CHAPTER-4

SECTION-I

Introduction of 2,5-disubstituted pyrrolidines
Introduction

4.1 2,5-Disubstituted pyrrolidines

Pyrrolidines, the 5-membered aza-heterocycles substituted at 2nd and 5th positions, are often encountered in the living organisms. The first pyrrolidine alkaloids were found in the solenopsis ant’s venom. These compounds have been extracted from plants, animals and microorganisms, but only in very micro quantities. Because of scarcity of these naturally occurring products, only few studies on their biological activity and mechanism of action have been performed.

2,5-Dialkylated pyrrolidines extracted from venomous ants and frogs\(^1\) have shown insecticide\(^2,3\) hemolytic and antiendinergic\(^4\) activities. Polyhydroxy pyrrolidines isolated from several plants of the companulaceae and fabaceae families have shown very potent activity as enzyme inhibitors (e.g. codonosine).\(^5\) Apart from the medicinal uses, these compounds possessing a C\(_2\) symmetry axis, may be used as very powerful catalyst in numerous asymmetric reactions.\(^6\) All these reasons make these compounds interesting targets for synthetic chemist.

This section briefly presents the stereoselective synthesis of 2,5-disubstituted pyrrolidines and will be subdivided in two main sections: (1) where the 5-memberd ring is formed by stereospecific methods and (2) where the already formed ring is functionalized at the 2nd and 5th positions.
4.1.1 Synthesis with formation of the pyrrolidine ring:

4.1.1.a Radical cyclization:

Several methods have been reported in the literature for the synthesis of 2,5-substituted pyrrolidines by means of intramolecular cyclization of \( \delta \)-alkenyl amines via

![Chemical structure](image)

Figure 1. Amido and amino mercuration

the aminyl radical as an intermediate. Photolysis,\(^7\) thermolysis, of \( N \)-chloroamines\(^8\) and anodic oxidation of lithium amides and hydroxylamines\(^9,10\) are the most encountered methods. Anodic oxidation of \( \gamma\delta \)-unsubstituted lithium amides furnish the exclusively \( cis \)-2,5-substituted pyrrolidines, where as \( N \)-chloroalkenylmine in the presence of tributyltin hydride and azoisobutyronitrile (\( n-Bu_3SnH-AIBN \)) giving rise almost to \( trans \) 2,5-substituted pyrrolidines.

![Chemical structure](image)

Figure 2. Radical cyclization of bis homoallylic amines
4.1.1.b Electrophilic cyclisation

This is subdivided into intramolecular cyclization and intermolecular cyclization.

![Figure 3. Iodocyclisation](image)

A. Intramolecular cyclization:

Iodocyclization\(^{11}\) and amino and amido mercuration\(^{12}\) are the two prominent methods employed in the synthesis of 2,5-substituted pyrrolidines. Iodocyclization of \(\delta\)-alkenylamines in presence of I\(_2\) and aqueous CH\(_3\)CN preferentially furnish the trans 2,5-substituted pyrrolidines.

![Structure](image)

Amino and amido mercuration of \(\delta\)-alkenylamines have been studied by Perie in 1972. Treatment of \(\delta\)-alkenylamines with Hg(OAc)\(_2\) leads to the formation of both cis-trans products, in case of amino mercuration, exclusively trans product was observed. The stereochemistry of the cyclization may be explained by the preferred chair transition state with the equatorial methyl group.
B. Intermolecular cyclization.

Intermolecular cyclization of chiral silanes:

![Chemical structures](image)

**Figure 4. Cyclization of chiral allylsilanes**

This method was discovered by Panek and Naresh in which chiral allylsilanes were treated with N-Acylimines, generated in situ at temp -100 °C to -78 °C formation of N-acyl pyrrolidines was observed, when the temperature raised to -78 °C to -20 °C N-acylhomooallylic amines were formed.

4.1.2 1,3-Dipolar cycloadditions:

The 1,3-dipolar cycloadditions are among the efficient methods for the synthesis of pyrrolidines and pyrrolines. These reactions are concerted and exhibit high stereo- and regioselectivity.

![Dipolar cycloaddition](image)

Compounds with 4π-electrons named as 1,3-dipolar, which is formed by 3 atoms a-b-c, of which a has a sextet of electrons in outer shell and c has octet with at least one unshared pair and it can be drawn as zwitterions, where the +ve charge localizes at
central atom, negative charge distributes at terminal atoms. Compound with 2π-electrons is known as alkene and named as dipolarophile. Azomethine ylides and nitrones are two allylic dipoles used for the synthesis of polysubstituted pyrrolidines.

4.1.2.a Azomethine ylides:

Imines of α-amino esters react with electron deficient alkenes in the presence of Lewis acids to give polysubstituted pyrrolidines. Reaction proceeds via the formation of metalldipole, which is formed by co-ordination of metal with nitrogen atom and carboxy of the imine, followed by deprotection. Use of a tertiary amine favors the formation of metalldipole.

![Figure 5. Formation of metalldipole](image)

Asymmetric 1,3-dipolar cycloadditions of azomethineylides were performed by using (i) chiral dipolarophiles (ii) chiral azomethine ylides and (iii) chiral catalyst.
4.1.2.b 1,3-Dipolar cycloadditions of nitrones:

Tufariello and Puglis\textsuperscript{19} noted in 1986 that cyclo adducts 16, obtained by addition of 1-oxy-1-pyrrolidine 15 on mono substituted alkene in the presence of a carboxylic peracid, allowed the regiospecific access to nitrone 17. A second cycloaddition will stereoselectively lead to trans 2,5-dialkyl pyrrolidines generally with good de.

![Figure 6](image)

4.1.2.c Cycloaddition of azapentadienyl anions:

In 1994\textsuperscript{20} Pearson and Jacobs reported the synthesis of 2-alkenyl pyrrolidines 24, by anionic cyclization of 2-azapentadienyl anion 23 with electron rich alkenes. This reaction is contrary to the cycloaddition of azomethine ylides in which electron deficient alkene takes part for the formation of pyrrolidine rings depending on the nature of the electrophiles and alkenes yields are ranging from 43-93%.
4.1.3.1 Reduction-cyclization of γ-aza-derivative ketones:

This section briefly describes the reductive amination of γ-azaderivative ketones in the presence of hydrogen and a metal such as Pt or Pd.

4.1.3.1a Hydrogenation of nitrones:

In 1990 Yoshikoshi et al.\textsuperscript{21} reported the synthesis of 2,5 dialkyl pyrrolidines from hydrogenation of acetylnitronates 27, prepared from nitroalkanes & enolates, low diastereoselectivity was observed in this procedure. Oppolzer\textsuperscript{22} used chiral cyclic nitrones for the synthesis of 2,5-dialkyl pyrrolidines.
4.1.3.1b Hydrogenation of nitroketones:

Hydrogenation of nitroketones is very often used method for the synthesis of aza-heterocycles Kloetzel\textsuperscript{23} in 1947 described first synthesis of polysubstituted pyrrolidine through this method. Stenens and Lee\textsuperscript{24} in 1982 synthesized compound 30 from $\gamma$-nitroketones.

4.1.3.1c Reductive amination of azidoketones:

Paulsen et al.\textsuperscript{25} first used this method for the synthesis of 2,3,4,5-tetrasubstituted pyrrolidine from chiral $\alpha$-azidoaldehydes and dihydroxyacetonephosphatase as shown in Figure 11.
Chiral α-azidoaldehydes 32 were first condensed with DHAP (dihydroxyacetone phosphate) 33, through an aldolase catalyzed reaction. Then the azidoketone 34, after removal of the phosphate group, is hydrogenated on palladium to give the expected azasugars 35.

