CHAPTER I

Stereoselective Formal Synthesis of (+)- and (–)-Cyclophellitol, (–)-Conduritol-B and Stereoselective Synthesis of (–)-Conduramine-B Derivative

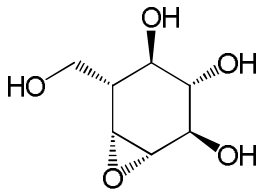
This chapter deals with a brief account of the synthesis of Cyclophellitol, Conduritol-B, Conduramine-B reported by the various research groups and an elaborate account of the present work on the stereoselective formal synthesis of (+)- and (–)-Cyclophellitol, (–)-Conduritol-B in section A and stereoselective synthesis of (–)-Conduramine-B derivative in section B.

Section-A

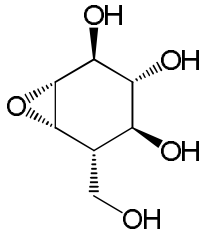
Stereoselective Formal Synthesis of (+)- and (–)-Cyclophellitol, (–)-Conduritol-B

(+)-Cyclophellitol (**1**, **Figure 1**) was isolated in 1990 from the mushroom *Phellinus sp.* and shown to possess potent β-glucosidase inhibitory activity and activity against HIV. Glycosidase inhibitors, in addition to providing insight into glycoprotein processing also find applications in immunology, diabetes, virology and cancer. It is a carbocyclic analogue of D-glucopyranose with an epoxide ring. The inhibition of β-glucosidase is irreversible, which is presumably due to protonation and ring opening of the epoxide by a carboxylate in the active site of the enzyme. Conduritols (5-cyclohexene-1,2,3,4-tetrols) are precursors for the synthesis of cyclitols, pseudosugars and conduritol derivatives have interesting biological activities.

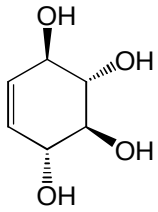
Figure 1: Structures of (+)- and (–)-Cyclophellitol and (–)-Conduritol-B



(+)-Cyclophellitol 1



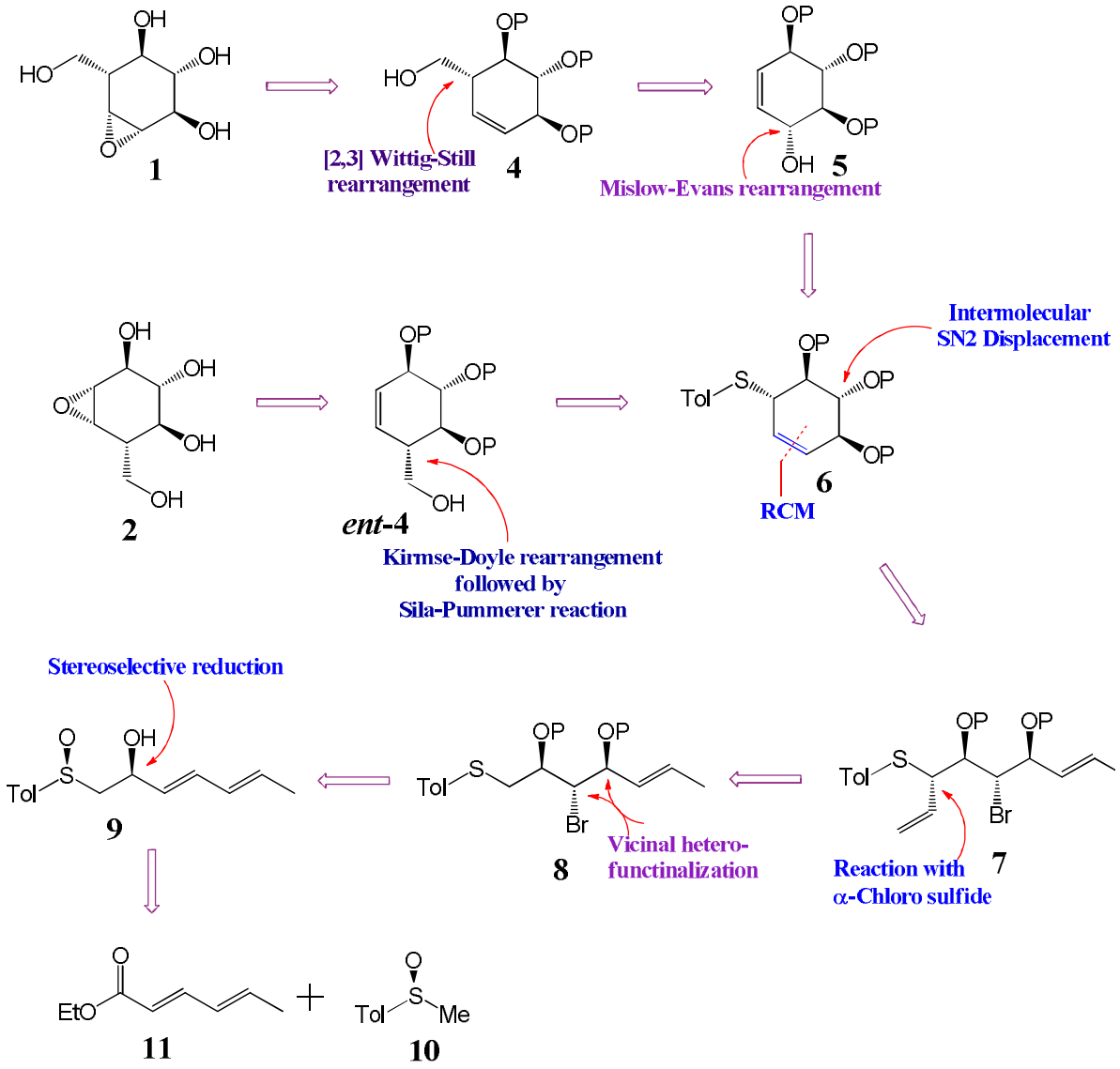
(–)-Cyclophellitol 2



(–)-Conduritol-B 3

Cyclophellitol has stimulated a great deal of attention due to their biological activity and low natural abundance.

Scheme-1: Retrosynthetic disconnection of (+)- and (–)-cyclophellitol

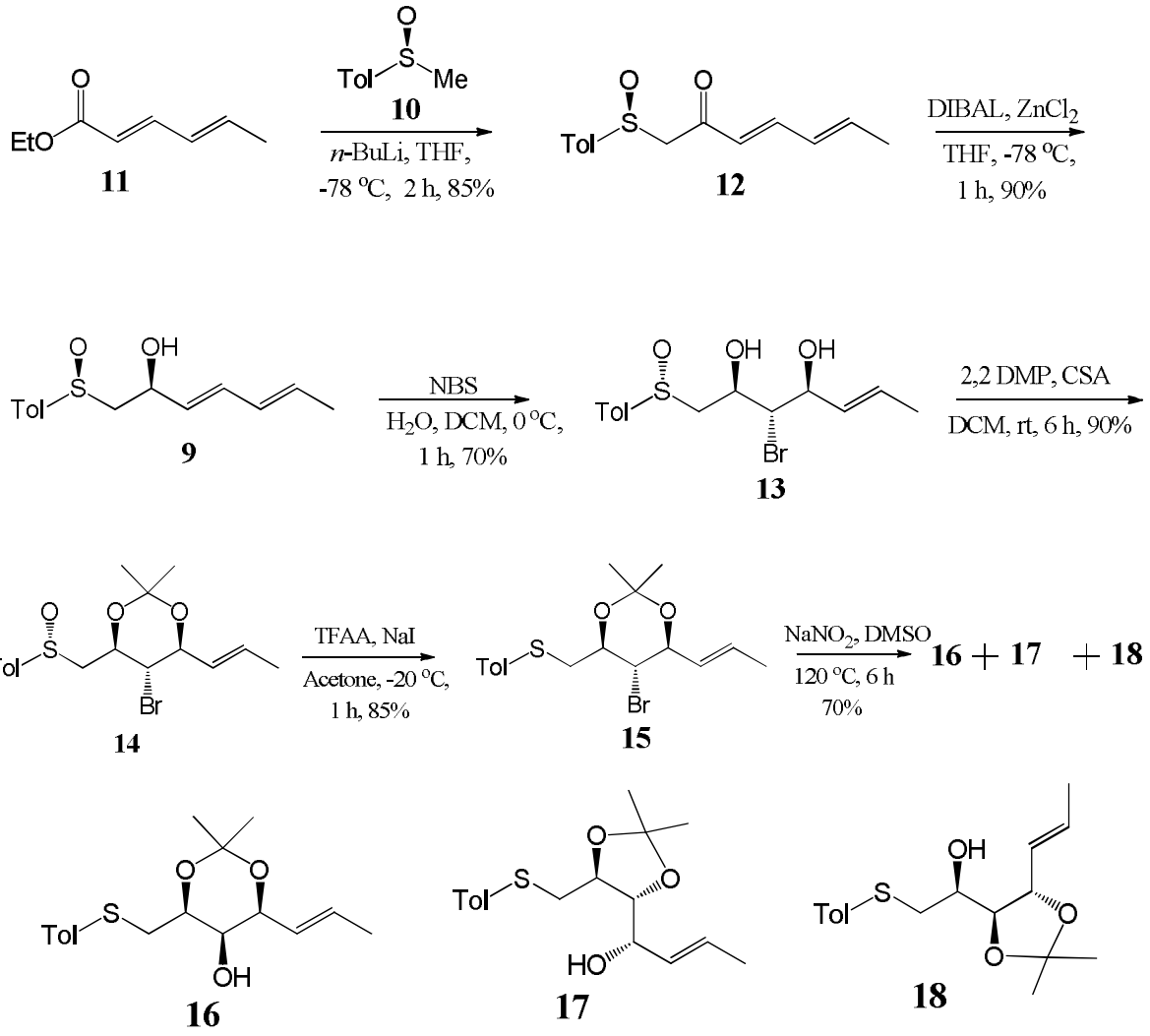


The retrosynthetic analysis of (+)- and (–)-Cyclophellitol is depicted in Scheme-1. (+)-Cyclophellitol **1**, was envisaged to obtain by a hydroxyl-directed epoxidation of a protected homoallylic alcohol **4**, which would result from a [2,3] Wittig-Still rearrangement of protected conduritol-B derivative **5**. Enantiomerically enriched conduritol-B derivative **5** was envisaged to be obtained by Mislow-Evans rearrangement of the allylic sulfide **6.** As depicted (–)-Cyclophellitol **2**, would be available through a hydroxyl-directed epoxidation of a protected homoallylic alcohol ***ent*-4**, which would result from a Kirmse-Doyle rearrangement from sulfide **6** followed by sila-Pummerer reaction and reduction of the ensuing aldehyde. Sulfide **6**

can be obtained by the metathesis of the diene **7** which in turn can be obtained from α-chloro sulfide derived from sulfide **8**. Compound **8** can in turn be obtained from the diene sulfoxide **9** which can be traced to sulfoxide **10** and commercially available ethyl sorbate **11**.

The synthesis began with the addition of the lithiated anion of **10**, obtained by the reaction of LDA with (–)-(*S*)-methyl *p*-tolyl sulfoxide **10** at –78 °C, to commercially available ethyl sorbate **11**, which afforded the ketosulfoxide **12** in 85% yield. (–)- (*S*)-Methyl *p*-tolyl sulfoxide **10** was prepared according to Jackson's protocol. The carbonyl group in **12** was stereoselectively reduced using Dibal-H / $ZnCl_2$ system to furnish alcohol **9** with excellent diasteroselectivity (de>99%) in multigram quantities.

