"Synthetic Studies Toward Amphidinolide C and Some Biologically Active Natural Products"

A THESIS

SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)

TO

PUNE UNIVERSITY

BY

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DIVISION OF ORGANIC CHEMISTRY

NATIONAL CHEMICAL LABORATORY

PUNE-411008

JULY 2008

DEDICATED

TO MY BELOVED

PARENTS

DECLARATION

The research work embodied in this thesis has been carried out at National Chemical Laboratory, Pune under the supervision of **Dr. M. K. Gurjar**, Former Deputy Director, and Head, Division of Organic Chemistry, National Chemical Laboratory, Pune-411 008. This work is original and has not been submitted part or full, for any degree or diploma of this or any other University.

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CERTIFICATE

The research work presented in thesis entitled "**Synthetic Studies Toward Amphidinolide C and Some Biologically Active Natural Products**" has been carried out under my supervision and is a bonafide work of **Mr. Hasibur Rahaman**. This work is original and has not been submitted for any other degree or diploma of this or any other University.

Pune-411008

July 2008

(Dr. M. K. Gurjar)

Research Guide

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Hasibur Rahaman

ABBREVIATIONS

Ac	-	Acetyl
Ac_2O	-	Acetic anhydride
AIBN	-	Azaisobutyronitrile
BF_3:OEt_2	-	Boron trifluoride diethyl ether complex
Bn	-	Benzyl
BnBr	-	Benzyl bromide
BzCl	-	Benzoyl chloride
BuLi	-	Butyl Lithium
DCC	-	Dicyclohexylcarbodiimide
DCM	-	Dichloromethane
DDQ	-	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DET	-	Diethyltartrate
DIAD	-	Diisopropylazodicarboxylate
DIBAL-H	-	Diisobutylaluminiumhydride
DMP	-	2,2-Dimethoxypropane
DMA	-	*N, N'*-Dimethylacetamide
DMF	-	*N, N'*-Dimethylformamide
DMAP	-	*N,N'*-Dimethylaminopyridine
DMSO	-	Dimethyl sulfoxide
CuCN	-	Copper (I) Cyanide
EtOH	-	Ethanol
Et	-	Ethyl
Et_2O	-	Diethyl ether
EtOAc	-	Ethyl acetate
Et_3N	-	Triethylamine
IBX	-	Iodoxybenzoic acid
Im	-	Imidazole
LAH	-	Lithium Aluminium Hydride

MeOH	-	Methanol
MsCl	-	Methanesulfonyl chloride
Ms	-	Methanesulfonyl
Me	-	Methyl
MeI	-	Methyl iodide
MOM	-	Methoxy Methyl
NaH	-	Sodium hydride
NMR	-	Nuclear Magnetic Resonance
Ph	-	Phenyl
PMB	-	*p*-Methoxybenzyl
PPTS	-	Pyridinium *p*-toluenesulfonate
PCC	-	Pyridinium chlorochromate
Pd/C	-	Palladium on Carbon
Py	-	Pyridine
PDC	-	Pyridiniumdichromate
PNB	-	*p*-Nitro Benzoyl
p-TSA	-	*p*-Toluenesulfonic acid
RCM	-	Ring closing metathesis
TBAF	-	Tetra-*n*-butylammonium fluoride
TBDMSCl	-	*tert*-Butyldimethyl chlorosilane
TBDMS	-	*tert*-Butyldimethyl silyl
TBDPSCl	-	*tert*-Butyldiphenyl chlorosilane
TBDPS	-	*tert*-Butyldiphenyl silyl
TBHP	-	*tert*-Butylhydroperoxide
TBTH	-	Tri-n-butyltin hydride
TEA	-	Triethylamine
THF	-	Tetrahydrofuran
TPP	-	Triphenylphosphine
TsCl	-	*p*-Toluenesulphonyl chloride
TFA	-	Trifluoroacetic acid

GENERAL REMARKS

❋ ^{1}H NMR spectra were recorded on AC-200 MHz, MSL-300 MHz, and DRX-500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.

❋ ^{13}C NMR spectra were recorded on AC-50 MHz, MSL-75 MHz, and DRX-125 MHz spectrometer

❋ EI Mass spectra were recorded on Finngan MAT-1020 spectrometer at 70 *eV* using a direct inlet system.

❋ Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}.

❋ Optical rotations were measured with a JASCO DIP 370 digital polarimeter.

❋ Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected.

❋ All reactions are monitored by Thin Layer chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV light, I_2 and anisaldehyde in ethanol as development reagents.

❋ All solvents and reagents were purified and dried by according to procedures given in Vogel's Text Book of Practical Organic Chemistry. All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.

❋ All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 40 °C.

❋ Silica gel (60–120) used for column chromatography was purchased from ACME Chemical Company, Mumbai, India.

CONTENTS

Research Student	Hasibur Rahaman
Research Guide	Dr. Mukund K. Gurjar
Title of Thesis	"Synthetic Studies Toward Amphidinolide C and Some Biologically Active Natural Products"
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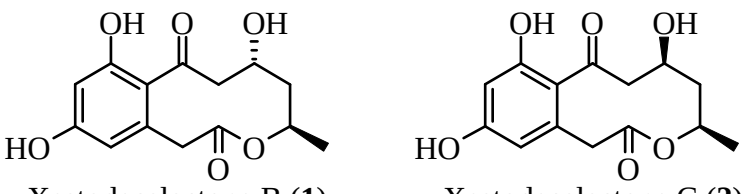
Abstract

The thesis entitled "**Synthetic Studies Toward Amphidinolide C and Some Biologically Active Natural Products"** consists of three chapters and each chapter is further subdivided into following sections: Introduction, Present work, Experimental, Spectroscopic data and References. Chapter 1, sections I, describes the synthesis of xestodecalactone C, whereas section II deals with the synthesis of xestodecalactone B. Chapter 2 provides the total synthesis of (−)-curvularin. The syntheses of C19-C34 (Section I) and C1-C9 segment (Section II) of amphidinolide C, and C14-C29 segment (Section III) of amphinolide U have been described in the concluding chapter 3.

CHAPTER 1: Synthetic studies of xestodecalactone B and C

Section I: Total synthesis of xestodecalactone C

Xestodecalactone B (**1)**, and C (**2)** have been recently characterized as a new secondary metabolite obtained from the marine sponge *Xestospongia exigua*. The salient feature of the structure of xestodecalactone B (**1**) and C (**2**) is the presence of a 1,3-dihydroxybenzene ring embedded in macrolactone moiety with two stereogenic centers (Figure 1). Xestodecalactone B **(1)** was found to be active against the yeast *C. albicans.*

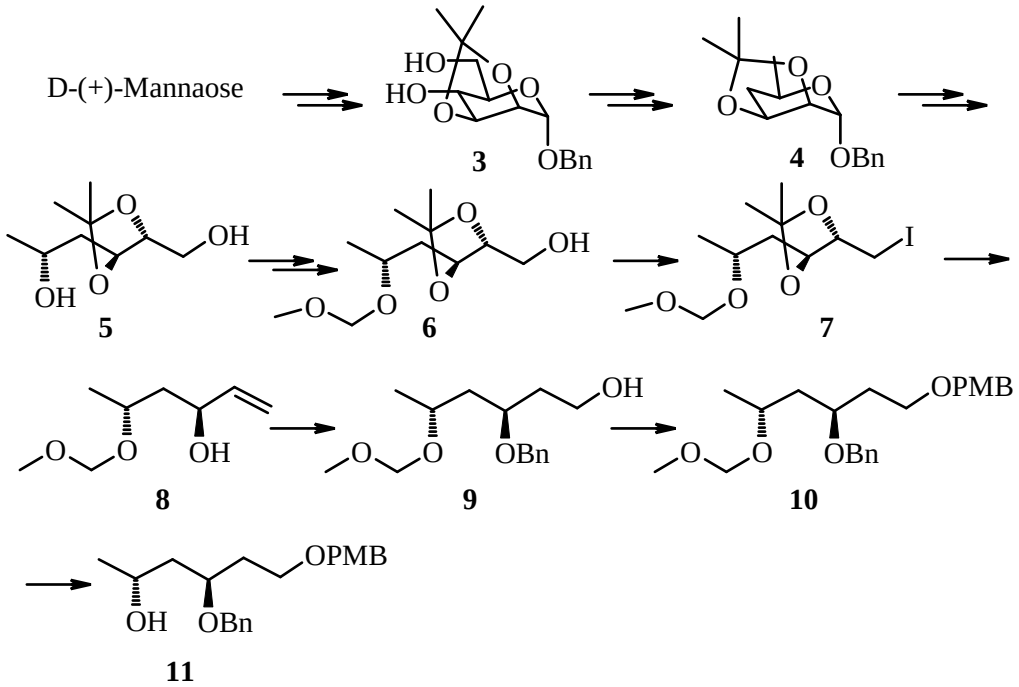


Xestodecalactone B (**1**) Xestodecalactone C (**2**)

Figure 1

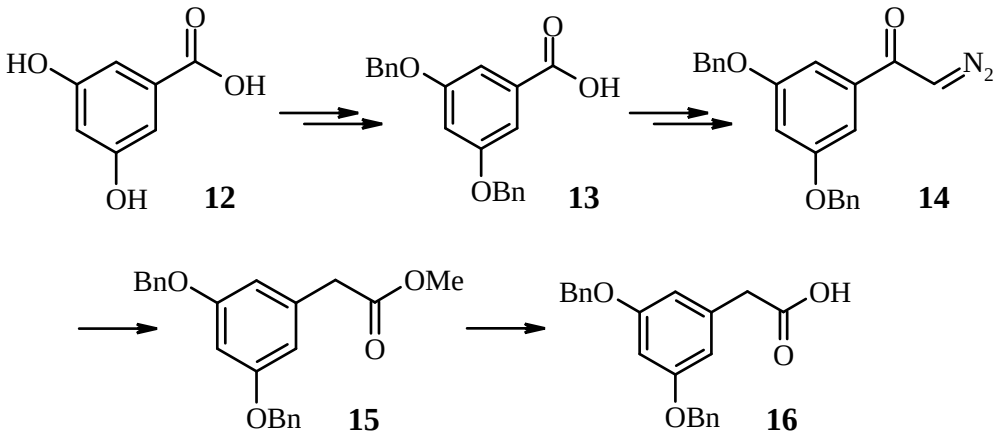
using the agar diffusion assay, it caused inhibition zones of 25, 12, and 7 mm at concentrations of 100, 50, and 20 μmol, respectively.

Our synthetic strategy towards the total synthesis of xestodecalactone C relies on the synthesis of fragment **11** from D-mannose as a chiral pool source. For the preparation of coupling partner **16**, Arndt-Eistert homologation played a key role.



Scheme 1

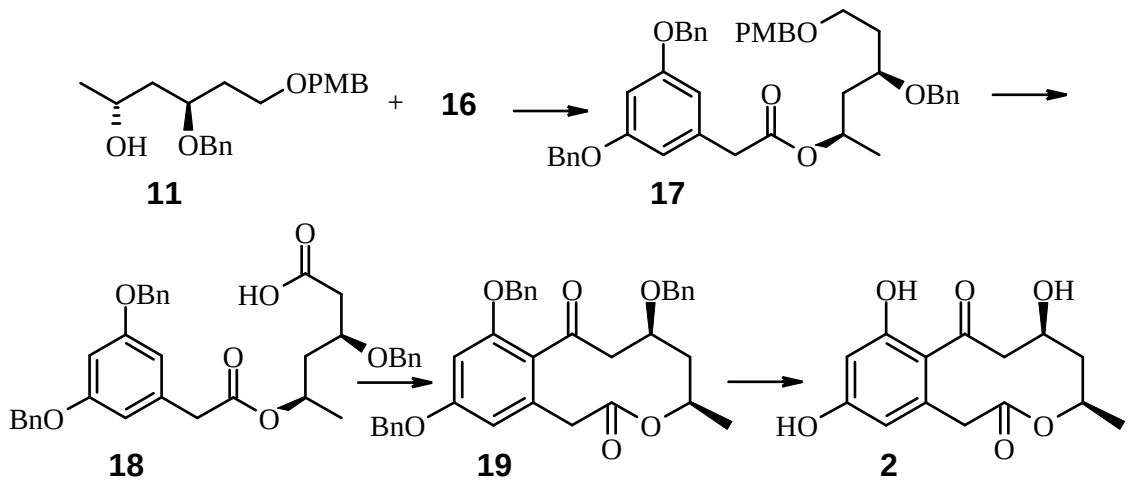
The synthesis of alcohol component **11** commenced with **3**, which was synthesized from D-mannose (Scheme 1). Deoxygenation at C4 and C6 were performed by two-step sequence, first formation of the dihalo derivative, followed by radical dehalogenation to obtain **4**. Debenzylation of benzyl mannopyranoside in presence of Na/naphthaline, followed by exposure to LAH resulted in the formation of the diol derivative **5**. A sequential protection deprotection strategy provided alcohol **6**. Primary hydroxyl group of **6** was converted to its iodo derivative **7** by Corey's protocol. A facile elimination of **7** in presence of activated Zn resulted the corresponding allylic alcohol **8**. The free hydroxyl group of **8** was converted to the benzyl ether, sequential hydroboration oxidation of the olefin and subsequent protection of the hydroxyl group as its *PMB* ether afforded **10**. Finally, acid mediated cleavage of *MOM* ether of **10** accomplished the coupling partner **11**.



Scheme 2

The synthetic endeavor for acid segment **16** began with commercially available 3,5-dihydroxybenzoic acid **12**, which was converted into its tribenzyl derivative and subsequent hydrolysis of ester provided 3,5-dibenzyloxybenzoic acid **13** (Scheme 2). Acid **13** was transformed to acid chloride, which on exposure to diazomethane furnished the diazoketone **14**. Diazoketone **14** underwent Arndt-Eistert rearrangement to give ester **15**, followed by basic hydrolysis accomplished the acid component **16**.

The coupling reaction of **11** and **16** was carried out via DCC mediated esterification reaction to give ester **17**. Cleavage of the *p*-methoxybenzyl ether of **17** using DDQ, oxidation of the resulting alcohol to the corresponding aldehyde by IBX and further oxidation using Pinnick reaction conditions in presence of buffer afforded the acid **18**. The macrolide **19** was constructed by intramolecular acylation reaction. On deprotection



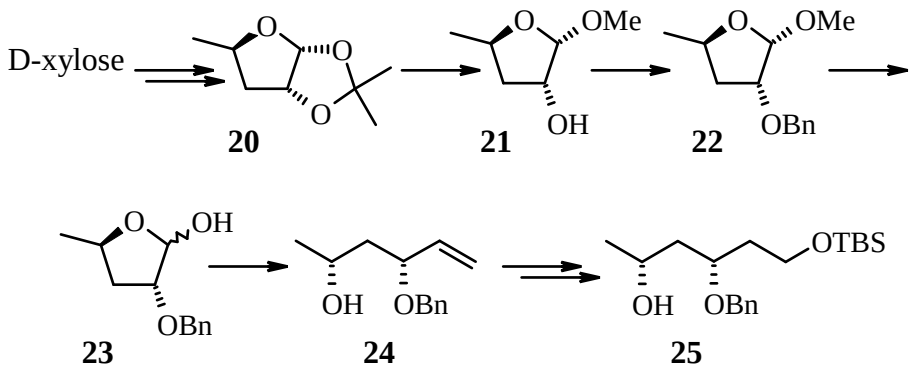
Scheme 3

of the benzyl groups of **19** by catalytic hydrogenation completed the total synthesis of xestodecalactone C (**2**).

Chapter 1: Section II: Total synthesis of xestodecalactone B

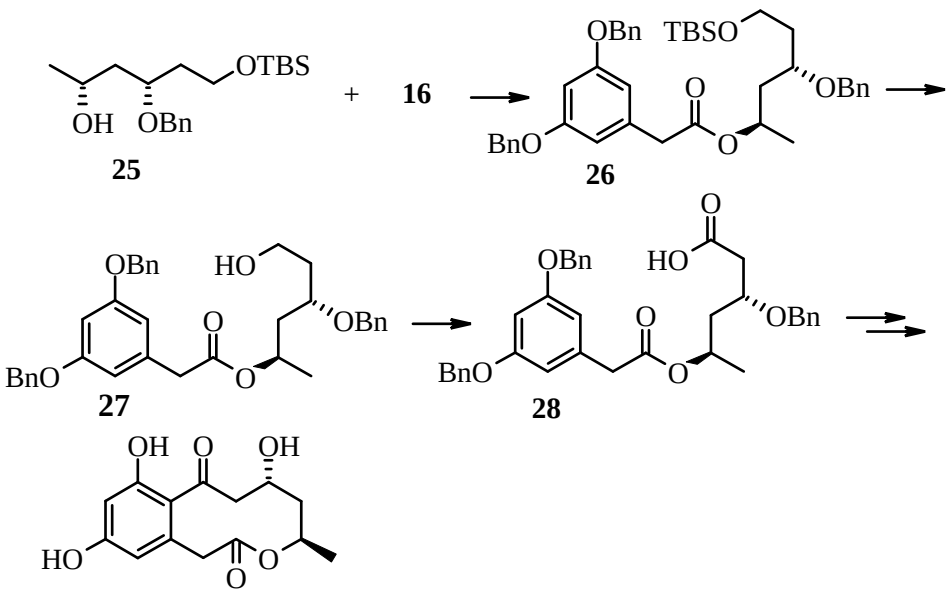
An appealing strategy for the convergent synthesis of xestodecalactone B (**1**) was envisaged by the efficient synthesis of the hydroxyl segment **20** from D-xylose by appropriate fuctionalizations of sugar backbone and the installation of macrolide core using intramolecular acylation.

The synthesis of alcohol component **25** began with **20**, which was synthesized according to the literature procedure from D-xylose (Scheme 4). The acid mediated cleavage of the 1,2-*O*-isopropylidene moiety and concomitant methyl glycosidation afforded **21**, which on exposure to BnBr furnished **22**. Compound **22** on acidic hydrolysis afforded lactol **23**, which on Wittig reaction furnished olefin derivative **24**. Hydroboration-oxidation of **24**, followed by a protection of the primary hydroxyl group as TBDMS ether furnished the alcohol segment **25**.



Scheme 4

The esterification between **25** and **16** was accomplished using DCC to furnish the ester **26**. Compound **26** was desilylated with TBAF to give the hydroxyl compound **27**, oxidation of the free hydroxyl group to aldehyde and subsequent Pinnick oxidation afforded the acid **28**. Finally, compound **28** was subjected to intramolecular acylation, followed by cleavage of the benzyl ethers by catalytic hydrogenation accomplished the total synthesis of xestodecalactone B (**1**).

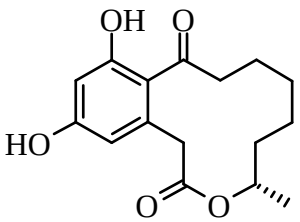


Xestodecalactone B (**1**)

Scheme 5

CHAPTER 2: Total synthesis of (−)-curvularin: a ring closing metathesis based construction of the macrocyclic framework

Curvularin belongs to a unique class of 12-membered fused resorcinylic macrolides. Curvularin **29**, and related compounds have been reported as metabolites produced by members of the *Curvularia*, *Alternaria*, and *Penicillium* genera. These macrolides possess interesting biological properties, including phytotoxicity, cytotoxicity toward sea urchin embryogenesis, inhibition of cell division, inhibition of expression of human inducible nitric oxide synthase, and growth-promoting activity in farm animals.

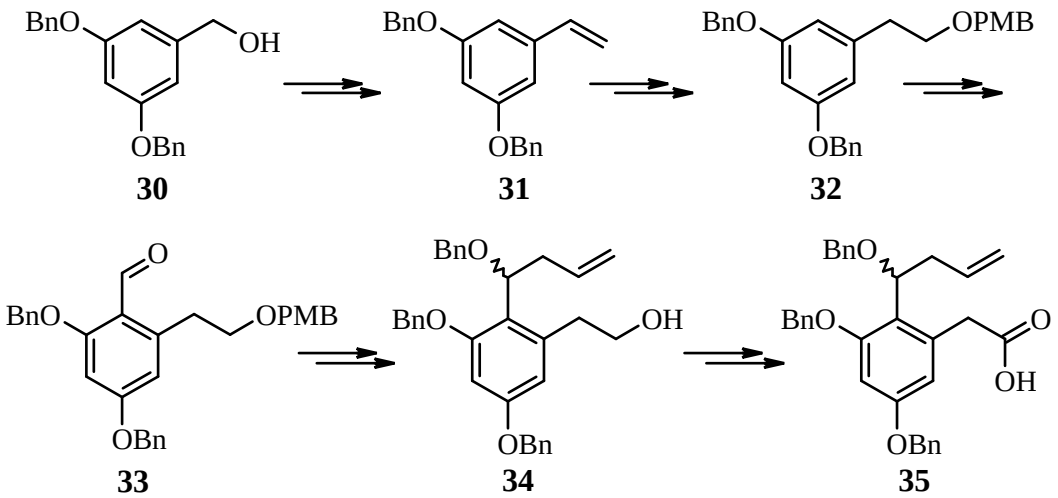


(-)-Curvularin **29**

Figure 2

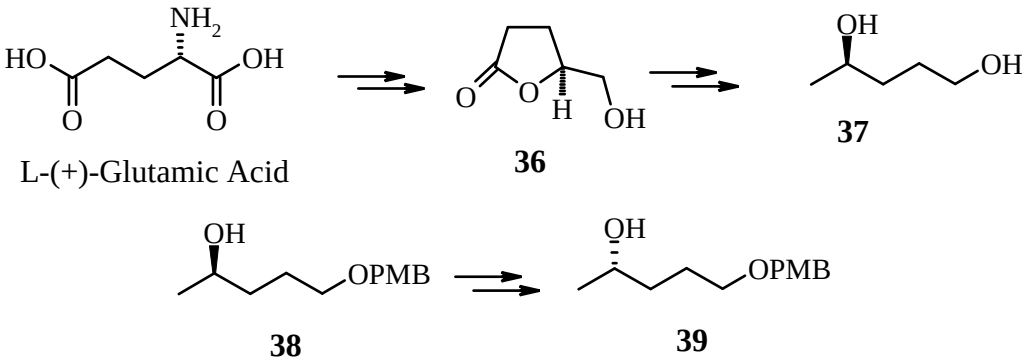
Synthesis of densely functionalized substituted aromatic acid began with commercially available 3,5-benzyloxybenzyl alcohol **30**, which was oxidized to aldehyde, followed by one carbon Wittig olefination provided olefin **31**. The sequential

hydroboration-oxidation of the olefin **31**, protection of the hydroxyl group as its *PMB* ether and subsequent formylation provided **33**. Grignard reaction of **33**, followed by a protection-deprotection sequence furnished the olefin derivative **34**. IBX oxidation of alcohol **34**, followed by Pinnick oxidation provided the required acid **35**.



Scheme 6

The synthesis of segment **39** was technically more expedient, commencing with commercially available L-glutamic acid. The synthesis of (*R*)-2,5-pentane diol synthon **37** was achieved over four steps following a standard procedure. A regioselective protection

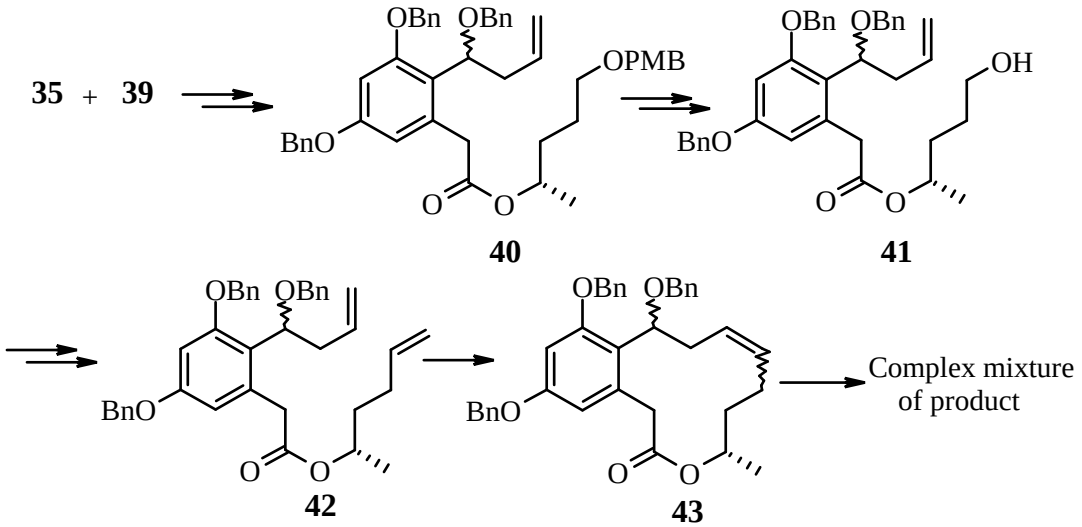


Scheme 7

of the primary hydroxyl group as *p*-methoxybenzyl ether **38**, followed by inversion of the secondary hydroxyl group using Mitsunobu reaction conditions provided the desired segment **39** (Scheme 7).

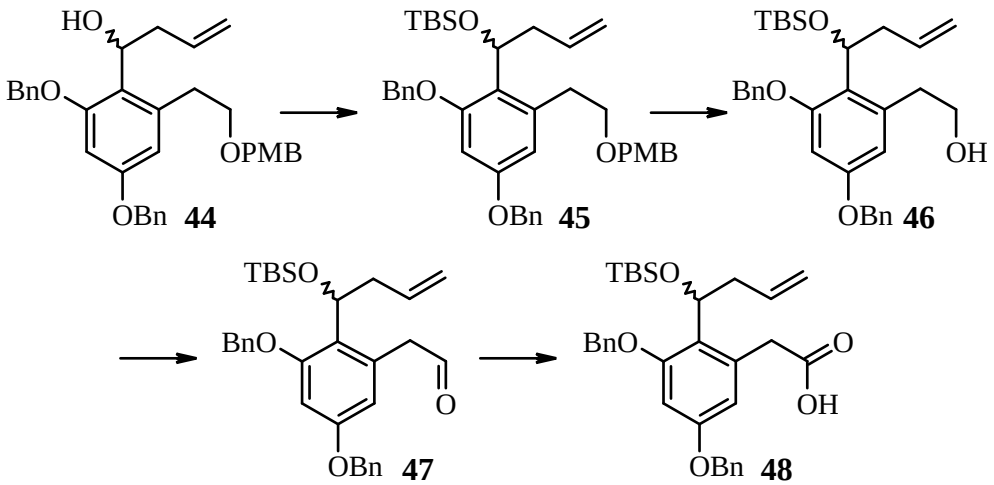
With two coupling partner in hand, the engagement was accomplished using DCC to afford **40**. Unmasking of *PMB* ether, followed by oxidation of the resulting alcohol,

and subsequent Wittig reaction gave the requisite diene intermediate **42**. Ring closing metathesis of **42** afforded the desired macrolactone **43**. The next objective of our synthetic endeavor needed global deprotection of benzyl group as well as reduction of the olefin in a single shot. Accordingly, compound **43** was subjected to catalytic hydrogenation as well as Lewis acid ($TiCl_4$) to obtain the desired product. Unfortunately, the major isolated product didn't provide the clear image over the structure. Hence, we stopped at this juncture and looked for alternative.



Scheme 8

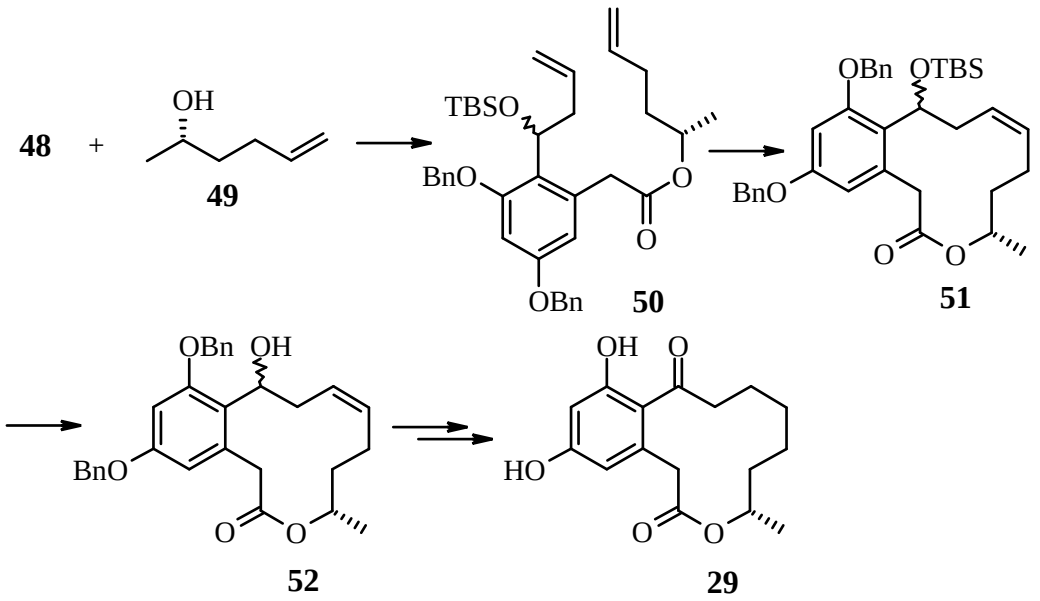
With the failure of aforementioned route, the mission for conquering the synthesis of curvularin solely rested on the alternative protecting group for hydroxy group of **40** rather than benzyl ether. To reduce the steps in the journey to reach target, we have furnished the alcohol **58** in an alternative way.



Scheme 9

The alcohol **44** was protected as its *TBS* ether using TBSCl to obtain **45**. Cleavage of *PMB* ether by treating with DDQ followed by IBX oxidation of alcohol **46** afforded the corresponding aldehyde which on Pinnick oxidation gave the required acid **48**. With the aromatic segment readily in hand, alcohol **49** was synthesized from commercially available (*S*)-(−)-methyloxirane following standard method.

With two subunits were in our hand, we proceeded to couple both intermediates **48** and **49** as described in scheme 10. Accordingly, the esterification was accomplished using DCC to furnish **50**. On exposure of **50** to Grubbs' 2nd generation catalyst led to the formation of *E/Z* mixture of unsaturated macrocycle **51**. Macrolactone **51** was converted



Scheme 10

to hydroxyl lactone **52** by treating with TBAF. Finally, IBX oxidation of the secondary hydroxyl functionality in **52** led to the keto-lactone, followed by global deprotection and concomitant reduction of the olefin with catalytic hydrogenation using 10% Pd/C afforded curvularin **29**.

In conclusion, a convergent synthesis of (−)-curvularin has been achieved via ring-closing metathesis reaction as the key step starting from easily available starting materials.

CHAPTER 3: Synthetic studies of amphidinolide C and U

Section I: Synthesis of the C19-C34 segment of amphidinolide C

The growing importance of amphidinolide group of naturally occurring macrolides from the marine dinoflagellates of the genus amphidinium has been attributed to the potent biological activities and novel structural features. The target molecule amphidinolide C (**53**; Figure 3), isolated from the marine dinoflagellates *Amphidinium sp*. (strain Y–5), is a unique 25-membered macrolide having two tetrahydrofuran rings decorated with vicinally located one-carbon branches, showed extremely potent *in vitro* cytotoxic activity against murine lymphoma L1210 and epidermoid carcinoma KB cells (IC_{50} = 0.0058 and 0.0046 mg $mL,^{-1}$ respectively).

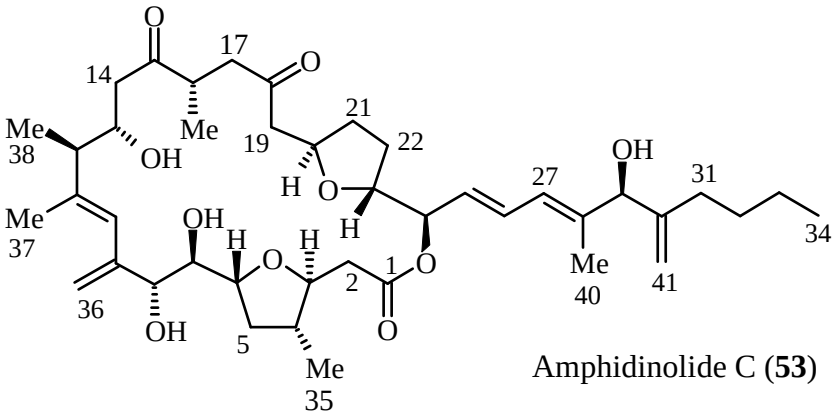
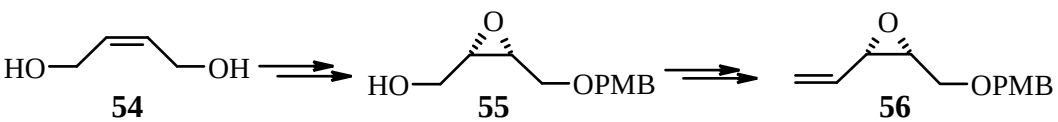


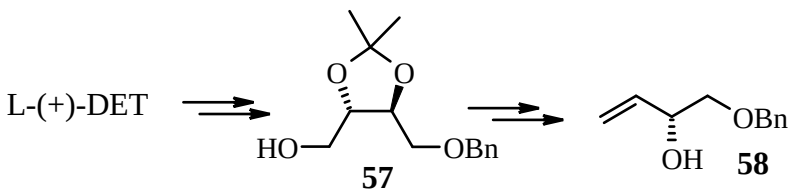
Figure 3

The synthesis of **56** began with *cis*-2-butene-1,4-diol (**54**), which was converted into **55** by employing the Sharpless asymmetric epoxidation following established procedure. Subsequent oxidation of **55**, followed by one-carbon Wittig reaction gave the vinyl substituted epoxide **56**.



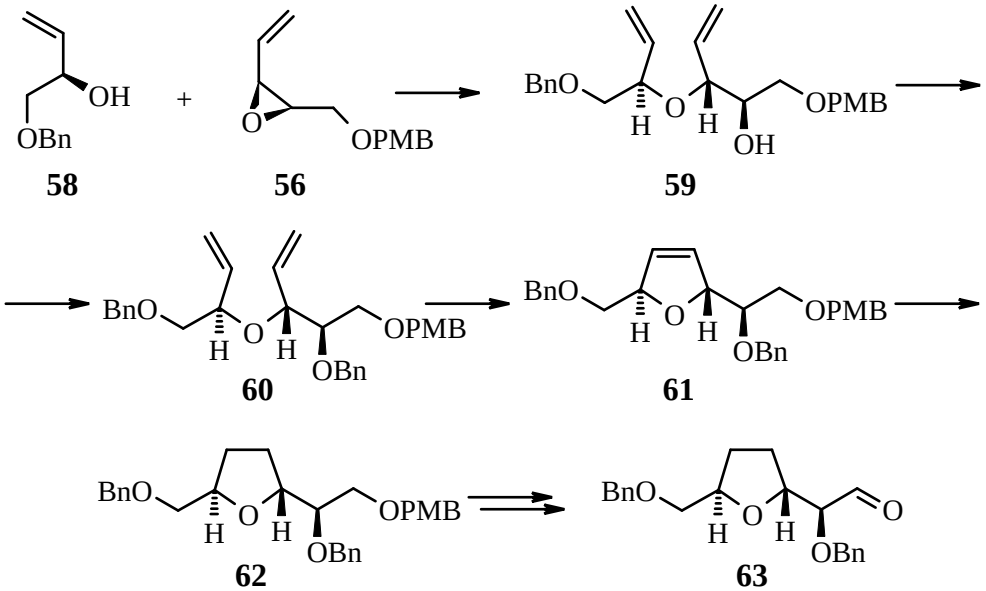
Scheme 11

The chirally pure allylic alcohol **58** was prepared by following a sequence of reaction staring from L-(+)-DET (Scheme 12).



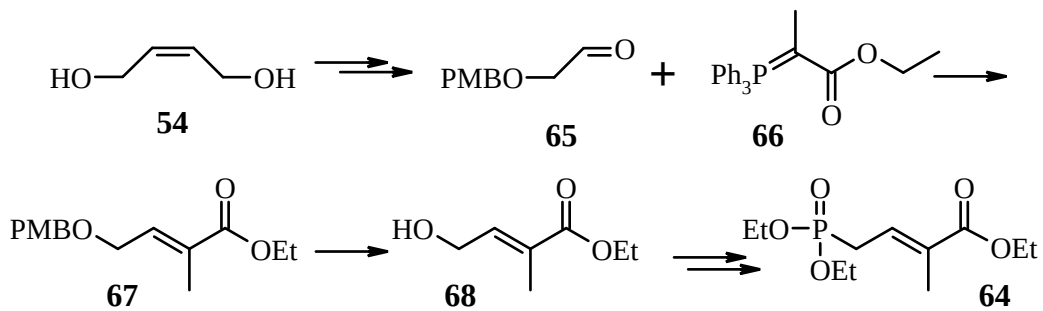
Scheme 12

The coupling reaction between **56** and **58** was carried out in the presence of catalytic amount of $Cu(OTf)_2$. The absolute stereochemistry of the secondary hydroxyl group at C24 was confirmed by modified Mosher's method. The secondary hydroxyl group of **59** was then protected as its benzyl ether and ring-closing metathesis reaction was carried out to afford the dihydrofuran derivative **61** whose hydrogenation was carried out in the presence of 10% Pd/ C to afford the tetrahydrofuran derivative **62** (Scheme 13). The removal of the *PMB* group, followed by oxidation of the free alcohol provided aldehyde **63**. Having in hand the aldehyde **63**, we next envisaged the synthesis of phosphonate **64**.



Scheme 13

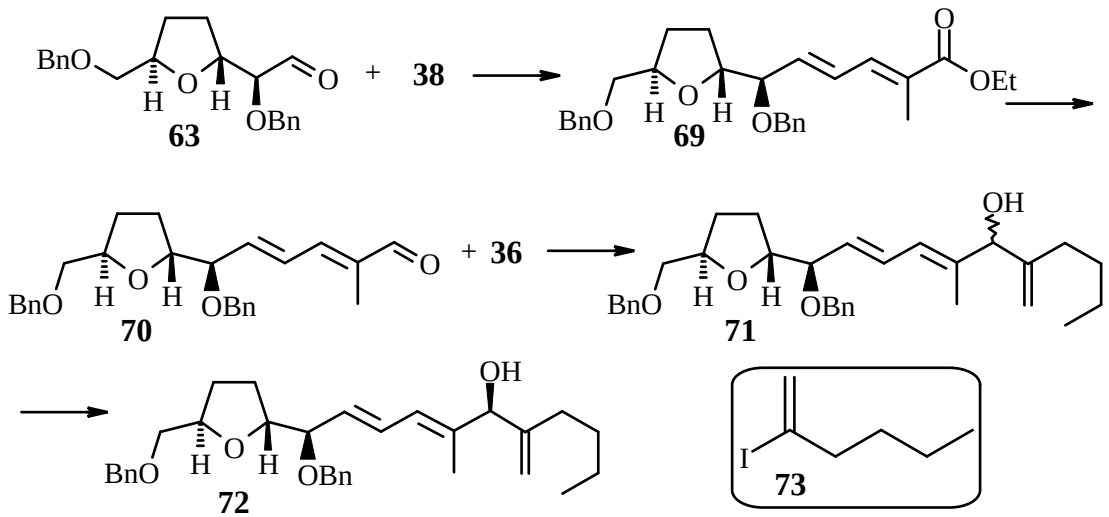
The next synthetic target was the phosphonate derivative **64**, for which aldehyde **65** was identified as the starting material. *Cis*-2-butene-1,4-diol **42** was protected as di-*PMB*



Scheme 14

ether and then subjected to oxidative cleavage of olefin to afford **65** (Scheme 14). The aldehyde **65** was subjected to Wittig reaction to provide the (*E*)-α,β-unsaturated ester **67**. Removal of *p*-methoxybenzyl ether in **67** afforded the allyl alcohol **68**. Conversion of alcohol **68** to the corresponding bromo derivative, followed by Michaelis-Arbuzov reaction of the resulting bromo intermediate afforded **64**.

Our next concern was the introduction of the densely olefinated side chain for which the Wittig–Horner reaction with **64** in the presence of LDA was performed to obtain **69**. Reduction of **69** with DIBAL-H gave the allylic alcohol, which was converted into the aldehyde derivative **70**. The Nozaki–Hiyama–Kishi coupling reaction between **70** and **73** provided **71** as diastereomeric mixture (1:1) (Scheme 15). The diastereomers were separated by preparative liquid chromatography and the absolute stereochemistry of secondary hydroxyl group bearing center was assigned following a modification of Mosher's method.



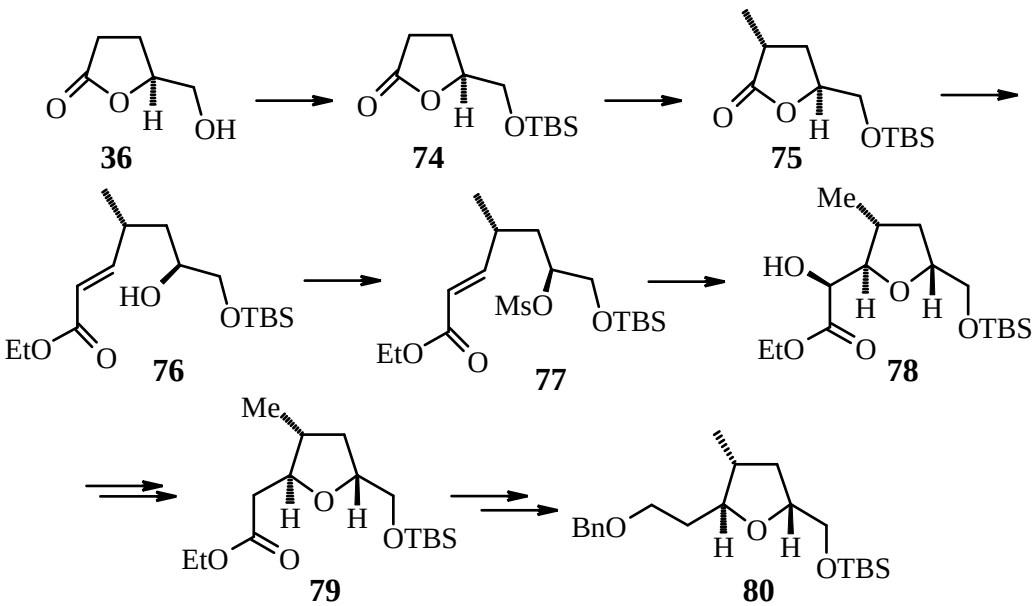
Scheme 15

In conclusion, a versatile synthetic strategy towards the C19-C34 segment of amphidinolide C (**72**) has been achieved which could lead to the easy access of its diastereomers as well. For the construction of the tetrahydrofuran framework, the Lewis acid-catalyzed regiospecific opening of vinyl substituted epoxide **56** by alcohol **58**, followed by ring closing metathesis (RCM) were the key steps

Chapter 3: Section II: Synthesis of the densely functionalized C1-C9 segment of amphidinolide C

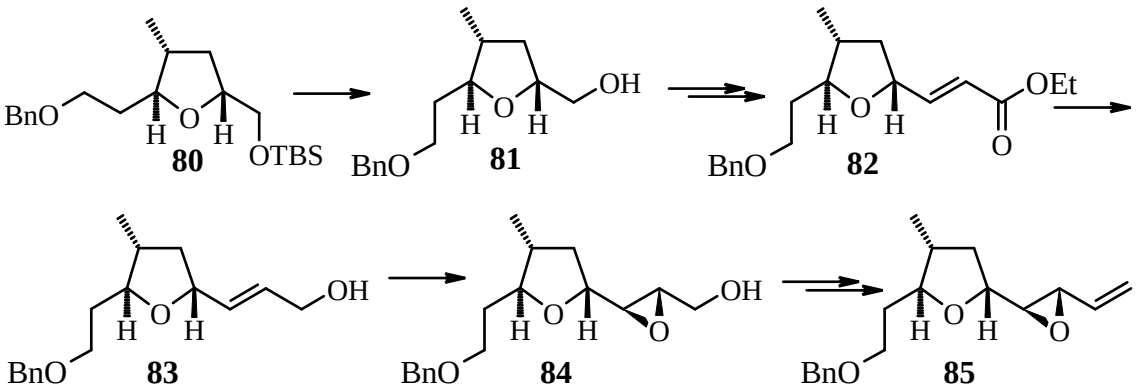
After successful achievement of the expedient assembly of substituted tetrahydrofuran containing segment C19-C34 of amphidinolide C (**72**), our next endeavor was the synthesis of the densely functionalized segment C1-C9. The synthetic pathway adapted a comparatively short, highly stereoselective synthesis from (*S*)-hydroxymethyl-γ-butyrolactone **36**. The latter could be inexpensively prepared in two steps from naturally abundant L-(+)-glutamic acid. The central transformation of the synthetic sequence, *i.e.*, formation of the THF ring with appropriate stereochemistry, *trans*-fusion, through a tendem dihydroxylation-S_N2 cyclization sequence was investigated next.

Accordingly, we have started with the lactone alcohol **36**. The hydroxyl group was protected as *TBS* ether to get the *TBS* protected lactone **74**. Stereoselective methylation of the lactone **74** resulted in **75** as a major diastereomer (ratio 11:1). The *trans* relationship between the two substituents on the five-membered ring lactone **75** was confirmed by NOESY experiment. Lactone **75** was reduced by DIBAL to the corresponding hemiacetal **76**, which was quickly exposed to Wittig reaction provided the α,β-unsaturated ester **76**. The alcohol **76** was converted into its mesylate ester **77**, which was subjected to Sharpless dihydroxylation, whereupon the *trans*,*syn*-tetrahydrofuran **78** was obtained. Our next concern was to deoxygenate the hydroxyl group at C2 by using Barton's radical deoxygenation protocol to furnish the 2-deoxy derivative **79**. Compound **79** was treated with $LiAlH_4$ to afford the alcohol, which was converted to benzyl ether **80**.



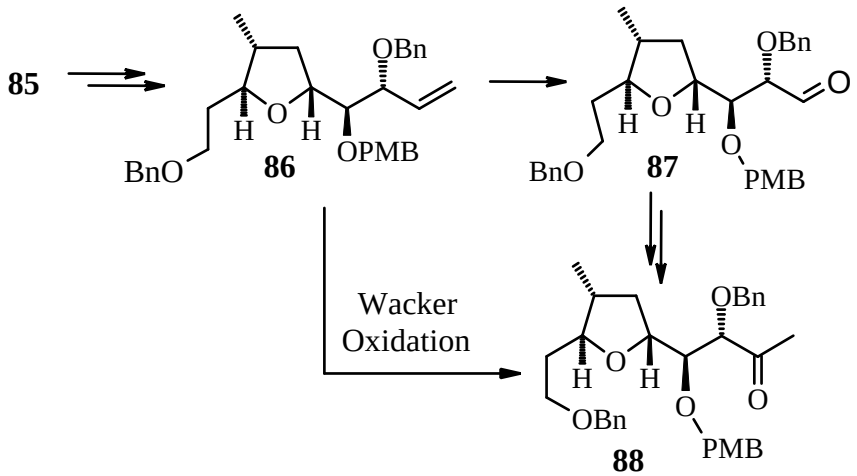
Scheme 16

For the installation of the side chain, cleavage of *TBS* ether of **80** was performed to give the alcohol **81**. The free hydroxyl group present in **81** was first subjected to Swern oxidation to furnish a highly labile aldehyde **84**, which was immediately transformed into the corresponding α,β-unsaturated ester **82**. Reduction of ester derivative **82** using DIBAL-H furnished the allylic alcohol derivative **83**. Sharpless asymmetric epoxidation of the *E*-allylic alcohol **83** using diethyl-(L)-tartrate provided the corresponding epoxy alcohol **84** (Scheme 17). The alcohol derivative **84** was efficiently oxidized to aldehyde, which underwent Wittig reaction to obtain the requisite vinyl epoxide intermediate **85**.



Scheme 17

Our next objective was the regiospecific opening of vinyl epoxide **85** with benzyl alcohol. Accordingly, the epoxide **85** was subjected to the treatment of BnOH in presence



Scheme 18

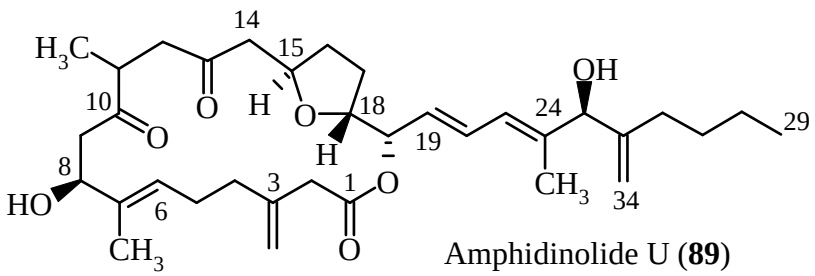
of $BF_3{\cdot}Et_2O$ to furnish β-hydroxy allyl ether. The secondary hydroxyl group was converted as its *PMB* ether to provide **86** (Scheme 18). Compound **86** was subjected to modified Wacker oxidation protocol to introduce carbonyl group. Despite the success in

accomplishing the desired product **88**, the poor yielding sequence forced us to seek for an easy alternative. In view of the simple reaction conditions, we opted for three step protocol, *viz*, oxidative cleavage, Grignard reaction and IBX oxidation to complete the targeted segment **88**.

In conclusion, we have achieved an asymmetric synthesis of C1-C9 segment of amphidinolide C (**53**) in a completely stereocontrolled linear approach. The construction of *trans*-2,5-disubstituted tetrahydrofuran ring was accomplished by a tandem dihydroxylation-S_N2 cyclization sequence. Stereocenter at C7 and C8 were fixed by Sharpless asymmetric epoxidation.

Chapter 3: Section III: Synthesis of the C14-C29 Segment of Amphidinolide U Utilizing a Tandem Dihydroxylation-S_N2 Cyclization

Amphidinolide U (**89**, Figure 4), a novel 20-membered macrolide, possessing a tetrahydrofuran ring, two *exo*-methylenes, three branched methyls, two ketones, two hydroxyl groups, and a C10 linear side chain, was isolated from laboratory cultured dinoflagellates of the *Amphidinium* sp. This section describes the synthesis of C14-C29 segment of amphidinolide U starting from L-(+)-glutamic acid.

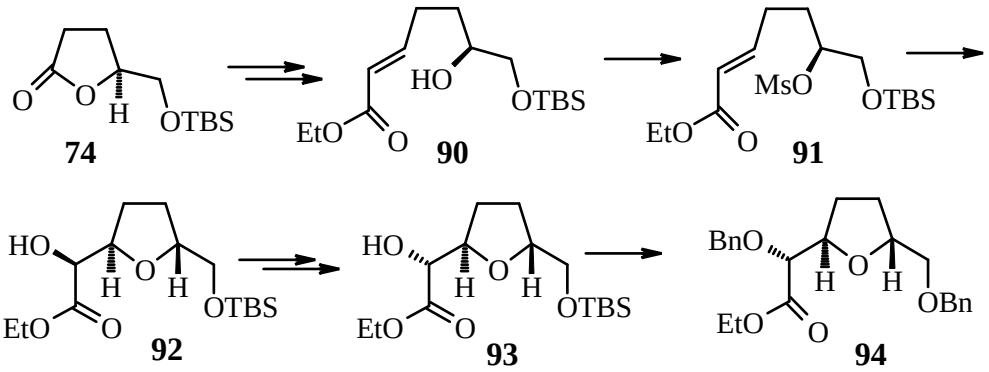


Amphidinolide U (**89**)

Figure 4

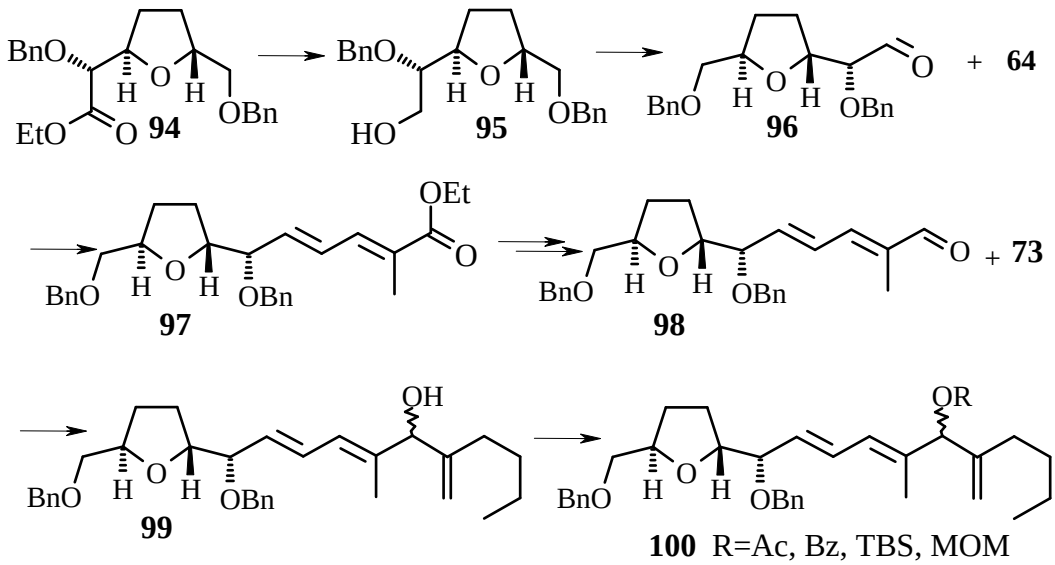
Accordingly, the journey began with lactone **74**, which could be obtained from commercially available optically pure L-(+)-glutamic acid. Compound **7** was treated with DIBAL-H, followed by Wittig reaction to afford *E*-olefin **90** as the only product. The secondary hydroxy group was then protected as its mesylate ester. The mesylate ester **91** was subjected to Sharpless dihydroxylation, where upon the *trans,syn*-tetrahydrofuran **92** was obtained with excellent diastereoselectivity (Scheme 19). Next, the inversion of the hydroxy group was achieved via standard Mitsunobu protocol to obtain required chiral

center. Modified Mosher's method and NOESY experiment was performed to assign the stereochemistry. Compound **93** was desilylated with TBAF to give the diol, which was subsequently converted to dibenzyl ether **105**.



Scheme 19

Treatment of **94** with LAH gave the primary alcohol **95**. Our next concern was to introduce the densely olefinated side chain. The primary hydroxyl group of **95** was then oxidized with IBX, followed by Wittig–Horner reaction with phosphorane **64** furnished



Scheme 20

the *E,E*-dienoate **97**. Subsequent reduction of **97** with DIBAL-H gave the allylic alcohol, which was converted into the aldehyde **98** using IBX oxidation (Scheme 20). The Nozaki–Hiyama–Kishi coupling reaction between **98** and **73** provided 1:1 diastereomeric mixture of our targeted segment **99**. We protected the secondary hydroxy group with different protecting groups to generate variously protected diastereomers **100**.

Unfortunately, no separation of diastereomers with different solvent systems was discernible.

In conclusion, we have achieved the first synthesis of the entire top half **99** of the amphidinolide U (**89**), offering the promise of the total synthesis of this molecule but also other structurally similar congeners. For the construction of *trans*-2,5-disubstituted tetrahydrofuran, a tandem Sharpless asymmetric dihydroxylation-S_N2 cyclization protocol has been used as the key step.

CHAPTER 1

Synthetic Studies of Xestodecalactone B and C

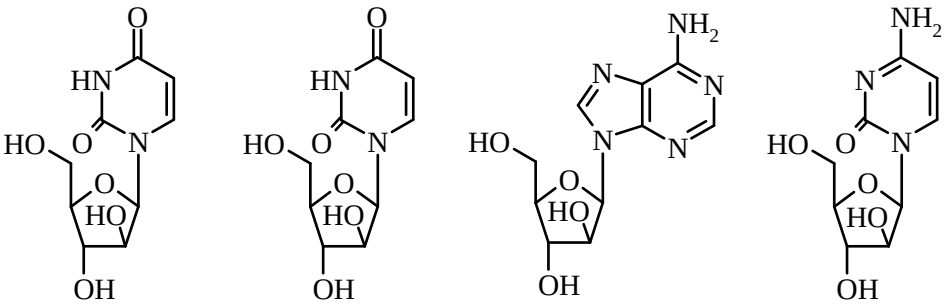
Introduction

The Ocean, which is called the '*mother of origin of life*', is also the source of structurally unique natural products that are mainly accumulated in living organisms. Several of these compounds show pharmacological activities and are helpful for the invention and discovery of bioactive compounds, primarily for deadly diseases like cancer, acquired immuno-deficiency syndrome (AIDS), arthritis, etc., while other compounds have been developed as analgesics or to treat inflammation, etc. The life saving drugs is mainly found abundantly in microorganisms, algae and invertebrates, while they are scarce in vertebrates. Modern technologies have opened vast areas of research for the extraction of biomedical compounds from oceans and seas.

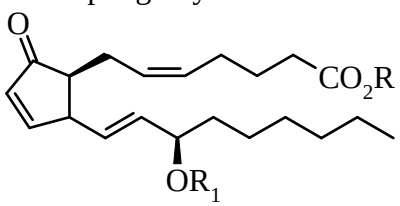
Marine microorganisms have evolved to biosynthesize biologically interesting and chemically diverse compounds. In the search for novel bioactive compounds more than 800 microorganisms have so far been isolated from marine sediments and organisms,[1-3] and about half of them belong to fungal genera. In the search for new pharmaceutical or agrochemical lead structures, sponge-associated fungi yielding cytotoxic metabolites have received increasing attention at a rate much faster than those of other unicellular organisms.[4,5] One group of compounds is the macrolides, which have been of much interest because of their flexible ring conformation and well-known antibiotic activities.[6] Recently, macrolides have also been reported as cytotoxic and potential antitumor agents.

Bioactive compounds of marine sponge origin

Marine sponges are pre-eminent producers of secondary metabolites and are also one of the richest sources of alkaloids and polyketides. The first compounds, isolated from marine organisms and used as tools in pharmaceutical development, were the unusual nucleosides spongouridine **1**[7a] and spongothymidine **2**[7a] from the sponge *Cryptotethya crypta*. These two compounds helped the development of the antiviral drugs, vidarabine **3**[7b] and cytarabine **4**.[7c] Also, an important milestone in the discovery of potential drugs from marine natural sources was the isolation and structural elucidation of the prostaglandins **5** from the gorgonian *Plexaura homomalla*.[8]



Spongouridine **1** Spongothymidine **2** Vidarabine **3** Cytarabine **4**



Prostaglandins **5**

$R = CH_3$, R_1= Ac

$R = CH_3$, R_1= H

$R = R_1$= H

Figure 1

Approximately 10,000 sponges have been described in the world and most of them live in Marine waters. A range of bioactive metabolites has been found in about 11 sponge genera. Three of these genera (*Haliclona*, *Petrosia* and *Discodemia*) produce powerful anti-cancer, anti-inflammatory agents, but their cultivation has not been studied.[9] The discovery of spongouridine **1**, a potent tumor-inhibiting arabinosyl nucleoside in Caribbean sponge *Cryptotethia crypta*, focused attention on sponges as a source of biomedically important metabolites. The identification of the pharmacophore led to the synthesis of a new class of arabinosyl nucleoside analogues, one of which is arabinosyl cytosine, which is converted into arabinosyl cytosine triphosphate and incorporated into cellular DNA where it inhibits DNA polymerase, is already in clinical use for the treatment of acute mylocytic leukemia and non-Hodgkin's lymphoma.[10] The compound manoalide from a Pacific sponge has spawned more than 300 chemical analogs, with a significant number of these going on to clinical trials as anti-inflammatory agents. An aminoacridine alkaloid, dercitin, has been isolated from the deep-water sponge, *Dercitus sp*. That possesses cytotoxic activities in the low nanomolar concentration range and in animal studies, prolongs the life of mice-bearing ascitic P388 tumours, and is also active against B16 melanoma cells and small cell Lewis lung carcinoma.[11] Theopederina A-E, sponge *Theonella sp.*, are highly cytotoxic against P388

murine leukemia cells. Theopederins A and B (**6** and **7**) showed promising antitumor activity.[12]

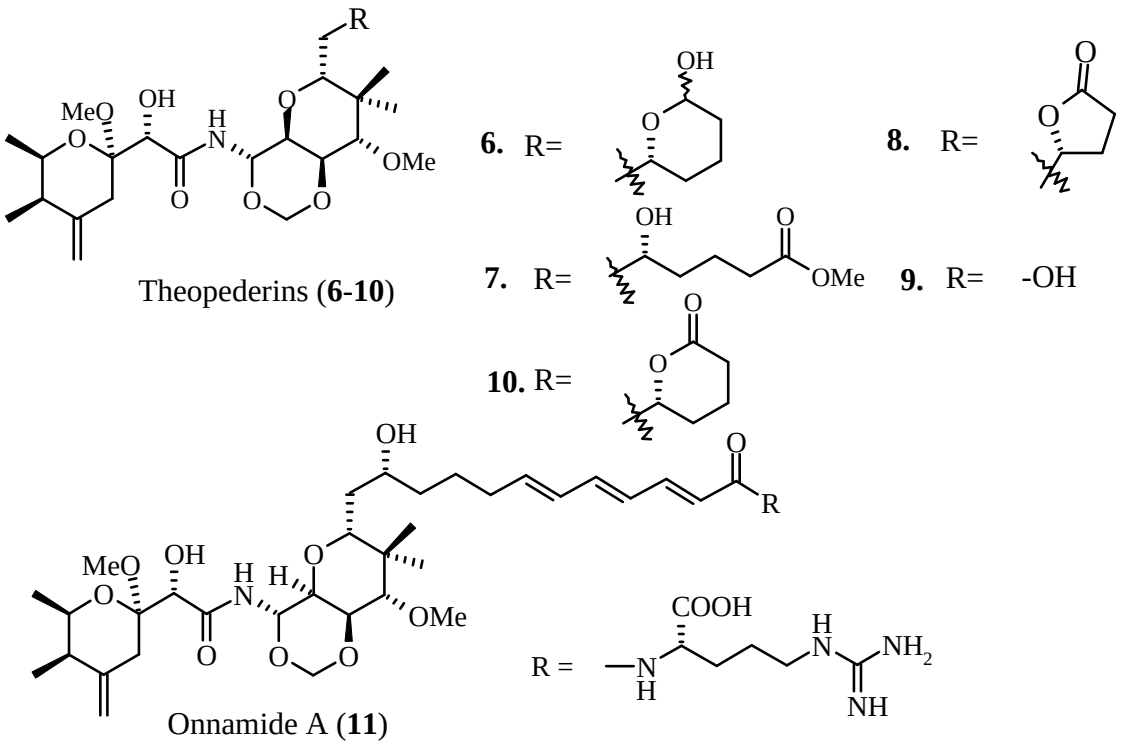


Figure 2

The theopederins (**6**-**10**) are structurally related to onnamide-A (**11**) from marine sponge, *Theonella sp*. collected in Okinawa,[13] which show *in vitro* cytotoxity and *in vivo* antitumour activity in many leukemia and solid tumour model systems.[14] Isoquinolinequinone metabolite cribostatin from the Indian Ocean sponge *Cribrochalina sp*. shows selective activity against all nine human melanoma cells in National Critical Technologies (NCT) panel.[15] Spongstatin (**13** and **14**), a macrocyclic lactone from the Indian Ocean collection of *Spongia* sp., is the most potent substance known against a subset of highly chemoresistant tumour types in the NCT tumour panel.[16] Two new pyrones (herbarin) along with a new phthalide, herbaric acid, were isolated from two cultured strains of the fungus *Cladosporium herbarum* from the sponges *Aplysina aerophoba* and *Callyspongia aerizusa* collected in the French Mediterranean and in Indonesian waters, respectively.[17] Herbarins displayed activity in the brine shrimp assay. A culture of the fungus *Emericella variecolor* isolated from a sponge collected in the Caribbean Sea off Venezuela yielded varitriol (**15**, **16**), varioxirane (**17**, **18**) varixanthone

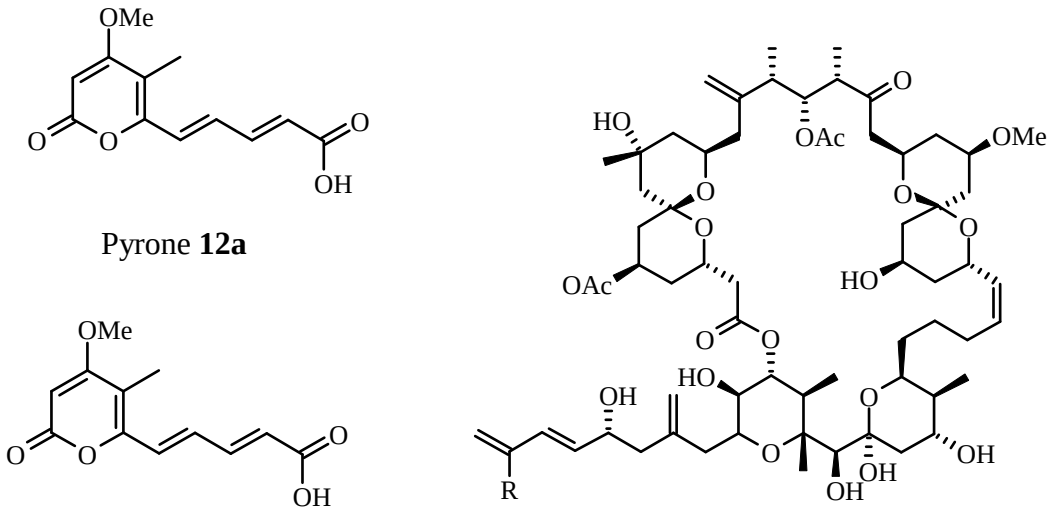


Figure 3

19, which were characterised by spectroscopic methods and chemical transformations.[18] Varitriol (**15**, **16**) displayed increased potency toward some renal, central nervous system and breast cancer cell-lines in the NCI's 60-cell line panel, while varixanthone **19** displayed antimicrobial activity against a range of bacteria.

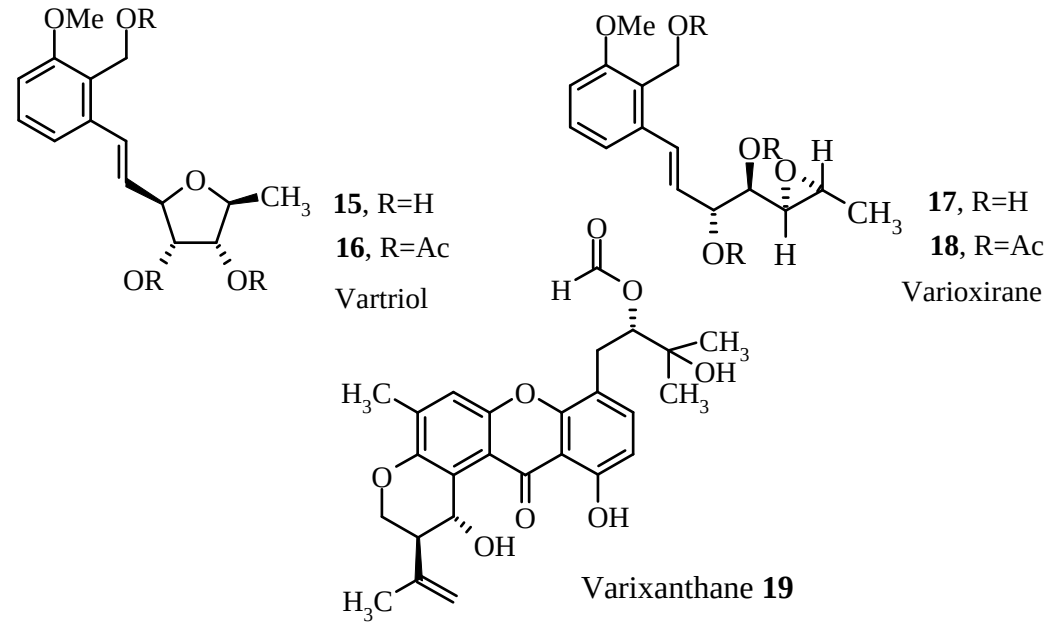


Figure 4

Potent phosphate inhibitors have been isolated from sponges like, okadaic acid from *Halichondria okadai*, motuporin (**20**, **21**) from *Theonella swinhoei* and calyculin-A (**22**) from *Discodermia calyx*.[19,20] Inhibitors of phospholipase such as manoalide and scalaradial have proved to be useful tools to study the role of this enzyme in the release of arachidonic acid, which is a key molecule, involved in the biochemical processes leading to inflammation.[21]

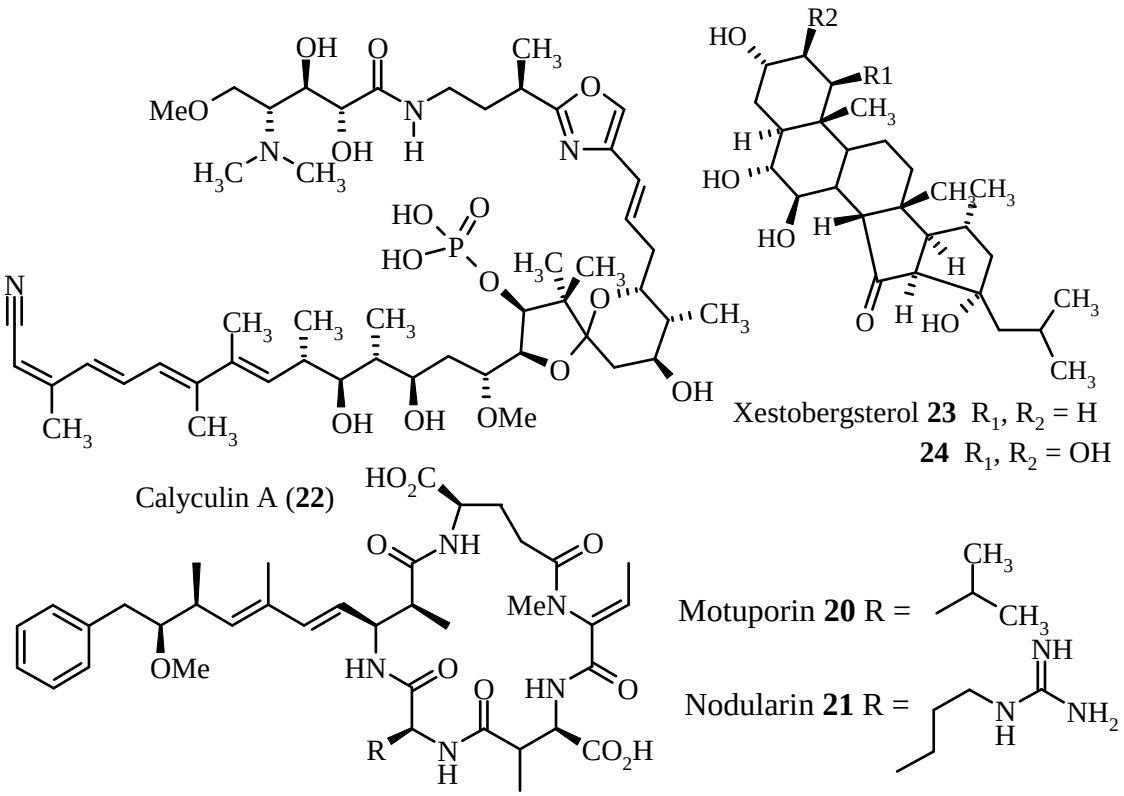
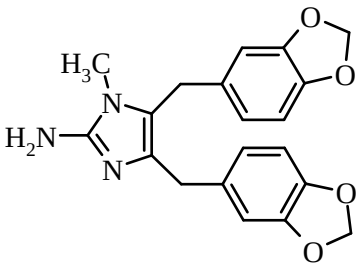


Figure 5

A number of receptor antagonists with potential as biochemical tools or structural leads to the development of therapeutics have been isolated from sponges. Examples include xestobergsterol (**23**, **24**) (isolated from *Xestospongia berguista*), which inhibits immunoglobulin E mediated histamine release from mast cells and is 5000 times more potent than the antiallergic drug disodium cromoglycate.[22] Leucettamine A (**25**) isolated from *Leucetta microraphis*, is a potent and selective antagonist for the receptor for leukotrine, a non-peptide metabolite of arachidonic acid produced mainly in inflammatory cells.[23]



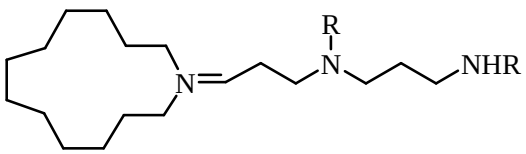
Leucettamine A (**25)**

Figure 6

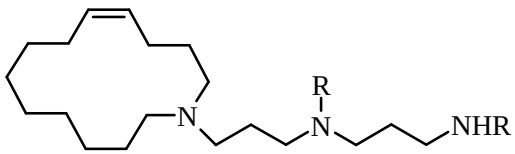
Metabolites isolated from marine sponge *Xestospongia exigua*

The ability of tumor cells to invade adjacent tissue through the extracellular matrix is critical to metastasis, the process by which a tumor cell leaves the primary tumor, travels to a distant site *via* the circulatory system, and establishes a secondary tumor.[24] Metastasis is the main cause of death in cancer patients and a major impediment to improving cures. Tumors also stimulate angiogenesis, the formation of new blood vessels. Without the formation of new blood vessels, tumors cannot increase in size and they cannot metastasize. Angiogenesis, which requires migration of vascular endothelial cells through the extracellular matrix toward tumors, shares many features with tumor invasion. Therefore, inhibition of extracellular matrix invasion represents an attractive chemotherapeutic approach to preventing metastasis and angiogenesis. Extracts of the sponge *Xestospongia exigua* collected in the waters off the coast of Papua New Guinea were positive in a new assay for anti-invasion activity.[25]

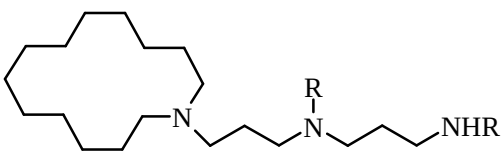
Bioassay-guided fractionation of the crude extract led to the identification of the three motuporamines, A (**26**), B (**30**), and C (**33**), **29** and the motuporamines D (**28**), E (**32**), F (**37**). Motuporamines A (**26**), B (**30**), and C (**33**) and the mixture of G, H, and I (i.e., **39**) were primarily responsible for the anti-invasion activity of the crude extract.



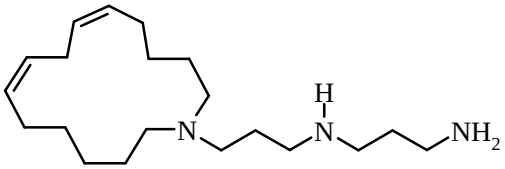
26 R=H, Motuporamine A
27 R=Ac



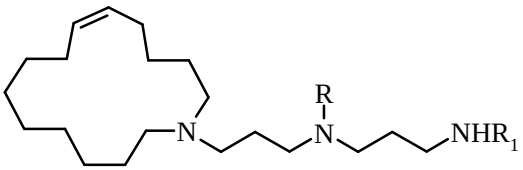
28 R=H, Motuporamine D
29 R=Ac



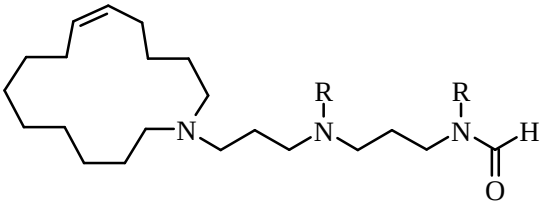
30 R=H, Motuporamine B
31 R=Ac



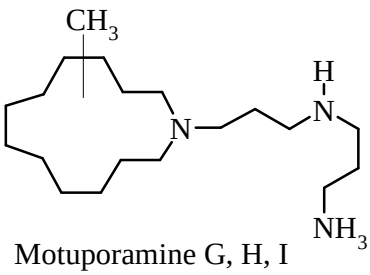
32 Motuporamine E



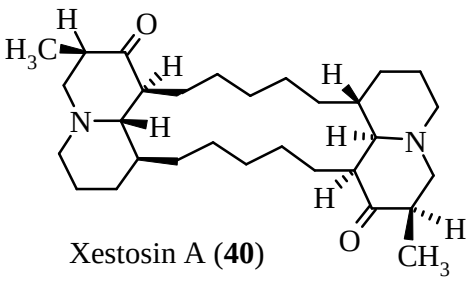
33 R = R_2 = H, Motuporamine C
34 R = H, R_1 = Ac
35 R = H, R1 = CF_3CO-
36 R = R1 = Ac



37 R=H, Motuporamine F
38 R=Ac



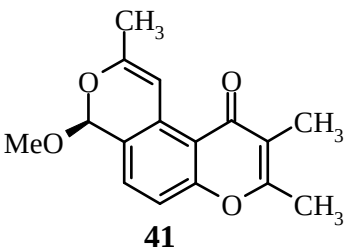
39 Motuporamine G, H, I



Xestosin A (**40**)

Figure 7

A new bis-quinolizidine alkaloid, xestosin A (**40**),[26] possessing *cis*- and *trans*-quinolizidine nuclei, has been isolated from the Papua New Guinean sponge *xestospongia*



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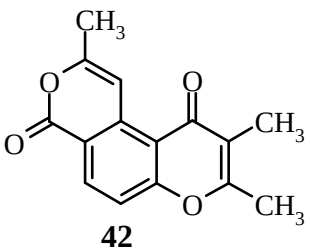

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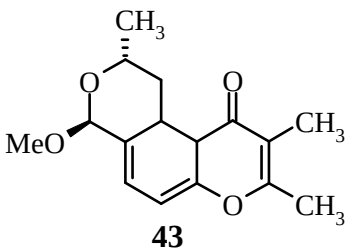

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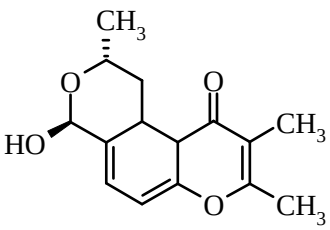

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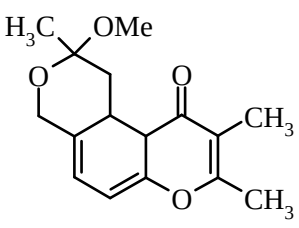

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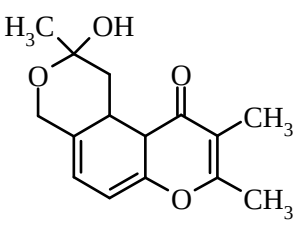
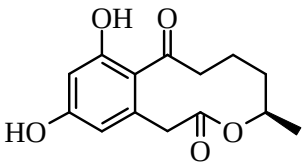


46

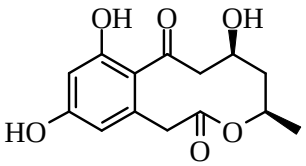
Figure 8

exigua. They possess either vasodilatory or ichthyotoxic activity. From the marine sponge *xestospongia exigua*, fungal isolates of *Aspergillus versicolor* (Vuill)Triab were obtained. Isolation and purification of ethyl acetate extracts from culture filtrates of the fungus led to yield six chromone derivatives[27] namely aspergione A (**41**), aspergione B (**42**), aspergione C (**43**), aspergione D (**44**), aspergione E (**45**), aspergione F (**46**). These are promising anti-microorganisms (*Escherio coli* HB101, *Candida albicans*, *Staphylococcus aureus, E. corl, Bacillus subtilwas*).

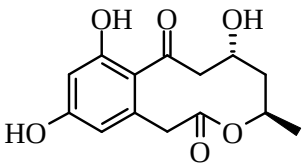
Fungal isolates of *Penicillium cf. montanense* were obtained from the marine sponge *Xestospongia exigua* collected from the Bali Sea, Indonesia. Culture filtrates of the fungi yielded three novel decalactone metabolites,[28] xestodecalactones A, B, and C (**47**, **48**, and **49**), consisting of 10-membered macrolides with a fused 1,3-dihydroxybenzene ring. Compound **48** was found to be active against the yeast *Candida albicans*. These new compounds are structurally related to a number of compounds (**50**, **51**) isolated from terrestrial fungi.



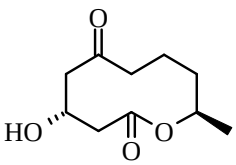
Xestodecalactone A (**47**)



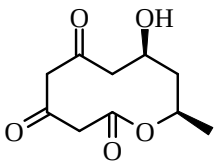
Xestodecalactone B (**48**)



Xestodecalactone C (**49**)



Diplodialide D (**50**)



Dicarestritin J (**51**)

Figure 9

Structural aspects of novel class benzo-fused lactones

Medium ring compounds in general

Medium ring compounds (those having a ring size in the range (8 to 11)[29] are becoming increasingly important in organic chemistry, as they are contained in an ever-growing number of natural products. Hydrocarbons, as well as heterocyclic compounds (ethers, lactones, amines, amides) have been isolated, and a number of reviews have already been published.[30] These compounds have specific characteristics which had been

recognized by at the beginning of this century,[31] and it was soon observed that they were much more difficult to synthesize by cyclization methods than other cyclic compounds including macrocyclic compounds (ring sizes >12). These difficulties are caused by the fact that the formation of these cyclic compounds are disfavoured by entropy as well as enthalpy[31] (*vide infra*). The carbon chain becoming too long disfavors the entropic factor, and thus the probability of a reaction taking place between the two chain termini decreases. The enthalpic factor is mainly created by steric interactions. There are three different interactions:

- *torsional effects in single bonds (Pitzer strain)*
- *deformation of bond angles from their optimal values (Baeyer strain)*
- *transannular strain, particularly important in medium ring compounds.*

The pioneering work of Hunsdiecker and Erlbach reported the yields obtained in the reaction of ω-bromo alkanoic acids with potassium carbonate to give the corresponding lactones.[32] Good yields were observed in the preparation of five- to eight- and twelve- to eighteen-membered ring lactones. The yield of the nine-membered ring lactone was almost zero. This work was subsequently reinvestigated and developed by the Illuminati group.[33] They measured with great precision the rate of lactone formation in the ring sizes 3 to 23 by reaction of ω-bromoalkanoic acids with a base (KOH or diisopropylethylamine) in 21% aqueous DMSO. A maximum rate of cyclisation was observed for the formation of γ- butyrolactone and then the rate decreased dramatically to the 8-membered ring lactone, which was formed more than 106 times less rapidly than the 5-membered ring lactone. A slow increase of the cyclisation rate was then observed, the cyclisation rate constant of the 18- membered ring lactone being close to that of the intermolecular reaction rate constant (formation of esters). From a synthetic point of view, these constant rate values mean that good yields (intramolecular reactions) should be obtained for the formation of 3- to 7- and 13- to 18-membered ring lactones, while polymerization (intermolecular reactions) should be the major pathway for 8- to 12-atom chains.[34] In medium ring lactones, stereoelectronic factors can, however decrease the strain energy slightly. Lactones can exist in *Z* (or *syn)* and *E* (or *anti)* forms. The *syn* form is in general more stable than the *anti* form (2-8 kcal/mole). For lactones with a ring sizes of atleast 7 the rings are forced into the disfavored *anti* conformation. In 8- and 9-

membered ring lactones, an equilibrium *syn anti* conformation was observed, while in 10- and 11-membered ring lactones (and macrolactones), the *syn* form is normal.[35]

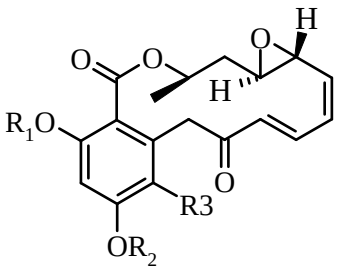
Benzolactone: a common structural view

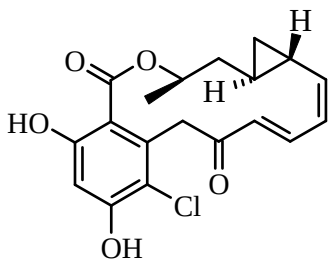
A variety of natural products can be viewed in the context of the fusion of a macrolactone moiety with a resorcinylic aromatic ring.[36] In most cases,[37] the fusion encompasses the carbons α and *β* to the lactonic carbonyl group and carbons 5 and 6 of the resorcinol. The resultant system corresponds to a lactone based on an orsellinic acid format, functionalized at its benzylic site with a side chain bearing a pendant *ω*-hydroxyl group. With regard to the biological activity, the unsaturated ketone is important. It follows that the benzolactones are important lead structures for the search of novel antitumor compounds.[38] Several benzolactones are discussed in the following section. Classic examples of such systems are the 12-membered orsellinic acid type lactone lasiodiplodin[38] (**65**) and the 14-membered orsellinic acid macrolides zearalenone[39] (**59**) and radicicol[40] **52**. Like radicicol **52**, relatively new members to this group such as 14-membered aigialomycin D[41] **55** and hypothemycin[42] **54** also possess potentially useful antitumor activity. Even though their structures are quite similar, each of them displays a characteristic and unique type of biological activity. Thus, the benzolactone core clearly is an important privileged structure.

14- membered benzolactone

Radicicol, (**52**) and monocillin I (**52a**) are resorcylic macrolides[40] which can both be isolated from *Monocillium nordinii* (Figure 10). While the skeletal structure of radicicol was determined in 1964, its relative and absolute stereochemical configuration was not unambiguously established until 1987.[43] The structure of monocillin I (**52a**) was confirmed by its direct conversion into radicicol (**52**).[43] Affirmation of these structures was achieved by their only total synthesis accomplished by Lett and Lampilas.[40c] Both radicicol (**52**) and monocillin I (**52a**) exhibit a variety of antifungal and antibiotic properties not shared by other members of this class of natural products. Recently, the antitumor properties of radicicol have come into focus. Its ability to suppress the transformed phenotype caused by various oncogenes such as *src, ras,* and *raf* has been linked to its high affinity binding (20 nM) and inhibition of the Hsp90 molecular chaperone. This “anti-chaperone” activity may stimulate depletion of oncogenic proteins

and could therefore be of clinical interest. Importantly, while radicicol displays this and other activities *in vitro*, the compound has not yet exhibited *in vivo* antitumor activity in animal models,[44] though some derivatives do manifest *in vivo* efficacy. Recently, Danishefsky *et al*. demonstrated the synthetic analogue of Radicicol, cycloproparadicicol (**53**), binds to Hsp90 at ca. 160 nM.[45]



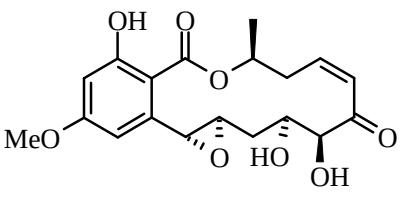


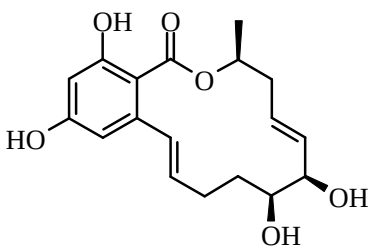
Radicicol (**52**) R1 = R2 = H, R3 = Cl
Monocillin (**52a**) R1 = R2 = R3 = H

Cycloproparadicicol (**53**)

Figure 10

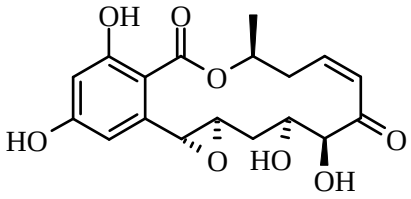
Hypothemycin (**54**)[42] is a 14-membered resorcylic acid lactone that has been isolated from the fungal fermentations of *Hypomyces trichothecoides*, *Coriolus* V*ersicolor*, and *Aigialus par*V*us*. It has been shown to exhibit moderate antimalarial[4] and antifungal activity as well as cytotoxicity against various murine and human cell lines. It has also been demonstrated to suppress the growth of murine and human tumor cells transplanted into the backs of mice. Both *in vitro* and *in vivo* studies by Zhao et al.[7] and Schirmer *et al*. have identified hypothemycin as a potent and selective inhibitor of the threonine/tyrosine-specific kinase, MEK, and other protein kinases that contain a conserved cysteine residue in their ATP-binding site. Because many of these kinases play an important role in the signal transduction pathways that regulate cell proliferation, cell differentiation, and apoptosis, their aberrant activation can lead to uncontrolled cell proliferation and transformation.