4.1.3.2 Reductive amination of 1,4-diketones:

The reductive amination of 1,4-diketones is one of the oldest methods for the preparation of 2,5-disubstituted pyrrolidines Figure 12.

![Figure-12](image)

This method is not stereoselective, Jones and Blum\textsuperscript{26} optimized this method and showed that a treatment of 1,4-diketones 36 by an excess of ammonium carbonate allows the formation of the non isolated pyrrole intermediates 37 which are hydrogenated to give the trans isomers as the major compounds (d.e. = 85:15). Alkaloids 38a-c were synthesized through this methodology and the trans isomer was always the major one (Figure 13).

![Figure-13](image)

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4.1.4 Cyclization by $S_N2$ reactions

4.1.4.1 Intramolecular cyclization

Synthesis of functionalized pyrrolidines 40 were prepared by intermolecular $S_N2$ substitution from aminoalcohol derivatives such as 39 are described in literature. The cyclization is usually stereospecific and a very little epimerisation occurs during the process (Figure 14).

![Figure 14](image)

**Figure 14**

4.1.4.1a Aminoalcohol derivatives:

Wightman et.al\textsuperscript{27} achieved the synthesis of 43 via the non isolable aminoalcohol derivative, which was obtained through a diastereoselective addition of ammonia to $\alpha,\beta$-unsaturated esters 41 (Figure 15).

![Figure 15](image)
MacGavrey et al.\textsuperscript{28} reported that addition of ammonia was dependent both on the stereochemical relationship of the alkene and the bulkiness of the acetal.\textsuperscript{29} The major isomer formed was the \textit{trans} pyrrolidine.

4.1.4.1b Nucleophilic opening of aziridines:

Depezay et al.\textsuperscript{30} described the nucleophilic opening of bis-aziridines 44 by phenylthiolates ions or azides, followed by cyclization into pyrrolidines. A mixture of polysubstituted pyrrolidines 46b and piperidines 46a was thus obtained (Figure 16). Usually, pyrrolidines 46b are the major compounds so formed (along with 7 % of piperidines 46a) with chemical yields ranging from 51 to 84 %.

![Figure 16]

4.1.4.1c Aminoepoxides:

Intramolecular cyclization of \( \gamma \)-aminoepoxides is a very attractive method for the preparation of 2,5-disubstituted pyrrolidines. Langlois et. al.\textsuperscript{31} in 1986 used this strategy for the synthesis of neothramycines (Figure 17).

![Figure 17]
Biellmann et al. in 1992 synthesized the compound 52 and 53 as shown in figure 18. The dianion of propynylamine 49 (Figure 18) is obtained by treatment with LDA, and reacted with the bromide 50 leading to an unseparable mixture (30:70) of amino carbamate epoxides 51 with 60% chemical yield. The mixture of 51 is then either treated by silica gel at 65 °C (2 giving a mixture of products 53 (cis:trans 11:9), or by trifluoroacetic acid at 0 °C leading to pyrrolidines 52 with a 15:85/cis:trans ratio.

4.1.4.1d Intramolecular cyclization of ω-azidoalkyl boronic esters:

Carboni et al. showed in 1989 that ω-azidoalkyl boronic esters 55, after reduction, cyclized in situ to give the corresponding heterocycles 57 (Figure 19). From diastereoisomerically and enantiomerically pure boronic esters (prepared by asymmetric
hydroboration), the corresponding pyrrolidines 58 are obtained with a total control of the configurations and with excellent yields (80 to 89 %, depending on the nature of $R^1$, $R^2$ and $R^3$).

4.1.4.2 Intermolecular cyclizations:

4.1.4.2a Aminocyclization of 2,5-dibromo adipic acid esters:

In 1960, Gignarella et al.\textsuperscript{34} described the synthesis of pyrrolidine-2,5-dimethyl dicyclohexylcarboxylate starting from dibromo adipicacidester and benzylamine (Figure-20). In 1992, Yamamoto\textsuperscript{35} replaced benzylamine by (-)-(S)-phenylethylamine and obtained enantiomerically pure compounds.

![Figure 20]

4.1.4.2b Trans amination of 1,4-dihydroxy derivatives:

Nucleophilic attack followed by cyclization of 1,4-dihydroxy derivatives by primary amine to form trans 2,5-disubstituted pyrrolidines is a well known reaction directly derived from the studies on the aminocyclizations of 2,5-dibromo adipic acid esters (Figure 21).

![Figure 21]

$X = Ts, Ms, Tf$
Numerous amines were used: e.g. ammonia, benzylamine, hydrazine, hydroxylamine, allylamine. Several leaving groups were also employed such as tosylates, triflates and mesylates. Usually the stereoselectivity, and the stereospecificity are excellent. In the non racemic cases, the chirality may be introduced by: (i) the diols may be enantiomerically pure and because the cyclization occurs through a $S_N2$ type reaction, inversions of both stereogenic centres are observed; (ii) a chiral auxiliary such as the amine allows the stereoselective formation of enantiomerically pure pyrrolidines from a racemic mixture of 1,4-dihydroxy derivatives.\textsuperscript{36}

4.2 Synthesis from aza-heterocycles:

4.2.1 Synthesis from proline:

Shono\textsuperscript{37,38} prepared the $\alpha$-methoxylated methyl ester of proline with 87% yield but without diastereomeric excess.

\begin{center}
\textbf{Figure 22}
\end{center}

Thaning and Wistrand \textsuperscript{39} studied the influence of the hydroxyl group at (4-hydroxyproline). He observed the formation of a mixture of compounds in a 58:26:16

\begin{center}
\textbf{Figure 23}
\end{center}
C-4 ratio (cis:trans α,α'-disubstituted products) and found that the cis isomer can be epimerized into the trans product by treatment with BF$_3$.Et$_2$O as depicted on Figure 23. These 2-methoxy-5 carbethoxy-proline derivatives are the good substrates to perform nucleophilic substitutions at the pseudo-anomeric positions. Barrett and Pilipauskas$^{40}$ synthesized bacterial metabolite bulgecinine by employing above strategy, anodic oxidation followed by radical reaction as shown in Figure 24.

4.2.2 Synthesis from glutamic acid

Glutamic acid, possesses three advantages which make this natural (R-amino acid a very versatile starting material: (i) it is a very inexpensive compound, (ii) commercially available as its -(R) or -(S) form, (iii) which can be quantitatively and stereospecifically converted into pyroglutamic acid, a cyclic analogue with a pyrrolidinone ring possessing a stereogenic center. Syntheses using pyroglutamic acid as starting material can be divided into 4 sections: (i) reductions of the lactam followed by a nucleophilic substitution of the acyliminiums ions, (ii) syntheses through a β-enaminoester
intermediate, (iii) or from a thiolactam, (iv) and reactions through an acyclic intermediate obtained by nucleophilic substitution.

4.2.2.1a Partial reduction:

The pyroglutamic acid obtained by pyrolysis of the corresponding glutamic acid is partially reduced into the hemiaminal. Then, functionalization of the free hydroxyl followed by nucleophilic substitution allows the access to 2,5-disubstituted pyrrolidines (Figure 25). The partial reduction can be performed under several reaction conditions (DIBAL-H, NaBH₄, and LiEt₃BH) in high yields.

![Figure 25](image)

4.2.2.1b Complete reduction:

Related hemiaminals can be obtained in a two steps sequence by a first reduction leading to the γ-hydroxylamine which after an oxidation step gives the desired

![Figure 26](image)
hemiaminal. For instance, Holmes et al. 45 in 1991 used a Swern oxidation for the last step (Figure 26).

