APPROACHES TOWARDS THE TOTAL SYNTHESIS OF BIOACTIVE MACROLIDES: LEUCASCANDROLIDE A, AMPHIDINOLACTONE A AND ASPERGILLIDE B

A THESIS

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BY

MANAS RANJAN PATTANAYAK

Reg. No: 09CHPH24

Supervisor

Dr. J. S. Yadav, FNA, FNASc, FTWAS

Director's Research Group

Natural Product Chemistry Division

INDIAN INSTITUTE OF CHEMICAL TECHNOLOGY

(An Associate Institution of UNIVERSITY OF HYDERABAD)

HYDERABAD-500 607, INDIA

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Dedicated
To
My Beloved Parents

INDIAN INSTITUTE OF CHEMICAL TECHNOLOGY

(Council of Scientific and Industrial Research)

Hyderabad – 500 007

Phone: +91-40-27193030
Fax: +91-40-27160387
E-mail: yadavpub@iict.res.in

Dr. J. S. Yadav FNA, FNASc, FTWAS
Director

CERTIFICATE

This is to certify that the research work incorporated in this thesis entitled *"Approaches Towards the Total Synthesis of Bio-active Macrolides: Leucascandrolide A, Amphidinolactone A and Aspergillide B"* has been carried out under my supervision and is a bonafide work of **Mr. MANAS RANJAN PATTANAYAK**. This work is original and has not been submitted in part or full, for any degree or diploma to this or any other university.

Place: Hyderabad
Date:

Dr. J. S. YADAV
(Supervisor)

DECLARATION

I hereby declare that the research work embodied in this thesis is the result of investigations carried out by me at Indian Institute of Chemical Technology, Hyderabad, under the supervision of **Dr. J. S. YADAV**, Director, Indian Institute of Chemical Technology, CSIR, Hyderabad-500 007, India. This work is original and has not been submitted, in part or full, for any degree or diploma to this or any other university.

Place: Hyderabad (**MANAS RANJAN PATTANAYAK)**

Date: **(Candidate)**

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Manas Ranjan Pattanayak

GENERAL REMARKS

- Infrared spectra were recorded on Perkin-Elmer infrared-683 spectrophotometer with NaCl optics. Spectra were calibrated against the polystyrene absorption at 1601 cm^{-1}.
- Mass measurements were carried out on CEC-21-110B double focusing mass spectrometer operating at 70 eV using direct inlet systems and are given in mass units (m/z).
- Proton magnetic resonance spectra were recorded on Varian Gemini-200, Avance 300 Varian Unity-400 and Varian FT-80A. Most of the samples were made in CCl_4/chloroform-d (1:1) using tetramethylsilane (Me_4Si) as the internal standard and are given in the δ scale. The standard abbreviations s, d, t, q, m, dd, dt, br s, refer to singlet, doublet, triplet, quartet, multiplet, double doublet, doublet triplet, broad singlet respectively.
- The optical rotations were measure on JASCO DIP-360 Digital polarimeter.
- All reactions involving air-sensitive compounds were conducted in oven-dried glassware at 90-110 ^oC for 6-12 h. Solutions were transferred with syringes or cannulas (double-ended needles) *via* nitrogen pressure.
- Analytical thin-layer chromatography (TLC) was performed on precoated silica gel-60 F_{254} (0.5 mm) glass plates. Visualization of the spots on TLC plates was achieved either by exposure to iodine vapour or UV light or by spraying sulphuric-*β*-naphthol or phosphomolybdic acid-sulphuric acid or sulphuric acid-anisaldehyde and heating the plates at 120 ^oC.
- All the reactions were monitored by employing TLC techniques using appropriate solvent systems for development. Anhydrous DMF, THF, diethyl ether, hexane and toluene were obtained from an Innovative Technologies solvent purification system. *n*-Pentane, petroleum-ether (boiling range 35 ^oC to 60 ^oC) were distilled over P_2O_5 and stored over pressed sodium wire; dry ether, and dry THF were made by distilling them from sodium-benzophenone ketyl. All chlorinated solvents, pyridine, DMF and TEA were distilled over CaH_2 and stored over 4 A^o molecular sieves. Acetone was distilled over potassium permanganate and potassium carbonate.

- All solvent extracts were concentrated at reduced pressure on Buchi-RE-121 rotary evaporator below 50 ^{o}C. Yields reported are isolated yields of material judged homogenous by TLC and ^{1}H NMR spectroscopy.
- All solvents used for silica gel column chromatography were distilled prior to use. Silica gel used was either 60-120 or 100-200 mesh.
- Moisture sensitive reactions were carried out using standard syringe septum techniques.
- Yields reported are isolated yields of material judged homogeneous by TLC and NMR spectroscopy.
- The names of all the compounds given in the experimental section were taken from ACD/Name, Version 1.0 and ChemDraw Ultra 9.0.

ABBREVIATIONS

[α]	:	Optical rotation
aq	:	aqueous
Ac_2O	:	Acetic anhydride
AcOH	:	Acetic acid
aq	:	Aqueous
atm	:	Atmosphere
BAIB	:	bis(acetoxy)iodobenzene
$BF_3.OEt_2$	:	boron trifluoride diethyl ether
Bn	:	Benzyl
n-BuLi	:	*n*-butyl lithium
^{t}Bu	:	*tert*-butyl
c	:	Concentration
CCl_4	:	Carbon tetrachloride
$CeCl_3$	:	Cerium Chloride
CBS	:	Corey-Bakshi-Sibata
m-CPBA	:	*meta*-Chloroperbenzoic acid
CuCN	:	Copper cyanide
cm	:	Centimetre
DCM	:	Dichloromethane
DET	:	diethyl tartrate
DHP	:	dihydro pyran
DIBAL-*H*	:	diisobutylaluminum hydride
L(+)-DIPT	:	L(+)- Diisopropyltartarate
DMAP	:	4-(dimethylamino)pyridine
DMF	:	*N*,*N*-dimethylformamide
DMP	:	2,2-dimethoxypropane
DMSO	:	Dimethyl sulphoxide
EI-MS	:	Electron impact mass spectrometry
ESI-MS	:	Electrospray ionization mass spectrometry
Et	:	Ethyl
EtMgBr	:	Ethyl magnesium bromide
EtOAc	:	Ethyl acetate

Fig	:	Figure
g	:	gram
h	:	hour (s)
HMPA	:	Hexamethyl phosphoramide
HRMS	:	High Resolution Mass Spectrometry
Hz	:	Hertz
IR	:	Infrared
IBX	:	Iodoxy benzoic acid
J	:	Coupling costant
$^{i}Pr_2EtN$	:	Diisopropyl ethyl amine (Hunig's base)
$LIALH_4$	:	Lithium aluminium hydride
LC-MS	:	Liquid chromatography mass spectrometry
Li	:	Lithium
$LiNH_2$	:	Lithiumamide
Liq	:	Liquid
MeI	:	Methyl iodide
mL	:	millilitre
mp	:	melting point
MOM	:	Methoxymethyl
MOMCl	:	Methoxymethylchloride
MsCl	:	Methanesulphonylchloride
MHz	:	Megahertz
NMR	:	Nuclear magnetic resonance
nOe	:	nuclear Overhauser enhancement
PMB	:	*p*-methoxybenzyl
PMBBr	:	*p*-methoxybenzylbromide
PMR	:	Proton magnetic resonance
PPTS	:	Pyridiniumparatolunesulphonate
^{i}Pr	:	*iso*-propyl
PTSA	:	*para*-toluenesulphonic acid
Py	:	Pyridine
R_f	:	Retardation factor
rt	:	room temperature
TBAF	:	tetrabutylammonium fluoride

TEMPO	:	2,2,6,6-tetramethyl-1-piperidinyloxy free radical
TBS	:	*tert*-butyldimethylsilyl
TBHP	:	*tert*-butyl hydroperoxide
TEA	:	Triethylamine
THF	:	Tetrahydrofuran
THP	:	Tetrahydropyran
$Ti(O_iPr)_4$	:	Titanium isopropoxide
TLC	:	Thin layer chromatography
TosMIC	:	Tosyl methyl isocyanide
TPP	:	Triphenylphosphine
Ts	:	Tosyl (*p*-toluenesulphonyl)
UV	:	ultraviolet

SYNOPSIS

SYNOPSIS

The thesis entitled **"Approaches Towards the Total Synthesis of Bioactive Macrolides: Leucascandrolide A, Amphidinolactone A and Aspergillide B"** has been divided into three chapters.

CHAPTER I: This chapter is further divided into two sections.

Section A: This section describes a brief introduction to pyran containing bioactive natural products and previous approaches for the macrolide core of Leucascandrolide A.

Section B: This section deals with the total synthesis of the macrolide core of Leucascandrolide A.

CHAPTER II: This chapter is again subdivided into two sections.

Section A: This section deals with a brief introduction to olefin metathesis reaction and previous approaches for Amphidinilactone A.

Section B: This section describes the synthesis of the macrolactone Core of Amphidinolactone A.

CHAPTER III: This chapter is further divided into two sections.

Section A: This section includes introduction and previous approaches for Aspergillide B.

Section B: This section describes stereoselective approach towards the total synthesis of Aspergillide B.

CHAPTER I: Section A:

This Section **describes** ***the introduction to*** **"Pyran Containing Bioactive Natural Products and Previous Approaches for Macrolide Core of Leucascandrolide A ".**

CHAPTER I: Section B:

This Section ***deals with*** **the "Total Synthesis of the Macrolide Core of Leucascandrolide A".**

In 1996, Pietra and co-workers identified a new genus of calcareous sponges *Leucascandra caveolata* obtained from the northeastern coast of New Calendonia Coral Sea, which resulted in the discovery of a highly complex natural product designated as leucascandrolide A (**1**). This macrolide exhibits high in vitro cytotoxicity against human KB and P388 tumor cell lines displaying IC_{50} values of 0.05 and 0.25 μg/mL, respectively. The

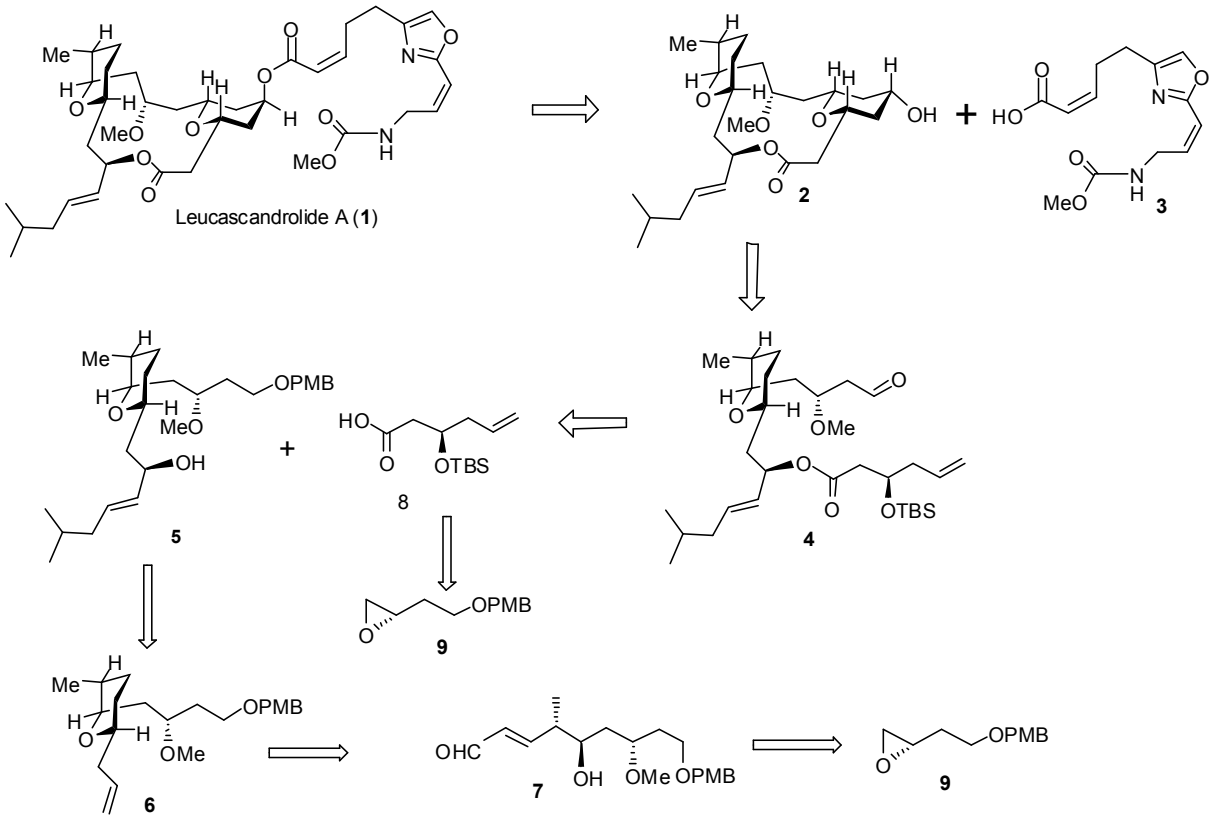
natural product also possesses potent antifungal ability against *Candida albicans*, pathogenic yeast that attacks AIDs patients and other immunocompromised individuals. Additionally, following hydrolysis of the C5 ester linkage, biological testing of the 18-membered macrocyclic core and the separated side chain demonstrated that the macrocyclic domain is solely responsible for the cytotoxicity, while the oxazole-containing unsaturated side chain appears to be responsible for the antifungal activity. The highly oxygenated 18-membered macrolide (**1**) has eight stereogenic centers and three alkenes and also features two trisubstituted tetrahydropyran rings, one of these having an unusual oxazole-containing side chain axially appended at C5. A subsequent report indicates that leucascandrolide A is no longer available from its initial natural source. It has been proposed that leucascandrolide A and its cometabolite leucascandrolide B are products of opportunistic microbial colonization of the sponge, as evidenced by the large amounts of dead tissue in the initial harvest of *Leucascandra caveolata*. Currently, there is no natural source of leucascandrolide A. Based on its impressive biological activity, inaccessibility from natural sources, and structural complexity associated with ample synthetic challenges, the construction of leucascandrolide A has spurred considerable synthetic interest, resulting in several total and formal syntheses.

We achieved a unique synthetic solution for the synthesis of leucascandrolide featuring a concise, convergent, and highly stereoselective approach to this complex natural product. Our interest for **1** arose from studies in which we demonstrated that the critical *trans*-2,6-disubstituted tetrahydropyran relevant to the C11-C15 fragment would be prepared following a recently developed iodocyclization of *δ*-hydroxy *α,β*-unsaturated aldehyde with allyltrimethyl silane in the presence of molecular iodine (Scheme 1). The second most important reaction was to apply a Prins-type macrocyclization which has recently emerged as a successful strategy in the synthesis of polyketide derived complex natural products.

Retrosynthetic analysis of the leucascandrolide A

The retrosynthetic analysis of Leucascandrolide A is shown in Scheme 1. From the retrosynthetic perspective, disconnection of Leucascandrolide A at the macrolactone core **2** and the oxazole containing side chain **3** at the C5 hydroxyl yeild two fragment **5** and **8**. The macrolactone core **2** could be obtained through a late stage Prins-cyclization. The alcohol fragment **5** could be prepared from the C11-C15 pyran of **6** which could be obtained

following our recently reported protocol. The *δ*-hydroxy *α,β*-unsaturated aldehyde **7** precursor for the iodocyclization reaction as well as the acid fragment **8** could be obtained starting from a known chiral epoxide **9**.

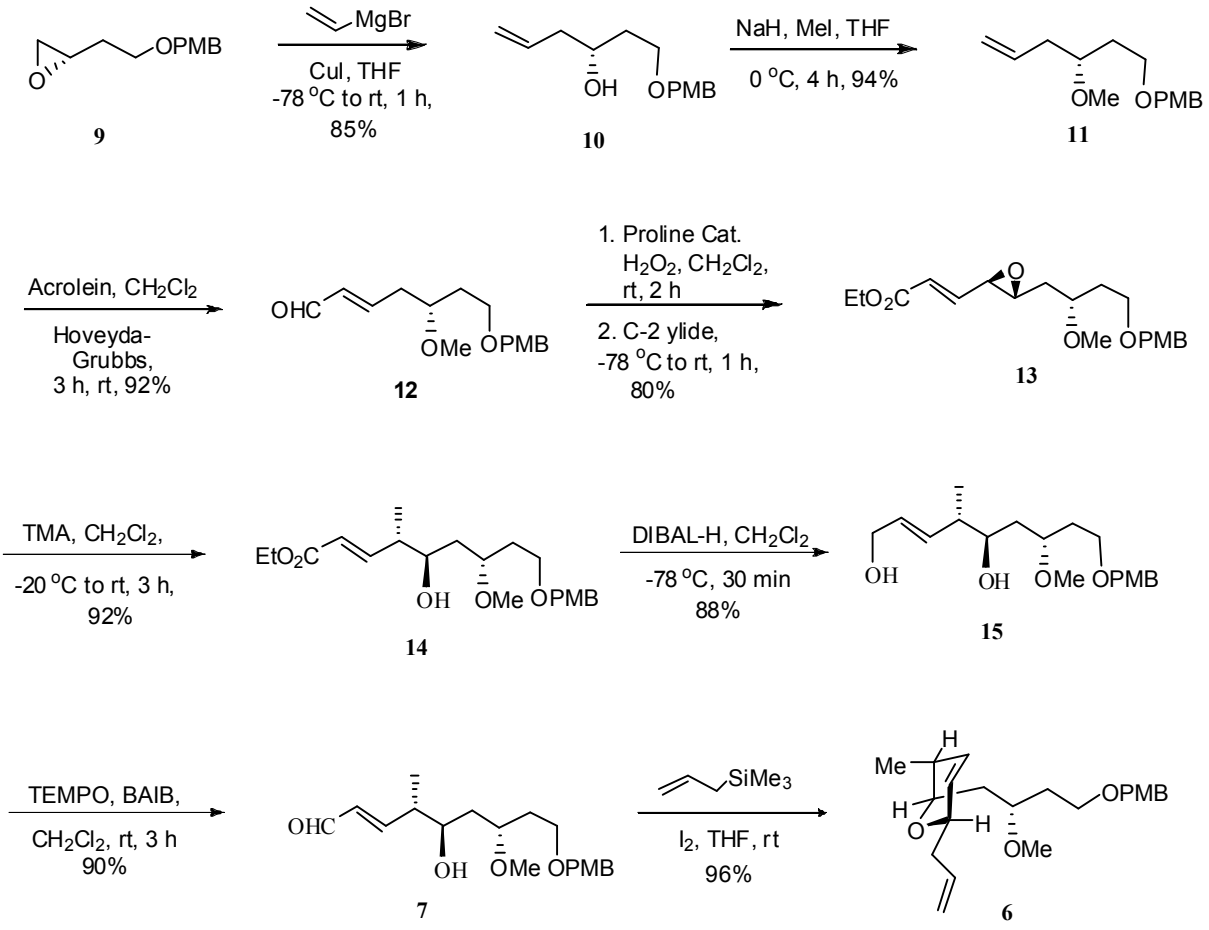


Scheme 1

Synthesis of the alcohol fragment, 5

The journey towards the synthesis of **2** commenced with the conversion of the epoxide **9** into a homoallyl alcohol **10** through the copper-(I)-catalyzed addition of a vinyl Grignard reagent. The hydroxyl group of alcohol **10** was converted to its methyl ether **11** by using MeI and sodium hydride followed by cross metathesis with Hoveyda-Grubbs catalyst affording the *α,β*-unsaturated aldehyde **12**. The aldehyde was then subjected to asymmetric epoxidation under Jørgensen's conditions with H_2O_2 in the presence of a proline-derived catalyst to furnish an epoxy aldehyde, which on condensation with $Ph_3P{=}CHCO_2Et$ afforded an epoxy ester **13** in 80% yield. The regioselective opening of epoxide of **13** was taken place by using trimethyl aluminum (TMA), followed by reduction of an *α,β*-unsaturated ester with DIBAL-*H*

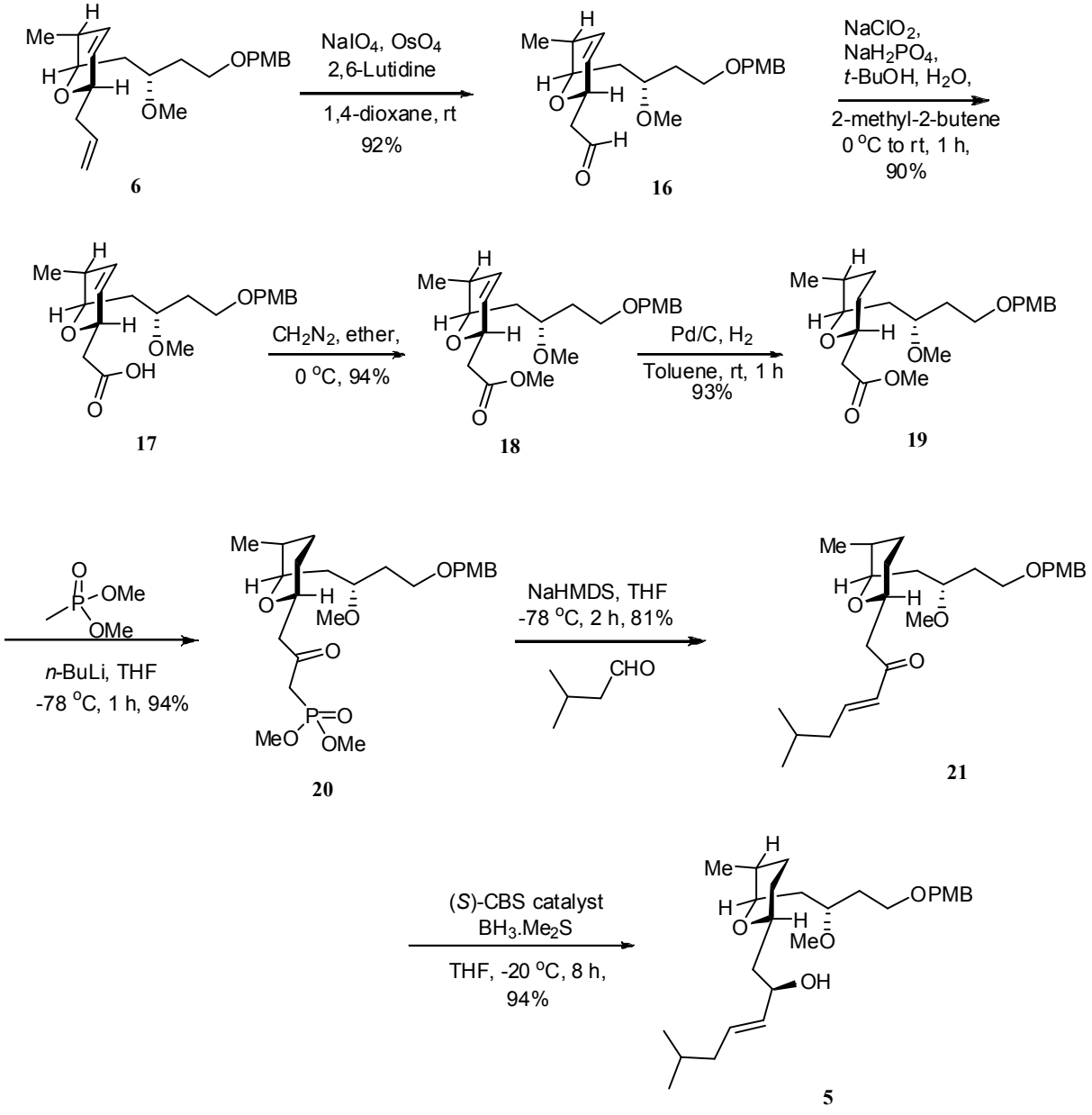
afforded the diol compound **15**. This diol **15** on selective oxidation in the presence of bis(acetoxy)iodobenzene (BAIB) and 2,2,6,6-tetramethylpiperidine-*N*-oxide (TEMPO) furnshied the desired *δ*-hydroxy *α,β*-unsaturated aldehyde **7** in 90% yield which on iodocyclization afforded the pyran containing compound **6**. The ^{1}H and ^{13}C NMR spectra revealed a single isomer which was supported by HPLC analysis data (de ≥ 99%).



Scheme 2

The terminal double bond was oxidatively cleaved following a modified method ($NaIO_4$ and 2,6-lutidine) to obtain aldehyde **16** and a subsequent oxidation of aldehyde under Pinnick conditions afforded carboxylic acid **17** which on treatment with diazomethane gave the ester **18**. Reduction of the double bond over Pd/C under hydrogen atmosphere furnished tetrahydropyran derivative **19** in 93% yield. Nucleophilic addition of the lithiated derivative of dimethyl methyl phosphonate furnished the *β*-keto phosphonate **20**. The *β*-keto phosphonate **20** on treatment with 3-methylbutanal in the presence of NaHMDS gave *α,β*-

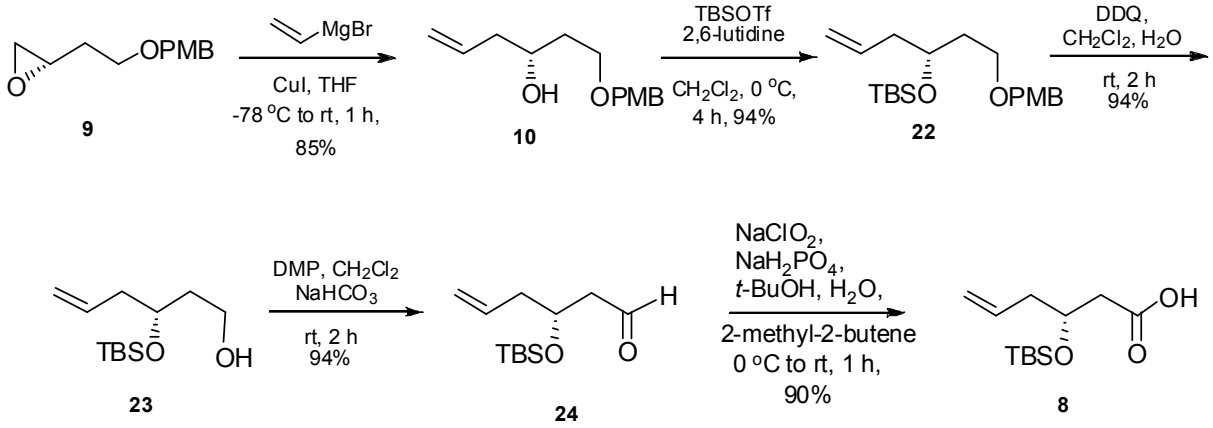
unsaturated ketone **21**. The crucial Corey-Bakshi-Shibata (CBS) reduction of α,β-unsaturated ketone **20** using the reagent (*S*)-2- methyloxazaborolidine in the presence of borane-dimethylsulfide complex installed the C17 stereogenic center present in **5** with a 12:1 diastereomeric ratio (by HPLC) in 82% yield as a separable mixture (Scheme 3).



Scheme 3

Synthesis of the acid fragment 8

The synthesis of acid fragment **8** commenced with the copper-(I)-catalyzed addition of the Grignard reagent vinyl magnesium bromide to the epoxide **9** to afford **10** in 85% yield. The resulting homoallylic alcohol was protected as its TBS-ether using TBSOTf and 2,6-lutidine in anhydrous CH_2Cl_2 to obtain **22** in 93%yield. Deprotection of the *p*-methoxybenzyl group of **22** with DDQ in CH_2Cl_2/H_2O (9:1) yielded the primary hydroxy compound **23** in 94% yield. The resulting primary hydroxy group **23** was oxidized with Dess-Martin periodinane to afford the corresponding aldehyde **24** (Scheme 4) which on further oxidation under Pinnick conditions ($NaClO_2/NaH_2PO_4$/*t*-BuOH/H_2O/2-methyl-2-butene) gave acid **8** whose spectral and analytical data were in good agreement with the reported values.

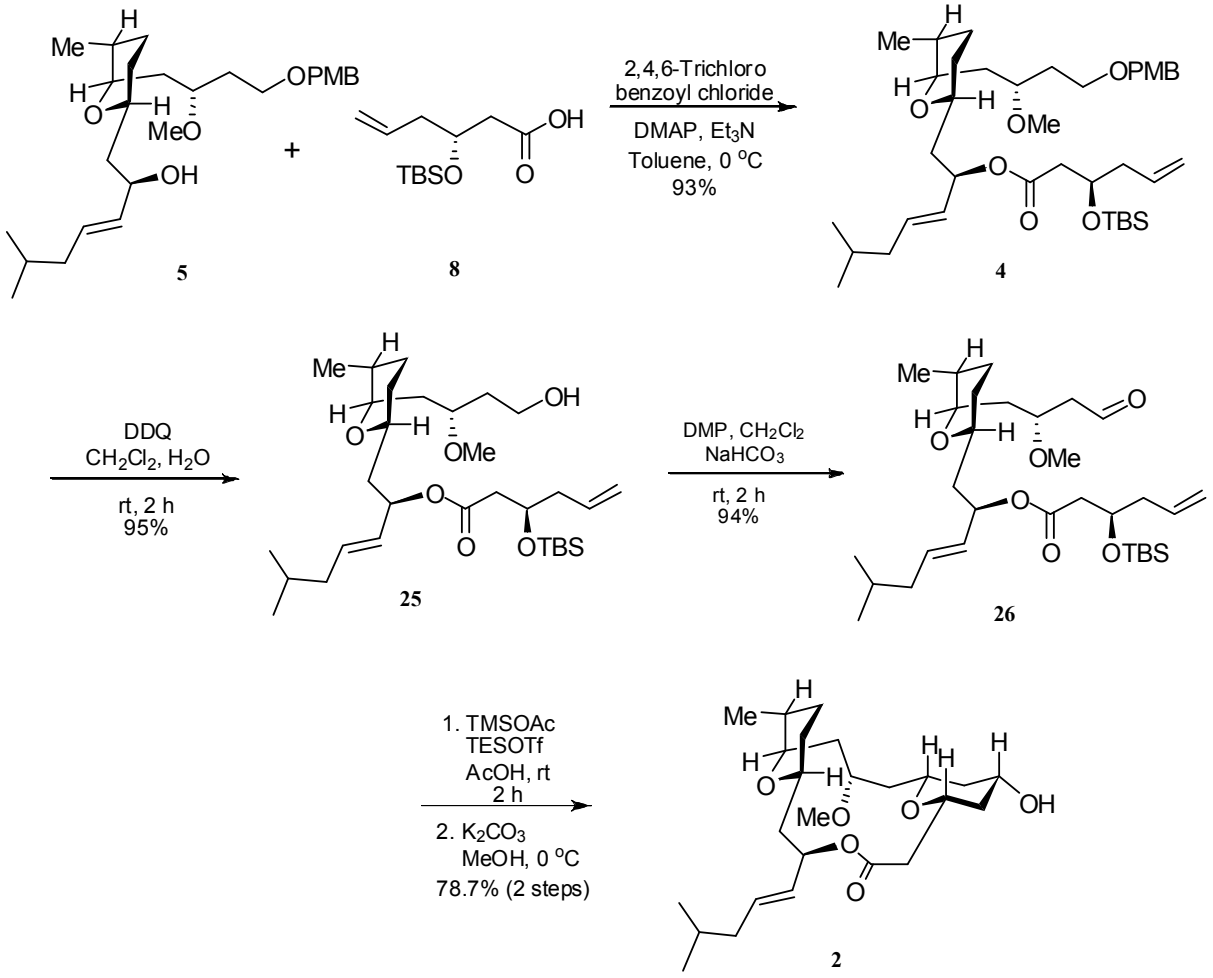


Scheme 4

Synthesis of the macrolide 2

With alcohol **5** and acid fragment **8** in hand, our next task was to couple both of the fragments and verify the Prins-type macrocyclization on an 18-membered macrolactone. The coupling of C1-C6 acid fragment **8** and C7-C23 alcohol fragment **5** was performed under Yamaguchi condition. The coupling of acid fragment **8** and alcohol fragment **5** was performed by using 2,4,6-trichlorobenzoyl chloride, Et_3N and DMAP in toluene to obtain ester **4** in 93% yield, which contains all 23 carbons of the target molecule (Scheme 5). Deprotection of the PMB ether in **4** upon treatment with DDQ afforded alcohol **25** in 95% yield. The primary hydroxyl group at C7 was then oxidized to an aldehyde **26** by treatment with Dess-Martin periodinane which was taken forward for the next reaction without further purification. The next important task was to perform the Prins-macrocyclization. As expected, the construction

of 18-membered macrolide **2** by intramolecular Prins-cyclization of aldehyde **26** was a significant challenge. After extensive investigations, we eventually found that treatment of **26** with >30 equiv of TMSOAc and TESOTf in 0.01M solution of AcOH resulted in the Prins adduct and hydrolysis furnished macrolide **2** in 72% yield over three steps. The outcome of **2** was in good agreement with the previously reported values *i.e* analytical as well as spectral values.



Scheme 5

In summary, our investigations into the allylation of a δ-hydroxy α,β-unsaturated aldehyde with an allyltrimethyl silane in the presence of a catalytic amount of molecular iodine as a protocol combined with the intramolecular Prins-macrocyclization has led to a concise formal total synthesis of leucascandrolide A, which proceeded only in a 20-step longest linear sequence with 11.5% overall yield starting from a known epoxide.

CHAPTER II: Section A:

This Section describes the introduction to **"Olefin Metathesis Reaction and Previous Approaches for Amphidinilactone A ".**

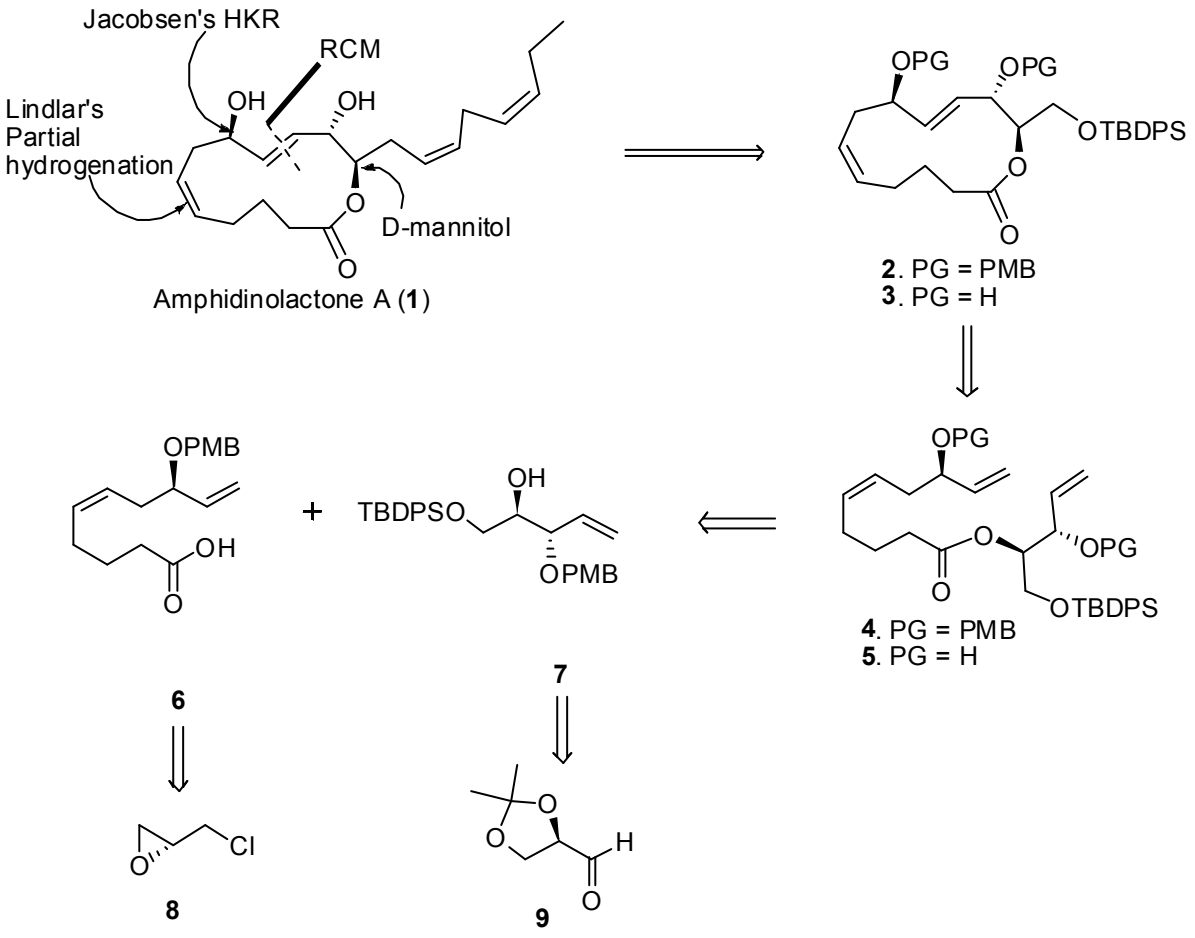
CHAPTER II: Section B:

This Section describes the "Synthesis of the Macrolactone Core of Amphidinolactone A**".**

In 2007, Kobayashi *et al.* isolated amphidinolactone A (**1**), a cytotoxic 13-membered macrolide isolated from a symbiotic dinoflagellate *Amphidinium* sp. (Y-25) separated from an Okinawa a marine acoel flatworm *Amphiscolops sp*. The relative and absolute stereo-chemistry of amphidinolactone A (**1**) has been elucidated on the basis of extensive spectral analysis followed by total synthesis. The interesting biological profile as well as the structural complexity of amphidinolactone A (**1**) has attracted the attention of synthetic organic chemists worldwide. Recently, we reported a concise and efficient total synthesis of amphidinolactone A via stereoselective intramolecular Nozaki-Hiyama-Kishi reaction. Construction of lactone through the formation of C-C bond and particularly by intramolecular ring-closing metathesis reaction stands as a promising tool for the synthesis of macrolides and heterocycles. The influence of protecting groups and the substrate specific nature of the ring-closing metathesis reaction have been reported previously. During our studies on the total synthesis of nonenolide and decarestrictine C1 and C2, we observed a complete control of the double bond geometry by the protecting groups during the ring-closing metathesis reaction. In continuation of our interest in exploring ring-closing metathesis reaction for macrolide synthesis and generality, its substrate and protecting group-based selectivity, we planned to synthesize initially the macrolactone core of amphidinolactone A.

Retrosynthetic analysis of the Amphidinolactone A

According to our retrosynthetic analysis of amphidinolactone A (**1**) shown in Scheme 1, core **3** could be achieved through ring-closing metathesis reaction of **5** which in turn could be obtained by coupling of acid fragment **6** and alcohol fragment **7**. Acid fragment **6** and alcohol fragment **7** could be obtained from (*R*)-epichlorohydrin (**8**) and (*R*)-2,3-*O*-isopropylidene glyceraldehyde **(9**) respectively.

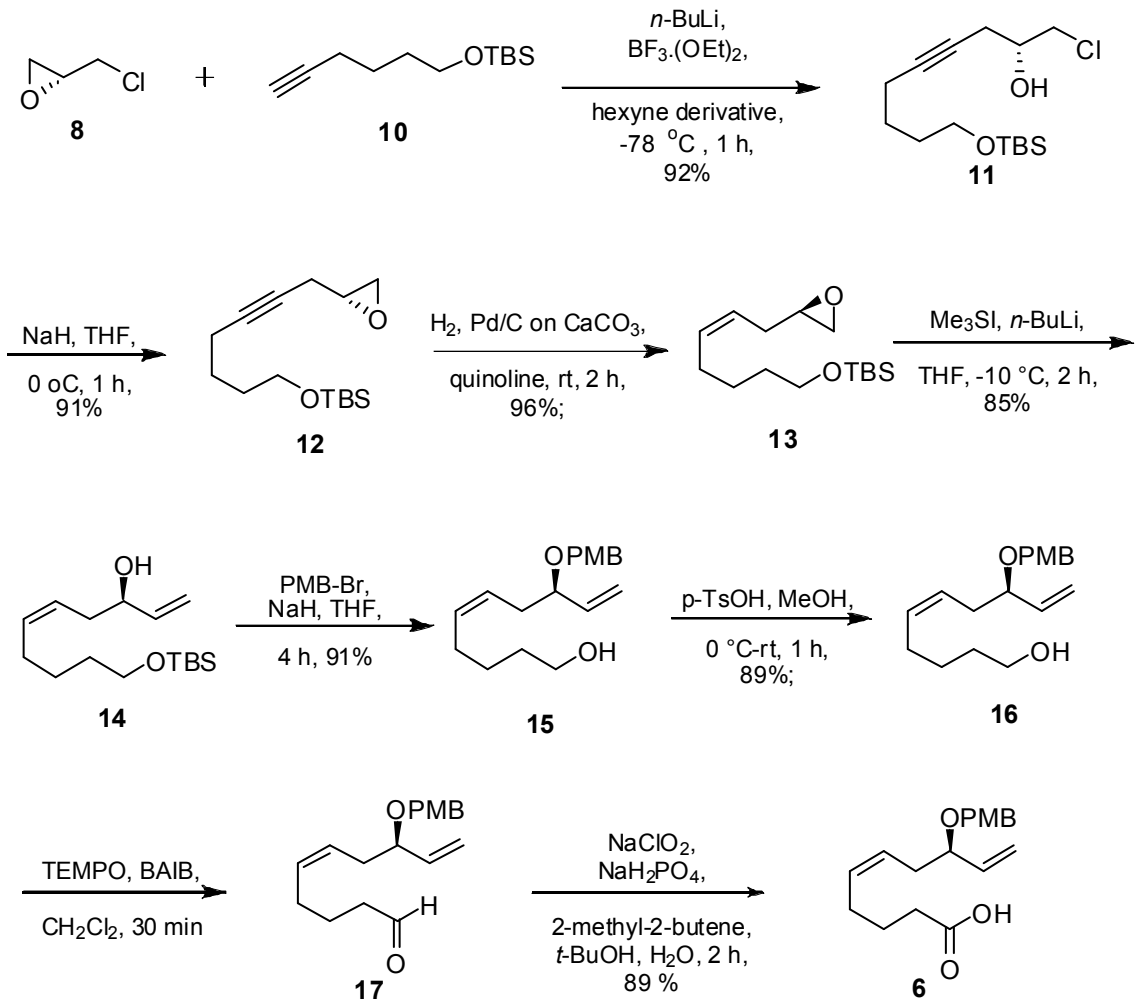


Scheme 1

Synthesis of the acid fragment 6

Chiral epoxide **8**, prepared by following Jacobsen's hydrolytic kinetic resolution protocol, was taken as the starting material for the synthesis of acid fragment **6.** The epoxide **8** was opened with lithium acetylide prepared from TBS-protected alkyne **10** using *n*-BuLi in THF at −78 ^{o}C to afford **11**. The epoxidation of the resulting homopropagyl alcohol **11** proceeded smoothly with NaH in THF at 0 ^{o}C to obtain **12**. Partial hydrogenation was achieved with Lindlar catalyst to furnish the *Z*-olefin derivative **13** in 96% yield. One-carbon homologation with dimethyl sulfonium methylide at −10 ^{o}C afforded the allylic alcohol **14**. Protection of the secondary hydroxyl group as its PMB ether followed by desillylation with *p*-TsOH in MeOH at room temperature gave the primary alcohol **15**. Treatment of the resulting primary hydroxyl group with TEMPO and BAIB furnished the corresponding aldehyde which on further

oxidation under Pinnick conditions with $NaClO_2$ in presence of 2-methyl-2-butene afforded the acid fragment **6** (Scheme 2).

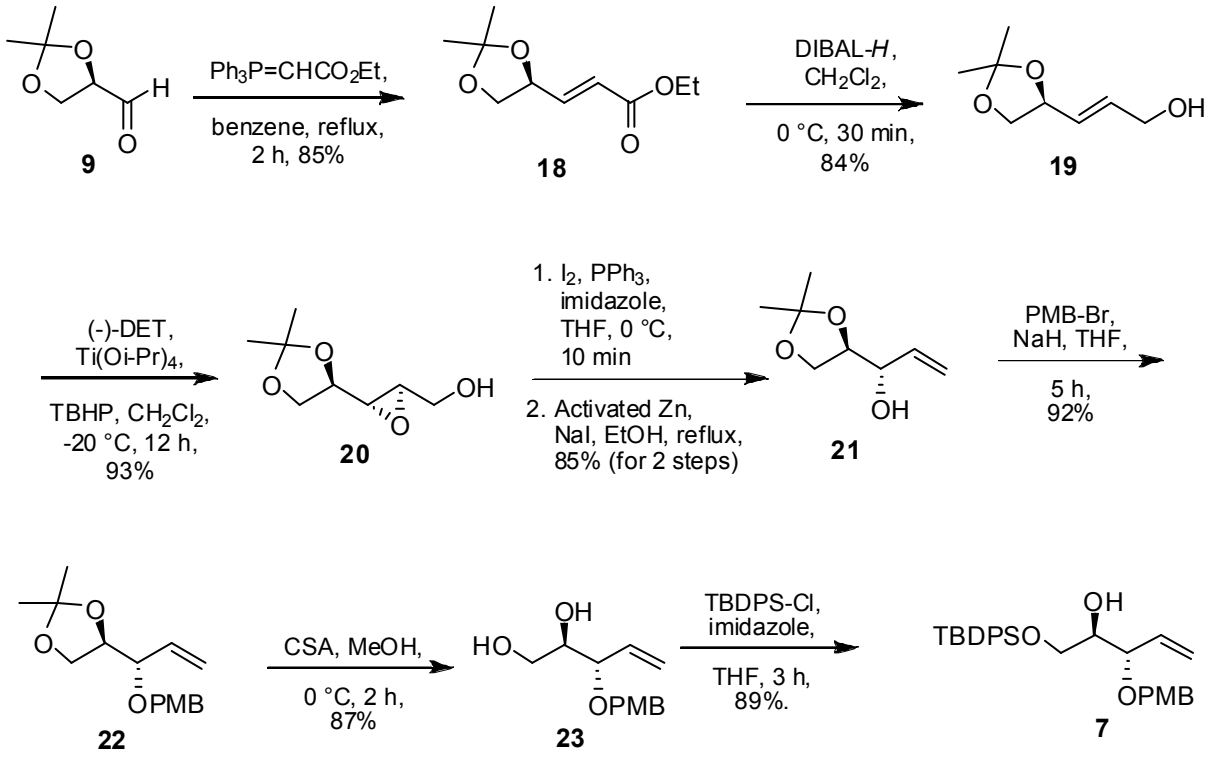


Scheme 2

Synthesis of the alcohol fragment 7

Synthesis of fragment **7** was commenced with two-carbon homologation of the known aldehyde (*R*)-2,3-*O*-isopropylidene glyceraldehyde (**8**) to obtain *α,β*-unsaturated ester **18** which was converted to the corresponding *E*-allylic alcohol **19** by using DIBAL-*H* to set the platform for introducing two more chiral centers via Sharpless asymmetric epoxidation. Thus the allyl alcohol **19** on treatment with (–)-DET, titanium(IV)isopropoxide and *tert*-butyl hydroperoxide in CH_2Cl_2 under anhydrous conditions at –20 ^oC to yield epoxy alcohol **20**. The epoxy alcohol was transformed to its iodo derivative by standard I_2, TPP, imidazole protocol which on treatment with activated Zn dust and NaI in refluxing MeOH, reductive

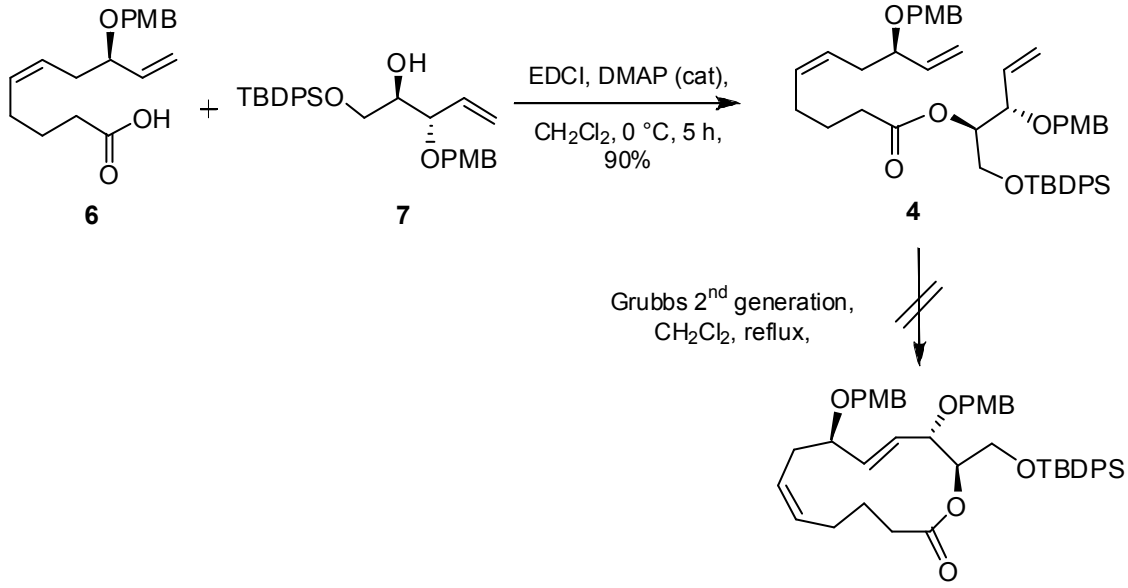
epoxide ring opening took place to produce the allyl alcohol **21**. The resulting secondary hydroxyl group was protected as its PMB ether to obtain **22** in 92% yield followed by deprotection of the isopropylidene group with *p*-TsOH in MeOH at room temperature afforded diol **23** in good yield. The primary hydroxyl group of the diol **23** (Scheme 3) was selectively protected as its TBDPS ether using TBDPSCl, imidazole in DCM at 0 ^{o}C.



Scheme 3

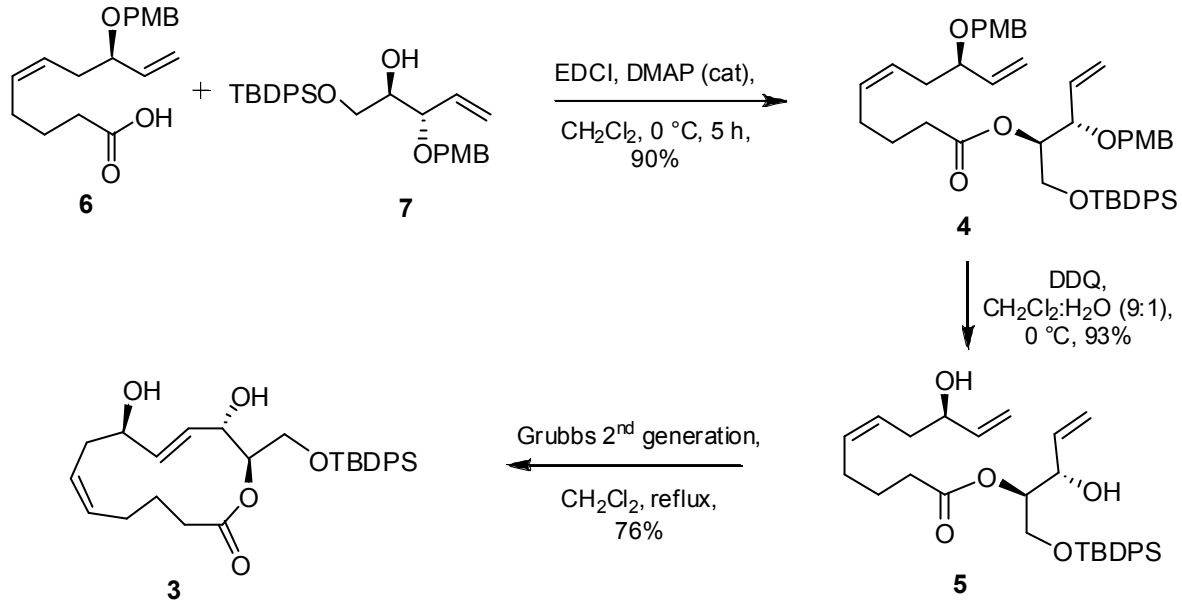
Synthesis of the macrolactone 3

Our next target was to couple both the fragments and investigate the critical ring-closing metathesis reaction. As per our investigation in Chapter I, we had followed the Yamaguchi conditions for the esterification reaction. In this case, the yield was only 30-35% with complete consumption of the starting matterials. However, a better result was achieved by uniting both the coupling partners with EDCI and DMAP in CH_2Cl_2 to afford the triene ester **4** (Scheme 4). Now, the stage was ready to perform the crucial RCM reaction. The ester **4** was refluxed with Grubbs II generation catalyst in CH_2Cl_2 under high dilution conditions (0.001 M) for 5 h. The reaction was failed to provide the lactone **2**. Again this RCM reaction was kept in different concentrations and extending the time, this attempt also proven unsuccessful.



Scheme 4

To further attempt to prepare the lactone, di-PMB protected ester **4** was treated with DDQ in CH_2Cl_2:H_2O (9:1) to obtain diol **5** in 93% yield (Scheme 5). Treatment of diol **5** with Grubbs 2nd generation catalyst in refluxing CH_2Cl_2 under high dilution (0.001 M) conditions smoothly furnished the required 13-membered lactone ring system **3** present in amphidinolactone A (**1**).



Scheme 5

Geometry (*trans*) of the newly formed double bond was established by its coupling constant, while one of the olefinic proton signals appeared at δ 5.66 ppm as a doublet of a doublet (J_{trans} coupling constant 15.7 Hz) and other olefinic proton signals appeared at their respective chemical shifts. The spectral and analytical data were in good agreement with the constitution and configuration of the assigned structure for **3**.

In summary, effect of protecting groups on the ring-closing metathesis reaction for the construction of 13-membered lactone ring system present in amphidinolactone A has been demonstrated. The coupling partners have been synthesized from commercially available starting materials in a concise manner.

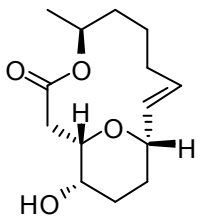
CHAPTER III: Section A:

This Section describes the introduction to **"Previous Approaches for Aspergillide B".**

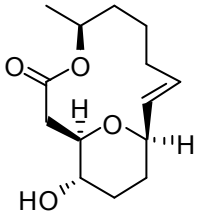
CHAPTER III: Section B:

This Section describes the "Stereoselective Study Towards the Total Synthesis of Aspergillide B".

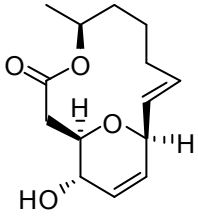
In 2007, three 14-membered macrolides, named aspergillides A, B and C were isolated by T. Kusumi *et al.* from marine-derived fungus *Aspergillus ostianus* strain 01F313. The biological assay of these compounds revealed a potent cytotoxicity against mouse lymphocytic leukemia cells (L1210) at 2–70 lg/L (LC50). The structures of the new compounds were determined by analyses of 1D and 2D NMR spectra. Their structures were proposed to be heptaketidic 14-membered macrolides and absolute configurations were elucidated by the modified Mosher's method and chemical conversions. Aspergillides are the



Aspergillide A



Aspergillide B



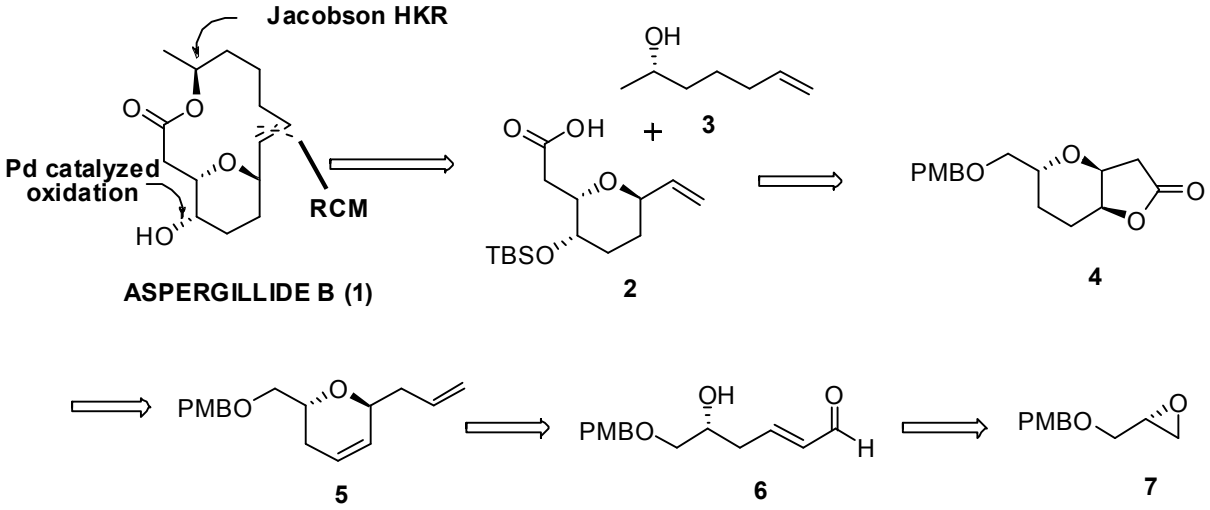
Aspergillide C

first examples of 14-membered macrolides incorporated with a *trans* tetrahydropyran ring. Our recent developed methodology, iodocyclization is going to be a potent protocol for

synthesis of pyran rings by using low cost reagents with a quantitative yield. In our group, iodocyclization reaction has been successfully implemented for synthesis of a number of natural products. The *trans* pyran ring present in the aspergillides attracted our attention for their synthesis following iodo-cyclization methodology developed in our laboratory.

Retrosynthetic analysis of the Aspergillide B

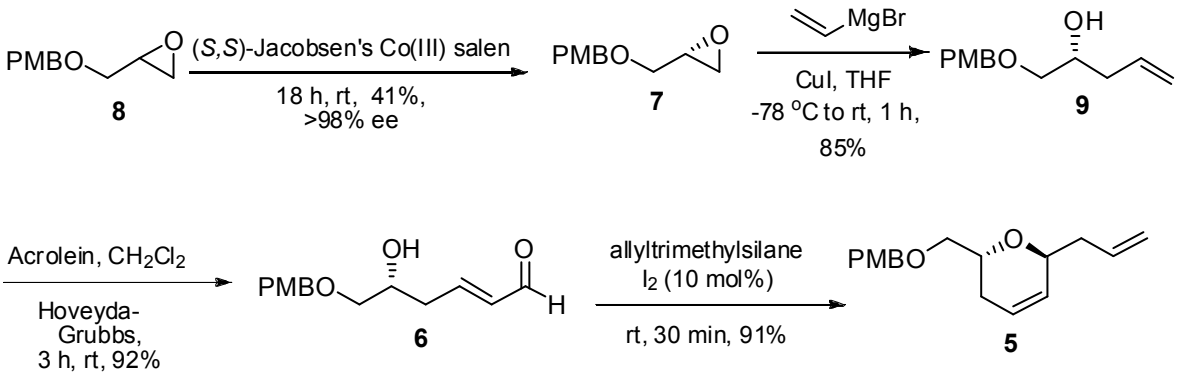
The retrosynthetic analysis for the total synthesis of Aspergillide B is illustrated in Scheme 1. Aspergillide B (**1**) could be derived from the diene compound via ring-closing metathesis which could be obtained from the lactone **4**. The lactone **4** could be obtained from the *trans*-2,6,-disubstituted-3,4-dihydropyrans compound **5** via palladium catalyzed Wacker type oxidation which in turn could be drived from the aldehyde **6** by utilizing our newly developed methodology *i.e* iodocyclization. The aldehyde **6** could be obtained from the known chiral epoxide **7.**



Scheme 1

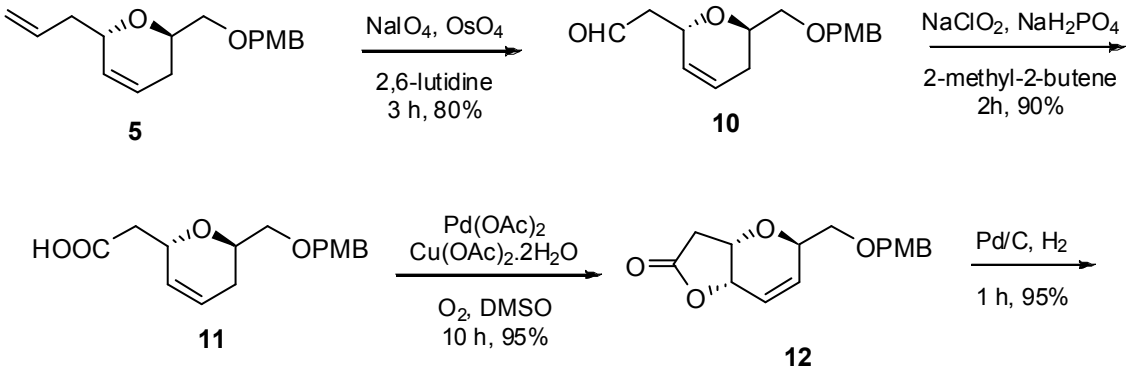
The study towards the synthesis of Aspergillide B (**1**) was started from a known chiral epoxide **7**. The Chiral epoxide **7**, which was prepared from the racemic terminal epoxide by following Jacobsen's hydrolytic kinetic resolution protocol, on treatment with CuI and vinyl magnesium bromide to afford the secondary homoallylic alcohol **9** in 85% yield. The resulted homoallylic alcohol **9** was exposed for a cross-metathesis (CM) reaction between the alcohol and acrolein using a Hoveyda-Grubbs catalyst (10 mol%) in CH_2Cl_2 at room temperature to

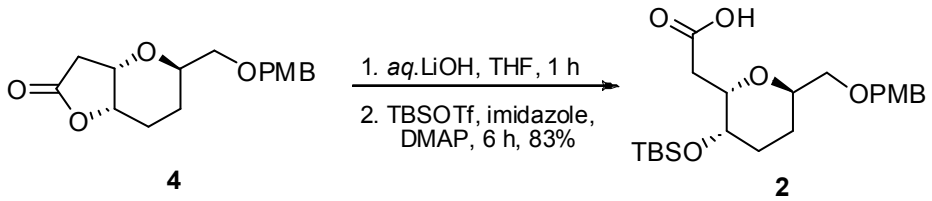
afford a α,β-unsaturated aldehyde **6** in 92% yield (Scheme 2). Then, the iodocyclization reaction was performed by using 10 mol% of iodine with allyl trimethylsilane to give the trans pyran compound **5**.



Scheme 2

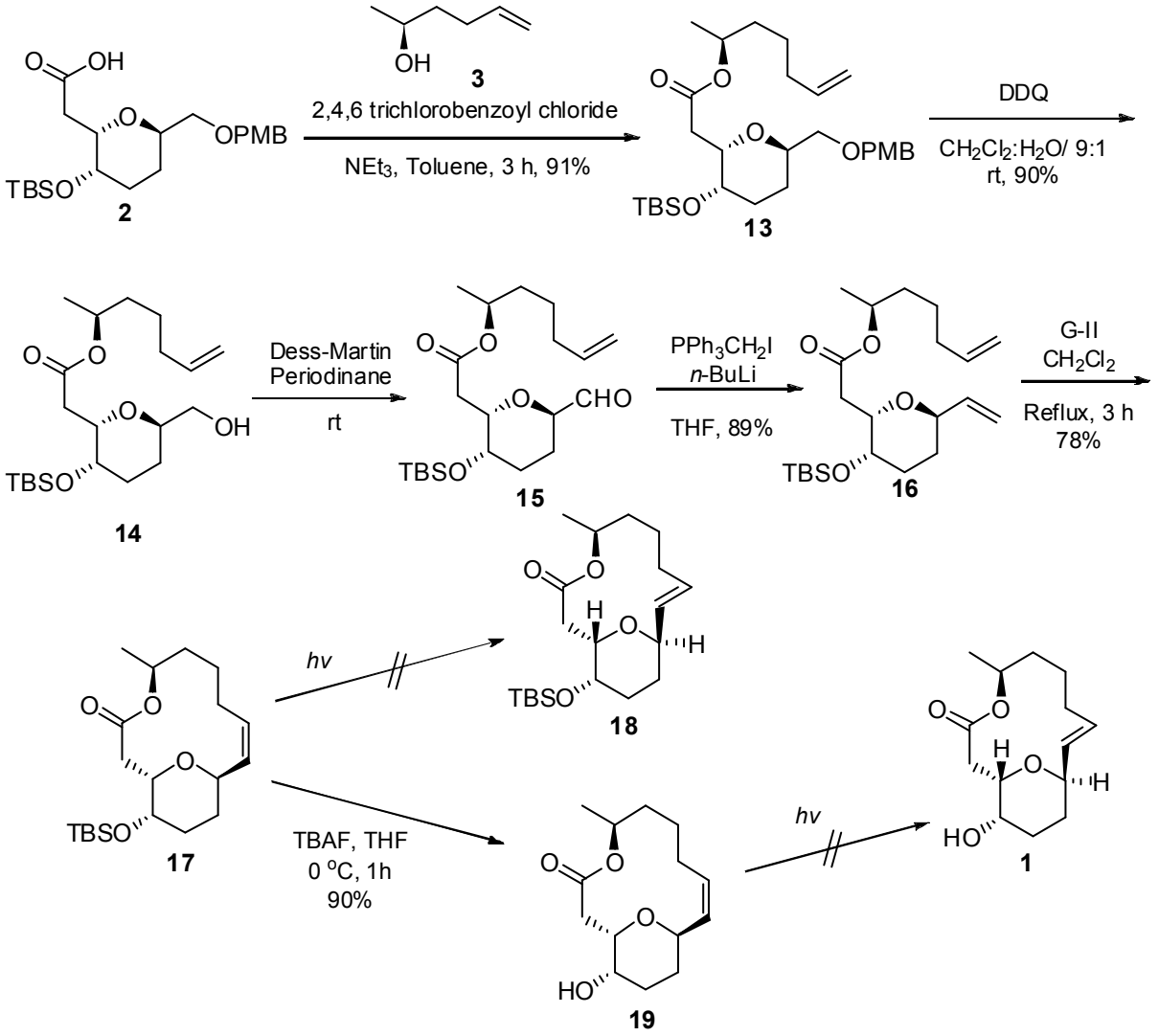
The terminal double bond was oxidatively cleaved following a modified method ($NaIO_4$ and 2,6-lutidine) to obtain aldehyde **10** and a subsequent oxidation of aldehyde under Pinnick conditions afforded a carboxylic acid **11** by using $NaClO_2$, $NaH_2PO_4.H_2O$, 2-methyl-2-butene (Scheme 3). The acid **11** underwent a palladium catalyzed wacker type oxidation with $Pd(OAc)_2$, $Cu(OAc)_2{\cdot}2H_2O$ under oxygen atmosphere in DMSO to afford the lactone **12** in 90% yield subsequent hydrogenation of the double bond containing lactone **12** to give the saturated lactone **4**. The hydrolytic cleavage of the lactone **4** was taken place by using aqueous lithium hydroxide in THF at 0 °C. The resulting lithiated salt of the hydroxyl acid was allowed to react with TBSOTf and imidazole in DMF to afford the TBS ether compound **2**.





