SYNTHETIC STUDIES TOWARD SUPERSTOLIDE A, CENTROLOBINE AND SOME RADICAL REARRANGEMENT

BY

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Synthetic Studies Toward Superstolide A, Centrolobine and Some Radical Rearrangement

A THESIS

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BY

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NATIONAL CHEMICAL LABORATORY

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JUNE 2008

DEDICATED

TO MY BELOVED

PARENTS

DECLARATION

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

Pune-411008 **(Rita Pal)**

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CERTIFICATE

The research work presented in thesis entitled "**Synthetic Studies Toward Superstolide A, Centrolobine and Some Radical Rearrangement**" has been carried out under my supervision and is a bonafide work of **Ms. Rita Pal**. This work is original and has not been submitted for any other degree or diploma of this or any other University.

Pune-411008

June 2008

(Dr. M. K. Gurjar)

Research Guide

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Rita Pal

ABBREVIATIONS

Ac	-	Acetyl
AcOH	-	Acetic acid
Ac_2O	-	Acetic anhydride
AIBN	-	Azaisobutyronitrile
BF3:OEt2	-	Boron trifluoride diethyl ether complex
Bn	-	Benzyl
BnBr	-	Benzyl bromide
BzCl	-	Benzoyl chloride
BuLi	-	Butyl Lithium
DBTO	-	Di-*tert*-butyltin oxide
DBU	-	1,8-Diazabicyclo [5.4.0]undec-7-ene
DCM	-	Dichloromethane
DDQ	-	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DET	-	Diethyltartrate
DIAD	-	Diisopropylazodicarboxylate
DIBAL-H	-	Diisobutylaluminiumhydride
DMP	-	2,2-Dimethoxypropane
DMF	-	*N*, *N'*-Dimethylformamide
DMAP	-	*N*,*N'*-Dimethylaminopyridine
DMSO	-	Dimethyl sulfoxide
CuCN	-	Copper (I) Cyanide
EtOH	-	Ethanol
Et	-	Ethyl
Et_2O	-	Diethyl ether
EtOAc	-	Ethyl acetate
Et_3N	-	Triethylamine
IBX	-	Iodoxybenzoic acid
Im	-	Imidazole

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

GENERAL REMARKS

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

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

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

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

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

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

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

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

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

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

CONTENTS

ABSTRACT

Research Student	Rita Pal
Research Guide	Dr. Mukund K. Gurjar
Title of Thesis	"Synthetic Studies Toward Superstolide A, Centrolobine and Some Radical Rearrangement"
Registration no	E1/83/Ph.D/2005
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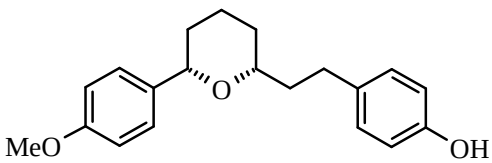
Abstract

The thesis entitled "**Synthetic Studies Toward Superstolide A, Centrolobine and Some Radical Rearrangement**" consists of three chapters and each chapter is further subdivided into following sections: Introduction, Present work, Experimental, Spectroscopic data and References. Chapter 1 describes the synthesis of (−)-centrolobine. Chapter 2, section I, deals with synthesis of C21-C26 fragment of superstolide A using chiral pool strategy, whereas section II involves stereoselective synthesis of C21-C26 fragment of superstolide A. The final chapter 3 highlights some radical rearrangements deals with extensive Ueno reaction.

Chapter 1: Synthetic studies toward (−)-centrolobine

(−)-Centrolobine **1** is a crystalline substance isolated from the heartwood of *Centrolobium robustum* and from the stem of *Brosinum potabile* in the Amazon forest. Although the basic structure was elucidated in 1964 by total synthesis of the racemic methyl ether, its absolute configuration has been unequivocally established in 2002.



(-)-Centrolobine **1**

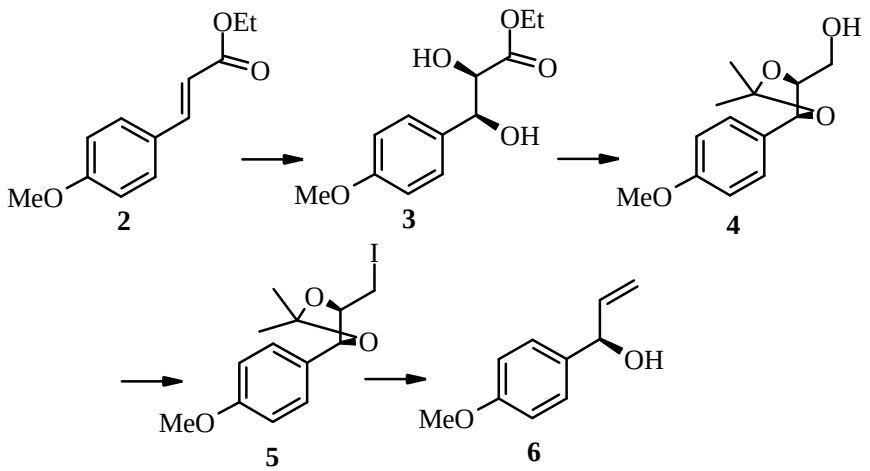
Figure 1

(−)-Centrolobine **1**, an antibiotic showed strong antilesmanial activity with calculated LD_{50} = 77nM. Our synthetic strategy for the construction of the crucial *syn*-

disubstituted tetrahydropyran ring of (−)-Centrolobine **1** was based on the ring closing metathesis as the key step.

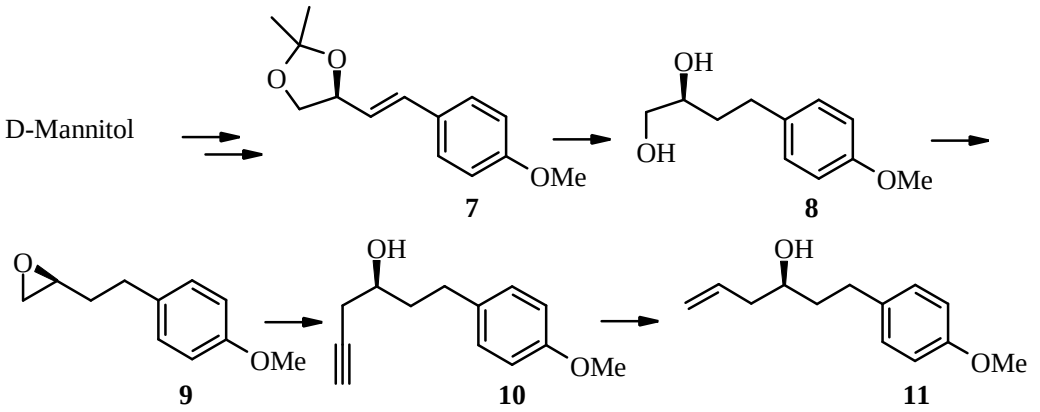
The synthetic strategy towards the total synthesis of (−)-centrolobine **1** relies on the enantioselective preparation of the key fragment **6** via a Sharpless asymmetric dihydroxylation and D-mannitol as a chiral pool source for the preparation of other coupling partner.

Synthesis of the olefinic alcohol **6** (Scheme 1) was initiated by the Sharpless asymmetric dihydroxylation of the unsaturated ester **2** with $(DHQ)_2PHAL$ as ligand. Isopropylidenation of the resulting diol **3** and subsequent reduction using DIBAL-H provided the alcohol **4.** Primary alcohol **4** was converted to its iodo derivative **5**. A facile elimination of **5** using freshly activated Zn in refluxing ethanol accomplished the corresponding substituted allylic alcohol **6**.



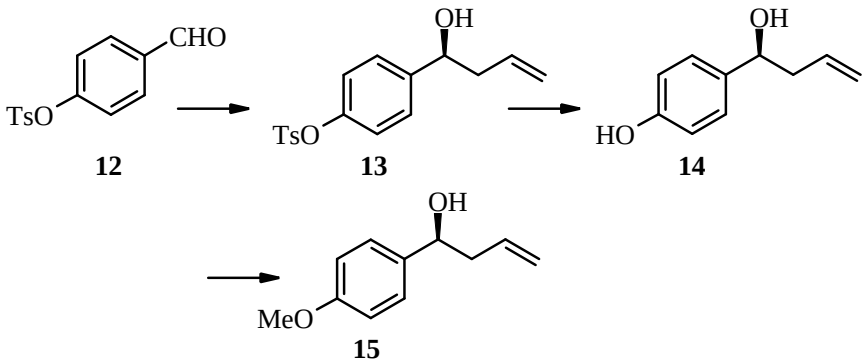
Scheme 1

The synthesis of the other component **11** commenced with **7**, which was synthesized according to the literature procedure from D-mannitol (Scheme 2). Hydrogenation using 10% Pd/carbon followed by acid catalyzed de-isopropylidenation gave the diol **8**. On selective mono tosylation, followed by substitution reaction, diol **8** was converted to epoxide **9**. Opening of the epoxide **9** with an excess of lithium acetylide and partial hydrogenation of the resulting acetylene **10** with Lindlar catalyst achieved the olefinic alcohol **11**. The attempted coupling reactions between fragment **6** and **11** were unsuccessful in our hand. So, we planned an alternative route to construct the pyran ring by coupling alcohol and vinyl epoxide, followed by RCM cyclization in a tandem fashion.



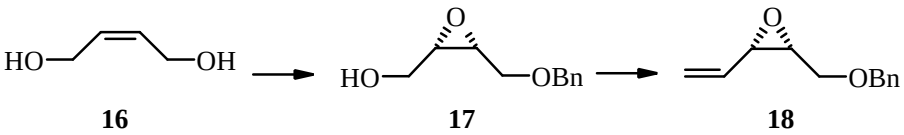
Scheme 2

In the revised route one of the stereogenic centers was established in a reagent-controlled fashion, whereas the other capitalized on a stereo-controlled asymmetric allylation. For synthesizing fragment **15**, we followed Keck allylation on 4-tosyloxybenzaldehyde **12**. Detosylation followed by selective methylation of phenolic hydroxy group accomplished the fragment **15**.



Scheme 3

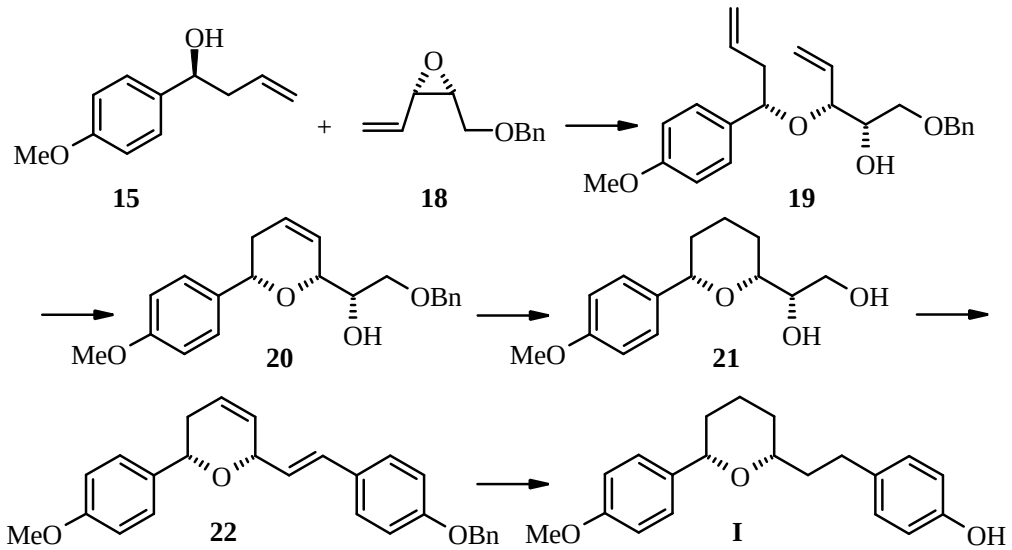
The other fragment **18** was synthesized starting from *cis*-2-butene-1,4-diol. Accordingly, the alcohol **16** was mono protected as its benzyl ether followed by Sharpless asymmetric epoxidation with L-(+)-DET afforded the epoxy alcohol **17**.



Scheme 4

IBX oxidation of the primary hydroxyl group to the corresponding aldehyde and Wittig reaction using methyltriphenylphosphonium bromide afforded vinyl substituted epoxide **18**.

After having enantiomerically pure homoallylic alcohol **15** and the vinyl epoxide derivative **18** in hand, we proceeded further for the Mioskowski's Lewis acid ($BF_3{\cdot}OEt_2$) mediated epoxide opening reaction to afford **19**. On exposure of **19** to Grubbs' second generation catalyst furnished the pyran ring **20**. Double bond reduction as well as benzyl ether cleavage was accomplished in one pot by exposure of **20** to Pd/C catalyst under hydrogen atmosphere to afford the diol **21**. Compound **21** was then treated with $NaIO_4$ impregnated over silica gel in dichloromethane to afford the aldehyde, which on Wittig reaction between the 4-benzyloxybenzyl triphenylphosphonium bromide furnished **22**. Reduction of the double bond and cleavage of the benzyl ether by catalytic hydrogenation gave (−)-centrolobine **1**.



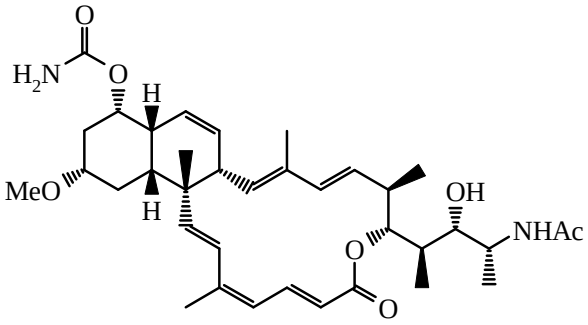
Scheme 5

In summary, a new synthetic approach has been designed for the stereoselective synthesis of (−)-centrolobine **1** following Lewis acid mediated epoxide opening followed by ring-closing metathesis reaction for the first time.

CHAPTER 2: Towards the synthesis of superstolide A (23)

Section I: A chiral pool approach for the synthesis of C21-C26 segment of superstolide A (23)

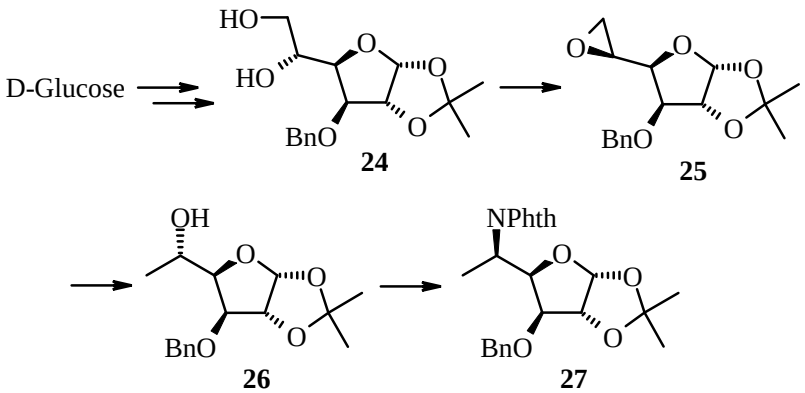
Superstolide A (**23**) is a member of a structurally unique family of cytotoxic macrolide, isolated by Minale and co-worker from the new Caledonian deep-water sponge *Neosiphonia superstes*. This structurally novel macrolide shows nM activity against murine and human leukemia, colon, and nasopharyngeal cells.



Superstolide A (**23**)

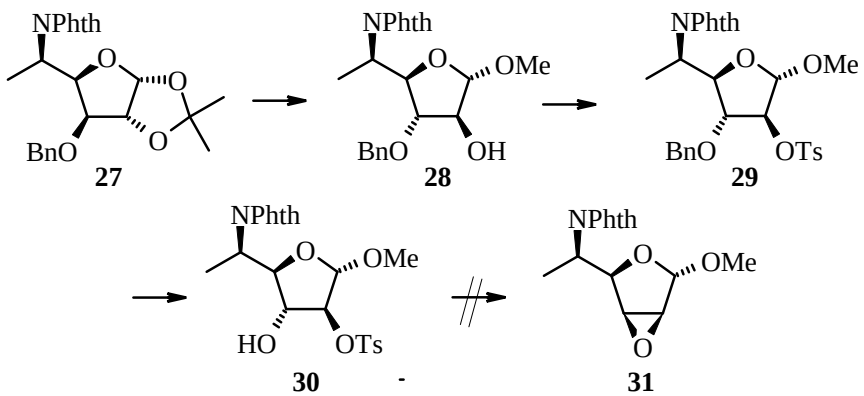
Figure 2

Our synthetic strategy commenced with **24**, which was easily obtained from D-(+)-glucose. The diol **24**, by a sequence of protection deprotection protocol, converted to the epoxide **25**, which on LAH treatment furnished alcohol **26**. Hydroxyl group of **26** was transformed to phthalimide derivative **27** following standard Mitsunobu reaction conditions.



Scheme 6

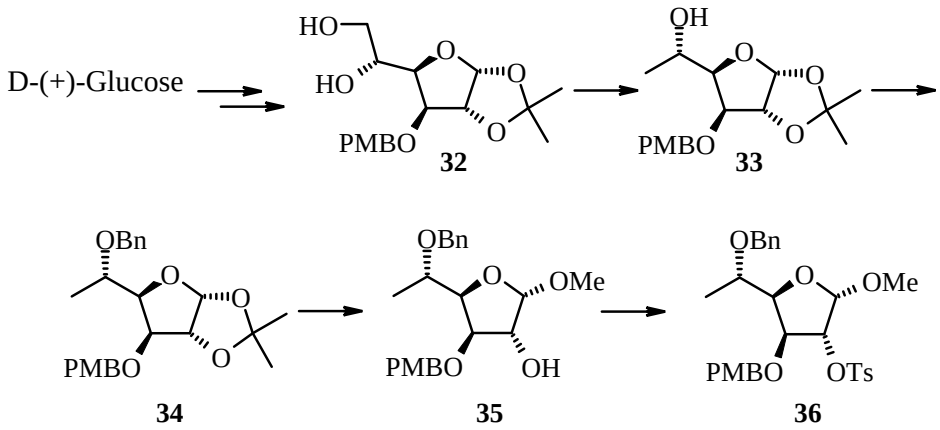
Deprotection of the 1,2-isopropylidene group and concomitant methyl glycosidation of **27** was accomplishd using conc. H_2SO_4(cat.) to obtain methyl acetal **28**. Derivatisation of newly generated hydroxyl group as its tosyl ester furnished **29**.



Scheme 7

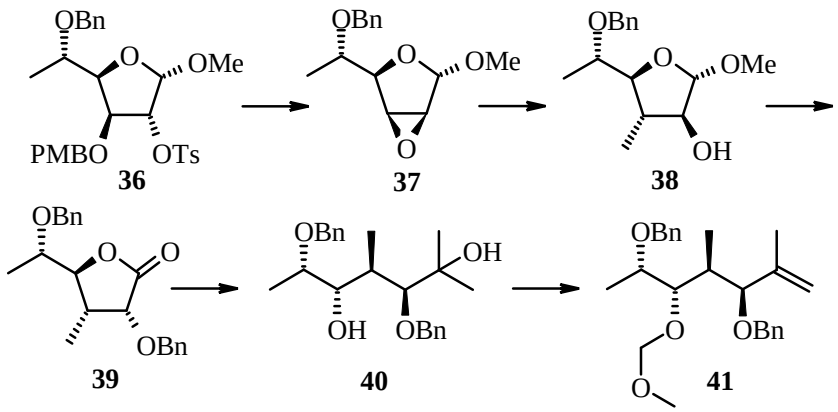
Cleavage of benzyl ether of **29** by $TiCl_4$ afforded compound **30**. Treatment of potassium carbonate in methanol to obtain epoxide **31** resulted in decomposition of starting material.

Having encountered the failure at this stage of our synthetic strategy, we decided to modify our synthetic pathway. We started with the known diol **32**, which was easily obtained from D-(+)-glucose. Following the standard synthetic sequence compound **33** was synthesized from **32**. The hydroxyl group of **33** was converted as its benzyl ether to obtain compound **34**. Cleavage of the 1,2-*O*-isopropylidene group of compound **34** and concomitant methyl glycosidation was achieved by methanolic HCl. The newly generated hydroxyl group was converted to its tosyl derivative **36**.



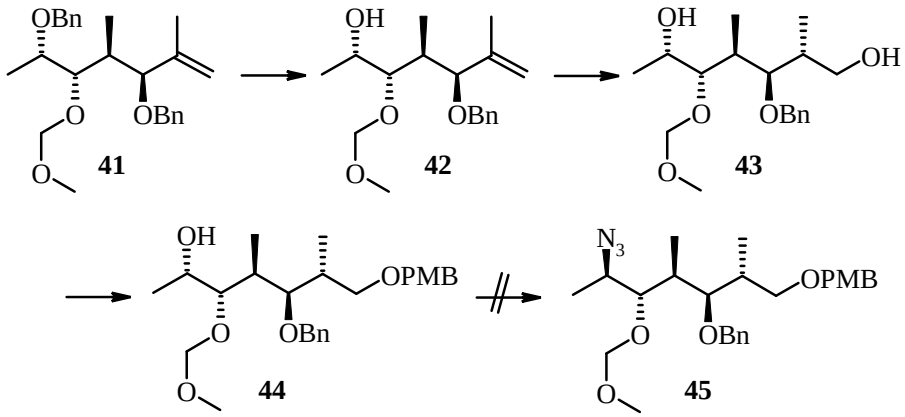
Scheme 8

The cleavage of PMB ether by DDQ afforded alcohol, which on potassium carbonate treatment converted to epoxide **37**. On treatment of excess MeMgCl, epoxide **37** was transformed to alcohol **38**. The free hydroxyl group was protected as its benzyl ether.



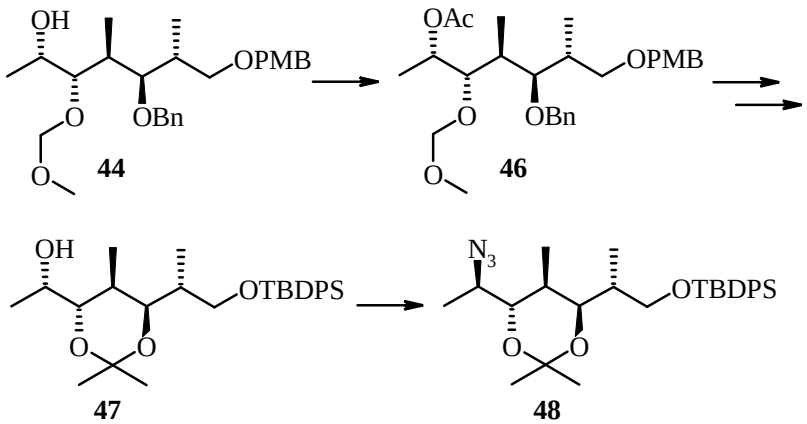
Scheme 9

Hydrolysis of methyl furanoside afforded the lactol, which was oxidized to lactone **39** by PDC. Treatment of excess methyl magnesium chloride on lactone **39** produced the diol **40**. The secondary alcohol was selectively protected as its methoxy methyl ether by MOMCl, whereas the tertiary alcohol was eliminated in basic medium to generate the *exo*-methylene moiety **41**.



Scheme 10

Both the benzyl ether was cleaved by Na-Napthaline treatment, and the hydroxyl group at allyl position was selectively protected as benzyl ether (Scheme 10). Regeioselective hydroboration of **42** was performed with 9-BBN to get the diol **43**. The primary hydroxyl group was selectively protected as its PMB ether **44**. For the introduction of amine functionality at this stage, we tried for Mitsunobu reaction, however only starting material was recovered. Being unsuccessful in the installation of the amine functionality in a single step, we opted for a stepwise procedure, mesylation followed by substitution. Unfortunately, the product obtained was not the desired azide **45**.



