ABSTRACT

The thesis entitled “Total synthesis of biologically active alkaloids: (1S, 8aS)-1-hydroxyindolizidine, (+)-radicamine B, (+)-5-epi-radicamine B, (-)-codonopsinol, (+)-2-epi-codonopsinol, some polyhydroxylated azepanes and (-)-deoxocuscohygrine” is divided into three chapters.

Chapter-I: It is further sub-divided into two sections

Section A: It describes with the “Introduction to alkaloids”.

Section B: This section describes “Stereoselective synthesis of (1S, 8aS)-1-hydroxy indolizidine”.

Chapter-II: It contains the synthesis of some naturally occurring polyhydroxy pyrrolidine alkaloids and its epimers. It is further sub-divided into two sections

Section A: It describes the “Total synthesis of (+)-radicamine B and (+)-5-epi-radicamine B”.

Section B: It describes the “Total Synthesis of (-)-codonopsinol and (+)-2-epi-codonopsinol via acid catalyzed amido cyclisation”.

Chapter-III: It consists of the synthesis of some unnatural alkaloids and it is further sub-divided into two sections

Section A: This section describes the “Stereoselective synthesis of polyhydroxylated azepane derivatives”.

Section B: It describes the “Chiron approach to (-)-deoxocuscohygrine”.

I
CHAPTER-I

Section A: Introduction to alkaloids

This chapter contains the introduction of alkaloids. It also describes history, occurrence, characteristics, classification and biological activities (glycosidase inhibition) of alkaloids.

Section B: Synthesis of (1S, 8aS)-1-hydroxyindolizidine using stereoselective Grignard addition on N-benzyl-3-deoxy sugarimine

This section describes the stereo selective synthesis of 1-hydroxy indolizidine 5, which is a key precursor in the biosynthesis of indolizidine alkaloids such as swainsonine 2 and slaframine 4.

Polyhydroxylated indolizidine alkaloids are frequently encountered in nature in variety of sources. Few such examples are castanospermine 1, swainsonine 2, lentiginosine 3 and slaframine 4. Compounds 1-3 are specific inhibitors of glycosidases and shown activity against HIV, cancer and diabetics. Slaframine 4 is a neurotoxin fungus metabolite that has potent use in the treatment of diseases involving cholinergic dysfunction. Because of their interesting biological activity and structural features, these indolizidine alkaloids attracted both biologists and synthetic chemists. As part of ongoing
programme for the synthesis of azasugars we recently developed an approach for the synthesis of (5,6), (6,6) and (6,7) bicyclic azasugars using highly stereoselective Grignard addition reaction on sugar imine as a key step, this process represents a unique source for the synthesis of chiral amines with proper alkyl chain. Here in we wish to report an extension of our methodology for the stereoselective synthesis of (1S, 8aS)-1-hydroxyindolizidine 5 which is a key precursor in the biosynthesis of indolizidine alkaloids such as swainsonine 2 and slaframine 4 in the fungus Rhizoctonia Legumiola (Figure 1). Although several approaches are known in the literature to the best of our knowledge none of them utilized carbohydrates as starting materials.

The retrosynthetic analysis of (1S, 8aS)-1-hydroxyindolizidine 5 is shown in scheme 6. The key aspect of present synthesis is to find the stereoselectivity in Grignard addition on 3-deoxy sugarimine derived from D-glucose 11 (Scheme-1).

**Scheme-1: Retrosynthesis**

Our synthesis starts from the aldehyde 12 which can be prepared from commercially available D-glucose 11 using standard literature procedure. Condensation of aldehyde 12 with benzyl amine in presence of 4Å molecular sieves afforded chiral imine 8 which was used as such without any purification for the next step. Treatment of the imine 8 with homoallyl magnesiumbromide 9 in THF at 0 °C gave syn amino olefin 7 as an exclusive isomer by 1H NMR (Scheme-2).
The absolute configuration of the newly created center was not known at this stage (Scheme-2). But based on our earlier observation we presumed it to be a syn isomer, because the ring oxygen chelates with Grignard reagent and it helps the nucleophile to undergo addition with high stereoselectivity. It was felt earlier that the presence of alkoxy group at C-3 position is also helping to get the exclusive stereoselectivity, but formation of 7 clearly shows that the chelation of ring oxygen is the only essential factor for the high selectivity (Figure 2).