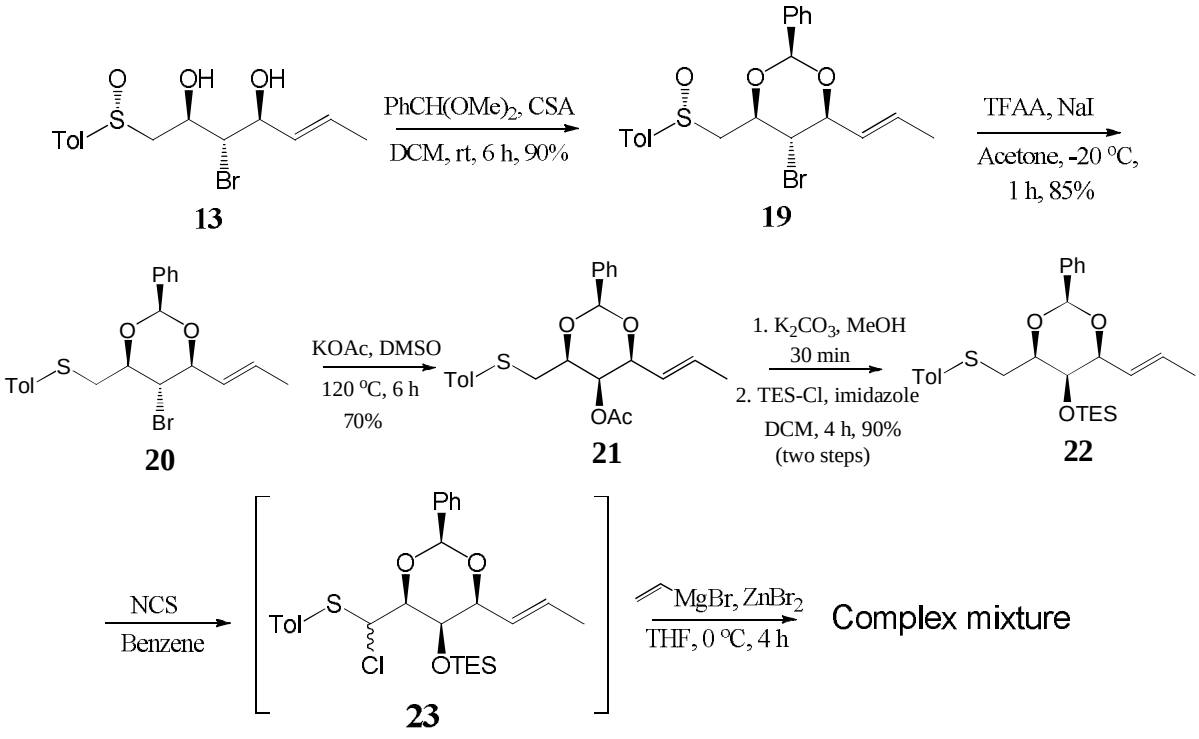
Scheme-2: Synthesis of triol derivative **16**



The alcohol **9** on subjecting to reaction with freshly recrystallized *N*-bromosuccinimide furnished the bromohydrin **13,** as the sole product regio- and stereoselectively. The hydroxyl groups in bromohydrin **13** were protected as the acetonide **14** by reaction with 2,2-dimethoxypropane. The sulfinyl group in compound **14** was reduced using sodium iodide and trifluoroacetic anhydride in acetone at -20 ^{o}C to afford the corresponding sulfide **15**. The next objective was to introduce the oxygen functionality by intermolecular displacement of bromide by an oxygen nucleophile. Toward this end sulfide **15** was reacted with $NaNO_2$ in DMSO at 120 ^{o}C to afford a mixture of compounds **16**, **17** and **18** by the displacement of bromide followed by isomerization of the acetonide group (Scheme 2).

Since 1,3-benzylidene is preferred to a 1,2-benzylidene derivative. The 1,3 diol **13** was protected as the benzylidene **19** by treatment with benzaldehyde dimethyl acetal. The compound **19** was then reduced using sodium iodide and trifluoroacetic anhydride in acetone at -20 ^{o}C to afford the corresponding sulfide **20** which was then subjected to displacement reaction by using KOAc in DMSO at 120 ^{o}C to obtain corresponding acetate compound **21** which was hydrolyzed with K_2CO_3 / MeOH. The hydroxyl group was protected as the triethyl silyl ether **22.**

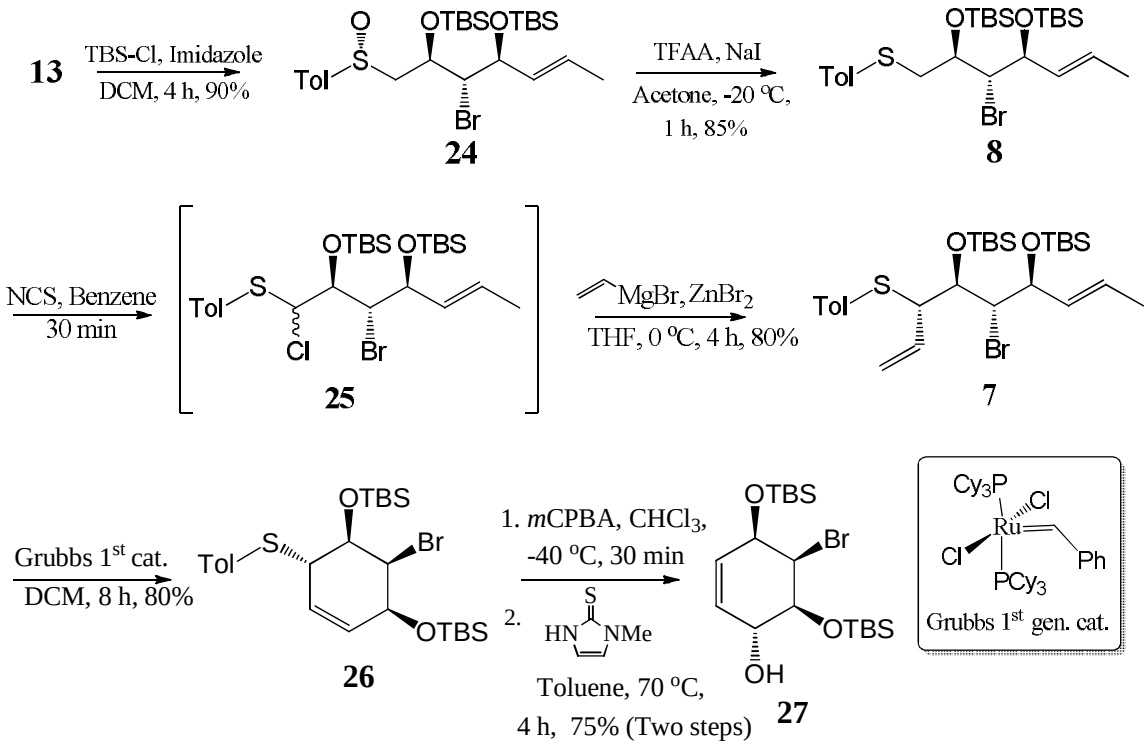
Scheme-3:



Treatment of sulfide **22** with *N*-chlorosuccinimide furnished the α-chloro sulfide **23**, which without isolation was reacted with vinylzinc bromide. Unfortunately, in this reaction a complex mixture of products was obtained. Being unsuccessful in forming the C–C bond with the α–chlorosulfide generated from **22**, attempts were made on substrates with different protecting groups on hydroxyl group. (Scheme 3).

Exploring alternatives, α-chloro sulfide generated from bromo acetal **20** was reacted with vinylzinc bromide only to obtain a complex mixture of products. Next the hydroxy groups in bromohydrin **13** were protected as their *tert*-butyldimethylsilyl ether **24**, which was then reduced using sodium iodide and trifluoroacetic anhydride in acetone at -20 °C to afford the corresponding thiol ether **8,** in 85% yield. Treatment of **8** with *N*-chlorosuccinimide furnished the α-chloro sulfide **25**, which without isolation was reacted with vinylzinc bromide to yield diene sulfide **7** (P = TBS) as the sole product. Ring-closing metathesis of **7** using Grubbs' first generation catalyst afforded allylic sulfide **26**.

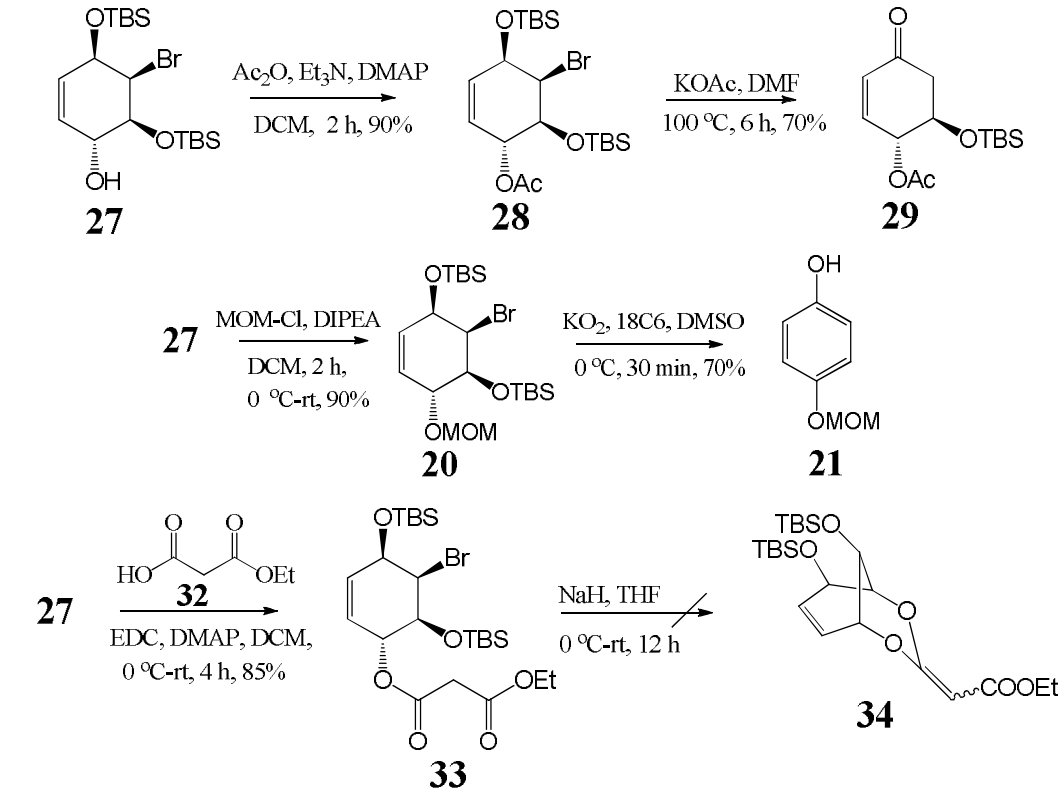
Scheme-4: Synthesis of bromotriol derivative **27**



The synthetic sequence called for the nucleophilic displacement of bromide in **26** by a suitable oxygen nucleophile and conversion of the sulfide to a carbinol. Toward this end, compound **26** was subjected to oxidation with *m*-CPBA to furnish a diastereomeric mixture of sulfoxides, which without isolation on warming in toluene in the presence of a thiophile, underwent Mislow-Evans rearrangement to furnish the bromotriol derivative **27** (Scheme 4).