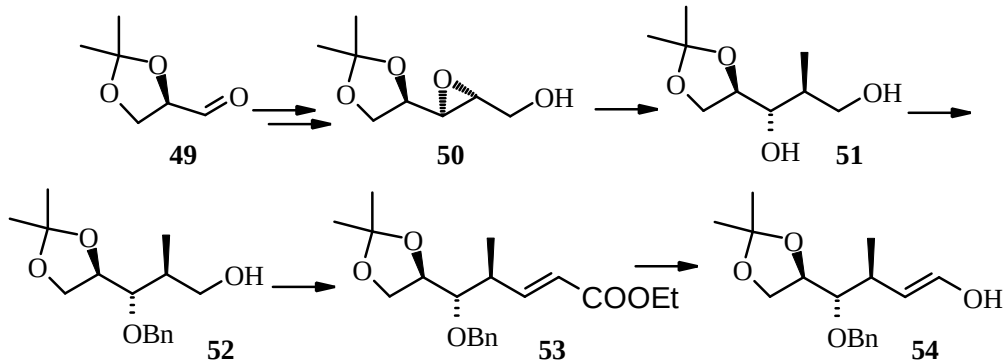
Scheme 11

So, we planed to change our protecting groups to overcome the aforesaid failure (Scheme 11). A series of protection deprotection afforded compound **47**. Finally, a two-step sequence based on the deprotection of the acetate group, mesylation of the resulting alcohol, and introduction of the azido group with NaN_3 through an S_N2 process readily afforded the desired azido polyol **48** without the need for purification of either intermediate.

In conclusion, a segment corresponding to C21-C26 (**48**) of superstolide A (**23**) has been successfully synthesized using chiron approach from D-(+)-glucose.

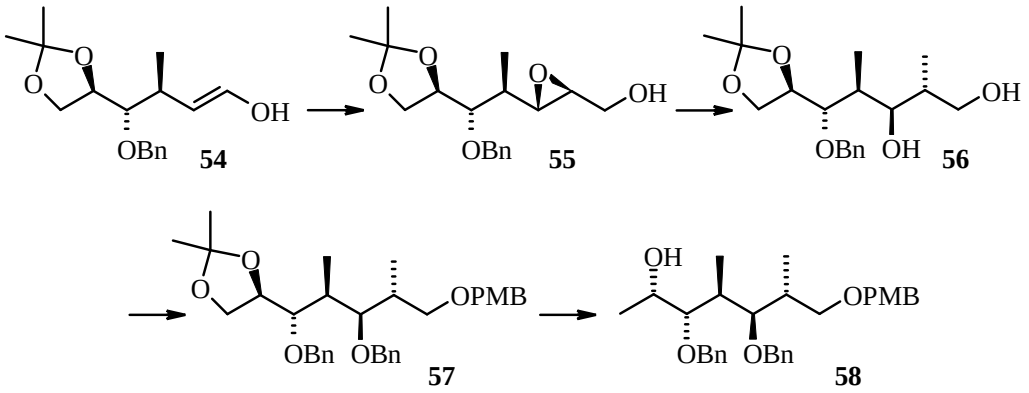
Section II: Stereoselective synthesis of C21-C26 fragment of superstolide A(23)

The synthesis of the targeted segment was initiated with the epoxide **50**, readily obtained from (*R*)-2,3-*O*-isopropylidene-D-glyceraldehydes **49**. Upon treatment of **50** with excess of MeMgCl in presence of CuCN at 0 ^oC, methylation took place at the α position of the hydroxyl group with complete regio and stereo-selectivity to afford the 1,3-diol **51** as the sole product. By some protection deprotection strategy, **51** was converted to compound **52**. The alcohol thus obtained was transformed into the unsaturated ester **53** by IBX oxidation followed by direct Wadsworth-Horner-Emmons reaction with exclusive *trans* isomer. Reduction of the ester with DIBAL-H, afforded the unsaturated alcohol **54**.



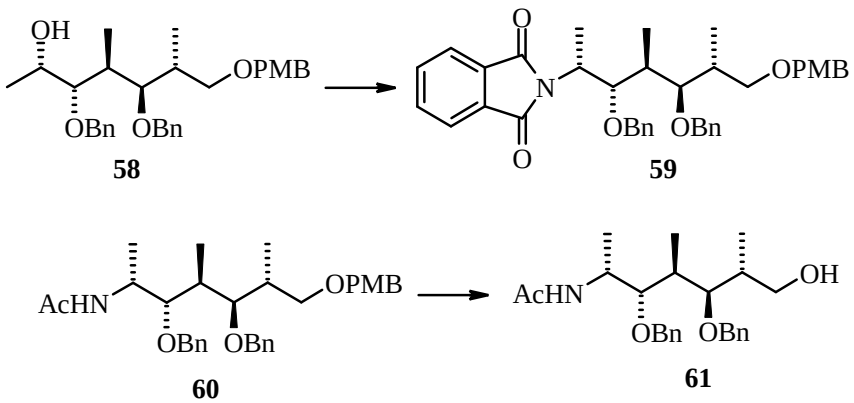
Scheme 12

The exposure of the ensuing allylic alcohol **54** to sharpless asymmetric epoxidation afforded the required epoxide **55**. The epoxide **55** by the same reaction condition, that is, regioselective ring opening with MeMgCl provided diol **56**. Primary alcohol selectively protected as its PMB ether, whereas the secondary hydroxyl group as benzyl ether to obtain **57**.



Scheme 13

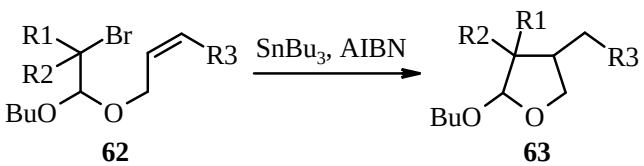
Our next concern was to introduce the amide functionality. After deprotection of isopropylidene group of compound **57**, the secondary hydroxyl group was inverted following a standard protocol to afford **58**. Mitsunobu reaction was effectively carried out on the alcohol **58** in presence of phthalimide to afford **59**. Phthalimide moiety was reduced to amine by hydrazine hydrate and direct protection with acetate provided compound **60**. Finally, PMB ether cleavage with DDQ afforded the target fragment **61**.



Scheme 14

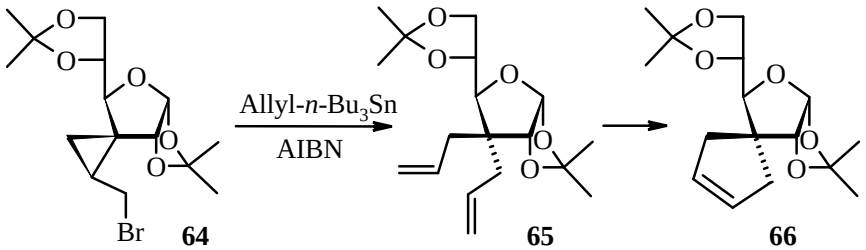
In conclusion, we have accomplished a stereoselective synthesis of C21-C26 (**61**) segment of superstolide A (**23**) in a linear fashion via shorter synthetic sequence starting from 2,3-*O*-isopropylidene-D-gleceraldehyde **49**.

Chapter-3: ***Studies of Some Useful Radical Rearrangement, Extensive Ueno Reaction***



Scheme 15

Stork and Ueno have demonstrated that mixed bromo acetal derived from the allylic alcohols undergo stereoselective radical cyclization to form the *trans*-tetrahydrofuran derivative. This cyclization method is particularly useful for C-C bond formation at the sterically bulky carbon.



Scheme 16

A novel methodology has been developed in our group for the installation of gem-diallyl functionality by trapping the homoallyl radical generated *in situ* with allyltri-*n*-butylstannane.

Ueno reaction is very useful for construction of those rings especially sterically hindered systems. Unfortunately, in Ueno substrates there were no such functional groups for further manipulation to the natural products.

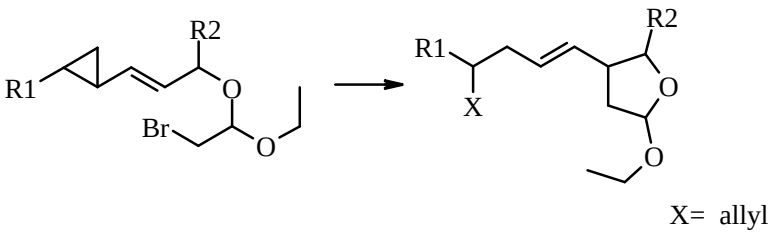
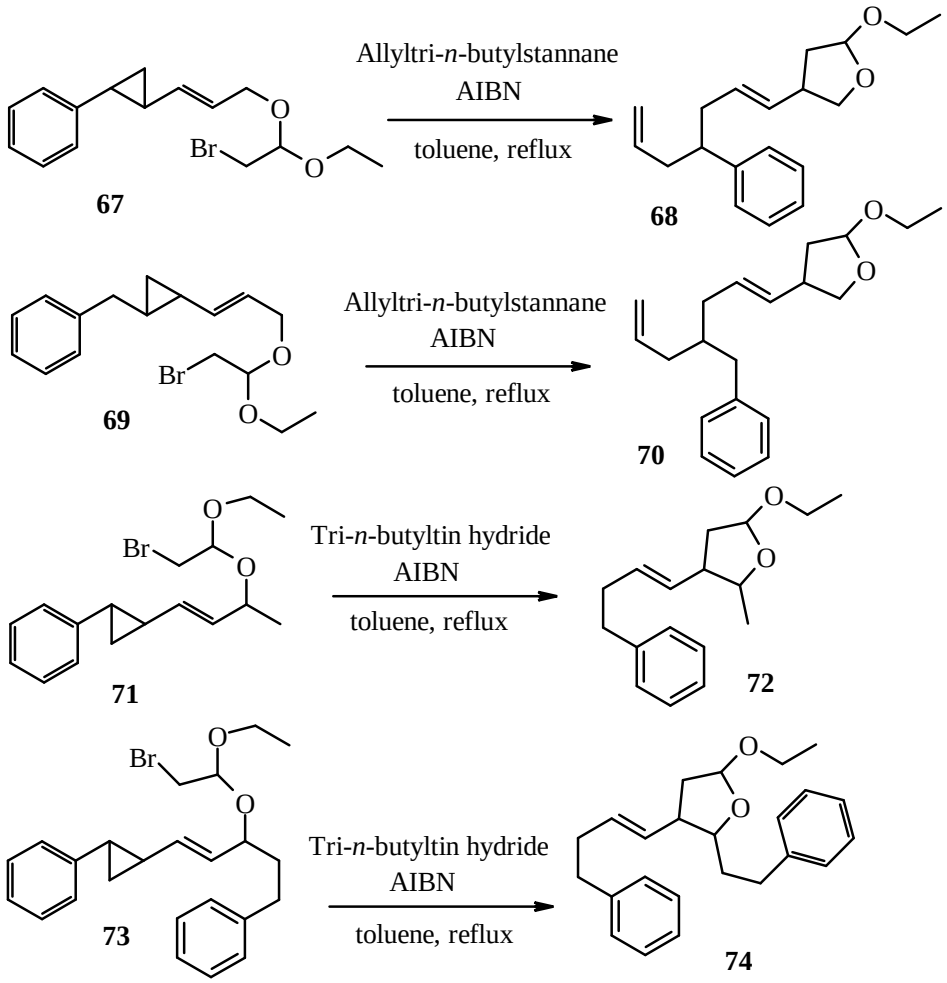


Figure 3

In our laboratory cyclopropyl methyl radical was utilized to generate diallyl compounds, which was very constructive to incorporate allyl group where active methylene group was not present. Based on Ueno reaction and our approach, we intended to utilize and couple these two approaches as a radical mediated domino reaction wherein the rearrangement is triggered by allyltri-*n*-butylstannane.

These reactions were conducted using azobisisobutyronitrile (AIBN) as initiator in refluxing toluene. In case of bromo acetal derived from primary alcohol, we obtained the expected product, however with bromo acetal derived from secondary alcohol there was no reaction with allyltri-*n*-butylstannane, only starting material was

recovered. Surprisingly, on treatment of tri-*n*-butyltin hydride, we obtained the furan derivative as well as cyclopropyl ring opening product with excellent yield.



Scheme 17

In conclusion, a useful extension of Ueno reaction has been developed as an alternative for the incorporation of allyl units in systems where active methylene group are not present. Unfortunately, the scope of the reaction with respect to substitution patterns of the stannane is much more restricted, as mentioned above.

CHAPTER 1

Synthetic Studies Toward (−)-centrolobine

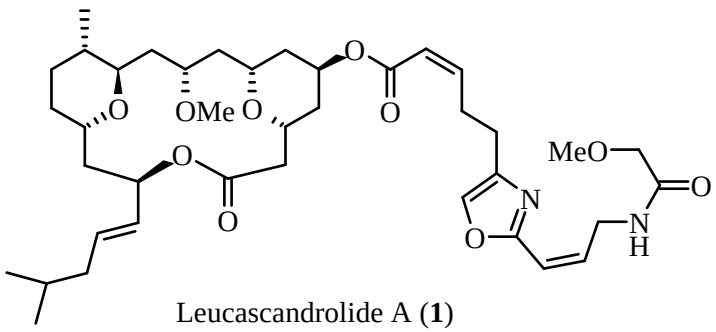
INTRODUCTION

Introduction

The search for biologically active natural products for the development of new drugs has a long tradition[1]. Most of such compounds were isolated from plants, animals, fungi, and microorganisms like bacteria, which exist in great variety on earth. Total synthesis is playing a major role in the drug discovery process since it allows exploration in chemical biology through molecular design and mechanistic study.[2]

2,6-Disubstituted tetrahydropyran scaffolds have gained prominence recently owing to their excellent biological properties. This unit is also present in several natural products with *cis* stereo connectivity at the 2,6-positions. Some recent examples which fall into this class, include leucascandrolides **1**, phorboxazoles **2**, (+)-SCH 351448 (**3**), dactylolide **4** etc. There are some diarylheptanoid natural products containing a tetrahydropyran ring with 2,6-disubstitution, as for examples, calyxin (**8a**-**12**), diospongins (**6**,**7**), (−)-centrolobine[1] **14**, (−)-de-*O*-methylcentrolobine **13** and others.

Leucascandrolide A (**1**)[3] (Figure 1) was isolated from the sponge *Leucascandra caVeolata* by Pietra and co-workers in 1996. The natural product displays strong *in vitro* cytotoxicity against KB and P388 cancer cell lines and is also a potent antifungal inhibiting the growth of *Candida albicans*.

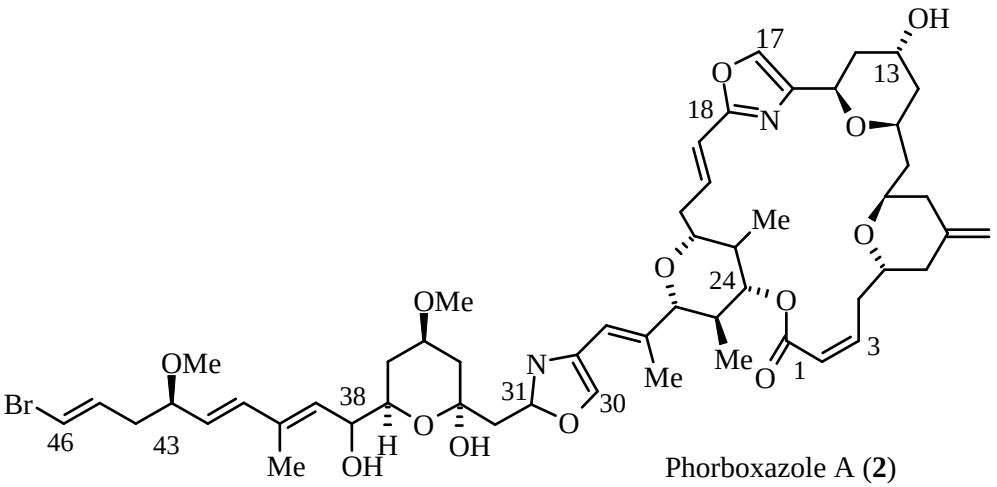


Leucascandrolide A (**1**)

Figure 1

Phorboxazole A (**2**)[4] (Figure 2) and its C13 epimer phorboxazole B are remarkable natural products isolated recently from an Indian Ocean sponge *Phorbas sp*. Bioassays against the National Cancer Institute panel of 60 human solid tumor cell lines revealed extraordinary activity against the entire panel; the mean GI_{50} value was 1.58 10^{-9} M for both **1** and **2**. Some cell lines were completely inhibited at the lowest level tested.

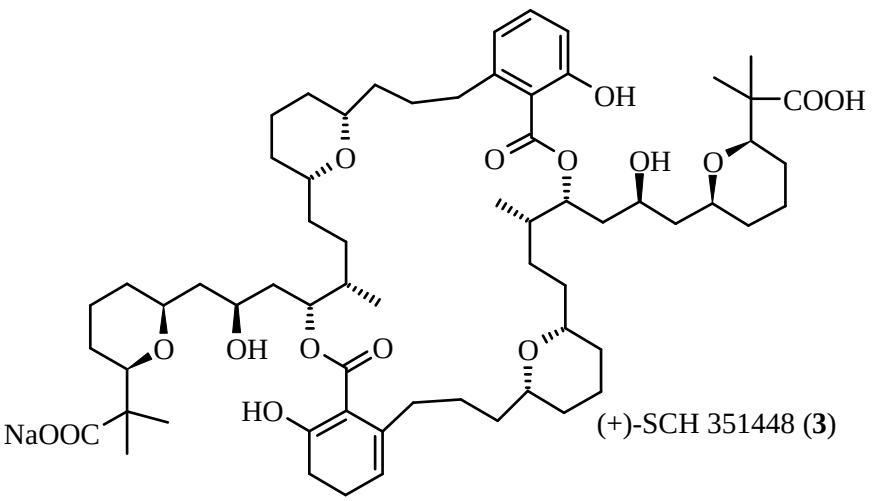
Particularly noteworthy, phorboxazole A (**2**) inhibited the human colon tumor cell line HCT-116 and the breast cancer cell line MCF7 with GI_{50} values of 4.36 10^{-10} M and 5.62 10^{-10} M, respectively.



Phorboxazole A (**2**)

Figure 2

SCH 351448 (**3**)[5] is a novel activator of low-density lipoprotein receptor (LDL-R) promoter with an IC_{50} of 25 μM, which was discovered from the organic extract of the fermentation groth of a *Micromonospora* microorganism (Figure 3).

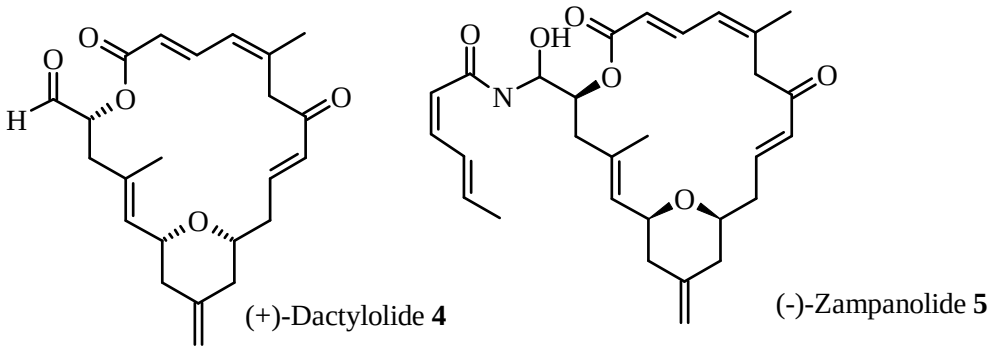


(+)-SCH 351448 (**3**)

Figure 3

Dactylolide **4** (Figure 4)[6] is a bicyclic macrolactone that was isolated from the Vanuatu sponge Dactylospongia in 2001 by Riccio and co-workers. While dactylolide is moderately cytotoxic toward L1210 (lymphatic leukemia) and SK-OV-3 (ovarian cancer) cells, causing 63% and 40% growth inhibition, respectively, at 3.2 $\mu g mL^{-1}$ (8.3 μM), the

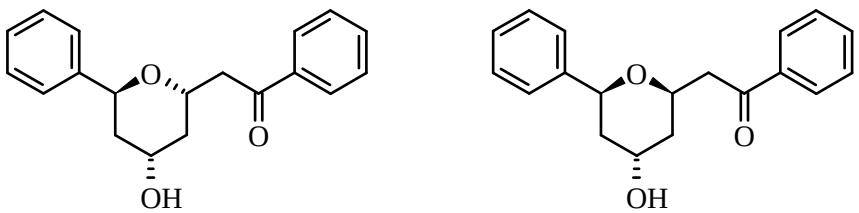
structurally related natural product zampanolide[7] **5** shows significantly greater cytotoxic activity, with IC_{50} values of 1–5 nM against several cell lines.



(+)-Dactylolide **4** (-)-Zampanolide **5**

Figure 4

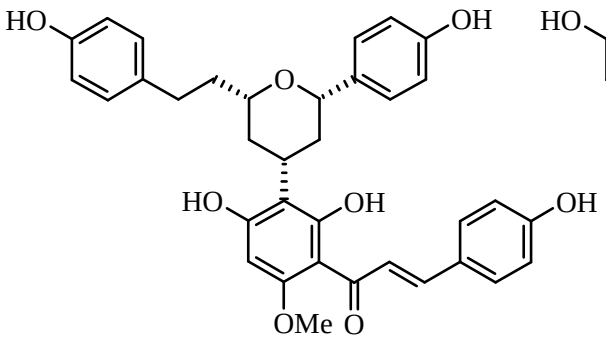
Diospongin A (**6**) and B (**7**)[8] (Figure 5) possess six-membered cyclic ether cores with aromatic side chains, isolated from the rhizomes of *Dioscorea spongiosa via* bioassay-guided fraction. These are exhibited potent inhibitory activity of ^{45}Ca release at 200 μM (30.5%) and 20 μM (18.2%), respectively.



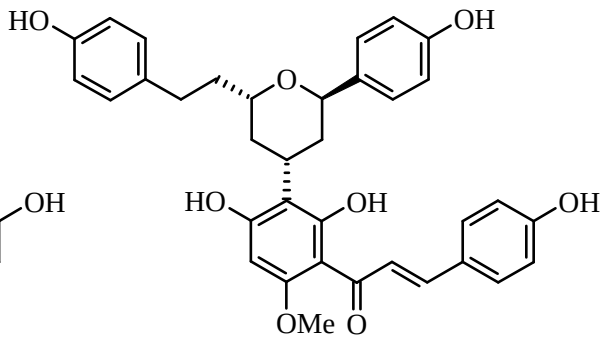
(-)-Diospongin B (**7**) (-)-Diospongin A (**6**)

Figure 5

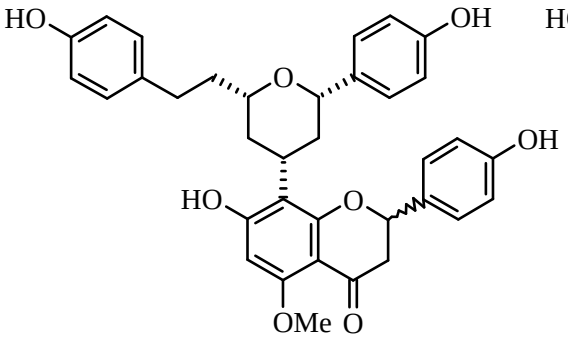
Calyxin F (**8b**),[9] calyxin G (**9a**) calyxin K (**10a**) and calyxin I (**11**) are novel diarylheptanoids, were isolated from the seed of *Alpinia blepharocalyx* seeds, which are used for the treatment of stomach disorders in Chinese medicine. Calyxins were showed interesting antiproliferative activity against carcinoma cells especially epicalyxin F is most potent membeb of the calss and possessed potent antiproliferative activity toward HT-1080 fibrosacoma which is stronger than that of 5-fluorouracil, a clinically used drug for the treatment of human tumor and it is also active towards colon 26-L5 carcinoma with ED_{50} values of 1.71 and 0.89 μM, respectively (Figure 6).