Scheme 3

The acid **2** was coupled with **3** under Yamaguchi condition by using 2,4,6-Trichloro benzoyl chloride, Et_3N and DMAP in toluene to give the couple product **13** followed by deprotection of the PMB group by using DDQ to produce the alcohol **14** which was oxidized with Dess-Martin periodinane to give the aldehyde **15**. The resulting aldehyde **15** was



Scheme 4

subjected for Wittig olefination to furnish the diene **16**. The diene **16** when treated with Grubbs 2nd generation catalyst, **17** was formed which was associated with the unrequired *cis* double bond with 78% yield. The compound **17** was exposed to *hv* for photoisomerisation of the *cis* double bond to *trans* double bond, but this reaction was proven unsuccessful by giving untraced compound. Finally, TBS group was deprotected with TBAF to furnish the *cis* isomer of aspergillide B (**19**). Again, the photoisomerisation of the compound **19** was also failed to give the target molecule Aspergillide B (**1**) (Scheme 4).

Thus, we envisioned the successful implementation of the iodine catalyzed cyclization of the *δ*-hydroxy *α,β*-unsaturated aldehyde towards the total synthesis of Aspergillide B.

CONTENTS

CHAPTER I

Section A

Introduction to pyran containing bioactive natural products and previous approaches for the macrolide core of Leucascandrolide A

1.1. Introduction to Natural Products Containing Pyran Rings:

Naural products have attracted the attention of biologists and chemists the world over for the last five decades as it continues to be one of the most important sources of pharmacologically active compounds[1] in the quest for drugs against life threatening diseases such a microbial infections, diseases of the heart and the circulatory system, cancer and others.[2] Marine soursces are considered as the potent source for highly bioactive natural products containing pyran ring. Marine natural products have been isolated from marine organisms and reported in approximately 6,800 publications. In addition to these publications there are approximately another 9,000 publications which cover syntheses, reviews, biological activity studies, ecological studies etc. on the subject of marine natural products.[3] Several of the compounds isolated from marine source exhibit biological activity. The ocean is considered to be a source of potential drugs. Marine organisms not only elaborate pharmaceutically useful compounds but also produce toxic substances. Most marine natural products, especially polyketides, possess polyhydroxy and polyoxy substituents in their structures. Polyketide macrolides continue to show promising biological activities. One of the most important societal contributions of marine natural products chemists have been the isolation and identification of toxins responsible for sea food poisoning. Outbreaks of seafood poisoning are usually sporadic and unpredictable because toxic fish or shellfish does not produce the toxins themselves, but concentrate them from organisms that they are eating. Most marine toxins are produced by microorganisms such as dinoflagellate or marine bacteria and may be passed through several levels of the food chain. The identification of marine toxins has been one of the most challenging areas of marine natural products chemistry. The major occupation of marine natural products chemists for the past two decades have been the search for potential pharmaceuticals. It is difficult to single out a particular bioactive molecule that is destined to find a place in a particular medicine. However, many compounds have shown promise. The marine organisms are produced some of the most cytotoxic compounds ever discovered, but their abudance in nature are very small for further studies.

The biological activities of an extract of marine organisms or isolated compounds could be assessed in several ways. Due to limited amount of the material availability and high cost of biological testing, it is impossible in any laboratory to examine all permutations of drug-animal interaction, to unmask the drug potential of materials. Besides, the candidate drugs have to pass through rigorous toxicological evaluation and clinical trials before they reach the clinician's armamentarium. A fair understanding of biological, toxicological and clinical evaluation is essential to those interested in searching potential drugs from marine organisms. Marine organisms produce some of the most cytotoxic compounds ever discovered, but the yields of these compounds are invariably so small that natural sources are unlikely to provide enough material for drug development studies. It's worthwhile at this juncture to discuss few pyran ring containing marine natural products such as which have been of paramount importance to the mankind and also to the researchers who have been actively involved in the synthesis and isolation of these natural products.

1.1.1. Bistramide A

Kozmin and co-workers[4c] have reported the first total synthesis of bistramide A (**1**), thus confirming Wipf's prediction of the stereochemical assignment of bistramide C which was isolated from the marine ascidian *Lissoclinum bistratum* by Gouiffes and co-workers (Figue 1).[4a] The bistramides demonstrate significant neuro- and cytotoxic properties as well as profound effects on cell cycle regulation. In particular, bistramide A has an IC_{50} of 0.03-0.32 μg/mL for the P388/dox, B16, HT29, and NSCLC-N6 cell lines.[4b] From the time of their original isolation, the bistramides have presented a challenging stereochemical conundrum. Synthetic efforts toward the bistramides were hampered by the lack of information regarding their relative and absolute configuration prior to Wipf's theoretical and synthetic studies.

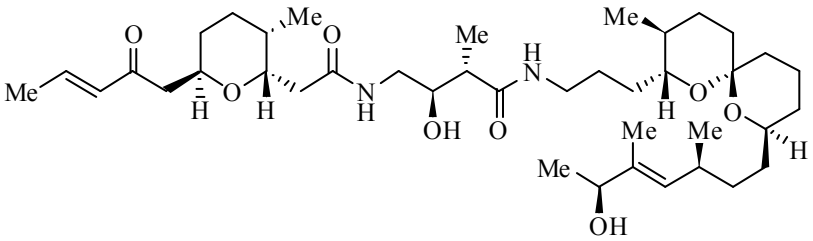


Figure 1. Bistramide A (1)

1.1.2. Zampanolide

In 1996 Tanaka and Higa have disclosed the isolation, partial structure elucidation, and biological activity of the architecturally novel macrolide (+)-zampanolide (**2**), obtained from *Fasciospongia rimosa*, an Okinawan sponge,[5a] which was associated with anticancer as well as antitumor cell growth inhibitory activities. The extreme scarcity and the impressive cytotoxicity displayed by these macrolides led to their synthesis in laboratory. The first total synthesis of (+)-zampanolide has been achieved by A. B Smith *et al*.[5b]

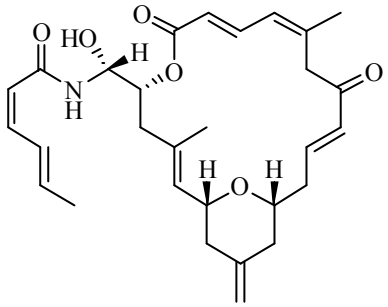
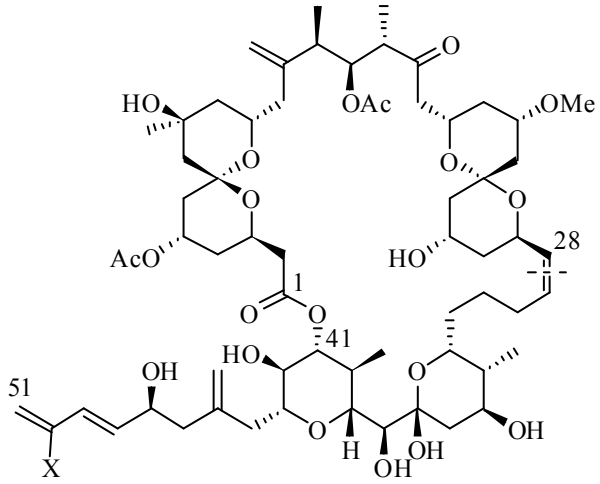


Figure 2. (+)-Zampanolide (2)

1.1.3. Spongistatins

The first members of the spongipyran family of antimitotic marine macrolides were reported independently by three research groups[6] in 1993 (Pettit and coworkers,



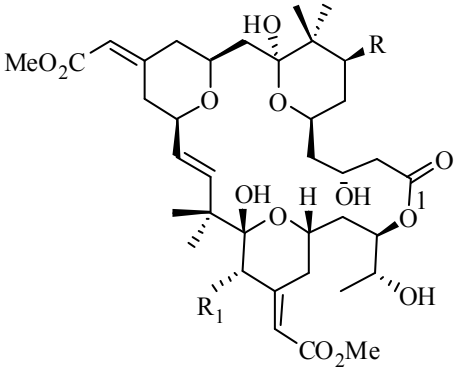
Spongistatin 3 : X = Cl
(Altohyrtin A)
Spongistatin 4 : X = H
(Altohyrtin C)

Figure 3. Spongistatins

Kitagawa/kobayashi group and Fusetani group). The spongistatins (altohyrtin A **3** and althohyrtin B **4**) have been found to be extraordinarily effective against a variety of chemoresistant tumor types, which comprise the NCI panel of 60 human cancer cell lines. Their structural novelties, limited availability, activity against a broad range of human cancer cell lines and microtubule assembly inhibitions, antifungal properties combined, led to make the spongistatins as important and challenging synthetic targets. Spongistatin possesses extraordinary activity compared to other members of the family (Figure 3).

1.1.4. Bryostatins

One potent antitumoral compounds, bryostatin (**5**) was isolated and characterized by Pettit *et al.,* in 1982 from the marine animal the bryozoan *Bugulu neritinu*[6c] (Figure 4) which are highly oxygenated macrolides with a unique polyacetate backbones. Bryostatin (**5**) has been found to cause differentiation of B-chronic lymphocytic leukemia in an unprecedented fashion,[12] and be capable of converting leukemia cells *in vitro* to those typical of hairy cell leukemia which is curable.[13] Successful extension of these experiments to the clinic may results in the first really curative techniques for human chronic lymphocytic leukemia. The potential for treating chronic myelogenous leukemia patients is also very promising.[14,15] Bryostatin (**5**) was found capable of inducing macrophage-like differentiation in maturing CML cells.[15] Most importantly, bryostatin was dramatically effective against cells that taken from patients in the CML blast phase. Against a line of acute lymphoblastic leukemia, bryostatin (**5**) was found to capable of inducing further differentiation along the B-cell lineage.[16,17]



Bryostatin 5 R = OAc, $R_1 = OCO(CH)_4{}^nPr$
Bryostatin 6 R = OH , $R_1 = OCO(CH)_4{}^nPr$

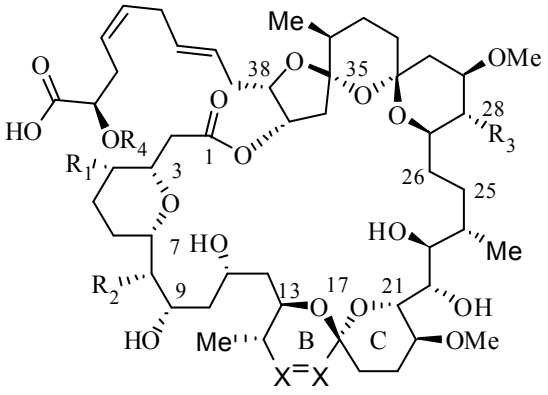
Figure 4. Bryostatins

Interestingly, bryostatin has been found to potentiate ARA-C apoptosis or programmed cell death, and this combination looks very promising for clinical evaluation.[18] Another facet of the activity of bryostatin against lymphomas is involved its ability to convert a high-grade lymphoma cell line 20 an intermediate grade, again offering clinical potential.[22]

1.1.5. Spirastrellolides

Spirastrellolide A and B (**7** and **8**, Figure 5) are two closely related polyketides that were isolated by Anderson and coworkers recently from the marine sponge *Spirastrella coccinea*.[8a] As part of ongoing examination of the *S. coccinea* extract, the same research group also identified the five new spirastrellolides C (**9**) to G (**13**).[8b] Spirastrellolides have a 47-carbon linear polyketide backbone incorporated into a highly functionalized 38-membered lactone containing a tetrahydropyran ring, a bicyclic spiroacetal ring system and a tricyclic bis-spiroacetal ring system, embedded in the macrocycle. Their structural novelty, limited availability, a potent inhibitory activity against protein phosphatase 2A combined, made the spirastrellolides as important and challenging synthetic target.

In addition to its ability to initiate premature entry into mitosis and untimely mitotic arrest in cells, spirastrellolides exhibit a potent inhibitory activity against protein phosphatase 2A (IC_{50} = 1 nM) with an excellent selectivity for PP2A over PP1 (ratio of IC_{50} values 1:50),[8c] and it does not inhibit PP2C. Its biological activities, therefore, resemble other known Ser/Thr phosphatase inhibitors fostriecin and okadaic acid. Developments of protein phosphatase inhibitors have lagged behind interest in kinase inhibitors because of the perceived notion that kinases are much more highly regulated and specific. However, there has been a renewed interest in recent years because reversible protein phosphorylation is critical "as the other half" of checkpoints in cell cycles, and protein phosphatases assume an equally important role in regulating cellular signal transductions and should not be ignored. Designing phosphatase inhibitor can lead to a new paradigm in developing cancer therapeutics.[8d]

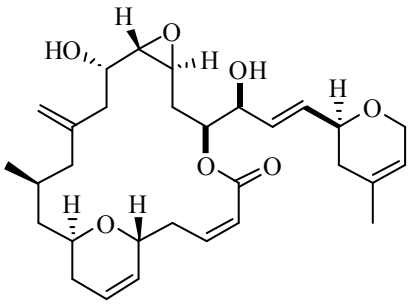


7 Spirastrellolide A: X=X = CH=CH, R_1=R_2=R_4=H, R_3=Cl
8 Spirastrellolide B: X=X = CH_2CH_2, R_1=R_2=R_3=R_4=H
9 Spirastrellolide C: X=X = CH_2CH_2, R_1=R_3=R_4=H, R_2=OH
10 Spirastrellolide D: X=X = CH=CH, R_2=R_4=H, R_1=R_3=Cl
11 Spirastrellolide E: X=X = CH=CH, R_1=R_2=R_3=R_4=H
12 Spirastrellolide F: X=X = CH_2CH_2, R_1=R_2=R_4=H, R_3=Cl
13 Spirastrellolide G: X=X = CH=CH, R_1=R_2=H, R_3=Cl, R_4=Me

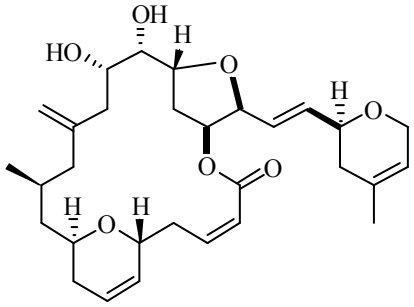
Figure 5. Spirastrellolides

1.1.6. Laulimalide and Isolaulimalide

Laulimalide (**14**) and Isolaulimalide (**15**) are 18-membered macrocyclic lactones isolated from the marine sponge *Cacspongia mycofijuensis*[9a] which are a new class of microtubule stabilizing agents having high therapeutic utility. They are Coincident with the microtubule change these two compounds induce nuclear convolution and the formation of multiple micronuclei. They promote elongating activity readily than paclitaxel.[9b] Several syntheses for laulimalide and isolaulimalide have been reported so far (Figure 6).[9c,d]



Laulimalide (14)

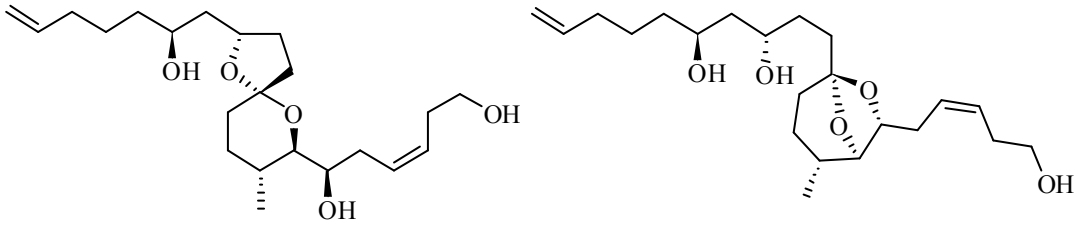


Isolaulimalide (15)

Figure 6. Laulimalide and Isolaulimalide

1.1.7. Attenols

Attenols A (**16**) and B (**17**), isolated from the EtOH extract of the Chinese bivalve *Pinna attenuata* by Uemura *et al*.,[10a] exhibited cytotoxicity against P388 cells (IC_{50} values of 24 and 12 μg/mL, respectively) (Figure 7). These compounds are unique isomeric triols: attenol A has a 1,5-dioxaspiro[4.5]decane core and attenol B has a 6,8-dioxabicyclo[3.2.1]octane framework, and equilibrium under acidic conditions is **16**/**17** = 3 : 1. They determined their relative structures by 2D NMR and absolute configurations by the modified Mosher method, however, those of the spiroacetal carbon of **16** were assumed by considering the anomeric effect. Uemura's group first synthesized these compounds to confirm the stereochemistry.[10b,10c]



Attenol A (16) **Attenol B (17)**

Figure 7. Attenol A and Attenol B

1.1.8. Halistatin

Halistatin (**18**) was found to be exceptionally potent antineoplastic constituents of two different marine sponges located in The Republic of Comoros.[11] Against the NCI human cancer cell lines panel, the negative $logI_{10}$ GI_{50} values range to over nine and represent an excellent selection of human cancer types. Briefly stated, the halistatins offer considerable promise for improving future human cancer treatment(Figure 8).

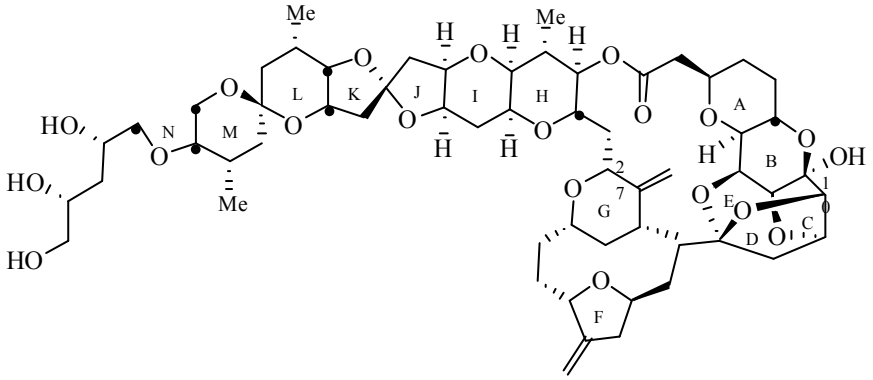


Figure 8. Halistatin (18)

1.1.9. Dactylolide

(+)-Dactylolide (**19**), a new cytotoxic natural product which was derived from a marine sponge of the genus *Dactylospongia*, collected off the coast of the Vanuatu islands[12] as a tumor cell growth inhibitory macrolides (Figure 9). The less abudance and the impressive biological activities displayed by this macrolide led to their laboratory synthesis. The first asymmetric total syntheses of (+)-dactylolide, has been achieved by A. B Smith *et al*.[12b]

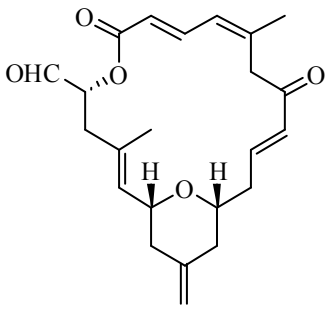


Figure 9. (+)-Dactylolide (19)

1.1.10. Scytophycins

One polyketides with *trans*-2,6-disubstituted dihydropyrans named scytophycins (isolated from the cultured terrestrial blue-green algae *Scytonema pseudohofmanni*) were first reported bye Moore *et al.*, in 1986.[13a] Along with scytophycin C (**20**, Figure 10), four related polyketide-derived macrolides scytophycins A, B, D and E were also isolated from same algae. These are novel series of polyoxygenated 22 membered macrolide, differing in substitution at C_{16} and C_{27}, with a C_{21} side chain terminating in an *N*-methyl vinyl formamide group. These are exhibiting potent cytotoxicity against a variety of human carcinoma cell lines, as well as broad-spectrum antifungal activity.[13b] The first total synthesis was described by Paterson[13c] followed by many other syntheses.[13d]

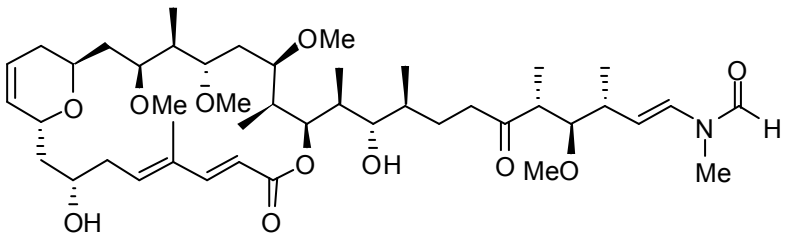


Figure 10. Scytophycin C (20)

1.1.11. Phorboxazole A

Isolation of phorboxazole A (**21**) by Molinski and Searle in 1995,[14a] the structurally complex and potent biological actvity (Figure 11) had sparked a flurry of interest from the synthetic community. Comprising 15 asymmetric centers, four diversely substituted hydropyran rings, a 21-membered macrolactone, two oxazole rings, and a variety of unsaturations, the phorboxazoles present a considerable challenge for synthetic organic chemist. A total of six research groups have reported synthesis of the phorboxazole, beginning with Forsyth's synthesis of phorboxazole A (**21**) in 1998,[14b] followed by Evans's synthesis of phorboxazole B in 2000.[14c] Subsequent synthesis of phorboxazole A has been completed by the research groups led by Smith (2001,[14d] 2005[14e]), In addition, numerous other formal and total synthetic efforts have been described.[14e] The phorboxazole is among the most potent cytostatic agents yet discovered, exhibiting a mean GI_{50}<1.58 against the NCI panel of 60 tumor cell lines.[14h] While it is known that the phorboxazole is induce S-phase cell cycle arrest without interference of the microtubules, the exact mode of activity is not fully understood. Recently, Forsyth, La Clair *et al*. have shown that fluorescently labeled phorboxazole derivatives induceed association of cell-cycle-dependent kinase 4 (cdk4) with extranuclear cytokeratin intermediate filaments (KRT10),[14i] and perturbation of cdk4 is known to inhibit cells cycle progression at the G1/S phase.[14j] In addition, new, potent analogues are beginning to shed some light on the phorboxazole pharmacophore.[14k,l]

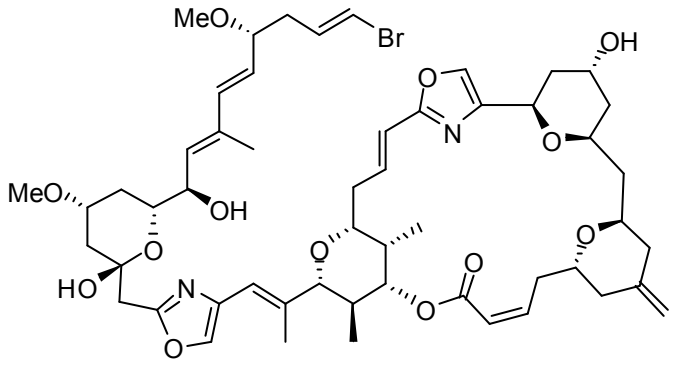


Figure 11. (+)-Phorboxazole A (21)

1.1.12. (–)-Lasonolide A

One potent anticancer activity containing compound, Lasonolide A (**22**, Figure 12) was isolated from shallow water Caribbean sponge; species of *Forcepia*.[15] It shows a

potent activity against A-549 human lung carcinoma. Lee's seminal synthetic work included a correction of the structure and a reassignment of the absolute configuration.[16] Lee prepared the tetrahydropyran scaffold of lasonolide through a cyclisation with silyl ether. Later, several groups have synthesized the tetrahydropyran core of lasonolide A.[17] Interesting structure of lasonolide A, potent anticancer activity and natural scarcity have made it an attractive target for synthetic organic chemists. As a result lots of syntheses were resulted by applying a veriety of key reactions.

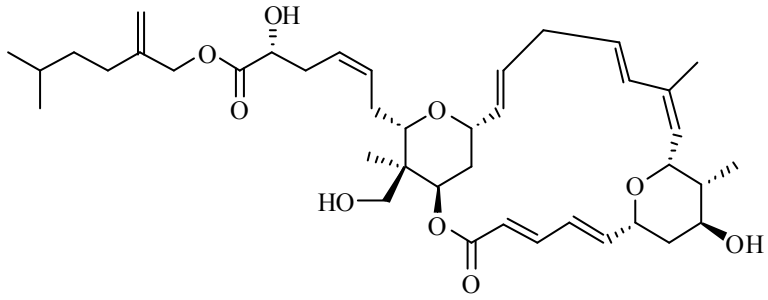


Figure 12. **(-)-Lasonolide A (22)**

1.1.13. (–)-Kendomycin

(–)-Kendomycin (**23**), a novel macrocyclic polyketide was first isolated in 1996 from *Streptomyces violaceoruber*, possesses potent activity as both an endothelin receptor antagonist and an antiosteoporotic agent.[18] Reisolation by the Zeeck's group[19] revealed, in addition, significant antibacterial activities against multiresistant bacteria, including vancomycin–resistant strains and remarkable cytotoxicity against a series of human tumor cell lines (GI_{50} < 0.1 μM). The impressive biological profiles, in conjunction with the challenging architecture, defined by X-ray and Mosher ester analysis, triggered considerable synthetic efforts,[20] culminating in 2004 with the first total synthesis (Figure 13)[21].

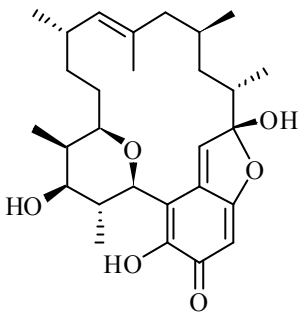


Figure 13. (-)-Kendomycin (23)

1.1.14. (+)-SCH 351448

SCH 351448 (**24**, Figure 14) is a hexane soluble material purified from a *Micromonospora* sp. fermentation broth.[22] The reported ability of natural SCH 351448 to activate transcription from the low-density lipoprotein (LDL) receptor promoter is of mechanistic and biomedical importance.[23] The single-crystal X-ray structure of SCH 351448 shows a remarkable topology. The ionized and un-ionized carboxyl groups are intramolecularly hydrogen-bonded and together with the phenol and hydroxyl groups to accommodate a heptacoordinate sodium ion in interior cavity of a hydrophobic globular structure. At this point, it is remained unclear whether SCH 351448 functions by mediating sodium or other ion transport across membranes or whether the role of the chelated sodium ion is structural *i.e*., does SCH 351448 behave as a hydrophobic small molecule ligand for a cellular receptor. To answer all related questions, synthetic program was started to provide materials for future structural, physicochemical and biological studies.

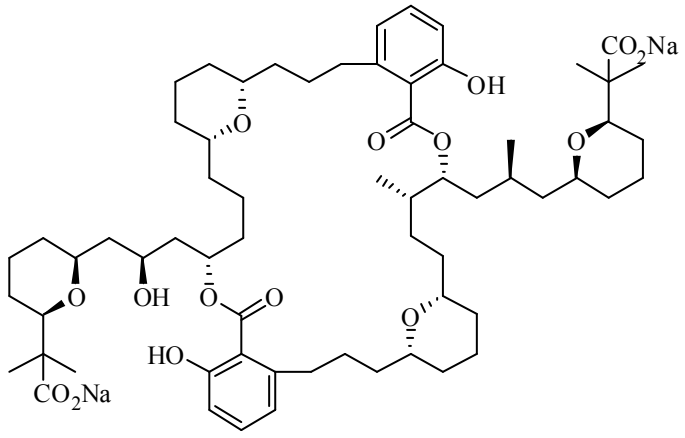


Figure 14. (+)-SCH 351448 (24)

1.1.15. Latrunculin A

Among the most prolific sponges in the Red Sea is the red colored *Latrunculia magnifica* that enjoys immunity from attack by fish. Two toxins, latrunculin A (**25**) and latrunculin B (**26**), were isolated from this sponge, known to be particularly toxic to fish (Figure 15). They are the first marine macrolides known to contain 16- and 14-membered rings and are also further characterized by the rare natural occurrence of the thiazolidinone

group.[24a] Studies of their mode of action indicates that both compounds are able to disrupt microfilament organization in cultured cells.[24b] The stereochemistry of the 8-methyl group in latrunculin B is presently unknown.

Latrunculin A (25) **Latrunculin B (26)**

Figure 15. Latrunculin A and Latrunculin A

1.1.16. Sorangicin A

Ho¨fle and co-workers had reported the isolation of members of another family of architecturally complex macrolides from the *cellulosum* strain So ce 90,[25a] were termed as sorangicins.[25b] Importantly, (+)-sorangicin A (**27**), the most potent and prevalent congener, is demonstrated remarkable antibiotic activity against a broad spectrum of both Gram-positive [minimum inhibitory concentration (MIC) 0.01-0.3 μg/mL] and Gram-negative bacteria (MIC 3-25 μg/mL).[25c]

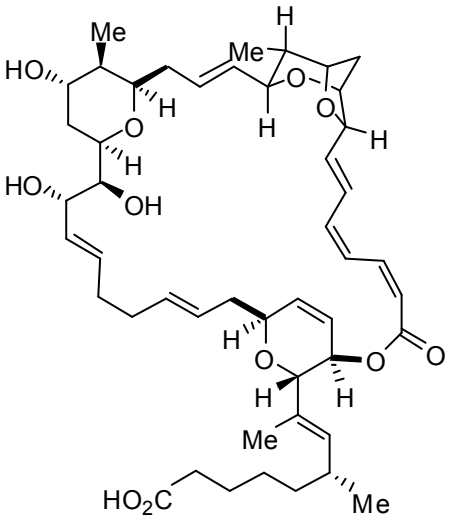


Figure 16. (+)-Sorangicin A (27)

1.1.17. Apoptolidin

First reported by Hayakawa and co-workers,[26a] apoptolidin (**28**) is a cytotoxic agent found during the course of a screening programs directed towards the discovery of novel apoptosis inducers. Isolated from the cultivation broth of an actinomycete identified as *Nocardiopsis* sp., apoptolidin was found to selectively induce cell death via apoptosis in rat glia cells transformed with adenovirus E1A and E1A/E1B19K oncogenes with considerable potency (Figure 17). Using a series of molecular and cell-based tools and techniques, Khosla and co-workers later had identified the mitochondrial F0F1-ATPase as the cellular target of apoptolidin.[26b]

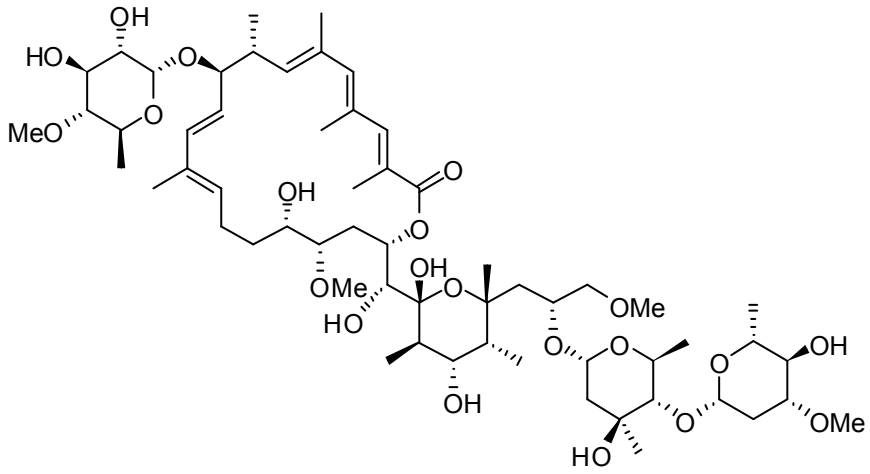
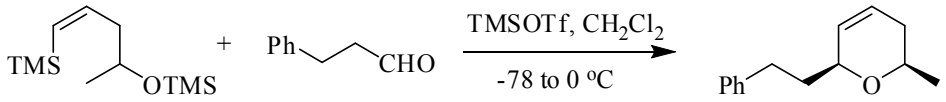


Figure 17. Apoptolidin (28)

1.2. Syntheis of Dihydropyrans

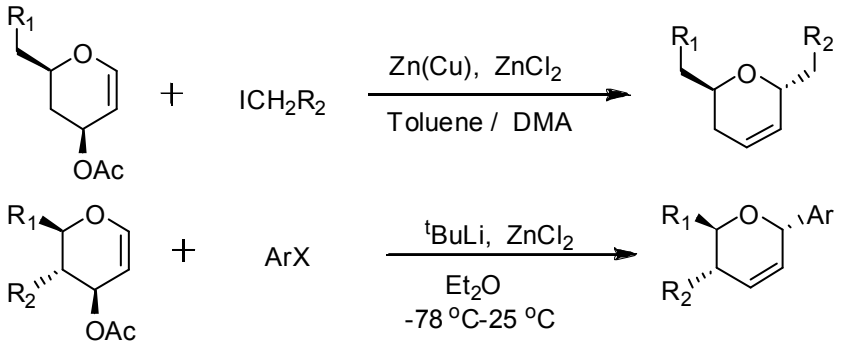
Several approaches have been reported for the preparation of dihydropyrans and some of the more varied methodologies include electrophile-initiated alkylation of glycals, hetero-Diels–Alder cycloadditions, bis(oxazoline)-copper-catalyzed asymmetric hetero-Diels-Alder reaction, olefin metathesis, intramolecular Wadsworth-Emmons, Ireland-Claisen rearrangement, and an intramolecular silyl-modified Sakurai reaction.

The condensation of vinylsilanes with aldehydes or acetals is resulted dihydropyrans with a good yield. An oxonium ion intermediate is involved in this stereoselective reaction (Scheme 1).[27]



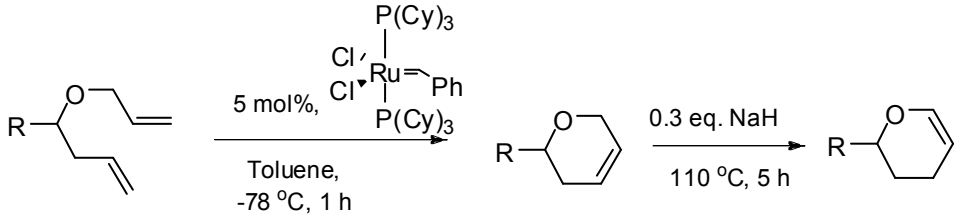
Scheme 1

For the first time, Steinhuebel *et al*. showed that arylzinc couplings with 1,2-dihydropyran that had given high *α*/*β* anomeric stereocontrol dihydropyrans. Nucleophilic addition of organozincs to 1,2-dihydropyranyl acetates represent a new, broadly defined method for the stereocontrolled synthesis of *α*-substituted pyrans (Scheme 2).[28]



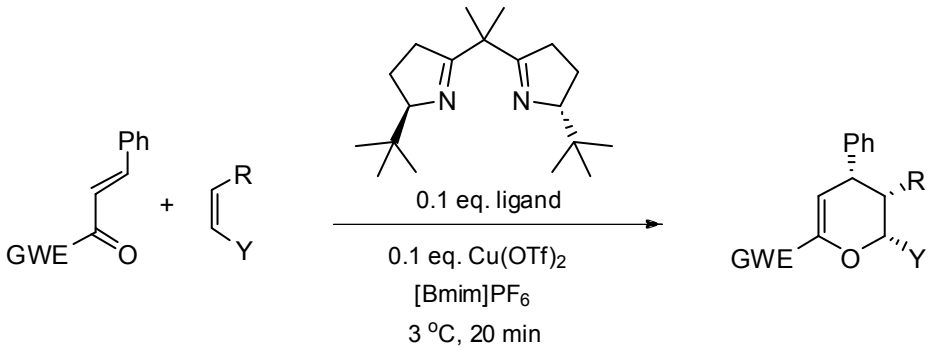
Scheme 2

An olefin metathesis or a double bond migration sequence of allyl ethers to cyclic enol ethers was catalyzed by first and second generation Grubbs' catalysts. These ruthenium carbene complexes were activated to catalyze the double bond migration by implementation of hydride sources such as NaH or $NaBH_4$ (Scheme 3).[29]



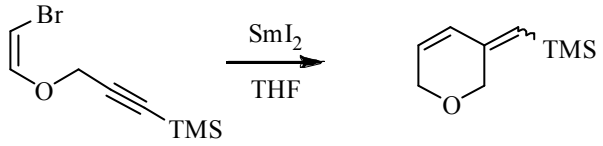
Scheme 3

Hydrophobic ionic liquid such as [Bmim]PF_6 are powerful media for bis(oxazoline)-copper-catalyzed asymmetric hetero-Diels-Alder reactions, that allow a convenient catalyst recycling. The reactivities and stereoselectivities were comparable to those of corresponding homogeneous reactions. Furthermore, the reaction was remarkably accelerated in [Bmim]PF_6 compared to dichloromethane (Scheme 4).[30]



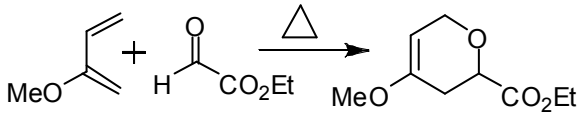
Scheme 4

Propenyl ether undergo a 6-*exo* cyclization by using SmI_2 as catalyst to afford the dihydropyran as 2:1 mixture of the *E* and *Z* isomers (Scheme 5).[31]



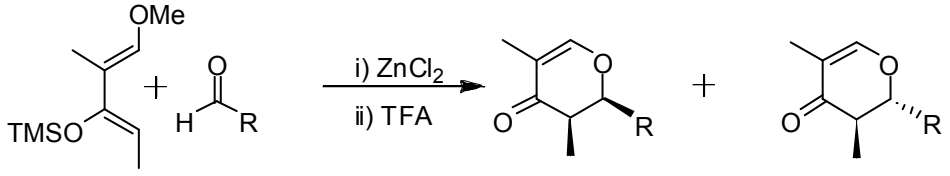
Scheme 5

First report of a hetero Diels-Alder (HDA) reaction was appeared in literature in 1951 by Gresham and Steadman (Scheme 6).[32]



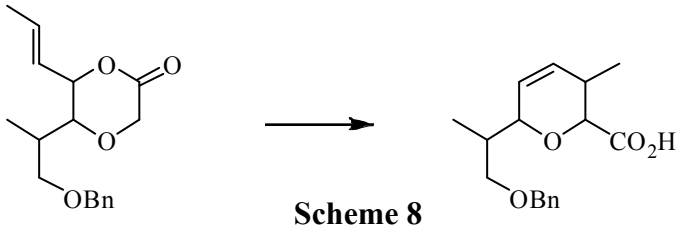
Scheme 6

In presence of Lewis acid catalyst, reaction proceeded smoothly at room temperature with better yield and selectivity (Scheme 7).[33]



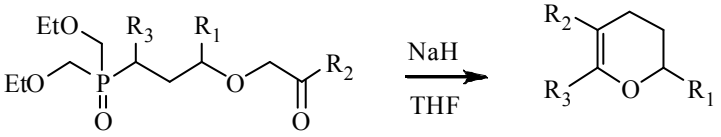
Scheme 7

An Ireland-Claisen rearrangement of the 1,4-dioxanone gave the substituted dihydropyran carboxylic acid (Scheme 8) for use in a macrolide synthesis.[34]



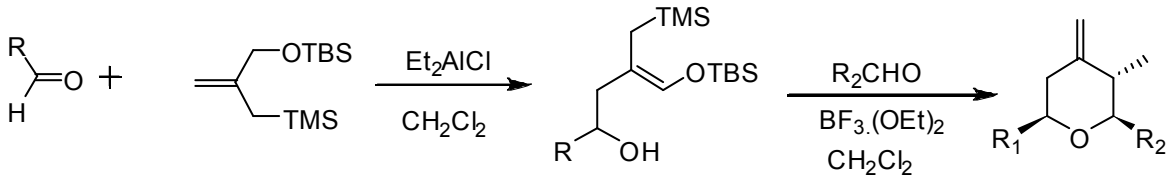
Scheme 8

An intramolecular Wadsworth-Emmons reaction features in a conversion of phosphonates to dihydropyran (Scheme 9).[35]



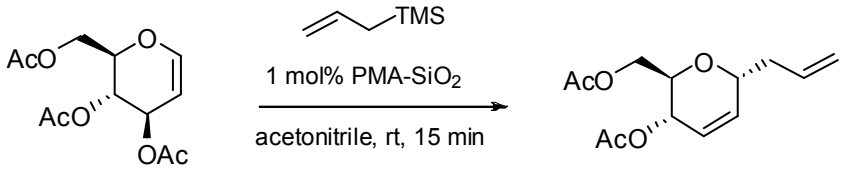
Scheme 9

Intramolecular Sakurai Cyclization (IMSC) of aldehydes was an efficient procedure for the preparation of a variety of diastereometrically pure *exo*-methylene tetrahydropyrans (Scheme 10).[36]



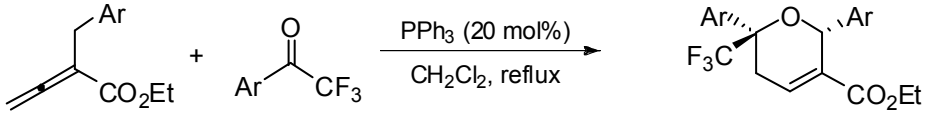
Scheme 10

Phosphomolybdic acid (PMA-SiO_2) catalysed Ferrier type rearrangement of glucals for synthesis of 2,3-unsaturated glycopyranosides (Scheme 11).[37]



Scheme 11

The diastereoselective synthesis of 6-trifluoromethyl-5,6-dihydropyrans was realized by the triphenyl phosphine-catalyzed [4 + 2] annulation of ethyl α-benzylallenoates and trifluoromethyl ketone (Scheme 12).[38]

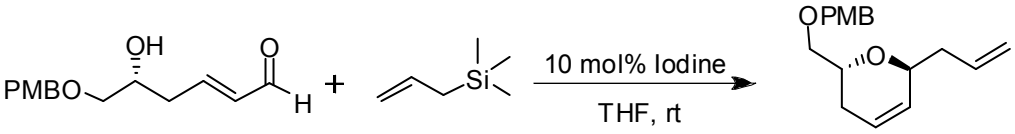


Scheme 12

1.2.1. Iodocyclization and applications in Natural Product:

Among all the heterocycle, 2,6-disubstituted dihydropyrans are probably one of the most common structural motifs spread across various natural products, from simple glucose to structurally complex secondary metabolites such as luminaolide, leucascandrolide A, aspergillide A, B and C, misakinolides, phorboxazole, laulimalide, swinholides, scytophycins, and even more elaborated architectures present in polytoxins, maitotoxins, and other marine derived natural products.

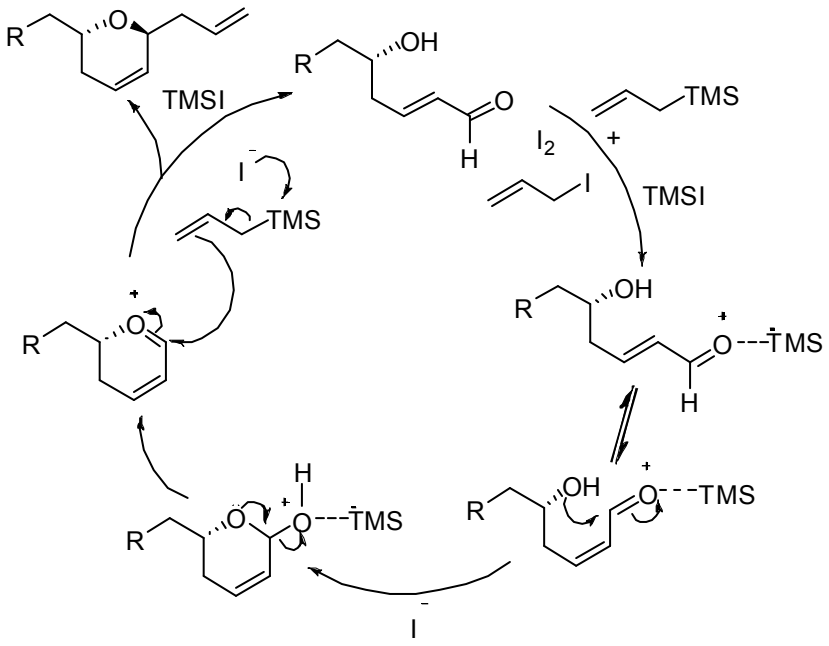
Many of the methods were discussed previously require long reaction times, stoichiometric use of expensive reagents, harsh reaction conditions, and some time gives poor yield and selectivity. To avoid the above limitations, in our group we have searched for a catalyst with high catalytic activity, easy availability, short reaction time, environment friendly and simple work-up procedure. Molecular iodine attracted our attention, as recently it has attained considerable importance in organic synthesis because of low cost, nontoxic nature, ready availability, environment friendly, easy handling, high efficiency for various organic transformations to the corresponding products in excellent yields with excellent diastereoselctivity. Since it has been used as a mild Lewis acid[39] catalyst for the activation of carbonyl compounds, including acetalization reactions, we envisaged that iodine could catalyze the reaction for the formation of 2,6-di-substituted-3,4-dihydropyrans starting from *δ*-hydroxy *α,β*-unsaturated aldehydes (Scheme 13).[40]



Scheme 13

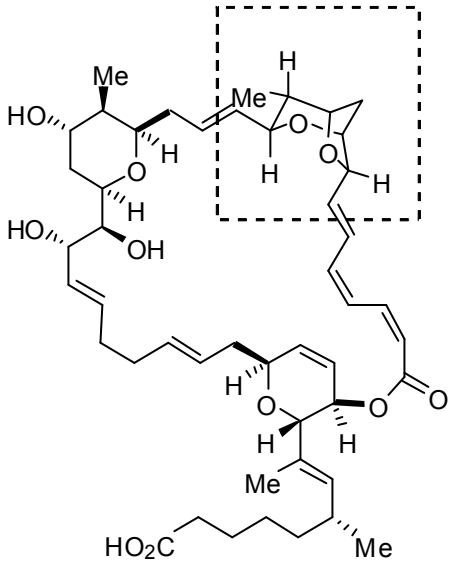
The formation of the *trans*-2,6-disubstituted-3,4-dihydropyran from *δ*-hydroxy *α,β*-unsaturated aldehydes by uing molecular iodine was explained bellow (Scheme 14).

Our recent developed methodology,[40] Iodocyclization is going to be a potent protocol for synthesis of pyran rings by using low cost reagents with a quantitative yield. In our group, Iodocyclization reaction has been successfully implemented for synthesis of a number of natural products such as (+)-Sorangicin A, Polyrhacitide A, *epi*-Cryptocaryolone



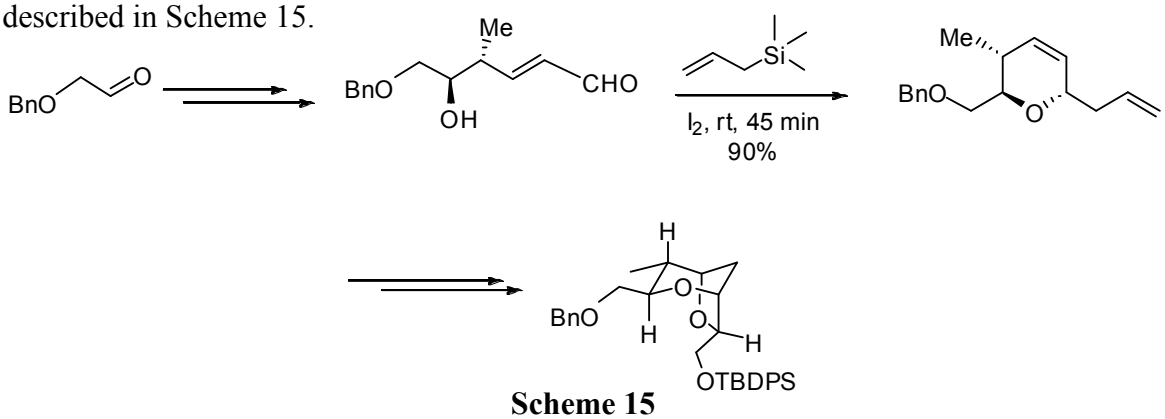
Scheme 14: Proposed mechanism

(+)-Sorangicin A (**27**) was disconnected into three major fragments and the iodocyclization protocol was initially applied for the synthesis of the Bicyclic Core .[40]



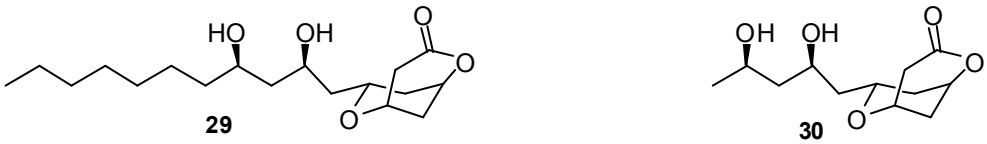
(+)-Sorangicin A

The highlights of the synthesis of the Bicyclic Core of (+)-Sorangicin A (**45**) was described in Scheme 15.

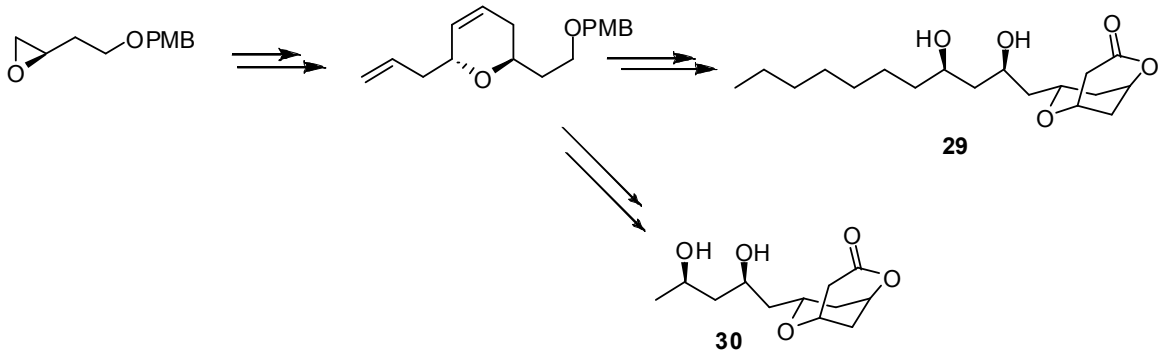


Scheme 15

Successively, the total synthesis of Polyrhacitide A and *epi*-Cryptocaryolone had been achieved by our group.[41]



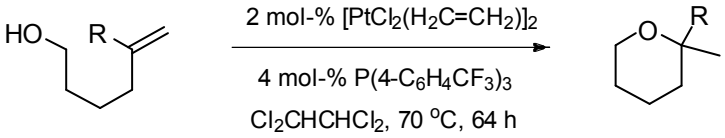
The total synthesis of Polyrhacitide A (**29**) and *epi*-Cryptocaryolone (**30**) was highlighted below (Scheme 16).



Scheme 16

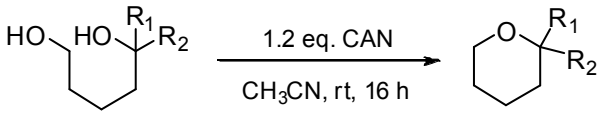
1.3. Synthesis of Tetrahydropyrans:

The platinum-catalyzed hydroalkoxylation of *γ*- and *δ*-hydroxy olefins tolerated various substitution pattern and a number of functional group including pivaloate and acetate esters, amides, silyl and benzyl ethers, and pendant hydroxyl and olefinic groups.[42]



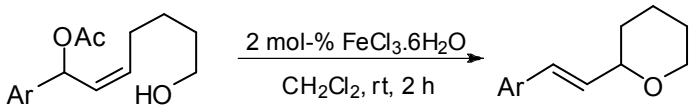
Scheme 17

The reaction of tertiary 1,4-diols and 1,5-diols with cerium ammonium nitrate at room temperature gave tetrahydrofuran and tetrahydropyran derivatives in high yield and stereoselectivity. Various fragrant compounds have been synthesized using this method.[43]



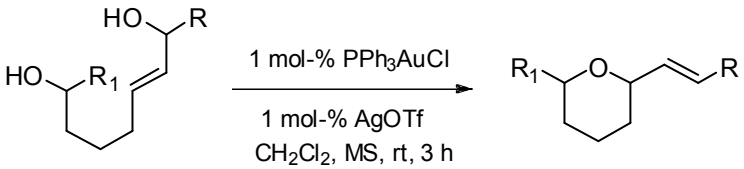
Scheme 18

Key step of an eco-friendly, commercially cheap and highly diastereoselective synthesis of substituted *cis*-2,6-piperidines and *cis*-2,6-tetrahydropyrans is an iron-catalyzed thermodynamic equilibration of 2-alkenyl 6-substituted piperidines and 2-alkenyl 6-substituted tetrahydropyrans allowing the isolation of enriched mixtures of the most stable *cis*-isomers (Scheme 19).[44]



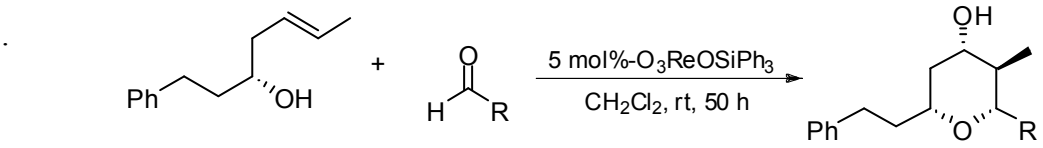
Scheme 19

The gold(I)-catalyzed cyclization of chiral monoallylic diols to form tetrahydropyrans is highly stereoselective. Substrates that differ only in olefin geometry are provided enantiomeric products from formal S_N2' reactions in high yields with excellent chirality transfer. In the presence of additional stereocenters the allylic alcohol stereochemistry efficiently controls the facial selectivity (Scheme 20).[45]



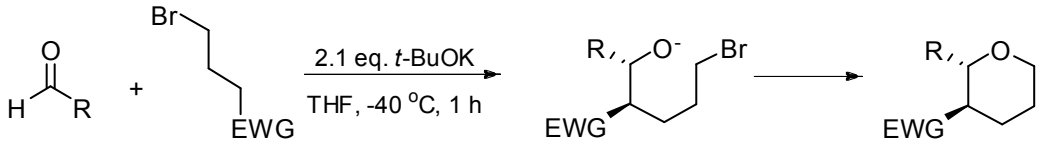
Scheme 20

The ruthenium(VII) complex $O_3ReOSiPh_3$ is a particularly effective catalyst for Prins cyclizations using aromatic and α,β-unsaturated aldehydes. The reaction conditions are mild, and the highly substituted 4-hydroxytetrahydropyran products were formed stereoselectively (Scheme 21).[46]



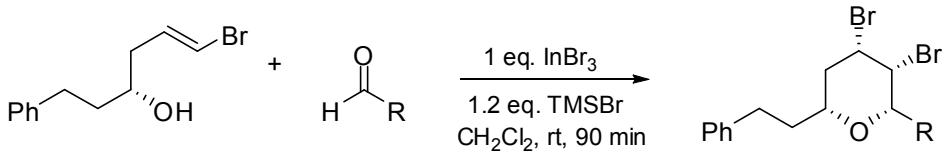
Scheme 21

Cyclization of δ-halocarbanions to cyclobutanes is a very slow process, thus formation of tetrahydropyran derivatives via addition to aldehydes and subsequent cyclization is possible in excellent yield. A simple mechanistic discussion, optimization of the reaction conditions, and the scope of the reaction are discussed (Scheme 22).[47]



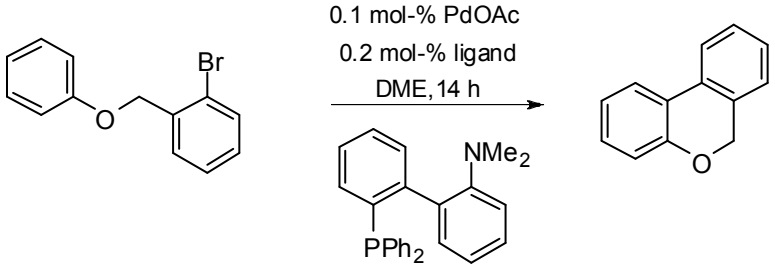
Scheme 22

An efficient method allow the construction of 2,6-*cis*-4,5-dibromo-tetrasubstituted tetrahydropyran rings with wellcontrolled stereochemistry by using $InBr_3$ in good yields.[48]



Scheme 23

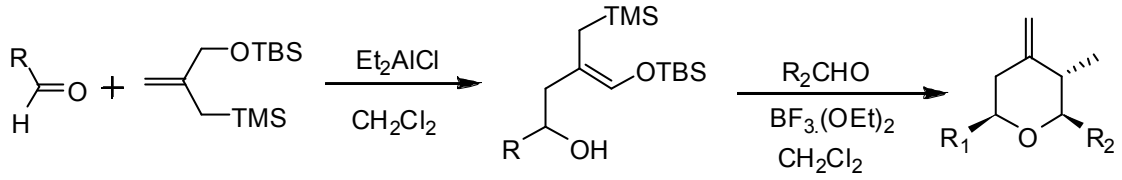
A Pd-catalyzed arylation reaction for the intramolecular formation of biaryl compounds using a novel phosphine ligand offers enhanced catalytic activity for transformations of previously unreactive substrates (Scheme 24).[49]



ligand

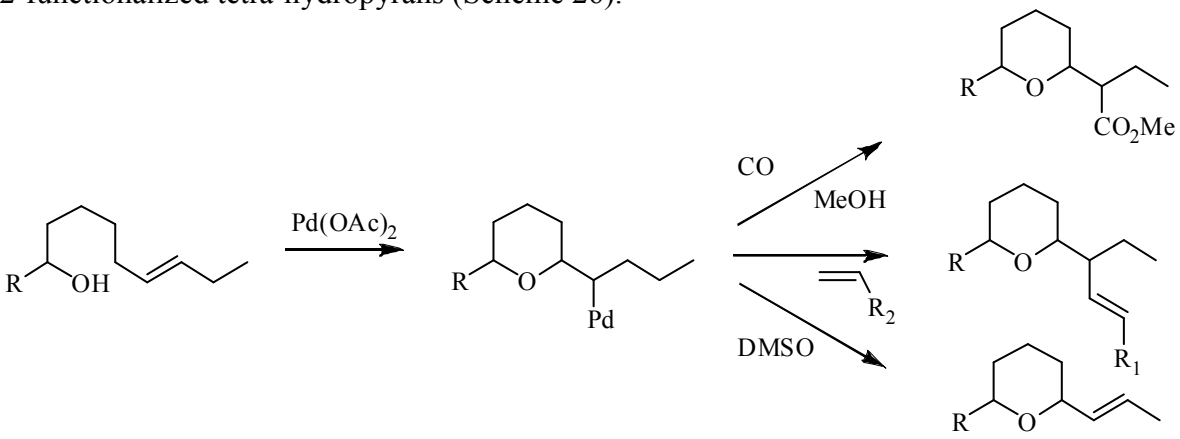
Scheme 24

Recently, Marko and co-workers have reported that the tandem Ene reaction-Intra Molecular Sakurai Cyclisation (IMSC) of aldehydes was a particularly efficient procedure for the synthesis of a variety of diastereometrically pure *exo*-methylene tetrahydropyrans (Scheme 25).[50]



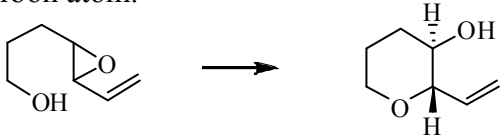
Scheme 25

Intramolecular palladium catalyzed cyclization of alkenols allows additional functionalization of the tetrahydropyran through the trapping of an intermediate palladium species. Thus, methoxy-carbonylation[51a,b], vinylation[51c], and hydride elimination[51d] lead to 2-functionalized tetra-hydropyrans (Scheme 26).



Scheme 26

A significant variation on the alkenol theme is the stereo- and regio- selective ring opening of hydroxyepoxides (Scheme 27).[52] 5-*exo*-Cyclization compete with the 6-*endo* mode but the latter is dominant when an electron-rich unsaturated function is present α-position to the epoxide carbon atom.



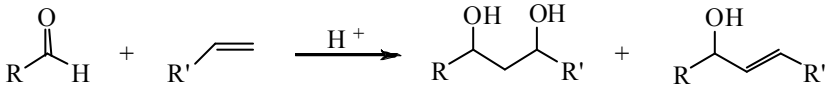
Scheme 27

1.3.1. Prins-cyclization and Prins-Type Macrocyclization:

1.3.1a. Introduction to Prins cyclization:

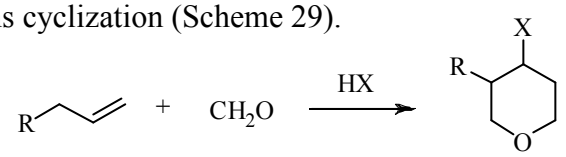
The Prins reaction is an organic reaction consisting of an electrophilic addition of an aldehyde or ketone to an alkene or alkyne followed by capture of a nucleophile or the acid catalyzed condensation of olefins with aldehydes.[54] A variety of Lewis acids[55] have been used to mediate such a cyclization. In 1919, Prins reported the condensation of formaldehyde with styrene in the presence of an acid catalyst to form a diol product. This reaction afforded a mixture of compounds; the major products of classical Prins reaction are normally 1,3-glycols, unsaturated alcohols and the products obtained from acid-catalyzed polymerization of the olefins (Scheme 28).

The Prins reaction has become a powerful tool for constructing carbocyclic and heterocyclic compounds. The Prins cyclization has wide applications including, among others, the synthesis of polyether antibiotics and other complex natural products that contain tetrahydropyran backbones are significant.



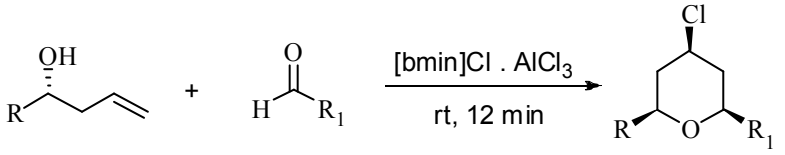
Scheme 28

In the late 1960s, Stapp[56] briefly examined the direct synthesis of tetrahydropyran derivatives via the Prins cyclization (Scheme 29).



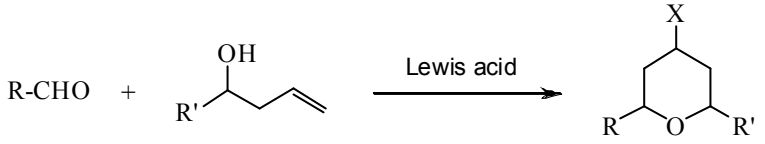
Scheme 29

1-*n*-Butyl-3-methylimidazolium chloroaluminate [bmin]Cl·$AlCl_3$ was successfully employed as a reaction medium for Prins cyclizations, to produce 4-chlorotetrahydropyran derivatives in short reaction times with good yield (Scheme 30).[53]



Scheme 30

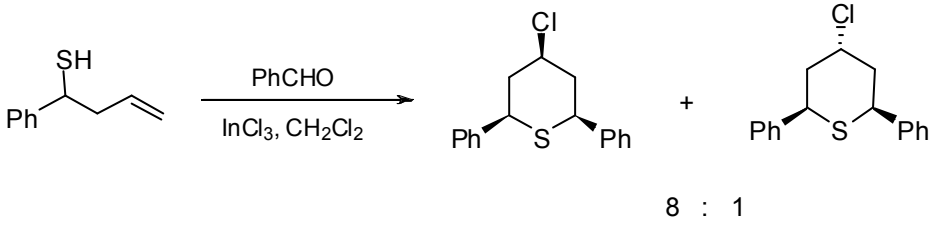
Chan[57] as well as Coppi reported that the coupling between allylsilanes and aldehydes could be used to prepare 2,6-disubstituted-4-halotetrahydropyrans.Coppi and co-workers[58] found that an analogous condensation could be achieved by directly mixing aldehydes and unsaturated alcohols at 0 °C in the presence of Lewis acid (Scheme 31).



Scheme 31

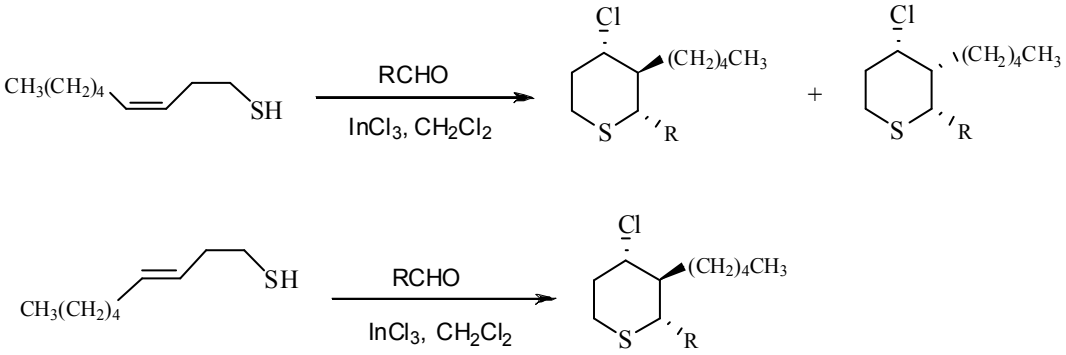
A variety of Lewis acids have been used to mediate such a cyclization. In most cases, the cyclization products are 2,6-disubstituted dihydropyran or 2,4,6-trisubstituted tetrahydropyran derivatives.

The Prins-cyclization of homoallyl mercaptans with aldehydes in the presence of indium trichloride afforded 2,4,6–trisubstituted thiacyclohexanes[59] as an 8:1 mixture of diastereomers (Scheme 32).



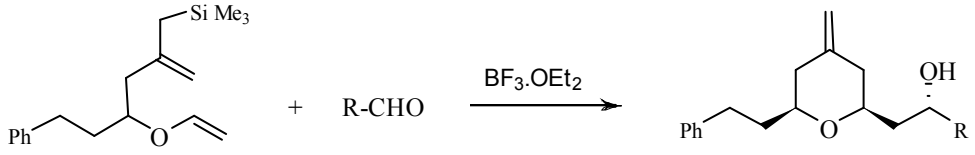
Scheme 32

The reaction of *cis*-mercaptan gave a mixture of *cis-cis-cis* and *cis-trans-cis*-thiacyclohexane derivatives with the latter as the predominant product whereas *trans*-mercaptan generated exclusively a *cis-trans-cis* thiacyclohexane derivative (Scheme 33).



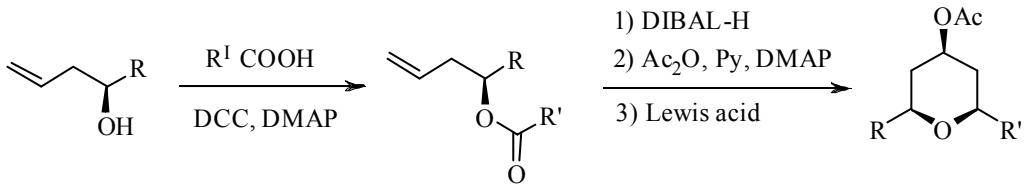
Scheme 33

The aldol-Prins reactions of enol allylsilanes in the presence of camphorsulphonic acid afforded the tetrahydropyran derivative with *cis*-diastereo-selectivity.[60] The aldol-Prins reactions of enol allylsilanes with aldehydes led to the formation of *cis*-2,6-disubstituted tetrahydropyran derivatives (Scheme 34).



Scheme 34

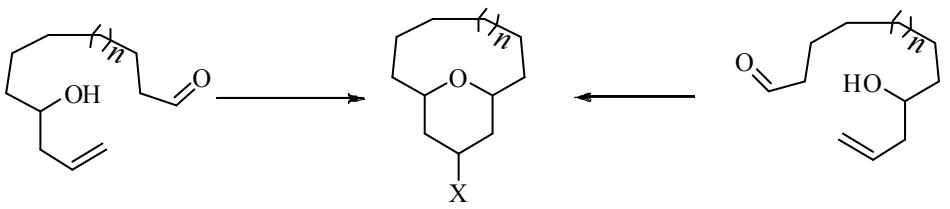
Recently, the segment-coupling Prins-cyclization has been reported[61] involving esterification, reductive acetylation and Lewis acid promoted cyclization (Scheme 35).