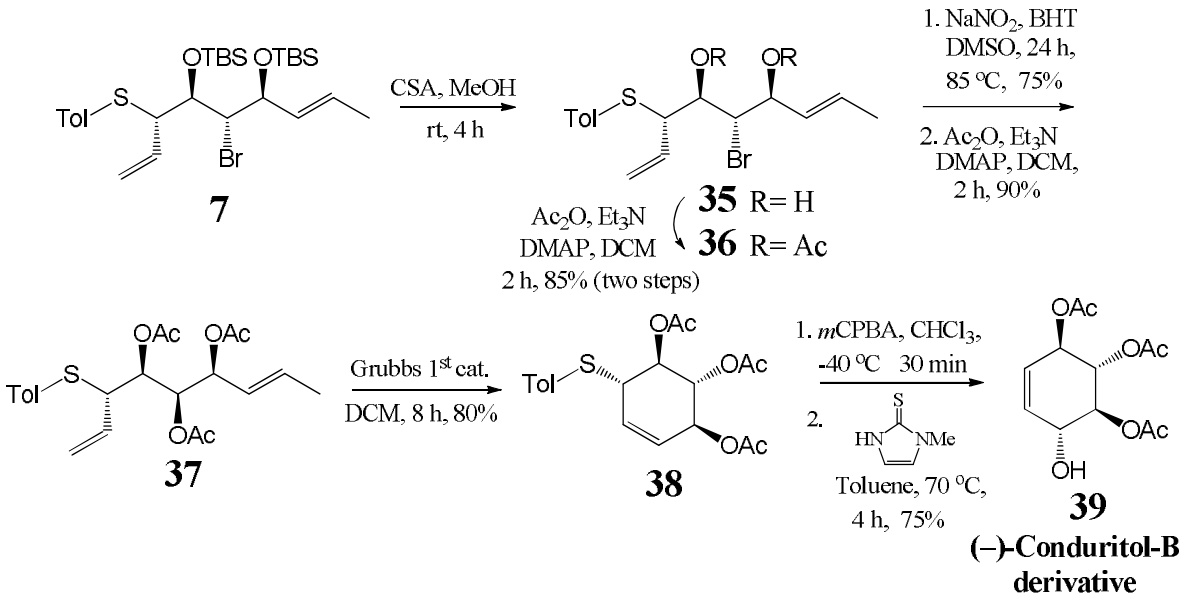
The compound **27** in hand, S_N2 displacement of bromide would provide (–)-conduritol B derivative. Toward this end, the hydroxyl group in **27** was protected as its acetate **28** and was further subjected to reaction with potassium acetate as the oxygen nucleophile in DMF at 100 °C. Unfortunately, instead of the desired tetrol derivative, the unsaturated ketone **29** was only obtained. In another trial, the MOM-ether **30**, prepared from alcohol **27**, on reaction with potassium superoxide in DMSO furnished the hydroquinone derivative **31**. In yet another experiment an intramolecular displacement of bromide by the anion derived from the malonate derivative **33** which was prepared from the compound **27** by coupling with mono ethyl malonate **32**, was attempted only to recover unreacted starting material (Scheme 5).

Scheme-5:



Having been unsuccessful in preparing conduritol-B derivative by nucleophilic displacement on a cyclic compound, the same was attempted on the acyclic sulfide **7**. Reaction of **7** with an excess of potassium acetate / sodium nitrite in DMF or DMSO at 80-120 ^{o}C for extended periods of time led to only recovered starting materials. Assuming steric hindrance of the silyl groups to be the cause for the failure, the silyl groups were deprotected in compound **7** under acidic conditions to furnish the bromodiol **35**. Acetylation furnished the diacetate **36**, which on reaction with an excess of sodium nitrite in the presence of BHT furnished a mixture of diacetates as a consequence of migration. The crude reaction mixture was therefore subjected to acetylation to yield the triacetate **37**. Ring-closing metathesis with grubbs first generation catalyst furnished the allylic sulfide **38**. Oxidation of sulfide with *m*CPBA yielded an epimeric mixture of sulfoxides followed by warming in toluene in the presence of 2-mercapto-1-methyl imidazole yielded (–)-conduritol-B derivative **39** via Mislow-Evans rearrangement **(**Scheme 6).

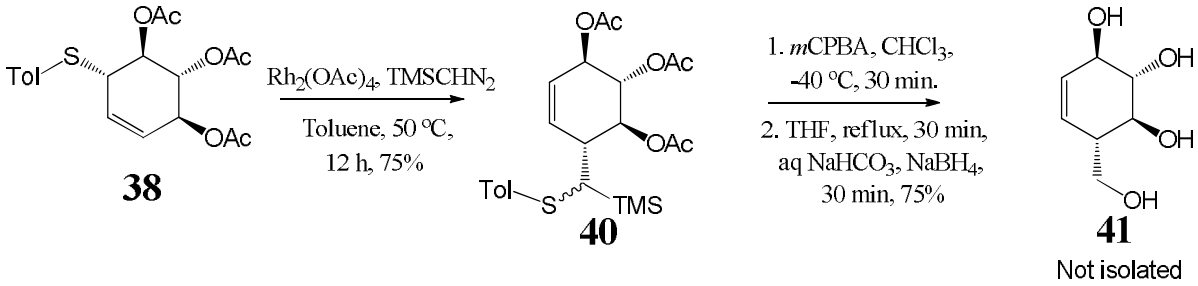
Scheme-6: Synthesis of (–)-conduritol-B derivative **39**



The synthesis of (–)-cyclophellitol **2** was envisioned by a Kirmse-Doyle rearrangement of the ylid obtained by the reaction of **38** with trimethylsilyl diazomethane. Indeed, the reaction proceeded cleanly in the presence of $Rh_2(OAc)_4$ and excess TMS-diazomethane to yield an epimeric mixture of sulfides **40**. Oxidation of sulfide with *m*-CPBA and warming the reaction mixture resulted in the sila-

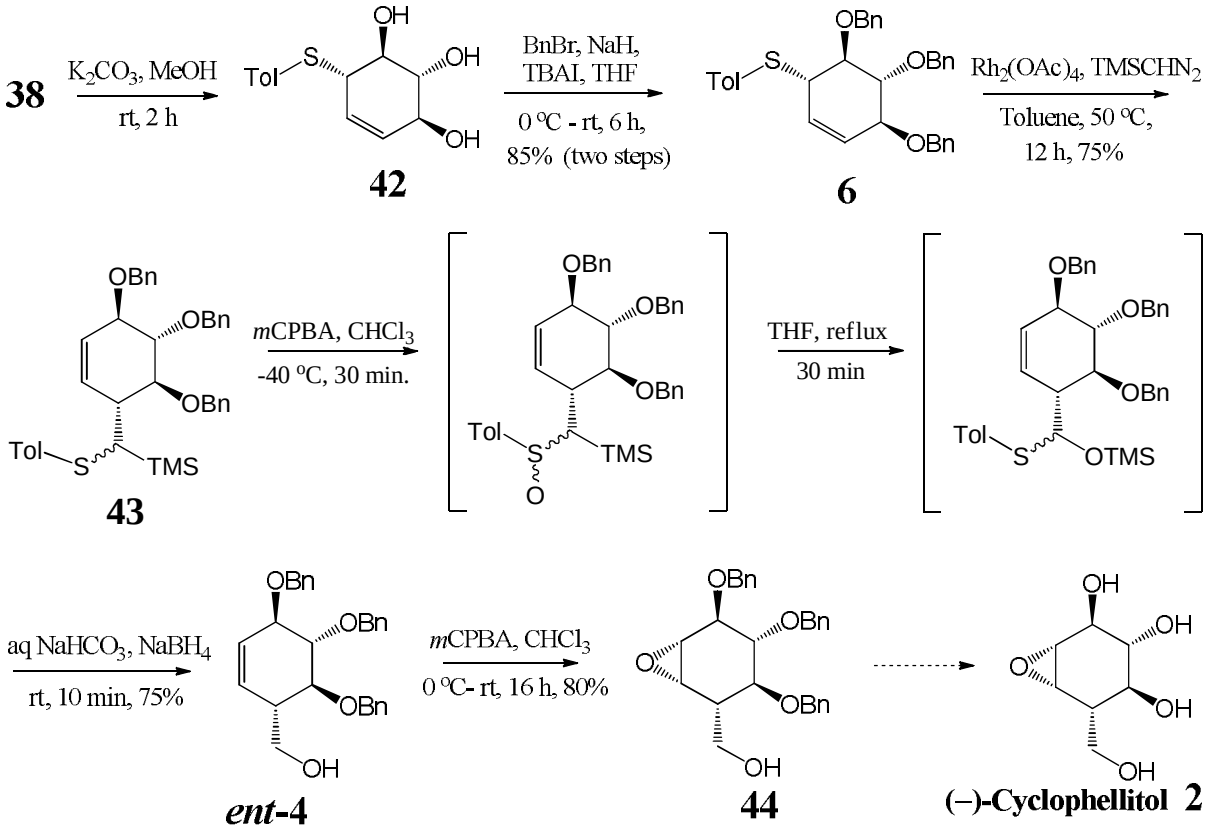
Pummerer rearrangement, hydrolysis followed by reduction of the ensuing aldehyde with sodium borohydride furnished a very polar compound **41**, probably resulting from the hydrolysis of the acetate groups, which however, could not be isolated (Scheme 7).

Scheme-7:



Then changed the protecting group that would be stable to the conditions of Pummerer followed by reduction reactions. Therefore, the acetate groups in compound **38** were hydrolyzed and the resulting triol **42** protected as its benzyl ethers **6.** Reaction of **6** with TMS-diazomethane and Rh(II) catalyst yielded an epimeric mixture of sulfides **43**.

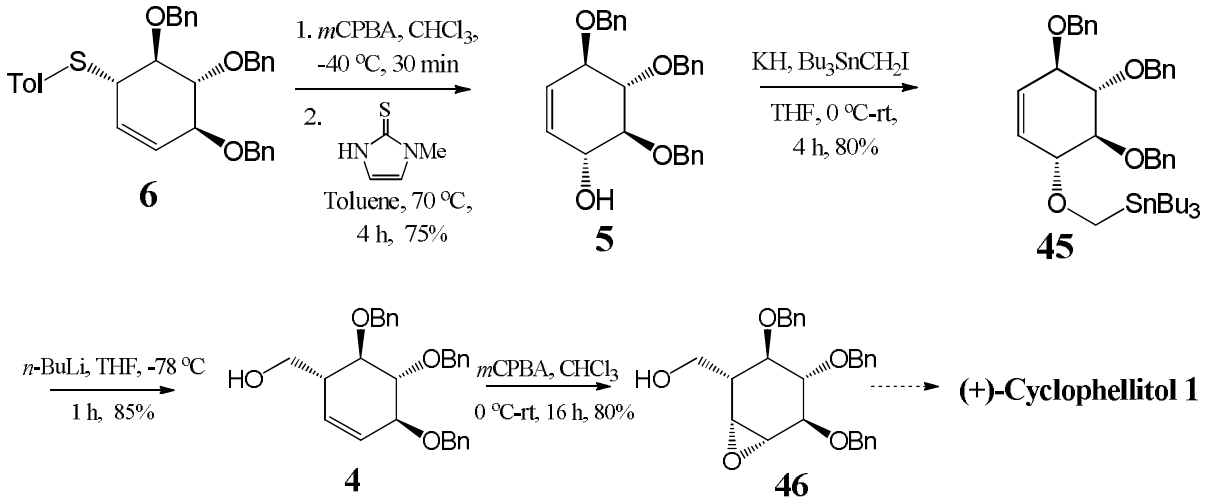
Scheme-8: Synthesis of (–)-cyclophelliol **2**



Oxidation of the sulfide with *m*CPBA yielded an epimeric mixture of sulfoxides and warming in THF led to Pummerer rearrangement. Hydrolysis of the intermediate with aq sodium bicarbonate and reduction of the resulting aldehyde in the same pot resulted in alcohol ***ent*-4**. Stereoselective epoxidation with *m*CPBA directed by homoallylic alcohol completed the formal synthesis of (–)-cyclophellitol **2** (scheme 8).

