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.[1] A large number of azasugars have been extracted from natural sources, mainly from plants, microorganisms and more recently from insects and sea sponges.[2] 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.[3] 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.[4] 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]
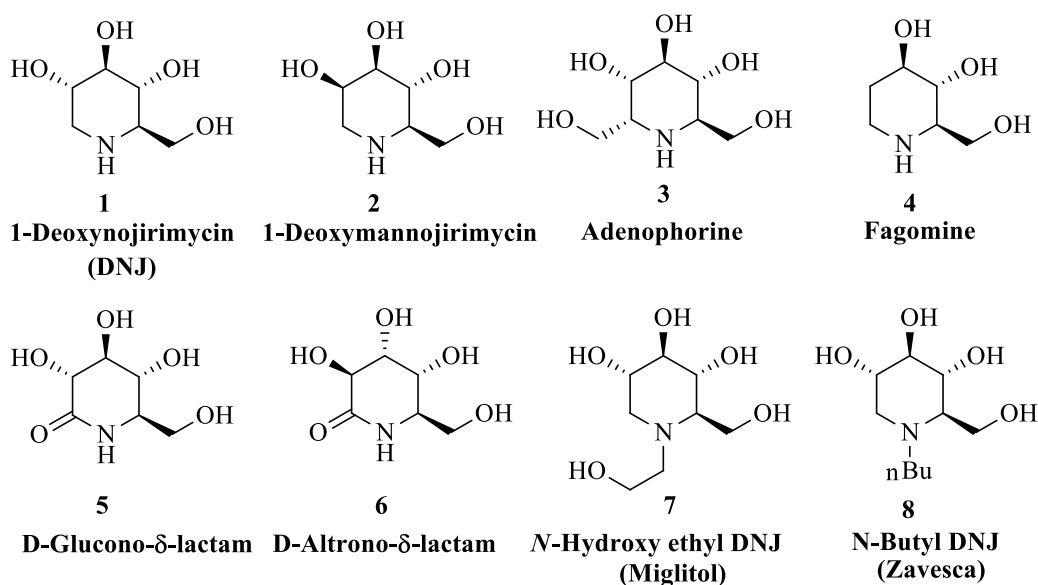

1
1-Deoxynojirimycin
(DNJ)

2
1-Deoxymannojirimycin

3
Adenophorine

4
Fagomine

5
D-Glucono-δ-lactam

6
D-Altrono-δ-lactam

7
***N*-Hydroxy ethyl DNJ**
(Miglitol)

8
N-Butyl DNJ
(Zavesca)

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-δ-lactam (**5**) and D-altrono-δ-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.

1. R, R^3 = H, R^1, R^2 = OH; X = 2H
5. R, R^3 = H, R^1, R^2 = OH; X = O
6. R, R^3 = OH, R^1, R^2 = H, X = O
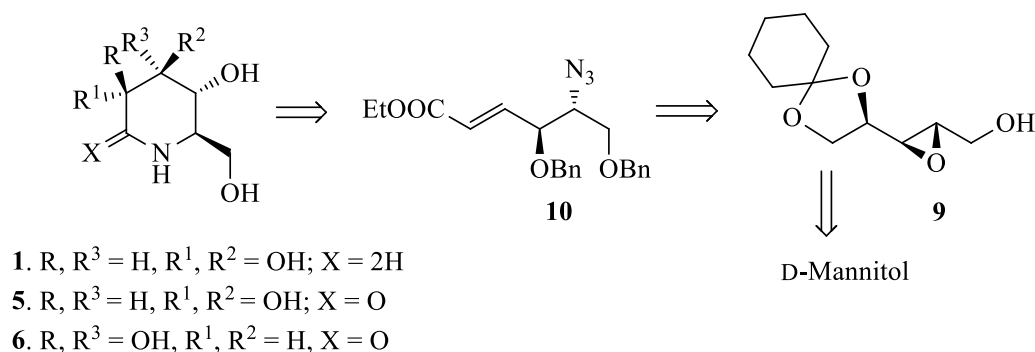
Scheme 1. Retrosynthetic plan for the synthesis of the title compounds **1**, **5** and **6**.