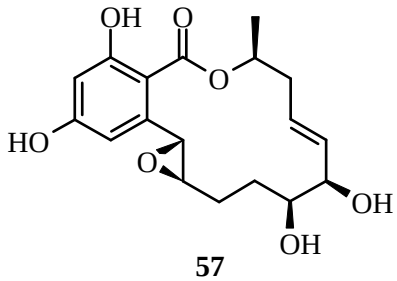


Hypothemycin (**54**)

Agialomycin D (**55**)



4-*O*-Demethylhypothemycin **56**



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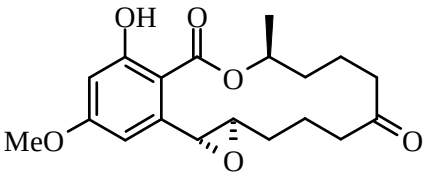
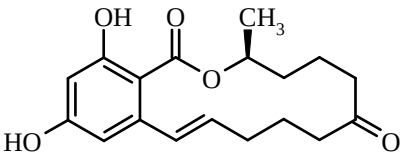


58

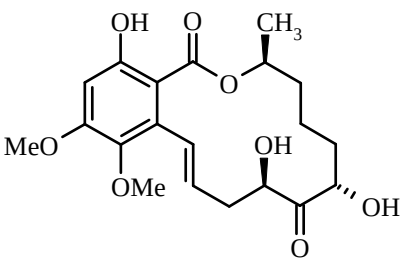


Zearalenone **59**

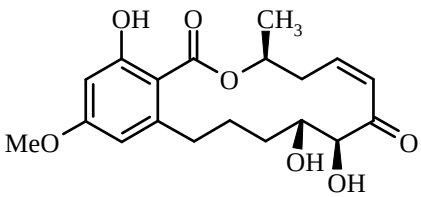
Figure 11

Hence, compounds that are specific inhibitors of these target proteins are promising candidates as anticancer agents. Recently three new hypothemycin analogues (**55**-**58**)[47] were isolated from the fermentations of *H. subiculosus* DSM 11931 and DSM 11932, in addition to hypothemycin, the major secondary metabolite (Figure 11).

Benzolactones represent an important subclass among the polyketides. The ones that feature an acetate as a starter unit normally contain a 14-membered macrolactone. The aliphatic sector is generally functionalized with hydroxyl or keto groups. Queenslandon **60**[47] was isolated from the strain *Chrysosporium queenslandicum* IFM51121. This macrolactone showed distinct activity against fungi but was devoid of antibacterial activity. The classical benzolactone, the fungal metabolite zearalenone **59** (Figure 11), shows oestrogenic activity. The antitumor activity seems to be connected to the inhibition of cyclin-dependent kinases. The resorcylic acid lactone L-783,277 (**61**), a fungal metabolite as well, was reported to be a selective inhibitor of MEK, a threonine/ tyrosine specific kinase resulting in antitumor activity.[48]



Queenslandon **60**

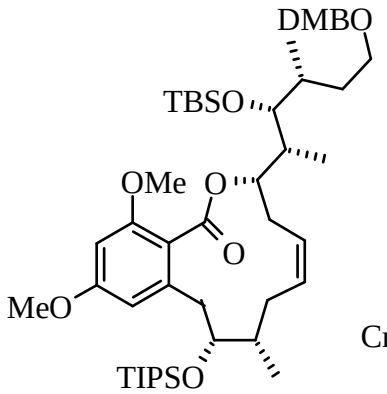


L-783277 (**61**)

Figure 12

12-membered benzolactone

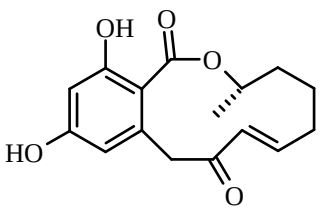
The macrolide cruentaren A (**62**)[49] is a highly cytotoxic and antifungal natural product which was isolated by the Ho¨fle group from the myxobacterium *Bysso*V*orax cruenta* (Figure 13). With an IC_{50} value of 1.2 ng mL^{-1} against the L929 cell line, it is among the most cytotoxic compounds found in myxobacteria. Initially, cruentaren A (**62**) was patented as a pesticide, but in the meantime it turned out that it is an inhibitor of mitochondrial F-ATPase from yeast. Interestingly, it does not inhibit V-ATPase, which is the molecular target of the benzolactone enamides.



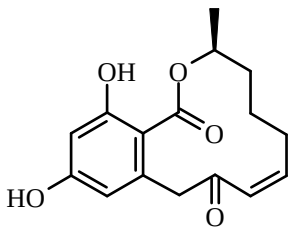
Cruentaren A (**62**)

Figure 13

Trans- and *cis*-resorcylide (**63**, **64**) are both natural macrocyclic plant growth inhibitors, isolated independently from different *Penicillium* species.[50] Along with zearalenone, **59** lasiodiplodin, **65** and the important antitumor agent radicicol **52**, they constitute an important class of bioactive resorcylic macrolides.



Trans-resorcyclide **63**

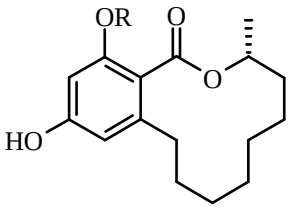


cis-resorcyclide **64**

Figure 14

The 12-membered ring lactones lasiodiplodin **65**[38] and de-*O*-methyl lasiodiplodin **66** isolated from a culture broth of the fungus *Botrysdiplodia theobromae* (formerly *Lasiodiplodia theobromae)* exhibit plant growth regulating properties. Macrolide **66** has

also been found in the roots of *Arnebia euchroma*, which is used in traditional Chinese medicine. This metabolite may well be responsible, at least in part, for the pharmacological properties of the plant extracts, because it efficiently inhibits the prostaglandin biosynthesis.

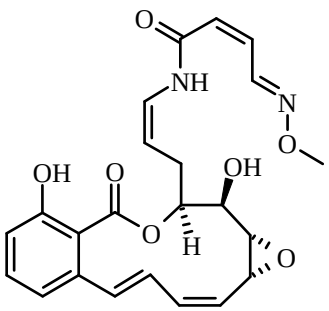


Lasiodiplodin **65**

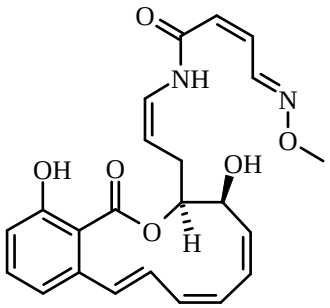
De-O-methyl lasiodiplodin **66**

Figure 15

Novel active compounds oximidines I (**67**) and II (**68**),[51] the cell-cycle inhibitors in transformed cells, were isolated from *Pseudomonas* sp. Q52002. The molecular formulas of **67** and **68** were established as $C_{23}H_{24}N_2O_7$ and $C_{23}H_{24}N_2O_6$, respectively, by high-resolution FABMS. The structures of the oximidines were elucidated by NMR spectral analysis, including a variety of two-dimensional techniques. The absolute stereochemistry of **65** was determined by using the modified Mosher method. The oximidines are novel 12-membered macrolides containing an *O*-methyloxime moiety. Oximidines I (**67**) and II (**68**) selectively inhibited the growth of rat 3Y1 cells transformed with E1A, *ras*, or *src* oncogenes.



Oximidin I (**67**)

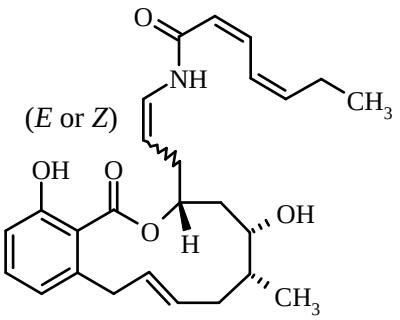


Oximidin II (**68**)

Figure 16

Sponges of the genus *Haliclona* are well-known for producing a variety of secondary metabolites, most commonly bioactive alkaloids.[2] In the screening of crude extracts for differential cytotoxicity, the organic extract of an Australian collection of an

unidentified species of *Haliclona* (phylum Porifera, class Demospongiae, order Haplosclerida, family Haliclonidae) displayed a potent and unique differential cytotoxicity profile in the NCI-60 cell line human tumor assay. Bioassay-guided fractionation of this extract afforded salicylihalamide A (**69**),[52] a novel salicylate macrolide with a highly unsaturated amide side chain.



Salicyllihalamide A (**69**): (*E*)

Salicyllihalamide B (**70**): (*Z*)

Figure 17

Among methods of controlling hypercholesterolemia and hyperlipidemia is the derectstimulation of hepatic low density lipoprotein (LDL) receptors. Two novel lactone compounds,[53] CJ-12950 (**71**) and CJ-13357 (**72**), containing an unusual oxime moiety, were isolated from a zygomycete Mortierella verticillata. These lactones are potent inducers of the LDL receptor gene *in vitro*, that enhanced LDL receptor expression in human hepatocytes 2-fold at 100 nM.

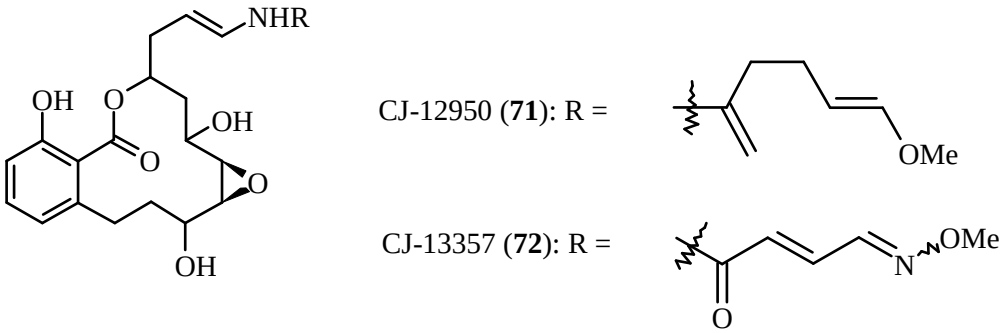
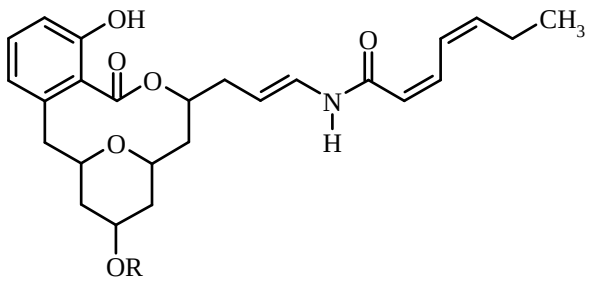


Figure 18

10 - membered benzolactone

A novel highly cytotoxic metabolite, apicularen A (**73**),[54] was isolated in a screening of the myxobacterial genus *Chondromyces*. The structure of **73** is characterized

by a salicylic acid residue as part of a 10-membered lactone, which bears an acylenamine side chain. Compound **73** is an inhibitor of the proliferation of human cancer cell lines and induces apoptosis. Habitually **73** is accompanied by different amounts of a more polar variant, apicularen B (**74**), which was identified as 11-*O*-(2-*N*-acetamido-2-deoxy-α-D-glucopyranosyl)apicularen.

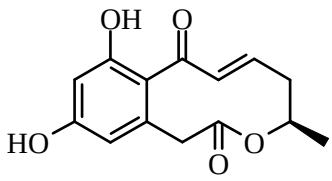


Apecularen A (**73**) R=H

Apecularen B (**74**) R=N-acetyl-β-D-glucosamine

Figure 19

There is another unique class of fused resorcinylic macrolides, which contain a keto rather than an ester group at the benzylic position. The ester bond corresponds to a macrolide of a formal phenylacetic acid. These macrolides have received much interest in agrochemical and pharmaceutical settings. Sporostatin[55] was isolated (M5032, **75**) as a new inhibitor of cyclic adenosine 3',5'-rnonophosphate phosphodiesterase (cAMP-PDE) from the fermentation filtrate of *Sporormiella sp*. M5032 (FERM P-9506)1). Sporostatin represents a 10-membered phenylacetic macrolactone macrolide that exhibits anti-cancer activity.

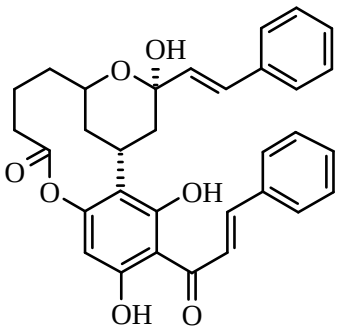


Sporostatin **75**

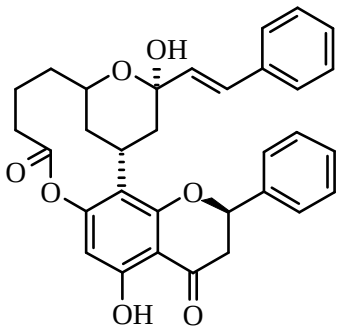
Figure 20

Four 10 membered benzolactone, flavanones, kurziflavolactones A, B, C and D, (**77-80**) and a chalcone, kurzichalcolactone **76**, have been found recently in the leaves of

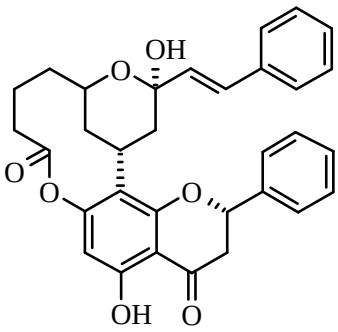
a Malaysian plant, *Cryptocarya kurzeii* (Lauracae) and have a weak cytotoxicity against KB cells.[56]



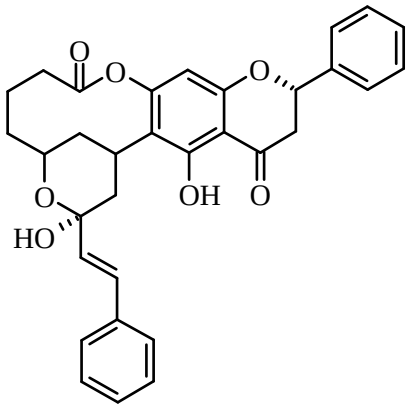
Kuzichalcolactone **76**



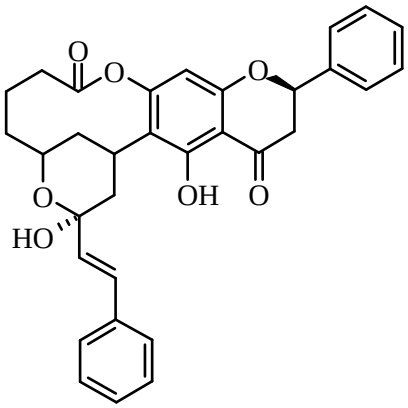
Kurziflavolactone A (**77**)



Kurziflavolactone B (**78**)



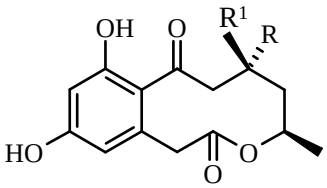
Kurziflavolactone C (**79**)



Kurziflavolactone D (**80**)

Figure 21

Structure elucidation of Xestodecalactone B (48) and C (49) [28]



Xestodecalactone A (**47**): R = R' = H

Xestodecalactone B (**48**): R =H, R' = OH

Xestodecalactone C (**49**): R = OH, R' = H

Figure 22

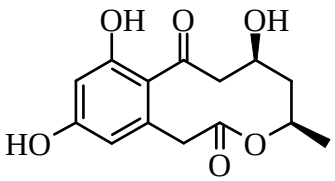
Xestodecalactones A, B, and C (**47**, **48**, and **49**), consisting of 10-membered macrolides with a fused 1,3-dihydroxybenzene ring. Online HPLC-NMR, ESI-MS/MS,

and -CD spectra were acquired, and the structures of the new compounds were established and confirmed on the basis of offline NMR spectroscopic (^{1}H, ^{13}C, COSY, ROESY, ^{1}H-detected direct and long-range ^{13}C-^{1}H correlations) and mass spectrometric (EIMS) data. Quantum chemical calculations of the CD spectra proved to be difficult because of the conformational flexibility of the xestodecalactones. Xestodecalactones B (**48**) and C (**49**) are in agreement with a molecular composition of $C_{14}H_{16}O_6$ as determined by HREIMS (M^+ 280.0965 and M^+ 280.0927, respectively). Each of the Xestodecalactone B and C has one hydroxyl group. The COSY spectra of **48** and **49** indicated the presence of a partial structure CH_2-CH-(OH)-CH_2-CH(O-)-Me. These compounds are diastereomeric compounds.

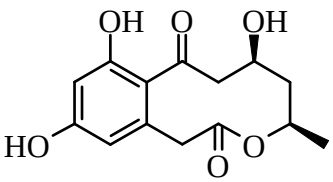
The unique structural parameters associated with 1,3-dihydroxybenzene fused macrolide in xestodecalactone B (**48**) and C (**49**) and limited availability prompted us to undertake the carbohydrate based total synthesis of this synthetically challenging molecule.

Present Work

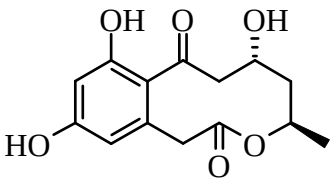
Secondary metabolites from fungi *penicillium cf. montanense* have been receiving a great deal of attention in recent years, and a number of peculiar structures with specific bioactivities have been discovered so far. Along this line, xestodecalactone A (**47)**, B (**48)**, and C (**49)**[28] have been recently characterized as a new secondary metabolite obtained from the marine sponge *Xestospongia exigua*. As shown in Figure 23, these compounds constitute 10-membered macrolides with a fused 1,3-dihydroxybenzene ring.



Xestodecalactone A (**47**)



Xestodecalactone C (**49**)



Xestodecalactone B (**48**)

Figure 23

The interesting structural feature and promising biological activity directed us toward the total synthesis of xestodecalactone C (**49**). Keeping this in mind, the retrosynthetic analysis for our endeavor was planned as outlined in Figure 24.

The target molecule could be obtained by mass deprotection of benzyl ether by cat. hydrogenation of tribenzyl derivative **81**. The macrocyclic framework of xestodecalactone C (**49**) was retrosynthetically disassembled into fragments **84** and **85** by means of two key disconnections. In the first disconnections at C6-C7 revealed the acid **82**, with intramolecular acylation playing crucial role in the synthetic strategy. The acid **82** in turn could be synthesized from ester **83** through cleavage of *PMB* ether **83**, followed by Pinnick oxidation of the corresponding aldehyde. The second disconnection discloses the DCC mediated coupling of the alcohol **84** and the acid **85**.

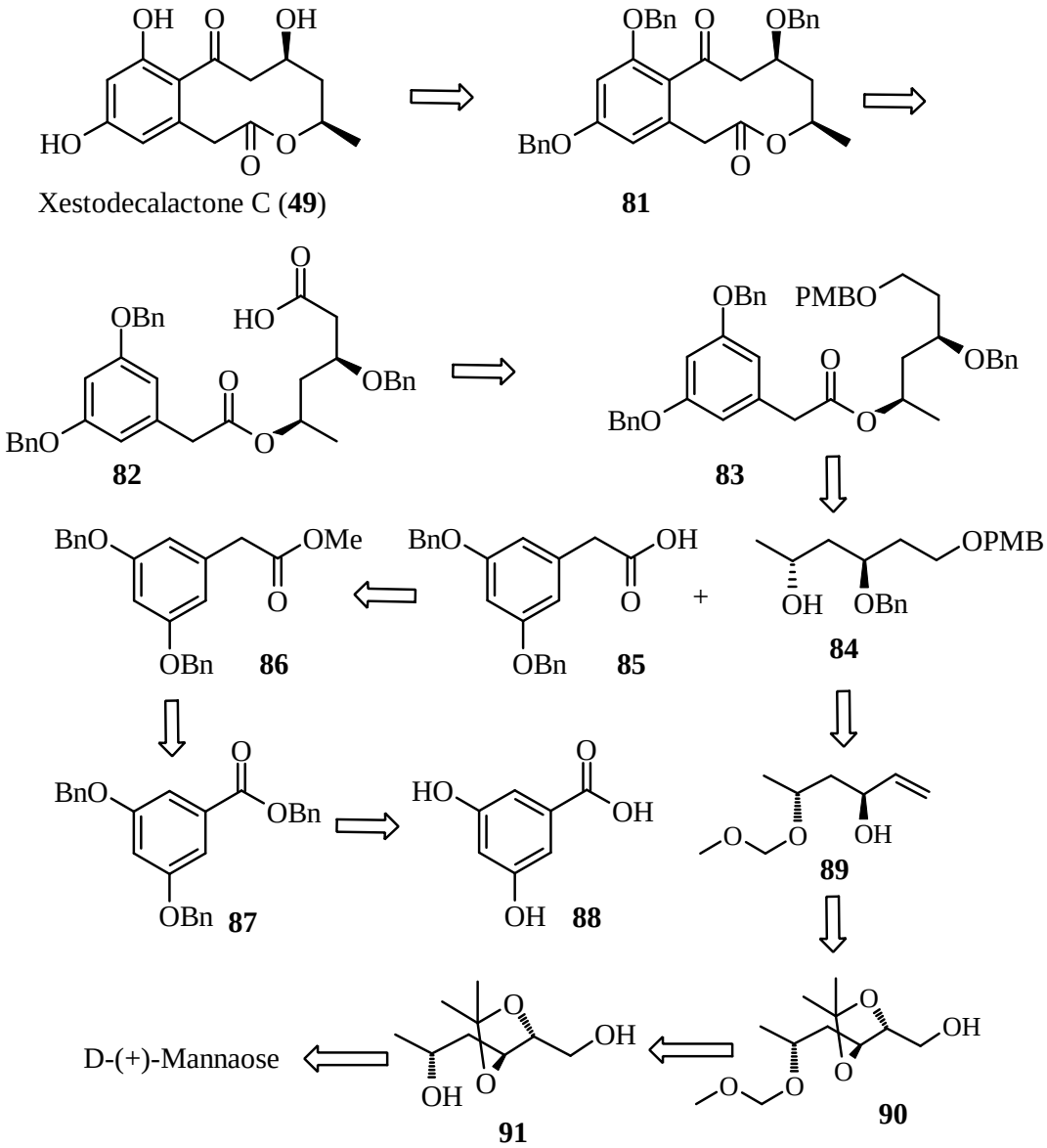


Figure 24: *Retrosynthetic analysis of xestodecalactone C (**49**)*

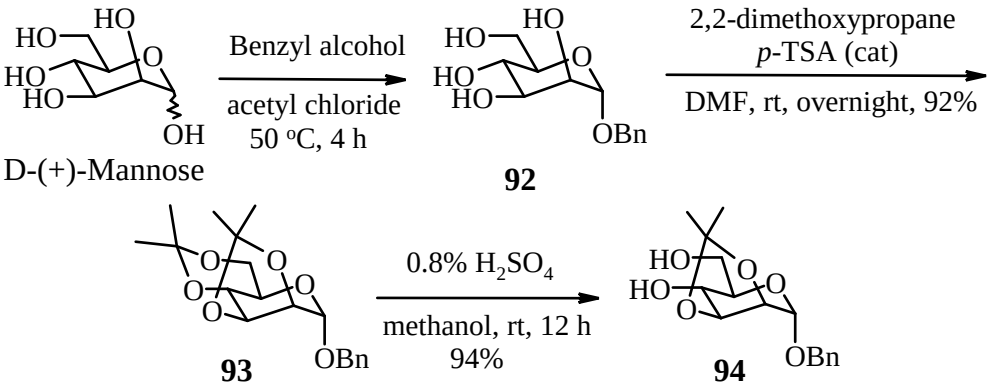
The alcohol **84** could be furnished by adapting linear approach using naturally occurring D-(+)-mannose as readily available starting material. Fragment **84** represents a 4,6-disubstituted 2-hexenol consisting of two stereocenters present in xestodecalactone C (**49**), arranged in *anti* fashion with (*R*,*S*) absolute configurations. A chiral pool approach has been intended in this context. After analyzing the relative stereochemistry of the hydroxyl substituents of the target segment **84**, an iterative regression analysis led to identify D-(+)-mannose as the required starting material. **84** could be obtained from **89** by performing suitable functional group manipulations. It was envisaged that compound **89**

could be obtained from **90** on iodination, followed by zinc mediated facile elimination reaction. The hydroxyl compound **90** could be furnished from **91** by the judicious combination of functional group manipulations. Compound **91** could be easily obtained starting from commercially available D-(+)-mannose.

The substituted phenyl acetic acid **85** could be obtained by simple hydrolysis of the ester **86**. A careful observation revealed that compound **86** could be obtained from **87** by employing Arndt-Eistert homologation and a series of transformation, which could be traced back to the commercially available 3,5-dihydroxybenzoic acid **88**.

Synthesis of Alcohol Segment

This part contains the two stereogenic centers of xestodecalactone C (**49**). Retrosynthetic analysis outlined in Figure 24 identified compound **90** as one of the potential synthetic intermediate and the construction of **90**, which would mark the first synthetic objective in the construction of fragment **84**. As it turned out, the synthesis of **90** began with commercially available D-(+)-mannose, which was converted to benzyl mannopyranoside **92**[57] by protecting the anomeric hydroxyl group with acetyl chloride in benzyl alcohol. Subsequent protection of rest of the four hydroxyl groups by the action of 2,2-dimethoxypropane in DMF as solvent in presence of cat. *p*-TSA afforded the 2,3:4,6-di-*O*-isopropylidene-α-D-benzylmannopyranoside **93**. Selective deprotection of the

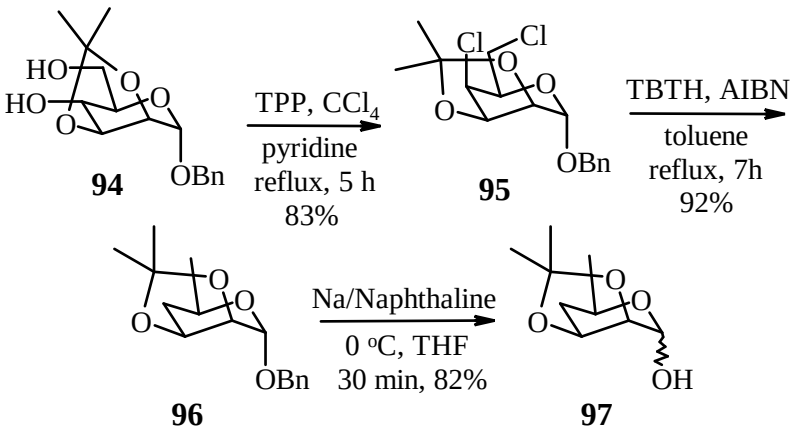


Scheme 1

4,6-*O*-isopropylidene group in **93** with aqueous 0.8% H_2SO_4 in methanol furnished the diol **94**. The ^{1}H NMR spectrum indicated the presence of two singlets at δ 1.34 (3H) and 1.51 (3H) ppm for one isopropylidene moiety, and two free hydroxyl groups (brs, at δ 2.59 ppm), rest of the protons resonated at their expected position. The structure was also

supported by ^{13}C NMR and elemental analysis. In the IR spectrum, a characteristic peak observed at 3493 cm^{-1} indicating the presence of free hydroxyl group (Scheme 1).

According to our retrosynthetic plan, deoxygenation at C4 and C6 were required. So, we performed a two-step sequence, first formation of the dihalo derivative, followed by radical dehalogenation (Scheme 2). Thus, the diol **94** on refluxing with TPP in carbon tetrachloride for 5 h afforded the 4,6-dideoxy-4,6-dichloro derivative **95**. The ^{1}H NMR, ^{13}C NMR spectra and elemental analysis supported the assigned structure **95**. In the ^{1}H NMR spectrum of **95**, the diastereotopic C6 protons appeared as multiplet at δ 3.70-3.85 (m, 2H) ppm, whereas C4 proton appeared as a double doublet at δ 4.39 (dd, *J* = 2.7, 5.0 Hz, 1H) ppm. In the ^{13}C NMR spectrum of **95**, C6 appeared at δ 43.98 ppm. The other features, *viz*., the isopropylidene groups (singlets at δ 1.37 and 1.61 accounting for two CH_3 groups) and H1 (singlet at δ 5.13 ppm) were secured the structure beyond doubt. The halogenated compound **95** was then deoxygenated under Barton-McCombie protocol [(*n*-Bu_3SnH/AIBN (catalytic)/toluene, reflux)] to provide the corresponding 4,6-dideoxy product **96** in 92% yield. This was clearly conveyed in the ^{1}H NMR spectrum by the characteristic doublet due to the methyl group at δ 1.22 (*J* = 6.4 Hz) ppm, while C4 methylene protons appeared at δ 1.43-1.55 (m, 1H) and 1.87 (ddd, *J* = 2.2, 6.8, 13.2 Hz, 1H) ppm. In the ^{13}C NMR spectrum of **96**, the C4 and C6 carbons appeared at δ 36.1 and 21.1 ppm, respectively. Debenzylation of benzyl mannopyranoside in presence of Na/nap

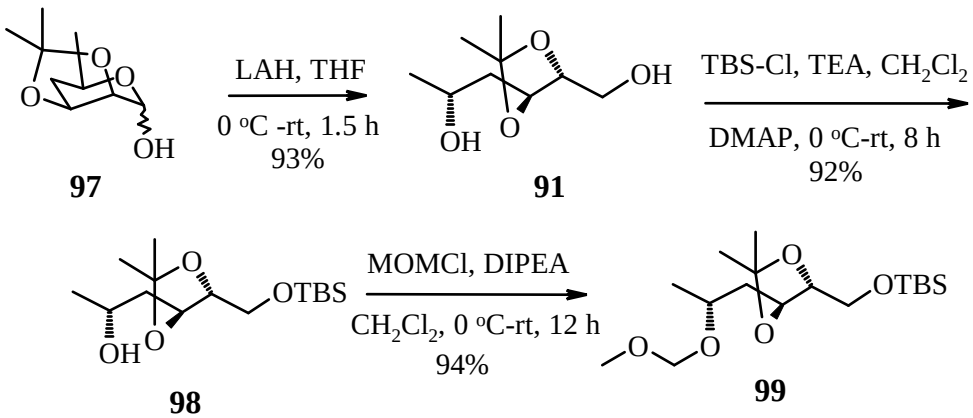


Scheme 2

-hthaline[59] in THF at 0 °C afforded a mixture of α and β-hexose derivatives **97**. The disappearance of peaks due to aromatic and benzylic protons and a new appearance of peaks at δ 5.29 (s, anomeric) and 5.42 (brs, anomeric) ppm in the ^{1}H NMR spectrum

evidently indicated the product formation. ^{13}C NMR, IR spectra further supported the structure of **97**.

Compound **97** on exposure to LAH in anhydrous THF resulted in the formation of the diol derivative **91** in 92 % yield. In its ^{1}H NMR spectrum, H1 and H5 (numbering based on D-Mannose) appeared as multiplet in the region δ 3.53-4.09 ppm, and a broad singlet at δ 2.26 ppm was assigned to –*OH*. While H2 appeared as quartet (*J* = 6.04 Hz) at δ 4.18 ppm, all other protons had the expected chemical shift confirming the structure of **91**. The structure was also supported by ^{13}C NMR spectral data together with combustion data. The next task in the synthetic endeavor dwells up on the conversion of the newly generated primary hydroxyl group to the corresponding iodide. However, methodologies for selective iodination are scarce and thus protection of secondary hydroxyl group was warranted. So, compound **98** was attained by the selective[60] masking of primary hydroxyl group of **91** as silyl ether by treating with TBSCl and TEA in dichloromethane at room temperature for 8 h in 92 % yield. The structure of product **98** was confirmed by its ^{1}H NMR and ^{13}C NMR spectra. In the ^{1}H NMR spectrum, two singlets at δ 0.08 ppm for Me_2Si and at δ 0.89 ppm for $C(CH_3)_3$ of TBS-group were accounted. The peaks at δ –5.50, ─5.47, 18.27 and 25.42 ppm in the ^{13}C NMR spectrum were in support of **98**. Subsequently, the secondary hydroxyl group was protected as its methoxymethyl ether using *N*,*N*-diisopropylethylammine and MOMCl in anhydrous dichloromethane at ambient temperature to provide *MOM* ether **99** in 94% yield. The

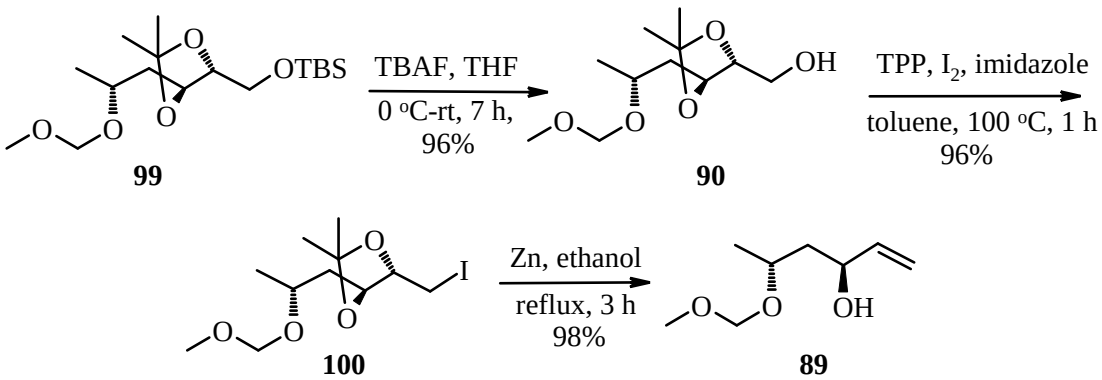


Scheme 3

structural identity was secured by the interpretation of the ^{1}H NMR and ^{13}C NMR spectra. The characteristic signals for *MOM* group were observed, for example, a singlet

resonated at δ 3.38 (−O<u>CH₃</u>), and two doublets at 4.64 (*J* = 6.77 Hz, 1H), 4.72 (*J* = 6.77 Hz, 1H) ppm (−O<u>CH₂</u>O−) corresponding with *MOM* group, while rest of the protons appeared at expected chemical shifts. The ^{13}C NMR spectrum showed resonances at δ 36.93 and 55.25 ppm for newly introduced *MOM* group (Scheme 3).

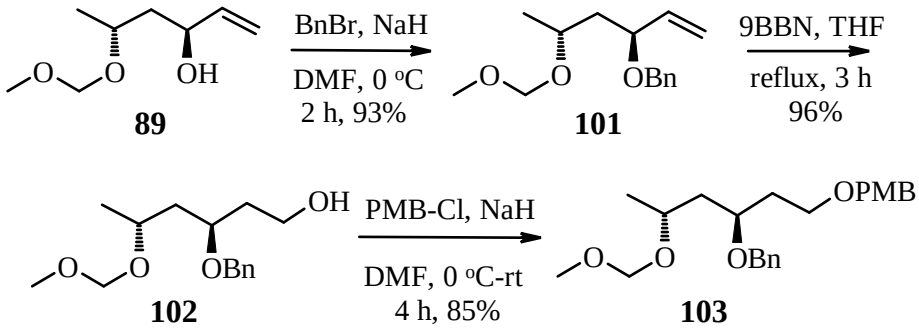
The cleavage of the silyl ether **99** with TBAF in anhydrous THF afforded the alcohol **90** in excellent yield. The ^{1}H NMR, ^{13}C NMR spectrum and elemental analysis were in agreement with the assigned structure. Having had the compound **90** in hand, our next concern was to transform **90** in to the corresponding iodo derivative **100**. Thus, compound **90** was subjected to Corey's deoxyhalogenation protocol[61] by treating with I_2, TPP and imidazole in toluene at 100 ^{o}C, 1 h, which led to the formation of iodo derivative **100** in 96% yield. The ^{1}H NMR, ^{13}C NMR spectrum and elemental analysis supported the structure **100**. In the ^{1}H NMR spectrum of **100**, the upfield shift of resonance due to H1 was observed. In the ^{13}C NMR spectrum, resonance due to C1 appeared at δ 4.26 ppm, rest of the carbons resonated at the expected positions (Scheme 4). Compound **89** was accomplished from **100** through zinc mediated elimination[62] reaction in refluxing ethanol for 3 h in 98% yield. In the ^{1}H NMR spectrum of **89**, peaks owing to −*CH₂I* and isopropylidene group were absent. The terminal olefinic group showed peaks at δ 5.17 (dt, *J* = 1.6, 20.7 Hz, 1H) and 5.26 (dt, *J* = 1.6, 17.2 Hz, 1H) ppm and at δ 5.88 (ddd, *J* = 5.3, 10.4, 17.2 Hz, 1H) ppm. The ^{13}C NMR spectrum displayed peaks at δ 113.89, 140.91 ppm corresponding to olefinic carbons at C2 and C1.



Scheme 4

For further progress, it was required to protect the newly generated hydroxyl group. So, the alcohol **89** was converted to the benzyl ether derivative **101** using BnBr and NaH in anhydrous DMF at 0 °C in 93% yield. In the ^{1}H NMR spectrum, the benzylic protons

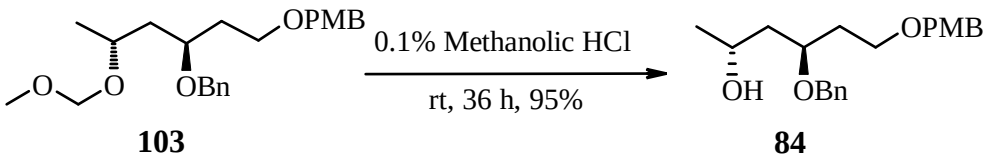
appeared at δ 4.31 (d, *J* = 11.5 Hz, 1H), 4.59 (d, *J* = 11.5 Hz, 1H) ppm and the aromatic protons were observed as multiplet at δ 7.24-7.36 (m, 5H) ppm. The olefin **101** was exposed to 9BBN[63] in THF in refluxing condition for 3 h, followed by oxidative work up with H_2O_2 and NaOAc to produce the desired primary alcohol **102** in 96% yield. In the ^{1}H NMR spectrum, a characteristic multiplet at δ 3.54-3.89 (m, 4H) ppm clearly revealed the presence of C1-H(*OH*), C3-H(*OBn*), C5-H(*OMOM*) group. In addition, the ^{13}C NMR spectrum showed a peak at δ 59.43 ppm corresponding to −*CH_2OH*.



Scheme 5

The primary hydroxyl group of **102** was treated with NaH, *p*-methoxybenzyl chloride in DMF to obtain the *p*-methoxybenzyl ether **103**. ^{1}H NMR spectrum of **103** showed singlet of aromatic methyl ether at δ 3.71 ppm. The ^{13}C NMR spectrum, mass spectra and elemental analysis further suggested the structure to be **103**.

To complete the synthesis of the alcohol segment, compound **103** was subjected to the acid mediated cleavage[64] of *MOM* ether, using 0.1% methanolic HCl at room temperature for 36 h to accomplish the alcohol **84** in 95% yield. The resonances relevant to *MOM* group were absent in the ^{1}H NMR and ^{13}C NMR spectrum, whereas rest of the protons resonated at the expected positions (Scheme 6).

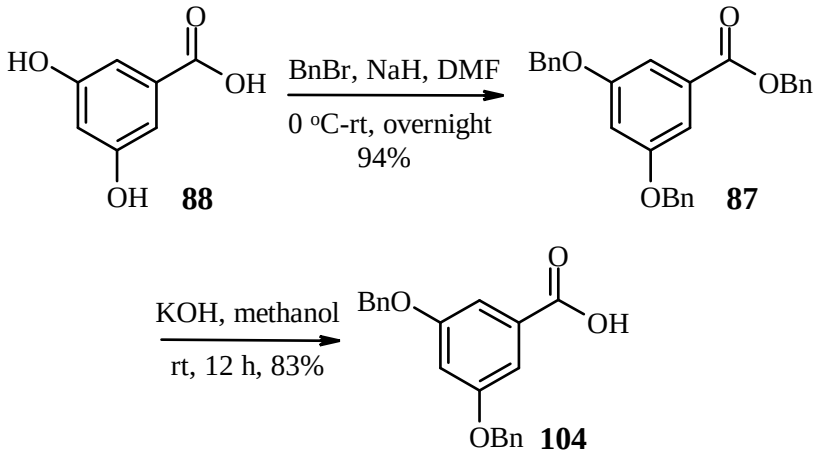


Scheme 6

Synthesis of substituted Aromatic acid

The synthetic endeavor began with commercially available 3,5-dihydroxybenzoic acid **88**. Thus, hydroxy acid **88** was converted into its tribenzyl derivative **87** by the

combined action of NaH, BnBr in anhydrous DMF at 0 ºC-rt in 94% yield. In the ^{1}H spectrum of **87**, the characteristic three benzylic peaks appeared at δ 5.08 (s, 4H), 5.36 (s, 2H) ppm. Further confirmation for **87** came from its ^{13}C NMR spectrum.

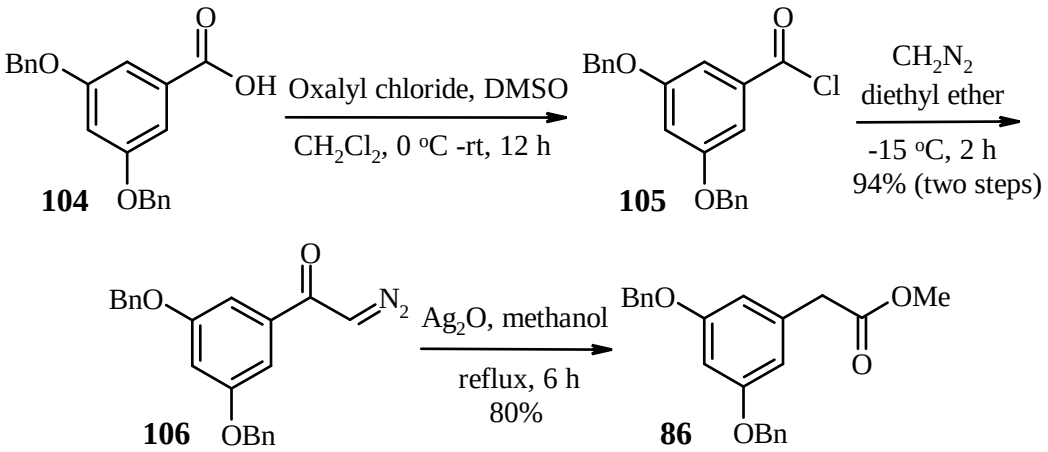


Scheme 7

The benzyl ester **87** was subjected to basic hydrolysis with KOH in methanol to provide 3,5-dibenzyloxybenzoic acid **104** in 83% yields. The product was unambiguously established by the ^{1}H NMR spectrum with benzylic protons resonating at δ 5.14 (s, 4H) ppm, while the aromatic protons in the region of δ 7.35-7.43 (m, 10H) ppm. The IR spectrum of **104** revealed the absorption at 1709 cm^{-1} pertinent to carbonyl moiety of acid (Scheme 7).

Next, we envisaged the Arndt-Eistert homologation[65] of the acid **104**. Thus, acid **104** was subjected to the treatment of oxaloyl chloride in dichloromethane to provide acid chloride **105**, which on exposure to the ethereal solution of diazomethane [generated from nitrosomethylurea (NMU) by treating with 50% aqueous KOH solution in diethyl ether at –15 ºC by established procedure[66]] at −15 ºC furnished the diazoketone **106**. The formation of **106** was confirmed by its ^{1}H NMR, ^{13}C NMR spectroscopy and elemental analysis. For example, in the ^{1}H NMR spectrum, a singlet at δ 5.78 ppm integrating for one proton was due to olefinic proton. A characteristic IR value at 2105 cm^{-1} clearly showed the presence of the diazo functionality (-N_2).

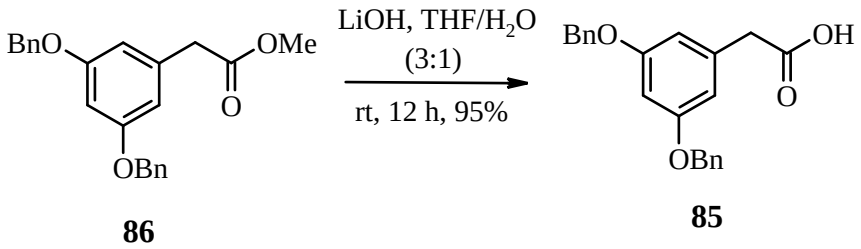
On refluxing with silver oxide (Ag_2O) in methanol for 6 h, diazoketone **106** underwent Arndt-Eistert rearrangement to give ester **86**. In ^{1}H NMR spectrum, disappearance of peak due to olefinic proton and appearance of a sharp singlet integrating



Scheme 8

for three protons was appeared at δ 3.58 ppm confirming the presence of methyl ester moiety. The ^{13}C NMR (165.95 ppm, =CO), mass, IR (1717 cm^{-1}) spectra and elemental analysis secured the assigned structure (Scheme 8).

Ester **86** was hydrolyzed to the free acid **85** using LiOH in a mixture of THF and water (3:1) at room temperature for 12 h. The acid **85** was characterized thoroughly by spectral and elemental analysis. In the mass spectrum, *m/z* 371.11 for $[(M+Na)]^+$ was observed. In ^{1}H NMR spectrum, a downfield shift of the methylene protons next to carboxylic acid was observed (Scheme 9). In ^{13}C NMR spectrum, a characteristic peak corresponding to carbonyl moiety of carboxylic acid at δ 177.8 ppm indicated the product formation.

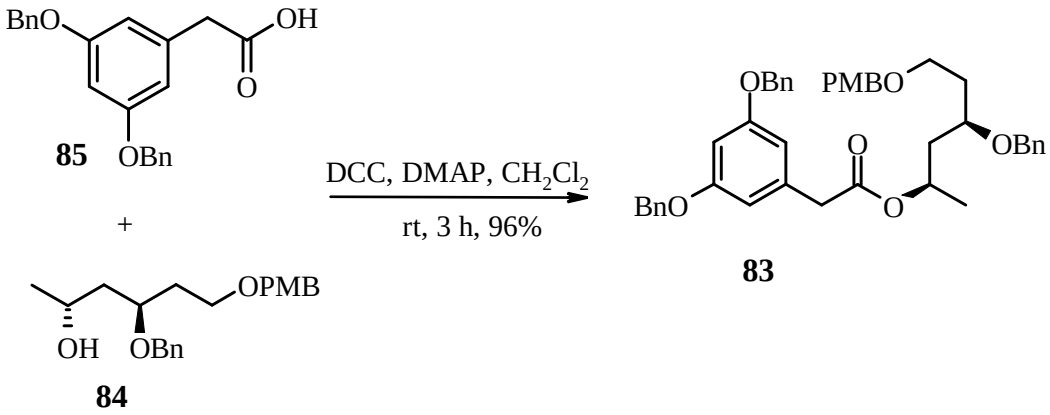


Scheme 9

Coupling reaction between 84 and 85

With the key intermediates **84** and **85** in hand, the stage was set to couple both the partners. Coupling reaction of alcohol **84** and acid **85** was accomplished using DCC[67] in presence of catalytic amount of DMAP in anhydrous CH_2Cl_2 for 3 h to give ester **83** in 96 % yield. The structure of **83** was proven by the ^{1}H NMR, ^{13}C NMR spectrum, IR, mass

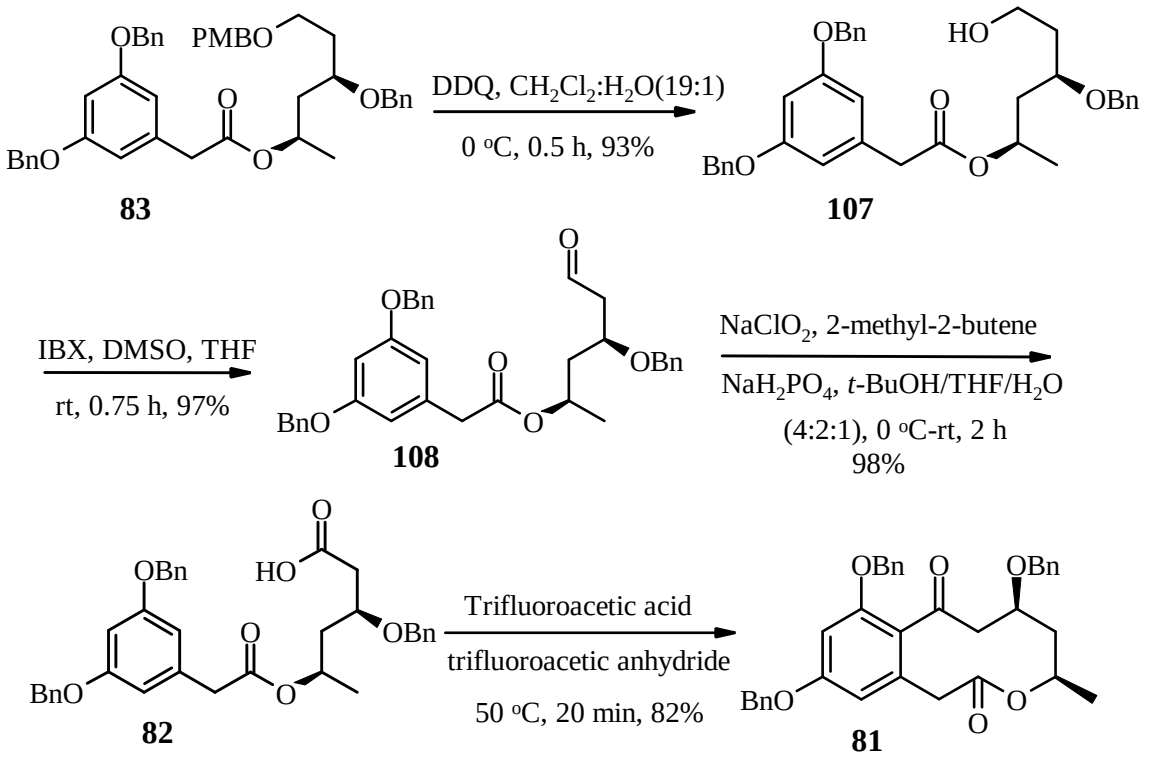
and elemental analysis (Scheme 10). In the ^{1}H NMR spectrum, a prominent down field shift of H11 signals (numbering based on Fig.1) was observed which indicates that the ester formation indeed occurred. In the ^{13}C spectrum, appearance of signal due to ester moiety at δ 170.6 ppm also supported the assigned structure.



Scheme 10

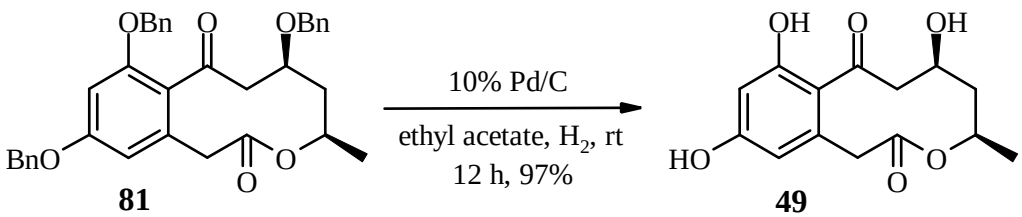
The *p*-methoxybenzyl ether of **83** was cleaved by treatment of DDQ in CH_2Cl_2: H_2O (19:1) at 0 ^{o}C to obtain the alcohol **107**. In ^{1}H NMR spectrum, the absences of signals due to −*OPMB* ether protons were the clear indication of product formation. The rest of the protons were localized at their expected regions. Moreover, the structure of the product was unambiguously supported by its ^{13}C NMR, IR, mass and elemental analysis. The alcohol was oxidized using IBX[68] in DMSO/THF at room temperature to furnish the aldehyde **108**, which was immediately transformed into the corresponding acid **82** by treating with $NaClO_2$, NaH_2PO_4 in *t*-BuOH/THF/H_2O[69] in presence of 2-methyl-2-butene at room temperature. The ^{1}H NMR and ^{13}C NMR spectrums of **82** were compatible with the assigned structure (Scheme 11). The ^{1}H NMR spectrum of **82** indicated the absence of methylenic protons (−*CH_2OH*) due to oxidation and the downfield shift of protons adjacent to the carbonyl moiety. The ^{13}C NMR spectrum of **82** showed the corresponding resonance for carbonyl group at δ 176.5 ppm. The macrolide **81** was constructed by intramolecular acylation[70] reaction of the carboxylic acid **82** in a mixture of trifluoroacetic acid and trifluoroacetic anhydride in 82 % yield (50 °C, 20 min). The yield of this reaction was higher than the 41% yield reported for the corresponding cyclization reaction in the previous synthesis[71]. This result may be correlated with the fact that the

aromatic ring has become more electron rich due to the presence of aromatic benzyl ether instead of methyl ether (as in the previous synthesis). The formation of **81** was well supp-



Scheme 11

orted by ^{1}H NMR, ^{13}C NMR and mass spectral studies together with elemental analysis. The ^{13}C NMR and DEPT spectra of **81** showed the corresponding resonances for the carbonyl moieties, *viz*, in the ^{13}C NMR spectrum of **81**, signals due to carbonyl and methylene carbons appeared at δ 204.74, 40.35, 43.96 and 52.28 respectively. The mass spectra recorded $[M+Na]^{+}$ peak at *m/z* 573.62 in support of the assigned structure (Scheme 12). The IR spectrum of **81** revealed the absorption at 1731 and 1680 cm^{-1} pertinent to lactone and carbonyl moieties.



Scheme 12

On deprotection of the benzyl groups of **81** by catalytic hydrogenation using 10% Pd/C in ethyl acetate under hydrogen atmosphere accomplished the desired

xestodecalactone C (**49**), whose spectral data corresponded with those of natural product[28].

Table 1. ***NMR spectral data of xestodecalactone C (Natural product)[28] and compound 49***

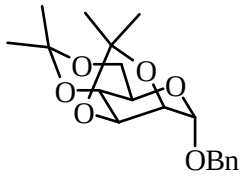
^{1}H NMR (400 MHz, DMSO-d_6) Natural product	**^{1}H NMR (400 MHz, DMSO-d_6) compound 49**	**^{13}C NMR 125MHz, DMSO-d_6) Natural product**	**^{13}C NMR (125 MHz, DMSO-d_6) compound 49**
1.08 (d, *J* = 6.2Hz)	1.07 (d, *J* = 6.2 Hz, 3H)	20.77 (q)	20.94 (q)
1.65 (ddd, *J* = 9.8, 11.4, 14.5 Hz)	1.65 (ddd, *J* = 9.8, 11.4, 14.4 Hz, 1H)	38.66 (t)	39.13 (t)
1.83 (bd, *J* = 14.5 Hz)	1.82 (d, *J* = 14.2 Hz,1H)	46.03 (t)	46.20 (t)
2.81 (bd, *J* = 15.1 Hz)	2.81 (d, *J* = 15.0 Hz, 1H)	55.29 (t)	55.46 (t)
3.08 (dd, *J* = 10.4, 15.1 Hz)	3.08 (dd, *J* = 10.3, 15.01 Hz, 1H)	67.82 (d)	68.00 (d)
3.48 (d, 18.7 Hz)	3.47 (d, *J* = 18.9 Hz, 1H)	70.60 (d)	70.78 (d)
3.82 (d, *J* = 19.0 Hz)	3.82 (d, *J* = 18.9 Hz, 1H)	101.26 (d)	101.44 (d)
3.95 (bt, *J* = 10.0 Hz)	3.95 (bt, *J* = 9.9 Hz, 1H)	109.25 (d)	109.43 (d)
4.70 (ddq, 2.5, 11.4, 6.2 Hz)	4.71-4.75 (m, 2H)	121.15 (s)	121.34 (s)
4.83 (d, *J* = 2.9 Hz)		134.43 (s)	134.61 (s)
6.10 (d, *J* = 2.1 Hz)	6.09 (s, 1H)	157.08 (s)	157.24 (s)
6.27 (d, *J* = 2.1 Hz)	6.27 (d, *J* = 1.6 Hz, 1H)	159.11 (s)	159.27 (s)
9.87 (s)	9.70 (s, 1H)	168.85 (s)	169.01 (s)
9.98 (s)	9.90 (s, 1H)	204.60 (s)	204.77 (s)

In summary, a carbohydrate based total synthesis of the promising antifungal agent xestodecalactone C (**49)**, a secondary metabolite produced by *penicillium cf. montanense* fungus, has been accomplished. Formation of the required 10-membered macrolactone was achieved through DCC mediated coupling, intramolecular acylation in an efficient manner. Finally global deprotection of protective groups was achieved by employing

catalytic hydrogenation, thus completing the total synthesis of xestodecalactone C. Though, the spectral data was in close agreement with the isolation paper, it corresponded with the diastereomer of the reported synthesis. We have therefore embarked on a study of the synthesis of the other diastereomer that is xestodecalactone B (Chapter 1 Section II), which would lead to a structural reassignment and determination of the absolute configuration of both the dastereomers.

Experimental

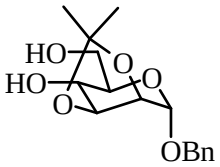
Benzyl 2,3:4,6-di-*O*-isopropylidene-α-D-mannopyranoside (93):



To an ice-cooled solution of **92** (20.1 g, 73.897 mmol) in dry DMF (200 mL), 2,2-dimethoxypropane (27.3 mL, 221.691 mmol) and *p*-TSA(cat.) were added. After 12 h of stirring, the reaction mixture was partitioned between water and ethyl acetate. The organic layer was washed with water, brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography (3% ethyl acetate in pet-ether) to afford **93** (23.99 g) as a colorless liquid.

Yield	: 92%
Mol. Formula	: $C_{19}H_{26}O_6$
Optical Rotation $[\alpha]_D^{25}$	: +22.5 (*c* 0.65, $CHCl_3$).
IR ($CHCl_3$) cm^{-1}	: 2991, 2938, 2914, 2876, 1738, 1607, 1497, 1455, 1382, 1372, 1313, 1265, 1199, 1170, 1116, 1044, 984, 860, 759, 699.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.35 (s, 3H), 1.43 (s, 3H), 1.55 (s, 6H), 3.59-3.84 (m, 4H), 4.13-4.24 (m, 2H), 4.52 (d, *J* = 11.7 Hz, 1H), 4.71(d, *J* = 11.7 Hz, 1H), 5.10 (s, 1H), 7.30-7.38 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 18.74, 26.16, 28.17, 29.04, 61.48, 61.96, 69.33, 72.71, 74.85, 76.10, 97.02, 99.59, 109.32, 127.97, 128.11, 128.46, 136.84 ppm.
ESI MS (*m/z*)	: 373.42 $[M+Na]^+$
Elemental Analysis	**Calcd:** C, 65.13; H, 7.48.
	Found: C, 65.02; H, 7.39.

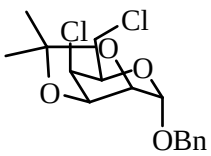
Benzyl-2,3-*O*-isopropylidene-α-D-mannopyranoside (94):



The compound **93** (15.47 g, 44.152 mmol) was stirred with aq. 0.8% H_2SO_4 (cat.) in methanol (500 mL) at ambient temperature for 24 h. After neutralization with solid $NaHCO_3$, the reaction mixture was filtered, concentrated and the residue purified by silica gel column chromatography (50% ethyl acetate in pet-ether) to afford **94** (12.82 g) as colourless thick liquid.

Yield	: 94%
Mol. Formula	: $C_{16}H_{22}O_6$
Optical Rotation $[\alpha]_D^{25}$	: + 56.9 (*c* 1.65, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	: 3493, 3360, 2987, 2935, 1696, 1670, 1624, 1553, 1370, 1216, 1139, 1077, 993, 861, 754, 699.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.34 (s, 3H), 1.51 (s, 3H), 2.59 (bs, 2H), 3.62-3.78 (m, 2H), 3.82 (d, *J* = 3.5 Hz, 2H), 4.13-4.21 (m, 2H), 4.51 (d, *J* = 11.8 Hz, 1H), 4.72 (d, *J* = 11.8 Hz, 1H), 5.10 (s, 1H), 7.28-7.40 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 28.23, 29.09, 61.53, 62.02, 69.38, 72.76, 74.89, 76.14, 97.05, 99.67, 109.40, 127.90, 128.19, 128.53, 136.88 ppm.
ESI MS (*m/z*)	: 333.35 $[M+Na]^+$
Elemental Analysis	**Calcd:** C, 61.92; H, 7.15.
	Found: C, 61.80; H, 7.13.

Benzyl 4,6-dichloro- 4,6-dideoxy-2,3-*O*-isopropylidene-α-D-talopyranoside (95):

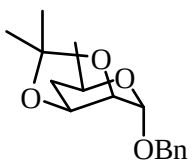


A mixture of **94** (4.5 g, 14.499 mmol) and triphenylphosphine (19.00 g, 72.495 mmol) containing pyridine (50 mL) was refluxed in CCl_4 (180 mL) for 5 h. Removal of

solvent and residue purification by silica gel column chromatography (5% ethyl acetate in pet-ether) gave **95** (4.19 g) as a colourless liquid.

Yield	: 83%
Mol. Formula	: $C_{16}H_{20}Cl_2O_4$
Optical Rotation $[\alpha]_D^{25}$	: +94.3 (*c* 1.9, $CHCl_3$).
IR ($CHCl_3$) cm^{-1}	: 3358, 2979, 2925, 1697, 1670, 1554, 1380, 1365, 1213, 1070, 862, 756, 700.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.37 (s, 3H), 1.61 (s, 3H), 3.70-3.85 (m, 2H), 4.07-4.16 (m, 2H), 4.38 (dd, *J* = 2.7, 5.0 Hz, 1H), 4.48 (dd, *J* = 5.1, 6.3 Hz, 1H), 4.61 (d, *J* = 11.7 Hz, 1H), 4.83 (d, *J* = 11.7 Hz, 1H), 5.13 (s, 1H), 7.30-7.38 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 25.17, 25.39, 43.98, 55.42, 69.49, 69.81, 72.06, 73.87, 96.83, 110.30, 128.04, 128.29, 128.46, 136.67 ppm.
ESI MS (*m/z*)	: 370.24 $[M+Na]^+$
Elemental Analysis	**Calcd:** C, 55.34; H, 5.81.
	Found: C, 55.40; H, 5.72.

Benzyl 4,6-dideoxy-2,3-*O*-isopropylidene-α-D-*lxyo*-hexopyranoside (96):



To a solution of halo compound **95** (5.62 g, 16.176 mmol) and AIBN (cat.) in toluene (80 mL), TBTH (22.4 mL, 80.88 mmol) was added. The reaction mixture was refluxed for 7 h, concentrated *in vacuo* and purified by silica gel column chromatography (10% ethyl acetate in hexane) to afford **96** (4.12 g) as a colourless oil.

Yield	: 92%
Mol. Formula	: $C_{16}H_{22}O_4$
Optical Rotation $[\alpha]_D^{25}$	: +84.0 (*c* 1.6, $CHCl_3$).

IR ($CHCl_3$) cm^{-1} : 3392, 3089, 3065, 3031, 2982, 2933, 1965, 1607, 1497, 1380, 1302, 1220, 1067, 863, 758, 698, 602, 515.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.22 (d, *J* = 6.4 Hz, 3H), 1.33 (s, 3H), 1.51(s, 3H), 1.55-1.65 (m, 1H), 1.87 (ddd, *J* = 2.2, 6.8, 13.2 Hz, 1H), 3.84 (d sextate, *J* = 2.3, 6.3 Hz, 1H), 3.96-4.02 (m, 1H), 4.28-4.41 (m, 1H), 4.52 (d, *J* = 11.8 Hz, 1H), 4.72 (d, *J* = 11.8 Hz, 1H), 5.10 (s, 1H), 7.28-7.35 (m, 5H) ppm.

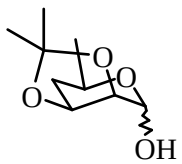
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 21.13, 26.27, 28.13, 36.10, 62.11, 68.76, 70.79, 72.64, 96.73, 108.53, 127.65, 127.93, 128.28, 137.33 ppm.

ESI MS (*m/z*) : 301.35 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 69.04; H, 7.97.

Found: C, 67.77; H, 7.68.

4,6-Dideoxy-2,3-*O*-isopropylidene-α/β-D-*lxyo*-hexopyranoside (97):



To a solution of naphthalene (10.43 g, 81.492 mmol) in THF (60 mL) was added sodium metal (1.87 g, 81.492 mmol) at room temperature under N_2. The mixture was stirred at room temperature until a dark green solution was formed. Then it was cooled to 0 °C and a solution of **96** (5.67 g, 20.373 mmol) in THF (40 mL) was added. The mixture was stirred at 0 °C for 30 min. The reaction mixture was then partitioned between ether and saturated aqueous NH_4Cl. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give lactol **97** as colorless oil (3.15 g).

Yield : 82%

Mol. Formula : $C_9H_{16}O_4$

IR ($CHCl_3$) cm^{-1} : 3369, 2930, 1594, 1385, 1045, 772, 662.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.20 (d, *J* = 6.3 Hz, 2H), 1.26 (d, *J* = 6.4 Hz, 1H),

1.34 (s, 2H), 1.35 (s, 1H), 1.40-1.48 (m, 1H), 1.51 (s, 2H), 1.53 (s, 1H), 1.86 (ddd, *J* = 2.3, 6.8, 13.3 Hz, 1H), 3.18 (brs, 1H), 3.94-4.09 (m, 2H), 4.29-4.40 (m, 1H), 5.29 (s, 0.38H), 5.42 (bs, 0.67H) ppm.

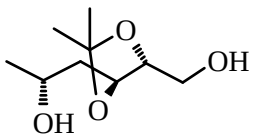
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 21.12, 21.34, 26.16, 26.22, 27.94, 28.02, 36.01, 36.28, 62.16, 67.07, 67.39, 70.61, 72.68, 72.91, 73.02, 76.34, 92.17, 92.86, 97.40, 108.58, 111.66 ppm.

ESI MS (*m/z*) : 211.23 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 57.43; H, 8.57.

Found: C, 61.54; H, 7.29.

(*R*)-1-((4*S*,5*R*)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propan-2-ol (91):



To a solution of compound **97** (2.13 g, 11.3 mmol) in THF (60 mL) at 0 ^oC was added $LiAlH_4$ (0.51 g, 13.56 mmol) and stirred at room temperature for 1.5 h. Excess of $LiAlH_4$ was quenched by the addition of ethyl acetate. The solid formed was filtered, and the filtrate was concentrated, purified by silica gel column chromatography eluting with light petroleum ether: EtOAc (1:4) to afford **91** (1.99 g) as colourless liquid.

Yield : 93%

Mol. Formula : $C_9H_{18}O_4$

Optical Rotation $[\alpha]_D^{25}$: −4.11 (*c* 0.7, $CHCl_3$).

IR ($CHCl_3$) cm^{-1} 3459, 3017, 2985, 2958, 1620, 1472, 1463, 1379, 1218, 1168, 1091, 938, 758, 666, 513.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.25 (d, *J* = 6.2 Hz, 3H), 1.36 (s, 3H), 1.44 (s, 3H), 1.55-1.69 (m, 1H), 1.78 (ddd, *J* = 3.2, 8.4, 14.2 Hz, 1H), 2.26 (bs, 2H), 3.53-3.69 (m, 2H), 3.94-4.09 (m, 1H), 4.18 (q, *J* = 6.0 Hz, 1H), 4.42 (ddd, *J* = 5.1, 6.1, 8.3 Hz, 1H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 24.23, 25.44, 28.11, 37.51, 61.07, 65.39, 74.63,

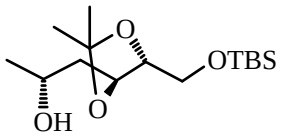
77.77, 107.56 ppm.

ESI MS (*m/z*) : 213.24 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 56.82; H, 9.54.

Found: C, 53.22; H, 9.61.

(*R*)-1-((4*S*,5*R*)-5-((*tert*-butyldimethylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propan-2-ol (98):



A solution of **91** (2.14 g, 11.222 mmol), TBSCl (2.20 g, 14.588 mmol) and triethylamine (3.1 mL, 22.272 mmol) in CH_2Cl_2 (50 mL) was stirred for 8 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 and washed with water. The organic layer was dried (Na_2SO_4), concentrated and the residue purified on silica gel column chromatography using EtOAc:light petroleum ether (1:4) as an eluent to obtain **98** (3.156 g) as clear oil.

Yield : 92%

Mol. Formula : $C_{15}H_{32}O_4Si$

Optical Rotation $[\alpha]_D^{25}$: −7.63 (*c* 1.25 $CHCl_3$).

IR ($CHCl_3$) cm^{-1} : 3453, 2959, 2932, 2859, 1472, 1371, 1255, 1219, 1169, 1093, 838, 776.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.08 (s, 6H), 0.89 (s, 9H), 1.22 (d, *J* = 6.3 Hz, 3H), 1.33 (s, 3H), 1.38 (s, 3H), 1.64-1.91 (m, 2H), 2.34 (bs, 1H), 3.53 (dd, *J* = 4.4, 10.2 Hz, 1H), 3.65 (dd, *J* = 8.4, 18.7 Hz, 1H), 3.88-4.03 (m, 1H), 4.09-4.18 (m, 1H), 4.40 (q, *J* = 6.3 Hz, 1H) ppm.

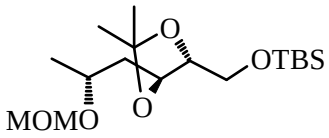
^{13}C NMR ($CDCl_3$, 50 MHz) : δ −5.50, −5.47, 18.27, 24.28, 25.42, 25.87, 28.15, 37.34, 61.86, 65.51, 74.94, 77.63, 107.26 ppm.

ESI MS (*m/z*) : 327.16 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 59.17; H, 10.59.

Found: C, 59.40; H, 10.69.

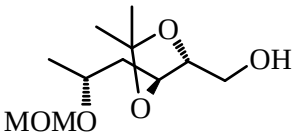
***tert*-butyl (((4*R*,5*S*)-5-(R)-2-(methoxymethoxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)dimethylsilane (99):**



To a solution of **98** (1.41 g, 4.5 mmol) in CH_2Cl_2 (10 mL) was added diisopropylethylamine (1.6 mL, 9.272 mmol) followed by MOMCl (0.55 mL, 6.955 mmol) at 0 ^oC. The mixture was stirred at room temperature overnight. The reaction was quenched with H_2O. The aqueous layer was extracted with CH_2Cl_2 twice. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (5% EtOAc/Hexanes) afforded **99** (1.52 g) as a clear oil.

Yield	: 94%
Mol. Formula	: $C_{17}H_{36}O_5Si$
Optical Rotation $[\alpha]_D^{25}$	: −20.1 (*c* 1.4, $CHCl_3$).
IR ($CHCl_3$) cm^{-1}	3358, 3014, 2955, 2888, 2401, 1696, 1670, 1552, 1398, 1370, 1215, 1098, 1040, 861, 838, 758, 667.
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 0.05 (s, 6H), 0.88 (s, 9H), 1.21 (d, *J* = 6.2 Hz, 3H), 1.32 (s, 3H), 1.40 (s, 3H), 1.54-1.68 (m, 1H), 1.72-1.85-m, 1H), 3.38 (s, 3H), 3.51-3.68 (m, 2H), 3.83-3.96 (m, 1H), 4.05 (q, *J* = 6.2 Hz, 1H), 4.38 (ddd, *J* = 2.7, 5.9, 10.4 Hz, 1H), 4.64 (d, *J* = 6.8 Hz, 1H), 4.72 (d, *J* = 6.8 Hz, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ −5.54, −5.47, 18.15, 21.24, 25.43, 25.80, 28.14, 36.93, 55.25, 61.99, 70.54, 73.66, 77.71, 95.19, 107.60 ppm.
ESI MS (*m/z*)	: 371.27 $[M+Na]^+$
Elemental Analysis	**Calcd:** C, 58.58; H, 10.41.
	Found: C, 58.24; H, 10.70.

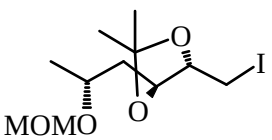
((4*R*,5*S*)-5-(R)-2-(methoxymethoxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)methanol (90):



A solution of **99 (**1.52 g, 4.373 mmol) in THF (20 mL) was added tetrabutylammonium fluoride **(**1 M in THF, 6.6 mL, 6.559 mmol) at 0 ^{o}C. The mixture was stirred at room temperature for 7 h, concentrated in *vacuo,* and then added to water. The aqueous layer was extracted with ether. The combined organic layers were dried (Na_2SO_4) and evaporated in *vacuo.* Flash column chromatography of the residue on silica gel column chromatography with ethyl acetate:pet ether (1:4) yielded alcohol **90** (986 mg) as a colorless oil.

Yield	: 96%
Mol. Formula	: $C_{11}H_{22}O_5$
Optical Rotation $[\alpha]_D^{25}$	: −7.9 (*c* 2.0, $CHCl_3$).
IR ($CHCl_3$) cm^{-1}	: 3467, 2984, 2934, 2824, 1638, 1456, 1379, 12401217, 1140, 1100, 919, 839, 756, 627, 515.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.21 (d, *J* = 6.2 Hz, 3H), 1.34 (s, 3H), 1.43 (s, 3H), 1.64-1.75 (m, 2H), 2.09 (bs, 1H), 3.36 (s, 3H), 3.50-3.66 (m, 2H), 3.88 (sextate, *J* = 6.4 Hz, 1H), 4.13 (dd, *J* = 4.9, 6.4 Hz, 1H), 4.36 (q, *J* = 6.3 Hz, 1H), 4.61 (d, *J* = 6.8 Hz, 1H), 4.70 (d, *J* = 6.8 Hz, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 21.04, 25.40, 28.14, 36.76, 55.40, 61.67, 70.68, 73.74, 77.82, 95.06, 107.72 ppm.
ESI MS (*m/z*)	: 257.29 $[M+Na]^+$
Elemental Analysis	**Calcd:** C, 56.39; H, 9.46.
	Found: C, 55.60; H, 9.76.

((4*S*,5*S*)-4-(iodomethyl)-5-((R)-2-(methoxymethoxy)propyl)-2,2-dimethyl-1,3-dioxolane (100):



A mixture of **90** (1.02 g, 4.362 mmol), I_2 (2.22 g, 8.726 mmol), Ph_3P (2.28 g, 8.724 mmol) and imidazole (1.19 g, 17.448 mmol) in toluene (30 mL) were heated to 100 ^oC for 1 h. The reaction mixture was cooled to room temperature, diluted with ether, washed with 20% $Na_2S_2O_3$ solution, water, brine, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel column chromatography using light petroleum: EtOAc (97:3) as an eluent to give **100** (1.44 g) as thick oil.

Yield : 96%

Mol. Formula : $C_{11}H_{21}IO_4$

Optical Rotation $[\alpha]_D^{25}$: +12.2 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$) cm^{-1} : 2986, 2932, 2890, 1619, 1455, 1380, 1372, 1218, 1153, 1099, 1036, 918, 757, 667, 513.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.22 (d, *J* = 6.2 Hz, 3H), 1.34 (s, 3H), 1.45 (s, 3H), 1.55-1.73 (m, 2H), 3.01-3.22 (m, 2H), 3.37 (s, 3H), 3.82-3.97 (m, 1H), 4.26-4.38 (m, 2H), 4.62 (d, *J* = 6.8 Hz, 1H), 4.70 (d, *J* = 6.8 Hz, 1H) ppm.

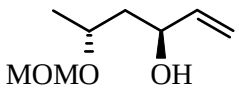
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 4.26, 21.16, 25.67, 28.43, 37.04, 55.31, 70.25, 74.41, 78.14, 95.08, 108.07 ppm.

ESI MS (*m/z*) : 357.19 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 38.39; H, 6.15.

Found: C, 39.49; H, 6.41.

(3*S*,5*R*)-5-(methoxymethoxy)hex-1-en-3-ol (89):



A mixture of **100** (1.3 g, 3.761 mmol), zinc (2.46 g, 37.61 g) in refluxing ethanol (30 mL) under nitrogen was stirred for 3 h. The zinc was filtered, filtrate concentrated, and the residue purified by silica gel column chromatography by using light petroleum: EtOAc (85:15) to obtain **89** (589 mg) as colorless oil.

Yield : 98%

Mol. Formula : $C_8H_{16}O_3$

Optical Rotation $[\alpha]_D^{25}$: −39.4 (*c* 1.1, $CHCl_3$).

IR ($CHCl_3$) cm^{-1} : 3487, 3030, 2968, 2930, 2884, 1950, 1643, 1610, 1496, 1454, 1376, 1239, 1210, 1102, 1039, 920, 756, 698, 666, 574.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.22 (d, *J* = 6.3 Hz, 3H), 1.55-1.79 (m, 2H), 2.82 (bs, 1H), 3.39 (s, 3H), 3.90-4.06 (m, 1H), 4.27-4.46 (m, 1H), 4.62 (d, *J* = 6.8 Hz, 1H), 4.70 (d, *J* = 6.8 Hz, 1H), 5.17 (dt, *J* = 1.6, 20.7 Hz, 1H), 5.26 (dt, *J* = 1.6, 17.2 Hz, 1H), 5.88 (ddd, *J* = 5.3, 10.4, 17.2 Hz, 1H) ppm.

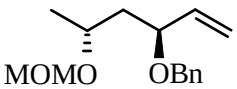
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 20.46, 43.62, 55.48, 69.20, 71.04, 95.26, 113.89, 140.91 ppm.

ESI MS (*m/z*) : 183.21 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 59.97, H, 10.07.

Found: C, 59.81; H, 9.96.

(((3*S*,*5R*)-5-(methoxymethoxy)hex-1-en-3-yloxy)methyl)benzene (101):



Compound **89** (515 mg, 3.215 mmol) in DMF (5 mL) was added to a stirred suspension of NaH (257 mg, 60% dispersion in oil, 6.43 mmol) in DMF (10 mL) at 0 ^oC. The resulting solution was stirred at the same temperature for 30 min; BnBr (0.6 mL, 4.823 mmol) was added. After 1.5 h, the reaction was quenched by ice-cold water and extracted with EtOAc. The combined organic layer was washed with water, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel column chromatography using EtOAc-light petroleum ether (3:97) to obtain **101** (752 mg) as yellowish liquid.

Yield : 93%

Mol. Formula : $C_{15}H_{22}O_3$

Optical Rotation $[\alpha]_D^{25}$: − 44.01 (*c* 1.3, $CHCl_3$).

IR ($CHCl_3$) cm^{-1} : 3083, 3010, 2971, 2935, 1644, 1448, 1378, 1217, 1145, 1101, 1036, 921, 757, 667, 618.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.19 (d, *J* = 6.2 Hz, 3H), 1.65-1.72 (m, 2H), 3.34 (s, 3H), 3.86-4.08 (m, 2H), 4.31 (d, *J* = 11.5 Hz, 1H), 4.52 (d, *J* = 6.8 Hz, 1H), 4.59 (d, *J* = 11.5 Hz, 1H), 4.61 (d, *J* = 6.8 Hz, 1H), 5.21-5.32 (m, 2H), 5.69-5.86 (m, 1H), 7.24-7.36 (m, 5H) ppm.

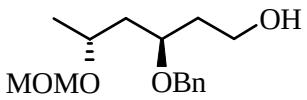
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 21.26, 43.95, 55.19, 70.23, 70.51, 77.13, 95.54, 116.81, 127.46, 127.89, 128.27, 138.48, 138.97 ppm.

ESI MS (*m/z*) : 273.33 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 71.97; H, 8.86.

Found: C, 71.82; H, 8.72.

(3*S*,5*R*)-3-(benzyloxy)-5-(methoxymethoxy)hexan-1-ol (102):



To a solution of **101** (461 mg, 1.841 mmol) in THF (10 mL) was added 9-BBN (674 mg, 5.525 mmol) at 0 ^oC. The reaction mixture was warmed up to reflux. After stirring at the same temperature for 3 h, 2 N NaOH and H_2O_2 were added. The mixture was extracted with ether, washed with brine. The organic layers were combined and dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure vacuum. The residue was purified on a silica gel column chromatography using petroleum ether /EtOAc (6/4) as the eluant to afford **102** as colorless oil (474 mg).

Yield : 96%

Mol. Formula : $C_{15}H_{24}O_4$

Optical Rotation $[\alpha]_D^{25}$: −22.3 (*c* 1.15, $CHCl_3$).

IR ($CHCl_3$) cm^{-1} : 3443, 3064, 3030, 2930, 1951, 1605, 1586, 1496, 1454, 1376, 1212, 1107, 918, 846, 752, 698, 610.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.13 (d, *J* = 6.2 Hz, 3H), 1.60-1.67 (m, 2H), 1.70-1.90 (m, 2H), 2.80 (brs, 1H), 3.28 (s, 3H), 3.54-3.89 (m, 4H), 4.40-4.59 (m, 4H), 7.16-7.29 (m, 5H) ppm.

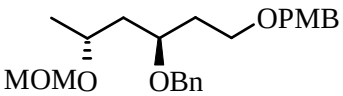
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 21.10, 36.17, 42.41, 55.28, 59.43, 70.93, 71.01, 74.48, 95.22, 127.58, 127.81, 128.30, 138.23 ppm.

ESI MS (*m/z*) : 291.35 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 67.14; H, 9.01.

Found: C, 67.01; H, 8.93.

1-(((3*S*,5*R*)-3-(benzyloxy)-5-(methoxymethoxy)hexyloxy)methyl)-4-methoxybenzene (103):



To an ice-cooled solution of **102** (500 mg, 1.863 mmol) in dry DMF (10 ml), NaH (60% dispersion in oil, 148 mg, 3.726 mmol) was added. After 30 minutes, PMBCl (0.47 ml, 3.354 mmol) was introduced and stirred for additional 3.5 h at room temperature. The reaction mixture was partitioned between water and ethyl acetate. The organic layer was washed with water, brine, dried (Na_2SO_4) and concentrated. The residue was purified on a silica gel column chromatography using petroleum ether /EtOAc (17/3) as the eluant to afford **103** (612 mg) as colorless oil.

Yield : 85%

Mol. Formula : $C_{23}H_{32}O_5$

Optical Rotation $[\alpha]_D^{25}$: −14.0 (*c* 1.2, $CHCl_3$).

IR ($CHCl_3$) cm^{-1} : 3063, 2933, 2005, 1882, 1613, 1586, 1513, 1455, 1362, 1302, 1172, 1091, 917, 821, 754, 698, 567.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.10 (d, *J* = 6.2 Hz, 3H), 1.54-1.60 (m, 2H), 1.74-1.85 (m, 2H), 3.26 (s, 3H), 3.38-3.56 (m, 2H), 3.71 (s, 3H), 3.61-3.88 (m, 2H), 4.34 (s, 2H), 4.40-4.49 (m, 3H), 4.56 (d, *J* = 6.9 Hz, 1H), 6.77 (d, *J* = 8.6 Hz, 2H), 7.15-7.24 (m, 7H) ppm.

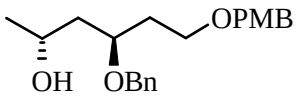
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 21.28, 34.48, 43.14, 55.08, 55.30, 66.27, 70.89, 71.15, 72.60, 73.36, 95.38, 113.65, 127.47, 127.82, 128.27, 129.20, 130.46, 138.67, 159.06 ppm.

ESI MS (*m/z*) : 411.50 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 71.11; H, 8.30.

Found: C, 71.01; H, 8.20.

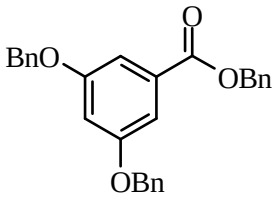
(2*R*,4*R*)-4-(benzyloxy)-6-(4-methoxybenzyloxy)hexan-2-ol (84):



A solution of **103** (464 mg, 1.194 mmol) in methanol (5 mL), 0.1% methanolic HCl (1 mL) was stirred at room temperature for 36 h. Triethylamine (excess) was added to neutralize acid and the stirring continued for 30 minutes. Evaporation of the solvent and purification of the crude product by silica gel column chromatography (10% ethyl acetate in pet-ether) afforded **84** (389 mg) as an oil.

Yield	: 95%
Mol. Formula	: $C_{21}H_{28}O_4$
Optical Rotation $[\alpha]_D^{25}$	: +5.47 (*c* 1.0, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	: 3435, 3030, 2932, 2862, 1713, 1612, 1513, 1454, 1363, 1302, 1248, 1173, 1067, 1035, 820, 739, 698, 596.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.08 (d, *J* = 6.2 Hz, 3H), 1.50 (ddd, *J* = 2.8, 6.3, 14.6 Hz, 1H), 1.60-1.79 (m, 2H), 1.82-1.99 (m, 1H), 2.49 (bs, 1H), 3.35-3.54 (m, 2H), 3.71 (s, 3H), 3.75-3.86 (m, 1H), 3.92-4.07 (m, 1H), 4.32 (bs, 2H), 4.41 (d, *J* = 11.4 Hz, 1H), 4.49 (d, *J* = 11.4 Hz, 1H), 6.78 (d, *J* = 8.6 Hz, 2H), 7.12-7.31 (m, 7H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 23.71, 33.94, 41.77, 55.10, 64.62, 66.25, 71.47, 72.62, 74.48, 113.69, 127.70, 127.93, 128.37, 129.30, 130.26, 138.13, 159.13 ppm.
ESI MS (*m/z*)	: 367.44 $[M+Na]^+$
Elemental Analysis	**Calcd:** C, 73.23; H, 8.19.
	Found: C, 73.18; H, 8.10.

