# ABSTRACT

**Thesis Title:** "**Enantioselective syntheses of (+)-*epi*-Muricatacin and *cis*, *trans*-cyclopropyl containing molecules**"

The thesis deals with the chiral hydrobenzoin auxiliary mediated enantioselective syntheses of (+)-*epi*-Muricatacin and *cis*, *trans*-cyclopropyl containing molecules.

The thesis comprises of three chapters, **Chapter I** describes chiral hydrobenzoin auxiliary mediated intramolecular iodoetherification and its application of Enantioselective total synthesis of (+)-*epi*-muricatacin. **Chapter II** deals with the Syntheses of *cis* cyclopropyl containing molecules, Using Cu Catalyzed Intramolecular cyclopropanation as a key Step. **Chapter III** describes the studies directed towards the total Synthesis of Constanolactone A, Using chiral hydrobenzoin auxiliary mediated Wadsworth–Emmons cyclopropanation as a key Step.

**Chapter I: Enantioselective total synthesis of (+)-*epi*-muricatacin, Using Asymmetric hydrogenation/intramolecular iodoetherification as key Steps.**

*γ*-Butyrolactone is a very common structural building block in organic compounds, present in about 10% of all natural products. Among *γ*-butyrolactones, compounds with chiral *δ*-hydroxy-*γ*-butanolides occupy central position equally as target bioactive molecules and also as constructive synthetic equivalents in total syntheses. Muricatacin **1a-d**, constitute a representative example of this class of compounds **(Figure 1)**. Muricatacins were isolated in **1991** by McLaughlin and co-workers as an approximate 62:38 mixture (25% *ee*) of the (-)-(*4R,5R*)-**1a** and (+)-(*4S,5S*)-**1b** enantiomers from the seeds of *Annona Muricata L.* (Annonaceae) from the Dominican Republic.

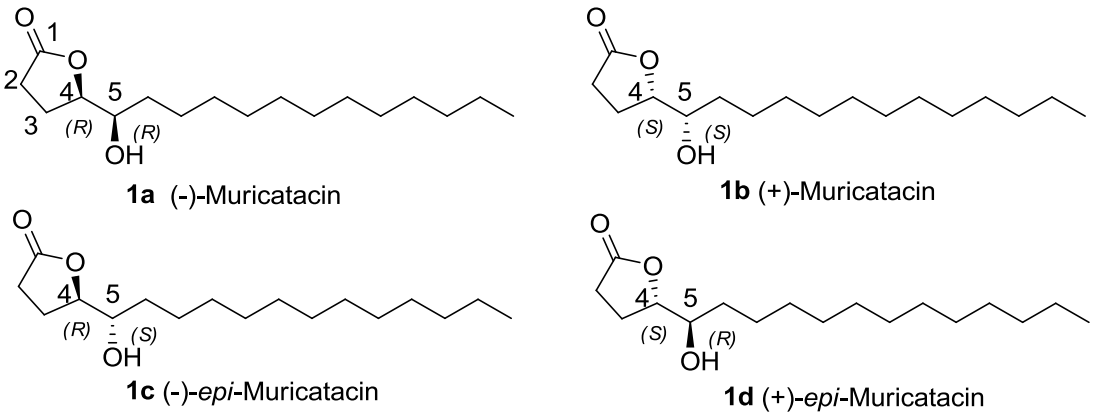
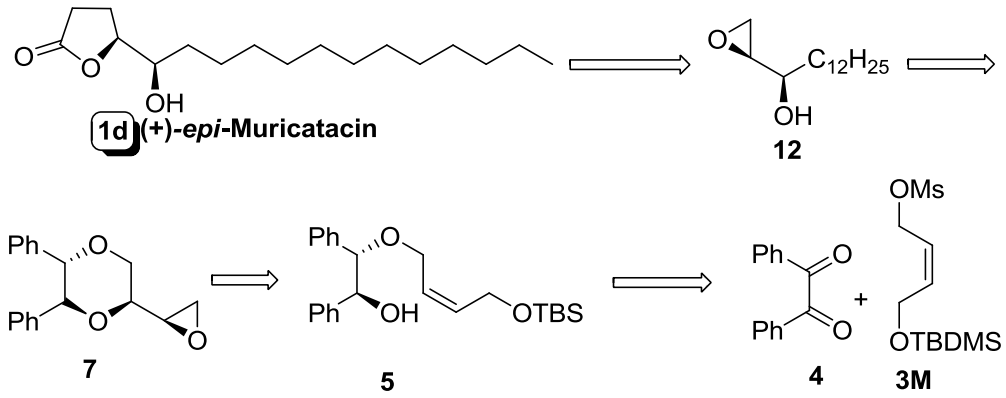



**Figure 1**

**Retro synthetic analysis:**

Our retro synthetic analysis revealed that the Muricatacin could be obtained by nucleophilic ring opening of terminal epoxide **12**, which could be generated from 7. Further **7** can be generated using electrophilic cyclization of **5** (**Scheme 1**).

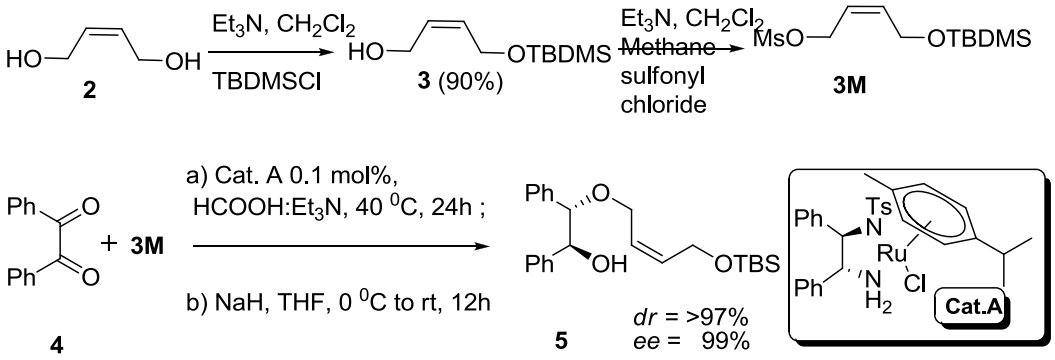



**Scheme 1**

It was envisioned that the chiral auxiliary unit in **7** will act as an inherent protecting group of corresponding diol. We have opted silyl protecting group in view of the fact that desilylation of silylated halohydrin and instantaneous intramolecular nucleophilic displacement of $\alpha$-halo atom could be occur with TBAF. We wanted to generate our critical starting material, that is, the $C_2$-symmetric (*S*,*S*)-diol tethered with

*tert*-butyldimethylsilyloxy *cis*-butene **5**, in a one pot procedure via a catalytic asymmetric hydrogenation of benzil **4** and subsequent monoprotection of the $C_2$-symmetric (*S*,*S*)-diol with *tert*-butyldimethylsilyloxy *cis*-butene mesylate **3M**.