R = R^1 = -(CH$_2$)$_5$-
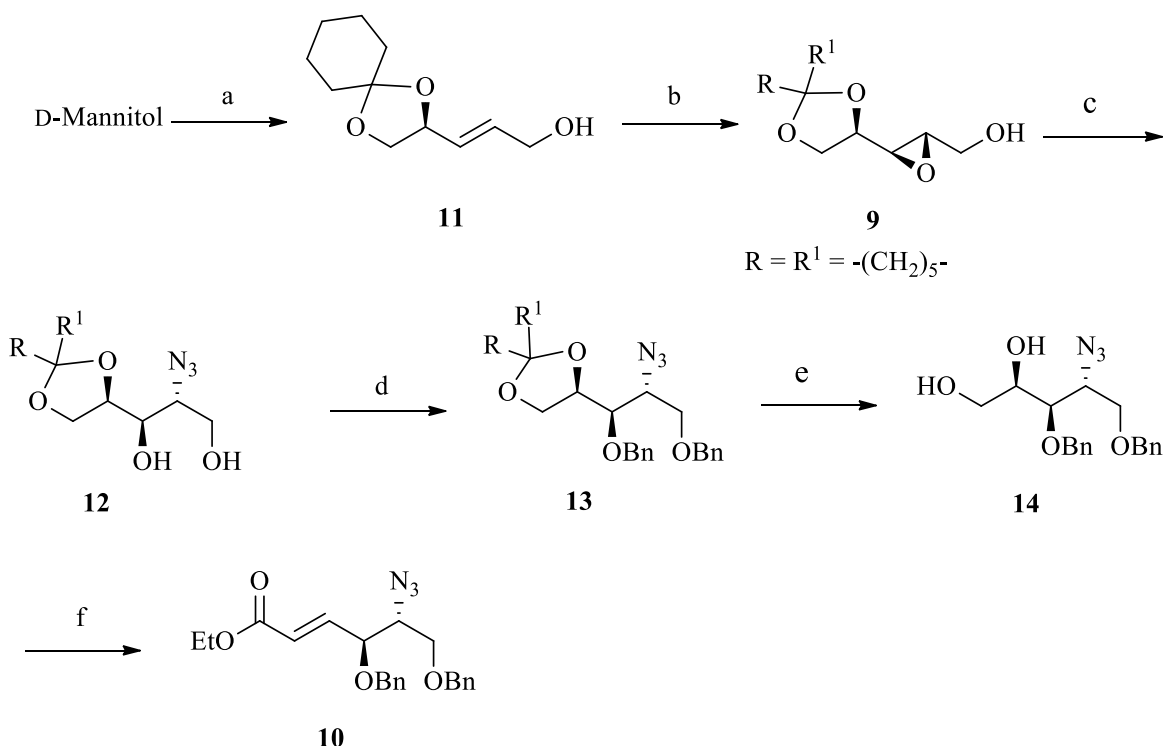
Reagents and conditions: (a) ref. 9; (b) diethyl L-tartrate, Ti(O^{i}Pr)$_4$, cumene hydroperoxide, 4Å MS, DCM, -20 °C, 72 h, 93%, 94% *de*; (c) (MeO)$_3$B, NaN$_3$, DMF, 50 °C, 6 h, then NaIO$_4$, 95%; (d) benzyl bromide, NaH, THF, *n*-Bu$_4$NI, 0 °C-rt, 16 h, 94%; (e) 10% HCl, CH$_3$CN, rt, 4 h, 95%; (f) (i) NaIO$_4$, aq.CH$_3$CN (60%), rt, 30 min, quantitative; (ii) (EtO)$_2$P(O)CH$_2$CO$_2$Et, LiCl, (^{i}Pr)$_2$NEt, CH$_3$CN, 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.[9] Thus synthesized *E*-allyl alcohol **11** was subjected to Sharpless catalytic asymmetric epoxidation[10] by using diethyl L-tartrate, Ti(O^{i}Pr)$_4$ and cumene

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 NaN_3-$(CH_3O)_3B$ system developed by Miyashita *et al.*[11] 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[12] 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 CH_3CN, afforded the 4-azido-1,2-diol **14** in good yield. The obtained azido-diol compound **14** was subjected to oxidative cleavage with $NaIO_4$ 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[13] to afford the desired, highly *E*- selective α,β-unsaturated ethyl ester **10** in 93% yield (*E:Z*, 98:2 based on ^{1}H 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.
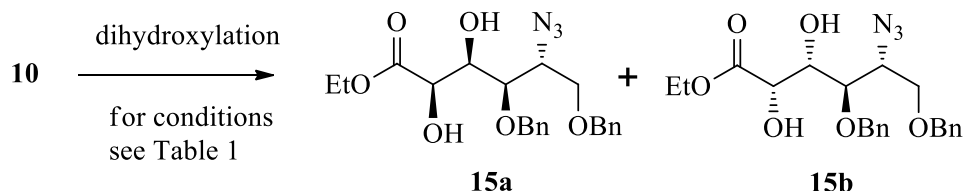
Scheme 3. Dihydroxylation of azido ester **10**.

Initially, compound **10** was treated with the recommended amount of AD-mix α (1.4 g/ 1mmol)[14] 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[15] 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 OsO_4 and *N*-methylmorpholine oxide (NMO)[16] 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.[14,17] This type of interaction between the catalyst and the bulkiness of the substrate in stereoselective dihydroxylation has been reported earlier.[18]

