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A 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**, pyrrolizidine **6**, *etc.*, are widespread in plants and microorganisms[3] (Fig. 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} = 5 μg mL^{-1}. 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 with the natural substrate for occupying the enzyme active site.

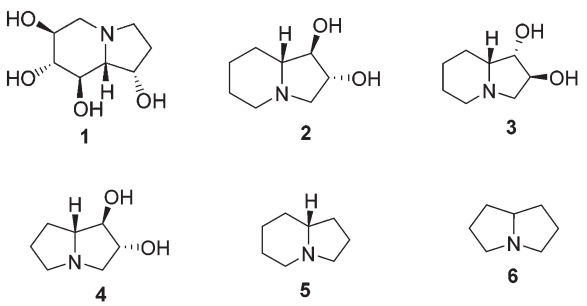

Fig. 1 Some indolizidine and pyrrolizidine alkaloids.

Owing to its potent biological activity, lentiginosine and its analogues have attracted a great deal of interest among synthetic organic chemists, in spite of 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 syntheses 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 these literature reports have used a chiral pool approach, they proved 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 necessary. We have

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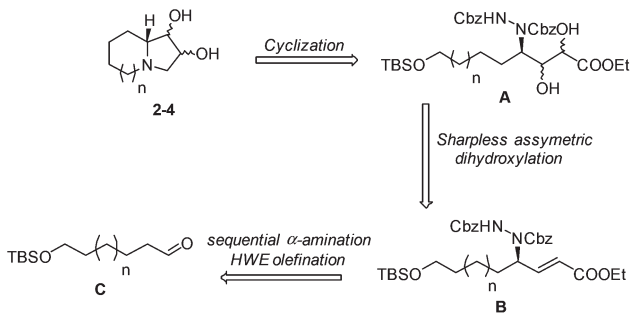
recently reported the synthesis of indolizidine and pyrrolizidine in our preliminary communication[11] employing the sequential α-amination[12] and Horner–Wadsworth–Emmons (HWE) olefination as the key step. In continuation of our interest in developing new methodologies[13] using proline catalyzed sequential amination/aminoxylation followed by HWE olefination, we report here a general and efficient strategy for the synthesis of lentiginosine, *epi*-lentiginosine and dihydroxy pyrrolizidine.

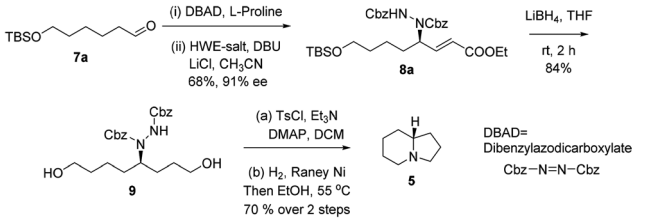
Results and discussion

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 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 ditosylate which was subjected to hydrogenation conditions for the cleavage of N–N bonds using RANEY®-Ni to give the free amine which on nucleophilic displacement of ditosylate 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.

The synthesis of the target molecules (−)-lentiginosine and its 1,2-epimer commenced with γ-amino-α,β-unsaturated ester

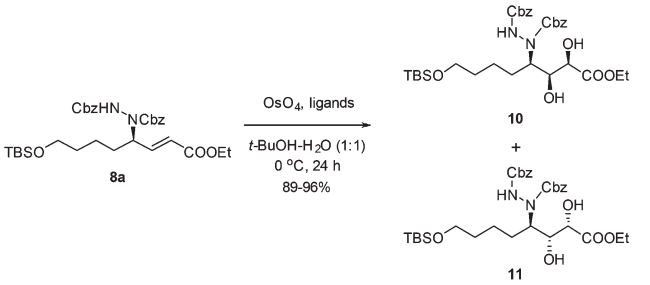


Scheme 1 Retrosynthetic route to indolizidine and pyrrolizidine alkaloids (**2–4**).



Scheme 2 Synthesis of indolizidine alkaloid coniceine.

Table 1 Optimization of Sharpless asymmetric dihydroxylation reaction conditions



Entry	Ligands[a]	Yield (%)	Ratio (**10** : **11**)
1	No ligand	94	83 : 17
2	$(DHQD)_2PHAL$ (5 mol%)	95	2 : 3
3	$(DHQ)_2PHAL$ (5 mol%)	93	99 : 1
4	$(DHQD)_2PYR$ (5 mol%)	89	2 : 3
5	$(DHQD)_2AQN$ (5 mol%)	96	1 : 3
6	$(DHQ)_2AQN$ (5 mol%)	96	99.8 : 0.2

[a] Reactions were carried out in the presence of 1 mol% of OsO_4 and 3 equivalents of K_2CO_3 and K_3FeCN_6.

