Chapter 3

Synthesis of dihydroxylated and monohydroxylated izidines using proline catalyzed α-amination followed by Sharpless asymmetric dihydroxylation
3.1. SECTION A

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

3.1.1 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 and pyrrolizidines. These “izidines” show different patterns of oxygenation, for instance, the highly oxygenated castanospermine, its less hydroxylated congeners such as lentiginosine, 8a-epi-lentiginosine, dihydroxypyrrolizidine or the non oxygenated ring systems such as coniceine and pyrrolizidine etc. are widespread in plants and microorganisms (Figure 1).

Lentiginosine was isolated in 1990 by Elbein and co-workers from the source Astralagus Lentiginosus. It is known to exhibit excellent anti-HIV, anti-tumour and immunomodulating activities apart from being a significant inhibitor of amyloglycosidases (lowering the absorption of carbohydrates in the GI tract) with IC_{50}=5μg/mL. Lentiginosine is an interesting compound from a biochemical standpoint. It was found to be the first glycosidase inhibitor with only two hydroxyl groups. All the other reported glycosidase inhibitors have three or more hydroxyl functions. The fact that a pyrrolizidine alkaloid can also inhibit these glycosidases indicates that a six-membered ring is not essential for inhibitory activity. It seems likely that the nitrogen in the ring is an essential requirement. The mechanism of action is related to inhibition of the biosynthesis of glycoproteins which are responsible for recognition and adhesion of exogenous agents. Effective inhibitors are known to mimic the terminal unit of oligosaccharides competing the natural substrate for occupying the enzyme active site.
Interestingly, its pyrrolizidines analogue was also found to belong to an important class of alkaloids that display a wide range of biological activities mainly due to their action as specific glycosidase inhibitors. Both the hydroxylated indolizidine and pyrrolizidine derivatives have gained considerable interest as antiviral and anticancer agents. Since the biological activity varies substantially with the number, the position and the stereochemistry of the hydroxyl groups on the aza bicyclic skeleton, the synthesis of both naturally occurring compounds and their stereoisomers and analogues have been very interesting targets.

Figure 1. Some indolizidine and pyrrolizidine alkaloids

3.1.2. Review of Literature

Owing to its potent biological activity, lentiginosine and its analogues have aroused a great deal of interest among synthetic organic chemists, resulting in a number of syntheses. Majority of the syntheses reported employ chiral pool starting materials such as sugars and amino acids and involve many steps. A detailed report of recent syntheses is described below.

Pohmakotr et al. (2014)

Pohmakotr and coworkers have synthesized (+)-lentiginosine using chiral pool starting material (+)-tartaric acid 7. Aminosulfide 8 and (+)-tartaric acid 7 was refluxed in xylene to afford the corresponding chiral hydroxyimides 9. Protection of both the hydroxyl groups as
their silyl ethers using TBSCl gave compound 10 which on oxidation with NaI04 in aqueous methanol at 0 °C furnished the required sulfinylimides 11. Sulfinylimides 11 on treatment with LiHMDS gave α-sulfinyl carbanions which undergo intramolecular cyclization reaction to give the dihydroxylated 1-azabicyclic compound 12 as a diastereomeric mixture. Reductive cleavage of the phenylsulfinyl group of compound 12 was accomplished by using a combination of NiCl2·6H2O/NaBH4 in aqueous methanol to get corresponding indolizidinone 13 as a single isomer. Subsequently, reduction of indolizidinone 13 with LiAlH4 in THF furnished (+)-lentiginosine 2.

Scheme1. Synthesis of (+)-lentiginosine (Pohmakotr’s method)

Ham et al. (2014)10th

Ham and coworkers successfully synthesized (-)-lentiginosine starting from γ-allyl benzamide 14 which in the presence of Pd(PPh3)4, NaH and n-Bu4NI gave anti, syn-oxazine 15 with high stereoselectivity. The bulk of the protecting group on the secondary alcohol is responsible for controlling the diastereoselectivity of oxazine ring formation. Anti,syn-
oxazine 15 under Schotten–Baumann conditions afforded the carbamate product 16. Ozonolysis of the terminal olefin of carbamate 16 gave the corresponding aldehyde which on hydrogenolysis gave aminoaldehyde intermediate which undergoes cyclization to get pyrrolidine ring 17. The pyrrolidine ring 17 was protected with Boc₂O and N-Boc compound was reacted with HF–pyridine to afford the selectively deprotected free primary alcohol 18. Oxidation of the primary hydroxyl group of compound 18 with Dess–Martin periodinane produced the corresponding aldehyde, which was subsequently reacted with (3-benzyloxypropyl)triphenylphosphonium bromide in the presence of n-BuLi to give the debenzoylated olefin 19. Catalytic hydrogenation of 19 with Pd/C produced by simultaneous deprotection of the benzyl group and reduction of the internal olefin to get compound 20. Mesylation of the primary alcohol of compound 20 gave the mesylate compound which on removal of the Boc and TBS groups with 4 M HCl–dioxane solution resulted into cyclization to afford (-)-lentiginosine 2.

Scheme 2. Synthesis of (-)-lentiginosine (Ham’s method)
Vankar et al. (2014)\textsuperscript{8k}

Vankar and coworkers successfully synthesized 8a-epi-(\textit{\textendash})-lentiginosine starting from sugar derivative. 3,4,6-Tri-O-acetyl-D-glycals 21 which was converted to its corresponding 6-O-trityl-3,4-dibenzyl-D-glycals 22, following a literature procedure.\textsuperscript{81} Glucal 22 was subjected to dihydroxylation reaction using a catalytic amount of OsO\textsubscript{4} to obtain a 2.2:1 mixture of diols 23 which were not separated at this stage. Subsequent oxidative cleavage of the diol 23 gave dicarbonyl compound 24 which on further reduction furnished the diol 25.

Scheme 3. Synthesis of 8a-epi-(\textit{\textendash})-lentiginosine (Vankar's method)
Mesylation of diol 25 was carried out using mesyl chloride to get dimesyl compound 26 which on treatment with benzylamine undergoes double nucleophilic displacement reaction to obtain pyrrolidine 27. The trityl protection on pyrrolidine 27 was removed to yield compound 28. Benzyl group protection on the amine of compound 28 was replaced with tert-butylcarbamate to get compound 29. Primary alcohol present in compound 29 was oxidized using Cornforth conditions to obtain aldehyde in a facile manner and the crude aldehyde was directly subjected to Wittig olefination using methyltriphenylphosphonium bromide to furnish alkene 30. Subsequently, the carbamate group of compound 30 was deprotected and the crude amine was treated with butenyl bromide to furnish diene 31. Ring closing metathesis of diene 31 gave cyclized product 32 which was subjected to hydrogenolysis to get 8a-epi-(−)-lentiginosine 3.

Dhavale et al. (2007)\textsuperscript{8i}

Dhavale and coworkers successfully synthesized 8a-epi-(−)-lentiginosine starting from D-glucose-derived aziridine carboxylate. Aziridine carboxylate 33 on DIBAL-H reduction at -78 °C gave aldehyde 34 which on 2-C Wittig olefination reaction gave compound 35. Compound 35 on reductive aziridine ring opening furnished δ-lactam 36 which was subjected to benzyl protection to get compound 37. δ-Lactam 36 was reduced to piperidine 38, which on acetonide deprotection, oxidation and hydrogenation gave 8a-epi-(−)-lentiginosine 3.
Scheme 4. Synthesis of 8α-epi-(−)-lentiginosine (Dhavale’s method)

**Jung et al. (2010)**

Jung and coworkers successfully synthesized dihydroxypyrrolizidine using chiral pool approach. Their synthesis started with benzylated pyranose 39 which on Wittig reaction gave compound 40. The hydroxy moiety of compound 40 was then converted into the bromide 41 which on treatment with chlorosulfonyl isocyanate afforded the \textit{anti}-3,4-amino alcohol 42. The intramolecular cyclization of compound 42 provided the corresponding pyrrolidine 43, which on removal of the Cbz moiety afforded pyrrolidine 44. Allylation of the pyrrolidine 44 gave diene 45 which on ring closing metathesis afforded the pyrrolizidine core 46. Finally, catalytic hydrogenation of 46 provided the 1,2-dihydroxypyrrolizidine 4.
Scheme 5. Synthesis of dihydroxytryrrolizidine (Jung’s method)

Angle et al. (2007)\textsuperscript{8f}

Angle and coworkers successfully synthesized dihydroxytryrrolizidine starting from prolinol derivative derived from D-mannitol. Prolinol 47 on Swern oxidation followed by Wittig olefination gave α,β-unsaturated ester 48. The olefin moiety of compound 48 was reduced to get compound 49, which on deprotection of Ts group afforded lactam 50. Reduction of the lactam and cleavage of the protecting groups of 50 gave 1,2-dihydroxytryrrolizidine 4.
3.1.3. Present work

Objective

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. 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.

