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Synthesis of polyhydroxylated indolizidines and piperidines from Garner's aldehyde: total synthesis of (−)-swainsonine, (+)-1,2-di-*epi*-swainsonine, (+)-8,8a-di-*epi*-castanospermine, pentahydroxy indolizidines, (−)-1-deoxynojirimycin, (−)-1-deoxy-*altro*-nojirimycin, and related diversity

Priyanka Singh, Sudipta Kumar Manna, Gautam Panda *

Medicinal and Process Chemistry Division, CSIR – Central Drug Research Institute, Lucknow 226031, UP, India

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ABSTRACT

Diastereoselective and diverse synthesis of polyhydroxylated indolizidines and piperidines have been described, where a common chiral intermediate 2-(hydroxymethyl) piperidine-3-ol is converted into (−)-swainsonine, (+)-1,2-di-*epi*-swainsonine, (+)-8,8a-di-*epi*-castanospermine, pentahydroxy indolizidines, (−)-1-deoxynojirimycin, (−)-1-deoxy-*altro*-nojirimycin, and related diversity. The key steps were hydroxy directed intramolecular aminomercuration, Mitsunobu cyclization, and diastereoselective dihydroxylation.

1. Introduction

New applications of natural and synthetic glycosidase inhibitors continue to mount interest in basic research and medicine. Swainsonine,[1] Castanospermine,[2] and their derivatives belong to indolizidine class of glycosidase inhibitors, and have generated much interest due to their potent and selective glycosidase inhibition activities and consequently exhibit significant anticancer, antitumor,[3] antimetastatic, immunoregulating,[4] and anti-HIV[5] properties. In addition to this, it was established that structural modifications in iminosugars induce significant changes in their biological activity, their potency, or their specificity as inhibitors of immunomodulators[6] as well as glycosidases.[7] Therefore several analogues have been synthesized and used as biochemical tools and have been examined as chemotherapeutic agents against diabetes,[8] cancers,[9] and HIV.[10] It is believed that their activity is the result of their ability to mimic the transition state involved in substrate hydrolysis. For example, the similarity of the six-membered ring of castanospermine to the glucosyl cation, is responsible for the activity of castanospermine against glucosidases.[11] In a less evident way, resemblance of the five membered ring of swainsonine to the mannosyl cation is responsible for the anti-mannosidase activity.[12] It has been suggested that their rigid, bicyclic structures are responsible for their potent activity. 1-Deoxynojirimycin (DNJ)[13] belongs to polyhydroxylated piperidine class of glycosidase inhibitors and inhibits α-glucosidases I and II.[14] In addition to this, it also exhibits promising antiviral[15] and anticancer activities. Miglitol[16] and Miglustat,[17] two of these synthetic analogues of polyhydroxylated piperidines are drugs against type-2 diabetes and Gaucher's disease, respectively. (−)-1-Deoxy-*altro*-nojirimycin; an analogue of nojirimycin, also shows modest activity towards glycosidases.[18] The biological activity of these above mentioned indolizidine and piperidines, coupled with their complex structural features, have led to many stereoselective syntheses of these natural alkaloids to date. Majority of syntheses of these alkaloids involve chemical transformations of monosaccharides, however, with the development in field of enantioselective synthesis, non-carbohydrate syntheses have also been reported.[19–21] Even though, the development of new expeditious stereodivergent approaches furnishing compounds in enantiomerically pure form from a common precursor remains a worthwhile job.

Recently, we reported,[22] the total syntheses of natural alkaloids Epiquinamide and Conhydrin, using ring-closing metathesis.[23,24] We envisaged that key intermediate **1**, readily prepared in a few steps from Garner aldehyde[24] derived from L-serine, could be a versatile precursor for the diastereoselective total synthesis of the natural isomer of swainsonine. We also demonstrate here that compound **1** is

* Corresponding author. E-mail addresses: gautam.panda@gmail.com, gautam_panda@cdri.res.in (G. Panda).

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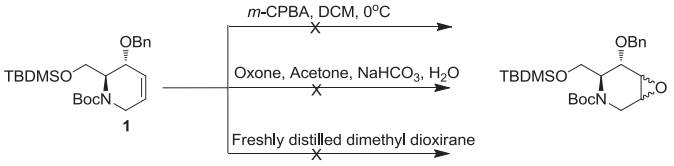
a versatile precursor for the diastereoselective synthesis of the alkaloids (+)-8,8a-di-*epi*-castanospermine, (+)-1,2-di-*epi*-swainsonine, (1*S*,2*R*,6*S*,7*R*,8*S*,8a*S*)-ctahydroindolizidine-1,2,6,7,8-pentol, (1*R*,2*S*,6*S*,7*R*,8*S*,8a*S*)-octahydroindolizidine-1,2,6,7,8-pentol, (−)-1-deoxy-*altro*-nojirimycin, *N*-(3-hydroxypropyl)-*altro*-DNJ, *N*-(2-hydroxyethyl)-*altro*-DNJ and *N*-butyl-*altro*-DNJ, and (−)-1-deoxynojirimycin.

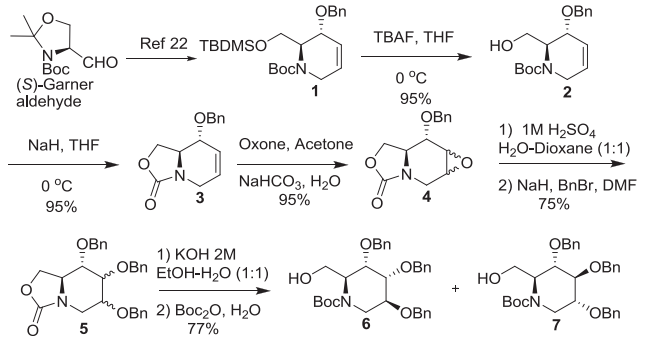
2. Results and discussions

The synthesis of (+)-8,8a-di-*epi*-castanospermine, (−)-1-deoxy-*altro*-nojirimycin, *N*-(3-hydroxypropyl)-*altro*-DNJ, *N*-(2-hydroxyethyl)-*altro*-DNJ and *N*-butyl-*altro*-DNJ and (−)-1-deoxynojirimycin, L-*altro*-deoxy-nojirimycin, (1*S*,2*R*,6*S*,7*R*,8*S*,8a*S*)-octahydroindolizidine-1,2,6,7,8-pentol, and (1*R*,2*S*,6*S*,7*R*,8*S*,8a*S*)-octahydroindolizidine-1,2,6,7,8-pentol commenced from **1**.

Our first aim was to introduce epoxy functionality on the double bond of **1**, while it yielded a complex mixture of products under standard conditions, (Scheme 1). The silyl ether **1**, upon desilylation followed by NaH treatment at 0 °C furnished oxazolidinone **3**, which on stereoselective epoxidation via in situ generated dimethyldioxirane (DMDO)[25] gave mixture of epoxides **4**[26] (overall yield 85.7% from **1**), (Scheme 2). ^{1}H NMR spectra of **4** showed that diastereomers were in 70:30 ratios. As the diastereoisomers were inseparable, the stereochemistry of epoxidation was determined from the subsequent steps.



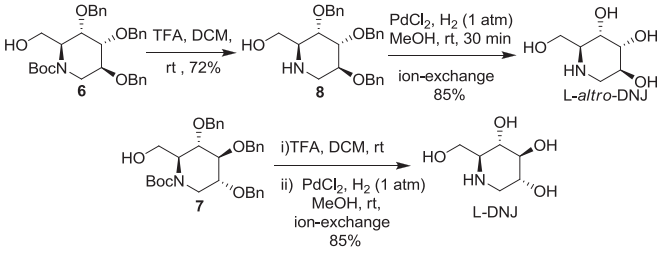
Scheme 1.



Scheme 2. Conversion of **1** to advanced precursor **6**.

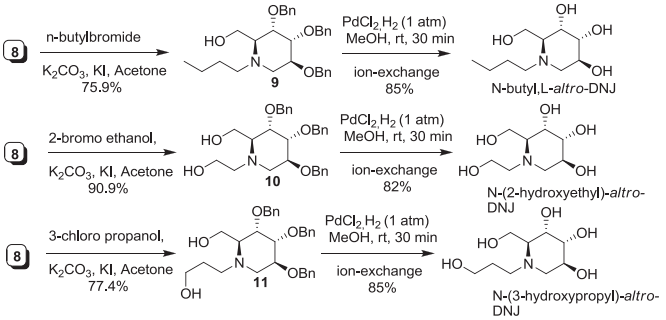
With the mixture of epoxides in hand, opening of this ring was explored. Towards this objective, use of $BF_3 \cdot OEt_2$ and benzyl alcohol in DCM on epoxides **4** was unsuccessful. On the other hand, $NaHSO_4$ and water treatment on epoxides **4** led to the recovery of starting material. It was decided that more strongly acidic conditions were necessary to provide the desired products. Treatment of epoxides **4** with sulfuric acid (1 M) in a 1:1 water/dioxane[27] mixture afforded the diols, which were protected as benzyl ethers **5** in 75% yields. ^{1}H NMR spectra of **5** showed the mixture of diastereomers. Moreover, diastereomers were inseparable at this stage as well, thus we proceeded further with the mixture of diastereomers. Hydrolysis of the oxazolidinone **5** under basic condition followed by protection of amine using Boc anhydride furnished two pure diastereomers **6** and **7** (95:5) in seven synthetic steps with 47% and 3% overall yield, respectively, from **1**. The exact stereochemistry of compound **6** was confirmed from the ultimate conversion of major intermediate **6** into L-*altro*-deoxynojirimycin.

With compound **6** and **7** in hand, we proceeded towards total synthesis of L-*altro*-1-deoxy-nojirimycin and L-1-deoxy-nojirimycin. Removal of *N*-Boc of **6** by acid treatment provided amino alcohol **8** (Scheme 3), which on hydrogenolysis with $PdCl_2/H_2$[28] afforded L-*altro*-1-DNJ in 29% overall yield from **1**. The ^{1}H, ^{13}C NMR, IR, and mass spectra of L-*altro*-1-DNJ were in agreement with those reported earlier.[20] Using the similar synthetic sequence, minor isomer **7** was converted in L-DNJ in 85% yield from **7**. The ^{1}H, ^{13}C NMR, IR, and mass spectra of L-1-DNJ were in agreement with those reported earlier.[20]



Scheme 3. Synthesis of L-*altro*-1-DNJ and L-DNJ.

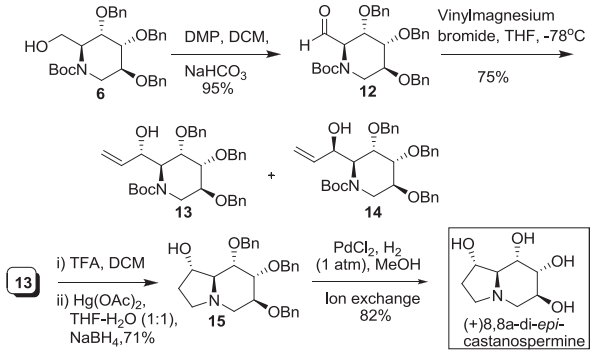
Synthesis of *N*-butyl-*altro*-DNJ, *N*-(2-hydroxyethyl)-*altro*-DNJ, and *N*-(3-hydroxypropyl)-*altro*-DNJ were easily achieved in two steps from amino alcohol **8** (Scheme 4). *N*-Butyl-DNJ was obtained through N-alkylation of **8** with *n*-butyl bromide giving **9** followed by hydrogenolysis with $PdCl_2/H_2$ in 85% yield after ion-exchange chromatography. Similarly *N*-(2-hydroxyethyl)-DNJ and *N*-(3-hydroxypropyl)-DNJ were obtained by N-alkylation of **8** with 2-bromoethanol and 3-bromo propanol providing **10** and **11**, respectively, followed by hydrogenolysis in 82% and 85% yields, respectively, after ion-exchange chromatography.



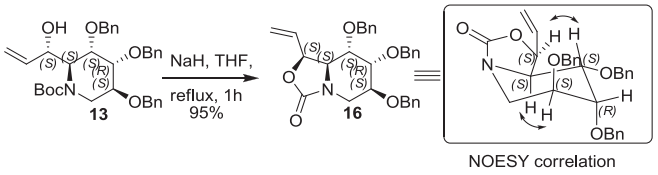
Scheme 4. Synthesis of L-*altro*-DNJ analogues.