Accordingly, Our synthesis began with the monosilylation of commercially available (*Z*)-but-2-ene-1,4-diol **2** using 1.2 equivalent of triethylamine, 1.0 equivalent of TBDMSCl in $CH_2Cl_2$ through usual and high yielding reaction to yield (*Z*)-4-(*tert*-butyldimethylsilyloxy)but-2-en-1-ol **3** (90%). The monosilylated butenediol **3** was then mesylated by treating with methanesulphonyl chloride and triethyl amine to furnish **3M (**mesylate of **3)**. The crude mesylate **3M** was used for next step without purification (**Scheme 2**).

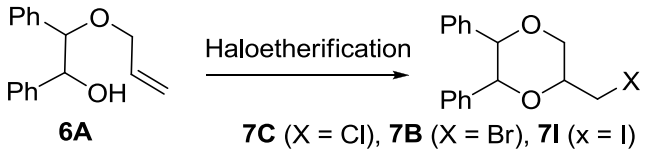



**Scheme 2**

**One-pot procedure:**

First of all, benzil **4** was subjected to Noyori's catalytic asymmetric transfer hydrogenation in the presence of 0.1 mol % of catalyst **A** RuCl[(*R*,*R*)-Tsdpen)( $\eta^6$-*p*-cymene) (TsDPEN, *N*-(*p*toluenesulfonyl)-1,2-diphenylethylenediamine). After 24 h at 40 $^0$C, the volatiles were removed from the reaction mixture under reduced pressure and the resulting crude residue was dissolved in THF and to it sequentially added NaH and **3M** (mesylate of *tert*-butyldimethylsilyloxy *cis*-butene **3)**. The expected product **5** was isolated in 70% yield with >97% diastereoselectivity with >99% enantiomeric

excess **(Scheme 2)**. The diastereomeric ratio and enantiomeric excess were estimated based on the specific rotation in comparison with an authentic sample of **5** prepared independently from (*S*,*S*)-diphenylethanediol (Aldrich) and compound **3M** (NaH, THF, rt, 12 h). The resulting compound's specific rotation was found to be$[\alpha]_D^{24}$ = -43.5 (*c* 1, $CHCl_3$) and the one-pot procedure also showed approximately same magnitude $[\alpha]_D^{24}$ = -43.0 (*c* 1, $CHCl_3$).




**6A** **7C** (X = Cl), **7B** (X = Br), **7I** (x = I)

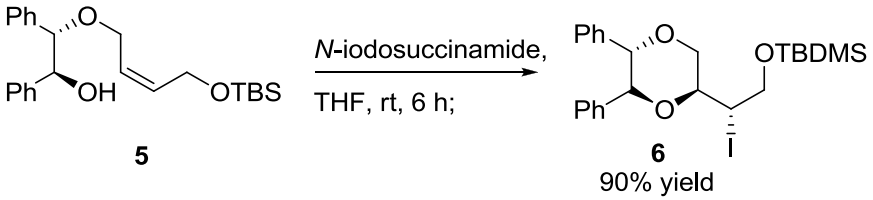
**Scheme 3**

**Table 1**

| entry | reagent | product | Yield (%) |
|---|---|---|---|
| 1 | *N*-chlorosuccinamide (toluene or $CH_2Cl_2$) | **7C** (X = Cl) | ~70 |
| 2 | *N*-bromosuccinamide (toluene or $CH_2Cl_2$) | **7B** (X = Br) | ~73 |
| 3 | *N*-iodosuccinamide (THF) | **7I** (X = I) | ~90 |
| 4 | $K_2CO_3$ +$I_2$ (THF) | **7I** (X = I) | ~85 |

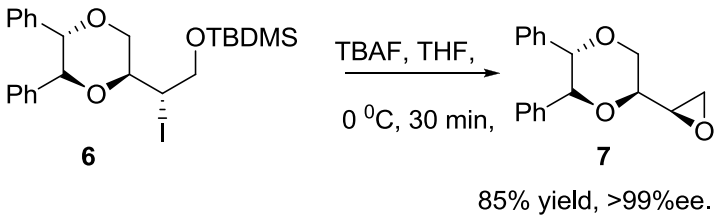
Having prepared the hydroxylalkene **5**, the envisaged enantioselective intramolecular iodoetherification using chiral hydrobenzoin auxiliary was evaluated for not only creation of two new streogenic centres but also as the oxygen atom source of Muricatacin. We have prepared allylated hydrobenzoin **6A** as a testing substrate for this reaction and conducted intramolecular haloethrification using a wide variety of electrophiles and conditions **(Scheme 3)**, some of these results are summarized in

**Table 1** and better yields were observed in enantioselective intramolecular iodoetherification using either *N*-iodosuccinamide or $K_2CO_3 + I_2$.




**Scheme 4**

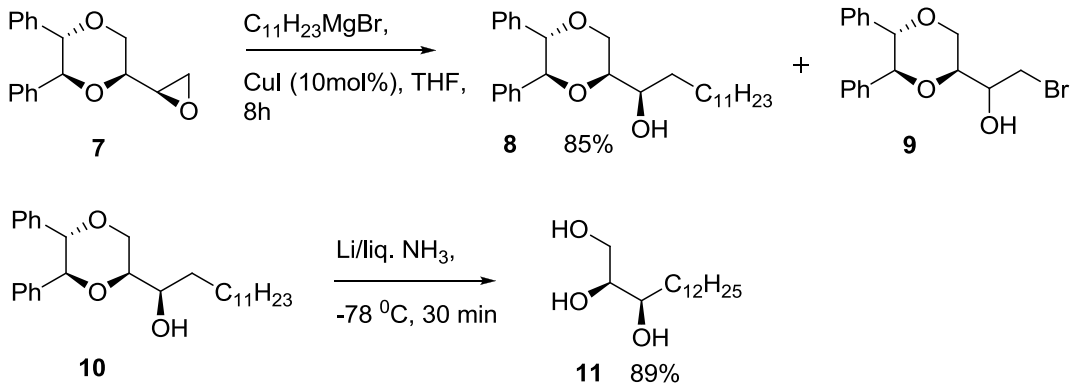
After considering above results, we preferred *N*-iodosuccinamide mediated enantioselective intramolecular iodoetherification of **5** in various solvent systems such as toluene, $CH_2Cl_2$, $^t$BuOMe, and THF. Only THF gave better results. The iodoetherifications were conducted in the dark, however, the iodo ethers are enough stable to be manipulated without special care. Reactions conducted at sub-zero and 0 $^0$C resulted in **6** lower yields. Thus, the reaction of **5** with *N*-iodosuccinamide (NIS) in THF at ambient temperature for 6 h resulted **6** with 9:1 separable diastereomers in a yield of 90%. **(Scheme 4)**.




