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ARTICLE TYPE

Stereoselective Approach to Indolizidine and Pyrrolizidine Alkaloids: Total Synthesis of (-)-Lentiginosine, (-)-*epi*-Lentiginosine and (-)-Dihydroxypyrrolizidine

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A simple and highly efficient approach to hydroxylated pyrrolizidine and indolizidine is developed from an aldehyde as a starting material using organocatalytic and asymmetric dihydroxylation reactions as key steps. Its application to the total synthesis of (-)-lentiginosine, (-)-*epi*-1,2-lentiginosine and (-)-dihydroxypyrrolizidine is also reported.

Introduction

The synthesis of enantiopure therapeutics with a high medicinal value has always been a prime concern among synthetic chemists. Among them, azasugars have gained much attention in recent years as they mimic carbohydrates. Structurally, they are known to contain fused bicyclic systems with nitrogen at the bridge head and variable ring size based on which they may be classified as indolizidines[1] and pyrrolizidines.[2] These "izidines" show different patterns of oxygenation, for instance, the highly oxygenated castanospermine **1,** its less hydroxylated congeners such as lentiginosine **2,** *epi*-lentiginosine **3**, and dihydroxypyrrolizidine **4** or the non oxygenated ring systems such as coniceine **5** and pyrrolizidine **6** *etc.* are widespread in plants and microorganisms[3] (Figure 1).

Lentiginosine was isolated in 1990 by Elbein and co-workers from the source *Astralagus Lentiginosus.*[4] It is known to exhibit excellent anti-HIV, anti-tumour and immunomodulating activities apart from being a significant inhibitor of amyloglycosidases with IC_{50}=5µg/mL. The mechanism of action is related to inhibition of the biosynthesis of glycoproteins which are responsible for recognition and adhesion of exogenous agents.[5] Effective inhibitors are known to mimic the terminal unit of oligosaccharides competing the natural substrate for occupying the enzyme active site.

Owing to its potent biological activity, lentiginosine and its analogues have aroused a great deal of interest among synthetic organic chemists, inspite the relatively low degree of hydroxylation as evident from the number of literature reports. Lentiginosine was first synthesized in 1993 by Yoda *et al*. from a tartaric acid derived imide.[6a] Several synthesis followed that employed a chiral pool approach using tartaric acid,[6] nitrones,[7] carbohydrates[8] or amino acids[9] as starting materials. Although the majority of the literature reports have used a chiral pool approach, they prove to be useful protocols for only a limited number of molecules and also involve a large number of synthetic steps. Shibasaki and co-workers were the first to report an enantioselective approach using a Heck cyclization as a key step.[10a] Subsequently a number of groups have reported the synthesis of lentiginosine and its analogues using an enantioselective approach.[10] Therefore, a general enantioselective synthetic approach to several azasugars and their unnatural analogues that are amenable to implementation of requisite stereochemical variations and different forms of substitution has become essential. We have recently reported the synthesis of indolizidine and pyrrolizidine in our preliminary communication[11] employing the sequential α-amination[12] and Horner–Wadsworth–Emmons (HWE) olefination as the key step. In continuation of our interest to develop new methodologies[13] using proline catalyzed sequential amination/aminoxylation followed by HWE olefination, we report here a general and an efficient strategy to the synthesis of lentiginosine, *epi*-lentiginosine and dihydroxy pyrrolizidine.

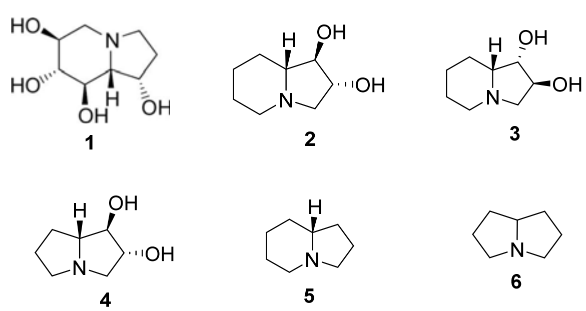
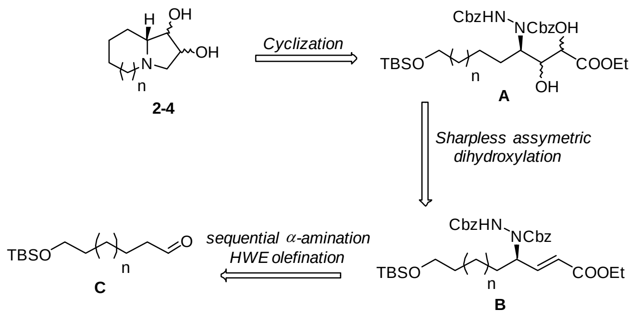


Figure 1. Some indolizidine and pyrrolizidine alkaloids

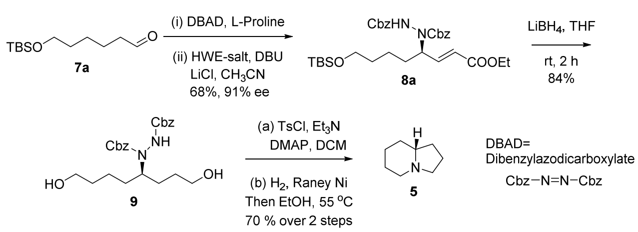
Results and Discussion

Our general synthetic strategy is outlined in Scheme 1. Lentiginosine **2**, *epi*-lentiginosine **3** and dihydroxy pyrrolizidine **4** could be obtained by cyclization of **A**. Compound **A** could be synthesized by Sharpless asymmetric dihydroxylation[14] of the α,β-unsaturated ester **B** for the introduction of the two hydroxy groups adjacent to the amine functionality which in turn could be synthesized from aldehyde **C** via a proline catalyzed α-amination reaction. Before embarking on the synthesis of the target molecules, we considered exploring a model synthesis to test the devised strategy, in particular, the concomitant cleavage of the N-N bond and nucleophilic displacement under hydrogenation



