\textsuperscript{d}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AD-mix α (1.4 g/1 mmol), MeSO\textsubscript{2}NH\textsubscript{2} (1 equiv.)</td>
<td>t-BuOH-H\textsubscript{2}O (1:1)</td>
<td>5 days</td>
<td>84:16</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>AD-mix α (1.4 g/1 mmol), (DHQ)\textsubscript{2}-PHAL (1 mol%), MeSO\textsubscript{2}NH\textsubscript{2} (1 equiv.), NaHCO\textsubscript{3} (3 equiv.), OsO\textsubscript{4} (1 mol%)\textsuperscript{a}</td>
<td>t-BuOH-H\textsubscript{2}O (1:1)</td>
<td>3 days</td>
<td>94:6</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>AD-mix β (1.4 g/1 mmol), MeSO\textsubscript{2}NH\textsubscript{2} (1 equiv.)</td>
<td>t-BuOH-H\textsubscript{2}O (1:1)</td>
<td>5 days</td>
<td>10:90</td>
<td>44</td>
</tr>
<tr>
<td>4</td>
<td>AD-mix β (1.4 g/1 mmol), MeSO\textsubscript{2}NH\textsubscript{2} (1 equiv.), NaHCO\textsubscript{3} (3 equiv.), NaHCO\textsubscript{3} (3 equiv.), OsO\textsubscript{4} (1 mol%)\textsuperscript{a}</td>
<td>t-BuOH-H\textsubscript{2}O (1:1)</td>
<td>3 days</td>
<td>3:97</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>OsO\textsubscript{4} (5 mol%),\textsuperscript{a} NMO (3 equiv.)</td>
<td>Acetone-H\textsubscript{2}O (9:1)</td>
<td>7 h</td>
<td>1:99</td>
<td>92</td>
</tr>
</tbody>
</table>

\textsuperscript{a} 0.04 molar solution; \textsuperscript{b} all the reaction were carried out at 0 °C; \textsuperscript{c} based on integration of the crude \textsuperscript{1}H NMR spectra; \textsuperscript{d} combined isolated yields.

After completion of these dihydroxylation experiments on the ester 10, we turned our attention to the synthesis of 1-deoxynojirimycin (Scheme 4). Towards that, azido dihydroxy ester 15a was converted into corresponding acetonide azido ester 16 using 2,2-dimethoxy propane and acetone in presence of PTSA followed by selective reduction of ester group of the compound 16 by LiBH\textsubscript{4}, generated in situ,\textsuperscript{19} to afford the corresponding alcohol 17 in 87% yield. In accord with our strategy, a leaving group is required for the construction of the piperidine ring through reductive amino cyclization at the penultimate stage, then the primary hydroxyl group of compound 17 was mesylated with MsCl in presence of triethylamine to afford compound 18 in 93% yield.
The piperidine ring closure was achieved by reductive cleavage of the azido group of compound 18 using Lindlar’s catalyst (Pd/CaCO₃) under hydrogen, followed by base treatment, in 86% yield. The final target compound 1-deoxynojirimycin (1) was obtained by global deprotection of the benzyl and acetonide groups of 19 with Pd/C under hydrogen atmosphere in MeOH containing 6N HCl, followed by treatment with ion-exchange resin Dowex 50Wx8, in 75% yield (Scheme 4). The spectroscopic and analytical data of 1-deoxynojirimycin 1 were in agreement with literature values.²⁰

\[ \text{Reagents and conditions: (a) 2,2-DMP, acetone, PTSA, rt, overnight, 96%}; \ (b) \text{LiCl, NaBH}_4, \text{THF, EtOH, rt, overnight, 87%}; \ (c) \text{MsCl, Et}_3\text{N, DCM, 0°C- rt, 3 h, 93%}; \ (d) \text{Pd/ CaCO}_3 / \text{H}_2, \text{MeOH, rt, 6 h, then K}_2\text{CO}_3 \text{reflux, 3 h, 86%}; \ (e) \text{Pd/C, H}_2, \text{MeOH, 6N HCl, rt, 48 h, then Dowex 50wx8 treatment, 75%}. \]

**Scheme 4.** Synthesis of 1-deoxynojirimycin 1.

After the successful synthesis of 1-deoxynojirimycin 1, we turned our attention to the synthesis of azasugar lactams using the synthesized azido-dihydroxy esters 15a and 15b. Under hydrogen atmosphere, using Pd/C, we have efficiently converted the azido-dihydroxy esters 15a and 15b independently into the corresponding D-glucono-δ-lactam 5 and D-altrono-δ-lactam 6 in one pot, involving debenzylation and reductive lactamization steps, as shown in Scheme 5. The spectroscopic and analytical data of gluconolactam 5 and altronolactam 6 were in good agreement with the literature values.²⁰⁻²¹

Conclusions

In conclusion, the total synthesis of 1-deoxynojirimycin and the related compounds D-glucono-δ-lactam and D-altrono-δ-lactam has been achieved in a highly stereoselective manner from a common intermediate derived from D-mannitol. A combination of Miyashita C-2 selective endo-mode azide opening of epoxy alcohol, and Sharpless asymmetric dihydroxylation were employed to generate chiral centers at the desired positions and to obtain the products in good yields. We believe that the synthetic intermediates described in this paper are useful synthons for other natural products and the work is currently under way in this laboratory.