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

Entry	Reagents	Solvent[b]	Time	**15a:15b**[c]	Yield (%)[d]
1	AD-mix α (1.4 g/1 mmol), MeSO$_2$NH$_2$ (1 equiv.)	t-BuOH-H$_2$O (1:1)	5 days	84:16	40
2	AD-mix α (1.4 g/1 mmol), (DHQ)$_2$-PHAL (1 mol%), MeSO$_2$NH$_2$ (1 equiv.), NaHCO$_3$ (3 equiv.), OsO$_4$ (1 mol%),[a]	t-BuOH-H$_2$O (1:1)	3 days	94:6	78
3	AD-mix β (1.4 g/1 mmol), MeSO$_2$NH$_2$ (1 equiv.)	t-BuOH-H$_2$O (1:1)	5 days	10:90	44
4	AD-mix β (1.4 g/1 mmol), MeSO$_2$NH$_2$ (1 equiv.), NaHCO$_3$(3 equiv.), NaHCO$_3$(3 equiv.), OsO$_4$ (1 mol%),[a]	t-BuOH-H$_2$O (1:1)	3 days	3:97	82
5	OsO$_4$ (5 mol%),[a] NMO (3 equiv.)	Acetone-H$_2$O (9:1)	7 h	1:99	92

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

After completion of these dihydroxylation experiments on the ester **10**, we turned our attention to the synthesis of 1-deoxynojirimcycin (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$_4$, generated in situ,[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/CaCO$_3$) 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]
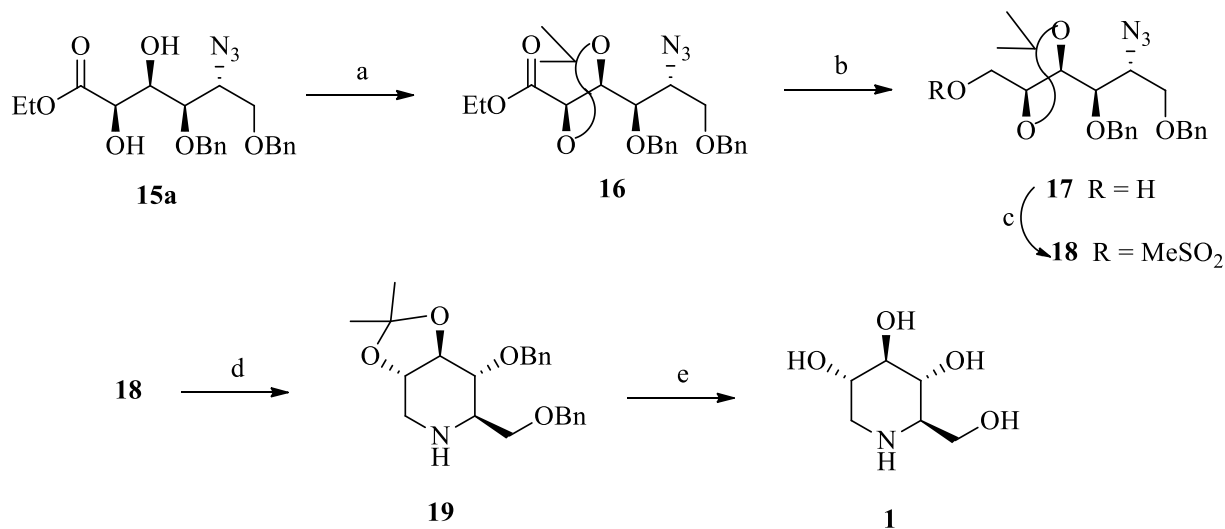
Reagents and conditions: (a) 2,2-DMP, acetone, PTSA, rt, overnight, 96%; (b) LiCl, NaBH$_4$, THF, EtOH, rt, overnight, 87%; (c) MsCl, Et$_3$N, DCM, 0 °C- rt, 3 h, 93%; (d) Pd/ CaCO$_3$ / H$_2$, MeOH, rt, 6 h, then K$_2$CO$_3$ reflux, 3 h, 86%; (e) Pd/C, H$_2$, MeOH, 6N HCl, rt, 48 h, then Dowex 50wx8 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.[20a,21]
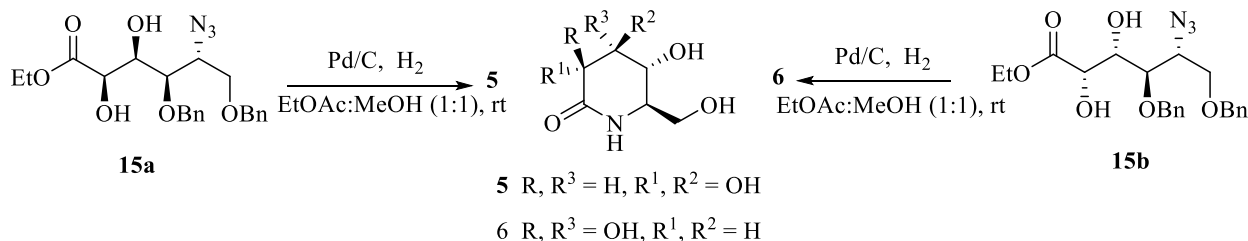
Scheme 5. Synthesis of D-glucono-δ-lactam **5** and D-altrono-δ-lactam **6**.

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-septa 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 ^{0}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 ^{1}H NMR and CDCl$_3$ for ^{13}C 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.

