SYNOPSIS

The thesis entitled "**Total synthesis of Achaetolide, Pectinolide-A, Pectinolide-H and asymmetric Michael reactions using carbohydrate-pyrrolidine based organocatalyst**" is divided into three chapters.

CHAPTER I	:	Chapter **I** describes the "Total synthesis of Achaetolide".
CHAPTER II	:	Chapter **II** is divided into two sections.
Section A	:	Describes the "Total synthesis of Pectinolide -A"
Section B	:	Describes the "Total synthesis of Pectinolide -H "
CHAPTER III	:	Chapter **III** describes the development of a new carbohydrate-pyrrolidine based organocatalyst for enantioselective Michael addition of carbonyls to nitroolefins.

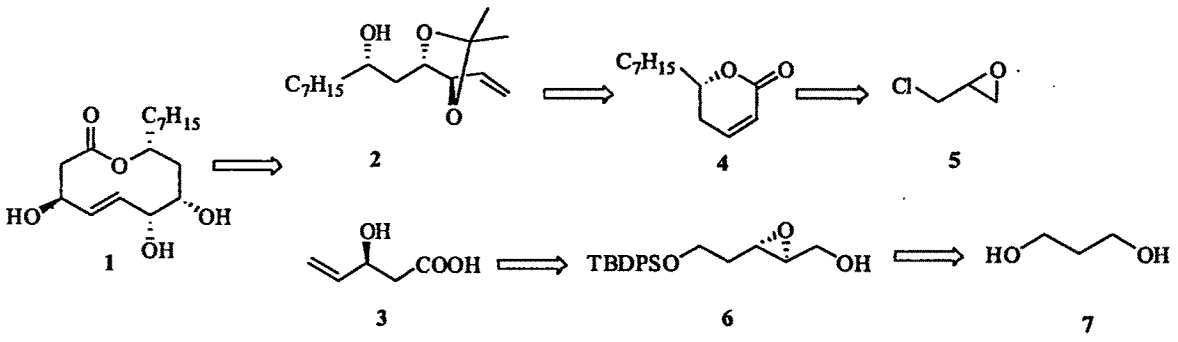
CHAPTER I

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 acylic 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)

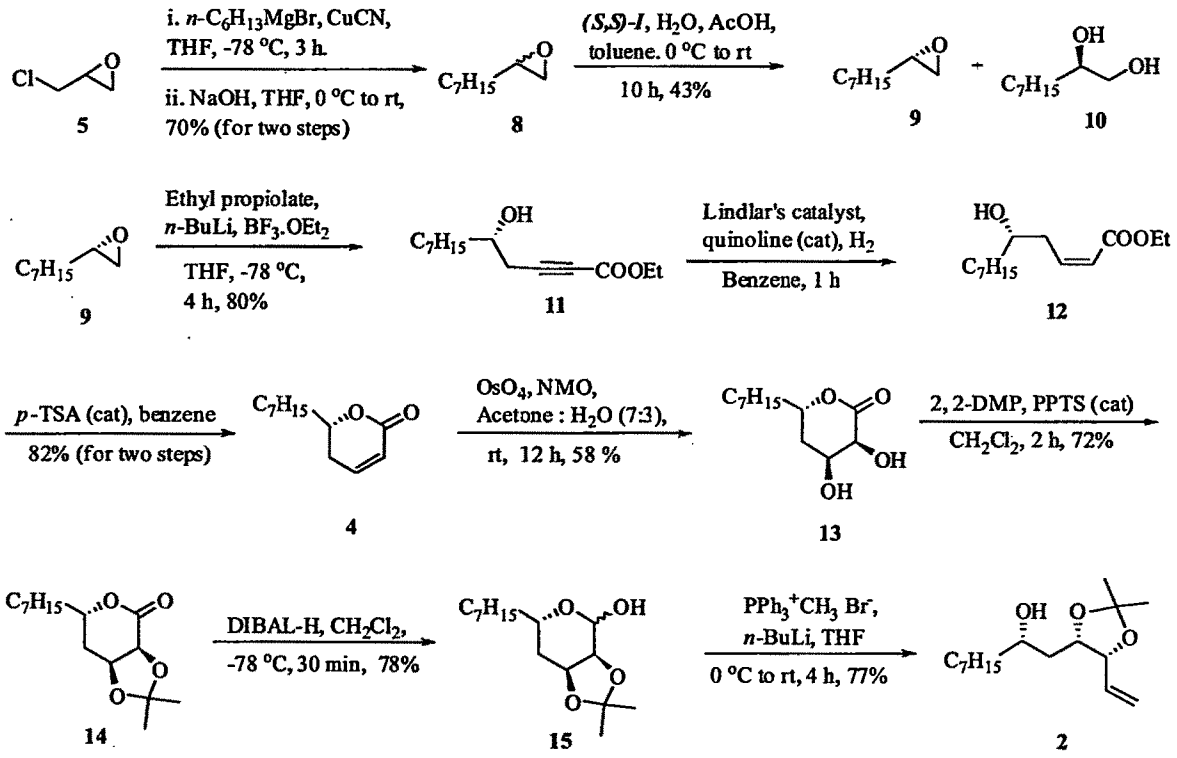


Scheme 1

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

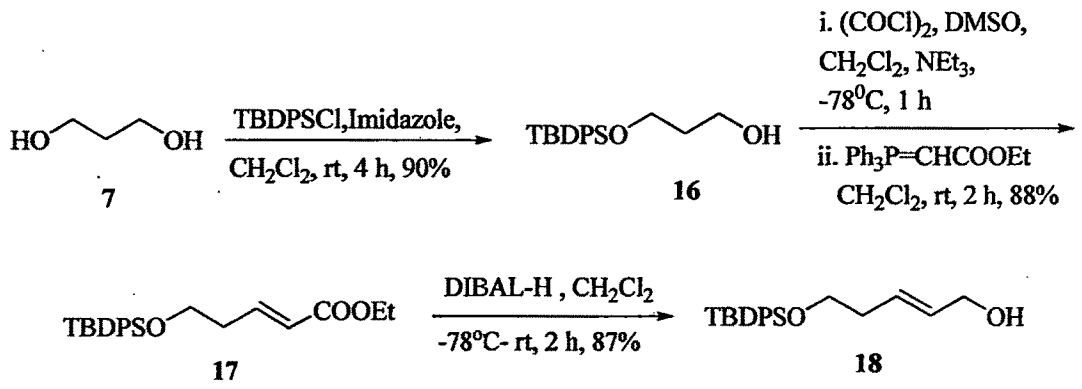
the homopropargylic alcohol **11** in 80% yield, which was then subjected to partial hydrogenation using Lindlar's catalyst [Pd-$CaCO_3$/Quinoline] to provide syn olefinic compound **12**. Exposure of **12** to catalytic *p*-TSA led to the formation of lactone **4**. Dihydroxylation of lactone **4** using OsO_4 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