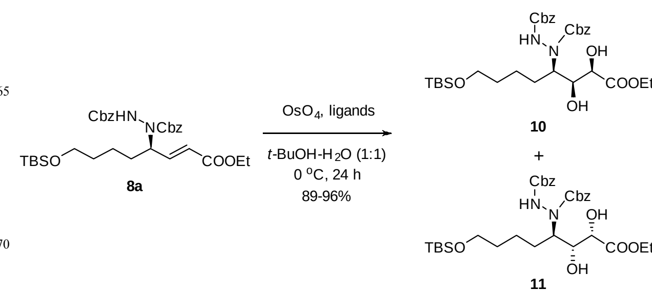
Scheme 1. Retrosynthetic route to indolizidine and pyrrolizidine alkaloids (**2-4**)

conditions. The synthesis commenced with the aldehyde **7a** which on proline-catalyzed sequential α-amination followed by a HWE olefination furnished the γ-amino-α,β-unsaturated ester **8a** in 68% yield (91% ee).[15] Compound **8a** was then subjected to ester reduction ensuing double bond reduction and TBS deprotection in one step using $LiBH_4$ in THF to provide the diol **9**. Compound **9** on treatment with toluenesulfonyl chloride and triethylamine resulted in the formation of di-tosylate which was subjected to hydrogenation conditions for the cleavage of N-N bond using Raney-Ni to give the free amine which on nucleophilic displacement of di-tosylate led to the formation of indolizidine alkaloid (*R*)-coniceine **5** (Scheme 2). The extrapolation of this strategy allowed the successful completion of the synthesis of all the three target molecules in a very short and efficient manner.



Scheme 2. Synthesis of indolizidine alkaloid coniceine

The synthesis of the target molecules (-)-lentiginosine and its 1,2-epimer commenced with γ-amino-α,β-unsaturated ester **8a** (Table 1). At this stage we investigated the use of the Sharpless asymmetric dihydroxylation reaction used for the embedding two hydroxy groups in the substrate containing a pre-existing chiral centre with a bulky substituent at the allylic nitrogen. The use of cinchona alkaloid ligand variants to achieve the two requisite stereocentres provided a general synthetic pathway to the family of hydroxylated azasugars in a highly diastereoselective manner. Dihydroxylation of **8a** under Sharpless conditions in the absence of a chiral ligand interestingly gave "*syn* facial selectivity" (*syn*-**10**/*anti*-**11**:83/17) where both products were easily separable by silica gel column chromatography. This result showed that the bulk of the allylic NCbz substituent had little impact on the stereodifferentiation of the two π faces. The probable explanation for this diastereofacial bias could be attributed to the presence of H-bonding between the OsO_4 and NCbz-NHCbz group that facilitates the formation of *syn*-diastereomer **10** as a major product (Figure 2).[16] We then examined the efficacy of various cinchona alkaloid containing ligands and the results are summarized in Table 1. To achieve the "*anti* facial selectivity" (based on the Sharpless mnemonic device) we used $(DHQD)_2$ PHAL, surprisingly the diastereomeric outcome (*anti*-**11**/*syn*-**10**) was found to be 3/2. Switching the ligand to $(DHQD)_2$ PYR gave a similar result (*anti*-**11**/*syn*-**10**:3/2). Finally, $(DHQD)_2$AQN was found to be a better ligand as the dr for the *anti* compound **11** increased to 3/1. To favour the "*syn* antipode" both $(DHQ)_2$PHAL and $(DHQ)_2$AQN were found to be useful ligands. In these case, the reaction progressed with high diastereoselectivity and we obtained *syn*-**10** essentially as a single diastereomer (Table 1, entries 3,6). In all the cases, however the yield remained almost the same.



Entry	Ligands*	yield (%)	Ratio (**10**:**11**)
1	no ligand	94	83:17
2	$(DHQD)_2$PHAL (5 mol %)	95	2:3
3	$(DHQ)_2$PHAL (5 mol %)	93	99:1
4	$(DHQD)_2$PYR (5 mol %)	89	2:3
5	$(DHQD)_2$AQN (5 mol %)	96	1:3
6	$(DHQ)_2$AQN (5 mol %)	96	99.8:0.2

* Reactions were carried out in the presence of 1 mol% of OsO_4 and 3 equivalents of K_2CO_3 and K_3FeCN_6

Table 1. Optimization of Sharpless asymmetric dihydroxylation reaction conditions

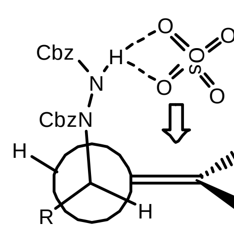
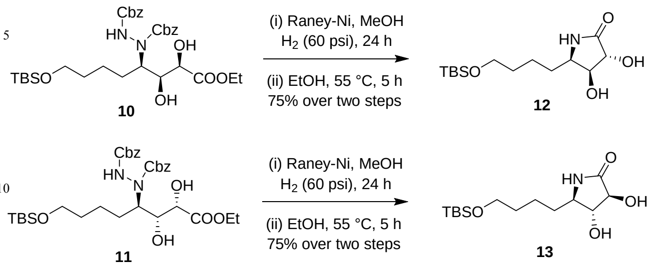