**Scheme 5**

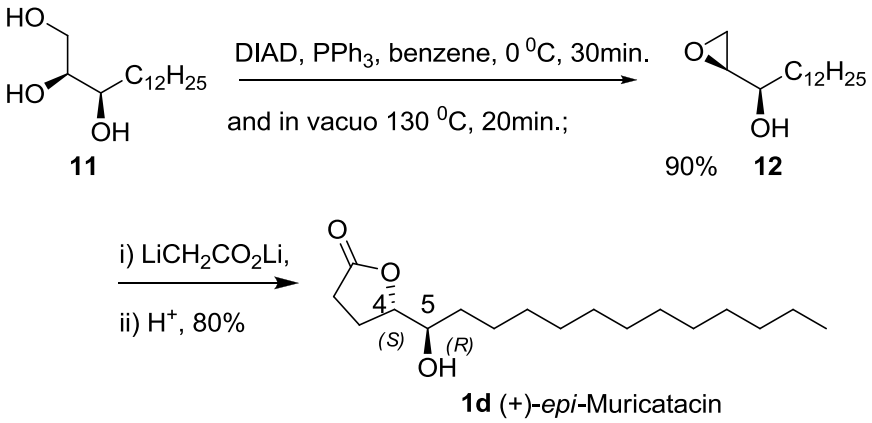
Exposure of **6** to TBAF in THF at ambient temperature not only led to desilylation, but also to the concomitant nucleophilic substitution of the resulting alcohol onto iodine to give highly enantioenriched epoxy intermediate **7** in 85% isolated yield. **(Scheme 5)**.

Grignard reaction with undecylmagnesium bromide in the presence of catalytic amount of CuI in THF led to **8** (89%) **(scheme 6)**. We examined the removal of the chiral auxiliary unit of **8** using Birch reduction with Li/liq.$NH_3$ at -78 $^0$C or $Pd(OH)_2$/C as the catalyst in the presence of a trace amount of conc. HCl. Both processes proceeded smoothly and afforded the corresponding chiral 1,2,3-triol **11** in good yields **(Scheme 6)**.




**Scheme 6**

Initially we synthesized the required epoxy alcohol from 1,2,3-triol **11** using *N*-tosylimidazole and NaH in THF but with lower yield, better yield 90% was achieved under Mitsunobu conditions ($Ph_3P$/DIAD, THF) **(Scheme 7)**. Finally, the substrate **12** treated with dilithioacetate dianion followed by acidification of resulting lithium carboxylate furnished the title compound **1d** in 80% isolated yield. The spectral and optical data of **1d** were in full agreement with that reported in the literature {$[\alpha]_D^{25}$ = +32.0 (*c* 0.9, $CHCl_3$), lit. $[\alpha]_D^{25}$ = 34.3 (*c* 2, $CHCl_3$)}.




**Scheme 7**

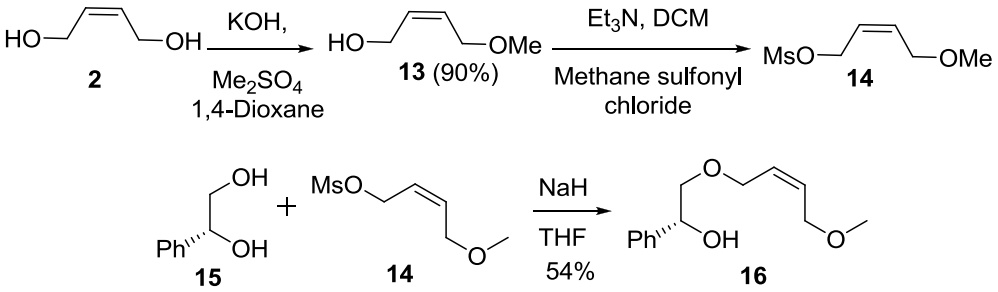
We have accomplished a concise enantioselective total synthesis of (+)-*epi*-Muricatacin **1d**. A key feature of this protocol is a catalytic asymmetric hydrogenation as the genesis of chirality and a chiral auxiliary mediated intramolecular iodoetherification to ensure a high degree of distereo- and enantiocontrol. The critical starting material **5** was prepared in high efficiency with a substrate/ catalyst molar ratio of 1000:1 using asymmetric hydrogenation. Moreover, the flexibility built into the synthesis to generate a library of analogues will be amenable to large-scale synthesis. We demonstrated that the present methodology employing (*S*,*S*)-hydrobenzoin as the chiral source and as the oxygen source would be very useful for the synthesis of (+)-*epi*-Muricatacin from simple achiral substances. Another merit of the present methodology is that an identical procedure using (*R*,*R*)- hydrobenzoin would provide the enantiomers of those obtained using (*S*,*S*)-hydrobenzoin.

## Chapter II: Syntheses of *cis* cyclopropyl containing molecules, Using Cu Catalyzed Intramolecular cyclopropanation as a key Step.

The smallest cycloalkane is found as a basic structural unit present in a wide range of biologically active naturally occurring compounds and hence it was attracted by Organic chemists. The cyclopropanes are not only synthetic targtets but also stood