Experimental Section

General. All reactions were carried out under an inert atmosphere unless mentioned otherwise, and standard syringe-septum techniques were followed. Solvents were freshly dried and purified by conventional methods prior to use. The progress of all the reactions was monitored by TLC, using glass plates precoated with silica gel 60 F254 to a thickness of 0.5 mm (Merck). Column chromatography was performed on silica gel (Acme, 60–120 mesh, India); EtOAc and hexane were used as eluents. Optical rotation values were measured either on a Perkin Elmer P241 polarimeter or Jasco DIP-360 digital polarimeter at 25 °C, and IR spectra were recorded on a Perkin Elmer FT-IR spectrophotometer. NMR spectra were recorded on a Varian Gemini 200 MHz or Bruker Avance 300 MHz or Varian Unity 400 MHz spectrometer upon their availability, using TMS as an internal standard for 1H NMR and CDCl3 for 13C NMR (chemical shift values in δ, J in Hz). Mass spectra were recorded on Thermo-Finnigan MAT1020B or Micromass 7070H spectrometer operating at 70 eV using direct inlet system. All high resolution mass spectra (HRMS) were recorded on QSTAR XL hybrid MS/MS system equipped with an ESI source. GC-MS were recorded on Agilent 6890 series GC-MS system, GC (Agilent Technologies, Palo Alto, CA) equipped with a model 5973N mass selective detector and HP-5MS capillary column (5% phenyl, 95% PDMS; 30 m × 0.25 mm i.d. × 0.25 µm film thickness) was used.
(2R,3R,4R)-2,3-Epoxy-4,5-(cyclohexylidenedioxy)pentan-1-ol (9). To powdered, activated 4Å molecular sieves (2.8 g 35% wt/wt) in dry CH₂Cl₂ (175 mL) under nitrogen were sequentially added titanium tetraisopropoxide (0.95 mL, 3.2 mmol) and diethyl L-(-)-tartrate (0.67 mL, 4 mmol) at -20 °C, and the mixture was stirred for 30 min. A solution of 11 (8 g, 40.4 mmol) in CH₂Cl₂ (50 mL) was added, and the resulting mixture was stirred at -20 °C for 30 min. Cumene hydroperoxide (11.8 mL, 80.8 mmol) was added dropwise to the reaction mixture, and the resulting solution was stored at -20 °C in freezer for 72 h. Aqueous tartaric acid (10%, 40 mL) was added at -20 °C, and the whole reaction mass was allowed to warm to room temperature. After being stirred for 1 h, the reaction mixture was filtered, and the filtrate was extracted with CH₂Cl₂ (2 × 75 mL). The combined organic layers were treated with a pre-cooled (0 °C) solution of 25 mL of 30% NaOH (w/v) in brine at 0 °C (25 mL of 30% NaOH solution in brine are prepared by adding 1.25 g of NaCl to a solution of 7.5 g of NaOH in 22.5 mL of water) and stirred for 20 min. The two layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2 × 20 mL). The combined organic layers were washed with Na₂SO₄, filtered and concentrated. The residue was chromatographed on silica gel with EtOAc-hexane (1:4) to afford pure compound 9 (8 g, 93%; 94%de based on GC-MS analysis) as colorless oil: \( R_f = 0.35 \) (hexanes-EtOAc, 1:1); [α]D²⁵ = -23.8 (c 1.4, MeOH); IR (neat): (νmax, cm⁻¹) 3446, 2934, 2859, 1448, 1367, 1162, 1096; ¹H NMR (CDCl₃, 300 MHz): δH 4.10-4.03 (m, 2H, CH₂CH), 3.91 (br d, J 13.1 Hz, 1H, CH₃H₅OH), 3.81 (dd, J 5.1, 7.3 Hz, 1H, CH₂CH), 3.64 (br d, J 13.1 Hz, 1H, CH₂H₃OH), 3.12 (dt, J 2.1, 3.6 Hz, 1H, oxirane-H₁), 3.04 (dd, J 2.1, 3.6 Hz, 1H, oxirane-H₂), 2.09 (br s, 1H, OH), 1.59-1.55 (m, 8H, Cy-H), 1.39 (br s, 2H, Cy-H); ¹³C NMR (CDCl₃, 50 MHz): δC 110.5, 74.6, 65.5, 60.8, 55.4, 55.1, 35.8, 34.9, 24.9, 23.8, 23.7; ESIMS: m/z 237 [M+Na]⁺; HRMS (EI): m/z [M+Na]⁺ calcd for C₁₁H₁₈O₄Na: 237.1102, found: 237.1088.

GC-MS data: The inlet and GC-MS interface temperatures were kept at 280 °C, Helium was used as the carrier gas at flow rate of 1 mL/min., and the sample was injected in split mode 1:10 ratio. Oven program was 80 °C for 2 min.; raised temperature 10 °C/min to 280 °C; hold 5 min. The major peak was found at the retention time of 14.07 min. with mass m/z 214 [M⁺] and the minor peak was found at 13.75 min. with mass m/z 214 [M⁺].