In order to construct the piperidine ring the amino compound 7 was treated with benzyloxy carbonyl chloride in presence of NaHCO₃ in MeOH to afford compound 13 in 92% yield. Hydroboration of compound 13 with BH₃.DMS at 0 ºC gave amino alcohol 14 in good yield. Then compound 14 was subjected to debenzylation with Pd/C in presence of ammonium formate in methanol for 3 h at 60 ºC gave free amine and it was immediately protected as Cbz derivative 15 in 86% yield. For the construction of piperidine ring, compound 15 was treated with MsCl, Et₃N in CH₂Cl₂ at 0 ºC to produce 16.
mesyl derivative which was used as such without purification. The cyclization was carried out on crude mesyl derivative using KO'Bu in THF to yield compound 6 in 80%. The next stage is to construct the pyrrolidine unit, for this acetonide moiety in 6 was removed using TFA-H₂O to give hemiacetal 16 in 85% yield. Oxidative cleavage of 16 with NaIO₄ in methanol-water gave eliminated α, β-unsaturated aldehyde 17 in 82% yield (Scheme-3). The formation of 17 can be explained through β-formyloxy elimination of the aldehyde derived from 16 during oxidative cleavage.

**Scheme 3: Reagents and conditions** (a) CbzCl, NaHCO₃, MeOH, rt, 4 h, 92%; (b) BH₃·DMS, THF, 0 °C, 2 h; (c) i) Pd/C, ammonium formate, 60 °C, 2 h; ii) CbzCl, NaHCO₃, MeOH, rt, 4 h, 86%; (d) i) MsCl, TEA, DMAP, CH₂Cl₂, 30 min, 80%; ii) KO'Bu, THF, 0 °C-rt, 3 h, 85%; (e) TFA: H₂O (3:2), rt, 3 h; (f) NaIO₄, MeOH-H₂O, 2 h, 82%.

To circumvent the elimination problem, hemiacetal 16 was treated with NaBH₄ in methanol to give triol 18 in 80% yield. Subsequent oxidative degradation of compound 18 with NaIO₄ gave aldehyde which was used as such to the next step without any purification. Deprotection of Cbz and simultaneously reductive amino cyclization under Pd/C and H₂ atmosphere in methanol gave 1-hydroxyindolizidine 5 in 73% yield (Scheme-4), whose NMR and physical properties were in perfect agreement with the reported values.
Scheme 4: Reagents and conditions (a) NaBH₄, MeOH, rt, 1 h, 80%; (b) NaIO₄, MeOH-H₂O, 2 h, then H₂, Pd/C, MeOH, 12 h, 73%.

In conclusion a highly stereoselective Grignard addition reaction on 3-deoxy sugarimine derived from D-glucose was utilized for the synthesis of 1-hydroxyindolizidine. This approach is also helpful for the preparation of other indolizidine and quinolizidine alkaloids and the work is under progress in our laboratory.

CHAPTER II

This chapter contains the total synthesis of polyhydroxylated pyrrolidines. Synthesis of natural and synthetic polyhydroxylated pyrrolidines is gaining more and more importance because of their highly active and efficient glycosidase inhibitory activity. Polyhydroxylated pyrrolidine alkaloids containing an aromatic substituent on the iminosugar ring at C-2 position are of a rare class found in nature (Figure 3). (−)-Codonopsine 19 and (−)-codonopsine 20 are the first two examples in this unusual category, initially isolated in 1969 from Codonopsis clematidea. These two compounds display antibiotic as well as hypotensive activities without affecting the central nervous system in animal tests. Recently, another new codonopsine related alkaloid (−)-codonopsinol 21 was isolated from the aerial parts of C. clematidea. The (−)-codonopsinol 21 is also known for its inhibitory activity against the α-glucosidase of yeast and Bacillus stearothermophilus lymph. Radicamine A 23 and radicamine B 24 are another examples for this category, isolated from Lobelia chinensis LOUR (campanulaceae) and exhibited glycosidase inhibitory activity.
Our continued interest in the development of new and efficient synthetic routes to some important chiral pyrrolidine compounds and azasugars, recently we have developed a stereoselective acid mediated amido cyclisation protocol for constructing the 2-aryl pyrrolidine skeleton, where presence of acetate group adjacent to the reaction site induces the stereoselectivity by its participation as neighbouring group and applied it for the synthesis of codonopsinine 20. Here in we present further application of this methodology to codonopsinol 21 and radicamine B 24 and the confirmation of amido cyclisation mechanism and importance of acetate as neighbouring group for stereoselectivity.