The formal synthesis of (+)-cyclophellitol **1** was completed following the sequence of reactions using compound **6** as the building block. Oxidation of **6** with *m*-CPBA yielded an epimeric mixture of sulfoxides followed by warming in toluene in the presence of 2-mercapto-1-methyl imidazole yielded (–)-conduritol-B derivative **5** via Mislow-Evans rearrangement. Deprotonation of **5** with potassium hydride followed by reaction with iodomethyltributyltin yielded the tin derivative **45**. Treatment of **45** with *n*-BuLi led to homoallylic alcohol **4** via Wittig-Still rearrangement. Stereoselective epoxidation with *m*CPBA directed by homoallylic alcohol completed the formal synthesis of (+)-cyclophellitol **1** (Scheme 9).

Scheme-9: Synthesis of (+)-cyclophelliol **1**



CHAPTER I

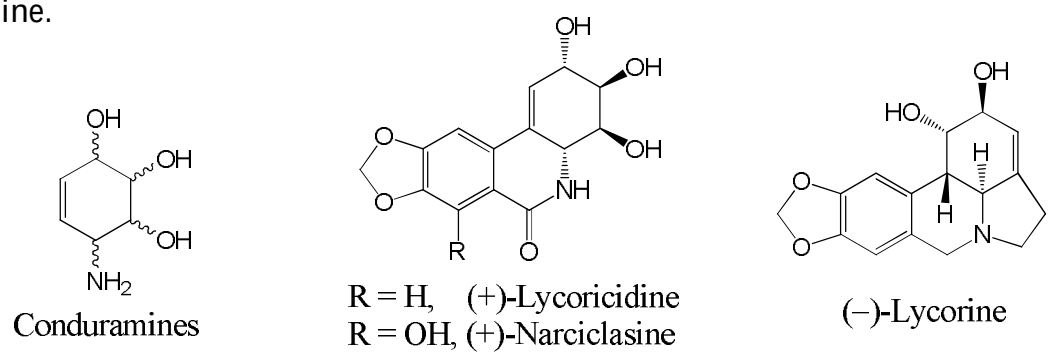
Section-B

Stereoselective Synthesis of (–)-Conduramine-B Derivative

Conduramines are aminocyclohexenetriols formally derived from conduritols, in which one of the hydroxyl groups is exchanged with an amino group.

Conduramines and their derivatives are important not only because of their glycosidase inhibitory effects, which derive from their structural features, but also for the synthesis of amino- and diamino-cyclitols. Glycosidase inhibitors have exhibited the potential to produce antidiabetic, antiviral, and anticancer effects. Conduramines are serve as important precursors of a wide variety of natural products, such as (+)-lycoricidine, (+)-narciclasine, (–)- lycorine (**Figure 1**).

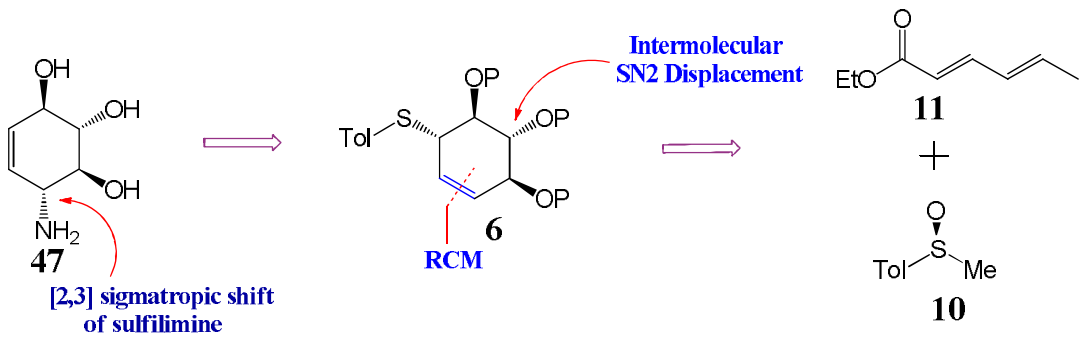
Figure 1: Structures of conduramines, (+)-lycoricidine, (+)-narciclasine, and (–)-lycorine.



As illustrated in the previous section, conduramine has stimulated a great deal of attention due to their biological activity and low natural abundance.

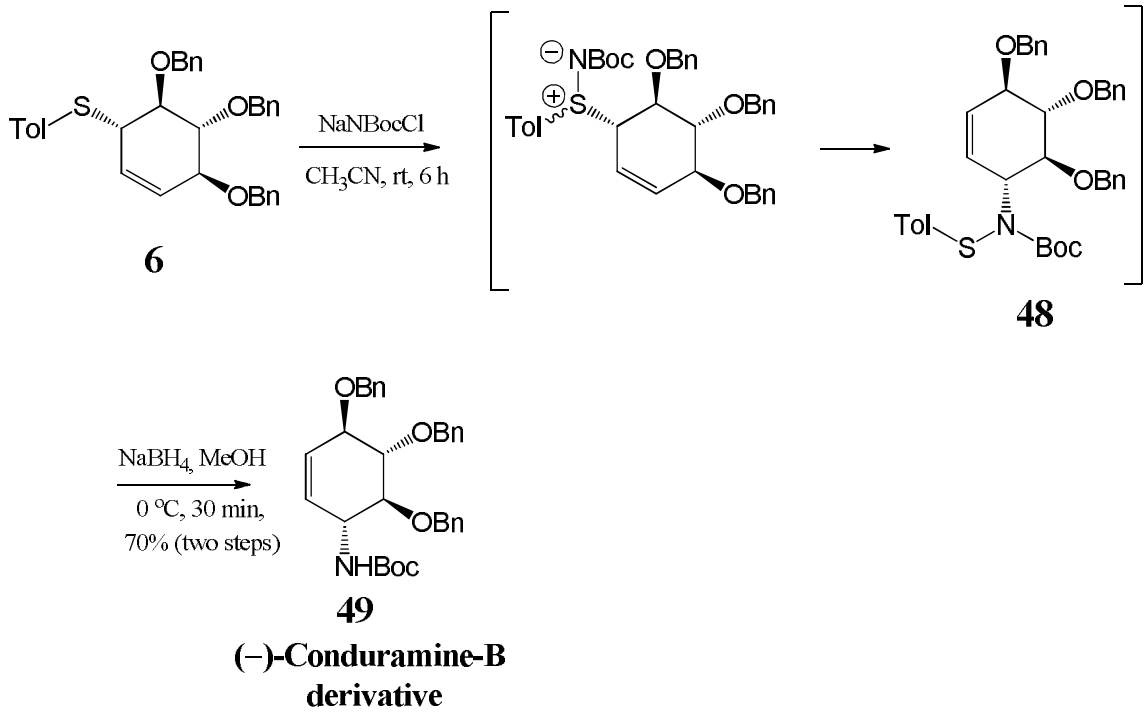
The retrosynthetic analysis of (–)-conduramine-B is depicted in Scheme-10. (–)-Conduramine-B **47**, was envisaged to obtain by [2,3] sigmatropic rearrangement of sulfilimine derived from allylic sulfide **6** followed by cleavage of N–S bond. Sulfide **6** would come from the metathesis of the diene **7** which in turn can be obtained from α-chloro sulfide derived from sulfide **8**. Compound **8** would result from the diene sulfoxide **9** which could be synthesized from compound **10** and commercially available ethyl sorbate **11** respectively.

Scheme-10: Retrosynthetic disconnection of (–)-conduramine-B



As illustrated in the chapter I, section-A, the same allylic sulfide **6** was utilized for the synthesis of (–)-Conduramine-B. Treatment of the allylic sulfide **6** with *N*-chloro-*N*-*tert*-butyloxy carbamate at 0 °C and warming to rt led to allylic amino derivative **48** which without isolation on treatment with sodium borohydride in methanol led to the cleavage of the N–S bond to furnish the carbamate **49** completed the synthesis of (–)-conduramine-B derivative (Scheme 11).

Scheme-11: Synthesis of (–)-conduramine-B derivative **49**



6 **48** **49**

(–)-Conduramine-B derivative

CHAPTER II

Experimental Procedures for Stereoselective Formal Synthesis of (+)- and (–)-Cyclophellitol, (–)-Conduritol-B and (–)-Conduramine-B Derivative

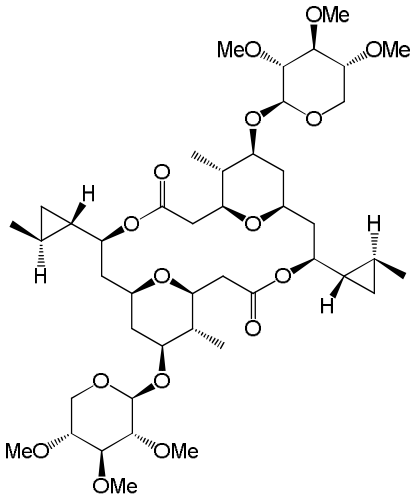
This chapter deals with an account on the experimental procedure for the synthesis of (+)- and (–)-cyclophellitol, (–)-conduritol-B and (–)-conduramine-B derivative.

CHAPTER III

Stereoselective Formal Synthesis of (–)-Clavosolide A

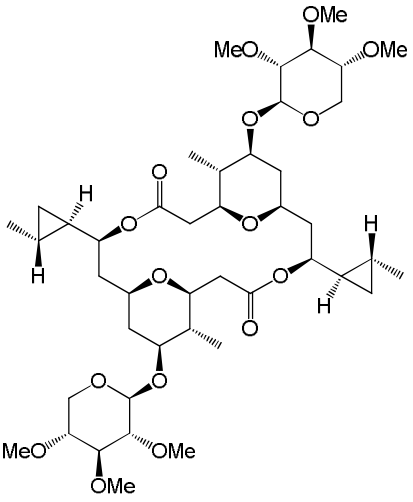
Marine sponges have provided an inexhaustible supply of bioactive metabolites. The clavosolides A–D are a family of unusual diolides isolated from extracts of the marine sponge *Myriastra clavosa* collected in the Phillipines by Faulkner and co-workers in 2002. The structure of (–)-clavosolide A was assigned originally as diolide (**1**, **Figure 1**) on the basis of extensive spectroscopic studies combined with molecular modeling. It is characterized by an unusual symmetrical 16-membered ring dilactone assembled on a highly functionalized tetrahydropyran core with a permethylated D-xylose moiety. The macrocycle is further adorned by two cyclopropyl containing side chains which were assigned the configuration 9*S*,9'*S*,10*S*,10'*S*,11*S*,11'*S*. A second disclosure by Erickson corrected the absolute and relative configuration of (–)-clavosolide A as 9*S*,9'*S*,10*R*,10'*R*,11*R*,11'*R* (**2**, **Figure 1**).