(2R,3R,4R)-2-Azido-4,5-(cyclohexylidenedioxy)pentane-1,3-diol (12). A mixture of epoxy alcohol 9 (7.5 g, 35 mmol), B(OMe)₃ (7.9 mL, 70 mmol), and NaN₃ (4.55 g, 70 mmol) in DMF (50 mL) under nitrogen atmosphere were stirred at 50 °C for 6 h. After cooling to 0 °C, a saturated aqueous solution of NaHCO₃ (50 mL) was added, and the mixture was stirred for 30 min at the same temperature. The mixture was separated, and the aqueous layer was extracted with diethyl ether (3 × 70 mL). The combined organic layers were successively washed with water (30 mL), saturated aqueous NaHCO₃ solution (40 mL), brine (50 mL), and dried over Na₂SO₄. Concentration under reduced pressure gave an oily residue, that was dissolved in CH₂CN (60 mL) and treated with sodium periodate (3.75 g, 17.5 mmol) dissolved in 40 mL water at room temperature for 30 min and filtered. The filtrate was mixed with water (10 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with
water (20 mL), brine (30 mL) and dried over Na₂SO₄, filtered and concentrated. The residue was chromatographed on silica gel with EtOAc-hexane (1:4) to give pure 1,3-diol 12 (8.55 g, 95%) as colorless oil; Rf = 0.4 (hexanes-EtOAc, 1:1); [α]D²⁵ = -41.6 (c 1, MeOH); IR (neat): (νmax, cm⁻¹) 3421, 2636, 2860, 2100, 1448, 1276, 1099; ¹H NMR (CDCl₃, 300 MHz): δH 4.34 (td, J 3.3, 6.7 Hz, 1H, CH₂CH), 4.13 (dd, J 6.7, 14.4 Hz, 1H, CH₃H₂CH), 4.02 (dd, J 3.3, 11.8 Hz, 1H, CH₃H₂CH), 3.92 (dd, J 6.7, 8.3 Hz, 2H, CH₂OH), 3.56-3.48 (m, 2H, CHOH, CHN₃), 2.56 (br d, J 6.7 Hz, 1H, OH), 2.43 (br s, 1H, OH), 1.64-1.57 (m, 8H, Cy-H), 1.44-1.40 (m, 2H, Cy-H); ¹³C NMR (CDCl₃, 50 MHz): δC 110.2, 74.8, 70.7, 65.6, 64.5, 62.6, 35.8, 34.3, 24.9, 23.9, 23.6; ESI-MS: m/z 280 [M+Na]+; HRMS (ESI): m/z [M+Na]+ calcd for C₁₁H₁₉N₃O₄Na: 280.1273, found: 280.1267.

**Page 295**

(2R,3R,4R)-2-Azido-4,5-(cyclohexylidenedioxy)-1,3-(bisbenzlyoxy)pentane (13). To a well stirred solution of NaH (60% dispersion in mineral oil, 3.73 g, 93 mmol) in dry THF (100 mL) under nitrogen was added azido diol 12 (8 g, 31 mmol) dissolved in THF (40 mL) via syringe very slowly at 0 °C and allowed to stir at same temperature for 20 min. Then tetrabutylammonium iodide (100 mg) followed by benzyl bromide (9.26 mL, 77 mmol) were added and allowed to stir at room temperature until completed the reaction (16 h). The reaction mixture was quenched by addition of water until clear solution results. THF was removed under reduced pressure, the residue was diluted with water (20 mL) and extracted with Et₂O (3 × 70 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The residue was chromatographed on silica gel with hexane (100%) followed by EtOAc-hexane (1:19) to give pure compound 13 (12.8 g, 94 %) as colorless oil; Rf = 0.6 (hexanes-EtOAc, 4:1); [α]D²⁵ = -8.6 (c 1.4, MeOH); IR (neat): (νmax, cm⁻¹) 2935, 2860, 2097, 1451, 1274, 1102; ¹H NMR (CDCl₃, 300 MHz): δH 7.29-7.23 (m, 10H, Ar-H), 4.75 (d, J 11.3 Hz, 1H, benzylic CH), 4.52 (s, 2H, benzylic C₂H), 4.24 (dd, J 7.5, 11.3 Hz, 1H, CH₂H₂CH), 3.98 (dd, J 6.0, 7.5 Hz, 1H, CH₂CH), 3.80 (dd, J 2.2, 9.8 Hz, 1H, CH₂H₂CH), 3.70-3.64 (m, 2H, CH₂OBN), 3.54-3.48 (m, 2H, CHOBN, CHN₃), 1.59-1.56 (m, 8H, Cy-H), 1.38 (br s, 2H, Cy-H); ¹³C NMR (CDCl₃, 50 MHz): δC 137.8, 137.5, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 109.7, 78.7, 76.7, 74.5, 73.3, 69.1, 65.6, 62.1, 36.0, 35.0, 25.1, 24.0, 23.8; ESI-MS: m/z 460 [M+Na]+; HRMS (ESI): m/z [M+Na]+ calcd for C₂₅H₃₁N₅O₄Na: 460.2212, found: 460.2204.