As a part of our research interest on developing new methodologies and their subsequent application to bioactive compounds,\textsuperscript{11} we envisioned that the proline-catalyzed $\alpha$-amination\textsuperscript{12} of aldehydes could easily give us sterecontrolled synthetic access to indolizidine and pyrrolizidine. Since the $\alpha$-amino aldehydes are prone to recemization, they have been successzfully trapped \textit{in situ} by various methods to furnish 1,2-amino alcohol, $\gamma$-amino-$\alpha,\beta$-unsaturated ester, $\beta$-amino alcohol etc. We chose to trap them by HWE olefination to furnish $\gamma$-amino-$\alpha,\beta$-unsaturated ester using a mild procedure developed by Sudalai \textit{et al.}\textsuperscript{13} It is noteworthy that $\gamma$-amino-$\alpha,\beta$-unsaturated ester, an allylic amines serve as useful building blocks and can further be elaborated to the synthesis of a variety of compounds of biological importance.
3.1.4. Results and Discussion

Our synthetic approach for the synthesis of target aza sugars was envisioned through the retrosynthetic route shown in Scheme 7. We were interested in a versatile approach using Sharpless asymmetric dihydroxylation reaction for introducing the hydroxyl groups, while a proline catalysed α-amination reaction was utilised to stereoselectively introduce the amine functionality. 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\(^\text{14}\) 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.

Scheme 7. Retrosynthetic analysis of of lentiginosine and its analogue.

Before embarking on the synthesis of the target molecules, we considered exploring a model synthesis to test the devised strategy (Scheme 8), in particular, by the concomitant cleavage of the N-N bond and nucleophilic displacement under hydrogenation conditions. Thus previously synthesized γ-amino-α, β-unsaturated ester 51 was subjected to ester reduction ensuing double bond reduction\(^\text{15}\) and TBS deprotection in one step using LiBH\(_4\) in THF to provide the diol 52. The disappearance of ester and olefinic protons in the range of δ 1.28 as triplet, 4.18 as quartet, 5.92 as doublet and 6.87 as dd in \(^1\)H NMR spectrum confirmed the formation of the product. Compound 52 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. 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 8. 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 51. 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.

In general, Kishi’s empirical rule is used to determine the stereochemical outcome of the
osmylation products. The presence of a bulky substituent at the allylic position generally
determines the formation of dihydroxylation product. This rule is however seen to be
generalised in case of carbohydrates. In the present method, dihydroxylation of 51 under
Sharpless conditions in the absence of a chiral ligand interestingly gave “syn facial
selectivity” (syn-53/anti-54:83/17)\(^6\) where the diastereomers were easily separable by silica
gel column chromatography. The disappearance of olefinic protons in the \(^1\)H NMR
confirmed the formation of the dihydroxylated product which was further confirmed by IR
spectroscopy which showed strong absorption at 3748 and 3421 cm\(^{-1}\). This result showed that
the bulk of the allylic NCbz substituent had little impact on the stereodifferentiation of the
two π faces and did not follow the Kishi empirical rule. 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 \(\text{syn-}\)-diastereomer 53 as a major product
(Figure 2).\(^7\) 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-54/syn-53) was found to be 3/2. Switching the ligand to (DHQD)$_2$ PYR gave a similar result (anti-54/syn-53-10:3/2). Finally, (DHQD)$_2$ AQN was found to be a better ligand as the dr for the anti compound 54 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-53 essentially as a single diastereomer (Table 1, entries 3.6). In all the cases, however the yield remained almost the same.

![Chemical Structure]

<table>
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<th>Entry</th>
<th>Ligands$^*$</th>
<th>yield (%)</th>
<th>Ratio (53:54)</th>
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<td>no ligand</td>
<td>94</td>
<td>83:17</td>
</tr>
<tr>
<td>2</td>
<td>(DHQD)$_2$ PHAL (5 mol %)</td>
<td>95</td>
<td>2:3</td>
</tr>
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<td>93</td>
<td>99:1</td>
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<td>(DHQ)$_2$ AQN (5 mol %)</td>
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</table>

Table 1. Optimization of Sharpless asymmetric dihydroxylation reaction conditions

*Reactions were carried out in the presence of 1 mol% of OsO$_4$ and 3 eq of K$_2$CO$_3$ and K$_3$FeCN$_6$. 

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The relative stereochemistry of the three stereocenters generated were unambiguously
determined using 2D NMR spectroscopy. For this purpose, diols 53 and 54 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 55 and 56, respectively.
Extensive NMR studies were carried out on compounds 55 and 56 to determine the relative
stereochemistry (Scheme 9).

**Scheme 9. Preparation of cyclic derivatives**

The two cyclic isomers 55 and 56 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 56 showed
resolved peaks for the methine protons $\alpha$, $\beta$ and $\gamma$ whereas this was not the case for
compound 55. Acetone-$d_6$ proved to be a more suitable solvent for a better quality NMR
spectra. The compounds 55 and 56 were then characterized using the 1D NMR experiments
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\(^1\text{H}, \text{\textsuperscript{13}C DEPT\textsuperscript{\textdagger}}\) as well as 2D homonuclear (COSY, and NOESY) and heteronuclear (HSQC and HMBC) NMR spectroscopy.

For compound 55, the \(\alpha, \beta, \gamma\) protons resonated at \(\delta\ 4.04, 4.22\) and 3.55 ppm respectively. The \(\alpha\) proton shows the distinct doublet at 4.04 ppm having a coupling constant of 6.63 Hz which indicated the \textit{trans} stereochemistry between the \(\alpha\) and \(\beta\)-methine protons. The \(\beta\) and \(\gamma\)-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 \(\beta\) and \(\gamma\)-position. The NOESY spectra of compound 55 shows cross peak between the \(\beta\) and \(\gamma\) proton which confirmed their \textit{syn} relationship between the \(\beta\) and \(\gamma\) methine protons, the \(\alpha\) and \(\beta\) protons did not show NOESY correlation which indicated their \textit{trans} relationship as shown in the Fig. 3.

![NOESY spectrum of compound 55](image)

**Figure 3**: NOESY spectrum of compound 55

For compound 56, the \(\alpha, \beta, \gamma\) protons resonated at \(\delta\ 4.06, 3.77\) and 3.28 respectively. The \(\alpha\) proton showed as a distinct doublet at 4.06 ppm having coupling constant of 7.3 Hz which indicated the \textit{trans} stereochemistry between \(\alpha\) and \(\beta\) methine protons. The \(\beta\) and \(\gamma\) 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 56 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 56

After determining the relative stereochemistry of compounds 53 and 54, we proceeded to the synthesis of target molecules. For the synthesis of 8a-epi-(−)-lentiginosine 3, diol 53 was subjected to LiBH₄ reduction to give tetrol 57. The disappearance of ester and olefinic protons in the range of δ 1.28 as triplet, 4.18 as quartet, 5.92 as doublet and 6.87 as dd in ¹H NMR spectrum confirmed the formation of the product. Compound 57 was then subjected to selective primary tosylation using TsCl and Et₃N to give the di-tosyl intermediate, which was subjected to hydrogenation conditions using freshly prepared Raney-Ni to deliver a free amine which on nucleophilic displacement of di-tosylate led to the formation of the desired 8a-epi-(−)-lentiginosine 3 (Scheme 10). The characterisation of 3 was in good agreement with the reported literature.
Scheme 10: Synthesis of 8a-epi-lentiginosine

In a similar way, as illustrated in Scheme 11, (-)-lentiginosine 2 was synthesized from diol 54 by an analogous series of reactions to those shown in Scheme 10. 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 11: Synthesis of (-)-lentiginosine.

After the successful completion of the synthesis of lentiginosine and its 8a-epimer we thought to extrapolate our strategy to other analogues. Thus, by simply altering the chain length to C5 aldehyde, the synthesis of dihydroxy pyrrolizidine 4 was achieved. As illustrated in Scheme 12, the synthesis started with previously synthesized γ-amino-α,β-unsaturated ester 59. The olefinic compound 59 was subjected to Sharpless asymmetric...
dihydroxylation using (DHQD)$_2$AQN as the ligand to give the diol 60. Diol 60 was converted to give the target compound 4 using same set of reactions as described in Scheme 11.

**Scheme 12: Synthesis of dihydroxy pyrrolizidine 4**

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.

**3.1.5. 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.
3.1.6. Experimental section

Dibenzyl \((R,E)-1-(8-((\text{tert}-\text{butyldimethylsilyl})\text{oxy})-1\text{-ethoxy}-1\text{-oxooct-2-en-4-yl})\text{hydrazine-1,2-dicarboxylate}\) (51):

The spectral data for compound 51 have been reported in chapter 2A.

