APPROACHES TOWARDS THE TOTAL SYNTHESIS OF BIOACTIVE NATURAL PRODUCTS: NHATRANGIN A, (-)-BREVISAMIDE, PUTAMINOXIN, 11-α- AND 11-β-METHOXYCURVULARINS

A THESIS

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BY

RAJU ANDE

Reg. No: 09CHPH27

Supervisor

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

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

सी एस आई आर - भारतीय रासायनिक प्रौद्योगिकी संस्थान
वैज्ञानिक तथा औद्योगिक अनुसंधान परिषद
CSIR - Indian Institute of Chemical Technology
Council of Scientific & Industrial Research
उप्पल रोड Uppal Road, हैदराबाद Hyderabad - 500 007, भारत India

Dr. J.S. YADAV, FNA, FTWAS
CSIR-Bhatnagar Fellow
Former Director, CSIR-IICT

डॉ. जे. एस. यादव,
एफएनए, एफटीडब्ल्यूएस
सी.एस.आई.आर. - भटनागर फेलो
पूर्व निदेशक, सी.एस.आई.आर. - आई.आई.सी.टी.

CERTIFICATE

This is to certify that the research work incorporated in this thesis entitled "*Approaches Towards the Total Synthesis of Bioactive Natural Products: Nhatrangin A, (–)-Brevisamide, Putaminoxin, 11-α and 11-β-Methoxycurvularins*" has been carried out under my supervision and is a bonafide work of **Mr. RAJU ANDE**. 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
(Research Supervisor)

email: jsyadav@iict.res.in / yadavfna@gmail.com | Tel No: 91-40-27193737 | Fax: 91-40-27193241/27160512

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-500 607, 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 (**ANDE RAJU)**

Date: **(Candidate)**

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At this moment of submission of my thesis, I invariably feel short of words to express my sincere thanks to my father Ande Ramulu and mother Ande Rajamani whose efforts have brought me to this stage. My thanks are also due to my brother Lingamurthi, Veeraswamy and father-in-law Adepu Chakrapani and mother-in-law Adepu Shobarani and brather-in-law Santhosh, Barath Chandra who have been a source of relief while I am away from the work.

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Finally, I thank the Director, IICT, for allowing me to submit this work in the form of a thesis.

Ande Raju

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
ACN	:	Acetonirile
Ac_2O	:	Acetic anhydride
AcOH	:	Acetic acid
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
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
Na	:	Sodium
NaH	:	Sodium hydride
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
TPP	:	Triphenylphosphine
Ts	:	Tosyl (*p*-toluenesulphonyl)
UV	:	ultraviolet

CONTENTS

SYNOPSIS

SYNOPSIS

Title of the thesis: "Approaches Towards the Total Synthesis of Bioactive Natural Products: Nhatrangin A, (-)-Brevisamide, Putaminoxin, 11-α- and 11-β-Methoxycurvularins"

Name of the student: RAJU ANDE (09CHPH27)

Research supervisor: Dr. J. S. Yadav

The thesis entitled **"Approaches Towards the Total Synthesis of Bioactive Natural Products: Nhatrangin A, (–)-Brevisamide, Putaminoxin, 11-α- and 11-β-Methoxycurvularins"** has been divided into three chapters.

CHAPTER I: This chapter describes the "total synthesis of Nhatrangin A".

CHAPTER II: This chapter describes the "formal stereoselective synthesis of (–)-Brevisamide".

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

Section A: This section describes the "stereoselective total synthesis of Putaminoxin".

Section B: This section describes "stereoselective total synthesis of 11-α- and 11-β-Methoxycurvularin".

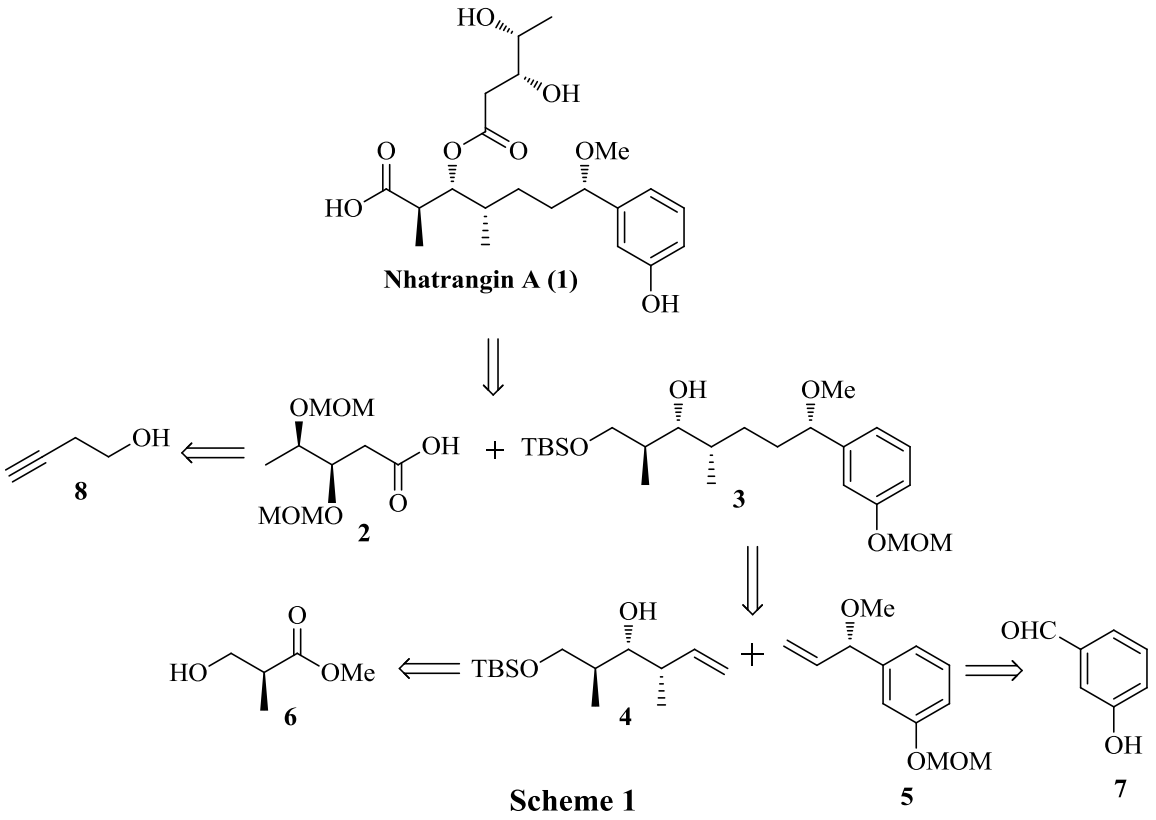
CHAPTER I:

This Chapter describes the "Total Synthesis of Nhatrangin A".

In 2007, Jimmy Orjala and co-workers isolated the polyketide natural product Nhatrangin A from a Vietnamese collection of *Lyngbya majuscula* at Vietnam, and named after the collection site of Nha Trang Bay Cynobacteria, in particular *Lyngbya majuscula*, have shown to be a rich source of biologically active secondary metabolites. The carbon skeleton of this molecule appears to be related to the Aplysiatoxin, which have been indicated as a causative agent for "swimmers itch'', were originally isolated from *Stylocheilus longicauda*, a sea hare. An initial organic extracts (2.5 g) of *Lyngbya majuscula* displayed significant antiproliferative activity in a colon cancer cell line (Col-2). To the best of our knowledge, total synthesis of this interesting natural product is not been reported.

Inspired by interesting structural features, biological profile (antiproliferative activity) in combination with lowest natural abundance and in continuation of our interest in the area total synthesis of biologically potent natural products, we initiated a program on total synthesis of nhatrangin A. Herein, we report an efficient synthetic route for the nhatrangin A from commercially available and cost-effective homopropargyl alcohol and 3-hydroxy benzaldehyde as starting materials. The key features of this synthetic approaches are the Sharpless asymmetric dihydroxylation, Sharpless asymmetric epoxidation, Browns crotyl boration, Birch reduction and Yamaguchi esterification.

Retrosynthesis of Nhatrangin A:



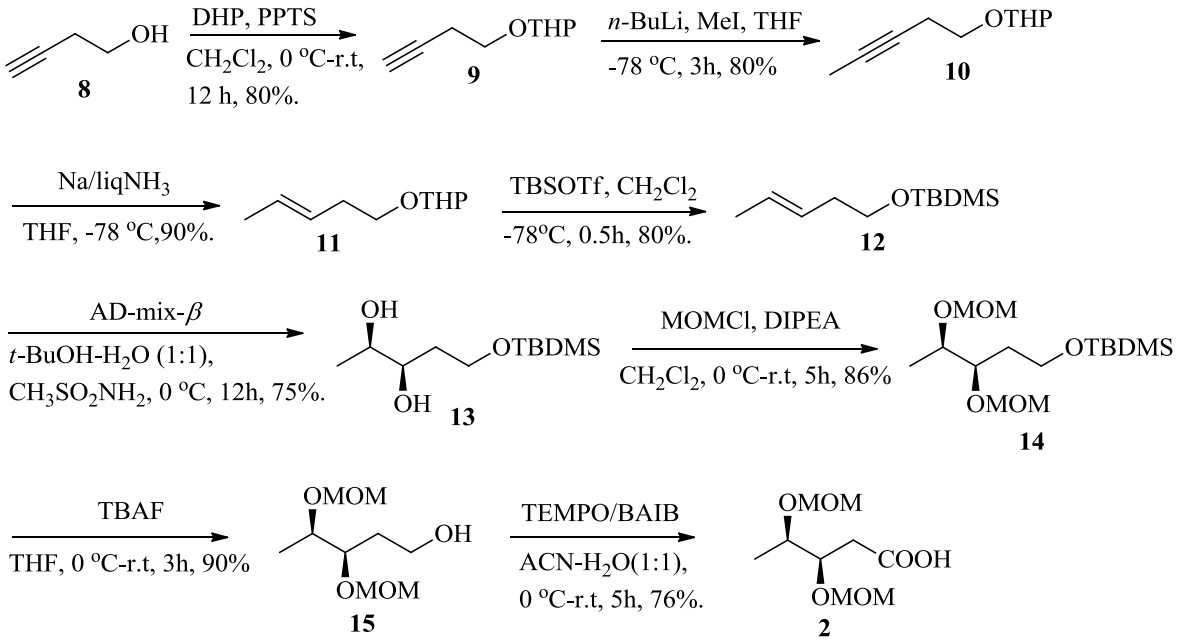
Scheme 1

Retrosynthetic analysis of Nhatrangin A (**1**) is delineated in Scheme 1. Nhatrangin A (**1**) could be accomplished by Yamaguchi esterification of the carboxylic acid fragment **2** and the secondary hydroxyl fragment **3**. Carboxylic acid **2** was prepared from commercially available homo propargyl alcohol **8**. The alcohol fragment **3** was obtained by the olefin-cross metathesis of two terminal alkene coupling partners **4** and **5**, which

were synthesized from (*S*)-methyl 3-hydroxy-isobutyrate **6** and 3-hydroxybenzaldehyde **7,** respectively (Scheme 1).

Synthesis of fragment 2

Synthesis of carboxylic acid fragment **2** commenced from commercially available homo propargyl alcohol **8**, which was protected as its THP-ether **9** using DHP and catalytic amount of PPTS in anhydrous CH_2Cl_2. THP-ether **9** was subjected to C-methylation using *n*-BuLi and MeI in THF at –78 ^oC to afford the methylated alkyne **10** in 80% yield. Alkyne **10** was treated with Sodium in liquid ammonia (Na/liq NH_3) in THF to furnish the alkene **11** with exclusively *E* stereo chemistry in 90% yield (Scheme 2).



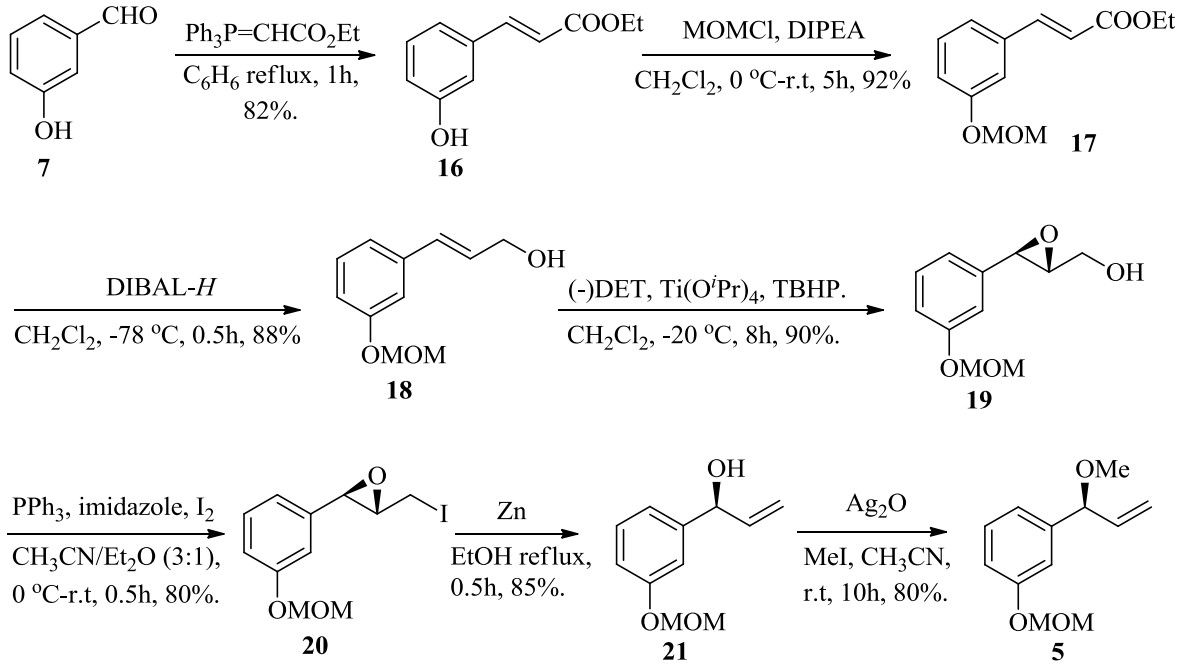
Scheme 2

Deprotection of THP ether group followed by TBS protection of **11** using TBSOTf, DMS and TEA in CH_2Cl_2 at –78 ^oC to afford TBS-ether **12** in 80% yield (Scheme 2). Sharpless asymmetric dihydroxylation of alkene **12** using AD-mix-β, $CH_3SO_2NH_2$ in *t*-BuOH/H_2O provided diol **13** in 75% yield in 9:1 well seperable diastereomeric mixture. The diol **13** was converted to its di-MOM ether **14** in 86% yield

using MOMCl in the presence of Hunig's base in anhydrous CH_2Cl_2. Deprotection of TBS group in compound **14** using TBAF in THF gave the primary alcohol **15** in good yield (Scheme 2). Oxidation of primary alcohol **15** by using TEMPO and BAIB in CH_3CN/H_2O (1:1) at 0 ^oC afforded the desired carboxylic acid **2** in 76% yield (Scheme 2).

Synthesis of Fragment 5

The synthesis of olefin fragment **5** was commenced from commercially available 3-hydroxybenzaldehyde **7**, which was treated with Wittig ylide ($Ph_3P=CHCO_2Et$) in refluxing benzene to afford the *α, β*-unsaturated ester **16** in 82% yield with *E* stereochemistry (Scheme 3).



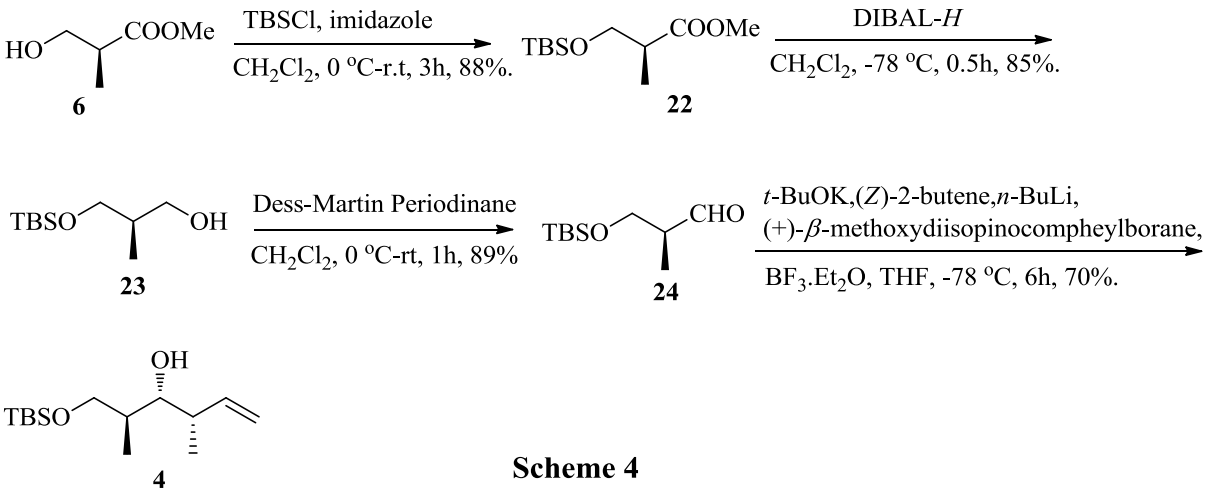
Scheme 3

The hydroxy group of **16** was protected as its MOM-ether **17** using MOMCl, DIPEA in CH_2Cl_2 in 92% yield. Chemo selective reduction of *α, β*-unsaturated ester **17** using DIBAL-*H* in CH_2Cl_2 at −78 ^oC provided the allylic alcohol **18** in good yield. Sharpless asymmetric epoxidation of allylic alcohol **18** using D-(–)-DET, $Ti(O^iPr)_4$ and TBHP in CH_2Cl_2 afforded the epoxy-alcohol **19** in 90% yield. Treatment of epoxy alcohol **19** with TPP, imidazole and I_2 in CH_3CN/Et_2O (1:1) afforded the corresponding *α*-

iodooxirane **20** in 80%. The α-iodooxirane **20** was converted into secondary allyl alcohol **21** in 85% yield by refluxing with activated Zn in dry EtOH. The secondary allyl acohol **21** was subjected to O-methylation using MeI, Ag_2O in the presence of CH_3CN to obtain the fragment **5** in 80% yield (Scheme 3).

Synthesis of Fragment 4

The fragment **4** was synthesized from commercially available (*S*)-Roche ester **6**, which was protected as its TBS-ether **22** using TBDMSCl and imidazole in CH_2Cl_2 in good yield. Reduction of ester **22** using DIBAL-*H* in CH_2Cl_2 at −78 ^oC afforded the primary alcohol **23** in 85% yield (Scheme 4).



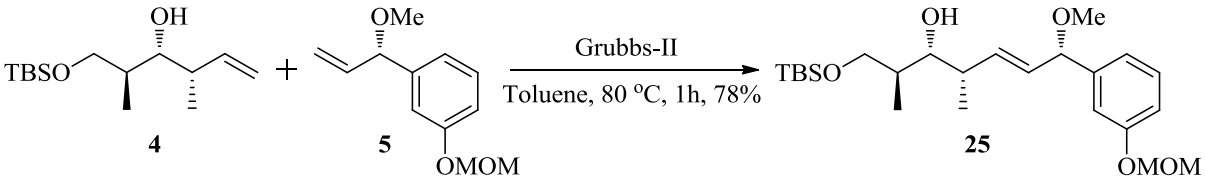
Scheme 4

Oxidation of primary alcohol **23** using Dess-Martin periodinane in anhydrous CH_2Cl_2 provided the aldehyde intermediate **24** in 89% yield. Crotylation of aldehyde **24** with (*Z*)-2-butene, (+)-β-methoxydiisopinocopheylborane, *n*-BuLi and $BF_3{\cdot}Et_2O$ in dry THF gave the homoallylalchol **4** in 70% yield with 9:1 diastereoselctivity (Scheme 4). The optical purity of allylalcohol **4** was confirmed by the comparison with reported data (optical rotation $[\alpha]_D^{25}$ +8.9 (*c* = 2.0, $CHCl_3$); lit $[\alpha]_D^{20}$ +9.1 (*c* = 2.0, $CHCl_3$). Spectral and analytical data of allylalcohol **4** were in good agreement with the reported literature.

Coupling of both the fragments 4 & 5 by Cross-Metathesis approach:

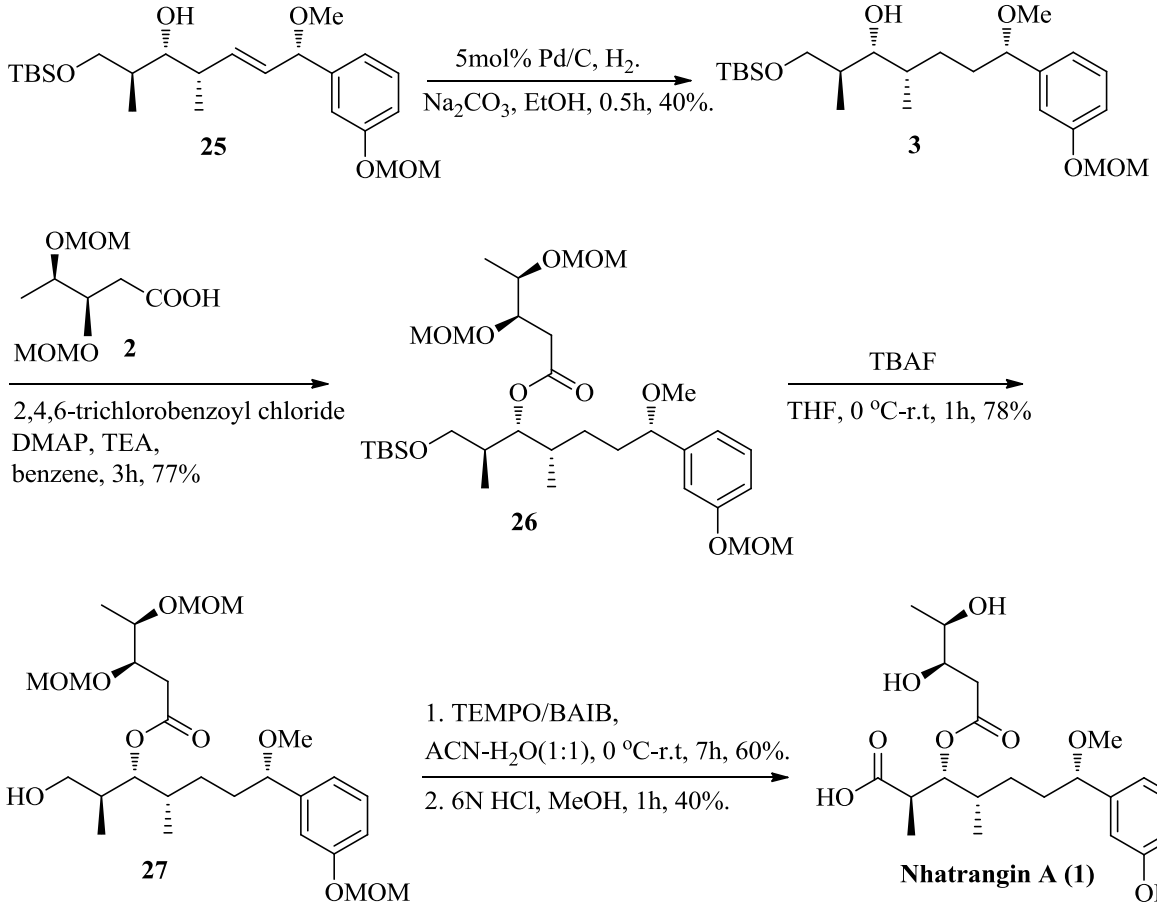
Having both the terminal olefin fragments **4** and **5** in hand, we performed olefin cross-metathesis reaction using Grubbs 2nd generation catalyst (10% mol) in toluene under

reflux conditions to provide the coupled product **25** in 78% yield (with separable *E*, *Z* isomers in 90:5 ratio, and homodimers of **5** and **4** in remaining 3:2 ratio respectively).



Scheme 5

Reduction of double bond **25** was carried out by using Pd/C (5 mol %) and Na_2CO_3 in EtOH at room temperature to afford the corresponding saturated analogue **3** in 40% yield. Now the stage was set for the coupling of carboxylic acid fragment **2** with alcohol fragment **3**.



Scheme 6

Accordingly acid fragment **2** was coupled with **3** under Yamaguchi lactonization conditions (2,4,6-trichlorobenzoyl chloride, DMAP and TEA) in toluene to afford the ester **26** in 77% yield. Deprotection of TBS group of ester **26** using TBAF in THF provided the primary alcohol **27** in 78% yield (Scheme 6). The primary alcohol **27** was oxidized using TEMPO and BAIB in CH_3CN/H_2O (1:1) to afford the corresponding carboxylic acid, which was subsequently subjected to the acid (6N aq HCl in MeOH) mediated cleavage of MOM protecting groups to afford the target natural product Nhatrangin A (**1**) in 40% yield (Scheme 6). The ^{1}H NMR, ^{13}C NMR, and mass spectral data of the synthetic Nhatrangin A (**1**) were in good agreement with reported in the literature.

In conclusion, we have accomplished an efficient asymmetric total synthesis of Nhatrangin A (**1**) in highly convergent manner using Sharpless asymmetric dihydroxylation, Sharpless asymmetric epoxidation, Browns crotyl boration, Birch reduction and Yamaguchi esterification as key transformations.

CHAPTER II:

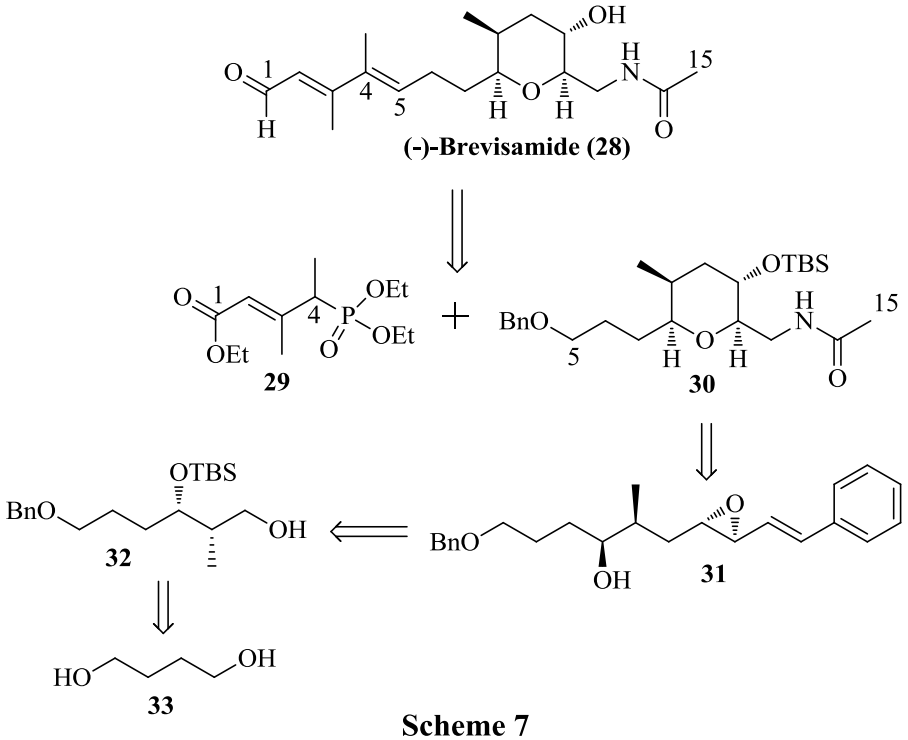
This Chapter describes the "Formal Stereoselective Synthesis of (–)-Brevisamide".

In 2008, Satake, Tachibana, Wright and co-workers reported the isolation and structural elucidation of (–)-Brevisamide (**28**), a marine derived monocyclic ether alkaloid from *Karenia brevis* (Red tide dinoflagellate) a species well known to produce various cyclic polyether toxins such as the **B**revetoxins A & B, Ciguatoxins and Maitotoxin. The absolute and relative stereochemistry of Brevisamide was determined by the groups of Satake, Tachibana and Wright by its stereoselective total synthesis employing Brown crotylation, Curtius rearrangement and Suzuki-Miyaura cross coupling as key transformations. Very interesting structural features of this natural product, which include, a tetra-substituted tetrahydropyran core coupled with dienal side chain and terminal amide subunit have attracted the attention of many synthetic research groups in last four years, resulting in several elegant total syntheses.

In light of interesting structural features of Brevisamide (**28**) and in continuation of our interest in total synthesis of oxygen containing heterocyclic natural products, we

established an efficient synthetic route for (–)-Brevisamide (**28**) employing *syn*-aldol reaction, Sharpless asymmetric epoxidation and stereoselective construction of tetrahydropyran moiety via 6-*endo*-cyclization of hydroxy-styrylepoxide.

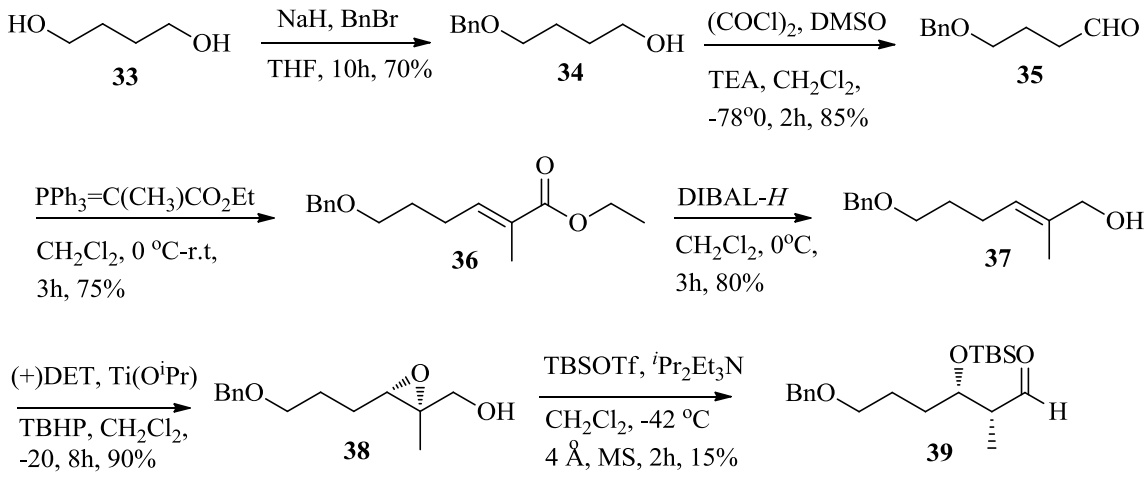
Retrosynthesis of Brevisamide:



Scheme 7

The retro synthetic analysis of (–)-Brevisamide (**28**) is depicted in Scheme 7. (–)-Brevisamide (**28**) could be readily synthesized *via* Horner-Wadsworth-Emmons (HWE) reaction between two coupling partners of C1-C4 side chain **29** and C5-C15 tetrahydropyran derived fragments **30** (by the use of corresponding C5 aldehyde intermediate). Tetrahydropyran derived segment (C5-C15 fragment) **30** would be achieved *via* base induced 6-*endo*-cyclization of hydroxy styrylepoxide **31**, which can be in turn prepared from commercially available 1,4-butanediol **33** via *syn*-stereo-diad **32** employing *syn*-aldol reaction, Sharpless asymmetric epoxidation and Wittig olefination as key transformations. Accordingly, our synthesis of (–)-Brevisamide (**28**) began from the commercially available 1,4-butanediol **33**, which on treatment with NaH, BnBr in THF

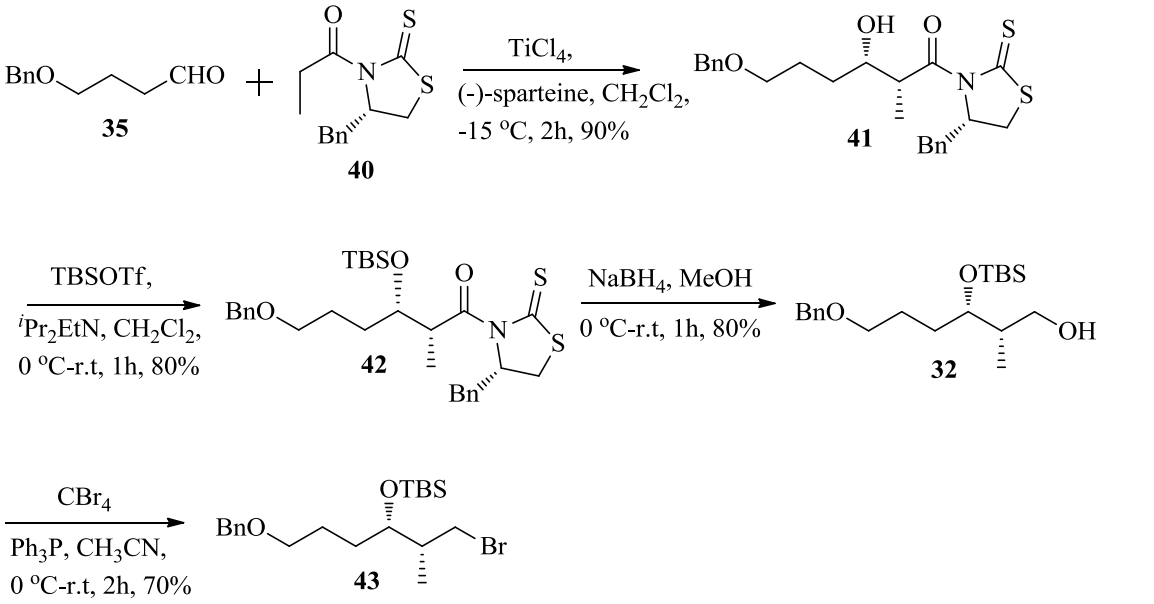
resulted in mono-benzyl ether **34** in 70% (Scheme 8). The hydroxyl group of **34** was oxidized under Swern oxidation conditions in CH_2Cl_2 to afford the aldehyde **35** in 85% yield. Aldehyde **35** on treatment with the C3-Wittig ylide (Ethyl-2-(triphenyl phosphoranylidene) propanoate) in CH_2Cl_2 gave exclusively the *E*-isomer of ester **36** in 75% yield. The ester **36** was reduced using DIBAL-*H* in CH_2Cl_2 at 0 ^oC to furnish the allylic alcohol **37** in 80% yield (Scheme 8).



Scheme 8

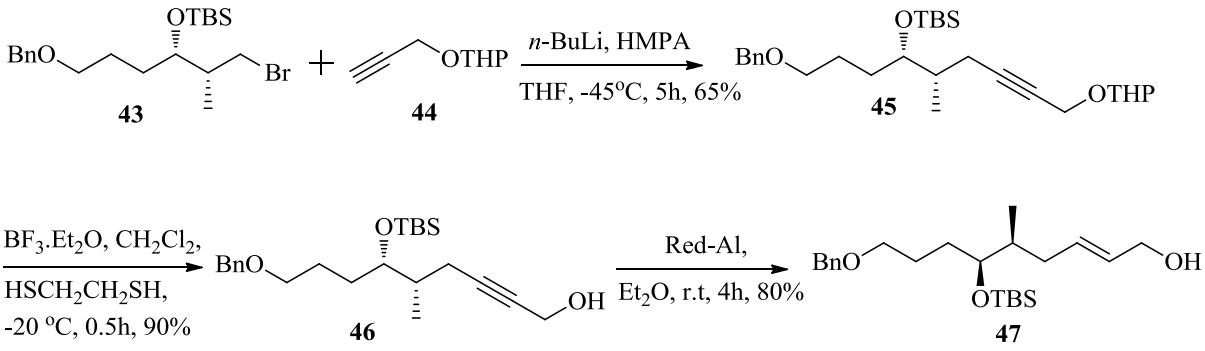
The allyl alcohol **37** was subjected to Sharpless asymmetric epoxidation using L-(+)-diethyltartarate, *t*-Butylhydroperoxide (TBHP), and titanium-tetraisopropxide ($Ti(O^iPr)_4$) in CH_2Cl_2 at –20 °C to afford the epoxy alcohol **38** in 90% yield. The epoxyalcohol **38** on treatment with *tert*-butyldimethylsilyl triflate (TBSOTf) and diisopropylethylamine (DIPEA) in CH_2Cl_2 at –42 ^oC gave the (M. E. Jung's protocol) TBS protected *syn*-aldol product **39**.

Unfortunately here we have ended up with poor yield of 15%, which could be due to the interference of C6-OBn functional group as judged by the reported literature (Scheme 8). Unsatisfying with above result, we adopted well precedented asymmetric Aldol addition reaction of thiazolidinethione propionate **40** onto the benzyloxybutanal **35** using $TiCl_4$ and (–)-sparteine in CH_2Cl_2 to give the alcohol **41** in 90% yield (Scheme 9).



Scheme 9

The alcohol **41** was protected as TBS-ether using TBSOTf and $^{i}Pr_2EtN$ in dry CH_2Cl_2 to afford the TBS-ether **42** in 80% yield (Scheme 9). Reductive removal auxillary of compound **42** using $NaBH_4$ in MeOH at 0 ^{o}C gave the primary alcohol **32** in 80% yield. Alcohol **32** was converted to bromide 43 using TPP, CBr_4 in CH_3CN in 70% yield.

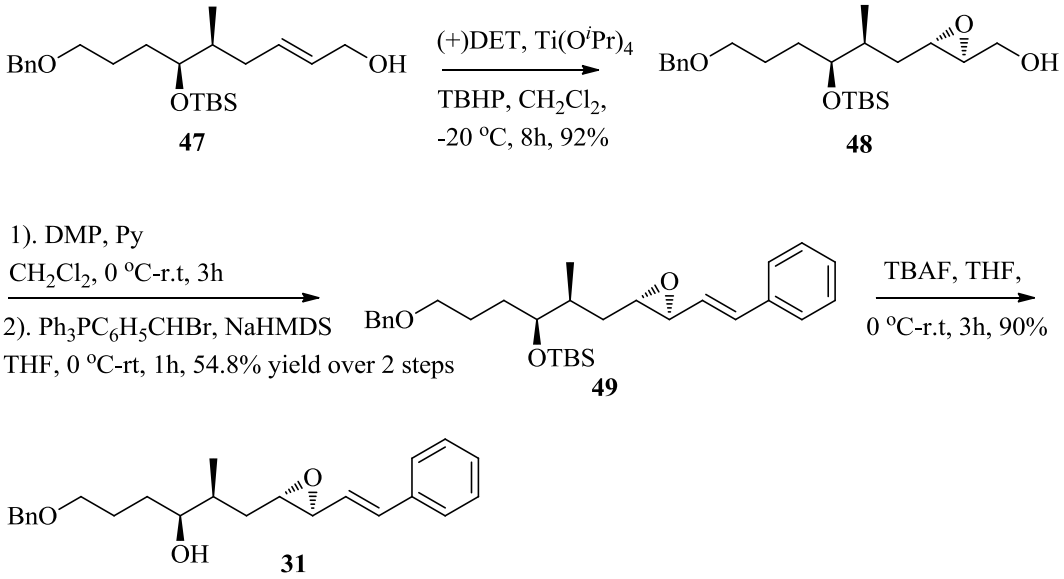


Scheme 10

Bromo **43** was coupled with 2-(prop-2-yn-1-yloxy)tetrahydro-2*H*-pyran **44** in the presence of *n*-BuLi, HMPA in THF at -45 ^{o}C to afford the compound **45** in 65% yield (Scheme 10). Selective deprotection of THP-ether using Boron trifluoride diethyl etherate ($BF_3{\cdot}Et_2O$) ethanedithiol ($HSCH_2CH_2SH$) in CH_2Cl_2 at −20 ^{o}C afforded propargyl alcohol

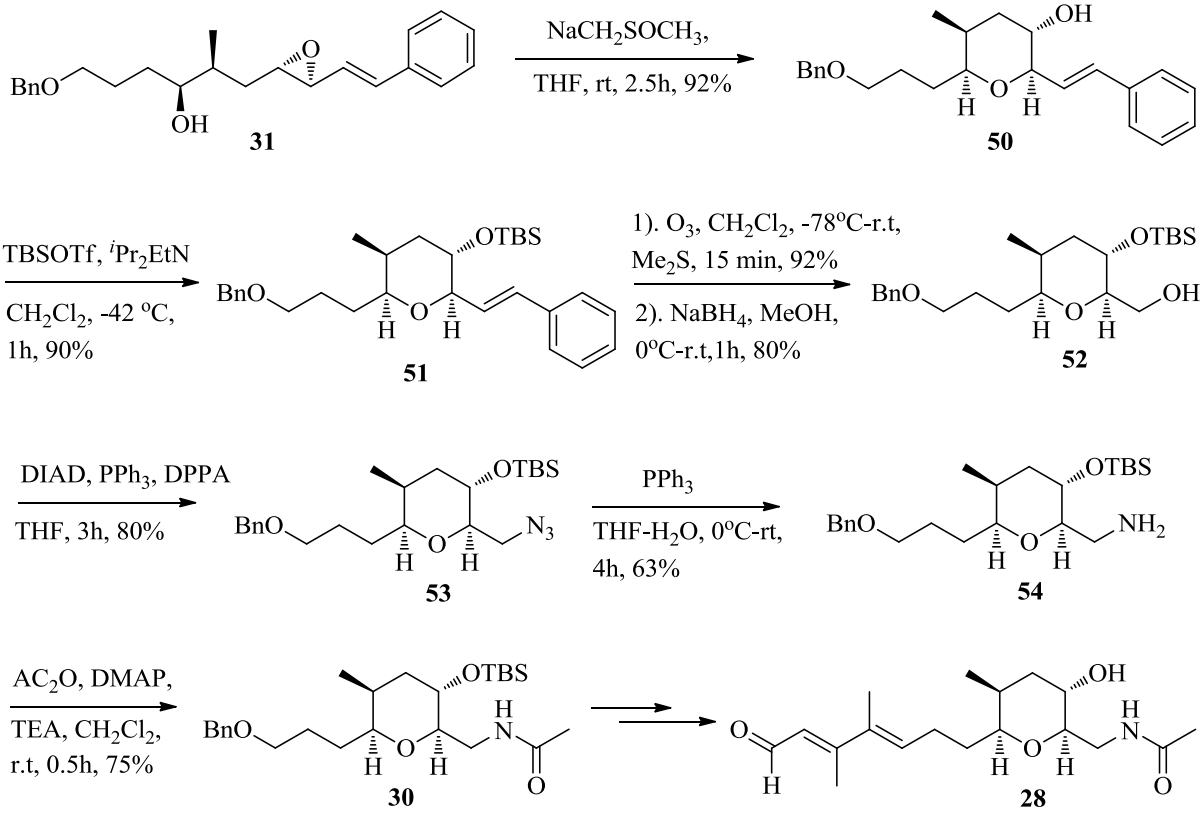
46 in 90% yield. propargyl alcohol **46** was treated with Red-Al in Et_2O to afford the *E* primary allylalcohol **47** in good yield (Scheme 10).

Sharpless asymmetric epoxidation of allylicalcohol **47** using L-(+)-DET, $Ti(^iPrO)_4$ and TBHP in dry CH_2Cl_2 at –20 ^oC gave the epoxy alcohol **48** in 92% yield. Dess-Martin periodinane oxidation of epoxyalcohol **48** and subsequent Wittig olefination using benzyltriphenylphosphonium bromide, NaHMDS in THF provided the styrylepoxide **49** in good yield (9:1, *E*/*Z* ratio) (Scheme 11).



Scheme 11

The deprotection of silyl group of compound **49** using TBAF in THF at 0 ^oC afforded the corresponding alcohol **31** in 90% yield . The styryl epoxide **94** was treated with NaH, DMSO (Tadashi Nakata protocol) in THF at room temperature to provide the 6-*endo*-cyclization product **50** in 92% yield (Scheme 12). The alcohol **50** was protected as its TBS-ether with TBSOTf and $^iPr_2EtN$ in dry CH_2Cl_2 to furnish **51** in 90% yield (Scheme 12). Ozonolysis of olefin **51** in CH_2Cl_2 at –78 ^oC followed by $NaBH_4$ reduction in MeOH gave the primary alcohol **52** in good yield (Scheme 12). The alcohol **52** was treated with DIAD, PPh_3, DPPA in THF to afford azide **53** in 80% yield. The azide **53** was treated with PPh_3, THF-H_2O to give the amine **54** in 63% yield.



Scheme 12

Acylation of primary amine **54** using Ac_2O, TEA and DMAP in CH_2Cl_2 provided the known amide **30** (C1-C15 fragment **30** of (–)-Brevisamide), which was readily converted to the target molecule by further few transformations as reported by Lindsley *et al*. Thus the present strategy completes the formal total synthesis of (–)-Brevisamide (**28**).

In conclusion, we have been accomplished the novel formal synthesis of (–)-Brevisamide (**28**) by constructing the advanced tetra substituted-tetrahydropyran core unit (C1-C15 fragment). *syn*-Aldol reaction, Sharpless asymmetric epoxidation and base induced 6-*endo*-cyclization of hydroxy styrylepoxide are used as key transformations in this synthetic strategy.

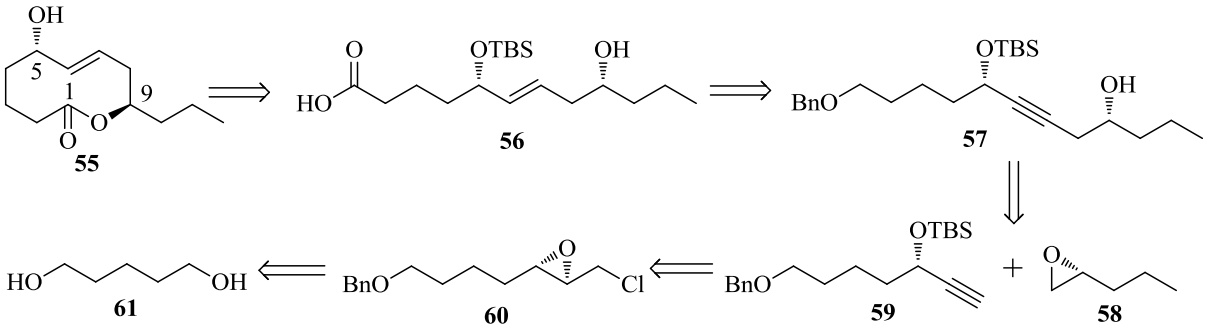
CHAPTER III: Section A:

This Section describes the "Stereoselective Total Synthesis of Putaminoxin".

Natural products containing 10-membered macrolide skeletons such as Putaminoxin (**55**) was isolated from fungal sources and are known to possess potent phytotoxic properties. In particular, Putaminoxin (**55**), a disubstituted phytotoxic nonenolide was first isolated by Evidenta *et al* in 1995, from the culture filtrates of *Phoma Putaminum* fungus, which is responsible for a necrotic leaf disease of *Erigeron annus* (Annual fleabane). Putaminoxin (**55**) is known to exhibit a range of phytotoxicities on mandarin and annual dog's mercury and also shows severe toxicity on *Erigeron annus*. The absolute stereochemistry of Putaminoxin (**55**) was determined by its total synthesis and the stereochemistry of C5 and C9 were revealed as *S* and *R* respectively. Fascinating structural features coupled with inherent phytotoxic activities of these macrolides have attracted the attention of synthetic chemists to develop elegant approaches for the synthesis of natural products and their analogues to invent leads for potent herbicides.

In continuation of our interest on the total synthesis of biologically active natural products, we developed an efficient synthetic approach for the phytotoxic natural product, Putaminoxin (**55**).

Retrosynthesis of Putaminoxin:

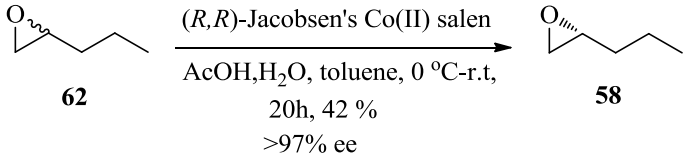


Scheme 13: Retrosynthesis of putaminoxin 1 (**55**)

Retrosynthetic analysis of Putaminoxin (**55**) is depicted in Scheme 13. Putaminoxin (**55**) could be obtained from hydroxy acid **56** *via* Yamaguchi macrolactonization. The hydroxy acid **56** would easily be prepared from a homopropargyl alcohol **57.** The intermediate alcohol **57** could be synthesized by the coupling of terminal alkyne **59** with chiral oxirane **58**, which could in turn be prepared from a commercially

available 1,5-pentanediol **61** and the racemic 2-propyloxirane **62** using known transformations such as Sharpless asymmetric epoxidation and Jacobsen's kinetic resolution. In this section, we describe the total synthesis of putaminoxin (**55**) (Scheme 13).

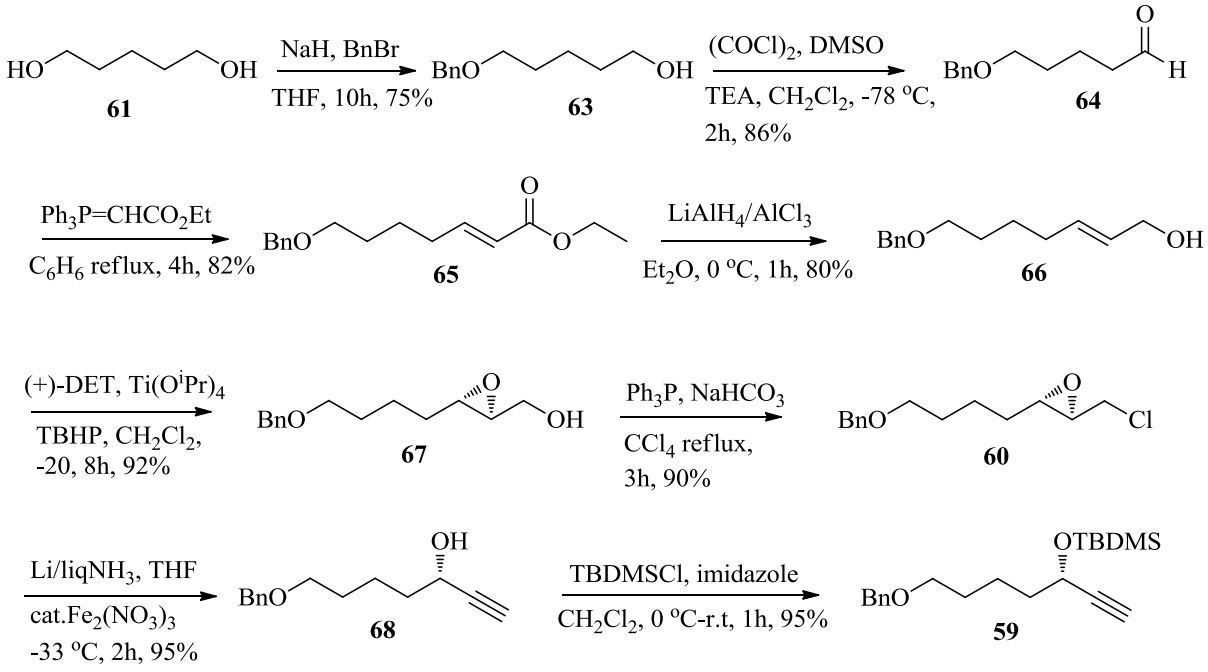
Chiral epoxide **58** was prepared form the commercially available racemic 2-propyloxirane **62** *via* hydrolytic kinetic resolution (HKR) using (*R*,*R*)-(+)-*N*,*N*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) and AcOH in toluene at room temperature with excellent optical purity (97% ee, determined by chiral HPLC) in 42% yield (Scheme 14), which was further confirmed by the comparison of optical rotation data reported in literature ($[\alpha]_D^{25}$ +11.0 (*c* = 1.0, $CHCl_3$); lit $[\alpha]_D^{20}$ +12.0 (*c* = 1.89, $CHCl_3$).



Scheme 14

The synthesis of propargylic alcohol fragment **59** began from the commercially available 1,5-pentane diol **61**, which was treated with NaH, BnBr in THF to afford the benzyl-ether **63** in 75% yield. The alcohol **63** was oxidized under Swern conditions to afford the aldehyde **64** in 86% yield. The aldehyde **64** was subjected to Wittig olefination using stable ylide (carboethoxymethylenetriphenyl phosphorane) to provide the unsaturated ester **65** in 82% yield. The ester **65** was reduced using $LiAlH_4$ and $AlCl_3$ in dry THF to afford allylic alcohol **66** in good yield (Scheme 15). Asymmetric epoxidation of allylic alcohol **66** using (+)-DET, $Ti(^iPrO)_4$ and TBHP in dry CH_2Cl_2 at –20 °C afforded desired epoxy alcohol **67** in 92% yield. The epoxy alcohol **67** was converted epoxy chloride **60** using PPh_3, $NaHCO_3$ in CCl_4 in 90% yield (Scheme 15). The epoxy chloride **60** was subjected to reductive ring opening reaction under Birch conditions (Li, liquid NH_3, THF, –33 °C) to afford the secondary propargylic alcohol **68** in 95% yield. The propargylic alcohol **68** was protected as its TBS-ether **59** using TBDMSCl and

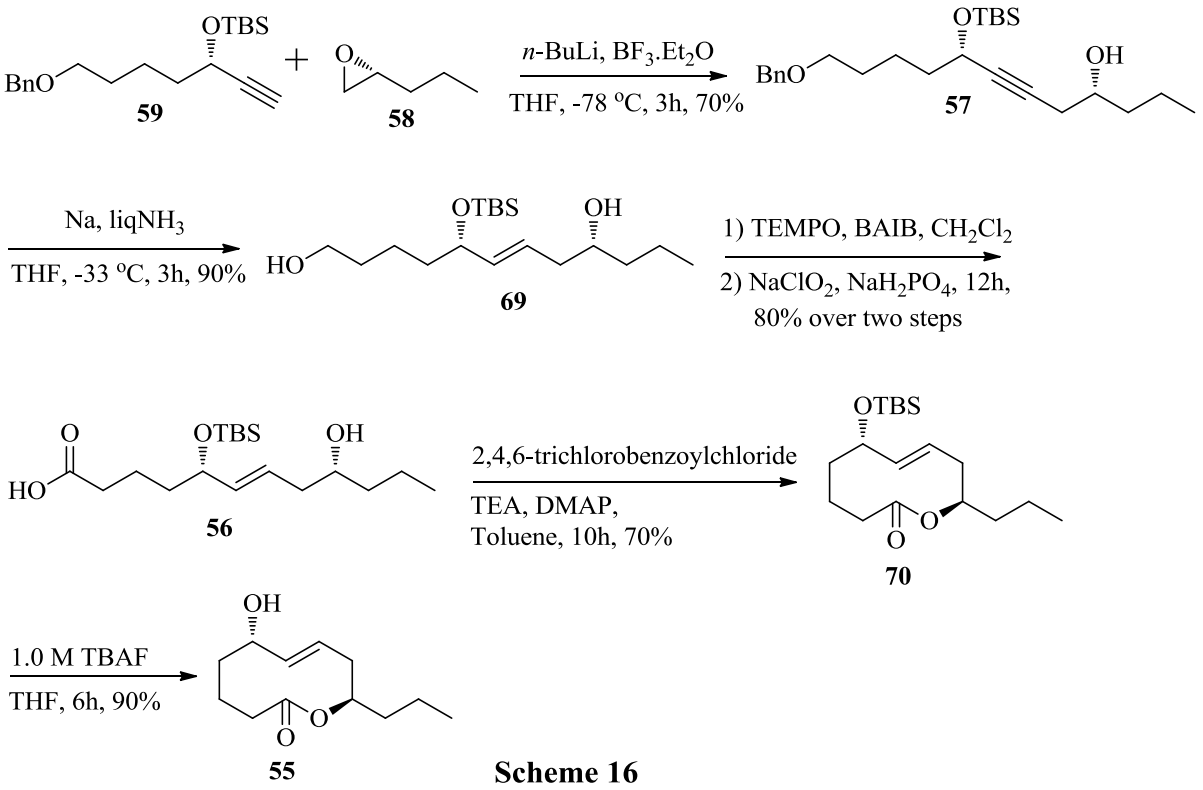
imidazole in anhydrous CH_2Cl_2 in 95% yield (Scheme 15). The (*R*)-2-propyloxirane **58** was opened regio-selectively with a terminal alkyne **59** using *n*-BuLi and $BF_3{\cdot}Et_2O$ in THF to afford the homopropargyl alcohol **57** in 70% yield (Scheme 16).



Scheme 15

Compound **57** was treated with Na in liquid NH_3 in THF at −33 °C to give the homoallylalcohol **69** with *E* stereochemistry in 90% yield. The primary hydroxyl group of 1,9-diol **69** was oxidized chemoselectively using TEMPO/BAIB in CH_2Cl_2 at ambient temperature to afford the hydroxyaldehyde, which was subsequently converted to corresponding hydroxyacid fragment **56** using *Pinnick's* oxidation ($NaClO_2/NaH_2PO_4.2H_2O$) (Scheme 16).

Hydroxyacid **56** was then subjected to Yamaguchi macrolactonization using 2,4,6-trichlorobenzoylchloride, Et_3N and DMAP in toluene reflux to afford the macrolide **70** in 70% yield. Removal of TBS ether in macrolide **70** using 1.0 M TBAF in THF gave the target molecule, Putaminoxin 1 (**55**) in 90% yield (Scheme 16). The ^1H NMR, ^{13}C NMR, IR, Mass spectral data and optical rotation of the synthetic Putaminoxin 1 (**55**) was in good agreement with that of the natural product reported in literature.



Scheme 16

In conclusion, we have accomplished an efficient linear synthetic approach to the phytotoxic macrolide, Putaminoxin (**55**)**.** This approach utilizes readily available precursors following simple and high yielding protocols such as Sharpless asymmetric epoxidation, Birch reduction, Jacobsen's kinetic resolution of racemic epoxide and Yamaguchi lactonization as key steps which makes it attractive for the generation of new derivatives of the natural product.

CHAPTER III: Section B:

This Section describes "Stereoselective Total Synthesis of 11-*α*- and 11-*β*-Methoxy curvularin".

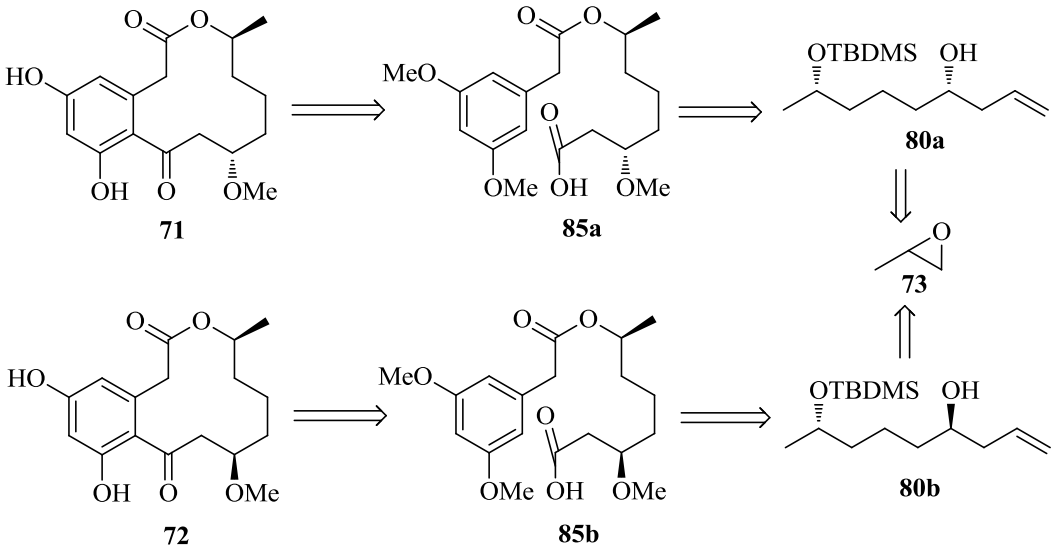
11-*α*-Methoxycurvularin (**71**) and 11-*β*-Methoxycurvularins (**72**) were isolated by Yamamura and co-workers in 1991 from the mycelium of the hybrid strain ME005, which is derived from *Penicillium citreoviride* 4692 and 6200. These substances showed considerable cytotoxicity against four types of human cancer cell lines (NCI-H460, MCF-7, SF-268, MIA. Pa Ca-2). They have also been found to be specific inhibitors of sea

urchin embryogenesis by acting on components of the mitotic apparatus, 90 (HSP90), which is a promising target for anticancer drug development.

It is structurally related to a number of compounds isolated from terrestrial fungi. The absolute configurations of 11-*α*-Methoxycurvularin (**71**) and 11-*β*-Methoxycurvularin (**72**) were determined by Xinfu Pan *et al*. by their stereoselective syntheses.

In continuation of our interest in the total synthesis of biologically active natural products, we have developed a novel synthetic route for 11-*α*-Methoxycurvularin (**71**) and 11-*β*-Methoxycurvularin (**72**) using Jacobsen hydrolytic kinetic resolution (HKR) and Maruoka asymmetric allylation reactions to create the two stereogenic centers. An intramolecular Friedel–Crafts acylation strategy was used to construct the macrolide.

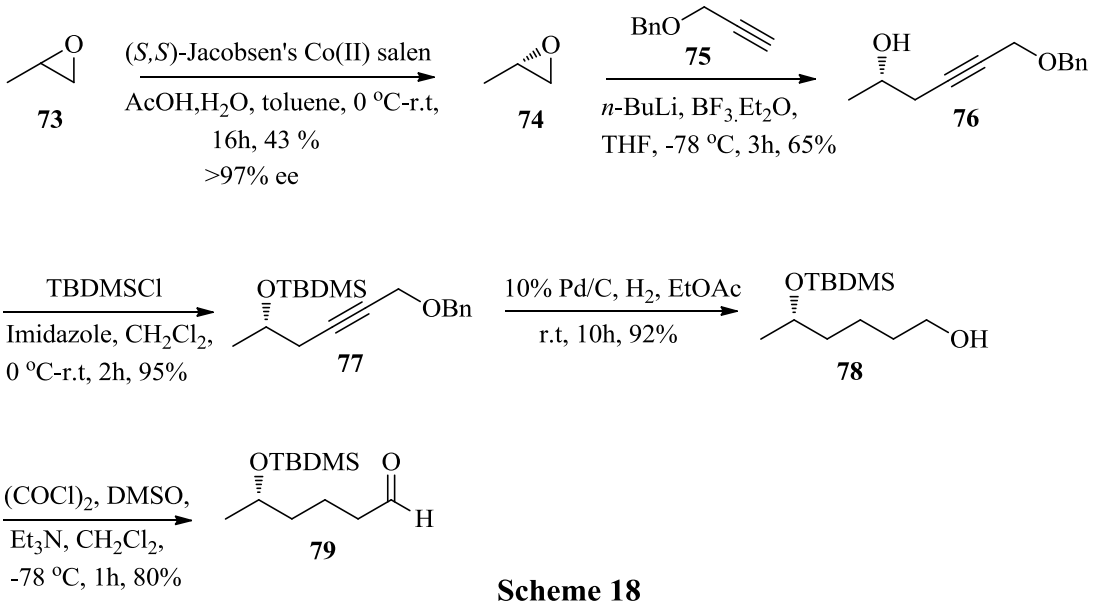
Retrosynthesis of 11-*α*-Methoxycurvularin (71) and 11-*β*-Methoxycurvularin (72):



Scheme 17

In our retrosynthetic analysis (Scheme 17), we envisioned that the construction of 11-*α*-Methoxycurvularin (**71**) and 11-*β*-Methoxycurvularin (**72**) could be achieved from carboxylic acids **85a** and **85b** respectively. These key fragments **85a** and **85b** could be synthesized from compounds **80a** and **80b** respectively, which in turn could be prepared from propylene oxide **73** by using Jacobsen resolution and Maruoka asymmetric allylation.

The synthesis of fragment **79** commenced from the commercially available racemic propylene oxide **73**. The oxirane **73** was subjected to hydrolytic kinetic resolution (HKR) using (*S,S*)-(−)-*N,N*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt (II) and AcOH in toluene at room temperature to afford the (*S*)-propylene oxide **74** in 43% yield (97% ee, determined by chiral HPLC) in Scheme 18. The resolution of (*S*)-propylene oxide **74** was confirmed by optical rotation analysis ($[\alpha]_D^{25}$ +10.8 (*c* = 1.0, $CHCl_3$); lit $[\alpha]_D^{20}$ +12.0 (*c* = 1.89, $CHCl_3$). Spectral and analytical data of compound **74** were in good agreement with the reported literature values.