(2R,3R,4R)-4-Azido-3,5-bis(benzyleoxy)pentane-1,2-diol (14). To a cooled (0 °C) solution of 13 (8.74 g, 20 mmol) in acetonitrile (100 mL) was added 1N HCl (100 mL) and allowed to stir at room temperature until starting material disappeared on TLC (4 h). Then reaction was neutralized with solid sodium bicarbonate at room temperature. The solvent was removed under vacuum, then it was diluted with ethyl acetate (75 mL) and after separation of the layers, the aqueous layer was further extracted with ethyl acetate (3 × 35 mL). The combined organic layers were washed with brine and dried over Na₂SO₄, filtered and concentrated. The residue was chromatographed on silica gel with EtOAc-hexane (1:4) to give pure compound 14 (6.785 g, 95%) as white color solid; mp 88-90 °C; Rf = 0.2 (hexanes-EtOAc, 1:1); [α]D²⁵ = -8.82 (c 1, MeOH); IR (KBr): (νmax, cm⁻¹) 3325, 2923, 2135, 2100, 1451, 1317, 1064; ¹H NMR (CDCl₃, 400
Ethyl (4S,5R,2E)-5-azido-4,6-bis(benzyloxy)hex-2-enoate (10). To a stirred solution of 14 (3.57 g, 10 mmol) in 48 mL of acetonitrile at room temperature was added NaIO₄ (4.27 g, 20 mmol) dissolved in 32 mL water over a period of 10 min. The mixture was stirred about 30 min, filtered through pad of celite and repeatedly washed with ethyl acetate. The filtrate was mixed with water (20 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water (20 mL), brine (40 mL) and dried over Na₂SO₄. Solvent removal under reduced pressure afforded the corresponding aldehyde in almost quantitative yield. This was sufficiently pure and hence used as such for the next step. 

To a well stirred solution of anhydrous LiCl (492 mg, 11.6 mmol) in dry acetonitrile (35 mL) under nitrogen were sequentially added triethyl phosphonoacetate (2.3 mL, 11.6 mmol), N,N-diisopropylethylamine (2 mL, 11.6 mmol) and above freshly prepared aldehyde (3.15 g, 9.7 mmol) dissolved in 32 mL water over a period of 10 min. The mixture was stirred about 30 min, filtered through pad of celite and repeatedly washed with ethyl acetate. The filtrate was mixed with water (20 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water (20 mL), brine (40 mL) and dried over Na₂SO₄. Solvent removal under reduced pressure afforded the corresponding aldehyde in almost quantitative yield. This was sufficiently pure and hence used as such for the next step. 

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IR (neat): (νmax, cm⁻¹) 2866, 2100, 1720, 1454, 1271, 1175, 1097; 

¹H NMR (CDCl₃, 300 MHz): δH 7.32-723 (m, 10H, Ar-H), 6.85 (dd, J 6.7, 15.8 Hz, 1H, =CH), 6.05 (d, J 15.8 Hz, 1H, =CH), 4.62 (d, J =12.0 Hz, 1H, benzylic CH₃H₅), 4.49 (s, 2H, benzylic CH₂H₅), 4.40 (d, J 12.0 Hz, 1H, benzylic CH₃H₅), 4.25 (q, J 7.5 Hz, 2H, CH₂CH₃), 4.16 (t, J 5.2 Hz, 1H, CHOBr), 3.68 (dd, J 5.8, 11.7 Hz, 1H, CH₂N₃), 3.60 (d, J 5.2 Hz, 2H, CH₂OBn), 1.34 (t, J 7.5 Hz, 3H, CH₃); 

¹³C NMR (CDCl₃, 50 MHz): δC 165.5, 143.4, 137.4, 137.2, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 124.9, 77.5, 73.4, 71.5, 68.8, 63.7, 60.6, 14.2; ESI-MS: m/z 418 [M+Na]+; 