Scheme 35

1.3.1b. Prins-Type Macrocyclization and applications in Natural Product Synthesis:

Prins-type macrocyclizations have recently emerged as a successful strategy in the synthesis of polyketide-derived natural products. This reaction provides a concise and selective means to form tetrahydropyran containing macrocyclic ring of varying size. A high degree of functionality within the macrocycle is tolerated and the yields for these transformations are typically good to excellent. Since the initial report of a Prins macrocyclization reaction in 1979, examples of this approach did not re-emerge until 2008. However, the use of this method in natural product synthesis has rapidly gained momentum in the synthetic community, with multiple examples of this macrocyclization tactic reported in the recent literature such as synthetic strategies toward neopeltolide by Lee,[62a] Formal synthetic strategy toward neopeltolide by Yadav and Kumar,[62b] Synthetic strategy toward bryostatin analogues by Wender,[62c] formal synthetic strategy toward kendomycin by Rychnovsky and Bahnck,[62d] synthetic studies toward clavosolide A by Rychnovsky[62e] and synthetic strategy toward polycavernoside A by Lee and Woo.[62f] The general strategy for Prins macrocyclization is given below in Scheme 36.

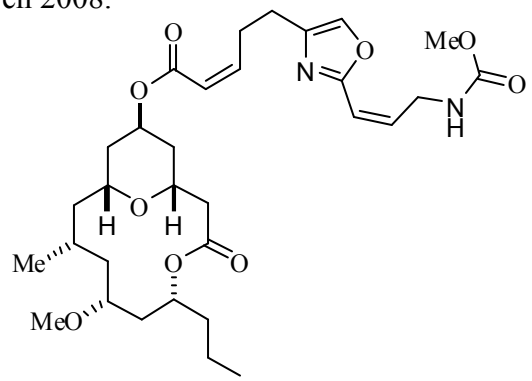


n = two or more than two
x= trapped nucleophile

Macrocycle embedded
with THP-ring

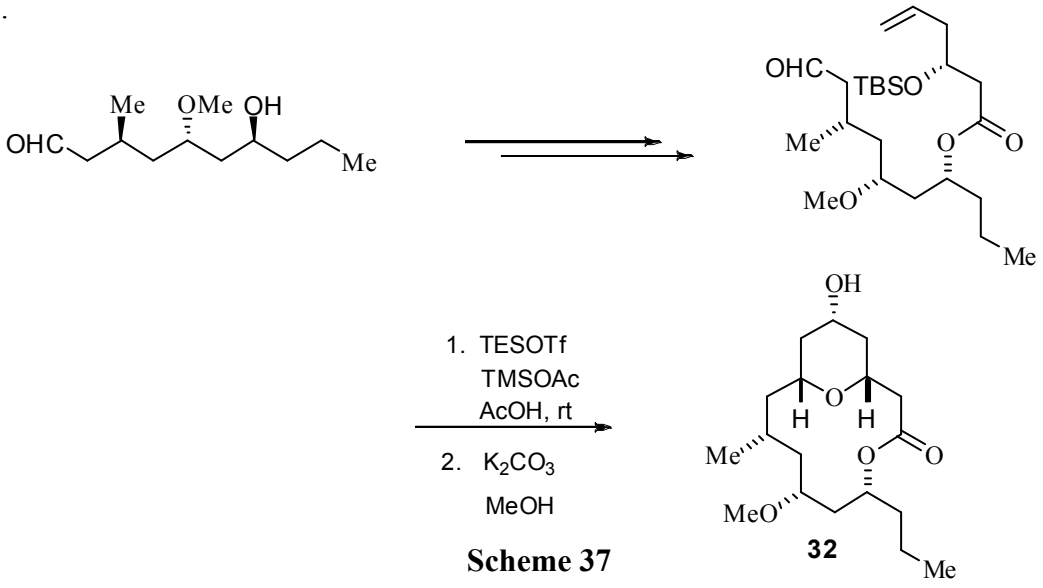
Scheme 36

Lee and co-workers reported the total synthesis of neopeltolide (**31**) utilizing a Prins macrocyclization in March 2008.[62a]



Neopeltolide (31)

The applications of this macrocyclisation in neopeltolide of two different macrocyclization precursors from a common advanced intermediate are given below (Scheme 37).



Scheme 37

In November 2009, Yadav and Kumar reported a formal synthesis of neopeltolide,[62b] in which the macrolactonisation was achieved by a Prins macrocyclization in a simillar manner to Lee's strategy.

By utilizing the above macrocyclisation, we have successfully prepared the core of leucacsandrolide A with good yield and high diastereoselectivity which is described briefly in this article.

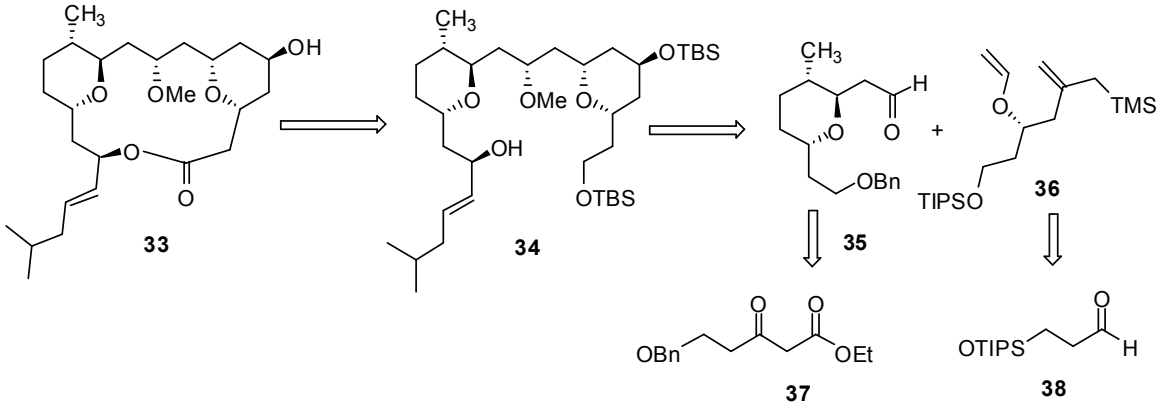
1.4. Previous Approaches:

In 1996, Pietra and co-workers identified a new genus of calcareous sponges *Leucascandra caveolata* obtained from the northeastern coast of New Calendonia Coral Sea, which resulted in the discovery of a highly complex natural product designated as leucascandrolide A. This macrolide exhibits high in vitro cytotoxicity against human KB and P388 tumor cell lines displaying IC_{50} values of 0.05 and 0.25 μg/mL, respectively. The natural product also possesses potent antifungal ability against *Candida albicans*, pathogenic yeast that attacks AIDs patients and other immunocompromised individuals. Additionally, following hydrolysis of the C5 ester linkage, biological testing of the 18-membered macrocyclic core and the separated side chain demonstrated that the macrocyclic domain is solely responsible for the cytotoxicity, while the oxazole-containing unsaturated side chain appears to be responsible for the antifungal activity. The highly oxygenated 18-membered macrolide has eight stereogenic centers and three alkenes and also features two trisubstituted tetrahydropyran rings, one of these having an unusual oxazole-containing side chain axially appended at C5. A subsequent report indicates that leucascandrolide A is no longer available from its initial natural source. It has been proposed that leucascandrolide A and its cometabolite leucascandrolide B are products of opportunistic microbial colonization of the sponge, as evidenced by the large amounts of dead tissue in the initial harvest of Leucascandra caveolata. Currently, there is no natural source of leucascandrolide A. Based on its impressive biological activity, inaccessibility from natural sources, and structural complexity associated with ample synthetic challenges, the construction of leucascandrolide A has spurred considerable synthetic interest, resulting in several total and formal syntheses.

1.4.1. Rychnovsky's approach:[63]

Williams and co-workers published the total synthesis of leucascandrolide A macrolide (**50**) by aldol-Prins reaction that developed by the same group for the synthesis of some natural products which was shown in Scheme 38.

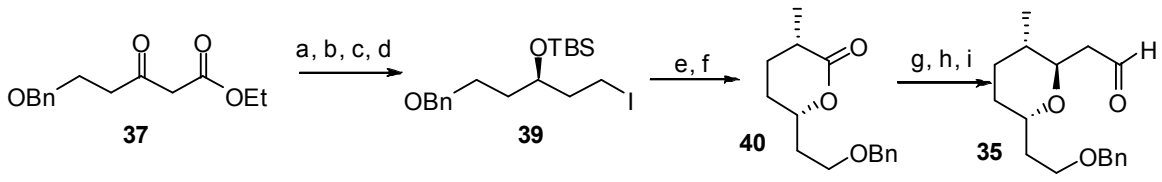
1.4.1a. Retrosynthesis:

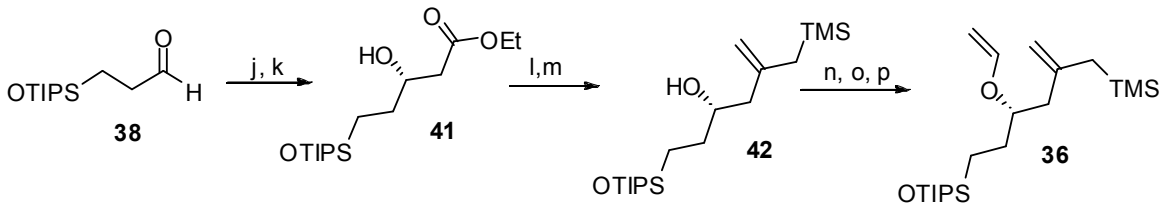


Scheme 38: Retrosynthetic analysis

1.4.1b. Discussion:

Synthesis of the optically pure aldehyde **35** was prepared by using some well established reactions from the known compound **37**. The first stereogenic center of **37** was introduced by Noyori reaction followed by TBS protection, DIBAL-*H* reduction and iodination gave the iodo compound **39**. Myers' pseudoephedrine auxiliary was used to introduce the C12 stereocenter by alkylation of iodide **39** and acid treatment gave the lactone **40**. Reductive acetylation axial allylation and ozonolysis completed the synthesis of **35**. The synthesis of fragment **36** was commenced from the known aldehyde **38**. Noyori hydrogenation of a α-keto ester generated the only stereogenic center in the target **36**. Bunnelle's method was used to convert the ester **41** to the 2-substituted allylsilane **42.** The sensitive enol ether was introduced using esterification with chloroacetyl chloride, reductive acetylation and elimination of the acetate and chloride groups by Li/NH_3 reduction to isolate the enol ether **36** (Scheme 39).

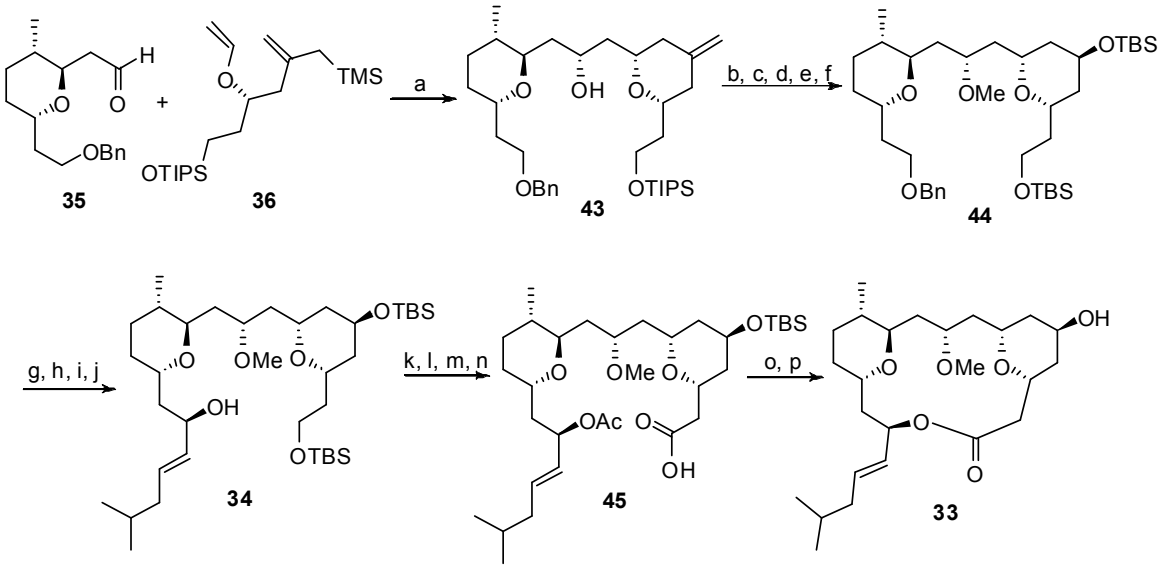




Scheme 39

Reagents and conditions: a) (*R*)-BINAP-RuCl(C_6H_6), 80 atm H_2, EtOH, 96%, 94% ee; b) TBSCCl, imidazole, DMF, 86%; c) DIBAL-*H*, THF, –25 ^oC, 88%; d) PPh_3, I_2, imidazole, CH_2Cl_2, quant; e) combine LDA, (–)-pseudoephedrine propionamide, LiCl, then add 15, THF, –78 ^oC, 98%, >20:1 dr; f) 2N H_2SO_4, dioxane, 95 ^oC, 77%; g) i. DIBAL-*H*, CH_2Cl_2, –78 ^oC, ii. Ac_2O, DMAP, pyridine, 95%; h) Allyl-trimethylsilane, $BF_3.OEt_2$, CH_2Cl_2; –78 ^oC, 97%, >20:1 dr; i) O_3, CH_2Cl_2, –78 ^oC, then PPh_3, 95%; j) N_2CHCO_2Et, $SnCl_2$, CH_2Cl_2, 72%; k) (*S*)-BINAP-RuCl(C_6H_6), 4 atm H_2, EtOH, 100 ^oC, 51%, >95%ee; l) TMSCl, Et_3N, CH_2Cl_2, 91%; m) i. $CeCl_3$, $TMSCH_2MgCl$, THF/Et_2O, –78 ^oC to 23 ^oC, ii. SiO_2 gel, CH_2Cl_2, 87% n) $ClCH_2COCl$, pyridine, CH_2Cl_2, 95%; o) i. DIBAL-*H*, CH_2Cl_2, –78 ^oC, ii.Ac_2O, DMAP, pyridine, CH_2Cl_2, 95%; p) Li , NH_3, THF, –78 ^oC, 65%

Aldehyde **35** and enol ether **36** were coupled using the same conditions $BF_3.OEt_2$ and 2,6-*di-tert*butylpyridine at –78 °C, to give the product **43** as a 5.5:1 mixture of epimers at



Scheme 40

Reagents and conditions: a) i. $BF_3.Et_2O$, 2,6-di-tert-butylpyridine, CH_2Cl_2, –78 ^oC, ii. $NaBH_4$, EtOH, 78%, 5,5:1 dr at C9; b) $MeO.BF_4$-, proton Sponge, 4 A^o M.S., CH_2Cl_2, 79% (single epimer) plus C9 epimer (15%), c) i. OsO_4, NMO, ii. NaIO4, 80%; d) *L*-Selectride, THF, –90 to –60 ^oC, 82% (single epimer) plus C5 epimer (10%); e) TBAF,

THF, 92%; f) TBSOTf, 2,6-lutidine, CH_2Cl_2, 89%; g) H_2, $Pd(OH)_2$, EtOAc, 96%; h) Swern, 94%; i) Me_2AlCl, $Me_3SnCCCH_2CH(CH_3)_2$, $PhCH_3$, –78 ^oC, 80%, 3.5:1 dr at C17; j) Red-Al, Et_2O, 60% (Single epimer) plus recovered SM and C17 epimer; k) Ac_2O, DMAP, pyridine, CH_2Cl_2, 89%; l) Neutral Al_2O_3, hexanes, 96%; m) Swern, 97%; n) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, 71%; o) K_2CO_3, MeOH, ii. $Cl_3C_6H_2COCl$, Et_3N, DMAP, C_6H_6, 23 ^oC, 56%; p) HF-Pyridine, THF, 96%.

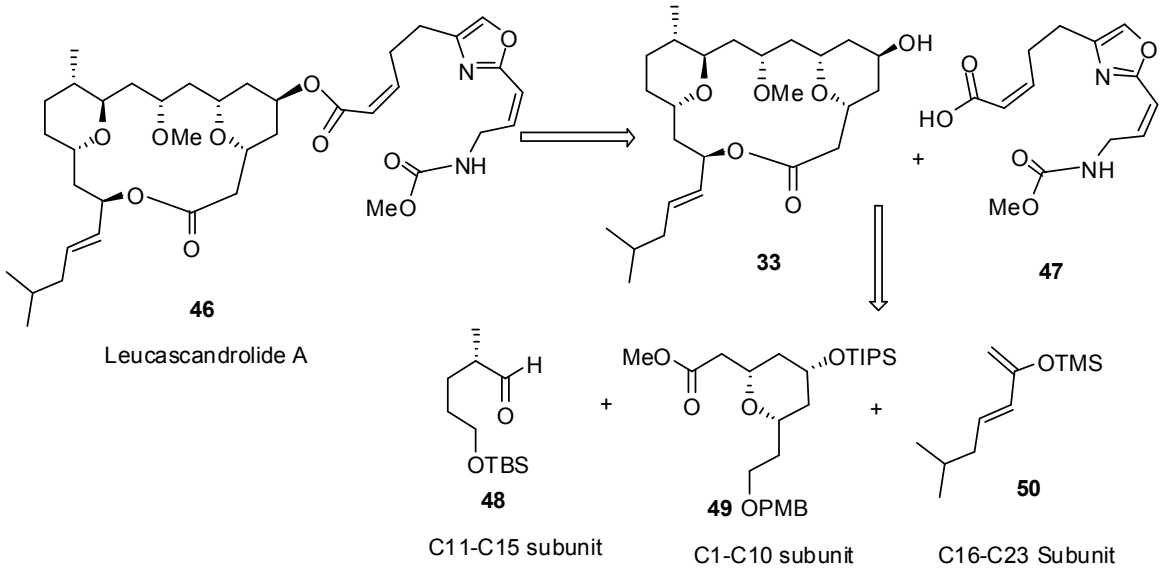
C9. The crucial methylation of C9 was carried out with trimethyloxonium tetrafluoroborate and proton Sponge and the C9 epimers were separated at this stage. Oxidative cleavage of the alkene and *L*-Selectride reduction introduced the axial C5 alcohol and reprotection gave **44** (Scheme 40). The C17 substituent was introduced by a chelation-controlled alkynylstannane addition to the corresponding aldehyde. Red-Al reduction gave the *(E)*-alkene **34** and deprotection of TBS and oxidation of the C1 alcohol gave the seco acid ester **45**. Hydrolysis, Yamaguchi-type cyclization and desilylation completed the synthesis of the leucascandrolide A macrolide **33**.

1.4.2. Paterson's approach:[64]

Paterson and co-workers published the total synthesis of core of leucascandrolide A (**50**) by utilizing Jacobsen asymmetric hetero Diels-Alder and 1,5-anti aldol coupling reaction.

1.4.2a. Retrosynthesis:

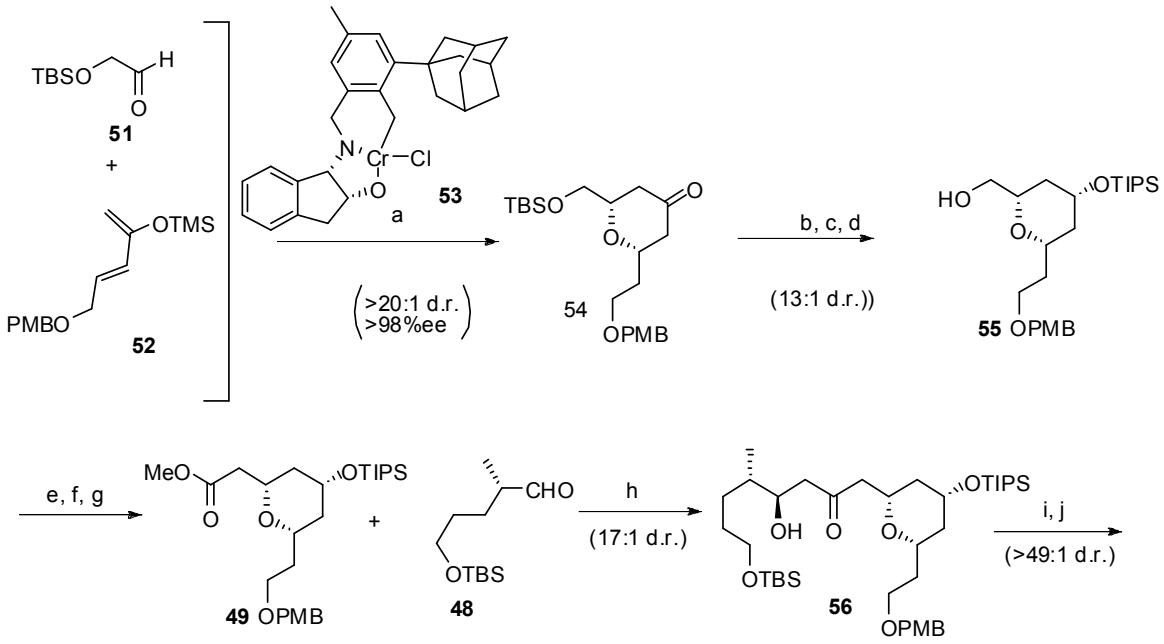
The retrosynthetic nalysis of this compound was shown in Scheme 41.

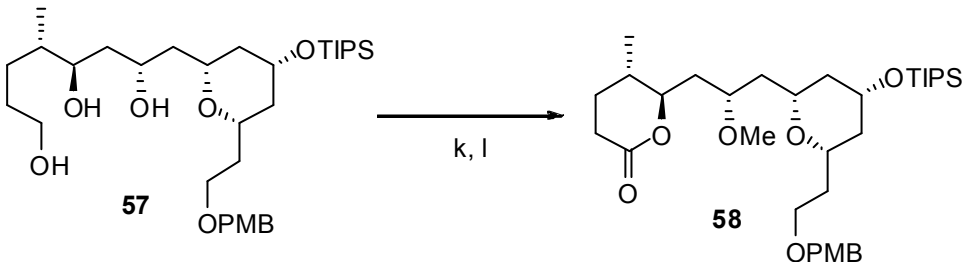


Scheme 41: Retrosynthetic analysis

1.4.2b. Discussion:

The synthesis of the trisubstituted tetrahydropyran **49** began with a Jacobsen asymmetric hetero Diels-Alder reaction of aldehyde **51** and readily available 2-siloxydiene **52**, promoted by the chromium tridentate catalyst **53**. Installation of the equatorial C5 hydroxy group was achieved by treatment with $NaBH_4$ in MeOH to give secondary alcohol following TIPS ether formation, selective acidic removal of the TBS group gave primary alcohol **55**. Homologation to the methyl ketone involved activation of alcohol **55** as its triflate derivative, displacement with lithium trimethylsilyl acetylide and basic methanolysis to give alkyne. Subsequent Hg(II)mediated hydration gave the methyl ketone **49** cleanly. Thus, treatment of **49** with *c*Hex_2BCl and Et_3N in Et_2O generated the corresponding less substituted enolate, which on addition of aldehyde **48** provided, after oxidative workup, aldol adduct was obtained and 1,3-anti reduction of b-hydroxy ketone **56** with $Me_4NBH(OAc)_3$ provided diol. Next, acidic removal of the TBS group gave triol **57**, which was oxidized selectively at the primary hydroxy group by using catalytic TEMPO and iodobenzene diacetate to give d-lactone. Methylation of the isolated C9 hydroxy group with Me_3OBF_4 and proton sponge gave advanced intermediate **58**. Suitable activation of the anomeric position was achieved by treating d-lactone **58**

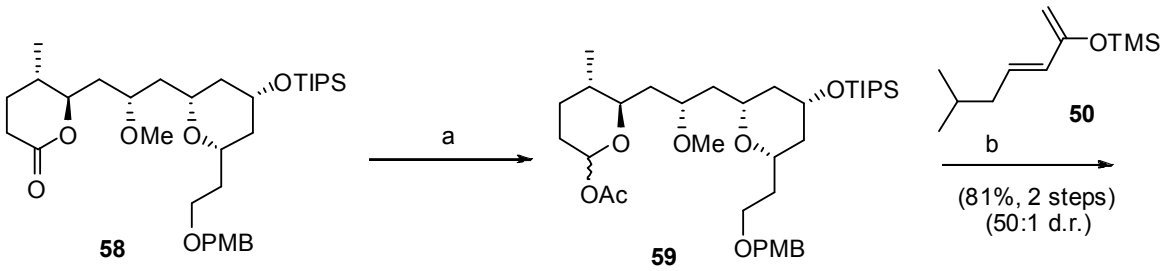


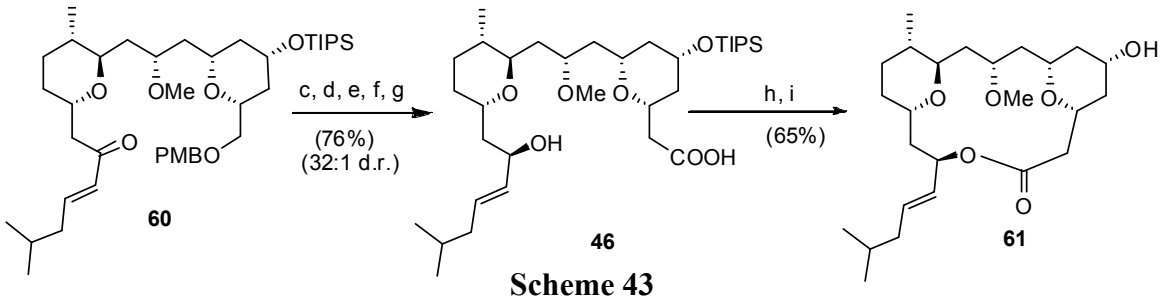


Scheme 42

Reagents and conditions: a) 4 A^{o} M.S, 20 ^{o}C, 20 h; acidified $CHCl_3$, 20 ^{o}C, 4 h, 80%; b) $NaBH_4$, MeOH, 20 ^{o}C, 2 h, 99%; c) TIPSOTf, lut, CH_2Cl_2, –78 ^{o}C, 2 h, d) CSA, 2:1 MeOH/ CH_2Cl_2, 20 ^{o}C, 1 h, 82% (over two steps); e) Tf_2O, pyr, CH_2Cl_2, –10 ^{o}C, 1 h; f) LDA, TMSC, HMPA, –78 to 20 ^{o}C, 1 h; K_2CO_3, MeOH, 20 ^{o}C, 12 h, 84% (over two steps); g) cat. $Hg(OAc)_2$, PPTS, wet THF, 40 ^{o}C, 1 h, 86%; h) *c*Hex_2BCl, NEt_3, Et_2O, O ^{o}C, 30 min; –78 ^{o}C, 2 h; –78 to –30 ^{o}C, 24 h, 99%; i) $Me_4NBH(OAc)_3$, 3:1 MeCN/AcOH, –40 to –20 ^{o}C, 24 h, 99%; j) CSA, 2:1 MeOH/ CH_2Cl_2, 25 oC, 1 h; k) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, –20 ^{o}C, 12 h, 79% (over two steps); l) Me_3OBF_4, proton sponge, CH_2Cl_2, 0 to 20 ^{o}C, 1 h, 84%.

with DIBAL- *H* followed by in situ acetylation to afford acetate **59** . Treatment of **59** with an excess of silyl enol ether **50** in the presence of catalytic $ZnBr_2$ afforded ketone **60** cleanly. Next, a 1,3-syn reduction was achieved by using $LiAlH(O\textit{t}Bu)_3$ alone gave allylic alcohol. Acetylation of the resultant (17*S*)-hydroxy group followed by oxidative removal of the PMB group gave alcohol followed by oxidation to the corresponding acid and saponification afforded seco-acid **46** which set the stage for the Mitsunobu macro-lactonization with treatment of **46** with DEAD and Ph_3P in degassed benzene for 5 min proceeded to give the desired macrocycle (Scheme 43). Cleavage of the equatorial C5 TIPS ether was achieved by HF.pyr in THF to furnish macrocycle **61** for the introduction of the axially oriented side chain at C5.





Scheme 43

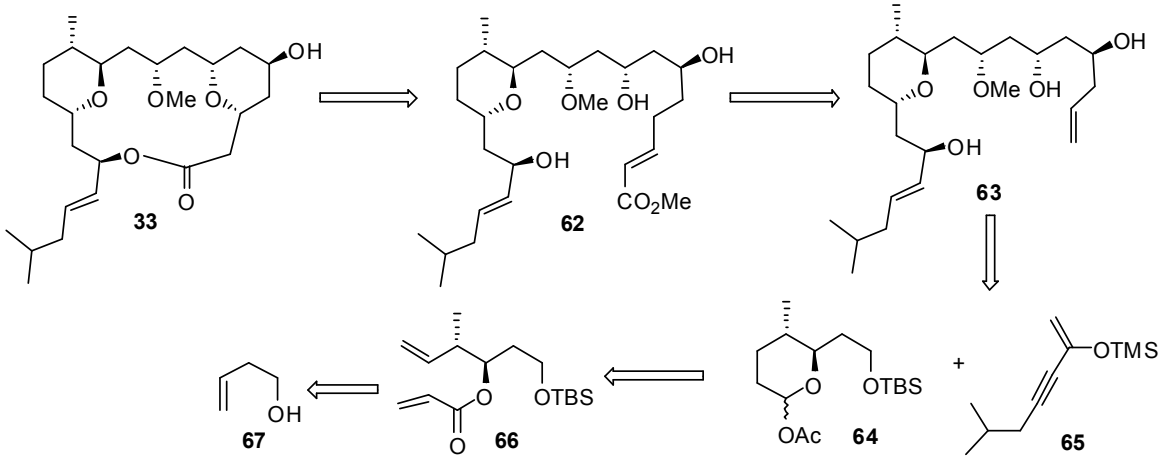
Reagents and conditions: a) DIBAL-*H*, CH_2Cl_2, then Ac_2O, pyr, DMAP, –78 to –20 ^oC, 15 h; b) $ZnBr_2$, CH_2Cl_2, 20 ^oC, 4 h; c) $LiAlH(OtBu)_3$, CH_2Cl_2, –78 to –10 ^oC, 1.5 h; d) Ac_2O, pyr, DMAP, CH_2Cl_2, 0 to 20 ^oC, 15 h; e) DDQ, 10:1 CH_2Cl_2/pH 7 buffer, 20 ^oC, 1 h; f) TEMPO, $Ph(OAc)_2$, CH_2Cl_2, 20 ^oC, 1 h; $NaClO_2$, $NaHPO_4$, 2-methyl-2-butene, aq. *t*-BuOH, 0 to 20 ^oC, 1 h; g) K_2CO_3, MeOH, 20 ^oC, 18 h; h) DEAD, PPh_3, PhH, 20 ^oC, 5 min; i) HF.pyr, THF, 0 to 20 ^oC, 5 h.

In summary, a highly stereocontrolled synthesis of the potent cytotoxic macrolide core of leucascandrolide A was proceeded in 23 steps from 8 (longest linear sequence) and 5.3% overall yield.

1.4.3. Cossy's approach:[65]

In 2007, Cossy and co-workers published the total synthesis of the macrolide ol leucascandrolide A. A chemoselective synthesis of the macrocyclic core of leucascandrolide A has been achieved, utilizing highly enantioselective allylmetalations, an enantioselective Noyori reduction of a propargylic ketone and olefin metatheses as the key steps.

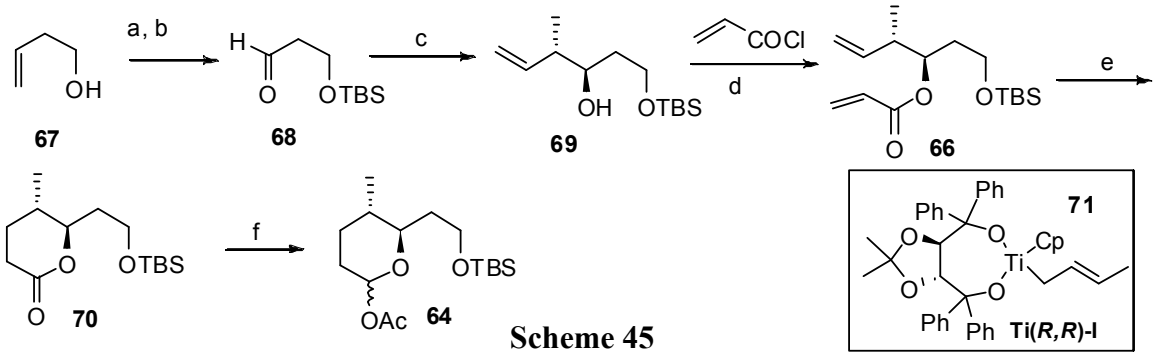
1.4.3a. Retrosynthesis:



Scheme 44: Retrosynthetic analysis

1.4.3b. Discussion:

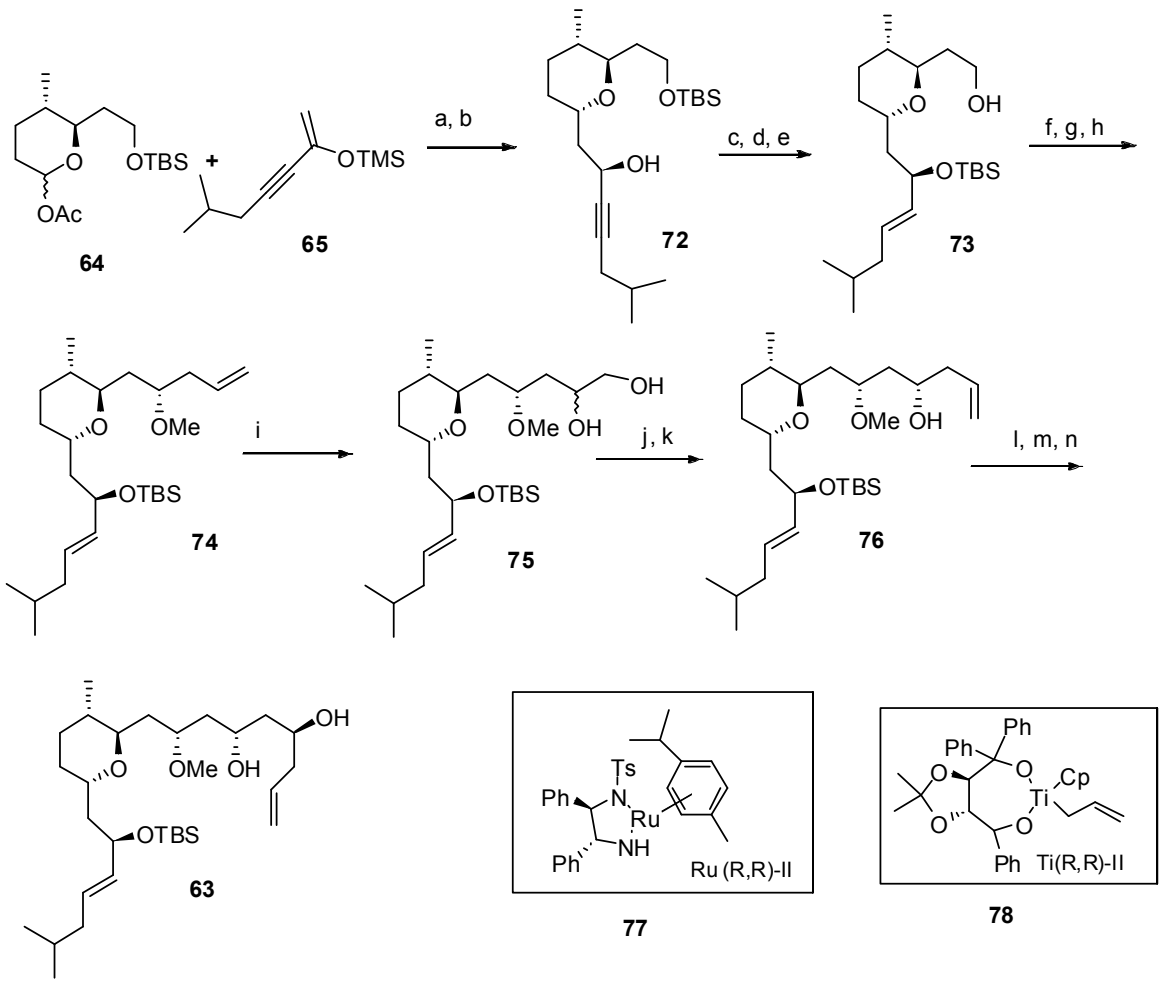
The synthesis of fragment C9-C15 started with the transformation of but-3-en-1-ol to aldehyde **68** which was obtained after protection of the alcohol (TBDMSCl, imidazole) and ozonolysis (O_3, –78 °C, then Et_3N). The addition of the highly face selective titanium complex Ti(*R,R*)-**I 71** to aldehyde **68** (Et_2O, –78 °C) allowed us to control the stereogenic centers at C11 and C12, producing the desired homoallylic alcohol **69**. After transformation of **69** to the unsaturated ester **66** by using acryloyl chloride, Et_3N and CH_2Cl_2. The first one-pot reaction involved a tandem RCM/hydrogenation10 (Ru-**I**, 3 mol %, then H_2, Pd/C) forming lactone **70**. The second one-pot reaction was the transfomation to **64** followed by acylation of the alkoxy aluminum intermediate. Silyl enol ether **65** was prepared in two steps from the commercially available 4-methyl pent-1-yne. The starting alkyne was acylated via an organozinc intermediate (*n*-BuLi, $ZnBr_2$ and AcCl) providing the propargylic ketone which was treated with LiHMDS to furnish the corresponding lithium enolate which was trapped with TMSCl gave the silyl enol ether **65** (Scheme 45).



Scheme 45

Reagents and conditions: a) TBSCl, imidazole, DMF; b) O_3, CH_2Cl_2, –78 ^oC, then Et_3N, 76% (2 steps); c) Ti(*R,R*)-1, Et_2O, -78 ^oC, 86%; d) Et_3N, CH_2Cl_2, 92%; e) Ru-I, CH_2Cl_2, 40 ^oC, 48 h, then Pd/C, 5%, H_2, 1 atm, rt, 70%; f) DIBAL-*H*, CH_2Cl_2, –78 ^oC, then Ac_2O, Py, DMAP, 98%.

Fragment **65** was then coupled with the C9-C15 fragment **64** by using a Mukaiyama-type reaction by treatment with $ZnCl_2$ at –78 °C to afford tetrahydropyran. After reduction of ketone by using Noyori catalyst Ru(*R,R*)-**II** (**78**) under phase transfer conditions (HCO_2Na, *n*-Bu_4NCl, H_2O/CH_2Cl_2), the desired propargylic alcohol **72** was isolated. The propargyl alcohol was reduced with Red-*Al* to the (*E*)-allylic alcohol, the crude material

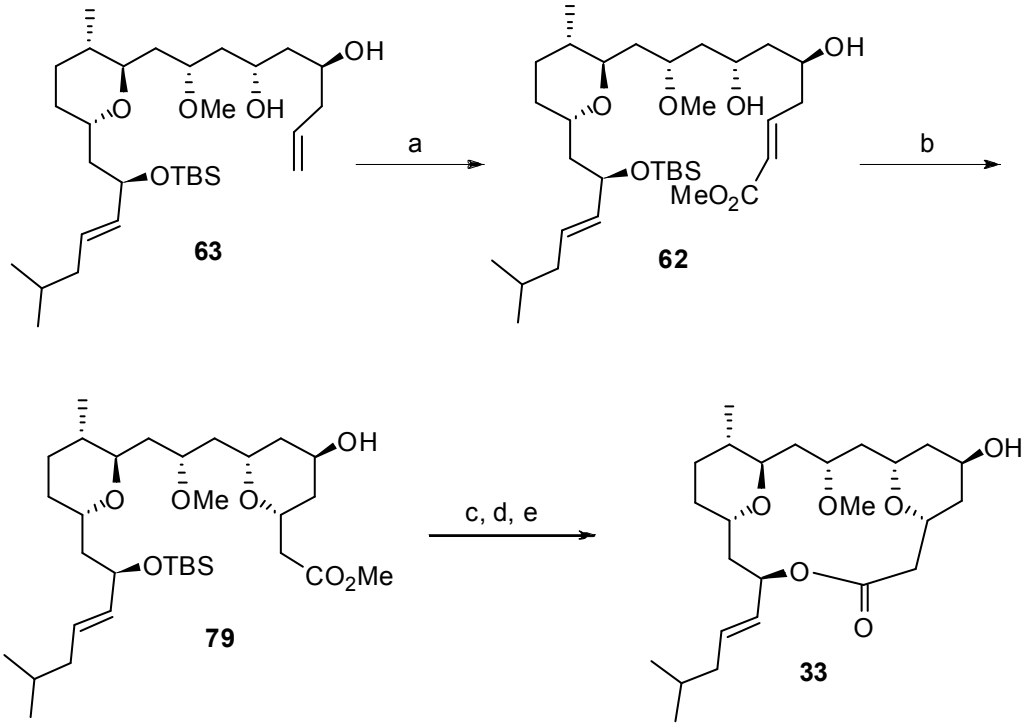


Scheme 46

Reagents and conditions: a) $ZnCl_2$, CH_2Cl_2, –78 ^oC to rt, 89%; b) HCOONa, *n*-Bu_4NCl cat Ru(*R,R*)-II (3mol %), H_2O/ CH_2Cl_2 (1/1), 4 days, rt; c) Red Al, 30 ^oC, THF, 24 h; d) TBSOTf, 2,6 Lutidine, 0 ^oC, 92% (over two steps); e) NH_4F, MeOH 60 ^oC, 4h; f) DMP, CH_2Cl_2, g) Ti(*R,R*)-II, Et_2O, –78 ^oC, 80% (over 2 steps); h) Ag_2O, MeI, rt, Drierite, Et_2O, 96%; i) OsO_4 5 mol %, NMO 1 eqiv, 24 h, 0 ^oC, *t*-BuOH/H_2O (2/1), j) $NaIO_4$, THF/H_2O, *n*-Bu_4NCl, 30 min, rt, k) Ti(*R,R*)-II, Et_2O, –78 ^oC, 78% (2 steps); l) OsO_4 5 mol %, NMO 1 eqiv, 24 h, 0 ^oC, *t*-BuOH/H_2O (2/1), 66%; m) $NaIO_4$, THF/H_2O, *n*-Bu_4NCl, 30 min, rt; n) AllylTMS, $SnCl_4$, CH_2Cl_2, –78 ^oC, 74% (2 steps).

was directly treated with TBSOTf to give TBS protected compound. The primary alcohol was chemoselectively deprotected (NH_4F, MeOH) to afford alcohol **73**. The primary alcohol **73** was oxidized to an aldehyde (Dess-Martin periodinane) which was directly treated with the highly face-selective titanium complex Ti(*R,R)*-**II**, (**77**) to produce homoallylic alcohol. The hydroxy group in compound, was then transformed to a methyl

ether compound **74** had to be converted to an aldehyde by selective oxidative cleavage of the terminal double bond furnish the desired aldehyde. This aldehyde was directly subjected to a stereoselective allylation using Ti(*R,R*)-**II** to produce homoallylic alcohol **76**. At first, triol was obtained by dihydroxylation (OsO_4 cat, NMO) and its subsequent oxidative cleavage with $NaIO_4$ generated the corresponding aldehyde. The obtained hydroxy-aldehyde was then directly treated with a premixed solution of allyltrimethylsilane and $SnCl_4$ at –78 °C producing *syn*-1,3-diol (Scheme 46). Compound **63** was treated with methyl acrylate in the presence of Hoveyda-Grubbs catalyst Ru-**III** (15 mol %) to provide chemoselectively the unsaturated ester **62**. The elaboration of *cis*-tetrahydropyran **62** was realized under basic conditions by using a catalytic amount of *t*-BuOK (20 mol %) which afforded **79**. After treatment with TBAF in THF, diol *cis*- was isolated as a single diastereoisomer. At first, a mild saponification of the methyl ester with TMSOK in Et_2O afforded the hydroxyl acid, the cyclization of which provided selectively the macrocyclic core of leucascandrolide A (**33**) under the Yonemitsu-modified Yamaguchi protocol.



Scheme 47

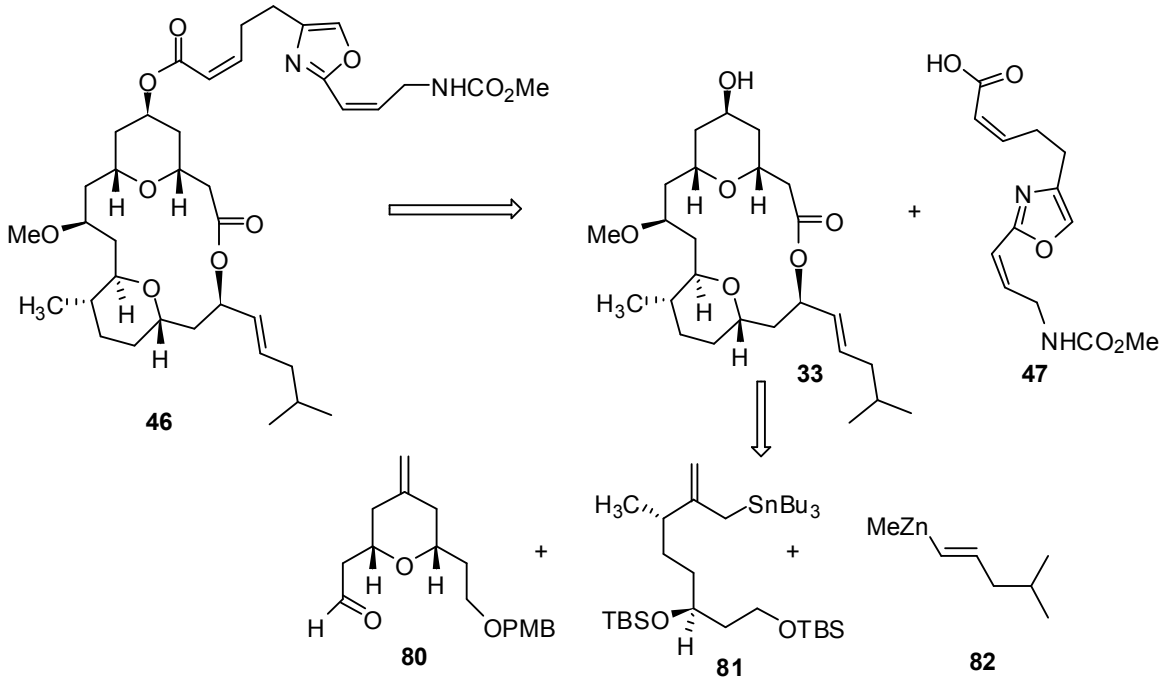
Reagents and conditions: a) Ru-III (15 mol %), CH_2Cl_2, 84%; b) *t*-BuOK (20 mol %), THF, 0 ^oC, (*cis*/*trans*=3/1); c) TBAF, THF, rt, 38% (2 steps); d) TMSOK, Et_2O, e) 2,4,6-trichlorobenzoyl- -chloride, Et_3N, DMAP, Toluene, 75%.

Thus, macrolide was synthesized in 25 steps and 1.2% overall yield from but-3-en-1-ol. Synthetic highlights include highly stereoselective allylmetalations, an enantioselective Noyori reduction, a cross-metathesis followed by an intramolecular 1,4-addition to build up the *cis*-tetrahydropyran.

1.4.4. Williams's approach:[66]

Williams and co-workers published the formal total synthesis of leucascandrolide A macrolide by asymmetric allylation as a key reaction.

1.4.4a. Retrosynthesis:

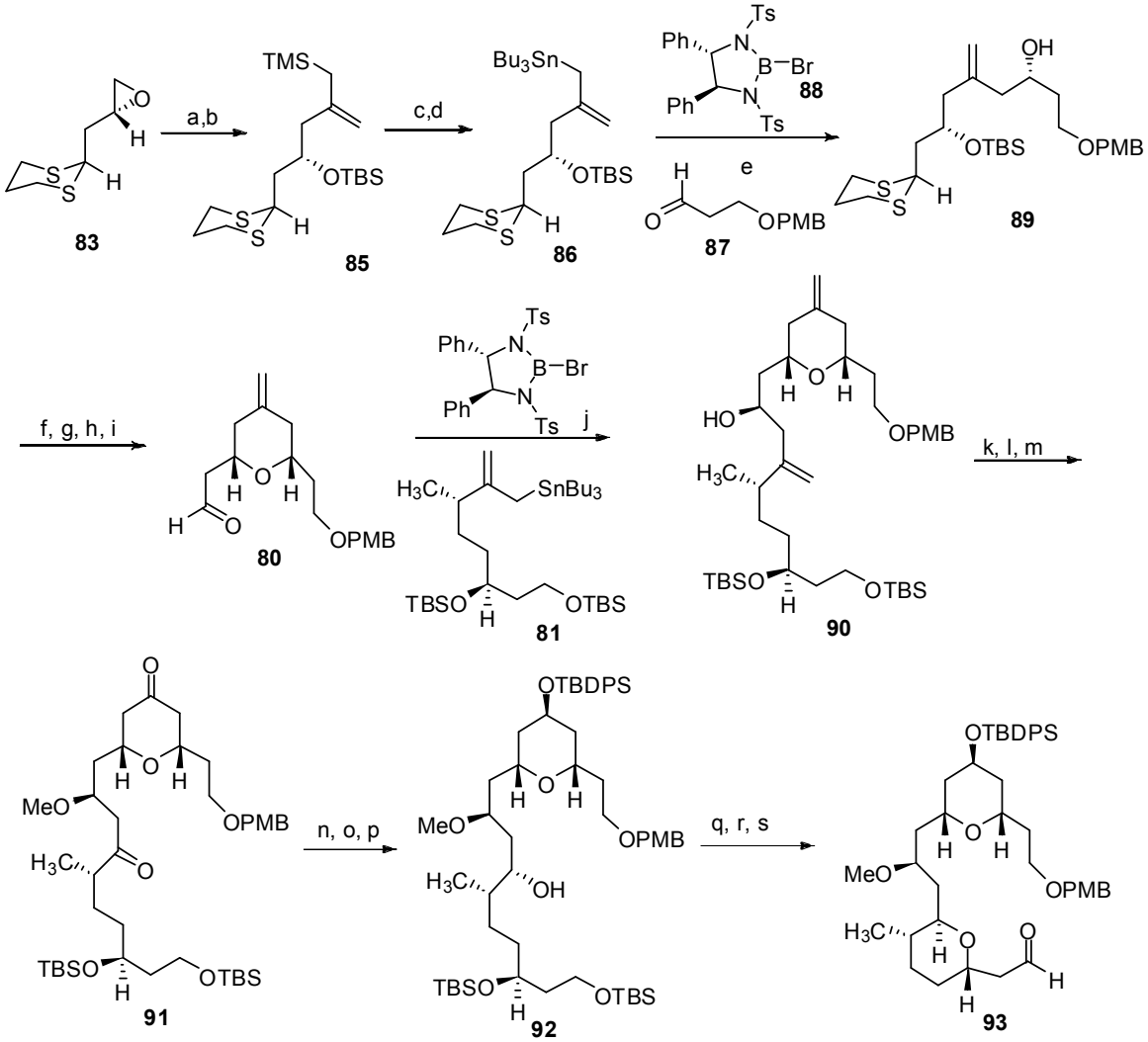


Scheme 48: Retrosynthetic analysis

1.4.4b. Discussion:

The preparation of the C1–C9 aldehyde **80** commenced with the conversion of the known epoxide **83** into the allyl silane **85** through the copper-catalyzed addition of the Grignard reagent prepared from 2-bromo-3 trimethylsilylpropene (Scheme 49). Subsequent protection of the resulting homoallylic alcohol gave the TBS ether. Treatment of **85** with freshly recrystallized NBS at –78 ^oC led to the immediate formation of the

labile corresponding allylic bromide which was displaced directly with a tributylstannylcuprate to give the allyl stannane **86** and subsequent asymmetric allylation was effected following the tin-boron transmetalation of the allylstannane by using the boron bromide reagent **88** developed by Corey et al. Nucleophilic addition to the aldehyde **87** provided the *S* homoallylic alcohol **89** and ring closure of resulted alcohol to afford the 2,6-*cis*-tetrahydropyranyl moiety of **80**. The homoallyl alcohol **90** was prepared by using some well known reaction.[66] Methylation of the homoallylic alcohol at **90** was followed by oxidative cleavage (OsO_4, NMO; $NaIO_4$) to provide the corresponding diketone **91**.

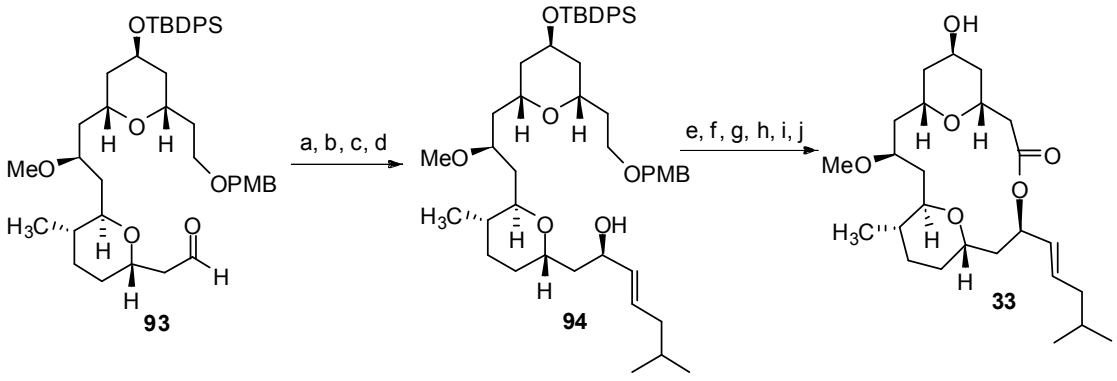


Scheme 49

Reagents and conditions: a) Mg, THF, (2-bromoallyl)trimethylsilane; then epoxide, CuI, –50 ^{o}C to –10 ^{o}C, 2 h; 79%; b) TBSCl, imidazole, DMF; 100 %; c) NBS, propylene oxide, CH_2Cl_2/DMF (2:3), –78 ^{o}C; d) Bu_3SnLi, CuBr.DMS, THF, –78 ^{o}C to –40 ^{o}C; 77% (2 steps); e) the (*S,S*)-1,2-diphenylethane bis (sulfonamide), BBr_3, CH_2Cl_2, 0 ^{o}C, 1 h; then

comp, rt, 10 h; then aldehyde, –78 ^{o}C, 1.5 h; 100%, d.r. 11:1; f) TsCl, Et_3N, DMAP, CH_2Cl_2, 100%; g) HF.pyr, CH_3CN, 99%; h) NaH, PhH, 90 ^{o}C, 75%; i) MeI, $CaCO_3$, CH_3CN/H_2O (9:1), 16 h, 100%; j) the (*R,R*)-1,2-diphenylethane bis (sulfonamide), BBr_3, CH_2Cl_2, 0 ^{o}C, 1 h ; then comp, rt, 10 h, then aldehyde, –78 ^{o}C, 1.5 h, 96%, d.r., 8.5:1; k) Me_3OBF_4, proton sponge, 4-A^{o} M.S., CH_2Cl_2, 96%; l) OsO_4, NMO, acetone/H_2O (2:1), 16 h, m) $NaIO_4$, THF/phosphate buffer (pH 7; 1:1), 16 h, 80%, (2 steps), n) *L*-Selectride, THF, –78 ^{o}C., 1.5 h, 84%; o) TBDPSCl, imidazole, DMF, 40 h; 73%; p) $LiAlH_4$ (2 equiv), (-)-N-methylephedrine (2 equiv), N-ethylaniline (4 equiv), Et_2O, –78 ^{o}C, 2 h, 95%; q) Ts_2O, pyridine, THF, 84%; r) NaH, PhH, 60 ^{o}C, 16 h, 73%; s) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, 95%.

L-Selectride promoted selective reduction at C5 of the tetrahydropyranone, which led to the corresponding axial alcohol and this alcohol was protected as its TBDPS ether. The asymmetric reduction of the ketone at C11 and formation of the 2,6-trans-tetrahydropyran was done and followed by selective removal of the TBS groups and treatment with sodium hydride. The Dess–Martin oxidation of the primary alcohol yielded the aldehyde **93**. The hydrozirconation of 4-methyl-1-pentyne with the Schwartz reagent was followed by transmetalation with dimethylzinc to give allylic alcohols which was oxidized directly to the enone which was allowed for Corey–Bakshi–Shibata (CBS) borohydride reduction and subsequent acetylation to give **94** was followed by oxidative deprotection of the alcohol at C1 and the acid was obtained by oxidation of the resulting primary alcohol to the carboxylic acid and subsequent basic methanolysis of the acetate at C17. The crude product was subjected to the Yonemitsu-modified Yamaguchi protocol to give the macrolide. Finally, deprotection of the alcohol at C5 by treatment with fluoride provided the leucascandrolide A macrolactone **33**.



Scheme 50

Reagents and conditions: a) 4-methyl-1-pentyne, CH_2Cl_2, $Cp_2Zr(H)Cl$, rt, then Me_2Zn, –78 ^{o}C, then comp, –78 to 0 ^{o}C, 1 h, 87%; b) Dess-Martin periodinane, $NaHCO_3$,

CH_2Cl_2, 75%; c) (*S*)-2-methyloxazaborolidine, BH_3.THF, –10 ^oC, 89%, d.r. 5:1; d) Ac_2O, pyridine, DMAP, CH_2Cl_2, 97%; e) DDQ, CH_2Cl_2/phosphate buffer (pH 7) / *t*-BuOH (40:10:1), 1.5 h; quant; f) Dess-Marton periodinane, $NaHCO_3$, CH_2Cl_2; g) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, aqueous *t*-BuOH, 0 ^oC, 45 min, 56% (2 steps); h) K_2CO_3, MeOH, 16 h; i) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, benzene, 63%, (2 steps); j) TBAF, THF, 67%.

In summary, investigations into asymmetric allylation methodology have extended this fundamental technique to the efficient, convergent construction of leucascandrolide A macrolactone.

CHAPTER I

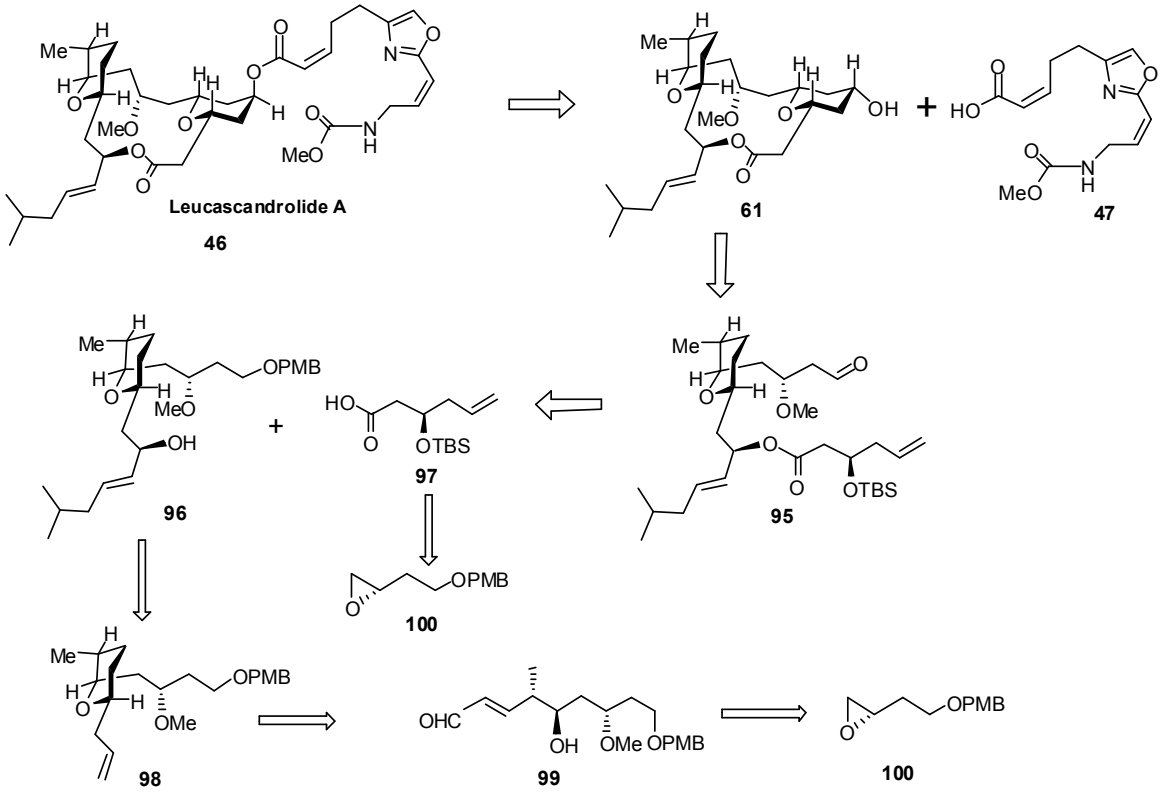
Section B

Total synthesis of the macrolide core of Leucascandrolide A

1.5. PRESENT WORK

We achieved a unique synthetic solution for the synthesis of leucascandrolide featuring a concise, convergent, and highly stereoselective approach to this complex natural product. Our interest for macrolactone core of leucascandrolide A arose from studies in which we demonstrated that the critical *trans*-2,6-disubstituted tetrahydropyran relevant to the C11-C15 fragment would be prepared following a recently developed iodocyclization of *δ*-hydroxy *α,β*-unsaturated aldehyde with allyltrimethyl silane in the presence of molecular iodine (Scheme 51). The second most important reaction was to apply a Prins-type macrocyclization which has recently emerged as a successful strategy in the synthesis of polyketide derived complex natural products. Here we disclose an effective and concise formal total synthesis of leucascandrolide A by utilizing some recent protocols like iodocyclization and intramolecular Prins-macrocyclization.

1.5.1. Retrosynthesis:



Scheme 51: Retrosynthetic analysis of the leucascandrolide A

The retrosynthetic analysis of leucascandrolide A was shown in Scheme 51. From the retrosynthetic perspective, disconnection of Leucascandrolide A at the macrolactone core **61** and the oxazole containing side chain at the C5 hydroxyl yeild two fragment **47**. The macrolactone core **61** could be obtained from aldehyde **95** through a late stage Prins-cyclization. The alcohol fragment **96** could be prepared from the C11-C15 pyran of **98** which could be obtained following our recently reported protocol. The *δ*-hydroxy *α,β*-unsaturated aldehyde **99** precursor for the iodocyclization reaction as well as the acid fragment **97** could be obtained starting from a known chiral epoxide **100**.

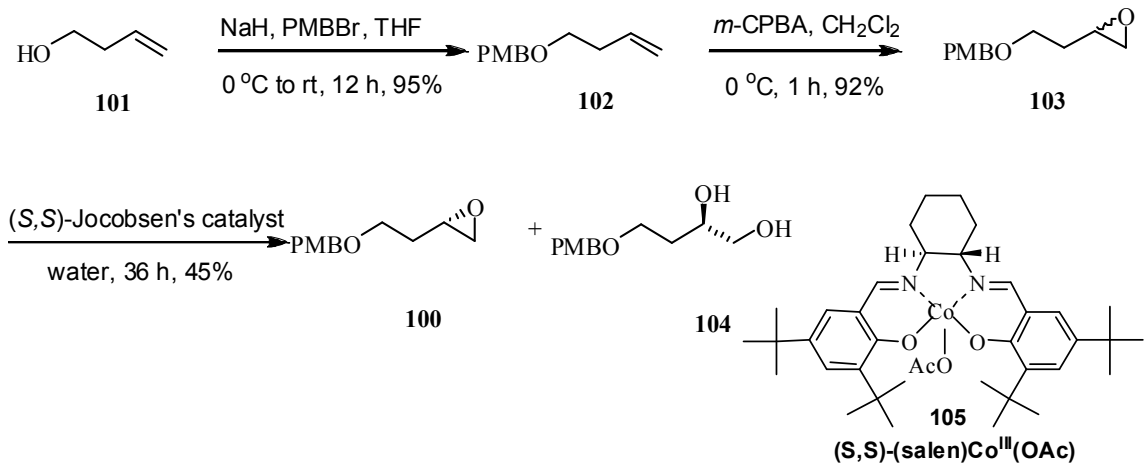
The crucial reactions involved in the synthesis of the core of leucascandrolide A are Jocobsen's hydrolytic kinetic resolution, cross-metathesis, Jørgensen's asymmetric epoxidation, iodine-catalyzed cyclization, CBS-reduction, Yamaguchi esterification and intramolecular Prins-macrocyclization.

1.5.2. Synthesis of the alcohol fragment (96):

The journey towards the synthesis of subtarget **96** began with the kinetic resolution of 2-(*p*-methoxybenzyloxyethyl)oxirane **103** (obtained from 3-butenol **101** in two steps as shown in Scheme 52).[67] The commercially available homoallyl alcohol **101** was converted to its *p*-methoxybenzyl ether **102** by treating with sodium hydride (60% w/v dispersion in oil) and benzyl bromide in dry THF at 0 ^{o}C in 95% yield. *p*-Methoxybenzyl ether **102** was confirmed by it ^{1}H NMR spectrum, which showed resonances at their corresponding chemical shift as a singlet for two benzylic protons and a multiplet for aromatic protons. Absence of hydroxyl functionality was also confirmed by IR spectrum, which showed no absorption band for hydroxyl functionality. Treatment of **102** with *m*-CPBA in dichloromethane at 0 ^{o}C afforded the racemic epoxide **103** in 92% yield. Compound **103** in ^{1}H NMR spectrum showed the absence of olefinic protons at their respective chemical shifts and the appearance of three oxirane protons at 2.98, 2.71 and 2.45 ppm as multiplets manifested the formation of epoxide.

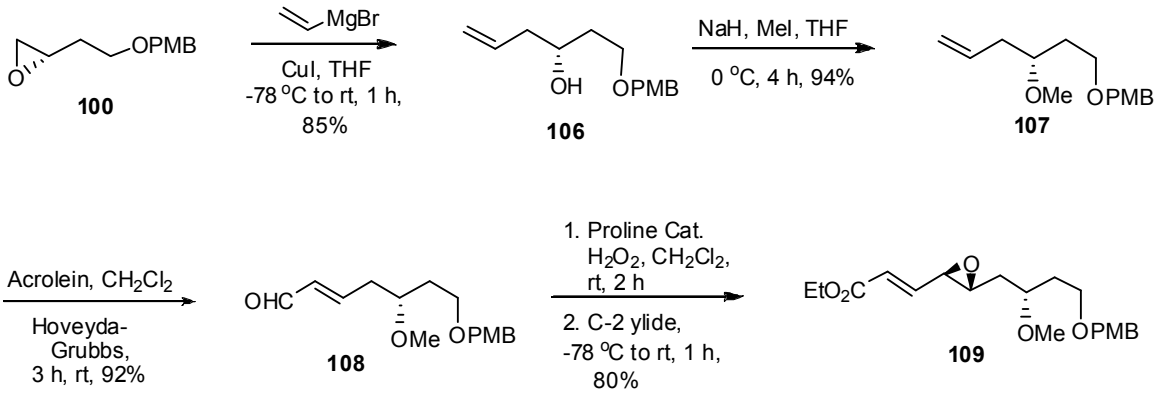
The recemic terminal epoxide **103** was converted to the chiral epoxide **100** in 45% yield along with chiral diol **104** by hydrolytic kinetic resolution employing 0.55 eq of water in the presence of 0.005 mol% of (*S,S'*)-(-)-*N*-*N*'-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino-cobalt (II) (Scheme 52).[68] The optical rotation of the compound **100** was found to be $[\alpha]^{25}_{D}$ -10.8 (*c* 2, $CHCl_3$) which was correlated with that of the earlier

reported value. Chiral epoxide **116** was confirmed by its ^{1}H NMR studies, which exhibited the resonance at the respective chemical shifts.