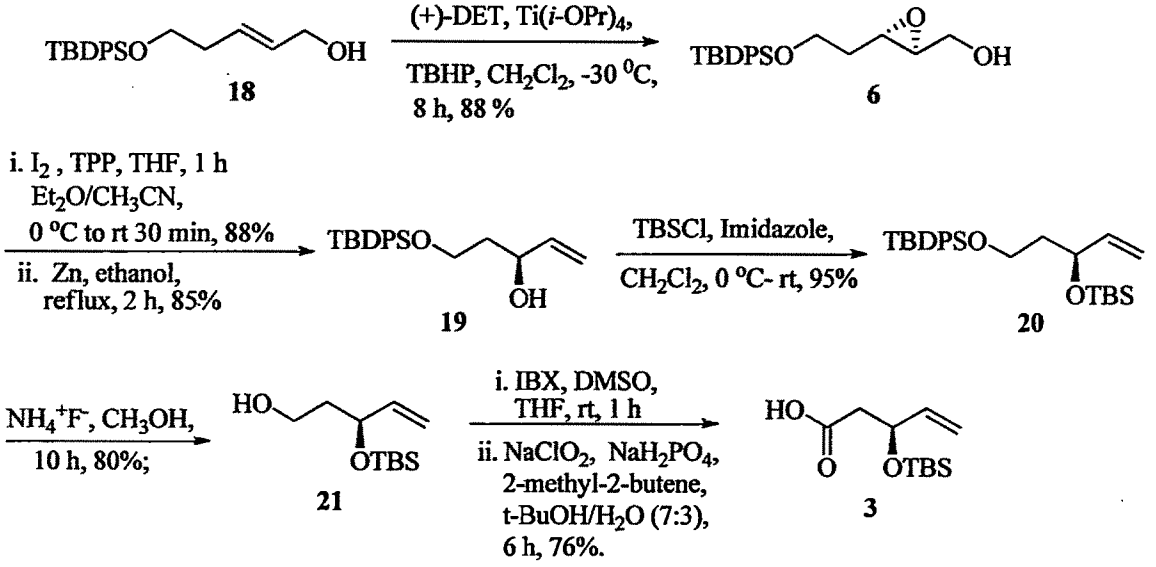
Synthesis of acid 3

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, [$COCl_2$, DMSO, NEt_3] at -78 °C, which was then subjected to Wittig reaction using Ph_3P=CHCOOEt to form two carbon homologated α,β-unsaturated ester **17** in 88% yield. The ester **17** was reduced to the allylic alcohol **18** using DIBAL-H in 87% yield (Scheme 3).



Scheme 3

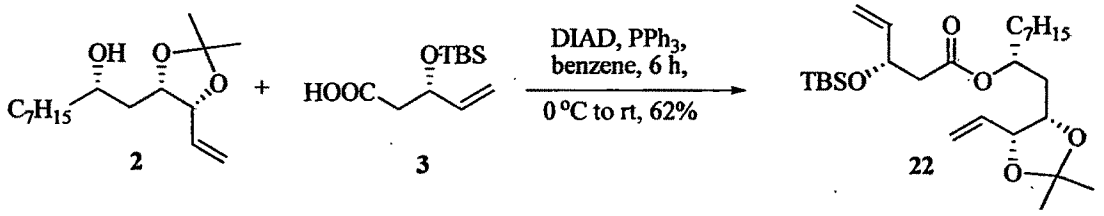
Sharpless asymmetric epoxidation of the allylic alcohol **18** using (+) DET, TBHP, $Ti(^iO\text{-}Pr)_4$ afforded the epoxy alcohol **6** in 88% yield. The epoxy alcohol **6** was converted into iodo compound using TPP, I_2 and imidazole, which on reductive elimination with activated Zn dust afforded 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 $NaClO_2$ and NaH_2PO_4 (Pinnick conditions) in 76% yield (Scheme 4).



Scheme 4

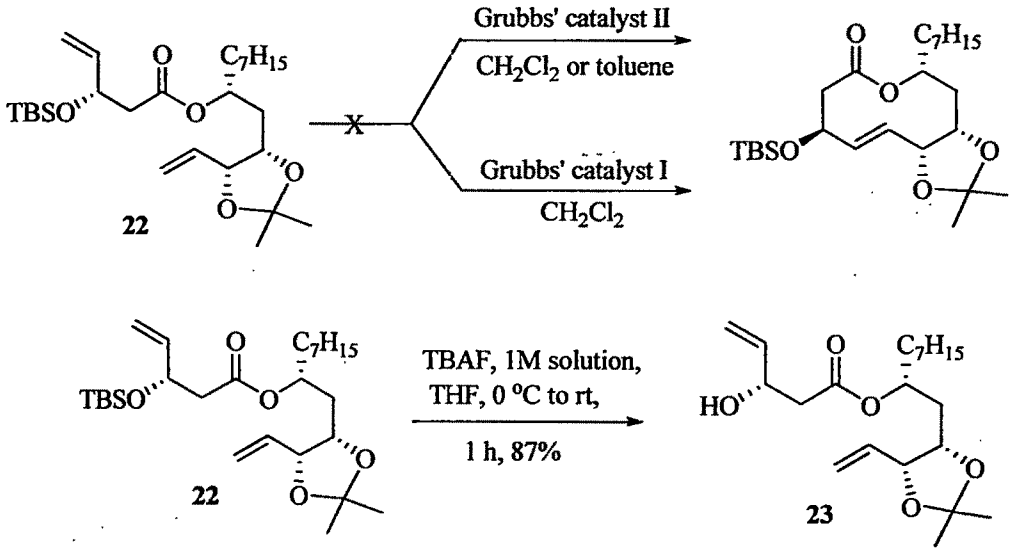
Coupling of the alcohol 2 and acid 3 fragments and completion of synthesis

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).



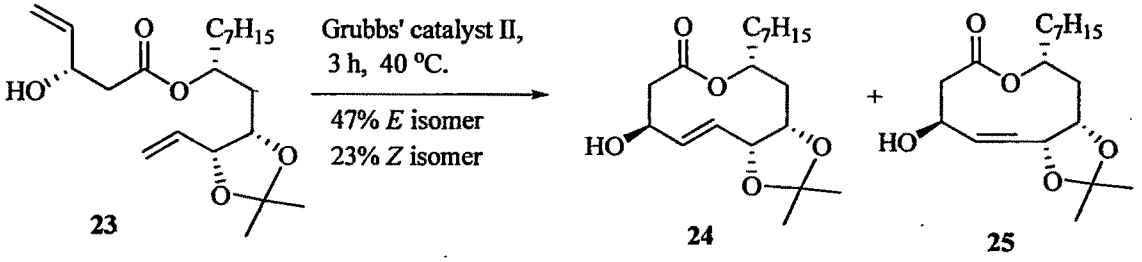
Scheme 5

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 macrolacatone. The TBS was deprotected using TBAF to give the diene **23** in 87% yield (Scheme 6).