Next, we turned our attention to conversion of **6** into (+)-8,8a-di-*epi*-castanospermine containing stereochemically well-defined hydroxylated carbon center C-1. Thus, the construction of pyrrolidine ring was initiated through intramolecular aminomercuration strategy.[29]

The synthesis commenced with oxidation of alcohol **6** to corresponding aldehyde **12** by the use of Dess–Martin periodinane[30] (DMP) as an oxidant in basic media, followed by addition of vinyl magnesium bromide at −78 °C furnishing separable diastereomeric mixture (3:1) of anti/syn products[31] **13** and **14** (Scheme 5). In order to establish the stereochemistry of newly generated carbinol in **13**, it was converted into oxazolidinone **16** and its 2D NMR studies confirmed the structure of **13** (Scheme 6).



Scheme 5. Synthesis of (+) 8,8a-di-*epi*-castanospermine.



Scheme 6. Stereochemical assignment of **13**.

Treatment of **13** under acidic condition provided β-hydroxy-γ-alkenylamine, which on exposure with mercury (II) acetate in THF/water at room temperature, followed by the reductive demercuration with $NaBH_4$, afforded exclusively 5-*endo*-*trig*-cyclized product **15** in 71% yield. Similar treatment on **14** did not yield any cyclized product because of unfavorable conformation. It could be explained by the fact that products were formed due to hydroxyl directed mercuration.[32] The reactivity difference towards mercuration of compounds **13** and **14** may depend on the possible transition states arising from amines derived from **13** and **14**, respectively.[33] As shown in hydroxyl directed mercuration (Fig. 1), Hg^{2+} approaches from the same side of hydroxyl in **13** and **14** but experiences less steric interaction in **13** compared to **14**. Subsequently, from the opposite side, nucleophilic attack of secondary amine in **13** furnished compound **15** whereas **14** did not.

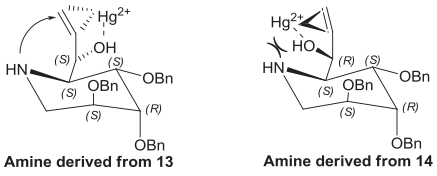
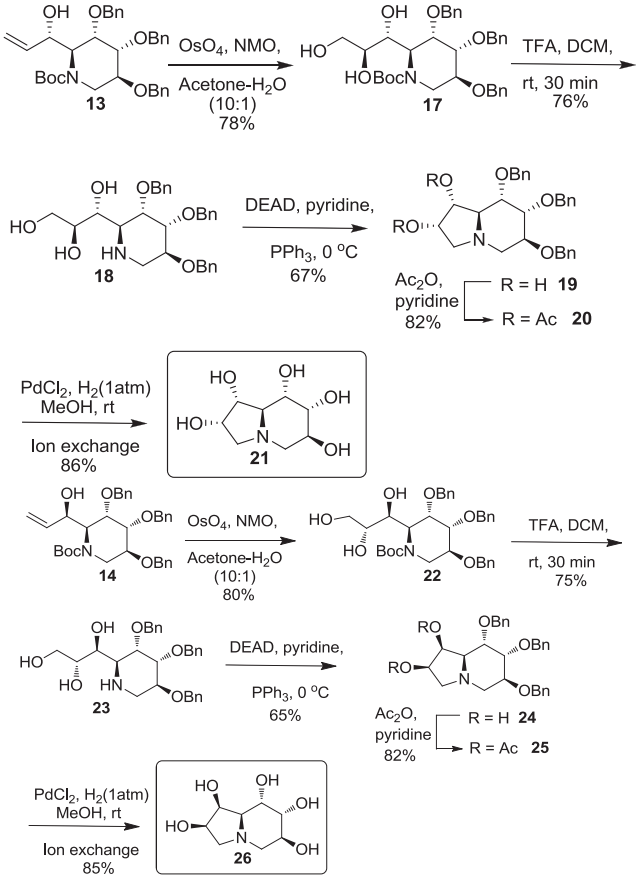


Fig. 1. Possible transition states of amines derived from **13** and **14**.

Hydrogenolysis of **15** with $PdCl_2/H_2$ furnished (+) 8,8a-di-*epi*-castanospermine with 82% yields after ion-exchange chromatography and overall 15% yield from intermediate **1**. The ^1H, ^{13}C NMR, IR, and mass were in agreement with those reported earlier.[21]

A modified strategy is required for the synthesis of pentahydroxylated indolizidine derivatives as they have one extra hydroxyl group at 2-position of indolizidine ring than castanospermine, Scheme 7. To achieve this goal allylic alcohol **13** and **14** underwent dihydroxylation[34] reaction using Upjohn condition to furnish triol **17** as the only isolable diastereomer in case of **13** in 78% yield and the major diastereomers **22** along with its minor isomer in ratio 4:1 in case of **14**.

The stereochemical outcome of this dihydroxylation (DH) reaction could be explained by Kishi's model.[35] Addition of bulky osmium reagent occurred from the face opposite to the hydroxy group because of the repulsion of the oxygen lone pairs with OsO_4.



Scheme 7. Synthesis of pentahydroxylated indolizidines.

In Kishi's empirical model, the substrate reacts in such conformation that minimizes $A^{1,3}$ strain. For **13**, conformation I is highly favored as there is no $A^{1,3}$ strain, yielding only one diastereoisomer. Whereas in **14**, conformation II is disfavored due to $A^{1,3}$ strain furnishing two diastereomers (4:1), Fig. 2.

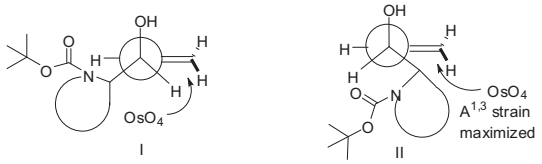


Fig. 2. Conformational model of **13** and **14**.

Treatment of triol **17** with trifluoroacetic acid resulted in *N*-Boc hydrolysis and gave the amino triol **18** in 76% yields, which was further used in next step without purification. Finally under Mitsunobu reaction conditions[36] with pyridine as the solvent, **18** underwent cyclization to give indolizidine **19** in a combined yield of 39.7% from **13** after purification of the crude reaction mixture by column chromatography. Hydrogenolysis of **19** under conditions using $PdCl_2/H_2$ gave **21** in 86% yields after ion-exchange chromatography. A similar reaction sequence, with triol **22**, afforded **26**. The target molecules were characterized by spectral and analytical techniques.

The stereochemistry of final compounds was confirmed on the basis of NOESY spectrum of acetylated products **20** and **25**. The significant NOESY correlations are shown in Fig. 3. In **20**, H-1 showed the NOESY correlation to H-2 and H-8 whereas in **25** H-1 showed the NOESY correlation with H-2 and H-8a. All these correlations confirmed the stereochemistry of final compounds.

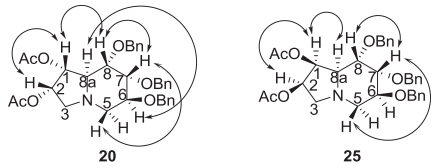
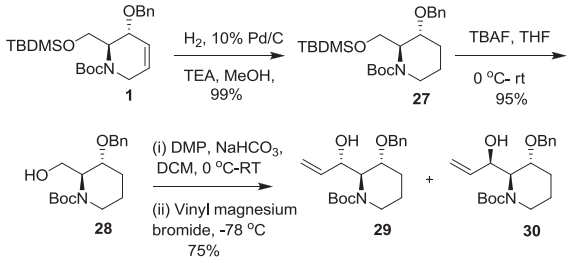


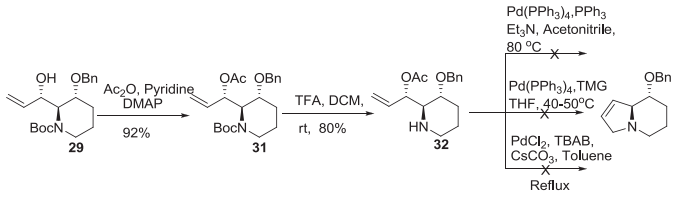
Fig. 3. NOESY correlation for **20** and **25**.

The synthetic sequences involved the selective double bond reduction through hydrogenation using H_2/10% Pd–C/triethyl amine followed by desilylation of TBS ether of **27**. The resulting alcohol **28** was oxidized to the corresponding aldehyde, which on addition of vinyl magnesium bromide at −78 °C, afforded the separable diastereomeric mixture (3:1) of anti/syn products **29** and **30**, respectively, in good yields (Scheme 8).



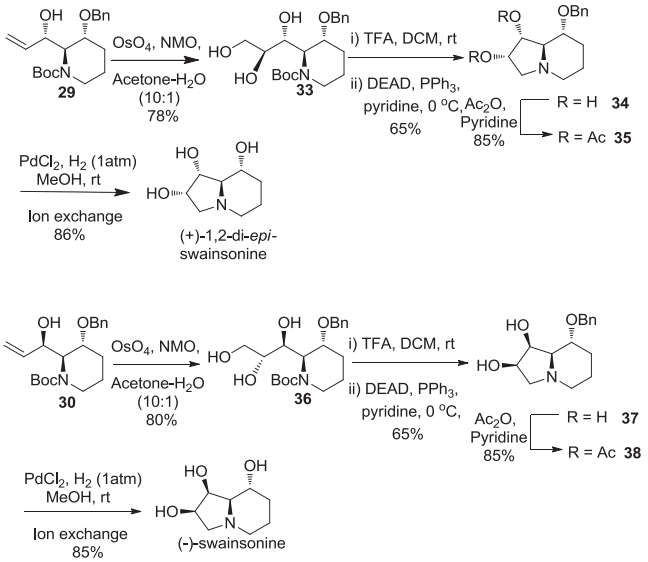
Scheme 8. Conversion of compound **1** into key intermediates **28** and **29**.

Now having the intermediate **29** with all the stereocenters in place as of the target molecule, we set out to prepare for the cyclization followed by dihydroxylation (Scheme 9). The palladium-catalyzed intramolecular amination are very much known in literature so we thought to use this methodology for cyclization. Hydroxy group of intermediate **29** was converted to its acetate derivative **31**. Acidic hydrolysis of *N*-Boc carbamate gave **32**. The intramolecular amination of amine **32** by using [$Pd(PPh_3)_4$], triphenylphosphine and triethyl amine as the base at 80 °C in acetonitrile was unsuccessful. Whereas use of $Pd(PPh_3)_4$ and trimethylguanidine as base in THF under nitrogen atmosphere at 40–55 °C led to recovery of starting material.[37] However use of strong basic condition, $PdCl_2$ and tetrabutylammonium bromide (TBAB) as a stabilizer in the presence of Cs_2CO_3 led to decomposition of starting material.[38] Disappointing with these results, we planned to modify our strategy. Modified synthetic plan involved, dihydroxylation of intermediate followed by cyclization.



Scheme 9. Attempted cyclization of **29**.

Application of Upjohn dihydroxylation (DH)[32] on another key intermediate **29**, furnished the triol **33** as the only isolable diastereomer in 78% yield whereas **30** gave triol **36** as major product (85%) along with its minor diastereomeric triol (15%). With *N*-Boc cleavage of triols **33** and **36** under acidic condition (TFA/DCM) yielded corresponding amino triols, which were further used in subsequent steps without purification (Scheme 10). Nevertheless, our effort to cyclize the amino-triol under Appel cyclization reaction conditions[39] were unsuccessful and resulted into a complex mixture of products. Finally treatment of amino triols under



Scheme 10. Synthesis of (+)-1,2-di-*epi*-swainsonine and (−)-swainsonine.

Mitsunobu reaction conditions[36] with pyridine as solvent produced the desired indolizidine products **34** and **37** in 65% yields. Hydrogenolysis of **34** and **37** by $PdCl_2/H_2$ gave (+)1,2-di-*epi*-swainsonine and (−)-Swainsonine in 86% and 85% yield, respectively, after ion-exchange chromatography and overall 23% and 7% from intermediate **1**. The ^1H and ^{13}C NMR spectral data were in consonance with that reported in the literature.[12] The stereochemistry was also determined by 2D NMR spectra of their acetate derivatives **35** and **38**. The stereochemical outcome of this DH reaction could be explained by the same way as has been described in **13** and **14**.

3. Conclusions

Diverse and straightforward syntheses of (−)-swainsonine, (+)-1,2-di-*epi*-swainsonine, (+)-8,8a-di-*epi*-castanospermine, (1*S*,2*R*,6*S*,7*R*,8*S*,8a*S*)-octahydroindolizidine-1,2,6,7,8-pentol and (1*R*,2*S*,6*S*,7*R*,8*S*,8a*S*)-octahydroindolizidine-1,2,6,7,8-pentol, (−)-1-deoxy nojirimycin, (−)-1-deoxy-*altro*-nojirimycin, *N*-(3-hydroxypropyl)-*altro*-DNJ, *N*-(2-hydroxyethyl)-*altro*-DNJ, and *N*-butyl-*altro*-DNJ have been described from easily accessible common chiral intermediate. Hydroxy directed intramolecular aminomercuration, and diastereoselective dihydroxylation were the key easily executable synthetic sequences, which gave access to a large number of polyhydroxylated indolizidines, piperidines, and their related diversity. Bioevaluation of this series is underway.

