SYNOPSIS

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Thesis entitled "Application of Ring-Closing Metathesis Reaction Towards the Syntheses of Zoapatanol, Stagonolide C, Modiolide A and Development of Novel Methodologies" has been divided into three chapters.

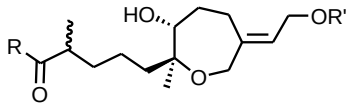
- **Chapter I:** This chapter is further subdivided into two sections.
    - **Section A**: This section deals with the historical and biological background of Zoapatanol including their isolations and previous synthetic approaches.
    - **Section B**: This section deals with the studies towards the total synthesis of Zoapatanol.
- **Chapter II:** This chapter is further subdivided into two sections.
    - **Section A**: This section emphasizes the brief introduction of ten-member lactones including their isolation, biological activity and synthetic approaches.
    - **Section B**: This section describes the stereoselective total synthesis of Stagonolide C and formal total synthesis of Modiolide A.
- **Chapter III:** This chapter is further subdivided into two sections.
    - **Section A**: Indium (III) bromide catalyzed cleavage of cyclic and acyclic ethers: An efficient and practical ring opening reaction.
    - **Section B**: Gallium (III) Chloride Catalyzed Stereoselective Synthesis of *E*-Configured α,β-Unsaturated Ketones.

Chapter I:

Section A: Historical and biological background of Zoapatanol including their isolations and previous synthetic approaches.

Zoapatanol (**1**), montanol (**2**), tomentol (**3**) and tomentanol (**4**) are novel diterpenoide oxepanes (Figure 1) isolated from the leaves of Mexican zoapatle plant *Montanoa tomentosa*. For centuries, Mexican women have been using 'tea', the aqueous extracts of the plant as a

contraceptive in local folk medicine. It was first isolated in 1979 by S. D Levine *et al*. Because of its challenging structure and excellent biological profile, it prompted us to take up Zoapatanol as our synthetic target.

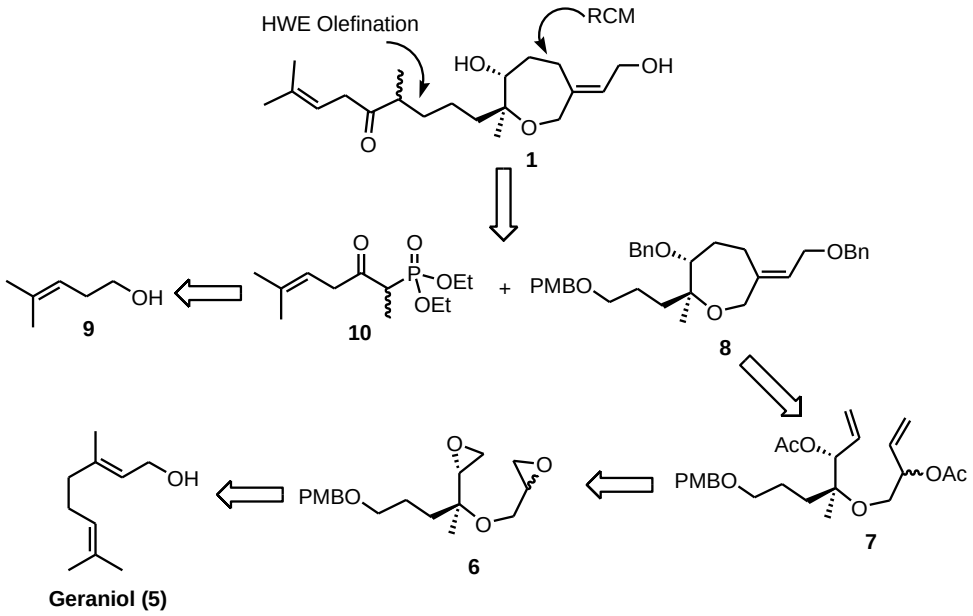


1. R = $(CH_3)_2C=CHCH_2$ R' = H Zoapatanol
2. R = $(CH_3)_2CHC(CH_3)=CH$ R' = H Montanol
3. R = $(CH_3)_2C(OH)CH=CH$ R' = Ac Tomentol
4. R = $H_2C=C(CH_3)CH(CH_3)CH_2$ R' = H Tomentanol

Figure 1

Section B: Studies towards the total synthesis of Zoapatanol.

Key issue for the successful synthesis of zoapatanol includes the stereocontrolled formation of oxepane ring, introduction of stereoselective exocyclic double bond and installation of nonenyl side chain. According to our retrosynthetic analysis, the stereoselective exocyclic

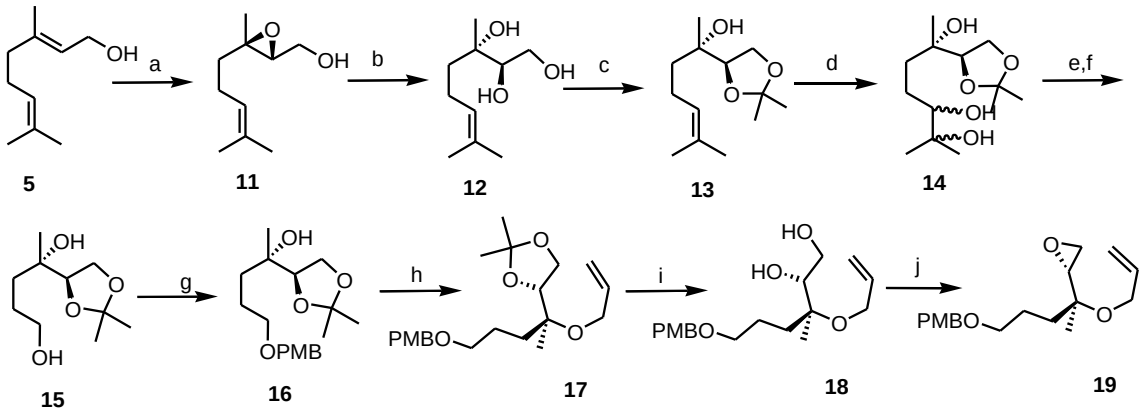


Scheme 1. Retrosynthetic analysis

double bond and nonenyl side chain would arise through Horner-Wordsworth-Emmons olefination reaction. And the stereocontrolled oxepane ring could be constructed ring-closing

metathesis reaction of diolefine **7** which synthesized from commercially available geraniol **5** by using Sharpless asymmetric epoxidation reaction and bis-epoxide opening reaction with Corey-Chaykovsky reagent (Scheme 1).

