SYNTHETIC STUDIES TOWARD PELORUSIDE A, CLAVOSOLIDES AND TEMPERATURE DEPENDENT ISOMERISATION VERSUS NET FRAGMENTATION OF SECONDARY ALLYLIC ALCOHOLS WITH GRUBBS' CATALYST

A THESIS
SUBMITTED TO THE
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IN CHEMISTRY

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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**, Deputy director, and Head, Division of Organic Chemistry: Technology, National Chemical Laboratory, Pune - 411008. This work is original and has not been submitted part or full, for any degree or diploma of this or any other University.

(Pedduri Yakambram)

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CERTIFICATE

The research work presented in thesis entitled "**Synthetic studies toward Peloruside A, Clavosolides and Temperature dependent isomerisation versus net fragmentation of secondary allylic alcohols with Grubbs' catalyst**" has been carried out under my supervision and is a bonafide work of **Mr. Pedduri Yakambram**. This work is original and has not been submitted for any other degree or diploma of this or any other University.

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Research Guide

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CONTENTS

GENERAL REMARKS

- ^{1}H NMR spectra were recorded on AC-200 MHz, MSL-300 MHz, DRX-400 and DRX-500 MHz spectrometers 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 spectrometers.
- 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 were 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.

List of abbreviations

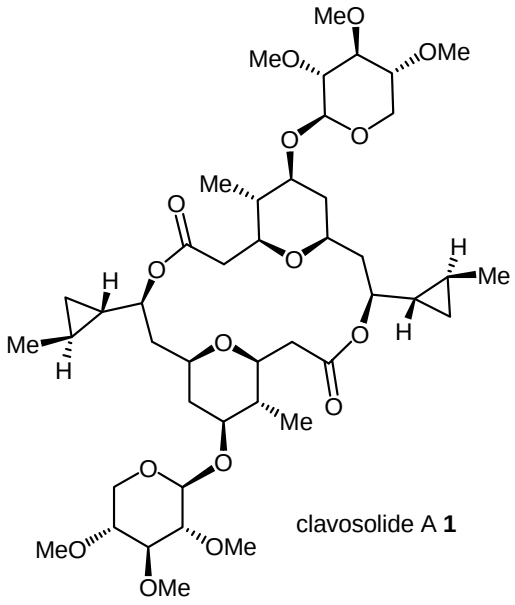
Ac	-	Acetyl
Ac_2O	-	Acetic anhydride
AcOH	-	Acetic acid
AIBN	-	2,2'-Azobisisobutyronitrile
$H_3B{:}SMe_2$	-	Borane-dimethyl sulfide complex
BnBr	-	Benzyl bromide
n-BuLi	-	*n*-Butyl lithium
n-Bu_3SnH	-	*n*-Tributyltin hydride
m-CPBA	-	*m*-Chloroperbenzoic acid
CSA	-	Camphor sulfonic acid
Cy_2BCl	-	Chlorodicyclohexylborane
DBU	-	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	-	Dicyclohexylcarbodiimide
DDQ	-	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	-	Diisopropyl azodicarboxylate
DIPEA	-	Diisopropyl ethylamine
2,2-DMP	-	2,2-Dimethoxypropane
DMP	-	Dess-Martin Periodinane
DIBAL	-	Diisobutylaluminum hydride
DMF	-	Dimethylformamide
DMSO	-	Dimethylsulfoxide
4-DMAP	-	4-Dimethylaminopyridine
Et_3N	-	Triethylamine (TEA)
EtOH	-	Ethanol
Im	-	Imidazole
LAH or $LiAlH_4$	-	Lithium aluminium hydride
LiHMDS	-	Lithium hexamethyl disilazane
LDA	-	Lithium diisopropylamine
MeI	-	Methyl iodide

MeOH	-	Methanol
Ms or Mesyl	-	Methanesulfonyl
MsCl	-	Methanesulfonyl chloride
NaOAc	-	Sodium acetate
NMM	-	*N*-Methylmorpholine
NMO	-	*N*-Methylmorpholine *N*-oxide
Pd/C	-	Palladium on Carbon
$Pd(OH)_2/C$	-	Palladium hydroxide on Carbon
PivCl	-	Trimethylacetyl chloride
PMB-Br	-	*p*-Methoxybenzyl bromide
PMB-Cl		*p*-Methoxybenzyl chloride
Py	-	Pyridine
PPh_3	-	Triphenylphosphine
PPTS	-	Pyridinium *p*-toluenesulfonate
TBSCl	-	*tert*-Butyldimethylsilyl chloride
TBSOTf	-	*tert*-Butyldimethylsilyl triflate
p-TSA	-	*p*-Toluenesulfonic acid
TBAF	-	Tetra-*n*-butylammonium fluoride
TBAI	-	Tetra-*n*-butylammonium iodide
Tf_2O	-	Trifluoromethanesulphonic anhydride
TIPSCl	-	Triisopropylsilyl chloride
TMSOTf	-	Trimethylsilyl trifluoromethanesulphonate
TPAP	-	Tetra-*n*-propylammonium perruthenate (VII)
Trt or Tr	-	Triphenylmethyl (trityl)
TsCl	-	*p*-Toluenesulfonyl chloride

Abstract

The thesis entitled “Synthetic studies toward Peloruside A, Clavosolides and Temperature dependent isomerisation versus net fragmentation of secondary allylic alcohols with Grubbs’ catalyst” consists of three chapters and each chapter is further sub-divided into following sections: Introduction, Present work, Experimental, Spectroscopic data and References. Chapter I describes the synthesis of clavosolide A. Chapter II, section I, deals with synthesis of C1-C11 fragment of anti-tumor macrolide peloruside A using chiral-pool strategy, whereas section II involves stereoselective synthesis of C1-C9 fragment of peloruside A. The final chapter III highlights a new transformation with Grubbs’ I generation metathesis catalyst involving isomerisation of secondary allylic alcohols into corresponding ethyl ketones.

CHAPTER 1: Towards the total synthesis of clavosolide A



clavosolide A **1**

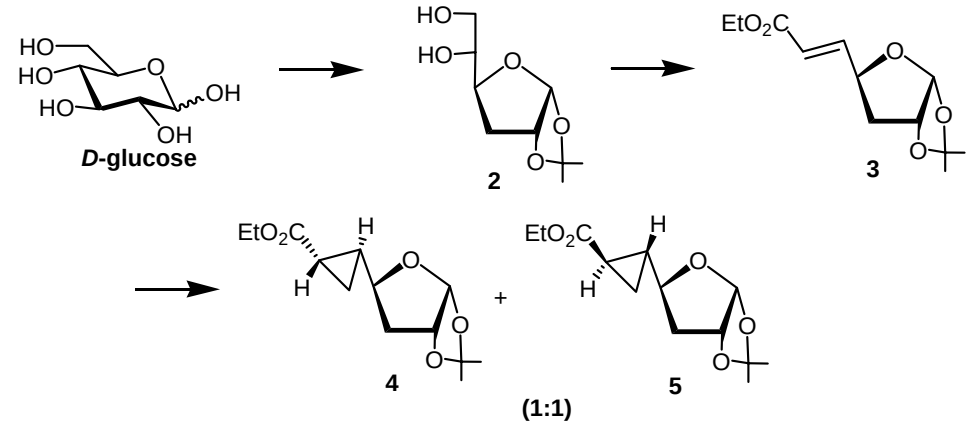
Marine organisms, particularly sponge invertebrates and associated bacteria, are enormously rich source of structurally diverse secondary metabolites with unique molecular architectures and marine macrolides isolated from sponges found to possess profound biological activities (*e.g.* anti cancer), making them valuable molecular probes for the investigation of biochemical transformations. Marine sponge *Myriastra Clavosa* collected from Phillipines provided structurally distinct unusual diolide clavosolide A (**4**)

in very minute quantity. Extensive spectroscopic studies coupled with molecular modeling provided the structure and stereochemistry of clavosolide A. Clavosolide A (**1**) is a symmetric 16-membered diolide whose monomeric unit contains a densely functionalized tetrahydropyran ring glycosylated with permethylated β-xylopyronose and a rare 1,2-disubstituted cyclopropane ring.

Carbohydrate embedded with cyclopropane ring can provide interesting class of compounds containing strained, reactive cyclopropane ring on optically dense chiral template to develop new synthetic pathways to access complex bioactive compounds. Similarly, our synthetic strategy was based on the study of stereoselective cyclopropanation of unsaturated furanose (**3** or **10**) as the key step to obtain the crucial *syn*-cyclopropyl moiety in clavosolide A (**1**).

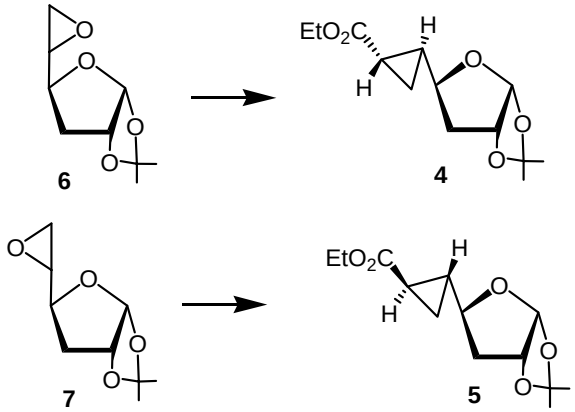
Thus, D-Glucose was converted into 3-deoxy-1,2-*O*-isopropylidene-α-D-*ribo*-hexofuranose **2** using Barton-McCombie deoxygenation followed by acid hydrolysis. The diol **2** was subjected to oxidative cleavage and subsequent two carbon Wittig homologation with $Ph_3P{=}CHCO_2Et$ afforded α,β-unsaturated ester **3**. In order obtain the requisite 5,6-cycloprpopane furanose derivative, compound **3** was treated with enolate of triethylphosphonoacetate under Corey-Chaykovsky reaction conditions to furnish a diastereomeric mixture (1:1) of *trans*-5,6-cyclopropane derivatives **4** and **5** (Scheme 1).

Scheme 1



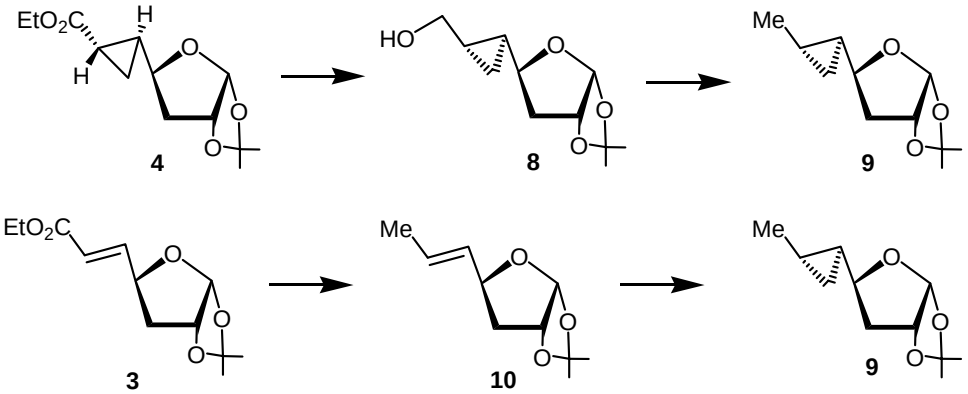
Stereochemistry of the cyclopropane of **4** and **5** was determined *via* chiral pool approach using Wadsworth-Emmons cyclopropanation of anhydrosugars **6** and **7**. Accordingly, anhydrosugars **6** and **7** were prepared from the diol **2**. Wadsworth-Emmons cyclopropanation of **6** and **7** was studied by using different bases (*n*-BuLi, NaH, *t*-BuOK) to obtain **4** and **5** respectively (Scheme 2). Furthermore, the structure of **5** was

Scheme 2



unambiguously determined by its single crystal X-ray studies. The requisite 5,6-cyclopropyl derivative **4**was transformed into cyclopropyl methane derivative **9** in three steps, (i) reduction of ester **4**, (ii) nucleophilic displacement with phenyl sulfide of the resulting alcohol and (iii) desulfurisation of corresponding sulphide derivative using Raney-Ni (Scheme 3). Having established the stereochemistry of **9**, a scalable approach was devised following a sequence of reactions, involving reduction of ester **3** using DIBAL-H at −78 °C, chlorination and subsequent reductive dehalogenation to afford the *trans*-olefinic derivative **10**. Simmons-Smith cyclopropanation of **10** using Et_2Zn-CH_2I_2 at −40 °C gave **9** exclusively in quantitative yield (Scheme 3).

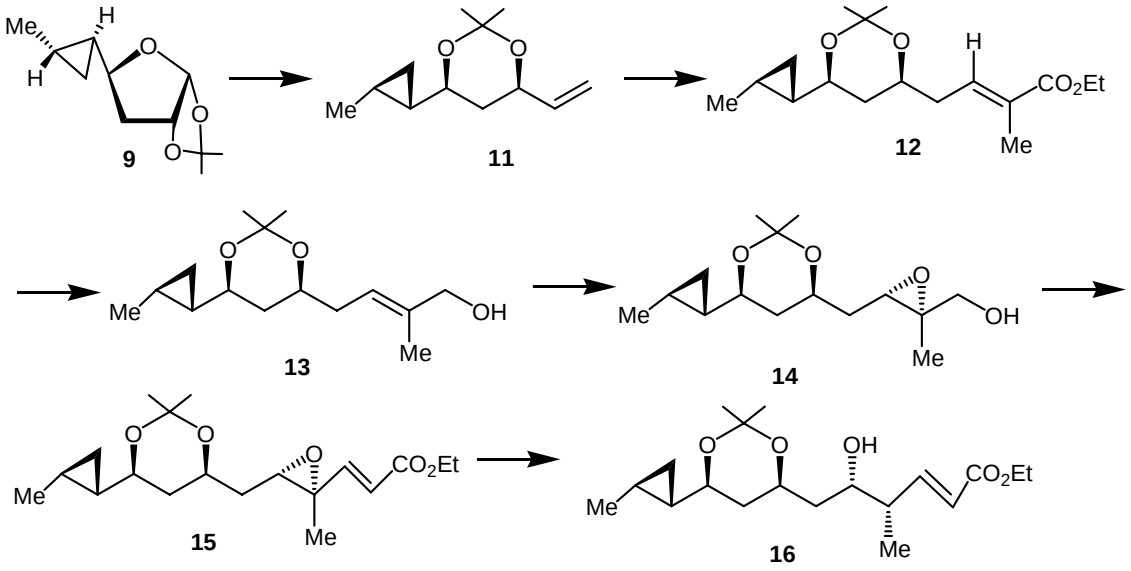
Scheme 3



The compound **9** undewent a sequence of simple and straightforward reactions involving acid hydrolysis of 1,2-acetonide in **9**, one carbon Wittig olefination and protection of resulting 1,3-diol to provide α-olefinic derivative **11**. Hydroboration, oxidation of **11** and Wittig homologation with PPh_3=CH(Me)CO_2Et afforded the α,β-unsaturated ester **12** whose reduction with DIBAL-H gave the allylic alcohol **13**. Sharpless

asymmetric epoxidation of **13** using (+)-DIPT at –20 ^{o}C gave the epoxy alcohol **14** (Scheme 4). Subsequent oxidation and Wittig reaction with $Ph_3P{=}CH_2CO_2Et$ on **14** provided the key epoxy enoate **15**. The regio- and stereoselective hydrogenolysis of the epoxy enoate **15** using BH_3:Me_2NH-AcOH in the presence of catalytic amount of $Pd[PPh_3]_4$ provided the requisite homoallylic alcohol **16**. The derived TBS-ether derivative

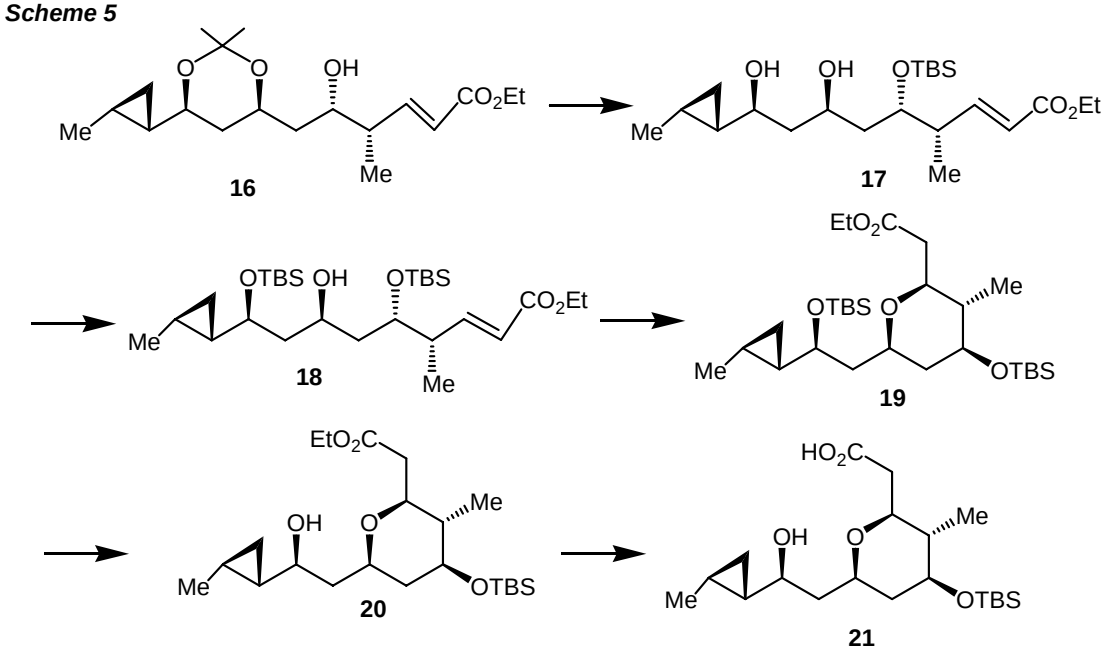
Scheme 4



from **16** was subjected to acetonide deprotection to give the diol **17** and the difference in reactivity of the two hydroxyl groups was exploited to protect selectively cyclopropyl alcohol giving rise to the *bis*-TBS ether derivative **18**. The intramolecular 1,4-Michael addition was carried out in the presence catalytic LiOH in THF to convert **18** in to the tetrahydropyran ring derivative **19** along with the other diastereomer. The 2D NOESY spectrum of **19** established the relative stereochemistry of three new chiral centers generated in the synthetic sequence followed. Selective deprotection of TBS group in compound **19** was achieved with catalytic PPTS in MeOH to afford the hydroxy ester compound **20**. Finally, the hydrolysis of the ester group of **20** gave the monomeric seco acid **21** of clavosolide A **1** (Scheme 5).

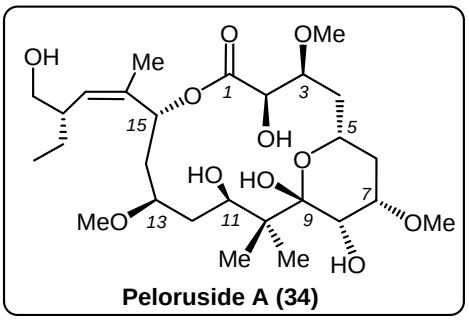
In conclusion, we have accomplished the synthesis of proposed structure of monomeric seco acid unit of diolide clavosolide A, starting from D-glucose using a flexible strategy to determine the stereochemistry of cyclopropane moiety in the early stages of synthesis.

Scheme 5



CHAPTER II: Towards the synthesis of peloruside A

Section I: A chiral pool approach for the synthesis of C_1-C_{11} segment of peloruside A

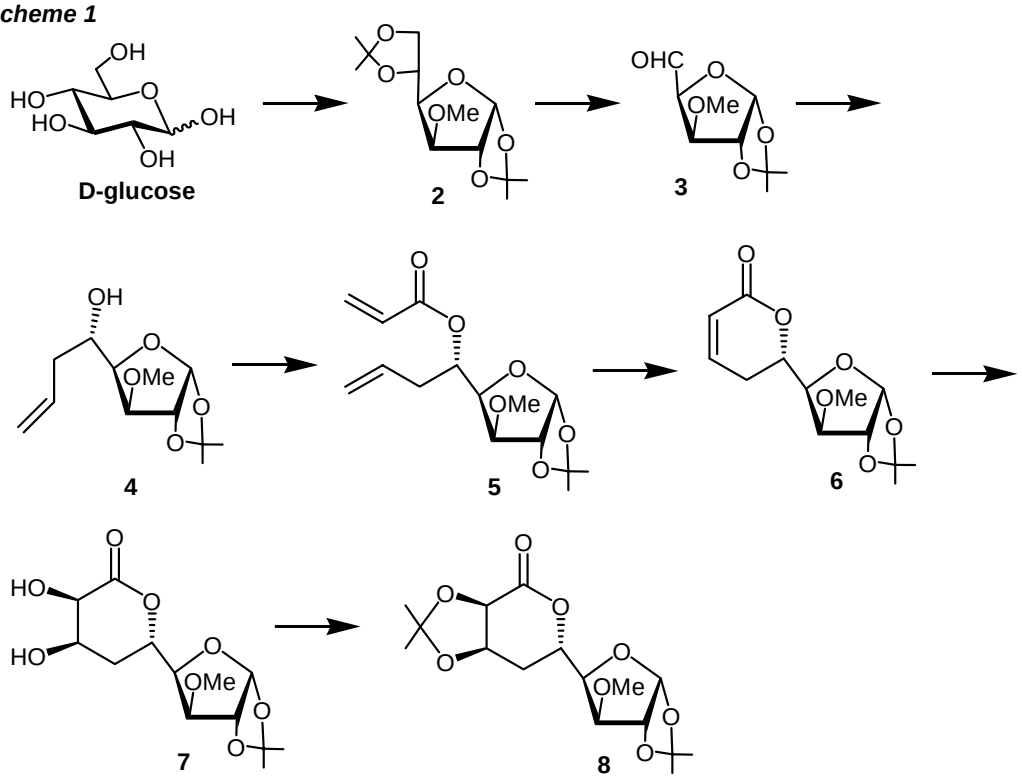


Peloruside A (**1**) is a recently discovered antimitotic macrolide isolated from New Zealand Marine sponge *Mycale sp*. Northcore and co-workers established its structure as a polyoxygenated 16-membered macrolide with an integrated pyranose ring and a branched unsaturated side chain, and its relative stereochemistry. Peloruside A was found to be cytotoxic to P388 murine leukemia cells as well to other cancer cells and recent studies demonstrated that the peloruside functions by promoting tubulin polymerization by interfering with microtubule dynamics like taxol and other microtubule stabilizing agents. In light of the inherent interest generated by promising biological activity, and with a

necessity to determine its absolute structure, peloruside A has been identified as an appropriate target for total synthesis.

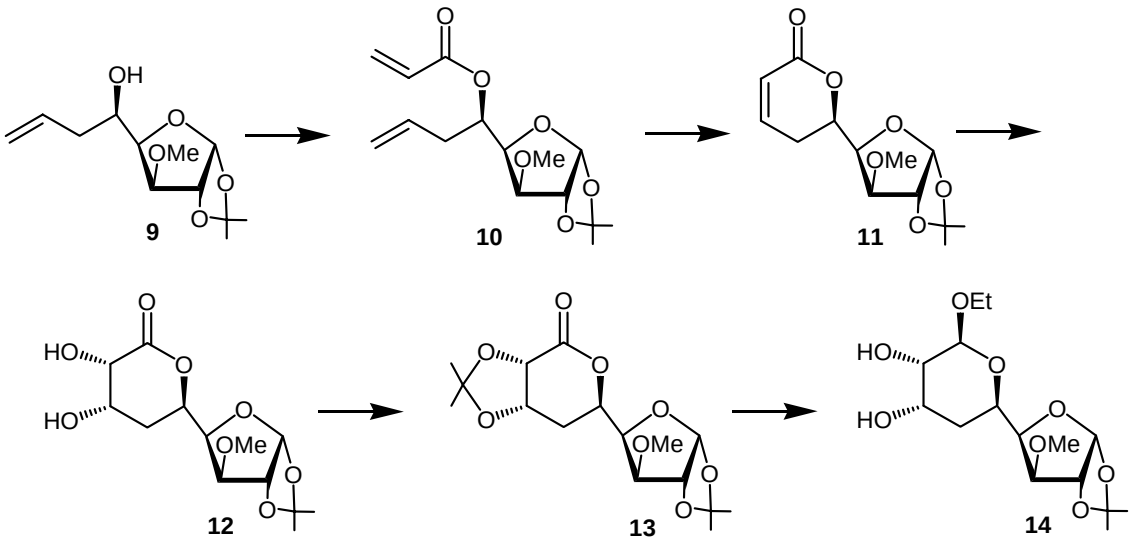
Our initial strategy for the synthesis of C_1-C_{11} segment of peloruside A **1** was envisaged from D-glucose. In this regard, asymmetric induction of L-idofuranose monosachharide unit to its emerging side chain, α,β-unsaturated-δ-valerolactone moiety (**6**) in the dihydroxylation reaction was studied. Thus, synthesis of **6** was initiated by using ring closing metathesis reaction on the corresponding diene **5**, obtained from 3-*O*-methyl-1,2:5,6-di-*O*-isopropylidene-α-*D*-glucofuranose **2**. Allylation of aldehyde **3** under Sakurai conditions using allyltrimethylsilane and $TiCl_4$ gave required 5*S*-homoallylalcohol derivative **4** which was treated with acryloyl chloride and DIPEA to provide the diene **5**. Ring-closing metathesis of **5** with Grubbs' catalyst gave theα,β-unsaturated δ-valerolactone **6** and the dihydroxylation of **6** provided a single diastereomer **7** which was characterized as its acetonide derivative **8** (Scheme 1). The structure of **8** was established by 2D NOESY experiment. Furthermore, the structure of **8** was unambiguously deduced by its X-ray diffraction studies. As the dihydroxylaiton **6** having correct stereochemistry at C-5 gave the undesired diol compound **7**, an alternate dihydroxylation on C_5-epimeric δ-

Scheme 1



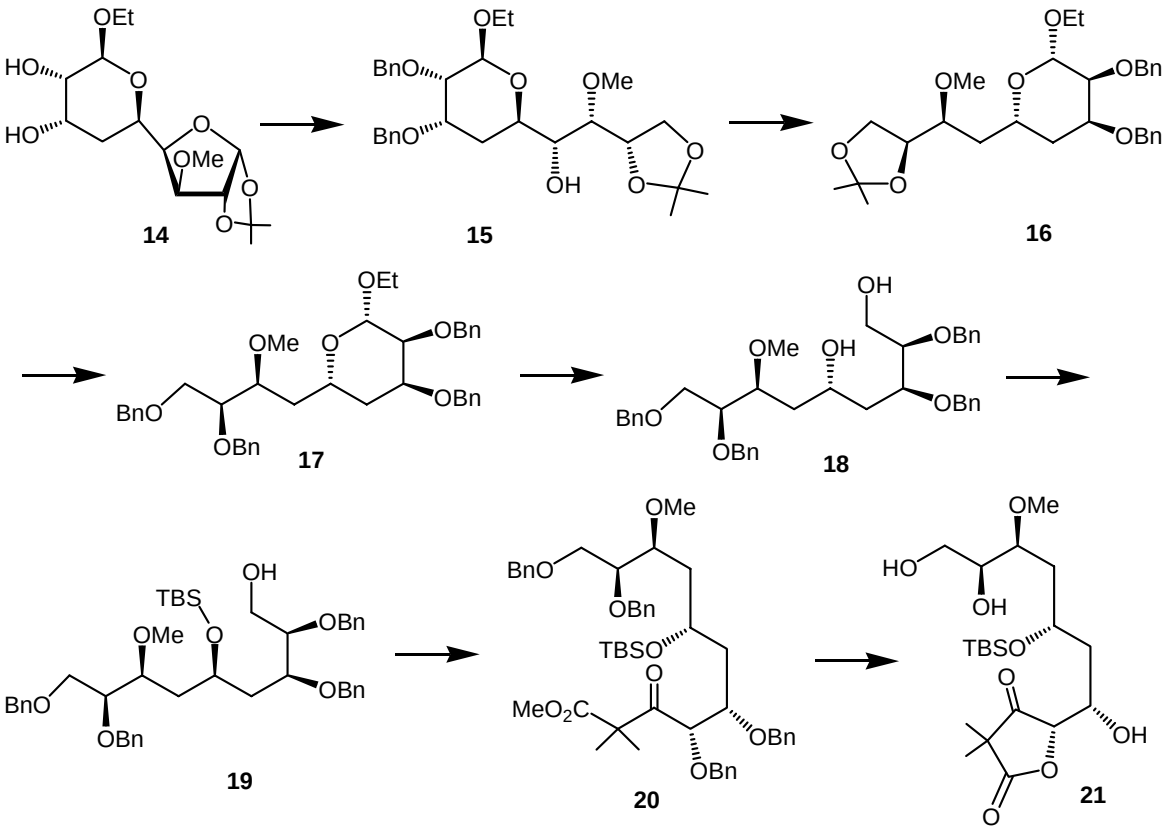
valerolactone **11** was planned using similar reactions established abovr starting from the homoallyl alcohol **9**.Dihydroxylation followed by acetonide protection of **11** gave **13** whose stereochemistry was adjudged by the 2D NOESY experiment. Furthermore, the structure of **13** was unambiguously established by the single crystal X-ray studies on the corresponding diol **14** (Scheme 2).

Scheme 2



With the required stereochemistry at C-7, C-8 in **14** and possibility of inversion of C-5 chiral center at late stages of synthesis, we intended to perform the selective manipulations that will address the inversion at C-5 and the chain extension at C-9. As shown in Scheme 3, benzylation of the diol **14** followed hydrolysis of furanoside acetonide, reduction of acetal, selective acetonide protection and subsequent Barton-McCombie deoxygenation of C4-OH in **15** gave the deoxygenated product **16**. Deprotection of isopropylidene in **16** with PPTS in methanol and protection as dibenzylether, hydrolysis of ethyl glycoside and reduction of the resulting lactol provided the open chain derivative **18**. Inversion of stereochemistry at the C-5 center in **18** was accomplished by using Mitsunobu reaction conditions on the corresponding pivolate derivative. Subsequent reductive deprotection, primary pivaloylation, TBS protection and pivalate deprotection gave the requisite alcohol **19**. The chain extension at C_9-alcohol of **19** was carried out by the addition of enolate of methyl isobutyrate to the corresponding aldehyde and subsequent oxidation of the resulting secondary alcohol gave the corresponding ketone derivative **20**. Finally, hydrogenation of **20** with 10% Pd-C gave the ketolactone **21** (Scheme 3).

Scheme 3

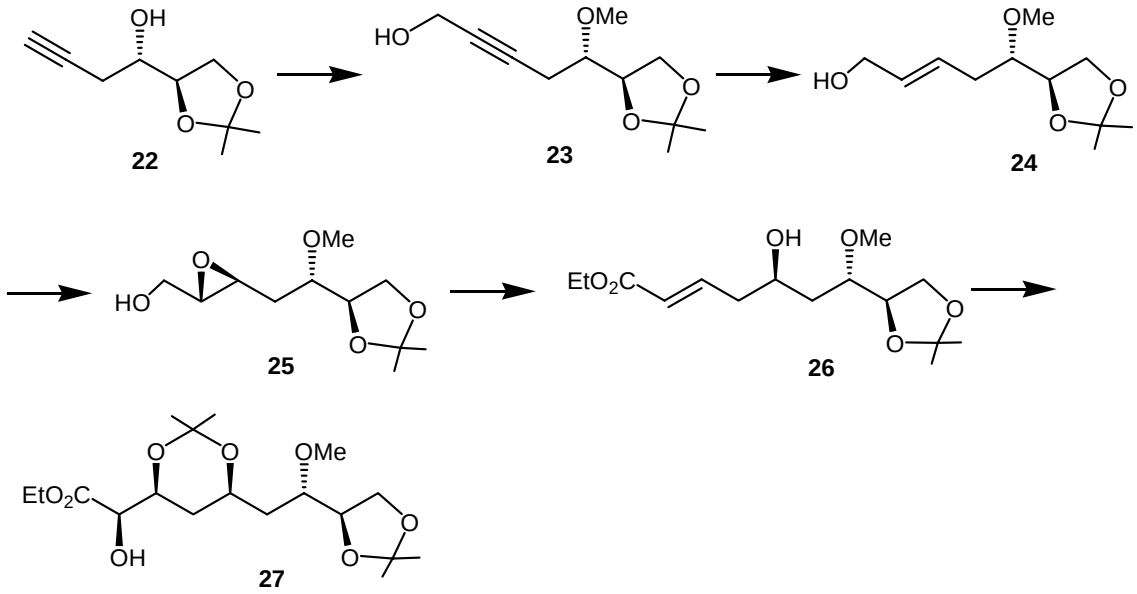


In conclusion a fragment corresponding to C_1-C_{11} of peloruside A has been successfully synthesised using chiron approach from D-glucose.

***Section II*: Stereoselective synthesis of C_1-C_9 fragment of peloruside A**

Synthesis of stereochemically important pentahydroxy C_1-C_9 segment (**27**) of peloruside A **1** was commenced with (*R*)-2,3-*O*-isopropylideneglyceraldehyde. Zn-mediated Babier-type propargylation of (*R*)-2,3-*O*-isopropylideneglyceraldehyde provided the alcohol **22**. Methyl ether of the homopropargylic alcohol **22** was transformed into allylic alcohol **24** with *n*-BuLi-paraformaldehyde and reduction. Sharpless asymmetric epoxidation of **24** using L(+)-DIPT gave the epoxy alcohol **25**. Subsequent oxidation of **25** and Wittig reaction with $Ph_3P{=}CH_2CO_2Et$ provided the key epoxy enoate intermediate which was subjected to the Pd(0) catalyzed regio- and stereoselective hydrogenolysis with BH_3:Me_2NH-AcOH to obtain the advanced intermediate **26**. Asymmetric dihydroxylation of **26** followed by isopropylidene protection of the triol afforded the C_1-C_9 fragment **27** of peloruside A (**1**) (Scheme 4).

Scheme 4

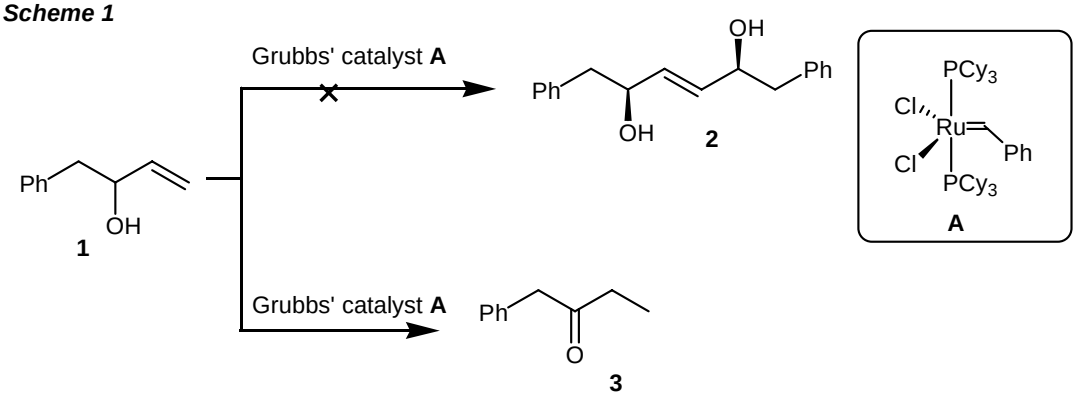


In conclusion we have developed a short route for the stereoselctive synthesis of C_1-C_9 segment **28** of peloruside A (**1**) in a linear sequence of total eleven steps starting from D-mannitol.

CHAPTER III: Temperature dependent isomerisation versus. net fragmentation of secondary allylic alcohols with Grubbs' catalyst

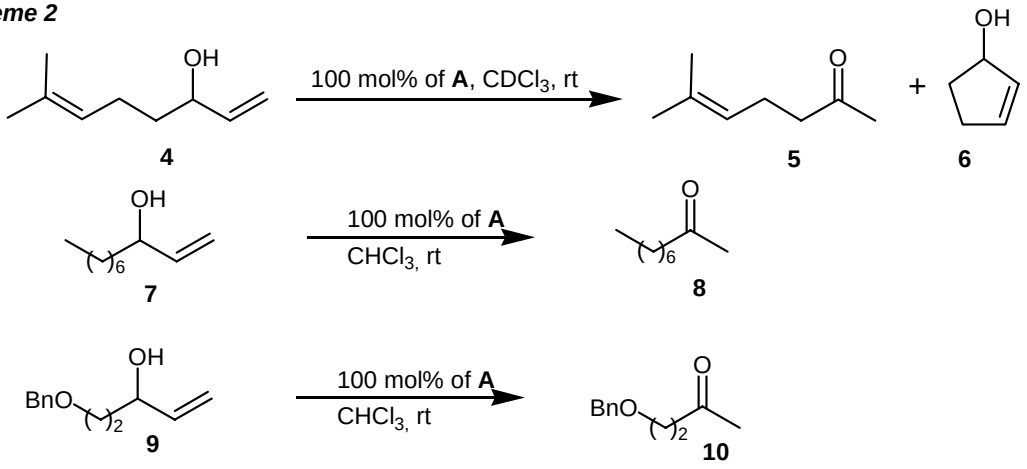
Ring closing metathesis (RCM) is widely being used in organic synthesis for the construction of medium to large ring structures. In this regard, Grubbs' catalyst **A** was used widely due to its inherent characteristic properties particularly functional group compatibility, tolerance to very many solvent systems, air and moisture insensitivity, and thermal stability. Whereas Cross-metathesis an emerging area of research has received relatively less attention, and as a part of our interest in HIV protease inhibitors, we sought to develop a simple approach to construct dimer **2** by self-metathesis the α-allylic alcohol **1** using Grubbs' catalyst **A**. Thus, compound **1** was subjected to self-metathesis using 10 mol % of catalyst **A** in refluxing toluene to give a product, which was not in conformity with the expected dimer product **2**. However, based on ^{1}H-NMR, ^{13}C-NMR, IR spectra and elemental analysis, structure of new product was proposed as saturated ethyl ketone **3**. It was apparent that compound **3** was formed as a result of intramolecular hydrogen transfer isomerisation of **1**(Scheme 1).

Scheme 1



Our results were contrary to the observations recently reported by Hoye and Zhao who noticed that a secondary allylic alcohol undergoes the net fragmentation reaction with 100 mol % of **A** at room temperature, leading to a methyl ketone, with a loss of one carbon atom (Scheme 2). Hence, temperature dependent isomerisation verus. net fragmentation of secondary allylic alcohols with Grubbs' was studied on several allylic alcohols under the above stated reaction conditions.

Scheme 2

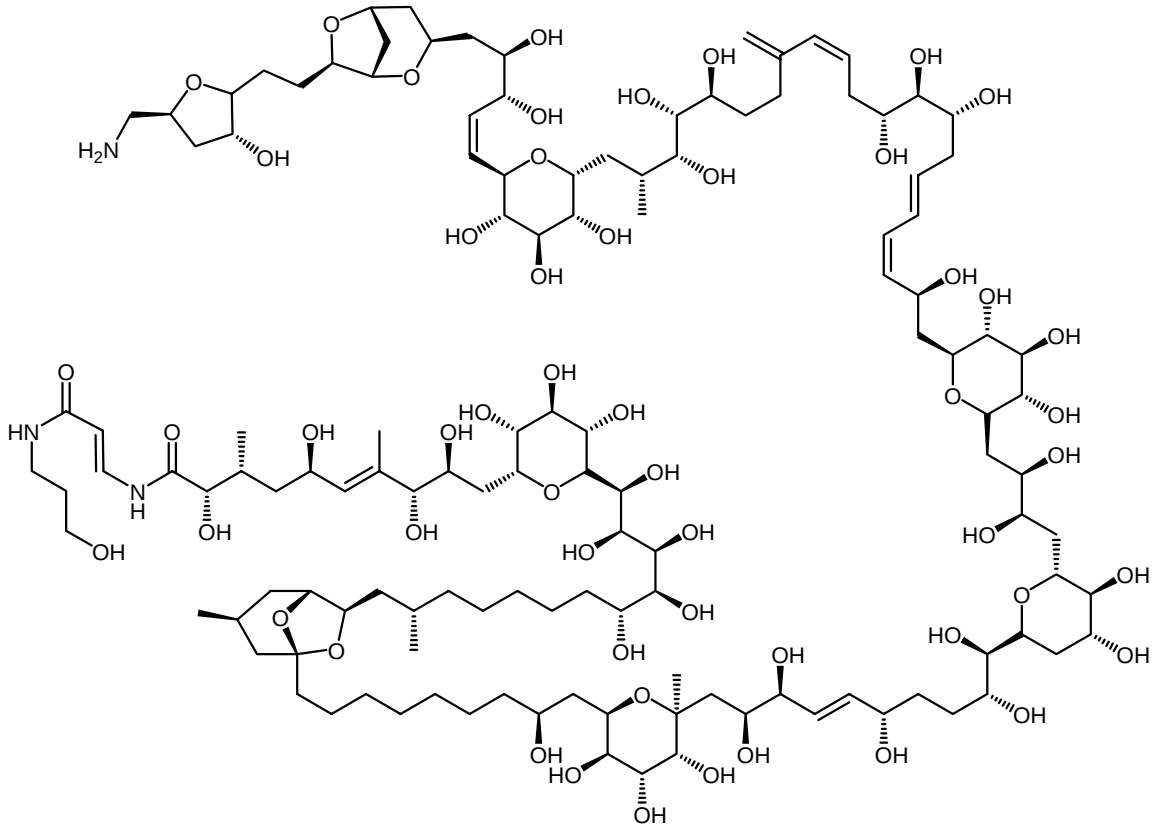


Chapter I

Towards the total synthesis of clavosolide A

Introduction

Early studies on variety of bioactive compounds originating from natural sources such as terrestrial plants, fungi and bacteria provided useful compounds, e.g. well known antibiotics from actinomycetes, and the anti-tumour agent Taxol[1] from the yew tree *Taxus brevifolia*. With the oceans making up more than 95% of the biosphere, researchers began to view the oceans as a new and untouched source of potentially useful compounds and found inexhaustible source of complex molecules. Often, the structural complexity of marine natural products posed challenge to the synthetic chemists, for example: palytoxin **1**[2] has been a source of much inspiration. The contemporary trends in drug discovery from natural sources also emphasize investigation of marine environment to obtain such compounds. Many of these compounds have served as lead molecules for novel pharmaceuticals or as cure for diseases. These substances are called secondary metabolites and are probably synthesized for the survival of the host organism as opposed to primary metabolites, which are essential for the survival and maintenance



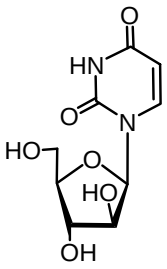
Palytoxin (1)

of the cell and its machinery. Traditionally, secondary metabolites have been regarded as evolutionary neutral or waste products. However, the presently most accepted view is that many secondary metabolites are adaptive and play a key role in the host defence against pathogens, parasites, predators, competitors and biofouling.[3] Although a striking number of secondary metabolites have been discovered from a wide array of organisms, molecules possessing a potent biological activity, i.e. display of activity in the submicromolar range, are still quite rare. Firn and Jones recently proposed a model for the evolution of secondary metabolism, which distributes secondary metabolites between molecules lack of biological activity and molecules with very potent activity.[4] They proposed that enzymes involved in the production of secondary metabolites favors substrate with chemical diversity over functional diversity for the evolution of a putative biologically potent molecule. Therefore, to ensure chemical diversity the enzymes involved will have to tolerate a range of substrates and thus a range of new compounds can be produced, one of which may have the desired potent biological activity.

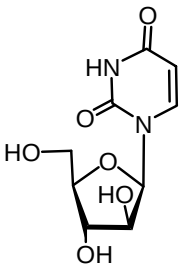
The sources commonly explored for the discovery of marine compounds are sessile invertebrate organisms like sponges, tunicates, bryozoans and molluscs. These organisms not only carry the large number of secondary metabolites, they also have the ability to synthesise a diverse range of organic compounds, i.e. polyketides, alkaloids, peptides, terpenes and others.[5]

Bioactive compounds of marine origin

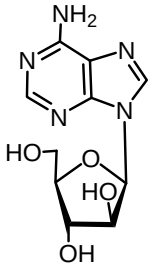
Marine sponges are pre-eminent producers of secondary metabolites and are also one of the richest sources of alkaloids and polyketides. The first compounds, isolated from marine organisms and used as tools in pharmaceutical development, were the unusual nucleosides spongouridine **2**[6a] and spongothymidine **3**[6a] from the sponge *Cryptotethya crypta*. These two compounds helped the development of the antiviral drugs, vidarabine **4**[6b] and cytarabine **5**[6c]. Also, an important milestone in the discovery of potential drugs from marine natural sources was the isolation and structural elucidation of the prostaglandins **6** from the gorgonian *Plexaura homomalla*.[7] To date, about 10.000 different natural compounds of marine origin have been discovered. Among them, alkaloids have long been recognized as one of the most potent groups of compounds and



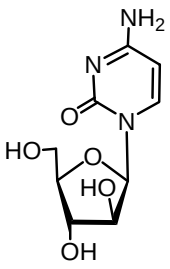
Spongouridine **2**



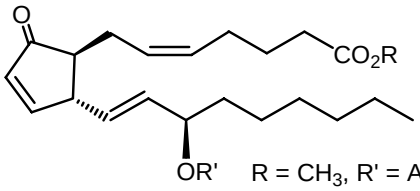
Spongothymidine **3**



Vidarabine **4**

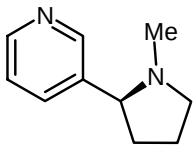


Cytarabine **5**

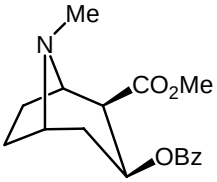


$R = CH_3$, R' = Ac
$R = CH_3$, R' = H
R = R' = H

Prostaglandins **6**

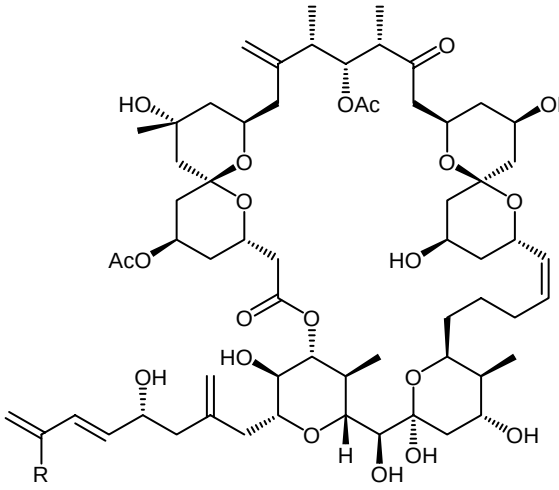


Nicotine **7**



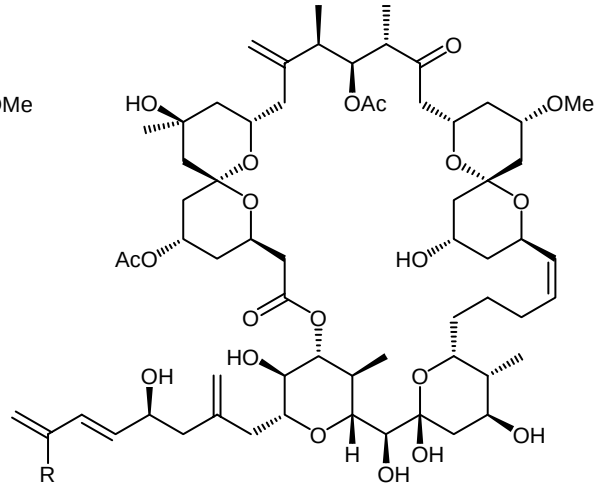
Cocaine **8**

several toxins and bioactive compounds belong to this group (e.g. nicotine **7**[8a], cocaine **8**[8b]). And equally diverse as their structural properties are many polyketides with valuable therapeutic utility, like spongistatin **9**, altohyrtin **10**, dictyostatin **11**, scytophycin **12**, swinholide **13**, misakinolide **14**, discodermolide **15**, peloruside **16** etc.[9]



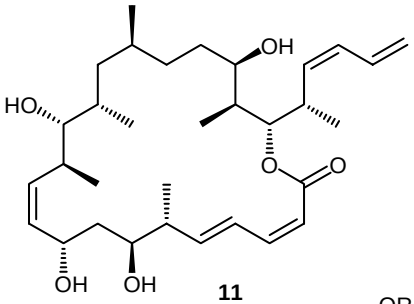
9

Spongistatin 1, R = Cl
2, R = H

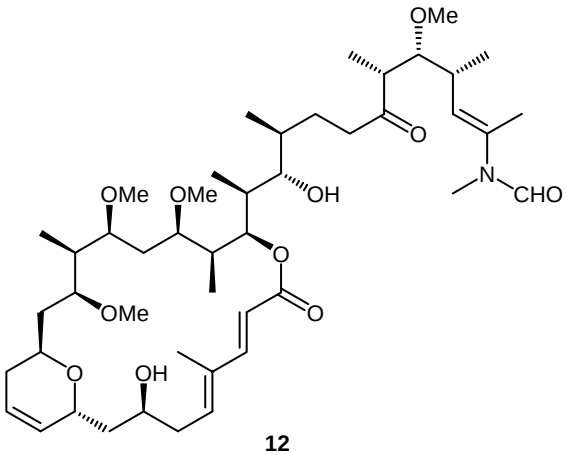


10

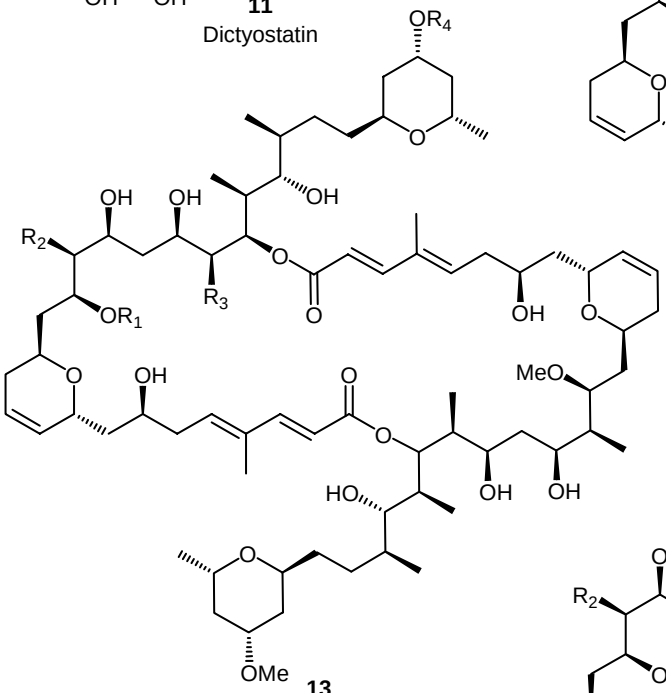
Altohytrin A, R = Cl
B, R = Br
C, R = H



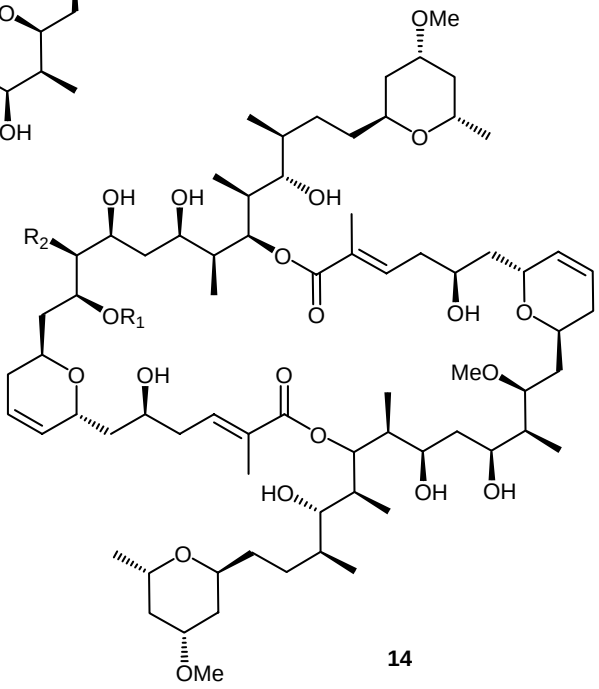
11
Dictyostatin



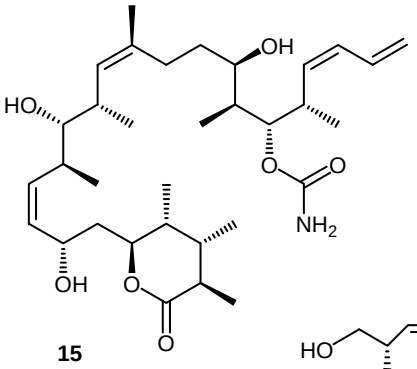
12
Scytophycin C



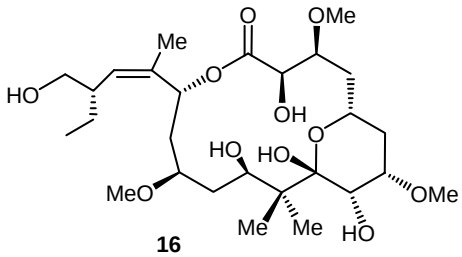
13
Swinholide A: $R_1 = R_2 = R_3 = R_4 = Me$
B: $R_1 = R_3 = R_4 = Me$, $R_2 = H$
C: $R_1 = R_2 = R_3 = Me$, $R_4 = H$
D: $R_1 = H$, $R_2 = R_3 = R_4 = Me$
G: $R_1 = R_2 = R_4 = Me$, $R_3 = H$



14
Misakinolide A: $R_1 = R_2 = Me$
B: $R_1 = Me$, $R_2 = H$
C: $R_1 = H$, $R_2 = Me$



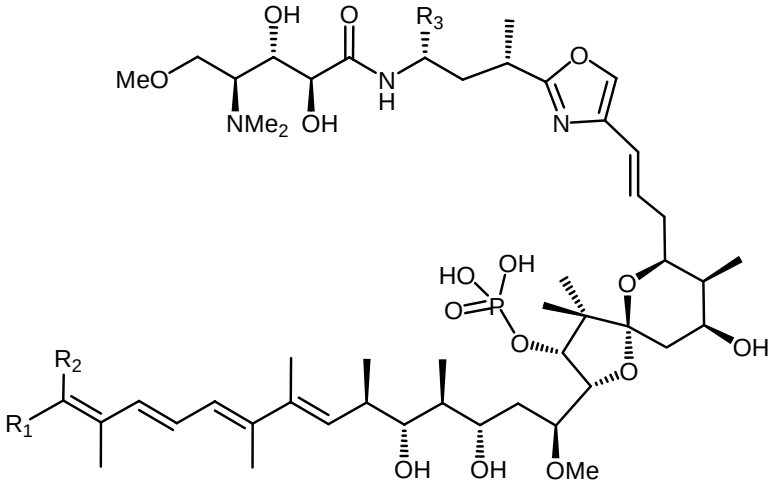
15
Discodermolide



16
Peloruside A

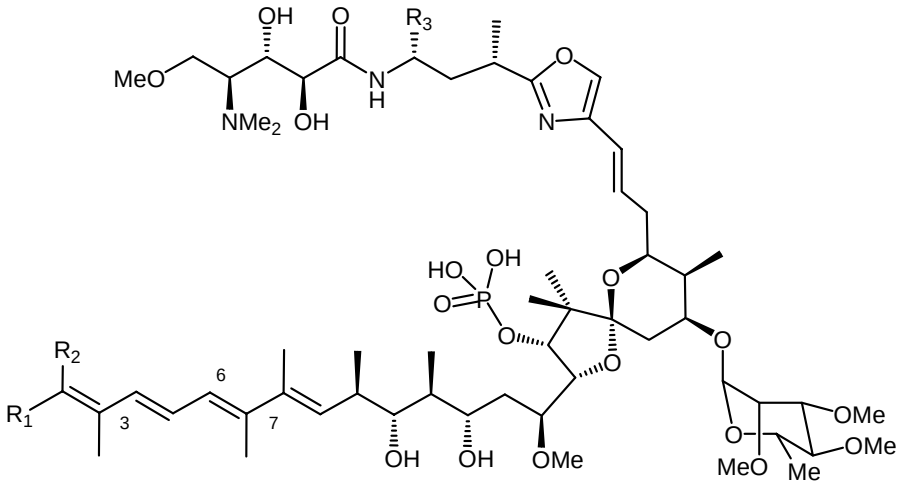
Metabolites isolated from marine sponge *Myriastra clavosa*

Investigations of marine sponge *Myriastra clavosa* Ridley 1884 (Order Astrophorida, Family Ancorinidae) collected from Chuuk exhibited cytotoxicity against human breast (MDA-MB435) and human lung (A549) tumor cell lines, but scarcity of the sample rendered the detailed chemical studies. Subsequently, more amount of sponge collected near Palau showed cytotoxicity comparable to that of Chuuk specimens. The MeOH extracts of lyophilized specimens were concentrated and partitioned with several organic solvents, CH_2Cl_2 soluble material shown bioactivity and further purification led to clavosines A-C (**21**-**23**).[10] These highly functionalized cytotoxins are structurally related to the calyculins (**17**-**18**)[11] and calyculinamides (**19**-**20**)[11], and they have been shown to inhibit serine/threonine protein phosphatases.[10] Whereas, sponge collected from the Philippines produced a distinctive pattern of differential cytotoxicity and antiproliferative effects in the National Cancer Institute's 60-cell antitumor screen. Isolation and structural elucidation of ethyl acetate soluble material from the MeOH extract of this specimen provided a suite of unusual metabolites, whose ^{1}H NMR spectral data indicated the presence of protons in the cyclopropane chemical shifts region. Detailed spectral study of the these compounds provided interesting four novel dimeric macrolide glycosides, clavosolides A-D (**26**-**29**)[12] and found to be noncytotoxic to select set of human tumor cell lines. The novel dimeric macrolide glycosides clavosolides A-D are not related to any known sponge metabolites.

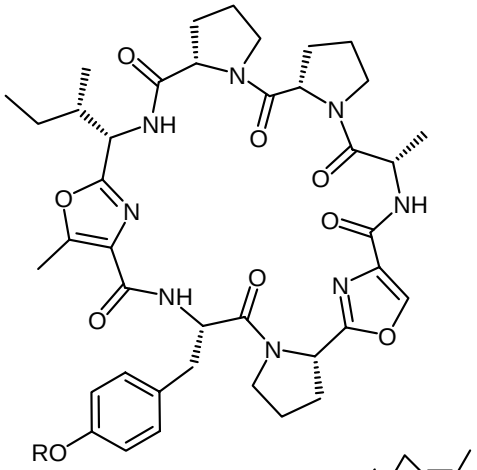


Calyculin A **17**: R_2 = CN, R_1, R_3 = H
Calyculin B **18**: R_1 = CN, R_2 = R_3 = H
Calyculinamide A **19**: R_1 = $CONH_2$, R_2 = R_3 = H
Calyculinamide B **20**: R_2 = $CONH_2$, R_1 = R_3 = H

Figure 1: **secondary metabolites isolated from marine sponge *Myriastra Clavosa***

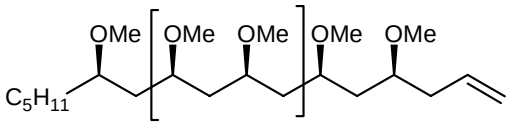


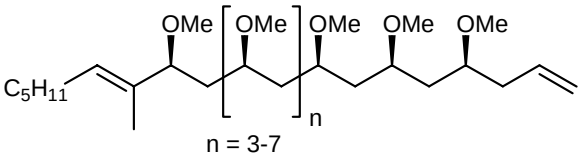
Clavosine A **21**: R_1 = H, R_2 = $CONH_2$, R_3 = Me, R_4 = X
Clavosine B **22**: R_1 = $CONH_2$, R_2 = H, R_3 = Me, R_4 = X
Clavosine C **23**: 6*Z* isomer of 2



Myriastramide A **24**: R =

Myriastramide B **25**: R =



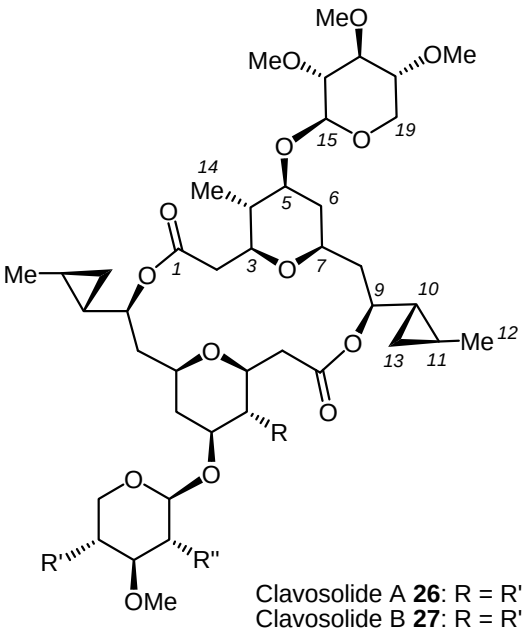


Polymethoxydienes **30**

Further isolation and purification afforded a homologous series of polymethoxydienes (**30**) which was responsible for the cytotoxicity observed in ethyl acetate soluble fraction.[13] Interestingly, specimens of *M. clavosa* collected from the Philippines did not any of clavosines. In continuation of isolation studies, the above specimen also yielded three new modified octapeptides myriastramides A-C from both organic and aqueous extracts.[14] First three classes of secondary metabolites clavosines, clavosolides and polymethoxydienes are appeared to be produced *via* polyketide biosynthesis, whereas myriastramides from nonribosomal peptide synthase.

The origin of bioactivity shown by crude extracts isolated from *M. clavosa* is elusive. The insufficient amount of all four classes of compounds rendered their detailed biological studies.

Structural elucidation of clavosolide A (26) [12]



Clavosolide A **26**: R = R' = R'' = Me
Clavosolide B **27**: R = R' = Me, R'' = H
Clavosolide C **28**: R = R'' = Me, R' = H
Clavosolide D **29**: R = H, R' = R'' = Me

Extensive spectroscopic studies coupled with molecular modeling established the structure of clavosolides A-D. The molecular formula of clavosolide A (**26**), $C_{44}H_{72}O_{16}$ was established by FABMS and the only 22 signals appeared in the ^{13}C NMR spectrum suggested that the clavosolide A as a symmetrical dimer. The IR spectrum showed only 1730 cm^{-1} band due to ester group and absence of hydroxyl band suggested that all 16 oxygen atoms were involved in ether or ester linkage. The ^{1}H, ^{13}C NMR coupled with various 2D NMR spectroscopic experiments (COSY, NOESY, ROESY and HMBC) indicated the presence of five methyl, five methylene, eleven methine and one carbonyl carbons in the monomer, and also established the carbon framework embedded with a tetrahydropyran, and relative stereochemistry of attached protons in clavosolide A. Two contiguous sequences of signals from H_2-2 to Me-12 (H_2-13, Me-14) and from H-15 to H_2-19 revealed the C-1 to C-12 (C-13, C-14) linear carbon sequence with an appendage at C_5 (C-15 to C-19). The 2D-correlations and signal overlapping of H-3:H-7 (δ 3.42), H-4_{ax}:H-6_{ax} (δ 1.87) suggested that it contains symmetrically substituted tetrahydropyran moiety

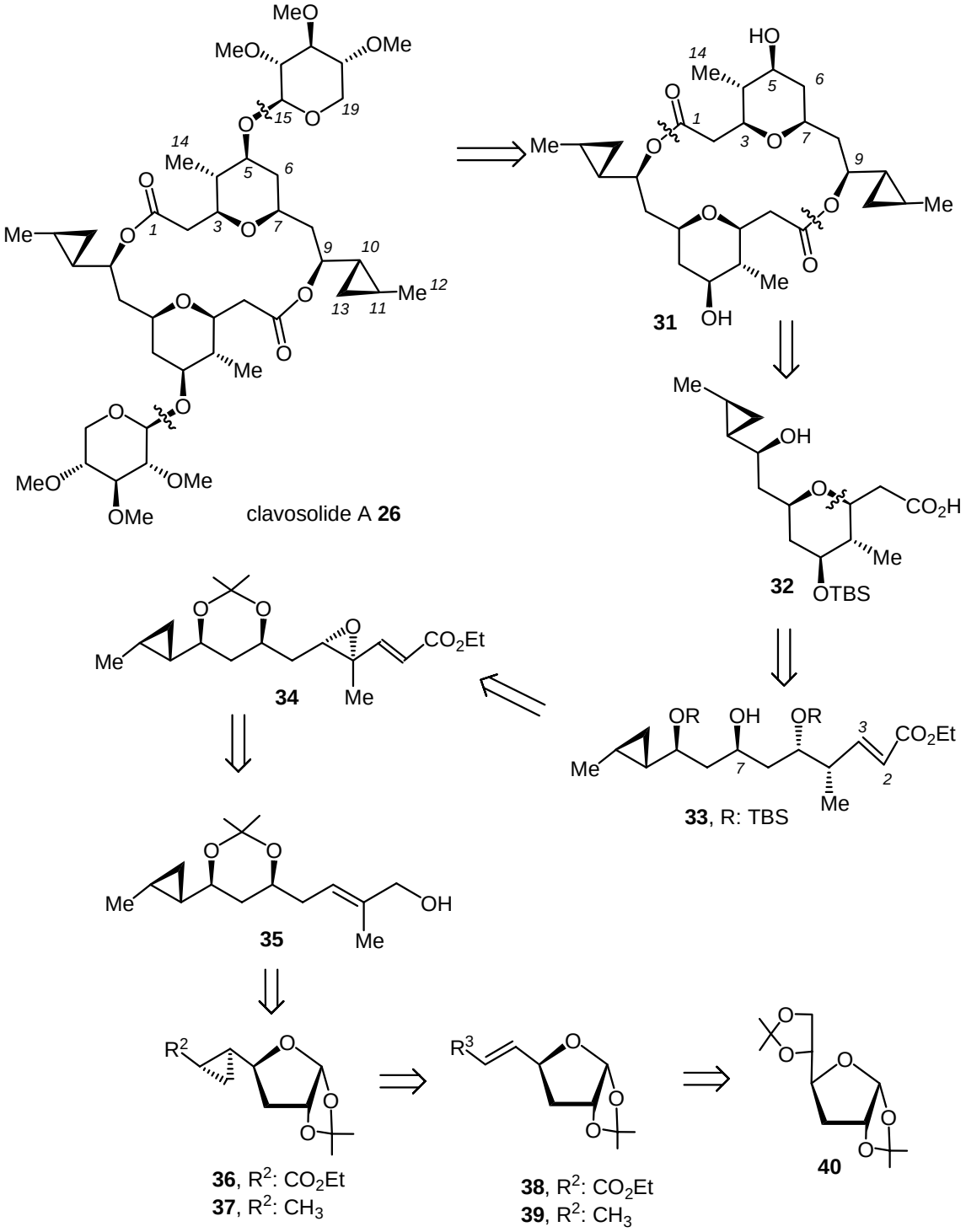
with all the substituents at the equatorial positions. Further 2D-correlations of H-9 (δ 4.41, showed correlation with C-1') with cyclopropane protons and Me-12 revealed connectivity of C-9 to C12 side chain. Interpretation of the coupling constant and ROESY correlations exposed the presence of *trans* cyclopropyl group at C-10, C-11. Molecular modeling of four possible symmetrical isomers of dimer indicated the presence of rigid flat rings with a dihydral angle >160° between cyclopropyl methylene and carbonyl group, which in turn indicated the *syn* conformation of cyclopropane methylene (C_{13}) with adjacent C9-O bond in clavosolide A. The glycosyl substituent attached at C-5 was confirmed as a trimethoxy-β-xylopyranoside by comparing the coupling constant exhibited by ring protons. By assuming the normal D-configuration for the xylose, the stereochemistry of clavosolide A (**26**) was derived as 3*S*, 3'*S*, 4*R*, 4'*R*, 5*S*, 5'*S*, 7*S*, 7'*S*, 9*S*, 9'*S*, 10*S*, 10'*S*, 11*S*, 11'*S*. The unique structural parameters associated with rare cyclopropane moiety in calvosolide A (**26**) and the necessity to determine its absolute stereochemistry coupled with the limited availability prompted us to undertake the total synthesis of this synthetically challenging molecule.