Figure 2. Proposed transition state for *syn* selectivity

The relative stereochemistry of the three stereocenters generated were unambiguously determined using 2D NMR spectroscopy. For this purpose, diols **10** and **11** were subjected to hydrogenation conditions using Raney-Ni to cleave N-N bond to get free amine which subsequently undergoes cyclization to give cyclic derivatives **12** and **13**, respectively (Scheme 3). Extensive NMR studies were carried out on compounds **12** and **13** to determine the relative stereochemistry.



Scheme 3. Preparation of cyclic derivatives

The two cyclic isomers **12** and **13** were subjected to 2D NMR spectroscopy after carefully studying their peak patterns in 1D NMR. ^{1}H, ^{13}C and DEPT NMR spectra of the cyclized compounds were determined in $CDCl_3$ initially, it was found that the compound **13** showed resolved peaks for the methine protons α, β and γ whereas this was not the case for compound **12**. Acetone-d_6 proved to be a more suitable solvent for a better quality NMR spectra. The compounds **12** and **13** were then characterized using the 1D NMR experiments (^{1}H, ^{13}C DEPT) as well as 2D homonuclear (COSY, and NOESY) and heteronuclear (HSQC and HMBC) NMR spectroscopy.

For compound **12**, the α, β, γ protons resonated at δ 4.04, 4.22 and 3.55 ppm respectively. The α proton shows the distinct doublet at 4.04 ppm having a coupling constant of 6.63 Hz which indicated the *trans* stereochemistry between the α and β-methine protons. The β and γ- protons showed multiplet like pattern which prohibited extraction of the coupling constants from 1D

spectrum. Therefore the 2D NOESY spectrum was used to determine the relative stereochemistry at the β and γ-position. The NOESY spectra of compound **12** shows cross peak between the β and γ proton which confirmed their *syn* relationship between the β and γ methine protons, the α and β protons did not show NOESY correlation which indicated their *trans* relationship as shown in the Fig. 3.

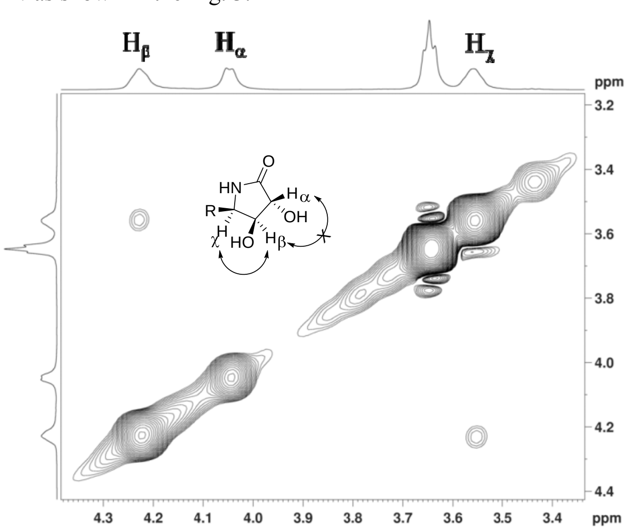


Figure 3.NOESY spectrum of compound **12**

For compound **13**, the α, β, γ protons resonated at δ 4.06, 3.77 and 3.28 respectively. The α proton showed as a distinct doublet at 4.06 ppm having coupling constant of 7.3 Hz which indicated the *trans* stereochemistry between α and β methine protons. The β and γ protons showed multiplet like patterns which prohibited extraction of their coupling constants. Therefore the 2D NOESY spectrum was used to find out the relative stereochemistry at the β and γ positions. The NOESY spectra of compound **13** did not show a correlation between the β and γ protons which confirmed their *anti* stereochemistry. The α and β protons did not show NOESY correlation which indicated the *trans* relationship between them as shown in the Fig. 4.

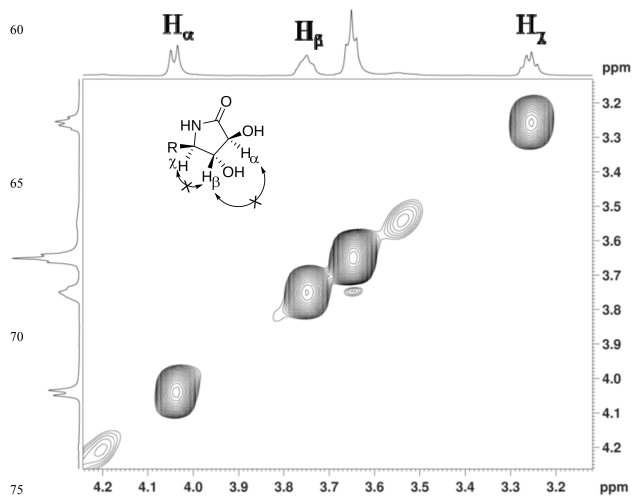
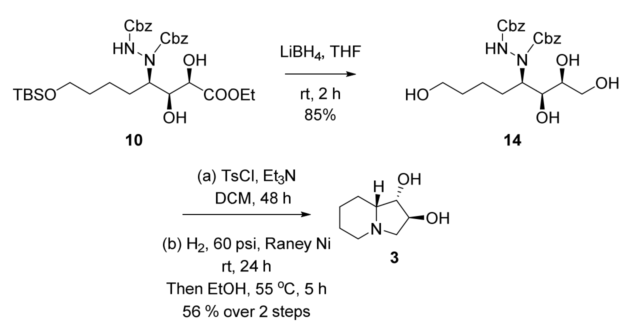