4. Experimental

4.1. General methods

Organic solvents were dried by standard methods. All the products were characterized by ^1H, ^{13}C, two-dimensional homonuclear COSY (correlation spectroscopy), heteronuclear single quantum coherence (HSQC), Nuclear Overhauser effect spectroscopy (NOESY), IR, ESI-MS, HRMS (direct analysis in real time, DART), and HRMS (quadrupole time of flight, Q-TOF). Analytical TLC was performed using 2.5×5 cm plates coated with a 0.25 mm thickness of silica gel (60F-254) using UV light as visualizing agent and an acidic solution of ninhydrin, and heat as developing agents. Column chromatography was performed using silica gel (60–120 and 100–200 mesh). NMR spectra were recorded on 300 MHz (^1H) and 50, 75 MHz (^{13}C). Experiments were recorded in $CDCl_3$ and D_2O at 25 °C. Chemical shifts are given on the δ scale and are referenced to

the TMS at 0.00 ppm for proton and 0.00 ppm for carbon. For ^{13}C NMR reference $CDCl_3$ appeared at 77.00 ppm. IR spectra were recorded on FT-IR spectrophotometers. Optical rotations were determined by using a 1 dm cell at 25 °C in chloroform, methanol, and water as the solvents; concentrations mentioned are in g/100 mL.

4.1.1. (8R,8aS)-8-(Benzyloxy)-8,8a-dihydro-1H-oxazolo[3,4-a]pyridin-3(5H)-one: ***3****.* To a cooled (0 °C) solution of alcohol **2** (50.0 mg, 0.15 mmol) in dry THF (2.25 mL) was added sodium hydride (7.48 mg, 0.31 mmol), in one portion, under nitrogen atmosphere and allowed to stir for 1 h at same temperature. After completion of reaction, it was quenched by addition of saturated aqueous NH_4Cl, and extracted with ethyl acetate (3×5 mL). The combined organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography to afford **3** (36.43 mg, 95%) as a white semi solid. Eluent for column chromatography: EtOAc/Hexane (17.5/32.5, v/v), $[\alpha]_D^{28}$ −1.5 (*c* 0.37, CH_3OH); R_f 0.50 (1/1 EtOAc/Hexane) ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.31 (5H, m, ArH), 5.98–5.79 (2H, m, CH=CH), 4.72 (1H, d, *J*=11.6 Hz, OCH_2Ph), 4.54–4.43 (2H, m, OCH_2Ph, CH_AH_BO), 4.13–4.06 (2H, m, $2CH_AH_BO$, CHOBn), 3.95–3.92 (1H, m, CHN), 3.69–3.57 (2H, m, NCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 137.3, 128.6, 128.2, 127.9, 126.4, 124.9, 74.0, 71.2, 67.4, 54.5, 40.9, 29.6; IR (neat, cm^{-1}) 3021, 2365, 1752, 1520, 1426, 1216, 1087, 763, 671; mass (ESI-MS) *m*/*z* 246 $[M+H]^{\bullet+}$; HRMS (DART) calcd for $C_{14}H_{16}NO_3$ $[M+H]^{\bullet+}$: 246.11302, measured 246.11522.

4.1.2. (6aS,7S)-7-(Benzyloxy)tetrahydro-1aH-oxazolo[3,4-a]oxireno[2,3-d]pyridin-4(2H)-one: ***4****.* To a stirred mixture of **3** (860 mg, 3.51 mmol), $NaHCO_3$ (4.42 g, 52.60 mmol), acetone (75.57 mL), and water (37.74 mL), oxone (10.82 g, 17.60 mmol) was added in portions over half an hour at 0 °C. The resulting mixture was stirred at room temperature, for four hours. After completion of reaction, it was diluted with ethyl acetate and washed with water followed by brine. The organic layer was dried over Na_2SO_4. The solvent was evaporated, and the residue was purified by silica gel column chromatography to furnish **4** (870 mg, 95%) as white semi solid. Eluent for column chromatography EtOAc/Hexane (30/20, v/v); R_f 0.55 (EtOAc); IR (Neat, cm^{-1}) 3428, 3022, 2364, 1744, 1652, 1522, 1427, 1216, 765, 672; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.35 (m, 5H, ArH), 4.80 (1H, dd, *J*=11.8, 2.0 Hz, OCH_2Ph), 4.6 (1H, m, OCH_2Ph) 4.30–4.10 (1H, m, CH_AH_BO), 4.06–3.70 (m, 3H, CH_AH_BO, CHN, NCH_AH_B), 3.57–3.40 (m, 3H, NCH_AH_B, CHO), 3.36–3.29 (m, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 137.0, 136.6, 128.8, 128.7, 128.5, 128.4, 128.1, 128.0, 75.4, 73.0, 72.1, 71,5, 67.3, 65.9, 53.9, 52.8, 52.6, 52.5, 51.6, 49.6, 39.5, 38.8; mass (ESI-MS) *m*/*z* found 262 $[M+H]^{\bullet+}$, HRMS (ESI TOF (+)): calcd for $C_{14}H_{16}NO_4$ $[M+H]^{\bullet+}$: 262.10793, measured 262.10723.

4.1.3. (8S,8aS)-6,7,8-Tris(benzyloxy)tetrahydro-1H-oxazolo[3,4-a]pyridin-3(5H)-one: ***5****.* To the solution of **4** (420 mg, 1.60 mmol) in a mixture of dioxane and water (1:1, 80 mL), an aqueous H_2SO_4 solution (1 M, 4.8 mL, 4.81 mmol) was added, and the mixture was allowed to stir at 80 °C for 12 h. A saturated aqueous $NaHCO_3$ solution (50 mL) was added, and the mixture was stirred at room temperature for 10 min. The aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with brine, and dried over Na_2SO_4. The organic fraction was concentrated in vacuo to give diols as a white gum. The residue was used without further purification. To a solution of the crude diols (426 mg, 1.52 mmol) in dry DMF (20 mL), NaH (182.9 mg, 60% mineral oil dispersion, and 7.62 mmol) was slowly added at 0 °C. The suspension was stirred at 0 °C until the evolution of H_2 had ceased (10 min) followed by the addition of benzyl bromide (400 μl, 3.35 mmol), and the mixture was allowed to stir at room temperature for 3 h. At 0 °C, saturated aqueous NH_4Cl solution (30 mL) was slowly added, and the resulting aqueous phase was extracted with Et_2O. The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography to furnish **5** as a white semi solid (553 mg, 75%). Eluent for column chromatography: EtOAc/Hexane (10/40, v/v); R_f 0.35 (1.5/3.5 EtOAc/Hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.23 (15H, m, ArH), 4.73–4.61 (2H, m, OCH_2Ph), 4.54 (2H, d, *J*=11.1 Hz, OCH_2Ph), 4.38–4.29 (m, 3H, OCH_2Ph, CH_AH_BO), 4.06–4.01 (m, 1H, CHOBn), 3.99–3.75 (m, 3H, 2CHOBn, CH_AH_BO), 3.74–3.68 (2H, m, NCH_AH_B, CHN), 3.20 (1H, dd, *J*=14.3, 1.4 Hz, NCH_AH_B); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.0, 137.8, 137.5, 137.3, 128.5, 128.4, 128.0, 127.9, 127.8, 127.77, 127.73, 127.6, 75.5, 73.3, 72.9, 72.7, 71.3, 70.8, 65.7, 52.9, 38.6; IR (neat, cm^{-1}) 3398, 3020, 2363, 1752, 1218, 1077, 766; mass (ESI-MS) *m*/*z* 460 $[M+H]^{\bullet+}$; HRMS (ESI TOF (+)): calcd for $C_{28}H_{30}NO_5$ $[M+H]^{\bullet+}$: 460.21240, measured 460.21250.

4.1.4. (2S,3S,4R,5S)-tert-Butyl 3,4,5-tris(benzyloxy)-2-(hydroxymethyl)piperidine-1-carboxylate: ***6****.* To the solution of oxazolidinone **5** (1 g, 2.18 mmol) in EtOH (7.72 mL), an aqueous solution of KOH (2 M, 7.72 mL) was added. The mixture was allowed to reflux for 12 h. After completion of reaction, it was cooled to room temperature, diluted with water, and extracted with ethyl acetate. The combined organic fraction was washed with water, followed by brine, and dried over anhydrous Na_2SO_4. Then organic fraction was concentrated under reduced pressure to give colorless oil. The residue was used without further purification. To the solution of crude amino alcohol (946 mg, 2.18 mmol) in water (2.18 mL), $(Boc)_2O$ (2.62 mmol, 0.60 mL) was added, and allowed to stir for 1 h. The reaction mixture was diluted with water, and extracted with ethyl acetate (35 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vacuo. Purification by flash chromatography afforded compound **6** as major (850 mg, 73.2%) and **7** as minor products (44 mg, 3.8%).

For **6**: white gum, eluent for column chromatography: EtOAc/Hexane (13/37, v/v); $[\alpha]_D^{28}$ +2.2 (*c* 0.94, MeOH); R_f 0.48 (2/3 EtOAc/Hexane); IR (neat, cm^{-1}) 3442, 2926, 1671, 1419, 1368, 1107, 745, 698; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.23 (15H, m, ArH), 4.74–4.55 (6H, m, OCH_2Ph), 4.50 (1H, s, CH_AH_BOH), 4.4–4.26 (1H, m, CH_AH_BOH), 3.91 (1H, q, *J*=13.3 Hz, CHOBn), 3.79 (1H, t, *J*=2.6 Hz, CHOBn), 3.71–3.64 (1H, m, OH), 3.56 (2H, m, CHN, NCH_AH_B), 2.78 (1H, t, *J*=10.9 Hz, NCH_AH_B), 1.42 (9H, s, CMe_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 138.4, 138.1, 128.3, 128.2, 127.8, 127.6, 127.58, 127.5, 127.4, 80,4, 79.1, 74.7, 73.7, 72.9, 72.3, 71.5, 59.9, 55.9, 42.9, 28.3; mass (ESI-MS) *m*/*z* 556 $[M+Na]^{\bullet+}$; HRMS (ESI TOF (+)): calcd for $C_{32}H_{39}NNaO_6$ $[M+Na]^+$: 556.26751, measured 556.26621.

4.1.5. (2S,3S,4S,5R)-tert-Butyl 3,4,5-tris(benzyloxy)-2-(hydroxymethyl)piperidine-1-carboxylate: ***7****.* White gum, eluent for column chromatography: EtOAc/Hexane (13/37, v/v); $[\alpha]_D^{28}$ +0.6 (*c* 1.04, MeOH); R_f 0.47 (2/3 EtOAc/Hexane); IR (neat, cm^{-1}) 3442, 2926, 1671, 1419, 1368, 1107, 745, 698; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32–7.29 (15H, m, ArH), 4.77–4.64 (5H, m, OCH_2Ph), 4.54 (d, *J*=11.7 Hz, 1H, OCH_2Ph), 3.85 (m, 1H, CH_AH_BOH), 3.78–3.75 (m, 1H, CHOBn), 3.73–3.65 (m, 2H, CHOBn, CH_AH_BOH), 3.62–3.55 (m, 3H, CHOBn, CHN, NCH_AH_B), 3.16 (m, 1H, NCH_AH_B), 1.42 (9H, s, CMe_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.7, 138.1, 138.08, 138.04, 128.4, 128.3, 127.9, 127.8, 127.7, 83.3, 80.6, 77.9, 76.0, 73.6, 73.5, 71.2, 61.5, 59.3, 43.2, 28.3; mass (ESI-MS) *m*/*z* 556 $[M+Na]^+$; HRMS (ESI TOF (+)): calcd for $C_{32}H_{39}NNaO_6$ $[M+Na]^+$: 556.26751, measured 556.26621.