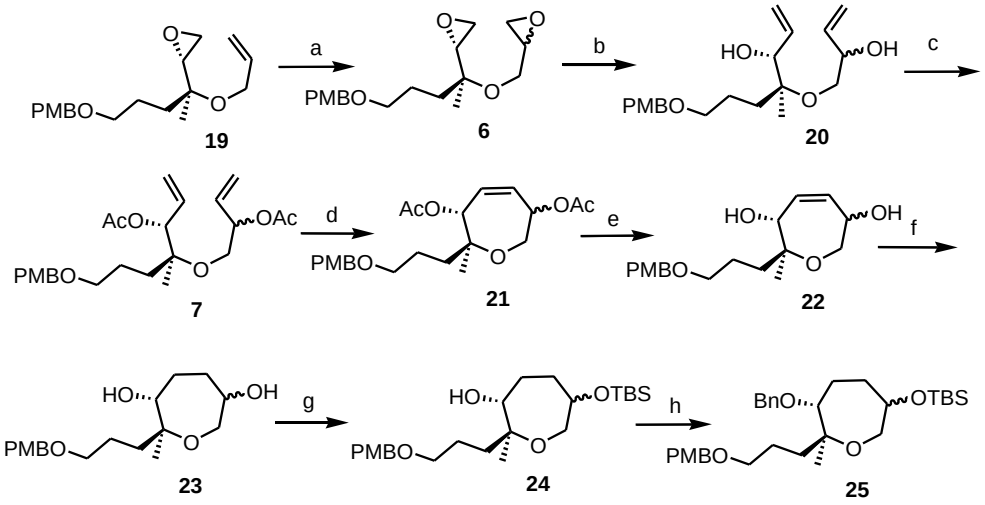
Our synthesis started from commercially available geraniol (**5**) which was subjected to Sharpless asymmetric epoxidation using (–)-DIPT, $Ti(O^iPr)_4$ and TBHP to get the epoxy alcohol **11** (Scheme 2). The alcohol **11** was then regeoselectively hydrolyzed by catalytic $HClO_4$ in THF-H_2O system followed by selective protection of primary and secondary hydroxyl group as its acetonide **13** using 2,2-DMP. Compound **13** was then treated with OsO_4 followed by oxidative cleavage with silica supported $NaIO_4$ and reduction with $NaBH_4$ afforded diol **15**. The primary hydroxyl group in **15** was selectively protected as its PMB ether **16** using PMBBr, NaH in THF in 96% yield. The quaternary hydroxyl group was then converted to its allyl ether **17** using allyl bromide and subsequent deprotection of acetonide by using CSA yielded diol **18**. Diol **18** was then subjected to



Scheme 2. *Reagents and conditions:* (a) $Ti(O^iPr)_4$, (–)-DIPT, TBHP, CH_2Cl_2, MS 4 Å, −30 ^oC, 10 min, 95%, (b) $HClO_4$, THF-H_2O, 0 ^oC-rt, 3 h, 78%, (c) 2,2-DMP, DMF, 0 ^oC-rt, 1 h, 96%, (d) OsO_4, NMO, Acetone-H_2O, rt, 48 h, 95%, (e) SiO_2-$NaIO_4$, CH_2Cl_2, 10 min, 97%, (f) $NaBH_4$, MeOH, rt, 30 min, 94%, (g) PMBBr, NaH, THF, 0 ^oC-rt, 5 h, 96%, (h) NaH, Allylbromide, DMF, 0 ^oC-rt, 3 h, 87%, (i) CSA, MeOH, rt, 24 h, 85%, (j) NaH, Trisylimidazole, THF, 0 ^oC-rt, 15 min, 82%.

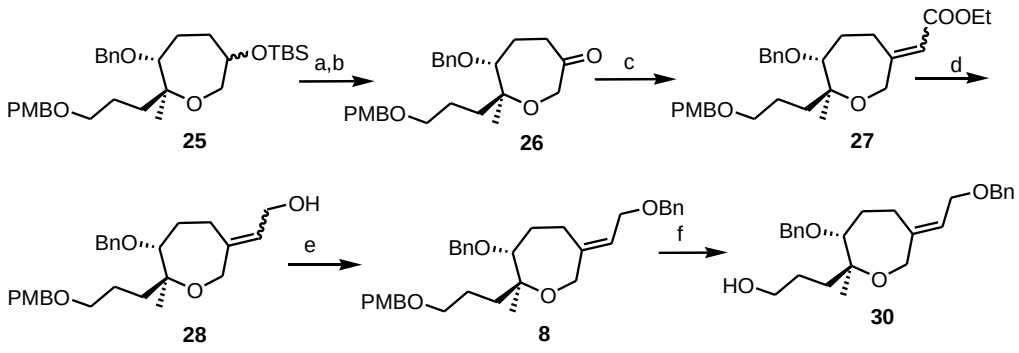
trisylimidazole, NaH in THF to furnish the epoxide **19** in single step. Olefin **19** was then reacted with *m*-CPBA (Scheme 3) to get the inseparable diastereomeric mixture of diepoxide **6**. As the newly formed chiral center has to be oxidized after few steps, so we proceeded with the mixture of diastereomers. Upon treatment of **6** with Me_3SI in presence of *n*-BuLi

followed by protection with acetic anhydride, Et_3N produce the ring-closing metathesis (RCM) precursor **7** in good yield. Ring-closing metathesis (RCM) reaction using Grubbs 1st generation catalyst yielded the oxepane **21** which was subjected to K_2CO_3, MeOH to furnish the diol **22**. The olefin **22** was then hydrogenated in ethyl acetate to produce its saturated derivative **23**. Regeoselective TBS protection of the less crowded



Scheme 3. *Reagents and conditions:* (a) *m*-CPBA, CH_2Cl_2, 0 ^oC-rt, 8 h, 83%, (b) Me_3SI, *n*-BuLi, THF, –10 ^oC, 45min, 94% (c) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 ^oC-rt, 4 h, 95%, (d) Grubbs-I, CH_2Cl_2, reflux, 28 h, 70%, (e) K_2CO_3, MeOH, 0 ^oC-rt, 10 h, 90%, (f) Pd/C, EtOAc, rt, 10 min, 78%, (g) TBSCl, Imidazole, CH_2Cl_2, 0 ^oC-rt, 2 h, 88%, (h) NaH, BnBr, DMF, 0 ^oC-rt, 12 h, 87%.