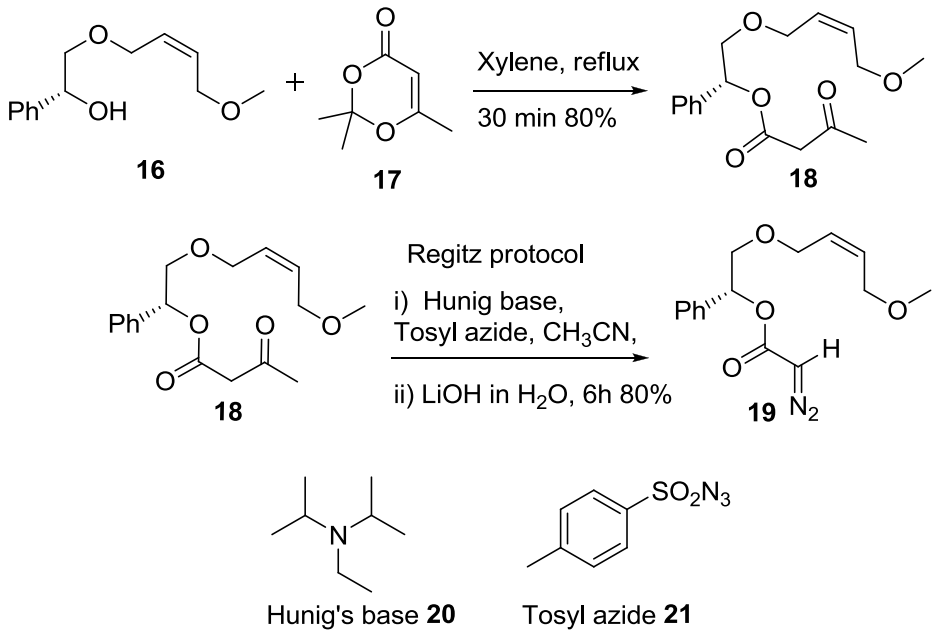
as versatile synthetic intermediates in the synthesis of more functionalized cycloalkanes and acyclic compounds.

Accordingly, Our synthesis began with the monomethylation of (*Z*)-but-2-ene-1,4-diol **2** using KOH and $Me_2SO_4$. The monomethylated butenediol **13** was then mesylated by treating with methanesulphonyl chloride and triethyl amine to furnish **14 (**mesylate of **13)**. The crude mesylate was used for next step without purification. The (*R*)-Mandelic acid was reduced using Lithium aluminium hydride to give (*R*)-1-phenylethane-1,2-diol **15** in a quantitative yield, which was dissolved in THF and to it sequentially added NaH and **14** (*Z*)-4-methoxybut-2-enyl methanesulfonate. The expected product **16** was isolated in 54% yield (**Scheme 11**).



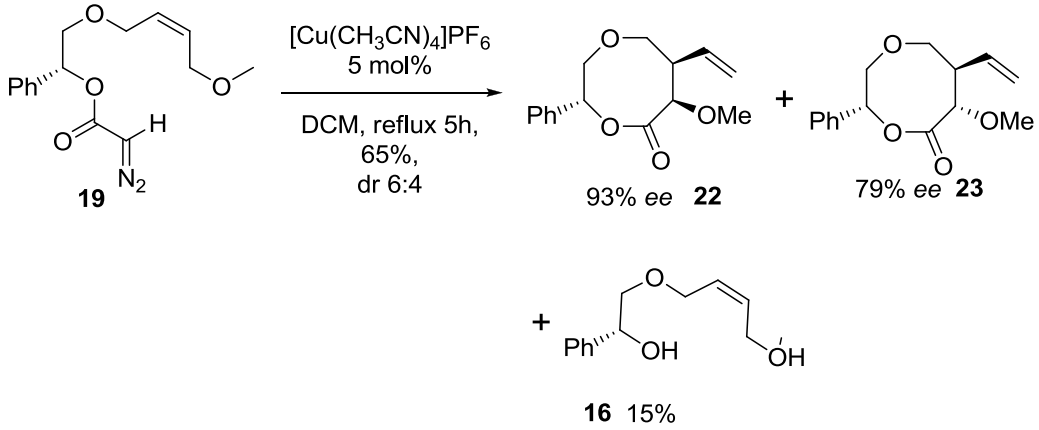

**Scheme 11**

The Acetoacetylation of (*R,Z*)-2-(4-methoxybut-2-enyloxy)-1-phenylethanol **16** has been attained using 1.1 equivalent of 2,2,6-trimethyl-1,3-dioxin-4-one **17** with a yield of 80% of **18**.




**Scheme 15**

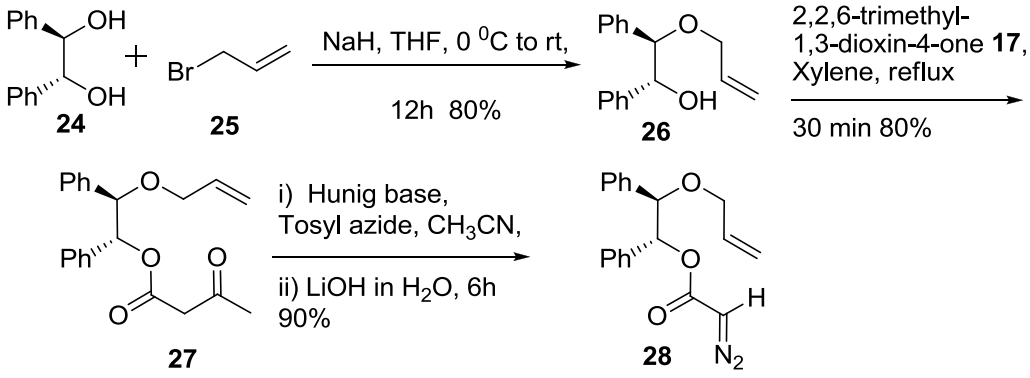
We followed the one pot procedure that is Regitz diazo transfer and saponification for the conversion of (*R,Z*)-2-(4-methoxybut-2-enyloxy)-1-phenylethyl 3-oxobutanoate **18** ($\beta$ keto ester) to (*R,Z*)-2-(4-methoxybut-2-enyloxy)-1-phenylethyl 2-diazoacetate **19** (terminal diazo product) with a 80% yield of **19** using 1.3 equivalent of Hunig's base **20**, 1.3 equivalent of Tosyl azide **21** and LiOH for Saponification.




**Scheme 16**

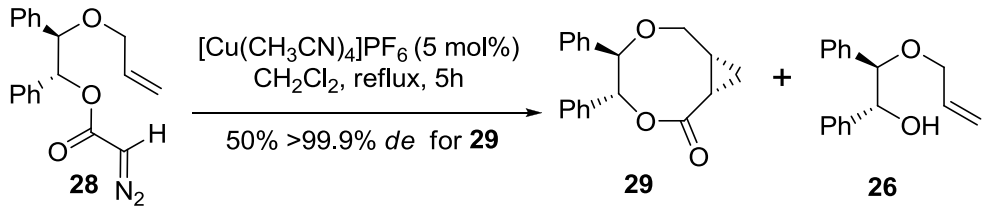
The Cu(I) catalyzed (5 mol%) reaction of **19** in $CH_2Cl_2$ at reflux temperature led to a diastereomeric mixture of **22** and **23** in a 6 : 4 ratio (*syn* : *anti*) and the diastereomeric excess was found to be good (**22**, 93% *de* and **23**, 79% *de*). Along with **22** and **23**, 15% of **16** were also isolated. Significantly, in contrast to the previous reports, no trace of intramolecular cyclopropanation product was observed in this transformation. The diastereomers **22** and **23** were separated by silica gel column chromatography. The *de* values of **22** and **23** were determined by chiral HPLC analysis in comparison with a racemic mixture which were prepared using Racemic Mandelic acid.