**Dibenzyl \((R)-1-(1,8\text{-dihydroxyoctan-4-yl})\text{hydrazine-1,2-dicarboxylate} \) (52):**

![](image)

To a solution of ethyl ester 51 (0.5 g, 0.80 mmol) in THF (7 mL), was added LiBH₄ (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 (1N) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine, dried over anhyd. Na₂SO₄ and concentrated under reduced pressure to give the crude product. Silica gel column chromatography of the crude product using ethyl acetate as eluent gave 52 as a waxy solid.

**Yield:** 0.312 g, 84%

**Mol. Formula:** C₂₄H₃₂O₆N₂

\([\alpha]_D^{25} : +0.32 \text{ (c 1.0, CHCl₃)}\)

**IR (CHCl₃, cm⁻¹):** \(v_{\text{max}} \) 3289, 2292, 1709, 1662, 1218

**¹H NMR (200 MHz, CDCl₃):** δ 1.26-1.60 (m, 1OH), 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, 1OH)

**¹³C NMR (100 MHz, CDCl₃):** 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):** \(m/\zeta \) 467.15 (M+Na)⁺

**HRMS (ESI) \(m/\zeta \):** [M+H]⁺ Calcd for C₂₄H₃₃O₆N₂ 445.2333; Found 445.2328

Dibenzyl 1-(2R,3S,4R)-8-((\text{tert}-\text{butyldimethylsilyl})\text{oxy})-1\text{-ethoxy}-2,3\text{-dihydroxy-1-oxooctan-4-yl})\text{hydrazine-1,2-dicarboxylate} \) (53):
General procedure for Sharpless asymmetric dihydroxylation: To a mixture of K$_3$Fe(CN)$_6$ (0.825 g, 2.50 mmol), K$_2$CO$_3$ (0.345 g, 2.50 mmol), (DHQ)$_2$AQN (6.5 mg, 1 mol%) in t-BuOH/H$_2$O (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 51 (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$_2$SO$_4$ and concentrated. Silica gel column chromatography purification ($R_f$ = 0.40, EtOAc/petroleum ether, 3:7) of the crude product gave 53 as a white waxy solid.

Yield: 0.507 g , 96%

Mol. Formula: C$_{32}$H$_{48}$O$_9$N$_2$Si

$[\alpha]_D^{25}$: + 0.22 (c 1.0, CHCl$_3$)

IR (CHCl$_3$, cm$^{-1}$) : $\nu_{max}$ 3474, 3250, 3036, 2925, 2855, 1718, 1682, 1462

$^1$H NMR (200 MHz, CDCl$_3$) : $\delta$ -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)

$^1$C NMR (50 MHz, CDCl$_3$) : $\delta$ -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$_9$N$_2$SiNa 655.3021; Found 655.3018

HPLC: Kromasil RP-18 (150 X 4.6mm) (methanol : H$_2$O = 85:15, flow rate 1ml/min, ($\lambda$ = 254 nm). Retention time (min) : 6.42 and 7.43
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Dibenzyl 1-((2S,3R,4R)-8-((tert-butyldimethylsilyl)oxy)-1-ethoxy-2,3-dihydroxy-1-oxoheptan-4-yl)hydrazine-1,2-dicarboxylate (54):

Product 54 was prepared using the general procedure for Sharpless asymmetric dihydroxylation starting from γ-amino-α,β-unsaturated ester 51 and using (DHQD)$_2$AQN as a ligand.

Yield: 0.380 g, 96%

Mol. Formula: C$_{32}$H$_{48}$O$_6$N$_2$Si

$[\alpha]_D^{25}$: + 8.04 (c 1.0, CHCl$_3$)

IR (CHCl$_3$, cm$^{-1}$): $\nu_{max}$ 3748, 3421, 3019, 1734, 1541

$^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 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)

$^1$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$_6$N$_2$SiNa 655.3021; Found 655.3018

HPLC: Kromasil RP-18(150 X 4.6mm) (methanol : H$_2$O = 85:15, flow rate 1ml/min. ($\lambda$ = 254 nm). Retention time (min): 7.33 and 8.23

Dibenzyl 1-((2S,3R,4R)-7-((tert-butyldimethylsilyl)oxy)-1-ethoxy-2,3-dihydroxy-1-oxoheptan-4-yl)hydrazine-1,2-dicarboxylate (60):

\[ \text{TBSO} \quad \text{CBz} \quad \text{N} \quad \text{OH} \quad \text{COOEt} \]
Product 60 was prepared using the general procedure for Sharpless asymmetric dihydroxylation starting from γ-amino-α,β-unsaturated ester 51 and using (DHQD)$_2$AQN as a ligand.

**Yield:** 0.378 g, 95%

**Mol. Formula:** C$_{31}$H$_{46}$O$_9$N$_2$Si

$[\alpha]_D^{25}$: +10.96 (c 1.0, CHCl$_3$)

**IR (CHCl$_3$, cm$^{-1}$):** $\nu_{\text{max}}$ 3456, 2956, 2857, 1731, 1416

**$^1$H NMR (200 MHz, CDCl$_3$):**

$\delta$ -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$_3$):**

$\delta$ -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$_9$N$_2$SiNa 641.2868; Found 641.2869

**HPLC:** Kromasil RP-18 (150 X 4.6mm) (methanol : H$_2$O = 85:15), flow rate 1ml/min. (λ = 254 nm). Retention time (min) : 6.18 and 7.28

(3R,4S,5R)-5-(4-((tert-Butyldimethylsilyl)oxy)butyl)-3,4-dihydroxypyrrolidin-2-one (55): General procedure for cyclization:

Determination of relative configuration:

A solution of compound 53 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 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 55 as a syrupy liquid.

**Yield:** 0.359 g, 75%
Mol. Formula: C$_{31}$H$_{46}$O$_3$N$_2$Si
[α]$_D^{25}$: +31.25 (c 0.5, CHCl$_3$)
IR (CHCl$_3$, cm$^{-1}$): $\nu_{\text{max}}$ 3285, 2930, 2858, 1712, 1255

$^1$H 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)

$^1$H 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$_3$NSiNa 326.1758; Found 326.1764

(3S,4R,5R)-5-(4-((tert-Butyldimethylsilyl)oxy)butyl)-3,4-dihydroxypyrrolidin-2-one (56):

Lactam 56 was prepared using the procedure described for compound 55 and starting from diol 54.

Yield: 0.180 g, 75%
Mol. Formula: C$_{14}$H$_{29}$O$_4$NSi
[α]$_D^{25}$: + 3.77 (c 0.5, CHCl$_3$)
IR (CHCl$_3$, cm$^{-1}$): $\nu_{\text{max}}$ 3354, 2922, 1711, 1463, 1377

$^1$H 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) $^1$H 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)
Dibenzyll-((2S,3S,4R)-1,2,3,8-tetrahydroxyoctan-4-yl)hydrazine-1,2-dicarboxylate (57):

General procedure for LiBH₄ reduction:

To a solution of ethyl ester 53 (0.5 g, 0.79 mmol) in THF (7 ml), was added LiBH₄ (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 x 5 ml). The combined organic layers were washed with brine, dried over anhyd. Na₂SO₄ and concentrated under reduced pressure to give the crude product. Silica gel column chromatography (methanol: CH₂Cl₂: 1:20) of the crude product gave 57 as a white solid.

Yield: 0.32 g, 85%

Mol. Formula: C₂₄H₃₂O₈N₂

M.P.: 123-125 °C

[α]D²⁵: +0.13 (c 0.3, CH₃OH)

IR (CHCl₃, cm⁻¹): νmax 3384, 3282, 3019, 2926, 1749, 1720, 1646, 1215

¹H NMR (200 MHz, CDCl₃): 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)

¹³C NMR (50 MHz, CDCl₃): 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
Dibenzyl 1-((2R,3R,4R)-1,2,3,8-tetrahydroxyoctan-4-yl)hydrazine-1,2-dicarboxylate (58):

Tetrol 58 was prepared using general procedure for LiBH₄ reduction and starting from diol 54.

Yield: 0.32 g, 85%

Mol. Formula: C₂₄H₃₂O₈N₂

M.P: 116-118 °C

[α]D²⁵: +0.34 (c 0.85, CH₃OH)

IR (CHCl₃, cm⁻¹): vmax 3384, 3282, 3019, 2926, 1749, 1720, 1646, 1215, 760

¹H NMR (200 MHz, CDCl₃): 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)

¹³C NMR (100 MHz, CDCl₃): 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

MS (ESI) : m/z 499.22(M+Na)⁺

HRMS (ESI) m/z: [M+Na]⁺ Calcd for C₂₄H₃₂O₈N₂Na 499.2051; Found 499.2047

Dibenzyl 1-((2R,3R,4R)-1,2,3,7-tetrahydroxyheptan-4-yl)hydrazine-1,2-dicarboxylate (61):
Tetrol 61 was prepared using general procedure for LiBH₄ reduction and starting from diol 60.