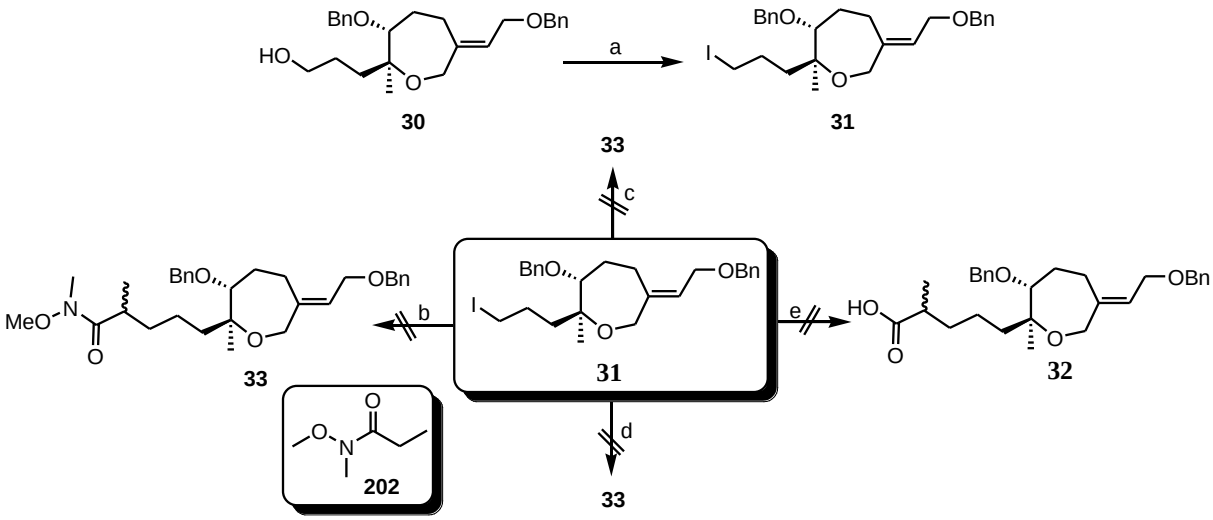
hydroxyl in **23** and subsequent protection of the crowded hydroxyl by BnBr, NaH in DMF furnished **25**. The TBS group was then deprotected by CSA, MeOH and subsequent oxidation (Scheme 4) using Dess-Martin periodinane (DMP) yielded **26** in good yield. Compound **26** when subjected to Horner-Wadsworth-Emmons olefination afforded



Scheme 4. *Reagents and conditions:* (a) CSA, MeOH, rt, 15 h, (b) Dess-Martin-periodinane, DCM, 0 ^{o}C, 1 h, 69%, (c) $EtO_2CCH_2P(O)(OEt)_2$, NaH, THF, rt, 97%, (d) LAH, THF, 0 ^{o}C-rt, 2 h, 90%, (e) Ag_2O, BnBr, TBAI, DCM, rt, 16 h, 94%, (f) CAN, CH_3CN-Water, 0 ^{o}C-rt, 11 h, 90%.

inseparable stereoisomer **27** (*E:Z* = 67:33) which upon treatment with LAH in THF produced the allyl alcohol **28.** Benzylation of **28** with Ag_2O, BnBr and TBAI furnished **29** in good yield. It is noteworthy to mention here that, at this stage the two isomers ware separated by simple silica gel column chromatography. PMB group was then selectively deprotected with CAN in acetonitrile-water system to furnish the alcohol **30** in 90%**.**

After successful construction of the oxepane **30**, our next task was to perform the Horner-Wordsworth-Emmons olefination reaction for introduction of the side chain. Accordingly, we tried to oxidize the primary hydroxyl group present in **30** with IBX in DMSO-THF system, but we got intractable mixture of products. Under other oxidation conditions such as Dess-Martin periodinane, TEMPO-BAIB, SO_3-Py, PCC and PDC also produced intractable mixture of products. To circumvent the problem, we changed our strategy to introduce the side chain based on alkylation reaction. The hydroxyl group in **30** was then converted to its iodo derivative **31** in presence of TPP, imidazole and iodine in THF at 0 ^{o}C. The reaction of iodo **31** with Weinreb amide **202** in presence of KHMDS in THF at −78 ^{o}C resulted complete



Scheme 6. *Reagents and conditions*: (a) TPP, imidazole, I_2, THF, 0 ^{o}C, 10 min, 85% (b) **202**, KHMDS, THF, −78 ^{o}C to rt, (c) **202**, KHMDS, HMPA, −78 ^{o}C to rt, (d) **202**, LDA, THF, −78 ^{o}C, (e) propanoic acid, LDA, THF, 0 ^{o}C.

recovery of starting material **31**. The same reaction even failed in different condition such as LDA in THF and KHMDS in presence of HMPA in THF. Reaction of iodo **31** with propanoic acid in presence of LDA in THF at -78 ^{o}C to rt was also failed to give desired product **32** (Scheme 6).

In conclusion, we have successfully completed the stereocontrolled synthesis of oxepane core structure of (+)-zoapatanol following a novel protocol which included Sharpless asymmetric epoxidation, bis-epoxide opening reaction with Corey reagent, Grubbs ring-closing metathesis reaction and Horner-Wadsworth-Emmons olefination reaction as key steps.

Chapter II:

Section A: brief introduction of ten-member lactones including their isolation, biological activity and synthetic approaches.

Many natural occurring ten-membered lactones isolated from fungal metabolites, commonly known as decanolides. They have attracted significant attention from synthetic organic chemists as well as medicinal chemists, because of their interesting structural features and exhibit various biological activities like plant growth inhibition, anti-feedant, anti-fungal and anti-bacterial activities. The previous synthetic approaches to synthesize ten member lactones including their isolations and biological activities have been described briefly.

