CHAPTER I

This chapter describes the Total synthesis of Achaetolide

Achaetolide 1 is a naturally occurring ten-membered lactone isolated from the culture broth of *Achaetomium crisalliferum*. Though first isolated in 1983, the absolute stereochemistry of the compound was not known. In 2009, Takada and co-workers extracted the same compound from culture broth of *Ophiobolus sp.* and determined the absolute stereochemistry of the compound by spectroscopic techniques. The structural features of achaetolide along with our interest in the synthesis of macrolactones prompted us to undertake the synthesis of achaetolide and it would also ultimately prove the absolute configuration of the molecule.

Retrosynthetic analysis of achaetolide

Our retrosynthetic plan revealed the achaetolide 1 can be obtained by ring-closing metathesis (RCM) reaction. The acyclic precursor required for the RCM could be obtained by coupling the secondary alcohol 2 and acid 3 through a Mitsunobu esterification. The fragment 2 could be obtained from epichlorohydrin 5 using Jacobson hydrolytic kinetic resolution and dihydroxylation of the lactone 4. The acid 3 is accessible from the known epoxy alcohol 6 which in turn could be made from 1,3-propane diol 7 (Scheme 1).

Synthesis of alcohol 2

Commercially available epi-chlorohydrin 5 was subjected to regioselective ring opening by *n*-hexylmagnesium bromide at -78 °C in the presence of catalytic CuCN to give chlorohydrin, which was converted to nonene oxide 8 under basic conditions. The racemic nonene oxide on Jacobsen hydrolytic kinetic resolution employing 0.55 eq. of water in the presence of 0.005 mol% of (S,S-1) catalyst afforded chiral oxirane 9 in 43% and diol 10 in 45% yield. The oxirane 9 was opened using lithiated ethyl propiolate at -78 °C to provide
the homopropargylic alcohol 11 in 80% yield, which was then subjected to partial hydrogenation using Lindlar’s catalyst [Pd-CaCO₃/Quinoline] to provide syn olefinic compound 12. Exposure of 12 to catalytic $p$-TSA led to the formation of lactone 4. Dihydroxylation of lactone 4 using OsO₄ and NMO was highly stereoselective, as diol 13 was the only product obtained in 58% yield, which was subsequently protected as its acetonide 14 using 2,2 dimethoxy propane with catalytic PPTS in 72% yield. The lactone 14 was reduced to lactol 15 using DIBAL-H at -78 °C, which on subsequent one carbon homologation using triphenyl methyl phosphonium ylide afforded the alcohol 2 in 77% yield (Scheme 2).

**Scheme 2**

**Synthesis of acid 3**

Propane diol 7 was selectively mono protected as its TBDPS ether 16 using TBDPS ether and imidazole. The mono protected alcohol 16 was oxidized to aldehyde under Swern reaction conditions, [COCl₂, DMSO, NEt₃] at -78 °C, which was then subjected to Wittig reaction using Ph₃P=CHCOOEt to form two carbon homologated $\alpha,\beta$-unsaturated ester 17 in 88% yield. The ester 17 was reduced to the allylic alcohol 18 using DIBAL-H in 87% yield (Scheme 3).
Sharpless asymmetric epoxidation of the allylic alcohol 18 using (+) DET, TBHP, Ti(\text{O-Pr})_4 afforded the epoxy alcohol 6 in 88% yield. The epoxy alcohol 6 was converted into iodo compound using TPP, I₂ and imidazole, which on reductive elimination with activated Zn dust afforded the allylic alcohol 19 in good yield. The exposed hydroxyl group was protected as its TBS ether 20 using TBS-Cl in 95% yield. The TBDPS ether is selectively deprotected using ammonium fluoride in methanol and the alcohol is oxidized to aldehyde using IBX and then to acid 3 using NaClO₂ and NaH₂PO₄ (Pinnick conditions) in 76% yield (Scheme 4).