Present work

Clavosolide A (**26**) is a symmetrical dimeric 16-membered ring dilactone, embedded with a highly substituted tetrahydropyran glycosylated at C-5 with permethylated β-xylopyranose. It also contains a side chain with rare disubstituted *trans*-cyclopropane ring. Keeping the unique structural parameters in mind, we planned straightforward disconnection approach for clavosolide A as shown in Scheme 1. The obvious disconnection of glycosidic bond in clavosolide A led to the C_2-symmetric diol **31**. The next logical saponification of ester functionality of suitably protected C_2-symmetric diol **31** gave simplified seco acid **32**. A mild direct esterification method was expected to provide the diolide **31** directly from the seco acid **32** due to rigid conformation of tetrahydropyran ring, which hinders the formation of monomeric 8-membered ring lactone. The seco acid **32**, with all the substituents at the equatorial position in the tetrahydropyran ring was envisaged *via* an intramolecular 1,4-addition of free C_7-OH to the conjugated ester moiety at C_2-C_3 of the intermediate **33**. The installation of *syn* hydroxymethyl isostere moiety at C_4-C_5 required a mild method without perturbing the active cyclopropane ring. Thus, a mild regio- and stereoselective hydrogenolysis of trisubstituted epoxyenoate **34** was planned for the same. Synthesis of relatively simplified intermediate **34** was envisioned from the corresponding allylic alcohol **35** by using Sharpless asymmetric epoxidation protocol, and the key intermediate **35** was designed using a chiral pool strategy in order to establish the stereochemistry of cyclopropane without any ambiguity. Thus, the allylic alcohol **35** was correlated to cyclopropane sugar derivative (**36** or **37**) with its flexible anomeric functionality for the chain extension. The olefin precursor (**38** or **39**) of the cyclopropane sugar compound (**36** or **37**) was in turn correlated to the 3-deoxy derivative of D-glucose diacetonide (**40**), which represents as an ideal starting material for the synthesis of proposed structure of clavosolide A.

Based on the retrosynthetic analysis, we intended to prepare the 5,6-cyclopropane derivative **36** from the corresponding α,β-unsaturated ester **38**. D-Glucose was converted into 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **41** by combined action of acetone and anhydrous $CuSO_4$ in the presence of catalytic H_2SO_4. Subsequent deoxygenation of

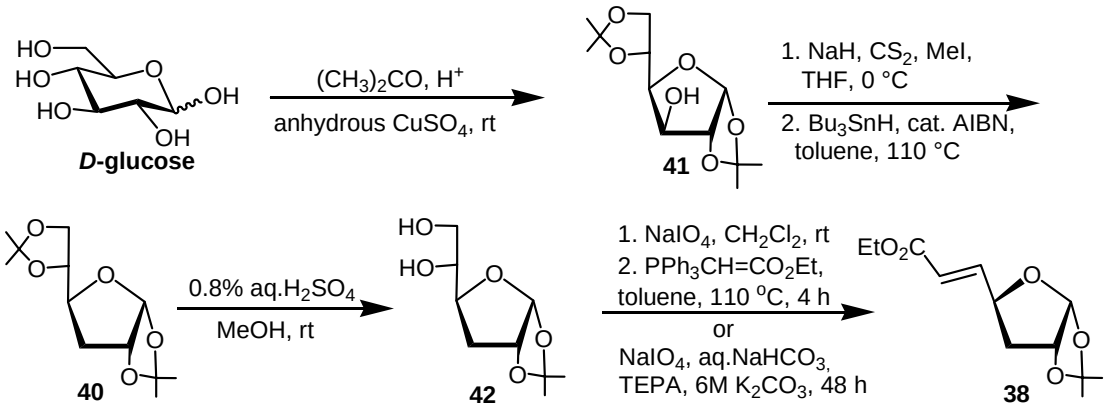
Scheme 1*: *Retrosynthetic analysis



free OH group at C-3 in **41** was accomplished by using the Barton-McCombie reaction involving the synthesis of the xanthate derivative, followed by treatment with Bu_3SnH-

AIBN to yield 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose **40**. Selective cleavage of the 5,6-isopropylidene group in **40** was accomplished with 0.8% aq. H_2SO_4 in

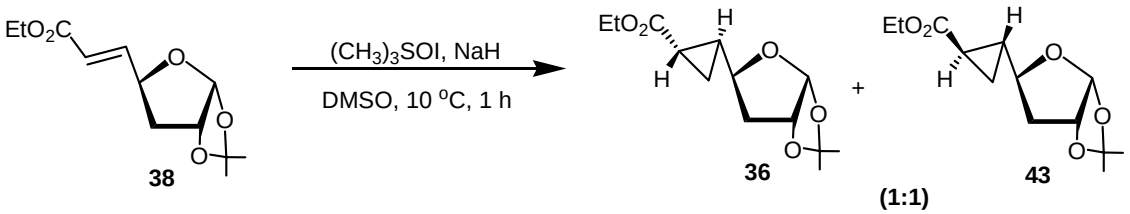
Scheme 2



methanol to give 3-deoxy-1,2-*O*-isopropylidene-α-D-*ribo*-hexofuranose **42**.[15] Oxidative cleavage of the diol **42** using silica gel supported $NaIO_4$ in dichloromethane afforded 3-deoxy-1,2-*O*-isopropylidene-α-D-*erythro*-pentodialdo-1,4-furanose[16] which was immediately used for the two-carbon homologation with $PPh_3CH{=}CO_2Et$ in toluene under reflux to provide the required *trans*-α,β-unsaturated ester **38** in good yield. However we encountered stability issues while scaling up the reaction. This warranted an alternative approach, and we followed one-pot oxidative cleavage and Horner-Emmons olefination in aqueous media.[17] Accordingly, oxidative cleavage of diol **42** with $NaIO_4$ in aqueous $NaHCO_3$ yielded the dialdofuranose, which without isolation was treated with triethylphosphonoacetate (TEPA) and 6M aq.K_2CO_3 to afford exclusively the *trans*-α,β-unsaturated ester **38** in quantitative yield (Scheme 2). In the ^{1}H NMR spectrum of **38**, the olefinic protons appeared as two double-doublets at δ 6.06 ($J_{6,5}$ = 15.7 Hz, $J_{6,4}$ =1.5 Hz) and at δ 6.90 ($J_{5,6}$ = 15.7 Hz, $J_{5,4}$ = 4.9 Hz). The signals due to methyl and methylene protons of carboethoxy group appeared at δ 1.29 (t, J = 7.0 Hz), 4.18 (q, J = 7.0 Hz) respectively. The ^{13}C NMR, IR (1718, 1661 cm^{-1}) spectral data and elemental analysis also supported the structure of **38**. The cyclopropanation of α,β-unsaturated ester **38** under Corey-Chaykovsky reaction conditions[18] with sulfur methylide (prepared from trimethylsulfoxonium iodide and NaH) in DMSO at 10 °C for 1 h provided a 1:1 mixture of diastereomers **36** and **43** in poor yield, and both the diastereomers were separated by chromatography (Scheme 3). Based on Michael intiated ring closure (MIRC) mechanism involved in the above reaction, the formation of the two *trans* cyclopropyl esters **36** and **43**

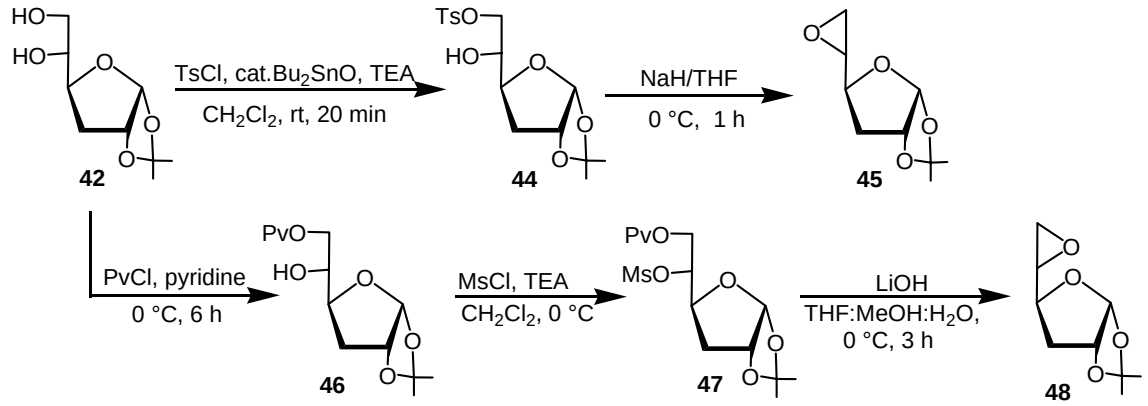
was predicted.[19] The ^{1}H NMR spectrum of **36** displayed characteristic signals due to cyclopropane protons as multiplets at δ 0.95-1.05, 1.15-1.20 and 1.55-1.70. The IR (1727 cm^{-1}) spectrum and elemental analysis also supported the structure of **36**. Whereas, the ^{1}H NMR spectrum of **43** showed resonances due to cyclopropane protons at δ 0.88 (ddd, 1H, *J* = 8.4, 6.3, 4.3 Hz) and a multiplet at δ 1.50-1.75 (2H) along with two new signals due to carboethoxy group at δ 1.22 (t, 3H, *J* = 7.2 Hz), 4.07 (q, 2H, *J* = 7.2 Hz). In the ^{13}C NMR spectrum of **43**, resonances due to cyclopropane carbons appeared at δ 11.83, 14.11 and 18.00. The structure of **43** was further supported by its IR (1725 cm^{-1}) and MS spectroscopic data.

Scheme 3



In order to establish the stereochemistry of cyclopropane of **36** and **43**, we prepared the both diastereomeric cyclopropane derivatives *via* chiral pool approach using Wadsworth-Emmons cyclopropanation[20] from the respective anhydrosugars **45** and **48**. Accordingly, anhydrosugars **45** and **48** were prepared from the diol **42** as reported (scheme 4).[21] Selective monotosylation of **42** at the primary alcohol using TsCl and triethylamine in the presence of catalytic amount of dibutyltin oxide in dichloromethane afforded 3-deoxy-6-*O*-tosyl-1,2-*O*-isopropylidene-α-D-*ribo*-hexofuranose **44** in quantitative yield. Treatment of compound **44** with base (NaH) cleanly provided 5,6-anhydro-3-deoxy-1,2-*O*-isopropylidene-α-D-*ribo*-hexofuranose **45**. The anhydrosugar **48** was prepared from diol **42** by sequence of reactions involving the selective protection of primary alcohol as its pivolate **46** using PivCl and pyridine, followed by mesylation of **46** with MsCl and triethylamine gave 5-*O*-mesyl-6-*O*-pivaloyl-3-deoxy-1,2-*O*-isopropylidene-α-D-*ribo*-hexofuranose **47**, and whose subsequent basic hydrolysis directly lead to required anhydrosugar **48**. The ^{1}H and ^{13}C NMR spectral data and optical rotation value of **45** and **48** were in agreement with reported values.[21] Wadsworth- Emmons cyclopropanation of **45** was studied by using different bases (*n*-BuLi, NaH, *t*-BuOK). The optimized conditions were observed where **45** was treated with the enolate of triethylphopsphonoacetate

Scheme 4



(generated *in situ* by addition of NaH to triethylphosphonoacetate at 0 °C) in refluxing THF to furnish ethyl 3,5,6-trideoxy-5,6-*C*-methylene-1,2-*O*-isopropylidene-α-D-*gulo*-hepto-1,4-furanos-7-onate **43** as a crystalline compound (Scheme 5). The structure of **43** was derived based on mechanism involving the intramolecular S_N^2 attack of enolate intermediate on the C_5-phosphate leading to *trans* C_5,C_6-cyclopropane furanose derivative.[22] The new chiral centers in **43** were assigned as 5*R*, 6*R* (numbering given according to the monosaccharide furanose unit) (Figure 2). Furthermore, the structure of **43** was unambiguously determined by its single crystal X-ray studies. The details of crystal data and structure refinement (Table 1), bond lengths and bond angels (Table 2) and torsion angles (Table 3) are given at the end of this section. In order to compare the data of the second diastereomer **36** obtained in the Corey-Chaykovsky cyclopropanation of **38** (Scheme 3), the anhydrosugar **48** was subjected to Wadsworth-Emmons cyclopropanation. The anhydrosugar **48** did not undergo Wadsworth-Emmons cyclopropanation smoothly. After several attempts, **48** was treated with enolate of triethylphosphonoacetate (generated *in situ* by addition of NaH to triethylphosphono acetate at 0 °C) in refluxing toluene to obtain the required cyclopropyl ester **36** in poor yield (Scheme 5). The spectral data and optical rotation of **43** and **36** were matched with that of diastereomers obtained by Corey-Chaykovsky cyclopropanation of **38**, and the stereochemistry of C_5,C_6-cyclopropane in **36** was assigned as 5*S*,6*S* without any ambiguity.

Scheme 5

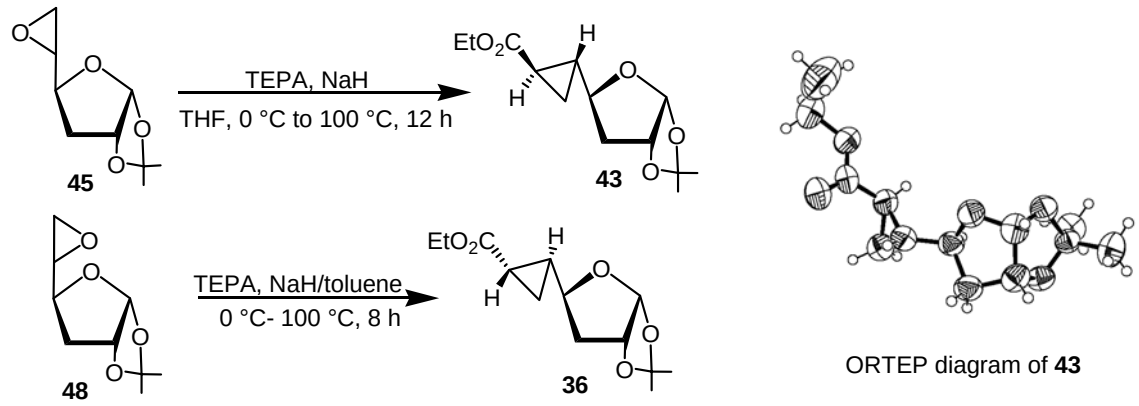
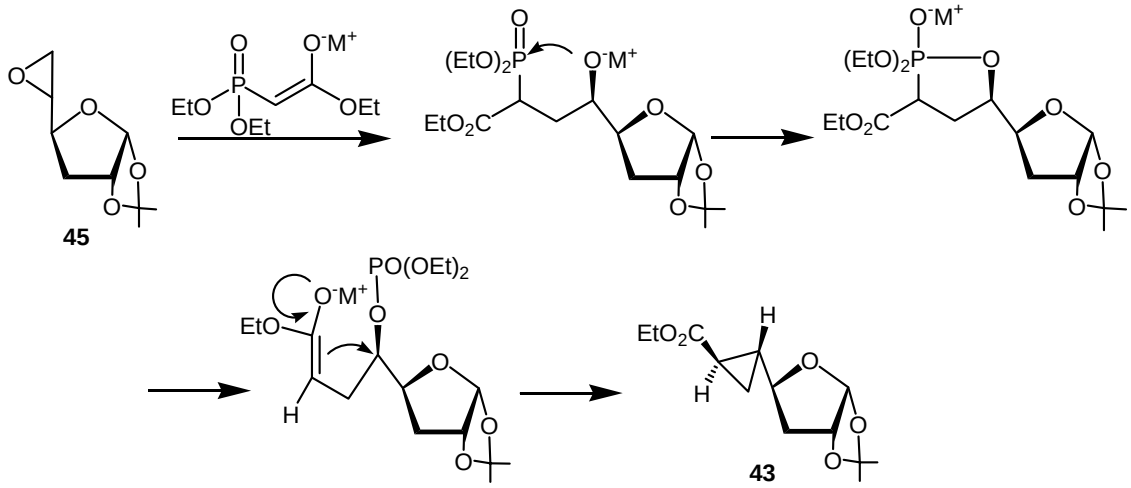
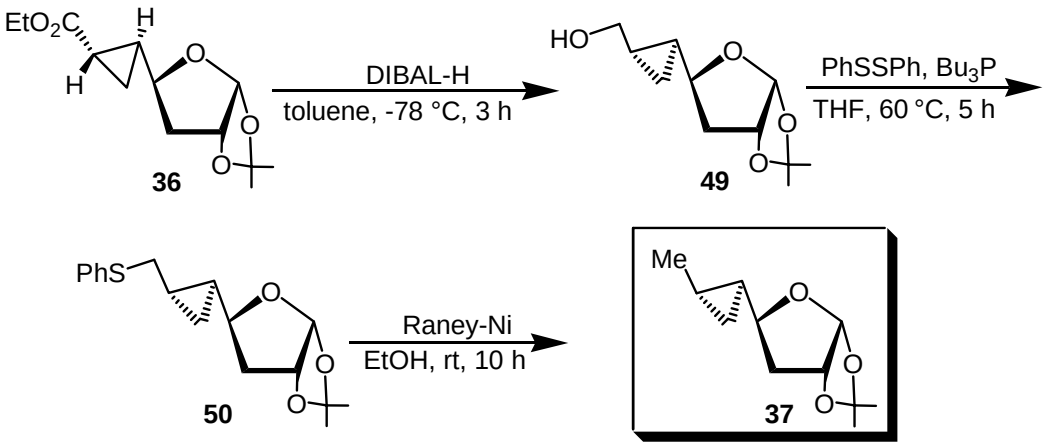


***Figure 2*:** Mechanism of Wadsworth-Emmons cyclopropanation



Reduction of ester in **36** with DIBAL-H in toluene at –78 °C afforded the 3,5,6-trideoxy-5,6-*C*-methylene-1,2-*O*-isopropylidene-β-L-*talo*-hepto-1,4-furanose **49** (Scheme 6). The ^{1}H, ^{13}C NMR spectral data and elemental analysis of **49** were in agreement with the assigned structure. Deoxygenation of alcohol in **49** was achieved by nucleophilic displacement of OH group with diphenyl disulfide and subsequent desulfurisation of corresponding sulfide derivative **50** using Raney Ni afforded the required 3,5,6,7-tetradeoxy-5,6-*C*-methylene-1,2-*O*-isopropylidene-β-L-*talo*-hepto-1,4-furanose **37**.[23] In the ^{1}H NMR spectrum of **37**, characteristic cyclopropane protons appeared as two multiplets at δ 0.29-0.36 (1H) and 0.55-0.71 (3H), whereas the methyl group (cypC*H*$_3$) resonated as a doublet at δ 1.04 (J = 5.8 Hz). The ^{13}C NMR spectrum of **37** showed resonances due to cyclopropane carbons at δ 9.93, 11.63, 18.39 and cyclopropylmethyl carbon appeared at δ 22.25 ppm.

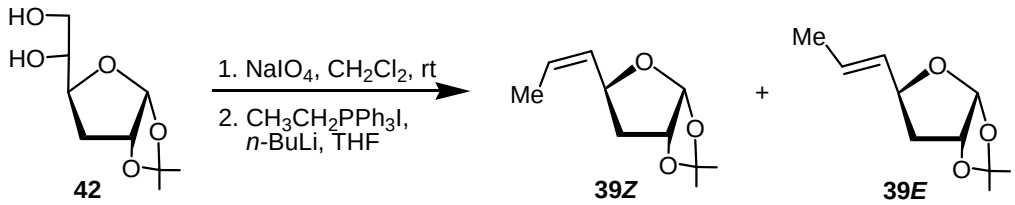
Scheme 6



Synthesis of 3,5,6,7-tetradeoxy-1,2-*O*-isopropylidene-5,6-*C*-methylene-β-L-*talo*-hepto-1,4-furanose (37): Second-generation strategy

Although we were successful in the preparation of requisite cyclopropane compound **37**, considering the poor selectivity in Chaykovsky cyclopropanation of **38** (Scheme 3) and lengthy sequence of reactions involved from anhydrosugar **48** (Scheme 5 & 6), we opted an alternative approach. Preparation of **37** from alkene **39*E*** was planned by using Simmons-Smith reaction to obtain *syn* selective cyclopropanation product.[24] Thus, synthesis of alkene **39*E*** was initiated from the diol **42** following the two carbon Wittig homologation of corresponding dialdofuranose using ethyltriphenylphosphonium iodide and *n*-BuLi in THF at −78 °C afforded *cis* olefin derivative **39*Z*** (Scheme 7).[25] Varying the

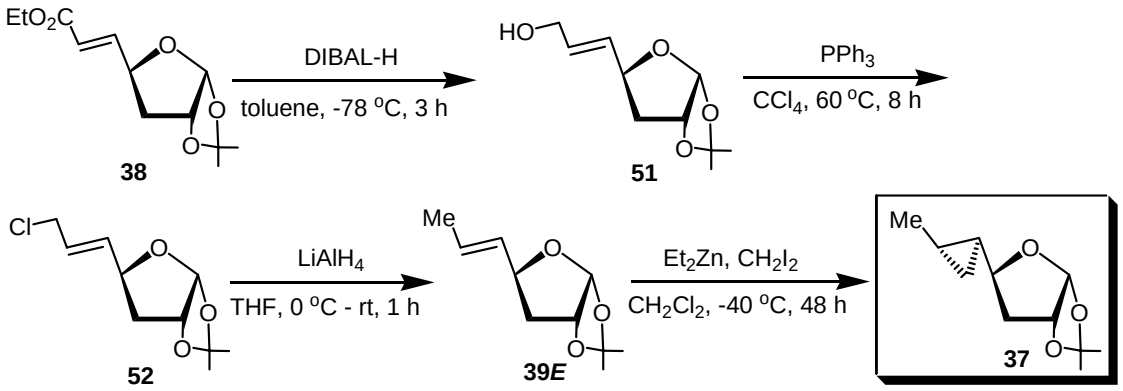
Scheme 7



reaction conditions of the Wittig olefination to 0 °C afforded inseparable mixture of *E* and *Z* diastereomers (**39*E***, **39*Z***) in 1:9 ratio. A three-step synthesis was followed from ester derivative **38** to prepare **39*E*** exclusively (Scheme 8). Reduction of ester derivative **38** using DIBAL-H in toluene at −78 ^{o}C furnished the allylic alcohol derivative **51**. The ^{1}H NMR, ^{13}C NMR, IR spectroscopic data and elemental analysis of **51** supported the structure of **51**. Chlorination reaction of **51** using triphenylphosphine in refluxing CCl_4

gave the required allyl chloride **52** whose reductive dehalogenation using $LiAlH_4$ gave the compound **39*E***. The ^1H and ^{13}C NMR spectral data confirmed the structure of **39*E***. In the ^1H NMR spectrum of **39*E***, the vinylic methyl group appeared as a double-doublet at δ 1.72 (*J* = 6.61, 1.5 Hz), whereas the olefinic protons appeared at δ 5.45 (ddq, 1H, *J* = 15.2, 7.4, 1.5 Hz) and 5.85 (dq, 1H, *J* = 15.2, 6.6 Hz) ppm. Having the desired *trans* olefin **39*E*** in hand, we attempted its cyclopropanation reaction under Simmons-Smith conditions. Gratifyingly, the cyclopropanation of **39*E*** under Furukawa modified conditions[26] using Et_2Zn-CH_2I_2 at –40 °C gave exclusively the required diastereomer **37** (Scheme 8). The spectral and optical rotation of the compound **37** were identical with those observed for the sample prepared earlier.

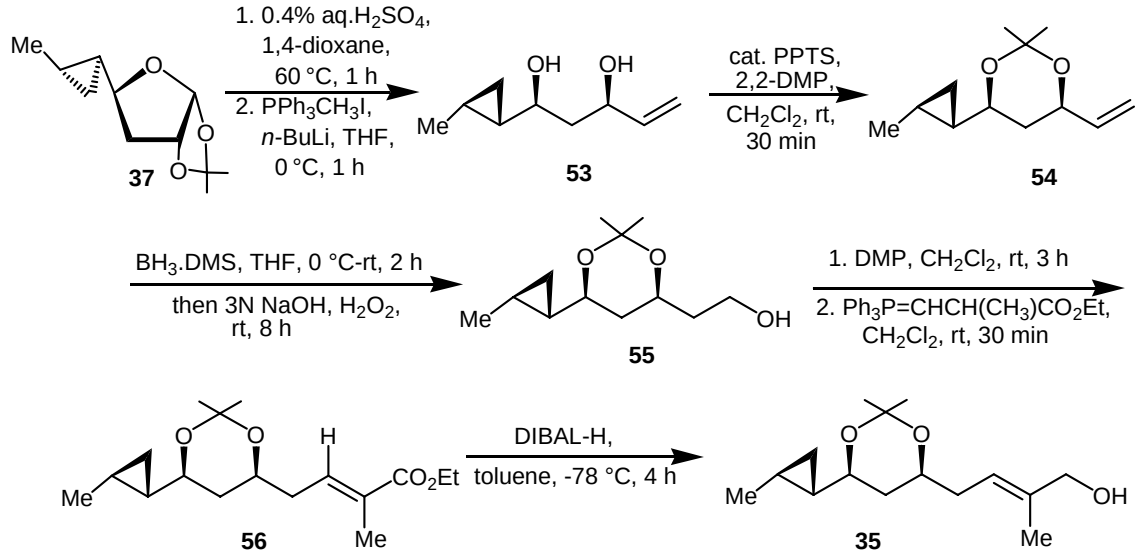
Scheme 8



Elaboration of intermediate 37 into seco acid 32

Our next concern involved was synthesis of prochiral allylic alcohol **35** from **37** by chain extension at its anomeric position (Scheme 9). Accordingly, compound **37** was converted into the lactol derivative by deprotecting the 1,2-*O*-isopropylidene moiety with 0.4% H_2SO_4 in 1,4-dioxane at 70 °C followed by one carbon Wittig olefination with methylenetriphenylphosphorane afforded the diol **53**. The ^1H NMR spectrum of **53** displayed signals due to olefin protons at δ 5.05 (dt, 1H, *J* = 10.3, 1.4 Hz), 5.22 (dt, 1H, *J* = 17.1, 1.4 Hz) and 5.84 (ddd, 1H, *J* = 17.1, 10.3, 5.9) ppm. Correspondingly, the ^{13}C NMR spectrum of **53** displayed resonance due to olefin carbons at δ 114.19 and 140.62 ppm. The diol **53** was protected as its isopropylidene derivative **54** using 2,2- dimethoxypropane in the presence of catalytic amount of pyridinium *p*-toluenesulfonate in CH_2Cl_2.

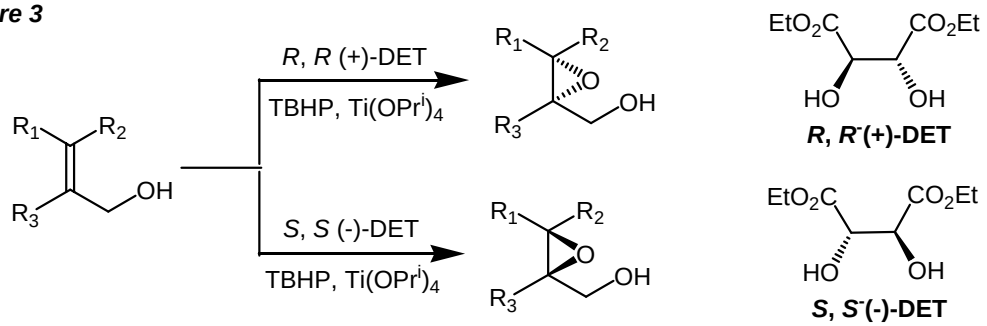
Scheme 9



In the ^{1}H NMR spectrum of **54**, resonances due to two methyl groups of isopropylidene moiety appeared as two singlets at δ 1.39 and 1.42. The hydroboration of olefin derivative **54** using $H_3B.SMe_2$ in THF followed by oxidative workup with H_2O_2 and 3N NaOH produced the desired primary alcohol **55**. In the ^{1}H NMR spectrum of **55**, a characteristic signal due to presence of -*CH*$_2$OH group appeared as two multiplets at δ 3.80-3.90 (1H) and 3.95-4.15 (1H) ppm. In addition, the ^{13}C NMR spectrum of **55** showed a signal at δ 59.43 corresponding to *C*H_2OH. The Dess-Martin periodinane oxidation of **55** followed by the Wittig reaction with Ph_3P=C(Me)CO_2Et in toluene under reflux gave the α,β-unsaturated ester **56** exclusively. In the ^{1}H NMR spectrum of **56**, the characteristic signal of olefinic proton appeared at δ 6.75 (tq, 1H, *J* = 7.2, 1.2 Hz). The methyl group of the carbethoxy ester appeared as a triplet at δ 1.30, whereas methylene group resonated as a quartet at δ 4.20. In the ^{13}C NMR spectrum of **56**, the olefinic carbons resonated at δ 129.5 and 137.0. The α,β-unsaturated ester **56** was then reduced to the allylic alcohol **35** with DIBAL-H at –78 °C. In the ^{1}H NMR of spectrum of **35**, the olefinic proton and the vinylic methyl resonated in the upfield region at δ 5.44 (tq, 1H, *J* = 7.0, 1.2 Hz) and 1.67 (s, 3H) respectively. The ^{13}C NMR spectroscopic data was also in support of **35**. Our next objective was Sharpless asymmetric epoxidation[27] of allylic alcohol **35** followed by stereoselective opening of corresponding trisubstituted epoxyenoate **34** (Scheme 10).

Sharpless asymmetric epoxidation (SAE) is one of the most popular reactions used for the enantioselective epoxidation of achiral allylic alcohols in organic synthesis. When a prochiral Z- or E-allylic alcohol is treated with dialkyl tartarate (generally Et or ^{i}Pr), titanium tetraisopropoxide and ter-butylhydroperoxide, produces the corresponding chiral epoxyalcohol with high ee. Easy availability of reagents involved, and high enantiomeric (or diastereomeric) excess obtained in the reaction made the Sharpless asymmetric epoxidation to find wide spread application in the introduction of chirality in the complex target molecules. The easy and accurate prediction of stereochemical outcome irrespective of substitution on the allylic alcohol further asserted the reaction application (Figure 3).

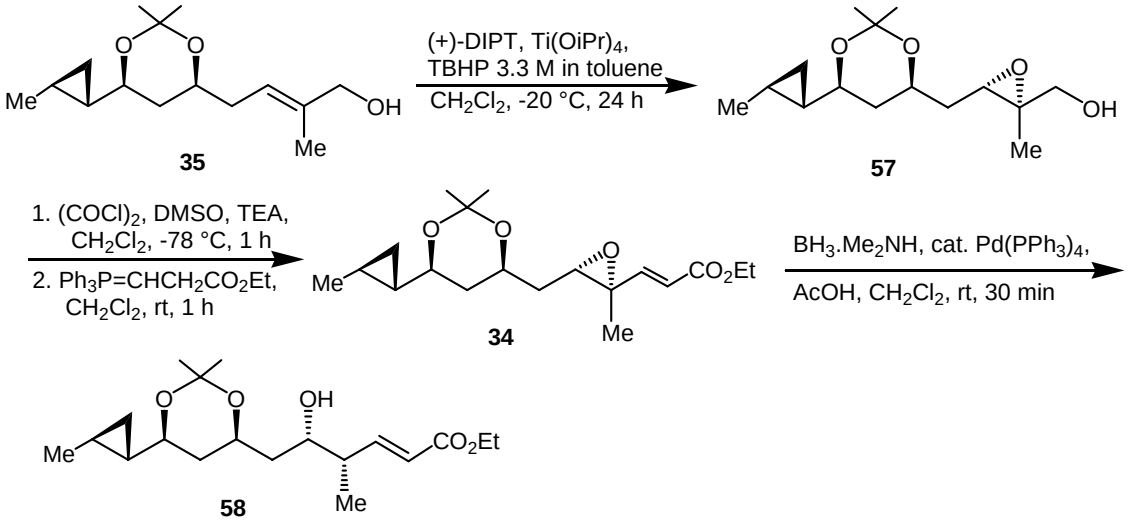
Figure 3



Sharpless asymmetric epoxidation of the *E*-allylic alcohol **35** using diisopropyl-L-tartarate, titanium tetraisopropoxide and *t*-butylhydroperoxide in the presence of 4Å molecular sieves powder in CH_2Cl_2 at –20 °C provided the corresponding epoxy alcohol **57** with excellent diastereoselectivity based on spectroscopic analysis (Scheme 10). The absolute configuration of **57** was established based on the empirical rules published by Sharpless.[27] The ^{1}H NMR spectrum of **57** displayed the epoxy proton as a double-doublet at δ 3.20 (*J* = 7.5, 4.2 Hz). All the other protons resonated at their expected chemical shifts. Further ^{13}C NMR spectrum of **57** showed signals due to the epoxy carbons at δ 57.12 and 60.08 ppm. Installation of *syn*-hydroxymethyl moiety with the suitable functionality from **57** for further reactions was planned from a recently reported[28] modification of Tsuzi-Shimizu protocol. Thus, the epoxy alcohol **57** was oxidized under Swern conditions to provide the aldehyde which was subjected to the Wittig olefination with $Ph_3P{=}CHCO_2Et$ in CH_2Cl_2 to give the (*E*)-α,β-unsaturated ester **34** (Scheme 10). In the ^{1}H NMR spectrum of **34**, the characteristic olefinic protons appeared as two doublets at δ 6.00 (*J* = 15.6 Hz) and at δ 6.75 (*J* = 15.6 Hz). The signal due to epoxy proton was observed at δ 3.00 (*J* = 7.3, 4.2 Hz) as a double-doublet. All other protons resonated at their respective values,

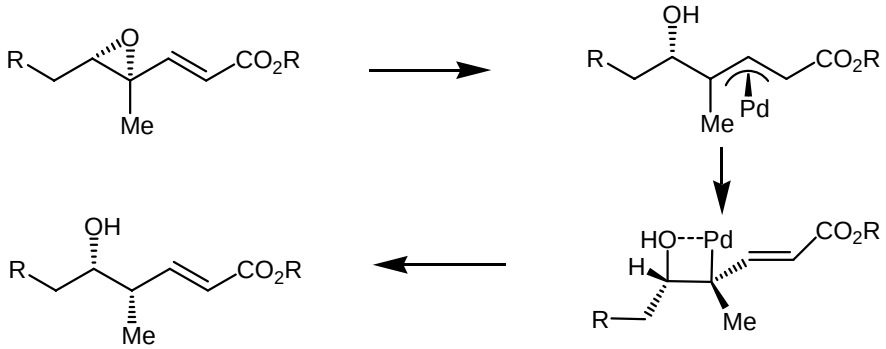
thereby confirming the structure of **34**. In the ^{13}C NMR spectrum of **34**, resonances due to olefinic carbons appeared at δ 121.5 and 149.6. The epoxyenoate compound **34** was treated

Scheme 10

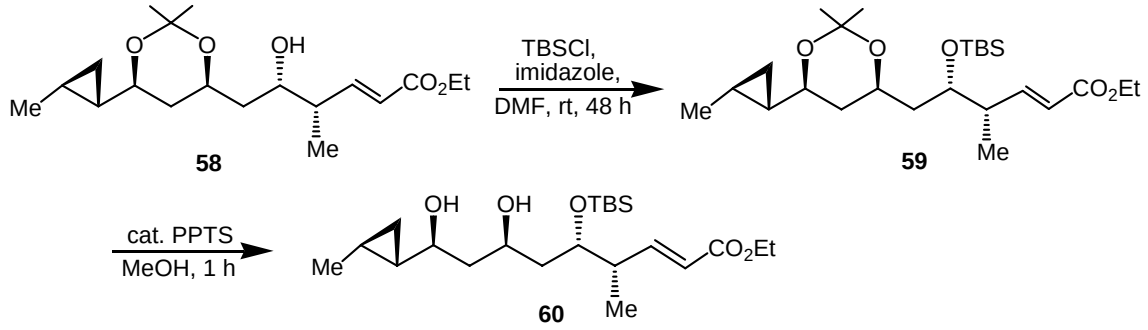


with 5 mol% of $Pd(PPh_3)_4$, $Me_2NH:BH_3$ and 3 equivalents of AcOH in CH_2Cl_2 to provide the compound **58**. The diastereoselectivity obtained in the above reaction was observed as 9:1 by the NMR spectroscopy. The formation of major *syn* isomer **58** was based on the literature precedents[28] and the stereoselectivity obtained was rationalized by stereospecific formation π-allylic complex, which proceeds with inversion of configuration at the allylic C-O bond (Figure 4).[29] The stereochemistry of new chiral centers in **58** was established by 2D NMR experiments on the corresponding group in **58** was protected as the silyl ether **59** using TBSCl and imidazole in DMF. The tetrahydropyran derivative **64** at a later stages of the synthesis (Scheme 14). The hydroxyl ^1H NMR spectrum of **59** displayed singlets at δ 0.06, 0.07, 0.90 due to TBS group and all other signals appeared at their respective positions. The ^{13}C NMR spectral data also supported the formation of **59**.

Figure 4**:** mechanism proposed for Pd(0) catalysed stereo- and regio selective opening of trisubstituted epoxyenoate

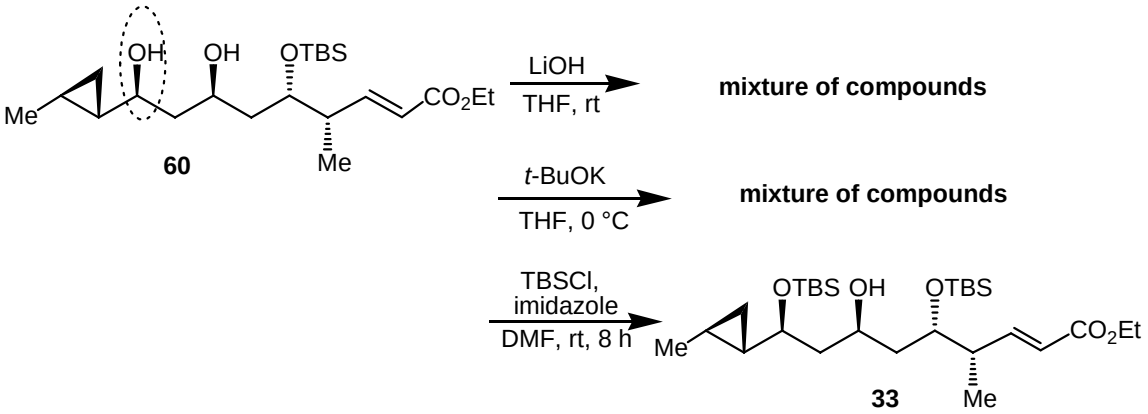


Scheme 11



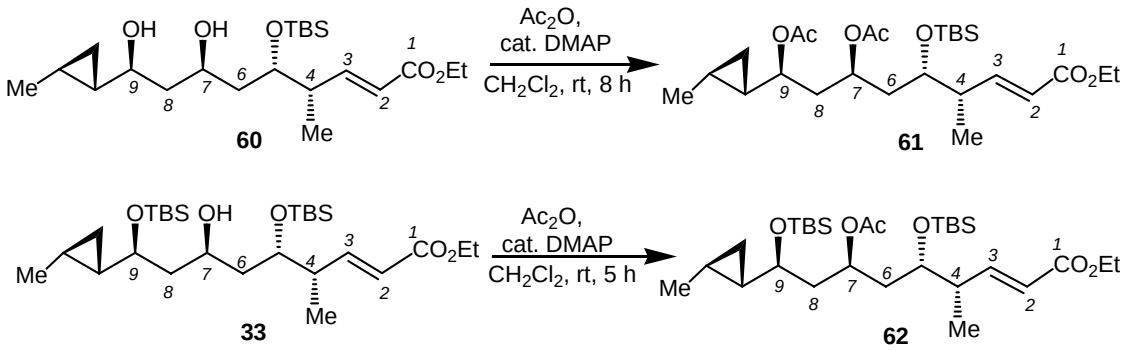
Selective deprotection of acetonide group in **59** was accomplished by using catalytic PPTS in methanol to afford the diol **60** (Scheme 11). The ^{1}H NMR spectrum of **60** showed the disappearance of signals due to isopropylidene group. The ^{13}C NMR spectral data also supported the structure of **60**. The diol **60** was subjected to the proposed intramolecular 1,4-Michael addition by using base (LiOH and KOBu^{t}) to yield an inseparable mixture of compounds, whose ^{1}H NMR spectrum tragent with many signals resulted from the formation of mixture of products (Scheme 12). The mixture of products were formed by Michael addition reaction of both hydroxyl groups giving rise to six (favorable) and eight (unfavorable) membered ring compounds due to the presence of reactive cyclopropane C_9-OH in **60**. In order to differentiate the reactivity of two hydroxyl groups in **60**, it was necessary to protect selectively the cyclopropyl alcohol. Gratifyingly, 60 on treatment with TBSCl-imidazole gave the *bis*-TBS-ether **33** (Scheme 12). The ^{1}H, ^{13}C NMR, and MS spectral data of **33** confirmed formation of *bis*-silylated product. In the ^{1}H NMR spectrum of **33**, signals due to two TBS groups were appeared as singlets at δ 0.08, 0.11, 0.13, 0.90 and 0.91 ppm. The regioselectivity obtained in the silyl protection was confirmed by converting the compound **33** into its acetate derivative **62**. In addition to acetylation of **60**

Scheme 12



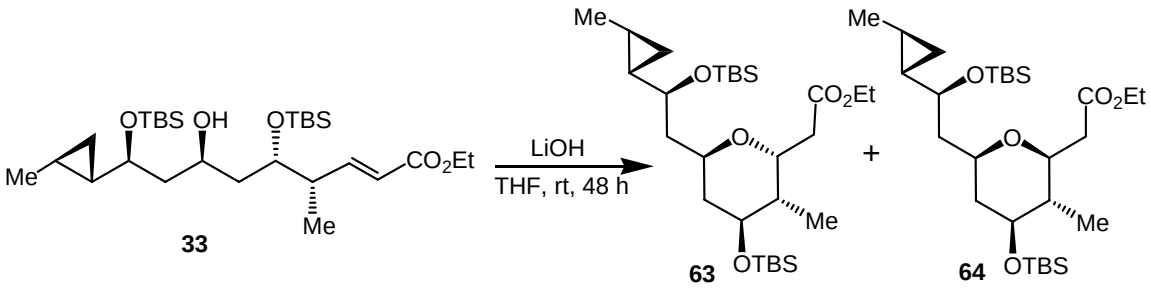
gave the diacetate **61** (Scheme 13). Comparison of ^{1}H NMR spectrum of **33**, **61** and **62** clearly showed that the hydroxyl group at C-7 was free. For example, the resonances due to H-7 in **62** showed a downfield shift indicating the presence of acetyl group at this position. The ^{1}H NMR spectrum of **61** displayed two singlets due to acetate methyl groups at δ 2.02 and 2.05 and while the methine protons bearing acetyl group appeared in the down field region as multiplets.

Scheme 13



Signal at δ 4.27–4.38 (multiplet) was assigned to H-9 (next to cyclopropane) while the signal at δ 4.92–5.07 (multiplet) to H-7 in the ^{1}H NMR spectrum of **61**. The ^{1}H NMR spectrum of the mono acetylated product **62** showed only one multiplet at δ 5.05–5.15 due to H-7 confirming the presence of a free OH group at C-7 in **33**. The intramolecular 1,4-Michael addition of *bis*-silylether derivative **33** in the presence of LiOH in THF provided two separable diastereomers **63** and **64** with moderate selectivity of 5:2 (Scheme 14). The ^{1}H NMR spectrum of **63** displayed signals due to oxymethine protons (H3, H5, H7 and H9) at δ 3.21 (q, 1H, *J* = 6.6 Hz), 3.54 (dt, 1H, *J* = 9.1, 4.4 Hz), 3.85-3.99 (m, 1H), and 4.41 (dt, 1H, *J* = 10.3, 4.6 Hz) ppm. Whereas, the ^{1}H NMR spectrum of **64** showed the corresponding four oxymethine signals at δ 3.19 (dt, 1H, *J* =7.7, 5.7 Hz), 3.34 (dt, 1H, *J* = 10.0, 4.5 Hz), 3.43 (dt, 1H, *J* = 9.3, 3.1 Hz), and 3.43-3.58 (m, 1H) ppm. Stereochemistry of **63** and **64** was deduced based on the 2D NOESY and COSY spectroscopic studies (Figure 5 & 6). The 2D NOESY spectrum of major diastereomer **63** showed a strong NOE between C_5-methine proton and C_7-methine proton indicating their *cis* relationship in the tetrahydropyran ring and thus conformed the stereochemistry of epoxide obtained in the Sharpless asymmetric epoxidation as predicted by choosing appropriate (+)-tartarate ligand (Scheme 10). Further strong NOE between C_4-methyl and C_5-methine protons confirmed the *syn* stereoselectivity obtained in the reductive opening of epoxyenoate (Scheme 10).

Scheme 14



Absence of NOE between C_3-methine and C_5-methine protons, and strong NOE between C_2-methylene and C_5-methine protons indicated the C_3-substituent in the axial position thereby confirming the structure of **63** as unwanted isomer (Figure 5). The NOESY spectrum of **64** displayed strong NOE interactions between C_3, C_5 and C_7-methine protons confirming their *cis* relation ship. Further NOE interactions between C_4-methyl and C_5-methine protons confirmed their *cis* relationship. Accounting all other NOE interactions, spatial arrangement of all the substituents in the tetrahydropyran asserted to be in the required equatorial position in **64** (Figure 6). The epimerization studies of **63** into **64** was conducted. Thus major diastereomer **63** was treated with *t*-BuOK for several hours to get a new compound whose spectroscopic data was compared with the previously isolated compound **64**.

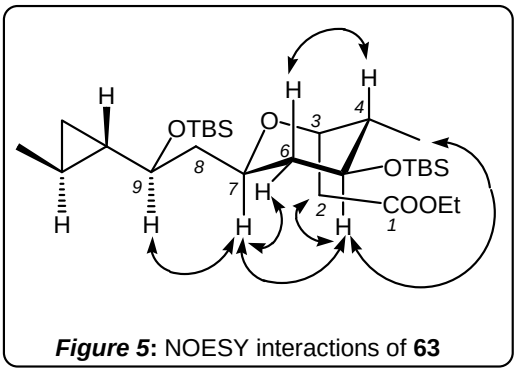


***Figure 5*: NOESY interactions of **63**

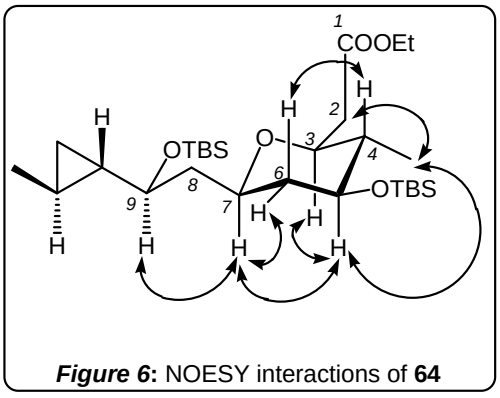
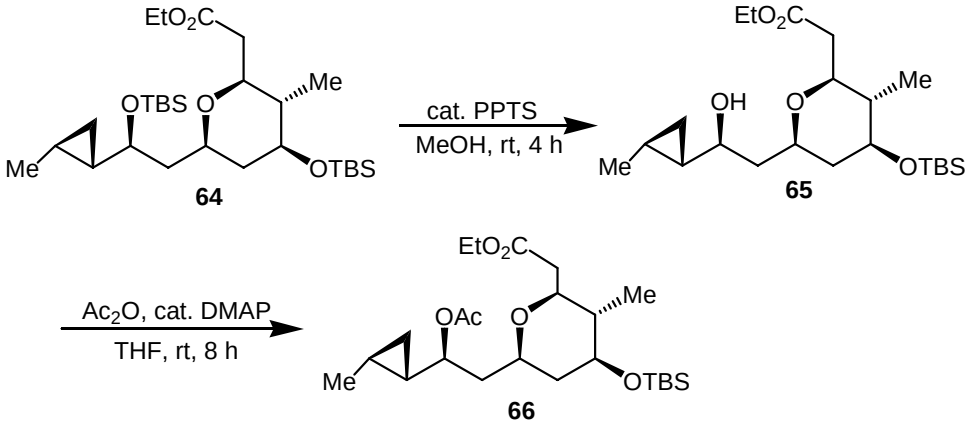


***Figure 6*: NOESY interactions of **64**

Compound **64** equipped with all the required chiral centers, was converted into the seco acid **32** by two step sequence. Thus, **64** was subjected to mild acid treatment with PPTS to afford the hydroxy ester **65**. The ^{1}H and ^{13}C NMR spectral data supported the structure of **65** (Scheme 15). The ESI MS spectrum gave a molecular ion peak (*m*/z) at 414 and further supported the structure of **65**. It is interesting to note that **64** has two TBS-groups, one in the side chain and second in the tetrahydropyran frame work. Our interest to

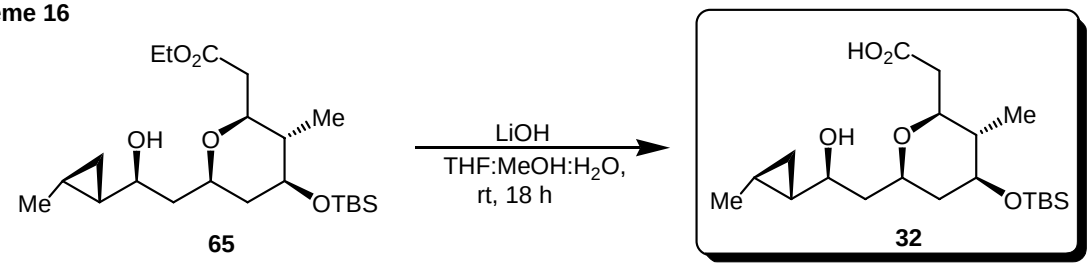
deprotect one TBS group selectively was by the differential reactivity. Thus **64** was treated with mild acidic PPTS in MeOH at room temperature for 1 h to give a slower moving product which was assigned tentatively the structure **65**. However in order to exclusively prove the structure **65**, it was converted into the acetate derivative **66**. Now it would be possible to differentiate the resonance of the proton in the ^{1}H NMR spectrum. The ^{1}H NMR spectrum of **66** displayed signal due to proton attached to the acetate group as a multiplet at δ 4.35–4.41. The chemical shift was characteristic of oxymethine proton adjacent to cyclopropane and thus structure of **66** was adjudged (Scheme 15).

Scheme 15

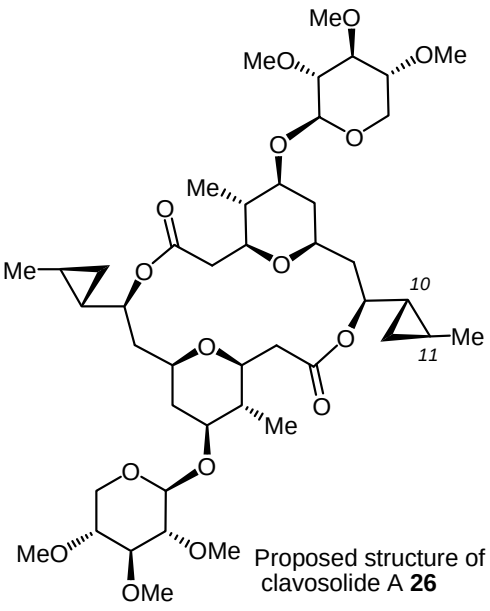


Finally, hydrolysis of ester group of **65** was accomplished using LiOH in THF:MeOH:H_2O in 10:1:1 ratio to afford the seco acid **32** (Scheme 16). The ^{1}H NMR and optical rotation of **32** was comparable to the data provided by Prof. Lee (personnel communication), thus confirmed the structure of **32** without any doubt. Recently, Lee et al[31a] dimerised the seco acid (**32**) into the natural product clavosolide A. However, the spectral data of synthetic clavosolide A and natural product was not in agreement. Willis and co-workers reported the first total synthesis of clavosolide A (**26**). [30] They proposed that the stereochemistry of C_{10} and C_{11} carbons were wrongly assigned as 10*S*, 10'*S*, 11*S*, 11'*S* instead of 10*R*, 10'*R*, 11*R*, 11'*R*. Later, Chakraborty et al completed the total synthesis of clavosolide A (**26**) and arrived at the same conclusion.[32] The exact structure of clavosolide A was also confirmed by total synthesis of revised structure of natural product clavosolide A (**66**).[31b,33,34]

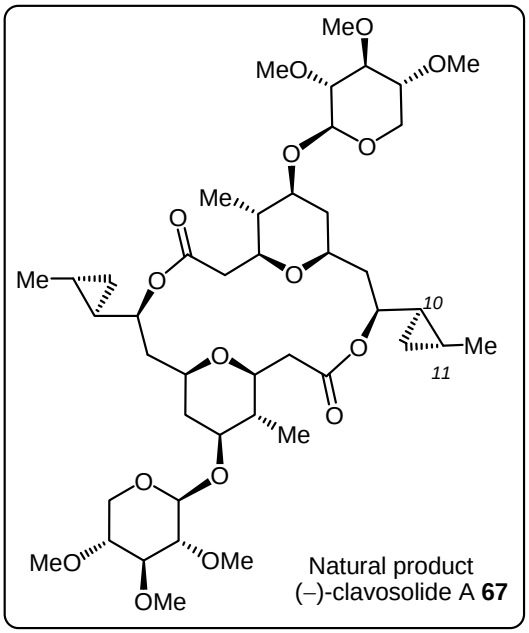
Scheme 16



In conclusion, we have completed the synthesis of monomeric seco acid of proposed structure of diolide clavosolide A (**26**) using stereoselective Simmons-smith cyclopropanation, Sharpless asymmetric epoxidation, regio- and stereoselective reductive opening of epoxyenoate and stereoselective intramolecular 1,4-michael addition as key steps to introduce five stereogenic centers (C_3-O, C_4-Me, C_5-OH, C_{10}, C_{11}-cypropane), while two other chiral centers (C_7-OH, C_9-OH) were adopted from starting material D-glucose. In addition, our flexible strategy to clavosolide A allowed to determine the stereochemistry of cyclopropane moiety in the initial stage, and with the revision of stereochemistry at cyclopropane functionality made this method viable for the synthesis of natural product (–)-clavosolide A from the intermediate **43** by following the same sequence of reactions discussed and established in this section.



Proposed structure of clavosolide A **26**



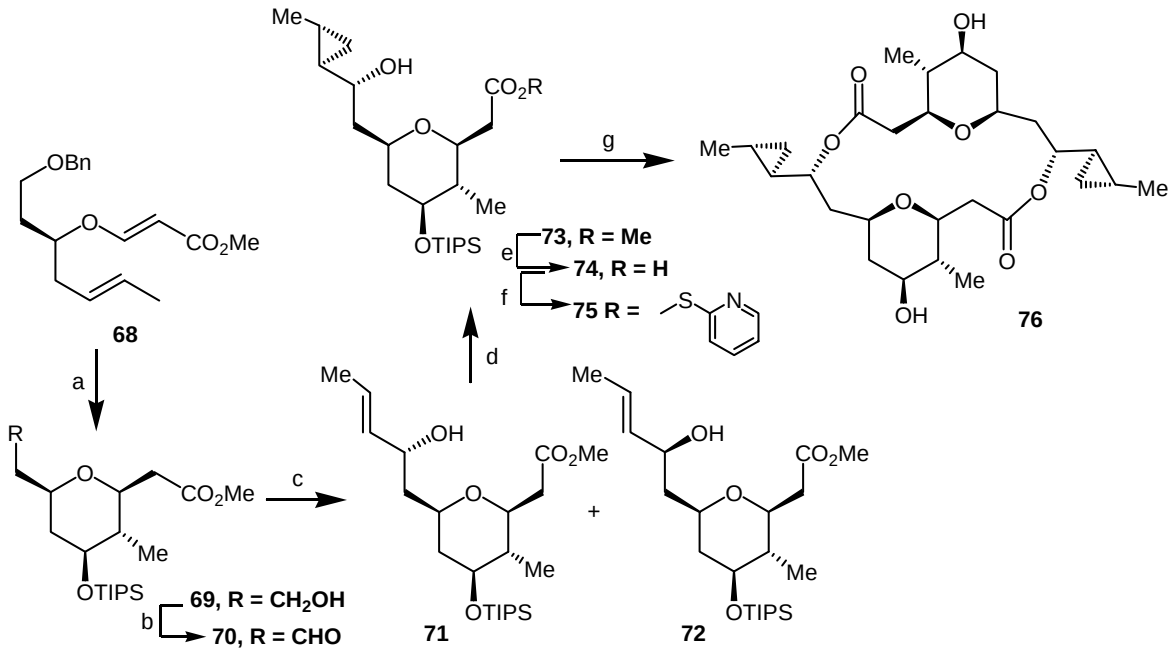
Natural product (–)-clavosolide A **67**

OTHER APPROACHES

Willis approach[30]

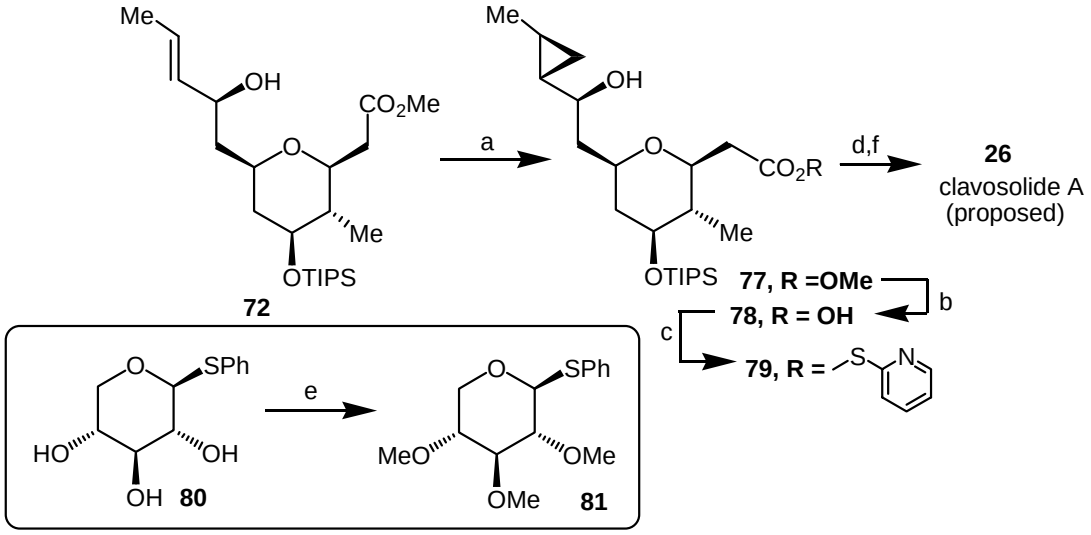
First total synthesis of proposed structure of clavosolide A (**26**) was accomplished by Willis and co-workers in an elegant and concise manner. Their synthetic endeavor relied on stereoselective synthesis of highly substituted tetrahydropyran (THP) ring based on the TFA mediated prins-type cyclisation of *S*-homoallylic enol ether **67** to install requisite chiral centers. The side chain of the THP was introduced using Nozaki-Hiyama-Kishi reaction (Scheme 16). Subsequent Charette's *syn*-selective cyclopropanation reaction on **71** and **72** afforded the corresponding cyclopropyl derivatives **73** and **77** respectively. Stereochemistry of **73** was adjudged by X-ray studies of derived diolide **76** and the requisite **77** was converted the corresponding C_2 symmetric diol **31**. Finally, glycosidation of diolide **31** using D-xylose thioglycoside **81** completed the synthesis of proposed structure of clavosolides A **26** (Scheme 17), and the spectral data of **26** was not in conformity with the natural product, particularly in the cyclopropane region. Thus, Willis et al proposed revision of stereochemistry at C10-C11 cyclopropane ring in **26** as 10*R*, 10'*R*, 11*R* and 11'*R* (**67**).

Scheme 16



Reagents and Conditions: a) (i) TFA, CH_2Cl_2; (ii) K_2CO_3, MeOH; (iii) TIPSCl, DMF, imidazole; (iv) H_2, Pd-C, EtOH; b) Dess-Martin periodinane; (c) *E*-1-bromo-1-propene, $CrCl_2$, $NiCl_2$, DMF; (d) Et_2Zn, CH_2I_2; e) TMSONa, CH_2Cl_2, AcOH; f) 2,2'-dipyridyl disulfide, PPh_3, toluene; g) (i) toluene, reflux; (ii) TBAF, THF.

Scheme 17

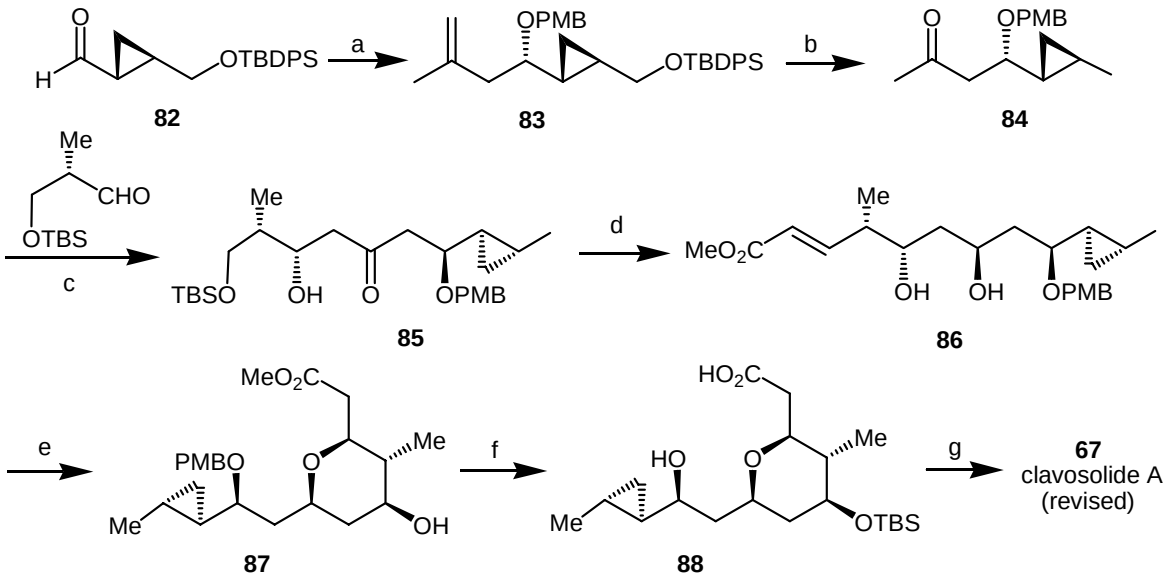


Reagents and Conditions: a) Et_2Zn, CH_2I_2; b) TMSONa, CH_2Cl_2, AcOH; c) 2,2'-bipyridyl disulfide, PPh_3, toluene; d) (i) toluene, reflux; (ii) TBAF, THF; e) NaH, MeI, DMF; f) **81**, NBS, CH_2Cl_2.