Section B: Stereoselective total synthesis of Stagonolide C and formal total synthesis of Modiolide A.

The main phytotoxic metabolites produced by *S. Cirsii* in liquid culture, named stagonolide (**34**) was isolated and characterized as a new nonenolides. Eight other stagonolides, named stagonolide B-I (**35-42**) were isolated and chemically characterized including their biological properties. Stagonolide G-I (**40-42**) were structurally similar to stagonolide (**34**) and stagonolide B-F (**35-39**), isolated from the same fungus (Figure 2). Another structurally similar 10-membered lactone known as modiolide A (**43**) was isolated by Kobayashi and co-workers as an anti-bacterial and anti-fungal compound from marine-origin microorganisms and the first total synthesis was achieved by Sugai *et al.*

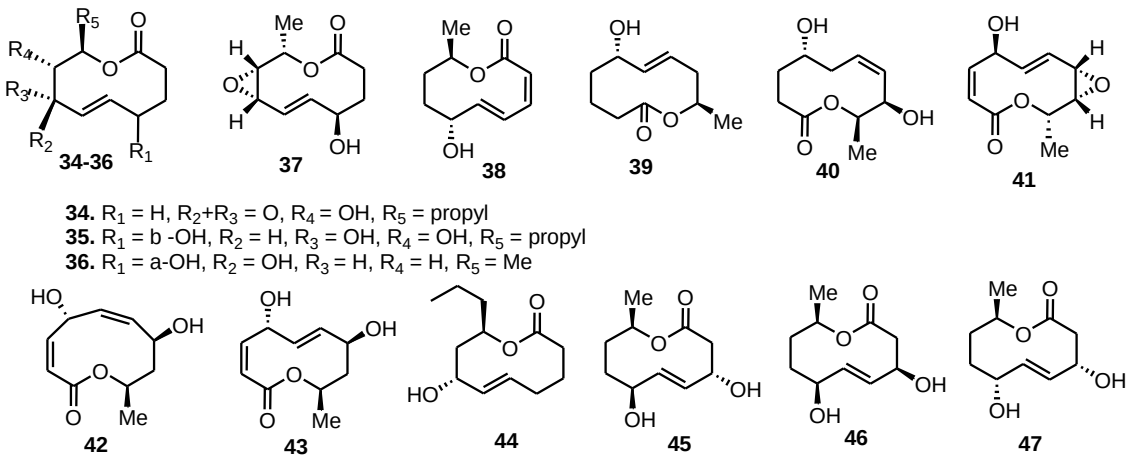
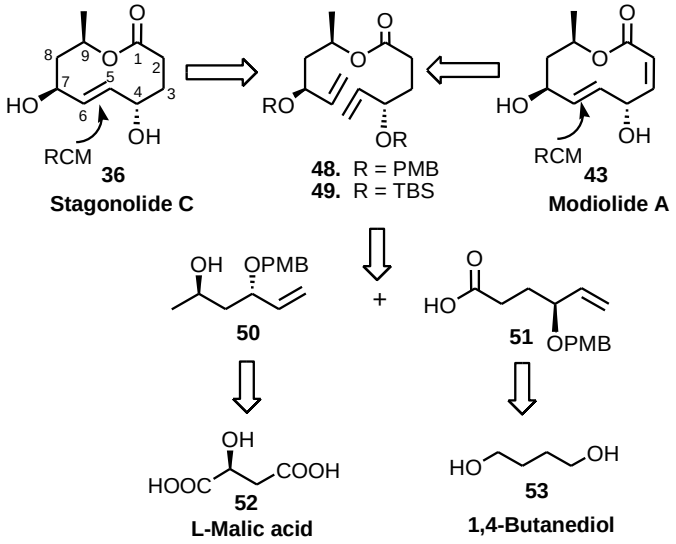


Figure 2. Stagonolide, stagonolide B-I, modiolide A, herbarumin III, nonenolide, and decarestrictine C1 and C2

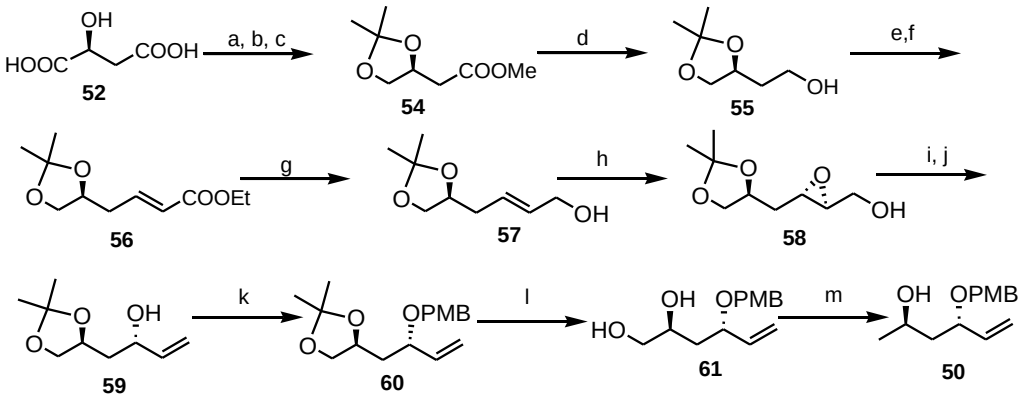
According to our retrosynthetic analysis (Scheme 7), the construction of the ten-membered lactone would arise from the formation of the C5-C6 olefinic linkage from bis-alkene which in turn would be prepared via esterification of alcohol **50** and acid **51**. Both the fragments would be prepared from malic acid **52** and 1,4-butane diol **53,** respectively.



