Chapter-I

Section IA

Studies towards the total synthesis of some piperidine alkaloids

Section IA deals with review of previous work done on synthesis piperidine natural products. In this section a general introduction to versatile C-N-bond forming reactions, i.e. reductive amination, scaffold based construction, conjugate addition, catalytic methods, Ring-closing metathesis approach, cycloaddition reaction and nucleophilic displacement reaction is described. Emphasis has been given to those studies where these reactions have been utilized in the synthesis of piperidine alkaloids.

Review of Literature
Introduction

Nitrogen-containing natural products are abundant in nature and exhibit diverse and important biological properties. Substituted piperidines and their analogues are key structural units in numerous naturally occurring alkaloids and in a number of successful pharmaceutical compounds. Accordingly, novel strategies for the stereoselective syntheses of azacyclic systems found in the alkaloid kingdom continue to receive considerable attention in the field of synthetic organic chemistry. A number of methodologies for the elaboration of these structures have been described. In particular, Domino reactions, multi-component reactions, and the so-called “telescopying” of reactions allow for a rapid increase in molecular complexity in a single chemical operation. The term “cascade” and “tandem” have also been applied to all three of these reaction types and are thus used as general descriptors in this field. Because of the rate at which they increase molecular complexity, the use of domino reactions for the synthesis of nitrogen heterocycles has drawn much more attention in recent chemistry.

Piperidines possessing chiral center at C-2 and/or C-6, stereoselectivity that is essential for the defined activity, have attracted a great attention because they are one of the most common framework encountered in many interesting compounds that exhibit a broad range of biological activities. For example, pelletierine (1.1, Figure-1.1), sedamine (1.2), sedridine(1.3) and allosedridine (1.4) containing 2-hydroxyalkyl side chain constitutes a framework frequently found in the structure of drug candidates and are usually available in only trace amounts from the natural source sedum acre. Especially these are used in the treatment for disease like asthma, bronchitis and pneumonia. (+)-Dumetorine (1.5) was isolated in 1985 from the tubers of Discorea dumetorum Pax, a yam, the extracts of which have found extensive use in African folk medicine. A number of synthetic methodologies established for the syntheses of valuable 2-substituted piperidine alkaloids.

Since its introduction in 1930s, the red imported fire ant, Solenopsis invicta Buren, has spread throughout the southern United States affecting agriculture, wildlife, and human well-being. These fire ants can create rich source of alkaloid venoms, which have antibacterial, fungicidal, insecticidal and hemolytic properties (Blum et al., 1958; Javors et al., 1993). The venoms are stored in the poison sac and delivered through the
stinger (MacConnell et al., in 1970 and latter Blum et al., in 1992 exploited the characteristics of the venom chemistry of *Solenopsis* fire ants). The venom of *S. invicta* is composed mainly of 2-methyl-6-alkyl or -alkenylpiperidines known as solenopsins. Both *cis* and *trans* stereoisomers of the solenopsins are present in *S. Invicta* with although *trans* stereoisomers predominating. Therefore, these 2,6-disubstituted piperidine alkaloids (−)-solenopsins (1.6)8 and (−)-isosolenopsins (1.7) were explicitly investigated as possessing a broad range of biological activities.

![Figure-1.1](image)

**Figure-1.1.** selected 2- and 2,6-disubstituted piperidine natural products.

Alkaloid andrachcinidine (1.8)9 having *cis*-2,6-disubstitution pattern have been extracted from *Andrachne aspera* also possess a range of useful pharmacological activities.

Another privileged scaffold found in nature is the 3-hydroxypiperidine motif10, which is present in a variety of natural products. A subclass of, the 2,6-disubstituted piperidin-3-ol, is commonly encountered in nature and most of its members show interesting pharmacological activities. Representative examples are prosopinine (1.9, Figure-1.2)11, prosophylline (1.10)12 those have been isolated from the *Prosopis africana*13 displays antibiotic and anaesthetic activities. Other interesting alkaloids of this series are (−)-morusimic acid D (1.11), which was isolated14 from riped fruit of the Turkish white mulberry plant and (−)-Cassine (1.12)15 was extracted from the leaves and twigs of the *Cassia excel* in 1964. These alkaloids are medicinally important due to their well-established actions on anaesthetic, analgesic, and antibiotic activities. Such type of alkaloids containing a hydrophobic aliphatic tail and a hydrophilic head group and resemble to the cyclic structure of safingol and
sphingosine. While the polar head group is essential for glycosidase inhibition and aliphatic long chain facilitates lipid membrane penetration. These distinctive properties also enhance the therapeutic potential of these compounds for the treatment of diseases like diabetes, viral infection, and cancer.

![Chemical structures](image1)

**Figure-1.2.** selected 3-hydroxy-2,6-dialkylpiperidine natural products

4-hydroxy-2,6-dialkyl piperidine alkaloids such as dendrobate alkaloid (+)-241D (1.13) isolated\(^6\) from methanolic skin extracts of Panamanian poison frogs *Dendrobates speciosus* is active on nicotinic acetylcholine receptors. Cyclopamine (1.14)\(^7\) and veratramine (1.15, Figure-1.3) having the 2,3,5-substituted pattern are the most prominent member of the biologically and structurally highly diverse family of *Veratrum* steroid alkaloids. These natural products possess characteristic trisubstituted piperidine substructure that are linked by either a furan (jervine-type) or a carbon atom (veratramine-type) to the steroid skeleton. Especially cyclopamine as the first inhibitor of the Hedgehog signaling pathway (Hh), which is of vital importance for both correct embryonic development and adult tissue homeostasis, has received a lot of attention in this decade\(^8\).

![Chemical structures](image2)

**Figure-1.3**
Indolizidine alkaloids, isolated from the skin secretions of certain neotropical frogs, represent a class of pharmacologically important compounds. Even a structurally simple member of this class of natural products such as indolizidine 209D (1.16, Figure-1.4), 195B (1.17), and 167B (1.18) etc can act as non-competitive blocker of neuromuscular transmission. The simple bicyclic skeleton having one or two alkyl substituents at indolizidine ring has made them attractive synthetic objects, since these are available in limited amount from natural sources. 8-ethyl indolizidine poison-frog alkaloids, 219F (1.21) detected in the Madagascan mantellid frog, *Mantella betsileo*, and the relative stereochemistry of natural 219F was thus determined by its first asymmetric total synthesis (Daly and co-worker in 2005).

![Indolizidine alkaloids](image)

**Figure-1.4.** selected indolizidine natural products

Cyclizidine (1.23) (antibiotic M146791) appears to be most representative member of indolozidine framework, isolated from a *Streptomyces* species. And its closest congener, indolizomycin (1.22) was reported to obtain from the protoplast fusion of microorganisms both of them has been found to displayed important biological activities.

The uleine-type alkaloids (1.24-1.27, Figure-1.5) constitute another important subgroup of the *Strychnos* alkaloids which are characterized by the presence of the 1,5-methanooazocino[4,3-b]indole moiety bearing an ethyl group at the bridge carbon atom. Uleine (1.24) was first isolated from *Aspidosperma ulei Mg* by Schmutz and co-workers and its correct structure was proposed by Buchi and Warnhoft in the late
1950s. After the isolation of uleine, different pathways to their total syntheses were reported in a number of publications over a long span of time.

Figure-1.5. selected biologically active indole alkaloids

Lythraceae plants is a rich source of quinolizidine alkaloids, among them aryl quinolizidine alkaloids (−)-Lasubine I (Figure-1.6), (−)-lasubine II (1.29), and subcosine II (1.30) were isolated from the leaves of Lagerstroemia subcostata koehne by Fuji et al. in 1978. Vertine (1.28) was first isolated in 1962 by Ferris from Decodon verticillatus (L.) Ell and also classified as a member of the Lythraceae alkaloids.

Figure-1.6. examples of some naturally occurring quinolizidine alkaloids

They display a wide range of biological activities, including anti-inflammatory, sedative, and antispasmodic properties. It also plays a role in glucose level regulation in blood and lowers blood pressure. Another important quinolizidine alkaloid lupinine (1.33) and epiquinamide (1.31) which found naturally as a secondary metabolite in
members of the lupin family, has been shown to exhibit in vitro inhibitory activity against leukaemia. Several research groups continue to elaborate the attractive syntheses of the quinolizidine alkaloids\(^\text{30}\).

\((\pm)\)-Aspidospermidine (1.37, Figure-1.7) a most representative member of the indole alkaloids isolated\(^\text{31}\) from the bark of the \textit{Aspidosperma quebracho-blanco} tree by Biemann and co-workers in 1961, due to unique fused-ring system it has attracted great attention towards synthetic chemists and large number of synthetic pathways\(^\text{32}\) are found in the literature for the construction of this complex molecular framework.

\[
\begin{align*}
\text{Aspidospermidine 1.37} & & \begin{array}{c}
\text{Aspidospermidin-21-oic acid 1.38} \\
\text{Aspidoalbine 1.39}
\end{array}
\end{align*}
\]

Figure-1.7. selected polycyclic natural products containing piperidine framework

Alkaloids having structural and conformational resemblance to sugar derivatives are reported to being mimicking the monosaccharides are believed to be widespread in plants and microorganisms. These sugar mimics can inhibit several glycosidases\(^\text{33}\) enzymes because of this resemblance to the natural substrate. Glycosidases are involved in a wide range of important biological processes, such as intestinal digestion, post-translational processing of glycoproteins and the lysosomal catabolism of glycoconjugates. The realization that alkaloidal sugar mimics might have enormous therapeutic potential in many diseases like viral infection\(^\text{34}\), cancer\(^\text{35}\) and diabetes has led to increasing interest and demand for these compounds. Most of these effects were shown to result from the direct or indirect inhibition of glycosidases. The glyco-sphingolipid (GSL) storage diseases\(^\text{36}\) are relatively rare hereditary disorders that are severe in nature and frequently fatal. Possible strategies for the treatment of these lysosomal storage diseases include enzyme replacement therapy, gene therapy and substrate deprivation. Naturally occurring iminosugars are classified into polyhydroxylated piperidines, pyrrolidines, indolizidines, pyrrolizidines and nortropanes.

Among the different kinds of imino sugars, the alkaloids containing piperidine substructure are our prime interest and a large number of natural and synthetic
piperidine polyhydroxylated compounds were shown to exploit a useful biological array.