Lee's approach[31b]

Lee et al completed the synthesis of the revised structure of clavosolide A (**67**) and unambiguously proved the natural product structure. Their total synthesis was based on stereoselective boron aldol reactions and stereoselective reduction of ketone to introduce the C5-OH, C7-OH and C9-OH centers of **67**. Construction of THP ring by a stereoselective intramolecular1,4-Micheal addition was accomplished by using NaH.

Scheme 18

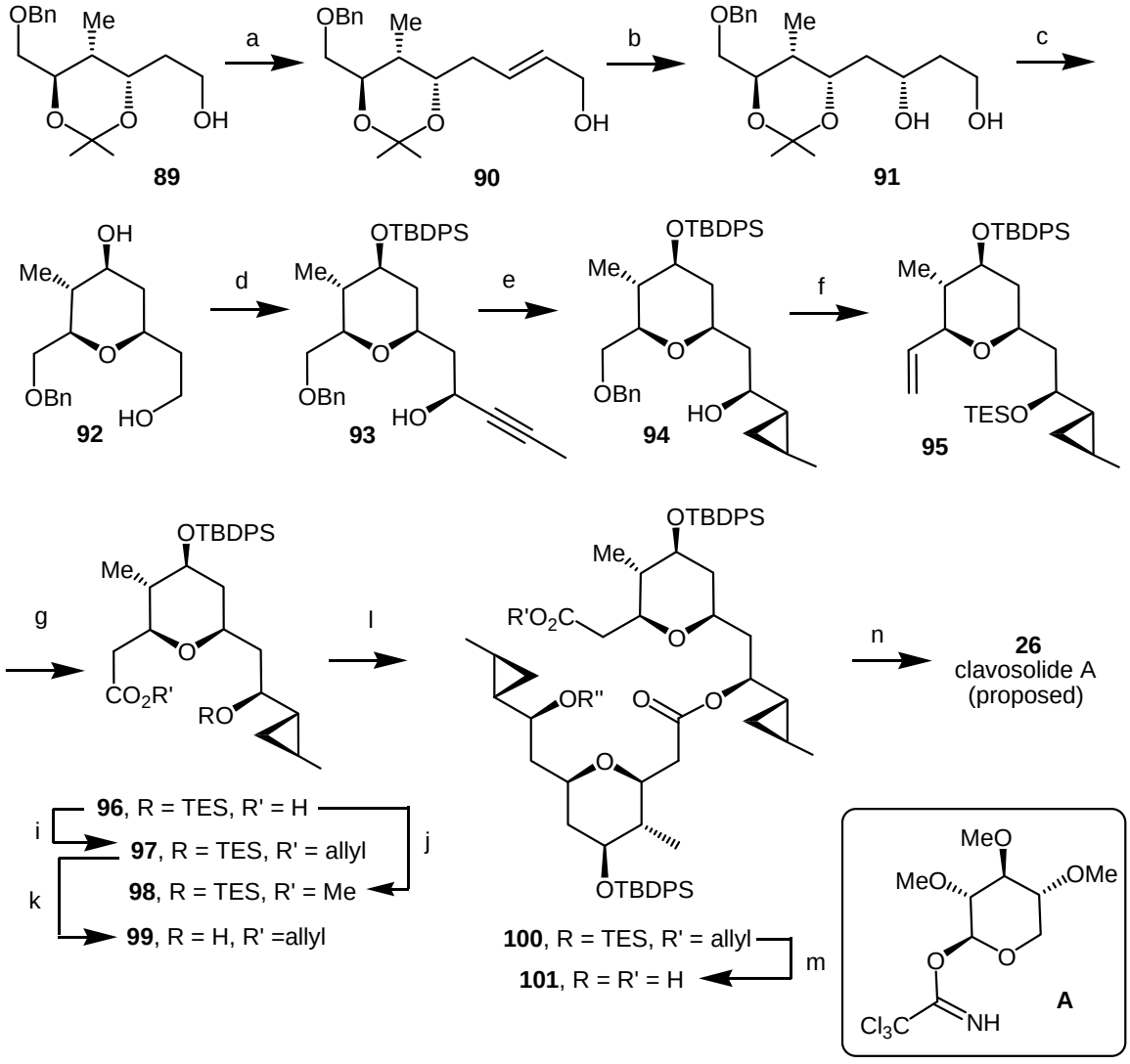


***Reagents and Conditions**:* a) (i) Isobutene, TMEDA, *n*-BuLi,(–)-$(Ipc)_2BOMe$, ether, –78 °C; (ii) $PMBO(C{=}NH)CCl_3$, TsOH, rt; b) (i) TBAF, THF, rt; (ii) CBr_4, PPh_3, THF, rt; (iii) LAH, THF, rt; (iv) O_3, pyridine, MeOH, –78 °C; c) *i*-Pr_2NEt, Bu_2BOTf, ether, –78 °C; d) (i) $Me_4NB(OAc)_4H$, MeCN-AcOH; (ii) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, rt; (iii) TBAF, THF, rt; (iv) Dess-Martin periodinane, $NaHCO_3$, rt; (v) $MeO_2CCH_2P(O)(OMe)_2$, LiCl, e) (i) *i*-Pr_2NEt, MeCN, 0 °C-rt; (ii) CSA, MeOH-H_2O, rt; (iii) NaH, THF, rt; f) (i) TBSOTf, Et_3N, CH_2Cl_2, 0 °C; (ii) DDQ, CH_2Cl_2-H_2O, rt; (iii) LiOH, THF-H_2O-MeOH, rt; g) (i) 2,4,6-$Cl_3PhCOCl$, Et_3N, THF, rt, (ii) DMAP, toluene, reflux; (iii) TBAF, THF, 0 °C; (iv) **A**, BF_3:OEt_2, 4Å MS, CH_2Cl_2, –78 °C-rt.

Dimerisation of derived seco acid **88** and subsequent glycosidation accomplished the first total synthesis of natural product **67** (Scheme 18).

Chakraborty's approach[32]

Scheme 19



Reagents and Conditions: a) (i) $(COCl)_2$, DMSO, Et_3N, DCM, −78 °C to 0 °C, 1 h; (ii) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, rt, 4 h; (iii) DIBAL-H, CH_2Cl_2, −78 °C, 20 min; bi) (i) D(−)-DIPT, $Ti(O^iPr)_4$, TBHP, 4 Å MS powder, CH_2Cl_2, −20 °C, 3 h; (ii) Red-Al, THF, −10 °C, 3 h; c) (i) TBDPSCl, Et_3N, DMAP (cat), DMF, 0 °C to rt, 5 h; (ii) MsCl, Et_3N, DMAP (cat), DCM, 0 °C to rt, 30 min; (iii) CSA (cat), MeOH, rt, 48 h; d) (i) TBDPSCl, imidazole, DMAP (cat), DMF, 0 °C to rt, 24 h; (ii) TBAF, THF, 0 °C, 3 h; (iii) $(COCl)_2$, DMSO, Et_3N, DCM, −78 °C to 0 °C, 1 h; (iv) propyne, LDA, THF, −78 °C; e) (i) Red-Al, Et_2O, 0 °C to rt, 2 h; (ii) Et_2Zn, CH_2I_2, CH_2Cl_2, −20 to 0 °C, 4 h; (iii) TESCl, Et_3N, DMAP, DCM, 0 °C to rt, 1 h; f) (i) H_2, Pd–C, hexane, rt, 1 h; (ii) SO_3–py, Et_3N, DCM, 0 °C to rt, 1 h; (iii) $Ph_3P{=}CH_2$, Et_2O, 0 °C to rt, 1 h; g) (i) $H_3B.SMe_2$, THF, 0 °C, 30 min, then H_2O_2, NaOH; (ii) $(COCl)_2$, DMSO, Et_3N, DCM, −78 °C to 0 °C, 1 h; (iii) $NaClO_2$, $NaH_2PO_4.2H_2O$, 2-methyl-2-butene, *t*-BuOH, rt, 1 h; i) allyl alcohol, K_2CO_3, rt, 1 h j) CH_2N_2, Et_2O, 0 °C, 10 min; k) CSA, MeOH–DCM (1:4), 0 °C, 10 min; l) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, rt, 3 h, then DMAP; m) (i) CSA, MeOH–DCM (1:4), 0 °C, 10 min; (ii) $Pd(PPh_3)_4$, morpholine, THF, rt, 1 h; n) (i) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, rt, 3 h, DMAP, toluene, 10^{-3} M, 80 °C, 5 h; (ii) TBAF, AcOH (cat), THF, 0 °C to rt, 8 h; (iii) **A**, TMSOTf, DCM, 4Å MS, 0 °C to rt, 2 h.

More recently Chakraborty et al also completed the total synthesis of proposed structure of clavosolide A (**26**) and suggested same revision of stereochemistry in clavosolide A (**26**). They constructed the key THP ring using a cycloetherification reaction by a S_N^2 type ring closure from a chiral tetrad system **91** which in turn obtained from reductive opening trisubstituted epoxide by sequence reactions. Side chain extension, *syn*-selective Simmons-Smith cyclopropanation and functional group manipulations led to **96**. Finally, a two step dimerisation, coupling and maclolactonisation by using Yamaguchi protocol gave macrocyclic diolide, whose global deprotection followed glycosidation with 2,3,4-tri-*O*-methyl-β-D-xylopyranosyl trichloroacetimidate (**A**) furnished the proposed structure of clavosolide **26** (Scheme 19). Chakraborty and co-workers also came to same conclusion as suggested by Willis et al.

Table 1: Crystal data and structure refinement for Compound 43

Empirical formula	$C_{13}\ H_{20}\ O_5$
Formula weight	256.29
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, C2
Unit cell dimensions	a = 25.246(3) Å
	b = 5.3144(6) Å beta = 92.231(2)º
	c = 10.5370(12) Å
Volume	1412.7(3) $Å^3$
Z, Calculated density	4, 1.205 mg/m^3
Absorption coefficient	0.092 mm^{-1}
F(000)	552
Crystal size	0.55 x 0.27 x 0.10 mm
Theta range for data collection	2.47º to 24.99º
Limiting indices	-29<=h<=29, -6<=k<=6, -8<=l<=12
Reflections collected / unique	3535 / 2323 [R(int) = 0.0149]
Completeness to theta = 24.99	99.4 %
Max. and min. transmission	0.9908 and 0.9515
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2323 / 1 / 166
Goodness-of-fit on F^2	1.031
Final R indices [I>2sigma(I)]	R1 = 0.0505, wR2 = 0.1293
R indices (all data)	R1 = 0.0604, wR2 = 0.1362
Absolute structure parameter	0.7(19)
Largest diff. peak and hole	0.259 and -0.194 e. $Å^{-3}$

Table 2: Bond lengths [Å] and angles [deg] for compound 43

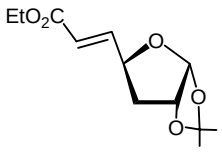
O(1)-C(1)	1.407(4)	C(3)-C(2)-C(1)	104.2(2)
O(1)-C(9)	1.412(3)	C(2)-C(3)-C(4)	101.7(2)
O(2)-C(2)	1.423(3)	O(3)-C(4)-C(5)	109.9(2)
O(2)-C(9)	1.424(3)	O(3)-C(4)-C(3)	103.7(3)
O(3)-C(1)	1.397(3)	C(5)-C(4)-C(3)	115.7(2)
O(3)-C(4)	1.435(4)	C(7)-C(5)-C(4)	119.9(3)
O(4)-C(8)	1.190(4)	C(7)-C(5)-C(6)	60.0(2)
O(5)-C(8)	1.321(4)	C(4)-C(5)-C(6)	118.3(2)
O(5)-C(12)	1.455(6)	C(8)-C(6)-C(7)	117.9(3)
C(1)-C(2)	1.519(4)	C(8)-C(6)-C(5)	118.6(3)
C(2)-C(3)	1.510(4)	C(7)-C(6)-C(5)	58.7(2)
C(3)-C(4)	1.514(4)	C(5)-C(7)-C(6)	61.2(2)
C(4)-C(5)	1.480(4)	O(4)-C(8)-O(5)	124.1(3)
C(5)-C(7)	1.471(5)	O(4)-C(8)-C(6)	125.6(3)
C(5)-C(6)	1.508(4)	O(5)-C(8)-C(6)	110.2(3)
C(6)-C(8)	1.473(5)	O(1)-C(9)-O(2)	104.9(2)
C(6)-C(7)	1.490(5)	O(1)-C(9)-C(11)	108.5(2)
C(9)-C(11)	1.494(4)	O(2)-C(9)-C(11)	108.3(3)
C(9)-C(10)	1.501(4)	O(1)-C(9)-C(10)	110.9(3)
C(12)-C(13)	1.397(9)	O(2)-C(9)-C(10)	110.9(3)
C(1)-O(1)-C(9)	108.9(2)	C(11)-C(9)-C(10)	112.9(3)
C(2)-O(2)-C(9)	107.4(2)	C(13)-C(12)-O(5)	110.3(5)
C(1)-O(3)-C(4)	107.4(2)		
C(8)-O(5)-C(12)	118.1(3)		
O(3)-C(1)-O(1)	110.9(2)		
O(3)-C(1)-C(2)	107.7(2)		
O(1)-C(1)-C(2)	105.6(2)		
O(2)-C(2)-C(3)	109.8(3)		
O(2)-C(2)-C(1)	104.1(2)		

Table 3: Torsion angles [deg] for compound 43

C(4)-O(3)-C(1)-O(1)	93.8(3)	C(4)-C(5)-C(6)-C(8)	-142.9(3)
C(4)-O(3)-C(1)-C(2)	-21.2(3)	C(4)-C(5)-C(6)-C(7)	110.0(3)
C(9)-O(1)-C(1)-O(3)	-128.4(2)	C(4)-C(5)-C(7)-C(6)	-107.4(3)
C(9)-O(1)-C(1)-C(2)	-12.1(3)	C(8)-C(6)-C(7)-C(5)	-108.2(4)
C(9)-O(2)-C(2)-C(3)	134.5(2)	C(12)-O(5)-C(8)-O(4)	1.1(7)
C(9)-O(2)-C(2)-C(1)	23.4(3)	C(12)-O(5)-C(8)-C(6)	179.1(5)
O(3)-C(1)-C(2)-O(2)	111.5(2)	C(7)-C(6)-C(8)-O(4)	38.4(6)
O(1)-C(1)-C(2)-O(2)	-7.0(3)	C(5)-C(6)-C(8)-O(4)	-29.3(6)
O(3)-C(1)-C(2)-C(3)	-3.6(3)	C(7)-C(6)-C(8)-O(5)	-139.6(4)
O(1)-C(1)-C(2)-C(3)	-122.1(3)	C(5)-C(6)-C(8)-O(5)	152.8(3)
O(2)-C(2)-C(3)-C(4)	-86.0(3)	C(1)-O(1)-C(9)-O(2)	26.7(3)
C(1)-C(2)-C(3)-C(4)	25.0(3)	C(1)-O(1)-C(9)-C(11)	142.3(3)
C(1)-O(3)-C(4)-C(5)	161.8(2)	C(1)-O(1)-C(9)-C(10	-93.2(3)
C(1)-O(3)-C(4)-C(3)	37.5(3)	C(2)-O(2)-C(9)-O(1)	-31.3(3)
C(2)-C(3)-C(4)-O(3)	-38.0(3)	C(2)-O(2)-C(9)-C(11)	-147.1(2)
C(2)-C(3)-C(4)-C(5)	-158.4(3)	C(2)-O(2)-C(9)-C(10)	88.5(3)
O(3)-C(4)-C(5)-C(7)	150.8(3)	C(8)-O(5)-C(12)-C(13)	104.8(6)
C(3)-C(4)-C(5)-C(7)	-92.2(3)		
O(3)-C(4)-C(5)-C(6)	81.0(4)		
C(3)-C(4)-C(5)-C(6)	-162.0(3)		
C(7)-C(5)-C(6)-C(8)	107.0(4)		

Experimental

Ethyl 3,5,6-trideoxy-1,2-*O*-isopropylidene-α-D-*erythro*-hept-5*E*-eno-1,4-furanose-7-uronate (38):



Method A: To a solution of **42** (1.0 g, 4.89 mmol) in CH_2Cl_2 (40 mL) was added silica supported $NaIO_4$ (10 g, 5 mmol) at room temperature. After stirring for 10 min, the reaction mixture was filtered and concentrated. The residue was dissolved in toluene (30 mL), charged with PPh_3=$CHCO_2Et$ (2.55 g, 7.33 mmol) and heated under reflux for 4 h. The reaction mixture was concentrated and residue purified on silica gel using EtOAc:light petroleum ether (1:9) as an eluent to obtain **38** (70%) as a colorless viscous liquid.

Method B: To a solution of **42** (9 g, 44.07 mmol) in 5% aq. $NaHCO_3$ (100 mL) was added $NaIO_4$ (12 g, 56.10 mmol) portionwise over period of 30 min at room temperature. After 1 h, triethylphosphonoacetate (15 mL, 75.60 mmol) and 6 M K_2CO_3 (100 mL) were introduced in succession and stirred for 48 h. The reaction mixture was extracted with CH_2Cl_2. The combined organic layer was washed with water, brine, dried (Na_2SO_4), concentrated and the residue purified on silica gel using EtOAc:light petroleum ether (1:9) to afford **38**.

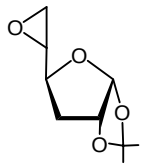
Yield	: 10.46 g (98%)
Mol. Formula	: $C_{12}H_{18}O_5$
Optical Rotation $[\alpha]_D^{25}$	: –56.9 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3444, 2984, 1718, 1661, 1445, 1371, 1305, 1184, 1030, 981 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.29 (t, 3H, *J* = 7.0 Hz), 1.32, 1.51 (2 s, 6H), 1.61 (ddd, 1H, *J* = 13.3, 10.9, 4.7 Hz), 2.25 (dd, 1H, *J* = 13.3, 4.3 Hz), 4.18 (q, 2H, *J* = 7.0 Hz), 4.70-4.80 (m, 2H), 5.85 (d, 1H, *J* = 3.5 Hz), 6.06 (dd, 1H, *J* = 15.7, 1.5 Hz), 6.90 (dd, 1H, *J* = 15.7, 4.9 Hz) ppm.
^{13}C NMR	: δ 13.74 (q), 25.61 (q), 26.20 (q), 38.66 (t), 59.94 (t), 75.79

($CDCl_3$, 50 MHz) (d), 79.90 (d), 105.08 (d), 110.82 (s), 120.93 (d), 144.67 (d), 165.59 (s) ppm.

Elemental Analysis **Calcd.:** C, 59.49; H, 7.49%.

Found: C, 59.70; H, 7.51%.

5,6-Anhydro-3-deoxy-1,2-*O*-isopropylidene-α-D-*ribo*-hexofuranose (45):



To a solution of **42** (2.5 g, 12.24 mmol), Bu_2SnO (60 mg, 0.24 mmol) and *p*TsCl (2.5 g, 13.11 mmol) in CH_2Cl_2 (40 mL) was added Et_3N (1.8 mL, 12.91 mmol) slowly over a period of 5 min at room temperature. After stirring for 20 min, reaction mixture was filtered through a plug of Celite, concentrated and the residue purified on silica gel using EtOAc:light petroleum ether (1:4) to give **44** (4.30 g, 98%).

To a stirred solution of **44** (4.30 g, 11.99 mmol) in THF (40 mL) was added NaH (60% dispersion in mineral oil, 1.0 g, 25.00 mmol) portionwise over a period of 20 min at 0 °C. After 1 h, the reaction was quenched with ice-cold aq. saturated NH_4Cl and extracted with EtOAc. Combined organic layer was washed with water, brine, dried (Na_2SO_4) and the residue purified on silica gel using EtOAc: light petroleum ether (1:9) to afford **45** (1.78 g, 80%) as a colorless light liquid.

Mol. Formula : $C_9H_{14}O_4$

Optical Rotation $[\alpha]_D^{25}$: –18.7 (*c* 1.3, $CHCl_3$), lit., –18.0 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3444, 2988, 2937, 1637, 1438, 1383, 1316, 1259, 1217, 1165, 1084, 1064, 1022, 943 cm^{-1}.

^{1}H NMR : δ 1.32, 1.50 (2 s, 6H), 1.72 (ddd, 1H, *J* = 13.3, 10.7, 4.7 Hz),

($CDCl_3$, 200 MHz) 2.07 (dd, 1H, *J* = 13.3, 4.4 Hz), 2.61 (dd, 1H, *J* = 4.9, 2.7 Hz), 2.83 (dd, 1H, *J* = 4.9, 4.1 Hz), 3.15 (dt, 1H, *J* = 4.1, 2.7 Hz), 4.20 (dt, 1H, *J* = 10.7, 4.4 Hz), 4.75 (dd, 1H, *J* = 4.7, 3.6 Hz), 5.85 (d, 1H, *J* = 3.6 Hz) ppm.

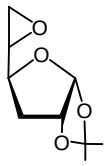
^{13}C NMR : δ 25.87 (q), 26.49 (q), 33.92 (t), 44.69 (t), 51.34 (d), 77.59 (d),

($CDCl_3$, 50 MHz) 79.98 (d), 105.27 (d), 110.96 (s) ppm.

Elemental Analysis **Calcd.:** C, 58.05; H, 7.58%.

Found: C, 58.15; H, 7.61%.

5,6-Anhydro-3-deoxy-1,2-*O*-isopropylidene-β-L-*lyxo*-hexofuranose (48):



A solution of **42** (1.0 g, 4.89 mmol) and pivaloyl chloride (0.6 mL, 4.87 mmol) in pyridine (5 mL) was stirred at 0 °C for 6 h. The reaction mixture was concentrated and the residue partitioned between EtOAc and 0.1 M HCl. The organic layer was washed with water, brine, dried ($NaSO_4$), concentrated, and the residue purified on silica gel using EtOAc:light petroleum ether (2:8) to afford **46** (1.27 g, 90%) as a white solid.

To a stirred solution of **46** (1.27g, 4.40 mmol) and Et_3N (0.7 mL, 5.02 mmol) in CH_2Cl_2 (20 mL) was added MsCl (0.36 mL, 4.65 mmol) at 0 °C. After 1 h, the reaction was quenched with ice-cold water and extracted with EtOAc. Combined organic layer was washed with brine, dried (Na_2SO_4), concentrated and the residue dissolved in THF:MeOH:H_2O (4:2:1, 10 mL), charged with LiOH (0.20 g, 8.35 mmol) at room temperature. After stirring for 3 h, the reaction mixture was concentrated and the residue partitioned between EtOAc and water. Combined organic layer was washed with brine, dried (Na_2SO_4), concentrated and the residue purified on silica gel using EtOAc:light petroleum ether (1:6) to afford **48** (0.623 g, 76%) as a thick liquid.

Mol. Formula : $C_9H_{14}O_4$

Optical Rotation $[\alpha]_D^{25}$: –5.4 (*c* 1.2, $CHCl_3$), lit. –5.0 (*c* 2.7, $CHCl_3$).

^{1}H NMR : δ 1.29, 1.47 (2 s, 6H), 1.85 (ddd, 1H, *J* = 13.3, 10.7, 4.7 Hz), 2.15 (dd, 1H, *J* = 13.3, 4.5 Hz), 2.80 (br d, 2H, *J* = 3.4 Hz), 2.99-3.07 (m, 1H), 4.17 (dt, 1H, *J* = 10.7, 4.5 Hz), 4.74 (dd, 1H, *J* = 4.7, 3.6 Hz), 5.85 (d, 1H, *J* = 3.6 Hz) ppm.

($CDCl_3$, 200 MHz)

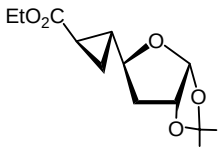
^{13}C NMR : δ 25.92 (q), 26.52 (q), 35.31 (t), 43.85 (t), 51.98 (d), 76.81 (d), 79.98 (d), 105.39 (d), 111.00 (s) ppm.

($CDCl_3$, 50 MHz)

Elemental Analysis **Calcd.:** C, 58.05; H, 7.58%.

Found: C, 58.13; H, 7.60%.

Ethyl 3,5,6-trideoxy-5,6-*C*-methylene-1,2-*O*-isopropylidene-α-D-*gulo*-hepto-1,4-furanos-7-uronate (43):



To a stirred solution of triethylphosphonoacetate (6.0 mL, 30.24 mmol) in THF (10 mL) was added NaH (60% dispersion in mineral oil, 1.2 g, 30.00 mmol) portionwise over period of 10 min at 0 °C, and a solution of **45** (2.8 g, 15.03 mmol) in THF (5 mL) introduced at the same temperature. After 30 min, reaction mixture was warmed to room temperature and then heated under reflux for 12 h. The reaction was quenched aq. saturated NH_4Cl and extracted with ethyl acetate. Combined organic layer was washed with water, concentrated, dried (Na_2SO_4) and the residue purified on silica gel using EtOAc:light petroleum ether (1:9) as an eluent to give **43** as a colorless solid. Recrystallisation of **43** in CH_2Cl_2 furnished colorless crystalline solid.

Yield : 2.31 g (60%)

Mol. Formula : $C_{13}H_{20}O_5$, solid,

Melting Point : 62-64 °C

Optical Rotation $[\alpha]_D^{25}$: –100.6 (*c* 1.2, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3433, 2984, 2937, 1725, 1457, 1417, 1376, 1311, 1297, 1263, 1244, 1210, 1181, 1086, 1055, 1021, 966, 941 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.90 (ddd, 1H, *J* = 8.4, 6.3, 4.3 Hz), 1.10-1.20 (m, 1H), 1.22 (t, 3H, *J* = 7.2 Hz), 1.27, 1.45 (2 s, 6H), 1.50-1.75 (m, 3H), 2.14 (dd, 1H, *J* = 13.3, 4.2 Hz), 3.77 (ddd, 1H, *J* = 10.9, 6.9, 4.2 Hz), 4.07 (q, 2H, *J* = 7.2 Hz), 4.69 (dd, 1H, *J* = 4.7, 3.6 Hz), 5.75 (d, 1H, *J* = 3.6 Hz).

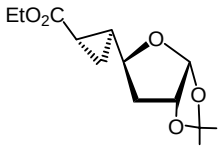
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 11.83 (d), 14.11 (q), 18.00 (t), 24.44 (d), 25.94 (q), 26.53 (q), 38.62 (t), 60.46 (t), 78.84 (d), 80.31 (d), 105.19 (d), 110.89 (s), 173.60 (s) ppm.

ESI MS (m/z): 279 (M+Na)

Elemental Analysis **Calcd.:** C, 60.92; H, 7.87%.

Found: C, 60.98; H, 7.92%.

Ethyl 3,5,6-trideoxy-5,6-*C*-methylene-1,2-*O*-isopropylidene-β-L-*talo*-hepto-1,4-furanos-7-onate (36):



To a solution of triethylphosphonoacetate (0.2 mL, 6.10 mmol) in toluene (6 mL) was added NaH (60% dispersion in mineral oil, 0.24 g, 6.00 mmol) portionwise over a period of 10 min at 0 °C and then introduced a solution of **48** (0.5 g, 2.68 mmol) in toluene (2 mL). After stirring for 30 min, reaction mixture was warmed to room temperature and then refluxed for 8 h. After usual work as reported earlier, the residue was purified on silica gel using EtOAc:light petroleum ether (1:6) as an eluent to afford **36** as a thick syrup.

Yield : 240 mg (35%)

Mol. Formula : $C_{13}H_{20}O_5$

Optical Rotation $[\alpha]_D^{25}$: +35.5 (*c* 2.0, $CHCl_3$).

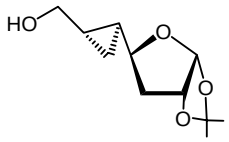
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.95-1.05 (m, 1H), 1.15-1.20 (m, 1H), 1.26 (t, 3H, *J* = 7.1 Hz), 1.29, 1.47 (2 s, 6H), 1.55–1.70 (m, 3H), 2.15 (dd, 1H, *J* = 13.3, 4.2 Hz), 3.90 (ddd, 1H, *J* = 10.6, 6.9, 4.2 Hz), 4.10 (q, 2H, *J* = 7.1 Hz), 4.72 (dd, 1H, *J* = 4.7, 3.8 Hz), 5.77 (d, 1H, *J* = 3.8 Hz) ppm.

ESI MS (m/z): 279 (M+Na)

Elemental Analysis **Calcd.:** C, 60.92; H, 7.87%.

Found: C, 61.13; H, 7.98%.

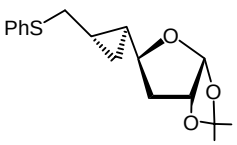
3,5,6-Trideoxy-5,6-*C*-methylene-1,2-*O*-isopropylidene-β-L-*talo*-hepto-1,4-furanose (49):



To a solution of **36** (1.0 g, 3.90 mmol) in toluene (20 mL) was added DIBAL-H (2.85M solution in toluene, 3 mL, 8.55 mmol) dropwise over a period of 5 min at –78 °C. After stirring for 3 h, the reaction was quenched with saturated sodium potassium tartarate solution, filtered through a pad of silica and concentrated. The residue was purified on silica gel using EtOAc:light petroleum ether (1:1) as an eluent to afford **49**.

Yield	: 777 mg (93%)
Mol. Formula	: $C_{11}H_{18}O_4$
Optical Rotation $[\alpha]_D^{25}$	: +8.2 (*c* 1.3, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3428, 2993, 2937, 1636, 1456, 1433, 1383, 1374, 1317, 1294, 1216, 1161, 1100, 1054, 1020, 932, 879, 847 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.54 (dt, 1H, *J* = 8.4, 5.0 Hz), 0.69 (dt, 1H, *J* = 8.4, 5.0 Hz), 0.85 (tt, 1H, *J* = 8.0, 4.6 Hz), 1.05–1.17 (m, 1H), 1.31, 1.48 (2 s, 6H), 1.60 (ddd, 1H, *J* = 13.3, 10.7, 4.8 Hz), 2.15 (dd, 1H, *J* = 13.3, 4.2 Hz), 3.42 (dd, 1H, *J* = 11.2, 7.0 Hz), 3.52 (dd, 1H, *J* = 11.2, 6.8 Hz), 3.75 (ddd, 1H, *J* = 10.7, 7.3, 4.2 Hz), 4.71 (dd, 1H, *J* = 4.8, 3.8 Hz), 5.80 (d, 1H, *J* = 3.8 Hz).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 7.93 (t), 17.67 (d), 19.07 (d), 25.73 (q), 26.29 (q), 38.07 (t), 65.18 (t), 80.05 (d), 80.24 (d), 104.83 (d), 110.37 (s) ppm.
Elemental Analysis	**Calcd.:** C, 61.66; H, 8.47%. **Found:** C, 61.75; H, 8.50%.

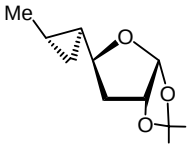
7-Phenythio-3,5,6,7-tetradeoxy-5,6-*C*-methylene-1,2-*O*-isopropylidene-β-L-*talo*-hepto-1,4-furanose (50):



A stirred solution of **49** (1.3 g, 6.07 mmol), PhSSPh (6.0 g, 27.48 mmol) and Bu_3P (6.0 mL, 24.08 mmol) in THF (20 mL) was heated under reflux for 5 h. The reaction mixture was concentrated and residue chromatographed on silica gel using EtOAc:light petroleum ether (1:9) as an eluent to give **50**.

Yield	: 1.58 g (85%)
Mol. Formula	: $C_{17}H_{22}O_3S$
IR ($CHCl_3$) $\tilde{\nu}$	: 3017, 2938, 2401, 1722, 1584, 1481, 1456, 1438, 1383, 1374, 1294, 1263, 1215, 1160, 1073, 1053, 1018, 932, 844 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.59 (dt, 1H, *J* = 8.1, 4.9 Hz), 0.75 (dt, 1H, *J* = 8.1, 4.9 Hz), 0.78-0.90 (m, 1H), 0.95-1.10 (m, 1H), 1.30, 1.46 (2 s, 6H), 1.57 (ddd, 1H, *J* = 13.3, 10.7, 4.7 Hz), 2.10 (dd, 1H, *J* = 13.3, 4.2 Hz), 2.87 (dd, 1H, *J* = 13.0, 7.8 Hz), 2.91 (dd, 1H, *J* = 13.0, 6.0 Hz), 3.59 (ddd, 1H, *J* = 10.8, 7.5, 4.2 Hz), 4.68 (dd, 1H, *J* = 4.7, 3.8 Hz), 5.77 (d, 1H, *J* = 3.8 Hz), 7.10-7.40 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 11.34 (t), 15.37 (d), 22.19 (d), 25.89 (q), 26.49 (q), 38.06 (t), 38.56 (t), 80.23 (d), 80.70 (d), 105.08 (d), 110.44 (s), 125.76, 128.67, 129.12, 136.50 (s) ppm.
Elemental Analysis	**Calcd.:** C, 66.63; H, 7.24%. **Found:** C, 66.67; H, 7.30%

3,5,6,7-Tetradeoxy-5,6-*C*-methylene-1,2-*O*-isopropylidene-β-L-*talo*-hepto-1,4-furanose (37):



Method A: To a suspension of Raney nickel (20 mL, in EtOH) was added to **50** (1.0 g, 3.26 mmol) in EtOH (10 mL) and stirred for 10 h. The reaction mixture was filtered through a plug of Celite, concentrated and the residue purified by silica gel column chromatography using EtOAc:light petroleum ether (1:20) as an eluent to afford **37** as a light liquid.

Method B: To a solution of **39*E*** (4.4 g, 23.88 mmol) in CH_2Cl_2 (20 mL) was added a 1 M solution of Et_2Zn (1M solution in heptane, 100 mL, 100 mmol) slowly over period of 30 min at –20 °C and stirred for 1 h. Then, reaction mixture was cooled to –40 °C, introduced CH_2I_2 (10 mL, 124.14 mmol) dropwise and warmed upto –20 °C. After 48 h, the reaction was quenched with slow addition of saturated NH_4Cl solution. The organic layer was separated and aqueous layer further extracted with CH_2Cl_2. Combined organic layer was dried (Na_2SO_4), concentrated and the residue purified on silica gel using EtOAc:light petroleum ether (1:20) as an eluent to afford **37** as a light liquid.

Yield : 563 mg (87%) and 4.21 g (89%)

Mol. Formula : $C_{11}H_{18}O_3$

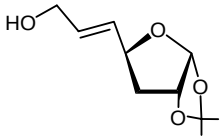
Optical Rotation $[\alpha]_D^{25}$: +20.0 (*c* 2.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 0.29-0.36 (m, 1H), 0.55-0.71 (m, 3H), 1.04 (d, 3H, *J* = 5.8 Hz), 1.29, 1.46 (2 s, 6H), 1.57 (ddd, 1H, *J* = 13.3, 10.5, 4.6 Hz), 2.10 (dd, 1H, *J* = 13.3, 4.1 Hz), 3.60 (ddd, 1H, *J* = 10.5, 7.0, 4.1 Hz), 4.67 (dd, 1H, *J* = 4.7, 3.9 Hz), 5.75 (d, 1H, *J* = 3.9 Hz) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz) : δ 9.93 (d), 11.63 (q), 18.39 (t), 22.25 (d), 25.99 (q), 26.56 (q), 38.77 (t), 80.45 (d), 81.67 (d), 105.10 (d), 110.53 (s) ppm.

Elemental Analysis **Calcd.:** C, 66.64; H, 9.15.
Found: C, 66.65; H, 9.38.

3,5,6-Trideoxy-1,2-*O*-isopropylidene-α-D-*erythro*-hept-5*E*-eno-1,4-furanose (51):



To a solution of **38** (7 g, 28.89 mmol) in toluene (100 mL) was added DIBAL-H (3.43 M solution in toluene, 17 mL, 58.31 mmol) slowly over period of 15 min at –78 °C and stirred for 3 h. After usual work up as described earlier, the residue was purified on silica gel using EtOAc:light petroleum ether (1:1) as an eluent to afford **51** as a viscous liquid.

Yield : 5.21 g (90%)

Mol. Formula : $C_{10}H_{16}O_4$

Optical Rotation $[\alpha]_D^{25}$: –42.7 (*c* 1.6, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3423, 2987, 2936, 1724, 1384, 1256, 1216, 1161, 1070, 1017 cm^{-1}.

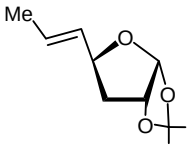
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.30, 1.50 (2 s, 6H), 1.59 (ddd, 1H, *J* = 13.3, 10.9, 4.7 Hz), 1.75 (br s, 1H), 2.15 (dd, 1H, *J* = 13.3, 4.3 Hz), 4.15 (d, 2H, *J* = 4.7 Hz), 4.55-4.70 (m, 1H), 4.71 (dd, 1H, *J* = 4.7, 3.8 Hz), 5.60-5.75 (m, 1H), 5.80 (d, 1H, *J* = 3.8 Hz), 5.85-6.00 (m, 1H) ppm

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 25.82 (q), 26.37 (q), 39.22 (t), 62.01 (t), 77.52 (d), 80.30 (d), 105.05 (d), 110.72 (s), 128.58 (d), 132.39 (d) ppm.

Elemental Analysis **Calcd.:** C, 59.98; H, 8.05%.

Found: C, 60.05; H, 8.09%.

3,5,6,7-Tetradeoxy-1,2-*O*-isopropylidene-α-D-*erythro*-hept-5*E*-eno-1,4-furanose (39*E*):



A stirred solution of **51** (3 g, 14.98 mmol) and TPP (4.71 g, 17.98 mmol) in CCl_4 (100 mL) was heated under reflux for 8 h. The reaction mixture was cooled to room temperature, concentrated and residue purified on silica gel using EtOAc:light petroleum ether (1:20) as an eluent to give **52** (2.55 g, 78%).

To a solution of **52** (2.55 g, 11.68 mmol) in THF (60 mL) was added $LiAlH_4$ (1 g, 26.35 mmol) in small portions over a period of 30 minutes at 0 °C, and stirred for 1 h at room temperature. The reaction mixture was cooled to 0 °C, quenched with EtOAc and water, filtered through a plug of Celite and concentrated. The residue was purified on silica gel using EtOAc:light petroleum ether (1:20) as an eluent to give **39*E*** (1.87 g, 78%)

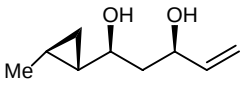
Mol. Formula : $C_{10}H_{16}O_3$,

Optical Rotation $[\alpha]_D^{25}$: –35.9 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3434, 2985, 1741, 1638, 1448, 1374, 1241, 1162, 1097, 1046, 938 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.32, 1.52 (2 s, 6H), 1.58 (ddd, 1H, *J* = 13.3, 10.6, 4.5 Hz), 1.72 (d, 3H, *J* = 6.6 Hz), 2.12 (dd, 1H, *J* = 13.3, 4.3 Hz), 4.56 (ddd, 1H, *J* = 10.6, 7.4, 4.3 Hz), 4.72 (dd, 1H, *J* = 4.7, 3.8 Hz), 5.45 (ddq, 1H, *J* = 15.2, 7.4, 1.5 Hz), 5.80 (d, 1H, *J* = 3.8 Hz), 5.85 (dq, 1H, *J* = 15.2, 6.6 Hz) ppm.
^{13}C NMR ($CDCl_3$, 125 MHz)	: δ 17.38 (q), 25.75 (q), 26.31 (q), 39.19 (t), 78.01 (d), 80.16 (d), 104.82 (d), 110.29 (s), 128.85 (d), 129.23 (d) ppm.
Elemental Analysis	**Calcd.:** C, 65.19; H, 8.75%. **Found:** C, 65.34; H, 8.88%.

(1*S*, 3*R*)-1-[(1*S*, 2*S*)-2-Methylcyclopropyl]-pent-4-ene-1,3-diol (53):



A stirred solution of compound **37** (500mg, 2.52 mmol) and 0.4% aq. H_2SO_4 (1 mL) in 1,4-dioxane (5 mL) was heated under reflux for 1 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) and concentrated and residue purified on silica gel using EtOAc:light petroleum ether (6:4) to obtain lactol.

Lactol was dissolved in THF and added to a solution of CH_2=PPh_3 [generated from PPh_3CH_3I (3.055 g, 7.56 mmol) and 1.6 M solution of *n*-BuLi (4.4 mL, 7.04 mmol)] at 0 °C. After stirring for 1 h, reaction mixture was quenched with saturated aq. NH_4Cl and extracted with EtOAc. Combined organic layer was dried (Na_2SO_4), concentrated and the residue purified on silica gel using EtOAc:light petroleum ether (1:4) as an eluent to give **53**.

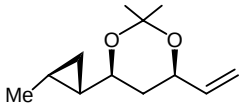
Yield	: 307 mg (78%)
Mol. Formula	: $C_9H_{16}O_2$
Optical Rotation $[\alpha]_D^{25}$	: +21.8 (*c* 1.4, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.25 (dt, 1H, *J* = 8.3, 4.2 Hz), 0.42-0.65 (m. 3H), 1.00 (d, 3H, *J* = 5.3 Hz), 1.70-1.78 (m, 2H), 3.08–3.20 (m, 1H), 3.63 (br s, 2H), 4.27 (ddd, 1H, *J* = 12.4, 5.9, 1.1 Hz), 5.05 (dt, 1H, *J* =

10.3, 1.4 Hz), 5.22 (dt, 1H, *J* = 17.1, 1.4 Hz), 5.84 (ddd, 1H, *J* = 17.1, 10.3, 5.9) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz): δ 10.41(d), 11.37 (t), 18.30 (q), 26.67 (d), 42.94 (t), 72.97 (d), 76.18 (d), 114.19 (t), 140.62(d) ppm.

Elemental Analysis **Calcd.:** C, 69.19; H, 10.32%.
Found: C, 69.50; H, 10.44%.

(1*S*, 3*R*)-1-[(1*S*, 2*S*)-2-Methylcyclopropyl]-1,3-*O*-isopropylidene-pent-4-ene (54):



A solution of **53** (450 mg, 2.88 mmol), 2,2-dimethoxypropane (0.5 mL, 4.06 mmol) and *p*TSA (20 mg, 0.10 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 30 min, neutralized with Et_3N and concentrated. The residue partitioned between EtOAc and water. The organic layer was washed with brine, dried (Na_2SO_4), concentrated and the residue purified on silica gel using EtOAc:light petroleum ether (1:15) to obtain **54**.

Yield : 542 mg (96%)

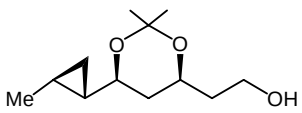
Mol. Formula : $C_{12}H_{20}O_2$

Optical Rotation $[\alpha]_D^{25}$: +41.5 (*c* 1.6, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.30 (dt, 1H, *J* = 8.0, 4.9 Hz), 0.40-0.65 (m, 3H), 1.03 (d, 3H, *J* = 5.3 Hz), 1.30-1.45 (m, 1H), 1.39, 1.42 (2 s, 6H), 1.63 (dt, 1H, *J* = 12.9, 2.8 Hz), 3.12 (ddd, 1H, *J* = 11.2, 7.4, 2.7 Hz), 4.20–4.35 (m, 1H), 5.10 (dt, 1H, *J* = 10.4, 1.3 Hz), 5.23 (dt, 1H, *J* = 17.3, 1.3 Hz), 5.80 (ddd, 1H, *J* = 17.3, 10.4, 5.8) ppm.

Elemental Analysis **Calcd.:** C, 73.43; H, 10.27%.
Found: C, 73.48; H, 10.41%.

(3*S*, 5*S*)-5-[(1*S*, 2*S*)-2-Methylcyclopropyl]-3,5-*O*-isopropylidene-pent-1-ol (55):

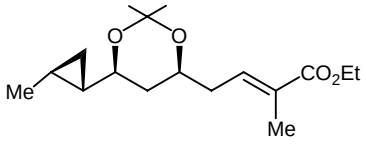


To a solution of **54** (250 mg, 1.27 mmol) in THF (10 mL) at 0 °C was added $H_3B.SMe_2$ (0.5 mL, 5.27 mmol) slowly over a period of 5 min. After stirring for 2 h, 3N aq. NaOH

solution (2.5 mL) and 30% H_2O_2 solution (2.5 mL) were introduced in succession at the same temperature. The reaction mixture was diluted with EtOAc, washed with saturated aq. Na_2SO_3, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel using EtOAc:light petroleum ether (1:6) as an eluent to obtain **55**.

Yield	: 207 g (76%)
Mol. Formula	: $C_{12}H_{22}O_3$
Optical Rotation $[\alpha]_D^{25}$	: +15.9 (*c* 1.4, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3429, 3068, 2997, 2947, 2871, 1719, 1453, 1417, 1380, 1262, 1200, 1172, 1115, 1089, 1052, 1023, 984, 964 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200MHz)	: δ 0.30 (dt, 1H, *J* = 8.0, 4.2 Hz), 0.40-0.68 (m. 3H), 1.03 (d, 3H, *J* = 5.3 Hz), 1.40 (s, 6H), 1.35-1.45 (m, 1H), 1.50–1.75 (m, 3H), 2.55 (br s, 1H), 3.12 (ddd, 1H, *J* = 10.9, 7.4, 3.1 Hz), 3.76 (ddd, 1H, *J* = 6.1, 4.5, 2.5 Hz), 3.80-3.90 (m, 1H), 3.95-4.15 (m, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 9.33 (d), 11.37 (t), 18.29 (d), 19.44 (q), 24.61 (q), 29.94 (q), 36.56 (t), 38.15 (t), 59.43 (t), 67.92 (d), 72.99 (d), 98.19 (s) ppm.
Elemental Analysis	**Calcd.:** C, 67.26; H, 10.35%. **Found:** C, 67.30; H, 10.35%.

Ethyl (5*S*, 7*S*, 2*E*)-2-methyl-7-[(1*S*, 2*S*)-2-methylcyclopropyl]-5,7-*O*-isopropylidene-hept-2-enoate (56):



To a solution of **55** (1.6 g, 7.46 mmol) in CH_2Cl_2 (20 mL) was added freshly prepared Dess-Martin Periodinane (6.0 g, 14.14 mmol) at room temperature. After stirring for 3 h, the reaction mixture was filtered through a plug of Celite and concentrated. The residue was dissolved in CH_2Cl_2 (20 mL) and charged with PPh_3=C(Me)CO_2Et (3.0 g, 8.28 mmol). After stirring for 30 min, the reaction mixture was concentrated and the residue purified on silica gel using EtOAc:light petroleum ether (1:12) to obtain **56**.

Yield : 1.46 g (66%)

Mol. Formula : $C_{17}H_{28}O_4$

Optical Rotation $[\alpha]_D^{25}$: +25.1 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3452, 3019, 2953, 2400, 1703, 1649, 1518, 1446, 1381, 1265, 1215, 1170, 1109, 1085, 1036, 983, 950, 929 cm^{-1}.

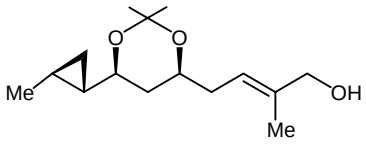
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.30 (dt, 1H, *J* = 8.0, 4.5 Hz), 0.41-0.65 (m, 3H), 1.03 (d, 3H, *J* = 5.3 Hz), 1.30 (t, 3H, *J* = 7.2 Hz), 1.30-1.45 (m, 1 H), 1.37, 1.41 (2 s, 6H), 1.63 (dt, 1H, *J* = 12.9, 2.8 Hz), 1.85 (br s, 3H), 2.22–2.50 (m, 2H), 3.06 (ddd, 1H, *J* = 11.4, 7.6, 2.5 Hz), 3.87 (ddt, 1H, *J* = 11.4, 6.3, 2.4 Hz), 4.20 (q, 2H, *J* = 7.2 Hz), 6.75 (tq, 1H, *J* = 7.2, 1.2 Hz) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 9.54 (d), 11.56 (t), 12.54 (d), 14.17 (q), 18.46 (q), 19.52 (q), 24.78 (q), 30.04 (q), 35.65 (t), 36.62 (t), 60.25 (t), 68.06 (d), 73.11 (d), 98.36 (s), 129.53 (d), 137.03 (s), 167.63 (s) ppm.

Elemental Analysis **Calcd.:** C, 68.89; H, 9.52%.

Found: C, 68.91; H, 9.81%.

(5*S*, 7*S*, 2*E*)-2-Methyl-7-[(1*S*, 2*S*)-2-methylcyclopropyl]-5,7-*O*-isopropylidene-hept-2-enol (35):



To a solution of **56** (3.0 g, 10.12 mmol) in anhydrous toluene (20 mL) was added DIBAL-H (2.0 M solution in toluene, 11 mL, 22.0 mmol) dropwise over a period of 15 min at –78 °C and stirred for 4 h. After usual workup as described earlier, the residue was purified on silica gel using EtOAc:light petroleum ether (1:9) to obtain **35**.

Yield : 2.31 g (90%)

Mol. Formula : $C_{15}H_{26}O_3$

Optical Rotation $[\alpha]_D^{25}$: +26.4 (*c* 1.0, $CHCl_3$).

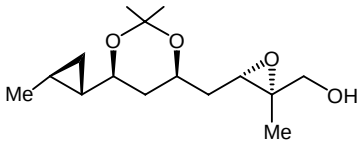
IR ($CHCl_3$) $\tilde{\nu}$: 3612, 3452, 3018, 3000, 2949, 2870, 2400, 1653, 1518, 1454, 1381, 1215, 1168, 1110, 1087, 1039, 983, 948 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.30 (dt, 1H, *J* = 8.0, 4.5 Hz), 0.40-0.65 (m, 3H), 1.04 (d, 3H, *J* = 5.3 Hz), 1.35–1.45 (m, 1H), 1.36, 1.40 (2 s, 6H), 1.63 (dt, 1H, *J* = 12.9, 2.8 Hz), 1.67 (s, 3H), 2.10–2.35 (m, 2H), 3.05 (ddd, 1H, *J* = 11.4, 7.4, 2.4 Hz), 3.70-3.85 (m, 1H), 4.00 (br s, 2H), 5.44 (tq, 1H, *J* = 7.0, 1.2 Hz) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 9.64 (d), 11.69 (t), 13.88 (d), 18.54 (q), 19.63 (q), 24.86 (q), 30.13 (q), 34.61 (t), 36.53 (t), 68.30 (t), 68.89 (d), 73.47 (d), 98.37 (s), 120.57 (d), 136.87 (s) ppm.

Elemental Analysis **Calcd.:** C, 70.83; H, 10.30%.
Found: C, 70.91; H, 10.55%.

(2*S*, 3*S*, 5*R*, 7*S*, 2*E*)-2-Methyl-2,3-epoxy-5,7-*O*-isopropylidene-7-[(1*S*, 2*S*)-2-methylcyclopropyl]-heptanol (57):



To a solution of (+)-DIPT (1.0 g, 4.27 mmol) and 4Å molecular sieves powder (6 g) in CH_2Cl_2 (40 mL) was added titanium tetraisopropoxide (1.2 mL, 4.06 mmol) at -20 °C. After 15 minutes, a solution of allylic alcohol **35** (3.0 g, 11.79 mmol) in CH_2Cl_2 (10 mL) was introduced and stirred for 45 min. Then reaction mixture was charged with TBHP (3.3 M solution in toluene, 4 mL, 13.20 mmol) slowly over period of 15 min at the same. After 24 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 using EtOAc:light petroleum ether (1:3) as an eluent to obtain **57**.

Yield : 2.80 g (88%)

Mol. Formula : $C_{15}H_{26}O_4$

Optical Rotation $[\alpha]_D^{25}$: –4.2 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3446, 3019, 2954, 2871, 2400, 1654, 1518, 1454, 1383, 1215, 1174, 1108, 1083, 1036, 950 cm^{-1}.

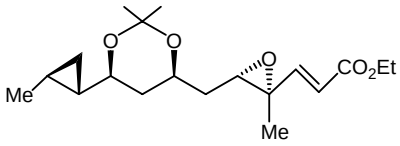
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.32 (dt, 1H, *J* = 8.0, 4.5 Hz), 0.40-0.65 (m, 3H), 1.04 (d, 3H, *J* = 5.2 Hz), 1.29, 1.39, 1.41 (3 s, 9H), 1.30–1.45 (m, 1H),

1.50–1.65 (m, 1H), 1.75–1.90 (m, 2H), 3.08 (ddd, 1H, *J* = 11.3, 7.5, 2.4 Hz), 3.20 (dd, 1H, *J* = 7.5, 4.2 Hz), 3.50–3.75 (m, 2H), 3.92–4.10 (m, 1H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 9.61 (d), 11.62 (t), 14.28 (d), 18.41 (q), 19.59 (q), 24.71 (q), 30.02 (q), 35.32 (t), 37.10 (t), 57.12 (d), 60.88 (s), 65.37 (t), 66.99 (d), 73.39 (d), 98.46 (s) ppm.

Elemental Analysis **Calcd.:** C, 66.64; H, 9.69%.
Found: C, 66.70; H, 9.80%.

Ethyl (4*S*, 5*S*, 7*R*, 9*S*, 2*E*)-4-methyl-4,5-epoxy-7,9-*O*-isopropylidene-9-[(1*S*, 2*S*)-2-methylcyclopropyl]-non-2-enoate (34):



To a solution of oxalyl chloride (0.8 mL, 9.17 mmol) in CH_2Cl_2 (25 mL) was added DMSO (0.8 mL, 11.27 mmol) dropwise over period of 10 min at –78 °C and stirred for 30 min. A solution of **57** (2.0 g, 7.39 mmol) in CH_2Cl_2 (20 mL) was then introduced and stirred for 1 h at the same temperature. The reaction was quenched with Et_3N (3 mL, 21.52 mmol) and poured into ice-water. The organic layer was separated, washed with water, dried (Na_2SO_4) and concentrated (below 35 °C). The residue was dissolved in CH_2Cl_2 (30 mL) and charged with PPh_3=$CHCO_2Et$ (3.0 g, 8.61 mmol). After stirring for 1 h, the reaction mixture was concentrated and the residue purified on silica gel using EtOAc:light petroleum ether (1:9) as an eluent to obtain **34**.

Yield : 1.90 g (76%)

Mol. Formula : $C_{19}H_{30}O_5$

Optical Rotation $[\alpha]_D^{25}$: +15.6 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3686, 3469, 3019, 3000, 2954, 2871, 2400, 1713, 1656, 1520, 1454, 1382, 1370, 1308, 1266, 1215, 1174, 1109, 1096, 1033, 979, 948, 928 cm^{-1}.

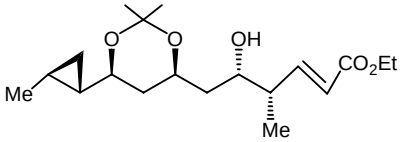
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.32 (dt, 1H, *J* = 8.0, 4.5 Hz), 0.42-0.65 (m, 3H), 1.02 (d, 3H, *J* = 5.2 Hz), 1.30 (t, 3H, *J* = 7.2 Hz), 1.35–1.45 (m, 1H),

1.38, 1.39, 1.43 (3 s, 9H), 1.52–1.72 (m, 2H), 1.85 (ddd, 1H, *J* = 14.2, 8.3, 4.4 Hz), 3.00 (dd, 1H, *J* = 7.3, 4.2 Hz), 3.04–3.19 (m, 1H), 3.90–4.05 (m, 1H), 4.2 (q, 2H, *J* = 7.2 Hz), 6.00 (d, 1H, *J* = 15.6 Hz), 6.75 (d, 1H, *J* = 15.6 Hz) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz): δ 9.64 (d), 11.66 (t), 14.17 (d), 15.45 (q), 18.53 (q), 19.66 (q), 24.83 (q), 30.11 (q), 35.76 (t), 37.19 (t), 58.32 (d), 60.38 (t), 62.58 (s), 66.79 (d), 73.20 (d), 98.49 (s), 121.50 (d), 149.64 (d), 165.90 (s) ppm.

Elemental Analysis **Calcd.:** C, 67.43; H, 8.93%.
Found: C, 67.61; H, 9.08%.

Ethyl (4*S*, 5*S*, 7*S*, 9*S*, 2*E*)-4-methyl-5-hydroxy-7,9-*O*-isopropylidene-9-[(1*S*, 2*S*)-2-methylcyclopropyl]-non-2-enoate (58):



To a solution of freshly prepared $Pd(PPh_3)_4$ (500 mg, 0.43 mmol) and $H_3B.NHMe_2$ (280mg, 4.75 mmol) in CH_2Cl_2 (10 mL) was added a mixture of AcOH (0.7 mL, 12.22 mmol) and **34** (1.5 g, 4.43 mmol) in CH_2Cl_2 (2 mL) at room temperature. After stirring for 30min, the reaction mixture was concentrated and residue purified on silica gel using EtOAc:light petroleum ether (1:20) as an eluent to obtain **58**.

Yield : 995 mg (66%)

Mol. Formula : $C_{19}H_{32}O_5$

Optical Rotation $[\alpha]_D^{25}$: –14.5 (*c* 1.3, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3392, 2945, 2834, 2536, 2043, 1705, 1652, 1449, 1373, 1282, 1193, 1109 cm^{-1}.

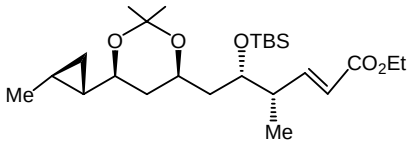
^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.31 (dt, 1H, *J* = 8.0, 5.0 Hz), 0.47 (dt, 1H, *J* = 8.0, 5.0 Hz), 0.54-0.61 (m, 2H), 1.04 (d, 3H, *J* = 5.6 Hz), 1.12 (d, 3H, *J* = 6.7 Hz), 1.30 (t, 3H, *J* = 7.2 Hz), 1.31–1.36 (m, 1H), 1.37, 1.40 (2 s, 6H), 1.41-1.57 (m, 3H), 2.35-2.45 (m, 1H), 2.90 (br s, 1H), 3.07–3.20 (m, 1H), 3.80-3.87 (m, 1H), 4.07-4.14 (m, 1H), 4.18

(q, 2H, *J* = 7.2 Hz), 5.84 (dd, 1H, *J* = 15.8, 1.0 Hz), 6.92 (dd, 1H, *J* = 15.8, 8.0 Hz) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 9.46 (d), 11.53 (t), 14.15 (d), 14.61 (q), 18.44 (q), 19.44 (q), 24.75 (q), 30.12 (q), 36.18 (t), 39.36 (t), 42.66 (d), 60.00 (t), 66.93 (d), 70.56 (d), 73.12 (d), 98.49 (s), 121.29 (d), 150.80 (d), 166.24 (s) ppm.

Elemental Analysis **Calcd.:** C, 67.03; H, 9.47%.
Found: C, 67.11; H, 9.53%.

Ethyl (4*S*, 5*S*, 7*S*, 9*S*, 2*E*)-4-methyl-5-*ter*butyldimethylsilyloxy-7,9-*O*-isopropylidene-9-[(1*S*, 2*S*)-2-methylcyclopropyl]-non-2-enoate (59):



A solution of **58** (500 mg, 1.47 mmol), TBSCl (250 mg, 1.66 mmol) and imidazole (130 mg, 1.91 mmol) in DMF (1 mL) was stirred for 48 h at room temperature. 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 (1:40) as an eluent to obtain **59**.

Yield : 432 mg (81%)

Mol. Formula : $C_{25}H_{46}O_5Si$

Optical Rotation $[\alpha]_D^{25}$: –34.3 (*c* 1.0, $CHCl_3$).

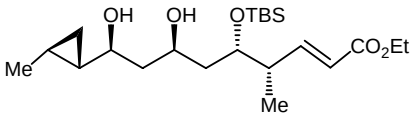
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.06, 0.07 (2 s, 6H), 0.25-0.35 (m, 1H), 0.42-0.62 (m, 3H), 0.90 (s, 9H), 1.02 (d, 6H, *J* = 6.2 Hz), 1.25-1.35 (m, 1H), 1.30 (t, 3H, *J* = 7.2 Hz), 1.36, 1.38 (2 s, 6H), 1.35–1.42 (m, 2H), 1.47 (dt, 1H, *J* = 12.0, 2.0 Hz), 2.45-2.75 (m, 1H), 3.07 (ddd, 1H, *J* = 11.0, 7.5, 3.0 Hz), 3.79-3.94 (m, 2H), 4.20 (q, 2H, *J* = 7.2 Hz), 5.78 (dd, 1H, *J* = 15.9, 1.5 Hz), 7.08 (dd, 1H, *J* = 15.9, 6.3 Hz) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ –4.36 (q), –3.95 (q), 9.61 (d), 11.72 (t), 13.81 (d), 14.33 (q), 18.17 (s), 18.62 (q), 20.18 (q), 25.06 (q), 25.97 (q), 30.37 (q),

37.84 (t), 40.88 (t), 42.22 (d), 60.00 (t), 65.50 (d), 71.78 (d), 73.16 (d), 98.30 (s), 121.18 (d), 150.09 (d), 166.43 (s) ppm.

Elemental Analysis **Calcd.:** C, 66.03; H, 10.20%.
Found: C, 66.31; H, 10.43%.

Ethyl (4*S*, 5*S*, 7*S*, 9*S*, 2*E*)-4-methyl-5-*ter*butyldimethylsilyloxy-7,9-dihydroxy-9-[(1*S*, 2*S*)-2-methylcyclopropyl]-non-2-enoate (60):



A solution of **59** (500 mg, 1.09 mmol) and PPTS (20 mg, 0.08 mmol) in MeOH (10 mL) was stirred for 1 h. The reaction mixture was neutralized with Et_3N, concentrated and the residue purified on silica gel using EtOAc:light petroleum ether (1:2) as an eluent to obtain **59**.

Yield : 285 mg (71%)

Mol. Formula : $C_{22}H_{42}O_5Si$

Optical Rotation $[\alpha]_D^{25}$: –28.7 (*c* 1.2, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3468, 3019, 2930, 2857, 1714, 1471, 1256, 1215, 1081 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.09, 0.12 (2 s, 6H), 0.18-0.30 (m, 1H), 0.34-0.66 (m, 3H), 0.91 (s, 9H), 1.03 (d, 3H, *J* = 5.5 Hz), 1.07 (d, 3H, *J* = 6.8 Hz), 1.30 (t, 3H, *J* = 7.2 Hz), 1.43 (dd, 1H, *J* = 7.5, 2.8 Hz), 1.50 (dd, 1H, *J* = 9.0, 2.8 Hz), 1.60-1.75 (m, 2H), 2.54-2.65 (m, 1H), 3.06-3.19 (m, 1H), 3.89-4.01 (m, 2H), 4.19 (q, 2H, *J* = 7.2 Hz), 5.80 (dd, 1H, *J* = 15.8, 1.0 Hz), 7.00 (dd, 1H, *J* = 15.8, 7.0 Hz) ppm.

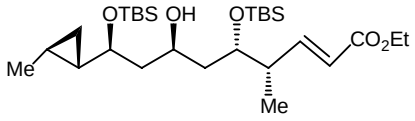
^{13}C NMR ($CDCl_3$, 50 MHz) : δ –4.48 (q), 10.53 (d), 11.27 (t), 14.27 (d), 14.93 (q), 18.09 (s), 18.37 (q), 25.94 (q), 27.13 (q), 40.79 (t), 42.11 (d), 44.02 (t), 60.12 (t), 68.57 (d), 72.76 (d), 77.06 (d), 121.30 (d), 150.76 (d), 166.47 (s) ppm.

ESI MS (m/z): 415 (M+1)

Elemental Analysis **Calcd.:** C, 63.72; H, 10.21%.

Found: C, 63.81; H, 10.43%.

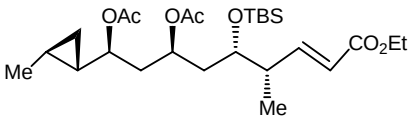
Ethyl (4*S*, 5*S*, 7*S*, 9*S*, 2*E*)-4-methyl-5,9-di-*ter*butyldimethylsilyloxy-7-hydroxy-9-[(1*S*, 2*S*)-2-methylcyclopropyl]-non-2-enoate (33):



A solution of **60** (250 mg, 0.60 mmol), imidazole (50 mg, 0.73 mmol) and TBSCl (90 mg, 0.59 mmol) in DMF (1 mL) was stirred for 8 h. After usual workup as described earlier, the residue was purified on silica gel using EtOAc:light petroleum ether (1:9) as an eluent to obtain **33**.