Scheme 6

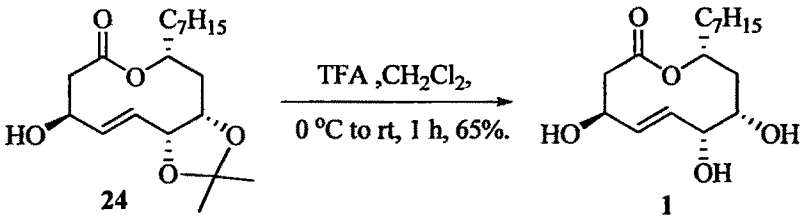
The diene **23** underwent the RCM reaction smoothly with Grubbs'-II catalyst, but a mixture of *E* isomer **24** and Z isomer **25** of the newly formed alkene unit were formed (Scheme 7)



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 CH_2Cl_2 afforded the achaetolide **1** in 65% yield as a white solid (Scheme 8). The

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.



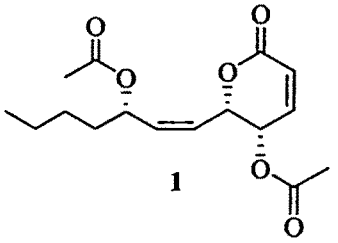
Scheme 8

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

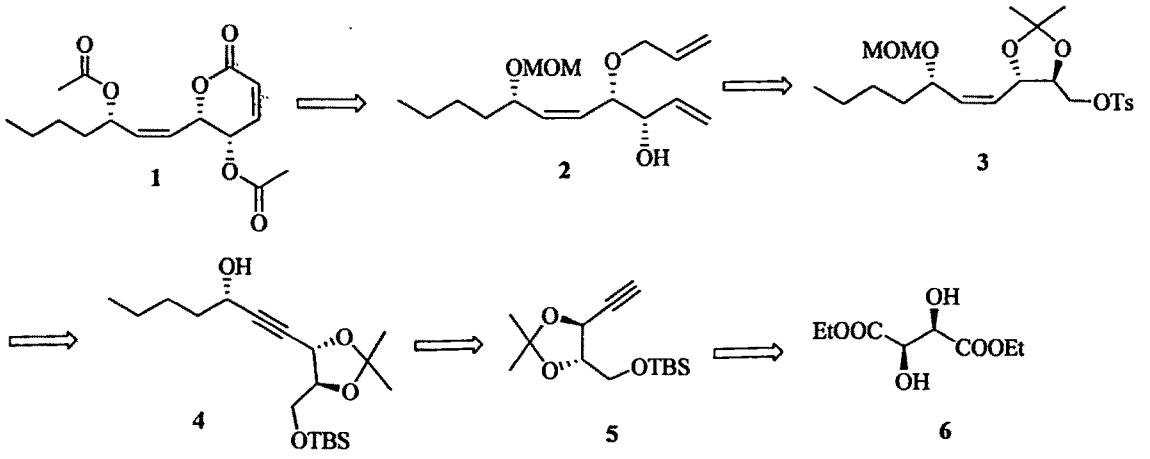
This section describes Total synthesis of Pectinolide-A

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-α-pyrone, it was isolated from this plant species along with other α-pyrones. Pectinolide-A showed anti-bacterial activity and exhibits cytotoxic properties against several tumor cell lines. As part of our efforts towards the synthesis of biologically active α-pyrones, we attempted a total synthesis of pectinolide-A.



Retrosynthetic analysis of Pectinolide-A

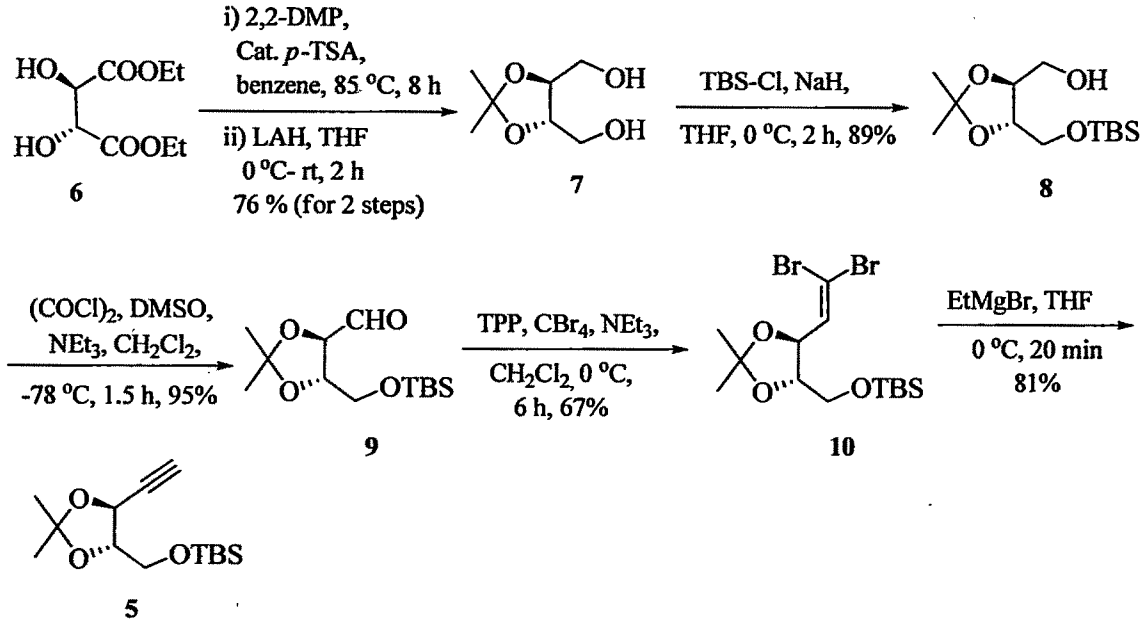
We envisaged to construct 5,6-dihydropyran-2-one ring of the pectinolide A through a ring closing metathesis of the triene **2**. The triene could be obtained from the tosyl intermediate **3** through an intramolecular substitution reaction to form an epoxide, allylation and one carbon homolgation of 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

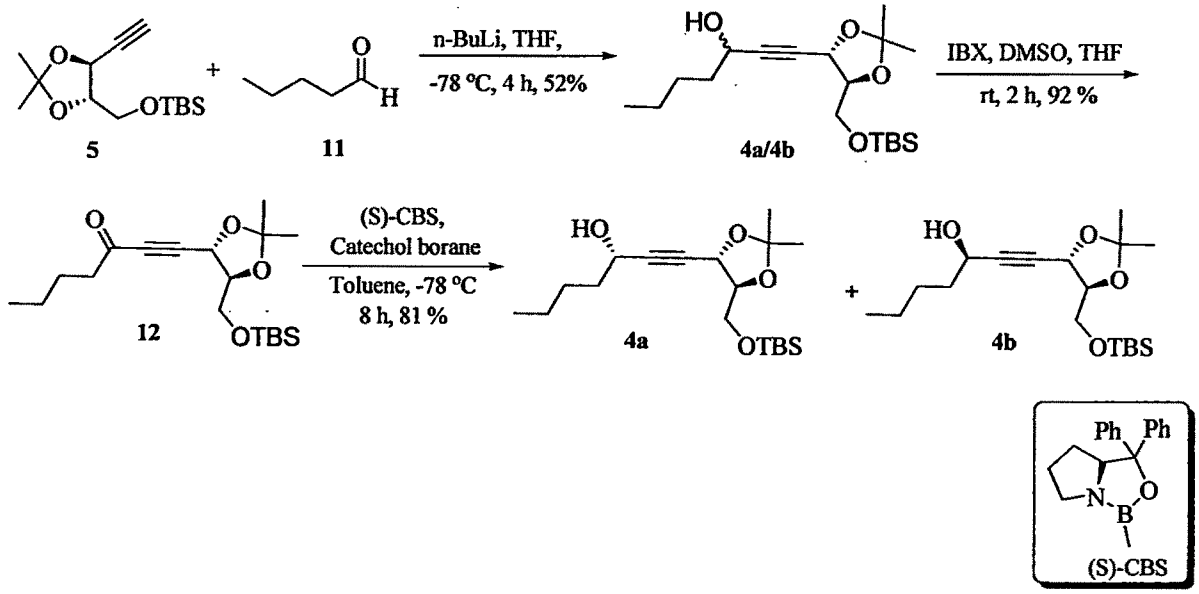
Our synthesis commenced from of cheaply available *L*-(+) diethyl tartrate **6**. The hydroxyl groups of the *L*-(+) DET were protected as its isopropylidene acetal using 2,2-dimethoxy propane with catalytic *p*-TSA. Reduction of the ester functionality using LAH afforded the diol **7** in 76% yield (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 CBr_4 and Ph_3P in CH_2Cl_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