at room temperature were added 0.04 molar toluene solution of OsO₄ (1 mL, 0.04 mmol, 1 mol%), (DHQ)₂PHAL (125 mg, 0.16 mmol), NaHCO₃(1 g, 12 mmol) and MeSO₂NH₂ (380 mg, 4 mmol) sequentially. After 20 min the clear solution was cooled to 0 °C and was added compound 10 (1.58 g, 4 mmol)) dissolved in t-BuOH (10 mL) at once and allowed to stir at 0 °C until the reaction was completed (72 h), then the reaction mixture was quenched with solid Na₂SO₃ (3.5 g) at 0 °C and stirred for 30 min then warmed to room temperature. Ethyl acetate (50 mL) was added to the reaction mixture and separated the aqueous layer from organic layer. The aqueous layer further extracted with ethyl acetate (2 × 40 mL), the combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude residue was chromatographed on silica gel with EtOAc-hexane (1:9) to give pure compound 15a (1.26 g, 73%) as pale yellow solid; mp 43-45 °C; R₇ = 0.33 (hexanes-EtOAc, 7:3); [α]D²⁵ = -21.7 (c 0.47, CHCl₃); IR (neat): (νmax, cm⁻¹) 3545, 3358, 2866, 2108, 1730, 1202, 1107, 1055; ¹H NMR (CDCl₃, 300 MHz): δH 7.34-7.26 (m, 1OH, Ar-H), 4.74 (d, J 10.4 Hz, 1H, benzylic CH₂), 4.61 (d, J 10.4 Hz, 1H, benzyl CH₃), 4.58 (dd, J 12.4, 14.5 Hz, 2H, benzyl CH₂), 4.41 (br d, J 3.1 Hz, 1H, CHOH), 4.28 (m, 2H, CH₂CH₃), 4.05 (dd, J 3.1, 5.2 Hz, 1H, CHOH), 4.01 (dd, J 6.2, 14.5 Hz, 1H, CHOBN), 3.81 (dd, J 5.2, 10.4 Hz, 1H, CH₃H₂OBN), 3.73-3.69 (m, 2H, CH₃H₂OBN, CH₃N), 3.07 (br d, J 4.1 Hz, 1H, OH), 2.55 (br d, J 8.3 Hz, 1H, OH), 1.30 (t, J 7.2 Hz, 3H, CH₃); ¹³C NMR (CDCl₃, 75 MHz): δC 172.9, 137.4, 137.3, 128.4, 128.0, 127.8, 127.7, 77.6, 74.2, 73.4, 71.4, 71.2, 69.2, 62.2, 62.0, 14.0; ESI-MS: m/z 452 [M+Na]⁺; HRMS (ESI): m/z [M+Na]⁺ calcd for C₄₂H₇₇N₅O₆Na: 452.1797, found: 452.1813.

Ethyl (25S,3S,4R,5R)-5-azido-4,6-bis(benzyloxy)-2,3-dihydroxyhexanoate (15b). The dihydroxy compound 15b was synthesized using AD-mix β (1.4 g/1 mmol) from 10 without employing a specific ligand (Table 1, entry 4) according to the procedure described for the synthesis of 15a from 10. The same dihydroxy compound 15b was synthesized using a catalytic amount of OsO₄ as described below.

To a cooled (0 °C) solution of ester compound 10 (1.58 g, 4 mmol) and NMO (1.62 g, 12 mmol) in acetone:H₂O (20 mL, 9:1) was added 0.04 M toluene solution of OsO₄ (5 mL, 5 mol%). The solution was stirred until the reaction was completed at 0 °C (TLC analysis ca. 7 h). The reaction was quenched by saturated aqueous sodium sulfite (8 mL) and the organic solvent was removed in vacuo. CH₂Cl₂ (40 mL) was added, separated the layers and the aqueous layers was extracted with CH₂Cl₂ (2 × 20 mL) and the combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, and concentrated. The crude residue was chromatographed on silica gel using EtOAc-hexane (1:9) as eluent to give pure compound 15b (1.55 g, 91%) as colorless oil; R₇ = 0.3 (hexanes-EtOAc, 7:3); [α]D²⁵ = -14.8 (c 0.5, CHCl₃, compound synthesized using AD-mix-β); [α]D²⁵ = -15.2 (c 0.5, CHCl₃, compound synthesized using OsO₄); IR (neat): (νmax, cm⁻¹) 3414, 2937, 2861, 2103, 1448, 1277, 1099; ¹H NMR (CDCl₃, 300 MHz): δH 7.34-7.29 (m, 10H, Ar-H), 4.76 (d, J 10.9 Hz, 1H, benzylic CH₂), 4.63 (d, J 10.9 Hz, 1H, benzyl CH₂), 4.56 (s, 2H, benzyl CH₂), 4.45 (br d, J 4.1 Hz, 1H, CHOH), 4.30-4.20 (m, 2H, CH₂CH₃), 4.09-4.02 (m, 2H, CH₂CH₂OBn), 3.82-3.70 (m, 3H, CH₂OBn, CH₃N), 3.12 (br d, J 5.2 Hz, 1H, OH), 2.65 (br d, J 8.6 Hz, 1H, OH), 1.30 (t, J 7.1 Hz, 3H, CH₃); ¹³C NMR (CDCl₃, 75 MHz): δC 172.9, 137.4,
137.4, 128.4, 128.0, 127.9, 127.8, 127.7, 78.8, 74.1 73.4, 71.5, 70.3, 69.2, 62.6, 62.2, 14.1; ESI-MS: m/z 452 [M+Na]⁺; HRMS (ESI): m/z [M+Na]⁺ calcd for C_{22}H_{27}N_{3}O_{6}Na: 452.1797, found: 452.1808.