4.1.6. ((2S,3S,4R,5S)-3,4,5-Tris(benzyloxy)piperidin-2-yl)methanol: ***8****.* To a stirred solution of compound **6** (150 mg, 0.34 mmol) in dry DCM (15 mL), 50% TFA in DCM was added at 0 °C. After completion of the reaction, it was quenched by saturated solution of $NaHCO_3$, and aqueous layer was extracted with DCM. The combined organic

layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vacuo to a colorless oil, which on column chromatographic purification gave the pure compound **8** (white gum, 87 mg, 72%). Eluent for column chromatography: MeOH/$CHCl_3$ (2.5/47.5, v/v). $[\alpha]_D^{28}$ −2.5 (*c* 1.0, MeOH); R_f 0.5 (1/9, MeOH/$CHCl_3$); IR (neat, cm^{-1}) 3449, 2925, 2856, 2364, 1688, 1218, 1094, 771; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.23 (15H, m, ArH), 4.67–4.39 (6H, m, OCH_2Ph), 4.07 (1H, t, J=6.5 Hz, CH_AH_BOH), 3.98 (1H, d, J=1.2 Hz, CHOBn), 3.80–3.69 (3H, m, OH, 2CHOBn), 3.65–3.59 (1H, m, CH_AH_BOH), 3.07–2.99 (1H, m, CHN), 2.89 (1H, dd, J=11.9, 3.1 Hz, NCH_AH_B), 2.66 (1H, dd, J=11.9, 2.3 Hz, NCH_AH_B), 2.27 (1H, br s, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 138.1, 137.9, 128.4, 128.3, 128.2, 127.7, 127.6, 85.6, 75.0, 73.8, 72.8, 71.7, 71.4, 69.6, 59.3, 46.5; (ESI-MS) *m*/*z* 434 $[M+H]^{\bullet+}$; HRMS (ESI TOF (+)): calcd for $C_{27}H_{32}NO_4$ $[M+H]^{\bullet+}$ 434.23313, measured 434.23093.

4.1.7. (2S,3S,4R,5S)-2-(Hydroxymethyl)piperidine-3,4,5-triol [L-altro-1-deoxynojirimycin]. To a solution of compound **8** (50 mg, 0.11 mmol) in MeOH (1 mL) was added catalytic amount of $PdCl_2$. The mixture was stirred at room temperature under an atmosphere of H_2 (balloon) for 1 h. The mixture was filtered through a Celite pad, and the filtrates were evaporated in vacuo. The residue was dissolved in water (1 mL), and applied to a column of Amberlite IRA-400 basic ion-exchange resin. Elution with water (30 mL) followed by evaporation of the eluent in vacuo, gave the title product L-*altro*-1-deoxynojirimycin (16 mg, 85%). $[\alpha]_D^{28}$ −3.73 (*c* 0.2, H_2O); ^1H NMR (300 MHz, D_2O) δ 3.87 (1H, m, CH_AH_BOH), 3.82 (1H, m, CH_AH_BOH), 3.75 (1H, dd, J=9.4, 2.8 Hz, CHOH), 3.69–3.68 (2H, m, CHOH), 2.81 (1H, dd, J=14.2, 1.87 Hz, CHN), 2.77–2.67 (2H, m, CH_2N); ^{13}C NMR (75 MHz, D_2O) δ 70.7, 69.4, 66.4, 60.9, 55.7, 44.6; IR (neat, cm^{-1}) 3600–3200; (ESI-MS) *m*/*z* 164 $[M+H]^{\bullet+}$; HRMS (ESI TOF (+)): calcd for $C_6H_{14}NO_4$ $[M+H]^{\bullet+}$: 164.09228, measured 164.09258.

4.1.8. (2S,3S,4S,5R)-2-(Hydroxymethyl)piperidine-3,4,5-triol (L-DNJ). Reaction was performed in same manner as for compound **8** and L-DNJ, compound **7** (50 mg, 0.115 mmol), afforded L-DNJ. (16 mg, 85%). $[\alpha]_D^{28}$ −10.7 (*c* 0.6, H_2O); IR (neat, cm^{-1}) 3600–3200; ^1H NMR (300 MHz, D_2O) δ 3.71 (dd, J=11.8, 3.0 Hz, 1H, CH_AH_BOH), 3.52 (dd, J=11.3, 6.0 Hz, 1H, CH_AH_BOH), 3.42–3.34 (m, 1H, CHOH), 3.21 (t, J=9.3 Hz, 1H, CHOH), 3.12 (t, J=9.3 Hz, 1H, CHOH), 3.05 (dd, J=12.3, 5.0 Hz, 1H, CHN); 2.49–2.46 (m, 1H, NCH_AH_BOH), 2.37 (dd, J=12.2, 11.0 Hz, 1H, NCH_AH_BOH); ^{13}C NMR (75 MHz, D_2O) δ 81.1, 74.2, 73.6, 64.1, 63.3, 51.4; (ESI-MS) *m*/*z* 164 $[M+H]^{\bullet+}$; HRMS (ESI TOF (+)): calcd for $C_6H_{14}NO_4$ $[M+H]^{\bullet+}$: 164.09228, measured 164.09258.

*4.1.9. ((2S,3S,4R,5S)-3,4,5-Tris(benzyloxy)-1-butylpiperidin-2-yl) methanol: **9**.* To the stirred solution of compound **8** (42 mg, 0.0968 mmol) in dry acetone (6 mL) was added 1-bromobutane (0.0156 mL, 0.1453 mmol), K_2CO_3 (26.75 mg, 0.1936 mmol), and catalytic amount of KI (1.6 mg, 0.00968 mmol). The reaction mixture was allowed to reflux for overnight. After completion of reaction, it was cooled to room temperature and acetone was removed in vacuum, diluted with water, and extracted with ethyl acetate (5 mL×3). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4 and concentrated under vacuum to colorless oil, which on column chromatographic purification gave the pure compound (white gum, 36 mg, 75.9%).

White semi solid, eluent for column chromatography: EtOAc/Hexane (7/43, v/v). $[\alpha]_D^{28}$ 4.6 (*c* 1.55, MeOH); R_f 0.8 (1/1, EtOAc/Hexane); IR (neat, cm^{-1}) 3473, 2949, 2839, 1649, 1454, 1024, 751; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32–7.28 (15H, m, ArH), 4.65–4.46 (6H, m, $3OCH_2Ph$), 3.87 (1H, d, J=7.18 Hz, CH_AH_BOH), 3.78–3.69 (m, 4H, CH_AH_BOH, 3CHOBn), 2.85–2.69 (m, 5H, NCH_2CHOBn, NCH_2CH_2, OH), 2.56 (m, 1H, CHN), 1.45–1.38 (m, 4H, $CH_2CH_2CH_3$), 0.90 (t, J=7.19 Hz, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.6, 138.5, 138.3, 128.3, 127.9, 127.6, 75.1, 74.8, 73.6, 72.5, 72.3, 71.5, 60.6, 57.9, 53.4, 49.0, 28.2, 20.5, 13.9; (ESI-MS) *m*/*z* 490 $[M+H]^{\bullet+}$; EI-HRMS: calcd for $C_{31}H_{40}NO_4$ $[M+H]^{\bullet+}$ 490.29573, measured 490.29383.

4.1.10. (2S,3S,4R,5S)-1-Butyl-2-(hydroxymethyl) piperidine-3,4,5-triol: (N-butyl, L-altro-DNJ). To a solution of compound **9** (50 mg, 0.102 mmol) in MeOH (1 mL) was added catalytic amount of $PdCl_2$. The mixture was stirred at room temperature under an atmosphere of H_2 (balloon) for 3 h. The mixture was filtered through a Celite pad and the filtrates were evaporated in vacuo, then the residue was dissolved in water (1 mL) and applied to a column of Amberlyst IRA-100 basic ion-exchange resin. Elution with water (30 mL) followed by evaporation of the eluent in vacuo gave the title product (19.0 mg, 85%) as a white foam. $[\alpha]_D^{28}$ +1.8 (*c* 0.24, H_2O); IR (neat, cm^{-1}) 3600–3200; ^1H NMR (300 MHz, D_2O) δ 4.06 (1H, t, J=4.6 Hz, CH_AH_BOH), 3.93–3.87 (2H, m, CHOH, CH_AH_BOH), 3.81–3.75 (2H, m, CHOH), 2.94–2.93 (1H, m, CHN), 2.86 (1H, dd, J=12.5, 4.3 Hz, NCH_AH_BCHOH), 2.69 (2H, t, J=7.5 Hz, NCH_2CH_2, NCH_AH_BCHOH), 2.63–2.56 (1H, m, NCH_AH_BCHOH), 1.56–1.48 (2H, m, CH_2CH_2), 1.41–1.31 (2H, m, CH_2CH_3), 0.95 (3H, s, CH_3); ^{13}C NMR (75 MHz, D_2O) δ 71.5, 68.6, 67.6, 62.2, 56.8, 53.1, 51.9, 27.6, 20.2, 13.3; (ESI-MS) *m*/*z* 220 $[M+H]^{\bullet+}$; EI-HRMS: calcd for $C_{10}H_{22}NO_4$ $[M+H]^{\bullet+}$: 220.15488, measured 220.15368.

*4.1.11. 2-((2S,3S,4R,5S)-3,4,5-Tris(benzyloxy)-2-(hydroxymethyl)piperidin-1-yl)ethanol: **10**.* To the stirred solution of compound **8** (55 mg, 0.126 mmol) in dry acetone (8 mL) was added 2-bromoethanol (17.43 mg, 0.139 mmol), K_2CO_3 (26.12 mg, 0.189 mmol), and catalytic amount of KI (2.09 mg, 0.0126 mmol). The reaction mixture was allowed to reflux for overnight. After completion of reaction it was cooled to room temperature and acetone was removed in vacuum, diluted with water, and extracted with ethyl acetate (5 mL×3). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4 and concentrated under vacuum to colorless oil, which on column chromatographic purification gave the pure compound (white gum, 55 mg, 90.9%).

White semi solid, eluent for column chromatography: EtOAc/Hexane (25/25, v/v). $[\alpha]_D^{28}$ −2.6 (*c* 0.82, MeOH); R_f 0.3 (1/1 EtOAc/Hexane); IR (neat, cm^{-1}) 3416, 2925, 2856, 2364, 1647, 1454, 1218, 1094, 768; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.25 (15H, m, ArH), 4.67–4.30 (9H, m, $3OCH_2Ph$, 2OH, CHOBn), 3.98 (1H, dd, J=11.56, 3.51 Hz, CH_AH_BOH), 3.79 (t, J=2.91 Hz, 1H, CHOBn), 3.67–3.54 (m, 4H, CH_AH_BOH, CHOBn, CH_2OH), 2.69–2.62 (2H, m, $NCH_AH_BCH_2OBn$, CHN), 2.57–2.53 (2H, m, $NCH_AH_BCH_2OH$, $NCH_AH_BCH_2OBn$), 2.27 (d, J=10.9 Hz, 1H, $NCH_AH_BCH_2OH$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 138.1, 137.9, 128.4, 127.9, 127.7, 127.6, 76.1, 73.9, 72.6, 71.8, 71.4, 71.2, 64.4, 63.1, 62.5, 57.7, 52.2; (ESI-MS) *m*/*z* 478 $[M+H]^{\bullet+}$; EI-HRMS: calcd for $C_{29}H_{36}NO_5$ $[M+H]^{\bullet+}$ 478.25935, measured 478.25815.

4.1.12. (2S,3S,4R,5S)-1-(2-Hydroxyethyl)-2-(hydroxymethyl)piperidine-3,4,5-triol: N-(2-hydroxyethyl)-altro-DNJ. To a solution of compound **10** (50 mg, 0.105 mmol) in MeOH (1 mL) was added catalytic amount of $PdCl_2$. The mixture was stirred at room temperature under an atmosphere of H_2 (balloon) for 3 h. The mixture was filtered through a Celite pad and the filtrates were evaporated in vacuo, then the residue was dissolved in water (1 mL) and applied to a column of Amberlyst IRA-100 basic ion-exchange resin. Elution with water (30 mL) followed by evaporation of the eluent in vacuo gave the title product (17.8 mg, 82%) as a colorless solid. $[\alpha]_D^{28}$ −1.8 (*c* 0.23, H_2O); IR (neat, cm^{-1}) 3600–3200; ^1H NMR (300 MHz, D_2O) δ 4.15–4.06 (2H, m, CH_AH_BOH, CHOH), 4.01 (d, J=3.5 Hz, 1H, CHOH), 3.98 (d, J=2.5 Hz, 1H, CHOH), 3.95 (br s, 2H, CH_AH_BOH, $CH_AH_BOHCH_2$), 3.57 (s, 1H, $CH_AH_BOHCH_2$), 3.35 (d, J=12.5 Hz, 1H, NCH_AH_BCHOBn, CHN), 3.26–3.24 (m, 2H, $NCH_AH_BCH_2$,

NCH_AH_BCHOBn), 3.12 (d, J=12.5 Hz, 1H, $NCH_AH_BCH_2$); ^{13}C NMR (75 MHz, D_2O) δ 68.4, 66.4, 63.9, 62.5, 59.0, 58.4, 54.1, 43.9; (ESI-MS) m/z 208 $[M+H]^+$; EI-HRMS: calcd for $C_8H_{15}NO_5$ $[M+H]^+$: 208.11850, measured 208.11891.