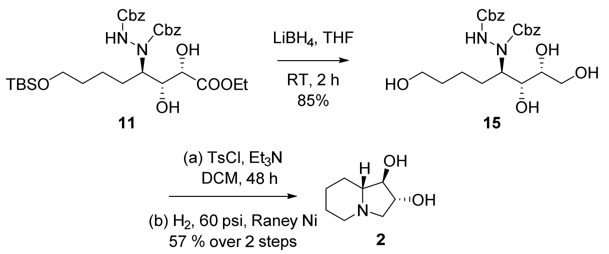
Figure 4. NOESY spectrum of compound **13**

After determining the relative stereochemistry of compounds **12** and **13**, we proceeded to the synthesis of target molecules. For the synthesis of (-)-1,2-*epi*-lentiginosine **3**, diol **10** was subjected to $LiBH_4$ reduction to give tetrol **14**. Compound **14** was subjected to selective primary tosylation using TsCl and Et_3N to give the di-tosyl, which was subjected to hydrogenation conditions using freshly prepared Raney-Ni to deliver the free amine which on nucleophilic displacement of di-tosylate led to the formation of the desired (-)-1,2-*epi*-lentiginosine **3** (Scheme 4).



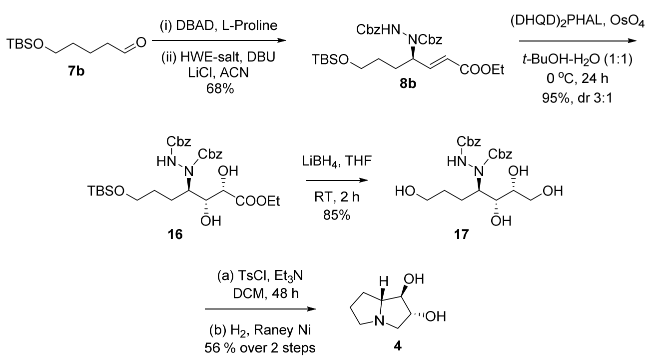
Scheme 4. Synthesis of 1,2-*epi*-lentiginosine

In a similar way, as illustrated in Scheme 5, (-)-lentiginosine **2** was synthesized from diol **11** by an analogous series of reactions to those shown in Scheme 4. The strategy can also be extended to the synthesis of the natural enantiomer and other stereoisomers by simply using the other enantiomer of proline for the α-amination and different ligands for dihydroxylation.



Scheme 5. Synthesis of (-)-lentiginosine

After the successful completion of the synthesis of lentiginosine and its 1,2-epimer we thought to extrapolate our strategy to other analogues. Thus, by simply altering the chain length, the synthesis of dihydroxy pyrrolizidine **4** was achieved. As illustrated in Scheme 6, the synthesis started with the aldehyde **7b**, which on sequential α-amination followed by HWE olefination furnished the γ-amino-α, β-unsaturated ester **8b** in 68% yield and 94% enantioselectivity.[15] The olefinic compound **8b** was subjected to Sharpless asymmetric dihydroxylation using $(DHQD)_2AQN$ as the ligand to give the diol **16**. Diol **16** was converted to give the target compound **4** using same set of reactions as described in Schemes 3 and 4.



Scheme 6. Synthesis of dihydroxy pyrrolizidine

Our synthetic approach afforded the target compound **3** in a linear sequence of 4 steps with an overall yield of 31%, target compound **2** with an overall yield of 23% and target compound **4** with an overall yield of 23%.This strategy is the shortest synthesis reported so far from easily available starting materials with high yields.

Conclusions

In conclusion, we have developed a new, highly efficient and concise protocol to dihydroxylated indolizidine and pyrrolizidine alkaloids using a proline catalyzed α-amination followed by Sharpless asymmetric dihydroxylation reaction as the key steps. Its utility was illustrated by the total synthesis of (-)-lentiginosine, (-)-*epi*-lentiginosine and (-)-dihydroxypyrrolizidine. The synthetic strategy allows implementation of the desirable stereocenters at C-1, C-2 and C-8a and can be extended to the synthesis of other stereoisomers and analogues with variable ring size and different degrees of hydroxylation.

Experimental section

Dibenzyl (*R,E*)-1-(8-((*tert*-butyldimethylsilyl)oxy)-1-ethoxy-1-oxooct-2-en-4-yl)hydrazine-1,2-dicarboxylate (8a): (For procedure to prepare **8a**, see the reference 11) $[\alpha]_D^{25}$: + 2.67 (*c* 1.0, $CHCl_3$) HPLC: Kromasil 5–Amycoat (250 X 4.6mm) (2-propanol : petroleum ether = 10:90, flow rate 0.5ml/min, (λ = 230 nm). Retention time (min):13.30 (major) and 16.23 (minor). The racemic standard was prepared in the same way using *dl*-proline as a catalyst. ee 91%.