Scheme 7. Retrosynthetic analysis of stagonolide C and modiolide A

The synthesis of fragment **50** began with the commercially available malic acid (**52**). Malic acid was first esterified with catalytic BF_3-Et_2O in MeOH (Scheme 8) to give diester compound. Then the diester was subjected to selective reduction with BH_3-Me_2S in presence

of catalytic $NaBH_4$ in THF and successive protection of 1,2-diol by 2,2-DMP in CH_2Cl_2 yielded **54** in good yield. The ester **54** was then reduced with LAH in THF to afford the

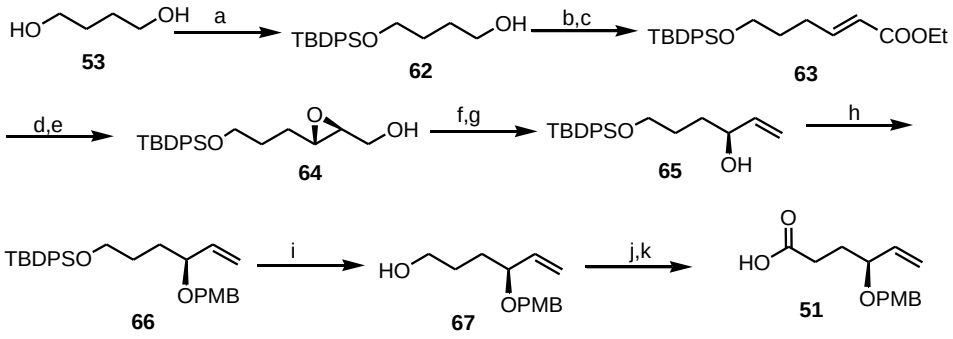


Scheme 8. *Reagents and conditions*: (a) BF_3-Et_2O, MeOH, rt, 15 h, 95%, (b) BH_3-Me_2S, cat. $NaBH_4$, THF, −20 °C to rt, 2 h, 90%, (c) 2,2-DMP, DCM, 0 °C-rt, 12 h, 80%, (d) LAH, THF, 0 °C-rt, 3 h, 94%, (e) IBX, DMSO-THF, rt, 3 h, (f) $Ph_3PCHCOOEt$, Benzene, reflux, 12 h, 85% for two steps, (g) DIBAL-H, CH_2Cl_2, −15 °C, 15 min, 81%, (h) (+)-DIPT, $Ti(O^iPr)_4$, TBHP, CH_2Cl_2, −20 °C, 4 Å MS, 10 h, 85%, (i) TPP, Imidazole, I_2, THF, 0 °C, 10 min, (j) Zn dust, NaI, MeOH, reflux, 3 h, 68% for 2 steps, (k) NaH, PMBBr, THF, 0 °C-rt, 4 h, 84%, (l) *p*-TSA, MeOH, 0 °C-rt, 3 h, 90%, (m) **(**1**)** *p*-TsCl, CH_2Cl_2, Et_3N, 0 °C-rt, 6 h, (2) LAH, THF, 0 °C-rt, 2 h, 76% for two steps.

alcohol **55** in 94% yield. The alcohol was subjected to oxidation followed by homologation by C2 Wittig ylide in benzene under reflux conditions furnished α,β-unsaturated ester **56** in 85% yield over two steps. The ester **56** was then reduced with DIBAL-H at −15 °C in CH_2Cl_2 to afford allyl alcohol **57** in 81% yield. The allyl alcohol **57** under Sharpless asymmetric epoxidation condition with (+)-DIPT produced 2,3-epoxy alcohol **58** in 85% yield with 95:5 ratio with the required isomer. Conversion of hydroxyl to iodo derivative with TPP, I_2 and imidazole in THF followed by activated Zn-dust mediated reductive elimination furnished allylic alcohol **59**, which was protected as its *p*-methoxybenzyl ether to afford **60** in 84% yield. Deprotection of isopropylidene group with *p*-TSA in methanol followed by selective protection of the primary hydroxyl group with TsCl and Et_3N which on treatment with $LiAlH_4$ gave the required alcohol fragment **50** in 76% yield over two steps.

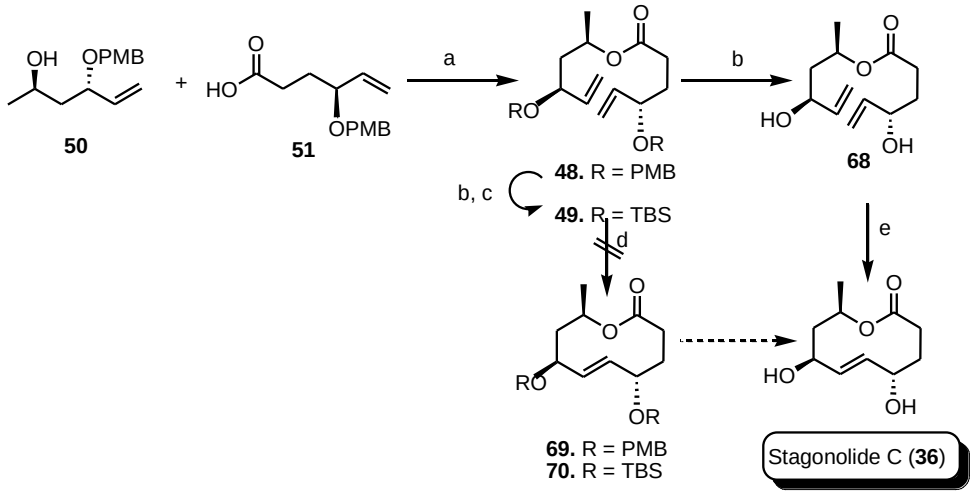
The synthesis of fragment **51** began from a known intermediate **63** prepared from commercially available 1,4-butane diol (**53**) and followed by the same sequence of reactions as performed during the preparation of **60**. Treatment of compound **66** with 1M solution of

TBAF in THF afforded **67** in 94% yield (Scheme 9). The primary hydroxyl group was then oxidized with IBX to afford the corresponding aldehyde; further oxidation with $NaClO_2$ in presence of NaH_2PO_4 and 2-methyl-2-butene as a scavenger furnished acid **51** in 84% yield over two steps.