Yield	: 229 mg (80%)
Mol. Formula	: $C_{28}H_{56}O_5Si_2$
Optical Rotation $[\alpha]_D^{25}$	: –8.9 (*c* 0.8, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3436, 3020, 2955, 2929, 2857, 1713, 1651, 1471, 1463, 1383, 1255, 1216, 1184, 1081, 1036, 1005, 939 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.08, 0.11, 0.13 (3 s, 12H), 0.29 (dt, 1H, *J* = 7.2, 4.5 Hz), 0.51-0.59 (m, 3H), 0.90, 0.91 (2 s, 18H), 1.03 (d, 3H, *J* = 5.0 Hz), 1.06 (d, 3H, *J* = 6.7 Hz), 1.30 (t, 3H, *J* = 7.2 Hz), 1.42 (ddd, 1H, *J* = 8.0, 5.2, 2.8 Hz), 1.55-1.75 (m, 3H), 2.49-2.59 (m, 1H), 3.30 (dt, 1H, *J* = 7.5, 4.4 Hz), 3.35-3.47 (br d, 1H), 3.85-3.97 (m, 1H), 3.98-4.10 (m, 1H), 4.19 (q, 2H, *J* = 7.2 Hz), 5.81 (dd, 1H, *J* = 15.8, 1.0 Hz), 6.93 (dd, 1H, *J* = 15.8, 7.4 Hz) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz)	: δ –4.62, –4.47, –3.39, 10.65, 13.76, 14.28, 18.01, 18.14, 18.48, 25.97, 26.92, 29.70, 41.15, 42.75, 45.25, 60.16, 66.88, 71.71, 77.21, 121.36, 150.94, 166.58 ppm.
ESI MS (m/z):	551 (M+Na)
Elemental Analysis	**Calcd.:** C, 63.58; H, 10.67%.
	Found: C, 63.81; H, 10.83%.

Ethyl (4*S*, 5*S*, 7*S*, 9*S*, 2*E*)-4-methyl-5-*ter*butyldimethylsilyloxy-7,9-diacetoxy-9-[(1*S*, 2*S*)-2-methylcyclopropyl]-non-2-enoate (61):



A solution of **60** (10 mg, 0.02 mmol) in CH_2Cl_2 (2 mL) was added to a mixture of Ac_2O (0.1M solution in CH_2Cl_2, 0.2 mL, 0.2 mmol) and DMAP (2 mg, 0.01 mmol) in CH_2Cl_2 (1 mL). After stirring for 8 h, the reaction mixture was concentrated and residue purified on silica gel using EtOAc:light petroleum ether (1:4) as an eluent to obtain **61**.

Yield : 8 mg (81%)

Mol. Formula : $C_{26}H_{46}O_7Si$

Optical Rotation $[\alpha]_D^{25}$: –27.7 (*c* 1.1, $CHCl_3$).

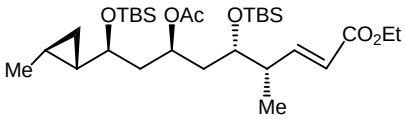
IR ($CHCl_3$) $\tilde{\nu}$: 3442, 3021, 2957, 2898, 2858, 1728, 1651, 1472, 1463, 1370, 1311, 1253, 1216, 1185, 1081, 1024, 989, 939 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.05 (2 s, 6H), 0.17-0.30 (m, 1H), 0.55-0.71 (m, 3H), 0.90 (s, 9H), 1.05 (d, 6H, *J* = 6.5 Hz), 1.30 (t, 3H, *J* = 7.2 Hz), 1.40-1.75 (m, 4H), 2.02, 2.05 (2 s, 6H), 2.45–2.55 (m, 1H), 3.72 (dt, 1H, *J* = 8.0, 3.7 Hz), 4.20 (q, 2H, *J* = 7.2 Hz), 4.27–4.38 (m, 1H), 4.92–5.07 (m, 1H), 5.79 (dd, 1H, *J* = 15.7, 1.5 Hz), 7.05 (dd, 1H, *J* = 15.7, 6.5 Hz) ppm.

ESI MS (m/z): 521 (M+Na)

Elemental Analysis **Calcd.:** C, 62.62; H, 9.30%.
Found: C, 62.81; H, 9.43%.

Ethyl (4*S*, 5*S*, 7*S*, 9*S*, 2*E*)-4-methyl-5,9-di-*ter*butyldimethylsilyloxy-7-hydroxy-9-[(1*S*, 2*S*)-2-methylcyclopropyl]-non-2-enoate (62):



A solution of **33** (20 mg, 0.03 mmol), Ac_2O (0.1 M solution in CH_2Cl_2, 0.1 mL, 0.1 mmol) and DMAP (2 mg, 0.01 mmol) in CH_2Cl_2 (2 mL) was stirred for 8 h. The reaction mixture

was concentrated and residue purified on silica gel using EtOAc:light petroleum ether (1:30) as an eluent to obtain **62**.

Yield : 13 mg (77%)

Mol. Formula : $C_{30}H_{58}O_6Si_2$

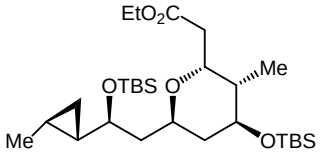
Optical Rotation $[\alpha]_D^{25}$: +18.1 (*c* 1.6, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3463, 3020, 2956, 2930, 2896, 2857, 1727, 1651, 1472, 1463, 1369, 1254, 1216, 1186, 1144, 1110, 1082, 1034, 985, 967, 940 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz) : δ 0.02, 0.04, 0.06 (3 s, 12H), 0.16-0.24 (m, 1H), 0.42 (dt, 1H, *J* = 8.0, 4.5 Hz), 0.55–0.64 (m, 2H), 0.88, 0.90 (2 s, 18H), 1.02 (d, 3H, *J* = 5.5 Hz), 1.07 (d, 3H, *J* = 6.5 Hz), 1.32 (t, 3H, *J* = 7.2 Hz), 1.50-1.60 (m, 1H), 1.61-1.79 (m, 2H), 1.93 (dt, 1H, *J* = 13.3, 5.7 Hz), 2.04 (s, 3H), 2.50–2.57 (m, 1H), 3.15-3.24 (m, 1H), 3.80 (dt, 1H, *J* = 8.3, 3.0 Hz), 4.20 (q, 2H, *J* = 7.2 Hz), 5.05–5.15 (m, 1H), 5.81 (dd, 1H, *J* = 15.7, 1.0 Hz), 6.90 (dd, 1H, *J* = 15.7, 7.0 Hz) ppm.

Elemental Analysis **Calcd.:** C, 63.11; H, 10.24%.
Found: C, 63.18; H, 10.43%.

(2*R*, 3*S*, 4*S*, 6*R*)-4-*ter*-Butyldimethylsilyloxy-6-{[2-*ter*-butyldimethylsilyloxy-2-[(1*S*, 2*S*)-2-methylcyclopropyl]ethyl}-3-methyl-tetrahydropyran-2-yl-acetic acid ethyl ester (63)



A solution of **33** (100 mg, 0.19 mmol) and LiOH (3 mg, 0.12 mmol) in 5 mL of THF was stirred at room temperature for 48 h. The reaction was diluted water and extracted with ether. Combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel using EtOAc:light petroleum ether (1:30) as an eluent to obtain **63** and further elution provided **64**.

Yield : 42 mg (42%)

Mol. Formula : $C_{28}H_{56}O_5Si_2$

Optical Rotation $[\alpha]_D^{25}$: +43.3 (*c* 1.3, $CHCl_3$).

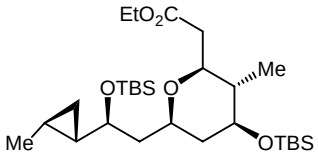
IR ($CHCl_3$) $\tilde{\nu}$: 3464, 3019, 2956, 2930, 2896, 2857, 2400, 1730, 1471, 1463, 1410, 1372, 1361, 1313, 1255, 1215, 1183, 1088, 1066, 1034, 1005, 939, 897 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.05 (br s, 12H), 0.18 (dt, 1H, *J* = 8.0, 4.5 Hz), 0.41 (dt, 1H, *J* = 8.0, 4.0 Hz), 0.51-0.64 (m, 2H), 0.89 (br s, 21H), 1.02 (d, 3H, *J* = 5.5 Hz), 1.15-1.25 (m, 1H) 1.27 (t, 3H, *J* = 7.1 Hz), 1.45-1.65 (m, 1H), 1.70-1.98 (m, 3H), 2.36 (dd, 1H, *J* = 14.4, 4.6 Hz), 2.59 (dd, 1H, *J* = 14.4, 10.3 Hz), 3.21 (q, 1H, *J* = 6.6 Hz), 3.54 (dt, 1H, *J* = 9.1, 4.4 Hz), 3.85-3.99 (m, 1H), 4.16 (q, 2H, *J* = 7.1 Hz), 4.41 (dt, 1H, *J* = 10.3, 4.6 Hz) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz) : δ –4.75, –4.70, –4.18, –3.95, 10.18, 11.68, 13.51, 14.29, 18.05, 18.11, 18.51, 25.84, 26.17, 34.07, 39.65, 41.01, 44.20, 60.43, 66.70, 70.39, 72.02, 72.93, 171.69 ppm.

Elemental Analysis **Calcd.:** C, 63.58; H, 10.67%.
Found: C, 63.81; H, 10.93%.

(2*S*, 3*S*, 4*S*, 6*R*)-4-*ter*-Butyldimethylsilyloxy-6-{[2-*ter*-butyldimethylsilyloxy-2-[(1*S*, 2*S*)-2-methylcyclopropyl]ethyl}-3-methyl-tetrahydropyran-2-yl-acetic acid ethyl ester (64):



Yield : 18 mg (20%)

Mol. Formula : $C_{28}H_{56}O_5Si_2$

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

^{1}H NMR ($CDCl_3$, 400 MHz) : δ 0.01, 0.04, 0.07 (3 s, 12H), 0.19 (dt, 1H, *J* = 8.1, 4.7 Hz), 0.38 (dt, 1H, *J* = 8.4, 4.7 Hz), 0.51 (tt, 1H, *J* = 7.8, 4.6 Hz), 0.57-0.65 (m, 1H), 0.87, 0.90 (2s, 18H), 0.91 (d, 3H, *J* = 4.0 Hz), 1.04 (d, 3H, *J* = 5.9 Hz), 1.27 (t, 3H, *J* = 7.1 Hz), 1.27-1.35

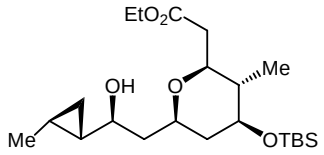
(m, 2H), 1.51-1.55 (m, 1H), 1.76-1.87 (m, 2H), 2.36 (dd, 1H, *J* = 14.5, 9.5 Hz), 2.60 (dd, 1H, *J* = 14.3, 3.0 Hz), 3.19 (dt, 1H, *J* = 7.7, 5.7 Hz), 3.34 (dt, 1H, *J* = 10.0, 4.5 Hz), 3.43 (dt, 1H, *J* = 9.3, 3.1 Hz), 3.43-3.58 (m, 1H), 4.13 (q, 2H, *J* = 7.1 Hz) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ –4.71, –4.63, –4.07, –3.93, 10.41, 11.52, 13.30, 14.23, 18.01, 18.63, 25.82, 25.92, 39.59, 41.85, 44.03, 44.93, 60.36, 72.26, 72.69, 74.06, 77.21, 77.83, 171.81 ppm.

ESI MS (m/z): 551 (M+Na)

Elemental Analysis **Calcd.:** C, 63.58; H, 10.67.
Found: C 63.81; H 10.83.

(2*S*, 3*S*, 4*S*, 6*R*)-4-*ter*-Butyldimethylsilyloxy-6-{[2-hydroxy-2-[(1*S*, 2*S*)-2-methylcyclopropyl]ethyl}-3-methyl-tetrahydropyran-2-yl-acetic acid ethyl ester (65):



A solution of **64** (50 mg, 0.09 mmol) and PPTS (5 mg, 0.02 mmol) in MeOH (5 mL) was stirred for 4 h. After usual workup as described earlier, the residue was purified on silica gel using EtOAc:light petroleum ether (1:9) as an eluent to give **65**.

Yield : 27 mg (84%)

Mol. Formula : $C_{22}H_{42}O_5Si$

Optical Rotation $[\alpha]_D^{25}$: +30.2 (*c* 0.8, $CHCl_3$); lit.[31a] + 31.4(*c* 0.340, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.05 (br s, 6H), 0.27 (dt, 1H, *J* = 8.0, 4.0 Hz), 0.50-0.60 (m, 3H), 0.90 (s, 9H), 0.92 (d, 3H, *J* = 6.6 Hz), 1.03 (d, 3H, *J* = 5.5 Hz), 1.25 (t, 3H, *J* = 7.1 Hz), 1.29-1.45 (m, 1H), 1.57-1.61 (m, 1H), 1.65 (dt, 1H, *J* = 14.5, 2.5 Hz), 1.75-1.83 (m, 2H), 2.39 (dd, 1H, *J* = 14.5, 9.8 Hz), 2.64 (dd, 1H, *J* = 14.5, 2.5 Hz), 3.12 (dt, 1H, *J* = 8.0, 2.8 Hz), 3.20 (br s, 1H), 3.35 (dt, 1H, *J* = 10.0, 4.7 Hz), 3.49 (dt, 1H, *J* = 10.0, 2.0 Hz), 3.58 (tt, 1H, *J* = 10.6, 2.0 Hz), 4.12-4.18 (m, 2H) ppm.

^{13}C NMR : δ –4.67, –3.92, 9.92, 11.51, 13.26, 14.18, 18.03, 18.53, 25.84,

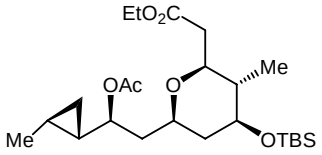
($CDCl_3$, 100 MHz) 26.31, 38.91, 42.10, 43.00, 43.63, 60.78, 73.59, 75.59, 76.25, 77.20, 77.98, 171.61 ppm.

ESI MS (m/z): 437 (M+Na)

Elemental Analysis **Calcd.:** C, 63.72; H, 10.21%.

Found: C, 63.81; H, 10.43.

(2*S*, 3*S*, 4*S*, 6*R*)-4-*ter*-Butyldimethylsilyloxy-6-{[2-aceyoxy-2-[(1*S*, 2*S*)-2-methylcyclopropyl]ethyl}-3-methyl-tetrahydropyran-2-yl-acetic acid ethyl ester (66):



A solution of **65** (20 mg, 0.03 mmol), Ac_2O (0.1M solution in CH_2Cl_2, 0.1 mL, 0.10 mmol) and DMAP (2 mg, 0.01 mmol) in CH_2Cl_2 (2 mL) was stirred for 8 h. The reaction mixture was concentrated and residue purified on silica gel using EtOAc:light petroleum ether (1:20) as an eluent to obtain **66**.

Yield : 11 mg (79%)

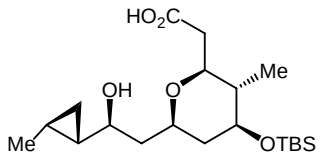
Mol. Formula : $C_{24}H_{44}O_6Si$

^{1}H NMR ($CDCl_3$, 400MHz) : δ 0.05, 0.07 (2 s, 6H), 0.22 (dt, 1H, *J* = 8.0, 4.8 Hz), 0.52 (dt, 1H, *J* = 8.4, 4.8 Hz), 0.57-0.64 (m, 1H), 0.70-0.77 (m, 1H), 0.90 (s, 9H), 0.95 (d, 3H, *J* = 7.0 Hz), 1.04 (d, 3H, *J* = 6.0 Hz), 1.27 (t, 3H, *J* = 7.1 Hz), 1.61–1.69 (m, 3H), 1.80 (dt, 1H, *J* = 13.3, 4.3 Hz), 2.01 (s, 3H), 2.43–2.52 (m, 2H), 2.59 (dd, 1H, *J* = 14.2, 5.5 Hz), 3.88–3.98 (m, 2H), 4.10–4.20 (m, 3H), 4.35–4.41 (m, 1H) ppm.

Elemental Analysis **Calcd.:** C, 63.12; H, 9.71%.

Found: C, 63.39; H, 9.83%.

(2*S*, 3*S*, 4*S*, 6*R*)-4-*ter*-Butyldimethylsilyloxy-6-{[2-hydroxy-2-[(1*S*, 2*S*)-2-methylcyclopropyl]ethyl}-3-methyl-tetrahydropyran-2-yl-acetic acid (32):



A 1M aqueous solution of LiOH (0.08 mL, 0.08 mmol) was added to a solution of **65** (10 mg, 0.02 mmol) in 2.4 mL of THF:H_2O:MeOH (10:1:1). After stirring for 18 h, the reaction mixture was diluted with buffer (pH = 7) and extracted with EtOAc. Combined organic layer was dried (Na_2SO_4) concentrated and the residue purified on silica gel using EtOAc:light petroleum ether (1:2) as an eluent to obtain **32**.

Yield : 5 mg (60%)

Mol. Formula : $C_{20}H_{38}O_5Si$

Optical Rotation $[\alpha]_D^{25}$: +15.1 (*c* 0.5, $CHCl_3$); lit.[31a] +17.7 (*c* 0.240, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 400MHz) : δ 0.05, 0.06 (2 s, 6H), 0.23-0.28 (m, 1H), 0.50-0.61 (m, 3H), 0.90 (s, 9H), 0.91 (d, 3H, *J* = 6.6 Hz), 1.01 (d, 3H, *J* = 5.5 Hz), 1.30-1.47 (m, 2H), 1.64-1.71 (m, 1H), 1.77-1.88 (m, 2H), 2.39 (dd, 1H, *J* = 15.0, 10.0 Hz), 2.66 (dd, 1H, *J* = 15.0, 2.5 Hz), 3.18 (br t, 1H, *J* = 9.0 Hz), 3.34 (dt, 1H, *J* = 10.5, 5.0 Hz), 3.49 (dt, 1H, *J* = 10.0, 2.0 Hz), 3.61 (br t, 1H, *J* = 11.5 Hz) ppm.

Elemental Analysis **Calcd.:** C, 62.14; H, 9.91%.

Found: C, 62.25; H, 9.93%.

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Chapter II

Towards the synthesis of peloruside A

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. Based on mode of action on cell division, anticancer agents are classified as alkylating agents, antimetabolites, antimitotic agents, anticancer antibiotics and others.[1] Of these, antimitotic agents occupies the vital space in cancer treatment due to the striking mechanism involved in disrupting the mitotic spindle via perturbation of microtubule function with net result of cell death or apoptosis. Mitosis is the stage in the process of cell division where segregation of chromosomes occurs prior to cell replication. During the cell division, the dynamic pipe-like protein fibers known as microtubules play an essential role in the segregation of chromosomes (mitotic spindle). Tubulin is a heterodimeric protein composed of α- and β-subunits, and in the presence of GTP this heterodimer combines in a head-to-tail manner to form protofilaments. Each protofilament, by the association of 13 α-β heterodimers forms a pipe like rigid structure, and its polymerization leads to the formation of microtubules. Microtubules grow at each end by the polymerization of tubulin dimers, and shrink at each end by the release of tubulin dimers (depolymerization). However, both processes always occur more rapidly at one (+) end.[2] Microtubules are highly sensitive to any tubulin-interacting agent (spindle poisons), and the change in their function in cell division process can lead to apoptosis (Figure 1).

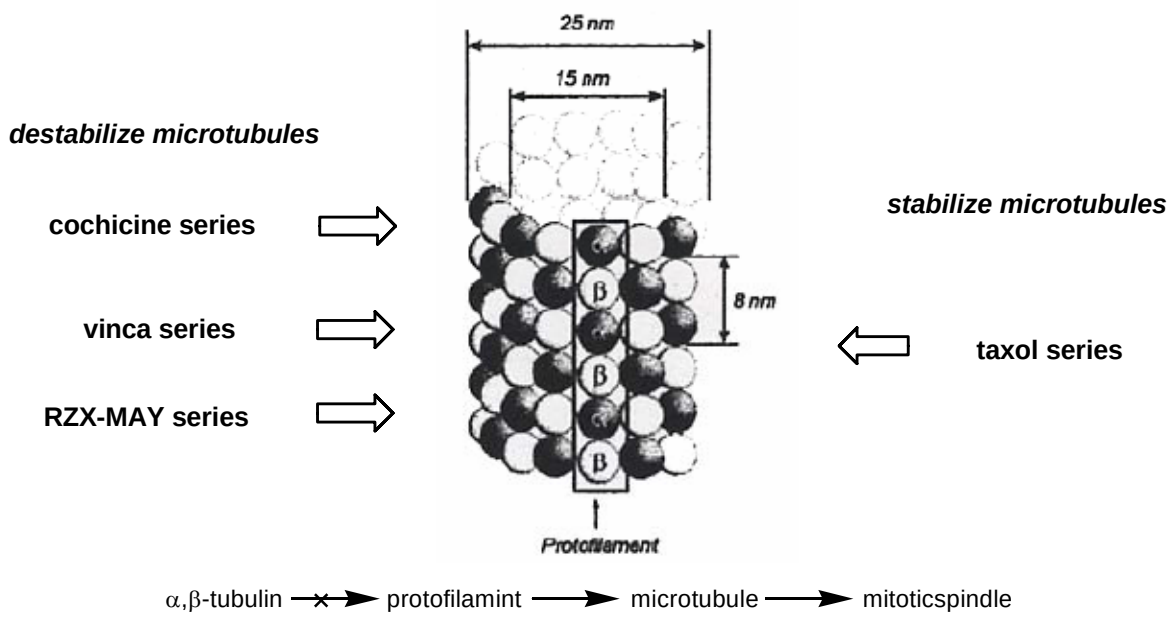


Figure 1: **Spindle poisons which affects the formation of microtubule**

The microtubule interacting agents or spindle poisons are targeted to alter the microtubule dynamics, and classified into various group of chemicals that bind different sites on tubulin: the colchicine group (Figure 2), the vinca alkaloid group (Figure 3), the rhizoxin/maytansin (RZX/MAY) group (Figure 4), and the paclitaxel group (Figure 5).[3] Interestingly, among these spindle poisons, the colchicine, vinca, and RZX/MAY series destabilize microtubules by inhibiting the formation of the polymer, whereas the paclitaxel series stabilizes microtubules formation. Colchicine (**1**)[4] has long been associated with microtubule biology and is the classic tubulin binding alkaloid. Combretastatin A-4 (**8**)[5], isolated from *Combretum cattrum*, is one of the simpler, most potent inhibitors of colchicine binding site and it is active only in *cis* form (Figure 2). Among the vinca binding domain series, spongistatins (**14-18**)[6] are the most potent compounds known to date, with antiproliferative activities as low as 10 fM (Figure 3). Among the RZX/MAY series, cryptophycin 1 (**20**)[7] has a reported 2 pM activity (Figure 4). Most promising therapeutic agents obtained from the paclitaxel series and thus occupied the major research arena of anticancer agents (Figure 5).

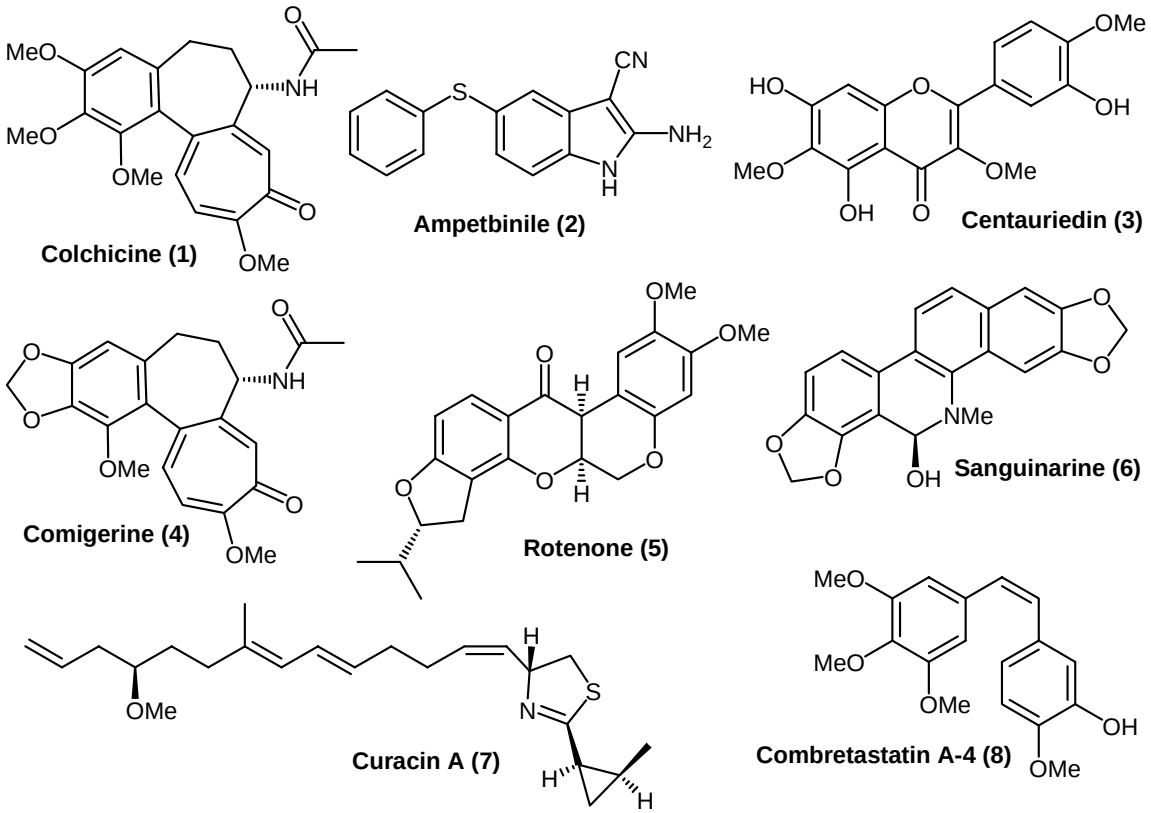
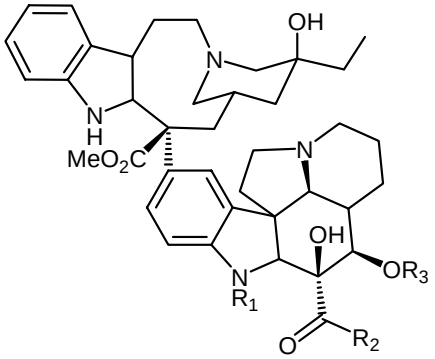
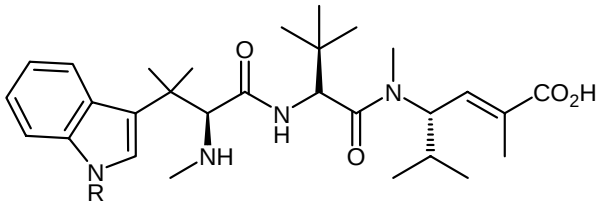


Figure 2: **Some representative molecules associated with the colchicine building site**

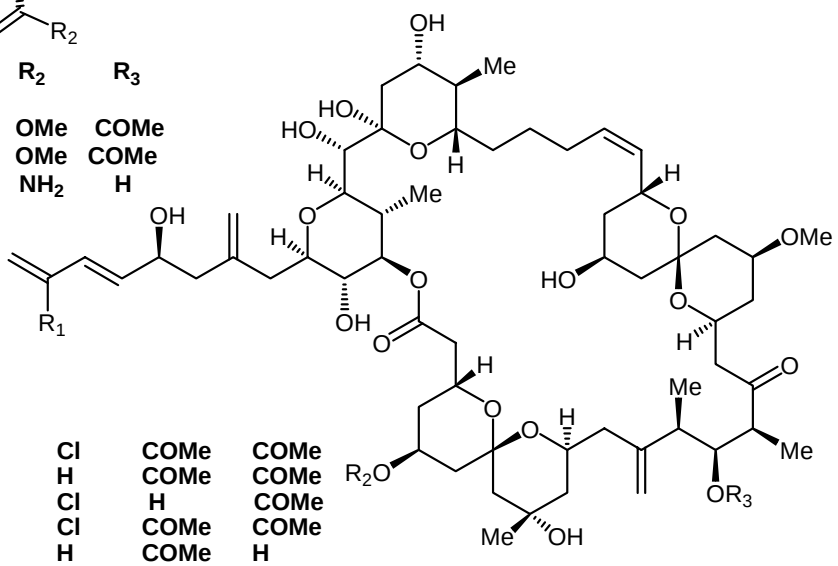
Paclitaxel (**23**)[8] has a unique mode of action, since it is the first compound known to favor the assembly of α- and β-tubulin into microtubules. It promotes this assembly *in vitro* in the absence of guanosine triphosphate (GTP), which is usually required for the polymerization of tubulin, and the formed microtubules are stable to depolymerization conditions.[9] Another unique characteristic of paclitaxel is its capacity to form microtubule bundles in cells. Suppressing microtubule dynamics at the cell cycle checkpoint between the G_2 and M phases provokes apoptosis.[10] Though these are very encouraging characteristics, formulation difficulties and the appearance of paclitaxel-resistant cancers became problematic, because of its high hydrophobicity, paclitaxel has to be dissolved in Cremophor EL for intravenous injections. Cremophor EL is a polyethoxylated castor oil, which is used as a vehicle for oral and intravenous administration of water-insoluble compounds in humans. It is thought to be responsible for hypersensitivity (mainly dyspnea with bronchospasm, urticaria, and hypotension) observed in some patients.[11] Additionally,



	R_1	R_2	R_3
Vinblastatin (9)	**Me**	**OMe**	**COMe**
Vincristine (10)	**CHO**	**OMe**	**COMe**
Vindesine (11)	**Me**	**NH_2**	**H**

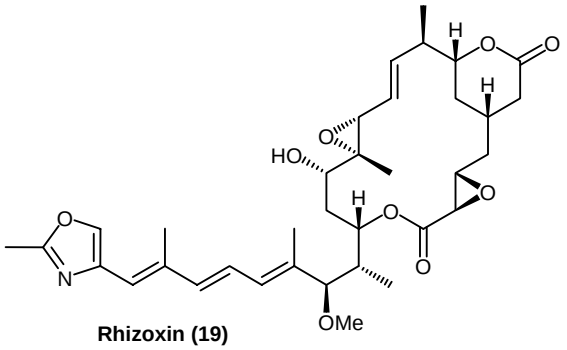


R = Me Hemiasterlin A (12)
R = H Hemiasterin B (13)

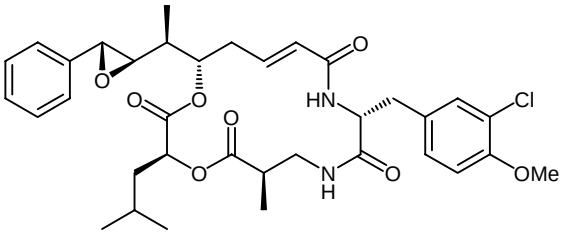


Spongistatin (14)	**Cl**	**COMe**	**COMe**
Spongistatin (15)	**H**	**COMe**	**COMe**
Spongistatin (16)	**Cl**	**H**	**COMe**
Spongistatin (17)	**Cl**	**COMe**	**COMe**
Spongistatin (18)	**H**	**COMe**	**H**

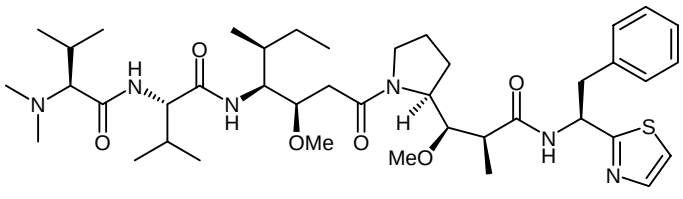
Figure 3: **Some representitive molecules associated with the vinca binding site**



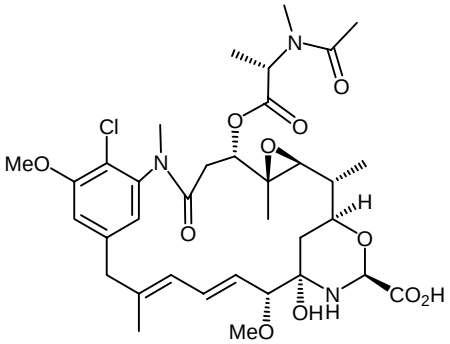
Rhizoxin (19)



Cryptophycin (20)



Dolastatin (21)



Maytansine (22)

Figure 4: **Some representative molecules associated with the RZX-MAY binding site**

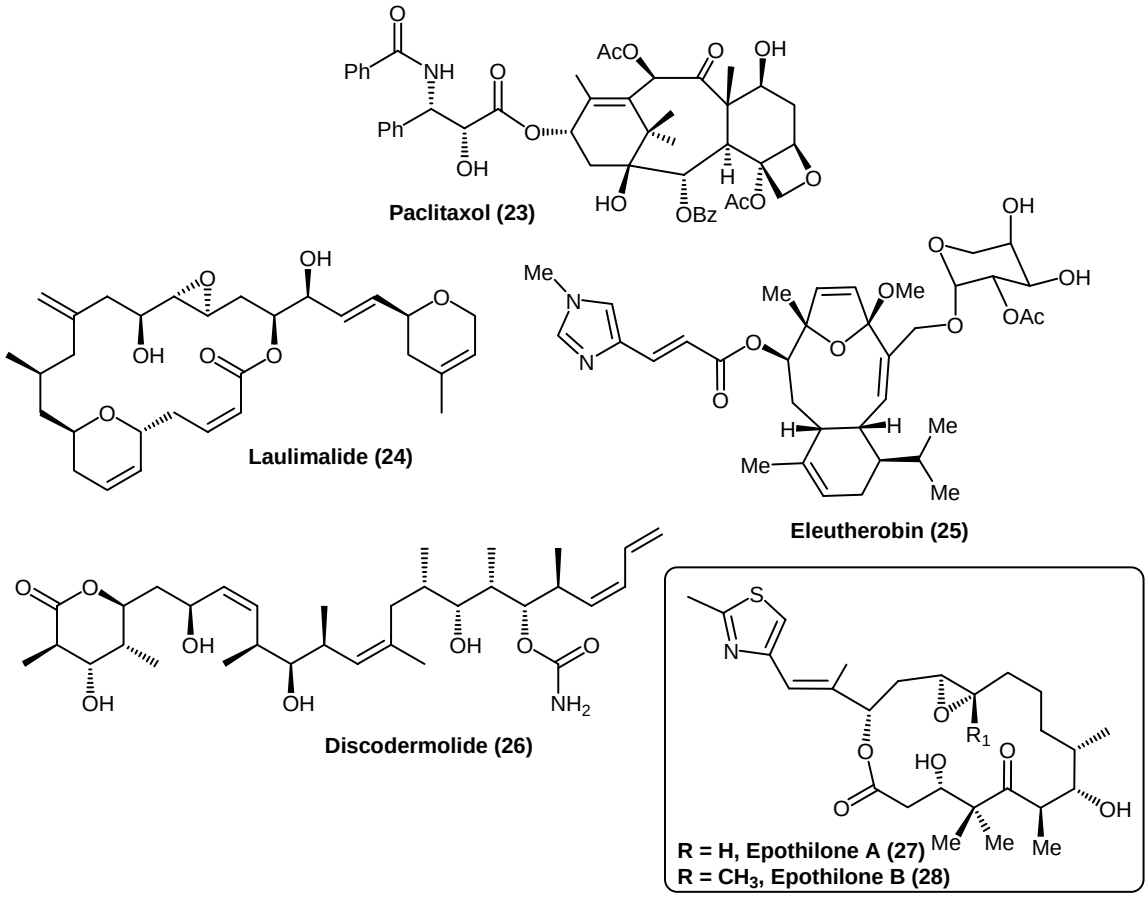


Figure 5: **Some representitive microtubule stabilizing agents**

cancer cells treated with paclitaxel (**23**) can become resistant by acquiring the multiple drug resistance (MDR) phenotype, characterized by the over expression of P-glycoprotein pump (P-gp), a transmembrane transporter that significantly lowers the concentration of the drug inside the cell.[12] These problems have led to the search for new microtubule stabilizing drugs to fight cancer. In the late 1980's, Höfle and co-workers reported a new family of polyketide macrolides called the epothilones (**27**-**28**).[13] They had been isolated from culture extracts of the cellulose-degrading myxobacterium *Sorangium cellulosum* strain. They have been shown to exhibit a narrow antifungal spectrum against the fungus *Mucor hiemalis*.[14] Scientists at Merck had independently isolated epothilones A (**27**) and B (**28**) and discovered that they are anticancer agents. Displacement experiments showed that they are competitive inhibitors of [^{3}H]-labeled paclitaxel with almost identical IC_{50} values (inhibitory concentration).[13] Both promote microtubule assembly in the absence of guanosine triphosphate (GTP), and this polymer is stable to depolymerization conditions.[15]

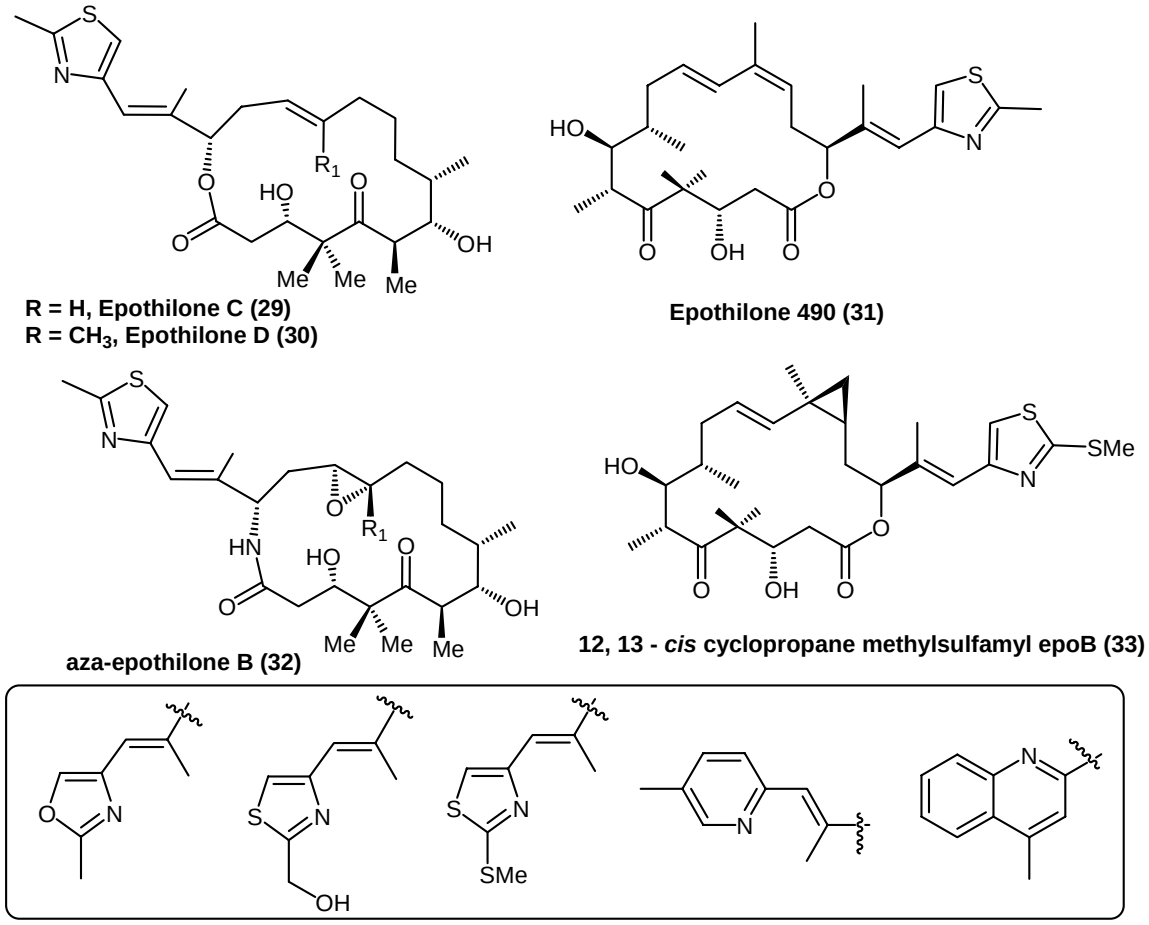


Figure 6: **Various analogues with side chain modification of natural product epothilone**

Moreover, cells treated with epothilone exhibit microtubule bundles, a change also observed with paclitaxel. Better still, epothilones show enhanced toxicity against multi drug resistant cells, since they retain their activity in P-gp expressing cells.[13] Two groups proposed that epothilones and taxanes possess a common pharmacophore for microtubule binding,[16] and recent studies in yeast highlight potential differences in the interaction between these drugs and microtubules; epothilones stabilize *saccharomyces cerevisiae* microtubules, whereas paclitaxel does not, presumably as a result of differences in the binding interactions.[17] A large number of epothilone analogs have been synthesized in efforts to improve antitumor efficacy relative to both paclitaxel and the originally identified natural products epothilone A and B (Figure 6). Existing structure-activity data provide some insight into the interaction between epothilones and microtubules (Figure 7). Although there are currently insufficient data to make conclusions regarding the usefulness of epothilones in specific cancers, early clinical results with several different epothilones

analogs are promising. Results from several groups indicate that modifications at or near the C12-C13 epoxide can affect microtubule-stabilizing activity.[18] For example, addition of a methyl group to epothilone A (**27**) at position C12 yields epothilone B (**28**), which is approximately twice as potent as epothilone A or paclitaxel (**23**) in inducing tubulin polymerization *in vitro*.[19,20] In addition, it is clear that an epoxide at C12-C13 is not required for microtubule binding, because desoxyepothilone B or epothilone D (**30**) lacks the C12-C13 epoxide and is a more potent microtubule stabilizer *in vitro* than epothilone A or B.[20] By contrast, replacement of lactone oxygen of epothilone B with a nitrogen to lactam **32** does not impair microtubule-polymerization activity.[21] Indeed, replacement of the methyl at C12-position of epothilone D with a propanol group results in a compound that is as effective as epothilone D against the luekemic cell line CCRF-CEM but is significantly less active against a P-gp-overexpressing subline.[22]

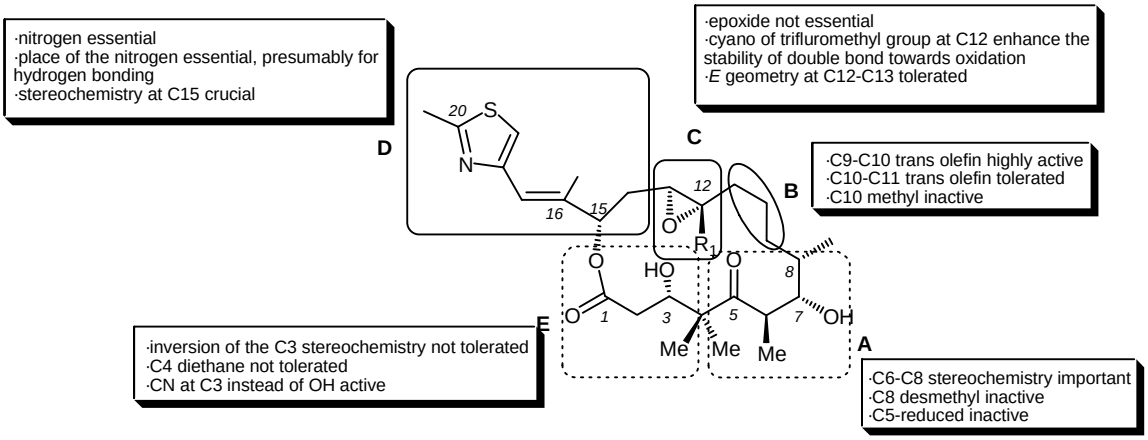
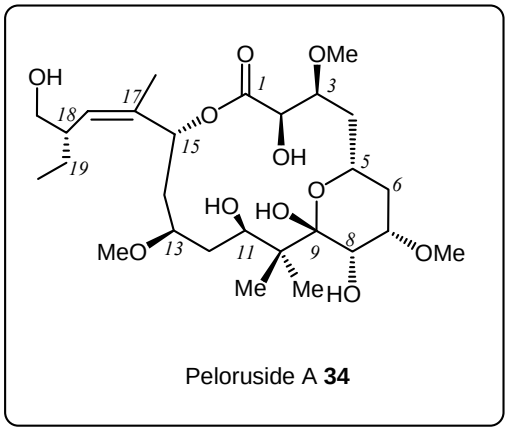
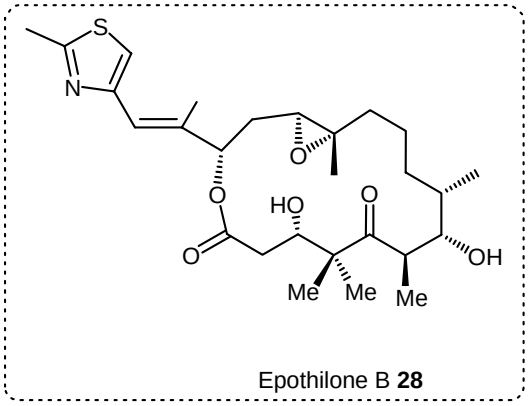


Figure 7: **Structure activity relationships of ephothilone**

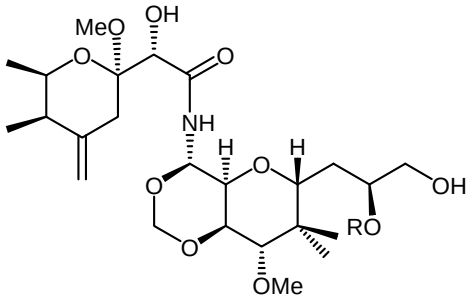
The marine sponge *Mycale hentscheli*, which is common throughout New Zealand's coastal waters, has been the focus of intense research into the sustainable supply of potent therapeutic compounds.[23] Particularly a *Mycale* species collected near Otago Harbor was found to contain the antiviral and antitumor agents mycalamide A (**35**) and mycalamide B (**36**).[24] In a subsequent study, a population of the same species was collected at Thompson Sound and provided with an immunosuppressive agent pateamine **37**.[25] Whereas, Northcote and coworkers collected the specimens of same species at a deeper range from Pelorus Sound and isolated a new cytotoxic macrolide peloruside A (**34**) in minute quantity (3 mg) together with mycalamide A **35** and pateamine **37**.[26] Peloruside A



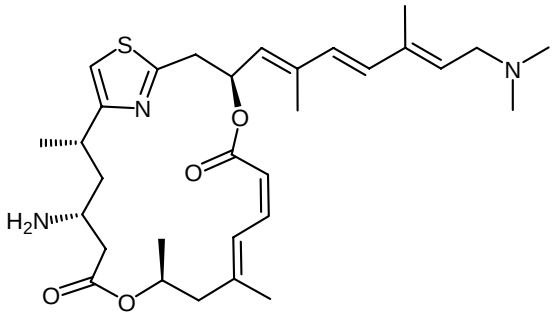
Peloruside A **34**



Epothilone B **28**



R = H Mycalamide A **35**
R = Me Mycalamide B **36**

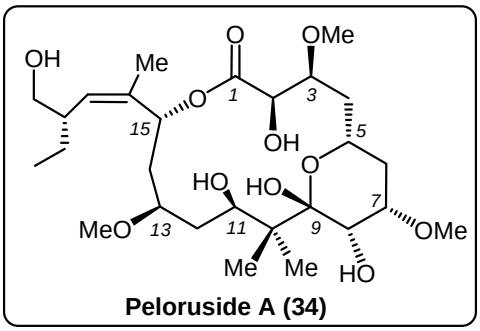


Pateamine **37**

was found to be cytotoxic to P388 murine leukemia cells as well to other cancer cells. The structure and relative stereochemistry of peloruside A was established by NMR studies and the relative stereochemistry assigned based on extensive data gathered from a variety of high-field NMR experiments.[26] Peloruside A induced biochemical changes consistent with apoptosis in a number of cultured mammalian cell lines at nM concentrations. Peloruside **34** is a macrolide similar to epothilone containing a 16-membered ring, whereas the laulimalides (**24**)[27] have a 20-membered ring. Despite the similarity of the primary mode of action of peloruside to the taxanes, epothilones, and laulimalides, it is interesting that in H441 cells, peloruside was less effective than paclitaxel at causing mitotic arrest.[28] The unique structure properties of peloruside may present novel benefits for anticancer targeting drugs. Peloruside (**34**) is less lipophilic than paclitaxel (**23**), and this property should aid the clinical application of peloruside or its analogs. Epothilones (**27**-**30**) are reported to be 30-50 times more soluble than paclitaxel, and discodermalide (**26**) is estimated to be 160-fold more soluble than paclitaxel.[29] Competition for binding between peloruside, paclitaxel and laulimalide (**24**) revealed that peloruside binds to a different site

on β-tubulin to paclitaxel and laulimalide was able to displace peloruside, indicating that peloruside and laulimalide may compete for the same or overlapping binding sites.[28] It was concluded that peloruside (**34**) and laulimalide (**24**) have different binding properties that are distinct from other microtubule stabilizing agents. The IC_{50} results in cell lines that overexpress the P-gp efflux pump indicate that peloruside is effective against P-gp pump and comparable with epothilone B (**28**), discodermalide (**26**), and laulimalide (**24**).[28] These results establish a new perspective in tumor chemotherapy because peloruside and laulimalide may prove more effective than other microtubule-stabilizing drugs against tumor cells that have developed paclitaxel/taxotere resistance through both P-gp over expression and β-tubulin gene mutation. Interestingly, isolaulimalide, the degradation product of laulimalide (**24**) is only cytotoxic at micromolar concentrations and is not affected by an increased level of P-gp overexpression, suggesting that the epoxide moiety of laulimalide (**24**) is required for its interaction with MDR efflux pump.[28] Thus, a potential advantage of peloruside (**34**) over laulimalide as a drug for additional anticancer development is the fact that peloruside is more stable than laulimalide, which may convert into its less potent isolaulimalide form. This has implications in terms of the pharmacokinetic effects that control the duration of action of laulimalide *in vivo*.[28] The identification of peloruside (**34**) as a microtubule-stabilizing drug increased the small number of microtubule-stabilizing agents available for development of anticancer drugs.

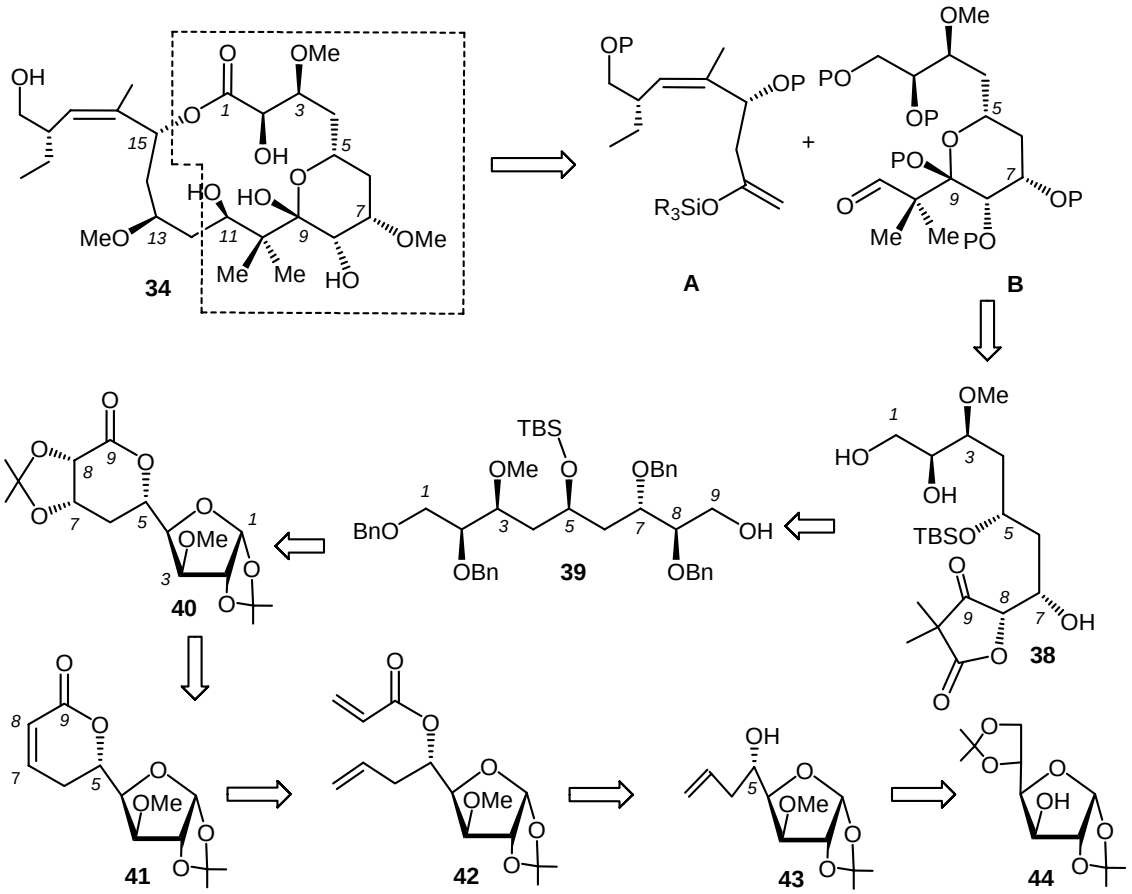
Present work



Peloruside A (34)

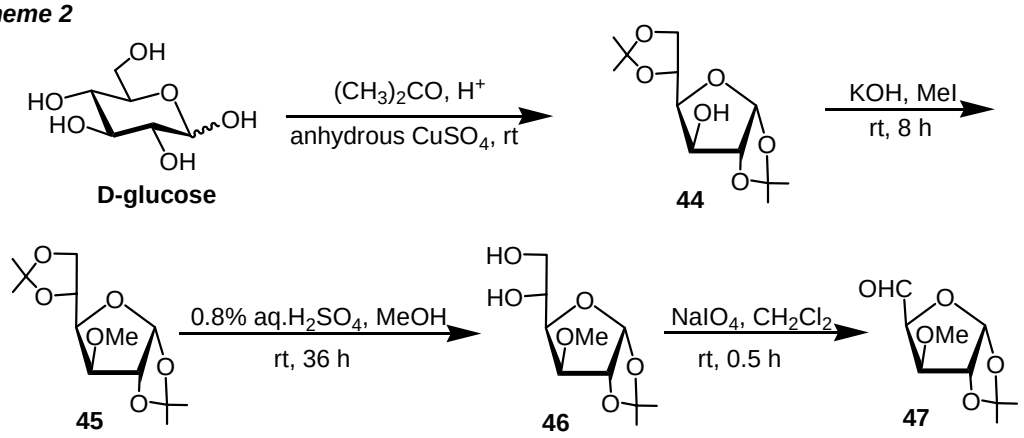
The 16-membered macrocyclic lactone peloruside A (**34**) contains an array of ten stereogenic centers with *Z*-configured trisubstituted olefin in the side chain. It also contains a sterically crowded tetrahydropyran ring ketal embedded on macrolactone system, and optimal minimization studies of peloruside A in the solution-phase indicated that its C_8-C_{11} segment adopts a conformation to accommodate strong intramolecular hydrogen bonding between the C-9 and C-11 hydroxyl groups. Our projected program towards the total synthesis of peloruside A (**34**) was envisaged by a Mukaiyama aldol reaction between segment **A** and segment **B** as a key transformation for fabricating the total carbon framework of peluroside A followed by subsequent macrolactonization as a final step (Scheme 1). First, we initiated the synthesis of C_1-C_{11} fragment **B** containing complex most stereochemical centers. Deprotection of C9-ketal moiety in fragment **B** provided an open chain β-keto-γ-lactone **38**, which can be further simplified by an aldol disconnection at C_8-C_9 bond to envision synthesis of fragment **B** from a simple straight chain polyhydroxy derivative **39**. The open chain polyol **39** was correlated to a duly protected C_4-C_5 linked deoxy disaccharide **40**. And as a part of our interest in the observations[30] on asymmetric induction of furanose monosaccharide unit to its emerging side chain, we planned a substrate induced stereoselective dihydroxylation on rigid α,β-unsaturated-δ-valerolactone moiety emerging from L-idofuranose monosachharide (**41**) to synthesize the lactone **40**. Synthesis of α,β-unsaturated lactone **41** was designed using ring closing metathesis reaction on the corresponding diene **42** which can be obtained from allyl alcohol **43**. In turn compound **43** can be obtained from readily available 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **44** (Scheme 1).

Scheme 1: Retrosynthetic analysis



Following the lines of retrosynthetic analysis (Scheme 1), synthesis of the lactone **41** was initiated from D-glucose. Thus, D-glucose was converted into 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **44**, and protection of alcohol functionality of **44** as methyl ether with NaH and methyl iodide in anhydrous THF afforded the known 3-*O*-methyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **45**. Although we obtained the desired methyl ether **45** in good yield, its large scale preparation was adopted by a new and efficient method in which KOH and neat methyl iodide were employed.[31] Selective deprotection of the 5,6-isopropylidene group in **45** with 0.8% aq. H_2SO_4 in MeOH furnished 3-*O*-methyl-1,2-*O*-isopropylidene-α-*D*-glucofuranose **46**. Subsequent oxidative cleavage of the 5,6-diol present in **46** by using $NaIO_4$ in CH_2Cl_2 gave rather unstable 3-*O*-methyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose **47** (Scheme 2).[32] Diastereoselective C-5 allylation of **47** was studied using various allylation conditions (Table 1). Treatment of **47** with freshly prepared allylmagnesium bromide in anhydrous

Scheme 2



THF gave the mixture of homoallyl alcohols **48** and **43** with poor diastereoselectivity (3:2) as judged by the NMR spectrum (Scheme 3). Alternately, the Sakurai allylation of **47** with allyltrimethylsilane in the presence of Lewis acid $TiCl_4$ yielded 6,7,8-trideoxy-3-*O*-methyl-1,2-*O*-isopropylidene-β-L-*ido*-oct-6-enofuranose **43** with high stereoselectivity.[33] The stereochemical out come observed was rationalized by mode of nucleophile approach from the α-face to the locked *s-cis* conformer (**47c**, C=O *syn* to sugar ring) of **47.**

Scheme 3

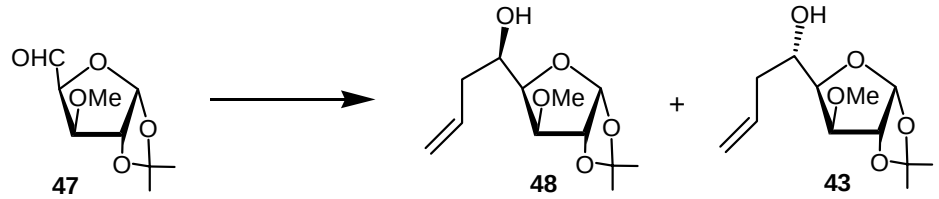


Table 1

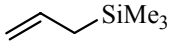
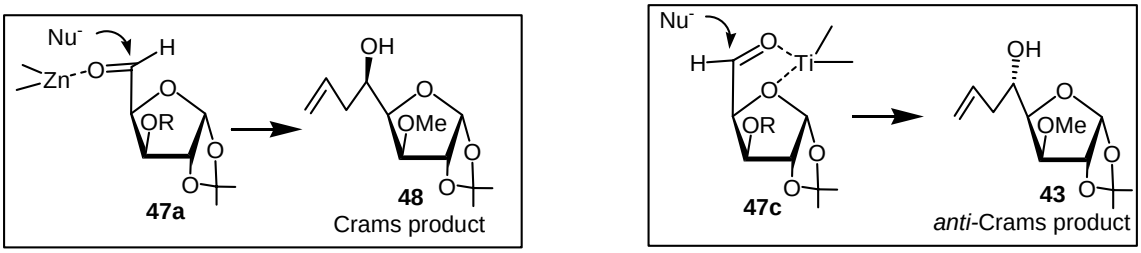
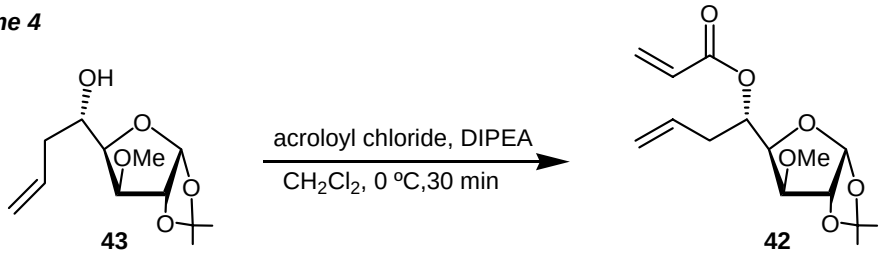
Entry	Reagents	Lewis Acid	Yield	Ratio of Products (48:43)
1.	 /CH_2Cl_2	$TiCl_4$	88%	1:20
2.	/THF	--	91%	3:2
3.	 , Zn/THF	--	95%	100:0
4.	 , Zn, aq.NH_4Cl/THF	--	99%	9:1

Figure 7



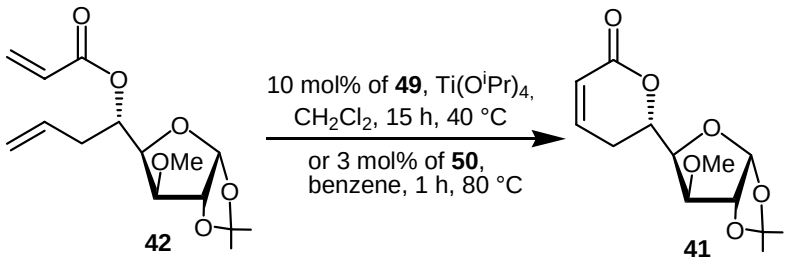
The chelation of $TiCl_4$ to C=O and ring oxygen was envisaged (Figure7).[33] Whereas under Barbier conditions, **47** and allyl bromide in the presence of zinc provided 6,7,8-trideoxy-3-*O*-methyl-1,2-*O*-isopropylidene-α-D-*gluco*-oct-6-enofuranose **48** as the sole product.[34] The formation of Crams product **48** was explained by α-attack of allyl nucleophile on *s-trans* conformer (**47a**, carbonyl *anti* to furanose ring) of **47** (Figure 7).[34] The requisite lactone **41** was prepared from homoallyl alcohol **43** by following two step sequence. The homoallyl alcohol **43** was treated with acroloyl chloride and DIPEA in CH_2Cl_2 to furnish the diene **42** (Scheme 4). The ^{1}H NMR spectrum of **42** displayed signals due to olefinic

Scheme 4



protons as set of three double-doublets at δ 5.80 (1H, J = 10.2, 1.7 Hz), 6.12 (1H, J = 17.2, 10.2 Hz) and 6.40 (1H, J = 17.2, 1.7 Hz). The protons H-1 (anomeric, d, J = 3.9 Hz), H-2 (d, J = 3.9 Hz), H-3 (d, J = 3.4 Hz), H-4 (dd, J = 8.3, 3.4 Hz) and H-5 (ddd, J = 8.3, 6.7, 4.6 Hz) resonated at δ 5.90, 4.56, 3.67, 4.20 and 5.35 respectively. The IR spectrum (1726 cm^{-1}) and microanalysis data also supported the structure of **42**. The ring closing metathesis of the diene **42** was initially performed with the 10 mol% of Grubbs' 1st generation catalyst **49**[41] in refluxing CH_2Cl_2, and found to be very sluggish probably due to the chelation of metal carbene with ester carbonyl (seven membered intermediate **42a**) (Figure 8). However, addition of 3 equivalent of $Ti(O^iPr)_4$ to the reaction mixture containing the substrate **42** and 10 mol% catalyst **49** led to the formation of the lactone **41**.[38] But, alternate use of Grubbs' 2nd generation catalyst **50**[43] in refluxing benzene provided the required δ-valerolactone **41** without any additive (Scheme 5).