(*R,E*)-Dibenzyl 1-(7-((*tert*-butyldimethylsilyl)oxy)-1-ethoxy-1-oxohept-2-en-4-yl)hydrazine-1,2-dicarboxylate (8b): (For procedure to prepare **8b** see the reference 11) $[\alpha]_D^{25}$: + 4.73 (*c* 1.0, $CHCl_3$) HPLC: Kromasil 5 –Amycoat (250 X 4.6mm) (2-propanol: pet ether = 10:90, flow rate 0.5ml/min, λ = 254 nm). Retention time (min): 13.46 (major) and 18.07 (minor). The racemic standard was prepared in the same way using *dl*-proline as a catalyst, ee 94%.[11]

Dibenzyl (*R*)-1-(1,8-dihydroxyoctan-4-yl)hydrazine-1,2-dicarboxylate (9): To a solution of ethyl ester **8a** (0.5 g, 0.80 mmol) in THF (7 mL), was added $LiBH_4$ (0.035 g, 1.6 mmol) at 0 ^oC. The reaction mixture was stirred at rt for 2 h. It was then quenched with ice cold aq. HCl (1N) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude product. Silica gel column chromatography of the crude product using ethyl acetate as eluent gave **9** as a waxy solid (0.312 g, yield 84%). $[\alpha]_D^{25}$: + 0.32 (*c* 1.0, $CHCl_3$), IR ($CHCl_3$, cm^{-1}): ν^{max} 3289, 2292, 1709, 1662, 1218. ^1H NMR (200 MHz, $CDCl_3$): δ 1.26-1.60 (m, 10H), 1.96 (brs, 2H), 3.47-3.67 (m, 4H), 4.02-4.29 (m, 1H), 4.96-5.26 (m, 4H), 7.04 (brs, 1H), 7.31-7.35 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): as a rotameric mixture δ 22.1, 25.5, 28.7, 29.3, 29.7, 31.9, 32.6, 61.8, 62.2, 62.3, 62.8, 67.7, 67.8, 67.9, 68.3, 127.6, 128.0, 128.2, 128.3, 128.4, 128.5, 135.5, 135.8, 136.0, 156.4, 156.8, 156.9,157.3. MS (ESI) : *m/z* 467.15 $(M+Na)^+$ HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{24}H_{33}O_6N_2$ 445.2333; Found 445.2328

Dibenzyl 1-((2*R*,3*S*,4*R*)-8-((*tert*-butyldimethylsilyl)oxy)-1-ethoxy-2,3-dihydroxy-1-oxooctan-4-yl)hydrazine-1,2-dicarboxylate (10): General procedure for Sharpless asymmetric dihydroxylation: To a mixture of $K_3Fe(CN)_6$ (0.825 g, 2.50 mmol), K_2CO_3 (0.345 g, 2.50 mmol), $(DHQ)_2AQN$ (6.5mg, 1 mol%) in *t*-BuOH/H_2O (1:1, 10 mL) at 0 °C was added osmium tetroxide (0.32 mL, 0.1 M solution in toluene, 0.4 mol%), followed by methane sulfonamide (0.079 g, 0.83 mmol). After stirring for 5 min at 0 °C, the olefin **8a** (0.500 g, 0.83 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 24 h and then quenched with solid sodium sulfite (0.5 g). Stirring was continued for additional 15 min and then the solution was extracted with EtOAc (3 x 20 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated. Silica gel column chromatography purification (R_f = 0.40, EtOAc /petroleum ether, 3:7) of the crude product gave **10** as a white waxy solid. (0.507 g, 96%). $[\alpha]_D^{25}$: + 0.22 (*c* 1.0, $CHCl_3$), IR ($CHCl_3$, cm^{-1}): ν^{max} 3474, 3250, 3036, 2925, 2855, 1718, 1682, 1462. ^1H NMR (200 MHz, $CDCl_3$): δ -0.01 (m, 6H), 0.85 (m, 9H), 1.21-1.32 (m, 6H), 1.39-1.53 (m, 3H), 3-3.29 (m, 1H), 3.45-3.82 (m, 3H), 4.02-4.17 (m, 1H), 4.27 (q, *J* = 7 Hz, 2H), 5.04-5.34 (m, 4H), 6.68 -7.02 (m, 1H), 7.14-7.37 (m, 10H). ^{13}C NMR (50 MHz, $CDCl_3$): δ -5.3, -5.4, 14.1, 18.3, 21.7, 25.9, 31.8, 61.8, 62.2, 68.5, 71.1, 71.3, 71.9, 72.1, 127.7, 127.9, 128.1, 128.2, 128.3, 128.5, 128.6, 134.9, 135.7, 156.0, 157.1, 172.7. MS (ESI) : *m/z* 655.29 $(M+Na)^+$ HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{32}H_{48}O_9N_2SiNa$ 655.3021; Found 655.3018

HPLC: Kromasil RP-18 (150 X 4.6mm) (methanol : H_2O = 85:15, flow rate 1ml/min, (λ = 254 nm). Retention time (min) : 6.42 and 7.43