![Chemical structures](image.jpg)

**Figure-1.8.** selected polyhydroxylated iminosugars

In 1966 nojirimycin (NJ, 1.40) (Figure-1.8) was discovered\(^{37}\) as the first natural glucose mimic, as well as first described as an antibiotic produced by *Streptomyces roseochromogenes* R-468 and *S. lavendulae* SF-425, and was shown to be a potent inhibitor of α- and β-glucosidases from various sources. (+)-Lentiginosine (1.42), trans-1,2-Dihydroxyindolizidine originally extracted\(^{38}\) by Elbein and co-workers in 1990 from the leaves of *Astragalus lentiginosus*, is a potent and selective indolizidine inhibitor of the fungal α-glucosidase and amyloglucosidase (IC\(_{50}\) 5 mg/mL). Interestingly, the non-natural laevorotatory enantiomer (−)-lentiginosine was found to be able to induce remarkable levels of apoptosis in some tumour cell lines which was not observed for the natural isomer.

Swainsonine (1.43), isolated\(^{39}\) from the fungus *Rhizoctonia leguminicola* and in an Australian plant *Swainsona canescens*, was found to be an effective inhibitor of both lysosomal α-mannosidase and mannosidase II. It also has antimetastatic, antitumor-proliferative, anticancer (swainsonine is the first glycoprotein\(^{40}\) processing inhibitor to be selected for clinical testing as an anticancer drug) and immunoregulating activity.

Castanospermine (1.44), a tetrahydroxy indolizidine isolated\(^{41}\) from the trees *Castanospermum australe* and *Alexa leiopetale* and possesses a plethora of interesting biological activities such as the inhibition of HIV infectivity, angiogenesis, antitumor agent and thyroglobulin secretion. These wide ranges of biological effects in vivo and
in vitro are produced mainly due to the strong inhibition of some types of α and β-glycosidases. Surprisingly, modification of the stereocenters in castanospermine has also been proven to cause significant changes in these biological activities. Several synthetic efforts have been drawn towards the synthesis of natural aza-sugars or their diaistereomeric analogues since long span of time.

**Synthetic methodologies: A brief overview**

**A. Reductive amination:**

Nucleophilic nature of the nitrogen atom makes it suitable for the intramolecular reaction with carbonyl functionalities to give the five or six member cyclic imine intermediate which after in situ hydrogenation/reduction produces aza-cyclic derivatives. There are several examples in which the piperidine ring is formed by this nucleophilic approach and several natural products or their derivatives thereof have been synthesized.

A particular example of synthesis of (−)-deoxocassine 1.49 as demonstrated by Kumar et al. The readily available sorbate 1.45 (Scheme-1.1) under selective dihydroxylation using osmium tetroxide and (DHQD)$_2$- PHAL as a chiral ligand followed by hydrogenation of the α,β-unsaturation provided cis-diol 1.46 in good yield and enantioselectivity. The diol 1.46 was then converted into lactone 1.47 via six steps synthetic sequences. Coupling of lactone 1.47 with a sulfone fragment under

**Scheme-1.1**

basic condition, followed by treatment with sodium amalgam gave the cyclization precursor a δ-aminoketone 1.48 in moderate yield. Finally, hydrogenolysis of the
amine protection led directly the reductive amination to afford targeted alkaloid 1.49 in quantitative yield.

Wei et al. recently established\(^\text{45}\) a one-pot approach for highly diastereoselective synthesis of versatile chiral substituted piperidones by treatment of Grignard reagents to \(\alpha\)-alkoxyaldimines containing the \(\omega\)-ester group. The investigation of this Intramolecular reaction of \(\alpha\)-chiral aldimines with variety Grignard reagents are listed in table 1.1. The reaction proceeded through tandem sequence of addition–cyclization and the stereogenic center of C-6 was assumed to be controlled by \(\alpha\)-alkoxy substitution.

![Diagram of chemical reaction](image)

**Table-1.1.** list of Grignard reagents used for addition and their corresponding yields.

<table>
<thead>
<tr>
<th>R</th>
<th>Yield (%)</th>
<th>trans:cis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.51a Ph</td>
<td>77</td>
<td>98:2</td>
</tr>
<tr>
<td>1.51b 4-MeC(_6)H(_5)</td>
<td>93</td>
<td>99:1</td>
</tr>
<tr>
<td>1.51c 4-OMe C(_6)H(_5)</td>
<td>89</td>
<td>99:1</td>
</tr>
<tr>
<td>1.51d 4-F C(_6)H(_5)</td>
<td>93</td>
<td>99:1</td>
</tr>
<tr>
<td>1.51e 4-PhC(_6)H(_5)</td>
<td>82</td>
<td>99:1</td>
</tr>
<tr>
<td>1.51f 3-MeC(_6)H(_5)</td>
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<td>99:1</td>
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<td>1.51g 3-MeO C(_6)H(_5)</td>
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<td>99:1</td>
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<td>1.51h 3-CF(_3) C(_6)H(_5)</td>
<td>84</td>
<td>99:1</td>
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<tr>
<td>1.51i 3-F C(_6)H(_5)</td>
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<td>99:1</td>
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<tr>
<td>1.51j 2-Me C(_6)H(_5)</td>
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<td>99:1</td>
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<tr>
<td>1.51k 2-MeO C(_6)H(_5)</td>
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<td>99:1</td>
</tr>
<tr>
<td>1.51l (\beta)-naphthyl</td>
<td>92</td>
<td>99:1</td>
</tr>
<tr>
<td>1.51m (\alpha)-naphthyl</td>
<td>53</td>
<td>99:1</td>
</tr>
<tr>
<td>1.51n cyclopropyl</td>
<td>74</td>
<td>99:1</td>
</tr>
<tr>
<td>1.51o pentyl</td>
<td>65</td>
<td>99:1</td>
</tr>
<tr>
<td>1.51p isopropyl</td>
<td>48</td>
<td>99:1</td>
</tr>
<tr>
<td>1.51q tert-butyl</td>
<td>Nr</td>
<td>---</td>
</tr>
<tr>
<td>1.51r benzyl</td>
<td>51</td>
<td>99:1</td>
</tr>
<tr>
<td>1.51s allyl</td>
<td>complex</td>
<td>---</td>
</tr>
</tbody>
</table>
The approach provided an efficient synthesis of libraries of chiral trans-5-hydroxy-6-substituted-2-piperidinones as well as 3-hydroxy 2-substituted piperidines which are the key skeleton of various naturally occurring bioactive molecules. One of the chiral δ-lactam 1.51a was demonstrated for an efficient enantioselective synthesis of an important non-peptidic neurokinin NK₁ receptor antagonist (−)-CP-99,994. Thus, lactam 1.51a (Scheme-1.2) was reduced to piperidine which after protection of the amine functionality gave 1.52. Oxidation of 1.52 with Dess-Mertin periodinane followed by oxime formation with NH₂-OMe and subsequent reduction with borane complex provides the cis-2,3-disubstituted aminopiperidine 1.53 in good diastereoselectivity. The alklylation of the 3-amino group was achieved by dehydrative condensation-reduction protocol followed by acidic removal of Boc-protection led to desired target 1.54 in good yield.

Another interesting example of reductive amination method was applied by Szolcsanyi and co-workers for the synthesis of a number of piperidine alkaloids. They utilised regioselective Wacker Tsuji oxidation on alkenylazide to install the azidoketone derivatives for readiness of the subsequent reductive amination. Thus, commercially available (S)-epi-chlorohydrin (Scheme-1.3) was chosen as starting source which, after some synthetic sequences alkenyl azide 1.55 was obtained. The cupper free Wacker-Tsuji oxidation of this provided azidoketone 1.56, the hydrogenation of 1.56 afforded targeted alkaloids under definite conditions. Thus,
catalytic hydrogenation of this azidoketone gave selectively the (−)-dihydropinidine **1.57** in good yield.

![Diagram of reaction](image)

**Scheme-1.3**

Surprisingly, when azidoketone **1.56** was treated with Ph₃P under refluxing conditions it underwent intramolecular Staudinger-aza-Wittig condensation to furnish the cyclic imine **1.58**. This was subsequently subjected to the reaction screening of low-temperature C=N reduction in presence of LiAlH₄ and N-chelating Lewis acid (Me₃Al) in order to obtain the highest diastereoselectivity favouring the formation of the 2,6-<i>trans</i>-arrangement of substituents on the piperidine and epi-dihydropinidine **1.59** was afforded with good overall yield. Similar approach was also effective for the synthesis of alkaloid (−)-pinidinone (Scheme-1.4) starting from the diketoazide **1.60** in good overall yield and selectivity.

![Diagram of reaction](image)

**Scheme-1.4**

Taylor and co-worker recently developed⁴⁷ a novel, bio-inspired method for the synthesis of 2,6-disubstituted piperidines. They described a remarkable one-pot rearrangement for the conversion of readily available acyl cyclohexenones into 2,6-disubstituted 2,3,4,5-tetrahydropyridines and then into 2,6-syndisubstituted piperidines (Scheme-1.5) through the selective reduction.
Thus, treatment of diketones of the type \( \text{1.62} \) with ammonia resulted in a tandem amination–imination sequence to produce a cyclic imine derivative \( \text{1.63} \), which was given rise a single diastereomer on hydrogenation in an excellent manner. Diverse cis-disubstituted piperidines were prepared by this protocol with good to excellent yield and selectivity shown in table-1.2.