**Ethyl (2R,3S,4R,5R)-5-azido-2,3-(isopropylidenedi oxy)-4,6-bis(benzyloxy) hexanoate (16).** A solution of ester 15a (2.15 g, 5 mmol) and PTSA (11 mg, 0.5 wt%) in 2,2-dimethoxypropane (DMP) (4 mL) and dry acetone (8 mL) was stirred at room temperature for overnight. 0.5 mL saturated aqueous NaHCO₃ solution was added to the mixture and excess of DMP and acetone was removed under reduced pressure. The residue was treated with water and the mixture was extracted with ethyl acetate (2 × 50 mL). The combined organic layer was washed with brine (30 mL) and dried over Na₂SO₄, the solvent was removed in vacuo and the crude product was purified by column chromatography using silica gel and EtOAc-hexane (1:9) as eluent to give pure compound 16 (2.25 g, 96%) as a colorless oil; R_f = 0.4 (hexanes-EtOAc, 4:1); [α]_D^{25} = -33.6 (c 0.59, CHCl₃); IR (neat): (ν_max, cm⁻¹) 2987, 2930, 2100, 1757, 1375, 1206, 1102; ¹H NMR (CDCl₃, 400 MHz): δ_H 7.31-7.21 (m, 10H, Ar-H), 4.63 (s, 2H, benzylic CH₂), 4.58 (d, J 11.7 Hz, 1H, benzyl CH₃), 4.54 (d, J 12.6 Hz, 1H, benzyl CH₃), 4.38 (d, J 7.8 Hz, 1H, C(2)H), 4.33 (dd, J 2.9, 7.8 Hz, 1H, C(3)H), 4.23 (t, J 6.8 Hz, 2H, CH₂CH₃), 3.83 (dd, J 4.8, 11.7 Hz, 1H, CH₃CH₂OBn), 3.74-3.68 (m, 3H, CH₂CH₂OBn, CHOBn, CH₃N), 1.42 (s, 6H, 2 × CH₃), 1.31 (t, J 6.8 Hz, 3H, CH₂CH₃); ¹³C NMR (CDCl₃, 75 MHz): δ_C 170.4, 137.5, 137.3, 128.4, 127.9, 127.8, 127.7, 127.6, 111.2, 79.0, 75.9, 74.8, 74.7, 73.3, 69.2, 61.7, 61.5, 26.6, 25.8, 14.1. ESI-MS: m/z 492 (18%) [M+Na], 487 (100%) (M+NH₃), 442 (98%) (M+H-N₂); HRMS (ESI): m/z [M+Na]⁺ calcd for C_{23}H_{31}N_{3}O_{6}Na: 492.2110, found: 492.2107.

**(2S,3S,4R,5R)-5-Azido-2,3-isopropylidenedi oxy-4,6-bis(benzyloxy) hexan-1-ol (17).** An ice cooled solution of anhydrous LiCl (637 mg, 15 mmol) and NaBH₄ (567 mg, 15 mmol) in dry ethanol (15 mL) was stirred for 30 min, to it azido ester 16 (2.35 g, 5 mmol) dissolved in dry THF (15 mL) was added over 10 min. The reaction mixture was brought to room temperature and stirred for overnight. The solid precipitate was filtered and washed with EtOAc (20 mL) and EtOH (10 mL). The filtrate was concentrated in vacuo and the residue was dissolved in EtOAc, treated with saturated NH₄Cl (50 mL) at 0 °C and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and the solvent was removed under vacuo. The residue was purified by column chromatography using silica gel and EtOAc-hexane (1:9 followed by 1:4) as eluent to give pure compound 17 (1.85 g, 87%) as colorless oil; R_f = 0.25 (hexanes-EtOAc, 4:1); [α]_D^{25} = -24.2 (c 0.62, CHCl₃); IR (neat): (ν_max, cm⁻¹) 3421, 2925, 2101, 1722, 1265, 1098; ¹H NMR (CDCl₃, 300 MHz): δ_H 7.33-7.21 (m, 10H, Ar-H), 4.64 (d, J 11.5 Hz, 1H, benzylic CH₃), 4.56 (d, J 11.5 Hz, 1H, benzylic CH₃), 4.55 (s, 2H, benzylic CH₂), 4.05 (dd, J 2.4, 8.3 Hz, 1H, C(3)H), 3.95 (dt, J 4.3, 8.3 Hz, 1H, C(2)H), 3.82-3.69 (m, 3H, CH₂OH, CHOBn), 3.59-3.53 (m, 2H, CH₃CH₂OBn, CH₃N), 3.43 (dd, J 3.9, 11.8 Hz, 1H, CH₃CH₂OBn), 1.76 (br s, 1H, OH), 1.36 (s, 6H, 2 × CH₃); ¹³C NMR (CDCl₃, 75 MHz): δ_C 137.5, 137.4, 128.4, 128.3, 128.2, 128.0, 127.8, 109.0, 77.6, 76.7, 75.7, 74.3, 73.5, 69.3, 62.1, 61.7, 27.3, 26.9; ESI-MS: m/z 428 [M+H]⁺; HRMS (ESI): m/z [M+Na]⁺ calcd for C_{23}H_{29}N_{3}O_{6}Na: 450.0204, found: 450.0202.
(2S,3S,4R,5R)-5-Azido-4,6-bis(benzyloxy)-2,3-isopropylidenedioxy-1-methanesulfonyloxy-hexane (18). To a stirred cooled (0 °C) solution containing alcohol 17 (1.71 g, 4 mmol) and Et3N (2.3 mL, 16 mmol) in DCM (40 mL) was added methanesulfonyl chloride (MsCl, 0.92 mL, 8 mmol) and the mixture was allowed to warm to room temperature and stirred until the alcohol disappeared on TLC (3 h). Then the reaction was quenched with water (5 mL), extracted with hexanes MeOH and the filtrate was concentrated in vacuo to remove the solvents. The crude mass was chromatographed on silica gel using DCM (2 × 25 mL) and the organic layer was washed with brine, then dried over Na2SO4, concentrated, and the residue was purified by column chromatography using silica gel and EtOAc-hexanes (1:19) as eluent to give pure compound 18 (1.92 g, 93%) as colorless oil; Rf = 0.6 (hexanes-EtOAc, 4:1); [α]25D = -39.7 (c 0.39, CHCl3); IR (neat): (νmax, cm⁻¹) 3030, 2936, 2999, 1454, 1358, 1215, 1175; ¹H NMR (CDCl3, 300 MHz): δH 7.33-7.21 (m, 10H, Ar-H), 4.64 (d, J 11.3 Hz, 1H, benzylic CH₄H₃), 4.57 (d, J 3.9 Hz, 2H, benzylic CH₂), 4.54 (d, J 11.3 Hz, 1H, benzylic CH₆H₆), 4.14-4.06 (m, 2H, C(2)H), 4.03-3.97 (m, 2H, CH₂OMs), 3.84-3.77 (m, 2H, CH₂OBn), 3.74 (dd, J 4.5, 7.7 Hz, 1H, CHOBr), 3.59 (dd, J 2.0, 7.3 Hz, 1H, CHN₃), 2.96 (s, 3H, CH₃), 1.38 (s, 3H, CH₃), 1.37 (s, 3H, CH₃); ¹³C NMR (CDCl₃, 75 MHz): δC 137.4, 137.0, 128.5, 128.4, 128.3, 127.8, 110.0, 77.4, 74.9, 74.3, 74.1, 73.4, 69.0, 68.3, 61.8, 37.6, 26.9, 26.7; ESI-MS: m/z 528 [M+Na]+; HRMS (ESI): m/z [M+Na]+ calcd for C₂₉H₃₁N₃O₇SNa: 528.1780, found: 528.1804.