Scheme 5



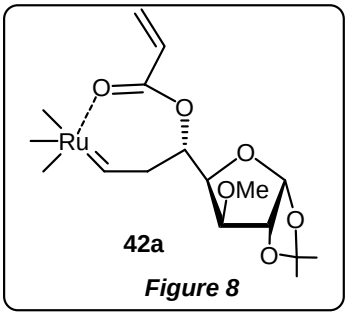
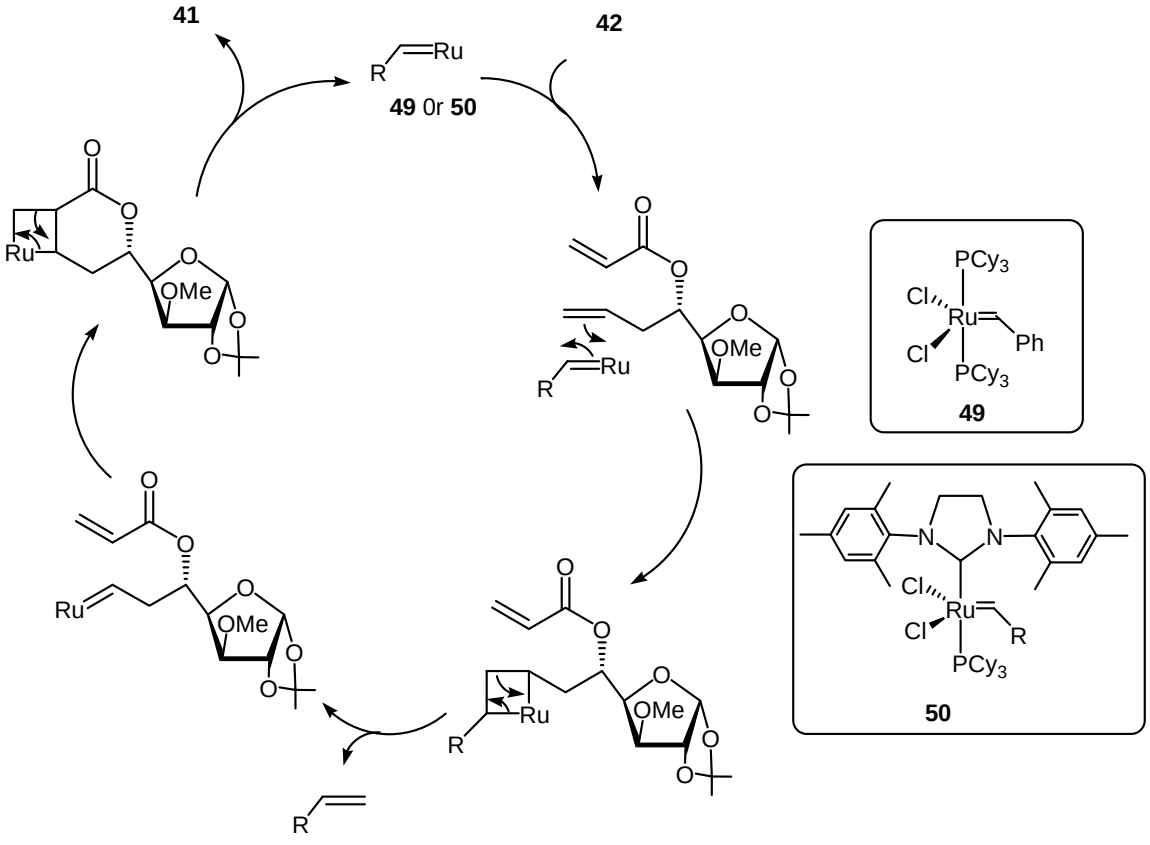


Figure 8

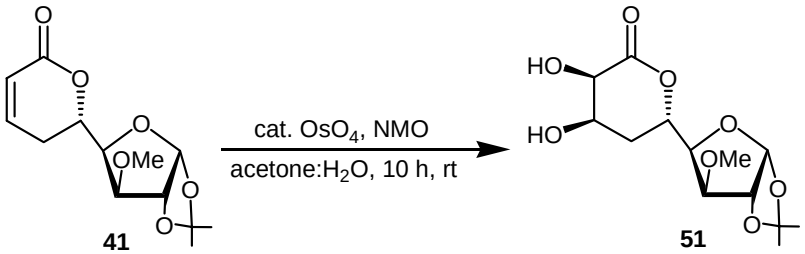
The proposed mechanism for the ring closing metathesis is outlined in Figure 9.[39] The ^{1}H NMR spectrum of α,β-unsaturated-δ-valerolactone **41** displayed signals due to olefinic protons as a multiplet at δ 6.01-6.09 and a doublet of double-doublet at δ 6.89 (J = 9.7, 6.0, 2.5 Hz). The signal due to H-5 moved upfield and appeared as doublet of double-doublet at δ 4.71 (J = 11.7, 7.5, 4.5 Hz). All other protons appeared at their expected chemical shift values. The ^{13}C NMR spectrum of **41** showed olefinic carbons at δ 120.85 and 144.63, and carbonyl carbon resonated at δ 163.09. The IR (1726 cm^{-1}) and MS (M+1, 271) spectroscopic data further supported the structure of **41**. In accordance with

***Figure 9*:** Mechanism of ring closing metathesis



retrosynthetic analysis, the unsaturated lactone **41** was subjected to dihydroxylation reaction by using catalytic OsO_4 along with co-oxidant NMO in acetone:water (9:1) to afford the diol **51** (Scheme 6), whose NMR spectral data indicated the formation of a single diastereomer. The ^{1}H NMR spectrum of **51** showed two hydroxymethine protons as a doublet at δ 4.20 (J = 3.1 Hz) and as a multiplet at δ 4.30-4.34, the methylene of valerolactone moiety moved upfield and appeared as a multiplet at δ 2.08-2.20 and as a double-triplet at δ 2.22 (J = 13.9, 4.2 Hz). All other protons resonated at their respective chemical shift values. The ^{13}C NMR spectrum of **51** displayed two new hydroxymethine carbons at δ 67.56 and 71.62, and methylene carbon resonated at δ 31.04. The stereochemistries of newly formed centers were assigned by the COSY and the 2D NOESY studies (Figure 10). In the 2D NOESY spectrum of **51**, a strong NOE between

Scheme 6



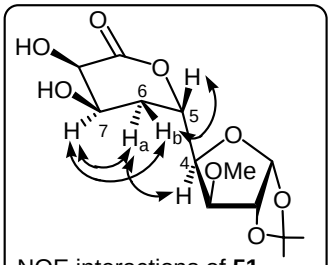
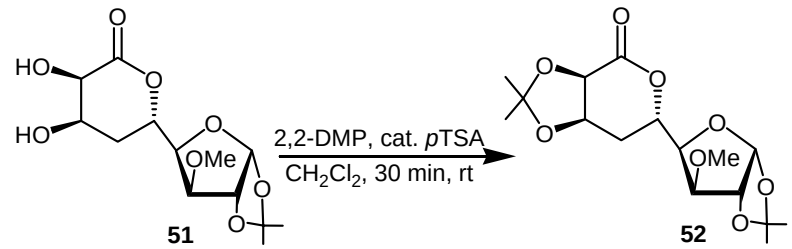


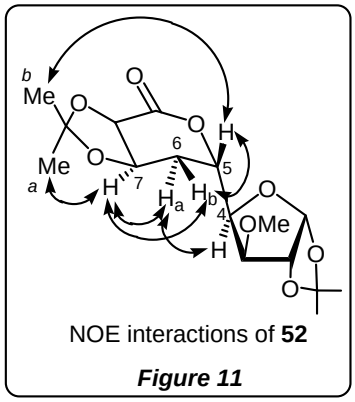
Figure 10

H-6_b, H-5 and H-7 methine protons, and between H-6_a, H-4 and H-7 methine protons were observed indicating their *cis* relationship. The structure of lactone **51** was further confirmed by transforming it into its isopropylidene derivative **52** (Scheme 7). The ^{1}H NMR spectrum of **52** displayed two new singlet signals at δ 1.48, 1.50 due to isopropylidene methyl groups while signals due to H-7 and H-8 appeared at δ 4.64-4.67 (m, 1H) and 4.58 (d, 1H, J = 6.7 Hz). All other protons appeared at their respective chemical shifts. The ^{13}C NMR spectrum of **52** showed two new signals due to isopropylidene methyl carbons at δ 24.10 and 25.82 along with an acetonide quaternary carbon at δ 111.88. The structure of diisopropylidene derivative **52** was also studied by the 2D NOESY experiments (Figure11). In the 2D NOESY spectrum of **52**, the correlations among δ-valerolactone protons observed were in accordance with its precursor **51** and additional strong NOE interaction was observed between isopropylidine methyl and H-5. Furthermore, the structure of **52** was unambiguously deduced by its X-ray diffraction

Scheme 7



51 **52**



NOE interactions of **52**

Figure 11

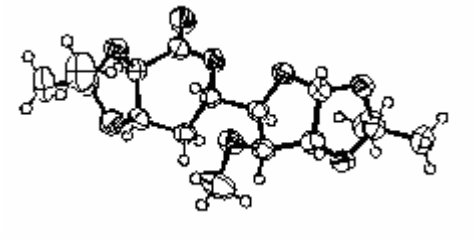
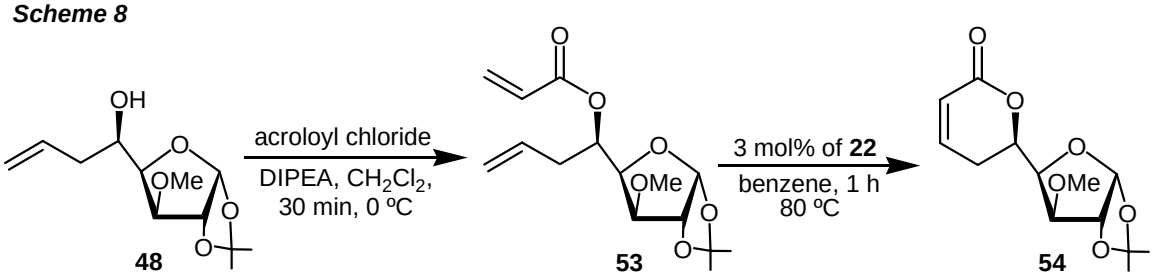


Figure 12: ORTEP diagram of **52**

studies. The ORTEP diagram of **52** clearly established the a*nti* periplaner selectivity in the dihydroxyaltion reaction (Figure 12). The details of crystal data and structure refinement (Table 2), bond lengths and bond angels (Table 3) and torsion angles (Table 4) are given at the end of this section.

The attributes of **51** have the correct stereochemistry at C-5 but undesired stereochemistry at C-7 and C-8 positions. In order to correct this situation, we planned to study the dihydroxylation on C_5-epimeric δ-valerolactone **54**. Thus, we initiated same sequence of reactions from homoallyl alcohol **48** (Scheme 8). The formation of the

Scheme 8



48 **53** **54**

lactone compound **54** from homoallyl alcohol **48** was a straightforward sequence by following acrylate formation and subsequent ring closing metathesis of the diene compound **53**. The ^{1}H NMR spectrum of **54** displayed resonances due to characteristic olefinic protons at δ 6.02 (ddd, 1H, J = 9.8, 2.3, 1.0 Hz) and 6.92 (ddd, 1H, J = 9.8, 5.9, 2.3

Hz). The methylene protons appeared at δ 2.50 (ddt, 1H, J = 18.6, 10.8, 2.5 Hz) and 2.60 (dt, 1H, J = 18.6, 5.0 Hz). The same dihydroxylation reaction as described above on **54** afforded the corresponding lactone-diol **55** exclusively as indicated by NMR spectroscopic data. The ^{1}H NMR spectrum of **55** displayed signals due to H-7 as a multiplet at δ 4.32-4.40 and H8 as a doublet at δ 4.12 (J = 3.2 Hz). In the ^{13}C NMR spectrum of **55**, resonances due to C-7 and C-8 appeared at δ 66.18 and 70.60. The IR spectral data and elemental analysis was also in support of **55**. The relative stereochemistry at C_7-C_8 segment was established by the 2D NOESY experiment of the derived acetonide compound. Thus, the diol **55** was subjected to isopropylidene protection with 2,2-dimethoxypropane in the presence of catalytic amount of *p*TSA in refluxing benzene under azeotropic conditions to yield the diacetonide derivative **56** (Scheme 9). The ^{1}H NMR

Scheme 9

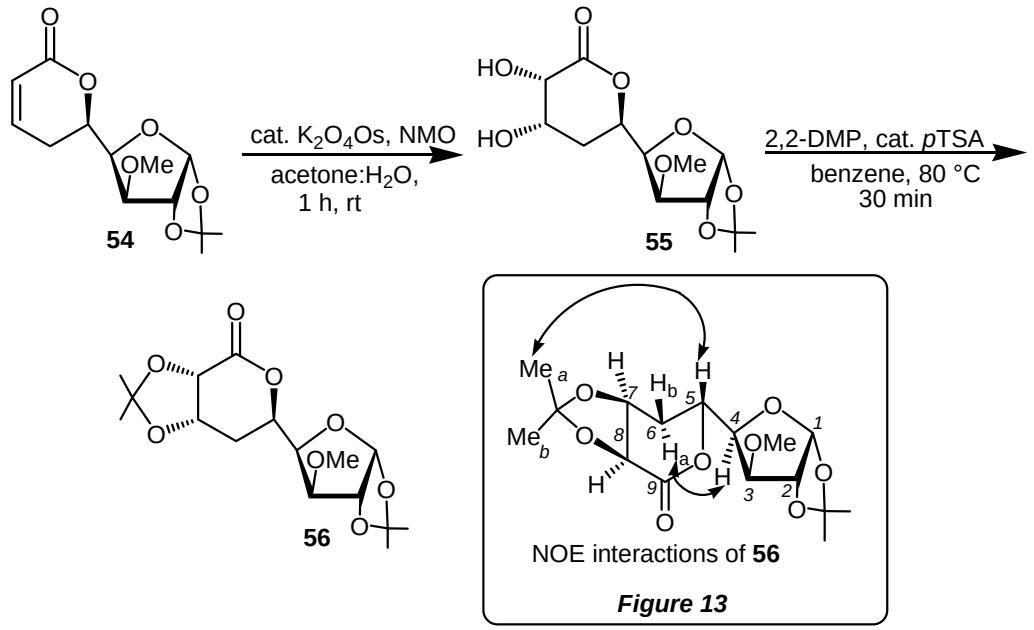
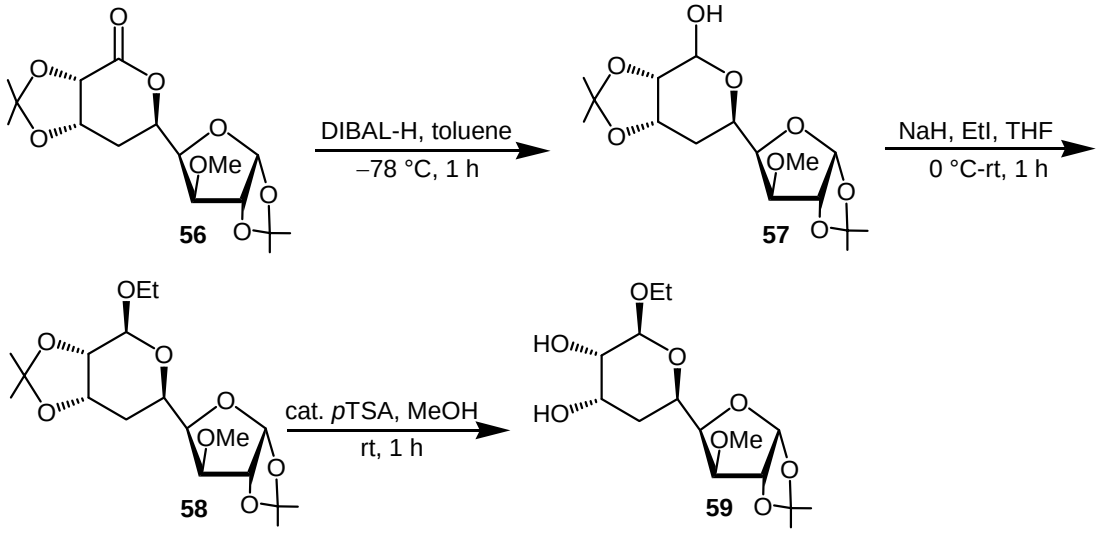


Figure 13

spectrum of **56** displayed two singlets due to isopropylidene methyl groups at δ 1.48 and 1.50, while methylene protons resonated at 1.84 (ddd, 1H, J = 15.1, 11.1, 3.4 Hz), 2.37 (dt, 1H, J = 15.1, 1.9 Hz) and all other protons appeared at the expected positions. The ^{13}C NMR, IR spectroscopic data and elemental analysis also supported the structure of **56**. In the 2D NOESY spectrum of the diacetonide derivative **56**, NOE between H_5-Me(a), H_4-H_{6a} and absence of NOE between H-5, H-7 and H-8 were observed (Figure 13). The consistent *anti* π-facial selectivity in the stereoselective dihydroxylation of unsaturated lactones

clearly indicated the limited role of furanosyl sugar moiety in the asymmetric induction evidenced. With the required stereochemistry at C-7and C-8 of **56** and possibility of inversion of C-5 center at late stages of synthesis, the compound **56** appeared as most probable diastereomer to synthesize the target fragment **B** of peloruside A. The deoxygenation of C_4-OH present in **56** required modification of the furanose ring. This was achieved by (i) hydrolysis of the 1,2-acetonide group (ii) reduction of corresponding lactol and (iii) selective protection with isopropylidene group. In order to perform this reaction sequence, it was necessary to mask the lactone functionality (Scheme 10). Accordingly, the lactone **56** was reduced to the lactol **57** using DIBAL-H at –78 °C in toluene followed by base mediated glycosidation with NaH and ethyl iodide in anhydrous THF to furnish the ethyl pyranoside **58**. In the ^{1}H NMR spectrum of **58**, signals due to ethyl group appeared at δ 1.26 (t, 3H, *J* = 7.0 Hz) and 3.77-3.84 (m, 2H). The anomeric proton resonated at δ 4.42 (*J* = 6.3 Hz) as a doublet. The coupling constant value of H-1 showed β-configuaration of the ethoxyl group. The ^{13}C NMR spectrum of **58** showed resonances due to ethyl group

Scheme 10



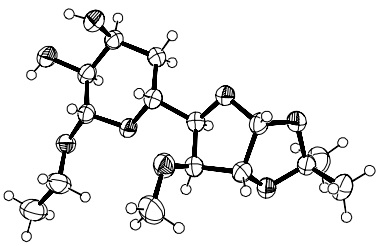
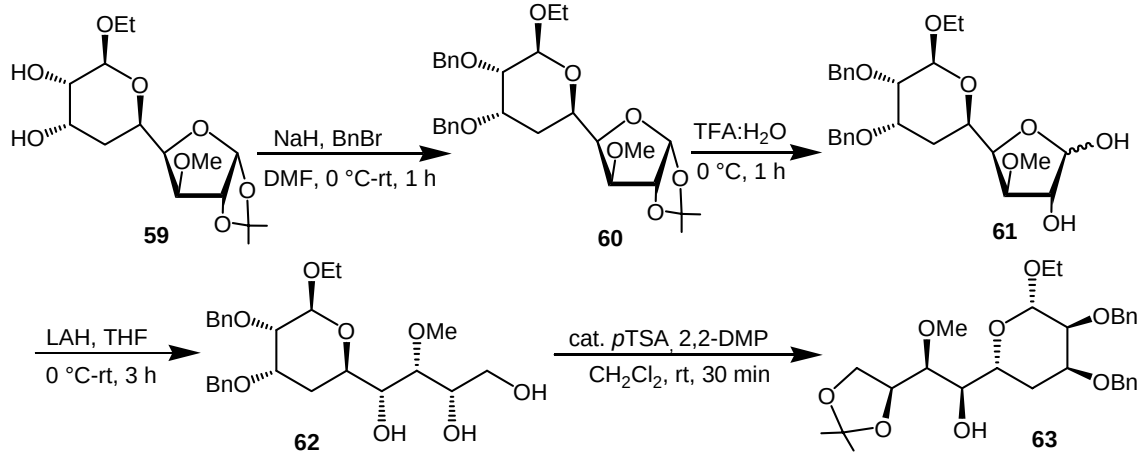


Figure 14: ORTEP diagram of **59**

carbons at δ 14.95 and 64.21, anomeric carbon of the pyranose ring resonated at δ 101.19. Subsequent deprotection of the acetonide group of **58** was accomplished using catalytic amount of *p*TSA in MeOH to yield the diol **59**. The ^{1}H, ^{13}C NMR spectral data and elemental analysis supported structure of **59**. The ^{1}H NMR spectrum of **59** showed the anomeric proton as a doublet at δ 4.65 with the diaxial coupling constant (J = 7.9 Hz). The structure of C_4-C_5 linked disaccharide **59** was further established without any ambiguity by its X-ray crystallographic studies. The ORTEP diagram provided the stereostructure of **59** (Figure 14). The details of crystal data and structure refinement (Table 5), bond lengths and bond angels (Table 6) and torsion angles (Table 7) are given at the end of this section. The hydroxyl groups of **59** was protected as dibenzyl ethers by the treatment with NaH-BnBr in DMF to afford the dibenzylether derivative **60** (Scheme 11). The ^{1}H NMR

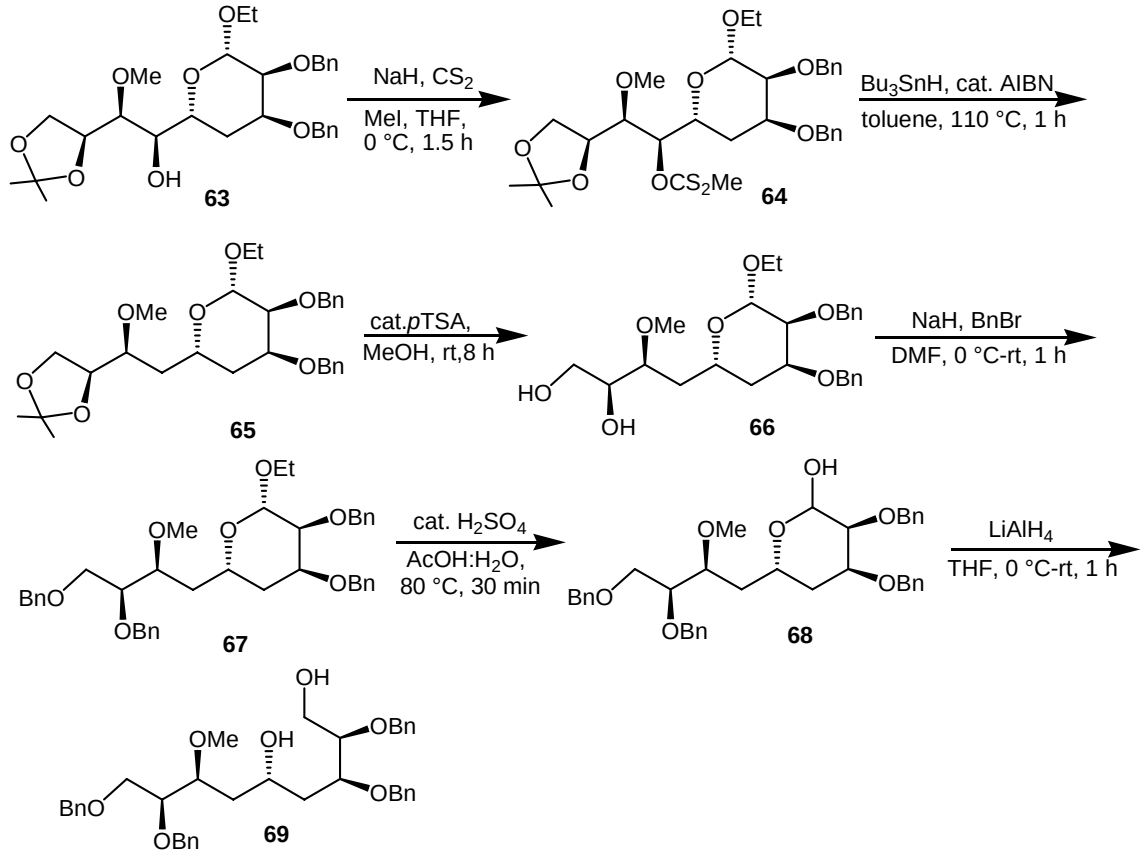
Scheme 11



spectrum of **60** displayed resonances due to aromatic protons at δ 7.15-7.40 as multiplet while benzylic protons resonated at δ 4.57-4.81 as several doublets. The ^{13}C NMR spectrum of **60** showed resonances due to benzylic carbons and all other carbons appeared at the expected chemical shifts. Having the stable orthogonal protecting groups at C-7 & C-8, deprotection of 1,2-isopropylidene group in **60** was performed by the treatment with mixture of TFA:H_2O (4:1) at 0 °C to afford the lactol **61**, and subsequent LAH reduction of **61** in THF was performed which led to the triol **62**. The ^{1}H, ^{13}C NMR spectral data and elemental analysis were in agreement with the structure of **62**. The triol **62** was treated with 2,2-DMP in the presence catalytic amount of *p*TSA in CH_2Cl_2 to afford the isopropylidene derivative **63**. The spectral and other data of compound **63** was in agreement with deduced structure. Compound **63** was subjected to Barton-McCombie deoxygenation[40] for which

the free OH group was converted into xanthate derivative **64** by treating with NaH, CS_2 and MeI in THF at 0 °C (Scheme 12).

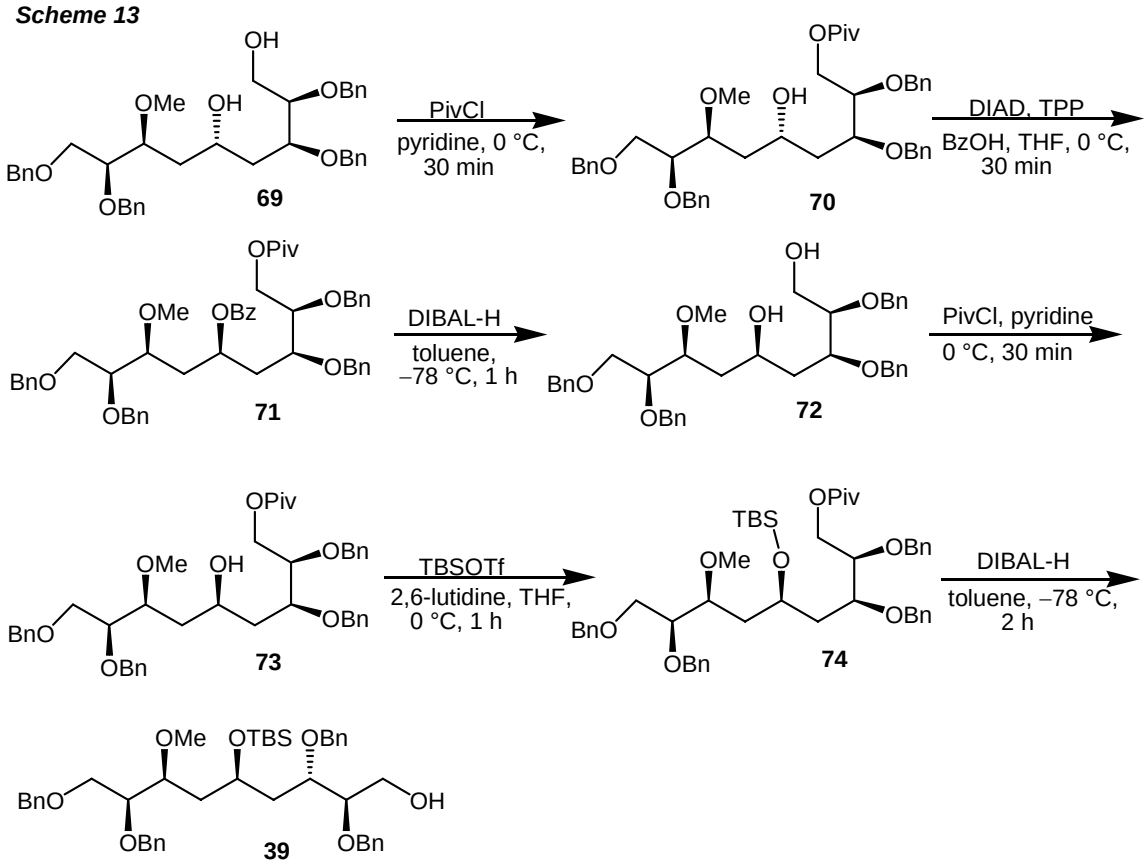
Scheme 12



Subsequent radical deoxygenation of **64** with *n*-Bu_3SnH-AIBN in refluxing toluene gave the deoxy derivative **65**. The acetonide group in **65** was cleaved to obtain the diol **66** and then benzylated to the corresponding dibenzyl ether **67** in usual manner. The spectral data of **66** and **67** was in complete agreement with the derived structures. The dibenzyl ether derivative **67** was subjected to acid hydrolysis using 80% aq. AcOH and H_2SO_4 (catalytic amount) at 80 °C to give the lactol **68**, whose reduction with LAH afforded the open chain diol **69**.

The projected Mitsunobu reaction[46] for inverting the configuration at C-5 was executed by first protecting the primary hydroxyl group as pivalate (**70**) with PivCl in pyridine at 0 °C. Subsequent Mitsunobu reaction[41] of **70** in presence of DIAD, benzoic acid and TPP in THF at 0 °C provided the benzoate derivative **71** (Scheme 13). The ^1H NMR spectrum of **71** showed a multiplet at δ 5.52-5.59 due to methine proton bearing OBz group. The ^{13}C NMR and other spectral data also supported the structure of **71**. Both the

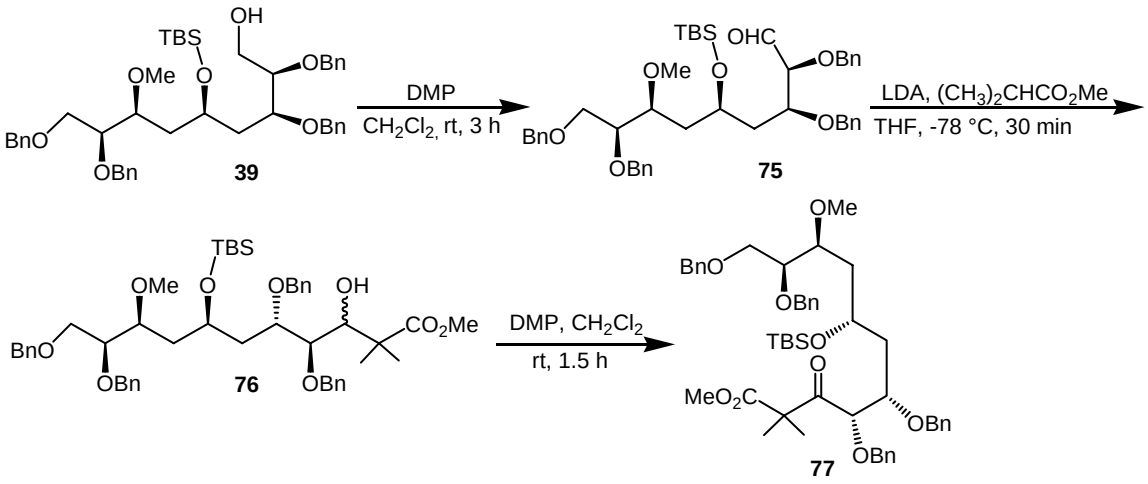
Scheme 13



protecting groups in **71** were removed under reductive conditions using DIBAL-H to afford the diol **72**. For the convenience of structural elucidation of **72**, it was selectively protected at the primary hydroxyl group with PivCl in pyridine at 0 °C to give the mono pivalate **73**. Comparison of the spectral data of two diastereomers **70** and **73** clearly indicated that the inversion had indeed occurred at C-5. Subsequent protection of secondary alcohol in **73** as silyl ether using TBSOTf and 2,6 lutidine gave the silyl derivative **74**, which upon treatment with DIBAL-H gave the C_1-C_9 fragment (**39**) of pelorusode A. The ^1H and ^{13}C NMR spectral data and other data of **39** were in agreement with assigned structure. The alcohol derivative **39** was oxidized using Dess-Martin periodinane[42] in CH_2Cl_2 to give the aldehyde **75**, which was immediately treated with the enolate derived from methyl isobutyrate in the presence of LDA in THF at –78 °C to furnish the diastereomeric mixture (**76**). The spectroscopic data and elemental analysis of **76** were compatible. The final stage of our synthetic planning was initiated by the oxidation of free OH group of **76** with Dess-Martin periodinane to afford the β-ketoester **77** (Scheme 14). The ^1H NMR spectrum of **77** showed the three singlets due to Me groups of isopropyl and carbomethoxy at δ 1.35, 1.39 and 3.41 respectively, while all other

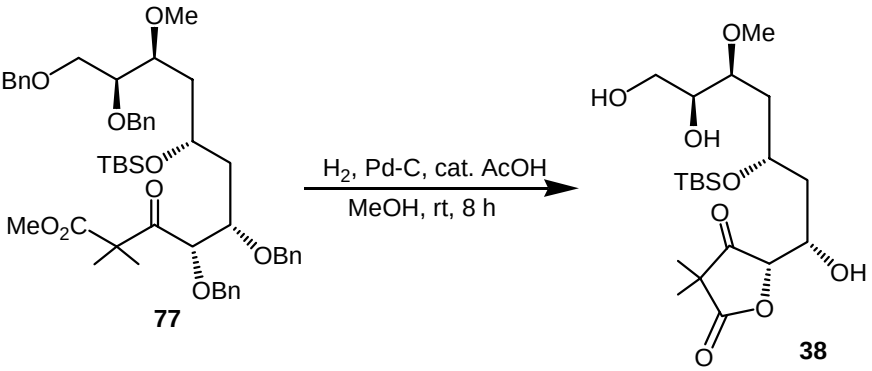
protons resonated at their expected chemical shifts. In the ^{13}C NMR spectrum of **77**, resonances due to ester and ketone carbons appeared at δ 173.59 and 206.74 respectively.

Scheme 14



Finally, the deprotection of four benzyl ethers was accomplished under hydrogenation conditions in the presence of catalytic amount Pd/C and AcOH in MeOH at normal temperature and pressure to afford the C_1-C_{11} fragment **38** (Scheme 15) whose ^1H NMR spectrum showed characteristic signals due to the methine proton (O-CH-C=O) as a doublet at δ 4.59 (J = 2.5 Hz) indicating the formation of β-keto-γ-butyrolactone. Presence of TBS ether was also evidenced in the ^1H NMR spectrum. The structure of **38** was further supported by the ^{13}C NMR spectroscopic data and elemental analysis. The ^{13}C NMR spectrum of **38** showed signals due to TBS group appeared at δ –4.67, –4.60, 17.86 and 19.20. All other carbons had expected δ values.

Scheme 15



In conclusion we have completed the synthesis of C_1-C_{11} fragment of peloruside A using ring closing metathesis and stereoselective dihydroxylation as key steps to construct the C_1-C_9 pentad core, and extended the carbon chain by aldol reaction. *En route* we

observed limited role of L-idofuranose moiety in asymmetric induction resulted during dihydroxylation of α,β-unsaturated-δ-valerolactones **41** and **54** into C4-C5 linked deoxy disaccharides **51** and **55**.

Table 2: Crystal data and structure refinement for Compound 52

Empirical formula	$C_{16}\ H_{24}\ O_8$
Formula weight	344.35
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P2(1)
Unit cell dimensions	a = 8.172(4) Å alpha = 90º
	b = 8.579(4) Å beta = 102.855(7)º
	c = 12.657(5) Å gamma = 90º
Volume	865.1(6) $Å^3$
Z, Calculated density	2, 1.322 mg/m^3
Absorption coefficient	0.106 mm^{-1}
F(000)	368
Crystal size	0.78 x 0.51 x 0.20 mm
Theta range for data collection	1.65º to 28.17º.
Limiting indices	-7<=h<=10, -11<=k<=10, -16<=l<=15
Reflections collected / unique	4888 / 3321 [R(int) = 0.0250]
Completeness to theta = 28.17	89.1 %
Max. and min. transmission	0.9791 and 0.9218
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3321 / 1 / 222
Goodness-of-fit on F^2	1.121
Final R indices [I>2sigma(I)]	R1 = 0.0448, wR2 = 0.1152
R indices (all data)	R1 = 0.0469, wR2 = 0.1169
Absolute structure parameter	-0.8(10)
Largest diff. peak and hole	0.248 and -0.163 e. $Å^{-3}$

Table 3. Bond lengths [Å] and angles [deg] for compound 52

O(7)-C(1)	1.335(3)	C(12)-O(3)-C(10)	119.2(2)
O(7)-C(3)	1.465(2)	O(5)-C(1)-O(7)	106.24(16)
O(8)-C(9)	1.410(2)	O(5)-C(1)-C(12)	122.3(2)
O(8)-C(2)	1.440(3)	O(7)-C(1)-C(12)	118.50(17)
O(6)-C(16)	1.413(3)	C(8)-O(2)-C(7)	110.68(17)
O(6)-C(6)	1.421(2)	O(8)-C(2)-C(3)	110.21(15)
O(3)-C(12)	1.422(3)	O(8)-C(2)-C(6)	105.09(15)
O(3)-C(10)	1.429(3)	C(3)-C(2)-C(6)	113.71(15)
C(1)-O(5)	1.194(3)	O(7)-C(3)-C(2)	105.24(14)
C(1)-C(12)	1.519(3)	O(7)-C(3)-C(5)	109.35(16)
O(2)-C(8)	1.415(3)	C(2)-C(3)-C(5)	112.01(16)
O(2)-C(7)	1.426(3)	O(4)-C(4)-C(5)	108.92(17)
C(2)-C(3)	1.515(3)	O(4)-C(4)-C(12)	103.48(17)
C(2)-C(6)	1.525(3)	C(5)-C(4)-C(12)	112.87(17)
C(3)-C(5)	1.516(3)	C(10)-O(4)-C(4)	109.60(16)
C(4)-O(4)	1.430(3)	C(9)-O(1)-C(7)	110.99(16)
C(4)-C(5)	1.510(3)	C(4)-C(5)-C(3)	110.42(17)
C(4)-C(12)	1.539(3)	O(6)-C(6)-C(8)	109.89(17)
O(4)-C(10)	1.402(3)	O(6)-C(6)-C(2)	108.82(16)
O(1)-C(9)	1.400(2)	C(8)-C(6)-C(2)	101.23(15)
O(1)-C(7)	1.422(3)	O(1)-C(7)-O(2)	105.99(16)
C(6)-C(8)	1.521(3)	O(1)-C(7)-C(11)	108.6(2)
C(7)-C(11)	1.503(3)	O(2)-C(7)-C(11)	110.24(19)
C(7)-C(14)	1.508(4)	O(1)-C(7)-C(14)	110.1(2)
C(8)-C(9)	1.532(3)	O(2)-C(7)-C(14)	108.6(2)
C(10)-C(13)	1.502(4)	C(11)-C(7)-C(14)	113.0(2)
C(10)-C(15)	1.510(3)	O(2)-C(8)-C(6)	110.41(18)
C(1)-O(7)-C(3)	118.90(15)	O(2)-C(8)-C(9)	104.15(16)
C(9)-O(8)-C(2)	109.73(15)	C(6)-C(8)-C(9)	104.51(16)

C(16)-O(6)-C(6)	113.29(19)	O(1)-C(9)-O(8)	113.19(17)
O(1)-C(9)-C(8)	104.55(17)	O(3)-C(12)-C(1)	107.18(17)
O(8)-C(9)-C(8)	106.95(16)	O(3)-C(12)-C(4)	104.19(16)
O(4)-C(10)-O(3)	104.39(15)	C(1)-C(12)-C(4)	115.93(16)
O(4)-C(10)-C(13)	109.2(2)		
O(3)-C(10)-C(13)	108.5(2)		
O(4)-C(10)-C(15)	110.9(3)		
O(3)-C(10)-C(15)	110.5(2)		
C(13)-C(10)-C(15)	112.9(2)		

Table 4: Torsion angles [deg] for compound 52

C(3)-O(7)-C(1)-O(5)	-177.5(2)	C(9)-O(1)-C(7)-C(11)	-127.1(2)
C(3)-O(7)-C(1)-C(12)	3.7(3)	C(9)-O(1)-C(7)-C(14)	108.7(2)
C(9)-O(8)-C(2)-C(3)	150.83(15)	C(8)-O(2)-C(7)-O(1)	-4.5(2)
C(9)-O(8)-C(2)-C(6)	27.94(19)	C(8)-O(2)-C(7)-C(11)	112.8(2)
C(1)-O(7)-C(3)-C(2)	165.02(18)	C(8)-O(2)-C(7)-C(14)	-122.8(2)
C(1)-O(7)-C(3)-C(5)	44.5(2)	C(7)-O(2)-C(8)-C(6)	126.10(19)
O(8)-C(2)-C(3)-O(7)	57.22(19)	C(7)-O(2)-C(8)-C(9)	14.4(2)
C(6)-C(2)-C(3)-O(7)	174.91(17)	O(6)-C(6)-C(8)-O(2)	163.36(15)
O(8)-C(2)-C(3)-C(5)	175.93(15)	C(2)-C(6)-C(8)-O(2)	-81.70(19)
C(6)-C(2)-C(3)-C(5)	-66.4(2)	O(6)-C(6)-C(8)-C(9)	-85.19(19)
C(5)-C(4)-O(4)-C(10)	131.08(19)	C(2)-C(6)-C(8)-C(9)	29.8(2)
C(12)-C(4)-O(4)-C(10)	10.8(2)	C(7)-O(1)-C(9)-O(8)	-98.9(2)
O(4)-C(4)-C(5)-C(3)	-79.6(2)	C(7)-O(1)-C(9)-C(8)	17.1(2)
C(12)-C(4)-C(5)-C(3)	34.7(2)	C(2)-O(8)-C(9)-O(1)	106.29(19)
O(7)-C(3)-C(5)-C(4)	-63.7(2)	C(2)-O(8)-C(9)-C(8)	-8.3(2)
C(2)-C(3)-C(5)-C(4)	-179.97(15)	O(2)-C(8)-C(9)-O(1)	-18.9(2)
C(16)-O(6)-C(6)-C(8)	-95.5(2)	C(6)-C(8)-C(9)-O(1)	-134.80(17)
C(16)-O(6)-C(6)-C(2)	154.5(2)	O(2)-C(8)-C(9)-O(8)	101.39(19)

O(8)-C(2)-C(6)-O(6)	80.49(18)	C(6)-C(8)-C(9)-O(8)	-14.5(2)
C(3)-C(2)-C(6)-O(6)	-40.1(2)	C(4)-O(4)-C(10)-O(3)	-28.7(2)
O(8)-C(2)-C(6)-C(8)	-35.24(18)	O(5)-C(1)-C(12)-C(4)	148.1(2)
C(3)-C(2)-C(6)-C(8)	-155.85(17)	O(7)-C(1)-C(12)-C(4)	-33.1(3)
C(9)-O(1)-C(7)-O(2)	-8.7(2)	O(4)-C(4)-C(12)-O(3)	11.2(2)
C(12)-O(3)-C(10)-C(13)	152.3(2)	C(5)-C(4)-C(12)-O(3)	-106.37(18)
C(12)-O(3)-C(10)-C(15)	-83.4(3)	O(4)-C(4)-C(12)-C(1)	128.70(19)
C(10)-O(3)-C(12)-C(1)	-152.14(16)	C(5)-C(4)-C(12)-C(1)	11.1(2)
C(10)-O(3)-C(12)-C(4)	-28.75(19)		
O(5)-C(1)-C(12)-O(3)	-96.0(3)		
O(7)-C(1)-C(12)-O(3)	82.7(2)		
C(4)-O(4)-C(10)-C(13)	-144.6(2)		
C(4)-O(4)-C(10)-C(15)	90.3(2)		
C(12)-O(3)-C(10)-O(4)	35.9(2)		

Table 5. Crystal data and structure refinement for Compound 59.

Empirical formula	C_{15} H_{26} O_8
Formula weight	334.36
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, C2
Unit cell dimensions	a = 17.913(16) Å
	b = 7.410(7) Å beta = 114.16(1) º
	c = 13.754(12) Å
Volume	666(3) $Å^3$
Z, Calculated density	4, 1.333 mg/m^3
Absorption coefficient	0.108 mm^{-1}
F(000)	720
Crystal size	0.93 x 0.73 x 0.34 mm
Theta range for data collection	1.62 to 23.46º.
Limiting indices	-19<=h<=20, -8<=k<=8, -15<=l<=15
Reflections collected / unique	6707 / 2424 [R(int) = 0.0273]
Completeness to theta = 23.46	99.6 %
Max. and min. transmission	0.9643 and 0.9061
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2424 / 1 / 215
Goodness-of-fit on F^2	1.084
Final R indices [I>2sigma(I)]	R1 = 0.0294, wR2 = 0.0757
R indices (all data)	R1 = 0.0296, wR2 = 0.0757
Absolute structure parameter	0.0(8)
Extinction coefficient	0.0198(13)
Largest diff. peak and hole	0.126 and -0.154 e. $Å^{-3}$

Table 6. Bond lengths [A] and angles [deg] for Compound 59

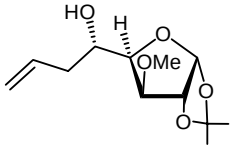
O(1)-C(1)	1.395(2)	C(9)-O(5)-C(5)	11.20(11)
O(1)-C(4)	1.426(2)	C(9)-O(8)-C(10)	14.05(13)
O(2)-C(1)	1.398(2)	O(1)-C(1)-O(2)	11.60(15)
O(2)-C(13)	1.428(2)	O(1)-C(1)-C(2)	107.53(13)
O(3)-C(2)	1.407(2)	O(2)-C(1)-C(2)	105.30(13)
O(3)-C(13)	1.413(2)	O(3)-C(2)-C(3)	109.77(15)
O(4)-C(12)	1.395(3)	O(3)-C(2)-C(1)	104.00(15)
O(4)-C(3)	1.409(2)	C(3)-C(2)-C(1)	104.44(14)
O(5)-C(9)	1.407(2)	O(4)-C(3)-C(4)	109.76(14)
O(5)-C(5)	1.429(2)	O(4)-C(3)-C(2)	110.52(15)
O(6)-C(7)	1.413(2)	C(4)-C(3)-C(2)	101.04(15)
O(7)-C(8)	1.414(2)	O(1)-C(4)-C(5)	109.35(12)
O(8)-C(9)	1.388(2)	O(1)-C(4)-C(3)	104.78(13)
O(8)-C(10)	1.428(3)	C(5)-C(4)-C(3)	115.22(14)
C(1)-C(2)	1.517(3)	O(5)-C(5)-C(4)	104.22(12)
C(2)-C(3)	1.512(3)	O(5)-C(5)-C(6)	108.94(13)
C(3)-C(4)	1.510(3)	C(4)-C(5)-C(6)	113.84(14)
C(4)-C(5)	1.507(3)		
C(5)-C(6)	1.508(3)		
C(6)-C(7)	1.510(3)		
C(7)-C(8)	1.513(3)		
C(8)-C(9)	1.503(3)		
C(10)-C(11)	1.486(3)		
C(13)-C(14)	1.487(3)		
C(13)-C(15)	1.496(3)		
C(1)-O(1)-C(4)	108.16(12)		
C(1)-O(2)-C(13)	109.03(14)		
C(2)-O(3)-C(13)	107.56(14)		
C(12)-O(4)-C(3)	112.83(18)		

Table 7. Torsion angles [deg] for Compound 59.

C(4)-O(1)-C(1)-O(2)	98.70(15)	C(4)-C(5)-C(6)-C(7)	171.28(13)
C(4)-O(1)-C(1)-C(2)	-16.30(17)	C(5)-C(6)-C(7)-O(6)	73.77(18)
C(13)-O(2)-C(1)-O(1)	-123.96(15)	C(5)-C(6)-C(7)-C(8)	-48.1(2)
C(13)-O(2)-C(1)-C(2)	-7.59(17)	O(6)-C(7)-C(8)-O(7)	50.70(19)
C(13)-O(3)-C(2)-C(3)	138.48(15)	C(6)-C(7)-C(8)-O(7)	170.67(15)
C(13)-O(3)-C(2)-C(1)	27.21(17)	O(6)-C(7)-C(8)-C(9)	-71.85(18)
O(1)-C(1)-C(2)-O(3)	107.28(15)	C(6)-C(7)-C(8)-C(9)	48.12(19)
O(2)-C(1)-C(2)-C(3)	-126.95(15)	C(10)-O(8)-C(9)-O(5)	68.74(18)
C(12)-O(4)-C(3)-C(4)	165.31(17)	C(10)-O(8)-C(9)-C(8)	-173.07(15)
C(12)-O(4)-C(3)-C(2)	-84.1(2)	C(1)-O(1)-C(4)-C(5)	158.27(14)
O(3)-C(2)-C(3)-O(4)	159.70(14)	C(1)-O(1)-C(4)-C(3)	34.23(16)
C(1)-C(2)-C(3)-O(4)	-89.32(18)	C(5)-O(5)-C(9)-O(8)	-176.69(13)
O(3)-C(2)-C(3)-C(4)	-84.15(16)	C(5)-O(5)-C(9)-C(8)	65.86(16)
C(1)-C(2)-C(3)-C(4)	26.84(17)	O(7)-C(8)-C(9)-O(8)	67.54(18)
O(2)-C(1)-C(2)-O(3)	-11.84(17)	C(7)-C(8)-C(9)-O(8)	-173.20(13)
O(1)-C(1)-C(2)-C(3)	-7.83(18)	O(7)-C(8)-C(9)-O(5)	-175.68(12)
O(4)-C(3)-C(4)-O(1)	79.51(16)	C(7)-C(8)-C(9)-O(5)	-56.42(17)
C(2)-C(3)-C(4)-O(1)	-37.21(15)	C(9)-O(8)-C(10)-C(11)	174.66(17)
O(4)-C(3)-C(4)-C(5)	-40.69(19)	C(2)-O(3)-C(13)-O(2)	-32.19(17)
C(2)-C(3)-C(4)-C(5)	-157.41(13)	C(2)-O(3)-C(13)-C(14)	-147.85(16)
C(9)-O(5)-C(5)-C(4)	172.97(13)	C(2)-O(3)-C(13)-C(15)	86.65(19)
C(9)-O(5)-C(5)-C(6)	-65.17(16)	C(1)-O(2)-C(13)-O(3)	24.20(18)
O(1)-C(4)-C(5)-O(5)	-177.50(13)	C(1)-O(2)-C(13)-C(14)	140.33(16)
C(3)-C(4)-C(5)-O(5)	-59.84(17)	C(1)-O(2)-C(13)-C(15)	-94.78(19)
O(1)-C(4)-C(5)-C(6)	63.95(18)		
C(3)-C(4)-C(5)-C(6)	-178.39(14)		
O(5)-C(5)-C(6)-C(7)	55.46(17)		

Experimental

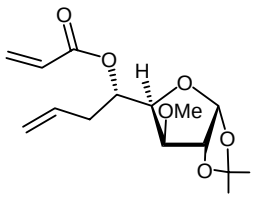
6,7,8-Trideoxy-3-*O*-methyl-1,2-*O*-isopropylidene-β-L-*ido*-oct-7-enofuranose (43)



To a solution of **47** (1.0 g, 4.94 mmol) in CH_2Cl_2 (40 mL) was added $TiCl_4$ (0.82 mL, 7.47 mmol) slowly over a period of 5 min at –78 ºC and stirred for 15 min. Then allyltrimethylsilane (0.94 mL, 5.91 mmol) was added slowly over a period of 5 min. After 3 h, the reaction mixture was poured into saturated aq. $NaHCO_3$ solution and extracted with Et_2O. Combined organic layer was washed with brine, dried (Na_2SO_4), concentrated and the residue purified on silica gel using EtOAc:light petroleum (1:4) to give **43**.

Yield	: 1.061 g (88%)
Mol. Formula	: $C_{12}H_{20}O_5$.
Optical Rotation $[\alpha]_D^{25}$	: –65.9 (*c* 3.0, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.32, 1.47 (2 s, 6H), 2.33 (ddt, 2H, *J* = 7.0, 6.0, 1.0 Hz), 2.78 (br s, 1H), 3.41 (s, 3H), 3.72 (d, 1H, *J* = 3.2 Hz), 3.93-4.06 (m, 2H), 4.58 (d, 1H, *J* = 3.8 Hz), 5.05-5.13 (m, 1H), 5.16-5.20 (m, 1H), 5.78-5.99 (m, 1H), 5.93 (d, 1H, *J* = 3.8 Hz), ppm.
^{13}C NMR ($CDCl_3$, 100 MHz)	: δ 26.31 (q), 26.78 (q), 37.76 (t), 57.54 (q), 69.42 (d), 81.64 (d), 81.83 (d), 85.25 (d), 104.73 (d), 111.77 (s), 117.38 (t), 134.45 (d) ppm.
Elemental Analysis	**Calcd.:** C, 59.00; H, 8.25%. **Found:** C, 59.35; H, 8.40%.

6,7,8-Trideoxy-6-*O*-acryloyl-3-*O*-methyl-1,2-*O*-isopropylidene-β-L-*ido*-oct-7-enofuranose (42)



To a solution of compound **43** (1.0 g, 4.09 mmol) and DIPEA (1.0 mL, 5.74 mmol) in CH_2Cl_2 (20 mL) was added acryloyl chloride (0.4 mL, 4.92 mmol) slowly over a period of 5 min at 0 ºC. After stirring for 30 min, the reaction mixture was poured into ice-cold water and repeatedly extracted with ethyl acetate. The combined organic layer was washed with water, brine, dried (Na_2SO_4), concentrated and the residue purified on silica gel using EtOAc:light petroleum (1:19) as an eluent to afford **42** as a thick syrup.

Yield : 927 mg (76%)

Mol. Formula : $C_{15}H_{22}O_6$

Optical Rotation $[\alpha]_D^{25}$: –32.6 (*c* 1.1, $CHCl_3$).

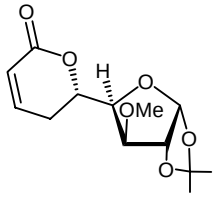
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) : 3078, 3018, 2989, 2935, 1726, 1406, 1375, 1295, 1262, 1216, 1194, 1166, 1128, 1082, 1058, 1024.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.31, 1.49 (2 s, 6H), 2.20-2.80 (m, 2H), 3.38 (s, 3H), 3.67 (d, 1H, *J* = 3.4 Hz), 4.20 (dd, 1H, *J* = 8.3, 3.4 Hz), 4.56 (d, 1H, *J* = 3.9 Hz), 5.03-5.16 (m, 2H), 5.35 (ddd, 1H, *J* = 8.3, 6.7, 4.6 Hz), 5.70-5.90 (m, 1H), 5.80 (dd, 1H, *J* = 10.2, 1.7 Hz), 5.90 (d, 1H, *J* = 3.9 Hz), 6.12 (dd, 1H, *J* = 17.2, 10.2 Hz), 6.40 (dd, 1H, *J* = 17.2, 1.7 Hz) ppm.

ESI MS (m/z): 299 (M+1)

Elemental Analysis **Calcd.:** C, 60.39; H, 7.43%.
Found: C, 60.46; H, 7.77%.

6,7,8-Trideoxy-3-*O*-methyl-1,2-*O*-isopropylidene-β-L-*ido*-non-7*Z*-enofuranuronic acid-5,9-δ-lactone (41)



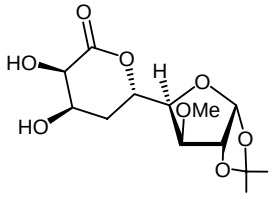
Method A: A solution of **42** (100 mg, 0.33 mmol) and titaniumtetraisopropoxide (0.3 mL, 1.00 mmol) in CH_2Cl_2 (40 mL) was heated under reflux for 15 min. The reaction mixture cooled to room temperature, charged with **49** (27 mg, 0.03 mmol) and degassed. Then the reaction mixture was heated under reflux for15 h, concentrated and the residue purified on

silica gel using EtOAc:light petroleum (1:3) as an eluent to afford **41** (63 mg, 70%) as a thick syrup.

Method B: A solution of **50** (70 mg, 0.08 mmol) and **42** (500 mg, 1.67 mmol) in 40 mL of benzene was degassed and heated at 80 ºC. After 1 h, reaction mixture was concentrated and the residue purified on silica gel using EtOAc:light petroleum (1:3) as an eluent to give **41** as a thick syrup.

Yield	: 324 mg (72%)
Mol. Formula	: $C_{13}H_{18}O_6$.
Optical Rotation $[\alpha]_D^{25}$	: −143.8 (*c* 0.6, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$ **(cm^{-1})**	: 3019, 2991, 2937, 1729, 1457, 1328, 1249, 1217, 1163, 1119, 1080, 1022.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.34, 1.51 (2 s, 6H), 2.35-2.55 (m, 2H), 3.41 (s, 3H), 3.77 (d, 1H, *J* = 3.8 Hz), 4.34 (dd, 1H, *J* = 7.7, 3.8 Hz), 4.62 (d, 1H, *J* = 3.8 Hz), 4.71 (ddd, 1H, *J* = 11.7, 7.5, 4.5 Hz), 5.98 (d, 1H, *J* = 3.8 Hz), 6.01-6.09 (m, 1H), 6.89 (ddd, 1H, *J* = 9.7, 6.0, 2.5 Hz) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 24.80 (t), 26.09 (q), 26.57 (q), 57.26 (q), 76.60 (d), 80.53 (d), 80.71 (d), 83.69 (d), 105.05 (d), 111.77 (s), 120.85 (d), 144.63 (d), 163.09 (s) ppm.
ESI MS (m/z):	271 (M+1)
Elemental Analysis	**Calcd.:** C, 57.77; H, 6.71%; **Found:** C, 58.01; H, 6.68%.

6-Deoxy-3-*O*-methyl-1,2-*O*-isopropylidene-L-*erythro*-β-L-*ido*-nonofuranuronic acid-5,9-δ-lactone (51)



A solution of **41** (500 mg, 1.85 mmol), 50% aq. NMO (0.9 mL, 3.84 mmol) and OsO_4 (0.05 M in toluene, 0.2 mL) in a mixture of acetone:H_2O (9 mL:1 mL) was stirred at room

temperature for 10 h. Excess OsO_4 was quenched with saturated aq. $NaHSO_3$, concentrated and the residue partitioned between water and ethyl acetate. The organic layer was washed with brine, dried ($NaSO_4$), concentrated and the crude product purified on silica gel with EtOAc;light petroleum (1:3) as an eluent to give **51**.

Yield : 439 mg (78%)

Mol. Formula : $C_{13}H_{20}O_8$.

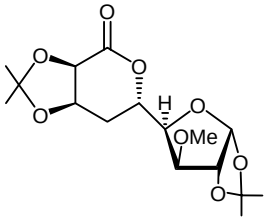
^{1}H NMR (Acetone-d_6, 500 MHz) : δ 1.31, 1.43 (2 s, 6H), 2.08-2.20 (m, 1H), 2.22 (dt, 1H, *J* = 13.9, 4.2 Hz), 2.78-2.90 (br s, 2H), 3.42 (s, 3H), 3.80 (d, 1H, *J* = 3.1 Hz), 4.20 (d, 1H, *J* = 3.1 Hz), 4.23 (dd, 1H, *J* = 8.5, 3.2 Hz), 4.30-4.34 (m, 1H), 4.71 (d, 1H, *J* = 3.8 Hz), 4.85 (ddd, 1H, *J* = 12.0, 8.3, 3.9 Hz), 5.91 (d, 1H, *J* = 3.8 Hz) ppm.

^{13}C NMR (Acetone-d_6, 125 MHz) : δ 26.50 (q), 27.08 (q), 31.04 (t), 57.47 (q), 67.56 (d), 71.62 (d), 77.47 (d), 81.77 (d), 83.21 (d), 84.81 (d), 106.21 (d), 112.05 (s), 173.52 (s) ppm.

Elemental Analysis **Calcd.:** C, 51.31; H, 6.62%.

Found: C, 51.44; H, 6.80%.

6-Deoxy-3-*O*-methyl-1,2:7,8-*bis*-*O*-isopropylidene-L-*erythro*-β-L-*ido*-nonofuranuronic acid-5,9-δ-lactone (52)



A solution of **51** (500 mg, 1.64 mmol), 2,2-dimethoxypropane (0.4 mL, 3.28 mmol) and *p*TSA (20 mg, 0.10 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 30 min, neutralized with Et_3N and concentrated. The residue was partitioned between EtOAc and water. The organic layer was washed with brine, concentrated, dried (Na_2SO_4) and purified on silica gel using EtOAc:light petroleum ether (1:4) as an eluent to obtain **52**.

Yield : 480 mg (85%)

Mol. Formula : $C_{16}H_{24}O_8$.

M. **P**. 121-124 ºC

Optical Rotation $[\alpha]_D^{25}$: –65.3 (*c* 0.9, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz) : δ 1.32, 1.36 (2 s, 6H), 1.48, 1.50 (2 s, 6H), 1.87 (ddd, 1H, *J* = 14.7, 11.2, 3.6 Hz), 2.01 (dt, 1H, *J* = 14.7, 1.9 Hz), 3.40 (s, 3H), 3.75 (d, 1H, *J* = 3.7 Hz), 4.22 (dd, 1H, *J* = 7.5, 3.7 Hz), 4.58 (d, 1H, *J* = 6.7 Hz), 4.60 (d, 1H, *J* = 3.8 Hz), 4.64-4.67 (m, 1H), 4.91 (ddd, 1H, *J* = 11.1, 7.7, 1.9 Hz), 5.96 (d, 1H, *J* = 3.8 Hz) ppm.

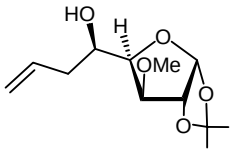
^{13}C NMR ($CDCl_3$, 125 MHz) : δ 24.10 (q), 25.82 (q), 26.19 (q), 26.69 (q), 29.99 (t), 57.49 (q), 71.57 (d), 72.77 (d), 74.16 (d), 80.80 (d), 81.03 (d), 83.94 (d), 105.13 (d), 110.61 (s), 111.88 (s), 167.08 (s) ppm.

ESI MS (m/z): 345 (M+1)

Elemental Analysis **Calcd.:** C, 55.81; H, 7.02%.

Found: C, 55.86; H, 7.10%.

6,7,8-Trideoxy-3-*O*-methyl-1,2-*O*-isopropylidene-α-D-*gluco*-oct-7-enofuranose (48)



To a mixture of **47** (4.0 g, 19.78 mmol) and allyl bromide (3.2 mL, 36.97 mmol) in THF:saturated aq. NH_4Cl (45 mL:30 mL) was added Zinc dust (3.573 g, 54.66 mmol) in portions over a period of 30 min at 0 °C. After stirring for 30 min, the reaction mixture was filtered through a Celite pad, extracted with EtOAc, washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified on silica gel using EtOAc:light petroleum (1:4) to afford **48** as a colorless liquid.

Yield : 4.78 g, (99%)

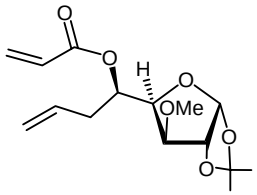
Mol. Formula : $C_{12}H_{20}O_5$.

Optical Rotation $[\alpha]_D^{25}$: –80.3 (*c* 1.5, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.32, 1.48 (2 s, 6H), 2.20-2.40 (m, 2H), 2.45-2.60 (m, 1H), 3.46 (s, 3H), 3.68 (d, 1H, *J* = 2.8 Hz), 3.98 (d, 1H, *J* = 2.9 Hz), 3.98-4.06 (m, 1H), 4.57 (d, 1H, *J* = 3.8 Hz), 5.10-5.23 (m, 2H),

	5.91 (d, 1H, *J* = 3.8 Hz), 5.76-6.00 (m, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 26.03 (q), 26.53 (q), 38.90 (t), 57.45 (q), 68.02 (d), 81.15 (d), 81.47 (d), 84.15 (d), 104.73 (d), 111.29 (s), 117.71 (t), 134.20 (d) ppm.
Elemental Analysis	**Calcd.:** C, 59.00; H, 8.25%.
	Found: C, 59.09; H, 8.37%.

6,7,8-Trideoxy-5-*O*-acryloyl-3-*O*-methyl-1,2-*O*-isopropylidene-α-D-*gluco*-oct-7-enofuranose (53)



To a stirred solution of **48** (8.0 g, 32.75 mmol) and DIPEA (7.5 mL, 43.05 mmol) in CH_2Cl_2 (15 mL) was added acryloyl chloride (3.0 mL, 36.92 mmol) slowly over a period of 10 min at 0 °C. After 30 min, reaction mixture was worked up as described earlier to give a residue, which was chromatographed on silica gel using EtOAc:light petroleum (1:19) to afford **53** as a colorless syrup.

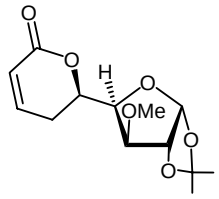
Yield	: 7.42 g (76%)
Mol. Formula	: $C_{15}H_{22}O_6$.
Optical Rotation $[\alpha]_{Na}^{25}$	: –53.2 (*c* 1.1, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.32, 1.49 (2 s, 6H), 2.40 (dt, 1H, *J* = 15.0, 7.4 Hz), 2.60-2.75 (m, 1H), 3.31 (s, 3H), 3.62 (d, 1H, *J* = 2.9 Hz), 4.20 (dd, 1H, *J* = 8.7, 3.4 Hz), 4.52 (d, 1H, *J* = 3.4 Hz), 5.00-5.15 (m, 2H), 5.25 (ddd, 1H, *J* = 8.7, 7.0, 3.6 Hz), 5.70-5.85 (m, 1H), 5.82, (dd, 1H, *J* = 10.3, 1.7 Hz), 5.89 (d, 1H, *J* = 3.8 Hz), 6.10 (dd, 1H, *J* = 17.3, 10.3 Hz), 6.42 (dd, 1H, *J* = 17.3, 1.5 Hz) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 25.91 (q), 26.46 (q), 35.72 (t), 57.44 (q), 69.32 (d), 79.65 (d), 81.19 (d), 83.25 (d), 104.86 (d), 111.33 (s), 117.54 (t), 128.13 (d), 130.26 (t), 132.84 (d), 164.15 (s) ppm.

ESI MS (m/z): 299 (M+1)

Elemental Analysis **Calcd.:** C, 60.39; H, 7.43%.

Found: C, 60.43; H, 7.50%.

6,7,8-Trideoxy-3-*O*-methyl-1,2-*O*-isopropylidene-α-D-*gluco*-non-7*Z*-enofuranuronic acid-5,9-δ-lactone (54)



A degassed solution of **53** (1.6 g, 5.36 mmol) and **50** (45 mg, 0.053 mmol) in benzene (100 mL) was heated under reflux for 1 h. After usual workup, the residue was purified on silica gel using EtOAc:light petroleum ether (1:3) as an eluent to obtain **54** as a colorless liquid.

Yield : 1.18 g, (78%)

Mol. Formula : $C_{13}H_{18}O_6$.

Optical Rotation $[\alpha]_D^{25}$:+4.7 (*c* 1.1, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) : 3442, 3019, 2938, 2400, 1723, 1524, 1384, 1252, 1215, 1163, 1119, 1081, 1023, 959, 929.

^{1}H NMR ($CDCl_3$, 500 MHz) : δ 1.32, 1.48 (2 s, 6H), 2.50 (ddt, 1H, *J* = 18.6, 10.8, 2.5 Hz), 2.60 (dt, 1H, *J* = 18.6, 5.0 Hz), 3.47 (s, 3H), 3.91 (d, 1H, *J* = 3.0 Hz), 4.22 (dd, 1H, *J* = 8.8, 3.0 Hz), 4.57 (d, 1H, *J* = 3.8 Hz), 4.71 (ddd, 1H, *J* = 10.8, 8.8, 4.3 Hz), 5.84 (d, 1H, *J* = 3.8 Hz), 6.02 (ddd, 1H, *J* = 9.8, 2.3, 1.0 Hz), 6.92 (ddd, 1H, *J* = 9.8, 5.9, 2.3 Hz) ppm.