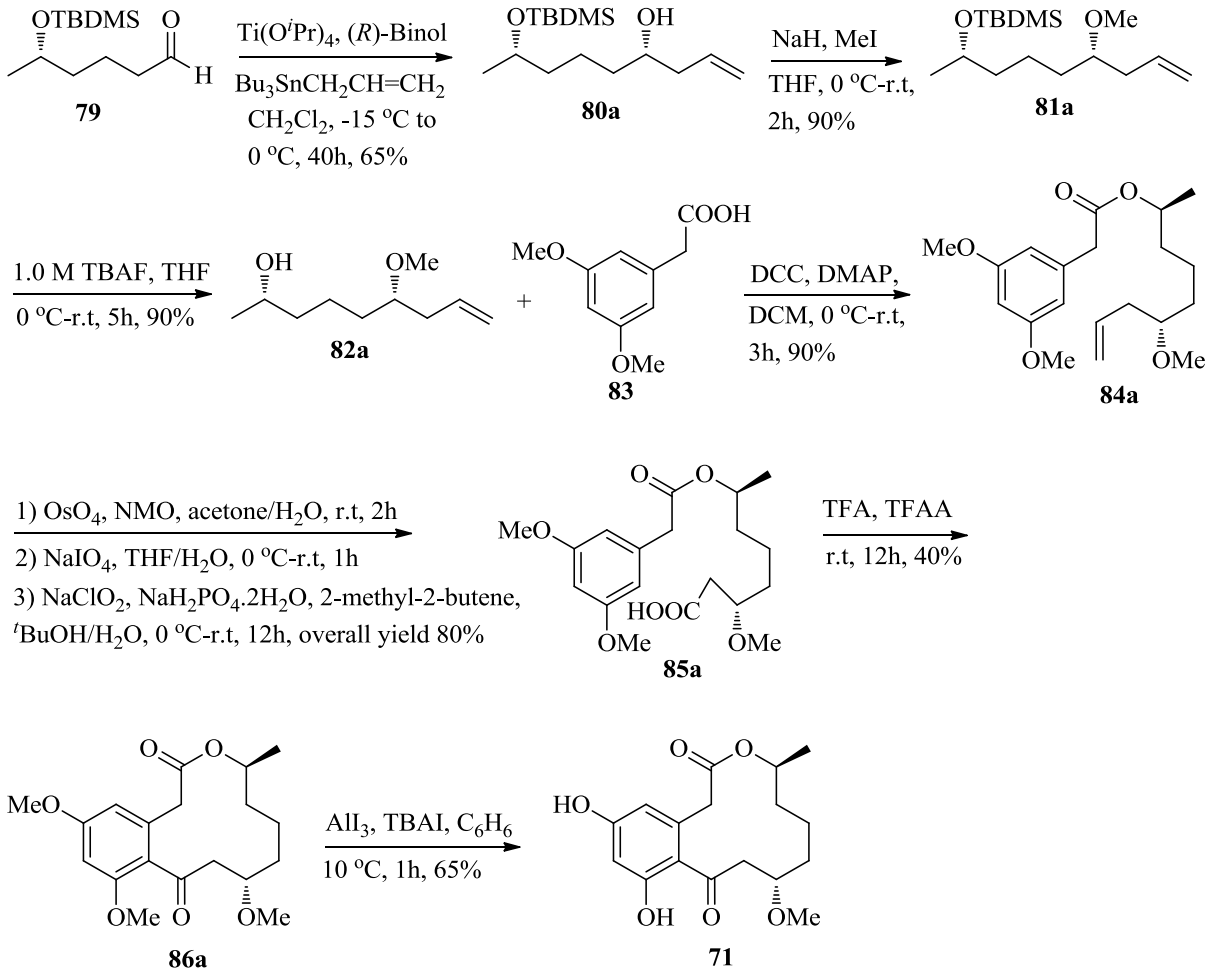
Scheme 18

The regioselective opening of epoxide **74** with ((prop-2-yn-1-yloxy)methyl)benzene **75** provided the secondary alcohol **76** in good yield. The homo propargylic alcohol **76** was protected as its TBS-ether **77** using TBDMSCl and imidazole in dry CH_2Cl_2 in 95% yield. Compound **77** was subjected to hydrogenolysis using Pd/C in EtOAc at room temperature to provide the primary alcohol **78** in 92% yield. The primary alcohol **78** was oxidized under Swern conditions in CH_2Cl_2 to afford the aldehyde **79** in 80% yield (Scheme 18).

Synthesis of 11-*α*-Methoxycurvularin (71)

The aldehyde **79** was subjected to an enantioselective Maruoka allylation using $Ti(O^iPr)_4$, (*R*)-Binol and allyltri-*n*-butyltin to furnish the homoallylic alcohol **80a** in 65%

yield. The homoallylic alcohol **80a** was protected as its methyl ether **81a** using MeI and NaH in THF in 90% yield. The deprotection of TBDMS group of compound **81a** using TBAF in THF afforded the corresponding alcohol **82a** in 90% yield. The secondary alcohol **82a** was treated with 3,5-dimethoxyphenyl acetic acid **83** in the presence of DCC and DMAP to afford the ester **84a** in 90% (Scheme 19).



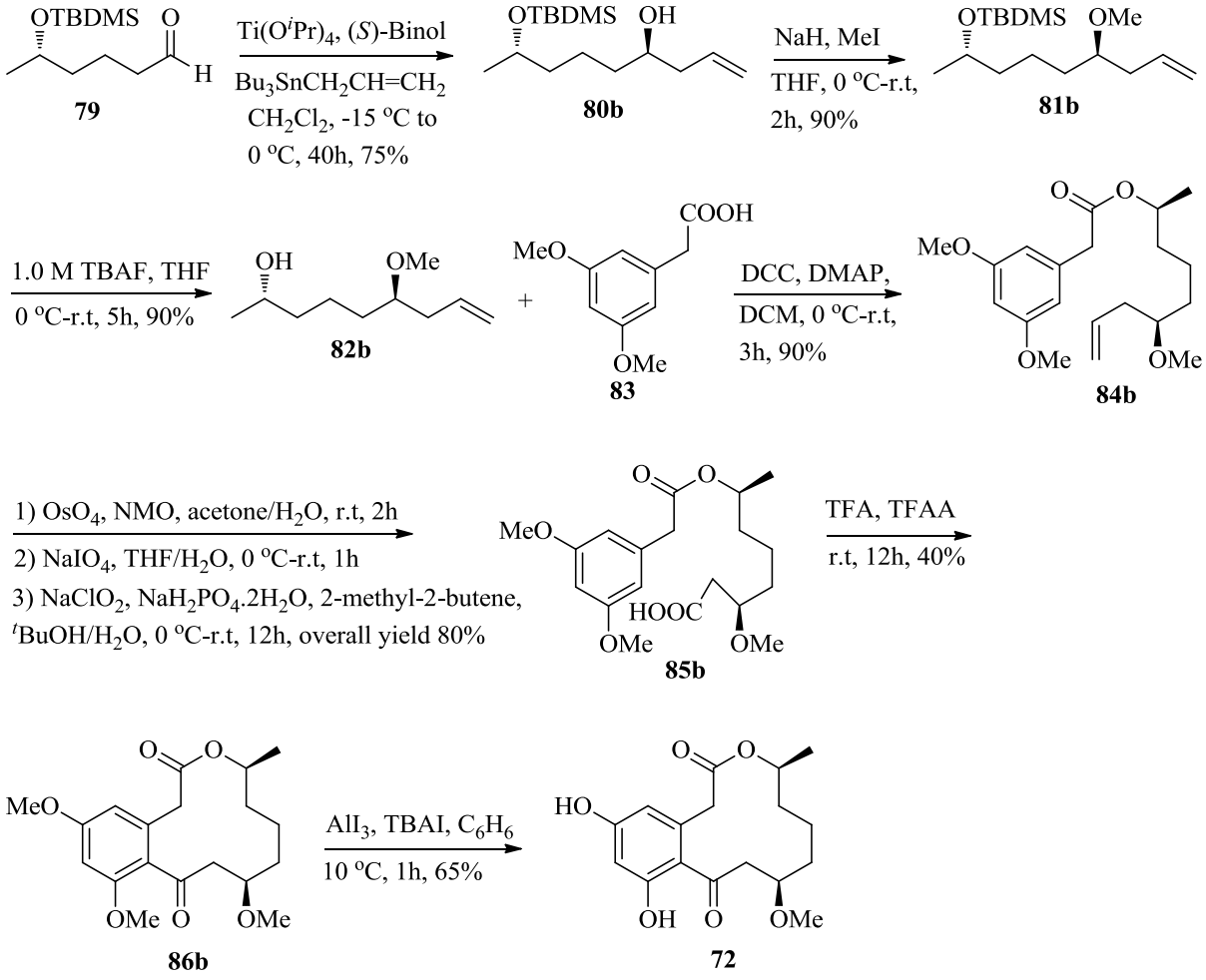
scheme 19

The compound **84a** was subjected to dihydroxylation using OsO_4, NMO followed by sodium metaperiodate ($NaIO_4$) mediated cleavage and oxidation with sodium chlorite ($NaClO_2$) to afford carboxylic acid **85a** (overall yield 80%). Intramolecular Friedel-Crafts acylation of the carboxylic acid **85a** using TFA and TFAA afforded the macrolide **86a** in 40% yield. Selective deprotection of the aromatic methoxy groups of macrolide **86a** using

aluminium iodide (AlI_3) and TBAI in benzene gave the target natural product 11-*α*-Methoxycurvularin (**71**) in good yield (Scheme 19). The spectral and analytical data were in good agreement with the reported values.

Synthesis of 11-*β*-Methoxycurvularin (72):

The aldehyde **79** was subjected to an enantioselective Maruoka allylation using $Ti(O^iPr)_4$ (*S*)-Binol and allyltri-*n*-butyltin to furnish the homoallylic alcohol **80b** in 75% yield.



scheme 20

The homoallylic alcohol **80b** was protected as its methyl ether **81b** using MeI and NaH in 90% yield (Scheme 20). The deprotection of TBDMS group of compound **81b** using TBAF in THF afforded corresponding alcohol intermediate **82b** in 90% yield. The secondary alcohol **82b** was treated with 3,5-dimethoxyphenyl acetic acid **83** in the

presence of DCC and DMAP to furnish the ester **84b** in 90% yield. The compound **84b** was subjected to dihydroxylation using OsO_4, NMO followed by sodiummetaperiodate ($NaIO_4$) mediated cleavage and oxidation with sodium chlorite ($NaClO_2$) to afford carboxylic acid **85b** (80% yield over 3 steps). Intramolecular Friedel-Crafts acylation of compound **85b** using TFA and TFAA afforded the macrolide **86b** in 40% yield (Scheme 20). Selective deprotection of the aromatic methoxy groups of macrolide **86b** using aluminium iodide (AlI_3) and TBAI in benzene gave the target natural product 11-*β*-Methoxycurvularin (**72**) in good yield. The spectral and analytical data were in good agreement with the reported values.

In conclusion, we have achieved the stereoselective total synthesis of 11-*α*-Methoxycurvularin (**71**) and 11-*β*-Methoxycurvularin (**72**) using the Jacobsen hydrolytic kinetic resolution, Maruoka asymmetric allylation and intramolecular Friedel–Crafts reaction as key transformations.

CHAPTER I

Total synthesis of Nhatrangin A

1.1. Introduction:

Cancer is the second leading cause of death in the United States and the Western World. Epidemiological studies of this insidious disease have now clearly shown that most human cancers are caused by environmental (exogenous) rather than endogenous factors. In recent years the emphasis of research on cancer has switched from studies on the treatment of cancer to studies on its cause and prevention. The rationale for this change is simple. If one could identify the causative exogenous factors, then presumably most human cancer could be eliminated either by reducing the human exposure or by developing protections for the human host against the responsible environmental agents.[1]

As a result of this change the present emphasis of research on cause and prevention is a reasonable one, since the control of this very complex disease will undoubtedly come only when the biochemistry of tumor formation is completely understood. Only then will it be possible to rationally develop new drugs that will not only specifically kill cancer cells (chemotherapeutic agents) but prevent their formation as well (chemopreventive agents), both in the early and late stages of tumor development. As a result scientists will move a step closer to the day when their better understanding of the disease will permit a more scientific approach to finding new drugs for controlling cancer.

When the natural products chemist began to examine marine organisms in detail about four decades ago, the marine plants and animals contained an exciting array of structurally unusual organic compounds, frequently very different from those found in terrestrial plants and animals. The initial screening reports were encouraging, at least for extracts of certain marine animals[2] and plants.[3] Several new cytotoxins with novel structures have been isolated and identified, but to the author's knowledge none of these compounds have been shown yet to be effective in the treatment of human cancer .[4]

Mice are used exclusively in primary screens for antineoplastic activity. Since curative activity is a rare occurrence, a substance that prolongs the life of the diseased animal to a significant extent (50% or better) is considered to be active and worthy of further study. Ehrlich ascites tumor, P-388 lymphocytic leukemia, Lewis lung carcinoma, and B16 melanoma. Once it has been established by *in vivo* testing that an extract has antineoplastic activity, use of *in vivo* assays to monitor isolation and purification of the

active principles is extremely tedious, slow, and expensive. Uses of cell culture assays alleviate most of these problems. *In vitro* assays, however, only indicate cytotoxicity. Unfortunately there is no clear cut correlation between cytotoxicity and antineoplastic activity. Anticancer compounds are generally cytotoxic, but cytotoxins do not always display antineoplastic activity when tested *in vivo*.

Many researchers have become side-tracked with *in vitro* cytotoxicity data which have not been correlated with animal testing data. Consequently, much effort can be spent on the isolation and identification of cytotoxic compounds that have no value as antineoplastic agents. Cytotoxicity assays in various cancer cell lines (e.g. KB, a human epidermoid carcinoma of the nasopharnx, and NIH 3T3; which are two systems are currently using) are useful for monitoring isolation and purification of the active compounds only after it has been established that the crude extract is active *in vivo*. After each purification step the cytotoxic fraction is checked for antineoplastic activity *in vivo*.

1.1.1. Blue-Green Algae:

For a several year's blue-green algae has been the source of new anticancer agents. Extracts of blue-green algae, especially those belonging to the *Oscillatoriaceae*, are frequently very active against P-388 lymphocytic mouse leukemia *in vivo*. Dennis Russell collected a marine *Phormidium sp*. at Pohakuloa on the island of Molokai. The methanolic extract of the cyanophyte showed a T/C (ratio of the average death time of treated mice to average death time of control mice x 100) value of 210 at a dose of 12.5 mg/kg in the P-388 lymphocytic leukemia test, with no signs of chronic toxicity.

1.1.2. Bacteria and Other Prokaryotes:

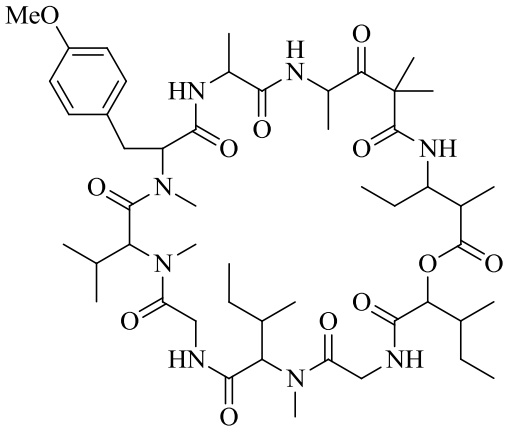
The antineoplastic activity of many marine animals may be due to the presence of symbiotic prokaryotes. Palytoxin, for example, is an exceedingly poisonous, water-soluble substance that is found in coelenterates belonging to the genus Palythoa.[5] Palytoxin is a powerful cytotoxin which shows some anticancer activity *in vivo*. For example, it completely cures Ehrlich ascites tumor in mice at doses as low as 1/10 the minimum lethal dose, but shows only marginal activity against P-388 leukemia.[6]

Didemnin B is a cyclic depsipeptide that the Rinehart group at the University of Illinois has isolated from a species of a Caribbean tunicate belonging to the genus

Tridemnum.[4d] Didemnin B shows very good activity against P-388 leukemia and B16 melanoma in mice.

In this discovery Jon Mynderse had isolated a cytotoxic cyclic depsipeptide, majusculamide C, from the blue-green alge *Lyngbya majuscula*, which showed cell cycle activity that was similar to the mitosis blocker cytoclasin B.[7] Majusculamide C, however, only showed 35% inhibition against X-5563 myeloma (0.5 mg/kg) and had marginal to nil activity against P-388 leukemia, 6C3HED lymphoma, and 755 carcinoma. A tentative structure has been proposed for majusculamide C by Daniel Carter.[8]

The didemnins could be metabolites of a *Prochloron sp*. that is associated symbiotically with all didemnid ascidians. This prokaryotic organism was originally thought to be a blue-green alga.[9] *Prochloron*, however, belongs to a phylum (*Prochlorophyta*) that is different from the phyla that other prokaryotes, such as bacteria and blue-green algae, belong to. Gregory Patterson and Nancy Withers[10] have recently discovered that Prochloron is an algal mutant that requires tryptophan for growth outside of its host.



Majusculamide C (1)

Figure 1

The alga apparently obtains this essential amino acid in its symbiotic relationship with the ascidian. The *Prochloron sp*. in the didemnid ascidian *Diplosoma similis* from Kaneohe Bay, Oahu was isolated and grown in culture. Testing of the extracts of the ascidian and the cultured prokaryote is planned.

1.1.3. Antineoplastic activity and Chemical carcinogenesis:

Most anticancer compounds that are used clinically for the treatment of human cancer are carcinogenic. Since there is generally a long lag time between carcinogen exposure and tumor formation, one wonders whether the drugs that are presently being used to treat and cure cancers are initiating new tumor cells that will emerge as different cancers 20-30 years from now.

Anticancer agents from blue-green algae, were isolated and identified representatives, e.g. debromoaplysiatoxin[11] and lyngbyatoxin A,[12] of two classes of compounds which show activity against P-388 lymphocytic mouse leukemia. Unlike most antineoplastic agents, however, the aplysiatoxins and lyngbyatoxins do not appear to be carcinogenic, but rather cocarcinogenic.[1b,13] Cocarcinogens, which are generally called tumor promoters, accelerate the development of benign and malignant tumors from cells that have been exposed to carcinogens. Many carcinogens can act as tumor promoters, but usually much higher concentrations of the carcinogen are required to accomplish this second stage.

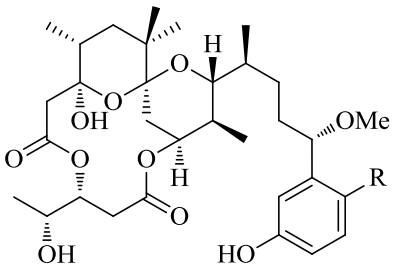
The blue-green algae that contain these tumor promoters may play a role in human stomach cancer, possibly among the Hawaiians who consume large amounts of seaweed and who have the highest incidence of gastrointestinal cancer in the world. The Hawaiians frequently eat seaweeds that contain carcinogenic and mutagenic halogen-containing compounds (*Asparagopsis taxiformis* and *Laurencia nidifica*).[14] Since the tumor promoter-containing blue-green algae sometimes grow epiphytically on edible seaweeds[15], the possibility exists that the Hawaiians are obtaining in their seaweed diet alone all of the necessary exogenous ingredients for developing gastrointestinal cancer.

1.1.4. Anticancer Compounds from Oscillatoriaceae:

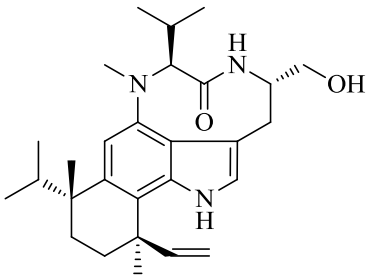
One of the most common and accessible marine cyanophytes in the subtropical and tropical oceans is *Lyngbya majuscula*. The *L. majuscula* was tested for antineoplastic activity was a deep-water variety found abundantly on many of the pinnacles of Enewetak Atoll in the Marshall Islands.[11] The crude lipophilic extract of this blue-green alga consistently displayed activity in the P-388 screen at a T/C value of 140 (0.6 mg/kg dose). Using an *in vivo* bioassay to monitor the isolation of the drug, Jon Mynderse showed that the active principle was debromoaplysiatoxin, one of the toxic constituents that Kato and

Scheuer had isolated from the digestive gland of the sea hare *Stylocheilus longicauda*.[16] While collecting the *L. majuscula* at Enewetak, Mynderse found several *S. longicauda* feeding on the alga. This discovery provided clear evidence that debromoaplysiatoxin was being accumulated in the digestive tract of this gastropod mollusk through diet. Aplysiatoxin, a second major toxin that had been isolated from the Hawaiian sea hare, however, was not found in this deep water variety of *L. majuscula*.

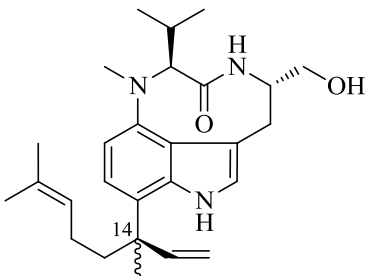
When extracts of shallow water varieties of *L. majuscula* from Hawaii were examined, antineoplastic activity could generally be attributed to debromoaplysiatoxin and aplysiatoxin. The marginal activity of the shallow water *L. majuscula* on leeward Oahu, however, was shown to be due primarily to a different compound, lyngbyatoxin A.[12] Debromoaplysiatoxin was also identified as one of the compounds responsible for the antineoplastic activity of the lipophilic extract of a mixture of two blue-green algae, tentatively identified as *Schizothrix calcicola* and *Oscillatoria nigroviridis*, found on the seaward side of Enewetak Atoll.[17]



Aplysiatoxin (2) R = Br
Debromoaplysiatoxin (3) R = H



Teleocidin B-4 (4)



Lyngbyatoxin A (5) 14R
Teleocidin A-2 (6) 14S

Figure 2

A second antineoplastic compound in this algal mixture, oscillatoxin A, was isolated and shown to be 31-nordebromoaplysiatoxin, it showed the same activity against P-388 leukemia *in vivo* as debromoaplysiatoxin. Small amounts of 17-bromooscillatoxin A, 17,19-dibromooscillatoxin A, and 19-bromoaplysiatoxin were also found in this algal mixture, but aplysiatoxin was not detected. The brominated toxins were not isolated in sufficient quantities for evaluation against P-388 *in vivo*. Debromoaplysiatoxin and oscillatoxin A are fairly toxic substances. The minimum lethal dose of each compound in

mice is roughly 0.2 mg/kg. Their best anticancer activities are observed only at the chronic toxicity levels and therefore do not appear to be potentially useful as anticancer drugs.

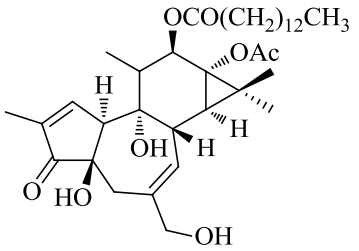
1.1.5. Seaweed Dermatitis:

Lyngbya majuscula is the causative agent of a severe contact dermatitis that sometimes affects swimmers and bathers in Hawaii during the summer months. To date outbreaks of the dermatitis have only been observed on the windward side of the island of Oahu. Fortunately seaweed dermatitis is rare and large outbreaks occur several years apart. The most recent outbreak, where a total of 86 persons with symptoms were reported to the Hawaii Department of Health, occurred at the Kailua, Kalama, and Pilapu beaches on windward Oahu in August, 1980.[18] The symptoms of the dermatitis were a burning rash, generally involving the genital and/or perianal areas, which was followed by blister formation and deep desquamation. The dermatitis had resulted from the swimmer's contact with filaments of the blue-green alga, which had been broken loose from the ocean floor by the heavy surf and were floating freely in the water.

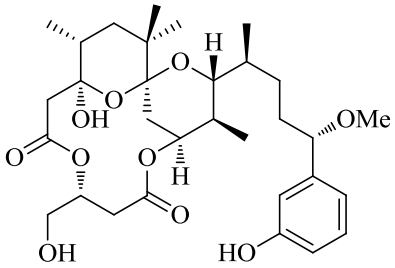
Lyngbyatoxin A is an indole alkaloid which is structurally related to teleocidin B, a potent inflammatory agent found in the soil fungus *Streptomyces mediocidicus*.[19] Lyngbyatoxin A appears to be a minor constituent in the dermatitis-producing strains of *L. mjuscula*.

1.1.6. Structures of Teleocidins and Lyngbyatoxins:

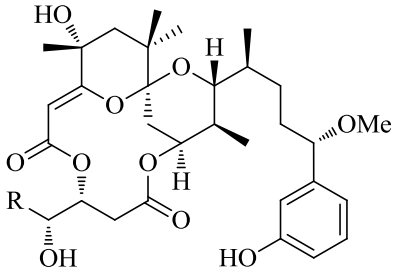
The teleocidins are the first representatives of this class of indole alkaloids and are so-named for their ichthyotoxicity. The teleocidins was isolated from the mycelia of several strains of Streptomyces.[20] *S. mediocidicus* contains two dermatitis-producing components, teleocidin A, and teleocidin B.



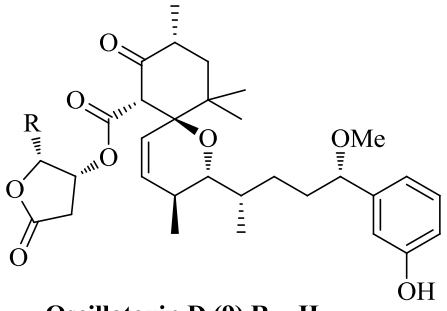
12-*O*-Tetradecanoylphorbol 13-acetate (7)



Oscillatoxin A (8)



Oscillatoxin B (11) R = CH_3
31-noroscillatoxin B (12) R = H



Oscillatoxin D (9) R = H
30-Methyloscillatoxin D (10) R = Me

Figure 3

1.1.7. Inflammation and Tumor Promotion:

Until recentally there was only a single class of chemical substances known, the phorbol esters, that were capable of inducing tumor promotion at nanomolar concentrations, i.e. levels at which hormonal activity is observed. The most potent tumor promoter of these diterpenoid esters is 12-*O*-tetracarbonylphorbol-13-acetate (TPA), a highly inflammatory agent found in Croton oil. Detailed studies of the tumor promoting activity of TPA by many investigators has strongly suggested that inflammation is an important event in the development of a tumor after carcinogen exposure.

About three decades ago Hirota Fujiki and Takashi Sugimura began an intensive search to find other inflammatory agents that could act as tumor promoters. They screened over 270 substances and found that 43 of these were skin irritants. Of these 43 only two compounds, teleocidin B and its catalytic hydrogenation product, dihydroteleocidin B, proved to be tumor promoters. Both compounds were found to be equipotent with TPA, acting at nanomolar concentrations, at about the time that the tumor promoting activity of the teleocidins was discovered. The Sugimura group immediately recognized the

similarity of lyngbyatoxin A and teleocidin B, not only in structure but in bioactivity, and requested samples of lyngbyatoxin A and its catalytic hydrogenation product, tetrahydrolyngbyatoxin A, both compounds were found to be powerful tumor promoters, essentially identical in potency with the teleocidins. Aplysiatoxin was found to be a potent tumor promoter, comparable in potency with TPA, teleocidin B, and lyngbyatoxin A. To everyone's surprise, however, debromoaplysiatoxin was found to be a much weaker tumor promoter, about a hundred times less effective.

1.1.8. Tumor Promotion and Skin Cancer:

Over two hundred years ago the British surgeon Sir Percivall Pott recognized that cancer of the scrotum, a common disease among chimney sweeps, was associated with their occupational exposure to soot.[21] This clever observation marked the first time that a human cancer had been linked to an environmental agent. It is now well established that most of the causative agents in the soot are certain polycylic aromatic hydrocarbons such as benzo[α] pyrene. These compounds represent major potential public health hazards even today. In the early 1970's it was estimated that about 1300 tons of benzo[α]pyrene was being emitted into the air of the United States annually.[22]

Chemically induced skin cancer proceeds in two major stages. This has been known for at least four decades and was first observed in mouse skin.[23] The first stage, initiation, is accomplished when the skin is exposed to a single small dose of a carcinogen (initiator). This one time contact with the carcinogen, however, is insufficient for visible tumors to be produced over the life-span of the animal. Tumors will only develop when the skin is repeatedly exposed a cocarcinogen (tumor promoter) in the second stage, promotion. Generally a carcinogen can act as both initiator and promoter at high doses. Tumor promoters alone are not carcinogenic. It is only after initiation has occurred that tumor promoters can cause cancer.

In the case of TPA[24] it has been shown that skin tumors will develop even if a year has elapsed between the application of the initiator and the promoter. Once application of the tumor promoter has commenced, it must be continued at frequent intervals for tumors to develop. If the application schedule is interrupted or changed so that there are longer intervals between applications, tumors are not produced. Tumor promotion, therefore, is a reversible process.

Initiation leads to a permanent change in the genetic machinery of the cell, presumably by irreversible interactions of the metabolized carcinogen with the DNA. Although enzymatic mechanisms for removing DNA defects exist in murine and human cells, the repair processes appear to be very slow. For this reason, tumors can be produced even when a long period has elapsed between initiation and exposure to the promoter.

The promotion process appears to begin when a promoter such as TPA, teleocidin, lyngbyatoxin A, or aplysiatoxin binds to a receptor on the plasma membrane of the cell,[25] frequently referred to as the phorboid receptor. Associated with this phorboid receptor binding are a number of biologic responses, for example, inhibition of binding of epidermal growth factor (EGF), a hormone-like protein which stimulates several events in cell division,[26] to its receptor[25a] and stimulation of choline and arachidonic acid release from cellular phospholipids,[25a] resulting in increased prostaglandin synthesis as one consequence.[27]

The binding potency of a promoter to the phorboid receptor and the degree to which a promoter inhibits EGF binding to its receptor appear to correlate with the promoter's strength as a tumor promoter *in vivo*. Interestingly debromoaplysiatoxin binds much weaker to the phorboid receptor and is a weaker inhibitor of binding of EGF to its receptor.[25a] TPA, the teleocidins, lyngbyatoxin A, and aplysiatoxin have all been shown to be strong tumor promoters *in vivo*. debromoaplysiatoxin, however, is a very weak tumor promoter. Curiously debromoaplysiatoxin stimulates the release of choline and arachidonic acid from cellular phospholipids to the same degree as teleocidin, lyngbyatoxin A, and aplysiatoxin. These results strongly suggest that induction of the phospholipid metabolism is mediated by a receptor that is different from the phorboid receptor.

The phorboid and EGF receptors might be one and the same as tumor promoters and EGF show some similar biologic effects.[26] EGF, however, does not inhibit phorboid receptor binding. Inhibition of binding of EGF to its receptor is an indirect consequence of binding of a tumor promoter to the phorboid receptor and not to binding of EGF and tumor promoters to the same receptor site.[28] Apparently the binding of the tumor promoter to the phorboid receptor causes alternations in the membrane as a result, EGF is no longer able to recognize its receptor.

The normal function of EGF is to initiate and maintain a complex network of biochemical and morphological events leading to cell growth and multiplication. When a cell undergoes division in the normal situation, one of the daughter cells replaces the parent (stem) cell whereas the other daughter cell is programmed to perform a special function (differentiation). In the case of the skin cell, the daughter cell that is destined to differentiate does so by becoming keratin. The switches that control the cell's capability to proliferate or differentiate are on the surface of the cell membrane. When cellular contact is broken, for example by a wound, the cellular biochemistry is reorganized to allow proliferation and a transient inhibition of terminal differentiation. When the tissue is restored so that cellular contact is reestablished at the healed wound site, proliferation ceases and terminal differentiation proceeds once again. The phorboid receptor system has been proposed to play a role in inhibiting terminal differentiation and stimulating cell growth during wound healing. This would necessitate the generation of an endogenous factor on wounding that would bind to the phorboid receptor to shut off the differentiation process and stimulate stem cell growth. Recently evidence was obtained that such factors exist.[28b] Stimulation of the phorboid receptor by a tumor promoter, however, might result in inhibition of terminal differentiation and preferential growth stimulation of aberrant stem cells formed during initiation.

The ability of tumor promoters to inhibit terminal differentiation may be central to heir ability to develop tumors from initiated cells.[1] TPA, teleocidin, lyngbyatoxim A, and aplysiatoxin are potent inhibitors of terminal differentiation in a variety of cell systems; for example, these compounds inhibit induced differentiation (hemoglobin synthesis) in Friend erythroblastic leukemia cells,[13] inhibit induced melanogenesis in Bl6 melanoma cells, and inhibit induced myogenesis in human myoblasts. TPA, teleocidin, lyngbyatoxin A, and aplysiatoxin are also potent inducers of differentiation in other cell systems. These compounds induce differentiation of human promyelocytic leukemia cells (HL-60) into macrophage-like cells, characterized by induction of cell adhesion and increased release of lysozyme.[29] The weak tumor promoter, debromoaplysiatoxin, is a much weaker inhibitor and inducer of terminal differentiation in all of the above cell systems.

Inflammation and hyperplasia are necessary events for tumor promotion. Evidence for this intimate connection comes from the fact that tumor development in mouse skin is

inhibited by pretreatment with indomethacin, an aspirin-like drug, prior to application of the tumor promoter.[30] The causative gent of the inflammation and hyperplasia appears to be prostaglandin E_2, which is produced from the arachidonic acid released on deacylation of membrane phospholipids by the tumor promoter.[27,31] Prostaglandin synthesis is blocked by the cyclooxygenase inhibitor indomethacin and other aspirin-like drugs.[32] In mouse skin inflammation and hyperplasia are inhibited when indomethacin is applied before the tumor promoter.[24] This inhibition is reversed if prostaglandin E_2 is applied simultaneously with the tumor promoter. Inflammation and hyperplasia induced by tumor promoters are also inhibited by corticosteroidal drugs, such as dexamethasone, which blocks the formation of arachidonic acid from phospholipids.[32] The inhibition of inflammation and hyperplasia, and also tumor development, by indomethacin and corticosteroids is only effective, however, when the drug is applied prior to the tumor promoter.

The role of prostaglandin E_2 in tumor promotion is not clear. It is suspected that prostaglandin-induced inflammation is necessary to attract leukocytes to the inflammatory site by chemotaxis.[33] After arrival of polymorphonuclear leukocytes (PMNLs) into the inflammed area, lipoxygenase products,[34] such as (5*S*,12*R*)-dihydroxy-6,8,10,l4-icosatetraenoic acid (leukotriene B), might then become more important as chemotactic factors in attracting more leukocytes to the area. Leukotriene production may be stimulated in PMNLs by tumor promoters; in support of this proposal, divalent cation ionophore A23187, which produces some biologic effects that are similar to tumor promoters,[31] stimulates the production of leukotriene B from human PMNLs.[35] To date, however, the importance, if any, of the leukotrienes[36] in tumor promotion has not been determined. It will be interesting to test whether lipoxygenase blockers[37] inhibit tumor promotion.

Generally a burst of oxygen consumption accompanies the activation of phagocytic cells during the inflammatory process, resulting in the production of superoxide anion radical O_2) and hydrogen peroxide. The function of these active oxygen species is to kill microbes, but these potent oxidants are also potentially genotoxic.[38] Superoxide anion radical production by human PMNLs is stimulated by TPA, teleocidin B, and the second stage promoter mezerein.[39] Active oxygen species generated during the activation of phagocytic cells could act on the DNA of the initiated cell to cause

expression of the tumor phenotype, perhaps by causing rearrangements of the genetic material. Protease inhibitors, vitamin A derivatives, and dexamethasone block superoxide formation by tumor promoter-stimulated phagocytes.[39a,40] Protease inhibitors[41] and vitamin A derivatives such as 13-*cis*-retinoic acid[30] inhibit tumorigenesis in mouse skin.

Tumor promoters express in normal cells the phenotype of the tumor cell. Increases ornithine decarboxylase (ODC) activity, an activity which is characteristic of cells of fast-growing neoplasms, is observed in normal cells that have been treated with a tumor promoter. When a tumor promoter is applied topically to mouse skin, increased ODC activity is noted almost immediately, reaching a maximum about four hours after application. ODC activity is inhibited if 13-*cis*-retinoic acid is applied to the skin prior to the tumor promoter. TPA, the teleocidins, lyngbyatoxin, aplysiatoxin, and even debromoaplysiatoxin show the same amount of activity,[13] indicating that this activity is associated with the second stage of tumor promotion. The significance of increased ODC activity, however, is unclear.

What happens in tumor promotion from this point on is uncertain. This discussion has presented only some of the current concepts in chemical carcinogenesis. It is obvious that the dermatitis-producing toxins of *Lyngbya majuscula* are playing and will continue to play an important role in determining the mechanisms of tumor promotion.

1.1.9. Structure-Activity Relationships of Tumor Promoters:

Three classes of chemical compounds are known to act as tumor promoters at nanomolar concentrations, *viz*. diterpenoid esters (12-*O*-Tetradecanoylphorbol-13-acetate), indole alkaloids (teleocidin B and lyngbyatoxin A) and phenolic bislactones (aplysiatoxin). Even though these three groups of compounds have totally different structures, all three of them act essentially the same way in several biologic systems. TPA, the teleocidins, lyngbyatoxin A and aplysiatoxin bind to the same phorboid receptor and produce the same biologic responses to this binding. In addition, these compounds show similar potencies as tumor promoters *in vivo*. Interestingly all three classes display antileukemic activities.[11,12,39b,42] Their similar bioactivities, in particular the same binding behavior to the phorboid receptor, suggest that the compounds in these three distinct classes have certain structural features in common.

The activities of the teleocidins and lyngbyatoxin A are not changed by hydrogenation of the monoterpenoidal portion. In fact the activity does not depend at all whether the monoterpenoidal portion of the molecule is cyclic or acyclic, saturated or unsaturated, C10 or C11. Lipophilic character in this region of the indole alkaloid is necessary for non-specific binding to the hydrophorbic region of the phorboid receptor. The indole alkaloid without its monoterpenoid moiety may exhibit activities similar to those of phorbol which has no tumor-promoting activity. Proof of this is needed. The intact lactam ring is needed for maximum toxicity, as is a free OH on C-24,[20b] these two functionalities are probably also needed for maximum tumor promoting activity.

To aid in this comparison was begun activity studies of derivatives of aplysiatoxin. It is already known that the OH on C-3, is necessary for activity. Anhydroaplysiatoxin is non-toxic and inactive in all of the test screens for tumor promoting activity. Aplysiatoxin 30-acetate has also been found to be non-toxic, tumor promoter activity. Toxicity is also lost when the phenolic OH is methylated. It is not clear at all why the bromine on C-l7 markedly enhances the potency of this compound as a tumor promoter. Recent studies by Hirota Fujiki and Takashi Sugimura indicate that 19-bromoaplysiatoxin shows less ODC activity in mouse skin than aplysiatoxin and that 19, 21-dibromoaplysiatoxin exhibits no ODC activity, suggesting that 19-bromoaplysiatoxin will probably be a weaker tumor promoter in vivo and 19, 21-dibromoaplysiatoxin a nonpromoter.

1.1.10. Chemical Carscinogenesis and Chemoprevention:

Since initiation requires only a single exposure to a carcinogen, there is not much hope that this stage of chemical carcinogenesis can be completely eliminated or avoided. Since tumor promotion requires prolonged contact with the causative agent for cancer to occur, however, there is a real possibility that this stage can be effectively controlled by limiting exposure to tumor promoters and by using chemopreventive agents to protect the human host. Some of these protective substances, like the vitamins, are dietary constituents.[43]

There is already evidence[43] that tumorigenesis is inhibited by vitamin A derivatives, protease inhibitors,[44] non-steroidal and steroidal antinflammatory agents, antioxidants,[45] certain trace elements, and other compounds[46] are found as the secrets of tumor promotion are uncovered.

The promotion stage, at least of some cancers, appears to commence when a tumor promoter interacts with the phorboid receptor. One wonders whether chemopreventives could be developed that would inhibit tumor promoters from binding to the phorboid receptor. It would be interesting therefore, to examine the cells of sea hares to find out why tumor promoters fail to elicit the biologic responses noted in murine[47] and human cells. Are inhibitors of phorboid receptor binding present in the digestive gland of the sea hare or is the lipid character[48] of the cell membrane sufficiently different to allow binding of an endogenous growth factor but not an exogenous tumor promoter.

Certain fish are also resistant to the tumor promoters of *Lyngbya majuscula*. The rabbitfish Siganus fuscescens, for example, has been observed to feed on sea grass entangled with *L. majuscula* with no apparent ill effects. Human intoxication in the Ryukyus Islands from rabbitfish may result from eating the viscera of the fish that has accumulated *L. majuscula* toxins. This suggests that the tumor promoters of *L. majuscula* might be found in the digestive tract and viscera of other fish, thereby contributing to gastrointestinal cancer in Japan.

1.1.11. Biological Material:

Samples of *Lyngbya majuscula* Harvey *ex* Gomont (Oscillatoriaceae), growing on rocks, dead corals, and gravel in the lower intertidal to subtidal zone of shores and exposed to calm to moderate wave action, they were collected in Vietnam at Hon Do locality (N 12°16.05′, E 109°12.23′) in Nhatrang of Khanh Hoa Province (Figure 4).

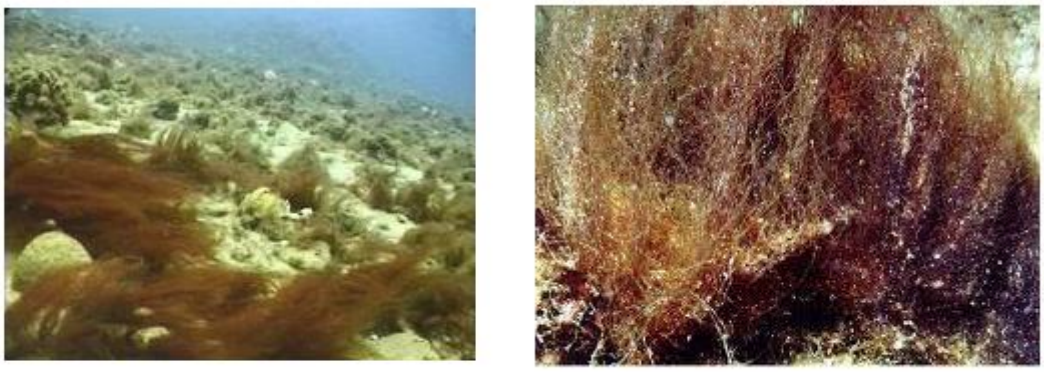


Figure 4: *Lyngbya majuscula*.

The sample (Pham Huu Tri 038/PHT 038) deposited at the Marine Museum of the Institute of Oceanography, Nhatrang. The thallus of PHT 038 expanded up to 3 cm long, dull blue-green to brown or yellowish-brown in color, with very long and curved filaments, seldom only slightly coiled, the sheath colorless, lamellated, the trichomes blue-green, not constricted at the cross-wall, not attenuated at both ends, the calyptra absent.

1.1.12. Extraction and Isolation:

A *Lyngbya majuscula* (PHT 038) yield 10.58 g of extract (CH_2Cl_2/CH_3OH, 1:1). This extract was subjected to silica gel liquid column chromatography with a solvent gradient of CH_2Cl_2/CH_3OH to yield 17 fractions.

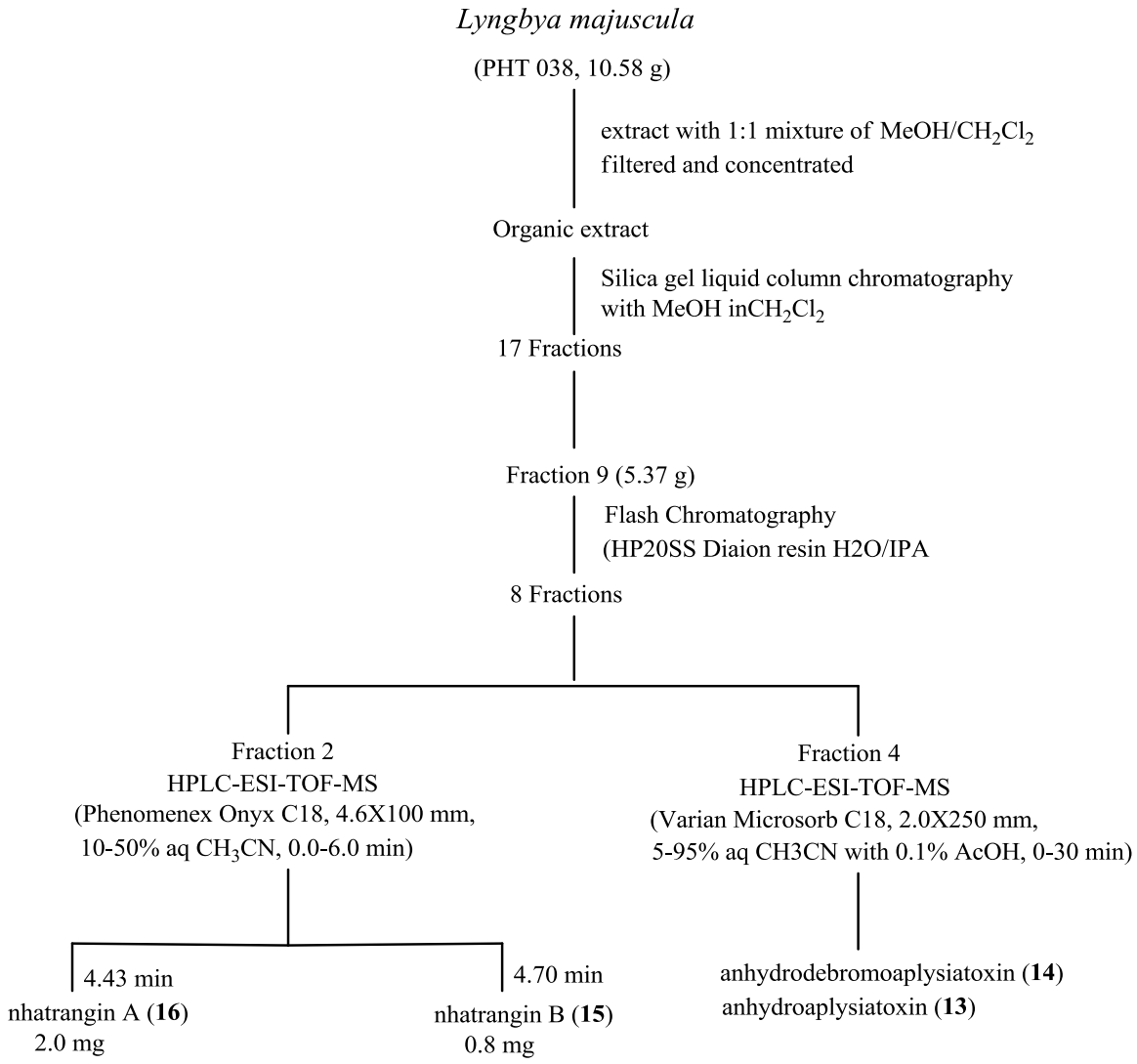
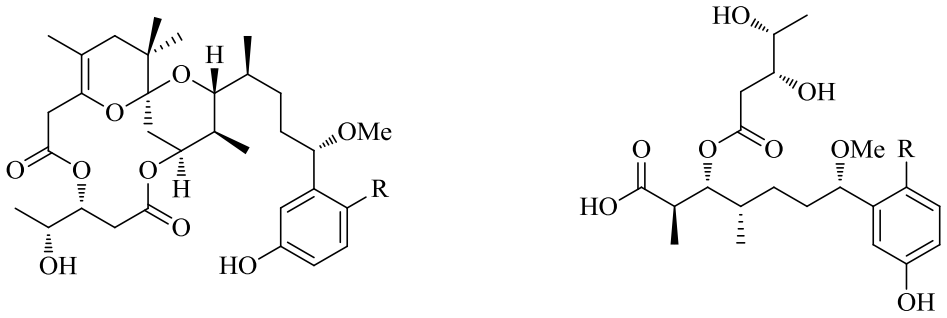


Figure 5: Scheme for the isolation and purification

Fraction 9 (5.37 g) was subjected to flash chromatography utilizing HP20SS Diaion resin and a H_2O/IPA gradient to yield eight fractions. These fractions were subjected to HPLC-ESI-TOF-MS analysis (Varian Microsorb C18, 2.0 X 250 mm, 5-95% aqueous CH_3CN with 0.1% AcOH, 0-30 min) to determine the presence of previously isolated metabolites. Data were acquired in negative scan mode, 200-1000 *m*/*z*, with event loop duration of 0.12 s. The mass spectrometric chromatogram (Figure 2) of subfraction 2 (F9.2) revealed the presence of nhatrangin A (**16**) as well as nhatrangin B (**15**). The chromatogram of subfraction 4 (F9.4) revealed the presence of anhydrodebromoaplysiatoxin (**14**) and anhydroaplysiatoxin (**13**) (Figure 6). Semipreparative reversed-phase HPLC (Phenomenex Onyx C18, 4.6 X 100 mm, 10-50% aqueous acetonitrile, 0.0-6.0 min) of F9.2 yielded 2.0 mg of (**16**) (4.43 min) and 0.8 mg of (**15**) (4.70 min).



Anhydroaplysiatoxin (13) R = Br
Anhydrodebromoaplysiatoxin (14) R = H

Nhatrangin B (15) R = Br
Nhatrangin A (16) R = H

Figure 6

1.1.13. Structure elucidation:

Nhatrangin A (**16**) was obtained as pale orange oil. Both positive and negative mode HRESI-FTMS indicated a molecular formula of $C_{21}H_{32}O_8$ (435.1984 *m*/*z* $[M + Na]^+$ and 411.2034 *m*/*z* $[M - H]^+$) containing six degrees of unsaturation. The ^1H NMR spectrum was consistent with a 1,3-disubstituted aromatic ring (δ_H 6.63, 6.65, 6.67, and 7.10), four heteroatom-bearing methines (δ_H 3.48, 3.75, 3.93, and 4.74), a methoxy moiety (δ_H 3.07), and three tertiary methyl groups (δ_H 0.74, 0.83, and 0.95). The DEPTQ spectrum[49] confirmed the carbonyl moiety (δ_C 171.1, C-1′). The HSQC spectrum showed that two of the protons in the ^1H spectrum (δ_H 2.35 and 2.05) shared the same carbon (C-

2′, δ_C 38.3). The ^1H and DEPTQ data accounted for $C_{20}H_{28}O_6$ and five of the six degrees of unsaturation. However there was still one carbon, two oxygen atoms, and one degree of unsaturation unassigned. Further evaluation of the HMBC spectra revealed a strong correlation from H-14 to a carbonyl carbon at δ_C 176.5. This additional carbonyl moiety (C-1) accounted for the missing one carbon and two oxygen atoms, as well as satisfied the missing degree of unsaturation. Interpretation of COSY, TOCSY, and HMBC experiments allowed the elucidation of two separate parts of the molecule, C-1 through C-15 and C-1′ through C-5′ (Figure 7). The main chain of the molecule consisted of C-1 through C-15. The seven-membered carbon alkyl chain (C-14, 2-7) with a methyl (C-15) attached at C-4 was deduced from the COSY spectrum (Figure 7). The downfield chemical shifts of C-3 and C-7, δ_C 78.0 and 83.3, respectively, and corresponding ^1H chemical shifts at δ_H 4.74 and 3.93 respectively, were consistent with carbons attached to an oxygen atom. Correlations from the HMBC spectrum revealed that the methoxy moiety was linked to the main chain via the oxygen attached at C-7. In addition, the HMBC spectrum showed correlations from H-7 to the carbons of the aromatic ring (C-9 and C-13).

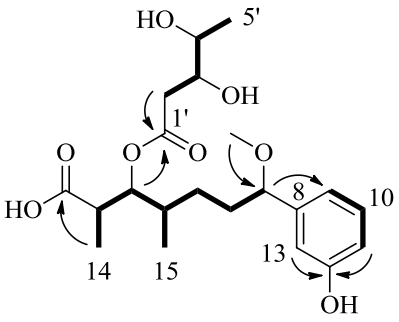


Figure 7: COSY data and HMBC correlations of **16**

Thus, the aromatic ring was attached to the main chain by a bond between C-7 and C-8. The downfield shift of C-12 (δ_C 157.5) and the lack of additional HMBC correlations beyond the aromatic ring were consistent with a phenolic hydroxy moiety at C-12. The previously mentioned HMBC correlation from H-14 to C-1 revealed that the carbonyl was attached to C-2 (δ_C 40.4).

The second partial structure consisted of C-1′ to C-5′. The COSY spectrum displayed correlations consistent with an unbranched chain from C-2′ to C-5′. The DEPTQ

and associated ^{1}H data for C-3′ (δ_C 70.6, δ_H 3.75) and C-4′ (δ_C 68.4, δ_H 3.48) indicated that these two carbons were substituted with oxygen. The HMBC correlations from H_2-2′ to C-1′ attached the carbonyl (C-1′) to C-2′. The downfield chemical shift of H-3 suggested an ester at the C-3 position. In order to support this ester linkage, a semiselective HMBC experiment focused around the two carbonyls (C-1 and C-1′) was performed. A correlation was observed between H-3 and C-1′. Thus, the two portions of the molecule are connected via an ester bond from C-1′ to C-3, and the planar structure was determined as shown above.

1.1.14. Configurational analysis:

The two-dimensional structure of nhatrangins A (**16**) the presence of six stereocenters (C-2, C-3, C-4, C-7, C-3′, and C-4′). The absolute configuration of C-7 was determined by circular dichroism and comparison with the CD spectrum of debromoaplysiatoxin.[50] Nhatrangin A (**16**) displayed positive molar ellipticities ($[\theta]_{274}$ +316) in their CD spectra, which was similar to the values in the published CD spectrum of debromoaplysiatoxin, and thus **16** was identical absolute configurations at the benzylic carbon (C-7) as **14** and **13** (C-15). The relative configurations of the other five carbons (C-2, C-3, C-4, C-3′, and C-4′) were determined using 3-bond coupling constants, which included $^{3}J_{H,H}$ and $^{3}J_{C,H}$ values, and NOE correlations acquired from selective 1D ROE experiments.

Protons H-2 and H-3 displayed a large coupling constant ($^{3}J_{H\text{-}2,H\text{-}3}$ = 8.2 Hz), indicating them to be in an *anti* conformation. This allowed for only two of the six possible relative conformations for C-2 and C-3. A selective ROE experiment displayed a NOE correlation between H_3-14 and H-4, which indicated a relative configuration of 2*R* and 3*R*. The protons H-3 and H-4 displayed a small coupling constant ($^{3}J_{H\text{-}3,H\text{-}4}$ = 3.6 Hz), which is consistent with a *gauche* conformation and produces four possible relative conformations. Three of these conformations would satisfy a NOE correlation between H_3-15 and H-2; however only one, 3*R* and 4*S*, can also satisfy the previously described NOE correlation of H_3-14 (attached at C-2) and H-4. This relative configuration (2*R*, 3*R*, 4*S*) is identical to the relative configurations of C-10, C-11, and C-12 of anhydrodebromoaplysiatoxin (**14**).

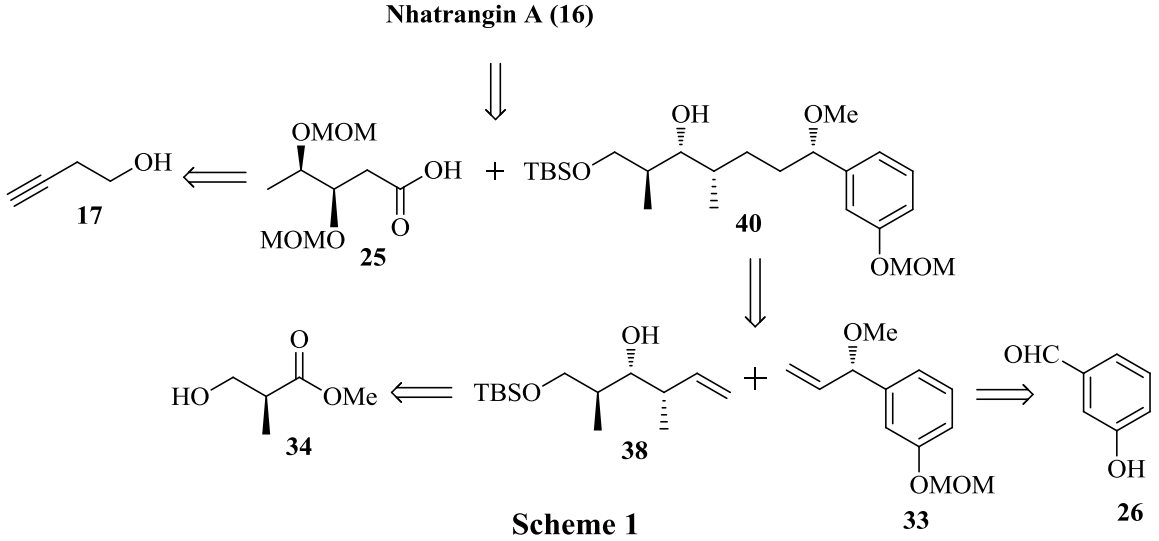
The ester side chain of (**16**) contained two stereocenters (C-3′ and C-4′). The protons H-3′ and H-4′ displayed a small coupling constant ($^3J_{\text{H-3′,H-4′}}$ = 4.2 Hz). The NOE correlation between H_3-5′ and H-2′a/b would be satisfied by three possible relative conformations, two 3′*R*, 4′*S* and one 3′*R*, 4′*R*. Since there were no other NOE correlations available to distinguish between these conformations, carbon-proton coupling constant analysis was used to determine the relative configuration.[51] The $^3J_{\text{C,H}}$ coupling constants were ascertained using a HSQMBC experiment.[52] The values for $^3J_{\text{C-2′,H-4′}}$ and $^3J_{\text{C-5′,H-3′}}$ were determined to be 4.6 and 5.0 Hz respectively. Both of these values were considered to be "large" (5-7 Hz) and were consistent with a configuration of 3′*R* and 4′*R*. The relative configurations of these carbons, C-3′ and C-4′, are identical to the relative configurations of C-29 and C-30 of anhydrodebromoaplysiatoxin (**14**).

1.2. Present Work:

The polyketide metabolites, Nhatrangin A (**16**) and Nhatrangin B (**15**), were isolated from a Vietnamese collection of *Lyngbya majuscula*. These compounds are related to the aplysiatoxin series of metabolites, which have also been isolated from the species of marine cynobacterium. Cynobacteria, in particular *Lyngbya majuscula*, have been shown to be a rich source of biologically active secondary metabolite.[53-55]

Nhatrangin A (**16**) was named after the collection site of Nha Trang Bay, Vietnam. The carbon skeleton of this molecule appears to be related to the carbon skeleton of the aplysiatoxin. An initial organic extract (2.5 g) of *Lyngbya majuscula* displayed significant antiproliferative activity in a colon cancer cell line (Col-2). To the best of our knowledge, total synthesis of this interesting natural product is not been reported. Inspired by interesting structural features, biological profile (antiproliferative activity) in combination with lowest natural abundance and in continuation of our interest in the area total synthesis of biologically potent natural products, we initiated a program on total synthesis of Nhatrangin A (**16**). Herein, we report an efficient synthetic route for the nhatrangin A (**16**) from commercially available and cost-effective homopropargyl alcohol and 3-hydroxy benzaldehyde as starting materials. The key features of this synthetic approach are the Sharpless asymmetric dihydroxylation, Sharpless asymmetric epoxidation, Browns crotyl boration, Birch reduction and Yamaguchi esterification (Scheme 1).

1.2.1a. Retrosynthesis of Nhatrangin A (16):

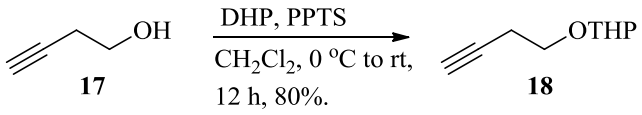


Scheme 1

Retrosynthetic analysis of Nhatrangin A (**16**) is delineated in Scheme 1. Nhatrangin A (**16**) could be accomplished by Yamaguchi esterification of the carboxylic acid fragment **25** and the secondary hydroxyl fragment **40**. Carboxylic acid **25** was prepared from commercially available homo propargyl alcohol **17**. The alcohol fragment **40** was obtained by the olefin-cross metathesis of two terminal alkene coupling partners **38** and **33**, which were synthesized from (*S*)-methyl 3-hydroxy-isobutyrate **34** and 3-hydroxybenzaldehyde **26**, respectively (Scheme 1)

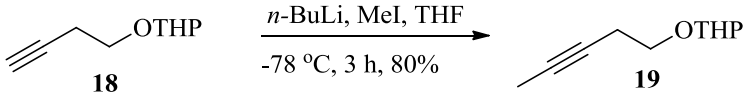
1.2.1b. Results and discussions:

1.2.2. Synthesis of fragment (25):



Scheme 2

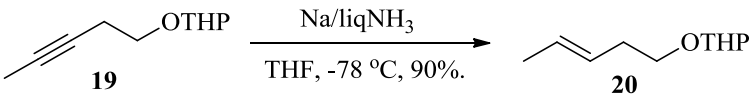
Synthesis of carboxylic acid fragment **25** commenced from commercially available homo propargyl alcohol **17**, which was protected as its THP-ether **18** using DHP and catalytic amount of PPTS in anhydrous CH_2Cl_2 (Scheme 2).[56] The compound **18** was characterized by its spectral analysis. In ^{1}H NMR spectrum, compound **18** clearly showed a triplet at δ 4.66 (*J* = 2.66 Hz, 1H) ppm and other THP protons showed at their expected chemical shift values. Appearance of molecular ion peak in the mass spectrum at *m/z* 154 $[M]^+$ further confirmed the formation of the product.



Scheme 3

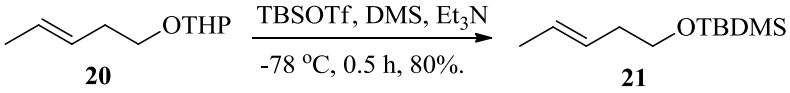
The THP-ether **18** was subjected to C-methylation using *n*-BuLi and MeI in THF at -78 °C to afford the methylated-alkyne **19** in 90% yield (Scheme 3),[57] which was confirmed by the analysis of its ^{1}H NMR spectrum resonating signal at δ 1.78 (t, *J* = 2.64 Hz, 3H) ppm. It was further confirmed by ^{13}C NMR spectrum which showed all the representative peaks for all carbons and EIMS showed peak at *m/z* 168 $[M]^+$. Compound

19 was treated with Sodium in liquid ammonia (Na/liq NH_3) reduction in THF to give the alkene **20** with exclusively *E* stereo chemistry in 90% yield (Scheme 4).[58]



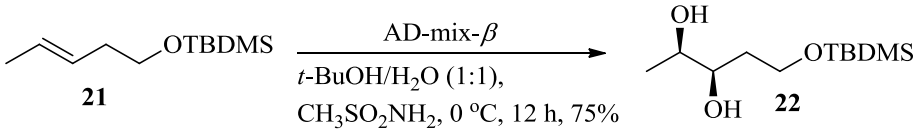
Scheme 4

Alkene **20** was well characterized by ^{1}H NMR spectrum, in which olefinic protons appeared at δ 5.55-5.35 (m, 2H) ppm. Compound **20** was also characterized by its EIMS data, which showed $[M]^+$ peak at *m/z* 170.



Scheme 5

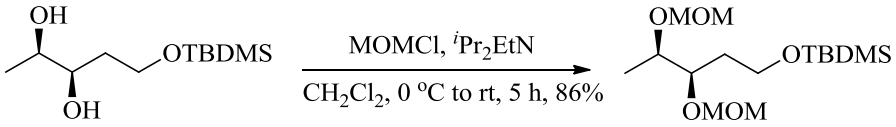
Replacement of THP-ether in compound **20** with TBS-ether using TBSOTf, DMS and TEA in CH_2Cl_2 at -78 °C provided the corresponding TBS-ether **21** in 80% yield (Scheme 5).[59] The structure was confirmed by the appearance of signals at δ 0.88 (s, 9H) and 0.03 (s, 6H) ppm in ^{1}H NMR spectrum. This was further confirmed by ^{13}C NMR spectrum which showed all the representative peaks for aliphatic and TBS carbons. Its EIMS spectrum showed peak at *m/z* 200 $[M]^+$.



Scheme 6

Sharpless asymmetric dihydroxylation[60] of alkene **21** was performed using AD-mix-*β*, $CH_3SO_2NH_2$ in *t*-BuOH/H_2O to obtain diol **22** in 75% yield as a separable 9:1 diastereomeric mixture. The formation of **22** was confirmed by disappearance of signal for olefinic protons between δ 5.55-5.35 (m, 2H) ppm and appearance of two multiplets of

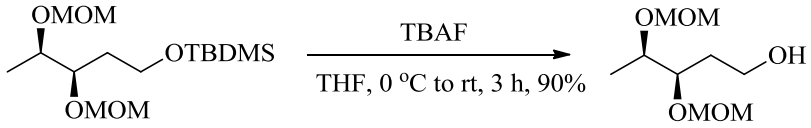
two hydroxy protons between δ 3.94-3.78 (m, 2H) ppm in ^{1}H NMR spectrum. IR spectrum also revealed a characteristic peak of hydroxyl moiety at 3392 cm^{-1}. Its ESI-HRMS spectrum showed peak at *m/z* 257.15455 $[M + Na]^+$ (Scheme 6) also confirmed the product **22**.



22 **23**

Scheme 7

The diol **22** was converted into a diMOM-ether **23** in 86% yield by treating with MOMCl in the presence of Hunig's base (Scheme 7).[61] Compound **23** was characterized by its ^{1}H NMR spectrum signals at δ 4.66-4.58 (m, O-**CH$_2$**-O, 4H), 3.36 (s, O-CH$_2$-O-**CH$_3$**, 3H) and 3.34 (s, O-CH$_2$-O-**CH$_3$**, 3H) ppm. This was further characterized by ESI-HRMS data, which showed a peak at *m/z* 345.20718 $[M + Na]^+$.

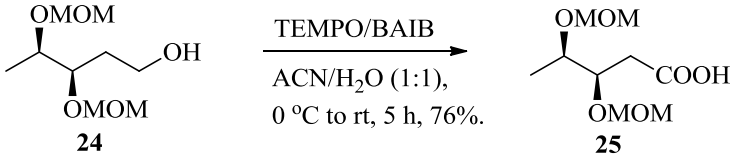


23 **24**

Scheme 8

Removal of TBS group of compound **23** using TBAF in THF afforded the alcohol **24** in 90% yield (Scheme 8). ^{1}H NMR spectrum showed disappearance of the singlet at δ 0.89 ppm, corresponding to nine *t*-butyl protons as well as the doublet at δ 0.04 ppm for six methyl protons of the TBS group confirmed the deprotection of TBS group and this was further confirmed by its ^{13}C NMR spectrum, which showed all the representative peaks for all carbons. IR spectrum also revealed a characteristic peak of hydroxyl moiety at 3446 cm^{-1}. Presence of peak at *m/z* 231.12041 $[M + Na]^+$ in ESI-HRMS spectrum further confirmed the structure of alcohol **24**. Oxidation of primary hydroxy group of alcohol **24** using TEMPO and BAIB in CH_3CN/H_2O (1:1) mixture, at 0 °C afforded the

carboxylic acid **25** in good yield of 76% (Scheme 9).[62] The ^{1}H NMR spectrum of compound **25** revealed the disappearance of the protons resonance at δ 4.12-3.86 (m, 2H) of the methylenic protons attached to primary hydroxyl functionality.

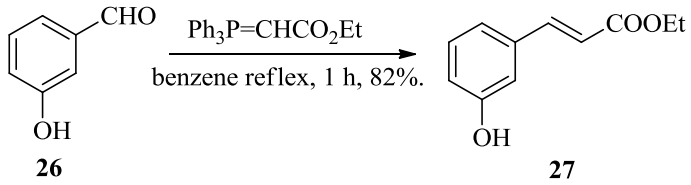


Scheme 9

All other protons of the structure **25** resonated at their expected chemical shift values. Compound **25** was further confirmed by its ESI-HRMS data, which showed peak at *m/z* 245.09972 $(M + Na)^+$ and IR spectrum showed a characteristic peak of acid moiety at 1773 cm^{-1}.