Scheme 52

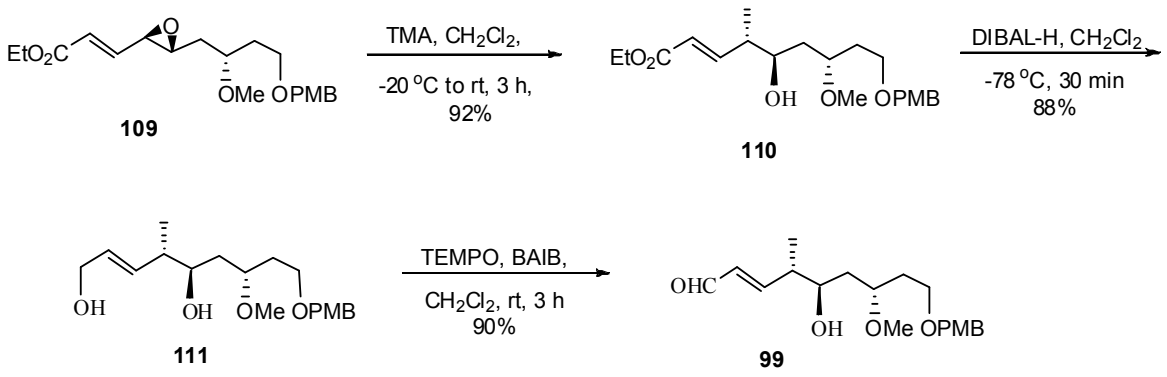
Conversion of epoxide **100** into a homoallyl alcohol **106** through the copper(I)-catalyzed addition of a vinyl Grignard reagent at –20 °C in 85% yield.[69] The ^{1}H NMR spectrum of compound **106** revealed two methylene protons adjacent to the double bond at δ 2.23 ppm and characteristic terminal olefin protons at δ 5.83 ppm and 5.10 ppm. IR absorption showed characteristic band at 3434 cm^{-1} for hydroxyl functionality. The hydroxyl group of alcohol **106** was converted to its methyl ether **107** using MeI and sodium hydride in 94% yield and it revealed by the appearance of characteristic protons at δ 3.32 ppm as singlet and disappearance of broad singlet for hydroxyl protons at 2.94 ppm and ^{13}C NMR spectrum also showed appearance of one peaks at δ 56.7 ppm. Then one carbon homologation of the methyl protected homoallylic alcohol **107** was performed by a cross-metathesis (CM) between the alcohol and acrolein using a Hoveyda-Grubbs catalyst[70] (10 mol%) in CH_2Cl_2 at room temperature to afford a *α,β*-unsaturated aldehyde **108** in 92% yield. ^{1}H NMR revealed a downfield shift for olefenic protons. The characteristic *α,β*-unsaturated olefenic protons resonated at δ 6.81ppm as multiplate and δ 6.12 ppm as doublet. A doublet at δ 9.48 ppm appeared for aldehyde proton and similarly a peak at δ 193.7 ppm appeared in ^{13}C NMR spectrum for aldehyde carbon. IR spectrum showed a peak at 1690 cm^{-1} and, ESI-HRMS also showed $(M+Na)^+$ peak at *m/z* 301.1407 which proved the presence of conjugated aldehyde.



Scheme 53

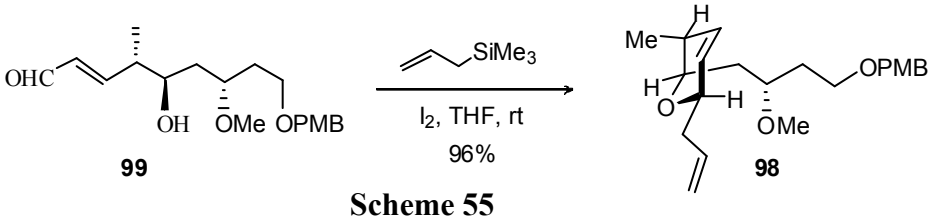
The aldehyde **108** was then subjected to asymmetric epoxidation under Jørgensen's conditions[71] with H_2O_2 in the presence of a proline-derived catalyst to furnish an epoxy aldehyde, which on condensation with $Ph_3P{=}CHCO_2Et$ afforded an epoxy ester **109** in 80% yield. The structure was confirmed by its ^{1}H NMR study which showed the appearance of ester protons at δ 1.18 ppm as quartet and 1.29 ppm as triplet and the opoxide protons at δ 3.17 and 2.97 ppm. The epoxy ester **109** was also confirmed by ^{13}C NMR spectrum on the appearance of carbonyl group of ester peak at δ 165.6 and all eight oxirane carbons at their corresponding positions and a new peak at δ 14.2. IR absorption spectrum revealed a sharp peak at 1720 cm^{-1} which unambiguously proved the formation of epoxy ester. A peak at m/z $[M + Na]^+$ 387.1791 in ESI-HRMS spectrum was helped us to confirm product formation.

The regioselective opening of epoxide of **109** was taken place by using trimethyl aluminum (TMA) followed by slow addition of water in CH_2Cl_2 at –40 °C to afford *δ*-hydroxy compound **110** in 92% yield.[72] The structure was confirmed by its ^{1}H NMR study which showed the absence of oxirane protons and the presence of three methyl protons at δ 1.06 ppm as doublet while the IR spectrum disclosed the absorption band at 3472 cm^{-1} indicating the presence of –OH functionality. The ester functionality in **109** was reduced to hydroxyl functionality using DIBAL-*H* at – 78 °C to afford the diol **111** in 88% yield (Scheme 54). The diol was characterized by ESI-HRMS which showed $[M +Na]^+$ peak at *m/z* 361.1982 and ^{1}H NMR spectrum showed the disappearance of characteristic peaks at δ 4.17 ppm and δ 1.29 ppm. IR absorption showed characteristic broad band at 3408 cm^{-1}



Scheme 54

which indicate the presence of hydroxyl functionalities. The product was characterized by ESI-HRMS which showed $[M + Na]^+$ peak at *m/z* 361.1982. This diol **111**, on selective oxidation in the presence of bis(acetoxy)iodobenzene (BAIB) and 2,2,6,6-tetramethylpiperidine-*N*-oxide (TEMPO) afforded the desired *δ*-hydroxy *α,β*-unsaturated aldehyde **99** in 90% yield.[73] ^{1}HNMR revealed a downfield shift for olefenic protons. The characteristic *α,β*-unsaturated olefenic protons resonated at δ 7.09 ppm as multiplate and δ 6.08 ppm as double doublet, a doublet at δ 9.49 ppm appeared for aldehyde proton in ^{1}H NMR and similarly a peak at δ 194.1 ppm appeared in ^{13}C NMR spectrum for aldehyde carbon. IR spectrum also showed a peak at 1689 cm^{-1} which proved the presence of conjugated aldehyde.Thus with a sizable amount *δ*-hydroxy *α,β*-unsaturated aldehyde in hand, we turned our attention to the most crucial cyclizations step where we tried various reaction conditions to get the desired 2,6-disubstituted-3,4-dihydropyran ring systems.

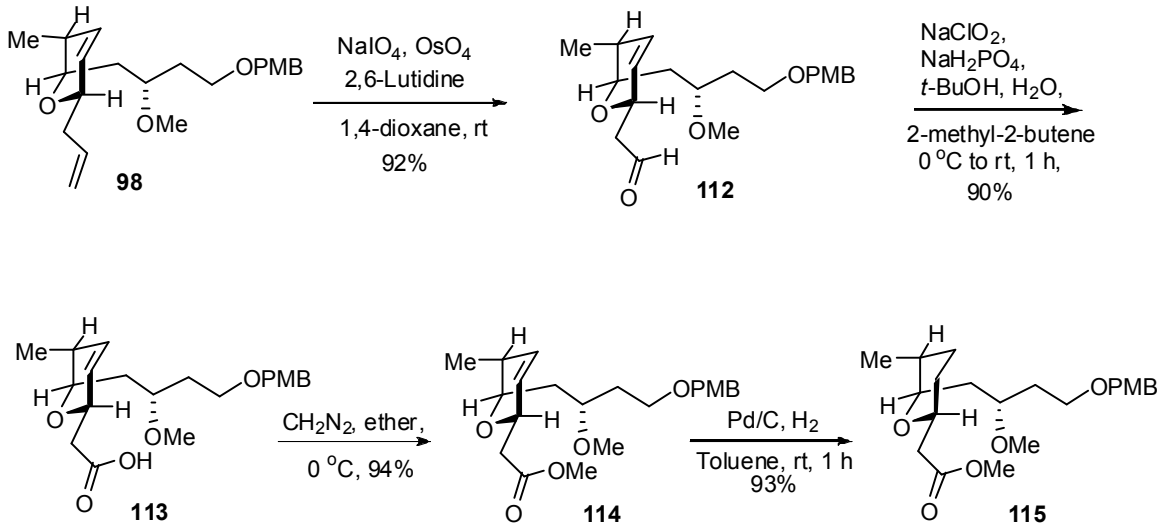


Scheme 55

Initially, we investigated the effect of 5 mol% iodine on the conversion of **99**, with allyltrimethyl silane in CH_3CN at room temperature to obtain **98**. After 12 h at room temperature, the reaction afforded the expected *trans*-2,6-disubstituted-3,4-dihydropyran **98** in 38% yield (Scheme 55). The reaction was incomplete even after 48 h of stirring at

room temperature. We had employed 10 mol% iodine for completion of the reaction. Even though, increasing the iodine concentrations did not help in improving the yield and reduction of reaction time expectedly. However, no reaction was observed in absence of iodine even after a long time (48 h). To optimize the reaction conditions, screening was performed on several parameters, such as solvents, temperature, and catalyst concentration. Initially, the reaction was performed in different solvent systems (CH_2Cl_2, TBME, THF) at room temperature with 5 mol% of iodine; THF was found to be superior to other solvents. Next, the reaction was examined carefully under reflux conditions which led to an intractable mixture of products. The experiment was also conducted carefully under the influence of different concentrations of the catalyst at room temperature with THF as solvent. The use of 10 mol% molecular iodine (based on δ-hydroxy α,β-unsaturated aldehyde) gave the best result with a yield of 96% after 45 min of reaction.[40] The ^1H and ^{13}C NMR of the product **98** revealed a single diastereomer which was supported by HPLC analysis data (de >99%). ^1H NMR spectrum showed extra olefin protons at δ 5.86 (m, 1H), δ 5.16-5.0 (m, 2H) and disappearance of aldehyde peak resonated at δ 9.49 ppm in compound **99**.

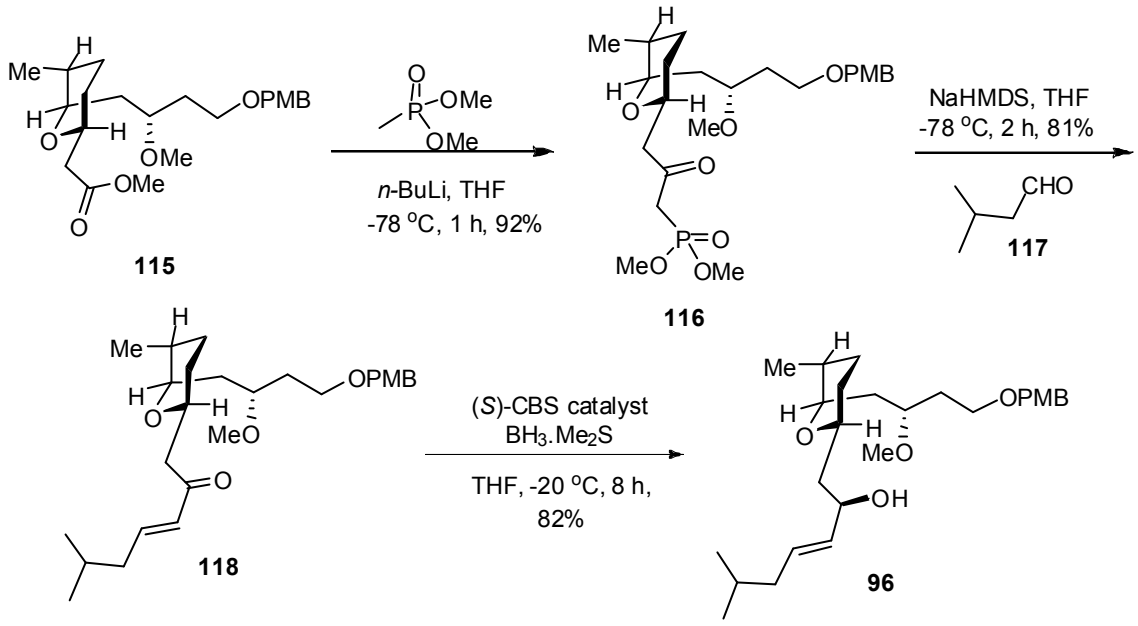
Then, selective oxidation of the terminal olefin in presence internal olefin of **98** was carried out under different conditions. First, we tried two step process- dihydroxylation and then chopping of diol to aldehyde by $NaIO_4$. When OsO_4, NMO was employed for dihydroxylation,[74] both internal and terminal olefin took part in raection and thus we got mixture of products with moderate yield of the desired product. Next, dihydroxylation reaction under Sharpless asymmetric dihydroxylation (SAD)[75] condition using $K_3Fe(CN)_6$, OsO_4 and $(DHQD)_2$- PHAL was performed. Although reaction was selective for terminal olefin, it was slow and never went to completion. Finally, recently developed one step dihydroxylation-oxidation protocol[76] was applied where OsO_4, 2,6 lutidine, $NaIO_4$ were used as reagents and 1,4 dioxane-H_2O (3:1) mixture used as solvent system. Fortunately, reaction went to completion in 1 h and the desired aldehyde **112** was produced in 92% yield. The aldehyde thus obtained was unstable in nature, passed through a bed of silia gel and immidiately used for the next step without further characterization. Subsequent oxidation of aldehyde **112** under Pinnick conditions[77] using $NaClO_2$,



Scheme 56

$NaH_2PO_4.H_2O$, 2-methyl-2-butene (Scheme 56) afforded a carboxylic acid **113** in 90% yield. A very broad absorption trough at 3029 cm^{-1} and another at 1732 cm^{-1} in IR spectra indicating the presence of acid group. It's ^1H NMR revealed absence of peaks for terminal olefenic protons whereas other spectral data were in complete agreement with the product. The carboxylic acid **113** which on treatment with diazomethane in ether at 0 ^oC gave the ester **114** in 94% yield. The ^1H NMR spectrum of **114** showed a singlet at δ 3.32 ppm for three protons corresponding to the methyl ester and ^{13}C NMR spectrum also showed appearance of one peaks at δ 51.6 ppm. . IR spectrum also revealed a peak at 1737 cm^{-1}, a characteristic peak of ester moiety. The saturation of olefinic functionality using Pd-$CaCO_3/H_2$ smoothly delivered the corresponding saturated ester **115** in 93% yield. The compound **115** was characterized by ESI-HRMS which showed $(M + Na)^+$ peak at *m/z* 417.2240 and ^{13}C NMR spectrum shows absence of olefinic carbons at δ 132.1 and 127.0 ppm. The absence of characteristic olefenic protons in ^1H NMR confirmed the reduction of double bond in **114**.

The saturated ester **115** was allowed for a nucleophilic addition of the lithiated derivative of dimethyl methyl phosphonate furnished the *β*-keto phosphonate **116** in 92% yield. The *β*-keto phosphonate thus obtained was unstable to coloumn chromatography in nature, passed through a bed of silia gel and immidiately used for the next step without



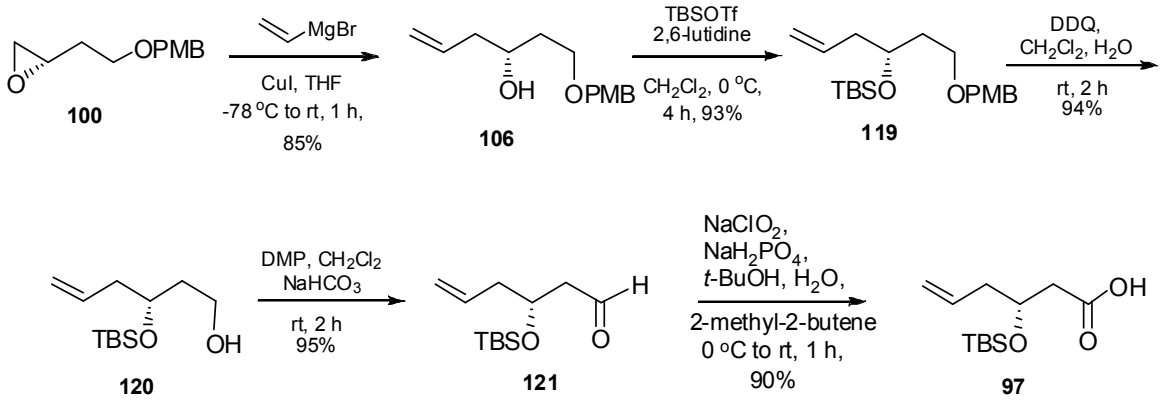
Scheme 57

further characterization. The *β*-keto phosphonate **116** on treatment with 3-methylbutanal **117** in the presence of NaHMDS gave *α,β*-unsaturated ketone **118** in 81% yield. The ^{1}H NMR spectrum of compound **118** showed characteristic olefinic resonances for *α,β*-unsaturated ketone at δ 6.81 as double doublet and δ 6.11 as doublets corresponding to two adjacent olefinic protons with a coupling constants $J_{CH=CH}$ = 15.6 Hz providing the *trans* geometry of the double bond and the ^{13}C NMR spectrum showed a peak at 198.4 ppm which corresponding to keto carbon. IR absorption showed characteristic band at 1717 cm^{-1} for ketone functionality. The product was further confirmed by ESI-HRMS showed (M + Na)$^{+}$ peak at *m/z* 469.2940. The crucial Corey-Bakshi-Shibata[78] (CBS) reduction of *α,β*-unsaturated ketone **118** was done by appling the reagent [(*S*)-2-methyloxazaborolidine at –20 ^{o}C in the presence of borane-dimethylsulfide complex installed the C17 stereogenic center present in **96** with a 12:1 diastereomeric ratio (by HPLC) in 82% yield as a separable mixture (Scheme 57). The product **96** was confirmed by ^{1}H NMR, ^{13}CNMR, IR, HRMS spectra. The ^{1}H NMR spectrum shows absence of *α,β*-unsaturated protons of ketone and appearance of olefinic protons as multiplate at δ 5.62 ppm as multiplate and double doublet at δ 5.46 ppm with *J* = 15.3 Hz and also disappearance of peak at 6.81 ppm and 6.11 ppm. The ^{13}C NMR showed the absence of ketone carbon which was situated at 198.4 ppm. IR spectrum of compound **96** disclosed

the absorption band at 3454 cm^{-1} corresponding to hydroxyl functional group and HRMS showed $(M + Na)^+$ peak at *m/z* 471.3069.

1.5.3. Synthesis of the acid fragment (97):

Having the required alcohol fragment **96** in hand, our next target was to synthesize acid fragment **97**. The synthesis commenced with the copper(I)-catalyzed addition of the Grignard reagent vinyl magnesium bromide to the chiral epoxide **100** to afford the homoallyl alcohol **106** in 85% yield. The characterization of the chiral epoxide **100** and homoallyl alcohol **106** was described in Scheme 58. The resultant secondary hydroxyl group which was obtained by opening of epoxide **100**, was protected as its TBS-ether using TBSOTf and 2,6-lutidine in anhydrous CH_2Cl_2 to obtain **119** in 93% yield. The ^{13}C NMR spectra of compounds **119** was revealed the presence of silyl methyl protons at δ –4.4 and –4.8 ppm and ESI-HRMS showed $(M + Na)^+$ peak at *m/z* 373.2181. PMB deprotection was achieved by the treatment of DDQ[79] in CH_2Cl_2/H_2O (9:1) and the



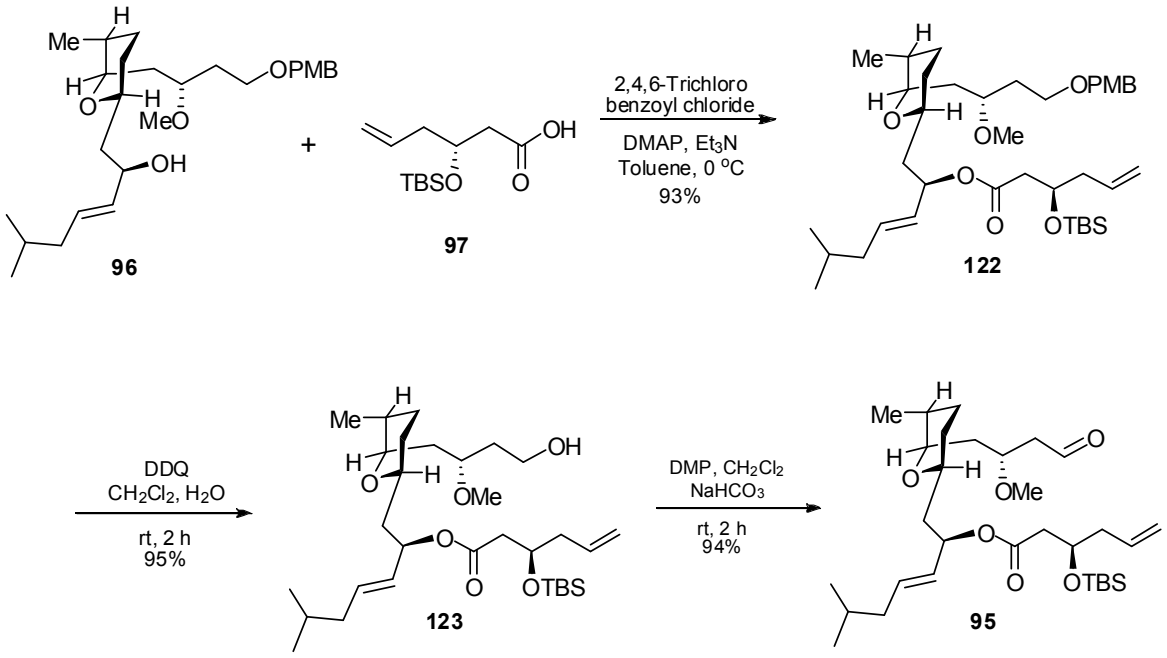
Scheme 58

desired primary alcohol **120** was produced with 94% yield. Its ^1H NMR revealed the absence of a set of two doublets at δ 7.19, 6.81 ppm, and a quartet at δ 4.36 ppm for two benzylic protons and a singlet at δ 3.78 ppm for three methoxy protons of PMB group. A peak at *m/z* 231.1775 $[M + Na]^+$ in ESI-HRMS spectrum was an additional proof in this favor. The primary alcohol **120** when subjected to Dess-Martin-Periodinane[80] oxidation, it afforded smoothly the aldhyde **121** which was immediately used for further oxidation under Pinnick conditions[77] using $NaClO_2$, NaH_2PO_4, *t*-BuOH, H_2O and 2-methyl-2-butene gave acid **97** in 90% yield (scheme 58). The acid functionality showed a peak at 1713

cm^{-1} in IR whereas the corresponding peak for carbonyl carbon appeared at δ 177.6 ppm in ^{13}C NMR spectrum. Along with above data, a peak at *m/z* 267.1385 $[M + Na]^+$ in ESI-HRMS spectrum was given additional support in this favor.

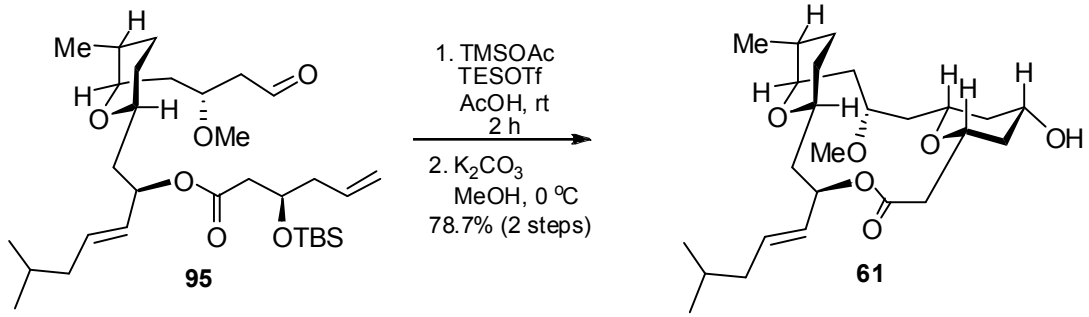
1.5.4. Synthesis of the macrolide (61):

With alcohol **96** and acid fragment **97** in hand, our next task was to couple both of the fragments and verify the Prins-type macrocyclization on an 18-membered macrolactone. The coupling of C1-C6 acid fragment **96** and C7-C23 alcohol fragment **97** was performed in different conditions to optimize the yield. Initially, the reaction was performed in employing dicyclohexyl carbodiimide (DCC) and a catalytic amount of DMAP in CH_2Cl_2 to afford ester **122** in 42% yield.[81] To improve the yield, again the coupling was examined with EDCI and DMAP in CH_2Cl_2 furnished the ester in 57% yield.[82] However, a better result was achieved under Yamaguchi conditions[83] by employing 2,4,6-Trichloro benzoyl chloride, Et_3N and DMAP in toluene to obtain the ester **122** in 93% yield, which contains all 23 carbons of the target molecule (Scheme 59). The ^1H NMR and ^{13}C NMR spectra were in full accord with the product where TBS, PMB, olefins and other functionalities resonated at their respective positions. IR absorption showed the absence of characteristic band for hydroxyl functionality whereas a peak at *m/z* 692.4883 $[M + NH_4]^+$ in ESI-HRMS spectrum was confirmed the formation of ester. Deprotection of the PMB ether in **122** upon treatment with DDQ[79] afforded the desired primary alcohol **123** in 95% yield. ^1H NMR revealed the absence of a set of two doublets at δ 7.21, 6.81 ppm, a quartet at δ 4.39 ppm for two benzylic protons and a singlet at δ 3.36 ppm for three methoxy protons of PMB group and also ^{13}C NMR spectra revealed the absence of characteristic peaks for PMB group. A peak at 3466 cm^{-1} appeared in IR specteum further confirmed the introduction of a hydroxyl group. The resulting primary alcohol **123** was oxidized to aldehyde **95** with Dess-Martin periodinane[80] reagent which was unstable in nature and quickly purified by a short flash column chromatography and directly used for the next step without further characterization.



Scheme 59

The next important task was to perform the Prins macrocyclization. As expected, the construction of 18-membered macrocycle **61** by intramolecular Prins-cyclization[84] of aldehyde **95** was a significant challenge. Initially, macrocyclization was taken place by using 10 equiv of TESOTf and 15 equiv of TMSOAc in 0.01M solution of AcOH and subsequent hydrolysis afforded the macrolide **61** with very low yield. After extensive investigations, we eventually found that treatment of the aldehyde **95** with >30 equiv of TMSOAc and TESOTf in 0.01M solution of AcOH resulted in the Prins adduct and hydrolysis with K_2CO_3 in MeOH furnished macrolide **61** in 72% yield over three steps. This macrocyclization with high diastereoselectivity (dr > 97:3) and good yield provides an additional example of the powerful and versatile nature of the Prins-macrocyclization strategy. The final target was characterized by ^{1}H NMR, ^{13}C NMR, IR, ESI-HRMS spectra which were in good agreement with the data mentioned by Kozmin and co-workers and also the analytical data *i.e.* optical rotation value was in complete agreement with the reported values.[85]



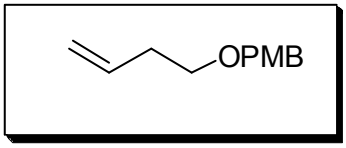
Scheme 60

In conclusion, our investigations into the allylation of a *δ*-hydroxy *α,β*-unsaturated aldehyde with an allyltrimethyl silane in the presence of a catalytic amount of molecular iodine as a protocol combined with the intramolecular Prins-macrocyclization has led to a concise formal total synthesis of leucascandrolide A, which proceeded in only a 20-step longest linear sequence with a 11.5% overall yield starting from a known epoxide.

Experimental Section

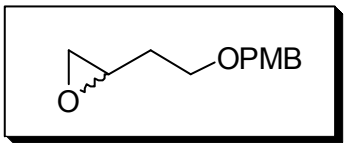
1.6. EXPERIMENTAL SECTION

1.6.1. 1-((but-3-enyloxy)methyl)-4-methoxybenzene (102)



To a suspension of NaH (10.0 g, 417 mmol, 60% w/v dispersion in mineral oil) in anhydrous THF (400 mL) was added dropwise a solution of 3-buten-1-ol **101** (15.0 g, 208 mmol) at 0 ^{o}C. To this reaction mixture TBAI (0.05 g) and PMB bromide (30 mL, 250 mmol) were added subsequently and stirring was continued for 2 h at the same temperature and overnight at room temperature. The reaction mixture was quenched by small crushed ice flakes until a clear solution (biphasic) has formed. The reaction mixture was extracted with EtOAc (2 x 200 mL). The organic extracts were washed with water (1 x 100 mL), brine (1 x 100 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvents followed by column chromatography afforded the pure product **102** (32.06 g, 95% yield) as a colorless liquid.

1.7.2. 2-(2-(4-methoxybenzyloxy)ethyl)oxirane (103)



To an olefin **102** (31.75 g, 196 mmol) in dry CH_2Cl_2 (300 mL) at 0 ^{o}C was added slowly *m*-chloroperbenzoic acid (50.71 g, 294 mmol) as a solid and the reaction mixture was stirred for 1 h. The solution was washed thoroughly with cold aqueous NaOH solution (19.60 g, 490 mmol) and the organic layer was separated. Evaporation of the solvent after drying over anhydrous Na_2SO_4 yielded the crude epoxide, which was purified by column chromatography to afford **103** as a viscous liquid (32.09 g, 92% yield).

IR (Neat) : ν_{max} 3033, 2860, 1603, 1495, 1258, 1100, 1013, 911 cm^{-1};

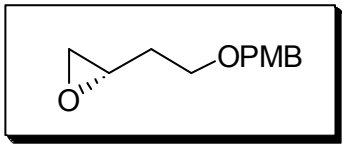
^{1}H NMR ($CDCl_3$, 300MHz) : δ 7.20 (d, J = 8.3 Hz, 2H), 6.82 (d, J = 8.3 Hz, 2H), 4.42 (s, 2H), 3.78 (s, 3H), 3.54 (m, 2H), 2.98

(m, 1H), 2.71 (q, J = 5.2 Hz, 1H), 2.45 (q, J = 5.2 Hz, 1H), 1.91-1.70 (m, 1H), 1.77-1.65 (m, 1H) ppm;

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 159.2, 130.3, 129.1, 113.7, 72.7, 66.6, 55.0, 49.8, 46.8, 33.0 ppm;

ESI-MS : m/z 208 $[M]^+$.

1.6.3. (S)-2-(2-(4-methoxybenzyloxy)ethyl)oxirane (100)



A mixture of (*S,S*)-(-)-*N*-*N*'-Bis(3,5-di*tert*-butyl salicylidene)-1,2-cyclohexanediamino-cobalt-II **105** (0.54 g, 0.89 mmol) toluene (4 mL) and acetic acid (0.1 mL, 1.78 mmol) was stirred while open to the air for 1 h at room temperature. The solvent was removed under reduced pressure and the brown residue was dried over high vacuum. The oxirane **103** (31.68 g, 178 mmol) was added in one portion, and the stirred mixture was cooled in an ice water bath. Water (1.8 mL, 98 mmol) was slowly added and the temperature of the reaction mixture was maintained in such a way that it never rises more than 20 ^{o}C. After 1 h, addition was complete. The ice bath was removed and the reaction mixture was stirred for 36 h. The crude reaction mixture was purified by column chromatography to afford the chiral epoxide **100** (14.16, 45% yield) as colorless oil.

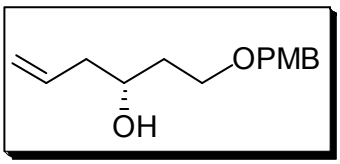
^{1}H NMR and ^{13}C NMR are similar to that of compound **103**.

$[\alpha]_D^{25}$: –10.8 (*c* 2.0, $CHCl_3$).

IR (KBr) : ν_{max} 3032, 2860, 1603, 1495, 1258, 1101, 912 cm^{-1}.

EIMS : *m/*z Calcd for $C_{13}H_{20}O_5Na$ $[M+Na]^+$: 231.0628, found 231.0631.

1.6.4. (*R*)-1-(4-Methoxybenzyloxy)hex-5-en-3-ol (106):



A freshly prepared vinyl magnesium bromide (76.9 mL, 76.92mmol) (1 M solution in THF) was added drop wise to a solution of CuI (0.73 g, 3.85 mmol) in THF (50 mL) at –20 °C. The mixture was stirred from 30 minutes and chiral epoxide **100** (8.0 g, 38.46

mmol) was added in THF (50 mL) dropwise to the above mixture. After 2 h, the reaction (monitored by TLC) was quenched with saturated solution of NH_4Cl (75 mL) and diluted with diethyl ether (50 mL). The two layers were separated and the aqueous layer extracted with diethyl ether (3 x 75 mL). The combined organic layer was washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get the crude mass. Purification by flash column chromatography over silica gel (ethyl acetate: hexane = 1:9) afforded the desired homoallyl alcohol **106** (7.7 g, 85%) as a colorless oil.

$[\alpha]_D^{25}$: +4.2 (*c* 1.1, $CHCl_3$);

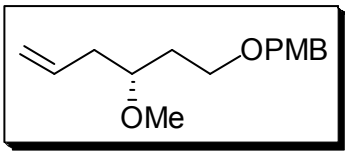
IR (neat, KBr) : ν_{max} 3434, 3074, 2933, 2862, 1613, 1513, 1464, 1302, 1249, 1174 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) : δ 7.25 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.83 (m, 1H), 5.14-5.06 (m, 2H), 4.45 (s, 2H), 3.85 (m, 1H), 3.80 (s, 3H), 3.76-3.57 (m, 2H), 2.94 (br s, 1H), 2.23 (t, *J* = 6.8 Hz, 2H), 1.81-1.71 (m, 2H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) : δ 159.2, 134.8, 130.0, 129.3, 117.4, 113.8, 72.9, 70.4, 68.6, 55.2, 41.9, 35.8 ppm;

ESI-HRMS : *m/z* Calcd for $C_{13}H_{20}O_5Na$ $[M+Na]^+$: 259.1305, found 259.1306.

1.6.5. (*R*)-1-Methoxy-4-((3-methoxyhex-5-enyloxy)methyl)benzene (107):



To a suspension of NaH (1.38 g, 34.74 mmol, 60% in mineral oil) in dry THF (50 mL), homoallyl alcohol **106** (4.1 g, 17.37 mmol) dissolved in dry THF (100 ml), was slowly added at 0 ^oC under N_2 atmosphere. The suspension was stirred for 1 h at room temperature. Then, methyl iodide (2.35 mL, 34.74 mmol) was added slowly at 0 ^oC to the above reaction mixture and then it was allowed to stir at room temperature for 4 h. After completion of the reaction (monitored by TLC), it was quenched with saturated solution of NH_4Cl (50 mL) at 0 ^oC and diluted with ethyl acetate (100 mL). The two layers were separated and the aqueous layer was

extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine (2 x 75 mL), dried over anhydrous Na_2SO_4 and solvent was removed under reduced pressure to obtain the crude mass which on purification over silica gel column chromatography (ethyl acetate: hexane = 1:19) afforded methyl ether **107** (4.08 g, 94%) as a light yellow liquid.

$[\alpha]_D^{25}$: −15.5 (*c* 0.95, $CHCl_3$);

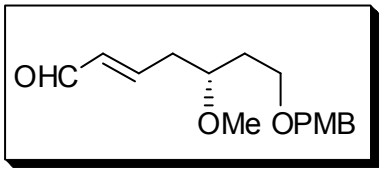
IR (neat, KBr) : ν_{max} 3074, 2932, 2854, 2837, 1613, 1513, 1464, 1248, 1094, 1036, 915, 821 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) : δ 7.21 (d, *J* = 8.3 Hz, 2H), 6.83 (d, *J* = 9.1 Hz, 2H), 5.77 (m, 1H), 5.09-5.00 (m, 2H), 4.40 (s, 2H), 3.78 (s, 3H), 3.56-3.44 (m, 2H), 3.38 (m, 1H), 3.32 (s, 3H), 2.25 (t, *J* = 6.3 Hz, 2H), 1.8-1.63 (m, 2H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) : δ 159.0, 134.4, 130.5, 129.1, 116.9, 113.6, 77.3, 72.5, 66.4, 56.6, 55.1, 37.8, 33.8 ppm;

ESI-HRMS : *m/z* calcd. for $C_{15}H_{22}NaO_3$ $[M + Na]^+$: 273.1461, found 273.1455.

1.6.6. (*R*,*E*)-5-Methoxy-7-(4-methoxybenzyloxy)hept-2-enal (108):



To a solution of methyl ether compound **107** (4.0 g, 16.0 mmol) in CH_2Cl_2 (10 mL) was added Hoveyda-Grubbs catalyst (0.98 mg, 1.6 mmol) followed by acrolein (9.0 g, 160.0 mmol) at room temperature under nitrogen atmosphere and the resulting mixture was stirred at the same temperature for 3 h. After completion of the reaction (monitored by TLC), it was concentrated to dryness under reduced pressure and the crude oil was directly purified by short flash column chromatography over silica gel (ethyl acetate: hexane = 1:7) furnished the desired *α,β* unsaturated aldehyde **108** (4.1 g, 92%) as a colorless liquid.

$[\alpha]_D^{25}$: −10.4 (*c* 0.55, $CHCl_3$);

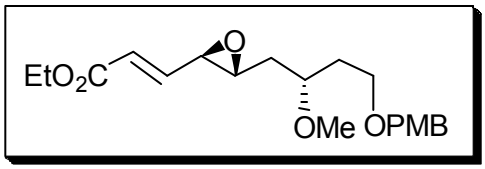
IR (neat, KBr) : ν_{max} 2935, 2861, 2837, 2740, 1690, 1513, 1248, 1093, 1034, 821 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) : δ 9.48 (d, *J* = 7.9 Hz, 1H), 7.20 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 6.78 (m, 1H), 6.12 (dd, *J* = 7.9, 15.9 Hz, 1H), 4.40 (s, 2H), 3.79 (s, 3H), 3.57-3.42 (m, 3H), 3.33 (s, 3H), 2.63-2.40 (m, 2H), 1.85-1.63 (m, 2H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) : δ 193.7, 159.1, 154.4, 134.8, 129.2, 113.7, 76.6, 72.6, 66.0, 56.9, 55.1, 36.7, 34.0 ppm;

ESI-HRMS : *m/z* calcd. for $C_{16}H_{22}NaO_4$ $[M+Na]^+$: 301.1410, found 301.1407.

1.6.7. (*E*)-Ethy 3-((2*R*,3*R*)-3-((*S*)-2-methoxy-4-(4-methoxybenzyloxy)butyl)oxiran-2-yl)acr- ylate (109):



To a stirred solution of *α,β* unsaturated aldehyde **108** (3.9 g, 14.03 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added TMS-protected diphenyl prolinol catalyst (0.46 g, 1.40 mmol) followed by H_2O_2 (35 % aq., 1.23 mL, 18.23 mmol). The reaction mixture was stirred vigorously at room temperature until total consumption of the starting material (monitored by TLC). Then $Ph_3P{=}CHCO_2Et$ (5.8 g, 16.83 mmol) was added in one portion at 0 °C and stirred for another 1 h at room temperature. After removal of the solvents under reduced pressure, the residue was purified by column chromatography over silica gel (ethyl acetate: hexane = 1:8) to give the desired epoxy compound **109** (3.69 g, 80%) as a colorless oil.

$[\alpha]_D^{25}$: +5.4 (*c* 1.25, CHCl3);

IR (neat, KBr) : ν_{max} 2979, 2935, 2861, 1720, 1657, 1613, 1513, 1303, 1249, 1182, 1092, 1035, 853, 821 cm^{-1};

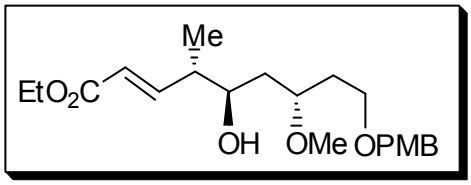
^1H NMR (300 MHz, $CDCl_3$) : δ 7.19 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 6.64 (dd, *J* = 6.8, 15.3 Hz, 1H), 6.07 (d, *J* = 15.9 Hz, 1H), 4.39 (s, 2H), 4.18 (q, *J* = 6.7 Hz, 2H),

3.79 (s, 3H), 3.55-3.41 (m, 3H), 3.34 (s, 3H), 3.17 (d, J = 7.6 Hz, 1H), 2.97 (dd, J = 6.8, 15.4 Hz, 1H), 1.86-1.64 (m, 4H), 1.29 (t, J = 7.6 Hz, 3H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) : δ 165.6, 159.2, 144.5, 130.4, 129.3, 123.8, 113.8, 75.9, 72.7, 66.1, 60.6, 58.6, 57.4, 56.7, 55.2, 37.0, 34.4, 14.2 ppm;

ESI-HRMS : *m/z* calcd. $C_{20}H_{28}NaO_6$ for $[M + Na]^+$: 387.1778, found 387.1791.

1.6.8. (4*S*,5*R*,7*S*,*E*)-Ethyl 5-hydroxy-7-methoxy-9-(4-methoxybenzyloxy)-4-methylnon-2-enoate(110):



The epoxy compound **109** (3.5 g, 9.3 mmol) was taken in a 250 mL RB and to it, CH_2Cl_2 (70 mL) was added under nitrogen atmosphere. The reaction mixture was cooled to −40 °C. Trimethyl aluminium (46.6 mL, 93.1 mmol, 2M in toluene) was slowly added under nitrogen atmosphere at the same temperature. After 10 min, H_2O (1.0 mL, 55.9 mmol) was added very carefully and slowly so that the internal temperature did not change. After effervescence ceased, it was allowed to stir for further 3 h at −40 ^oC and TLC showed the complete consumption of the starting material. It was quenched very slowly with saturated NH_4Cl (50 mL) and diluted with CH_2Cl_2 (100 mL). HCl (1.0 N, 50 mL) was added and vigorously stirred until a clear separation of the two layers took place. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layer was washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4, evaporated to dryness and then purified by silica gel column chromatography (ethyl acetate: hexane = 1:5) to get the desired product **110** (3.35 g, 92%) as a colorless oil.

$[\alpha]_D^{25}$: −4.5 (*c* 1.45, CHCl3);

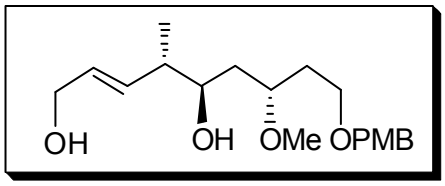
IR (neat, KBr) : ν_{max} 3472, 2936, 2874, 2836, 1713, 1651, 1613, 1513, 1301, 1250, 1180, 1092, 1036, 847, 821 cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$) : δ 7.18 (d, *J* = 8.3 Hz, 2H), 6.93 (dd, *J* = 7.5, 15.9 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 2H), 5.78 (d, *J* = 15.9 Hz, 1H), 4.38 (s, 2H), 4.17 (q, *J* = 6.8 Hz, 2H), 3.85 (m, 1H), 3.79 (s, 3H), 3.61 (m, 1H), 3.51-3.42 (m, 2H), 3.33 (s, 3H), 2.95 (br. s, 1H), 2.31 (m, 1H), 1.92 (m, 1H), 1.77-1.63 (m, 2H), 1.45 (m, 1H), 1.29 (t, *J* = 6.8 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) : δ 166.5, 159.1, 150.6, 130.3, 129.3, 121.8, 113.7, 76.8, 72.7, 71.4, 66.3, 60.2, 57.1, 55.2, 42.8, 36.6, 33.1, 15.5, 14.2 ppm;

ESI-HRMS : *m/z* calcd. for $C_{21}H_{32}NaO_6$ $[M + Na]^+$: 403.2096, found 403.2083.

1.6.9. (4*S*,5*R*,7*S*,*E*)-7-Methoxy-9-(4-methoxybenzyloxy)-4-methylnon-2-ene-1,5-diol (111):



To astirred solution of *α,β*-unsaturated ester **110** (3.2 g, 8.2 mmol) was dissolved in CH_2Cl_2 (60 mL) and cooled to −78 °C under nitrogen atmosphere. DIBAL-*H* (14.5 mL, 20.4 mmol) was slowly added to it over a period of 5 min. After 30 min of stirring at the same temperature, TLC was checked which showed complete consumption of starting material. It was quenched by slow addition of saturated solution of sodium potassium tartrate (50 mL), diluted with CH2Cl2 (40 mL) and allowed to stir at room temperature for another 2 h to get a clear two separated layers. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layer was washed with brine (2 x 75 mL), dried over anhydrous Na_2SO_4, evaporated to dryness under vacuum which on silica gel column chromatography (ethyl acetate: hexane = 2:3) produced the desired *α,β*-unsaturated alcohol **111** (2.43 g, 88%).

$[\alpha]_D^{25}$: +3.9 (*c* 0.73, $CHCl_3$);

IR (neat, KBr) : ν_{max} 3408, 2933, 2871, 1612, 1513, 1302, 1248,

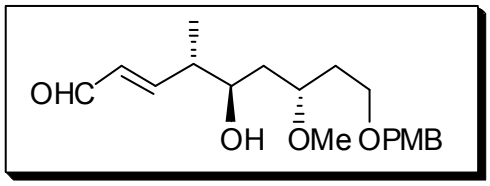
1087, 1035, 847, 821 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) : δ 7.19 (d, *J* = 8.9 Hz, 2H), 6.82 (d, *J* = 8.3 Hz, 2H), 5.60 (d, *J* = 5.3 Hz, 2H), 4.39 (s, 2H), 4.02 (d, *J* = 3.8 Hz, 2H), 3.78 (s, 3H), 3.67-3.55 (m, 2H), 3.52-3.41(m, 2H), 3.34 (s, 3H), 2.13 (m, 1H), 1.94-1.63 (m, 2H), 1.61-1.46 (m, 2H), 0.98 (d, *J* = 6.8 Hz, 3H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) : δ 159.1, 134.3, 130.0, 129.3, 113.7, 76.6, 72.3, 71.9, 66.4, 63.4, 57.1, 55.2, 42.7, 37.1, 33.4, 16.3 ppm;

ESI-HRMS : *m/z* calcd. for $C_{19}H_{30}NaO_5$ $[M + Na]^+$: 361.1985, found 361.1982.

1.6.10. (*4S*,5*R*,7*S*,*E*)-5-Hydroxy-7-methoxy-9-(4-methoxybenzyloxy)-4-methylnon-2-enal (99):



To a stirred solution of diol **111** (2.35 g, 6.95 mmol) in CH_2Cl_2 (40 mL) at 0 °C, iodobenzenediacetate (2.46 g, 7.65 mmol) followed by TEMPO (0.217 g, 1.39 mmol) was added and allowed to stir at ambient temperature for 3 h. After conversion of the primary alcohol completely to aldehyde (monitored by TLC), the reaction mixture was quenched with saturated solution of $Na_2S_2O_3$ (20 mL) and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporation of solvent led to crude aldehyde which on purification by short flash chromatography over silica gel (ethyl acetate: hexane = 3:7) afforded aldehyde **99** (2.1 g, 90%) as a thick viscous liquid and used immediately for the next reaction.

$[\alpha]_D^{25}$: +2.1 (*c* 1.0, $CHCl_3$);

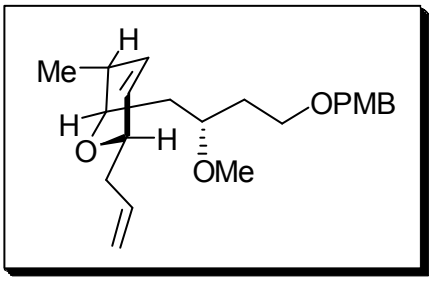
IR (neat, KBr) : ν_{max} 3459, 2936, 2874, 2837, 1689, 1613, 1513, 1302, 1248, 1089, 1034, 821 cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$) : δ 9.49 (d, *J* = 8.3 Hz, 1H), 7.20 (d, *J* = 9.1 Hz, 2H), 6.94 (m, 1H), 6.84 (d, *J* = 9.1 Hz, 2H), 6.08 (m, 1H), 4.40 (s, 2H), 3.84 (m, 1H), 3.80 (s, 3H), 3.64 (m, 1H), 3.52-3.43 (m, 2H), 3.34 (s, 3H), 2.43 (m, 1H), 1.95 (m, 1H), 1.80-1.67 (m, 2H), 1.55-1.44 (m, 2H), 1.10 (d, *J* = 6.8 Hz, 2H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) : δ 194.1, 160.4, 159.2, 132.9, 130.2, 129.3, 113.7, 80.1, 72.7, 71.6, 66.2, 57.1, 55.2, 43.3, 36.7, 32.9, 15.6 ppm;

ESI-HRMS : *m/z* calcd. for $C_{19}H_{28}NaO_5$ $[M + Na]^+$: 359.1829, found 359.1830.

1.6.11. (2*R*,3*S*,6*R*)-6-Allyl-2-((*S*)-2-methoxy-4-(4-methoxybenzyloxy)butyl)-3-methyl-3,6-dihydro-2*H*-pyran (98):



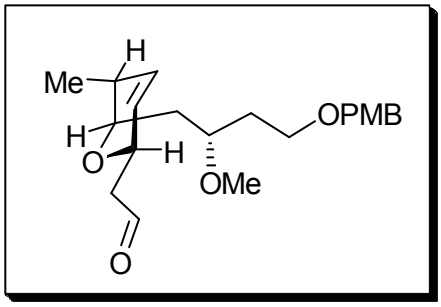
To a stirred solution of *δ*-hydroxy *α,β*-unsaturated aldehyde **99** (2.0 g, 5.95 mmol), and allyltrimethyl silane (1.45 mL, 8.93 mmol) in THF (30 mL) was added iodine (0.15 g, 0.59 mmol) at 0 ^oC and allowed to come to room temperature. After completion of the reaction (as indicated by TLC), it was quenched with saturated solution of $Na_2S_2O_3$ (10 mL) and diluted with *tert*-butyl methyl ether (20 mL). The organic layer was separated and the aqueous layer extracted with *tert*-butyl methyl ether (TBME) (2 x 40 mL). The combined organic layer was washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give pale yellow oil. This was finally purified by column chromatography over silica gel (ethyl acetate: hexane = 1:19) to obtain the cyclized product **98** (2.1 g, 96%).

$[\alpha]_D^{25}$: +14.2 (*c* 0.8 , $CHCl_3$);

IR (neat, KBr) : ν_{max} 3482, 2925, 2857, 1729, 1612, 1513, 1459, 1367, 1300, 1247, 1178, 1091, 1037, 914, 820, 723

	cm^{-1};
^1H NMR (300 MHz, $CDCl_3$)	: δ 7.27 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.86 (m, 1H), 5.70-5.59 (m, 2H), 5.16-5.00 (m, 2H), 4.45-4.38 (m, 2H), 4.16 (m, 1H), 3.81-3.74 (m, 3H), 3.62 (m, 1H), 3.57-3.46 (m, 3H), 3.36-3.26 (m, 3H), 2.41 (m, 1H), 2.26 (m, 1H), 2.00-1.66 (m, 4H), 1.53 (m, 1H), 0.97 (d, *J* = 7.2 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$)	: δ 159.0, 135.2, 131, 130.6, 129.2, 127.9, 116.7, 113.7, 74.8, 72.6, 71.5, 71.0, 66.5, 57.0, 55.2, 38.8, 38.8, 34.2, 34.0, 18.0 ppm;
ESI-HRMS	: *m/z* calcd. for $C_{22}H_{32}NaO_4$ $[M + Na]^+$: 383.2198, found 383.2195.

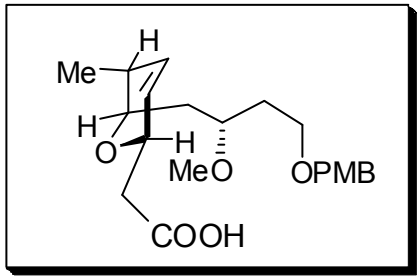
1.6.12. 2-((2*R*,5*S*,6*R*)-6-((*S*)-2-methoxy-4-(4-methoxybenzyloxy)butyl)-5-methyl-5,6-dihydro -2*H*-pyran-2-yl)acetaldehyde (112):



To a stirred solution of the compound **98** (1.8 g, 5.0 mmol) in 1,4-dioxane (25 mL) was added 2,6-lutidine (2.33 mL, 20.0 mmol) at room temperature. $NaIO_4$ (4.28 g, 20.0 mmol) was dissolved in distilled water (10 mL) and then added to the above reaction mixture. Finally, OsO_4 (0.5 mL, 0.5 mmol, 1 M solution in toluene) was added and stirring was continued for 3 h under dark at room temperature. After completion of the reaction (as indicated by TLC), the reaction mixture was quenched with saturated aq. $NaHSO_3$ (30 mL) solution. Organic solvent was removed under reduced pressure and the residual aqueous layer was extracted with *t*-butyl methyl ether (3 x 50 mL). The combined organic layer was washed with 1 N HCl (3 x 50 mL) to remove excess 2,6-lutidine. The organic layer was washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude mass which was passed through a small pad of

silica gel (ethyl acetate: hexane = 1:3) to afford aldehyde **112** as a colorless liquid which was immediately used for the next step.

1.6.13. 2-((2*R*,5*S*,6*R*)-6-((*S*)-2-Methoxy-4-(4-methoxybenzyloxy)butyl)-5-methyl-5,6-dihydro -2*H*-pyran-2-yl)acetic acid (129):



To a solution of aldehyde **112** (1.78 g, 4.92 mmol) in *tert*-butyl alcohol (25 mL), 2-methyl-2-butene (5.8 mL, 5.8 mmol, 1 M solution in THF) was added at room temperature. NaH_2PO_4 (1.8 g, 11.6 mmol) and sodium chlorite (0.59 g, 7.38 mmol) were dissolved in water (10 mL) to make a clear solution which subsequently added to the reaction mixture at 0 ^oC. It was then allowed to stir for further 3 h at room temperature. The reaction mixture was diluted with water (15 mL). The organic solvent was removed under reduced pressure and the aqueous layer extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate: hexane = 2:5) to afford the acid **113** (1.53 g, 81% over two steps) as a colorless oil.

$[\alpha]_D^{25}$: +28.9 (*c* 1.16, $CHCl_3$);

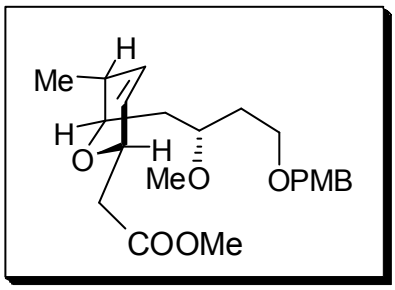
IR (neat, KBr) : ν_{max} 3029, 2931, 2876, 1732, 1713, 1612, 1513, 1301, 1248, 1094, 1035, 847, 821 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) : δ 7.24 (d, *J* = 8.3 Hz, 2H), 6.84 (d, *J* = 8.3 Hz, 2H), 5.66 (s, 2H), 4.60 (m, 1H), 4.42 (s, 2H), 3.79 (s, 3H), 3.36-3.41 (m, 4H), 3.31 (s, 3H), 2.64 (dd, *J* = 9.1, 15.1 Hz, 1H), 2.45 (dd, *J* = 4.5, 15.1 Hz, 1H), 1.98 (t, *J* = 6.8 Hz, 1H), 1.81 (q, *J* = 6.0 Hz, 1H), 1.72 (m, 1H), 1.52 (dt, *J* = 1.5, 9.0 Hz, 1H), 0.96 (d, *J* = 6.8 Hz, 1H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) : δ 174.8, 159.1, 132.1, 130.3, 129.3, 126.6, 113.7, 75.1, 72.7, 71.5, 68.7, 66.6, 56.6, 55.2, 39.0, 38.0, 34.1, 34.0, 17.7 ppm;

ESI-HRMS : *m/z* calcd. for $C_{21}H_{30}NaO_6$ $[M + Na]^+$: 401.1935, found 401.1949.

1.6.14. Methyl 2-((2*R*,5*S*,6*R*)-6-((*S*)-2-methoxy-4-(4-methoxybenzyloxy)butyl)-5-methyl-5,6-dihydro-2*H*-pyran-2-yl)acetate (114):



To a stirred solution of acid **113** (1.3 g, 3.44 mmol) in ether at 0 ^oC, was added freshly prepared diazomethane solution in ether (25 mL). It was stirred for 10 min at the same temperature and then quenched with saturated solution of $Na_2S_2O_3$ (10 mL) at 0 ^oC. The reaction mixture was stirred at room temperature for 1 h to evaporate excess diazomethane. The organic layer was separated and the aqueous layer extracted with diethyl ether (2 x 40 mL). The combined organic layer was washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get the crude mass. The crude mass was purified by silica gel column chromatography (ethyl acetate: hexane = 1:8) to afford methyl ester **114** (1.29 g, 96%) as a light yellow liquid.

$[\alpha]_D^{25}$: +25.1 (*c* 2.0, $CHCl_3$);

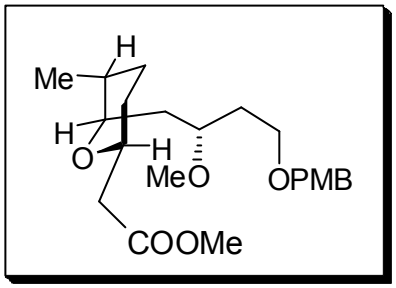
IR (neat, KBr) : ν_{max} 3027, 2951, 2875, 1737, 1612, 1513, 1458, 1301, 1248, 1197, 1095, 1036, 847, 821 cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$) : δ 7.20 (d, *J* = 9.0 Hz, 2H), 6.81 (d, *J* = 8.3 Hz, 2H), 2.64 (s, 2H), 4.58 (m, 1H), 4.39 (s, 2H), 3.78 (s, 3H), 3.64 (s, 3H), 3.55-3.36 (m, 4H), 3.32 (s, 3H), 2.61 (dd, *J* = 9.1, 15.1 Hz, 1H), 2.41 (dd, *J* = 4.5, 15.1 Hz, 1H), 1.98-1.42 (m, 5H), 0.97 (d, *J* = 6.8 Hz, 3H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) : δ 171.5, 159.1, 132.1, 131.9, 129.2, 127.0, 113.7, 74.8, 72.6, 71.3, 68.7, 66.6, 57.0, 55.2, 51.6, 39.1, 38.8, 36.7, 34.1, 17.8 ppm;

ESI-HRMS : *m/z* calcd. for $C_{22}H_{32}NaO_6$ $[M + Na]^+$: 415.2096, found 415.2087.

1.6.15. Methyl 2-((2*S*,5*S*,6*R*)-6-((*S*)-2-methoxy-4-(4-methoxybenzyloxy)butyl)-5-methyl-tetra-hydro-2*H*-pyran-2-yl)acetate (115):



Pd/C (10%) (50 mg) was added to a stirred solution of the compound **114** (1.2 g, 3.06 mmol) in toluene (20 mL) followed by catalytic amount of triethylamine at room temperature under hydrogen atmosphere. The mixture was stirred for 1 h at room temperature. After complete consumption of the starting material (monitored by TLC), the black reaction mass was filtered through a pad of Celite and then thoroughly washed with ethyl acetate (3 x 15 mL). The filtrate was concentrated under reduced pressure and purification of the crude product by silica gel column chromatography (ethyl acetate: hexane = 1:7) furnished the desired product **115** (1.12 g, 93%) as a colorless liquid.

$[\alpha]_D^{25}$: +30.4 (*c* 1.9, $CHCl_3$);

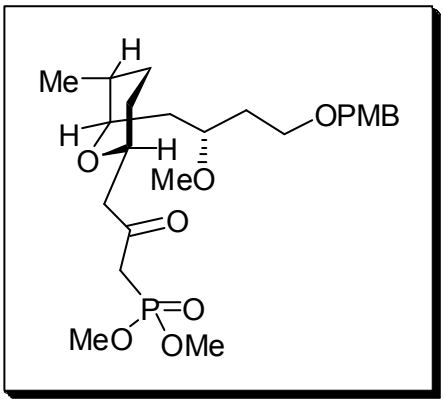
IR (neat, KBr) : ν_{max} 2933, 2873, 1740, 1612, 1513, 1460, 1301, 1248, 1171, 1092, 1036, 846, 821 cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$) : δ 7.29 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.47 (s, 2H), 4.26 (m, 1H), 3.86 (m, 3H), 3.60-3.42 (m, 4H), 3.37 (s, 3H), 2.70 (dd, *J* = 8.1, 14.9 Hz, 1H), 2.50 (dd, *J* = 5.8, 14.9 Hz, 1H), 1.89-1.32 (m, 7H), 1.03 (d, *J* = 6.2 Hz, 3H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) : δ 171.9, 159.1, 130.7, 129.2, 113.7, 74.9, 73.3, 72.6, 68.0 66.7, 57.2, 55.2, 51.5, 38.3, 38.2, 34.3, 33.6, 27.5, 26.3, 18.3 ppm;

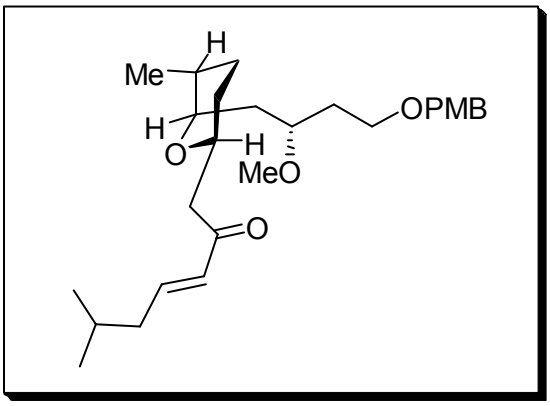
ESI-HRMS : *m/z* calcd. for $C_{22}H_{34}NaO_6$ $[M + Na]^+$: 417.2248, found 417.2240.

1.6.16. Dimethyl 3-((2*S*,5*S*,6*R*)-6-((*S*)-2-methoxy-4-(4-methoxybenzyloxy)butyl)-5-methyl-tetrahy-dro-2*H*-pyran-2-yl)-2-oxopropylphosphonate (116):



To a stirred solution of the dimethyl methyl phosphonate (1.26 g, 10.15 mmol) in THF (30 mL), *n*-BuLi (4.1 mL, 10.15 mmol, 2.5 M in hexane) was slowly added at −78 ^{o}C under nitrogen atmosphere and allowed to slowly warm to 0 ^{o}C. After 1 h, the reaction mixture was again cooled to −78 ^{o}C and to it, ester **115** (1.0 g, 2.54 mmol) dissolved in THF (15 mL) was slowly added and stirred at the same temperature for 1 h. After complete consumption of the starting material (monitored by TLC), the reaction mixture was quenched with saturated NH_4Cl (30 mL), diluted with ethyl acetate (50 mL) and allowed to come to room temperature. The two layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with brine (100 mL) and dried over Na_2SO_4. The organic layer was concentrated under reduced pressure to obtain the crude mass which on purification by silica gel column chromatography (ethyl acetate: hexane = 5:1) afforded the desired keto phosphonate **116** (1.12 g, 92%) as a colorless liquid which was immediately used for next step without further characterization.

1.6.17. (*E*)-1-((2*S*,5*S*,6*R*)-6-((*S*)-2-Methoxy-4-(4-methoxybenzyloxy)butyl)-5-methyl-tetra-hydro-2*H*-pyran-2-yl)-6-methylhept-3-en-2-one (118):



To a stirred solution of the keto phosphonate **116** (1.0 g, 2.06 mmol) in THF (20 mL) was added NaHMDS (2.67 mL, 2.67 mmol, 1M in THF) at −78 oC under nitrogen atmosphere and allowed to come to 0 ^{o}C. After 1 h, the reaction mixture was again cooled to −78 oC and isovaleraldehyde **117** (0.354 g, 4.12 mmol) was slowly added to it and stirred at the same temperature for 1 h. After complete consumption of the starting material (monitored by TLC), the reaction mixture was quenched with saturated NH_4Cl (20 mL), diluted with ethyl acetate (50 mL) and allowed to come to room temperature. The two layers were separated and the aqueous layer extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with brine (2 x 50 mL) and dried over anhydrous Na_2SO_4. The organic layer was concentrated to dryness under reduced pressure to get the crude product which on purification by silica gel column chromatography (ethyl acetate: hexane = 1:6) furnished the desired keto **118** (0.74 g, 81%) as a colorless liquid.

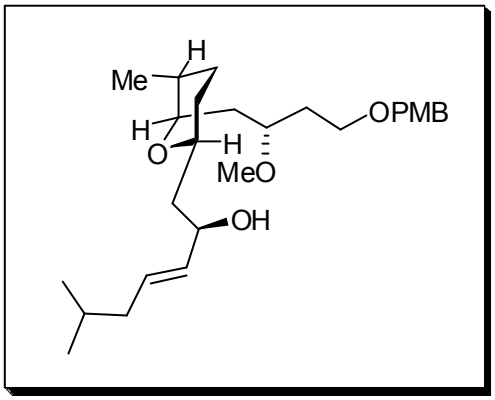
$[\alpha]_D^{25}$: +19.1 (*c* 1.4, $CHCl_3$);

IR (neat, KBr) : ν_{max} 2956, 2927, 2854, 1717, 1606, 1513, 1463, 1256, 1169, 1091, 1034, 848, 821 cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$) : δ 7.27 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 8.3 Hz, 2H), 6.81 (dd, *J* = 8.3, 15.9 Hz, 1H), 6.11 (d, *J* = 15.9 Hz, 1H), 4.43 (s, 2H), 4.30 (m, 1H), 3.80 (s, 3H), 3.56-3.46 (m, 4H), 3.30 (s, 3H), 2.90 (dd, *J* = *6.*8, 15.9 Hz, 1H), 2.70 (dd, *J* = 6.8, 15.9 Hz, 1H), 2.09 (t, *J* = 6.8 Hz, 2H), 1.85-1.24 (m, 10H), 0.96 (d,

	J = 6.0 Hz, 3H), 0.92 (dd, J = 6.8, 15.9 Hz, 6H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$)	: δ 198.4, 159.0, 146.6, 131.6, 130.6, 129.2, 113.6, 74.8, 73.2, 72.6, 67.6, 66.6, 57.1, 55.2, 43.5, 41.6, 38.2, 36.2, 34.0, 33.6, 27.8, 27.6, 26.4, 22.3, 18.3 ppm;
ESI-HRMS	: *m/z* calcd. for $C_{27}H_{42}NaO_5$ $[M + Na]^+$: 469.2924, found 469.2940.