4.2.2.1c Nucleophilic substitution of N-acyliminium ions obtained from L-proline or glutamic acid:

Nucleophilic substitution of N-acyliminium ions obtained from L-proline or L-glutamic acid N-acyliminium ions obtained from the 2-OAc or -OMe pyrrolidinic precursors are very convenient intermediates for nucleophilic additions. The influences on the stereoselectivity of the reaction of several factors have been studied: e.g. Lewis acid used, nature of the nucleophile and the nature of the protection groups used.

4.2.2.2a Syntheses via the β-enaminoesters:

The β-enaminoesters 87 are obtained by reaction of the corresponding lactams 84 with dimethylsulfate followed by condensation with either the Meldrum acid 46,47,48 or with 2-acetylbutyrolactone47 (Figure 27). The β-enaminoesters 87 are decarboxylated (H3BO3/Δ or HCl, 3N) leading to the corresponding 2,5-disubstituted.
pyrrolines 88 with chemical yields from 37 to 90% depending on the nature of R1 and R2. Then, Lhommet 49 studied the reduction of the pyrrolines 88 with various reducing agents (AILiH₄-Me₃Al, A1LiH₄-Ni(acac)₂, DIBAL-H, NaBH₃CN, NaBH₄, H₂,Pd/C, HCl 10%, H₂-Pd/BaSO₄ 47) to obtain the pyrrolidines 89.

4.2.2.2b Syntheses via the thiolactams

In 1985, Shiosaki and Rapoport 50 achieved the diastereo- and enantioselective synthesis of trans and cis 5-butyl-2-heptylpyrrolidines from either D or L-glutamic acid via a thiolactam as intermediate. The importance of their strategy is that either trans product is obtained or cis product is obtained with ee 94% from the same intermediate via an Eschenmoser reaction (Figure 28).

![Syntheses via the thiolactams](image)

Figure 28

Brossi et al. 51 in 1987 synthesized some (+)-trans-2,5-dialkylpyrrolidines via a thiolactam which was obtained from the Lukes-Sorm dilactams 98 (Figure 29).
4.2.2.2c Synthesis via nucleophilic opening of the pyroglutamic ring:

Ezquerra in 1993\textsuperscript{52} synthesized the cis and trans-2,5-dicarboxylic acid pyrrolidines, through the acyclic compound 106 (Figure 30) which was obtained by the opening of N-Boc ethyl pyroglutamate with methyl p-tosyloxynyl lithium anion.
4.3. Syntheses from commercially available pyrrolidines and pyrrolines:

3.1.a Electrophilic substitutions: In 1976, Fraser and Passananti synthesized 2,5-dialkylated pyrrolidines 110 via alkylation of metallated nitrosamines (Figure 30). Compound 111 is alkylated twice at the α and α ' positions with an excellent regioselectivity and a good stereoselectivity hence the cis:trans ratios are in favor of the trans compounds (de 85:15 to 62:38), depending on the nature of both the lithium amide and the alkylating reagent. Mac Donald described the same type of reaction but starting with a pyrroline derivative and found that the regio- (>97% at α, α'-positions) and diastereoselectivity were excellent (trans >95%) (Figure 31). Meyers et al. in 1985, studied the electrophilic substitutions of derivatives of formamidine anions for the preparation of 2,5-dialkylated pyrrolidines [e.g. from enamidine 109, obtained par lithiation-selenation-elimination of N-tert-butylformamidine (TBF) heptylpyrrolidine] (Figure 31). Unfortunately, no selectivity was observed and a 50:50 mixture of cis and trans isomers was obtained.
4.3.1.b Nucleophilic substitution:

Moore et.al\textsuperscript{56} described the synthesis of acid 83 (Figure 32) starting from nitrone 113, which on treatment with KCN afforded N-hydroxynitriles in high yields.

\[
\begin{array}{c}
\text{Nitrone} \\
113 \\
\text{KCN} \quad \text{HCl} \\
\text{Nitrile} \\
114 \\
\text{HCl} \quad \text{H}_2\text{Pd} \\
\text{Carboxylic Acid} \\
115
\end{array}
\]

\textbf{Figure 32}

Magnus\textsuperscript{57} in 1994 described the synthesis of 2,5-diazides pyrrolidines 86 by treatment of N-acylated pyrrolidines 116 with the mixture of PhIO/TMSN\textsubscript{3} at -25°C (Figure 33). Magnus found that pyrrolidines are more reactive than piperidines, and that \(\alpha\)-azidonation increases with the electron donating power of \(X\). The \(\alpha\) and \(\alpha'\) disubstitution is favored with the \(N\)-Boc and \(N\)-C\(_6\)H\(_2\)(-3,4,5-OMe) derivatives leading to the major trans compounds.

\[
\begin{array}{c}
\text{Pyrrolidine} \\
116 \\
\text{PhIO/TMSN\textsubscript{3}} \quad \text{PhIO/TMSN\textsubscript{3}} \\
\text{Pyrazole} \\
117 \\
\text{N\textsubscript{3}} \\
118 \quad X = \text{NPh\textsubscript{3}, OPh} \\
\text{C\(_6\)H\(_2\)(3,4,5-OMe)} \\
\text{C\(_6\)H\(_4\)OMe-p,Ph} \\
\text{C\(_6\)H\(_2\)NO\textsubscript{2}-p,OCH\(_2\)Ph} \\
\text{OtBu,Me}
\end{array}
\]

\textbf{Figure 33}

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4.3.2 Synthesis from pyrrole derivatives:

Casiraghi and Rassu\textsuperscript{58} developed the use of N-Boc-2-ert-butyldimethylsilyloxy-pyrrole 120 for the synthesis of natural products. He has shown that N-Boc-2-tertbutyldimethylsilyloxypyrrole (TBSOP) 87 adds regio- and stereoselectively on several synthons 121 (Figure 34) leading to $\alpha,\beta$-unsaturated-$\gamma$-lactams 122, which can be further reduced and substituted as L-proline or glutamic derivatives 123. This strategy has been used for the synthesis of azasugars e.g. N-Boc-4'-azauridine.\textsuperscript{59}

\[ \text{N} \quad \text{Boc} \quad \text{O} \quad \text{SiR}_3 \quad + \quad \text{H} \quad \text{R}^* \quad \text{H} \quad \text{X}_2 \quad \rightarrow \quad \text{O} \quad \text{Boc} \quad \text{XH} \quad \text{R}^* \]

\[ \text{R}^* = \text{Chiral center} \]
\[ \text{X} = \text{O, N, S}, \]

\[ \text{Polysubstituted pyrrolidines} \]

**Figure 34**

4.3.3 Syntheses from bicyclic amino derivatives:

Shibuya et.al\textsuperscript{60} in 1994 proposed the synthesis of 2,5-disubstituted pyrrolidines via stereospecific radical cyclization of $\Delta^{4,5}$ oxazolidin-one 92 (Figure 35). The same year, Shibuya synthesized (+) bulgecinine using the identical strategy.
Momose synthesized Bulgecinine through the intermediate 128 (Figure 36) obtained by palladium catalyzed N→π cyclization of γ-unsaturated oxazolidin-2-one 127.

In 1987, Fleet and Smith\textsuperscript{61} reported the synthesis of 2,5-dideoxy-2,5-imino-D-mannitol 133 (Figure 37) via the bicyclic [2.2.1] amine intermediate 132 obtained by hydrogenation of azide 131.
4.3.4 Resolution of racemic mixtures of pyrrolidines:

Resolution of racemic mixtures of pyrrolidines is still a very efficient method for the preparation of enantiomerically pure compounds. In 1985, Ohno et al. used the enzymatic desymmetrization of meso pyrrolidines for the preparation of carbapenem antibiotics (Figure 38).