Figure 1: Structure of (–)-Clavosolide A



1

Originally proposed structure



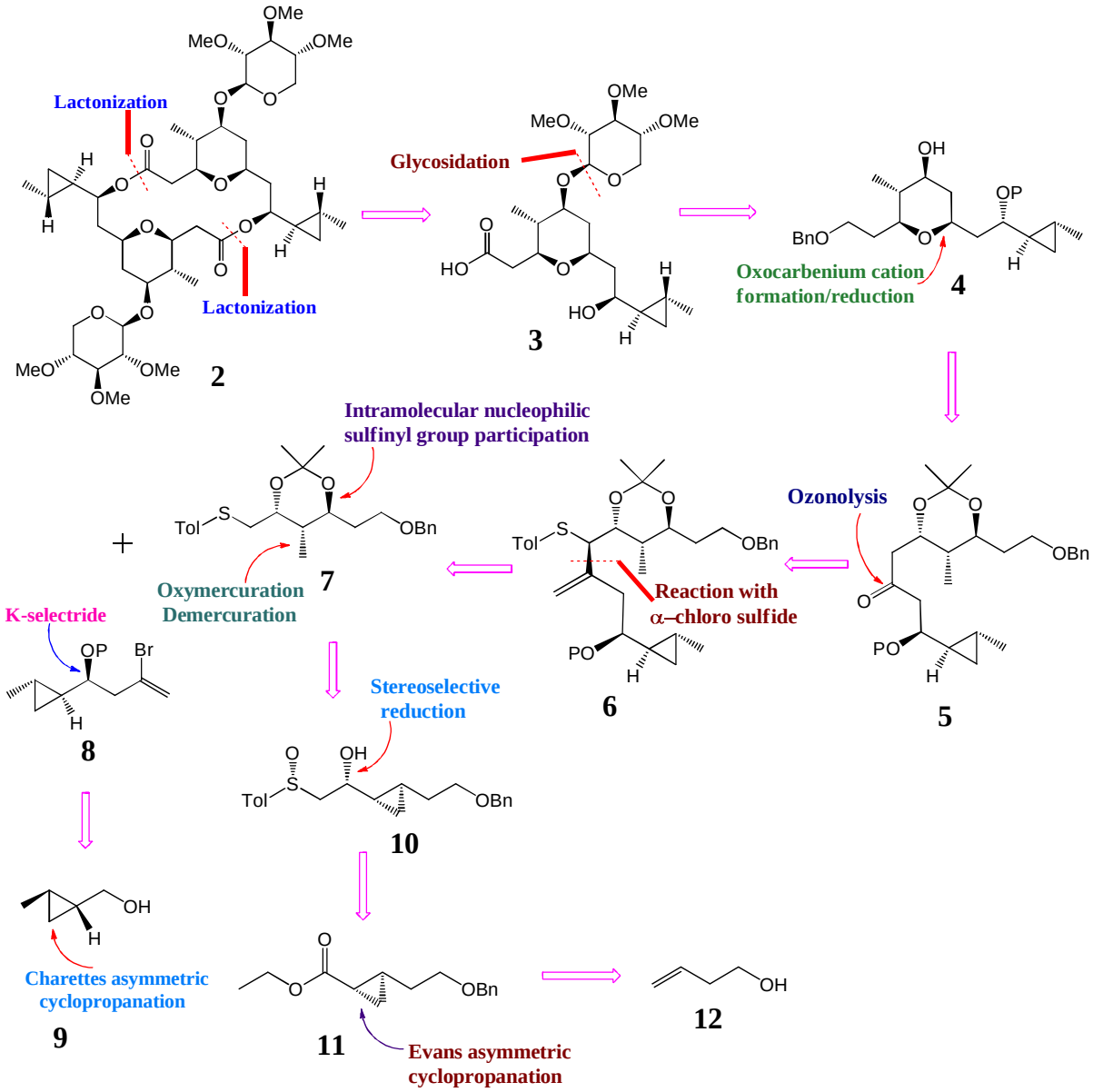
2

Revised structure for natural product

The retrosynthetic analysis of (–)-clavosolide A is depicted in Scheme-1. Clavosolide A **2** was envisaged to be obtained by the dimerization of the monomer **3**. The monomer **3** could be obtained from the tetrahydropyran derivative **4** by glycosidation of D-Xylose moiety. The highly functionalized tetrahydropyran derivative **4** could be obtained from the ketone **5** by reduction of oxocarbenium cation

with triethyl silane. The keto compound **5** can be prepared from the allylic sulfide derivative **6** by ozonolysis and reductive removal of sulfide. Sulfide **6** was envisaged to be obtained by the reaction of α-chloro sulfide prepared from sulfide **7** with vinylzinc bromide derivative prepared from **8**. The sulfide **8** could be prepared from the cyclopropyl carbinol **10** by mercury mediated cleavage of cyclopropane ring by using sulfinyl moiety as an intramolecular nucleophile.

Scheme-1: Retrosynthetic disconnection of (–)-Clavosolide A

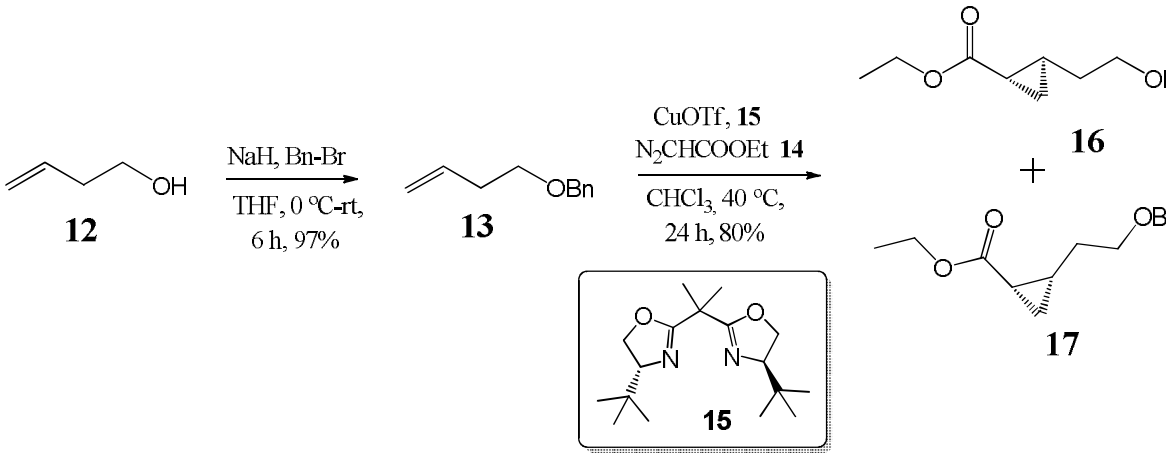


The cyclopropyl carbinol **10** could be synthesized from ester **11** which in turn can be obtained from commercially available 3-butene-1-ol **12** by employing Evans

asymmetric cyclopropanation protocol. The vinyl bromide derivative **8** was planned to be synthesized by the reaction of the aldehyde derived from cyclopropyl carbinol **9** and 2,3 dibromo 1 propene. Carbinol **9** can be prepared from crotyl alcohol by employing Charrette's asymmetric cyclopropanation protocol (Scheme 1).

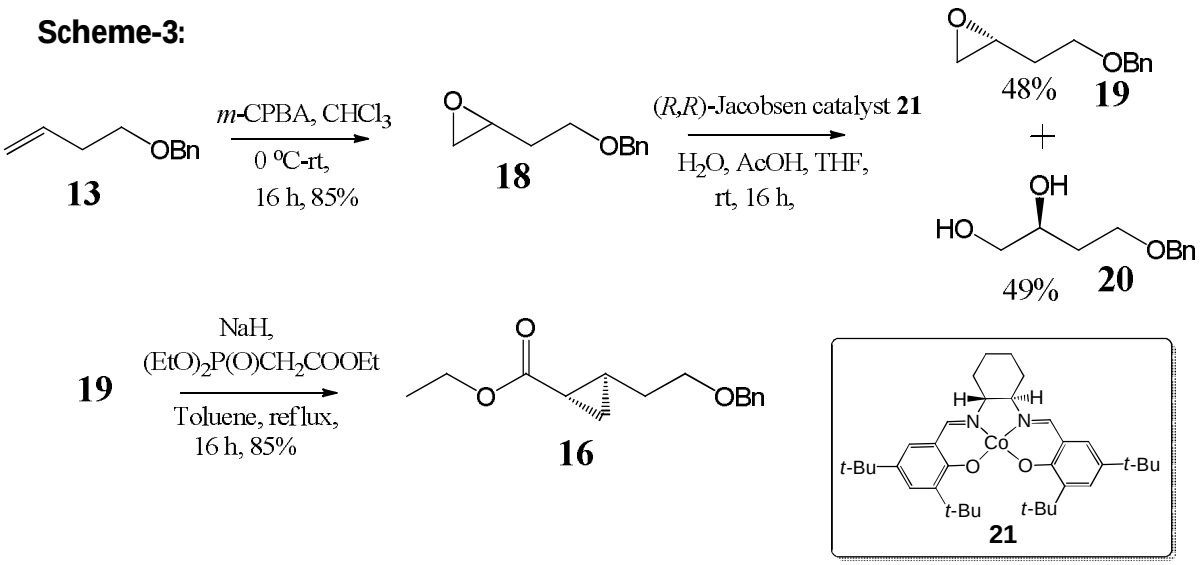
The synthesis started with the commercially available 3-butene-1-ol **12** which was protected as its benzyl ether **13**. Terminal alkene **13** was subjected to Evans' asymmetric cyclopropanation with ethyldiazoacetate **14** catalysed by CuOTf and the (*R*,*R*)-Box ligand **15** to furnish a 2:1 ratio of *trans*- and *cis*-cyclopropyl esters **16** and **17** with >95% enantioselectivity that could not be separated (Scheme 2).

Scheme-2: Synthesis of cyclopropyl esters **16**



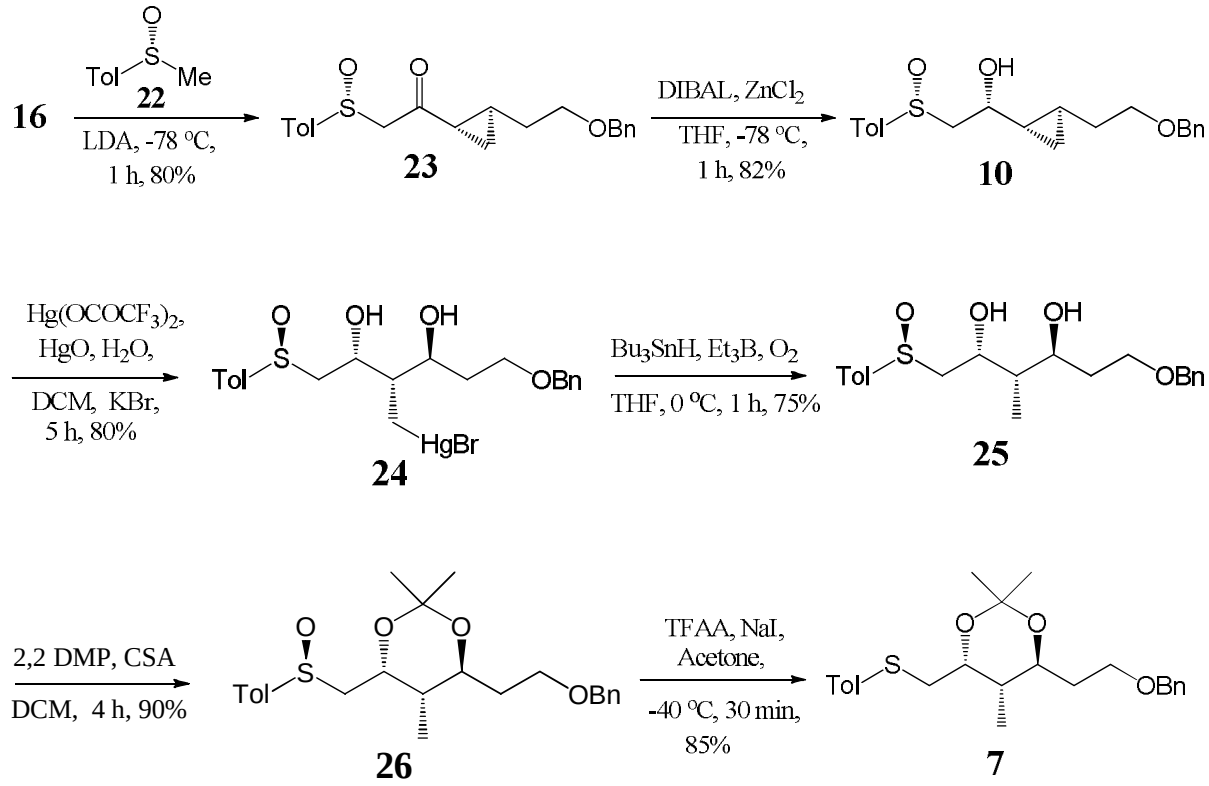
Although the *trans*-cyclopropane derivative **16** was obtained with excellent enantioselectivity, yields were not satisfactory since a third of the product was the undesired *cis*-cyclopropane ester. An alternate route was therefore explored. Benzyl ether **13** was oxidized with *m*-CPBA to afford racemic epoxide **18,** which was resolved using (*R*,*R*)-Jacobsen's protocol to obtain optically active epoxide **19**. The optically pure epoxide **19** was subjected to reaction with the anion of triethyl phosphonoacetate, generated using sodium hydride as the base, to afford exclusively the *trans*-cyclopropyl ester **16** (Scheme 3).