1.6.18. (*R*,*E*)-1-((2*S*,5*S*,6*R*)-6-((*S*)-2-Methoxy-4-(4-methoxybenzyloxy)butyl)-5-methyl-tetrahydro-2*H*-pyran-2-yl)-6-methylhept-3-en-2-ol (96):



To a 50 mL round bottom flask charged with a magnetic stir bar was added *S*-CBS catalyst (0.087 g, 0.314 mmol) in THF (15 mL) under argon. The reaction was cooled to –20 °C and BH_3•Me_2S (1.57 mL, 3.14 mmol, 2M in THF) was added. To this reaction mixture, a solution of ketone **118** (0.71 g, 1.57 mmol) dissolved in THF (8 mL) was added dropwise. The reaction was stirred for 8 h at –20 °C and TLC checked which showed complete consumption of the starting material. MeOH (5 mL) was carefully added to quench excess BH_3. The reaction was diluted with saturated aqueous NH_4Cl (20 mL) and extracted with ethyl acetate (3 x 40 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude oil was purified by silica gel column chromatography (ethyl acetate: hexane = 1:5) giving the desired alcohol **96** (0.576 g, 82%) as a colorless liquid.

$[\alpha]_D^{25}$	: +17.9 (*c* 0.9, $CHCl_3$);
IR (neat, KBr)	: ν_{max} 3454, 2951, 2929, 2869, 1613, 1513, 1302,

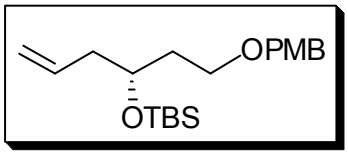
1248, 1090, 1038, 820 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) : δ 7.26 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 8.3 Hz, 2H), 5.62 (m, 1H), 5.46 (dd, *J* = 6.0, 15.3 Hz, 1H), 4.44 (s, 2H), 4.33 (m, 1H), 3.95 (m, 1H), 3.80 (s, 3H), 3.67-3.57 (m, 2H), 3.57-3.50 (t, *J* = 6.0 Hz, 2H), 3.35 (s, 3H), 1.94-1.32 (m, 14H), 1.01 (d, *J* = 6.2 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 6H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) : δ 159.1, 134.2, 133.8, 130.3, 129.4, 113.7, 74.9, 73.6, 72.6, 68.7, 66.9, 66.5, 57.2, 55.2, 41.6, 40.8, 37.3, 34.0, 32.9, 28.2, 27.5, 26.0, 22.3, 22.2, 18.5 ppm;

ESI-HRMS : *m/z* calcd. for $C_{27}H_{44}NaO_5$ $[M + Na]^+$: 471.3081, found 471.3069.

1.6.19. (*R*)-*tert*-Butyl(1-(4-methoxybenzyloxy)hex-5-en-3-yloxy)dimethylsilane (119):



To a stirred solution of alcohol **106** (0.5 g, 2.12 mmol) in CH_2Cl_2 (30 mL) under nitrogen atmosphere, was added 2,6-lutidine (0.6 mL, 5.29 mmol) followed by TBSOTf (0.97 mL, 4.24 mmol) at 0 ^oC and allowed to stir for 30 min. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with water (20 mL) and diluted with CH_2Cl_2 (50 mL). The organic layer was separated and quickly washed with 1 N HCl (2 x 50 mL) to remove excess 2,6-lutidine. The organic layer was washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4, evaporated to dryness under vacuum to obtain the crude product which on purification by silica gel column chromatography purification (ethyl acetate: hexane produced = 1:19) furnished the desired TBS ether **119** (0.69 g, 93%).

$[\alpha]_D^{25}$: −8.1 (*c* 0.33, $CHCl_3$);

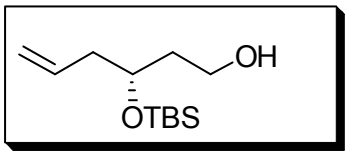
IR (neat, KBr) : ν_{max} 3075, 2999, 2953, 2930, 2857, 1613, 1513, 1463, 1249, 1093, 1040, 912, 836 cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$) : δ 7.19 (d, *J* = 9.1 Hz, 2H), 6.81 (d, *J* = 8.3 Hz, 2H), 5.77 (m, 1H), 5.04-4.96 (m, 2H), 4.36 (q, *J* = 7.5, 18.8 Hz, 2H), 3.87 (m, 1H), 3.78 (s, 3H), 3.45 (m, 2H), 2.19 (m, 2H), 1.68 (m, 2H), 0.87 (s, 9H), 0.03 (d, *J* = 3.7 Hz, 6H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) : δ 159.0, 134.9, 130.6, 129.2, 116.9, 113.6, 72.5, 68.9, 66.6, 55.1, 42.2, 36.6, 25.8, 18.0, −4.4, −4.8 ppm;

ESI-HRMS : *m/z* calcd. for $C_{20}H_{34}NaO_3Si$ [M + Na]+: 373.2169, found 373.2181.

1.6.20. (*R*)-3-(*tert*-Butyldimethylsilyloxy)hex-5-en-1-ol (120):



To a solution of PMB protected compound **119** (0.55 g, 1.57 mmol) in CH_2Cl_2 (20 mL) and water (2 mL) was added DDQ (0.535 g, 2.36 mmol) at room temperature and allowed to stir for 2 h at the same temperature. After completion of the reaction, it was quenched with saturated $NaHCO_3$ (20 mL) solution. The two layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layer was washed with brine (2 x 40 mL), dried over anhydrous Na_2SO_4 and evaporated to dryness to give red colored crude product which on purification by silica gel column chromatography (ethyl acetate: hexane = 1:7) to afford the desired primary alcohol **120** (0.34 g, 94%) as a colorless liquid.

$[\alpha]_D^{25}$: −26.0 (*c* 0.46, $CHCl_3$);

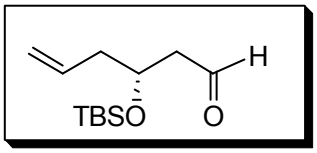
IR (neat, KBr) : ν_{max} 3350, 3078, 2953, 2930, 2858, 1641, 1463, 1255, 1071 cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$) : δ 5.74 (m, 1H), 5.09-4.99 (m, 2H), 3.95 (m, 1H), 3.83-3.62 (m, 2H), 2.28 (t, *J* = 6.6 Hz, 2H), 2.16 (br s, 1H), 1.76 (m, 1H), 1.63 (m, 1H), 0.89 (s, 9H), 0.09 (d, *J* = 2.4 Hz, 6H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) : δ 134.5, 117.2, 71.0, 59.9, 41.6, 25.7, 35.7, 17.9, −4.5, −4.9 ppm;

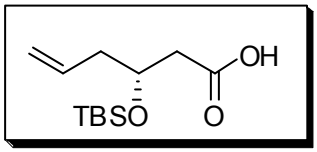
ESI-HRMS : *m/z* calcd. for $C_{12}H_{26}NaO_2Si$ [M + H]+: 231.1780, found 231.1775.

1.6.21. (*R*)-3-(*tert*-Butyldimethylsilyloxy)hex-5-enal (121):



To a stirred solution of primary alcohol **120** (0.25 g, 1.09 mmol) and solid anhydrous $NaHCO_3$ (1.0 g) in CH_2Cl_2 (25 mL) at 0 ^oC, was added Dess-Martin periodinane (0.69 g, 1.63 mmol). The reaction mixture was stirred at 0 ^oC for 3 h. After completion of the reaction (monitored by TLC), the reaction mixture was filtered through a Celite bed and washed with CH_2Cl_2 (50 mL). The filtrate was washed with saturated $NaHCO_3$ (2 x 30 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 40 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and solvent removed under reduced pressure to get crude aldehyde **121** (0.24 g) as a pale yellow liquid which was directly used in the next step.

1.6.22. (*R*)-3-(*tert*-Butyldimethylsilyloxy)hex-5-enoic acid (97):



To a solution of aldehyde **121** (0.24 g, 1.05 mmol) in *tert*-butyl alcohol (15 mL), 2-methyl-2-butene (1.59 mL, 1.56 mmol, 1M solution in THF) was added at room temperature. Sodium dihydrogen phosphate (0.49 g, 3.15 mmol) and sodium chlorite (0.14 g, 1.56 mmol) were dissolved in water (5 mL) to make a clear solution which subsequently added to the reaction mixture at 0 ^oC. It was allowed to stir for further 3 h at room temperature. After completion of the reaction (monitored by TLC), it was diluted with ethyl acetate (30 mL). The two layers were separated and the aqueous layer extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4 and evaporated to dryness under reduced pressure.

The crude product was purified by column chromatography over silica gel (ethyl acetate: hexane = 1:9) to afford the desired acid **97** (0.22 g, 86% over two steps) as a colorless oil.

$[\alpha]_D^{25}$: −18.9 (*c* 0.7, $CHCl_3$);

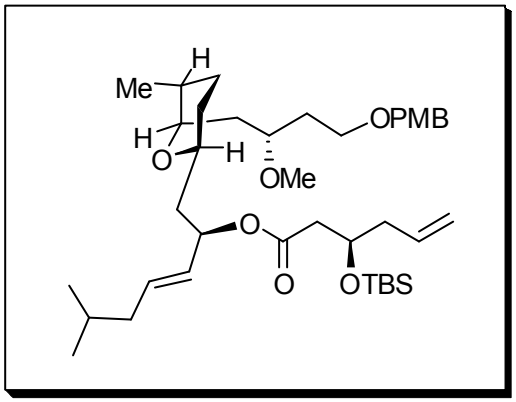
IR (neat, KBr) : ν_{max} 3079, 2956, 2930, 2858, 1713, 1642, 1463, 1256, 1089 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) : δ 5.78 (m, 1H), 5.12-5.02 (m, 2H), 4.18 (m, 1H), 2.52-2.37 (m, 2H), 2.28 (t, *J* = 6.8 Hz, 2H), 0.86 (s, 9H), 0.06 (d, *J* = 6.6 Hz, 6H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) : δ 177.6, 133.7, 118.1, 68.8, 41.9, 41.7, 25.7, 17.9, −4.5, −5.0 ppm;

ESI-HRMS : *m/z* calcd. for $C_{12}H_{24}NaO_3$ [M + Na]+: 267.1387, found 267.1385.

1.6.23. (*R*)-((*R*,*E*)-1-((2*S*,5*S*,6*R*)-6-((*S*)-2-Methoxy-4-(4-methoxybenzyloxy)butyl)-5-methyl tetra-hydro-2*H*-pyran-2-yl)-6-methylhept-3-en-2-yl) 3-*(tert*-butyldimethylsilyloxy)- hex-5-enoate (122):



To a stirred solution of the acid **97** (0.49 g, 2.01 mmol) in dry toluene (10 mL) at 0 oC, Et_3N (0.31 mL, 4.02 mmol) followed by 2,4,6-trichlorobenzoyl chloride (0.63 mL, 4.02 mmol) was added and stirred for 30 min at room temperature. DMAP (1.22, 10.04 mmol) and alcohol **96** (0.45 g, 1.004 mmol) was dissolved in dry toluene (10 mL) and this was added to the above mentioned solution at 0 ^oC and allowed to stir at room temperature for 6 h. After completion of the reaction (monitored by TLC), it was diluted with ethyl acetate (50 mL) and water (25 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 x 40 mL). The combined organic layer was washed

with Na_2CO_3 (2 x 250 mL), brine (2 x 50 mL), dried over anhydrous Na_2SO_4 and solvent evaporated under reduced pressure to give a colorless oil which on purification by silica gel column chromatography (ethyl acetate: hexane = 1:12) furnished the desired coupled product **122** (0.63 g, 93%, based on the starting alcohol) as a colorless liquid.

$[\alpha]_D^{25}$: +14.3 (*c* 0.7,, $CHCl_3$);

IR (neat, KBr) : ν_{max} 3076, 2953, 2928, 2856, 1734, 1613, 1513, 1463, 1302, 1249, 1171, 1091, 1037, 836 cm^{-1};

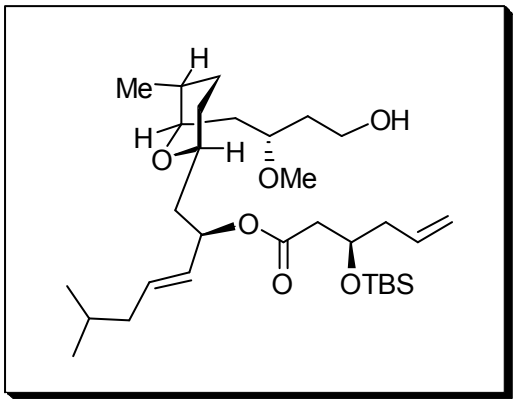
^1H NMR (300 MHz, $CDCl_3$) : δ 7.21 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 8.9 Hz, 2H), 5.83-5.62 (m, 2H), 5.40-5.19 (m, 2H), 5.07-4.99 (m, 2H), 4.39 (s, 2H), 4.16 (m, 1H), 3.81 (m, 1H), 3.78 (s, 3H), 3.60-3.42 (m, 3H), 3.36 (s, 3H), 2.41-2.35 (m, 2H), 2.31-2.18 (m, 2H), 2.01-1.23 (m, 14H), 0.92-0.83 (m, 18H), 0.03 (d, *J* = 15.8 Hz, 6H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) : δ 170.7, 159.0, 134.3, 132.9, 129.7, 129.2, 128.2, 117.6, 113.7, 74.3, 72.6, 71.8, 68.7, 67.7, 66.5, 56.8, 55.2, 42.3, 41.9, 41.5, 38.8, 36.5, 34.7, 33.5, 28.2, 28.0, 26.9, 25.8, 22.3, 22.2, 18.2, 18.0, −4.6, −4.8 ppm;

ESI-HRMS : *m/z* calcd. for $C_{39}H_{70}NO_7Si$ $[M + NH_4]^+$: 692.4916, found 692.4883.

1.6.24. (*R*)-((*R*,*E*)-1-((2*S*,5*S*,6*R*)-6-((*S*)-4-Hydroxy-2-methoxybutyl)-5-methyl-tetrahydro-2-pyran-2-yl)-6-methylhept-3-en-2-yl) 3-(*tert*-butyldimethylsilyloxy)hex-5-enoate (123):

To a solution of the compound **122** (0.31 g, 0.445 mmol) in CH_2Cl_2 (15 mL) and water (1 mL) at 0 ^oC, was added DDQ (0.152 g, 0.667 mmol) and allowed to stir for 2 h at room temperature. The reaction mixture was quenched with saturated $NaHCO_3$ solution (10 mL) and diluted with CH_2Cl_2 (15 mL). The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layer was washed with brine (2 x 40 mL), dried over anhydrous Na_2SO_4 and evaporated to give red colored



crude product which on purification by silica gel column chromatography (ethyl acetate: hexane = 1:5) afforded the desired primary alcohol **123** (0.23 g, 95%) as a colorless liquid.

$[\alpha]_D^{25}$: +23.0 (*c* 0.52, $CHCl_3$);

IR (neat, KBr) : ν_{max} 3466, 3077, 2953, 2930, 1734, 1641, 1462, 1253, 1171, 1087, 836 cm^{-1};

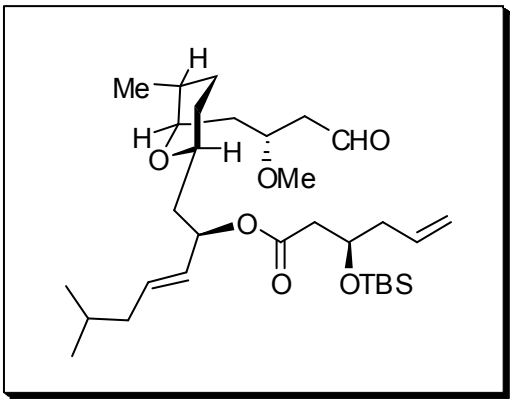
^1H NMR (300 MHz, $CDCl_3$) : δ 5.87-5.62 (m, 2H), 5.43-5.26 (m, 2H), 5.08-4.99 (m, 2H), 4.17 (m, 1H), 3.87-3.72 (m, 2H), 3.72-3.60 (m, 2H), 3.42 (s, 3H), 3.6 (m, 2H), 2.41 (d, *J* = 5.5 Hz, 2H), 2.34-2.15 (m, 2H), 2.06-1.24 (m, 14H), 0.94 (d, *J* = 5.7 Hz, 3H), 0.9-0.8 (m, 15H), 0.04 (d, *J* = 11.9 Hz, 6H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) : δ 171.1, 134.3, 133.0, 129.5, 117.6, 76.4, 72.9, 71.7, 68.7, 67.5, 59.8, 56.8, 42.2, 41.9, 41.5, 38.0, 36.6, 36.1, 35.1, 34.7, 28.4, 28.2, 28.0, 26.9, 25.8, 22.2, 18.3, −4.6, −4.8 ppm;

ESI-HRMS : *m/z* calcd. for $C_{31}H_{58}NaO_6Si$ $[M + Na]^+$: 577.3895, found 577.3916.

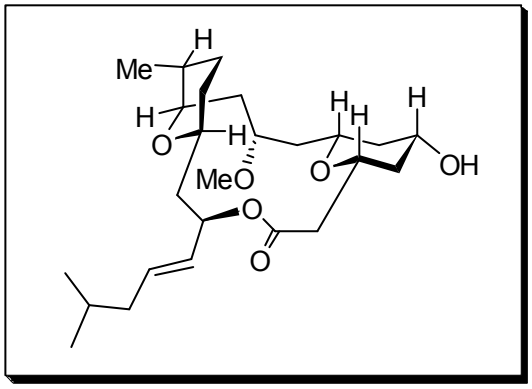
1.6.25. (*R*)-((*R*,*E*)-1-((2*S*,5*S*,6*R*)-6-((*R*)-2-Methoxy-4-oxobutyl)-5-methyl-tetrahydro-2*H*-pyran-2-yl)-6-methylhept-3-en-2-yl) 3-(*tert*-butyldimethylsilyloxy)hex-5-enoate (95):

To a stirred solution of primary alcohol **123** (0.15 g, 0.271 mmol) and solid anhydrous $NaHCO_3$ (0.2 g) in CH_2Cl_2 (10 mL), Dess-Martin periodinane (0.173 g, 4.062 mmol) was added at 0 oC under nitrogen atmosphere. The reaction mixture was stirred at



0 ^{o}C for 4 h. After completion of reaction (monitored by TLC), the reaction mixture was filtered through a Celite bed and thoroughly washed with CH_2Cl_2 (50 mL). The filtrate was washed with saturated $NaHCO_3$ (30 mL) solution. The aqueous layer was again extracted with CH_2Cl_2 (2 x 40 mL). The combined organic layer was washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get the crude aldehyde **95** (0.16 g) which was immediately used for next step without further purification and characterization.

1.6.26. Macrolide (61):



TMSOAc (1.71 mL, 11.21 mmol) was added to a solution of aldehyde **95** (0.16 mg, 0.28 mmol) in AcOH (15.0 mL) at room temperature. TESOTf (1.23 mL, 7.02 mmol) was added dropwise to the resulting solution at the same temperature. After 30 min, the reaction mixture was poured into diethyl ether (100 mL) and washed with $NaHCO_3$ (4 x 100 mL). The aqueous layer was again extracted with diethyl ether (3 x 50 mL). The combined organic layer was washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to obtain the crude product which was dissolved in MeOH (10 mL) and then treated with K_2CO_3 (0.37 g, 2.89 mmol) at room

temperature. The reaction mixture was stirred for 3 h at room temperature. After completion of the reaction (monitored by TLC), it was concentrated under reduced pressure. The residue was dissolved in water (10 mL) and diethyl ether (20 mL). The two layers were separated and the aqueous layer extracted with diethyl ether (3 x 20 mL). The combined organic layer was washed with brine (2 x 25 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was finally purified by flash column chromatography over silica gel (ethyl acetate: hexane = 1:2) to afford the macrolide **61** (0.104 g, 72% over three steps).

$[\alpha]_D^{25}$: +54.7 (*c* 1.18, EtOH);

IR (neat, KBr) : ν_{max} 3452, 2954, 2925, 2854, 1736, 1643, 1261, 1083, 1034 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) : δ 5.71 (m, 1H), 5.41-5.32 (m, 2H), 3.91 (m, 1H), 3.87 (m, 1H), 3.77-3.66 (m, 1H), 3.59-3.47 (m, 2H), 3.36 (s, 3H), 3.22 (m, 1H), 2.57 (dd, *J* = 4.5, 13.6 Hz, 1H), 2.44-2.30 (m, 3H), 2.09-1.96 (m, 3H), 1.95-1.83 (m, 4H), 1.36-1.23 (m, 8H), 1.17 (d, *J* = 6.8 Hz, 3H), 1.03 (m, 1H), 0.85 (d, *J* = 6.8 Hz, 6H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) : δ 169.3, 132.4, 130.0, 73.6, 73.5, 73.0, 72.2, 70.8, 68.0, 63.0, 57.3, 43.0, 42.8, 41.6, 41.0, 40.8, 39.1, 35.4, 30.9, 28.1, 27.1, 24.1, 22.2, 18.2 ppm;

ESI-HRMS : *m/z* calcd. for $C_{25}H_{42}NaO_6$ $[M + Na]^+$: 461.2874, found 461.2876.

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1.7. REFERENCES

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CHAPTER II

Section A

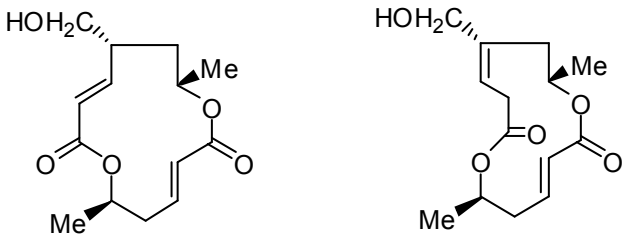
Introduction to olefin metathesis reaction and previous approaches for Amphidinilactone A

2.1. Introduction:

Ever since the first isolation of Exaltolide in 1927 by Kerschbaum,[1] interest in macrocyclic lactones, defined as lactones with more than 8 atoms in the ring, has been increasing. Indeed, natural macrocyclic lactones, the term macrolide[2] has been for years a synonym for "macrolactone glycoside antibiotics" and thus will not be used herein, present a large spectrum of interesting properties from perfume, to pheromone or insecticide activity, to medicinal (antibiotic, cytotoxic, antiangiogenesis) properties and a wide range of structures from 8-membered ones such as octalactins[3] to the 60-membered quinolidomicins. From their first isolation in the 50s, macrolide antibiotics, such as erythromycin[5] were widely used for treatment of bacterial infections, and because of their safety and efficacy, they are still the preferred therapeutic agents for treatment of respiratory infections. Another important class of macrolactones with a wide range of biological activities is the cyclodepsipeptides[6]

The term "macrolide" is used to describe natural products with a macrocyclic lactone ring of 12 or more elements. The term macrolide was introduced in 1957 by Woodward to denote the class of substances produced by *Streptomyces* species containing a macrocyclic lactone ring.[7] The macrolide class is large and structurally diverse. Macrolides are produced by the fermentation of microorganisms and/or are found in marine invertebrates, such as sponges, bryozoa, or marine cyanobacteria, and in dinoflagellate species belonging to the genera *Amphidinium*, *Gambierdiscus*, *Prymnesium,* and *Protoceratium*. The polyether and macrolide antibiotics have been the focus of a great deal of attention since the 1950's, when the first of these metabolites were isolated. Around 80 polyethers[8] and 100 macrolides[9] have now been characterized. Among several macrolides, most of them are polymethylated, polyhydroxy(methoxy)lated, or polyether compounds, whilst a few embed contiguous isoxazole units. In general, such compounds exhibit potent biological activities. The synthesis of macrolides has received considerable attention in pharmaceutical industry. The introduction of macrolide rings onto organic molecule often increases the stability, bioactivities and also alters the lipophilicity. Natural macrolides having odd number of ring atoms are comparatively less abundant than even numbers. Recently, cytotoxic Irimotiolide[10] (15-membered macrolide), Amphidinolide Y[11] (17-

membered macrolide), Amphidinolide T[12] (19-membered macrolide) has been isolated. Before the isolation of Amphidinolactone A, only two 13-memdered macrolides, bartanol **9** and bartallol **10** were known.[13] These were isolated[13a] from a *Cytospora* sp. and their structures established by a detailed study of their high field ^{1}H and ^{13}C NMR spectra. Unlike the other 14-membered ring macrodiolides isolated from this source, bartanol and bartallol have a novel rearranged 13-membered macrocyclic ring.



Bartanol (1) **Bartallol (2)**

Figure 1

In 2007, Kobayashi *et al.* isolated amphidinolactone A (**1**), a cytotoxic 13-membered macrolide isolated from a symbiotic dinoflagellate *Amphidinium* sp. (Y-25) separated from an Okinawa a marine acoel flatworm Amphiscolops sp.[14]

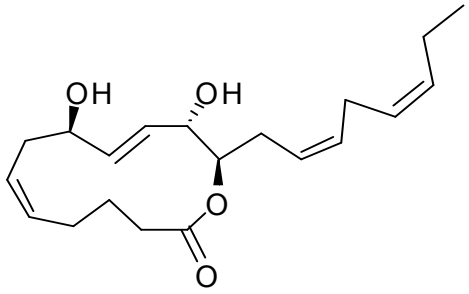


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Fig. 2 Structure of amphidinolactone A (**3**)

Construction of lactone through the formation of C-C bond and particularly by intramolecular ring-closing metathesis[15] reaction stands as a promising tool for the synthesis of macrolides and heterocycles. As per literature review, to make 13 membered macrolide by utilizing ring closing metathesis reaction was proven difficult. In this article, the influence of protecting groups and the substrate specific nature of the ring-closing metathesis reaction was studied.

2.2. Olefin metathesis reaction:

Ever since the birth of the art of organic synthesis, as marked by Wohler's synthesis of urea in 1828, progress in this field has, to a large degree, been dependent on our ability to construct carbon frameworks through carbon–carbon bond forming reactions. Olefin metathesis is an organic reaction that entails the union of fragments of alkenes (olefins) by the scission and regeneration of carbon-carbon double bonds.[16] Carbon-carbon bond forming reactions are among the most important family of reactions in organic synthesis. Olefin metathesis is now become a strong and potent synthetic technique and is a powerful method for the clean construction of innumerable classes of chemical architectures. The wide use of this reaction successively in the total synthesis of natural product led to the awarding of Nobel Prize in Chemistry to the pioneers in olefin metathesis: Yves Chauvin, Robert H. Grubbs, and Richard R. Schrock in the 2005. The functional group tolerance of these catalysts and their ability to be handled without the use of glove box or Schlenk techniques have propelled this synthetic methodology in to the forefront of carbon–carbon bond forming techniques in total synthesis. Therefore herein, we have discussed briefly about the ruthenium alkylidenes participation in olefin metathesis reaction.[17]

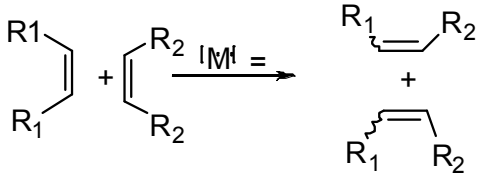
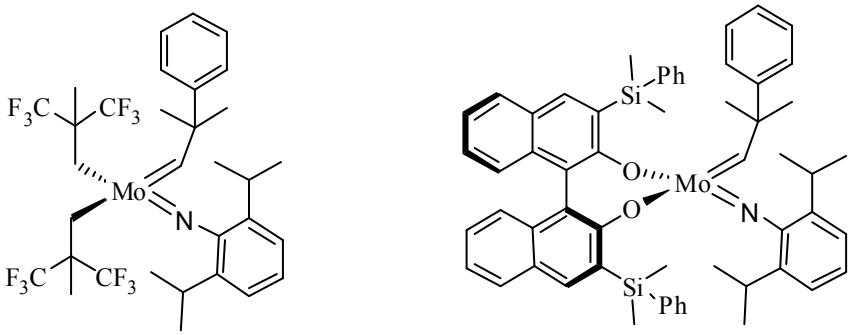


Figure 3

Metathesis reaction represents a bimolecular process involving the exchange of bonds between the two reacting chemical species and in the olefin metathesis is a reaction which involves the redistribution of olefin bond. The term metathesis was first introduced by Colderon in 1967 although this reaction was initially observed in 1950s during the study on Ziegler-Natta polymerization process. The first report of the processes involving olefin metathesis was reported by Eleuterio. Traditional catalysts are prepared by a reaction of the metal halides with alkylation agents. Historically, olefin metathesis has been studied both from a mechanistic standpoint[18] and in the context of polymer synthesis.[19] The traditional, industrial catalysts are ill-defined and used mainly for petroleum products.

Modern catalysts are well-defined organometallic compounds that come in two main categories, commonly known as Schrock catalysts and Grubbs' catalysts. Schrock catalysts are molybdenum(VI)- and tungsten(VI)-based, and are examples of Schrock alkylidenes. Schrock entered the olefin metathesis field in 1979 as an extension of work on tantalum alkylidenes.20 Schrock in 1990, prepared the alkylidenes for olefin metathesis and in 1993, prepared the asymmetric catalyst in which the saturated part was replaced with a binol ligand.21(figure 4)



Shrock's catalyst **S**hrock's asymmetric catalyst

Figure 4

On the other hand, Grubbs' catalysts are ruthenium(II) carbenoid complexes.[22]

1st generation Grubbs' catalyst I 2nd generation Grubbs' catalyst II

Figure 5

By utilization the so called catalyst in different type of metathesis reactions, resulted several types of olefin metathesis processes.

Some important classes of olefin metathesis include:

- Cross Metathesis (CM)
- Ring-Opening Metathesis (ROM)
- Ring-closing metathesis (RCM)
- Ring opening metathesis polymerisation (ROMP)
- Acyclic diene metathesis (ADMET)
- Ethenolysis

Cross-metathesis (CM) and Ring closing metathesis (RCM) reactions are widely used in total synthesis of a lot of complex bioactive natural products. Herein, a brief discussion about CM and RCM reactions has been given.

2.2.1. Cross-Metathesis (CM):

Carbon-carbon bond construction is an interesting part of organic research. Numbers of procedures are there to construct c-c bond, olefin metathesis has come to the fore in recent years owing to the wide range of transformations that are possible with commercially available and easily handled catalysts. Consequently, olefin metathesis is now widely considered as one of the most powerful synthetic tools in organic chemistry. Until recently the intermolecular variant of this reaction, cross-metathesis, had been neglected despite its potential. With the evolution of new catalysts, the selectivity, efficiency, and functional-group compatibility of this reaction have improved to a level that was unimaginable just a few years ago. These advances, together with a better understanding of the mechanism and catalyst–substrate interactions, have brought us to a stage where more and more researchers are employing cross-metathesis reactions in multistep procedures and in the synthesis of natural products. The recent inclusion of alkynes and hindered bi cyclic olefins as viable substrates for bimolecular metathesis coupling, the discovery of enantioselective cross-metathesis and cross-metathesis in water, and the successful marriage of metathesis and solid-phase organic synthesis has further widened the scope of this versatile reaction. Progress in the development of the metathesis reaction has been directly correlated to improvements in the functional group compatibility and the reactivity of the catalysts. Cross metathesis reactions have numerous advantages typical of modern olefin-metathesis reactions *i.e.* to carry out this reaction 1–5 mol% of catalyst required and high yields can obtain under mild conditions in relatively short reaction times, a wide range of functional groups are tolerated, with minimal substrate protection necessary, this is a well adoptable process for industrial applications due its reversibility character and relatively atom-economic and ethylene is usually the only by-product which is a gas, the olefin substrates are generally easier and less expensive to prepare than those associated with other common catalytic C-C bond-forming reactions (e.g. unsaturated boranes, stannanes, halides, triflates), the olefinic products are suitable for further structural elaboration (e.g. hydrogenation, epoxidation,

halogenation, cycloaddition), high levels of chemo-regio and stereoselectivity can be attained.

Cross-metathesis between two acyclic olefins offers interesting possibilities for synthesizing higher-substituted alkenes. The use of highly substituted asymmetric olefins is not practical because of the expected complex spectrum of products. Use of terminal olefins in the formation of volatile ethylene as a byproduct provides the driving force for the reaction. The volume of work reported in the areas of RCM, ROMP, and novel combinations there of has dramatically overshadowed that reported for olefin cross-metathesis (CM). This unique method for the intermolecular formation of carbon-carbon double bonds has not yet found wide spread application in organic synthesis because general reaction conditions that give high product and *trans/cis* selectivity have not been developed. The simplified CM reaction between two terminal olefins is depicted below.

Mecanism of cross-metathesis:

Hérisson and Chauvin first proposed the widely accepted mechanism of transition metal alkene metathesis. The direct [2 + 2] cycloaddition of two alkenes is formally symmetry forbidden and thus has a high activation energy. The Chauvin mechanism involves the [2 + 2] cycloaddition of an alkene double bond to a transition metal alkylidene to form a metallacyclobutane intermediate. The metallacyclobutane produced can then cyclorevert to give either the original species or a new alkene and alkylidene. Interaction with the d-orbitals on the metal catalyst lowers the activation energy enough that the reaction can proceed rapidly at modest temperatures.

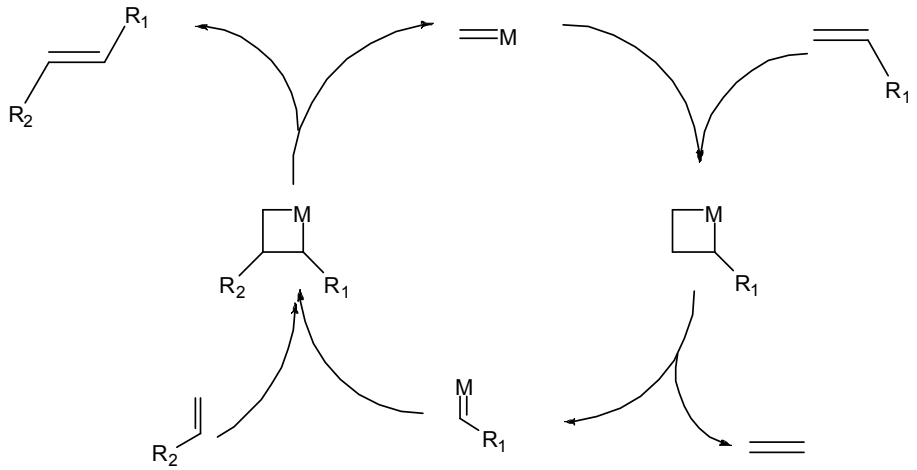
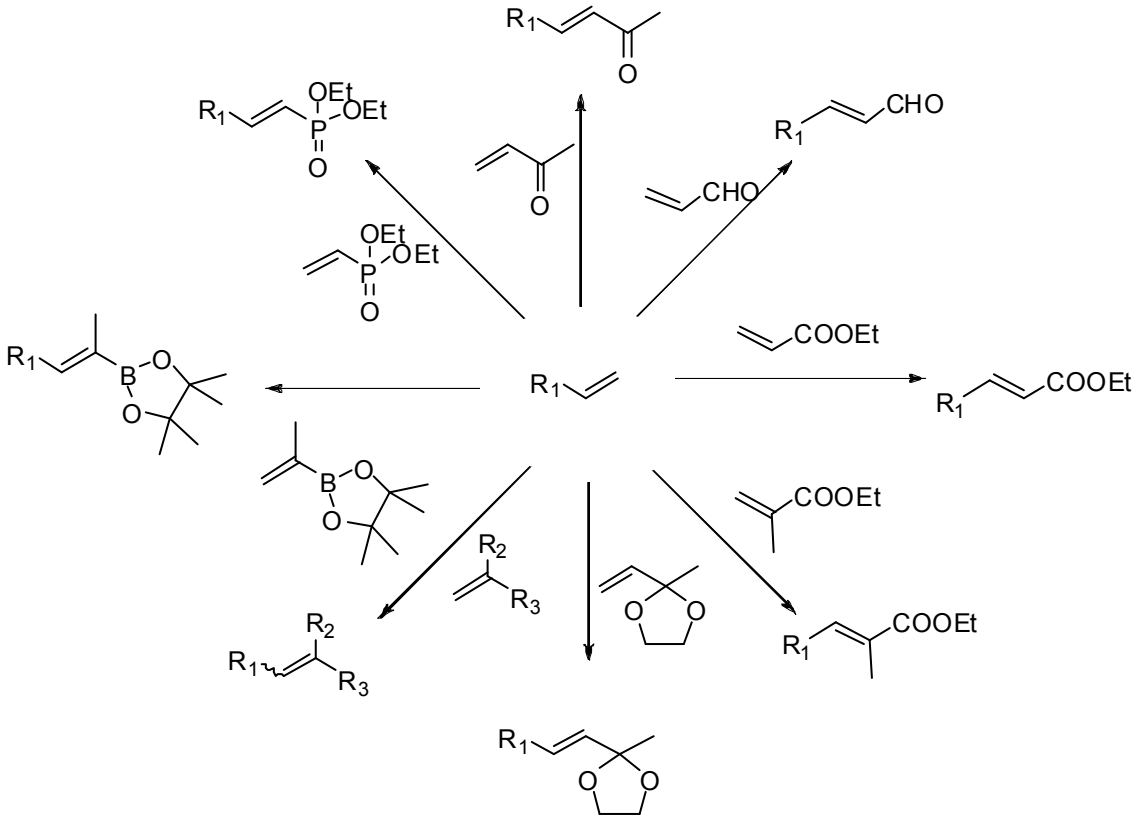


Figure 6

Commonly employed alkene metathesis reactions

Cross-metathesis is a powerful method for the rapid synthesis of simple and complex olefinic building blocks. Grubbs catalyst and Hoveyda-Grubbs catalyst are generally used for this reaction to lead high yield of desired product. Some examples by using grubbs II generation catalyst were shown in Scheme 1.

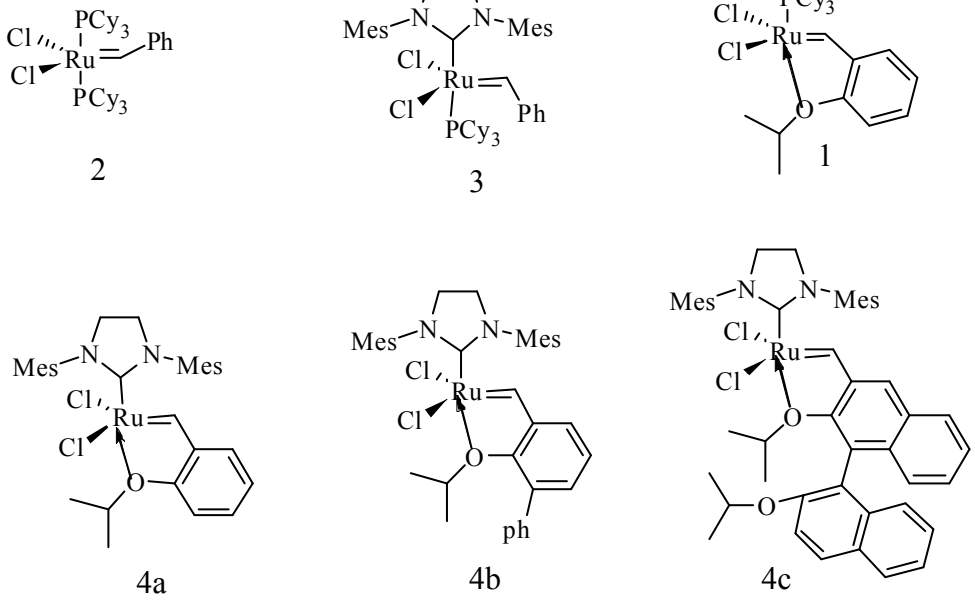


Scheme 1

2.2.2. Ring-closing metathesis (RCM)

The olefin metathesis reaction has been known since the 1960s, but it was not until the early 1990s that this transformation became an important tool in synthetic organic chemistry. It was thus in 1992 that Grubbs and Fu published two seminal papers describing the application of ring-closing metathesis (RCM) to the synthesis of simple five-, six-, and seven-membered monocyclic systems containing oxygen and nitrogen atoms using a molybdenum catalyst that had been first prepared by Schrock.[23] From onwards RCM became an interesting and exciting protocol for total synthesis of number of natural products. Ruthenium and the molybdenum catalysts are very reactive and well tolerance behaviors towards all types of functional groups, but the Mo-based complexes

suffer the potential disadvantage of being more air and moisture sensitive. Therefore ruthenium-based catalysts were treated as ideal catalyst worldwide.



Recently modified, highly efficient, ruthenium-based catalycts

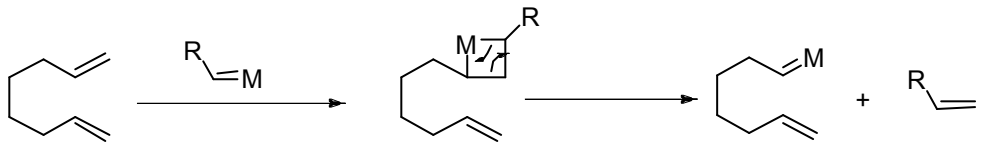
Figure 7

The high selectivity and reactivity of all ruthenium catalyst for carbon-carbon π-bonds minimizes protecting group manipulations while enabling the use of RCM as an excellent alternative to other ring-forming reactions for the efficient construction of complex cyclic targets having a variety of ring sizes. The Ring-Closing Metathesis (RCM) allows synthesis of 5- up to 30-membered cyclic alkenes. The *E/Z*-selectivity depends on the ring strain.

Chauvin's Mechanism for RCM:

Chauvin had suggested the following mechanism which was universally accepted.

Initiation:



Catalytic Cycle:

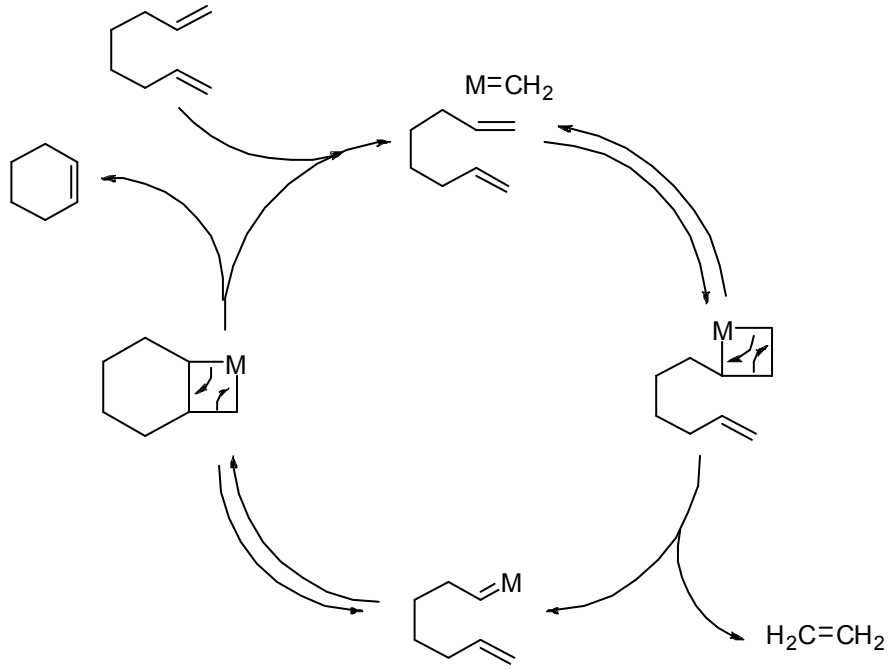
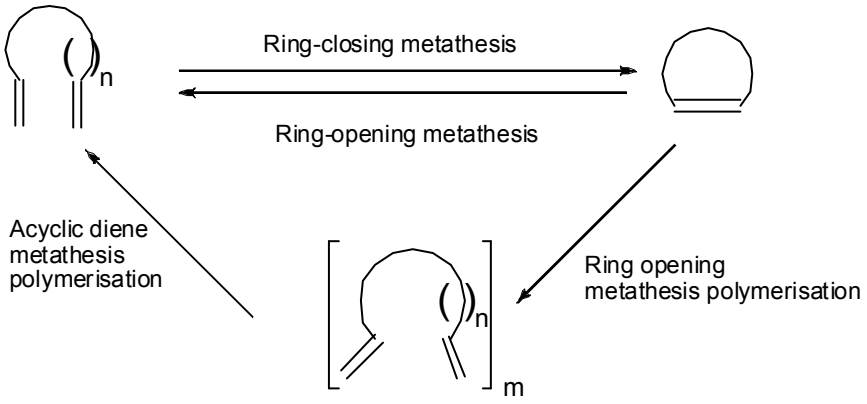


Figure 8

It is now generally accepted that the mechanism of both cyclic and acyclic olefin metathesis proceeds through a series of metalla cyclobutanes and carbene complexes. Although the relative stabilities of the carbenes and metalla cyclo butanes can change with



(Diagram for most commonly employed different types of alkene metathesis reactions.)

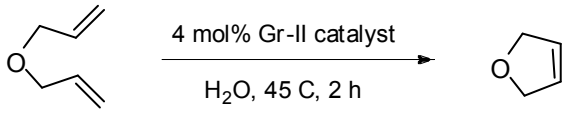
Scheme 2

reaction conditions, catalyst composition and alkene substitution, the mechanism of olefin metathesis (Figure 8) appears to be the same for all catalysts. The key intermediate is a metallacyclobutane, which can undergo cycloreversion either towards products or back to

starting materials. When the olefins of the substrate are terminal, the driving force for RCM is the removal of ethene from the reaction mixture.

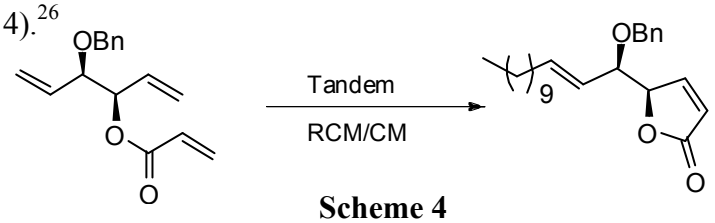
As with any other cyclization method, the synthetic efficiency of RCM is limited by the competition between intramolecular ring-closing and intermolecular oligomerization reactions. Olefin metathesis is represented as a fully reversible set of [2 + 2] cyclo-addition-cycloreversion equilibria, implying a thermodynamic distribution of "living" metathesis products.[24] The emergence of metathesis reactions in chemical synthesis over the last few years has been dramatic. It has been delightful to review the field and highlight some of its most exciting applications in total synthesis. Some excellent use of ring closing metathesis had been demonstrated bellow.

Olefin ring closing metathesis and hydrosilylation reaction in aqueous medium by Grubbs second generation ruthenium catalyst was demonstrated in 2008 by Verma etc (scheme 3).[25]



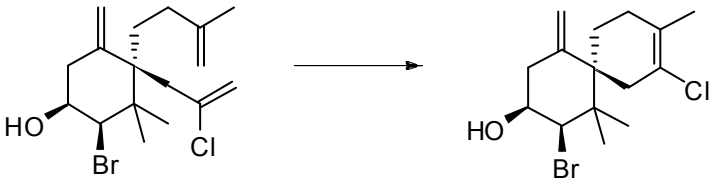
Scheme 3

The total synthesis of (−)-muricatacin had been achived via highly regioselective and stereoselective tandem ring-closing/cross metathesis reaction in which both lactone formation (scheme 4).[26]



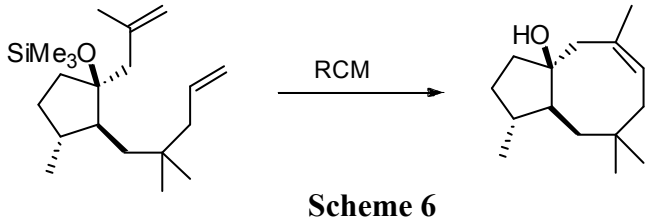
Scheme 4

The first total synthesis of elatol which is a halogenated sesquiterpene in the chamigrene natural product family had been achieved a ring-closing olefin metathesis to concomitantly form the spirocyclic core as well as the fully substituted chlorinated olefin (scheme 5).[27]



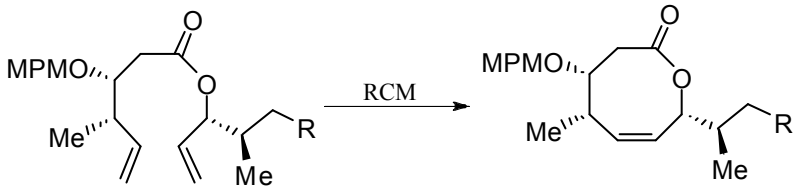
Scheme 5

A straightforward total synthesis of the cyclooctenoid sesquiterpene dactylol has been achieved via ring-closing metathesis (RCM) of the resulting dienes to form the cyclooctene ring using Schrocks molybdenum carbene as a precatalyst (scheme 6).[28]



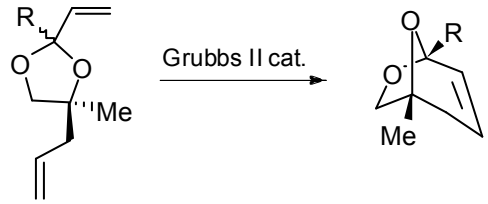
Scheme 6

The total synthesis of the novel lactone natural product octalactin A was done. The key step involves the facile construction of the eight-membered lactone core via ring-closing metathesis (RCM) (scheme 7).[29]



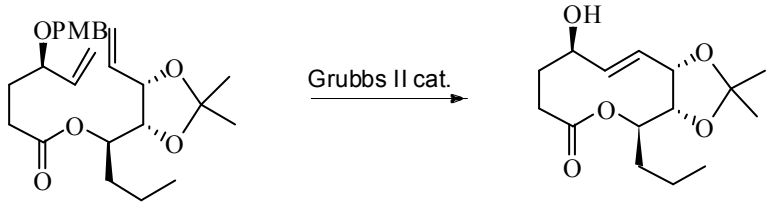
Scheme 7

Racemic and enantiopure targets containing the 6,8-dioxabicyclo[3.2.1]octaine skeleton, was conveniently synthesized from monocyclic diene precursors using an intramolecular ruthenium-catalyzed ring-closing metathesis reaction as the key step (scheme 8).[30]



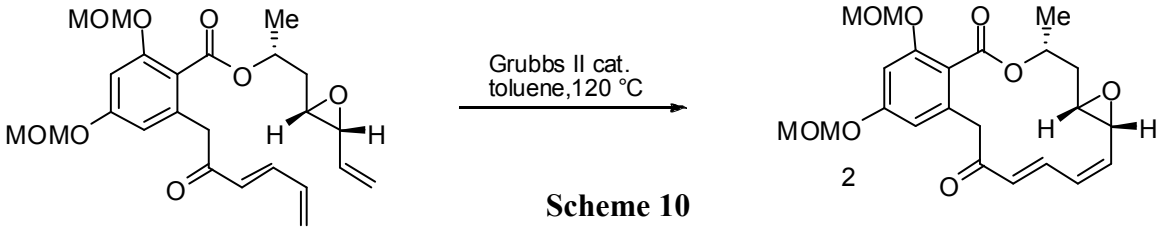
Scheme 8

The ring closing reaction was widely demonstrated in 10 membered lactones. In this context, we are going to discuss about some similar lactones. The total syntheses of stagonolide B and its 4-epimer were carried out to probe into how the relative stereochemistry of allylic hydroxy groups and their protecting groups influence the efficiency of the ring closing metathesis (scheme 9).[31]



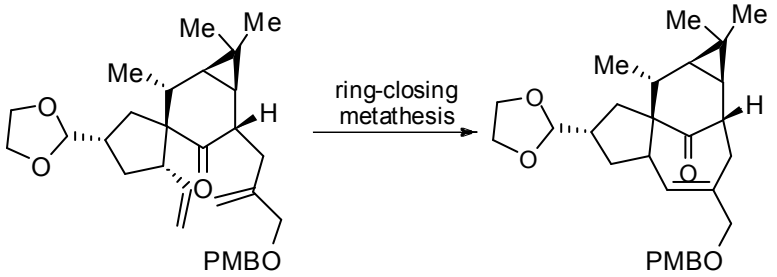
Scheme 9

Ring-closing metathesis to form a diene system in the total synthesis of pochonin C was completed by Winssinger and co-workers in 2004 (scheme 10).[32]



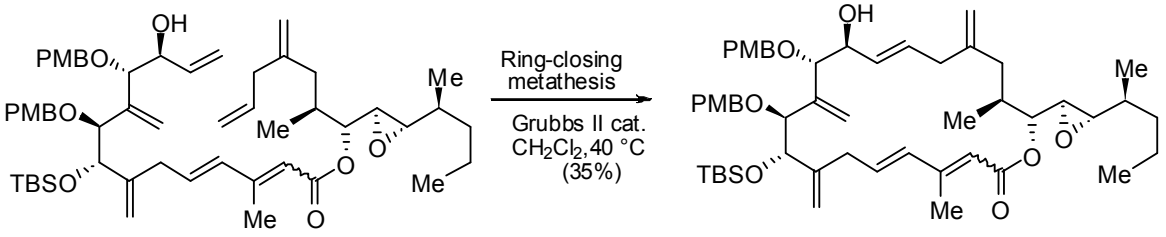
Scheme 10

Wood and co-workers in 2004 had reported the total synthesis of ingenol via ring-closing-metathesis reaction (scheme 11).[33]



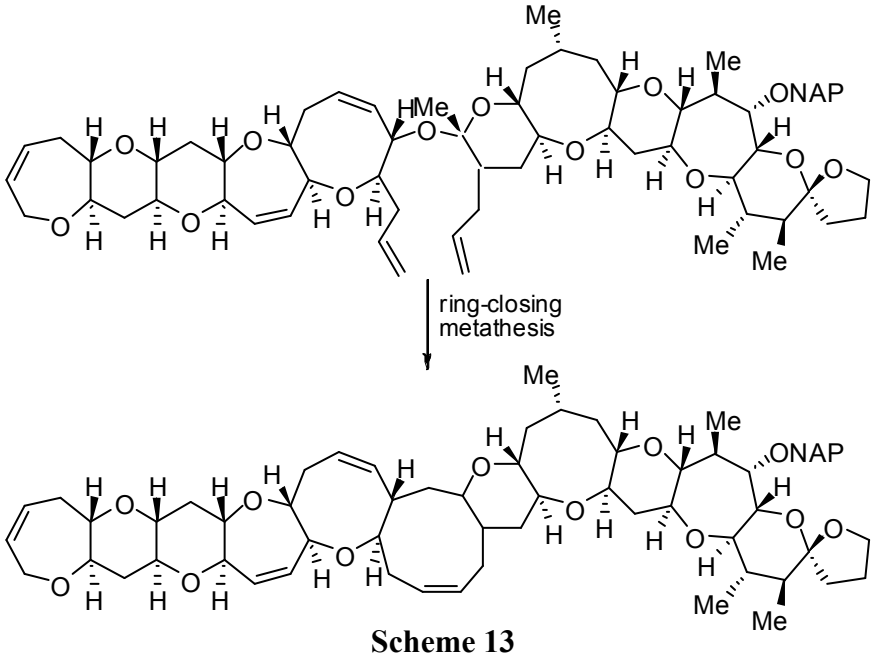
Scheme 11

Ring-closing-metathesis reactions in the total synthesis of amphidinolide A and its stereoisomers was successfully demonstrated by Maleczka and co-workers (scheme 12).[34]



Scheme 12

Hirama and co-workers in 2002 published the total synthesis of ciguatoxin CTX3C by using multiple use of ring-closing-metathesis reaction (scheme 13).[35]



Scheme 13

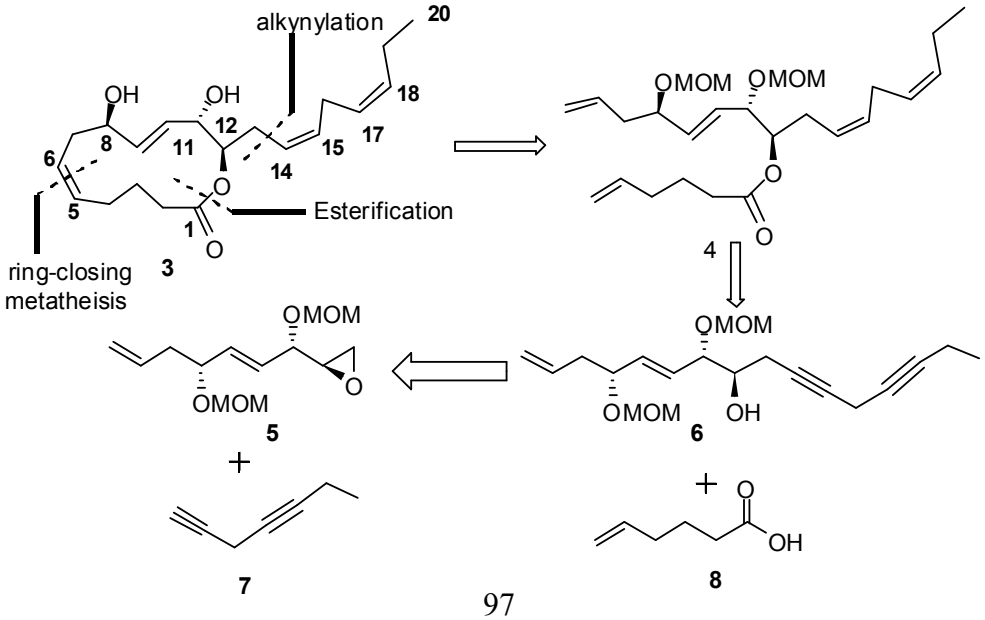
2.3. Previous approaches:

Herein, a brief account of the previous works carried out the total synthesis of amphidinolactone A has been reviewed.

2.3.1 Kobayashi's Approach: [36]

Kobayashi *et al.* reported first total synthesis Amphidinolactone A and thus they confirmed that the absolute stereochemistry was identical with the proposed one. [20]

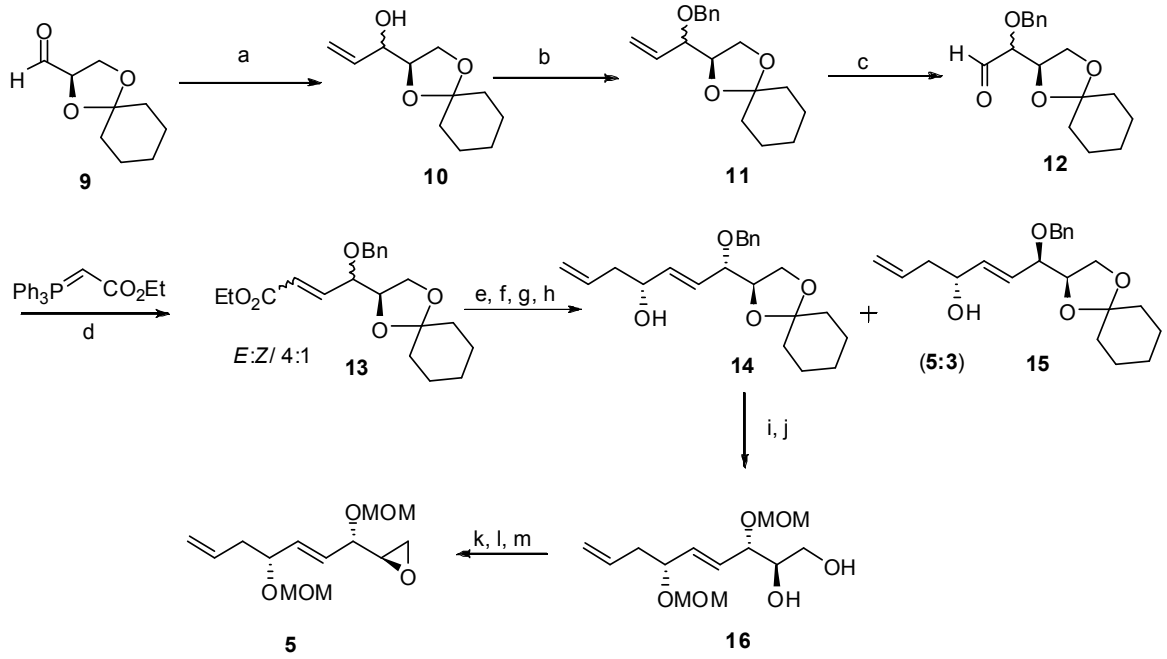
2.2.2a. Retrosynthesis:



Scheme 14: Retrosynthetic analysis

2.3.1b. Synthesis:

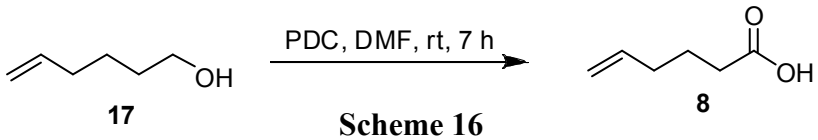
The synthesis of the C-6–C-13 segment **5** of **3** is summarized in Scheme 5. 2,3-Di-*O*-cyclohexylidene-(*R*)-(+)-glyceraldehyde **9** was treated with vinylmagnesium bromide to give **10** as an inseparable 5:3 diastereomeric mixture. Protection of the hydroxy group at C-11 in **10** as benzyl ether yielded **11**, which was subjected to oxidative cleavage of terminal olefin followed by Wittig reaction to provide a 4:1 (*E*:*Z*) mixture of ester **13**. Reduction of ester **13** with DIBAL-*H* gave alcohol, which was oxidized with Dess–Martin periodinane and then subjected to Yamamoto's silver-catalyzed asymmetric allylation to give a 5:3:2 mixture of **14**, **15** and *Z* isomers, respectively. At this stage, alcohols **14** and **15** were separated by silica gel column chromatography. Removal of benzyl group in **14** followed by protection of hydroxy groups provided MOM ether, which was treated with *p*-TsOH.H_2O to afford diol **16**. Selective mesylation of diol **16** followed by treatment with K_2CO_3 in MeOH provided the C-6–C-13 segment **5** (scheme 15).



Scheme 15

Reagents and conditions: a) THF,0 ^oC, 40 min, 60%, b) BnBr, NaH, DMF, 50 ^oC, 1 h, c) OsO_4, dioxane:H_2O/ 3:1, d) CH_2Cl_2, rt, e) DIBAL-*H*, CH_2Cl_2, –40 ^oC, f) DMP, CH_2Cl_2, rt, g) Allyltrimethoxy silane, AgF, h) (*R*)-*p*-Tol- BINAP, MeOH, –20 ^oC, i)Na, Liq-NH_3, –78 ^oC j) MOMCl, iPr_2NEt, CH_2Cl_2, rt, k) *p*-TSOH.H_2O, MeOH, l) MsCl, pyridine, 0 ^oC, m) K_3CO_3, MeOH.

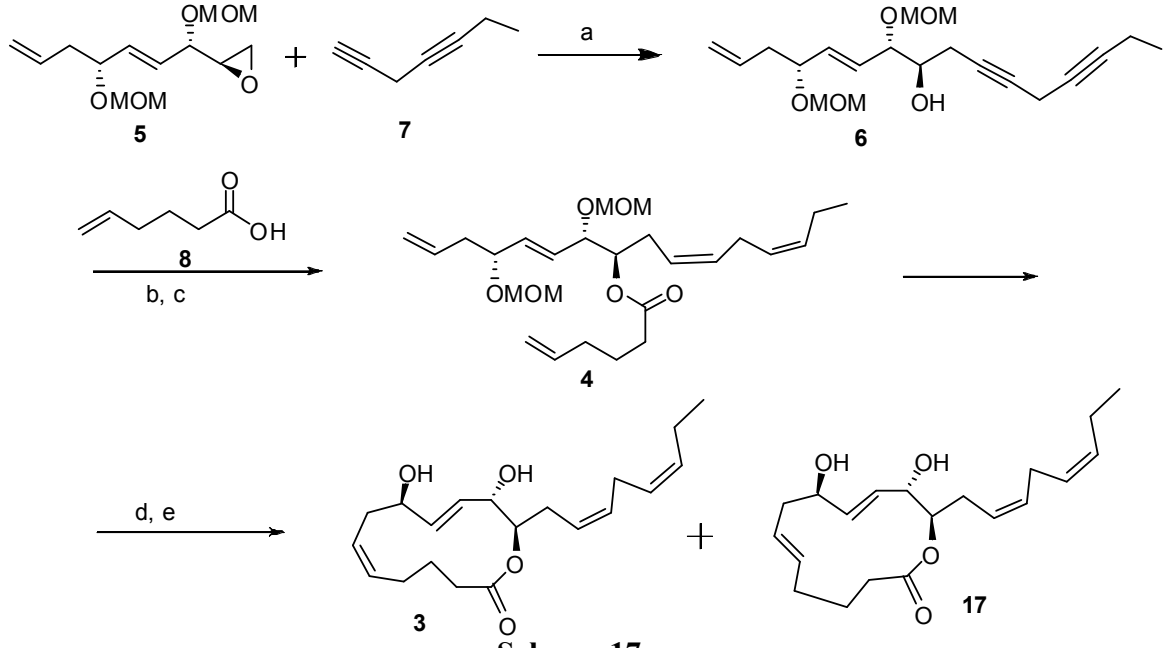
The synthesis of the C-1–C-5 segment **8** is summarized in Scheme 16. Commercially available alcohol **17** was treated with PDC in DMF to provide the C-1–C-5 segment **8**. Known acetylene **7** and the C-6–C-13 segment **5** in hand, they turned to alkynylation of oxirane under Yamaguchi condition (Scheme 17). Coupling of **25** with known acetylene 1**6** using *n*-BuLi and $BF_3.OEt_2$ provided the alcohol **6**. Reduction of **6** with hydrogen and Lindlar's catalyst followed by esterification with the resulted alcohol and acid **8** using 1-ethyl-3-(dimethylaminopropyl)carbodiimide (EDC) gave ester **4**.



17 **8**

Scheme 16

The ester was subjected to RCM by using Grubbs' first-generation catalyst followed by removal of MOM groups to furnish Amphidinolactone A (**3**). The synthetic material was spectroscopically (IR, ^{1}H and ^{13}C NMR, HRMS) identical with natural product. Thus, the absolute stereochemistry of Amphidinolactone A (**3**) was established as 8*R*, 11*S* and 12*R*.



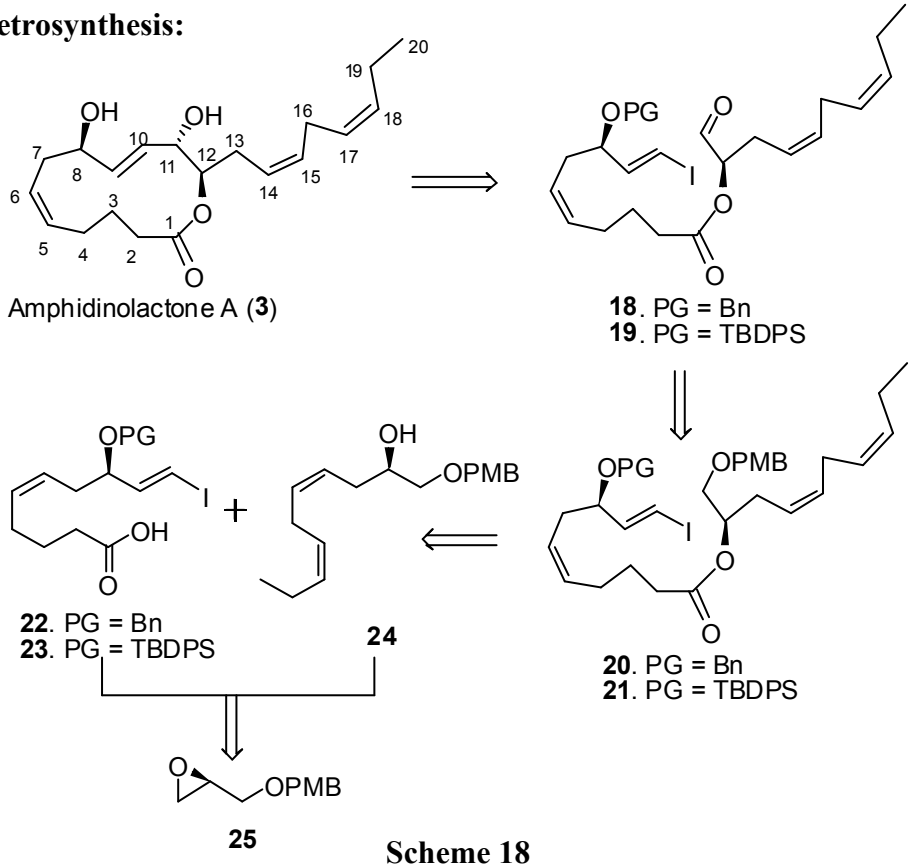
Scheme 17

Reagents and conditions: a) *n*-BuLi, $BF_3.OEt_2$, –78 ^oC, 20 min, b) H_2, Lindlar's Pd-cat, quinoline, c) 4, EDC, CH_2Cl_2, rt, d) Grubbs Ist gereration catalyst, e) *p*-$TsOH.H_2O$, MeOH, 0 ^oC.