Dibenzyl 1-((2*S*,3*R*,4*R*)-8-((*tert*-butyldimethylsilyl)oxy)-1-ethoxy-2,3-dihydroxy-1-oxooctan-4-yl)hydrazine-1,2-dicarboxylate (11) : waxy solid; (0.380 g, 96%, dr 3:1); $[\alpha]_D^{25}$: + 8.04 (*c* 1.0, $CHCl_3$), IR ($CHCl_3$, cm^{-1}): ν^{max} 3748, 3421, 3019, 1734,1541. ^1H NMR (200 MHz, $CDCl_3$): δ 0.00 (m , 6H) , 0.82-0.91 (m , 9H), 1.22-1.54 (m, 8H), 1.78-1.98 (m, 1H), 3.55-3.64 (m, 2H), 3.90-4.09 (m, 1H), 4.14-4.38 (m, 3H), 4.90-5.34 (m, 4H) , 6.68-6.84 (m,1H), 7.26-7.45 (m, 10H). ^{13}C NMR (50 MHz, $CDCl_3$): -5.3, 14.1, 18.3, 25.9, 25.8, 31.4, 32.3, 61.8, 62.4, 67.8, 68.5, 70.3, 70.4, 72.9, 127.8, 128.0, 128.2, 128.3, 128.5, 135.5, 156.6, 156.9, 172.8. MS (ESI) : *m/z* 655.29 $(M+Na)^+$ HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{32}H_{48}O_9N_2SiNa$ 655.3021; Found 655.3018

HPLC: Kromasil RP-18(150 X 4.6mm) (methanol : H_2O = 85:15, flow rate 1ml/min, (λ = 254 nm). Retention time (min) : 7.33 and 8.23

Dibenzyl 1-((2*S*,3*R*,4*R*)-7-((*tert*-butyldimethylsilyl)oxy)-1-ethoxy-2,3-dihydroxy-1-oxoheptan-4-yl)hydrazine-1,2-dicarboxylate (16): waxy solid; (0.378 g, 95%, dr 3:1); $[\alpha]_D^{25}$: + 10.96 (*c* 1.0, $CHCl_3$) IR ($CHCl_3$, cm^{-1}): ν^{max} 3456, 2956, 2857,1731, 1416. ^1H NMR (200 MHz, $CDCl_3$) : δ -0.02 (m, 6H), 0.80 (m, 9H), 1.17-1.31 (m, 3H), 1.38-1.68 (m, 3H), 1.87-2.03 (m, 1H), 3.28-3.68 (m, 3H), 3.85-3.99 (m,1H), 4.16-4.30 (m, 3H), 4.86-5.27(m, 4H), 7.26(m, 10H), 7.48-7.70 (m,1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ -5.6, 13.9, 18.2, 25.8, 28.7, 60.2, 61.6, 62.2, 68.0, 68.3, 70.9, 71.8, 126.8, 127.5, 127.7, 128.0, 128.3, 128.4, 135.0, 135.7, 156.1, 156.9, 172.7. MS (ESI) : *m/z* 641.31$(M+Na)^+$ HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{31}H_{46}O_9N_2SiNa$ 641.2868; Found 641.2869

HPLC: Kromasil RP-18 (150 X 4.6mm) (methanol : H_2O = 85:15), flow rate 1ml/min, (λ = 254 nm). Retention time (min) : 6.18 and 7.28

(3*R*,4*S*,5*R*)-5-(4-((*tert*-Butyldimethylsilyl)oxy)butyl)-3,4-dihydroxypyrrolidin-2-one (12): General procedure for cyclization: Determination of relative configuration: A solution of compound **10** in MeOH (10 mL) and acetic acid (5 drops) was treated with Raney nickel (1g, excess) under a H_2 (60 psi) atmosphere for 24 h. The reaction mixture was then filtered over celite and concentrated to the give the crude free amine which was further subjected to cyclisation by stirring in EtOH at 55 °C for 5 h. The reaction mixture was concentrated in vacuo to give the crude product Silica gel column chromatography (ethyl acetate: petroleum ether/ 6:4) of the crude product gave **12** as a syrupy liquid. (0.359 g, 75%). $[\alpha]_D^{25}$: +31.25 (*c* 0.5, $CHCl_3$) IR ($CHCl_3$, cm^{-1}): ν^{max} 3285, 2930, 2858, 1712, 1255. ^1H NMR (200 MHz, $CDCl_3$) : δ 0.05 (s, 6H), 0.89 (s, 9H), 1.29-1.56 (m, 5H), 1.71-1.89 (m, 1H), 3.60- 3.66 (m, 3H), 4.24-4.45 (m, 2H), 6.29 (brs,1H). ^1H NMR (500 MHz, Acetone-d_6) : δ 0.07 (s, 6H), 0.91 (s, 9H), 1.40 (m, 2H), 1.56 (m, 3H), 1.81 (m, 1H), 2.92 (brs, 2H), 3.58 (m, 1H), 3.67 (t, *J* = 5.72 Hz, 2H), 4.06 (d, *J* = 5.35 Hz, 1H), 4.25 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ -5.3, 18.4, 22.5, 25.9, 29.7, 32.5, 55.1, 62.9, 74.1, 74.9, 175.4. MS (ESI) : *m/z* 326.18 $(M+Na)^+$ HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{29}O_4NSiNa$ 326.1758; Found 326.1764