Achiwa reported that the Pig Liver Esterase (PLE) gave different e.e. and chemical yields depending on the substituent on the nitrogen atom (for \( N \)-benzylpyrrolidines yield 54%, e.e. 23% for \( SS \)-isomer and for NH compounds, yield 71%, e.e. 10% for the \( RR \) isomer). Boutelje studied the influence of the co-solvent on the enantiomeric purity of the \( cis \) \( N \)-benzyl monoester obtained in this reaction without dimethylsulfoxide ee. is 17%, whereas in the presence of 25% of DMSO the ee. is 100%. Sibi in 1994 converted the racemic \( trans \) 2,5-dihydroxymethyl-\( N \)-benzylpyrrolidine into the corresponding enantiomerically pure mono or diacetate compound by treatment with the PS enzyme (Figure 39).
4.4 Conclusion

2,5-Disubstituted pyrrolidines have attracted many synthetic chemists, because of the challenge in synthesizing in an enantiospecific way such products, and because of the biological potential of these bioactive compounds. Furthermore, 2,5-disubstituted pyrrolidines possessing a C2 symmetry axis are very interesting chiral auxiliaries for numerous asymmetric reactions\(^6\). The discovery in the next future of new natural 2,5-disubstituted pyrrolidines is probably to come, and efficient syntheses of these products will be still needed for their access in large quantities for biological studies.
Figure 40 Various pathways for the synthesis of substituted pyrrolidines
4.5 Reference

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SECTION II

Studies towards the synthesis of (2S, 5S)-Pyrrolidine-2,5-dicarboxylic acid and (2S, 4S, 5R)- Bulgecinine
4.6 (2S,5S)-Pyrrolidine-2,5-dicarboxylic acid:

The (2S,5S)-pyrrolidine-2,5-dicarboxylic acid (1) has been isolated\(^1\) as marine natural product from the red alga *Schizmenia dubyi* and it has been used as a potential chiral building block in \(\beta\)-lactams synthesis,\(^2\) also as an elegant chiral auxiliary in asymmetric synthesis\(^3\) and synthesis of peptides and proteins with unusual conformational properties of therapeutic utility.\(^4\)

4.6.1 Earlier Synthesis of (2S,5S)-pyrrolidine-2,5-dicarboxylic acid:

Till date eight synthesis of 1 starting from enantiomerically pure (S)-pyroglutamate derivatives,\(^5\)\(^-\)\(^7\) (S)-O-benzyl-glycidol,\(^8\) pyrrolidine derivatives\(^9\)\(^,\)\(^10\) and *meso* dimethyl 2,5-dibromoadipate\(^11\) using variety of elegant synthetic strategies are known in the literature.

![Chemical structure diagram](image)

**Figure 1** Earlier synthesis of (2S,5S)-pyrrolidine-2,5-dicarboxylic acid
First synthesis was reported by Shigeo nozoe et al in 1987. The synthesis involves chain elongation reaction of N-carbamoyl pyroglutamates at C₅ and a pyrrolidine ring formation.

Yukio Yamamoto achieved the synthesis by employing (-)-1-phenylethylamine as a chiral auxiliary, three diastereomeric isomers of 2,5-bis(methoxycarbonyl)pyrrolidine derivatives are prepared from dimethyl rac-2,5-dibromoadipate and separated by crystallization and chromatographic fraction involving stereoselective hydrolysis.

B. Ganem et al reported the synthesis in 2002, by using Cp₂ZrHCl (Schwartz’s reagent) for the reduction of pyrrolidone to Pyrrole, which was isolated and cyanated this on hydrolysis resulted the target molecule.

The (2S,5S)-pyrrolidine dicarboxylic acid 1 has been isolated from the red alga Schizmnenia duby. It has been used as a potential chiral building block in β-lactam synthesis, and as an elegant chiral auxiliary in asymmetric synthesis of peptides and proteins with unusual conformational properties.

![Diagram](image)

(2S,5S) Pyrrolidine dicarboxylic acid (1)

4.6.2 Present work:

We envisaged the stereoselective synthesis of 1 starting from readily available (S)-proline derivative 2 via an electrochemical oxidation route¹² (Scheme 1).
Scheme 1

Reagents and conditions (i) Electrochemical oxidation (Carbon electrode, 230 mA/28 cm²), MeOH, TBATFB (0.5 M solution), 0-15 °C, 10 h (95%, 3:4 = 7:3); (ii) TMSOTf (0.1 equiv), TMSiCN (1.1 equiv), DCM, −35 °C, 30 min (70%, 5:6 = 3:7); (iii) t-BuOK (1 equiv), THF, rt, 6 h (80%, racemic mixture); (iv) 6 N HCl, reflux, 24 h (92%); (v) SOCl₂, MeOH, rt, 12 h (75%); (vi) H₂O, reflux, 24 h (92%).

The methyl ester of BOC-protected (S)-proline 2 on stereoselective electrochemical oxidation at 230 mA current in methanol using tetrabutylammonium tetrafluoroborate (TBATFB) as an electrolyte furnished mixture of 5-methoxylated proline derivatives 3 and 4 in 7:3 ratio (by ¹H NMR) with 95% yield. The mixture of diastereomers 3 and 4 was not separable using column chromatography. The mixture of compounds 3 plus 4 on treatment with trimethylsilyl cyanide (1.1 equiv) in CH₂Cl₂ at −30 °C gave the mixture of cyano compounds 5 and 6 with complete inversion of
configuration at C5-chiral centre in 7:3 ratio (by 1H NMR) with 70% yield. We could very easily separate the mixture of cyano compounds 5 and 6 using neutral alumina column. The major cis-isomer 5 in the mixture of 5 plus 6 or as pure 5 on treatment with potassium tert-butoxide (1 equiv) in THF at room temperature underwent very smooth isomerization to furnish the thermodynamically more stable trans-isomer 6 in 80% yield, but with complete racemization. We search for conditions to obtain the desired trans-isomer 6, without loss of optical purity. The trans-cyanoester 6 in refluxing 6 N hydrochloric acid yielded the hydrochloride salt of the natural product 1 in 92% yield and the conversion of hydrochloride salt to 1 using propylene oxide treatment with 87% yield is known. The hydrochloride of 1 on reaction with methanol-thionyl chloride followed by base induced neutralization of formed hydrochloride yielded the trans dimethyl ester 8 in 75% yield, which on refluxing in water for 24 hours furnished the natural product (2S,5S)-pyrrolidine-2,5-dicarboxylic acid (1) in 92% yield. The analytical and spectral data obtained for 1 and 8 were in complete agreement with the reported data. The enantiomerically pure cis-isomer 5 on repetition of similar reaction sequence gave the meso diester 7 and diacid 9.

4.7 Experimental Procedure

Methyl (2S)-N-(tert-butoxycarbonyl)-5(R/S)-methoxyprolinecarboxylate (3 + 4)

Methyl ester of N-(tert-butoxycarbonyl)-L-proline (2, 8.0 g, 34.9 mmol) was dissolved in a 0.5 M solution of tetrabutylammonium tetrafluoroborate in methanol (100 mL). The reaction mixture was cooled to 5 °C in an ice bath and the stirred solution was oxidized at carbon anode and cathode using a constant current (230 mA/28 cm²) for 10 h. The reaction mixture was concentrated under vacuo and the residue was treated with
diethyl ether (3 x 75 mL) leaving the supporting electrolyte as a crystalline solid. The combined ether layer was concentrated in vacuo to get the crude product as an oil which was purified by chromatography on 230-400 silica gel by isocratic elution using 10% ethyl acetate/petroleum ether as eluent to obtain the mixture of diastereomers 3 + 4; yield 8.32 g (95%). Thick oil (mixture of diastereomers).