(2R,3R,4R,5S)-3-Benzzyloxy-2-benzyloxymethyl-4,5-isopropylidenedioxypiperidine (19). A mixture of mesyl compound 18 (1 g, 2 mmol) and Lindlar’s catalyst (20% content, 30% wt/wt, 300 mg) in EtOAc (20 mL) was stirred at room temperature under H₂ (balloons) atmosphere for 6 h. Then the reaction mixture was filtered through celite and washed with EtOAc (5 mL), K₂CO₃ (276 mg, 2 mmol) was added to the filtrate, and the mixture was refluxed for 3 h, then it was concentrated in vacuo to remove the solvents. The crude mass was chromatographed through silica gel using EtOAc-hexanes (1:9) as eluent to give pure compound 19 (665 mg, 86%) as colorless oil; Rf = 0.5 (hexanes-EtOAc, 1:1); [α]25D = +67.4 (c 0.5, CHCl₃); IR (neat): (νmax, cm⁻¹) 3338, 2922, 2853, 1456, 1374, 1231, 1084, 750; ¹H NMR (CDCl₃, 300 MHz): δH 7.31-7.21 (m, 10H, Ar-H), 4.85 (d, J 11.7 Hz, 1H, benzylic CH₄H₃), 4.53 (d, J 11.7 Hz, 1H, benzylic CH₆H₆), 4.47 (d, J 11.7 Hz, 1H, benzylic CH₄H₃), 4.39 (d, J 11.8 Hz, 1H, benzylic CH₆H₆), 3.69-3.61 (m, 2H, C(3)H, C(4)H ), 3.53-3.36 (m, 2H, C(5)H, CH₂OBn), 3.27-3.22 (m, 1H, CH₆H₆OBn ), 2.89 (br s, 1H, NH), 2.61 (m, 1H, C(2)H), 2.41-2.31 (m, 2H, C(6)H₂ ), 1.43 (s, 6H, 2 × CH₃); ¹³C NMR (CDCl₃, 75 MHz): δC 138.3, 137.8, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6, 110.3, 84.5, 76.5, 75.7, 73.3, 72.6, 68.7, 58.9, 46.4, 26.9, 26.7; ESI-MS: m/z 384 [M+H]+; HRMS (ESI): m/z [M+H]+ calcd for C₃₁H₄₅N₃O₂Na: 384.1742, found: 384.1745.