1.2.3. Synthesis of Fragment (33):

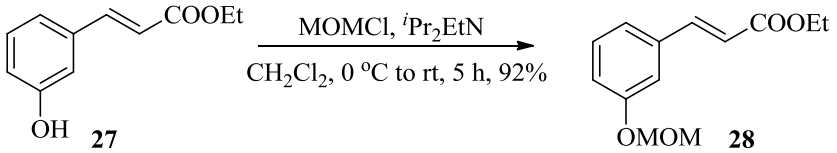
The synthesis of fragment **33** was started from commercially available 3-hydroxy benzaldehyde **26**, which was homologated using a Wittig ylide[63] ($Ph_3P=CHCO_2Et$) in benzene under reflux to afford the *α, β*-unsaturated ester **27** in 82% yield with 96% *E* stereochemistry (Scheme 10). The appearance of signals of the two olefinic protons at δ 7.63 (d, *J* = 16.0 Hz 1H) and δ 6.41 (d, *J* = 15.56 Hz, 1H) ppm in ^{1}H NMR spectrum confirmed the product as *trans*-olefin.



Scheme 10

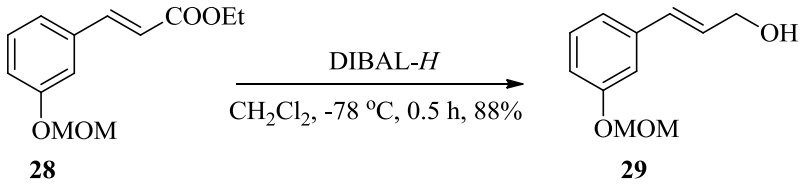
The conversion was confirmed by the appearance of a quartet at δ 4.27 (q, *J* = 6.98, Hz, 2H) ppm and a triplet at δ 1.34 (t, *J* = 6.98 Hz, 3H) ppm in ^{1}H NMR spectrum which correspond to the presence of the ethyl group in unsaturated ester. The formation of **27** was further confirmed by ^{13}C NMR spectrum, which showed all the representative

peaks and further supported by EIMS with $(M)^+$ peak at *m/z* 192, and a characteristic peak at 1713 cm^{-1} in IR spectrum.



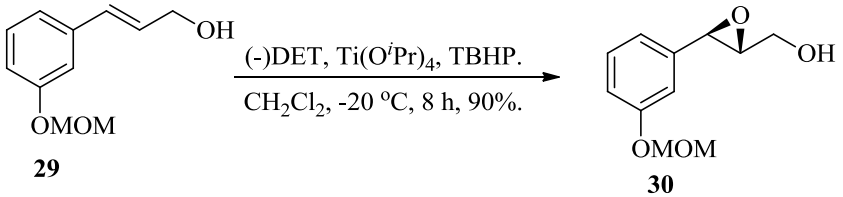
Scheme 11

The hydroxy group of **27** was protected as a MOM-ether using MOMCl, DIPEA in CH_2Cl_2 to give **28** in 92% yield (Scheme 11). Compound **28** was characterized by ^{1}H NMR spectrum signals at δ 5.20 (s, O-**CH_2**-O, 2H) ppm and 3.49 (s, O-CH_2-O-**CH_3**, 3H) ppm. Further it was characterized by ESI-HRMS data which showed a peak at *m/z* 259.09417 $[M + Na]^+$.



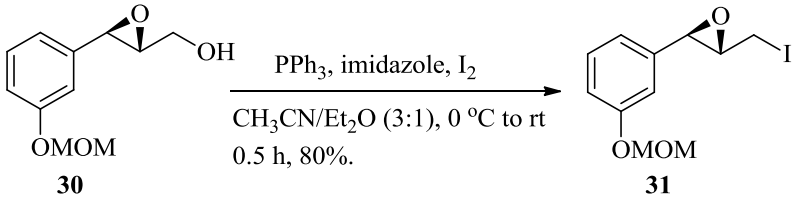
Scheme 12

Chemo selective reduction of *α, β*-unsaturated ester **28** using DIBAL-*H* in anhydrous CH_2Cl_2 at -78 ^{o}C afforded the allylic alcohol **29** in 88% yield (Scheme 12). The product was characterized by ^{1}H NMR, where the disappearance of signals corresponding to ethyl group and appearance of signal at δ 4.29 (d, *J* = 5.28 Hz, 2H) corresponds to allylic protons. This was further confirmed by ^{13}C NMR spectrum which showed all the representative peaks for olefinic as well as aliphatic and aromatic carbons. A peak at *m/z* 194 $[M]^+$ in EIMS spectrum was further confirmed this transformation. IR spectrum also revealed a characteristic peak of hydroxyl moiety at 3376 cm^{-1}.



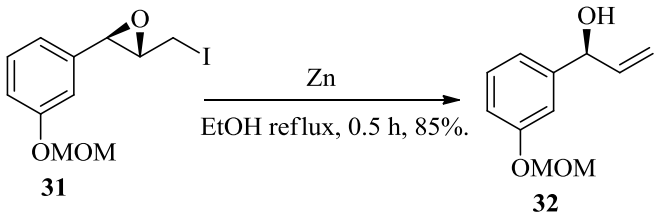
Scheme 13

Sharpless asymmetric epoxidation[64] of allylic alcohol **29** using (-)-DET, $Ti(O^iPr)_4$ and TBHP in CH_2Cl_2 afforded the epoxy alcohol **30** in 90% yield (Scheme 13). The formation of **30** was confirmed by disappearance of signal for olefinic protons between δ 6.59-6.50 (m, 1H), 6.37-6.27 (m, 1H) ppm and appearance of two multiplets of two epoxy protons between δ 3.23-3.19 (m, 1H) and 3.91 (d, J = 2.26 Hz, 1H) ppm in ^{1}H NMR spectrum. ESI-HRMS data, showed peak at *m/z* 233.07816. $(M + Na)^+$ and confirmed this transformation.



Scheme 14

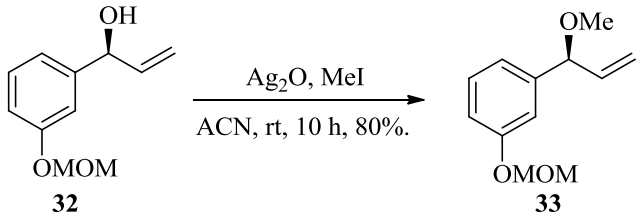
Treatment of **30** with TPP, imidazole and I_2 in CH_3CN/Et_2O (1:1) gave the corresponding α-iodooxirane **31** in 80% yield (Scheme 14).[65] The ^{1}H NMR spectrum showed slight up field shift for iodo attached methylene protons at δ 3.32-3.23 as a multiplet compared to alcohol **31**. In IR spectrum, a characteristic peak of hydroxyl moiety at 3419 cm^{-1} is disappered. Compound **31** was further confirmed by its ESI-HRMS data, which showed peak at *m/z* 343.98093 $(M + Na)^+$.



Scheme 15

The α-iodooxirane **31** was converted into secondary allyl alcohol **32** in 85% yield by refluxing with activated Zn in dry EtOH (Scheme 15). The compound **32** was confirmed by its spectral data analysis. The olefin protons resonated as multiplet at δ 6.11-5.98 (m, 1H), 5.41-5.32 (m, 1H) and 5.25-5.14 (m, 1H) in ^{1}H NMR spectrum. This was further confirmed by ^{13}C NMR spectrum which showed all the representative peaks for

olefinic as well as aliphatic and aromatic carbons. The IR spectrum showed a strong and broad hydroxyl absorption band at 3380 cm^{-1}. Compound **32** was further confirmed by its EIMS data, which showed peak at *m/z* 194 $(M)^+$.

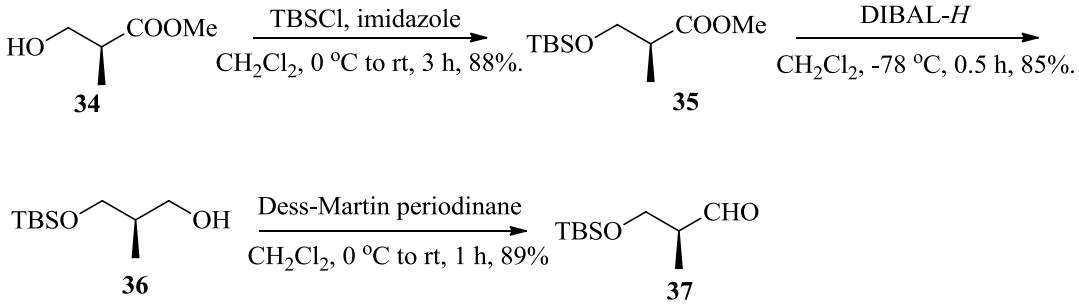


Scheme 16

The secondary allyl alcohol **32** was methylated using MeI, Ag_2O in the presence of CH_3CN to give the fragment **33** in 80% yield (Scheme 16),[66] which was confirmed by ^1H NMR spectrum signal resonating at δ 3.34 (s, 3H) and ESI-HRMS showed peak at *m/z* 231.09944 $[M + Na]^+$.

1.2.4. Synthesis of Fragment (38):

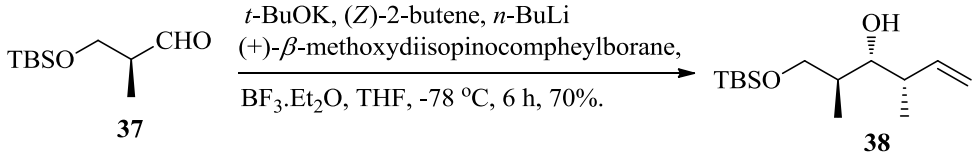
The fragment **38** was obtained from commercially available (*S*)-Roche ester **34**, which was protected as its TBS-ether **35** using TBDMSCl and imidazole in CH_2Cl_2 (Scheme 17). The structure of compound **35** was confirmed by its ^1H NMR analysis, in which the appearance of signals at δ 0.87 (s, 9H) ppm and δ 0.04 (s, 6H) ppm were observed. This was further confirmed by ^{13}C NMR spectrum, which showed all the representative peaks for aliphatic and silyl carbons. Its ESI-HRMS spectrum showed peak at *m/z* 233.07264 $[M + H]^+$ provided aditional proof for formation of the product.



Scheme 17

Reduction of ester **35** using DIBAL-*H* in CH_2Cl_2 at -78 ^oC afforded the primary alcohol **36** in 85% yield (Scheme 17). The product was characterized by ^1H NMR, where the disappearance of signals corresponding to methyl group and appearance of signal at δ 3.75-3.51 ppm corresponds to hydroxyl attached protons (-C**H$_2$**-OH). This was further confirmed by ^{13}C NMR spectrum which showed all the representative peaks for all carbons. A peak at *m/z* 204 $[M]^+$ in EIMS spectrum further confirmed this transformation. In IR spectrum, ester stretching frequency 1741 cm^{-1} disappeared and a characteristic peak of hydroxyl moiety appeared at 3378 cm^{-1} also confirmed this conversion.

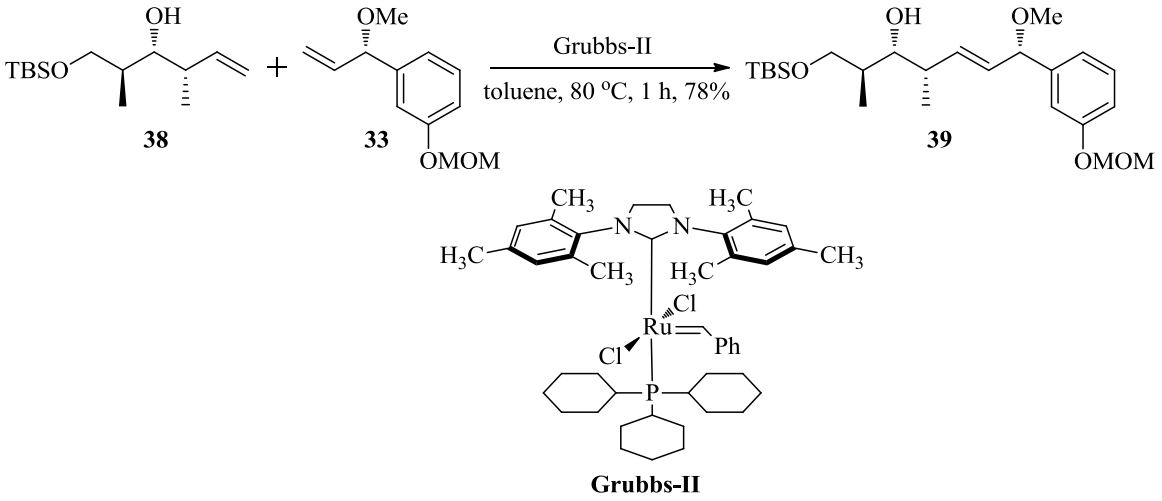
Oxidation of primary alcohol **36** using DMP in CH_2Cl_2 at 0 ^oC at room temperature gave the aldehyde **37** in 89% yield (Scheme 17).[67] This was clearly conveyed in the ^1H NMR spectrum, by the resonance as a singlet at δ 9.75 ppm indicating alcohol **36** was converted into aldehyde **37**. The other protons of the compound resonated at their expected chemical shift values. The compound **37** was also characterized by ESI-HRMS with $(M - H)^+$peak at *m/z* 201.13049. IR spectrum also revealed a characteristic peak of aldehyde at 1734 cm^{-1} which confirmed this conversion.



Scheme 18

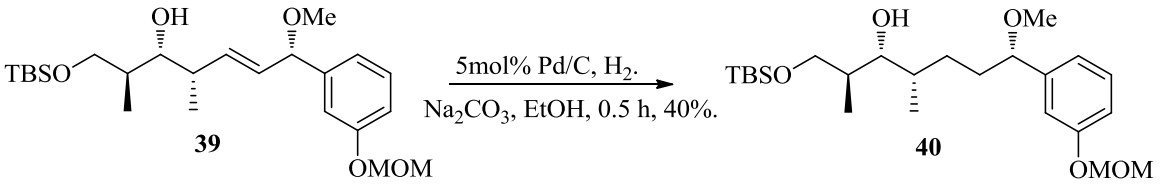
Crotylation of aldehyde **37** using (+)-*β*-methoxydiisopinocopheylborane, *n*-BuLi and $BF_3.Et_2O$ in dry THF gave the homo allyl alchol **38** in 70% yield and with 9:1 diastereoselectivity (Scheme 18).[68] The aldehyde proton disappeared and olefin protons resonated as multiplet at δ 5.94-5.79 (m, 1H), 5.11-4.95 (m, 2H) in ^1H NMR spectrum. The aldehyde carbon δ 204.6 ppm disappeared and terminal olefin carbons resonated at δ 142.3, 113.7 ppm in ^{13}C NMR spectrum. The IR spectrum showed a strong and broad hydroxyl absorption band at 3380 cm^{-1}. The compound **38** was also characterized by ESI-HRMS with $(M + Na)^+$ peak at *m/z* 281.19064 and above spectral data confirmed the transformation. The optical purity of allyl alcohol **38** was also confirmed by its optical rotation value $[\alpha]_D^{25}$ +8.9 (*c* = 2.0, $CHCl_3$), which was compared with the literature

value[69] ($[\alpha]_D^{20}$ +9.1 (*c* = 2.0, $CHCl_3$)). Remaining spectral and analytical data were in good agreement with the reported literature values.



Scheme 19

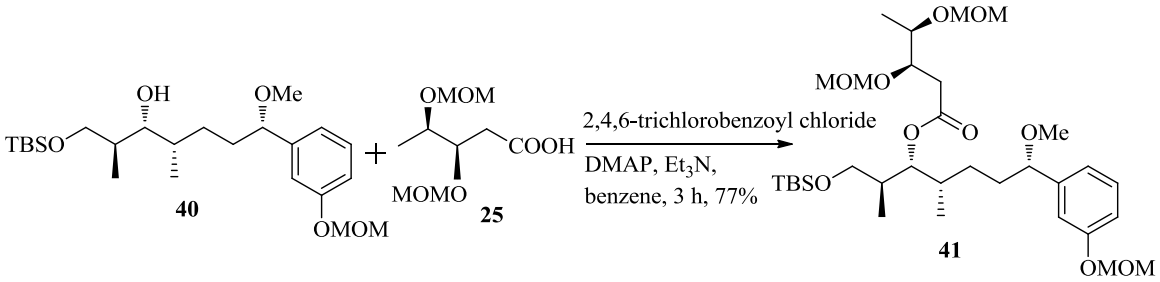
Treatment of fragments **38** and fragment **33** (2eq) with Grubbs 2nd generation catalyst (10% mol)[70] in Toluene under reflux conditions provided the cross metathesis product **39** in 78% yield with separable *E*, *Z* isomers, homodimer of **33** and **38** in 90:5:3:2 mixture (Scheme 19). In the ^{1}H NMR spectrum of **39** newly introduced two protons resonated at δ 5.84-5.72 (m, 1H), 5.60-5.49 (m, 1H). ^{13}C NMR spectrum showed all the carbons at their expected chemical shifts values. The compound **39** was also characterized by ESI-HRMS , which showed $(M + Na)^+$ peak at *m/z* 461.26983.



Scheme 20

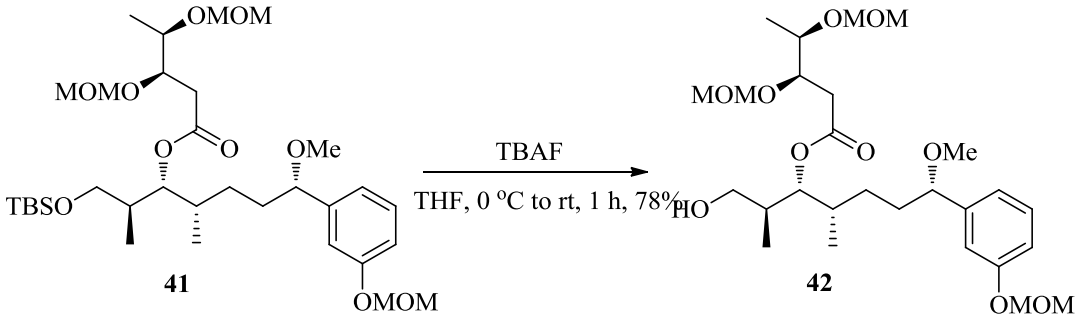
Reduction of the internal double bond of **39** was carried out by hydrogenation using Pd/C (5 mol %) and Na_2CO_3 in EtOH at room temperature afford alcohol **40** in 40% yield (Scheme 20).[71] Disappearance of olefin protons δ 5.84-5.72 (m, 1H), 5.60-5.49 (m,

1H) and appearance of all the protons at their expected chemical shift values in ^{1}H NMR spectrum confirmed the product formation. Its ESI-HRMS spectrum, which showed peak at *m/z* 441.3040 $[M + H]^+$ provided aditional proof for formation of the product.



Scheme 21

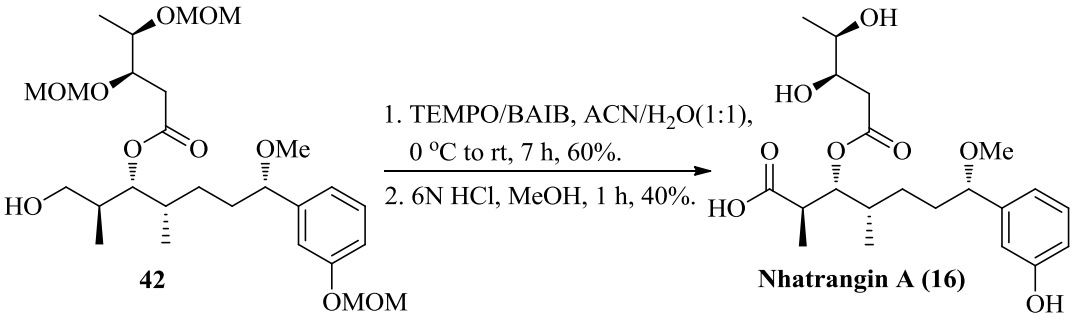
The alcohol **40** was subjected to Yamaguchi esterification[72] with acid **25** using 2,4,6-trichlorobenzoyl chloride, DMAP and TEA in toluene to afford the ester **41** in 77% yield (Scheme 21). The structure of the compound **41** was established from its IR and mass spectral data. In the IR spectrum, an absorbance is seen at 1737 cm^{-1} for the ester functional group and ESI-HRMS data showed a value of *m/z* 667.38606 for the $[M + Na]^+$. ^{13}C NMR showed a ester-carbonyl carbon resonance at δ 171.5 ppm to confirm the transformation.



Scheme 22

Deprotection of TBS group of ester **41** using TBAF in THF gave the primary alcohol 4**2** in 78% yield (Scheme 22). ^{1}H NMR spectrum showed disappearance of the singlet at δ 0.89 ppm, corresponding to nine *t*-butyl protons as well as the doublet at δ 0.01 ppm for six methyl protons of the TBS group. This was further confirmed by ^{13}C NMR spectrum which showed all the carbons expected their chemical shift values. IR

spectrum also revealed a characteristic peak of hydroxyl moiety at 3448 cm^{-1} . Peak at *m/z* 553.29895 $[M + Na]^+$ in ESI-HRMS spectrum further confirmed the structure of product.



Scheme 23

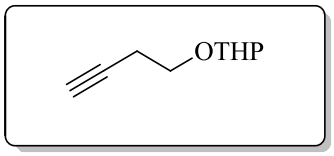
The primary alcohol **42** was oxidised[62] using TEMPO and BAIB in CH_3CN/H_2O to give the corresponding carboxylic acid, which was without further purification treated with 6N aq HCl in MeOH at 0 °C to rt for 1h to afford the target molecule Nhatrangin A (**16**) in 40% yield (Scheme 23). In ^1H NMR three MOM-ether protons disappeared. This was further confirmed by its ^{13}C NMR spectrum, which showed carboxylic acid carbon resonance at δ 175.5 ppm and all other carbons at their expected chemical shift values. IR spectrum also revealed a characteristic peaks corresponding to carboxylic acid and ester moiety at 1670, 1737 cm^{-1} respectively. The compound (**16**) was also characterized by ESI-HRMS analysis, which showed $(M + Na)^+$ peak at *m/z* 435.19932. The spectral data of synthetic nhatrangin A (**16**) was in full agreement (IR, ^1H NMR, ^{13}C NMR and HRMS) with that of natural product.[73]

In conclusion, we have been accomplished an efficient asymmetric total synthesis of Nhatrangin A (**16**) in highly convergent manner using Sharpless asymmetric dihydroxylation, Sharpless asymmetric epoxidation, Browns crotyl boration, Birch reduction and Yamaguchi esterification as key transformations.

Experimental Section

1.3. EXPERIMENTAL SECTION

1.3.1. 2-(But-3-yn-1-yloxy)tetrahydro-2*H*-pyran (18):



To a stirred solution of but-3-yn-1-ol **17** (9.0 g, 128.57 mmol) in CH_2Cl_2 (150 mL) were added 3,4-dihydro-2*H*-pyran (14.0 mL, 154.28 mmol) and a catalytic amount of PPTS (1.5 g, 6.42 mmol) at 0 ^oC. The mixture was stirred overnight, solid K_2CO_3 was added and the resulting suspension was stirred for 30 min. The solids were then removed by filtration and the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexanes, 0.2:9.8) to afford the compound **18** (15.84 g, 80%) as a colorless liquid.

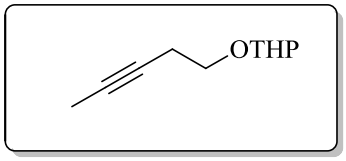
^1H NMR ($CDCl_3$, 300 MHz): δ 4.66 (t, *J* = 2.66 Hz, 1H), 3.95-3.79 (m, 2H), 3.63-3.47(m, 2H), 2.50 (dt, *J* = 3.02, 7.55 Hz, 2H), 1.98 (t, *J* = 2.66, 5.28 Hz, 1H), 1.90-1.48 (m, 6H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 98.5, 81.2, 69.0, 65.3, 62.0, 30.3, 25.2, 19.7, 19.2 ppm.

IR (neat): 3289, 2944, 2874, 1736, 1441, 1352, 1182, 1135, 1123, 1034, 905,814, 642 cm^{-1}.

EIMS: *m/z* 154 $(M)^+$.

1.3.2. 2-(Pent-3-yn-1-yloxy)tetrahydro-2*H*-pyran (19):



To a stirred solution of THP ether **18** (15.6 g, 101.3 mmol) in THF (130 mL) was added *n*-BuLi (2.5 M solution in hexane, 42.45 mL, 106.36 mmol) at –78 °C. After being stirred for 30 min, CH_3I (7 mL, 111.43 mmol) was added. After 2 h the reaction was quenched with addition of saturated aqueous NH_4Cl (30 mL) the phases were separated

and the aqueous phase was extracted with EtOAc (3 x 40 mL). The combined organic layers were dried over Na_2SO_4, the solvents were evaporated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexanes, 0.2:9.8) to afford the methylated compound **19** (13.6 g, 80%) as a colorless liquid.

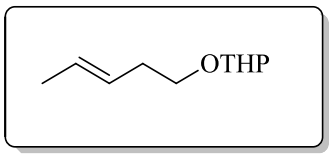
^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.64 (t, *J* = 2.83 Hz, 1H), 3.93-3.75 (m, 2H), 3.57-3.47(m, 2H), 2.48-2.39 (m, 2H), 1.78 (t, *J* = 2.64 Hz, 3H), 1.74-1.47 (m, 6H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 98.6, 76.4, 75.8, 66.0, 62.0, 30.4, 25.3, 20.0, 19.3, 3.3 ppm.

IR (neat): 2943, 2923, 2873, 1441, 1352, 1201, 1135, 1121, 1033, 970, 869, 771 cm^{-1}.

EIMS: *m/z* 168 $(M)^+$.

1.3.3. (*E*)-2-(Pent-3-en-1-yloxy)tetrahydro-2*H*-pyran (20):



To a freshly condensed solution of anhydrous NH_3 (125 ml), in a two-necked round-bottomed flask fitted with a cold condenser was added cautiously a freshly cut Na metal (10.95 g, 476.2 mmol) portion-wise at –78 ^{o}C. The resulting deep blue suspension was stirred for 30 min at the same temperature. A solution of THP-protected homopropargylic alcohol **19** (8.0 g, 47.62 mmol) in dry THF (30 mL) was added dropwise and then stirred for another 2 h at –78 ^{o}C. After completion of the reaction, the mixture was quenched with solid NH_4Cl, and the mixture was warmed to room temperature overnight, during which time the ammonia was evaporated. The residue was dissolved in ether (40 mL) and then filtered though small pad of Celite. The combined organic fraction was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexanes, 0.5:9.5) to afford the olefin compound **20** (7.36 g, 90%) as a clear colorless liquid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.5-5.35 (m, 2H), 4.56 (t, *J* = 2.64 Hz, 1H), 3.87-3.77 (m, 1H), 3.73-3.63(m, 1H), 3.51-3.42 (m, 1H),

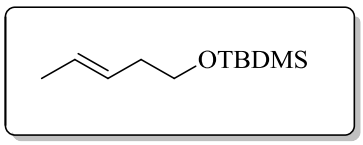
3.39-3.30 (m, 1H), 2.25 (q, *J* = 6.42, 13.29 Hz, 2H), 1.90-1.75 (m, 2H), 1.66 (d, *J* = 4.72, 3H), 1.62-1.44 (m, 4H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 128.0, 127.6, 98.5, 76.2, 75.9, 35.6, 30.6, 25.3, 20.2, 19.5 ppm.

IR (neat): 2940, 2928, 2860, 1450, 1250, 1100, 830, 750, cm^{-1}.

EIMS: *m/z* 170 $(M)^+$.

1.3.4. (*E*)-*tert*-Butyldimethyl(pent-3-en-1-yloxy)silane (21):



To stirred solution of THP ether **20** (5.77 g, 33.94 mmol) in CH_2Cl_2 (50 mL) at –50 ^oC was added TBSOTf (44.123 mmol, 10.133 mL). The mixture was stirred for 30 min at the same temperature. To this mixture $(CH_3)_2S$ (7.47 mL, 101.82 mmol) was added dropwise and the mixture was stirred for another 30 min at –50 °C, and excess amount of triethylamine (23.68 mL, 169.7 mmol) was added and allowed to rt. The mixture was diluted with H_2O (40 mL) and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic phase was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexanes, 0.5:9.5) to afford the TBS-olefin **21** (5.43 g, 80%) as a colourless yellow oil.

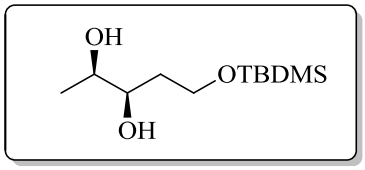
^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.57-5.28 (m, 2H), 3.59 (t, *J* = 6.04 Hz, 2H), 2.18 (q, *J* = 6.04, 12.08 Hz, 2H), 1.64 (m, 3H), 0.88 (s, 9H), 0.03 (s, 6H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 127.6, 126.8, 63.3, 36.3, 30.3, 25.9, 17.9, -5.2 ppm.

IR (neat): 2926, 2855, 1467, 1254, 1100, 836, 749 cm^{-1}.

EIMS: *m/z* 200 $(M)^+$.

1.3.5 (2*R*,3*R*)-5-((*tert*-Butyldimethylsilyl)oxy)pentane-2,3-diol (22):



To a stirred 1:1 mixture of *t*-BuOH (40 mL) and H_2O (40 mL) was added AD-mix-*β* (25.9 g, 1.4g of AD-mix-*β* per 1 mmol of olefin) and $CH_3SO_2NH_2$ (1.76 g, 18.5 mmol). The mixture was stirred for 10 to 15 min to get a clear solution. The reaction bath was cooled to 0 ^oC and then olefin **21** (3.7 g, 18.5 mmol) dissolved in minimum volume of *t*-BuOH (5 mL) was added. The reaction mixture was stirred for 12 h at 0 ^oC. Then the reaction mixture was quenched with solid Na_2SO_3 (25.9 g) at room temperature and stirred for another 30 min. The reaction mixture was diluted with EtOAc and two layers were separated. The aqueous layer was extracted with EtOAc (3 x 40 mL). The combined organic fraction was dried over anhydrous Na_2SO_4 and the solvent was evaporated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexanes, 4:6) to afford the diol compound **22** (3.24 g, 75%) as a clear colorless liquid.

$[\alpha]_D^{21}$: –6.40 (*c* 0.5, $CHCl_3$).

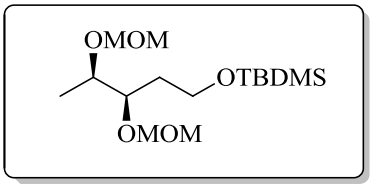
^1H NMR ($CDCl_3$, 300 MHz): δ 3.94-3.78 (m, 2H), 3.63-3.40 (m, 2H), 2.60 (brs, 1), 1.74-1.61 (m, 2H), 1.16 (d, *J* = 6.04 Hz, 3H), 0.91 (s, 9H), 0.09 (s, 6H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 75.4, 70.4, 61.7, 34.8, 29.5, 25.7, 18.9, -5.6 ppm.

IR (neat): 3392, 2956, 2931, 2859, 1467,1389, 1255, 1082, 981, 938, 836, 774, 665 cm^{-1}.

ESI-HRMS: calcd for $C_{11}H_{26}NO_3NaSi$ $(M + Na)^+$ 257.15434, found 257.15455.

1.3.6. (5*R*,6*R*)-6-(Methoxymethoxy)-5,10,10,11,11-pentamethyl-2,4,9-trioxa-10-siladodecane (23):



To a stirred solution of diol compound **22** (1.11 g, 4.74 mmol) in anhydrous CH_2Cl_2 (15 mL) at 0 ^oC under nitrogen, $^iPr_2EtN$ (4.88 mL, 28.45 mmol) was added followed by drop wise addition of MOMCl (1.43 mL, 18.972 mmol). After stirring for 5 h at room temperature, the reaction mixture was diluted with water, and extracted with CH_2Cl_2 (3 x 20 mL). The organic layer was washed with saturated aqueous NH_4Cl (5 mL), brine (5 ml) and then dried over anhydrous Na_2SO_4. The residue was concentrated

under reduced pressure and purified by silica gel column chromatography (EtOAc/hexanes, 2:8) to afford the compound **23** (1.32 g, 86%) as a clear colorless liquid.

$[\alpha]_D^{21}$: –2.30 (*c* 1.0, $CHCl_3$).

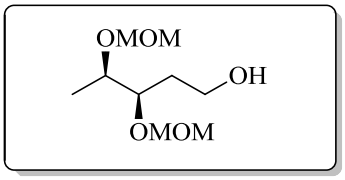
^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.66-4.58 (m, 4H), 3.83-3.62 (m, 4H), 3.36 (s, 3H), 3.34 (s, 3H), 1.85-1.54 (m, 2H), 1.16 (d, *J* = 6.04 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 97.1, 95.5, 77.5, 74.3, 59.6, 55.7, 55.4, 33.2, 25.8, 18.2, 17.7, -5.3 -5.4 ppm.

IR (neat): 2954, 2930, 2858, 1468, 1385, 1255, 1151, 1104, 1038, 919, 836, 774 cm^{-1}.

ESI-HRMS: calcd for $C_{15}H_{34}O_5NaSi$ $(M + Na)^+$ 345.20677, found 345.20718.

1.3.7. (3*R*,4*R*)-3,4-bis(Methoxymethoxy)pentan-1-ol (24):



To a stirred solution of TBS compound **23** (627 mg, 1.947 mmol) in dry THF (3 mL) was added TBAF (2.92 mL, 2.92 mmol) at 0 ^oC. The mixture was stirred for 3 h and quenched with saturated $NaHCO_3$ (10 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic phase was washed with brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexanes, 3:7) to afford the alcohol **24** (365 mg, 90%) as a colourless oil.

$[\alpha]_D^{21}$: +26.3 (*c* 1.0, $CHCl_3$).

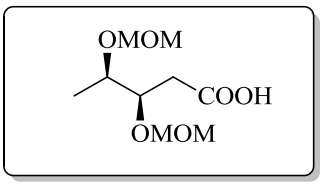
^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.77-4.59 (m, 4H), 3.81-3.65 (m, 4H), 3.41 (s, 3H), 3.36 (s, 3H), 1.90-1.76 (m, 1H), 1.69-1.55 (m, 1H), 1.16 (d, *J* = 6.23 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 97.6, 95.6, 78.9, 74.8, 59.4, 55.9, 55.4, 33.8, 15.7 ppm.

IR (neat): 3446, 2926, 2857, 1458, 1219, 1031, 772 cm^{-1}.

ESI-HRMS: calcd for $C_9H_{20}O_5Na$ $(M + Na)^+$ 231.12029, found 231.12041.

1.3.8. (3*R*,4*R*)-3,4-bis(Methoxymethoxy)pentanoic acid (25):



To a stirred solution of alcohol **24** (283 mg, 1.36 mmol) in CH_3CN/H_2O (1:1, 2 mL), were added BAIB (876 mg, 2.72 mmol) followed by TEMPO (21 mg, 0.136 mmol) at 0 °C and allowed to warm to room temperature gradually and then stirred for 5h. The reaction mixture was quenched with saturated $Na_2S_2O_3$ (2 mL) solution at 0 °C. The reaction mixture was stirred for another 15 minutes and then solvent was evaporated *in vacuo*. EtOAc (5 mL) and water (3 mL) were added to the residue and the two layers were separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexanes, 4:6) to afford the acid **25** (230 mg, 76%) as a colourless oil.

$[\alpha]_D^{21}$: –7.0 (*c* 0.5, $CHCl_3$).

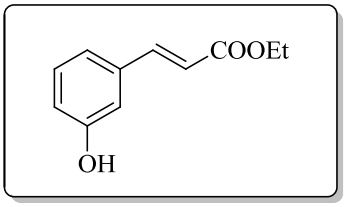
^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.78-4.62 (m, 4H), 4.12-4.03 (m, 1H), 3.96-3.86 (m, 1H), 3.38 (s, 3H), 3.37 (s, 3H), 2.79-2.53 (m, 2H), 1.21 (d, *J* = 6.04 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 177.3, 97.0, 95.4, 76.6, 73.4, 55.6, 55.4, 33.3, 15.0 ppm.

IR (neat): 2927, 2851, 1773, 1219, 1103, 1035, 772, 673 cm^{-1}.

ESI-HRMS: calcd for $C_9H_{18}O_6Na$ $(M + Na)^+$ 245.09956, found 245.09972.

1.3.9. (*E*)-Ethyl 3-(3-hydroxyphenyl)acrylate (27):



To a stirred solution of Ph_3P=CH-CO_2Et (50.22 g, 147.54 mmol) in benzene (70 mL) at 80 ^oC, was added the aldehyde **26** (15.0 g, 122.95 mmol) in benzene (50 mL). After 1h, the solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (EtOAc/hexanes, 0.5:9.5) to afford the ester compound **27** (19.35 g, 82%) as a white solid.

m.p: 58 ^oC.

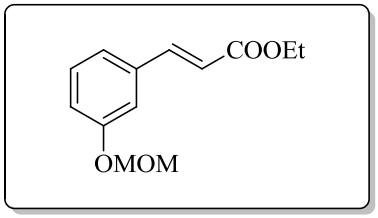
^1H NMR ($CDCl_3$, 300 MHz): δ 7.63 (d, *J* = 16.0 Hz 1H), 7.30-6.81 (m, 4H), 6.41 (d, *J* = 15.56 Hz, 1H), 4.27 (q, *J* = 6.98, 14.16 Hz, 2H), 1.34 (t, *J* = 6.98 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.8, 156.4, 145.0, 135.6, 129.9, 120.45, 117.9, 117.7, 114.6, 60.9, 14.2 ppm.

IR (KBr): 3376, 2904, 2981, 1713, 1639, 1487, 1367, 1311, 1204, 1151, 1081, 1018, 859, 680 cm^{-1}.

EIMS: *m/z* 192 $(M)^+$.

1.3.10. (*E*)-Ethyl 3-(3-(methoxymethoxy)phenyl)acrylate (28):



To a stirred solution of hydroxy compound **27** (12.6 g, 65.62 mmol) in anhydrous CH_2Cl_2 (120 mL) at 0 ^oC under nitrogen atmosphere, $^iPr_2EtN$ (34.23 mL, 196.86 mmol) was added followed by drop wise addition of MOMCl (9.88 mL, 131.24 mmol). After stirring for 2 h at room temperature, the reaction mixture was diluted with water (40 mL), and the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure followed by purification on silica gel column chromatography (EtOAc/hexanes, 0.5:9.5) afforded the alcohol **28** (14.2 g, 92%) as a colourless liquid.

^1H NMR ($CDCl_3$, 300 MHz): δ 7.65 (d, *J* = 15.8 Hz, 1H), 7.35-7.03 (m, 4H), 6.43 (d, *J* = 15.8 Hz, 1H), 5.20 (s, 2H), 4.26 (q, *J* = 6.79,

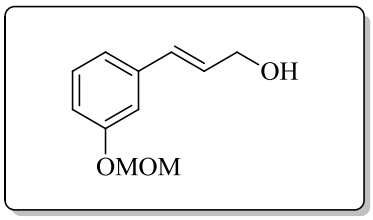
14.35 Hz, 2H), 3.49 (s, 3H), 1.34 (t, *J* = 6.79 Hz, 2H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz). δ 166.7, 157.5, 144.1, 135.7, 129.7, 121.7, 118.5, 118.0, 115.20, 94.2, 60.3, 55.8, 14.1 ppm.

IR (neat): 2980, 2958, 2900, 1715, 1639, 1601, 1440, 1367, 1310, 1240, 1178, 1081, 1018, 925, 850, 778, 681 cm^{-1}.

ESI-HRMS: calcd for $C_{13}H_{16}O_4Na$ $(M + Na)^+$ 259.09408, found 259.09417.

1.3.11. (*E*)-3-(3-(Methoxymethoxy)phenyl)prop-2-en-1-ol (29):



To a stirred solution of ester **28** (13.0 g, 55.084 mmol) in CH_2Cl_2 (120 mL) at –78 ^oC was added slowly DIBAL-*H* (69.3 mL, 20 % solution in toluene, 132.19 mmol) and the mixture was stirred for 30 min at the same temperature. The reaction was quenched with saturated aqueous sodium potassium tartarate (50 mL) and stirring was continued for 3 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4. Removal of the solvent under reduced pressure followed by purification by silica gel column chromatography (EtOAc/hexanes, 2:8) afforded the alcohol **29** (9.40 g, 88%) as a colourless oil.

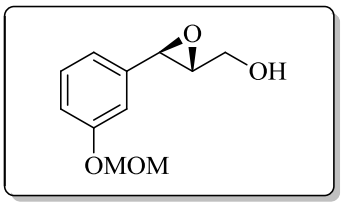
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.18 (t, *J* = 7.93 Hz, 1H), 7.03-6.84 (m, 3H), 6.59-6.50 (m, 1H), 6.37-6.27 (m, 1H), 5.14 (s, 2H), 4.29 (d, *J* = 5.28 Hz, 2H), 3.46 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz). δ 157.4, 138.2, 130.5, 129.5, 129.2, 120.0, 115.4, 114.0, 95.3, 63.4, 55.9 ppm.

IR (neat): 3376, 3030, 2919, 2828, 1581, 1486, 1245, 1151, 1080, 1016, 922, 773, 689, 532 cm^{-1}.

EIMS: *m/z* 194 $(M)^+$.

1.3.12. ((2*R*,3*R*)-3-(3-(Methoxymethoxy)phenyl)oxiran-2-yl)methanol (30):



To a stirred suspension of activated 4 Å molecular sieves (9.0 g) in dry CH_2Cl_2 (80 mL) was added D-(–)-DET (1.44 mL, 7.23 mmol) and $Ti(O^iPr)_4$ (2.47 mL, 8.71 mmol) at –20 ^oC. The mixture was stirred for 30 min at the same temperature. To this mixture, a solution of allyl alcohol **29** (8.45 g, 43.55 mmol) in dry CH_2Cl_2 (15 mL) was added dropwise and the mixture was stirred for another 30 min at –20 °C. Then a solution of TBHP (46.82 mL, 4.0 M in toluene, 98.00 mmol) was added and the resulting mixture stirred at the same temperature for 8 h. It was then warmed to 0 °C and then quenched with water (15 mL) and a solution of NaOH (20%, 12mL). The resulting mixture was vigorously stirred for 3 h at room temperature and then filtered through Celite. The residue was washed well with CH_2Cl_2 (3 x 40 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. Removal of the solvent under reduced pressure followed by purification on silica gel column chromatography (EtOAc/hexanes, 3:7) afforded the epoxy alcohol **30** (8.23 g, 90%) as a colourless viscous liquid.

$[\alpha]_D^{20}$: +34.0 (*c* 1.0, $CHCl_3$).

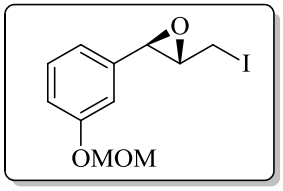
^1H NMR ($CDCl_3$, 300 MHz): δ 7.25 (t, *J* = 7.55 Hz, 1H), 7.01-6.92 (m, 3H), 5.17 (s, 2H), 4.16-4.00 (m, 1H), 3.91 (d, *J* = 2.26 Hz, 1H), 3.84-3.71 (m, 1H), 3.48 (s, 3H), 3.23-3.19 (m, 1H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.2, 138.3, 129.3, 119.0, 115.9, 113.2, 94.1, 62.3, 61.1, 55.7, 55.3 ppm.

IR (neat): 3419, 2932, 2905, 2828, 1594, 1488, 1250, 1151, 1079, 1017, 922, 773, 697 cm^{-1}.

ESI-HRMS: calcd for $C_{11}H_{14}O_4Na$ $(M + Na)^+$ 233.07843, found 233.07816.

1.3.13. (2*S*,3*R*)-2-(Iodomethyl)-3-(3-(methoxymethoxy)phenyl)oxirane (31):



To a stirred solution of epoxy alcohol **30** (4.35 g, 20.714 mmol) in 3:1 mixture of CH_3CN (30 mL) and Et_2O (30 mL) were added TPP (8.15 g, 31.07 mmol), imidazole (4.23 g, 62.14 mmol) and iodine (6.31 g, 24.85 mmol) at 0 ^oC. The resulting mixture was stirred at room temperature for 30 min. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (20 mL), the solids were filtered and washed with ether. The filtrate was extracted with ether (3 x 30 mL). The combined organic layers were dried over Na_2SO_4. Removal of the solvent under reduced pressure followed by purification on silica gel column chromatography (EtOAc/hexanes, 05:9.5) afforded the epoxy Iodo compound **31** (5.3 g, 80%) as a colourless oil.

$[\alpha]^{20}_D$: +3.70 (*c* 1.0, $CHCl_3$).

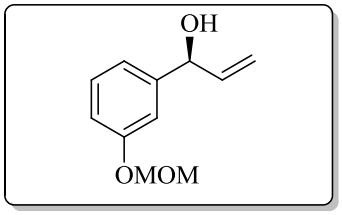
^1H NMR ($CDCl_3$, 300 MHz): δ 7.30-7.23 (m, 1H), 7.02-6.90(m, 3H), 5.18 (s, 2H), 3.75 (d, *J* = 1.51 Hz, 1H), 3.48 (s, 3H), 3.32-3.23 (m, 3H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.2, 137.6, 129.4, 118.8, 116.0, 112.9, 94.0, 61.9, 61.6, 55.7, 4.3 ppm.

IR (neat): 2956, 2902, 2847, 2826, 1589, 1488, 1244, 1152, 1080, 1013, 924, 871, 789, 695, 624 cm^{-1}.

ESI-HRMS: calcd for $C_{11}H_{13}IO_3Na$ $(M + Na)^+$ 343.98016, found 343.98093.

1.3.14. (*S*)-1-(3-(Methoxymethoxy)phenyl)prop-2-en-1-ol (32):



A stirred solution of epoxy iodo compound **31** (4.46 g, 13.93 mmol) and zinc (9.11 g, 139.3 mmol) in anhydrous EtOH (30 mL) was refluxed for 30 min. The reaction mixture was filtered on small pad of Celite and the solvent was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (EtOAc/hexanes, 1:9) to afford the allylic alcohol **32** (2.3 g, 85%) as a colourless oil.

$[\alpha]_D^{20}$: +5.20 (*c* 1.0, $CHCl_3$).

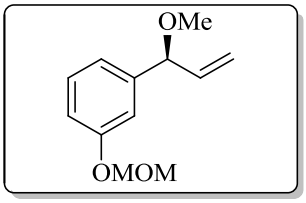
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.31-7.23 (m, 1H), 7.08-6.93 (m, 3H), 6.11-5.98 (m, 1H), 5.41-5.32 (m, 1H), 5.25-5.14 (m, 4H), 3.48 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.1, 144.2, 139.9, 129.4, 119.7, 115.2, 114.9, 114.0, 94.1, 74.8, 55.8 ppm.

IR (neat): 3380, 2957, 2903, 2828, 1595, 1486, 1451, 1247, 1151, 1079, 1018, 924, 771, 701 cm^{-1}.

EIMS: *m/z* 194 $(M)^+$.

1.3.15. (*S*)-1-(1-Methoxyallyl)-3-(methoxymethoxy)benzene (33):



To a stirred solution of allyl alcohol **32** (1.48 g, 7.62 mmol) in CH_3CN (15 mL) was added Ag_2O (5.32 g, 22.88 mmol) at 0 °C in dark place. After 10 min, MeI (2.37 mL, 38.14 mmol) was added dropwise. The resulting mixture was stirred for 10 h, and the solid was filtered over small pad of celite with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, the solvents were evaporated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexanes, 0.5:9.5) to afford the methyl protected compound **33** (1.27 g, 80%) as a colorless liquid.

$[\alpha]_D^{20}$: +7.40 (*c* 1.0, $CHCl_3$).

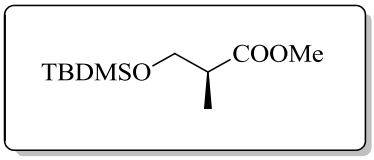
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.33-7.23 (m, 1H), 7.06-6.92 (m, 3H), 5.99-5.84 (m, 1H), 5.35-5.16 (m, 4H), 4.59 (d, *J* = 6.79 Hz, 1H), 3.49 (s, 3H), 3.34 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.3, 142.4, 138.4, 129.3, 120.0, 116.2, 115.1, 114.4, 94.2, 84.3, 56.1, 55.7 ppm.

IR (neat): 2929, 2824, 1590, 1486, 1449, 1277, 1220, 1152, 1080, 1017, 992, 924, 772, 701 cm^{-1}.

ESI-HRMS: calcd for $C_{12}H_{16}O_3Na$ $(M + Na)^+$ 231.09917, found 231.09944.

1.3.16. (*S*)-methyl 3-((*tert*-Butyldimethylsilyl)oxy)-2-methylpropanoate (35):



To a stirred solution of (*S*)-methyl-3-hydroxyisobutyrate **34** (4.27 g,36.18 mmol) in dry CH_2Cl_2 (50 mL) under N_2 atmosphere, was addded imidazole (3.7 g, 54.28 mmol) followed by TBDMSCl (7.63 g, 50.6 mmol) at 0 °C and stirred for 3 h at room temperature. The reaction mixture was treated with saturated aqueous NH_4Cl solution (30 mL) and extracted with CH_2Cl_2 (3 x 40 mL). The organic layer was washed with brine (20 mL), dried over Na_2SO_4, concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexanes, 0.5:9.5) to afford the ester **35** (7.4 g, 88%) as a colorless liquid.

$[\alpha]_D^{20}$: +18.7 (*c* 1.0, $CHCl_3$).

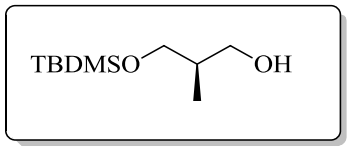
^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.82-3.61 (m, 5H), 2.72-2.58 (m, 1H), 1.14 (d, *J* = 6.79 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 6H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.4, 65.1, 51.4, 42.4, 25.6, 18.0, 13.3, -5.6 ppm.

IR (neat): 2954, 2932, 2858, 1741, 1466, 1432, 1389, 1256, 1219, 1097, 837, 773, 664 cm^{-1}.

ESI-HRMS: calcd for $C_{11}H_{25}O_3$ $(M + H)^+$ 233.07250, found 233.07264.

1.3.17. (*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-2-methylpropan-1-ol (36):



To a stirred solution of ester **35** (7.0 g, 30.17 mmol) in CH_2Cl_2 (50 mL) at –78 ^oC was added slowly DIBAL-*H* (38.00 mL, 20 % solution in toluene, 72.41 mmol) and the mixture was stirred for 30 min at the same temperature. The reaction was quenched with saturated aqueous sodium potassium tartarate (30 mL) and stirring continued for 3 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were dried over Na_2SO_4. Removal of the solvent under reduced pressure followed by purification on silica gel column chromatography (EtOAc/hexanes, 2:8) afforded the alcohol **36** (5.52 g, 85%) as a colourless oil.

$[\alpha]_D^{20}$: +14.2 (*c* 0.7, $CHCl_3$).

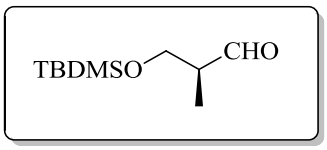
^1H NMR ($CDCl_3$, 300 MHz): δ 3.75 (dd, *J* = 4.52, 9.83 Hz, 1H), 3.69-3.51(m, 3H), 2.88 (dd, *J* = 4.52 Hz, 1H), 2.01-1.89 (m, 1H), 0.90 (s, 9H), 0.84 (d, *J* = 6.79 Hz, 3H), 0.08 (s, 6H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 68.44, 67.89, 36.98, 25.76, 18.08, 13.02, -5.62, -5.68 ppm.

IR (neat): 3378, 2956, 2859, 1255, 1100, 1032, 669 cm^{-1}.

EIMS: *m/z* 204 $(M)^+$.

1.3.18. (*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-2-methylpropanal (37):



To a stirred solution of alcohol **36** (4.87 g, 23.87 mmol) in CH_2Cl_2 (30 mL) was added Dess-Martin periodinane (11.11g, 26.26 mmol) at 0 ^oC. The reaction mixture was stirred for 10 min and then warmed to room temperature. After 45 min, the reaction was quenched with aqueous $Na_2S_2O_3$ (10 mL) and saturated $NaHCO_3$ (10 mL). The mixture was stirred vigorously until a clear solution resulted. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). Combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated in *vacuo*. The crude product was purified by silica gel column chromatography (EtOAc/hexanes, 1:9) to afford the aldehyde **37** (4.3 g, 89%) as a colourless oil.

$[\alpha]_D^{20}$: +9.20 (*c* 0.5, $CHCl_3$).

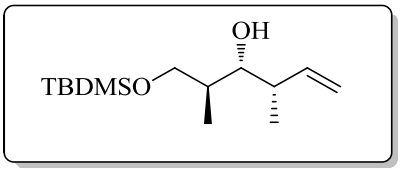
^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.75 (d, *J* = 1.51 Hz, 1H), 3.90-3.77 (m, 2H), 2.59-2.47 (m, 1H), 1.09 (d, *J* = 6.79 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 6H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 204.6, 63.3, 48.7, 25.6, 18.1, 10.1, -5.6 ppm.

IR (neat): 2955, 2932, 2889, 2859, 1734, 1467, 1391, 1255, 1100, 1032, 838, 777, 669 cm^{-1}.

ESI-HRMS: calcd for $C_{10}H_{21}O_2Si$ $(M - H)^+$ 201.13053, found 201.13049.

1.3.19. (2*S*,3*R*,4*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-2,4-dimethylhex-5-en-3-ol (38):



To a stirred solution of Potassium *tert*-butoxide (1.41 g, 12.87 mmol) in dry THF (10 mL) was added *cis*-2-Butene (2.35 mL, 24.75 mmol) *via* cannula at –78 ^{o}C. After 5 min, *n*-BuLi (5.13 mL, 2.5 M solution, 12.87 mmol) was added and the mixture was stirred for 30 min at –45 ^{o}C. The reaction mixture cooled to –78 ^{o}C, and (+)-*β*-methoxydiisopinocampheylborane [(+)-Ipc_2BOMe] (4.71 g, 14.85 mmol) dissolved in THF (20 mL) was added and stirred for 1 h. $BF_3.Et_2O$ (2.11 mL, 16.83 mmol) was added dropwise followed by the dropwise addition of a -78 ^{o}C cooled solution of aldehyde **37** (2.0 g, 9.90 mmol) in THF (10 mL) *via* cannula. The reaction mixture was stirred at –78 ^{o}C for 4 h and then oxidized by a slow addition of 3M NaOH solution (5.94 mL, 17.82 mmol) and H_2O_2 (30% solution, 5.94 mL, 17.82 mmol) at –78 ^{o}C, warming to rt and then refluxing for 5 h. Layers were separated and the aqueous layer was extracted with ether (3 x 30 mL). Combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (EtOAc/hexanes, 1:9) to afford the homoallylic alcohol **38** (1.78 g, 70%) as a colourless oil.

$[\alpha]_D^{20}$: +8.9 (*c* 2.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.94-5.79 (m, 1H), 5.11-4.95 (m, 2H), 3.89-3.82 (m, 1H), 3.66-3.55 (m, 2H), 3.41 (brs, 1H), 2.41-2.28

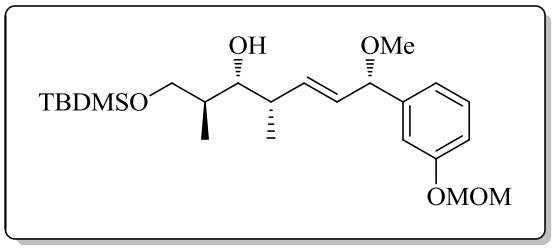
(m, 1H), 1.88-1.73 (m, 1H), 1.06 (d, *J* = 6.79 Hz, 3H), 0.93-0.87 (m, 12H), 0.08 (s, 6H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 142.3, 113.7, 79.4, 67.7, 41.2, 36.6, 25.7, 18.0, 14.0, 13.4, -5.7 ppm.

IR (neat): 3502, 2957, 2931, 2859, 1466, 1255, 1079, 1003, 911, 837, 775, 695 cm^{-1}.

ESI-HRMS: calcd for $C_{14}H_{30}O_2NaSi$ $(M + Na)^+$ 281.19073, found 281.19064.

1.3.20. (2*S*,3*R*,4*S*,7*S*,*E*)-1-((*tert*-Butyldimethylsilyl)oxy)-7-methoxy-7-(3-(methoxymethoxy)phenyl)-2,4-dimethylhept-5-en-3-ol (39):



The solution of TBS compound **38** (427 mg, 1.655 mmol), and MOM compound **33** (686 mg, 3.310 mmol), in dry Toluene (2 mL) was degassed and Grubbs' 2nd generation catalyst (140 mg, 0.165 mmol) was added at rt under nitrogen atmosphere. The resulted pale purple color solution was stirred at 80 ^oC for 1 h. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (EtOAc/hexanes, 1.5:8.5) to afford the compound **39** (565 mg, 78%) as a colorless oil.

$[\alpha]_D^{20}$: +32.8 (*c* 0.5, $CHCl_3$).

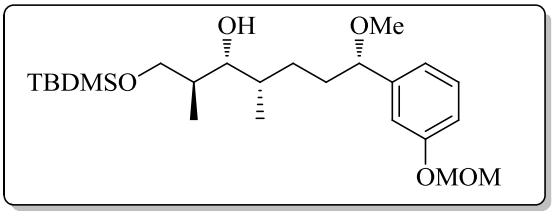
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.29-7.21 (m, 1H), 7.02-6.89 (m, 3H), 5.84-5.72 (m, 1H), 5.60-5.49 (m, 1H), 5.18 (s, 2H), 4.57 (d, *J* = 7.55 Hz, 1H), 3.83-3.77 (m, 1H), 3.66-3.50 (m, 1H), 3.48 (s, 3H), 3.40-3.33 (m, 1H), 3.31 (s, 3H), 2.42-2.29 (m, 1H), 1.80-1.69 (m, 1H), 1.07 (d, *J* = 6.04 Hz, 3H), 0.92-0.85 (m, 12H), 0.06 (m, 6H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.3, 143.3, 137.1, 129.6, 129.3, 120.1, 115.0, 114.5, 94.3, 84.1, 79.6, 67.8, 56.8, 55.9, 40.2, 36.6, 29.6, 25.7, 14.2, 14.0, -5.6 ppm.

IR (neat): 3480, 2921, 2851, 1579, 1457, 1373, 1270, 1150, 1120, 1032, 920, 771, 701 cm^{-1}.

ESI-HRMS: calcd for $C_{24}H_{42}O_5NaSi$ $(M + Na)^+$ 461.26937, found 461.26983.

1.3.21. (2*S*,3*R*,4*S*,7*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-7-methoxy-7-(3-(methoxymethoxy)phenyl)-2,4-dimethylheptan-3-ol (40):



To a stirred solution of double bond compound **39** (207mg, 0.47 mmol) in EtOH (10 mL) was added Na_2CO_3 (250 mg, 2.36 mmol) and 5 mol % Pd/C (50 mg) at room temperature. The flask was evacuated and pressurized with H_2 (balloon) and the mixture was then stirred for 0.5 h. The mixture was then filtered through a small pad of Celite. After washing thoroughly with EtOAc, the filtrate was concentrated, purified by silica gel column chromatography (EtOAc/hexanes, 3:7) to afford the hydroxy compound **40** (83 mg, 40%) as a colourless oil.

$[\alpha]_D^{20}$: –10.4 (*c* 0.5, $CHCl_3$).

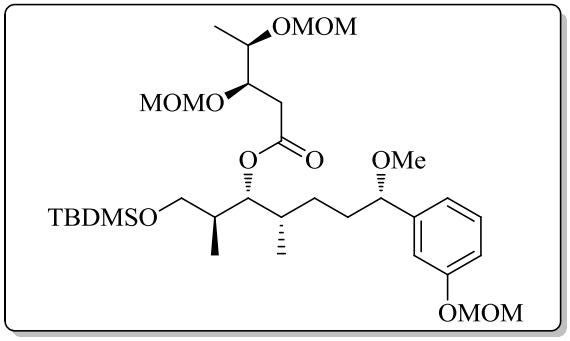
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.43-7.21 (m, 2H), 6.99-6.91 (m, 2H), 5.17 (s, 2H), 4.04 (t, *J* = 7.65 Hz, 1H), 3.75-3.70 (m, 1H), 3.63 (brs, 1H), 3.56 (t, *J* = 8.61 Hz, 1H), 3.49 (s, 3H), 3.37 (d, *J* = 7.65 Hz, 1H), 3.21 (s, 3H), 1.86-1.74 (m, 2H), 1.69-1.61 (m, 1H), 1.57-1.35 (m, 3H), 0.94-0.85 (m, 12H), 0.74 (d, *J* = 6.70 Hz, 3H), 0.07 (s, 6H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.3, 144.4, 129.3, 120.3, 114.9, 114.5, 94.4, 84.1, 79.1, 69.4, 56.6, 56.0, 37.1, 36.2, 35.3, 30.1, 25.8, 25.6, 13.1, 12.4, -5.7 ppm.

IR (neat): 3482, 2923, 2852, 1581, 1548, 1457, 1373, 1274, 1152, 1118, 1080, 1023, 923, 772, 702 cm^{-1}.

ESI-HRMS: calcd for $C_{24}H_{45}O_5Si$ $(M + H)^+$ 441.3036, found 441.3040.

1.3.22. (3*R*,4*R*)-(2*S*,3*R*,4*S*,7*S*)-1-((tert-Butyldimethylsilyl)oxy)-7-methoxy-7-(3-(methoxy methoxy)phenyl)-2,4-dimethylheptan-3-yl 3,4-bis(methoxymethoxy)pentanoate (41):



To a stirred solution of carboxylic acid **25** (89.8 mg, 0.40 mmol) in THF (2 mL) at room temperature were added triethylamine (84.7 μL, 0.606 mmol) and 2,4,6-trichlorobenzoyl chloride (82.16 μL, 0.52 mmol). The mixture was stirred for 2 h at room temperature, and the solids were filtered off and washed with hexane (5 mL). The combined solution was concentrated under reduced pressure. The residue was dissolved in benzene (2 mL), the solution was added to a refluxing solution of alcohol **40** (44.5 mg, 0.1011 mmol) and DMAP (123.5 mg, 1.01 mmol) in benzene (3 mL). After being stirred for 1 h, the reaction mixture was diluted with ether (10 mL), and washed with aqueous saturated $NaHCO_3$ (5 mL). Layers were separated and the aqueous layer was extracted with ether (2 x 10 mL). Combined organic layers were washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexanes 1:9) to afford the desired ester **41** (50 mg, 77%) as a colorless oil.

$[\alpha]_D^{20}$: –7.0 (*c* 1.0, $CHCl_3$).

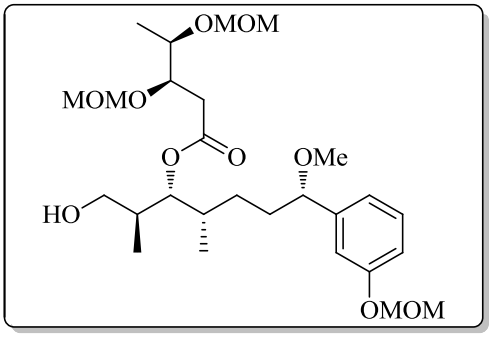
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.29-7.19 (m, 1H), 6.98-6.86 (m, 3H), 5.18 (s, 2H), 4.84-4.59 (m, 4H), 4.12-3.86 (m, 4H), 3.56 (dd, *J* = 3.77, 9.82 Hz, 1H), 3.50 (s, 3H), 3.37 (s, 6H), 3.28 (dd, *J* = 7.55, 9.82 Hz, 1H), 3.19 (s, 3H), 2.59 (dq, *J* = 3.77, 15.86 Hz, 2H), 1.99-1.85 (m, 2H), 1.77-1.55 (m, 4H), 1.21 (d, *J* = 6.043 Hz, 3H), 0.90-0.84 (m, 15H), 0.01 (s, 6H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.51, 158.51, 144.40, 129.39, 120.04, 115.0, 114.41, 97.40, 95.68, 95.53, 94.47, 84.09, 77.78, 73.83, 64.72, 56.69, 56.01, 55.80, 55.49, 37.56, 34.09, 31.91, 31.40, 30.15, 29.68, 25.87, 15.27, 14.10, 13.53, -5.48 ppm.

IR (neat): 2933, 2853, 1737, 1579, 1448, 1375, 1255, 1150, 1103, 1038, 921, 746, 697 cm^{-1}.

ESI-HRMS: calcd for $C_{33}H_{60}O_{10}NaSi$ $(M + Na)^+$ 667.38480, found 667.38606.

1.3.23. (3*R*,4*R*)-(2*S*,3*R*,4*S*,7*S*)-1-Hydroxy-7-methoxy-7-(3-(methoxymethoxy)phenyl)-2,4-dimethylheptan-3-yl 3,4-bis(methoxymethoxy)pentanoate (42):



To a stirred solution of TBS-ester **41** (46.8 mg, 0.072 mmol) in dry THF (1 mL), was added TBAF (72.6 µL, 0.072 mmol) at 0 ^{o}C. The mixture was stirred for 1 h and quenched with saturated $NaHCO_3$ (3 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic phase was washed with brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was

purified by silica gel column chromatography (EtOAc/hexanes 3:7) to afford the hydroxy ester **42** (30 mg, 78%) as a colorless oil.

$[\alpha]_D^{20}$: +8.3 (*c* 0.5, $CHCl_3$).