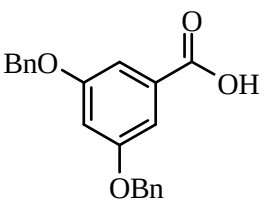
Benzyl 3,5-bis(benzyloxy)benzoate (87):



To a solution of hydroxy acid **88** (15.0 g, 97.402 mmol) in DMF (250 mL) was added sodium hydride (15.58 g, 389.608 mmol, 60% in mineral oil) portionwise with stirring at 0 ^{o}C. After stirring for 0.5 h at 0 ^{o}C, benzyl bromide (41.6 mL, 340.907 mmol) was added over 20 min, and stirring was continued for 12 h at room temperature. The reaction was quenched with ice-water, the mixture was extracted with EtOAc and the combined extract was washed with brine, dried (Na_2SO_4) and evaporated. Purification of the crude by silica gel column chromatography (3% ethyl acetate in pet-ether) afforded **87** (39.92 g) as an oil.

Yield	: 94%
Mol. Formula	: $C_{28}H_{24}O_4$
IR ($CHCl_3$) cm^{-1}	: 3090, 3032, 2936, 2876, 1717, 1595, 1497, 1454, 1444, 1345, 1297, 1224, 1160, 1080, 1028, 764, 696.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 5.08 (s, 4H), 5.36 (s, 2H), 6.81(t, *J* = 2.4 Hz, 1H), 7.31-7.46 (m, 17H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 66.78, 70.20, 107.12, 108.48, 127.54, 128.07, 128.12, 128.21, 128.57, 131.97, 135.91, 136.39, 159.72, 165.95 ppm.
ESI MS (*m/z*)	: 447.50 $[M+Na]^+$
Elemental Analysis	**Calcd:** C, 79.23; H, 5.70.
	Found: C, 79.18; H, 5.61.

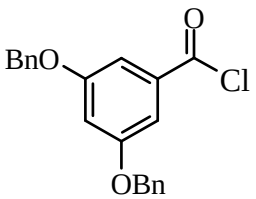
3,5-bis(benzyloxy)benzoic acid (104):



A methanolic solution of KOH (2.64 g in 20 mL methanol, 47.114 mmol) was added to a solution of **87** (10.0 g, 23.557 mmol) in 80 mL of MeOH. After stirring for 12 h, the reaction mixture was neutralized with 6 N HCl and extracted with ether. Combined organic layer was dried (Na_2SO_4) concentrated and the residue purified on silica gel column chromatography EtOAc: hexane (6:4) as an eluent to obtain **104** (6.51 g).

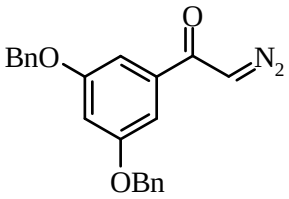
Yield	: 83%
Mol. Formula	: $C_{21}H_{18}O_4$
IR (Nujol) cm^{-1}	: 2923, 2853, 2725, 2638, 2208, 2051, 1688, 1596, 1497, 1461, 1377, 1300, 1168, 1028, 852, 752, 694, 502.
^{1}H NMR (DMSO-*d_6*, 200 MHz)	: δ 5.14 (s, 4H), 6.93 (s, 1H), 7.17 (bs, 2H), 7.35-7.43 (m, 10H) ppm.
^{13}C NMR (DMSO-*d_6*, 50 MHz)	: δ 69.76, 106.81, 108.29, 127.93, 128.16, 128.71, 133.16, 136.99, 159.68, 167.21 ppm.
ESI MS (*m/z*)	: 357.38 $[M+Na]^+$
Elemental Analysis	**Calcd:** C, 75.43; H, 5.43.
	Found: C, 75.32; H, 5.31.

3,5-bis(benzyloxy)benzoic chloride (105):



3,5-dibenzyloxybenzoic acid **104** (10.0 g, 29.906 mmol) in CH_2Cl_2 (54 mL) was treated with DMF (0.2 mL) and oxalyl chloride (25.4 mL, 2 M in CH_2Cl_2, 50.84 mmol) at 0 °C, and the suspension was stirred at 0 °C for 4.5 h. The resultant clear solution was stirred at room temperature overnight and evaporated under reduced pressure to give a yellow solid of crude acid chloride **105** (12.31 g).

1-(3,5-bis(benzyloxy)phenyl)-2-diazoethanone (106):



50% aq. solution of NaOH was added slowly to a solution of nitrosomethylurea (NMU) (20.6 g, 200.058 mmol) in anhydrous ether (100 mL) while shaking at –15 ^{o}C. The ether layer containing diazomethane was decanted into another conical flask and dried over KOH pellets. It was then added to the solution of crude **105** (12.31 g) in anhydrous ether (100 mL) at –15 ^{o}C and stirred for 2 h at same temperature. The solvent was removed and the residue purified by silica gel column chromatography using EtOAc–light petroleum (5:95) as an eluent to afford **106** (10.11 g,) as colorless syrup.

Yield : 94% (over two steps)

Mol. Formula : $C_{22}H_{18}N_2O_3$

IR ($CHCl_3$) cm^{-1} : 3369, 3090, 2923, 2105, 1589, 1440, 1355, 1294, 1150, 1053, 1026, 845, 785, 739, 697,

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 5.05 (s, 4H), 5.78 (s, 1H), 6.75 (t, *J* = 2.28 Hz, 1H), 6.96 (d, *J* = 2.25 Hz, 2H), 7.24-7.43 (m, 10H) ppm.

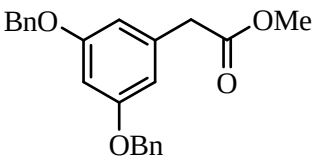
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 54.13, 70.15, 105.64, 106.17, 127.46, 128.05, 128.53, 136.26, 138.53, 159.91, 185.55 ppm.

ESI MS (*m/z*) : 381.40 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 73.73; H, 5.06; N, 7.82.

Found: C, 73.82; H, 5.55; N, 7.56.

Methyl 2-(3,5-bis(benzyloxy)phenyl)acetate (86):



A mixture of diazoketone **106** (3.0 g, 8.37 mmol) and Ag_2O (freshly prepared) (3.879 g, 16.741 mmol) in methanol (15 mL) was reflux for 6 h. The solid was filtered off, washed with ethyl acetate. The filtrate was concentrated, dried (Na_2SO_4), and the

residue purified on silica gel column chromatography using EtOAc:light petroleum ether (1:9) as an eluent to obtain **86** (2.43 g) as yellowish liquid.

Yield : 80%

Mol. Formula : $C_{23}H_{22}O_4$

IR ($CHCl_3$) cm^{-1} : 3379, 3032, 2949, 1738, 1698, 1594, 1497, 1454, 1378, 1292, 1156, 1057, 1028, 834, 737,698, 632.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 3.44 (s, 2H), 3.58 (s, 3H), 4.91 (s, 4H), 6.43 (s, 3H), 7.20-7.35 (m, 10H) ppm.

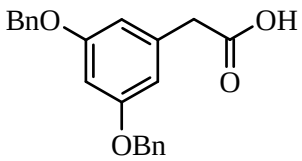
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 40.95, 53.48, 69.22, 126.87, 128.64, 128.89, 135.75, 159.75 ppm.

ESI MS (*m/z*) : 385.43 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 76.22; H, 6.12.

Found: C, 76.09; H, 6.01.

3,5-bis(benzyloxy)phenyl acetic acid (85):



LiOH (134 mg, 6.394 mmol) was added to a solution of **86** (1.16 g, 3.197 mmol) in 16 mL of H_2O/MeOH (1:3). After stirring for 12 h, the reaction mixture was neutralized with 6 N HCl and extracted with ether. Combined organic layer was dried (Na_2SO_4) concentrated and the residue purified on silica gel using EtOAc:light petroleum ether (7:3) as an eluent to obtain **85** (1.07 g) as a thick liquid.

Yield : 95%

Mol. Formula : $C_{22}H_{20}O_4$

IR ($CHCl_3$) cm^{-1} : 3066, 3017, 2930, 1709, 1595, 1453, 1376, 1294, 1216, 1160, 1057, 846, 757, 697, 668.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 3.59 (s, 2H), 5.03 (s, 4H), 6.55 (s, 3H), 7.32-7.44 (m, 10H) ppm.

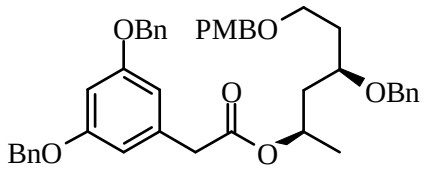
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 41.29, 69.98, 100.97, 108.57, 127.52, 127.97, 128.53, 135.22, 136.69, 160.01, 177.77 ppm.

ESI MS (*m/z*) : 371.11 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 75.84; H, 5.79.

Found: C, 74.98; H, 6.39.

(2*R*,4*R*)-4-(benzyloxy)-6-(4-methoxybenzyloxy)hexan-2-yl 2-(3,5-bis(benzyloxy)phenyl)acetate (83):



To a solution of alcohol **84** (146 mg, 0.424 mmol) and acid **85** (295 mg, 0.848 mg) in CH_2Cl_2 (5 mL) was added DCC (192 mg, 0.932 mmol) followed by DMAP (cat.). The mixture was stirred at room temperature for 3 h, filtered, and concentrated in vacuo. Purification of the crude product by flash column (5% EtOAc/hexanes) afforded ester **83** (275 mg) as a clear oil.

Yield : 96%

Mol. Formula : $C_{43}H_{46}O_7$

Optical Rotation $[\alpha]_D^{25}$: −20.1 (*c* 0.95, $CHCl_3$).

IR ($CHCl_3$) cm^{-1} 3031, 2931, 1730, 1594, 1512, 1497, 1455, 1382, 1247, 1159, 1059, 755, 697.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.11 (d, *J* = 6.2 Hz, 3H), 1.55-1.73 (m, 4H), 3.22-3.47 (m, 5H), 3.66 (s, 3H), 4.09 (d, *J* = 11.0 Hz, 1H), 4.21-4.29 (m, 3H), 4.73-4.92 (m, 4H), 5.01-5.14 (m, 1H), 6.38-6.44 (m, 3H), 6.74 (d, *J* = 8.6 Hz, 2H), 7.09-7.30 (m, 17H) ppm.

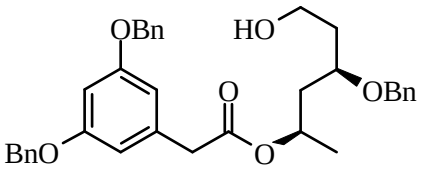
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 20.62, 34.42, 41.57, 42.05, 55.04, 66.11, 68.58, 69.85, 71.70, 72.54, 73.03, 100.66, 108.27, 113.64, 127.41, 127.48, 127.87, 127.95, 128.25, 128.44, 129.21, 130.32, 136.31, 136.68, 138.32, 159.05, 159.93, 170.64 ppm.

ESI MS (*m/z*) : 697.82 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 76.53; H, 6.87.

Found: C, 75.54; H, 7.87.

(2*R*,4*R*)-4-(benzyloxy)-6-hydroxyhexan-2-yl 2-(3,5-bis(benzyloxy)phenyl)acetate (107):



To a solution of PMB ether **83** (375 mg, 0.556 mmol) in dichloromethane/water (19:1) (5 mL) at 0 °C was added DDQ (252 mg, 1.112 mmol). The resultant slurry stirred for 0.5 h at the same temperature, and diluted with additional dichloromethane and saturated sodium bicarbonate. The organic layer was washed with sodium bicarbonate, dried (Na_2SO_4), concentrated and purified by chromatography on silica gel column chromatography (20% EtOAc/hexanes to afford alcohol **107** (289 mg,) as a clear oil.

Yield : 93%

Mol. Formula $C_{35}H_{38}O_6$

Optical Rotation $[\alpha]_D^{25}$: −32.4 (*c* 1.4, $CHCl_3$).

IR ($CHCl_3$) cm^{-1} 3436, 2927, 1728, 15.94, 1497, 1454, 1383, 1291, 1159, 1055, 849, 756, 697.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.16 (d, *J* = 6.3 Hz, 3H), 1.55-1.77 (m, 4H), 3.39-3.48 (m, 3H), 3.52-3.74 (m, 2H), 4.15 (d, *J* = 11.02 Hz, 1H), 4.28 (d, *J* = 11.01 Hz, 1H), 4.84-4.94 (m, 4H), 5.00-5.13 (m, 1H), 6.42-6.47 (m, 3H), 7.16-7.32 (m, 15H) ppm.

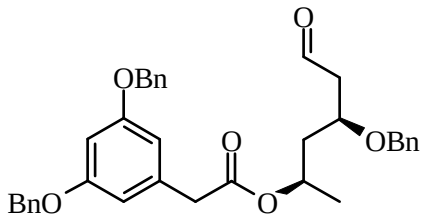
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 20.69, 36.21, 41.20, 42.19, 59.65, 68.70, 69.98, 71.81, 74.37, 100.61, 108.44, 127.49, 127.74, 127.97, 128.04, 128.43, 128.53, 136.31, 136.65, 137.97, 159.98, 170.64 ppm.

ESI MS (*m/z*) : 554.67 577.67 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 75.79; H, 6.91.

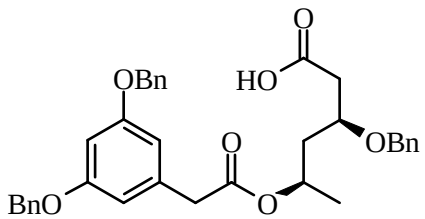
Found: C, 75.62; H, 6.81.

(2*R*,4*R*)-4-(benzyloxy)-6-oxohexan-2-yl 2-(3,5-bis(benzyloxy)phenyl)acetate (108):



To a solution of IBX (132 mg, 0.479 mmol) in DMSO (0.3 mL) at room temperature, was added alcohol **107** (133 mg, 0.239 mmol) in dry THF (5 mL). After 0.75 h of stirring, water (H_2O) was added, and diluted with ether and stirred it for additional 30 min. The solid was filtered off and from the filtrate organic layer was isolated, washed with brine, dried over Na_2SO_4, concentrated and purified by column chromatography on silica gel (20% EtOAc/hexanes to give 129 mg (97%) of **108** as a yellow colour liquid.

(3*S*,5*R*)-3-(benzyloxy)-5-(2-(3,5-bis(benzyloxy)phenyl)acetoxy)hexanoic acid (82):



The aldehyde **108** (129 mg, 0.233 mmol) was dissolved in a mixture of THF (2.9 mL), *t*-BuOH (5.6 mL), H_2O (1.4 mL) and 2-methyl-2-butene (1.8 mL). To this solution was added NaH_2PO_4 (58 mg, 0.489 mmol) and $NaClO_2$ (65 mg, 0.722 mmol) and the resulting mixture was stirred vigorously for 2 h. The volatiles were removed by evaporation, and the residue was partitioned between EtOAc and brine. The phases were separated and the aqueous phase was extracted with EtOAc(three times). The combined extract was dried (Na_2SO_4) evaporated and purified by chromatography on silica gel column chromatography (30% EtOAc/hexanes) to obtain carboxylic acid **82** (130 mg).

Yield : 98%

Mol. Formula : $C_{35}H_{36}O_7$

Optical Rotation $[\alpha]_D^{25}$: −38.6 (*c* 1.4, $CHCl_3$).

IR ($CHCl_3$) cm^{-1} : 3064, 3032, 2925, 2871, 1730, 1594, 1454, 1377, 1292, 1258, 1160, 834, 750, 698.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.12 (d, *J* = 6.3 Hz, 3H), 1.59-1.70 (m, 2H), 2.33 (dd, *J* = 6.3, 15.3 Hz, 1H), 2.48 (dd, *J* = 5.6, 15.4 Hz, 1H), 3.37 (s, 2H), 3.59-3.71 (m, 1H), 4.09 (d, *J* = 10.9 Hz, 1H), 4.29 (d, *J* = 11.0 Hz, 1H), 4.80-4.92 (m, 4H), 4.96-5.08 (m, 1H), 6.39-6.44 (m, 3H), 7.11-7.29 (m, 15H) ppm.

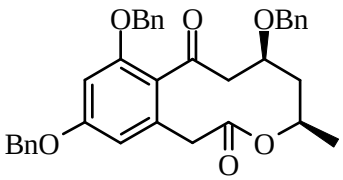
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 20.56, 39.42, 41.58, 42.10, 68.30, 69.93, 72.07, 72.26, 100.84, 108.37, 127.48, 127.78, 127.93, 128.05, 128.40, 128.51, 136.23, 136.77, 137.70, 160.03, 170.75, 176.54 ppm.

ESI MS (*m/z*) : 591.66 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 73.92; H, 6.38.

Found: C, 73.81; H, 6.21.

(4*R*,6*S*)-6,9,11-tris(benzyloxy)-4-methyl-4,5,6,7-tetrahydro-1*H*-benzo[*d*]oxecine-2,8-dione (81):



The acid **82** (115 mg, 0.202 mmol) was dissolved in a mixture of trifluoroacetic acid (4 mL) and trifluoroacetic acid anhydride (0.8 mL) under argon. The solution was stirred for 20 min at 50 ^oC, poured into an excess of sodium hydrogen carbonate, extracted with ether, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (hexanes/EtOAc, 4:1) to give the macrolactone **81** (91 mg) as a colorless liquid.

Yield : 82%

Mol. Formula : $C_{35}H_{34}O_6$

Optical Rotation $[\alpha]_D^{25}$: −4.4 (*c* 0.9, $CHCl_3$).

IR ($CHCl_3$) cm^{-1} : 3064, 3031, 2923, 2853, 1731, 1680, 1601, 1579, 1497, 1454, 1434, 1378, 1334, 1240, 1158, 1072, 913, 753, 697.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.14 (d, *J* = 6.2 Hz, 3H), 1.77-1.86 (m, 1H), 1.98 (d, *J* = 14.5 Hz, 1H), 3.11 (d, *J* = 15.1 Hz, 1H), 3.18 (dd, *J* = 9.6, 15.4 Hz, 1H), 3.35 (d, *J* = 18.9 Hz, 1H), 3.92 (t, *J* = 9.6 Hz, 1H), 4.18 (d, *J* =18.9 Hz, 1H), 4.36 (d, *J* = 11.3 Hz, 1H), 4.43 (d, *J* = 11.3 Hz, 1H), 4.85-4.91(m, 1H), 4.97 (s, 2H), 5.60-5.05 (m, 2H), 6.30 (s, 1H), 6.48 (d, *J* = 2.1 Hz, 1H), 7.19-7.33 (m, 15H) ppm.

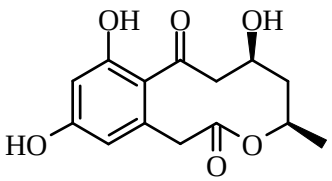
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 20.91, 29.68, 40.35, 43.96, 52.28, 70.24, 70.51, 70.85, 71.79, 99.08, 109.05, 124.88, 127.55, 127.63, 127.73, 128.28, 128.41, 128.71, 134.51, 136.03, 136.23, 138.17, 158.15, 160.54, 168.84, 204.74 ppm.

ESI MS (*m/z*) 573.62 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 76.34; H, 6.22.

Found: C, 76.21; H, 6.09.

(4*R*,6*S*)-6,9,11-trihydroxy-4-methyl-4,5,6,7-tetrahydro-1*H*-benzo[*d*]oxecine-2,8-dione (49):



To a solution of **81** (91 mg, 0.165 mmol) was added 10% Pd/C (cat.) and stirred under H_2 atmosphere at normal temperature and pressure for 12 h. The reaction mixture was filtered through a pad of Celite, concentrated and the residue purified on silica gel column chromatography using EtOAc:$CHCl_3$ (1:1) as an eluent to give **49** (47 mg).

Yield : 97%

Mol. Formula $C_{14}H_{16}O_6$

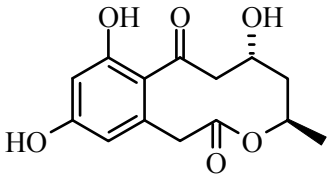
Optical Rotation $[\alpha]_D^{25}$: + 50.9 (*c* 0.9, $CHCl_3$).

IR ($CHCl_3$) cm^{-1}	: 3352, 2923, 2853, 1703, 1640, 1618, 1590, 1463, 1376, 1214, 1158, 1048, 836, 761, 669.
^{1}H NMR (DMSO-d_6, 400 MHz)	: δ 1.07 (d, *J* = 6.20 Hz, 3H), 1.65 (ddd, *J* = 9.8, 11.40, 14.40 Hz, 1H), 1.82 (d, *J* = 14.22 Hz,1H), 2.81 (d, *J* = 15.01 Hz, 1H), 3.08 (dd, *J* = 10.34, 15.01 Hz, 1H), 3.47 (d, *J* = 18.9 Hz, 1H), 3.82 (d, *J* = 18.9 Hz, 1H), 3.95 (bt, *J* = 9.9 Hz, 1H), 4.71-4.75 (m, 2H), 6.09 (s, 1H), 6.27 (d, *J* = 1.65 Hz, 1H), 9.70 (s, 1H), 9.90 (s, 1H) ppm.
^{13}C NMR (DMSO-d_6, 100 MHz)	: δ 20.94, 31.43, 46.20, 55.46, 6800, 70.78, 101.44, 109.43, 121.34, 134.61, 157.24, 159.27, 169.01, 204.77 ppm.
ESI MS (*m/z*)	: 303.27 $[M+Na]^+$
Elemental Analysis	**Calcd:** C, 59.99; H, 5.75.
	Found: C, 59.88; H, 5.63.

CHAPTER 1

SECTION II

Total Synthesis of Xestodecalactone B



Xestodecalactone B (**48**)

Figure 25

The salient feature of the structure of xestodecalactone B (**48**) is the presence of a 1,3-dihydroxybenzene ring embedded in macrolactone moiety with two stereogenic centers (Figure 25). Xestodecalactone B **(48)**[28] was found to be active against the yeast *C. albicans.* Using the agar diffusion assay, it caused inhibition zones of 25, 12, and 7 mm at concentrations of 100, 50, and 20 μmol, respectively.

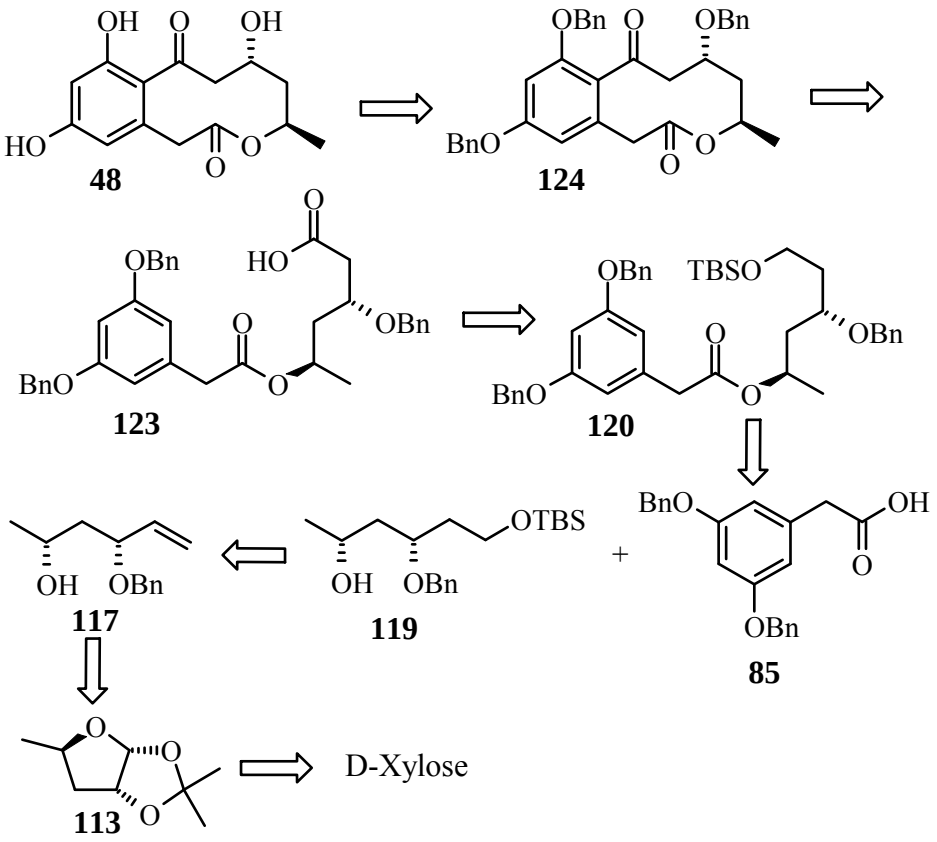
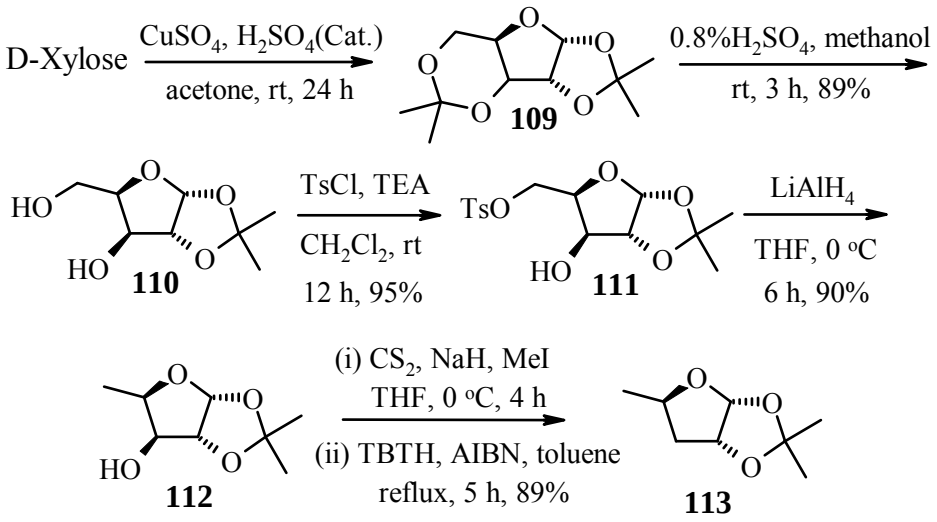


Figure 26: *Retrosynthetic analysis of xestodecalactone B (**48**)*

The basic strategy for the synthesis of xestodecalactone B (**48**) is delineated in the retrosynthetic analysis (Figure 26). An appealing strategy for the convergent synthesis of xestodecalactone B (**48**) could be envisaged by the efficient synthesis of the hydroxyl segment **119** from D-xylose by appropriate functionalization of sugar backbone and the installation of macrolide core using intramolecular acylation. In the synthetic direction, it was anticipated that the acid precursor **123** required for intramolecular acylation approach could be obtained from **120** by DCC mediated coupling between alcohol **119** and acid **85**, and the subsequence functional group transformations of ester **120** moiety. The sequential hydroboration and oxidation of olefinic group and the concomitant selective conversion to TBS ether of primary hydroxyl group of **117** would lead to alcohol **119**. The olefin **117** could easily be synthesized from 3,5-dideoxy-xylose derivative **113** that in turn could be realized from D-xylose by employing literature procedures.[72]

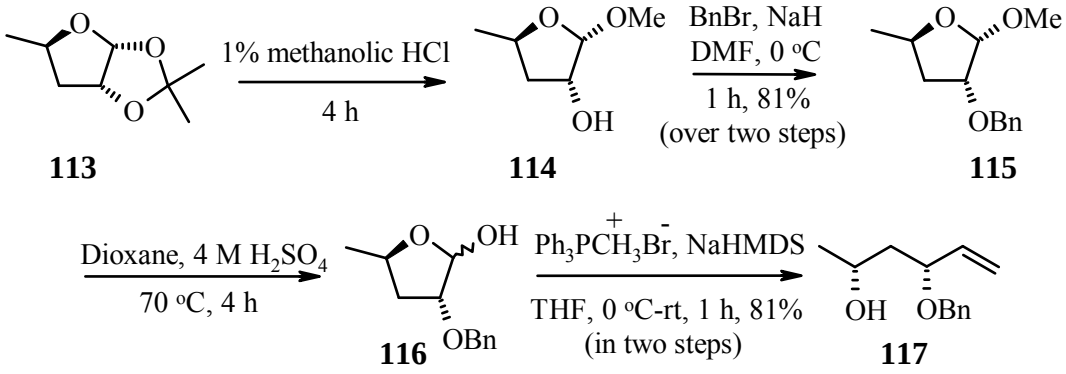
The retrosynthetic analysis outlined in Figure 26 identified compound **117** as a potential synthetic intermediate, and its synthesis would be the first milestone of the synthetic objective in the total synthesis of xestodecalactone B (**48**). For that task, compound **113** was chosen as an appropriate precursor, which could be obtained from D-xylose in six steps. Thus, D-xylose was transformed into 1,2:3,5-di-*O*-isopropylidene-α-D-xylofuranose **109** by combined action of acetone and anhydrous $CuSO_4$ in presence of conc. H_2SO_4 (cat.). Subsequent cleavage of the 3,5-isopropylidene group was carried out using aqueous 0.8% H_2SO_4 (cat) in methanol to afford 1,2-*O*-isopropylidene-α-D-xylofuranose **110**. The primary hydroxyl group of **110** was deoxygenated by making it tosyl ester **111,** followed by LAH treatment. For the execution of Barton-McCombie reaction, the compound **112** was first converted into the corresponding xanthate derivative using CS_2, NaH, MeI in THF at 0 ^oC, and then treatment of *n*-Bu_3SnH and catalytic AIBN was affected to furnish the 3,5-dideoxy product **113** in 89% yield, for two steps. The C3 deoxygenation in **113** was well supported by ^1H NMR, ^{13}C NMR and mass spectral studies together with elemental analysis. The ^{13}C NMR and DEPT spectrum of **38** showed the corresponding resonances for C3 methylenic moieties, and the mass spectrum also in support of the assigned structure (Scheme 13). The rotation value of this

compound was {$[\alpha]_D^{25}$ −10.8 (*c* 1.1, $CHCl_3$)}, which was agreeable with reported value { $[\alpha]_D^{25}$ −11.2 (*c* 1.0 $CHCl_3$)}.[72]



Scheme 13

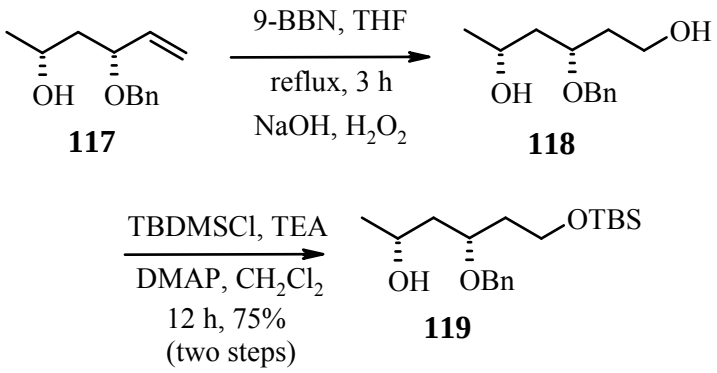
The treatment of **113** with 1% methanolic HCl resulted in the cleavage[73] of the 1,2-isopropylidene moiety and concomitant methyl glycosidation to give **114** with inseparable mixture of byproduct. The crude product was subjected to the treatment of BnBr, NaH in DMF to furnish **115**. The product formation was secured by spectral as well as elemental analysis beyond doubt. The ^{1}H NMR spectrum of **115** indicated the corresponding resonances at δ 4.29-4.52 ppm (m, *Ph-<u>CH2</u>*) and at δ 7.14-7.30 (m, *<u>Ph</u>-CH2*) supporting the presence of benzyl ether moiety (Scheme 14).



Scheme 14

Having had the compound **115** in hand, our immediate concern was the transformation of **115** into the corresponding olefin derivative **117**. Thus, **115** was hydrolyzed using aqueous 0.4% H_2SO_4 in dioxane[74] at 70 °C to afford **116**, which was

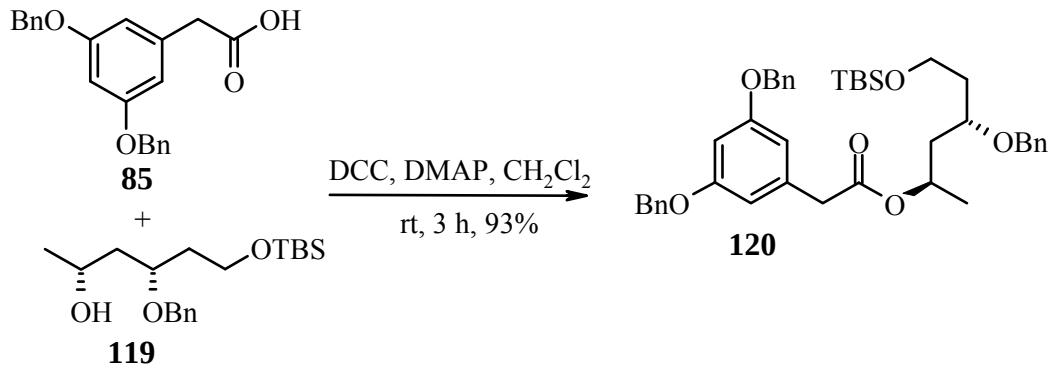
immediately reacted with methylenetriphenylphosphorane [generated from $Ph_3P^+CH_3Br^-$ by the action of *n*-BuLi in THF at 0 ^oC] to furnish olefin derivative **117** without any further purification. The structure of olefin **117** was well supported by ^1H NMR, ^{13}C NMR studies together with elemental analysis. The ^1H NMR spectrum indicated presence of two olefinic protons in the region of δ 5.12-5.19 (*CH*$_2$=) and 5.57-5.75 (*CH*=) ppm, while the EI mass recorded the mass peak at *m/z* 229.3 $[M+Na]^+$.



Scheme 15

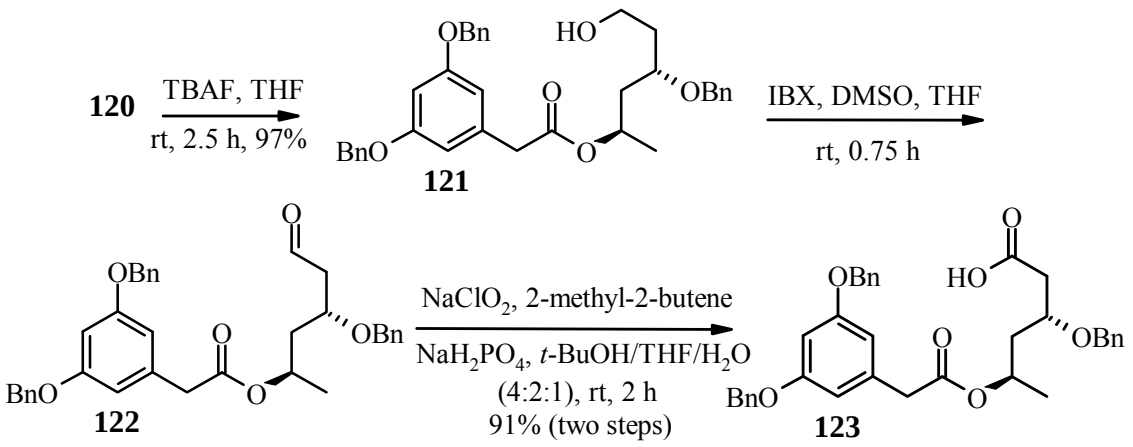
Hydroboration of olefin **117** using 9-BBN[63] in THF in refluxing condition followed by the *in vivo* oxidation of the resulted alkyl boronate with H_2O_2 provided diol **118** (Scheme 15). At this juncture, the spectral characterization was a difficult job since the polarity of diol compound **118** and 9-BBN byproduct was indistinguishable. Consequently, we proceeded forward to our synthetic direction without further purification. Selective protection of the primary hydroxyl moiety of **118** as TBDMS ether[60] was accomplished using TBDMSCl and triethylamine in anhydrous CH_2Cl_2 at room temperature to deliver **119** in 86% yield. The ^1H NMR spectrum of **119** revealed three clear singlet resonances corresponding to TBDMS group at δ 0.02 (3 H), 0.04 (3 H) and 0.88 ppm (9 H). It was further confirmed by the ^{13}C NMR spectrum of **119**, which showed resonances at δ –5.40, 18.20, and 25.80 ppm.

Having accomplished the synthesis of both the fragments **119** and **85 (**synthesis of acid **85** discussed in the previous section**)**, the esterification was accomplished using DCC[67], DMAP in anhydrous dichlomethane to furnish the ester **120**. In the IR spectrum, ester carbonyl absorption was observed at 1729 $cm.^{-1}$ The ^1H NMR, ^{13}C NMR spectra and elemental analysis data were in good agreement with the assigned structure (Scheme 16).



Scheme 16

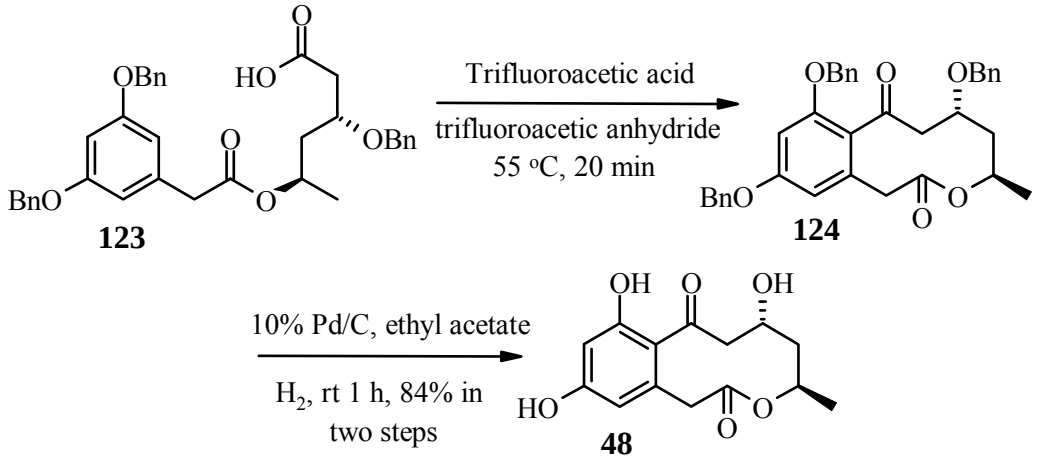
Compound **120** was desilylated with TBAF in anhydrous THF at 0 °C to give the hydroxyl compound **121**. The ^{1}H NMR, ^{13}C NMR spectra and elemental analysis were in support of the structure of **121** (Scheme 17). The hydroxyl compound **121** was first subjected to the treatment of IBX in DMSO/THF at room temperature to furnish the aldehyde **122** which was transformed in to the corresponding acid **123** by using $NaClO_2$ in *t*-BuOH/THF/H_2O in the presence of phosphate buffer.[69] The ^{1}H NMR and ^{13}C NMR spectra of **123** were compatible with the assigned structure.



Scheme 17

Now the stage was set to perform the central transformation of our synthetic endeavor to accomplish the macrolactone core. Accordingly, the acid **123** was treated with trifluoroacetic acid/trifluoroacetic anhydride[70] at 55 °C to provide **124**. Unfortunately, attempted purification of the reaction mixture was failed due to the decomposition of the desired product **124** on standing (Scheme 46). Thus, we proceeded for the next reaction without further purification. Finally, cleavage of the benzyl ethers

were accomplished using Pd/C in ethyl acetate to afford **48** whose spectral data matched with those reported by Proksch *et al* for the natural product.[28]



Scheme 18

Table 2. ***NMR spectral data of xestodecalactone B (Natural product)[28] and compound 48***

^{1}H NMR (400 MHz, DMSO-d_6) Natural product	**^{1}H NMR (200 MHz, DMSO-d_6) compound 48**	**^{13}C NMR 125MHz, DMSO-d_6) Natural product**	**^{13}C NMR (50 MHz, DMSO-d_6) compound 48**
1.15 (d, J = 6.4Hz)	1.15 (d, 6.4 Hz, 1H)	19.53 (q)	19.83(q)
1.73 (ddd, J = 3.2, 6.9, 14.6 Hz)	1.70-1.75 (m, 1H)	37.83 (t)	40.41 (t)
1.87 (ddd, J = 4.0, 7.3, 14.6 Hz)	1.83-1.87 (m, 1H)	41.98 (t)	42.25(t)
2.60 (dd, J = 9.5, 14.4 Hz)	2.60(dd, J = 9.5, 14.5 Hz, 1H)	52.48 (t)	52.74(t)
3.48 (bdd, J = 2.6, 14.5 Hz)	3.42-3.46 (m, 2H)	64.13 (d)	64.48(d)
3.53 (d, 17.3 Hz)		68.18 (d)	68.55(d)
3.63 (d, J = 17.3 Hz)	3.58-3.63 (m, 1H)	101.22 (d)	101.58(d)
4.02 (m)	3.98-4.03 (m, 1H)	109.85 (d)	110.19(d)
4.81 (ddq, 4.3, 6.4, 6.4 Hz)	4.78-4.86 (m, 2H)	119.67 (s)	120.07(s)
		135.48 (s)	135.77(s)
6.11 (d, J = 2.2 Hz)	6.11(d, J = 2.2 Hz, 1H)	156.84 (s)	157.13(s)
6.27 (d, J = 2.2 Hz)	6.25 (d, J = 2.2 Hz, 1H)	159.07 (s)	159.36(s)

9.8 (brs)	9.83 (brs, 1H)	169.18 (s)	169.42(s)
9.8 (brs)	10.05 (brs, 1H)	205.04 (s)	205.48(s)

There was a very good correlation of the ^{1}H NMR, ^{13}C NMR spectrum of our synthetic compounds (**48**, **49**) with that of isolation paper (natural products) as can be seen in table 2 (and table 1, Previous section), but opposes the spectral data of the previously reported synthesis.[71] In isolation paper[28], the *cis*,*trans*-stereochemistry about the protons at C9 and C11 (of **48** and **49**) was based on HPLC-WET-ROESY data and other spectral analysis.

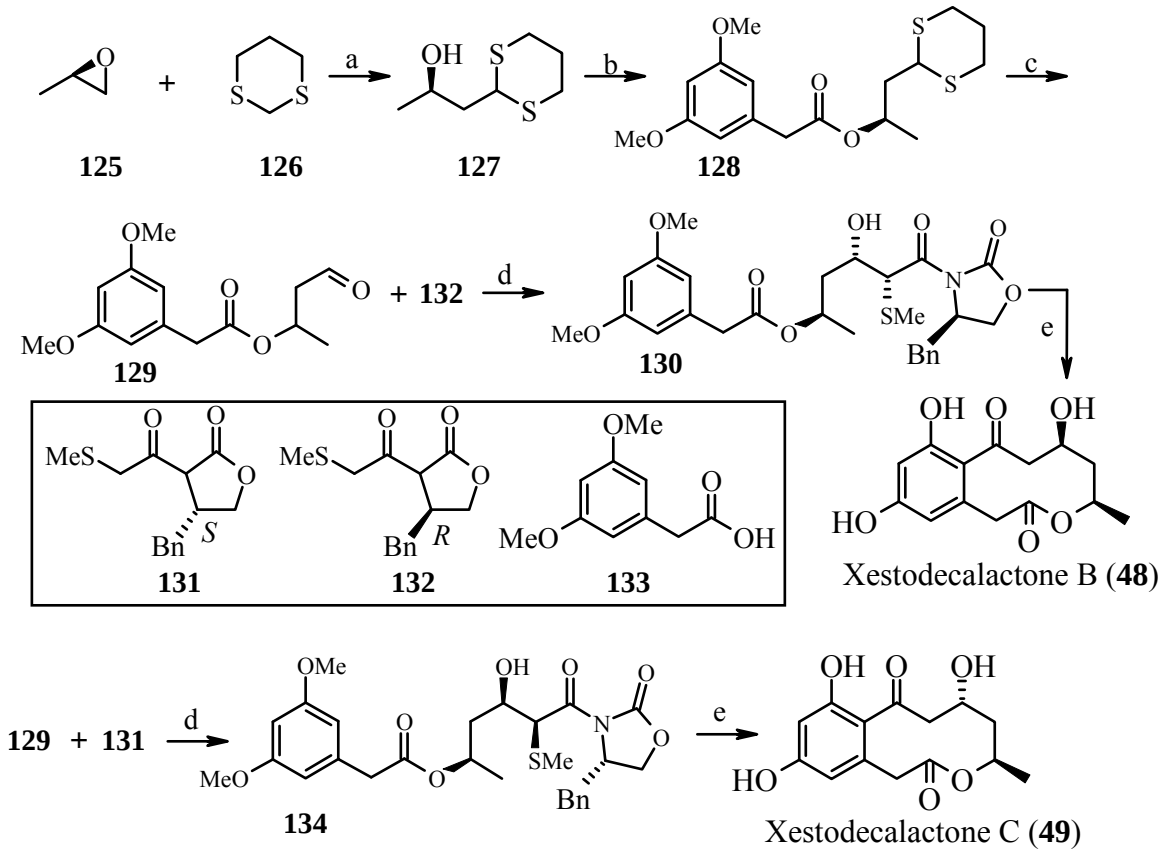
The absolute stereochemistry of xestodecalactone B (**48**) and C (**49**) had been assigned on the assumption that the carbohydrate moiety (Xylose and Mannose) has the usual D-configuration. The close correlations of the ^{1}H-NMR data of the natural product and **48** (and **49**) as well as the ^{13}C NMR data are in accord with the proposed relative stereochemistry of the sugar moiety and macrocycle. Hence, on the basis of the synthetic and spectroscopic studies reported herein, we propose that the assign structures of xestodecalactone C (**49**) and B (**48**) should be interchanged. However, the absolute configurations assigned are allright, the unexpected diastereoselection in Evans reactions might have helped Pan and co-workers to arrive at the wrongly assigned structure.

In conclusion we have completed the chiral pool based total synthesis of the isolated structure for xestodecalactone B (**48**) and C (**49**) and found that these were in fact a diastereomer of the reported synthesis.

Other Approach

1. *Pan's et al.(2007)*[71]

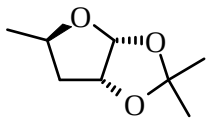
The first asymmetric total syntheses of xestodecalactones **B** (**48**) and **C** (**49**) had been accomplished by Pan *et al.* The key steps involved the utility of Evans oxazolidinone-mediated *syn*-aldol condensations to establish the C-9 configuration and the macrolide ring formation by intramolecular acylation. The absolute configurations of xestodecalactones **B** (**48**) and **C** (**49**) were first determined via these syntheses.



Scheme 19: *Reagents and conditions*: a) *n*-BuLi, HMPA, THF, 0 to −78 °C; b) **133**, DCC, DMAP, Et_2O, rt; c) PdO_2, $BF_3{\cdot}Et_2O$, THF/H_2O, rt; d) *n*-Bu_2BOTf, TEA, CH_2Cl_2, −78 °C; e) (i) Ac_2O, pyridine, rt; (ii) AIBN, *n*-Bu_3SnH, benzene, reflux; (iii) H_2O_2, LiOH, THF/H_2O, 0 °C; (iii) TFA/TFAA, reflux; (iv) AlI_3, $Bu_4N^+I^-$, benzene, rt; (v) AcCl/MeOH, 0 °C.

Experimental

3,5-Dideoxy-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranose (113)



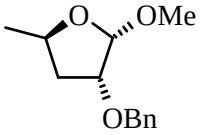
To a solution of hydroxyl compound **112** (5.0 g, 28.73 mmol) in THF (90 mL) at 0 ^{o}C, NaH (1.72 g, 60% in oil, 43.10 mmol) was added. After being stirred for 30 minutes, carbon disulphide (3.4 mL, 57.47 mmol) was added. After an interval for 30 minutes, MeI (3.6 mL, 57.47 mmol) was added. The reaction mixture was stirred for 2.5 h, quenched with water and evaporated to leave the residue, which was taken in ethyl acetate. The organic layer was washed with water and brine, dried (Na_2SO_4), and concentrated to afford the crude, which was used for next reaction without further purification.

To a solution of xanthate and AIBN (cat.) in toluene (100 mL), TBTH (15.2 mL, 57.47 mmol) was added. The reaction mixture was refluxed for 6 h, concentrated *in vacuum* and purified by silica gel column chromatography (ethyl acetate in hexane) to afford **113** (4.0 g) as colourless oil.

Yield	: 89% over two steps.
Mol. Formula	: $C_8H_{14}O_3$
IR ($CHCl_3$) cm^{-1}	: 2989, 2936, 1384, 1217, 1165, 1075, 1013, 760.
Optical Rotation $[\alpha]_D^{25}$	: −10.8 (c 1.0 $CHCl_3$).
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.28 (d, J = 6.21 Hz, 3H), 1.30 (s, 3H), 1.40 (dd, J = 2.45, 4.75 Hz, 1H), 1.49 (s, 3H), 2.09 (dd, J = 4.07, 13.26 Hz, 1H), 4.24-4.35 (m, 1H), 4.68-4.72 (m, 1H), 5.78 (d, J = 3.85 Hz, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 19.26, 26.07, 26.57, 40.75, 73.74, 80.91, 105.34, 110.62 ppm.
ESI MS (*m/z*)	: 181.2 $[M+ Na]^+$
Elemental Analysis	**Calcd:** C, 60.74; H, 8.92.

Found: C, 60.64; H, 8.75.

Methyl 2-benzyloxy-3,5-dideoxy-α-D-*erythro*-pentofuranoside (115):

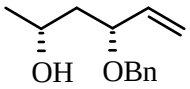


A solution of compound **(113)** (3.0 g, 18.98 mmol) in 1% methanolic HCl (200 mL) was stirred at room temperature for 4 h. Triethylamine (excess) was added to neutralize acid and the stirring continued for 30 minutes. Evaporation of the solvent provided crude **114**, which was used for next reaction without further purification.

To an ice-cooled solution of **114** in dry DMF (80 ml), NaH (60% dispersion in oil, 1.52 g, 37.97 mmol) was added. After 30 minutes, benzyl bromide (3.4 mL, 28.48 mmol) was introduced and stirred for additional 1 h. The reaction mixture was partitioned between water and ethyl acetate. The organic layer was washed with water, brine, dried (Na_2SO_4) and concentrated. The residue was purified on a silica gel column chromatography using petroleum ether /EtOAc (10/1) as the eluant to afford **115** (3.4 g) as colorless oil.

Yield	: 81% over two steps.
Mol. Formula	: $C_{13}H_{18}O_3$
IR ($CHCl_3$) cm^{-1}	: 2973, 2929, 1454, 1376, 1192, 1131, 1065, 1028, 755, 697.
Optical Rotation $[\alpha]_D^{25}$	: −48.2 (c 1.95, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.22 (d, J = 6.25 Hz, 3H), 1.64 (ddd, J = 5.11, 8.93, 18.93 Hz, 1H), 1.04 (dd, J = 6.22, 13.25 Hz, 1H), 3.26 (s, 3H), 3.90 (d, J = 5.11 Hz, 1H), 4.29-4.52 (m, 3H), 4.82 (S, 1H), 7.14-7.30 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 22.95, 37.30, 54.13, 71.12, 75.81, 83.73, 106.96, 127.51, 127.59, 128.32, 137.94 ppm.
ESI MS (*m/z*)	: 245.3 $[M+ Na]^+$
Elemental Analysis	**Calcd:** C, 70.24; H, 8.16.
	Found: C, 70.06; H, 8.10.

(2*R*,4*R*)-4-(benzyloxy)hex-5-en-2-ol (117):

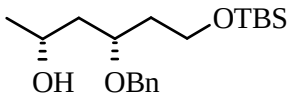


A stirred solution of compound **115** (2.0 g, 8.99 mmol) and aq. 0.4% H_2SO_4 (9.7 mL) in 1,4-dioxane (30 mL) was heated at 70 ^oC for 6 h. Reaction mixture was neutralized by addition of solid $NaHCO_3$, filtered, concentrated and the residue partitioned between EtOAc and water. Combined organic layer was washed with brine, dried (Na_2SO_4), concentrated and residue purified on silica gel column chromatography using EtOAc:light petroleum ether (6:4) to obtain lactol **116**, the crude lactol was used immediately for the next reaction.

To a suspension of salt $Ph_3P^+CH_3Br^-$ (9.6 g, 26.99 mmol) in THF (80 mL) at 0 ^oC, was added NaHMDS (13.5 mL, 1M solution in toluene) dropwise. After 1 h stirring at the same temperature, the crude lactol **116** in THF was added slowly. After stirring at room temperature for overnight reaction was quenched with saturated solution of NH_4Cl, and extracted with ether. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. Purification was done by silica gel (60-120 mesh) column chromatography to afford alkene **117** (1.5 g) as yellow colour liquid.

Yield	: 81% over two steps
Mol. Formula	: $C_{13}H_{18}O_2$
IR ($CHCl_3$) cm^{-1}	: 3401, 2969, 2930, 1497, 1454, 1218, 1070, 1026, 934, 755, 698.
Optical Rotation $[\alpha]_D^{25}$	: + 50 (c 0.8 $CHCl_3$).
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.06 (d, J = 6.28 Hz, 3H), 1.46-1.73 (m, 2H), 3.46 (bs, 1H), 3.88-3.97 (m, 2H), 4.27 (d, J = 11.62 Hz, 1H), 4.55 (d, J = 11.62 Hz, 1H), 5.12-5.19 (m, 2H), 5.57-5.75 (m, 1H), 7.17-7.23 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 23.31, 44.02, 67.45, 70.09, 81.17, 117.71, 127.71, 127.83, 128.45, 129.36, 137.91 ppm.
ESI MS (*m/z*)	: 229.3 $[M+ Na]^+$
Elemental Analysis	**Calcd:** C, 75.69; H, 8.80.
	Found: C, 75.55; H, 8.65.

(2*R*,4*S*)-4-(benzyloxy)-6-(*tert*-butyldimethylsiloxy)hexan-2-ol (119):

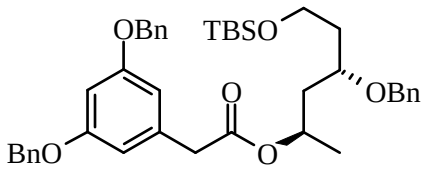


To a solution of **117** (1 g, 4.85 mmol) in THF (15 mL) was added 9-BBN (1.78 g, 14.56 mmol) at 0 ^{o}C. The reaction mixture was warmed up to reflux. After 3 h of stirring, NaOH and H_2O_2 (30%) were added. The mixture was extracted with ether, washed with brine. The organic layers were combined and dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure vacuum. The residue was used for next reaction without further purification.

To a solution of crude **118**, Et_3N (1.0 mL, 7.28 mmol) and DMAP (catalytic) in CH_2Cl_2 (20 mL) was added TBDMSCl (800 mg, 5.34 mmol) at room temperature. The reaction mixture was stirred for over night, diluted with CH_2Cl_2, washed with water, brine, dried (over Na_2SO_4) and concentrated. The residue was purified on silica gel column chromatography by using EtOAc:hexane (1:3) to give **119** (1.37 g) as colourless liquid.

Yield	: 86% over two steps
Mol. Formula	: $C_{19}H_{34}O_3Si$
IR ($CHCl_3$) cm^{-1}	: 3369, 2929, 2856, 1384, 1255, 1094, 835, 755, 697.
Optical Rotation $[\alpha]_D^{25}$	: + 26.0 (c 0.6 $CHCl_3$).
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.02 (s, 3H), 0.04 (s, 3H), 0.88 (s, 9H), 1.13 (d, J = 6.22 Hz, 3H), 1.64-1.69 (m, 4H), 3.65-3.82 (m, 4H), 4.44 (d, J = 11.31 Hz, 1H), 4.63 (d, J = 11.31 Hz, 1H), 7.26-7.31 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ –5.40, -3.62, 18.20, 23.50, 25.87, 36.81, 43.13, 59.37, 67.60, 70.83, 77.42, 127.79, 127.92, 128.49, 137.91 ppm.
Elemental Analysis	**Calcd:** C, 67.40; H,10.12.
	Found: C, 67.24; H, 10.23.

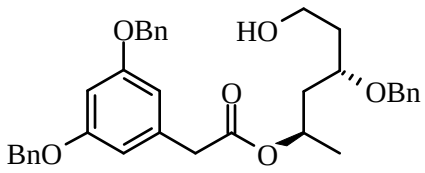
(2*R*,4*S*)-4-(benzyloxy)-6-(*tert*-butyldimethylsiloxy)hexan-2-yl 2-(3,5-bis(benzyloxy)phenyl)acetate (120):



To a solution of alcohol **119** (250 mg, 0.74 mmol) and acid **85** (515 mg, 1.48 mg) in CH_2Cl_2 (8 mL) was added DCC (335 mg, 1.63 mmol) followed by DMAP (cat.). The mixture was stirred at room temperature for 2 h, filtered, and concentrated in vacuo. Purification by flash column chromatography (5% EtOAc/hexanes) afforded ester **120** (459 mg) as a clear oil.

Yield	: 93%
Mol. Formula	: $C_{41}H_{52}O_6Si$
IR ($CHCl_3$) cm^{-1}	: 2928, 1729, 1595, 1453, 1218, 1158, 1059, 835, 772, 697.
Optical Rotation $[\alpha]_D^{25}$	: −9.1 (c 1.1 $CHCl_3$).
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.30 (s, 6H), 1.15 (s, 9H), 1.44 (d, J = 6.19 Hz, 3H), 1.85-1.92 (m, 1H), 1.95-2.05 (m, 2H), 2.15-2.29 (m, 1H), 3.74 (s, 2H), 3.78-3.98 (m, 3H), 4.70 (s, 2H), 5.20-5.37 (m, 5H), 6.78 (s, 3H), 7.51-7.66 (m, 15H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ –5.32, 18.25, 20.24, 25.97, 37.12, 40.29, 41.95, 49.36, 69.12, 69.98, 70.72, 73.10, 108.44, 127.50, 127.78, 127.95, 128.32, 128.55, 136.29, 136.81, 138.63, 159.98, 170.56 ppm.
ESI MS (*m/z*)	: 668.35 $[M+ Na]^+$
Elemental Analysis	**Calcd:** C, 73.62; H, 7.84.
	Found: C,73.55; H, 7.77.

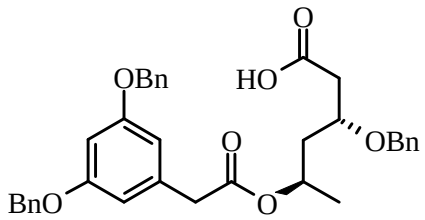
(2*R*,4*S*)-4-(benzyloxy)-6-hydroxyhexan-2-yl 2-(3,5-bis(benzyloxy)phenyl)acetate (121):



To a solution of **120 (**350 mg, 0.52 mmol) in THF (5 mL) was added tetrabutylammonium fluoride **(**1 M in THF, 0.8 mL) at 0 ^{o}C. The mixture was stirred at room temperature for 4 h, concentrated in *vacuo*, and then added to water. The aqueous layer was extracted with ether**.** The combined organic layers were dried (Na_2SO_4) and evaporated in *vacuo.* Flash column chromatography of the residue on silica gel with ethyl acetate: petroleum ether (3:7) yielded alcohol **121** (281 mg) as a colorless oil

Yield	: 97%
Mol. Formula	: $C_{35}H_{38}O_6$
IR ($CHCl_3$) cm^{-1}	: 3393, 2929, 1728, 1594, 1453, 1292, 1158, 1054, 770, 697.
Optical Rotation $[\alpha]_D^{25}$	: −18.5 (c 1.77 $CHCl_3$).
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.14 (d, J = 6.25 Hz, 3H), 1.48-1.77 (m, 3H), 1.88-2.01 (m, 1H), 2.36 (bs, 1H), 3.42-3.63 (m, 5H), 4.25 (d, J = 11.36 Hz, 1H), 4.39 (d, J = 11.36 Hz, 1H), 4.85-4.97 (m, 5H), 6.45 (s, 3H), 7.15-7.33 (m, 15H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 20.48, 35.94, 39.84, 41.99, 60.27, 68.65, 69.99, 70.80, 75.27, 100.60, 108.43, 127.48, 127.70, 127.76, 127.94, 128.40, 128.50, 136.21, 136.66, 138.02, 159.98, 170.76 ppm.
ESI MS (*m/z*)	: 577.27 $[M+ Na]^+$
Elemental Analysis	**Calcd:** C, 75.79; H, 6.91.
	Found: C, 75.64; H, 7.09.

(3*R*,5*R*)-3-(benzyloxy)-5-(2-(3,5-bis(benzyloxy)phenyl)acetoxy)hexanoic acid (123):



To a solution of IBX (199 mg, 0.72 mmol) in DMSO (0.5 mL) at room temperature, was added alcohol **121** (200 mg, 0.36 mmol) in dry THF (5 mL). After 0.75 h of stirring, water (H_2O) was added, and diluted with ether and stirred it for additional 30 min. The solid was filtered off and from the filtrate organic layer was isolated, washed with brine, dried over Na_2SO_4, concentrated and purified by column chromatography on silica gel (20% EtOAc/hexanes) to give **122** as a yellow colour liquid

The aldehyde **122** was dissolved in a mixture of THF (2.9 mL), *t*-BuOH (5.6 mL), H_2O (1.4 mL) and 2-methyl-2-butene (2.8 mL). To this solution was added NaH_2PO_4 (90 mg, 0.76 mmol) and $NaClO_2$ (101 mg, 1.11 mmol) and the resulting mixture was stirred vigorously for 2 h. The volatiles were removed by evaporation, and the residue was partitioned between EtOAc and brine. The phases were separated and the aqueous phase was extracted with EtOAc(three times). The combined extract was dried (Na_2SO_4), evaporated and purified by chromatography on silica gel column chromatography (30% EtOAc/hexanes) to obtain carboxylic acid **123** (186 mg)

Yield : 91% over two steps

Mol. Formula : $C_{35}H_{36}O_7$

IR ($CHCl_3$) cm^{-1} :3361, 2926, 1720, 1706, 1594, 1292, 1159, 1058, 771, 697.

Optical Rotation $[\alpha]_D^{25}$: −3.6 (c 0.95, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.12 (d, J = 6.24 Hz, 3H), 1.63-1.67 (m, 1H), 1.91-1.96 (m, 1H), 2.48-2.51 (m, 2H), 3.40 (d, J = 15.10 Hz, 1H), 3.44 (d, J = 15.10 Hz, 1H), 3.75-3.81 (m, 1H), 4.35 (d, J = 11.41 Hz, 1H), 4.41 (d, J = 11.41 Hz, 1H), 4.90-5.01 (m, 5H), 6.45 (s, 3H), 7.17-7.33 (m, 15H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 20.16, 39.05, 40.05, 41.91, 68.53, 69.99, 71.32,

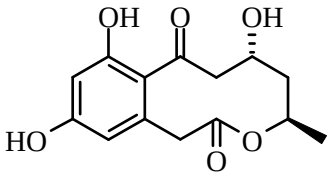
72.71, 100.78, 108.43, 127.52, 127.74, 127.81, 127.94, 128.38, 128.53, 131.90, 133.35, 136.13, 136.76, 137.79, 141.83, 159.99, 170.80, 176.35 ppm.

ESI MS (*m/z*) : 591.25 $[M+ Na]^+$

Elemental Analysis **Calcd:** C, 73.92; H, 6.38.

Found: C, 74.09; H, 6.21.

(4*R*,6*R*)-6,9,11-trihydroxy-4-methyl-4,5,6,7-tetrahydro-1*H*-benzo[*d*]oxecine-2,8-dione (48):



The acid **123** (27 mg, 0.05 mmol) was dissolved in a mixture of trifluoroacetic acid (1 mL) and trifluoroacetic acid anhydride (0.2 mL) under argon. The solution was stirred for 20 min at 50 ^oC, poured into an excess of sodium hydrogen carbonate, extracted with ether, dried (Na_2SO_4), and concentrated in vacuo. The residue was used for next reaction without further purification.

To a solution of crude **124** in ethyl acetate (3 mL) was added 10% Pd/C (cat.) and stirred under H_2 atmosphere at normal temperature and pressure for 12 h. The reaction mixture was filtered through a pad of Celite, concentrated and the residue purified on silica gel using EtOAc:$CHCl_3$ (1:1) as an eluent to give **48** (11 mg)

Yield : 84%

Mol. Formula : $C_{14}H_{16}O_6$

IR ($CHCl_3$) cm^{-1} : 3420, 2920, 2853, 1710, 1650, 1617, 1580, 1376, 1214, 1043, 826, 761, 669.

Optical Rotation $[\alpha]_D^{25}$ +16.5 (c 0.5 CH_3OH).

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.15 (d, *J* = 6.4 Hz, 1H), 1.70-1.75 (m, 1H), 1.83-1.87 (m, 1H), 2.60 (dd, *J* = 9.5, 14.5 Hz, 1H), 3.42-3.46 (m, 2H), 3.58-3.63 (m, 1H), 3.98-4.03 (m, 1H), 4.78-4.86 (m, 2H), 6.11 (d, *J* = 2.2 Hz, 1H), 6.25 (d, *J*

	= 2.2 Hz, 1H), 9.83 (brs, 1H), 10.05 (brs, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 19.83, 40.41, 42.25, 52.74, 64.48, 68.55, 101.58, 110.19, 120.07, 135.77, 157.13, 159.36, 169.42, 205.48 ppm.
ESI MS (*m/z*)	: 303.20 $[M+Na]^+$
Elemental Analysis	**Calcd:** C, 59.99; H, 5.75.
	Found: C, 59.79; H, 5.59.

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CHAPTER 2

Total Synthesis of (−)-Curvularin: A Ring Closing Metathesis Based Construction of the Macrocyclic Framework

Introduction

Inflammation is the response of the human body to numerous noxious stimuli (e.g., infection; chemical injury such as impaired blood supply or a chemical burn; trauma including flame, electric burn, and frostbite injury; and antigen-antibody interactions). Clinically, inflammation is characterized by redness, swelling, heat, pain, loss of function, and tenderness. A classic example would be a scald burn or a wasp sting. The inflammatory response is used by the body to control the injury and is intrinsically the same for all stimuli with minor variations based on the nature of the offending agent. The body's ability to mount an inflammatory response is a survival mechanism, but on occasion can be overwhelming (e.g. dying from a bee sting) or remain active for a prolonged time (as in rheumatoid arthritis). *Uncontrolled inflammation damages healthy cells and has been implicated in many diseases including cancer, cardiovascular disease, diabetes, Alzheimer's disease, cystic fibrosis, multiple sclerosis, ulcerative colitis, inflammatory bowel disease, and autoimmune diseases including arthritis and psoriasis.* The exact events at the cellular and biochemical level, which make up inflammation are extremely complex and are not yet entirely known. Cells involved include white and red blood cells, "helper" cells such as tissue lymphocytes, and scar tissue forming cells. But it is at the biochemical level where the complexities become extreme.

Inflammatory Pathways

The Arachidonic Acid/COX Pathway

In 1971, Professor John Vane from Cornell University was awarded the Nobel Prize for his work in elucidating the mechanism of action of aspirin **4** on prostaglandins.[1] Prostaglandins are short-lived localized hormones that can be released by any cell of the body during tissue, chemical, or traumatic injury, and can induce fever, inflammation, and pain once they are present in the intercellular space. Thromboxanes, which are also hormone activators, regulate blood vessel tone, platelet aggregation, and clot formation; are manufactured in every cell of the body; and can be released in response to injury. There is a complex biochemical pathway which, once stimulated by injury, will lead to the production of these and other inflammatory mediators whose initial effect is pain and

tissue destruction, followed by healing and recovery.[2] This is called the arachidonic acid pathway, because arachidonic acid is released in the early stages from traumatized cellular membranes. This substance is transformed into prostaglandins and thromboxanes through the action of COX.[2] Vane[3] discovered that aspirin **4** works by irreversibly disabling the COX enzymes so that they no longer produce the inflammatory prostaglandins and thromboxanes (Fig. 1). Aspirin **4** therefore reduces inflammation, pain, fever, and blood clotting by decreasing prostaglandin and thromboxane production.

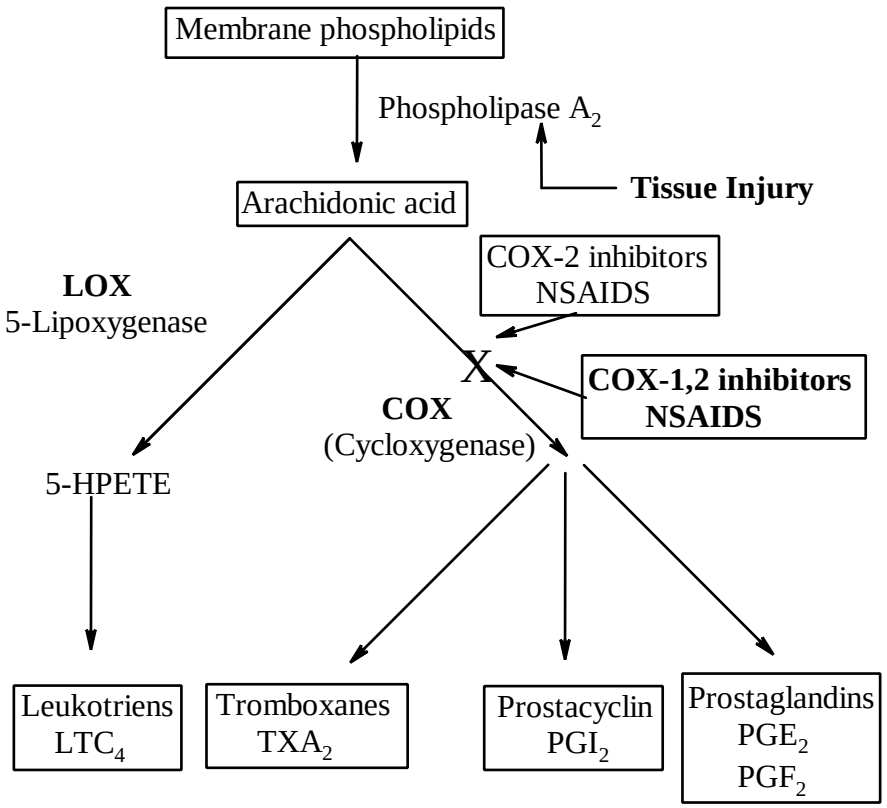


Fig 1: *Schematic showing that when a cell membrane is injured, the arachidonic Acid pathway is activated to initiate the local inflammatory response through the production of prostaglandins, thromboxanes, and leukotrienes. Their activation, however, requires the enzymes COX and LOX. The NSAIDs can block COX action and thereby prevent the formation of the COX-derived inflammatory mediators. 5-HPETE = 5-hydroperoxyeicosatetraenoic acid; LTC_4 = lukotriene C4; PGE_2 = prostaglandin E2; PGF_2 = prostaglandin F2; PGI_2 = prostacyclin; TXA_2 = thromboxane.*

Nonselective COX Inhibitors

The COX enzyme is found in two forms in the human body: COX-1, a constitutive enzyme that normally protects the gastrointestinal mucosa; and COX-2, which is

activated by tissue damage and is considered to be an inducible enzyme because it exists during injury only (Fig. 2).[2] Gastrointestinal side effects associated with COX inhibitors, such as aspirin **4** and the nonselective NSAIDs, which block both COX-1 and COX-2, have pushed researchers to find a way to block COX-2 selectively and thereby limit the complications of gastritis and ulcers that are common with long-term use.

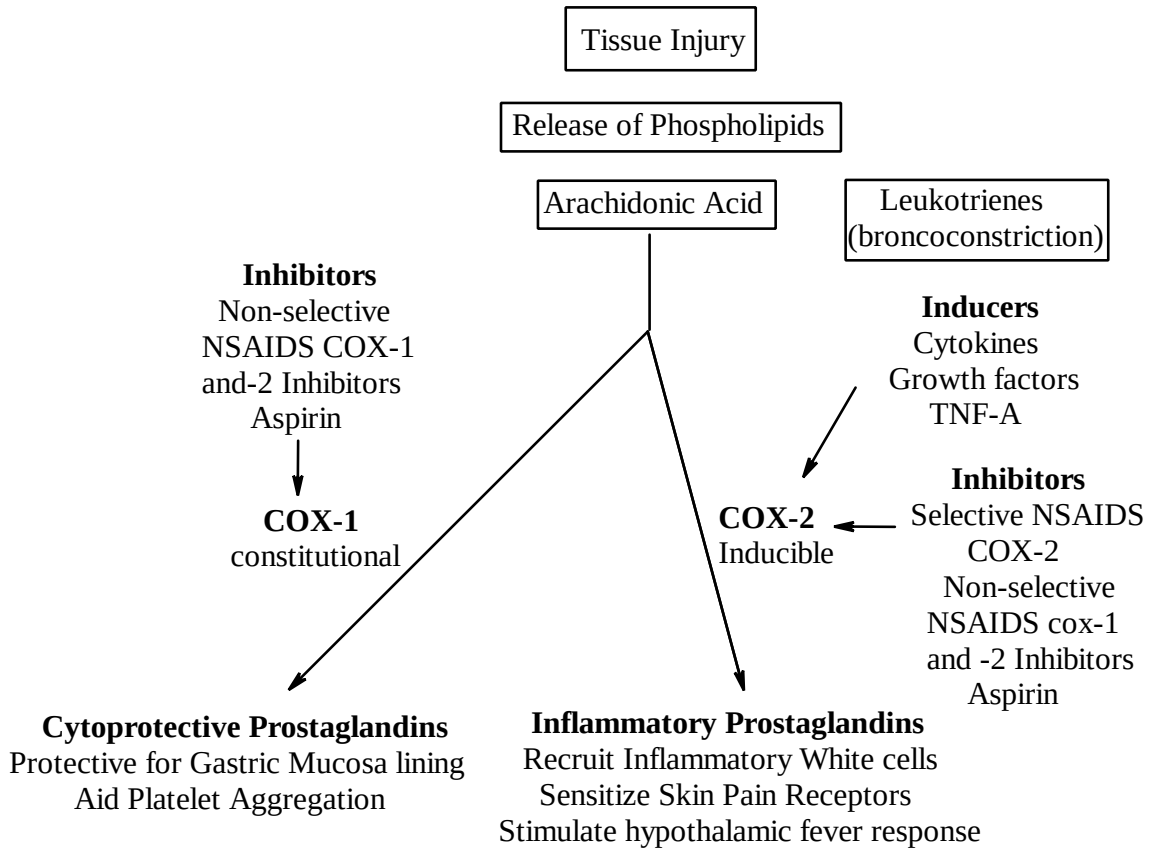


Figure 2: *Schematic showing that the COX enzyme can exist in two forms: COX-1, constitutional or existing in small amounts at all times; or COX-2, inducible or only present during the inflammatory response. By selectively blocking only the COX-2-produced inflammatory prosglandins, COX-2-inhibiting medications were believed to be superior to nonselective COX-1 and -2 inhibitors; they were thought to have fewer gastric side effects.*

Selective COX Inhibitors

In December 1998, celecoxib (Celebrex)[4] was approved by the FDA as the first selective COX-2 inhibitor for treatment of arthritis pain. Rofecoxib (Vioxx) was approved several months later, followed by valdecoxib (Bextra). These NSAIDs were designed to allow continued production of the gastrointestinally protective prostaglandins

produced through the COX-1 enzyme system while blocking the COX-2 enzyme that produces the inflammatory prostaglandins.[2] The number of prescriptions for nonselective (COX-1 and -2) inhibitors such as ibuprofen (Motrin) quickly dropped as the new selective COX-2 inhibiting NSAIDs began to grow in popularity.[5] By its 7th week on the market, Celebrex had surpassed Viagra in generating record numbers of daily prescriptions early in its marketing.[5] The Big 3 (Celebrex, Vioxx, and Bextra) quickly became the mainstay for the treatment of chronic pain conditions related to inflammation.[1]. It was estimated that 5 to 10% of the adult population used NSAIDs, and among the elderly (a group at higher risk of NSAID-induced gastrointestinal complications), use of these drugs was as high as 15%. In 2003, the sales of these three drugs surpassed $9 billion in the US alone. The general acceptance of these drugs was due to the perceived lack of serious gastrointestinal side effects that had been associated with the nonselective class of NSAIDs.

Anti-Inflammatory Agents

There exists in medical practice at the close of the 20th century two basic categories of anti-inflammatory drugs: steroidal (from steroid compounds) and non-steroidal. Steroids are potent inhibitors of inflammation and the immune system, but also have a host of serious, even deadly, side effects. The non-steroidal agents are in general less potent but also have fewer side effects.

In the mid 1700s, Reverend Edmund Stone wrote a letter to the English Royal Society noting the ability of the bark of the willow tree to cure fever. He was reiterating an observation known for ceturies by many cultures, but the actual ingredient remained unknown until 1829, when Leroux isolated salicin (**3**). Salicin (**3**) indeed proved to decrease fever. Chemically salicin (**3**) can be converted to salicilic acid, a very successful treatment of fever and gout. In 1875, Hoffman, a chemist working for the Bayer Company, synthesized acetylsalicilic acid, which was made available for clinical use under the name aspirin **4**. Many synthetic variations of aspirin were used in the early 1900s, but in 1999 only acetaminophen (Tylenol) remains.

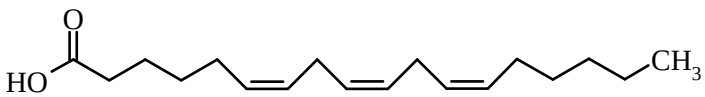
Aspirin and sodium salicylate are now believed to target NF-κB as well as the COX system. These agents inhibit the NF-κB pathway in endothelial cells and block NF-κB

activation to inhibit leukocyte recruitment.[3] Other nonsteroidal agents have also been found to inhibit both the COX system and the NF-κB pathway. Immunosuppressant drugs also reduce nuclear expression of NF-κB.

The natural anti-inflammatory agent

Gamma-linolenic acid

Gamma-linolenic acid **1** (GLA; *cis*-6, *cis*-9, *cis*-12-octadecatrienoic acid) is an *omega*-6 fatty acid that is naturally present in breast milk, beef, pork, chicken, and egg yolk. Over the past four decades, human and animal studies have confirmed anti-inflammatory properties of three commercialized sources of GLA: the oils of evening primrose (Oenothera biennis; 8 to 12% GLA), borage (Borago officinalis; 18 to 26% GLA), and black currant (Ribes nigrum; 13 to 17% GLA), for treating inflammatory conditions including arthritis and psoriasis.

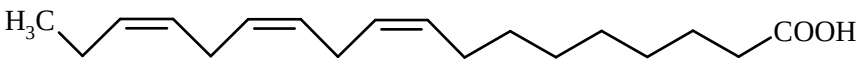


Gamma-Linolenic acid **1**

Figure 3

Omega-3 EFAs (Fish Oil)

Research has shown that the omega-3 (**2**) polyunsaturated fatty acids are some of the most effective natural antiinflammatory agents available.[1] With the discovery that vascular inflammation is the underlying cause of coronary artery disease, fish and fish oil supplements are now recommended by the American Heart Association for the prevention of this disease.[18] Countries in which the highest fish consumption occurs have



Omega-3 (**2**)

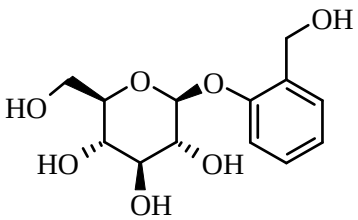
Figure 4

populations with a lower incidence of neurodegenerative disease and depression.[1] The biological basis for the effectiveness of fish oil in treating arthritis has been well

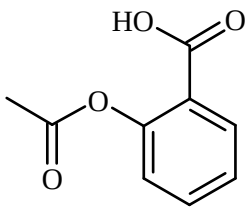
documented, with many positive clinical studies when compared with traditional pharmaceutical anti-inflammatory agents.

White Willow Bark

Bark from the white willow tree is one of the oldest herbal remedies for pain and inflammation. It has been used by the ancient Egyptian, Roman, Greek, and Indian civilizations as an analgesic and antipyretic agent.[7] In fact, the first record of its use is found in the Ebers papyrus, written more than 3500 years ago. Because the drug caused gastric irritation, the French chemist Charles Gerhardt neutralized salicylic acid and created acetylsalicylic acid.[7] In 1897, Felix Hoffmann used the agent to treat his father's rheumatoid arthritis, and because of his success, the Bayer Corporation marketed the product under the trade name of aspirin (**4**). Because of the side effects of aspirin, there has been resurgence in the use of white willow bark for the treatment of inflammatory syndromes. Salix alba, or white willow, is the species most commonly used for medicinal purposes. The mechanism of action of white willow bark is similar to that of aspirin in that it is also a nonselective inhibitor of COX-1 and COX-2, thus reducing the inflammatory prostaglandins.[8] Various randomized placebocontrolled studies comparing white willow bark with nonsteroidal agents have show an efficacy comparable to these agents and aspirin.[7] Salicin **3** from white willow bark is converted to salicylic acid by the liver and is considered to have fewer side effects than aspirin **4**.[8] However, it is more costly than aspirin **4**, and should not be used in children (to avoid the risk of Reye syndrome), or in patients with peptic ulcer disease, diabetes, hepatic or renal disorders, or other conditions in which aspirin **4** would be contraindicated. The usual dose of white willow bark is 240 mg per day.



D-(-)-Salicin **3**

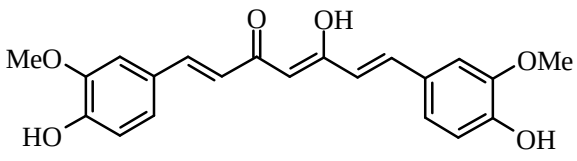


Acetylsalicylic acid (Aspirin) (**4**)

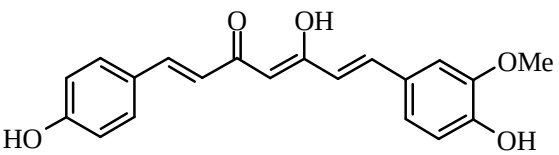
Figure 5

Curcumin (Turmeric)

Curcumin **5** is a naturally occurring yellow pigment derived from turmeric (Curcuma longa), a flowering plant in the ginger family.[9] It has traditionally been used as a coloring and flavoring spice in food products. Curcumin **5** has long been used in both Ayurvedic and Chinese medicine as an antiinflammatory agent, a treatment for digestive disorders, and to enhance wound healing. Several clinical trials have demonstrated curcumin's antioxidant, antiinflammatory, and antineoplastic effects.[9] In a recent article in the *New England Journal of Medicine*, Zandi and Karin[10] suggested that curcumin might be efficacious in the treatment of cystic fibrosis because of its antiinflammatory effect. Curcumin **5** has been suggested as a treatment for colitis, chronic neurodegenerative diseases, arthritis, and cancer. In addition, it regulates the activity of several enzymes and cytokines by inhibiting both COX-1 and-2.86 Most studies to date have been performed in animals, but given the centuries of use of curcumin **5**, as well as its now demonstrated activity in the NF-κB, COX-1, and COX-2 inflammatory pathways, it may be considered a viable natural alternative to nonsteroidal agents for the treatment of inflammation. The usual dosage of standardized turmeric powder is 400 to 600 mg taken three times per day.



Curcumin **5**



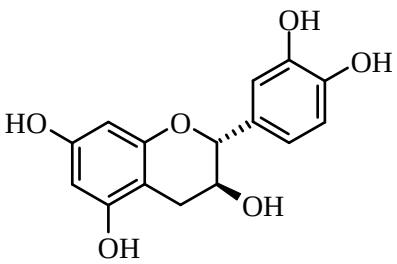
Demethoxycurcumin **6**

Figure 6

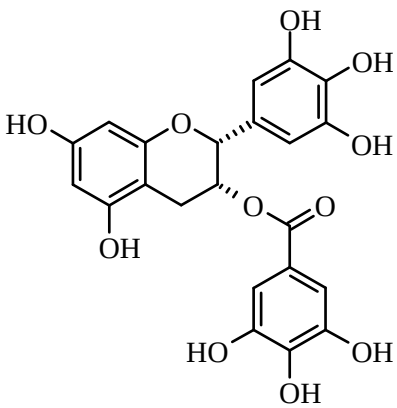
Side effects are few, but with extended use this agent can cause stomach upset, and in extreme cases gastric ulcers may occur at very high doses. Caution should be used if the patient is taking anticoagulant medications or high doses of nonsteroidal drugs. Studies have shown that curcumin **5** may be used in combination with lower doses of nonsteroidal medications. Curcumin's therapeutic effects are considered comparable to pharmaceutical nonsteroidal medications such as phenylbutazone, but with a major difference in that this compound is relatively nontoxic and free of side effects.

Green Tea

Green tea has long been recognized to have cardiovascular and cancer preventative characteristics due to its antioxidant properties.[11] Its use in the treatment of arthritic disease as an anti-inflammatory agent has been recognized more recently. The constituents of green tea are polyphenolic compounds called catechins **7**, and epigallocatechin 3 galate **8** is the most abundant catechin in green tea.[11] Epigallocatechin-3 galate inhibits IL-1–induced proteoglycan release and Type 2 collagen degradation in cartilage explants.[11] In human *in vitro* models, it also suppresses IL-1b and attenuates activation of the transcription factor NF-κB.[12] Green tea also inhibits the aggrecanases, which degrade cartilage. From various studies, the molecular basis of the anti-inflammatory and chondroprotective effects of green tea is being discovered. A recent review article from Yale University regarding green tea as the Asian paradox summarizes its currently recognized therapeutic effects: as a cardiovascular and neuroprotective agent, an inhibitor of carcinogenesis, and an anti-inflammatory agent.[13] The usual recommendation is 3 to 4 cups of tea a day. If the patient is taking green tea extract, a dosage of 300 to 400 mg is typical. Green tea can cause stomach irritation in some, and because of its high caffeine content, a decaffeinated variety should be considered.