**Methyl (2S)-N-(tert-butoxycarbonyl)-5(R/S)-cyanoprolinecarboxylate (5 and 6)**

The mixture of 3 & 4 (2.46 g, 9.5 mmol) was dissolved in anhydrous dichloromethane (25 mL) and cooled to −35 °C by a cryostat. To this was added 1% of TMSOTf (0.25 mL) and TMSCN (1.46 mL, 10.9 mmol) in a drop wise fashion at −35 °C with stirring. The reaction mixture was further stirred for 30 min and diluted with methanol (1 mL). The reaction mixture was concentrated under vacuo and the residue was purified by neutral alumina column using 12% ethyl acetate/petroleum ether to obtain the diastereomeric nitriles, yield: major isomer 5, 1.4 g (70%); minor isomer 6, 0.69 g (30%).

Major isomer 5 (more polar), thick oil.

\([\alpha]_D^{25} = +41.8 \text{ (c = 0.665, CHCl}_3)\).

**(2S,5R)-Pyrrolidine-2,5-dimethyl dicarboxylate (7)**

Solution of isomer 5 (0.4 g, 1.57 mmol) in 6 N HCl (10 mL) was refluxed for 24 h, and reaction mixture was concentrated under vacuo to obtain the hydrochloride salt of dicarboxylic acid, yield 0.28 g (92%). The resultant salt was dissolved in methanol and cooled to 0 °C and SOCl₂ (0.25 mL) was added in a dropwise fashion. The reaction mixture was further stirred at room temperature for 12 h and concentrated under vacuo. The residue was treated with saturated aqueous NaHCO₃ solution and the aqueous layer
was extracted with ethyl acetate (3 x 10 mL), dried over Na₂SO₄, concentrated in vacuo to obtain 7, yield 0.2 g (75%). Thick oil.

\[ \text{MeO}_2\text{C}^\text{N} \text{H} \text{MeO}_2\text{C}^\text{N} \text{H} \]

**1H NMR** (CDCl₃, 300 Hz): \( \delta = 1.80-2.05 \) (m, 2H), 2.05-2.25 (m, 2H), 2.90 (bs, 1H), 3.70 (s, 6H), 3.90-4.05 (m, 2H). **13C NMR** (CDCl₃, 125 MHz): \( \delta = 28.8, 51.8, 59.2, 174.7 \). Ms: \( m/z = 187 \) (21%), 128 (69%). IR (CHCl₃): 3005, 1741 cm⁻¹. \( [\alpha]_D^{25} = -38.0 \) (c = 0.001, CHCl₃).

\[ \text{MeO}_2\text{C}^\text{N} \text{H} \text{MeO}_2\text{C}^\text{N} \text{H} \]

**1H NMR** (CDCl₃, 300 MHz): \( \delta = 1.85-2.00 \) (m, 2H), 2.05-2.20 (m, 2H), 2.77 (bs, 1H), 3.73 (s, 6H), 3.75-3.85 (m, 2H). **13C NMR** (CDCl₃, 125 MHz): \( \delta = 29.4, 51.8, 59.8, 174.2 \). Ms: \( m/z = 187 \) (25%), 128 (60%). IR (CHCl₃): 3000, 1740 cm⁻¹.

*(2S,5S)-Pyrrolidine-2,5-dimethylidicarboxylate (8)*

Repetition of the above procedure with 5 furnished 7; yield: 75%; thick oil.

*(2S,5S)-Pyrrolidine-2,5-dicarboxylic acid (1)*

The solution of diester 8 (200 mg, 1.08 mmol) in water (10 mL) was refluxed for 24 h, concentrated in vacuo and dried to obtain 1 as a free flowing solid, yield 0.16 g (92%).

\[ \text{HO}_2\text{C}^\text{N} \text{H} \text{CO}_2\text{H} \]

**1H NMR** (D₂O, 500 MHz): \( \delta = 2.05-2.15 \) (m, 2H), 2.30-2.40 (m, 2H), 4.28-4.35 (m, 2H).

**13C NMR** (D₂O, 125 MHz) \( \delta = 28.2, 60.9, 172.6 \). \( [\alpha]_D^{25} = -105 \) (c = 0.001, H₂O), (lit.\(^{12}\) [\( \alpha \])_D^{25} = -108). IR (Nujol): 3170, 1710 cm⁻¹. Mp 278 °C (lit.\(^{12}\) 272-277 °C).

*(2S,5R)-Pyrrolidine-2,5-dicarboxylic acid (9)*

The repetition of same procedure with 7 furnished 9, 92% yield.

\[ \text{HO}_2\text{C}^\text{N} \text{H} \text{CO}_2\text{H} \]

**1H NMR** (D₂O, 500 MHz): \( \delta = 1.95-2.15 \) (m, 2H), 2.20-2.40 (m, 2H), 4.15-4.30 (m, 2H).

**13C NMR** (D₂O, 125 MHz): \( \delta = 28.4, 61.0, 172.5 \). Ms: \( m/z = 159 \) (5%). IR (Nujol): 3170, 1709 cm⁻¹. Mp 268 °C.
4.8 Chemical studies towards the synthesis of Bulgecinine:

![Chemical structure of Bulgecinine](image)

Bulgecins are glycopeptide bacterial metabolites isolated from the cultures of *Pseudomonas acidophilia* and *Pseudomonas mesoacidophilia*. These compounds do not show any antibacterial activity on their own but when used with the β-lactam antibiotics, show synergetic effects. Bulgecinine 10 is a constituent amino acid of the Bulgecins. Till date 30 syntheses of 10 are known in the literature starting from D-glucose, 2-amino pentanoic acid, D-glucuronolactone, D-Serine, N-carbamoyl-L-pyroglutamate using variety of elegant synthetic strategies are known in the literature.

4.8.1 Earlier synthesis

First synthesis of bulgecinine was reported by Tetsuo Shiba and co-workers in 1985, employing the D-glucose as a chiral precursor.

Chavan et al. achieved the synthesis of Bulgecinine starting from the readily available non-chiral pool starting material cis-2-butene-1,4-diol in which a Claisen orthoester rearrangement and a Sharpless asymmetric dihydroxylation were used as the key steps with 43% overall yield.

Karen E. Holt reported a scaleable route to both isomers of Z-2-tert-butoxycarbonylamino-6-hydroxyhex-4-enoic acid from 2-butyne-1,4-diol, utilizing L- and D-acylase enzymes. These intermediates were readily converted to multigram quantities of *N*-Boc-(2S,4S,5R)- and *N*-Boc-(2R,4R,5S)-Bulgecinine.
In 1997 Klaus Burger\textsuperscript{22} reported the synthesis of bulgecineine starting from (S)-aspartic acid, [Rh(OAc)]\textsubscript{2} catalyzed stereospecific transformation (de >98\%) of the hexafluoroacetone protected diazoketone into the 4-oxoproline derivative. is the key step of the synthesis.