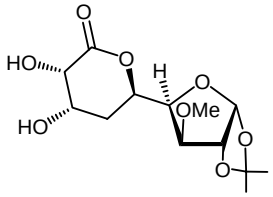
^{13}C NMR ($CDCl_3$, 125 MHz) : δ 25.96 (t), 26.57 (q), 26.62 (q), 58.07 (q), 73.40 (d), 80.30 (d), 81.49 (d), 82.65 (d), 104.90 (d), 111.78 (s), 120.91 (d), 145.12 (d), 162.90 (s) ppm.

ESI MS (m/z): 271 (M+1)

Elemental Analysis **Calcd.:** C, 57.77; H, 6.71%.

Found: C, 57.83; H, 6.79%.

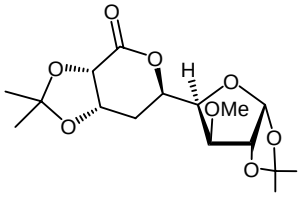
6-deoxy-3-*O*-methyl-1,2-*O*-isopropylidene-D-*erythro*-α-D-*gluco*-nonofuranuronic acid-5,9- δ-lactone (55)



To a solution of **54** (1.3 mg, 4.80 mmol) and 50% aq. NMO (2.2 mL, 9.60 mmol) in acetone:H_2O (9:1, 20 mL) was added potassium osmate (18 mg, 0.048 mmol) at room temperature and stirred for 1 h. After usual workup as described earlier, the residue was purified on silica gel using EtOAc:light petroleum ether (1:3) as an eluent to give **55**.

Yield	: 1.14 g (78%)
Mol. Formula	: $C_{13}H_{20}O_8$
^{1}H NMR ($CDCl_3$, 300 MHz)	: δ 1.33, 1.50 (2 s, 6H), 1.95-2.10 (m, 1H), 2.47 (dt, 1H, *J* = 15.1, 4.1 Hz), 2.75 (br s, 1H), 3.47 (s, 3H), 3.85 (d, 1H, *J* = 3.2 Hz), 4.12 (d, 1H, *J* = 3.2 Hz), 4.17 (dd, 1H, *J* = 7.5, 3.1 Hz), 4.32-4.40 (m, 1H), 4.55 (d, 1H, *J* = 3.8 Hz), 5.05 (ddd, 1H, *J* = 11.7, 7.5, 3.6 Hz), 5.87 (d, 1H, *J* = 3.8 Hz) ppm.
^{13}C NMR ($CDCl_3$, 125 MHz)	: δ 25.79 (q), 26.39 (q), 31.33 (t), 57.89 (q), 66.18 (d), 70.60 (d), 73.83 (d), 81.14 (d), 81.27 (d), 82.89 (d), 104.69 (d), 111.59 (s), 173.22 (s) ppm.
Elemental Analysis	**Calcd.:** C, 51.31; H, 6.62%. **Found:** C, 51.53; H, 6.90%.

6-Deoxy-3-*O*-methyl-1,2:7,8-*bis*-*O*-isopropylidene-D-*erythro*-α-D-*gluco*-nonofuranuronic acid-5,9-δ-lactone (56)

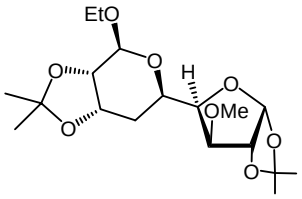


A solution of **55** (1.0 g, 3.30 mmol), 2,2-dimethoxypropane (0.8 mL, 6.5 mmol), *p*TSA (62 mg, 0.33 mmol) in benzene (40 mL) was heated under azeotropic conditions. After 30 min,

the reaction was cooled to room temperature, neutralized with Et_3N, concentrated and the residue chromatographed on silica gel using EtOAc:light petroleum ether (1:4) as an eluent to furnish **56**.

Yield	: 954 mg (84%)
Mol. Formula	: $C_{16}H_{24}O_8$.
Optical Rotation $[\alpha]_D^{25}$	: –86.6 (*c* 1.4, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 500 MHz)	: δ 1.31, 1.36 (2 s, 6H), 1.48, 1.50 (2 s, 6H), 1.84 (ddd, 1H, *J* = 15.1, 11.1, 3.4 Hz), 2.37 (dt, 1H, *J* = 15.1, 1.9 Hz), 3.44 (s, 3H), 3.87 (d, 1H, *J* = 2.9 Hz), 4.10 (dd, 1H, *J* = 8.5, 3.1 Hz), 4.54-4.60 (m, 2H), 4.63-4.72 (m, 1H), 4.89 (ddd, 1H, *J* = 11.1, 8.6, 2.0 Hz), 5.86 (d, 1H, *J* = 3.8 Hz) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 23.91 (q), 25.85 (q), 25.98 (q), 26.59 (q), 31.20 (t), 58.13 (q), 71.37 (d), 71.58 (d), 72.86 (d), 80.39 (d), 81.55 (d), 82.86 (d), 104.90 (d), 110.58 (s), 111.75 (s), 167.33 (s) ppm.
ESI MS (m/z):	345 (M+1)
Elemental Analysis	**Calcd.:** C, 55.81; H, 7.02%. **Found:** C, 55.97; H, 7.30%

Ethyl, (9*S*)-6-deoxy-3-*O*-methyl-1,2:7,8-*bis*-*O*-isopropylidene-D-*erythro*-α-D-*gluco*-nonodialdo-1,4-furanose-9,5-pyranoside (58)



To a solution of **56** (500 mg, 1.45 mmol) in toluene (20 mL) was added DIBAL-H (2.5 M in toluene, 0.6 mL, 1.5 mmol) slowly over a period of 10 min at –78 °C. After stirring for 1 h, the reaction was quenched with saturated aq. sodium potassium tartarate, filtered through a pad of Celite and concentrated. The residue was purified on silica gel using EtOAc:light petroleum ether (1:3) as an eluent to give **57** (492 mg, 98%).

To a stirred solution of **57** (492 mg, 1.42 mmol) in THF (10 mL) was added NaH (60% dispersion in mineral oil, 85 mg, 2.125 mmol) portionwise over a period of 5 min at 0 °C.

After15 min, EtI (0.22 mL, 2.84 mmol) in THF (1 mL) was introduced and the reaction mixture warmed to room temperature. The reaction was quenched with saturated aq. NH_4Cl after 1h and extracted with EtOAc. Combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel using EtOAc:light petroleum ether (1:6) as an eluent to afford **58** (462 mg, 87%) as a colorless liquid.

Mol. Formula : $C_{18}H_{30}O_8$.

Optical Rotation $[\alpha]_D^{25}$: +40.6 (*c* 1.1, $CHCl_3$).

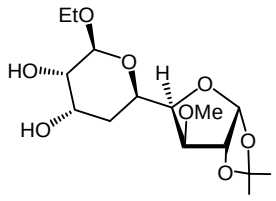
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) : 3498, 3020, 2991, 2937, 1748, 1376, 1264, 1244, 1215, 1164, 1123, 1080, 1042, 1024.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.26 (t, 3H, *J* = 7.0 Hz), 1.32, 1.36 (2 s, 6H), 1.48, 1.51 (2 s, 6H), 1.75-1.95 (m, 1H), 2.30 (dt, 1H, *J* = 14.8, 2.1 Hz), 3.45 (s, 3H), 3.55 (dd, 1H, *J* = 9.4, 7.0 Hz), 3.77-3.84 (m, 2H), 3.85-3.92 (m, 1H), 3.96-4.02 (m, 2H), 4.40-4.50 (m, 1H), 4.42 (d, 1H, *J* = 6.3 Hz), 4.55 (d, 1H, *J* = 3.8 Hz), 5.87 (d, 1H, *J* = 3.8 Hz) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 14.95 (q), 25.47 (q), 26.09 (q), 26.61 (q), 27.60 (q), 29.99 (q), 57.78 (q), 64.21 (t), 66.08 (d), 71.85 (d), 74.98 (d), 81.52 (d), 82.07 (d), 83.32 (d), 101.19 (d), 104.90 (d), 108.76 (s), 111.30 (s) ppm.

Elemental Analysis **Calcd.:** C, 57.74; H, 8.08%.
Found: C, 57.75; H, 8.38%.

Ethyl, (9*S*)-6-deoxy-3-*O*-methyl-1,2-*O*-isopropylidene-D-*erythro*-α-D-*gluco*-nonodialdo-1,4-furanose-9,5-pyranoside (59)

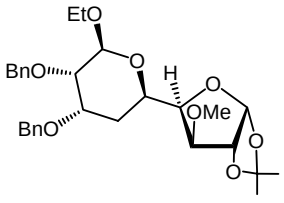


A solution of compound **58** (500 mg, 1.33 mmol) and *p*TSA (25 mg) in MeOH (10 mL) was stirred at room temperature for 1 h. After usual work up as described earlier, the

residue was purified on silica gel using EtOAc:light petroleum ether (5:7) as an eluent to give **59** as a colorless crystalline solid.

Yield	: 369 g (83%)
Mol. Formula	: $C_{15}H_{26}O_8$.
M. P.	: 142-145 °C
Optical Rotation $[\alpha]_{Na}^{25}$	: +34.1 (*c* 1.4, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1})	: 3473, 3018, 2984, 2933, 2900, 1376, 1215, 1136, 1124, 1081, 1027.
^{1}H NMR ($CDCl_3$, 500 MHz)	: δ 1.28 (t, 3H, *J* = 7.0 Hz), 1.31, 1.47 (2 s, 6H), 1.65 (ddd, 1H, *J* = 14.1, 11.4, 2.7 Hz), 2.18 (dt, 1H, *J* = 13.3, 2.5 Hz), 2.47 (br s, 1H), 2.51 (br s, 1H), 3.39 (dt, 1H, *J* = 8.0, 2.5 Hz), 3.42 (s, 3H), 3.58 (dq, 1H, *J* = 9.5, 7.0 Hz), 3.77 (d, 1H, *J* = 2.9 Hz), 3.91 (dq, 1H, *J* = 9.5, 7.0 Hz), 4.01 (dd, 1H, *J* = 9.0, 2.8 Hz), 4.16 (ddd, 1H, *J* = 11.2, 8.0, 2.0 Hz), 4.21-4.25 (m, 1H), 4.54 (d, 1H, *J* = 3.8 Hz), 4.65 (d, 1H, *J* = 7.9 Hz), 5.87 (d, 1H, *J* = 3.8 Hz) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 14.73 (q), 25.72 (q), 26.20 (q), 34.62 (t), 57.59 (q), 64.36 (t), 66.08 (d), 66.82 (d), 71.05 (d), 81.34 (d), 82.99 (d), 99.83 (d), 104.49 (d), 110.93 (s) ppm.
Elemental Analysis	**Calcd.:** C, 53.88; H, 7.84%. **Found:** C, 53.90; H, 7.91%.

Ethyl, (9*S*)-6-deoxy-3-*O*-methyl-1,2-*O*-isopropylidene-7,8-*bis*-*O*-benzyl-D-*erythro*-α-D-*gluco*-nonodialdo-1,4-furanose-9,5-pyranoside (60)



To a solution of **59** (300 mg) in DMF (2 mL) was added NaH (60% dispersion in paraffin oil, 100 mg, 2.5 mmol) portionwise over a period of 10 min at 0 °C and then introduced BnBr (0.3 mL, 2.5 mmol). After stirring for 1 h, the reaction was quenched with ice-cold

water and extracted with Et_2O. Combined organic layer was washed with water, brine, dried (Na_2SO_4), concentrated and the residue purified on silica gel using EtOAc:light petroleum ether (1:9) as an eluent to give **60** as a thick liquid.

Yield : 412 mg (90%)

Mol. Formula : $C_{29}H_{38}O_8$.

Optical Rotation $[\alpha]_D^{25}$: +30.7 (*c* 0.9, $CHCl_3$).

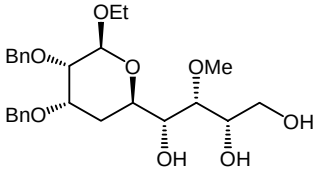
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.29 (t, 3H, *J* = 7.1 Hz), 1.30, 1.44 (2 s, 6H), 1.40-1.50 (m, 1H), 2.23 (ddd, 1H, *J* = 14.0, 3.6, 2.2 Hz), 3.20 (dd, 1H, *J* = 7.9, 3.0 Hz), 3.44 (s, 3H), 3.61 (dq, 1H, *J* = 9.5, 7.1 Hz), 3.78 (d, 1H, *J* = 2.9 Hz), 3.88-3.96 (m, 2H), 4.00 (d, 1H, *J* = 2.9 Hz), 4.06-4.20 (m, 1H), 4.52 (d, 1H, *J* = 3.8 Hz), 4.57 (d, 1H, *J* = 7.7 Hz), 4.65 (s, 1H), 4.68 (d, 1H, *J* = 12.3 Hz), 4.81 (d, 1H, *J* = 12.3 Hz), 4.89 (d, 1H, 8.0 Hz), 5.84 (d, 1H, *J* = 3.8 Hz), 7.15-7.40 (m, 10H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 15.25 (q), 26.09 (q), 26.53 (q), 32.93 (t), 58.07 (q), 65.02 (t), 66.49 (d), 71.30 (d), 72.59 (d), 73.14 (d), 78.76 (d), 81.78 (d), 83.32 (d), 100.75 (d), 104.90 (d), 111.41 (s), 127.43 (d), 127.62 (d), 128.02 (d), 138.50 (s), 138.72 (s) ppm.

Elemental Analysis **Calcd.:** C, 67.68; H, 7.44%.

Found: C, 67.77; H, 7.49%.

Ethyl, 4-deoxy-7-*O*-methyl-2,3-*bis*-*O*-benzyl-L-*threo*-β-L-*allo*-nonopyranoside (62)



A solution of compound **60** (240 mg, 0.46 mmol) in TFA:H_2O (1:1, 4 mL) was stirred at 0 °C for 1 h, concentrated and the resulting residue partitioned between EtOAc and water. Organic layer was washed with saturated aq. Na_2CO_3, brine, dried (Na_2SO_4), concentrated and the residue purified on silica gel using EtOAc;light petroleum ether (2:3) as an eluent to give **61** (168 mg, 77%).

To a solution of **61** (168 mg, 0.35 mmol) in THF (10 mL) was added $LiAlH_4$ (26 mg, 7.0 mmol) portion wise over a period of 15 min at 0 °C and then stirred for 3 h at room temperature. The reaction was quenched by the slow addition of EtOAc followed by ice water, filtered through a plug of Celite, concentrated and the residue purified on silica gel using EtOAc:light petroleum ether (4:1) as an eluent to afford **62** (146 mg, 81%).

Mol. Formula : $C_{26}H_{36}O_8$.

Optical Rotation $[\alpha]_D^{25}$: +41.4 (*c* 0.7, $CHCl_3$).

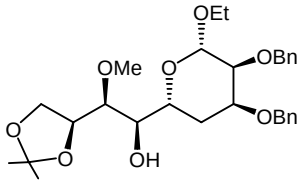
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.29 (t, 3H, *J* = 7.0 Hz), 1.40-1.50 (m, 1H), 2.26 (ddd, 1H, *J* = 14.0, 3.5, 2.0 Hz), 2.92-3.05 (br s, 3H), 3.20 (dd, 1H, *J* = 8.0, 3.0 Hz), 3.53 (s, 3H), 3.50-3.60 (m, 1H), 3.60-3.70 (m, 4H), 3.75-4.00 (m, 4H), 4.70 (s, 2H), 4.75 (AB_q, 2H, *J* = 12.2 Hz), 4.89 (d, 1H, *J* = 8.0 Hz), 7.25-7.40 (m, 10H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz) : δ 15.38 (q), 29.77 (q), 32.60 (t), 60.87 (q), 62.49 (t), 62.76 (d), 65.38 (d), 69.69 (d), 71.85 (d), 72.44 (d), 72.89 (d), 73.56 (d), 73.82 (d), 78.94 (d), 79.05 (d), 101.06 (d), 127.47 (d), 127.60 (d), 127.77 (d), 128.81 (d), 138.65 (s), 138.66 (s) ppm.

Elemental Analysis **Calcd.:** C, 65.53; H, 7.61%.

Found: C, 65.74; H, 7.88%.

Ethyl, 4-deoxy-7-*O*-methyl-8,9-*O*-isopropylidene-2,3-*bis*-*O*-benzyl-L-*threo*-β-L-*allo*-nonopyranoside (63)



A solution of **62** (150 mg, 0.31 mmol), 2,2-dimethoxypropane (0.1 mL, 0.81 mmol), *p*TSA (10 mg) in CH_2Cl_2 (10 mL) was stirred at room temperature for 0.5 h and neutralized with Et_3N. After usual work up as described earlier, the residue was purified on silica gel using EtOAc:light petroleum ether (1:9) as an eluent to give **63**.

Yield : 156 g, (98%)

Mol. Formula : $C_{29}H_{40}O_8$.

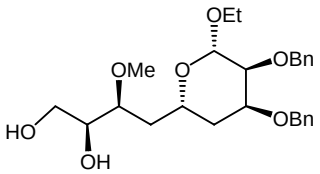
Optical Rotation $[\alpha]_D^{25}$: +38.1 (*c* 0.8, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.30 (t, 3H, *J* = 7.0 Hz), 1.37, 1.43 (2 s, 6H), 2.27 (ddd, 1H, *J* = 14.0, 8.0, 3.3 Hz), 2.40 (br d, 1H, *J* = 8.5 Hz), 3.20 (dd, 1H, *J* = 8.0, 3.3 Hz), 3.47-3.61 (m, 2H), 3.60 (s, 3H), 3.65-3.89 (m, 3H), 3.91-4.05 (m, 3H), 4.30 (q, 1H, *J* = 6.8 Hz), 4.70 (s, 2H), 4.75 (AB_q, 2H, *J* = 12.0 Hz), 4.90 (d, 1H, *J* = 8.0 Hz), 7.25-7.40 (m, 10H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz) : δ 15.47 (q), 25.63 (q), 26.58 (q), 32.70 (t), 60.97 (q), 65.35 (t), 65.92 (t), 69.54 (d), 71.87 (d), 72.94 (d), 73.65 (d), 74.48 (d), 77.75 (d), 78.97 (d), 79.36 (d), 101.16 (d), 109.47 (d), 127.44 (d), 127.50 (d), 127.65 (d), 127.81 (d), 128.24 (d), 128.28 (d), 138.76 (s), 138.82 (s) ppm.

Elemental Analysis **Calcd.:** C, 67.42; H, 7.80%.
Found: C, 67.34; H, 7.88%.

Ethyl, 4,6-dideoxy-7-*O*-methyl-2,3-*bis*-*O*-benzyl-L-*glycero*-α-D-*talo*-nonopyranoside (66)



To a solution of **63** (200 mg, 0.39 mmol) in THF (10 mL) was added NaH (60% dispersion in mineral oil, 40 mg, 1.0 mmol) in portion wise over a period of 5 min at 0 °C, stirred for 15 min and CS_2 (0.1 mL, 1.65 mmol), MeI (0.1 mL, 1.60 mmol) added in succession. After 30 min, the reaction was quenched with water and extracted with EtOAc. Combined organic layer was washed with water, brine, dried (Na_2SO_4) and concentrated to afford **64**, which was heated to reflux with Bu_3SnH (0.2 mL, 0.74 mmol) and AIBN (10 mg) in toluene (10 mL) for 1 h. The reaction mixture was concentrated and the residue purified on silica gel using EtOAc:light petroleum ether (1:9) as an eluent to give **65** (107 mg, 55%) .
A solution of **65** (107 mg, 0.21 mmol) and *p*TSA (5 mg) in MeOH (10 mL) was stirred at room temperature for 8 h. After usual workup as described earlier, the residue was purified on silica gel using EtOAc:light petroleum ether (1:2) as an eluent to give **66** (91 mg, 93%).

Mol. Formula : $C_{26}H_{36}O_7$.

Optical Rotation $[\alpha]_D^{25}$: +45.7 (*c* 1.4, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) : 3444, 3018, 2929, 2979, 2401, 1722, 1602, 1582, 1495, 1452, 1384, 1276, 1215, 1177, 1149, 1112, 1070, 1029, 928.

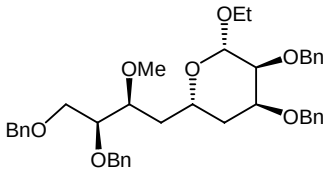
^{1}H NMR ($CDCl_3$, 300 MHz) : δ 1.30 (t, 3H, *J* = 7.2 Hz), 1.20-1.40 (m, 1H), 1.50-1.70 (m, 2H), 1.80-1.90 (m, 1H), 3.22 (dd, 1H, *J* = 8.0, 3.0 Hz), 3.47 (s, 3H), 3.55-3.80 (m, 4H), 3.85-4.20 (m, 3H), 4.50-4.75 (m, 2H), 4.70 (s, 2H), 4.80 (d, 1H, *J* = 12.0 Hz), 4.90 (d, 1H, *J* = 8.0 Hz), 7.25-7.55 (m, 10H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 15.26 (q), 36.32 (t), 37.08 (t), 59.33 (q), 63.66 (d), 65.16 (t), 66.71 (t), 71.99 (d), 72.79 (d), 73.89 (d), 78.59 (d), 78.92 (d), 100.84 (d), 127.24 (d), 127.30 (d), 127.48 (d), 127.54 (d), 128.06 (d), 138.65 (s), 138.74 (s) ppm.

Elemental Analysis **Calcd.:** C, 67.80; H, 7.88%.

Found: C, 67.87; H, 7.94%.

Ethyl, 4,6-dideoxy-7-*O*-methyl-2,3,8,9-*tetrakis*-*O*-benzyl-L-*glycero*-α-D-*talo*-nonopyranoside (67)



To a solution of **66** (200 mg, 0.43 mmol) in DMF (2 mL) was added NaH (60% dispersion in mineral oil, 50 mg, 1.3 mmol) portionwise at 0 °C and then charged with BnBr (0.1 mL, 0.84 mmol). After stirring for 1 h at room temperature, reaction mixture was subjected to usual workup as described earlier and the residue purified on silica gel using EtOAc:light petroleum ether (1:9) as an eluent to give **67** as a thick liquid.

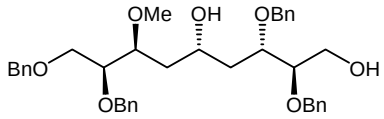
Yield : 267 mg (97%)

Mol. Formula : $C_{40}H_{48}O_7$.

Optical Rotation $[\alpha]_{Na}^{25}$: +27.6 (*c* 0.8, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1})	: 3317, 3011, 2926, 1723, 1453, 1216, 1148, 1089, 1044, 1028.
^{1}H NMR ($CDCl_3$, 500 MHz)	: δ 1.29 (t, 3H, *J* = 7.2 Hz), 1.20-1.40 (m, 1H), 1.47-1.60 (m, 2H), 1.72-1.85 (m, 1H), 3.17 (dd, 1H, *J* = 8.0, 3.2 Hz), 3.42 (s, 3H), 3.50-3.70 (m, 4H), 3.80-3.88 (m, 1H), 3.90-4.05 (m, 2H), 4.15 (q, 1H, *J* = 6.8 Hz), 4.55 (s, 2H), 4.62-4.75 (m, 4H), 4.71 (s, 2H), 4.90 (d, 1H, *J* = 8.0 Hz), 7.17-7.40 (m, 20H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 15.47, 36.35, 36.90, 59.61, 64.98, 66.56, 70.27, 71.93, 72.88, 73.03, 73.29, 74.17, 77.51, 79.13, 79.65, 100.93, 127.47, 127.62, 127.98, 128.20, 128.94, 129.71, 134.34, 138.39, 138.68, 138.86, 139.05 ppm.
ESI MS (m/z):	641 (M+1)
Elemental Analysis	**Calcd.:** C, 74.97; H, 7.55%. **Found:** C, 74.99; H, 7.91%.

4,6-Dideoxy-3-*O*-methyl-1,2,7,8-*tetrakis*-*O*-benzyl-D-*glycero*-D-*gluco*-nonitol (69)



To a solution of **67** (500 mg, 0.78 mmol) in 80% aq. AcOH (5 mL) was added conc. H_2SO_4 (2 drops) and heated at 80 °C for 30 min. The reaction mixture was neutralized with solid Na_2CO_3 and concentrated. The residue was partitioned between EtOAc and water, organic layer dried (Na_2SO_4), concentrated, and the residue purified on silica gel using EtOAc:light petroleum ether (1:2) as an eluent to give **68** (368 mg, 77%) as a thick syrup.

To a solution of **68** (368 mg, 0.60 mmol) in THF (10 mL) was added $LiAlH_4$ (45 mg, 1.2 mmol) in one portion at 0 °C and stirred for 1 h at room temperature. Reaction mixture was cooled to 0 °C, quenched with EtOAc, filtered through a plug of Celite, concentrated and the residue was purified on silica gel using EtOAc–light petroleum (2:3) as an eluent to give **69** (334 mg, 87%).

Mol. Formula : $C_{38}H_{46}O_7$.

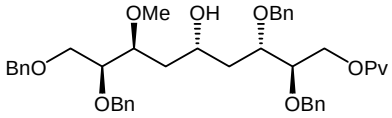
Optical Rotation $[\alpha]_D^{25}$: –10.9 (*c* 1.2, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.45-1.69 (m, 2H), 1.60-1.72 (m, 2H), 3.40 (s, 3H), 3.50-3.75 (m, 7H), 3.82-3.88 (m, 2H), 4.54 (s, 2H), 4.57-4.75 (m, 6H), 7.20-7.36 (m, 20H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 38.24, 38.85, 58.81, 61.40, 66.90, 70.22, 72.27, 72.30, 72.82, 73.25, 77.98, 78.68, 79.29, 81.03, 127.45, 127.69, 127.75, 128.09, 128.30, 137.83, 138.07, 138.22, 138.53 ppm.

Elemental Analysis **Calcd.:** C, 74.24; H, 7.54%.
Found: C, 74.47; H, 7.67%.

4,6-Dideoxy-3-*O*-methyl-1,2,7,8-*tetrakis*-*O*-benzyl-9-*O*-pivaloyl-D-*glycero*-D-*gluco*-nonitol (70)



To an ice-cold solution of **69** (550 mg, 0.89 mmol) in pyridine (2 mL) was added pivaloyl chloride (0.12 mL, 0.97 mmol) and stirred at that temperature for 30 min. The reaction mixture was concentrated and residue partitioned between ethyl acetate-aqueous 0.1 N HCl. The organic layer was washed with water, brine, dried (Na_2SO_4), concentrated and the residue purified on silica gel using EtOAc:light petroleum ether (1:4) as an eluent give **70** as a light liquid.

Yield : 578 mg (93%)

Mol. Formula : $C_{43}H_{54}O_8$.

Optical Rotation $[\alpha]_D^{25}$: –9.8 (*c* 0.6, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz) : δ 1.20 (s, 9H), 1.30-1.35 (m, 1H), 1.58-1.65 (m, 2H), 1.82 (dt, 1H, *J* = 14.5, 8.7 Hz), 3.24-3.33 (m, 1H), 3.39 (s, 3H), 3.55 (dd, 1H, *J* = 10.0, 6.4 Hz), 3.59-3.63 (m, 1H), 3.66 (d, 1H, *J* = 3.5 Hz), 3.67-3.70 (m, 1H), 3.75 (dt, 1H, *J* = 6.0, 3.5 Hz), 3.83 (dt, 1H, *J* = 8.0, 3,7 Hz), 3.89-3.94 (m, 1H), 4.17 (dd, 1H, *J* = 12.0, 6.2 Hz), 4.37 (dd, 1H, *J* = 12.0, 3.7 Hz), 4.53 (s, 2H), 4.57 (d, 1H, *J* = 11.6 Hz), 4.63 (d, 1H, *J* = 11.6 Hz), 4.64 (d, 1H, *J* =

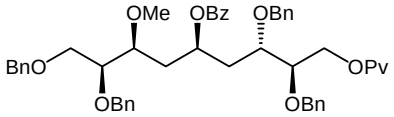
12.0 Hz), 4.67-4.75 (m, 3H), 7.17-7.38 (m, 20H) ppm.

^{13}C NMR (CDCl$_3$, 125 MHz) : δ 21.93, 27.21, 38.45, 38.60, 38.70, 59.02, 63.48, 66.93, 70.28, 72.27, 72.56, 72.86, 73.32, 77.79, 78.66, 78.92, 79.20, 127.67, 127.72, 127.86, 127.95, 128.18, 128.28, 128.33, 128.44, 137.73, 138.01, 138.25, 138.59, 178.09 ppm.

Elemental Analysis **Calcd.:** C, 73.90; H, 7.79%.

Found: C, 74.07; H, 7.77%.

4,6-Dideoxy-3-*O*-methyl-1,2,7,8-*tetrakis*-*O*-benzyl-5-*O*-benzoyl-9-*O*-pivaloyl-D-*glycero*-D-*galacto*-nonitol (71)



To a mixture of **70** (400 mg, 0.57 mmol), TPP (300 mg, 1.14mmol) and benzoic acid (104 mg, 0.85 mmol) in THF was added a solution of DIAD (0.22 mL, 1.14 mmol) in THF (1 mL) at 0 ºC. After stirring at that temperature for 0.5 h, the reaction mixture was concentrated and the residue purified on silica gel (200-400 mesh) using EtOAc:light pet. ether (1:14) as an eluent to afford **71**.

Yield : 361 mg (79%)

Mol. Formula : $C_{50}H_{58}O_9$.

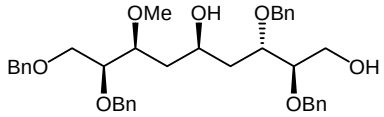
Optical Rotation $[\alpha]_D^{25}$: –6.8 (*c* 1.2, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) : 3463, 2974, 2932, 2401, 1723, 1603, 1496, 1479, 1454, 1398, 1283, 1216, 1162, 1093, 1028, 927.

NMR (CDCl$_3$, 400 MHz) : δ 1.13 (s, 9H), 1.16-1.20 (m, 2H), 1.90-1.98 (m, 2H), 3.24 (s, 3H), 3.44-3.50 (m, 1H), 3.58 (dd, 1H, *J* = 10.0, 6.5 Hz), 3.61-3.70 (m, 2H), 3.72-3.79 (m, 2H), 4.17 (dd, 1H, *J* = 11.7, 5.8 Hz), 4.30 (dd, 1H, *J* = 11.7, 4.5 Hz), 4.44 (d, 1H, *J* = 10.8 Hz), 4.49 (s, 2H), 4.56 (d, 1H, *J* = 10.8 Hz), 4.57 (d, 1H, *J* = 11.8 Hz), 4.62 (d, 1H, *J* = 11.8 Hz), 4.68 (d, 1H, *J* = 11.8 Hz), 4.70 (d, 1H, *J* = 11.8 Hz), 5.52-5.59 (m, 1H), 7.20-7.35 (m, 20H), 7.41 (t, 1H, *J* = 7.8 Hz), 7.47 (t, 1H, *J* = 7.8 Hz), 7.53-7.63 (m,

	1H), 8.01 (dd, 1H, *J* = 7.8, 1.3 Hz), 8.10 (dd, 1H, *J* = 7.8, 1.3 Hz) ppm.
^{13}C NMR ($CDCl_3$, 125 MHz)	: δ 27.01, 29.58, 35.12, 36.25, 38.57, 57.80, 63.08, 69.96, 72.42, 72.88, 73.00, 73.12, 76.02, 78.05, 78.25, 127.41, 127.52, 127.58, 127.78, 128.12, 128.18, 128.28, 129.51, 130.05, 133.44, 137.98, 138.08, 138.16, 138.40, 165.94, 170.20, 178.00 ppm.
Elemental Analysis	**Calcd.:** C, 74.79; H, 7.28%. **Found:** C, 74.87; H, 7.37%.

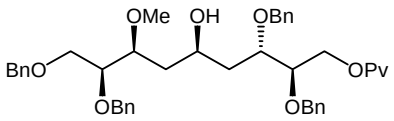
4,6-Dideoxy-3-*O*-methyl-1,2,7,8-*tetrakis*-*O*-benzyl-D-*glycero*-D-*galacto*-nonitol (72)



To a solution of **71** (500 mg, 0.62 mmol) in toluene (20 mL) was added DIBAL-H (3.0 M in toluene, 1 mL, 3.0 mmol) at –78 ºC and stirred at that temperature for 1 h. After usual workup as described earlier, the residue was purified on silica gel using EtOAc:light petroleum ether (2:3) as an eluent to give **72**.

Yield	: 340 mg (89%)
Mol. Formula	: $C_{38}H_{46}O_7$.
Optical Rotation $[\alpha]_D^{25}$	: –11.4 (*c* 1.3, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 300 MHz)	: δ 1.45-1.72 (m, 4H), 3.40 (s, 3H), 3.50-3.61 (m, 3H), 3.65-3.80 (m, 4H), 3.90-4.20 (m, 2H), 4.52 (s, 2H), 4.60 (d, 1H, *J* = 11.4 Hz), 4.61 (d, 1H, *J* = 11.8 Hz), 4.62 (d, 1H, *J* = 11.4 Hz), 4.71 (d, 1H, *J* = 11.8 Hz), 4.75 (d, 1H, *J* = 11.4 Hz), 4.76 (d, 1H, *J* = 11.8 Hz), 7.23-7.41 (m, 20H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz)	: δ 37.45, 39.16, 58.17, 61.40, 67.60, 70.07, 72.18, 72.91, 73.15, 73.37, 76.60, 78.62, 81.15, 127.54, 127.66, 127.75, 127.85, 128.27, 138.13, 138.34, 138.50 ppm.
Elemental Analysis	**Calcd.:** C, 74.24; H, 7.54%. **Found:** C, 74.47; H, 7.57%.

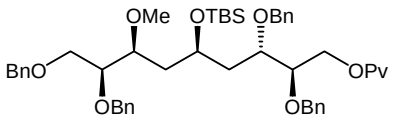
4,6-Dideoxy-3-*O*-methyl-1,2,7,8-*tetrakis*-*O*-benzyl-9-*O*-pivaloyl-D-*glycero*-D-*galacto*-nonitol (73)



To a solution of **72** (600 mg, 0.97 mmol) in pyridine (2 mL) was added pivaloyl chloride (0.12 mL, 0.97 mmol) and stirred at 0 ºC for 30 min. After usual workup as described earlier, the residue was purified on silica gel using EtOAc:light petroleum ether (1:4) to afford **73** as a syrup.

Yield	: 474 mg (70%)
Mol. Formula	: $C_{43}H_{54}O_8$.
Optical Rotation $[\alpha]_D^{25}$	: –12.6 (*c* 1.2, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 300 MHz)	: δ 1.20 (s, 9H), 1.47-1.74 (m, 4H), 3.39 (s, 3H), 3.52-3.63 (m, 2H), 3.67 (d, 1H, *J* = 3.0 Hz), 3.70-3.78 (m, 2H), 3.91-4.02 (m, 2H), 4.17 (dd, 1H, *J* = 11.8, 6.3 Hz), 4.37 (dd, 1H, *J* = 11.8, 3.8 Hz), 4.47 (s, 2H), 4.54 (d, 1H, *J* = 11.4 Hz), 4.55 (d, 1H, *J* = 11.8 Hz), 4.59 (d, 1H, *J* = 11.4 Hz), 4.64 (d, 1H, *J* = 11.8 Hz), 4.66 (d, 1H, *J* = 11.4 Hz), 4.70 (d, 1H, *J* = 11.8 Hz), 7.25-7.40 (m, 20H) ppm.
^{13}C NMR ($CDCl_3$, 125 MHz)	: δ 27.04, 37.29, 38.55, 38.95, 58.10, 63.51, 77.14, 69.96, 72.27, 72.79, 72.97, 73.25, 76.04, 78.42, 79.26, 80.97, 127.38, 127.44, 127.69, 127.77, 128.13, 128.18, 138.01, 138.17, 138.37, 178.10 ppm.
Elemental Analysis	**Calcd.:** C, 73.90; H, 7.79%. **Found:** C, 73.87; H, 7.97%.

4,6-Dideoxy-5-*O*-*ter*butyldimethylsilyl-3-*O*-methyl-1,2,7,8-*tetrakis*-*O*-benzyl-9-*O*-pivaloyl-D-*glycero*-D-*galacto*-nonitol (74)



To a solution of **73** (250 mg, 0.35 mmol) and 2,6-lutidine (0.16 mL, 1.37 mmol) in CH_2Cl_2 was added TBSOTf (0.12 mL, 0.68 mmol) at 0 ºC. After 1 h, reaction was quenched by addition of water and extracted with EtOAc. The organic layer was dried (Na_2SO_4), concentrated and the residue purified on silica gel using EtOAc:light pet. ether (1:20) as an eluent to furnish **74** as a light liquid

Yield : 276 mg (97%)

Mol. Formula : $C_{49}H_{68}O_8Si$.

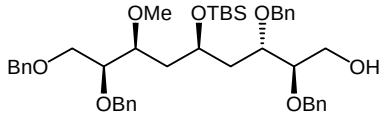
Optical Rotation $[\alpha]_D^{25}$: –55.4 (*c* 0.4, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz) : δ -0.02, -0.01 (2 s, 6H), 0.83 (s, 9H), 1.16 (s, 9H), 1.57-1.68 (m, 2H), 1.79 (ddd, 1H, *J* = 13.7, 10.2, 3.2 Hz), 1.89-1.95 (m, 1H), 3.26 (s, 3H), 3.42-3.46 (m, 1H), 3.53 (dd, 1H, *J* = 9.3, 6.2 Hz), 3.56-3.60 (m, 1H), 3.63 (dd, 1H, *J* = 9.2, 3.6 Hz), 3.69-3.72 (m, 1H), 3.84-3.88 (m, 1H), 4.03-4.08 (m, 1H), 4.18 (dd, 1H, *J* = 11.9, 6.6 Hz), 4.25 (dd, 1H, *J* = 11.9, 3.8 Hz), 4.45-4.48 (m, 3H), 4.54 (d, 1H, *J* = 11.9 Hz), 4.61-4.63 (m, 2H), 4.66 (d, 1H, *J* = 11.9 Hz), 4.72 (d, 1H, *J* = 11.5 Hz), 7.27-7.40 (m, 20H) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz) : δ –4.49, –3.79, 17.95, 25.94, 27.17, 39.27, 39.53, 58.71, 64.01, 67.11, 70.25, 72.34, 72.91, 73.35, 76.94, 78.01, 79.35, 79.72, 127.34, 127.46, 127.54, 127.81, 128.15, 128.21, 128.24, 138.30, 138.46, 138.65, 138.79, 178.18 ppm.

Elemental Analysis **Calcd.:** C, 72.38; H, 8.43%.
Found: C, 72.48; H, 8.67%.

4,6-Dideoxy-5-*O*-terbutyldimethylsilyl-3-*O*-methyl-1,2,7,8-*tetrakis*-*O*-benzyl-D-*glycero*-D-*galacto*-nonitol (39)

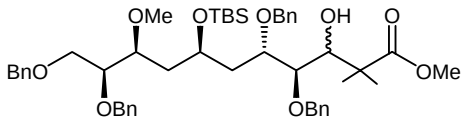


To a solution of **74** (200 mg, 0.24 mmol) in toluene (10 mL) was added DIBAL-H (2.0 M in toluene, 0.3 mL, 0.6 mmol) dropwise at –78 ºC and stirred at that temperature for 1 h.

After usual work up, the residue was purified on silica gel using EtOAc:light petroleum ether (1:12) as an eluent to give **39.**

Yield	: 166 mg (95%)
Mol. Formula	: $C_{44}H_{60}O_7Si$.
Optical Rotation $[\alpha]_D^{25}$	: –13.3 (*c* 0.9, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 300 MHz)	: δ 0.03, 0.04 (2 s, 6H), 0.89 (s, 9H), 1.50-1.64 (m, 2H), 1.64-1.74 (m, 1H), 1.80-1.90 (m, 1H), 3.32 (s, 3H), 3.37-3.44 (m, 1H), 3.55-3.80 (m, 6H), 3.89-3.96 (m, 1H), 4.01-4.15 (m, 1H), 4.50-4.56 (m, 3H), 4.58 (d, 1H, *J* = 12.4 Hz), 4.61 (d, 1H, *J* = 11.7 Hz), 4.72 (d, 1H, *J* = 11.7 Hz), 4.75 (d, 1H, *J* = 11.7 Hz), 4.85 (d, 1H, *J* = 11.7 Hz), 7.20-7.42 (m, 20H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz)	: δ –4.52, –3.79, 17.94, 25.91, 39.06, 39.77, 58.69, 61.68, 67.26, 70.19, 72.03, 72.67, 72.91, 73.37, 77.21, 77.95, 79.29, 81.55, 127.42, 127.54, 127.60, 127.82, 128.15, 128.24, 128.36, 138.25, 138.34, 138.60, 138.65 ppm.
Elemental Analysis	**Calcd.:** C, 72.49; H, 8.30%. **Found:** C, 72.48; H, 8.67%.

(3*R* and 3*S*)-2,6,8-Trideoxy-7-*O*-*ter*butyldimethylsilyl-2,2-dimethyl-9-*O*-methyl-4,5,10,11-*tetrakis*-*O*-benzyl-L-*glycero*-D-*manno*-undeconic acid, methyl ester (76)



To a stirred solution of **39** (100 mg, 0.14 mmol) in CH_2Cl_2 (10 mL) was added freshly prepared Dess-Martin Periodinane (118 mg, 0.28 mmol) at room temperature. After 3 h, reaction mixture was filtered through a plug of Celite and concentrated to give **75**.

To a solution of methyl isobutyrate (0.1 mL, 1.0 mmol) in THF (5 mL) was added a 1M solution of LDA (1.0 mL, 1.0 mmol) at 0 ºC. After 15 min, solution of **75** in THF (1 mL) was introduced at –78 ºC. The reaction mixture was stirred for 30 min at the same temperature, quenched with saturated aq. NH_4Cl and extracted with EtOAc. Combined organic layer was dried (Na_2SO_4), concentrated and the residue purified on silica gel using EtOAc:light petroleum ether (1:4) as an eluent to afford **76**.

Yield : 80 g, (69%)

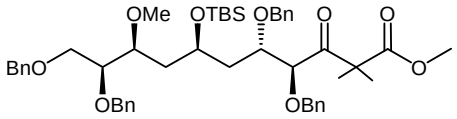
Mol. Formula : $C_{49}H_{68}O_9Si$.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ –0.05, –0.03, –0.02 (3 s, 6H), 0.81, 0.83 (s, 9H), 1.10, 1.12, 1.14 (3 s, 6H), 1.50-1.70 (m, 4H), 3.20, 3.24 (2 s, 3H), 3.45 (s, 3H), 3.47-3.52 (m, 1H), 3.55-3.65 (m, 3H), 3.99-4.06 (m, 2H), 4.28, 4.37 (2 d, 1H, *J* = 10.5 Hz), 4.42-4.46 (m, 3H), 4.52 (d, 1H, *J* = 11.4 Hz), 4.62, 4.63 (2 d, 1H, *J* = 11.4 Hz), 4.70, 4.72 (2 d, 1H, *J* = 11.4 Hz), 4.75, 4.82 (2 d, 1H, *J* = 11.4 Hz), 7.15-7.32 (m, 20H) ppm.

Elemental Analysis **Calcd.:** C, 70.98; H, 8.27%.

Found: C, 71.00; H, 8.44%.

2,6,8-Trideoxy-7-*O*-*ter*butyldimethylsilyl-2,2-dimethyl-9-*O*-methyl-4,5,10,11-*tetrakis*-*O*-benzyl-L-*glycero*-D-*manno*-3-undeculosonic acid, methyl ester (77)



To a solution of **76** (80 mg, 0.10 mmol) in CH_2Cl_2 (10 mL) was added freshly prepared Dess-Martin Periodinane (127 mg, 0.30 mmol) and stirred for 1.5 h at room temperature. The reaction mixture was filtered through a plug of Celite, concentrated and the residue purified on silica gel using EtOAc:light petroleum ether (1:12) as an eluent to obtain **77**

Yield : 65 g, (79%)

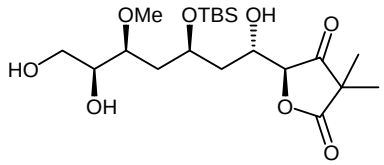
Mol. Formula : $C_{49}H_{66}O_9Si$.

Optical Rotation $[\alpha]_D^{25}$: –34.6 (*c* 2.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz) : δ 0.05, 0.06 (2 s, 6H), 0.93 (s, 9H), 1.35, 1.39 (2 s, 6H), 1.44-1.50 (m, 1H), 1.55-1.75 (m, 2H), 2.00-2.10 (m, 1H), 3.31 (s, 3H), 3.41 (s, 3H), 3.41-3.43 (m, 1H), 3.60 (dd, 1H, *J* = 9.2, 5.6 Hz), 3.65-3.75 (m, 2H), 4.10-4.15 (m, 1H), 4.33-4.37 (m, 1H), 4.51 (d, 1H, *J* = 11.2 Hz), 4.52-4.58 (m, 4H), 4.61 (d, 1H, *J* = 11.8 Hz), 4.71 (d, 1H, *J* = 11.6 Hz), 4.75 (d, 1H, *J* = 11.6 Hz), 4.90 (d, 1H, *J* = 11.2 Hz), 7.25-7.37 (m, 20H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz)	: δ –4.40, –3.63, 18.13, 21.67, 22.83, 26.12, 29.76, 38.61, 39.16, 51.61, 53.32, 58.60, 67.08, 70.58, 71.84, 72.97, 73.49, 73.86, 78.16, 79.32, 79.41, 83.71, 127.42, 127.54, 127.63, 127.88, 128.24, 128.33, 137.76, 138.50, 138.83, 173.59, 206.74 ppm.
Elemental Analysis	**Calcd.:** C, 71.15; H, 8.04%. **Found:** C, 71.48; H, 8.37%.

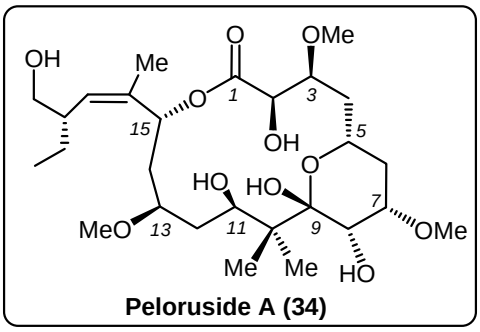
2,6,8-Trideoxy-7-*O*-*ter*butyldimethylsilyl-2,2-dimethyl-9-*O*-methyl-L-*glycero*-D-*manno*-3-undeculosonic acid-1,4-δ-lactone (38)



To a solution of **77** (50 mg, 0.06 mmol) and AcOH (2 drops) in MeOH (4 mL) was added 10% Pd/C (0.01 g) and stirred under H_2 atmosphere at normal temperature and pressure for 8 h. The reaction mixture was filtered through a pad of Celite, concentrated and the residue purified on silica gel using EtOAc:light petroleum ether (3:1) as an eluent to give **38**.

Yield	: 21 mg (82%)
Mol. Formula	: $C_{20}H_{38}O_8Si$.
Optical Rotation $[\alpha]_D^{25}$	: –7.5 (*c* 0.3, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 500 MHz)	: δ 0.10, 0.12 (2 s, 6H), 0.88 (s, 9H), 1.32, 1.33 (2 s, 6H), 1.68 (ddd, 1H, *J* = 14.7, 5.0, 2.2 Hz), 1.88 (t, 2H, *J* = 6.3 Hz), 2.22 (ddd, 1H, 15.0, 11.3, 4.2 Hz), 3.37-3.40 (m, 1H), 3.42 (s, 3H), 3.64-3.67 (m, 2H), 3.73 (dd, 1H, *J* = 13.3, 6.3 Hz), 4.11-4.19 (m, 1H), 4.38 (dt, 1H, *J* = 11.2, 2.5 Hz), 4.59 (d, 1H, *J* = 2.5 Hz) ppm.
^{13}C NMR ($CDCl_3$, 125 MHz)	: δ –4.67, –4.60, 17.86, 19.20, 21.96, 25.73, 36.11, 44.67, 57.95, 63.86, 67.93, 68.93, 72.53, 78.76, 85.97, 177.71, 211.48 ppm.
Elemental Analysis	**Calcd.:** C, 55.27; H, 8.81%; **Found:** C, 55.48; H, 8.37%.

Present Work

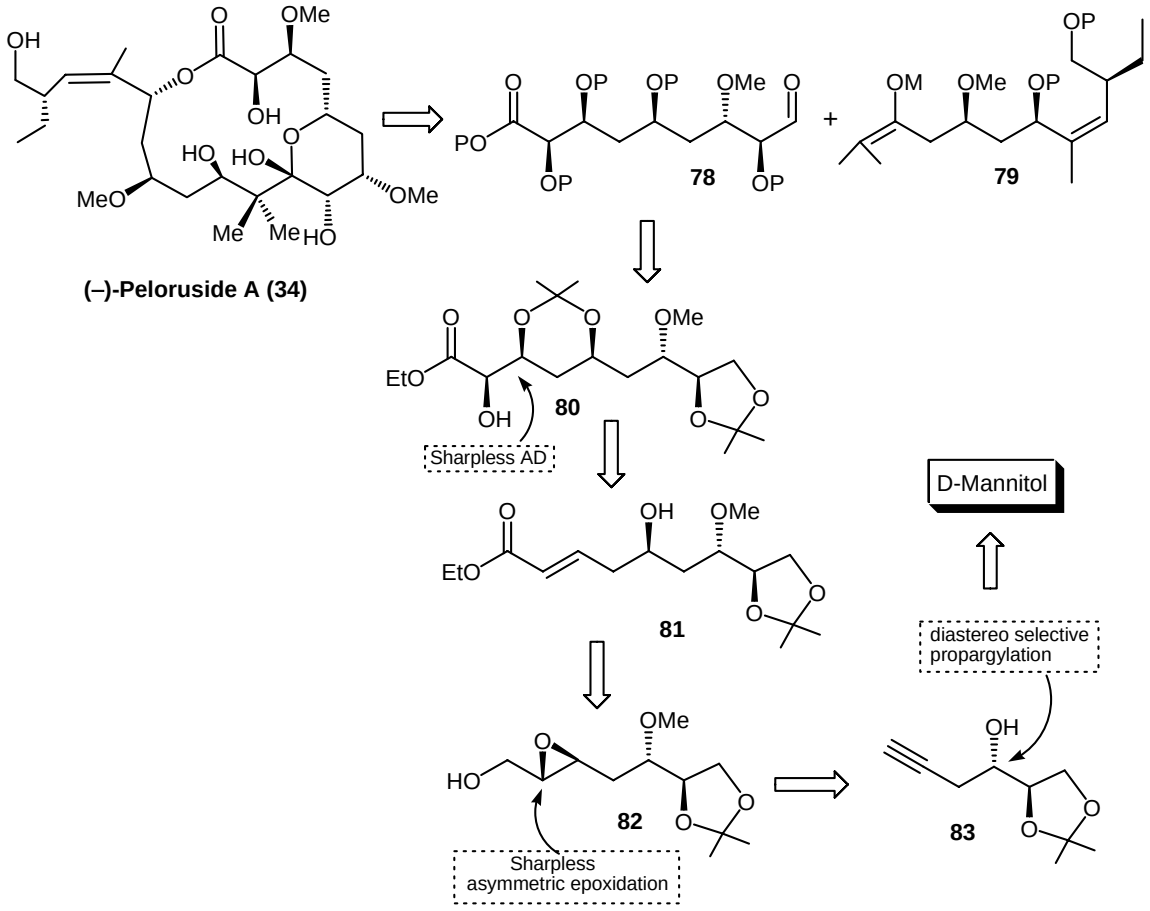


Peloruside A (34)

In the previous section, we have shown the synthesis of C_1-C_{11} fragment of peloruside A (**34**). While the earlier work was in progress, an alternative route leading to C_1-C_9 segment of **34** was also in progress. This section deals with new studies on C_1-C_9 fragment. We planned a new concise synthetic strategy for stereopentad region, C_1-C_9 fragment of peloruside A, with least protection-deprotection transformations and stereoselective reactions. Retrosynthetic analysis for the C_1-C_9 fragment of peloruside A is depicted in Scheme 16. Based on our successful coupling reaction in the earlier approach towards C_1-C_{11} fragment of peloruside A, we disconnected the seco acid of **34** at C_9-C_{10} bond via a thermodynamically controlled aldol reaction to obtain stereochemically comparable two fragments **78** and **79**. The stereochemically dense deoxy aldose fragment **78** was then explored by Sharpless asymmetric dihydroxylation/epoxidation and diastereoselective propargylation to install the required five chiral centers in it.

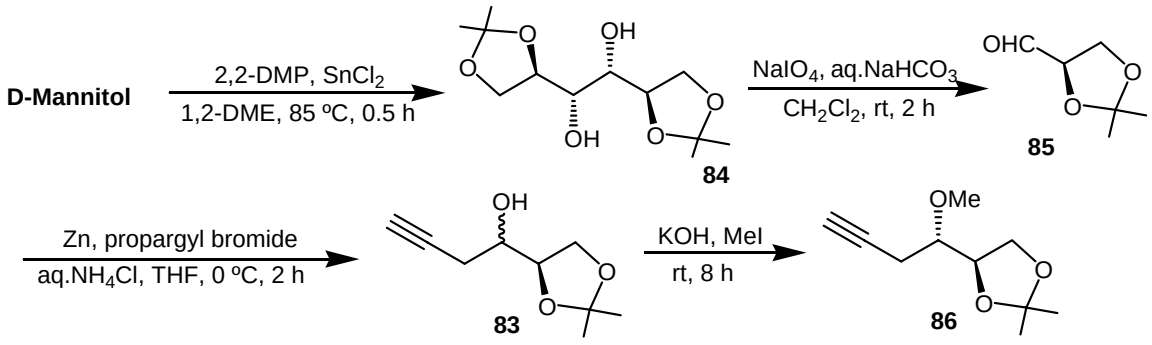
Our synthetic endeavor started with the homopropargyl alcohol **83** obtained by known sequence of reactions.[43] Isopropylidenation of commercially available D-mannitol followed by oxidative cleavage of the corresponding 1,2:5,6-di-*O*-isopropylidene-D-mannitol **84** using $NaIO_4$ in CH_2Cl_2 yielded 2,3-*O*-isopropylidene-*R*-glyceraldehyde **85**. The Barbier-type propargylation of aldehyde **85** was carried out with propargyl bromide and Zinc in a mixture of THF and saturated aqueous NH_4Cl (4:1) at 0 °C to afford predominantly the *anti* homopropargyl alcohol **83** along with *syn* isomer as an inseparable mixture in 10:1 ratio.[44] The diastereomeric mixture of **83** was subjected to etherification using KOH in neat MeI to provide corresponding methyl ethers.[31]

Scheme 16: **Retrosynthetic analysis**



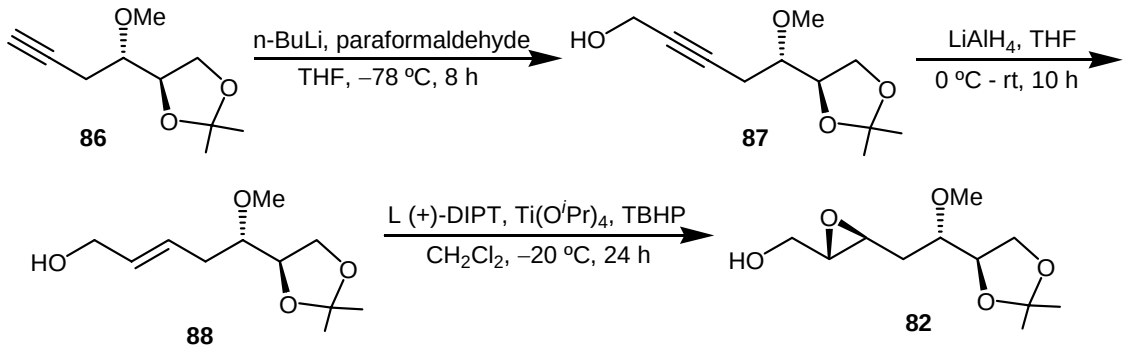
At this stage the major diastereomer **86** was separated by silica gel chromatography (Scheme 17). The ^{1}H NMR spectrum of **86** displayed a signal at δ 1.99 (J = 2.6 Hz) due to acetylene proton as a triplet, and methylene adjacent to C≡C appeared as a doublet of a double-doublet at δ 2.45 (1H, J = 17.2, 4.9, 2.6 Hz) and at δ 2.62 (1H, J = 17.2, 4.5, 2.6 Hz), whereas methyl group appeared as a singlet at δ 3.46. In the ^{13}C NMR spectrum of

Scheme 17



86, resonances due to acetylene carbons appeared at δ 79.65, 80.13 and methyl resonated at δ 57.79. Furthermore, the IR spectrum (3309, 2121 cm^{-1}) and elemental analysis also supported the structure of **86**. The terminal acetylenic derivative **86** was transformed into the allylic alcohol **88** by first alkylation with *n*-BuLi and parafarmaldehyde in anhydrous THF to **87** followed by $LiAlH_4$ reduction (Scheme 18). The ^1H NMR spectrum of **87** displayed signal for hydroxymethylene group as a triplet at δ 4.23 (J = 2.1 Hz). All other protons appeared at their expected chemical shift values. The ^{13}C NMR spectrum of **87** displayed signal due to new methylene carbon at δ 57.74 along with characteristic signal due to acetylene carbons at δ 80.50, 81.17. The IR spectrum and elemental analysis were also in accordance with the structure of **87**. The ^1H and ^{13}C NMR spectroscopic data confirmed the structure of **88** by displaying characteristic olefin signals. The IR spectral data (1688, 1670 cm^{-1}) also supported the formation of allyl alcohol **88**. The Sharpless asymmetric epoxidation of **88** was performed using L(+)-DIPT as a ligand and $Ti(O^iPr)_4$ in the presence of oxidant TBHP in CH_2Cl_2 to obtain the epoxy alcohol **82**.[45] Formation of a

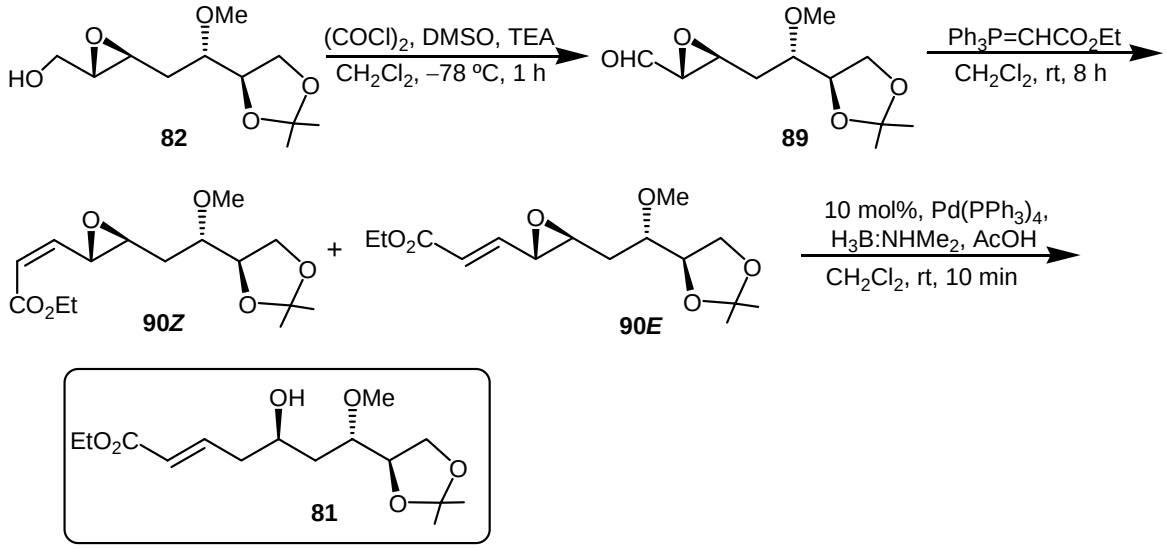
Scheme 18



single diastereomer **82** was adjudged by the analysis of its ^1H and ^{13}C spectral data. The ^1H NMR spectrum of **82** displayed characteristic signals due to epoxy protons as a double-triplet at δ 2.97 (J = 4.7, 2.1 Hz), 3.12 (J = 5.8, 2.2 Hz). In the ^{13}C NMR spectrum of **82**, the epoxy carbons displayed signals at δ 58.51, 58.99 and all other carbons resonated in accordance with the structure of **82**. The IR spectral data and elemental analysis also supported the structure of **82**. The absolute stereochemistry of newly generated epoxide moiety of **82** was determined at the late stage of synthesis. The epoxy alcohol **82** was subjected to oxidation under the Swern conditions to furnish the corresponding aldehyde **89** which was immediately subjected to the Wittig reaction using $Ph_3P{=}CHCO_2Et$ in

CH_2Cl_2 to afford the diastereomeric mixture of *cis* and *trans* olefin derivatives **90*Z*** and **90*E*** (Scheme 19). The ^1H and ^{13}C spectral data of diastereomeric mixture (**90*Z*** and **90*E*** 1:3) displayed the characteristic olefin signals at 5.76 and 6.68 (dd, 1H, J = 11.6 and 15.6, 8.2 and 7.0 Hz), 5.98 and6.13 (dd, 1H, J = 11.6 and 15.6, 0.7 Hz). The structure of **90** was further supported by ^{13}C NMR data and elemental analysis. The mixture of *cis* and *trans* alkene derivatives (**90*Z*** and **90*E***) was subjected to Pd(0) catalysed regio- and stereoselective reductive opening of epoxide ring with the treatment of $BH_3.NHMe_2$-AcOH. The diastereomer **81** was isolated in pure form.[46] Stereochemistry of C_5-OH in **81** was confirmed by modified Mosher ester analysis of derived MTPA esters.

Scheme 19



Modified Mosher's ester method: Application for stereochemical assignment of C_5-OH of 81

Determination of the absolute stereochemistry of organic compounds has become an important aspect for natural product chemistry. The limitations involved in physical methods such as *Exciton* chirality method and X-ray crystallography method forced synthetic chemists to look 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 used most frequently. Mosher proposed that, in solution, the β C-H bond, ester carbonyl, and trifluoromethyl group of the MTPA derivative lie in the same plane (Figure

15).[47] 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 this concept for more accuracy.[48] The modified Mosher's ester method is one of the simple and efficient methods to determine the absolute stereochemistry of the secondary alcohols and amine stereo centers in organic molecules.

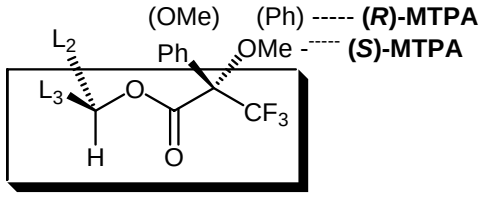


Figure 15: Configurational correlation model fro (*R*)-MTPA and (*S*)-MTPA derivatives proposed by Mosher

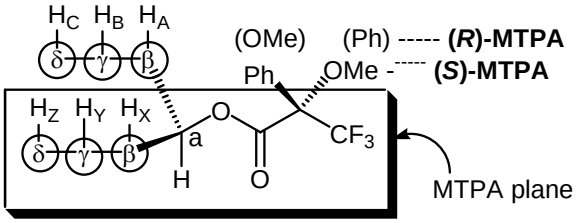


Figure 16: MTPA plane of an MTPA ester is shown. $H_{A,B,C,.....}$ and $H_{X,Y,Z.....}$ are on the right and left sides of the plane respectively.

The basic concept of the modified Mosher's ester method is essentially the same as Mosher proposed. The idealized conformation is depicted in Figure 16. The plane with the hypothesized conformation of MTPA group is as the MTPA plane with ideal conformation. Due to the diamagnetic effect of the benzene ring, the H_A,H_B,H_C….signals of (*R*)-MTPA ester in the ^{1}H NMR spectrum should appear upfield to those of the (*S*)-MTPA ester. The reverse should hold true for protons, H_X,H_Y,H_Z…… Hence, when $\Delta\delta = (\delta S - \delta R)$ x 1000 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 ($\Delta\delta < 0$) as illustrated in simpler model A (Figure 17).