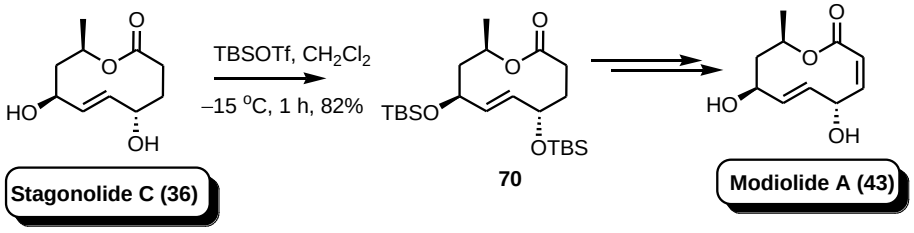
Scheme 9. *Reagents and conditions*: (a) TBDPSCl, NaH, THF, 0 ^oC-rt, 5 h, 88%, (b) IBX, DMSO-THF, rt, 4 h, (c) $CH(PPh_3)CO_2Et$, benzene, reflux, 10 h, 80% for two steps, (d) DIBAL-H, CH_2Cl_2, –20 ^oC, 10 min, 90%, (e) (+)- DIPT, $Ti(O^iPr)_4$, TBHP, CH_2Cl_2, –20 ^oC, 4 Å MS, 3 h, 92%, (f) TPP, imidazole, I_2, THF, 0 ^oC, 10 min, (g) Zn dust, NaI, MeOH, reflux, 4 h, 76% for two steps, (h) PMBBr, NaH, THF, 0 ^oC-rt, 4 h, 84%, (i) TBAF, THF, 0 ^oC-rt, 7 h, 94%, (j) IBX, THF, DMSO, rt, 3 h, (k) $NaClO_2$, $NaH_2PO_4.2H_2O$, 2-methyl-2-butene, ^tBuOH-H_2O, 0 ^oC-rt, 2 h, 84% over two-steps.

Our next task was to couple the two fragments and investigate the critical ring-closing metathesis reaction. Accordingly, condensation of fragments **50** and **51** was achieved under



Scheme 10. *Reagents and conditions*: (a) EDCI, DMAP, CH_2Cl_2, 0 ^oC, 14 h, 85%, (b) DDQ, CH_2Cl_2:H_2O (9:1), 0 ^oC-rt, 40 min, 85%, (c) TBDMSCl, imidazole, CH_2Cl_2, rt, 10 h, 86%, (d) Grubbs 2nd Generation, CH_2Cl_2 or toluene, reflux, 48 h, (e) Grubbs 2nd Generation, CH_2Cl_2, reflux, 30 h, 68%.

EDCI (*N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride) and DMAP (4-di(methylamino)pyridine) conditions to afford the (Scheme 10) bis-olefinic ester **48** in 85% yield. As per our report, a 0.001 M solution of **48** and 10 mol% of Grubbs' second-generation catalyst was heated at reflux for 8-48 h in dry, degassed CH_2Cl_2 failed to provide the required ten-membered lactone. The crucial ring-closing metathesis reaction even failed in dry benzene and by changing the protecting groups from PMB-ethers to TBS-ethers. Finally, reaction with diol **68** (0.001 M in CH_2Cl_2) with Grubbs' second-generation catalyst afforded the required ten- membered lactone (stagonolide C) **36** as the sole product in 68% yield. The geometry of the newly formed double bond was unequivocally assigned by detection of the olefinic J_{trans} coupling constant (15.6 Hz between the protons at δ 5.41 and 5.58 ppm, respectively). The constitution and configuration of the assigned structure was unambiguous as the spectral and analytical data were in excellent accord with the proposed structure and perfectly matched those reported in the literature.



Scheme 11. Formal total synthesis of modiolide A (**43**)

As the RCM reaction failed with TBS-protected and PMB-protected bis-olefins, we proceeded to have an advanced intermediate for the total synthesis of modiolide A. The free hydroxyl groups present at C4 and C7 were protected as its TBS-ethers with TBSOTf in CH_2Cl_2 at −15 °C to afford the bis-TBS compound **70** (Scheme 11), whose spectral and analytical data were in good agreement with the reported values.

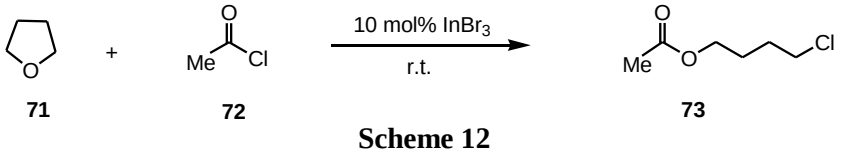
In conclusion, the first stereoselective total synthesis of stagonolide C and formal total synthesis of modiolide A were achieved starting from commercially available malic acid and 1,4-butane diol.

Chapter III:

Section A: Indium(III) bromide catalyzed cleavage of cyclic and acyclic ethers: an efficient and practical ring opening reaction:

The cleavage of ethers is a versatile reaction in organic synthesis, mainly in degradation or transformation of complex molecules especially in biologically active natural products such as carbohydrates and macrolide antibiotics. Particularly, aliphatic, benzylic and allylic ethers are frequently used as protecting groups for hydroxyl functions and subsequent cleavage is a very interesting route to poly functional molecules useful in organic synthesis. Therefore, the development of simple, convenient and practical procedures for the cleavage of cyclic and acyclic ethers continues to be a challenging target in synthetic organic chemistry. Recently, there have been remarkable interest on the catalytic use of indium(III) halides in organic synthesis. Due to their unique catalytic properties, indium(III) bromide have been widely used for a range of organic transformations including glycosidation, thioacetalization, cyanation of ketones and conjugate addition reactions.

Herein, we report our research on the use of indium(III) bromide as novel and efficient catalyst for the cleavage of cyclic and acyclic ethers with acyl chloride under solvent-free conditions. Initially, we attempted the cleavage of tetrahydrofuran (**71**) with acetyl chloride (**72**) in the presence of indium(III) bromide. The reaction went to completion in 2.5 h and the product **73** was obtained in 89% yield (Scheme 12).