(+)-Catechin **7**



(+)-Epigalocatechin-3-gallate **8**

Figure 7

Pycnogenol (Maritime Pine Bark)

Pycnogenol, like white willow bark, is a nutraceutical material that has been used since ancient times. Pycnogenol is derived from the bark of the maritime pine tree (Pinus maritima) and has been used for more than 2000 years.[14] Hippocrates mentions its use as

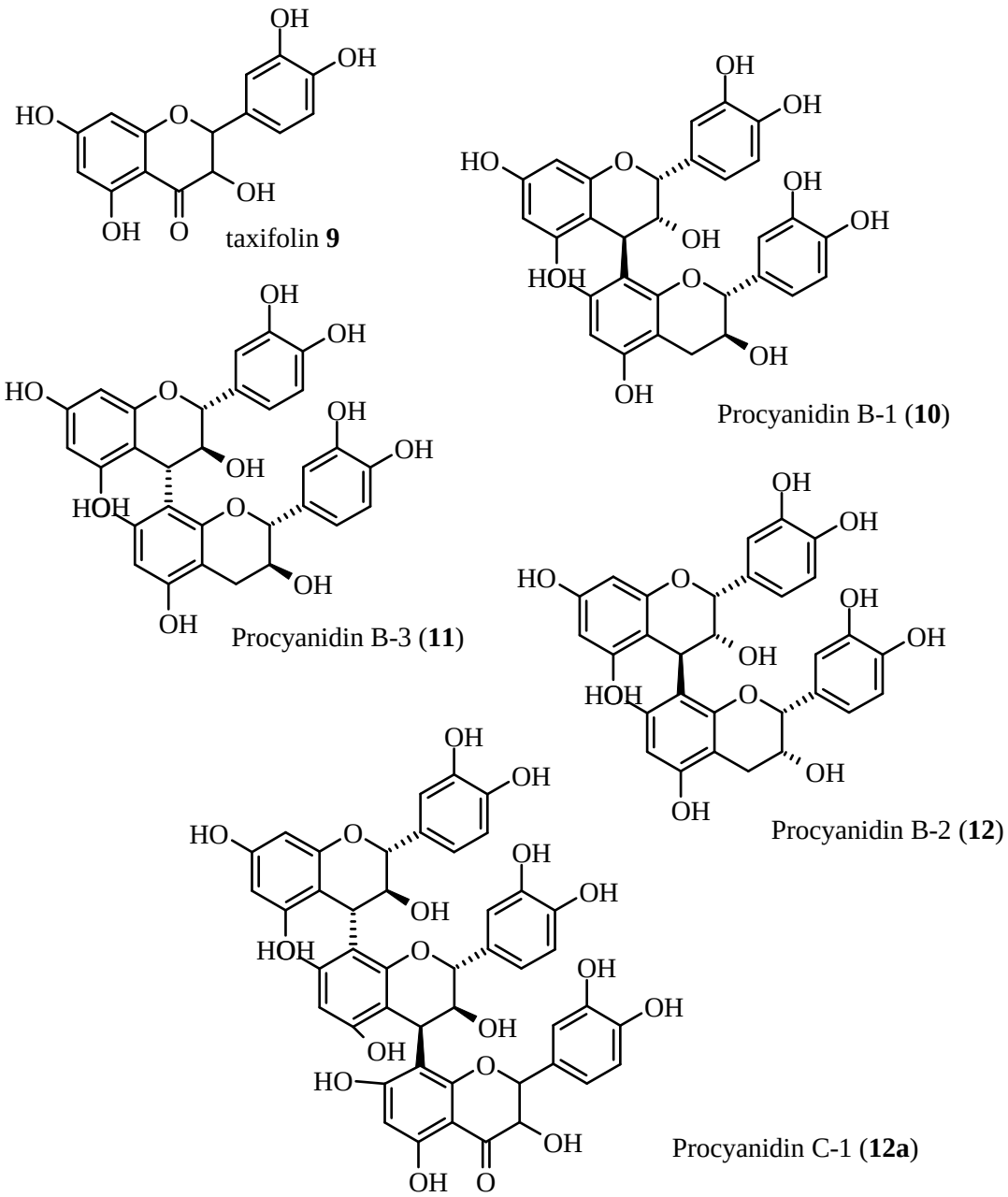


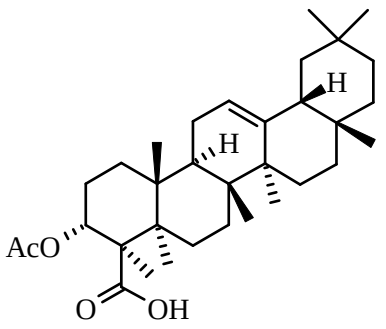
Figure 8

an anti-inflammatory agent. It has been considered helpful for wound healing, treating scurvy, healing of ulcers, and reducing vascular inflammation. It contains a potent blend of active polyphenols that includes catechin **7**, taxifolin **9**, and procyanidins (**10**-**12a**). It is one of the most potent antioxidant compounds currently known.[14] Pycnogenol inhibitsTNFα-induced NF-κB activation as well as adhesion molecule expression in the

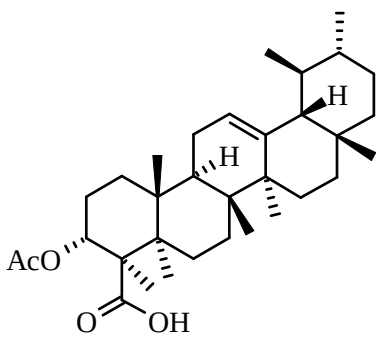
Endothelium.[15] Grimm and colleagues[16] recently reported that oral intake of pycnogenol inhibited NF-κB activation in lipopolysaccharide stimulated monocytes as well, thus decreasing the inflammatory response. It also statistically significantly inhibited matrix metalloproteinase-9.[16] This matrix-degrading enzyme is highly expressed at sites of inflammation, and contributes to the pathogenesis of various chronic inflammatory diseases.

Boswellia serrata Resin (Frankincense)

The Boswellia species (**13**, **14**) are trees located in India, Ethiopia, Somalia, and the Arabian peninsula that produce a gum resin called olibanum, better known in the western world as frankincense.[17] This resin possesses antiinflammatory, antiarthritic, and analgesic properties.[18] It is known to inhibit the leukotriene biosynthesis in neutrophilic granulocytes by inhibiting 5-LOX. Various inflammatory diseases are perpetuated by leukotrienes, hence some of the antiinflammatory activity of this agent.[17] Clinically, the substance is used in the treatment of degenerative and inflammatory joint disorders. It reduces the total white blood cell count in joint fluid,[18] and it also inhibits leukocyte elastase, which is released in rheumatoid arthritis.[17] In one recent study, a statistically significant improvement in arthritis of the knee was shown after 8 weeks of treatment with 333 mg B. serrata extract taken three times a day. The treatment improved function, but radiographically there was no change in the affected joints.[18]



Acetyl-alfa-boswellic acid **13**



Acetyl-beta-boswellic acid **14**

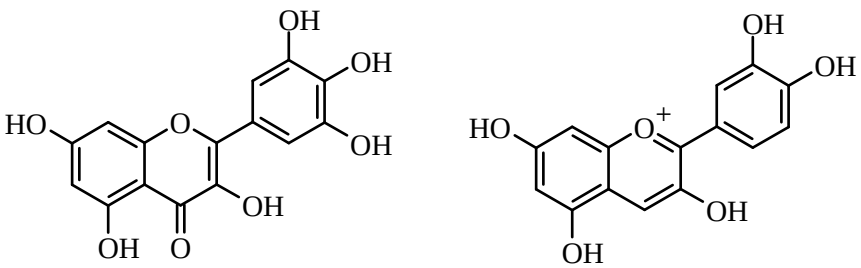
Figure 9

Another study by Kulkarni, *et al*,[19] demonstrated a significant drop in pain severity and disability. A combination of Boswellia and curcumin showed superior efficacy and tolerability compared with nonsteroidal diclofenac for treating active osteoarthritis.

Boswellia typically is given as an extract standardized to contain 30 to 40% boswellic acids (300– 500 mg two or three times/day). Boswellia has been well tolerated in most studies, although some people may experience stomach discomfort, including nausea, acid reflux, or diarrhea.

Uncaria tomentosa (Cat's Claw)

Uncaria tomentosa [20] and U. guianensis100 are Peruvian herbs derived from woody vines with small clawlike thorns (hence the vernacular name, cat's claw) at the base of the leaf that allows the plant to climb to heights of up to 100 ft. Traditionally, a decoction of the bark of the cat's claw is used to treat arthritis, bursitis, and intestinal disorders. The active ingredients appear to be polyphenols (**15**, **16**). Various studies indicate that this Peruvian herb induces a generalized reduction in proinflammatory mediators. This herb has been shown to prevent the activation of the transcriptional factor NF-κB and it directly inhibits TNFα production by up to 65 to 85%. It inhibits the expression of inducible genes associated with inflammation, specifically negating the expression of inducible nitric oxide synthase, and hence attenuates nitrous oxide production.[21]



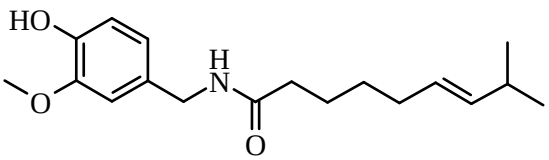
Myricetin **15** Cyanidin **16**

Figure 10

Side effects may include nausea, although it has shown an impressive protective effect on indomethacin induced enteritis in laboratory studies. Although, toxicity and side effects are usually minimal, two case reports of acute renal failure in a patient with lupus erythematosus have been recorded. Cat's claw can be consumed as a tea (1000 mg root bark to 8 oz water), or as a dry, standardized extract in a capsule (20–60 mg daily).

Capsaicin (Chili Pepper)

Capsicum annum is a small spreading shrub originally cultivated in the tropical regions of the Americas but now is grown throughout the world, including the US. The small red fruit commonly used to accentuate chili owes its stinging pungency to the chemical capsaicin **17**. This was isolated by chemists more than a century ago and constitutes approximately 12% of the chili pepper. This fruit has been used for medicinal purposes by the native peoples of the American tropics for hundreds of years. More recently, various preparations have become available over the counter for the treatment of peripheral neuropathies and chronic musculoskeletal pain. Capsaicin **17** produces highly selective regional anesthesia by causing degeneration of capsaicin-sensitive nociceptive nerve endings, which can produce significant and long-lasting increases in nociceptive thresholds.[22] Capsaicin potently activates transient receptor potential vanilloid 1, which is a main receptor underlying nociception. It also inhibits NF-κB, thus producing an anti-inflammatory effect. Capsaicin can cause a burning sensation when it comes in contact with human flesh, and also in the digestive tract. This herb is rarely used alone but is generally mixed into other natural antiarthritic preparations. There are topical capsaicin formulations now available to treat postherpetic neuralgia.

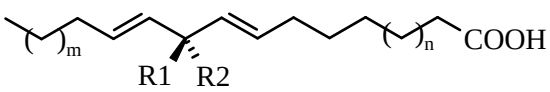


Capsaicin **17**

Figure 11

Recently isolated anti-inflammatory drug

A chemical study on the anti-inflammatory components of the red alga *Gracilaria* V*errucosa* led to the isolation of oxygenated fatty acids[23] (**18**, **19**). Their structures were elucidated on the basis of NMR and MS data. The anti-inflammatory activity of the isola-



18 n = 2 m = 5 R_1, R_2 = O

19 n = 2 m = 4 R_1 = H, R_2 = OH

Figure 12

ted compounds (**18**, **19**) was evaluated by determining their inhibitory effects on the production of pro-inflammatory mediators (NO, IL-6, and TNF-R) in lipopolysaccharide (LPS)-activated RAW 264.7 murine macrophage cells. Compounds **18** and **19** exhibited potent anti-inflammatory activity.

Recently isolated compounds,[24] (7′*S*,8′*S*)-5-demethoxybilagrewin (**20**), (7′*S*,8′*S*)-4′-*O*-methylcleomiscosin D (**21**) and (+)-9′-*O*-(*Z*)-feruloyl-5,5′-dimethoxylariciresinol (**22**) have been isolated from the stem wood of *Zanthoxylum a*V*icennae*. The structures of these compounds were determined through spectroscopic and MS analyses. (7′*S*, 8′*S*)-4′-*O*-Methylcleomiscosin D (**21**) exhibited inhibition ($IC_{50} \leq 18.19\ \mu M$) of superoxide anion generation by human neutrophils in response to formyl-L-methionyl-L-leucyl-L-phenylalanine/cytochalasin B (FMLP/CB).

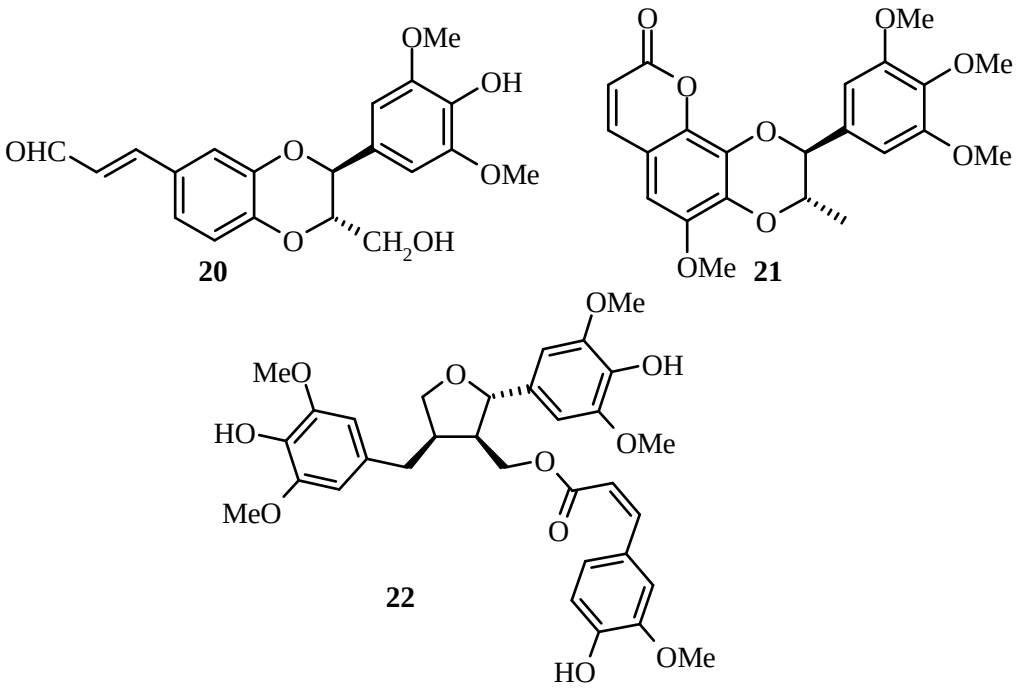
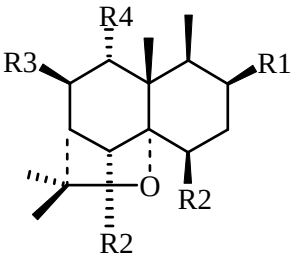


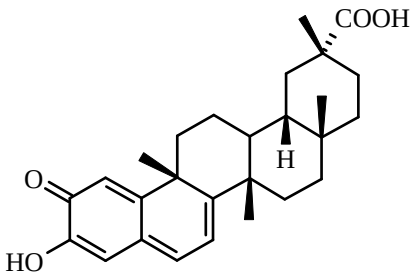
Figure 13

The anti-inflammatory effects of compounds isolated from the stem wood of *Z. a*V*icennae* were evaluated by suppressing formyl-L-methionyl-L-leucyl-L-phenylalanine/cytochalasin B (FMLP/CB) induced superoxide radical anion ($O_2^{\cdot -}$) generation and elastase release by human neutrophils. Diphenyleneiodonium and phenylmethylsulfonyl fluoride were used as positive controls for $O2^{\bullet -}$ generation and elastase release, respectively. From the results of anti-inflammatory tests, the following

conclusions can be drawn: (a) (7′*S*,8′*S*)-5-demethoxybilagrewin (**20**), (7′*S*,8′*S*)-4′-*O*-methylcleomiscosin D (**21**), (+)-9′-*O*-(*Z*)-Feruloyl-5,5′-dimethoxylariciresinol (**22**), exhibited inhibitory activities ($IC_{50} \leq 27.97\ \mu M$) on human neutrophil $O_2^{\bullet-}$ generation. (b) (+)-9′-*O*-(*Z*)- Feruloyl-5,5′-dimethoxylariciresinol (**22**) inhibited FMLP/CB-induced elastase release with IC_{50} values $\leq 32.55\ \mu M$.



	R1	R2	R3	R4
23	H	OFu	OAc	OFu
24	OFu	OFu	H	OFu
25	OAc	OBz	H	OBz

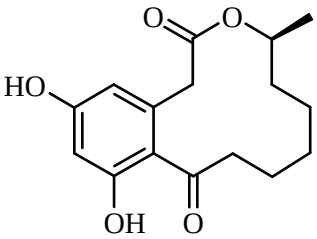


26

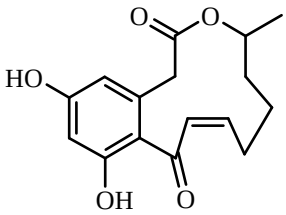
Figure 14

Two new sesquiterpene esters,[25] 1*β*,8*β*-diacetoxyl-6α,9α-difuroyloxydihydro-*β*-agarofuran (**23**) and 1*β*-acetoxyl-2*β*,6α,9α-trifuroyloxydihydro-*β*-agarofuran (**24**), celastrol (**25**), and celaphanol A (**26**) were isolated from the roots of *Celastrus orbiculatus* in a search for inhibitors of NF-κB activation and nitric oxide production. Compound **25** was the most active, while compounds **23**, **24**, and **26** showed moderate inhibition in both NF-κB activation and nitric oxide production.

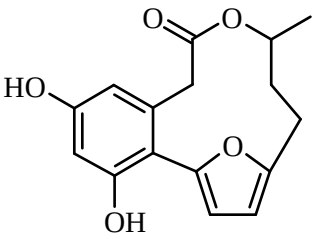
The fungal macrocyclic lactone (*S*)-curvularin **27**, previously isolated from *Curvularia,*[26,27] *Alternaria,*[28,29] *and penicillium*[30,31,32] sp., inhibits inducible transcripstion and synthesis of the pro-inflammatory enzymes iNOS and COX2 in A549/8 cells without affecting the activity of the constitutive human eNOS promoter or displaying cytotoxic effects. Studies on the mode of action revealed that (*S*)-curvularin **27** blocks the phoshphorylation (and activation) of the transcription factor STAT-1α (signal transducer and activator of transcription) by the upstream tyrosine kinase JAK2 (Janus kinase), thereby interfering with a signal transduction pathway responsible for the inducible expression of many pro-inflammatory genes.



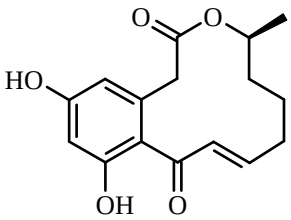
curvularin **27**



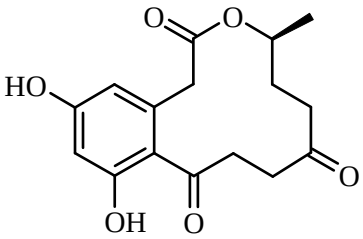
cis-dehydrocurvularin **27a**



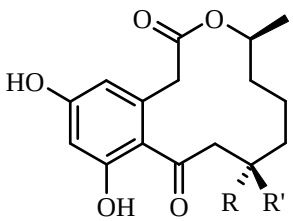
citreofuran **27b**



trans-dehydrocurvularin **27c**



12-oxocurvularin **27d**



27e R = OH, R' = H
27f R = H, R' = OH
27g R = OMe, R' = H
27h R = H, R' = OMe

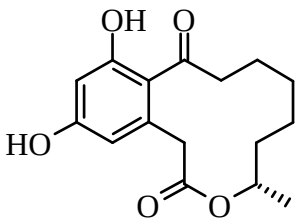
Figure 15

Therefore, (*S*)-curvularin (**27**) is an ant-inflammatory compound with an interesting mode of action and almost no negative effects on eNOS expression, as is desirable for anti-inflammatory drug, thus, may offer an alternative to standard glucocorticoid therapy. (*S*)-curvularin **27** was also reported to arrest the cell cycle. This is why natural products (**27a**-**27h**) related to (*S*)-cuvularin (**27**) have received increasing attention from chemist interested in the total synthesis of biologically active natural products.

Present Work

Curvularins[33,34] are macrocyclic lactones produced by a number of fungi of the genera *Curvularia,*[26,27] *Alternaria,*[28,29] and *Penicillium.*[30,31,32] These macrocyclic lactones have been reported to possess a variety of biological activities, including phytotoxicity,[28] cytotoxicity[31] toward sea urchin embryogenesis, inhibition of cell division, inhibition of expression of human inducible nitric oxide synthase,[35] and growth-promoting activity in farm animals.[36]

This class of compound is a fused resorcinylic macrolides. In these target systems, a keto group is presented at the benzylic position. The ester bond corresponds to a macrolide of a formal phenyl acetic acid. These macrolides have received much interest in agrochemical and pharmaceutical settings. A representative of a 12-membered phenylacetic macrolactone is curvularin **27** (Figure 16) as well as its metabolites.



Curvularin **27**

Figure 16

Several syntheses have been reported[37a-g] for curvularin **27** involving intramolecular acylation as the key step, which describes very poor yield at the final acylation step. Hence, a practical route for the construction of this molecule is still desirable. So, in search of some alternative synthetic route, we had planned to develop the ring closing metathesis approach towards the total synthesis of curvularin **27**. Key steps featured in our synthetic plan were the DCC mediated coupling of acid **31** and alcohol **32**, followed by ring closing metathesis reaction.

The retrosynthetic analysis for our synthetic endeavour was planned using a convergent approach as outlined in Figure 17 and employed a ring closing metathesis reaction to form the macrolide **28**. The formation of diene **29**, following some synthetic sequence starting from **30** was a straightforward exercise. The intermediate **30** could be

obtained by the esterification of alcohol **32** with substituted benzoic acid **31**, the former being envisaged from the diol intermediate **33** through selective *PMB* protection, Mitsunobu inversion, which in turn could be obtained from L-(+)-glutamic acid. The latter fragment **31** could be obtained from aldehyde **34** through allyl Grignard protocol, protection of the alcohol as benzyl ether, cleavage of *PMB* ether and Pinnick oxidation. The aldehyde **34** could be furnished by Vilsmeier-Haack formylation on **35**, which could be obtained from commercially available **36** through a sequence of reactions.

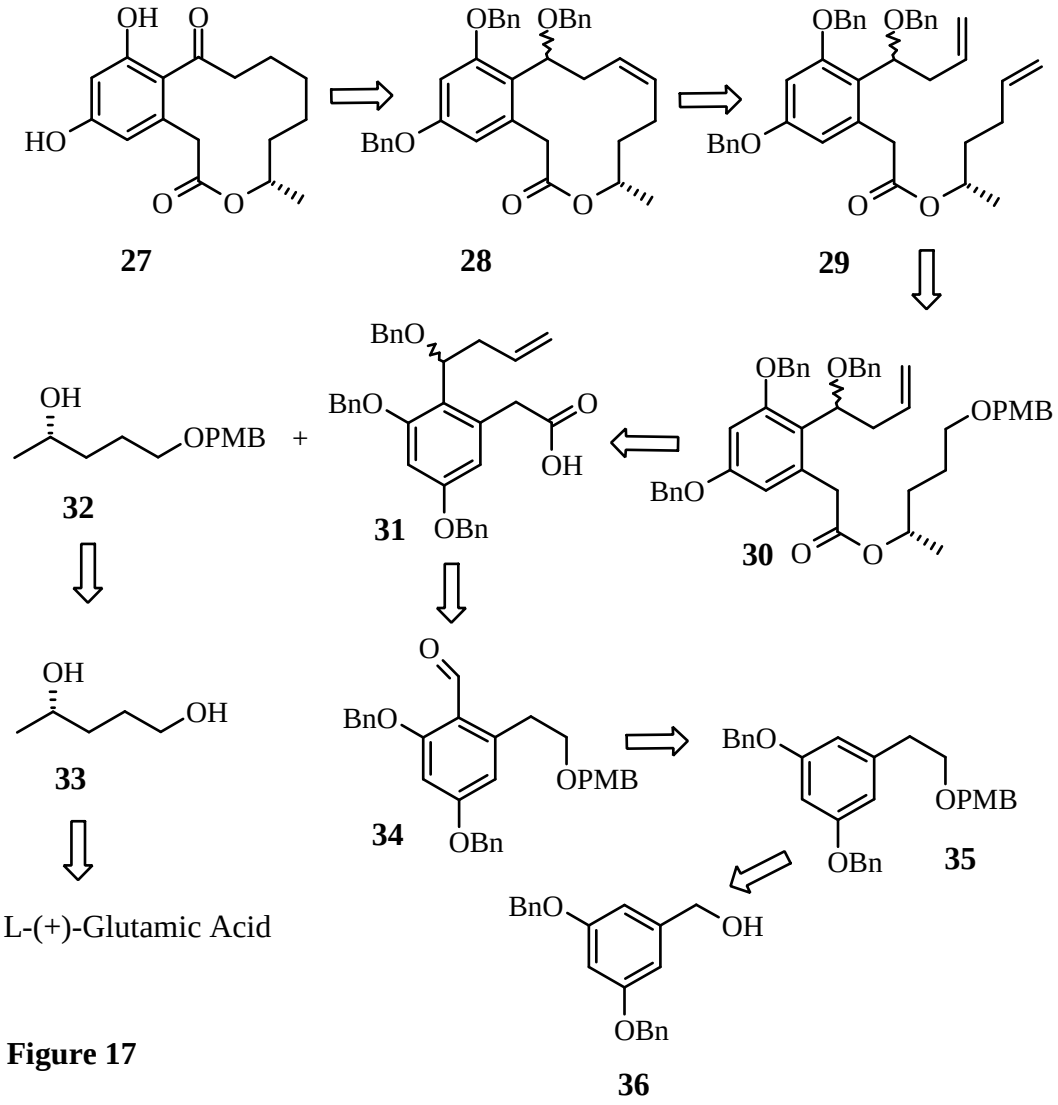


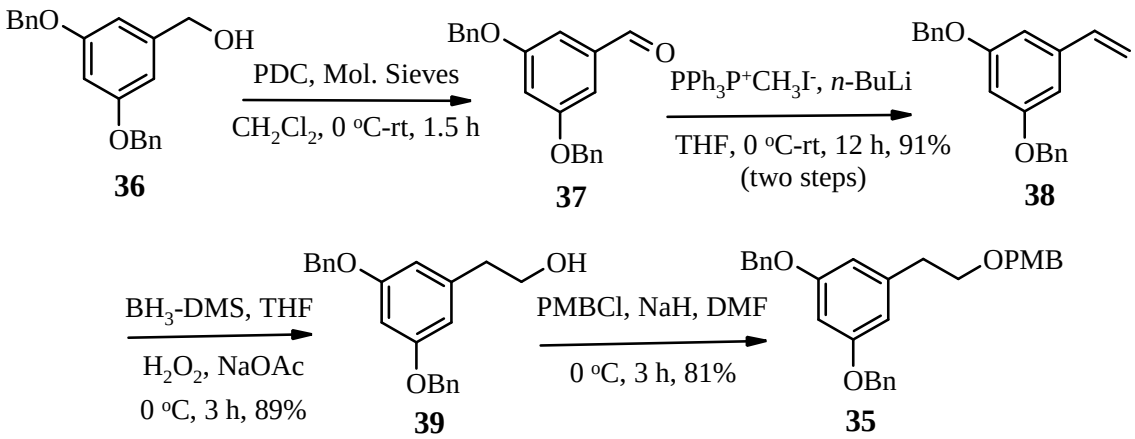
Figure 17

Synthesis of the Acid segment

Accordingly, our synthesis began with readily available 3,5-dibenzyloxy benzyl alcohol **36**,[38] which was oxidised to aldehyde **37** with PDC[39] in dichloromethane, followed by one carbon Wittig olefination with methylenetriphenylphosphorane

[generated *in situ* from $CH_3P^+Ph_3I^-$ and *n*-BuLi] in THF to afford **38**. ^{1}H NMR, ^{13}C NMR spectroscopy and elemental analysis confirmed the formation of **38**. For example, in the ^{1}H NMR spectrum, a double doublet at δ 5.29 (dd, *J* = 0.8, 10.8 Hz) ppm integrating for one proton and another double doublet at δ 5.75 (dd, *J* = 0.8, 17.4 Hz) ppm integrating for one proton were due to terminal double bond proton.

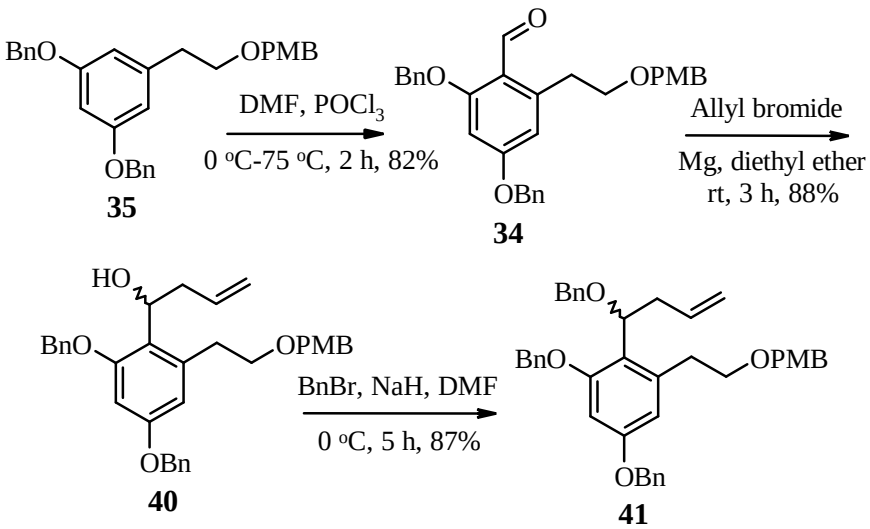
With a vision to transform the olefin **38** into the corresponding alcohol **39**, **38** was exposed to $H_3B{\cdot}SMe_2$[40] in THF followed by oxidative workup with H_2O_2 and NaOAc to produce the desired primary alcohol **39** (Scheme 1). The structural feature was unambiguously corroborated from the combined spectral data from ^{1}H NMR, ^{13}C NMR, IR and EIMS. In the ^{1}H NMR spectrum, a characteristic triplet at δ 3.82 (t, *J* = 6.4 Hz, 2H) ppm clearly revealed the presence of $-CH_2OH$ group. In addition, the ^{13}C NMR spectrum showed a peak at δ 63.18 ppm corresponding to $-\underline{CH_2}OH$.



Scheme 1

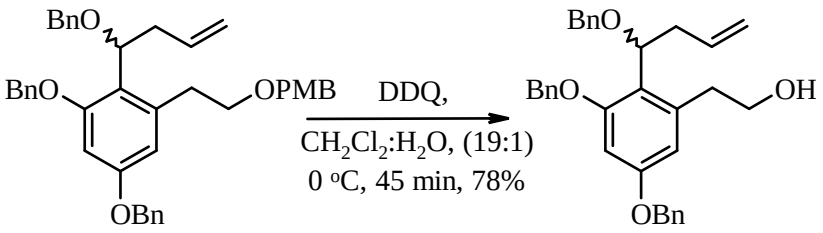
The free hydroxyl group of **39** was protected as its *p*-methoxybenzyl ether by PMBCl/NaH in DMF at 0 ^{o}C to obtain compound **35**. The product **35** was confirmed by the presence of additional peaks in the ^{1}H NMR spectrum due to *p*-methoxybenzyl group, *i.e.*, a singlet at δ 3.67 (3H) ppm for aryl methyl ether and two doublets at δ 6.76 (*J* = 8.6 Hz, 2H) and 7.14 (*J* = 8.6 Hz, 2H) ppm of A2B2 pattern. The next step of regioselective formylation[41] was conveniently achieved with $POCl_3$ in DMF as per the Vilsmeier-Haack protocol. The resulting aromatic aldehyde **34** was confirmed by analyzing spectroscopic data. In the ^{1}H NMR spectrum of **34**, aldehydic proton was situated at δ 10.45 (s, 1H) ppm. Moreover, in the ^{13}C NMR spectrum, the aldehydic carbon was resonated at δ 190.3 ppm. In the IR spectrum, absorption due to C=O was observed at 1673 cm.$^{-1}$ Allylation

by Grignard reaction on aldehyde **34** with allylmagnesium bromide in diethyl ether at room temperature furnished the homoallylic alcohol **40**. Disappearance of signal due to the aldehydic proton in the ^{1}H NMR spectrum indicated the transformation had occurred. In addition, the multiplets at δ 4.88-5.02 ppm integrating for two protons and at δ 5.66-5.87 ppm integrating for one proton indicated the presence of terminal double bond. The structure of **40** was further confirmed by its ^{13}C NMR spectroscopy, elemental analysis and mass spectroscopy. The free hydroxyl group present in **40** was then protected conveniently as the corresponding benzyl ether **41** using NaH and BnBr in DMF at 0 ^{o}C (at higher temperature byproducts predominates over the desired product) (Scheme 2). The ^{1}H NMR spectrum showed the resonances due to aromatic protons of the benzyl group between δ 7.10-7.33 ppm as a multiplet and the characteristic of benzylic methylene group was located at δ 4.17 (d, *J* = 12.0 Hz, 1H) and 4.33 (d, *J* = 12.0 Hz, 1H) ppm. All other proton signals appeared at their respective chemical shift values. The mass spectroscopy showed a peak at *m/z* 637.7 due to $[M+Na]^{+}$ ion.



Scheme 2

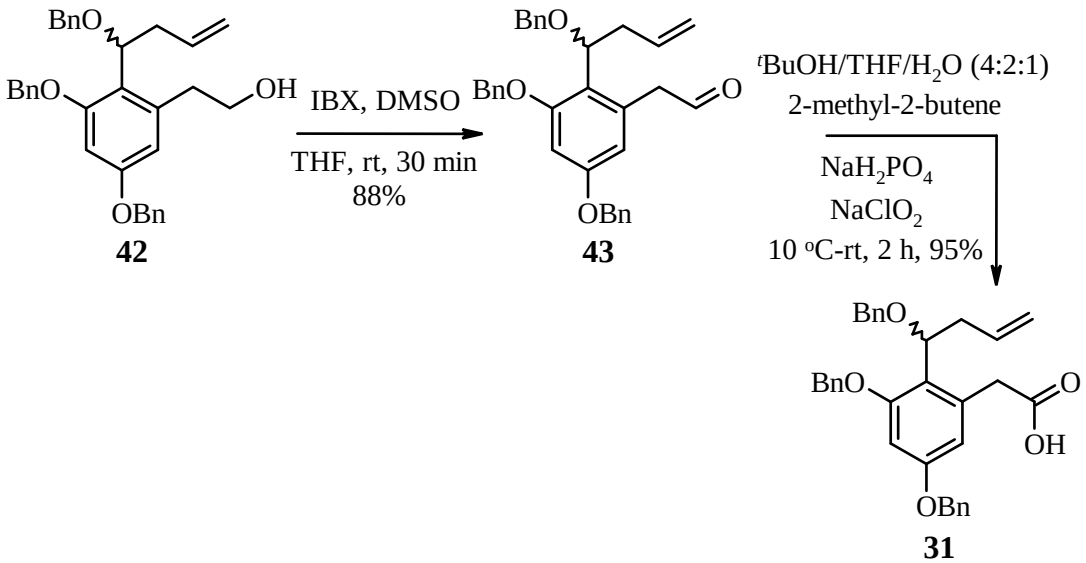
The *p*-methoxy benzyl ether was cleaved using DDQ[42] in CH_2Cl_2/H_2O (19:1) at 0 ^{o}C to provide alcohol **42**. The product was confirmed by ^{1}H NMR, ^{13}C NMR, IR and elemental analysis. In ^{1}H NMR spectrum, disappearances of peaks corresponding to *PMB* group were noticed. Moreover, IR spectra showed a characteristic signal due to hydroxyl group at 3393 cm.$^{-1}$



41 **42**

Scheme 3

The free hydroxyl group of **42** was converted into the aldehyde (**43**) with IBX[43] in DMSO/THF at room temperature. The aldehyde **43** was transformed into the corresponding acid fragment **31** using $NaClO_2$, NaH_2PO_4 in *tert*-BuOH/THF/H_2O in presence of 2-methyl-2-butene.[44] The structure of **31** was supported by its ^1H NMR, ^{13}C NMR, mass spectroscopy and elemental analysis. The ^{13}C NMR spectrum of **31** revealed the characteristic signals at δ 170.28 ppm corresponding to carbonyl moiety of acid group. The mass spectroscopy showed a peak at *m/z* 531.5 due to $[M+Na]^+$ ion. The IR spectrum revealed absorption due to acid carbonyl at 1736 cm^{-1} (Scheme 4).



42 **43** **31**

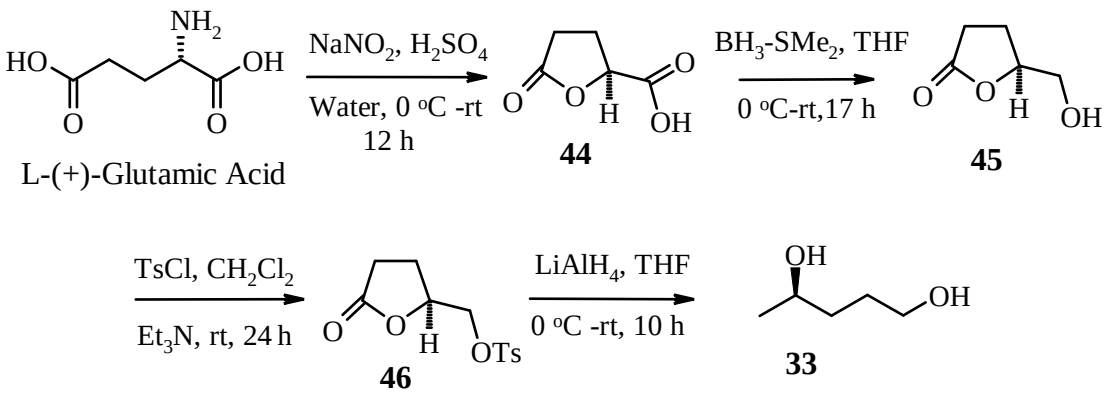
Scheme 4

Synthesis of the Alcohol segment

The synthesis of alcohol segment **32** rested on the prospects of "chiron approach" which over the years has been nurtured by the synthetic chemists to manoeuvre chemically and stereochemically with obvious operational and practical advantages to

realize the asymmetric targets. Readily available chiral starting materials such as amino acids have their unique place in the practice of art of synthetic design, particularly when one or two chiral centers are sought. The scrutinization of the molecular architecture of our target to locate the elements of symmetry, chirality and functionality, decoding such information and transposing it onto the carbon framework of suitable synthetic precursors (chirons) should imply 2,5-pentane diol **33**[45] by systematic functionalization. Essentially, 2,5-pentane diol **33** poses as a replica of a segment of our target, *i.e.*, as chiral template. This precarious planning should reveal L-(+)-glutamic acid, the precursor of 2,5-pentane diol **33** as the chiron progenitor to start with.

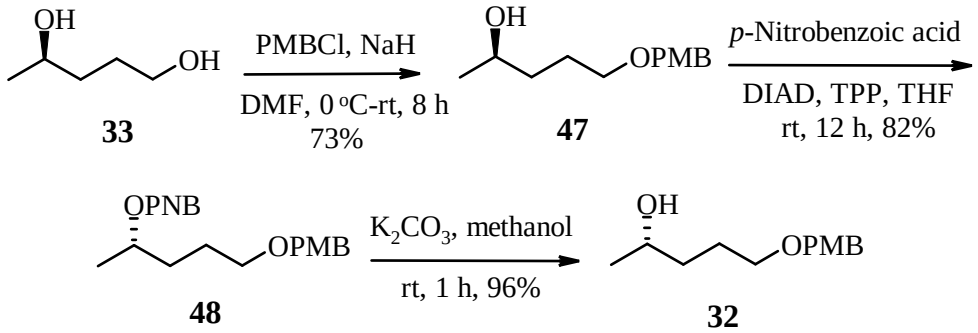
Accordingly, L-(+)-glutamic acid was converted to acid lactone **44**, which involved the treatment with $NaNO_2/H_2SO_4$ (cat.), water. Reduction of acid **44** was next performed with borane dimethyl sulphide complex in THF to afford the alcohol **45** according to lit[46] procedure. The primary hydroxyl group of **45** was converted to tosyl derivative **46**, followed by reduction with LAH to provide (*R*)-2,5-pentane diol synthon **33**. The diol **33** was confirmed by the relevant signals in the ^1H NMR, ^{13}C NMR spectrum and well corresponded with the reported value[45] (Scheme 5).



Scheme 5

A regioselective protection of the primary hydroxyl group as *p*-methoxybenzyl ether **47** was accomplished by using PMBCl, NaH in DMF. The −*OPMB* group was identified by a singlet at δ 3.80 ppm due to aromatic −OCH_3 group, a singlet at δ 4.44 (s, 2H) ppm due to benzylic methylene (−$\underline{CH_2}Ph$) group and two doublets at δ 6.86 (J = 8.6 Hz, 2H), 7.24 (J = 8.6 Hz, 2H) ppm corresponding to aromatic protons. The methylene protons of −$\underline{CH_2}OPMB$ resonated at δ 3.48 (t, J = 5.8 Hz, 2H) ppm.

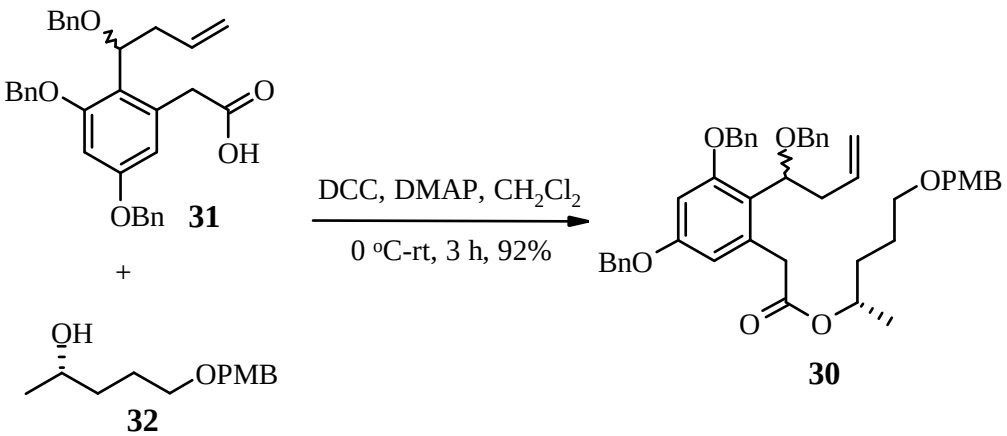
The projected Mitsunobu reaction[47] for inverting the configuration at C4 of **47** was executed in presence of DIAD, *p*-nitrobenzoic acid and TPP in THF at room temperature provided the *p*-nitrobenzoate derivative **48** (Scheme 6). The ^{1}H NMR spectrum of **48** showed doublet at δ 8.17 (*J* = 8.9 Hz, 2H), 8.27 (*J* = 8.9 Hz, 2H) ppm (A2B2 doublets) due to −*OPNB* group. The ^{13}C NMR and other spectral data also supported the structure. In the ^{1}H NMR spectrum, a clear-cut down field shift of C4-H signals was observed, which indicates that the ester formation indeed occurred. Finally, the ester **48** was hydrolyzed in presence of K_2CO_3 in methanol to furnish the alcohol **32**, one of the coupling partners.



Scheme 6

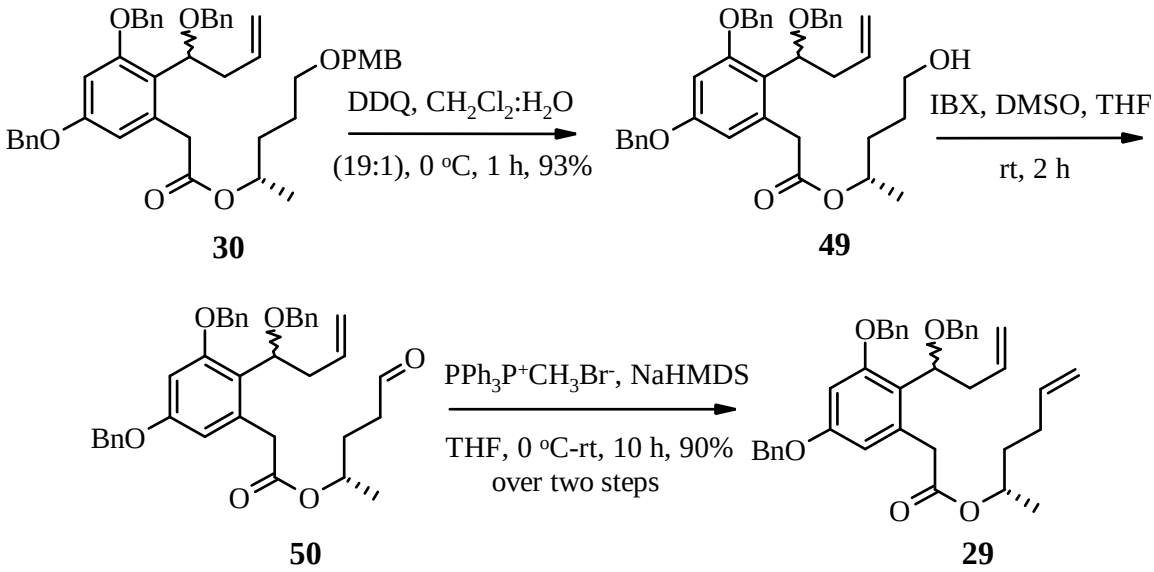
Coupling reaction between 31 and 32

With two coupling partners in hand, the engagement was accomplished using DCC[48], DMAP in dichloromethane to afford **30**. The structure was fully secured on the basis of information from ^{1}H NMR, ^{13}C NMR, DEPT and IR spectral data.



Scheme 7

Unmasking of *PMB* ether in **30** was accomplished in presence of DDQ in CH_2Cl_2/H_2O (19:1) to provide the free alcohol **49** in 93% yields. This deprotection was supported by the ^1H NMR spectrum by the disappearance of peaks due to −*PMB* group. The ^{13}C NMR, IR, EI MS [$(M+Na^+)$ at *m/z* 737.8] spectral studies also supported the structure. The alcohol **49** was oxidized by IBX in DMSO/THF at room temperature to give rise to aldehyde **50**. Wittig methylenation of **50** with incipient methylenetriphenylphosphorane [generated *in situ* from $CH_3P^+Ph_3Br^-$ and NaHMDS] in THF gave the requisite diene intermediate **29** in 90% yields (in two steps). The structure of acyclic diene was elucidated from the ^1H, ^{13}C NMR, IR and mass spectral analysis. The ^1H NMR spectrum indicated presence of olefinic groups in the region of δ 4.81-5.04 (two CH_2=) and 5.64-5.88 (two *CH*=) ppm, while the EI mass recorded peak at *m/z* 613.6 $[M+Na]^+$Now, the stage is set to have the RCM reaction.



Scheme 8

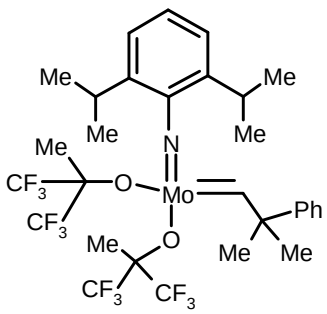
Ring Closing Metathesis: a brief view

Olefin metathesis is a unique carbon skeleton redistribution in which unsaturated C-C bonds are rearranged in the presence of metal carbine complexes. This can be utilized in three closely related type of reactions such as ring-opening metathesis polymerization (ROMP), ring-closing metathesis (RCM) and acyclic cross metathesis (CM). Ring closing metathesis, in which two un-substituted (or substituted) olefins

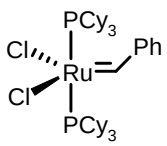
undergo ring closure with formal loss of ethylene, is one of the most popular methods of present time. It has received a great deal of attention in recent years for the synthesis of medium or large size ring systems from acyclic diene precursors. The reasons being:

1) *well designed, stable and highly active catalysts;*
2) *very high turnover number was observed in the catalytic process;*
3) *its efficiency in medium to macro-ring cyclization;*
4) *its superiority over other cyclization method like macrocyclisation, Diels-Alder etc., because of favourable thermodynamic profile;*
5) *adaptable for both solution and solid phase reactions;*
6) *water solubility enabling the metathesis in water and methanol;*
7) *design of recyclable and polymer bound catalysts;*
8) *applicability to broad scope of substrates like ene –yne and yne-yne metathesis, in addition to tri and tetra-substituted systems;*
9) *combinatorial RCM libraries;*
10) *eco-friendly profile, including viability in solvents like super critical CO_2;*
11) *compatible with various functional groups.*

*Although a number of titanium and tungsten catalyst have been developed for metathesis and related reaction the Schrock's catalyst **(51)**, Grubbs' 1st **(52)** and 2nd generation catalysts **(53)** have greatly attracted the attention of synthetic chemists because of their high reactivity and commercial availability. This reaction has changed the strategy of synthetic chemist and it is very common to find RCM as key transformation in the recent total synthesis of natural products.*

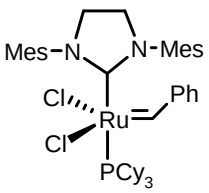


Schrock's catalyst **51**



Grubbs' 1st generation catalyst

52



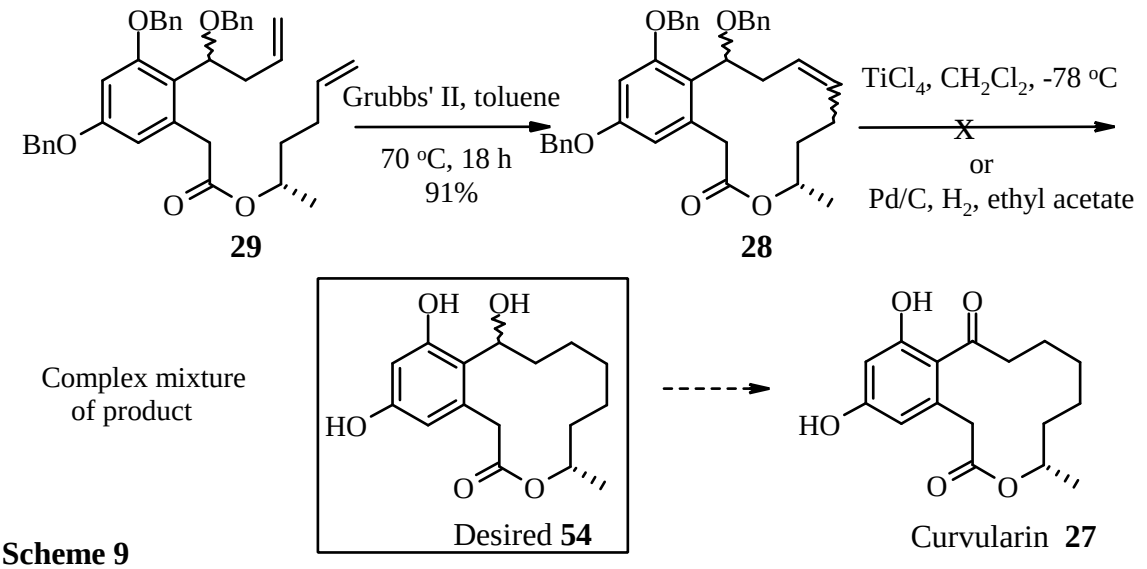
Grubbs' 2nd generation catalyst

53

Figure 18

Ring closing metathesis[49] of **29** on exposure to Grubbs' second generation catalyst (3 mol%) in anhydrous toluene at 70 ^{o}C was found to be facile and afforded the desired macrolactone **28** in 91% yield as an inseparable mixture of diastereomers. Since, the newly formed olefin would be hydrogenated at a later stage of synthetic sequence, we have proceeded further. The structural integrity of compound **28** was established by ^{1}H NMR and ^{13}C NMR spectrum. The ^{1}H NMR spectrum of **28** showed the resonances accounting for only two internal olefinic protons at δ 5.18-5.41 (m, 2H) ppm and the absence of peaks belonging to terminal olefinic protons, thereby confirming the ring closure.

The next objective of our synthetic endeavor needed global deprotection of benzyl group as well as reduction of the olefin in a single shot. Accordingly, compound **28** was subjected to catalytic hydrogenation with 10% Pd/C in ethyl acetate to obtain the triol **54**. Unfortunately, we got a complex mixture of products.



Scheme 9

So, the compound **28** was then treated with $TiCl_4$[50,51] at –78 ^{o}C to obtain triol **54**. However, the major isolated product didn't provide the clear image over the structure, as the ^{1}H NMR spectrum was complex and suggested mixture of compounds formed probably due to destructive decomposition of **28**. Hence, we stopped at this juncture and looked for alternative.

With the failure of aforemention route, the mission for conquering the synthesis of curvularin **27** solely rested on the alternative protecting group for hydroxyl group of **40**

rather than benzyl ether. To reduce the steps in the journey to reach target, we have furnished the alcohol **58** in another way. The retrosynthetic analysis is outlined in Figure 19.

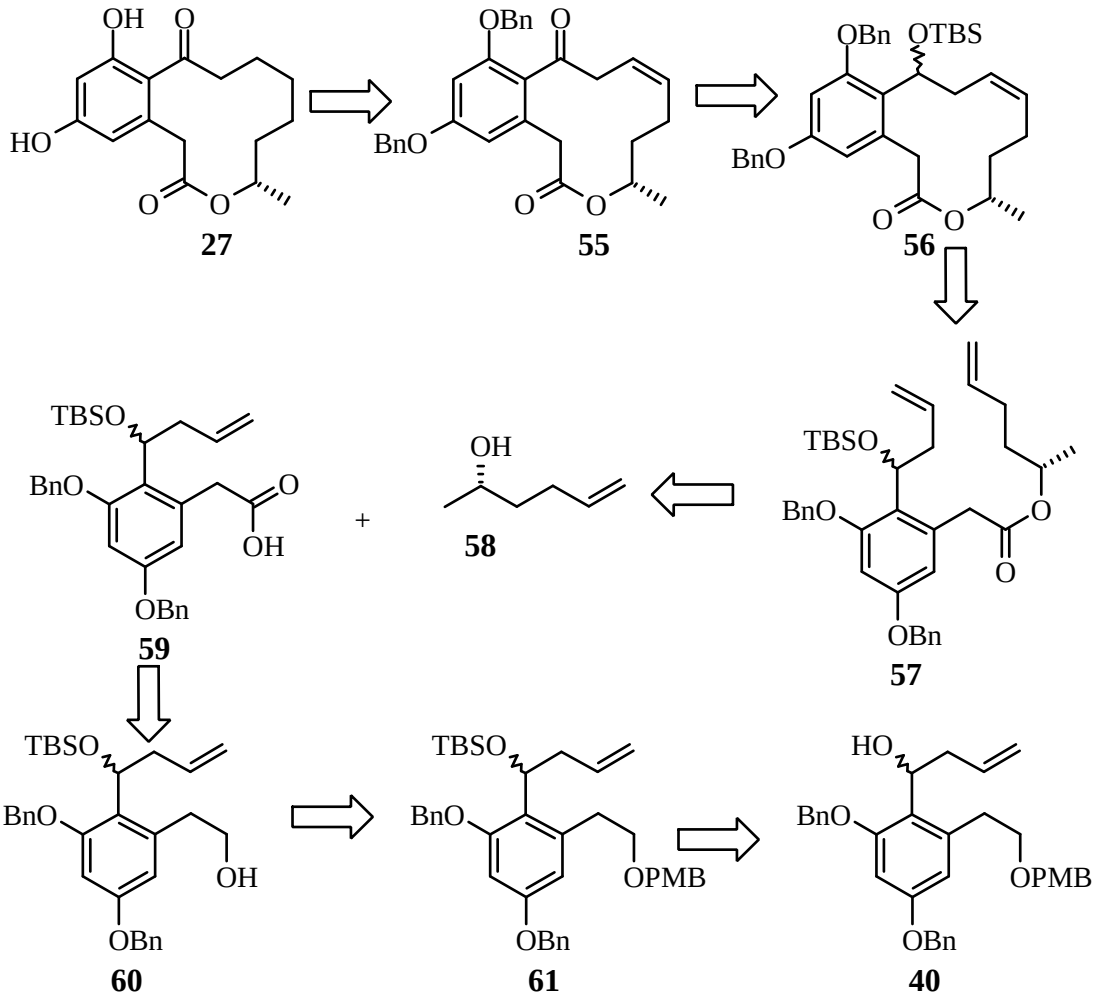
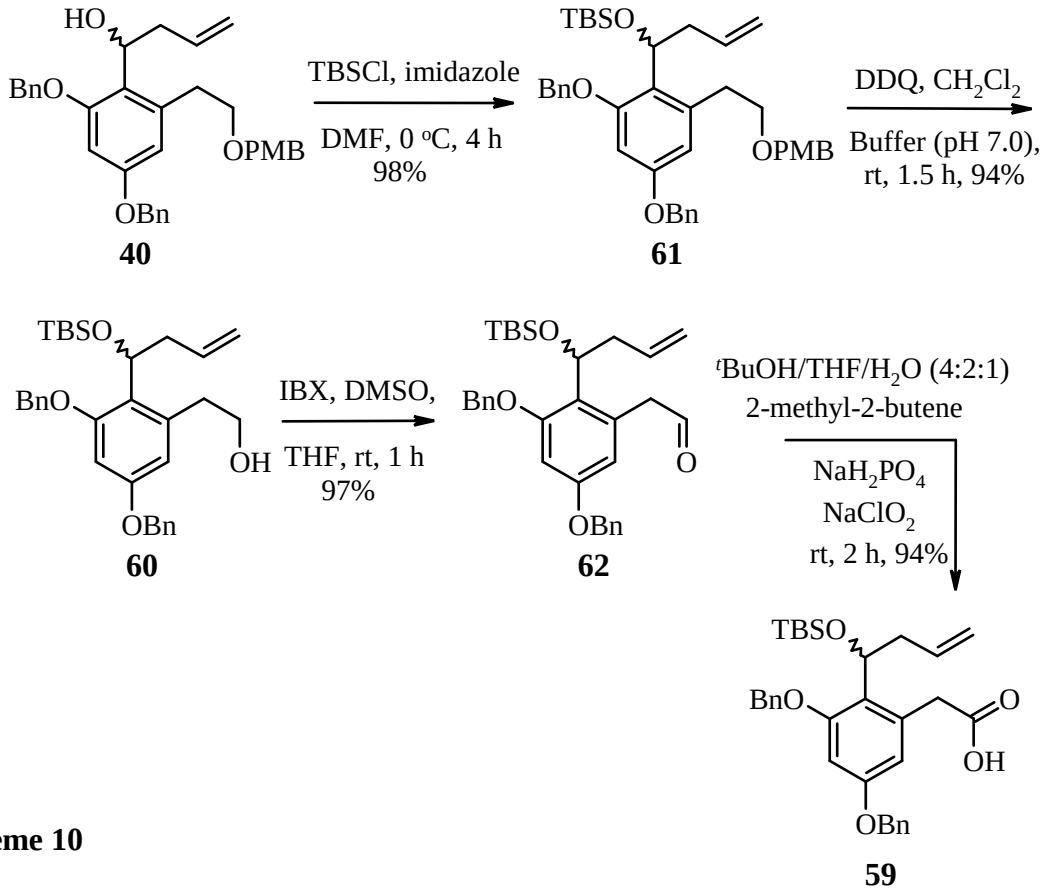


Figure 19

Synthesis of the Acid Segment

The homoallylic alcohol **40** was protected as silyl ether **61** using TBSCl[52] and imidazole in DMF. The ^{1}H NMR spectrum of **61** displayed singlets at δ −0.07 (s, 3H), 0.10 (s, 3H), and 0.95 (s, 9H) ppm due to −*TBS* group and all other signals appeared at their respective positions. The ^{13}C NMR spectral data was also supported the formation of **61**. In order to accomplish the required acid, the *p*-methoxybenzyl ether of **61** was cleaved using DDQ in CH_2Cl_2 at room temperature in the presence of phosphate buffer[53] (pH, 7.0) to provide **60**.

Our next endeavor was the conversion of **60** into the corresponding acid derivative **59**. Thus, **60** was first subjected to oxidation by using IBX[43] in DMSO/THF to furnish aldehyde **62** in 97% yield, which was subjected to the treatment of $NaClO_2$, 2-methyl-2-butene in *tert*-BuOH/THF/H_2O[44] in presence of phosphate buffer NaH_2PO_4 to afford the corresponding acid **59**. The ^{1}H NMR spectrum of **59** indicated the absence of methylenic protons due to oxidation and the downfield shift of protons adjacent to the carbonyl moiety. The ^{13}C NMR spectrum of **59** showed the corresponding resonance for carbonyl group at δ 170.4 ppm.

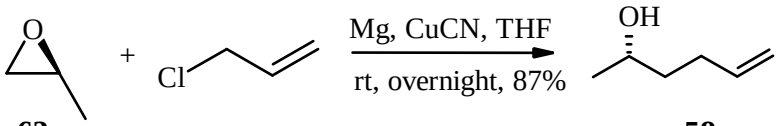


Scheme 10

Synthesis of the Alcohol Segment

The synthesis of alcohol **58** was accomplished with commercially available (*S*)-(−)-methyloxirane **63**. The epoxide **63** was subjected to CuCN coordinated regioselective nucleophilic opening[54] with allylmagnesium chloride to provide the alcohol **58** in 87% yield, which was adequately substantiated by spectral studies. In the ^{1}H NMR spectrum, the olefinic protons showed peaks at δ 4.90-5.07 (m, 2H) ppm (*H_2C*=, due to terminal protons) and 5.71-5.91 (m, 1H) ppm (*HC*=). Two set of methylene protons, homoallylic

and allylic, resonated as multiplets in the region δ 1.46-1.58 (2H) and 2.06-2.20 (2H) ppm, respectively. The EI mass spectrum gave a peak at $[M+Na]^+$ 123.1. The ^{13}C NMR spectrum showed characteristic peak at δ 114.7 ppm accounting for terminal methylene carbon (=CH_2).

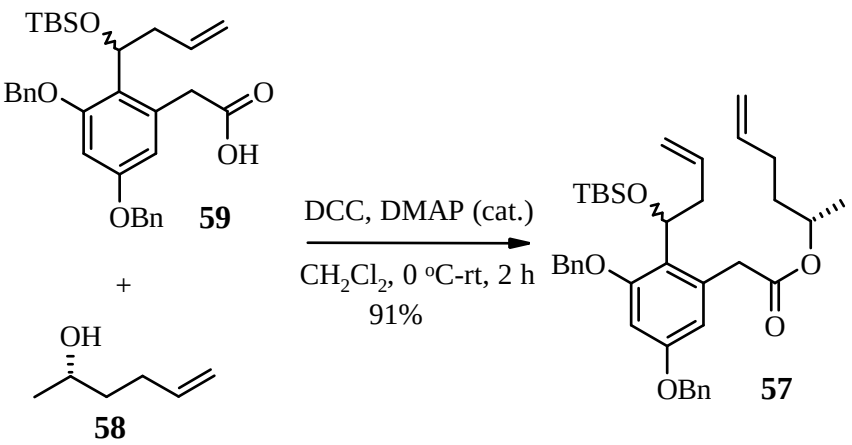


63 **58**

Scheme 11

Coupling reaction between 58 and 59

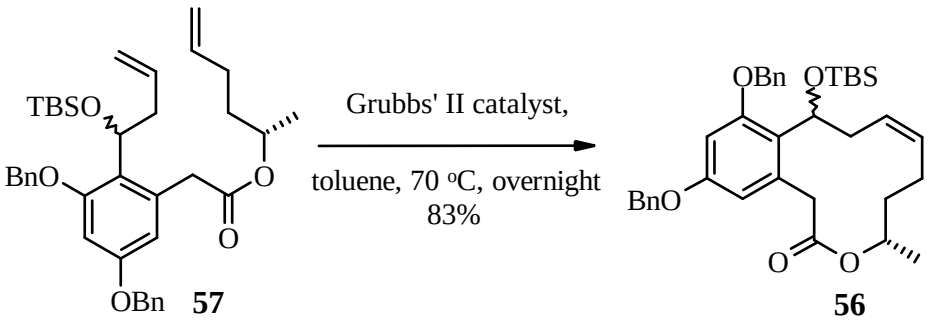
Coupling of the alcohol **58** and acid **59** in the presence of DCC[48] and DMAP gave the ester **57**. This readied the substrate for RCM. The structure of acyclic diene was elucidated from the ^1H NMR and mass spectral analysis. The ^1H NMR spectrum indicated presence of two olefinic groups in the region of δ 4.92-5.07 (two CH_2=) and 5.67-5.91 (two *CH*=) ppm, while the EI mass recorded the mass peak at *m/z* 637.8 $[M+Na]^+$ The ^{13}C NMR spectrum of **57** showed the corresponding resonance for ester carbonyl group at δ 170.9, 171.9 ppm. All the other resonances were in support of the assigned structure.



Scheme 12

After having synthesized the diene derivative **57**, our next endeavor was to apply the ring closing metathesis reaction[49] to achieve the synthesis of macrocyclic framework**.** Thus, the ring closing metathesis reaction of **57** was successfully accomplished using 3 mol% Grubbs' 2nd generation catalyst in toluene at 70 ^oC to furnish the macrolide **56** in

83% yield. The structure of **56** was adequately secured by ^{1}H NMR, ^{13}C NMR, mass spectrum and elemental analysis. The ^{1}H NMR spectrum of **56** showed characteristic olefinic protons at δ 5.17-5.74 (m, 2 H) ppm. The rest of the protons had the expected chemical shifts (Scheme 13). In the ^{13}C NMR spectrum, disappearance of terminal methylene peak confirmed the product formation.

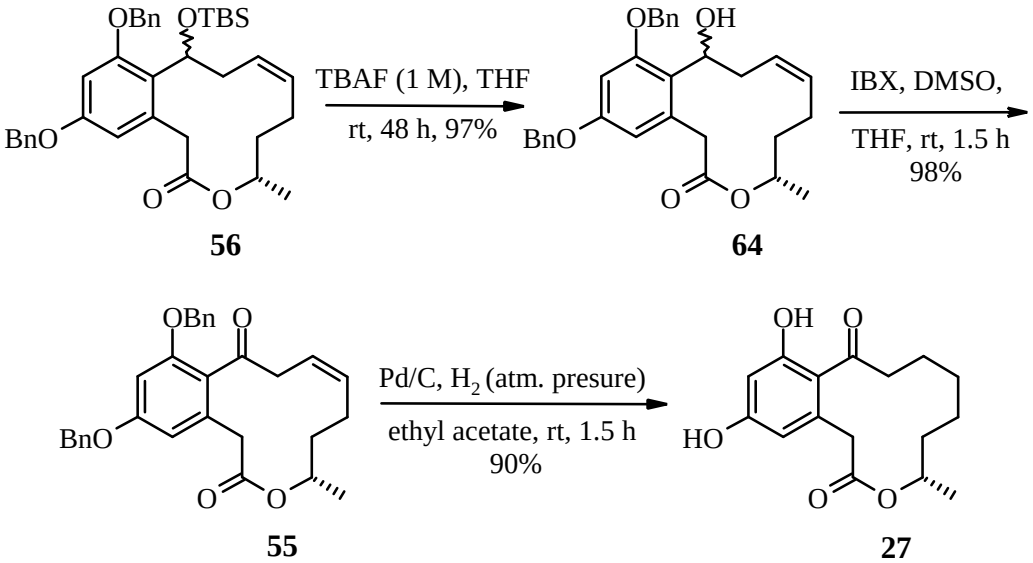


Scheme 13

The cleavage of silyl ether was accomplished by exposing **56** with $Bu_4N^+F^-$ in THF at room temperature to obtain hydroxyl lactone **64**. The ^{1}H NMR, ^{13}C NMR spectrum and elemental analysis of **64** were in agreement with the assigned structure. Oxidation of **64** to the corresponding keto lactone **55** was accomplished with IBX[43] in DMSO/THF at room temperature. A downfield shift of signal due to the methylene group adjacent to keto group as a multiplet at δ 3.05-3.34 (m, 2H) and the disappearance of the C-2 benzylic proton signal were in favor of the transformation. In the ^{13}C NMR spectrum, the carbonyl carbon of the keto group appeared at δ 204.6 ppm.

Hydrogenation of **55** over 10% Pd/C in ethyl acetate at atmospheric pressure and temperature took place with concomitant cleavage of benzyl ether to accomplish curvularin **27** in 90% yields. The spectroscopic (^{1}H NMR, ^{13}C NMR) (Table-1) and analytical data were in all respects identical to those reported in the literature.[37h] The structure of **27** was supported by spectral and analytical data. In the ^{1}H NMR spectrum of **27**, the H2 and H2[1] were resonated as two doublet at δ 3.71 (d, *J* = 15.7 Hz, 1H) and 3.79 (d, *J* = 15.6 Hz, 1H) ppm, respectively, and the protons adjacent to lactone moiety, *i.e.* at C10 were resonated as two doublet of double doublet at δ 2.78 (ddd, *J* = 2.9, 9.8, 15.5 Hz, 1H) and 3.12 (ddd, *J* = 2.9, 8.7, 15.5 Hz, 1H) ppm and a multiplet at δ 4.90-4.96 (m, 1H) ppm due to proton at C15 in accordance with the structure. The IR spectrum of **27**

revealed the absorption at 1719 and 1661 cm^{-1} pertinent to keto-lactone moiety (Scheme 14).



Scheme 14

Table 1. ***NMR Spectral data of (-) curvularin (Kunz et al.)[37h] and compound 27***

^{1}H NMR (300 MHz, acetone-d_6) *(Kunz et al.)*[37h]	**^{1}H NMR (400 MHz, acetone-d_6) compound 27**	**^{13}C NMR 75.5MHz, acetone-d_6) *(Kunz et al.)*[37h]**	**^{13}C NMR (50 MHz, acetone-d_6) compound 27**
1.10 (d, *J* = 6.3Hz, 3H)	1.13 (d, *J* = 6.3 Hz, 3H)	20.6	20.53
1.63-1.22 (m, *7H*)	1.24-1.28 (m, 2H), 1.40-150 (m, 3H), 1.52-1.57 (m, 1H), 1.59-1.64 (m, 1H),	23.5	23.40
1.78-1.70 (m, 1H)	1.73-1.80 (m, 1H)	24.6	24.51
2.75 (ddd, *J* = 15.5, 9.6, 2.9 Hz, 1H)	2.78 (ddd, *J* = 15.5, 9.9, 2.9 Hz, 1H)	27.5	27.44
3.10 (ddd, *J* =15.5, 8.5, 2.9 Hz, 1H)	3.12 (ddd, *J* = 15.5, 8.7, 2.9 Hz, 1H)	32.9	32.81
3.68 (d, *J* =15.5 Hz, 1H)	3.71 (d, *J* = 15.7 Hz, 1H)	39.7	39.63
3.77 (d, *J* = 15.5 Hz, 1H)	3.79 (d, *J* = 15.6 Hz, 1H)	44.0	43.90
4.94-4.87 (m, 1H)	4.90-4.96 (m, 1H)	72.6	72.57
6.33 (d, *J* = 2.2 Hz, 1H)	6.36 (d, *J* = 2.2 Hz, 1H)	102.4	102.46
6.38 (d, *J* = 2.2 Hz,	6.41 (d, *J* = 2.2 Hz,	112.2	112.15

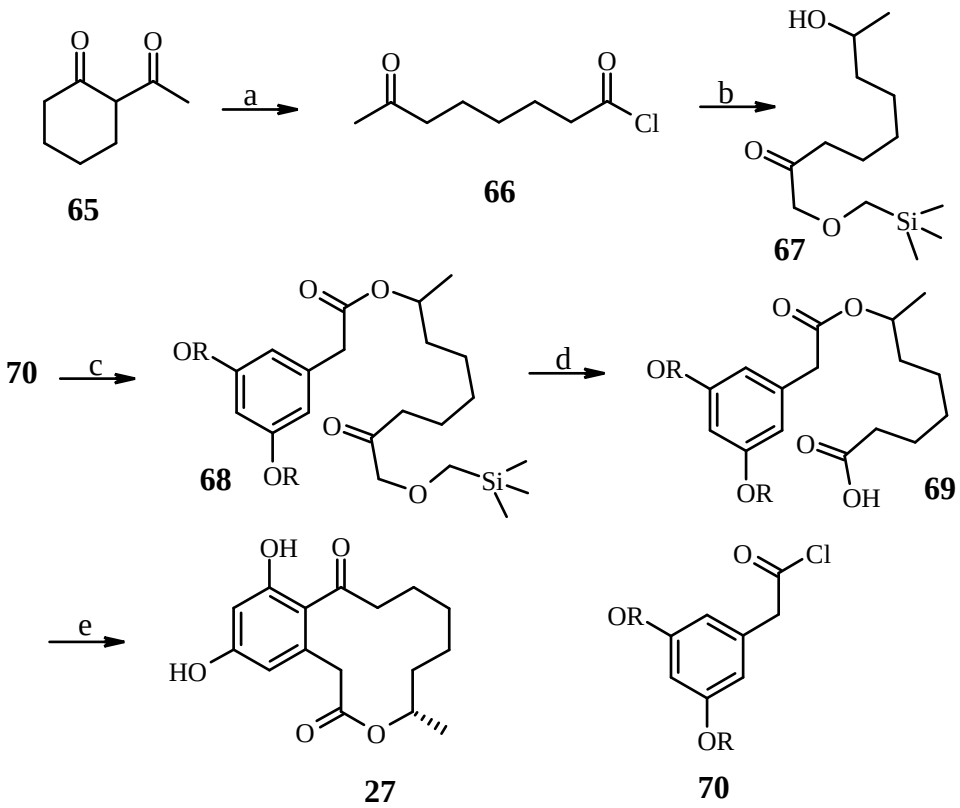
1H)	1H)		
8.75 (brs, 1H)	8.82 (bs, 1H)	121.3	121.27
9.17 (brs, 1H)	9.19 (bs, 1H)	136.9	136.89
		158.2	158.17
		160.1	160.07
		171.0	170.97
		206.7	206.65

In conclusion, we have accomplished a total synthesis of curvularin **27** in a complete convergent fashion. The assembly of macrolactone ring with requisite stereochemistry through the central transformation “ring closing metathesis” constitutes a flexible and highly efficient synthetic strategy. We anticipate that the synthetic strategy, detailed above, could be extended to prepare the analogues through functional group manipulation of the appropriate alcohol partner in the coupling stage. This protocol will be promising for gram quantity synthesis of curvularin **27**, a nonsteroidal anti-inflammatory drugs.

Other Approaches

(I) *Gerlach's approach (1977)*[37b]

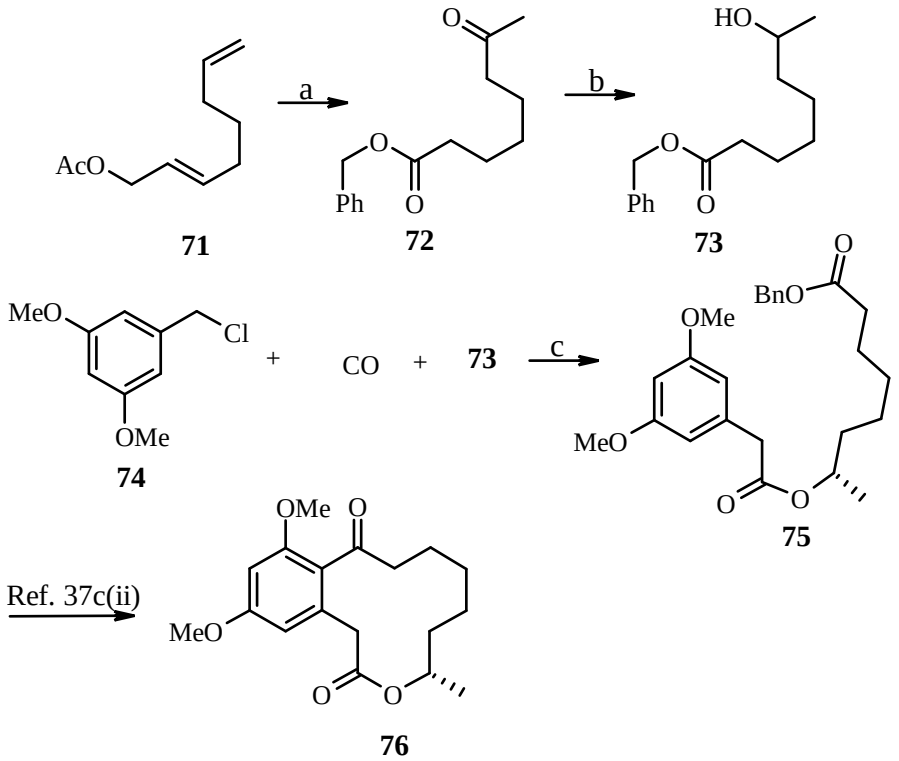
The mould metabolite curvularin **27** has been synthesized with the help of a new carboxyl protecting group that can be removed selectively with fluoride ions. 2-(Trimethylsilyl)ethyl 7-hydroxy-octanoate **67** was acylated with 3,5-dibenzyloxyphenacetyl chloride **70** to form **68** with two different ester groups. Tetrabutylammonium fluoride in tetrahydrofuran cleaved the 2-(trimethylsily1)ethyl ester in **68** selectively to form the carboxylate anion of **40** together with ethylene and trimethylsilyl fluoride. Curvularin dibenzyl ether was formed by intramolecular acylation of **69**. Removal of the benzyl ether groups by hydrogenolysis led to *(R)*-curvularin. The naturally occurring (*S*)-enantiomer was formed when (+)-(*S*)-**67** served as starting material.



Scheme 15: *Reagent and conditions*: a) (i) KOH, (ii) $(COCl)_2$; b) $(CH_3)_3SiCH_2CH_2OH$, (ii) $NaBH_4$; c) **67**, K_2CO_3; d) TBAF; e) (i) $(CF_3CO)O$, CF_3COOH, (ii) Pd/C, H_2.

II) *Takahashi's approach (1980)*[37c(i)]

The formal synthesis of (±) dimethyl curvularin **76** was accomplished using palladium-catalyzed carbonylation of 3,5-dimethoxybenzyl chloride **74** with benzyl 7-hydroxyoctanoate **73** afforded benzyl 7-(3,5-dimethoxyphenylacetoxy) octanoate **75**. The ester **75** was easily prepared from the butadiene telomer obtained by the palladium-catalyzed reaction of butadiene with acetic acid.

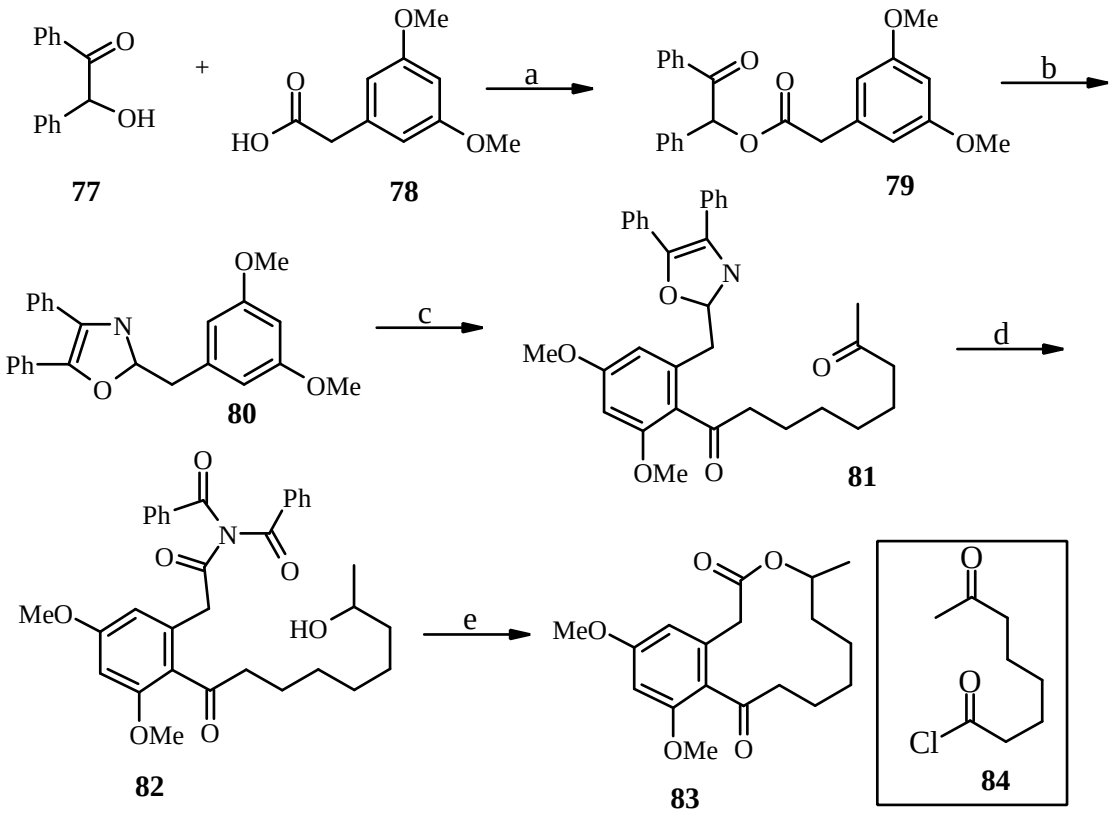


Scheme 16: *Reagent and conditions*: a) (i) $PdCl_2$, CuCl, O_2, aqueous DMF, (ii) aqueous KOH, (ii) Pd/C, H_2, ethanol, (iv) Jones oxidation, (v) BnBr, NaH, HMPA, 0 ^oC; b) $NaBH_4$, ethanol; c) NaOAc, $PdCl_2(PPh_3)_2$, CO(10 atm), dry benzene, 100 ^oC.

(IV) *Wasserman's approach (1981)*[37d]

Starting with the readily available methyl 3,5-dimethoxyphenyl acetate, the oxazole **80** was prepared in 68% overall yield in standard fashion by saponification with potassium hydroxide in ethanol to form acid **78**, condensation with benzoin **77** in the presence of DCC and 4-dimethylaminopyridine yielding the ester **79**, followed by treatment with excess ammonium acetate in refluxing glacial acetic acid. Friedel-Crafts

acylation of **80** with 7-oxooctanoyl chloride and anhydrous aluminum chloride in carbon disulfide gave the diketo oxazole **81**, which was selectively reduced at the aliphatic carbonyl with sodium borohydride in aqueous ethanol to provide the hydroxy oxazole **82**. Dye-sensitized photooxygenation of the hydroxy oxazole **82** in chloroform readily yielded the intermediate triamide, which, under acid catalysis and high dilution was converted to (±)-di-*O*-methylcurvularin **83**.

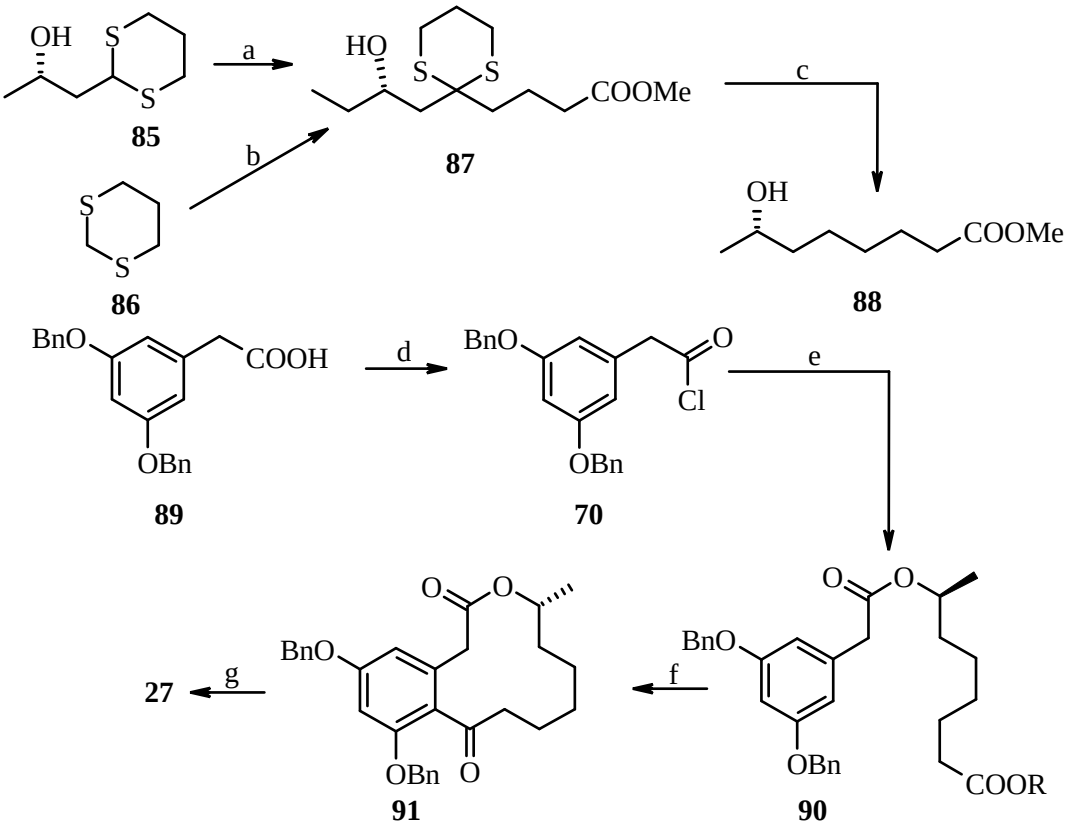


Scheme 17: *Reagent and conditions*: a) DCC, DMAP, Et_2O; b) NH_4OAc, HOAc, Δ; c) **84**, $AlCl_3$, CS_2; d) (i) NBH_4; (ii) O_2, $CHCl_3$; e) *p*-TSA, benzene, Δ.

(V) *Bracher's approach (1997)*[37g]

The macrocyclic lactone (*S*)-curvularin **27** was prepared in an enantiodivergent manner from (*S*)-methyl 7-hydroxyoctanoate **88**, which was easily obtained on two different ways. (*S*)-2-(2-hydroxypropyl)-1,3-dithiane **85** was converted to a dianion and alkylated with trimethyl 4-bromoorthobutyrate to give the hydroxy ester **87**. Alternatively, **87** can be prepared in a convenient one-pot procedure from commercially available starting materials. Thus, 1,3-dithiane **86** was deprotonated, alkylated with trimethyl 4-bromoorthobutyrate, then deprotonated again and treated with (*S*)-propylene

oxide, aqueous workup gave the 2,2-disubstituted dithiane **87**. Reductive desulfurization of the dithiane **87** with Raney nickel occurred smoothly to give the (5')-methyl 7-hydroxyoctanoate **88**. Esterification of **88** under either retention or inversion of the chiral centre gave the enantiomeric diesters **90**. Chemoselective cleavage of the methyl ester groups of these diesters, followed by intramolecular acylation and *O*-debenzylation gave curvularin **27**.