Scheme-3:



Proceeding, the *trans*-ester **16** was reacted with lithio anion of (+)-(*R*)-methyl *p*-tolyl sulfoxide **22** generated by reaction of **22** with LDA furnish the β-keto sulfoxide **23**. The carbonyl group in **23** was stereoselectively reduced using Dibal-H / $ZnCl_2$ system to yield the desired *syn*-alcohol **10** with excellent diasteroselectivity (de >99%) in multigram quantities.

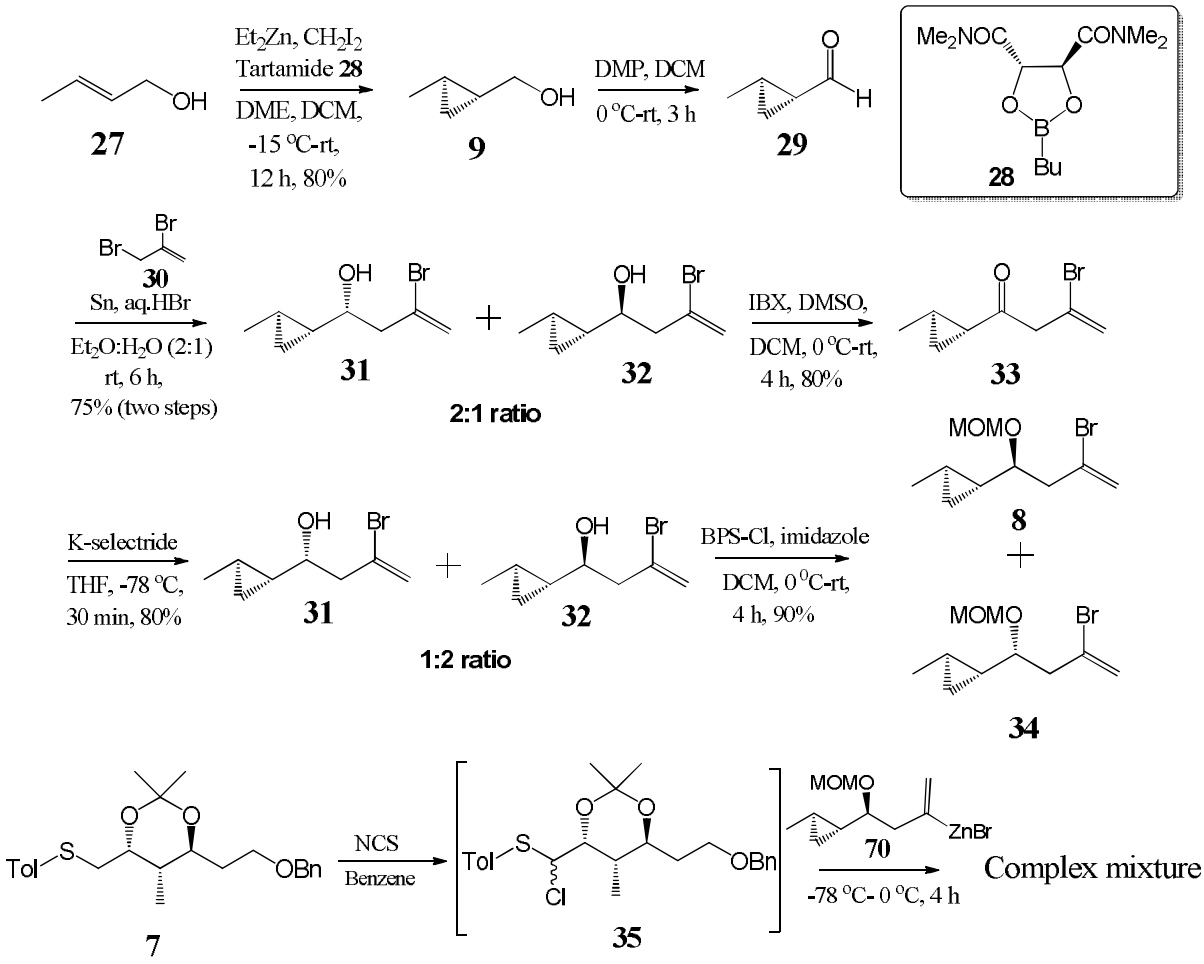
Scheme-4:



The next objective was to introduce methyl and hydroxyl centers. For this purpose, mercuric trifluoroacetate promoted cyclopropane ring opening by using the intramolecular sulfinyl moiety as the nucleophile was employed. Thus, reaction of cyclopropyl carbinol **10** with $Hg(OCOCF_3)_2$ and HgO in the presence of water in dichloromethane as the solvent afforded the mercuric trifluoroacetate which on treatment with aq KBr furnished mercuric bromide derivative **24**. Demercuration of **24** using Bu_3SnH/Et_3B in the presence of oxygen afforded diol **25**. The hydroxyl groups in diol **25** were protected as their acetonide **26** which was reduced using sodium iodide and trifluoroacetic anhydride in acetone at -40 ^oC to afford the corresponding sulfide **7** (Scheme 4).

The synthesis of cyclopropane derivative **8** began with the commercially available *trans*-crotyl alcohol **27** which was reacted with Et_2Zn, CH_2I_2 and tartamide ligand **28** under Charrette's asymmetric cyclopropanation conditions to afford cyclopropyl carbinol **9**. Oxidation of cyclopropyl carbinol **9** using Dess-Martin periodinane afforded aldehyde **29** which was reacted with 2,3 dibromo propane **30** in the presence of tin metal to furnish an epimeric mixture of alcohols **31** and **32** in a 2:1 ratio respectively. Compound **32** obtained as the minor isomer has the required relative stereochemistry. In an effort to obtain compound **32** as the exclusive or at the minimum, the major product, the mixture of alcohols was oxidized to ketone **33** and subjected to reduction with K- Selectride at -78 ^oC. Unfortunately, in this reaction also a 1:2 ratio of its diastereomers **31** and **32** was obtained. With the enough quantity of alcohols **31** and **32** being available these were converted into their MOM derivatives **8** and **33** which were separated in column chromatography. The bromo olefin **8** was treated with *t*-BuLi to generate the alkenyl lithium species and further treated with $ZnBr_2$ to afford the alkenylzinc compound **34**. Reaction of alkenylzinc compound **34** with the α-chloro sulfide **35**, generated by treating sulfide **7** with NCS in benzene, a complex mixture of products afforded (Scheme 5).

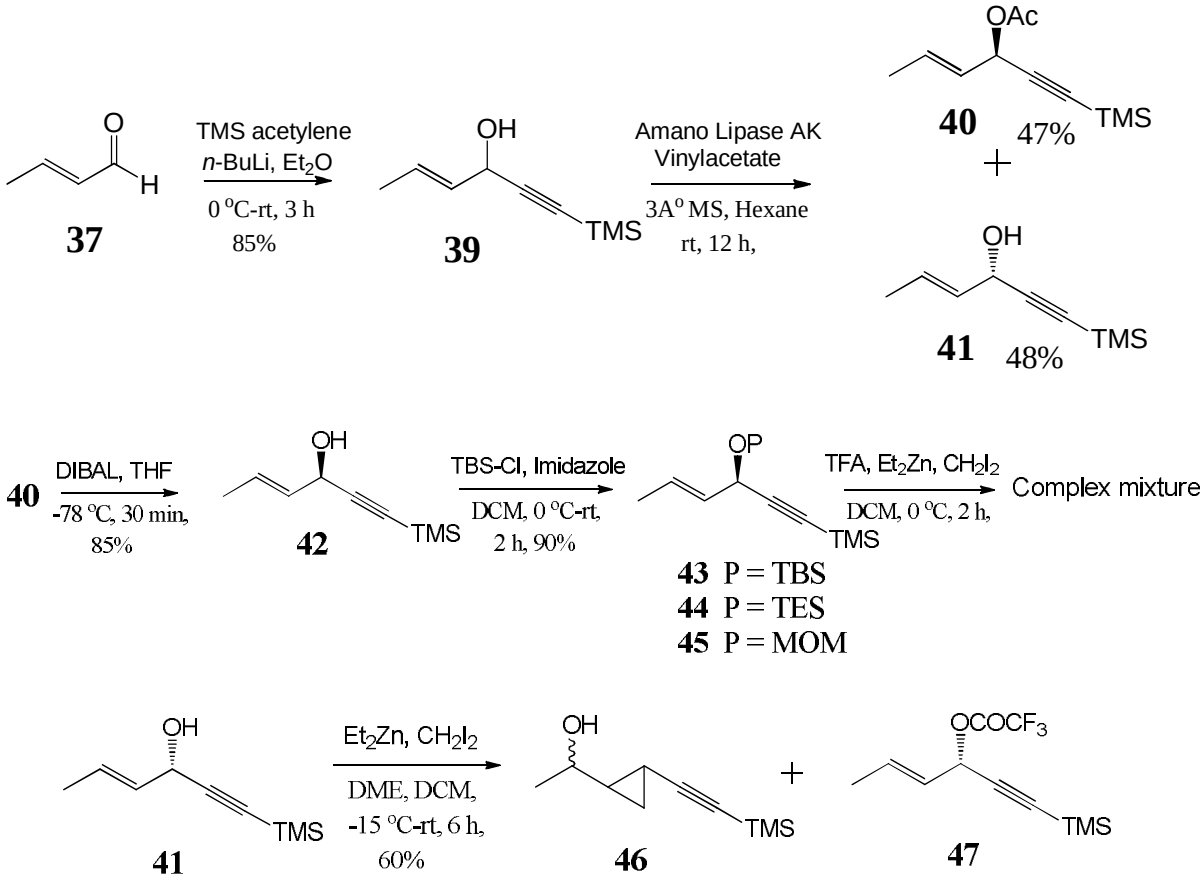
Scheme-5:



Since bromo alkene **8** could not be prepared as the sole isomer, stoichiometric ligands were required for preparing the cyclopropyl alcohol **9** and C–C bond formation between α-chloro sulfide **35** and sp^2 hybridized alkenylzinc bromide **34**, prepared from **8**, was unsuccessful, an alternate route was explored to prepare an appropriate less basic nucleophile alkynylzinc species for reaction with α-chloro sulfide **35**. The efforts to obtain alkyne **36** are described below. Commercially available *trans*-crotonaldehyde **37** was treated with lithiated anion of TMS acetylene **38** to furnish the racemic alcohol **39**. Enzymatic resolution of alcohol **39** using Amano lipase Ak afforded the optically pure acetate **40** and alcohol **41.** Both the alcohols **41** and **42** were envisioned as suitable precursors of alkyne **36,** the silyl ether of **42** by *anti*-cyclopropanation and alcohol **41** by hydroxyl directed *syn*-cycloprpanation followed by inversion. For *anti*-cyclopropanation the compound **42** was converted into its silyl

ethers **43**, **44** and MOM ether **45** which were then treated with $CF_3COOZnCH_2I$, generated by adding TFA to Furukawa's reagent. Unfortunately, a complex mixture of products resulted with no trace of the desired product being observed. The hydroxyl directed *syn*-cyclopropanation of alcohol **41** with Shi's reagent afforded the non stereoselective migration of the allylic alcohol to the conjugated enyne followed by hydroxyl directed cyclopropanation. In addition, the allylic alcohol was converted to its trifluoroacetate ester (Scheme 6).