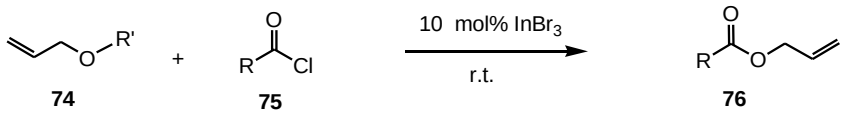


71 **72** **73**

Scheme 12

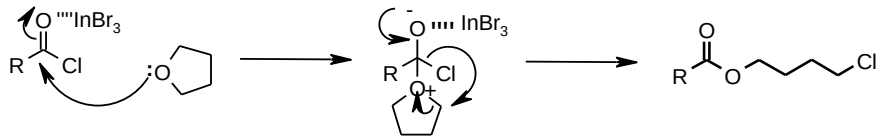
Encouraged by the results obtained with tetrahydrofuran and acetyl chloride, we turned our attention to various acyl chlorides. Interestingly, several acyl chloride derivatives such as benzoyl chloride, 3-methyl-, 2-chloro-benzoylchloride and the acid chloride derived from cyhalothrin involved in the cleavage of tetrahydrofuran to afford the corresponding halo esters in excellent yields (entries **b**-**e**, Table 1). Like tetrahydrofuran, several other cyclic and

acyclic ethers also cleaved by a range acyl chloride derivatives to afford the corresponding halo-esters in good yields. (entries **f-s**, Scheme 13, Table 1).



Scheme 13

The probable mechanism seems to be the activation of carbonyl group of acyl chloride, by indium tribromide and a subsequent attack of furan onto activated carbonyl group. This

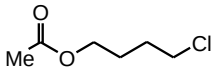
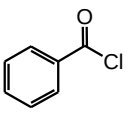
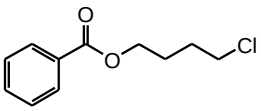


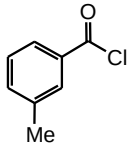
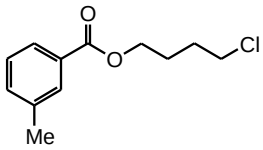
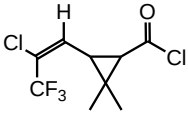
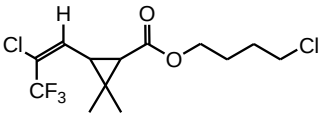
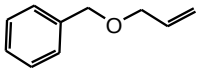
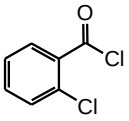
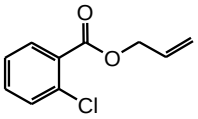
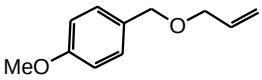
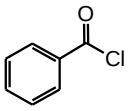
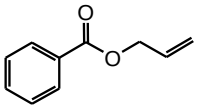
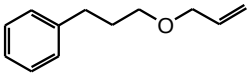
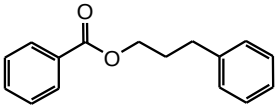
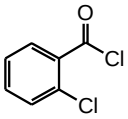
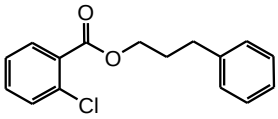
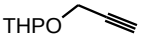
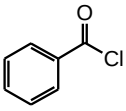
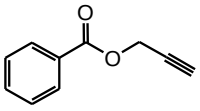
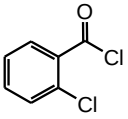
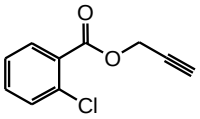
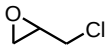
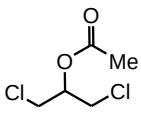
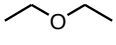
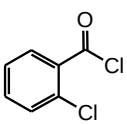
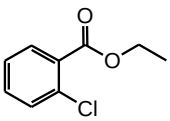
Scheme 14

facilitates an intramolecular attack of leaving chloride ions onto the electronically deficient carbon of tetrahydrofuran moiety would result the required product (Scheme 14).

In all cases, the reactions proceeded smoothly at room temperature with high efficiency. In the absence of catalyst, no cleavage was observed between ethers and acyl chloride. Among various Indium(III) salts such as $InCl_3$, $In(ClO_4)_3$, and $In(OTf)_3$ tested, $InBr_3$ was found to be the most effective for this cleavage in the terms of reaction rates and yields. The scope and generality of this process is illustrated with respect to various cyclic and acyclic ethers and acyl chlorides and the results are presented in Table 1.

Table: 1 Indium(III) bromide catalyzed cleavage of ethers

Entry	Ether **74**	Acyl chloride **75**	Product[a] **76**	Time (h)	Yield(%)[b]
a				2.5	89
b	"			3.5	87

Entry	Ether **74**	Acyl chloride **75**	Product[a] **76**	Time (h)	Yield(%)[b]
c	"			4.0	91
d	"			3.5	82
e				2.5	86
f				3.5	85
g		"		4.0	78
h	"			2.5	87
i				3.0	83
j	"			3.5	85
k				2.0	80
l				2.5	84

[a] All products were characterized by ^{1}H NMR, IR spectra and mass spectrometry.
[b] Yields obtained after column chromatography.

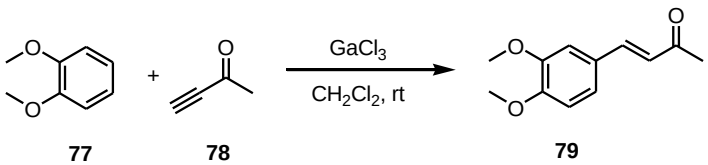
In conclusion, we have described a simple, convenient, efficient and practical method for the cleavage of cyclic and acyclic ethers with acyl chloride using indium(III) bromide as the novel catalyst under solvent-free conditions.

Chapter III:

Section B: Gallium(III) chloride catalyzed stereoselective synthesis of *E*-configured α,β-unsaturated ketones:

Lewis acid catalyzed carbon–carbon bond-forming reactions are of great importance in organic synthesis because of their mild reaction conditions, unique reactivity and improved selectivities. Several Lewis acid promoted reactions have been reported and many have been employed in industry. α,β-Unsaturated ketones are one of the most useful building block to prepare various poly-functionalized organic compounds and have been widely used in organic synthesis. The stereoselective synthesis of α,β-unsaturated ketones has been extensively developed and is generally achieved by condensation, oxidation, elimination and acylation reactions. However, in most of these syntheses, the stereoselective control of the carbon-carbon double-bond formation remains unsolved. Due to their unique Lewis acid activity, gallium halides have been widely used for a variety of organic transformations. Particularly, gallium(III) compounds are being considered as effective Lewis acids to activate alkynes under extremely mild conditions.