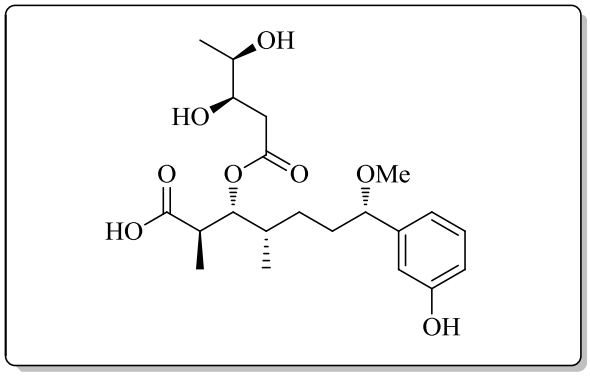
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.26 (q, *J* = 5.93, 7.91 Hz, 1H), 6.98-6.89 (m, 3H), 5.18 (s, 2H), 4.63 (s, 4H), 4.38-4.28 (m, 2H), 4.21 (dd, *J* = 3.95, 10.88 Hz, 1H), 4.05 (t, , *J* = 5.93 Hz, 1H), 3.63-3.57 (m, 1H), 3.49 (s, 3H), 3.37 (s, 3H), 3.29 (dd, *J* = 1.98, 8.90 Hz, 1H), 3.24 (s, 6H), 2.68 (dq, *J* = 3.77, 15.86 Hz, 2H), 2.10- 1.73 (m, 3H), 1.71-1.37 (m, 3H), 1.08 (d, *J* = 6.92 Hz, 3H), 0.90 (d, *J* = 6.92 Hz, 3H), 0.84 (d, *J* = 6.92 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.23, 158.39, 144.53, 129.43, 120.04, 115.10, 114.43, 97.41, 95.67, 95.54, 94.57, 83.91, 77.87, 72.23, 64.01, 56.52, 56.00, 55.78, 55.02, 37.57, 34.29, 31.91, 31.40, 30.12, 23.86, 14.56, 13.64 ppm.

IR (neat): 3448, 2935, 2856, 1738, 1540, 1443, 1218, 1143, 1100, 1038, 921, 858, 697 cm^{-1}.

ESI-HRMS: calcd for $C_{27}H_{46}O_{10}Na$ $(M + Na)^+$ 553.29832, found 553.29895.

1.3.24. (2*R*,3*R*,4*S*,7*S*)-3-(((3*R*,4*R*)-3,4-Dihydroxypentanoyl)oxy)-7-(3-hydroxyphenyl)-7-methoxy-2,4-dimethylheptanoic acid (16):



To a stirred solution of alcohol **42** (26.8 mg, 0.05 mmol) in 1:1mixture of CH_3CN (1 mL) and H_2O (1 mL) were added TEMPO (1.6mg, 0.01 mmol) and BAIB (40 mg, 0.125 mmol). The mixture was stirred vigorously until TLC-analysis showed complete

conversion of the starting material. Aqueous saturated $Na_2S_2O_3$ (5 mL) was added and the resulting mixture was stirred for 15 min. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 10mL). The combined organic layers were dried over Na_2SO_4 and concentrated in *vacuo*.

To the crude residue (16.5 mg) in MeOH (1 mL) was added 6N aqueous HCl (1 mL). After 1 h the reaction mixture was extracted with CH_2Cl_2 (3 x 10mL). The combined organic layers were dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure followed by purification on silica gel column chromatography (MeOH/$CHCl_3$, 1:9) afforded the target molecule Nhatrangin A (**16**) (5 mg, 40%) as a colourless oil.

$[\alpha]_D^{20}$: (*c* 0.25, MeOH).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.13 (t, *J* = 7.84 Hz, 1H), 6.73-6.61 (m, 3H), 5.70 (brs, 1H), 4.53 (dd, *J* = 3.77, 9.82 Hz, 1H), 3.72-3.58 (m, 1H), 3.54-3.47 (m, 1H), 3.09-3.04 (m, 1H), 3.03 (s, 3H), 2.58 (dd, *J* = 5.22, 16.99 Hz, 2H), 2.29 (dd, *J* = 3.77, 15.88 Hz, 1H), 1.68-1.57 (m, 1H), 1.55-1.43 (m, 2H), 1.41-1.22 (m, 2H), 1.08 (d, *J* = 6.53 Hz, 3H), 0.82 (d, *J* = 7.84 Hz, 3H), 0.76 (d, *J* = 6.53 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz): δ 175.50, 171.60, 158.19, 144.29, 129.44, 119.50, 114.79, 113.82, 82.81, 77.54, 71.14, 66.37, 56.14, 40.14, 37.62, 34.33, 32.61, 30.09, 19.76, 14.49, 13.48 ppm.

IR (neat): 3446, 2930, 2856, 1737, 1670, 1449, 1375, 1275, 1149, 1104, 1037, 977, 922, 837, 782, 699 cm^{-1}.

ESI-HRMS: calcd for $C_{21}H_{32}O_8Na$ $(M + Na)^+$ 435.19894, found 435.19932.

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Spectra

CHAPTER II

Formal stereoselective synthesis of (-)-Brevisamide

2.1. Introduction:

In recent years, natural marine toxins are becoming more prevalent around the world, affecting an estimated 500,000 individuals annually, and having deleterious impacts on health resulting in a global mortality rate of 1.5%.[2] These toxins, which poison wildlife as well as humans are known to be produced by a very large and diverse group of eukaryotic algae in the marine ecosystem, dinoflagellates during the course of harmful algal blooms (also known as the red tides).[1] Interestingly, many marine toxins are known to have fascinating complex structures. In particular, the dinoflagellate toxins are structurally and functionally diverse, usually possessing multiple cyclic-ether rings which are often aligned in a ladder frame, and in a long carbon chain backbone bearing many hydroxyl groups.[3] These polycyclic ether marine natural products have shown unique and extreme potent biological activities such as neurotoxicity, anticancer and antifungal properties.[3]

Karenia brevis is a marine dinoflagellate known for producing complex fused polyethers, which found in the Gulf of Mexico, Caribbean Sea and along New Zealand coasts. This organism is responsible for the blooms along the coasts of Florida and Texas.[4] Brevetoxin A (**1**), B (**2**) and hemibrevetoxin B (**3**) (Figure 1) were isolated from the red tide dinoflagellates, *Karenia brevis*, and they are the first members of this class of natural product to be structurally elucidated.[5] This group of natural products consists of a lactone ring fused to 9 to 10 contiguous trans-fused cyclic ether rings. The brevetoxins bind with high affinity to site 5 of the voltage-sensitive sodium channel (VSSC) in neurons, responsible for the passage of sodium ions through a cell's plasma membrane. These voltage-sensitive channels are responsible for inducing a channel mediated sodium ion reflux, nerve membrane depolarization, and spontaneous firing. This process causes the disruption of the neurological activities leading to illness known as neurotoxic shellfish poisoning (NSP). Brevetoxins are easily absorbed into the body due to their lipid-solubility properties and can pass through cell membranes including the blood brain barrier (BBB).[6] Nicolaou and co-workers reported the first total syntheses of brevetoxin A (**1**) and B (**2**) in 1995 and 1998 respectively.[7] Nakata's, Yamamoto/Kadota's and Crimmins's group have also completed syntheses of either brevetoxin A (**1**) or B (**2**).[8]

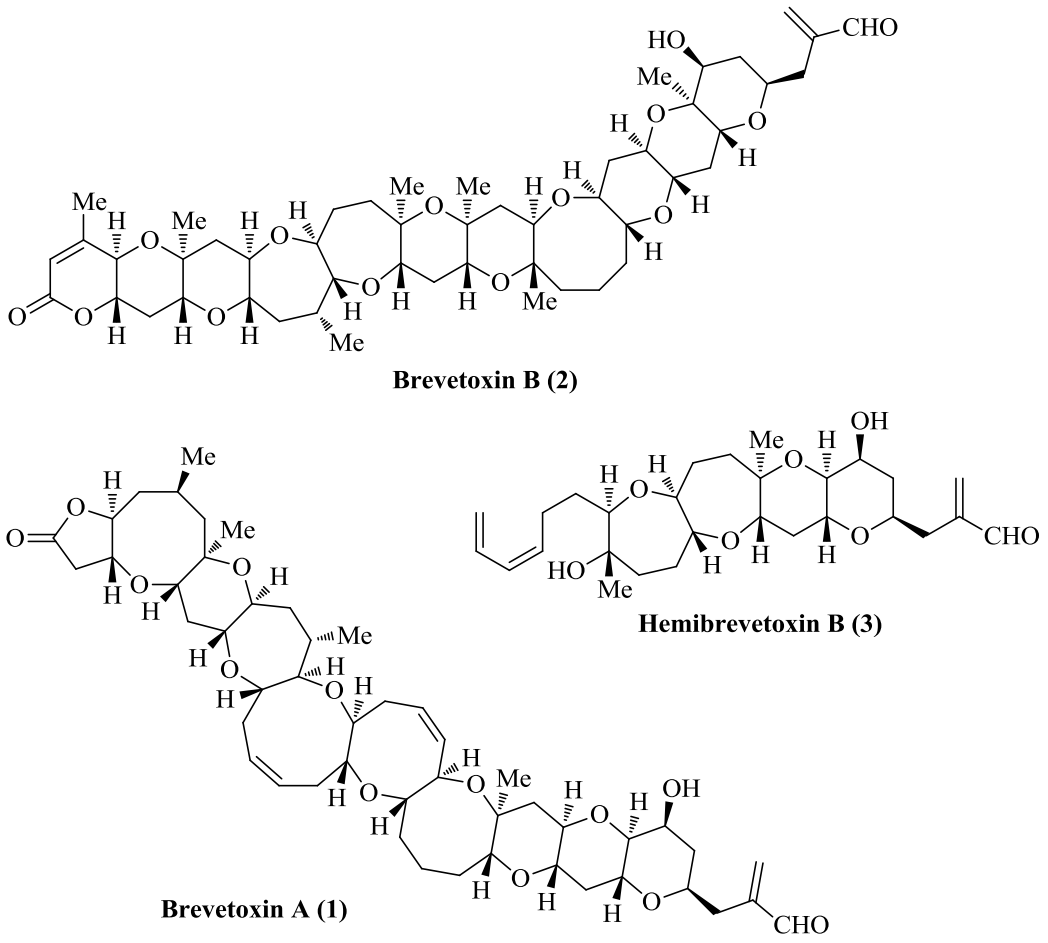
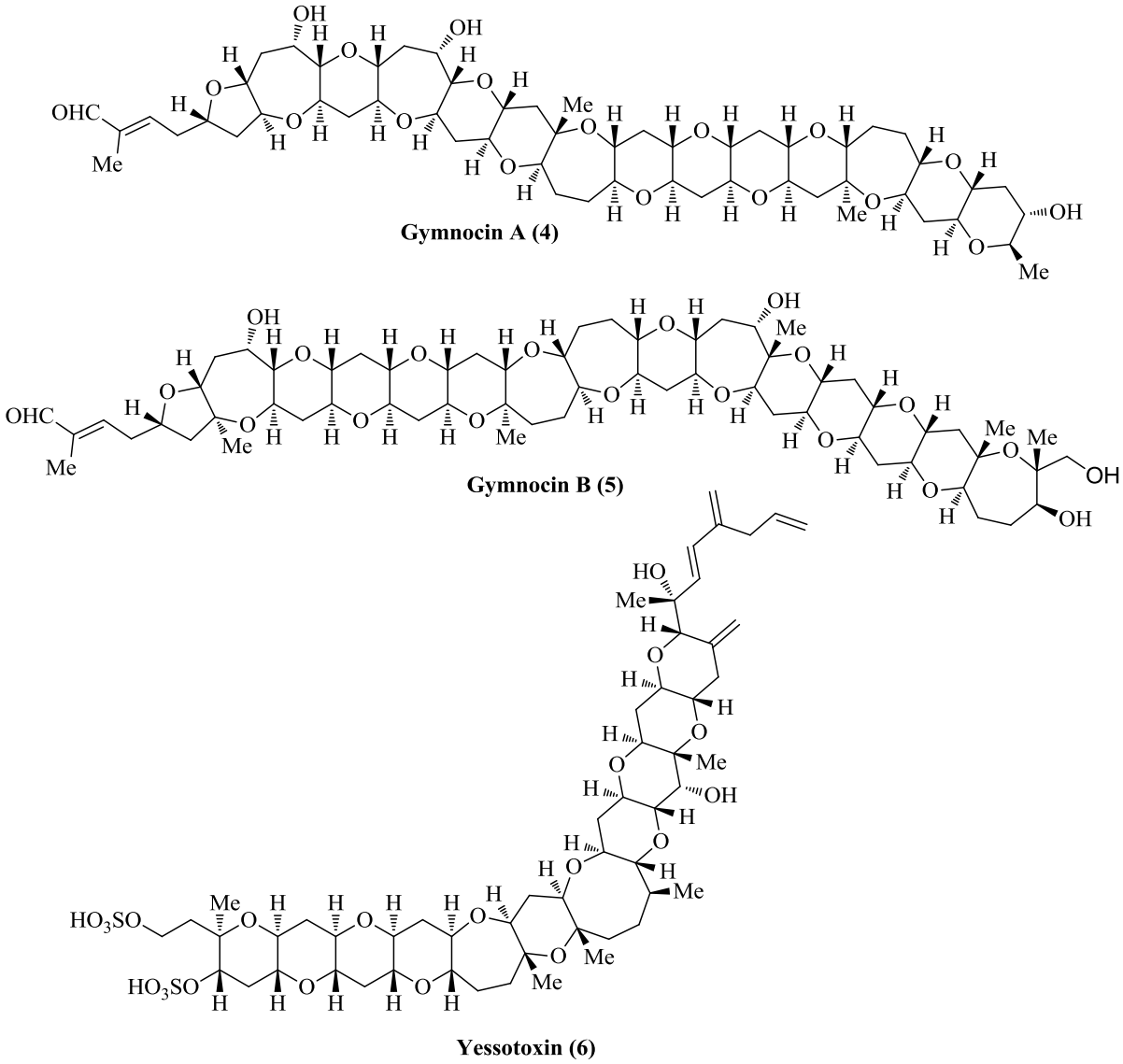


Figure 1

Other known marine toxins include gymnocin A (**4**), gymnocin B (**5**) (isolated from *Gymnodinium mikimotoi*) and yessotoxin (**6**) which was isolated from the marine dinoflagellate *Protoceratium reticulatum* (Figure 2).

Gambierdiscus toxicus another marine dinoflagellate is considered to produce some of the most poisonous toxins, including ciguatoxin (CTX-3C) (**7**), gambierol (**8**), gambieric acid A-D (**9-12**) (Figure 3) and maitotoxin (**13**) (Figure 4).



Gymnocin A (4)

Gymnocin B (5)

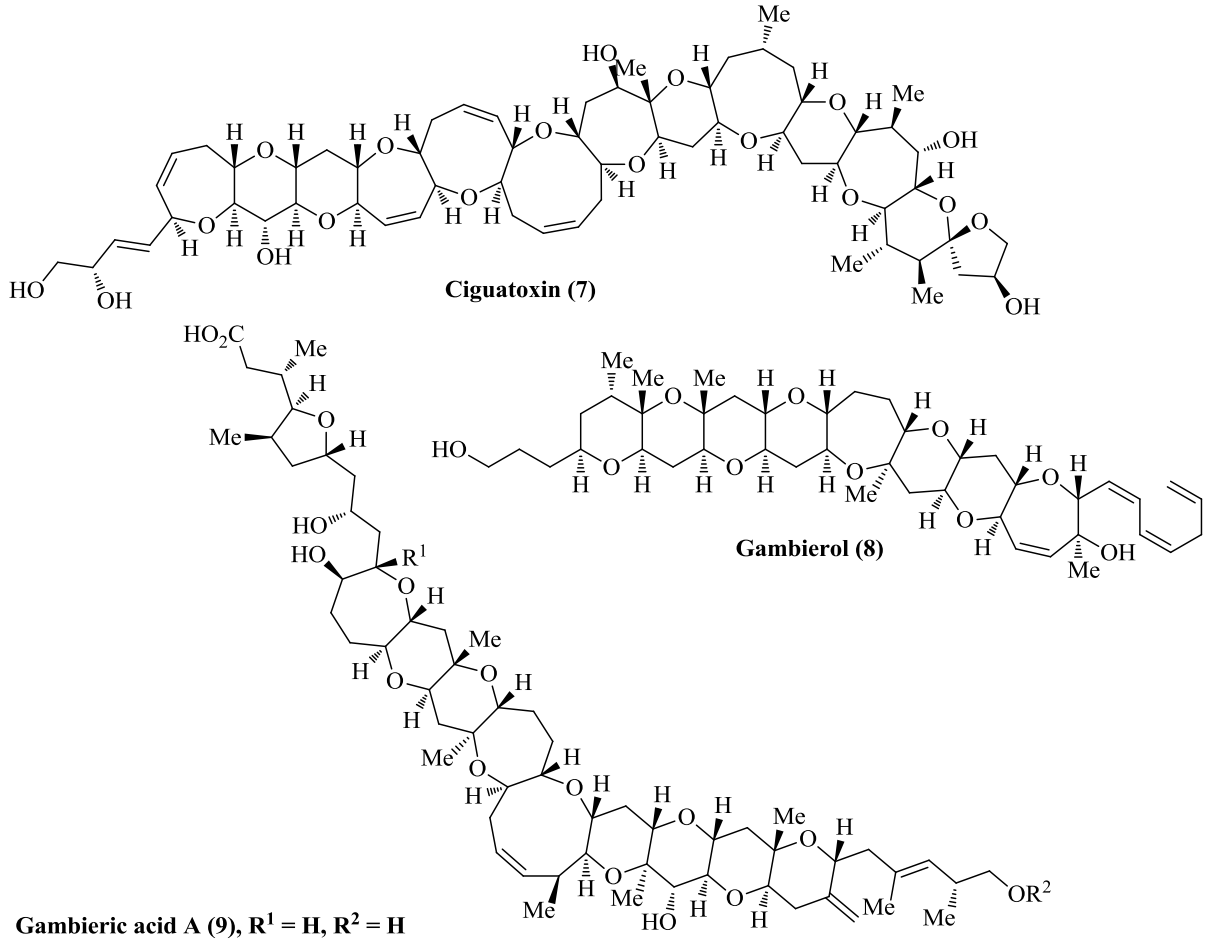
Yessotoxin (6)

Figure 2

Ciguatera, a type of seafood poisoning caused by ciguatoxins is estimated to affect approximately 20,000 people annually.[9] Ciguatoxins are lipophilic polycyclic ethers with 13 five to nine membered fused cyclic ether rings. Similar to brevetoxin, ciguatoxins are extremely potent neurotoxins that lower the threshold for opening voltage-gated sodium channels, thus causing membrane depolarization.[10] These effects could cause heart contractions and paralysis. In 1984, Scheuer's group reported the isolation of ciguatoxin and later Yasumoto and co-workers disclosed its structure. In 2001, the first total synthesis

of ciguatoxin congener CTX-3C (**7**) (Figure 3) was accomplished by Hirama and co-workers.[11]

Gambierol (**8**) (Figure 3), a polycyclic ether family of marine neurotoxin was isolated from the cultured cells of the ciguatera causative dinoflagellate *Gambierdiscus toxicus* in 1993.[12] Structurally, gambierol consists of 8 ether rings, 18 stereocenters, and 2 pyranyl rings. Similar to ciguatoxins, gambierol (**8**) is responsible for ciguatera seafood poisoning, showing potent toxicity in mice at LD_{50} 50 μg/kg (ip).



Gambieric acid A (9), R^1 = H, R^2 = H

Gambieric acid B (10), R^1 = Me, R^2 = H

Gambieric acid C (11), R^1 = H, R^2 = $COCH_2CH(Me)CH_2CO_2H$

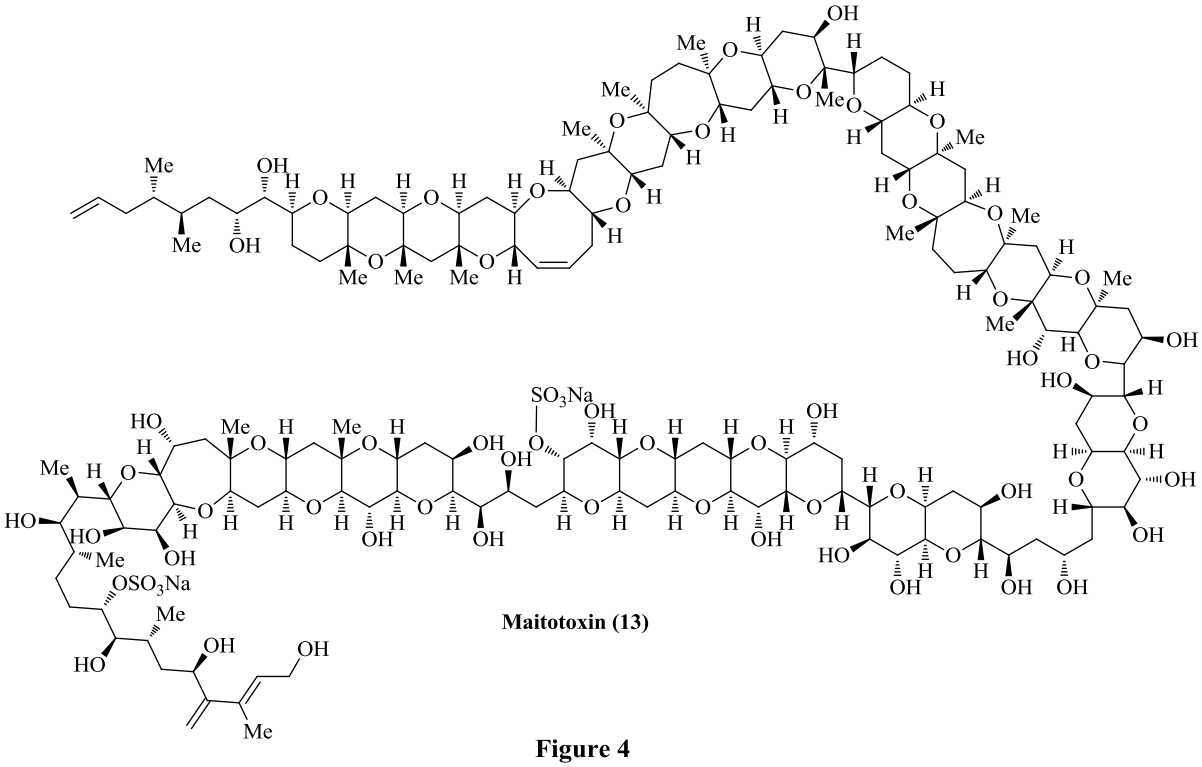
Gambieric acid D (12), R^1 = Me, R^2 = $COCH_2CH(Me)CH_2CO_2H$

Figure 3

It is believed that gambierols bind to ion channels like other similar neurotoxins. In 2003, Yasumoto, Hirama, and co-workers reported that gambierol inhibits the binding

of brevetoxin PbTx-3 to its target, site 5 of voltage gated sodium channels, thus acting as a competitive antagonist of PbTx-2.[13] Later, Bigiani and co-workers reported that gambierol (**8**) is also capable of binding to potassium channels.[14] The first total synthesis of gambierol (**8**) was accomplished by Sasaki and co-workers in 2002.[15] Yamamoto/Kadota and Rainier groups have also completed the synthesis of the natural product.[16] In 1992, gambieric acids A-D (**9**-**12**) (Figure 3) were isolated from *Gambierdiscus toxicus* which were shown to inhibit the growth of *Aspergillus niger* showing potency that exceeds amphotericin B by 2000-fold.[17] A competitive inhibition assay performed by Hirama and co-workers showed that gambieric acid A (**9**) inhibits the binding of isotope-labeled dihydro-brevetoxin ([3H]-PbTx-3).[18]

Maitotoxin (**13**), the largest molecule made by nature (excluding bio-polymers) was first discovered from the surgeon fish *Ctenochaetus striatus*[19] and later isolated from cultured cells of *Gambierdiscus toxicus*.[20] The structure of maitotoxin (**13**) contains 32 rings and 98 stereogenic centers (Figure 4). Maitotoxin (**13**) is extremely potent and the most poisonous marine toxin known, showing lethality (LD_{50}) value of 50 ng/kg against mice.[21]



Maitotoxin (13)

Figure 4

In 2005, Baden, Bourdelais and co-workers isolated a new member of polycyclic ether from the culture of *Karenia brevis* called brevenal (**14**) (Figure 5), a smaller, ladder-frame polycyclic ether that competitively displaced brevetoxin from its binding site in rat brain synaptosomes.[22] Brevenal (**14**) was shown to displace ([^{3}H]-PbTx-3) from receptor site 5 of VSSC. Also recently, it has been demonstrated that brevenal (**14**) is a potent antagonist of PbTx-2-induced Ca^{2+} influx in neurons.[23] Molgo and co-workers have recently shown that brevenal (**14**) can potently inhibit ciguatoxin's stimulatory effect on exocytosis and can be used as the first treatment of ciguatera.[24] For the treatment of cystic fibrosis and neurotoxic shellfish poisoning, brevenal (**14**) has been identified as a lead compound. Brevisin (**15**), a polycyclic ether, which was isolated from the dinoflagellate *karenia brevis* by Wright and co-workers in 2008. It contains two separate fused polyether rings linked by a methylene group. One of the polyether rings contains the same conjugated aldehyde side chain found in brevenal (**14**) (Figure 5).[25]

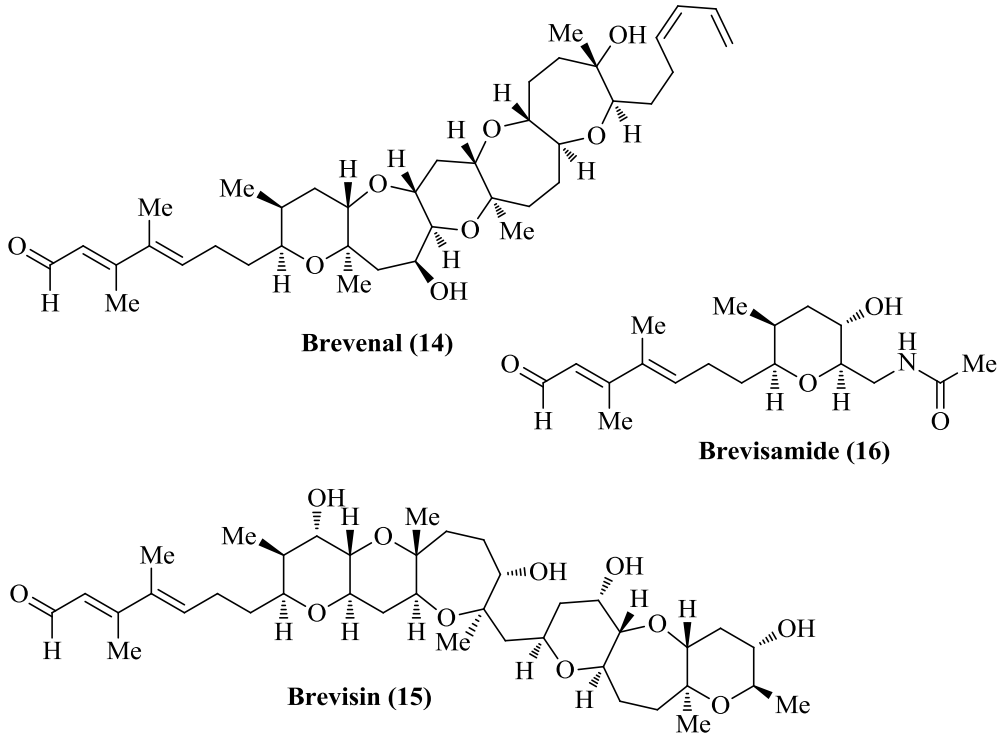


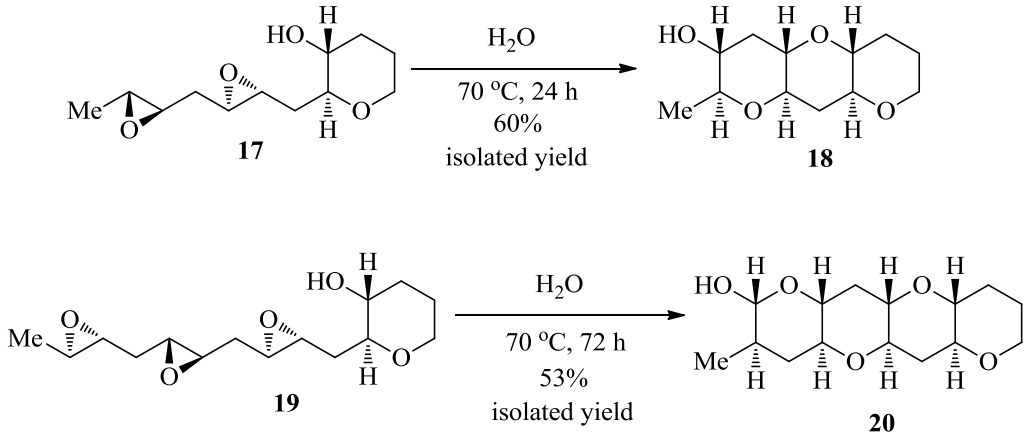
Figure 5

Thus, this unprecedented polycyclic ether could provide more insight into the biogenesis of fused polyether ring systems. Wright and co-workers reported that brevisin

(**15**) inhibits the binding of [^{3}H]-PhTx-3 to its binding site on the voltage -sensitive sodium channels in rat synaptosomes. In 2011, the total synthesis was reported by the Satake group, who were involved in the isolation of this polycyclic ether natural product.[26]

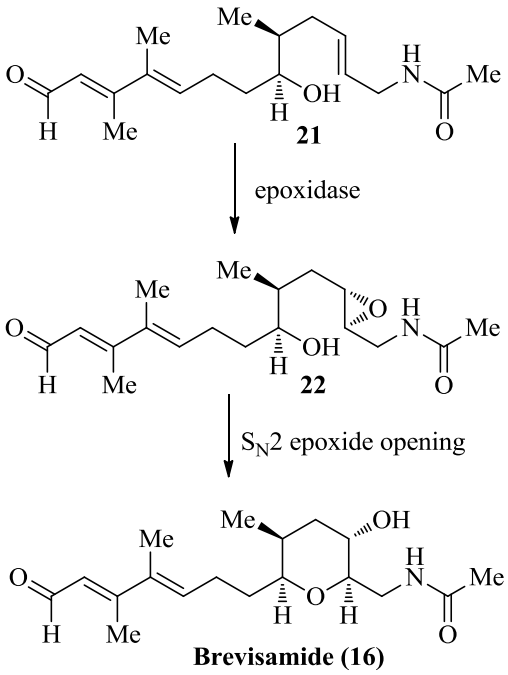
Proposed biosynthesis of brevisamide

Recently, an important breakthrough in understanding the formation of ladder polyether marine natural products was reported by Jamison's group. Their work explained the importance of the first ring towards the cascade formation of multiple ether rings present in the ladder frame polyethers. It was reported that the *endo*-tet cyclization of a polyepoxide precursors for the formation of ladder-frame polyethers can only proceed in aqueous media of neutral pH, and an initial 3-hydroxy-tetrahydropyranyl ring moiety must be built into the polyepoxide intermediate (Scheme 1).[27] Jamison's work suggests that after enzyme catalyzed formation of the first ether ring, the cascade polyepoxide opening should proceed spontaneously, relying on the spatial and configurational properties of the epoxide-intermediate.[27,28]



Scheme 1

An epoxide based biosynthetic mechanism for the formation of the ether ring of brevisamide was proposed by Wright and co-workers (Scheme 2). It involves epoxidation of polyketide olefin chain **21** to give hydroxyl epoxide intermediate **22**, which undergoes intramolecular S_N2 cyclization of the *β*-hydroxy group on a flow from left to right-opposite the flow of polyketide chain assembly to provide brevisamide (**16**).[29]



Scheme 2

Consequently, the isolation of brevisamide as the smallest known ether-containing metabolite produced by dinoflagellate provides further support for the model of ladder-frame initiation in the biosynthesis of polycyclic ether natural products.

Isolation of Brevisamide

In 2008, Satake, Tachibana, Wright, and co-workers reported the isolation and characterization of brevisamide (**16**), an unprecedented monocylic ether alkaloid, from the dinoflagellate *Karenia brevis*. The extraction of 400 L of cultured cells lead to 0.2 mg of brevisamide (**16**) as an amorphous solid.[29] Brevisamide (**16**), which displayed similar UV data to brevenal (**14**), had a very distinctive ^{1}H NMR spectra compared to other known brevetoxins. The structural assignment was elucidated by 500 MHz 2D-NMR experiments including ^{1}H-^{1}H COSY, ^{1}H-^{13}C HMBC, TOSCY, HSQC and NOE experiments.

Brevisamide (**16**), contains the same conjugated 3,4-dimethyl-2,4-dienal side chain as the more complex polycylic ether brevenal (**14**) and brevisin (**15**) (Figure 5). Thus, brevisamide (**16**) is believed to be a biosynthectic precursor for these complex polyether natural products **14** and **15**.[22] Interestingly, the brevisamide (**16**) skeleton matches well with Jamison's template ring system in the formation of ladder polyethers (Scheme 1), with the ether ring oxygen *anti* to the hydroxyl oxygen and a carbon-carbon-oxygen

unit.[27,28] These features are consistent with the structural and stereochemical trend found in complex ladder polyethers such as Brevetoxins. Brevisamide (**16**) might prove the existence of the tetrahydropyran template in nature.[29] Wright, and co-workers suggested that based on the established biosynthesis pathway of other dinoflagellate metabolites, glycine could be the source of the amide nitrogen of brevisamide (**16**) and acts as a starter unit in a NRPS/PKS hybrid pathway.[29]

Due to the unique role Brevisamide (**16**) could play in further understanding the biogenetic origin of fused, ladder-frame polyether marine natural products, it has garnered a great deal of interest among the synthetic community, with six total syntheses and three formal syntheses reported.

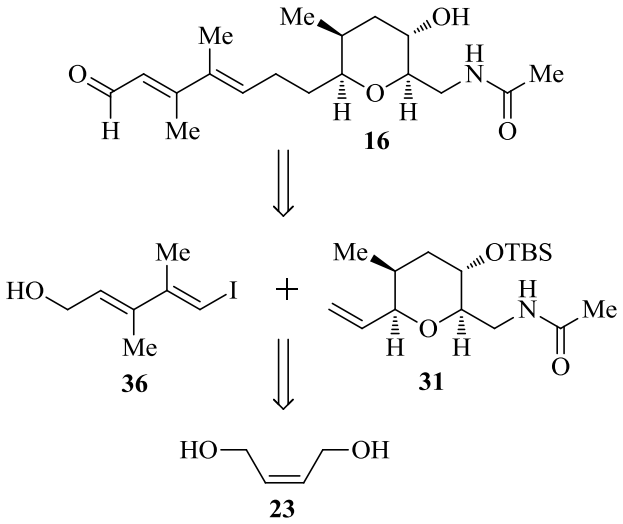
2.2. Previous approaches:

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

2.2.1. Kazuo Tachibana approach:[30]

Tachibana *et al.* reported first total synthesis Brevisamide and thus they confirmed that the absolute stereochemistry was identical with the proposed one.

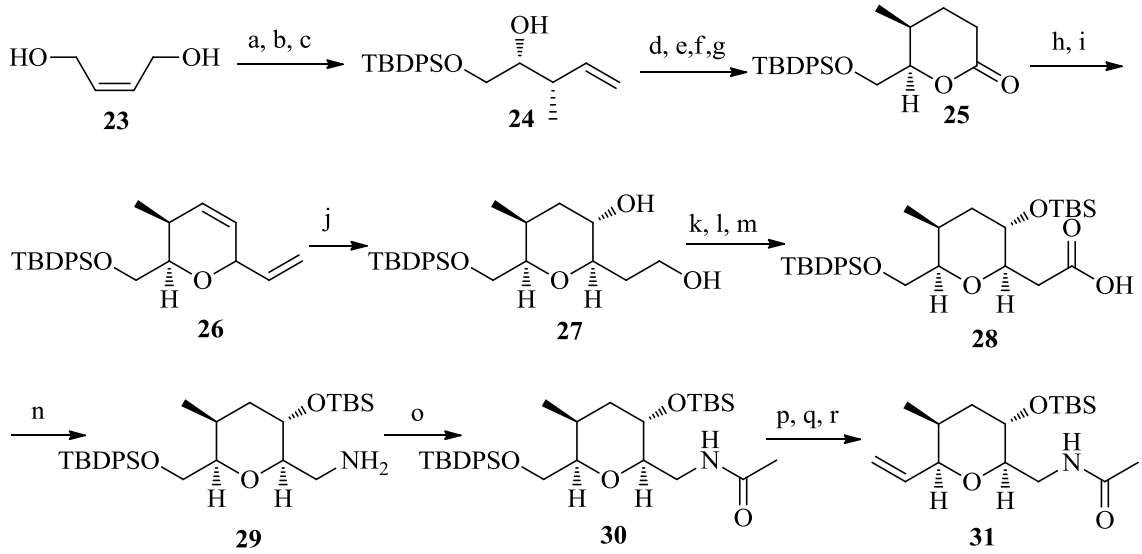
2.2.1a. Retrosynthesis:



Scheme 3

2.2.1b. Synthesis:

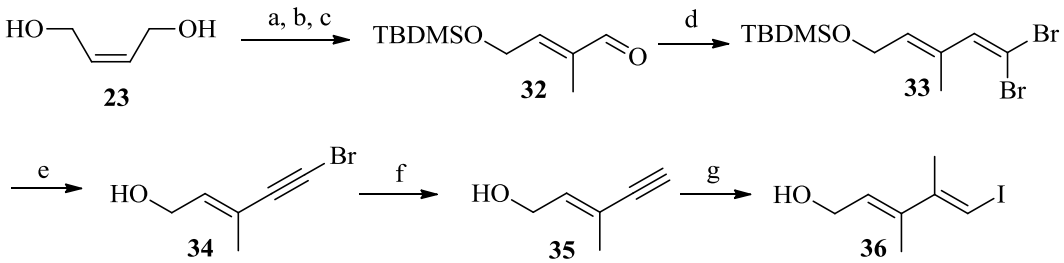
Tachibana *et al.* reported the total synthesis of Brevisamide, starting from *cis* butene 1,4 diol **23** (Scheme 4). Diol **23** was mono protected with TBDPSCl and then oxidatively cleaved with O_3 to give the aldehyde. Brown crotylation of this aldehyde with (+)-(Z)-crotyldiisopinocampeylborane gave the *syn*-homoallylic alcohol **24** with excellent selectivity. The alcohol was oxidized with O_3 and Wittig homologation followed by hydrogenation and transesterification afforded the lactone **25**. The Stille coupling of lactone with CH_2=CHSn*n*-Bu_3 gave dienol ether **26**.



Scheme 4

Reagents and conditions: (a) TBDPSCl, imidazole, DMF, rt; (b) O_3, CH_2Cl_2, -78 ^oC, PPh_3, rt; (c) (+)-*Z*-IpcBCH_2CH=$CHCH_3$, Et_2O, -78 ^oC, 3N NaOH, 30% H_2O_2, 50 ^oC, 78% for 3 steps; (d) O_3, -78 ^oC, PPh_3, rt; (e) Ph_3P=$CHCO_2Me$, THF, rt; (f) H_2, Pd/C, EtOAc, rt; (g) PPTS, benzene, reflux, 70% for 4 steps; (h) KHMDS, Tf_2NPh, DPMU, THF, -78 ^oC; (i) CH_2=CHSn*n*-Bu_3, $Pd(PPh_3)_4$, LiCl, THF, reflux, 85% for 2 spteps; (j) thexylborane, THF, 0 ^oC, 30% H_2O_2, sat. $NaHCO_3$ aq, rt, 50%; (k) TBSCl, imidazole, DMF, rt; (l) CSA, MeOH-CH_2Cl_2, 0 ^oC; (m) TEMPO, NaOCl, KBr, TBAC, NaCl, $NaHCO_3$, CH_2Cl_2-H_2O, 0 ^oC, 80% for 3 steps; (n) DPPA, Et_3N, toluene, 80 ^oC, 4N LiOH, THF, rt, 1 h, 85%; (o) Ac_2O, pyridine; (p) TBAF, AcOH, THF, 0 ^oC to rt, 83%; (q) SO_3·pyridine, Et_3N, CH_2Cl_2-DMSO, 0 ^oC; (r) $Ph_3P^+CH_3Br^-$, NaHMDS, THF, -78 ^oC to rt, 56% for 2 steps.

The ether **26** was converted to diol **27** using hydroboration and subsequent base indused hydrolysis reactions. The obtained diol **27** was protected with TBS ether. Selective primary silyl deprotection followed by oxidation gave the carboxylic acid **28**. Curtius rearrangement of acid **28** produced primary amine **29**. The amine **29** was acetylated with Ac_2O in CH_2Cl_2 to give amide **30** in good yield. Selective deprotection of TBDPS group using TBAF in AcOH gave the corresponding alcohol. The primary alcohol oxidation with SO_3·Py followed by Wittig reaction gave the ether ring fragment **31** (Scheme 4).

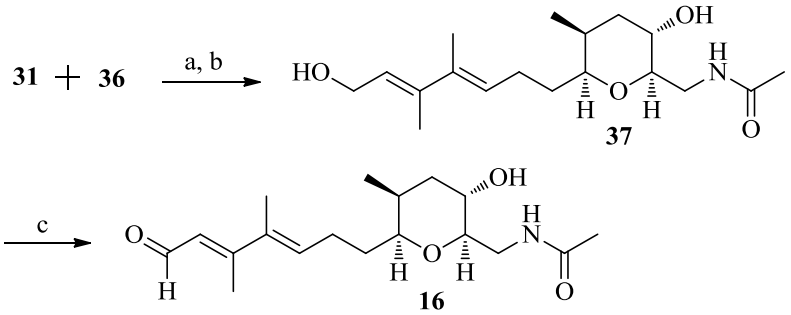


Scheme 5

Reagents and conditions: (a) TBDMSCl, imidazole, DMF, rt; (b) O_3, CH_2Cl_2, -78 ^oC, PPh_3, rt; (c) $Ph_3P{=}CH(CH_3)CHO$, benzene reflux, 63% for 3 steps; (d) CBr_4, PPh_3, Et_3N, CH_2Cl_2, -40 to 0 ^oC, 88%; (e) TBAF, THF, 45 ^oC; (f) *n*-BuLi, Et_2O, -78 ^oC, H_2O, rt, 63% for 2 steps; (g) Me_3Al, $ZrCp_2Cl_2$, CH_2Cl_2-heptane, rt, I_2, THF, -78 ^oC to 0 ^oC, 32%.

Unsaturated aldehyde **32** was prepared from 1,4-*cis* butene diol **33** in three steps. The aldehyde **32** was treated with CBr_4, PPh_3, and Et_3N to give dibromo olefin **33** in good yield. Dehydrobromination using TBAF gave bromoacetylene **34** and subsequent debromination with *n*-BuLi at -78 °C afforded alkyne **35** (Scheme 5)**.** Methylalumination-iodination of enynol **35** in the presence of $ZrCp_2Cl_2$ proceeded by *syn*-addition, which afforded the side chain fragment **36** with the desired *E,E* geometry (Scheme 5).

Connection of fragments **31** and **36** by Suzuki-Miyaura cross-coupling using 9-BBN, aqueous Cs_2CO_3 and $PdCl_2$(dppf) followed by treatment with TBAF at 0 °C gave dienol **37** in 40% yield. Finally, chemoselective oxidation of the allylic alcohol at C-1 in **37** with MnO_2 produced Brevisamide (**16**) in 55% yield (Scheme 6).



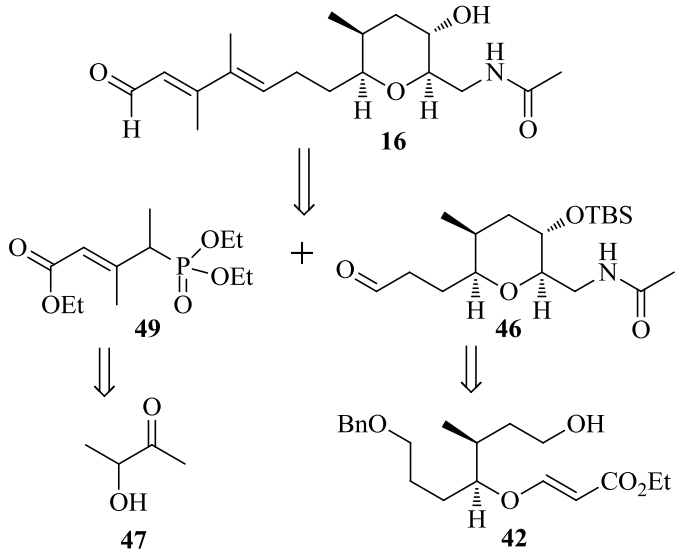
Scheme 6

Reagents and conditions: (a) 9-BBN, THF, rt, 3M Cs_2CO_3, $PdCl_2$(dppf), DMF, 45 ^oC; (b) TBAF, 0 ^oC, 40% for 2 steps; (c) MnO_2, CH_2Cl_2, rt, 55%.

2.2.2. Craig W. Lindsley *et al*. approach:[31]

The total synthesis of brevisamide proceeds in 21 steps, with a longest linear sequence of the 14 steps in 5.2% overall yield. Reductive cyclization using SmI_2 to produce tetrasubstituted pyran core is a key step in this approach.

2.2.2a. Retrosynthesis:

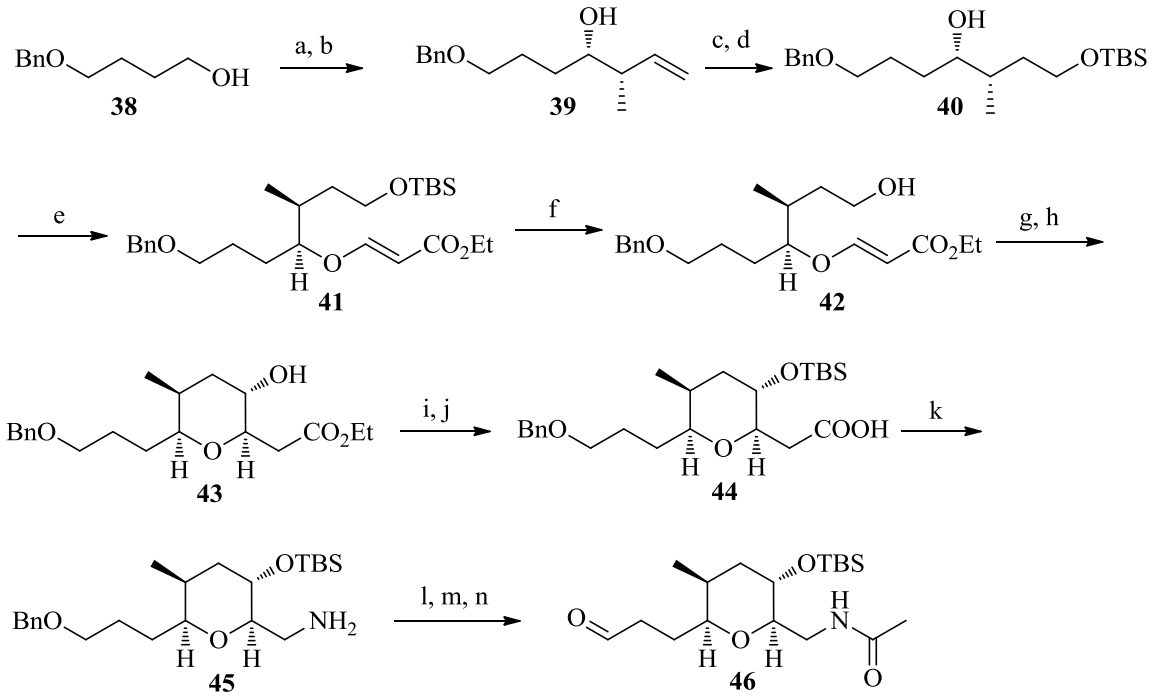


Scheme 7

2.2.2b. Synthesis:

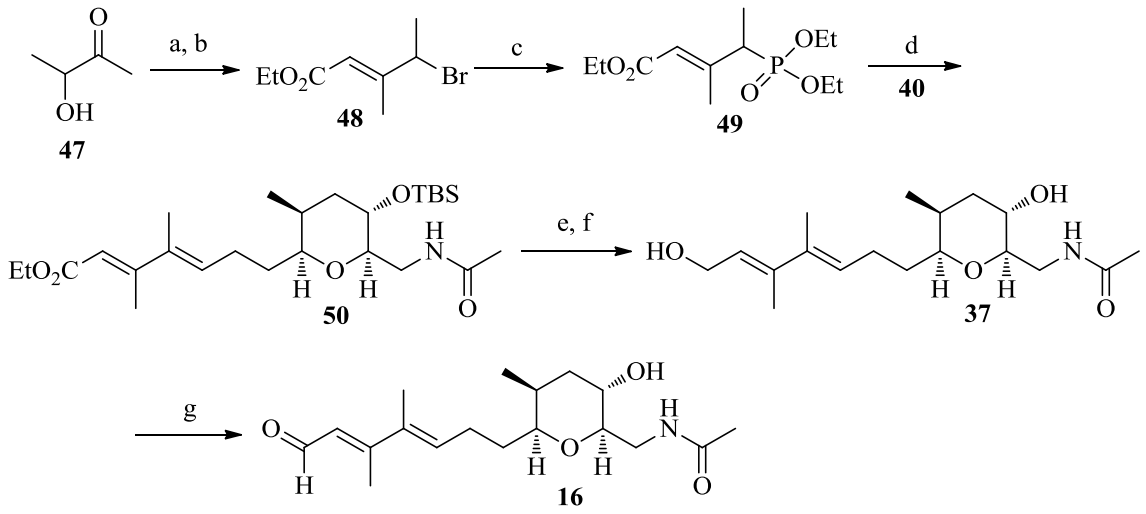
In this approach, monobenzyl protected-1,4-butane diol **38** was oxidized under Swern conditions and followed by Brown crotylation reaction to afford **39** as a single diastereomer in 87% ee. Hydroboration and chemoselective TBS protection of the primary alcohol provided **40**. 1,4-Addition of **40** using ethyl propiolate, NMM in CH_3CN gave the

key intermediate **41**. Removal of the TBS group using few drops of conc HCl in MeOH at 0 °C gave the alcohol **42** in good yield. Oxidation under Swern conditions followed by reductive cyclization using SmI_2 gave the pyran **43**. The secondary alcohol of **43** was protected as its TBS ether and ester was hydrolyzed using LiOH to furnish the acid **44**. Curtius rearrangement with DPPA gave amine **45** in good yield. Finally, an acetylation, benzyl deprotection, and oxidation with SO_3·Py afforded key fragment of pyran ring **46** (Scheme 8).



Scheme 8

Reagents and conditions: (a) DMSO, $(COCl)_2$, CH_2Cl_2, -78 ^oC, Et_3N; (b) (+)-*Z*-IpcB $CH_2CH{=}CHCH_3$, THF, -78 ^oC, 3N NaOH, 30% H_2O_2, 46.8% for 2 steps; (c) 9-BBN, THF then H_2O_2/NaOH; (d) TBDMSCl, imidazole, CH_2Cl_2 89% for 2 steps; (e) Ethyl propiolate, NMM, CH_3CN, 93%; (f) con HCl, MeOH, 0 ^oC; (g) DMSO, $(COCl)_2$, CH_2Cl_2, -78 ^oC, Et_3N; (h) SmI_2, MeOH, THF, 0 ^oC, 69% for 3 steps; (i) TBDMSCl, imidazole, CH_2Cl_2; (j) LiOH, THF-H_2O, 75 ^oC, 85% for 2 steps; (k) DPPA, Et_3N, toluene, 80 ^oC, 81%; (l) Ac_2O, pyridine, 85 ^oC; (m) H_2, Pd/C, MeOH; (n) SO_3.Py, Et_3N, DMSO, 81% for 3 steps.



Scheme 9

Reagents and conditions: (a) $Ph_3P{=}CHCO_2Et$, toluene reflux, over night, 96%; (b) CBr_4, PPh_3, imidazole, CH_2Cl_2, 90%; (c) $P(OEt)_3$, 140 ^oC, 92%; (d) *n*-BuLi, THF, -78 ^oC to rt then **40**, 80%; (e) DIBAL-H, -78 ^oC, CH_2Cl_2; (f) TBAF, THF, 0 ^oC to rt, 71% for 2 steps; (g) MnO_2, CH_2Cl_2, 74%.

Wittig reaction with 3-hydroxybutan-2-one **47**, C2-Wittig reaction and bromination with CBr_4, PPh_3 gave the secondary bromide **48**. An Arbuzov reaction with bromide **48** gave the phosphoate ester **49** in 90% yield (Scheme 9). The Horner-Wadsworth Emmons reaction between the fragments **46** and **49** afforded dienol moiety **50** in 78% (Scheme 9). DIBAL-H reduction of the ester followed by TBAF-mediated deprotection afforded compound **37**. Finally selective oxidation with MnO_2 gave brevisamide **16** in 74% yield.

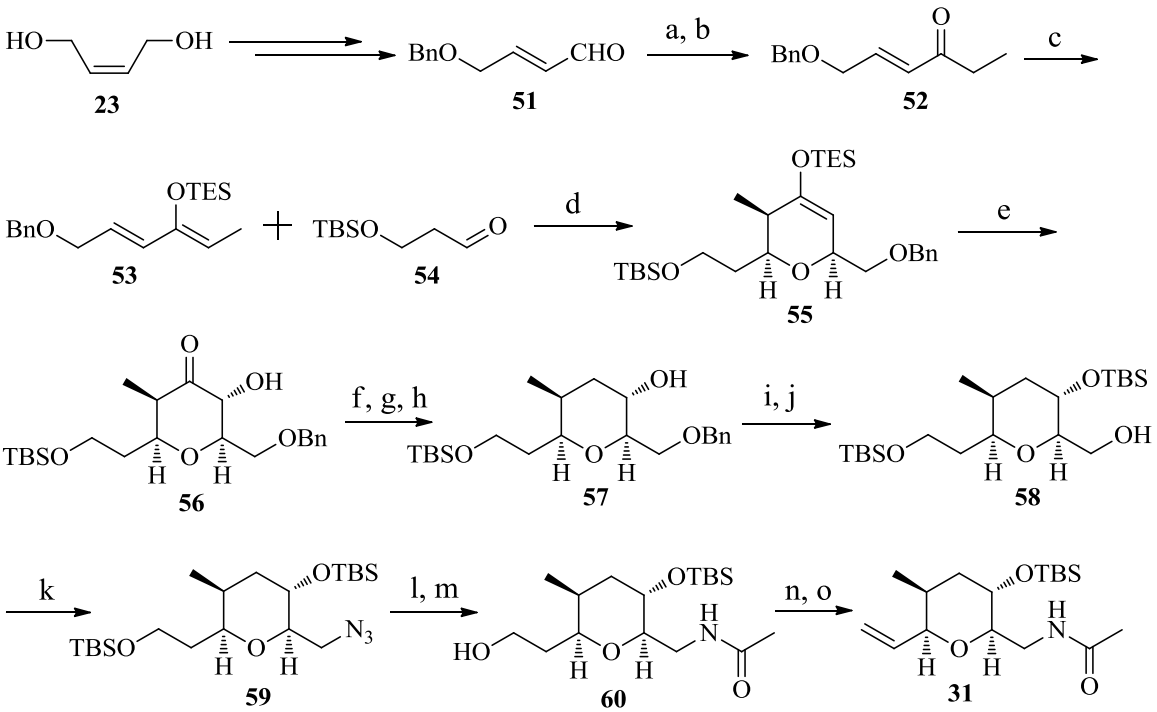
2.2.3. Arun k. Ghosh *et al*. approach:[32]

This approach utilized an enantioselective hetero-Diels-Alder reaction which sets three chiral centers. The synthesis also features a modified Wolff-Kishner reduction, Rubottom oxidation, and Suzuki-Miyaura coupling to furnish brevisamide.

2.2.3a. Synthesis:

According to the reported procedure staring with *cis* butene 1,4 diol **23,** which was benzylated and subjected to Swern oxidation to afford the aldehyde **51**. The aldehyde **51** was converted to enone **52** *via* addition of ethylmagnesium bromide and Swern oxidation.

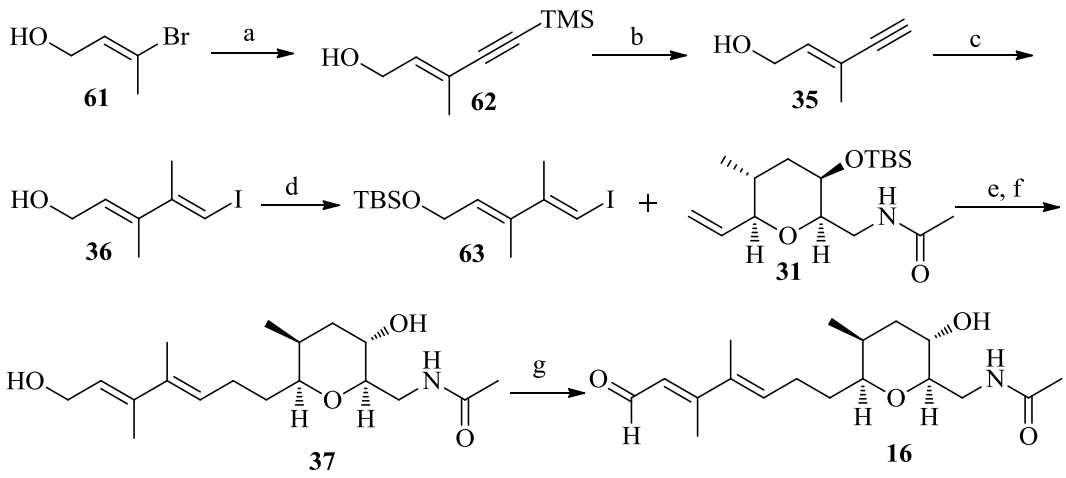
It was treated with TESOTf, Et_3N to afford the diene **53** in 84% yield (Scheme 10). Hetero-Diels-Alder reaction of diene **53** and aldehyde **54** with 10 mol% Jacobsen's chromium catalyst in the presence of 4Å MS at 23 °C for 7 days afforded the highly diastereoselective (dr:95%) cycloadduct **55** in 52% yield (Scheme 10). Rubottom oxidation of **55** using *m*-chloroperoxybenzoic acid solution in toluene in the presence of aqueous $NaHCO_3$ buffer at 0 °C gave **56** as a single isomer in 60% yield.



Scheme 10

Reagents and conditions: (a) EtMgBr, THF, 1 h, 90%; (b) DMSO, $(COCl)_2$, CH_2Cl_2, -78 ^oC, Et_3N, 93%; (c) TESOTf, Et_3N, -78 ^oC, 84%; (d) 10 mol % Jacobsen's chromium catalyst, 4Å ms, 23 ^oC, 7 days, 52%; (e) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 60%; (f) $TsNHNH_2$, EtOH, 3 h; (g) $NaBH_3CN$, EtOH, 0 ^oC, 15 min; (h) NaOAc, EtOH, 75 ^oC, 76% for 3 steps; (i) TBSOTf, Et_3N, CH_2Cl_2, 0 ^oC, 93%; (j) H_2, Pd/C, EtOH, 40 min, 88%; (k) PPh_3, DIAD, HN_3, CH_2Cl_2, 94%; (l) H_2, Pd/C, EtOH, 1 h, $NaHCO_3$, Ac_2O; (m) PPTS, EtOH, 24 h, 77%; (n) 2-NO_2PhSeCN, *n*-Bu_3P, 2 h; (o) Na_2HPO_4, *m*-CPBA, *i*-Pr_2NH, 12 h, 50% for 2 steps.

A modified Wolff-Kishner reduction protocol was utilized for the reduction of ketone **56**, which was first converted into its corresponding hydrazone using tosylhydrazine in ethanol. The hydrazone was reduced with $NaBH_3CN$ to provide the hydrazine. Treatment of this hydrazine with NaOAc in EtOH at 75 °C afforded deoxygenated product **57** in 76% yield (Scheme 10). Protection of the alcohol **57** as TBS ether followed by removal of the benzyl ether by hydrogenation with 10% Pd/C gave **58**. Mitsunobu reaction of **58** using hydrazoic acid afforded the azide **59** in 94% yield. Reduction of the azide by hydrogenation, acetylation and selective desilylation of the primary TBS-ether using a catalytic amount of pyridinium *p*-toluenesulfonate gave primary alcohol **60**. Using Grieco's protocol the alcohol **60** was treated with *o*-nitrophenylselenic cyanide and *n*-Bu_3P and followed by oxidation with *m*-CPBA to result in olefin **31**.



Scheme 11

Reagents and conditions: (a) TMSC≡CH, $Pd(Ph_3P)_4$, CuI, *i*-Pr_2EtN, DMF, 96%; (b) K_2CO_3, MeOH, 1 h, 77%; (c) Me_3Al, CH_2Cl_2, -78 ^oC to 0 ^oC, 2.5 h, Cp_2ZrCl_2, 23 ^oC, I_2, 39%; (d) TBDMSCl, imidazole, CH_2Cl_2, 0 ^oC to rt, 3.5 h, 87%; (e) 9-BBN, Cs_2CO_3, I_2, **3**, $PdCl_2(dppf)\cdot CH_2Cl_2$, THF; (f) TBAF, THF, 0 ^oC to rt, 3 h, 40% for 2 steps; (g) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, 2 h, 87%.

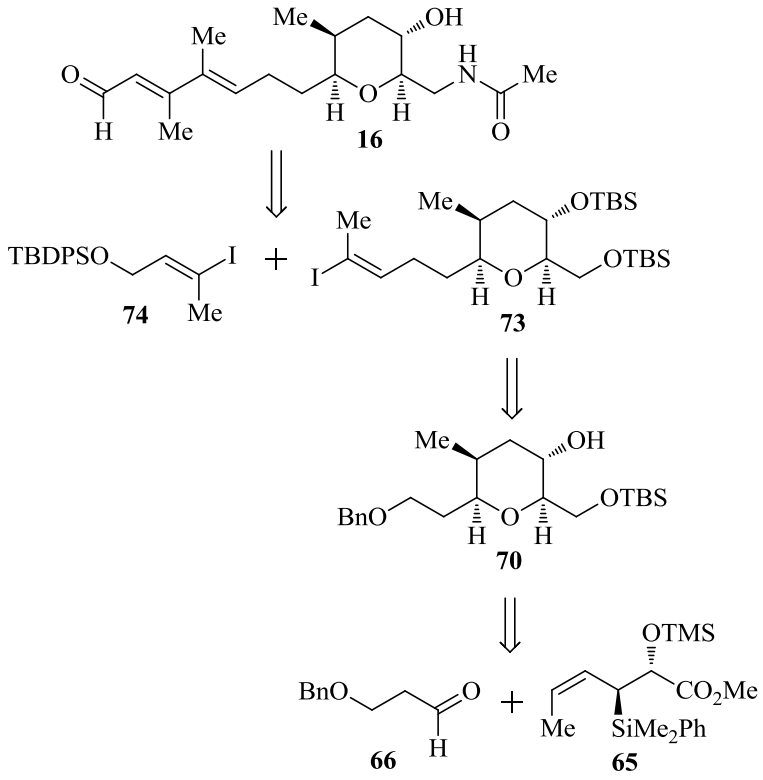
The *E*-bromocrotyl alcohol **61** was treated with trimethylsilylacetylene in the presence of diisopropylethylamine, $Pd(PPh_3)_4$ and CuI to provide enyne derivative **62** in

96% yield (Scheme 11). Desilylation of **62** using K_2CO_3 in methanol afforded alkynol **35**. It was treated with trimethylaluminum, dichlorozirconocene and elemental iodine to provide the desired diene **36** in 39% yield. Treatment of **36** with TBSCl and imidazole furnished silyl ether **63**. Connection of fragments **63** and **31** was done by Suzuki-Miyaura cross-coupling using 9-BBN, aqueous Cs_2CO_3 and $PdCl_2$(dppf). This crude product was treated with TBAF at 0 °C to give dienol **37** in 40% yield. Finally, selective oxidation of the allylic alcohol in **37** was carried out using TEMPO in the presence of $PhI(OAc)_2$ in CH_2Cl_2 at 23 °C to provide Brevisamide (**16**) in 87% yield (Scheme 11).

2.2.4. James S. Panek *et al*. approach:[33]

In this approach synthesis of Brevisamide (**16**) is described based on the application of the crotyl silane-based [4 + 2]-annulation used for the preparation of the advanced oxygenated tetrahydropyran intermediate. The side chain bearing a conjugated (*E*,*E*)-diene was efficiently constructed under modified Negishi cross-coupling conditions.