2.3.2. Mohapatra's Approach: [37]

Mohapatra *et al.* reported a concise and efficient total synthesis Amphidinolactone via a protecting group directed stereoselective intramolecular Nozaki-Hiyama-Kishi (NHK) reaction for macrocyclization.

2.3.2a. Retrosynthesis:

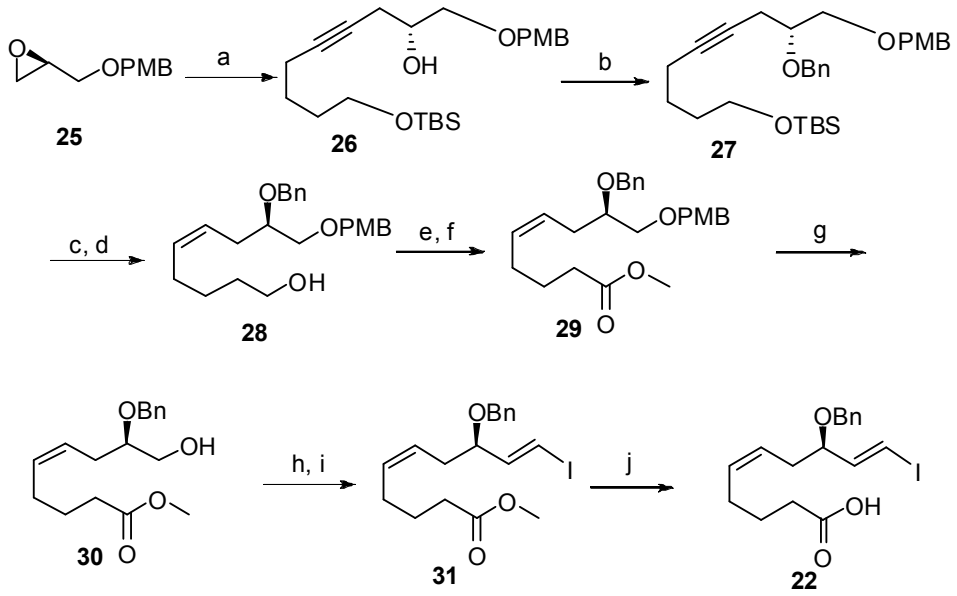


Scheme 18

2.3.2b. Synthesis:

Synthesis of fragment **22** was initiated starting from a known chiral epoxide **25** which was prepared by using Jacobsen's hydrolytic kinetic resolution protocol. The epoxide **25** underwent clean addition of lithium acetylide prepared from TBS-protected alkyne by treatment with *n*-BuLi in THF at −78 ^{o}C and the resulting secondary hydroxyl group was protected as its benzyl ether with NaH and benzyl bromide at 0 ^{o}C to afford **27** followed by deprotection of the silyl group with *p*-TsOH in MeOH at room temperature followed by Lindlar-catalyzed partial hydrogenation[6] afforded the *Z*-olefin derivative **28** (Scheme 19). Oxidation of the resulting hydroxyl group with TEMPO and BAIB followed by further Pinnick oxidation with $NaClO_2$ in presence of 2-methyl-2-butene afforded acid which on treatment with CH_2N_2 in ether at 0 ^{o}C gave ester **29**. Deprotection of the PMB

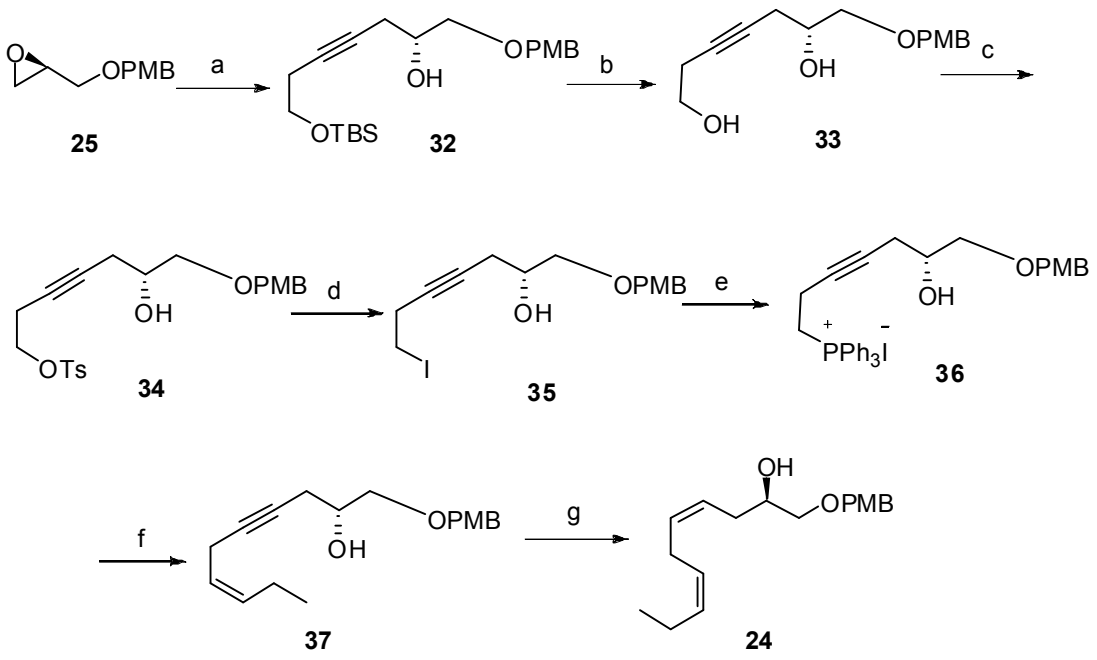
group with DDQ in CH_2Cl_2:H_2O (19:1) at room temperature gave alcohol **30** which on Dess-Martin periodinane oxidation followed by Takai olefination afforded the *trans*-vinyl iodide **31** as the only product. Saponification of the ester functionality with LiOH in THF:H_2O (3:2) afforded the required acid fragment **22**.



Scheme 19

Reagents and conditions: (a) *n*-BuLi, $BF_3.(OEt)_2$, hexyne derivative, −78 ^oC, 1 h, 89%; (b) NaH, BnBr, 0 ^oC-rt, 5 h, 90%; (c) *p*-TsOH, MeOH, 0 ^oC-rt, 1 h, 91%; (d) H_2, Pd/C on $CaCO_3$, quinoline, rt, 2 h, 95%; (e) TEMPO, BAIB, CH_2Cl_2, rt; (f) (1) $NaClO_2$, NaH_2PO_4, *t*-BuOH, H_2O, 2-methyl 2-butene, rt, 3 h, 85% over two steps; (2) CH_2N_2, ether, 0 ^oC-rt, 10 min, 96%; (g) DDQ, CH_2Cl_2:H_2O (9:1), rt, 2 h, 89%; (h) DMP, CH_2Cl_2, $NaHCO_3$, rt, 3 h,92%; (i) $CrCl_2$, CHI_3, THF, 16 h, 82%: (j) LiOH, THF:H_2O (3:1), rt, 3 h, 91%.

The chiral epoxide **25** on treatment with lithium acetylide followed by deprotection of the TBS-ether linkage with *p*-TsOH in MeOH afforded **33**. The primary hydroxyl group of **33** was converted to iodide **35** via tosylation and treatment of the tosylate derivative with NaI in acetone. The Wittig salt **36** was prepared by treating **35** with triphenylphosphine in acetonitrile under reflux conditions (Scheme 20). *Cis*-geometry at C17-C18 was then introduced by performing Wittig reaction of **36** with *n*-propanal by generating *in situ* ylide with *n*-BuLi at −78 ^oC to obtain **37** as the only product followed by partial hydrogenation using Lindlar's catalyst (Pd on $CaCO_3$) in presence of quinoline (catalytic) afforded alcohol **24**.

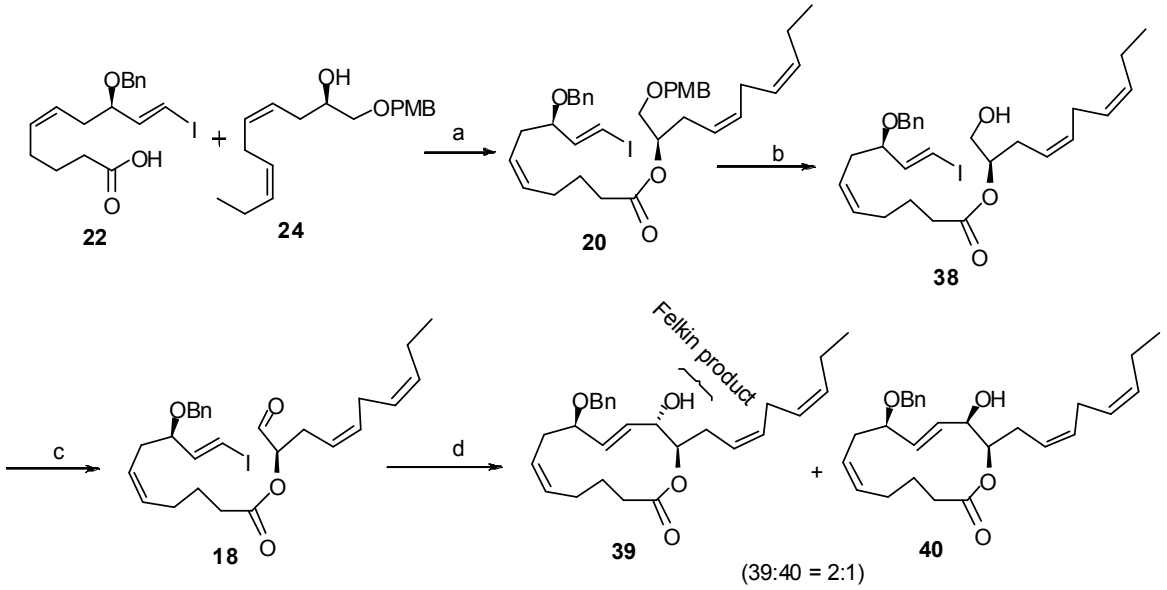


Scheme 20

Reagents and conditions: (a) *n*-BuLi, $BF_3.(OEt)_2$, alkyne derive., −78 ^oC, 1 h, 86%; (b) *p*-TsOH, MeOH, 0 ^oC-rt, 1 h, 94%; (c) TsCl, Et_3N, CH_2Cl_2, 0 ^oC, 6 h, 80%; (d) NaI, acetone, reflux, 3 h, 90%; (e) TPP, CH_3CN, 100 ^oC, 12 h, 94%; (f) *n*-BuLi, propionaldehyde, −78 ^oC, 4 h, 83%; (g) H_2, Pd/C on $CaCO_3$, quinoline (catalytic), benzene, rt, 3 h, 91%.

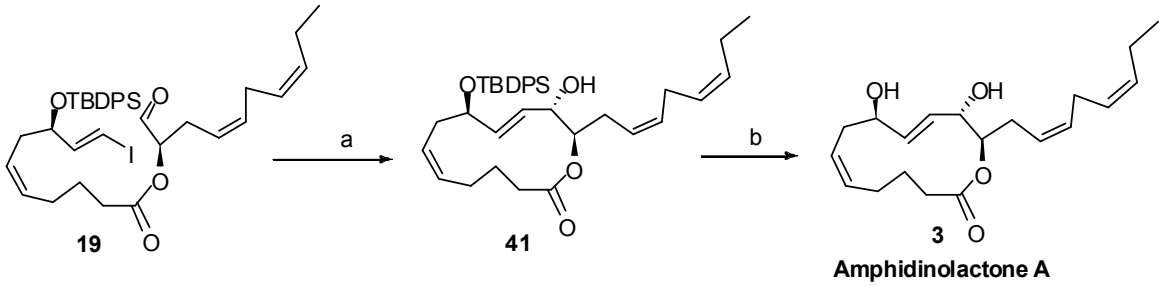
The coupling of fragment **22** and fragment **24** was achieved under Yamaguchi conditions to obtain the ester **20**, which contains all 20-carbons of the target molecule (Scheme 20). Deprotection of the PMB ether in **20** upon treatment with DDQ afforded alcohol **38** and a subsequen**t** Dess-Martin periodinane oxidation of **38** gave the required aldehyde **18**. The critical macrocyclization of **18** via Nozaki-Hiyama-Kishi coupling reaction was performed in DMSO and THF (3:1) mixture, high yield was obtained although the reaction took about 24 h to completely consume the starting material to afford a 2:1 mixture of inseparable diastereomeric allylic alcohols **39** and **40**.

To obtain a single isomer, the OBn protecting group was replaced by OTBDPS group and followed same sequence of reactions as illustrated above. Then, the critical macro-cyclization of **19** via Nozaki-Hiyama-Kishi coupling reaction was performed to afford the required isomer as a only product as **41**. Finally, deprotection of the TBDPS ether linkage with TBAF and acetic acid afforded the target natural product amphidinolactone A (**3**).



Scheme 21

Reagents and conditions: (a) (i) DCC, DMAP, CH_2Cl_2, 0 ^oC-rt, 12 h, 58%; (ii) EDCI, DMAP, CH_2Cl_2, 0 ^oC-rt, 12 h, 70%; (iii) 2,4,6-trichlorobenzoyl chloride, DMAP, THF, toluene, rt, 6 h, 89%; (b) DDQ, CH_2Cl_2:H_2O (9:1), rt, 3 h, 91%; (c) DMP, CH_2Cl_2, rt, 4 h; (d) $CrCl_2$, $NiCl_2$, DMSO:THF (3:1), rt, 24 h, 81% over two steps.



Scheme 22

Reagents and conditions: (a) $CrCl_2$, $NiCl_2$, DMSO, rt, 24 h, 85% over two steps; (b) TBAF, AcOH, THF, 0 ^oC-rt, 18 h, 87%.

A convergent total synthesis of amphidinolactone A is described in 13 longest linear steps in 22% overall yield involving macrolactonization using intramolecular Nozaki-Hiyama-Kishi (NHK) reaction for the construction of 13-membered lactone ring.

CHAPTER II

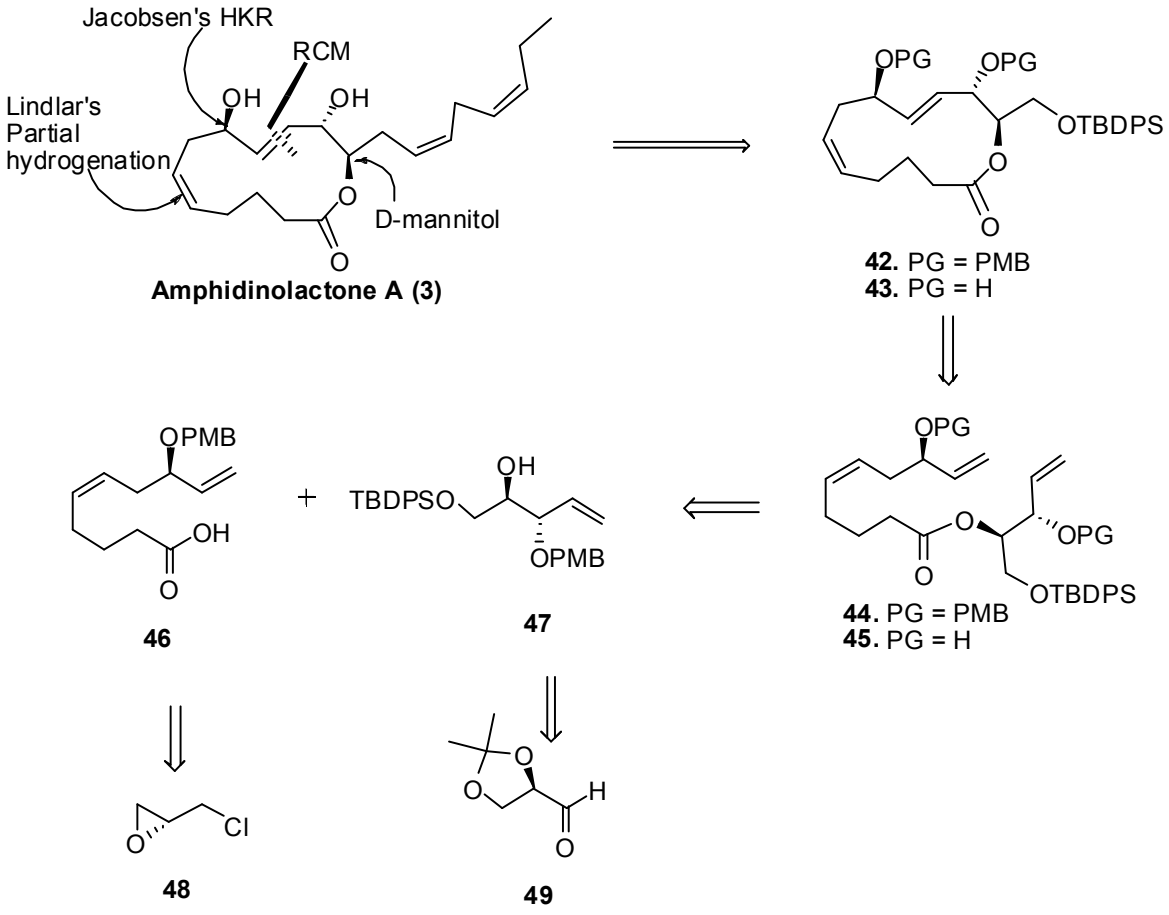
Section B

Synthesis of the macrolactone Core of Amphidinolactone A

2.4. Present Work:

The interesting biological profile as well as the structural complexity of amphidinolactone A (**3**) has attracted the attention of synthetic organic chemists worldwide. Herein, we provide a complete account of our synthetic studies. We envisioned a convergent synthesis of macrolactone core of amphidinolactone A and we expected that this synthetic strategy would provide a highly stereoselective route to amphidinolactone A (**3**). Moreover, the synthetic protocol could sort out all the selectivity problems faced by Kobayashi et al. during the total synthesis.

2.4.1. Retrosynthesis



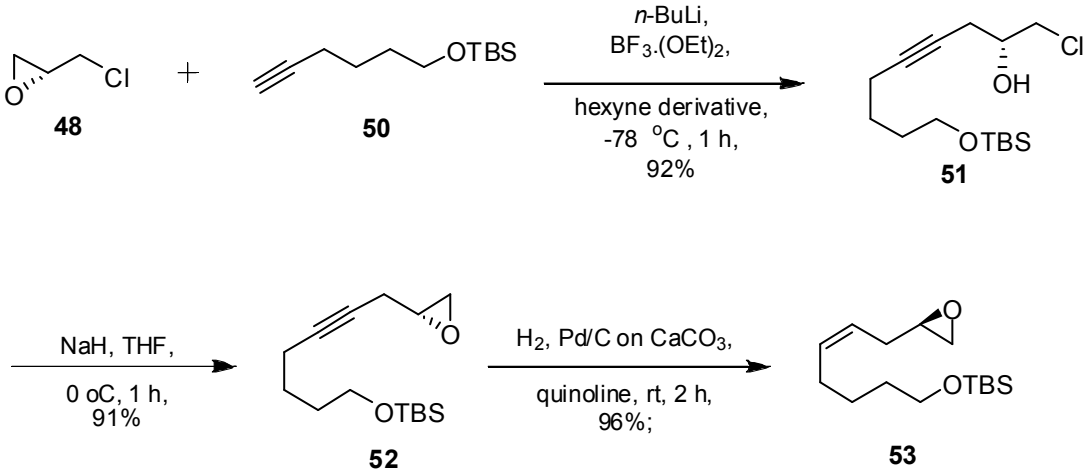
Scheme 23

According to our retrosynthetic analysis of amphidinolactone A (**3**) shown in Scheme 23, **43** could be achieved through ring-closing metathesis reaction of **45** which in turn could be obtained by coupling of acid fragment **46** and alcohol fragment **47**. Acid fragment **46** and alcohol fragment **47** could be obtained from (*R*)-epichlorohydrin **48** and (*R*)-2,3-*O*-isopropylidene glyceraldehyde **49**, respectively. The crucial reactions involved in the synthesis of the individual fragments are Jocobsen's hydrolytic kinetic resolution, Sharpless asymmetric epoxidation, Lindlar's hydrogenation, Ring closing metathesis and Yamaguchi esterification.

2.4.2 Results and Discussions:

Synthesis of the fragment 46:

Chiral epoxide **48** prepared by following Jacobsen's hydrolytic kinetic resolution protocol,[38] was taken as the starting material for the synthesis of acid fragment **46.** The racemic epoxide was subjected to solvent free hydrolytic kinetic resolution employing 0.55 eq of water in the presence of 0.005 mol% of (*S,S'*)-(−)-*N*-*N*'-bis-(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino-cobalt(II) to afford the chiral epoxide **48** in 45% yield along with the chiral diol. The epoxide **48** was opened with lithium acetylide prepared from TBS-protected alkyne **50** using *n*-BuLi, $BF_3.OEt_2$ in THF in THF at −78 ^oC to afford the secondary hydroxyl compound **51** in 92% yield[39] (Scheme 24). The product **51** formation was confirmed by ^1H NMR which showed two singlet at δ 9.1 and 0.05 ppm, characteristics of TBS group. ^{13}C NMR also showed resonance characteristics

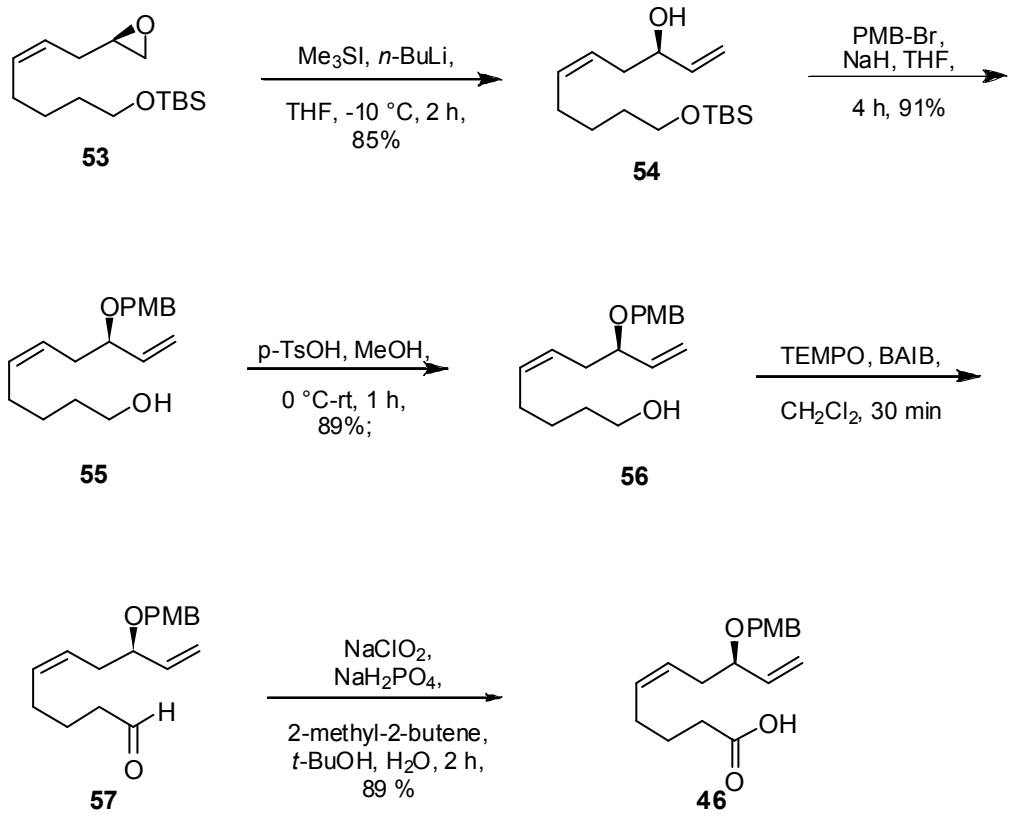


Scheme 24

peak for triple bond carbons at δ 83.6 and 74.6 ppm. Product formation was further confirmed by its ESI-HRMS which showed a peak at m/z 327.1509 $[M + Na]^+$ and a broad peak at 3416 cm^{-1} due the presence of hydroxyl group in IR. The epoxidation of the resulting homopropagyl alcohol **51** proceeded smoothly with NaH in THF at 0 ^oC to obtain the epoxy compound **52** in 91% yield. The epoxy compound **52** was confirmed by it ^1H NMR spectrum, which showed resonance at δ 3.62, 3.07, 2.78 ppm as multiplates for three oxirane protons. Absence of hydroxyl functionality was also confirmed by IR spectrum, which showed no absorption band for hydroxyl functionality. Partial hydrogenation was taken place by treating with Lindlar's catalyst[40] in presence of catalytic amount of quinoline under hydrogen atmosphere to afford **53** with the required *Z* olefin in 96% yield. The appearance of two multiplet for double bond at δ 5.53 and 5.41 ppm in ^1H NMR and two new peaks at δ 132.9, 123.2 ppm and disappearance of two alkyne peaks at δ 83.6 and 74.6 ppm in ^{13}C NMR confirmed the transformation to a Z-olefin. The compound was characterized by ESI-HRMS which showed $(M + Na)^+$ peak at *m/z* 293.1893.

One-carbon homologation[41] with trimethyl sulfonium iodide and *n*-BuLi in THF at −10 ^oC afforded the allylic alcohol **54** in 85% yield. The terminal three olefinic protons of the product resonated as a multiplet at δ 5.85, 5.22, 5.09 ppm where as the allylic oxygen attached proton resonated at δ 4.11 ppm as a quartet in ^1H NMR. ^{13}C NMR revealed two new peaks at δ 140.5, 114.5 ppm for olefinic carbons whereas peak at *m/z* 307.2051 $[M + Na]^+$ in ESI-HRMS spectrum further confirmed this transformation. The newly formed secondary hydroxyl group was protected as its PMB ether **55** by treating with NaH, PMBBr in 91% yield. The ^1H NMR of **55** revealed two new peaks as doublet at δ 7.21, 6.82 ppm for aromatic group and ABq pattern at δ 4.37 (J = 11.3 Hz) ppm for the two benzylic protons. Next, TBS group was deprotected using *p*-TsOH (cat.) in MeOH to afford the primary alcohol **56** with 89% yield (scheme 25). The structure was confirmed by its ^1H NMR study which showed the absence of TBS protons and carbon peaks at δ 5.3 for TBS in ^{13}C NMR. IR spectrum of compound **56** disclosed the absorption band at 3406 cm^{-1} and ESIMS showed $(M + H)^+$ peak at *m/z* 313.1794 clearly indicating the absence TBS ether. Treatment of the resulted primary hydroxyl compound **56** with BAIB and TEMPO[42] in DCM produced aldehyde **57** which was quickly purified by flash column

chromatography and directly subjected to Pinnick oxidation[43] by $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene in *t*-BuOH:H_2O to convert to acid **46** in 89% yield (over two steps). The disappearance of two protons in ^1H NMR at δ 3.58 ppm region and appearance of two extra protons (*α* to the acid) at δ 2.31 ppm as multiplate confirmed the conversion. The mass spectroscopy showed $(M + Na)^+$ peak at *m/z* 327.1182.



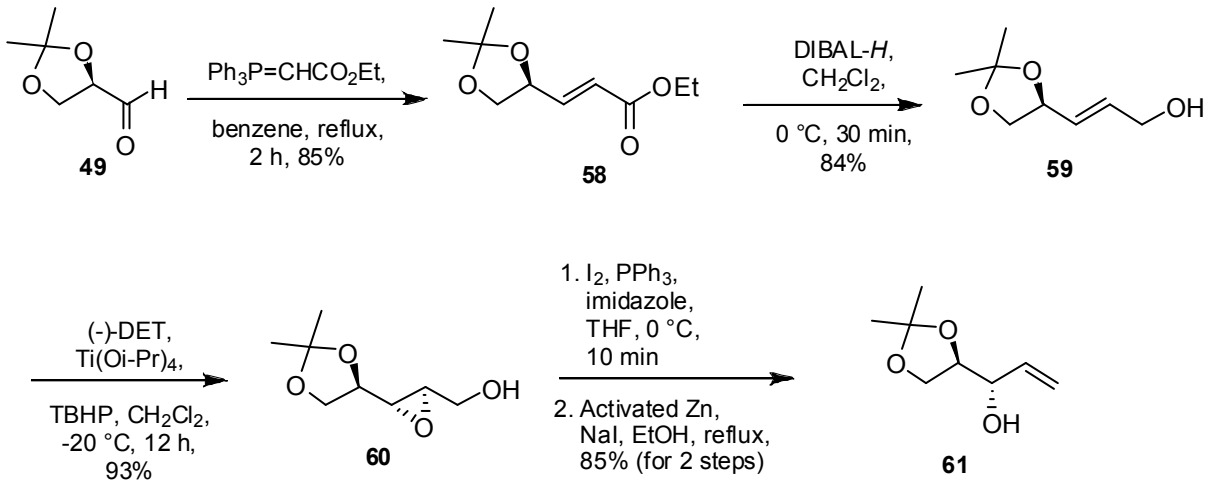
Scheme 25

Its 1710 cm^{-1} peak in IR spectrum and δ 179.3 ppm peak in ^{13}C NMR spectrum provided additional proof in favor of acid formation.

Synthesis of the alcohol fragment 4:

Synthesis of fragment **47** was commenced with two-carbon homologation of the known aldehyde (*R*)-2, 3-*O*-isopropylidene glyceraldehyde (**49**) to give *α,β*-unsaturated ester **58** in 85% yield. The ester was converted to the corresponding *E*-allylic alcohol **59** by using DIBAL-*H* set the platform for introducing two more chiral centers via Sharpless

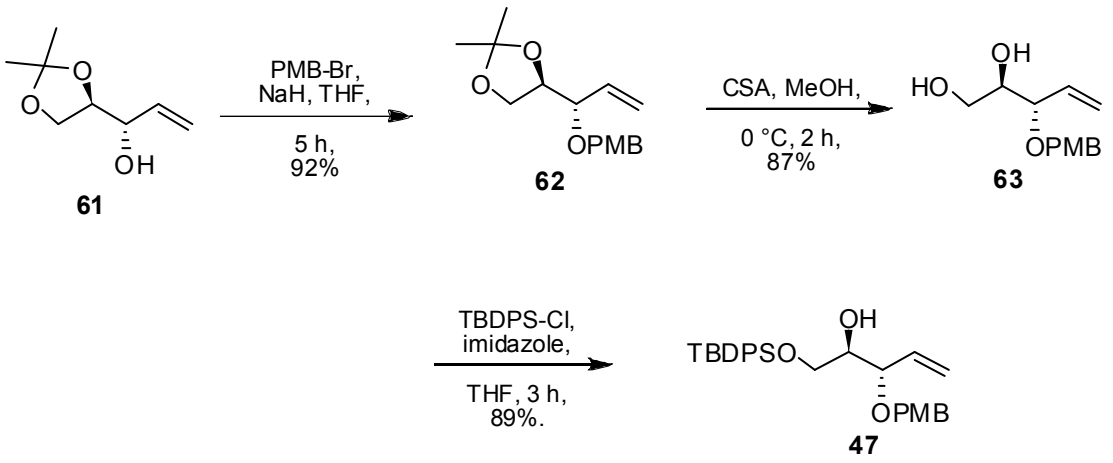
asymmetric epoxidation.[44] Thus the allyl alcohol **59** on treatment with (–)-DET, titanium(IV)isopropoxide and *tert*-butyl hydroperoxide in dichloromethane in anhydrous condition at -20 ^{o}C to yield epoxy alcohol **60** in 92% yield (94:6 ratio with the required isomer as the major product) (Scheme 26). The structure was confirmed by its ^{1}H NMR study which showed the absence of olefinic protons and the presence of two oxirane protons at 3.14-3.07 ppm as multiplets and methylene protons adjacent to hydroxyl group with an upfield shift at 4.02-3.84 ppm as a multiplet (versus 4.14 ppm for allyl alcohol). The epoxy alcohol was transformed to its iodo derivative (Scheme 14) by standard I_2, TPP, imidazole protocol and the iodo derivative immediately used for next



Scheme 26

step without further charecterisation. When the iodo derivative was treated with activated Zn dust and NaI in refluxing MeOH, reductive epoxide ring opening[45] took place to produce the allyl alcohol **61**. The geminal protons of the olefin resonated as a set of singlets at δ 5.0 and 4.83 ppm, while two olefenic carbons resonated at δ 110.7 and 145.5 ppm. A peak at *m/z* [M + H]+ 423 further confirmed the product. The resulting secondary hydroxyl group of **61** was protected as its PMB ether by using PBB bromide and sodium hydride in THF at 0 ^{o}C to obtain **62** in 92% yield. Its ^{1}H NMR revealed two doublets at δ 7.21 (J = 8.7 Hz), 6.80 (J = 8.7 Hz) ppm for aromatic protons of PMB group along with the other required protons. ^{13}C NMR revealed two new peaks at δ 133.1, 123.9 for olefenic carbons and three new peaks at δ 20.4, 17.0, 13.9 ppm for aliphatic carbons

whereas peak at *m/z* 311.1628 $[M + Na]^+$ in HRMS spectrum further confirmed this transformation. Then, deprotection of the isopropylidene group with *p*-TsOH in MeOH[46] at room temperature afforded diol **63** in 87% yield. Its ^1H NMR revealed the absence of a set of two doublets at δ 1.36, 1.31 ppm, and a broad singlet at δ 4.36 ppm for two hydroxyl protons. In IR spectroscopy a broad peak at 3409 cm^{-1} and a peak at *m/z* 261.1115 $[M+Na]^+$ in ESI-HRMS spectrum was an additional proof in the favor of formation of diol. The primary hydroxyl group of the diol **63** (Scheme 27) was selectively protected as its TBDPS ether **47** by TBDPSCl, imidazole in DCM at 0 °C with 89%



Scheme 27

yield. In ^1H NMR, the two phenyl group of TBDPS resonated as a set of two multiplets at δ 7.68-7.61 ppm integarting for four protons and δ 7.46-7.32 ppm integrating for six protons where as the nine protons of *t*-Butyl group resonated as a singlet at δ 1.05 ppm and the ^{13}C NMR spectra were in full accord with the incorporation of TBDPS group. A peak at *m/z* [M + H]+ 499.2275 thus confirmed the formation of the alcohol fragment **47**.

Coupling of fragment 46 and 47:

Our next target was to couple both the fragments and investigate the critical ring-closing metathesis reaction. As per our investigation in chapter I, we had followed the Yamaguchi conditions[47] for the esterification reaction. In this case, the yield was only 30-35% with complet destruction of the starting matterials. However, a better result was achieved by uniting both the coupling partners with EDCI and DMAP in CH_2Cl_2 to afford the triene ester **44** in 90% yield (Scheme 4).[48] The ^1H NMR and ^{13}C NMR spectra were in full accord with the product where PMB, olefins and other functionalities resonated at

their respective positions. IR absorption showed the absence of characteristic band for hydroxyl functionality whereas a peak at *m/z* 785.3847 $[M + NH_4]^+$ in ESI-HRMS spectrum was confirmed the formation of ester. Now the stage was ready to perform the crucial RCM reaction. The ester **44** was refluxed with Grubbs II generation[49] catalyst in CH_2Cl_2 under high dilution conditions (0.001 M) for 5 h. The reaction was failed to provide the lactone **42**. Again this RCM reaction was kept in different solvent concentrations and exending the time, this attempt also proven unsuccess. The extent of bias if any conferred by the protecting groups on the outcome of the ring-closing metathesis reaction could not be predicted with certainty. We envisaged that PMB-protecting groups around the reacting centers might act as a temporary constraint to adequately come closer for the reaction to happen. This prediction was also supported by computational analysis (Fig. 9) as well as further experimental studies. In order to unravel the observed experimental trends quantum chemical

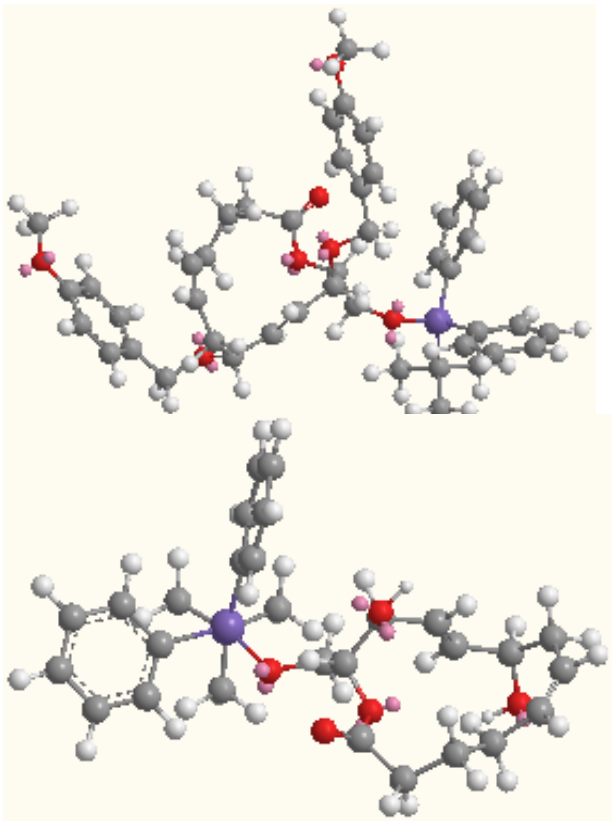
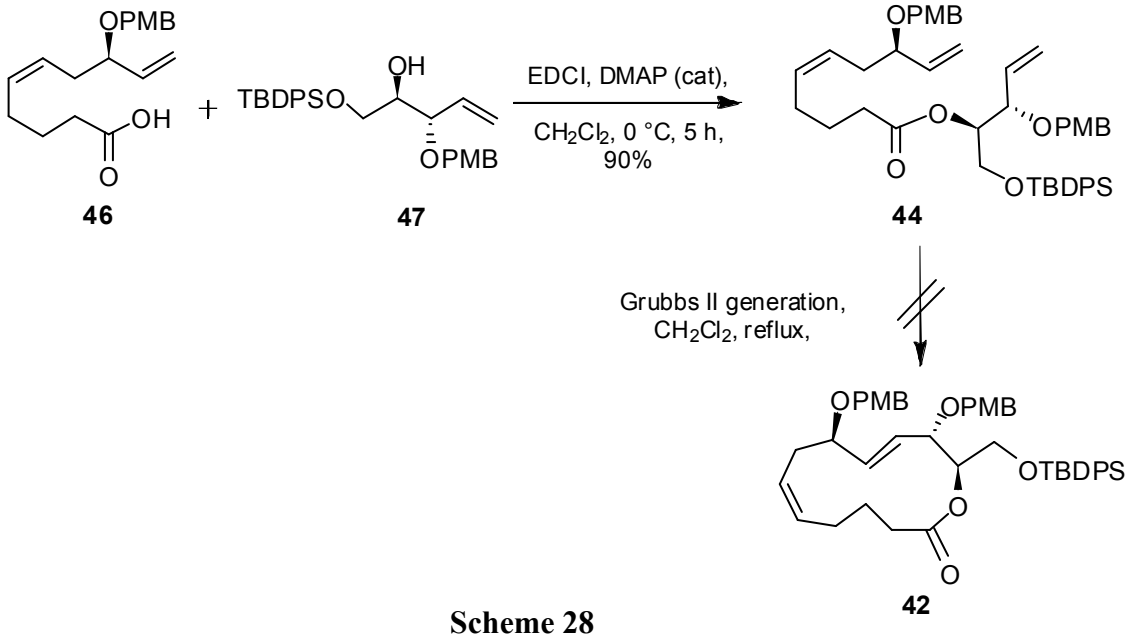


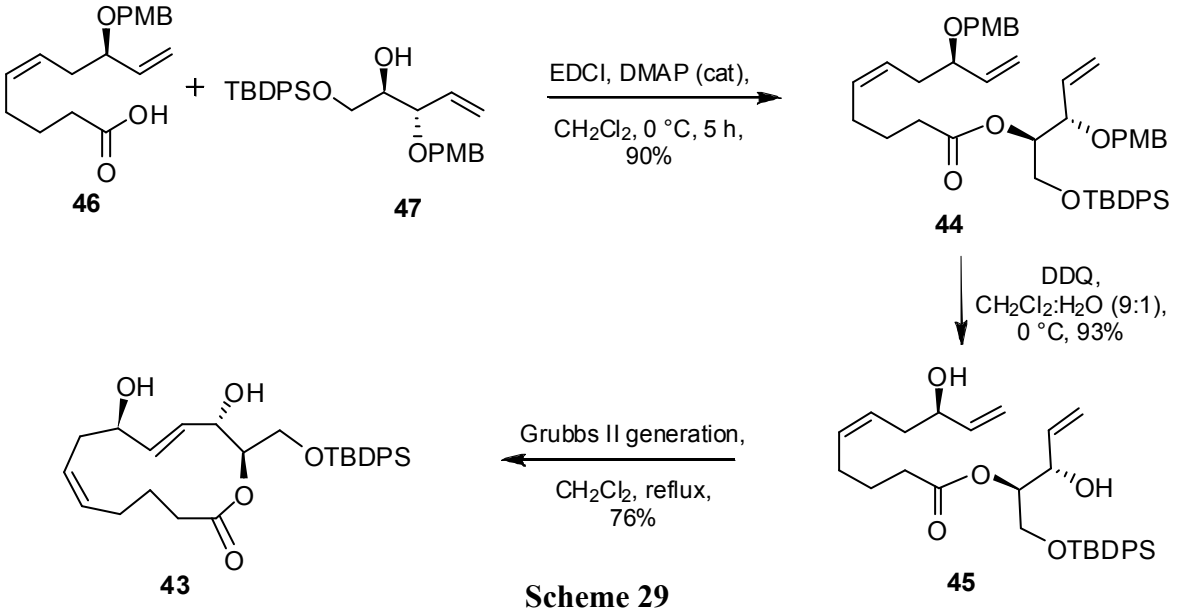
Fig. 9 Minimum energy calculated for di-PMB protected lactone core **2** (44.18 kcal/mol) and diol-lactone **3** (24.71 kcal/mol) of amphidinolactone A.

calculations are carried out on the PMB proctected lactone and PMB deprotected lactone. This trends quantum chemical calculation were revealed that Minimum energy calculation for di-PMB protected lactone core **42** was found 44.18 kcal/mol and diol-lactone **43** was found 24.71 kcal/mol of amphidinolactone A (**3**). To further prove our predictions, di-PMB protected ester **44** was treated with DDQ[50] in CH_2Cl_2:H_2O (9:1) to obtain diol **--** in 93% yield (Scheme 28). Its ^{1}H NMR revealed the absence of a set of two doublets at δ 7.20, 6.83 ppm, a peak at δ 4.43 ppm for two benzylic protons and a singlet at δ 3.79 ppm for three methoxy protons of PMB group. A peak at *m/z* 723.2354 $[M + Na]^+$ in ESI-HRMS spectrum and a very big peak at 3445 cm^{-1} revealed the deprotection of PMB group. Treatment of diol **45** with Grubbs II generation catalyst[18] in refluxing CH_2Cl_2 under high dilution (0.001 M) conditions smoothly furnished the



Scheme 28

required 13-membered lactone ring system **43** present in amphidinolactone A (**3**) in 76% yield. Geometry (*trans*) of the newly formed double bond was established by its coupling constant, while one of the olefinic proton signals appeared at δ 5.66 ppm as a doublet of a doublet (J_{trans} coupling constant 15.7 Hz) and other olefinic proton signals appeared at their respective chemical shifts. The ^{13}C NMR data were in good agreement with the constitution and configuration of the assigned structure for **43**. Along with above data, a peak at *m/z* 517.2400 $[M + Na]^+$ in ESI-HRMS spectrum was given additional support for the formation of 13 membered lactone (scheme 29).



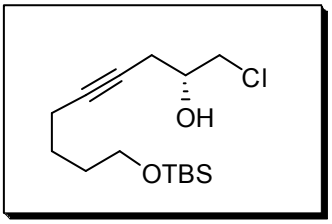
Scheme 29

Thus, a convergent synthesis of macrolactone core of amphidinolactone A has been achieved through ring-closing metathesis reaction as the macrolactonization step. The RCM precursor was obtained by the union of acid and alcohol fragments derived from (*R*)-epichlorohydrin and (*R*)-2,3-*O*-isopropylidene glyceraldehyde, respectively.

Experimental Section

2.5. EXPERIMENTAL SECTION

2.5.1. ((*R*)-9-(*tert*-Butyldimethylsilyloxy)-1-chlorononon-4-yn-2-ol (51).



A flame-dried 250 mLtwo necked round bottom flask was charged with TBS protected 5-hexyne 1-ol **50** (3.0 g, 14.12 mmol) in THF (100 mL) and cooled to −78 °C. To this solution, *n*-BuLi (2.5M in hexanes, 5.64 mL, 14.12 mmol) was added drop-wise via syringe, warmed slowly to 0 °C. During this period, the reaction mixture turned to dark red in color. After 30 min, (*R*)-epichlorohydrin **48** (1.1 g, 11.29 mmol) was slowly added followed by $BF_3.OEt_2$ (1.43 mL, 11.29 mmol) at −78 °C and stirred for an additional 30 min. The reaction was then quenched with saturated $NaHCO_3$ (50 mL), diluted with ethyl acetate (50 mL), and warmed to room temperature. The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 x 60 mL). The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash column chromatography (ethyl acetate/hexane = 1:19) provided the desired secondary alcohol **51** (3.96 g, 92%) as a colorless oil.

$[\alpha]_D^{25}$: –5.0 (*c* 0.9, $CHCl_3$);

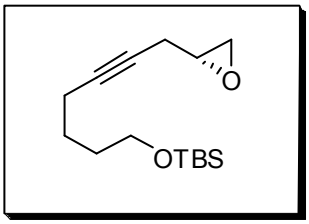
IR (neat, KBr) : ν_{max} 3074, 2932, 2854, 2837, 1613, 1513, 1464, 1248, 1094, 1036, 915, 821 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) : δ 3.93 (m, 1 H), 3.73-3.56 (m, 4 H), 2.55-2.48 (m, 2H), 2.32-2.15 (m, 2 H), 1.65-1.50 (m, 4 H), 0.91 (s, 9 H), 0.05 (s, 6 H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) : δ 83.6, 74.6, 70.0, 62.6, 48.3, 31.9, 25.9, 25.3, 24.7, 18.5, 18.3, −5.3ppm;

ESI-HRMS : *m/z* calcd for $C_{15}H_{29}ClNaO_2Si$ [M + Na]+ 327.1518; found 327.1509.

2.5.2. (*R*)-*tert*-Butyldimethyl-(7-(oxiran-2-yl)hept-5-ynyloxy)silane (52).



To a suspension of NaH (0.69 g, 28.78 mmol, 60% w/v dispersion in mineral oil) in dry THF (25 mL), was added dropwise a solution of chlorohydrins **51** (3.5 g, 11.51 mmol) in dry THF (50 mL) under N_2 atmosphere at 0 ^oC. The reaction mixture was allowed to stir at room temperature for 30 min. After completion of the reaction (monitored by TLC), it was quenched with ice cold water (50 mL) at 0 ^oC. The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. The crude mass was purified by silica gel chromatography (ethyl acetate/hexane = 1:49) to afford the epoxide **52** (2.70 g, 91%) as a light yellow liquid.

$[\alpha]_D^{25}$: –9.2 (*c* 0.8, $CHCl_3$);

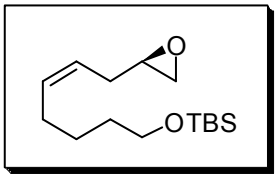
IR (neat, KBr) : ν_{max} 3051, 2933, 2859, 1741, 1613, 1467, 1392, 1252, 1102, 996, 838, 776 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) : δ 3.62 (t, *J* = 5.8 Hz, 2 H), 3.07 (m, 1 H), 2.78 (t, *J* = 4.7 Hz, 1 H), 2.65 (m, 1 H), 2.57 (m, 1 H), 2.44 (m, 1 H), 2.23-2.14 (m, 2 H), 1.70-1.48 (m, 4 H), 0.9 (s, 9 H), 0.05 (s, H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) : δ 82.5, 74.2, 62.7, 50.3, 46.4, 31.9, 25.9, 25.2, 22.5, 18.5, 18.3, −5.3ppm;

ESI-HRMS : *m/z* calcd for $C_{15}H_{28}NaO_2Si$ [M + Na]+ 291.1751; found 291.1739.

2.5.3. (*R*,*Z*)-*tert*-Butyldimethyl-(7-(oxiran-2-yl)hept-5-enyloxy)silane (53).

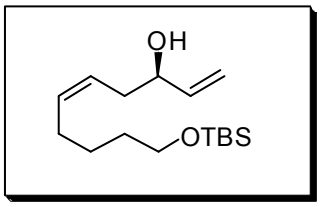


Lindlar catalyst (Pd/C on $CaCO_3$,) (10 mol%) was added to a stirred solution of alkyne **52** (2.5 g, 9.32 mmol)) in benzene (10 mL) followed by catalytic amount of quinoline (0.02 mL, 0.093 mmol) at room temperature under hydrogen atmosphere. The mixture

was vigorously stirred for 3 h at room temperature. After complete consumption of the starting material (monitored by TLC), the black reaction mass was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and purification of the crude product by silica gel column chromatography (ethyl acetate/hexane = 1:49) to yield the desired *Z*olefin **53** (2.41 g, 96%).

$[\alpha]_D^{25}$	: –5.5 (*c* 1.35, $CHCl_3$);
IR (neat, KBr)	: ν_{max} 2932, 2858, 1742, 1467, 1389, 1253, 1101, 836, 775 cm^{-1};
^1H NMR (300 MHz, $CDCl_3$)	: δ 5.53 (m, 1 H), 5.41 (m, 1 H), 3.62 (t, *J* = 6.4Hz, 2 H), 2.95 (m, 1 H), 2.74 (t, *J* = 4.5 Hz, 1 H), 2.51 (m, 1 H), 2.38 (m, 1 H), 2.26 (m, 1H), 2.06 (q, *J* = 7.2 Hz, 2 H), 1.58-1.47 (m, 2 H), 1.46-1.35 (m, 2 H), 0.89 (s, 9 H), 0.05(s, 6 H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$)	: δ 132.9, 123.2, 63.0, 51.6, 46.5, 32.4, 30.1, 27.1, 25.9, 25.8, 18.3, −5.3 ppm;
ESI-HRMS	: *m/z* calcd for $C_{15}H_{30}NaO_2Si$ [M + Na]+ 293.1907; found 293.1893.

2.5.4. (*R*,*Z*)-10-(*tert*-Butyldimethylsilyloxy)deca-1,5-dien-3-ol (54).



To a stirred solution of trimethylsulfonium iodide (predried by azeotropic method using dry toluene) (4.53 g, 22.2 mmol) in THF (30 mL) was cooled to −20 °C, added *n*-BuLi (7.4 mL, 2.5M in hexane, 18.5 mmol) and stirred for 30 min. After stirring the reaction mixture for 30 min at −20 °C, the epoxide **53** (2.0 g, 7.4 mmol) in THF (20 mL) was added *via* syringe over 20 min at the same temperature. After complete addition, the cooling bath was removed and the reaction mixture was allowed to warm to room temperature over 30 min. After stirring at room temperature for 2 h, the reaction was quenched with saturated ammonium chloride (40 mL) water and diluted with diethyl ether (60 mL). The organic layer was separated and the aqueous layer extracted with diethyl

ether (2x 50 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane = 1:19) to obtain the secondary allylic alcohol **54** (1.79 g, 85%) as colorless syrup.

$[\alpha]_D^{25}$: +9.7 (*c* 0.8, $CHCl_3$);

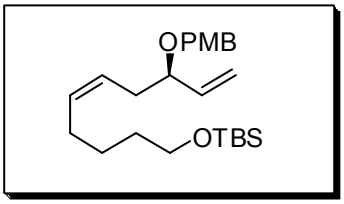
IR (neat, KBr) : ν_{max} 3410, 3011, 2932, 2858, 1466, 1389, 1253, 1101, 837, 775 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) : δ 5.85 (m, 1 H), 5.53 (m, 1 H), 5.37 (m, 1H), 5.22 (d, *J* = 16.8 Hz, 1 H), 5.09 (d, *J* = 10.3 Hz, 1 H), 4.11 (q, *J* = 6.0, 12.2 Hz, 1 H), 3.58 (t, *J* = 6.2 Hz, 2 H), 2.28 (t, *J* = 6.7 Hz, 2 H), 2.12 (q, *J* = 6.9, 13.9 Hz, 2 H), 1.57-1.35 (m, 4 H), 0.88 (s, 9 H), 0.03 (s, 6 H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) : δ 140.5, 133.0, 124.5, 114.5, 72.4, 63.0, 35.0, 32.3, 27.1, 25.9, 18.3, -5.3 ppm;

ESI-HRMS : *m/z* calcd for $C_{16}H_{32}NaO_2Si$ [M + Na]+ 307.2064; found 307.2051.

2.5.5.(*R*,*Z*)-*tert*-Butyl(8-(4-methoxybenzyloxy)deca-5,9-dienyloxy)dimethylsilane (55):



To a suspension of NaH (0.28 g, 7.04 mmol, 60% w/v dispersion in mineral oil) in dry THF (25 mL) was added dropwise a solution of resulting allylic alcohol **54** (1.0 g, 3.52 mmol) at 0 ^oC and continued the stirring for the next 45 min at room temperature. At 0 oC, freshly prepared *p*-methoxy benzyl bromide (0.71 g, 3.52 mmol) was added and stirred further for 4 h at room temperature with frequent monitoring of the progress of the reaction by TLC. The reaction mixture was quenched with crushed ice flakes until a clear solution (biphasic) was formed. The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with water (2 x 70 mL), brine (100 mL), and dried over anhydrous Na_2SO_4. Solvent was

removed under reduced pressure and the crude was purified by column chromatography on silica gel (ethyl acetate/hexane = 1:49) to afford the PMB-ether **55** (1.29 g, 91%) as a colorless liquid.

$[\alpha]_D^{25}$: +11.7 (*c* 1.1, $CHCl_3$);

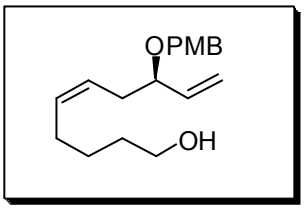
IR (neat, KBr) : ν_{max} 2933, 2857, 1613, 1513, 1464, 1301, 1249, 1174, 1099, 835, 775cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) : δ 7.21 (d, *J* = 9.0 Hz, 2 H), 6.82 (d, *J* = 9.0 Hz, 2 H), 5.73 (m, 1 H), 5.48-5.32 (m, 2 H), 5.24-5.14 (m, 2 H), 4.51 (d, *J* = 11.3 Hz, 1 H), 4.47 (d, *J* = 11.3 Hz, 1 H), 3.79 (s, 3 H), 3.71 (q, *J* = 6.9, 14.5 Hz, 1 H), 3.58 (t, *J* = 6.0 Hz, 2 H), 2.43-2.19 (m, 2 H), 2.08-2.01 (m, 2 H), 1.54-1.30 (m, 4 H), 0.90 (s, 9 H), 0.04 (s, 6 H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) : δ 158.9, 138.6, 131.6, 130.7, 129.1, 125.0, 117.1, 113.6, 80.0, 69.6, 63.0, 55.1, 33.4, 32.4, 27.1, 25.9, −5.3 ppm;

ESI-HRMS : *m/z* calcd for $C_{24}H_{40}NaO_3Si$ [M + Na]+ 427.2639; found 427.2623.

2.5.6. (*R*,*Z*)-8-(4-Methoxybenzyloxy)deca-5,9-dien-1-ol (56).



To a stirred solution of TBS ether **55** (1.0 g, 2.47 mmol) in MeOH (20 mL) was added *p*-TsOH (catalytic) at 0 °C and the resulting solution was stirred for 1 h at ambient temperature. The reaction mixture was quenched with aqueous $NaHCO_3$ (20 mL). MeOH was removed under reduced pressure, the residue extracted with EtOAc (3 x 50 mL), the combined organic layer washed with brine (50 mL), dried over Na_2SO_4, and evaporated to dryness which on silica gel column chromatography (EtOAc/hexane: 1/7) furnished the desired primary alcohol **56** (0.64 g, 89%) as a viscous colorless liquid.

$[\alpha]_D^{25}$: +19.3 (*c* 0.9, $CHCl_3$);

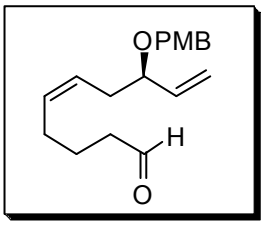
IR (neat, KBr) : ν_{max} 3406, 3074, 2933, 2861, 1612, 1513, 1459, 1301, 1247,1175, 1037, 821,774 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) : δ 7.21 (d, *J* = 8.3 Hz, 2 H), 6.81 (d, *J* = 8.3 Hz, 2 H), 5.72 (m, 1 H), 5.47-5.3 (m, 2 H), 5.24-5.12 (m, 2 H), 4.50 (d, *J* = 11.5 Hz, 1 H), 4.25 (d, *J* = 11.5 Hz, 1 H), 3.78 (s, 3 H), 3.69 (q, *J* = 6.9, 13.9 Hz, 1 H), 3.53 (t, *J* = 6.2 Hz, 2 H), 2.36 (m, 1 H), 2.22 (m, 1 H), 2.08-1.97 (m, 2 H), 1.56-1.32 (m, 4 H) ppm;

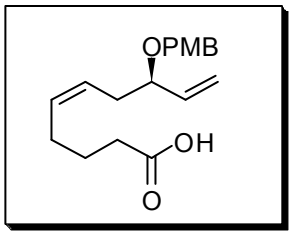
^{13}C NMR (75 MHz, $CDCl_3$) : δ 158.9, 138.5, 131.4, 130.6, 129.2, 125.3, 117.2, 113.6, 79.9, 69.7, 62.7, 55.2, 33.4, 32.2, 27.0, 25.6 ppm;

ESI-HRMS : *m/z* calcd for $C_{18}H_{26}NaO_3$ [M + Na]+ 313.1774; found 313.1794.

2.5.7. (*R*,*Z*)-8-(4-Methloxy)deca-5,9-dienoioxybenzyc acid (46):



To a stirred solution of primary alcohol **56** (0.35 g, 1.21 mmol) in CH_2Cl_2 (30 mL) at 0 °C, were added iodobenzenediacetate (0.43 g, 1.33 mmol) followed by TEMPO (0.04 g, 0.24 mmol) and allowed to stir at ambient temperature for 30 min. After complete consumption of the starting material (monitored by TLC), the reaction mixture was quenched with saturated solution of $Na_2S_2O_3$ (20 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporation of solvent led to crude aldehyde which was passed through a small pad of silica gel (ethyl acetate/hexane = 1:4) to afford the corresponding aldehyde **57** (0.32 g, 94%) as a thick viscous liquid and used immediately for the next reaction.



To a solution of resulting aldehyde **57** (0.32 g, 1.04 mmol) in *tert*-butyl alcohol (10 mL), 2- methyl-2-butene (0.5 mL, 1.04 mmol, 2M solution in THF) was added at room temperature. Sodium dihydrogenphosphate (0.49 g, 3.12 mmol) and sodium chlorite (0.14 g, 1.56 mmol) were dissolved in water (5 mL) to make a clear solution which was subsequently added to the above mentioned reaction mixture at 0 ^{o}C. It was allowed to stir for further 3 h at room temperature. The reaction mixture was extracted with EtOAc (3 x 20 mL), the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by silica gel chromatography (EtOAc/hexane: 3/7) to afford the corresponding acid **46** (0.29 g, 93%) as a colorless oil.

$[\alpha]_D^{25}$: +5.5 (*c* 1.1, $CHCl_3$);

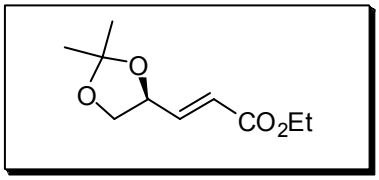
IR (neat, KBr) : ν_{max} 3450, 3007, 2932, 2857,1741, 1613, 1513, 1420, 1248, 1172, 1034, 821 cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$) : δ 7.19 (d, *J* = 8.5 Hz, 2 H), 6.8 (d, *J* = 8.7 Hz, 2 H), 5.72 (m, 1 H), 5.47-5.33 (m, 2 H), 5.24-5.12 (m, 2 H), 4.49 (d, *J*= 11.7 Hz, 1 H), 4.25 (d, *J* = 11.7, 1 H), 3.77 (s, 3 H), 3.69 (q, *J* = 6.6, 13.9 Hz, 1 H), 2.45-2.17 (m, 4 H), 2.07 (m, 1 H), 1.73-1.61 (m, 2 H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) : δ 178.5, 158.9, 138.4, 130.3, 129.2, 126.1, 117.2, 113.6, 79.8, 69.6, 55.1, 33.4, 33.3, 26.6, 24.6 ppm;

ESI-HRMS : *m/z* calcd for $C_{18}H_{24}NaO_4$ [M + Na]+ 327.1203; found 327.1182.

2.5.8. (*S,E*)-ethyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (58):



To the crude aldehyde **49** in benzene (50 mL) was added ethoxycarbonylmethylene triphenylphosphorane (19.49 g) at room temperature and stirred for 2 h. The reaction mixture was concentrated *in vacuo* and purified by silica gel column chromatography using petroleum ether/EtOAc (95:5) to give pure product **58** (6.80 g, 95% yield).

$[\alpha]_D^{25}$: +82.3 (*c* 0.7, $CHCl_3$).

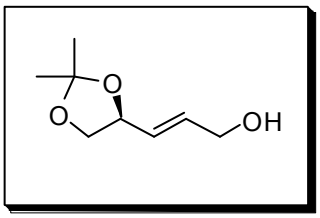
IR (KBr) : ν_{max} 2983, 2925, 2851, 1718, 1306, 1267, 1175, 1032, 980, 774 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) : 6.84 (dd, *J* = 5.4 Hz, 15.7 Hz, 1 H), 6.06 (d, *J* = 15.8 Hz, 1 H), 4.62 (q, J = 6.0 Hz, 1H), 4.24-4.12 (m, 3H), 3.64 (t, *J* = 7.5 Hz, 1H), 1.42 (s, 3H), 1.38 (m, 3H), 1.3 (t, *J* = 6.8 Hz, 3H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) : δ 166.0, 144.5, 122.4, 110.1, 74.9, 68.7, 60.5, 26.4, 25.7, 14.1 ppm;

ESI-HRMS : Calcd for $C_{10}H_{16}O_4Na$ $[M+Na]^+$: 223.0939.

2.5.9. (*S,E*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-ol (59):



To astirred solution of *α,β*-unsaturated ester **58** (6.2 g, 23.2 mmol) was dissolved in CH_2Cl_2 (60 mL) and cooled to −78 °C under nitrogen atmosphere. DIBAL-*H* (34.5 mL, 42.4 mmol) was slowly added to it over a period of 5 min. After 30 min of stirring at the same temperature, TLC was checked which showed complete consumption of starting material. It was quenched by slow addition of saturated solution of sodium potassium tartrate (50 mL), diluted with CH_2Cl_2 (40 mL) and allowed to stir at room temperature for another 2 h to get a clear two separated layers. The organic layer was separated and the

aqueous layer extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layer was washed with brine (2 x 75 mL), dried over anhydrous Na_2SO_4, evaporated to dryness under vacuum which on silica gel column chromatography (ethyl acetate: hexane = 2:3) produced the desired α,β-unsaturated alcohol **59** (5.8 g, 88%).

$[\alpha]_D^{25}$: +28.1 (*c* 0.5, $CHCl_3$).

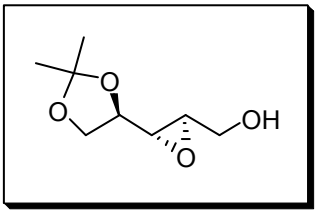
IR (KBr) : ν_{max} 3414, 2987, 2873, 1374, 1245, 1218, 1058, 1009, 856, 770 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) : δ 5.92 (m, 1H), 5.68 (dd, *J* = 7.9 Hz, 11.3 Hz, 1 H), 4.49 (m, 1H), 4.14 (s, 2H), 4.05 (t, *J* = 6.8 Hz, 1H), 3.55 (t, J = 6.8 Hz, 1H), 1.42 (s, 3H), 1.34 (s, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) : δ 133.5, 128.3, 109.3, 76.4, 69.3, 62.6, 26.6, 25.8 ppm;

EI-MS : Calcd for $C_8H_{14}O_3Na$ $[M+Na]^+$: 181.

2.5.10. (*R*)-4-((*S*)-1-(4-Methoxybenzyloxy)allyl)-2,2-dimethyl-1,3-dioxolane (60):



To a freshly flame dried double necked round bottom flask equipped with activated 4 A^o molecular sieves (~15 g) and dry CH_2Cl_2 (200 mL) at –20 ^oC were added $Ti(O^iPr)_4$ (2.3 mL, 1.9 mmol), (–)-diethyl tartrate (1.4 mL, 1.3 mmol) and the mixture was stirred for 30 min. To this reaction mixture it was added allyl alcohol **59** (5.25 g, 21.1 mmol) in an interval of 30 min. and TBHP (26 mL, 104 mmol, 4 M solution in toluene) were added and stirring was continued till completion of the reaction (8 h). The reaction mixture was warmed to 0 ^oC, filtered through Celite. The filtrate was quenched with water (34 mL), 15% aq. NaOH solution (5.6 mL) and stirred vigorously for 1 h. The biphasic solution was separated and aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under *vacuum*. The crude residue was purified by column chromatography to afford the pure epoxide **60** as colorless oil (4.8 g, 95% yield).

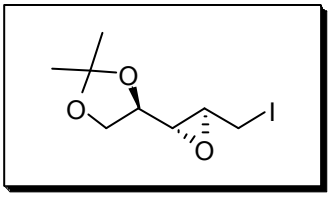
$[\alpha]_D^{25}$: +11.0 (*c* 0.5, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) : δ 4.17-4.06 (m, 2H), 4.02-3.84 (m, 3H), 3.69 (bs, 1H), 3.14-3.07 (m, 2H), 1.45 (s, 3H), 1.43 (s, 3H);

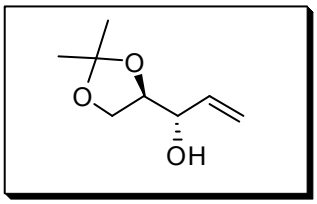
^{13}C NMR (75 MHz, $CDCl_3$) : δ 110.0, 75.1, 65.9, 60.7, 55.3, 54.9, 26.3, 25.5 ppm;

ESI-MS : Calcd for $C_8H_{14}O_4Na$ $[M+Na]^+$: 197.