(2*R*,3*R*,4*R*)-2,3-Epoxy-4,5-(cyclohexylidenedioxy)pentan-1-ol (**9**). To powdered, activated 4Å molecular sieves (2.8 g 35% wt/wt) in dry CH_2Cl_2 (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 CH_2Cl_2 (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 CH_2Cl_2 (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 CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, 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); $[\alpha]_D^{25}$ = -23.8 (*c* 1.4, MeOH); IR (neat): (ν_{max}, cm^{-1}) 3446, 2934, 2859, 1448, 1367, 1162, 1096; ^{1}H NMR (CDCl$_3$, 300 MHz): δ_H 4.10-4.03 (m, 2H, C*H*$_2$CH), 3.91 (br d, *J* 13.1 Hz, 1H, C*H*$_a$H$_b$OH), 3.81 (dd, *J* 5.1, 7.3 Hz, 1H, CH$_2$C*H*), 3.64 (br d, *J* 13.1 Hz, 1H, CH$_a$*H*$_b$OH), 3.12 (dt, *J* 2.1, 3.6 Hz, 1H, oxirane-*H*), 3.04 (dd, *J* 2.1, 3.6 Hz, 1H, oxirane-*H*), 2.09 (br s, 1H, O*H*), 1.59-1.55 (m, 8H, Cy-*H*), 1.39 (br s, 2H, Cy-*H*); ^{13}C NMR (CDCl$_3$, 50 MHz)**:** δ_C 110.5, 74.6, 65.5, 60.8, 55.4, 55.1, 35.8, 34.9, 24.9, 23.8, 23.7; ESI-MS: *m/z* 237 [M+Na]$^+$; HRMS (ESI): *m/z* [M+Na]$^+$ calcd for C$_{11}$H$_{18}$O$_4$Na: 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]$^+$.

(2*R*,3*R*,4*R*)-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 NaN$_3$ (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 NaHCO$_3$ (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 NaHCO$_3$ solution (40 mL), brine (50 mL), and dried over Na$_2$SO$_4$. Concentration under reduced pressure gave an oily residue, that was dissolved in CH$_3$CN (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 Na_2SO_4, 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; R_f = 0.4 (hexanes-EtOAc, 1:1); $[\alpha]_D^{25}$ = -41.6 (*c* 1, MeOH); IR (neat): (ν_{max}, cm^{-1}) 3421, 2636, 2860, 2100, 1448, 1276, 1099; ^{1}H NMR (CDCl$_3$, 300 MHz): δ_H 4.34 (td, *J* 3.3, 6.7 Hz, 1H, CH$_2$C*H*), 4.13 (dd, *J* 6.7, 14.4 Hz, 1H, C*H*$_a$H$_b$CH), 4.02 (dd, *J* 3.3, 11.8 Hz, 1H, CH$_a$*H*$_b$CH), 3.92 (dd, *J* 6.7, 8.3 Hz, 2H, C*H*$_2$OH), 3.56-3.48 (m, 2H, C*H*OH, C*H*N$_3$), 2.56 (br d, *J* 6.7 Hz, 1H, O*H*), 2.43 (br s, 1H, O*H*), 1.64-1.57 (m, 8H, Cy-*H*), 1.44-1.40 (m, 2H, Cy-*H*); ^{13}C NMR (CDCl$_3$, 50 MHz): δ_C 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 C$_{11}$H$_{19}$N$_3$O$_4$Na: 280.1273, found: 280.1267.

(2*R*,3*R*,4*R*)-2-Azido-4,5-(cyclohexylidenedioxy)-1,3-(bisbenzyloxy)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 ^{o}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 Et$_2$O (3 × 70 mL). The combined organic layers were dried over Na$_2$SO$_4$, 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; R_f = 0.6 (hexanes-EtOAc, 4:1); $[\alpha]_D^{25}$ = -8.6 (*c* 1.4, MeOH); IR (neat): (ν_{max}, cm^{-1}) 2935, 2860, 2097, 1451, 1274, 1102; ^{1}H NMR (CDCl$_3$, 300 MHz): δ_H 7.29-7.23 (m, 10H, Ar-*H*), 4.75 (d, *J* 11.3 Hz, 1H, benzylic C*H*$_a$H$_b$), 4.59 (d, *J* 11.3 Hz, 1H, CH$_a$*H*$_b$), 4.52 (s, 2H, benzylic C*H*$_2$), 4.24 (dd, *J* 7.5, 11.3 Hz, 1H, C*H*$_a$H$_b$CH), 3.98 (dd, *J* 6.0, 7.5 Hz, 1H, CH$_2$C*H*), 3.80 (dd, *J* 2.2, 9.8 Hz, 1H, CH$_a$*H*$_b$CH), 3.70-3.64 (m, 2H, C*H*$_2$OBn), 3.54-3.48 (m, 2H, C*H*OBn, C*H*N$_3$), 1.59-1.56 (m, 8H, Cy-*H*), 1.38 (br s, 2H, Cy-*H*); ^{13}C NMR (CDCl$_3$, 50 MHz): δ_C 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 C$_{25}$H$_{31}$N$_3$O$_4$Na: 460.2212, found: 460.2204.