**Table 1.2.**

<table>
<thead>
<tr>
<th>Starting material</th>
<th>Intermediate</th>
<th>Piperidine derivative</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{162a} )</td>
<td>( \text{163a} )</td>
<td>( \text{164a} )</td>
</tr>
<tr>
<td>( \text{162b} )</td>
<td>( \text{163b} )</td>
<td>( \text{164b} )</td>
</tr>
<tr>
<td>( \text{162c} )</td>
<td>( \text{163c} )</td>
<td>( \text{164c} )</td>
</tr>
<tr>
<td>( \text{162d} )</td>
<td>( \text{163d} )</td>
<td>( \text{164d} )</td>
</tr>
<tr>
<td>( \text{162e} )</td>
<td>( \text{163e} )</td>
<td>( \text{164e} )</td>
</tr>
<tr>
<td>( \text{162f} )</td>
<td>( \text{163f} )</td>
<td>( \text{164f} )</td>
</tr>
</tbody>
</table>
This novel sequence of reaction was rapidly utilized for the syntheses of related natural products. For example, a naturally occurring alkaloid \textbf{1.67} isolated from ladybirds of the species \textit{Calvia guttata} was nicely synthesised using this method from readily available diketone \textbf{1.65} (Scheme-\textbf{1.6}), which, when treated with ammonia in methanol underwent addition/imine formation/methanolysis followed by catalytic hydrogenation of intermediate \textbf{1.66} gives directly to the natural product \textbf{1.67} in an yield of 68\% from starting cyclohexenone.

\begin{center}
\textbf{Scheme-\textbf{1.6}}
\end{center}

The synthetic protocol was also applied to report a first total synthesis of (\textendash\textendash)-grandisine G, an important bio-active natural product isolated from an extract of Australian rainforest tree \textit{Elaeocarpus grandis}. Thus, grandisine \textbf{D 1.68} (Scheme-\textbf{1.7}) a diketo derivative superior for this amination gives grandisine \textbf{B 1.69} as an intermediate followed by micro wave assisted methanolysis afforded the desired alkaloid \textbf{1.70}.

\begin{center}
\textbf{Scheme-\textbf{1.7}}
\end{center}

A recent report\textsuperscript{48} that provides the mild, expedient, and stereoselective method for the synthesis of a variety of azacyclic natural products was developed by Hanessian and co-workers. A stereo controlled one-pot cascade reaction between a ketone \textbf{1.71} (Scheme-\textbf{1.8}) derived from L-homoproline and cyclohexanone in presence of a Lewis acid directly provided tricyclic indolizidine skeleton \textbf{1.72}. 

\textbf{Scheme-\textbf{1.8}}
The reaction was assumed to take place via the formation of the iminium intermediate I (Scheme-1.9) which after tautomerisation produces an enamine II followed by cyclization to III and dehydration to the azadienium ion IV. Finally stereoselective reduction of this iminium intermediate using NaBH₄ yielded the intended prototypical tricycle.

Scheme- 1.9

Therefore judicial choice of the alkyl groups, carbonyl compounds, and the ring size in amine led to the syntheses of diverse indolizidine and quinolizidine alkaloids especially aryl substituted natural products like (+)-septicine 1.74, (+)-seco-antofine 1.75 and (+)-julandine 1.76 with least number of synthetic steps(Scheme-1.10).

Scheme-1.10
Huang and co-workers have developed an important method for the one-pot reductive alkylation of lactam to generate the alkylated piperidines. A variety of Grignard reagents and several reducing conditions were used for this reductive alkylation reaction, which displayed good to excellent 1,3- asymmetric induction in cyclic systems. The reductive alkylation of the lactams was achieved by successive treatment of lactam derivatives with Tf₂O/DTBMP at −78 to 0 °C, followed by Grignard reagents along with reducing agent. Thus, treatment of lactam 1.77 (Scheme-1.11) with the described protocol gave the piperidine derivative 1.78 in good yield. The stereochemistry of the C-2 position was controlled by the reducing agents used, and the best result was obtained using Pd(OH)₂/C/H₂ in favour of cis-2,6-diastereoselectivity (20:1).

Using this methodology they achieved an efficient five-step stereoselective synthesis of (−)-morusimic acid D (Scheme-1.12). The silyl ether 1.78 was treated with the Br₂/PPh₃ complex, which gave the bromide 1.79 in good yield. Reaction of 1.79 with the dianion generated in situ from benzyl 3-oxobutanoate produced 1.80. The Noyori catalytic asymmetric hydrogenation of the HCl salt of 1.80 produced β-hydroxy ester 1.81 as the single diastereomer in 73% yield. Subsequent catalytic hydrogenation afforded the desired (−)-morusimic acid D 1.82 in good yield.
B. Scaffold based synthesis:

Organometallic enantiomeric scaffolds \(^{50}\) offer strategic advantage for the systematic variation of structure in three dimensions about the periphery of \(N\)-based ring heterocycles. The synthesis of diverse piperidine alkaloids from a common precursor using “Molecular scaffolding” provides a means of challenging work in current organic synthesis. Functionalization of the organometallic scaffold periphery uses some elements of reaction control that are standard in synthetic purpose, but owing to the organometallic nature of the system, strategically bond formation and regio- and stereocontrol are also feasible. The scaffolds provide a single source of planar chirality that controls, in a predictable and systematic fashion, the regio- and stereocontrolled introduction of multiple substituents about nonplanar heterocycles over multiple steps. Not only this, comparing to traditional metal catalysis where one metal atom influences one step of many turnovers, in organometallic enantiomeric scaffolding the efficiency is achieved with one metal atom influencing multiple, different steps, each of one turnover, for the controlled introduction of variety of substituents along with number of stereocenters.

Liebeskind and co-workers disclosed \(^{51}\) a recent report on organometallic enantiomeric scaffolding and the methodology was successful for the construction of regio- and stereodivergent pieridine motif in a good overall yield. The readily available, single enantiomer of stable organometallic π-complexes of unsaturated heterocyclic ligands \(\text{e.g.} \ (\text{-})(\text{-})\text{-Tp(CO)}_2[\eta-2,3,4]-(1S,2S)-1\text{-benzyloxycarbonyl-5-oxo-5,6-dihydro-2H-pyridin-2-yl})\text{molybdenum (Tp = hydridotrispyrazolylborato) was used to function as enantiomeric scaffold. The potential of this strategy for the synthesis of substituted piperidines is specifically demonstrated by the stereodivergent construction of 2,3,6-}cis\text{ and 2,6-cis-3-trans piperidines from the high enantiopurity organometallic scaffold (--)\text{-Tp(CO)}_2[\eta-2,3,4]-(2S)-1\text{-benzyloxycarbonyl-5-oxo-5,6-dihydro-2H-pyridin-2-yl})\text{molybdenum in a substituent-independent fashion. Thus, oxopyridinylmolybdenum scaffold 1.84 (Scheme-1.13) underwent Grignard addition to its keto functionality to afford corresponding alcohol 1.85. Next, the complexes of} \)

the type 1.83 were subjected bromine-induced oxidative dimethoxylation to provide 2,6- dimethoxy-functionalized molybdenum complexes 1.86 in excellent yields. With this general route to 5-substituted η³-pyridinylmolybdenum complexes in hand, they achieved stereodefined procedure to introduced second and third alkyl groups into these complexes, thus a range of different alkyl groups were introduced leading to the trisubstituted complex of type 1.87. Finally the demetalation of these complexes provided an easy access of the substituted piperidines in a stereo-defined position.

Table-1.3

<table>
<thead>
<tr>
<th>compounds</th>
<th>PG</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>yield</th>
</tr>
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<tr>
<td>1.90</td>
<td>(S)-CO₂CH(n-Pr)Ph</td>
<td>Me</td>
<td>BnO(CH₂)₃-</td>
<td></td>
<td>81</td>
</tr>
<tr>
<td>1.91</td>
<td>CO₂Me</td>
<td>Me</td>
<td></td>
<td></td>
<td>90</td>
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<td>1.92</td>
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<td>1.94</td>
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<tr>
<td>1.95</td>
<td>CO₂Me</td>
<td>Et</td>
<td>Me</td>
<td>n-Bu</td>
<td>92</td>
</tr>
</tbody>
</table>

Demetalation using a CO/NO⁺ ligand exchange followed by nucleophilic attack of hydride on the resulting cationic intermediate resulted all cis- configuration at 2,3,6-
piperidines 1.88, while protodemetalation under acidic condition gave rise to the 
trans-configuration 1.89 at C-3 position.

These studies include synthesis of diverse piperidine derivatives (Table-1.3) having 
potential importance in the field of alkaloid syntheses and they reported the total 
syntheses of numerous alkaloids (−)-indolizidine 209I, indolizidine (−)-251N, (−)- 
quinolizidine 251AA and (−)-dehydroindolizidine 233E and epi-indolizidine 219F 1.99 (Scheme-1.14).

\[
\text{Scheme-1.14}
\]

Kobayashi et al. recently reported\(^{52}\) a stereocontrolled synthesis of the chiral 2,4-
disubstituted and 2,4,6-trisubstituted piperidines from a common intermediate, 
obtained by the unique one-pot protocol of the stereoselective asymmetric 
aza-electrocyclization.

\[
\text{Scheme-1.15}
\]

one-pot 6π-azaelectrocyclization of alkenyl vinyl stannane, ethyl (Z)-2-iodo-4-
oxobutenoate, and (−)-7-isopropyl-cis-aminoindanol 1.101 (Scheme-1.15) in presence 
of a Pd(0) catalyst stereoselectively produced the tetracyclic aminoacetals 1.103 or 
1.104, resulting from the four-bond formation accompanying by controlling the 
stereochemistry at the two asymmetric centres. cyclic aminoacetals were found to be 
good synthetic precursors for substituted piperidines. Thus, compound 1.103 provides 
cis-2,4-disubstituted piperidine 1.106 (Scheme-1.16) by stereoselective reduction with
Ni/H₂ followed by deprotection of the auxiliary. Whereas, reduction with Mg/MeOH led to the trans-analogue 1.108 through same sequence.

Scheme-1.16

Having established a stereoselective pathway to 2,4-disubstituted piperidines they next, achieved to introduce another alkyl group to the C-6 position in piperidine to access several diastereomeric 2,4,6-trisubstituted piperidine derivatives. Thus, the chemoselective reduction of the C-4 ester group in both 1.105 and 1.107 led to the alcohols 1.109 and 1.114 in good yield (Scheme-1.17), which after stereoselective alkylation with Grignard reagents provided compounds 1.110 and 1.111 with good selectivity.

Scheme-1.17
Oxidative cleavage of the indane moiety delivered corresponding piperidine derivatives 1.112 and 1.113. one of the aminoacetal 1.114 having an alkoxy side chain undergo simple synthetic operation to yield the natural product (+)-epi-dendoprimine 1.116 in a good manner to describe the efficacy of this methodology.

An interesting example of a configurational switch for Ir-catalyzed allylic cyclizations was demonstrated by Helmchen and co-workers. The methodology was applied for the preparation of 2,6-disubstituted or 2,4,6-trisubstituted piperidines with all possible diastereoisomeric products in high degree of selectivity. The Ir-catalysed cyclization of the chiral amine 1.117 (Scheme-1.18) using 4 mol% of the catalyst with L2 as ligand the all cis- piperidine derivative 1.118 was obtained in 90% yield with perfect diastereoselectivity. Whereas, use of enantimeric ligand ent-L2 provides selectively the trans configuration 1.119 at 2,4-position.