To ascertain chemoselectivity, we have synthesized an allyltethered diazo $C_2$-symmetric substrate **28** starting from (*1R,2R*)-1,2-diphenylethane-1,2-diol **24**. We performed the monoallylation of (*1R,2R*)-1,2-diphenylethane-1,2-diol **24** using NaH and allyl bromide **25** followed by acetoacetylation using 1.1 equivalent of 2,2,6-trimethyl-1,3-dioxin-4-one **17** with an overall yield of 64 % (**Scheme17**). The *β*-keto ester **27** was converted to terminal diazo product **28** using one pot procedure which combines Regitz protocol and saponification furnished the required cyclopropanation precursor that is (*1R,2R*)-2-(allyloxy)-1,2-diphenylethyl 2-diazoacetate **28** in a yield of 90%.




**Scheme 17**

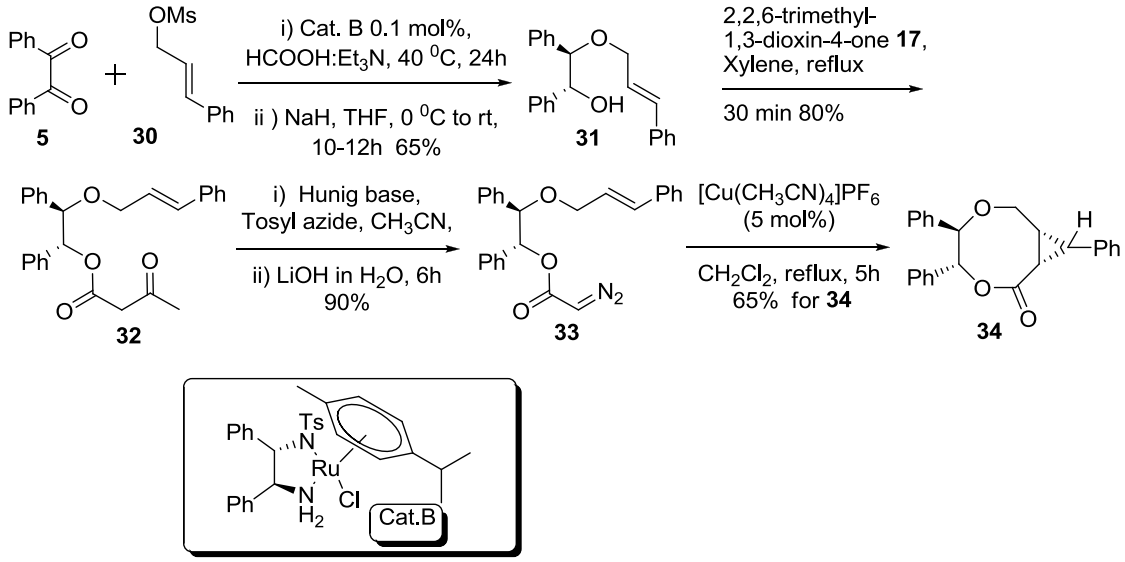
The Cu-catalyzed (5 mol%) diazodecomposition of **28** in $CH_2Cl_2$ at reflux temperature resulted exclusively in the *cis*-cyclopropanation product **29** in 50% yield with >99.9% *de* along with **26** (15%) (**Scheme 19**).




**Scheme 19**

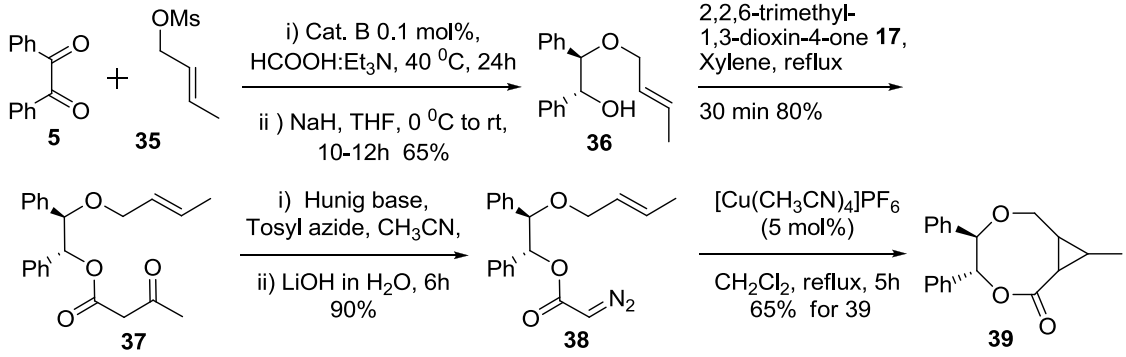
The *de* values of **29** were determined by chiral HPLC analysis in comparison with a racemic mixture, which was prepared using Racemic hydrobenzoin. The structure of compound **29** was confirmed by its $^{13}C$ NMR and $^{1}H$ NMR spectrum, which showed the appearance of cyclopropane moity, while rest of the protons appeared at the expected chemical shifts. The products were further confirmed depending on ESIMS and IR. The relative stereochemistry (*S,R*) of **29** was confirmed by X-ray crystallography. For this transformation, among the surveyed catalysts $Cu(CH_3CN)_4PF_6$ turned out to be the best. The electropositive Cu attached to a large counter anion appears to be essential to the reaction. We have also evaluated other Cu sources such as $Cu(OTf)_2$, $CuCl_2$, $Cu(OAc)_2$, Cu(pivalate)$_2$, Cu(acac)$_2$, $CuSO_4$, and CuI, gave the observed product but with lower yields.

We extended this methodology with cinnamyltethered diazo $C_2$-symmetric substrate **33** which was synthesized starting from benzil **5**. We extended one pot procedure which includes both noyori's asymmetric transfer hydrogenation and monocinnamylation of the resulting chiral hydrobenzoin to furnish **31** (**Scheme 20**).