(2*R*,3*R*,4*R*)-4-Azido-3,5-bis(benzyloxy)pentane-1,2-diol (**14**). To a cooled (0 ^{o}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 Na$_2$SO$_4$, 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 ^{o}C; R_f = 0.2 (hexanes-EtOAc, 1:1); $[\alpha]_D^{25}$ = -8.82 (*c* 1, MeOH); IR (KBr): (ν_{max}, cm^{-1}) 3325, 2923, 2135, 2100, 1451, 1317, 1064; ^{1}H NMR (CDCl$_3$, 400

MHz): δ_H 7.36-7.24 (m, 10H, Ar-*H*), 4.68 (d, *J* 10.8 Hz, 1H, benzylic C*H*$_a$H$_b$), 4.59 (d, *J* 10.8 Hz, 1H, benzylic CH$_a$*H*$_b$), 4.56 (s, 2H, benzylic C*H*$_2$), 3.90 (dt, *J* 4.4, 6.6, 1H, C*H*OH), 3.81 (dd, *J* 4.4, 10.2 Hz, 1H, C*H*$_a$H$_b$OH), 3.75 (dd, *J* 2.9, 10.2 Hz, 1H, CH$_a$*H*$_b$OH), 3.70-3.64 (m, 3H, C*H*$_2$OBn, C*H*N$_3$), 3.64 (dd, *J* 4.4, 6.6 Hz, 1H, C*H*OBn), 2.83 (br s, 1H,O*H*), 1.99 (br s, 1H, O*H*); ^{13}C NMR (CDCl$_3$, 75 MHz): δ_C 137.4, 137.1, 128.5, 128.4, 128.2, 128.1, 127.9, 127.7, 77.4, 74.4, 73.5, 71.2, 69.2, 63.9, 61.6; ESI-MS: *m/z* 380 [M+Na]$^+$; HRMS (ESI): *m/z* [M+Na]$^+$ calcd for C$_{19}$H$_{23}$N$_3$O$_4$Na: 380.1586, found: 380.1597.

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 NaIO$_4$ (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 × 50 mL). The combined organic layers were washed with water (20 mL), brine (40 mL) and dried over Na$_2$SO$_4$. 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. R_f = 0.5 (hexanes-EtOAc, 3:1); $[\alpha]_D^{25}$ = +16.0 (*c* 1, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz): δ_H 9.56 (d, *J* 1.5 Hz, 1H, C*H*O), 7.33-7.23 (m, 10H, Ar-*H*), 4.73 (d, *J* 11.3 Hz, 1H, benzylic C*H*$_a$H$_b$), 4.65 (d, *J* 11.3 Hz, 1H, benzylic CH$_a$*H*$_b$), 4.49 (s, 2H, benzylic C*H*$_2$), 3.92 (dd, *J* 1.5, 3.7 Hz, 1H, C*H*OBn), 3.87 (dt, *J* 3.7, 6.0 Hz, 1H, C*H*N$_3$), 3.71 (dd, *J* 6.7, 9.8 Hz, 1H, C*H*$_a$H$_b$OBn), 3.63 (dd, *J* 6.0, 9.8 Hz, 1H, CH$_a$*H*$_b$OBn). ^{13}C NMR (CDCl$_3$, 75 MHz): δ_C 200.8, 137.2, 136.5, 128.5, 128.4, 128.3, 128.1, 127.8, 127.6, 82.5, 73.4, 67.6, 61.4; ESI-MS: *m/z* 348 [M+Na]$^+$.

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 acetonitrile (25 mL) at room temperature and the mixture was stirred at rt for 16 h. The reaction mixture was diluted with water (40 mL), extracted with EtOAc (2 × 75 mL) and the combined organic layers were washed with brine (40 mL), dried over Na$_2$SO$_4$, filtered and concentrated gave an oily residue which was chromatographed on silica gel with EtOAc-hexane (1:49) gave highly predominant *E*-isomer **10** (inseparable *E* and *Z* isomers in 98:2 ratio, based on crude ^{1}H-NMR; 3.66 g, 93%) as colorless oil; R_f = 0.55 (hexanes-EtOAc, 3:1); $[\alpha]_D^{25}$ = +29.8 (*c*, 1.0, CHCl$_3$); IR (neat): (ν_{max}, cm^{-1}) 2866, 2100, 1720, 1454, 1271, 1175, 1097; ^{1}H NMR (CDCl$_3$, 300 MHz): δ_H 7.32-723 (m, 10H, Ar-*H*), 6.85 (dd, *J* 6.7, 15.8 Hz, 1H, =C*H*), 6.05 (d, *J* 15.8 Hz, 1H, =C*H*), 4.62 (d, *J* =12.0 Hz, 1H, benzylic C*H*$_a$H$_b$), 4.49 (s, 2H, benzylic C*H*$_2$), 4.40 (d, *J* 12.0 Hz, 1H, benzylic CH$_a$*H*$_b$), 4.25 (q, *J* 7.5 Hz, 2H, C*H*$_2$CH$_3$), 4.16 (t, *J* 5.2 Hz, 1H, C*H*OBn), 3.68 (dd, *J* 5.8, 11.7 Hz, 1H, C*H*N$_3$), 3.60 (d, *J* 5.2 Hz, 2H, C*H*$_2$OBn), 1.34 (t, *J* 7.5 Hz, 3H, C*H*$_3$); ^{13}C NMR (CDCl$_3$, 50 MHz): δ_C 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]$^+$; HRMS (ESI): *m/z* [M+Na]$^+$ calcd for C$_{22}$H$_{25}$N$_3$O$_4$Na: 418.1742, found: 418.1745.