2.5.11. (*S*)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-ol (61):



To a stirred solution of epoxy alcohol **60** (6.5 g, 14.84 mmol) in dry THF (75 mL), TPP (5.83 g, 22.26 mmol) followed by imidazole (3.02 g, 44.52 mmol) was added under nitrogen atmosphere and stirred for 5 min to dissolve it completely. It was cooled to 0 ^oC and then iodine (5.65 g, 22.26 mmol) was added portionwise to it. After completion of reaction (monitored by TLC), it was quenched with saturated solution of hypo (50 mL). The organic layer was diluted with Ethyl acetate (100 mL), washed with brine (2 x 50 mL), dried over Na_2SO_4, concentrated and then purified rapidly by short silica gel flash column chromatography (Ethyl acetate: hexane =1: 49) to get red colored iodo product which was immediately used for the next step.



The iodo compound after column purification was immediately dissolved in MeOH (50 mL) and to it, activated Zn dust (2.9 g, 44.52 mmol) and NaI (6.67 g, 68 mmol) was successively added. It was refluxed for 3 h. After completion of the reaction, excess Zn dust was filtered out and the filtarte was removed under reduced pressure to get a semisolid. It was diluted with Ethyl acetate (100 mL), washed with saturated NH_4Cl (2 x 50 mL), brine (2 x 30 mL), dried over Na_2SO_4, evaporated under reduced pressure and purified by silicagel column chromatography (Ethyl acetate: hexane = 5: 95) to get colorless liquid **61** (5.13 g, 82% over two steps) as a colorless liquid.

$[\alpha]_D^{25}$: +8.4 (*c* 0.6, $CHCl_3$);

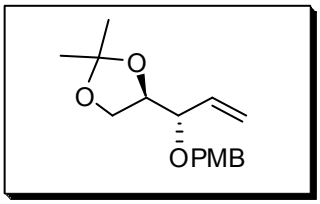
IR (KBr) : ν_{max} 3452, 2988, 2936, 2889, 1375, 1247, 1218, 1157, 1067, 848, 772 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) : δ 5.77 (m, 1H), 5.28 (d, *J* = 17.3 Hz, 1H), 5.14 (d, *J* = 10.5 Hz, 1H), 1.14 (m, 1H), 4.0 (m, 1H), 3.93-3.76 (m, 2H), 2.83 (bs, 1H), 1.35 (s, 3H), 1.32 (s, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) : δ 136.0, 116.5, 109.2, 78.0, 71.9, 64.9, 26.2, 25.0 ppm;

ESI-MS : Calcd for $C_8H_{14}O_3Na$ $[M+Na]^+$: 181.

2.5.12. (*R*)-4-((*S*)-1-(4-Methoxybenzyloxy)allyl)-2,2-dimethyl-1,3-dioxolane (62):



To a suspension of NaH (0.8 g, 21.56 mmol, 60% w/v dispersion in mineral oil) in dry THF (125 mL) was added dropwise a solution of secondary allylic alcohol **61** (3.2 g, 17.56 mmol) at 0 ^oC and continued the stirring for the next 45 min at room temperature. At 0 oC, freshly prepared *p*-methoxy benzyl bromide (1.53 g, 7.56 mmol) was added and stirred further for 4 h at room temperature with frequent monitoring of the progress of reaction by TLC. The reaction mixture was quenched by small crushed ice flakes until a clear solution (biphasic) had formed. The combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4. After removing the volatiles under reduced pressure, crude *p*-methoxy benzyl ether was purified by column chromatography on silica gel (ethyl acetate/hexane = 1:49) to afford the pure product **62** (3.6 g, 92%) as a colorless liquid.

$[\alpha]_D^{25}$: +12.5 (*c* 1.0, $CHCl_3$);

IR (neat, KBr) : ν_{max} 3070,2985, 2926, 1727, 1639, 1427, 1249, 1115, 1066, 821 cm^{-1};

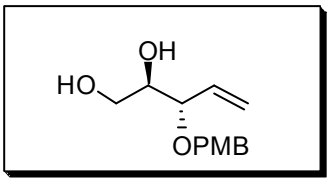
^1H NMR (300 MHz, $CDCl_3$) : δ 7.18 (d, *J* = 8.6 Hz, 2 H), 6.81 (d, *J* = 8.6Hz, 2 H), 5.77 (m, 1 H), 5.40-5.27 (m, 2 H), 4.54 (d, *J* = 11.5 Hz, 1 H), 4.30 (d, *J* = 11.3Hz, 1 H), 4.4-3.6 (m,

2 H), 3.79 (s, 3 H), 3.76 (m, 1 H), 3.67 (m,1 H), 1.36 (s, 3 H) 1.31(s, 3 H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) : δ 159.1, 135.2, 130.1, 129.4, 119.6, 113.7, 109.4, 80.6, 77.5, 70.1, 66.8, 55.2, 26.5, 25.2 ppm;

ESI-MS : *m/z* calcd ($C_{16}H_{22}O_4$): m/z 301 [M +Na]+.

2.5.13. (2*R*,3*S*)-3-(4-Methoxybenzyloxy)pent-4-ene-1,2-diol (63):



To a solution of **62** (1.5 g, 5.39 mmol) in methanol (50 mL), CSA (cat.) was added at 0 oC and stirred at room temperature for 2 h after which it was quenched with Et3N (3 mL), and the solvent evaporated under reduced pressure. The residue was purified by column chromatography (Silica gel, ethyl acetate/hexane = 2:3) to give **63** (1.1 g, 87%).

$[\alpha]_D^{25}$: +25.4 (*c* 0.42, $CHCl_3$);

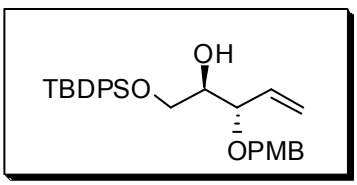
IR (neat, KBr) : ν_{max} 3408,2924, 1612, 1513, 1301, 1248, 1176, 1035, 932,821 cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$) : δ 7.18 (d, *J* = 8.5 Hz, 2 H), 6.82 (d, *J* = 8.5Hz, 2 H), 5.79 (m, 1 H), 5.39-5.27 (m, 2 H), 4.53 (d, *J* = 11.3 Hz, 1 H), 4.27 (d, *J* = 11.3Hz, 1 H), 3.84 (m, 1 H), 3.78 (s, 3 H), 3.66-3.57 (m, 3 H) 2.89 (br s, 2 H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) : δ 159.2, 134.9, 129.8, 129.4, 120.0, 113.8, 81.6, 73.1, 70.2, 63.2, 55.2 ppm;

ESI-HRMS : *m/z* calcd for $C_{13}H_{18}NaO_4$ [M + Na]+ 261.1097; found 261.1115.

2.5.14. (2*R*,3*S*)-1-(*tert*-Butyldiphenylsilyloxy)-3-(4-methoxybenzyloxy)pent-4-en-2-ol (47):



To a stirred solution of diol **63** (1.0 g, 4.2 mmol) in CH_2Cl_2 (50 mL) under nitrogen atmosphere at room temperature, was added TBDPSCl (1.12 mL, 4.2 mmol) and imidazole (0.57 g, 8.4 mmol). The reaction mixture was stirred at room temperature for 3 h. After completion (monitored by TLC), the reaction was quenched with water (20 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel column chromatography to give **47** (1.78 g, 89%) as colorless viscous liquid.

$[\alpha]_D^{25}$: +6.4 (*c* 0.5, $CHCl_3$);

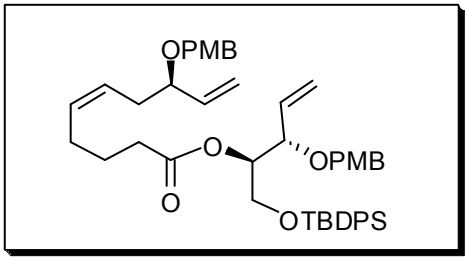
IR (neat, KBr) : ν_{max} 3453, 2932, 2859, 1613, 1513, 1426, 1301, 1247, 1109, 1069, 930, 820, 703 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) : δ 7.68-7.61 (m, 4 H), 7.46-7.32 (m, 6 H), 7.16 (d, *J* = 8.6 Hz, 2 H), 6.82 (d, *J* = 8.6 Hz, 2 H), 5.84 (m, 1 H), 5.39-5.27 (m, 2 H), 4.52 (d, *J* = 11.3 Hz, 1 H), 4.26 (d, *J* = 11.3 Hz, 1 H), 3.79 (s, 3 H), 3.77-3.73 (m, 3 H) 2.45 (br s, 1 H), 1.05 (s, 9 H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) : δ 159.1, 135.5, 135.2, 133.2, 130.2, 129.7, 129.3, 127.7, 119.5, 113.7, 80.3, 73.5, 70.0, 64.4, 55.2, 26.8, 19.2 ppm;

ESI-HRMS : *m/z* calcd for $C_{29}H_{36}NaO_4Si$ [M + Na]+ 499.2275; found 499.2252.

2.5.15. (*R*,*Z*)-((2*R*,3*S*)-1-(*tert*-Butyldiphenylsilyloxy)-3-(4-methoxybenzyloxy)pent-4-en-2-yl)-8-(4-methoxybenzyloxy)deca-5,9-dienoate (44).



To a stirred solution of acid **46** (0.28 g, 0.92 mmol) in CH_2Cl_2 (15 mL) at 0 oC, Et3N (0.30 mL, 1.68 mmol) followed by EDCI (0.24 g, 1.26 mmol) and DMAP (0.84 mmol,

0.09 g) were added and stirred for 30 min. Alcohol **47** (0.4 g, 0.84 mmol) was dissolved in CH_2Cl_2 (10 mL) and slowly added to the resulting reaction mixture at the same temperature and then allowed to stir for 12 h at room temperature. After completion of the reaction (monitored by TLC), it was quenched with water (20 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layer was dried over Na_2SO_4 and the solvent evaporated under reduced pressure to give a colorless oil which on purification by silica gel column chromatography (ethyl acetate/hexane = 3:97) furnished the desired coupled product **44** (0.576 g, 90%, based on the starting alcohol) as a colorless liquid.

$[\alpha]_D^{25}$: +17.4 (*c* 0.48, $CHCl_3$);

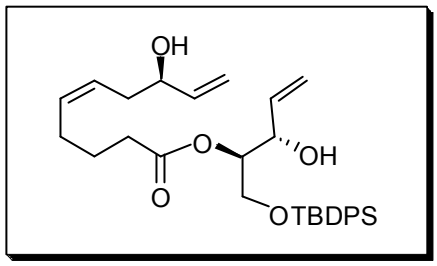
IR (neat, KBr) : ν_{max} 2923, 2855, 1738, 1612, 1512, 1462, 1381, 1245, 1107, 1069, 929, 819, 701 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) : δ 7.61 (d, *J* = 6.9 Hz, 4 H), 7.43-7.29 (m, 6 H), 7.20 (d, *J* = 8.7 Hz, 2 H), 7.12 (d, *J* = 8.5 Hz, 2 H), 6.81 (d, *J* = 8.7Hz, 2 H), 6.77 (d, *J* = 8.5 Hz, 2 H), 5.78-5.64 (m, 2 H), 5.44-5.35 (m, 2 H), 5.31-5.14 (m, 4 H), 5.04 (q, *J* = 5.8, 9.6 Hz, 1 H), 4.5 (d, *J* = 11.5 Hz, 2 H), 4.26 (d, *J* = 11.7 Hz, 2 H), 3.98 (t, *J* = 6.9 Hz, 1 H),3.85 (m, 1 H), 3.78 (s, 6 H), 3.71 (m, 2 H), 2.40-2.14 (m, 4 H), 2.08-1.98 (m, 2 H), 1.68-1.54 (m, 2 H), 1.02 (s, 9 H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) : δ 172.7, 159.0, 138.6, 135.6, 135.5, 135.0, 130.5, 129.6, 129.2, 127.6, 126.0, 119.6, 117.3, 113.7, 79.9, 78.4, 74.7, 70.1, 69.7, 62.2, 55.2,33.9, 33.4, 29.7, 26.7, 24.7, 19.2ppm;

ESI-HRMS : *m/z* calcd for $C_{47}H_{58}NaO_7Si$ [M + Na]+ 785.3844; found 785.3847.

2.5.16. (*R*,*Z*)-((2*R*,3*S*)-1-(*tert*-Butyldiphenylsilyloxy)-3-hydroxypent-4-en-2-yl)-8-hydroxy-deca-5,9-dienoate (45).



To a stirred solution of di-PMB ether **44** (255 mg, 0.33 mmol) in CH_2Cl_2 (15 mL), was added DDQ (227 mg, 1.0 mmol) at pH7 with phosphate buffer solution (1.6 mL) at 0 oC. The reaction mixture was allowed to stir for 2 h at room temperature. After completion of the reaction (monitored by TLC), it was quenched with saturated $NaHCO_3$ (10 mL) solution. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layer was washed with brine (40 mL), dried over anhydrous Na_2SO_4 and evaporated to give the crude product which on purification by silica gel column chromatography (ethyl acetate/hexane = 1:5) to afford the desired diol **45** (162 mg, 93%) as a colorless viscous liquid.

$[\alpha]_D^{25}$: –7.5 (*c* 1.4, $CHCl_3$);

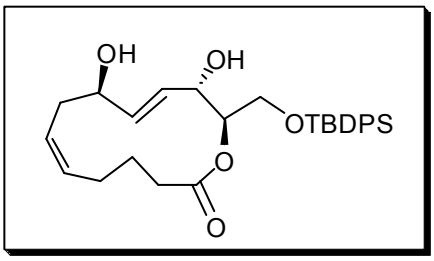
IR (neat, KBr) : ν_{max} 3446, 2927, 2856, 1728, 1637, 1426, 1218, 1111, 768, 702 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) : δ 7.70-7.61 (m, 4 H), 7.46-7.34 (m, 6 H), 5.93-5.76 (m, 2 H), 5.60-5.34 (m, 3 H), 5.28-5.08 (m, 3 H), 4.93 (q, *J* = 4.5, 9.1 Hz, 1 H), 4.42 (t, *J* = 4.5 Hz, 2 H), 4.12 (q, *J* = 6.8, 12.1 Hz, 1 H), 3.92 (dd, *J* = 5.3, 11.3 Hz, 1 H), 3.77 (dd, *J* = 3.8, 11.3 Hz, 1 H), 2.41-2.20 (m, 4 H), 2.17-2.15 (m, 3 H), 1.77-1.63 (m, 2H), 1.05 (s, 9 H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) : 173.2, 140.3, 136.3, 135.6, 135.5, 132.6, 131.8, 129.9, 127.8, 125.8, 117.0, 114.8, 75.5, 73.1, 72.4, 63.1, 35.1, 33.6, 26.7, 26.6, 24.6, 19.1 ppm;

ESI-HRMS : *m/z* calcd for $C_{31}H_{42}NaO_5Si$ [M + Na]+ 545.2694; found 545.2712.

2.5.17. (6*Z*,9*R*,10*E*,12*S*,13*R*)-13-((*tert*-Butyldiphenylsilyloxy)methyl) 9,12dihydroxyoxacyclotrideca-6,10-dien-2-one (43).



Grubbs second generation catalyst (16 mg, ca. 0.02 mmol) was dissolved in dry, deoxygenated CH_2Cl_2 (200 mL) under argon atmosphere. After the solution was heated to reflux, diene **45** (0.1 g, 0.2 mmol) was added slowly via syringe (30 min) in dry, deoxygenated CH_2Cl_2 (30 mL) to the reaction mixture. The reaction mixture was then stirred at reflux for an additional 8 h. After completion of the reaction (monitored by TLC), solvent was evaporated under reduced pressure. Purification of the crude residue by silica gel column chromatography (ethyl acetate/hexane = 3:7) afforded **43** (71 mg, 76%) (single stereoisomer) as a colorless viscous oil.

$[\alpha]_D^{25}$: −12.5 (*c* 0.8, $CHCl_3$);

IR (neat, KBr) : ν_{max} 3421, 2926, 2855, 1733, 1463, 1428, 1379, 1110, 1035, 969, 767, 702 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) : 7.69-7.62 (m, 4 H), 7.48-7.35(m, 6 H), 5.66 (dd, *J* = 7.7 Hz, 15.7 Hz, 1 H), 5.60-5.46 (m, 2 H), 5.23 (q, *J* = 6.2, 10.9Hz, 1 H), 4.8 (m, 1 H), 4.40-4.26 (m, 2 H), 3.99-3.78 (m, 2 H), 2.47-2.12 (m, 6 H), 2.20-1.82 (m, 2 H), 1.06 (s, 9 H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) : δ 172.6, 135.9, 135.6, 131.3, 131.1, 130.4, 129.9, 127.8, 126.6, 124.4, 74.9, 73.6, 72.6, 63.9, 35.1, 32.5, 26.7, 25.7, 22.9, 19.2ppm;

ESI-HRMS : *m/z* calcd for $C_{29}H_{38}NaO_5Si$ [M + Na]+ 517.2381; found 517.2400.

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CHAPTER III

Section A

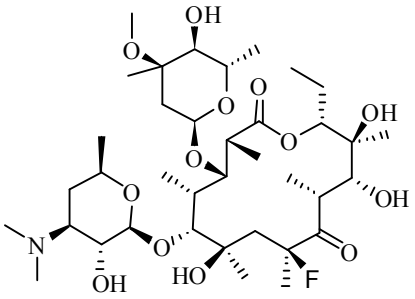
Introduction and previous approaches for Aspergillide B

3.1. Introduction:

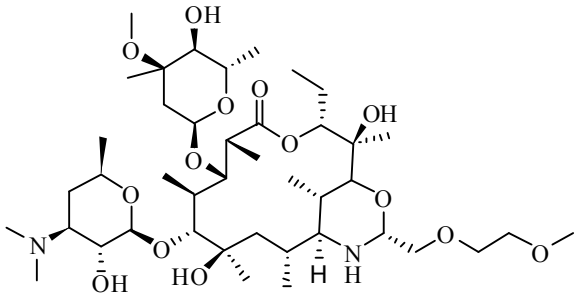
If we will go to historical era, from that day onwards nature has proven itself as a rich source of bioactive natural product which all display a wide range of pharmacological activities[1] and also nature has long been recognized as a major reservoir of molecular diversity, with natural products making an indispensable contribution to the discovery and development of effective medicinal agents.[2] Traditionally plants and terrestrial micro-organisms have been in the focus for the search of new drug candidates from nature. In recent years, however, marine organisms[3] such as sponges, tunicates, shell less mollusks and others are increasingly attracting attention due to their structurally unique and pharmacologically active compounds. The marine environment has proven to be a rich source of bioactive compounds, many of which belong to novel chemotypes not found in terrestrial sources.[4] It's worthwhile at this juncture to discuss few pyran ring containing marine natural products, which have been of paramount importance to the mankind and also to the researchers who have been actively involved in the synthesis and isolation of these natural products. Biological activity of these types of molecules, their structural complexities, and the challenge to synthesize them in optically pure form made them an attractive target for their total syntheses.

The macrocycle ia an important structural motif amongst bioactive natural products and in parts favorable physiochemical and pharmacological attributes. Macrocyclic geometry maintains a delicate balance between flexibility and rigidity that commonly affects solubility, permeability and bind to biological targets. Macrolide is used to describe drugs with a macrocyclic lactone ring of 12 or more elements.[5] This class of compounds includes a variety of bioactive agents, including antibiotics, antifungal drugs, prokinetics, and immunosuppressants. The 14-, 15-, and 16-membered macrolides are a widely used family of antibiotics. The 14-membered macrolides (Figure 1) erythromycin, dirithromycin, roxithromycin, clarithromycin, the 15-membered compound azithromycin and the 16-membered macrolides josamycin, spiramycin and midecamycin acetate are associated with antibiotic activities (Figure 2). They have excellent tissue penetration and antimicrobial activity, mainly against Gram-positive cocci and atypical pathogens.[6]

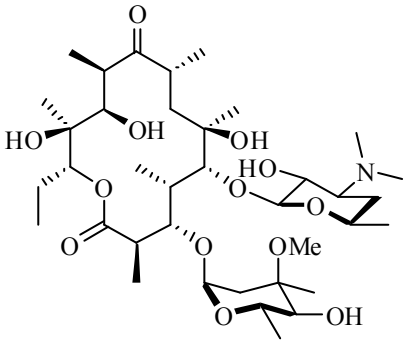
Erythromycin A, a 14-membered macrolide, was isolated more than 50 years ago from cultures of Streptomyces and was the first macrolide introduced into clinical practice.[5,7]



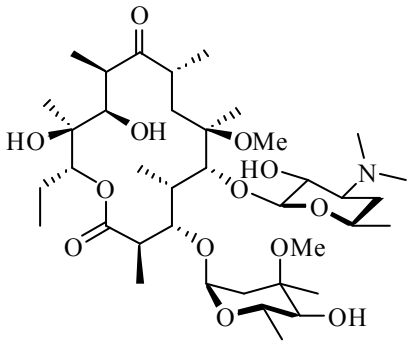
Flurithromycin (1)



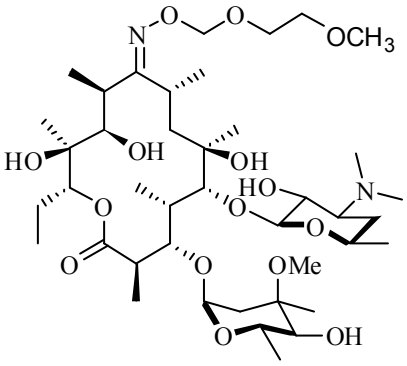
Dirithromycin (2)



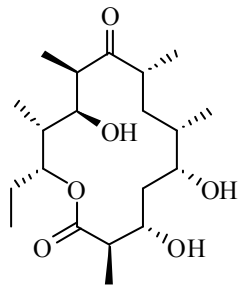
Erithromycin (3)



Clarithromycin (4)



Roxithromycin (5)

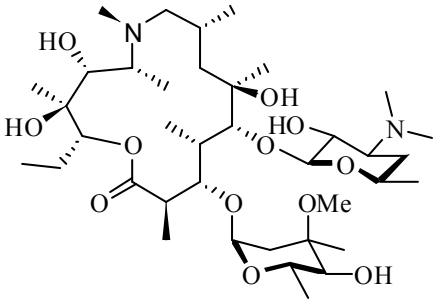


6-Deoxyerythronolide B (6)

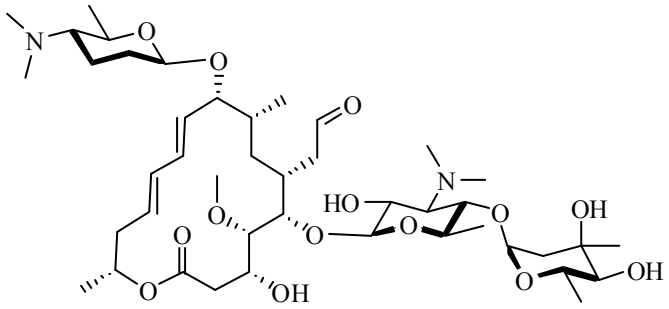
Figure 1

(14-membered macrolides)

Clarithromycin is highly effective against H.pylori and atypical mycobacteria (M.avium) and azithromycin is highly effective against H.influenzae. Spiramycin, azithromycin and roxithromycin are active against some protozoa (T.gondii, Cryptosporidium spp.). Enterobacteriaceae, Pseudomonas spp. and Acinetobacter spp. strains have a natural resistance to all macrolides.



Azithromycin (7)
(15-membered macrolide)



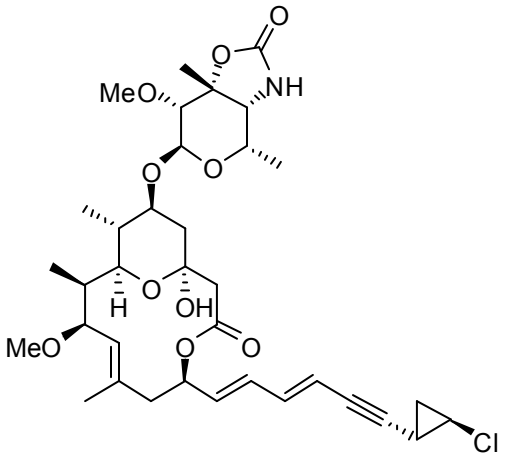
Spiramycin (8)
(16-membered macrolide)

Figure 2

A lot of 14-membered known macrolides are there which were exhibiting very effective antibiotic activities towards different type of bacterial infection. But there are a few 14-membered natural products with pyran (*cis* and *trans*) moiety (described below). The unusual structures of those natural products are associated with interesting biological activities like anticancer as well as antibacterial activities.

CallipeltosideA (**9**) (Figure 3) is a cytotoxicmacrolide isolated in 1996 from the marine lithistida sponge (*Callipelta sp*.).[8] The stereochemical features of callipeltoside A were deduced on the basis of extensive NMR studies. The first total synthesis as well as the absolute configuration determination was done by Trost group in 2002.[9]

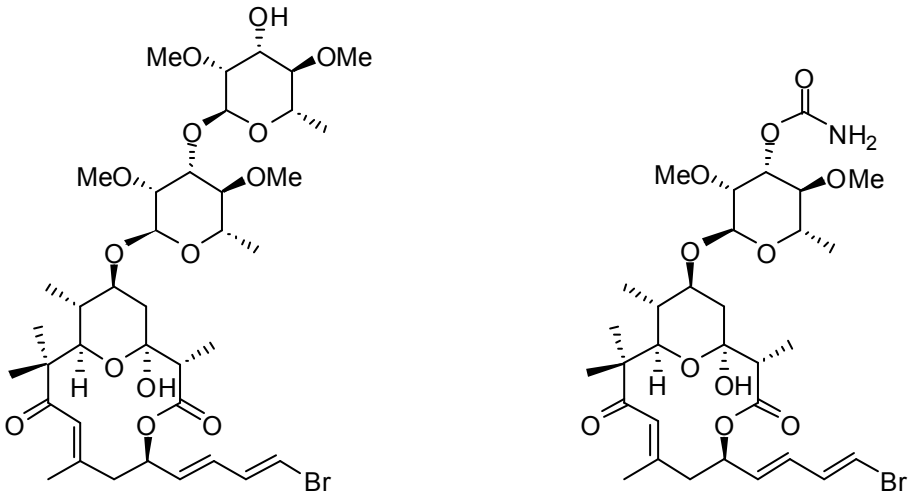
In 1996, Aurisides A (**10**) and B (**11**) (Figure 4) are unique marine polyketides isolated by Yamada and co-workers from the Japanese sea hare *Dolabella auricularia*,[10] an organism that has proved to be a rich source of bioactive secondary metabolites.[11] The



Callipeltoside A (9)

Figure 3

first total synthesis of aurisides A (**10**) and B (**11**) was done by Paterson and co-workers in 2005 by appropriate attachment of the required sugar residue, which involves a highly convergent and expedient aldol-based route for the stereocontrolled construction of the common macrolide core.[12]

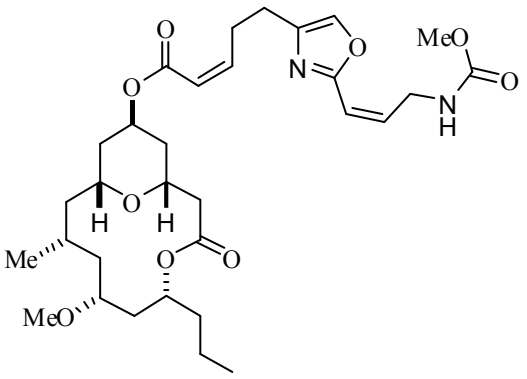


Auriside A (10) **Auriside B (11)**

Figure 4

Neopeltolide (**12**) (Figure 5) was first isolated from deep-water sponges most closely related to the genus Daedalopelta Sollas in 2007 by Wright and co-workers.[13] Neopeltolide is an extremely potent inhibitor of in vitro proliferation of A-549 human lung adenocarcinoma and P388 murine leukemia cell lines with IC_{50} values in the nanomolar range (1.2 and 0.56 nM, respectively) as well as potent inhibition (MIC =

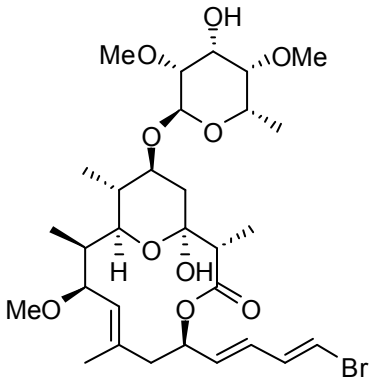
0.625 μg/mL) of the fungal pathogen *Candida albicans*, which can greatly threaten the health of advanced AIDS patients.[14] The first total synthesis was achieved by Panek and co-workers in 2007.[15]



Neopeltolide (12)

Figure 5

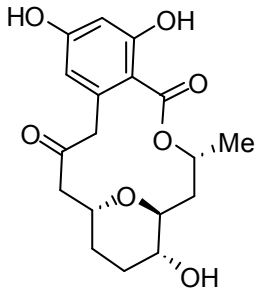
In 2004, Dolastatin (**13**) (Figure 6) is a 14 membered macrolide was isolated by Pettit and co-workers from the marine sponge which has associated with some interesting biological activities like cytotoxic as well as antifingal activities.[16]



Dolastatin (13)

Figure 6

In 2009, Shinonaga and co-workers disclosed a unique pochonin J (**14**) (Figure 7) from the culture broth of Pochonia *chlamydosporia var. chlamydosporia*.[17] This compound was isolated via bioassay-guided fractionation against WNT-5A expression in search of novel hair-growth stimulants.

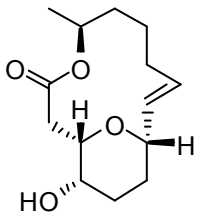


Prochonin J (14)

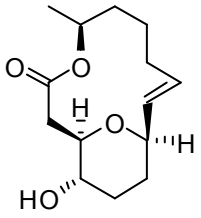
Figure 7

Such structural motifs are extremely rare. Recently three 14-membered macrolides those possess a tetrahydropyran ring inside were isolated, known as Aspergillides A (**15**), B (**16**) and C (**17**).

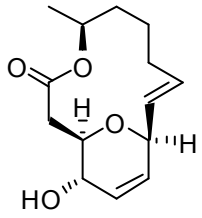
In 2007, three 14-membered macrolides, named aspergillides A, B and C were isolated by T. Kusumi *et al.* from marine-derived fungus *Aspergillus ostianus* strain 01F313. The biological assay of these compounds revealed a potent cytotoxicity against mouse lymphocytic leukemia cells (L1210) at 2–70 lg/L (LC50).[18] The structures of the new compounds were determined by analyses of 1D and 2D NMR spectra. Structurally, aspergillides A-C all bear a 14-membered lactone ring incorporating a 2,6 *trans*-trisubstituted pyran subunit and an *E*-olefin bond at C8-C9, which is very rare in natural products. Their structures were proposed to be heptaketidic 14-membered macrolides and absolute configurations were elucidated by the modified Mosher's method and chemical



Aspergillide A (15)



Aspergillide B (16)



Aspergillide C (17)

Figure 8

conversions. Aspergillides are the first examples of 14-membered macrolides incorporated with a trans tetrahydropyran ring. Our recent developed methodology, iodocyclization[19] is going to be a potent protocol for synthesis of pyran rings by using low cost reagents with a quantitative yield. In our group, iodocyclization reaction has been successfully implemented for synthesis of a number of natural products. The *trans* pyran ring inside the

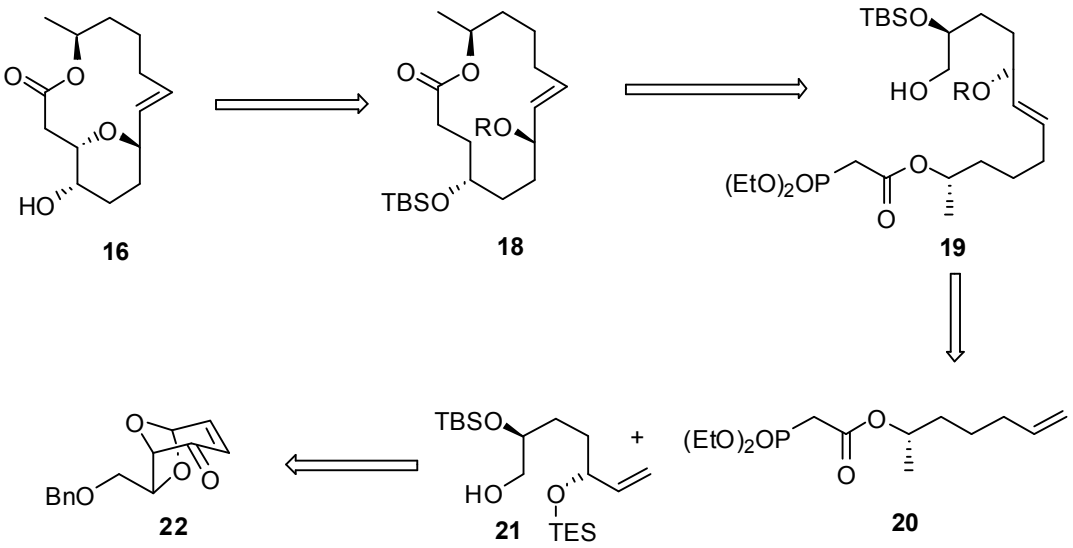
aspergillides attracted our attention to synthesize following our own developed iodo-cyclization protocol.

3.2. Previous Approaches:

3.2.1. Shishido's approach:[20]

Shishido and co-workers had reported the total synthesis of the aspergillides A and B via first application of a highly efficient and diastereoselective transannular oxy-Michael reaction as key reaction. The synthesis had been commenced from the chiral building block as shown in Scheme 1.

3.2.1a. Retrosynthesis:

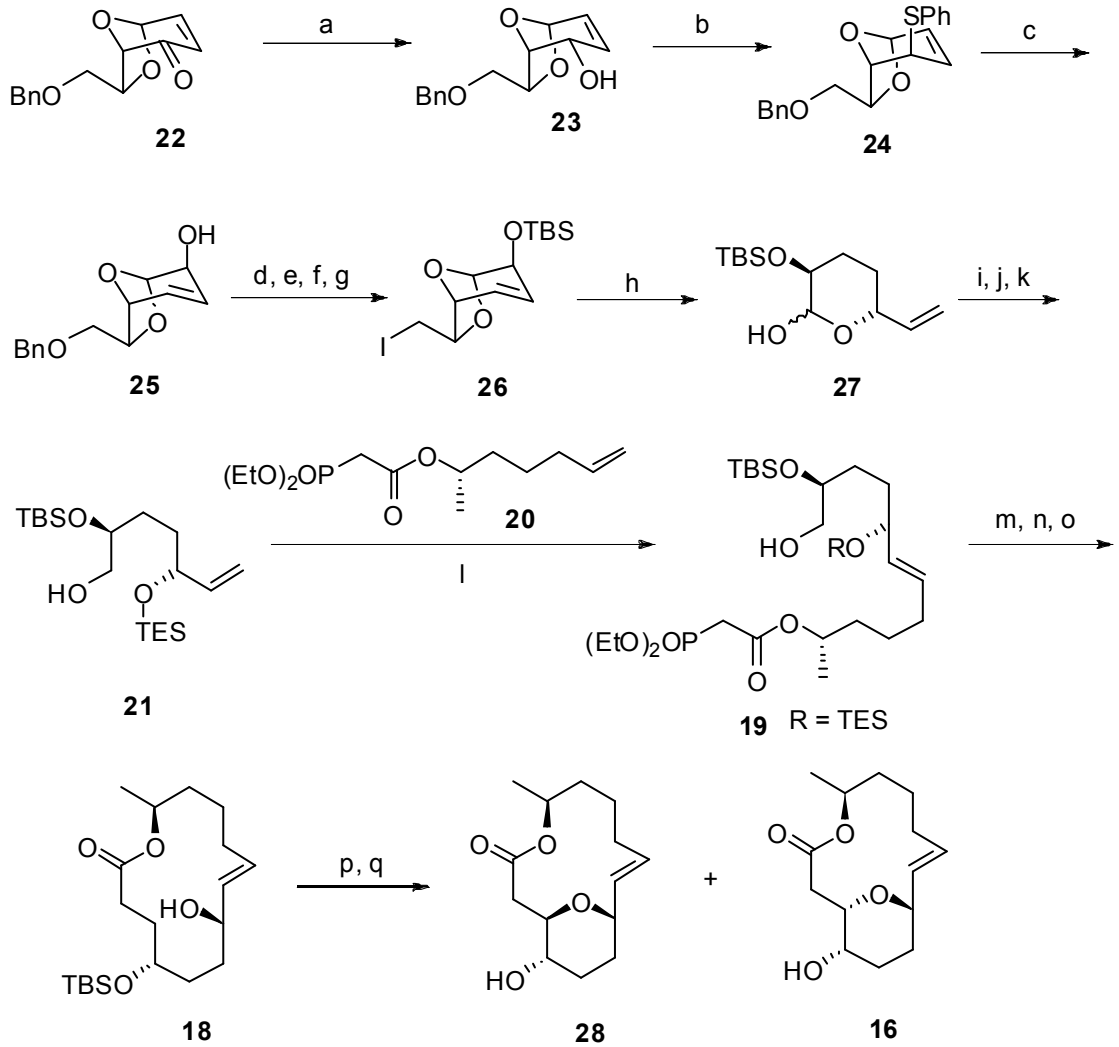


Scheme 1: Retrosynthetic analysis

3.2.1b. Discussion:

The optically pure enone **22** with a bicyclo[3.2.1]octane framework, prepared from 2-furfural by a six-step sequence was served as the starting material for the synthesis of the synthesis aspergillide B (**16**). Reduction with $NaBH_4$ followed by the Hata reaction of the resulting **23** produced the inverted sulfide **24**, which was treated with *m*-CPBA and $(MeO)_3P$ in ethanol at reflux to give the alcohol **25** in 60% yield from **22**. After protection of the alcohol moiety as its TBS ether, sequential hydrogenation, debenzylation, mesylation, and iodination gave the iodide **26**, which was reduced with zinc in ethanol at reflux to afford the hemiacetal **27**. Reduction with $LiBH_4$ gave the diol, the primary and the secondary alcohols of which were sequentially protected as the pivalate and the TES

ether, respectively. The pivalate was reduced with $LiBH_4$ to give the alkenyl alcohol **21**. Cross-metathesis of **21** with the phosphonoacetate **20** prepared from (*R*)-2-methyloxirane through a two-step sequence, in the presence the second-generation Grubbs catalyst (5 mol%) in methylene chloride at reflux provided the coupled product **19**, as the E alkene (>20:1). Oxidation of **19** with Dess–Martin periodinane and a subsequent intramolecular Horner–Wadsworth–Emmons reaction gave the macrolactone. Selective removal of the TES ether was realized by treatment with PPTS to afford the alcohol **18** followed by a treatment of the resulted alcohol **18** with KH, [18]crown-6 in THF to give the anti-adduct as major and was treated with acidic conditions (3M aqueous HCl in THF at room temperature for 3 h) to give quantitatively the aspergillides B (**16**).



Scheme 2

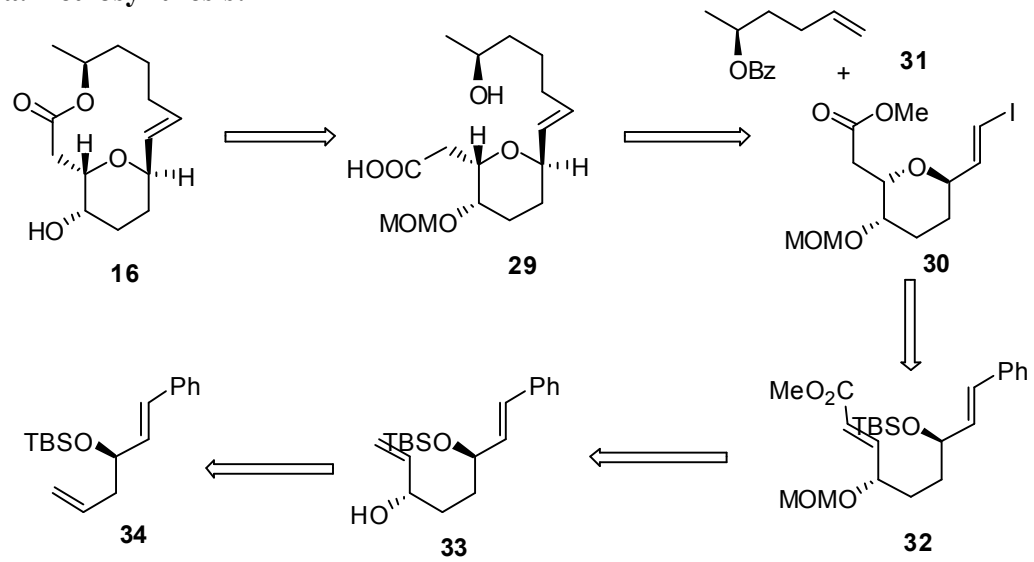
Reagents and conditions: a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, RT, 1 h, 98%; b) PhSSPh, *n*-Bu_3P, pyridine, 60 8C, 16 h, 86%; c) *m*-CPBA, CH_2Cl_2, –78 ^oC, 1.5 h; then $(MeO)_3P$, EtOH, reflux, 6 h, 71%; d) TBSCl, imidazole, DMAP, CH_2Cl_2, RT, 1 h, 94%; e) H_2, $Pd(OH)_2$-C, THF, 60 ^oC, 8 h, 99%; f) MsCl, Et_3N, CH_2Cl_2, RT, 1 h; g) LiI, THF, reflux, 8 h, 94% (over 2 steps); h) Zn, EtOH, reflux, 3 h, 94%; i) $LiBH_4$, THF, 0 ^oC, 2 h, quant.; j) PivCl, Et_3N; then TESCl, DMAP, CH_2Cl_2, RT, 1 h; k) $LiBH_4$, THF, 0 ^oC, 3 h, 96%; l) Grubbs II gen. catalyst, CH_2Cl_2, reflux, 9 h, 98%; m) DMP, $NaHCO_3$ CH_2Cl_2, reflux, 2 h; n) LiCl, DBU, CH_3CN, rt, 1 h, 78% (over two steps); o) PPTS, MeOH/THF (1:2), rt, 1 h, 82%; p) KH (1.1 eq.), THF, rt, 0.5 h, 79%; q) 3M HCl (aq), THF, rt, 3 h,

Thus, the synthesis of the aspergillides A and B illustrated in Scheme 2, proposes the formation of the trisubstituted pyran moiety through a base-mediated transannular oxy-Michael reaction from the 14-membered macrolactone.

3.2.2. Haruhiko Fuwa's approach:[21]

Haruhiko Fuwa and co-workers had reported an enantioselective total synthesis of aspergillides B has been accomplished based on a unified strategy, wherein a hydroxy-directed, highly chemoselective olefin cross-metathesis and a diastereoselective intramolecular oxa-conjugate cyclization were employed to forge the 2,6-substituted tetrahydropyran substructure.

3.2.2a. Retrosynthesis:

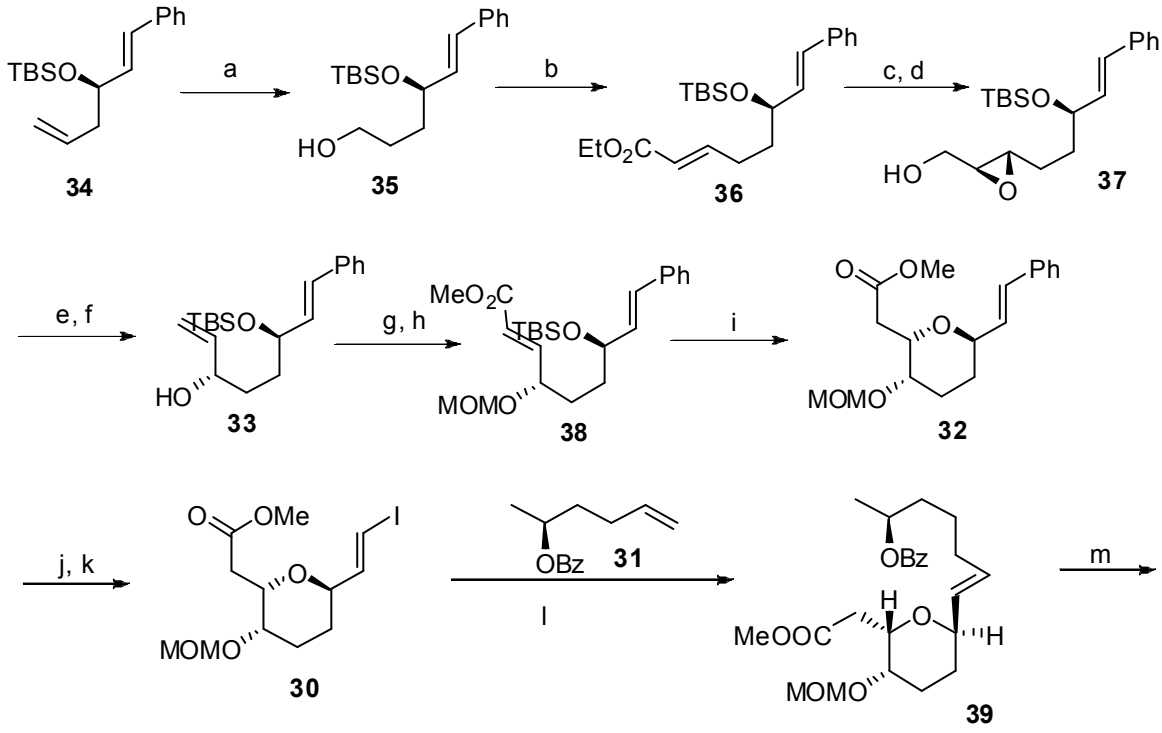


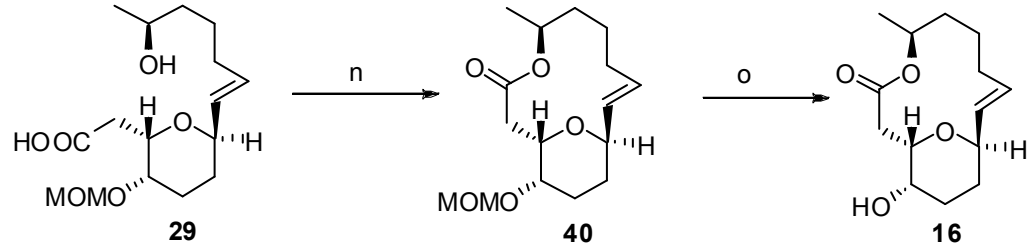
Scheme 3: Retrosynthetic analysis

2.2.2b. Discussion:

The synthesis of the target molecule **16** is illustrated in Scheme 4. The known homo-allylic alcohol was protected with TBSCl/imidazole to give silyl ether **34**. Chemoselective hydroboration of the terminal olefin of **34** with disiamylborane followed by oxidative

workup afforded alcohol **35**. TEMPO/ BAIB oxidation of **35** and one-pot Wittig reaction afforded enoate **36** in. DIBAL-*H* reduction of **36** gave allylic alcohol which was subjected to Sharpless asymmetric epoxidation to yield epoxy alcohol **37**. Iodination under standard conditions followed by zinc reduction of the derived iodo-epoxide afforded allylic alcohol **33**. Chemoselective olefin CM of **33** with methyl acrylate proceeded smoothly to deliver enoate followed by protection of the hydroxy group within enoate using MOMCl and *i*-Pr_2NEt to give **38**. Removal of the TBS group with TBAF buffered with AcOH led to enoate followed by intramolecular oxa-conjugate cyclization by exposure to KO*t*-Bu (0.05 equiv) in THF at –78 °C for 30 min gave rise to 2,6-*trans*-tetrahydropyran *trans*-**32** with excellent diastereoselectivity (dr 17:1) (Scheme 4). Ozonolysis of the double bond of *trans*-**32** followed by Takai olefination of the derived aldehyde gave (*E*)-vinyl iodide **30** as the major isomer (*E*/*Z*) (5:1). Suzuki-Miyaura coupling of **30** with an alkylborane, derived from olefin **31**,under the influence of the $PdCl_2(dppf)\cdot CH_2Cl_2/Ph_3As$ catalyst system and aqueous Cs_2CO_3 (DMF, room temperature) afforded *E*-olefin **39**. Hydrolysis gave hydroxyl acid **29**, whose macrolactonization under Yamaguchi condition successfully delivered the 14- membered macrolactone **40**. Finally, cleavage of the MOM group with furnished synthetic aspergillide B (**16**).





Scheme 4

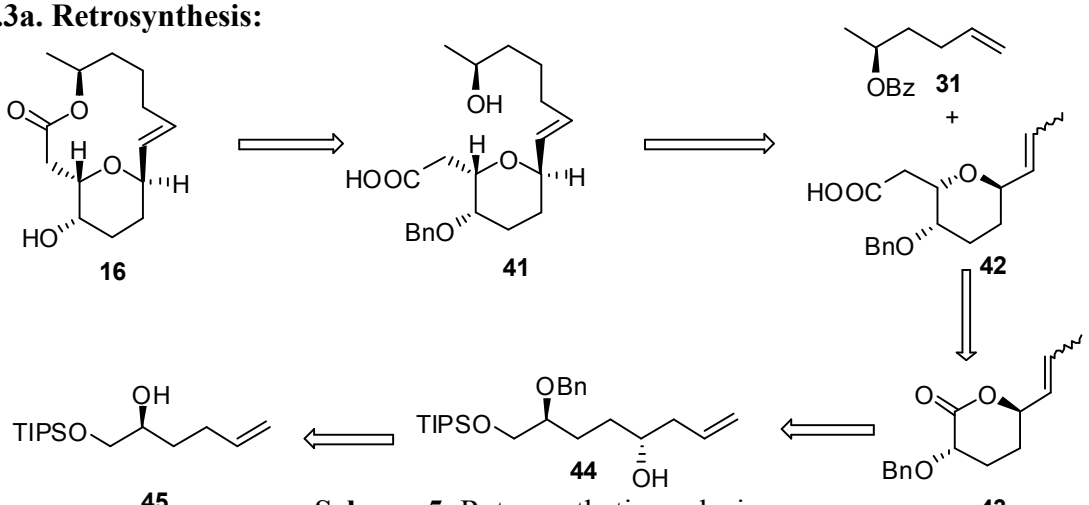
Reagents and conditions: a) $(Sia)_2BH$, THF, 0 ^oC, 1 h, then $NaHCO_3$, H_2O_2, rt, 1 h, 88%; b) TEMPO, BAIB, CH_2Cl_2, rt, 8 h, then $Ph_3P{=}CO_2Et$, rt, 15 h, 95%; c) DIBAL-*H*, CH_2Cl_2, –78 ^oC, 1 h, 100%; d) Ti(O*i*-Pr)$_4$, (+) DET, TBHP, MS, CH_2Cl_2, –25 ^oC, 24 h, 89%; e) I_2, TPP, imidazole, THF, rt, 20 min; f) Zn, AcOH, EtOH, rt, 30 min, 100%; g) Grubbs II gen. catalyst, metyl acrylate, Toluene,, rt, 2 h, 90%; h) MOMCl, $(i\text{-Pr})_2Net$, CH_2Cl_2, 50 ^oC, 7.25 h, 90%; i) TBAF, AcOH, THF, rt, 89%, then KH (1.1 eq.), THF, rt, 0.5 h, 79%; j) O_3, CH_2Cl_2, –78 ^oC, 15 min, rt, then TPP, rt overnight, 93%; k) $CrCl_2$, CHI_3, THF/dioxane, 0 ^oC, 2 h, 70% (*E:Z*/5:1); l) 9-BBN-H, THF, rt, 105 min, then aq $CsCO_3$, $PdCl_2$(dppf), Ph_3As,DMF, rt, 11 h, 73%; m) aq. NaOH, MeOH, rt, overnight, 88%; n) 2,4,6-trichlorobenzoyl chloride, NEt_3, rt, 3.5 h, then DMAP, Toluene, 100 ^oC, 6.5 h, 73%; o) $LiBF_4$, MeCN, 72 ^oC, 9 h, 94%.

In conclusion, the total synthesis of aspergillides B based on a interesting protocols that involves (i) a hydroxy-directed, highly chemoselective olefin cross-metathesis reaction of allylic alcohol **33** and (ii) a diastereoselective intramolecular oxa-conjugate cyclization of **38** to construct either 2,6-*cis*- or 2,6-*trans*-substituted tetrahydropyran substructure.

3.2.3. Macro's approach:[22]

Macrolides B was found to show cytotoxic activities, its total synthesis was reported by Macro via a cross metathesis and a C-glycosidation and a Mukaiyama-type aldol reaction.

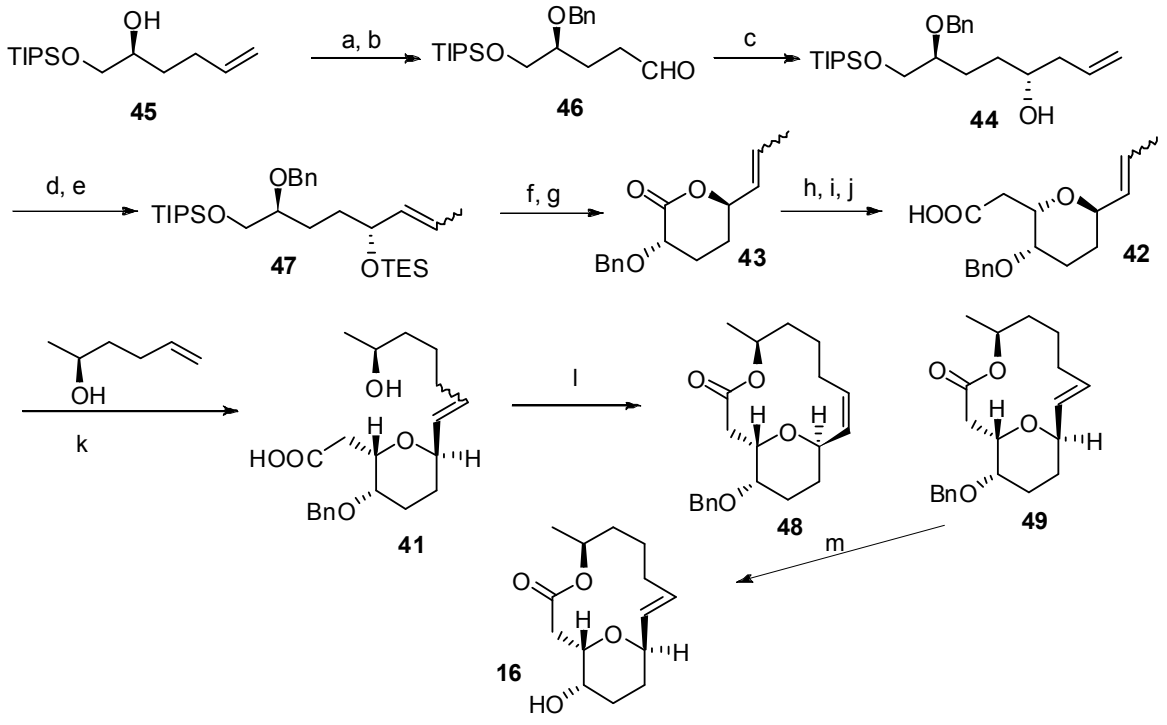
3.2.3a. Retrosynthesis:



Scheme 5: Retrosynthetic analysis

3.2.3b. Discussion:

Alcohol **45** was benzylated under mild, nonbasic conditions and ozonolytic cleavage of the olefinic bond yielded aldehyde **46**, which was first purified and then subjected to Brown's asymmetric allylboration. This gave homoallyl alcohol **47** was subsequently protected as its triethylsilyl derivative. Isomerization of the terminal olefinic bond to the internal position in **47** was achieved by utilizing the catalytic method of Wipf et al. Cleavage of the two silyl groups and selective oxidation of the primary alcohol with $PhI(OAc)_2$/TEMPO afforded *d*-lactone **43**. Reduction of **43** by using DIBAL-*H* followed by acetylative quenching yielded the acetylated lactol and the mixture was subsequently treated with the trimethylsilyl enolate of tert-butyl thioacetate in the presence of BF_3-etherate and TMSOTf. This furnished the trans-2,6-disubstituted tetrahydropyran and subsequent alkaline hydrolysis of the ester provided acid **42** in high yield. Treatment of **42** with 5 equiv of olefinic alcohol in the presence of 20% of ruthenium catalyst caused cross metathesis and afforded hydroxy acid **41** as a (7:3) *E/Z* mixture. Macrolactonization was performed on the mixture by means of the Yamaguchi procedure and gave a separable mixture of (*E*)-**49** and (*Z*)-**48**. Cleavage of the benzyl group in the former was performed with DDQ in wet CH_2Cl_2 to afford aspergillide B (**16**).



Scheme 6

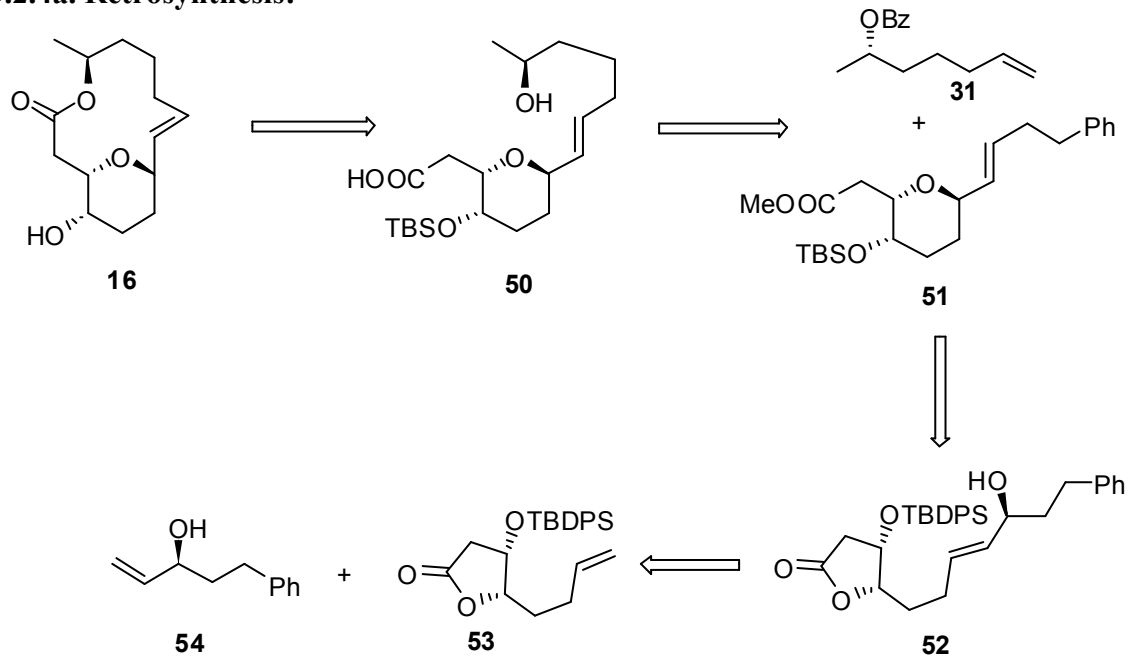
Reagents and conditions: (a) BnBr, Ag_2O, Et_2O, rt, 3 h, 83%; (b) O_3, CH_2Cl_2, –80 ^oC, 30 min, then Ph_3P, rt, 2 h, 78%; (c) allylBIpc$_2$ from (–)-DIP-Cl and allylmagnesium bromide, Et_2O, –90 ^oC, 2 h (dr >95:5); (d) TESOTf, Et_3N, CH_2Cl_2, –80 ^oC, 2 h, 77% (overall from 10); (e) Grubbs II cat. (5 mol%), N-trityl allylamine, EtNiPr_2, CH_2Cl_2, 16 h 96%, (*E/Z* 9:1); (f) TBAF, THF, rt, 16 h, 98%; (g) PhI(OAc)$_2$, TEMPO (cat.), CH_2Cl_2, 0 ^oC, 16 h (84%); (h) DIBAL, CH_2Cl_2, –80 ^oC, 2 h, then addition of Ac_2O, py, DMAP, 14 h 93%; (i) CH_2=C(OTMS)S*t*Bu, 4 Å MS, BF_3-Et_2O, TMSOTf, MeCN, 16 h, –18 ^oC, 55%; (j) NaOH, aq MeOH, rt, 16 h, 94%; (k) Grubbs II gen. cat. (20 mol%), CH_2Cl_2, reflux, 6 h 89%, (*E/Z* 7:3); (l) $Cl_3C_6H_2COCl$, Et_3N, THF, rt, 1.5 h, then DMAP, toluene, 50 ^oC, 6 h, 57%; (m) DDQ, CH_2Cl_2/H_2O 10:1, rt, 20 h, 51%.

Thus, total synthesis of aspergillide B was achieved via a cross metathesis and a C-glycosidation and a Mukaiyama-type aldol reaction were key features of the synthesis. The macrocyclic lactone ring was created by means of the Yamaguchi procedure.

3.2.4. Uenishi's approach:[23]

Uenishi and co-workers published the total synthesis of aspergillide B by the Pd^{II}-catalyzed stereospecific synthesis of tetrahydropyrans that developed by the same group for the synthesis of some natural products.

3.2.4a. Retrosynthesis:

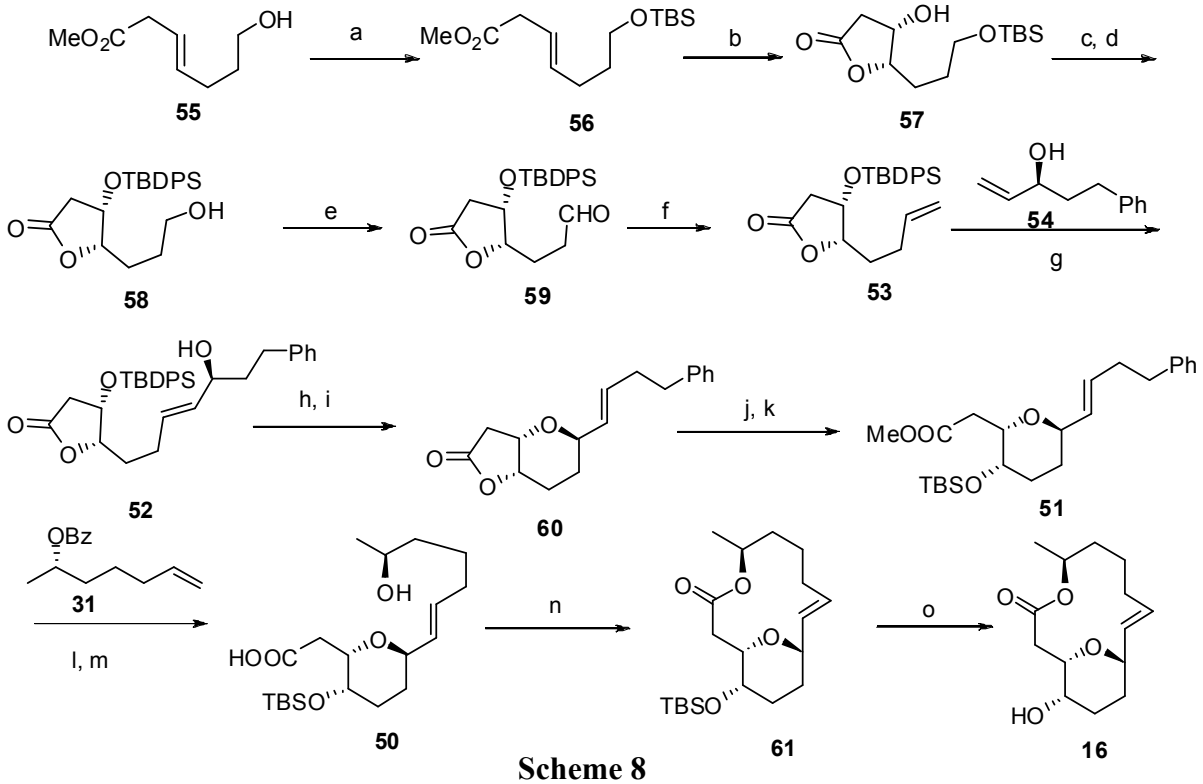


Scheme 7: Retrosynthetic analysis

3.2.4b. Discussion:

The synthesis commenced from the known methyl (*E*)-7-hydroxyhept-3-enoate (**55**). After the protection of the primary alcohol of **55** with TBSCl, alkene **56** was subjected to

the Sharpless asymmetric dihydroxylation reaction using AD-mix-α accompanied by lactonization to give the chiral β-hydroxy-γ-lactone **57**. Protection of the secondary hydroxy group with TBDPSCl and selective deprotection of TBS group by the treatment with BF3.OEt2 at -10 ^{o}C afforded **58**. The Swern oxidation of the primary alcohol gave aldehyde **59** followed by a Wittig olefination provided **53**. Next, olefin **53** was subjected to the cross-metathesis reaction with the coupling partner (*S*)-5-phenylpent-1-en-3-ol (**54**) to afford **52**. Desilylation of **52** with TBAF gave the cyclization precursor and subsequently the cyclization was carried out to give **60** by the treatment with 15 mol % of $PdCl_2(CH_3CN)_2$ in THF at 0 ^{o}C for 45 min. Methanolysis of **60** by treatment with sodium methoxide in absolute methanol and successive silylation of the axial hydroxyl group with TBSOTf in the presence of 2,6-lutidine in CH_3CN gave **51**. The required heptenol side chain on the tetrahydropyran ring for the seco acid **51** was introduced through a second cross-metathesis of the sequence with (S)-hept-6-en-2-yl benzoate (**31**) followed by hydrolysis of benzoate and methyl ester was performed in one step to give **50** and the standard Yamaguchi macrolactonization of **50** provided **61**. The final deprotection of silyl ether by the treatment of **61** with TBAF gave aspergillide B (**16**).