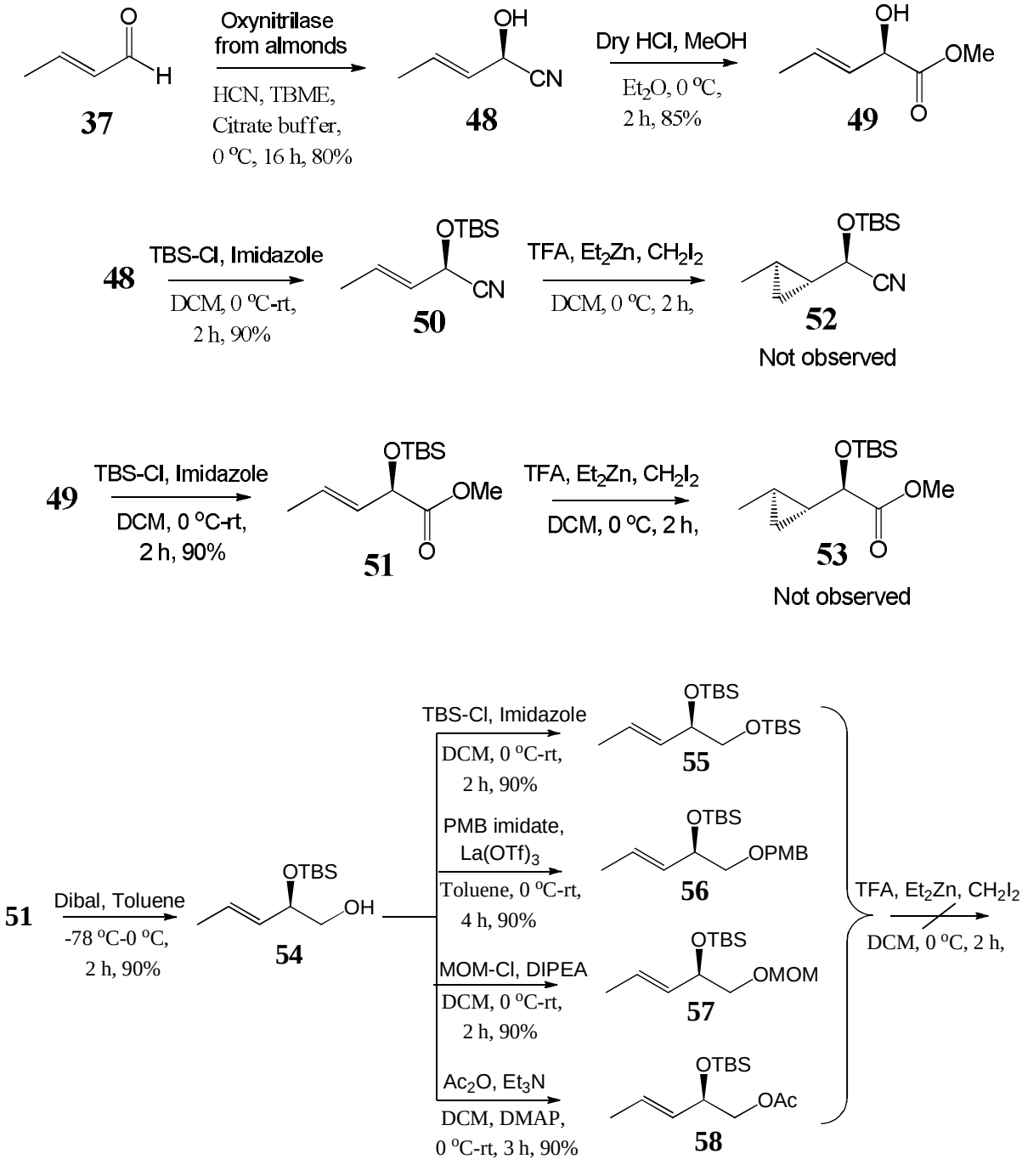
Scheme-6:

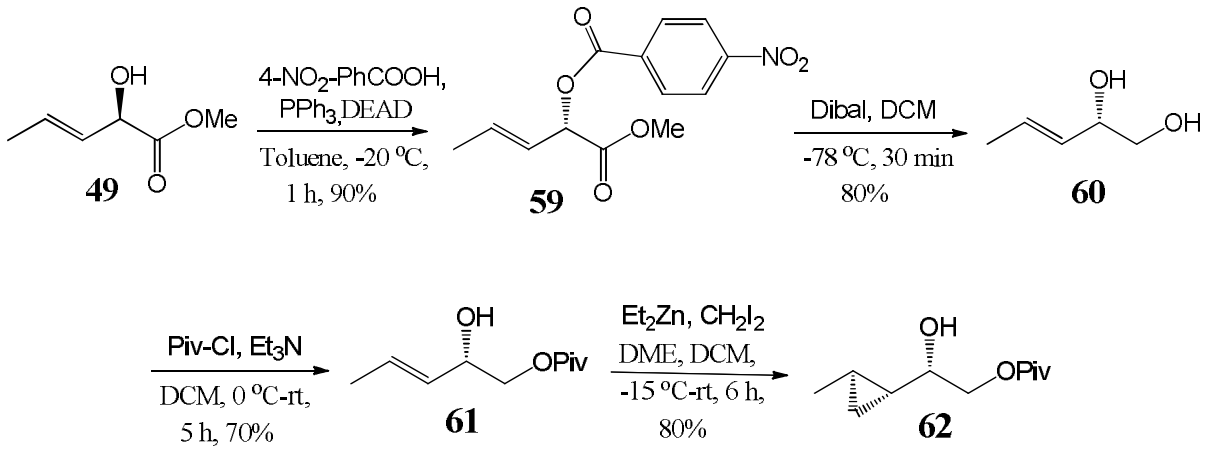


It was decided to introduce the triple bond after creating the cyclopropane ring. Thus, crotonaldehyde **37** was treated with oxynitrilase from bitter almonds to furnish the (*R*)-cyanohydrin **48** with high levels of enantioselectivity (>99% ee) which was transformed into the methyl ester **49** by reacting it with dry HCl gas in MeOH. The componds **48** and **49** were converted into their silyl ethers **50** and **51** respectively and subjected to cyclopropanation under $CF_3COOZnCH_2I$ only to the recover unreacted starting material. Assuming the electron withdrawing nature of the nitrile and ester

groups to be cause for recovery of the starting material, the ester **49** was reduced using Dibal-H to furnish the corresponding alcohol **54.** It was further protected as its TBS ether **55**, PMB ether **56**, MOM ether **57** and acetate derivative **58** and cyclopropanation was attempted on each of these substrates under Shi's condition to obtain the corresponding cyclopropyl carbinol derivatives. The cyclopropanation did not proceeded with any of these substrates.

Scheme-7:

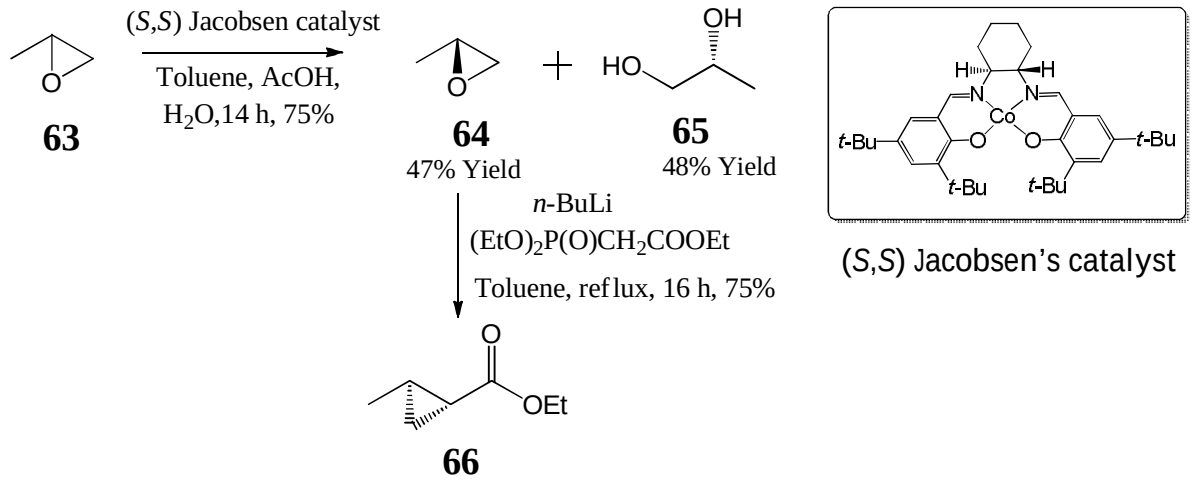




After being unsuccessful with *anti*-cyclopropanation of silyl ethers under Shi's condition, the hydroxyl directed cyclopropanation was considered. Thus, the hydroxy centre of the ester **49** was inverted using Mitsunobu protocol to afford the diester **59.** Reduction with Dibal-H furnished the diol **60**. Selective monoprotection of the diol **60** using pivaloyl chloride afforded the pivalate derivative **61** which underwent cyclopropanation following Furukawa's protocol to yield alcohol **62** (Scheme 7).

After many attempts at cyclopropanation, one successful reaction could be accomplished. However, conversion of compound **62** to alkyne **36** was calculated to be lengthy. Therefore **62** was not considered an appropriate substrate for the preparation of **36**.

Scheme-8:

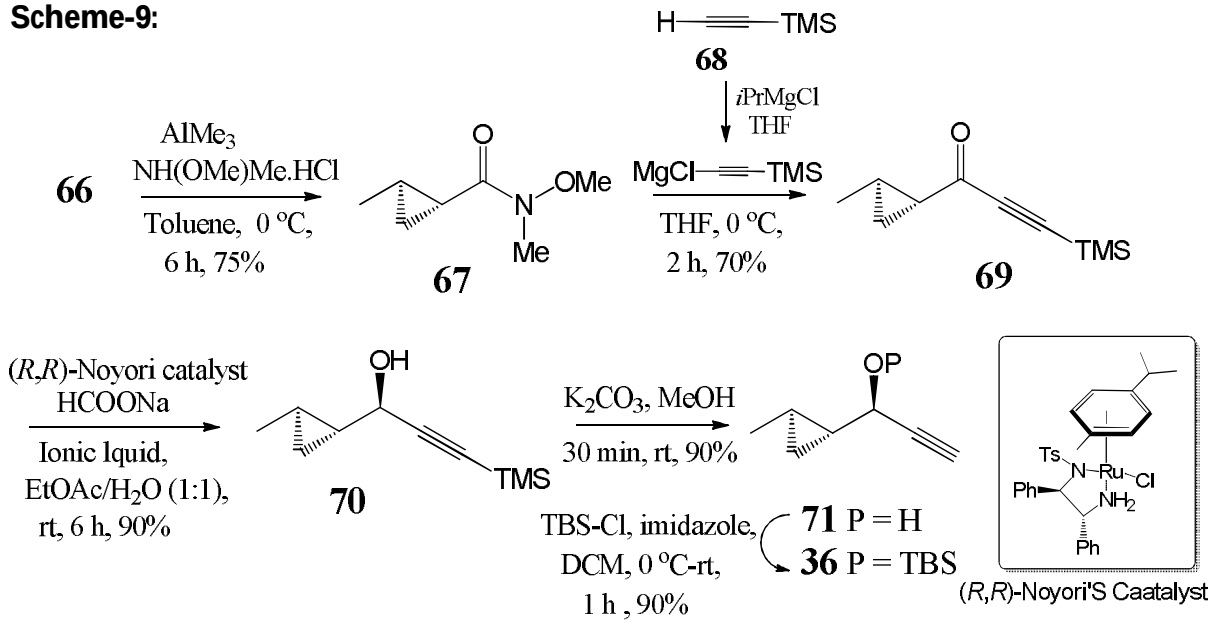


(*S*,*S*) Jacobsen's catalyst

Thus, alternatives were explored for the preparation of the alkyne **36** in less number of steps. The optically pure (*S*)-propylene oxide **64** was prepared hydrolytic kinetic resolution of the commercially available racemic propylene oxide **63** using (*S*, *S*)-Jacobsen's catalyst. (*S*)-Propylene oxide **64** on treatment with lithio anion of triethylphosphono acetate, generated by treatment with *n*-BuLi afforded *trans*-cyclopropyl ester **66** exclusively (>99% ee) (Scheme 8).