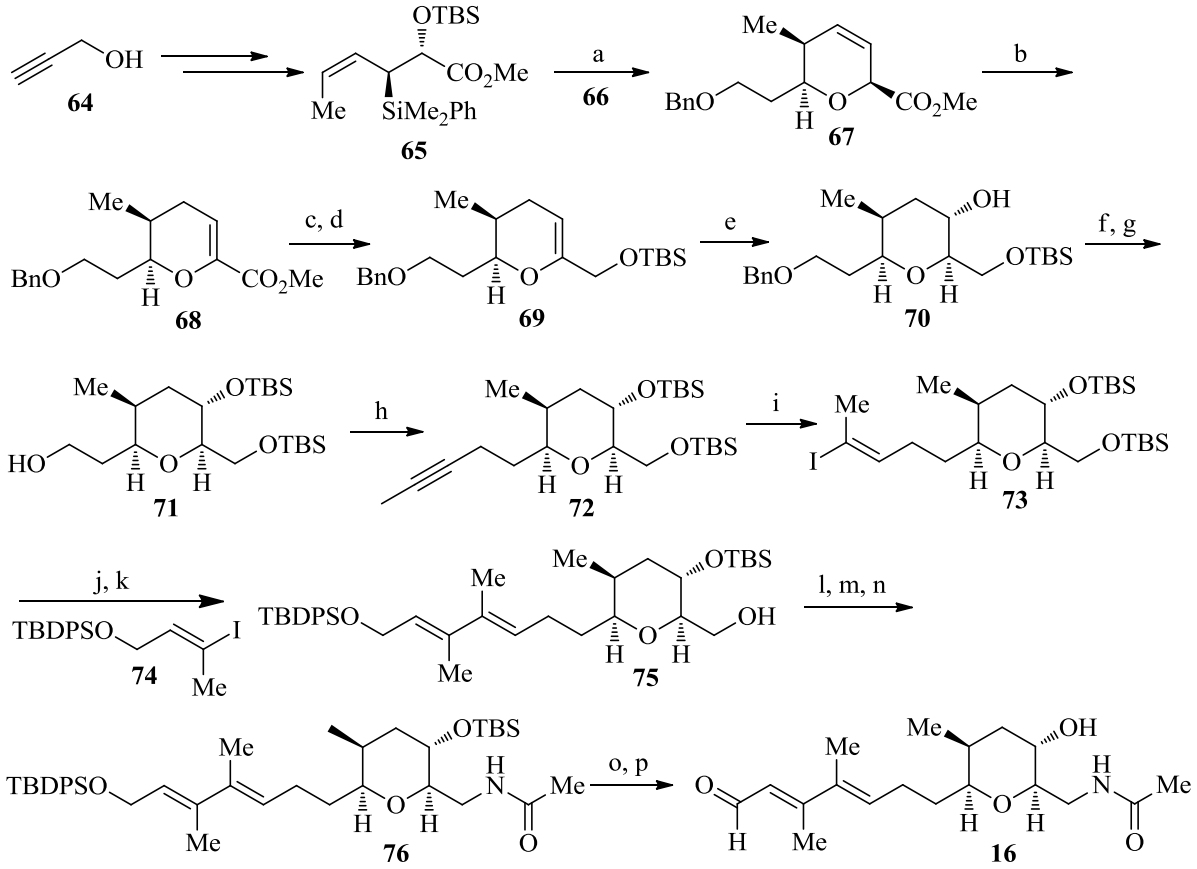
2.2.4a. Retrosynthesis:



Scheme 12

2.2.4b. Synthesis:

According to literature procedure, (*Z*)- crotylsilane **65** was prepared from 2-propyne-1-ol **64**. [4 + 2]-annulation of crotylsilane **65** with aldehyde **66** afforded dihydropyran **67** in 70% yield (Scheme 13). Isomerization of the olefin **67** using DBU in THF in 12h gave the conjugated ester **68** in 86% yield. Reduction of methyl ester **68** using $LiAlH_4$ in Et_2O followed by protection of the resulting allylic alcohol as its TBS ether gave a precursor **69**. Subsequently, hydroboration using $BH_3{\cdot}SMe_2$ at 0 °C afforded the desired oxygenated tetrahydropyran **70** in 90% yield, with high diastereoselectivity (90%, dr >11:1). Alcohol intermediate **70** was protected as its TBS ether, and hydrogenolysis of benzyl ether using Pd/C in EtOAc afforded primary alcohol **71** in high yield. S_N2-type alkyne substitution was employed. Triflation of primary alcohol **71** using Tf_2O, 2,6-lutidine in THF at -78 ^oC gave an unstable intermediate triflate ester that was used without purification.



Scheme 13

Reagents and conditions: (a) TMSOTf, CH_2Cl_2, C_6H_6, -50 ^oC, 70%; (b) DBU, THF, rt, 86%; (c) $LiAlH_4$, Et_2O, 0 ^oC; (d) TBDMSCl, imidazole, DMF, rt, 84% for 2 steps; (e) $BH_3{\cdot}SMe_2$, THF, 0 ^oC to rt, 30% H_2O_2, 1N NaOH, 90%; (f) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 ^oC, 98%; (g) H_2, Pd/C, EtOAc, rt; (h) Tf_2O, 2,6-lutidine, CH_2Cl_2, -78 ^oC, 1-propynyllithium, THF, -78 ^oC, to rt, 78% for 2 steps; (i) Cp_2ZrHCl, THF, 50 ^oC, I_2, 88%; (j) *t*-BuLi, $ZnCl_2$, THF, -78 ^oC, to 0 ^oC, $Pd(PPh_3)_4$; (k) CSA, MeOH, CH_2Cl_2, 58% for 2 steps; (l) DIAD, PPh_3, DPPA, THF, 80%; (m) PPh_3, NH_4OH, Dioxane/MeOH, rt; (n) Ac_2O, DMAP, TEA, CH_2Cl_2, rt, 83%; (o) TBAF, THF, 0 ^oC to rt, 83%; (p) MnO_2, CH_2Cl_2, rt, 66%.

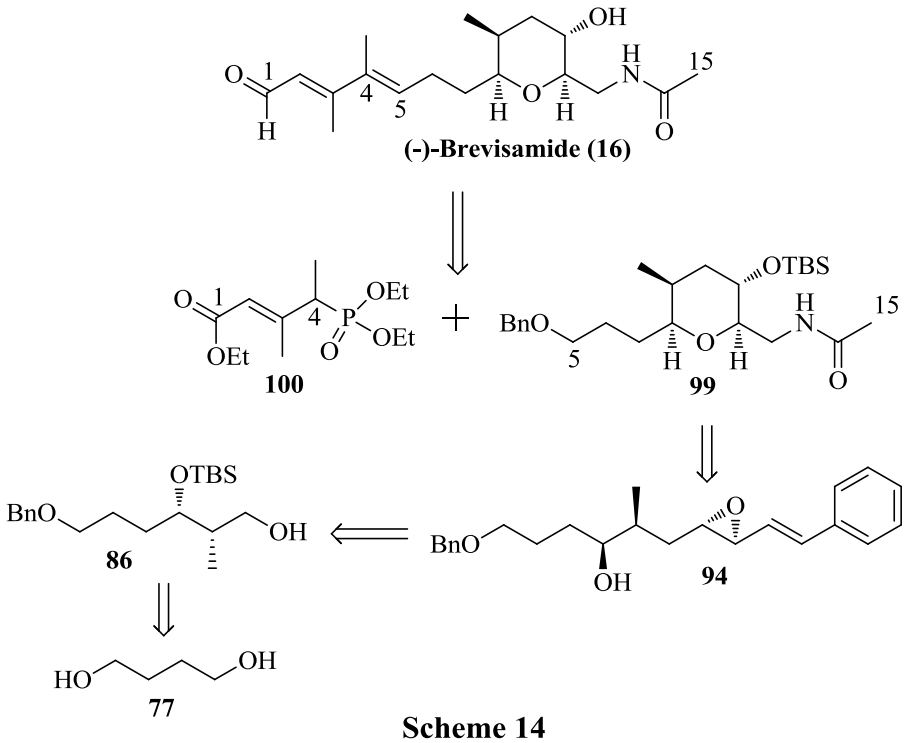
The triflate ester was treated with 5 equiv of propynyllithium in THF for 3 h, affording the alkyne **72** in 78% yield over two steps (Scheme 13). Regioselective hydrozirconation of the internal alkyne **72** using 2 equiv of Schwartz reagent in THF, I_2 furnished the coupling precursor (*E*)-iodoalkene **73** in 88% yield (*E*/*Z* = 10:1). Coupling between two different (*E*)-vinyl iodide fragments **73** and **74** was accomplished using *t*-BuLi, $ZnCl_2$ and $Pd(PPh_3)_4$ in THF under modified Negishi coupling conditions and the selective cleavage of primary TBS ether using CSA afforded (*E*,*E*)-diene **75** in 58% as a single regioisomer (Scheme 13).

The primary alcohol **75** was converted to azide using diphenylphosphoryl azide (DPPA) under Mitsunobu conditions. Reduction of the azide in the presence of NH_4OH followed by acetylation of the primary amine gave the acetyl amide **76** in 83% yield. Deprotection of the two silyl ethers using TBAF gave a diol intermediate, and chemoselective oxidation of the primary allylic alcohol in the presence of the secondary alcohol using excess amount of MnO_2 afforded Brevisamide (**16**) (Scheme 13).

2.3. Present Work:

In continuation of our interests in the synthesis of biologically active oxygen containing natural products,[34] herein we report the synthesis of (-)-Brevisamide (**16**). The tetrahydropyran ring is an important structural feature of a good number of natural products. We initiated a program on the formal total synthesis of (–)-Brevisamide (**16**). Brevisamide was isolated from a marine *Kerenia brevis* (Red tide dinoflagellate) a species well known to produce various cyclic polyether toxins such as the Brevetoxins A (**1**), B (**2**), Ciguatoxins (**7**) and Maitotoxin (**13**). The key features of this synthetic approach are the *syn*-aldol reaction, Sharpless asymmetric epoxidation and stereoselective construction of tetrahydropyran moiety via 6-*endo*-cyclization of hydroxy-styrylepoxide.

2.3.1. Retrosynthesis Brevisamide:



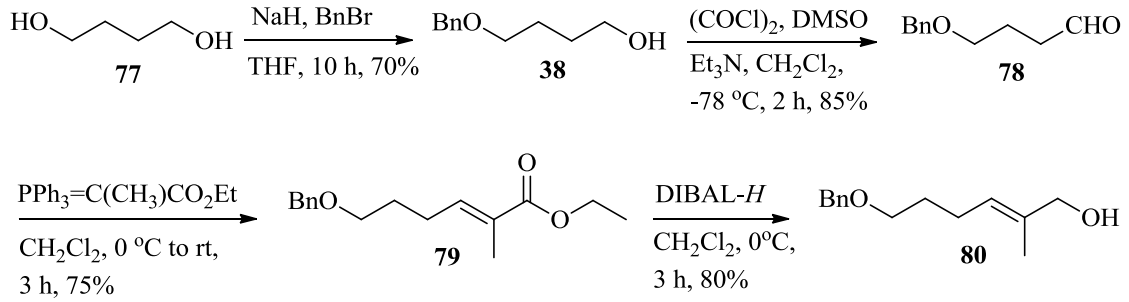
Scheme 14

The retro synthetic analysis of (–)-Brevisamide (**16**) is depicted in Scheme 14. (–)-Brevisamide (**16**) could be readily synthesized using Horner-Wadsworth-Emmons (HWE) reaction between two coupling partners of C1-C4 side chain **100** and C5-C15 tetrahydropyran derived fragments **99** (by the use of corresponding C5 aldehyde

intermediate). Tetrahydropyran derived segment (C5-C15 fragment) **99** would be achieved *via* base induced 6-*endo*-cyclization of hydroxy styrylepoxide **94**, which can be in turn prepared from commercially available 1,4-butanediol **77** via *syn*-stereo-diad **86** employing *syn*-aldol reaction, Sharpless asymmetric epoxidation and Wittig olefination as key transformations.

2.3.2. Results and Discussions:

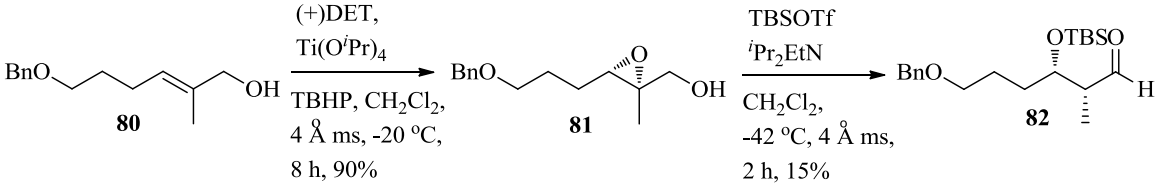
Our synthesis of (–)-Brevisamide (**16**) began from the commercially available 1,4-butanediol **77**, which on treatment with NaH, BnBr in THF resulted in mono-benzyl ether **38** in 70% (Scheme 15). ^{1}H NMR spectrum of compound **38** showed a characteristic signal resonating as singlet at δ 4.52 ppm for benzylic protons and multiplet protons at δ 7.38-7.24 ppm for aromatic attached protons. The compound **38** was also confirmed by ESIMS with $(M + Na)^+$ peak at *m/z* 203. The hydroxyl group of **38** was oxidized under Swern conditions to afford the aldehyde **78** in 85%. This was clearly conveyed in the ^{1}H NMR spectrum by the resonance as a singlet at δ 9.79 ppm indicating that alcohol was converted into aldehyde (Scheme 15). The other protons of the compound resonated at their respected chemical shift values. The compound **78** was also characterized by ESIMS with $(M + Na)^+$ peak at *m/z* 201, and a characteristic peak at 1720 cm^{-1} in IR spectrum.



Scheme 15

Aldehyde **78** on treatment with the C3-Wittig ylide (ethyl-2-(triphenyl phosphoranylidene) propanoate) in CH_2Cl_2 gave exclusively the *E*-isomer of unsaturated ester **79** in 75% yield[35]. The ester **79** was confirmed by its ^{1}H NMR spectrum which showed triplet of olefinic proton at δ 6.71 (J = 7.55 Hz), singlet of 3 protons (CH_3) at δ 1.82 showed the presence of allylic-methyl group, the 2H quartet at δ 4.16 (J = 6.79 Hz),

3H triplet at δ 1.28 (J = 6.79) observed, which was characteristic of ethyl ester functionality, and the other protons resonated at the expected chemical shift values. IR spectrum showed absorption at 1710 cm^{-1} due to stretching of ester carbonyl (Scheme 15). The ester group **79** was reduced by using DIBAL-*H* in CH_2Cl_2 at 0 ^oC to furnish the allylic alcohol **80** in 80% yield (Scheme 15).[36] The formation of allylic alcohol **80** was confirmed by ^1H NMR spectrum in which a allylic oxygen attached protons appeared at δ 3.86 (s, 2H), allylic protons appeared at δ 3.41 (t, J = 5.95 Hz, 2H) and olefinic proton appeared at δ 5.33 (t, J = 7.93 Hz, 1H). This allylic alcohol **80** was also confirmed by HRMS analysis which showed peak at *m/z* 243.1639 $[M + Na]^+$ and absorption peak at 3421cm^{-1} in IR spectrum. The allyl alcohol **80** was subjected to Sharpless asymmetric epoxidation[37] by using L-(+)-diethyltartarate, *t*-butylhydrogenperoxide (TBHP), and titanium-tetraisopropxide ($Ti(O^iPr)_4$) in CH_2Cl_2 at –20 °C to afford the epoxy alcohol **81** in 90% yield. The ^{1}HNMR spectrum of compound **81** revealed the disappearance of olefinic hydrogen, appearance of proton at δ 2.99 (t, J = 6.0 Hz, 1H) showed the presence of epoxy group, and methyl protons appeared at δ 1.26 (s, 3H). Compound **81** was also characterized and confirmed by its ^{13}C NMR, IR, and HRMS analysis (Scheme 16).

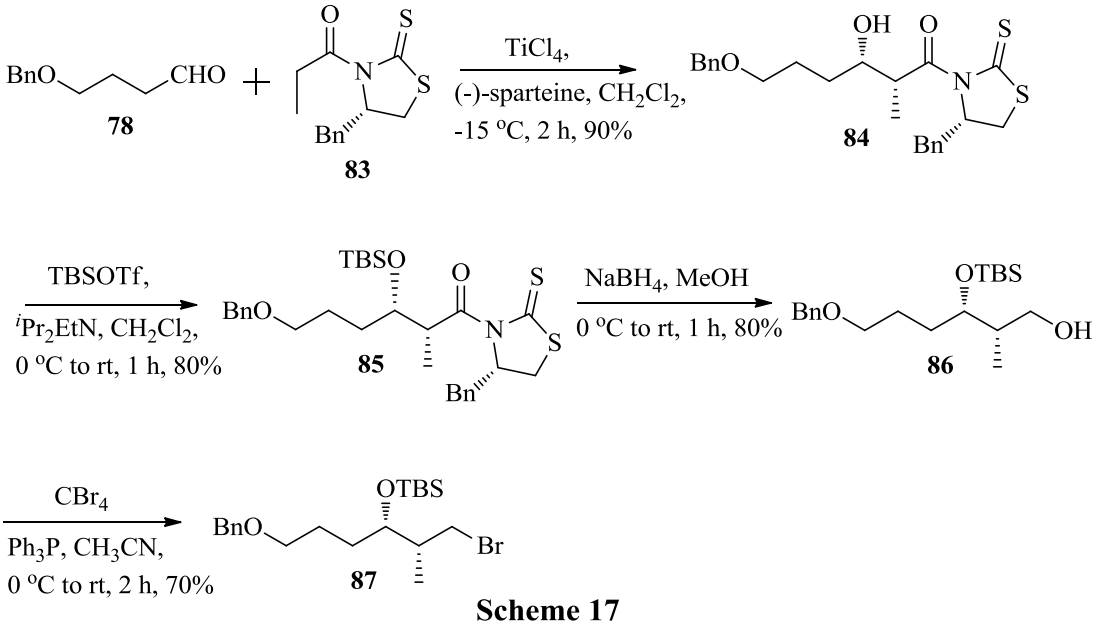


Scheme 16

The epoxyalcohol **81** on treatment with *tert*-butyldimethylsilyl triflate (TBSOTf) and diisopropylethylamine (DIPEA) in dichloromethane at –42 ^oC gave the (M. E. Jung's protocol)[38] TBS protected *syn*-aldol product **82**. Unfortunately here we have ended up with poor yield of 15%, which could be due to the interference of C6-OBn functional group as judged by the reported literature (Scheme 16).[39] The structure assigned to compound **82** was confirmed by its ^1H NMR spectrum. It showed aldehyde proton at δ 9.39 (s, 1H), methyl at δ 0.91 (d, J = 2.07 Hz, 3H) and TBDMS ether protons appeared at

δ 0.87 (s, 9H), 0.07 (s, 6H). Absorption peak at 1718 cm^{-1} in IR and peak at *m/z* 373(M + $Na)^+$ in ESIMS spectrum confirmed this transformation.

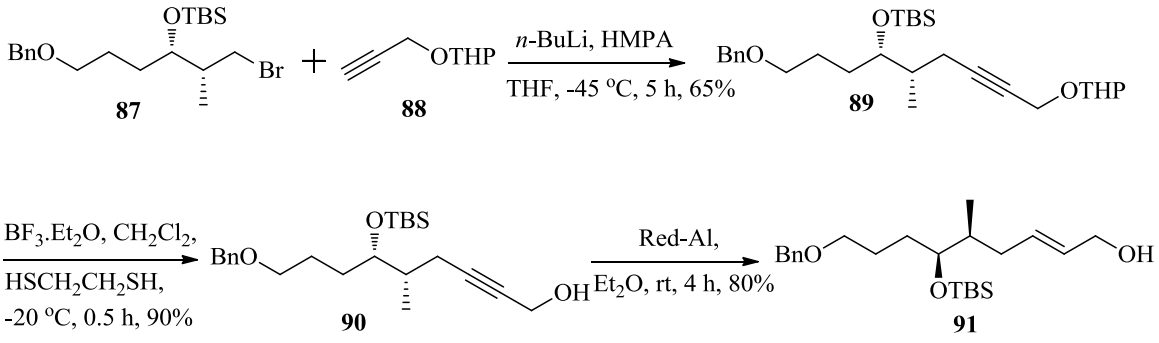
Unsatisfying with the above result, we adopted well precedented asymmetric Aldol addition reaction of thiazolidinethione propionate **83** to the benzyloxybutanal **78** using $TiCl_4$ and (–)-sparteine in CH_2Cl_2 to give the alcohol **84** in 90% yield (Scheme 17). ^1H NMR spectrum of compound **84** showed the presence of aromatic protons at δ 7.37-7.15 (m, 10H), oxygen attached (HO-C**H**) proton at δ 4.65 (dq, *J* = 2.74, 6.56 Hz, 1H) and all protons resonated at their expected values. The ^{13}C NMR spectrum showed peak at δ 201 ppm corresponding to keto functionality. Broad absorption peak at 3446 cm^{-1} in IR spectrum confirm the hydroxy functionality and ESI-HRMS spectrum showed peak at *m/z* 466.1500 $(M + Na)^+$ confirmed this conversion.



Scheme 17

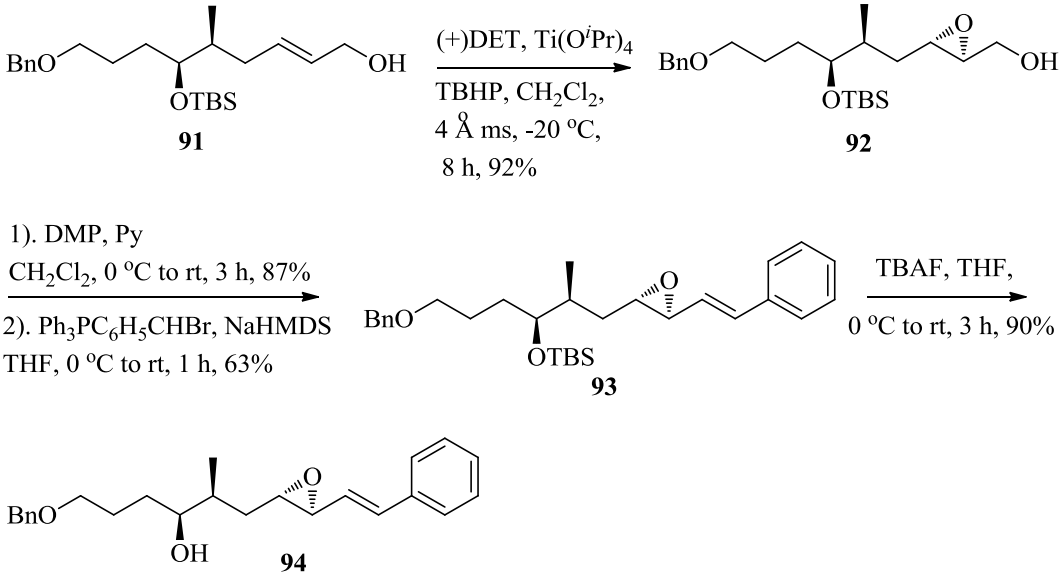
The alcohol **84** was protected as its TBS-ether **85** using TBSOTf and $^iPr_2EtN$ in dry CH_2Cl_2 in 80% yield (Scheme 17). The structure was confirmed by the appearance of signals at δ 0.89 (s, 9H) and *δ* 0.06 (d, *J* = 3.88 Hz, 6H) ppm in ^1H NMR spectrum. This was further confirmed by ^{13}C NMR spectrum, which showed all the representative peaks for aliphatic, aromatic and silyl carbons. Its ESI-HRMS spectrum, which showed peak at *m/z* 580.2362 $[M + Na]^+$ confirmed the TBS protection. Compound **85** on reduction with $NaBH_4$ in MeOH at 0 °C gave the primary alcohol **86** in 80% yield (Scheme 4).[40]

Aromatic proton signals at δ 7.31-7.13 (m, 5H) and benzylic protons signals at δ 4.19-4.13 (m, 1H), 3.46-3.37 (m, 1H) disappeared and all protons appeared at their expected chemical shift values. Broad absorption peak at 3449 cm^{-1} in IR spectrum confirm the hydroxy functionality. ESI-HRMS spectrum showed peak at *m/z* 375.2237 $(M + Na)^+$ which confirms this conversion. Hydroxy compound **86** on treatment with TPP, CBr_4 in CH_3CN afforded bromo compound **87** in 70% yield (Scheme 17).[41] ^1H NMR showed proton signals at δ 3.50 (dd, *J* = 6.04, 9.82 Hz, 1H), and δ 3.24 (dd, *J* = 7.55, 9.82 Hz, 1H) with decreasing chemical shift values, which could be corresponding to bromo attached protons (Br-C**H_2**). ^{13}C NMR spectrum showed all the carbons with expected chemical shift values. ESI-HRMS spectrum showed peak at *m/z* 437.1470 $(M + Na)^+$, which was further confirmed this conversion. Bromo compound **87** was coupled with 2-(prop-2-yn-1-yloxy)tetrahydro-2H-pyran **88** in the presence of *n*-BuLi, HMPA in THF at -45 ^oC to afford the compound **89** in 65% yield (Scheme 18). The formation of compound **89** was confirmed by its ^1H NMR spectrum analysis, which showed methylenic proton at δ 4.75 (t, *J* = 3.02 Hz, 1H) and showed all expected chemical shift values. ESIMS showed peak at 475 $(M + H)^+$ to confirm this conversion. Selective deprotection of THP-ether using Borontrifluoride diethyl etherate ($BF_3.Et_2O$), ethanedithiol ($HSCH_2CH_2SH$) in CH_2Cl_2 at –20 ^oC gave the compound **90** in 90% (Scheme 18). In ^1H NMR spectrum THP ether protons disappeared and ^{13}C NMR spectrum showed expected chemical shift values. Broad absorption peak at 3423 cm^{-1} was seen in IR. ESI-HRMS spectrum showed peak at *m/z* 391.2662 $(M + H)^+$, which confirm the formation of compound **90**.



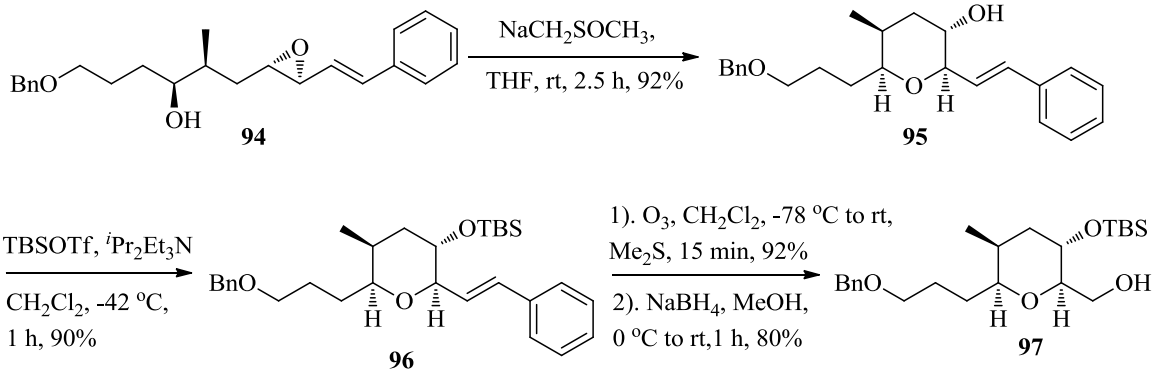
Scheme 18

Compound **90** was treated with Red-Al in Et_2O to afford the allyl alcohol **91** in good yield (Scheme 18).[42] The ^1H NMR spectrum of compound **91** revealed the appearance of the olefinic protons resonance at δ 5.66-5.57 (m, 2H). In IR spectrum absorption peak at 3438 cm^{-1} confirmed the hydroxyl group. ESI-HRMS spectrum showed peak at *m/z* 415.26557 $(M + Na)^+$, the above spectral analysis conformed this conversion. Asymmetric epoxidation[37] of allylic alcohol **91** with L-(+)-DET, $Ti(O^iPr)_4$ and TBHP in dry CH_2Cl_2 at –20 °C gave the epoxy alcohol **92** in 92% yield (Scheme 19). The formation of **92** was confirmed by disappearance of signal for olefinic protons between δ 5.66-5.57 (m, 2H) ppm and appearance of two epoxy protons resonating at δ 2.98-2.90 (m, 1H), 2.28-2.13 (m, 1H) ppm in ^1H NMR spectrum. Its ESI-HRMS spectrum, which showed peak at *m/z* 503.29482 $[M + Na]^+$ provided aditional proof for this conversion. The epoxy alcohol **92** was oxidized[43] using Dess-Martin periodinane, pyridine in CH_2Cl_2 and followed by Wittig olefination[44] using benzyltriphenylphosphonium bromide, NaHMDS in THF to give the styrylepoxide **93** in good yield with 9:1 of *E*/*Z* ratio (Scheme 19). The appearance of signals of the two olefinic protons resonance at δ 6.73 (d, *J* = 12.08 Hz, 1H), 5.96-5.84 (m, 1H) and aromatic protons resonance at δ 7.41-7.17(m, 5H) in ^1H NMR spectrum confirmed the formation of *trans*-olefin. ESI-HRMS spectrum showed peak at *m/z* 503.29482 $(M + Na)^+$, which further confirmed the formation of compound **93**.



Scheme 19

The deprotection of silyl group of compound **93** using TBAF in THF at 0 ^{o}C afforded corresponding alcohol **94** in 90% yield (Scheme 19). The compound **94** was confirmed by its ^{1}H NMR spectrum which showed disappearance of signals at δ 0.89 (s, 9H), 0.05 (s, 6H). The compound **94** was also characterized by its ESI-HRMS data, which showed peak at *m/z* 389.20753 $[M + Na]^{+}$ and absorption peak at 3415 cm^{-1} in IR spectrum. The styryl epoxide **94** was treated with NaH, DMSO in THF at room temperature to afford the product **95** of 6-*endo*-cyclization[45] in 92% yield (Scheme 20). ^{1}H NMR revealed the disappearance of epoxy protons resonance at δ 2.98-2.92 (m, 1H), 2.27-2.13 (m, 1H), appeared signals resonated at δ 4.26-4.18 (m, 1H), 3.71-3.64 (m, 1H) ppm and methyl protons resonance at δ 0.88 (d, *J* = 7.90 Hz, 3H). In ^{13}C NMR, all carbons expected at their chemical shifts values. The compound **95** was also characterized by ESI-HRMS analysis, which showed peak at *m/z* 389.20764 $(M + Na)^{+}$. The alcohol **95** was protected as its TBS-ether **96** using TBSOTf and $^{i}Pr_2EtN$ in dry CH_2Cl_2 in 90% yield (Scheme 20). The structure was confirmed by the appearance of signals resonating at δ 0.82 (s, 9H), 0.06 (s, 6H) ppm in ^{1}H NMR spectrum. This was further confirmed by ^{13}C NMR spectrum, which showed all the representative peaks for aliphatic, aromatic and silyl carbons. Its ESI-HRMS spectrum showed peak at *m/z* 503.29468 $[M + Na]^{+}$ which further confirmed the TBS protection.

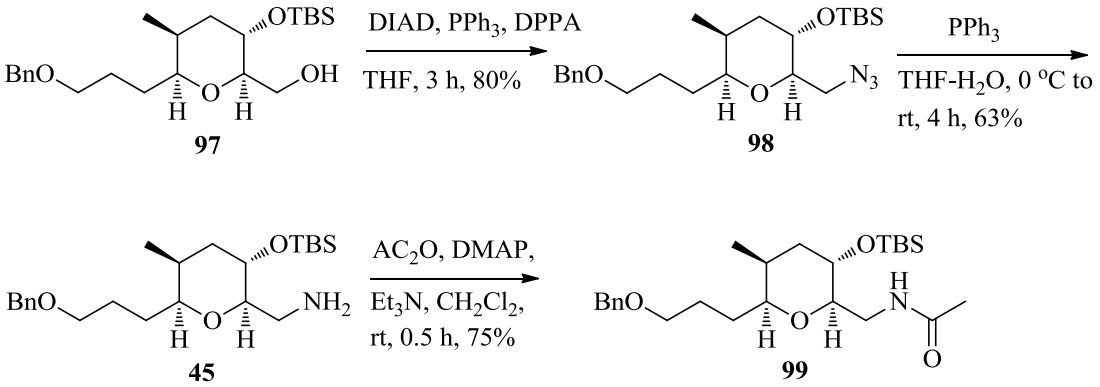


Scheme 20

A one-pot ozonolysis[44,46] of olefin **96** in CH_2Cl_2 at −78 ^{o}C followed by reduction with $NaBH_4$ in MeOH gave the primary alcohol **97** in good yield (Scheme 20). The

formation of **97** was confirmed by disappearance of signal for olefinic protons at δ 6.72 (d, *J* = 11.70 Hz, 1H), 5.68-5.49 (m, 1H) and five aromatic protons at δ 7.49-7.19(m, 5H) ppm in ^{1}H NMR spectrum. ^{13}C NMR showed all the carbons at their expected chemical shift values. In IR spectrum absorption peak at 3455 cm^{-1} conform the hydroxyl group. ESI-HRMS spectrum showed peak at *m/z* 431.25894 $(M + Na)^{+}$. The above spectral analysis confirmed this conversion.

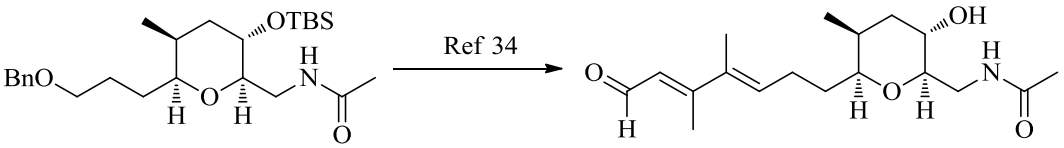
The alcohol **97** was treated with DIAD, TPP, DPPA in THF to afford the azide **98** in 80% yield (Scheme 21). ^{1}H NMR revealed the disappearance of hydroxyl attached protons resonance at δ 3.96-3.38 (m, 2H) and new signals appearance at δ 1.94-1.73 (m, 2H) ppm. In ^{13}C NMR all carbons appeared at expected chemical shifts values. IR absorption peak at 2169 cm^{-1} clearly indicated the installation of azide group.



Scheme 21

ESI-HRMS showed peak at *m/z* 456.2663 $[M + Na]^{+}$ which confirmed the formation of azide **98**. The azide **98** was treated with TPP, THF-H_2O to give the amine **45** in 63% yield (Scheme 21).[33] ^{1}H NMR revealed the primary amine attached protons (NH_2-C**H_2**) shifted to upfield at δ 1.86-1.72 (m, 2H). IR spectrum showed disappearance of azide absorption at 2169 cm^{-1} and peak at *m/z* 430.2752 $[M + Na]^{+}$ in its ESI-HRMS spectrum conformed this transformation. The primary amine **45** acylation[33] with Ac_2O, TEA and DMAP in CH_2Cl_2 gave the target C1-C15 fragment **99** of (–)-Brevisamide (**16**) 75% yield (Scheme 21). The ^{1}H NMR spectrum of compound **99** revealed the appearance of the methyl protons resonance at δ 1.97 (s, 3H) ppm. ^{13}C NMR showed carbonyl carbon

at δ 169.5 and all other carbons at their expected chemical shift values. IR absorption peak at 1762 cm^{-1} clearly indicated the installation of keto functional group. ESI-HRMS spectrum showed peak at *m/z* 472.28795 $(M + Na)^+$, the above spectral analysis rigorously conformed this conversion. The spectral data and optical rotation values of this intermediate **99** (C1-C15 fragment) were in agreement with known compound reported in literature.[31]



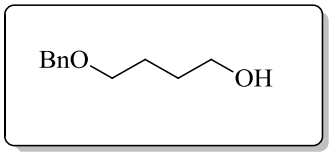
Scheme 22

In conclusion, we have accomplished the novel formal synthesis of (–)-brevisamide by constructing the advanced tetra substituted-tetrahydropyran core unit (C1-C15 fragment). *syn*-Aldol reaction, Sharpless asymmetric epoxidation and base induced 6-*endo*-cyclization of hydroxystyrylepoxide are used as key transformations in this synthetic strategy.

Experimental Section

2.4. EXPERIMENTAL SECTION

2.4.1. 4-(Benzyloxy)butan-1-ol (38):



To a stirred suspension of 60% dispersion of NaH in mineral oil (6.93 g, 289 mmol) in THF (300 mL) was added a solution of 1, 4-butanediol **77** (13.0 g, 144.5 mmol) in dry THF (50 mL) drop wise over a period of 15 min at 0 ^{o}C and the reaction mixture was stirred at room temperature for 2 h. Then benzyl bromide (17.6 mL, 144.5 mmol) was added at 0 °C over a period of 15 min followed by addition of TBAI (1.512 mg, 14.45 mmol) and the reaction mixture was stirred at room temperature for additional 12 h. The reaction mixture was quenched with cold water and THF was removed *in vacuo*. The crude mixture was extracted with EtOAc (3 x 100 mL) and the organic layer was washed with brine and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexanes, 2:8) to afford the alcohol **38** (18.0 g, 70 %) as a colorless liquid.

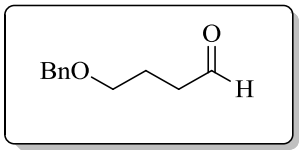
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.38-7.24 (m, 5H), 4.52 (s, 2H), 3.62 (t, *J* = 5.28 Hz, 2H), 3.51 (t, *J* = 6.04 Hz, 2H), 2.61-2.39 (brs, 1H), 1.76-1.60 (m, 4H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 137.8, 128.0, 127.3, 127.2, 72.5, 69.9, 61.8, 29.3, 26.0 ppm.

IR (neat): 3397, 2940, 2864, 1451, 1363, 1276, 1206, 1101, 1065, 956, 739, 700, 611 cm^{-1}.

ESI-MS: *m/z* 203 $(M + Na)^{+}$.

2.4.2. 4-(Benzyloxy)butanal (78):



To a solution of oxalyl chloride (17.25 mL, 198.25 mmol) in CH_2Cl_2 (200 mL) at –78 °C was added DMSO (28.6 mL, 396.5 mmol) and the resultant solution stirred at the same temperature for 30 min. To it was added the solution of alcohol **38** (17.84 g, 99.12 mmol) in CH_2Cl_2 (50 mL) dropwise at –78 °C and resulting cloudy white mixture was stirred for 1 h and was treated with triethylamine (83.0 mL, 594.73 mmol) and stirred for 30 min at the same temperature. The reaction mixture was warmed to 0 °C for 40 min then warmed to room temperature for 20 min and quenched with saturated $NaHCO_3$ (100 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 100 mL), the combined organic layers were dried over Na_2SO_4, and concentrated. Purification by silica gel column chromatography (EtOAc/hexanes, 5:95) afforded aldehyde **78** (15.0 g, 85%) as a oily yellow liquid.

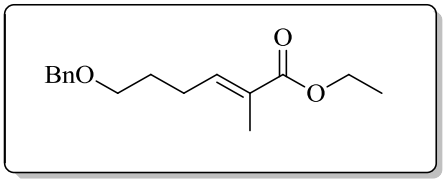
^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.79 (s, 1H), 7.39-7.25 (m, 5H), 4.50 (s, 2H), 3.51 (t, *J* = 6.04 Hz, 2H), 2.55 (t, *J* = 7.55 Hz, 2H), 2.0-1.90 (m, 2H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 202.0, 138.2, 128.0, 127.3, 127.2, 72.5, 68.8, 40.5, 22.2 ppm.

IR (neat): 2931, 2862, 1720, 1511, 1412, 1365, 1260, 1100, 1030, 740, 699, 600 cm^{-1}.

ESI-MS: *m/z* 201 $(M + Na)^+$.

2.4.3. (*E*)-Ethyl 6-(benzyloxy)-2-methylhex-2-enoate (79):



To a stirred solution of ethyl-2-(triphenyl phosphoranylidene) propanoate (48.86 g, 13.46 mmol) in CH_2Cl_2 (50 mL) was added aldehyde **78** (2.08 g, 11.22 mmol) at 0 °C and stirred at rt. The reaction was slightly exothermic and in one hour the reaction was completed. The solvent was removed under atmospheric pressure and the residue was purified by silica gel column chromatography (EtOAc/hexanes, 5:95) to afford the ester **79** (2.30 g, 75%) as a colourless oil.

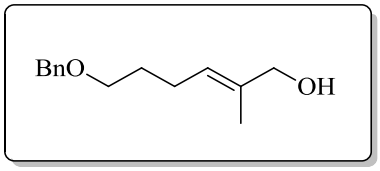
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.34-7.19 (m, 5H), 6.71 (t, *J* = 7.55 Hz, 1H), 4.46 (s, 2H), 4.16 (q, *J* = 6.79, 14.35 Hz, 2H), 3.45 (t, *J* = 6.04 Hz, 2H), 2.28 (q, *J* = 7.55, 14.35 Hz, 2H), 1.82 (s, 3H), 1.74 (t, *J* = 7.55 Hz, 2H), 1.28 (t, *J* = 6.79 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.1, 141.3, 138.4, 128.3, 128.2, 127.5, 127.4, 72.9, 69.4, 60.3, 28.6, 25.3, 14.2, 12.2 ppm.

IR (neat): 2932, 2860, 1710, 1648, 1451, 1366, 1266, 1096, 1028, 742, 699, 538 cm^{-1}.

ESI-HRMS: calcd for $C_{16}H_{22}O_3Na$ $(M + Na)^+$ 285.1466, found 285.1476.

2.4.4. (*E*)-6-(Benzyloxy)-2-methylhex-2-en-1-ol (80):



To a stirred solution of unsaturated ester **79** (2.23 g, 8.51mmol) in CH_2Cl_2 (20 mL) at 0 ^oC was added slowly DIBAL-*H* (10.72 mL, 20 % solution in toluene, 20.42 mmol) and the mixture was stirred for 3 h at 0 ^oC. The reaction was quenched with saturated aq. sodium potassium tartarate (30 mL) and stirring continued for 1 h. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 x 30 mL). The combined organic layers were dried over Na_2SO_4. Removal of the solvent under reduced pressure followed by purification on silica gel column chromatography (EtOAc/hexanes, 2.5:7.5) afforded the alcohol **80** (1.50 g, 80%) as a colourless liquid.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.30-7.18 (m, 5H), 5.33 (t, *J* = 7.93 Hz, 1H), 4.43 (s, 2H), 3.86 (s, 2H), 3.41 (t, *J* = 5.95 Hz, 2H), 2.09 (q, *J* = 6.96, 14.88 Hz, 2H), 1.66-1.58 (m, 5H) ppm.

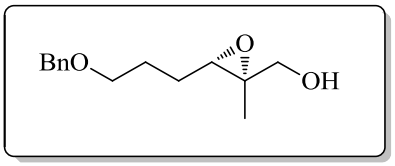
^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.6, 135.4, 128.4, 127.7, 127.6, 125.1, 72.9, 69.8, 68.5, 29.6, 24.2, 13.7 ppm.

IR (neat): 3421, 932, 1452, 1363, 1274, 1099, 739, 698 cm^{-1}.

ESI-MS: *m/z* 243 $(M + Na)^+$.

ESI-HRMS: calcd for $C_{14}H_{20}O_2Na$ $(M + Na)^+$ 243.1360, found 243.1369.

2.4.5. ((2*S*,3*S*)-3-(3-(Benzyloxy)propyl)-2-methyloxiran-2-yl)methanol (81):



To a stirred suspension of activated 4 Å molecular sieves, (1.5 g) in dry CH_2Cl_2 (10 mL) was added L-(+)-DET (0.21 mL, 1.09 mmol) and $Ti(O^iPr)_4$ (0.37 mL, 1.32 mmol) at -20 ^oC. The mixture was stirred for 30 min at the same temperature. To this mixture, a solution of allyl alcohol **80** (1.45 g, 6.60 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise and the mixture was stirred for another 30 min at -20 °C. Then a solution of TBHP (3.46 mL, 4.0 M in toluene, 7.26 mmol) was added and the resulting mixture stirred at the same temperature for 8 h. It was then warmed to 0 °C and then quenched with water (5 mL) and a solution of NaOH (20%, 2mL). The resulting mixture was vigorously stirred for 3 h at room temperature and then filtered through Celite. The residue was washed well with CH_2Cl_2 (3 x 20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. Removal of the solvent under reduced pressure followed by purification by silica gel column chromatography (EtOAc/hexanes, 3:7) afforded the epoxy alcohol **81** (1.40 g, 90%) as a colourless viscous liquid.

$[\alpha]^{22}_D$: –7.0 (*c* 1.0, $CHCl_3$).

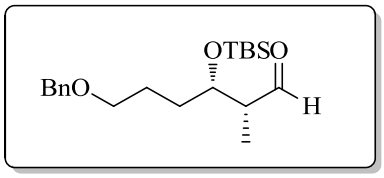
^1H NMR ($CDCl_3$, 500 MHz): δ 7.32-7.21 (m, 5H), 4.47 (s, 2H), 3.61-3.44 (m, 4H), 2.99 (t, *J* = 6.0 Hz, 1H), 1.84-1.60 (m, 4H), 1.26 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.0, 128.0, 127.3, 127.2, 72.5, 69.3, 65.3, 60.94, 59.8, 26.3, 24.7, 13.7 ppm.

IR (neat): 3435, 2929, 2862, 1453, 1364, 1275, 1097, 1035, 741, 698 cm^{-1}.

ESI-HRMS: calcd for $C_{14}H_{20}O_3Na$ $(M + Na)^+$ 259.1310, found 259.1315.

2.4.6. (2*R*,3*S*)-6-(Benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-2-methylhexanal (82):



To a stirred suspension of activated 4 Å molecular sieves (1.7 g) in dry CH_2Cl_2 (15 mL) was added a solution of epoxy alcohol **81** (1.40 g, 5.93 mmol) and *N*,*N*-diisopropylethylamine (1.4 mL, 8.29 mmol) in CH_2Cl_2, after 20 min *tert*-butyldimethylsilyltrifluoromethanesulfonate (TBSOTf, 1.77 mL, 7.71 mmol) was added drop wise over 15 min. The resulting solution was stirred for 1 h at -42 °C, then quenched by addition of pH 7.0 buffer (15 mL) and allowed to warm to room temperature. The mixture was diluted with hexane and the phases were separated. The organic phases were washed with saturated copper(II) sulfate two times and brine, then dried over anhydrous Na_2SO_4, filtered through celite, and concentrated under reduced pressure, then purified by silica gel column chromatography (EtOAc/hexanes, 1:9) to afford the aldehyde **82** (310 mg, 15%) as colorless oil.

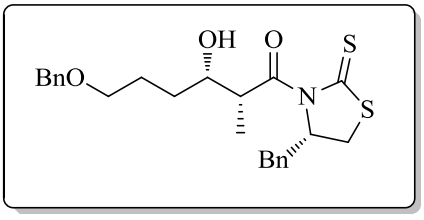
^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.39 (s, 1H), 7.46-7.24 (m, 5H), 4.51 (s, 2H), 3.82-3.46 (m, 3H), 2.53-2.42 (m, 1H), 1.91-1.67 (m, 4H), 0.91 (d, *J* = 2.07 Hz, 3H), 0.87 (s, 9H), 0.07 (s, 6H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 195.1, 138.2, 128.4, 127.6, 126.8, 73.4, 68.1, 67.7, 60.6, 29.6, 28.3, 26.8, 25.6, 13.1, -4.0, -5.1 ppm.

IR (neat): 2930, 2862, 1718, 1454, 1374, 1274, 1086, 1058, 986, 769, 701 cm^{-1}.

ESI-MS: *m/z* 373 $(M + Na)^+$.

2.4.7. (2*R*,3*S*)-1-((*S*)-4-Benzyl-2-thioxothiazolidin-3-yl)-6-(benzyloxy)-3-hydroxy-2-methylhexan-1-one (84):



To a dry 1000 mL round-bottom flask, under nitrogen, was added *N*-acetylthiazolidinethione **83** (14.7 g, 55.47 mmol) in 250 mL CH_2Cl_2. The solution was cooled to -15 °C and titanium tetrachloride (30.63 mL, 61.01 mmol, 2M solution in CH_2Cl_2) was added dropwise. The thick suspension was stirred for 15 min upon which (−)-sparteine was added (11.75 mL, 55.47 mmol). The dark red solution was stirred for 30 min at -15 °C. Then aldehyde **78** (11.75 g, 65.93 mmol) was added in 60 mL CH_2Cl_2. The reaction mixture was stirred for 1 h at -15 °C and the reaction was quenched with saturated NH_4Cl (100 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 150 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (EtOAc/hexanes, 1.5:8.5) to afford the alcohol **84** (26.30 g, 90%) as a yellow viscous oil.

$[\alpha]^{25}_D$: +71.8 (*c* 1.1, $CHCl_3$).

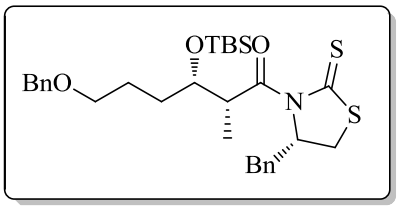
^{1}H NMR ($CDCl_3$, 500 MHz). δ 7.37-7.15 (m, 10H), 5.38-5.32 (m, 1H), 4.65 (dq, *J* = 2.74, 6.56 Hz, 1H), 4.49 (s, 2H), 4.05-4.01 (brs, 1H), 3.50 (t, *J* = 6.56 Hz, 2H), 3.33 (dd, *J* = 3.73, 11.18 Hz, 1H), 3.22 (dd, *J* = 3.73, 13.04 Hz, 1H), 3.00 (dd, *J* = 10.53, 13.04 Hz, 1H), 2.97-2.85 (m, 2H), 1.85-1.50 (m, 4H), 1.19 (d, *J* = 6.56 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz). δ 201.4, 178.0, 138.2, 136.3, 129.3, 129.1, 128.9, 128.8, 128.3, 127.6, 127.4, 127.4, 127.1, 72.8, 70.83, 70.1, 68.8, 42.8, 40.0, 36.8, 31.7, 26.3, 10.5 ppm.

IR (neat): 3446, 3062, 3028, 2937, 2854, 1688, 1493, 1343, 1294, 1259, 1190, 1160, 1032, 963, 744, 700, 659 cm^{-1}.

ESI-HRMS: calcd for $C_{24}H_{29}NO_3S_2Na$ $(M + Na)^+$ 466.1486, found 466.1500.

2.4.8. (2*R*,3*S*)-1-((*S*)-4-Benzyl-2-thioxothiazolidin-3-yl)-6-(benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-2-methylhexan-1-one (85):



To a stirred solution of alcohol **84** (26.24 g, 59.25 mmol) in 200 mL CH_2Cl_2 at 0 ^oC was added *N*,*N*-diisopropylethyl amine (15.23 mL, 88.86 mmol), followed by addition of TBSOTf (17.67 mL, 77.01 mmol). After 1 h, the reaction was quenched by the addition of aqueous saturated $NaHCO_3$ (30 mL). The two layers were separated, and the aqueous layer was further extracted with CH_2Cl_2 (3 x 30 mL). The combined organics were then washed with brine (30 mL), dried, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (EtOAc/hexanes 1:9) to provide the product **85** (29.7 g, 90%) as a bright yellow oil.

$[\alpha]^{25}_D$: +88.0 (*c* 0.5, $CHCl_3$).

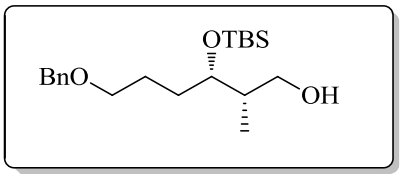
^1H NMR ($CDCl_3$, 400 MHz): δ 7.31-7.13 (m, 10H), 5.32-5.24 (m, 1H), 4.75-4.67 (m, 1H), 4.43 (s, 2H), 4.19-4.13 (m, 1H), 3.46-3.37 (m, 1H), 3.27 (dd, *J* = 7.28 Hz, 1H), 3.15 (dd, *J* = 3.23, 12.95 Hz, 1H), 2.93 (dd, *J* = 10.93, 12.95 Hz, 1H), 2.80 (d, *J* = 11.33 Hz, 1H), 1.70-1.53 (m, 4H), 1.17 (d, *J* = 6.88 Hz, 3H), 0.89 (s, 9H), 0.06 (d, *J* = 3.88 Hz, 6H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 201.0, 176.6, 136.5, 129.3, 128.8, 128.2, 127.5, 127.4, 127.3, 127.1, 72.6, 70.4, 69.0, 62.9, 43.4, 37.0, 32.1, 31.4, 25.9, 25.0, 18.1, 14.3, -4.0, -4.3 ppm.

IR (neat): 3064, 3030, 2951, 2930, 2856, 1650, 1604, 1495, 1460, 1363, 1340, 1294, 1255, 1192, 159, 1103, 1060, 1029, 837, 777, 699 cm^{-1}.

ESI-HRMS: calcd for $C_{30}H_{43}NO_3SiS_2Na$ $(M + Na)^+$ 580.2351, found 580.2362.

2.4.9. (2*S*,3*S*)-6-(Benzyloxy)-3-(*tert*-butyldimethylsilyoxy)-2-methylhaxan-1-ol (86):



To a stirred solution of auxiliary **85** (29.66g, 53.25 mmol) in MeOH (200 mL), was added $NaBH_4$ (3.62 g, 95.85 mmol) at 0 ^oC. Then the reaction mixture was stirred at the same temperature for 1 h. After completion of the reaction, solvent was removed through rotavapour *in vacuo*, quenched with saturated aqueous NH_4Cl (30 mL) at 0 ^oC. Add EtOAC (50 mL), the two layers were separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed on rotavapour *in vacuo*. The residue was purified through silica gel column chromatography EtOAc/petroleum ether (1:9) to afford the alcohol **86** (15.0 g, 80%) as oily liquid.

To a stirred solution of aldehyde **82** (310 mg, 0.885 mmol) in MeOH (10 mL), was added $NaBH_4$ (37 mg, 0.974 mmol) at 0 ^oC. Then the reaction mixture was stirred at the same temperature for 1 h. After completion of reaction, solvent was removed on rotavapour *in vacuo*, quenched with saturated NH_4Cl (2 mL) at 0 ^oC. The two layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed using rotavapour *in vacuo*. The residue was purified by column chromatography (EtOAc/hexanes, 2:8) to afford the alcohol **86** (250 mg, 80%) as oily liquid.

$[\alpha]^{25}_D$: +1.9 (*c* 0.5, $CHCl_3$).

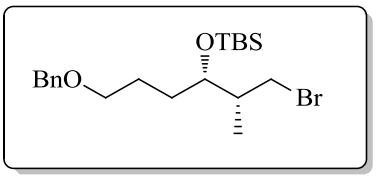
^1H NMR ($CDCl_3$, 300 MHz): δ 7.34-7.18 (m, 5H), 4.46 (s, 2H), 3.82-3.35 (m, 5H), 1.97-1.82 (m, 1H), 1.76-1.43 (m, 4H), 0.96 (d, *J* = 7.17 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.5, 128.3, 127.6, 127.5, 79.6, 72.9, 70.2, 65.23, 55.8, 38.1, 28.0, 26.3, 25.6, 10.9, -4.2, -4.6 ppm.

IR (neat): 3449, 2931, 2877, 1453, 1363, 1097, 1034, 917, 731, 698 cm^{-1}.

ESI-HRMS: calcd for $C_{20}H_{36}O_3SiNa$ $(M + Na)^+$ 375.2326, found 375.2237.

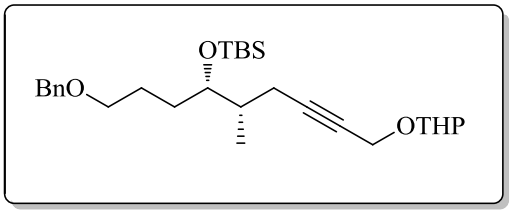
2.4.10. ((2*R*,3*S*)-6-(Benzyloxy)-1-bromo-2-methylhexan-3-yloxy)(*tert*-butyl)dimethylsilane (87):



To a stirred solution of alcohol **86** (15.0 g, 42.61 mmol) and Ph_3P (13.412 g, 51.13 mmol) in CH_3CN (150 mL) at 0 ^oC was added CBr_4 (3.27g, 51.13 mmol). The reaction mixture was stirred at 0 ^oC for 5 min and then at room temperature for 2 h. After completion of the reaction, the reaction mixture was quenched with water (30 mL) and stirred for 30 min, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL), the combined organic layer was washed with brine (20 mL) dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexanes, 1:9) to afford the bromo compound **87** (12.3 g, 70%) as a light brown liquid.

$[\alpha]^{25}_D$:	+4.30 (*c* 0.2, $CHCl_3$).
^1H NMR ($CDCl_3$, 300 MHz):	δ 7.33-7.21 (m, 5H), 4.47 (s, 2H), 3.67-3.60 (m, 1H), 3.50 (dd, *J* = 6.04, 9.82 Hz, 1H), 3.47-3.40 (m, 2H), 3.24 (dd, *J* = 7.55, 9.82 Hz, 1H), 2.07-1.98 (m, 1H), 1.70-1.52 (m, 4H), 1.03 (d, *J* = 6.79 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 6H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz):	δ 138.3, 128.2, 127.7, 127.3, 78.6, 72.0, 70.2, 66.2, 42.3, 37.4, 28.4, 26.5, 25.2, 10.7, -4.1, -4.4 ppm.
IR (neat):	3450, 2930, 2885, 1240, 1150, 1034, 744, 698 cm^{-1}.
ESI-HRMS:	calcd for $C_{20}H_{35}BrO_2SiNa$ $(M + Na)^+$ 437.1482, found 437.1470.

2.4.11. ((4*S*,5*S*)-1-(Benzyloxy)-5-methyl-9-(tetrahydro-2*H*-pyran-2-yloxy)non-7-yn-4-yloxy)(*tert*-butyl)dimethylsilane (89):



To a stirred solution of THP-protected 2-propyn-1-ol **88** (3.0 g, 21.41 mmol) in dry THF (20 mL) and HMPA (15 mL) at –45 ^{o}C, was slowly added a 2.5 M solution of *n*-BuLi in hexanes (9.4 mL, 23.55 mmol), maintaining the internal temperature below -30 ^{o}C. After stirring the yellow solution for 5 min at –45 ^{o}C, a solution of bromo compound **87** (11.82 g, 28.55 mmol) in HMPA (30 mL) was added dropwise *via* cannula. The resulting mixture was stirred for 2 h at –40 ^{o}C, then warmed up to 0 ^{o}C over 2 h. After an additional 1 h of stirring at 0^{o}C, saturated aqueous NH_4Cl (30 mL) was added. The mixture was diluted with ether (30 mL) and aqueous 1.2 M HCl (10 mL). The two layers were separated and the aqueous layer was washed with brine (100 mL), and then dried over Na_2SO_4. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexanes, 1:9) to afford the compound **89** (8.8g, 65%) as an oily liquid.

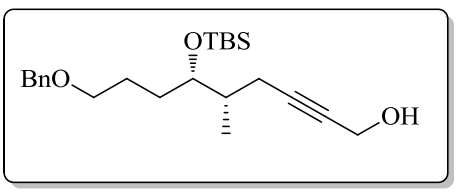
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.31-7.17 (m, 5H), 4.75 (t, *J* = 3.02 Hz, 1H), 4.43 (s, 2H), 4.27-4.09 (m, 2H), 3.82-3.72 (m, 1H), 3.52-3.35 (m, 4H), 2.36-2.20 (m, 1H), 2.11-1.98 (m, 1H), 1.88-1.40 (m, 11H), 0.91 (d, *J* = 6.79 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 6H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.5, 128.3, 127.5, 127.4, 96.2, 85.5, 80.1, 72.8, 70.2, 61.9, 55.6, 54.5, 36.0, 30.2, 30.4, 27.7, 26.0, 25.7, 25.3, 22.3, 19.1, 14.4, -4.2, -4.4 ppm.

IR (neat): 3421, 2943, 2850, 1514, 1249, 1178, 1080, 1025, 836, 770, 740 cm^{-1}.

ESI-MS: *m/z* 475 $(M + H)^{+}$.

2.4.12. (5*S*,6*S*)-9-(Benzyloxy)-6-(*tert*-butyldimethylsilyloxy)-5-methylnon-2-yn-1-ol (90):



To a stirred solution of propargyl-OTHP **89** (8.65 g, 18.25 mmol) in dry CH_2Cl_2/EtSH (49/1 mL), was added $BF_3.Et_2O$ (0.26 mL, 1.82 mmol) at -20 ^{o}C. The

mixture was stirred for 0.5 h. The mixture was poured into saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phase was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexanes, 2:8) to afford compound **90** (6.4g, 90%) as a colorless oil.

$[\alpha]^{25}_D$: –4.70 (*c* 1.0, $CHCl_3$).

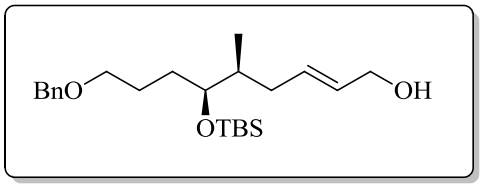
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.38-7.25 (m, 5H), 4.51 (s, 2H), 4.28-4.2 (m, 2H), 3.72-3.64 (m, 1H), 3.47 (t, *J* = 6.04 Hz, 2H), 2.35-2.01(m, 2H), 1.83-1.42 (m, 5H), 0.92 (d, *J* = 6.79 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.5, 128.3, 127.5, 127.5, 85.9, 79.1, 74.0, 72.8, 70.4, 51.3, 37.5, 30.4, 29.6, 25.9, 22.5, 18.1, 13.9, -4.1, -4.5 ppm.

IR (neat): 3423, 2928, 2855, 1461, 1362, 1254, 1090, 1027, 836, 774, 738 cm^{-1}.

ESI-HRMS: calcd for $C_{23}H_{39}O_3Si$ $(M + H)^+$ 391.2668, found 391.2662.

2.4.13. (5*S*,6*S*,*E*)-9-(Benzyloxy)-6-(*tert*-butyldimethylsilyloxy)-5-methylnon-2-en-1-ol (91):



To a stirred suspension of Red-Al (4.15 g, 6.38 mL, 20.53 mmol) in anhydrous THF (20 mL) at 0 ^oC was added dropwise, a solution of compound **90** (5.34 g, 13.7 mmol) in anhydrous THF (20 mL). The reaction mixture was allowed to warm to room temperature and stirred for 4 h. It was then cooled to 0 ^oC, diluted with ether and quenched with dropwise addition of saturated aqueous Na_2SO_4 (20 mL). The solid material was filtered and washed thoroughly with hot ethyl acetate for several times. The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed

under vacuum and the residue was purified by silica gel column chromatography (EtOAc/hexanes, 2:8) to afford the compound **91** (4.30 g, 80%) as a viscous liquid.

$[\alpha]^{25}_{D}$: +1.90 (*c* 1.0, $CHCl_3$).

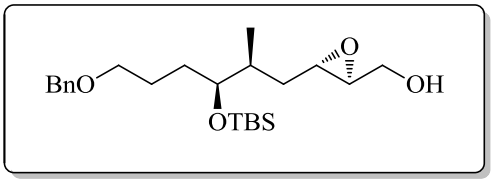
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.36-7.21 (m, 5H), 5.66-5.57 (m, 2H), 4.47 (s, 2H), 4.09-4.00 (m, 2H), 3.59-3.49 (m, 1H), 3.42 (t, *J* = 6.04 Hz, 2H), 2.28-2.09 (m, 2H), 1.85-1.38 (m, 5H), 0.88-0.80 (m, 12H), 0.04 (s, 6H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.4, 131.9, 129.9, 128.2, 127.5, 127.4, 75.3, 72.6, 70.4, 63.6, 38.2, 34.9, 29.5, 28.8, 26.0, 25.8, 14.2, -4.2, -4.4 ppm.

IR (neat): 3438, 2954, 2930, 2856, 1461, 1363, 1253, 1070, 972, 835, 773 cm^{-1}.

ESI-HRMS: calcd for $C_{23}H_{40}O_3NaSi$ $(M + Na)^+$ 415.26389, found 415.26557.

2.4.14. ((2*S*,3*S*)-3-((2*S*,3*S*)-6-(Benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-2-methylhexyl)oxiran-2-yl)methanol (92):



To a stirred suspension of activated 4 Å molecular sieves (3.0 g) in dry CH_2Cl_2 (15 mL) was added L-(+)-DET (0.26 mL, 1.33 mmol) and $Ti(O^iPr)_4$ (0.45 mL, 1.60 mmol) at -20 ^oC. The mixture was stirred for 30 min at the same temperature. To this mixture, a solution of allyl alcohol **91** (3.14 g, 8.01 mmol) in dry CH_2Cl_2 (15 mL) was added dropwise and the mixture was stirred for further 30 min at -20 °C. Then a solution of TBHP (4.2 mL, 4.0 M in toluene, 8.81 mmol) was added and the resulting mixture stirred at the same temperature for 8 h. It was then warmed to 0 °C and then quenched with water (5 mL) and a solution of NaOH (20%, 2mL). The resulting mixture was vigorously stirred for 3 h at room temperature and then filtered through Celite. The residue was washed well with CH_2Cl_2 (3 x 20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were washed with brine

and dried over Na_2SO_4. Removal of the solvent under reduced pressure followed by purification on silica gel column chromatography (EtOAc/hexanes, 3:7) afforded the epoxy alcohol **92** (3.0 g, 92%) as a colourless viscous liquid.

$[\alpha]^{23}_D$: –6.5 (*c* 1.0, $CHCl_3$).

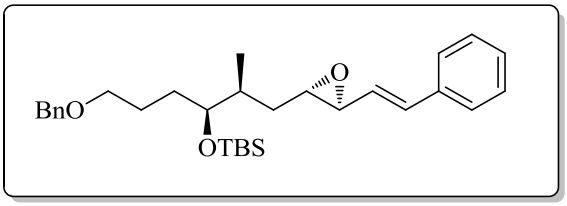
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.33-7.21 (m, 5H), 4.46 (s, 2H), 3.88-3.79 (m, 1H), 3.64-3.53 (m, 2H), 3.47-3.37 (m, 2H), 2.95-2.88 (m, 1H), 2.85-2.76 (m, 1H), 1.86-1.22 (m, 7H), 0.91 (d, *J* = 5.93 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.8, 129.6, 128.9, 128.8, 76.9, 74.1, 71.7, 62.9, 60.6, 56.4, 37.9, 36.9, 35.6, 30.9, 27.5, 27.2, 15.7, -3.0, -3.1 ppm.

IR (neat): 3445, 2954, 2930, 2856, 1462, 1362, 1252, 1072, 1032, 835, 772, 697 cm^{-1}.

ESI-HRMS: calcd for $C_{23}H_{40}O_4NaSi$ $(M + Na)^+$ 431.52881, found 431.25802.

2.4.15. ((2*S*,3*S*)-6-(Benzyloxy)-2-methyl-1-((2*S*,3*S*)-3-styryloxiran-2-yl)hexan-3-yloxy)(*tert*-butyl)dimethylsilane (93):



To a stirred solution of epoxy alcohol **92** (2.32 g, 5.69 mmol) in dry CH_2Cl_2 (20 mL) was added pyridine (5.35 mL) and Dess-Martin periodinane (3.62 g, 8.54 mmol) at 0 ^oC. The reaction mixture was stirred for 3 h at room temperature. After completion of reaction quenched with saturated aqueous $NaHCO_3$ (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The crude residual aldehyde (2.01 g, 87 %) was used as such in next step immediately.

The benzyltriphenylphosphonium bromide (3.21 g, 7.42 mmol) was dissolved in dry THF (20 mL) and cooled to 0 ^oC. NaHMDS (5.9 mL, 5.94 mmol, 1M in THF) was added dropwise. After stirring for 30 min, the resulting orange solution was cooled to -78

^{o}C and added to a solution of adehyde (2.01 g, 4.95 mmol) in THF (15 mL) *via* syringe. After 20 min the reaction was quenched with H_2O. The aqueous layer was extracted with Et_2O (3 x 20 ml). Combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and purified by silica gel column chromatography (EtOAc/hexanes, 0.5:9.5) to afford the olefin **93** (1.5g, 63%) as a viscous liquid.