Coupling of the alcohol 2 and acid 3 fragments and completion of synthesis

The alcohol 2 and acid 3 were coupled under Mitsunobu conditions (TPP, DIAD) to afford the diene 22 in 62% yield with the inversion of configuration at the hydroxyl carbon (Scheme 5).
Ring closing metathesis of 22 was not successful using either Grubbs’-II or Grubbs’-I catalyst. We assumed the bulky nature of the TBS group would hinder the approach of dienes and pose a strain for the formation of the macrolactone. The TBS was deprotected using TBAF to give the diene 23 in 87% yield (Scheme 6).

The diene 23 underwent the RCM reaction smoothly with Grubbs’-II catalyst, but a mixture of E isomer 24 and Z isomer 25 of the newly formed alkene unit were formed (Scheme 7).

The isomers were separated by column chromatography and deprotection of the isopropylidene unit of E isomer of the macrolactone 23 using trifluoroacetic acid in CH₂Cl₂ afforded the achaetolide 1 in 65% yield as a white solid (Scheme 8).
compound was characterized by $^1$H NMR, $^{13}$C NMR, ESIMS, HRMS, IR and specific rotation and they agree well with the literature for the naturally occurring achaetolide.

![Chemical structure](image)

**Scheme 8**

In conclusion, the total synthesis of achaetolide has been achieved from commercially available epichlorohydrin. The key steps include Mitsunobu reaction and Grubbs’ ring closing metathesis reaction and Jacobsen hydrolytic kinetic resolution.

**CHAPTER-II, Section-A**

This section describes Total synthesis of Pectinolide-A

Hyptis pectinata (L) poit is a herbaceous plant found in Central America and it is widely used for its medicinal properties. Pectinolide-A 1 is a 5,6 dihydro-$\alpha$-pyrone, it was isolated from this plant species along with other $\alpha$-pyrones. Pectinolide-A showed antibacterial activity and exhibits cytotoxic properties against several tumor cell lines. As part of our efforts towards the synthesis of biologically active $\alpha$-pyrones, we attempted a total synthesis of pectinolide-A.

![Chemical structure](image)

**Retrosynthetic analysis of Pectinolide-A**

We envisaged to construct 5,6-dihydropyran-2-one ring of the pectinolide A through a ring closing metathesis of the triene 2. The triene could be obtained from the tosyl intermediate 3 through an intramolecular substitution reaction to form an epoxide, allylation and one carbon homolagation of the epoxide. The tosyl intermediate would be realized from the reaction of alkyne 5 with $n$-valeraldehyde through progargylic alcohol 4. The alkyne 5 could be made from L-(+)-diethyl tartrate 6 (Scheme 1).
Scheme 1

Synthesis of alkyne 5

Our synthesis commenced from of cheaply available L-(+) diethyl tartrate 6. The hydroxyl groups of the L-(+) DET were protected as its isopropylidene acetal using 2,2-dimethoxy propane with catalytic \( p \)-TSA. Reduction of the ester functionality using LAH afforded the diol 7 in 76% yield (for two steps). The diol 7 was mono protected as its TBS-ether using TBS-Cl followed by oxidation of the alcohol under Swern conditions afforded the aldehyde 9. The aldehyde 9 was immediately treated with a mixture of \( \text{CBr}_4 \) and \( \text{Ph}_3\text{P} \) in \( \text{CH}_2\text{Cl}_2 \) to give dibromoalkene 10 in 67% yield. The dibromo compound on reaction with freshly prepared ethylmagnesium bromide gave alkyne 5 in 81% yield (Scheme 2).

Scheme 2
Synthesis of alkynol 4a

\( n \)-Valeraldehyde 11 was allowed to react with lithated alkyne at -78 °C for 4 h to give propargylic alcohol 4a and 4b in 52% yield with 1:1 diasteromeric ratio. To prepare the required propargylic alcohol, the mixture was oxidized to ynone 12 using IBX which upon stereoselective reduction using (S)-CBS catalyst and catechol borane as a reducing agent afforded the propargylic alcohol 4a/4b in 9:1 diastereomeric ratio in 81% yield (Scheme 3).