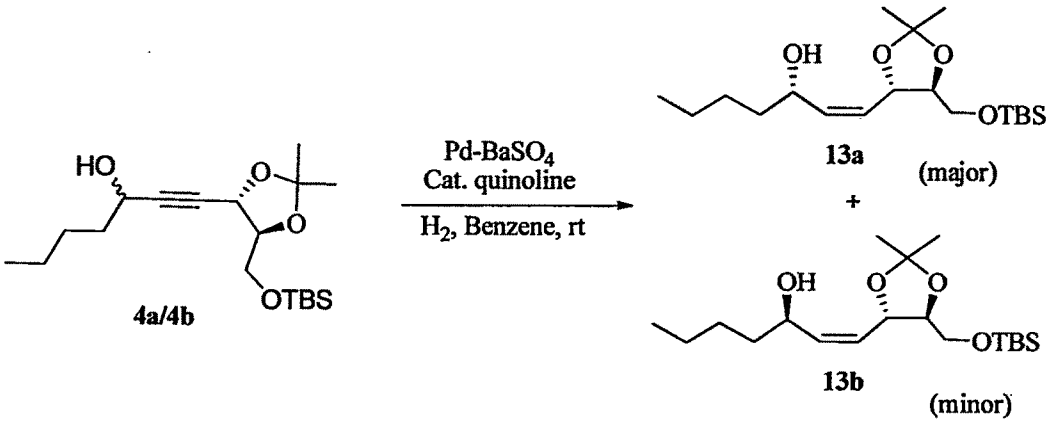
Synthesis of alkynol 4a

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 steroselective 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

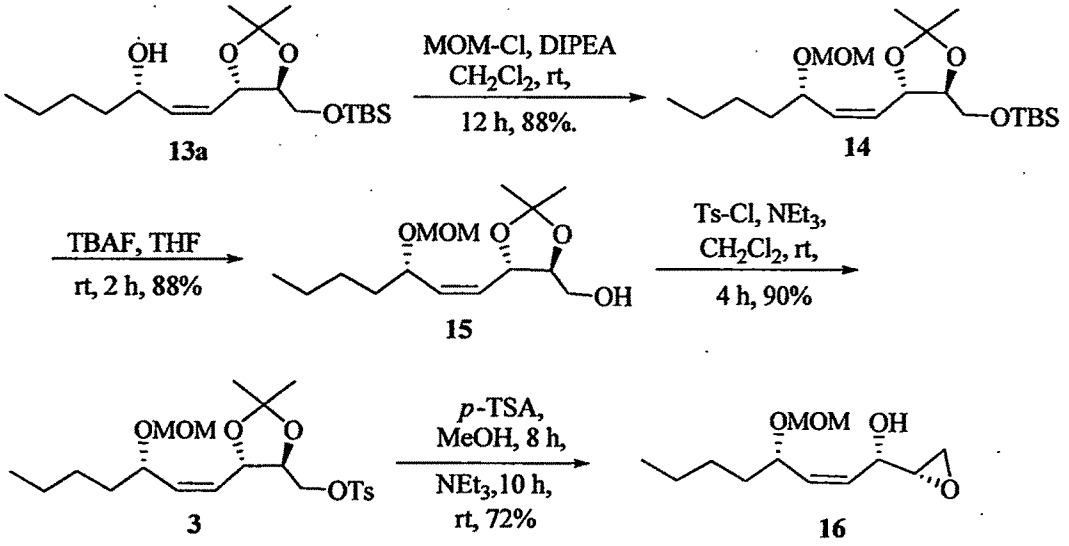
The propargylic alcohol mixture **4a/4b** was then subjected to *syn* reduction using Lindlar's catalyst and cat. quinoline under H_2 atmosphere to afford allylic alcohols **13a** and **13 b**, which were separated by column chromatography to give **13a** in 86% and **13b** in 10% yield (Scheme 4).



Scheme 4

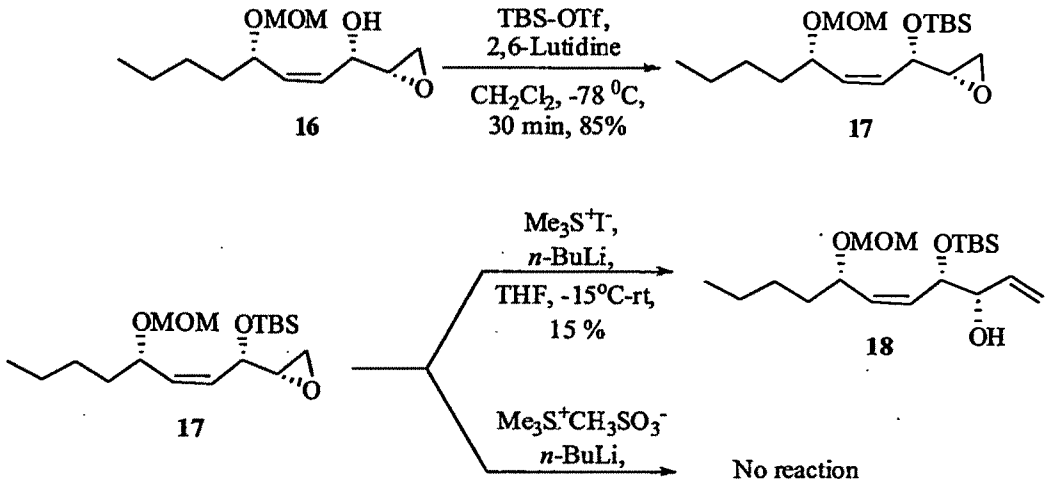
The allylic alcohol **13a** was protected as its MOM-ether using MOM-Cl/ DIPEA in CH_2Cl_2.in 88% yield, then the silyl group was deprotected using TBAF to give the primary

alcohol **15** in 88% yield. The primary alcohol **15** was tosylated 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).