$[\alpha]^{25}_{D}$: +14.5 (*c* 1.0, $CHCl_3$).

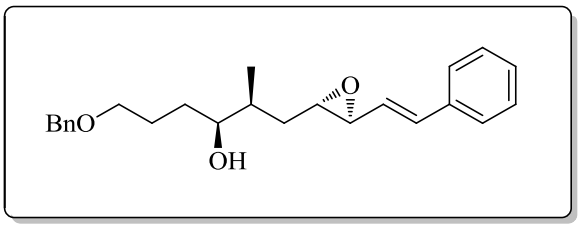
^{1}H NMR ($CDCl_3$, 300 MHz). δ 7.41-7.17 (m, 10H), 6.73 (d, *J* = 12.08 Hz, 1H), 5.96-5.84 (m, 1H), 4.49 (s, 2H), 3.64-3.53 (m, 1H), 3.49-.34 (m, 2H), 2.98-2.90 (m, 1H), 2.28-2.13 (m, 1H), 1.76-1.21 (m, 7H), 0.94 (d, *J* = 6.79 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.4, 137.0, 130.9, 129.1, 128.9, 128.5, 128.1, 127.7, 127.3, 127.0, 76.1, 74.0, 71.9, 62.4, 60.7, 40.0, 35.4, 30.0, 29.4, 27.5, 17.5, -4.2, -4.4 ppm.

IR (neat): 2925, 2858, 1717, 1453, 1380, 1272, 1101, 1073, 766, 699 cm^{-1}.

ESI-HRMS: calcd for $C_{30}H_{44}O_3NaSi$ $(M + Na)^+$ 503.29519, found 503.29482.

2.4.16. (2*S*,3*S*)-6-(Benzyloxy)-2-methyl-1-((2*S*,3*S*)-3-styryloxiran-2-yl)hexan-3-ol (94):



To a stirred solution of TBS-epoxide **93** (1.20 g, 2.5 mmol) in dry THF (10 mL), was added TBAF (3.75 mL, 3.75 mmol) at 0 ^{o}C. The mixture was stirred for 3 h and quenched with saturated $NaHCO_3$ (10 mL) solution. The resulting mixture was extracted with EtOAc (2 x 100 mL). The combined organic phases were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue

was purified by silica gel column chromatography (EtOAc/hexanes, 2:8) to afford the hydroxy epoxide **94** (823 mg, 90%) as a colorless oil.

$[\alpha]^{25}_{D}$: +2.0 (*c* 0.25, $CHCl_3$).

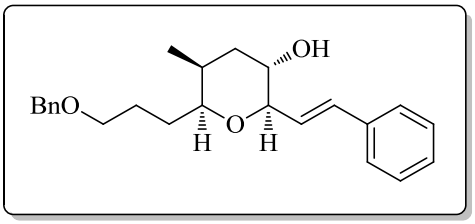
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.39-7.17 (m, 10H), 6.66 (d, *J* = 8.30 Hz, 1H), 6.09 (dd, *J* = 8.30, 16.61 Hz, 1H), 4.69-4.60 (brs, 1H), 4.48 (s, 2H), 3.57-3.33 (m, 3H), 2.98-2.92 (m, 1H), 2.27-2.13 (m, 1H), 1.75-1.19 (m, 7H), 0.96 (d, *J* = 6.79 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.6, 137.1, 130.1, 129.2, 128.8, 128.5, 128.1, 127.4, 127.2, 127.0, 76.3, 74.1, 72.2, 62.2, 60.8, 35.9, 35.2, 30.4, 29.5, 17.6 ppm.

IR (neat): 3415, 2925, 2850, 1452, 1381, 1252, 1073, 767 cm^{-1}.

ESI-HRMS: calcd for $C_{24}H_{30}O_3Na$ $(M + Na)^+$ 389.20872, found 389.20753.

2.4.17. (2*R*,3*S*,5*S*,6*S*)-6-(3-(Benzyloxy)propyl)-5-methyl-2-styryltetrahydro-2*H*-pyran-3-ol (95):



A stirred solution of hydroxy epoxide **94** (782 mg, 2.13 mmol) in THF (15 mL) was treated with dimsylsodium (1.0 M solution in DMSO, 0.42 mL, 4.27 mmol). The resulting pale brown solution was stirred at room temperature for 2.5 h. After completion of the reaction, quenched with ice water (5 mL) and diluted with EtOAc (30 mL). The reaction mixture was extracted with EtOAc (2 x 10 mL) and washed with water (5 mL), brine (5 mL), and dried over anhydrous Na_2SO_4, combined organic layers were concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (EtOAc/hexanes, 2:8) to afford the THP-ether **95** (720 mg, 92%) as a colourless oil.

$[\alpha]^{25}_{D}$: +8.70 (*c* 1.0, $CHCl_3$).

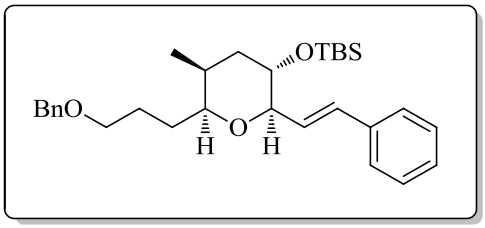
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.44-7.16 (m, 10H), 6.81 (d, *J* = 11.86 Hz, 1H), 5.63 (dd, *J* = 9.80, 11.86 Hz, 1H), 4.52-4.46 (brs, 1H), 4.37 (s, 2H), 4.26-4.18 (m, 1H), 3.71-3.64 (m, 1H), 3.55-3.43(m, 1H), 3.40-3.33 (m, 1H), 3.32-3.25 (m, 1H), 1.70-1.18 (m, 7H), 0.88 (d, *J* = 7.90 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.8, 136.9, 130.1, 129.0, 128.7, 128.3, 128.0, 127.6, 127.0, 127.4, 92.2, 85.3, 72.8, 71.6, 70.2, 36.1, 35.6, 29.5, 29.2, 17.8 ppm.

IR (neat): 3426, 2924, 2854, 1456, 1260, 1097, 1023, 699 cm^{-1}.

ESI-HRMS: calcd for $C_{24}H_{30}O_3Na$ $(M + Na)^+$ 389.20872, found 389.20764.

2.4.18. (2*R*,3*S*,5*S*,6*S*)-6-(3-(Benzyloxy)propyl)-5-methyl-2-styryltetrahydro-2*H*-pyran-3-yloxy)(*tert*-butyl)dimethylsilane (96):

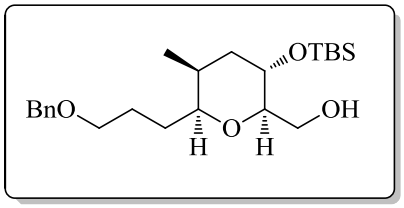


To a stirred solution of alcohol **95** (0.6g, 1.64 mmol) in CH_2Cl_2 (10 mL), *N*,*N*-diisopropylethyl amine (0.428mL, 2.459 mmol) and *tert*-butyldimethylsilyltrifluoromethanesulfonate (0.49 mL, 2.13 mmol) were added sequentially at -42 ^oC nitrogen atmosphere. After being stirred for 1 h at the same temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (2.5 mL). The reaction mixture was extracted with CH_2Cl_2 (2 x 10 mL) and washed with water (5 mL), brine (5 mL), and dried over anhydrous Na_2SO_4, combined organic layers were concentrated under reduced pressure gave crude residue. The crude residue was purified by silica gel column chromatography (EtOAc/hexanes, 1:9) to afford the compound **96** (700 mg, 90%) as a clear oil.

$[\alpha]^{25}_D$: +50.78 (*c* 1.0, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$):	δ 7.49-7.19 (m, 10H), 6.72 (d, *J* = 11.70 Hz, 1H), 5.68-5.49 (m, 1H), 4.49 (s, 2H), 4.18-3.85 (m, 2H), 3.75-3.32 (m, 3H), 1.95-1.40 (m, 7H), 0.92 (d, *J* = 6.04 Hz, 3H), 0.82 (s, 9H), 0.06 (s, 6H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz):	δ 138.6, 136.8, 130.2, 129.0, 128.7, 128.3, 128.0, 127.5, 127.4, 126.9, 86.2, 82.0, 72.8, 70.9, 70.4, 38.4, 35.8, 29.6, 29.4, 26.7, 25.7, 17.6, -4.4, -4.8 ppm.
IR (neat):	3029, 2856, 1453, 1274, 1206, 1169, 1102, 973, 748, 699 cm^{-1}.
ESI-HRMS:	calcd for $C_{30}H_{44}O_3NaSi$ $(M + Na)^+$ 503.29519, found 503.29468.

2.4.19. ((2*R*,3*S*,5*S*,6*S*)-6-(3-(Benzyloxy)propyl)-3-(*tert*-butyldimethylsilyloxy)-5-methyltetrahydro-2*H*-pyran-2-yl)methanol (97):



The olefinic compound **96** (513 mg, 1.06 mmol) in CH_2Cl_2 (10 mL) was cooled to –78 ^oC and then ozone gas was passed through the reaction mixture for 15 min. After completion of reaction, added $(CH_3)_2S$ (0.1 mL) to the reaction mixture and stirred for 5 minutes at the same temperature. Then, the reaction mixture was diluted with water (10 mL). The reaction mixture was brought to room temperature and separated the layers. The organic layer was washed with brine (8 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude aldehyde (400 mg 92 %) was used as such in next step immediately.

To a stirred solution of aldehyde (400 mg, 0.98 mmol) in MeOH (10 mL), was added $NaBH_4$ (41 mg, 1.08 mmol) at 0 ^oC. Then the reaction mixture was stirred at the same temperature for 1h. After completion of the reaction, solvent was removed through rotavapour *in vacuo*, quenched with saturated NH_4Cl (2 mL) at 0 ^oC. The two layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined

organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed through rotavapour *in vacuo*. The residue was purified by column chromatography (EtOAc/hexanes, 2:8) to afford the alcohol **97** (320 mg, 80%) as oily liquid.

$[\alpha]^{25}_D$: +8.80 (*c* 0.5, $CHCl_3$).

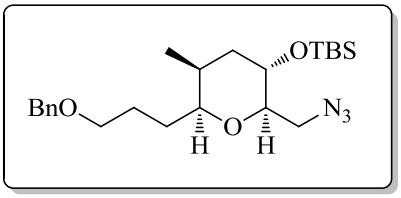
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.39-7.24 (m, 5H), 4.50 (s, 2H), 3.96-3.38 (m, 7H), 1.90-1.48 (m, 7H), 1.33-1.29 (m, 1H), 0.94 (d, *J* = 6.79 Hz, 3H), 0.87 (s, 9H), 0.05 (s, 6H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.5, 128.3, 127.6, 127.4, 82.6, 79.4, 72.8, 70.2, 65.3, 64.5, 40.9, 35.8, 32.6, 29.6, 26.5, 25.8, 17.8, -4.1, -4.6 ppm.

IR (neat): 3455, 2954, 2929, 2856, 1461, 1396, 1253, 1101, 837, 777, 736 cm^{-1}.

ESI-HRMS: calcd for $C_{23}H_{40}O_4NaSi$ $(M + Na)^+$ 431.25881, found 431.25946.

2.4.20. ((2*R*,3*S*,5*S*,6*S*)-2-(Azidomethyl)-6-(3-(benzyloxy)propyl)-5-methyltetrahydro-2H-pyran-3-yloxy)(*tert*-butyl)dimethylsilane (98):



To a stirred solution of alcohol **97** (300 mg, 0.73 mmol) and diisopropyl azodicarboxylate (0.29 mL, 1.47 mmol) in THF (5 mL) was added PPh_3 (385 mg, 1.47 mmol) at 0 ^oC. After 5 min, diphenylphosphoryl azide (0.32 mL, 1.47 mmol) was added. The reaction mixture was warm to rt and stirred for 3 h. EtOAc (10 mL) and H_2O (2 mL) were added and the layers were separated. The organic phase was dried over anhydrous Na_2SO_4, concentrated *in vacuo*, purification over silica gel column chromatography (EtOAc/hexanes, 0.5:9.5) gave the azide **98** (254 mg, 80%) as a clear oil.

$[\alpha]^{25}_D$: −1.60 (*c* 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.44-7.23 (m, 5H), 4.50 (s, 2H), 3.72-3.64 (m, 1H), 3.57-3.36 (m, 2H), 3.32-3.21 (m, 2H), 1.94-1.73 (m,

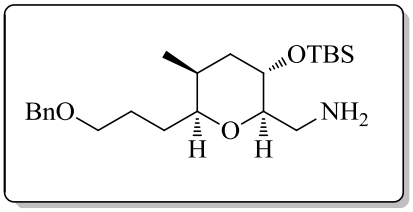
3H), 1.69-1.37 (m, 6H), 0.97 (d, *J* = 6.73 Hz, 3H), 0.86 (s, 9H), 0.05 (d, *J* = 2.07 Hz, 6H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 139.5, 128.2, 127.6, 127.4, 82.3, 79.7, 72.7, 70.1, 64.4, 51.8, 40.9, 32.7, 31.4, 30.1, 29.2, 25.6, 17.8, -4.1, -4.9 ppm.

IR (neat): 2930, 2857, 2169, 2097, 1591, 1488, 1271, 1183, 1102, 965, 776, 688, 508 cm^{-1}.

ESI-HRMS: calcd for $C_{23}H_{39}N_3O_3NaSi$ $(M + Na)^+$ 456.2653, found 456.2663.

2.4.21. ((2*R*,3*S*,5*S*,6*S*)-6-(3-(Benzyloxy)propyl)-3-(*tert*-butyldimethylsilyloxy)-5-methyltetrahydro-2H-pyran-2-yl)methanamine (45):



To a stirred solution of azide **98** (160 mg, 0.37 mmol) in THF/H_2O (3/1 mL) was added Ph_3P (106 mg, 0.40 mmol) at 0 °C and the reaction was stirred for 4 h, after completion of reaction, added water (5 mL) and EtOAc (5 mL). Extract with EtOAc (3 x 5 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 0.5:9.5) to afford the amine **45** (95 mg, 63%) as a clear oil.

$[\alpha]^{25}_D$: +14.8 (*c* 0.2, $CHCl_3$).

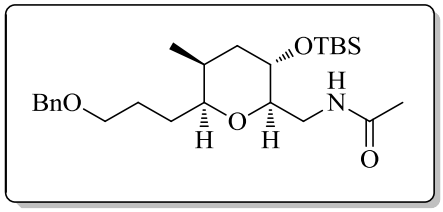
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.44-7.25 (m, 5H), 4.51 (s, 2H), 3.70-3.65 (m, 1H), 3.40-3.31 (m, 2H), 3.29-3.14 (m, 2H), 3.03-2.96 (m, 1H), 2.52-2.46 (m, 1H), 1.86-1.72 (m, 2H), 1.69-1.38 (m, 4H), 1.30-1.28 (m, 1H), 0.90 (d, *J* = 6.98 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.4, 128.6, 127.7, 127.4, 80.2, 79.3, 72.9, 70.3, 65.4, 40.7, 33.0, 28.8, 26.3, 25.8, 25.5, 17.9, 12.6, -4.1, -4.6 ppm.

IR (neat): 3073, 2928, 2840, 1600, 1472, 1273, 1204, 1183, 1104, 965, 776, 685, 508 cm^{-1}.

ESI-HRMS: calcd for $C_{23}H_{41}NO_3SiNa$ $(M + Na)^+$ 430.2748, found 430.2752.

2.4.22. *N*-(((2*R*,3*S*,5*S*,6*S*)-6-(3-(Benzyloxy)propyl)-3-(*tert*-butyldimethylsilyloxy)-5-methyltetrahydro-2*H*-pyran-2-yl)methyl)acetamide (99):



To a stirred solution of amine **45** (48 mg, 0.11 mmol), in CH_2Cl_2 (1.5 mL) was added DMAP (1.5 mg, 0.012 mmol), Ac_2O (13.4 μL, 0.142 mmol), and triethylamine (19 μL, 0.142 mmol) at 0 ^oC. After 30 min, the reaction mixture was concentrated under reduced pressure and purified by silica gel column chromatography ($MeOH/CH_2Cl_2$, 0.3:9.7) to afford the amide **99** (40 mg, 75%) as a clear oil.

$[\alpha]^{25}_D$: +11.8 (*c* 0.25, $CHCl_3$).

^1H NMR ($CDCl_3$, 300 MHz): δ 7.35-7.26 (m, 5H), 5.89-5.80 (brs, 1H), 4.52 (s, 2H), 3.76-3.72 (m, 1H), 3.55-3.44 (m, 3H), 3.40-3.37 (m, 1H), 3.12-3.00 (m, 2H), 1.97 (s, 3H), 1.88-1.60 (m, 4H), 1.52-1.30 (m, 3H), 0.94 (d, *J* = 6.74 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.5, 138.4, 128.2, 127.5, 127.4, 81.2, 79.4, 72.9, 70.1, 65.5, 41.4, 40.8, 32.5, 29.3, 26.5, 25.7, 23.3, 17.7, 12.6, -4.2, -4.8 ppm.

IR (neat): 2925, 2855, 1762, 1698, 1369, 1204, 11o5, 1015, 762, 702 cm^{-1}.

ESI-HRMS: calcd for $C_{25}H_{43}O_4NNaSi$ $(M + Na)^+$.472.28536, found 472.28795.

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Spectra

CHAPTER III

Section A

Stereoselective total synthesis of Putaminoxin

3.1.1. Introduction:

Phytotoxic means harmful or lethal to plants, phytotoxicity is the degree to which a chemical or other compound is toxic to plants. All types of pesticides, herbicides are hazardous to plants because they are designed to kill or suppress plants. Some insecticides and fungicides can also harm plants. Phytotoxic effects caused by herbicides can be from spray droplets, soil residues or vapours contacting sensitive plants. Plants can also be harmed by herbicides which move off target in water or soil or when sensitive crops are planted in fields too soon after an herbicide treatment was applied for a previous crop. Phytotoxic properties of pesticides are usually associated with specific formulations (wettable powder, emulsifiable concentrate, granule, etc) or specific plants rather than groups of pesticides or plants. A pesticide label may indicate whether the pesticide could be phytotoxic, and may list plants or varieties that are sensitive. Phytotoxic effects can range from slight burning or browning of leaves to death of the plant. Sometimes the damage appears as distorted leaves, fruit, flowers or stems. Damage symptoms vary with the pesticide and the type of plant that has been affected. Phytotoxicity is not necessarily caused by the active ingredient. Plant damage can also be caused by the solvents in a formulation, impurities in spray water, using more pesticide than listed on the label, or poorly mixing the spray solutions. Condition of the plant at the time of treatment can affect phytotoxicity; stressed plants may be more susceptible. Environmental conditions such the temperature, humidity, and light can influence phytotoxicity. High temperatures can speed up pesticide degradation and volatilization, but may also result in increased phytotoxicity for some products. UV light rapidly breaks down many pesticides. Soil properties such as texture, temperature, moisture, microbial activity and pH also influence phytotoxicity. Higher pH soils are less binding and may increase photoxicity. High microbial activity can reduce phytotoxicity.

Phytotoxins are metabolites produced by pathogenic fungi or bacteria when infecting the host plant and are often responsible for the characteristic symptoms of plant disease. A number of new phytotoxins have been reported recently but most of them have structures related to previously reported phytotoxins. The discovery of the 10-membered macrolide, putaminoxin A, was reported in the last review.[1-3] Many 10-membered

lactones have been isolated as secondary metabolites of terrestrial and marine organisms, such as bacteria, fungi, and plants. Synthetic studies on these compounds are meaningful, as well as biological studies, because their bioactivities are frequently concerned with structure. The first naturally occurring 10-membered lactone is Jasmine ketolactone (**1**), which was isolated in 1942[4] as a component of essential oil of *Jasminum grandiflorium*, and whose structure was confirmed in 1964.[5] Diplodiade A is the first bioactive 10-membered lactone isolated from a fungus as a steroid hydroxylase inhibitor, in 1975.[6] After that this class of compounds attracted many organic chemists, and many synthetic studies have been reported. In synthesizing these compounds, the key reaction is the construction of a 10-membered ring.

3.1.1.1. Naturally occurring 10-membered ring lactones

Natural products containing a medium ring lactone framework are found in plants, insects (pheromones) and bacteria (antibiotics), they can have a terrestrial, fungal or a marine origin. In the present context the emphasis was made only on 10-membered lactones. The oldest natural product possessing an oxecan-2-one framework would appear to be the jasmine ketolactone (**1**) (Figure 1).

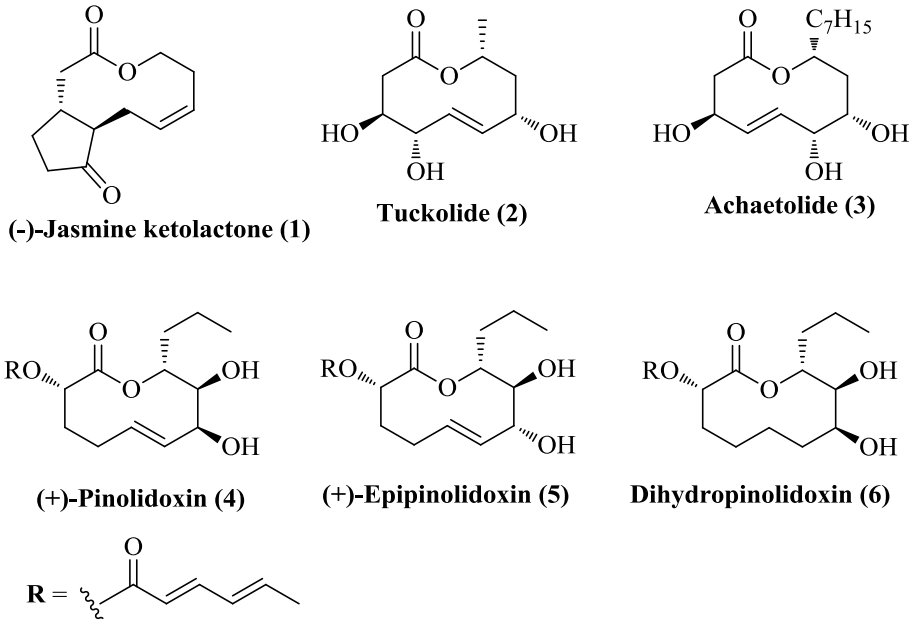


Figure 1

More recently, Tuckolide (**2**) was isolated as metabolite of the Canadian tuckahoe, the sclerotium of *Polyporus tuberaster*, a subterranean fungus.[7] Achaetolide (**3**), a

compound with a very similar structure, was also isolated from the fungus, *Achaetomium cristalliferum.*[8a] Pinolidoxin (**4**), a phytotoxin (anthraenose of pea) was produced by the fungus *Aschochyta pinodes*.[8b] Subsequently, two new metabolites of this fungus were found epipinolidoxin (**5**) and dihydropinolidoxin[8c] (**6**) (Figure 1).

Diplodialides A (**7**), B (**8**), C (**9**) and D (**10**), the metabolites of the phytopathogenic fungus *Diplodia pinea*, have more simple structures than pinolidoxine derivatives.[9] Diplodialide A (**7**) has been reported to be a steroid hydroxylase inhibitor. Another phytopathogenic fungus, *Pyrenophora teres*, produces metabolites, pyrenolides A (**11**), B (**12**) and C (**13**) (Figure 2), which have similar structures to the diplodialides.[10a]

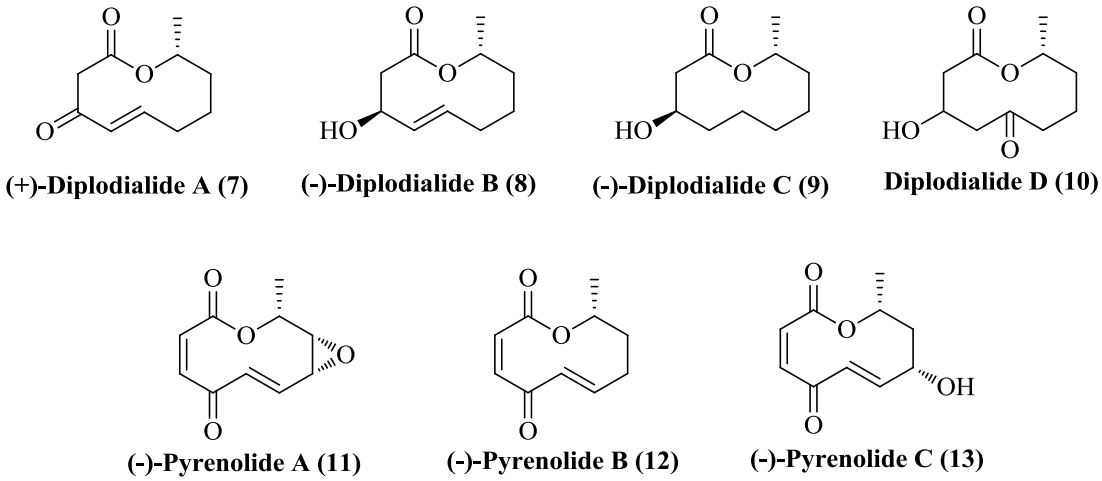
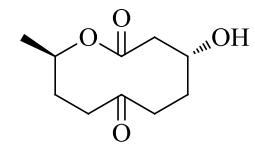
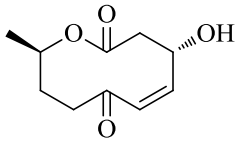


Figure 2

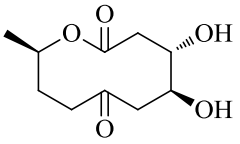
These compounds show inhibitory activity against fungi.[10b] Two other similar structures, Cephalosporolides B (**15**) and C (**16**) (Figure 3), are metabolites of the fungus *Cephalosporium aphidicola*.[11a] Another interesting metabolite, Thiobiscephalosporolide A (**17**), was isolated during the fermentation of *Cephalosporium aphidicola* and found to be a dimeric 10-membered ring lactone.[11b] On degradation, it led to a compound which is a regioisomer of Diplodialide D (**10**). The biogenesis of these different compounds has been discussed recently.[11c]



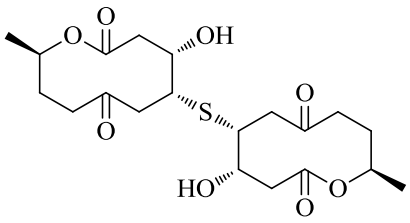
Cephalosporolide A (14)



Cephalosporolide B (15)



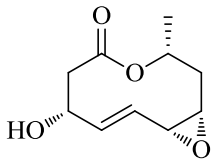
Cephalosporolide C (16)



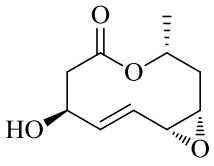
Thibiscephalosporolide A (17)

Figure 3

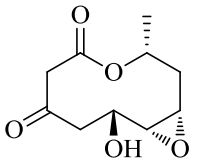
Various oxygenated oxecan-2-ones, Decarestrictines A (**18**)-J (**29**) (Figure 4)**,** were formed during the fermentation of *Penicillium simplicissimum*.[12] These compounds show important inhibitory effects on cholesterol biosynthesis.[13] Decarestritine D (**23**) is identical to Tuckloide (**2**), and its isolation was published simultaneously.[7]



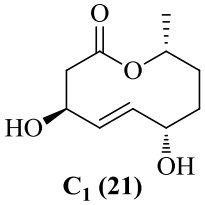
A_1 (18)



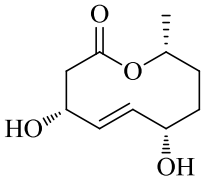
A_2 (19)



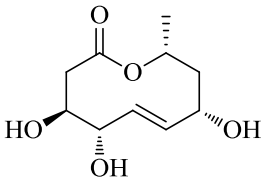
B (20)



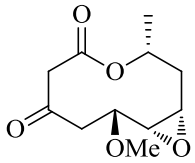
C_1 (21)



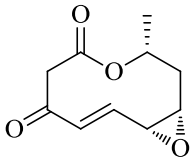
C_2 (22)



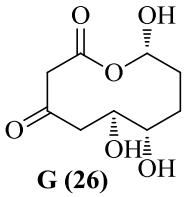
D (23)



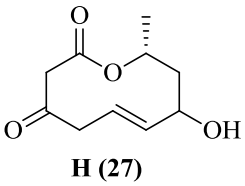
E (24)



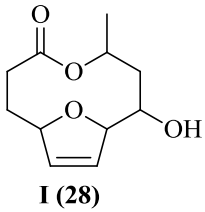
F (25)



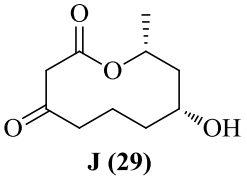
G (26)



H (27)



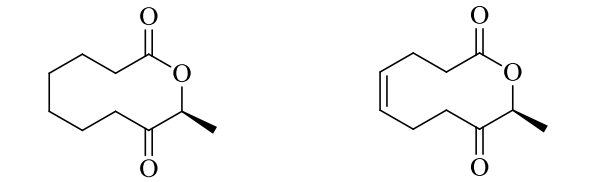
I (28)



J (29)

Fgure 4

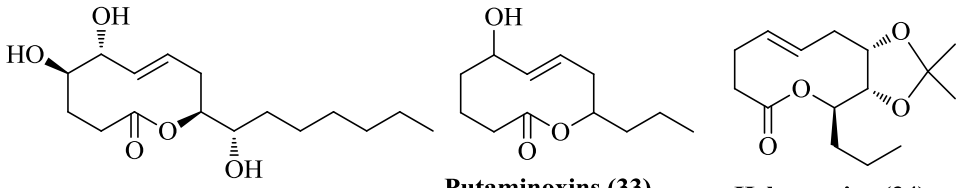
The metastemal gland secretion of the common eucalypt longicom, *Phoracantha semipunctata* contains two lactones as major components, phoracantholide I (**30**) and phoracantholide J[14] (**31**) (Figure 5).



Phorocantholide I (30) **Phorocantholide J (31)**

Figure 5

Microcarpalide (**32**) represents novel alkyl-substituted nonenolide structurally related to a family of phytotoxins such as achaetolide[8a] (**3**) pinolidoxin[8b] (**4**) (Figure 1), putaminotoxins[15a] (**33**) and herbarumins[15b] (**34**) (Figure 6), from which it differs in the hydroxylation pattern and the double bond position within the 10-membered lactones, as well as in the length of the side chain at C-10.



Microcarpalide (32) **Putaminoxins (33)** **Hebarumins (34)**

Figure 6

Stagonospora cirsii, a fungal pathogen isolated from *Cirsium arvense*[16] and proposed as a potential mycoherbicide of this perennial noxious weed, produces phytotoxic metabolites in liquid and solid cultures. Recently, the main metabolite, stagonolide A (**35**), with interesting phytotoxic properties, was isolated from a liquid culture and characterized as a new nonenolide. The same fungus, grown in solid culture, exhibited an increased capacity to produce nonenolides. Five new nonenolides, named stagonolides B (**36**)-F (**40**) (Figure 7), were isolated and characterized using spectroscopic methods.

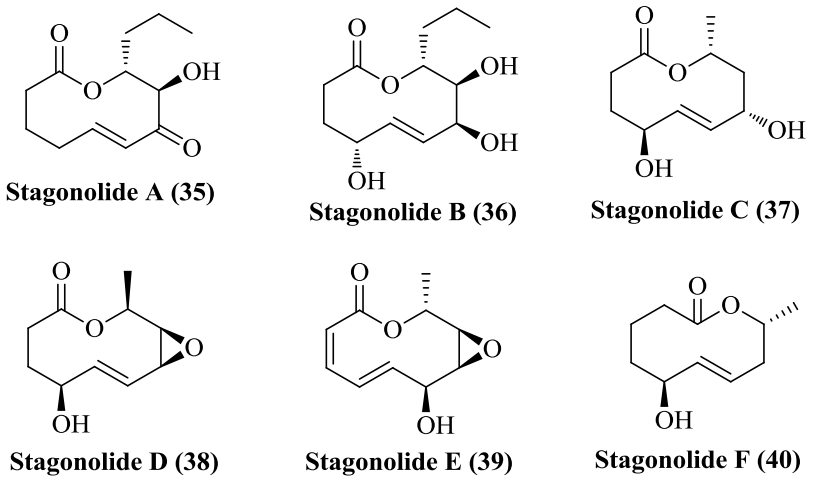


Figure 7

When tested by a leaf disk puncture assay at a concentration of 1 mg/mL, these compounds showed no toxicity to *C. arvense* and *Sonchus arvensis*, whereas stagonolide A (**35**) was highly toxic. Stagonolide B (**36**) and stagonolide C (**37**) were weakly toxic to *Colpoda steinii*, a protozoan, when tested at 0.05 mg/mL, with the other stagonolides nontoxic. A number of structure–activity relationship observations were made.

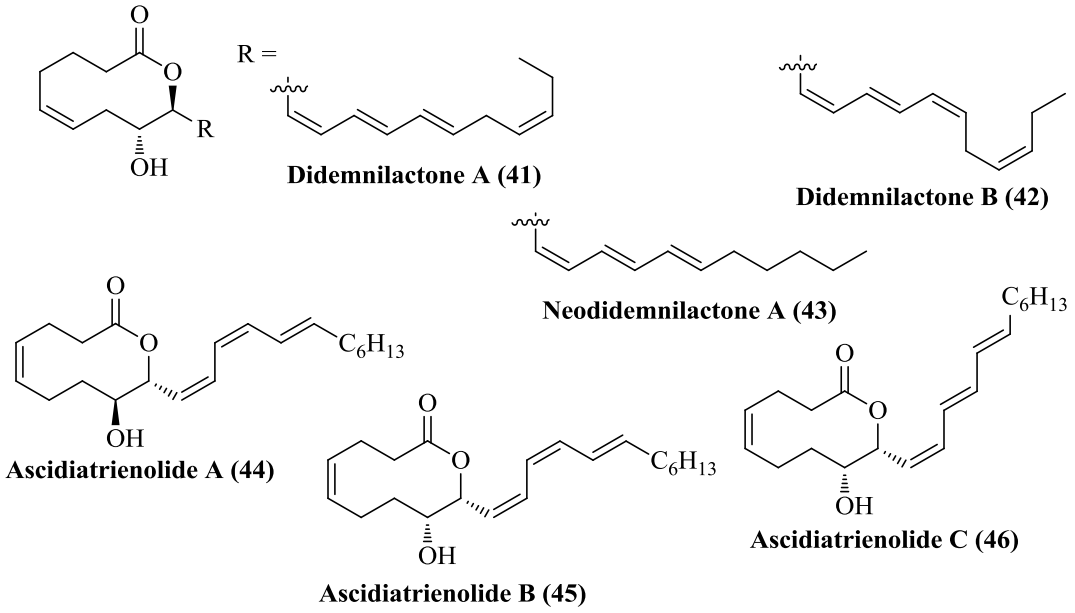
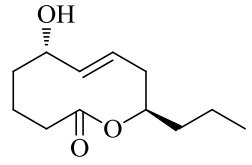


Figure 8

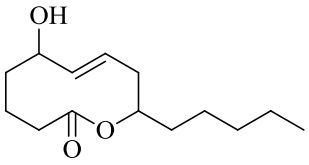
Metabolites of *Didenmum moseleyi* (Herdman), a tunicate living in the sea in Japan, didemnilactones A (**41**), didemnilactones B (**42**) and neodidemnilactone A (**43**),

were also found to be 10-membered ring lactones.[17] These compounds exhibit weak binding activity to leukotriene B_4 receptors in human polymorphonuclear leukocyte membrane fractions. Ascidiatrienolides A (**44**), B (**45**) and C[18a] (**46**) (Figure 8) whose structures were recently reinvestigated,[18b] were found in marine ascidian (*Didemnum candidum*) and corresponded to oxidation products of C20 fatty acid.

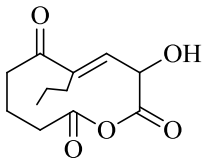
During a survey on the production of phytotoxins by weed and crop phytopathogenic fungi, several new phytotoxic nonenolides were isolated, identified and characterized. Nonenolides belong to macrolides, a family of natural compounds with interesting biological properties. In particular, putaminoxin (**47**) a disubstituted nonenolide, has been isolated as the main toxin from culture filtrates of *Phoma putaminum* [19] a fungal pathogen of *Erigeron annuus* (L.) Pers., an indigenous weed from North America widely present in fields and pastures all over Europe. Later on, other metabolites were isolated from the same culture filtrates, namely putaminoxins B (**48**), D (**50**) and E (**51**) (Figure 9) respectively, three new nonenolides structurally related to puaminoxin and putaminixins D and E were characterized by spectroscopic and chemical methods as a new disubstituted nonen and nonanolide, respectively.



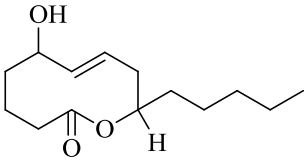
Putaminoxin (47)



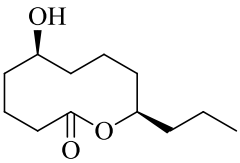
Putaminoxin B (48)



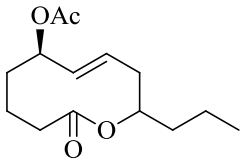
Putaminoxin C (49)



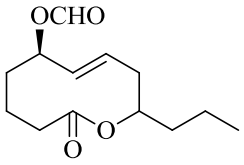
Putaminoxin D (50)



Putaminoxin E (51)



5-*O*-Acetylputaminoxin (52)



5-*O*-Formylputaminoxin 1 (53)

Figure 9

Moreover, putaminoxins D (**50**), E (**51**) and 5-*O* formylputaminoxin (**53**) showed no toxicity, unlike other putaminoxins. Putaminoxin C (**49**) a disubstituted cyclononendione containing some structural features similar to those of putaminoxin (**47**). Macrolides, particularly lactones with medium-sized rings (8-10 membered), have continued to attract the attention of both biologists and chemists during recent years, due to the interesting biological properties and scarce availability of macrolides. A few examples, in particular of ten-membered-ring containing macrolides that display potent biological activity is putaminoxin (**47**), the nonenolide (5*S*) 5-hydroxy-(9*R*)-propyl -(6*E*)-nonen-9-olide.

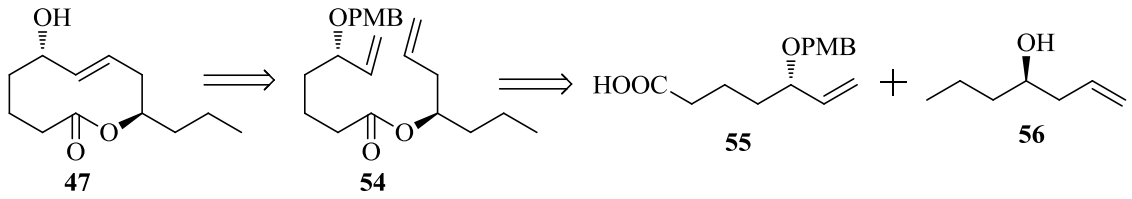
This macrolide has been isolated from *phoma putaminum*, a fungal pathogen isolated from diseased leaves of *Erigeron annuus* (L), the main phytotoxin produced by *phoma putaminum* named putaminoxin, which is disubstituted nonenolide.

3.1.2. Previous Approach:

3.1.2.1. Yadav's Approach:[20]

Asymmetric synthesis of putaminoxin, a phytotoxic macrolide from the cultured dinoflagellate *Amphidinium* sp., has been accomplished. Absolute configuration of putaminoxin was concluded to be putaminoxin (**47**) from comparison of the NMR data and $[\alpha]_D$ values of synthetic and natural putaminoxin.

3.1.2.1a. Retrosynthesis:

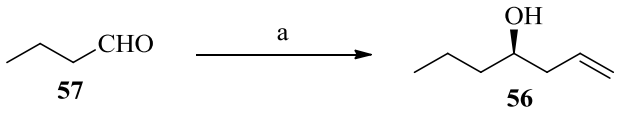


Scheme 1: Retrosynthetic analysis

3.1.2.1b. Discussion:

Our synthesis was started with commercially available *n*-butyraldehyde **57**, which was subjected to an enantioselective Keck allylation using (*S*)-Binol and allyl-tri-*n*-

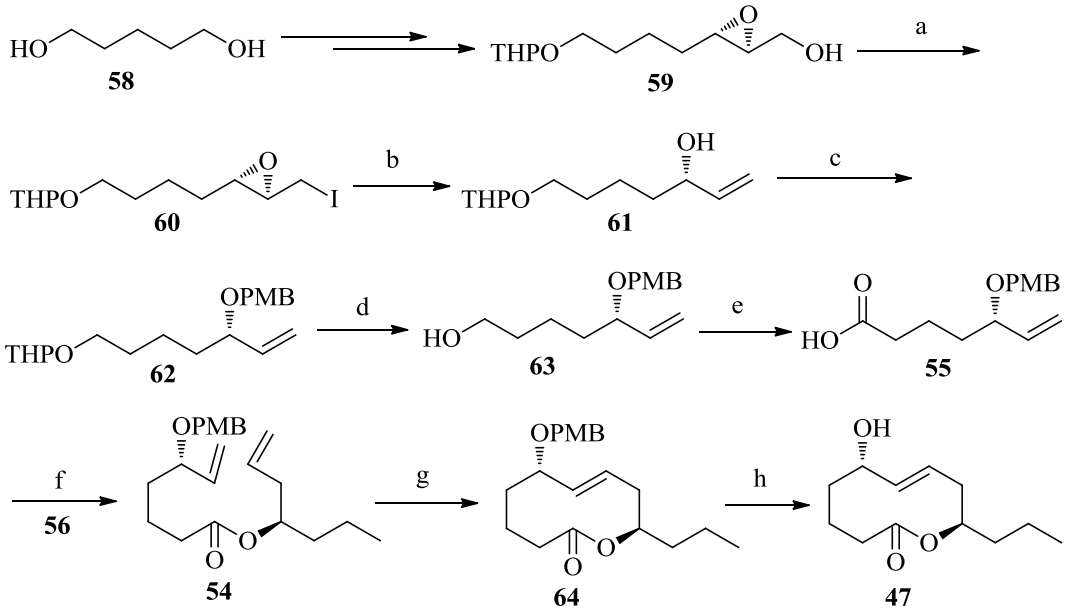
butyltin to gave the homoallylic alcohol **56** in 75% yield with excellent enantioselectivity of 95% ee (determined by chiral HPLC) (Scheme 2).



Scheme 2

Reagents and conditions: (a) $^{n}Bu_3SnCH_2CH=CH_2$, $Ti(O^{i}Pr)_4$, (*S*)-Binol, CH_2Cl_2, -78 ^{o}C to -20 ^{o}C, 72 h, 75%, 95% ee.

Epoxy alcohol **59** was prepared from commercially available 1,5 pentane diol **58** using well precedented literature procedure. The epoxy alcohol **59** was converted to the corresponding epoxy iodide **60** in 78% yield by treating with triphenylphosphine (PPh_3), iodine, and imidazole in a mixture of dry Et_2O and CH_3CN.



Scheme 3

Reagents and conditions: (a) imidazole, PPh_3, iodine, Et_2O/CH_3CN (3:1), 0 ^{o}C to rt, 2 h, 78%; (b) Zn, dry EtOH, reflux, 4 h, 85%; (c) NaH, PMBBr, dry THF, 0 ^{o}C to rt, 4 h, 86%; (d) PPTS, MeOH, 0 ^{o}C to rt, 6 h, 72%; (e) (i) IBX, dry DMSO, dry CH_2Cl_2, rt, 2 h; (ii) $NaClO_2$, $NaH_2PO_4.2H_2O$, 0 ^{o}C to rt, 1 h, 80%; (f) DCC, DMAP, **56**, CH_2Cl_2, 0 ^{o}C to rt, 18

h, 73%; (g) $(PCy_3)_2Cl_2Ru$=CHPh (20 mol %), CH_2Cl_2 reflux, 28 h, 60%; (h) DDQ, H_2O/CH_2Cl_2 (1:9), 0 ^oC to rt, 1 h, 80%.

The compound **60** was converted into a secondary allylic alcohol **61** in 85% yield by refluxing with activated zinc in dry ethanol. After protecting the secondary hydroxyl group as its 4-methoxybenzyl ether using sodium hydride and 4- methoxybenzyl bromide, the compound **62** was subjected to deprotection of the tetrahydropyran to give alcohol **63**. The alcohol **63** was oxidized to corresponding aldehyde using 2-iodoxybenzoic acid followed by subsequent oxidation using $NaClO_2$ gave the required acid fragment **55** in 80% yield (Scheme 3).

Next the union of the two fragments **55** and **56** was achieved by using N,N'-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) in CH_2Cl_2 afforded the diene ester **54**. Treatment of **54** with the Grubbs' first generation catalyst (20% mol) under high dilution furnished a 9:1 *E*:*Z* mixture of macrocyclic lactones, from which the (*E*)-isomer **64** was isolated in 60% yield. Removal of 4-methoxybenzyl ether group in compound **64** using with DDQ in H_2O and CH_2Cl_2 (1:9) gave the target molecule putaminoxin (**47**) in excellent yield (Scheme 3).

3.1.3. Present Work:

Natural products containing 10-membered macrolide skeletons such as putaminoxin,[21] aspinolide[22] and nonenolide[23] were isolated from fungal sources and are known to possess potent phytotoxic properties. In particular, putaminoxin (**47**), a disubstituted phytotoxic nonenolide was isolated by Evidenta et al. from the culture filtrates of *Phoma Putaminum* fungus,[21] which is responsible for a necrotic leaf disease of *Erigeron annus* (Annual fleabane). Putaminoxin (**47**) is known to exhibit a range of phytotoxicities on mandarin and annual dog's mercury and also shows severe toxicity on *Erigeron annus*. Putaminoxins B (**48**), D (**50**) and E (**51**) were also isolated by the same research group[21] from *Phoma Putaminum,* which are structurally closely related to putaminoxin (**47**).[24] The absolute stereochemistry of putaminoxin (**47**) was determined by its total synthesis and the stereochemistry of C5 and C9 were revealed as *S* and *R* respectively.[20] Fascinating structural features coupled with inherent phytotoxic activities of these macrolides have attracted the attention of synthetic chemists to develop elegant approaches for the synthesis of natural products and their analogues to invent prominent leads for potent herbicides.

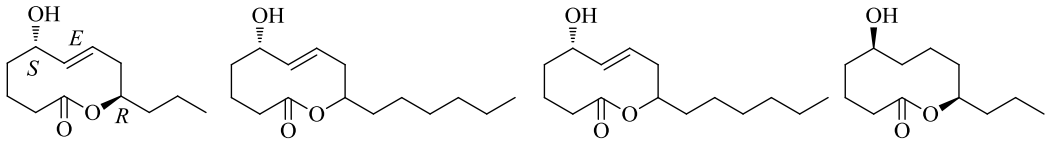


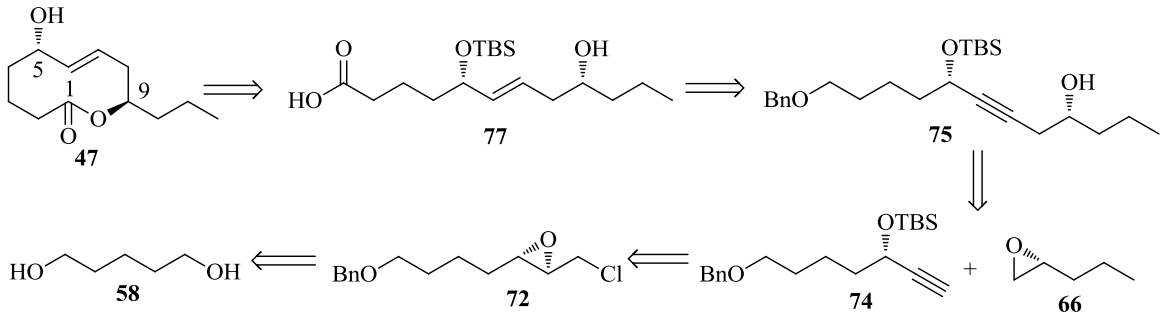
Figure 10: Putaminoxin (**47**) Putaminoxin B (**48**), D (**50**) and E (**51**).

In continuation of our interest on the total synthesis of biologically active natural products, we developed an efficient synthetic approach for the phytotoxic natural product, putaminoxin (**47**) as shown in Scheme 4.

3.1.3.1. Retrosynthetic analysis:

We retrosynthetically envisioned that, putaminoxin (**47**) could be obtained from hydroxy acid **77** *via* Yamaguchi macrolactonization. The hydroxy acid **77** would easily be prepared from a homopropargyl alcohol **75.** Alcohol **75** could be synthesized by the

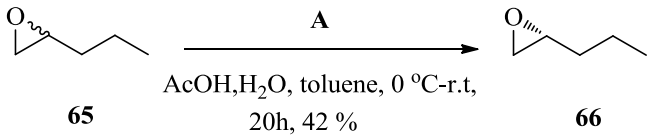
coupling reaction of terminal alkyne **74** with chiral oxirane **66**, which could in turn prepared from a commercially available 1,5-pentanediol **58** and the racemic 2-propyloxirane **65** using known transformations such as Sharpless asymmetric epoxidation and Jacobsen's kinetic resolution. In this section, we describe the total synthesis of putaminoxin (**47**) (Scheme 4).

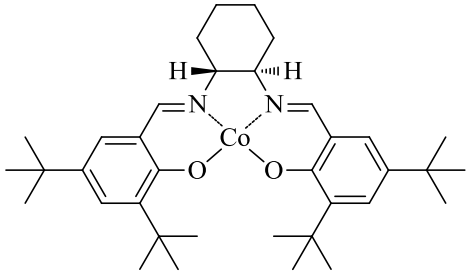


Scheme 4: Retrosynthesis of putaminoxin **(47)**

3.1.3.2. Results and discussions:

Synthesis of chiral epoxide **66** commenced form the commercially available racemic 2-propyloxirane **65**. Accordingly the racemic oxirane **65** was subjected to hydrolytic kinetic resolution (HKR)[25] using (*R*,*R*)-(+)-*N*,*N*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) and AcOH in toluene at room temperature to afford the excellent enantiorich (*R*)-2-propyloxirane **66** (94% ee, determined by chiral HPLC) in 42% yield (Scheme 5).





(*R*,*R*)-(salen)Co^{II}

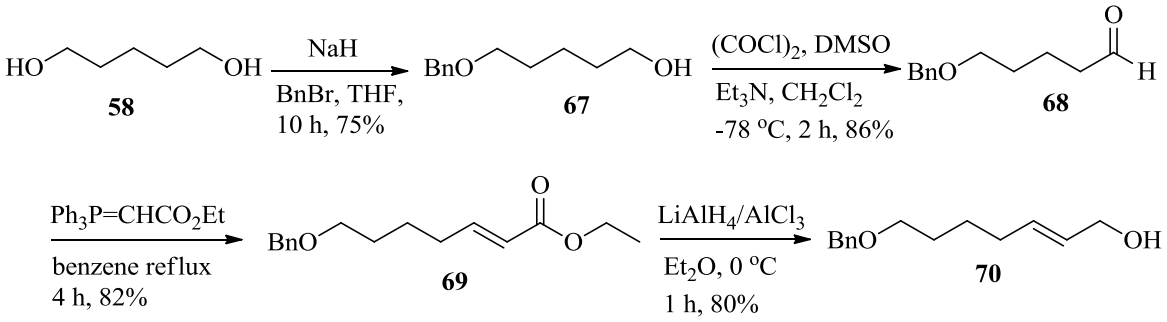
A

Scheme 5

The resolution of propyloxirane **66** was confirmed by the comparision of its optical rotation value with reported data $[\alpha]_D^{25}$ +11.0 (*c* = 1.0, $CHCl_3$); lit$^{25}[\alpha]_D^{20}$ +12.0 (*c* = 1.89, $CHCl_3$). Remaining spectral and analytical data were in good agreement with the reported literature.

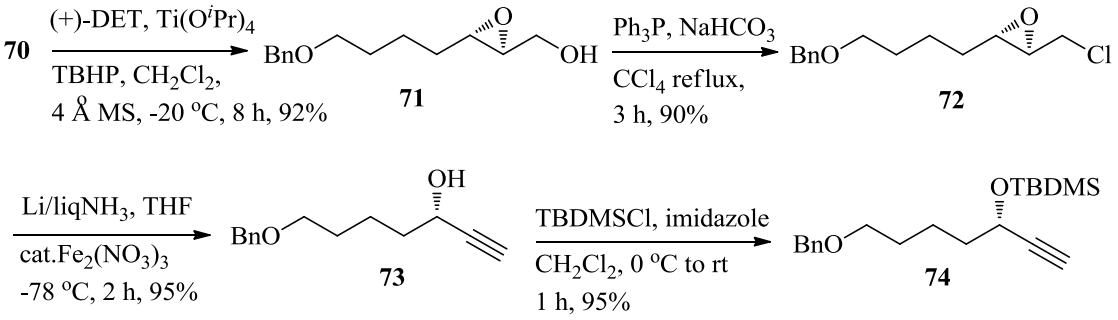
The synthesis of propargylic fragment **74** began from the 1,5-pentane diol **58** which was treated with NaH, BnBr in THF to provide the benzylprotected[26] compound **67** in 75% yield. ^{1}H NMR spectrum of compound **67** showed a characteristic signal resonationg as singlet at δ 4.47 ppm for benzylic protons and multiplet protons at δ 7.34-7.17 ppm for aromatic attached protons. The compound **67** was also confirmed by ESI-MS with $(M + H)^+$ peak at *m/z* 195. The alcohol **67** was oxidized under Swern[27] conditions in CH_2Cl_2 to afford the aldehyde **68** in 86% yield. This was clearly conveyed in the ^{1}H NMR spectrum by the resonance as a singlet at 9.74 ppm indicating alcohol was converted into aldehyde, the other protons of the compound resonated at their respected chemical shift values. The compound **68** was also characterized by ESI-MS with $(M + H)^+$ peak at *m/z* 193, and a characteristic peak at 1724 cm^{-1} in IR spectrum. The aldehyde **68** was subjected to Wittig[28] olefination reaction using stable ylide (carboethoxymethylenetriphenyl phosphorane) to produce *trans* unsaturated ester **69** in 82% yield. The appearance of signals of the two olefinic protons at δ 6.99-6.83 (m, 1H) and δ 5.77 (d, *J* = 15.26 Hz, 1H) in ^{1}H NMR spectrum confirmed the product as *trans*-olefin. The conversion was confirmed by the appearance of a quartet at δ 4.15 (*J* = 7.03 Hz, 2H) and a triplet at δ 1.29 (t, *J* = 7.03 Hz, 3H) in ^{1}H NMR spectrum which correspond to the presence of the ethyl group in unsaturated ester. The formation of **69** was further confirmed by ^{13}C NMR spectrum, which showed all the representative peaks and further supported by ESI-MS with $(M + Na)^+$ peak at *m/z* 285, and a characteristic peak at 1720 cm^{-1} in IR spectrum. The ester **69** was reduced[29] using $LiAlH_4$ and $AlCl_3$ in dry Et_2O to afford allylic alcohol **70** in 1 h with excellent yield (Scheme 6). The product was characterized by ^{1}H NMR, where olefinic protons were resonated as one set of multiples at δ 5.70-5.54 ppm and the disappearance of signals corresponding to ethyl group and appearance of signal at δ 4.03 (d, *J* = 3.77 Hz, 2H) correspond to allylic protons confirmed the conversion. This was further confirmed by ^{13}C NMR spectrum which showed all the representative peaks for olefinic as well as aliphatic and aromatic carbons.

Whereas peak at *m/z* 243 $[M + Na]^+$ in ESI-MS spectrum further confirmed this transformation. IR spectrum also revealed a characteristic peak of hydroxyl moiety at 3399 cm^{-1}.



Scheme 6

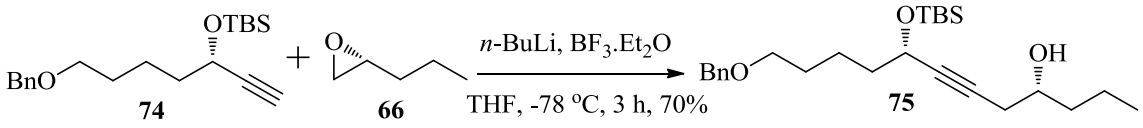
Asymmetric epoxidation[29a, 30] of allylic alcohol **70** with (+)-DET, $Ti(^iPrO)_4$ and TBHP in dry CH_2Cl_2 at –20 °C produced desired epoxy alcohol **71** in 92% yield (Scheme 7). The formation of **71** was confirmed by disappearance of signal for olefinic protons between δ 5.65-5.57 (m, 2H) ppm and appearance of two multiplets of two epoxy protons between δ 2.89-2.83 (m, 1H) and 2.80-2.76 (m, 1H) ppm in ^1H NMR spectrum. Mass peak at *m/z* 259 $[M + Na]^+$ in ESI-MS spectrum further confirmed this transformation.



Scheme 7

The epoxy alcohol **71** was subjected to chlorination[29] with Ph_3P, $NaHCO_3$ in CCl_4 reflux to produced desired epoxy chloride **72** in 90% yield (Scheme 7), whose structure was confirmed by observing the disappearance of OH stretching frequency at 3422 cm^{-1} in IR spectrum and an up field shift of hydroxyl ethylene CH_2-OH protons from δ 3.82-3.74 ppm to *δ* 3.77-.3.69 ppm in ^1H NMR spectrum. Compound **72** was also confirmed by

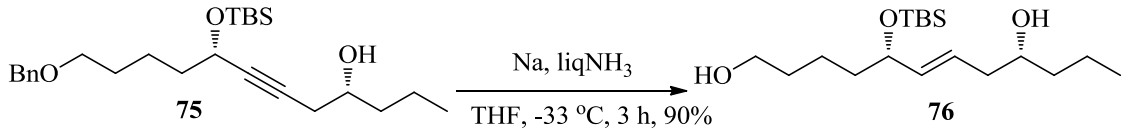
mass analysis which showed peak at *m/z* 255 $[M + H]^+$ in ESI-MS spectrum further confirmed this transformation. The chloro compound **72** was subjected to reductive ring opening using Birch reaction conditions[31] (Li, liquid NH_3, THF, –33 ^oC) to afford the propargylic alcohol **73** in 95% yield. ^1H NMR analysis revealed one new C≡C**H** proton resonance at δ 2.38 (d, *J* = 2.26 Hz, 1H) ppm and signals disappered at δ 4.14-4.07 (m, 1H) ppm, *δ* 4.00-3.86 (m, 1H) ppm, 3.77-3.69 (m, 1H) ppm.The mass spectrum analysis showed peak at *m/z* 241 $[M + Na]^+$ and further confirmed this transformation. The newly formed propargylic alcohol **73** was protected as TBS-ether using TBSCl and imidazole in dry CH_2Cl_2 to afford the TBS-ether **74** in 95% yield (Scheme 7), whose structure was confirmed by appearance of signals due to 9 protons as singlet at δ 0.90 ppm and δ 0.10 (s, 6H) ppm in ^1H NMR spectrum. This transformation was further confirmed by ^{13}C NMR spectrum which showed all the representative peaks for aliphatic, aromatic and silyl carbons. Its ESI-MS spectrum showed peak at *m/z* 333 $[M + H]^+$ provided additional proof for formation of the product. The (*R*)-2-propyloxirane **66** was opened[32] regioselectively with a terminal alkyne **74** using *n*-BuLi and $BF_3{\cdot}Et_2O$ in THF to afford the homopropargyl alcohol **75** in 70% yield (Scheme 8). The formation of compound **75** was determined by the appearance of proton signals at δ 4.36-4.26 (m, 1H), δ 3.75-3.61 (m, 1H), δ 2.47-2.21 (m, 2H), δ 1.24-1.81 (m, 10H) and δ 1.06-0.80 (m, 12H) in its ^1H NMR. It was further confirmed by ^{13}C NMR spectrum which showed all representative peaks for all carbons and whereas peak at *m/z* 441 $[M + Na]^+$ in ESI-MS spectrum further confirmed this transformation.



Scheme 8

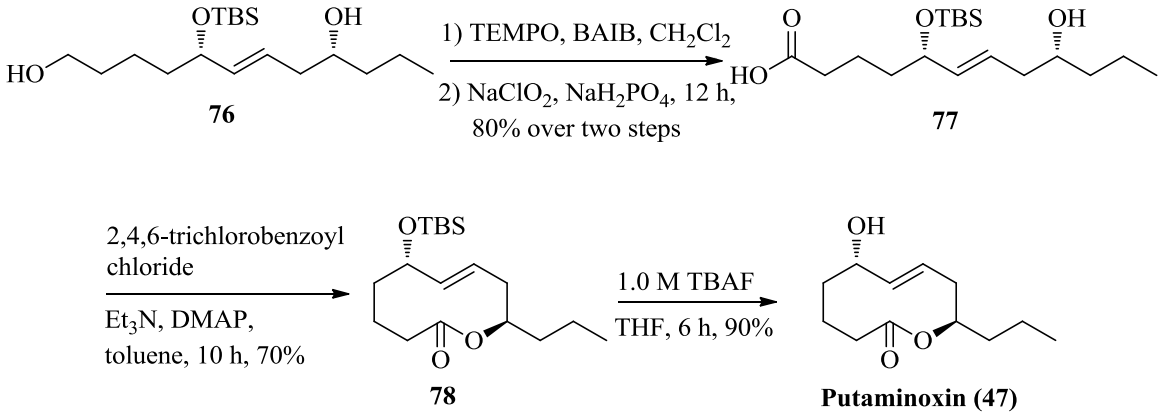
Compound **75** treated with Na in liquid NH_3 in anhydrous THF at –33 ^oC to give the debenzylated homoallylic alohol **76** with *E* stereochemistry in 90% yield[33] (Scheme 9). Diol **76** was characterized by ^1H NMR spectrum, in which aromatic peaks

corresponding to benzyl group and benzylic (Ph-$\mathbf{CH_2}$) peaks were absent and olefinic protons appered at δ 5.60-5.41 (m, 2H). Compound **76** was also characterized by ESI-MS data, which showed $(M + Na)^+$ peak at *m/z* 353.



Scheme 9

The primary hydroxyl group of 1,9-diol **76** was oxidized chemoselectively using TEMPO/BAIB in CH_2Cl_2 at ambient temperature to afford the 9-hydroxy aldehyde. Without further purification this hydroxyaldehyde was converted to 9-hydroxy carboxylic acid **77** by using *Pinnicks* conditions ($NaClO_2/NaH_2PO_4.2H_2O$) (Scheme 10).[34] The ^1H NMR spectrum of compound **77** revealed the disappearance of the protons resonance at δ 3.61 (t, *J* = 6.79 Hz, 2H) of the methylinic protons attached to primary hydroxyl functionality. All other protons of the structure **77** resonated at their expected chemical shift values.



Scheme 10

Compound **77** was further confirmed by its ESI-MS data, which showed $(M + H)^+$ peak at *m/z* 367 and in IR spectrum characteristic peak of acid moiety at 1712 cm^{-1}. Hydroxy acid **77** was then subjected to Yamaguchi macrolactonization[35] using 2,4,6-

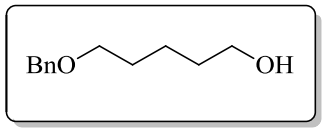
trichlorobenzoylchloride, Et_3N and DMAP in toluene reflux to afford the macrolide **78** in 70% (Scheme 10). Macrolide **78** showed a characteristic sharp absorption peaks at 1730 cm^{-1} correspond to carbonyl group in IR spectrum. Formation of **78** was further confirmed by appearance of signal for OC**H** proton as a multiplate at δ 5.05-4.90 ppm in ^{1}H NMR spectrum. This was further sufforted by ^{13}C NMR spectrum which showed all the representative peaks for olefinic as well as aliphatic carbons and peak at *m/z* 349 $[M + Na]^+$ in ESI-MS. Removal of TBS ether in macrolide **78** using 1.0 M TBAF in THF gave the target molecule, putaminoxin (**47**) in 90% yield (Scheme 10). ^{1}H NMR spectrum showed disappearance of the singlet at δ 0.87 ppm, corresponding to nine *t*-butyl protons as well as the doublet at δ 0.03 (d. J = 7.40 Hz, 6H) ppm for six methyl protons of the TBS group. This was further confirmed by ^{13}C NMR spectrum which showed all the representative peaks for olefinic as well as aliphatic corbans and peak at *m/z* 235 $[M + Na]^+$ in ESI-MS spectrum. The ^{1}H NMR, ^{13}C NMR, IR, Mass spectral data and optical rotation value of the synthetic putaminoxin (**47**) were in good agreement with a natural product reported in literature.[21, 20]

In conclusion, we have demonstrated an efficient linear synthetic approach to the phytotoxic macrolide, putaminoxin (**47**)**.** This approach utilizes readily available precursors, simple and very interesting protocols such as Sharpless asymmetric epoxidation, Birch reduction, Jacobsen's kinetic resolution of racemic epoxide and Yamaguchi lactonization's makes it an attractive strategy for the generation of new and more biologically potent analogues of the natural product.

Experimental Section

3.1.4. EXPERIMENTAL SECTION

3.1.4.1. 5-(Benzyloxy)pentane-1-ol (67):



To a stirred suspension of 55% dispersion of NaH in mineral oil (0.92 g, 38.4 mmol) in dry THF (20 mL) was added a solution of 1,5-pentanediol **58** (2.0 g, 19.2 mmol) in dry THF (25 mL) dropwise over a period of 15 min at 0 °C. The mixture was then allowed to stir at room temperature for 45 min. To this solution was added benzyl bromide (2.32 mL, 19.2 mmol) at 0 °C over a period of 10 min and then TBAI (40 mg, 1.92 mmol). The resulting mixture was stirred at room temperature for 10 h and then quenched with cold water at 0 °C. The crude mixture was extracted with EtOAc (3 x 20 mL) and the organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (EtOAc/hexanes, 3:7) to afford the mono-benzyl ether **67** (2.78 g, 75 %) as a colorless liquid.

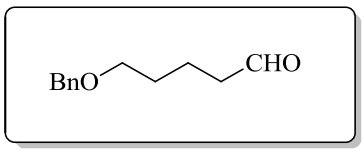
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.17-7.34 (m, 5H), 4.17 (s, 2H), 3.61 (t, *J* = 5.1 Hz, 2H), 3.45 (t, *J* = 6.6 Hz, 2H), 1.37-1.71 (m, 6H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.3, 128.1, 127.5, 127.3, 72.7, 70.1, 62.2, 32.3, 29.3, 22.3 ppm.