(3*S*,4*R*,5*R*)-5-(4-((*tert*-Butyldimethylsilyl)oxy)butyl)-3,4-dihydroxypyrrolidin-2-one (13): syrupy liquid; (0.180 g, 75%); $[\alpha]_D^{25}$: + 3.77(*c* 0.5, $CHCl_3$) IR ($CHCl_3$, cm^{-1}): ν^{max} 3354, 2922, 1711, 1463, 1377. ^1H NMR (200 MHz, $CDCl_3$) : δ 0.05 (s, 6H), 0.89 (s, 9H), 1.50-1.53 (m, 4H), 1.73-2.12 (m, 2H), 3.31- 3.42 (m, 1H), 3.63 (t, *J* = 5.9 Hz, 2H), 3.87-3.94 (m, 1H), 4.29-4.32 (m, 1H), 6.67 (brs,1H) ^1H NMR (500 MHz, Acetone-d_6) : δ 0.07 (s, 6H), 0.91 (s, 9H), 1.51-1.58 (m, 5H), 1.75 (m, 1H), 2.94 (brs, 2H), 3.26-3.30 (m, 1H), 3.67 (t, *J* = 6.10 Hz, 2H), 3.77(m, 1H), 4.06 (d, *J* = 7.3 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.3, 18.3, 22.1, 25.9, 32.5, 33.3, 56.8, 62.9, 76.3, 79.8, 175.3. MS (ESI) : *m/z* 326.15 $(M+Na)^+$ HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{14}H_{29}O_4NSiNa$ 326.1758; Found 326.1764

Dibenzyl 1-((2*S*,3*S*,4*R*)-1,2,3,8-tetrahydroxyoctan-4-yl)hydrazine-1,2-dicarboxylate (14): General procedure for $LiBH_4$ reduction: To a solution of ethyl ester **10** (0.5 g, 0.79 mmol) in THF (7 ml), was added $LiBH_4$ (0.05 g, 0.24 mmol) at 0 °C. The reaction was mixture was stirred at rt for 2 h. It was then quenched with aq. HCl (1N) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude product. Silica gel column chromatography (methanol: CH_2Cl_2: 1:20) of the crude product gave **14** as a white solid (0.32 g, yield 85%). mp: 123-125 °C; $[\alpha]_D^{25}$: +0.13 (*c* 0.3, CH_3OH), IR ($CHCl_3$, cm^{-1}): ν^{max} 3384, 3282, 3019, 2926, 1749, 1720, 1646, 1215. ^1H NMR (200 MHz, $CDCl_3$): δ 1.32-1.58 (m, 6H), 3.45-3.68 (m, 6H), 4.5-4.59 (m, 1H), 5.02-5.24 (m, 4H), 7.24-7.44 (m, 10H). ^{13}C NMR (50 MHz, $CDCl_3$): as a rotameric mixture 23.4, 30.5, 30.8, 33.1, 33.3, 62.8, 65.0, 69.1, 69.2, 69.4, 71.7, 71.8, 72.2, 72.5, 128.7, 129.1, 129.3, 129.4, 129.7, 137.4, 137.7, 158.6, 158.7, 158.9. MS (ESI) : *m/z* 499.17 $(M+Na)^+$ HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{24}H_{32}O_8N_2Na$ 499.2051; Found 499.2047

Dibenzyl 1-((2*R*,3*R*,4*R*)-1,2,3,8-tetrahydroxyoctan-4-yl)hydrazine-1,2-dicarboxylate (15): white solid (0.32 g, yield 85%); mp: 116-118 °C; $[\alpha]_D^{25}$: +0. 34 (*c* 0.85, CH_3OH), IR ($CHCl_3$, cm^{-1}): ν^{max} 3384, 3282, 3019, 2926, 1749, 1720, 1646, 1215, 760. ^1H NMR (200 MHz, $CDCl_3$): δ 1.36-1.41 (m, 1H), 1.49-1.66 (m, 5H), 3.48 -3.69 (m, 6H), 4.16-4.36 (m, 1H), 5.02-5.24 (m, 4H), 7.29-7.47 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): as a rotameric mixture δ 27.1, 30.5, 31.1, 33.8, 33.9, 63.0, 63.2, 63.3, 68.7, 69.4, 69.7, 71.8, 72.2, 72.4, 128.9, 129.3, 129.4, 129.5, 129.6, 129.7, 129.9, 137.9, 138.0, 158.5, 158.9, 159.1. MS (ESI) : *m/z* 499.22(M+Na)$^+$ HRMS (ESI) *m/z*: [M+Na]$^+$ Calcd for $C_{24}H_{32}O_8N_2Na$ 499.2051; Found 499.2047

Dibenzyl 1-((2*R*,3*R*,4*R*)-1,2,3,7-tetrahydroxyheptan-4-yl)hydrazine-1,2-dicarboxylate (17): white solid (0.32 g, yield 85%); mp: 125-127 °C; $[\alpha]_D^{25}$: -0.19 (*c* 0.55, CH_3OH). IR ($CHCl_3$, cm^{-1}): ν^{max} 3376, 3280, 3022, 2929, 1716, 1638, 1190. ^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.27-1.44 (m, 2H), 1.70-1.90 (m, 2H), 3.54-3.66 (m, 5H), 3.83-4.05 (m, 1H), 4.15-4.40 (m, 1H), 5.05-5.15 (m, 4H), 7.10-7.36 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$): as a rotameric mixture δ 23.3, 33.5, 34.1, 63, 64.6, 68.5, 69.3, 72.7, 75.6, 77.5, 80.2, 128.0, 128.7, 129.1, 129.2, 129.4, 129.5, 129.6, 129.7, 137.5, 137.7, 143.5, 157.7, 158.8. MS (ESI) : *m/z* 485.22 (M+Na)$^+$ HRMS (ESI) *m/z*: [M+Na]$^+$ Calcd for $C_{23}H_{30}O_8N_2Na$ 485.1894; Found 485.1891

(1*S*,2*S*,8a*R*)- Octahydroindolizine-1,2-diol (3): General procedure for cyclization: To an ice-cold stirred solution of **14** (0.25g, 0.5 mmol) and triethylamine (0.22 mL, 1.5mmol) in anhydrous CH_2Cl_2 6mL) was added toluenesulfonyl chloride (0.20 g, 1.0 mmol) over 15 min. The resulting mixture was allowed to warm up to room temperature and stirred for 48 h. After diluting with 6 mL CH_2Cl_2, the solution was washed with water (3 x 15 mL), brine, dried over anhyd. Na_2SO_4 and concentrated to give the crude di-tosylated product which was subjected to next step without further purification.