Scheme 8

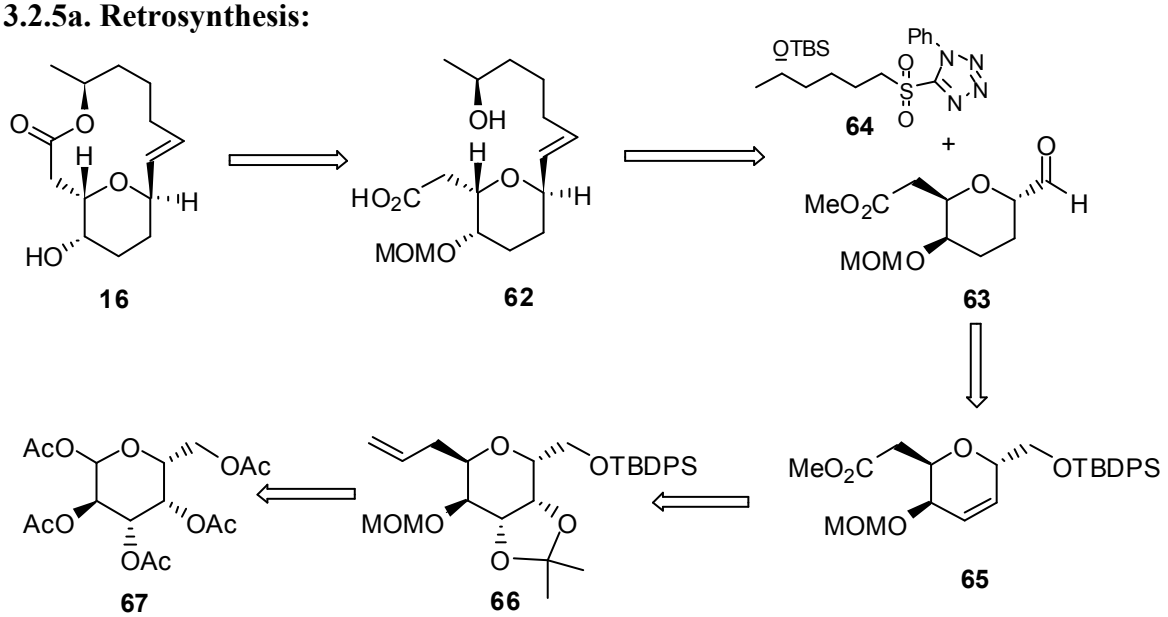
Reagents and conditions: (a) TBSCl, Et_3N, DMAP, CH_2Cl_2, 3 h, 83%; (b) AD-mix-α, $CH_3SO_2NH_2$, t-BuOH:H_2O (1:1), 0 ºC, 20 h, 89%; (c) TBDPSCl, imidazole, DMAP, CH_2Cl_2, rt, 36 h; (d) BF_3 OEt_2, CH_2Cl_2, –10 ºC, 1.5 h, 91%; (over 2 steps); (e) Swern oxidation, 98%; (f) Ph_3PCH_2, toluene, –40 - 0 ºC, 30 min, 57%; (g) Grubbs II cat. (10 mol%), $CHCl_3$, 40 ºC, 2 h, 63%; (h) TBAF, THF, 15 min, 98%; (i) $PdCl_2(CH_3CN)_2$, (15 mol%) THF, 0 ºC, 45 min, *trans* 76%; (j) MeONa, MeOH, 0 ºC, 30 min; (k) TBSOTf, 2,6-lutidine, CH_3CN, –20 ºC, 20min; 60% (over 2steps); (l) Grubbs II cat. (10 mol%), $CHCl_3$, 40 ºC, 2 h, 73%; (m)) NaOH, aq MeOH, rt, 16 h, 91%; (n) $Cl_3C_6H_2COCl$, Et_3N, THF, rt, 1.5 h, then DMAP, toluene, 50 ^oC, 6 h, 86%; (o) TBAF, THF, rt, 3 h, 98%.

Thus, fourteen-membered cytotoxic macrolide B was synthesized from a known alcohol in a 15 steps utilizing stereospecific Pd(II)-catalyzed cyclization of γ-hydroxy chiral allylic alcohol.

3.2.5. Xuegong She's approach:[24]

Xuegong She and co-workers had disclosed an efficient total synthesis of (+)-aspergillide B, which features the *C* glycosylation reaction for constructing the 2,6-*trans*-substituted pyran core, a highly effective four-step sequence without purification to produce the key intermediate **9** and an advantageous *E*-selective Julia-Kocienski olefination on a highly elaborate substrate.

3.2.5a. Retrosynthesis:

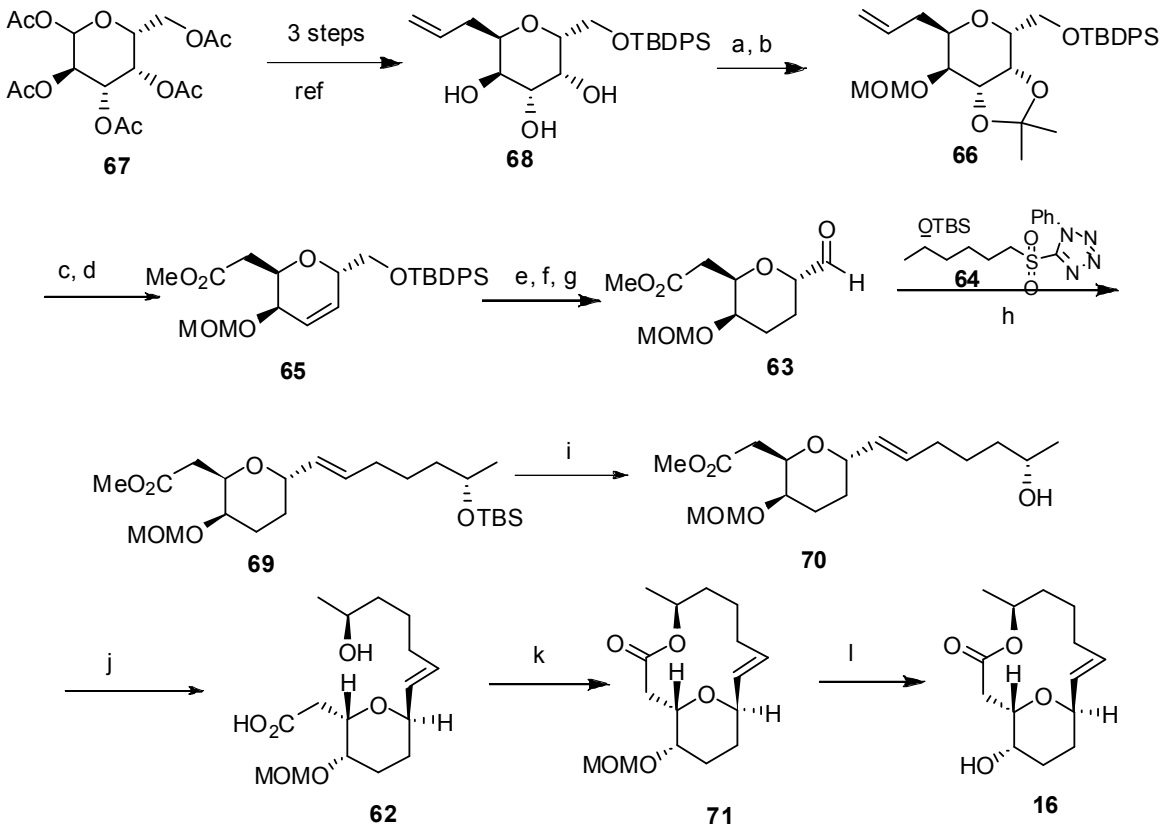


Scheme 9: Retrosynthetic analysis

3.2.5b. Discussion:

To syntheses aspergillide B, D-galactose pentaacetate **67** was chosen as a starting material. After three chemical transformations, the known triol **68** was prepared in good

selectivity and high yield.[24] The compound **65** could be easily obtained through a highly efficient sequence of reactions (protection of *syn*-dihydroxy with trimethyl orthoformate; protection the residual hydroxy as MOM ether; ozonolysis of olefin in methanolic NaOH; elimination of the orthoformate ester) without purification. Treatment of **65** with $3HF\cdot NEt_3$ deprotected the TBDPS ether smoothly and furnished dihydropyran alcohol and the Pd/ C-catalyzed hydrogenation of the dihydropyran compound was done to give alcohol and the resulting alcohol was then subjected to IBX oxidation to give the aldehyde **63**. JuliaKocienski olefination of segments **64** and **63** was done with LiHMDS in THF/HMPA at -78 °C to room temperature, and the desired *E*-olefin **69** was obtained. Removal of TBS and hydrolysis of methyl ester gave the desired *seco* acid **70**. The completion of the macrolactone **17** required the inversion of chiral center at C-13. To this end, treatment of the hydroxy acid **62** with PPh_3 and DIAD in anhydrous benzene in high dilution (1 mM) gave the desired macrolactone **71**. Deprotection of MOM group smoothly by $LiBF_4$ in CH_3CN/H_2O completed the synthesis of aspergillide B (**16**).



Scheme 10

Reagents and conditions: (a) $CH(OMe)_3$, CSA, $CHCl_3$, 0 ºC, (b) MOMCl, NaI, DIEPA, reflux, (c) NaOH, NeOH, CH_2Cl_2, O_3, –78 ºC, (d) Ac_2O, 120 ºC; 41% (over four steps.) (e) HF. Py, Et_3N, 0 ºC, 85%; (f) Pd/C, H_2, rt, (g) IBX, DMSO, rt, (h) LiHMDS, HMPA, –78 ºC, 57%; (i) HF.Py, Et_3N, CH_2Cl_2, (j) $LiOH.H_2O$, (k) Ph_3P, DIAD, Benzene, 65%; (l) $LiBF_4$, CH_3CN/H_2O 77%.

CHAPTER III

Section B

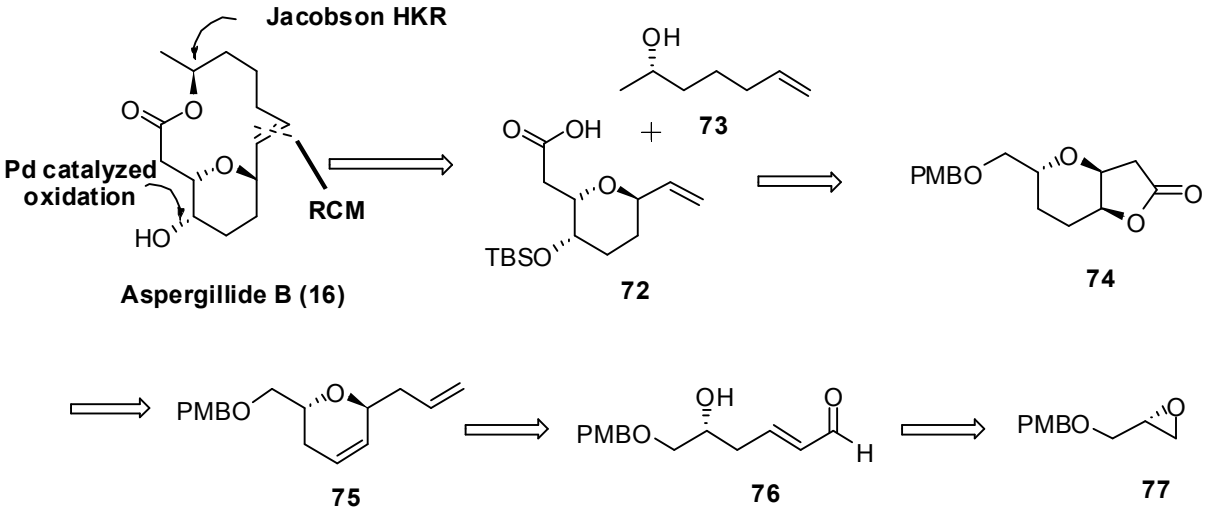
Stereoselective approach towards the total synthesis of Aspergillide B

3.3. Present Work:

The interesting biological profile and the bridged tetrahydropyran ring with required *trans*-stereochemistry had attracted us to achieve the total synthesis of Aspergillide B. Now days, our recent developed methodology, Iodocyclization is going to be a potent protocol for synthesis of trans-pyran rings by using low cost reagents with a quantitative yield. Successful implementation of iodine catalyzed cyclization to construct *trans*-pyran as well as ring-closing metathesis reaction was envisioned in the study towards the synthesis of aspergillide B (**16**).

3.3.1. Retrosynthetic analysis:

The retrosynthetic analysis for the total synthesis of Aspergillide B (**16**) is illustrated in Scheme 11. Aspergillide B **(16)** could be derived from the diene compound via ring closing metathesis which could be obtained from the acid **72**. The lactone **74** could be obtained from the *trans*-2,6,-disubstituted-3,4-Dihydropyrans compound **75** via palladium catalyzed wacker type oxidation which in turn could be drived from the aldehyde **76** by utilizing the our own developed methodology *i.e* iodocyclization. The aldehyde **76** could be obtained from the known chiral epoxide **77**.

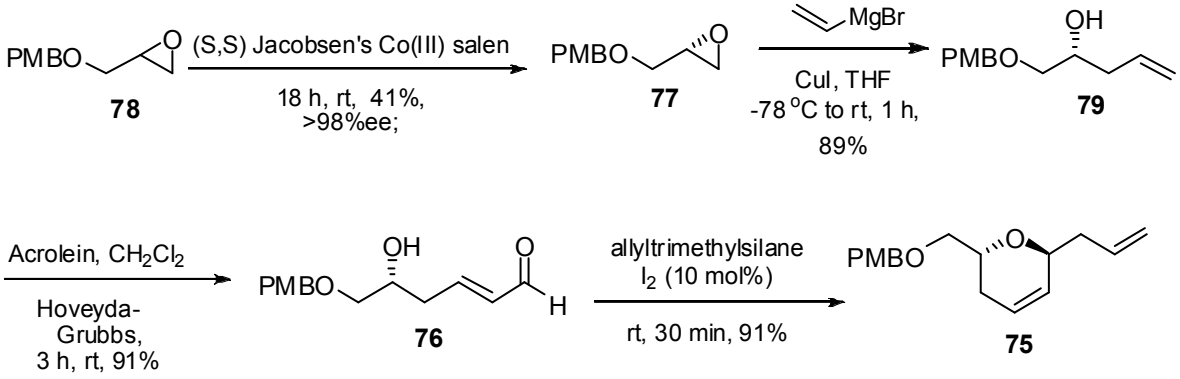


Scheme 11

3.3.2. Results and discussions:

Synthesis of acid fragment 72:

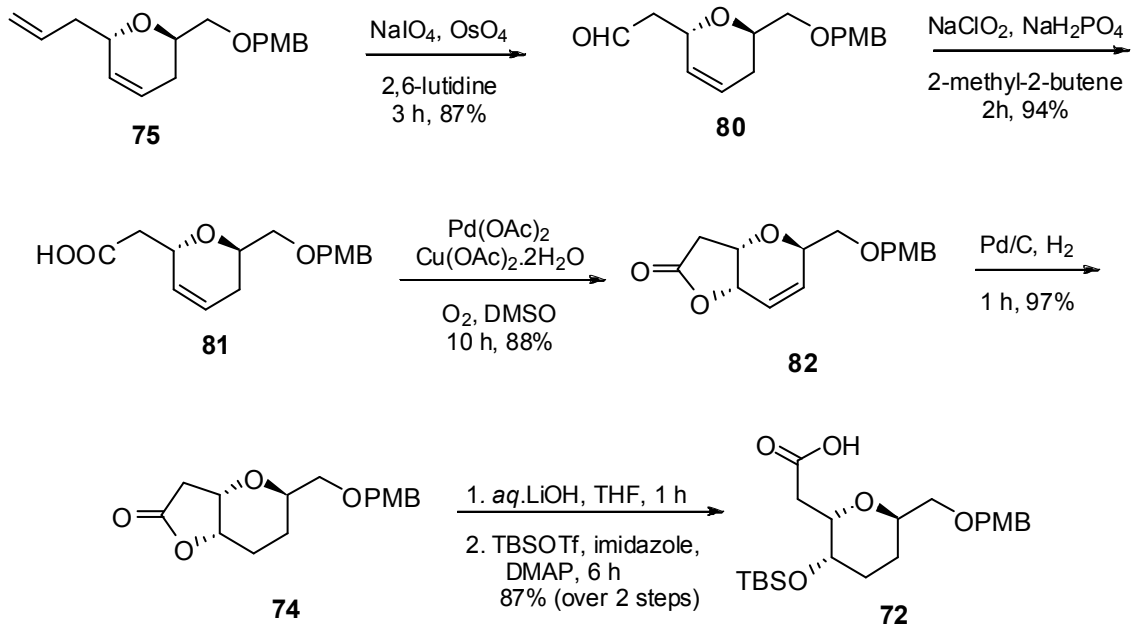
The journey towards the synthesis of subtarget **72** began the kinetic resolution of 2-(*p*-methoxybenzyloxyethyl)oxirane **78**.[25] The commercially available epichlorohydrin was converted to its *p*-methoxybenzyl ether **78** by treating with sodium hydride (60% w/v dispersion in oil) and PMB bromide in dry THF at 0 ^{o}C in 95% yield. *p*-Methoxybenzyl ether **78** was confirmed by it ^{1}H NMR spectrum, which showed resonance at 4.49 ppm as a singlet for two benzylic protons and two sets of doublet for aromatic protons at 7.26 and 6.86 ppm. The recemic terminal epoxide **78** was converted to the chiral epoxide **77** in 41% yield along with chiral diol by hydrolytic kinetic resolution employing 0.55 eq of water in the presence of 0.005 mol% of (*S,S'*)-(-)-*N*-*N*'-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt (II) (Scheme 12). The optical rotation of the compound **77** was found to be $[\alpha]_D^{25}$ –3.8 (*c* 1.4, $CHCl_3$) which was correlated with that of the earlier reported on $[\alpha]_D^{25}$ –4.0 (*c* 2.0, $CHCl_3$). Chiral epoxide was also confirmed by its ^{1}H NMR studies, which exhibited the resonance at the respective chemical shifts.



Scheme 12

Conversion of epoxide **77** into a homoallyl alcohol **79** through the copper(I)-catalyzed[26] addition of a vinyl Grignard reagent at –20 ^{o}C in 89% yield. The ^{1}H NMR spectrum of compound **79** revealed two methylene protons adjacent to the double bond at δ 2.25 ppm and characteristic terminal olefin protons at δ 5.81 ppm and 5.17 ppm. IR absorption showed characteristic band at 3431 cm^{-1} for hydroxyl functionality. The resulted homoallylic alcohol **79** was exposed for a cross-metathesis (CM) reaction between the alcohol and acrolein using a Hoveyda-Grubbs[27] catalyst (10 mol%) in CH_2Cl_2

at room temperature to afford a α,β-unsaturated aldehyde **76** in 91% yield (Scheme 12). ^{1}H NMR revealed a downfield shift for olefenic protons. The characteristic α,β-unsaturated olefenic protons resonated at δ 6.9 ppm as multiplate and δ 6.15 ppm as doublet. A doublet at δ 9.48 ppm appeared for aldehyde proton and similarly a peak at δ 193.9 ppm appeared in ^{13}C NMR spectrum for aldehyde carbon. IR spectrum showed a peak at 1686 cm^{-1} and ESI-MS also showed $(M + Na)^+$ peak at *m/z* 273 which proved the presence of conjugated aldehyde. Then, the iodocyclization reaction was performed by using 10 mol% of Iodine[19] with allyl trimethylsilane to give the trans pyran compound **75** in 91% yield. The ^{1}H and ^{13}C NMR of the product revealed a single diastereomer which was supported by HPLC analysis data (de >99%). ^{1}H NMR spectrum showed additional olefin protons at δ 5.72 (m, 1H), δ 5.15-5.03 (m, 2H) and disappearance of aldehyde peak resonated at δ 9.49 ppm in compound **76**.



Scheme 13

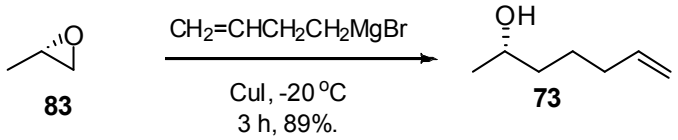
The selective oxidation of the terminal olefin in presence internal olefin in **75** was carried out under different conditions (Scheme 13). Dihydroxylation reaction under Sharpless asymmetric dihydroxylation (SAD)[28] condition using $K_3Fe(CN)_6$, OsO_4 and $(DHQD)_2$-PHAL was performed. Although reaction was selective for terminal olefin, it was slow and never went to completion. The resulted diol was chopped to corresponding aldehyde by silica gel absorbed $NaIO_4$. To avoid such type of lengthy and repeated

process, finally, we have adopted a recently developed one step dihydroxylation-oxidation protocol[29] where OsO_4, 2,6 lutidine, $NaIO_4$ were used as reagents and 1,4 dioxane-H_2O (3:1) mixture used as solvent system. Reaction completed in 1 h the and the desired aldehyde **80** was produced in 87% yield. The aldehyde thus obtained was unstable in nature, passed through a bed of silia gel and immidiately used for the next step without further characterization followed by oxidation of the resulted aldehyde **80** under Pinnick[30] conditions using $NaClO_2$, $NaH_2PO_4.H_2O$, 2-methyl-2-butene (Scheme 13) afforded a carboxylic acid **81** in 94% yield. A peak at m/z $[M + Na]^+$ 315 in ESI-MS spectrum was helped us to confirm product formation. A very broad absorption trough at 3036 cm^{-1} and another at 1729 cm^{-1} in IR spectra are indicating the presence of acid group. It's ^1H NMR revealed absence of peaks for terminal olefenic protons whereas other spectral data were in complete agreement with the product. The acid **81** underwent a palladium catalyzed wacker type oxidation[31] with $Pd(OAc)_2$, $Cu(OAc)_2 2H_2O$ under oxygen atmosphere in DMSO to afford the lactone **82** in 88% yield. The product ^1H NMR showed a new peak as multiplates at δ 6.18-6.08 ppm for olefenic protons and also showed disappearance methelene peak at δ 2.07-1.98 ppm. ^{13}C NMR spectrum also showed disappearance of one peaks at δ 26.6 ppm and appearance of another peak for oxirane carbons. IR absorption spectrum revealed a sharp peak at 1771 cm^{-1} which unambiguously proved the formation of a γ-lactone. A peak at m/z $[M + Na]^+$ 313 in ESI-MS spectrum was helped us to confirm product formation. Hydrogenation of the double bond in the lactone **82** was taken place with Pd/C under high pressure hydrogen atmosphere to give the saturated lactone **74** in 97% yield. The compound **74** was characterized by ESI-MS which showed $(M + Na)^+$ peak at *m/z* 315 and ^{13}C NMR spectrum shows absence of olefinic carbons at 133.4 and 121.3 ppm. The absence of characteristic olefenic protons and appearance of a multiplates at δ 2.11-1.84 ppm for 4 saturated protons in ^1H NMR confirmed the reduction of double bond in **82**. The hydrolytic cleavage of the lactone **74** was performed by using aqueous lithium hydroxide in THF at ^oC in 2 h. The resulting lithiated salt of the hydroxyl acid was allowed to react with TBSOTf and imidazole[32] in DMF at rt to afford the di-TBS ether to which water was added and stirred for another 2 h in at rt to obtain the required TBS protected hydroxyl acid compound **72** in 87 % yield (over two steps). The ^{13}C NMR spectra of compounds **72** was revealed the formation of TBS acid due to the presence of

silyl methyl carbons at δ -4.8 and -4.9 ppm and ESI-MS showed $(M + Na)^+$ peak at *m/z* 447. The characteristic protons for TBS in ^1H NMR was further confirmed the product.

Synthesis of alcohol fragment 73:

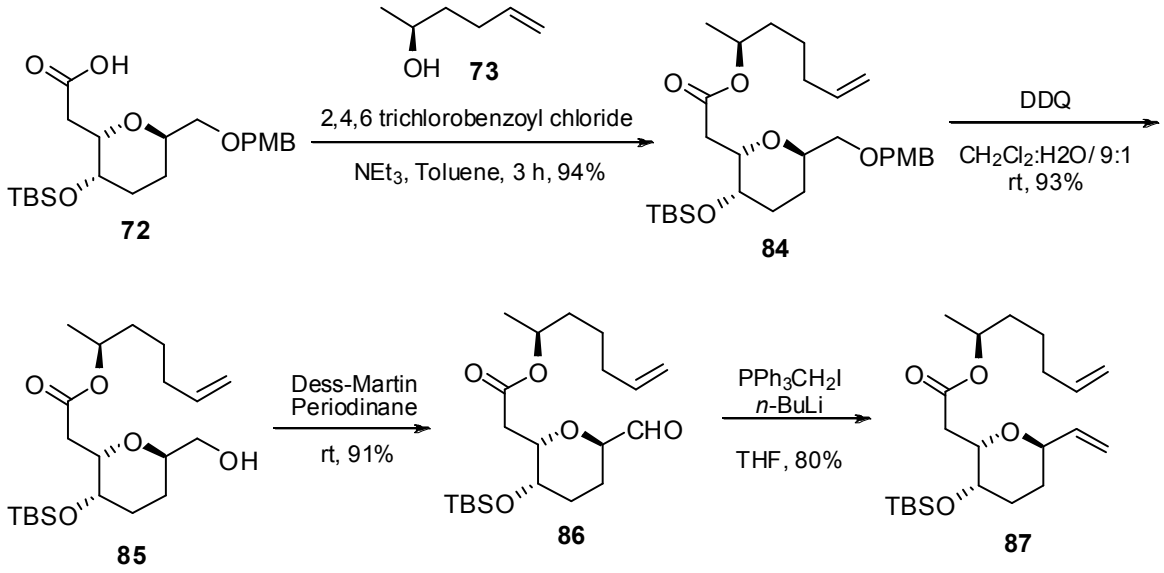
Chiral propylene oxide **83** was taken as the starting material for the synthesis of the alcohol fragment **73** which was prepared by the well known reaction Jcobsen Hydrolytic kinetic resolution[25]. SN_2 type epoxide opening of Chiral propylene oxide was achieved through CuI catalyzed epoxide opening with the Grignard reagent generated from homoallyl bromide furnished the known alcohol **73** in 89% yield **(**Scheme 14**)** and all data of the product were completely matched with the reported one.



Scheme 14

Synthesis of Aspergillide B:

With alcohol fragment **73** and acid fragment **72** in hand, our next task was to couple both of the fragments. The coupling of acid and alcohol was performed under Yamaguchi condition[33] by using 2,4,6-Trichloro benzoyl chloride, Et_3N and DMAP in toluene to give the couple product **84** in 94% yield. The terminal olefin of the product resonated as two set of multiplets at δ 5.77 and 5.02-4.86 ppm and a doublet at δ 1.18 ppm in ^1H NMR spectrum. ^{13}C NMR spectra were in full accord with the product where TBS, PMB, olefins and other functionalities resonated at their respective positions. A peak at *m/z* $[M + Na]^+$ 543.2768 in ESI-HRMS further confirmed its formation. IR absorption spectrum also showed a peak at 1731 cm^{-1} for the ester moiety. Deprotection of the PMB ether in **84** upon treatment with DDQ[34] afforded the desired primary alcohol **85** in 93% yield. ^1H NMR revealed the absence of a set of two doublets at δ 7.23, 6.86 ppm, a singlet at δ 4.45 ppm for two benzylic protons of ^1H NMR group and also ^{13}C NMR spectra revealed the absence of characteristic carbon peaks at δ 159.1, 130.4, 129.2 and 113.6 ppm for PMB group. A peak at 3465 cm^{-1} appeared and simultaneously a peak at 1513 disappered in IR specteum further confirmed the introduction of a hydroxyl group and deprotection of the PMB group respectively. The primary alcohol **85** was oxidized to the corresponding aldehyde **86** with Dess-Martin periodinane[35] reagent (Scheme 15) which was unstable in

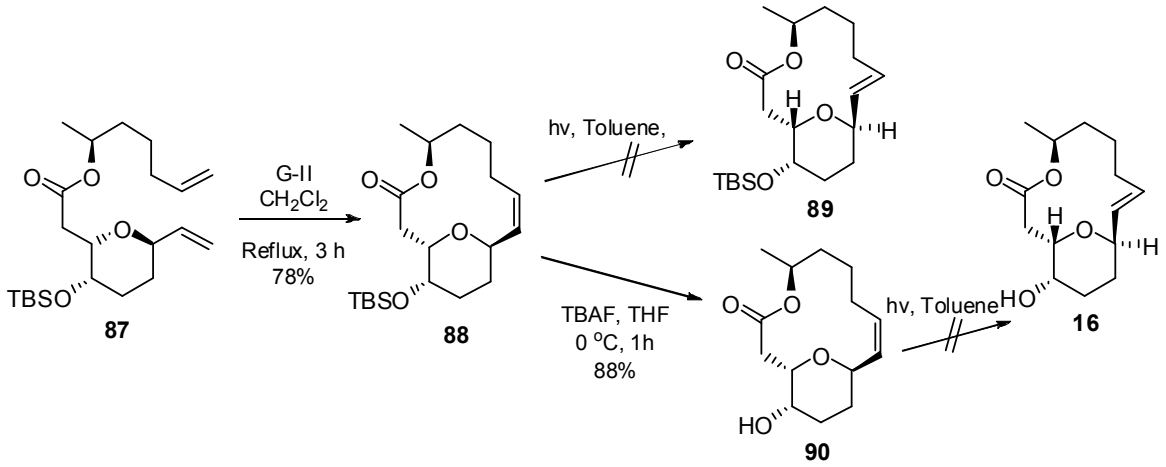


Scheme 15

nature and quickly purified by a short flash column chromatography and directly used for the one carbon homologation without further characterization. The aldehyde **86** was then subjected to one carbon homologation[36] with the methyltriphenyl phosphoniumiodide and *n*-BuLi as base at –20 ^{o}C furnished the terminal olefin **87** in 80% yield. The product ^{1}H NMR showed some new peaks at δ 5.90-5.69 and 5.29-5.10 ppm for olefenic protons and also showed disappearance of the peak at δ 3.61 and 3.47 ppm for terminal hydroxyl group. ^{13}C NMR spectrum also showed appearance of two peaks at δ 138.0 and 115.6 ppm was confirmed the introduction of the double bond. A peak at m/z $[M + Na]^{+}$ 419.2582 in ESI-HRMS spectrum was helped us to confirm product formation.

Now the diene in hand, our next plan was to perform the crucial ring closing metathesis[37] reaction. The diene **87** when treated with Grubbs 2nd generation catalyst in CH_2Cl_2 at refluxing condition, **88** was formed which was associated with the unrequired *cis* double bond with 78% yield. The formation of the unrequired macrolide was confirmed by the relative studies of ^{1}H NMR and ^{13}C NMR. ESI-HRMS showed $(M + Na)^{+}$ peak at *m/z* 391.2269 which gave additional information regarding the RCM product. The compound **88** was exposed to *hv* for photochemical isomerisation of the *cis* double bond to *trans* double bond, but this reaction was proven unsuccessful by giving untraced compound. Finally, TBS group in **88** was deprotected with TBAF in THF as solvent at 0 ^{o}C to furnish the *cis* isomer of aspergillide B (**90**) in 88% yield. The product was

characterized by showing the presence of all required peaks in ^{1}H NMR, ^{13}C NMR, IR spectra and also the absence of characteristic peaks for TBS group. Also a peak at m/z [M + Na]$^{+}$ 419.2582 in ESI-HRMS spectrum was helped us to confirm formation cis isomer of Aspergillide B (**90**). The photochemical iso-merisation[38] of the compound **90** was again failed to give the target molecule Aspergillide B (**16**) (Scheme 16).



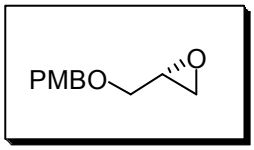
Scheme 16

Thus, we successfully implemented the iodine catalyzed cyclization of the *δ*-hydroxy *α,β*-unsaturated aldehyde followed by ring closing metathesis reaction towards the total synthesis of Aspergillide B.

Experimental Section

3.4. EXPERIMENTAL SECTION

3.4.1. Jacobsen hydrolytic kinetic resolution: (2*S*)-2-[(4 Methoxybenzyl)oxy]methyl-oxirane (77):



A mixture of (*R*,*R*)-*N*,*N*'-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino-Co (II) complex (94 mg, 0.157 mmol), toluene (5 mL) and acetic acid (0.017 mL, 0.31 mmol) was stirred in an open air for 1 h at room temperature. The solvent was removed in a rotary evaporator under reduced pressure and the brown residue (*S*,*S*)-*N*,*N*'-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino-$Co^{(III)}$-acetate, (Salen)$Co^{(III)}$(OAc) complex was dried under vacuum. The brown residue was then added to racemic epoxide **78** (12.0 g, 62.54 mmol) and the stirred mixture was then cooled in an ice-water bath. Water (0.64 mL, 34.4 mmol) was slowly added keeping the bath temperature 15 °C. After 1 h, the ice-water bath was removed and the reaction mixture was stirred at room temperature for 16 h. The crude reaction was purified by silica gel column chromatography to afford the chiral epoxide **77** (5.2 g, 42%) as a liquid product. Chiral HPLC (Gilson): 96% ee was found using CHIRAL CEL OD-H column. Column size: 0.46 cm I.D. × 15 cm. Eluent: Hexane/IPA (9/1) with flow rate1.0 ml/min at 25 °C (λ_{max} = 214 nm).

$[\alpha]_D^{25}$: -3.8 (*c* 1.4, $CHCl_3$);

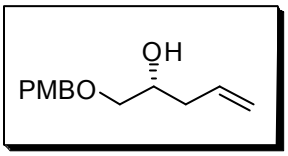
IR (neat, KBr) : ν_{max} 3000, 2922, 2860, 1612, 1513, 1248, 1176, 1090, 1033, 823, 771 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) : δ 7.26 (d, *J* = 8.3 Hz, 2 H), 6.86 (d, *J* = 8.3 Hz, 2 H), 4.49 (q, *J* = 11.5 Hz, 2 H), 3.77 (s, 3H), 3.71 (dd, *J* = 3.0, 11.3 Hz, 1H), 3.38 (dd, *J* = 5.8, 11.3 Hz, 1H), 3.15 (m, 1H), 2.76 (m, 1H), 2.58 (m, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) : δ 159.1, 129.8, 129.1, 113.6, 72.8, 70.3, 55.0, 50.6, 44.0 ppm;

ESI-MS : *m/z* calcd for $C_{29}H_{38}NaO_5Si$ [M + Na]+ 217.

3.4.2. (*R*)-1-(4-methoxybenzyloxy)pent-4-en-2-ol (79):



A freshly prepared vinyl magnesium bromide (51.5 mL, 51.54 mmol) (1 M solution in THF) was added drop wise to a solution of CuI (0.49 g, 2.58 mmol) in THF (80 mL) at –20 °C. The mixture was stirred from 30 minutes and chiral epoxide **77** (5.0 g, 25.77 mmol) was added in THF (50 mL) dropwise to the above mixture. After 2 h, the reaction (monitored by TLC) was quenched with saturated solution of NH_4Cl (75 mL) and diluted with diethyl ether (50 mL). The two layers were separated and the aqueous layer extracted with diethyl ether (3 x 75 mL). The combined organic layer was washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get the crude mass. Purification by flash column chromatography over silica gel (ethyl acetate: hexane = 1:9) afforded the desired homoallyl alcohol **79** (75.09 g, 89%) as a colorless oil.

$[\alpha]_D^{25}$: +3.5 (*c* 0.8, $CHCl_3$);

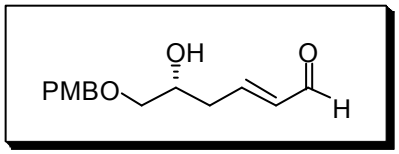
IR (neat, KBr) : ν_{max} 3431, 3004, 2934, 2910, 2864, 1708, 1640, 1608, 1513, 1253, 1171, 1101, 1032, 771 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) : δ 7.25 (d, *J* = 8.3 Hz, 2 H), 6.88 (d, *J* = 8.3 Hz, 2 H), 5.81 (m, 1H), 5.17-5.04 (m, 2H), 4.48 (s, 2 H), 3.86 (m, 1H), 3.8 (s, 3H), 3.50 (m, 1H), 3.34 (m, 1H), 2.25 (t, *J* = 6.8 Hz, 2H);

^{13}C NMR (75 MHz, $CDCl_3$) : δ 159.0, 134.1, 129.8, 129.1, 117.2, 113.5, 73.4, 72.7, 69.4, 54.9, 37 ppm;

ESI-MS : *m/z* calcd for $C_{29}H_{38}NaO_5Si$ [M + Na]+ 245.

3.4.3. (*R*,*E*)-5-hydroxy-6-(4-methoxybenzyloxy)hex-2-enal (76):



To a solution of methyl ether compound **79** (4.9 g, 22.07 mmol) in CH_2Cl_2 (15 mL) was added Hoveyda-Grubbs catalyst (0.98 mg, 2.2 mmol) followed by acrolein (12.0 g, 220.7 mmol) at room temperature under nitrogen atmosphere and the resulting mixture was stirred at the same temperature for 3 h. After completion of the reaction (monitored by TLC), it was concentrated to dryness under reduced pressure and the crude oil was directly purified by short flash column chromatography over silica gel (ethyl acetate: hexane = 1:7) furnished the desired *α,β* unsaturated aldehyde **76** (45.03 g, 91%) as a colorless liquid.

$[\alpha]_D^{25}$: −12.5 (*c* 0.8, $CHCl_3$);

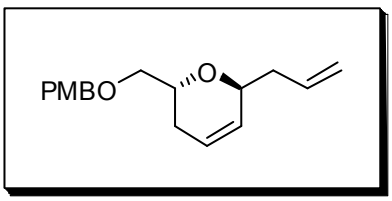
IR (neat, KBr) : ν_{max} 3006, 2908, 2867, 1686, 1612, 1513, 1247, 1220, 1091, 1033, 771 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) : δ 9.48 (d, *J* = 7.74 Hz, 1H), 7.24 (d, *J* = 8.49 Hz, 2H), 6.93-6.83 (m, 3H), 6.15 (d, *J* = 7.74, 15.67 Hz, 1H), 4.47 (s, 2H), 3.96 (m, 1H), 3.79 (s, 3H), 3.49 (dd, *J* = 3.5, 9.8 Hz, 1H), 3.36 (dd, *J* = 6.9, 9.8 Hz, 1H), 2.47 (t, *J* = 6.9 Hz, 2H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) : δ 193.9, 159.3, 154.2, 134.6, 129.5, 129.4, 113.8, 73.2, 73.0, 68.9, 55.2, 36.5 ppm;

ESI-MS : *m/z* calcd for $C_{29}H_{38}NaO_5Si$ [M + Na]+273 .

3.4.4. (2*R*,6*S*)-6-allyl-2-((4-methoxybenzyloxy)methyl)-3,6-dihydro-2H-pyran (75):



To a stirred solution of δ-hydroxyl *α,β*-unsaturated aldehyde **76** (5.0 g, 20.0 mmol), and allyltrimethylsilane (3.42 g, 30.0 mmol) in THF (40 mL) was added iodine (0.5 g, 2 mmol) at 0 ^oC under nitrogen atmosphere and allowed to come to room temperature. After completion of the reaction (as indicated by TLC) (30 min), the reaction mixture was quenched with saturated solution of $Na_2S_3O_3$ (15 mL). The reaction mixture was extracted with *t*-butyl methyl ether (TBME) (2 x 30 mL), combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a pale yellow oil

which was purified by silica gel column chromatography using (ethyl acetate: hexane = 3: 97) as eluent to obtain the cyclized product **75** (4.98 g, 91%) as a colourless liquid.

$[\alpha]_D^{25}$: +98.8 (*c* 1.2, $CHCl_3$);

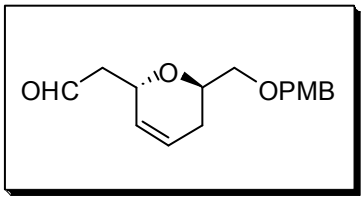
IR (neat, KBr) : ν_{max} 3034, 2928, 2912, 2862, 1640, 1612, 1513, 1248, 1089, 1036, 825 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) : δ 7.27 (d, *J* = 8.49 Hz, 2H), 6.87 (d, *J* = 8.68 Hz, 2H), 5.94-5.79 (m, 2H), 5.72 (m, 1H), 5.15-5.03 (m, 2H), 4.51 (q, *J* = 11.7 & 15.29 Hz, 2H), 4.24 (m, 1H), 3.96 (m, 1H), 3.80 (s, 1H), 3.55 (m, 1H), 3.45 (m, 1H), 2.45 (m,1H), 2.28 (m, 1H), 2.05-1.98 (m, 2H) ppm;

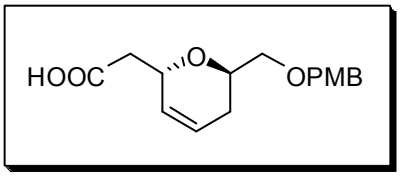
^{13}C NMR (75 MHz, $CDCl_3$) : δ 159, 134.8, 129.2, 129.0, 123.8, 116.9, 113.6, 72.8, 72.2, 72.1, 67.1, 55.1, 38.8, 27.0 ppm;

ESI-HRMS : *m/z* calcd for $C_{29}H_{38}NaO_5Si$ $[M + Na]^+$ 297.

3.4.5. 2-((2*S*,6*R*)-6-((4-Methoxybenzyloxy)methyl)-5,6-dihydro-2*H*-pyran-2-yl)acetic acid (81):



To a stirred solution of **75** (4.9 g, 17.88 mmol) in 1,4-dioxane (50 mL), was added 2,6- lutidine (2.7 mL, 71.53 mmol). $NaIO_4$ (15.3 g, 71.53 mmol) was dissolved in distilled water (20 mL) and then added to the reaction mixture. Finally, OsO_4 (1.8 mL, 1.78 mmol, 1 M solution in toluene) was added and stirring was continued under dark condition. After completion of the reaction (as indicated by TLC), the reaction mixture was quenched with saturated aq. $NaHSO_3$ (10 mL) solution. Organic solvent was removed under reduced pressure, aqueous layer extracted with *t*-butyl methyl ether (3 x 50 mL), the combined organic layer was washed with 1 N HCl (3 x 50 mL) to remove excess lutidine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a colorless oil which was purified by silica gel column chromatography using 20% ethyl acetate: hexane as eluent to give aldehyde **80** (4.29 g, 87%) as a colorless liquid which was immediately used for next step without further characterization.



To a solution of aldehyde **80** (4.1 g, 14.80 mmol) in *tert*-butyl alcohol (45 mL), 2-methyl-2-butene (14.8 mL, 14.8 mmol, 1M solution in THF) was added at room temperature. Sodium dihydrogenphosphate (6.5 g, 44.56 mmol) and sodium chlorite (2.0 g, 22.28 mmol) were dissolved in water (20 mL) to make a clear solution which was subsequently added to the above mentioned reaction mixture at 0 ^{o}C. It was allowed to stir for further 3 h at room temperature. The reaction mixture was extracted with ethyl acetate (3 x 100 mL), the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by silica gel chromatography (EtOAc: hexane = 3:7) to afford acid **81** (4.07 g, 94%) as a colorless oil.

$[\alpha]_D^{25}$: +27.0 (*c* 0.9, $CHCl_3$);

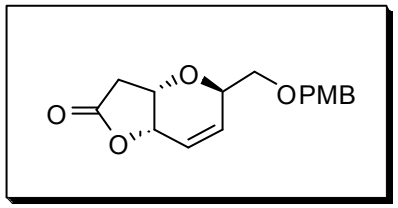
IR (neat, KBr) : ν_{max} 3036, 2923, 1729, 1712, 1612, 1513, 1248, 1092, 1035, 824, 715 cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$) : δ 7.22 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 5.88 (m, 1H), 4.66 (m, 1H), 4.48 (s, 2H), 3.90 (m, 1H), 3.79 (s, 3H), 3.51 (dd, *J* = 6.4, 10.2 Hz, 1H), 3.43 (dd, *J* = 4.5, 10.2 Hz, 1H), 2.71 (dd, *J* = 9.2, 15.3 Hz, 1H), 2.50 (dd, *J* = 4.9, 15.3 Hz, 1H), 2.07-1.98 (m, 2H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) : δ 174.4, 159.2, 130.0, 129.4, 127.5, 125.1, 113.7, 73.0, 71.7, 69.1, 67.5, 55.2, 38.7, 26.6 ppm;

ESI-MS : *m/z* calcd for $C_{16}H_{20}NaO_5$ $[M + Na]^+$ 315;

3.4.6. (3a*S*,5*R*,7a*S*)-5-((4-Methoxybenzyloxy)methyl)-3,3a,5,7a-tetrahydro-2H-furo[3,2-b]pyran-2-one (82):



A solution of acid **81** (4.0 g, 13.69 mmol), $NaOAc.3H_2O$ (43.7 g, 27.39 mmol), $Cu(OAc)_2$ (4.9 g, 27.39 mmol) and $Pd(OAc)_2$ (0.3 g, 1.37 mmol) in DMSO was stirred at 80 ^oC under O_2 atmosphere for 8h. After dilution with saturated NH_4Cl (50 ml) and extraction with DCM (5x50 ml). The combined layer were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by flash chromatography (EtOAc: hexane = 1:2) afforded the lactone **82** (3.49 g, 88%) as a colorless oil.

$[\alpha]_D^{25}$: −12.5 (*c* 0.8, $CHCl_3$);

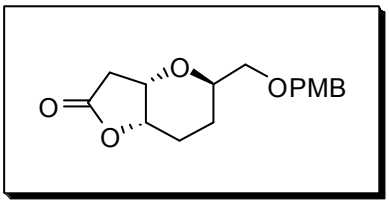
IR (neat, KBr) : ν_{max} 2932, 2859, 1788, 1771, 1611, 1513, 1249, 1155, 1036, 835 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) : δ 7.19 (d, *J* = 8.3 Hz, 2 H), 6.82 (d, *J* = 8.3 Hz, 2 H),), 6.18-6.08 (m, 2H), 4.60 (m, 1H), 4.48 (m, 3H), 4.32 (m, 1H), 3.79 (s, 3H), 3.52 (d, *J* = 6.4 Hz, 2H), 3.43 (dd, *J* = 4.5, 10.2 Hz, 1H), 2.72 (dd, *J* = 9.2, 15.3 Hz, 1H), 2.50 (d, *J* = 15.3 Hz, 1H)ppm;

^{13}C NMR (75 MHz, $CDCl_3$) : δ 175.2, 159.4, 133.4, 129.7, 129.3, 121.3, 113.9, 73.0, 72.2, 71.3, 69.7, 55.3, 37.0 ppm;

ESI-MS : *m/z* calcd for $C_{16}H_{18}NaO_5$ $[M + Na]^+$ 313;

3.4.7. (3a*S*,5*R*,7a*S*)-5-((4-Methoxybenzyloxy)methyl)-hexahydrofuro[3,2-b]pyran-2-one (74):



Pd/C (10%) (50 mg) was added to a stirred solution of the compound **82** (3.2 g, 11.03 mmol) in toluene (30 mL) followed by catalytic amount of triethylamine at room temperature under hydrogen atmosphere. The mixture was stirred for 1 h at room temperature. After complete consumption of the starting material (monitored by TLC), the black reaction mass was filtered through a pad of Celite and then thoroughly washed with ethyl acetate (3 x 25 mL). The filtrate was concentrated under reduced pressure and

purification of the crude product by silica gel column chromatography (ethyl acetate: hexane = 1:7) furnished the desired product **74** (3.14 g, 97%) as a colorless liquid.

$[\alpha]_D^{25}$: − 31.8(*c* 0.8, $CHCl_3$);

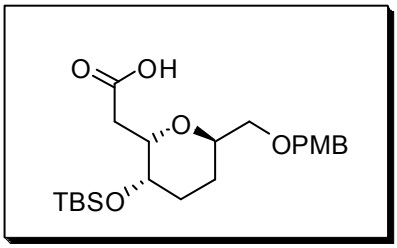
IR (neat, KBr) : ν_{max} 2929, 2857, 1730, 1712, 1612, 1513, 1248, 1095, 1037, 821 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) : δ 7.2 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 4.46 (s, 2H), 4.43-4.36 (m, 2H), 3.94 (pentet, 1H), 3.80 (s, 3H), 3.56 (dd, *J* = 5.9, 10.0 Hz, 1H), 3.48 (dd, *J* = 4.9, 10.2 Hz, 1H), 2.62 (dd, *J* = 4.7, 17.6 Hz, 1H), 2.53 (dd, *J* = 1.2, 17.4 Hz, 1H), 2.11-1.84 (m, 4H);

^{13}C NMR (75 MHz, $CDCl_3$) : δ 175.8, 159.2, 131.7, 129.3, 113.8, 77.0, 72.9, 70.4, 69.6, 68.3, 55.2, 37.1, 21.5, 19.7 ppm;

ESI-MS : *m/z* calcd for $C_{16}H_{20}NaO_5$ $[M^+ Na]$+ 315;

3.4.8. 2-((2*S*,3*S*,6*R*)-3-(*tert*-Butyldimethylsilyloxy)-6-((4-methoxybenzyloxy)methyl-tetrahydro-2H-pyran-2-yl)acetic acid (72):



To a solution of lactone **74** (3.05 g, 10.37 mmol) in THF (15 mL) was added LiOH soluiton (0.75 g, 31.12 mmol, dissolved in 1 mL H_2O) was added. The resulting solution was stirred for 3 h at room temperature. After completion of reaction (monitored by TLC), THF was removed under reduced pressure. The reaction mixture was further dried to get a solid mass via azeotropic removal of residual water with benzene. The solid mass was then dissolved in dry DMF (8 mL) and to it, imidazole followed by TBSOTf (9.4 mL, 39.35 mmol), DMAP (0.2 g, 1.03 mmol) were added at 0 ^oC. The resulting mixture was stirred for 12 h. TLC was checked and it showed complete consumption of the starting material. The reaction mixture was quenched with H_2O (15 mL) and stirred for 1 h. Then saturated solution of $KHSO_4$ (15 mL) was added and stirred for 3 h to ensure the

deprotection of acid TBS group. Finally, organic compound was extracted with diethyl ether (5 x 30 mL). The combined organic layer was washed with brine (2 x 20 mL), dried over anhydrous Na_2SO_4, evaporated to dryness under reduced pressure which on silica gel column chromatography (EtOAc: hexane = 1: 4) gave the desired TBS acid **72** (3.82 g, 87%) as a colorless thick liquid.

$[\alpha]_D^{25}$: − 20.8 (*c* 1.2, $CHCl_3$);

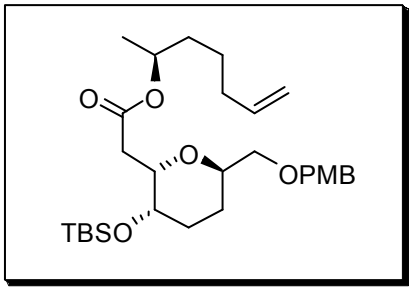
IR (neat, KBr) : ν_{max} 2935, 2858, 1712, 1612, 1513, 1250, 1104, 1038, 838, 777 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) : δ 7.2 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 4.43 (s, 2H), 4.30 (pentet, 1H), 3.88-3.78 (m, 2H), 3.75 (s, 3H), 3.42 (dd, *J* = 5.8, 10.2 Hz, 1H), 3.33 (dd, *J* = 4.3, 10.0 Hz, 1H), 2.74-2.59 (m, 2H), 1.78-1.68 (m, 2H), 1.58-1.34 (m, 2H), 0.82 (s, 9H), 0.01 (s, 6H);

^{13}C NMR (75 MHz, $CDCl_3$) : δ 176.9, 159.1, 130.1, 129.3, 113.7, 73.1, 72.8, 71.6, 68.7, 67.8, 55.2, 32.0, 27.2, 25.7, 17.9, - 4.8, -4.9 ppm;

ESI-MS : *m/z* calcd for $C_{22}H_{36}NaO_6Si$ [M + Na]+ 447.

3.4.9. (*R*)-hept-6-en-2-yl 2-((2*S*,3*S*,6*R*)-3-(*tert*-Butyldimethylsilyloxy) -6-((4-Methoxy-benzyloxy)methyl)-tetrahydro-2H-pyran-2-yl)acetate (84):



To a stirred solution of the acid **72** (3.6 g, 8.49 mmol) in dry toluene (30 mL) at 0 ^oC, Et_3N (4.7 mL, 33.96 mmol) followed by 2,4,6-trichlorobenzoyl chloride (5.3 mL, 33.96 mmol) was added and stirred for 30 min at room temperature. DMAP (0.9, 8.49 mmol) and alcohol **73** (1.7 g, 16.98 mmol) was dissolved in dry toluene (10 mL) and this was added to the above mentioned solution at 0 oC and allowed to stir at room temperature for

6 h. After completion of the reaction (monitored by TLC), it was diluted with ethyl acetate (50 mL) and water (50 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (5 x 50 mL). The combined organic layer was washed with Na_2CO_3 (2 x 100 mL), brine (2 x 50 mL), dried over anhydrous Na_2SO_4 and solvent evaporated under reduced pressure to give a colorless oil which on purification by silica gel column chromatography (ethyl acetate: hexane = 1:12) furnished the desired coupled product **84** (4.33 g, 94%, based on the starting acid) as a colorless liquid.

$[\alpha]_D^{25}$: − 34.0 (*c* 0.6, $CHCl_3$);

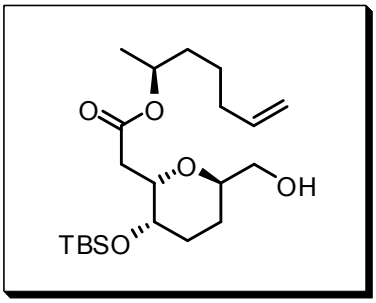
IR (neat, KBr) : ν_{max} 2930, 2857, 1731, 1612, 1513, 1251, 1099, 1057, 836, 777 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) : δ 7.23 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 5.77 (m, 1H), 5.02-4.86 (m, 3H), 4.45 (s, 2H), 4.35 (pentet, *J* = 5.0 Hz, 1H), 3.88 (m, 1H), 3.80 (s, 3H), 3.78 (m, 1H), 3.43 (dd, *J* = 4.9, 9.8 Hz, 1H), 3.36 (m, 1H), 2.7 (m, 1H), 2.57 (dd, *J* = 4.4, 15.4 Hz, 1H), 2.07-1.99 (m, 2H), 1.80-1.71 (m, 2H), 1.62-1.53 (m, 6H), 1.18 (d, *J* = 5.9 Hz, 3H), 0.87 (s, 9H), 0.05 (s, 6H);

^{13}C NMR (75 MHz, $CDCl_3$) : δ 171.7, 159.1, 138.4, 130.4, 129.2, 114.6, 113.6, 73.9, 72.9, 72.1, 70.8, 68.2, 68.0, 55.2, 35.3, 33.5, 31.9, 27.4, 26.4, 25.7, 24.5, 19.9, 17.9, − 4.7, − 4.9 ppm;

ESI-HRMS : *m/z* calcd for $C_{29}H_{48}NaO_6Si$ [M + Na]+ 543.2749; found 543.2768.

3.4.10. (*R*)-hept-6-en-2-yl 2-((2*S*,3*S*,6*R*)-3-(tert-butyldimethylsilyloxy)-6--(hydroxymethyl)-tetrahydro-2H-pyran-2-yl)acetate (85):



To a solution of PMB ether **84** (4.2 g, 7.73 mmol) in CH_2Cl_2 (70 mL) and water (8 mL) at room temperature was added DDQ (2.6 g, 11.60 mmol) and allowed to stir for 2 h at the same temperature. The reaction mixture was quenched with saturated $NaHCO_3$ (50 mL) solution. The organic compound was extracted with CH_2Cl_2 (2 x 80 mL). The combined organic layer was washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4 and evaporated to give red colored crude product which was purified by silica gel column chromatography (EtOAc: hexane = 1: 4) to afford the desired primary alcohol **85** (2.87 g, 93%) as a colorless liquid.

$[\alpha]_D^{25}$: −14.0 (*c* 0.4, $CHCl_3$);

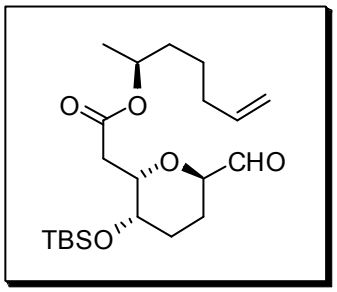
IR (neat, KBr) : ν_{max} 3465, 2937, 2860, 1732, 1642, 1463, 1286, 1255, 1187, 1106, 837, 777 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) : δ 5.77 (m, 1H), 5.04-4.95 (m, 2H), 4.93 (m, 1H), 4.25 (dt, *J* = 4.0, 10.6 Hz, 1H), 3.81 (m, 1H), 3.75 (m, 1H), 3.61 (dd, *J* = 7.5, 11.5 Hz, 1H), 3.47 (dd, *J* = 3.6, 12.3 Hz, 1H), 2.70 (dd, *J* = 10.6, 15.7 Hz, 1H), 2.49 (dd, *J* = 3.4, 15.9 Hz, 1H), 2.06 (q, *J* = 7.2 Hz, 2H), 1.81-1.71 (m, 2H), 1.62-1.48 (m, 3H), 1.48-1.31 (m, 3H), 1.22 (d, *J* = 6.2 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H);

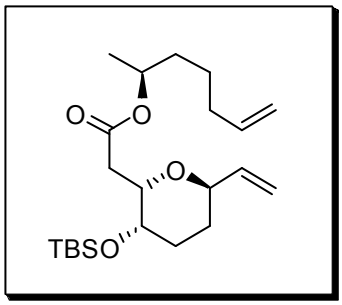
^{13}C NMR (75 MHz, $CDCl_3$) : δ 171.9, 138.4, 114.7, 72.5, 71.1, 69.9, 67.9, 64.0, 35.3, 33.4, 32.7, 27.4, 25.7, 24.6, 24.2, 24.2, 20.0, 18.0, − 4.9, − 4.7 ppm;

ESI-HRMS : *m/z* calcd for $C_{21}H_{40}NaO_5Si$ [M + Na]+ 423.2537; found 423.2502.

3.4.11. (*R*)-hept-6-en-2-yl 2-((2*S*,3*S*,6*R*)-3-(tert-butyldimethylsilyloxy)-6-vinyl-tetrahydro-2H-pyran-2-yl)acetate (87):



To a stirred solution of primary alcohol **85** (1.5 g, 3.75 mmol) and solid anhydrous $NaHCO_3$ (1.0 g) in CH_2Cl_2 (5 mL) at 0 ^oC was added Dess-Martin periodinane (2.4 g, 5.62 mmol). The reaction mixture was stirred at 0 ^oC for 3 h. After completion of reaction (TLC monitored), the reaction mixture was diluted with CH_2Cl_2 (75 mL) and then filtered filtered through a filter paper. The filtrate was washed with saturated $NaHCO_3$ (2 x 40 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic fraction was dried over anhydrous Na_2SO_4 and solvent was removed under reduced pressure. The crude mass was purified by flash chromatography (EtOAc: hexane = 1:6) to afford the pure aldehyde **86** (1.35 g, 91%) as a pale yellow liquid which was immediately used for the next step.



The aldehyde **86** (1.2 g, 3.01 mmol) was dissolved in dry THF (25 mL) under nitrogen. In another RB, methyltriphenylphosphonium iodide $[(PPh)_3P^+I^-(CH_3)]$ (2.4 g, 6.03 mmol) was taken in dry THF (50 mL) under nitrogen atmosphere and cooled to 0 ^oC. To it, BuLi (3.8 mL, 1.6 M in hexane) was slowly added and allowed to stir for 30 min. During this time the reaction mixture turned yellow which ensured the formation of ylide. This yellow solution was cooled to −78 ^oC and then aldehyde was added to it. The resulting solution was slowly warm to 0 ^oC and stirred at the same temperature for 3 h.

The reaction mixture was quenched with saturated NH_4Cl solution (40 mL). The organic compound was extracted in diethyl ether (2 x 50 mL). The combined organic layer was washed with brine (3 x 50 mL), dried over anhydrous Na_2SO_4, evaporated to dryness under reduced pressure which on silica gel column chromatography (EtOAc: hexane = 1: 49) afforded the desired diene **87** (0.9 g, 80%).

$[\alpha]_D^{25}$: −18.2 (*c* 0.8, $CHCl_3$);

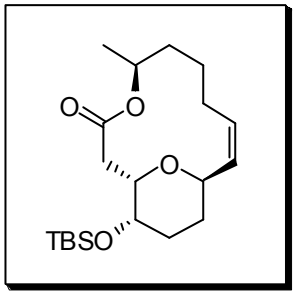
IR (neat, KBr) : ν_{max} 3077, 2928, 2856, 2125, 1732, 1462, 1378, 1286, 1186, 1106, 1035, 837, 777cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) : δ 5.90-5.69 (m, 2H), 5.29-5.10 (m, 2H), 5.07-4.91 (m, 2H), 4.38-4.16 (m, 2H),3.82 (m, 1H), 2.69 (dd, *J* = 9.8, 15.1 Hz, 1H), 2.52 (dd, *J* = 4.5, 15.1 Hz, 1H), 2.11-2.0 (m, 2H), 1.93 (m, 1H), 1.77 (m, 1H), 1.69-1.55 (m, 2H), 1.53-1.36 (m, 2H), 1.21 (d, *J* = 6.0 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H) ;

^{13}C NMR (75 MHz, $CDCl_3$) : δ 171.7, 138.4, 138.0, 115.5, 114.6, 72.6, 70.8, 70.5, 67.6, 35.3, 33.8, 33.5, 27.3, 27.1, 25.8, 24.5, 20.0, 18.0, –4.7, –4.9 ppm;

ESI-HRMS : *m/z* calcd for $C_{22}H_{40}NaO_4Si$ [M + Na]+ 419.2588; found 419.2582.

3.4.12. (1S,5R,11R,14S,Z)-14-(tert-butyldimethylsilyloxy)-5-methyl-4,15-dioxabicyclo[9.3.1]pentadec-9-en-3-one (88):



To a stirred solution of diene **87** (0.4 g, 1.01 mmol) in CH_2Cl_2 (350 mL), nitrogen gas was bubbled for 15 min.Then Grubbs 2nd generation catalyst (45 mg, 0.101 mmol) was added and refluxed for 3h. TLC showed complete disappearence of the starting material. CH_2Cl_2 layer was evaporated to dryness under reduced pressure and purified by silica gel

column chromatography (EtOAc: hexane = 1: 9) to furnish the desired product **88** (0.29 g, 78%) as a colorless liquid.

$[\alpha]_D^{25}$: −45.5 (*c* 0.5, $CHCl_3$);

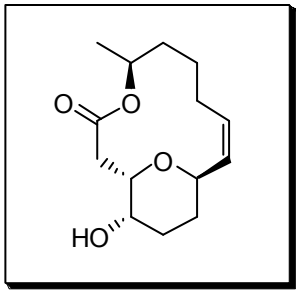
IR (neat, KBr) : ν_{max} 3008, 2923, 2851, 1724, 1446, 1368, 1219, 1176, 1059, 772 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) : δ 5.57 (td, *J* = 4.7, 10.5 Hz, 1H), 5.34 (t, *J* = 9.0 Hz, 1H), 5.21 (m, 1H), 4.52 (t, *J* = 9.8 Hz, 1H), 4.31 (m, 1H), 3.93 (m, 1H), 2.94 (t, *J* = 12.8 Hz, 1H), 2.59 (m, 1H), 2.46 (dd, *J* = 3.2, 13.0 Hz, 1H), 1.92 (m, 1H), 1.84-1.73 (m, 2H), 1.67 (m, 1H), 1.61-1.40 (m, 4H), 1.23 (d, *J* = 6.4 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 6H) ;

^{13}C NMR (75 MHz, $CDCl_3$) : δ 172.6, 135.3, 129.7, 76.0, 71.3, 68.1, 63.9, 32.2, 31.9, 30.4, 28.2, 27.8, 25.8, 24.5, 19.4, -4.7, -4.8 ppm;

ESI-HRMS : *m/z* calcd for $C_{20}H_{36}NaO_4Si$ [M + Na]+ 391.2280; found 391.2269.

3.4.13. (1S,5R,11R,14S,Z)-14-hydroxy-5-methyl-4,15-dioxabicyclo[9.3.1]pentadec-9-en-3-one (90):



A solution of the TBS ether **88** (0.13 g, 0.353 mmol) in THF (30 mL) was treated with TBAF (0.8 ml, 0.77 mmol) at 0 ^oC and stirred for 2 h at room temperature. After completion of the reaction, the reaction mixture was concentrated *in vacuo*, and then purified by silica gel chromatography using petroleum (EtOAc/hexane = 1:4) to give pure product **90** (0.78 g, 88% yield).

$[\alpha]_D^{25}$: −53.4 (*c* 0.7, $CHCl_3$);

IR (neat, KBr) : ν_{max} 3496, 2928, 2857, 1732, 1640, 1459, 1275, 1174, 1106, 1061, 861, 773 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) : δ 5.61 (td, *J* = 4.9, 10.8 Hz, 1H), 5.37 (t, *J* = 9.8 Hz, 1H), 5.20 (m, 1H), 4.56 (t, *J* = 9.8 Hz, 1H), 4.35 (dt, *J* = 2.9, 11.8 Hz, 1H), 3.94 (m, 1H), 2.91 (t, *J* = 12.8 Hz, 1H), 2.62 (m, 1H), 2.47 (dd, *J* = 2.9, 13.8 Hz, 1H), 2.0-1.17 (m, 8H), 1.71-1.57 (m, 2H), 1.53 (m, 1H), 1.43 (m, 1H), 1.23 (d, *J* = 6.9 Hz, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) : δ 172.5, 136.0, 129.1, 74.8, 71.6, 67.6, 64.7, 32.8, 32.2, 29.3, 27.7, 27.3, 24.4, 19.2 ppm;

ESI-HRMS : *m/z* calcd for $C_{14}H_{22}NaO_4$ [M + Na]+ 277.1410; found 277.1404.

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2.6. REFERENCES

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LIST OF PUBLICATIONS

1. "Iodine-Catalyzed Highly Diastereoselective Synthesis of trans-2,6-Disubstituted-3,4- Dihydropyrans: Application to Concise Construction of C28-C37 Bicyclic Core Of (+)-Sorangicin A" Debendra K. Mohapatra,* Pragna P. Das, **Manas R. Pattanayak** and J.S. Yadav*; ***Chem. Eur. J***. **2010**, *16*, 2072 – 2078.
2. "Iodocyclization and Prins-Type Macrocyclization: An Efficient Formal Synthesis of Leucascandrolide A." J. S. Yadav,* **Manas R. Pattanayak**, Pragna P. Das and Debendra K. Mohapatra*; ***Org. Lett***., **2011,** *13, 7*, 1710-1713.
3. "Protecting-Group Directed Stereoselective Intramolecular Nozaki–Hiyama–Kishi Reaction: A Concise and Efficient Total Synthesis of Amphidinolactone A." Debendra K. Mohapatra,* Pragna P. Das, **Manas R. Pattanayak,** Gaddamanugu Gayatri, G. Narahari Sastry and J.S. Yadav *; ***Eur. J. Org. Chem***. **2010**, 4775–4784.
4. "Ring-closing metathesis (RCM) based synthesis of the macrolactone core of Amphidinolactone A." Debendra K. Mohapatra,* **Manas R. Pattanayak**, Pragna P. Das, Tapas R. Pradhan and J. S. Yadav*; ***Org. Biomol. Chem***., **2011**, *9*, 5630–5632.
5. "Iodocyclization: Sterioselective Formal Total Synthesis of Aspergillide B." Debendra K. Mohapatra,* **Manas R. Pattanayak**, Tapas R. Pradhan and J. S. Yadav.* Manuscript under preparation.

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1. "Inside Cover: Iodine-Catalyzed Highly Diastereoselective Synthesis of *trans*-2,6-Disubstituted-3,4-Dihydropyrans: Application to Concise Construction of C28–C37 Bicyclic Core of (+)-Sorangicin A (Chem. Eur. J. 7/2010)." Debendra K. Mohapatra* , Pragna P. Das, **Manas R. Pattanayak**, J. S. Yadav.*; ***Chem. Eur. J***. *16*, *9*, 2648, April 1, **2010**.
2. "Protecting-Group Directed Stereoselective Intramolecular Nozaki–Hiyama–Kishi Reaction: A Concise and Efficient Total Synthesis of Amphidinolactone A." (Eur. J. Org. Chem. 25/2010). Debendra K. Mohapatra,* Pragna P. Das, **Manas R. Pattanayak,** Gaddamanugu Gayatri, G. Narahari Sastry and J.S. Yadav *; ***Eur. J. Org. Chem***. **2010**, 25, September **2010,** 4737-4944.
3. "Ring-closing metathesis (RCM) based synthesis of the macrolactone core of Amphidinolactone A." Debendra K. Mohapatra,* **Manas R. Pattanayak**, Pragna P. Das, Tapas R. Pradhan and J. S. Yadav*; ***Org. Biomol. Chem.***, *9*, *16*, 21 Augest **2011**, 5581–5880.