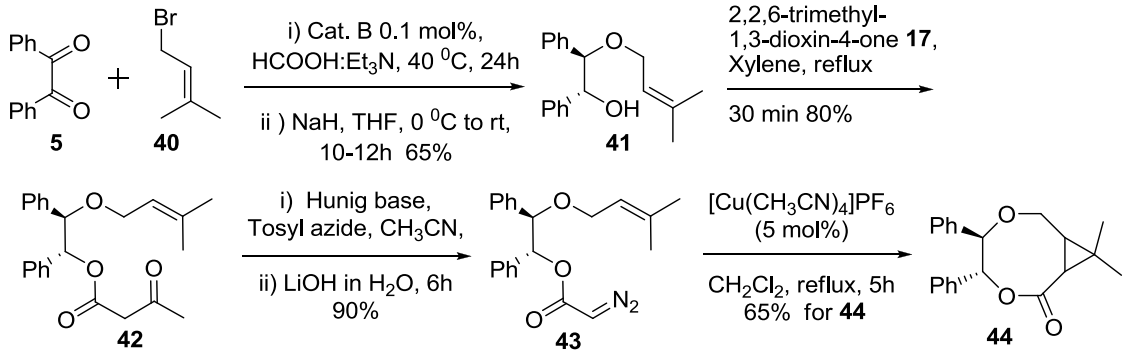

**Scheme 20**

The acetoacetylation of **32** followed by one pot procedure which combines Regitz protocol and saponification furnished the required cyclopropanation precursor that is (*1R,2R*)-2-(cinnamyloxy)-1,2-diphenylethyl 2-diazoacetate **33**. The Cu-catalyzed (5 mol%) diazodecomposition of **33** in $CH_2Cl_2$ at reflux temperature resulted exclusively the cyclopropanation product **34** in 65% yield. The NOE study confirmed the *cis* geometry of the cyclopropane. The structure of compound **34** was confirmed by its $^{13}C$ NMR and $^{1}H$ NMR spectrum, which showed the appearance of cyclopropane moity, while rest of the protons appeared at the expected chemical shifts. The products were further confirmed depending on ESIMS and IR.




**Scheme 21**

We have followed above sequence of reactions which includes One pot preparation of monocrotylated hydrobenzoin **36**, followed by acetoacetylation and finally one pot procedure which combines Regitz diazo transfer and saponicfication resulted the crucial (*R,R*)-Chiral hydrobenzoin tethered with prenyl and diazoacetate substrate **38** starting from benzil and mesylate of crotyl alcohol **35** (**Scheme 21**). The Cu-catalyzed (5 mol%) diazodecomposition of **38** in $CH_2Cl_2$ at reflux temperature resulted exclusively the cyclopropanation product **39** in 65% yield.

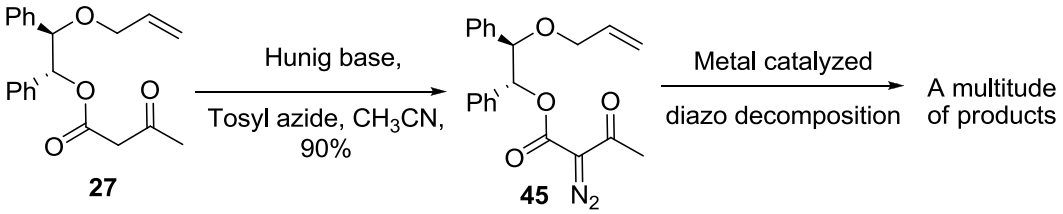



**Scheme 22**

We have followed above sequence of reactions which includes One pot preparation of monoprenylatedylated hydrobenzoin **41**, followed by acetoacetylation and finally one

pot procedure which combines Regitz diazo transfer and saponicfication resulted the crucial (*R,R*)-Chiral hydrobenzoin tethered with prenyl and diazoacetate substrate **43** starting from benzil and prenyl bromide **35** (**Scheme 22**). The Cu-catalyzed (5 mol%) diazodecomposition of **43** in $CH_2Cl_2$ at reflux temperature resulted exclusively in the cyclopropanation product **44** in 65% yield.

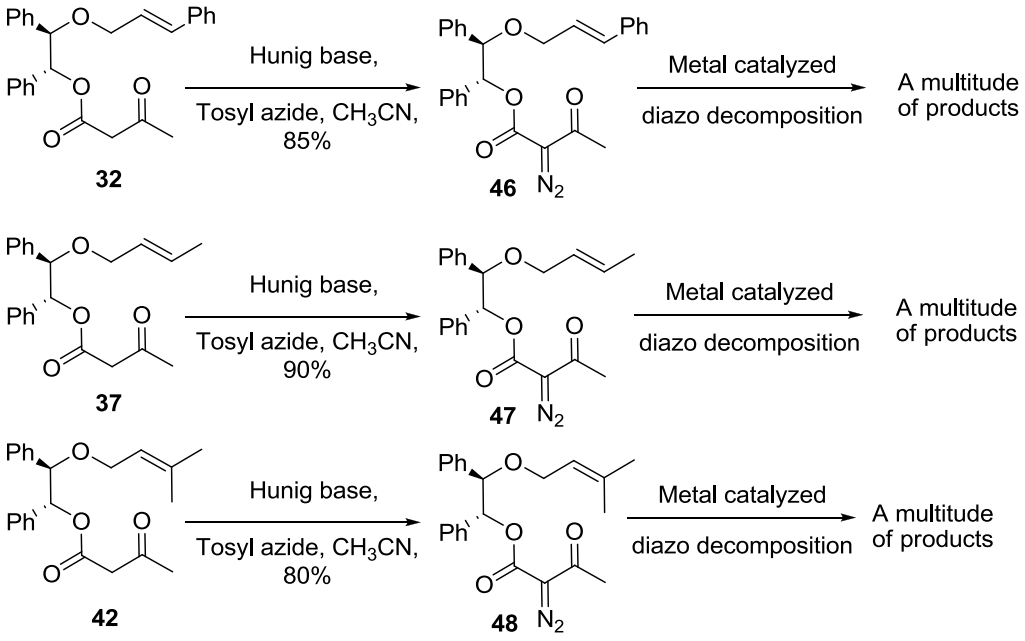
We have prepared internal diazo substrate using Regitz protocol starting from the acetoacetylated molecule. The Regitz diazo transfer reaction of (*1R,2R*)-2-(allyloxy)-1,2-diphenylethyl 2-diazoacetate **27** using Hunig'sbase and tosyl azide furnished the (*1R,2R*)-2-(allyloxy)-1,2-diphenylethyl-2-diazo-3-oxobutanoate (internal diazo compound) **45**.We have tried to extend our methodology for internal diazo substrate also using Metal catalyzed diazo decomposition but a multitude of products were observed (**Scheme 23**).