4.1.13. 3-((2S,3S,4R,5S)-3,4,5-Tris(benzyloxy)-2-(hydroxymethyl)piperidin-1-yl)propan-1-ol: ***11****.* To the stirred solution of compound **8** (40 mg, 0.09 mmol) in dry acetone (8 mL) was added 3-chloro propanol (0.007 mL, 0.10 mmol), K_2CO_3 (19.07 mg, 0.14 mmol), and catalytic amount of KI (1.52 mg, 0.01 mmol). The reaction mixture was allowed to reflux for overnight. After completion of reaction it was cooled to room temperature and acetone was removed in vacuum, diluted with water, and extracted with ethyl acetate (5 mL×3). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4, and concentrated under vacuum to colorless oil, which on column chromatographic purification gave the pure compound (white gum, 35 mg, 77%).

Off white semi solid, eluent for column chromatography: EtOAc/Hexane (25/25, v/v). $[\alpha]_D^{28}$ −2.6 (*c* 0.82, MeOH); R_f 0.35 (3/2, EtOAc/Hexane); IR (neat, cm^{-1}) 3391, 2925, 2363, 1588, 1217, 1091, 771; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32–7.25 (15H, m, ArH), 4.69–4.40 (6H, m, $3OCH_2Ph$), 3.92–3.88 (2H, m, CH_2OH), 3.85–3.76 (2H, m, CH_2OH), 3.69–3.68 (1H, m, CHOBn), 3.62 (1H, br s, CHOBn), 3.15–3.05 (1H, m, CHOBn), 2.98–2.83 (4H, m, CHN, CH_2N), 2.72–2.64 (1H, m, CH_AH_BN), 2.54–2.59 (1H, m, CH_AH_BN), 2.05–2.00 (2H, m, CH_2CH_2OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 138.3, 138.0, 128.4, 128.38, 128.36, 128.3, 128.1, 127.71, 127.67, 127.62, 74.7, 73.8, 72.9, 72.6, 72.3, 71.5, 71.4, 63.2, 62.4, 52.6, 50.1, 33.8; (ESI-MS) m/z 492 $[M+H]^{\bullet+}$; EI-HRMS: calcd for $C_{30}H_{38}NO_5$ $[M+H]^{\bullet+}$ 492.27500, measured 492.27540.

4.1.14. (2S,3S,4R,5S)-2-(Hydroxymethyl)-1-(3-hydroxypropyl)piperidine-3,4,5-triol: (N-(3-hydroxypropyl)-altro-DNJ). To a solution of compound **11** (50 mg, 0.10 mmol) in MeOH (1 mL) was added catalytic amount of $PdCl_2$. The mixture was stirred at room temperature under an atmosphere of H_2 (balloon) for 3 h. The mixture was filtered through a Celite pad and the filtrates were evaporated in vacuo, then the residue was dissolved in water (1 mL) and applied to a column of Amberlyst IRA-100 basic ion-exchange resin. Elution with water (30 mL) followed by evaporation of the eluent in vacuo gave the title product (19.1 mg, 85%) as a colorless foam. $[\alpha]_D^{28}$ −1.4 (*c* 0.4, H_2O); IR (neat, cm^{-1}) 3600–3200; ^1H NMR (300 MHz, D_2O) δ 4.05 (1H, m, CH_AH_BOH), 3.92–3.89 (m, 2H, CH_AH_BOH, CHOBn), 3.82–3.76 (m, 2H, 2CHOBn), 3.70 (2H, t, J=6.0 Hz, CH_2OH), 2.92 (2H, m, CH_AH_BN,CHN), 2.81 (2H, t, J=7.8 Hz, NCH_2CH_2), 2.63–2.57 (1H, m, CH_AH_BN), 1.85–1.76 (2H, m, CH_2CH_2OH); ^{13}C NMR (75 MHz, D_2O) δ 71.5, 68.6, 67.58, 62.9, 60.7, 56.8, 51.6, 50.6, 21.9; (ESI-MS) m/z 222 $[M+H]^{\bullet+}$; EI-HRMS: calcd for $C_9H_{20}NO_5$ $[M+H]^{\bullet+}$: 222.13415, measured 222.13155.

4.1.15. (2S,3S,4R,5S)-tert-Butyl 3,4,5-tris(benzyloxy)-2-((S)-1-hydroxyallyl)piperidine-1-carboxylate: ***13****.* To a solution of alcohol **6** (200 mg, 0.37 mmol) in anhydrous CH_2Cl_2 (20 mL) under a nitrogen atmosphere, was added Dess–Martin periodinane (238.4 mg, 0.56 mmol) at 0 °C. The reaction mixture was allowed to stir at ambient temperature for 30 min. Then, the reaction was quenched with aqueous saturated $Na_2S_2O_3$ (10 mL), the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, and concentrated under vacuo to obtain the aldehyde **12**, which was used as such for the next step without purification. To a solution of aldehyde in dry THF under N_2 atmosphere at −78 °C, vinyl magnesium bromide was added and allowed to stir for one hour at same temperature. After completion of reaction, it was quenched with saturated solution of NH_4Cl, and extracted with ethyl acetate (10 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vacuo to a colorless oil, which on column chromatographic purification, gave the pure compound Colorless oil, **13** (118 mg, 56%). Eluent for column chromatography: EtOAc/Hexane (6.5/43.5, v/v); $[\alpha]_D^{28}$ +9.8 (*c* 1.08, $CHCl_3$); R_f 0.4 (2/8, EtOAc/Hexane); IR (neat, cm^{-1}) 3451, 2921, 2858, 2348, 1680, 1218, 1102, 769; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.24 (15H, m, ArH), 5.86–5.79 (1H, m, $CH{=}CH_2$), 5.23–5.12 (2H, m, $CH_2{=}CH$), 4.78–4.74 (1H, m, CHOH), 4.67–4.50 (6H, m, $3OCH_2Ph$), 4.26–4.22 (2H, m, 2CHOBn), 4.08 (1H, s, CHOBn), 3.97 (1H, br s, OH), 3.76–3.74 (1H, m, CHN), 2.69–2.49 (2H, m, CH_2NBoc), 1.42 (9H, s, CMe_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 138.6, 138.5, 138.3, 137.9, 128.3, 128.2, 127.7, 127.6, 127.4, 117.2, 80.2, 79.2, 74.7, 73.2, 72.1, 71.6, 71.3, 57.9, 42.5, 28.3; (ESI-MS) m/z 582 $[M+Na]^{\bullet+}$; HRMS (ESI TOF (+)): calcd for $C_{34}H_{42}NO_6$ $[M+H]^{\bullet+}$: 560.30121, measured 560.30120.

4.1.16. (2S,3S,4R,5S)-tert-Butyl 3,4,5-tris(benzyloxy)-2-((R)-1-hydroxyallyl)piperidine-1-carboxylate: ***14****.* Colorless oil, (39 mg, 19%) eluent for column chromatography: EtOAc/Hexane (7/43, v/v); $[\alpha]_D^{28}$ +3.7 (*c* 0.98, $CHCl_3$); R_f 0.35 (2/8, EtOAc/Hexane); IR (neat, cm^{-1}) 3747, 2925, 2860, 2365, 1684, 1219, 1102, 769; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.24 (15H, m, ArH), 5.65–5.53 (1H, m, $CH{=}CH_2$), 5.07–4.99 (2H, m, $CH_2{=}CH$), 4.76 (1H, br s, CHOH), 4.68–4.40 (6H, m, OCH_2Ph), 4.21–4.12 (1H, m, CHOBn), 4.06 (1H, t, J=7.9 Hz, CHOBn), 3.94 (1H, br s, CHOBn), 3.67 (1H, t, J=2.8 Hz, CHN), 3.52 (1H, d, J=6.2 Hz, OH), 2.75–2.66 (2H, m, CH_2NBoc), 1.43 (9H, s, CMe_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 138.5, 138.4, 137.9, 128.4, 128.3, 128.2, 127.8, 127.7, 127.6, 127.5, 118.1, 80.6, 78.5, 74.8, 73.2, 72.2, 70.4, 71.5, 71.3, 58.0, 43.5, 28.2; (ESI-MS) m/z 582 $[M+Na]^{\bullet+}$; HRMS (ESI TOF (+)): calcd for $C_{34}H_{42}NO_6$ $[M+H]^{\bullet+}$: 560.30121, measured 560.30121.

4.1.17. (1S,6S,7R,8S,8aS)-6,7,8-Tris(benzyloxy)octahydroindolizin-1-ol: ***15****.* To a stirred solution of compound **13** (150 mg, 0.26 mmol) in dry DCM (15 mL), 50% TFA in DCM was added at 0 °C. After completion of the reaction, it was quenched by saturated solution of $NaHCO_3$, and aqueous layer was extracted with DCM. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. After concentration in vacuo, the crude amine was used in the next step without further purification. To a stirred solution of amine (100 mg, 0.21 mmol) in THF/water (1:1, 1.6 mL) was added $Hg(OAc)_2$ (138.8 mg, 0.43 mmol), and the reaction mixture was stirred at room temperature for 3 h. Sodium borohydride (32.95 mg, 0.87 mmol) was added over a period of 10 min. THF was removed under reduced pressure, and the residue was extracted with chloroform. The combined organic portion was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum to a colorless oil, which on column chromatographic purification gave the pure compound **15** (87.5 mg, 71%).

White gum, eluent for column chromatography: EtOAc/Hexane (36/14, v/v). $[\alpha]_D^{28}$ +2.1 (*c* 0.26, MeOH); R_f 0.35 (EtOAc); IR (neat, cm^{-1}) 3416, 2925, 2856, 2364, 1647, 1454, 1218, 1094, 768; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.24 (15H, m, ArH), 4.61–4.36 (6H, m, OCH_2Ph), 4.15–4.07 (m, 1H, CHOH), 3.78–3.73 (m, 2H, 2CHOBn), 3.58 (1H, d, J=2.3 Hz, CHOBn), 2.99 (1H, dt, J=8.5, 2.21 Hz, CHN), 2.89 (1H, dd, J=12.0, 1.7 Hz, CH_AH_BN), 2.51–2.39 (3H, m, CH_2N, CH_AH_BN), 2.32–2.22 (1H, m, CH_AH_BCHOH), 1.63–1.54 (1H, m, CH_AH_BCHOH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 138.3, 137.9, 128.6, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 79.5, 75.4, 74.9, 72.5, 72.1, 71.8, 70.9, 67.1, 52.1, 51.5, 30.5; (ESI-MS) m/z 460 $[M+H]^{\bullet+}$; HRMS (ESI TOF (+)): calcd for $C_{29}H_{34}NO_4$ $[M+H]^{\bullet+}$ 460.2487, measured 460.2475.

4.1.18. (1S,6S,7R,8S,8aS)-Octahydroindolizine-1,6,7,8-tetraol [(+)-8-8a-di-epi-castanospermine]. To a solution of compound **15** (50 mg, 0.11 mmol) in methanol (1 mL) was added catalytic amount of $PdCl_2$. The mixture was stirred at room temperature under an

atmosphere of H_2 (balloon) for 1 h. The mixture was filtered through a Celite pad, and the filtrates were evaporated in vacuo, then the residue was dissolved in water (1 mL) and applied to a column of Amberlyte IRA-400 basic ion-exchange resin. Elution with water (35 mL) followed by evaporation of the eluent in vacuo gave the title product (+)-8,8a-di-*epi*-castanospermine (16.8 mg, 82%). $[\alpha]_D^{28}$ +13.8 (*c* 0.15, H_2O); IR (neat, cm^{-1}) 3600–3200; ^1H NMR (300 MHz, D_2O) δ 4.29 (1H, m, CHOH), 4.00 (1H, m, CHOH), 3.98 (1H, br s, CHOH), 3.89 (1H, dd, *J*=9.0, 3.0 Hz, CHOH), 3.01 (1H, dt, *J*=9.5, 2.1 Hz, CHN), 2.94 (1H, dd, *J*=12.4, 2.3 Hz, CH_AH_BN), 2.67–2.56 (2H, m, CH_2N), 2.36 (1H, t, *J*=9.0 Hz, CH_AH_BN), 2.28–2.25 (1H, m, CH_AH_BCHOH), 1.67–1.64 (1H, m, CH_AH_BCHOH); ^{13}C NMR (75 MHz, D_2O) δ 76.3, 73.4, 72.3, 72.0, 70.2, 54.6, 53.7, 33.6; (ESI-MS) *m*/*z* 190 $[M+H]^{\bullet+}$; HRMS (ESI TOF (+)): calcd for $C_8H_{17}NO_4$ $[M+H]^{\bullet+}$: 190.10793, measured 190.10813.