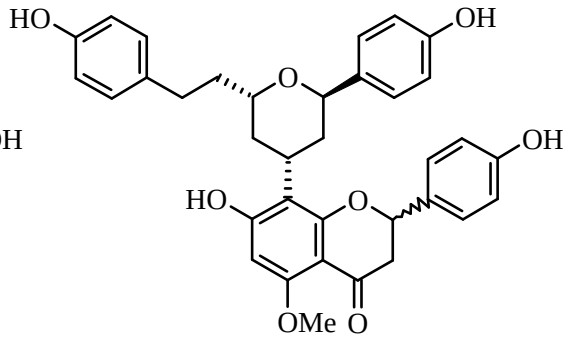
Epicalyxin F (**8a**)



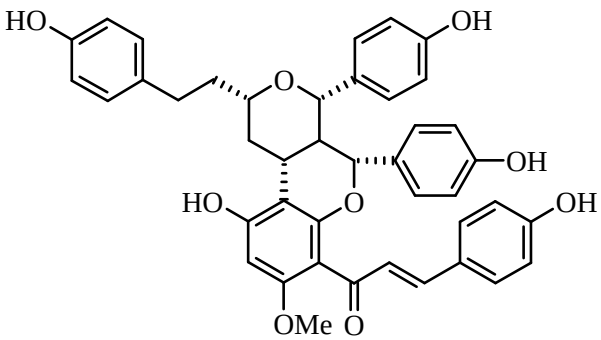
Calyxin F (**8b**)



Calyxin K (**10a**) and
Epicalyxin K (**10b**)



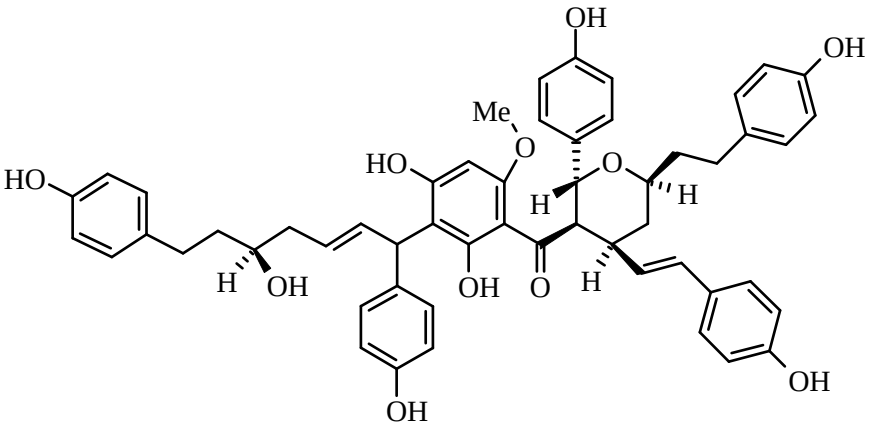
Calyxin G (**9a**) and
Epicalyxin G (**9b**)



Calyxin I (**11**)

Figure 6

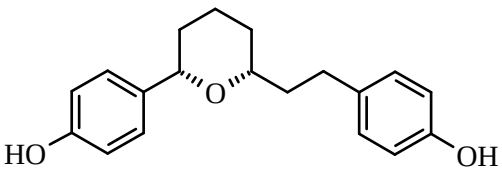
There was another calyxin named as belpharocalyxin A (**12**)[10] isolated from the same seed *Alpinia blepharocalyx*, possessing the diarylheptanoied structure (Figure 7).



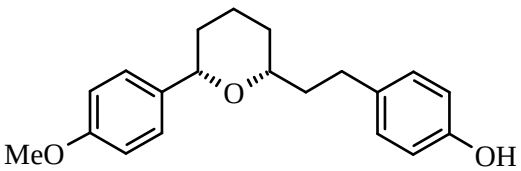
Belpharocalyxin A (**12)**

Figure 7

(−)-Centrolobine **14**[11] (Figure 8) was isolated from the heartwood of *Centrolobium robustum* and from the stem of *Brosinum potabile*.[1,2] Recently, (−)-centrolobine **14** and related natural products (−)-de-*O*-methylcentrolobine **13** have been shown to be active against Leishmania amazonensis promastigotes; a parasite associated with leishmaniasis (Figure 8).



(-)-De-*O*-methylcentrolobine **13**



(-)-Centrolobine **14**

Figure 8

What is leishmaniasis?

Leishmaniasis[12] is a major health problem in Brazil. This is a parasitic disease transmitted by the sand fly and is related to Indian dum dum fever (or Kalaazar). There is an important incidence of Leishmania co-infection in HIV patients, due to the opportunistic character of parasite. There are several different forms of leishmaniasis e.g. Cutaneosu, Mucocutaneous, and Visceral Leismania. The most common forms are cutaneous leishmaniasis, which causes skin sores and visceral leishmaniasis, which affects some of the internal organs of the body (for example, spleen, liver, and bone marrow). Mucocutaneous leishmaniasis begins just like the cutaneous form with dermal

lesions. Visceral leishmaniasis, the most fatal form is also the form of leishmaniasis least likely to be clinically apparent. Visceral Leishmania, or kala-azar, is primarily cause by *L.* donovani on the Indian subcontinent and in Africa. Once in its human host; the parasite attacks the spungiform organs of the body, especially the liver and spleen, where the initial symptoms include a high fever, meaning that the disease is often mistaken for malaria. If the parasite attacks the skin, similar symptoms to leprosy arise, often leading to the wrong treatment being given to the patient.

What are the signs and symptoms of leishmaniasis?

People who have cutaneous leishmaniasis have one or more sores on their skin. The sores can change in size and appearance over time. They often end up looking somewhat like a volcano, with a raised edge and central crater. Some sores are covered by a scab. The sores can be painless or painful. Some people have swollen glands near the sores (for example, under the arm if the sores are on the arm or hand). People who have visceral leishmaniasis usually have fever, weight loss, and an enlarged spleen and liver (usually the spleen is bigger than the liver). Some patients have swollen glands. Certain blood tests are abnormal. For example, patients usually have low blood counts, including a low red blood cell count (anemia), low white blood cell count, and low platelet count.

In what parts of the world is leishmaniasis found?

Leshmaniasis is found in parts of about 88 countries. Approximately, 350 million people live in these areas. Most of the affected countries are in the tropics and subtropics. The settings in which leishmaniasis is found range from rain forests in Central and South America to deserts in West Asia. More than 90% of the world's cases of visceral leishmaniasis are in India, Bangladesh, Nepal, Sudan, and Brazil. The number of new cases of cutaneous leishmaniasis each year in the world is thought to be about 1.5 million. The number of new cases of visceral leishmaniasis is thought to be about 500,000.

How is leishmaniasis spread?

Leishmaniasis is spread by the bite of some types of phlebotomine sand flies. Sand flies become infected by biting an infected animal (for example, a rodent or dog) or person. Since sand flies do not make noise when they fly, people may not realize they are present. Sand flies are very small and may be hard to see; they are only about one-third

the size of typical mosquitoes. Sand flies usually are most active in twilight, evening, and night-time hours (from dusk to dawn). Sand flies are less active during the hottest time of the day. However, they will bite if they are disturbed such as when a person brushes up against the trunk of a tree where sand flies are resting. Rarely, leishmaniasis is spread from a pregnant woman to her baby. Leishmaniasis also can be spread by blood transfusions or contaminated needles.

People of all ages are at risk for leishmaniasis if they live or travel where leishmaniasis is found. Leishmaniasis usually is more common in rural than urban areas; but it is found in the outskirts of some cities. The risk for leishmaniasis is highest from dusk to dawn because this is when sand flies are the most active. All it takes to get infected is to be bitten by one infected sand fly. Adventure travelers, Peace Corps volunteers, missionaries, ornithologists (people who study birds), other people who do research outdoors at night, and soldiers are examples of people who may have an increased risk for leishmaniasis (especially cutaneous leishmaniasis).

Anti-Leishmania drugs

Co-infection with HIV, now quite common in many of the endemic areas, accounts for new challenges to the effective treatment of leishmaniasis. Immunocompromised patients need to be given a suppressive regimen in order to minimize the chance of recurrence. For the past 80 years, the only available drug for this distressing disease has been the pentavalent antimonials, which have been recently linked to cardiac and renal toxicity and are expensive. Besides, the precise chemical structure and mechanism of action of these drugs are unknown up to date. The second choice for the treatment of the disease is a diamidine (pentamidine isethionate), which also cause serious side effects. One alternative therapy is based on amphotericin B (**15**) (AmB),[13] an antifungal polyenic antibiotic that can be nephrotoxic. Liposome formulations of AmB showed fewer side effects, but are unaffordable in the areas of high prevalence. Other compounds [Paramomycin **16**[14], Miltefosine **18**[15], Azithromycin **17**[16], Fluconazole[17] *etc*] are being used now but the same problems of toxicity, difficulty in route of administration, and cost are great obstacles in their effective delivery.

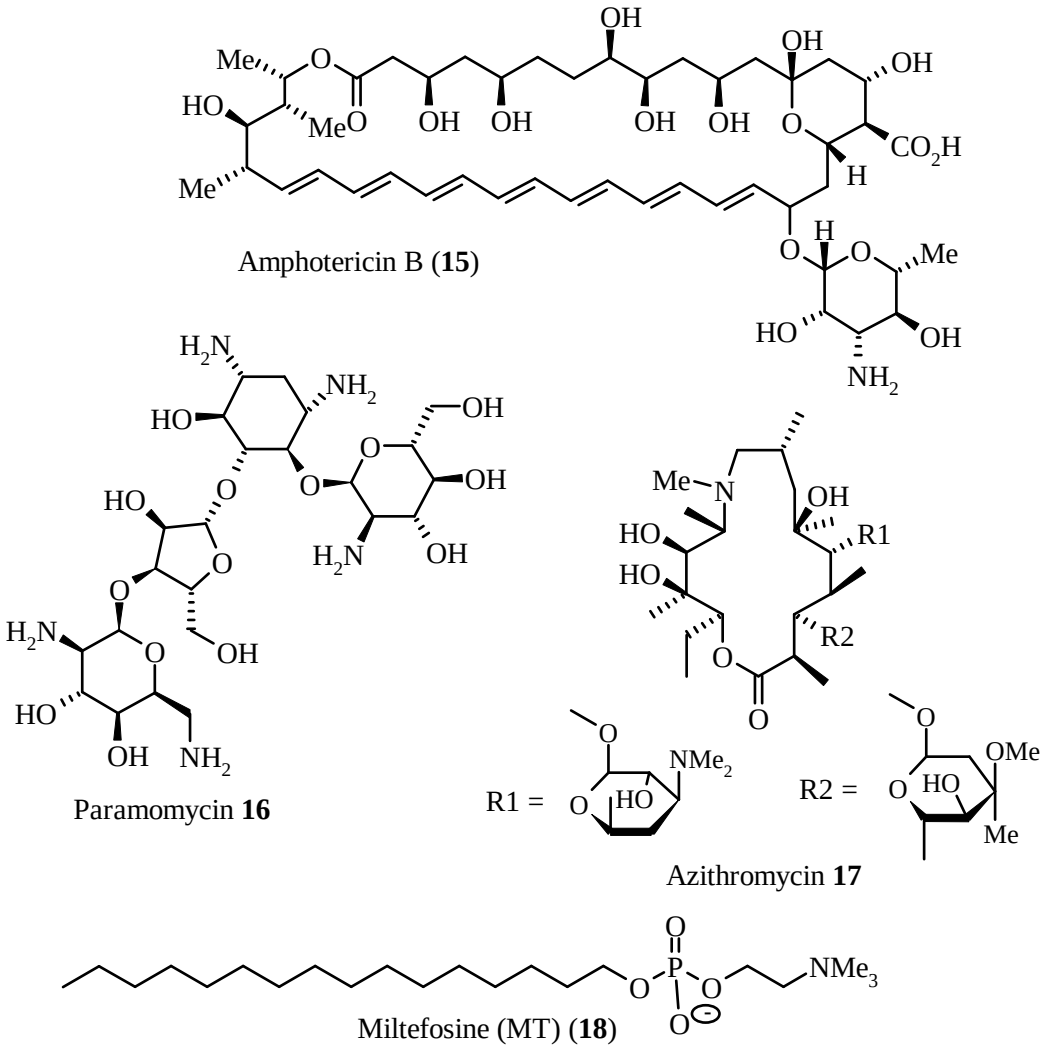


Figure 9

It is for this reason that Leon and co-workers conducted a screen of traditional remedies from the Amazon rainforest to find new antileishmanial compounds. Interestingly, (−)-centrolobine **14** had already been shown to be one of the active ingredients in a herbal tea made from the wood of *Centrolobum robustum* that is used by the native peoples of the Amazon as a tonic cure for a variety of ailments. Guided fractionation of a chloroform extract of the wood of *Centrolobium sclerophyllum* led to the isolation of two diarylheptanoids. Samples of those classes of compounds, extracted and characterized from other plant species, had been shown to have some anti-inflammatory and anti-bacterial, activity and highly effective against the extracellular form (promastigotes) of *L. amazonensis.*

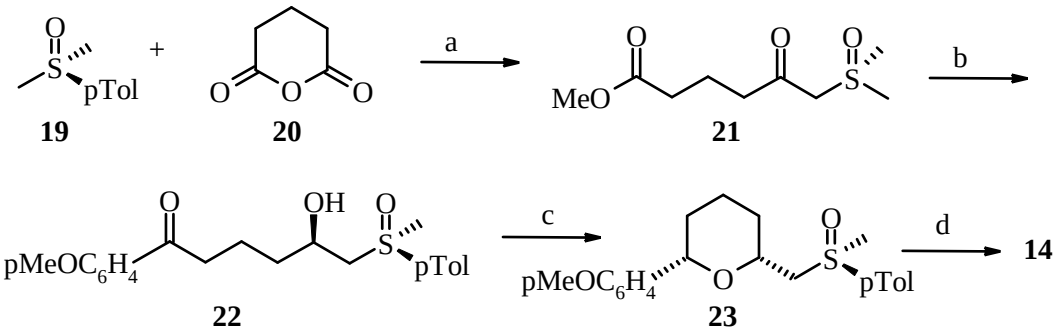
Both (−)-centrolobine **14** and de-OMe-(−)-centrolobine **13** showed a good anti-leishmanial activity[18] with calculated LD_{50} = 77nM and LD_{50} = 86nM, respectively. These compounds showed a high activity when compared with glucantime, which is a drug used in clinical practice.

Previous work

Various approaches leading to (−)-centrolobine **14** have been reported. Solladie and co-workers accomplished the first asymmetric total synthesis of (−)-centrolobine **14** in 2002, which also established the absolute configuration of **14**. Since then, a number of groups have achieved the synthesis of **14** in both racemic and optically active forms. A variety of approaches starting with optically active building blocks, obtained by well-established asymmetric reactions or the chiral pool method, have been devised to provide access to the *cis*-2,6-disubstituted tetrahydropyran rings. These include the Prins and related cyclizations, reductive etherification, one-pot cross metathesis–hydrogenation–lactonization procedure, radical cyclization, nucleophilic addition–stereoselective reduction protocol, intramolecular oxy-Michael reaction, diastereoselective ring rearrangement metathesis–isomerization sequence, $FeCl_3$-mediated cyclization of 1,5-diol, and hetero-Diels-Alder reaction.

1. ***Solladie's approach***[19] ***(2002)***:

Solladie *et al* reported the first enantioselective total synthesis of (−)-centrolobine **14** (Scheme 1). The key reaction was the synthesis of the *cis*-disubstituted tetrahydropyran framework by intramolecular cyclization of the enantiopure hydroxyketone **22** with Et_3SiH and TMSOTf. The stereoselective reduction of the *β*-ketosulfoxide **21** was the

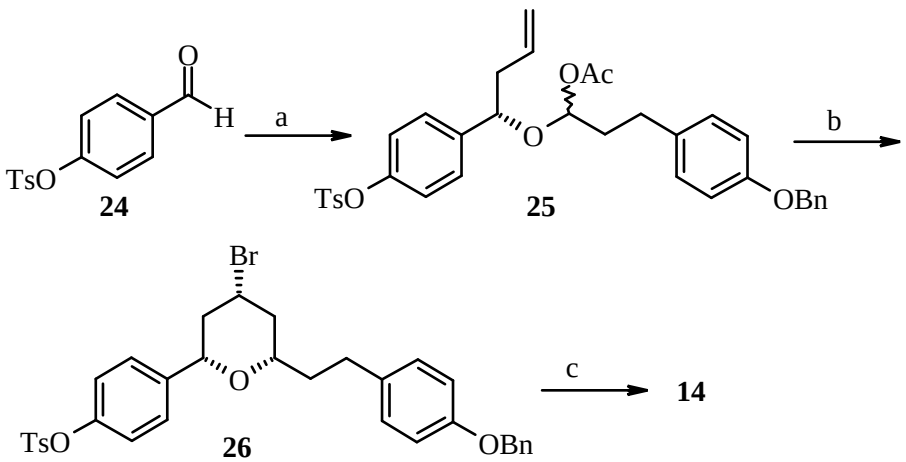


Scheme 1: ***Reagents and conditions*****:** (a) i) LDA, THF, −78 ^{o}C; ii) K_2CO_3, rt, acetone; iii) Me_2SO_4, reflux, 82%; (b) i) DIBAL-H/$ZnBr_2$, THF; ii) HCl·HN(OMe)$_2$, $AlMe_3$, CH_2Cl_2, reflux, 93%; iii) *p*-(MeO)C_6H_4MgBr, ether/THF, reflux, 71%; (c) TMSOTf, Et_3SiH, CH_2Cl_2, 0 ^{o}C, 81%; (d) i) TFAA, 2,4,6-collidine, MeCN, 0 ^{o}C, $NaHCO_3$; ii) 4-benzyloxybenzyltriphenylphosphonium salt, *n*-BuLi, 0 ^{o}C, 96%; iii) H_2, Pd/Al_2O_3, 50 bar, rt, 93%.

source of chirality. β-Ketosulfoxide (+)-(*R*) **21** was prepared by condensation of glutaric anhydride **20** and the carbanion of (+)-(*R*)-methyl *p*-tolyl sulfoxide **19**. The sulfoxide **23** was converted to aldehyde, followed by Wittig reaction and subsequent hydrogenation provided (−)-centrolobine **14**.

2. ***Rychnovsky's approach***[20] ***(2002)***:

The synthesis of (−)-centrolobine **14** commenced with a Keck enantioselective allylation of aldehyde **24** to give the homoallylic alcohol (Scheme 2), followed by esterification and reductive acetylation led to the (*R*)-acetoxy ether **25**. Cyclization, promoted by $SnBr_4$, generated the all-equatorial tetrahydropyran **26**. The tosylate protecting group was replaced with methyl ether by basic hydrolysis and alkylation. The synthesis was completed by radical reduction to cleavage of the bromide and hydrogenation to remove the benzyl ether.

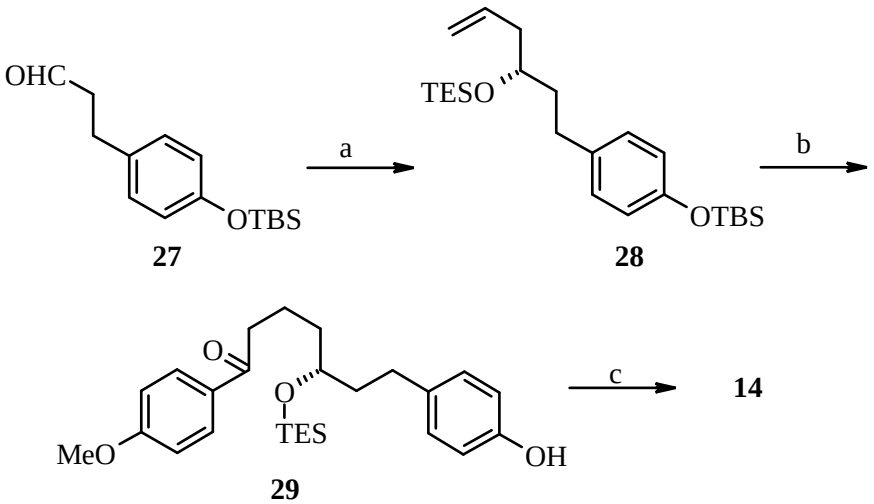


Scheme 2: ***Reagents and conditions***: (a) i) (*S*)-BINOL, Ti(O^{i}Pr)$_4$, allylSnBu_3, 79%, 94% ee.; ii) DCC, DMAP, 4-(BnO)$C_6H_4CH_2CH_2CO_2H$, 94%; iii) (1) DIBAL-H, −78 °C; (2) Ac_2O, DMAP, pyridine, 93%; (b) $SnBr_4$, CH_2Cl_2, −78 °C, 84%; (c) i) K_2CO_3, MeOH,

reflux; ii) MeI, K_2CO_3, acetone, rt, 85%; iii) Bu_3SnH, AIBN (cat.), $PhCH_3$, reflux, 86%; iv) H_2, 10% Pd/C, 72%.

3. ***Evans's approach***[21] ***(2003)****:*

The stereoselective intramolecular reductive etherification of *δ*-trialkylsilyloxy substituted ketones with catalytic bismuth tribromide and triethylsilane was the key step for the synthesis of (−)-centrolobine **14** (Scheme 3). Enantioselective allylation of aldehyde **27** and protection of the resulting secondary alcohol furnished the triethysilyl ether **28**. The alkene **28** was then subjected to cross-metathesis by using the Grubbs' 2nd generation catalyst to afford the corresponding *α,β*-unsaturated ketone. Selective hydrogenation of the alkene with Wilkinson's catalyst furnished the aryl ketone **29**. Treatment of the *δ*-triethylsilyloxy aryl ketone **29** with bismuth tribromide and triethylsilane at room temperature followed by *in situ* removal of the *tert*-butyldimethylsilyl group afforded (−)-centrolobine **14**.