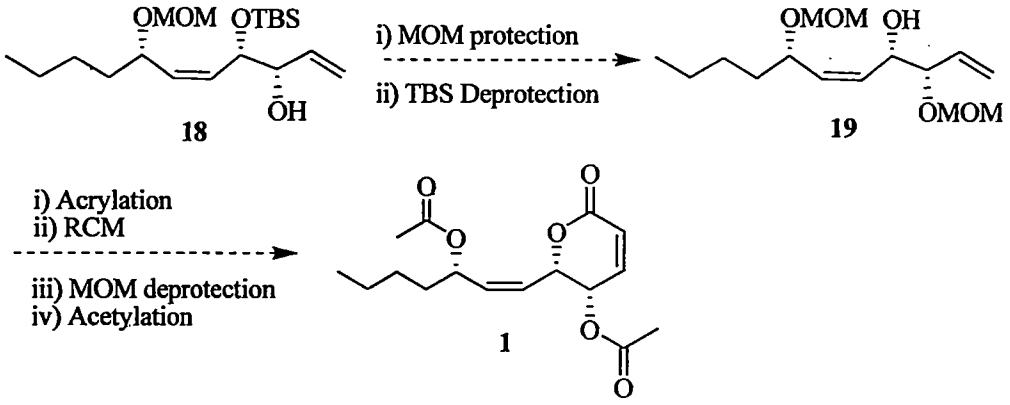
Scheme 5

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).



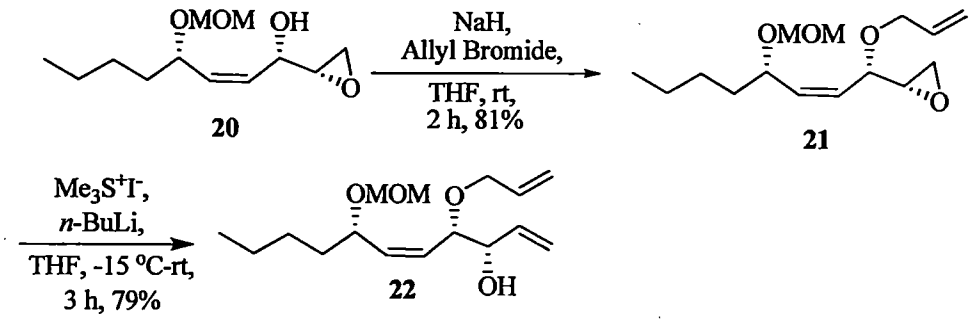
Scheme 6

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



Scheme 7

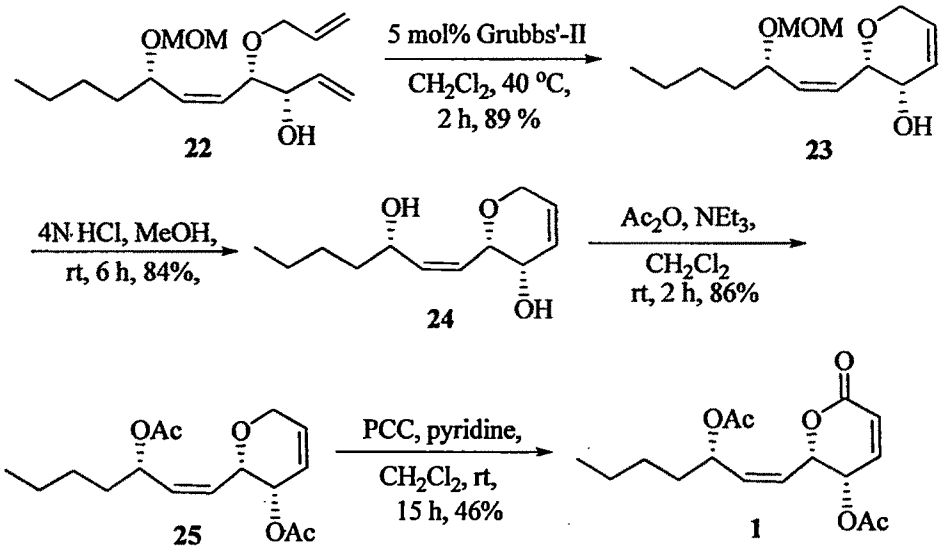
As allyl ether can be converted to the acryl group on oxidation. The hydroxyl group was protected as its allyl ether **21** using allyl bromide/NaH in 81% yield. The epoxide **21** when exposed to trimethylsulfonium ylide, it smoothly underwent one carbon homologation to afford the triene **22** in 79%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



Scheme 8

Completion of synthesis

The triene **22** was subjected to undergo ring closing metathesis using 5 mol% of Grubbs'-II catalyst in anhydrous CH_2Cl_2, 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 NEt_3 in CH_2Cl_2 to afford compound **25** in 86% yield. Oxidation of the acetylated dihydropyran **25** using PCC/pyridine in CH_2Cl_2 at refluxing temperature afforded pectinolide-A **1** in 46% yield (Scheme 9).



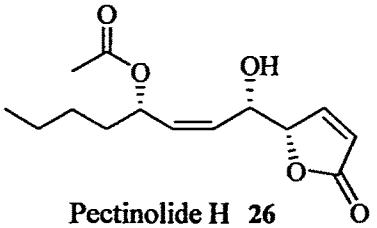
Scheme 9

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 **1** has been achieved using RCM reaction of allylic ether which acts a masked acrylic ester moiety and stereoselctive reduction of *α,β*-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.