Section A: Total synthesis of radicamine B and 5-epi-radicamine B

It describes the total synthesis of radicamine B 24 and 5-epi-radicamine B 25 by using acid mediated cyclisation protocol. In 2001, Kusano et al. isolated radicamines A 23 and B 24 from Lobelia chinensis LOUR (Campanulaceae). The plant, Lobelia chinensis LOUR is distributed throughout China, Taiwan, Korea, and Japan. The whole plants have been used as a diuretic, an antidote, hemostat, and as carcinostatic agents for stomach cancer in Chinese folk medicine. Both the compounds 23 and 24 were found to exhibit inhibitory activity on α-glucosidase. Kusano et al. proposed the relative stereochemistry of radicamine A 23 and B 24 as 2S,3S,4S,5S. Later, Yu et al. and
Ramana et al. independently synthesized natural radicamines 23 and 24 at the same time and assigned the absolute configuration as 2R,3R,4R,5R (Figure 3).

For the last ten years, half a dozen methods were developed for the synthesis of radicamine B 24 from sugars and amino acids. Herein we present the application of our acid mediated amido cyclisation protocol to the synthesis of radicamine B 24 starting from simple and readily available starting material p-hydroxy benzaldehyde 29. Our retrosynthetic disconnections are outlined in scheme-5. The key transformations in the proposed strategy will involve Wittig olefination followed by Sharpless asymmetric dihydroxylation to install the chirality and an intramolecular acid catalysed amido cyclisation protocol to construct the pivotal pyrrolidine core of the target molecule.

\[ 
\text{Radicamine B 24} \quad \text{Cyclisation with NGP} \quad \text{BnO} \quad \text{Ac} \quad \text{Ac} \quad \text{Ac} \quad \text{26} \\
\text{Wittig olefination} \quad \text{Sharpless asymmetric dihydroxylation} \\
\text{Cyclisation without NGP} \\
\text{5-Ep-radicamine B 25} \\
\text{BnO} \quad \text{Ac} \\
\text{p-Hydroxy benzaldehyde 29} \\
\text{28} \\
\]

Scheme 5: Retrosynthetic pathway

Accordingly, reaction of the compound 29 with K₂CO₃ and BnBr in dry DMF at 60 °C for 12 h gave compound 30 in 91% yield. The aldehyde of compound 30 was submitted to the Wittig reaction with Ph₃PCHCO₂Et in toluene under reflux for 4 h to give exclusively trans olefin 31 in 88% yield. The treatment of compound 31 with ADmix-α at 0 °C for 24 h gave the desired diol derivative 32 in 91% yield. Compound 32 on treatment with 2,2-DMP in presence of catalytic amount of p-TSA in CH₂Cl₂ afforded the
compound 33 in 97% yield. Reduction of the ester functionality of 33 with LAH afforded alcohol 34 in 92% yield. The alcohol functionality of the compound 34 was oxidized to aldehyde under Swern conditions. The resultant aldehyde on Wittig reaction with \( \text{Ph}_3\text{PCHCO}_2\text{Et} \) in toluene reflux for 6 h gave corresponding trans olefin 35 in 83% yield, along with the cis olefin in 9:1 ratio. Further, the compound 35 was subjected to dihydroxylation with \( \text{OsO}_4 \), we got 7:3 ratio of 36 and 28. Based on the Kishi rules we assumed that the stereochemistry of the major isomer would be as shown in Scheme 6.

We again tried the dihydroxylation with ‘AD-mix-β’ which is a matched ligand based on the Kishi rules, it gave 36 and 28 in 19:1 ratio. In order to get the required isomer 28 in excess, we utilized ‘AD-mix-α’ for dihydroxylation. Initially we tried with 1 mol% which gave us 36 and 28 in 4:6 ratio. The poor de is because of unmatched nature of ‘Admix α’ with the substrate. To improve the ratio further in favour of 28, we utilized excess ligand (4 mol %) which gave us the separable products 36 and 28 in 1:5.5 ratio, as per our earlier observation.