Ethyl (2R,3R,4R,5R)-5-azido-4,6-bis(benzyloxy)-2,3-dihydroxyhexanoate (15a). To a stirred solution of AD-mix α (5.6 g, 1.4 g/1 mmol) in t-BuOH and H$_2$O (10 mL *t*-BuOH + 20 mL H$_2$O)

at room temperature were added 0.04 molar toluene solution of OsO_4 (1 mL, 0.04 mmol, 1 mol%), (DHQ)$_2$PHAL (125 mg, 0.16 mmol), NaHCO$_3$(1 g, 12 mmol) and MeSO$_2$NH$_2$ (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 completed the reaction (72 h), then the reaction mixture was quenched with solid Na$_2$SO$_3$ (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 Na$_2$SO$_4$, 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; R_f = 0.33 (hexanes-EtOAc, 7:3); [α]$_D^{25}$ = -21.7 (*c* 0.47, CHCl$_3$); IR (neat): (ν$_{max}$, cm^{-1}) 3545, 3358, 2866, 2108, 1730, 1202, 1107, 1055; ^{1}H NMR (CDCl$_3$, 300 MHz): δ$_H$ 7.34-7.26 (m,10H, Ar-*H*), 4.74 (d, *J* 10.4 Hz, 1H, benzylic C*H*$_a$H$_b$), 4.61 (d, *J* 10.4 Hz, 1H, benzylic CH$_a$*H*$_b$), 4.58 (dd, *J* 12.4, 14.5 Hz, 2H, benzylic C*H*$_2$), 4.41 (br d, *J* 3.1 Hz, 1H, C*H*OH), 4.28 (m, 2H, C*H*$_2$CH$_3$), 4.05 (dd, *J* 3.1, 5.2 Hz, 1H, C*H*OH), 4.01 (dd, *J* 6.2, 14.5 Hz, 1H, C*H*OBn), 3.81 (dd, *J* 5.2, 10.4 Hz, 1H, C*H*$_a$H$_b$OBn), 3.73-3.69 (m, 2H, CH$_a$*H*$_b$OBn, C*H*N$_3$), 3.07 (br d, *J* 4.1 Hz, 1H, O*H*), 2.55 (br d, *J* 8.3 Hz, 1H, O*H*), 1.30 (t, *J* 7.2 Hz, 3H, C*H*$_3$); ^{13}C NMR (CDCl$_3$, 75 MHz): δ$_C$ 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 C$_{22}$H$_{27}$N$_3$O$_6$Na: 452.1797, found: 452.1813.

Ethyl (2*S*,3*S*,4*R*,5*R*)-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 OsO_4 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:H$_2$O (20 mL, 9:1) was added 0.04 M toluene solution of OsO_4 (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.* CH$_2$Cl$_2$ (40 mL) was added, separated the layers and the aqueous layers was extracted with CH$_2$Cl$_2$ (2 × 20 mL) and the combined organic layers were washed with brine (30 mL), dried over Na$_2$SO$_4$, 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; R_f = 0.3 (hexanes-EtOAc, 7:3); [α]$_D^{25}$ = -14.8 (*c* 0.5, CHCl$_3$, compound synthesized using AD-mix-β); [α]$_D^{25}$ = -15.2 (c 0.5, CHCl$_3$, compound synthesized using OsO$_4$); IR (neat): (ν$_{max}$, cm^{-1}) 3414, 2937, 2861, 2103, 1448, 1277, 1099; ^{1}H NMR (CDCl$_3$, 300 MHz): δ$_H$ 7.34-7.29 (m, 10H, Ar-*H*), 4.76 (d, *J* 10.9 Hz, 1H, benzylic C*H*$_a$H$_b$), 4.63 (d, *J* 10.9 Hz, 1H, benzylic CH$_a$*H*$_b$), 4.56 (s, 2H, benzylic C*H*$_2$), 4.45 (br d, *J* 4.1 Hz, 1H, C*H*OH), 4.30-4.20 (m, 2H, C*H*$_2$CH$_3$), 4.09-4.02 (m, 2H, C*H*OH, C*H*OBn), 3.82-3.70 (m, 3H, C*H*$_2$OBn, C*H*N$_3$), 3.12 (br d, *J* 5.2 Hz, 1H, O*H*), 2.65 (br d, *J* 8.6 Hz, 1H, O*H*), 1.30 (t, *J* 7.1 Hz, 3H, C*H*$_3$); ^{13}C NMR (CDCl$_3$, 75 MHz): δ$_C$ 173.5, 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 $C_{22}H_{27}N_3O_6Na$: 452.1797, found: 452.1808.