A solution of crude tosylated compound in MeOH (10 mL) and acetic acid (5 drops) was treated with Raney nickel 1 g, excess) under H_2 (60 psi) atmosphere for 24 h. The reaction mixture was then filtered over celite and concentrated to give crude free amine which was further subjected to cyclization by stirring in EtOH at 55 ^{o}C for 20 h. The reaction mixture was concentrated in vacuo to give crude product. Silica gel (neutralized) column chromatography (methanol: CH_2Cl_2: 1:15) of the crude product gave **3** as a white solid (0.046 g, 56%). mp: 134-136 °C [lit.[6e]: 137-138]; $[\alpha]_D^{25}$: - 6.48 (*c* 1, CH_3OH). [lit.[6e]: $[\alpha]_D^{25}$: - 5.3 (*c* 0.3, CH_3OH)]; ^{1}H NMR (200 MHz, D_2O) : δ 1.34-1.55 (m, 3H), 1.67-1.88 (m, 3H), 2.16-2.34 (m, 2H) , 2.42-2.49 (m, 1H), 3.15 (d, *J* =11.2 Hz, 1H), 3.52 (dd, *J* = 7Hz, 11.2 Hz, 1H), 3.98 (d, *J* = 4.1 Hz, 1H), 4.08 – 4.15 (m, 1H). ^{13}C NMR (50 MHz, D_2O) : 25.0, 25.9, 26.0, 55.1, 62.1, 69.6, 77.9, 80.6. (^{1}H and ^{13}C NMR data were in good agreement with those reported in lit.[6e]). MS (ESI) : *m/z* 158.11(M+H)$^+$ HRMS (ESI) *m/z*: [M+H]$^+$ Calcd for $C_8H_{16}O_2N$ 158.1176; Found 158.1175

(1*R*,2*R*,8a*R*)-Octahydroindolizine-1,2-diol (2): white solid, (0.047 g, 57%). mp: 106-108 °C [lit.[5a]: 106-107]; $[\alpha]_D^{25}$: - 2.92 (*c* 0.5, CH_3OH), [lit.[5a]: $[\alpha]^{23}_D$ −1.6 (*c* 0.24, CH_3OH), lit.[7c] $[\alpha]_D$ −3.05 (*c* 1.0, CH_3OH)]. ^{1}H NMR (200 MHz, D_2O): δ 1.28 -1.34 (m, 2H), 1.47-1.53 (m, 1H), 1.68-1.70 (m, 1H), 1.82-1.86 (m, 1H), 1.94-1.98 (m, 1H), 2.13-2.27 (m, 2H), 2.81 (dd, *J* = 7.59, 11.3 Hz , 1H), 2.94 (d, *J*=11.3 Hz, 1H), 3.06 (d, *J* = 11.7 Hz, 1H), 3.70 (dd, *J* = 3.4, 9.1Hz, 1H) 4.10- 4.13 (m, 1H). ^{13}C NMR (50 MHz, D_2O): 25.5, 26.4, 29.9, 55.4, 62.7, 71.4, 78.1, 85.1. (^{1}H and ^{13}C NMR data were in good agreement with those reported in lit.[10g]). MS (ESI) : *m/z* 158.11 (M+ H)$^+$ HRMS (ESI) *m/z*: [M+H]$^+$ Calcd for $C_8H_{16}O_2N$ 158.1176; Found 158.1174

(1*R*,2*R*,7a*R*)-Hexahydro-1H-pyrrolizine-1,2-diol (4): colorless solid, (0.047 g, 56%). mp: 138-140 °C [lit.[8f]: 141-143]; $[\alpha]_D^{25}$: - 6.67 (*c* 1.3, CH_3OH), [lit.[8f]: $[\alpha]^{24}_D$ − 6.4 (*c* 1, CH_3OH), lit.[10e] $[\alpha]_D$ + 7.6 (c 1.3, CH_3OH)]. ^{1}H NMR (200 MHz, CD_3OD): δ 1.63-1.80 (m, 2H), 1.84-1.99 (m, 2H), 2.50 (dd, *J* = 7 Hz , 10.7 Hz ,1H), 2.63-2.74 (m, 1H), 2.84-2.92 (m, 1H), 3.14-3.19 (m, 1H), 3.23-3.26 (m,1H), 3.60 (t, *J* = 5.6 Hz, 1H), 3.94- 4.05 (m,1H). ^{13}C NMR (50 MHz, CD_3OD): 26.4, 31.5, 56.8, 59.7, 71.0, 78.8, 82.9 (^{1}H and ^{13}C NMR data were in good agreement with those reported in lit.[8f]). MS (ESI) : *m/z* 144.12 (M+H)$^+$ HRMS (ESI) *m/z*: [M+H]$^+$ Calcd for $C_7H_{14}O_2N$ 144.1019; Found 144.1020

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