**Scheme 6:** *Reagents and conditions* (a) BnBr, \( \text{K}_2\text{CO}_3 \), TBAI, dry DMF, 60 °C, 12 h, 91%; (b) \( \text{Ph}_3\text{PCHCO}_2\text{Et} \), toluene, reflux, 4 h, 88%; (C) AD-mix-α, \( \text{CH}_3\text{SO}_2\text{NH}_2 \), tBuOH:water, 24 h, 91%; (d) 2,2-DMP, \( \rho\text{-TSA} \), \( \text{CH}_2\text{Cl}_2 \), 12 h, 97%; (e) LiAlH\_4, THF, 0 °C-rt, 3 h, 92%; (f) i) (COCl)_2, DMSO, \( \text{CH}_2\text{Cl}_2 \), -78 °C; ii) \( \text{Ph}_3\text{PCHCO}_2\text{Et} \), toluene, reflux, 6 h, 83%; (g) (DHQ)_2PHAL, \( \text{OsO}_4 \), \( \text{K}_2\text{CO}_3 \), \( \text{K}_3\text{Fe(CN)}_6 \), \( \text{CH}_3\text{SO}_2\text{NH}_2 \), tBuOH:water, 92%. 

**IX**
The diol 28 on further treatment with thionyl chloride/Et3N in CH2Cl2 afforded the cyclic sulphite, which was immediately treated with sodium azide in dry DMF, to undergo stereoselective ring opening with azide to give the azido alcohol 37 in 84% yield. Reduction of the azido functionality with TPP/ethanol gave amine, which was immediately treated with CbzCl/Na2CO3 in ethanol to afford the fully protected compound 38 in 76% yield. The ester functionality of compound 38 was reduced under LiBH4 conditions to give diol 27 in 78% yield. Treatment of compound 27 with TFA:CH2Cl2 (1:1) for 4 h at room temperature gave directly diastereomeric cyclic pyrrolidine compounds 39 and 40 (1.3:1) in 78% yield (Scheme-7). The formation of cyclic compounds 39 and 40 from 27 can be explained through intramolecular SN1 reaction where the acetonide deprotection followed by intramolecular cyclisation is taking place simultaneously. It seems plausible to suggest that the N-nucleophilic attack on the sp2 carbon of the stabilised benzylic carbocation yielded diastereomeric cyclic pyrroilidine compounds 39 and 40 (1.3:1).

Scheme 7: Reagents and conditions (a) i) SOCl2, N(Et)3, CH2Cl2, 0 °C-rt, 30 min; ii) NaN3, DMF, 80 °C, 2 h, 84%; (b) i) TPP, ethanol, 0 °C-rt, 6 h; ii) CbzCl, Na2CO3, ethanol, 0 °C-rt, 8 h, 76%. (c) LiCl, NaBH4, ethanol, THF, 0 °C-rt, 3 h, 78%; (d) TFA:CH2Cl2 (1:1), 0 °C-rt, 4 h, 78%.

To get complete stereoselectivity in cyclisation we required tetraacetyl derivative as per our earlier observation. Keeping this in mind, we planned for tetraacetate
derivative 26 from the diol compound 27. When compound 27 was subjected to mild acidic condition (80% acetic acid in water) it gave corresponding tetrol derivative as a single product, which on acetylation with acetic anhydride in presence of Et₃N afforded tetraacetyl derivative 26 in 67%. Treatment of compound 26 with trifluoroacetic acid in CH₂Cl₂ (1:3) indeed afforded the cyclic triacetyl derivative 41 as an exclusive isomer in 90% yield. The stereoselective formation of pyrrolidine compound 41 from 26 can be explained through intramolecular Sₐ,N₁ reaction via resonance-stabilized benzylic carbocation. The benzylic carbocation can be further stabilized by the neighboring acetoxy group to give a trans dioxolane carbocation (acetoxonium ion) intermediate, thereby further facilitating the approach of the N-nucleophile preferentially from the opposite face and giving more stable 2,5-trans-substituted pyrrolidine.

Scheme 8: Reagents and conditions (a) i) 80% aq. AcOH, rt, 8 h, 94%; ii) Ac₂O, Et₃N, CH₂Cl₂, DMAP, 0 °C-rt, 4 h, 67%; (b) TFA:CH₂Cl₂ (1:3), 0 °C-rt, 4 h, 90%; (c) K₂CO₃, MeOH, 0 °C-rt, 1 h, 84%; (d) PdCl₂/H₂ MeOH, 12 h, 84%; (e) i) 6N HCl soln, ethanol, reflux, 3 h, 80%; ii) DOWEX 5WX8-200, 30% ammonia solution.