IR (neat): 3387, 3030, 2928, 2858, 1454, 1362, 1206, 1097, 737, 697, 610 cm^{-1}.

ESI-MS: *m/z* 194 $[M + H]^+$.

3.1.4.2. 5-(Benzyloxy)pentanal (68):



To a solution of oxalylchloride (1.64 mL, 18.6 mmol) in dry CH_2Cl_2 (10 mL) at –78 °C under N_2 atmosphere was added DMSO (1.58 mL, 22.3 mmol) dropwise over 10

min. The mixture was stirred for an additional 10 min and then a solution of alcohol **67** (2.4 g, 12.4 mmol) in CH_2Cl_2 (20 mL) was added dropwise. The resulting mixture was stirred for 30 min and then Et_3N (10.3 mL, 74.4 mmol) was added dropwise at −78 °C and then stirring was continued at room temperature for 30 min. After completion, the mixture was quenched with ice cold water (10 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent and purification on small pad of silica gel gave the 5-(benzyloxy)pentanal **68** (2.04 g, 86%) as a colourless liquid.

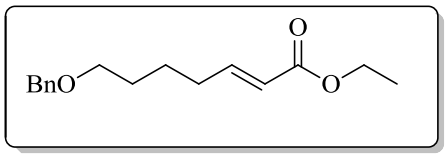
^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.74 (s, 1H), 7.21-7.33 (m, 5H), 4.46 (s, 2H), 3.45 (t, *J* = 6.04 Hz, 2H), 2.44 (t, *J* = 6.78 Hz, 2H), 1.58-1.79 (m, 4H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 202.5, 138.0, 128.3, 127.5, 127.4, 72.8, 69.6, 43.4, 28.9, 18.8 ppm.

IR (Neat): 3030, 2937, 2860, 2722, 1724, 1453, 1363, 1205, 1101, 1026, 909, 739, 698, 610 cm^{-1}.

ESI-MS: *m/z* 193 $(M + Na)^+$.

3.1.4.3. (*E*)-Ethyl-7-(benzyloxy)hept-2-enoate (69):



A solution of the above aldehyde **68** in anhydrous benzene (10 mL) was added dropwise to the solution of $Ph_3P{=}CHCO_2Et$ (3.2 g, 9.4 mmol) in benzene (15 mL) and refluxed at 80 ºC. After 1h, the solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (EtOAc/hexanes, 1:9) to afford the ester **69** (1.67 g, 82%) as a colorless liquid.

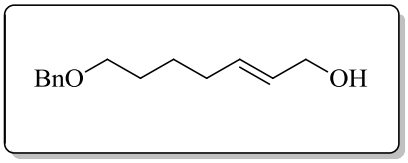
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.20-7.35 (m, 5H), 6.83-6.99 (m, 1H), 5.77 (d, *J* = 5.6 Hz, 1H), 4.46 (s, 2H), 4.15 (q, *J* = 7.0, 14.0 Hz, 2H), 3.44 (t, *J* = 5.4 Hz, 2H), 2.22 (q, *J* = 7.3, 14.0 Hz, 2H), 1.54-1.68, (m, 4H), 1.29 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.4, 148.6, 138.3, 127.3, 127.2, 127.1, 121.2, 72.7, 69.5, 60.0, 31.6, 28.9, 24.5, 14.0 ppm.

IR (neat): 2927, 2856, 1720, 1654, 1455, 1366, 1266, 1197, 1165, 1105, 1024, 982, 737, 698 cm^{-1}.

ESI-MS: *m/z* 285 $[M + Na]^+$.

3.1.4.4. (*E*)-7-(Benzyloxy)hept-2-en-1-ol (70):



To a stirred suspension of $LiAlH_4$ (326 mg, 8.6 mmol) in dry Et_2O (10 mL) at −78 °C under N_2 atmosphere was added a solution of $AlCl_3$ (392 mg, 2.9 mmol) in Et_2O (7 mL) over a period of 5 min. After complete addition, the mixture was allowed to stir at room temperature for 30 min. To this stirred suspension was added a solution of *α,β*-unsaturated ester **69** (1.5 g, 5.73 mmol) in dry Et_2O (10 mL) over a period of 10 min. After stirring at 0 °C for 30 min, the mixture was quenched with saturated Na_2SO_4 and filtered through the pad of celite. The residue was washed with EtOAc (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the crude residue by silica gel column chromatography (EtOAc/hexanes, 2:8) afforded the compound **70** (1.0 g, 80%) as a colourless viscous liquid.

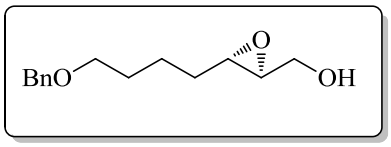
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.20-7.33 (m, 5H), 5.54-5.70 (m, 2H), 4.46 (s, 2H), 4.03 (d, *J* = 3.7 Hz, 2H), 3.43 (t, *J* = 6.0 Hz, 2H), 2.05 (q, *J* = 6.7, 12.8 Hz, 2H), 1.41-1.66, (m, 4H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): 138.4, 132.4, 129.2, 128.6, 127.5, 127.3, 72.7, 70.2, 63.2, 31.7, 29.0, 25.5 ppm.

IR (neat): 3399, 3029, 2929, 2857, 1454, 1364, 1206, 1096, 1006, 971, 737, 697, 610 cm^{-1}.

ESI-MS: *m/z* 243 $[M + Na]^+$.

3.1.4.5. ((2*S*,3*S*)-3-(-4-(Benzyloxy)butyl)oxiran-2-yl)methanol (71):



To a stirred suspension of activated 4 Å molecular sieves (1.0 g) in dry CH_2Cl_2 (10 mL) was added L-(+)-DET (0.2 mL, 1.0 mmol) and $Ti(O^iPr)_4$ (0.30 mL, 1.0 mmol) and the mixture was stirred for 30 min at –20 °C. To this mixture, a solution of allyl alcohol **70** (0.9 g, 4.0 mmol) in dry CH_2Cl_2 (15 mL) was added dropwise and the mixture was stirred for another 30 min at –20 °C. Then a solution of TBHP (4.3 mL, 4.0 M in toluene, 9.0 mmol) was added and the resulting mixture stirred at the same temperature for 8 h. It was then warmed to 0 °C and then quenched with water (5 mL) and a solution of NaOH (20%). The resulting mixture was vigorously stirred for 3 h at room temperature and then filtered through celite. The residue was washed well with CH_2Cl_2 (3 x 20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. Removal of the solvent under reduced pressure followed by purification on silica gel column chromatography (EtOAc/hexanes, 3:7) to afford the epoxy alcohol **71** (888 mg, 92%) as a colourless viscous liquid.

$[\alpha]_D^{27}$: –19.3 (*c* 1.0, $CHCl_3$).

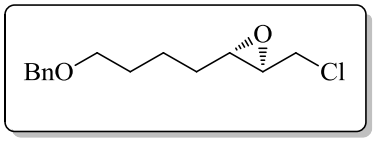
^{1}H NMR ($CDCl_3$, 300 MHz): 7.17-7.32 (m, 5H), 4.43 (s, 2H), 3.74-3.82 (m, 1H), 3.47-3.57 (m,1H), 3.41 (t, *J* = 6.0 Hz, 2H), 2.83-2.89 (m, 1H), 2.76-2.80 (m, 1H), 1.44-1.70 (m, 6H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): 138.3, 128.2, 127.5, 127.4, 72.7, 69.9, 61.6, 58.4, 55.8, 31.2, 29.3, 22.5 ppm.

IR (neat): 3422, 2928, 2859, 1727, 1455, 1365, 1276, 1099, 1026, 877, 740, 698 cm^{-1}.

ESI-MS: *m/z* 259 $[M + Na]^+$.

3.1.4.6. ((2*S*,3*R*)-2-(-4-(Benzyloxy)butyl)-3-(chloromethyl)oxirane (72):



To a stirred solution of triphenylphosphine (0.95 g, 3.6 mmol) in anhydrous CCl_4 (10 mL) were added a solution of epoxy alcohol **71** (0.7 g, 3.0 mmol) in CCl_4 (10 mL) followed by $NaHCO_3$ (25 mg, 0.3 mmol). The reaction mixture was stirred at reflux temperature for 3 h. After completion, it was cooled to room temperature and then solvent was removed under reduced pressure. Purification of the crude product by silica gel column chromatography (EtOAc/hexanes, 0.5:9.5) afforded the compound **72** (0.678 g, 90%) as a colourless liquid.

$[\alpha]_D^{25}$: +18.7 (*c* 1.0, $CHCl_3$).

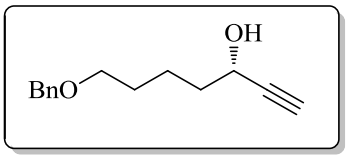
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.21-7.35 (m, 5H), 4.47 (s, 2H), 4.35-4.42 (m, 1H), 4.07-4.14 (m, 1H), 3.86-4.00 (m, 1H), 3.70-3.77 (m, 1H), 3.46 (t, *J* = 5.8 Hz, 2H), 1.49-2.02 (m, 6H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.3, 128.2, 127.4, 127.3, 72.7, 69.7, 58.7, 56.9, 44.6, 31.0, 29.2, 22.4 ppm.

IR (neat): 3030, 2935, 2860, 1493, 1454, 1362, 1258, 1207, 1102, 1026, 739, 710, 649 cm^{-1}.

ESI-MS: *m/z* 255 $[M + H]^+$.

3.1.4.7. (*S*)-7-(Benzyloxy)hept-1-yn-3-ol (73):



To a freshly condensed solution of anhydrous NH_3 (20 mL) in a two-necked round-bottomed flask fitted with a cold condenser, were added a catalytic amount of $Fe(NO_3)_3$ followed by cautious addition of Li metal pieces (100 mg, 14.16 mmol) at –33 ^oC. The resulting grey suspension was stirred for 1h at the same temperature. A solution of epoxy chloride **72** (0.6 g, 2.36 mmol) in dry THF (10 mL) was added dropwise and then stirring was continued for another 2 h at –33 ^oC. To this mixture, solid NH_4Cl was added and then ammonia was allowed to evaporate slowly. The residue was dissolved in ether and then filtered though small pad of celite. The filtrate was dried over Na_2SO_4 and

the crude product was purified by silica gel column chromatography (EtOAc/hexanes, 2:8) to afford the propargyl alcohol **73** (4.9 g, 95%) as a colourless liquid.

$[\alpha]_D^{25}$: –7.3 (*c* 1.0, $CHCl_3$).

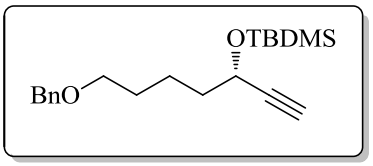
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.19-7.34 (m, 5H), 4.48 (s, 2H), 4.32 (t, *J* = 5.2 Hz, 1H), 3.46 (t, *J* = 6.0 Hz, 2H), 2.28 (d, *J* = 2.2 Hz, 1H), 1.40-1.76 (m, 6H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.3, 128.2, 127.5, 127.4, 84.9, 72.8, 72.7, 70.0, 61.9, 37.26, 29.2, 21.7 ppm.

IR (neat): 3416, 2927, 2858, 1697, 1456, 1385, 1259, 1214, 1175, 1096, 759, 697, 668 cm^{-1}.

ESI-MS: *m/z* 241 $[M + Na]^+$.

3.1.4.8. ((*S*)-7-(Benzyloxy)hept-1-yn-3-yloxy)(*tert*-butyl)dimethylsilane (74):



To a solution of propargyl alcohol **73** (0.4 g,1.84 mmol) in dry CH_2Cl_2 (10 mL) under N_2 atmosphere, were added imidazole (20 mg, 2.76 mmol) followed by TBDMSCl (0.331 g, 2.20 mmol) at 0 °C and the stirring was continued for 1h at room temperature. Then the mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The organic layer was washed with water (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexanes, 0.5:9.5) to give the TBSDMS ether **74** (0.578 g, 95%) as a colorless liquid.

$[\alpha]_D^{25}$: –9.3 (*c* 1.0, $CHCl_3$).

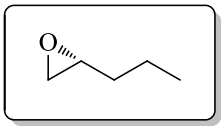
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.21-7.36 (m, 5H), 4.47 (s, 2H), 4.27-4.36 (m, 1H), 3.45 (t, *J* = 6.2 Hz, 2H), 2.31 (d, *J* = 2.3 Hz, 1H), 1.43-1.77 (m, 6H), 0.90 (s, 9H), 0.10 (s, 6H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 136.7, 128.4, 127.5, 127.4, 85.5, 72.8, 72.0, 70.2, 62.6, 38.3, 29.3, 25.8, 21.8, 18.2, -5.1 ppm.

IR (neat): 3308, 2930, 2857, 1461, 1361, 1254, 1104, 936, 837, 776, 736, 696, 665 cm^{-1}.

ESI-MS: *m/z* 333 $[M + Na]^+$.

3.1.4.9. (*R*)-2-Propyloxirane (66):



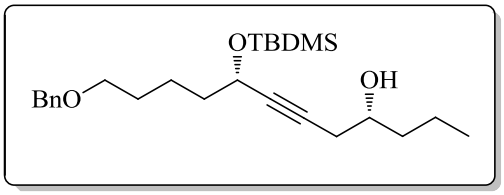
A mixture of (*R,R*)-(+)-*N*-*N*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt (II) (42 mg, 0.07 mmol) in toluene (0.2 mL) and acetic acid (84 mg, 0.140 mmol) was stirred under open air for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure and the brown residue was dried under reduced pressure. The 2-propyl oxirane **65** (3.0 g, 34.8 mmol) was added in one portion at 0 ºC and then water (0.35 mL, 19.2 mmol) was added dropwise over 10 min. The mixture was then allowed to room temperature and stirred for 20 h. The desired (*R*)-2-propyloxirane **66** (1.26 g, 42%) was isolated as a colourless liquid by distillation from the reaction mixture at atmospheric pressure.

$[\alpha]_D^{25}$: +11.0 (*c* 1.0, $CHCl_3$).

^1H NMR ($CDCl_3$, 300 MHz): δ 2.81-2,88 (m, 1H), 2.69 (dd, *J* = 3.7, 5.2 Hz, 1H), 2.40 (dd, *J* = 2.6, 5.2 Hz, 1H), 1.44-1.55 (m, 4H), 0.98 (t, *J* = 6.7 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 46.3, 41.0, 31.2, 23.4, 15.8 ppm.

3.1.4.10. (4*R*, 8*S*)-12-(Benzyloxy)-8-(*tert*-butyldimethylsilyloxy)dodec-6-yn-4-ol (75):



To a stirred solution of ((*S*)-7-(Benzyloxy)hept-1-yn-3-yloxy)(*tert*-butyl)dimethylsilane **74** (0.5 g, 1.5 mmol) in anhydrous THF (10 mL) was added a solution of *n*-BuLi (1.6 M in hexane, 1.04 mL, 1.65 mmol) under an N_2 atmosphere at –78 °C. The mixture was allowed to stir for 30 min at the same temperature. $BF_3 \cdot OEt_2$ (0.2 mL, 1.65 mmol) was then added slowly. After 10 min, a solution of (*R*)-2-propyloxirane **66** (0.5 g, 5.81mmol) in anhydrous THF (10 mL) was added and the mixture was stirred

for further 3h at –78 °C. The mixture was then quenched with sat.$NaHCO_3$ (10 mL) and sat.NH_4Cl (10 mL) at –78 °C. The mixture was allowed to warm to room temperature and then extracted with EtOAc (3 x 20 mL) and dried over Na_2SO_4. Removal of the solvent followed by purification on silica gel column chromatography (EtOAc/hexanes, 30:70) to afford compound **75** (0.44 g, 70%) as a colourless viscous liquid.

$[\alpha]_D^{25}$: –10.7 (*c* 1.0, $CHCl_3$).

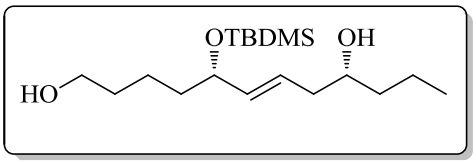
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.21-7.35 (m, 5H), 4.47 (s, 2H), 4.26-4.36 (m, 1H), 3.69 (m, 1H), 3.44 (t, *J* = 6.2 Hz, 2H), 2.21-2.47 (m, 2H), 1.24-1.81 (m, 10H), 0.80-1.06 (m, 12H), 0.09 (d, *J* = 4.6 Hz, 6H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.6, 128.2, 127.5, 127.4, 84.5, 80.5, 72.8, 70.2, 69.7, 63.0, 38.6, 38.3, 29.3, 27.7, 25.7, 22.0, 18.7, 18.2, 13.9, -4.5, -5.0 ppm.

IR (neat): 3415, 2925, 2855, 1630, 1383, 1272, 1106, 1036, 840, 703cm^{-1}.

ESI-MS: *m/z* 441 $[M + Na]^+$.

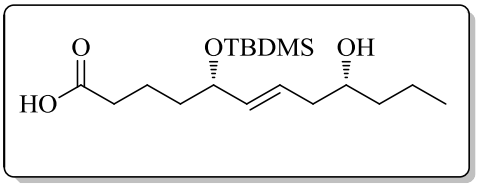
3.1.4.11. (5*S*,9*R*,*E*)-5-(*tert*-Butyldimethylsilyloxy)dodec-6-ene-1,9-diol (76):



To a freshly condensed solution of anhydrous NH_3 (25 ml), in a two-necked round-bottomed flask fitted with a cold condenser was added cautiously a freshly cut Na metal (230 mg, 10 mmol) portion-wise at –78 ^oC. The resulting deep blue suspension was stirred for 30 min at the same temperature. A solution of homopropargylic alcohol **75** (0.4 g, 1.0 mmol) in dry THF (10 mL) was added dropwise and then stirred for another 2 h at –78 ^oC. After completion, the mixture was quenched with solid NH_4Cl and then ammonia was allowed to evaporate slowly. The residue was dissolved in ether and then filtered through small pad of celite. The filtrate was dried over Na_2SO_4 and the crude product was purified by silica gel column chromatography (EtOAc/hexanes, 70:30) to afford the title compound **76** (0.284 g, 90%) as a colourless liquid.

$[\alpha]_D^{25}$:	+7.7 (*c* 2.0, $CHCl_3$).
^1H NMR ($CDCl_3$, 300 MHz):	δ 5.41-5.60 (m, 2H), 4.03-4.15 (m, 1H), 3.69-3.76 (m, 1H), 3.61 (t, *J* = 6.7 Hz, 2H), 2.0-2.29 (m, 2H), 1.21-1.62 (m, 10H), 0.94 (t, *J* = 7.5 Hz, 3H), 0.89 (s, 9H), 0.03 (d, *J* = 6.7 Hz, 6H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz):	δ 137.1, 125.8, 73.2, 70.7 62.7, 40.2, 38.8, 37.9, 32.5, 25.8, 21.3, 18.8, 18.1, 14.0, -4.3, -4.7 ppm.
IR (neat):	3351, 2931, 2860, 1463, 1362, 1242, 1065, 973, 836, 775, 670 cm^{-1}.
ESI-MS:	*m/z* 353 $[M + Na]^+$.

3.1.4.12. (5*S*, 9*R*, *E*)-5-(*tert*-Butyldimathylsilyloxy)-9-hydroxydodec-6-enoic acid (77):



BAIB (0.3 g, 0.935 mmol) was added to a solution of **76** (0.28 g, 0.85 mmol) and TEMPO (0.014 g, 0.085 mmol) in dry CH_2Cl_2 (5 mL) at 0 ^oC. The mixture was stirred for 20 min at room temperature. After complete conversion, the mixture was diluted with CH_2Cl_2 (20 mL) and washed with saturated aqueous $Na_2S_2O_3$ solution (10 mL) and then extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (10 mL) followed by brine solution (10 mL), and then dried over Na_2SO_4 and concentrated *in vacuo*. The crude aldehyde was immediately used for the next reaction.

A solution of $NaClO_2$ (0.12 g, 1.27 mmol) in water (2 mL) was added dropwise within 5 min at room temperature. To a stirred solution of above aldehyde in DMSO (3 mL) was added NaH_2PO_4 (0.27 g, 1.7 mmol) in water (3 mL). The mixture was left overnight at room temperature, and then 5% aqueous $NaHCO_3$ (10 mL) solution was added. The aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL) and the organic layer was washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The

residue was purified by silica gel column chromatography (EtOAc/hexnaes, 30:70) to afford the title compound **77** (0.233 g; 80% yield over the two steps) as a yellow oil.

$[\alpha]_D^{25}$: –18.1 (*c* 0.33, $CHCl_3$).

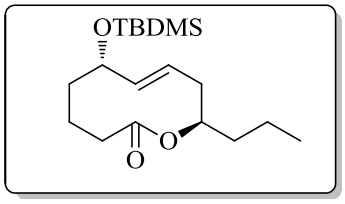
^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.44-5.59 (m, 2H), 4.06-4.16 (m, 1H), 3.56-3.66 (m, 1H), 2.35 (t, *J* = 6.79 Hz, 2H), 2.03-2.28 (m, 2H), 1.19-1.74 (m, 8H), 0.94 (t, *J* = 7.5 Hz, 3H), 0.89 (s, 9H), 0.03 (d, *J* = 7.5 Hz, 6H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 178.8, 136.7, 126.0, 72.8, 70.7, 40.1, 38.8, 37.4, 31.8, 25.8, 22.5, 20.4, 18.7, 14.0, -4.7, -4.8 ppm.

IR (Neat): 2956, 2927, 2855, 1712, 1463, 1253, 1084, 973, 835, 776, 668 cm^{-1}.

ESI-MS: *m/z* 367 $[M + Na]^+$.

3.1.4.13. (6*S*,10*R*,*E*)-6-(*tert*-Butyldimethylsilyloxy)-10-propyl-3,4,5,6,9,10-hexahydro-2*H*-oxecin-2-one (78):



To a stirred solution of compound **77** (0.15 g, 0.47 mmol) and Et_3N (100 mg, 0.71 mmol) in dry THF (3 ml), 2,4,6-trichlorobenzoyl chloride (0.13 ml, 0.71 mmol) was added at room temperature. The resulting mixture was stirred at room temperature for 3 h and then a solution of DMAP (0.29 g, 2.35 mmol) in dry toluene (20 mL) was added. The mixture was refluxed for 10 h and then cooled to room temperature. After complete conversion the mixture was quenched with a saturated $NaHCO_3$ solution and then aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (EtOAc/hexanes, 20:80) to afford the macrolide **78** (0.099 g, 70%) as a colourless oil.

$[\alpha]^{25}_D$: –8.7 (*c* 0.30, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.43 (ddd, *J* = 4.3, 10.0, 15.0 Hz, 1H), 5.27 (dd, *J* = 9.0, 15.0 Hz, 1H), 4.90-5.05 (m, 1H), 4.0 (dt, *J* = 3.0,

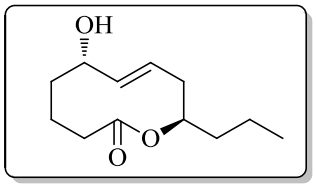
10.0, 19.0 Hz, 1H), 2.37-2.57 (m, 2H), 1.80-2.0 (m, 4H), 1.22-1.75 (m, 6H), 0.90 (t, *J* = 7.40 Hz, 3H), 0.87 (s, 9H), 0.03 (d, *J* = 7.4 Hz, 6H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz,): δ 174.6, 138.3, 129.5, 75.6, 72.3, 40.3, 39.6, 36.7, 35.8, 22.2, 18.9, 18.2, 14.0, 13.8, -4.3, -4.7 ppm.

IR (neat): 3433, 2962, 2935, 2890, 1730, 1670, 1450, 1366, 1183, 1007.

ESI-MS: *m/z* 249 $[M + Na]^+$.

3.1.4.14. (6*R*,10*R*,*E*)-6-Hydroxy-10-propyl-3,4,5,6,9,10-hexahydro-2*H*-oxecin-2-one (47):



To a stirred solution of **78** (0.07 g, 0.215 mmol) in dry THF (7 mL) was added 1.0 M TBAF in THF (0.34 ml, 0.34 mmol) at 0 ^oC. The mixture was stirred for 6 h and then diluted with water and extracted with EtOAc (3 x 10 mL). The organic layers were washed with brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Removal of the solvent followed by purification using silica gel column chromatography (EtOAc/hexanes, 3:7) afforded the target molecule putaminoxin (**47**) (35 mg, 90%) as a colourless oil.

$[\alpha]^{25}_D$: –25.3 (*c* 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.54 (ddd, *J* = 4.7, 10.4, 15.3 Hz, 1H), 5.32 (dd, *J* = 9.3, 15.5 Hz, 1H), 4.97-5.10 (m, 1H), 4.01 (dt, *J* = 3.4, 10.2 Hz, 1H), 2.31-2.50 (m, 2H), 1.83-2.09 (m, 4H), 1.20-1.75 (m, 6H), 0.93 (t, *J* = 7.3 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.7, 137.2, 131.7, 75.4, 40.3, 38.7, 36.4, 35.7, 22.3, 19.2, 13.9 ppm.

IR (neat): 3433, 2959, 2930, 2871, 1729, 1641, 1442, 1365, 1182, 1007 cm^{-1}.

ESI-MS: *m/z* 235 $[M + Na]^+$.

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Spectra

CHAPTER III

Section B

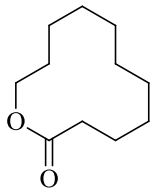
Stereoselective total synthesis of 11-α- and 11-β-Methoxycurvularin

3.2.1. Introduction:

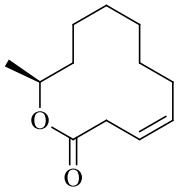
Marine microorganisms have evolved to biosynthesize biologically interesting and chemically diverse compounds. Sponge-associated fungi yielding cytotoxic metabolites have received increasing attention at a rate much faster than those of other unicellular organisms.[1,2] One group of compounds is the macrolides, which have been of much interest because of their flexible ring conformation and well-known antibiotic activities[3]. Recently, macrolides have also been reported as cytotoxic and potential antitumor agents[4]. Macrocyclic structures that have one or more ester linkages are generally referred to as macrolides or macrocyclic ring lactones, in some cases, macrocyclic lactams have also been described as macrolides. Medium ring compounds, those containing 8-11 atoms in the ring[5], are the subject of continuous interest in organic synthesis, as they constitute the framework of many natural products. The useful properties of macrolides range from perfumery to biological and medicinal activities. The new findings in the field of antitumor activity and other antibiotic macrolides, together with pheromones and plant growth regulators with macrolactone framework are an inspiration to chemists to study macrolides. The nomenclature of macrolides is something new but straightforward. Trivial names are widely used, especially for naturally occurring macrocyclic lactones. According to IUPAC rules, macrolides as well as other lactones formed from aliphatic acids should be named by adding "olide" as a suffix to the name of the hydrocarbon with the same number of carbon atoms. The numbering starts from the ester carbonyl carbon. The IUPAC rules also gave an alternative way of naming lactones based on the rules for naming heterocycles. According to this rule, the lactones are named as oxacyclo ketones and the numbering starts from the ring oxygen. AutoNom[6] naming program uses this latter rule, although the "olide" naming is generally used in the literature. By way of example, Figure 1 shows the alternative names of two macrolides **1** and **2**. The macrolide structures of this work are sometimes identified by their trivial names.

The isolation and structural elucidation of almost all of the known ten-membered-ring lactones were reported in the last 30 years. Before 1975, the only described decalactone was the jasmine ketolactone, identified in Italian jasmine oil in 1942. From the monocyclic lactones diplodialides (isolated in 1975) to the bicyclic lactone Sch

642305 (isolated in 2003) and very recently isolated Botryolides (isolated in 2008), more than ten structural groups, several of which possess three or even more lactones with different structures, were isolated. The isolation and structural elucidation of almost all of the known ten-membered-ring lactones were reported in the last 30 years. Before 1975, the only described decalactone was the jasmine ketolactone, identified in Italian jasmine oil in 1942. From the monocyclic lactones diplodialides (isolated in 1975) to the bicyclic lactone Sch 642305 (isolated in 2003) and very recently isolated Botryolides (isolated in 2008), more than ten structural groups, several of which possess three or even more lactones with different structures, were isolated.



Undecanolide
Oxacyclododecan-2-one (1)



(3*Z*, 11*S*)-3-Dodecene-11-olide
Ferrulactone II (trivialname) (2)
(12*S*, 4*Z*)-methyloxacyclododecen-2-one

Figure 1

The chemistry of macrocyclic compounds originated in 1926 when Ruzicka[7] elucidated the structures of civetone (**3**) and muscone (**4**) as large-ring ketones. Before it was believed on the basis of Baeyer's strain theory that large-ring compounds would be too unstable to exist because the internal bond angles in large planar rings do not have tetrahedral geometry. In fact, large rings are able to adopt non-planar conformations and they are flexible and almost strain free. In 1927 Kerchbaum isolated the first macrocyclic lactones, exaltolide (**5**) and ambrettolide (**6**) from *Angelica* root and *Ambrette* seed oil respectively[8]. The discovery of these vegetable musk oils aroused interest in finding synthetic routes to these and related macrolides owing to commercial importance in the fragrance industry[9]. Even today exaltolide (**5**) is one of the most widely produced macrocyclic musk lactone. The production was estimated at 200 tons in 1996, the importance of macrocyclic musks is increasing due to their ready biodegradability[10] (Figure 2).

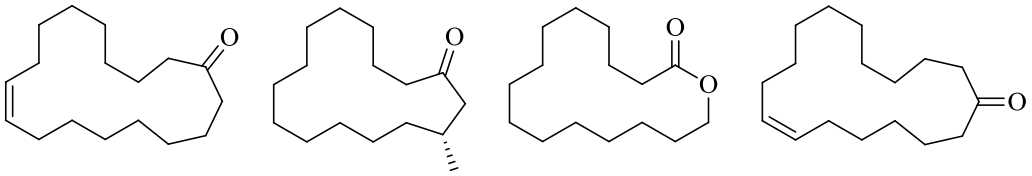


Figure 2

3.2.1.1. Bicyclic Aromatic Ring Lactones

Some important biologically active 10, 12 and 14 membered ring lactones are described below.

3.2.1.2. Xestodecalactones

Sporostatin (M5032) (**7**), isolated from the fungus of *Sporormiella* sp.[11] is an inhibitor of cyclic adenosine 3′,5′-monophosphate phosphodiesterase (cAMP-PDE).[12] Sporostatin showed inhibitory activities against cAMP-PDE from bovine heart expressed in terms of 50% inhibition (IC_{50}) was 41 µg/mL and it was noncompetitive against cAMP. It was found to be a specific inhibitor of epidermal growth factor (EGF) receptor, tyrosine kinase *in vitro*.

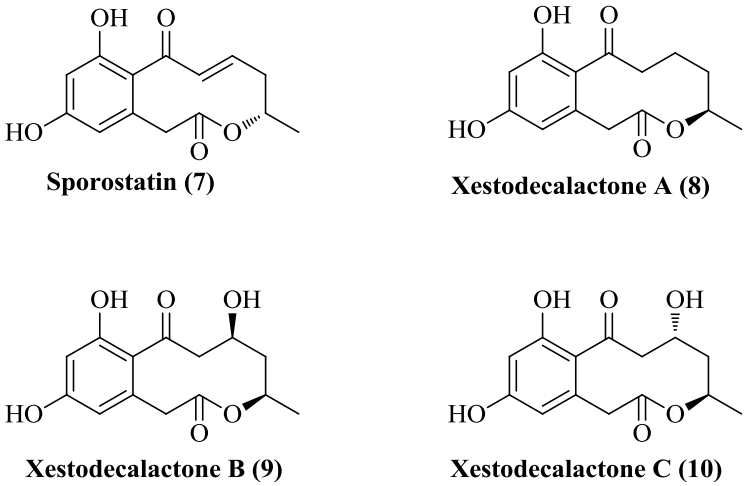
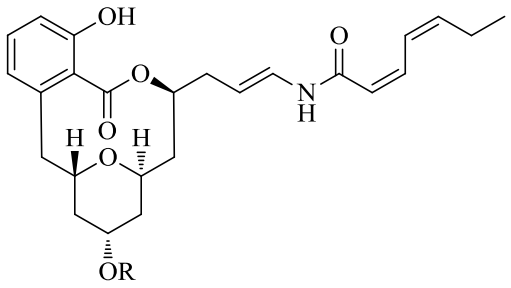


Figure 3

The xestodecalactones **A** (**8**), **B** (**9**), and **C** (**10**) are secondary metabolites of an isolate of the fungus *Penicillium cf. montanense* obtained from the marine sponge *Xestospongia exigua* (Figure 3). These compounds possess pronounced toxic effects that

may be related to fungal pathogenic effects in plants.[13] Xestodecalactone **B** (**9**) has been shown to exhibit antifungal activity against *Candida albicans*.[14]

3.2.1.3. Apicularens



(-)-Apicularen A (R = H) (11)

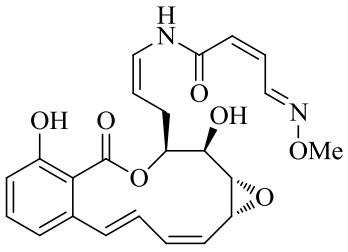
(-)-Apiclarin B (R = *N*-acetyl-*b*-glucosamine) (12)

Figure 4

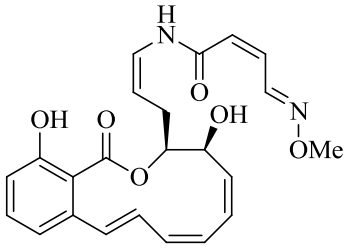
(-)-Apicularen A (**11**) a highly cytostatic 12-membered macrolide, was first isolated from a variety of strains of the myxobacterial genus Chondromyces in 1998 (Figure 4).[15] Apicularens not only showed the potent cytostatic activity against a wide range of human cancer cell lines, such as ovarian, prostate, lung, kidney, cervix, leukaemia, and histiocytic cells, with IC_{50} values in the range of 0.23-6.79 nM, but also exhibited antiangiogenesis properties,[16a] induction of apoptosis,[16b] production of nitric oxide,[16c] and inhibition of vacuolar (H^+)-ATPase (V-ATPase).[16d]

3.2.1.4. Benzolactone enamides

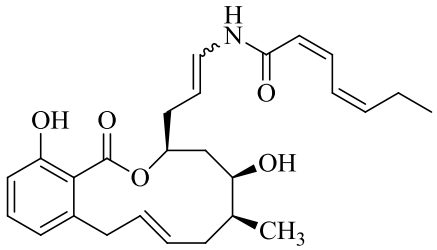
The benzolactone enamides such as oximidines and salicylihalamides show potent activity against human cancer cell lines. For some of the benzolactone enamides, it could be shown that the antitumor activity is due to the inhibition of vacuolar ATPase membrane bound enzymes. These enzymes utilize the hydrolysis of ATP to generate a potential across the membrane that can be used to transport ions and small molecules. The oximidines, first isolated in 1999 from *Pseudomonas* sp. Q52002, shows promising biological activity.[17] Oximidines I (**13**) and II (**14**) exhibit selective cytotoxicity at ng/mL levels for *ras* and *src* oncogene transformed cells. This biological inhibition was determined to affect the cell cycle at the G1 phase. As is the case with the salicylihalamides, V-ATPases appear to be the cellular target of these molecules.[18]



Oximidine I (13)



Oximidine II (14)



Salicylihalamide A (*E*) (15)

Salicylihalamide B (*Z*) (16)

Figure 5

Salicylihalamide **A** (**15**) was isolated[19] from the sponge *Haliclona sp.* (southwestern Australian coast) by Boyd and co-workers in 1997 with the minor component salicylihalamide **A** (**15**) Salicylihalamide **B** (**16**), possesses potent cytotoxicity against human tumor cell lines. Salicylihalamide **A** (**15**) and **B** (**16**) are selective inhibitors of mammalian vacuolar type H^+ ATPase (V-ATPase), and are distinct from V-ATPase inhibitors.

3.2.1.5. Nargenicin-type Antibiotics

Nargenicin $\mathbf{A_1}$ or CP-47,444 (**17**) (isolated from *Nocardia argentinensis*),[20] nodusmicin (**18**) (from *Saccharopolysporahirsuta*)[21] and coloradocin (from *Actinoplanes coloradoensis*)[22] belong to a family of antibiotics possessing a highly oxygenated *cis*-fused decalin moiety and a 1,4-oxygen bridge, in addition to a ten-membered-ring lactone (Figure 6). A synthesis of the complete carbon skeleton of the nargenicins was developed by Roush *et al*.,[23] where as several approaches to the synthesis of nodusmicin (**18**)[24] and coloradocin (**19**)[25] are described in the literature.

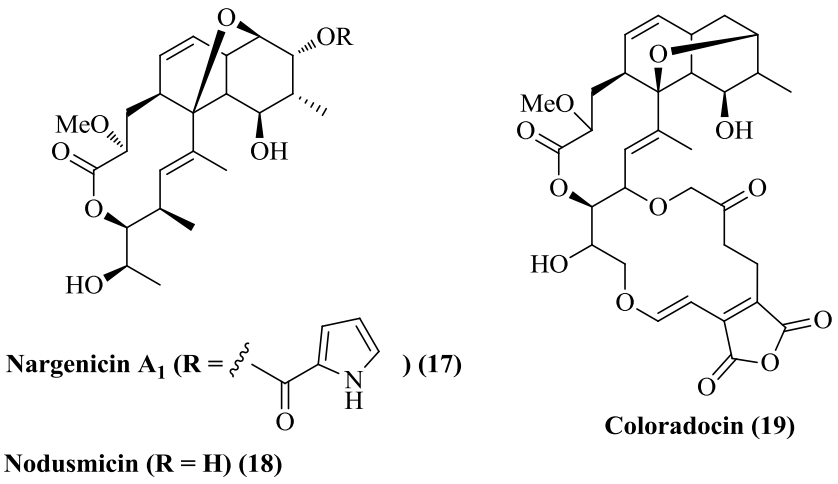


Figure 6

Hypothemycin (**20**), Aigialomycins D (**21**) macrolides were isolated from the mangrove fungus, *Aigialus parvus* BCC 5311. Hypothemycin (**20**) and aigialomycin D (**21**) exhibited in vitro antimalarial activity with IC_{50} values of 2.2 and 6.6 µg/mL. Cytotoxicities of these compounds were also evaluated. Zearalenone (**22**) was first isolated from the mycelium of the fungus *Gibberella zeae* (*Fusarium graminearum*) growing as a mould on corn.[26]

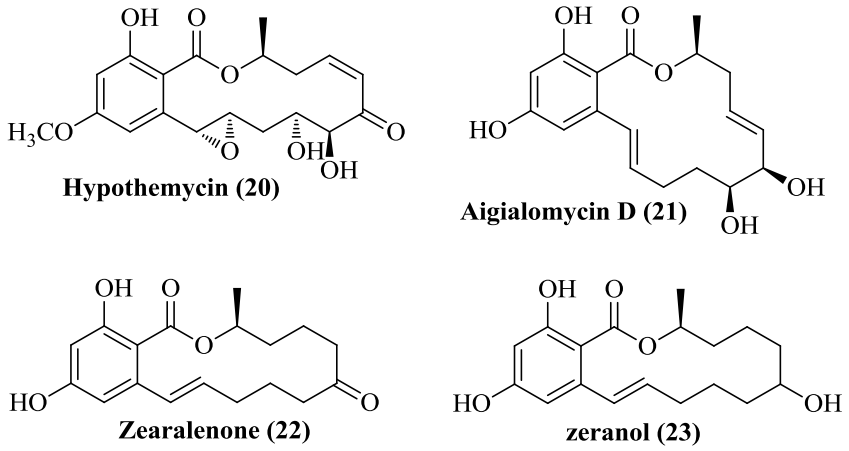


Figure 7

Zearalenone (**22**) is a 14-membered macrolactone exhibits anabolic, estrogenic, uterotropic, and antibacterial activity.[27] Zeranol (**23**) also belongs to this class of

macrolide and is closely related to (*S*)-zearalenone (**22**). Zeranol (**23**) is a non-steroidal estrogen agonist and animal growth-promoting agent and is under clinical trials as a potential treatment for menopausal and post-menopausal syndrome.[28] These compounds show more number of biological activities. Curvularin (**24**) and related polyketide metabolites such as (**25**) and (**26**) isolated from various *Curvularia*, *Penicillium*, *Alternaria*, and *Cochliobolus* species are known to elicit diverse biological effects ranging from phytotoxicity to antibacterial and antifungal activity.[29] Citreofuran (**27**), Curvularin (**24**), 11-*α*-hydroxycurvularin (**28**), 11-β-hydroxycurvularin (**29**), 11-*α*-Methoxycurvularin (**30**) and 11-*β*-methoxycurvularin (**31**) are isolated from the mycelium of the hybrid strain ME 005 derived from *penicillium citreoviride* 4692 and 6200 (Figure 8).[30] They were discovered to exhibit cytotoxicity towards human cancer cell lines [NCI-H460, MCF-7, SF-268, MIA. Pa Ca-2].[31]

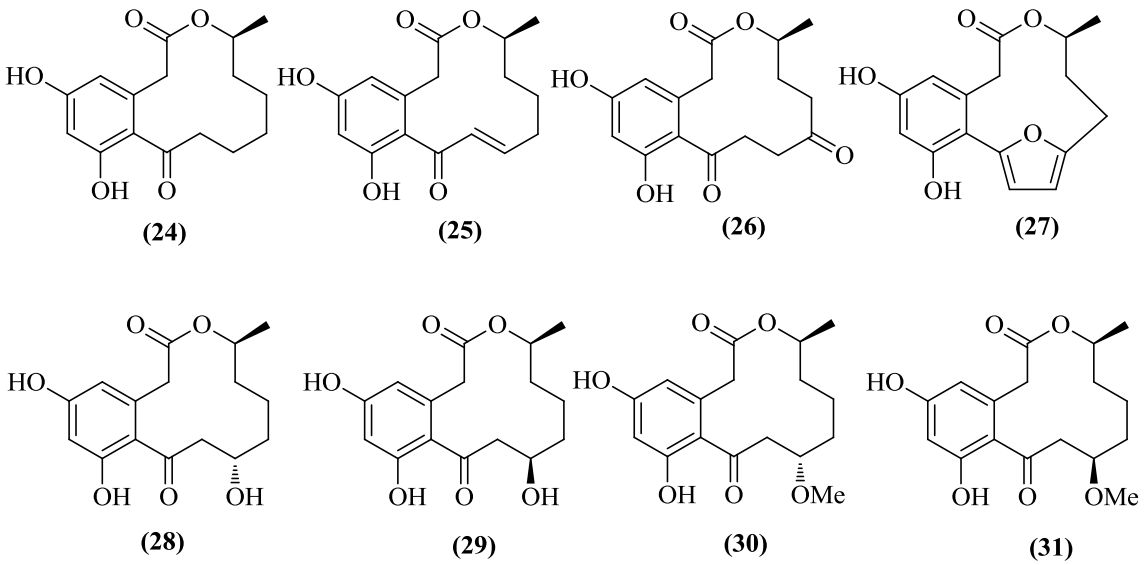


Figure 8

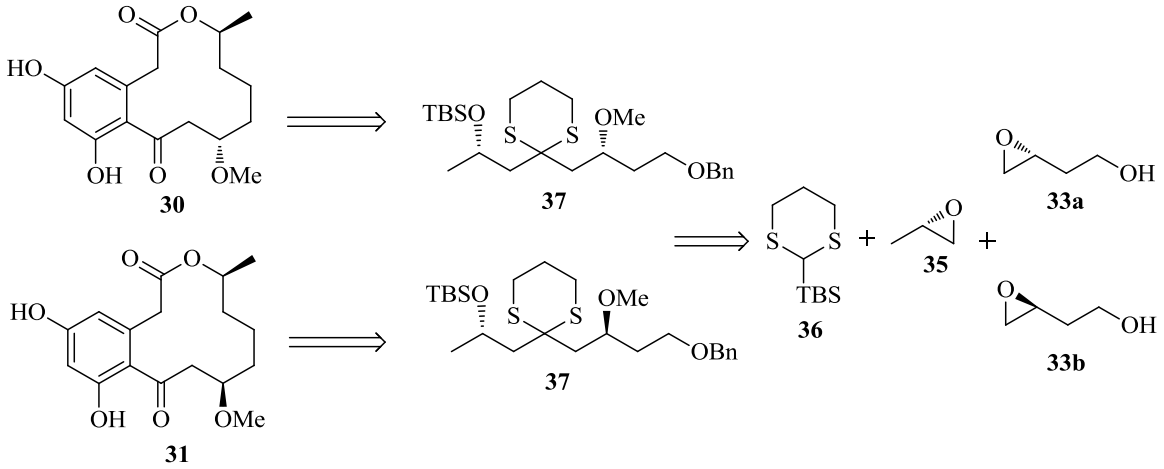
The activity and structural complexity has attracted us to synthesize 11-*α*-Methoxycurvularin (**30**) and 11-*β*-methoxycurvularin (**31**). It's worthwhile at this juncture to discuss few earlier approaches for the total syntheses of curvularins.

3.2.2. Previous Approaches:

3.2.2.1. Xuegong She approach:[32]

Xuegong She *et al.* reported the first total synthesis of 11-*α*-methoxycurvularin (**30**) and 11-*β*-methoxycurvularin (**31**). Both were accomplished in three-component linchpin coupling and intramolecular acylation reactions.

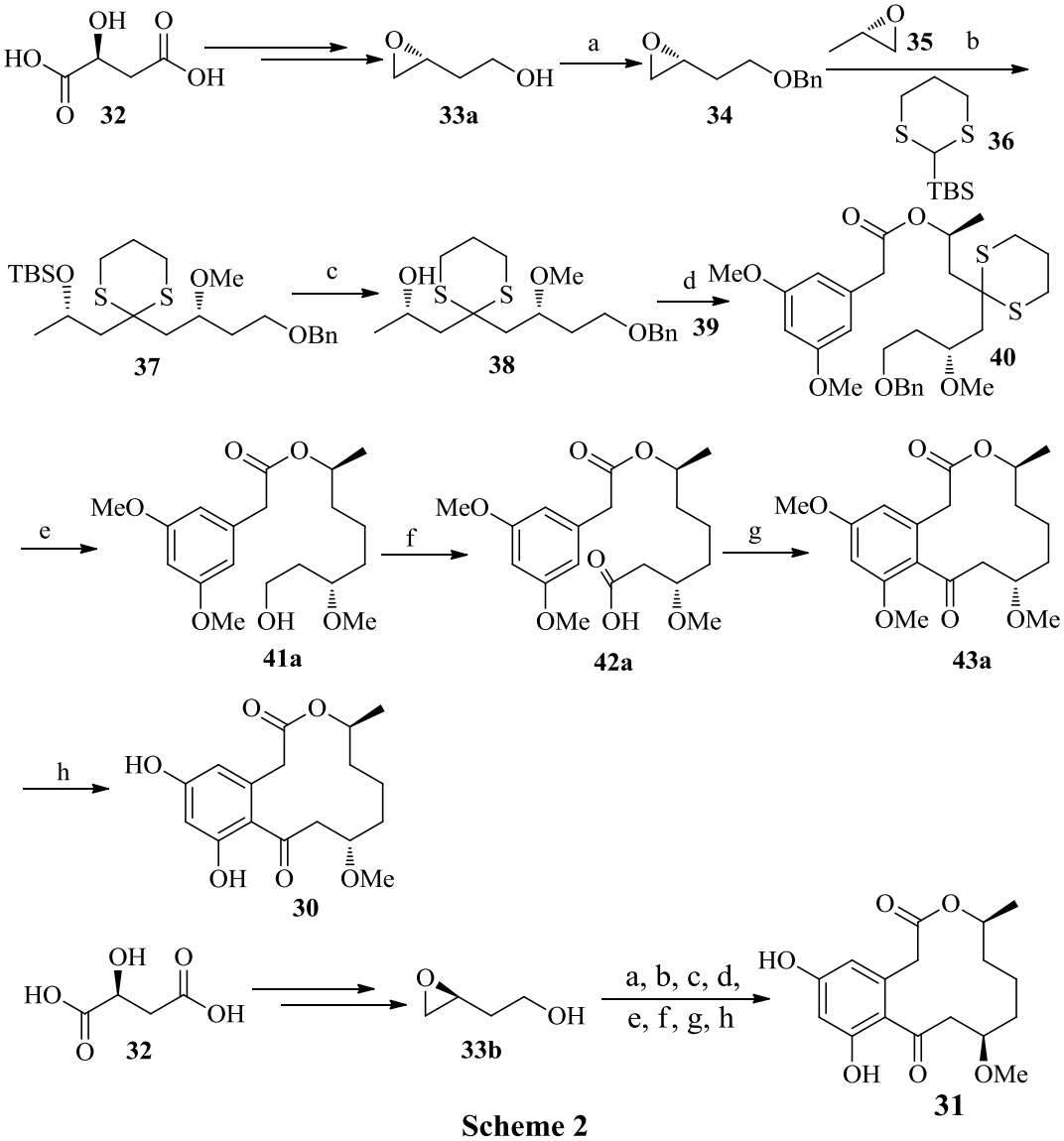
3.2.2.1a. Retrosynthesis:



Scheme 1: Retrosynthetic analysis

3.2.2.1b. Discussion:

According to the reported literature procedure, synthesis of 11-*α*-methoxycurvularin (**30**) began with (*R*)-1,2-epoxy-4-butanol **33a** prepared from (*S*)-(-)-malic acid **32**. Epoxide **33a** was treated with BnBr, NaH in THF to give benzylether **34**. The linchpin coupling with (*S*)-(-)-methyloxirane **35**, epoxide **34**, and dithiane **36** in *n*-BuLi, HMPA, MeI furnished **37** in 74% yield (Scheme 2). The deprotection of the TBS group in **37** with 1% HCl in MeOH gave **38** in 99% yield. Esterification of **38** with 3,5-dimethoxyphenylacetic (**39**) acid using DCC and DMAP provided the ester **40**. The dithiane and benzyl groups of **40** were removed with Raney Ni to afford **41a** in 75.4% yield. Oxidation of the hydroxy group of **41a** with Jones reagent in acetone at 0 °C for 15 min gave the acid **42a** in good yield. The macrolide **43a** was obtained by intramolecular Friedel-Crafts reaction of the acid **42a** in a mixture of TFA and TFAA. Selective deprotection of the methoxy groups at C5 and C7 of macrolide **43a** with AlI_3 gave 11-*α*-Methoxycurvularin (**30**). 11-*β*-Methoxycurvularin (**31**) was synthesized by using the same strategy as the synthesis of 11-*α*-Methoxycurvularin (**30**). The 11-*β*-Methoxycurvularin (**31**) began with (*S*)-1,2-epoxy-4-butanol **33b** prepared from (*S*)-(-)-malic acid **32**.



Scheme 2

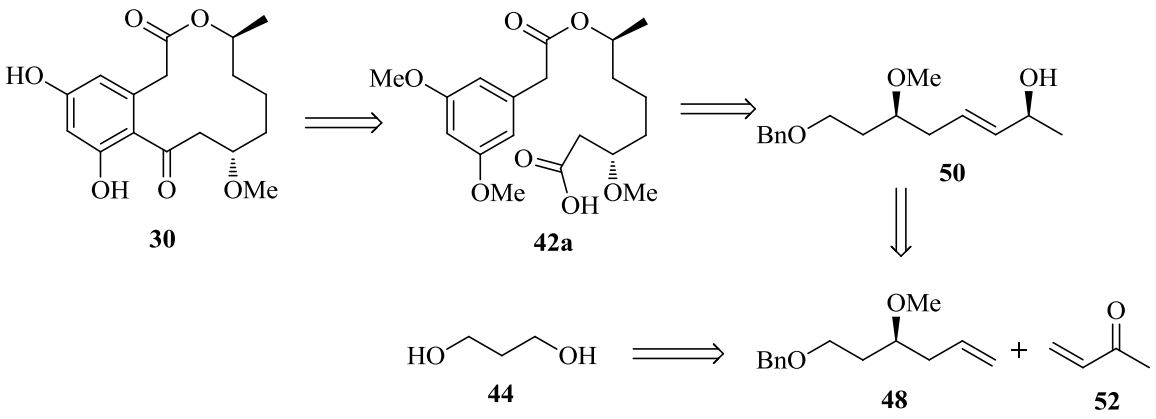
Reagents and conditions: (a) NaH, BnBr, $Bu_4N^+I^-$, rt, 99%; (b) *n*-BuLi, HMPA, MeI, THF, -78 ^oC, 74%; (c) HCl, 1% solution in MeOH, rt, 99%; (d) 3,5-dimethoxyphenyl acetic (39), DCC, DMAP, Et_2O, rt, 4 h, 98%; (e) Raney Ni, H_2, EtOH, 80 ^oC, 8 h, 75%; (f) CrO_3, H_2O, H_2SO_4, acetone, 0 °C to rt, 15 min, 86%; (g) TFA, TFAA, rt, 8 h, 42%; (h) AlI_3, $Bu_4N^+I^-$, C_6H_6, 10 ^oC, 15 min, 68%.

In summary a concise and efficient total synthesis of 11-*α*-methoxycurvularin (**30**) and 11-*β*-methoxycurvularin (**31**) were accomplished in 8 steps with an overall yield of 10.0% and 13.3%, respectively.

3.2.2.2. J. Madhusudana Rao Approach:[33]

In this approach total synthesis of 11-α-methoxycurvularin (**30**) and 11-β-methoxycurvularin (**31**) has been accomplished with Maruoka asymmetric allylation to introduce the stereocenter at C-11 and the key fragment was installed by using Grubbs cross-metathesis followed by CBS-reduction.

3.2.2.2a. Retrosynthesis:

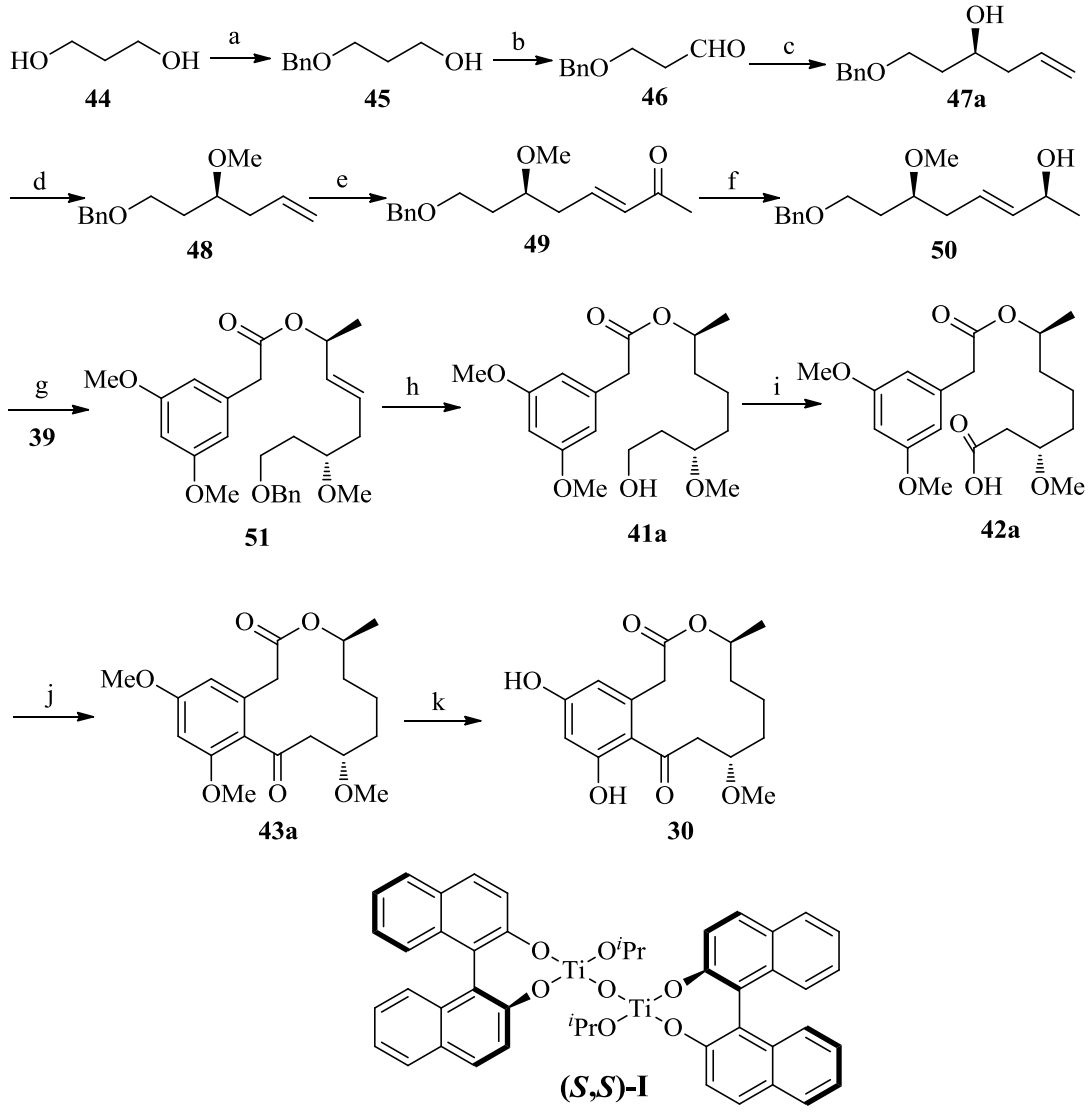


Scheme 3: Retrosynthetic analysis

3.2.2.2b. Discussion:

The total synthesis was initiated with the 1,3-propanediol **44**, which was selectively protected as benzyl ether **45** using BnBr, NaH and a catalytic amount of TBAI in THF (Scheme 4). IBX oxidation of **45** afforded aldehyde **46**, which was subjected to an enantioselective Maruoka allylation using titanium complex (***S,S*)-I** and allyl tri-*n*-butyltin to furnish the homoallylic alcohol **47a** in 86% yield with excellent enantio-selectivity of 97.96% ee (determined by chiral HPLC). Homoallylic alcohol **47a** was then converted to its corresponding methyl ether **48** using MeI and NaH in THF in 96% yield. The merging of two alkenes **48** and methyl vinyl ketone **52** with Grubbs catalyst (5 mol% Grubbs II) in CH_2Cl_2 under reflux conditions provided the cross metathesis product **49** in 86% yield. The unsaturated ketone **49** was treated with (*R*)-(+)-2-methyl-CBSoxazaborolidine and BH_3·DMS at –40 ^oC to furnish allyl alcohol **50** with an (***S***)-configuration in 90% yield with 97% de. Esterification of **50** with 3,5-dimethoxyphenyl acetic acid **39** using DCC and DMAP at room temperature afforded **51** in 96% yield. Deprotection of benzyl ether group and reduction of double bond were carried out by hydrogenation using 10% Pd/C in

EtOAc to furnish alcohol **41a**. Oxidation of **41a** using Jones' reagent (CrO_3, H_2O, H_2SO_4, acetone, 0 °C to rt) gave carboxylic acid **42a**.

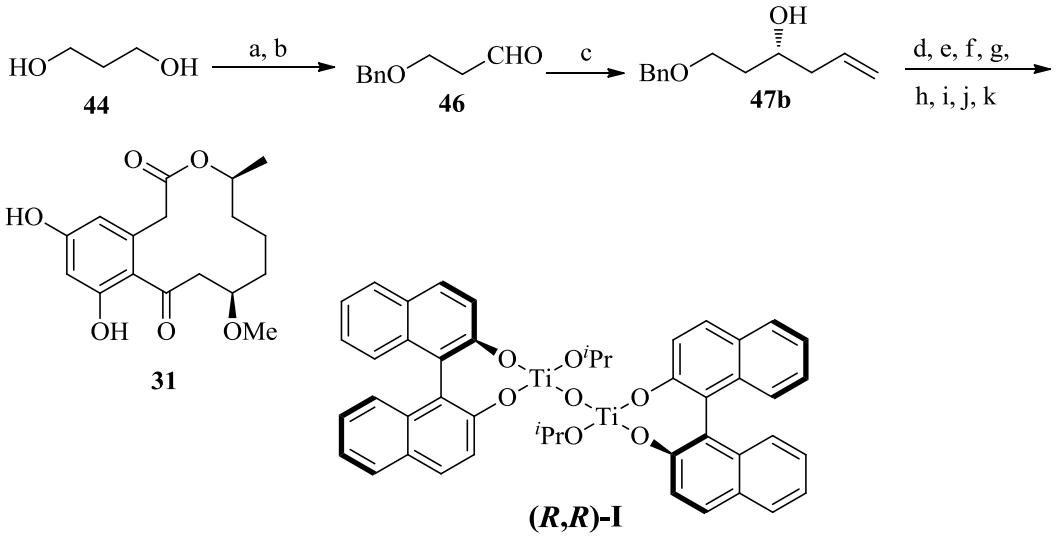


Scheme 4

Reagents and conditions: (a) NaH, BnBr, THF, 0 ^oC to rt, 2 h, 95%; (b) IBX, DMSO, THF, rt, 1 h, 92%; (c) 10 mol% (***S*,*S*)-I**, $Bu_3SnCH_2CH{=}CH_2$, CH_2Cl_2, -15 ^oC to 0 ^oC, 24 h, 86%; (d) NaH, MeI, 0 ^oC to rt, 3 h, 96%; (e) Methyl vinyl ketone (**52**), 5 mol% Grubbs 2nd generation, CH_2Cl_2, reflux, 6 h, 86%; (f) *R*-CBS catalyst, THF, -40 ^oC, BH_3·DMS, 3 h, 90%, 97% *de*; (g) 3,5-dimethoxyphenyl acetic (39), DCC, DMAP, Et_2O, 0 ^oC to rt, 3 h, 96%; (h) H_2, 10% Pd/C, EtOAc, 10h, 90%; (i) CrO_3, H_2O, H_2SO_4, acetone, 0 °C to rt, 15

min, 85%; (j) TFA, TFFA, reflux, 30 min, 42%; (k) AlI_3, $Bu_4N^+I^-$, C_6H_6, 10 ^oC, 15 min, 68%.

The macrolide **43a** was obtained by intramolecular Friedel-Crafts acylation of the acid **42a** using in a mixture of TFA and TFAA. Treatment of **43a** with freshly prepared AlI_3 in benzene afforded 11-*α*- methoxycurvularin (**30**) in 68% yield.



Scheme 5

Reagents and conditions: (a) NaH, BnBr, THF, 0 ^oC to rt, 2 h, 95%; (b) IBX, DMSO, THF, rt, 1 h, 92%; (c) 10 mol% (***R***,***R***)-**I**, $Bu_3SnCH_2CH{=}CH_2$, CH_2Cl_2, -15 ^oC to 0 ^oC, 24 h, 86%; (d) NaH, MeI, 0 ^oC to rt, 3 h, 96%; (e) Methyl vinyl ketone, 5 mol% Grubbs 2nd generation, CH_2Cl_2, reflux, 6 h, 86%; (f) *R*-CBS catalyst, THF, -40 ^oC, BH_3·DMS, 3 h, 90%, 97% de; (g) 3,5-dimethoxyphenyl acetic (**39**), DCC, DMAP, Et_2O, 0 ^oC to rt, 3 h, 96%; (h) H_2, 10% Pd/C, EtOAc, 10 h, 90%; (i) CrO_3, H_2O, H_2SO_4, acetone, 0 °C to rt, 15 min, 85%; (j) TFA, TFFA, reflux, 30 min, 42%; (k) AlI_3, $Bu_4N^+I^-$, C_6H_6, 10 ^oC, 15 min, 68%.

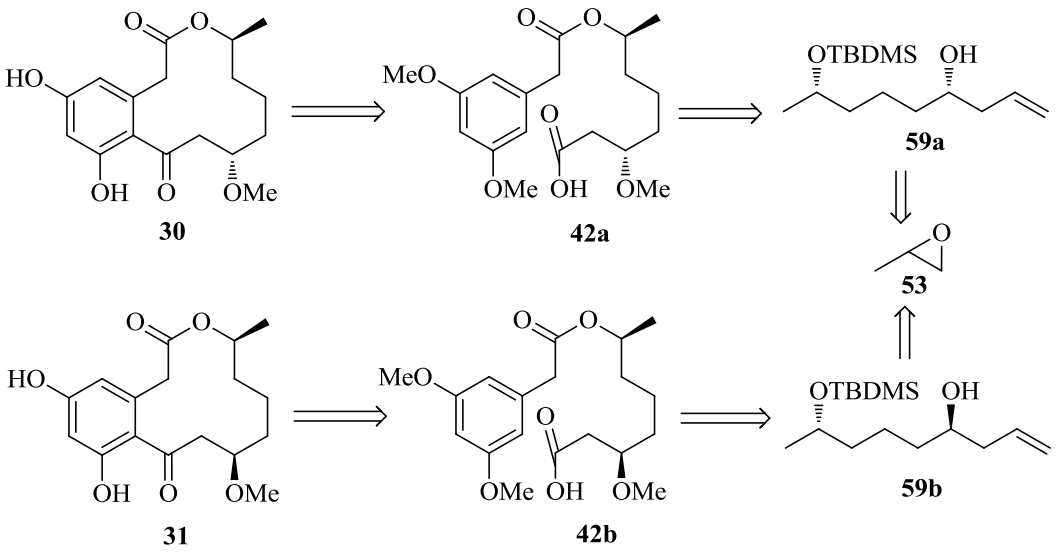
The synthesis of 11-*β*-methoxycurvularin (**31**) was achieved by using the same strategy as the synthesis of 11-*α*-methoxycurvularin (**30**). The aldehyde **45** was subjected to Maruoka allylation using titanium complex (***R,R***)-**I** and allyl tri-*n*-butyltin to give the alcohol **46b** in 86% yield (Scheme 5). 11-*β*-methoxycurvularin (**31**) was synthesized, by repeating of all the same steps as in the case of 11-*α*-methoxycurvularin (**30**).