Ethyl (2*R*,3*S*,4*R*,5*R*)-5-azido-2,3-(isopropylidenedioxy)-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 NaHCO$_3$ solution were 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 Na$_2$SO$_4$, 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, CHCl$_3$); IR (neat): (ν$_{max}$, cm^{-1}) 2987, 2930, 2100, 1757, 1375, 1206, 1102; ^{1}H NMR (CDCl$_3$, 400 MHz): δ$_H$ 7.31-7.21 (m, 10H, Ar-*H*), 4.63 (s, 2H, benzylic C*H*$_2$), 4.58 (d, *J* 11.7 Hz, 1H, benzylic C*H*$_a$H$_b$), 4.54 (d, *J* 12.6 Hz, 1H, benzylic CH$_a$*H*$_b$), 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 (q, *J* 6.8 Hz, 2H, C*H*$_2$CH$_3$), 3.83 (dd, *J* 4.8, 11.7 Hz, 1H, C*H*$_a$H$_b$OBn), 3.74-3.68 (m, 3H, CH$_a$*H*$_b$OBn, C*H*OBn, C*H*N$_3$), 1.42 (s, 6H, 2 × C*H*$_3$), 1.31 (t, *J* 6.8 Hz, 3H, CH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, 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+NH$_3$), 442 (98%) (M+H-N$_2$); HRMS (ESI): *m/z* [M+Na]$^+$ calcd for $C_{25}H_{31}N_3O_6Na$: 492.2110, found: 492.2107.

(2*S*,3*S*,4*R*,5*R*)-5-Azido-2,3-isopropylidenedioxy-4,6-bis(benzyloxy)-hexan-1-ol (17). An ice cooled solution of anhydrous LiCl (637 mg, 15 mmol) and NaBH$_4$ (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 NH$_4$Cl (50 mL) at 0 ºC and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried over Na$_2$SO$_4$ 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, CHCl$_3$); IR (neat): (ν$_{max}$, cm^{-1}) 3421, 2925, 2101, 1722, 1265, 1098; ^{1}H NMR (CDCl$_3$, 300 MHz): δ$_H$ 7.33-7.21 (m, 10H, Ar-*H*), 4.64 (d, *J* 11.5 Hz, 1H, benzylic C*H*$_a$H$_b$),4.56 (d, *J* 11.5 Hz, 1H, benzylic CH$_a$*H*$_b$), 4.55 (s, 2H, benzylic C*H*$_2$), 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, C*H*$_2$OH, C*H*OBn), 3.59-3.53 (m, 2H, C*H*$_a$H$_b$OBn, C*H*N$_3$), 3.43 (dd, *J* 3.9, 11.8 Hz, 1H, CH$_a$*H*$_b$OBn), 1.76 (br s, 1H, O*H*), 1.36 (s, 6H 2 × C*H*$_3$); ^{13}C NMR (CDCl$_3$, 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 $C_{23}H_{29}N_3O_5Na$**:** 450.2004, found: 450.2002.

(2*S*,3*S*,4*R*,5*R*)-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 Et_3N (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 DCM (2 × 25 mL) and the organic layer was washed with brine, then dried over Na_2SO_4, 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; R_f = 0.6 (hexanes-EtOAc, 4:1); $[\alpha]_D^{25}$ = -39.7 (*c* 0.39, $CHCl_3$); IR (neat): (ν_{max}, cm^{-1}) 3030, 2936, 2099, 1454, 1358, 1215, 1175; ^1H NMR ($CDCl_3$, 300 MHz): δ_H 7.33-7.21 (m, 10H, Ar-*H*), 4.64 (d, *J* 11.3 Hz, 1H, benzylic C*H*aHb), 4.57 (d, *J* 3.9 Hz, 2H, benzylic C*H*2), 4.54 (d, *J* 11.3 Hz, 1H, benzylic CHa*H*b), 4.14-4.06 (m, 2H, C(2)*H*, C(3)*H*), 4.03-3.97 (m, 2H, C*H*2OMs), 3.84-3.77 (m, 2H, C*H*2OBn), 3.74 (dd, *J* 4.5, 7.7 Hz, 1H, C*H*OBn), 3.59 (dd, *J* 2.0, 7.3 Hz, 1H, C*H*N3), 2.96 (s, 3H, C*H*3), 1.38 (s, 3H, C*H*3), 1.37 (s, 3H, C*H*3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 137.4, 137.0, 128.5, 128.4, 128.3, 128.2, 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 $C_{24}H_{31}N_3O_7SNa$: 528.1780, found: 528.1804.