Yield: 0.32 g, 85%

Mol. Formula: C₂₃H₃₀O₈N₂

M.P: 125-127 °C

[a]D²⁵ = -0.19 (c 0.55, CH₃OH)

IR (CHCl₃, cm⁻¹): νmax 3376, 3280, 3022, 2929, 1716, 1638, 1190

¹H NMR (200 MHz, CDCl₃): 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)

¹³C NMR (125 MHz, CDCl₃): 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 C₂₃H₃₀O₈N₂Na 485.1894: Found 485.1891

(1S,2S,8aR)- Octahydroindolizine-1,2-diol (3):

General procedure for cyclization:

To an ice-cold stirred solution of 57 (0.25g, 0.5 mmol) and triethylamine (0.22 mL, 1.5mmol) in anhydrous CH₂Cl₂ (6mL) was added tolenesulfonyl 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 CH₂Cl₂, the solution was washed with water (3 x 15 mL), brine, dried over anhyd. Na₂SO₄ 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 H₂ (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 crude product. Silica gel (neutralized) column chromatography (methanol: CH₂Cl₂: 1:15) of the crude product gave 3 as a white solid.

**Yield:** 0.046 g, 56%

**Mol. Formula:** C₈H₁₅O₂N

**M.P:** 134-136 °C [lit.⁶⁻: 137-138]

[α]D²⁵⁻ : - 6.48 (c 1. CH₃OH), [lit.⁶⁻: [α]D²⁵⁻ : - 5.3 (c 0.3, CH₃OH)]

**¹H NMR (200 MHz, D₂O):** 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)

**¹³C NMR (50 MHz, D₂O):** 25.0, 25.9, 26.0, 55.1, 62.1, 69.6, 77.9, 80.6

**MS (ESI):** [M+H]^⁺ 158.11

**HRMS (ESI):** [M+H]^⁺ Calcd for C₈H₁₅O₂N 158.1176; Found 158.1175

**(-)-Lentiginosine 2:**

(-)-Lentiginosine 2 was prepared using general procedure for cyclization reaction and starting from tetrol 58.

**Yield:** 0.047 g, 57%

**Mol. Formula:** C₈H₁₅O₂N

**M.P:** 106-108 °C [lit.⁶⁻: 106-107];

[α]D²⁵⁻ : - 2.92 (c 0.5, CH₃OH), [lit.⁶⁻: [α]D²⁵⁻ : -1.6 (c 0.24, CH₃OH), lit.⁸⁻ [α]D⁻ : -3.05 (c 1.0, CH₃OH)].

**¹H NMR (200 MHz, D₂O):** 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$_2$O): 25.5, 26.4, 29.9, 55.4, 62.7, 71.4, 78.1, 85.1

MS (ESI) : m/z 158.11 (M+H)$^+$

HRMS (ESI) m/z: [M+H]$^+$ Calcd for C$_8$H$_{16}$O$_2$N 158.1176; Found 158.1174

(1R,2R,7aR)-Hexahydro-1H-pyrrolizine-1,2-diol (4):

![Chemical Structure Image]

Dihydroxypyrrolizidine 4 was prepared using general procedure for cyclization reaction and starting from tetrol 61.

Yield: 0.047 g, 56%

Mol. Formula: C$_7$H$_{13}$O$_2$N

M.P: 138-140 °C [lit.: 141-143]

$[\alpha]_D^{25}$ : - 6.67 (c 1.3, CH$_3$OH), [lit.]: $[\alpha]^{24}$D - 6.4 (c 1, CH$_3$OH), lit. $[\alpha]_D^{10}$ + 7.6 (c 1.3, CH$_3$OH)]

$^1$H NMR (200 MHz, CD$_3$OD) : $\delta$ 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$_3$OD): 26.5, 31.5, 56.8, 59.7, 71.0, 78.8, 82.9

MS (ESI) : m/z 144.12 (M+H)$^+$

HRMS (ESI) m/z: [M+H]$^+$ Calcd for C$_7$H$_{14}$O$_2$N 144.1019; Found 144.1020

3.1.7. Spectra
Chapter 3: Section A

$^1$H NMR (CDCl$_3$, 200 MHz) of Dibenzyl ($R$)-1-(1,8-dihydroxyoctan-4-yl) hydrazine-1,2-dicarboxylate (52):

$^{13}$C NMR (CDCl$_3$, 50 MHz) of Dibenzyl ($R$)-1-(1,8-dihydroxyoctan-4-yl) hydrazine-1,2-dicarboxylate (52):
$^1$H NMR (CDCl$_3$, 200 MHz) of Dibenzyl 1-((2R,3S,4R)-8-((tert-butyldimethylsilyl)oxy)-
1-ethoxy-2,3-dihydroxy-1-oxooctan-4-yl)hydrazine-1,2-dicarboxylate (53):

$^{13}$C NMR (CDCl$_3$, 50 MHz) of Dibenzyl 1-((2R,3S,4R)-8-((tert-butyldimethylsilyl)oxy)-
1-ethoxy-2,3-dihydroxy-1-oxooctan-4-yl)hydrazine-1,2-dicarboxylate (53):
\(^1\)H NMR (CDCl\(_3\), 200 MHz) of Dibenzyl 1-((2S,3R,4R)-8-((tert-butyldimethylsilyl)oxy)-
1-ethoxy-2,3-dihydroxy-1-oxooctan-4-yl)hydrazine-1,2-dicarboxylate (54):

\[^{13}\]C NMR (CDCl\(_3\), 50 MHz) of Dibenzyl 1-((2S,3R,4R)-8-((tert-butyldimethylsilyl)oxy)-
1-ethoxy-2,3-dihydroxy-1-oxooctan-4-yl)hydrazine-1,2-dicarboxylate (54):
\(^1\)H NMR (CDCl\(_3\), 200 MHz) of Dibenzyl 1-\((2S,3R,4R)-7-((\text{tert-butyldimethylsilyl})\text{oxy})-1\text{-ethoxy-2,3-dihydroxy-1-oxoheptan-4-yl})\text{hydrazine-1,2-dicarboxylate (60):}

\(^1\)C NMR (CDCl\(_3\), 50 MHz) of Dibenzyl 1-\((2S,3R,4R)-7-((\text{tert-butyldimethylsilyl})\text{oxy})-1\text{-ethoxy-2,3-dihydroxy-1-oxoheptan-4-yl})\text{hydrazine-1,2-dicarboxylate (60):}
\textbf{Chapter 3: Section A}

$^1$H NMR (CDCl$_3$, 200 MHz) of (3R,4S,5R)-5-(4-((\textit{tert}-\text{butyldimethylsilyl})oxy)butyl)-3,4-dihydroxypyrrolidin-2-one (55):

\begin{figure}
\centering
\includegraphics[width=\textwidth]{hnmr}
\caption{$^1$H NMR (CDCl$_3$, 200 MHz) of (3R,4S,5R)-5-(4-((\textit{tert}-\text{butyldimethylsilyl})oxy)butyl)-3,4-dihydroxypyrrolidin-2-one (55).}
\end{figure}

$^{13}$C NMR (CDCl$_3$, 50 MHz) of (3R,4S,5R)-5-(4-((\textit{tert}-\text{butyldimethylsilyl})oxy)butyl)-3,4-dihydroxypyrrolidin-2-one (55):

\begin{figure}
\centering
\includegraphics[width=\textwidth]{cnmr}
\caption{$^{13}$C NMR (CDCl$_3$, 50 MHz) of (3R,4S,5R)-5-(4-((\textit{tert}-\text{butyldimethylsilyl})oxy)butyl)-3,4-dihydroxypyrrolidin-2-one (55).}
\end{figure}
$^1$H NMR in Acetone-d$_6$ of (3R,4S,5R)-5-(4-((tert-butyldimethylsilyl)oxy)butyl)-3,4-dihydroxypyrrolidin-2-one (55):
$^1$H NMR (CDCl$_3$, 200 MHz) of (3S,4R,5R)-5-(4-((tert-butyldimethylsilyl)oxy)butyl)-3,4-dihydroxypyrrolidin-2-one (56):

$^{13}$C NMR (CDCl$_3$, 50 MHz) of (3S,4R,5R)-5-(4-((tert-butyldimethylsilyl)oxy)butyl)-3,4-dihydroxypyrrolidin-2-one (56):
$^1$HNMR in Acetone-<sub>d6</sub> of (3S,4R,5R)-5-(4-((tert-butyldimethylsilyl)oxy)butyl)-3,4-dihydroxypyrrolidin-2-one (56):
$^1$H NMR (CDCl$_3$, 200 MHz) of Dibenzyl 1-((2S,3S,4R)-1,2,3,8-tetrahydroxyoctan-4-yl)hydrazine-1,2-dicarboxylate (57):