The triacetyl compound 41 on deacetylation with K₂CO₃ in methanol gave interestingly the bicyclic carbamate 42 in 84% yield instead of the corresponding N-Cbz triol compound. The O-benzyl group in compound 42 was deprotected by catalytic hydrogenation to give compound 43 in 84% yield. This on treatment with 6N HCl in ethanol at reflux gave the hydrochloride salt of radicamine B 24. The spectral and
analytical data of the hydrochloride salt of radicamine B 24 were in excellent agreement with the reported values. When the compound 24.HCl passed through DOWEX W8–200 exchange resin column with 30% NH₃ solution afforded 24 as the free base (Scheme-8), whose physical and spectroscopic data were also identical with reported values. The cyclized compound 39 on hydrogenation also gave radicamine 24 in 80% yield. In similar way, the minor isomer 40 was transferred to 5-epi-radicamine B 25 on hydrogenation in 80% yield (Scheme-9), whose spectral data were also in excellent agreement with the reported values.

Scheme 9: Reagents and conditions (a) PdCl₂/H₂, MeOH, 12 h, 80%.

In conclusion, the stereoselective synthesis of radicamine B 24 and its epimer 5-epi-radicamine B 25 were achieved from p-hydroxy benzaldehyde 29 with simple reaction sequences and intramolecular S_N1 cyclisation strategy as the key step. This further confirms our earlier proposed mechanism where the acetate is participating as neighboring group during amido cyclisation reaction.

Section B: Total synthesis of (−)-codonopsinol and (+)-2-epi-codonopsinol via acid catalyzed amido cyclisation

Recently, Ishida and co-workers reported another new codonopsine related alkaloid (−)-codonopsinol 21 from the aerial parts of C. clematidea. The aerial parts of C. clematidea are well known for their medicinal properties in treating liver diseases. The (−)-codonopsinol 21 is also known for its inhibitory activity against the α-glucosidase of yeast and bacillus stearothermophilus lymph.

In continuation of our efforts in the synthesis of polyhydroxylated pyrrolidine alkaloids and azasugars, here in we wish to report the total synthesis of (−)-codonopsinol
21 and 2-epi-codonopsinol 22 (Figure 3) and their inhibitory activity against glucosidases and galactosidases. So far only one synthesis for 21 is reported. Based on our earlier amido cyclisation protocol we envisaged the following retrosynthesis for (-)-codonopsinol 21 (Scheme-10). The pyrrolidine core skeleton can be obtained from protected amino alcohol 44 by means of acid catalyzed cyclisation. The compound 44 can be obtained from commercially available D-1,5-gluconolactone 45.

Scheme 10: Retrosynthetic pathway

D-Gluconolactone 45 on treatment with 2,2-DMP in presence of catalytic amount of PTSA in acetone, methanol gave α-hydroxy ester 46 in 76% yield. Reduction of the ester functionality of 46 with LAH afforded diol 47. Regioselective benzylation of diol 47 with dibutyl tin oxide in toluene followed by the addition of benzyl bromide in presence of catalytic TBAI gave compound 48 in 89% yield. Compound 48 on treatment with MsCl/Et₃N gave corresponding mesylate derivative, which up on treatment with NaN₃/DMF yielded corresponding azido derivative 49 in 80% yield. Reduction of the azido functionality with LiAlH₄/THF gave amine, which was immediately treated with CbzCl/Na₂CO₃ in CH₂Cl₂ affording the fully protected compound 50 (Scheme-11).
Scheme 11. Reagents and conditions (a) 2,2-DMP, PTSA, acetone, MeOH, 0 °C-r.t., 50 h, 76%; (b) LiAlH₄, THF, 0 °C-r.t., 4 h, 93%; (c) i) Bu₂SnO, toluene, reflux, 8 h; ii) BnBr, TBAI, reflux, 16 h, 89%; (d) i) MsCl, N(Et)₃, CH₂Cl₂, 0 °C-r.t., 3 h; ii) NaN₃, DMF, 80 °C, 24 h, 80%; (e) i) LiAlH₄, THF, 0 °C-r.t., 5 h; ii) CbzCl, Na₂CO₃, CH₂Cl₂, 0 °C-r.t., 8 h, 87%.

Selective deprotection of the terminal acetonide of 50 and in situ oxidative cleavage of the resulting diol with periodic acid in ether gave aldehyde 51. The aldehyde 51 was treated with the freshly prepared Grignard reagent 52 from 3,4-dimethoxybromobenzene and Mg in THF to give diastereomeric mixture 53 in 65% yield (~3:1 ratio based on ¹H NMR signals). The alcoholic mixture 53 was treated with TFA:CH₂Cl₂ (1:1) for 4 hours gave directly trans pyrroloidine compound 54 as a major isomer along with cis isomer 55 (2.5:1) in 80% isolated yield (Scheme-12). The formation of mixture of products (54/55) further confirmed our earlier proposed mechanism where acetate presence directs the nucleophile to under go cyclisation to give single isomer.