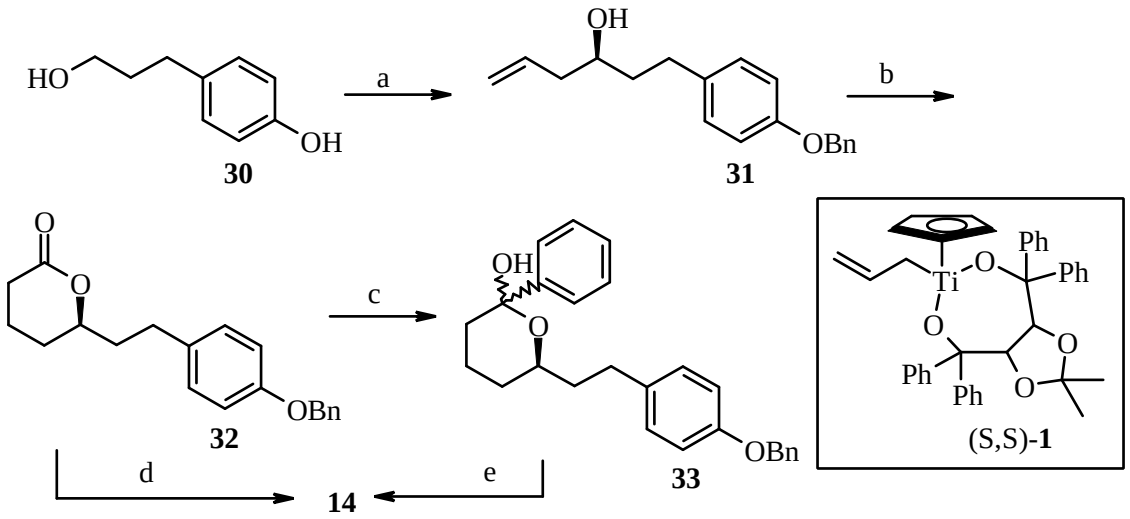
27 **28** **29**

Scheme 3: ***Reagents and conditions*****:** (a) i) (*R*)-BINOL, $Ti(O^iPr)_4$, Allyltri-*n*-butyltin; ii) TESOTf, CH_2Cl_2, 2,6-Lutidine, 77%; (b) i) Grubbs' cat, $ArCOHC{=}CH_2$; ii) $RhCl(PPh_3)_3$, H_2, PhH, 74%; (c) 10 mol% $BiBr_3$, Et_3SiH, MeCN, rt, TBAF, 93%.

4. ***Boulard's approach***[22] ***(2004)***:

L. Boulard *et al* employed asymmetric allylation on aldehyde derived from compound **30** by PCC oxidation (Scheme 4). The homoallylic alcohol **31** was converted to lactone **32** by one-pot four reactions, cross metathesis (CM), hydrogenation, lactonization and debenzylation. On treatment of **32** with 4-methoxyphenylmagnesium bromide, lactol **33** was obtained. The addition of Et_3SiH in the presence of $BF_3{\cdot}Et_2O$ to

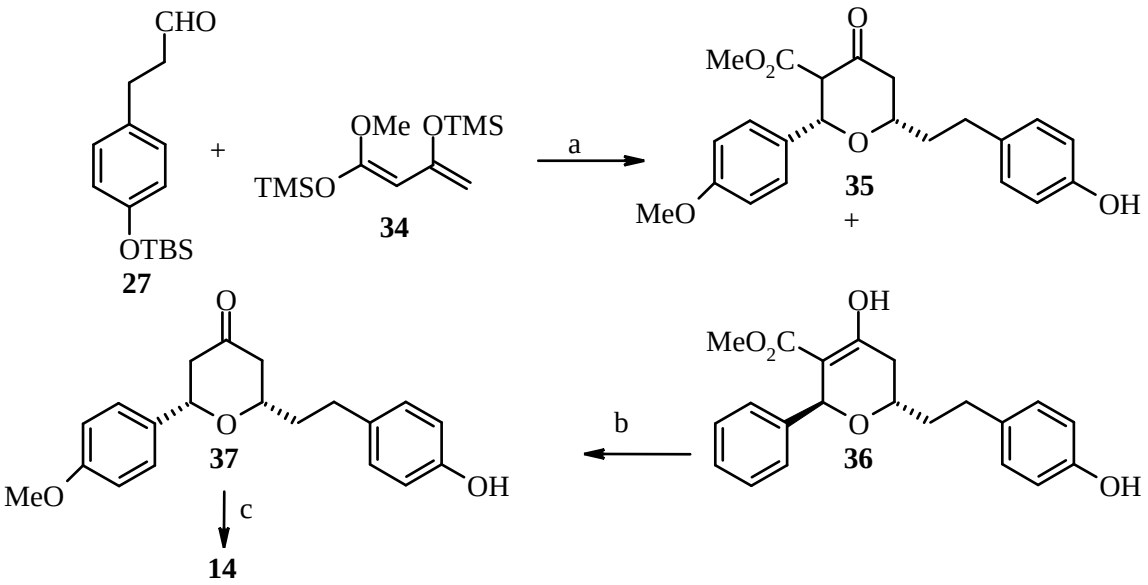
the crude lactol **33** offered (−)-centrolobine **14**. A one-pot transformation from **32** to **14** also achieved by addition of 4-methoxyphenylmagnesium bromide followed by TMSOTf and Et_3SiH.



Scheme 4: ***Reagents and conditions*****:** (a) NaH, BnBr, DMF, 50 ^oC, 90%; (b) i) PCC, CH_2Cl_2, rt, quantitative; ii) (*S,S*)-**I**, ether, −78 ^oC, 61%; (iii) Acrylic acid (4.2 equiv), Grubbs' II (3.7 mol%), CH_2Cl_2, two days then Pd/C (2.2 mol%), H_2, four days, 56%; (c) i) 4-methoxyphenylmagnesium bromide (4 equiv) THF, −78 ^oC, 1 h; ii) TMSOTf (4 equiv) and Et_3SiH (4 equiv), −78 ^oC then rt, 1 h, 23%; (d) 4-methoxyphenylmagnesium bromide (3 equiv) THF, −78 ^oC, 1 h; (e) $BF_3{\cdot}Et_2O$ (3equiv) and Et_3SiH (4 equiv), CH_2Cl_2, −78 ^oC then rt, 1 h, 40%.

5. ***Clark's approach***[23] ***(2004)***:

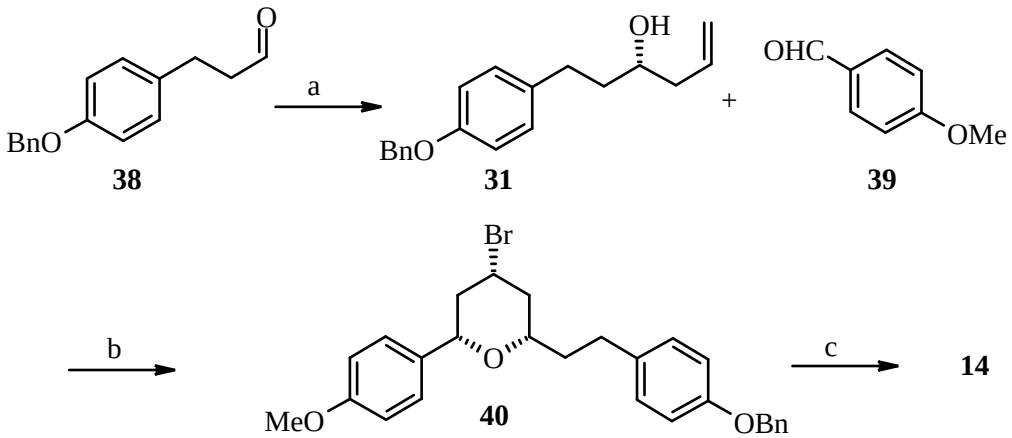
In the synthesis of centrolobine **14** (Scheme 5), Clark *et al* utilized the one pot three-component revisited Maitland–Japp reaction of Chan's diene **34**, followed by the addition of anisaldehyde furnished tetrahydropyran-4-ones **35** and **36** with an equilibrium ratio of 2:1. Decarboxylation of **35** provided **37**. Finally, reduction of keto afforded (−)-centrolobine **14**.



Scheme 5: ***Reagents and conditions*****:** (a) $Yb(OTf)_3$, TFA, anisaldehyde, 92%; (b) LiOH, H_2O_2, THF/H_2O, 100 ^oC, 60%; (c) i) $(CH_2SH)_2$, $BF_3{\cdot}OEt_2$, 100%; ii) Raney Ni, H_2, Et_2O, 100%.

6. ***Loh's approach***[24] ***(2005)*****:**

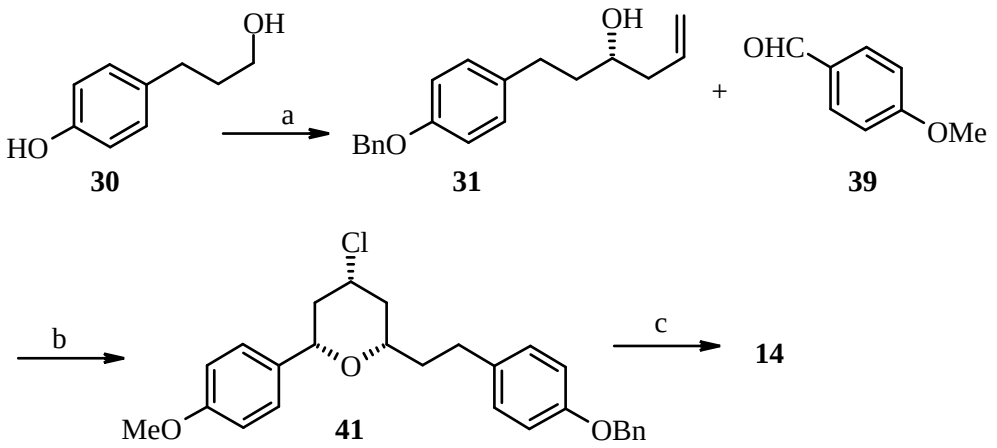
In Loh's approach, the synthesis based on an asymmetric allylation of aldehyde **38** using (*R*)-BINOL indium complex and allyltri-*n*-butyltin as allylating agent to install one of the chiral center. The formation of 4-Bromo THP ring **40** was accomplished via catalytic Prince cyclization using $InBr_3$ in presence of TMSBr. Finally, dehalogenation and catalytic hydrogenation provided (−)-centrolobine **14** (Scheme 6).



Scheme 6: ***Reagents and conditions:*** (a) $InCl_3$, (*R*)-BINOL, $allylSnBu_3$, molecular sieves 4Å, CH_2Cl_2, −78 ^oC to 25 ^oC, 24 h, 68%; (b) $InBr_3$, TMSBr, CH_2Cl_2, −78 ^oC, 1 h, 83%;

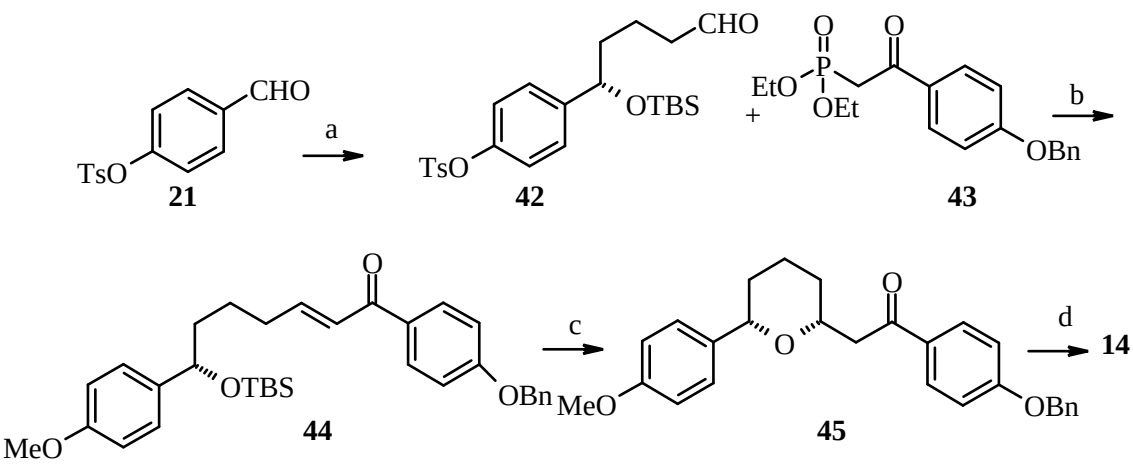
(c) i) Bu_3SnH, ABCCN, PhH, reflux, 24 h, 98%; ii) H_2, 10% Pd/C, MeOH/EtOAc, 7 h, 71%.

The same group published one more similar synthetic approach,[25] where $InCl_3$ was used for the Prince cyclisation step, keeping all other synthetic sequence as before (Scheme 7).



Scheme 7: ***Reagents and conditions*****:** (a) i) BnBr, Ag_2O, CH_2Cl_2, 0 ^oC, 80%; ii) Dess–Martin periodinane, CH_2Cl_2, 0 ^oC, 76%; (b) camphor-derived homoallylic alcohol, CSA, CH_2Cl_2, 15 ^oC, 68%, 90% ee; (c) i) $InCl_3$, 0 ^oC, 70%, 90% ee; ii) ABCCN, Bu_3SnH, C_6H_6, reflux, 94%; iii) H_2, 10% Pd/C, 86%, MeOH/EtOAc, 7 h.

7. ***Chandarshekhar's approach***[26] ***(2005)***:



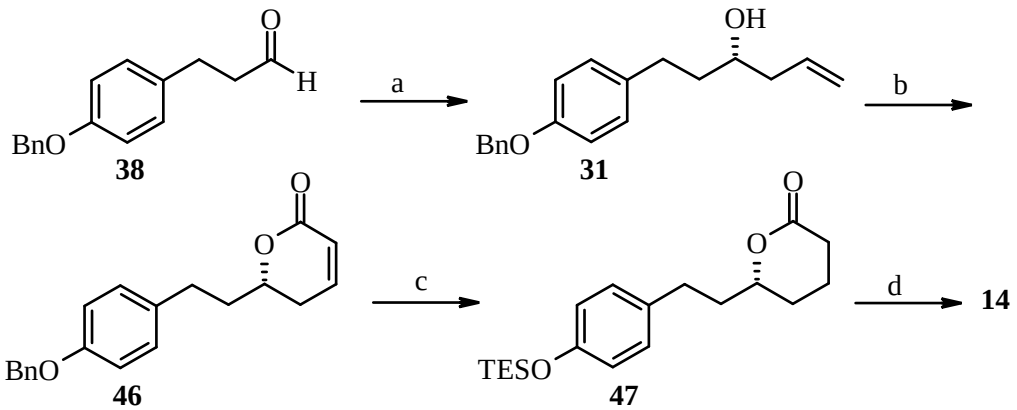
Scheme 8***: Reagents and conditions:*** (a) i) (*S*)-BINOL, $Ti(O^iPr)_4$, allyltributyltin, 4Å MS, CH_2Cl_2, −20 ^oC, 70 h, 73%; ii) TBDMSCl, imidazole, CH_2Cl_2, 0 ^oC, 4 h, 87%; iii)

Mg/MeOH, rt, 3 h, 85%; iv) K_2CO_3, MeI, acetone, 0 ^oC to reflux, 4 h, 73%; v) O_3, CH_2Cl_2, −78 ^oC, 1 h, then TPP; vi) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, rt, 2 h, 84% (for two steps); vii) Mg/MeOH, rt, 3 h, 81%; viii) LAH, THF, 0 ^oC to rt, 3 h, 76%; ix) IBX, DMSO, rt, 4 h, 80%; (b) $Ba(OH)_2/8H_2O$, THF/H_2O (4:1), rt, 5 h, 81%; (c) HF-Py, THF, 0 ^oC to reflux, 4 h, 80%; (d) Pd/C, H_2 atm., HCl, EtOH/EtOAc/H_2O (5:1:1), 10 h, 70%.

Chandarshekhar *et al.* efficiently utilized the Keck allylation on **21** (Scheme 8), which was processed forward through some functional group manipulations: oxidation, Wittig olefination, reduction of ester as well as double bond, followed by oxidation to obtain aldehyde **42**. Wittig-Horner olefination with phosphonate **43** provided the key intermediate **44**, which on exposure to HF-pyridine triggered *in situ* silyl cleavage followed by intramolecular oxy-anion Michael addition to provide substituted pyran **45**. Benzyl ether cleavage and keto reduction by hydrogenation provided (–)-centrolobine **14**.

8. ***M. P. Jennings's approach***[27] ***(2005):***

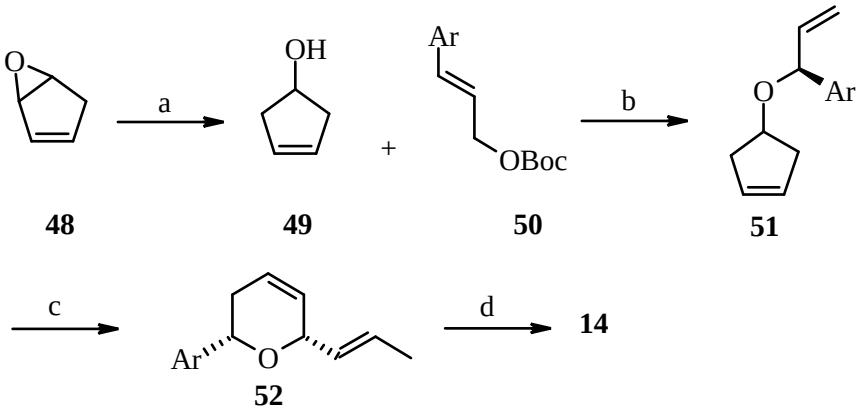
The synthesis was initiated with the asymmetric allylation of aldehyde **38** to get homoallylic alcohol **31**. Esterification of **31** with acryloyl chloride and subsequent ring closing olefin metathesis with Grubbs' second-generation catalyst provided lactenone **46**. (−)-Centrolobine **14** had been achieved from lactone **47** by two steps, Grignard reaction followed by dehydration (Scheme 9).



Scheme 9: ***Reagents and conditions*****:** (a) allylMgBr (2.0 equiv), Et_2O, −78 ^oC, 1 h, 84%; (b) i) acryloyl chloride (5.0 equiv), Et_3N (10 equiv), DMAP (5% mol), CH_2Cl_2, 0 ^oC, 6 h, 86%; ii) Grubbs'-II, (5% mol), CH_2Cl_2, reflux, 5 h, 87%; (c) i) Pd/C (3% mol), EtOH, rt, 40 h, 84%; ii) TESCl (12 equiv), imidazole (5 equiv), DMF, rt, 87%; (d) 4-MeOPhMgBr (1.0 equiv) THF, −78 ^oC, 2.5 h; then Et_3SiH (10.0 equiv), CH_3CN, −40 ^oC, 96%.

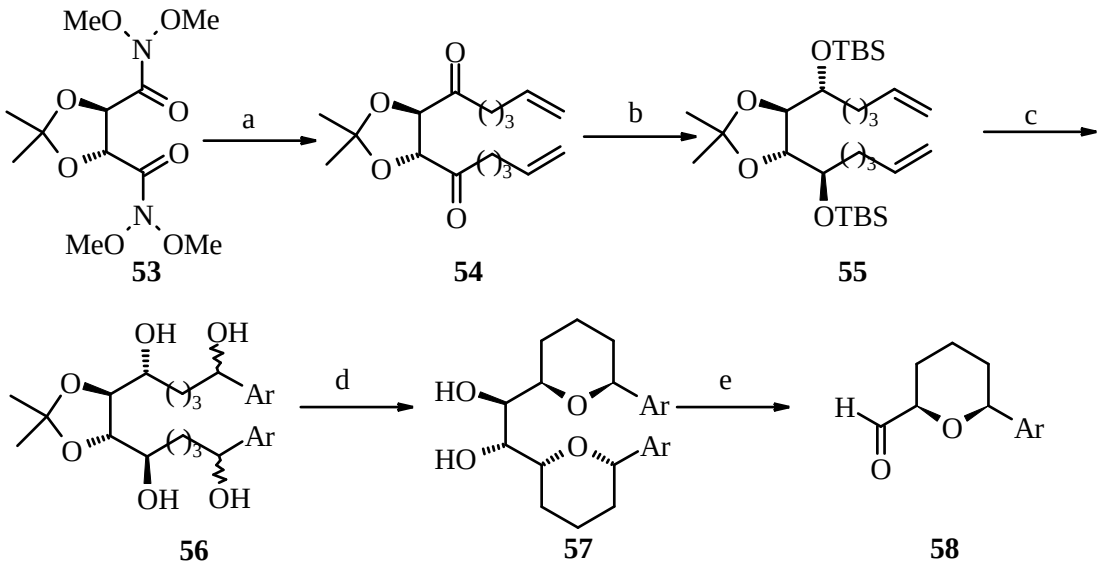
9. ***Blechert's approach (2006)***:[28]

In Blechert's approach, reductive opening of epoxide **48** with $LiAlH_4$ (Scheme 10) afforded the alcohol **49**. Transition metal catalysed asymmetric allylation on **49** provided compound **51**. On exposure of **51** to Grubbs' catalyst, it rearranged into **52**. Cross metathesis with styrene derivative followed by hydrogenation completed the synthesis.



Scheme 10: ***Reagents and conditions***: (a) $LiAlH_4$, Et_2O, 98%; (b) *n*-BuLi, CuI; then $[Ir(COD)Cl]_2$, THF, 0 ^oC-rt, 87%; (c) i) 2 × 5% $[Ru(IH_2Mes)PCy_3(=CHPh)Cl_2]$, benzene/ethylene, 50 ^oC, 6 h; (ii) 0.4 equiv. $NaBH_4$, 55%; (d) 10% $(IH_2Mes)RuCl_2PCy_3((O^iPr)CHPh)$, toluene, rt then 5% Pd/C (50 wt% water), H_2 (1 atm), 50%.

10. ***Prasad's approach***[29] ***(2007)***:



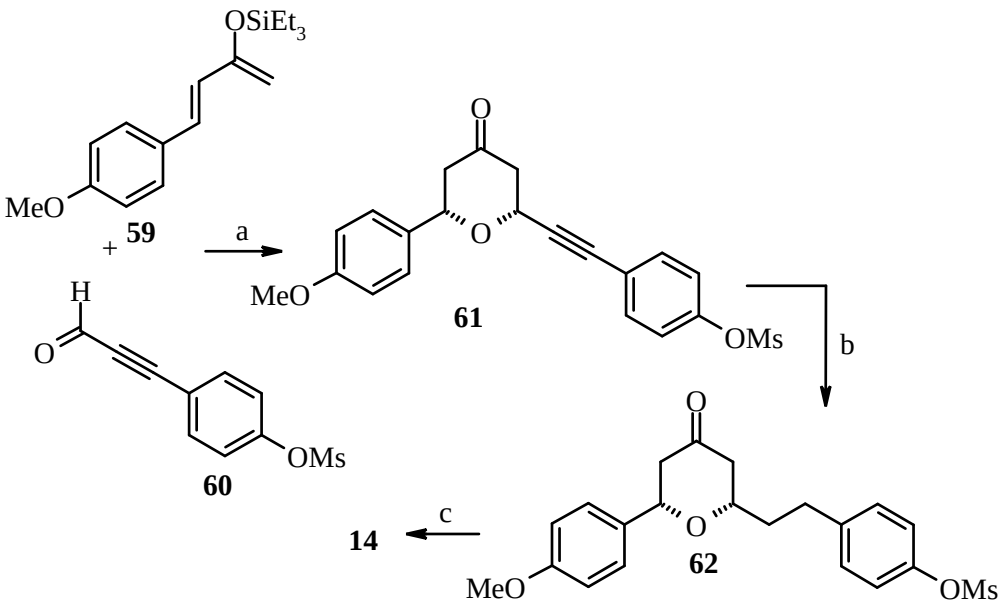
Scheme 11: ***Reagents and conditions*****:** (a) C_5H_9MgBr, THF, 0 ^oC, 1 h, 96%; (b) i) L-Selectride, THF −78 °C, 2.5 h, 94%; ii) TBSCl, imidazole, DMAP, DMF, 80 °C, 3 h, 94%; (c) i) O_3/O_2, Me_2S, $NaHCO_3$, CH_2Cl_2, MeOH, 0 °C, 5h; ii) *p*-$OMeC_6H_4MgBr$,

THF, 0 °C, 1 h, 90% for 2 steps; iii) TBAF, THF, rt, 8 h, 89%; (d) $FeCl_3$, rt, 30 min, 70%; (e) $Pb(OAc)_4$, benzene, rt, 1.5 h.