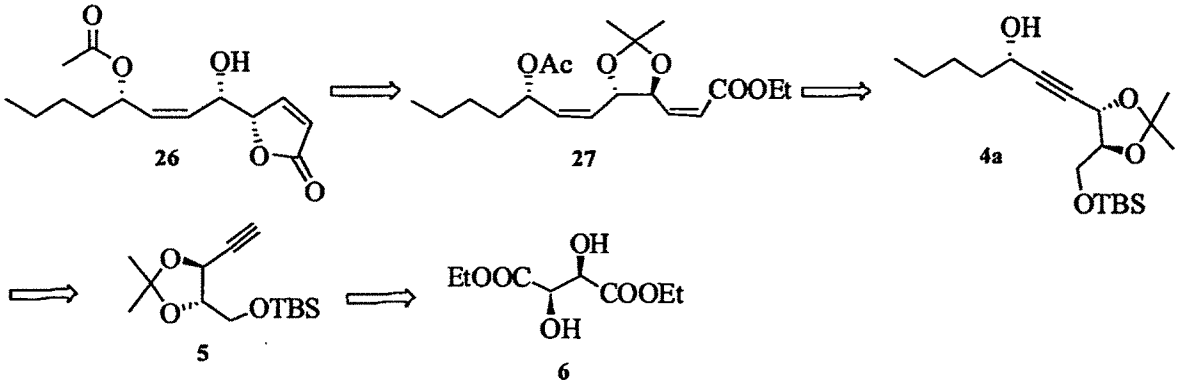


Pectinolide H **26**

Retrosynthetic analysis

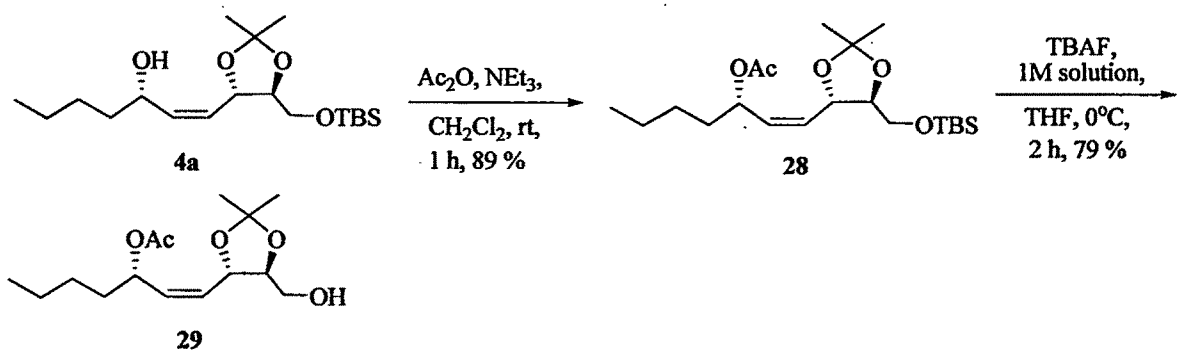
Being structurally related to pectinolide A, we devised a strategy to synthesize pectinolide H from **4a**, an intermediate used for the synthesis of pectinolide A. Pectinolide H **26** could be obtained by the concomitant deprotection of the isopropylidene acetal and

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.**



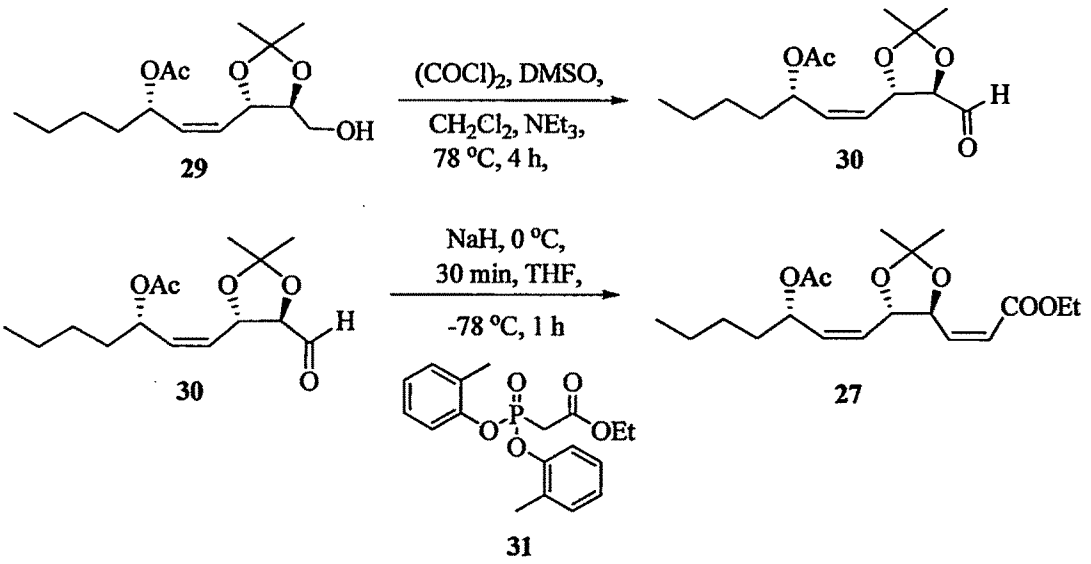
Scheme 11

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, NEt_3 in CH_2Cl_2 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)



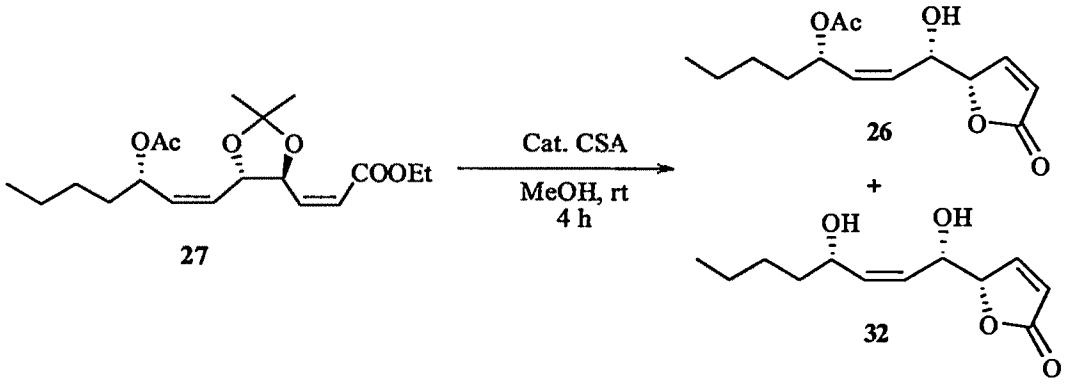
Scheme 12

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(*o*-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 cycliczation 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.



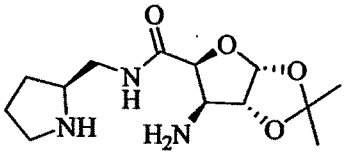
Scheme 14

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 concominant deprotection and lactionazation 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.



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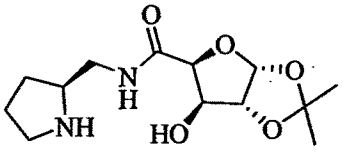
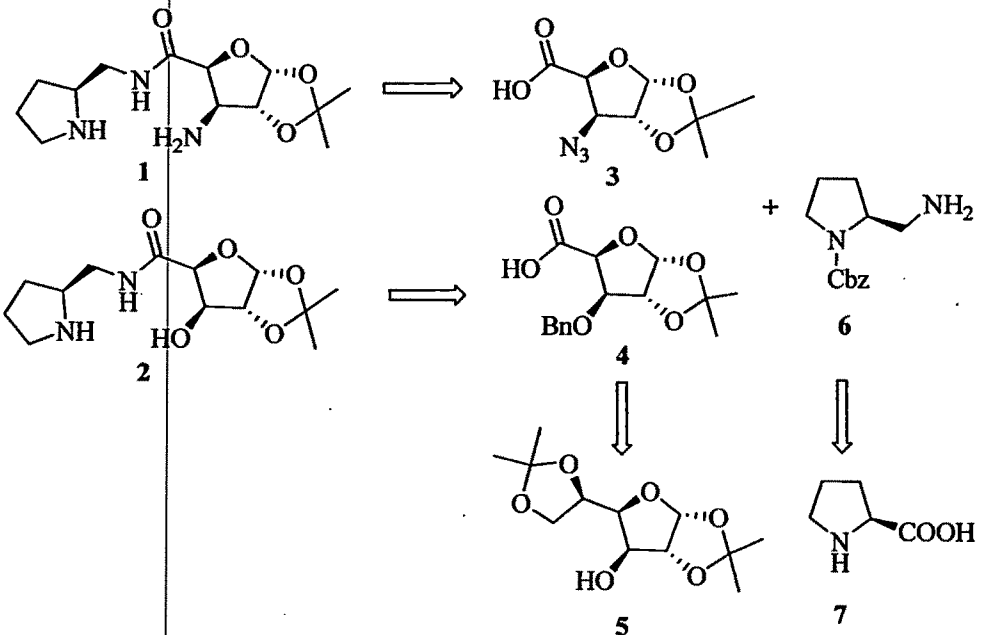