$^{13}$C NMR (CDCl$_3$, 50 MHz) of Dibenzyl 1-((2S,3S,4R)-1,2,3,8-tetrahydroxyoctan-4-yl)hydrazine-1,2-dicarboxylate (57):
\(^1\)H NMR (CDCl\(_3\), 200 MHz) of Dibenzyl 1-((2\(R\),3\(R\),4\(R\))-1,2,3,8-tetrahydroxyoctan-4-yl)hydrazine-1,2-dicarboxylate (58):

\(^{13}\)C NMR (CDCl\(_3\), 50 MHz) of Dibenzyl 1-((2\(R\),3\(R\),4\(R\))-1,2,3,8-tetrahydroxyoctan-4-yl)hydrazine-1,2-dicarboxylate (58):
\(^1\)H NMR (CDCl\(_3\), 200 MHz) of Dibenzy l-((2^,3^,4^)-1,2,3,7-tetrahydroxyheptan-4-yl)hydrazine-1,2-dicarboxylate (61):

\(^1\)C NMR (CDCl\(_3\), 50 MHz) of Dibenzy l-((2^,3^,4^)-1,2,3,7-tetrahydroxyheptan-4-yl)hydrazine-1,2-dicarboxylate (17):
Chapter 3: Section A

$^1$H NMR (CDCl$_3$, 200 MHz) of (1S,2S,8aR)-octahydroindolizine-1,2-diol (3):

$^{13}$C NMR (CDCl$_3$, 50 MHz) of (1S,2S,8aR)-octahydroindolizine-1,2-diol (3):
$^1$H NMR (CDCl$_3$, 200 MHz) of (1$R$,2$R$,8$a$R)-octahydroindolizine-1,2-diol (2):

\begin{center}
\includegraphics[width=\textwidth]{image1}
\end{center}

$^{13}$C NMR (CDCl$_3$, 50 MHz) of (1$R$,2$R$,8$a$R)-octahydroindolizine-1,2-diol (2):

\begin{center}
\includegraphics[width=\textwidth]{image2}
\end{center}
$^1$H NMR (CDCl$_3$, 200 MHz) of (1$R$,2$R$,7a$R$)-hexahydro-1H-pyrrolizine-1,2-diol (4):

![NMR spectrum of (1$R$,2$R$,7a$R$)-hexahydro-1H-pyrrolizine-1,2-diol (4)](image)

$^{13}$C NMR (CDCl$_3$, 50 MHz) of (1$R$,2$R$,7a$R$)-hexahydro-1H-pyrrolizine-1,2-diol (4):

![NMR spectrum of (1$R$,2$R$,7a$R$)-hexahydro-1H-pyrrolizine-1,2-diol (4)](image)
Diastereomeric ratio of compounds 53, 54 and 60

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Retention Time (min)
**Chapter 3: Section A**

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3.1.8. References


16. Diastereoselectivity were determined using HPLC.

Stereoselective approach to the synthesis of 1-hydroxyindolizidines and pyrrolizidines

3.2.1 Introduction

Biosynthesis of many hydroxylated indolizidine and pyrrolizidine alkaloids reveal the formation of useful intermediates such as D/L-1-hydroxy indolizidines other than amino acids such as pipecolinic acid.1,2 These compounds were found to be useful precursors for the synthesis of toxic indolizidine and pyrrolizidine alkaloids such as slaframine and swainsonine in the fungus Rhizoctonia leguminola.3 A close study of both the isomers of hydroxyl indolizidines reveled an insight to the biosynthesis of swainsonine. Cytotoxicity and other biological properties have attracted many chemists to take up hydroxyl indolizidines and pyrrolizidines as target compound for synthesis.4

Both indolizidines and pyrrolizidines have been molecules of great interest to us as evident from our earlier communications.2 We have used tools like HKR, proline catalyzed α-aminoxilation as key tools in our previous strategies for the synthesis of molecules like swainsonine, conine and conicine.3a We then devised a short and an efficient strategy using proline catalyzed α-amination and Sharpless asymmetric dihydroxylation to achieve the synthesis of lentiginosine and analogues in high enantio- and diastereoselectivity. We have reported the synthesis of core azabicyclic systems and also their dihydroxylated derivatives in our previous communication.3b These studies further prompted us to devise a new strategy for the synthesis of 1-hydroxy indolizidines and pyrrolizidines in a high enantio- and diastereomanner.

![Figure 1. Some indolizidine and pyrrolizidine alkaloids](image)
Literature reports as mentioned below show that the azabicylic system can be assembled in numerous ways. However an approach that addresses issues like fewer steps, high yields, good enantio and diastereoselectivity is always a quest and therefore highly desirable.

3.2.2. Review of Literature

Literature reports show that the hydroxylated indolizidine and pyrrolizidine alkaloids can be assembled in numerous ways. A detailed report of recent syntheses is described below.

**Huang et al. (2007)**

Huang and coworkers synthesized the hydroxylated indolizidine starting from maleimide derivative. Grignard reaction of the THP-protected 4-hydroxybutyl magnesium bromide with maleimide derivative 3 at -20°C gave $N,O$-acetal 4 which was then subjected to acidic conditions for 30 min to afford the aza-spiropyran. This aza-spiropyran on reduction with borane-dimethyl sulfide gave pyrrolidine compound 5. Free alcohol of pyrrolidine 5 was mesylated to get compound 6 which on hydrogenation conditions gave (1S,8aR)-1-hydroxyindolizidine 1.

![Scheme 1. Synthesis of 1-hydroxyindolizidine (Huang’s method)](image)

**Chandrasekhar et al. (2010)**

Chandrasekhar and coworkers synthesized the hydroxylated indolizidine starting from pyrrolidine aldehyde which in turn was prepared from D-glucose using a known literature procedure. Condensation of aldehyde 7 with benzylamine in the presence of 4 Å molecular sieves afforded chiral imine 8 which on treatment with homoallyl magnesium bromide in
THF at 0 °C gave syn-amino olefin 9 as the exclusive isomer. The amino compound 9 was treated with benzyloxy carbonyl chloride to afford compound 10. Hydroboration of compound 10 with BH$_3$DMS gave amino alcohol 11. Debenzylation of amino alcohol 11 with Pd/C in the presence of ammonium formate gave the free amine, which was immediately protected as the Cbz derivative 12. Compound 12 was treated with MsCl and Et$_3$N to get the mesyl derivative, which on cyclization using KO'Bu in THF afforded compound 13. The acetonide moiety present in compound 13 was removed using TFA–H$_2$O to give hemiacetal 14 which on treatment with NaBH$_4$ in methanol gave triol 15. The subsequent oxidative degradation of compound 15 with NaIO$_4$ gave the aldehyde, which was used as such in the next step without any purification. Deprotection of Cbz and simultaneous reductive amino cyclization under Pd/C gave 1-hydroxyindolizidine 1.

Scheme 2. Synthesis of 1-hydroxyindolizidine (Chandrasekhar’s method)
Zapata Machina *et al.* (2015)*\textsuperscript{c}\*

Zapata Machina and co-workers synthesized the hydroxylated pyrrolizidine starting from epoxy-pyrrolidine derivative which in turn was prepared from an epoxy-aldehyde using a known literature procedure. Epoxy-pyrrolidine derivative 16 on reduction with LiAlH\textsubscript{4} delivered the alcohol and the secondary hydroxyl group was protected as its t-butyldiphenylsilyl (TBDPS) ether to get compound 17. Compound 17 on oxidative functionalization of the olefin using hydroboration reaction followed by treatment with peroxide and NaOH afforded the pyrrolidine compound 18. N-Deprotection under Pd/C-catalyzed hydrogenolysis afforded the deprotected pyrrolidine which on Appel conditions with PPh\textsubscript{3}/CCl\textsubscript{4} and Et\textsubscript{3}N in DMF gave the pyrrolizidine 19. Finally deprotection of TBDPS group using TBAF delivered the targeted hydroxylated pyrrolizidine 2.

Scheme 3. Synthesis of 1-hydroxy pyrrolizidine (Zapata Machina’s method)

Murray *et al.* (2007)*\textsuperscript{b}\*

Murray and co-workers synthesized the hydroxylated pyrrolizidine starting from N-methoxy-N-methyl amide. Amide 20 upon treatment with LiHMDS was successfully cyclised to ketone 21 which was then reduced with sodium borohydride to give the exo-alcohol 22. Subsequent reduction under LiAlH\textsubscript{4} conditions gave (1S,8aR)-1-hydroxyindolizidine 2.
Scheme 4. Synthesis of 1-hydroxy pyrrolizidine (Murray’s method)

3.2.3. Present work

Objective

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. 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.