The cyclopropyl ester **66** was converted to the Weinreb amide **67** by treating with the reagent prepared from *N*,*O*-dimethyl hydroxylamine hydrochloride and trimethyl aluminium. The Weinreb amide **67** on reaction with TMS acetylide anion, generated by treating TMS acetylene **68** with *i*PrMgCl, afforded the ketone **69** which was stereoselectively reduced by using (*R*,*R*)-Noyori catalyst to furnish propargylic alcohol derivative **70** with excellent diastereoselectivty (>99% de). The TMS group in propargylic alcohol derivative **70** was deprotected under basic conditions to afford terminal alkyne **71** which was protected as its TBS ether **36** (Scheme 9).

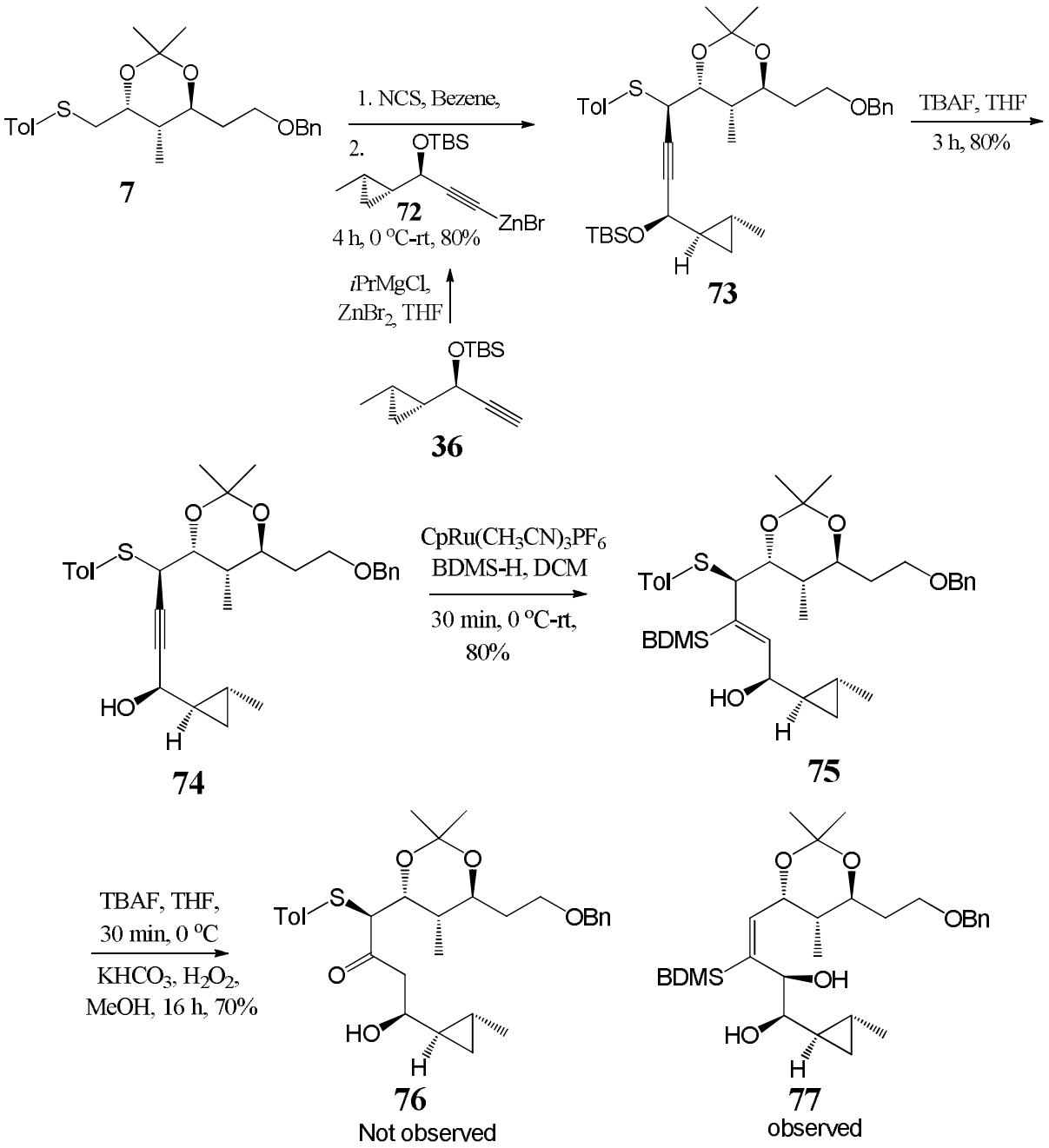
Scheme-9:



With the compound **36** being available the C–C bond formation by reaction of alkynylzinc reagent from **36** and α-chloro sulfide from sulfide **7** was investigated. The reaction of sulfide **7** with NCS in benzene furnished α-chlorosulfide **35** which was reacted with an excess of alkynylzinc bromide **72**, obtained by sequential treatment of **36** with *i*PrMgCl.LiCl and $ZnBr_2$, to afford propargyl sulfide **73** as the sole product.

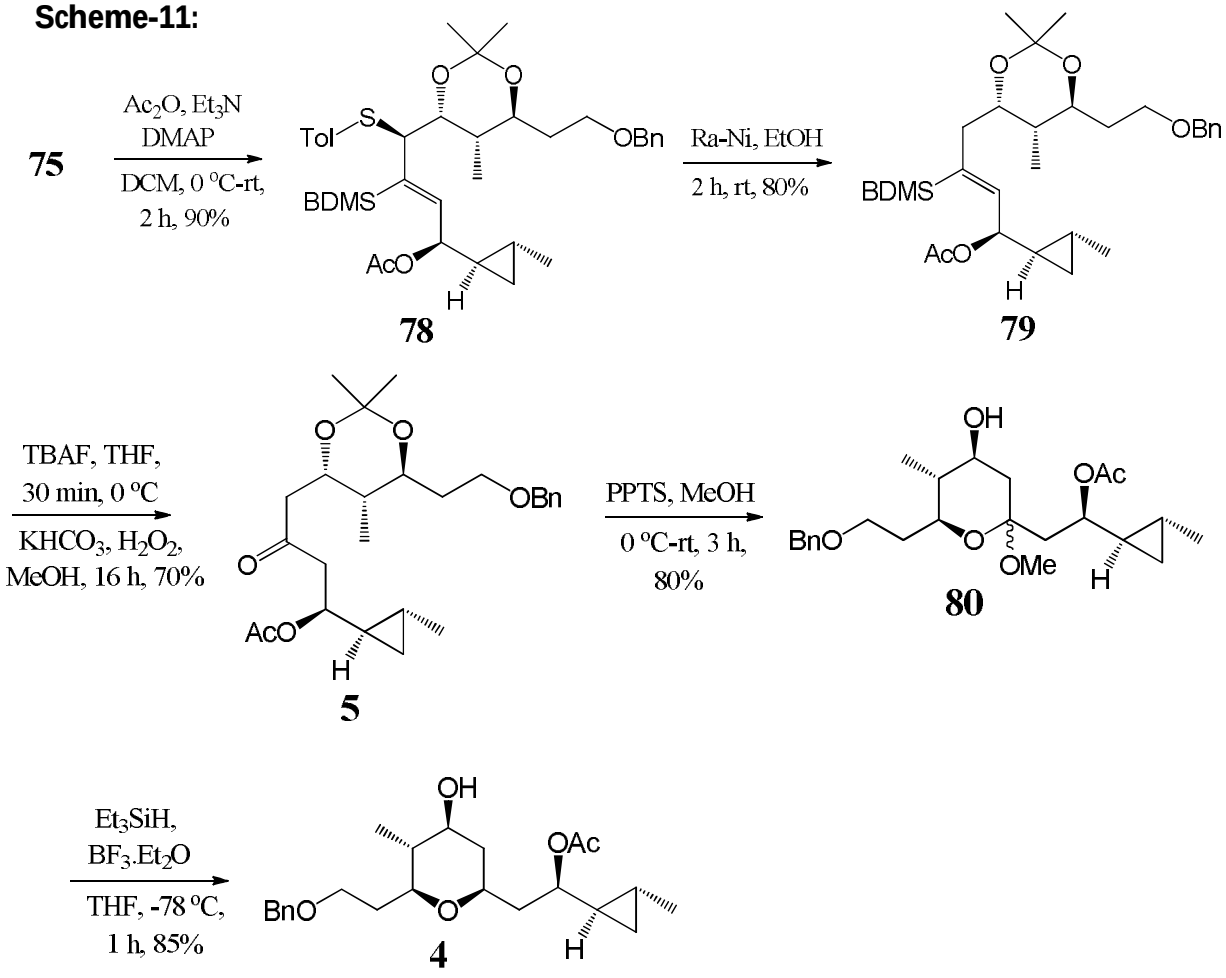
The TBS ether in propargyl sulfide **73** was deprotected with TBAF to afford the corresponding alcohol **74** which was used for the hydroxyl directed hydrosilylation following Trost's protocol. Thus, the compound **74** was treated with benzyldimethyl silane in DCM using [CpRu(CH_3CN)$_3PF_6$] catalyst to furnish vinyl silane derivative **75.** Fleming-Tamao oxidation with the vinyl silane was expected to furnish a keto sulfide **76**. However, under the experimental condition of the Fleming-Tamao oxidation, the sulfide **75** was oxidized to sulfoxide and it underwent Mislow-Evans rearrangement to afford product **77** (Scheme 10).

Scheme-10:



Thus, the hydroxy group in compound **75** was protected as its acetate **78** and the thio ether was hydrogenolyzed by treatment with deactivated Ra-Ni to furnish the acetate **79**. Fleming-Tamao oxidation of compound **79** afforded ketone **5.** The acetonide group in ketone **5** was deprotected under mild acidic condition to afford acetal **80**. The acetal **80** was treated with $BF_3.Et_2O$ to form oxocarbenium cation which was reduced with Et_3SiH to furnish tetrahydropyron derivative **4** (Scheme 11).

Scheme-11:



CHAPTER IV

Experimental Procedures for Stereoselective Formal Synthesis of (–)-Clavosolide A

4.1 Experimental:

This chapter deals with an account on the experimental procedure for the synthesis of (–)-Clavosolide A