Prasad *et al.* started with bis-Weinreb amide **53** derived from L-(+)-tartaric acid (Scheme 11). With the controlled addition of 4-pentenylmagnesium bromide to the bis-Weinreb amide **53** furnished 1,4-diketone **54**. Stereoselective reduction of diketo with L-selectride, followed by protection with sillyl group provided diene **55**. Ozonolysis followed by Grignard reaction afforded racemic diol, which on desilylation provided compound **56**. $FeCl_3$ mediated cyclisation provided **57**, which on oxidative cleavage converted to aldehyde **58**, thus completed the formal synthesis of (−)-centrolobine **14**.

11. ***Hasimoto's approach (2007)***:[30]

In this synthetic approach hetero-Diels–Alder (HDA) reaction between 4-aryl-2-silyloxy-1,3-butadienes **59** and phenylpropargyl aldehyde **60** derivatives played as a key step (Scheme 12).

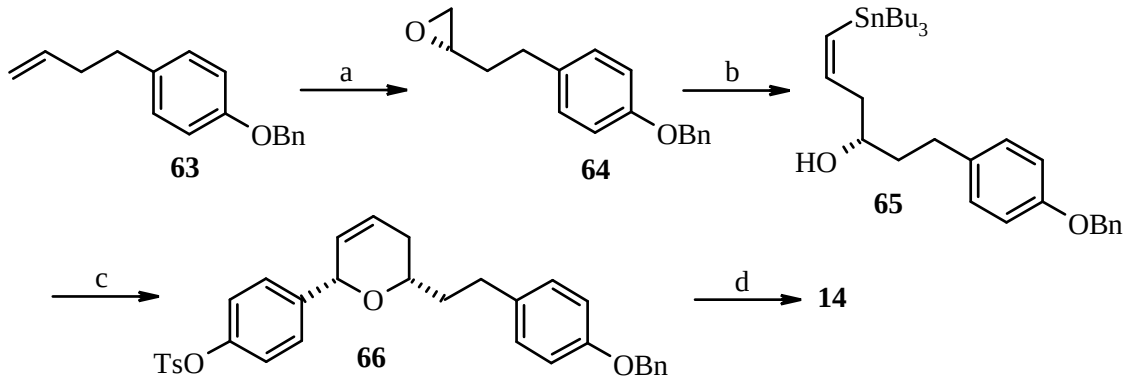


Scheme 12: ***Reagents and conditions*****:** (a) Rh_2(*R*-BPTPI)$_4$ (1 mol %), CH_2Cl_2 87%; (b) H_2, 10%Pd/C, EtOAc, 2 h; (c) i) $TsNHNH_2$, MeOH, reflux, 2 h; ii) $NaBH_3CN$, TsOH, DMF–sulfolane (1:1), 110 ^oC, 1 h; iii) K_2CO_3, MeOH, reflux, 3 h.

The HAD reaction between **59** and **60** occurred in presence of Rh_2(*R*-BPTPI)$_4$, as a chiral Lewis acid catalyst to provides exclusively *cis*-2,6-disubstituted tetrahydropyran-4-ones **61**. The triple bond was reduced by catalytic hydrogenation. Keto group reduction and some protecting group manipulation provided (−)-centrolobine **14**.

12**. *Furman's approach*[31] *(2008)***:

The stereoselective construction of 2,6-disubstituted dihydropyrans following Lewis acid catalyzed intramolecular reactions of oxocarbenium ions with vinylstannanes was used as the key reaction (Scheme 13). The starting epoxide **64** was synthesized from the corresponding olefin **63** via Sharpless asymmetric dihydroxylation followed by tosylation of the primary hydroxyl group and NaOH treatment. The ring opening of epoxide **64** with lithium acetylide–ethylenediamine complex and subsequent hydrostannylation afforded alcohol **65**. The Prins cyclization of **65** with 4-tosyloxybenzaldehyde in presence of TMSOTf yielded dihydropyran **66**, which on some synthetic sequence of reactions provided (−)-centrolobine **14**.

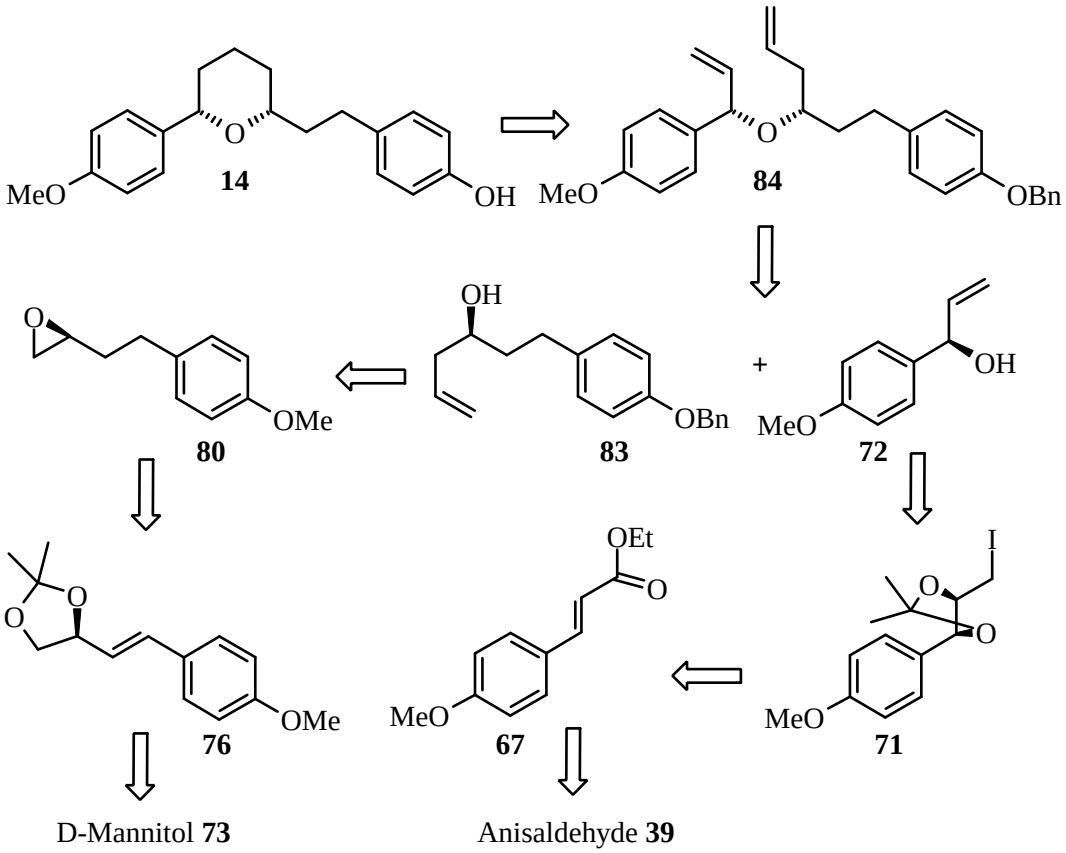


Scheme-13: ***Reagents and conditions***: (a) (i) AD-mix-α, *t*-BuOH–H_2O, 0 ^oC, 80%, 90% ee; (ii) TsCl, pyridine, 0 ^oC, 88%; (iii) NaOH, Et_2O/H_2O, 93%; (b) (i) lithium acetylide–EDTA, DMSO, 0 ^oC, 83%, 87% ee; (ii) $Bu_2Sn(OTf)H$ then *n*-BuLi, 72%; (c) benzaldehyde, TMSOTf (2.0 equiv), Et_2O, −78 ^oC, 87%; (d) (i) Pd/C, H_2, EtOAc, 78%; (ii) TBSCl, imidazole, 95%; (iii) Mg (10 equiv), MeOH, 25 ^oC, 50%; (iv) NaH, MeI, THF then Bu_4NF, THF, 0 ^oC, 73% (over two steps).

PRESENT WORK

Present Work

(−)-Centrolobine, 6[β(*p*-hydroxyphenyl)ethyl]-2-(*p*-methoxyphenyl) tetrahydro-pyran **14**, is a crystalline substance isolated from the heartwood of *Centrolobium robustum* and from the stem of *Brosinum potabile* in the amazon forest. Although the basic structure[11] was elucidated in 1964 by total synthesis of the racemic methyl ether, its absolute configuration has been unequivocally established by Francoise Colobert[19] *et al* in 2002. Unique structural feature and potential biological activity received increasing attention from chemist interested in the total synthesis of biologically active natural products.

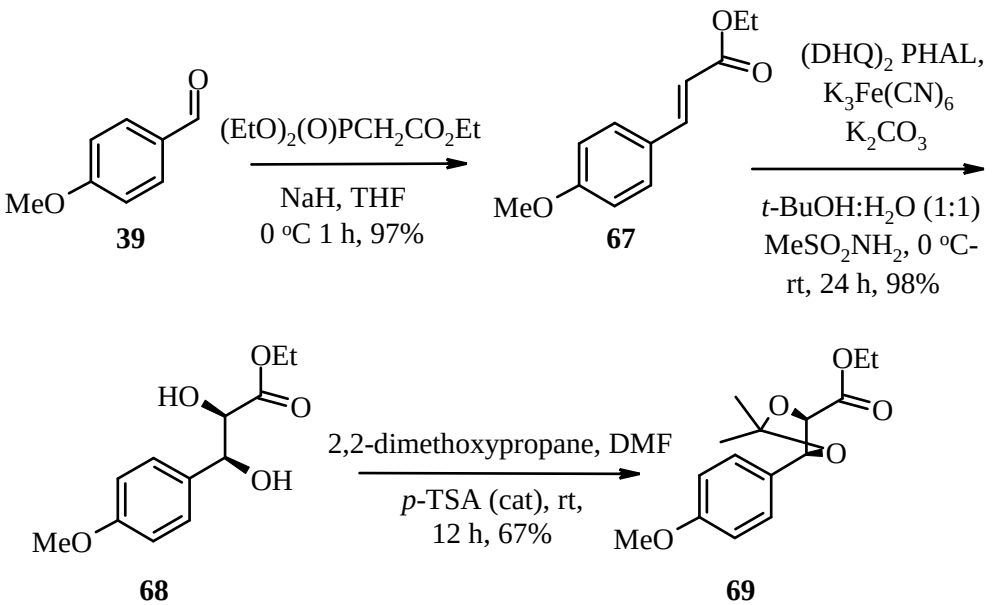


Scheme 14

Keeping in mind, the biological activity and its structural similarity with the other natural products prompted us to take up the synthesis of (−)-centrolobine **14**. Our own interest in the synthesis of enantiopure bioactive natural products[32] directed us to explore

the possibility of synthesizing (−)-centrolobine **14**. Flexible scheme was devised and is outlined in retrosynthetic plan (Scheme 14).

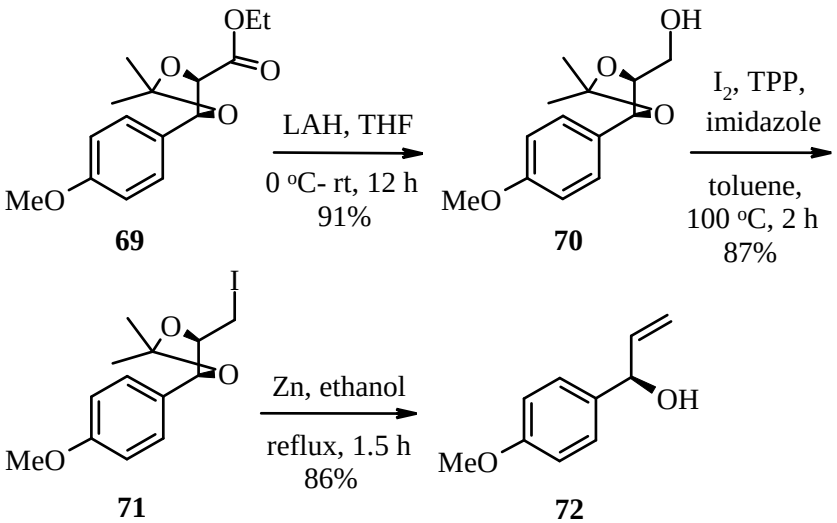
(−)-Centrolobine **14** was retrosynthetically disassembled into fragments **72** and **83** by means of two key disconnections, namely ring-closing metathesis reaction (RCM)[33] for the construction of the pyran ring and an etherification reaction for assembling the two alkene fragments. Both fragments contain one stereogenic carbon atom and bear a terminal alkene group, which is required for the key RCM reaction. Fragment **72** could be obtained from Zn mediated elimination reaction[34] of halide **71**, which in turn could be obtained by asymmetric dihydroxylation[35] on compound **67**. Olefinic compound **67** could be synthesized from anisaldehyde **39** following two carbon homologation using Wittig reaction. Other fragment **83** could be obtained by opening of epoxide **80** with vinyl Grignard reagent. The epoxide **80** could be obtained from D-mannitol by a sequence of standard reactions.



Scheme 15

The journey towards the synthesis of fragment **72** began with commercially available *p*-anisaldehyde **39**, which was subjected to Wadsworth-Horner-Emmons olefination[36] using triethylphosphonoacetate in presence of sodium hydride in anhydrous tetrahydrofuran at 0 ^{o}C to give **67** with 100% *trans*-selectivity (by ^{1}H NMR). The next task was to generate the requisite stereocenters, which was accomplished by employing Sharpless asymmetric dihydroxylation protocol. Thus, compound **67** was treated with

ligand $(DHQ)_2$ PHAL, $K_3Fe(CN)_6$, K_2CO_3, $MeSONH_2$ and OsO_4 in *t*-BuOH-H_2O (1:1) at 0 ^oC to afford the diol **68**. The compound **68** was thoroughly investigated by ^1H, ^{13}C NMR and elemental analysis. Enantioselectivity was determined by HPLC using CHIRACEL OD column to be 90%. The diol **68** was then ketalised under acidic condition (catalytic *p*-TSA) using 2,2-dimethoxypropane in *N*,*N*-dimethylformamide to furnish **69**. The structure was assigned by ^1H NMR and ^{13}C NMR spectra.



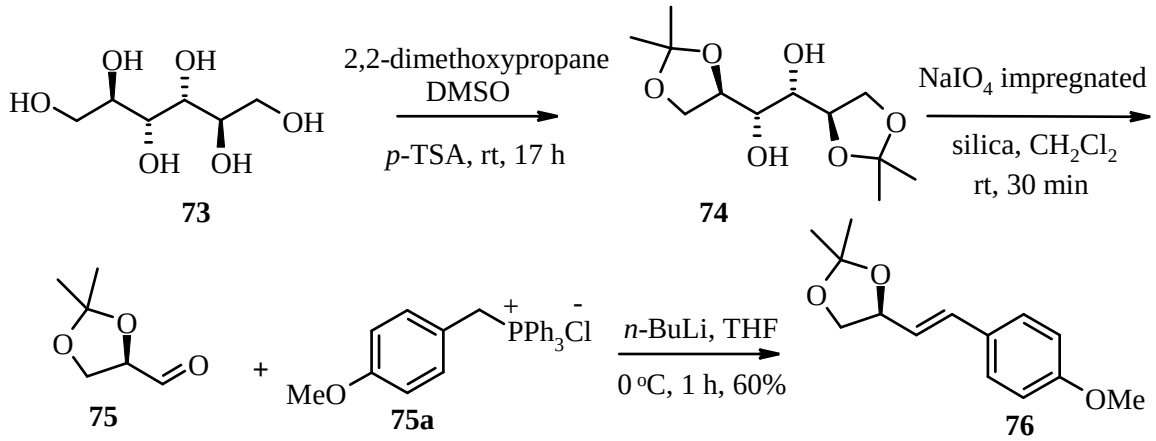
69 **70** **71** **72**

Scheme 16

Reduction of carboxylate group of **69** was performed using lithium aluminium hydride in anhydrous THF to obtain **70**. The structure was suggested by the ^1H NMR spectrum in which resonance at δ 3.81-3.88 ppm as a multiplet due to the $-CH_2OH$ group and the acetonide methyl peaks at δ 1.52 and 1.58 ppm were observed.

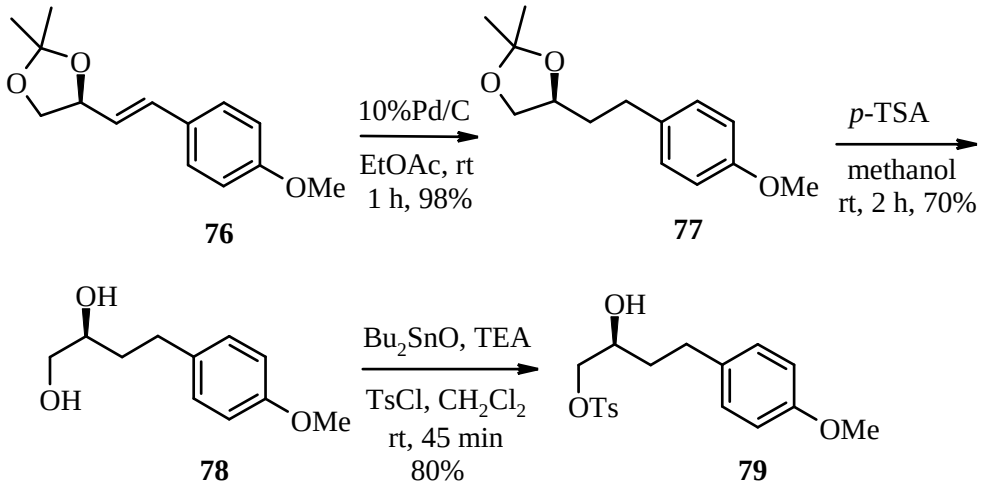
Having in hand the alcohol **70**, our next concern was to transform it to the corresponding iodo derivative **71**. Thus, **70** was subjected to Corey's[37] deoxyhalogenation protocol by treating with iodine, TPP, imidazole and pyridine in toluene at 100 ^oC to furnish **71** in 87% yield. Fragment **72** was accomplished from compound **71** through zinc mediated facile elimination reaction in refluxing ethanol. In ^1H NMR spectrum of **72**, peaks owing to $-CH_2I$ and isopropylidene group were absent, whereas Peaks at δ 5.0-5.26 and 5.84-6.01 ppm as two multiplets characteristic of terminal olefinic group were observed. All the other protons were resonated at their expected chemical shift. The ^{13}C NMR spectrum displayed signal at δ 114.46, 134.86 ppm corresponding to olefinic carbons.

For the synthesis of fragment **83**, we started from D-mannitol **73**, which was ketalised as 1,2;5,6-di-*O*-isopropylidene-D-mannitol, followed by oxidative cleavage to provide (*R*)-2,3-*O*-isopropylidene-D-glyceraldehyde synthon **75**.[38] The cheap and easy availability, high enantiomeric purity and equivalence to double unit of chiral building block because of C2 symmetry were the strong incentives for our interest to start with D-mannitol **73**.



Scheme 17

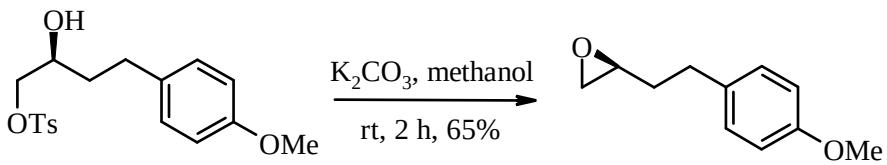
Thus, aldehyde **75** was reacted with Wittig salt **75a** (which was accomplished from *p*-methoxybenzyl chloride using TPP in refluxing benzene according to reported procedure[39]) in presence of *n*-BuLi in THF to obtain the olefinic compound **76** with a 2:3 ratio of *cis, trans* mixture, which was ascertained by NMR analysis. In ^{1}H NMR spectrum, the olefinic proton signals were observed at δ 5.61 (dd, *J* = 11.5, 8.9 Hz), 5.01 (dd, *J* = 15.8, 7.8 Hz), 6.66 (d, *J* = 11.5 Hz) and 6.61 (d, *J* = 15.7 Hz) ppm. All the other protons were resonated at their respective values confirming the structure of **76**. The olefin **76** was hydrogenated with 10% Pd/C in ethyl acetate at 60 *psi* to obtain the saturated compound **77** with excellent yield. Absence of signals due to olefinic protons in ^{1}H NMR was in accordance with the transformation. Deketalisation was performed by treating **77** with catalytic amount of *p*-TSA in methanol for 4 h to provide **78**. The structure was supported by the ^{1}H and ^{13}C NMR spectral analysis. The peaks owing to isopropylidene group were disappeared in the ^{1}H NMR spectrum. The structure was further confirmed by mass and elemental analysis. The primary hydroxyl group of **78** was selectively converted to the sulphonate derivative **79** using tosyl chloride, triethylamine in presence of dibutyltin oxide[40] at room temperature.



76 **77** **78** **79**

Scheme 18

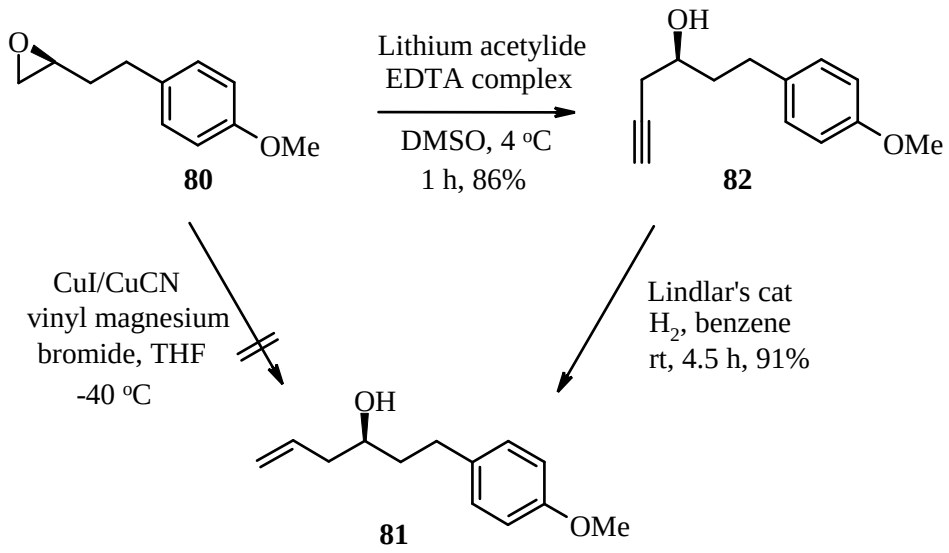
In the ^{1}H NMR spectrum of **79**, additional characteristic resonance for the tosyl group were observed as two dublets at δ 7.34 and 7.79 (J = 8.4 Hz) ppm, while the aromatic methyl group appeared as a singlet at δ 2.44 ppm. Rest of the spectral data was in full agreement with the assigned structure. The next step involved the oxirane derivatisation for which compound **79** was treated with potassium carbonate in methanol to furnish the terminal epoxide **80**. While the protons specifying *–OTs* group were no more, the characteristic signals due to typical epoxide at the region of δ 2.51-2.88 ppm were observed in the ^{1}H NMR spectrum. Rest of the protons was observed in their expected position. Other spectral data was in full agreement with the assigned structure.