4.1.19. (1S,6S,7R,8S,8aS)-6,7,8-Tris(benzyloxy)-1-vinyltetrahydro-1H-oxazolo[3,4-a]pyridin-3(5H)-one: ***16****.* To a cooled (0 °C) solution of **13** (50 mg, 0.11 mmol) in dry THF (1.5 mL) was added sodium hydride in one portion under nitrogen atmosphere (5.21 mg, 0.22 mmol), and the suspension was allowed to reflux for 1 h, quenched by addition of saturated aqueous NH_4Cl, and extracted with ethyl acetate (3×10 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography to afford **16** (41 mg, 95%) as a white gum.

Colorless oil, eluent for column chromatography: EtOAc/Hexane (7/43, v/v); $[\alpha]_D^{28}$ +5.1 (*c* 0.67, $CHCl_3$); R_f 0.5 (3/7, EtOAc/Hexane); IR (neat, cm^{-1}) 3021, 2365, 1752, 1216, 763; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23–7.12 (15H, m, ArH), 5.92–5.81 (1H, m, CH=CH_2), 5.45 (1H, d, *J*=17.1 Hz, CH_2=CH), 5.20 (1H, d, *J*=10.9 Hz, CH_2=CH), 5.0 (1H, t, *J*=6.5 Hz, CHN), 4.66 (1H, d, *J*=11.9 Hz, OCH_AH_BPh), 4.56 (1H, d, *J*=11.9 Hz, OCH_AH_BPh), 4.43 (1H, d, *J*=11.9 Hz, OCH_AH_BPh), 4.35–4.20 (3H, m, OCH_AH_BPh, OCH_2Ph), 4.08–4.01 (1H, m, CHOH), 3.92–3.87 (2H, m, CH_AH_BN, CHOH), 3.69 (1H, dd, *J*=10.3, 2.3 Hz, CH_AH_BN), 3.60 (1H, d, *J*=3.9 Hz, CHOH), 3.14 (1H, d, *J*=13.6 Hz, CHOH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 137.8, 137.6, 137.3, 131.2, 128.4, 128.37, 127.8, 127.6, 117.4, 76.2, 73.1, 73.0, 72.6, 72.5, 70.6, 70.4, 56.6, 38.7; (ESI-MS) *m*/*z* 486 $[M+H]^{\bullet+}$; HRMS (ESI TOF (+)): calcd for $C_{30}H_{32}NO_5$ $[M+H]^{\bullet+}$: 486.22805, measured 486.23105.

4.1.20. (2S,3S,4R,5S)-tert-Butyl 3,4,5-tris(benzyloxy)-2-((1R,2S)-1,2,3-trihydroxypropyl)piperidine-1-carboxylate: ***17****.* To a solution of allylic alcohol **13** (175 mg, 0.38 mmol) in a 10:1 mixture of acetone/H_2O (4.15 mL) was added *N*-methylmorpholine *N*-oxide (61.68 mg, 0.526 mmol) and 4% aqueous OsO_4, (1.1 mL). The reaction mixture was stirred at room temperature for 3 h. After addition of aqueous $NaHSO_3$ solution (1 mL), the mixture was stirred for an additional 1 h at room temperature and extracted with EtOAc (3×10 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4 and concentrated under vacuum to a colorless oil, which on column chromatographic purification gave the pure compound **17** (colorless thick liquid, 105 mg, 78%).

Colorless oil, eluent for column chromatography: EtOAc/Hexane (30/20, v/v); $[\alpha]_D^{28}$ +27.2 (*c* 0.32, $CHCl_3$); R_f 0.6 (EtOAc); IR (neat, cm^{-1}) 3470, 3394, 2927, 1722, 1640, 1217, 768; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24–7.18 (15H, m, ArH), 4.6–4.45 (6H, m, OCH_2Ph), 4.36 (1H, br s, CH_AH_BOH), 4.23 (1H, t, *J*=6.4 Hz, CHOH), 4.14 (1H, dd, *J*=5.8, 3.4 Hz, CH_AH_BOH), 4.02–4.00 (1H, m, CHOH), 3.91 (1H, br s, CHBn), 3.88 (1H, br s, CHBn), 3.70 (4H, m, CHBn), 3.37–3.36 (1H, m, CHN), 2.98 (1H, t, *J*=12.3 Hz, NCH_AH_B), 2.23 (1H, t, *J*=7.20 Hz, NCH_AH_B), 1.34 (9H, s, CMe_3); (ESI-MS) *m*/*z* 616 $[M+Na]^{\bullet+}$; EI-HRMS: calcd for $C_{34}H_{43}NO_8$ $[M]^{\bullet+}$: 593.29887, measured 593.30817.

4.1.21. (1R,2S,6S,7R,8S,8aR)-6,7,8-Tris(benzyloxy)octahydroindolizine-1,2-diyl diacetate: ***20****.* To the stirred solution of compound **17** (500 mg, 0.84 mmol) in dry DCM (5 mL), 50% TFA in DCM was added. After completion of the reaction, the mixture was basified at 0 °C with aqueous NH_3 solution (28%). The mixture was extracted with DCM, dried over Na_2SO_4, and concentrated under vacuo to give crude amine **18**, which was further used without purification. To a solution of triol amine (315 mg, 0.64 mmol) in pyridine, under nitrogen atmosphere at 0 °C was added triphenylphosphine (199.3 mg, 0.76 mmol) and diisopropyl azodicarboxylate (0.12 mL, 0.76 mmol). The mixture was stirred at same temperature for 1 h. After completion of reaction, solvent was removed under vacuo to give crude indolizidine (203 mg, 67%). To the stirred solution of **19** (203 mg, 0.47 mmol) in pyridine (10 mL) at 0 °C was added acetic anhydride (239.9 mg, 2.35 mmol) and catalytic amount of dimethylaminopyridine. The mixture was stirred at room temperature for overnight. The usual workup followed by separation by column chromatography afforded diacetate **20** (195.9 mg, 82%); R_f 0.6 (1:1 EtOAc/Hexane); IR (neat, cm^{-1}) 2364, 1742, 1617, 1225, 1098, 769; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23–7.15 (15H, m, ArH), 5.19–5.12 (2H, m, CHOAc), 4.61 (1H, d, *J*=12.6 Hz, OCH_2Ph), 4.45–4.28 (5H, m, OCH_2Ph), 3.69–3.66 (1H, m, CHOBn), 3.63 (1H, br s, CHOBn), 3.49 (2H, br s, CHOBn, CHN), 2.84–2.81 (2H, m, NCH_AH_B), 2.55–2.47 (1H, m, NCH_AH_B), 2.28–2.56 (1H, m, NCH_AH_B), 1.95 (3H, s, CH_3CO), 1.83 (3H, s, CH_3CO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 169.8, 138.4, 138.2, 138.1, 128.4, 128.3, 128.29, 127.85, 127.82, 127.7, 127.6, 78.7, 74.6, 73.5, 72.9, 72.5, 71.7, 71.4, 68.7, 61.4, 58.1, 50.5, 20.7, 20.6; (ESI-MS) *m*/*z* 560 $[M+H]^{\bullet+}$; EI-HRMS: calcd for $C_{33}H_{38}NO_7$ $[M+H]^{\bullet+}$: 560.26480, measured 560.26370.

4.1.22. (1R,2S,6S,7R,8S,8aS)-Octahydroindolizine-1,2,6,7,8-pentaol: ***21****.* To a solution of compound **19** (50 mg, 0.10 mmol) in MeOH (1 mL) was added catalytic amount of $PdCl_2$. The mixture was stirred at rt under an atmosphere of H_2 (balloon) for 3 h. The mixture was filtered through a Celite pad and the filtrates were evaporated in vacuo, then the residue was dissolved in water (1 mL) and applied to a column of Amberlyst IRA-100 basic ion-exchange resin. Elution with water (30 mL) followed by evaporation of the eluent in vacuo gave the title product **21** (18.5 mg, 86%) as a white foam. $[\alpha]_D^{28}$ +0.3 (*c* 0.7, D_2O); IR (neat, cm^{-1}) 3600–3200; ^1H NMR (300 MHz, D_2O) δ 4.28–4.25 (1H, m, CHOH), 3.98 (3H, br s, CHOH), 3.87 (1H, d, *J*=9.3 Hz, CHOH), 3.58–3.41 (2H, m, CHN, NCH_AH_B), 2.90 (1H, d, *J*=11.9 Hz, NCH_AH_B), 2.62 (1H, d, *J*=12.6 Hz, NCH_AH_B), 2.43 (1H, t, *J*=9.3 Hz, NCH_AH_B), 2.36–2.31 (1H, m, NCH_AH_B); ^{13}C NMR (75 MHz, D_2O) δ 73.5, 71.0, 70.2, 69.5, 67.3, 65.1, 59.5, 52.2; (ESI-MS) *m*/*z* 206 $[M+H]^{\bullet+}$; EI-HRMS: calcd for $C_8H_{16}NO_5$ $[M+H]^{\bullet+}$: 206.1028, measured 206.1038.

4.1.23. (2S,3S,4R,5S)-tert-Butyl 3,4,5-tris(benzyloxy)-2-((1S,2R)-1,2,3-trihydroxypropyl)piperidine-1-carboxylate: ***22****.* The reaction of *N*-methylmorpholine *N*-oxide (61.68 mg, 0.53 mmol) and OsO_4 (1.0 mL) with allylic alcohol (120 mg, 0.26 mmol) was performed under similar reaction conditions as described for **17** followed by purification by column chromatography gave pure product **22** (colorless thick liquid, 75 mg, 80%).

Colorless thick liquid, eluent for column chromatography: EtOAc/Hexane (25/25, v/v); R_f 0.5 (EtOAc); IR (neat, cm^{-1}) 3470, 3394, 2927, 1722, 1640, 1217, 768; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24–7.18 (15H, m, ArH), 4.60–4.45 (6H, m, OCH_2Ph), 4.36 (1H, br s, CH_AH_BOH), 4.23 (1H, t, *J*=6.4 Hz, CHOH), 4.14 (1H, dd, *J*=5.8, 3.4 Hz, CH_AH_BOH), 4.02–4.00 (1H, m, CHOH), 3.91 (1H, br s, CHOBn), 3.88 (1H, br s, CHOBn), 3.70 (4H, m, CHOBn), 3.37–3.36 (1H, m, CHN), 2.98 (1H, t, *J*=12.3 Hz, NCH_AH_B), 2.23 (1H, t, *J*=7.2 Hz, NCH_AH_B), 1.34 (9H, s, CMe_3); (ESI-MS) *m*/*z* 593; found 616 $[M+Na]^{\bullet+}$; EI-HRMS: calcd for $C_{34}H_{43}NO_8$ $[M]^{\bullet+}$: 593.29882, measured 593.30812.

4.1.24. (1S,2R,6S,7R,8S,8aR)-6,7,8-Tris(benzyloxy)octahydroindolizine-1,2-diyl diacetate: ***25****.* Reaction was performed in same manner as for

compound **20** (165 mg, 32% over four steps). Yellowish liquid, eluent for column chromatography: EtOAc/Hexane (12/38, v/v); $[\alpha]_D^{28}$ −18.5 (*c* 0.39, $CHCl_3$); R_f 0.4 (3:7 EtOAc/Hexane); IR (neat, cm^{-1}) 2364, 1742, 1617, 1225, 1098, 769; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25–7.11 (15H, m, ArH), 5.45–5.44 (1H, m, CHOAc), 5.20 (1H, t, *J*=6.3 Hz, CHOAc), 4.49–4.46 (2H, m, OCH_2Ph), 4.39–4.32 (2H, m, OCH_2Ph), 4.29–4.23 (2H, m, OCH_2Ph), 3.92 (1H, d, *J*=7.9 Hz, CHOBn), 3.70 (1H, t, *J*=2.8 Hz, CHOBn), 3.50 (1H, br s, CHOBn), 2.95–2.91 (2H, m, CHN, NCH_AH_B), 2.68 (m, 1H, NCH_AH_B), 2.58 (m, 1H, NCH_AH_B), 2.34 (d, *J*=9.4 Hz, 1H, NCH_AH_B), 1.95 (3H, s, CH_3CO), 1.92 (3H, s, CH_3CO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 170.1, 138.25, 138.23, 137.9, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 74.2, 74.0, 72.7, 72.2, 71.5, 71.46, 71.3, 70.2, 63.1, 58.9, 51.0, 20.6; (ESI-MS) *m/z* 560 $[M+H]^{\bullet+}$; EI-HRMS: calcd for $C_{33}H_{38}NO_7$ $[M+H]^{\bullet+}$: 560.26483, measured 560.26373.