Scheme 12. Reagents and conditions (a) H₂IO₄, Ether, 0 °C-r.t., 6 h; (b) 3,4-dimethoxy phenyl magnesium bromide (52), THF, 0 °C-r.t., 16 h, 65%; (c) TFA, CH₂Cl₂, 0 °C-r.t., 4 h, 80%.

The mechanism of formation of cyclic compounds 54 and 55 from 53 can be explained as shown in scheme-13. Where the acetonide deprotection followed by intramolecular cyclisation is taking place simultaneously. The N-nucleophile attack on the SP² carbon of quinonoid form or benzyl carbocation might have yielded the trans isomer 54 and cis isomer 55 in 2.5:1 ratio.
Scheme 13: Mechanism for acid catalysed amido cyclisation

The major isomer 54 was treated with LAH in THF under reflux for 5 h, to give N-methyl derivative 56 in 82%. Compound 56 on catalytic hydrogenation with PdCl₂/H₂ in methanol gave (−)-codonopsinol 21 in 85% isolated yield. The spectral and analytical data of synthetic (−)-codonopsinol 21 were in excellent agreement with the reported values⁷b (Scheme-14). Our synthesis further confirmed the absolute stereochemistry of the molecule 21.

Scheme 14: Reagents and conditions (a) LiAlH₄, THF, 0 °C-60 °C, 5 h, 82%; (b) PdCl₂/H₂, MeOH, 12 h, 70%.

The minor isomer 55 was transferred to (+)-2-epi-codonopsinol 22 following similar reaction pathway used for the preparation of 21 in 65% yield for 2 steps (Scheme-15). The stereochemistry of compound 22 was confirmed with 1D nuclear Overhauser enhancement (NOE) correlations (Figure 4).
Abstract

Scheme 15: Reagents and conditions: (a) LiAlH₄, THF, 0 °C-60 °C, 5 h, 82%; (b) PdCl₂/H₂ MeOH, 12 h, 70%.

Glycosidase inhibitory study:

The glycosidase inhibitory activity against α-glucosidase (yeast), β-glucosidase (almonds), α-galactosidase (green coffee beans) and β-galactosidase (Kluyveromyces lactis) for compounds 21 & 22 were studied and the IC₅₀ values are summarized in Table 1. The residual hydrolytic activities of the glycosidases were measured spectrometrically of the corresponding chromogenic nitrophenyl glycosides as substrates in aqueous phosphate buffer at pH 6.8. All the enzymes and substrates were purchased from Sigma-Aldrich Co., U.S.A.

The compound 21 shown better inhibition against α & β-glucosidases than 22 and these two compounds didn’t show inhibition against α & β-galactosidases.

Table 1: Glycosidase inhibitory activity, IC₅₀ values in μM

<table>
<thead>
<tr>
<th>Compound</th>
<th>α-glucosidase</th>
<th>β-glucosidase</th>
<th>α-galactosidase</th>
<th>β-galactosidase</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>54</td>
<td>53.8</td>
<td>NI*</td>
<td>NI*</td>
</tr>
<tr>
<td>22</td>
<td>457</td>
<td>137</td>
<td>NI*</td>
<td>NI*</td>
</tr>
</tbody>
</table>

No inhibition at 1mm.

In summary, we developed a novel synthetic approach for the natural (−)-codonopsinol 21 and its epimer, (+)-2-epi-codonopsinol 22 from D-1,5-gluconolactone 45, using stereoselective intramolecular SN1 cyclisation protocol as the key step.

XVI
This chapter consists of the synthesis of some unnatural alkaloids: polyhydroxylated azepane derivatives and (-)-deoxcuscohygrine.