79 **80**

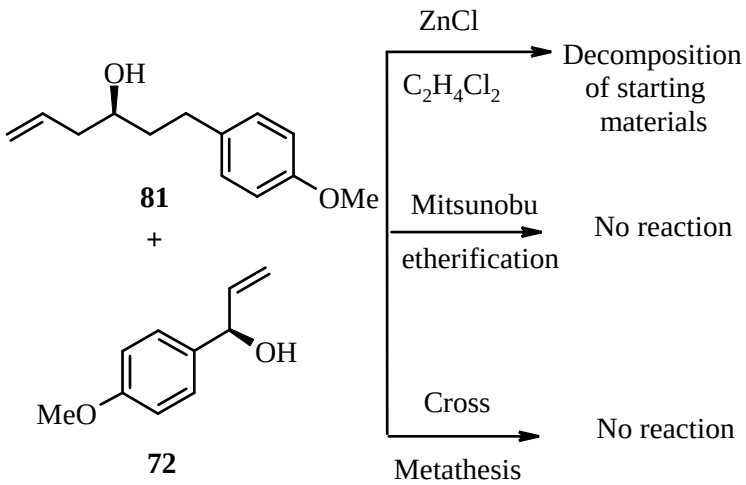
Scheme 19

The ring opening reaction of the oxirane **80** with vinyl magnesium bromide was our next job to get the intermediate **81**. Thus, on exposure of compound **80** to vinyl magnesium bromide in tetrahydrofuran at −40 ^{o}C led to a mixture of products in which the required product was minor. This was partly attributed to many side reactions particularly opening of the oxirane ring with halide (halohydrin formation).



Scheme 20

Based on aforesaid failure, we decided to make **81** by two step protocol in which **80** was treated with lithium acetylide-EDTA[41] complex in DMSO at 4 °C to afford **82** in 86% yield. In ^{1}H NMR spectrum of **82**, a triplet at δ 1.95 (J = 2.6 Hz) was attributed to acetylenic proton. Partial reduction of the triple bond of **82** was carried out by hydrogenation over Lindlar's catalyst[42] at normal temperature and pressure for 4.5 h to release the key intermediate **81** in excellent yield. The ^{1}H NMR spectrum of **81** showed resonance for olefin protons at δ 5.00-5.08 and 5.62-5.83 ppm as sets of multiplets, whereas ^{13}C NMR spectrum indicated olefinic carbons at δ 118.05, and 134.6 ppm.

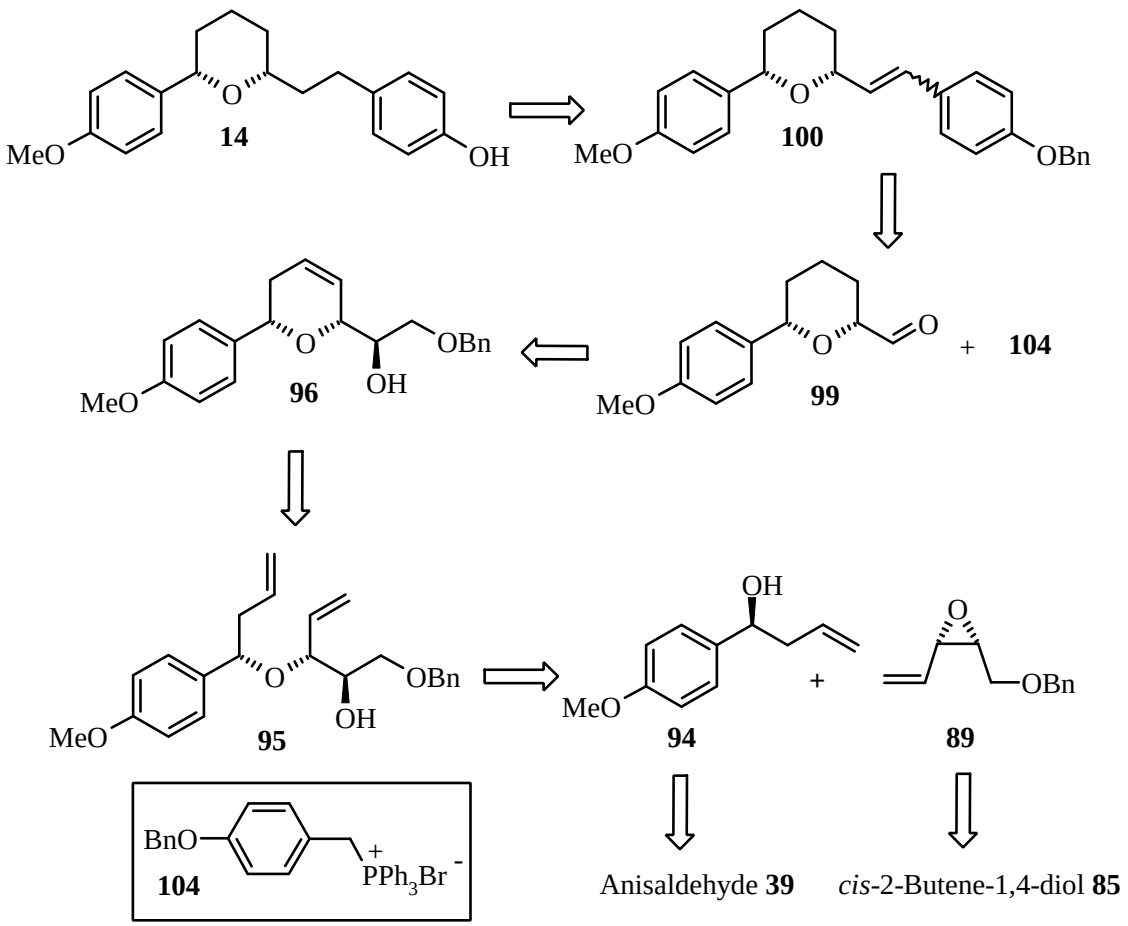


Scheme 21

With the key intermediate **81** and **72** in hand, our next target was to couple both the olefinic partner. Thus, the hydroxyl compounds **81** and **72** were treated with $ZnCl_2$[43] in 1,2-ethylenedichloride, unfortunately decomposition of starting material was observed within shorter period of addition. Since our initial attempt to couple both the fragment was failed, we opted for other alternatives such as Mitsunobu,[44] cross metathesis,[45] which were also unsuccessful in our hands.

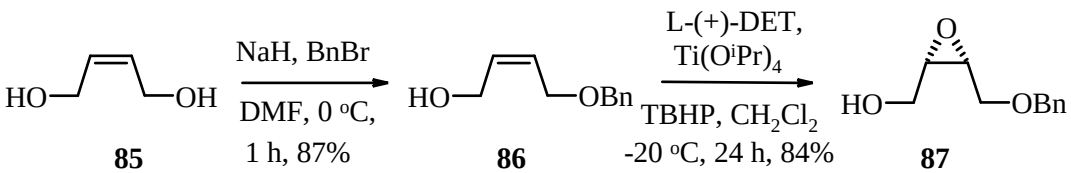
Based on the abovesaid failure, an alternative yet simplified approach to reach the target molecule was planned. After getting the experience in aforementioned etherification reaction, we planned to construct the pyran ring before chain elongation. While searching for potential routes for the construction of the pyran ring, which could be conveniently adapted and amplified towards target molecule, it occurred to us that a short access to the required pyran ring system could be devised by coupling alcohol and vinyl epoxide, followed by RCM cyclization in a tandem fashion. The stereogenic center could be generated via Keck asymmetric allylation[47] and Sharpless asymmetric epoxidation[48] as depicted in scheme 22.

The retrosynthetic analysis reveals that the key steps in the construction of pyran ring are the $BF_3 \cdot OEt_2$ mediated coupling of alcohol **94** and vinyl substituted epoxide **89**, followed by ring closing metathesis reaction. Starting materials were identified as anisaldehyde **39** and *cis*-2-butene-1,4-diol **85**. The homoallylic alcohol **94** could be generated by Keck allylation on anisaldehyde **39**, whereas epoxide **89** from *cis*-2-butene-1,4-diol **85** through some functional group manipulations. The double bond reduction as well as deprotection of benzyl ether could be achieved by hydrogenation on **96**. For the chain extension, Wittig reaction with *p*-benzyloxybenzyltriphenylphosphonium bromide **104** on aldehyde **99** could be opted.



Scheme 23: Retrosynthetic analysis of (−)-centrolobine **14**

In the revised strategy, the synthesis started with a readily available *cis*-2-butene-1,4-diol **85**, which was converted to the chiral intermediate, the (2*S*, 3*R*)-epoxy alcohol **87** by a two step protocol already reported in the literature[49] (Scheme 23). The mono protection of *cis*-2-butene-1,4-diol **85** was achieved by treating with benzyl bromide and sodium hydride in *N*,*N*-dimethylformamide at 0 ^{o}C with 87% yields. The ^{1}H NMR spectrum showed the appearance of the multiplets at δ 7.23-7.36 ppm corresponding to aromatic protons. All the other protons were resonated at their expected chemical shift values.



Scheme 23

***INTRODUCTION OF CHIRALITY**:*

The Sharpless asymmetric epoxidation (SAE) is one of the most useful reaction used in organic synthesis today. When a prochiral Z or E-allyl alcohol is treated with dialkyl tartarate (generally Et or ^{i}Pr), titanium(IV) isopropoxide and tert-butylhydroperoxide, produces the corresponding chiral epoxy alcohol.

***The salient features of SAE are**:*

(i) high yield; (ii) very high enantioselectivity; (iii) reagents are cheap, easily available and safe to handle; (iv) the dialkyl tartrate (6.5 mole percent) and titanium(IV) isopropoxide (5.0 mole percent) are used in catalytic amount; (v) the ease and accuracy of the prediction of the streochemical outcome irrespective of the substitution on the allylic alcohol.

Stereoselectivity:

The stereochemical outcome of the asymmetric epoxidation is consistent with (S,S)-(−)-DET inducing the epoxide formation on the Si face and the (R,R)-(+)-DET inducing the epoxide formation on the Re face of the substituted allylic alcohol as illustrated in Figure 10.

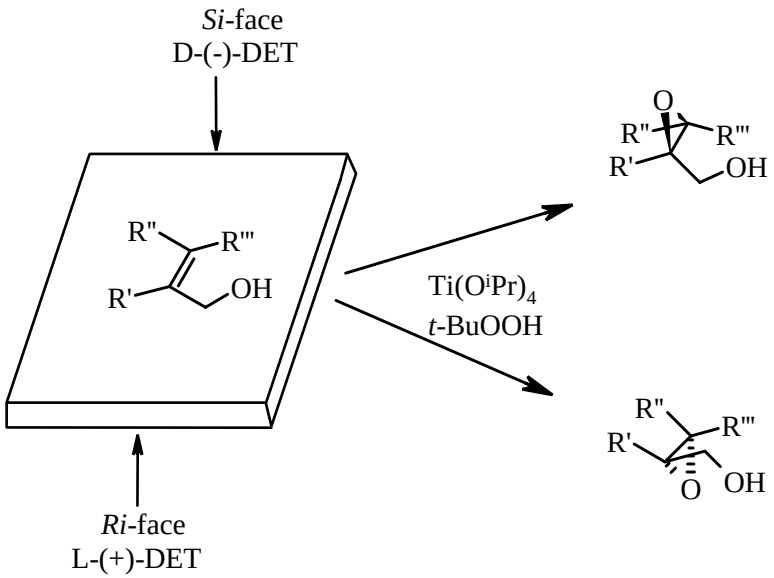
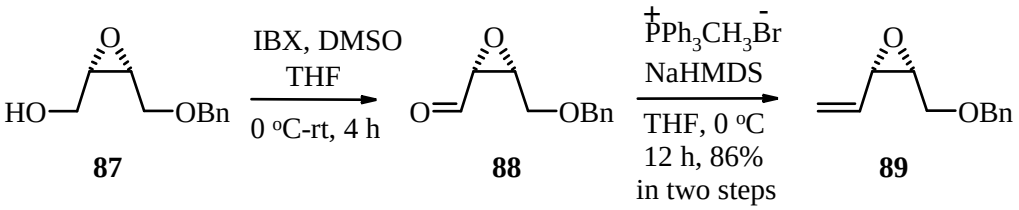


Figure 10

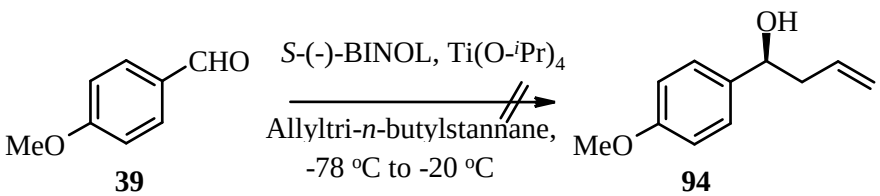
Accordingly, the *Z*-allyl alcohol **86** was treated with L-(+)-diethyltartrate, titanium tetraisopropoxide and *tert*-butylhydroperoxide in presence of 4Å molecular sieves in CH_2Cl_2 at −20 ^oC to give the (2*S*,3*R*)-epoxy alcohol **87** (Scheme 23) in 84% yield. The ^1H NMR spectrum of **87** showed the epoxy protons as two multiplets at δ 3.14-3.29 (1H) ppm and 3.63-3.70 (1H) ppm. All the other protons were resonated at their expected chemical shifts. Enantioselectivity was determined by HPLC using R.R. Whelk-01 column to be 85%.



87 **88** **89**

Scheme 24

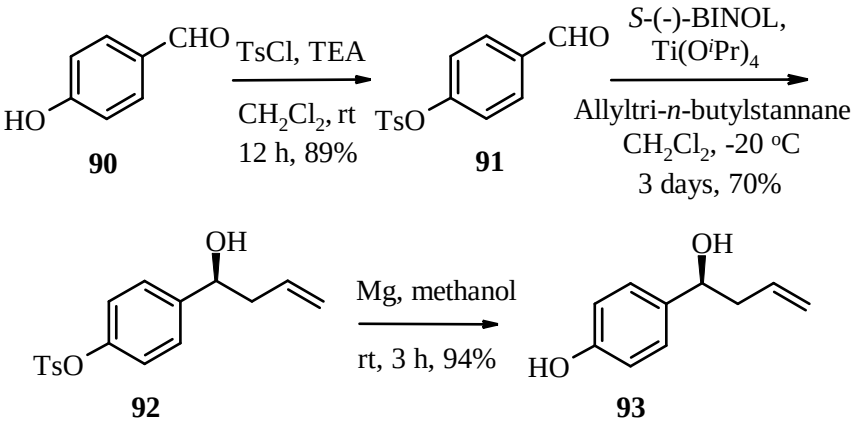
Consequently, **87** was oxidized to the corresponding aldehyde **88** by IBX, followed by one carbon Wittig extension with methyltriphenylphosphonium bomide and NaHMDS[50] in tetrahydrofuran to provide **89** in 86% overall yield in two steps. In the ^1H NMR spectrum of **89**, the olefinic proton signals appeared as two multiplets at δ 5.22-5.44 (2H) and 5.51- 5.68 (1H) ppm.



39 **94**

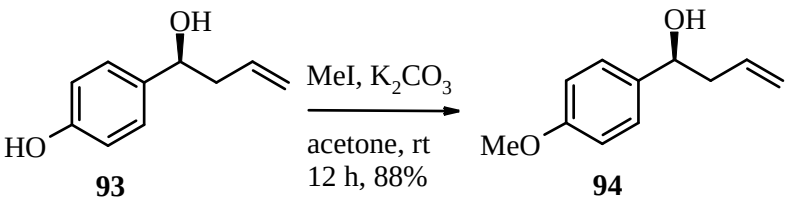
Scheme 25

For the synthesis of other coupling partner, we performed the Keck allylation on anisaldehyde **39** in presence of *S*-(−)-BINOL, titanium(IV) isopropoxide and allyltri-*n*-butylstannane, unfortunately the reaction failed in our hand (Scheme 25). Other asymmetric allylating agents like tin catalyzed allylation in presence of allyl bromide provided very poor ennantioselectivity. When we gone through literature,[51] it was learnt that aromatic aldehyde containing para substitution with an electron withdrawing group (such as nitro, tosyl) undergoes the Keck allylation with excellent stereoselectivity.



Scheme 26

Accordingly, phenolic hydroxyl group of **90** was converted to its tosyl derivative by treating with *p*-tolunesulphonyl chloride, triethylamine in dichloromethane. The spectral data was in full agreement with the desired compound. Aldehyde **91** was treated with *S*-(−)-BINOL, titanium(IV) isopropoxide and allyltri-*n*-butylstannane at −78 ^{o}C and stirred for 3 days at −20 ^{o}C to obtain homoallylic alcohol **92**. In the ^{1}H NMR spectrum, the olefinic protons appeared at δ 5.03-5.12 (m, 2H) and 5.59-5.80 (m, 1H) ppm. All the other protons resonated at their expected value confirming the structure of compound **92**.

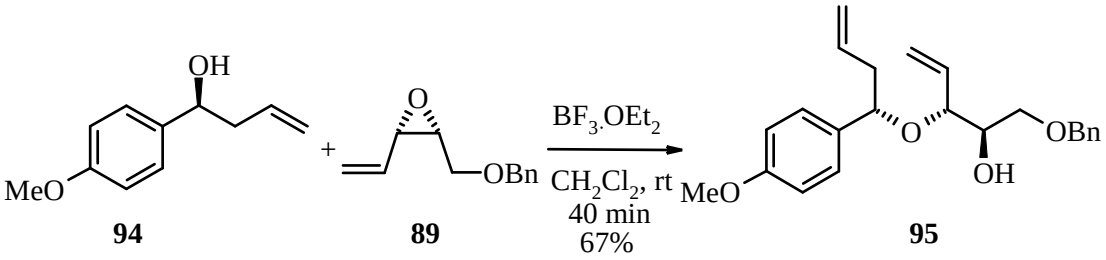


Scheme 27

Since, we required *p*-methyl ether substitution at the aromatic ring, some protection deprotection strategy was needed. Thus, the tosyl group was deprotected by treatment of compound **92** with magnesium in methanol at room temperature. In ^{1}H NMR spectrum of **93**, the disappearance of the singlet at δ 2.39 ppm and aromatic protons corresponding to the tosyl moiety were noted, and all other protons resonated at their expected chemical shift. Selective methylation of phenolic hydroxyl group of **93** was performed by treating with methyl iodide in presence of potassium carbonate in acetone at room temperature. In ^{1}H NMR spectrum of compound **94**, singlet at δ 3.71 ppm showed the presence of phenolic −*OMe* group. Other spectral data was in accordance with the structure. The

rotation value of this compound was {$[\alpha]_D^{25}$ −56 (*c* 1.0, benzene)}, which was agreeable with reported value { $[\alpha]_D^{25}$ −66 (*c* 1.0, benzene)}.[52]

The homoallyl alcohol **94** and the vinyl substituted epoxide **89**, precursors to the pyran skeleton were then ready to be coupled and further elaborated toward the target molecule.



94 **89** **95**

Scheme 28

The two segments were engaged by standard epoxide ring opening condition using $BF_3 \cdot Et_2O$ as catalyst in dichloromethane at room temperature to obtain diene **95** with 67% yield. In ^1H NMR spectrum, the protons appeared as multiplets at δ 4.88-5.25 (4H) and 5.40-5.76 (2H) ppm indicated the presence of two olefins. Other spectral data was in accordance with the structure.

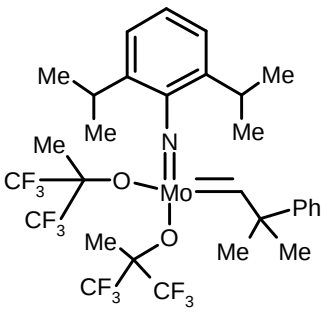
Ring Closing Metathesis: a brief view

Olefin metathesis is a unique carbon skeleton redistribution in which unsaturated C-C bonds are rearranged in the presence of metal carbine complexes. This can be utilized in three closely related type of reactions such as ring-opening metathesis polymerization (ROMP), ring-closing metathesis (RCM) and acyclic cross metathesis (CM). Ring closing metathesis, in which two un-substituted (or substituted) olefins undergo ring closure with formal loss of ethylene, is one of the most popular methods of present time. It has received a great deal of attention in recent years for the synthesis of medium or large size ring systems from acyclic diene precursors. The reasons being:

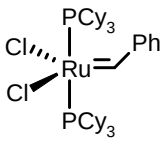
1) *Well designed, stable and highly active catalysts.*
2) *Very high turnover number was observed in the catalytic process.*
3) *Its efficiency in medium to macro-ring cyclization.*

4) *Its superiority over other cyclization method like macrocyclisation, Diels-Alder etc., because of favourable thermodynamic profile.*
5) *Adaptable for both solution and solid phase reactions.*
6) *Water solubility enabling the metathesis in water and methanol.*
7) *Design of recyclable and polymer bound catalysts.*
8) *Applicability to broad scope of substrates like ene –yne and yne-yne metathesis, in addition to tri and tetra-substituted systems.*
9) *Combinatorial RCM libraries.*
10) *Eco-friendly profile, including viability in solvents like super critical CO_2.*
11) *Compatible with various functional groups.*

*Although a number of titanium and tungsten catalyst have been developed for metathesis and related reaction the Schrock's catalyst (**107**), Grubbs' 1st (**108**) and 2nd generation catalysts (**109**) have greatly attracted the attention of synthetic chemists because of their high reactivity and commercial availability. This reaction has changed the strategy of synthetic chemist and it is very common to find RCM as key transformation in the recent total synthesis of natural products.*

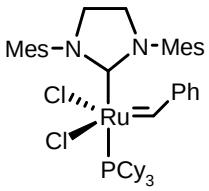


Schrock's catalyst **107**



Grubbs' 1st generation catalyst

108

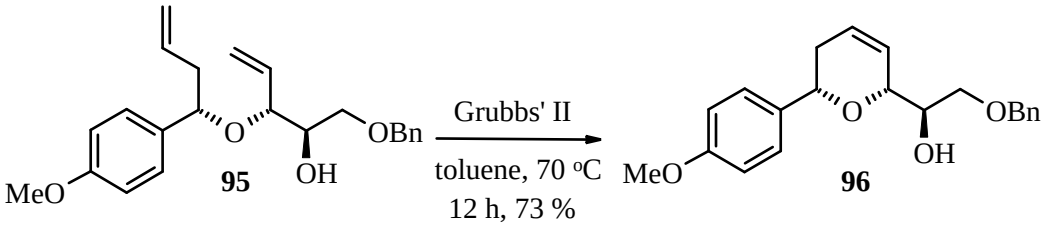


Grubbs' 2nd generation catalyst

109

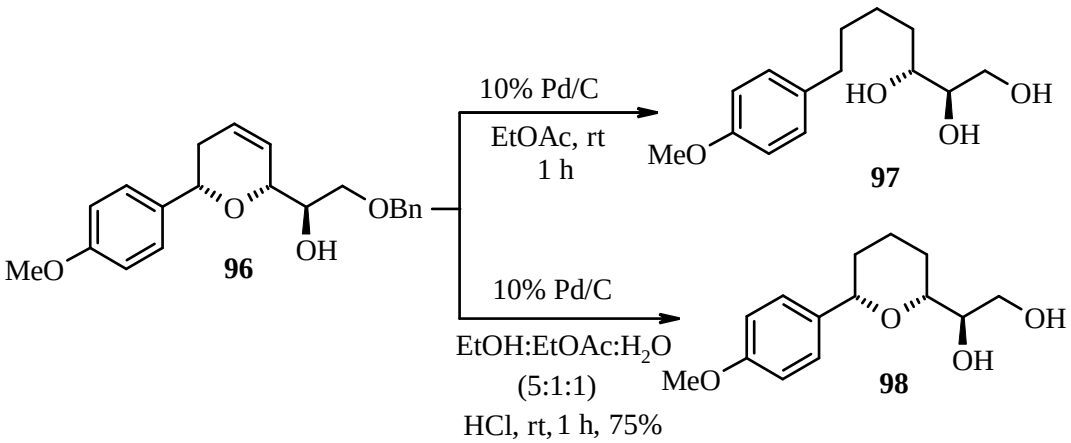
Figure 11

The two alkenyl side arms in **95** were in well position for effecting the RCM reaction. On exposure of **95** to Grubbs' second generation catalyst **109** in toluene heating at 70 ^{o}C for overnight furnished the pyran ring. In ^{1}H NMR spectra of compound **96**, mutiplets at δ 5.74-5.80 (1H) and 5.94-6.04 (1H) ppm corresponding to olefinic protons were present, whereas terminal olefinic protons were disappeared.