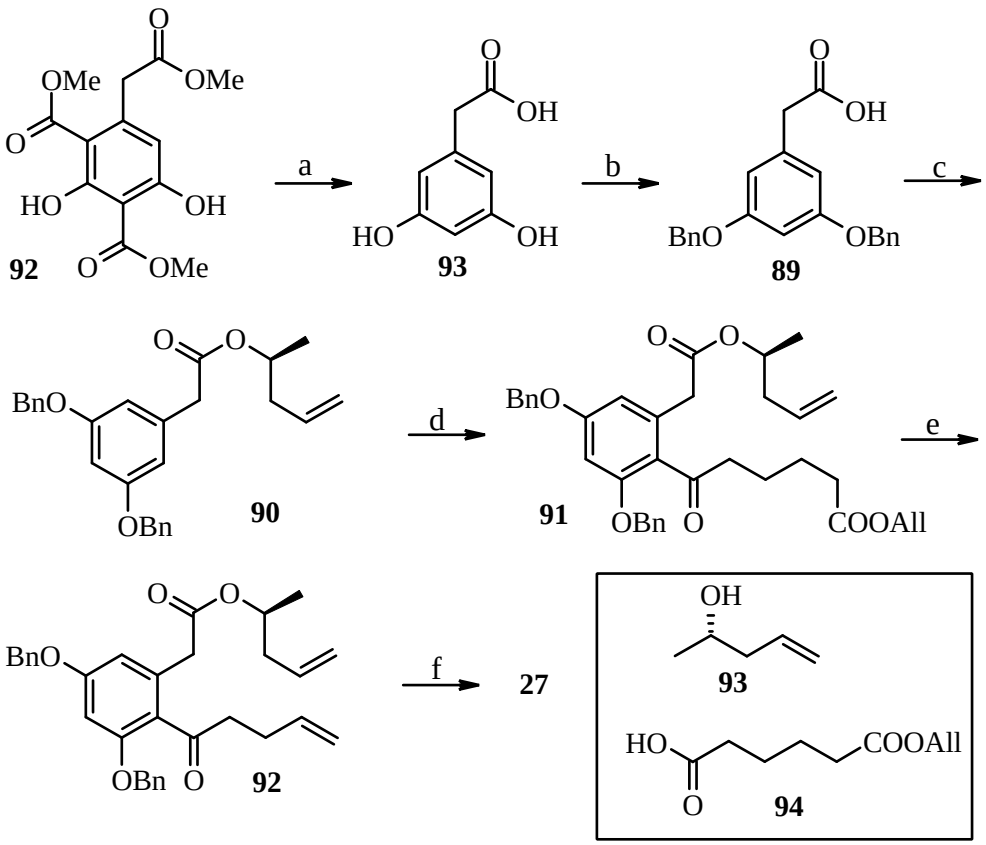


Scheme 18: *Reagent and conditions*: a) (i) *n*-BuLi (2 equiv.), $Br(CH_2)_3$-$C(OMe)_3$, THF; ii) HCl, H_2O (pH 5), b) (i) *n*-BuLi, $Br(CH_2)_3$-$C(OMe)_3$, THF; (ii) *n*-BuLi, (*S*)-propylene oxide; (iii) HCl, H_2O (pH 5), c) Raney nickel, THF, d) Oxalyl chloride, e) **88**, K_2CO_3, CH_2Cl_2 or **88**, Ph_3P, DEAD, diethyl ether; f) i) NaCN, HMPA, ii) TFAA, TFA; g) H_2, Pd/C, ethyl acetate.

(VI) *Kunz's Approach (2008)*[37h]

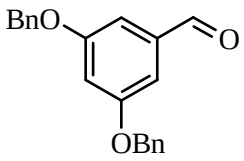
The synthetic plan adopted by Kunz *et al*. for the synthesis of curvularin **27** relied on a kochi oxidative decarboxylation and ring-closing metathesis reaction. The acid **89**

was accomplished from known triester **92** following some synthetic sequence. Esterification of phenylacetic acid **89** with alcohol **93** afforded compound **90**. Friedel-Craft acylation of **90** with **94** gave the diester **91**. Selective cleavage of the allyl ester, followed by Kochi decarboxylation furnished the divinyl compound **92**. RCM reaction of **92** using Grubbs' catalyst and subsequent hydrogenation over Pd/C afforded Curvularin **27**.



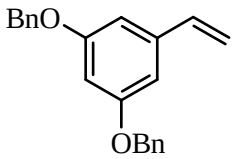
Scheme 19: *Reagent and conditions*: a) (i) 4 N NaOH, reflux, 30 min; (ii) H_2SO_4; b) (i) 2,2-dimethoxypropane, HCl, 20 ^oC; (ii) BnBr, K_2CO_3, acetone; (iii) 2 N NaOH; c) **93**, DCC, DMAP, CH_2Cl_2; d) (i) **94**, $(COCl)_2$, 20 ^oC; (ii) $SnCl_4$, −60 to −10 ^oC, CH_2Cl_2; e)(i) 4-Me-$PhSO_2Li$, $[Pd(PPh_3)_4]$, methanol/THF 1:1; (ii) $Pd(OAc)_4$, $Cu(OAc)_2$, pyridine, benzene; (iii) 80 ^oC, 1 h; f) (i) Grubbs' (II) catalyst, toluene, 80 ^oC; (ii) Pd/C, H_2, THF/MeOH (1:1).

3,5-bis(benzyloxy)benzaldehyde (37):



A mixture of compound **36** (25.0 g, 78.03 mmol), PDC (44.03 g, 117.04 mmol) and 4 Å mol. sieves powder (10.0 g) in CH_2Cl_2 (250 mL) were stirred at room temperature for 1.5 h and then concentrated. The residue was diluted with ethyl acetate and filtered. The filtrate was concentrated to afford crude **37** (27.65 g). The crude aldehyde was used for the next reaction without further purification.

(5-vinyl-1,3-phenylene)bis(oxy)bis(methylene)dibenzene (38):



n-BuLi (63.4 mL, 101.44 mmol, 1.6 M solution in hexane) was added at 0 ^oC to methyltriphenylphosphonium iodide (63.05 g, 156.06 mmol) in THF (150 mL). The resultant yellowish solution was stirred for 30 min. A solution of **37** (27.65 g) in THF (50 mL) was then added. After being stirred at 0 ^oC for 1 h, the reaction mixture was gradually warmed to room temperature and continued for overnight. After quenching with saturated NH_4Cl solution, the solvent was evaporated and the residue taken in diethyl ether. The organic phase was washed with water and brine, dried (Na_2SO_4), and concentrated. The residue on silica gel column chromatography purification gave **38** (22.4 g) as colourless oil.

Yield : 91%

Mol. Formula : $C_{22}H_{20}O_2$

IR ($CHCl_3$) cm^{-1} : 3064, 3032, 2929, 2870, 1590, 1496, 1453, 1376, 1291, 1216, 1157, 1048, 1028, 909, 832, 735, 696.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 5.08 (s, 4H), 5.29 (dd, *J* = 0.8, 10.8 Hz, 1H), 5.75

(dd, *J* = 0.8, 17.4 Hz, 1H), 6.58-6.61 (m, 1H), 6.67-6.75 (m, 2H), 7.32-7.50 (m, 10H) ppm.

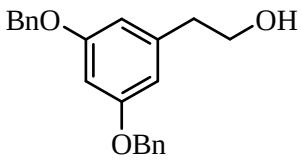
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 69.98, 101.60, 105.50, 114.35, 127.48, 127.94, 128.54, 136.79, 136.83, 139.58, 160.03 ppm.

ESI MS (*m/z*) : 339.291 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 83.51; H, 6.37.

Found: C, 83.29; H, 6.15.

2-(3,5-bis(benzyloxy)phenyl)ethanol (39):



To a solution of **38** (11.64 g, 36.79 mmol) in anhydrous THF (100 mL) was added $BH_3{\cdot}SMe_2$ (1.7 mL, 18.39 mmol) slowly at 0 ^oC and stirred for 3 h at the same temperature. MeOH and saturated aq. NaOAc were added to the reaction mixture at 0 ^oC until the effervescence ceased and stirring continued for 30 min. Then 30% H_2O_2 was added and stirred at room temperature for 30 min. THF and MeOH were removed on rotavapor, and extracted twice with EtOAc. The combined organic fractions were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel column chromatography using EtOAc-light petroleum (3:7) to give **39** (10.92 g).

Yield : 89%

Mol. Formula : $C_{22}H_{22}O_3$

IR ($CHCl_3$) cm^{-1} : 3393, 3064, 3032, 2927, 2873, 1593, 1497, 1452, 1376, 1345, 1291, 1216, 1157, 1048, 1028, 829, 753, 696.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.78 (t, *J* = 6.4 Hz, 2H), 3.82 (bt, *J* = 6.4 Hz, 2H), 5.01 (s, 4H), 6.42-6.52 (m, 3H), 7.28-7.43 (m, 10H) ppm.

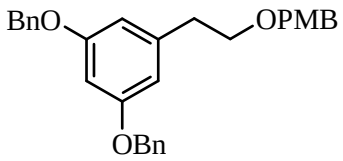
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 39.31, 63.18, 69.81, 99.92, 108.07, 127.40, 127.83, 128.43, 136.74, 140.83, 159.91 ppm.

ESI MS (*m/z*) : 357.39 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 79.02; H, 6.63

Found: C, 78.92; H, 6.79

2,4-bis(benzyloxy)-6-(2-(4-methoxybenzyloxy)ethane (35):



To an ice-cooled solution of **39** (4.98 g, 14.88 mmol) in dry DMF (50 mL), NaH (60% dispersion in oil, 893 mg, 22.23 mmol) was added at 0 ^{o}C. After 30 minutes, PMBCl (3.1 mL, 22.23 mmol) was introduced and stirred for additional 3 h at the same temperature. The reaction mixture was partitioned between water and ethyl acetate. The organic layer was washed with water, brine, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel column chromatography using EtOAc-light petroleum (1:9) to obtain **35** (5.51 g) as thick oil.

Yield : 81%

Mol. Formula : $C_{30}H_{30}O_4$

IR ($CHCl_3$) cm^{-1} : 3032, 2932, 2860, 1593, 1512, 1453, 1375, 1301, 1247, 1152, 1096, 1035, 822, 737, 696.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.76 (t, *J* = 7.1 Hz, 2H), 3.55 (t, *J* = 7.1 Hz, 2H), 3.67 (s, 3H), 4.35 (s, 2H), 4.90 (s, 4H), 6.39 (s, 3H), 6.76 (d, *J* = 8.6 Hz, 2H), 7.14 (d, *J* = 8.6 Hz, 2H), 7.21-7.34 (m, 10) ppm.

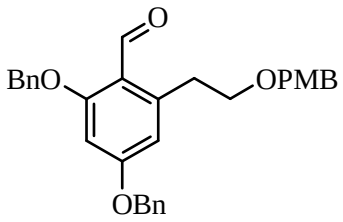
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 36.61, 55.10, 69.89, 70.59, 72.60, 99.87, 108.09, 113.69, 127.47, 127.87, 128.50, 129.23, 130.38, 136.96, 141.35, 159.10, 159.85 ppm.

ESI MS (*m/z*) : 477.32 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 79.27; H, 6.65.

Found: C, 79.49; H, 6.96.

2,4-bis(benzyloxy)-6-(2-(4-methoxybenzyloxy)ethyl)benzaldehyde (34):



$POCl_3$ (2.6 mL, 28.18 mmol) was dropped slowly into anhydrous DMF (7 mL) at 0 ^oC, and the resulting solution was stirred at 25 ^oC for 20 min. A solution of **35** (3.20 g, 7.04 mmol) in anhydrous DMF (23 mL) was added slowly and the reaction was warmed to 75 ^oC for 2 h. The reaction was then allowed to cool to 25 ^oC and poured into ice water. The mixture was neutralized with 2 N NaOH to pH = 7 and stirred 1.5 h at 25 ^oC. The reaction mixture was diluted with ethyl acetate, washed with H_2O, brine, dried over Na_2SO_4 and concentrated. The residue was purified on silica gel column chromatography using EtOAc-light petroleum (1:9) to obtain **34** (2.78 g) as colourless oil.

Yield : 82%

Mol. Formula : $C_{31}H_{30}O_5$

IR ($CHCl_3$) cm^{-1} : 3032, 2933, 1673, 1598, 1572, 1513, 1436, 1384, 1320, 1247, 1152, 1090, 1031, 820, 754, 698.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 3.21 (t, *J* = 6.6 Hz, 2H), 3.59 (t, *J* = 6.6 Hz, 2H), 3.67 (s, 3H), 4.35 (s, 2H), 4.95 (s, 2H), 4.99 (s, 2H), 6.40 (d, *J* = 2.2 Hz, 1H), 6.42 (d, *J* = 2.2 Hz, 1H), 6.73 (d, *J* = 8.6 Hz, 2H), 7.12 (d, *J* = 8.7 Hz, 2H), 7.22-7.32 (m, 10H), 10.45 (s, 1H) ppm.

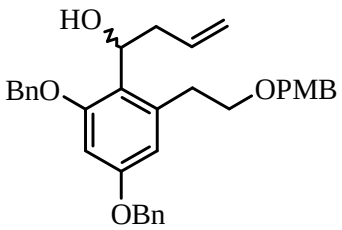
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 34.89, 55.19, 70.12, 70.16, 70.63, 72.34, 98.41, 110.13, 113.63, 117.42, 127.28, 127.58, 128.23, 128.32, 128.69, 129.20, 130.70, 135.92, 135.95, 145.34, 158.98, 163.45, 164.38, 190.34 ppm.

ESI MS (*m/z*) : 505.11 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 77.16; H, 6.27.

Found: C, 77.46; H, 6.21.

1-(2,4-bis(benzyloxy)-6-(2-(4-methoxybenzyloxy)ethyl)phenyl)but-3-en-1-ol (40):



To a suspension of Mg turning (1.20 g, 49.58 mmol) in anhydrous diethyl ether (15 mL) was added allyl bromide (2.6 mL, 29.71 mmol) at room temperature for 10 min. To the ash colored reaction mixture was added aldehyde **34** (4.78 g, 9.916 mmol) in diethyl ether (5 mL). After being stirred for 3 h, it was quenched by addition of saturated aqueous solution of NH_4Cl (20 mL). The two layers were separated, the organic layer dried (Na_2SO_4) and concentrated to form a residue, which was purified on silica gel column chromatography using EtOAc-light petroleum ether (1:9) to furnish **40** (4.62 g) as yellow color liquid.

Yield : 88%

Mol. Formula : $C_{34}H_{36}O_5$

IR ($CHCl_3$) cm^{-1} : 3400, 2930, 1600, 1512, 1454, 1383, 1302, 1247, 1151, 1084, 1030, 822, 738, 698.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.42-2.55 (m, 1H), 2.64-2.79 (m, 1H), 2.84-3.03 (m, 2H), 3.51-3.67 (m, 2H), 3.77 (s, 3H), 4.36-4.48 (m, 2H), 4.85-4.97 (m, 4H), 5.01-5.02 (m, 1H), 5.05 (s, 2H), 5.66-5.87 (m, 1H), 6.42 (d, *J* = 2.4 Hz, 1H), 6.51 (d, *J* = 2.4 Hz, 1H), 6.83 (d, *J* = 8.5 Hz, 2H), 7.20 (d, *J* = 8.5 Hz, 2H), 7.33-7.41 (m, 10H) ppm.

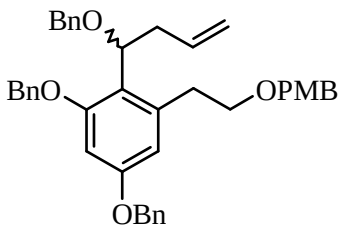
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 34.63, 55.16, 69.95, 70.11, 70.44, 72.61, 99.18, 108.22, 113.74, 114.27, 116.03, 118.67, 126.33, 126.96, 127.25, 127.57, 127.83, 128.02, 128.49, 128.59, 129.26, 130.37, 131.98, 134.03, 136.79, 136.85, 138.90, 139.34, 158.11, 158.27, 159.12 ppm.

ESI MS (*m/z*) : 547.62 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 77.84; H, 6.92.

Found: C, 77.69; H, 6.82.

(4-(1-(benzyloxy)but-3-enyl)-5-(2-(4-methoxybenzyloxy)ethyl)-1,3-phenylene)bis (oxy)bis(methylene)dibenzene (41):



Compound **40** (3.13 g, 5.96 mmol) in DMF (10 mL) was added to a stirred suspension of NaH (477 mg, 60% dispersion in oil, 5.96 mmol) in DMF (20 mL) at 0 ^{o}C. The resulting solution was stirred at the same temperature for 30 min; BnBr (1.1 mL, 8.95 mmol) was added. After 5 h, the reaction was quenched by ice-cold water and extracted with EtOAc. The combined organic layer was washed with water, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel column chromatography using EtOAc-light petroleum ether (1:9) to obtain **41** (3.22 g) as colourless liquid.

Yield : 87%

Mol. Formula : $C_{41}H_{42}O_5$

IR ($CHCl_3$) cm^{-1} : 3064, 3031, 3007, 2930, 2859, 1602, 1513, 1454, 1376, 1302, 1248, 1149, 1088, 1029, 912, 828, 754, 697.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.36-2.49 (m, 1H), 2.68-2.87 (m, 1H), 2.98-3.22 (m, 2H), 3.51 (t, *J* = 7.3 Hz, 2H), 3.68 (s, 3H), 4.15-4.36 (m, 4H), 4.84-4.96 (m, 6H), 5.08 (t, *J* = 5.2 Hz, 1H), 5.60-5.81 (m, 1H), 6.38 (d, *J* = 2.4 Hz, 1H), 6.44 (d, *J* = 2.4 Hz, 1H), 6.74 (d, *J* = 8.7 Hz, 2H), 7.12 (d, *J* = 8.7 Hz, 2H), 7.17-7.34 (m, 15H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 33.08, 40.42, 55.08, 69.87, 70.19, 70.49, 70.89, 72.46, 74.56, 98.68, 108.60, 113.66, 116.21, 120.51, 126.96, 127.12, 127.49, 127.60, 127.65, 127.97, 128.10, 128.43, 128.54, 129.23, 130.51, 135.86, 136.90, 137.06, 139.00, 140.57, 158.14, 158.54,

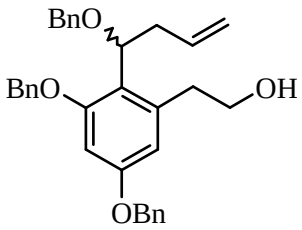
159.05 ppm.

ESI MS (*m/z*) : 637.76 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 80.10; H, 6.89.

Found: C, 80.12; H, 6.78.

2-(3,5-bis(benzyloxy)-2-(1-(benzyloxy)but-3-enyl)phenyl)ethanol (42):



To a solution of PMB ether **41** (1.12 g, 1.81 mmol) in dichloromethane/water (19:1) (20 mL) at 0 °C was added DDQ (618 mg, 2.72 mmol). The resultant reaction mixture was stirred for 45 min, and diluted with additional dichloromethane and saturated sodium bicarbonate. The organic layer was washed three times with sodium bicarbonate, dried over sodium sulfate, concentrated and purified by column chromatography on silica gel (20% EtOAc/ light petroleum ether) to afford alcohol **42** (698 mg) as a colourless liquid.

Yield : 78%

Mol. Formula : $C_{33}H_{34}O_4$

IR ($CHCl_3$) cm^{-1} : 3393, 2923, 1595, 1487, 1454, 1434, 1373, 1281, 1216, 1153, 1099, 1049, 914, 769, 700.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.65 (brs, 1H), 2.48-2.61 (m, 1H), 2.77-2.91 (m, 1H), 2.98-3.28 (m, 2H), 3.71-3.89 (m, 2H), 4.37 (d, *J* = 11.8 Hz, 1H), 4.49 (d, *J* = 11.8 Hz, 1H), 4.95-5.08 (m, 7H), 5.23 (t, *J* = 7.3 Hz, 1H), 5.68-5.88 (m, 1H), 6.49 (d, *J* = 2.4 Hz, 1H), 6.51 (d, *J* = 2.4 Hz, 1H), 7.25-7.31 (m, 5H), 7.34-7.44 (m, 10H) ppm.

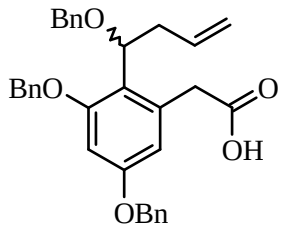
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 36.03, 40.45, 63.74, 69.93, 70.26, 70.86, 74.43, 98.68, 108.46, 116.43, 120.86, 127.01, 127.39, 127.60, 127.71, 128.03, 128.21, 128.46, 128.58, 135.59, 136.80, 136.95, 138.55, 140.31, 158.09, 158.70 ppm.

ESI MS (*m/z*) : 517.60 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 80.13; H, 6.93.

Found: C, 80.23; H, 6.85.

2-(3,5-bis(benzyloxy)-2-(1-(benzyloxy)but-3-enyl)phenyl)acetic acid (31):



To a solution of IBX (480 mg, 1.74 mmol) in DMSO (1.0 mL) at room temperature, was added alcohol **42** (430 mg, 0.87 mmol) in dry THF (5 mL). After 0.5 h of stirring, water (H_2O) was added, and diluted with ether and stirred it for additional 30 min. The solid was filtered off and from the filtrate organic layer was isolated, washed with brine, dried over Na_2SO_4, concentrated and purified by passing through a pad of silica gel (20% EtOAc/ light petroleum ether to obtain **43** (379 mg, 88%) as a yellow oil.

The aldehyde **43** (379 mg, 0.77 mmol) was dissolved in a mixture of THF (10 mL), *t*-BuOH (20 mL), H_2O (5 mL) and 2-methyl-2-butene (0.415 g). To this solution was added NaH_2PO_4 (204 mg, 1.7 mmol) and $NaClO_2$ (222 mg, 2.26 mmol) at 10 ^oC and the resulting mixture was stirred vigorously for 2 h at room temperature. The volatiles were removed by evaporation, and the residue was partitioned between EtOAc and brine. The aqueous phase was extracted with EtOAc (three times). The combined extract was dried (Na_2SO_4), evaporated and purified by column chromatography on silica gel (40% EtOAc/ light petroleum ether) to get carboxylic acid **31** (374 mg).

Yield : 95%

Mol. Formula : $C_{33}H_{32}O_5$

IR ($CHCl_3$) cm^{-1} : 3435, 3065, 3030, 2929, 1736, 1605, 1453, 1376, 1336, 1280, 1218, 1152, 1093, 1041, 755, 697

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.55 (t, *J* = 6.5 Hz, 2H), 3.50 (d, *J* = 20.0 Hz, 1H), 3.66 (d, *J* = 20.0 Hz, 1H), 4.61 (s, 2H), 4.91-5.08 (m, 6H), 5.60-5.80 (m, 2H), 6.26 (d, *J* = 2.0 Hz, 1H), 6.44 (d, *J* = 2.0 Hz, 1H), 7.17-7.36 (m, 15H) ppm.

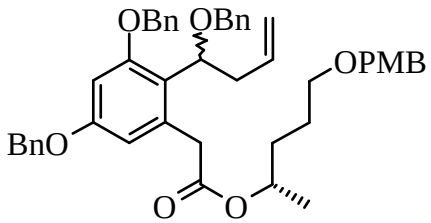
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 34.84, 40.23, 65.22, 70.06, 70.22, 77.54, 99.12, 104.28, 114.75, 119.26, 126.93, 127.10, 127.47, 127.55, 128.13, 128.47, 128.64, 131.81, 132.45, 136.18, 136.37, 154.92, 159.84, 170.22 ppm.

ESI MS (*m/z*) : 531.58 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 77.93; H, 6.34.

Found: C, 77.16; H, 6.45.

(*S*)-5-(4-methoxy)pentan-2-yl 2-(3,5-bis(benzyloxy)-2-(1-(benzyloxy)but-3-enyl) phenyl)acetate (30):



To a solution of alcohol **32** (110 mg, 0.49 mmol) and acid **31** (274 mg, 0.54 mmol) in CH_2Cl_2 (6 mL) was added DCC (222 mg, 1.08 mmol) at 0 ^oC followed by DMAP (cat.). The mixture was stirred at room temperature for 3 h, filtered and concentrated in vacuo. Purification by flash column (5% EtOAc/ light petroleum ether) afforded ester **30** (323 mg) as a clear oil.

Yield : 92%

Mol. Formula : $C_{46}H_{50}O_7$

Optical Rotation $[\alpha]_D^{25}$: +6.4 (*c* 1.25, $CHCl_3$).

IR ($CHCl_3$) cm^{-1} : 2930, 1728, 1603, 1513, 1453, 1382, 1303, 1248, 1152, 1038, 828, 755, 697.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.03 (d, *J* = 6.4 Hz, 1.5H), 1.07 (d, *J* = 6.3 Hz, 1.5H), 1.41-1.55 (m, 4H), 2.26-2.43 (m, 1H), 2.59-2.73 (m, 1H), 3.22-3.35 (m, 2H), 3.68 (s, 3H), 3.82 (d, *J* = 16.0 Hz, 1H), 3.96 (d, *J* = 16.0 Hz, 1H), 4.13 (dd, *J* = 1.1, 12.2 Hz, 1H), 4.28 (s, 2H), 4.34 (d, *J* = 12.1 Hz, 1H), 4.72-4.98 (m, 7H), 5.12 (dd, *J* = 6.4, 8.1 Hz, 1H), 5.58-5.79 (m, 1H), 6.42 (s, 2H), 6.74 (d, *J* = 8.6

Hz, 2H), 7.09-7.34 (m, 17H) ppm.

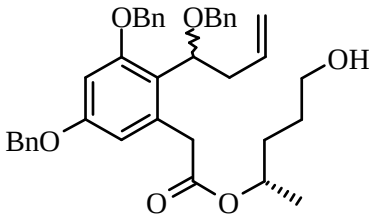
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 19.89, 25.63, 25.60, 32.55, 38.31, 40.64, 55.10, 69.55, 69.95, 70.22, 70.62, 70.97, 71.04, 72.43, 74.14, 74.24, 99.37, 108.98, 113.69, 116.30, 120.88, 126.96, 127.17, 127.60, 127.66, 127.97, 128.08, 128.43, 128.52, 129.11, 130.55, 135.54, 135.55, 135.73, 135.76, 136.82, 136.89, 138.77, 158.00, 158.02, 158.64, 159.08, 171.58 ppm.

ESI MS (*m/z*) : 737.87 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 77.28; H, 7.05.

Found: C, 77.13; H, 7.14.

(*S*)-5-hydroxypentan-2-yl 2-(3,5-bis(benzyloxy)-2-(1-(benzyloxy)but-3-enyl)phenyl) acetate (49):



To a solution of PMB ether **30** (0.8 g, 1.12 mmol) in dichloromethane/water (19:1) (20 mL) at 0 °C was added DDQ (0.38 g, 1.68 mmol). The reaction mixture was stirred for 1 h at the same temperature, and diluted with additional dichloromethane and saturated sodium bicarbonate. The organic layer was washed with sodium bicarbonate, dried over sodium sulfate, concentrated and purified by column chromatography on silica gel (20% EtOAc/ light petroleum ether) to afford alcohol **49** (0.61 g) as colorless liquid.

Yield : 93%

Mol. Formula : $C_{38}H_{42}O_6$

Optical Rotation $[\alpha]_D^{25}$: +4.9 (*c* 1.65, $CHCl_3$).

IR ($CHCl_3$) cm^{-1} : 3431, 2930, 1729, 1603, 1454, 1383, 1308, 1148, 1068, 737, 697.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.07 (d, *J* = 6.4, 1.5H), 1.11 (d, *J* = 6.4 Hz, 1.5H), 1.40-1.48 (m, 4H), 2.32-2.46 (m, 1H), 2.61-2.76 (m,

1H), 3.43-3.55 (m, 2H), 3.81-4.04 (m, 2H), 4.15 (dd, *J* = 1.5, 12.1 Hz, 1H), 4.36 (d, *J* = 12.1 Hz, 1H), 4.76-5.02 (m, 7H), 5.12-5.22 (m, 1H), 5.60-5.82 (m, 1H), 6.45 (s, 2H), 7.18-7.37 (m, 15H) ppm.

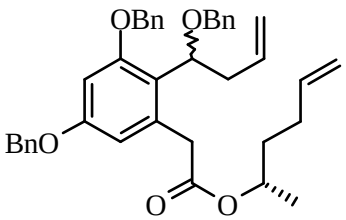
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 19.84, 28.34, 28.37, 32.02, 32.06, 38.29, 40.59, 62.19, 62.22, 69.94, 70.19, 70.59, 70.91, 70.98, 74.11, 74.24, 99.29, 109.06, 109.11, 116.31, 120.81, 126.93, 127.17, 127.57, 127.64, 127.68, 127.96, 128.05, 128.40, 128.51, 135.46, 135.50, 135.59, 135.62, 136.74, 136.81, 138.69, 157.96, 157.98, 158.58, 171.64, 171.68 ppm.

ESI MS (*m/z*) : 617.73 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 76.74; H, 7.12.

Found: C, 76.69; H, 7.11.

(*S*)-hex-5-en-2-yl 2-(3,5-bis(benzyloxy)-2-(1-(benzyloxy)but-3-enyl)phenyl)acetate (29):



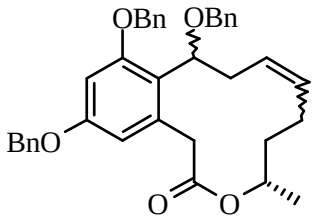
To a solution of IBX (287 mg, 1.04 mmol) in DMSO (0.6 mL) at room temperature, was added alcohol **49** (310 g, 0.52 mmol) in dry THF (10 mL). After 2 h of stirring, water (H_2O) was added, and diluted with ether and stirred it for additional 30 min. The solid was filtered off and from the filtrate organic layer was isolated, washed with brine, dried over Na_2SO_4, concentrated to give aldehyde **50** (305 mg, crude product) the crude aldehyde was used immediately for the next reaction without further purification.

To a suspension of $Ph_3P^+CH_3Br^-$ (557 g, 1.56 mmol) in THF (5 mL) at 0 ^oC, was added NaHMDS (1 mL, 1 M solution in toluene) dropwise. After 1 h stirring at the same temperature, the aldehyde **50** (305 mg) in THF was added slowly. After 9 h, reaction was quenched with saturated solution of NH_4Cl, and extracted with ether. The organic layers

were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. Purification was done by silica gel (60-120 mesh) column chromatography (5% EtOAc/ light petroleum ether) to afford diene **29** as yellow colour liquid (278 mg).

Yield	: 90% (two steps)
Mol. Formula	: $C_{39}H_{42}O_5$
Optical Rotation $[\alpha]_D^{25}$	: +6.7 (*c* 1.2, $CHCl_3$).
IR ($CHCl_3$) cm^{-1}	: 2928, 1728, 1603, 1453, 1382, 1308, 1218, 1149, 1068, 913, 770, 697.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.14 (t, *J* = 6.0 Hz, 3H), 1.50-1.69 (m, 2H), 1.94-2.06 (m, 2H), 2.39-2.53 (m, 1H), 2.68-2.82 (m, 1H), 3.91 (dd, *J* = 3.0, 15.9 Hz, 1H), 4.07 (dd, *J* = 3.4, 15.9 Hz, 1H), 4.22 (dd, *J* = 1.0, 12.0 Hz, 1H), 4.43 (d, *J* = 12.1 Hz, 1H), 4.81-5.04 (m, 9H), 5.22 (dd, *J* = 6.5, 8.1 Hz, 1H), 5.64-5.88 (m, 2H), 6.52 (s, 2H), 7.20-7.43 (m, 15H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 19.79, 29.57, 34.98, 38.34, 40.61, 70.00, 70.24, 70.57, 70.61, 70.80, 70.88, 74.10, 74.24, 99.35, 108.93, 114.87, 114.89, 115.26, 116.29, 120.38, 120.83, 126.98, 127.23, 127.58, 127.66, 128.02, 128.11, 128.44, 128.56, 129.52, 135.53, 135.68, 135.73, 136.76, 136.90, 137.73, 137.75, 138.74, 158.03, 158.06, 158.64, 171.79 ppm.
ESI MS (*m/z*)	: 613.72 $[M+Na]^+$
Elemental Analysis	**Calcd:** C, 79.29; H, 7.17.
	Found: C, 79.08; H, 7.12.

(*S*)-10,11,13-tris(benzyloxy)-4-methyl-5,6,9,10-tetrahydro-1*H*-benzo[*d*][1]oxacyclo dodecin-2(4*H*)-one (28):



Compound **29** (0.178 g, 0.30 mmol) was dissolved in anhydrous toluene (30 mL) and solution degassed with argon. Grubbs' catalyst **53** (8 mg, 3 mol %) was added and reaction mixture stirred at 70 ^{o}C for 18 h. The solvent was removed and residue purified by column chromatography on silica gel using EtOAc-light petroleum ether (3:97) to obtain **28** (0.154 g) as colorless oil.

Yield : 91%

Mol. Formula : $C_{37}H_{38}O_5$

Optical Rotation $[\alpha]_D^{25}$: +10.8 (*c* 1.3, $CHCl_3$).

IR ($CHCl_3$) cm^{-1} : 3031, 2926, 1723, 1603, 1497, 1454, 1378, 1306, 1261, 1153, 1067, 1028, 910, 832, 736, 697.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.24 (bs, 3H), 1.45-1.75 (m, 3H), 1.84-2.22 (m, 2H), 2.26-2.54 (m, 1H), 3.14-3.55 (m, 2H), 4.19-4.32 (m, 1H), 4.36-4.44 (m, 1H), 4.47-4.60 (m, 1H), 4.88-5.12 (m, 5H), 5.18-5.41 (m, 2H), 6.31-6.61 (m, 2H), 7.20-7.48 (m, 15H) ppm.

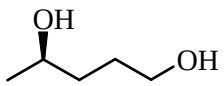
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 19.95, 20.99, 21.31, 22.69, 29.35, 29.69, 29.97, 31.01, 31.92, 33.09, 35.72, 36.23, 36.96, 38.08, 41.48, 41.81, 69.80, 70.00, 70.15, 70.53, 70.65, 70.85, 71.04, 72.53, 75.04, 76.15, 99.44, 100.56, 100.74, 100.87, 100.95, 108.73, 109.48, 110.00, 110.53, 114.29, 119.52, 120.02, 124.26, 124.34, 124.93, 126.90, 126.95, 127.06, 127.25, 127.51, 127.62, 127.71, 127.78, 128.03, 128.19, 128.46, 128.58, 133.54, 136.47, 136.72, 136.83, 136.93, 137.15, 137.27, 138.96, 157.08, 158.13, 158.58, 159.17, 159.38, 169.86, 170.46, 172.64 ppm.

ESI MS (*m/z*) : 585.67 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 78.98; H, 6.81.

Found: C, 78.17; H, 6.89.

(*S*)-5-pentan-2,5-diol (33):



Mol. Formula : $C_5H_{12}O_2$

Optical Rotation $[\alpha]_D^{25}$: −18.0 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$) cm^{-1} : 3411, 2931, 1666, 1375, 1642, 770

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.18 (d, *J* = 6.2 Hz, 3H), 1.42-1.72 (m, 4H), 3.52-3.69 (m, 2H), 3.76-3.93 (m, 3H) ppm.

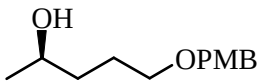
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 23.27, 28.94, 36.03, 62.29, 67.49 ppm.

ESI MS (*m/z*) : 127.48 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 57.66; H, 11.61.

Found: C, 57.57; H, 11.71.

(*R*)-5-(4-methoxybenzyloxy)pentan-2-ol (47):



To an ice-cooled solution of **33** (1.92 g, 18.38 mmol) in dry DMF (125 mL), NaH (60% dispersion in oil, 0.66 g, 27.58 mmol) was added. After 30 min, PMBCl (2.84 mL, 20.22 mmol) was introduced and stirred for additional 10 h at the same temperature. The reaction mixture was partitioned between water and ethyl acetate. The organic layer was washed with water, brine, dried (Na_2SO_4) and concentrated. The crude product purified by column chromatography on silica gel using EtOAc-light petroleum ether (15:85) to obtain **47** (3.01 g) as a colorless syrup.

Yield : 73%

Mol. Formula : $C_{13}H_{20}O_3$

Optical Rotation $[\alpha]_D^{25}$: −4.6 (*c* 1.3, $CHCl_3$)

IR ($CHCl_3$) cm^{-1} : 3410, 2934, 2859, 1669, 1612, 1513, 1463, 1364,

1302, 1248, 1096, 1035, 820.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.17 (d, *J* = 6.2 Hz, 3H), 1.38-1.77 (m, 4H), 2.36 (bs, 1H), 3.48 (t, *J* = 5.8 Hz, 2H), 3.80 (s, 3H), 3.70-3.86 (m, 1H), 4.44 (s, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 7.24 (d, *J* = 8.6 Hz, 2H) ppm.

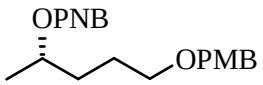
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 23.23, 26.08, 36.26, 54.92, 67.23, 70.02, 72.40, 113.53, 129.07, 130.04, 158.94 ppm.

ESI MS (*m/z*) : 247.28 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 69.61; H, 8.99.

Found: C, 69.56; H, 8.83.

(*S*)-5-(4-methoxybenzyloxy)pentan-2-yl 4-nitrobenzoate (48):



To a solution of alcohol **47** (2.71 g, 12.08 mmol), triphenylphosphine (12.67 g, 48.34 mmol), and 4-nitrobenzoic acid (8.28 g, 49.55 mmol) in THF (100 mL) was added diisopropylazodicarboxylate (9.3 mL, 47.13 mmol) at 0 °C under N_2. Then the mixture was stirred at room temperature for 8 h. All the volatiles were removed and the residue was chromatographed on silica gel using EtOAc-light petroleum ether (1:19) to obtain ester **48** as colorless oil (3.72 g).

Yield : 82%

Mol. Formula : $C_{20}H_{23}NO_6$

Optical Rotation $[\alpha]_D^{25}$: +19.7 (*c* 1.32, $CHCl_3$).

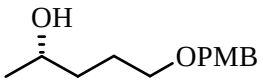
IR ($CHCl_3$) cm^{-1} : 2935, 2859, 1721, 1611, 1528, 1513, 1463, 1350, 1276, 1248, 1100, 1035, 822, 757, 666.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.37 (d, *J* = 6.3 Hz, 3H), 1.61-1.88 (m, 4H), 3.46 (t, *J* = 5.9 Hz, 2H), 3.80 (s, 3H), 4.42 (s, 2H), 5.13-5.28 (m, 1H), 6.85 (d, *J* = 8.6 Hz, 2H), 7.23 (d, *J* = 8.6 Hz, 2H), 8.17 (d, *J* = 8.9 Hz, 2H), 8.27 (d, *J* = 8.9 Hz, 2H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 19.89, 25.67, 32.60, 55.01, 69.34, 72.50, 72.64,

	113.61, 123.29, 129.04, 130.32, 130.48, 135.99, 150.31, 159.04, 163.98 ppm.
ESI MS (*m/z*)	: 396.38 $[M+Na]^+$
Elemental Analysis	**Calcd:** C, 64.33; H, 6.21.
	Found: C, 64.41; H, 6.29.

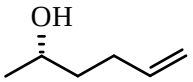
(*S*)-5-(4-methoxybenzyloxy)pentan-2-ol (32):



To a solution of ester **48** (3.72 g, 9.97 mmol) in MeOH (30 mL) was added finely powdered K_2CO_3 (2.75 g, 19.94 mmol) at 0 °C under N_2. Then the mixture was stirred at room temperature for 1 h and concentrated. The residue was then partitioned between CH_2Cl_2 and water. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel using EtOAc-light petroleum ether (3:17) to furnish alcohol **32** as colorless oil (2.1 g).

Yield	: 96%
Mol. Formula	: $C_{13}H_{20}O_3$
Optical Rotation $[\alpha]_D^{25}$	: +11.8 (*c* 1.1, $CHCl_3$).
IR ($CHCl_3$) cm^{-1}	: 3392, 2932, 1613, 1513, 1455, 1302, 1248, 1089, 1037, 821, 770.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.08 (d, *J* = 6.3 Hz, 3H), 1.29-1.68 (m, 4H), 2.10 (bs, 1H), 3.39 (t, *J* = 5.9 Hz, 2H), 3.62-3.81 (m, 1H), 3.71 (s, 3H), 4.35 (s, 2H), 6.77 (d, *J* = 8.6 Hz, 2H), 7.16 (d, *J* = 8.7 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 23.23, 26.13, 36.33, 55.06, 67.45, 70.10, 72.49, 113.63, 129.18, 130.09, 159.01 ppm.
ESI MS (*m/z*)	: 247.28 $[M+Na^+]$
Elemental Analysis	**Calcd:** C, 69.61; H, 8.99.
	Found: C, 69.79; H, 8.68.

(*S*)-5-en-hexane-2-ol (58):



To a mixture of magnesium (1.20 g, 49.89 mmol) and iodine (a small crystal) in THF (10 mL), a solution of allyl chloride (2.18 g, 28.51 mmol) in THF (10 mL) was slowly added. After stirring for 1 h at room temperature, cuprous cyanide (1.27 g, 14.25 mmol) was then added at once, resulting in immediate color change of reaction mixture into dark brown. After 5 min, cooling to 0 °C, epoxide **63** (414 mg, 7.13 mmol) in THF (10 mL) was added dropwise. The reaction mixture was stirred for overnight at room temperature, quenched with saturated aqueous NH_4Cl solution and the resulting suspension stirred for another 30 min. Inorganic solid material was filtered off and washed with ether. The combined ether layer was dried (Na_2SO_4) and concentrated to furnish the residue, which on filtration over silica gel column chromatography (20% ethyl acetate in hexane) gave **58** (626 mg) as colourless oil.

Yield : 87%

Mol. Formula : $C_6H_{12}O$

Optical Rotation $[\alpha]_D^{25}$: +9.8 (*c* 1.1, $CHCl_3$).

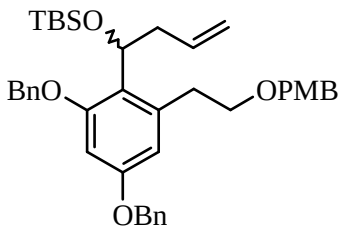
IR ($CHCl_3$) cm^{-1} : 3435, 3019, 1598, 1403, 1215, 1118, 758, 669.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.17 (d, *J* = 6.2 Hz, 3H), 1.46-1.58 (m, 2H), 1.99 (bs, 1H), 2.06-2.20 (m, 2H), 3.79 (quintate, *J* = 6.2 Hz, 1H), 4.90-5.07 (m, 2H), 5.71-5.91 (m, 1H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 23.39, 30.11, 38.17, 67.42, 114.69, 138.39 ppm.

ESI MS (*m/z*) : 123.16 $[M+Na]^+$

(1-(2,4-bis(benzyloxy)-6-(2-(4-methoxybenzyloxy)ethyl)phenyl)but-3-enyloxy)(*tert*-butyl)dimethylsilane (61):



A solution of **40** (7.51 g, 14.31 mmol), TBSCl (3.24 g, 21.47 mmol) and imidazole (1.95 g, 28.62 mmol) in DMF (40 mL) was stirred for 4 h at 0 ^oC. The reaction mixture

was diluted with diethyl ether and washed with water. The organic layer was dried (Na_2SO_4), concentrated and the residue purified on silica gel using EtOAc:light petroleum ether (3:97) as an eluent to obtain **61** (8.96 g) as thick liquid.

Yield : 98%

Mol. Formula : $C_{40}H_{50}O_5Si$

IR ($CHCl_3$) cm^{-1} : 3032, 2953, 2929, 2856, 1639, 1603, 1586, 1513, 1462, 1361, 1302, 1249, 1147, 1082, 913, 834, 756, 697.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ −0.07 (s, 3H), 0.10 (s, 3H), 0.95 (s, 9H), 2.50-2.93 (m, 2H), 3.21-3.64 (m, 2H), 3.71-3.82 (m, 2H), 3.84 (s, 3H), 4.54 (d, *J* = 11.5 Hz, 1H), 4.58 (d, *J* = 11.5 Hz, 1H), 5.04-5.13 (m, 7H), 5.81-5.92 (m, 1H), 6.54 (s, 1H), 6.63 (s, 1H), 6.96 (d, *J* = 8.6 Hz, 2H), 7.36-7.52 (m, 12H) ppm.

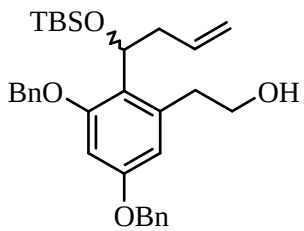
^{13}C NMR ($CDCl_3$, 50 MHz) : δ -4.78, -5.24, 18.15, 25.60, 25.87, 34.53, 55.10, 69.82, 70.08, 71.26, 72.54, 99.14, 108.50, 113.68, 116.11, 123.95, 126.84, 127.19, 127.51, 127.63, 127.90, 128.35, 128.47, 129.25, 130.50, 136.19, 136.89, 137.19, 138.12, 139.32, 158.08, 159.05 ppm.

ESI MS (*m/z*) : 661.12 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 75.20; H, 7.89.

Found: C, 75.19; H, 8.05.

2-(3,5-bis(benzyloxy)-2-(1-(*tert*-butyldimethylsilyloxy)but-3-enyl)phenyl)ethanol (60):

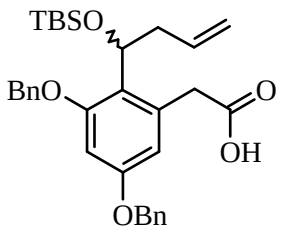


To a solution of PMB ether **61** (1.78 g, 2.79 mmol) in dichloromethane (27 mL) was added pH = 7 phosphate buffer (10.5 mL) and DDQ (1.27 g, 5.58 mmol). The

reaction mixture stirred for 1.5 h, and diluted with additional dichloromethane and saturated sodium bicarbonate. The organic layer was washed with sodium bicarbonate, dried over sodium sulfate, concentrated and purified by chromatography on silica gel (15% EtOAc/ light petroleum ether) to afford alcohol **60** (1.35 g) as a colourless liquid.

Yield	: 94%
Mol. Formula	: $C_{32}H_{42}O_4Si$
IR ($CHCl_3$) cm^{-1}	: 3373, 3071, 2920, 1595, 1487, 1454, 1434, 1377, 1254, 1154, 1049, 915, 822, 711, 702, 651.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.12 (s, 6H), 0.94 (s, 9H), 2.51-2.63 (m, 1H), 2.66-2.89 (m, 3H), 3.72-3.83 (m, 1H), 4.00-4.18 (m, 1H), 4.95-5.14 (m, 7H), 5.83-6.03 (m, 1H), 6.36 (d, *J* = 2.3 Hz, 1H), 6.46 (d, *J* = 2.3 Hz, 1H), 7.30-7.46 (m, 10H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ −3.56, 17.99, 25.67, 29.35, 37.96, 59.91, 69.76, 70.00, 72.16, 98.39, 105.59, 116.19, 119.45, 127.02, 127.49, 127.86, 127.95, 128.53, 128.54, 135.99, 136.11, 136.74, 136.91, 155.71, 158.06 ppm.
ESI MS (*m/z*)	: 661.71 $[M+Na]^+$
Elemental Analysis	**Calcd:** C, 74.09; H, 8.16.
	Found: C, 74.16; H, 8.09.

2-(3,5-bis(benzyloxy)-2-(1-(*tert*-butyldimethylsilyloxy)but-3-enyl)phenyl)acetic acid (59):



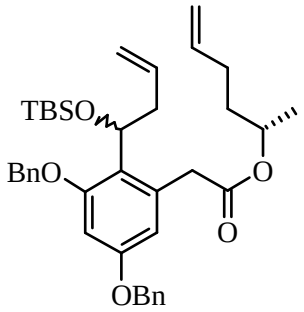
To a solution of IBX (899 mg, 3.26 mmol) in DMSO (2 mL) at room temperature, was added alcohol **60** (1.63 g, 1.63 mmol) in dry THF (10 mL). After 1 h of stirring, water (H_2O) was added, and diluted with ether and stirred it for additional 30 min. The solid was filtered off and from the filtrate organic layer was isolated, washed with brine,

dried over Na_2SO_4, concentrated and purified by chromatography on silica gel (20% EtOAc/hexanes to get **62** (819 mg, 97%) as a yellow oil.

The aldehyde **62** (819 mg, 1.58 mmol) was dissolved in a mixture of THF (14 mL), *t*-BuOH (28 mL), H_2O (7 mL) and 2-methyl-2-butene (8.32 g, 12.3 mL, 118.8 mmol). To this solution were added NaH_2PO_4 (396 mg, 3.33 mmol) and $NaClO_2$ (444 mg, 4.91 mmol) and the resulting mixture was stirred vigorously for 2 h. The volatiles were removed by evaporation, and the residue was partitioned between EtOAc and brine. The phases were separated and the aqueous phase was extracted with EtOAc (three times). The combined extract was dried (Na_2SO_4) and evaporated and purified by chromatography on silica gel (30% EtOAc/ light petroleum ether to obtain carboxylic acid **59** (798 mg).

Yield	: 94%
Mol. Formula	: $C_{32}H_{40}O_5Si$
IR ($CHCl_3$ cm^{-1}	: 3065, 3031, 2927, 2855, 1730, 1602, 1454, 1385, 1254, 1105, 836, 756, 616.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ −0.11 (s, 3H), 0.05 (s, 3H), 0.88 (s, 9H), 2.40-2.54 (m, 1H), 2.61-2.75 (m, 1H), 3.96 (d, *J* = 16.7 Hz, 1H), 4.45 (d, *J* = 16.7 Hz, 1H), 4.97-5.08 (m, 6H), 5.55-5.58 (m, 1H), 5.68-5.89 (m, 1H), 6.52-6.60 (m, 2H), 7.30-7.48 (m, 10H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ −3.68, 17.92, 25.57, 34.84, 40.23, 70.02, 70.19, 77.55, 99.08, 104.18, 114.25, 114.67, 119.31, 126.88, 127.09, 127.48, 127.76, 128.13, 128.42, 128.51, 128.63, 131.76, 132.42, 136.15, 136.33, 136.94, 141.71, 154.89, 159.81, 170.42 ppm.
ESI MS (*m/z*)	: 555.71 $[M+Na]^+$
Elemental Analysis	**Calcd:** C, 72.14; H, 7.57.
	Found: C, 72.31; H, 7.39.

(*S*)-hex-5-en-2-yl 2-(3,5-bis(benzyloxy)-2-(1-(tert-butyldimethylsilyloxy)but-3-enyl)phenyl)acetate (57):



To a solution of alcohol **58** (60 mg, 0.599 mmol) and acid **59** (319 mg, 0.599 mmol) in CH_2Cl_2 (3 mL) was added DCC (247 mg, 1.2 mmol) at 0 ^oC, followed by DMAP (cat.). The mixture was stirred at room temperature for 2 h, filtered, and concentrated in vacuo. Purification by flash column (5% EtOAc/ light petroleum ether) afforded ester **57** (335 mg) as clear oil:

Yield : 91%

Mol. Formula : $C_{38}H_{50}O_5Si$

Optical Rotation $[\alpha]_D^{25}$: +7.86 (*c* 1.5, $CHCl_3$).

IR ($CHCl_3$) cm^{-1} : 2929, 2371, 2361, 2341, 1730, 1604, 1383, 1257, 1146, 1068, 773, 696, 667.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ –0.16 (s, 3H), 0.01 (s, 3H), 0.86 (s, 9H), 1.22 (d, *J* = 5.7 Hz, 1.5H), 1.25 (d, *J* = 5.7 Hz, 1.5H), 1.47-1.79 (m, 2H), 1.99-2.16 (m, 2H), 2.37-2.50 (m, 1H), 2.61-2.75 (m, 1H), 3.70-3.88 (m, 1H), 4.37-4.50 (m, 1H), 4.92-5.07 (m, 9H), 5.50-5.56 (m, 1H), 5.67-5.91 (m, 2H), 6.48 (d, *J* = 2.3 Hz, 1H), 6.53 (bs, 1H), 7.31-7.42 (m, 10H) ppm.

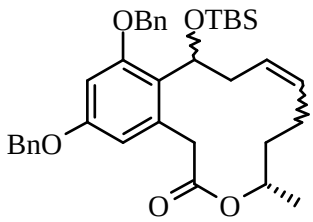
^{13}C NMR ($CDCl_3$, 50 MHz) : δ −5.18, −4.88, 18.19, 19.88, 19.99, 25.90, 29.61, 29.74, 35.05, 69.87, 70.16, 70.55, 70.66, 98.92, 108.46, 108.60, 115.02, 116.41, 124.20, 126.88, 127.17, 127.69, 127.96, 128.45, 128.51, 128.56, 135.94, 136.79, 137.04, 137.68, 158.21, 170.94, 171.90 ppm.

ESI MS (*m/z*) : 637.79 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 74.23; H, 8.20.

Found: C, 74.01; H, 8.22.

(*S*)-11,13-bis(benzyloxy)-10-(*tert*-butyldimethylsilyloxy)-4-methyl-5,6,9,10-tetrahydro-1*H*-benzo[*d*][1]oxacyclododecin-2(4*H*)-one (56):



Compound **57** (115 mg, 0.187 mmol) was dissolved in anhydrous toluene (15 mL) and solution degassed with argon. Grubbs' II catalyst **53** (5 mg, 3 mol %) was added and mixture stirred at 70 ^{o}C for overnight. The solvent was removed and residue purified by column chromatography on silica gel using EtOAc-light petroleum ether (1:9) to obtain **56** (91 mg) as colorless syrup.

Yield : 83%

Mol. Formula : $C_{36}H_{46}O_5Si$

Optical Rotation $[\alpha]_D^{25}$: +10.0 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$) cm^{-1} : 2929, 2856, 1724, 1604, 1454, 1381, 1305, 1256, 1151, 1068, 835, 758, 697.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ (–0.19)-(0.10) (m, 6H), 0.82-0.94 (m, 9H), 1.07-1.27 (m, 3H), 1.38 (dd, *J* = 2.0, 6.3 Hz, 1H), 1.60-1.76 (m, 1H), 1.83-2.49 (m, 4H), 3.10-3.78 (m, 2H), 4.73-4.92 (m, 1H), 4.97-5.09 (m, 4H), 5.17-5.74 (m, 3H), 6.30-6.60 (m, 2H), 7.31-7.61 (m, 10H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ −5.24, −5.07, −5.02, −4.75, −4.65, −4.61, 18.08, 18.11, 18.26, 18.30, 20.77, 20.94, 21.01, 21.21, 21.41, 25.65, 25.81, 25.92, 30.00, 30.52, 30.69, 30.81, 33.09, 33.19, 33.95, 34.43, 37.50, 38.86, 38.90, 39.06, 39.35, 39.57, 40.80, 41.47, 41.68, 68.86, 69.87, 70.00, 70.07, 70.17, 70.61, 70.71, 72.01, 72.59, 72.93, 73.14, 98.49, 98.87, 99.17, 101.00, 101.12, 108.52, 109.31, 110.40, 110.82, 122.83, 122.89, 123.19, 123.34, 123.73,

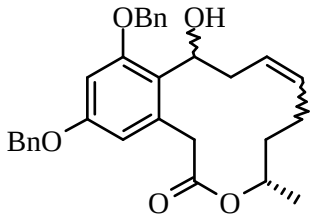
123.79, 124.03, 125.16, 125.56, 126.79, 126.83, 126.92, 127.15, 127.29, 127.33, 127.54, 127.74, 127.80, 127.92, 127.97, 128.24, 128.26, 128.53, 128.56, 133.32, 133.71, 133.98, 1343.23, 134.69, 135.39, 135.73, 136.11, 136.97, 137.01, 137.15, 137.26, 137.51, 155.76., 155.83, 157.47, 157.80, 158.24, 158.54, 159.40, 159.53, 170.04, 171.23, 172.10, 172.91 ppm.

ESI MS (*m/z*) : 609.82 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 73.68; H, 7.90.

Found: C, 73.57; H, 7.89.

(*S*)-11,13-bis(benzyloxy)-10-hydroxy-4-methyl-5,6,9,10-tetrahydro-1*H*-benzo[*d*][1]oxacyclododecin-2(4*H*)-one (64):



A mixture of **56** (95 mg, 0.16 mmol) and TBAF (1.6 mL, 1.61 mmol, 1.0 M solution in THF) was stirred at room temperature for 48 h. The reaction was quenched with saturated aqueous NH_4Cl solution. The aqueous layer was extracted with ethyl acetate twice. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column (10% EtOAc/ light petroleum ether) afforded **64** (74 mg) as a thick oil.

Yield : 97%

Mol. Formula : $C_{30}H_{32}O_5$

Optical Rotation $[\alpha]_D^{25}$: +18.3 (*c* 1.4, $CHCl_3$).

IR ($CHCl_3$) cm^{-1} : 3405, 3213, 2929, 1720, 1606, 1431, 1266, 1105, 756, 667, 616.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.15 (d, *J* = 6.4 Hz, 3H), 1.48-1.65 (m, 2H), 1.81-1.99 (m, 1H), 2.10-2.22 (m, 1H), 2.36-2.49 (m, 1H), 2.59-2.73 (m, 1H), 3.25 (d, *J* = 15.5 Hz, 1H), 3.62 (d. *J* = 15.5 Hz, 1H), 3.89 (bs, 1H), 4.56-4.64 (m, 1H), 4.69-4.84 (m, 1H), 4.91-5.01 (m, 4H), 5.07-5.20 (m, 1H), 5.34-5.48 (m, 1H), 6.54 (s, 2H), 7.23-7.37 (m, 10H) ppm.

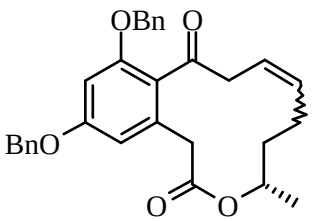
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 21.42, 21.51, 30.62, 30.98, 33.14, 36.64, 40.17, 40.53, 40.80, 70.01, 70.51, 72.35, 77.20, 100.15, 100.59, 109.29, 109.79, 122.03, 122.97, 124.50, 124.71, 127.45, 127.57, 127.62, 127.73, 128.05, 128.43, 128.58, 128.60, 128.91, 133.76, 133.81, 134.36, 135.09, 135.79, 135.89, 136.68, 136.72, 157.70, 157.85, 157.98, 158.31, 169.76, 171.18 ppm.

ESI MS (*m/z*) : 495.55 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 76.25; H, 6.83.

Found: C, 76.01; H, 6.79.

(*S*)-11,13-bis(benzyloxy)-4-methyl-5,6-dihydro-1*H*-benzo[*d*][1]oxacyclododecin-2,10(4*H*,9*H*)-dione (55):



To a solution of IBX (59 mg, 0.215 mmol) in DMSO (0.1 mL) at room temperature, was added alcohol **64** (51 mg, 0.107 mmol) in dry THF (10 mL). After 1.5 h of stirring, water (H_2O) was added, and diluted with ether and stirred it for additional 30 min. The solid was filtered off and from the filtrate organic layer was isolated, washed with brine, dried over Na_2SO_4, concentrated and purified by column chromatography on silica gel (15% EtOAc/ light petroleum ether to give **55** (50 mg) as a colourless liquid.

Yield : 98%

Mol. Formula : $C_{30}H_{30}O_5$

Optical Rotation $[\alpha]_D^{25}$: +45.1 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$) cm^{-1} : 3208, 2928, 1728, 1687, 1655, 1601, 1429, 1311, 1154, 1105, 754.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.09 (d, *J* = 6.3 Hz, 3H), 1.47-1.62 (m, 2H), 1.91-1.99 (m, 1H), 2.14-2.26 (m, 1H), 3.05-3.55 (m, 4H), 4.94-5.02 (m, 5H), 5.15-5.25 (m, 1H), 5.38-5.51 (m, 1H), 6.46 (d, *J* = 2.1 Hz, 1H), 6.52 (s, 1H), 7.22-7.36 (m, 10H) ppm.

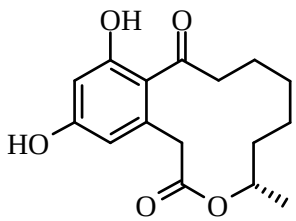
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 20.93, 30.43, 33.67, 38.00, 49.02, 70.21, 70.55, 72.44, 99.57, 109.54, 120.08, 124.33, 127.19, 127.61, 128.09, 128.14, 128.64, 134.14, 136.19, 136.47, 137.23, 156.62, 160.22, 170.76, 204.56 ppm.

ESI MS (*m/z*) 493.12 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 76.57; H, 6.43.

Found: C, 76.42; H, 6.49.

(*S*)-11,13-dihydroxy-4-methyl-4,5,6,7,8,9-hexahydro-1*H*-benzo[*d*][1] oxacyclodo decin-2,10-dione (27):



A solution of **55** (50 mg, 0.11 mmol) in ethyl acetate (2 mL) was hydrogenated in the presence of 10% Pd/C (cat.) at room temperature. After 1.5 h, the reaction mixture was filtered through a pad of Celite, concentrated; the residue was purified by silica gel column chromatography (ethyl acetate) to afford **27** (28 mg).

Yield : 91%

Mol. Formula : $C_{16}H_{20}O_5$

Optical Rotation $[\alpha]_D^{25}$: −32.9 (*c* 2.0, EtOH).

IR (Nujol) cm^{-1} : 3419, 3176, 2933, 2869, 2254, 1719, 1661, 1607,

	1589, 1463, 1316, 1264, 1105, 1006, 823, 616.
^{1}H NMR (acetone-d_6, 200 MHz)	: δ 1.13 (d, *J* = 6.3 Hz, 3H), 1.24-1.28 (m, 2H), 1.40-150 (m, 3H), 1.52-1.57 (m, 1H), 1.59-1.64 (m, 1H), 1.73-1.80 (m, 1H), 2.78 (ddd, *J* = 2.9, 9.9, 15.5 Hz, 1H), 3.12 (ddd, *J* = 2.9, 8.7, 15.5 Hz, 1H), 3.71 (d, *J* = 15.7 Hz, 1H), 3.79 (d, *J* = 15.6 Hz, 1H), 4.90-4.96 (m, 1H), 6.36 (d, *J* = 2.2 Hz, 1H), 6.41 (d, *J* = 2.2 Hz, 1H), 8.82 (bs, 1H), 9.19 (bs, 1H) ppm.
^{13}C NMR (acetone-d_6, 50 MHz)	: δ 20.53, 23.40, 24.51, 27.44, 32.81, 39.63, 43.90, 72.57, 102.46, 112.15, 121.27, 136.89, 158.17, 160.07, 170.97, 206.65 ppm.
ESI MS (*m/z*)	: 315.31 $[M+Na]^+$
Elemental Analysis	**Calcd:** C, 65.74; H, 6.90.
	Found: C, 65.68; H, 6.91.

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CHAPTER 3

Synthetic Studies of Amphidinolide C and V

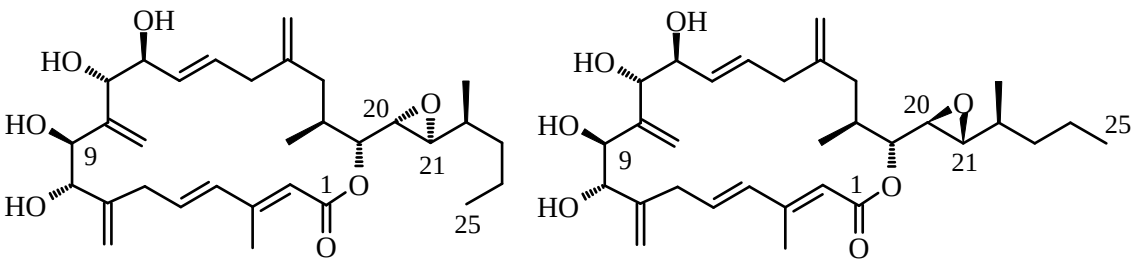
Introduction

Abnormal cell growth in an uncontrolled manner is called cancer and is the second most causative disease leading to death in humans after the cardiovascular disease. Cancerous cell growth can be treated with surgical removal, ionizing radiation and chemotherapy. Treatment by surgical and radiation methods are limited to the early stage of disease where locating the cancerous lesion is possible, but chemotherapy can be used in effective manner for both local and metastatic lesions by interfering with the cell division to cure the cancer. Anti-cancer drugs usually take advantage of the rapid replication of cancer cells and target the cell division process.

In the search for novel anticancer agents, natural products isolated from marine organisms have shown a wealth of pharmacological and structural diversity.[1] The sources of the active compounds (sponges in particular) contain very small amounts of the desired products, limiting the quantities that may be isolated and studied. During the 1980s, Jun'ichi Kobayashi and coworkers undertook the isolation of natural products originating from marine symbiotic microorganisms (such as bacteria, fungi, and microalgae) with the intent to cultivate the microorganisms and subsequently isolate larger amount of active compounds.[1a] Early on, Kobayashi focused on a marine microalga dinoflagellate from the genus *Amphidinium*, found in the inner tissue of the Okinawan flatworm *Amphiscolops*. Four novel bioactive macrolides were originally isolated, amphidinolides A–D,[2] exhibiting cytotoxicity against murine lymphoma cells (L1210) and human epidermoid carcinoma KB cells. Additional species of *Amphidinium* were subjected to the extraction procedure, leading to the discovery of amphidinolides E–H. During the process of isolation, several fractions were found to exhibit cytotoxicity of greater potency than any of the amphidinolides A–H. Further investigation of these cultures led to the discovery of related macrolides, amphidinolides J–Y.[3] Of all the amphidinolides, the most potent anticancer activities are displayed by amphidinolides B, C, G, H, and N (IC_{50} values against L1210 and KB cells <0.006 μg mL^{-1}). In addition to the striking biological activity of the amphidinolides, they possess several interesting structural features. This family of macrolides shows diversity in size, including lactones of odd-numbered ring size. They display an abundance of stereogenic centers, *exo*- and

endocyclic double bonds, and oxygen-containing substituents (including epoxides, THF and TFP rings, hydroxyl groups, and ketones). Due to their remarkable biological activity and structural functionality, the amphidinolides are challenging and attractive synthetic targets. Since the first reports of the amphidinolide family, considerable effort has been focused on synthesizing these macrolides, resulting in several innovative and efficient total syntheses.[4]

The cytotoxic macrolide, amphidinolide A (**1**), was isolated by Kobayashi from the culture broth of the marine dinoflagellate *Amphidinium* sp., which is symbiotically associated with an Okinawan flatworm.[5] The gross structure and relative stereochemistry were proposed after extensive 2D NMR experiments. Amphidinolide A (**1**) exhibits cytotoxicity against L1210 cells (IC_{50} 2.0 μg mL^{-1}) and KB cells (IC_{50} 5.7 μg mL^{-1}). Three groups synthesized the proposed structure independently. Pattenden and coworkers synthesized **1** and its epimer (**1a**) at C20 and C21, through inter- and intramolecular *sp*2–*sp*2 Stille coupling reaction.[6] Maleczka *et al.* have achieved the total synthesis of together with two analogues.[7] Their convergent synthesis was performed using a Stille coupling with copper thiophenecarboxylate and then a ring-closing metathesis, the latter compound being formed by Mitsunobu esterification. On the other hand, Trost and coworkers[8a,b] have succeeded in the total synthesis of **1** from three subunits using ruthenium catalyzed alkene–alkyne coupling.

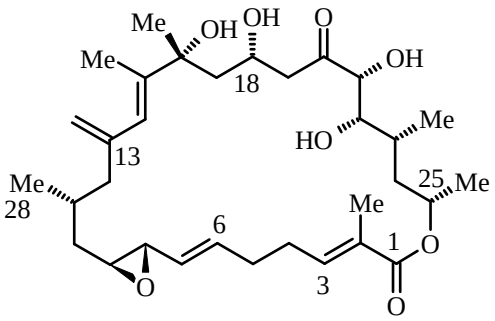


Amphidinolide A (**1**) Amphidinolide A1 (**1a**)

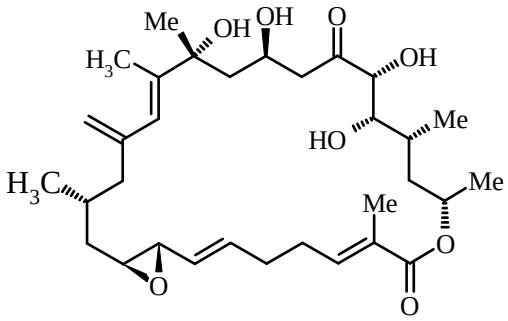
Figure 1

Amphidinolide B [9a,b] (**2**), a 26-membered macrolide isolated from culture of the symbiotic marine dinoflagellate *Amphidinium* sp. (strain Y-5), exhibits potent cytotoxicity against L1210 murine leukemia and KB human epidermoid carcinoma cells *in vitro* (IC_{50} 0.00014 and 0.0042 μg/mL, respectively). Shimizu and coworkers isolated

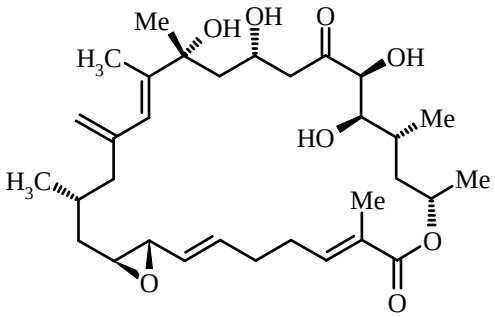
three amphidinolide B-congeners,[9c] amphidinolides B1 (**2**), B2 (**3**), and B3 (**4**) from a free-swimming dinoflagellate *Amphidinium operculatum* ver nov *Gibbosum*.[9d] The relative stereochemistry of nine chiral centers in B1 was determined by X-ray crystal analysis.[10] The absolute stereochemistry of **2** was assigned as 8*S*, 9*S*, 11*R*, 16*R*, 18*S*, 21*R*, 22*S*, 23*R* and 25*S* on the basis of synthesis of the C22-C26 segment.[11]



Amphidinolide B1 (**2**)



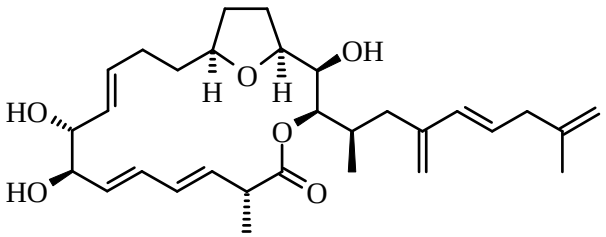
Amphidinolide B2 (**3**)



Amphidinolide B3 (**4**)

Figure 2

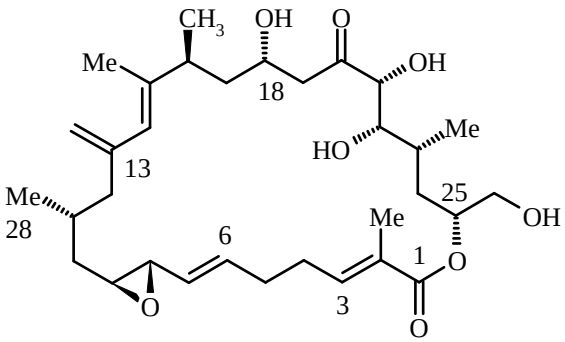
Amphidinolide E[12] (**5**) is a 19-membered macrolactone featuring an embedded *cis*-tetrahydrofuran, four C1 branches, two *exo*-methylene, and three hydroxyl groups. While this structural motif is common within the amphidinolide family, the C1-C6 α-chiral, *β,γ,δ,Є*-dienoate moiety of amphidinolide E (**5**) is not found in any of the other amphidinolides. Amphidinolide E (**5**) is cytotoxic to murine lymphoma L1210 and human epidermoid carcinoma KB cells, IC_{50} 2.0 and 10.0 μg/mL, respectively.[13] The relative and absolute stereochemistry was determined by 2D NMR studies and total synthesis. Lee has reported the total synthesis of amphidinolide E.[14a] Furthermore, Gurjar,[14b] Marshall1[14c] and Roush[14d] have published studies toward amphidinolide E (**2**). The absolute configurations at eight chiral centers in amphidinolide E (**5**) were elucidated to be 2*R*, 7*R*, 8*R*, 13*S*, 16*S*, 17*R*, 18*R* and 19*R*.



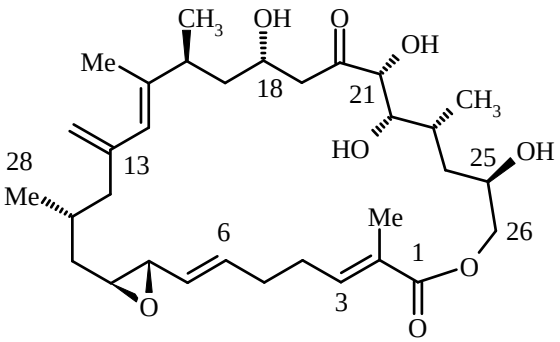
Amphidinolide E (**5**)

Figure 3

Amphidinolides G (**7**) and H (**6**), 27- and 26-membered macrolides, respectively, are regioisomers at C26 and C25, respectively, and are also different in the position of a hydroxyl group (C16 and C26, respectively).[15] The relative stereochemistry of 9 chiral centers in **6** was obtained from a single crystal X-ray diffraction analysis.[16] The absolute stereochemistry of amphidinolide H (**6**) was concluded to be 8*S*, 9*S*, 11*R*, 16*S*, 18*S*, 21*R*, 22*S*, 23*R* and 25*R* on the basis of 2D NMR data and modified Mosher's ester method of the C22–C26 segment of **6** by Kobayashi *et al*. On the other hand, treatment of amphidinolide H (**6**) with K_2CO_3 in EtOH at 4 ^oC for 18 h yielded a 1:1 mixture of **6** and **7**. All spectral data of amphidinolide G (**7**) isolated from this mixture were identical to those of natural product **7**. Thus, the absolute configurations of amphidinolide G (**7**) were concluded to be the same as those of amphidinolide H (**6**).



Amphidinolide H (**6**)

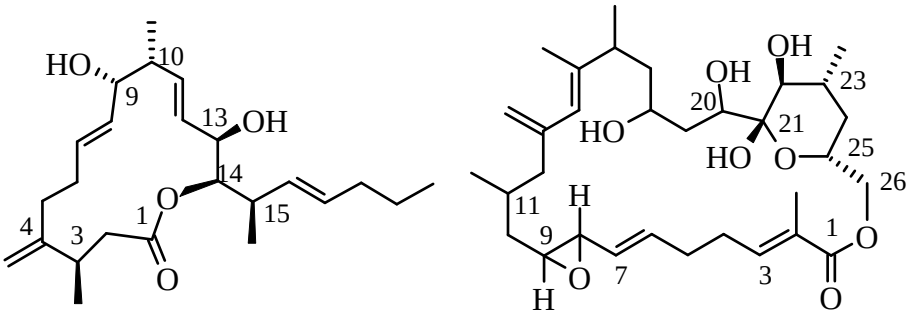


Amphidinolide G (**7**)

Figure 4

Amphidinolide J[17] **(8)**, a novel cytotoxic 15-membered macrolide with two hydroxyl groups and four C1 branches, two of which are adjacent to each other, has been isolated from the cultured dinoflagellate *Amphidinium* sp. Amphidinolide J **(8)** was cytotoxic against L1210 murine leukemia and KB human epidermoid carcinoma cells (IC_{50} 2.7 and 3.9 μg/mL, respectively). The absolute stereochemistry of **8** was determined by synthesis of the ozonolysis products by Kobayashi *et al*. Recently, Williams and

Kissel have succeeded in the total synthesis of amphidinolide J (**8**) through organozinc mediated coupling between C1–C12 and C13–C20 subunits, followed by macrocyclization by the Yamaguchi procedure.[18]

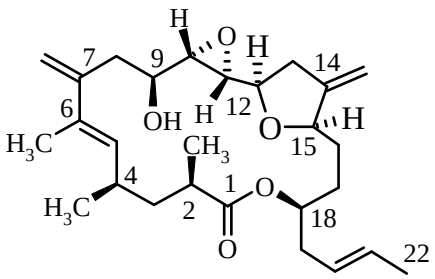


Amphidinolide J (**8**) Amphidinolide L (**9**)

Figure 5

Amphidinolide L (**9**),[19] cytotoxic 27-membered macrolide containing a hemiketal ring was isolated from extracts of the dinoflagellate *Amphidinium* sp. The relative stereochemistry was assigned by detailed analyses of NOESY data and ^{1}H-'H coupling constants, and the absolute configurations at C22, C23, and C25 were established by synthesis of the C21-C26 fragment.

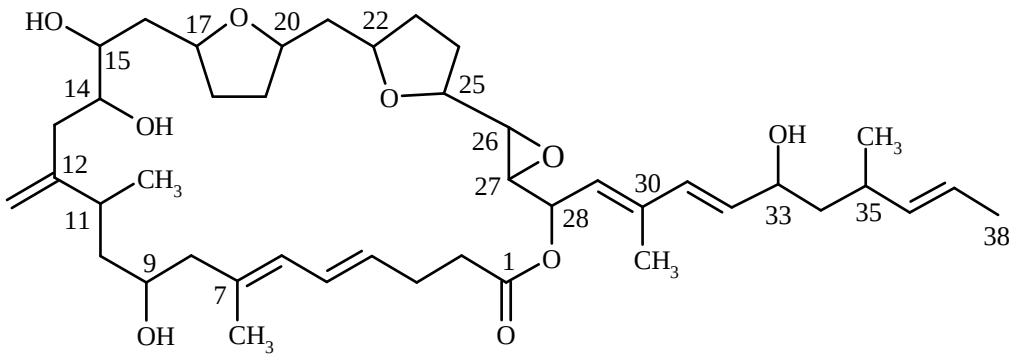
Amphidinolide K[20] (**10**) is a 19-membered macrolide isolated by Kobayashi *et al*. from a laboratory-cultured dinoflagellate *Amphidinium sp*.; it shows strong cytotoxic activity against murine lymphoma L1210 and epidermoic carcinoma KB cells[1] and as such is of interest to those involved in anticancer drug design. The structure of amphidinolide K (**10**) (established from 0.3 mg of sample!) was originally reported with some uncertainties regarding the relative stereochemistry at C2, C4, and C18. The relative and absolute stereochemistry was finally concluded by Williams and Meyer by the total synthesis of amphidinolide K[21] (**10**).



Amphidinolide K (**10**)

Figure 6

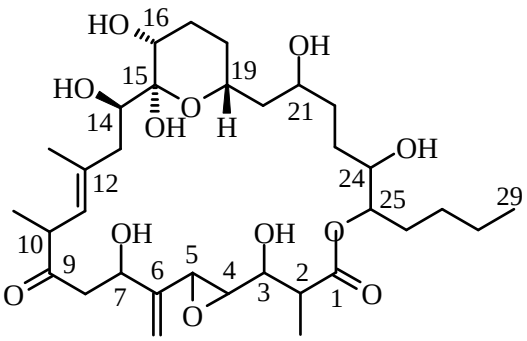
Amphidinolide M[22] (**11**), a novel 29-membered macrolide ring with two tetrahydrofuran rings, an epoxide, two diene moieties, and two vicinally located methyl or *exo*-methylene groups, isolated from the laboratory-cultured dinoflagellates *Amphidinium* sp. which live inside of Okinawan marine flatworms *Amphiscolops* sp. Amphidinolide M (**11**) exhibited cytotoxic activity against murine lymphoma L1210 and human epidermoid carcinoma KB cells *in vitro* with IC_{50} values of 1.1 and 0.44 μg/mL, respectively.



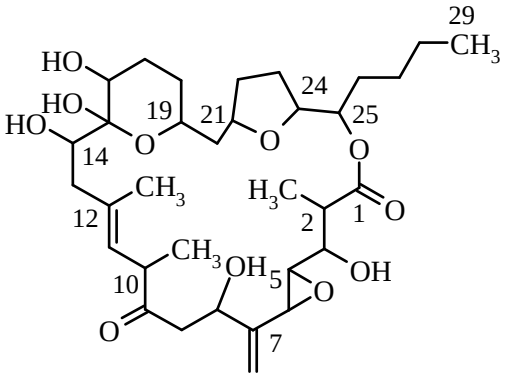
Amphidinolide M (**12**)

Figure 7

The structure of amphidinolide N[23] (**12**) was interpreted to be a 26-membered macrolide containing a 6-membered hemiacetal ring, an epoxide, a ketone carbonyl, four C1 branches, and seven hydroxyl groups. This compound was extremely cytotoxic against L1210 and KB cells (IC_{50}: 0.00005 and 0.00006 μg/mL, respectively). Although the relative stereochemistry of C14, C15, C16 and C19 was indicated as shown, the absolute stereochemistry of **12** was not determined. Shimizu and coworkers isolated an amphidinolide *N*-type macrolide, named Caribenolide I (**13**), from a free-swimming dinoflagellate *Amphidinium operculatum* ver nov *Gibbosum*.[24] Caribenolide I (**13**) was reported to show potent cytotoxicity against human colon tumor cells HCT116 and its drug-resistant strain HCT116/VM46 (IC_{50}: both 0.001 μg/mL), of which the IC_{50} value was about 100 times higher than that of amphidinolide B (IC_{50}: 0.122 μg/mL). Caribenolide I (**13**) showed antitumor activity against murine leukemia P388 (T/C: 150% at a dose of 0.03 mg kg^{-1}) *in vivo*.



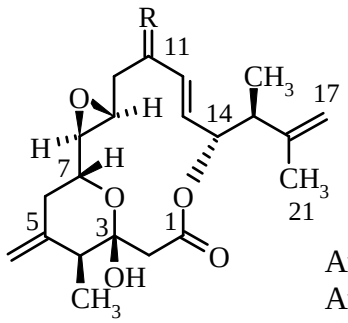
Amphidinolide N (**12**)



Caribenolide I (**13**)

Figure 8

Amphidinolides O (**14**) and P (**15**) are 15-membered macrolides possessing a tetrahydropyran ring, an epoxide, and two vicinally located methyl or *exo*-methylene groups.[25] The structural difference between **14** and **15** is at the C11 position, a ketone group for **14** and an *exo*-methylene group for **15**. Natural product analogs with this type of structural difference are quite rare. Williams *et al*. achieved the total synthesis of the enantiomer of (−)-amphidinolide P (**15**) in a convergent and highly enantio-controlled manner.[26] The optical rotation of **15** was opposite to that of synthetic one, thus indicating that the absolute stereochemistry of amphidinolide P (**15**) was enantiomeric to the synthetic (−)-amphidinolide P. Amphidinolides O (**14**) and P (**15**) were cytotoxic against L1210 (IC_{50}: 1.7 and 1.6 μg/mL, respectively) and KB cells (IC_{50}: 3.6 and 5.8 μg/mL, respectively).

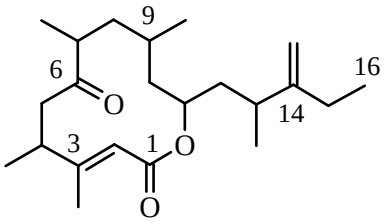


Amphidinolide O (**14**) R = O
Amphidinolide P (**15**) R = CH_2

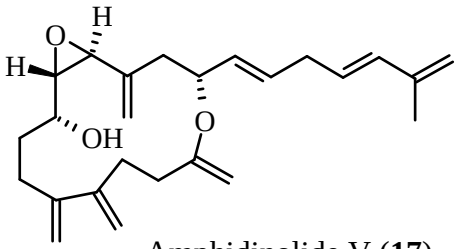
Figure 9

Amphidinolide Q[27] (**16**) is a 12-membered macrolide with four branched methyls, an *exo*-methylene, a ketone carbonyl, and a hydroxyl group. Convincing evidence for stereochemical assignment of **16** has not been provided. The 14-membered macrolide,

amphidinolide V (**17**), possessed five *exo*-methylenes and one epoxide.[28] The relative configurations at four chiral centers (C8, C9, C10, and C13) in **17** were deduced from the $^{1}H–^{1}H$ coupling constants and NOESY data. Amphidinolides Q (**16**) and V (**17**) showed cytotoxicity against L1210 (IC_{50}: 6.4 and 3.2 μg $mL,^{-1}$ respectively) and KB cells (IC_{50}: > 10 and 7 μg $mL,^{-1}$ respectively).



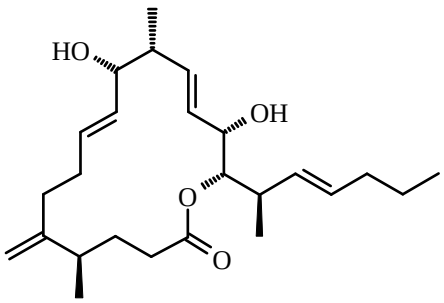
Amphidinolide Q (**16**)



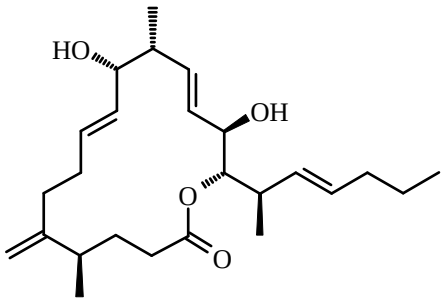
Amphidinolide V (**17**)

Figure 10

Amphidinolides[29] R (**18**) and S (**19**), cytotoxic 14- and 15-membered macrolides, respectively, possessing related structures to that of amphidinolide J (**8**), were isolated from the cultured marine dinoflagellate *Amphidinium* sp. Their structures including absolute stereochemistry were established on the basis of spectroscopic data as well as chemical derivatization experiments. Compounds **18** and **19** showed cytotoxicity against murine lymphoma L1210 (IC_{50}, 1.4 and 4.0 μg/mL) and human epidermoid carcinoma KB cells (IC_{50}, 0.67 and 6.5 μg/mL) *in vitro*, respectively.



Amphidinolide R (**18**)



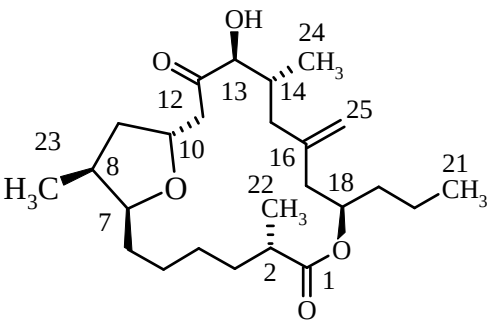
Amphidinolide S (**19**)

Figure 11

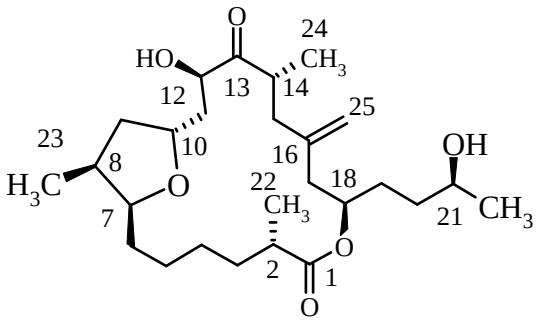
Amphidinolide T1[30] (**20**) is a 19-membered macrolide, which has been isolated from the dinoflagellate *Amphidinium* sp. (Y-56), possessing a tetrahydrofuran ring, an *exo*-methylene, three branched methyls, a ketone, and a hydroxyl group. Absolute configurations at four (C2, C13, C14, and C18) of seven chiral centers in amphidinolide T1 (**20**) were elucidated on the basis of the NMR data of the MTPA esters and the

degradation products, and the relative stereochemistry of the tetrahydrofuran ring was assigned from NOESY data.