Scheme 3

The propargylic alcohol mixture 4a/4b was then subjected to syn reduction using Lindlar’s catalyst and cat. quinoline under H\(_2\) atmosphere to afford allylic alcohols 13a and 13 b, which were separated by column chromatography to give 13a in 86% and 13 b in 10% yield (Scheme 4).

Scheme 4

The allylic alcohol 13a was protected as its MOM-ether using MOM-Cl/ DIPEA in CH\(_2\)Cl\(_2\) in 88% yield, then the silyl group was deprotected using TBAF to give the primary
alcohol 15 in 88% yield. The primary alcohol 15 was tosyliated using tosyl chloride to give the compound 3 in 90% yield. The tosyl compound 3, when exposed to p-TSA, the isopropylidene acetal unit got deprotected, which upon basifying with triethyl amine intramolecular substitution of tosyl functionality took place and epoxide 16 was formed in the same pot in 72% yield (Scheme 5).

Scheme 5

The hydroxyl group on the epoxy alcohol 16 was protected as its TBS ether using TBS-OTf to afford compound 17 in 85% yield. One carbon homologation of the epoxide 17 using ylide of trimethylsulfonium iodide gave the required product 18 in just 15% yield and using ylide of trimethylsulfonium mesylate did not yield any product (Scheme 6).

Scheme 6
A few more chemical transformations would have afforded pectinolide A 15 as shown in Scheme 7.

As allyl ether can be converted to the acryl group on oxidation. The hydroxyl group was protected as its allyl ether 21 using allyl bromide/NaH in 81% yield. The epoxide 21 when exposed to trimethylsulfonium ylide, it smoothly underwent one carbon homologation to afford the triene 22 in 79% yield (Scheme 8).

Completion of synthesis

The triene 22 was subjected to undergo ring closing metathesis using 5 mol% of Grubbs’-II catalyst in anhydrous CH₂Cl₂ which afforded dihydropyran 23 in 89% yield, then the MOM ether was deprotected using 4N HCl to give the diol 24. The diol was diacetylated using acetic anhydride in NEt₃ in CH₂Cl₂ to afford compound 25 in 86% yield. Oxidation of the acetylated dihydropyran 25 using PCC/pyridine in CH₂Cl₂ at refluxing temperature afforded pectinolide-A 1 in 46% yield (Scheme 9).
The optical rotation exhibited by synthetic pectinolide-A $[\alpha]_D^{27} = +208.5$ (c 0.43, MeOH) was in agreement with literature $[\alpha]_D^{25} = +202$ (c 0.15, MeOH). The IR, NMR and mass spectra of the synthetic product was identical with those of the naturally occurring pectinolide A. In conclusion, the total synthesis of Pectinolide A has been achieved using RCM reaction of allylic ether which acts a masked acrylic ester moiety and stereoselective reduction of $\alpha,\beta$-ynone using CBS catalyst as key steps.

CHAPTER-II, Section-B

This section describes the Total synthesis of Pectinolide-H

In 2004, Chemical reinvestigation of the same plant species Hyptis pectinata (L) poit led to the isolation of pectionlide H 26, a structurally related analogue pectinolide B. Pectinolide H displayed a reasonably high potency against two multidrug resistant strains of S.Aureus, XU-212.
Retrosynthetic analysis

Being structurally related to pectinolide A, we devised a strategy to synthesize pectinolide H from 4a, an intermediate used for the synthesis of pectinolide A. Pectinolide H 26 could be obtained by the concomitant deprotection of the isopropylidene acetal and laconisation of the compound 27, which in turn could be obtained from the propargylic alcohol 4a. Reaction between valeraldehyde and alkyne 29 would realize the propargylic alcohol. The alkyne 5 could be obtained from the L (+) DET 6.