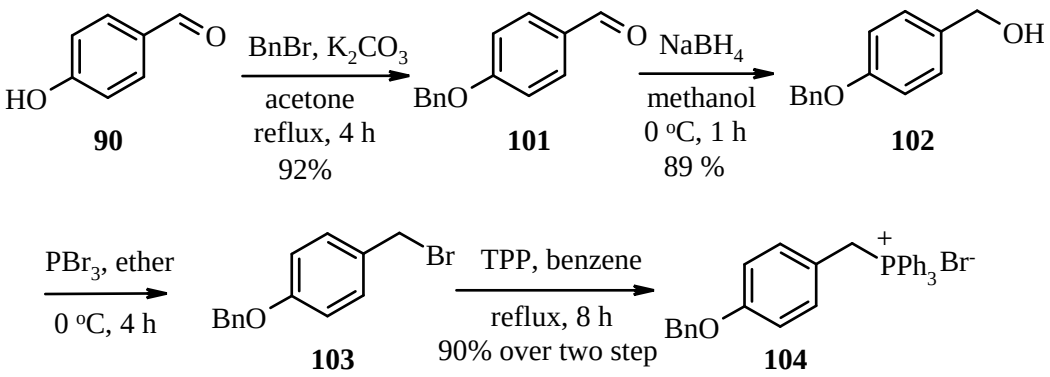
Scheme 29

Compound **96** on treatment with 10% Pd/C under hydrogen atmosphere in ethyl acetate converted to ring opening product **97**. Finally, hydrogenation of the double bond as well as benzyl ether deprotection of **96** was accomplished with 10% Pd/C in a solvent system EtOH:EtOAc:H_2O (5:1:1) in presence of conc. HCl (catalytic) to obtain diol **98**. Disappearance of olefinic as well as aromatic proton due to benzene ring was observed in accordance with the assigned structure.



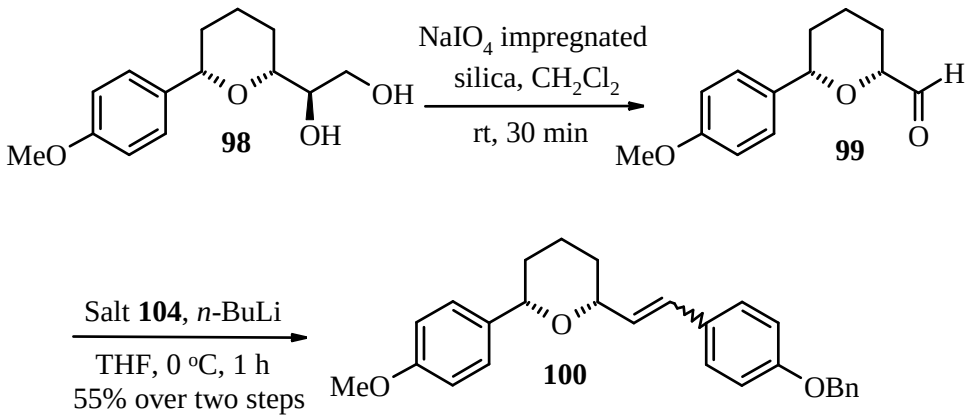
Scheme 30

Aldehyde **99** was obtained by oxidative cleavage of diol **98** with $NaIO_4$ impregnated silica [prepared by mixing 2.58 g sodium meta periodate with 10 g silica gel (200-400 mesh) in 5 mL water] in dichloromethane at room temperature. The crude aldehyde **99** was immediately used for the next reaction without further purification. Compound **99** was then subjected to a Wittig olefination enroute to (−)-Centrolobine **14**. The required 4-benzyloxybenzyltriphenylphosphonium bromide[19] **104** (Wittig salt) was synthesized from the commercially available 4-hydroxybenzaldehyde **90** by a reported procedure (Scheme 31).



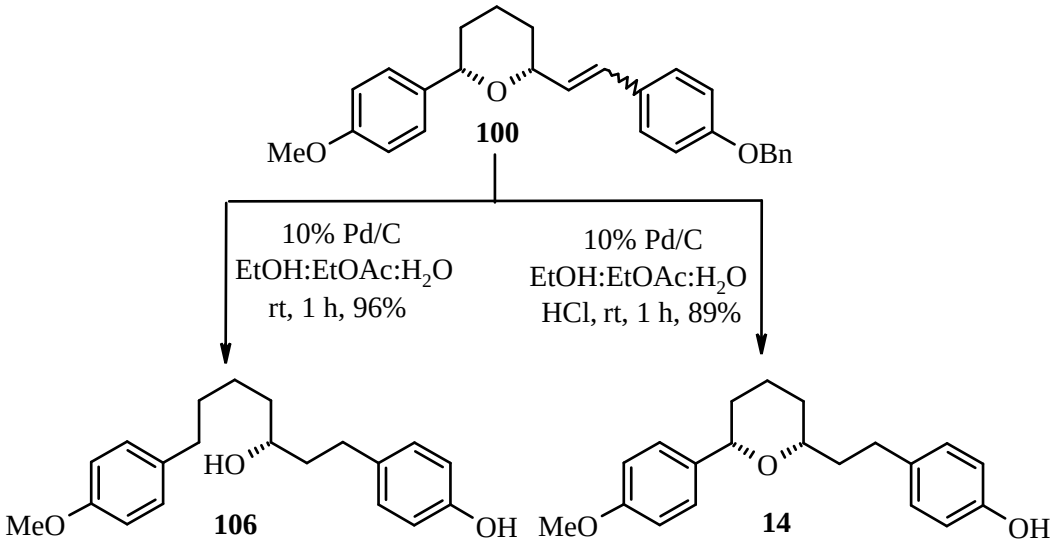
Scheme 31

The Wittig olefination between the salt **104** and the aldehyde **99** was carried out in the presence of *n*-BuLi in THF at 0 ^{o}C to generate the olefin **100** as *cis*:*trans* (3:7) (by ^{1}H NMR) mixture. All the other spectral data were in good agreement with the reported[19] one. Though this constitute a formal synthesis of (–)-centrolobine, we were interested to complete its synthesis and compare the data with the natural product.



Scheme 32

Simultaneous reduction of double bond and deprotection of benzyl ether of **100** by catalytic hydrogenation [in the same solvent system as mentioned for the transformation from **96** to **98**] afforded (−)-centrolobine **14** in 89% yield. ^{1}H, ^{13}C NMR and IR spectra were in good agreement with the natural product. The rotation value of this compound {$[\alpha]_D^{25}$ −91 (*c* 1.2, $CHCl_3$)}, which was agreeable with reported value {($[\alpha]_D$ –93 (*c* 1.0, $CHCl_3$)}. The peak at 344.4 for [M+ Na]$^{+}$ in the ESI MS spectrum was an additional support.



Scheme 33

Table 1: Comparison of ^{1}H and ^{13}C NMR spectral data of 14 with reported one[30]

^{1}H NMR (200 MHz, $CDCl_3$) compound 14	**^{1}H NMR (400 MHz, $CDCl_3$) reported**	**^{13}C NMR (100MHz, $CDCl_3$) compound 14**	**^{13}C NMR (100 MHz, $CDCl_3$) reported**
1.42-1.58 (m, 4H), 1.61-1.69 (m, 2H), 1.78-1.89 (m, 2H), 2.54-2.69 (m, 2H), 3.34-3.39 (m, 1H)	1.25-137 (m, 1H),1.45-1.55 (m, 1H), 1.61-1.66 (m, 2H), 1.67-1.76 (m, 1H), 1.80-1.95 (m, 3H), 2.61-2.76 (m, 2H), 3.41-3.46 (m, 1H)	24.04	23.9
3.73 (s, 3H)	3.80 (s, 3H)	30.74	30.6
4.22 (dd, *J* = 1.9, 11.1 Hz, 1H)	4.29 (dd, *J* = 2.1, 9.0 Hz, 1H)	31.25	31.1
6.67 (d, *J* = 8.4 Hz, 2H)	6.71-6.75 (m, 2H)	33.31	33.1
6.81 (d, *J* = 8.6 Hz, 2H)	6.86-6.90 (m, 2H)	38.28	38.1
6.98 (d, *J* = 8.4 Hz, 2H)	7.03-7.07 (m, 2H)	55.27	55.1
7.24 (d, *J* = 8.6 Hz, 2H)	7.29-7.33 (m, 2H)	76.12	76.9
		79.05	78.9
		113.6	113.4
		115.07	114.8

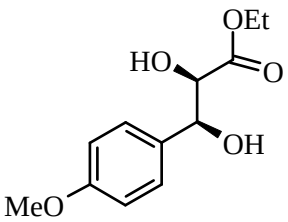
		127.06	126.9
		129.56	129.3
		134.70	134.4
		135.90	135.5
		153.46	153.2
		158.71	158.4

In conclusion, a convergent stereoselective total synthesis of (−)-centrolobine **14** has been achieved. For the construction of pyran ring, Mioskowski's protocol of Lewis acid catalyzed regiospecific opening of vinyl epoxide by alcohol, followed by RCM reaction was adapted. This general strategy for synthesizing the pyran skeleton should allow the preparation of structurally related targets.

EXPERIMENTAL

Experimental

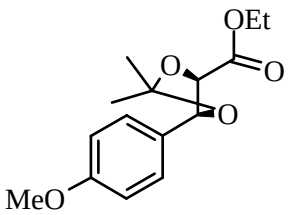
(2*R*,3*S*)-ethyl 2,3-dihydroxy-3-(4-methoxyphenyl)propanoate (68):



A mixture of $K_3Fe(CN)_6$ (24.0 g, 72.8 mmol), K_2CO_3 (10.0 g, 72.8 mmol), methane sulphonamide (2.3 g, 24.17 mmol), $(DHQ)_2PHAL$ (170 mg, 0.22 mmol) in ^{t}BuOH (200 mL) and water (100 mL) was stirred vigorously for 30 min. To this reaction mixture, was added OsO_4 solution (0.1M solution in toluene, 1.0 ml) and stirred for additional 30 min before the addition of olefin **67 (**5 g, 24.27 mmol) at 0 °C and stirred for 12 h. Excess OsO_4 was quenched with Na_2SO_3 solution. ^{t}BuOH was evaporated, residue was extracted with ethyl acetate, dried organic fraction over (Na_2SO_4), concentrated. The residue was purified on silica gel column with petroleum ether: ethyl acetate (1:1) to afford **68** (15.7 g) as a white solid (Melting point: 88.0- 91.2 ^{o} C).

Yield	: 98%
Mol. Formula	: $C_{12}H_{16}O_5$
Optical Rotation $[\alpha]_D^{25}$	: +11.2 (*c* 1.25, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	: 3437, 2982, 2937, 2837, 1734, 1612, 1585, 1514, 1465, 1388, 1303, 1249, 1178, 1110, 1032, 833, 757.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.29 (t, *J* = 7.1 Hz, 3H), 3.82 (s, 3H), 4.22-4.32 (m, 3H), 4.93 (d, *J* = 3.2 Hz, 1H), 6.90 (d, *J* = 8.6 Hz 2H) 7.34 (d, *J* = 8.6 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 13.96, 55.08, 61.76, 74.25, 74.94, 113.62, 127.60, 132.05, 159.05, 172.69 ppm.
Elemental Analysis	**Calcd:** C, 59.99; H, 6.71.
	Found: C, 59.84; H, 6.59.

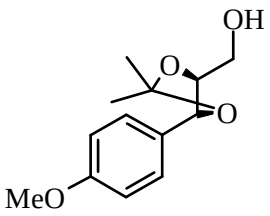
(4*R*,5*R*)-ethyl 5-(4-methoxyphenyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (69):



A solution of **68** (5.3 g, 22.08 mmol), 2,2-dimethoxypropane (4.0 mL, 33.12 mmol) and *p*-TSA (catalytic) in DMF (50 mL) was stirred at room temperature for 3 h, 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 (1:4) to obtain **69** (4.15 g).

Yield	: 67%
Mol. Formula	: $C_{15}H_{20}O_5$
Optical Rotation $[\alpha]_D^{25}$	: −23.0 (*c* 1.22, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	: 2989, 2937, 1754, 1615, 1515, 1464, 1381, 1301, 1215, 1193, 1098, 1033, 896, 830, 756.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.24 (t, *J* = 7.1 Hz, 3H), 1.56 (s, 3H), 1.61 (s, 3H), 3.82 (s, 3H), 4.19-4.31 (m, 3H), 5.09 (d, *J* = 7.7 Hz, 1H), 6.90 (d, *J* = 8.7 Hz, 2H), 7.34 (t, *J* = 8.7 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 14.06, 25.68, 25.89, 55.05, 61.16, 80.50, 81.21, 111.13, 113.83, 127.78, 129.44, 159.69, 170.12 ppm.
Elemental Analysis	**Calcd:** C, 64.27; H, 7.19. **Found:** C, 64.10; H, 7.09.

((4*S*,5*R*)-5-(4-methoxyphenyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (70):



A suspension of LAH (977 mg, 25.7 mmol), **69** (3.6 g, 12.85 mmol) in THF (50 mL) was stirred at room temperature for 12 h. The excess LAH was quenched with ice pieces and saturated solution of Na_2SO_4 and filtered and the residue thoroughly washed with EtOAc. The filtrate was concentrated and purified on silica gel using EtOAc:light petroleum ether (1:3) to afford **70** (2.9 g) as thick oil.

Yield : 91%

Mol. Formula : $C_{13}H_{18}O_5$

Optical Rotation $[\alpha]_D^{25}$: + 32.6 (*c* 1.35, $CHCl_3$)

IR ($CHCl_3$) cm^{-1} : 3436, 2986, 2934, 1614, 1515, 1461, 1371, 1245, 1171, 1059, 1033, 828, 771.

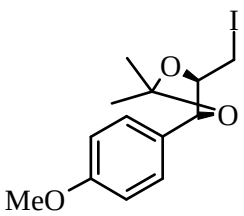
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.52 (s, 3H), 1.58 (s, 3H), 2.01 (bs, 1H), 3.60 (dt, *J* = 4.4 Hz, 13.0 Hz, 1H), 3.81-3.88 (m, 2H), 3.81 (s, 3H) 4.85 (d, *J* = 8.4 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 7.32 (d, *J* = 8.8 Hz, 2H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 26.95, 27.09, 55.05, 60.19, 78.33, 83.50, 108.86, 113.89, 127.79, 129.37, 159.53.

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

Found: C, 65.44; H, 7.49.

(4*R*,5*R*)-4-(iodomethyl)-5-(4-methoxyphenyl)-2,2-dimethyl-1,3-dioxolane (71):



A mixture of compound **70** (0.5 g, 2.02 mmol), Ph_3P (1.08 g, 4.04 mmol), iodine (1.04 g, 4.04 mmol) and imidazole (413 mg, 6.07 mmol) in toluene (10 mL) were heated

at 100 ^{o}C for 4 h and cooled to 0 ^{o}C. The reaction mixture was diluted with diethyl ether and saturated aq. $NaHCO_3$ solution was added and the organic layer separated, washed with water, aq. sodium thiosulphate, dried (Na_2SO_4) and evaporated. The residue was purified by silica gel column chromatography with light petroleum: EtOAc (97:3) as an eluent to afford **71** (630 mg).

Yield : 87%

Mol. Formula : $C_{13}H_{17}O_3I$

Optical Rotation $[\alpha]_D^{25}$: −27.1 (*c* 1.6, $CHCl_3$)

IR ($CHCl_3$) cm^{-1} : 2986, 2933, 2836, 1614, 1515, 1372, 1248, 1171, 1105, 1047, 830, 758.

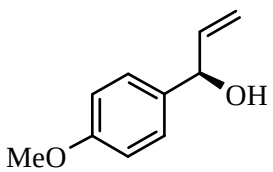
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.56 (s, 6H), 3.20 (dd, *J* = 4.9 Hz, 11.0 Hz, 1H), 3.36 (dd, *J* = 3.8, 11.0 Hz, 1H) 3.52-3.60 (m, 1H), 3.81 (s, 3H) 4.66 (d, *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 8.7, 2H), 7.30 (d, *J* = 8.7, 2H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 4.52, 27.33, 55.19, 81.16, 82.98, 109.15, 114.06, 127.97, 128.77, 159.84 ppm.

Elemental Analysis **Calcd:** C, 44.84; H, 4.92.

Found: C, 44.75; H, 4.86.

(*R*)-1-(4-methoxyphenyl)prop-2-en-1-ol (72):



A mixture of **71** (630 mg, 1.76 mmol), Zn (231mg, 3.53 mmol) was refluxed in ethanol (10 mL) under nitrogen for 1.5 h. The zinc was filtered off, filtrate concentrated, and the residue purified by silica gel column chromatography by using light petroleum: EtOAc (7:3) to obtain **72** (250 mg).

Yield : 86%

Mol. Formula : $C_{10}H_{12}O_2$

Optical Rotation $[\alpha]_D^{25}$: + 7.0 (*c* 1.15, $CHCl_3$)

IR ($CHCl_3$) cm^{-1} : 3400, 2932, 2836, 1611, 1586, 1511, 1464, 1248, 1174, 1034, 830, 758.

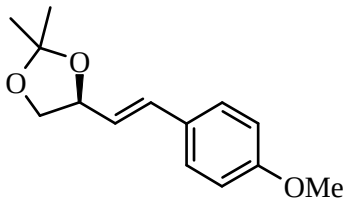
^{1}H NMR ($CDCl_3$, 200 MHz) : δ. 3.70 (s, 3H), 5.0-5.26 (m, 3H), 5.84-6.01 (m, 1H), 6.77 (d, *J* = 8.7 Hz, 2H), 7.17 (d, *J* = 8.7 Hz, 2H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 55.05, 74.57, 113.73, 114.46, 127.58, 134.86, 140.42, 158.95 ppm.

Elemental Analysis **Calcd:** C, 73.15; H, 7.37.

Found: C, 73.04; H, 7.29.

(*S*,*E*)-4-(4-methoxystyryl)-2,2-dimethyl-1,3-diooxolane (76):



To a stirred solution of *p*-methoxybenzyltriphenylphosphonium chloride **75a** (64.38 g, 153.84 mmol) in THF under nitrogen atm. was added *n*-butyllithium (72.1 mL, 115.38 mmole). After stirring for 2 h, aldehyde **75** (10.0 g, 76.92 mmol) was added and the reaction mixture stirred for an additional 4 h. The reaction was quenched with saturated ammonium chloride and then diluted with ether. The combined organic layers were washed with brine, dried ($NaSO_4$), concentrated and the residue was subjected to column chromatography using EtOAc:light petroleum (1: 10) to obtain **76** (10.68 g).

Yield : 60%

Mol. Formula : $C_{14}H_{18}O_3$

Optical Rotation $[\alpha]_D^{25}$: −37.4 (*c* 3.05, $CHCl_3$)

IR ($CHCl_3$) cm^{-1} : 2985, 2935, 2836, 1607, 1511, 1370, 1252, 1210, 1190, 1177, 1059, 1034, 843, 756.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.41 (s, 2.39H), 1.43 (s, 0.61H), 1.48 (s, 3H), 3.67 (t, *J* = 7.9 Hz, 1H), 3.81 (s, 0.64H), 3.83 (s, 2.26H), 4.15 (dt, *J* = 6.0, 8.1 Hz, 1H), 4.60-4.71 (m, 0.21H), 4.86-4.98 (m, 0.79H), 5.61 (dd, *J* = 11.5 Hz, 8.86 Hz, 0.8H), 6.01 (dd, *J* = 15.8, 7.8 Hz, 0.2H), 6.57-6.74 (m,

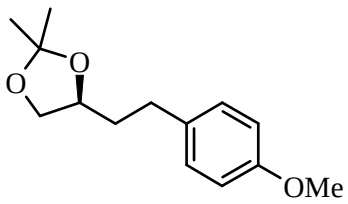
1H), 6.88 (d, *J* = 8.8 Hz, 2H), 7.22 (d, *J* = 8.8 Hz, 1.65H), 7.32 (d, *J* = 8.8 Hz, 0.37H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 25.90, 25.94, 26.75, 26.86, 55.10, 69.50, 69.69, 72.45, 77.44, 109.19, 113.65, 113.89, 124.24, 127.49, 127.79, 128.67, 128.92, 129.96, 133.06, 133.60, 159.01, 159.45 ppm.

Elemental Analysis **Calcd:** C, 71.77; H, 7.74.

Found: C, 71.61; H, 7.69.

(*S*)-4-(4-methoxyphenethyl)-2,2-dimethyl-1,3-dioxolane (77):



A solution of **76 (**10.68 g, 45.64 mmol) in EtOAc (5 mL) was hydrogenated in the presence of 10% Pd/C (400 mg) at rt. After 1 h, the reaction mixture was filtered through a pad of celite, concentrated and the residue purified on silica gel using EtOAc:light petroleum ether (1:10) to afford **77** (10.6 g) as colorless syrup.

Yield : 98%

Mol. Formula : $C_{14}H_{20}O_3$

Optical Rotation $[\alpha]_D^{25}$: + 5.1 (*c* 1.95, $CHCl_3$)

IR ($CHCl_3$) cm^{-1} : 2986, 2935, 1513, 1369, 1244, 1209, 1189, 1059, 756.

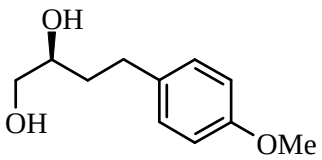
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.37 (s, 3H), 1.44 (s, 3H), 1.72-2.06 (m, 2H), 2.52-2.83 (m, 2H), 3.51 (t, *J* = 7.1 Hz, 1H), 3.80 (s, 3H), 3.97-4.15 (m, 2H), 6.83 (d, *J* = 8.6 Hz, 2H) 7.11 (d, *J* = 8.6 Hz, 2H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 25.70, 26.96, 31.06, 35.51, 55.05, 69.26, 75.23, 108.58, 113.74, 129.16, 133.43, 157.80 ppm.

Elemental Analysis **Calcd:** C, 71.16; H, 8.53.

Found: C, 71.00; H, 8.44.

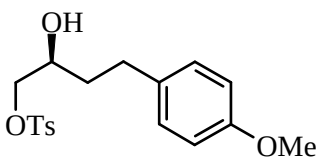
(*S*)-4-(4-methoxyphenyl)butane-1,2-diol (78):



A solution of **77** (10.6 g, 44.91 mmol) and *p*-TSA (20 mg, 0.08 mmol) in MeOH (60 mL) was stirred for 2 h. The reaction mixture was neutralized with Et_3N, concentrated and the residue purified on silica gel using EtOAc:light petroleum ether (7:3) as an eluent to obtain **78** (4.1 g).

Yield	: 70%
Mol. Formula	: $C_{11}H_{16}O_3$
Optical Rotation $[\alpha]_D^{25}$	: −12.90 (*c* 3.1, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	: 3401, 2931, 2849 1609, 1514, 1446, 1253, 1177, 1087, 1026, 872, 814, 773.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.64-1.75 (m, 2H), 2.53-2.82 (m, 2H), 3.29 (bs, 2H), 3.42 (dd, *J* = 7.7, 11.2 Hz, 1H), 3.58-3.72 (m, 2H), 3.77 (s, 3H), 6.83 (d, *J* = 8.6 Hz, 2H) 7.10 (d, *J* = 8.6 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 30.83, 34.78, 55.07, 66.62, 71.47, 113.74, 129.20, 133.66, 157.71 ppm.
Elemental Analysis	**Calcd:** C, 67.32; H, 8.22 **Found:** C, 67.10; H, 8.04.