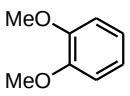
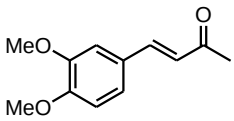
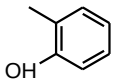
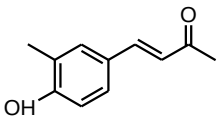
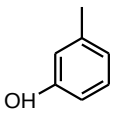
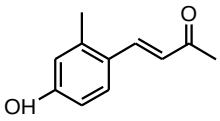
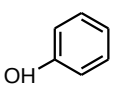
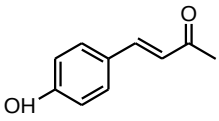
We herein report a novel and efficient protocol for the synthesis of *E*-configured α,β-unsaturated ketones from arenes and ynones. Initially, 1,2-dimethoxybenzene (**77**) was subjected to 3-butyn-2-one (**78**) in the presence of 10 mol% of gallium(III) chloride in CH_2Cl_2 to give (*E*)-4-(1,2-dimethoxy- phenyl)-3-buten-2-one **79** in high yield. The reaction went to completion in 40 minutes and the product was obtained in 88% yield with complete *E*-selectivity (Scheme 15). The assignment of structure and stereochemistry of the product

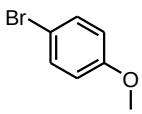
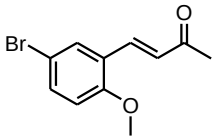
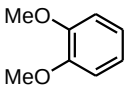
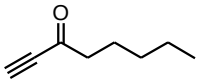
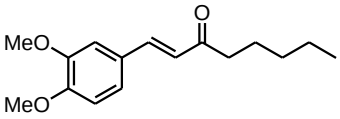
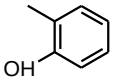
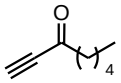
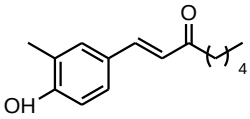
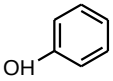
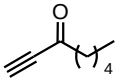
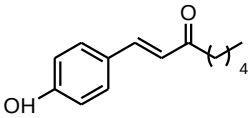
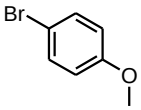
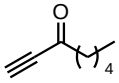
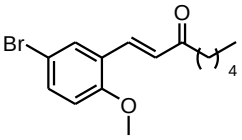
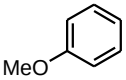
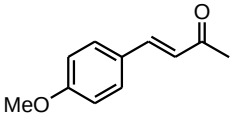
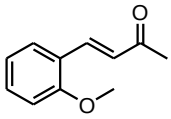
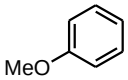
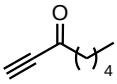
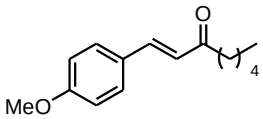
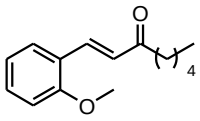
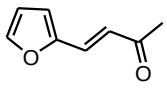


Scheme 15

was established by ^{1}H NMR spectroscopy. The *E*-stereochemistry of the product was determined on the basis of coupling constants of newly formed olefin protons in the ^{1}H NMR spectrum. Encouraged by the results obtained with 1,2-dimethoxybenzene, we turned our attention to various electron-rich arenes. Interestingly, substituted arenes such as *o*-cresol, *m*-cresol, phenol and 4-bromoanisole reacted well with 3-butyn-2-one to give the corresponding *E*-configured α,β unsaturated ketones in good yields (Entries b–e, Table 1). afterward, we turned our concentration towards various substituted ynones and observed that 1-octyn-3-one reacted smoothly with several arenes such as *o*-cresol, phenol and 4-bromoanisole to give the corresponding α,β-unsaturated ketones in good yields with complete selectivity (Entries f–i, Table 1). No *Z*-isomer was observed under these conditions. In the case of disubstituted arenes, the product was obtained as a single regioisomer. Surprisingly, anisole gave both *para* and *ortho* isomers with *para* as the major product (entries j and k, Table 1). These regioisomers could easily be separated by simple column chromatography. Interestingly, furan was also reacted efficiently with 3-butyn-2-one to give exclusively 2-substituted furan in 89% yield (entry l, Table 1). However, low conversions were obtained when reactions were performed with 1-phenyl-2-propyn-1-one. For example, treatment of anisole with 1-phenyl-2-propyn-1-one gave the corresponding α,β-unsaturated

Table: 2 Gallium(III) Chloride Catalyzed Synthesis of a,b-Unsaturated Ketones

Entry	Substrate **77**	Alkyne **78**	Product[a] **79**	**80**	Time (h)	Yield(%)[b]
a					40	88
b					45	89
c					35	85
d					30	80

Entry	Substrate **77**	Alkyne **78**	Product[a] **79**	**80**	Time (h)	Yield(%)[b]
e					30	90
f					30	90
g					35	81
h					30	85
i					35	91
j					55	82 (8:2)
k					30	79 (8:2)
l					45	89

[a] All products were characterized by NMR, IR and ESI-MS.
[b] Isolated yields after column chromatography.

ketone in 20% yield. Surprisingly, no reaction was observed with methyl propiolate. This may be due to intrinsically lower reactivity of methyl propiolate in comparison with 3-butyn-2-one and 1-octyn-3-one. This reaction was further studied with various metal triflates such as $Sc(OTf)_3$, $Yb(OTf)_3$, and $In(OTf)_3$. However, no reaction was observed with these metal

triflates. Other acid catalysts such as $BF_3 \cdot OEt_2$, $InCl_3$, $CeCl_3 \cdot 7H_2O$ and KSF clay also failed to produce the desired product. The scope and generality of this method was illustrated with respect to various arenes and ynones and the results were presented in Table 1.

In conclusion, we have developed a novel synthetic route for the stereoselective synthesis of α,β-unsaturated ketones from arenes and ynones using a catalytic amount of gallium(III) chloride under mild conditions. This method is quite simple, more convenient and high yielding with *E*-selectivity. It is entirely a new approach to produce α,β-unsaturated ketones directly from arenes and ynones in a single-step operation.