**Scheme 23**

We have performed the reaction with various Cu (I), Cu (II) and Rh reagents such as CuCl, CuBr, CuI, $Cu(OTf)_2$, $CuCl_2$, $Cu(acac)_2$, $CuSO_4$, $Rh_2(OAc)_4$, $Rh_2(Octanoate)_4$. We have conducted the reaction at various temparatures. We employed various solvent systems such as $CHCl_3$, $CCl_4$, benzene, toluene, DMSO, DMF and MeOH. We have changed the addition sequence (slow addition upto 10-24h) and the order of addition also but the formation of number of products was not reduced. Finally, We have tried even by varying the internal diazo substrates such as (1*R*,2*R*)-2-

(cinnamyloxy)-1,2-diphenylethyl 2-diazo-3-oxobutanoate **46**, (1*R*,2*R*)-2-((*E*)-but-2-enyloxy)-1,2-diphenylethyl 2-diazo-3-oxobutanoate **47**, (1*R*,2*R*)-2-(3-methylbut-2-enyloxy)-1,2-diphenylethyl 2-diazo-3-oxobutanoate **48** and performed the Metal catalyzed diazo decomposition but there is no reduction in the formation of number of products (**Scheme 24**).




**Scheme 24**

We have succeeded in developing a unified strategy for the synthesis of the cyclopropane containing molecules. The salient features of this concise convergent synthesis are i) The genesis of chirality through a catalytic asymmetric transfer hydrogenation. ii) We exended our one pot methodology which includes noyori's catalytic asymmetric transfer hydrogenation followed by monoetherification.

## Chapter III: Towards the total Synthesis of Constanolactone A, Using Wadsworth–Emmons cyclopropanation as a key Step.

Marine metabolites containing a *trans*-disubstituted cyclopropane subunit and saturated and unsaturated lactones of various ring sizes, which are called oxylipins, are a

growing class of natural products and are isolated from a wide spectrum of marine organisms.

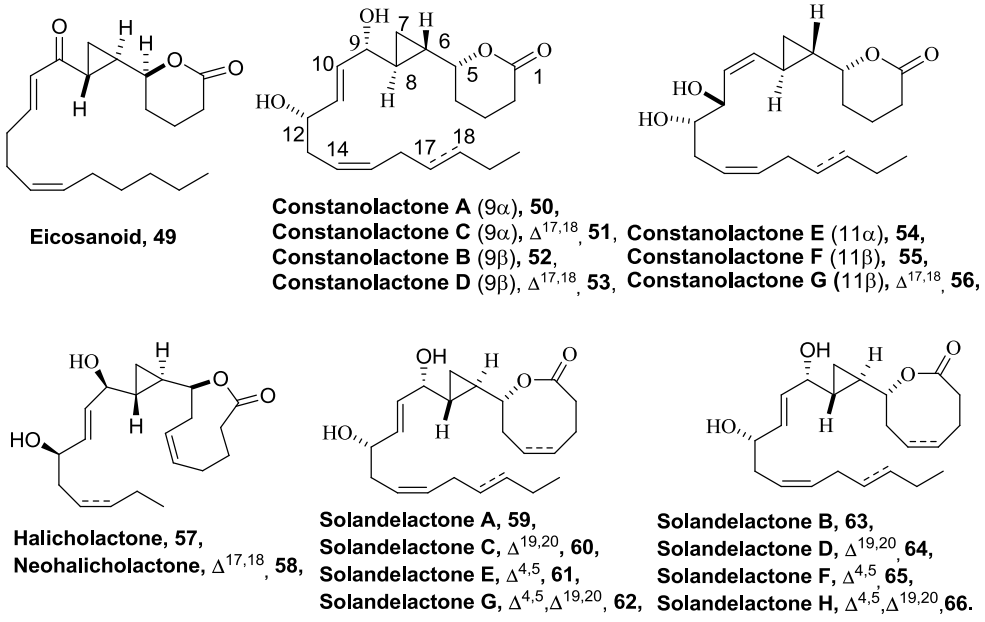



**Figure 2**

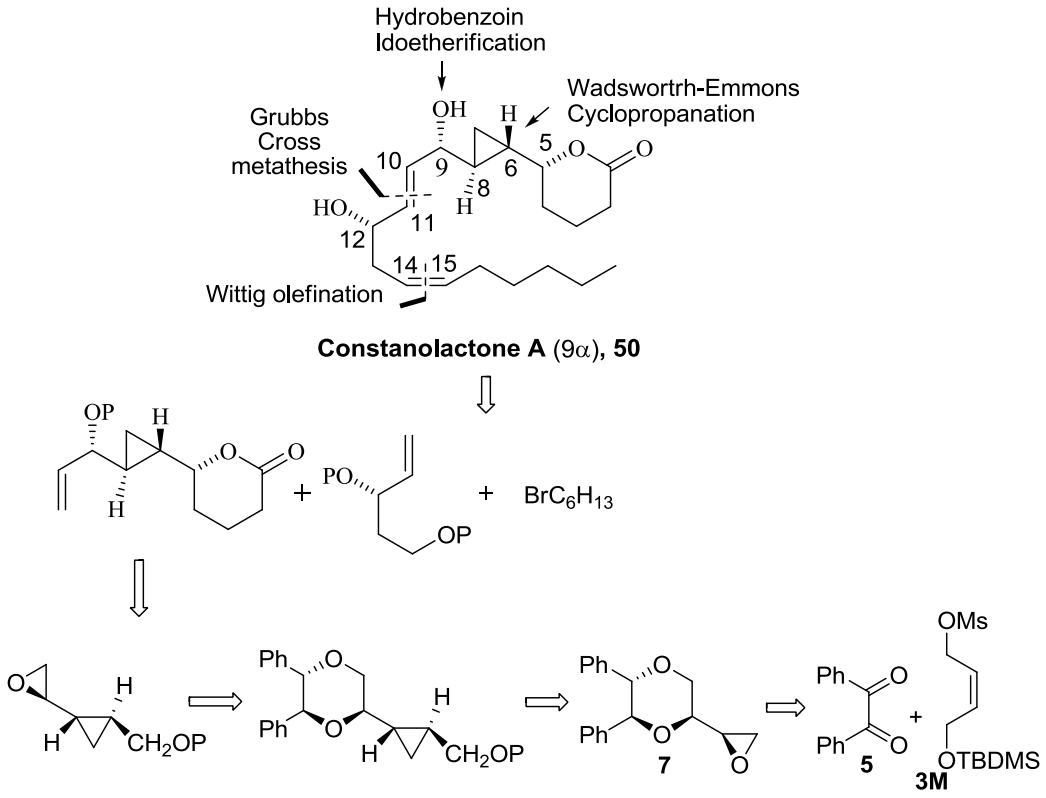
In **1990**, Nagle and Gerwick et. al., revealed the presence of two new cyclopropyl lactone containing oxylipins i.e. constanolactone, **50, 51** from the extracts of temperate red alga, harvested off the coast of Oregon. Interestingly, further studies revealed that the presence of additional new constanolactones, **52-56** in between **1990-1993** (**Figure 2**).