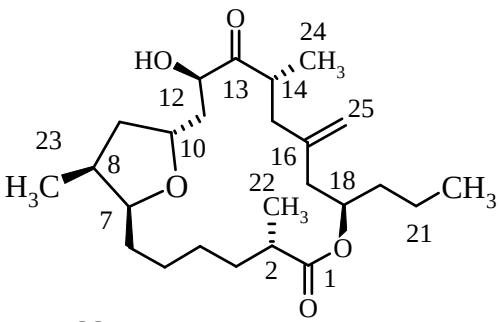
Amphidinolide T2[31] (**21**) is a congener of amphidinolide T1 (**20**) with one-carbon elongation at C21, while amphidinolides T3 (**22**),[31] T4 (**23**),[31] and T5 (**24**)[31] are 12-dihydro-13-dehydro isomers of **20**. The absolute stereochemistry of **21**–**23** was elucidated by chemical methods similar to those applied for the determination of **20**. The structure of amphidinolide T5 (**24**) was assigned by interconversion of **23** to **24** with K_2CO_3. Recently, Fürstner and coworkers achieved the total synthesis of amphidinolide T4 (**23**),[32] and the Ghosh group also reported the total synthesis of amphidinolide T1 (**20**).[33] Amphidinolides T1–T5 (**20** and 2**1**–**24**) exhibit modest cytotoxicity against L1210 cells *in vitro* with IC_{50} values of 18, 10, 7.0, 11, and 12 μg mL,$^{-1}$ respectively.



Amphidinolide T1 (**20**)



Amphidinolide T2 (**21**)



22

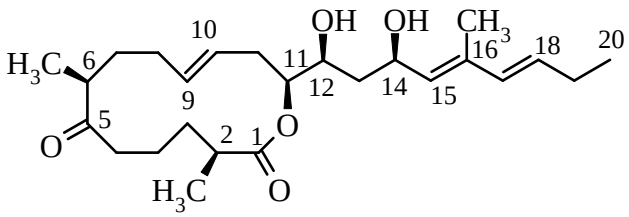
23: 12*S*-isomer of **22**

24: 12*S*, 14*S*-isomer of **22**

Figure 13

Amphidinolide W[34] (**25**), a novel 12-membered macrolide, has been isolated from the marine dinoflagellate *Amphidinolide* sp.[2] The chemical structure of **25** was elucidated mainly on the basis of spectroscopic studies. The absolute configurations of the five chiral centers of **25** have been determined by using NMR studies of the MTPA esters of

25 and its degradation products. Ghosh[35] *et al* completed the total synthesis of **25** and made revision of the C6 stereochemistry of structure **25** originally proposed for natural amphidinolide W. Amphidinolide W (**25**) is the first macrolide without an *exo*-methylene unit among all of the amphidinolides isolated so far. The gross structure of the C9–C16 moiety of **25** corresponds to that of C6–C15 of amphidinolide H **(8**), which was contained in strain Y-42, suggesting that amphidinolide W (**25**) may be biogenetically related to amphidinolide H (**6**). Amphidinolide W (**25**) exhibited potent cytotoxicity against murine lymphoma L1210 cells *in vitro* with an IC_{50} value of 3.9 μg $mL.^{-1}$



Amphidinolide W (**25**)

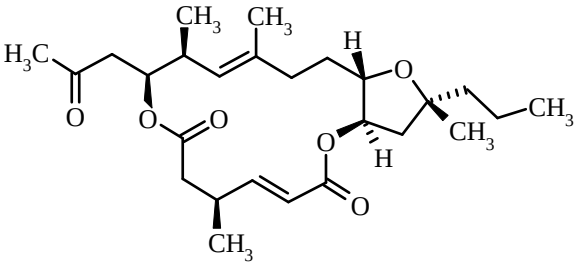
Figure 14

Amphidinolide X (**26)** was isolated by Kobayashi *et al*.[1] from a marine dinoflagellate of the genus *Amphidinium sp*. Amphidinolides usually embed a "conserved" set of structural elements into highly diverse macrolactone backbones. Amphidinolide X (**26**), however, is a significant exception to this rule.[2] This compound has neither the characteristic *exo*-methylene group, nor a vicinal one-carbon branch, nor a 1,3-diene unit found in virtually all other members of this series. Moreover, **26** is the only naturally occurring macrodiolide known to date that consists of a diacid and a diol unit rather than of two hydroxyacid entities.[2] The gross structure of **26** was elucidated on the basis of spectroscopic data including one-bond and long-range ^{13}C–^{13}C correlations obtained from 2D DEPT C–C Relay and 2D DEPT C–C Long-Range Relay experiments The relative stereochemistry for C10/C11 was elucidated to be *erythro* by *J*-based configuration analysis, while that of the tetrahydrofuran portion was assigned on the basis of NOESY data. The absolute configuration was determined by Mosher's method.

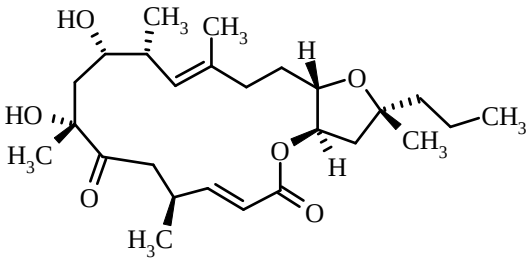
Amphidinolide Y (**27**), a 17-membered macrolide, was obtained from the same strain, and it was elucidated to exist as a 9:1 equilibrium mixture of 6-keto and 6(9)-hemiacetal forms (**27** and **27a**, respectively) on the basis of 2D NMR data. The structure and absolute stereochemistry of the 6-keto form **27** were assigned on the basis of

spectroscopic data and chemical conversion of **27** into amphidinolide X (**26**) by $Pb(OAc)_4$ oxidation. The 6-keto form **27a** of amphidinolide Y is a 17-membered macrolide possessing a tetrahydrofuran ring, five branched methyls, a ketone, and two hydroxyl groups.

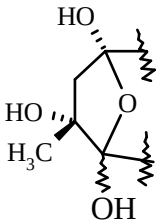
Amphidinolides X (**26**) and Y (**27**) show cytotoxicity against L1210 (IC_{50}: 0.6 and 0.8 μg $mL,^{-1}$ respectively) and KB cells (IC_{50}: 7.5 and 8.0 μg $mL,^{-1}$ respectively).



Amphidinolide X (**26**)



Amphidinolide Y (**27**)



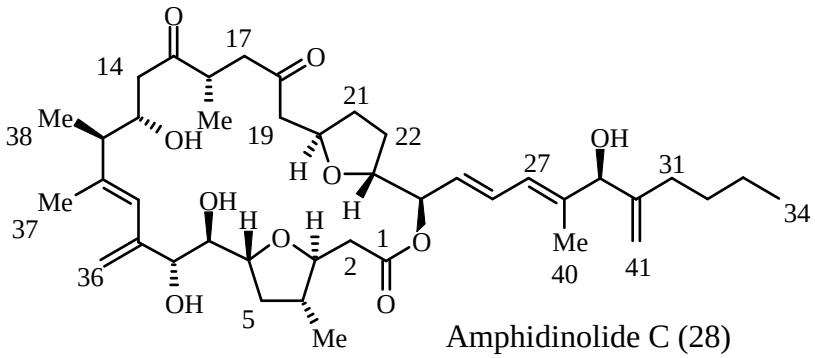
Amphidinolide Y (**27a)**

Figure 15

Amphidinolide C[36] (**28**), obtained from the marine dinoflagellate *Amphidinium* sp. (Y-5), is unique 25-membered macrolides having two tetrahydrofuran rings and vicinally located one-carbon branches, of which the gross structure has been elucidated by 2D NMR data. An *erythro* relationship for the C7–C8 bond was deduced from analysis of the NOESY spectrum of the 7,8-*O*-isopropylidene derivative of **28**.[37] On the other hand, the relative stereochemistry of H20/H23 and H23/H24 was assigned to be *anti* and *threo*, respectively, from analysis of the NOESY spectrum of **28**.[38] Recently, relatively large amounts of amphidinolide C (**28**) have been isolated from three strains (Y-56, Y-59, and Y-71) of the genus *Amphidinium*, which were separated from the inside cells of the marine acoel flatworms *Amphiscolops* sp. This sample allowed the elucidation of the absolute configurations of 12 chiral centers in **28**. The absolute configurations at C12, C13, C20, C23, and C29 were assigned as *R*, *S*, and *S* by *J*-based configuration analysis and the modified Mosher's method.[39] 3*S*, 4*R*, 6*R*, and 16*S*-configurations were

determined by comparison of the ^{1}H NMR spectra of the C1–C7 and C16–C18 segments obtained by oxidative degradation of **28** with those of the synthetic segments. For the absolute stereochemistry of C7 and C8, the Mosher's method for *erythro*-glycol proposed by Kusumi *et al.*[40] was applied. Therefore, the absolute configurations at twelve chiral centers in amphidinolide C (**28**) were assigned as 3*S*, 4*R*, 6*R*, 7*R*, 8*R*, 12*R*, 13*S*, 16*S*, 20*R*, 23*R*, 24*R*, and 29*S*.

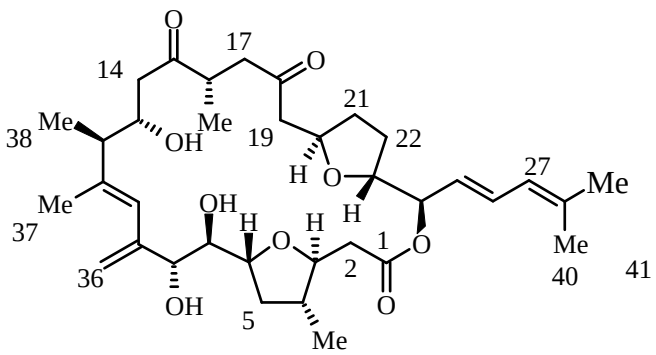
Amphidinolide C (**28**), the first 25-membered macrocyclic lactone, has powerful antineoplastic activity (IC_{50} 5.8 ng/mL) against L1210 murine leukemia cells *in vitro*.



Amphidinolide C (28)

Figure 16

Amphidinolide F [41] (**29**) is a congener of amphidinolide C (**28**) with a shorter side chain by a C6 unit than that of **28**. Since ^{1}H NMR and ^{13}C NMR chemical shifts of **29** were close to those of **28**, the relative stereochemistry of eleven chiral centers in **29** was suggested to be the same as that of amphidinolide C (**28**).

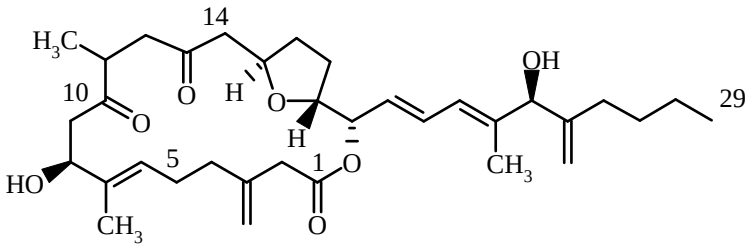


Amphidinolide F (**29**)

Figure 17

Amphidinolide[42] U **(30)**, A novel 20-membered macrolide possessing a tetrahydrofuran ring, two *exo*-methylenes, three branched methyls, two ketones, two hydroxyl groups, and a C10 linear side-chain, has been isolated from a marine

dinoflagellate *Amphidinium* sp. The structure was elucidated on the basis of spectroscopic data. The relative stereochemistry of C15, C18, and C19 was deduced from NOESY correlations, while the absolute configurations at C5 and C24 were assigned as both *S* on the basis of modified Mosher's method. The gross structure of the C9–C29 unit in amphidinolide U (**30**) corresponds to that of C14–C34 of amphidinolide C (**28**), while the carbon skeleton of the C1–C8 unit in 3**0** is very close to that of C1–C8 in amphidinolide A (**1**). This observation suggests that amphidinolide U (**30**) may be biogenetically related to amphidinolides C (**28**) and A (**1**).



Amphidinolide U (**30**)

Figure 18

Amphidinolide C (**28**) exhibited potent cytotoxic activity against L1210 and KB cells *in vitro* with IC_{50} values of 0.0058 and 0.0046 μg $mL,^{-1}$ respectively. Amphidinolides F (**29**) and U (**30**) showed cytotoxicity against L1210 (IC_{50}: 1.5 and 12 μg $mL,^{-1}$ respectively) and KB cells (IC_{50}: 3.2 and 20 μg $mL,^{-1}$ respectively). Thus, it was anticipated that the 25-membered macrolactone ring may be essential for cytotoxicity, and the length of side chain is considered to affect the potency of cytotoxic activity significantly.

The potential importance of the biological implication and complexity of structures made them an attractive target for total synthesis. Our current interest is the synthetic studies of amphidinolide C (**28**) and amphidinolide U (**30**).

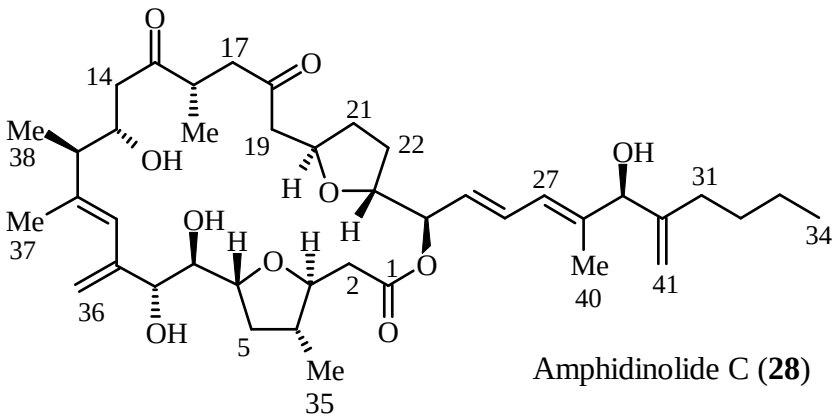
CHAPTER 3

SECTION I

Synthesis of C19-C34 fragment of Amphidinolide C

Present Work

The growing importance of amphidinolides group of naturally occurring macrolides from the marine dinoflagellates of the genus *amphidinium* has been attributed to the potent biological activities and novel structural features.[3] The complete biological profiling of amphidinolides has been hampered because they are found only in microscopic marine flatworms. The target molecule amphidinolide C (**28**; Figure 16), isolated from the marine dinoflagellates *Amphidinium* sp. (strain Y–5), is a unique 25-membered macrolide having two tetrahydrofuran rings decorated with vicinally located one-carbon branches.[36] The gross structure of **28** was elucidated by the 2D NMR data. It is interesting to point out that amphidinolide C (**28**) showed extremely potent *in vitro* cytotoxic activity against murine lymphoma L1210 and epidermoid carcinoma KB cells (IC_{50} = 0.0058 and 0.0046 mg $mL,^{-1}$ respectively). Based on these findings, it was but obvious that amphidinolides make attractive targets for total synthesis and therefore, we also embarked on one of their family members amphidinolide C (**28**) and we will discuss in this section the synthesis of the C19–C34 segment **34**.



Amphidinolide C (**28**)

Figure 16

Amphidinolide C (**28)** could be assembled from four building blocks: the alcohol part **31**, acid part **32**, stannane part **30** and thione part **29**. The thione moiety could be devised as a tool for coupling of the C17 of segment **30** and C19 of segment **31**. The macrolactonization between alcohol of part **31** and acid of part **32** could be achieved through DCC mediated coupling. The underlying concept is outlined in Figure 19.

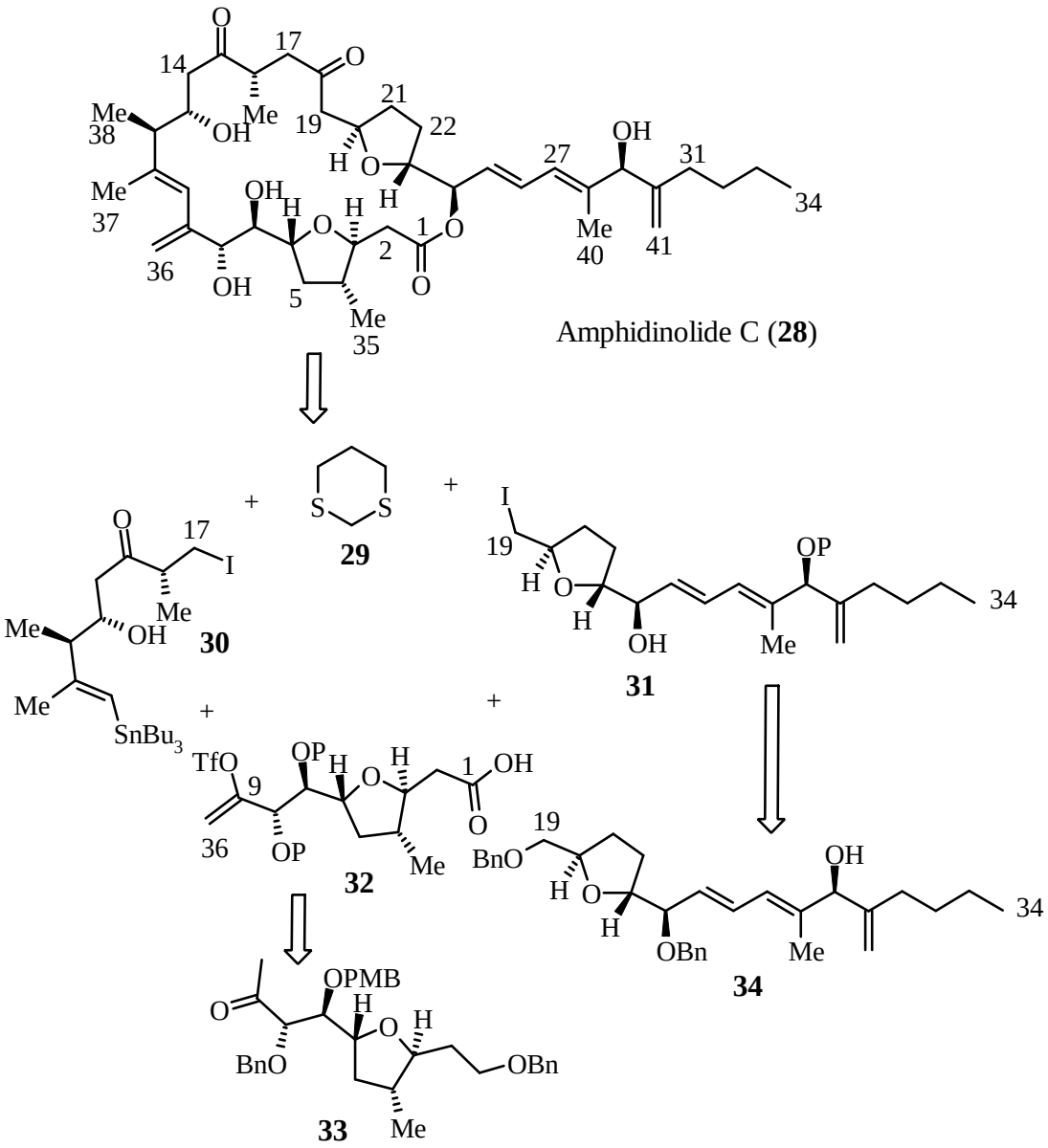
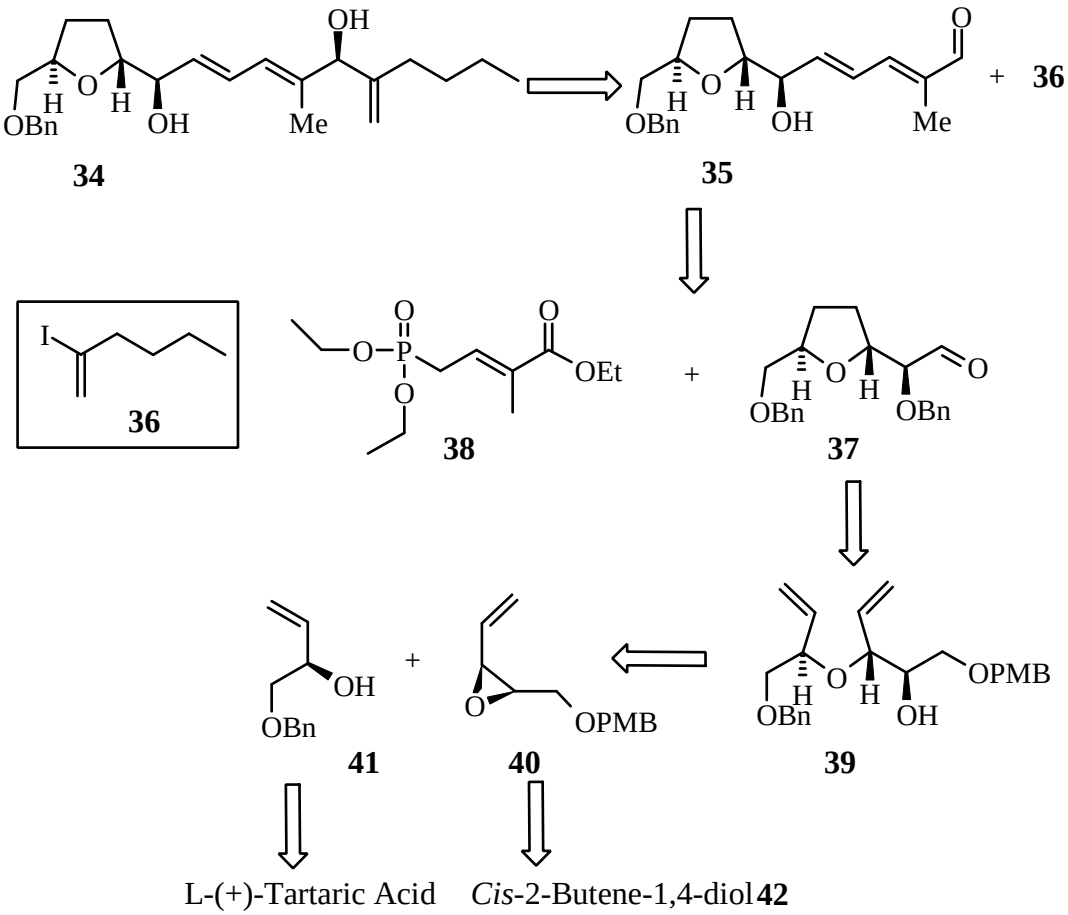


Figure 19: *Retrosynthetic analysis of amphidinolide C (**28**)*

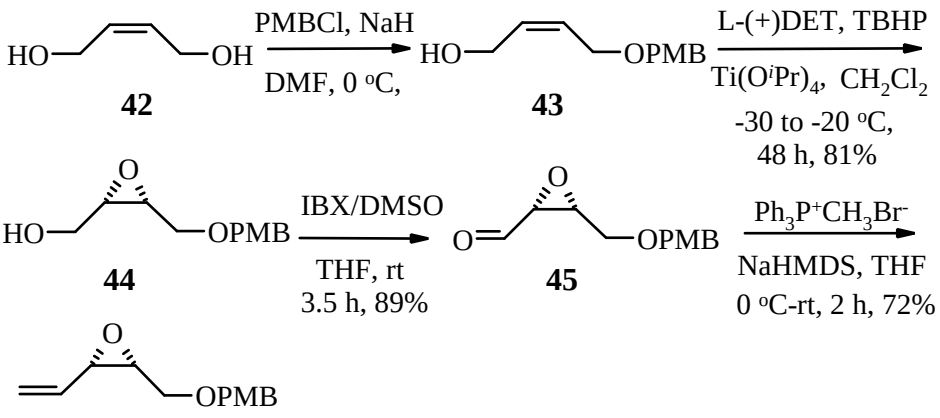
The retrosynthetic analysis of segment **34** has been outlined in scheme 1 whose salient features involved the Mioskowski's Lewis acid catalyzed regioselective epoxide **40** opening with the alcohol **41,** followed by the RCM reaction to construct the tetrahydrofuran unit. For the installation of the side chain, two well-known reactions–Wittig and Nozaki–Hiyama–Kishi coupling–were envisaged.

The synthesis of **40** began with *cis*-2-butene-1,4-diol **42** which was converted into **44** by employing the Sharpless asymmetric epoxidation as previously described.[43] The enantiomeric purity of **44** was determined to be 83% *ee* by chiral HPLC analysis (Scheme



Scheme 1: *Retrosynthetic analysis of segment **34***

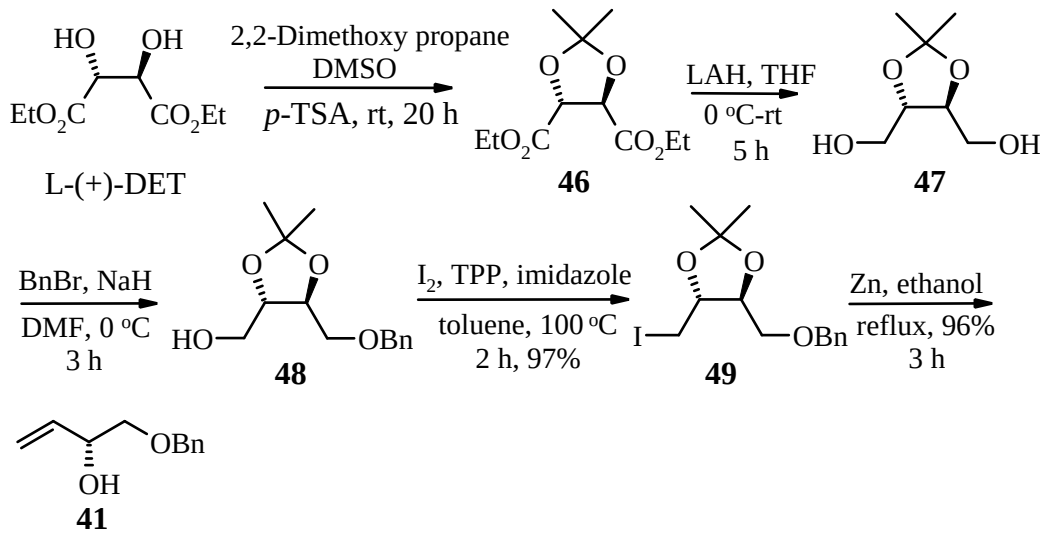
2). The spectroscopic data (^{1}H NMR and ^{13}C NMR) and the optical rotation of **44** were in close agreement with the reported values {observed: $[\alpha]_D^{25}$ –16.8 (*c* = 2.5, CH_2Cl_2); lit.[43] $[\alpha]_D^{25}$ –17.0 (*c* = 2.15, CH_2Cl_2)}. The preparation of aldehyde **45** was accomplished by IBX oxidation of **44** in DMSO/THF at room temperature. The aldehyde was subjected



Scheme 2

to one carbon Wittig homologation of **45** by treating with methyltriphenylphosphonium bromide and NaHMDS in THF to produce **40** in 72% yield. In the ^{1}H NMR spectrum of 4**0**, the internal olefinic protons resonated in the region of δ 5.58-5.75 (m, 1H) ppm and terminal olefinic protons appeared as a multiplet spanning between δ 5.30-5.51 (m, 2H) ppm. In the ^{13}C NMR spectrum of **40**, peaks for olefinic carbons were observed at *δ* 120.1 (t), 131.8 (d) and were in support of the assigned structure of **40**.

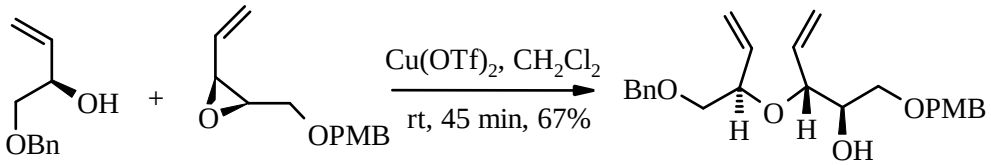
Synthesis of allylic alcohol part **41** is outlined in scheme 3. The strategy for the synthesis of fragment **41** takes the advantage of C_2 symmetry present in tartaric acid. The cheap and easy availability, high enantiomeric purity, were the strong incentives for our interest to start with L-(+)-tartaric acid which could be easily converted to L-(+)-diethyl tartarate following standard procedure. Accordingly, the journey began with L-(+)-DET, which was ketalized as 1,2-*O*-isopropylidene-D-diethyltartrate, followed by LAH reduction to provide diol **47**, and subsequent monobenzylation furnished the synthon **48**. Compound **48** was subjected to iodination by using TPP, imidazole, I_2 in toluene at 100 ^{o}C to afford compound **49**. The ^{1}H NMR, ^{13}C NMR spectra secured the assigned structure. The iodide **49** on refluxing with zinc in ethanol underwent a facile elimination reaction to furnish alcohol **41**. The ^{1}H NMR, ^{13}C NMR spectra, mass and elemental analysis were in good agreement with the reported data.[44]



Scheme 3

The allyl alcohol **41** and the vinyl substituted epoxide **40** precursors to the ring closing metathesis substrate were then ready to be coupled. The coupling reaction

between **41** and **40** was carried out in the presence[45] of catalytic amount of $BF_3 \cdot OEt_2$ in dichloromethane to afford the diene **39** in 32% yield, whereas the alcohol **41** was recovered in 45% yield. It is noteworthy that with catalytic amount of $Cu(OTf)_2$, the diene moiety was formed in 67% yield and the alcohol **41** was recovered in 18% yield. In the ^1H NMR spectrum of **39**, characteristic signals due to two olefinic groups were clearly observed. In addition, the resonances due to benzylic protons of −*Bn* and −*PMB* groups were located at δ 4.43 (d, *J* = 11.5 Hz, 1H), 4.49 (d, *J* = 11.5 Hz, 1H), 4.55 (s, 2H) ppm, respectively. The structure was further supported by the ^{13}C NMR and elemental analysis.



41 **40** **39**

Scheme 4

The absolute stereochemistry of the secondary hydroxyl group at C24 (numbering based on Figure 1) was confirmed by modified Mosher's method.[46(i)]

Modified Mosher's ester method: Application for stereochemical assignment of C24-OH of 39

Determination of the absolute stereochemistry of organic compounds has become an important aspect for natural product chemists as well as synthetic chemists. The limitations involved in physical methods such as exciton chirality method and X-ray crystallography forced synthetic chemists for a more reliable alternative. Although there are several chemical methods used to predict the absolute configuration of organic substances, Mosher's method using 2-methoxy-2-phenyl-2-(trifluoromethyl)acetic acid (MTPA) esters has been most frequently used. Mosher proposed that, in solution, the carbinyl proton, ester carbonyl and trifluoromethyl group of the MTPA moiety lie in the same plane (Figure 20).[46(ii)]

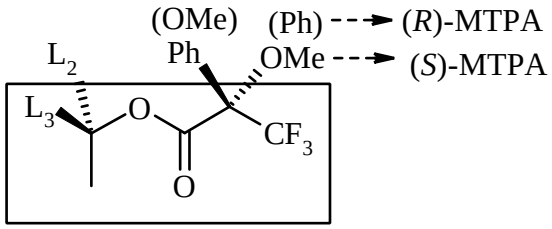


Figure 20: *Configurational correlation model for (R)-MTPA and (S)-MTPA derivatives proposed by Mosher.*

When the MTPA group is in the hypothesized conformation, Mosher pointed out that the ^{1}H NMR signal of L^{2} of the (R)-MTPA ester will appear upfield relative to that of the (S)-MTPA ester due to the diamagnetic effect of the benzene ring. The lack of reliability associated with Mosher's ^{19}F method using ^{19}F NMR motivated Kakisawa et al. to elaborate his concept for more accuracy.[46(i)] *The modified Mosher's ester method (^{1}H) is one of the simple and efficient ways to determine the absolute stereochemistry of the secondary alcohols and amine stereocenters in organic molecules.*

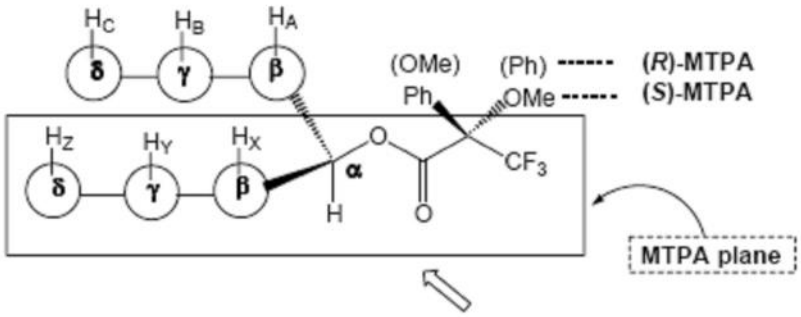


Figure 21*: MTPA plane of an MTPA ester is shown. $H_{A,B,C,\ldots}$ and $H_{X,Y,Z,\ldots}$ are on the right and left sides of the plane respectively.*

The basic concept of the modified Mosher's ester method is essentially the same as Mosher proposed. The idealized conformation is depicted in Figure 21. The plane and the conformation of MTPA group will be called as the MTPA plane and ideal conformation respectively. Due to the diamagnetic effect of the benzene ring, the $H_{A,B,C,\ldots}$ signals of (R)-MTPA ester in the ^{1}H NMR should appear upfield to those of the (S)-MTPA ester. The reverse should hold true for protons, $H_{X,Y,Z,\ldots}$ Hence, when $\Delta\delta = (\delta S - \delta R) \times 10^{3}$ protons on the right side of the MTPA plane must have positive values ($\Delta\delta > 0$), and the protons on the left side of the MTPA plane must have negative values ($\Delta\delta < 0$). This is illustrated in model A (Figure 22).

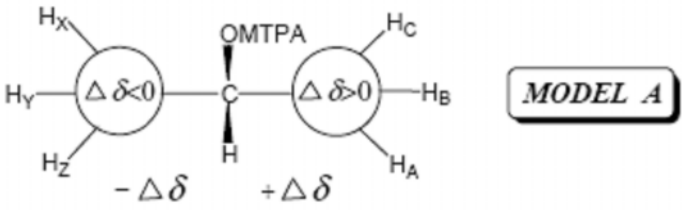


Figure 22: *A view of MTPA ester drawn in Figure 21 from the direction indicated by outlined arrow to determine the absolute configuration of secondary alcohol***.**

According to Kakisawa and coworkers, the Mosher's method can be extended as follows:

(i) *Assign as many proton signals as possible with respect to each of the (R)- and (S)-MTPA esters;*

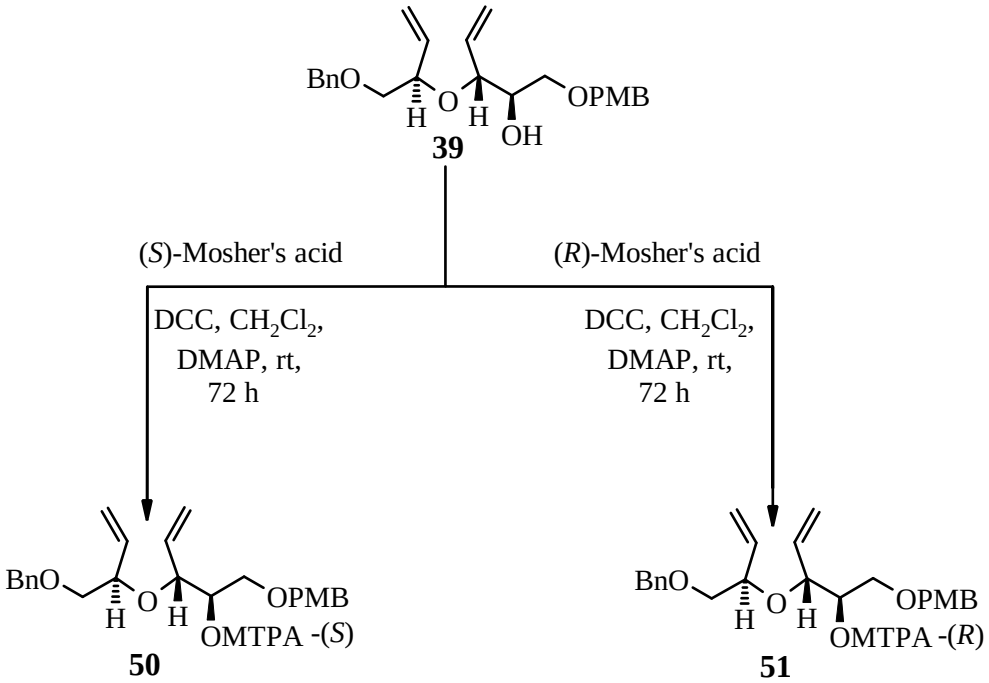
(ii) *Obtain Δδ values for the protons;*

(iii) *Arrange the protons with positive Δδ values right side and those with negative Δδ values on the left side of the model;*

(iv) *Construct a molecular model of the compound in question and confirm that all the assigned protons with positive and negative Δδ values are actually found on the right and left sides of the MTPA plane, respectively.*

The absolute values of Δδ must be proportional to the distance from the MTPA moiety. When these conditions are all satisfied, model A will represent the correct absolute configuration of the compound.

In order to assign the absolute stereochemistry of the side chain at C24, the (*S*)-MTPA ester **50** and (*R*)-MTPA ester **51** were independently prepared from **39** by using corresponding (*S*)-MTPA acid and (*R*)-MTPA acid in presence of coupling agent DCC and DMAP (cat.) in anhydrous dichloromethane at room temperature (Scheme 5). The $\Delta\delta = (\delta_S - \delta_R)$ X 10^3 values were calculated for as many protons as possible from the ^{1}H NMR spectrum of (*S*)-MTPA ester **50** and (*R*)-MTPA ester **51** (Table 1). Then, constructed a molecular model of the compound and the $\Delta\delta = (\delta_S - \delta_R)$ X 10^3 values were uniformly arranged as shown in Figure 23. On the basis of the model (Figure 23) we have assigned the absolute stereochemistry of side chain at C24 of **39** as (*R*)-configuration.



Scheme 5

Table 1: *Chemical shifts for (S) and (R)-MTPA esters of **39**.*

Sr. No.	**Protons**	δ_S	δ_R	$\triangle\delta = \delta_S - \delta_R$	$\triangle\delta$ **X** 10^3
1.	H^1	3.67,3.61,3.57	3.59,3.58, 3.53.	+0.06,+0.03, +0.04,	+60+30, +40,
2.	H^8	4.56,4.53,4.53	4.58,4.56,4.55	-0.02, -0.03	-20, –30,
3.	H^{18}	7.18,7.20.	7.14,7.12	+0.04, +0.08	+40, +80.
4.	H^{19}	6.85,6,83.	6.82,6.81	+0.03, +0.02	+30, +20
5.	H^3	4.07, 4.05	4.19, 4.16.	-0.12, -0.11	-120, -110.
6.	H^4	4.00, 3.97, 3.36.	4.09, 4.07, 4.05	-.09, 0-0.1, -0.69	-90,–100, -690
7.	H^5	3.37	3.46	-0.09	-90
8.	H^{17}	4.49,4.47,4.39	4.39,4.36,4.30	+0.1 +0.11, +0.09,	+100, +110, +90
9.	H^7	5.27,5.20, 5.17,5.15	5.36, 5.32, 5.24,5.22	-0.11, -0.08, -0.07, -0.09	-110, –80 –70, –90

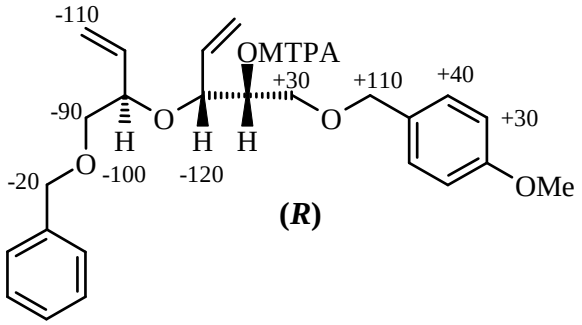
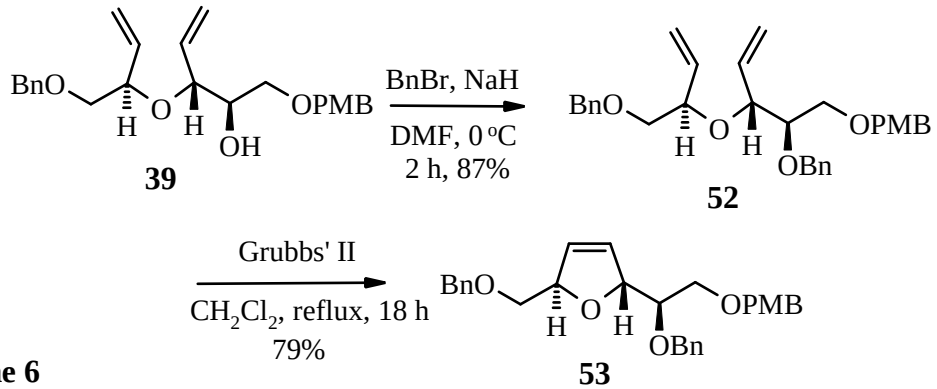


Figure 23: *$\Delta\delta = (\delta_S - \delta_R) \times 10^3$ for (S) and (R) MTPA esters of **39***

Having secured the absolute configuration of secondary hydroxyl group at C24 of **39** beyond doubt, we focused our attention on the construction of tetrahydrofuran ring from **39**. For that endeavor, the RCM[47] reaction was applied to diene **39**. Subjecting **39** to the Grubbs' second generation catalyst did not afford the RCM product but only led to recovery of starting material **39**. The lack of success in this RCM reaction was may be due to the presence of a free secondary alcohol in **39**. Thus, **39** was first subjected to benzylation of the free hydroxyl group using NaH and BnBr in DMF to provide the diene **52**, whose ^{1}H NMR and ^{13}C NMR spectrum showed the resonances in accordance with the structure.

The achievement of the protected diene derivative **52** set the stage for the application of ring closing metathesis reaction to obtain the tetrahydrofuran core, which would be a landmark towards the target segment. Thus, the diene **52** was treated with 3 mol% of Grubbs' 2nd generation catalyst in dichloromethane to afford the dihydrofuran intermediate **53** in 79% yields. The ^{1}H NMR spectrum of **53** indicated the resonances per

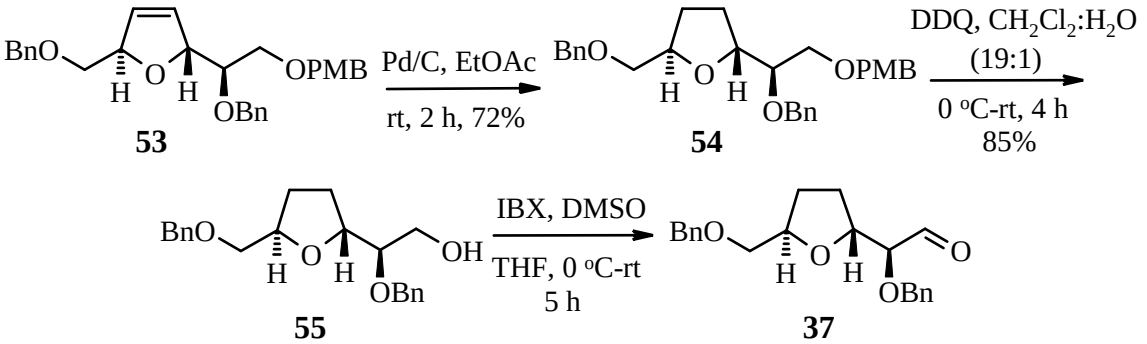


Scheme 6

-taining to olefinic protons at δ 5.82-5.90 (m, 2H) ppm, whereas the H20, H23 (numbering based on Figure 1) protons resonated in the downfield region at δ 4.93-5.06

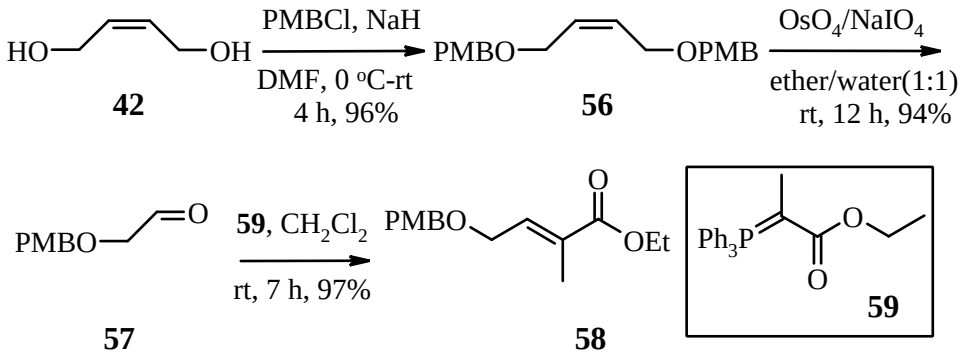
(m, 2H) ppm. The rest of the protons had the expected chemical shifts in support of the assigned structure of **53** (Scheme 6). ^{13}C NMR spectra, mass and elemental analysis also secured the product formation.

Catalytic hydrogenation of compound **53** in the presence of 10% Pd/C in ethyl acetate at normal temperature and pressure resulted in the reduction of olefinic double bond to provide the tetrahydrofuran derivative **54**. The ^{1}H NMR spectrum of **54** revealed the characteristic resonances at δ 1.62-1.69 (m, 1H), 1.71-1.78 (m, 1H), 1.88-1.94 (m, 1H) ppm. The removal of the −*PMB* group with DDQ in dichloromethane and water in a ratio of 19:1 gave the primary alcohol **55**. The structure of **55** was confirmed by the ^{1}H NMR, ^{13}C NMR and elemental analysis. Oxidation of the free alcohol **55** to the aldehyde **37** using IBX in DMSO/THF at room temperature occurred smoothly. Our next concern was the introduction of the densely olefinated side chain by Horner-Wadsworth-Emmons olefination (Scheme 10). Having in hand the aldehyde **37**, we next envisaged the synthesis of phosphonate **38**.



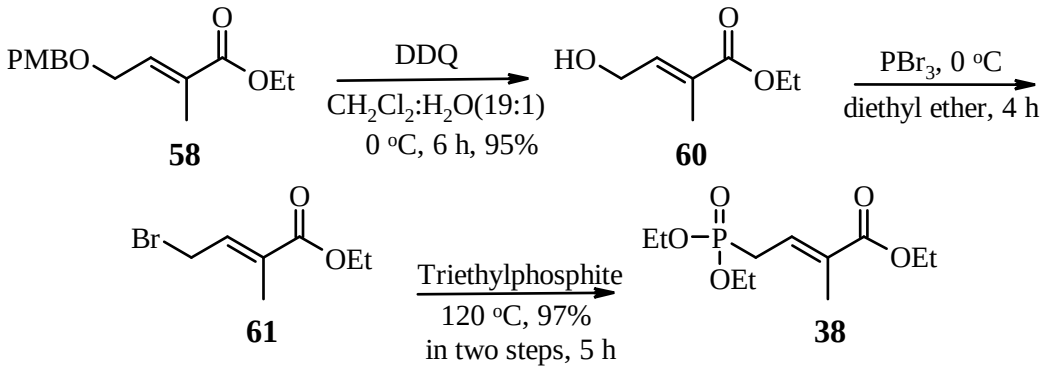
Scheme 7
Synthesis of Phosphonate 38

The next synthetic target was the phosphonate derivative **38**, for which aldehyde **57** was identified as the starting material. *Cis*-2-butene-1,4-diol **42** was protected as di-*PMB* ether **56** and then subjected to oxidative cleavage of olefin with OsO_4 in presence of sodium metaperiodate in ether/H_2O(1:1) (Scheme 8). This protocol gave the aldehyde **57** which was subjected to two-carbon homologation by Wittig reaction[49] with the stable ylide $Ph_3P{=}C(Me)CO_2Et$ **59** in CH_2Cl_2 at room temperature to provide the (*E*)-α,β-unsaturated ester. In the ^{1}H NMR spectrum of **58**, the olefinic proton appeared in the region δ 6.82-6.89 ppm, while the vinylic methyl group resonated at δ 1.82 (3H) ppm as a singlet.



Scheme 8

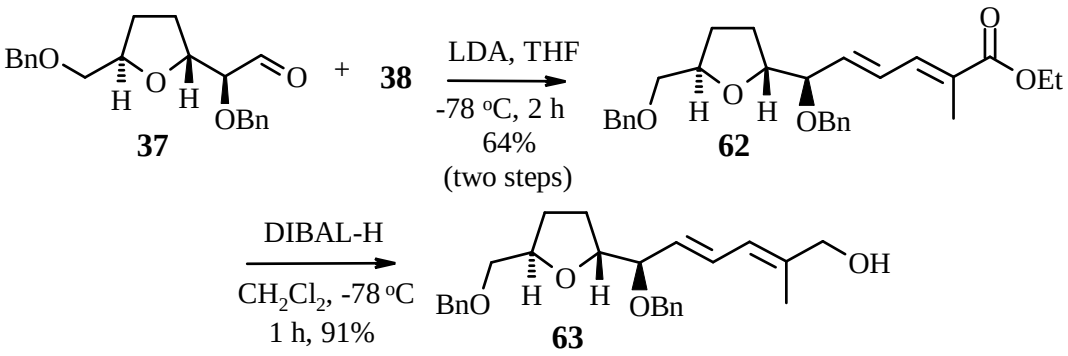
Removal of *p*-methoxybenzyl ether in **60** was effected with DDQ in CH_2Cl_2/H_2O (19:1) at 0 ^oC to afford the allyl substituted alcohol **60**. Disappearance of signals due to the methyl ether and related aromatic peaks of *−PMB* ether in the ^1H NMR spectrum clearly indicated the transformation. The methylene protons of C1 appeared at δ 4.35 (*J* = 6.0 Hz, 2H) ppm as a doublet. An attempt for the conversion of alcohol **60** to the corresponding bromo derivative **61** with TPP/CBr_4[50] resulted in the formation of unidentified products. However, the conversion was achieved with PBr_3 in diethyl ether at 0 ^oC (Scheme 9).[51] Michaelis-Arbuzov reaction of the resulting bromo derivative **61** with $P(OEt)_3$ at 120 ^oC afforded[52] the phosphonate **38,** whose structure was confirmed by ^1H NMR, ^{13}C NMR, IR spectra and elemental analysis.



Scheme 9

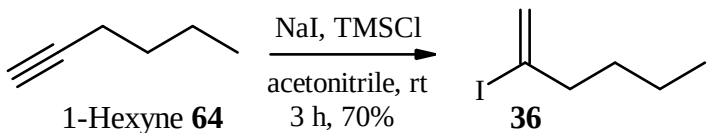
In the ^1H NMR spectrum of **38**, the active methylene protons appeared as a doublet of doublet at δ 2.73 (*J* = 8.2, 23.4 Hz, 2H) ppm. The methylene protons of the $P(OEt)_2$ group appeared as a multiplet in the region of δ 4.04-4.26 (6H) ppm, while the methyl protons spanning between δ 1.27-1.37 (9H) ppm as a multiplet. All the other resonances were in good agreement with the assigned structure.

Having made the two key intermediates **37** and **38**, our attention turned towards the introduction of the the *E*,*E*-dienoate moiety. For this endeavor, Horner-Wadsworth-Emmons[48] chain homologation of **37** using phosphonate **38** in the presence of LDA as base at –78 ^{o}C furnished exclusively *E*,*E*-dienoate **62** (Scheme 10). The structure of **62** was thoroughly investigated by its ^{1}H NMR, ^{13}C NMR spectroscopy and elemental analysis. The ^{1}H NMR of **62** showed H3 at δ 7.19 (*J* = 11.6 Hz, 1H) ppm as a doublet, H4 at δ 6.03 (*J* = 7.1, 15.3 Hz, 1H) ppm as a double-doublet and H4 as a doublet of double doublet at δ 6.57 (ddd, *J* = 1.0, 11.4, 15.3, 1H) ppm. From the above observations, it was clearly revealed the presence of *E*,*E*-dienoate moiety in **62**. Reduction of ester derivative **62** using DIBAL-H in dichloromethane at −78 ^{o}C furnished the allylic alcohol derivative **63**. The ^{1}H NMR, ^{13}C NMR, IR spectroscopic data and elemental analysis of **63** supported the structure. In the ^{1}H NMR spectrum, the olefinic proton and the vinylic methyl resonated in the upfield region at δ 5.56 (dd, *J* = 7.9, 15.2 Hz, 1H), 6.02 (d, *J* = 10.8 Hz, 1H), 6.40 (dd, *J* = 11.0, 15.3 Hz, 1H) and 1.70 (s, 3H) ppm, respectively.



Scheme 10

According to our synthetic plan, next we needed iodohexene **36**[53]. Thus, 1-hexyne was straightforwardly transformed into iodohexene using sodium iodide (NaI) in presence of TMSCl in CH_3CN (Scheme 11).

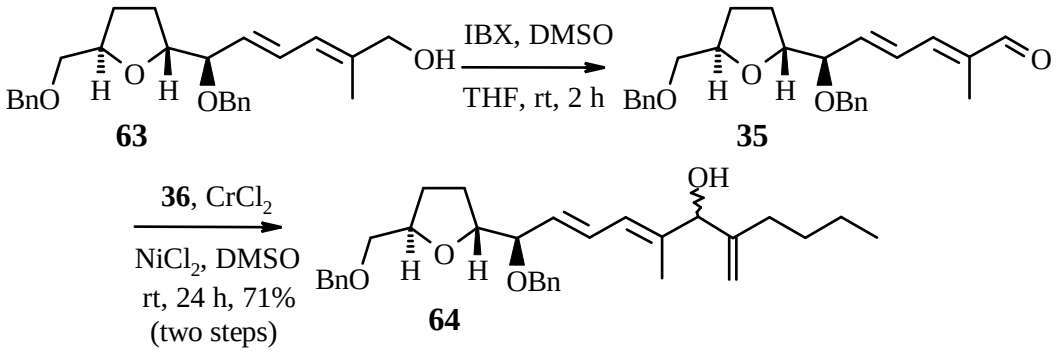


1-Hexyne **64** **36**

Scheme 11

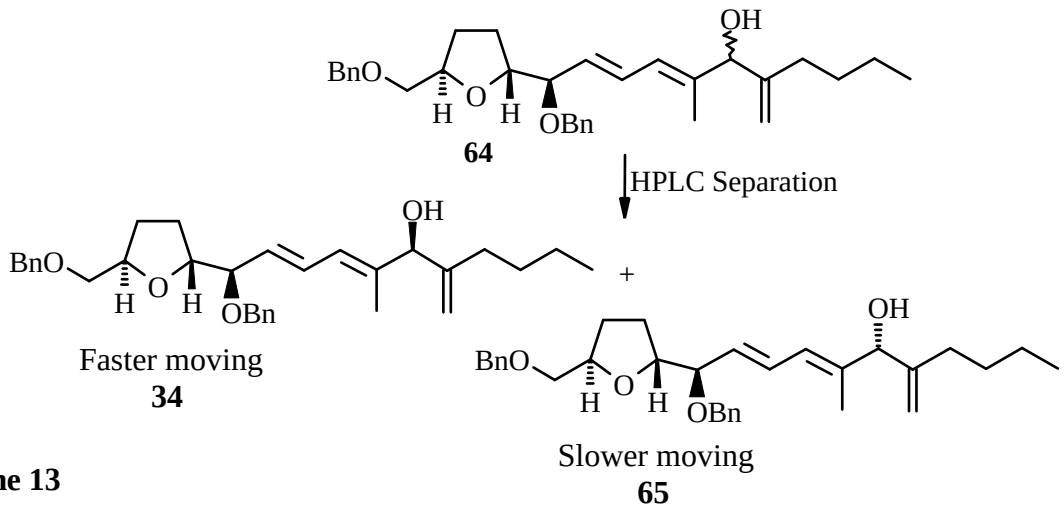
The allyl substituted alcohol **63** was next converted into the aldehyde **35** in presence of IBX in DMSO/THF at room temperature. Without further purification of the crude

aldehyde **35**, it was carried forward to Nozaki–Hiyama–Kishi coupling[54] reaction with **36** in the presence of $CrCl_2$ and catalytic amount of $NiCl_2$ to give a diastereomeric mixture of our target segment **64** in a 1:1 ratio (Scheme 12).



Scheme 12

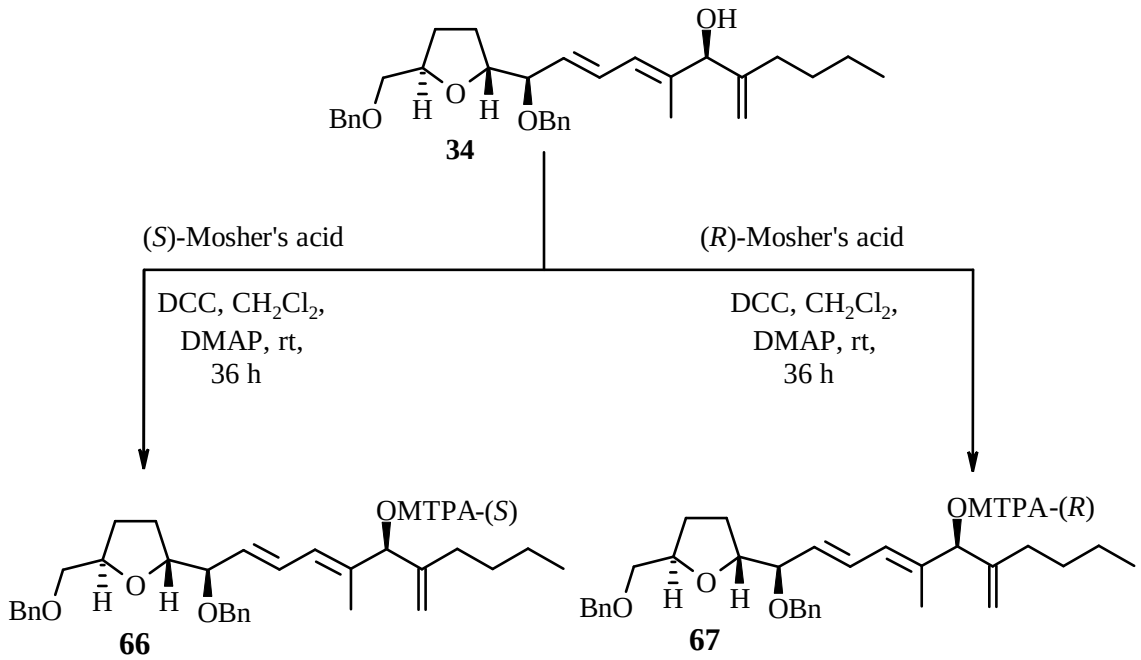
To separate the diastereomeric mixture, we had gone through HPLC separation of the mixture. Accordingly, the diastereomers were separated by preparative liquid chromatography to deliver two diastereomers **34** and **65** in pure form and structurally scrutinized.



Scheme 13

Although, both **34** and **65** showed NMR data in conformity with the assigned structure, it was difficult to correctly assign the absolute stereochemistry at the newly generated chiral center. The resonance due to H25, H26 and H27 were observed at 5.67, 6.48, and 6.17 ppm for compound **34** and 5.68, 6.48, and 6.17 for compound **65**, respectively. In compound **34**, the resonance for H34 was observed at δ 0.90 ppm (J = 7.2 Hz) matched with the value reported for **28**. The compound **65** showed H34 at δ 0.89 ppm (J = 7.3 Hz) (Scheme 13).

Although the gross structure of **34** was revealed by its spectral studies, the absolute stereochemistry at the newly born chiral center at C29 side chain could not be ascertained based on spectral studies. Hence, we had opted for modified Mosher's method[46] to establish the absolute stereochemistry.



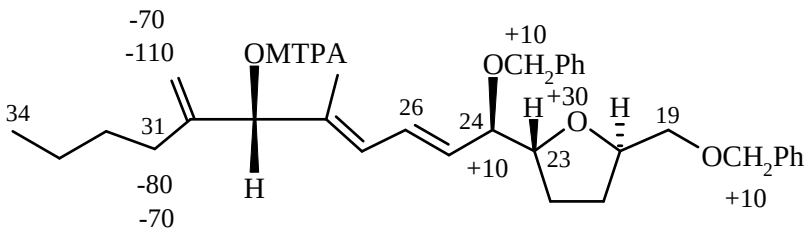
Scheme 14

Accordingly, the faster-moving spot **34** was converted into its (*R*)- and (*S*)-MTPA esters (**66** and **67**) autonomously by using corresponding (*S*)-MTPA acid and (*R*)-MTPA acid in presence of coupling agent DCC and DMAP (cat.) in anhydrous CH_2Cl_2 at room temperature (Scheme 14). The Mosher's esters showed negative chemical shift difference ($\Delta\delta = \delta_S - \delta_R$) for protons on C30–C34, while protons on C19–C28 showed positive differences, which is consistent with C29 bearing an (*S*) configuration.

Table 2: *Chemical shifts for (S) and (R)-MTPA esters (***66** and **67**) *of **34**.*

Protons	δ_S	δ_R	$\Delta\delta = \delta_S - \delta_R$	$\Delta\delta$ X 10^3
H31	2.32	2.40	-0.08	-80
	2.31	2.38	-0.07	-70
	2.29	2.36	-0.07	-70
H41	4.94	5.01	-0.07	-70
	5.01	5.12	-0.10	-110

H23	4.15	4.12	+0.03	+30
	4.17	4.14	+0.03	+30
H24-Benzylic	4.64	4.63	+0.01	+10
	4.67	4.66	+0.01	+10
H19-Benzylic	4.58	4.57	+0.01	+10
H24	3.92	3.91	+0.01	+10



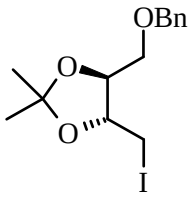
(*S*)

Figure 24: *$\Delta\delta = (\delta_S - \delta_R) \times 10^3$ for (S) and (R) MTPA esters of **34***

In conclusion, a versatile synthetic strategy towards the C19-C34 segment of amphidinolide C (**28**) has been achieved which could lead to the easy access of its diastereomers as well. For the construction of the tetrahydrofuran framework, the Lewis acid-catalyzed regiospecific opening of vinyl substituted epoxide **40** by alcohol **41**, followed by ring closing metathesis (RCM) were the key steps.

Experimental

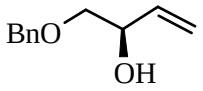
(4*S*,5*R*)-4-(benzyloxymethyl)-5-(iodomethyl)-2,2-dimethyl-1,3-dioxolane (49):



To a stirred solution of alcohol **48** (5.4 g, 21.46 mmol) in toluene (100 mL) was added successively triphenylphosphine (TPP) (11.25 g, 42.93 mmol), imidazole (4.39 g, 64.40 mmol) and iodine (I_2) (10.89 g, 42.93 mmol), at room temperature and stirred it for additional 30 min. The reaction was then allowed to warm to 100 ^oC. After 2 h, the reaction mixture cooled to room temperature and diluted with ether, and stirred it for additional 1 h (when clear solution appeared and TPP-oxide precipitated out). The clear solution was separated and washed with saturated sodium thiosulfate, $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated. Purification on silica gel column chromatography (EtOAc/light Petrolium.ether:5/95) afforded iodo compound **49** (7.52 g) as clear oil.

Yield	: 97%
Mol. Formula	: $C_{14}H_{19}IO_3$
Optical Rotation $[\alpha]_D^{25}$	: −9.20 (c 3.3, $CHCl_3$).
IR ($CHCl_3$) cm^{-1}	: 3392, 2986, 2932, 2864, 1605, 1453, 1380, 1217, 1093, 1028, 861, 754, 698.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.41(s, 3H), 1.47(s, 3H), 3.23-3.39 (m, 2H), 3.58-3.71 (m, 2H), 3.81-4.00 (m, 2H), 4.59 (s, 2H), 7.26-7.40 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 6.24, 27.24, 27.34, 70.35, 73.44, 77.54, 79.93, 109.56, 127.50, 127.64, 128.32, 137.67 ppm.
Elemental Analysis	**Calcd:** C, 46.42; H, 5.29.
	Found: C, 45.92; H, 4.81.

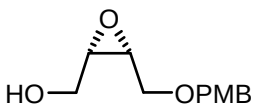
(*R*)-1-(benzyloxy)but-3-en-2-ol (41):



To a solution of iodo compound **49** (4.97 g, 13.72 mmol) in ethanol (130 mL), activated Zn (8.97 g, 137.18 mmol) was added. Reflux it for 3 h and filtered off the solid. The filtrate was concentrated and purified by silica gel (60-120 mesh) column chromatography (Ethyl acetate/Petroleum ether: 3/7) to afford vinyl alcohol **41** (2.36 g) colorless oil.

Yield	: 96%
Mol. Formula	: $C_{11}H_{14}O_2$
Optical Rotation $[\alpha]_D^{25}$	: +8.9 (*c* 2.6, $CHCl_3$).
IR ($CHCl_3$) cm^{-1}	: 3432, 3064, 3030, 2864, 1719, 1602, 1453, 1364, 1274, 1112, 930, 698, 608.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 2.49 (brs, 1H), 3.31-3.56 (m, 2H), 4.28-4.38 (m, 1H), 4.56 (bs, 2H), 5.15-5.40 (m, 2H), 5.74-5.90 (m, 1H), 7.25-7.36 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 71.13, 73.04, 73.88, 115.94, 127.52, 128.19, 136.66, 137.65 ppm.
Elemental Analysis	**Calcd:** C, 74.13; H, 7.92.
	Found: C, 73.29; H, 7.83.

((2*S*,3*R*)-3-((4-methoxybenzyloxy)methyl)oxiran-2-yl)methanol (44):

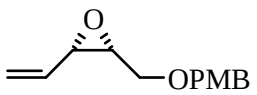


To a solution of L-(+)-DET (2.0 mL, 11.79 mmol) and 4Å molecular sieves powder (10 g) in CH_2Cl_2 (600 mL) was added titanium(IV) isopropoxide (2.5 mL, 8.42 mmol) at −20 °C. After 30 minutes, a solution of allylic alcohol **43** (17.53 g, 84.27 mmol) in CH_2Cl_2 (200 mL) was introduced and stirred for 45 min. Then reaction mixture was charged with TBHP (3.33 M solution in toluene, 76 mL, 252.8 mmol) slowly over period of 15 min at the same temperature. After 48 h, the reaction was quenched with 10% aq. tartaric acid and extracted with CH_2Cl_2. Combined organic layer was dried (Na_2SO_4), concentrated and the residue purified on silica gel column chromatography using

EtOAc:light petroleum ether (1:5) as an eluent to obtain **44** (15.33 g) as a thick liquid. Enantiomeric excess of the diol (**67**) was determined by chiral HPLC (analysis condition: column R1R. Whelk-ol, Mobile phase: PET: IPA: CH3COOH (95:5:0.5), flow- 0.5 mL/min, λ- 254 nm) and it was found to be 83%.

Yield	: 81 %
Mol. Formula	: $C_{12}H_{16}O_4$
Optical Rotation $[\alpha]_D^{25}$	: −16.7 (*c* 1.8, CH_2Cl_2).
IR ($CHCl_3$) cm^{-1}	: 3400, 2928, 1454, 1377, 1100, 1020, 923, 757.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 2.20 (brs, 1H), 3.16-3.30 (m, 2H), 3.54 –3.75 (m, 4H), 3.80 (s, 3H), 4.44 (d, *J* = 11.4, 1H), 4.54 (d, *J* = 11.4 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 54.64, 54.96, 55.66, 60.29, 67.47, 72.77, 113.67, 129.30, 159.19 ppm.
Elemental Analysis	**Calcd:** C, 64.27; H, 7.19.
	Found: C, 64.12; H, 7.02.

(2*S*,3*R*)-2-((4-methoxybenzyloxy)methyl)-3-vinyloxirane (40):



To a solution of IBX (3.83 g, 13.877 mmol) in DMSO (8 mL) at room temperature, was added pyridine (1.0 mL) followed by epoxy alcohol **44** (1.56 g, 6.938 mmol) in dry THF (10 mL). After 3.5 h of stirring, water was added, and diluted with ether and stirred it for additional 30 min. The solid was filtered off and from the filtrate organic layer was isolated, washed with brine, dried (Na_2SO_4) concentrated and purified by silica gel (deactivated with 3% TEA in pet-ether) column chromatography to get **45** (1.36 g).

To a suspension of salt ($Ph_3P^+CH_3Br^-$) (4.39 g, 12.28 mmol) in THF (15 mL) at 0 ^oC, was added NaHMDS (4.6 mL, 1M solution in toluene) dropwise. After 1 h stirring at the same temperature, the aldehyde **45** (1.36 g) in THF was added slowly. After 2 h, reaction was quenched with saturated aqueous solution of NH_4Cl, and extracted with ether. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated

under vacuum. Purification was done by silica gel (60-120 mesh) column chromatography using EtOAc:light petroleum ether (1:19) as an eluent to afford vinyl epoxide **40** as yellow colour liquid (978 mg).

Yield : 72%

Mol. Formula : $C_{13}H_{16}O_3$

Optical Rotation $[\alpha]_D^{25}$: +11.6 (*c* 2.2, $CHCl_3$).

IR ($CHCl_3$) cm^{-1} : 3015, 2936, 2861, 1613, 1586, 1513, 1442, 1302, 1249, 1216, 1087, 1036, 930, 821, 756, 667.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 3.27-3.34 (m, 1H), 3.42-3.66 (m, 3H), 3.79 (s, 3H), 4.44 (d, *J* = 11.5, 1H), 4.54 (d, *J* = 11.5 Hz, 1H), 5.30-5.51 (m, 2H), 5.58-5.75 (m, 1H), 6.86 (d, *J* = 8.6 Hz, 2H), 7.25 (d, *J* = 8.6, 2H) ppm.

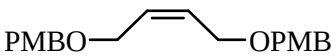
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 54.87, 55.67, 56.43, 67.27, 72.51, 113.55, 120.15, 129.04, 131.84, 159.10 ppm.

ESI MS (*m/z*) : 243.10 $[M+ Na]^+$

Elemental Analysis **Calcd:** C, 70.89; H, 7.32.

Found: C, 70.70; H, 7.29.

(*Z*)-1,4-bis(4-methoxybenzyloxy)but-2-ene (56):



To an ice-cooled solution of **42** (5.0 g, 56.82 mmol) in dry DMF (100 mL), NaH (60% dispersion in oil, 5.68 g, 142.04 mmol) was added. After 30 min, PMBCl (18.4 mL, 130.68 mmol) was introduced and stirred for additional 4 h at room temperature. The reaction mixture was partitioned between water and ethyl acetate. The organic layer was washed with water, brine, dried (Na_2SO_4) and concentrated. Purification was done by silica gel (60-120 mesh) column chromatography using EtOAc:light petroleum ether (1-3:97) as an eluent to afford PMB ether **56** as yellow colour liquid (17.99 g).

Yield : 96%

Mol. Formula : $C_{20}H_{24}O_4$

IR ($CHCl_3$) cm^{-1} : 3008, 2931, 2855, 1684, 1613, 1514, 1463, 1302,

1248, 1173, 1076, 1035, 820, 759.

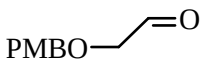
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 3.80 (s, 6H), 4.01 (d, *J* = 4.3 4H), 4.41 (s, 4H), 5.76 (t, *J* = 3.7 Hz, 2H), 6.85 (d, *J* = 8.2 Hz, 4H), 7.23 (d, *J* = 8.2 Hz, 4H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 54.95, 65.23, 71.66, 113.58, 129.20, 129.34, 130.02, 159.04 ppm.

Elemental Analysis **Calcd:** C, 73.15; H, 7.37.

Found: C, 73.02; H, 7.29.

2-(4-methoxybenzyloxy)acetaldehyde (57):



To a stirred solution of **56** (9.71 g, 29.57 mmol) and $NaIO_4$ (6.4 g, 54.54 mmol) in diethyl ether/H_2O (1:1, 100 mL) at room temperature was added OsO_4 (1.5 mL, 0.0295 mmol in toluene). The mixture was stirred at room temperature for 12 h and then quenched with aqueous sodium sulphite and extracted with ether. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc–light petroleum ether, 1:5); this gave aldehyde **57** (4.98 g) as colourless liquid.

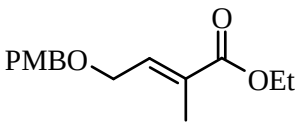
Yield : 94%

Mol. Formula : $C_{10}H_{12}O_3$

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 3.81 (s, 3H), 4.05 (bs, 2H), 4.56 (bs, 2H), 6.88 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 9.70 (s, 1H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 54.8, 72.9, 74.7, 113.6, 128.7, 129.3, 159.3, 200.1 ppm.

(*E*)-ethyl 4-(4-methoxybenzyloxy)-2-methylbut-2-enoate (58):



To a solution of aldehyde **57** (10.25 g, 56.897 mmol) in dichloromethane, Ph_3P=C(Me)COOEt (22.66 g, 62.58 mmol) was added at room temperature and the reaction mixture stirred for 7 h at the same temperature. Removal of the solvent followed by purification of the residue on silica gel column chromatography by eluting with EtOAc:light petroleum ether (3:97) afforded **58** (14.59 g) as clear oil.

Yield : 97%

Mol. Formula : $C_{15}H_{20}O_4$

IR ($CHCl_3$) cm^{-1} : 2936, 1713, 1554, 1612, 1514, 1464, 1367, 1302, 1250, 1173, 1069, 1034, 822, 738, 597.

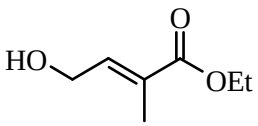
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.29 (t, *J* = 7.1 Hz, 3H), 1.81 (s, 3H), 3.80 (s, 3H), 4.14-4.24 (m, 4H), 4.47 (bs, 2H), 6.82-6.89 (m, 3H), 7.26 (d, *J* = 8.15, 2H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 12.70, 14.15, 55.01, 60.46, 66.34, 72.28, 113.71, 129.27, 129.75, 137.93, 159.24, 167.20 ppm.

Elemental Analysis **Calcd:** C, 68.16; H, 7.63.

Found: C, 68.05; H, 7.55.

(*E*)-ethyl 4-hydroxy-2-methylbut-2-enoate (60):



To a solution of PMB ether **58** (8.55 g, 32.35 mmol) in dichloromethane (152 mL)/H_2O (8 mL) at 0 °C was added DDQ (9.56 g, 42.05 mmol). The reaction mixture stirred for 6 h at the same temperature, and diluted with additional dichloromethane and saturated sodium bicarbonate. The organic layer was washed with sodium bicarbonate, dried over sodium sulfate, concentrated and purified by silica gel column chromatography eluting with 20% EtOAc/ light petroleum ether to afford alcohol **60** (4.46 g) as a clear oil.

Yield : 95%

Mol. Formula : $C_7H_{12}O_3$

IR ($CHCl_3$) cm^{-1} : 3434, 2984, 2939, 1716, 1651, 1514, 1447, 1369,

1260, 1193, 1133, 1030, 867, 777, 740, 619.

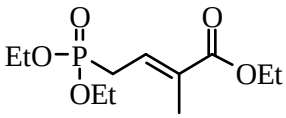
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.30 (t, *J* = 7.2 Hz, 3H), 1.83 (s, 3H), 2.35 (brd, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.35 (d, *J* = 6.0 Hz, 2H), 6.80-6.86 (m, 1H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 12.55, 14.11, 59.53, 60.73, 128.37, 140.20, 167.76 ppm.

Elemental Analysis **Calcd:** C, 58.32; H, 8.39.

Found: C, 58.22; H, 8.24.

(*E*)-ethyl 4-(diethoxyphosphoryl)-2-methylbut-2-enoate (38):



A solution of **60** (3.73 g, 25.86 mmol) and PBr_3 (1.3 mL, 12.93 mmol) in diethyl ether (60 mL) was stirred at 0 ^oC for 4 h. The reaction mixture was quenched by the addition of saturated aqueous solution of KBr and layers are separated. The aqueous layer was extracted with diethyl ether. The combined organic layer was washed with water, dried (Na_2SO_4) and evaporated. The resulting product **61** and triethylphosphite (5.3 mL, 31.03 mmol) were heated at 120 ^oC for 5 h and chromatographed on silica gel with light petroleum-EtOAc (2:3) as eluent to give **38** (6.65 g) as clear oil.

Yield : 97 %

Mol. Formula : $C_{11}H_{21}O_5P$

IR ($CHCl_3$) cm^{-1} : 2983, 2934, 2908, 1712, 1650, 1446, 1392, 1367, 1350, 1255, 1167, 1105, 1029, 966, 864, 834, 783, 748, 713, 649, 521.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 6.67-6.81 (m, 1H), 4.04-4.26 (m, 6H), 2.73 (dd, *J* = 8.2, 23.4 Hz, 2H), 1.89 (d, *J* = 4.4 Hz, 3H), 1.27-1.37 (m, 9H) ppm.

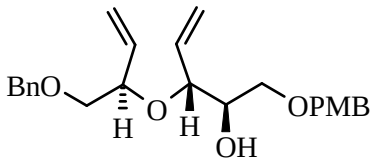
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 12.17, 13.90, 15.72, 16.15, 25.85, 28.61, 60.24, 61.63, 129.60, 131.60, 166.74 ppm.

ESI MS (*m/z*) : 287.09 $[M+ Na]^+$

Elemental Analysis **Calcd:** C, 50.00; H, 8.01.

Found: C, 49.91; H, 7.90.

(2*R*,3*R*)-3-(*R*)-1-(benzyloxy)but-3-en-2-yloxy)-1-(4-methoxybenzyloxy)pent-4-en-2-ol (39):



To a mixture of epoxide **40** (273 mg, 1.53 mmol) and alcohol **41** (375 mg, 1.70 mmol) in anhydrous dichloromethane (3 mL) was added dropwise a solution of $Cu(OTf)_2$ (6 mg, 0.015 mmol) in freshly distilled dichloromethane at room temperature. After 45 min of stirring at room temperature, the solution was diluted with dichloromethane and washed with a saturated aqueous sodium bicarbonate ($NaHCO_3$) solution, followed by brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (Petroleum ether/Ethyl acetate :9/1) afforded diene **39** (412 mg) as colorless liquid.

Yield : 67%

Mol. Formula : $C_{24}H_{30}O_5$

Optical Rotation $[\alpha]_D^{25}$: − 3.7 (*c* 1.1, $CHCl_3$).

IR ($CHCl_3$) cm^{-1} : 3431, 3009, 2924, 2854, 1724, 1610, 1513, 1454, 1249, 1102, 1036, 931, 758.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 3.41-3.48 (m, 2H), 3.51-3.56 (m, 2H), 3.71-3.74 (m, 1H), 3.79(s, 3H), 3.94-3.97 (m, 1H), 4.07-4.10 (m, 1H), 4.43 (d, *J* = 11.5 Hz, 1H), 4.49 (d, *J* = 11.5 Hz, 1H), 4.55 (singlet, 2H), 5.25-5.31 (m, 4H), 5.65-5.74 (m, 2H), 6.85 (d, *J* = 8.5, 2H), 7.22-7.34 (m, 7H) ppm.

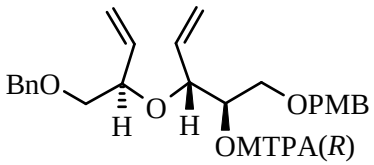
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 55.20, 70.31, 72.86, 73.11, 73.28, 76.76, 77.26, 78.25, 113.74, 119.16, 119.58, 127.57, 128.36, 129.38, 130.24, 135.06, 135.64, 138.24, 159.22 ppm.

ESI MS (*m/z*) : 421 $[M+ Na]^+$.

Elemental Analysis **Calcd:** C, 72.34; H, 7.59.

Found: C, 72.22; H, 7.48.

(*R*)-(2*R*,3*R*)-3-(*R*)-1-(benzyloxy)but-3-en-2-yloxy)-1-(4-methoxybenzyloxy)pent-4-en-2-yl) 3,3,3-trifluro-2-methoxy-2-phenylpropanoate (51):



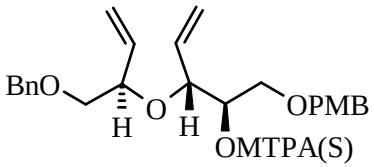
To a stirred solution of a mixture of alcohol **39** (25 mg, 0.062 mmol) and (*R*)-(−)-MTPA acid (29 mg, 0.125 mmol) in dichloromethane (1 mL) at room temperature were added DCC (26 mg, 0.125 mmol) and DMAP (cat). After 72 h of stirring, the separated precipitate was filtered off and concentrated under vacuum. The crude mass was purified by flash column chromatography (EtOAc/Petrolium Ether: 3/97) to afford the (*R*)-MTPA ester **51** (23 mg) as transparent oil.

Mol. Formula : $C_{34}H_{37}F_3O_7$

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 3.43-3.61 (m, 7H), 3.79 (s, 3H), 4.05-4.12 (m, 1H), 4.14-4.19 (m, 1H), 4.29 (d, *J* = 11.4 Hz, 1H), 4.37 (d, *J* = 11.4 Hz, 1H), 4.53 (d, *J* = 12.4 Hz, 1H), 4.57 (d, *J* = 12.4 Hz, 1H), 5.21-5.38 (m, 5H), 5.54-5.68 (m, 2H), 6.81 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.25-7.41 (m, 8H), 7.57 (d, *J* = 7.5 Hz, 2H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 55.20, 55.56, 68.30, 72.79, 72.85, 73.34, 75.72, 76.31, 77.37, 113.69, 119.51, 120.58, 127.58, 127.83, 128.19, 128.36, 128.56, 129.23, 129.44, 129.83, 133.73, 135.24, 138.27, 159.19, 166.18 ppm.

(*S*)-(2*R*,3*R*)-3-(*R*)-1-(benzyloxy)but-3-en-2-yloxy)-1-(4-methoxybenzyloxy)pent-4-en-2-yl) 3,3,3-trifluro-2-methoxy-2-phenylpropanoate (50):

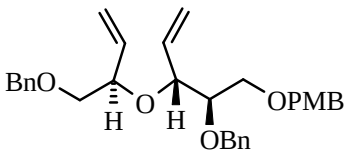


Alcohol **39** was treated with (*S*)-(+)-MTPA acid by the same procedure as described above to afford the (*S*)-MTPA ester **50**.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 3.34-3.37 (m, 1H), 3.41-3.45 (m, 1H), 3.54 (s, 3H), 3.57-3.61 (m, 1H), 3.65-3.67 (m, 1H), 3.79 (s, 3H), 3.96-4.00 (m, 1H), 4.06 (t, *J* = 6.9 Hz 1H), 4.38 (d, *J* = 11.4, 1H), 4.48 (d, *J* = 11.4, 1H), 4.53 (bs, 2H), 5.12-5.17 (m, 2H), 5.24-5.27 (m, 2H), 5.31-5.39 (m, 2H), 5.51-5.59 (m, 1H), 6.84 (d, *J* = 8.4 Hz, 2H), 7.18-7.34 (m, 10H), 7.56 (d, *J* = 7.7, 2H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 55.13, 55.46, 68.17, 72.59, 72.73, 73.21, 75.69, 75.78, 76.69, 76.94, 77.49, 113.70, 119.18, 120.19, 127.48, 127.53, 128.11, 128.27, 129.23, 129.41, 129.68, 132.47, 133.40, 135.20, 138.32, 159.20, 165.99 ppm.

1-(((2*R*,3*R*)-2-(benzyloxy)-3-((*R*)-1-(benzyloxy)but-3-en-2-yloxy)pent-4-enyloxy)methyl)-4-methoxybenzene (52):

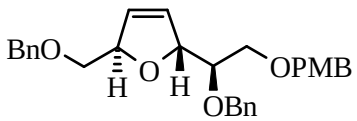


A solution of alcohol **39** (0.36 g, 0.903 mmol) in DMF (5 mL) was treated with sodium hydride (0.05 g, 60%, 1.354 mmol) at 0 ^{o}C. To this solution, kept at the same temperature, benzyl bromide (0.15 mL, 1.26 mmol) was added slowly. After 2 h of stirring at 0 ^{o}C, the whole reaction mixture poured in to ice-water, and extracted with diethyl ether. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The crude compound was purified by flash column

chromatography (petroleum ether/ethyl acetate: 97/3) to afford benzyl ether **52** (0.39 g) as thick liquid.

Yield	: 87%
Mol. Formula	: $C_{31}H_{36}O_5$
Optical Rotation $[\alpha]_D^{25}$	: +1.1 (*c* 0.85, $CHCl_3$).
IR ($CHCl_3$) cm^{-1}	: 3066, 3017, 2909, 2865, 2401, 1720, 1612, 1586, 1513, 1496, 1423, 1364, 1302, 1248, 1216, 1173, 1084, 1036.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 3.42-3.56 (m 3H), 3.59-3.70 (m, 2H), 3.79 (s, 3H), 4.00-4.17 (m, 2H), 4.43 (bs, 2H), 4.55 (bs, 2H), 4.71 (bs, 2H), 5.18-5.33 (m, 4H), 5.60-5.86 (m, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 7.19-7.37 (m, 12H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 55.05, 70.22, 72.93, 73.16, 73.23, 77.64, 77.97, 80.56, 113.58, 118.14, 118.48, 127.28, 127.36, 127.49, 127.76, 128.07, 128.19, 129.12, 130.40, 135.16, 135.94, 138.35, 138.83, 159.00 ppm.
ESI MS (*m/z*)	: 511.22 $[M+ Na]^+$
Elemental Analysis	**Calcd:** C, 76.20; H, 7.43.
	Found: C, 76.05; H, 7.32.

(2*R*,5*R*)-2-((*R*)-1-(benzyloxy)-2-(4-methoxybenzyloxy)ethyl)-5-(benzyloxymethyl)-2,5-dihydrofuran (53):



The diene **52** (0.57 g, 1.17 mmol) was dissolved in 50 mL of dichloromethane. After degassing, Grubbs' 2nd generation catalyst (0.050 g, 0.058 mmol) was added to the reaction mixture at room temperature. Once again the reaction mixture was degassed. The reaction was allowed to warm up to reflux for 18 h. After the solvent being removed, the obtained residue was purified by flash column chromatography (Petrolium Ether/Ethyl Acetate: 9/1) to get RCM product **53** (0.428 g) as colorless oil.

Yield : 79%

Mol. Formula : $C_{29}H_{32}O_5$

Optical Rotation $[\alpha]_D^{25}$: +87.53 (*c* 2.3, $CHCl_3$).

IR ($CHCl_3$) cm^{-1} : 3066, 3017, 2909, 2865, 2401, 1757, 1719, 1611, 1586, 1513, 1496, 1454, 1422, 1363, 1302, 1249, 1216, 1173, 1089, 1029.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 3.42-3.58 (m, 4H), 3.61-3.72 (m, 1H), 3.78 (s, 3H), 4.40 (d, *J* = 11.6 Hz, 1H), 4.46 (d, *J* = 11.0, 1H), 4.52 (d, *J* = 12.1 Hz, 1H), 4.60 (d, *J* = 12.7 Hz, 1H), 4.66 (d, *J* = 12.1 Hz, 1H), 4.74 (d, *J* = 11.9 Hz, 1H), 4.93-5.06 (m, 2H), 5.82-5.90 (m, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 7.19-7.25 (m, 12H) ppm.