**Section A: A stereoselective approach for polyhydroxylated iminoheptitols**

This section describes the stereoselective synthesis of polyhydroxy azepanes from D-1,5-gluconolactone, using RCM protocol as the key step. In recent years, attention has been increasingly focused on the structure-activity relationship of iminosugars, particularly in seven-membered iminocyclitols, commonly known as azaseptanoses or polyhydroxy azepanes. Some of these polyhydroxy azepane derivatives show potent glycosidase and glycosyltransferase inhibitory activity. In addition, azepanes are DNA minor groove-binding ligands (MGBLs) due to the high water solubility and flexibility (compared to five- or six-membered ring), which allow the hydroxyl groups to adopt a variety of positions, thus increasing the probability of them forming hydrogen bonds with the purine and pyrimidine bases, hence that make them potentially useful as DNA MGBL's. A number of synthetic approaches for trihydroxy, tetrahydroxy and hydroxymethyl/acetamido azepane analogues are reported in the literature. In 2004, Sinaï et al. reported for the first time the preparation and biological evaluation of iminoheptitols 58, 59 and 60, a novel family of polyhydroxylated azepanes (Figure 5). These derivatives have shown potent and specific glycosidase inhibition; for example, compound 59 is a selective inhibitor of coffee bean α-galactosidase and compound 60 strongly inhibits bovine liver β-galactosidase.
To best of our knowledge, only one synthesis for 58, 59 and 60 (Figure 5) has been described so far. In continuation of our efforts in the synthesis of polyhydroxylated iminocyclitols, here in we wish to report the total synthesis of 58, 59 and 60. As part of ongoing program in our group to utilize ring closing metathesis reaction to construct functionalized carbocycles and azasugars from diene precursors, now we are extending RCM approach to the synthesis of above polyhydroxylated azepane derivatives starting from carbohydrate.

Based on the retrosynthesis, the key intermediate 61 for azepanes can be obtained from the diene 62 through RCM. The diene compound 62 can be achieved from compound 63, which in turn can be obtained from D-1,5-gluconolactone 45 (scheme-16). The above strategy can give the required key intermediate 61 with high optical purity.

\[
\begin{align*}
\text{Scheme 16: Retrosynthetic pathway.}
\end{align*}
\]

Accordingly, D-1,5-gluconolactone 45 was transferred to compound 63 using our earlier procedure. The compound 63 was subjected to allylation with allyl chloride/NaH in DMF for 2 h to give N-allyl derivative 64 in 85% yield. Selective deprotection of the terminal acetonide of 64 with 80% AcOH in rt for 16h afforded the diol compound 65 in 95% yield. Diol functionality of 65 was converted to olefin 62 using Garegg’s protocol (TPP, I₂, imidazole and toluene) in 86% yield. Initially, the diene 62 was subjected to
ring closing metathesis using Grubbs first generation catalyst in CH₂Cl₂ under reflux conditions for 18 h, which produced the key cyclic intermediate 61 in 88% yield. Then we tried with Grubbs second generation catalyst in CH₂Cl₂ under reflux conditions to give compound 61 in 91% yield in 4 h (Scheme-17). Deprotection of O-benzyl and N-Cbz groups under catalytic hydrogenation condition followed by acetonide deprotection with 6N HCl in ethanol gave the hydrochloride salt of azepane 58. Finally the compound 58.HCl passed through DOWEX W8–200 exchange resin column with 30% NH₃ solution afforded 58 as the free base in 71% yield. The spectral and analytical data of synthetic compound 58 were in excellent agreement with the reported values.

Scheme 17: Reagents and conditions: (a) Allyl chloride, NaH, DMF, DMAP, 0 °C-rt, 2 h, 85%; (b) 80% AcOH, 0 °C-rt, 16 h, 95%; (c) I₂, TPP, imidazole, toluene, 110 °C, 3 h, 86%; (d) G-I, CH₂Cl₂, 40 °C, 18 h, 88% (or) G-II, CH₂Cl₂, 40 °C, 4 h, 91%; (e) (i) PdCl₂/methanol, rt, 12 h. (ii) 6N HCl, rt, 6 h; (iii) DOWEX 5WX8-200, 30% ammonia solution, 71%.

To get the 1,6-dideoxy-1,6-iminoheptitols 59 and 60, treatment of cyclised compound 61 with OsO₄ for 8 h gave the desired diol derivatives 66 and 67 (4:1) in 85% yield. The O-benzyl and N-Cbz group in compound 66 was deprotected by catalytic hydrogenation followed by the acetonide group deprotection with 6N HCl in ethanol to give the hydrochloride salt of azepane 59. Finally the compound 59.HCl passed through DOWEX W8–200 exchange resin column with 30% NH₃ solution afforded 59 in 72%
yield as the free base, whose spectroscopic data were also identical with reported values (Scheme-18). In similar way, the minor isomer 67 was transferred to compound 60 in 66% yield, whose spectral data were also in excellent agreement with the reported values.