Scheme 11

The synthetic intermediate 4a was obtained from L(+) DET 6 as shown in scheme 2 & 3 was used to synthesize pectinolide H. The propargylic alcohol 4a was acetylated using acetic anhydride, NEt₃ in CH₂Cl₂ to give compound the acetylated compound 28 in 89% yield, which upon deprotection of the TBS ether using TBAF afforded the alcohol 29 in 79% yield (Scheme 12)

Scheme 12

The alcohol 29 on oxidation using oxalyl chloride and DMSO in dichloromethane at -78 °C gave aldehyde 30, which was subjected to Wittig-Horner-Emmons olefination
using ethyl [bis(α-dimethylphenyl phosphono)] acetate 31 at -78 °C to afford the cis- α,β unsaturated ester 27 in 62% yield (for 2 steps).

![Scheme 13]

The unsaturated ester 27, when exposed to catalytic CSA, deprotection of the isopropylidene group and cyclization took place concomitantly to afford pectinolide H 26 along with the diol 32 due to the deprotection of acetyl group (Scheme 14). The spectral features were in complete agreement with those reported in literature.

![Scheme 14]

In conclusion, total synthesis of pectinolide H 26 was achieved through stereoselective CBS reduction of α,β-ynone, Z-selective Wittig-Horner olefination and one pot concomitant deprotection and lactonization as key steps.
CHAPTER-III

This section deals with development of a new class of carbohydrate-pyrrolidine based organocatalysts for asymmetric Michael addition reaction

Asymmetric Michael addition is one of the widely used C-C bond forming reaction. Last few years have seen an exponential growth in the synthesis and application of various pyrrolidine based asymmetric organocatalysts. Carbohydrates are highly oxygenated compounds and have a set of chemical and structural features. Due to their low cost and ease of poly-functionalization, they can be easily tuned for the steric, electronic and solubility requirements needed for a reaction. Herein, we describe the development and evaluation of a new class of carbohydrate based pyrrolidine organocatalysts 1 and 2 and their application in asymmetric Michael addition of carbonyl compounds to nitro olefins.

Retrosynthetic analysis

A retrosynthetic analysis of catalyst 1 and 2 is shown in Scheme 1. The carbohydrate-pyrrolidine catalysts 1 could be obtained by coupling of pyrrolidine amine 6 with β-azido-acid 3. The catalyst 2 can be obtained by coupling of pyrrolidine amine 6 with benzyl protected β-hydroxy-acid 4. Pyrrolidine amine 6 could be obtained from L-proline 7 and the β-acids from D-glucofuranose.

Scheme 1
The synthesis of organocatalyst commenced from L-proline. Proline 7 was protected as its carbamate 8 using Cbz-Cl followed by the reduction of the acid using borane dimethyl sulfide afforded the alcohol 9. The alcohol was converted to tosyl derivative 10 and subsequently to azide 11 using sodium azide. The azide group was chemoselectively reduced to its corresponding amine 6 using Pd-BaSO₄ (poisoned with lead) in methanol under hydrogen atmosphere (Scheme 2).

![Scheme 2](image)

The β-azido-acid 3 fragment was obtained from D-glucose as shown in scheme 3.

![Scheme 3](image)
Benzyl protected β-hydroxy-acid was obtained from D-glucose as shown in scheme 4.

\[
\begin{align*}
\text{i. } & \text{BnBr, NaH} \\
\text{ii. } & 0.8 \text{ H}_{2}\text{SO}_{4}, \text{MeOH} \\
& \text{rt, 12 h.} \\
& 84\% \text{ (for 2 steps)}
\end{align*}
\]

Scheme 4

Amine 6 and acid 3 were coupled using EDC.HCl and HOBt to afford the amide 19 in 81% yield. Deprotection of –N\text{Cbz} group and reduction of azide were carried out under hydrogenation conditions using Pd/C catalyst in methanol for 12 h to afford the catalyst 1 in 84% yield (Scheme 5).

\[
\begin{align*}
\text{Pd/C, } & \text{H}_2, \text{CH}_3\text{OH} \\
& \text{rt, 12 h, 84\%}
\end{align*}
\]