![Scheme-1.18](image)

The cyclization precursor 1.117 was accomplished with the diastereoselective allylation of an chiral aldehyde 1.120 with (+)-Ipc₂B(allyl) at low temperature, and the resulting homoallyl alcohol 1.121 under chain prolongation using cross-metathesis provides the allyl carbonate as E/Z mixture, which under acidic cleavage of the nitrogen protection gives the amine 1.117 in good yield. The methodology found application for the synthesis of alkaloids e.g. alkaloid 241D which bears the all cis stereochemistry at the 2,4,6-position of the piperidine ring. Thus the vinyl side chain...
in compound 1.118 was converted to a nonyl chain (Scheme-1.19) through a cross metathesis reaction after the protection of both amine and hydroxy functionalities. Catalytic hydrogenation in 1.123 followed by acetyl deprotection furnished the (+)-isomer of the alkaloid 241D.

Scheme-1.19

Hu et al. reported\textsuperscript{54} a general method for the preparation of enantiopure 2,6-disubstituted piperidines bearing alkene- or alkyne substituent by using non-racemic Betti base as a chiral auxiliary. The important step of this methodology involves deprotection of the N-benzylated auxiliary residue through non hydrogenative pathway, which accomplished the unsaturation at the substituents. They were successfully prepared a number of valuable 2,6-disubstituted piperidines, which are versatile building blocks for asymmetric syntheses of indolizidine or quinolizidine alkaloids.

Thus, the chiral auxiliary 1.126 (Scheme-1.20) was conveniently prepared from Betti base and tartaric acid as shown, which then treatment with Grignard reagents provided a series of alkenylated (1.127 a-c) or alkynylated (1.127 d-e) products with good yield and selectivity.

Scheme-1.20

They proposed that the alkylation of 1.126 may occurred through a S\textsubscript{N}2 reaction at 0 °C because the Bt-group was replaced with complete inversion of configuration and
the products obtained \textbf{1.127 a–e} were found to a single diastereoisomer as evident from the NMR spectral data. The method was quite general and showed high diastereoselectivity when \textbf{1.127 a–e} were treated separately with different Grignard reagents, followed by base catalysing removal of the \textit{N}-benzylated moiety, the corresponding 2,6-	extit{cis}-disubstituted piperidines were obtained again in good yield and stereoselectivity, as shown in case of propylmagnesium bromide treated in compound \textbf{1.127a} leads to compound \textbf{1.128} (Scheme-1.21).

```
\begin{center}
\begin{tikzpicture}
  \node[anchor=base] (1) at (0,0) {\textbf{1.127 a}};
  \node[anchor=base] (2) at (2,0) {\textbf{1.128}};
  \node[anchor=base] (3) at (1,1) {\textbf{1.129}};
  \node[anchor=base] (4) at (1,-1) {\textbf{1.130}};
  \node[anchor=base] (5) at (3,-1) {\textbf{1.131}};

  \draw (1) -- (2) node[midway,above] {1) C$_3$H$_7$MgBr,
  Et$_2$O, 0 \textdegree C, 1 h};
  \draw (2) -- (3) node[midway,above] {2) NaOH-MeOH-THF
  60 \textdegree C};
  \draw (3) -- (4) node[midway,above] {HG 2 Cat.};
  \draw (4) -- (5) node[midway,above] {H$_2$/Pd-C
  91\%};

\end{tikzpicture}
\end{center}
```

\textbf{Scheme-1.21}

A simple demonstration was undertaken, compound \textbf{1.128} after \textit{N}-protection underwent smooth cross metathesis with \textit{\alpha},\textit{\beta}-unsaturated ketone \textbf{1.129} (Type-I olefin) to delivered compound \textbf{1.130} (Scheme-1.22) which on one-pot reductive amination with saturation of the double bond led to the indolizidine alkaloid 223AB \textbf{1.131} in an excellent yield of 91%.

```
\begin{center}
\begin{tikzpicture}
  \node[anchor=base] (1) at (0,0) {\textbf{1.128}};
  \node[anchor=base] (2) at (2,0) {\textbf{1.129}};
  \node[anchor=base] (3) at (1,1) {\textbf{1.130}};
  \node[anchor=base] (4) at (3,-1) {\textbf{1.131}};

  \draw (1) -- (2) node[midway,above] {HG 2 Cat.};
  \draw (2) -- (3) node[midway,above] {\textbf{indolizidine 223AB 1.131}};
  \draw (3) -- (4) node[midway,above] {91\%};

\end{tikzpicture}
\end{center}
```

\textbf{Scheme-1.22}

Oxindole alkaloids are a diverse group of natural products characterized by the presence of a spiro ring system, a privileged heterocyclic motif associated with a variety of bioactivity profiles. Most of the oxindole alkaloids incorporate an unrearranged secologanin skeleton and are biogenetically formed by oxidative rearrangement of secoyohimbane- or heteroyohimbane-type indole alkaloids. Boscha et al. presented\textsuperscript{55} an enantioselective synthesis of \textit{ent}-rhynchophylline and \textit{ent}-isorhynchophylline using (S)-tryptophanol as the starting material, which incorporates
the tryptamine moiety of the natural products as well as acts as the source of chirality. The approach takes advantage of the methodology directed for the enantioselective spirocyclization of tryptophanol-derived oxazolopiperidone lactam 1.133, involving a Lewis acid-promoted cyclization of the corresponding N_{ind}-tosyl derivative 1.134 in the presence of Et_{3}SiH.

The bicyclic lactam 1.133 (Scheme-1.23), containing an acetate chain at the 4-position of the piperidone ring, prepared by cyclocondensation of (S)-tryptophanol with the prochiral aldehyde–diester 1.132, in a process that involves the enantioselective desymmetrization of two enantiotopic chains. Treatment of sulfonyl derivative with TiCl_{4} in the presence of Et_{3}SiH resulted in a regio- and stereocontrolled cyclization, with concomitant reduction of the initially formed spiroindoleninium intermediate, leading to the tetracyclic spiroindoline 1.134 as a single stereoisomer in an excellent yield.

Incorporation of some synthetic transformations (Scheme-1.24) on compound 1.134 led to the synthesis of rhynchophyllines viz. (i) removal of the hydroxymethyl group to 1.135, (ii) stereoselective introduction of the C-20 ethyl substituent to obtain 1.136, (iii) oxidation of the indoline moiety to the oxindole functionality, followed by chemoselective reduction of the lactam carbonyl 1.138 etc.
C. Conjugate addition:

With regards to the definition of an alkaloid, one crucial thought for the designing a synthetic pathway is the step which can incorporates the basic nitrogen atom into a carboxylic core. Conjugate addition is one of the most useful reactions for creating N-C bonds in a premeditated position and in a defined stereochemical topology and hence highly useful tools for the synthetic studies in alkaloid chemistry. In conjugate addition or addition of a nucleophilic nitrogen to an electrophilic olefin, the so-called “aza-Michael reaction”, is a valuable transformation that has been largely exploited for the construction of alkaloid-core structures. Indeed, the aza-Michael (AM) reaction in its intramolecular version constitutes the most straightforward manner to construct nitrogen containing heterocycles. On the other hand, both the AM reaction and the Mannich reaction are synthetically equivalent since both of them afford the same functionalized β-aminocarbonyl synthons and sometimes provided same skeletons.

Chandrakekhar et al. developed an efficient enantioselective route for the total synthesis of lasubine II using aza-Michael reaction as the key step. Their synthesis began with the preparation of chiral 1,3-amino alcohol \( \text{1.139} \) (Scheme-1.25) followed by its transformation of terminal olefin into a \( \alpha,\beta \)-unsaturated ester \( \text{1.140} \). The key
intramolecular AM reaction was then performed by releasing the primary amine under acidic condition to afford 2,6-cis-disubstituted piperidine 1.141 as the sole isomer.

\[
\text{(i) TBSOTf, DIPEA, 0}°\text{C, 1 h (ii) Dibal-H, toluene, -78}°\text{C, 2 h (iii) Ph}_3\text{P}=\text{CHCO}_2\text{Et, K}_2\text{CO}_3, \text{rt, 4 h) 1% HCl in i-PrOH, 60 °C 62% (four steps)}
\]

![Scheme-1.25](image)

The stereochemical outcome of the AM cyclisation could be rationalized on the basis of the stabilizing π-stacked geometry 1.140. Total synthesis of (-)-lasubine II was then achieved after side chain homologation, reduction and intramolecular S_N2 reaction.

Pirnot and co-worker described similar protocol for the synthesis of 2,4,6-trisubstituted piperidine derivatives through conjugate addition of the lithiated methyl pyridine to cyclic or acyclic enones. They were pleased to find out the optimized conditions to avoid the 1,2-addition product, surprisingly applying this methodology they were able to report a concise synthesis of quinolizidine alkaloids (+/-)-cermizine C and (+/-)-senepodine G. Thus, the addition product 1.144 (Scheme-1.26) was chosen and after simple protection of keto functionality, the ketal derivative 1.145 was vigorously hydrogenated to obtained a 1:1 separable diastereomeric mixture of 2-substituted piperidines 1.146 and 1.147.
Separate exposure of each diastereomer in acid gave the corresponding bicyclic alkaloids (+/-)-senepodine G 1.148 and (+/-)-epi-senepodine G 1.149. Borohydride reduction of these imine derivatives delivered the alkaloids (+/-)-cermizine C and (+/-)-epi-cermizine C respectively, as a single diastereomer.

Clive et al. described a good way to synthesize the piperidine derivatives containing the substitutions at the 2,6-position from the commercially available starting material serine. The methodology consisting of preparation of chiral aldehyde 1.154 (Scheme-1.27) following six synthetic steps from L-serine. The aldehyde 1.154 reacted efficiently with a range of lithium salts derived from terminal acetylenes to afford the expected propargylic alcohols, which were oxidized with MnO₂ to generate...
ketones of type 1.155. These ketones 1.155 a-c were readily undergo cyclisation in presence Cs$_2$CO$_3$ in methanol into the corresponding dihydropyridinones 1.156 a-c.

Scheme-1.27

Stereoselective reduction of the oxo group of these α,β-unsaturated ketones 1.156 a-c led to the corresponding allylic alcohols 1.157 a-c in good yields. The Claisen rearrangement led to corresponding piperidine derivatives 1.158 a-c, when heated with butyl vinyl ether in the presence of Hg(OAc)$_2$ and Et$_3$N. The rearrangement products are versatile intermediates for making a broad range of alkaloids containing a substituted piperidine subunit.