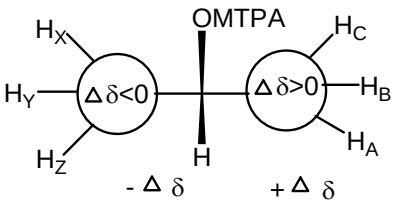


Figure 17: A projection of MTPA ester is shown in *Figure 16*

Thus, modified Mosher's method can be used following the 4 steps:

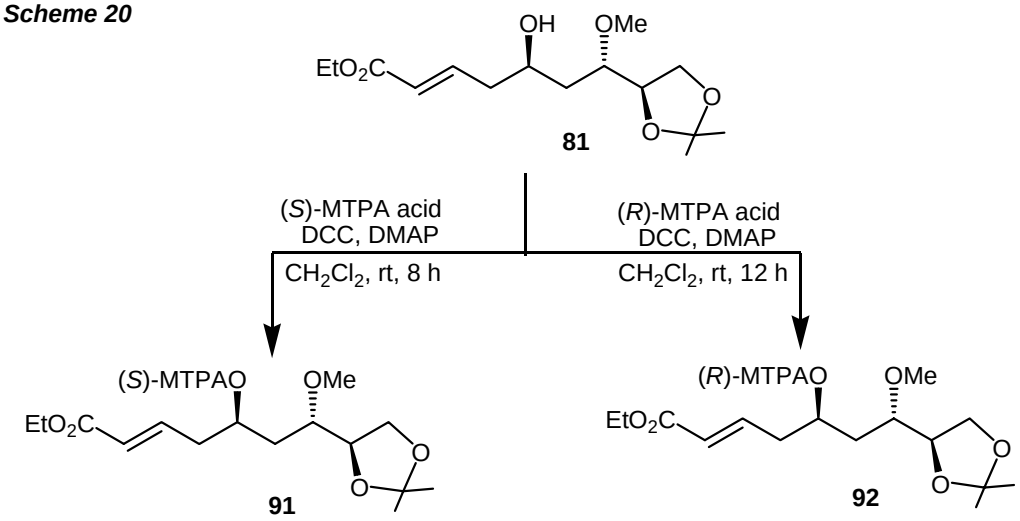
(i) Assign as many proton signals as possible with respect to each of the (*R*)- and (*S*)-MTPA esters,

(ii) Obtain $\Delta\delta$ values for the protons

(iii) Arrange the protons with positive $\Delta\delta$ values right side and those with negative $\Delta\delta$ 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 $\Delta\delta$ values are actually found on the right and left sides of the MTPA plane respectively.

Scheme 20



The absolute values of $\Delta\delta$ 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 *C5-OH* in **81**, the (*S*)- MTPA ester **91** and (*R*)-MTPA ester **92** were independently prepared from **81** 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 20). The $\Delta\delta = (\delta S - \delta R)$ x 1000 values were calculated for as many protons as possible from the ^{1}H

NMR spectrum of (*S*)-MTPA ester **91** and (*R*)-MTPA ester **92** (Table 2). The $\Delta\delta = (\delta S - \delta R)$ x 1000 values were uniformly arranged as shown in Figure 18. On the basis of the model (Figure 18) we have assigned the absolute stereochemistry of side chain at C-5 of **81** with (*R*)-configuration.

Table 2

Protons	**H_4**	**H_3**	**H_2**	**H_{13}**	**H_5**	**H_{6a}**	**H_{6b}**	**H_7**	**H_8**	**H_{9a}**	**H_{9b}**
δ_S	2.53	6.78	5.79	4.12	5.36	1.56	1.74	2.98	3.98	3.55	3.89
δ_R	2.47	6.70	5.72	4.10	5.37	1.58	1.82	3.11	4.05	3.65	3.95
$\Delta\delta$	+60	+80	+70	+20	–10	–20	–80	–130	–70	–100	–60

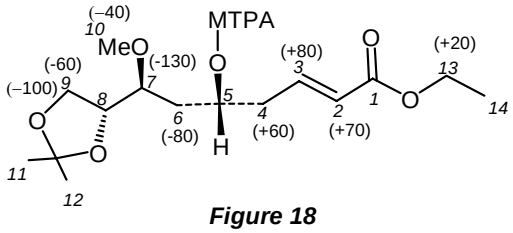
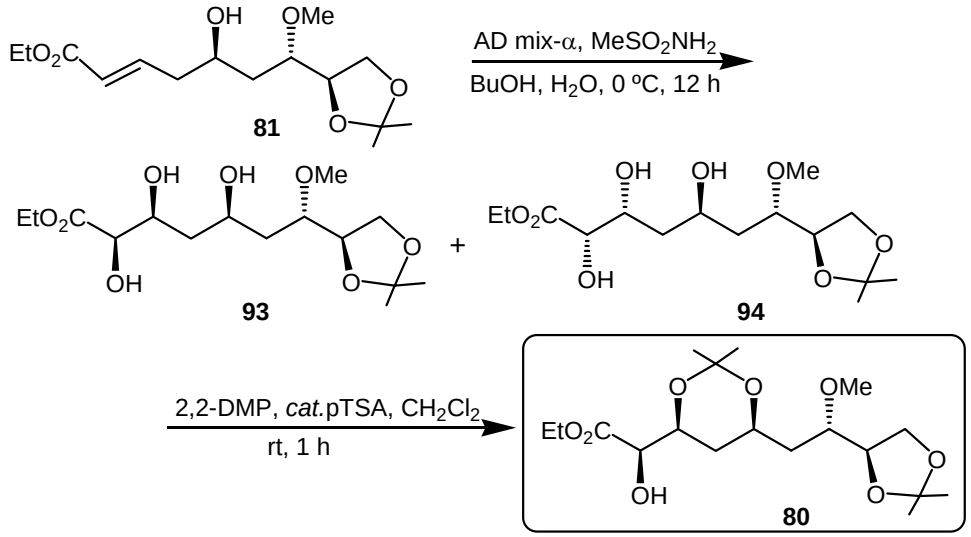


Figure 18

Finally, the Sharpless asymmetric dihydroxylation[49] of *trans*-α,β-unsaturated ester **81** by using AD mix-α and $MeSO_2NH_2$ in 1:1 mixture of *t*-BuOH and H_2O at 0 ºC gave the corresponding diol as a diastereomeric mixture of **93** and **94**. Without further purification, the product (**93**/**94**) was subjected to the isopropylidination reaction by using 2,2-dimethoxypropane in the presence of catalytic amount of *p*TSA in CH_2Cl_2 (Scheme 21). Gratifyingly, the diastereomer **80** was isolated after silica gel chromatography. The ^1H NMR spectrum of **80** displayed two oxymethine signals along with a singlet signal at δ1.26 due to the acetonide *gem*-dimethyl functionality. Resonances due to C4-methylene shifted upfield and appeared at δ 1.52, 1.60. In the ^{13}C spectrum of **80**, the quaternary carbon at δ 98.80 indicated the *syn*-dioxane isopropylidene formation, which in turn confirmed the stereochemistry of 2,3-diol moiety (*syn* w.r.t C-5 stereocenter).

Scheme 21



In conclusion, we have developed a concise route to the C_1-C_9 fragment of antitumor macrolide peloruside A from the homopropargyl alcolhol **83** in eight steps. Studies toward the other C_{10}-C_{24} fragment of peloruside A and short route towards its 16-membered macrolactone core is under progress in our laboratory.

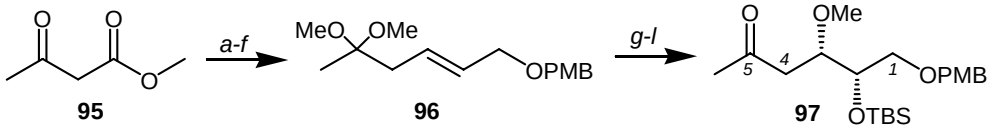
OTHER APPROACHES

Limited supply of peloruside A (**34**) from the sponge source and uncertainty over its absolute configuration prompted several synthetic chemists to develop an efficient total synthesis. Recently, two research groups[52,54] completed the total synthesis of natural product, and several others reported synthetic studies for peloruside A while our work was in progress.

Ian Paterson's approach[51]

Paterson et al simplified peloruside A **34** into three comparable polyol subunits **97**, **102** and **107** by the disconnection at C6-C7 and C11-C12. They envisioned the completion of synthesis of peloruside A by convergent assembly of three fragments via remote 1,5-stereoinduction in boron aldol reactions. Subunits **97** and **102** with 1,2-*syn* diol moiety were synthesized using asymmetric Sharpless asymmetric dihydroxylation conditions starting from methyl acetoacetate (**95**) and neopentylglycol (**98**) respectively (Scheme22 & 23). Whereas subunit **107** was prepared by asymmetric boron aldol reaction using (*S*)-lactate-derived ketone **103** (Scheme 24). Several model studies were conducted to couple the three fragments (Scheme 25). The *c*-Hex_2BCl-mediated aldol reactions between methyl ketone **107** - aldehyde **108** and methyl ketone **97** - isobutyraldehyde **114** proceeded with good 1,5-anti induction. Boron enolate of acetone and aldehyde **110** using (+)-Ipc_2BCl favored the desired (7*S*)-configuration to yield **112** in 75:25 diastereomeric ratio. Evans-Tishchenko reduction of aldol coupling product **109** with SmI_2 - EtCHO served the purpose of 1,3-anti reduction to obtain the requisite compound **116**.

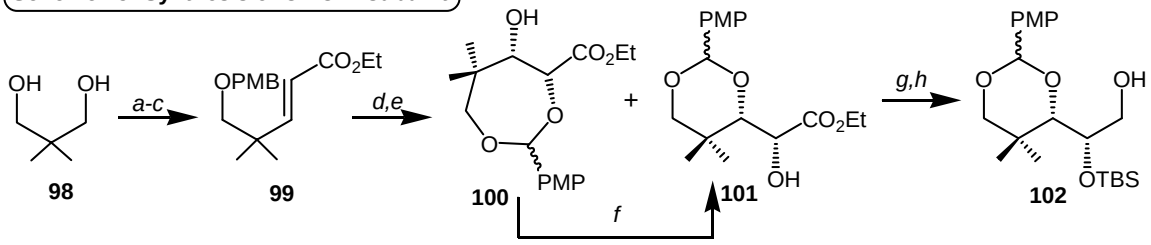
Scheme 22: **Synthesis of C1-C6 subunit**



95 **96** **97**

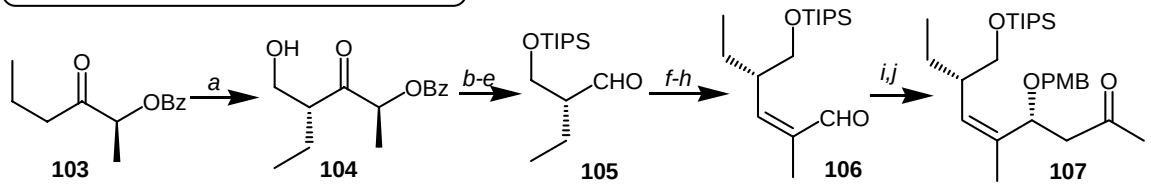
Reagents and Conditions: (a) $(MeO)_3CH$, CSA, MeOH; (b) $LiAlH_4$, THF, 0 °C; (c) PDC, 4 Å MS, CH_2Cl_2; (d) $(MeO)_2P(O)CH_2CO_2Me$, NaH,THF, 0 °C; (e) DIBAL, CH_2Cl_2, –78 °C; (f) PMBBr, NaH, THF, 0 °C; (g) $(DHQ)_2PYR$, K_2CO_3, $K_3Fe(CN)_6$, K_2OsO_4, $MeSO_2NH_2$,*t*-BuOH/H_2O, 4 °C; (h) PPTS, MeOH; (i) NaH, MeI, THF, 0 °C;(j) HCl_{aq}, CH_2Cl_2, 0 °C; (k) TBSOTf, 2,6-lutidine, CH_2Cl_2, –78 °C; (l) cat. TBAF, THF.

Scheme 23: Synthesis of C7-C11 subunit



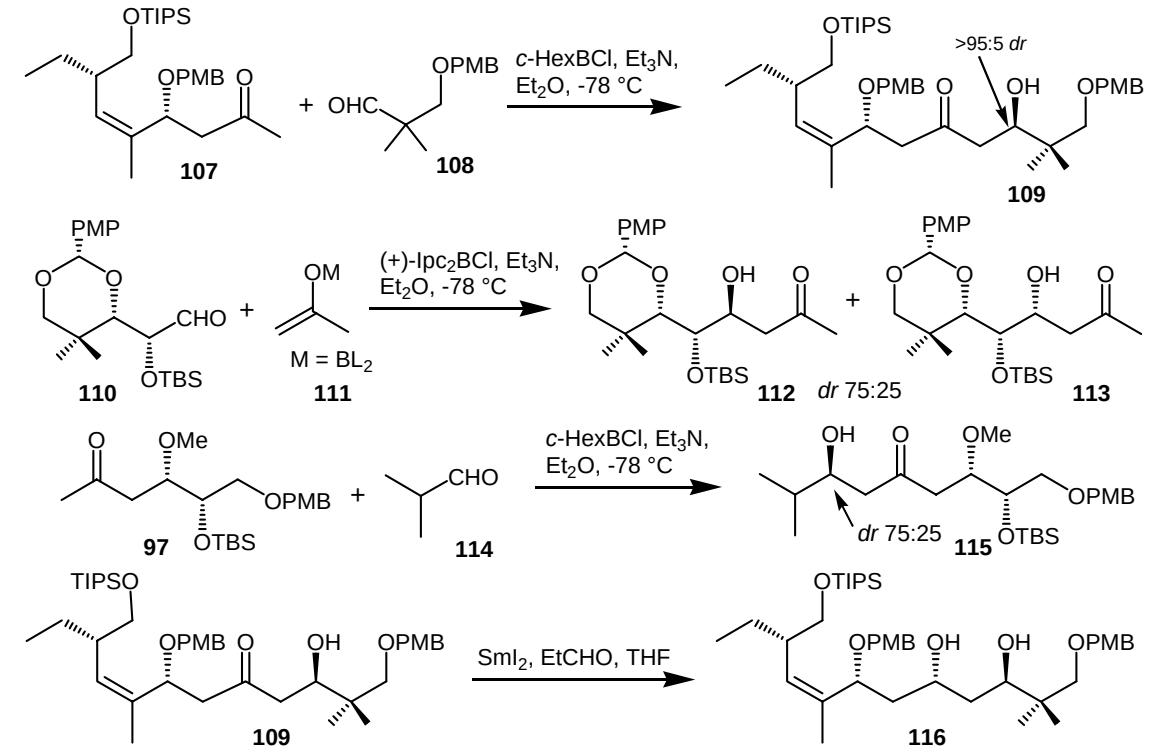
Reagents and Conditions: (a) PMBBr, NaH, Bu_4NI, THF, 0 °C; (b) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, NEt_3; (c) $(EtO)_2P(O)CH_2CO_2Et$, NaH, PhMe/THF, 0 °C; (d) (DHQ)PHN, K_2CO_3, $K_3Fe(CN)_6$, K_2OsO_4, SO_2NH_2, *t*-BuOH/H_2O, 4 °C; (e) DDQ, 4 Å MS, CH_2Cl_2; (f) CSA, 4 Å MS, CH_2Cl_2; (g) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (h) DIBAL, CH_2Cl_2/hexane, –50 °C.

Scheme 24: Synthesis of C12-C19 subunit



Reageants and Conditions: (a) c-Hex_2BCl, Me_2NEt, Et_2O; HCHO, –78 °C; MeOH, H_2O_2, pH 7 buffer; (b) TIPSCl, imidazole, DMAP, CH_2Cl_2; (c) $NaBH_4$, MeOH; (d) K_2CO_3, MeOH; (e) $Pb(OAc)_4$, Na_2CO_3, CH_2Cl_2, 0 °C; (f) $(CF_3CH_2O)_2P(O)CHMeCO_2Me$, 18-crown-6, KHMDS, THF, –78 °C; (g) DIBAL, CH_2Cl_2, –40 °C; (h) DMP, CH_2Cl_2; (i) (–)-Ipc_2BCl, Me_2CO, Et_3N, Et_2O, –78 °C; MeOH, H_2O_2, pH 7 buffer; (j) PMBTCA, TfOH, Et_2O.

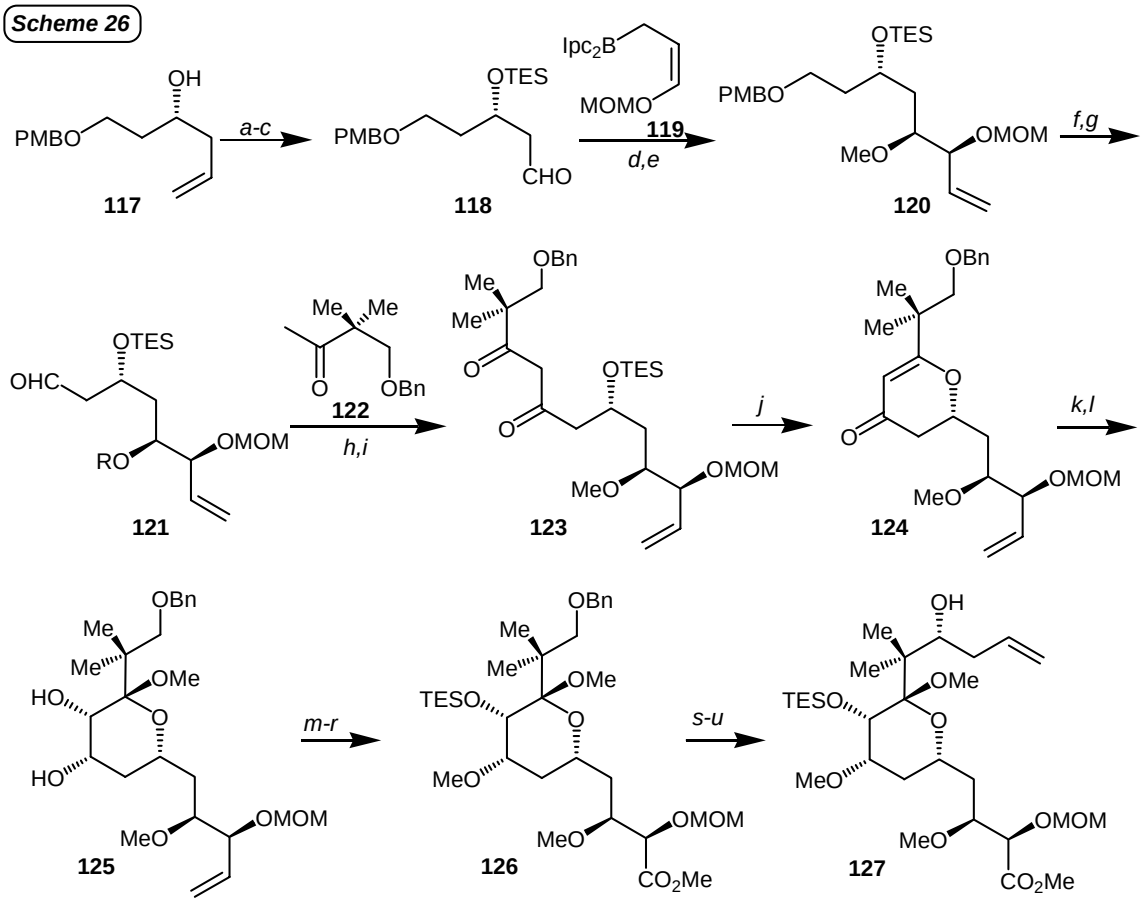
Scheme 25: Coupling Strategies



De Brabander's approach[52]

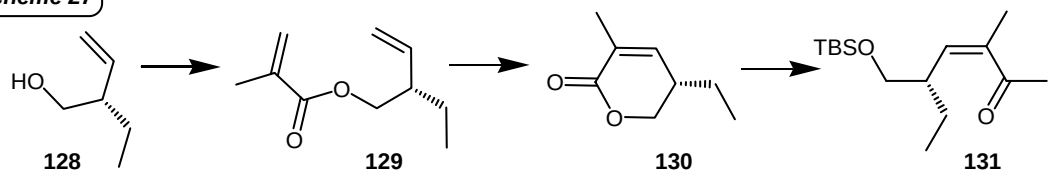
The synthetic plan adopted by De Brabander et al for the peloruside A **34** relied on a late-stage aldol coupling between the methyl ketone **131** to the fully elaborated aldehyde **132** to facilitate the flexibility in the macrolactonization step via reagent-controlled reduction of the C15 ketone group followed by either Yamaguchi or Mitsunobu-type cyclization (Scheme 28). Due to difficulties encountered in the deprotection of the C11-OH in the initial sequence, the C1-C13 segment **132** subjected to coupling reaction without any protecting group. The C11 stereocenter in **132** was created adventitiously in a challenging substrate-controlled allylboration of the sterically demanding *gem*-dimethyl-substituted aldehyde obtained by oxidation of **126** (scheme 26).

Scheme 26



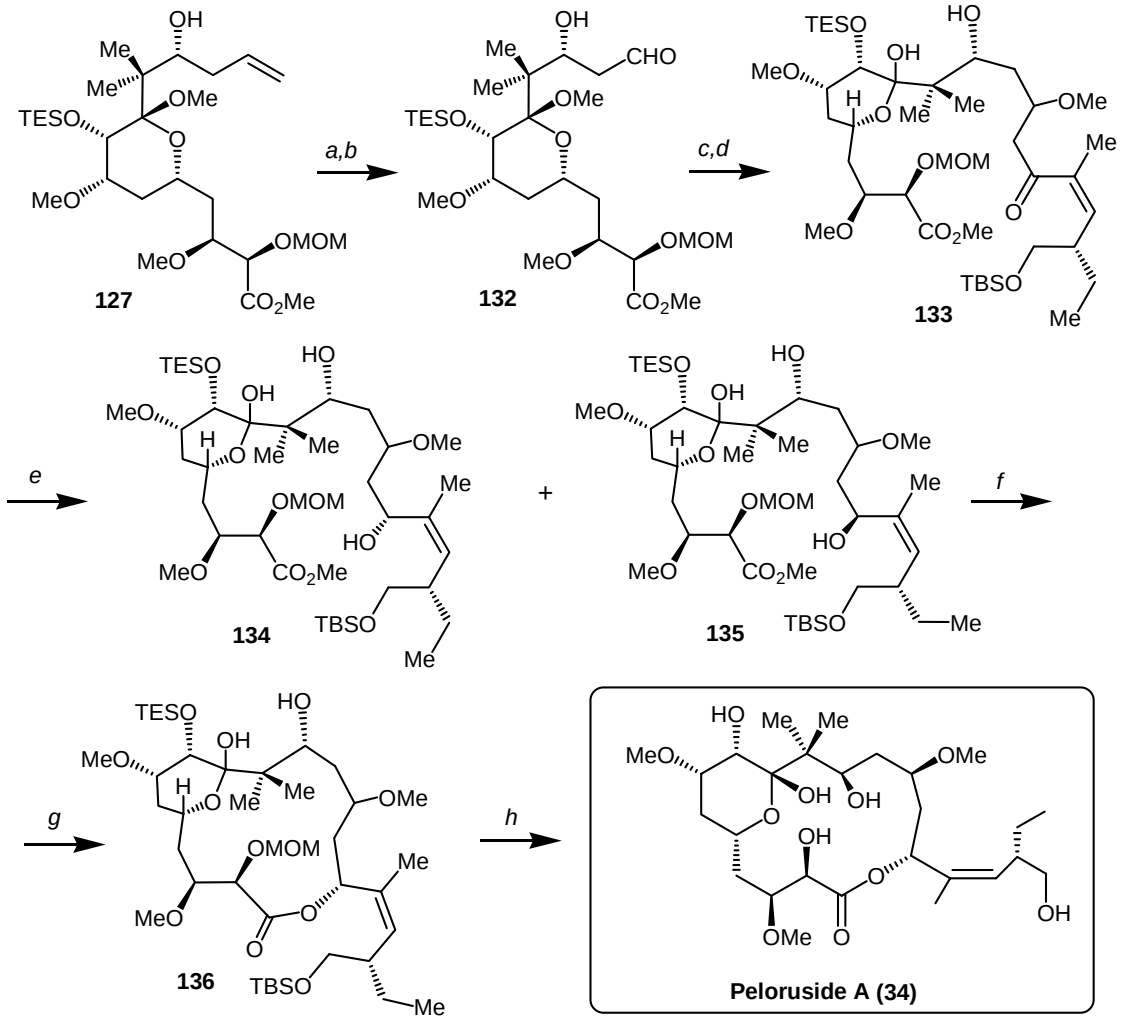
Reagents and conditions: a) TESOTf, 2,6-lutidine, CH_2Cl_2; b) cat. OsO_4, NMO, acetone/H_2O; c) $Pb(OAc)_4$, pyridine, CH_2Cl_2; d) THF, −78 °C to 0 °C, 1.5 h, −95°C, 3 h, slowly warm to RT; 30% H_2O_2, NaOH, 16 h; e) NaH, MeI, DMF, -5 °C; f) DDQ, CH_2Cl_2/H_2O, 0 °C; g) py·SO_3, Et_3N, DMSO, CH_2Cl_2, 0 °C; h) LDA, THF, −78 °C; i) Dess-Martin periodinane, CH_2Cl_2, 10 °C; j) PTSA, PhMe, RT; k) $NaBH_4$, $CeCl_3·7H_2O$, MeOH, -30 °C; l) mCPBA, $NaHCO_3$, CH_2Cl_2/MeOH, 0 °C; m) *t*BuOK, MeI, THF, 0 °C; n) TESOTf, 2,6-lutidine, CH_2Cl_2; o) cat. OsO_4, NMO, acetone/H_2O; p) $Pb(OAc)_4$, pyridine, CH_2Cl_2 ; q) $NaClO_2$, NaH_2PO_4, 2-Me-2-butene, *t*BuOH/H_2O; r) CH_2N_2, Et_2O, 0 °C; s) H_2, Pd/C (10 %), MeOH (quant.); t) py·SO_3, Et_3N, DMSO, CH_2Cl_2, 0 °C; u) allylBEt_2, Et_2O, −10 °C.

Scheme 27



Reagents and conditions: a) $CH_2CMeC(O)Cl$, $^iPr_2NEt$, DMAP, CH_2Cl_2; b) 10 mol% Grubs' catalyst, CH_2Cl_2 (0.0025M), reflux, 17 h; c) MeLi, THF, –78 °C; d) TBSCl, imidazole, DMAP, DMF

Scheme 28



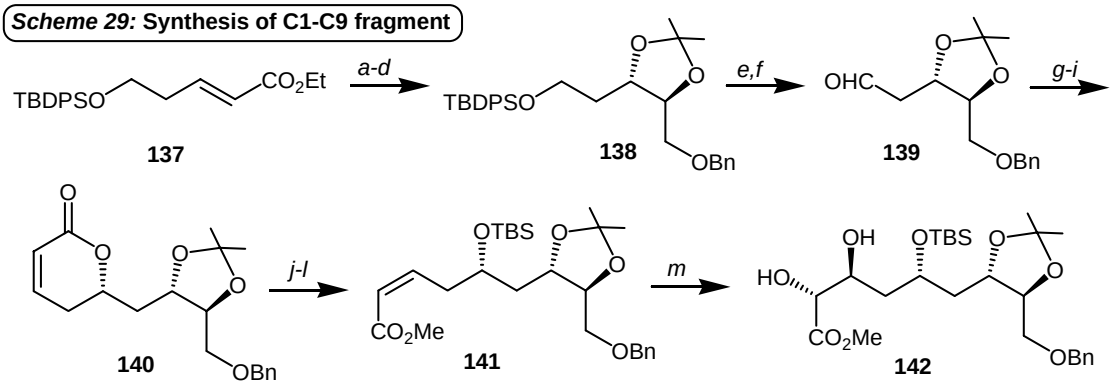
Reagents and Conditions: a) c*at.* OsO_4, NMO, acetone/H_2O; b) $Pb(OAc)_4$, pyridine, CH_2Cl_2; c) *i*Pr_2NEt, Et_2BOTf, CH_2Cl_2, 78 ºC, 15 min,30 ºC, 45 min, 78 ºC**, 131**, 78 ºC; d) Me_3OBF_4 (20 equiv), 2,6-di-tert-butyl-4-methylpyridine, CH_2Cl_2, RT; e) (*R*) or (*S*)-B-Me-CBS (20 equiv), $BH_3{\cdot}SMe_2$ (7 equiv), CH_2Cl_2, 30 ºC, 1 h, RT (4 h), add MeOH; f) 0.3N aq. LiOH, THF, RT (quant.); g) PPh_3, DIAD, THF (0.05 M), RT, 15 min, add seco-acid (0.003M in THF) through syringe pump over 2 h, then 1 h at 0 º; h) 4N HCl, THF, RT, 3 h.

However, the optical rotation of synthetic peloruside A (**34**) was found to be opposite sign ($[\alpha]_D^{23} = -16$; $c = 0.12$ in CH_2Cl_2) to the one reported for the natural product ($[\alpha]_D^{23} = +16$; $c = 0.30$ in CH_2Cl_2).

Ghosh's approach[53]

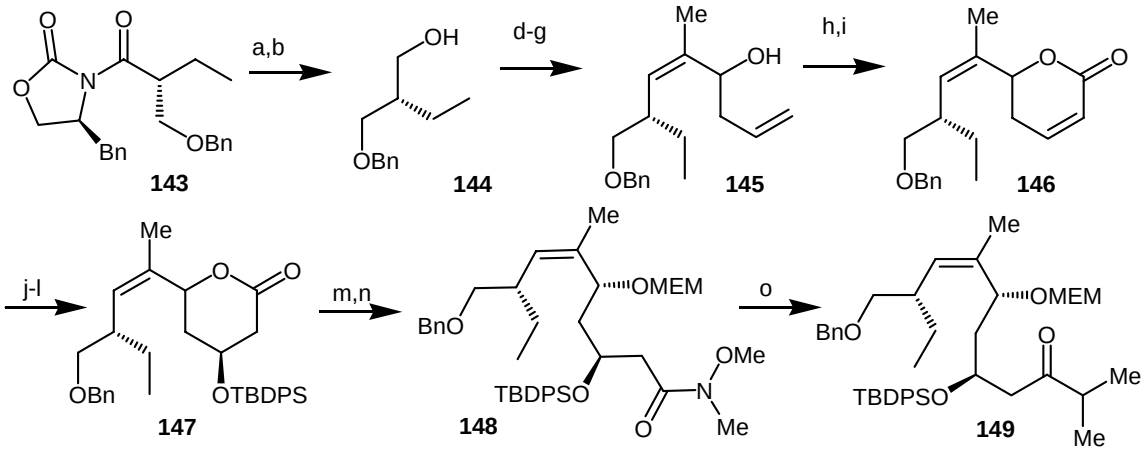
Enantioselective synthesis of the C1-C9 segment (**142**) and C10-C24 segment (**149**) corresponding to the natural product peloruside A **34** was described by Ghosh et al using Sharpless asymmetric dihydroxylation, Evans alkylation, Browns asymmetric allyl boration coupled with stereo controlled epoxide formation, Andos *Z*-selective olefination, chelation-controlled reduction of a chiral β-alkoxy ketone and ring closing metathesis as the key steps (Scheme 29 & 30).

Scheme 29: **Synthesis of C1-C9 fragment**



Reagents and Conditons: (a) AD mix-α,$CH_3SO_2NH_2$, *t*BuOH-H_2O (1:1), 0 °C, 36 h; (b) $Me_2C(OMe)_2$, PPTS (cat.), Me_2CO, 23°C, 5 h; (c) $LiBH_4$, THF, 0 °C, 2 h; (d) NaH, BnBr, DMF, 23 °C, 4 h; (e) *n*Bu4N$^+F^-$, THF, 23 °C, 2 h; (f) Dess-Martin, $NaHCO_3$, CH_2Cl_2, 23 °C, 2 h; (g) CH_2=$CHCH_2B[(-)\text{-Ipc}]_2$, THF, –78 °C, 3 h; (h) CH_2=$CHCH_2MgBr$, Et_2O, 0 °C, 1 h; (i) $Cl_2(PCy_3)_2Ru$=CHPh, CH_2Cl_2, 40 °C, 14 h; (j) NaOH, THF-H_2O, 0 °C, 14 h; (k) TBDMSCl, imidazole, DMF, 23 °C, 18 h; (l) CH_2N_2, Et_2O, 0 °C, 0.5 h; (m) AD mix-β,$CH_3SO_2NH_2$, *t*BuOH-H_2O (1:1), 0 °C, 72 h.

Scheme 30: **Synthesis of C10-C24 segment**

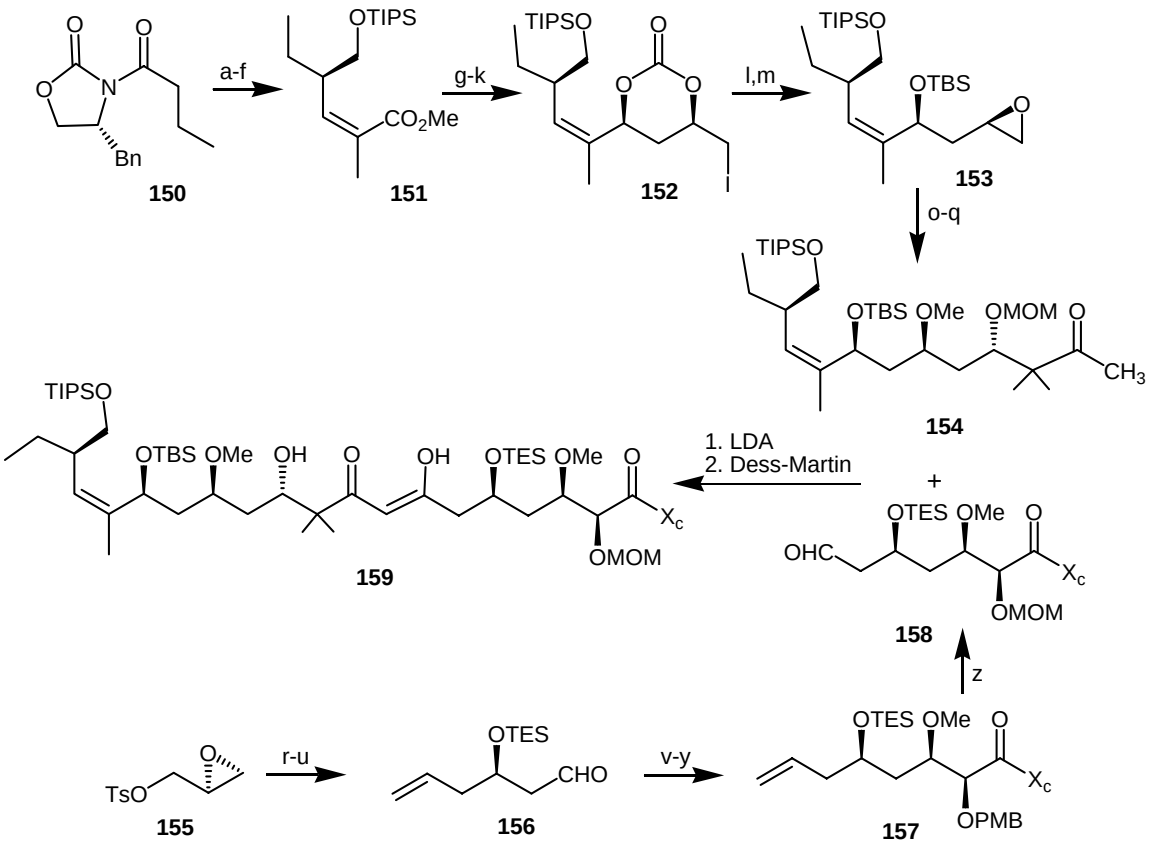


Reagents and conditions: (a) $TiCl_4$, Et_3N, CH_2Cl_2, $PhCH_2OCH_2Cl$, 0 °C, 1.5 h; (b) $LiBH_4$, MeOH, THF, 23 °C, 1 h; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -60 °C, 45 min; (d) $(o\text{-cresol})_2P(=O)(CH_3)CHCO_2Et$, NaH, THF, -78 to -20 °C, 2 h; (e) Dibal-H, CH_2Cl_2, -78 °C to -40 °C, 1 h; (f) DMP, $NaHCO_3$, CH_2Cl_2, 23 °C, 1.5 h; (g) CH_2=$CHCH_2B[(+)\text{-Ipc}]_2$, Et_2O, -80 °C, 3 h; (h) CH_2=CHCOCl, Et_3N, CH_2Cl_2, 0 °C, 2 h; (i) $Cl_2(Pcy_3)_2Ru$=CHPh, CH_2Cl_2, 40 °C, 12 h; (j) H_2O_2, 6N-aq NaOH, MeOH, 1.5 h; (k) $NaBH_4$, PhSeSePh, AcOH, *i*PrOH, 0 °C, 30 min (quant.); (l) TBDPSCl, imidazole, DMAP, DMF, 23 °C, 13 h (quant.); (m) $AlMe_3$, $HN(OCH_3)\text{-}CH_3\cdot HCl$, CH_2Cl_2, 23 °C, 2.5 h; (n) MEMCl, DIPEA, 23 °C, 9 h; (o) ^{i}PrMgCl, THF, 23 °C, 5 h.

Taylor's approach[54]

Taylor et al accomplished the second total synthesis of peloruside A **34**. Thier synthesis based on a key aldol coupling reaction between the C8-C19 methyl ketone **154** and the C1-C7 aldehyde **158** to give access to the elaborate β-diketone **159** that possesses the full carbon framework of peloruside A and a dehydrative cyclization to install a dihydropyranone ring (as in **160**) on which the three contiguous stereocenters at C7-C9 of the requisite tetrahydropyran were established (Scheme 31).

Scheme 31

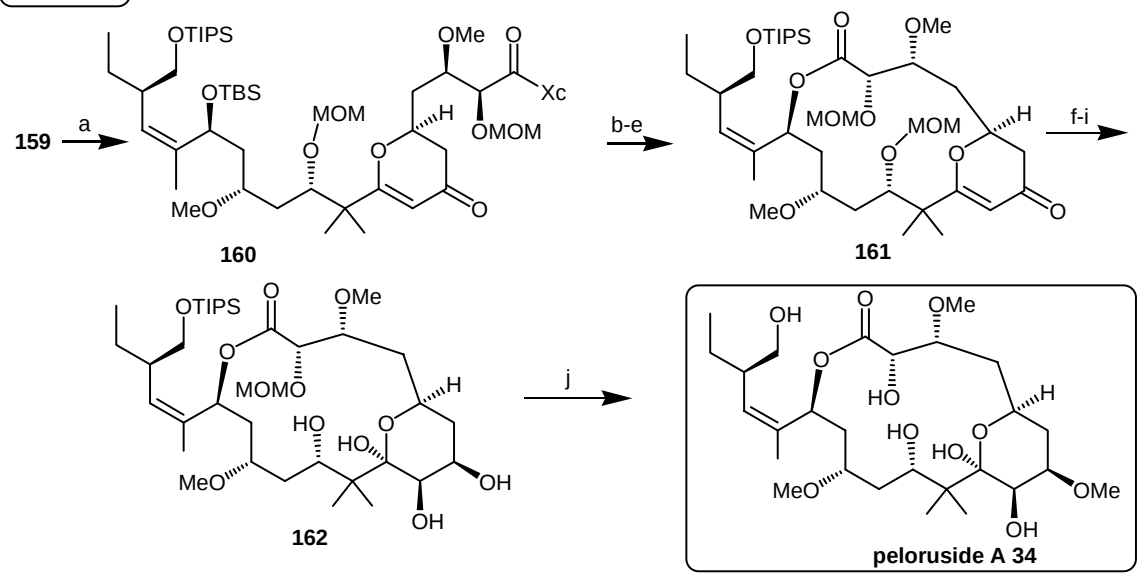


Reagents and conditions: a) $TiCl_4$, BOMCl; b) H_2, Pd/C; c) TIPSCl; d) $LiBH_4$; e) DMP ; f) Still-HWE; g) Dibal-H; h) DMP; i) (+)-Ipc_2B-allyl; j) Boc-ON; k) NIS, CH_3CN; l) K_2CO_3, MeOH; m) TBSCl, imid.; n) 1,3-dithiane, *n*BuLi; KO*t*Bu, CH_3I; o) MeI, CH_3CN/H_2O; p) BF_3:Et_2O, CH_2Cl_2, −78 ºC; q) MOMCl, DIPEA; r) *n*BuLi, dithiane; s) CH_2=CHMgBr, CuI; t) TESCl; u) MeI, $CaCO_3$; v) Bu_2BOTf, Et_3N; w) Me_3OBF_4; x) DDQ; y) MOMCl; z) O_3, TPP.

Deprotection at C15 and hydrolysis at C1 of **160** revealed the seco-acid derivative, which was subjected to Yamaguchi conditions to give the advanced 16-membered macrolactone intermediate **161**. The remaining C7-C9 stereocenters were installed by Luche reduction followed by epoxidation of the dihydropyranone unit. Selective methylation of the C7

equatorial hydroxyl group and acidic deprotection of **162** then delivered (+)-peloruside A **34** (Scheme 32).

Scheme 32

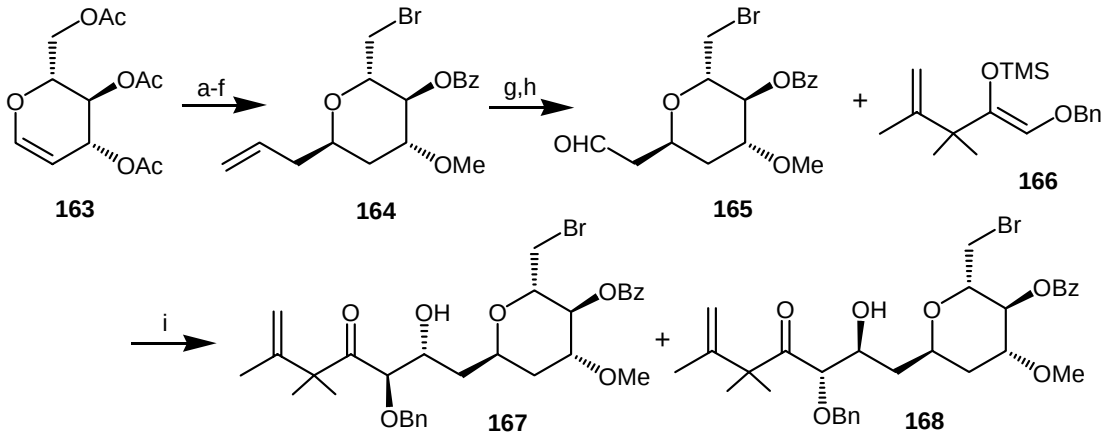


Reagents and conditions: a) PTSA, $PhCH_3$; b) HF.pyr; c) TIPSCl; d) LiOH, H_2O; e) TCBCl, TEA, DMAP; f) $NaBH_4$, $CeCl_3$; g) *m*CPBA; h) Me_3OBF_4; i) 2,6-di-*t*Bu-pyr; j) 4 N HCl.

Pagenkopf's approach [55]

Carbohydrate based synthesis of C1-C12 fragment **170** of peloruside A **34** was accomplished Pagenkopf et al using relatively unexplored *anti-anti* glycol aldol. Aldehyde **165** (C1-C7 subunit) coupling partner for the key *anti-anti* aldol reaction was

Scheme 33

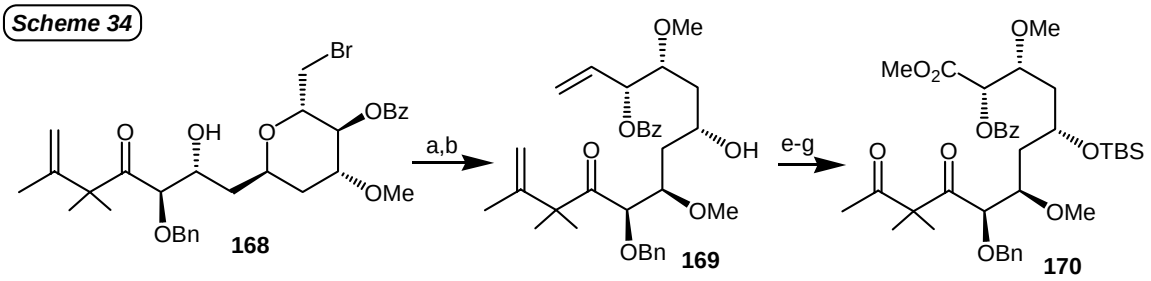


Reagents and Conditions: a) 10 mol% $Ph_3P.HBr$, 3 eq. MeOH, MeCN; b) Et_2NH; c) $PhCH(OMe)_2$, cat. TsOH; d) NaH, MeI; e) NBS, $BaCO_3$, CCl_4; f) allylTMS, TMSOTf, -20 ºC, MeCN; g) OsO4, NMO; h) $NaIO_4$; i) BF_3:Et_2O, CH_2Cl_2.

executed starting from commercially available D-glucol **163**. The F_3B:OEt_2 catalyzed Mukaiyama aldol reaction was identified as the most effective method for securing the 2,3-

anti-3,5-*anti* diastereomer required for the peloruside A with modest selectivity of 3.5:1 relative to 2,3-*anti*-3,5-*syn* diastereomer **168** (Scheme 33). Further functional group transformations gave requisite β-diketone **170** (Scheme 34).

Scheme 34

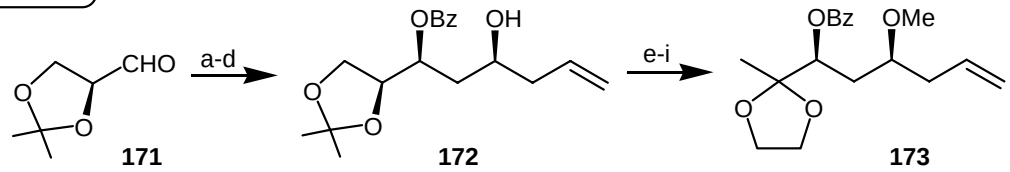


Reagents and conditions: a) Me_3OBF_4, proton sponge; b) ZN/Cu, EtOH; c) TBSCl, imid.; d) MeOH, H^+; e) O_3, Ph_3P; f) $NaClO_2$, NaH_2PO_4; g) $TMSCHN_2$.

Zhou's approach[56]

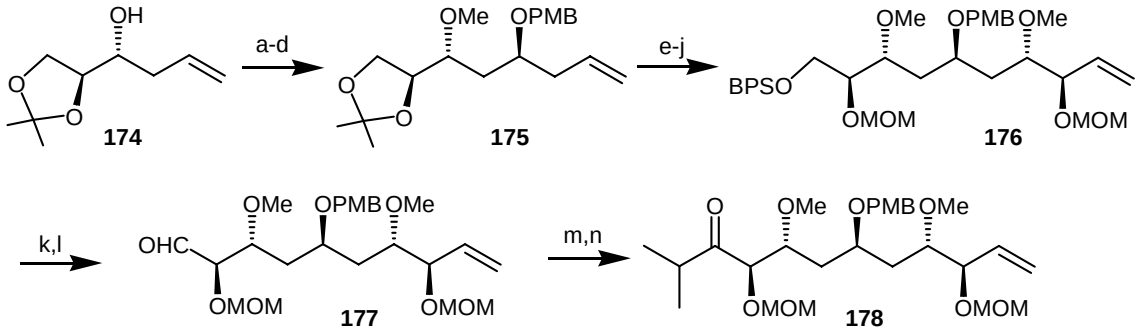
In the study aimed at total synthesis of peloruside A **34**, Zhou and co-workers prepared open-chain fragment C1-C17 (**180**) of 16-membered macrolactone core using thermodynamically controlled aldol reaction to couple the C1-C10 (**178**) and C11-C17 (**179**) subunits (Scheme 37). Synthesis of subunits C1-C10 (**178**) and C11-C17 (**173**) was

Scheme 35



Reagents and conditions: (a) diallyl zinc, THF, -10 to 20 °C, 85:15 dr; (b) PhCOOH, Ph_3P, DIAD, THF, rt; separation of diastereoisomers; (c) *Cat.* OsO_4, $NaIO_4$, THF-H_2O, rt; (d) allylB[(-)-Ipc_2], ether, -78 °C; (e) MeI, NaH, THF, rt; (f) H_5IO_6, EtOAc, 0 °C; (g) Me_3Al, CH_2Cl_2, 0 °C; (h) DMP, $NaHCO_3$, CH_2Cl_2, rt; (i) Ethylene glycol, *cat.* TsOH, PhH, reflux.

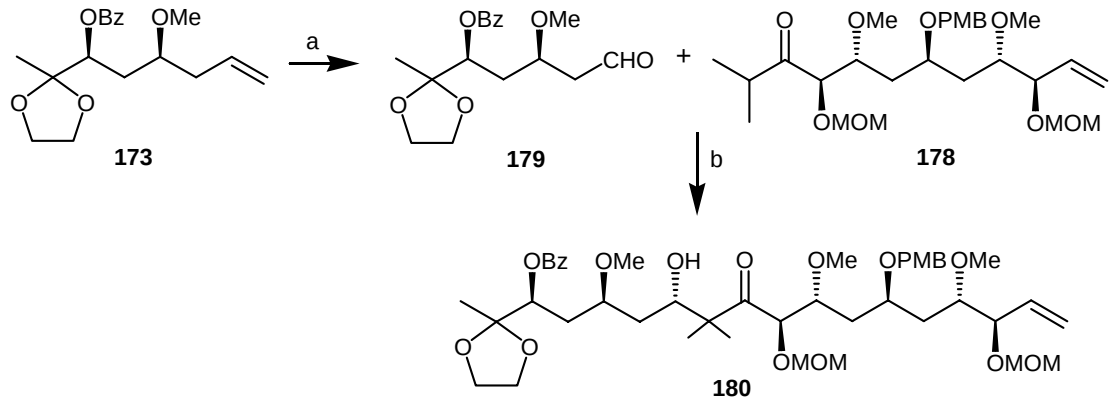
Scheme 36



Reagents and conditions: (a) MeI, KOH, DMSO, rt; (b) *Cat.* OsO_4, $NaIO_4$, THF-H_2O, rt. (c) allylB[(-)-Ipc_2], ether, -78 °C; (d) PMBCl, *cat.* TBAI, NaH, THF, reflux; (e) *Cat*. TsOH, MeOH, rt; (f) TBDPSCl, *cat.* DMAP, Et_3N, CH_2Cl_2, rt, quant. (g) MOMCl, *i*Pr_2NEt, CH_2Cl_2, rt; (h) *Cat*. OsO_4, $NaIO_4$, THF-H_2O, rt. (i) allylMOM, *s*BuLi, THF, -78 °C, 40 min; then (-)-Ipc_2BOMe, -78 °C, 1.5 h; then aldehyde, -78 °C, 3.5 h; NaOH, 30% H_2O_2, ether, rt, 8 h; (j) MeI, NaH, THF, rt; (k) TBAF, THF, rt; (l) Dess-Martin periodinane, CH_2Cl_2, rt. (m) isopropyllithium, toluene, -78 °C to rt; (n) Dess- Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt.

initiated with same homoallyl alcohol derived form 2,3-*O*-isopropylidene-L-glyceraldehyde **171** following iterative chiral allylation transformations (Scheme 35 & 36).

Scheme 37

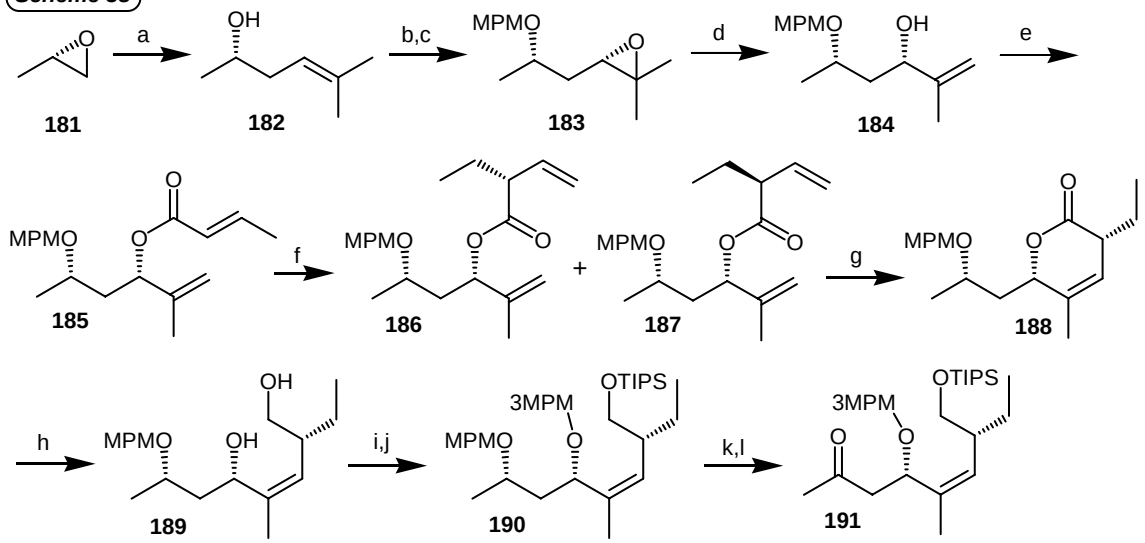


Reagents and conditions: (a) *Cat.* OsO_4, $NaIO_4$, THF-H_2O, rt; (b) LDA, THF, -78 °C; then aldehyde 30, THF, -78 to -40°C, 74:26 dr.

Ermolenko's approach[57]

A short and efficient asymmetric synthesis of the C12-C19 fragment (**191**) of peloruside A **34** was accomplished Emerlenko et al using a highly diastereo discriminating ring closing metathesis of α-branched but-3-enoate ester (**186**/**187**) of a methallylic alcohol **184** starting from hydrolytically resolved optically pure (–)-propylene oxide **181** (Scheme 38). Synthesis of diene precursor from allyl alcohol **184** and (*R*)-2-ethyl-but-3-enoic acid

Scheme 38

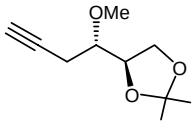


Reagents and conditions: Me_2C=CHMgBr, CuI/THF, -35 °C; b) *t*BuO_2H, $VO(acac)_2$, CH_2Cl_2, -25 °C; c) MPMCl, NaH, THF; d) *i*Pr_2NMgBr, THF; e) CH_3CH=CHCOCl, TEA; f) LDA, EtI, HMPA/THF, -78 °C; g) Grubbs' catalyst, CH_2Cl_2, reflux; h) $LiAlH_4$, THF; i) TIPSCl, py, 50 °C; j) 3-MPMCl, NaH, TBAi, THF, reflux; k) DDQ, CH_2Cl_2-H_2O, 0 °C; l) TPAP, NMO, CH_2Cl_2.

using classical coupling conditions (DCC/DMAP) resulted in epimeric mixture, and RCM reaction of epimeric mixture (**186** and **187**) in refluxing CH_2Cl_2 provided single diastereomeric *syn*-lactone **188** and unreacted diene ester recovered in almost pure 5*S* isomer. Thus, synthesis of *syn*-lactone **188** further simplified by alternate crotonylation of allylalcohol followed by alkylation and subsequent resolution of diene using RCM.

Experimental

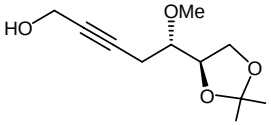
1,2-*O*-isopropylidene-3-*O*-methyl-4-ethynyl-4-deoxy-L-erythritol (86)



To a solution of **83** (6.800 g, 39.95 mmol) in neat MeI (10.0 mL, 160.06 mmol) was added KOH pellets (4.483 g, 54.66 mmol) and stirred vigorously at room temperature. After 8 h, excess MeI was distilled from the reaction mixture, residue dissolved in water and extracted with Et_2O. Combined organic layer was washed with brine, dried (Na_2SO_4), concentrated and the residue purified on silica gel using EtOAc:light petroleum ether (2:23) as an eluent to afford **86** as a colorless liquid.

Yield	: 2.280 g (98%)
Mol. Formula	: $C_{10}H_{16}O_3$.
Optical Rotation $[\alpha]_D^{25}$	: +21.5 (*c* 1.2, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1})	: 3309, 3014, 2989, 2935, 2828, 2121, 1956, 1643, 1456, 1423, 1382, 1372, 1349, 1216, 1156, 1105, 1079, 1052, 984.
^{1}H NMR ($CDCl_3$, 200MHz)	: δ 1.34, 1.40 (2 s, 6H), 1.99 (t, 1H, *J* = 2.6 Hz), 2.45 (ddd, 1H, *J* = 17.2, 4.9, 2.6 Hz), 2.62 (ddd, 1H, *J* = 17.2, 4.5, 2.6 Hz), 3.25-3.35 (m, 1H), 3.46 (s 3H), 3.85-3.95 (m, 1H), 4.01-4.19 (m, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 20.08, 25.01, 26.53, 57.79, 66.34, 70.10, 76.01, 79.65, 80.13, 108.97.
Elemental Analysis	**Calcd.:** C, 65.19; H, 8.75%. **Found:** C, 65.53; H, 8.99%.

1,2-*O*-isopropylidene-3-*O*-methyl-4-(3-hydroxy-1-propynyl)-4-deoxy-L-erythritol (87)



To a solution of **86** (5.000 g, 27.14 mmol) in THF (50 mL) was added *n*-BuLi (1.6 M solution in hexane, 25 mL, 40.71 mmol) dropwise over a period of 15 min at –78 ºC and

the reaction mixture allowed to warm up to –40 ºC. After 1 h, reaction mixture was cooled to –78 ºC and charged with paraformaldehyde (1.630 g, 57.28 mol). After 8 h, reaction was quenched with water and extracted with Et_2O. Combined organic layer was washed with brine, 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 give **87** as a thick syrup.

Yield : 4.710 g (81%)

Mol. Formula : $C_{11}H_{18}O_4$.

Optical Rotation $[\alpha]_D^{25}$: +13.0 (*c* 2.0, $CHCl_3$).

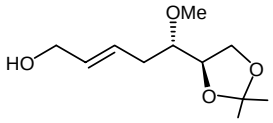
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) : 3433, 2987, 2935, 2288, 2227, 1642, 1456, 1423, 1372, 1257, 1214, 1156, 1076,1020. 974, 920.

^{1}H NMR ($CDCl_3$, 200MHz) : δ 1.34, 1.40 (2 s, 6H), 2.18 (br s, 1H), 2.49 (ddt, 1H, *J* = 17.2, 4.6, 2.1 Hz), 2.65 (ddd, 1H, *J* = 17.2, 4.5, 2.2 Hz), 3.23-3.34 (m, 1H), 3.45 (s 3H), 3.88-3.97 (m, 1H), 4.02-4.17 (m, 2H), 4.23 (t, 2H, *J* = 2.1 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 20.23, 25.02, 26.53, 50.61, 57.74, 66.31, 75.97, 79.74, 80.50, 81.17, 109.10.

Elemental Analysis **Calcd.:** C, 61.66; H, 8.47%.
Found: C, 61.53; H, 8.49%.

1,2-*O*-isopropylidene-3-*O*-methyl-4-(3-hydroxy-1-propenyl)-4-deoxy-L-erythritol (88)



To a solution of **87** (1.0 g, 4.66 mmol) in THF (20 mL) was added $LiAlH_4$ (250 mg, 6.59 mmol) in portionwise over a period of 15 min at 0 °C and then stirred for 10 h at room temperature. Reaction mixture was cooled to 0 °C, quenched with EtOAc and water, filtered, concentrated and the residue purified on silica gel using EtOAc:light petroleum ether (1:4) as an eluent to afford **88**.

Yield : 960 mg (95%)

Mol. Formula : $C_{11}H_{20}O_4$.

Optical Rotation $[\alpha]_D^{25}$: +19.48 (*c* 2.0, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) : 3451, 3017, 2990, 2888, 2830, 2436, 2400, 1688, 1622, 1670, 1519, 1455, 1429, 1382, 1372, 1216, 1156, 1134, 1070, 1091, 974, 929.

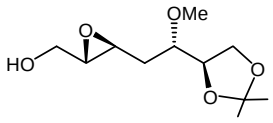
^{1}H NMR ($CDCl_3$, 200MHz) : δ 1.33, 1.40 (2 s, 6H), 1.85 (br s, 1H), 2.27-2.45 (m, 2H), 3.22-3.30 (m, 1H), 3.40 (s 3H), 3.82-3.90 (m, 1H), 3.95-4.03 (m, 2H), 4.08-4.11 (m, 2H), 5.70-5.76 (m, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 25.07, 26.35, 32.82, 57.75, 62.75, 66.16, 76.42, 80.87, 108.77, 126.80, 132.11

Elemental Analysis **Calcd.:** C, 61.09; H, 9.32%.

Found: C, 61.43; H, 9.49%.

1,2-*O*-isopropylidene-3-*O*-methyl-4-[(2*S*,3*S*)-3-hydroxymethyl-oxiranyl]-4-deoxy-L-erythritol (82)



To a stirred and cooled (–20 °C) solution of (+)-DIPT (1.900 g, 8.11 mmol) and 4Å molecular sieves powder (5 g) in CH_2Cl_2 (40 mL) was added titanium tetraisopropoxide (2.40 mL, 8.13 mmol). After 15 minutes, a solution of **88** (1.800 g, 8.32 mmol) in CH_2Cl_2 (10 mL) was introduced at –20 °C, stirred for 45 min and then charged with TBHP (3.3 M solution in toluene, 4 mL, 13.20 mmol) at the same temperature. The reaction was quenched after 24 h with 10% aq. tartaric acid solution and aqueous layer further extracted with CH_2Cl_2. Combined organic layer was dried (Na_2SO_4), concentrated and the residue purified on silica gel using EtOAc:light petroleum ether (1:4) as an eluent to give **82**.

Yield : 1.810 g (94%)

Mol. Formula : $C_{11}H_{20}O_5$.

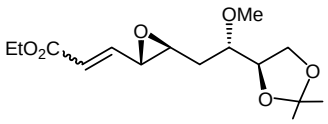
Optical Rotation $[\alpha]_D^{25}$: –38.1 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) : 3468, 3018, 2990, 2935, 2401, 1742, 1618, 1455, 1382, 1372, 1216, 1156, 1084, 928.

^{1}H NMR : δ 1.33, 1.40 (2 s, 6H), 1.76 (t, 2H, *J* = 5.8 Hz), 2.05 (br s, 1H),

($CDCl_3$, 200MHz)	2.97 (dt, 1H, *J* = 4.7, 2.1 Hz), 3.12 (dt, 1H, *J* = 5.8, 2.2 Hz), 3.34-3.44 (m, 1H), 3.47 (s 3H), 3.62 (dd, 1H, *J* = 12.6, 4.2 Hz), 3.75-3.95 (m, 2H), 4.00-4.15 (m, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 25.01, 26.32, 32.98, 52.68, 58.51, 58.99, 61.59, 66.29, 76.78, 79.29, 109.18.
Elemental Analysis	**Calcd.:** C, 56.88; H, 8.68%. **Found:** C, 56.97; H, 8.99%.

Ethyl (4*S*, 5*S*, 7*S*, 8*R*)-7-methoxy-8,9-*O*-isopropylidene-4,5-epoxy-non-2-enoate (90)



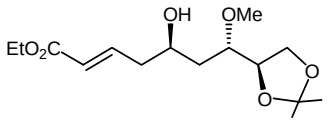
To a CH_2Cl_2 (10 mL) solution of oxalyl chloride (0.40 mL, 4.58 mmol) was added DMSO (0.60 mL, 8.45 mmol) at –78 °C, stirred 15 min, and then a solution of **82** (0.600 g, 2.58 mmol) in CH_2Cl_2 (5 mL) added. After 1 h, reaction was quenched with Et_3N (1.60 mL, 11.50 mmol) and poured into ice-cold water. The organic layer was dried (Na_2SO_4) and concentrated (below 35 °C) to obtain **89**.

A solution of **89** and PPh_3=CHCOOEt (1.100 g, 3.15 mmol) in CH_2Cl_2 (20 mL) was stirred for 8 h at room temperature and concentrated. The residue was purified on silica gel using EtOAc:light petroleum ether (3:17) as an eluent to obtain **90*Z***:**90*E*** (1:3).

Yield	: 604 mg (78%)
Mol. Formula	: $C_{15}H_{24}O_6$.
^{1}H NMR ($CDCl_3$, 200MHz)	: δ 1.30 and 1.32 (t, 3H), 1.34, 1.40(2 s, 6H), 1.65-1.95 (m, 2H), 3.28 (dd, 1H, *J* = 7.0, 2.0 Hz), 3.02-3.42 (m, 1H), 3.46 and 3.48 (s, 3H), 3.75-3.87 (m, 1H), 3.98-4.11 (m, 2H), 4.2 (q, 2H, *J* = 7.1 Hz), 5.76 and 6.68 (dd, 1H, *J* = 11.6 and 15.6, 8.2 and 7.0 Hz), 5.98 and 6.13 (dd, 1H, *J* = 11.6 and 15.6, 0.7 Hz).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 14.01, 24.97, 26.27 and 26.32, 33.15 and 33.44, 54.35, 56.63, 57.93, 58.41, 60.20 and 60.35, 66.17 and 66.45, 76.64, 79.19 and 79.24, 109.14, 123.71, 144.12 and 144.26, 165.35 and 165.55.
Elemental	**Calcd.:** C, 59.98; H, 8.05%.

Analysis **Found:** C, 59.97; H, 8.39%.

Ethyl (2*E*, 5*R*, 7*S*, 8*R*)-5-hydroxy-7-methoxy-8,9-*O*-isopropylidene-non-2-enoate (81)



To a CH_2Cl_2 (5 mL) solution of freshly prepared $Pd(PPh_3)_4$ (115 mg, 0.10 mmol) and $Me_2NH{:}BH_3$ (60 mg, 1.01 mmol) was added a mixture of AcOH (0.2 mL, 3.17 mmol) and **90** (300 mg, 1.00 mmol) in CH_2Cl_2 (5 mL) at room temperature. After 30 min, the reaction mixture was concentrated and the residue purified on silica gel using EtOAc:light petroleum ether (1:9) as an eluent to obtain **81**.

Yield : 266 mg, (88%)

Mol. Formula : $C_{15}H_{26}O_6$.

Optical Rotation $[\alpha]_D^{25}$: –3.1 (*c* 1.0, $CHCl_3$).

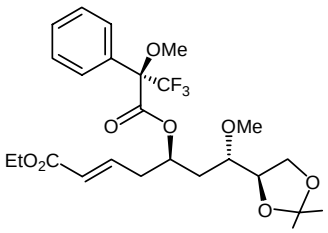
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) : 3474, 3017, 2989, 2937, 2831, 2439, 2401, 1712, 1655, 1446, 1455, 1382, 1371, 1317, 1264, 1159, 1216, 1089, 1047, 981, 926.