As a part of our research interest on developing new methodologies and their subsequent application to bioactive compounds, we envisioned that the proline-catalyzed α-amination of aldehydes could easily give us stereocontrolled synthetic access to indolizidine and pyrrolizidine. Since the α-amino aldehydes are prone to racemization, they have been successfully trapped in situ by various methods to furnish 1,2-amino alcohol, γ-amino-α,β-unsaturated ester, β-amino alcohol etc. We chose to trap them by HWE olefination to furnish γ-amino-α,β-unsaturated ester using a mild procedure developed by Sudalai et al. It is noteworthy that γ-amino-α,β-unsaturated esters, an allylic amines serve as useful building blocks and can further be elaborated to the synthesis of variety of compounds of biological importance.
3.2.4. Results and Discussion

Our general synthetic strategy is outlined in Scheme 5. The hydroxylated indolizidine 1 and pyrrolizidine alkaloids 2 could be obtained from compound A. Compound A could be obtained by Sharpless asymmetric dihydroxylation\(^{12}\) of \(\gamma\)-amino-\(\alpha,\beta\)-unsaturated ester B. Ester B could be obtained from aldehyde C via organocatalytic \(\alpha\)-amination reaction.\(^{11}\)

![Scheme 5](image)

**Scheme 5.** Retrosynthetic analysis of 1-hydroxy indolizidine and pyrrolizidine alkaloids

Our synthesis started from mono tosylated 1,6-hexane diol 23a. The choice of tosylation as protecting group was found to be an alternative to our previously reported silyl ethers in order to avoid protection and deprotection steps. Oxidation of the primary alcohol using IBX in ethyl acetate gave aldehyde 24a which was subjected to \(\alpha\)-amination reaction as a crude mixture using DBAD as a nitrogen source and L-proline as a catalyst followed by HWE olefination to furnish \(\gamma\)-amino-\(\alpha,\beta\)-unsaturated ester 25a in 60% yield and 98% enantioselectivity.\(^{12}\) The \(^1\)H NMR spectrum gave olefin protons at \(\delta\) 6.80 (doublet of doublet) with the coupling constant \(J = 6.0, 15.2\) Hz and \(\delta\) 6.57 (doublet) with the coupling constant \(J = 15.2\) Hz indicating trans-olefin. The \(\alpha,\beta\)-unsaturated hydrazino ester 25a was then treated with OsO\(_4\) in presence of \((\text{DHQ})_2\text{AQN}\) (5 mol %) as a ligand to give syn diastereomer 26a as the major product in 95% yield.\(^{11}\) The disappearance of olefinic protons
in the \(^1\)H NMR confirmed the formation of the dihydroxylated product which was further confirmed by IR spectroscopy which showed strong absorption at 3743 and 3470 cm\(^{-1}\).

In the dihydroxylation step, although a general behaviour of the ligands for diastereofacial selectivity was studied with respect to the silylated substrate. It was seen that no much difference was observed in the present case although the protecting group was changed. This was first observed on TLC that the ratio of diastereomers remained same which was further confirmed using HPLC where we observed similar results as in the previous case.\(^{3b}\) Therefore, our concept of hydrogen bonding between OsO\(_4\) and H of NCbz group facilitating syn isomer holds good in each case.

With the dihydroxylation product 26a in hand we proceeded to the cyclisation step where we treated compound 26a with freshly prepared Raney Ni in methanol with few drops of glacial acetic acid to simultaneously cleave N-N bond and cyclisation to give the aza bicyclic lactam 27a in 36% yield (over 2 steps). Disappearance of the Cbz proton peaks in the aromatic region ranging from \(\delta 7.49-7.17\) confirmed the formation of product. Formation of product was also confirmed using the IR spectroscopy where the ester peak at 1716 cm\(^{-1}\) was not observed, instead a new peak at 1690 was observed that corresponds to a 5 membered lactam. The \(\alpha\)-hydroxy group of lactam 27a was then selectively tosylated\(^{13}\) using tosyl chloride under highly dilute conditions for 48 hrs with triethyl amine as a base in CH\(_2\)Cl\(_2\) as a solvent to get monotosylate lactam which without column purification was subjected to LiAlH\(_4\) reduction in THF to get (1S,8aR)-1-hydroxyindolizidine 1 in 43% yield (over 2 steps). Formation of product was also confirmed using the IR spectroscopy due to the absence of lactam peak at 1690 cm\(^{-1}\).
Scheme 6. Synthesis of hydroxylated indolizidine and pyrrolizidine alkaloids

After successful completion of synthesis of 1-hydroxyindolizidine we thought to extrapolate our synthetic strategy to other analogues. Thus, by simply changing the chain length, the synthesis of 1-hydroxy pyrrolizidine 2 was achieved. As illustrated in Scheme 6, synthesis started with mono-tosylated pentane diol 23b which on IBX oxidation gave aldehyde 24b, which on sequential α-amination followed by HWE olefination gave the γ-amino-α, β-unsaturated ester 25b in 60% yield and 98% enantioselectivity. The olefinic compound 25b was subjected to Sharpless asymmetric dihydroxylation using OsO₄ as an oxidant and (DHQD)₂AQN as a ligand and to get diol 26b. Diol 26b was converted to target compound 2 using same set of reactions as described in scheme 6.

3.2.5. Conclusion

In conclusion, we have developed a new protocol employing proline-catalyzed sequential α-amination and Horner–Wadsworth–Emmons olefination approach to the synthesis of 1-
hydroxy indolizidine and pyrrolizidine systems. The present method is easily amenable for
the synthesis of a variety of monohydroxy alkaloids.

3.2.6. Experimental section

General Procedure for the preparation of aldehydes 24a,b:

To a solution of 1.6-hexanediol (1.0 g, 8.5 mmol) in CH₂Cl₂ (17 mL) was added imidazole
(0.58 g, 8.5 mmol) and toluene sulfonyl chloride (1.278 g, 8.5 mmol) at 0 °C and reaction
mixture was stirred at room temperature for 12 h. It was quenched with saturated solution of
NH₄Cl and extracted with CH₂Cl₂. The combined organic layer was washed with brine, dried
(Na₂SO₄) and concentrated to give crude product. Silica gel column chromatography of the
crude product using petroleum ether / ethyl acetate (9:1) provided mono tosylated alcohol
23a as a pale yellow oil.

To a suspension of mono tosylated alcohol 23a (0.5 g, 2.16 mmol) in ethyl acetate was
added IBX (1.21 g, 4.32 mmol) and refluxed (3 h) until complete consumption of alcohol.
The mixture was cooled to room temperature then filtered through a pad of celite, washing
with ethyl acetate. The filtrate was collected and concentrated under reduced pressure to
give aldehyde 24a which was subjected to further reaction without purification.

Using the same procedure as mentioned above, aldehyde 24b was prepared starting from
1.5-pentanediol.

Dibenzyl (R,E)-1-(1-ethoxy-1-oxo-8-(tosyloxy)oct-2-en-4-yl)hydrazine-1,2-dicarboxylate
(25a):

General procedure for sequential α-amination/Horner-Wadsworth-Emmons olefination: To a cooled solution of dibenzylazodicarboxylate (DBAD) (0.54 g, 1.81 mmol)
and L-proline (0.02 g, 8 mol%) in CH₃CN (34 mL) at 0 °C was added aldehyde 24a (0.5 g,
2.17 mmol) and the mixture was stirred for 2 h at 0 °C and further for 1 h at 10 °C. This was
followed by addition of lithium chloride (0.11 g, 2.7 mmol), triethylphosphonoacetate (0.54
ml., 2.71 mmol) and DBU (0.27 mL, 1.81 mmol) in that sequence and the whole mixture was stirred at 5 °C for 45 min. It was then quenched with aq. ammonium chloride solution (15 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine, dried over anhyd. Na₂SO₄ and concentrated under reduced pressure to give crude product. Silica gel column chromatography (petroleum ether: ethyl acetate: 85:15) of the crude product gave 25a as a colorless syrupy liquid.

**Yield:** 0.760 g, 60%

**Mol. Formula:** C₃₃H₃₈N₂O₉S

|α|b|²⁵| + 0.35 (c 1.0, CHCl₃)

**IR (CHCl₃, cm⁻¹):** νmax 3284, 2296, 1716, 1454, 1238, 1054

**¹H NMR (200 MHz, CDCl₃):** δ 7.77 (d, J = 8.3 Hz, 2H), 7.34 (s, 12H), 6.80 (dd, J = 15.2 Hz, 6.0 Hz, 1H), 6.57 (d, J = 15.2 Hz, 1H), 5.17 (s, 4H), 4.23-4.13 (m, 2H), 3.98 (t, J = 6.4 Hz, 2H), 2.43 (s, 3H), 1.71-1.55 (m, 4H), 1.48-1.38 (m, 2H) ppm.