The methodology was quite useful for the synthesis of naturally occurring piperidine, azaspiroyclic, indolizidine alkaloids. One such demonstration was shown for compound 1.158a which under Wittig olefination produces 1.159 (Scheme-1.28) followed by deprotection, oxidation and vinyl addition led to olein 1.161. The diene
was subjected to RCM reaction in presence of Grubb’s 2nd generation catalyst to yield spirocyclic compound 1.162.

![Chemical structure and reaction scheme]

Scheme-1.28

Synthesis both cis- and trans- 2,6-disubstituted piperidines from common substrates through an aza-Michael reaction (Scheme-1.29) was developed by Ying’s group\(^6\). In that case, the conjugate addition was shown to promoted by the iminium ion activation. The Aza-Michael precursor 1.163 was prepared by coupling of an (Z)-allyl alcohol 1.167 (Scheme-1.30) with readily available Ts-protected chiral aziridine 1.166, followed by an allylic oxidation with MnO\(_2\). This conjugated enal 1.163 failed to undergo Michael addition to form the cyclic product because of poor nucleophilicity of the sulphonamide.

![Chemical structures and reaction scheme]
However, tandem oxidation-cyclisation was successfully achieved through an activation of aldehyde via iminium ion using pyrrolidine-TFA. Thus, 2,6-cis-disubstituted piperidine 1.164 was obtained as major form along with trans-isomer 1.165. While the use of chiral organocatalysts improve the stereoselectivity and cis-isomer over trans-isomer in presence of catalyst (R)-I or (R)-II. Surprisingly, when enantiomeric catalyst (S)-I was used for the aza-Michael addition of 1.163, the 2,6-trans-piperidine 1.165 was found as the major diastereomer, demonstrating that the synthesis of both 2,6-cis- and 2,6-trans-piperidines could be achieved from a common substrate through the organocatalytic aza-Michael reactions.

Scheme-1.30

After the establishment of this diastereodivergent route to the synthesis of 2,6-disubstituted piperidine, they explored their strategy towards the straightforward total synthesis of quinolizidine alkaloids epi-myrtine and myrtine (Scheme-1.31) from corresponding intermediates 1.171 and 1.172.
Ma and co-workers reported two-component method for the synthesis of enantiopure quinolizidinones and indolizidinones using β-amino ester and halo-alkynoate under very normal reaction condition. The reaction of iodide 1.171 (Scheme-1.32) and enantiopure β-amino ester 1.172 mediated by mild bases e.g. potassium carbonate or cesium carbonate in acetonitrile under heating condition provides quinolizidinone 1.173, together with piperidine derivative 1.174. Conversion of this piperidine 1.174 through hydrolysis to the corresponding carboxylic acid followed by treatment of acetic anhydride/triethylamine transformed into desired quinolizidone 1.173.

![Chemical structures and reaction scheme](image)

**Scheme-1.32**

Applying this methodology they synthesized an important quinolizidine alkaloid (−)-lasubine II. Hydrolysis of the intermediate 1.173 by aqueous KOH followed by decarboxylation leading to 1.175 which, after diastereoselective hydrogenation provided corresponding alcohol epi-lasubine II 1.176 in good yield, which after Mitsunobu inversion of 4-OH group afforded (−)-lasubine II.

Vertine and Lythrine are two of the most studied alkaloids in Lythraceae containing Z-configured α,β-unsaturated 12-membered lactone which possess a quinolizidine ring substituted at C2 with an axially oriented oxygen group and, with an equatorially oriented aromatic ring at C4. The two alkaloids differ in the configuration in such that the quinolizidinidine ring is either cis-fused, as in vertine or trans-fused as in lythrine.
Kundig et al. reported the synthesis of both these alkaloids starting from 2-piperidineethanol (rac-1.177) (Scheme-1.33) which on resolution using (S)-10-camphorsulfonic acid gave optically pure (R)-1.177 and using L-leucine to access the optically pure (S)-1.177. Simple functional group transformations on these led to the optical pure (R)- or (S)-pelletierines 1.179.

\[
\text{NH} \quad \text{OH} \\
\begin{array}{c}
\text{Boc} \\
\text{O} \\
\text{I} \\
\text{OMe}
\end{array}
\quad \text{OH} \\
\begin{array}{c}
\text{Boc} \\
\text{O} \\
\text{I} \\
\text{MeO}
\end{array}
\quad \text{HO}
\]

\[
\text{3} \\
\begin{array}{c}
\text{SO} \\
\text{O}
\end{array} \\
\begin{array}{c}
\text{Me} \\
\text{O}
\end{array} \\
\begin{array}{c}
\text{Me} \\
\text{O}
\end{array}
\]

Scheme-1.33

The condensation between pelletierine (R)-1.179 with 6-iodoveratraldehyde by refluxing with methanolic NaOH gives the \(\alpha,\beta\)-unsaturated ketone 1.180. The compound 1.180 after acidic deprotection of \(N\)-Boc undergo aza-Michael addition, to gives a mixture of cis- and trans-quinolizidinones (1.182 : 1.181 = 1:8) ratio in favour of trans-isomer 1.181.

Suzuki–Miyaura coupling between 1.181 and boronic acid derivative afforded biaryl 1.183 (Scheme-1.34) in good yield. This on stereoselective reduction of keto functionality followed by benzylic oxidation and acrylation gave the product 1.184. The styrene derivative was prepared using Nysted’s reagent in presence of TiCl\(_4\) but it was failed to lactonise by means of several procedures. And achieved by replacing MOM protecting group by TBS followed by Ring Closing Metathesis to provide the \(Z\)-configured \(\alpha,\beta\)-unsaturated lactone which after silicon deprotection afforded the (+)-vertine in moderate yield.
Scheme-1.34

(+)‐lythrine, the trans‐fused quinolizidine alkaloid was also prepared by the same group. They offered a very good technique for the epimerization of the cis‐quinolizidinone 1.181 to the trans‐quinolizidinone ent-1.182 via a retro‐Michael/Michael addition. Epimerization occurred nicely in the presence of NaOH in methanol at room temperature with good yield and enantioselectivity. Following the same synthetic sequence as described for (+)-vertine (Scheme-1.35) they reported first total synthesis of the alkaloid (+)-lythrine.
D. Catalytic methods:
Gold catalysis has emerged as an important tool in various fields of synthetic organic chemistry. Recently, Nicolas and co-worker reported an intramolecular cyclisation of β-amino ynone for the formation of an enatio pure pyridinone using catalytic amount of gold catalyst PPh$_3$AuCl. The synthetic strategy was useful for the synthesis of 2,6- and 2,4,6-trisubstituted piperidine derivatives. The ynone 1.183 and 1.185 nicely provided the corresponding cyclised products 1.184 and 1.186 (Scheme-1.36) in good yield. Acidic deprotection followed by stereoselective reductions the olefin and carbonyl functionality in 1.184 gives the (+)-isomer of the dendrable alkaloid 241D in an excellent yield. The intermediate 1.186 was similarly provided the (−)-isomer of the alkaloid 241 D in a single step conversion through stereoselective hydrogenation.

![Scheme-1.36](image)

The methodology was also applied for the synthesis of the cis-2,6-disubstituted piperidines. They described the four step total synthesis of the natural products isosolenopsin 1.193 and isosolenopsin A 1.194 as hydrochlorides. The chiral synthons 1.187 and 1.188 under controlled hydrogenation gives the oxo-compounds 1.189 & 1.190 as single isomer in cis-stereochemistry (Scheme-1.37). The piperidones 1.189 & 1.190 then deoxygenation through enol triflet 1.191 and 1.192 which, subsequent acidic deprotection led to the natural products with good overall yields.
An elegant approach based on hydrozirconation/acylation sequence which allowed to access a variety of protected amino ketones. Szymoniak and co-worker applied these amino ketones as starting materials for the cyclic imines which are readily converted to the piperidine derivatives. The methodology thus consists of the sequential activation of the C- and N-termini of homoallylic amines toward a trivalent electrophile.

Thus, homoallylic amines 1.195 and 1.199 were undergo hydrozirconation with different acylation to obtain their corresponding amino ketone derivatives 1.196 and 1.200 (Scheme-1.38) respectively. Both of them undergo reductive amination to form the piperidine derivatives 1.197 and 1.201 in good yield and selectivity. Compound 1.197 was applied to diastereoselective synthesis of the piperidine alkaloid (−)-coniine 1.198. Similarly cis-2,6-disubstituted piperidine 1.201 was shown to have a potential to deliver the alkaloid (−)-indolizidine 209D.
Chiou et al. recently described a novel methodology, alkyne-mediated domino Rh-catalyzed hydroformylation/double cyclization, for the construction of indolizidine derivatives. The bicyclization process is initiated by Rh-catalyzed hydroformylation of olefin followed by intramolecular cyclization to yields \( N \)-acyliminium. Subsequent intramolecular cyclization of this with the alkyne moiety as a \( \pi \)-carbon nucleophile leads to formation of bicyclic skeleton.

\[
\text{Rh}(\text{acac})_2 (0.5 \text{ mol}%), \text{BIPHEPHOS} (1.0 \text{ mol}%), \text{CO} (2 \text{ atm}), H_2 (2 \text{ atm}), \text{pTSA, AcOH, 60 }^\circ \text{C}
\]

**Scheme-1.39**

Their observation commenced that the hydroformylation on \( N \)-allylamide having a phenyl substituent \( 1.202a \) undergo cyclization to afford compound \( 1.203a \) (Scheme-1.40) in only 32% yield, whereas for electron releasing substituent at para- position of the benzene ring increases the yield of bicyclized product up to 83%. This was thought to be due to the increased nucleophilicity of the triple bond. Thus, the nature of the substituent next to the alkyne group exerted a critical effect on the second cyclization. Treatment of \( E \)-enol acetate \( 1.203b \) in a basic methanol solution provided ketone \( 1.204b \) as only single stereoisomer in good yield.