8a (Table 1). At this stage we investigated the use of the Sharpless asymmetric dihydroxylation reaction used for 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 (Fig. 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 $(DHQD)_2PHAL$, surprisingly the diastereomeric outcome (*anti*-**11**/*syn*-**10**) was found to be 3/2. Switching the ligand to $(DHQD)_2PYR$ gave a similar result (*anti*-**11**/*syn*-**10** 3/2).

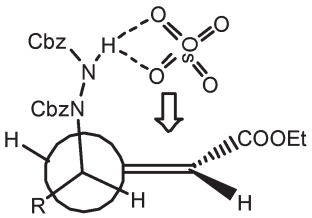


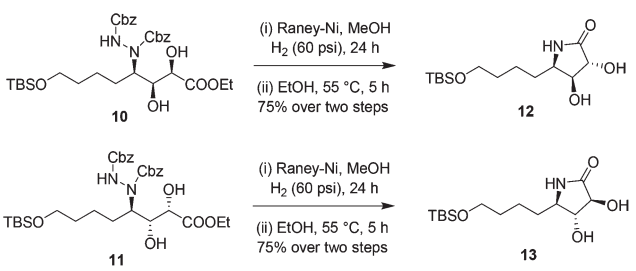
Fig. 2 Proposed transition state for *syn* selectivity.

Finally, $(DHQD)_2AQN$ 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 $(DHQ)_2PHAL$ and $(DHQ)_2AQN$ were found to be useful ligands. In these cases, the reaction progressed with high diastereoselectivity and we obtained *syn*-**10** essentially as a single diastereomer (Table 1, entries 3 and 6). In all the cases, however, the yield remained almost the same.

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 the N–N bond to obtain 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.

The two cyclic isomers **12** and **13** were subjected to 2D NMR spectroscopy after carefully studying their peak patterns in 1D NMR. ^1H, ^{13}C and DEPT NMR spectra of the cyclized compounds were determined in $CDCl_3$. Initially, it was found that 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 better quality NMR spectra. Compounds **12** and **13** were then characterized using the 1D NMR experiments (^1H, ^{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 the 1D spectrum. Therefore the 2D NOESY spectrum was used to determine the relative stereochemistry at the



Scheme 3 Preparation of cyclic derivatives.

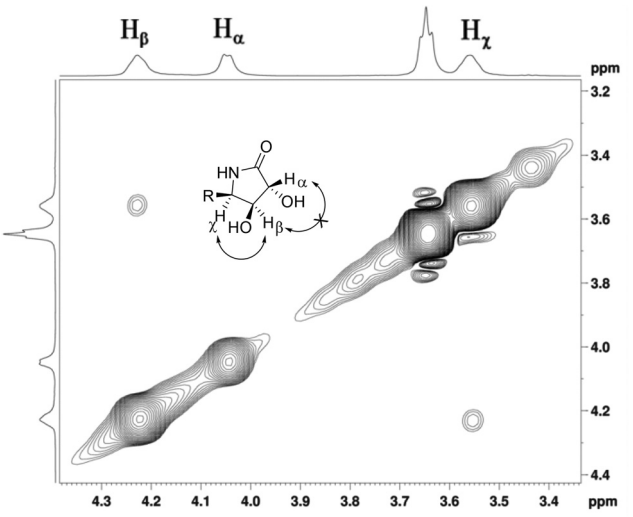


Fig. 3 NOESY spectrum of compound **12**.

β- and γ-position. The NOESY spectra of compound **12** show a cross peak between the β and γ protons 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 Fig. 3.

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 a 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 Fig. 4.

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 ditosyl, which was subjected to hydrogenation conditions using freshly prepared RANEY®-Ni to deliver the free amine which on nucleophilic displacement of ditosylate led to the formation of the desired (−)-1,2-*epi*-lentiginosine **3** (Scheme 4).

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.

After the successful completion of the synthesis of lentiginosine and its 1,2-epimer we thought to extrapolate our strategy