(+)-1-Deoxynojirimycin (1). A mixture of 19 (383 mg, 1 mmol) and Pd/C (10% content, 30% wt/wt, 115 mg) in EtOAc : MeOH (1:1, 10 mL) having 0.5 mL of 6N HCl was stirred for 48 h at room temperature under H₂ atmosphere (balloons). The catalyst was filtered through pad of celite, repeatedly washed with aqueous MeOH and the filtrate was concentrated in vacuo afforded a residue that was retained on a column packed with Dowex 50WX8 (200-400 mesh) ion-exchange resin. The column was washed with MeOH, water and then with 5% NH₄OH to afford pure compound 1 (121 mg, 75%) as white solid; mp 199-202 °C; [α]D²⁵ = +50 (c 0.2, 0.1% MeOH in H₂O).
H₂O), [lit.²⁰ᵇ mp 202-204 °C, [α]D²¹ = +47.1 (c 0.17, H₂O)]; IR (KBr): (ν_max, cm⁻¹) 3316, 2894, 2837, 1374, 1101, 1042, 990; ¹H NMR (D₂O, 300 MHz): δ_H 3.82 (dd, J 2.8, 11.7 Hz, 1H, CH₃H₂OH), 3.62 (dd, J 6.2, 11.7 Hz, 1H, CH₃H₂OH), 3.49 (dd, J 5.0, 10.5, 14.1 Hz, 1H, C(5)H), 3.31 (t, J 9.4 Hz, 1H, C(3)H), 3.2 (t, J 9.4 Hz, 1H, C(4)H), 3.11 (dd, J 5.0, 12.4 Hz, 1H, C(6)H₂H₂b), 2.54 (dd, J 2.8, 6.2, 9.4 Hz, 1H, C(2)H₂), 2.46 (t, J 11.8 Hz, 1H, C(6)H₂H₂b); ¹³C NMR (D₂O, 100 MHz): δ_C 81.0, 74.1, 73.4, 63.9, 63.1, 51.3; ESI-MS: m/z 164 [M+H]+; HRMS (ESI): m/z [M+H]+ calc'd for C₆H₁₄NO₃: 164.0922, found: 164.0925.

**D-Glucono-δ-lactam (5).** A mixture of dihydroxy-azide compound 15a (430 mg, 1 mmol) and Pd/C (10% content, 30% wt/wt, 130 mg) in EtOAc:MeOH (1:1, 20 mL) was stirred for 48 h at rt under H₂ atmosphere (balloons). Filtration of the mixture, washing with MeOH (30 mL), and evaporation gave only traces of 5. While washing the mixture with H₂O (50 mL), after evaporation, however afforded the crude compound 5 which was recrystallized from H₂O/EtOH to afford pure compound 5 (142 mg, 80%); white solid; mp: 203-205 °C; [α]D²⁵ = +54.3 (c 0.5, H₂O), [lit.²⁰ᵃ mp 204-205 °C, [α]D²⁰ = +57 (c 0.63, H₂O); [lit.²¹ᵇ mp 205-207 °C, [α]D²² = +59 (c 0.39, H₂O)]; IR (KBr): (ν_max, cm⁻¹) 3423, 3259, 3177, 2932, 1648, 1319, 1127; ¹H NMR (D₂O, 400 MHz): δ_H 3.98 (d, J 8.8 Hz, 1H, C(3)H), 3.80 (dd, J 3.2, 12.0 Hz, 1H, CH₃H₂OH), 3.73-3.67 (m, 3H, CH₃H₂OH, C(4)H, C(5)H), 3.36-3.30 (m, 1H, C(6)H); ¹³C NMR (D₂O, 75 MHz): δ_C 173.3, 73.2, 70.6, 67.5, 60.3, 56.9; ESI-MS: m/z 200 [M+Na]+; HRMS (ESI): m/z [M+Na]+ calc'd for C₆H₁₁NO₃Na: 200.0534, found: 200.0538.

**D-Altrono-δ-lactam (6).** The title compound 6 was prepared from 15b according to the procedure described for the synthesis of 5 from 15a. Yield: 138 mg, (78%); white solid; mp 136-138 °C; [α]D²⁵ = -28.8 (c 0.35, H₂O), [lit.²¹ᵇ mp 141-143 °C, [α]D²⁶ = -33.7 (c 0.30, H₂O)]; IR (KBr): (ν_max, cm⁻¹) 3420, 3257, 3272, 2937, 1654, 1322, 1125; ¹H NMR (D₂O, 400 MHz): δ_H 4.19 (d, J 8.7 Hz, 1H, C(3)H), 4.15 (t, J 2.9 Hz, 1H, C(4)H), 4.01 (dd, J 2.9, 8.7 Hz, 1H, C(5)H), 3.68 (dd, J 5.1, 11.7 Hz, 1H, CH₃H₂OH), 3.64 (dd, J 5.1, 11.7 Hz, 1H, CH₃H₂OH), 3.56 (dd, J 5.1, 8.7 Hz, 1H, C(6)H); ¹³C NMR (D₂O, 75 MHz): δ_C 173.8, 70.5, 69.8, 67.9, 62.7, 57.9; ESI-MS: m/z 200 [M+Na]+; HRMS (ESI): m/z [M+Na]+ calc'd for C₆H₁₁NO₃Na: 200.0534, found: 200.0528

**Acknowledgements**

The authors thank the Director, IICT for encouragement. This work is the Main Lab Project of IICT. MR thanks CSIR, New Delhi; TNR and BM thanks UGC, New Delhi for fellowships.
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