In 2004 Apruba datta\textsuperscript{23} achieved the synthesis of Bulgecineine in 13 steps, utilizing D-serine as a chiral template. Regio-stereoselective amido mercuration-oxidation protocol was the key step in the synthesis.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{diagram.png}
\caption{Earlier synthesis of (2S,4S,5R) Bulgecineine}
\end{figure}
4.9 Present work

4.9.a Synthesis of bulgecinine by hydroxyl directed ester reduction approach

Scheme 2

Reagents and conditions: (i) Acetone, K₂CO₃ (3 equiv.), DMS (2 equiv.), Reflux 5 h; (ii) THF, DEAD (1.2 equiv.), (Ph)₃P (1.1 equiv.), CH₂CO₂H (1.1 equiv), rt, 8 h; (iii) MeOH, TBATFB, 260mA, 0-5 °C, 6 h; (iv) DCM, TMSO-tf (3 equiv.), HMDS (2.5 equiv.), TMSiCN (3.5 equiv.); (v) DCM, (Boc)₂O, DMAP (cat), rt, 6h; (vi) (a) 6 N HCl, reflux, 12 h, (b) SOCl₂, MeOH, rt, 16 h; (vii) THF, BH₃-DMS, NaBH₄ (cat), rt 50h.
Synthesis of (2S,4S,5R) Bulgecinine was carried out as in Scheme-2 by employing 4-hydroxy proline as a starting material. On treatment with DMS (dimethylsulphate), K₂CO₃ in acetone furnished proline ester 12, which under Mitsunobu conditions using acetic acid furnished proline ester 13. Subjecting ester 13 to electrochemical oxidation 5-methoxyproline ester 14 was obtained as non-separable diastereomeric mixture. This on treatment with TMSCN/TMSOTF in DCM gave 5-nitrile proline ester as separable mixture. Nitriles 15 and 16 (major) were converted to diester compounds 19 and 20 by refluxing in 6 N HCl followed by esterification using SOCl₂ in MeOH. The configuration at C-5 was assigned from the small coupling constant of H-4 and H-5 of compounds 17 and 18 as reported in literature.²⁴ Diester 20 on treatment with with BH₃-DMS and NaBH₄ in THF gave 5-methyl hydroxyl ester 22.²⁵ Conversion of 22 and 21 to desired 10 and 10a are in progress.

4.10 Attempts to increase the diastereoselectivity of the reaction (Scheme-3)

Various reaction conditions were tried (Table 1) to improve the diastereoselectivity and yield of the cyanation reaction (Scheme 3). When reactions were performed at -78 °C, only starting material was recovered irrespective of the Lewis acid used in the reaction. In the case of ytterbium triflate no conversion was observed in the reaction at -78 °C and at room temperature. Employing TMSOTf and BF₃.Et₂O yielded both isomers in the ratio of 1:1 (a:b) and 2:1 respectively (Entry 4 and 6).

![Scheme 3](image-url)
<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis Acid</th>
<th>Reaction conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMSOTf (Cat)</td>
<td>DCM, -78 °C, 3h, TMSCN (1.2 eq)</td>
<td>No reaction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DCM, -78 °C - RT, TMSCN (1.2 eq)</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>TMSOTf (1.2 eq)</td>
<td>DCM, -78 °C - RT, TMSCN (1.2 eq)</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>TMSOTf (1.2 eq)</td>
<td>DCM, -78 °C - RT, TMSCN (1.2 eq)</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>TMSOTf (3 eq)</td>
<td>DCM, 0 °C - RT, TMSCN (3 eq)</td>
<td>1:1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Collidine, HMDS, 18h</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>TiCl₄</td>
<td>DCM, -78 °C - RT, TMSCN (1.2 eq)</td>
<td>2:1 (Poor Yields)</td>
</tr>
<tr>
<td>6</td>
<td>BF₃-O-(Et)₂ (3.5)</td>
<td>DCM, 0 °C - RT, TMSCN (3 eq)</td>
<td>2:1</td>
</tr>
<tr>
<td>7</td>
<td>Ytterbium triflate</td>
<td>DCM, 0 °C - RT, TMSCN (3 eq)</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

**Table 1**

In another approach compound 14 was subjected to reflux in presence of acetic acid and acetic anhydride to afford compound 14a (Scheme 4), where acyl group facilitates substitution by cyano group better than the methoxy at this position. Cyanation was performed on substrate 14a to get better yields, neither diastereoselectivity nor yield was improved. Reaction conditions have been tabulated in Table 2.

![Scheme 4](image)

**Table 2**

<table>
<thead>
<tr>
<th>S. No</th>
<th>Lewis Acid</th>
<th>Reaction conditions</th>
<th>Result</th>
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<tr>
<td>1</td>
<td>TMSOTf</td>
<td>DCM, -78 °C, 6h, TMSCN, HMDS</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>TMSOTf</td>
<td>DCM, 0 °C-RT, 18h, TMSCN, HMDS</td>
<td>1:1</td>
</tr>
</tbody>
</table>
In literature it is reported that cyanation reaction proceeds through intermediate 14b (Scheme-5) in which carbonyl of the acetyl group intramolecularly coordinates with the Imine function, we thought that the resultant intermediate may effect the course of the reaction in some or other way, to overcome this hurdle compound 22 was synthesized as shown in Scheme 6.

The ester 23 (Scheme 6) was subjected to electrochemical oxidation to obtained 5-methoxyproline ester 24 as separable diastereomeric mixture, the free hydroxyl of the 24 was reprotected as TBDMS, using pyridine as a solvent to furnish ester 25 as a mixture of diastereoisomers. When ester was subjected to cyanation in presence of TMSICN and TMSOTf, nitrile 26 was obtained with 30% yield. Due to the purification problems and low yield associated with nitrile 26, this scheme was abandoned.
Finally, cyanation reaction was performed on compound 29 (Scheme 7) in the presence of BF$_3$.Et$_2$O to get nitrile 30 (Scheme 7) with high diastereoselectivity, but very less conversion of starting material was observed in the reaction, hence reaction has to be repeated under suitable conditions.

![Chemical reaction diagram]

**Scheme 7**

The other low yielding reaction in the scheme is the conversion of nitriles 15, 16 to 17 and 18 respectively (Scheme 2). Several reaction conditions were tried to get the better yield of 19 and 20. Which have been tabulated in Table 3.

![Chemical reaction diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMS-Cl, MeOH, (1:1), rt-50 °C. $^{26a}$</td>
<td>Amide</td>
</tr>
<tr>
<td>2</td>
<td>PTSA (3eq), MeOH, reflux, 4h.</td>
<td>Complex reaction mixture</td>
</tr>
<tr>
<td>3</td>
<td>PTSA (1eq), MeOH, reflux, 4h.</td>
<td>Amide</td>
</tr>
<tr>
<td>4</td>
<td>Acidic MeOH, 0 °C, 16h. $^{26b}$</td>
<td>Amide</td>
</tr>
<tr>
<td>5</td>
<td>Acid (cat), MeOH, reflux, 16h. Base (cat), MeOH, reflux, 16h.</td>
<td>Amide</td>
</tr>
<tr>
<td>6</td>
<td>6N HCl, reflux, 16h. SOCl$_2$, MeOH, rt, 18h.</td>
<td>Diester, 20%</td>
</tr>
</tbody>
</table>

**Table 3** Various conditions tried for alcoholsysis of nitrile$^{26}$

280
4.11 Diazotisation approach:

In the diazotization approach (Scheme 8) catalytic reduction of the cyano compound 18 yielded the 5-aminomethyl derivative (not isolated), which on treatment with Fmoc-Cl in the presence of dioxane 4-hydroxy ester 31 as a white solid. On treatment of ester 31 with 50% DCM/DEA provided the 5-aminomethyl 4-hydroxy proline ester (not isolated). This was subjected to diazotisation under basic conditions in THF for the transformation of primary amine to hydroxyl group to obtain the target molecule 24. Search for the suitable reaction conditions for the conversion of 31 to desired 24 is in progress.

\[ \text{AcO} \quad \overset{\text{vii}}{\rightarrow} \quad \overset{\text{viii}}{\rightarrow} \quad \text{HO} \quad \overset{\text{HO}}{\rightarrow} \quad \text{NH} \quad \overset{\text{Boc}}{\rightarrow} \quad \overset{\text{Fmoc}}{\rightarrow} \quad \text{CO}_2\text{Me} \]

\[ \text{18} \quad \overset{\text{71}}{\rightarrow} \quad \overset{\text{81}}{\rightarrow} \quad \overset{\text{81}}{\rightarrow} \quad \text{31} \quad \overset{\text{24}}{\rightarrow} \quad \text{24} \]