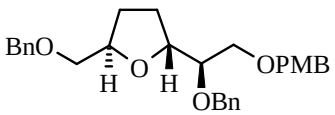
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 55.2, 70.6, 72.8, 73.0, 73.1, 73.4, 79.9, 85.6, 86.5, 113.8, 127.4, 127.5, 127.6, 127.7, 128.2, 128.3, 128.5, 128.9, 129.2, 130.5, 138.3, 138.9, 159.2 ppm..

ESI MS (*m/z*) : 483.21 $[M+ Na]^+$

Elemental Analysis **Calcd:** C, 75.63; H, 7.00.

Found: C, 75.53; H, 6.90.

(2*R*,5*R*)-2-((*R*)-1-(benzyloxy)-2-(4-methoxybenzyloxy)ethyl)-5-(benzyloxymethyl) tetrahydrofuran (54):



A solution **53** (0.68 g, 1.474 mmol) in ethyl acetate (75 mL) was hydrogenated with 10% Pd/C for 2 h on balloon pressure at room temperature. The catalyst was filtered off, concentrated, and crude mass purified by flush chromatography (EtOAc/Pet Ether: 1/9) to afford the reduced product **54** (0.49 g) as colorless oil.

Yield : 72%

Mol. Formula : $C_{29}H_{34}O_5$

Optical Rotation $[\alpha]_D^{25}$: + 45.6 (*c* 2.5, $CHCl_3$).

IR ($CHCl_3$) cm^{-1} : 3066, 3016, 2928, 1716, 1606, 1584, 1512, 1496, 1454, 1383, 1315, 1275, 1258, 1216, 1169, 1072.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.62-1.69 (m, 1H), 1.71-1.78 (m, 1H), 1.88-1.94 (m, 1H), 1.97-2.03 (m, 1H), 3.43-3.49 (m, 2H), 3.53 (q, *J* = 4.8, 9.6 Hz, 1H), 3.63-3.64 (m, 2H), 3.78 (s, 3H), 4.13-4.21 (m, 2H), 4.43 (d, *J* = 11.7 Hz, 1H), 4.47 (d, *J* = 11.7 Hz, 1H), 4.54 (d, *J* = 12.1 Hz, 1H), 4.57 (d, *J* = 12.1 Hz, 1H), 4.66 (d, *J* = 12.1 Hz, 1H), 4.77 (d, *J* = 12.0 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 2H), 7.21-7.36 (m, 12H) ppm.

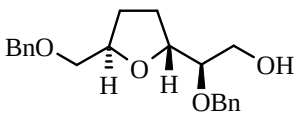
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 27.79, 28.71, 55.15, 70.88, 72.75, 73.01, 73.07, 73.26, 78.40, 79.60, 80.14, 113.69, 127.36, 127.47, 127.60, 127.81, 128.18, 128.29, 129.22, 130.39, 138.43, 138.93, 159.10 ppm.

ESI MS (*m/z*) : 485.22 $[M+ Na]^+$

Elemental Analysis **Calcd:** C, 75.30; H, 7.41.

Found: C, 75.21; H, 7.29.

(*R*)-2-(benzyloxy)-2-((2*R*,5*R*)-5-(benzyloxymethyl)tetrahdrofuran-2-yl)ethanol (55):



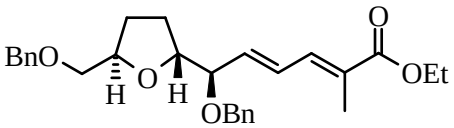
To a solution of compound **54** (0.639 g, 1.38 mmol) in CH_2Cl_2/H_2O (9.5 mL/0.5 mL) at 0 ^oC was added DDQ (0.47 g, 2.07 mmol). After 3 h at room temperature, the reaction mixture was diluted with an aqueous saturated solution of sodium bicarbonate. The aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated under vacuum. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate: 70/30) gave alcohol **55** (0.402 g) as yellowish liquid.

Yield : 85%

Mol. Formula : $C_{21}H_{26}O_4$

Optical Rotation $[\alpha]_D^{25}$	: +13.7 (*c* 2.15, $CHCl_3$).
IR ($CHCl_3$) cm^{-1}	: 3445, 3019, 2926, 2400, 1454, 1215, 1083, 928, 758, 669, 626.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.59-1.67 (m, 1H), 1.69-1.76 (m, 1H), 1.87-1.93 (m, 1H), 1.95-2.01 (m, 1H), 2.34 (bp, 1H) 3.37-3.44 (m, 3H), 3.56 (dd, *J* = 5.1 Hz, 11.7 Hz, 1H), 3.71 (dd, *J* = 4.1, 11.5 Hz, 1H), 4.10-4.20 (m, 2H), 4.48-4.53 (m,2H), 4.63 (d, *J* = 11.8, 1H), 4.68 (d, *J* = 11.8 Hz, 1H), 7.19-7.30 (m, 10H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 27.96, 28.48, 62.18, 72.53, 72.67, 73.31, 78.60, 80.40, 80.82, 127.57, 127.67, 127.87, 128.35, 128.41, 138.36, 138.54 ppm.
ESI MS (*m/z*)	: 364.22 $[M+ Na]^+$
Elemental Analysis	**Calcd:** C, 73.66; H, 7.65.
	Found: C, 73.53; H, 7.54.

(*R*,*2E*,*4E*)-ethyl 6-(benzyloxy)-6-((2*R*,5*R*)-5-(benzyloxymethyl)tetrahdrofuran-2-yl)-2-methylhexa-2,4-dienoate (62):



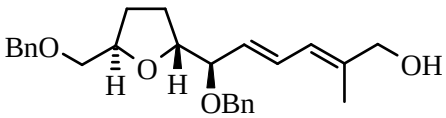
A solution of the alcohol compound **55** (0.21 g, 0.613 mmol) in THF (5 mL) was added to a solution of IBX (0.34 g, 1.226 mmol) in DMSO (0.7 mL) at room temperature and stirred it for 5 h. Then cooled to 0 ^oC, and added ice-cooled water, followed by ether. After additional 30 min of stirring, filtered, organic layer was separated. Aqueous layer washed further with ether. The combined organic layer was washed with brine, dried over sodium sulfate, and concentrated in vacuum to give crude aldehyde **37** (0.24 g). The crude aldehyde was not purified, but immediately used for the next reaction.

To a freshly prepared solution of LDA [1.226 mmol; prepared by adding 0.77 mL of 1.6 M *n*-BuLi to a solution of 0.14 mL (1.471 mmol) of diisopropylamine in dry THF at 0 ^oC, and stirring at the same temperature for 15 min] at –78 ^oC was added phosphonate **38** (486 mg, 1.83 mmol). After 30 mins at –78 ^oC, the crude aldehyde **37**

(241 mg) in THF was added. The reaction mixture was allowed to attain 0 ^{o}C over a period of 2 h, quenched with saturated aqueous ammonium chloride (NH_4Cl) solution, and the layers separated. The aqueous layer was extracted with ether, washed with water, dried over Na_2SO_4 and concentrated under vacuum. The crude compound was purified by flash column chromatography eluting with petroleum ether/ethyl acetate (3:97) to afford compound **62** (0.18 g) as yellowish transparent oil.

Yield	: 64%
Mol. Formula	: $C_{28}H_{34}O_5$
Optical Rotation $[\alpha]_D^{25}$	: −10.0 (*c* 0.9, $CHCl_3$).
IR ($CHCl_3$) cm^{-1}	3019, 2982, 2928, 2871, 2401, 1703, 1607, 1496, 1454, 1391, 1369, 1258, 1216, 1176, 1101, 1027, 977, 927, 878, 757, 698, 668, 625 ppm.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.31 (t, *J* = 7.1 Hz, 3H), 1.62-1.76 (m, 2H), 1.84-2.04 (m, 5H), 3.40-3.50 (m, 2H), 3.95-4.01 (m, 1H), 4.10-4.27 (m, 4H), 4.43-4.69 (m, 4H), 6.03 (dd, *J* = 7.1, 15.3 Hz, 1H), 6.57 (ddd, *J* = 1.01, 11.4, 15.3, 1H), 7.19 (d, *J* = 11.6 Hz, 1H), 7.25-7.34 (m, 10H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 12.77, 14.34, 27.51, 28.54, 60.57, 71.01, 72.76, 73.33, 78.60, 81.02, 81.15, 127.46, 127.51, 127.61, 127.66, 127.86, 128.32, 128.54, 137.07, 137.96, 138.36, 138.39, 168.21 ppm.
ESI MS (*m/z*)	: 473.22 $[M+ Na]^+$
Elemental Analysis	**Calcd:** C, 74.64; H, 7.61.
	Found: C, 73.90; H, 7.86.

(*R*,*2E*,*4E*)-6-(benzyloxy)-6-((2*R*,5*R*)-5-(benzyloxymethyl)tetrahdrofuran-2-yl)-2-methylhexa-2,4-dien-1-ol (63):

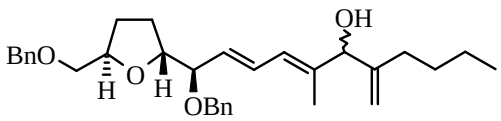


The ester **62** (0.178 g, 0.395 mmol) was dissolved in freshly distilled dichloromethane (5 mL) under a nitrogen atmosphere. The solution was cooled to –78 ^{o}C,

and DIBALH (1.412 M in toluene, 0.7 mL) was slowly added over a period of 5 min. The solution was stirred for 1 h at –78 ^{o}C before the reaction was quenched with methanol. The reaction mixture was allowed to warm to ambient temperature before an aqueous saturated solution of sodium potassium tartarate was added and stirred for 5 h. The aqueous phase was extracted with dichloromethane, and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under vacuum. Purification by silica gel column chromatography afforded alcohol **63** (0.15 g) as colorless oil.

Yield	: 91%
Mol. Formula	: $C_{26}H_{32}O_4$
Optical Rotation $[\alpha]_D^{25}$	: − 4.4 (*c* 1.1, $CHCl_3$).
IR ($CHCl_3$) cm^{-1}	: 3443, 3065, 3016, 2926, 2868, 2401, 1720, 1636, 1496, 1454, 1365, 1216, 1072, 1028, 976, 928, 756, 698, 668, 609.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.49-1.67 (m, 2H), 1.70 (s, 3H), 1.79-1.93 (m, 2H), 3.32-3.47 (m, 2H), 3.72-3.82 (m, 1H), 3.92-4.16 (m, 4H), 4.30-4.61 (m, 4H), 5.56 (dd, *J* = 7.9, 15.2 Hz, 1H), 6.02 (d, *J* = 10.8 Hz, 1H), 6.40 (dd, *J* = 11.0, 15.3 Hz, 1H), 7.14-7.28 (m, 10H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 14.21, 27.64, 28.61, 68.17, 70.32, 72.79, 73.30, 78.44, 81.32, 81.75, 124.02, 127.34, 127.48, 127.62, 127.64, 128.24, 128.30, 129.54, 130.17, 137.96, 138.42, 138.68 ppm.
Elemental Analysis	**Calcd:** C, 76.44; H, 7.90. **Found:** C, 76.29; H, 7.78.

(*R*,*2E*,*4E*)-1-(benzyloxy)-1-((2*R*,5*R*)-5-(benzyloxymethyl)tetrahdrofuran-2-yl)-5-methyl-7-methyleneundeca-2,4-dien-6-ol (64):



To a stirred solution of IBX (0.3 g, 1.07 mmol) in DMSO (0.6 mL), was added a solution of alcohol **63** (0.22 g, 0.54 mmol) in THF (5 mL) at room temperature and

stirring was continued for further 2 h. After completion of the reaction, water, followed by diethyl ether was added. Stirred it for additional 30 min before it was filtered. Organic layer was separated, and the aqueous layer was washed two times with ether. The combined organic layer was washed with brine, dried over Na_2SO_4, concentrated under vacuum. The crude product **35** (0.25 g) was used immediately used for the next reaction.

To a mixture of crude aldehyde **35** (0.25 g) and halide **36** (0.79 g, 3.75 mmol) in DMSO (properly degassed with argon) (50 mL) was added $CrCl_2$ (0.46 g, 3.75 mmol), followed by $NiCl_2$ (cat). The reaction mixture was stirred for 24 h at room temperature. Saturated aqueous ammonium chloride (NH_4Cl) was added and extracted with diethyl ether. The whole organic layer was washed with brine and dried over Na_2SO_4. The crude product was purified by flush column chromatography (Ethyl Acetate/petroleum Ether: 1/9) to afford the required fragment as a mixture of two diastereomers **64** (0.19 g) as a colorless oil, which were separated by chiral HPLC (analysis condition: column Chiral Cel OD-H, 25 cm, Mobile phase: PET: IPA (95:5), flow- 1.0 mL/min, λ- 220 nm).

Faster moving isomer: **(1*R*,2*E*,4*E*,6*R*)-1-(benzyloxy)-1-((2*R*,5*R*)-5-(benzyloxymethyl) tetrahdrofuran-2-yl)-5-methyl-7-methyleneundeca-2,4-dien-6-ol (34)**:

Yield	: 71%
Mol. Formula	: $C_{32}H_{42}O_4$
Optical Rotation $[\alpha]_D^{25}$	: −5.4 (*c* 1.5, $CHCl_3$).
IR ($CHCl_3$) cm^{-1}	: 3445, 3018, 2959, 2931, 2872, 2400, 1717, 1636, 1496, 1454, 1382, 1216, 1087, 1028, 927, 757, 698, 668, 625.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.90 (t, *J* = 7.2, 3H), 1.27-1.36 (m, 2H), 1.38-1.47 (m, 2H), 1.66 (s, 3H), 1.68-1.79 (m, 2H), 1.85-2.07 (m, 4H), 3.44-3.53 (m, 2H), 3.86-3.89 (m, 1H), 4.12-4.22 (m, 2H), 4.44 (d, *J* = 12.3 Hz, 1H), 4.51 (s, 1H), 4.55 (d, *J* = 12.2 Hz, 1H), 4.59 (d, *J* = 12.2 Hz, 1H), 4.65 (d, *J* = 12.3 Hz, 1H), 4.97 (s, 1H), 5.14 (s, 1H), 5.66 (dd, *J* = 7.7, 15.2 Hz, 1H), 6.17 (d, *J* = 10.9 Hz, 1H), 6.47 (dd, *J* = 11.0, 15.2, 1H), 7.23-7.36 (m, 10H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 12.43, 13.96, 22.50, 27.69, 28.59, 30.12, 31.60, 70.44, 72.81, 73.31, 78.47, 79.89, 81.35, 81.88, 110.10, 116.16, 125.73, 127.36, 127.50, 127.66, 127.68, 128.25, 128.32, 129.65, 130.55, 138.26, 138.43, 138.73, 149.36, 149.50 ppm.

ESI MS (*m/z*) : 513.29 $[M+ Na]^+$

Elemental Analysis **Calcd:** C, 78.33; H, 8.63.

Found: C, 78.63; H, 8.51

***Slower moving isomer:* (1*R*,*2E*,*4E*,*6S*)-1-(benzyloxy)-1-((2*R*,5*R*)-5-(benzyloxymethyl) tetrahdrofuran-2-yl)-5-methyl-7-methyleneundeca-2,4-dien-6-ol (65)**:

Optical Rotation $[\alpha]_D^{25}$: +12.0 (*c* 0.66, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.89 (t, *J* = 7.3, 3H), 1.28-1.36 (m, 2H), 1.39-1.47 (m, 2H), 1.66 (s, 3H), 1.68-1.80 (m, 2H), 1.86-2.02 (m, 4H), 3.44-3.53 (m, 2H), 3.87 (dd, *J* = 5.6, 7.7 Hz, 1H), 4.12-4.17 (m, 1H), 4.18-4.23 (m, 2H), 4.45 (d, *J* = 12.2 Hz, 1H), 4.45 (d, *J* = 12.2 Hz, 1H), 4.51 (s, 1H), 4.54 (d, *J* = 12.2 Hz, 1H), 4.59 (d, *J* = 12.2 Hz, 1H), 4.65 (d, *J* = 12.2 Hz, 1H), 4.97 (s, 1H), 5.15 (s, 1H), 5.68 (dd, *J* = 7.7, 15.2 Hz, 1H), 6.17 (d, *J* = 11.1 Hz, 1H), 6.47 (dd, *J* = 11.0, 15.2 Hz, 1H), 7.23-7.36 (m, 10H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 12.32, 13.97, 22.50, 27.67, 28.61, 30.12, 31.65, 70.42, 72.81, 73.32, 78.49, 79.92, 81.36, 81.83, 110.02, 116.17, 125.87, 127.36, 127.51, 127.66, 127.69, 128.26, 128.32, 129.65, 130.61, 138.24, 138.44, 138.72, 149.37, 149.51 ppm.

ESI MS (*m/z*) : 513.79 $[M+ Na]^+$

Elemental Analysis **Calcd:** C, 78.33; H, 8.63.

Found: C, 78.63; H, 8.51.

CHAPTER 3

SECTION II

Synthesis of the Densely Functionalized C1-C9 Segment of Amphidinolide C

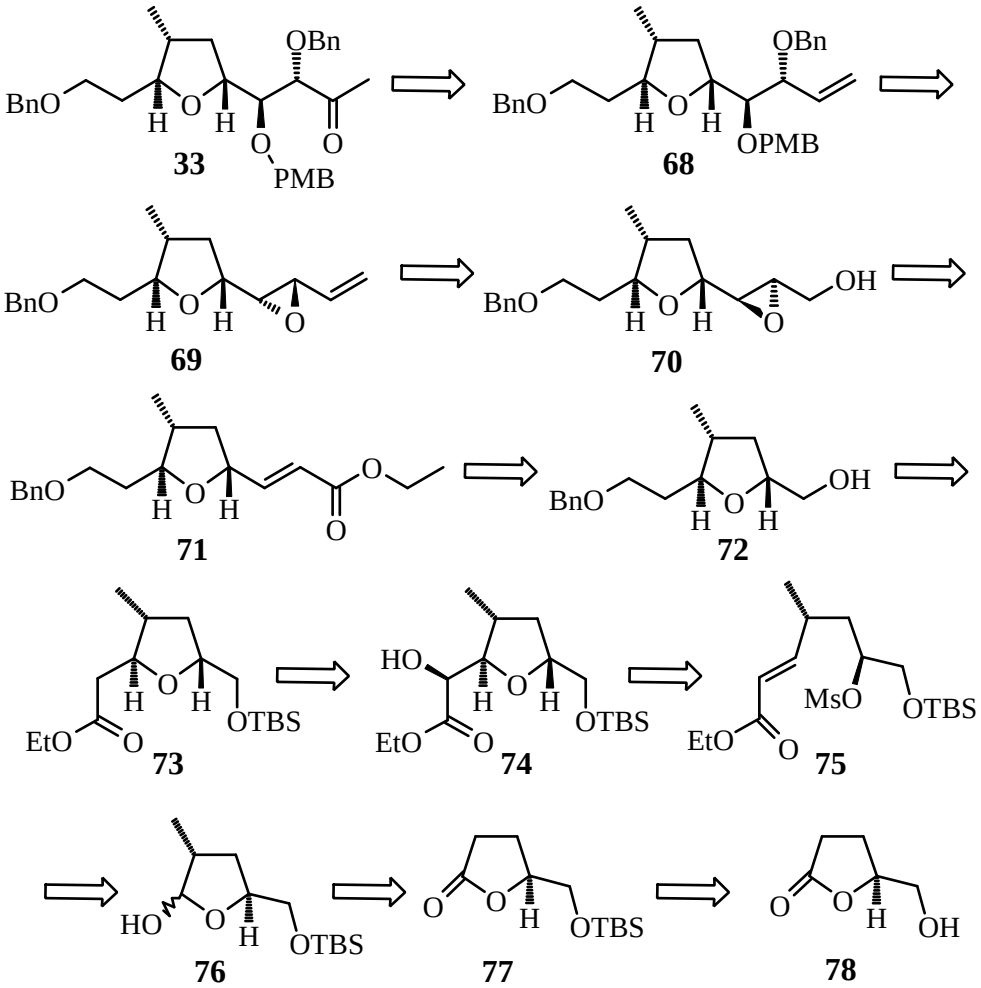
Present Work

After successful achievement of the expedient assembly of substituted tetrahydrofuran containing segment C19-C34 of amphidinolide C (**28**), our next endeavor was the synthesis of the densely functionalized segment C1-C9. As can be seen from the retrosynthetic analysis (Scheme 15), the synthetic pathway adapted a comparatively short, highly stereoselective synthesis of **33** from (*S*)-hydroxymethyl-γ-butyrolactone **78**. The latter could be inexpensively prepared in two steps from naturally abundant L-(+)-glutamic acid.[55]

For the synthesis of segment **33**, we have adopted a linear approach. The synthesis could be commenced with commercially available L-(+)-glutamic acid. The retrosynthetic analysis for our synthetic endeavour was planned using a 'tactical combination of transforms', as outlined in scheme 15. On scrutiny of the target segment, it is obvious that out of five chiral centers, four had been generated in a complete stereocontrolled manner. The keto functionality **33**, on the rightern side, was envisaged to arise from olefin **68** by employing modified Waker oxidation. The olefin intermediate **68** could be obtained by regioselective $BF_3 \cdot Et_2O$ mediated epoxide opening of the vinyl epoxide **69** using benzyl alcohol. The vinyl epoxide **69** in turn could be accomplished from **72** by performing a synthetic sequence, *viz*, Wadsworth Horner Emmons olefination, Sharpless asymmetric epoxidation, one carbon Wittig olefination. The tetrahydrofuran core **74** could be constructed by tandem Sharpless asymmetric dihydroxylation-S_N2 cyclization protocol from **75**. In the synthetic direction, the feasibility of this synthetic step (**75** to **74**) was more appealing, out of several strategies explored till now to construct tetrahydrofuran ring, since the outcome of the reaction through internal S_N2 displacement in a pre organized substrate would be completely stereospecific with predictability of stereochemistry at the ring junctions. The intermediate **75** could be obtained from **78** by standard functional group transformation.

Accordingly, we have started with the lactone alcohol **78**. The hydroxyl group of **78** was protected as TBS ether with TBSCl/triethylamine in dichloromethane to get the TBS

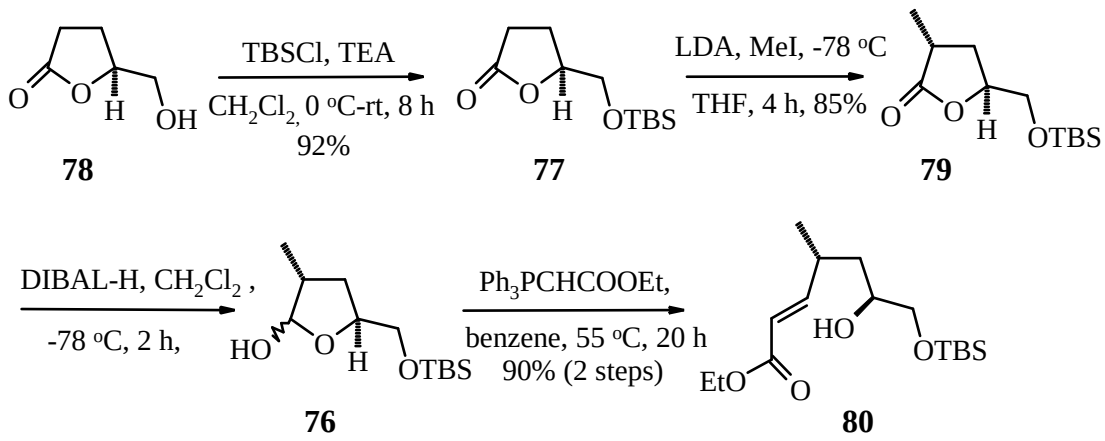
protected lactone **77**. The ^{1}H NMR spectrum of **77** displayed resonances at δ 0.07 (s, 6H), 0.88 (s, 9H) ppm characteristic of TBS group.



Scheme 15: *Retrosynthetic strategy of segment C1-C9 (**33**) of amphidinolide C (**28**)*

Stereoselective methylation[56] of the lactone **77** using LDA, MeI in THF at −78 ^{o}C resulted in **79** in 85% yield. The *trans* relationship between the two substituents on the five-membered ring lactone **79** was confirmed by NOESY experiment in the later stage of synthetic sequence. The structure of **79** was confirmed from its ^{1}H NMR spectroscopy. The two double-doublets due to H5 were appeared at δ 3.60 (dd, *J* = 2.9, 8.3 Hz, 1H), 3.78 (dd, *J* = 3.2, 11.3 Hz, 1H) ppm. The newly introduced methyl proton was observed as a clean doublet at δ 1.19 (*J*= 7.2 Hz, 3H) ppm. The structure of **79** was further confirmed by its ^{13}C NMR spectroscopy and elemental analysis. Lactone **79** was reduced by DIBAL-H at −78 ^{o}C to the corresponding hemiacetal **76**, which was quickly exposed to ethoxycarbonylmethylenetriphenylphosphorane[56] in benzene at 55 ^{o}C to provide the

corresponding α,β-unsaturated ester as a geometric mixture (9.5:0.5 by ^{1}H NMR). The minor (*Z*)-isomer was eliminated through column chromatography. The predominant (*E*)-isomer **80**, obtained in 90% yield, showed characteristic coupling constant (*J* = 15.6 Hz) for olefinic protons in the ^{1}H NMR spectrum. In ^{1}H NMR spectrum, the relevant resonances due to alkene were appeared as two double doublet at δ 5.84 (dd, *J* = 1.0, 15.6 Hz, 1H), 6.81 (dd, *J* = 8.6, 15.6 Hz, 1H) ppm, whereas ester group (─*CO*$_2$*CH*$_2$*CH*$_3$) was observed at δ 1.29 (t, *J* = 7.1 Hz, 3H) 4.18 (q, *J* = 7.1 Hz, 2H) ppm. In the IR spectrum, the carbonyl stretching at 1718 and 1651 cm^{-1}, characteristic of α,β- unsaturated ester was observed, whereas the EI mass spectrum showed peak at (*m*/*z*) 339.1 for [M+Na].$^+$



Scheme 16

The alcohol **80** was converted into its mesylate[57] ester **75** using $MeSO_2Cl$, Et_3N and DMAP (catalytic) in CH_2Cl_2. The purpose behind the introduction of mesyl ester at this stage was to utilize for dual role, as a protecting group and as a leaving group at the later stage. Mesylation of **80** was confirmed by the presence of new resonance at δ 3.04 ppm as a singlet (*CH*$_3$*SO*$_2$−) and downfield shift of methine proton carrying the mesylate group spanning between δ 4.57-4.68 ppm (from 4.0 ppm) in the ^{1}H NMR spectrum. This was supported by a peak at (*m*/*z*) 417.5 $[M+Na]^+$ in the EI MS spectrum.

The central transformation of the synthetic sequence, *i.e.*, formation of THF ring with appropriate stereochemistry, *trans*-fusion, through a tandem dihydroxylation-S_N2 cyclization sequence was investigated next.

A short account on Sharpless asymmetric dihydroxylation (AD):

The stereospecific cis-dihydroxylation of olefins achieved by OsO_4 is one of the most valued transformations for introducing functionality into organic molecules. Initially the AD using derivatives of cinchona alkaloids was performed under stoichiometric conditions. Lateron, with the advent of: i) use of two phase conditions with $K_3Fe(CN)_6$ as reoxidant; ii) $MeSO_2NH_2$ for rate acceleration and iii) second generation ligands (phthalazine and diphenylpyrimidine, with two independent cinchona alkaloid units) by Sharpless et al., catalytic AD came into focus. The enantioselectivity in the AD reaction is due to the enzyme-like binding pocket present in the dimeric cinchona alkaloid ligands. The cinchona alkaloid backbone is ideally suited for providing high ligand acceleration and enantioselectivity. The reaction rates are influenced by the nature of O-9 substituent of the Cinchona alkaloid. The rate enhancement is caused by a stabilization of the transition state due to aromatic stacking interactions. Although this

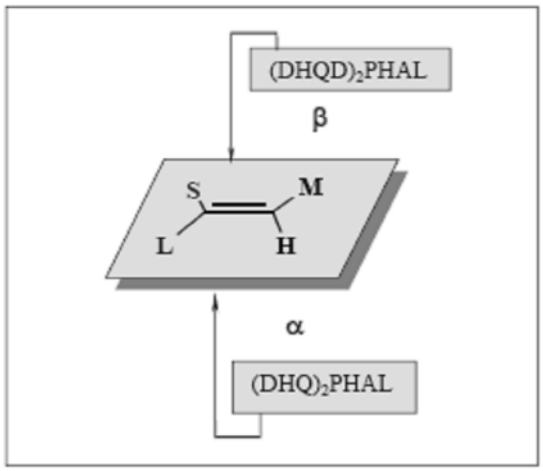
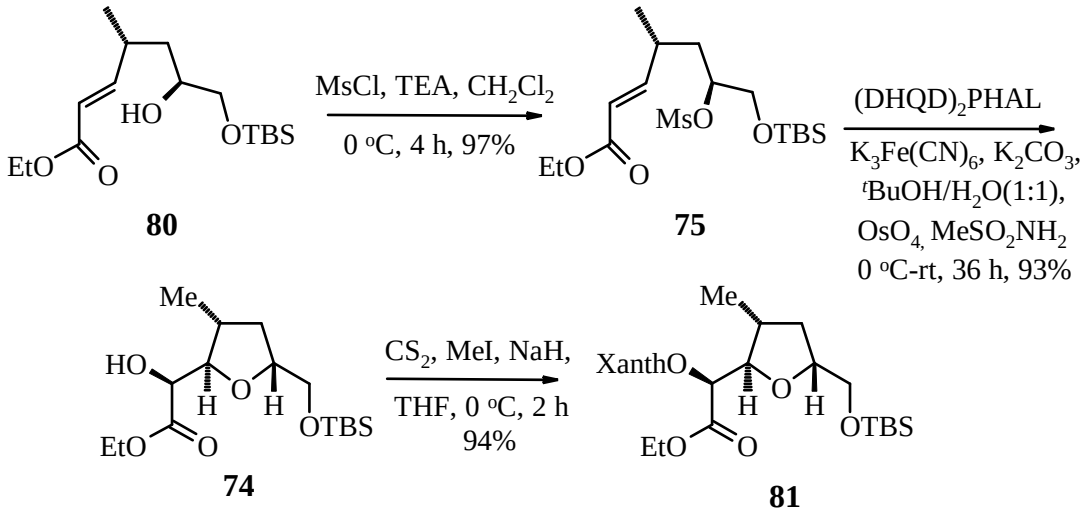


Figure 25: ***Mnemonic diagram*** *(S = small group, L = large group, M = medium group, H = proton).*

kind of stabilization is operative even in monomeric first generation ligand, it is most effective in the dimeric second-generation ligands due to the presence of a binding pocket. Thus the almost perfect match between the phthalazine ligands and aromatic olefins with respect to rates and enantioselectivities can be readily explained by an especially good transition state stabilization resulting from offset-parallel interactions between the aromatic substituent of the olefin and the phthalazine floor of the ligand, as well as favorable edge-to-face interactions with the bystander methoxyquinoline ring.

The above observations have led to a revised mnemonic device for predicting the enantiofacial selectivity in the reaction. An olefin positioned accordingly will be attacked either from the top face (β face) in the case of dihdroquinidine derivatives or from the bottom face (α face) in the case of dihydroquinine derived ligands.

Accordingly, the mesylate derivative **75** was subjected to dihydroxylation[58] with ligand $(DHQD)_2$ PHAL, $K_3Fe(CN)_6$, K_2CO_3, $MeSONH_2$ and OsO_4 in *t*-BuOH/H_2O (1:1) at 0 °C-rt for 36 h, whereupon the *trans,syn*-tetrahydrofuran **74** was obtained in high yeild with excellent diastereoselectivity. The compound **74** was thoroughly investigated by the ^1H NMR and ^{13}C NMR spectrum and elemental analysis. In the ^1H NMR spectrum, the H2 and H3 protons were resonated as multiplet at δ 4.17-4.34 (m, 2H) ppm. In the ^{13}C NMR spectrum, peaks corresponding to olefinic moiety were disappeared.



Scheme 17

Our next concern was to deoxygenate the hydroxyl group at C2 using Barton's radical deoxygenation protocol.[59] The free hydroxyl group of **74** was converted to its corresponding xanthate derivative **81** with NaH/CS_2/MeI in THF at 0 °C. The ^1H NMR spectrum confirmed the presence of xanthate group (a singlet at δ 2.62 ppm due to −*S<u>CH</u>*$_3$) and the other features, *viz*., the methyl protons (doublet at δ 1.09 ppm accounting for three protons) and ester group (at δ 1.29 and 4.24 ppm). Compound **81** was treated with TBTH in presence of AIBN in refluxing toluene for 8 h to furnish the 2-deoxy derivative **73**. The structure was confirmed by its ^1H NMR, ^{13}C NMR and elemental

analysis. For instance, the ^{1}H NMR spectrum of **73** showed characteristic resonances due to H-2, 2′ in the span of δ 2.36-2.57 (m, 2H) ppm. Other protons resonated at their respective values confirming the assigned structure.

To examine the relative stereochemistry present in **73**, we were interested to study the n*O*e interactions present in **73**. Gratifyingly, n*O*e correlations were observed for H3/H8, H3/ H5, H6/H4, H6/H5, indicating that relative stereochemistries between H3 and H6 and between H3 and H4 were *anti*- and *anti*-oriented, respectively (Figure 26).

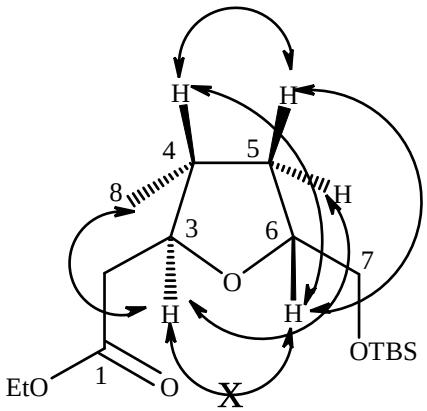
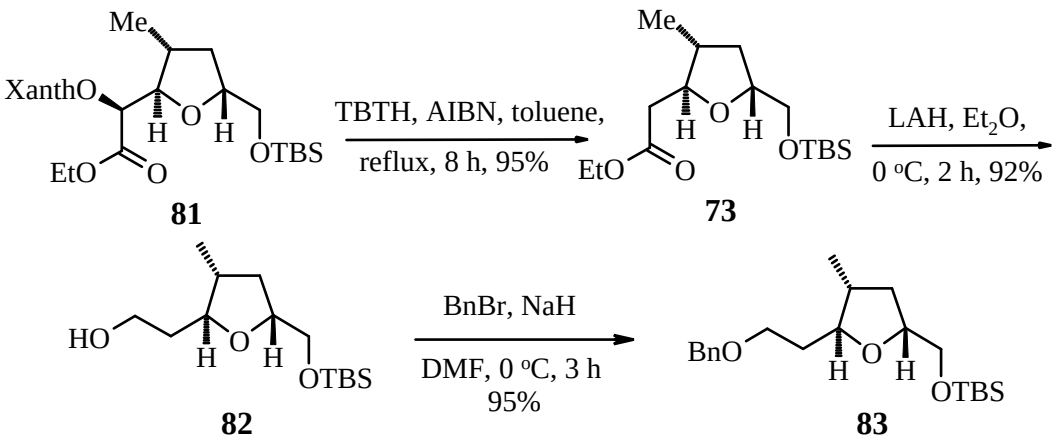


Figure 26: *Selected nOe Correlations of **73***

Now compound **73** was treated with $LiAlH_4$ in anhydrous diethyl ether at 0 ^{o}C to afford the alcohol derivative **82** in good yield. The absence of relevant resonances of carboethoxy moiety was evidenced by both ^{1}H NMR and ^{13}C NMR spectrum of **82**. In

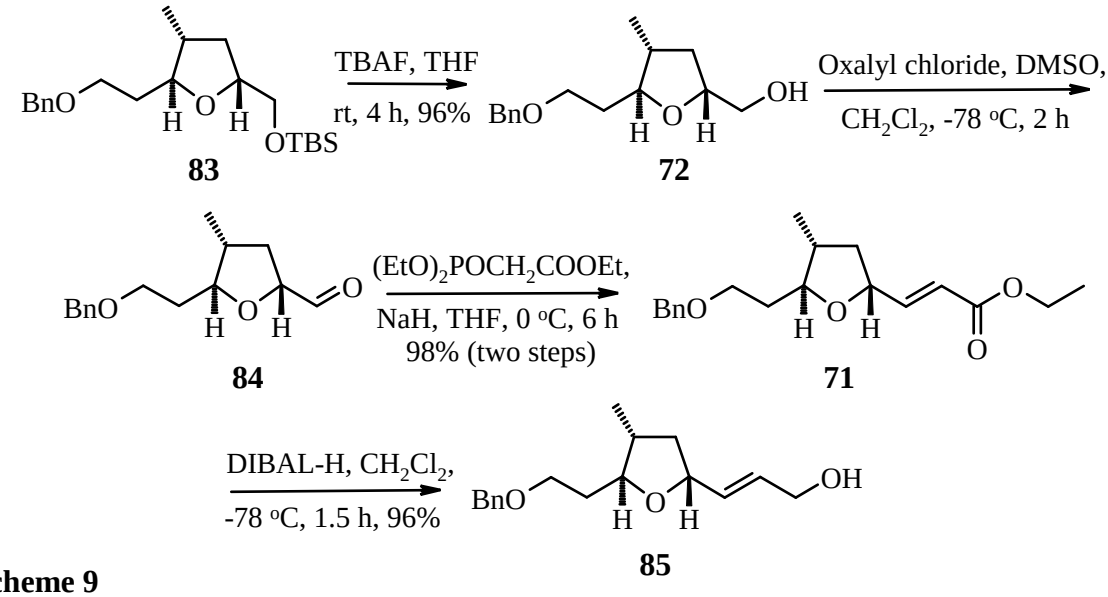


Scheme 18

the ^{1}H NMR spectrum of **82**, protons due to reduction of carboethoxy moiety were resonated as multiplet at δ 3.59-3.62 (2H) ppm. The newly generated primary hydroxyl functionality of **82** was protected as benzyl ether using benzyl bromide in the presence of

NaH in DMF to provide **83** in 95% yield. The ^{1}H NMR spectrum of **83** indicated the corresponding resonances at δ 4.51 ppm (s, *Ph-*$\underline{CH_2}$) and at δ 7.23-7.35 (m, *Ph-*$\underline{CH_2}$) supporting the presence of benzyl ether moiety (Scheme 18).

For the installation of the side chain, cleavage of TBS ether of **83** was needed. At this juncture, it was decided to first cleave the *TBS* group with $Bu_4N^+F^-$ in THF to give the alcohol **72**. The ^{1}H NMR spectrum of **72** showed the absence of resonance due to *TBS* moiety, while rest of the spectrum secured the assigned structure.



Scheme 9

Our next endeavor was the stereoselective construction of the α,β-unsaturated *E*-ester **71**, Thus the free hydroxyl group present in **72** was subjected to Swern oxidation[60] by using $(COCl)_2$, DMSO and Et_3N in CH_2Cl_2 at –78 ^{o}C to furnish a highly labile aldehyde **84**, which (without column purification) on treatment with the anion generated from the triethylphosphonoacetate and NaH at 0 ^{o}C afforded the desired *E*-unsaturated ester **71**, exclusively. In the ^{1}H NMR spectrum of **71**, the characteristic olefinic protons appeared as two double doublets at δ 5.94 (dd, J = 1.6, 15.6 Hz, 1H) and 6.85 (dd, J = 5.1, 15.6 Hz, 1H) ppm. The signals due to carbethoxy proton were observed at δ 1.24 (t, J = 7.1 Hz, 3H) and 4.14 (q, J = 7.2 Hz, 2H) ppm. All other protons resonated at their respective values, thereby confirming the structure of **71.** The ester carbonyl carbon was observed at δ 166.3 ppm, whereas the olefinic carbons were at 119.4 and 148.7 ppm in the ^{13}C NMR spectrum. In the mass spectrum, a signal for $[M+Na]^+$ was observed at *m/z* 341.3. Reduction of ester **71** using DIBAL-H in dichloromethane at −78 ^{o}C furnished the

allylic alcohol derivative **85**. In the ^{1}H NMR spectrum, the olefinic proton and the vinylic methyl protons resonated in the upfield region at δ 5.65-5.89 (m, 2H) ppm. The ^{13}C NMR and IR spectroscopic data was also in support of **85**.

INTRODUCTION OF CHIRALITY*:*

The Sharpless asymmetric epoxidation (SAE) is one of the most useful reactions used in organic synthesis today. When a prochiral Z or E-allyl alcohol is treated with dialkyl tartrate (generally Et or ^{i}Pr), titanium(IV) isopropoxide and tert-butylhydroperoxide, produces the corresponding chiral epoxy alcohol.

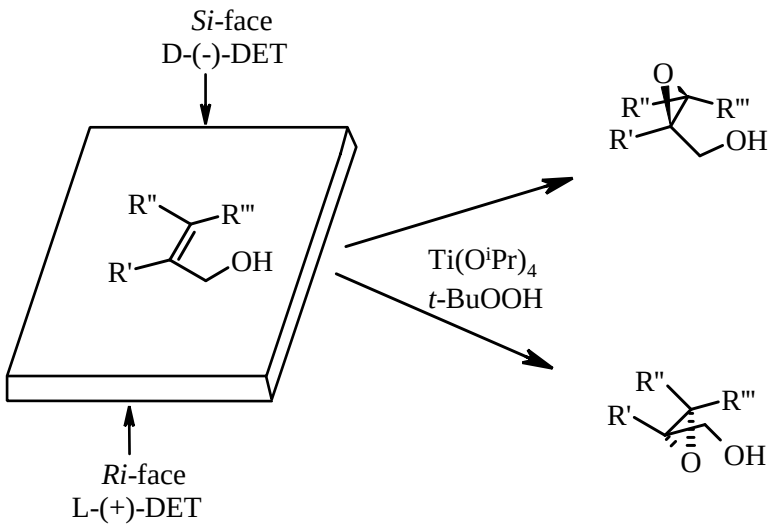


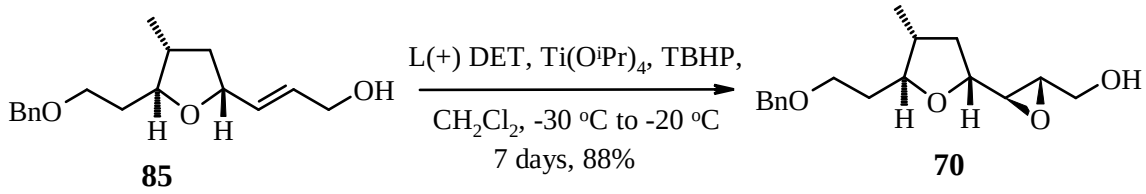
Figure 27

The salient features of SAE are*:*

(i) High yield; (ii) very high enantioselectivity; (iii) reagents are cheap, easily available and safe to handle; (iv) the dialkyl tartrate (6.5 mole percent) and titanium(IV) isopropoxide (5.0 mole percent) are used in catalytic amount; (v) the ease and accuracy of the prediction of the stereochemical outcome irrespective of the substitution on the allylic alcohol.

Stereoselectivity:

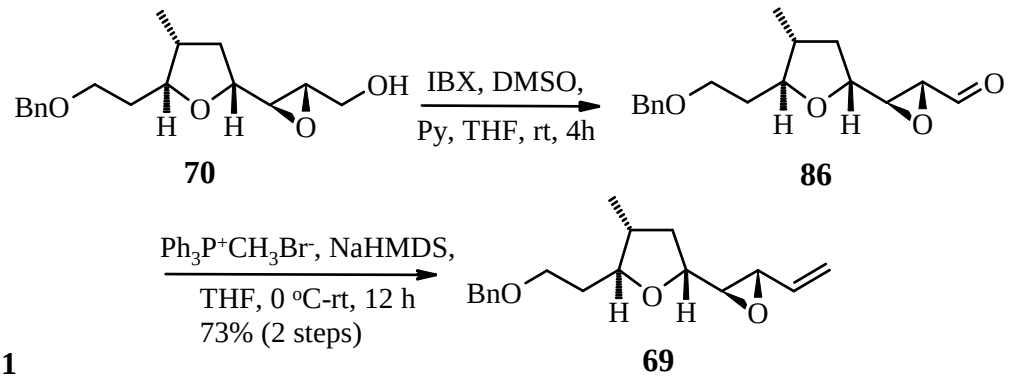
The stereochemical outcome of the asymmetric epoxidation is consistent with (S,S)-(−)-DET inducing the epoxide formation on the Si face and the (R,R)-(+)-DET inducing the epoxide formation on the Re face of the substituted allylic alcohol.



85 **70**

Scheme 20

Our next objective was the installation of chirality's at C7 and C8 of substituted allylic alcohol **85**. Thus, Sharpless asymmetric epoxidation of the *E*-allylic alcohol **85** using diethyl-(L)-tartrate, titanium(IV) isopropoxide and *tert*-butylhydroperoxide in the presence of 4Å molecular sieves powder in CH_2Cl_2 provided the corresponding epoxy alcohol **70** with excellent diastereoselectivity [based on spectroscopic analysis] (Scheme 20). The absolute configuration of **70** was established based on the empirical rules published by Sharpless.[61] The ^{1}H NMR spectrum of **70** displayed the epoxy protons as a multiplet at δ 2.95-2.99 (2H) ppm. All the other protons resonated at their expected chemical shifts. Further, ^{13}C NMR spectrum of **70** showed signals due to the epoxy carbons at δ 56.5 and 57.1 ppm.



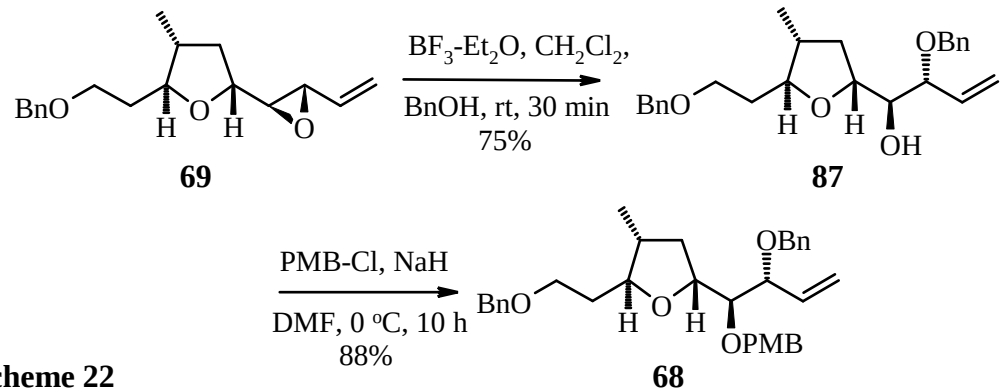
70 **86** **69**

Scheme 21

The alcohol derivative **70** was efficiently oxidized with IBX in DMSO/THF at ambient temperature to provide the aldehyde **86**, which was quickly exposed for the following Wittig reaction. Thus, Wittig methylenation of **86** with incipient methylenetriphenylphosphorane [generated *in situ* from $CH_3P^+Ph_3Br^-$ and NaHMDS] in THF gave the requisite vinyl substituted epoxide intermediate **69** in excellent yield. The structure of vinyl epoxide **69** was elucidated from the ^{1}H NMR, ^{13}C NMR and mass spectral analysis. ^{1}H NMR spectrum indicated the presence of olefinic protons at δ 5.20 (dd. *J* = 10.3, 1.4 Hz, 1H), 5.39 (dd, *J* = 1.4, 17.2 Hz, 1H) for terminal methylene group

(*CH*$_2$=) and 5.48-5.57 (m, *CH*=) ppm, for internal olefinic protons, while the epoxide protons resonated at δ 2.84 (dd, *J* = 2.1, 4.5 Hz, 1H), 3.13 (dd, *J* = 2.1, 7.5 Hz, 1H) ppm. The EI mass recorded peak at *m/z* 311.3 $[M+Na]^+$ also supported the assigned structure (Scheme 21).

Our next objective was the regiospecific opening of vinyl epoxide **69** with benzyl alcohol. Accordingly, the epoxide **69** was subjected to the treatment of BnOH in presence of $BF_3{\cdot}Et_2O$ in anhydrous dichloromethane to furnish β-hydroxy allyl ether **87**. The product **87** was confirmed for its structure by the ^{1}H NMR, ^{13}C NMR, IR and EI MS spectral data. The chemical shift of methine proton bearing the benzyl group shifted downfield (compared to **69)** and appeared in the region of δ 3.81-3.86 (m, 1H) ppm, whereas the protons in *Ph*CH_2− group showed resonances between δ 7.44–7.91 (m, 10H) ppm in the ^{1}H NMR spectrum. In the IR spectrum, two intense peaks at 1601 and 3436 $cm,^{-1}$ respectively, characteristic of olefin and newly generated hydroxyl group were observed. The EI mass spectrum gave a sodiated peak at *m*/*z* 419.5, which was subsequently confirmed by elemental analysis.



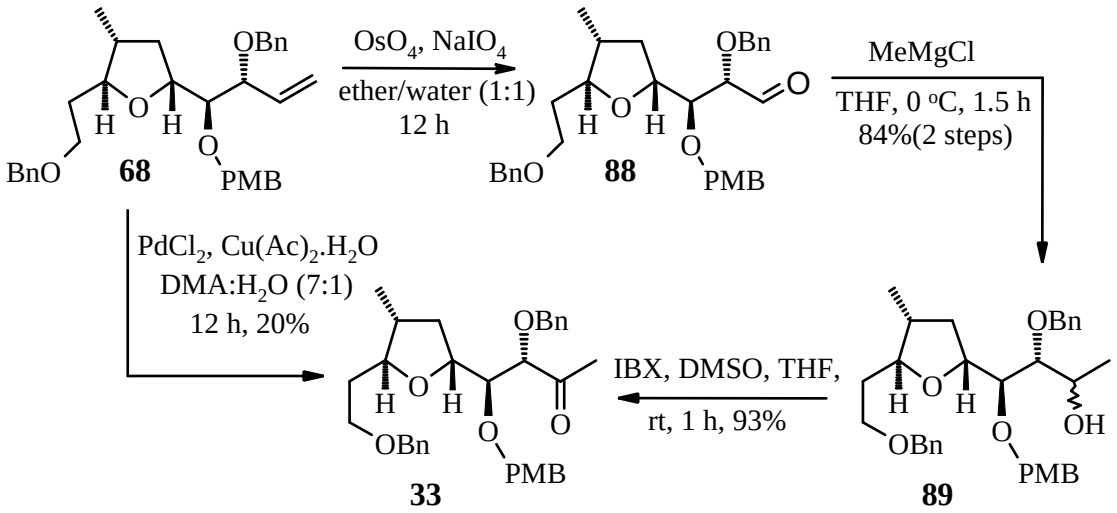
Scheme 22

The secondary hydroxyl group of **87** was converted as its *PMB* ether using PMBCl and NaH in DMF to provide **68** (Scheme 22). In the ^{1}H NMR spectrum of **68**, a characteristic singlet due to aromatic methyl ether proton was observed at δ 3.76 (s, 3H) ppm. Other resonances were in accordance with the assigned structure. The structure was further confirmed by its ^{13}C NMR spectroscopy and elemental analysis

Compound **68** was subjected to modified Wacker oxidation protocol[62] to introduce carbonyl group. Thus, **68** was treated with $Cu(OAc)_2$. H_2O (0.2 eq), 10 mol% of $PdCl_2$ in a mixture of DMA: H_2O (7:1) under oxygen atmosphere at ambient temperature for 16 h

to afford **33** in 20% yield. In the ^{1}H NMR spectrum of **33**, the distinct absence of olefinic protons was noticed. A sharp singlet at δ 2.07 ppm corresponding to the methyl group adjacent to the carbonyl group confirmed the structure of **33**. Further, the presence of carbonyl signals at δ 209.57 ppm in the ^{13}C NMR spectrum of **33** substantiated the assigned structure (Scheme 23).

Despite the success in accomplishing the desired product, the poor yielding sequence forced us to seek for an easy alternative. In view of the simple reaction conditions, we opted for three step protocol, *viz*, oxidative cleavage, Grignard reaction and IBX oxidation to complete the targeted segment **33**.



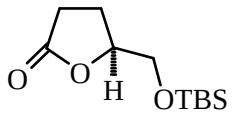
Scheme 23

Accordingly, the olefinic compound **68** was subjected to oxidative cleavage protocol on treatment of $OsO_4/NaIO_4$ in ether/water (1:1) to generate the aldehyde **88**, which was immediately subjected to the Grignard reaction with CH_3MgCl in THF at 0 ^{o}C to afford **89** (84%) (Scheme 23). The newly formed stereocenter of **89** was of no consequence, as it would finally be transformed into the keto functionality. The structure was supported by its ^{1}H NMR, ^{13}C NMR, mass spectroscopy and elemental analysis. For instance, the ^{1}H NMR spectrum confirmed the presence of the newly introduced methyl group which appeared as a doublet at δ 0.99 (d, J = 6.5 Hz, 3H) ppm. All other resonances were in accord with the assigned structure. Characteristic resonances at δ 67.8 and 67.9 ppm were observed due to C10 in the ^{13}C NMR spectrum.

Finally, IBX oxidation of the secondary hydroxyl group of **89** in DMSO/THF at room temperature accomplished the target segment **33**. Structure of **33** was confirmed by the ^{1}H NMR, ^{13}C NMR, IR (1719 cm^{-1}) spectroscopic data and elemental analysis

In conclusion, we have described an asymmetric synthesis of C1-C9 segment of amphidinolide C (**28**) in a completely stereocontrolled linear approach. The construction of *trans*-2,5-disubstituted tetrahydrofuran ring was accomplished by a tandem dihydroxylation-S_N2 cyclization sequence. We envisaged that the above mentioned enantioselective synthetic strategy, could be extended to prepare the corresponding antipode through stereotuning in the relevant steps. Stereocenter at C7 and C8 were fixed by sharpless asymmetric epoxidation protocol.

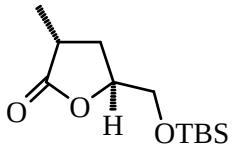
(*S*)-5-((*tert*-butyldimethylsilyloxy)methyl)dihydrofuran-2(3*H*)-one (77):



To a solution of alcohol **78** (27.47 g, 236.82 mmol) in CH_2Cl_2 (300 mL) was added triethyl amine (65.9 mL, 473.63 mmol) and TBDMSCl (39.26 g, 260.5 mmol) at 0 °C. The resulting mixture was allowed to warm to room temperature slowly and stirred for 8 h. The reaction mixture was then partitioned between CH_2Cl_2 and water. The combined organic extracts were dried (Na_2SO_4) and concentrated. Purification by silica gel column cromatography (3% EtOAc/Light petroleum ether) afforded silyl ether **77** as colorless oil (50.19 g).

Yield	: 92%
Mol. Formula	: $C_{11}H_{22}O_3Si$
Optical Rotation $[\alpha]_D^{25}$	: +7.6 (*c* 1.1, $CHCl_3$).
IR ($CHCl_3$) cm^{-1}	: 3533, 2954, 2886, 2857, 1780, 1472, 1361, 1256, 1175, 1083, 995, 942, 837, 778, 665.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.07 (s, 6H), 0.88 (s, 9H), 2.07-2.32 (m, 2H), 2.35-2.69 (m, 2H), 3.67 (dd, *J* = 3.1, 11.3 Hz, 1H), 3.85 (dd, *J* = 3.2, 11.2 Hz, 1H), 4.52-4.61 (m, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ −5.73, −5.66, 18.05, 23.34, 25.63, 28.35, 64.73, 79.78, 177.15 ppm.
ESI MS (*m/z*)	: 253.13 $[M+ Na]^+$
Elemental Analysis	**Calcd:** C, 57.35; H, 9.63.
	Found: C, 57.21; H, 9.49.

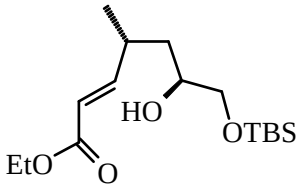
(3R,5S)-5-((*tert*-butyldimethylsilyloxy)methyl)-3-methyldihydrofuran-2(3*H*)-one (79):



n-BuLi (51.7 mL, 82.69 mmol, 1.6 M solution in hexane) was added to a solution of diisopropylamine (11.6 mL, 82.69 mmol) in THF (160 mL) at −78 °C, and the mixture was stirred at this temperature for 30 min. A solution of lactone **77** (15.0 g, 65.11 mmol) in THF (160 mL) was added to the above mixture, and the resulting mixture was stirred at –78 °C for 1 h. To the above orange mixture was added excess MeI (16.2 mL, 260.43 mmol) and the reaction was stirred at −78 °C for 2 h before it was warmed to room temperature for additional 1 h. The reaction was quenched by saturated aqueous NH_4Cl solution. The aqueous layer was extracted with EtOAc twice. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column cromatography (5% EtOAc/Hexanes) afforded *trans*-lactone **79** (13.46 g) as a clear oil.

Yield	: 85%
Mol. Formula	: $C_{12}H_{24}O_3Si$
Optical Rotation $[\alpha]_D^{25}$	: +19.5 (*c* 2.0, $CHCl_3$).
IR ($CHCl_3$) cm^{-1}	: 3526, 2955, 2931, 2883, 2858, 1771, 1471, 1378, 1361, 1256, 1201, 1173, 1130, 1023, 956, 838, 757, 694.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ −0.01 (s, 6H), 0.82 (s, 9H), 1.19 (d, *J* = 7.2 Hz, 3H), 1.81-1.96 (m, 1H), 2.27-2.40 (m, 1H), 2.58-2.81 (m, 1H), 3.60 (dd, *J* = 2.9, 8.3 Hz, 1H), 3.78(dd, *J* = 3.2, 11.2 Hz, 1H), 4.41-4.50 (m, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ −5.74, −5.66, 16.27, 18.08, 25.67, 32.05, 34.07, 64.89, 77.36, 180.01 ppm.
Elemental Analysis	**Calcd:** C, 58.97; H, 9.90.
	Found: C, 59.44; H, 9.96.

(*E*)-ethyl 7-(*tert*-butyldimethylsilyloxy)-6-hydroxy-4-methylhept-2-enoate (80):



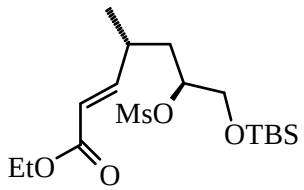
A solution of lactone **79** (24.94 g, 102.04 mmol) in CH_2Cl_2 (500 mL) was treated DIBAL-H (42.9 mL, 122.45 mmol, 2.85 M solution in toluene). After stirring at –78 °C for 1.5 h, the reaction was quenched with saturated aqueous potassium sodium tartrate. The mixture was diluted with CH_2Cl_2 and vigorously stirred at room temperature for 2 h. The aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to provide the crude hemiacetal **76** as colorless oil, which was immediately used in the next reaction without further purification.

A solution of the above hemiacetal **76** and (carbethoxyethylidene) triphenylphosphorane (70.82 g, 204.09 mmol) in benzene (500 mL) was heated to 55 ^oC for 20 h. The resulting mixture was cooled to room temperature, concentrated and the residue was purified by silica gel column chromatography (5%, 10% EtOAc/Light petroleum ether) to provide ester **80** (29.193 g) as clear oil.

Yield	: 90%
Mol. Formula	: $C_{16}H_{32}O_4Si$
Optical Rotation $[\alpha]_D^{25}$	: −17.7 (*c* 2.0, $CHCl_3$).
IR ($CHCl_3$) cm^{-1}	: 3482, 2956, 2930, 2858, 1718, 1651, 1463, 1369, 1257, 1209, 1178, 1039, 985, 845, 776, 667.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.07 (s, 6H), 0.90 (s, 9H), 1.09 (d, *J* = 6.8 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.38-1.63 (m, 2H), 2.36 (bs, 1H), 2.55-2.73 (m, 1H), 3.30-3.39 (m, 1H), 3.53-3.67 (m, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 5.84 (dd, *J* = 1.0, 15.6 Hz, 1H), 6.81 (dd, *J* = 8.6, 15.6 Hz, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ −5.48, −5.43, 14.20, 18.22, 25.82, 28.19, 31.16, 59.95, 67.08, 70.80, 121.59, 148.45, 166.34 ppm.
ESI MS (*m/z*)	: 339.51 $[M+ Na]^+$
Elemental Analysis	**Calcd:** C, 60.72; H, 10.19.

Found: C, 61.44; H, 9.85.

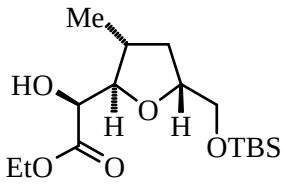
(4*R*,6*S*,*E*)-ethyl 7-(*tert*-butyldimethylsilyloxy)-4-methyl-6-(methylsulfonyloxy)hept-2-enoate (75):



To a solution of **80** (23.2 g, 73.37 mmol), and triethylamine (20.4 mL, 146.73 mmol), in CH_2Cl_2 (200 mL) was added a solution of methanesulphonyl chloride (8.5 mL, 110.053 mmol) in CH_2Cl_2 (100 mL) at 0 ^oC. The reaction mixture was stirred at room temperature for 4 h, washed with water and brine, dried (Na_2SO_4), and concentrated on rotavapor. The residue on purification by silica gel column chromatography (10% ethyl acetate in hexane) provided **75** (27.96 g) as colourless oil.

Yield	: 97%
Mol. Formula	: $C_{17}H_{34}O_6SSi$
Optical Rotation $[\alpha]_D^{25}$	: −21.4 (*c* 1.4, $CHCl_3$).
IR ($CHCl_3$) cm^{-1}	: 3421, 2965, 2935, 1716, 1652, 1458, 1342, 1278, 1227, 1174, 1098, 1041, 983, 917, 787, 756, 526.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.07 (s, 6H), 0.89 (s, 9H), 1.10 (d, *J* = 6.79 Hz, 3H), 1.28 (t, *J* = 7.14 Hz, 3H), 1.63-1.88 (m, 2H), 2.51-2.69 (m, 1H), 3.04 (s, 3H), 3.64-3.79 (m, 2H), 4.18 (dq, *J* = 0.64, 7.15 Hz, 2H), 4.57-4.68 (m, 1H), 5.95 (dd, *J* = 0.98, 15.73 Hz, 1H), 6.79 (dd, *J* = 8.37, 15.71 Hz, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ −5.60, 14.10, 18.18, 20.25, 25.72, 32.49, 37.61, 38.61, 60.12, 64.87, 81.50, 121.23, 151.88, 166.43 ppm.
ESI MS (*m/z*)	: 417.6 $[M+Na]^+$
Elemental Analysis	**Calcd:** C, 51.74; H, 8.68.
	Found: C, 61.44; H, 9.85.

(*S*)-ethyl 2-((2*R*,3*R*,5*R*)-5-((*tert*-butyldimethylsilyloxy)methyl)-3-methyl tetrahydrofuran-2-yl)-2-hydroxyacetate (74):



The mixture of $K_3Fe(CN)_6$ (29.14 g, 88.25 mmol), K_2CO_3 (2.28 g, 88.25 mmol), $(DHQD)_2PHAL$ (205 mg, 0.294 mmol), OsO_4 (1.2 mL, 0.098 M in toluene) and $MeSO_2NH_2$ (2.28 g, 23.92 mmol) in *t*-BuOH/H_2O (100 mL/100 mL) was stirred at room temperature for 15 min and then cooled to 0 °C. To this solution was added the enoate **75** (11.61 g, 29.42 mmol). The reaction was stirred at room temperature for 1.5 days and then quenched with saturated aqueous Na_2SO_3 at room temperature. Ethyl acetate was added to the reaction mixture, and after separation of the layers, the aqueous layer was further extracted with EtOAc twice. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (5% EtOAc/Light petroleum ether) afforded **74** (9.471 g) as a colorless oil.

Yield : 93%

Mol. Formula : $C_{16}H_{32}O_5Si$

Optical Rotation $[\alpha]_D^{25}$: −12.9 (*c* 1.65, $CHCl_3$).

IR ($CHCl_3$) cm^{-1} : 3478, 3018, 2930, 2858, 1738, 1471, 1384, 1256, 1216, 1129, 1023, 939, 838, 758, 667.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.03 (s, 6H), 0.88 (s, 9H), 1.09 (d, *J* = 6.6 Hz, 3H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.43-1.59 (m, 1H), 2.05-2.18 (m, 1H), 2.36-2.53 (m, 1H), 3.55 (dd, *J* = 4.3, 11.0 Hz, 1H), 3.64 (dd, *J* = 4.2, 11.0 Hz, 1H), 1.73 (dd, *J* = 1.3, 9.2 Hz, 1H), 4.01-4.14 (m, 2H), 4.17-4.34 (m, 2H) ppm.

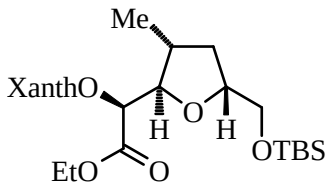
^{13}C NMR ($CDCl_3$, 50 MHz) : δ −5.34, 14.15, 15.98, 18.29, 25.89, 34.82, 36.59, 61.58, 65.54, 69.86, 80.18, 85.97, 173.30 ppm.

ESI MS (*m/z*) : 355.51 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 57.79; H, 9.70.

Found: C, 57.66; H 9.61.

(*S*)-ethyl 2-((2*R*,3*R*,5*R*)-5-((*tert*-butyldimethylsilyloxy)methyl)-3-methyltetrahydrofuran-2-yl)-2-(methylthiocarbonothioyloxy)acetate (81):



To a solution of hydroxyl compound **74** (12.31 g, 35.53 mmol) in THF (150 mL) at 0 ^{o}C, NaH (2.13 g, 60% in oil, 53.28 mmol) was added. After being stirred for 30 min, carbon disulphide (4.3 mL, 71.05 mmol) was added. After an interval for 30 min, MeI (4.4 mL, 71.05 mmol) was added. The reaction mixture was stirred for 1 h, quenched with water and evaporated to leave the residue, which was taken in ethyl acetate. The organic layer was washed with water and brine, dried (Na_2SO_4), and concentrated to afford the crude, which on silica gel column chromatography (5% ethyl acetate in light petroleum ether) gave **81** (14.19 g) as thick liquid.

Yield : 94%

Mol. Formula : $C_{18}H_{34}O_5S_2Si$

Optical Rotation $[\alpha]_D^{25}$: +17.4 (*c* 1.4, $CHCl_3$).

IR ($CHCl_3$) cm^{-1} : 2956, 2929, 2857, 1765, 1742, 1471, 1385, 1369, 1254, 1207, 1031, 940, 837, 778, 672.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.05 (s, 6H), 0.89 (s, 9H), 1.09 (d, *J* = 6.3 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.50-1.66 (m, 2H), 2.15-2.30 (m, 1H), 2.62 (s, 3H), 3.56-3.72 (m, 2H), 4.05 (dd, *J* = 2.6, 8.6 Hz, 1H), 4.10-4.18 (m, 1H), 4.24 (dq, *J* = 1.2, 7.2 Hz, 2H), 5.84 (d, *J* = 2.6 Hz, 1H) ppm.

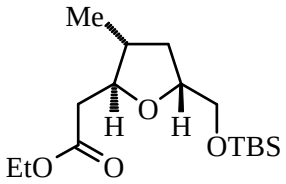
^{13}C NMR ($CDCl_3$, 50 MHz) : δ −5.35, 14.06, 16.60, 18.27, 19.26, 25.89, 35.25, 36.49, 61.64, 65.17, 79.14, 79.87, 84.52, 167.14, 216.12 ppm.

ESI MS (*m/z*) : 445.68 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 51.15; H, 8.11.

Found: C, 51.27; H, 8.87.

Ethyl 2-((2*S*,3*R*,5*R*)-5-((*tert*-butyldimethylsilyloxy)methyl)-3-methyltetrahydrofuran-2-yl)acetate (73):



To a solution of xanthate **81** (12.53 g, 29.64 mmol) and AIBN (cat.) in toluene (150 mL), TBTH (15.7 mL, 59.29 mmol) was added. The reaction mixture was refluxed for 8 h, concentrated *in vacuo* and purified by silica gel column chromatography (3% ethyl acetate in light petroleum ether) to afford **73** (8.98 g) as thick liquid.

Yield : 95%

Mol. Formula : $C_{16}H_{32}O_4Si$

Optical Rotation $[\alpha]_D^{25}$: −14.6 (*c* 1.05, $CHCl_3$).

IR ($CHCl_3$) cm^{-1} : 2956, 2929, 2858, 1777, 1739, 1472, 1462, 1385, 1253, 1042, 939, 837, 777, 671 ppm.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.05 (s, 6H), 0.89 (s, 9H), 1.03 (d, *J* = 6.4 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.39-1.55 (m, 1H), 1.85-2.01 (m, 1H), 2.04-2.19 (m, 1H), 2.36-2.57 (m, 2H), 3.54-3.65 (m, 2H), 3.83 (ddd, *J* = 4.7, 7.6, 8.7 Hz, 1H), 3.97-4.09 (m, 1H), 4.14 (q, *J* = 7.2 Hz, 2H) ppm.

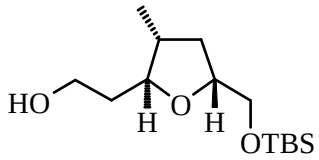
^{13}C NMR ($CDCl_3$, 50 MHz) : δ −5.35, 14.18, 16.25, 18.29, 25.91, 36.97, 39.43, 39.91, 60.31, 65.87, 78.56, 81.65, 171.31 ppm.

ESI MS (*m/z*) : 339.51 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 60.72; H, 10.19.

Found: C, 60.10; H, 11.80.

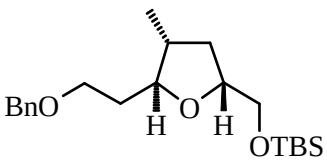
2-((2*S*,3*R*,5*R*)-5-((*tert*-butyldimethylsilyloxy)methyl)-3-methyltetrahydrofuran-2-yl)ethanol (82):



To a solution of LAH **(**1.46 g, 38.99 mmol) in dry THF **(**100 mL) was added dropwise ester **73 (**10.28 g, 32.49 mmol) in THF (50 mL) at 0 ^{o}C under nitrogen. After 3 h, the reaction was quenched by adding water, solid filtered off and washed with ethyl acetate, and dried (Na_2SO_4), and evaporated in *vacuo*. Flash column chromatography of the residue on silica gel with ethyl acetate:light petroleum ether (1:4) yielded alcohol **82 (**8.25 g**)** as a colorless oil.

Yield	: 92%
Mol. Formula	: $C_{14}H_{30}O_3Si$
Optical Rotation $[\alpha]_D^{25}$	: −14.8 (*c* 0.75, $CHCl_3$).
IR ($CHCl_3$) cm^{-1}	: 3391, 2957, 2930, 2858, 1599, 1462, 1384, 1254, 1106, 1051, 837, 757, 665.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.06 (s, 6H), 0.90 (s, 9H), 1.01 (d, *J* = 6.4 Hz, 3H), 1.33-1.48 (m, 1H), 1.54-1.72 (m, 1H), 1.78-1.99 (m, 2H), 2.03-2.16 (m, 1H), 2.60 (bs, 1H), 3.54 (dd, *J* = 2.9, 9.1 Hz, 1H), 3.59-3.62 (m, 2H), 3.74-3.80 (m, 2H), 4.01-4.14 (m, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ −5.35, 15.97, 18.25, 25.86, 35.32, 36.53, 40.11, 61.66, 65.84, 78.75, 85.69 ppm.
ESI MS (*m/z*)	: 297.47 $[M+Na]^+$
Elemental Analysis	**Calcd:** C, 61.26; H, 11.02.
	Found: C, 60.35; H, 10.90.

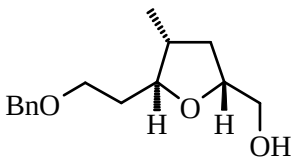
(((2*R*,4*R*,5*S*)-5-(2-(benzyloxy)ethyl)-4-methyltetrahydrofuran-2-yl)methoxy)(*tert*-butyl)dimethylsilane (83):



Compound **82** (6.17 g, 22.46 mmol) in anhydrous DMF (20 mL) was added to a stirred suspension of NaH (1.53 g, 60% dispersion in oil, 38.19 mmol) in DMF (30 mL) at 0 ^{o}C. The resulting solution was stirred at the same temperature for 30 min; BnBr (8.7 mL, 72.1 mmol) was added. After 2.5 h, the reaction was quenched by ice-cold water and extracted with EtOAc. The combined organic layer was washed with water, dried (Na_2SO_4) and concentrated. Purification on silica gel column chromatography [EtOAc-Light petroleum ether (1:19)] afforded **83** (7.79 g) as light yellow liquid.

Yield	95%
Mol. Formula	$C_{21}H_{36}O_3Si$
Optical Rotation $[\alpha]_D^{25}$	: −19.4 (*c* 1.25, $CHCl_3$).
IR ($CHCl_3$) cm^{-1}	2956, 2929, 2857, 1471, 1455, 1384, 1361, 1105, 938, 837, 757, 697.
^{1}H NMR ($CDCl_3$, 200 MHz)	δ 0.07 (s, 6H), 0.91 (s, 9H), 1.02 (d, *J* = 6.5 Hz, 3H), 1.40 (ddd, *J* = 8.9, 10.6, 11.9 Hz, 1H), 1.68-1.79 (m, 1H), 1.82-2.00 (m, 2H), 2.06-2.18 (m, 1H), 3.46-3.71 (m, 5H), 3.96-4.08 (m, 1H), 4.51 (s, 2H), 7.23-7.35 (m, 5H).
^{13}C NMR ($CDCl_3$, 50 MHz)	δ −5.24, −5.21, 16.34, 18.39, 25.99, 34.32, 37.38, 40.10, 66.22, 68.02, 73.02, 78.37, 82.40, 127.41, 127.63, 128.28, 138.61 ppm.
Elemental Analysis	**Calcd:** C, 69.18; H, 9.95. **Found:** C, 69.24; H, 10.71.

((2*R*,4*R*,5*S*)-5-(2-(benzyloxy)ethyl)-4-methyltetrahydrofuran-2-yl)methanol (72):

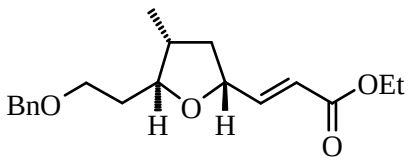


To a stirred solution of **83** (1.29 g, 3.53 mmol) in dry THF (15 mL) at room temperature was added 1.0 M TBAF in THF (5.3 mL, 5.30 mmol). After 4 h, brine was added, the layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue

was purified by silica gel column chromatography (Ethyl acetatec:Light petroleum ether, 1:3).

Yield	: 96%
Mol. Formula	: $C_{15}H_{22}O_3$
Optical Rotation $[\alpha]_D^{25}$	: −50.0 (*c* 1.3, $CHCl_3$).
IR ($CHCl_3$) cm^{-1}	: 3402, 3019, 1603, 1452, 1384, 1277, 1218, 1115, 1070, 770, 713, 666.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.94 (d, *J* = 6.4 Hz, 3H), 1.19-1.34 (m, 1H), 1.53-1.70 (m, 1H), 1.75-1.88 (m, 2H), 1.92-2.05 (m, 1H), 2.07-2.20 (m, 1H), 3.31-3.58 (m, 5H), 3.91-4.04 (m, 1H), 4.43 (s, 2H), 7.18-7.26 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 16.27, 34.12, 36.53, 39.99, 64.93, 67.50, 72.80, 78.46, 82.24, 127.39, 127.51, 128.21, 138.38 ppm.
ESI MS (*m/z*)	: 273.33 $[M+Na]^+$
Elemental Analysis	**Calcd:** C, 71.97; H, 8.86.
	Found: C, 70.00; H, 9.45.

(*E*)-ethyl 3-((2*R*,4*R*,5*S*)-5-(2-(benzyloxy)ethyl)-4-methyltetrahydrofuran-2-yl) acrylate (71):



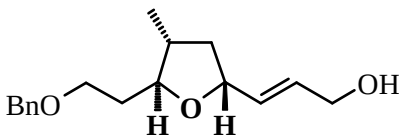
DMSO (5.1 mL, 72.26 mmol) was added to a solution of oxalyl chloride (15.1 mL, 2 M in CH_2Cl_2, 30.11 mmol) in CH_2Cl_2 (18 mL) at −78 ^oC. After 30 min at −78 ^oC, a solution of the alcohol **72** (3.01 g, 12.04 mmol) in CH_2Cl_2 (30 mL) was added dropwise, maintaining the internal temperature below −70 ^oC and was stirred at −78 ^oC for 1.5 h. Triethylamine (15 mL, 108.39 mmol) was added and the reaction was allowed to warm to room temperature, diluted with CH_2Cl_2, washed with brine, and concentrated to get **84** (3.53 g crude), which was used for next reaction without further purification.

To a stirred solution of $(EtO)_2P(O)CH_2CO_2Et$ (4.8 mL, 24.09 mmol) in THF (70 mL) was added NaH (722 mg, 60% dispersion in oil, 18.07 mmol) at 0 °C and the

mixture was stirred for 10 min. A soln of crude aldehyde **84** (3.53 g) in THF (30 mL) was added by syringe. The resulting mixture was stirred at 0 °C for 6 h. The mixture was quenched by the addition of saturated aqueous NH_4Cl solution and extracted with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate: light petroleum ether, 1:19) to obtain **71** (3.756 g) thick liquid.

Yield	: 98% (two steps)
Mol. Formula	: $C_{19}H_{26}O_4$
Optical Rotation $[\alpha]_D^{25}$	: −8.9 (*c* 1.6, $CHCl_3$).
IR ($CHCl_3$) cm^{-1}	: 2960, 2929, 2871, 1719, 1658, 1454, 1367, 1300, 1270, 1165, 1096, 1037, 755, 698.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.98 (d, *J* = 6.5 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.30-1.41 (m, 1H), 1.63-1.74 (m, 1H), 1.78-1.99 (m, 2H), 2.26 (dt, *J* = 6.7, 12.1 Hz, 1H), 3.48.3.62 (m, 3H), 4.14 (q, *J* = 7.2 Hz, 2H), 4.47 (s, 2H), 4.43-4.54 (m, 1H), 5.94 (dd, *J* = 1.6, 15.6 Hz, 1H), 6.85 (dd, *J* = 5.1, 15.6 Hz, 1H), 7.21-7.30 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 14.16, 16.09, 34.18, 40.28, 41.14, 60.06, 67.47, 72.90, 76.39, 82.58, 119.40, 127.33, 127.45, 128.18, 138.39, 148.73, 166.25 ppm.
ESI MS (*m/z*)	: 341.41 $[M+Na]^+$
Elemental Analysis	**Calcd:** C, 71.67; H, 8.23.
	Found: C, 68.78; H, 8.56.

(*E*)-3-((2*R*,4*R*,5*S*)-5-(2-(benzyloxy)ethyl)-4-methyltetrahydrofuran-2-yl)prop-2-en-1-ol (85):

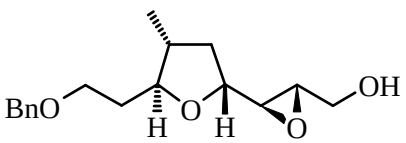


DIBAL-H (9.3 mL {2.6 M in toluene}, 24.03 mmol) was added dropwise to a solution of **71** (3.06 g, 9.61 mmol) at –78 °C under N_2 atm. After being vigorously stirred

for 1.5 h at –78 ^{o}C, the reaction was quenched with saturated aqueous potassium sodium tartrate. The mixture was diluted with CH_2Cl_2 and vigorously stirred at room temperature for overnight. The aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to provide a colorless oil, which was purified by silica gel column chromatography using ethyl acetate:light petroleum-ether(1:19) to give **85** (2.56 g) as colourless viscous oil.

Yield	: 96%
Mol. Formula	: $C_{17}H_{24}O_3$
Optical Rotation $[\alpha]_D^{25}$	: −20.0 (*c* 1.4, $CHCl_3$).
IR ($CHCl_3$) cm^{-1}	: 3400, 2924, 2858, 1620, 1454, 1364, 1218, 1094, 1018, 754, 698.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.03 (d, *J* = 6.5 Hz, 3H), 1.27-1.44 (m, 1H), 1.71-1.78 (m, 2H), 1.84-2.04 (m, 2H), 2.15-2.27 (m, 1H), 3.52-3.68 (m, 3H), 4.12 (d, *J* = 4.7 Hz, 2H), 4.33-4.44 (m, 1H), 4.51 (s, 2H), 5.65-5.89 (m, 2H), 7.24-7.34 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 16.42, 34.38, 40.33, 41.91, 62.49, 67.71, 72.89, 78.21, 82.44, 127.37, 127.53, 128.21, 130.47, 132,31, 138.39 ppm.
ESI MS (*m/z*)	: 299.37 $[M+Na]^+$
Elemental Analysis	**Calcd**: C, 73.88; H, 8.75.
	Found: C, 73.65; H, 8.64.

((*2S,3S*)-3-((2*R*,4*R*,5*S*)-5-(2-(benzyloxy)ethyl)-4-methyltetrahydrofuran-2-yl)oxiran-2-yl)methanol (70):

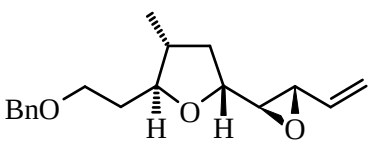


To a solution of (+)-diethyl D-tartrate (0.2 mL, 1.07 mmol) in dry CH_2Cl_2 (40 mL) was added titanium(IV) isopropoxide (0.2 mL, 0.76 mmol) at −30 to −20 °C. The mixture was stirred for 30 min. A solution of allylic alcohol **85** (2.11 g, 7.64 mmol) in CH_2Cl_2 (20

mL) was added, and the mixture was stirred at −30 to −20 °C for 20 min. *tert*-Butyl hydroperoxide (6.9 mL, 3.3 M in toluene, 22.93 mmol) was then added dropwise over 10 min. The resulting mixture was stirred at −20 °C for 7 days. Aqueous (+)-L-tartaric acid was added, then the mixture was stirred at −20 °C for 30 min, allowed to warm to room temperature, and stirred for 1 h. Aqueous NaOH (1 N) was added at 0 °C, and the resulting mixture was stirred for 1 h. The reaction mixture was then partitioned between water and CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel (ethyl acetate: petroleum ether 2:3) to obtain epoxide **70** as sticky oil (1.98 g).

Yield	: 88%
Mol. Formula	: $C_{17}H_{24}O_4$
Optical Rotation $[\alpha]_D^{25}$	: −21.82 (*c* 1.1, $CHCl_3$).
IR ($CHCl_3$) cm^{-1}	: 3430, 3063, 2957, 2929, 2871, 1635, 1496, 1454, 1364, 1276, 1099, 1074, 922, 739, 698, 609.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.97 (d, *J* = 6.58 Hz, 3H), 1.32-1.42 (m,1H), 1.58-1.68 (m, 1H), 1.80-1.88 (m, 2H), 2.09-2.17 (m, 1H), 2.95-2.99 (m, 2H), 3.43-3.59 (m, 4H), 3.83-3.90 (m, 2H), 4.44 (s, 2H), 7.19-7.33 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 16.11, 33.97, 37.31, 39.64, 56.52, 57.13, 61.26, 67.51, 72.91, 76.44, 82.85, 127.43, 127.55, 128.24, 138.37 ppm.
ESI MS (*m/z*)	: 315.37 $[M+Na]^+$
Elemental Analysis	**Calcd:** C, 69.84; H, 8.27.
	Found: C, 69.71; H, 8.17.

(2*S*,3*R*,5*R*)-2-(2-(benzyloxy)ethyl)-3-methyl-5-((2S,3S)-3-vinyloxiran-2-yl)tetrahydrofuran (69):



To a solution of IBX (2.89 g, 10.48 mmol) in DMSO (6 mL) at room temperature, was added pyridine (0.5 mL) followed by epoxy alcohol **70** (1.53 g, 5.239 mmol) in dry THF (20 mL). After 4 h of stirring, water (H_2O) was added, and diluted with diethyl ether and stirred it for additional 30 min. The solid was filtered off and from the filtrate organic layer was isolated, washed with brine, dried over Na_2SO_4, concentrated to give 1.60 g of **86**, which was used for next reaction without further purification.

A 1.0 M soln of NaHMDS in THF (10.5 mL, 10.48 mmol) was added dropwise to a stirred solution of $MeP^+Ph_3Br^-$ (5.61 g, 15.72 mmol) in THF (10 mL) at 0 °C. The resulting yellow suspension was stirred for 30 min at 0 °C. A soln of crude aldehyde **86** (1.60 g) in THF (10 mL) was added by syringe. After addition, the mixture was gradually warmed to room temperature over 1 h and stirred at this temperature for overnight. The mixture was quenched by the addition of saturated aqueous NH_4Cl solution and extracted with Et_2O. The combined organic extracts were washed with brine dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel column chromatography using EtOAc:light petroleum ether (4:96) to afford (1.105 g) as colorless liquid.

Yield : 73% (two steps)

Mol. Formula : $C_{18}H_{24}O_3$

Optical Rotation $[\alpha]_D^{25}$: −26.1 (*c* 1.15, $CHCl_3$).

IR ($CHCl_3$) cm^{-1} : 2960, 2928, 2871, 1601, 1454, 1363, 1218, 1100, 1027, 925, 757, 697, 665.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.97 (d, *J* = 6.6 Hz, 3H), 1.31-1.41 (m, 1H), 1.59-1.67 (m, 1H), 1.79-1.88 (m, 2H), 2.08-2.17 (m, 1H), 2.84 (dd, *J* = 2.1, 4.5 Hz, 1H), 3.13 (dd, *J* = 2.1, 7.49 Hz, 1H), 3.45-3.59 (m, 3H), 3.86 (ddd, *J* = 4.6, 6.6, 9.0 Hz, 1H), 4.44 (s, 2H), 5.20 (dd. *J* = 10.3, 1.4 Hz, 1H), 5.39 (dd, *J* = 1.4, 17.2 Hz, 1H), 5.48-5.57 (m, 1H), 7.17-7.26 (m, 5H) ppm.

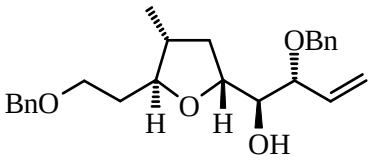
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 16.23, 34.13, 37.25, 39.76, 56.72, 61.67, 67.65, 73.03, 76.74, 82.94, 119.39, 127.47, 127.60, 128.32, 135.14, 138.52 ppm.

ESI MS (*m/z*) : 311.38 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 74.97; H, 8.39.

Found: C, 74.88; H, 8.28.