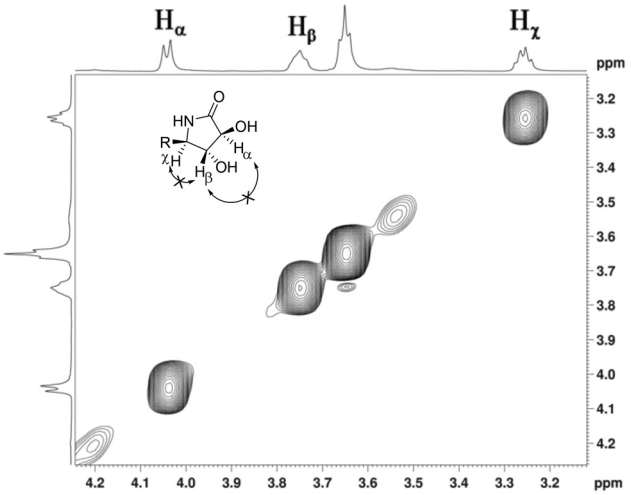
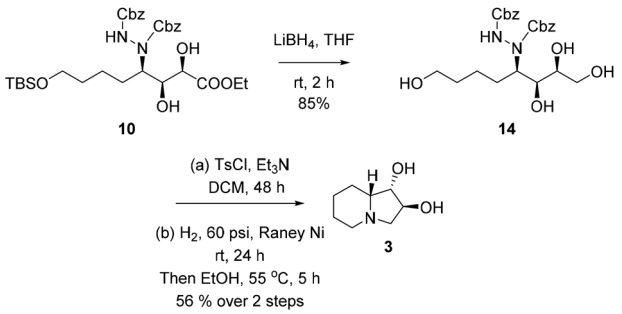
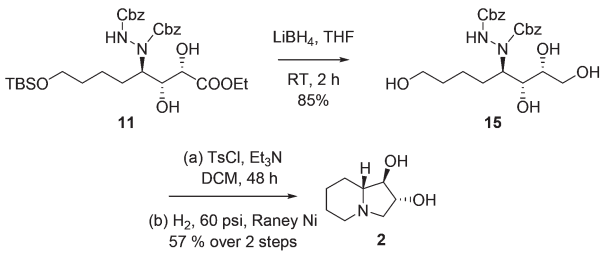


Fig. 4 NOESY spectrum of compound **13**.



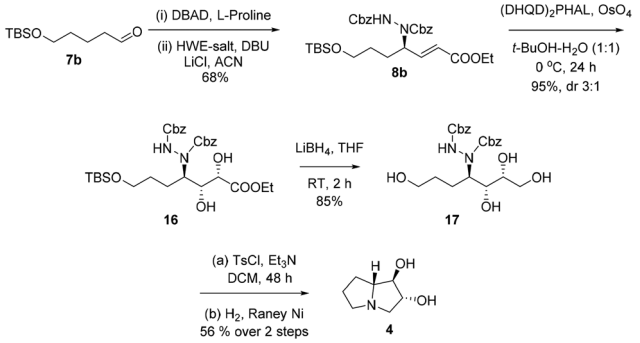
Scheme 4 Synthesis of 1,2-*epi*-lentiginosine.



Scheme 5 Synthesis of (–)-lentiginosine.

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 the same set of reactions as described in Schemes 3 and 4.

Our synthetic approach afforded the target compound **3** in a linear sequence of 4 steps with an overall yield of 31%, target



Scheme 6 Synthesis of dihydroxy pyrrolizidine.

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 synthesise 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 sizes 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 a procedure to prepare **8a**, see ref. 11.) $[\alpha]_D^{25}$: +2.67 (*c* 1.0, $CHCl_3$) HPLC: Kromasil 5-Amycoat (250 × 4.6 mm) (2-propanol–petroleum ether = 10 : 90, flow rate 0.5 mL min^{-1}, 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 a procedure to prepare **8b** see ref. 11.) $[\alpha]_D^{25}$: +4.73 (*c* 1.0, $CHCl_3$) HPLC: Kromasil 5-Amycoat (250 × 4.6 mm) (2-propanol–pet ether = 10 : 90, flow rate 0.5 mL min^{-1}, 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 °C. The reaction mixture was stirred at rt for 2 h. It was then quenched with ice-cold aq. HCl (1 N) 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 the 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), and $(DHQ)_2AQN$ (6.5 mg, 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 an additional 15 min and then the solution was extracted with EtOAc (3 × 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 × 4.6 mm) (methanol–H_2O = 85 : 15, flow rate 1 mL min^{-1}, 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 × 4.6 mm) (methanol–H_2O = 85 : 15, flow rate 1 mL min^{-1}, 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 × 4.6 mm) (methanol–H_2O = 85 : 15, flow rate 1 mL min^{-1}, 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 (1 g, 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 mixture was stirred at rt for 2 h. It was then quenched with aq. HCl (1 N) 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. ^1H 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** (0.25 g, 0.5 mmol) and triethylamine (0.22 mL, 1.5 mmol) in anhydrous CH_2Cl_2 (6 mL) 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 × 15 mL), brine, dried over anhyd. Na_2SO_4 and concentrated to give the crude ditosylated product which was subjected to the 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 a 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 °C for 20 h. The reaction mixture was concentrated *in vacuo* to give the 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)]; ^1H 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* = 7 Hz, 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. (^1H 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] $[\alpha]_D^{23}$ −1.6 (*c* 0.24, CH_3OH), lit.[7c] $[\alpha]_D$ −3.05 (*c* 1.0, CH_3OH)]. ^1H 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, 9.1 Hz, 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. (^1H 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-1*H*-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] $[\alpha]_D^{24}$ −6.4 (*c* 1, CH_3OH), lit.[10e] $[\alpha]_D$ +7.6 (c 1.3, CH_3OH)]. ^1H 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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