**Scheme 8**

*Reagents, conditions: (vii) (a) MeOH, NEt₃, Raney Ni, 65 Psi, 4 h, (b) MeOH, 2 N NaOH, rt. 45 min, (c) Dioxane/H₂O, 10% Na₂CO₃, Fmoc-Cl (1.5 equiv.); (viii) (a) DEA/DCM (50%), (b) Na₂NOFe(CN)₆, K₂CO₃, THF, rt. 16 h*

In another approach (Scheme 9) nitrile 17 was hydrolyzed in LiOH solution to furnish acid 32 as solid compound, which was treated with DIBAL at -78 °C in THF for about 3h, to obtain aldehyde, this on reduction in presence of NaBH₄ gives the N-protected form of bulgecinidine. Due to the solubility problem of the nitrile 32 DIBAL reaction did not proceed.
4.12 Experimental

All reagents were obtained from commercial sources and used without further purification. NaH was obtained from Aldrich as 60% suspension in paraffin oil and the paraffin coating was washed off with pet-ether before use to remove the oil. The supporting electrolyte tetrabutyl ammonium tetrafluoroborate was obtained from Aldrich and used as such without further purification. All the solvents were dried according to literature procedures. IR spectra were recorded on a Perkin Elmer 599B instrument. $^1$H NMR (200MHz), $^{13}$C NMR (50 MHz) spectra were recorded on Bruker ACF200 spectrometer fitted with an Aspect 3000 computer. All chemical shifts are with reference to TMS as an internal standard and are expressed in d scale (ppm). The values given are directly from the computer printout. TLCs were carried out on (E.Merck 5554) precoated silicagel 60 F254 plates. TLCs were visualized with UV light and/or ninhydrin spray, followed by heating after exposing the HCl for the deprotection of the tert-butoxycarbonyl group. Optical rotations were measured on JASCODIP-181 polarimeter. All TLCs were run in pet-ether containing appropriate amount of ethyl acetate or dichloromethane containing appropriate amount of methanol to get the rf value 0.5. All
the compounds were purified by column chromatography using 100-200 silica gel obtained from Sisco Research Laboratory. In NMR spectra that show splitting of peaks due to the presence of rotameric mixtures, arising from the tertiary amide linkage, the major rotamer is designated as maj. and the minor rotamer as min. The ratio of major minor is 80:20 unless otherwise mentioned. In cases, where minor isomer is <10% only the peaks of major rotamer are reported.

**Compound 14a**

To a solution of 14 (0.4 gm, 1.26 mmol) in CH₃CO₂H/AC₂O (1:1, 8 mL) was added sodium acetate (0.51 gm, 6.3 mmol) and reaction mixture was heated to 100 °C for about 12 h, after completion of the reaction solvent was evaporated under vacuo and extracted with ethyl acetate (3 x 10 mL). Evaporation of the solvent, and purification by column chromatography afforded 217 mg of 14a (50%) as an oily liquid.

\[
\text{1H NMR (CDCl₃, 200 Hz): } \delta = 1.46 \text{ (bs, 9H), 2.04-2.40 (m, 7H), 2.50-2.75 (m, 1H), 3.74-3.78 (d, } J = 8 \text{ Hz, 3H), 4.10-4.60 (m, 1H), 5.00-5.25 (m, 1H), 4.44 \text{ (m, 1H), 6.47-6.70 (m, 1H)}, \text{13C NMR (CDCl₃, 50 MHz): } \delta = 20.3, 20.7, 27.8, 51.9, 52.1, 57.6, 58.0, 74.9, 76.0, 79.0, 81.3, 84.1, 85.0, 152.5, 188.5, 188.9, 169.3, 171.1; \text{ IR (CHCl₃) } \gamma = 1670, 1770, 1771 \text{ cm}^{-1}.\]

**Compound 15 and 16**

To a solution of 14 (1 gm, 3.15 mmol) in DCM was added TMSICN (0.812 mL, 6.3 mmol) and reaction mixture was cooled to ice temperature, to this BF₃.Et₂O (0.997 gm, 7.8 mL) was added drop wise fashion and stirred at ambient temperature for 14 h, after completion of the reaction Na₂CO₃ (160 mg, 0.5 mmol) was added and stirred for
2h to quench the excess Lewis acid present in the reaction. Evaporation of the solvent, and purification by column chromatography using neutral alumina afforded 133 mg of 16 (19%) and 60 mg of 15 (8%) as an oily liquid.

**Compound 17**

To a solution of 15 (60 mg, 0.312 mmol) in DCM was added di-tertiarybutyloxy carbonate (300 mg, 1.352 mmol) followed by catalytic amount of DMAP (8.23 mg, 0.73 mmol) at ice temperature and stirred at ambient temperature for 8h. Evaporation of the solvent and purification by flash chromatography afforded 120 mg of 17 (70%) as a oily liquid.
Compound 18

Following the above procedure synthesis of compound 18 was achieved.

\[ \text{AcO} \quad \text{NC} \quad \text{N} \quad \text{CO}_2\text{Me} \]

\[ 1^H \text{ NMR (CDCl}_3 200 \text{ MHz)} \delta 1.54-1.45 (d, J = 18 \text{ Hz}, \text{COOC(CH}_3)_2); 2.05-2.04 (d, J = 2 \text{ Hz, -OCO-CH}_3), 2.47-2.40 (d, J = 16 \text{ Hz}, \text{H}_3), 2.81-2.64 (m, 1\text{H}, \text{H}_3), 3.76 (s, 3\text{H}), 4.61-4.47 (m, 1\text{H}) 4.68-4.64 (d, J = 8 \text{ Hz m, 1H}), 5.38-5.36 (d, J = 4 \text{ Hz, 1H, H}_4), \]

\[ ^{13}C \text{ NMR (CDCl}_3 200 \text{ MHz)} \delta 171.0, 170.6 (\text{CO}_2\text{CH}_3), 169.4, 169.0 (\text{OCO-CH}_3), 152.5, 152.21 (\text{COOC(CH}_3)_2), 115.7, 115.6 (\text{CN}), 82.8, 82.1, (\text{COOC(CH}_3)_2), 76 (\text{OCH}_3), 58.0, 57.7 (\text{C}_2), 53.6, 53.5 (\text{C}_2), 53.6, 53.5 (\text{C}_5), 52.5, 52.3 (\text{C}_4), 35.2, 34.1 (\text{C}_3), 20.5 (\text{OCO-CH}_3); \]

\[ \text{Ms: m/z = 333 [M+Na] (3%), 235.21(20%), 102.11 (100%).} \]

Compound 20

Solution of isomer 16 (0.2 g, 0.641 mmol) in 6 N HCl (10 mL) was refluxed for 24 h, and reaction mixture was concentrated under vacuo to obtain the hydrochloride salt of dicarboxylic acid, yield 0.122 g, (0.576 mmol, 90%). The resultant salt was dissolved in methanol and cooled to 0 °C and SOCl\(_2\) (0.25 mL) was added in a drop wise fashion. The reaction mixture was further stirred at room temperature for 12 h and concentrated under vacuo. The residue was treated with saturated aqueous NaHCO\(_3\) solution and the aqueous layer was extracted with ethyl acetate (3 x 10 mL), dried over Na\(_2\)SO\(_4\), concentrated in vacuo to obtain 20, yield 0.05 g (50%). Thick oil.
**Compound 22**

To a solution of 20 (6mg, 0.03 mol) in dry THF was added borane-dimethyl sulphate (5.04 mg) as drop wise fashion and reaction stirred at 0 °C for about 2 h, to this solution added NaBH₄ (powder, catalytic amount) and stirred at ambient temperature for about 50 h. Evaporation of the solvent and purification by flash chromatography afforded 5 mg of 24 as a sticky solid.