To demonstrate the ability of this novel methodology, they reported a facile total synthesis of an indolizidine alkaloid tashiromine. The bicyclic product \( 1.204b \) was treated with meta-chloroperbenzoic acid to gave ester \( 1.205 \) (Scheme-1.41), which, after one-pot reduction of the ester and lactam functionalities with LiAlH\(_4\) led to the natural product in 73% yield.
Another rhodium-catalysed one-pot hydroformylation protocol was applied\(^{66}\) by Bate’s group in the synthesis of pseudoconhydrine and its epimer. The homoallylic amine 1.206 was chosen for this hydroformylation (Scheme-1.42) and the reaction was carried using rhodium acetate (1 mol %) in THF under a mixture of CO and H\(_2\) (30 psi of each gas). With triphenyl phosphite as the ligand, the product of linear hydroformylation, ene-sulphonamide 1.207 was obtained in good yield.

**Scheme-1.42**

Stereoselective dihydroxylation of this ene-sulphonamide 1.207 subsequently gave to the \(\text{cis}\)-hydroxy piperidine 1.208 (Scheme-1.43). Facile rearrangement of the diol to the oxo-piperidine 1.209, followed by stereidivergent reduction of the keto functionality provided access to the pseudoconhydrine 1.211 and its epimer 1.210 in an excellent way.

**Scheme-1.43**
E. RCM approach:

An efficient approach is formation of the piperidine ring by a ring-closing metathesis (RCM) strategy. In this way, a tetrahydropyridine is obtained with the double bond in a specified position, providing obvious opportunities to functionalize the ring. A straightforward method was developed by Lebreton and co-workers involving diastereoselective allylation of a chiral imine and a RCM step. The efficacy of this methodology was demonstrated with a total synthesis of (–)-epi-deoxoprosopinine (1.212). Garner’s aldehyde 1.212 after HWE olefination afforded the corresponding E-product 1.213 (Scheme-1.44) as the sole isomer. Next, imine formation using dodecanal, followed by in situ alkylation with allylmagnesium bromide in a diastereoselective fashion (trans/cis = 87:13) provided compound 1.214. Both the nitrogen and the hydroxyl were protected by the corresponding oxazolidinone, and then elegant RCM reaction under Grubbs II condition provided bicyclic structure 1.215 in a yield of 90%. Epoxidation of the olefin followed by opening of the epoxide with LiEt₃BH gave 3-hydroxypiperidine derivative 1.216. Finally hydrolysis of the oxazolidinone 1.216, under harsh basic condition led to the desired product 1.217 in good yield.

An useful strategy for the synthesis of quinolizidine alkaloid (+)-lepadin F (118) was designed by Blechert and co-workers using tandem ene-yne-ene RCM (Scheme-45) starting material was chosen protected L-alanine 1.218 which upon condensation with cis-4-hexenal, followed by copper-catalyzed addition of benzyl propargyl ether led to a mixture of propargylamines 1.219 and its epimer (dr 1:2),
which could be separated after reduction with LiAlH$_4$. The minor isomer was converted into the desired allylic alcohol 1.220 by Swern oxidation and a Grignard reaction with vinylmagnesium bromide. Grubbs I turned out to be the best catalyst to carry out the tandem ene-yne-ene RCM reaction providing quinolizidine core 1.221 in an excellent yield. The latter was nicely converted by some side chain modifications into the natural product.

**Scheme-1.45**

Chattopadhyay and co-workers employed\textsuperscript{70} a very good example of RCM reaction for development a complementary route to the syntheses of both the enantiomers of pipenic acid derivatives from a single starting source. The methodology was involved a diastereodivergent synthesis of homoallylic amines 1.223 and 1.224 (Scheme-1.46) from a chiral imine 1.222 derived from protected

**Scheme-1.46**

N. Saha

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glyceraldehyde. Amines 1.223 and 1.224 were then separately subjected RCM reaction after a simple protection to amine functionality to obtained the unsaturated piperidine derivatives 1.225 and 1.227 respectively. Saturation of the double bond followed by oxidation of the side chain in each of them afforded enantiomeric pipecolic acid derivatives 1.226 and 1.228 in good yields.

The first asymmetric total synthesis of the enantiomer of the indolizidine alkaloid, cyclizidine, was accomplished by Hanessian and co-workers\textsuperscript{71} from readily available D-serine as the starting chiron. They utilised ring closing metathesis of the diene 1.229 (Scheme-1.47) for the construction of the piperidine derivative 1.230, which after protection-deprotection manipulation gave 1.231. The stereoselective epoxidation of the olefin followed by oxidation of primary alcohol led to chiral aldehyde 1.233. The aldehyde 1.233 was the key structure of the target synthesis and then it was treated with \( n \)-propynylmagnesium bromide to form the alcohol as a diastereomeric mixture this was further on oxidation-reduction protocol furnished the desired isomer 1.234 (Scheme-1.48) in good overall yield.

The indolizidine ring 1.236 was constructed by the intramolecular nucleophilic displacement of the prepared mesylate 1.235. A Pd-catalyzed hydrostannylation afforded the \( E \)-vinyl stannane which, upon treatment with iodine, led to the vinyl iodide 1.237 quantitatively. The vinyl cyclopropyl unit was coupled using Suzuki-Miyaura reaction with vinyl cyclopropyl boronate. Deprotection of the BOM ether provided the (+)-isomer of the cyclizidine 1.238.
F. Cycloaddition reaction:

The cycloaddition reaction is an important and fundamental reaction in organic chemistry. In this cascade contiguous stereocenters are formed in which relative stereochemistry of the substituents can be controlled by tuning the chirality of the substrate. These reactions have found general application in organic synthesis, especially in the synthesis of heterocyclic compounds. One recent example by Yang and co-workers have developed\textsuperscript{72} an Yb (III)-mediated aza-Diels–Alder reaction strategy between Danishefsky-type diene and a variety of chiral, cyclic aldimines with complete regioselectivity and high degree of diastereoselectivity. The stereoselectivity of the cycloaddition was reported to be control by the C\textsubscript{3} stereocenter of the heterodienophile. This methodology opens a convergent access to stereochemically riched indolizidine enaminones that are extremely useful synthons for transformation into diverse arrays of polyhydroxyindolizidine iminosugars. Thus, cycloaddition of imine 1.240 and diene 1.239 deliver the adduct 1.241 in good yield and selectivity (Scheme-1.49). The stereoselective hydrogenation of enone 1.241 produces alcohol 1.242 in an excellent manner. This trihydroxy indolizidine 1.242 was nicely transformed into the dihydroxylated aza-sugar lentiginosine after the elimination of this 4-OH group in 1.242 through Barton–McCombie radical deoxygenation method followed by acidic deprotection of the silyl ethers.
Micalizio et al. demonstrated\textsuperscript{73} a concise asymmetric synthesis of (\textendash)-205B utilising an important stereoselective intramolecular nitrone cycloaddition reaction. Therefore a Ti-mediated reductive cross-coupling reaction of an allylic alcohol \ref{1.244} (Scheme \ref{1.50}) with aldehyde \ref{1.243} to produced chiral amine \ref{1.245} in good manner. Then oxidation of this primary amine \ref{1.245} by treatment with (BzO)\textsubscript{2} and hydrazine gave the corresponding hydroxylamine derivative \ref{1.246} which under heating with butylglyoximate delivered the stereodefined oxazabicycle \ref{1.248} in an excellent manner. This annulation process was thought to be proceeded via the formation of E-alkenyl nitrone \ref{1.247} which under intramolecular cycloaddition deliver this complex heterocyclic structure.

\begin{align*}
\text{HO}_2-\text{Me} & \quad \text{TMS} & \quad \text{NH}_2
\end{align*}
\ref{1.243} \quad \ref{1.244} \quad \ref{1.245}

\begin{align*}
\text{OH} & \quad \text{TMS}
\end{align*}
\ref{1.242}

\begin{align*}
\text{HO}_2-\text{Bu} & \quad \text{TMS}
\end{align*}
\ref{1.246}

\begin{align*}
\text{HO}_2-\text{Me} & \quad \text{TMS}
\end{align*}
\ref{1.247}

\begin{align*}
\text{HO}_2-\text{Bu}
\end{align*}
\ref{1.248}

\begin{align*}
\text{HO}_2-\text{Bu}
\end{align*}
\ref{1.249}

\begin{align*}
\text{HO}_2-\text{Bu}
\end{align*}
\ref{1.250}

\textbf{Scheme-1.50}

The densely functionalised heterocycle \ref{1.248} after few synthetic steps led to compound \ref{1.250}, a designed compound for the synthesis of tricyclic core through
tandem aza-Sakurai cyclisation to provide the compound 1.252 (Scheme-1.51). Isomerisation of double bond in 1.252 accomplished the natural product (−)-205B.S

Scheme-1.51

Olmos and co-workers investigated a zeolite-catalyzed [4+2] cycloaddition as the basis of substituted piperidine synthesis. The developed approach utilizes a highly effective one-pot reaction cascade, through imine formation followed by an Imino-Diels–Alder reaction, promoted by scandium-loaded zeolites as heterogeneous catalyst. Such so-called imino-Diels–Alder reactions have been reported with various soft Lewis acid catalysts, such as zinc, zirconium, bismuth and lanthanide, and more recently niobium. Here the [4+2] cycloaddition between imines of the type 1.255 (Scheme-1.52) with various dienes has tested to access the functionalised piperidines 1.256 or piperidones 1.257 with good manner.

Scheme-1.52
One of these sequences of reaction was applied for the construction of important core present in naturally occurring indoloquinolizidine alkaloids such as reserpine, yohimbine hirsutine, and corynantheidol. Imine was obtained in situ by the dehydrocondensation between the tryptophan and benzaldehyde which after cycloaddition with Danishefsky diene afforded the cycloadducts 1.258 and 1.259 as diastereomeric mixture (dr = 1:3) (Scheme-1.53). The adducts are valuable intermediates because of having potential to deliver the indoloquinolizidine framework 1.260.