^{1}H NMR ($CDCl_3$, 200MHz) : δ 1.29 (t, 3H, *J* = 7.2 Hz), 1.34, 1.41 (2 s, 6H), 1.66-1.75 (m, 2H), 2.38 (ddd, 2H, *J* = 7.2, 5.9, 1.3 Hz), 3.03-3.09 (br s, 1H), 3.37-3.48 (m, 1H), 3.47 (s 3H), 3.78-3.89 (m, 1H), 4.00-4.15 (m, 3H), 4.18 (q, 2H, *J* = 7.2 Hz), 5.90 (dt, 1H, *J* = 15.6, 1.4 Hz), 6.98 (dt, 1H, *J* = 15.6, 7.3 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 14.09, 24.99, 26.29, 37.28, 40.57, 58.48, 60.04, 66.50, 67.15, 76.90, 79.70, 109.16, 123.51, 145.02, 166.15

Elemental Analysis **Calcd.:** C, 59.58; H, 8.67%.
Found: C, 59.77; H, 8.83%.

Ethyl (2*E*, 5*R*, 7*S*, 8*R*)-5-[(*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyloxy]-7-methoxy-8,9-*O*-isopropylidene-non-2-enoate (91)



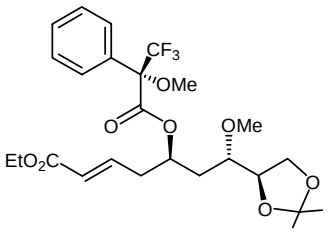
A solution of **81** (21 mg, 0.07 mmol), (*S*)-(–)-α-methoxy-α-trifluoromethylphenylacetic acid (*S*-MTPA) (23 mg, 0.10 mmol), DCC (20 mg, 0.10 mmol) and DMAP (2 mg, 0.02 mmol) in CH_2Cl_2 (4 mL) was stirred for 8 h at room temperature. The reaction mixture was diluted with water, extracted with CH_2Cl_2. Combined organic layer was washed with brine, dried (Na_2SO_4), concentrated and the residue purified on silica gel using EtOAc:light petroleum ether (1:9) as an eluent to afford **91**.

Yield : 10 mg (80% based on recovered starting material)

Mol. Formula : $C_{25}H_{33}F_3O_8$.

^{1}H NMR ($CDCl_3$, 400MHz) : δ 1.29 (t, 3H, *J* = 7.2 Hz), 1.33, 1.37 (2 s, 6H), 1.63 (ddd, 1H, *J* = 14.9, 10.0, 2.7 Hz), 1.83 (ddd, 1H, *J* = 14.9, 10.0, 2.1 Hz), 2.61 (br t, 2H, *J* = 6.7 Hz), 3.06 (ddd, 1H, *J* = 9.8, 4.7, 2.2 Hz), 3.36 (s 3H), 3.54 (br s, 3H), 3.62 (dd, 1H, *J* = 8.2, 6.4 Hz), 3.97 (dd, 1H, *J* = 8.2, 6.7 Hz), 4.05 (dt, 1H, *J* = 4.8, 4.5 Hz), 4.20 (q, 2H, *J* = 7.2 Hz), 5.41-5.47 (m, 1H), 5.87 (dt, 1H, *J* = 15.7, 1.3 Hz), 6.86 (dt, 1H, *J* = 15.7, 7.3 Hz), 7.39-7.43 (m, 3H), 7.53-7.55 (m, 2H).

Ethyl (2*E*, 5*R*, 7*S*, 8*R*)-5-[(*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyloxy]-7-methoxy-8,9-*O*-isopropylidene-non-2-enoate (92)



The reaction was carried out as described above using compound **81** (21 mg, 0.07 mmol), (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (*R*-MTPA) (23 mg, 0.10 mmol),

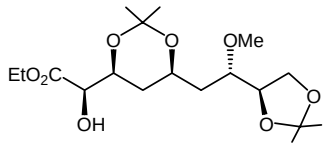
DCC (40 mg, 0.20 mmol) and DMAP (4 mg, 0.04 mmol) in CH_2Cl_2 (4 mL). The residue was purified by silica gel column chromatography with EtOAc:light petroleum ether (1:9) as an eluent to afford **92**.

Yield : 3 mg (78% based on recovered starting material)

Mol. Formula $C_{25}H_{33}F_3O_8$

^{1}H NMR ($CDCl_3$, 400MHz) : δ 1.29 (t, 3H, *J* = 7.2 Hz), 1.34, 1.40 (2 s, 6H), 1.66 (ddd, 1H, *J* = 14.8, 9.7, 2.7 Hz), 1.91 (ddd, 1H, *J* = 14.8, 9.7, 2.5 Hz), 2.53-2.58 (m, 2H), 3.19 (ddd, 1H, *J* = 7.3, 4.7, 2.5 Hz), 3.40 (s 3H), 3.52 (br s, 3H), 3.71-3.74 (m, 1H), 4.00-4.06 (m, 2H), 4.18 (q, 2H, *J* = 7.2 Hz), 5.44-5.48 (m, 1H), 5.80 (dt, 1H, *J* = 15.7, 1.3 Hz), 6.78 (dt, 1H, *J* = 15.7, 7.5 Hz), 7.40-7.43 (m, 3H), 7.53-7.56 (m, 2H).

Ethyl (2*R*, 3*S*, 5*S*, 7*R*, 8*R*)-3-hydroxy-7-methoxy-3,5:8,9-di-*O*-isopropylidene-non-2-enoate (80)



To a clear solution of AD mix-α (800 mg) in mixture of *t*-BuOH-H_2O (1:1, 10 mL) was added olefin compound **81** (150 mg, 0.49 mmol) in *t*-BuOH (1 mL) and $MeSO_2NH_2$ (50 mg. 0.50 mmol) in succession at 0 ºC. After 12 h, the reaction was quenched by the addition of saturated aq. Na_2SO_3 solution and the aqueous layer further extracted with EtOAc. Combined organic layer was dried (Na_2SO_4), concentrated and the residue dissolved in CH_2Cl_2 (10 mL). A solution of 2,2-DMP (0.1 mL, 0.81 mmol) and *p*TSA (5 mg) in CH_2Cl_2 was then introduced at room temperature. After 1 h, the reaction mixture was neutralized with Et_3N, concentrated and the residue purified on silica gel using EtOAc:light petroleum ether (1:9) as an eluent to obtain **80**.

Yield : 160 mg (86%)

Mol. Formula : $C_{18}H_{32}O_8$

Optical Rotation $[\alpha]_D^{25}$: –10.03 (*c* 0.6, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) : 3684, 3553, 3019, 2953, 2400, 1736, 1520, 1476, 1432, 1373, 1382, 1215, 1162, 1096, 1068, 1046, 979, 938.

^{1}H NMR ($CDCl_3$, 400MHz)	: δ 1.28 (t, 3H, *J* = 7.1 Hz), 1.34 (s, 6H), 1.40, 1.42 (2 s, 6H), 1.35-1.36 (m, 1H), 1.46 (ddd, 1H, *J* = 14.0, 10.0, 2.8 Hz), 1.57 (ddd, 1H, *J* = 14.0, 9.7, 2.8 Hz), 1.65 (AB_q, 1H, *J* = 12.0 Hz), 2.83-95 (br s, 1H), 3.45 (s, 3H), 3.55 (ddd, 1H, *J* = 10.0, 4.0, 2.8 Hz), 3.82 (dd, 1H, *J* = 8.0, 6.8 Hz), 3.95-4.00 (m, 2H), 4.05-4.14 (m, 2H), 4.15-4.35 (m, 3H).
^{13}C NMR ($CDCl_3$, 100 MHz)	: δ 14.24, 19.66, 25.22, 26.24, 29.85, 32.20, 38.36, 59.59, 61.40, 64.74, 65.43, 70.26, 73.12, 76.75, 77.94, 98.80, 109.08, 172.29.
Elemental Analysis	**Calcd.:** C, 57.43; H, 8.57%. **Found:** C, 57.77; H, 8.63%.

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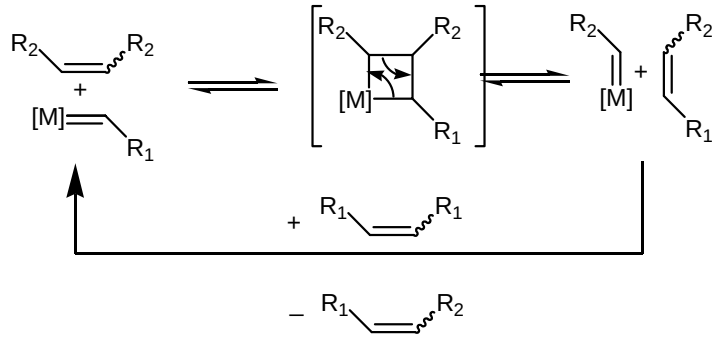
Chapter III

Temperature dependent isomerisation versus net fragmentation of secondary allylic alcohols with Grubbs' catalyst

Introduction

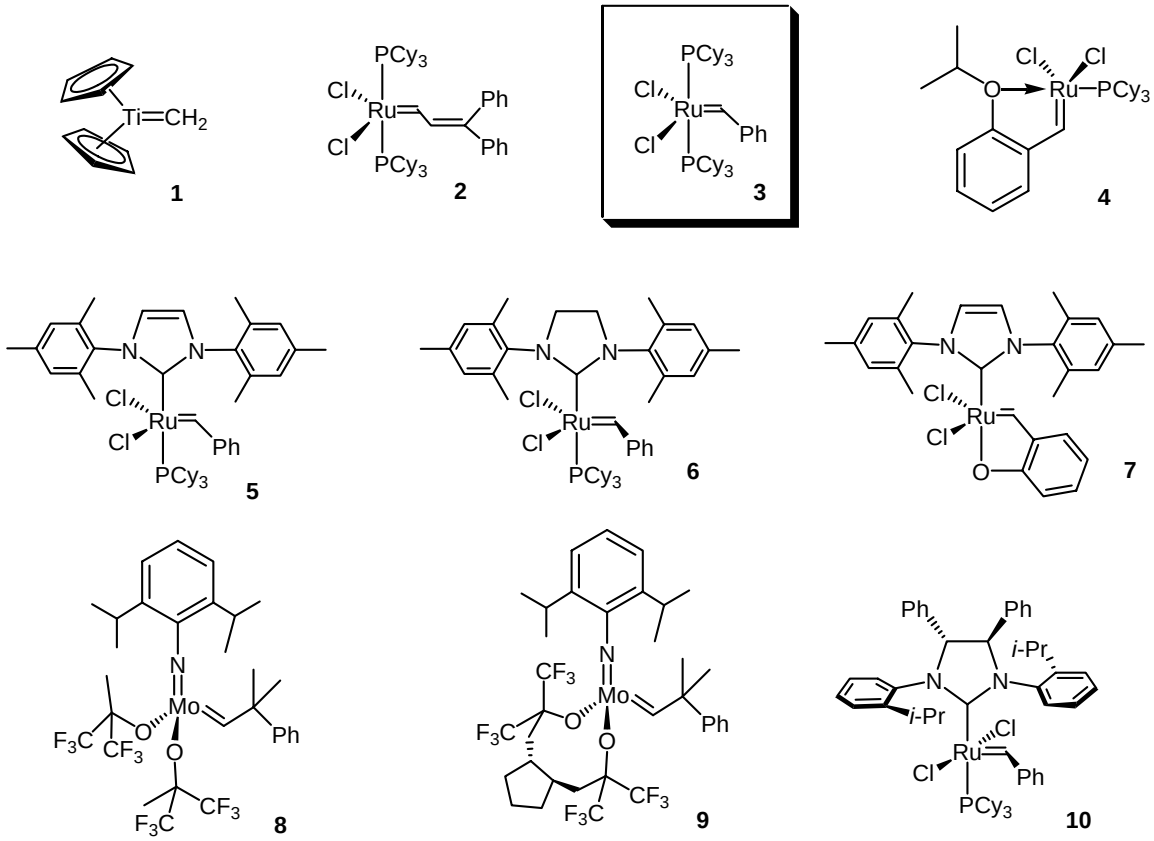
Olefin metathesis is nothing but disproportionation of two alkene compounds in the presence of certain metal catalysts, most often tungsten, molybdenum, or rhenium complexes.[1] Olefin metathesis can be classified into closely related reactions of type, such as ring-closing metathesis (RCM), ring-opening metathesis polymerization (ROMP), acyclic diene metathesis polymerization (ADMET), cross metathesis (CM), and ring-opening/cross-metathesis (ROX).[1] A common mechanistic pathway for metathesis reaction was suggested by Chauvin et al in 1971.[2] The postulated mechanism involves an iterative process of [2+2] cycloaddition and cycloreversion between the olefins, metal alkylidene and metallocyclobutane species (Figure 1). The initial retro-type intermolecular [2+2] cycloaddition between the metal-carbene complex and a C=C bond proceeds with the incorporation of the metal alkylidene into the substrate. And regenerated metal-carbene after cycloreversion takes up another olefin molecule and acts in same fashion to complete the catalytic cycle. In the first turn of the cycle, the volatile nature of the alkene by-product (the gaseous ethene in most cases) tends the reaction to proceed forward thermodynamically. The bond formation in metathesis reaction generally does not proceed under stereocontrol and often leads to mixture of alkenes.

Figure 1: **Chavuvin Mechanism for olefin metathesis**



With the advent of well defined new stable carbene metal complexes developed Robert H. Grubbs' (Ruthenium catalyst, **3**[3]) and Richard R. Schrock (Molybdenum catalyst, **8**[4]), metathesis reaction has seen tremendous progress in the last decade (Figure 2). Interestingly, both of these catalysts have developed a synergistic relationship in the metathesis literature. For example, while **8** has demonstrated greater catalytic activity

Figure 2: **Some of well-established metathesis catalysts**



than **3**, it is more difficult to handle in the presence of air and water, and can be poisoned by certain organic functional groups. Even though catalyst **3** exhibits lower metathesis activity to that of **8**, catalyst **3** is less susceptible to decomposition by air, water, and organic functional groups. However, the apparent compromise between functional group compatibility and activity has been overcome with the recent development of catalyst **6**[5]. These imidazoylidene based systems have been discovered due to a more detailed understanding of the initiation of this family of catalysts. While still maintaining the characteristics of ease in handling and functional group compatibility, catalyst **6** possesses greater electron density at the metal center due to σ-donation from the imidazoylidene ligand. This factor, coupled with reduced π-backbonding in imidazoylidene ligands versus phosphine, leads to greater preference for olefin binding and higher metathesis activity of these systems.

The ring closing metathesis (RCM), in which two un-substituted (or substituted) olefins undergoes ring closure with formal loss of ethylene, is one of the most exploited reaction by synthetic chemists to construct medium to large ring compounds of greater

complexity.[1] An acyclic diene substrate undergoes competitive polymerization metathesis (ADMET) verses ring closing metathesis (RCM) depending primarily on substrate dilution and ring size of the product.[1]

The metal-carbene catalyzed intermolecular coupling between two different olefins, often called as cross metathesis (CM), potentially yields three new types of alkenes **ab**, **aa**, **bb** (**aa** and **bb** are self-metathesis or dimerization products).[6] Minimization of self-metathesis, and control of regioselectivity and stereoselectivity of the newly formed double bonds are crucial issues that hindered the wide spread application of cross metathesis (Figure 3).[6] In comparison with metathesis reactions such as ring closing metathesis (RCM) and ring opening metathesis (ROMP), the cross metathesis (CM) reaction is not well established and several factors influenced the under development of this reaction, e.g. low catalyst activity to effect the reaction, lack of driving force such as strong enthalpic driving force of ROMP and the entropic advantage of intramolecular reactions of RCM. Various possible alkylidene intermediates and numerous primary and secondary metathesis pathways involved in the CM reaction makes it difficult to predict the selectivity in the product formation (Figure 5).[6] Recently, One of the limitation with the metathesis catalysts to construct the tetrasubstituted alkenes was overcome by using Relay Ring Closing Metathesis (RRCM) with slight substrate modification (Figure 4).[7]

Figure 3: **Statical Distribution of CM products**

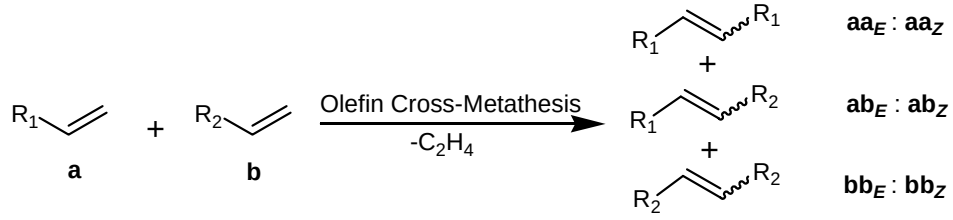


Figure 4

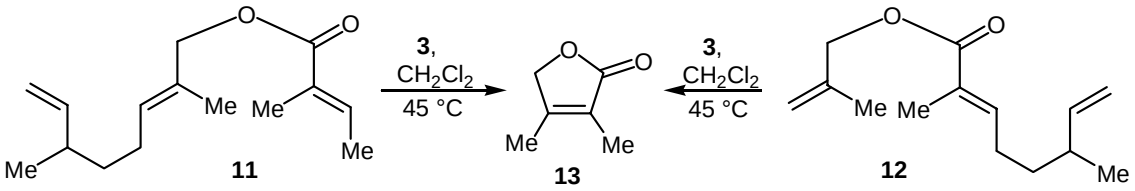
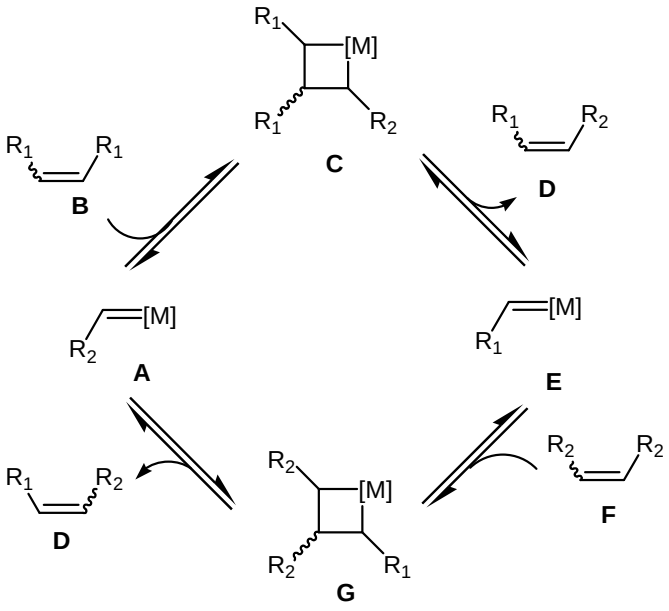


Figure 5: **mechanism of olefin cross metathesis**



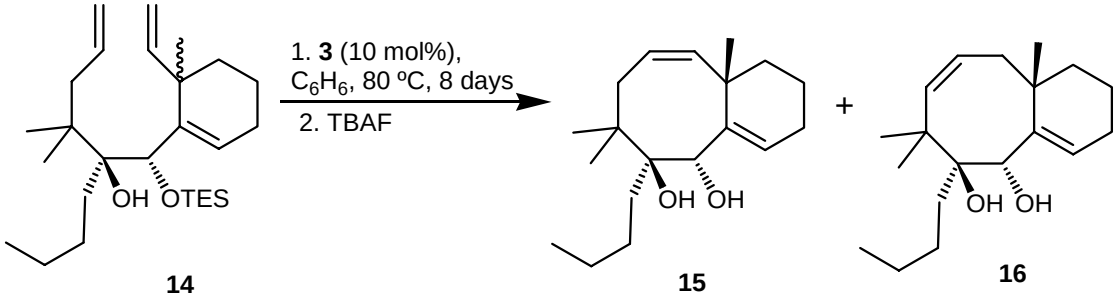
Non-metathesis side reactions with Grubbs' catalyst:

The discovery of stable and well defined metathesis catalysts provided easy access to the construction of C-C bond and gained much prominence in the recent past with few exceptional double bond migration side reactions. Over the past few years, several studies have indeed revealed new non-metathesis pathways with metathesis catalysts. Some of these with first generation Grubbs' catalyst (**3**) are given below.

Prunet et al [8]

Prunet et al investigated the ring closing metathesis of diene **14** with a view towards preparing the carbocyclic moiety of taxol and obtained only minor product amounts of two cyclised products with Grubbs' catalyst **3**: the expected cyclooctene **15** and an unexpected isomer **16**, which obviously results from an isomerisation subsequent to the metathesis step (Scheme 1).

Scheme 1

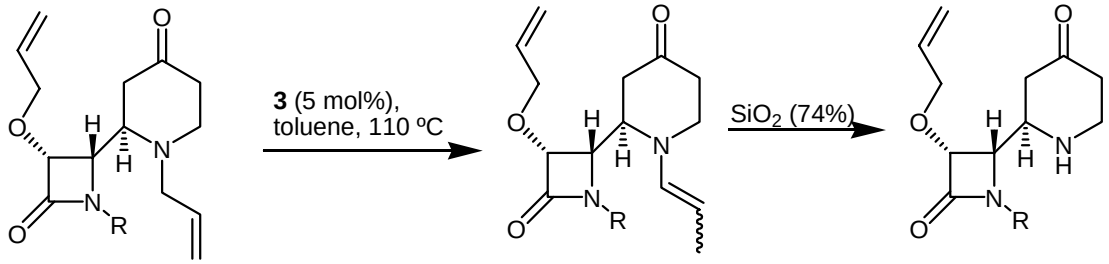


14 **15** **16**

Alcaide et al[9]

The isomerisation of C-C double bonds catalyzed by **3** in competition with metathesis reactions was strongly preferred in the studies led by Alcaide et al. Thus, they observed a useful protocol using catalyst **3** for the deprotection of allylamines, allyllactams with catalys that relies in the selective isomerisation to enamines and enamides, respectively, (Scheme 2).

Scheme 2

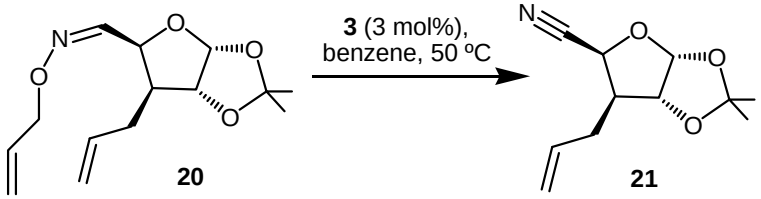


17 **18** **19**

Arindam et al[10]

Remarkably, no isomerisation of the second allyl ether function is observed in the conversion of sugar-derived oximes to nitriles that are catalyzed by Grubbs' catalyst **3**. For example, **20** does not cyclize to the expected ring closing metathesis product under metathesis conditions; instead, formal elimination of allyl alcohol occurs to yield the nitrile **21** (Scheme 3).

Scheme 3

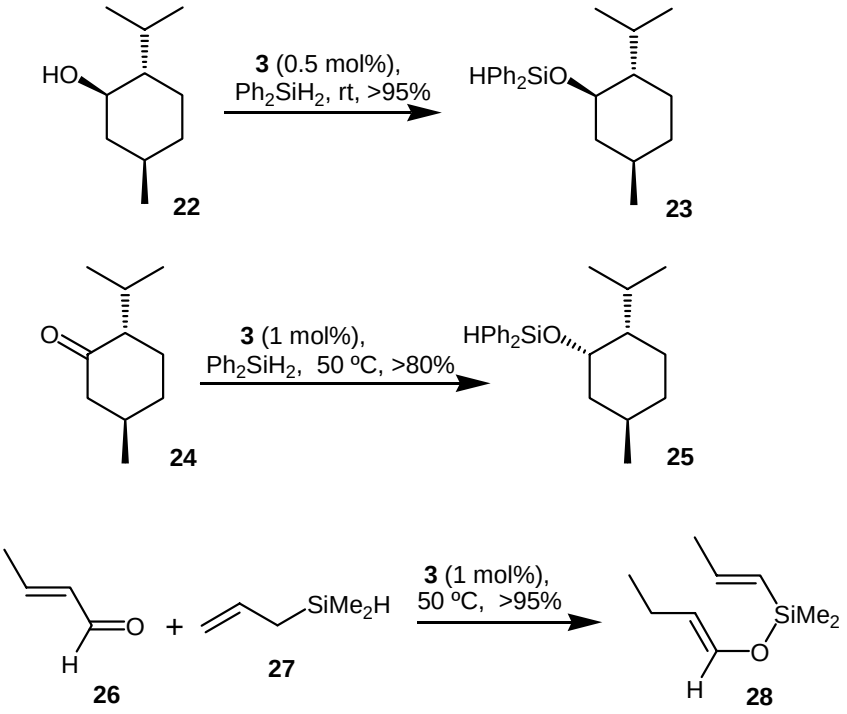


20 **21**

Lee et al [11]

Recently, ruthenium-carbene complex **3** was efficiently used to catalyze the dehydrogenative silylation of alcohols and hydrosilylation of carbonyl compounds to silyl ethers (Scheme 4). If an α,β-unsaturated aldehyde was employed in the reaction e.g. crotonaldehyde **26** in the presence of allyltrimethylsilane led to the corresponding silyl enolether **28** (Scheme 4).

Scheme 4

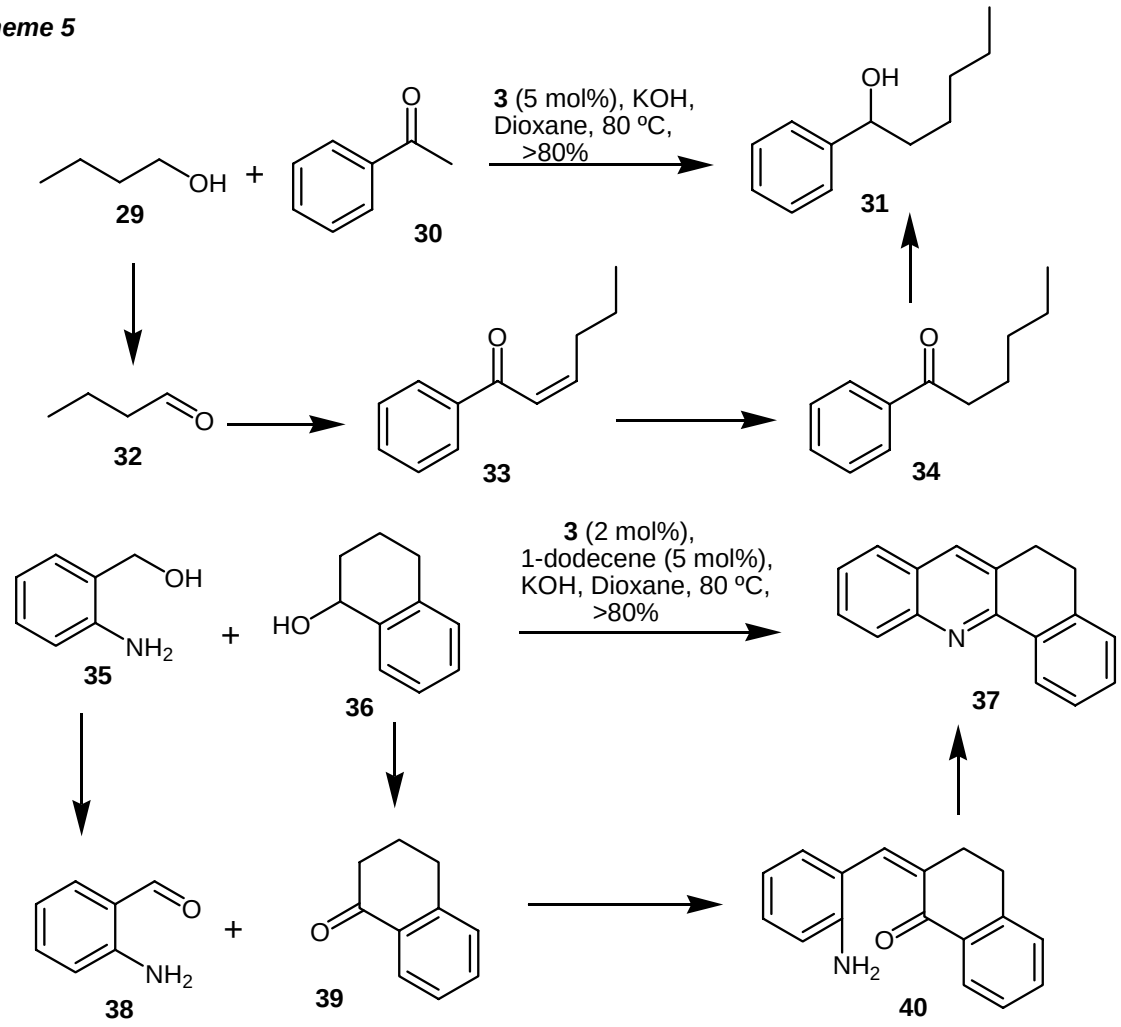


Cho et al[12]

Grubbs' catlyst **3** was also employed successfully in a transfer dehydrogenation/aldol condensation/double transfer hydrogenation sequence discovered by Cho, Shim et al. as outlined in the scheme 5. Primary alcohols, e.g., 1-butanol **29**, reacted with acetophenone **30** in the presence of a catalytic amount of **3** and KOH to give alcohol **31**. This result can be understood by assuming a transfer dehydrogenation of **29**to give butanal **32**, which then undergoes an aldol condensation with **30**, yielding enone **33**. The enone **33** undergoes two subsequent transfer hydrogenations to give the final product **31**. Later, the same authors demonstrated that the sequence does not necessarily require a ketone such as **30**. This was amicably demonstrated with *o*-amino-phenylethanol **35** with

another secondary alcohol **36** in the presence of catalyst **3** to afford quinoline **37** (Scheme 5).

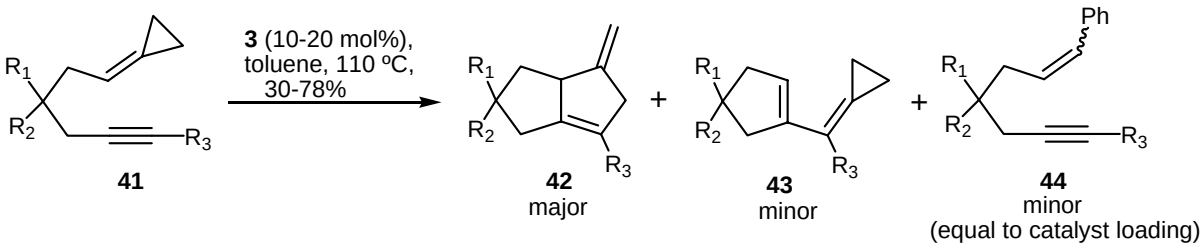
Scheme 5



Mascarenas et al[13]

In a recent publication, Mascarenas et al demonstrated the [3+2] cycloaddition of methylene cyclopropane to unsaturated bonds in the presence of Grubbs' catalyst **3** leading to interesting cyclopentanes containing bicycles such as **42**. They noticed this unusual non-metathetic pathway in the ring closing enyne metathesis reaction of **41** into **43**. And under the optimized reaction conditions Mascarenas et al were able to obtain the bicyclic compound **42** as the major product (Scheme 6).

Scheme 6



41

42
major

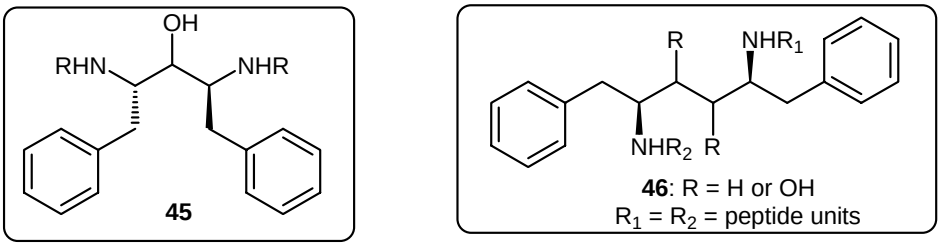
43
minor

44
minor
(equal to catalyst loading)

Present work

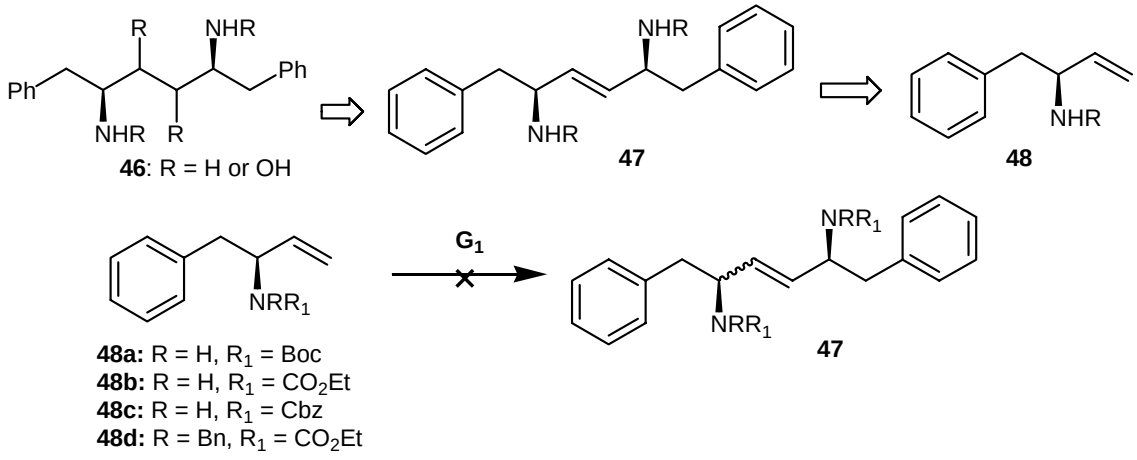
More than 40 million people affected with acquired immunodeficiency syndrome (AIDS) across the world and is the first major epidemic caused by a formerly unknown pathogen. Individual infected with AIDS suffers with disorder of immunological system and develops severe neurological dysfunction. [14] The HIV protease inhibitors synthesized from the C_2 symmetrical core structures **45** or **46** disrupts viral replication effectively and met with most success in developing efficient anti-HIV drugs (Figure 6).[15]

Figure 6



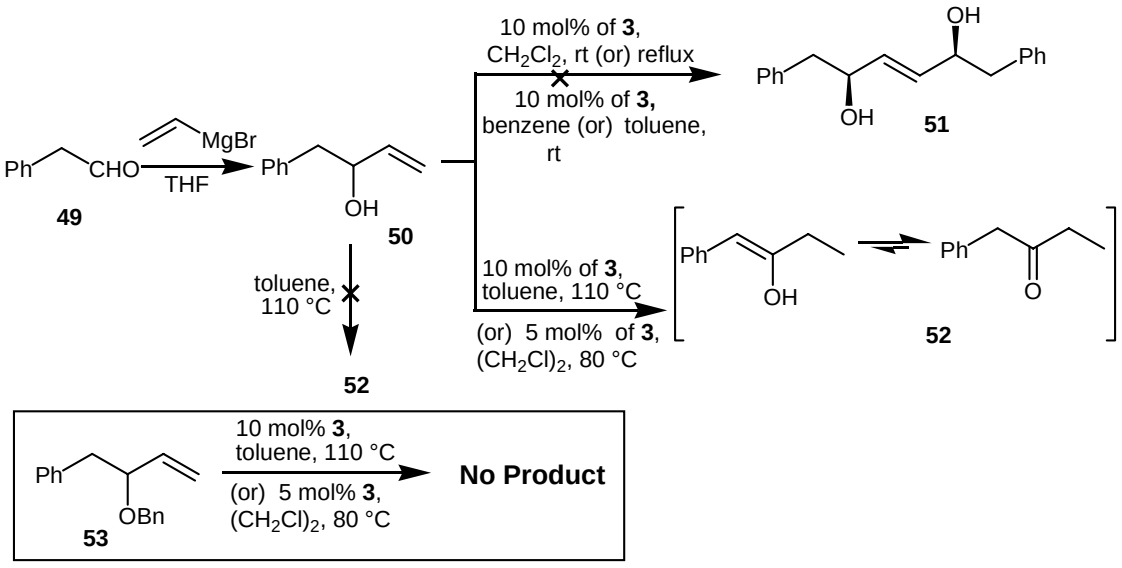
In this regard, we planned a simple dimerisation protocol of α-olefin **48** via Cross-metathesis reaction using Grubbs' catalyst **3** for the synthesis of **46** (Scheme 7). For this endeavor, we followed known methods to prepare the α-olefin **48** from L-phenylalanine.[16] The proposed self-metathesis (Cross-metathesis) of **48a** with 10 mol% of Grubbs' catalyst **3** was failed to provide the required dimer **47** under various reactions conditions. An analogues series of α-olefins (**48b**-**48d**) were prepared by changing the amine protecting groups and subjected to the cross metathesis. However, all the efforts met with failure (Scheme 7).

Scheme 7



Alternatively, cross metathesis of oxygen analogue **50**[17] of α-olefin **48** was planned to obtain self-metathesis product **51** (Scheme 8). Thus, phenyl acetaldehyde **49** was treated with freshly prepared vinyl magnesium bromide in THF at 0 ºC to furnish 1-phenylbut-3-en-2-ol (**50**). Cross metathesis of **50** in the presence of 10 mol% of **3** using high concentration or neat reaction conditions[6] were failed to provide any product even after 5 days at room temperature. However, 1M solution of α-olefin **50** in toluene under the reflux conditions in the presence of 10 mol% of **3** gave a new product **52**, whose spectral data did not match with expected structure of self-metathesis product **51** (Scheme 8). The ^{1}H NMR spectrum of new product showed disappearance of signals due olefin protons and new signals appeared at δ 1.03 (t, 3H, *J* = 7.3 Hz), 2.45 (q, 2H, *J* = 7.3 Hz) and 3.68 (s, 2H) indicating the presence of ethyl ketone (**52**) formed probably, via double bond isomerisation. Structure of **52** was also confirmed by the ^{13}C NMR, IR (1711 cm^{-1}) spectroscopic data and elemental analysis. In the ^{13}C NMR spectrum of **52**, signals due to carbonyl, methyl and methylene carbons appeared at δ 208.78, 7.64, 35.06 and 49.69 respectively. It was apparent that compound **52** was formed as a result of intramolecular hydrogen transfer isomerisation of **50**. Isomerisation of **50** into **52** was also observed in refluxing 1,2-dicholoroethane in the presence of 10 mol% of **3**. Absence of catalyst under the identical conditions failed to provide any product from **50**. Thus double bond migration leading to **52** from **50** under thermal conditions was ruled out. It was also observed that the presence of free allylic alcohol was essential for isomerisation of **50**, as the *O*-benzyl ether

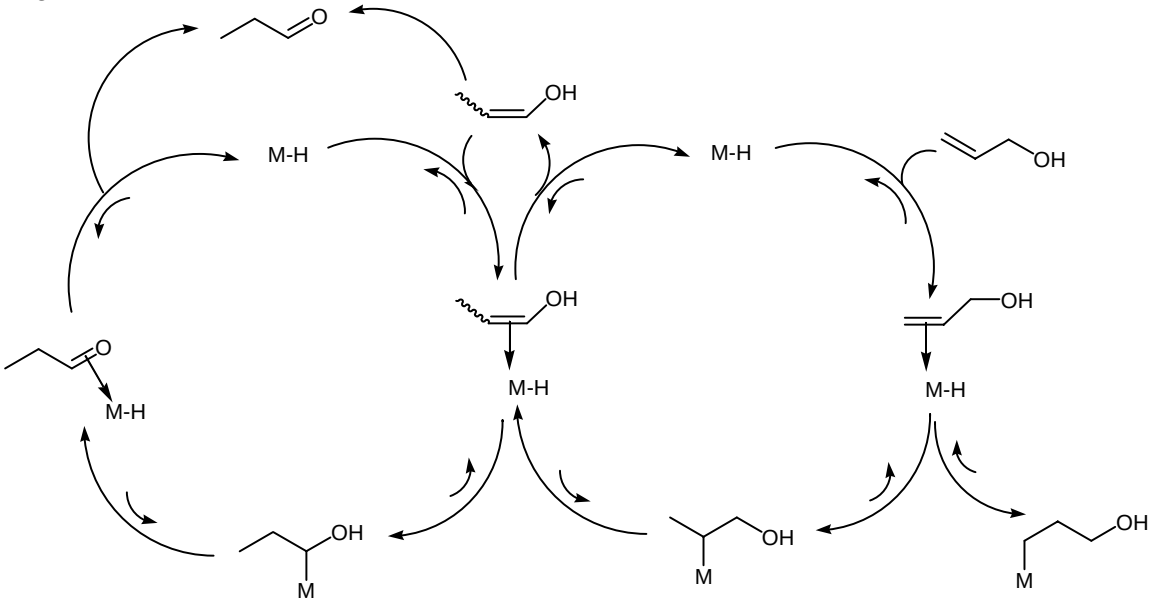
Scheme 8



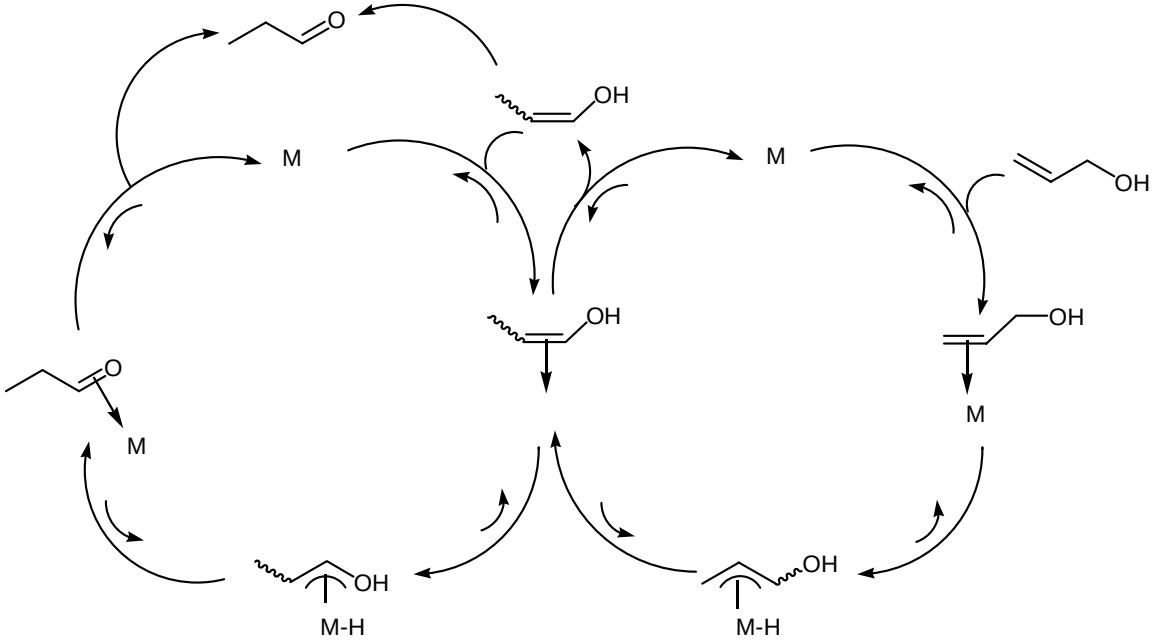
derivative **53** found to be inert to above reaction conditions. Thus we encountered a new synthetic transformation with Grubbs' catalyst **3**, involving isomerisation of secondary allylic alcohol into saturated ketone.

The conversion of allylic alcohols into saturated carbonyl compounds via double bond isomerization is conceptually attracting strategy as the conventional synthetic transformation requires two step sequential oxidation-reduction reactions, and involves

Figure 7



Type I mechanism: Intermolecular hyrogen transfer



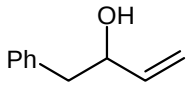
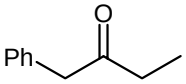
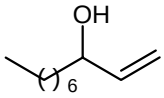
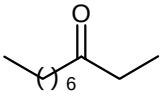
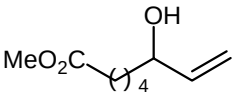
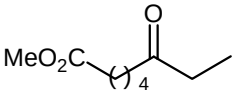
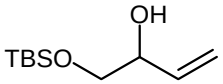
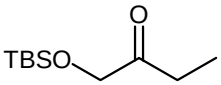
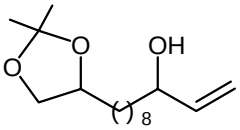
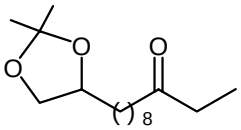
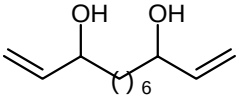
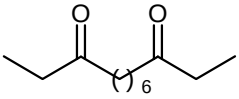
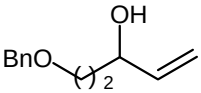
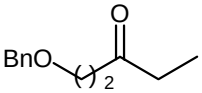
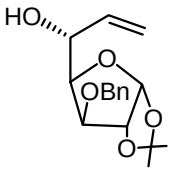
Type II mechanism: Intramolecular hydrogen transfer

use of costly and/or toxic reagents, particularly at the oxidation stage. The internal double bond isomerization of allyl alcohol to an enol intermediate, which on tautomerization can afford the saturated carbonyl compounds with complete atom economy. Over the last 40 years, 50 different catalytic systems have been prepared from Mo, group 8, 9 and 10 metals for this transposition and successfully employed for isomerization of allyl alcohols into saturated carbonyl compounds. Recently, Gree et al classified metal complexes known for this transformation based on the metal involved (Fe, Rh, Ru, Ni, Ir, Co, Pd, Pt, Os and Mo complexes).[18] It was observed that the scope of isomerisation reaction limited to simple allylic alcohols and the functional group compatibility needs further studies. The most accepted mechanistic pathways for the transition metal catalyzed isomerisation of allylic alcohols into corresponding saturated carbonyl compounds are given below (Figure 7).[18]

We initiated a systematic study for this attractive useful reaction pathway with Grubbs' catalyst **3**. Several secondary allylic alcohols were prepared by the Grignard reaction of aldehyde (Table 1). In all the cases, isomerisation of secondary allylic alcohols (**50**, **54-60**) proceeded smoothly into the corresponding ethyl ketone (**52**, **61-66**) in the presence of 10 mol% of catalyst **3**. As indicated in the Table 1, some of the subatrates (entry 1-4) were subjected to the isomerisation reaction in refluxing 1,2-dichloroethane to observe the temperature dependence of this transformation. In addition, this isomerisation reaction conditions tolerates wide range of sensitive functionalities such as ester in **55**, TBS-ether in **56**, and isopropylidene group in **57**. An interesting competitive ring closing metathesis verses isomerization was studied in case of *bis*-allylic alcohol **58** and observed the exclusive isomerization to *bis*-ketone **65** without trace amount of possible 10-membered carbocycle. Whereas, isomerization of sterically demanding allylic alcohol **60** was found to be sluggish under these reaction conditions. Traces of enone compounds were observed in the ^{1}H NMR spectrum of **51**, **64** and **66**.

In contrast, Hoye et al noticed that a secondary allylic alcohol undergoes a net fragmentation reaction with stoichiometric amount of Grubbs' catalyst **3** at room temperature, leading to a methyl ketone, with loss of one carbon atom (Scheme 9).[19] A systematic reactivity study of *bis*-olefin with α-allylic alcohol functionality in the ring closing metathesis reaction in the presence of **3** concluded that the unhindered α-allylic

Table 1

Entry	Substrate	Time	Solvent	Product	Yield %
1	 **50**	2 h	1,2-dichloroethane/ toluene	 **52**	70
2	 **54**	2 h	1,2-dichloroethane	 **61**	80
3	 **55**	3 h	1,2-dichloroethane/ toluene	 **62**	67
4	 **56**	4 h	1,2-dichloroethane/ toluene	 **63**	67
5	 **57**	2 h	toluene	 **64**	70
6	 **58**	1 h	toluene	 **65**	81
7	 **59**	1 h	toluene	 **66**	52
8	 **60**	24 h	toluene	---	---

alcohol functionality in the substrate increases the reaction rate comparatively depending upon catalyst loading. Use of 100 mol% of catalyst in the case of reactive allylic alcohol, rapidly converts into the corresponding ruthenium-carbene species **73**, and undergoes hydride shift (enolyl ruthenium hydride species **74**) then tautomerization to the oxoalkyl ruthenium hydride **75**, to produce the methyl ketone (path A in Figure 8).

We followed same reactions conditions with the allylic alcohols **54** and **69** using stoichiometric amount of **3** and delighted to find the net fragmentation leading to methyl ketones **70** and **71** respectively (Scheme 9). Although, the conventional type I or type II mechanisms (Figure 7) can not be ruled out in the present isomerisation reaction, we believed in Path B of Figure 8 with the analogy to the mechanism proposed by the Hoye et al, as a probable mechanism responsible for the isomerization of α-allylic secondary alcohols into the corresponding ethyl ketone by a double hydride migration pathway.

Scheme 9

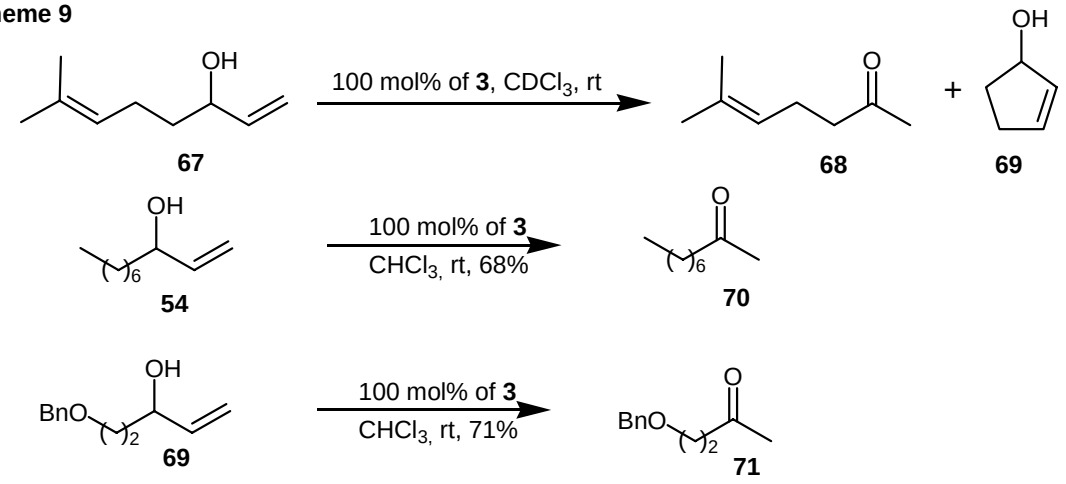
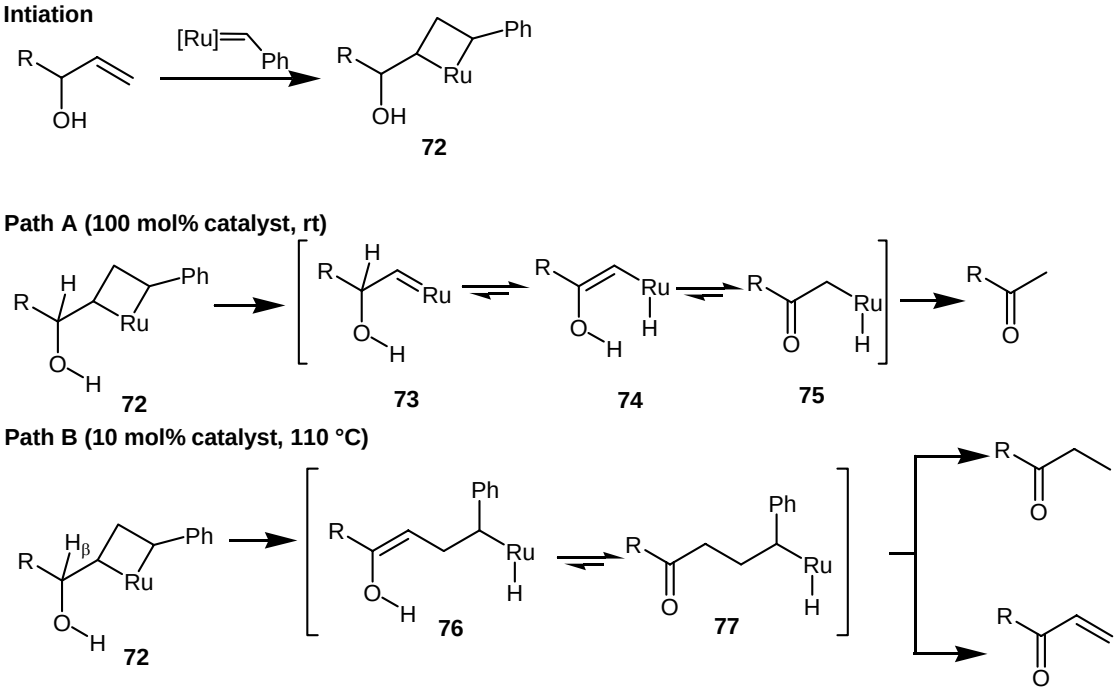


Figure 8: **Mechanism proposed for the isomerization *Vs* net fragmentaion of allylic alcohols**

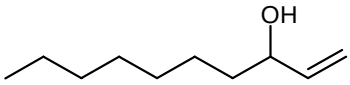


In conclusion, we have studied an unusual reaction pathway with the Grubbs' metathesis catalyst, which involves conversion of secondary allylic alcohols into the corresponding ethyl ketones and asserted the functional group tolerance in this isomerisation reaction.

General procedure for vinyl Grignard addition to the aldehydes:

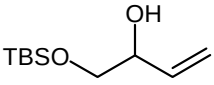
To a suspension of Mg turnings (0.24 g, 10.0 mmol) in anhydrous THF (15 mL) were added vinyl bromide (0.2 mL of total 2.0 mL of 5M solution in THF, 10.0 mmol) and a pinch of iodine. The mixture was stirred vigorously at room temperature, whereupon a rise in temperature and clouding of the reaction mixture occurred indicating the beginning of reaction. The remainder of the vinyl bromide (1.8 mL) solution was added dropwise with continued stirring at such a rate as to maintain a gentle reflux. The mixture was stirred for an additional 20 min at room temperature. The resulted vinyl magnesium bromide was added to a solution of aldehyde (5.0 mmol) in anhydrous THF (10 mL) through a cannula at 0 ^{o}C and stirred for 1 h at same temperature and slowly warmed upto room temperature. After 4-6 h, reaction was quenched with saturated aq. NH_4Cl solution, extracted with ether. Combined organic layer was washed with water, brine, dried (Na_2SO_4), and concentrated. The residue was purified on silica gel using EtOAc–light petroleum to afford the corresponding allylic alcohols.

Methyl 6-hydroxyoct-7-enoate (55)[20]:



Mol. Formula	: $C_{10}H_{20}O$
^{1}H NMR ($CDCl_3$, 200MHz)	: δ 0.90 (t, 3H, *J* = 6.7 Hz), 1.25 (br s, 10H), 1.42-1.60 (m, 2 H), 1.75 (br s, 1H), 4.00-4.15 (m, 1 H), 5.10 (dt, 1 H, *J* = 10.3, 1.2 Hz), 5.20 (dt, 1 H, *J* = 17.0, 1.2 Hz), 5.85 (ddd, 1 H, *J* = 17.0, 10.3, 6.2 Hz).
Elemental Analysis	**Calcd.:** C, 76.86; H, 12.90%.
	Found: C, 76.98; H, 13.19%.

1-^{t}Butyldimethylsilyloxy-2-hydroxy-But-3-ene (57)[21]:



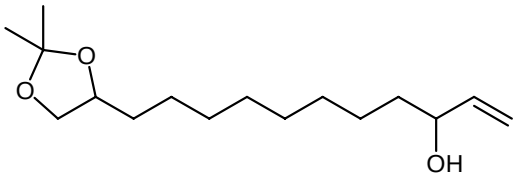
Mol. Formula : $C_{10}H_{22}O_2Si$

^{1}H NMR ($CDCl_3$, 200MHz) : δ 0.10 (s, 6H), 0.90 (s, 9H), 3.45 (dd, 1H, *J* = 10.0, 8.0 Hz), 3.65 (dd, 1H, *J* = 10.0, 3.5 Hz), 4.10-4.25 (m, 1H), 5.20 (dt, 1H, *J* = 10.2, 1.5 Hz), 5.35 (dt, 1H, *J* = 17.0, 1.5 Hz), 5.80 (ddd, 1H, *J* = 17.0, 10.2, 5.4 Hz).

Elemental Analysis **Calcd.:** C, 59.35; H, 10.96%.

Found: C, 59.65; H, 11.08%.

1,2-*O*-Isopropylidene-tridec-12-ene-11-ol (58):



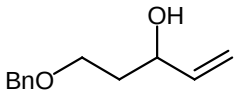
Mol. Formula : $C_{16}H_{30}O_3$

^{1}H NMR ($CDCl_3$, 200MHz) : δ 1.36, 1.41 (2 s, 14H), 1.55-1.70 (m, 8H), 3.49-3.55 (m, 1H), 3.90-4.17 (m, 3H), 5.11 (dq, 1H, *J* = 11.0, 1.5 Hz), 5.25 (dq, 1H, *J* = 16.8, 1.5 Hz), 5.80 (ddd, 1H, *J* = 16.8, 10.0, 6.0 Hz).

Elemental Analysis **Calcd.:** C, 71.07; H, 11.18%.

Found: C, 71.30; H, 11.21%.

1-(Benzyloxy)-pent-4-en-3-ol (60) [22]**:**



Mol. Formula : $C_{12}H_{16}O_2$

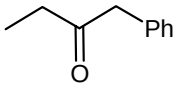
^{1}H NMR ($CDCl_3$, 200MHz) : δ 1.75-1.90 (m, 2H), 3.55-3.80 (m, 2H), 4.25-4.40 (m, 1H), 4.52 (br s, 2H), 5.10 (dq, 1H, *J* = 11.0, 1.0 Hz), 5.25 (dq, 1H, *J* = 16.8, 0 Hz), 5.85 (ddd, 1H, *J* = 16.8, 10.0, 5.5 Hz), 7.30-7.40 (m, 5H).

Elemental Analysis **Calcd.:** C, 74.97; H, 8.39%.

Found: C, 75.10; H, 8.41%.

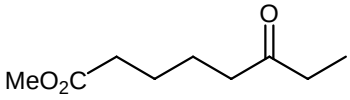
General procedure for isomerisation: To the allyl alcohol (0.5 mmol) in refluxing 1,2-dichloroethane or toluene (2 ml), Grubbs' catalyst **3** (0.05 mmol) was added portionwise. After the completion of reaction (TLC), solvent was evaporated and the residue purified on silica gel using light petroleum and ethyl acetate as an eluent.

1-Phenylbutan-2-one (52):



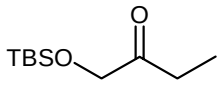
Yield	: 67%
Mol. Formula	: $C_{10}H_{12}O$.
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1})	: 3019, 2980, 2939, 1711, 1454, 1216.
^{1}H NMR ($CDCl_3$, 200MHz)	: δ 1.03 (t, 3H, *J* = 7.3 Hz), 2.45 (t, 2H, *J* = 7.3 Hz), 3.68 (s, 2H), 7.25-7.45 (m, 5H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 7.64, 35.06, 49.69, 126.84, 128.57, 129.27, 134.42, 208.78
Elemental Analysis	**Calcd.:** C, 81.04; H, 8.16%.
	Found: C, 81.36; H, 8.21%.

Methyl 6-oxooctonoate (63)[23]:



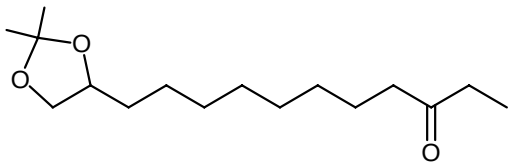
Yield	: 58%
Mol. Formula	: $C_9H_{16}O_3$.
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1})	: 2945, 1738, 1712, 1439, 1368, 1312, 1248, 1202, 1172, 1115.
^{1}H NMR ($CDCl_3$, 200MHz)	: δ 1.05 (t, 3H, *J* = 7.2 Hz), 1.51-1.69 (m, 4H), 2.25-2.50 (m, 6H), 3.66 (s, 3H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 7.57, 23.04, 24.23, 33.57, 35.62, 41.60, 51.21, 173.56, 210.83.
Elemental Analysis	**Calcd.:** C, 62.77; H, 9.36%.
	Found: C, 62.82; H, 9.44%.

1-^{t}Butyldimethylsilyloxy-butan-2-one (64)[24]:



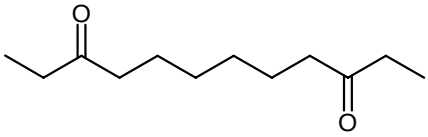
Mol. Formula	: $C_{10}H_{22}O_2Si$
Yield	: 67%
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1})	: 3019, 2953, 2400, 1715, 1465, 1215.
^{1}H NMR ($CDCl_3$, 200MHz)	: δ 0.01 (s, 6H), 0.90 (s, 9H), 1.00 (t, 3H, *J* = 7.3 Hz), 2.45 (q, 2H, *J* = 7.3 Hz), 4.08 (s, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ –5.59, 7.16, 18.22, 25.72, 31.53, 69.06, 211.42.
Elemental Analysis	**Calcd.:** C, 59.35; H, 10.96%. **Found:** C, 59.45; H, 11.88%.

1,2-*O*-Isopropylidene-tridecan-11-one (65):



Mol. Formula	: $C_{16}H_{30}O_3$
Yield	: 70%
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1})	: 2938, 2931, 2856, 1714, 1369, 1246, 1215, 1060.
^{1}H NMR ($CDCl_3$, 200MHz)	: δ 1.02 (t, 3H, *J* = 7.3 Hz), 1.26 (br s, 10H), 1.33, 1.38 (2 s, 6H), 1.45-1.65 (m, 4H), 2.30-2.45 (m, 4H), 3.40-3.55 (m, 1H), 3.95-4.10 (m, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 7.79, 23.85, 25.69, 26.90, 29.25, 29.51, 33.55, 35.79, 42.34, 69.46, 76.08, 108.50, 211.79.
Elemental Analysis	**Calcd.:** C, 71.07; H, 11.18%. **Found:** C, 71.26; H, 11.33%.

Dodecane-3,10-dione (66)[25]:



Mol. Formula : $C_{12}H_{22}O_2$

Yield : 81%

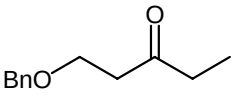
^{1}H NMR ($CDCl_3$, 200MHz) : δ 1.05 (t, 6 H, *J* = 7.3 Hz), 1.21-1.34 (m, 4 H), 1.50-1.65 (m, 4 H), 2.40 (q, 8 H, *J* = 7.2 Hz).

^{13}CNMR ($CDCl_3$, 50 MHz) : δ 7.67, 23.55, 28.88, 35.72, 42.12, 211.57.

Elemental Analysis **Calcd.:** C, 72.68; H, 11.18%.

Found: C, 72.59; H, 11.18%.

1-(Benzyloxy)-pentan-3-one (67)[26]:



Yield : 52%

Mol. Formula : $C_{12}H_{16}O_2$

IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) : 2936, 2868, 1713, 1107.

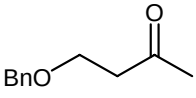
^{1}H NMR ($CDCl_3$, 200MHz) : δ 1.05 (t, 3 H, *J* = 7.2 Hz), 2.45 (q, 2 H, *J* = 7.2 Hz), 2.67 (t, 2 H, *J* = 6.0 Hz), 3.7 (t, 2 H, *J* = 6.0 Hz), 4.50 (s, 2 H), 7.25-7.35 (m, 5 H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ –5.59, 7.53, 36.46, 42.45, 65.38, 73.14, 127.58, 128.31, 138.13, 209.40.

Elemental Analysis **Calcd.:** C, 74.97; H, 8.39%.

Found: C, 74.77; H, 8.22%.

1-(Benzyloxy)-butan-3-one (72):



Yield : 71%

Mol. Formula	: $C_{11}H_{14}O_2$
^{1}H NMR (CDCl$_3$, 200MHz)	: δ 2.18 (s, 3H), 2.72 (t, 2H, *J* = 6.2 Hz), 3.74 (t, 2H, *J* = 6.2 Hz), 4.51 (s, 2H), 7.25-7.40 (m, 5H).
^{13}C NMR (CDCl$_3$, 50 MHz)	: δ 30.39, 43.77, 65.27, 73.21, 127.65, 128.35, 138.09, 207.09.
Elemental Analysis	**Calcd.:** C, 74.13; H, 7.92%.
	Found: C, 74.00; H, 7.88%.

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List of Publications

1. Towards the total synthesis of clavosolide A. **Pedduri Yakambram**; Vedavati G. Puranik; Mukund K. Gurjar, *Tetrahedron Letters*, **2006**, *47*, 3781-3783.
2. Toward a synthesis of the antitumor macrolide peloruside A: a chiral pool approach for the C(1)–C(11) segment. Mukund K. Gurjar; **Yakambram Pedduri**; C. V. Ramana; Vedavati G. Puranik; Rajesh G. Gonnade, *Tetrahedron Letters*, **2004**, *45*, 387-390.
3. Temperature-dependent isomerisation versus net fragmentation of secondary allylic alcohols with Grubbs' catalyst. Mukund K. Gurjar; Pedduri Yakambram, *Tetrahedron Letters*, **2001**, *42*, 3633-3636.