**Compound 25**

To a solution of 24 (0.4 gm, 1.45 mmol) in pyridine (10 mL) was added imidazole (0.147 gm, 2.17 mmol) and the reaction mixture was cooled to ice temperature, to this TBDMS-Cl (0.26 gm, 1.745 mmol) was added in portion wise and
the reaction mixture was stirred at ambient temperature for about 16 h, after completion of the reaction solvent was evaporated under vacuo and extracted with ethyl acetate (3 x 15 mL). Evaporation of the solvent, and purification by column chromatography afforded 537.25 mg of 25 (95%) as a oily liquid.

Compound 31

To a solution of 18 (120 mg, 0.384 mmol) in methanol (2 mL) were added NEt₃ (0.15 mL, 2.0 mmol) followed by raney Ni (250 mg). The mixture was subjected to hydrogenation at 65 psi, after completion of the reaction (4 h), reaction mixture was filtered through celite pad and the solvent was evaporated under reduce pressure to get amino ester (not isolated) as a oily liquid. This was redissolved in 10% Na₂CO₃ (1 mL) and the reaction mixture was cooled to 0 °C in an ice-bath. To this was added dioxane (2 mL) (peroxide free) followed by the slow addition of Fmoc-Cl (201 mg, 0.719 mmol), in dioxane at 0 °C. Stirring was continued at 0 °C for 4 h. followed by room temperature stirring for 18 h. The reaction as monitored by TLC, after the completion of the reaction solvent was evaporated under vacuo and extracted with ethyl acetate (3 x 10 mL). Evaporation of the solvent, and purification by column chromatography afforded 56 mg of 31 (30%) as a white solid.
\[ \text{ Compound 32 } \]

To a solution of 17 (0.1 gm, 0.370 mmol) in methano (2 mL) was added 0.4 mL 1N aq. NaOH (15.67 mg, 0.391 mmol) and the reaction mixture was stirred for about 4 h, after completion of the reaction, solvent was neutralized with cationic exchange resin filtration followed by evaporation afforded 74 mg of 32 (75%) as a hygroscopic solid.

\[ \text{ Compound 32 } \]

\[ ^1H \text{ NMR (CDCl}_3, \text{ 200 Hz): } \delta = 1.4-1.50 (d, J = 6 \text{ Hz, } 9H), 1.95-2.10 (m, 1H), 2.12-2.25 (m, 1H), 3.95-4.25 (m, 1H), 4.25-4.5 (m, 1H), 4.60-4.80 (m, 2H); ^13C \text{ NMR (CDCl}_3/\text{CD}_2\text{OD 50 MHz): } \delta = 26.6, 35.8, 36.1, 53.9, 54.8, 60.3, 69.5, 70.9, 80.6, 115.2, 153.6, 178.4. \]
4.13 Reference:


13. The stereochemical assignments are based on the optical rotation of the known compounds.
### 4.14 Appendix

<table>
<thead>
<tr>
<th>Entry</th>
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<tr>
<td>1</td>
<td>Compound 1; $^1$H NMR and Mass spectra</td>
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<tr>
<td>2</td>
<td>Compound 1; $^{13}$C and DEPT spectra</td>
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<td>Compound 7; $^1$H NMR and $^{13}$Cspectra</td>
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<td>Compound 7; DEPT and Mass spectra</td>
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<td>Compound 8$^1$; H NMR and $^{13}$Cspectra</td>
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<td>6</td>
<td>Compound 8$^1$; DEPT and Mass spectra</td>
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<td>Compound 9$^1$; H NMR and $^{13}$Cspectra</td>
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<tr>
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<td>Compound 9; DEPT spectrum</td>
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<td>Compound13; $^1$H NMR and $^{13}$Cspectra</td>
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<td>Compound 13; DEPT and Mass spectra</td>
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<td>Compound 14; $^1$H NMR and $^{13}$Cspectra</td>
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<td>Compound 14; DEPT and Mass spectra</td>
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<tr>
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<td>Compound 15; $^1$H NMR and $^{13}$Cspectra</td>
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<td>Compound 16; $^1$H NMR and $^{13}$Cspectra</td>
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<td>Compound 16; DEPT spectrum</td>
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<td>Compound 17; $^1$H NMR and $^{13}$Cspectra</td>
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<td>Compound 17; DEPT spectrum of</td>
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<td>Compound 20; $^1$H NMR and $^{13}$Cspectra</td>
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<td>Compound 20; DEPT spectrum</td>
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<td>Compound 22; $^1$HNMR spectrum</td>
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<td>Compound 24; $^1$H NMR spectrum</td>
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<td>Compound 25; $^1$H NMR and $^{13}$C spectra</td>
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<td>23</td>
<td>Compound 25; DEPT and Mass spectra</td>
<td>313</td>
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<tr>
<td>24</td>
<td>Compound 31; $^1$H NMR and Mass spectra</td>
<td>314</td>
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<tr>
<td>25</td>
<td>Compound 35; $^1$H NMR and $^{13}$Cspectra of</td>
<td>315</td>
</tr>
</tbody>
</table>
Figure 3 1H NMR and Mass spectra of compound 1

Compound 1
$M_{\text{calculated}} = 159$
$M_{\text{observed}} = 160.17$ (M+1)
Figure 4 $^{13}$C and DEPT spectra of compound 1
Figure 5 $^1$H NMR and $^{13}$C spectra of compound 7
Figure 6 DEPT and Mass spectra of compound 7
Figure 7 $^1$H NMR and $^{13}$C spectra of compound 8
Figure 8 DEPT and Mass spectra of compound 8
Figure 9 $^1$H NMR and $^{13}$C spectra of compound 9
Figure 10 DEPT spectrum of compound 9
Figure 11 $^1$H NMR and $^{13}$C spectra of compound 13
Figure 12 DEPT and Mass spectra of compound 13
Figure 13 $^1$H NMR and $^{13}$C spectra of compound 14
Figure 14 DEPT and Mass spectra of compound 14

M_{calculated} = 259
M_{observed} = 260.12
Figure 15 $^1$H NMR and $^{13}$C spectra of compound 15
Figure 16 $^1$H NMR and $^{13}$C spectra of compound 16
Figure 17 DEPT spectrum of compound 16
Figure 18 $^1$H NMR and $^{13}$C spectra of compound 17
Compound 17
DEPT, CDCl₃

Figure 19 DEPT spectrum of compound 17
Figure 20 $^1$H NMR and $^{13}$C spectra of compound 20
Compound 20
DEPT, CDCl₃
Major + Minor

Figure 21 DEPT spectrum of compound 20

CDCl₃, ¹H NMR

Figure 22 ¹HNMR spectrum of compound 22
$^1$H NMR, CDCl$_3$

Figure 23 $^1$H NMR of compound 24
Figure 24 $^1$H NMR and $^{13}$C spectra of compound 25
Compound 25
DEPT, CDCl₃

$M_{\text{calculated}} = 389$
$M_{\text{observed}} = 390.45$

Figure 25 DEPT and Mass spectra of compound 25
Compound 31

$M_{calculated} = 496$

$M_{observed} = 497.07$

**Figure 26** $^1$H NMR and Mass Spectra of Compound 31
Figure 27 $^1$H NMR and $^{13}$C spectra of compound 35