![Scheme-1.53](image)

An elegant method involving an intramolecular acylnitroso Diels–Alder reaction was discovered by Kibayashi and co-workers. The sequence started with an aldehyde 1.261, which some synthetic transformation leads to a hydroxamic acid 1.262 in very good fashion (Scheme-1.54). Upon periodate-mediated oxidation, the in situ generated acylnitroso derivative underwent intramolecular [4+2] cycloaddition to generate the trans-oxazinolactam 1.264 as the major isomer in a moderate diastereoselectivity of 6.6:1. This lactam 1.264 provided key structure for the diverse piperidine syntheses and served as an intermediate in a synthesis of alkaloids (−)-lepadins A, B and C 1.265.
Another organocatalytic synthesis of piperidines based on [4+2] cycloaddition of imines with α,β-unsaturated acyl chlorides developed\textsuperscript{76} by Ye \textit{et al.} This provided one of the most convenient approaches for the synthesis of N-containing six-member heterocycles. Cinchona alkaloid was used for this catalytic cycloaddition (Scheme-1.55). Thus, [4+2] cyclocondensation of α,β-unsaturated acyl chlorides 1.266 with imine 1.267 delivered dihydropyridinones of type 1.268.

\begin{align*}
\text{Ar} \text{COCl} + \text{Cl}_3\text{C} \text{NBoc} & \xrightarrow{\text{cat A or B (10 mol\%)} \text{ DIPEA, toluene, MS 4A}} \text{Ar} \text{N} = \text{CCl}_3 \\
\text{Ar} = 4-\text{Cl-C}_6\text{H}_4, 4-\text{Br-C}_6\text{H}_4, \text{-naphthyl, furyl, thieryl} & \\
\text{cat A} & \\
\text{cat B} &
\end{align*}

\textbf{Scheme-1.55}

It was observed that β-aryl-α,β-unsaturated acyl chlorides with electron-withdrawing groups or with electron-donating groups at para-position of the benzene ring, worked well to give the desired cycloadducts in good yields (66–95%) and high enantioselectivity (99% ee). The reaction of 2-naphthyl, 2-furyl, 2-thienyl-α,β-unsaturated acyl chlorides also gave the same results. Iminoester 1.270 also undergo cycloaddition with acylchloride 1.269 in presence of \textit{O}-trimethylsilyl quinidine (Cat.
A) as catalyst and proceeded better in mix-solvent ether–THF (3:1) (Scheme-1.56). The unsaturated lactam derivative obtained by this methodology was useful for synthesis of 2,4-disubstituted piperidine derivatives, one such demonstration was followed in which, the adduct 1.271 after hydrogenation and amide reduction produces piperidine 1.272 in good yield.

\[
\begin{align*}
\text{COCl} & \quad \text{NTs} \\
\text{EtO}_2\text{C} & \quad \text{cat A1 (10 mol%)} \\
\text{cat A1} & \quad \text{DIPEA, ether/THF, MS 4A, -40 °C} \\
\end{align*}
\]

\[
\begin{align*}
\text{1.269} & \quad + \\
\text{1.270} & \quad \rightarrow \\
\text{1.271} & \\
\end{align*}
\]

Scheme-1.56

Lycodine is a representative *Lycopodium* alkaloid that was isolated from *L. annotinum*. This class of alkaloids is structurally characterized by a bicyclo[3.3.1]nonane skeleton with a piperidine ring. Hirama and co-workers developed\(^7\) an efficient route towards the synthesis of this complex structure using regio- and stereoselective Diels–Alder reaction. The [4+2] cycloaddition reaction of dienophile 1.273 with known diene 1.274 proceeded smoothly under optimized condition to give the mixture of isomeric products. Which after chromatographic separation give the desired major isomer 1.275 (Scheme-1.57). After triflation of adduct 1.275, intramolecular Mizoroki–Heck reaction under optimized condition provided direct isomerised product 1.276 a bicyclo[3.3.1]nonane core. Stereoselective methylation at the C15 centre was the major challenge to complete the total synthesis. Thus, reduction of ketone 1.276 under conventional procedure led to compound 1.277 in good yield. Then alkaline hydrolysis of ester 1.277 results carboxylic acid, which was decarboxylated by Curtius rearrangement using DPPA followed by hydrolysis, gave ketone 1.278 in excellent yield. The stereoselective methylation was achieved by the formation of the silyl enol ether, which under reaction with iodomethane afford compound 1.279 in good manner. Thioacetalization of ketone 1.279 with ethanedithiol
and subsequent one-pot reduction and deprotection of the Cbz group completed the total synthesis of (−)-lycodine 1.280.

![Scheme-1.57]

G. **Nucleophilic displacement reactions:**

Another commonly used method to synthesize the piperidine motif proceeds via nucleophilic substitution of a good leaving group by the nitrogen atom. In this way, there is no need for reductive conditions and therefore there is a broader compatibility with functional groups.

A recent report on an efficient organocatalytic approach to the enantioslective synthesis of two important piperidine alkaloids, namely (+)-α-conhydrine and (−)-sedamine by Sudalai *et al*. They used L-proline-catalysed α-aminooxylation reaction as the key step for the installation of chirality present in desired alkaloids. The azido diol 1.282 was obtained from corresponding azido alcohol 1.281 through L-proline catalysed asymmetric α-aminooxylation as the key step followed by cleavage of the aminooxy moiety with CuSO₄ methanol (Scheme-1.58). The primary alcoholic group in diol 1.282 was then selectively protected as its silyl ether and the piperidine ring was constructed through intramolecular displacement of the OMs group by amine
functionality obtained by catalytic hydrogenation of the azido group in 1.283. Subsequent protection of nitrogen delivered the Boc-protected piperidine derivative 1.284 in good yield. Functional group manipulation of the hydroxymethyl side chain in 1.284 followed by a stereoselective Grignard addition completed the synthesis of (+)-conhydrine.

Scheme-1.58

The approach was also extended towards the synthesis of alkaloid sedamine having similar skeletal structure (Scheme-1.59). The azidodiol 1.282 was chosen for preparation of cyclisation precursor 1.285. This upon in situ mesylation-displacement led to the piperidine structure 1.286 with desired stereochemistry. Compound 1.286 under some synthetic transformations afforded (−)-isomer of sedamine in moderate yield.

Scheme-1.59

Schneider et al. recently documented the Bronsted acid catalyzed, enantioselective vinylogous Mukaiyama-Mannich reaction of acyclic silyl dienolates 1.289 with aldimine 1.288 to furnished δ-amino-α,β-unsaturated ester 1.290 (Scheme-1.60) in good yield and excellent enantio- and diastereoselectivity.
The ester-substituted aldimine was seen to a suitable partner for this reaction which should readily undergo a concomitant cyclization into the corresponding γ-lactam. This transformation would form the five-membered ring along with a bridgehead stereogenic center which is required for the assembly of the bicyclic framework. Thus, treatment of bifunctional aldehyde 1.288a, and vinylketene silyl-\(O,O\)-acetal 1.289a with catalytic amount of the TRIP phosphoric acid (TRIP-cat.) at -55 °C yielded the corresponding product which after subsequent reflux in acetic acid eventually afforded the lactam 1.291 in 80% yield over two steps (Scheme-1.61).

\[
\begin{align*}
1.288a & \quad + \quad 1.289a \\
& \xrightarrow{i. \text{7.5 mol\% TRIP cat.}} \xrightarrow{\text{-55 C, 16 h}} \xrightarrow{\text{ii. AcOH, reflux, 1 h}} \xrightarrow{85\% (96-99\% ee)} 1.291
\end{align*}
\]

\[
\begin{align*}
\text{i. LiEt}_3\text{BH, THF} \\
\text{ii. BF}_3\text{OEt}_2, 95\%
\end{align*}
\]

\[
\begin{align*}
1.288a & \quad + \quad 1.289a \\
& \xrightarrow{i. \text{Pd-C/H}_2} \xrightarrow{\text{ii. CAN}} \xrightarrow{\text{iii. Boc}_2\text{O, DMAP}} \xrightarrow{86\% (3 steps)} 1.292
\end{align*}
\]

\[
\begin{align*}
1.292 & \xrightarrow{i. \text{BuMgBr, THF}} \xrightarrow{\text{ii. B(ArF}_3)_3, \text{Ph}_3\text{SiH}} \xrightarrow{-78 \text{ C}, 82\%} 1.293, R = H \\
& \quad 1.294, R = \text{n-Bu}
\end{align*}
\]

\[
\begin{align*}
1.295, R = H, 99\% \\
1.296, R = \text{n-Bu, 89}\%
\end{align*}
\]
This vinylogous Mannich reaction when employed with γ-methyl-substituted dienolate 1.289b a second stereogenic centre was introduced and the lactam 1.297 was obtained with good yield and diastereoselectivity (Scheme-1.62).

These lactams 1.291 and 1.297 were subsequently transformed into the corresponding indolizidone derivatives through a tandem cyclisation protocol in good yield. They also adopted the Grignard addition reaction to N-acyliminium ion for the access of the diverse substituents into the indolizidine rings as in 1.294. Thus, intramolecular nucleophilic substitution of the aminoesters 1.293 and 1.294 delivered the indolizidine skeletons 1.295 and 1.296 in good way. The alkaloid (S)-coniceine, (+)-indolizidine 167B, (+)-monomorine, indolizidine 167A and indolizidine 195B were synthesized by this methodology.

Scheme-1.62

Haddad et al. presented a strategy to perform the cyclization by opening of an epoxide and applied this in the total synthesis of (2R,3R)-3-hydroxy-pipecolic acid. The starting material 1.299 was prepared from O-protected methyl mandelate. Next, the cyclization precursor 1.300 was obtained via a six step sequence including the key step, epoxidation under Sharpless condition (Scheme-1.63). The cyclization was then performed using PPh₃ in the presence of water, by intramolecular nucleophilic

Scheme-1.63
displacement at the benzylic position after Staudinger reduction of the azide function in 1.300. The desired 3-hydroxy 2-phenylpiperidine 1.301 was obtained in good yield, and the latter was converted to the pipecolic acid derivative.