3.2.3. Present Work:

11-*α*-Methoxycurvularin (**30**) and 11-*β*-Methoxycurvularin (**31**) were isolated from the mycelium of the hybrid strain ME005, which is derived from *Penicillium citreoviride* 4692 and 6200.[30] These substances showed considerable cytotoxicity against four types of human cancer cell lines (NCI-H460, MCF-7, SF-268, MIA. Pa Ca-2).[31] They have also been found to be specific inhibitors of sea urchin embryogenesis by acting on components of the mitotic apparatus,[34] 90 (HSP90),[35] which is a promising target for anticancer drug development.[36]

Structurally, these natural products are 12-membered macrolides with a fused 1,3-dihydroxy benzene ring, they are related to a number of compounds isolated from terrestrial fungi. The absolute configurations of 11-*α*-Methoxycurvularin (**30**) and 11-*β*-Methoxycurvularin (**31**) were determined by Xinfu Pan et al. by their stereoselective syntheses.[32] In continuation of our interest in the total synthesis of biologically active natural products, we herein report the total synthesis of 11-*α*-Methoxycurvularin (**30**) and 11-*β*-Methoxycurvularin (**31**) using Jacobsen hydrolytic kinetic resolution (HKR) and Maruoka asymmetric allylation reactions to create two stereogenic centres. An intramolecular Friedel-Crafts acylation strategy was used to construct the macrolide.

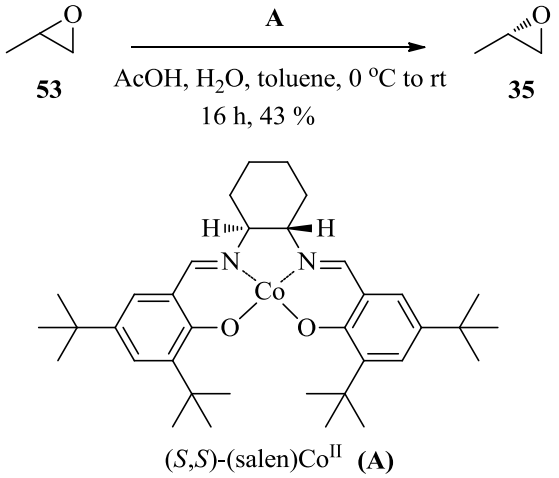
3.2.3.1. Retrosynthesis of 11-*α*-Methoxycurvularin and 11-*β*-Methoxycurvularin:



Scheme 6: Retrosynthetic analysis

3.2.3.2. Results and discussions:

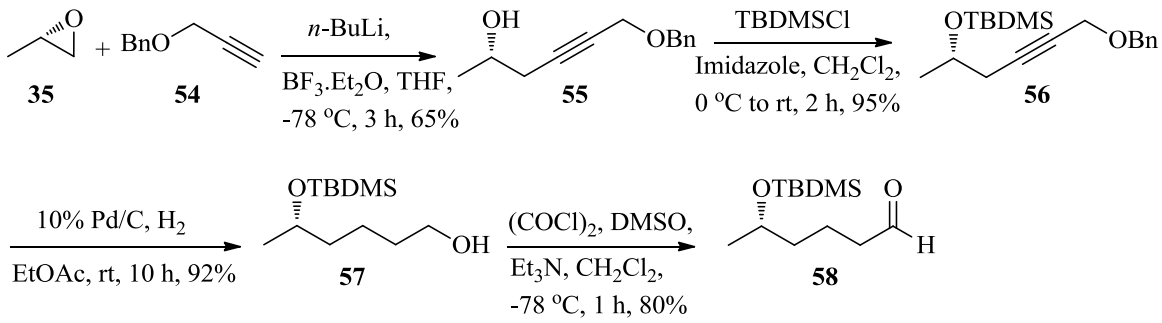
In our retrosynthetic analysis (Scheme 6), we envisioned that the construction of 11-*α*-Methoxycurvularin (**30**) and 11-*β*-Methoxycurvularin (**31**) could be achieved from carboxylic acids **42a** and **42b**. These key carboxylic acid intermediates could be synthesized from compounds **59a** and **59b** respectively, which could be prepared from propylene oxide **53** by using Jacobsen resolution and Maruoka asymmetric allylation. We commenced the synthesis of **35** from the commercially available racemic propylene oxide **53** as the starting material. The oxirane was subjected to hydrolytic kinetic resolution (HKR)[37] using (*S*,*S*)-(−)-*N*,*N*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino cobalt(II) and AcOH in toluene at room temperature to afford the excellent enantiorich (97% ee, determined by chiral HPLC) (*S*)-propylene oxide **35** in 43% yield (Scheme 7). The resolution of (*S*)-propylene oxide **35** was confirmed by optical rotation $[\alpha]_D^{25}$ +10.8 (*c* = 1.0, $CHCl_3$); lit[41] $[\alpha]_D^{20}$ +12.0 (*c* = 1.89, $CHCl_3$). Spectral and analytical data were in good agreement with the reported literature values.



Scheme 7

The regioselective opening of epoxide **35** with ((prop-2-yn-1-yloxy)methyl)benzene **54** provided the secondary alcohol **55** in good yield (Scheme 8). The ^{1}H NMR spectrum of compound **55** showed a characteristic signal resonating as singlet at δ 4.56 ppm for benzylic protons, multiplet protons at δ 7.33-7.22 ppm for aromatic ring attached protons and doublet at δ 1.25 (*J* = 6.04 Hz, 3H) ppm. The

compound **55** was also confirmed by ESI-HRMS peak at *m/z* 227.1056 $[M + Na]^+$ and IR absorption showed characteristic band at 3416 cm^{-1} for hydroxyl functionality. The homo propargylic alcohol **55** was protected as its TBS-ether **56** using TBDMSCl and imidazole in dry CH_2Cl_2 in 95% yield (Scheme 8). The structure was confirmed by the appearance of signals at δ 0.89 (s, 9H) and δ 0.07 (s, 6H) ppm in ^1H NMR spectrum. This was further confirmed by ^{13}C NMR spectrum which showed all the representative peaks for aliphatic, aromatic and silyl carbons. Its ESI-HRMS spectrum showed peak at *m/z* 341.1913 $[M + Na]^+$. Compound **56** was hydrogenated using Pd/C in EtOAc at room temperature to give the primary alcohol **57** in 92% yield (Scheme 8), which was confirmed by disappearance of aromatic proton signals at δ 7.34-7.21 (m, 5H) ppm in ^1H NMR and sharp absorption peak at 3347 cm^{-1} corresponding to OH fuctional group in the IR spectroscopy.

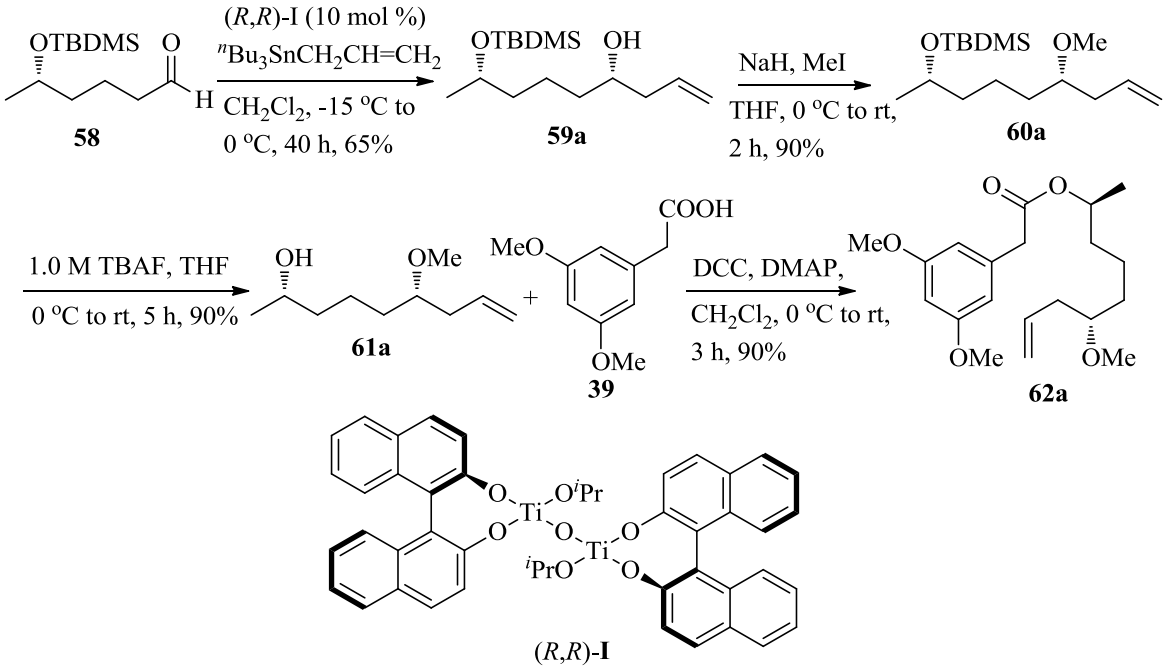


Scheme 8

The ^{13}C NMR spectrum of **57** showed all the representative peaks, and the peak at *m/z* 233.1933 $[M + H]^+$ in ESI-HRMS spectrum further confirmed this transformation. The hydroxyl group **57** was oxidized under Swern[38] conditions in CH_2Cl_2 to afford aldehyde **58**. This was clearly conveyed in the ^1H NMR spectrum by the resonance as a triplet at 9.74 ppm indicating alcohol was converted into aldehyde. The other protons of the compound resonated at their respected chemical shift values. The compound **58** was also characterized by ESI-MS with $(M + Na)^+$ peak at *m/z* 253, and a characteristic peak at 1722 cm^{-1} in IR spectrum.

3.2.3.3. Synthesis of 11-*α*-Methoxycurvularin (30)

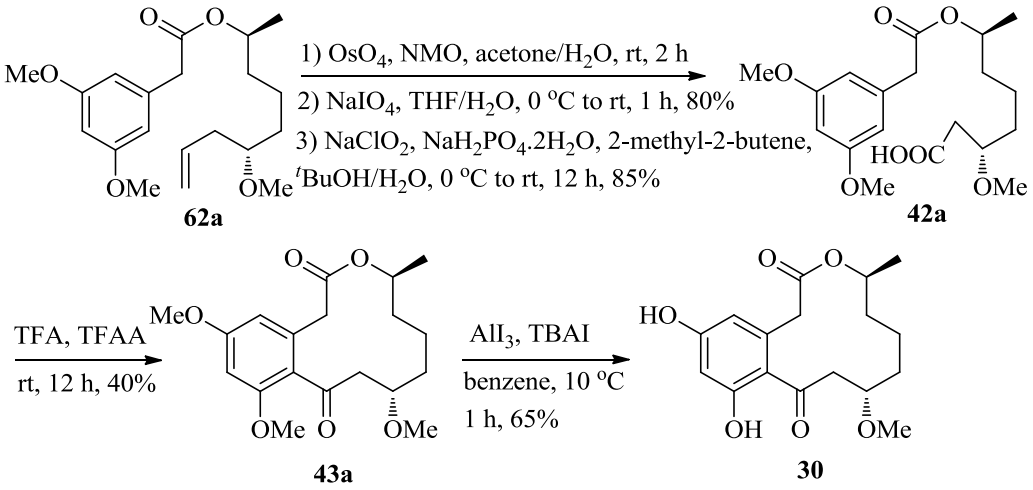
The aldehyde **58** was subjected to an enantioselective Maruoka allylation[39] using titanium complex (*R,R*)-**I** and allyltri-*n*-butyltin to furnish the homoallylic alcohol **59a** in 65% yield. Formation of product **59a** was ascertained from ^{1}H NMR spectrum, where the absence of aldehyde proton and presence of olefin protons at δ 5.90-5.75 (m, 1H), 5.17-5.13 (m, 1H) and 5.10 (d, *J* = 1.13 Hz, 1H) along with the other required protons confirmed the product. The presence of peak at *m/z* 295.2068 $[M + Na]^+$ in the ESI-HRMS spectrum further confirmed the formation of product **59a**. The homoallylic alcohol **59a** was protected as methyl-ether **60a** using MeI and NaH in 90% yield, which was confirmed by its ^{1}H NMR spectrum resonating signal at δ 3.32 (s, 3H) and also ESI-HRMS showed peak at *m/z* 309.2235 $[M + Na]^+$. The deprotection of TBDMS group of compound **60a** with TBAF in THF afforded corresponding alcohol **61a** in 90% yield. Compound **61a** was confirmed by its ^{1}H NMR spectrum which showed disappearance of signals corresponding to TBDMS group.



Scheme 9

Compound **61a** was also characterized by its ESI-HRMS data, which showed peak at *m/z* 195.1365 $[M + Na]^+$. The secondary alcohol **61a** was treated with 3,5-dimethoxyphenyl acetic acid **39** in the presence of DCC and DMAP to afford ester **62a** in

90% yield (Scheme 9).[40] It was confirmed by appearance of aromatic protons signals at δ 6.37 (d, *J* = 1.8 Hz, 2H), 6.29 (t, *J* = 2.07 Hz, 1H), olefinic protons at δ 5.79-5.64 (m, 1H), 5.01 (d, *J* = 6.42 Hz, 1H), 4.96 (s, 1H), and methyl protons resonating at δ 1.14 (d, *J* = 6.23 Hz, 3H) in ^{1}H NMR. The strong absorption peak at 1730 cm^{-1} in the IR spectroscopy corresponds to the ester functionality. It was further confirmed by ^{13}C NMR spectrum which showed all the representative peaks for alkene as well as aromatic carbons and showed peak at *m/z* 373.1993 $[M + Na]^+$ in ESI-HRMS. Dihydroxylation of compound **62a** OsO_4, NMO, followed by sodium metaperiodate ($NaIO_4$) mediated cleavage and oxidation with sodium chlorite ($NaClO_2$) afforded the carboxylicacid **42a** (overall yield 80%). The ^{1}H NMR spectrum of compound **42a** revealed the disappearance of olefinic protons, and acid attached methylinic protons resonance at δ 2.48 (dd, *J* = 6.98 Hz, 1H), 2.37 (dd, *J* = 5.47, 15.48 Hz, 1H). All other protons of the structure **42a** resonated at their expected chemical shift values. Compound **42a** was further confirmed by its ESI-HRMS data, which showed peak at *m/z* 319.1714 $[M + Na]^+$. The acid **42a** upon intramolecular Friedel-Crafts acylation using TFA and TFAA[40,41] afforded macrolide **43a** in 40% (Scheme 10).



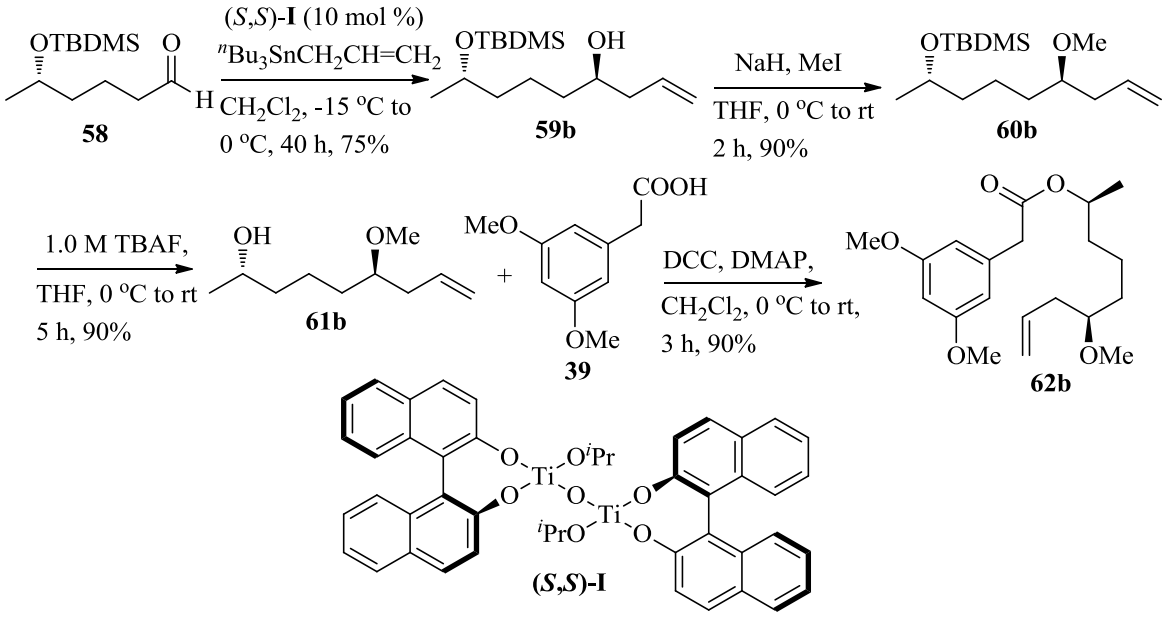
scheme 10

In ^{1}H NMR spectrum, showed disappearance of aromatic proton at δ 6.29 (t, *J* = 2.21 Hz, 1H) and all other protons resonated at their expected chemical shift values. Compound **43a** was further confirmed by its ESI-HRMS data, which showed peak at *m/z*

373.1623 $[M + Na]^+$. Selective deprotection of the aromatic methoxy groups of macrolide **43a** using aluminium iodide (AlI_3) and TBAI in benzene gave the target natural product 11-*α*-Methoxycurvularin (**30**) in good yield (Scheme 10).[42] ^1H NMR spectrum of (**30**) showed disappearance of aromatic methoxy (ph-O-**CH_3**) protons at δ 3.84 (s, 3H), 3.77 (s, 3H) ppm. This was further confirmed by ^{13}C NMR spectrum which showed all the representative peaks for aromatic as well as aliphatic carbons and peak at *m/z* 345.1315 $[M + Na]^+$ in ESI-HRMS. The spectral and analytical data were in good agreement with the reported values.[32,33]

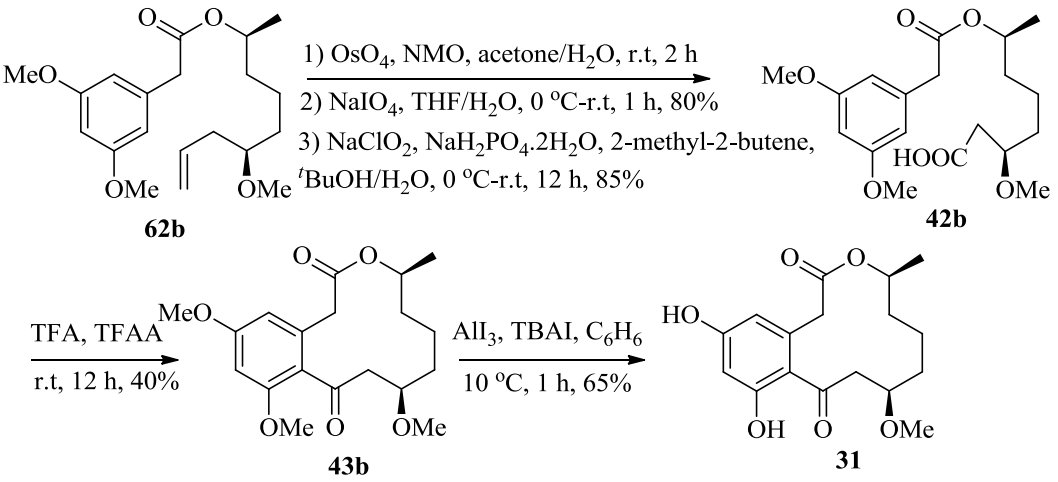
3.2.3.4. Synthesis of 11-*β*-Methoxycurvularin (31)

The aldehyde **58** was subjected to an enantioselective Maruoka allylation[39] using titanium complex (*S,S*)-**I** and allyltri-*n*-butyltin to furnish the homoallylic alcohol **59b** in 75% yield. Formation of product **59b** was ascertained from ^1H NMR spectrum, where the absence of aldehyde proton and presence of three olefin protons at δ 5.87-5.73 (m, 1H), 5.14 (s, 1H) and 5.09 (d, *J* = 3.02 Hz, 1H) along with the other required protons confirmed the product. ESI-HRMS spectrum showed peak at *m/z* 295.2068 $[M + Na]^+$ further confirmed the formation of product **59b** (Scheme 11).



Scheme 11

The homoallylic alcohol **59b** was protected as its methyl ether **60b** using MeI and NaH in THF in 90% yield, which was confirmed by ^{1}H NMR spectrum with resonating signal at δ 3.32 (s, 3H), and ESI-HRMS showed peak at *m/z* 309.2235 $[M + Na]^+$. The deprotection of TBDMS group of compound **60b** with TBAF in THF afforded corresponding alcohol **61b** in 90% yield. Compound **61b** was confirmed by its ^{1}H NMR spectrum which showed disappearance of signals corresponding to TBDMS group. Compound **61b** was also characterized by its ESI-HRMS data, which showed peak at *m/z* 195.1360 $[M + Na]^+$. The secondary alcohol **61a** was treated with 3,5-dimethoxyphenyl acetic acid **39** in the presence of DCC and DMAP to afford ester **62b** in 90% (Scheme 11).[40] It was confirmed by appearance of aromatic protons signals at δ 6.38 (d, *J* = 2.2 Hz, 2H), 6.28 (t, *J* = 2.2, Hz, 1H) ppm, olefinic protons at δ 5.85-5.62 (m, 1H), 5.13-4.96 (m, 2H), and methyl protons resonating at δ 1.20 (d, *J* = 6.6 Hz, 3H) ppm in ^{1}H NMR. The strong absorption peak at 1728 cm^{-1} in the IR spectrum corresponds to the ester functionality. It was further confirmed by ^{13}C NMR spectrum which showed all the representative peaks for alkene as well as aromatic carbons and showed peak at *m/z* 373.1990 $[M + Na]^+$ in ESI-HRMS. Dihydroxylation of compound **62b** using OsO_4, NMO followed by sodium metaperiodate ($NaIO_4$) mediated cleavage and oxidation with sodium chlorite ($NaClO_2$) afforded acid **42b** (80% yield over 3 steps).



Scheme 12

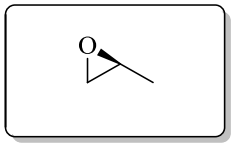
The ^{1}H NMR spectrum of compound **42b** revealed the disappearance of olefinic protons and acid attached methylinic protons (**CH$_2$**-COOH resonance at δ 2.47 (dd, *J* = 6.98 Hz, 1H), 2.33 (dd, *J* = 5.47 Hz, 1H). All other protons of the structure **42b** resonated at their expected chemical shift values. Compound **42b** was further confirmed by its ESI-HRMS data, which showed peak at *m/z* 319.1732[M + Na]$^+$. The acid **42b** upon intramolecular Friedel-Crafts acylation using TFA and TFAA[40,41] afford macrolide **43b** in 40% yield (Scheme 12). The ^{1}H NMR spectrum showed disappearance of aromatic proton at δ 6.29 ppm (t, *J* = 2.26 Hz, 1H) and all other protons resonated at their expected chemical shift values. Compound **43b** was further confirmed by its ESI-HRMS data, which showed peak at *m/z* 373.1627 [M + Na]$^+$. Selective deprotection of the aromatic methoxy groups of macrolide **43b** using aluminium iodide (AlI_3) and TBAI in benzene gave the target natural product 11-*β*-Methoxycurvularin (**31**) in good yield.[42] ^{1}H NMR spectrum of (**31**) showed disappearance of aromatic methoxy (ph-O-**CH$_3$**) protons at δ 3.80 (s, 3H), 3.74 (s, 3H) ppm. This was further confirmed by ^{13}C NMR spectrum which showed all the representative peaks for aromatic as well as aliphatic carbons and peak at *m/z* 345.1309 [M + Na]$^+$ in ESI-HRMS. The spectral and analytical data were in good agreement with the reported values.[32,33]

In conclusion, we have achieved the stereoselective total synthesis of 11-*α*-Methoxycurvularin (**30**) and 11-*β*-Methoxycurvularin (**31**) using the Jacobsen hydrolytic kinetic resolution, Maruoka asymmetric allylation and intramolecular Friedel–Crafts reaction as key steps.

Experimental Section

3.2.4. EXPERIMENTAL SECTION

3.2.4.1. (S)-2-Methyloxirane (35):

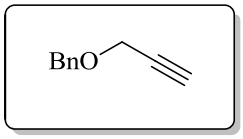


A mixture of (*S*,*S*)-(–)-*N*,*N*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino cobalt(II) (0.480 g, 0.80 mmol) in toluene (1.2 mL) and AcOH (0.96 g, 1.6 mmol) was stirred under air at room temperature for 1 h. After the reaction mixture was concentrated under reduced pressure, the resulting brown residue was dried under vacuum. The racemic epoxide **53** (23.2 g, 400 mmol) was added to the above residue in one portion at 0 °C then H_2O (3.96 mL, 220 mmol) was added dropwise over 10 min. The reaction mixture was allowed to stir at room temperature for 16 h. The desired (*S*)-propylene oxide **35** (10.0 g, 43%, >97% ee determined by chiral HPLC) was isolated as a colorless liquid by distillation of the reaction mixture at atmospheric pressure.

bp: 37 °C.

$[\alpha]_D^{23}$: +10.8 (*c* 1.0, $CHCl_3$).

3.2.4.2. ((Prop-2-yn-1-yloxy)methyl)benzene (54):



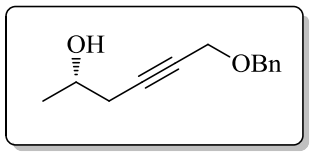
To a stirred suspension of 55% dispersion of NaH in mineral oil (1.71 g, 74.63 mmol) in dry THF (30 mL) was added a solution of propargyl alcohol (3.8 g, 67.85 mmol) in dry THF (20 mL) at 0 °C. The mixture was then allowed to stir at room temperature for 15 min. To this solution, benzyl bromide (8.0 mL, 67.85 mmol) was added at 0 °C. The resulting mixture was stirred at room temperature for 2h and then quenched with cold water at 0 °C. The crude mixture was extracted with EtOAc (3 x 25 mL) and the organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (EtOAc/hexanes, 0.5:9.5) to afford the benzyl ether **54** (9.3 g, 93 %) as a colorless liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.35-7.20 (m, 5H), 4.58 (s, 2H), 4.13 (d, *J* = 2.20 Hz, 2H), 2.38 (t, *J* = 2.20 Hz, 1H) ppm.

^{13}C NMR (CDCl3, 75 MHz): δ 137.4, 128.3, 127.8, 127.5, 79.2, 74.1, 71.4, 56.5 ppm.

IR (neat): 3296, 3032, 2116, 1088 cm^{-1}.

3.2.4.3. (*S*)-6-(Benzyloxy)hex-4-yn-2-ol (55):



n-BuLi (1.6 M in hexane, 43.5 mL, 69.3 mmol) was added dropwise to a solution of ((prop-2-yn-1-yloxy)methyl)benzene **54** (9.2 g, 63.0 mmol) in anhydrous THF (100 mL) at –78 °C under an N_2 atmosphere. The mixture was allowed to stir for 30 min, then treated with $BF_3{\cdot}OEt_2$ (8.73 mL, 69.3 mmol). After 10 min, a solution of (*S*)-propylene oxide **35** (9.15 g, 157.7 mmol) in anhydrous THF (30 mL) was added and the mixture was stirred for further 3h at –78 °C. The reaction mixture was quenched with saturated NH_4Cl solution (30 mL) then with saturated $NaHCO_3$ solution (20 mL) at –78 °C. The mixture was allowed to warm to room temperature then extracted with EtOAc (3 x 70 mL), washed with H_2O (20 mL) and dried over anhydrous Na_2SO_4. Removal of solvent followed by purification by silica gel chromatography (EtOAc/hexanes, 1.5:8.5) afforded the compound **55** (8.3 g, 65%) as a colourless oil.

$[\alpha]_D^{23}$: +9.3 (*c* 1.0, $CHCl_3$).

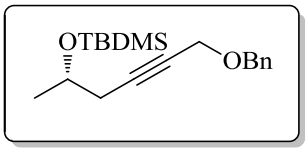
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.33-7.22 (m, 5H), 4.56 (s, 2H), 4.13 (t, *J* = 1.51 Hz, 2H), 3.96-3.86 (m, 1H), 2.46-2.29 (m, 2H), 2.01-1.92 (brs, 1H), 1.25 (d, *J* = 6.04 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.3, 128.2, 127.9, 127.7, 83.4, 78.1, 71.4, 66.1, 57.5, 29.2, 22.2 ppm.

IR (neat): 3416, 2927, 2953, 2857, 1452, 1354, 1070, 938, 741, 698 cm^{-1}.

ESI-HRMS: *m/z* calcd for $C_{13}H_{16}O_2Na$ $[M + Na]^+$ 227.1047, found 227.1056.

3.2.4.4. (*S*)-((6-(Benzyloxy)hex-4-yn-2-yl)oxy)(*tert*-butyl)dimethylsilane (56):



To a stirred solution of alcohol **55** (7.63 g, 37.4 mmol) in dry CH_2Cl_2 (100 mL) under N_2 atmosphere, were added imidazole (3.3 g, 48.62 mmol) and TBDMSCl (6.2 g, 41.14 mmol) at 0 °C and the stirring was continued for 1h at room temperature. Then the mixture was quenched with saturated aqueous NH_4Cl (30 mL) and extracted with CH_2Cl_2 (3 x 70 mL). The combined organic layers were washed with brine solution (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexanes, 0.2:9.8) to afford the silyl ether **56** (11.3 g, 95%) as a colorless liquid.

$[\alpha]_D^{23}$: –3.7 (*c* 1.0, $CHCl_3$).

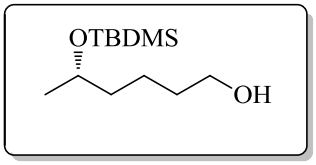
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.34-7.21 (m, 5H), 4.55 (s, 2H), 4.11 (t, *J* = 2.26 Hz, 2H), 3.99-3.89 (m, 1H), 2.43-2.21 (m, 2H), 1.24 (d, *J* = 6.04 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.5, 128.2, 127.9, 127.6, 83.4, 77.3, 71.2, 67.5, 57.5, 29.6, 25.7, 23.3, 18.0, -4.7, -4.8 ppm.

IR (neat): 2954, 2930, 2889, 2856, 1464, 1356, 1253, 1128, 1029, 998, 883, 738, 698 cm^{-1}.

ESI-HRMS: *m/z* calcd for $C_{19}H_{30}O_2Na$ $[M + Na]^+$ 341.1912, found 341.1913.

3.2.4.5. (*S*)-5-((*tert*-Butyldimethylsilyl)oxy)hexan-1-ol (57):



To a stirred solution of benzyl ether **56** (10.0 g, 31.44 mmol) in EtOAc (30 mL), 10% wt of Pd/C (0.157 g) was added and the mixture was stirred under H_2 atmosphere at room temperature for 12 h. When the reaction was completed the mixture was filtered

through small pad of celite. The filtrate was concentrated under reduced pressure and purified by silica gel column chromatography (EtOAc/hexanes, 2:8) to afford the alcohol **57** (6.73 g, 92%) as a colourless oil.

$[\alpha]_D^{23}$: +10.7 (*c* 1.0, $CHCl_3$).

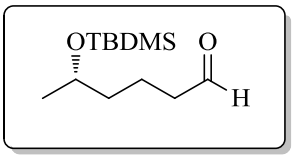
^1H NMR ($CDCl_3$, 300 MHz): δ 3.83-3.71 (m, 1H), 3.61 (t, *J* = 6.42 Hz, 2H), 1.59-1.26 (m, 6H), 1.11 (d, *J* = 6.04 Hz, 3H), 0.88 (s, 9H), 0.03 (d, *J* = 1.13 Hz, 6H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 68.5, 62.8, 39.3, 32.7, 25.8, 23.7, 21.8, 18.1, -4.4, -4.7 ppm.

IR (neat): 3347, 2932, 2859, 1465, 1372, 1253, 1057, 834, 774, 698 cm^{-1}.

ESI-HRMS: *m/z* calcd for $C_{12}H_{29}O_2Si$ $[M + Na]^+$ 233.1937, found 233.1933.

3.2.4.6. (*S*)-5-((*tert*-Butyldimethylsilyl)oxy)hexanal (58):



To a stirred solution of oxalylchloride (3.7 mL, 42.0 mmol) in dry CH_2Cl_2 (30 mL) at −78 °C under N_2 atmosphere was added DMSO (3.57 mL, 50.4 mmol) dropwise over 10 min. The mixture was stirred for an additional 10 min and then a solution of alcohol **57** (6.5 g, 28.0 mmol) in CH_2Cl_2 (40 mL) was added dropwise. The resulting mixture was stirred for 30 min and then Et_3N (25.2 mL, 168 mmol) was added dropwise at −78 °C and then stirring was continued at room temperature for 30 min. After completion of the reaction, the mixture was quenched with ice cold water (30 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure and purification by small pad of silica gel column chromatography (EtOAc/hexanes, 0.5:9.5) afforded the aldehyde **58** (5.2 g, 80%) as a pale yellow liquid.

$[\alpha]_D^{23}$: +7.8 (*c* 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.75 (t, *J* =1.46 Hz, 1H), 3.88-3.73 (m, 1H), 2.41 (dt, *J* = 1.46, 6.61 Hz, 2H), 1.80-1.33 (m, 4H), 1.13 (d, *J* = 5.87 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 202.0, 68.1, 42.2, 39.1, 25.8, 23.7, 20.8, 18.1, -4.4, -4.7 ppm.

IR (neat): 2932, 2859, 1722, 1253, 1058, 834, 774 cm^{-1}.

ESI-MS: *m/z* 253 $[M + Na]^+$.

3.2.4.7. (4*S*,8*S*)-8-((*tert*-Butyldimethylsilyl)oxy)non-1-en-4-ol (59a):

To a stirred solution of $TiCl_4$ (0.03 mL, 0.10 mmol) in CH_2Cl_2 (5 mL), was added anhydrous $Ti(O^iPr)_4$ (0.19 mL, 0.64 mmol) at 0 °C under an N_2 atmosphere. After 1 h, (*R*)-binaphthol (248 mg, 0.87 mmol) was added at room temperature and the resulting solution was stirred for 3 h. The mixture was cooled to 0 °C, treated with Ag_2O (99 mg, 0.43 mmol) and stirred at room temperature for 5 h in the dark to furnish chiral bis{[(*R*)-binaphthoxyisopropoxy]titanium}oxide, which was then treated with compound **58** (0.5 g, 2.15 mol) and allyl-*n*-tributyltin (0.73 mL, 2.374 mol) at –15 °C. The mixture was warmed to 0 °C and allowed to stir for 36 h. When the reaction was completed, sat. $NaHCO_3$ (5 mL) was added and the mixture was extracted with CH_2Cl_2 (4 x 30 mL). The organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The resulting crude residue was purified by column chromatography using silica gel (EtOAc/hexanes, 2:8) to give the allylated product **59a** (0.40 g, 65%) as a colourless oil.

$[\alpha]_D^{22}$: +5.7 (*c* 1.0, $CHCl_3$).

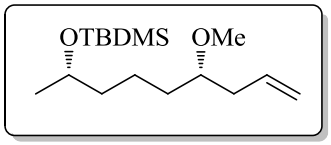
^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.90-5.75 (m, 1H), 5.17-5.13 (m, 1H), 5.10 (d, *J* =1.13, 1H), 3.84-3.73 (m, 1H), 3.69-3.59 (m, 1H), 2.35-2.07 (m, 2H), 1.53-1.20 (m, 6H), 1.12 (d, *J* = 6.04 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 134.8, 118.0, 70.5, 68.4, 41.8, 39.5, 36.7, 25.8, 23.7, 21.7, 17.4, -4.4, -4.7 ppm.

IR (neat): 3388, 2956, 2930, 2857, 1464, 1375, 1218, 1137, 1042, 999, 773, 661 cm^{-1}.

ESI-HRMS: *m/z* calcd for $C_{15}H_{32}O_2NaSi$ $[M + Na]^+$ 295.2069, found 295.2068.

3.2.4.8. *tert*-Butyl(((2*S*,6*S*)-6-methoxynon-8-en-2-yl)oxy)dimethylsilane (60a):



To a suspension of 55% dispersion of NaH in mineral oil (122 mg, 5.09 mmol) in THF (5 mL), was added alcohol **59a** (1.26 g, 4.63 mmol) at 0 °C. After stirring for 20 min, MeI (0.35 mL, 5.558 mmol) was added slowly and the resulting mixture was stirred for a further 2 h. After completion, the reaction was quenched with ice-cold H_2O (10 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexanes,0.5:9.5) to afford the compound **60a** (1.2 g, 90%) colourless oil.

$[\alpha]_D^{23}$: +7.7 (*c* 1.0, $CHCl_3$).

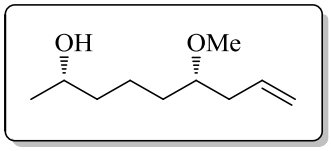
^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.83-5.71 (m, 1H), 5.07-4.99 (m, 2H), 3.80-3.71 (m, 1H), 3.32 (s, 3H), 3.19-3.12 (m, 1H), 2.29-2.15 (m, 2H), 1.64-1.21 (m, 6H), 1.11 (d, *J* = 5.86 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 6H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 134.9, 116.7, 80.4, 68.5, 56.5, 39.7, 37.7, 33.4, 25.9, 23.7, 21.4, 18.1, -4.4, -4.7 ppm.

IR (neat): 3450, 2928, 2856, 1463, 1372, 1255, 1146, 1036, 912, 767 cm^{-1}.

ESI-HRMS: *m/z* calcd for $C_{16}H_{34}O_2NaSi$ $[M + Na]^+$ 309.2225, found 309.2235.

3.2.4.9. (2*S*,6*S*)-6-Methoxynon-8-en-2-ol (61a):



To an ice-cold solution of silyl ether **60a** (534 mg, 1.867 mmol) in THF (10 mL), was added TBAF (1.0 M in THF, 2.4 mL, 2.24 mmol). The resulting solution was stirred at room temperature for 5 h and then diluted with saturated NH_4Cl (5 mL) and EtOAc (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to obtain an oily residue, which was purified by silica gel column chromatography (EtOAc/hexanes, 2:8) to afford the compound **61a** (288 mg, 90%) as a colourless oil.

$[\alpha]_D^{23}$: +5.7 (*c* 1.0, $CHCl_3$).

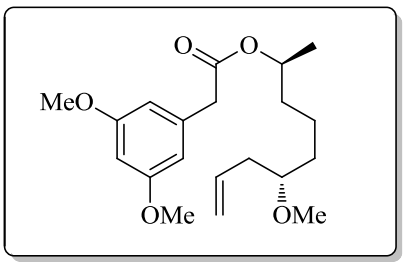
^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.87-5.69 (m, 1H), 5.12-4.96 (m, 2H), 3.85-3.70 (m, 1H), 3.34 (s, 3H), 3.25-3.14 (m, 1H), 2.31-2.17 (m, 2H), 1.54-1.35 (m, 6H), 1.18 (d, *J* = 6.04 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 134.7, 116.8, 80.4, 67.9, 56.5, 39.2, 37.6, 33.2, 23.4, 21.4 ppm.

IR (neat): 3045, 3070, 2928, 2856, 1641, 1462, 1372, 1095, 995, 776 cm^{-1}.

ESI-HRMS: *m/z* calcd for $C_{10}H_{20}O_2Na$ $[M + Na]^+$ 195.1360, found 195.1365.

3.2.4.10. (2*S*,6*S*)-6-Methoxynon-8-en-2-yl 2-(3,5-dimethoxyphenyl)acetate (62a):



To a solution of alcohol **61a** (220 mg, 1.28 mmol) and 3,5-dimethoxyphenylacetic acid **39** (300 mg, 1.53 mmol) in anhydrous Et_2O (10 mL) at room temperature were added DCC (318 mg, 1.532 mmol) and DMAP (16 mg, 0.128 mmol). After stirring for 3 h at room temperature, the mixture was filtered. The filtrate was diluted with Et_2O (20 mL) and washed with brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexanes, 1:9) to afford the olefin **62a** (400 mg, 90%) colourless oil.

$[\alpha]_D^{23}$: +8.3 (*c* 1.0, $CHCl_3$).

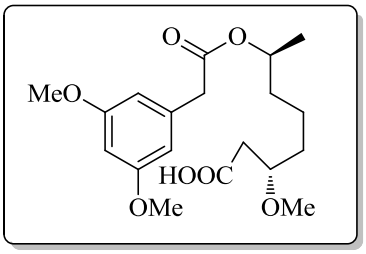
^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.37 (d, *J* = 1.8 Hz, 2H), 6.29 (t, *J* = 2.07 Hz, 1H), 5.79-5.64 (m, 1H), 5.01 (d, *J* = 6.42 Hz, 1H), 4.96 (s, 1H), 4.90-4.78 (m, 1H), 3.71 (s, 6H), 3.45 (s, 2H), 3.25 (s, 3H), 3.13-3.03 (m, 1H), 2.21-2.08 (m, 2H), 1.64-1.25 (m, 6H), 1.14 (d, *J* = 6.23 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.9, 160.7, 136.3, 134.7, 116.8, 107.1, 99.1, 80.2, 71.3, 56.5, 55.2, 42.0, 37.6, 35.8, 33.0, 21.0, 19.8 ppm.

IR (neat): 3446, 2933, 1730, 1603, 1461, 1295, 1150, 1096, 916, 770, 687 cm^{-1}.

ESI-HRMS: *m/z* calcd for $C_{20}H_{30}O_5Na$ $[M + Na]^+$ 373.1990, found 373.1993.

3.2.4.11. (3*S*,7*S*)-7-(2-(3,5-Dimethoxyphenyl)acetoxy)-3-methoxyoctanoic acid (42a):



To a solution of the alkene **62a** (150 mg, 0.42 mmol) in a mixture of *t*-BuOH (16 mL) and H_2O (4 mL), were added NMO (50% by wt in H_2O, 1.12 mL, 2.13 mmol) and OsO_4 (10 mg, 0.042 mmol) and the resulting mixture was stirred at rt for 12 h. The mixture was quenched with addition of granular $NaHSO_4$ (100 mg). After stirring for 15

min, the mixture was filtered and the filtrate was concentrated *in vacuo*. The crude residue was diluted with EtOAc (15 mL) and brine (5 mL), the organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure.

The crude diol was taken into a mixture of acetone (14 mL) and H_2O (4 mL), then solid $NaIO_4$ (184 mg, 0.84 mmol) was added to the reaction mixture. The resulting white suspension was stirred at room temperature for 1 h, filtered, and the filtrate was concentrated *in vacuo*. The residue was diluted with Et_2O (25 mL) and H_2O (10 mL), the layers were separated and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo.* The crude product was purified by silica gel column chromatography (EtOAc/hexanes,1:9) to give the aldehyde (68 mg, 80%), which was used directly in next reaction without further purification.

To a stirred solution of the crude aldehyde (60 mg, 0.19 mmol) were sequentially added 2-methylbut-2-ene (5 mL), *t*-BuOH (10 mL), $NaClO_2$ (50 mg, 0.57 mmol), NaH_2PO_4 (70 mg, 0.57 mmol) and H_2O (5 mL). After stirring at r.t. for 1.5 h, the reaction mixture was diluted with H_2O (5 mL) and extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to afford the acid **42a** (70 mg, 85%) as a colourless oil.

$[\alpha]_D^{23}$: +9.7 (*c* 1.0, $CHCl_3$).

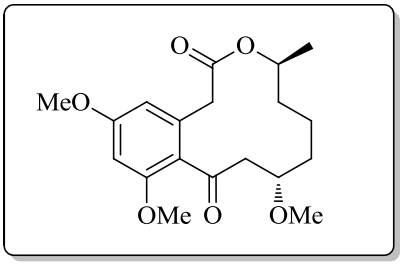
^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.40-6.35 (m, 2H), 6.29 (t, *J* = 2.21 Hz, 1H), 4.96-4.83 (m, 1H), 3.75 (s, 6H), 3.51-3.47 (m, 1H), 3.48 (s, 2H), 3.38 (s, 3H), 2.48 (dd, *J* = 6.98 Hz, 1H), 2.37 (dd, *J* = 5.47 Hz, 1H), 1.63-1.24 (m, 6H), 1.22 (d, *J* = 6.2 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.6, 171.2, 160.9, 136.2, 107.3, 99.2, 77.3, 71.2, 56.8, 55.2, 41.9, 38.9, 35.6, 33.3, 20.7, 19.8 ppm.

IR (neat): 3449, 2930, 1726, 1600, 1463, 1295, 1258, 1156, 1064, 772, 683 cm^{-1}.

ESI-HRMS: *m/z* calcd for $C_{19}H_{28}O_7Na$ $[M + Na]^+$ 391.1732, found 391.1714.

3.2.4.12. (4*S*,8*S*)-8,11,13-Trimethoxy-4-methyl-4,5,6,7,8,9-hexahydro-1H-benzo[d][1]oxacyclododecine-2,10-dione (43a):



Compound **42a** (50 mg, 0.21 mmol) was dissolved in a mixture of TFA (6 mL) and TFAA (1 mL) under an argon atmosphere. The solution was stirred overnight at room temperature and then poured into saturated $NaHCO_3$ solution (50 mL), extracted with Et_2O (3 x 50 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexanes, 2:8) to afford the compound **43a** (30 mg, 40%) as a colourless oil.

$[\alpha]_D^{23}$: −4.7 (*c* 1.0, $CHCl_3$).

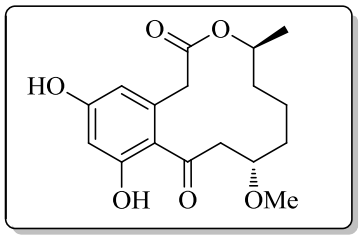
^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.46 (d, *J* = 1.8 Hz, 1H), 6.44 (d, *J* = 1.8 Hz, 1H), 4.89 (t, *J* = 6.4 Hz, 1H), 3.88 (s, 2H), 3.84 (s, 3H), 3.77 (s, 3H), 3.40 (d, *J* = 4.2 Hz, 3H), 2.35 (dd, *J* = 6.4, 13.0 Hz, 1H), 2.29 (t, *J* = 6.4 Hz, 1H), 2.20 (dd, *J* = 8.4 Hz, 1H), 1.93-1.80 (m, 1H), 1.60-1.41 (m, 4H), 1.17 (d, *J* = 6.6 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 197.3, 170.2, 162.0, 160.1, 156.7, 133.7, 132.8, 123.9, 107.2, 97.6, 78.1, 66.0, 55.7, 54.3, 40.3, 34.3, 34.0, 24.2, 20.1 ppm.

IR (neat): 3383, 2929, 1729, 1657, 1603, 1471, 1317, 1163, 1085, 1022, 849 cm^{-1}.

ESI-HRMS: *m/z* calcd for $C_{19}H_{26}O_6Na$ $[M + Na]^+$ 373.1627, found 373.1623.

3.2.4.13. (4*S*,8*S*)-11,13-Dihydroxy-8-methoxy-4-methyl-4,5,6,7,8,9-hexahydro-1H-benzo[d][1]oxacyclododecine-2,10-dione (30):



Iodine (542 mg, 1.54 mmol) was added to a mixture of aluminium (77 mg, 3 mmol) in anhydrous benzene (4 mL). The mixture was refluxed for 0.5 h and cooled to 0 °C, then TBAI (2 mg) and trimethoxy compound **43a** (25 mg, 0.07 mmol) in benzene (2 mL) were added. The mixture was stirred for 15 min at 0 °C, then quenched with 2N HCl (5 mL) at 0 °C and extracted with EtOAc (3 x 20 mL). The organic phase was washed with saturated $NaHCO_3$ (3 mL) and brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexanes, 3:7) to afford the target molecule **30** (15 mg, 65%) as a colourless oil.

$[\alpha]_D^{23}$: –16.3 (*c* 1.0, EtOH).

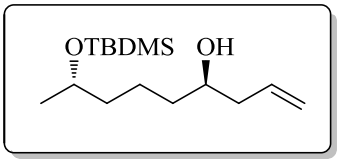
^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.30 (d, *J* = 2.0 Hz, 1H), 6.23 (d, *J* = 2.0 Hz, 1H), 4.90 (t, *J* = 6.9 Hz, 1H), 3.85 (d, *J* = 15.7 Hz, 1H), 3.82 (d, *J* = 3.6 Hz, 1H), 3.72 (dd, *J* = 6.9 Hz, 1H), 3.40 (d, *J* = 12.0 Hz, 1H), 3.35 (s, 3H), 3.04 (dd, *J* = 8.8, 1H), 1.65-1.52 (m, 6H), 1.20 (d, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 205.0, 172.0, 160.2, 159.1, 135.3, 120.0, 112.2, 103.0, 77.0, 74.0, 55.6, 49.1, 39.8, 32.7, 31.8, 20.8, 17.2 ppm.

IR (neat): 3393, 2924, 2854, 1710, 1613, 1454, 1320, 1267, 1030, 844, 758, 645 cm^{-1}.

ESI-HRMS: *m/z* calcd for $C_{17}H_{22}O_6Na$ $[M + Na]^+$ 345.1309, found 345.1315.

3.2.4.14. (4*R*,8*S*)-8-((*tert*-Butyldimethylsilyl)oxy)non-1-en-4-ol (59b):



To a stirred solution of $TiCl_4$ (1.04 mL, 1.0 M in CH_2Cl_2, 1.04 mmol) in CH_2Cl_2 (5 mL), was added anhydrous $Ti(O^iPr)_4$ (0.77 mL, 2.60 mmol) at 0 °C under an N_2 atmosphere and the mixture was allowed to warm to room temperature. After 1 h, (*S*)-binaphthol (0.99 g, 3.47 mmol) was added at room temperature and the resulting mixture was stirred for 3 h. The mixture was cooled to 0 °C, treated with Ag_2O (0.4 g, 1.74 mmol) and allowed to stir at room temperature for 5 h in the dark to furnish chiral bis{[(*S*)-binaphthoxyisopropoxy] titanium}oxide, which was subsequently treated with compound **58** (2.0 g, 8.69 mmol) and allyl-*n*-tributyltin (2.94 mL, 9.56 mol) at –15 °C. The mixture was warmed to 0 °C and stirred for 36 h, then quenched with saturated $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (EtOAc/hexanes, 1:9) to afford the allylated product **59b** (1.84 g, 75%) as a colourless oil.

$[\alpha]_D^{23}$: +17.0 (*c* 1.0, $CHCl_3$).

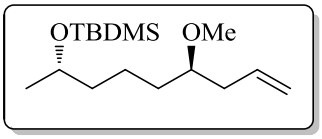
^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.87-5.73 (m, 1H), 5.14 (s, 1H), 5.09 (d, *J* = 3.02, 1H), 3.82-3.71 (m, 1H), 3.65-3.54 (m, 1H), 2.33-2.05 (m, 2H), 1.56-1.34 (m, 6H), 1.11 (d, *J* = 6.04 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 6H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz): δ 138.7, 117.9, 70.5, 68.4, 41.8, 39.5, 36.7, 25.8, 23.7, 21.8, 18.0, -4.5, -4.7 ppm.

IR (neat): 3388, 2956, 2930, 2857, 1464, 1375, 1218, 1134, 1042, 999, 834, 773 cm^{-1}.

ESI-HRMS: *m/z* calcd for $C_{15}H_{32}O_2NaSi$ $[M + Na]^+$ 295.2069, found 295.2068.

3.2.4.15. *tert*-Butyl(((2*S*,6*R*)-6-methoxynon-8-en-2-yl)oxy)dimethylsilane (60b):



To a suspension of 55% dispersion of NaH in mineral oil (122 mg, 5.09 mmol) in THF (5 mL), was added alcohol **59b** (1.26 g, 4.63 mmol) at 0 °C. After stirring for 20 min, MeI (0.35 mL, 5.55 mmol) was added slowly and the resulting mixture was stirred for a further 2 h. After complete conversion, the reaction was quenched with ice-cold H_2O (10 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexanes,0.5:9.5) to afford the compound **60b** (1.2 g, 90%) as a colourless oil.

$[\alpha]_D^{23}$: +9.7 (*c* 1.0, $CHCl_3$).

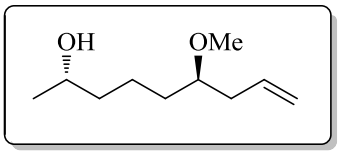
^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.82-5.72 (m, 1H), 5.07-5.00 (m, 2H), 3.80-3.71 (m, 1H), 3.32 (s, 3H), 3.19-3.12 (m, 1H), 2.29-2.15 (m, 2H), 1.65-1.22 (m, 6H), 1.11 (d, *J* = 5.86 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 6H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 134.9, 116.7, 80.4, 68.5, 56.6, 39.8, 37.7, 33.5, 25.9, 23.7, 21.6, 18.1, -4.4, -4.7 ppm.

IR (neat): 3450, 2928, 2857, 1462, 1372, 1255, 1035, 911, 832, 767 cm^{-1}.

ESI-HRMS: *m/z* calcd for $C_{16}H_{34}O_2NaSi$ $[M + Na]^+$ 309.2225, found 309.2235.

3.2.4.16. (2*S*,6*R*)-6-Methoxynon-8-en-2-ol (61b):



To an ice-cold solution of silyl ether **60b** (534 mg, 1.86 mmol) in THF (10 mL), was added TBAF (1.0 M in THF, 2.4 mL, 2.24 mmol). The resulting solution was stirred at room temperature for 5 h and then diluted with saturated NH_4Cl (5 mL) and EtOAc (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to obtain an oily residue, which was purified by silica gel column chromatography (EtOAc/hexanes, 2:8) to afford the compound **61b** (288 mg, 90%) as a colourless oil.

$[\alpha]_D^{23}$: +20.7 (*c* 1.0, $CHCl_3$).

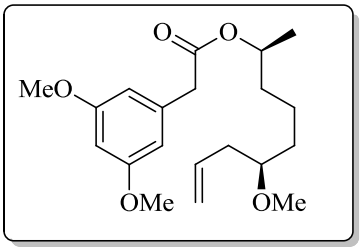
^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.84-5.68 (m, 1H), 5.09-4.99 (m, 2H), 3.82-3.70 (m, 1H), 3.33 (s, 3H), 3.21-3.13 (m, 1H), 2.40-2.15 (m, 2H), 1.52-1.25 (m, 6H), 1.17 (d, *J* = 6.04 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 134.6, 116.7, 80.4, 67.5, 56.4, 39.1, 37.5, 33.1, 23.3, 21.4 ppm.

IR (neat): 3048, 3076, 2927, 2857, 1641, 1460, 1372, 1096, 995, 770 cm^{-1}.

ESI-HRMS: *m/z* calcd for $C_{10}H_{20}O_2Na$ $[M + Na]^+$ 195.1360, found 195.1365.

3.2.4.17. (2*S*,6*R*)-6-Methoxynon-8-en-2-yl 2-(3,5-dimethoxyphenyl)acetate (62b):



To a solution of alcohol **61b** (220 mg, 1.28 mmol) and 3,5-dimethoxyphenylacetic acid **39** (300 mg, 1.53 mmol) in anhydrous Et_2O (10 mL) at room temperature were added DCC (318 mg, 1.53 mmol) and DMAP (16 mg, 0.12 mmol). After stirring for 3 h at room temperature, the mixture was filtered. The resulting filtrate was diluted with Et_2O (20 mL) and washed with brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*.

The residue was purified by silica gel column chromatography (EtOAc/hexanes, 1:9) to afford the compound **62b** (400 mg, 90%) as a colourless oil.

$[\alpha]_D^{23}$: +15.3 (*c* 1.0, $CHCl_3$).

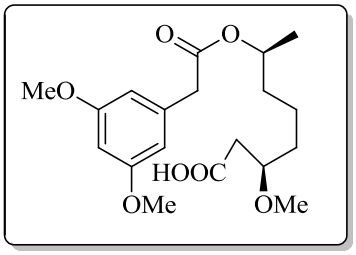
^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.38 (d, *J* = 2.20 Hz, 2H), 6.28 (t, *J* = 2.20 Hz, 1H), 5.85-5.62 (m, 1H), 5.13-4.95 (m, 2H), 4.94-4.79 (m, 1H), 3.76 (s, 6H), 3.46 (s, 2H), 3.28 (s, 3H), 3.16-3.02 (m, 1H), 2.25-2.09 (m, 2H), 1.64-1.25 (m, 6H), 1.20 (d, *J* = 6.61 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.9, 160.7, 136.3, 134.7, 116.8, 107.1, 99.0, 80.1, 71.3, 56.4, 55.2, 41.9, 37.5, 35.9, 33.0, 21.0, 19.8 ppm.

IR (neat): 2932, 1728, 1602, 1461, 1294, 1206, 1154, 1095, 915, 770, 687 cm^{-1}.

ESI-HRMS: *m/z* calcd for $C_{20}H_{30}O_5Na$ $[M + Na]^+$ 373.1990, found 373.1993.

3.2.4.18. (3*R*,7*S*)-7-(2-(3,5-Dimethoxyphenyl)acetoxy)-3-methoxyoctanoic acid (42b):



To a solution of the alkene **62b** (150 mg, 0.42 mmol) in a mixture of *t*-BuOH (16 mL) and H_2O (4 mL), was added NMO (50% by wt in H_2O, 1.12 mL, 2.13 mmol) and OsO_4 (10 mg, 0.04 mmol) and the resulting mixture was stirred at room temperature for 12 h. The mixture was quenched with the addition of granular $NaHSO_4$ (100 mg). After stirring for 15 min, the mixture was filtered and the filtrate was concentrated under *vacuo*. The crude residue was diluted with EtOAc (15 mL) and brine solution (5 mL), the organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude diol was taken into a mixture of acetone (14 mL) and H_2O (4

mL) and solid $NaIO_4$ (184 mg, 0.84 mmol) was added. The resulting white suspension was stirred at r.t. for 1 h, filtered, and the filtrate was concentrated *in vacuo*. The residue was diluted with Et_2O (25 mL) and H_2O (10 mL), the layers were separated and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (EtOAc/hexanes, 1:9) to give the aldehyde (68 mg, 80%), which was used directly in reaction without further purification.

To a stirred solution of the crude aldehyde (60 mg, 0.19 mmol), were sequentially added 2-methylbut-2-ene (5 mL), *t*-BuOH (10 mL), $NaClO_2$ (50 mg, 0.57 mmol), NaH_2PO_4 (70 mg, 0.57 mmol) and H_2O (5 mL). After stirring at room temperature for 1.5 h, the reaction mixture was diluted with H_2O (5 mL) and extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to afford the acid **42b** (70 mg, 85%) as a colourless oil.

$[\alpha]_D^{23}$: +9.3 (*c* 1.0, $CHCl_3$).

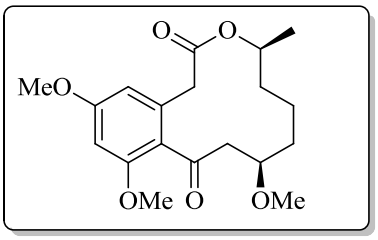
^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.41-6.36 (m, 2H), 6.29 (t, *J* = 2.26 Hz, 1H), 4.95-4.83 (m, 1H), 3.76 (s, 6H), 3.57-3.48 (m, 1H), 3.47 (s, 2H), 3.32 (s, 3H), 2.47 (dd, *J* = 6.98 Hz, 1H), 2.33 (dd, *J* = 5.47 Hz, 1H), 1.63-1.24 (m, 6H), 1.21 (d, *J* = 6.62 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.7, 171.0, 160.6, 136.2, 107.1, 98.9, 77.3, 71.2, 56.8, 55.2, 41.9, 38.8, 35.6, 33.3, 20.7, 19.8 ppm.

IR (neat): 3448, 2930, 1728, 1599, 1462, 1295, 1258, 1204, 1156, 1064, 771, 683 cm^{-1}.

ESI-HRMS: *m/z* calcd for $C_{19}H_{28}O_7Na$ $[M + Na]^+$ 391.1732, found 391.1714.

3.2.4.19. (4*S*,8*R*)-8,11,13-Trimethoxy-4-methyl-4,5,6,7,8,9-hexahydro-1H-benzo[d][1]oxacyclododecine-2,10-dione (43b):



Compound **42b** (50 mg, 0.21 mmol) was dissolved in a mixture of TFA (6 mL) and TFAA (1 mL) under an argon atmosphere. The solution was stirred overnight at room temperature and then poured into saturated $NaHCO_3$ (50 mL), extracted with Et_2O (3 x 50 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexanes, 2:8) to afford the compound **43b** (30 mg, 40%) as a colourless oil.

$[\alpha]_D^{23}$: –30.0 (*c* 1.0, $CHCl_3$).

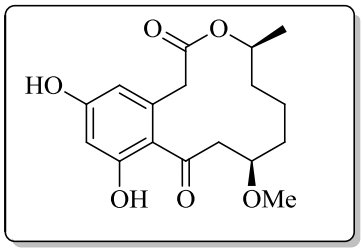
^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.47-6.34 (m, 2H), 4.93-4.85 (m, 1H), 3.86 (s, 2H), 3.80 (s, 3H), 3.74 (s, 3H), 3.43 (s, 3H), 3.32-3.26 (m, 1H), 2.30-2.20 (m, 2H), 1.93-1.80 (m, 6H), 1.21 (d, *J* = 6.23 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 198.4, 171.2, 162.3, 160.4, 155.2, 133.3, 132.7, 123.2, 107.7, 97.7, 78.1, 66.0, 55.7, 54.0, 40.1, 34.6, 34.0, 24.1, 20.0 ppm.

IR (neat): 3380, 2928, 1730, 1655, 1604, 1459, 1312, 1160, 1083, 1024, 849 cm^{-1}.

ESI-HRMS: *m/z* calcd for $C_{19}H_{26}O_6Na$ $[M + Na]^+$ 373.1627, found 373.1622.

3.2.4.20. (4*S*,8*R*)-11,13-Dihydroxy-8-methoxy-4-methyl-4,5,6,7,8,9-hexahydro-1H-benzo[d][1]oxacyclododecine-2,10-dione (31):



Iodine (542 mg, 1.54 mmol) was added to a mixture of aluminium (77 mg, 3 mmol) in anhydrous benzene (4 mL). The mixture was refluxed for 0.5 h and cooled to 0 °C, then TBAI (2 mg) and macrolide **43b** (25 mg, 0.07 mmol) in benzene (2 mL) were added. The mixture was stirred for 15 min at 0 °C, then quenched with 2 N HCl (5 mL) at 0 °C and extracted with EtOAc (3 x 20 mL). The organic phase was washed with

saturated $NaHCO_3$ solution (3 mL) and brine solution (5 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexanes, 3:7) to afford the target molecule **31** (15 mg, 65%) as a colourless oil.

$[\alpha]_D^{23}$:	–3.2 (*c* 1.0, EtOH).
^{1}H NMR ($CDCl_3$, 300 MHz):	δ 6.37 (d, *J* = 2.4 Hz, 1H), 6.13 (d, *J* = 2.4 Hz, 1H), 5.12 (t, *J* = 6.0 Hz, 1H), 3.97 (d, *J* = 15.7 Hz, 1H), 3.79 (d, *J* = 14.1 Hz, 1H), 3.58 (d, *J* = 16.5 Hz, 1H), 3.33 (d, *J* = 5.2 Hz, 1H), 3.25 (s, 3H), 3.12 (dd, *J* = 8.1 Hz, 1H), 1.85-1.53 (m, 6H), 1.24 (d, *J* = 5.2 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz):	δ 204.2, 171.8, 160.1, 159.4, 135.0, 118.4, 113.4, 102.7, 74.9, 72.8, 54.1, 49.3, 41.0, 31.3, 30.6, 19.0, 17.3 ppm.
IR (neat):	3392, 2925, 2853, 1711, 1620, 1454, 1321, 1268, 1169, 1031, 844, 758, 644 cm^{-1}.
ESI-HRMS:	*m/z* calcd for $C_{17}H_{22}O_6Na$ $[M + Na]^+$ 345.1309, found 345.1313.

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Spectra

LIST OF PUBLICATIONS

1. "First total synthesis of Nhatrangin A" Yadav, J. S.; Raju, A.; (Manuscript Ready for *Eur. J. Org. Chem*).
2. "A formal stereoselective synthesis of (-)-brevisamide" Yadav, J. S.; **Raju**, **A**.; Ravindar, K.; Subba Reddy, B. V.; (*Tetrahedron Letters* Accepted).
3. "Stereoselective Total Synthesis of Putaminoxin" Yadav, J. S.; **Raju**, **A**.; Ravindar, K.; Subba Reddy, B. V.; Ahmad Al Khazim Al Ghamdi.; (*Synthesis* **2012**, *44*, 585-590).
4. "Organocatalytic asymmetric aldol reaction: A facile enantioselective synthesis of *β*-hydroxyketones" Yadav, J. S.; Bhavani, K.; **Raju**, **A**.; Subba Reddy, B. V.; (*Tetrahedron Asymmetry*, **2011**, *22*, 881-886).
5. "Iodine as a versatile catalyst for the hydroalkylation of vinyl arenes with 1,3-diketones"CJ. S. Yadav, B. V. Subba Reddy, T. Srinivasa Rao, K. Bhavani. **A. Raju**. (*Tetrahedron Letters*, **2010**, 51, 2622-2624).
6. "Stereoseletive Total Synthesis of 11-*α*- and 11-*β*-Methoxycurvularins" J. S. Yadav, **A. Raju**, K. Ravindar, B. V. Subba Reddy (*Synthesis* **2010**, *5*, 797-802).
7. "The Hydroamination of Unactivated Alkenes with Sulfonamide Catalyzed by Phosphomolybdic Acid/SiO_2" J. S. Yadav, B. V. Subba Reddy, **A. Raju**, K. Ravindar and R. Narender (*Letters in Organic Chemistry* **2008**, *5*, 651-654).
8. "1-(Chloromethyl)-4-fluoro-1,4-diazoniabicyclo-[2,2,2]octane Bis(tetrafluoroborate) as Novel and Efficient Reagent for the Conjugate Addition of Indoles to *α*, *β*- Unsaturated Ketones" J. S. Yadav, B. V. Subba Reddy, **A. Raju**, K. Ravindar and Gakul Baishya ((*Chemistry letter*, **2007**, *36*, 1056-1057).
9. "Hydrothiolation of Unactivated Alkynes Catalyzed by Indium(III) Bromide" J. S. Yadav, B. V. Subba Reddy, **A. Raju**, K. Ravindar, and Gakul Baishya (*Chemistry letter*, **2007**, *36*, 1474-1475).