Scheme 5

Coupling of the amine 6 and acid 4 using EDC.HCl and HOBt gave the amide 20 in 77% yield. Both the -OBn and -N\text{Cbz} protecting groups were removed by hydrogenation using Pd/C as catalyst in methanol to afford the catalyst 2 (Scheme 6).

\[
\begin{align*}
\text{Pd/C, } & \text{H}_2, \text{CH}_3\text{OH} \\
& \text{rt, 15 h, 83\%}
\end{align*}
\]

Scheme 6
Evaluation of catalyst

With both the catalysts 1 and 2 in hand, we tested their efficiency in asymmetric Michael addition reaction of $\beta$-nitrostyrene 21a with cyclohexanone 22 (Scheme 7). The reactions were conducted in 10 mol% of catalyst in solvent free condition at room temperature. Both catalysts were able to catalyse the reaction however, catalyst 2 bearing hydroxyl functionality provided the product in good yield (88%) and good stereoselectivity (ee up to 66%, syn:anti 92:8, Table-1, entry-2). After that we screened THF, CHCl$_3$, methanol and dioxan as solvents for the same reaction with 20 mol% of the catalyst 2. Increasing the catalyst quantity improved both enantioselectivity and diastereoselectivity of the reaction (ee up to 91%, syn:anti 98:2 Table-1, entry-3). Usually Michael reactions employing pyrrolidine based catalyst needs small amount of acid catalyst as additive, in our study the reaction under solvent free condition proceeded at a reasonable rate without any additives.

![Scheme 7](image)

Table 1: Screening of catalyst and solvent.$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>mol%</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield (%)$^b$</th>
<th>dr (syn/anti)$^c$</th>
<th>ee (syn)$^d$</th>
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</thead>
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<td>neat</td>
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<td>98:2</td>
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<td>20</td>
<td>CHCl$_3$</td>
<td>60</td>
<td>72</td>
<td>95:5</td>
<td>92</td>
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<tr>
<td>6</td>
<td>2</td>
<td>20</td>
<td>Methanol</td>
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<td>78</td>
<td>93:7</td>
<td>88</td>
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<tr>
<td>7</td>
<td>2</td>
<td>20</td>
<td>Dioxan</td>
<td>52</td>
<td>82</td>
<td>85:15</td>
<td>90</td>
</tr>
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</table>

$^a$All reactions were performed with nitrostyrene (1 mmol), cyclohexanone (5 mmol), solvent (0.5 mL) at room temperature

$^b$Isolated yields; $^c$Determined by $^1$H NMR of the crude product

$^d$Determined by chiral HPLC of the syn product.
Under these optimized conditions, Michael reaction of various nitroolefin substrates (21a-21h) with cyclohexanone 22, cyclopentanone and acetone as Michael acceptors were investigated to check the generality of this procedure. All the β-nitrostyrenes bearing electron donating aryl groups as well as electron withdrawing aryl groups were reacted smoothly with cyclohexanone to give corresponding Michael adducts in good yields with high diastereoselectivity and enantioselectivity.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nitro olefin</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
<th>dr (syn/anti)</th>
<th>ee (syn)</th>
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<tbody>
<tr>
<td>1</td>
<td>21a</td>
<td>26</td>
<td>23a</td>
<td>94</td>
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<td>91</td>
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<tr>
<td>3</td>
<td>21c</td>
<td>24</td>
<td>23c</td>
<td>92</td>
<td>99:1</td>
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<tr>
<td>4</td>
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<tr>
<td>5</td>
<td>21e</td>
<td>60</td>
<td>23e</td>
<td>90</td>
<td>93:7</td>
<td>79</td>
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</table>
In summary, we have developed a new type of carbohydrate based pyrrolidine organocatalyst for asymmetric Michael reaction of ketones to β-nitrostyrenes under solvent free condition without any additives. Michael adducts were formed in high yields and diastereoselectivity with good to moderate enantioselectivities.