Aspidosperma family belonging to a very important class of pentacyclic alkaloid imbedded in an indoline substructure more than 250 compounds falls in this category. Qiu et al. in 2013 reported an enantioselective total synthesis\textsuperscript{81} of aspidophytine achieved in 18 steps starting from a known intermediate. The synthesis involved an application of a pivotal indole synthesis through C-H bond activation with a Heck-type coupling of 1.302 (Scheme-1.64). The allyl side chain was then converted to a primary alcohol 1.304 using hydroboration oxidation and hydroxy functionality was transformed into the azido group 1.305 by substitution method. The azido group in 1.305 after reduction leading to the amine functionality which after Michael addition to a Michael type acceptor formed from the acidic dehydration of the indolyl alcohol leads the stereoselective synthesis piperidine skeleton 1.306. Deprotection of Ts- and Cbz protection the piperidine amine in 1.306 was reacted with bromoethanol to obtain the alcohol 1.307. The iodo mediated cyclization through alkylation at the C3 position of the indole occurred simultaneously under the reaction conditions to give the desired intermediate, which after elimination reaction provided a stable intermediate 1.308. Targeted natural product 1.309 was achieved following the known protocol on compound 1.308.
A recent application\textsuperscript{82} of one-pot amino allylation protocol was established by Gomez et al. to synthesised stereocontrolled preparation of 2-allylpiperidine. They treated 5-bromopentanal \textbf{1.312} and chiral sulfinamide \textbf{1.311} into allylindium bromide at 60 °C followed by KHMDS provide directly to the 2-allylpiperidine derivative \textbf{1.313} in good yield and diastereoselectivity (Scheme-\textbf{1.65}).
Indium aided synthesis allylpiperidine was utilised for the synthesis of tricyclic natural products tetraponerines T3 and T4. Thus, compound 1.313 was converted to a chiral aldehyde 1.315 (Scheme-1.66) via a redox manipulation of the double bond. The aldehyde 1.315 underwent similar aminoallylation reactions using different set of enantiomeric sulfinamides to gives a set of diastereomeric diamino derivatives 1.316 and 1.317 which are the intermediates for the total synthesis of the tricyclic natural products tetraponerines T3 and T4 respectively.

![Scheme-1.66](image)

One such demonstration was undertaken, and hence free diamine 1.318 was prepared by acidic removal of the chiral auxiliary followed by catalytic hydrogenation of the olefin moiety and then crude diamine was treated with 4- bromobutanal in the presence of K$_2$CO$_3$ to obtain tetraponerine T3 in good yield.

An elegant procedure was developed by Back and co-workers for the total synthesis of (−)-deoxoprosophylline (Scheme-1.67). For this, long chain unsaturated ester 1.320 was taken for asymmetric conjugate addition with the chiral amine, the addition product after LiAlH$_4$ reduction and hydrogenolysis provide the desired γ-amino alcohol 1.321 in a yield of 78% over three steps. The second conjugate addition of long chain chiral amine 1.321 to an alkynone proceeded smoothly in DMF, which after and subsequent displacement to the alcohol leads bromide 1.322. Refluxing of this bromide in acetonitrile underwent nucleophilic displacement to afford the corresponding cyclic enamine in moderate yield. Stereoselective hydrogenation followed by protection of the amine functionality gave piperidine 1.323. Epimerization of the 3-acetyl group by treating with DBU followed by successful
Baeyer–Villiger oxidation with in situ generated trifluoroperacetic acid leads the intermediate acetate with desire stereochemistry, which on acidic hydrolysis provided alkaloid (−)-deoxoprosophyline.

Scheme-1.67

The phenanthroindolizidine alkaloids were found to be important bio-active molecules for example, hypoestestatin 1 and hypoestatin 2 shown to possess good cytotoxic activity (ED\textsubscript{50} = 10^{-5} \mu g/mL against the murine P-388 cell line). Wang and co-workers reported\textsuperscript{84} an enantioselective concise approach to 13α-methylphenanthroindolizidine alkaloids, utilising an efficient stereoselective Seebach’s alkylation and Pictet–Spengler cyclization. Their synthesis started from chief and commercially available phenanthryl alcohol \textbf{1.323} which under treatment with PBr\textsubscript{3} gives phenanthryl bromide \textbf{1.324} in quantitative yield (Scheme-1.68). The LDA mediated alkylation of the \textbf{1.324} with a \((R)\)-proline derivative (Oxazolidinone was prepared by a modified Seebach’s procedure from \((R)\)-proline) provided alkylated product \textbf{1.325} as a single diastereomer. The key intermediate \textbf{1.325} was then hydrolysed to furnish an enantio pure pyrrolidine derivative \textbf{1.326} in excellent yield.
Scheme-1.68

Compound 1.326 was then converted to the phenanthroindolizidine ester 1.327 through Pictet–Spengler cyclization. The required angular methyl group was successfully installed via two sequential reduction protocols led to the alkaloid hypoestestatin 1 (1.328).

A collective asymmetric synthesis\(^8^5\) of phenanthroindolizidine and phenanthroquinolizidine alkaloids \((-\)\)-antofine, \((-\)\)-cryptopleurine, \((-\)\)-tylophorine, and \((-\)\)-tylocrebrine was reported by Wang \textit{et al.} The reaction sequence involved an efficient generation of chiral homoallylic amine intermediates by asymmetric allylation of the corresponding tert-butanesulfinyl imine. From these intermediates, the pyrrolidine and piperidine rings were constructed by means of an intramolecular S\(_{N2}\) reaction and a RCM reaction.

The readily available phenanthrylmethyl bromides 1.329 or 1.330, which was converted to corresponding aldehydes 1.333 and 1.334 via intermediate formation of corresponding nitriles (Scheme-1.69). The aldehydes undergo condensation with tert-butanesulfinamide in the presence of copper (II) sulfate to access enantiomerically pure tert-butanesulfinylimines, which on stereoselective allylation afforded the
homoallylic amine derivatives 1.337 and 1.338 after acidic removal of the tert-butanesulfinyl auxiliary.

![Chemical structures and reactions]

**Scheme-1.69**

These amines were then converted to the primary alcohols 1.339 and 1.340 (Scheme-1.70) through Cbz-protection followed by hydroboration–oxidation. The desired pyrrolidine cyclisation was achieved by mesylation of alcohols followed by NaH promoted intramolecular substitution at 0 °C to afford 1.343 and 1.344.

![Chemical structures and reactions]

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Finally one-pot removal of the Cbz protecting group and Pictet–Spengler annulation under standard conditions (formaldehyde, HCl, EtOH, reflux) generate the indolizidine natural products (−)-antofine 1.345 and (−)-tylophorine 1.346. The common intermediate 1.337 also utilised for the construction of quinolizidine skeleton present in alkaloid (−)-cryptopleurine. Thus homoallylic amine 1.337 was treated with acryloyl chloride to afford diene 1.347 (Scheme-1.71), which after ring closure the lactam 1.348 was obtained, the latter after hydrogenation followed by amide reduction gives the piperidine derivative 1.349. Finally, Pictet–Spengler annulation reaction on 1.349 provided quinolizidine natural product 1.350 in high yield.

Scheme-1.71

A recent report by Yu et al. covering a diastereodivergent Grignard addition to a cyclic nitrone during the first synthesis of (+)-steviamine, and its natural enantiomer. The synthesis started from the readily available D-ribose derived cyclic nitrone 1.351 which after Grignard addition with 1.352 at 0 °C furnished the hydroxylamine 1.353 in an excellent yield and high selectivity (dr > 95%) (Scheme-1.72). The trans-selectivity could explain on the basis of Felkin-Anh transition-state model. Reduction of the resulting hydroxylamine 1.353 by Zn-Cu(OAc)₂-AcOH system followed by protection of the corresponding amine with (Boc)₂O gave 1.354 in good yield. Compound 1.354 was then converted to the key intermediate, N-Boc ketone, for the
preparation of the indolizidine skeleton either by reductive amination or by intramolecular nucleophilic displacement.

![Chemical Structures](image)

**Scheme-1.72**

Using intramolecular nucleophilic substitution the product obtained as 1:1 diastereomeric mixture of indolizidine derivatives 1.355 and 1.356. Hydrogenolysis of the benzyl ethers gave (+)-steviamine 1.357 and 5-epi-(+)-steviamine 1.358 with good yield. These two new isomers of the natural product (+)-steviamine and its C-5 epimer were found weak inhibitors of R-rhamnosidase.

Hurvois and co-workers reported the total syntheses of myrtine and alkaloid 241D based on the N-Boc-directed metalation of enantiopure 4-piperidone (−)-1.364, which was prepared in four steps from α-amino nitriles 1.360 and 1.361 (Scheme-1.73) through a stereoselective alkylation–reduction decyanation process. These α-amino nitriles were obtained at the anode through electrochemical oxidation of 4-piperidone (+)-1.359.
With this efficient enantiopure synthesis of 7-methyl-4-piperidone 1.364 they developed a regio- and stereodefined introduction of the second alkyl group into the piperidine ring system. Thus, lithiation followed by the addition of a CuCN-LiCl at \(-80\) °C led to the formation of the intermediary piperidylcuprate which reacted to \(1\)-chloro-4-iodobutane to afforded 1.365 with good selectivity (Scheme-1.74). Compound 1.365 after removal of nitrogen protection undergoes intramolecular displacement reaction directly to yield (+)-isomer of alkaloid myrtine. Similarly when lithiated piperidine was condensed with an excess of dimethylformamide (DMF) the aldehyde was obtained as a 75:25 mixture in favour of trans isomer 1.366. surprisingly, when this trans isomer was stirred in Et\(_2\)O in presence of silica gel and Et\(_3\)N epimerisation provide a cis predominating mixture 1.367 (dr = 80:20). Incorporating some simple synthetic transformations on aldehyde 1.367 provided piperidine alkaloid 241D in good manner.
Quinolizidine alkaloid (−)-217A was isolated from the Madagascan frog Mantellabaroni in 1993 by Daly and co-workers, and it displays a wide range of biological activities. Harrity and co-workers reported a synthetic strategy towards the 2,3,6-trisubstituted piperidine motifs utilising the annelation of aziridine with appropriate reagents. Thus aziridine derivative 1.370 prepared from aspartic acid, undergo [3+3] annelation with Trost’s conjunctive reagent 1.371 and Buchi Grignard 1.373 to form selectively the piperidine derivatives 1.372 and 1.374 respectively (Scheme-1.75).
Scheme-1.75

For the stereoselective preparation of the natural product core they used the cyclopropanation reaction to input the methyl group at 3-substitution. Therefore cyclopropanation of the enamide 1.374 (Scheme-1.76) proceeded smoothly and provide the bicycle 1.375 in good yield and stereo selectivity. NIS promoted cleavage of the cylopropane ring led the aminal 1.376 which after reduction of the iodide followed by allylation with ketene acetal 1.377 provided the desired intermediate 1.378 in good yield and selectivity.

With the 2,3,6-trisubstituted piperidine in hand they turned out their attention towards the target molecule which incorporate two consecutive reductions followed by tosyl deprotection to led the aminol derivative 1.379. Iodine promoted cyclisation of this aminol to quinolizidine derivative followed by hydrolysis of the silyl ether provide the alcohol 1.380 that was elaborated to the natural product according to previously described methods to provide 1.381.
Chapter-I

Section IB

References related to Section IA

Reference section
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