(2*R*,3*R*,4*R*,5*S*)-3-Benzyloxy-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 H_2 (balloons) atmosphere for 6 h. Then the reaction mixture was filtered through celite and washed with EtOAc (5 mL), K_2CO_3 (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; R_f = 0.5 (hexanes-EtOAc, 1:1); $[\alpha]_D^{25}$ = +67.4 (*c* 0.5, $CHCl_3$); IR (neat): (ν_{max}, cm^{-1}) 3338, 2922, 2853, 1456, 1374, 1231, 1084, 750; ^1H NMR ($CDCl_3$, 300 MHz): δ_H 7.31-7.21 (m, 10H, Ar-*H*), 4.85 (d, *J* 11.7 Hz, 1H, benzylic C*H*aHb), 4.53 (d, *J* 11.7 Hz, 1H, benzylic CHa*H*b), 4.47 (d, *J* 11.7 Hz, 1H, benzylic C*H*aHb), 4.39 (d, *J* 11.8 Hz, 1H, benzylic CHa*H*b), 3.69-3.61 (m, 2H, C(3)*H*, C(4)*H*), 3.53-3.36 (m, 2H, C(5)*H*, C*H*aHbOBn), 3.27-3.22 (m, 1H, CHa*H*bOBn), 2.89 (br s, 1H, NH), 2.61 (m, 1H, C(2)*H*), 2.41-2.31 (m, 2H, C(6)*H*2), 1.43 (s, 6H, 2 × C*H*3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 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 $C_{23}H_{30}NO_4$: 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 H_2 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% NH_4OH to afford pure compound **1** (121 mg, 75%) as white solid; mp 199-202 °C; $[\alpha]_D^{25}$ = +50 (*c* 0.2,

H$_2$O), [lit.[20b] mp 202-204 °C, [α]$_D^{21}$ = +47.1 (c 0.17, H$_2$O)]; IR (KBr): (ν$_{max}$, cm^{-1}) 3316, 2894, 2837, 1374, 1101, 1042, 990; ^{1}H NMR (D$_2$O, 300 MHz): δ$_H$ 3.82 (dd, J 2.8, 11.7 Hz, 1H, CH_aH$_b$OH), 3.62 (dd, J 6.2, 11.7 Hz, 1H, CH$_a$$H_b$OH), 3.49 (ddd, J 5.0, 10.5, 14.1 Hz, 1H, C(5)H), 3.31 (t, J 9.4 Hz, 1H, C(3)H), 3.2 (t, J 9.4 Hz, 1H, C(4)H), 3.11 (dd, J 5.0, 12.4 Hz, 1H C(6)H_aH$_b$), 2.54 (ddd, J 2.8, 6.2, 9.4 Hz, 1H, C(2)H), 2.46 (t, J 11.8 Hz, 1H, C(6)H$_a$$H_b$); ^{13}C NMR (D$_2$O, 100 MHz): δ$_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]$^+$ calcd for C$_6$H$_{14}$NO$_4$**:** 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 H$_2$ atmosphere (balloons). Filtration of the mixture, washing with MeOH (30 mL), and evaporation gave only traces of **5**. While washing the mixture with H$_2$O (50 mL), after evaporation, however afforded the crude compound **5** which was recrystallized from H$_2$O/EtOH to afford pure compound **5** (142 mg, 80%); white solid; mp: 203-205 °C; [α]$_D^{25}$ = +54.3 (c 0.5, H$_2$O), {[lit.[20a] mp 204-205 °C, [α]$_D^{20}$ = +57 (c 0.63, H$_2$O]; [lit.[21b] mp 205-207 °C, [α]$_D^{22}$ = +59 (c 0.39, H$_2$O]}; IR (KBr): (ν$_{max}$, cm^{-1}) 3423, 3259, 3177, 2932, 1648, 1319, 1127; ^{1}H NMR (D$_2$O, 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, CH_aH$_b$OH), 3.73-3.67 (m, 3H, CH$_a$$H_b$OH, C(4)$H$, C(5)$H$), 3.36-3.30 (m, 1H, C(6)H); ^{13}C NMR (D$_2$O, 75 MHz): δ$_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]$^+$ calcd for C$_6$H$_{11}$NO$_5$Na: 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]$_D^{25}$ = -28.8 (c 0.35, H$_2$O), [lit.[21b] mp 141-143 °C, [α]$_D^{26}$ = -33.7 (c 0.30, H$_2$O)]; IR (KBr): (ν$_{max}$, cm^{-1}) 3420, 3257, 3272, 2937, 1654, 1322, 1125; ^{1}H NMR (D$_2$O, 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, CH_aH$_b$OH), 3.64 (dd, J 5.1, 11.7 Hz, 1H, CH$_a$$H_b$OH), 3.56 (dd, J 5.1, 8.7 Hz, 1H, C(6)H); ^{13}C NMR (D$_2$O, 75 MHz): δ$_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]$^+$ calcd for C$_6$H$_{11}$NO$_5$Na: 200.0534, found: 200.0528

Acknowledgements

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