4.1.25. (1S,2R,6S,7R,8S,8aS)-Octahydroindolizine-1,2,6,7,8-pentaol: ***26***. To a solution of compound **25** (50 mg, 0.11 mmol) in MeOH (1 mL) was added catalytic amount of $PdCl_2$. The mixture was stirred at rt under an atmosphere of H_2 (balloon) for 3 h. The mixture was filtered through a Celite pad and the filtrates were evaporated in vacuo, then the residue was dissolved in water (1 mL) and applied to a column of Amberlyst IRA-100 basic ion-exchange resin. Elution with water (30 mL) followed by evaporation of the eluent in vacuo gave the title product **26** (18.2 mg, 85%) as a colorless foam. IR (neat, cm^{-1}) 3600–3200; ^1H NMR (300 MHz, D_2O) δ 4.38–4.32 (1H, m, CHOH), 4.2–4.18 (1H, m, CHOH), 4.06 (1H, dd, *J*=10.3, 3.3 Hz, CHOH), 3.95 (1H, t, *J*=3.3 Hz, CHOH), 3.89–3.88 (1H, m, CHOH), 2.88 (m, 1H), 2.84 (1H, m, CHN), 2.60–2.54 (1H, m, NCH_AH_B), 2.44 (1H, d, *J*=1.6 Hz, NCH_AH_B), 2.40 (1H, d, *J*=1.6 Hz, NCH_AH_B), 2.33 (1H, dd, *J*=10.2, 3.7 Hz, NCH_AH_B); ^{13}C NMR (75 MHz, D_2O) δ 70.6, 70.1, 69.6, 69.2, 65.3, 65.1, 59.9, 51.9; (ESI-MS) *m/z* 206 $[M+H]^{\bullet+}$; EI-HRMS: calcd for $C_8H_{16}NO_5$ $[M+H]^{\bullet+}$: 206.10285, measured 206.10315.

4.1.26. (2S,3R)-tert-Butyl 3-(benzyloxy)-2-((tert-butyl dimethylsilyloxy)methyl)piperidine-1-carboxylate: ***27***. To a solution of compound **1** (668.0 mg, 1.54 mmol) in methanol, catalytic amount of triethyl amine (31.17 mg, 0.04 mL, 0.31 mmol) and 10% Pd/C was added, and the solution was stirred under the pressure of H_2 atmosphere in balloon at room temperature for 4 h. After completion of the reaction, it was filtered through Celite, and the solvent was evaporated under vacuum, which on column chromatographic provided the pure product **27** (665 mg, 99%) as colorless oil. Eluent for column chromatography: EtOAc/Hexane (2/48, v/v). $[\alpha]_D^{28}$ +2.2 (*c* 0.24, MeOH); R_f 0.5 (1/9 EtOAc/Hexane); IR (neat, cm^{-1}) 3441, 3020, 2364, 1676, 1216, 762, 670; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.28 (5H, m, ArH), 4.64 (1H, d, *J*=10.4 Hz, OCH_2Ph), 4.52–4.35 (2H, m, OCH_2Ph), 4.08 (1H, br s, CH_AH_BO), 3.74–3.68 (3H, m, NCH_AH_B, CHN, CH_AH_BO), 2.79 (1H br s, NCH_AH_B), 1.87–1.68 (4H, m, CH_2CHOBn, CH_2CH_2NBoc), 1.47 (9H, s, CMe_3), 0.89 (9H, s, $SiCMe_3$), 0.06 (6H, s, $SiMe_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 138.8, 128.2, 127.3, 79.3, 71.2, 69.9, 61.1, 55.1, 39.1, 28.4, 25.8, 24.6, 19.4, 18.1, −5.4, −5.5; (ESI-MS) *m/z* 436 $[M+H]^{\bullet+}$, 336 [M-Boc]; HRMS (DART): calcd for $C_{24}H_{42}NO_4Si$ $[M+H]^{\bullet+}$ 436.28831, measured 436.28781.

4.1.27. (2S,3R)-tert-Butyl 3-(benzyloxy)-2-(hydroxymethyl)piperidine-1-carboxylate: ***28***. To a cooled solution of **27** (890 mg, 2.04 mmol) in dry THF (10 mL), solution of TBAF (1.0 M in THF, 5.0 mL) was added, and allowed to stir for 30 min. After completion of the reaction, mixture was concentrated in vacuo, the residue was diluted with ethyl acetate. The combined organic layer was washed with water followed by brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum to colorless oil, which on column chromatographic purification gave the pure compound **28** as white gum (636 mg, 95%). Eluent for column chromatography: EtOAc/Hexane (13.5/26.5, v/v). $[\alpha]_D^{28}$ +1.4 (*c* 0.83, MeOH); R_f 0.3 (1/1 EtOAc/Hexane); IR (neat, cm^{-1}) 3418, 2936, 2364, 1654, 1433, 1057, 745; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.24 (5H, m, ArH), 4.62 (1H, d, *J*=11.8 Hz, OCH_2Ph), 4.51–4.47 (2H, m, OCH_2Ph, CH_AH_BOH), 3.98 (1H, d, *J*=12 Hz, CH_AH_BOH), 3.75 (1H, t, *J*=8.2 Hz, NCH_AH_B), 3.64–3.57 (2H, m, NCH_AH_B), 2.9–2.82 (1H, m, CHN), 2.30 (1H, br s, OH), 1.96–1.85 (2H, m, CH_2CHOBn), 1.66–1.53 (2H, m, CH_2CH_2NBoc), 1.45 (9H, s, CMe_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 156.4, 138.6, 128.3, 127.4, 79.9, 71.5, 70.1, 60.7, 55.7, 39.6, 28.4, 25.3, 19.4; (ESI-MS) *m/z* 322 $[M+H]^{\bullet+}$; HRMS (DART): calcd for $C_{18}H_{28}NO_4$ $[M+H]^{\bullet+}$ 322.20183, measured 322.20179.

4.1.28. (2S,3R)-tert-Butyl 3-(benzyloxy)-2-((S)-1-hydroxyallyl)piperidine-1-carboxylate: ***29***. To a solution of **28** (180 mg, 0.56 mmol) in anhydrous CH_2Cl_2 (15 mL), under a nitrogen atmosphere was added Dess–Martin periodinane (356.28 mg, 0.84 mmol) at 0 °C and the reaction mixture was allowed to stir at ambient temperature for 30 min. Then, the reaction was quenched with aqueous solution of saturated $Na_2S_2O_3$ (10 mL), the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, and concentrated under vacuo to obtain the aldehyde, which was used as such for the next step without purification. To a solution of aldehyde in dry THF, under N_2 atmosphere at −78 °C, vinyl magnesium bromide (1 M solution in THF, 1.68 mL) was added and allowed to stir for one hour at same temperature. After completion of reaction, it was quenched with saturated solution of NH_4Cl, and extracted with ethyl acetate (10 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vacuo to a colorless oil, which on column chromatographic purification gave the pure compound **29** (colorless oil, 109 mg, 56.2% in two steps). Eluent for column chromatography: EtOAc/Hexane (7/43, v/v); $[\alpha]_D^{28}$ +17.5 (*c* 5.10, $CHCl_3$); R_f 0.4 (1.2/7.8, EtOAc/Hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.25–7.16 (5H, m, ArH), 5.83 (1H, m, $CH{=}CH_2$), 5.18 (1H, d, *J*=17.3 Hz, $CH_2{=}CH$), 5.08 (1H, d, *J*=10.3 Hz, $CH_2{=}CH$), 4.55 (1H, d, *J*=11.9 Hz, OCH_2Ph), 4.39 (1H, d, *J*=11.9 Hz, OCH_2Ph), 4.22 (2H, m, CHOH, CHOBn), 4.00 (1H, br s, OH), 3.83 (1H, m, CHN), 2.64 (br s, 1H, NCH_AH_B), 2.08 (br s, 1H, NCH_AH_B), 1.83–1.68 (m, 4H, CH_2CHOBn, CH_2CH_2NBoc), 1.35 (9H, s, CMe_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ 155.6, 138.9, 128.4, 128.1, 127.2, 116.8, 79.5, 71.1, 70.0, 57.2, 39.2, 28.4, 24.8, 19.4; (ESI-MS) *m/z* 370 $[M+Na]^{\bullet+}$; HRMS (ESI TOF (+)): calcd for $C_{20}H_{29}NNaO_4$ $[M+Na]^{\bullet+}$: 370.19943, measured 370.19833.

4.1.29. (2S,3R)-tert-Butyl 3-(benzyloxy)-2-((R)-1-hydroxyallyl)piperidine-1-carboxylate: ***30***. Colorless oil (36.5 mg, 18.8%) eluent for column chromatography: EtOAc/Hexane (8/42, v/v); $[\alpha]_D^{28}$ +10.8 (*c* 2.92, $CHCl_3$); R_f 0.35 (1.2/7.8, EtOAc/Hexane); IR (neat, cm^{-1}) 3399, 2928, 2360, 1665, 1424, 1150, 769; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.24 (5H, m, ArH), 5.91–5.79 (1H, m, $CH{=}CH_2$), 5.26 (1H, d, *J*=17.2 Hz, $CH_2{=}CH$), 5.15 (1H, d, *J*=10.3 Hz, $CH_2{=}CH$), 4.63 (1H, d, *J*=11.8 Hz, OCH_2Ph), 4.47 (1H, d, *J*=11.8 Hz, OCH_2Ph), 4.29 (2H, m, CHOBn, CHOH), 4.07 (1H, br s, CHN), 3.90 (1H, m, NCH_AH_B), 2.72 (1H, m, NCH_AH_B), 1.91–1.71 (4H, m, CH_2CHOBn, CH_2CH_2NBoc), 1.53 (9H, s, CMe_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.6, 138.9, 138.4, 128.2, 127.2, 116.8, 79.5, 71.1, 70.0, 57.0, 39.2, 28.4, 24.8, 19.4; (ESI-MS) *m/z* 370 $[M+Na]^{\bullet+}$; HRMS (ESI TOF (+)): calcd for $C_{20}H_{29}NNaO_4$ $[M+Na]^{\bullet+}$: 370.19943, measured 370.19833.

4.1.30. (2S,3R)-tert-Butyl 3-(benzyloxy)-2-((1R,2S)-1,2,3-trihydroxypropyl)piperidine-1-carboxylate: ***33***. To a solution of **29** (146 mg, 0.42 mmol) in a 10:1 mixture of acetone/H_2O (6.6 mL) was added *N*-methylmorpholine *N*-oxide (98.51 mg, 0.84 mmol) and 4% aqueous OsO_4, (1.0 mL). The reaction mixture was stirred at room temperature for 3 h. After addition of aqueous $NaHSO_3$ solution (1 mL), the mixture was stirred for an additional 1 h at room

temperature, and extracted with EtOAc (3×10 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vacuo to a colorless oil, which on column chromatographic purification gave the pure compound **33** (colorless oil, 125 mg, 78%). Eluent for column chromatography: EtOAc/Hexane (35/15, v/v); $[\alpha]_D^{28}$ +5.0 (*c* 1.04, $CHCl_3$); R_f 0.7 (EtOAc); IR (neat, cm^{-1}) 3417, 2370, 1629, 1219, 771; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32–7.23 (5H, m, ArH), 4.62 (1H, d, *J*=11.7 Hz, OCH_2Ph), 4.47 (1H, d, *J*=11.7 Hz, OCH_2Ph), 4.38 (1H, br s, CH_AH_BOH), 4.08 (1H, d, *J*=6.99 Hz, CHOH), 3.94 (2H, m, CHOH, CH_AH_BOH), 3.86–3.84 (1H, m, CHOBn), 3.71 (1H, m, CHN), 3.58 (1H, brs, NCH_AH_B), 2.77 (1H, t, *J*=12.4 Hz, NCH_AH_B), 1.90–1.72 (4H, m, CH_2CH_2N, CH_2CHOBn), 1.42 (9H, s, CMe_3); (ESI-MS) *m*/*z* 404 $[M+Na]^{\bullet+}$; HRMS (ESI TOF (+)): calcd for $C_{20}H_{31}NNaO_6$ $[M+Na]^{\bullet+}$: 404.20491, measured 404.20521.