2

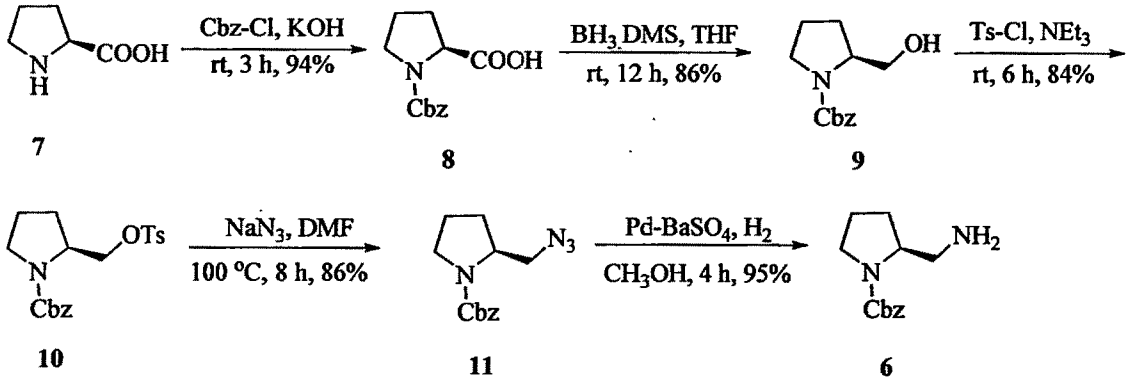
Retrosynthetic analysis

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.



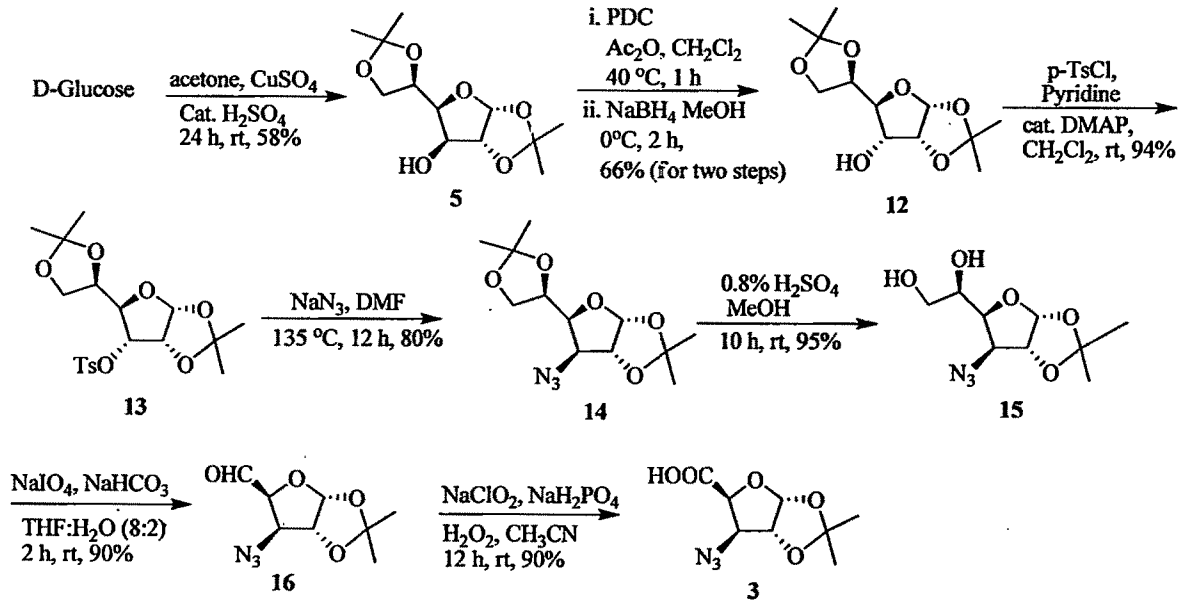
Scheme 1

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 sufide 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-$BaSO_4$ (poisoned with lead) in methanol under hydrogen atmosphere (Scheme 2)