**¹³C NMR (50 MHz, CDCl₃):** δ 156.5, 156.4, 144.7, 135.5, 129.8, 128.5, 128.4, 128.1, 127.8, 77.0, 70.0, 67.8, 60.6, 30.2, 28.4, 21.9, 21.6, 14.1 ppm.

**MS (ESI):** m/z 639.22 (M+H)+

**HPLC:** Kromasil 5-CelluCoat (250 X 4.6cm) (Ethanol: n-Hexane: DEA(1 :99:0.1), flow rate : 1 mL/min 465Psi, λ = 254 nm). Retention time (min): 16.625 (major) and 18.150 (minor). The racemic standard was prepared in the same way using d/-proline as a catalyst. ee 98%.

**Dibenzyl (R,E)-1-(1-ethoxy-1-oxo-7-(tosyloxy)hept-2-en-4-yl)hydrazine-1,2-dicarboxylate (25b):**

![Dibenzyl structure](image)

Compound 25b was prepared using the general procedure for sequential α-amination/ Horner-Wadsworth-Emmons olefination starting from aldehyde 24b.

**Yield:** 0.724 g, 58%

**Mol. Formula:** C₃₂H₃₆N₂O₈S
Chapter 3: Section B

[\alpha]_b^{25}: + 0.29 (c 1.0, CHCl₃)

IR (CHCl₃, cm⁻¹): νmax 3284, 2290, 1716, 1546, 1218, 1052

¹H NMR (200 MHz, CDCl₃): δ 7.89 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 2.8 Hz, 13H), 6.96 (dd, J = 7.1, 15.8 Hz, 1H), 6.00 (d, J = 15.8 Hz, 1H), 5.25 (s, 4H), 4.47-3.87 (m, 4H), 2.55 (s, 3H), 1.59 (d, J = 6.4 Hz, 2H), 1.49-1.26 (m, 6H) ppm.

¹³C NMR (50 MHz, CDCl₃): δ 165.9, 156.6, 155.4, 144.5, 135.4, 132.8, 129.6, 128.3, 128.1, 128.0, 127.9, 127.6, 122.8, 69.9, 68.1, 67.4, 60.4, 30.0, 29.4, 28.2, 21.6, 21.3, 13.9 ppm.

MS (ESI): m/z 647.29 (M+Na)

HPLC: Kromasil 5-CelluCoat (250 X 4.6cm) (Ethanol: n-Hexane: DEA (1:99:0.1). flow rate: 1 mL/min 465Psi. X = 254 nm). Retention time (min): 8.82 (major) and 10.09 (minor). The racemic standard was prepared in the same way using dl-proline as a catalyst, ee 98%.

Dibenzyld 1-((2R,3S,4R)-1-ethoxy-2,3-dihydroxy-1-oxo-8-(tosyloxy)octan-4-yl)hydrazine-1,2-dicarboxylate (26a):

\[
\begin{align*}
\text{Cbz} & \quad \text{Cbz} \\
\text{HN} & \quad \text{HN} \\
\text{TsO} & \quad \text{TsO} \\
\text{OH} & \quad \text{OH} \\
\text{COOEt} & \quad \text{COOEt}
\end{align*}
\]

General procedure for Sharpless asymmetric dihydroxylation: To a mixture of K₃Fe(CN)₆ (0.825 g, 2.50 mmol), K₂CO₃ (0.345 g, 2.50 mmol), (DHQ)₂AQN (6.5mg, 1 mol%) in t-BuOH/H₂O (1:1.10 mL) at 0 °C was added osmium tetroxide (0.32 mL, 0.1 M solution in toluene, 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 25a (0.500 g, 0.79 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 Na₂SO₄ and concentrated. Silica gel column chromatography purification (Rf = 0.40, EtOAc/petroleum ether: 3:7) of the crude product gave 26a as a white waxy solid.

Yield: 0.500 g, 95%

Mol. Formula: C₃₃H₄₀O₁₁N₂S
Dibenzyl 1-((2S,3S,4R)-1-ethoxy-2,3-dihydroxy-1-oxo-7-(tosyloxy)heptan-4-yl)hydrazine-1,2-dicarboxylate (26b):

![Chemical Structure Diagram]

Compound 26b was prepared using the general procedure for Sharpless asymmetric dihydroxylation starting from α,β-unsaturated ester 25b.

**Yield:** 0.490 g, 93%

**Mol. Formula:** C₃₂H₃₈O₁₁N₂S

**[α]_D^{25}**: +0.22 (c 1.0, CHCl₃)

**IR (CHCl₃, cm⁻¹):** ν_max 3423, 3016, 1732, 1545

**¹H NMR (200 MHz, CDCl₃)**: δ 7.78 (d, J = 8.3 Hz, 2H), 7.46-7.29 (m, 13H), 5.42-4.13 (m, 6H), 3.12 (s, 3H), 2.45 (s, 3H), 1.38-1.28 (m, 9H) ppm.

**¹³C NMR (50 MHz, CDCl₃)**: δ 172.0, 172.8, 165.9, 165.8, 156.8, 144.9, 135.6, 133.0, 129.9, 128.6, 128.2, 128.2, 127.9, 77.2, 70.3, 68.6, 67.9, 62.9, 62.8, 61.7, 43.2, 35.6, 33.6, 29.7, 28.6, 21.7, 16.4, 16.3, 14.2, 14.2, 14.1 ppm.

**MS (ESI)**: m/z 681.29 (M+Na)⁺
HPLC: Kromasil RP-8 (150 X 4.6mm) (methanol : H₂O = 75:25, flow rate 1ml/min, (λ = 254 nm). Retention time (min) : 6.41 and 7.48 (dr 95.5:4.5)

(1S,2R,8aR)-1,2-Dihydroxyhexahydroindolizin-3(2H)-one (27a):

General procedure of N-N bond cleavage using Raney-Ni: The solution of 27a (0.5 g, 0.74 mmol) in MeOH (10 mL) and acetic acid (8 drops) was treated with Raney nickel (1.0 g, excess) under H₂ (70 psig) atmosphere for 24 h. The reaction mixture was then filtered over celite and concentrated to give crude amino alcohol which was stirred in EtOH at 55 °C for 5 h. The reaction mixture was concentrated in vacuo to give crude product. Silica gel column chromatography (petroleum ether: ethyl acetate: 40:60) of the crude product gave lactam 27a as a colorless liquid.

Yield: 0.045 g, 36%

Mol. Formula: C₉H₁₃O₃N

[a]D²⁵: -6.1 (c 1.2, MeOH)

IR (CHCl₃, cm⁻¹): νmax 3280, 2933, 2856, 1690, 1254

¹H NMR (200 MHz, CDCl₃): δ 4.19-3.95 (m, 3H), 3.72-3.50 (m, 1H), 2.81-2.59 (m, 1H), 1.73 (t, J = 14.5 Hz, 2H), 1.57-1.20 (m, 4H) ppm.

¹³C NMR (50 MHz, CDCl₃): δ 173.1, 177.4, 74.4, 60.3, 41.9, 27.0, 26.0, 24.7 ppm.

MS (ESI): m/z 172.20 (M+H)⁺

(1S,2R,7aR)-1,2-Dihydroxyhexahydro-3H-pyrrolizin-3-one (27b):

Compound 27b was prepared using the general procedure for N-N bond cleavage starting from diol 26b.
Yield: 0.044 g. 35%

Mol. Formula: C_{7}H_{11}NO_{3}

[\alpha]_{D}^{25}: -5.83 (c 1.0, MeOH)

IR (CHCl_{3}, cm^{-1}): \nu_{\text{max}} 3352, 2926, 1690, 1462, 1375

^{1}H NMR (200 MHz, CDCl_{3}) : \delta 6.79 (d, J = 8.7 Hz, 1 H), 6.21 (dd, J = 7.2, 8.5 Hz, 1 H), 6.04 - 5.87 (m, 2 H), 5.61 - 5.46 (m, 2 H), 4.74 - 4.59 (m, 1 H), 4.54 - 4.39 (m, 2 H), 4.09 - 3.89 (m, 1 H)

^{13}C NMR (50 MHz, CDCl_{3}) : \delta 173.9, 83.3, 80.3, 64.4, 49.1, 43.4, 43.0, 31.1, 26.8

MS (ESI): m/z 158.20 (M+H)^{+}

(1S,8aR)-Octahydroindolizin-1-ol (1):

General procedure for reduction: To the stirred solution of lactam 27a (0.04 g, 0.23 mmol) in CH_{2}Cl_{2} (10 mL) was added tosyl chloride (0.044 g, 0.23 mmol) under high dilution conditions and stirred for 48 h under room temperature. After completion of the reaction as observed on TLC the reaction was quenched with water and the organic layer was extracted with CH_{2}Cl_{2} (3 x 20 mL) twice and concentrated in vacuo to give the crude monotosylated product which was further used for subsequent reaction without any purification.