4.1.31. (1R,2S,8R,8aS)-8-(Benzyloxy)octahydroindolizine-1,2-diol: ***34***. To the stirred solution of compound **33** (500 mg, 1.31 mmol) in dry DCM (5 mL), 50% TFA in DCM was added. After completion of the reaction, the mixture was basified at 0 °C with aqueous NH_3 solution (28%). The mixture was extracted with EtOAc, dried over Na_2SO_4, and concentrated under vacuo to give crude amine, which was further used without purification. To a solution of triol amine (0.792 g, 1.14 mmol) in pyridine, under nitrogen atmosphere at 0 °C was added triphenylphosphine (0.301 g, 1.15 mmol) and diisopropyl azodicarboxylate (0.56 mL, 2.84 mmol). The mixture was stirred at same temperature for 1 h. After completion of reaction, solvent was removed under vacuo to give crude indolizidine, which on column chromatographic purification gave the pure compound **34** (colorless oil, 224 mg, 65%). Eluent for column chromatography: EtOAc/Hexane (3.5/46.5, v/v); $[\alpha]_D^{28}$ −1.3 (*c* 0.82, MeOH); R_f 0.5 (1:4 MeOH:$CHCl_3$); IR (neat, cm^{-1}) 3417, 2370, 1629, 1219, 771; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.34 (5H, m, ArH), 4.72 (1H, d, *J*=11.6 Hz, OCH_2Ph), 4.51 (1H, d, *J*=11.6 Hz, OCH_2Ph), 4.21–4.15 (1H, m, CHOH), 3.88–3.83 (1H, m, CHOH), 3.50–3.36 (2H, m, CHOBn, CHN), 2.89 (1H, br d, *J*=8.9 Hz, NCH_AH_BCHOH), 2.66 (2H, brs, OH), 2.33–2.23 (2H, m, $NCH_AH_BCH_2$, NCH_AH_BCHOH), 2.08–2.03 (2H, m, CH_AH_B-CHOBn, $NCH_AH_BCH_2$), 1.77–1.72 (1H, m, CH_AH_BCHOBn), 1.58–1.47 (2H, m, CH_2CH_2N); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.8, 128.6, 128.3, 127.6, 73.2, 72.4, 71.0, 70.0, 69.1, 62.1, 52.0, 33.8, 23.2; (ESI-MS) *m*/*z* 264 $[M+H]^{\bullet+}$; HRMS (ESI TOF (+)): calcd for $C_{15}H_{22}NO_3$ $[M+H]^{\bullet+}$: 264.15997, measured 264.16077.

4.1.32. (1R,2S,8R,8aR)-8-(Benzyloxy)octahydroindolizine-1,2-diyl diacetate: ***35***. To the stirred solution of **34** (50 mg, 0.19 mmol) in pyridine (2 mL) at 0 °C was added acetic anhydride (58.2 mg, 0.57 mmol) and catalytic amount of DMAP. The mixture was stirred at room temperature for overnight. The usual workup followed by separation by column chromatography afforded diacetate **35** (56 mg, 85%). Colorless, eluent for column chromatography: EtOAc/Hexane (16/24, v/v); $[\alpha]_D^{28}$ +5.0 (*c* 1.04, $CHCl_3$); R_f 0.4 (1:1 EtOAc/Hexane); IR (neat, cm^{-1}) 3417, 2370, 1629, 1219, 771; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23–7.19 (5H, m, ArH), 5.18–5.07 (2H, m, 2CHOAc), 4.54 (1H, d, *J*=11.1 Hz, OCH_2Ph), 4.32 (1H, d, *J*=11.1 Hz, OCH_2Ph), 3.47 (1H, dd, *J*=9.7, 6.5 Hz, CHOBn), 3.30 (1H, ddd, *J*=12.8, 9.8, 4.3 Hz, $NCH_AH_BCH_2$), 2.86 (1H, br d, *J*=10.2 Hz, CHN), 2.28–2.17 (3H, m, NCH_2CH_2, NCH_AH_BCHOAc), 2.07–2.01 (1H, m, CH_AH_B-CHOBn), 1.95 (3H, s, CH_3CO), 1.83 (3H, s, CH_3CO), 1.65 (1H, br d, *J*=12.8 Hz, CH_AH_BCHOBn), 1.56–1.48 (1H, m, $CH_AH_BCH_2N$), 1.32–1.16 (1H, m, $CH_AH_BCH_2N$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.9, 169.7, 138.4, 128.3, 127.8, 127.6, 78.8, 73.6, 70.8, 68.4, 68.2, 58.2, 51.5, 29.9, 23.6, 20.6, 20.5; (ESI-MS) *m*/*z* 348 $[M+H]^{\bullet+}$; HRMS (ESI TOF (+)): calcd for $C_{19}H_{26}NO_5$ $[M+H]^{\bullet+}$: 348.18110, measured 348.18020.

4.1.33. (1R,2S,8R,8aR)-Octahydroindolizine-1,2,8-triol [(+)-1,2-di-epi-swainsonine]. To a solution of compound **34** (50 mg, 0.19 mmol) in MeOH (1 mL) was added catalytic amount of $PdCl_2$. The mixture was stirred at room temperature under an atmosphere of H_2 (balloon) for 1 h. The mixture was filtered through a Celite pad and the filtrates were evaporated in vacuo, then the residue was dissolved in water (1 mL) and applied to a column of Amberlyte IRA-100 basic ion-exchange resin. Elution with water (30 mL) followed by evaporation of the eluent in vacuo gave the title product (+)-1,2-di-*epi*-swainsonine (28.3 mg, 86%) as a colorless solid. $[\alpha]_D^{28}$ +6 (*c* 2.25, MeOH); IR (neat, cm^{-1}) 3600–3200; ^1H NMR (300 MHz, D_2O) δ 4.22 (1H, q, *J*=13.0 Hz, CHOH), 3.97 (1H, t, *J*=7.4 Hz, CHOH), 3.61–3.53 (1H, m, CHOH), 3.43 (1H, dd, *J*=7.4, 2.8 Hz, CH_AH_B), 2.96 (1H, d, *J*=9.32 Hz, CH_AH_B), 2.33–2.27 (1H, m, CH_AH_B), 2.19–1.99 (3H, m, CH_AH_B, CHN, CH_AH_B), 1.80 (1H, d, *J*=12.6 Hz, CH_AH_B), 1.63 (1H, m, CH_AH_B), 1.43–1.31 (1H, m, CH_AH_B); ^{13}C NMR (75 MHz, D_2O) δ 73.7, 72.0, 71.2, 67.1, 59.4, 51.0, 32.7, 23.1; (ESI-MS) *m*/*z* 174 $[M+H]^{\bullet+}$; HRMS (ESI TOF (+)): calcd for $C_8H_{16}NO_3$ $[M+H]^{\bullet+}$: 174.11302, measured 174.11242.

4.1.34. (2S,3R)-tert-Butyl 3-(benzyloxy)-2-((1S,2R)-1,2,3-trihydroxypropyl)piperidine-1-carboxylate: ***36***. To a solution of allylic alcohol **30** (146 mg, 0.42 mmol) in a 10: 1 mixture of acetone/H_2O (6.6 mL) was added *N*-methylmorpholine *N*-oxide (98.51 mg, 0.84 mmol) and 4% aqueous OsO_4 (1.0 mL). The reaction mixture was stirred at room temperature for 3 h. After addition of aqueous $NaHSO_3$ solution (1 mL), the mixture was stirred for an additional 1 h at room temperature and extracted with EtOAc (3×10 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vacuo to colorless oil, which on column chromatographic purification gave the pure compound (colorless oil, 125 mg, 80%). Colorless oil, eluent for column chromatography: EtOAc/Hexane (30/20, v/v); $[\alpha]_D^{28}$ +4.5 (*c* 1.23, $CHCl_3$); R_f 0.5 (EtOAc); IR (neat, cm^{-1}) 3417, 2370, 1629, 1219, 771; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.25 (5H, m, ArH), 4.59 (1H, d, *J*=12 Hz, OCH_AH_BPh), 4.51 (1H, d, *J*=12 Hz, OCH_AH_BPh), 4.44 (1H, m, CHN), 3.97 (1H, d, *J*=11 Hz, CH_AH_BOH), 3.83–3.81 (3H, m, CH_AH_BOH, CHOH, CH_AH_BN), 3.69 (1H, br s, OH), 3.48 (1H, m, CHOH), 3.17 (1H, m, CH_AH_BN), 2.88 (1H, br s, OH), 2.62–2.46 (1H, m, CHOBn), 2.04–1.81 (4H, m, CH_2CH_2), 1.46 (9H, s, CMe_3); (ESI-MS) *m*/*z* 404 $[M+Na]^{\bullet+}$; HRMS (ESI TOF (+)): calcd for $C_{20}H_{31}NNaO_6$ $[M+Na]^{\bullet+}$: 404.20491, measured 404.20901.

4.1.35. (1S,2R,8R,8aR)-8-(Benzyloxy)octahydroindolizine-1,2-diyl diacetate: ***38***. Reaction was performed in same manner as for compound **34** and **35**, compound **36** (500 mg, 1.31 mmol, 1.18 mmol), afforded diacetate **38** (276 mg 55% over three steps); colorless oil, eluent for column chromatography: EtOAc/Hexane (16/24, v/v); $[\alpha]_D^{28}$ −101 (*c* 2.01, $CHCl_3$); R_f 0.4 (1:1 EtOAc/Hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.32–7.28 (m, 5H), 5.56 (m, 1H), 5.29 (m, 1H), 4.58 (d, *J*=11.6 Hz, 1H), 4.42 (d, *J*=11.6 Hz, 1H), 3.63 (m, 1H), 3.07–3.0 (m, 2H), 2.57 (dd, *J*=11.1, 7.8 Hz, 1H), 2.31–2.28 (m, 1H), 2.07 (m, 1H), 2.01 (s, 6H), 1.90 (m, 1H), 1.80–1.5 (m, 2H), 1.28–1.1 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 138.1, 128.4, 127.8, 127.7, 72.9, 71.1, 70.5, 70.1, 69.8, 59.6, 52.1, 33.8, 23.3, 20.7, 20.6; IR (neat, cm^{-1}) 3417, 2370, 1629, 1219, 771; (ESI-MS) *m*/*z* 348 $[M+H]^{\bullet+}$; HRMS (ESI TOF (+)): calcd for $C_{19}H_{26}NO_5$ $[M+H]^{\bullet+}$: 348.1811, measured 348.1802.

4.1.36. (1S,2R,8R,8aR)-Octahydroindolizine-1,2,8-triol [(−)-swainsonine]. To a solution of compound **37** (50 mg, 0.11 mmol) in MeOH (1 mL) was added catalytic amount of $PdCl_2$. The mixture was stirred at room temperature under an atmosphere of H_2 (balloon) for 1 h. The mixture was filtered through a Celite pad and the filtrates were evaporated in vacuo, then the residue was dissolved in water (1 mL) and applied to a column of Amberlyte IRA-400 basic ion-exchange resin. Elution with water (35 mL) followed by evaporation of the eluent in vacuo gave the title product

(−)-swainsonine (28 mg, 85%) as a white solid; mp 140–141 °C $[\alpha]_D^{28}$ −68 (*c* 0.46, MeOH); IR (neat, cm^{-1}) 3367, 2944, 2800, 2723, 1347, 1127, 1073; ^1H NMR (300 MHz, D_2O) δ 4.27–4.21 (m, 1H, CHOH), 4.16–4.14 (m, 1H, CHOH), 3.69 (ddd, *J*=13.6, 10.8, 4.48 Hz, 1H, CHOH), 2.80–2.75 (m, 2H, CHN), 2.52–2.38 (m, 1H, CH_AH_BN), 1.98–1.78 (m, 3H, CH_AH_B, CH_2N), 1.62–1.58 (m, 1H, CH_AH_B), 1.50–1.37 (m, 1H, CH_AH_BN), 1.13 (m, 1H, CH_AH_BN); ^{13}C NMR (75 MHz, D_2O) δ 71.8, 68.7, 68.0, 65.4, 59.6, 50.7, 31.5, 22.2; (ESI-MS) *m/z* 174 $[M+H]^{\bullet+}$; HRMS (ESI TOF (+)): calcd for $C_8H_{16}NO_3$ $[M+H]^{\bullet+}$: 174.11302, measured 174.11242.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.11.074.

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