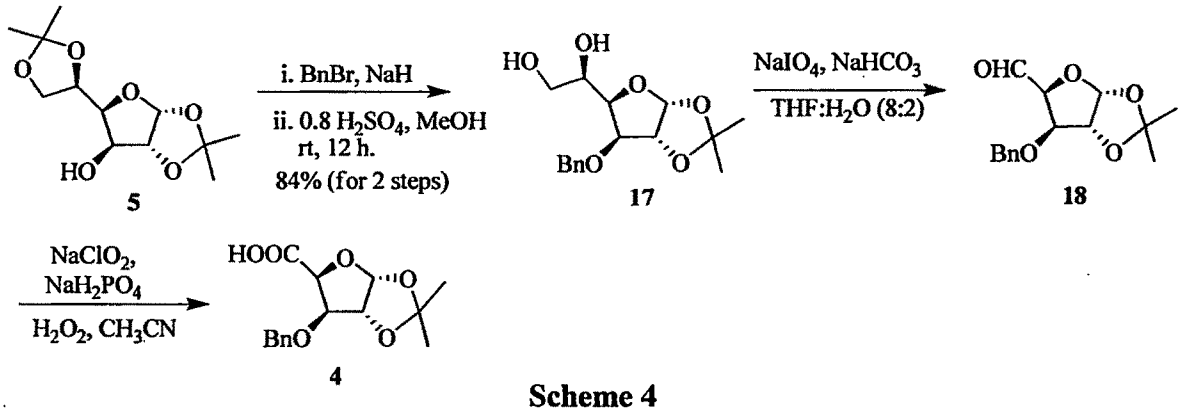
Scheme 2

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



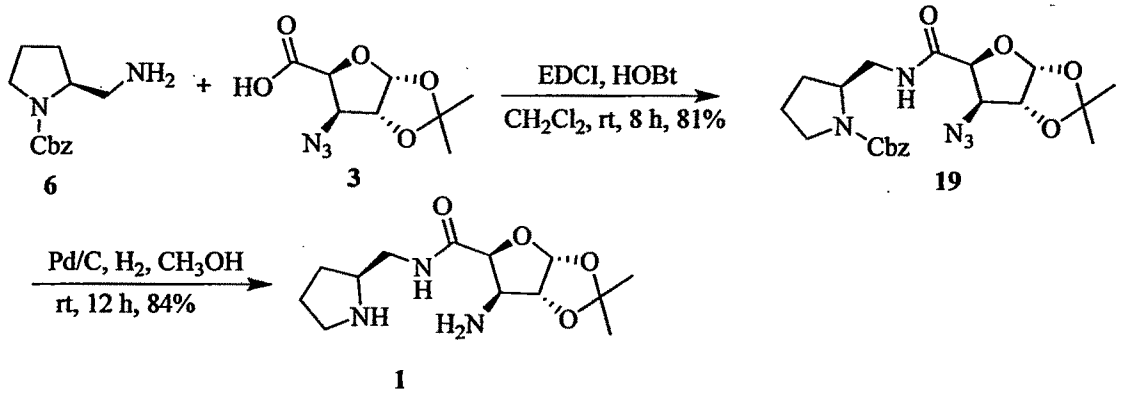
Scheme 3

Benzyl protected β-hydroxy-acid was obtained from D-glucose as shown in scheme 4



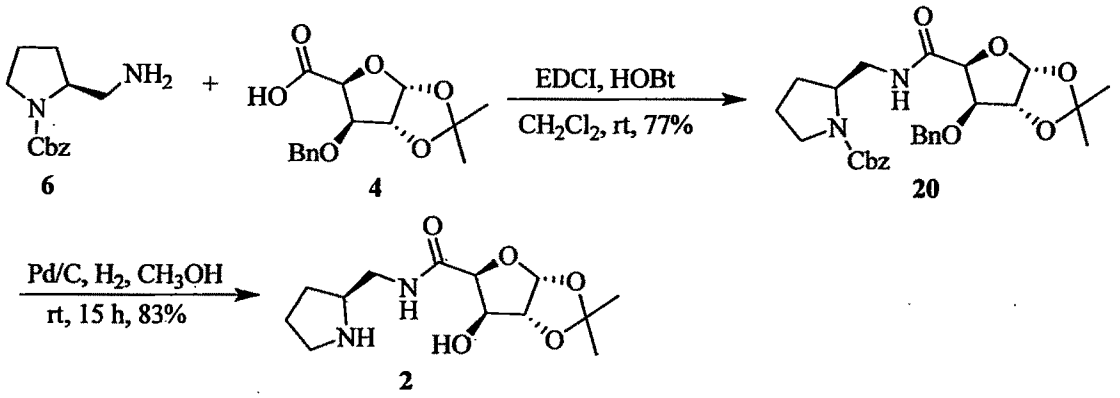
Scheme 4

Amine **6** and acid **3** were coupled using EDC.HCl and HOBt to afford the amide **19** in 81% yield. Deprotection of –NCbz 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)



Scheme-5

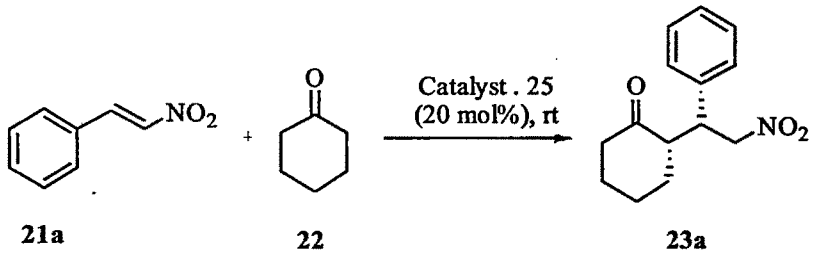
Coupling of the amine **6** and acid **4** using EDC.HCl and HOBt gave the amide **20** in 77% yield. Both the -OBn and -NCbz protecting groups were removed by hydrogenation using Pd/C as catalyst in methanol to afford the catalyst **2** (Scheme 6).



Scheme 6

Evaluation of catalyst

With both the catalysts **1** and **2** in hand, we tested their efficiency in asymmetric Michael addition reaction of *β*-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.



21a **22** **23a**

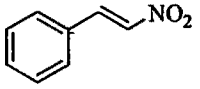
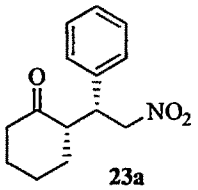
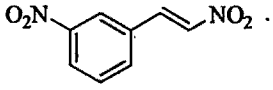
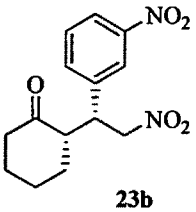
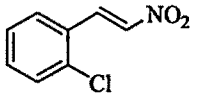
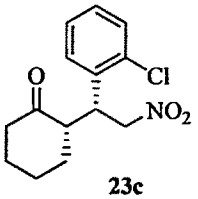
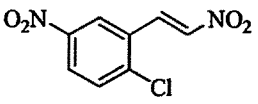
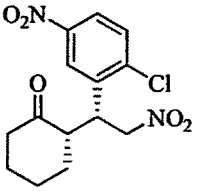
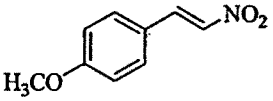
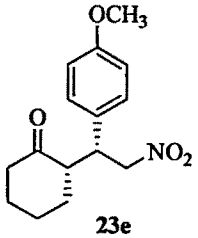
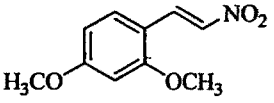
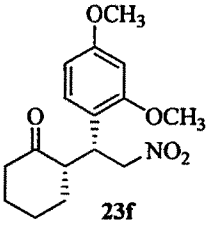
Scheme 7

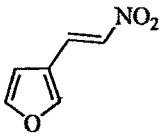
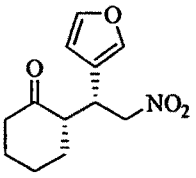
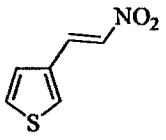
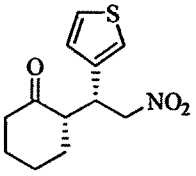
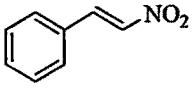
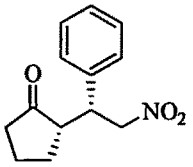
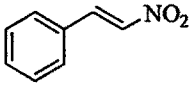
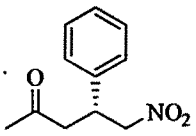
Table 1: Screening of catalyst and solvent. [a]

Entry	Catalyst	mol%	Solvent	Time (h)	Yield (%)[b]	dr (syn/anti)[c]	ee (syn)[d]
1	1	10	neat	36	85	90:10	18
2	2	10	neat	36	88	92:8	66
3	2	20	neat	26	94	98:2	91
4	2	20	THF	60	85	92:8	86
5	2	20	$CHCl_3$	60	72	95:5	92
6	2	20	Methanol	56	78	93:7	88
7	2	20	Dioxan	52	82	85:15	90

[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*-nitro styrenes 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

Entry	Nitro olefin	Time (h)	Product	Yield (%)[a]	dr (syn/anti)[b]	ee (syn)[c]
1	 **21a**	26	 **23a**	94	98:2	91
2	 **21b**	24	 **23b**	95	96:4	89
3	 **21c**	24	 **23c**	92	99:1	87
4	 **21d**	48	 **23d**	88	93:7	68
5	 **21e**	60	 **23e**	90	93:7	79
6	 **21f**	60	 **23f**	96	94:6	79

7	 **21g**	28	 **23g**	85	97:3	93
8	 **21h**	24	 **23h**	92	97:3	85
9	 **21a**	48	 **23i**	86	92:8	79
10	 **21a**	56	 **23j**	62	-	57

[a]Isolated yields.
[b] Determined by ^{1}H NMR and HPLC analysis.
[c]Determined by chiral HPLC using chiral pak-IA, IC

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.