To a stirred suspension of LiAlH_{4} (0.017 g, 0.46 mmol) in dry THF (1 mL) was added a solution of crude monotosylate product in THF (1 mL), and the mixture was refluxed for 6 h. After being cooled to ambient temperature, the mixture was treated with a saturated aqueous solution of sodium sulfate (2 mL) and extracted with CH_{2}Cl_{2} (3 x 5 mL). The combined organic layers were washed with brine, dried (Na_{2}SO_{4}), and concentrated under reduced pressure. Silica gel column chromatography (MeOH: CH_{2}Cl_{2}: 2:8) of the crude product gave as a colorless liquid.

Yield: 0.014 g. 43%

Mol. Formula: C_{8}H_{15}NO

[\alpha]_{D}^{25}: -16.2 (c 1.0, MeOH)

IR (CHCl_{3}, cm^{-1}): \nu_{\text{max}} 3420, 3220
1H NMR (500 MHz, CH3OD): δ 3.86-3.76 (m, 1H). 3.46 (t, J = 6.6 Hz, 1H). 3.04-2.85 (m. 2H). 2.68-2.55 (m, 1H). 2.45-2.34 (m, 1H). 2.27 (dd, J = 8.1, 10.5 Hz, 1H). 1.83-1.64 (m. 1H). 1.64-1.54 (m, 1H). 1.51-1.38 (m, 2H). 1.28 (t, J = 2.9 Hz, 1H) ppm.

13C NMR (101 MHz, CH3OD): δ 78.7, 71.1, 59.6, 56.8, 49.2, 43.5, 31.4, 26.3, 24.5 ppm.

MS (ESI): m/z 142.12 ([M+H]+)

(1S,7aR)-Hexahydro-1H-pyrrolizin-1-ol (2):

Yield: 0.013 g, 43%

Mol. Formula: C7H13NO

[α]D25: -15.4 (c 1.0, MeOH)

IR (CHCl3, cm⁻¹): νmax 3472, 3150

1H NMR (200 MHz, CH3OD) δ 4.36 (d, J = 8.7 Hz, 1H). 3.78 (dd, J = 7.1, 8.5 Hz, 1H). 3.61-3.45 (m, 2H). 3.16-2.94 (m, 4H). 2.33-1.90 (m, 3H). 1.68-1.40 (m, 1H) ppm.

13C NMR (50 MHz, CH3OD): 80.9, 77.6, 60.5, 43.4, 40.8, 31.7, 25.3 ppm.

MS (ESI): m/z 128.20 ([M+H]+)

3.2.7. Spectra
Dibenzyl \((R,E)-1-(1\text{-ethoxy}-1\text{-oxo}-8\text{-tosyloxy})\text{oct}-2\text{-en}-4\text{-yl})\text{hydrazine-1,2-dicarboxylate} (25a):

\[ \text{H NMR (CDCl}_3, 200 \text{ MHz)} \]

\[ \text{C NMR (CDCl}_3, 50 \text{ MHz)} \]
Dibenzyl(\(R,E\))-1-(1-ethoxy-1-oxo-7-(tosyloxy)hept-2-en-4-yl)hydrazine-1,2-dicarboxylate (25b):

\[\text{Chemical Shift (ppm)}\]

\[\text{\(1^H\) NMR (CDCl\(_3\), 200 MHz)}\]

\[\text{\(13^C\) NMR (CDCl\(_3\), 50 MHz)}\]
Dibenzyl-(2R,3S,4R)-1-ethoxy-2,3-dihydroxy-1-oxo-8-(tosyloxy)octan-4-yl)hydrazine-1,2-dicarboxylate (26a):

**$^{1}H$ NMR (CDCl$_3$, 200 MHz)**

**$^{13}C$ NMR (CDCl$_3$, 50 MHz)**
Dibenzyl 1-((2R,3S,4R)-1-ethoxy-2,3-dihydroxy-1-oxo-7-(tosyloxy)heptan-4-yl)hydrazine-1,2-dicarboxylate (26b):
(1S,2R,8aR)-1,2-Dihydroxyhexahydroindolizin-3(2H)-one (27a):

\[ \text{Chemical Shift (ppm)} \]

\[ \text{\( ^1H \text{ NMR (CDCl}_3, 200 \text{ MHz}) \)} \]

\[ \text{Chemical Shift (ppm)} \]

\[ \text{\( ^{13}C \text{ NMR (CDCl}_3, 50 \text{ MHz}) \)} \]
Chapter 3: Section B

\[(1S,2R,7aR)-1,2\text{-Dihydroxyhexahydro-3H-pyrrolizin-3-one (27b):}\]

\[\text{\textbf{H NMR (CDCl}_3, 200 \text{ MHz)}}\]

\[\text{\textbf{C NMR (CDCl}_3, 50 \text{ MHz)}}\]
(1S,8aR)-Octahydroindolizin-1-ol (1):

\[\text{H NMR (CH}_3\text{OD, 500 MHz)}\]

\[\text{C NMR (CH}_3\text{OD, 125 MHz)}\]
(1S,7αR)-Hexahydro-1H-pyrrolizin-1-ol (2):

$^1$H NMR (CD$_3$OD, 200 MHz)

$^{13}$C NMR (CD$_3$OD, 125 MHz)
Chapter 3: Section B

Detector A - 1 (254nm)

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<th>C Area</th>
<th>Area &quot;%&quot;</th>
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</tr>
<tr>
<td>18.325</td>
<td>500544</td>
<td>40.561</td>
</tr>
<tr>
<td>21.958</td>
<td>38149</td>
<td>3.061</td>
</tr>
<tr>
<td>23.667</td>
<td>45228</td>
<td>2.627</td>
</tr>
</tbody>
</table>

Totals

| 1246821        | 100.000  |

Detector A - 1 (254nm)

<table>
<thead>
<tr>
<th>Retention Time</th>
<th>C Area</th>
<th>Area &quot;%&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.625</td>
<td>4579705</td>
<td>99.483</td>
</tr>
<tr>
<td>18.150</td>
<td>23785</td>
<td>0.517</td>
</tr>
</tbody>
</table>

Totals

| 4603490        | 100.000  |
### Table 1: Chromatographic Analysis

<table>
<thead>
<tr>
<th>No.</th>
<th>RT</th>
<th>Height</th>
<th>Area</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.85</td>
<td>115115</td>
<td>1488123</td>
<td>98.689</td>
</tr>
<tr>
<td>2</td>
<td>7.51</td>
<td>1540</td>
<td>19763</td>
<td>1.311</td>
</tr>
</tbody>
</table>

|    | 116655 | 1507886 | 100.000 |

**Diagram:**

- **Rt:** Retention Time
- **Height:** Peak height
- **Area:** Peak area
### Detector A - 1 (214nm)

<table>
<thead>
<tr>
<th>Pk #</th>
<th>Retention Time</th>
<th>Area</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8.792</td>
<td>3878568</td>
<td>55.917</td>
</tr>
<tr>
<td>2</td>
<td>10.067</td>
<td>3057690</td>
<td>44.083</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>6936258</strong></td>
<td><strong>100.000</strong></td>
<td></td>
</tr>
</tbody>
</table>

![Diagram of retention time and area for Detector A - 1 (214nm)](image)

### Detector A - 1 (214nm)

<table>
<thead>
<tr>
<th>Pk #</th>
<th>Retention Time</th>
<th>Area</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8.817</td>
<td>3626206</td>
<td>99.289</td>
</tr>
<tr>
<td>2</td>
<td>10.092</td>
<td>33141</td>
<td>0.711</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>4659317</strong></td>
<td><strong>100.000</strong></td>
<td></td>
</tr>
</tbody>
</table>
### Peak Quantitation: AREA

<table>
<thead>
<tr>
<th>No.</th>
<th>RT</th>
<th>Height</th>
<th>Area</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.41</td>
<td>235219</td>
<td>3893904</td>
<td>95.306</td>
</tr>
<tr>
<td>2</td>
<td>7.48</td>
<td>11768</td>
<td>191646</td>
<td>4.694</td>
</tr>
</tbody>
</table>

**Calculation Method: AREA**

\[
\text{Area} = \sum \text{Height} 
\]

\[
\text{Total Area} = 401.500 
\]

\[
\text{Relative Area} = 100.000 
\]
3.2.8. References:


2. (a) V. Jha, P. Kumar, RSC Adv. 2014, 4, 3238; (b) V. Jha, P. Kumar, Synlett 2014, 25, 1089.


5. (a) F. P. Guengerich, J. J. Synder, H. P. Broquist, Biochemistry 1973, 12, 4264; (b) E. C. Clevenstine, P. Walter, T. M. Harris, H. P. Broquist, Biochemistry 1979, 18, 3663.


Chapter 3: Section B


14. Diastereomeric and enantiomeric excess were determined using HPLC (See experimental section).