The novel structural features and potential biological activity of these marine oxylipins encouraged us to initiate a programme on the total synthesis of Constanolactone A.

**Retro synthetic analysis:**

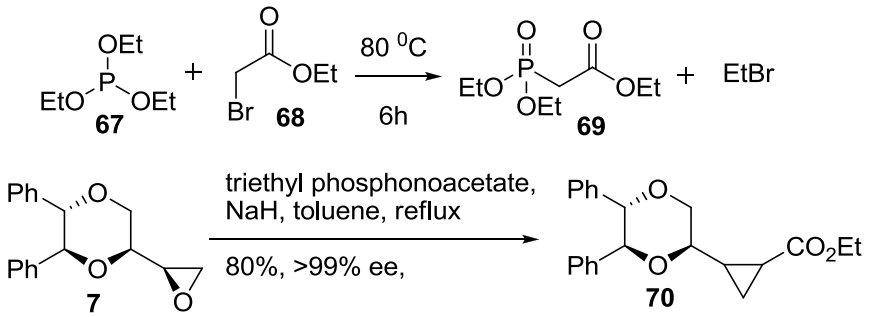
In retro synthetic analysis, the Wittig olefination ($C_{14}$-$C_{15}$) and Grubbs cross metathesis ($C_{10}$-$C_{11}$) could be useful for unsaturated double bonds synthesis (**Scheme**

**25**). The $\alpha$-hydroxy- *trans*-cyclopropyl moity could be obtained using Wadsworth-Emmons cyclopropanation on **7**. Further **7** can be generated starting from benzil and butene diol described in **Chapter I**.




**Scheme 25**

We have selected Wadsworth–Emmons cyclopropanation for the synthesis of cyclopropane as it provides a direct access to the required 1,2-disubstituted cyclopropanes in good yields using readily available and stable reagent TEPA (triethylphosphonoacetate) **69** which can be prepared from triethyl phosphite **67** and ethyl bromo acetate **68**. We have evaluated the Wadsworth-Emmons cyclopropanation reaction using various conditions on (2*S*,3*S*,5*S*)-5-((*R*)-oxiran-2-yl)-2,3-diphenyl-1,4-dioxane **7.** The convertion of epoxide **7** to cyclopropane **70** by employing NaH base and 3.5 equivalence of TEPA in Toluene solvent at reflux for 14h gave better results (80% **4$^{th}$** entry, **Table 2**).

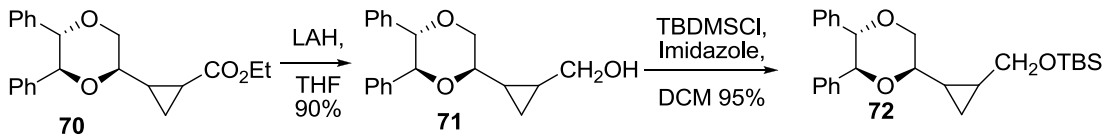



**Scheme 26**

**Table 2:**

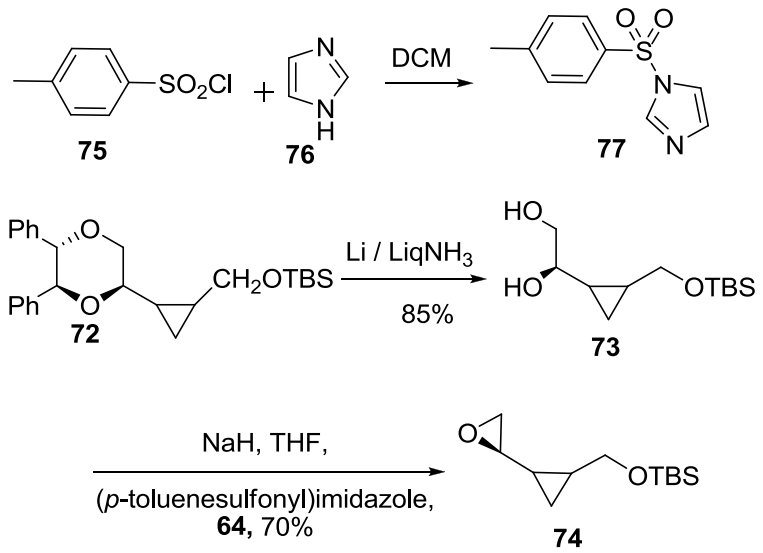
| Entry | Base | Solvent | TEPA (Eq.) | Temp/$^0$C | Time | Yield |
|---|---|---|---|---|---|---|
| 1 | NaH | DMF | 2.0 | 80 | 18h | 40% |
| 2 | | DME | 2.0 | 80 | 24h | 60% |
| 3 | | Toluene | 3.0 | 110 | 14h | 60% |
| **4** | | **Toluene** | **3.5** | **110** | **14h** | **80%** |
| 5 | K$^t$BuO | DMF | 3.0 | 80 | 18h | 30% |
| 6 | | DME | 3.0 | 80 | 24h | 60% |
| 7 | | Toluene | 3.5 | 110 | 18h | 70% |
| 8 | | THF | 3.5 | 65 | 24 | 60% |

Reduction of the Cyclopropyl ester with lithium aluminum hydride in THF furnished the Cyclopropylcarbinol **71** with a yield of 90% (**Scheme 7**). The Silylation of the Cyclopropylcarbinol **71** using TBDMSCl and Imidazole in $CH_2Cl_2$ resulted silylated product **72** with a yield of 95%.




**Scheme 27**

Removal of the chiral auxiliary unit of **72** has been carried out using Birch reduction with Li/liq.$NH_3$ at -78 $^0$C afforded the corresponding 1,2,-diol **73** with a yield of **85%**. Even $Pd(OH)_2$/C under Hydrogen atmosphere in the presence of a trace amount of conc. HCl proceeded smoothly but reaction was slow 30h (**Scheme 28**). A modification of a Fraser-Reid protocol was then employed to prepare **74** in nearly yield 70% via sequential treatment of **73** with NaH and *N*-tosylimidazole **77** which can be prepared from *p*-toluenesulfonyl chloride **75** and imidazole **76**.




**Scheme 28**

In conclusion, we have developed an efficient method for the synthesis of $\alpha$-epoxy cyclopropane using Chiral hydrobenzoin mediated Intermolecular Wadsworth-Emmons cyclopropanation. This is a key intermediate of Constanolactone A.