(1*S*,2*R*)-2-(benzyloxy)-1-((2*R*,4*R*,5*S*)-5-(2-(benzyloxy)ethyl)-4-methyl tetrahydrofuran-2-yl)but-3-en-1-ol (87):



To a mixture of epoxide **69** (250 mg 0.86 mmol) and benzyl alcohol (140 mg, 1.3 mmol) in CH_2Cl_2 (2 mL) was added dropwise $BF_3 \cdot Et_2O$ (0.5 mL, 0.079 M in dichloromethane, 0.043 mmol) at room temperature. After 30 min of stirring at room temperature, the solution was diluted with CH_2Cl_2 and washed with a saturated aqueous sodium bicarbonate ($NaHCO_3$) solution, followed by brine. The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash column chromatography (Petroleum ether/Ethyl acetate 9/1) afforded alcohol **87** (257 mg).

Yield : 75%

Mol. Formula : $C_{25}H_{32}O_4$

Optical Rotation $[\alpha]_D^{25}$: −4.4 (*c* 2.3, $CHCl_3$).

IR ($CHCl_3$) cm^{-1} : 3436, 3030, 2871, 1601, 1496, 1454, 1384, 1218, 1095, 1027, 927, 755, 697.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.99 (d, *J* = 6.5 Hz, 3H), 1.51 (dd, *J* = 21.6, 10.6 Hz, 1H), 1.61-1.69 (m, 1H), 1.81-1.90 (m, 2H), 1.95-1.99 (m, 1H), 2.21 (bs, 1H), 3.45-3.60 (m, 4H), 3.77 (t, *J* = 5.5 Hz, 1H), 3.81-3.86 (m, 1H), 3.93-3.99 (m, 1H), 4.32 (d, *J* = 11.9 Hz, 1H), 4.47 (s, 2H), 4.58 (d, *J* = 11.9 Hz, 1H), 5.29-5.36 (m, 2H), 5.81-5.90 (m, 1H), 7.22-7.32 (m, 10H) ppm.

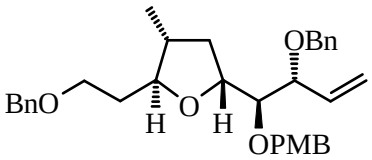
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 16.60, 34.45, 36.51, 40.06, 67.70, 70.22, 72.96, 74.83, 77.66, 81.40, 82.64, 119.71, 127.46, 127.57, 127.73, 128.32, 134.86, 138.27, 138.58 ppm.

ESI MS (*m/z*) : 419.52 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 75.73; H, 8.13.

Found: C, 75.62; H, 8.01.

((2*S*,4*R*,5*S*)-5-((1*S*,2*R*)-2-(benzyloxy)-1-(4-methylbenzyloxy)but-3-enyl)-2-(2-(benzyloxy)ethyl)-3-methyltetrahydrofuran (68):



To an ice-cooled solution of **87** (515 mg, 1.29 mmol) in dry DMF (5 mL), NaH (60% dispersion in oil, 62 mg, 2.59 mmol) was added. After 30 min, PMBCl (0.23 mL, 1.68 mmol) was introduced and stirred for additional 10 h at the same temperature. The reaction mixture was partitioned between water and ethyl acetate. The organic layer was washed with water, brine, dried (Na_2SO_4) and concentrated. Purification by flash column chromatography (Petroleum ether/Ethyl acetate: 9/1) afforded **68** (589 mg).

Yield : 88%

Mol. Formula : $C_{33}H_{40}O_6$

Optical Rotation $[\alpha]_D^{25}$: −23.2 (*c* 0.95, $CHCl_3$).

IR ($CHCl_3$) cm^{-1} : 3392, 2928, 1613, 1513, 1454, 1384, 1247, 1218, 1098, 1037, 883, 770, 697.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.95 (d, *J* = 6.3 Hz, 3H), 1.41-1.52 (m, 1H), 1.61-1.71 (m, 1H), 1.75-2.06 (m, 3H), 3.43-3.65 (m, 4H), 3.76 (s, 3H), 3.86 (dd, *J* = 4.7, 7.6 Hz, 1H), 4.00-4.11 (m, 1H), 4.31 (d, *J* = 11.9 Hz, 1H), 4.48 (bs, 2H), 4.56-4.69 (m, 3H), 5.22-5.33 (m, 2H), 5.86 (ddd, *J* = 7.8, 10.7, 16.9 Hz, 1H), 6.79 (d, *J* = 8.5 Hz, 2H), 7.18-7.29 (m, 12H) ppm.

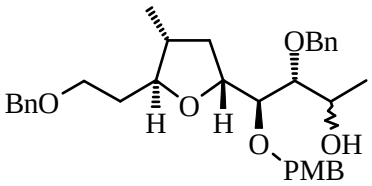
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 16.20, 34.18, 36.66, 40.07, 55.00, 67.87, 70.21, 72.91, 73.75, 77.61, 81.70, 82.04, 82.64, 113.47, 118.84, 127.23, 127.33, 127.41, 127.47, 128.13, 128.20, 129.63, 130.94, 135.59, 138.53, 138.63, 158.98 ppm.

ESI MS (*m/z*) : 539.67 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 76.71; H, 7.80.

Found: C, 76.59; H, 7.70.

(3*R*,4*S*)-3-(benzyloxy)-4-((2*R*,4*R*,5*S*)-5-(2-(benzyloxy)ethyl)-4-methyltetrahydrofuran-2-yl)-4-(4-methylbenzyloxy)butan-2-ol (89):



To a stirred solution of **68** (110 mg, 0.212 mmol) and $NaIO_4$ (74 mg, 0.636 mmol) in ether/H_2O (1:1, 2 mL) at room temperature was added OsO_4 (0.1 mL, 0.098 M in toluene, 0.01 mmol). The mixture was stirred at room temperature for 12 h and then quenched with aqueous sodium sulphite and extracted with ether. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to get 119 mg of **88** as yellow oil, which was used for the next reaction without further purification.

The above product **88** (119 mg) was dissolved in anhydrous THF (3 mL) and cooled to 0 ^oC. A 2 M solution of MeMgCl in THF (0.26 mL, 0.526 mmol) was added. After 1.5 h stirring at room temperature, it was quenched by addition of saturated aqueous solution of NH_4Cl. The organic layer separated, dried (Na_2SO_4) and concentrated to form a residue which was purified on silica gel column chromatography using ethyl acetate-light petroleum ether (1:9) to furnish **89** (96 mg) as clear oil.

Yield : 84% (three steps)

Mol. Formula : $C_{33}H_{42}O_6$

Optical Rotation $[\alpha]_D^{25}$: +16.2 (*c* 0.95, $CHCl_3$).

IR ($CHCl_3$) cm^{-1} : 3434, 2929, 1612, 1514, 1454, 1364, 1302, 1248, 1218, 1096, 1029, 822, 770, 698.

^{1}H NMR ($CDCl_3$, 400 MHz) : δ 0.99 (d, *J* = 6.5 Hz, 3H), 1.19 (d, *J* = 6.5 Hz, 1H), 1.21 (d, *J* = 6.4 Hz, 2H), 1.54-1.61 (m, 1H), 1.64-1.70 (m, 1H), 1.82-1.95 (m, 2H), 1.98-2.13 (m, 1H), 3.18 (brs, 1H), 3.32-3.41 (m, 1H), 3.49-3.64 (m, 3H), 3.73

(dt, *J* = 5.2, 15.6 Hz, 1H), 3.78 (s, 3H), 3.93-4.01 (m, 1H), 4.18-4.33 (m, 1H), 4.45-4.51 (m, 2H), 4.54-4.72 (m, 4H), 6.83 (d, *J* = 8.1 Hz, 2H), 7.22-7.31 (m, 12H) ppm.

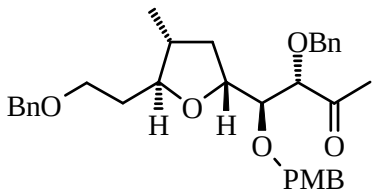
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 16.07, 16.14, 19.43, 19.57, 34.14, 34.21, 36.96, 37.44, 39.97, 40.08, 55.25, 67.10, 67.80, 67.86, 68.34, 73.07, 73.46, 73.59, 73.86, 77.61, 77.95, 81.40, 81.77, 81.85, 82.19, 82.31, 82.72, 113.79, 113.81, 127.47, 127.59, 127.62, 127.68, 127.76, 127.82, 128.03, 128.31, 128.37, 129.75, 129.81, 130.25, 138.09, 138.42, 138.45, 159.26 ppm.

ESI MS (*m/z*) : 557.68 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 74.13; H, 7.92.

Found: C, 74.01; H, 7.81.

(3*S*,4*S*)-3-(benzyloxy)-4-((2*R*,4*R*,5*S*)-5-(2-(benzyloxy)ethyl)-4-methyltetrahydro furan-2-yl)-4-(4-methylbenzyloxy)butan-2-one (33):



Method A: A solution of compound **68** (1.26 g, 2.45 mmol), Cu $(OAc)_2$. H_2O (0.097 g, 0.48 mmol), $PdCl_2$ (0.043 g, 0.24 mmol) in DMA: H_2O (7:1) (total volume 5 mL) were stirred under oxygen atmosphere at normal temperature and pressure for 12 h. The reaction was filtered, extracted with ether, washed with water, brine, dried (Na_2SO_4) and evaporated. The residue was purified on silica gel column chromatography by eluting with light petroleum: EtOAc (3:1) to afford **33** (0.26 g, 20%).

Method B: To a solution of IBX (99 mg, 0.359 mmol) in DMSO (0.2 mL) at room temperature was added alcohol **89** (96 mg, 0.179 mmol) in dry THF (2 mL). After 2 h of stirring, water (H_2O) was added, and diluted with ether and stirred it for additional 30 min. The solid was filtered off and from the filtrate organic layer was isolated, washed

with brine, dried over Na_2SO_4, concentrated to form a residue which was purified on silica gel column chromatography using EtOAc-light petroleum ether (1:4) to furnish **33** (89 mg, 93%) as viscous liquid.

Mol. Formula	: $C_{33}H_{40}O_6$
Optical Rotation $[\alpha]_D^{25}$	: +9.52 (*c* 1.05, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	: 3370, 2927, 1719, 1611, 1513, 1453, 1362, 1248, 1219, 1096, 1035, 770, 698.
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 0.86 (d, *J* = 6.6 Hz, 3H), 1.22-1.36 (m, 1H), 1.50-1.65 (m, 1H), 1.70-1.87 (m, 2H), 2.07 (s, 3H), 3.23 (dt, *J* = 2.8, 9.0 Hz, 1H), 3.34-3.54 (m, 2H), 3.67-3.73 (m, 1H), 3.73 (s, 3H), 3.88 (d, *J* = 3.2 Hz, 1H), 4.15 (q, *J* = 7.6 Hz, 1H), 4.34-4.49 (m, 4H), 4.50-4.63 (m, 2H), 6.77 (d, *J* = 8.6 Hz, 2H), 7.13 (d, *J* = 8.6 Hz, 2H), 7.17-7.25 (m, 10H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz)	: δ 16.21, 27.42, 34.00, 38.01, 40.19, 55.20, 67.91, 72.54, 73.04, 73.15, 76.16, (77.20), 82.05, 83.39, 83.56, 113.76, 127.48, 127.68, 127.85, 127.95, 128.32, 128.41, 129.75, 129.94, 131.88, 133.23, 137.64, 138.50, 141.85, 159.32, 209.57 ppm.
Elemental Analysis	**Calcd:** C, 74.41; H, 7.57. **Found:** C, 74.31; H, 7.48.

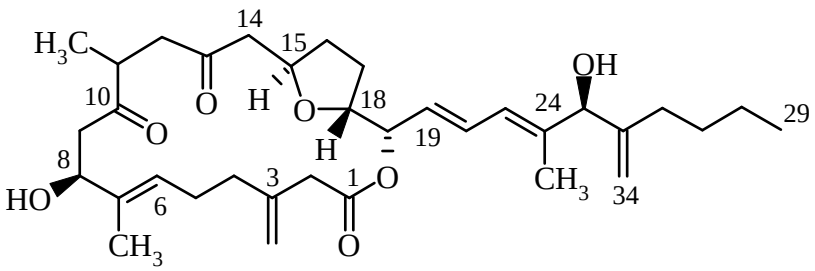
CHAPTER 3

SECTION III

Synthesis of the C14-C29 Segment of Amphidinolide U Utilizing a Tandem Dihydroxylation-S_N2 Cyclization

Present Work

Amphidinolides are a group of structurally unique macrolides isolated to date from laboratory-cultured dinoflagellates of the *Amphidinium* sp.[3] Many of the amphidinolides exhibit potent antitumor activity against lymphoma L1210 and human carcinoma KB cells. Despite their common origin and uniformly high cytotoxicity against various cancer cell lines, the amphidinolides possess a high degree of structural diversity incorporating many variegated molecular scaffolds. Continuing search for bioactive secondary metabolites resulted in the isolation of a novel 20-membered macrolide, amphidinolide U (**30**, Figure 18), possessing a tetrahydrofuran ring, two *exo*-methylenes, three branched methyls, two ketones, two hydroxyl groups, and a C10 linear side chain.[42] The structure of amphidinolide U (**30**) was elucidated by spectroscopy; relative stereochemistry was assigned by NOESY studies and absolute configurations were assigned on the basis of modified Mosher's method. The interesting biological profile coupled with structural parameters of amphidinolide U (**30)** prompted us to undertake its synthesis.



Amphidinolide U (**30**)

Figure 18

The retrosynthetic analysis for the total synthesis of **30** has been outlined in Figure 28. Amphidinolide U (**30**) could be assembled from three building blocks: the alcohol part **91**, acid part **90,** and thione part **29**. The thione moiety could be devised as a tool for coupling of the C12 of segment **90** and C14 of segment **91**. The alcohol segment **91** of amphidinolide U (**30)** contains four chiral centers with a terminal *E,E*-dienoic moiety. The macrolactonization between alcohol **91** and acid **90** could be achieved through DCC mediated coupling.

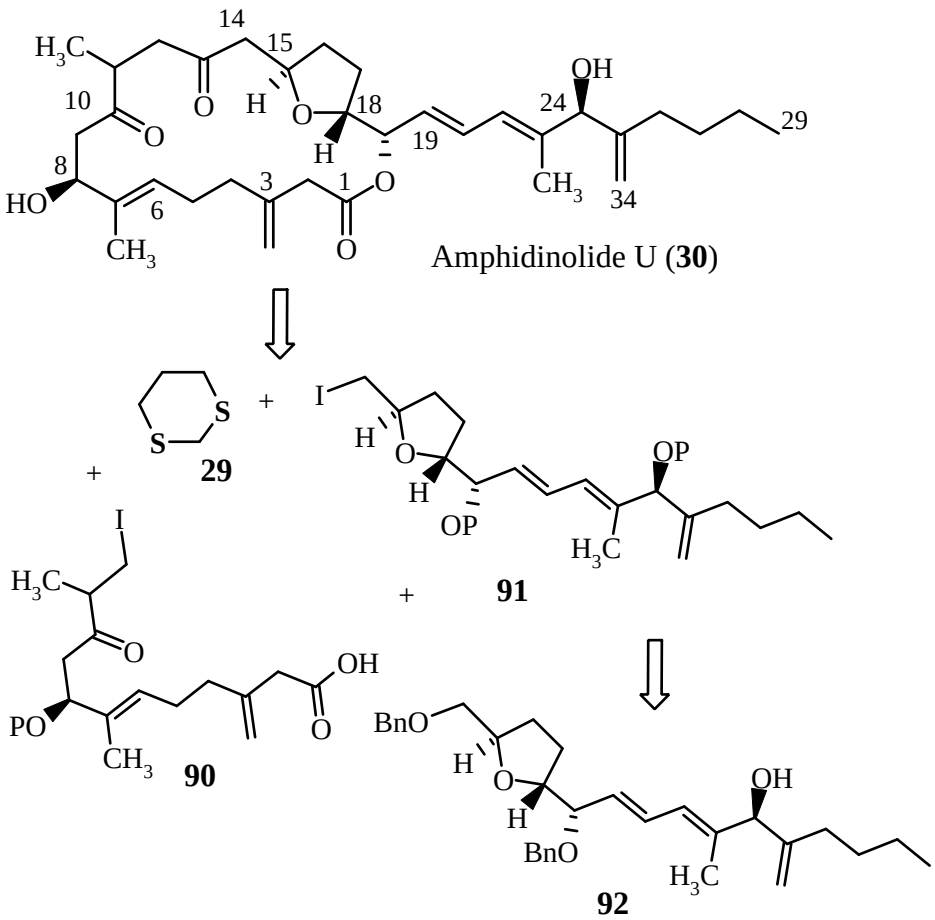
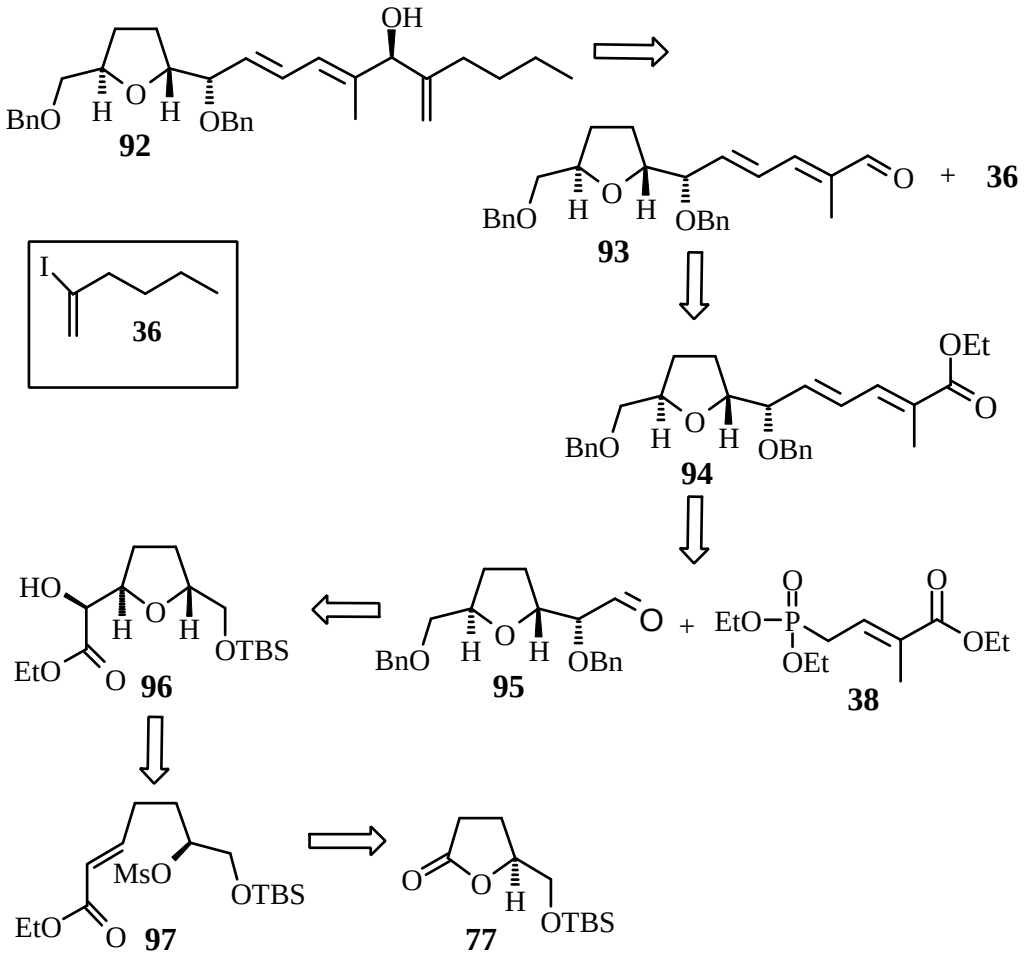


Figure 28: *Retrosynthetic analysis of amphidinolide U (**30**)*

Synthesis of the C14-C29 segment of amphidinolide U (30)

In our synthetic plan, we envisaged a disconnection into two segments **93** and **36**. For the synthesis of **92**, we planned to add hexenyl iodide **36** to aldehyde **93** following Nozaki-Hiyama-Kishi reaction (Scheme 24). The diene system **94** would be introduced by following a Horner-Wadsworth-Emmons reaction with the phosphorane **38** [Synthesis of **38** discussed in the previous section (Chapter-3: Section-I)]. We anticipated that the required *trans*-tetrahydrofuran would be obtained by tandem dihydroxylation-S_N2 cyclization protocol.

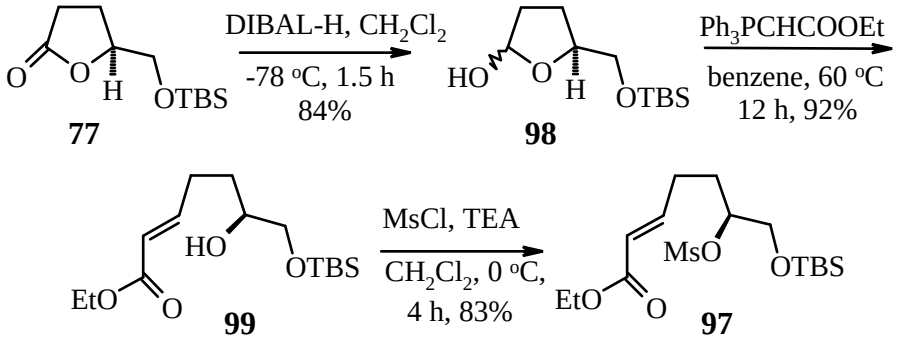
Accordingly, the journey began with lactone **77**, which could be obtained from commercially available optically pure L-(+)-glutamic acid **(**discussed in the previous section: Chapter 3; Section II). Reduction of **77** with DIBAL-H at –78 ^oC in CH_2Cl_2 provided the corresponding hemiacetal **98** as a diastereomeric mixture in quantitative yield.



Scheme 24

The lactol **98** without further purification was carried forward to the two carbons Wittig olefination using ethoxycarbonylmethylenetriphenylphosphorane in benzene at 60 ^{o}C to afford **99** as the only product. In ^{1}H NMR spectrum, signals due to ethyl (−*O*<u>*CH*$_2$*CH*$_3$</u>) protons were observed at δ 1.28 (t, *J* = 7.2 Hz) and 4.17 (q, *J* = 7.1 Hz) ppm integrating for three and two protons, respectively. For olefinic protons, the resonances were observed at δ 5.82 (dt, *J* = 1.6, 15.6 Hz, 1H) ppm and at δ (dt, *J* = 6.9, 15.7 Hz, 1H) ppm in the ^{1}H NMR spectrum. A resonance observed in ^{13}C NMR spectrum at δ 165.3 ppm was assigned for the ester carbonyl carbon, whereas the signals at δ 121.6 and 148.5 ppm were assigned for the olefinic carbons. IR (1722 cm^{-1} for C=O), mass spectral [*m/z* 325.4 for M+Na^{+}] and elemental analysis was in accordance to the assigned structure.

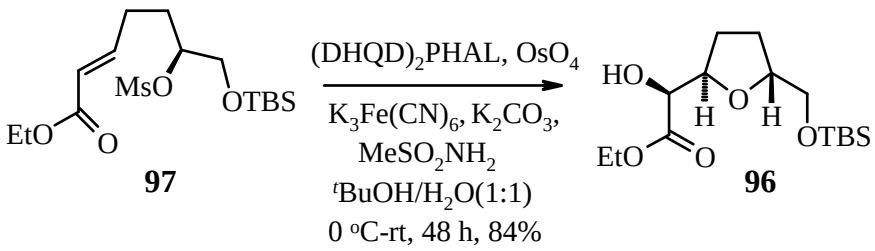
Our next concern was to construct the tetrahydrofuran derivative following the two-steps procedure as depicted in Scheme 25. Thus, the free hydroxyl group was converted to its mesylate ester **97** using $MeSO_2Cl$ (1.5 equiv.)/TEA/DMAP (catalytic) in CH_2Cl_2 at 0 ^oC. This mesylation was confirmed by the ^1H NMR spectrum in which the resonances due to $\underline{CH_3}SO_2$ group (one singlets at δ 3.05 ppm) and downfield shift of peaks due to H6 proton, compared to that of starting material, were observed.



Scheme 25

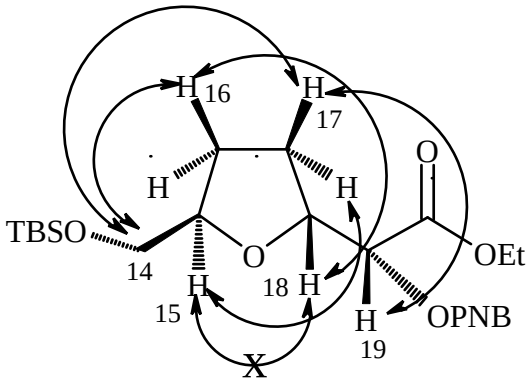
Now, the stage was set to carry out the tandem dihydroxylation–S_N2 cyclization reaction. The mesylate[57] derivative **97** was subjected to Sharpless asymmetric dihydroxylation with $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, $MeSONH_2$ and OsO_4 in *tert*-$BuOH/H_2O$ (1:1) for 10 h, whereupon the *trans*,*syn*-tetrahydrofuran **96** was obtained with excellent diastereoselectivity (Scheme 26). The compound was thoroughly investigated by the ^1H NMR and ^{13}C NMR spectrum and elemental analysis. In the ^1H NMR spectrum, the absence of signals due to olefinic and mesylate protons and the appearance of multiplets due to ring junction protons at C5 and C3 located between δ 4.08-4.35 (2H) ppm were the clear indication of the formation of the THF framework **96**. The rest of the protons were localized at their expected regions. ^{13}C NMR, IR and mass spectra also supported the assigned structure.

To get the required center, inversion of the hydroxyl group at C2 was needed. Accordingly, Mitsunobu reaction[57] of **96** in presence of DIAD, *p*-nitrobenzoic acid and TPP in THF provided the *p*-nitrobenzoate derivative **100** (Scheme 26). The ^1H NMR spectrum of **100** showed a doublet at δ 5.40 (J = 3.6 Hz, 1H) ppm due to methine proton bearing -*OPNB* group. The ^{13}C NMR and other spectral data also supported the structure of **100**.



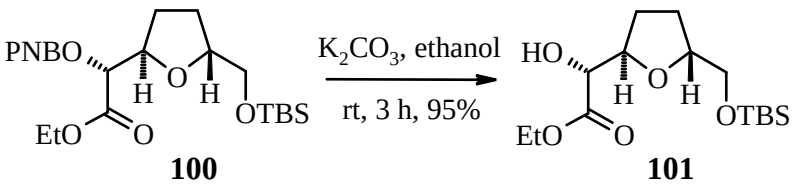
Scheme 26

We were interested to study the n*O*e interactions in compound **100** to check the relative configuration present in **100**. Gratifyingly, the n*O*e correlations were observed for H14a–H16a, H14a–H17a, H15–H17b, H16a–H18 and H17a–H19, indicating that relative stereochemistries between H15-H18 and between H18 and H19 were *anti*- and *syn*-oriented, respectively **(**Figure 29).



100

Figure 29: *Selected NOESY Correlations of **100***

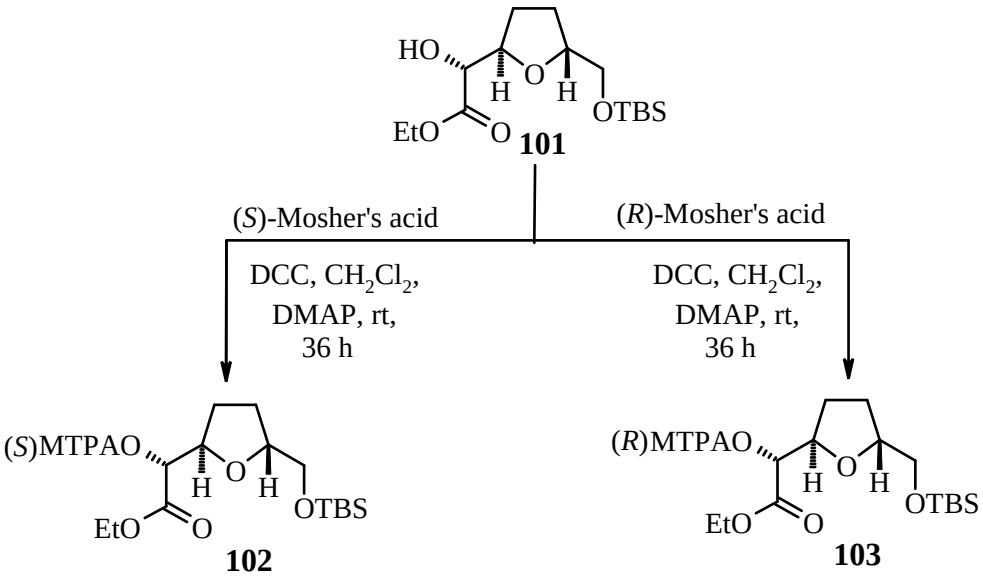


Scheme 27

The ester **100** was hydrolyzed by K_2CO_3 in ethanol to generate the inverted alcohol **101**. Although, we determined the relative stereochemistry of the chiral centers present in

100 at previous stage by n*O*e experiment, absolute stereochemistry of C2-OH in **101** was confirmed by modified Mosher's ester analysis[46] of derived MTPA esters.

In order to assign the absolute stereochemistry of C2-OH in **101**, the (*S*)- MTPA ester **102** and (*R*)-MTPA ester **103** were independently prepared from **101** by using corresponding (*S*)-MTPA acid and (*R*)-MTPA acid in presence of coupling agent DCC and DMAP (cat.) in anhydrous CH_2Cl_2 at room temperature (Scheme 28). The $\Delta\delta = (\delta_S - \delta_R) \times 10^3$ values were calculated for as many protons as possible from the ^{1}H NMR spectrum of (*S*)-MTPA ester **102** and (*R*)-MTPA ester **103** (Table 3). On the basis of the model (Figure 30) we have assigned the absolute stereochemistry of side chain at C5 of **101** as (*R*)-configuration.

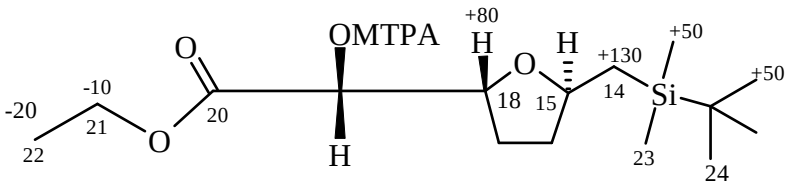


Scheme 28

Table 3 *Chemical shifts for (S) and (R)-MTPA esters of **101***

Sr. No.	**Protons**	δ_S	δ_R	$\Delta\delta = \delta_S - \delta_R$	$\Delta\delta$ **X** 10^3
1.	H^{14}	3.51, 3.53	3.38, 3.41	+0.13, +0.12	+130, +120
2.	H^{18}	4.49, 4.50, 4.52, 4.54, 4.55, 4.57	4.41, 4.43, 4.45, 4.47, 4.48, 4.50	+0.08, 0.07, +0.07, 0.07, +0.07, 0.07	+80, +70, +70, +70, +70, +70
3.	H^{21}	4.18, 4.22, 4.25, 4.29	4.20, 4.23, 4.27, 4.30	-0.02, -0.01, -0.02, -0.01	-20, -10, -20, -10
4.	H^{22}	1.24, 1.28, 1.31	1.26, 1.29, 1.33	-0.02, -0.01, -0.02	-20, -10, -20

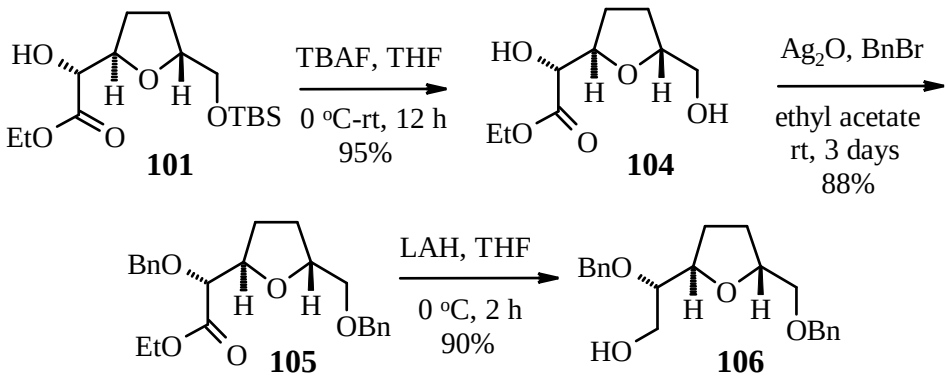
5.	H^{23}	0.06	0.01	+0.05	+50
6.	H^{24}	0.89	0.84	+0.05	+50



(*R*)

Figure 30

Compound **101** was desilylated with TBAF in anhydrous THF at 0 °C-rt to give the diol **104**. The ^{1}H NMR, ^{13}C NMR spectra and elemental analysis were in support of the structure **104** (Scheme 29). Protection of hydroxyl functionality of **104** as its benzylic ether was accomplished using benzyl bromide in the presence of a mild base, Ag_2O in ethyl acetate to yield **105** in 88% yield. The ^{1}H NMR spectrum of **105** indicated the corresponding resonances at δ 4.42 (d, *J* = 11.7 Hz, 1H), 4.48 (s, 2 H), 4.64 (d, *J* = 11.7 Hz, 1H) (two -*CH*$_2$ of *Ph*-*CH*$_2$) and 7.16-7.30 (m, two *Ph* of *Ph*-*CH*$_2$) ppm in support of the benzyl ether moiety.

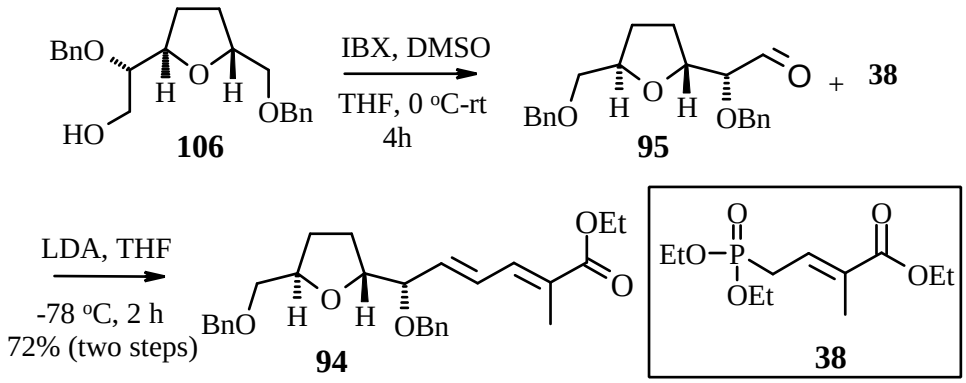


Scheme 29

Compound **105** on exposure to LAH in anhydrous THF at 0 °C for 2 h resulted in the formation of the hydroxy derivative **106** in 90 % yield. In its ^{1}H NMR spectrum, protons due to –*CH*$_2$*OH* group appeared as multiplet in the region of δ 3.54-3.70 (2H) ppm, a broad singlet at δ 2.26 (1H) ppm was assigned to –*OH*, while H-2 appeared as

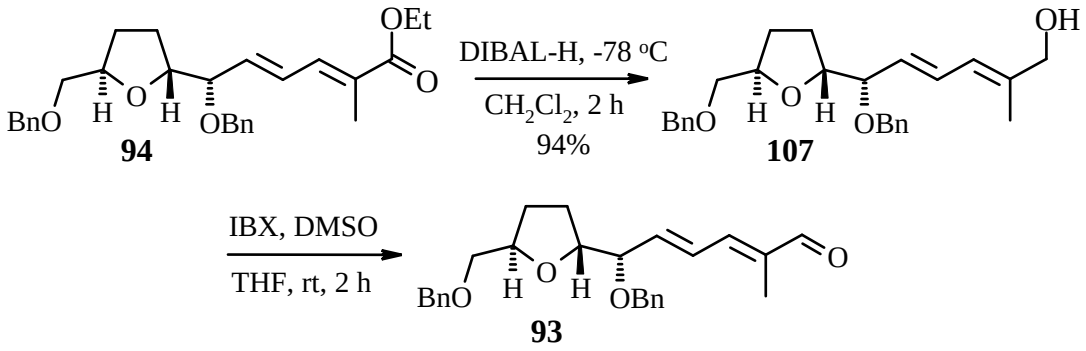
quartet at δ 3.44 (*J* = 5.4 Hz, 1H) ppm. H-7 appeared as a doublet at δ 3.38 (d, *J* = 5.0 Hz, 2H) ppm.

Our next concern was to introduce the densely olefinated side chain. The phosphorane **38** was prepared starting from *cis*-buten-1,4-diol following the sequence of reactions described in the previous section (Chapter 3 Section I). The primary hydroxyl group of **106** was then oxidized with IBX in DMSO/THF to provide aldehyde **95**, which was carried forward to the next reaction without further purification. The aldehyde **95** was immediately subjected to Horner-Wadsworth-Emmons reaction[48] with phosphorane **38** in the presence of LDA (*in situ* generated) to obtain **94**. Structure of **94** was investigated by spectroscopic data. For example, its ^{1}H NMR spectrum revealed signals (Scheme 30) due to olefinic protons at δ 6.02 (dd, *J* = 7.0, 15.3 Hz, 1 H), 6.56 (ddd, *J* = 1.0, 11.4, 15.3 Hz, 1 H), and 7.21 (d, *J* = 11.4 Hz, 1 H) ppm, which were characteristic of the *E,E*-dienoate group, whereas the resonances at δ 1.32 (t, *J* = 7.2 Hz, 3 H) and 4.22 (q, *J* = 7.1 Hz, 2H) ppm corresponding to the ethyl group (−*O*<u>*CH*$_2$*CH*$_3$</u>) were noted. The peak [M+Na^{+}] at *m*/*z* 473.5 was recorded in the EI mass spectrum.



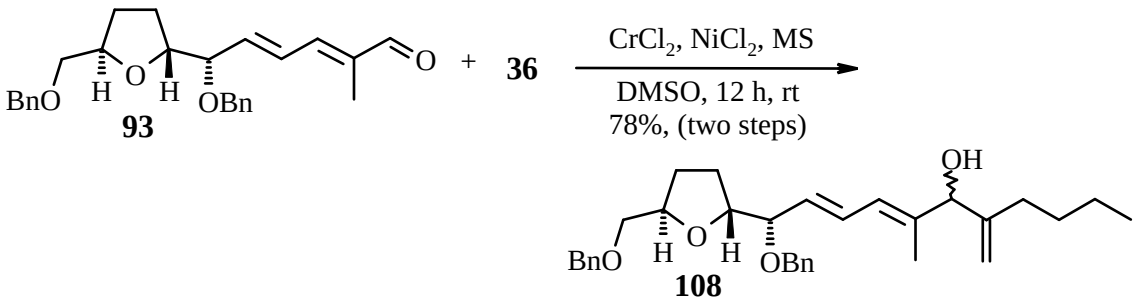
Scheme 30

Reductive chemistry was next undertaken with DIBAL-H in dichloromethane at −78 °C to provide the corresponding allyl alcohol **107** in 94% yield. The structure was elucidated on the basis of ^{1}H NMR, ^{13}C NMR, IR and EI mass spectral analysis. In the ^{1}H NMR spectrum, the resonances due to olefinic protons moved upfield and the −*CH*$_2$ group of allyl alcohol was localized at δ 4.07 (s, 2 H) ppm. In ^{13}C NMR spectrum, the disappearance of signal due to carboethoxy moiety also secured the assigned structure. The alcohol **107** was subjected to the treatment of IBX in DMSO/THF at ambient temperature to obtain aldehyde **93**.



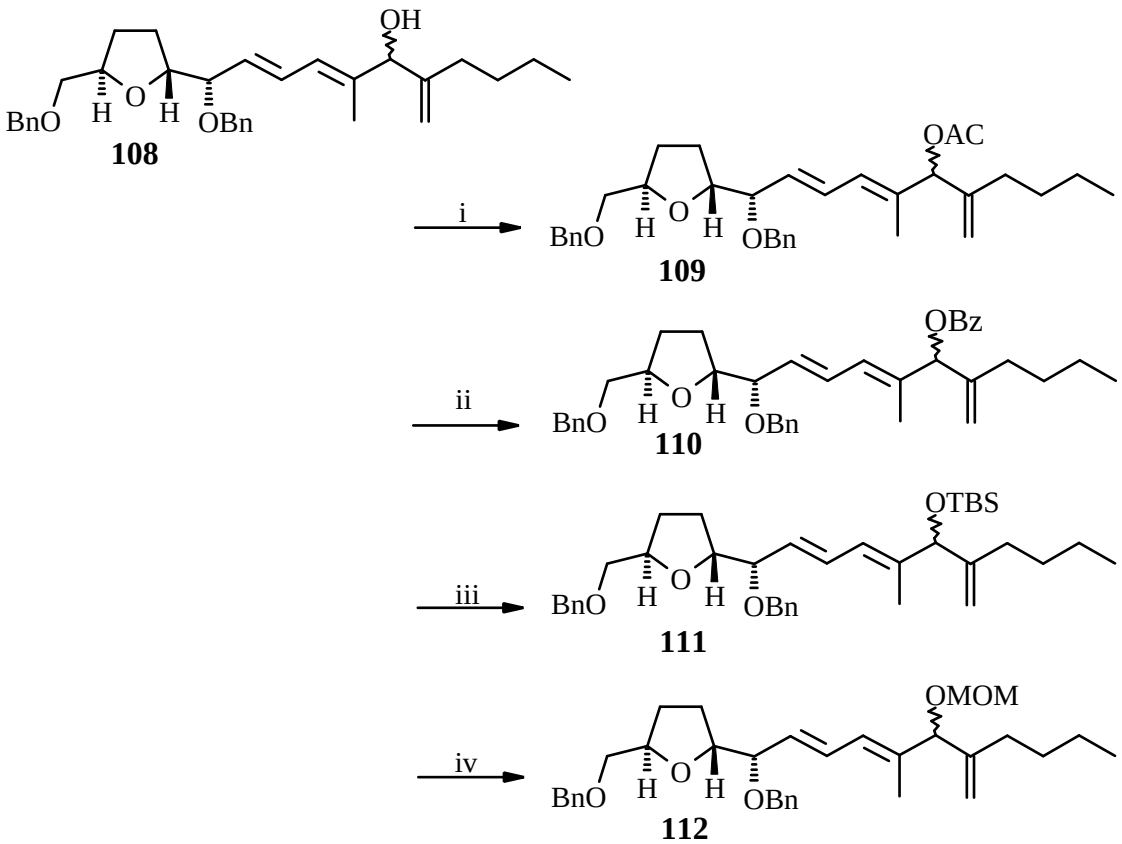
Scheme 31

The Nozaki–Hiyama–Kishi coupling[54] reaction between **93** and **36** was effected in the presence of $CrCl_2$ and catalytic amount of $NiCl_2$ to give a 1:1 diastereomeric mixture of our targeted segment **108**. The structure of **108** was confirmed by its ^{1}H NMR and ^{13}C NMR spectroscopic data. For example, its ^{1}H NMR spectrum revealed signals due to olefin protons at δ 5.66 (dd, *J* = 7.7, 15.2 Hz, 1 H), 6.47 (dd, *J* = 10.9, 15.2 Hz, 1 H), and 6.18 (d, *J* = 10.89 Hz, 1 H). Two characteristic singlets due to *exo*-methylene protons observed at δ 4.97 (s, 1 H) and 5.15 (s, 1 H) ppm. IR, mass and elemental analysis also supported the product formation.



Scheme 32

We protected the secondary hydroxy group with different protecting groups (Scheme 33) to generate variously protected diastereomers (**109-112**). Unfortunately, no separation of diastereomers with different solvent systems was discernible. The diastereomers could be separated by preparative liquid chromatography and assigned the absolute stereochemistry as reported for amphidinolide C (**28**).[64]

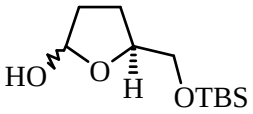


Scheme 33: ***Reagent and Conditions*****:** i) Ac_2O, CH_2Cl_2, DMAP, rt, 1 h; ii) Bz-Cl, Et_3N, DMAP, CH_2Cl_2, 0 ^oC-rt, 12 h; iii) TBSCl, DMF, imidazole, DMAP, 0 ^oC-rt, overnight; iv) MOMCl, CH_2Cl_2, DMAP, DIPEA, overnight, rt.

In conclusion, we have achieved the first synthesis of the entire top half **108** of the amphidinolide U (**30**), offering the promise of the total synthesis of this molecule but also other structurally similar congeners. For the construction of *trans*-2,5-disubstituted tetrahydrofuran, a tandem Sharpless asymmetric dihydroxylation-S_N2 cyclization protocol has been used as the key step. Further work is in progress.

Experimental

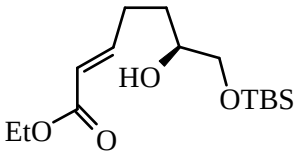
(*S*)-5-((*tert*-butyldimethylsilyloxy)methyl)tetrahydrofuran-2-ol (98):



A solution of lactone **77** (11.51 g, 49.952 mmol) in CH_2Cl_2 (250 mL) was treated DIBALH (30.0 mL, 59.94 mmol, 1.994 M solution in toluene) at −78 ^oC. After stirring at the same temperature for 2 h, the reaction was quenched with saturated aqueous potassium sodium tartrate. The mixture was diluted with CH_2Cl_2 and vigorously stirred at room temperature for 2 h. The aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to provide the crude hemiacetal. Purification by flash column chromatography (20% EtOAc/Light petroleum ether) afforded lactol **98** (9.85 g) as a colorless oil.

Yield	: 84%
Mol. Formula	: $C_{11}H_{24}O_3Si$
Optical Rotation $[\alpha]_D^{25}$	: −1.1 (*c* 1.15, $CHCl_3$).
IR ($CHCl_3$) cm^{-1}	: 3410, 2955, 2930, 2858, (1719, W), 1648, 1472, 1463, 1389, 1361, 1256, 1107, 1068, 1006, 972, 837, 758, 666.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.08-0.11 (m, 6H), 0.90-0.92 (m, 9H), 167-2.16 (m, 4H), 3.53-3.59 (m, 1H), 3.72-3.83 (m, 1H), 4.18-4.33 (m, 1H), 5.37 (d, *J* = 8.2 Hz, 0.67H), 5.54 (d, *J* = 4.2 Hz, 0.31H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ −5.50, −5.37, −3.61, 18.30, 18.35, 23.76, 25.65, 25.87, 32.64, 34.75, 65.42, 65.49, 78.80, 79.97, 98.33, 98.74 ppm.
ESI MS (*m/z*)	: 255.40 $[M+Na]^+$
Elemental Analysis	**Calcd:** C, 56.85; H, 10.41.
	Found: C, 56.01; H, 10.85.

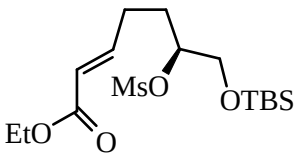
(*E*)-ethyl 7-(*tert*-butyldimethylsilyloxy)-6-hydroxyhept-2-enoate (99):



A solution of hemiacetal **98** (11.36 g, 48.87 mmol) and (carbethoxyethylidene) triphenylphosphorane (32.87 g, 97.73 mmol) in benzene (500 mL) was heated to 60 ^{o}C for 12 h. The resulting mixture was cooled to room temperature, concentrated and the residue was purified by silica gel column chromatography (10% EtOAc/ Light petroleum ether) to provide ester **99** (13.65 g) as colorless oil.

Yield	: 92%
Mol. Formula	: $C_{15}H_{30}O_4Si$
Optical Rotation $[\alpha]_D^{25}$	: −0.8 (*c* 1.2, $CHCl_3$).
IR ($CHCl_3$) cm^{-1}	: 34.86, 2954, 2930, 2858, 1722, 1654, 1472, 1463, 1368, 1258, 1160, 1123, 1045, 938, 838, 778, 668.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.07 (s, 6H), 0.90 (s, 9H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.49-1.61 (m, 2H), 2.26-2.48 (m, 2H), 3.39 (dd, *J* = 8.0, 10.5 Hz, 1H), 3.57-3.64 (m, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 5.82 (dt, *J* = 1.6, 15.6 Hz, 1H), 6.95 (dt, *J* = 7.0, 15.7 Hz, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ −5.48, −5.43, 14.20, 18.22, 25.82, 28.19, 31.16, 59.95, 67.08, 70.80, 121.59, 148.45, 166.34 ppm.
ESI MS (*m/z*)	: 325.48 $[M+Na]^+$
Elemental Analysis	**Calcd:** C, 59.56; H, 10.00.
	Found: C, 59.44; H, 9.89.

(6S,*E*)-ethyl 7-(*tert*-butyldimethylsilyloxy)-6-(methylsulfonyloxy)hept-2-enoate (97):

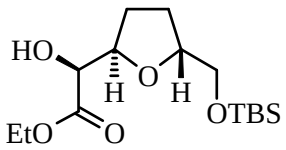


To a solution of **99** (16.03 g, 52.99 mmol), DMAP (cat.) and triethylamine (14.8 mL, 105.99 mmol) in CH_2Cl_2 (150 mL) was added a solution of methanesulphonyl

chloride (6.1 mL, 79.49 mmol) in CH_2Cl_2 (100 mL) at 0 ^oC. The reaction mixture was stirred at the same temperature for 2 h, washed with water and brine, dried (Na_2SO_4), and concentrated on rotavapor. The residue on purification by silica gel column chromatography (5% ethyl acetate in light petroleum ether) provided **97** (18.57 g) as colourless oil.

Yield	: 83%
Mol. Formula	: $C_{16}H_{32}O_6SSi$
Optical Rotation $[\alpha]_D^{25}$	: − 5.0 (*c* 1.05, $CHCl_3$).
IR ($CHCl_3$) cm^{-1}	: 3024, 2931, 2859, 1715, 1655, 1471, 1464, 1348, 1260, 1216, 1175, 1111, 1044, 923, 838, 757, 667.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.08 (s, 6H), 0.90 (s, 9H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.78-1.89 (m, 2H), 2.23-2.44 (m, 2H), 3.05 (s, 3H), 3.67-3.82 (m, 2H), 4.18(q, *J* = 7.15 Hz, 2H), 4.67 (quintate, *J* = 5.7 Hz, 1H), 5.86 (dt, *J* = 1.6, 15.7 Hz, 1H), 6.93 (dt, *J* = 6.8, 15.7 Hz, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ −5.57, 14.14, 18.20, 25.74, 27.44, 29.64, 38.45, 60.02, 64.57, 82.34, 122.22, 146.82, 166.05 ppm.
ESI MS (*m/z*)	: 403.57 $[M+Na]^+$
Elemental Analysis	**Calcd:** C, 50.50; H, 8.48.
	Found: C, 49.87; H, 8.32.

(*S*)-ethyl 2-((2*R*,5*R*)-5-(*tert*-butyldimethylsilyloxy)methyl)tetrahdrofuran-2-yl)-2-hydroxyacetate (96):

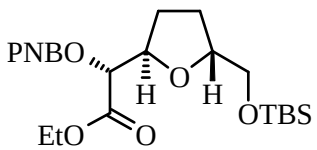


The mixture of $K_3Fe(CN)_6$ (39.74 g, 120.37 mmol), K_2CO_3 (16.85 g, 120.37 mmol), $(DHQD)_2PHAL$ (280 mg, 0.401 mmol), OsO_4 (8.4 mL, 0.019 M in toluene) and $MeSO_2NH_2$ (7.22 g, 75.78 mmol) in *t*-BuOH/H_2O (200 mL/200 mL) was stirred at room temperature for 15 min and then cooled to 0 °C. To this solution was added the enoate **97** (15.27 g, 40.12 mmol) in *t*-BuOH/H_2O (50 mL/50 mL). The reaction was stirred at room temperature for 48 h and then quenched with saturated aqueous Na_2SO_3 at room

temperature. EtOAc was added to the reaction mixture, and after separation of the layers, the aqueous layer was further extracted with EtOAc twice. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (5% EtOAc/ Light petroleum ether) afforded **96** (10.78 g) as a clear oil.

Yield	: 84%
Mol. Formula	: $C_{15}H_{30}O_5Si$
Optical Rotation $[\alpha]_D^{25}$	: −9.0 (*c* 1.85, $CHCl_3$).
IR ($CHCl_3$) cm^{-1}	: 3337, 3113, 3080, 3056, 2929, 2857, 1736, 1672, 1607, 1530, 1464, 1439, 1346, 1207, 1119, 837
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.03 (s, 6H), 0.88 (s, 9H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.73-1.91 (m, 1H), 1.95-2.11 (m, 3H), 2.88 (d, *J* = 8.2 Hz, 1H), 3.57 (d, *J* = 4.5 Hz, 2 H), 4.03 (dd, *J* = 2.2, 8.1 Hz, 1H), 4.08-4.16 (m, 1H), 4.18-4.35 (m, 3H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ −5.50, 14.00, 18.13, 25.74, 27.55, 27.84, 61.31, 65.44, 72.33, 79.77, 80.77, 172.78 ppm.
ESI MS (*m/z*)	: 341.13 $[M+Na]^+$
Elemental Analysis	**Calcd:** C, 56.57; H, 9.49.
	Found: C, 56.17; H, 9.29.

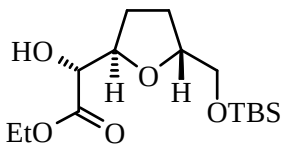
(*R*)-1-((2*R*,5*R*)-5-(*tert*-butyldimethylsilyloxy)methyl)tetrahdrofuran-2-yl)-2-ethoxy-2-oxoethyl 4-nitrobenzoate (100):



To a solution of alcohol **96** (3.13 g, 9.84 mmol), triphenylphosphine (10.06 g, 38.39 mmol), and 4-nitrobenzoic acid (6.74 g, 40.36 mmol) in THF (75 mL) was added diisopropyl azodicarboxylate (7.8 mL, 39.37 mmol) at 0 °C under N_2. Then the reaction mixture was stirred at room temperature for 12 h. All the volatiles were removed and the residue was chromatographed on silica gel (3% EtOAc/ Light petroleum ether) to give ester **100** as light yellow oil (3.8 g).

Yield	: 82%
Mol. Formula	: $C_{22}H_{33}NO_8Si$
Optical Rotation $[\alpha]_D^{25}$	: +9.1 (*c* 1.45, $CHCl_3$).
IR ($CHCl_3$) cm^{-1}	: 3381, 2955, 2930, 2857, 1733, 1608, 1530, 1470, 1439, 1346, 1286, 1257, 1210, 1032, 873, 830, 758, 720, 695.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.06 (s, 6H), 0.89 (s, 9H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.81-1.97 (m, 1H), 2.02-2.20 (m, 3H), 3.62 (d, *J* = 4.4 Hz, 2H), 4.09-4.17 (m, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 4.56 (dt, *J* = 3.6, 6.6 Hz, 1H), 5.40 (d, *J* = 3.6 Hz, 1H), 8.23 (d, *J* = 8.9 Hz, 2H), 8.32 (d, *J* = 8.9 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ −5.31, 14.16, 18.33, 25.92, 26.93, 27.81, 61.69, 65.59, 75.23, 78.11, 80.82, 123.60, 130.95, 134.88, 150.74, 163.98, 167.47 ppm.
ESI MS (*m/z*)	: 490.58 $[M+Na]^+$
Elemental Analysis	**Calcd:** C, 56.51; H, 7.11.
	Found: C, 56.39; H, 7.03.

(*R*)-ethyl 2-((2*R*,5*R*)-5-(*tert*-butyldimethylsilyloxy)methyl)tetrahdrofuran-2-yl)-2-hydroxyacetate (101):



To a solution of ester **100** (2.0 g, 4.26 mmol) in EtOH (10 mL) was added finely powdered K_2CO_3 (1.17 g, 8.52 mmol) under N_2. Then the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was then concentrated, partitioned between CH_2Cl_2 and water. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel using 15% EtOAc/light petroleum ether to furnish alcohol **101** as colorless oil (1.29 g).

Yield	: 95%
Mol. Formula	: $C_{15}H_{30}O_5Si$

Optical Rotation $[\alpha]_D^{25}$: −4.6 (*c* 1.4, $CHCl_3$).

IR ($CHCl_3$) cm^{-1} : 3413, 3019, 2956, 2930, 2858, 1729, 1600, 1518, 1471, 1419, 1255, 1215, 1130, 838, 758.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.04 (s, 6 H), 0.88 (s, 9 H), 1.29 (t, *J* = 7.2 Hz, 3 H), 1.72-2.06 (m, 4 H), 2.93 (brd, 1 H), 3.59 (d, *J* = 4.6 Hz, 2 H), 4.07-4.15 (m, 1 H), 4.19-4.37 (m, 4 H) ppm.

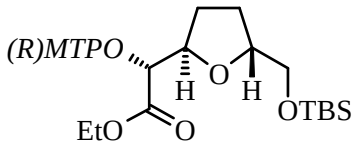
^{13}C NMR ($CDCl_3$, 50 MHz) : δ -5.39, -5.36, 14.15, 18.29, 25.66, 25.88, 27.87, 61.58, 65.69, 72.39, 80.40, 80.53, 172.42 ppm.

ESI MS (*m/z*) : 341.48 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 56.57; H, 9.49.

Found: C, 56.17; H, 9.43.

(*R*)-((*R*)-1((2*R*,5*R*)-5-((*tert*-butyldimethylsilyloxy)methyl)tetrahydrofuran-2-yl)-2ethoxy-2-oxoethyl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (103):



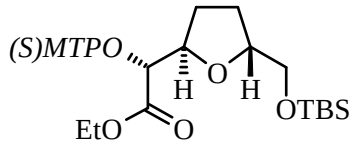
A solution of **101** (20 mg, 0.062 mmol), (*R*)-(−)-α-methoxy-α-trifluoromethyl phenylacetic acid (*R*-MTPA) (44 mg, 0.188 mmol), DCC (52 mg, 0.25 mmol) and DMAP (cat.) in CH_2Cl_2 (0.5 mL) was stirred for 48 h at room temperature. The reaction mixture was diluted with water, extracted with CH_2Cl_2. Combined organic layer was washed with brine, dried (Na_2SO_4), concentrated and the residue purified on silica gel column chromatography using 3% EtOAc in light petroleum ether (1:9) as an eluent to afford **103** (22 mg) as colorless liquid.

Yield : 65%

Mol. Formula : $C_{25}H_{37}F_3O_7Si$

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.01 (s, 6H), 0.86 (s, 9H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.77-1.92 (m, 4H), 3.40-3.50 (m, 2H), 3.67 (s, 3H), 4.04-4.30 (m, 3H), 4.41-4.49 (m, 1H), 5.33 (d, *J* = 3.5 Hz, 1H), 7.38-7.41 (m, 3H), 7.54-7.58 (m, 2H) ppm.

(*S*)-((*R*)-1((2*R*,5*R*)-5-((*tert*-butyldimethylsilyloxy)methyl)tetrahydrofuran-2-yl)-2ethoxy-2-oxoethyl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (102)



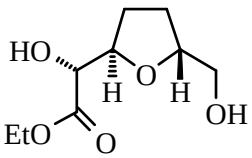
The reaction was carried out as described above using compound **101** (20 mg, 0.062 mmol), (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (*S*-MTPA) (44 mg, 0.188 mmol), DCC (52 mg, 0.25 mmol) and DMAP (cat.) in CH_2Cl_2 (0.5 mL). The residue was purified by silica gel column chromatography with EtOAc:light petroleum ether (3:97) as an eluent to afford **102** (19 mg) as thick oil.

Yield : 56%

Mol. Formula : $C_{25}H_{37}F_3O_7Si$

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.06 (s, 6H), 0.89 (s, 9H), 1.28 (t, *J* = 7.16 Hz, 3H), 1.68-1.79 (m, 1H), 1.83-1.99 (m, 3H), 3.53-3.65 (m, 5H), 3.98-4.08 (m, 1H), 4.23 (q, *J* = 7.17 Hz, 2H), 4.49-4.57 (m, 1H), 5.41 (d, *J* = 3.17 Hz, 1H), 7.37-7.44 (m, 3H), 7.56-7.63 (m, 2H) ppm.

(*R*)-ethyl 2-hydroxy-2-((2*R*,5*R*)-5-(hydroxymethyl)tetrahdrofuran-2-yl)acetate (104):



To a solution of **101** (1.29 g, 4.05 mmol) in THF (15 mL) was added TBAF (6.1 mL, 6.07 mmol, 1.0 M solution in THF) at 0 ^oC. The mixture was stirred at room temperature for 12 h. The reaction was quenched with saturated aqueous NH_4Cl solution. The aqueous layer was extracted with ethyl acetate twice. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (60% EtOAc/light petroleum ether) afforded **104** (789 mg) as a clear oil.

Yield : 95%

Mol. Formula : $C_9H_{16}O_5$

Optical Rotation $[\alpha]_D^{25}$: −14.2 (*c* 2.2, $CHCl_3$).

IR ($CHCl_3$) cm^{-1} : 3439, 3017, 2983, 2938, 1734, 1446, 1371, 1255, 1216, 1136, 1072, 930, 756, 667.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.27 (t, *J* = 7.2 Hz, 3H), 1.61-1.74 (m, 1H), 1.79-2.08 (m, 3H), 3.08 (bs, 2H), 3.45 (dd, *J* = 6.0, 11.8 Hz, 1H), 3.63 (dd, *J* = 3.1, 11.8 Hz, 1H), 4.10-4.36 (m, 5H) ppm.

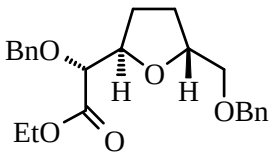
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 14.11, 25.73, 27.41, 61.42, 64.59, 72.28, 80.34, 80.83, 172.09 ppm.

ESI MS (*m/z*) : 227.22 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 52.93; H, 7.90.

Found: C, 52.21; H, 8.79.

(*R*)-ethyl 2-(benzyloxy)-2-((2*R*,5*R*)-5-(hydroxymethyl)tetrahdrofuran-2-yl)acetate (105):



A solution of **104** (500 mg, 2.45 mmol), Ag_2O (freshly prepared) (5.67 g, 24.48 mmol), BnBr (0.9 mL, 7.344 mmol) in EtOAc (15 mL) was stirred for 72 h at room temperature. The solid was filtered off, washed with ethyl acetate. The filtrate was concentrated, dried (Na_2SO_4), and the residue purified on silica gel column chromatography [EtOAc: Light petroleum ether (1:9)] to obtain **105** (826 mg).

Yield : 88%

Mol. Formula : $C_{23}H_{28}O_5$

Optical Rotation $[\alpha]_D^{25}$: +37.4 (*c* 0.9, $CHCl_3$)

IR ($CHCl_3$) cm^{-1} : 3063, 3030, 2927, 1745, 1496, 1454, 1368, 1262, 1199, 1087, 1028, 736, 697.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.21 (t, *J* = 7.2 Hz, 3 H), 1.58-1.72 (m, 1 H), 1.81-2.04 (m, 3 H), 3.37 (d, *J* = 5.0 Hz, 2 H), 4.01 (d, *J* = 4.4 Hz, 1 H), 4.06-4.23 (m, 3 H), 4.26-4.34 (m, 1 H), 4.42 (d, *J* = 11.7 Hz, 1 H), 4.48 (s, 2 H), 4.64 (d, *J* =

11.7 Hz, 1 H), 7.16-7.30 (m, 10 H) ppm.

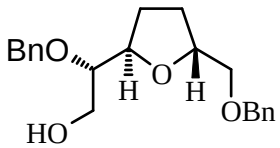
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 14.28, 26.51, 28.37, 60.83, 72.66, 72.83, 73.28, 79.00, 79.65, 80.67, 127.51, 127.60, 127.73, 127.86, 128.31, 137.60, 138.35, 170.73 ppm.

ESI MS (*m/z*) : 407.47 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 71.85; H, 7.34.

Found: C, 73.26; H, 7.61.

(*S*)-2-(benzyloxy)-2-((2*R*,5*R*)-5-(benzyloxymethyl)tetrahdrofuran-2-yl)ethanol (106):



To a solution of compound **105** (806 mg, 2.09 mmol) in THF (15 mL) at 0 ^oC was added $LiAlH_4$ (94 mg, 2.51 mmol) and stirred at 0 ^oC for 2 h. Excess of $LiAlH_4$ was quenched by the addition of ice-water. The solid formed was filtered off, and the filtrate was concentrated, purified by silica gel column chromatography eluting with light petroleum ether: EtOAc (1:4) to afford **106** (645 mg).

Yield : 90%

Mol. Formula : $C_{21}H_{26}O_4$

Optical Rotation $[\alpha]_D^{25}$: +15.4 (*c* 1.7, $CHCl_3$).

IR ($CHCl_3$) cm^{-1} : 3453, 3018, 2929, 1604, 1496, 1454, 1215, 1074, 1028, 928, 757, 698, 668.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.57-1.79 (m, 2H), 1.84-2.00 (m, 2H), 2.26 (bs, 1H), 3.38 (d, *J* = 5.0 Hz, 2H), 3.44 (q, *J* = 5.4 Hz, 1H), 3.54-3.70 (m, 2H), 3.96-4.06 (m, 1H), 4.09-4.18 (m, 1H), 4.49 (s, 2H), 4.60 (s, 2H), 7.19-7.26 (m, 10H) ppm.

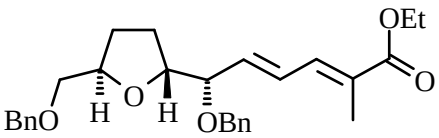
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 28.09, 28.32, 62.50, 72.55, 72.75, 73.22, 78.14, 80.16, 80.67, 127.50, 127.53, 127.68, 127.76, 128.27, 128.35, 138.16, 138.30 ppm.

ESI MS (*m/z*) : 365.43 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 73.66; H, 7.65.

Found: C, 72.73; H, 7.32.

(*S,2E,4E*)-ethyl 6-(benzyloxy)-6-((2*R*,5*R*)-5-(benzyloxymethyl)tetrahdrofuran-2-yl)-2-methylhexa-2,4-dienoate (94):



A solution of the alcohol compound **106** (0.94 g, 2.76 mmol) in THF (10 mL) was added to a solution of IBX (1.52 g, 5.52 mmol) in DMSO (3 mL) at room temperature. The reaction mixture was stirred for 4 h. Then cooled to 0 ^{o}C, and added ice-cooled water, followed by diethyl ether. After additional 30 min of stirring, filtered, organic layer was separated. Aqueous layer washed further with diethyl ether. The combined organic layer was washed with brine, dried over sodium sulfate (Na_2SO_4), and concentrated in vacuum to give crude aldehyde **95** (1.02 g). The crude aldehyde was used for the next reaction without further purification.

To a freshly prepared solution of LDA [(6.0 mmol; prepared by adding 3.75 mL of 1.6 M *n*-BuLi to a solution of 0.6 mL (6.6 mmol) of diisopropylamine in dry THF at 0 ^{o}C, and stirred at the same temperature for 15 min)] at –78 ^{o}C was added phosphonate **38** (2.18 g, 8.28 mmol). After 30 min at –78 ^{o}C, the crude aldehyde **95** (1.02 g) in THF was added. The reaction mixture was allowed to attain 0 ^{o}C over a period of 2 h, quenched with saturated aqueous ammonium chloride solution, and the layers separated. The aqueous layer was extracted with diethyl ether, washed with water, dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash column chromatography, eluting with light petroleum ether/ethyl acetate (19:1) to afford **94** (0.89 g) as yellowish transparent oil.

Yield : 72%

Mol. Formula : $C_{28}H_{34}O_5$

Optical Rotation $[\alpha]_D^{25}$: +51.4 (*c* 1.45, $CHCl_3$).

IR ($CHCl_3$) cm^{-1} : 3425, 3019, 2928, 1709, 1602, 1453, 1269, 1216,

1097, 1027, 757, 698, 668.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.32 (t, *J* = 7.2 Hz, 3H), 1.64-1.85 (m, 2H), 1.91-2.07 (m, 2H), 1.95(d, *J* = 1.3 Hz, 3H), 3.40-3.53 (m, 2H), 3.98 (dd, *J* = 4.7, 6.9 Hz, 1H), 4.07- 4.13 (m, 1H), 4.16-4.27 (m, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 4.46 (d, *J* = 12.1 Hz, 1H), 4.56-4.57 (m, 2H), 4.64 (d, *J* = 12.1 Hz, 1H), 6.02 (dd, *J* = 7.0, 15.3 Hz, 1H), 6.56 (ddd, *J* = 1.0, 11.4, 15.3 Hz, 1H), 7.21 (d, *J* = 11.4 Hz, 1H), 7.28-7.34 (m, 10H) ppm.

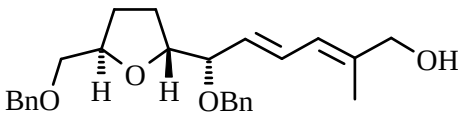
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 12.71, 14.27, 27.01, 28.37, 60.46, 71.09, 72.62, 73.19, 78.66, 81.39, 127.41, 127.46, 127.51, 127.57, 127.68, 128.21, 137.02, 138.27, 168.05 ppm.

ESI MS (*m/z*) : 473.57 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 74.64; H, 7.61.

Found: C, 74.94; H, 7.41.

(*S,2E,4E*)-6-(benzyloxy)-6-((2*R*,5*R*)-5-(benzyloxymethyl)tetrahdrofuran-2-yl)-2-methylhexa-2,4-dien-1-ol (107):

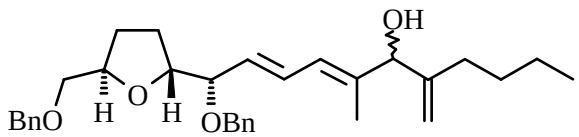


The ester **94** (0.45 g, 0.99 mmol) was dissolved in anhydrous dichloromethane (10 mL) under nitrogen (N_2) atmosphere. The solution was cooled to –78 ^oC, and DIBALH (1.534 M in toluene, 1.6 mL) was slowly added over a period of 5 min. The solution was stirred for 2 h at –78 ^oC before the reaction was quenched with methanol. The reaction mixture was allowed to warm to 0 ^oC before an aqueous saturated solution of sodium potassium tartrate was added. The reaction mixture was starred at room temperature for 12 h. The aqueous phase was extracted with dichloromethane, and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under vacuum. Purification by silica gel column chromatography afforded alcohol **107** (0.38 g) as colorless oil.

Yield : 94%

Mol. Formula	: $C_{26}H_{32}O_4$
Optical Rotation $[\alpha]_D^{25}$	: +47.7 (*c* 1.5, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	: 3418, 3019, 2927, 2400, 1719, 1600, 1453, 1421, 1215, 1072, 928, 757, 699, 669.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.56-1.75 (m, 1H), 1.80 (s, 3H), 1.84-2.05 (m, 3H), 3.40-3.56 (m, 2H), 3.87-3.96 (m, 1H), 4.07-4.24 (m, 4H), 4.43 (d, *J* = 12.1 Hz, 1H), 4.56 (s, 2H), 4.63 (d, *J* = 12.1, 1H), 5.63 (dd, *J* =7.7, 15.2 Hz, 1H), 6.11 (d, *J* = 11.0 Hz, 1H), 6.47 (dd, *J* = 11.0, 15.2 Hz, 1H), 7.27-7.33 (m, 10H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 14.21, 27.00, 28.52, 29.68, 68.10, 70.53, 72.76, 73.26, 78.66, 81.70, 81.93, 124.01, 127.34, 127.46, 127.60, 128.24, 128.27, 129.47, 130.47, 137.93, 138.37, 138.71 ppm.
ESI MS (*m/z*)	: 431.53 $[M+Na]^+$
Elemental Analysis	**Calcd:** C, 76.44; H, 7.90.
	Found: C, 76.41; H, 7.89.

(*R*,*2E*,*4E*)-1-(benzyloxy)-1-((2*R*,5*R*)-5-(benzyloxymethyl)tetrahdrofuran-2-yl)-5-methyl-7-methyleneundeca-2,4-dien-6-ol (108):

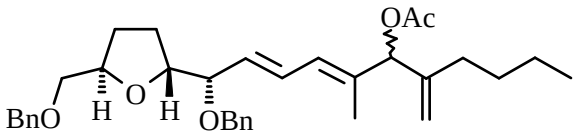


To a stirred solution of IBX (0.14 g, 0.51 mmol) in DMSO (0.3 mL), was added a solution of alcohol **107** (0.11 g, 0.26 mmol) in THF (10 mL) at room temperature, and stirring was continued for further 2 h. After completion of the reaction, water, followed by ether was added. Stirred it for additional 30 min before it was filtered. Organic layer was separated, and the aqueous layer was washed two times with ether. The combined organic layer was washed with brine, dried over Na_2SO_4, concentrated under vacuum. The crude product **93** (0.14 g) was used immediately for the next reaction without further purification.

To a mixture of crude aldehyde **93** (0.14 g) and halide **36** (0.38 g, 1.799 mmol) in DMSO (properly degassed) (25 mL) was added $CrCl_2$ (0.22 g, 1.799 mmol), followed by $NiCl_2$ (cat). The reaction mixture was stirred overnight at room temperature. Saturated aqueous ammonium chloride (NH_4Cl) was added and extracted with ether. The whole organic layer was washed with brine and dried over Na_2SO_4. The crude product was purified by flash chromatography (Ethyl Acetate/light petroleum Ether: 1/9) to afford the required fragment as two diastereomers **108** (0.98 g) as colorless oil.

Yield	: 78%
Mol. Formula	: $C_{32}H_{42}O_4$
Optical Rotation $[\alpha]_D^{25}$	: +11.1 (*c* 0.85, $CHCl_3$).
IR ($CHCl_3$) cm^{-1}	: 3445, 3018, 2959, 2931, 2872, 2400, 1717, 1636, 1496, 1454, 1382, 1216, 1087,1028, 927, 757, 698, 668, 625.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.90 (t, *J* = 7.1 Hz, 3H), 1.29-1.50 (m, 4H), 1.67 (s, 3H), 1.62-1.72 (m, 2H), 1.85-2.02 (m, 4H), 3.41-3.54 (m, 2H), 3.88-3.94 (m, 1H), 4.05-4.16 (m, 1H), 4.20-4.29 (m, 1H), 4.41-4.61 (m, 5H), 4.97 (s, 1H), 5.15 (s, 1H), 5.66 (dd, *J* = 7.7, 15.2 Hz, 1H), 6.18 (d, *J* = 10.9 Hz, 1H), 6.47 (dd, *J* = 10.9, 15.2 Hz, 1H), 7.28-7.38 (m, 10H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 12.35, 12.38, 13.97, 22.49, 27.00, 28.52, 30.10, 31.63, 70.63, 70.69, 72.82, 73.30, 78.68, 79.89, 81.74, 81.76, 81.89, 109.96, 110.01, 125.82, 125.88, 126.97, 127.36, 127.49, 127.65, 128.26, 128.30, 128.55, 129.50, 129.61, 138.20, 138.22, 138.4, 138.78, 140.87, 149.35, 149.37 ppm.
ESI MS (*m/z*)	: 513.67 $[M+Na]^+$
Elemental Analysis	**Calcd:** C, 78.33; H, 8.63.
	Found: C, 78.12; H, 8.49.

(*S*,*2E*,*4E*)-1-(benzyloxy)-1-((2*R*,5*R*)-5-(benzyloxymethyl)tetrahdrofuran-2-yl)-5-methyl-7-methyleneundeca-2,4-dien-6-yl acetate (109):



A mixture of **108** (30 mg, 0.061 mmol), triethylamine (0.09 mL, 0.61 mmol), acetic anhydride (0.05 mL, 0.61 mmol) and catalytic amount of DMAP in dichloromethane was stirred for 1 h at room temperature. The reaction mixture was diluted with dichloromethane, washed with brine, dried over sodium sulphate. After evaporation under reduced pressure, the residue purified by silica gel column chromatography using light petroleum: ethyl acetate (19:1) to obtain **109** (28 mg).

Yield : 86%

Mol. Formula : $C_{34}H_{44}O_5$

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.92 (t, *J* = 7.2 Hz, 3H), 1.30-1.38 (m, 2H), 1.42-1.48 (m, 2H), 1.68-1.74 (m, 1H), 1.72 (s, 3H), 1.87-2.05 (m, 5H), 2.13 (s, 3H), 3.46-3.54 (m, 2H), 3.93-3.97 (m, 1H), 4.11-4.16 (m, 1H), 4.21-4.29 (m, 1H), 4.47 (dd, *J* = 2.8, 12.1 Hz, 1H), 4.57 (d, *J* = 12.2 Hz, 1H), 4.61 (d, *J* = 12.2 Hz, 1H), 4.66 (d, *J* = 12.1 Hz, 1H), 4.99 (s, 1H), 5.08 (s, 1H), 5.60 (s, 1H), 5.70 (dd, *J* = 7.6, 15.3 Hz, 1H), 6.17 (d, *J* = 11.1 Hz, 1H), 6.48 (dd, *J* = 11.1, 15.3 Hz, 1H), 7.28-7.36 (m, 10H) ppm.

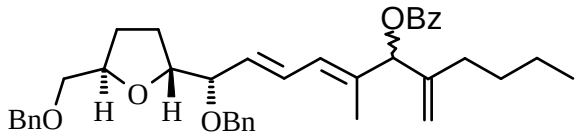
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 12.92, 12.95, 13.94, 21.20, 22.38, 26.95, 26.99, 28.50, 29.66, 29.79, 31.31, 31.94, 70.73, 70.75, 72.80, 73.29, 78.67, 80.44, 81.70, 81.74, 81.89, 111.12, 127.25, 127.29, 127.37, 127.49, 127.63, 128.25, 128.30, 129.04, 129.09, 131.74, 131.76, 134.33, 138.40, 138.74, 145.69, 145.71, 169.78 ppm.

ESI MS (*m/z*) : 555.71 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 76.66; H, 8.33.

Found: C, 76.49; H, 8.04.

(*S*,*2E*,*4E*)-1-(benzyloxy)-1-((2*R*,5*R*)-5-(benzyloxymethyl)tetrahdrofuran-2-yl)-5-methyl-7-methyleneundeca-2,4-dien-6-yl benzoate (112):



To a solution of **108** (19 mg, 0.038 mmol) in CH_2Cl_2 (5 mL) was added, Et_3N (0.05 mL, 0.385 mmol), benzoyl chloride (0.03 mL, 0.308 mmol) and DMAP (cat.) at 0 ^oC. The reaction mixture was stirred for 24 h at room temperature, diluted with CH_2Cl_2, washed with water, brine, dried (over Na_2SO_4) and concentrated. The residue was purified on silica gel column chromatography by using EtOAc:light petroleum ether (1:19) to obtain **112** (9 mg) as a yellow color liquid.

Yield : 39%

Mol. Formula : $C_{39}H_{46}O_5$

^{1}H NMR ($CDCl_3$, 400 MHz) : δ 0.91-0.97 (m, 3H), 1.35-1.41 (m, 2H), 1.48-1.55 (m, 1H), 1.64-1.75 (m, 3H), 1.82 (s, 3H), 2.00-2.08 (m, 4H), 3.47-3.54 (m, 2H), 3.95-3.99 (m, 1H), 4.13-4.19 (m, 1H), 4.24-4.30 (m, 1H), 4.48 (dd, *J* = 3.23, 12.02 Hz, 1H), 4.57 (d, *J* = 12.2 Hz, 1H), 4.61 (d, *J* = 12.2 Hz, 1H), 4.66 (d, *J* = 12.1 Hz, 1H), 5.04 (s, 1H), 5.20 (s, 1H), 5.72 (dd, *J* = 7.9, 15.6 Hz, 1H), 5.87 (s, 1H), 6.28 (d, *J* = 11.0 Hz, 1H), 6.51 (dd, *J* = 11.0, 15.1 Hz, 1H), 7.33-7.39 (m, 10H), 7.45-7.47 (m, 2H), 7.58-7.60 (m, 1H), 8.08-8.13 (m, 2H) ppm.

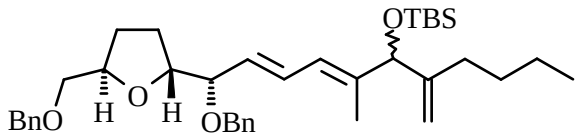
^{13}C NMR ($CDCl_3$, 100 MHz) : δ 13.01, 13.66, 13.98, 22.44, 22.70, 26.99, 27.86, 28.51, 29.70, 29.86, 32.05, 70.81, 72.78, 73.31, 78.73, 80.42, 81.06, 81.79, 81.90, 82.06, 111.38, 127.40, 127.52, 127.69, 128.28, 128.33, 128.49, 129.39, 129.66, 130.22, 131.69, 133.00, 133.78, 138.39, 138.76, 145.72, 165.30 ppm.

ESI MS (*m/z*) : 617.33 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 78.75; H, 7.80.

Found: C, 78.69; H, 7.57.

((*S*,*2E*,*4E*)-1-(benzyloxy)-1-((2*R*,5*R*)-5-(benzyloxymethyl)tetrahdrofuran-2-yl)-5-methyl-7-methyleneundeca-2,4-dien-6-yloxy)(*tert*-butyl)dimethylsilane (110):



To a solution of alcohol **108** (15 mg, 0.03 mmol) in DMF (1 mL) was added imidazole (6 mg, 0.091 mmol), DMAP (cat.) and TBDMSCl (9 mg, 0.061 mmol) at 0 °C. The resulting mixture was allowed to warm to room temperature slowly and stirred for 12 h. The reaction mixture was then partitioned between ethyl acetate and water. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel by using EtOAc: light petroleum ether (3:97) to give silyl ether **110** as colorless oil (5 mg).

Yield : 27%

Mol. Formula : $C_{38}H_{56}O_4Si$

^{1}H NMR ($CDCl_3$, 400 MHz) : δ −0.01-0.02 (m, 6H), 0.87-0.90 (m, 12H), 1.27-1.31 (m, 2H), 1.36-1.42 (m, 2H), 1.59 (s, 3H), 1.66-1.71 (m, 1H), 1.80-1.91 (m, 3H), 1.94-2.00 (m, 2H), 3.43-3.50 (m, 2H), 3.89-3.92 (m, 1H), 4.09-4.14 (m, 1H), 4.20-4.24 (m, 1H), 4.40 (s, 1H), 4.44 (d, *J* = 12.16 Hz, 1H), 4.53 (d, *J* = 12.4 Hz, 1H), 4.57 (d, *J* = 12.4 Hz, 1H), 4.62 (dd, *J* = 2.2, 12.15 Hz, 1H), 4.85 (s, 1H), 5.10 (s, 1H), 5.58 (dd, *J* = 7.81, 15.25 Hz, 1H), 6.09 (d, *J* = 11.04 Hz, 1H), 6.43 (dd, *J* = 11.03, 15.29, 1H), 7.29-7.36 (m, 10H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz) : δ −5.01, 12.11, 12.19, 14.02, 18.31, 22.55, 25.83, 26.94, 28.55, 29.69, 30.08, 30.70, 30.76, 53.40, 70.63, 72.84, 73.30, 78.69, 80.67, 81.83, 82.04, 82.11, 109.77, 109.83, 124.65, 124.82, 127.34, 127.49,

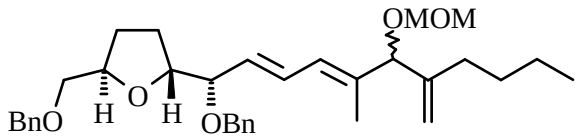
127.65, 128.25, 128.31, 129.64, 129.72, 129.99, 130.07, 138.45, 138.86, 139.36, 149.63, 149.66 ppm.

ESI MS (*m/z*) : 627.93 $[M+Na]^+$

Elemental Analysis **Calcd:** C, 75.45; H, 9.33.

Found: C, 75.19; H, 9.29.

((2*R*,5*R*)-2-((*S*,*2E*,*4E*)-1-(benzyloxy)-6-(methoxymethyl)-5-methyl-7-methyleneundeca-2,4-dienyl)-5-(benzyloxymethyl)tetrahdrofuran (111):



To a solution of **108** (20 mg, 0.04 mmol) in CH_2Cl_2 (0.5 mL) was added diisopropylethylamine (0.07 mL, 0.407 mmol) followed by MOMCl (6 mg, 0.081 mmol) at room temperature. The reaction mixture was stirred at room temperature for overnight. The reaction was quenched with H_2O. The aqueous layer was extracted with CH_2Cl_2 twice. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column cromatography (5% EtOAc/Light petroleum ether) afforded **111** (8 mg) as thick liquid.

Yield : 36%

Mol. Formula : $C_{34}H_{46}O_5$

^{1}H NMR ($CDCl_3$, 400 MHz) : δ 0.82 (t, *J* = 7.28 Hz, 3H), 1.21-1.26 (m, 2H), 1.30-1.39 (m, 2H), 1.57 (s, 3H), 1.60-1.65 (m, 1H), 1.78-1.94 (m, 4H), 3.30 (s, 3H), 3.38-3.44 (m, 2H), 3.84-3.89 (m, 1H), 4.02-4.07 (m, 1H), 4.13-4.19 (m, 1H), 4.34 (s, 1H), 4.38 (d, *J* = 12.11 Hz, 1H), 4.46-4.64 (m, 6H), 4.91 (s, 1H), 5.07 (s, 1H), 5.57 (dd, *J* = 7.71, 15.29 Hz, 1H), 6.10 (d, *J* = 11.17 Hz, 1H), 6.40 (dd, *J* = 11.02, 15.24 Hz, 1H), 7.22-7.31 (m, 10H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz) : δ 12.70, 13.99, 22.48, 26.97, 28.53, 29.68, 29.97, 31.58, 31.64, 55.52, 70.71, 72.82, 73.30, 78.67, 81.77, 82.00, 82.02, 82.68, 93.53, 111.12, 111.18, 126.74,

	126.79, 127.36, 127.49, 127.65, 128.26, 128.31, 129.51, 130.75, 130.79, 136.02, 138.44, 138.82, 146.85 ppm.
ESI MS (*m/z*)	: 557.73 $[M+Na]^+$
Elemental Analysis	**Calcd:** C, 76.37; H, 8.67.
	Found: C, 76.17; H, 8.49.

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List of Publications

1. Synthesis of C19-C34 Segment of Amphidinolide C. Debendra K. Mohapatra, **Hasibur Rahaman**, Mukund S. Chorghade and Mukund K. Gurjar. *Synlett* **2007**, 567.
2. Synthesis of C14-C29 Segment of Amphidinolide U: Utilizing a Tandem Dihydroxylation-S_N2 Cyclization Protocol. Debendra K. Mohapatra and **Hasibur Rahaman**. *Synlett* **2008**, 0837-0840.
3. Total Synthesis of (S)-(─)-Curvularin: A Ring-Closing Metathesis Based Construction of the Macrocyclic Framework. Debendra K. Mohapatra, **Hasibur Rahaman**, Rita Pal and Mukund K. Gurjar. *Synlett* **2008**, 1801-1804.
4. A Carbohydrade Based Total Synthesis of Xestodecalactone B and C: Revision of the Absolute Configuration. *(Under Manuscript).*
5. A Stereoselective Synthesis of the Densely Functionalized C1-C9 Fragment of Amphidinolide C. (*Under Manuscript*).