Scheme 18: Reagents and conditions: (a) OsO₄, acetone: H₂O (1:5), rt, 8 h, 85% (dr=3:1); (b) (i) PdCl₂-H₂/methanol, rt, 12 h; (ii) 6N HCl, rt, 6 h; (iii) DOWEX 5WX8-200, 30% ammonia solution.

In summary, we developed a synthetic approach for polyhydroxy azepanes 58, 59 and 60 from D-1,5-gluconolactone 45, using RCM protocol as the key step.

Section B: Chiron Approach to (-)-Deoxascuscohygrine

This chapter contains, the synthesis of (-)-deoxascuscohygrine 68 by using cross metathesis as the key step. The tropane alkaloids have been drawing considerable attention due to their significant biological properties such as hallucinogenic characteristics, and their utility as pharmacological probes. In 1981 Turner isolated (-)-dihydrocuscohygrine 68, a tropane alkaloid from the leaves of *Erythroxylon coca* and also it is distributed in some Erythroxylaceae families. Alkaloids having a tropane skeleton, for example, cocaine, atropine, and scopolamine, have some important activities and attracted considerable attention in medicinal chemistry.
Dyhidrocsuscohygrine 68 is a $C_2$-symmetrical diamine where propane side chain is attached to two pyrrolidine heterocyclic moieties. So far, one asymmetric approach has been developed to make the compound 68 and unnatural compound 69 (Figure 6). Due to the importance of these tropane molecule and our interest in the area of alkaloids synthesis, herein we report a short and efficient chiron approach for the (-)-deoxocsuscohygrine compound 69 utilizing the cross metathesis as the key step. The retrosynthetic analysis (Scheme-19) shows that the key intermediates 70 and 71 can be prepared from single starting material proline 72. The intermediate 71 in turn can be obtained from 70.

Scheme 19: Retrosynthetic analysis

Our synthetic strategy (Scheme-19) commences from the N-Boc proline ester 73. Reduction of ester functionality in 73 with LAH afforded alcohol 74, which was converted to olefin 70 by performing Swern oxidation followed by one carbon Wittig homologation. Hydroboration of compound 70 with BH$_3$.DMS at 0 °C gave amino alcohol 75 in 87% yield. Compound 75 was converted to olefin 71 in 70% yield by performing Swern oxidation followed by one carbon Wittig homologation (Scheme-20).
The key cross metathesis reaction between olefins 70 and 71 using Grubbs second generation catalyst (10 mol %) afforded the compound 76 as an inseparable E and Z mixture (69% yield based on the compound 70) along with the homodimers (Scheme-21). Initially reaction was performed with compound 70 (2 equivalents) and compound 71 (1 equivalent), which gave hetero dimer 76 (25% yield with respect to 71) along with the homodimer 77 (66% yield with respect to 71) and traces of dimer 78 was observed on TLC. The above result indicated that the reactivity of 70 is less due to steric and electronic effects of closely positioned N-Boc group. Therefore reaction preferentially has occurred on less hindered alkene group of 71, thus leading to dimer 77 and cross product 76. The formation of dimer 77 in better yields when compared to 76 also indicates that the rate of reversibility of 77 is low. Based on these results another reaction was carried out with compound 71 in excess. When compound 70 (1 equivalent) was treated with excess of 71 (1.6 equivalents) in presence of Grubbs second generation catalyst (10 mol %) indeed gave the compound 76 in 69% yield (with respect to compound 70) along with the dimer 77 (55% yield with respect to compound 71). In both the experiments, the unreacted material (compound 70) was recovered.
Scheme 21: Reagents and conditions (a) 10 mol% Grubbs II\textsuperscript{nd} generation catalyst, DCM, 40 °C, 12 h, 69%.

Hydrogenation of E & Z mixture of 76 with Pd-C/H\textsubscript{2} in methanol gave compound 79 in 90% yield. The compound 79 was treated with LAH in THF under reflux for 5 h to afford the (-)-deoxouscohygrine 69 in 77% yield (Scheme-22). The spectral and analytical data of (-)-deoxouscohygrine 69 were in excellent agreement with the reported values.

Scheme 22: Reagents and conditions (a) Pd-C/H\textsubscript{2}, MeOH, 2 h, 90%; (b) LiAlH\textsubscript{4}, THF, 0 °C-60 °C, 5 h, 77%.

In conclusion, we have demonstrated a short chiron approach for the synthesis of (-)-deoxouscohygrine 69 from single starting material L-proline 72 by using cross metathesis. Application of this strategy for some analogues is under progress.