(*S*)-2-hydroxy-4-(4-methoxyphenyl)but 4-methoxybenzenesulfonate (79):

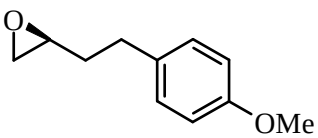


To a solution of **78** (2.5 g, 12.24 mmol), Bu_2SnO (60 mg, 0.24 mmol) and *p*-TsCl (2.5 g, 13.11 mmol) in CH_2Cl_2 (40 mL), Et_3N (1.8 mL, 12.91 mmol) was added slowly at room temperature. After stirring for 20 min, reaction mixture was filtered through a plug

of Celite, concentrated and the residue purified on silica gel using EtOAc:light petroleum ether (1:4) to give **79** (4.30 g).

Yield	: 80%
Mol. Formula	: $C_{18}H_{22}O_5S$
Optical Rotation $[\alpha]_D^{25}$	: + 2.6 (*c* 2.3, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	: 3401, 2931, 1611, 1513, 1359, 1246, 1189, 1175, 1096, 1035, 815, 771.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.64-1.76 (m, 2H), 2.44 (s, 3H), 2.55-2.76 (m, 2H), 3.78 (s, 3H), 3.70-4.03 (m, 3H), 6.81 (d, *J* = 8.7 Hz, 2H), 7.07 (d, *J* = 8.7 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H) 7.79 (d, *J* = 8.4 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 21.47, 30.24, 34.24, 55.05, 68.29, 73.80, 113.66, 127.76, 129.15, 129.81, 132.29, 133.04, 144.93, 157.65 ppm.
Elemental Analysis	**Calcd:** C, 61.69; H, 6.33.
	Found: C, 61.56; H, 6.21.

(*S*)-2-(4-methoxyphenethyl)oxirane (80):



Compound **79** (4.3 g, 16.7 mmol) was dissolved in MeOH (50 mL) and K_2CO_3 (4.6 g, 33.4 mmol) was added. The mixture was stirred at room temperature for 1 h and concentrated. The residue was dissolved in water and extracted with ethyl acetate, washed with water, dried (Na_2SO_4) and evaporated. Purification on silica gel using light petroleum: EtOAc (4:1) as an eluent afforded pure epoxide **80** (1.9 g).

Yield	: 65%
Mol. Formula	: $C_{11}H_{14}O_2$
Optical Rotation $[\alpha]_D^{25}$	: −11.8 (*c* 0.85, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	: 3018, 2934, 1612, 1513, 1409, 1247, 1217, 1178, 1037, 830, 769.

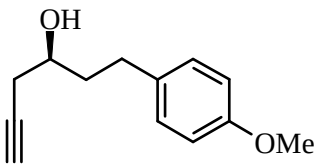
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.66-1.78 (m, 2H), 2.36 (dd, *J* = 2.7, 5.1 Hz, 1H), 2.51-2.72 (m, 3H), 2.76-2.88 (m, 1H), 3.69 (s, 3H), 6.72 (d, *J* = 8.7 Hz, 2H) 7.02 (d, *J* = 8.7 Hz, 2H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz) : δ 31.22, 34.41, 46.95, 51.50, 54.95, 113.68, 129.10, 133.08, 157.78 ppm.

Elemental Analysis **Calcd:** C, 74.13; H, 7.92.

Found: C, 74.00; H, 7.85.

(S)-1-(4-methoxyphenyl)hex-5-yn-3-ol (82):



To a solution of **80** (1.732 g, 9.71 mmol) in DMSO (20 mL) at 4 ^{o}C was added lithium acetylide-EDA complex (1.344 g, 14.6 mmol) in one portion. The reaction mixture was stirred at 4 ^{o}C for 1 h. The excess of reagent was quenched with saturated aq. ammonium chloride and extracted with diethyl ether, washed with water, brine, dried (Na_2SO_4), concentrated. The residue was purified by silica gel column chromatography by eluting with light petroleum ether: EtOAc (7:3) to afford **82** (1.42 g).

Yield : 86%

Mol. Formula : $C_{13}H_{16}O_2$

Optical Rotation $[\alpha]_D^{25}$: −14.3 (*c* 0.7, $CHCl_3$)

IR ($CHCl_3$) cm^{-1} : 3429, 3294, 2934, 2836, 2118, 1611, 1583, 1455, 1464, 1300, 1246, 1177, 1060, 1035, 827, 757, 353.

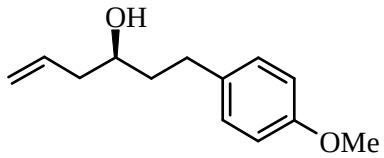
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.67-1.78 (m, 2H), 1.95 (t, *J* = 2.6 Hz, 1H), 2.09 (bs, 1H), 2.28 (dt, *J* = 2.6, 5.4 Hz, 1H), 2.53-2.62 (m, 3H), 3.68 (s, 3H), 3.60-3.72 (m, 1H), 6.72 (d, *J* = 8.64 Hz, 2H), 7.02 (d, *J* = 8.64 Hz, 2H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 27.43, 30.89, 37.94, 55.08, 68.92, 70.97, 80.72, 113.77, 129.23, 133.55, 157.72 ppm

Elemental Analysis **Calcd:** C, 76.44; H, 7.90

Found: C, 76.23; H, 7.80.

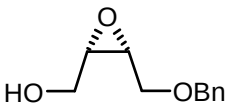
(*S*)-1-(4-methoxyphenyl)hex-5-en-3-ol (81):



Compound **82** (230 mg, 1.13 mmol), Lindlar catalyst (20 mg) and quinoline (5 mg) in benzene (10 mL) were stirred under hydrogen atmosphere at rt for 3.5 h. The catalyst was filtered, concentrated and the residue extracted with ethyl acetate, it was washed with 1N HCl, water, dried (Na_2SO_4) and purified by silica gel column chromatography eluting with light petroleum: EtOAc (8:2) to give **81** (0.93 g).

Yield	: 91%
Mol. Formula	: $C_{13}H_{18}O_2$
Optical Rotation $[\alpha]_D^{25}$	: −9.1 (*c* 1.92, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	: 3412, 2930, 1612, 1512, 1441, 1246, 1177, 1037, 758.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.60-1.71 (m, 2H), 2.01-2.29 (m, 2H), 2.45-2.74 (m, 2H), 3.50- 3.63 (m, 1H), 3.68 (s, 3H), 5.00-5.08 (m, 2H), 5.62- 5.83 (m, 1H), 6.73 (d, *J* = 8.7 Hz, 2H), 7.03 (d, *J* = 8.7 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 30.97, 38.53, 41.94, 55.09, 69.79, 113.66, 118.05, 129.20, 133.98, 134.60, 157.58 ppm.
Elemental Analysis	**Calcd:** C, 75.69; H, 8.80
	Found: C, 75.55; H, 8.65.

((2*S*,3*R*)-3-(benzyloxymethyl)oxiran-2-yl)methanol (87):

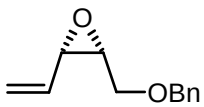


To a solution of L-(+)-DET (1.3 mL, 6.45 mmol) and 4Å molecular sieves powder (10 g) in CH_2Cl_2 (280 mL) was added titanium(IV) isopropoxide (1.3 mL, 4.61 mmol) at

−20 °C. After 30 minutes, a solution of allylic alcohol **86** (8.2 g, 46.06 mmol) in CH_2Cl_2 (50 mL) was introduced and stirred for 45 min. Then reaction mixture was charged with TBHP (5M solution in toluene, 27.6mL, 138.20 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 (1:5) as an eluent to obtain **87**.

Yield	: 84 %
Mol. Formula	: $C_{11}H_{14}O_3$
Optical Rotation $[\alpha]_D^{25}$	−22.4 (*c* 1.5, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	3400, 2928, 1454, 1377, 1100, 1020, 923, 757.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 2.60 (bs, 1H), 3.14-3.29 (m, 2H), 3.63-3.70 (m, 4H), 4.49 (d, *J* = 11.8 Hz, 1H), 4.59 (d, *J* = 11.8 Hz, 1H), 7.24-7.37 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 54.74, 55.69, 60.54, 67.99, 73.35, 127.79, 127.89, 128.45, 137.38 ppm.
Elemental Analysis	**Calcd:** C, 68.02; H, 7.27.
	Found: C, 67.84; H, 7.29.

(2*R*,3*S*)-2-(benzyloxymethyl)-3-vinyloxirane (89):



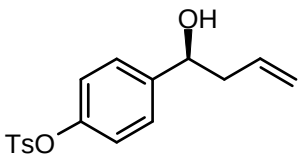
To a solution of IBX (6.5 g, 23.19 mmol) in DMSO (14 mL) at room temperature, was added pyridine (5 mL) followed by epoxy alcohol **87** (3.0 g, 15.46 mmol) in dry THF (10 mL). After 4 h of stirring water (H_2O) (30 mL) was added, and diluted with ether (100 mL) and stirred it for additional 30 min. The solid was filtered off and from the filtrate organic layer was isolated, washed with brine, dried over Na_2SO_4, concentrated to give aldehyde **88** (2.9 g, crude product) the crude aldehyde was used immediately for the next reaction.

To a suspension of salt (16.56 g, 46.39 mmol) in THF (25 mL) at 0 ^{0}C, was added NaHMDS (31 mL, 1M solution in toluene) dropwise. After 1 h stirring at the same temperature, the crude aldehyde **88** in THF was added slowly. After 2 h reaction was

quenched with saturated solution of NH_4Cl, and extracted with ether. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. Purification was done by silica gel (60-120 mesh) column chromatography to afford vinyl epoxide **89** as yellow colour liquid.

Yield	: 86 % over two steps.
Mol. Formula	: $C_{12}H_{14}O_2$
Optical Rotation $[\alpha]_D^{25}$	: −1.95 (*c* 1.65, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	: 3030, 2989, 2920, 2860, 1639, 1496, 1453, 1387, 1148, 1096, 1028, 929, 739.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 3.24 (dt, *J* = 4.5, 5.9 Hz, 1H), 3.38 (dd, *J* = 6.7, 4.4 Hz, 1H), 3.45-3.62 (m, 2H), 4.44 (d, *J* = 11.9 Hz, 1H), 4.53 (d, *J* = 11.9 Hz, 1H), 5.22-5.44 (m, 2H), 5.51-5.68 (m, 1H), 7.17-7.27 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 56.02, 56.69, 67.80, 73.18, 120.76, 127.73, 128.38, 131.85, 137.78 ppm
ESI MS *(m/z)*	: 213 $[M+ Na]^+$
Elemental Analysis	**Calcd:** C, 75.76; H, 7.42.
	Found: C, 75.59; H, 7.35.

(*S*)-4-(1-hydroxybut-3-enyl)phenyl 4-methoxybenzenesulfonate (92):



A mixture of *(S)*-(−)-BINOL (52 mg, 0.18 mmol), 1 M titanium tetraisopropoxide in CH_2C1_2 (0.05 mL, 0.18 mmol), and oven-dried powdered 4**Å** sieves (700 mg) in CH_2C1_2 **(**4 mL) was heated at reflux for 1 h. The red-brown mixture was cooled to room temperature and benzaldehyde **91** (500 mg, 1.81 mmol) was added. After being stirred for 10 min, the contents were cooled to −78 ^oC, and allyltri-*n*-butylstannane **(**0.6 mL, 1.99 mmol) was added. The reaction was stirred for 10 min and then placed in a −20 ^oC freezer for 70 h. Saturated $NaHCO_3$ (0.5 mL) was added, and the contents were stirred for 1 h and then poured over Na_2SO_4 and filtered through a plug of Celite. The crude

material was purified by flash chromatography, eluting with hexanes/acetone (17:3) to give **92** as colourless oil (403 mg).

Yield : 70%

Mol. Formula : $C_{17}H_{18}O_4S$

Optical Rotation $[\alpha]_D^{25}$: –6.1 (*c* 0.95, $CHCl_3$)

IR ($CHCl_3$) cm^{-1} : 3546, 3074, 2980, 2927, 1640, 1598, 1501, 1373, 1215, 1197, 1175, 1154, 1093, 867.

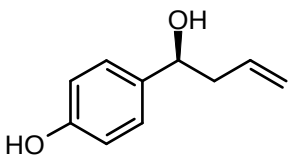
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.39 (s, 3H), 2.33-2.47 (m, 2H), 4.64 (dd, *J* = 5.3, 7.5 Hz, 1H), 5.03-5.12 (m, 2H), 5.59-5.80 (m, 1H), 6.89 (d, *J* = 8.6 Hz, 2H), 7.18-7.26 (m, 4H), 7.63 (d, *J* = 8.4 Hz, 2H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 21.74, 43.98, 72.38, 119.00, 122.30, 126.96, 128.53, 129.71, 132.40, 133.92, 142.74, 145.24, 148.76 ppm.

Elemental Analysis **Calcd:** C, 64.13; H, 5.70.

Found: C, 64.34; H, 5.79.

(*S*)-4-(1-hydroxybut-3-enyl)phenol (93):



A mixture of Mg turnings (264 mg, 11.0 mmol) and distilled MeOH (25 mL) was stirred at room temperature for 5 min under argon, before the mixture was cooled to 0 °C and a solution of **92** (700 mg, 2.2 mmol) in MeOH (5 mL) was added. The resulting mixture was warmed to room temperature and vigorously stirred for 30 min. The reaction was quenched by saturated aq. NH_4Cl, and extracted with CH_2Cl_2. The organic layer was washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to provide **93** (75 mg) as a yellow colour liquid.

Yield : 94 %

Mol. Formula : $C_{10}H_{12}O_2$

IR ($CHCl_3$) cm^{-1} : 3451, 3077, 3025, 2909, 1641, 1614 1599, 1515, 1448, 1372, 1238, 1172, 1046, 834.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.42 (t, *J* = 6.8 Hz, 2H), 4.59 (t, *J* = 6.6 Hz, 1H), 5.02-5.12 (m, 2H), 5.60-5.81 (m, 1H), 6.69 (d, *J* = 8.5 Hz, 2H), 7.21 (d, *J* = 8.5 Hz, 2H) ppm.

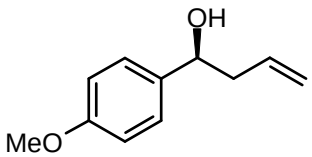
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 43.16, 73.47, 115.40, 118.27, 127.40, 134.29, 134.96, 155.29 ppm

ESI MS *(m/z)* : 187.2 $[M+ Na]^+$

Elemental Analysis **Calcd:** C, 73.15; H, 7.37

Found: C, 73.55; H, 7.20.

(*S*)-1-(4-methoxyphenyl)but-3-en-1-ol (94):



A 25 mL flask was charged with the phenol **93** (460 mg, 2.8 mmol), acetone (15 mL), K_2CO_3 (774 mg, 5.61 mmol) and MeI (0.2 mL, 3.36 mmol) and stirred for 12 h. The reaction was judged complete by TLC analysis, whereupon the reaction mixture was filtered (removal of K_2CO_3) and concentrated *in vacuo*. The resulting crude oil was purified by flash chromatography on silica gel eluting with (1:19 EtOAc/hexanes) to afford 440 mg of **94**.

Yield : 88 %

Mol. Formula : $C_{11}H_{14}O_2$

Optical Rotation $[\alpha]_D^{25}$: −56.1 (*c* 1.0, benzene)

IR ($CHCl_3$) cm^{-1} : 3400, 2934, 2837, 1612, 1586, 1514, 1463, 1247, 1174, 1037, 832, 768.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.91 (bs, 1H), 2.40 (t, *J* = 6.9 Hz, 2H), 3.71 (s, 3H), 4.58 (t, *J* = 6.5 Hz, 1H), 5.00-5.11 (m, 2H), 5.60-5.80 (m, 1H), 6.78 (d, *J* = 8.7 Hz, 2H), 7.18 (d, *J* = 8.7 Hz, 2H) ppm.

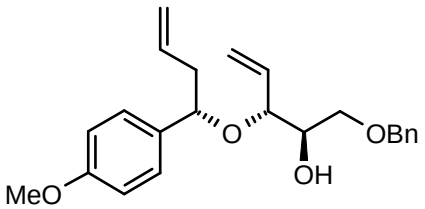
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 43.64, 55.08, 72.91, 113.63, 118.00, 126.99, 134.59, 136.04, 158.86 ppm

ESI MS *(m/z)* : 201.2 $[M + Na]^+$

Elemental Analysis **Calcd:** C, 74.13; H, 7.92

Found: C, 74.00; H, 7.87.

(2*S*,3*R*)-1-(benzyloxy)-3-((*S*)-1-(4-methoxyphenyl)but-3-enyloxy)pent-4-en-2-ol (95):



To a mixture of epoxide **89** (250 mg 1.31 mmol) and alcohol **94** (350 mg, 1.97 mmol) in CH_2Cl_2 (20 mL) was added dropwise a 19% solution of $BF_3{\cdot}Et_2O$ (0.4 mL, 0.065 mmol) in freshly dried CH_2Cl_2 at room temperature. After 45 minutes of stirring at room temperature, the solution was diluted with CH_2Cl_2 and washed with a saturated aqueous sodium bicarbonate ($NaHCO_3$) solution, followed by brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (Petroleum Ether/Ethyl Acetate: 9/1) afforded diene **95**.

Yield : 67 %

Mol. Formula : $C_{23}H_{28}O_4$

Optical Rotation $[\alpha]_D^{25}$: + 3.8 (*c* 2.6, $CHCl_3$)

IR ($CHCl_3$) cm^{-1} : 3436, 3009, 2906, 2862, 1639, 1611, 1512, 1496, 1454, 1302, 1247, 1175, 1035, 923, 832, 755, 698

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.24-2.58 (m, 2H), 3.30-3.65 (m, 3H), 3.71 (s, 3H), 3.84-3.96 (m, 1H), 4.24-4.48 (m, 3H), 4.88-5.25 (m, 4H), 5.40-5.76 (m, 2H), 6.72-6.80 (m, 2H), 7.07-7.25 (m, 7H) ppm.

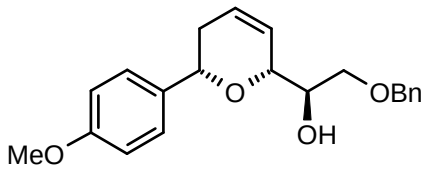
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 43.67, 55.08, 70.79, 72.87, 73.21, 77.39, 77.64, 113.64, 116.80, 118.03, 126.99, 127.58, 128.19, 133.04, 134.58, 134.75, 135.08, 159.08 ppm.

ESI MS (*m/z*) : 391.48 $[M+ Na]^+$

Elemental Analysis **Calcd:** C, 74.97; H, 7.66

Found: C, 74.79; H, 7.49.

(*S*)-2-(benzyloxy)-1-((2*R*,6*S*)-6-(4-methoxyphenyl)-5,6-dihydro-2*H*-pyran-2-yl)ethanol (96).



A mixture of compound **95** (0.31 g, 0.84 mmol) and Grubbs' II catalyst (0.021 g, 0.025 mmol) in degassed toluene (60 mL) was heated at 70 ^oC for 12 h. The reaction mixture evaporated and then purified on silica gel by eluting with light petroleum: EtOAc (19:1) to afford **96** (0.21 g).

Yield : 73 %

Mol. Formula : $C_{21}H_{24}O_4$

Optical Rotation $[\alpha]_D^{25}$: +4.3 (*c* 1.4, $CHCl_3$)

IR ($CHCl_3$) cm^{-1} : 3401, 2922, 2851, 1612, 1514, 1454, 1385, 1303, 1247, 1174, 1085, 829, 770.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.19-2.31 (m, 2H), 2.58 (bs, 1H), 3.53-3.72 (m, 2H), 3.78 (s, 3H), 3.78-3.90 (m, 1H), 4.48-4.61 (m, 4H), 5.74-5.80 (m, 1H), 5.94-6.04 (m, 1H), 6.85 (d, *J* = 8.7 Hz, 2H), 7.22-7.33 (m, 7H) ppm.

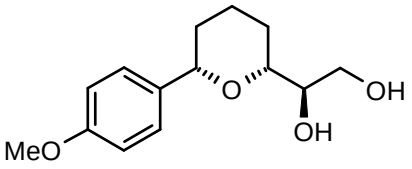
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 32.90, 55.16, 70.86, 72.32, 73.35, 75.16, 75.73, 113.67, 126.75, 126.83, 127.04, 127.67, 128.35, 134.47, 138.08, 158.97 ppm

ESI MS *(m/z)* : 363.42 $[M+ Na]^+$

Elemental Analysis **Calcd:** C, 74.09; H, 7.11.

Found: C, 73.97; H, 7.00.

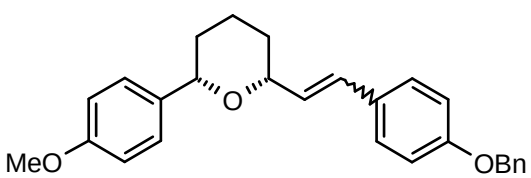
(*S*)-1-((2*R*,6*S*)-6-(4-methoxyphenyl)tetrahydro-2*H*-pyran-2-yl)ethane-1,2-diol (98).



A solution of **96** (0.34 g, 1.0 mmol) in EtOH:EtOAc:water (25:5:5) was hydrogenated in the presence of 10% Pd/C (20 mg) under acidic condition (conc. HCl) at rt. After 1 h, the reaction mixture was filtered through a pad of Celite, concentrated and the residue purified on silica gel using EtOAc:light petroleum ether (1:4) to afford **98** (0.19 g) as a liquid.

Yield	: 75 %
Mol. Formula	: $C_{14}H_{20}O_4$
Optical Rotation $[\alpha]_D^{25}$	: +4.8 (*c* 1.25, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	: 3392, 2932, 1613, 1514, 1384, 1246, 1175, 1035, 830, 771
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.43-1.48 (m, 2H), 1.56 (m, 1H), 1.61 (m, 1H), 1.70-1.73 (m, 1H), 1.89-1.93 (m, 1H), 2.55 (bs, 2H), 3.52-3.57 (m, 2H), 3.59 (dd, *J* = 4.5, 11.7 Hz, 1H), 3.67 (dd, *J* = 11.7, 3.4 Hz, 1H), 3.73 (s, 3H), 4.28 (dd, *J* = 11.4, 2.1 Hz, 1H), 6.80 (d, *J* = 8.7 Hz, 2H), 7.18 (d, *J* = 8.7 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 23.34, 26.80, 33.23, 55.22, 63.61, 74.16, 79.06, 79.70, 113.64, 127.12, 134.94, 158.93 ppm.
ESI MS (*m/z*)	: 275 $[M+ Na]^+$
Elemental Analysis	**Calcd:** C, 66.65; H, 7.99
	Found: C, 66.54; H, 7.80.

(2*R*,6*S*)-2-(4-(benzyloxy)styryl)-6-(4-methoxyphenyl)tetrahydro-2*H*-pyran (100):



Compound **98** (0.08 g, 0.32 mmol) in dichloromethane (5 mL) was stirred with sodium meta periodate impregnated silica gel (0.64 g, 2.0 g/ mmol) for 0.5 h. Silica was separated by filtration, organic layer concentrated under vacuum and crude aldehyde **99** was used for the next reaction.

To a stirred solution of **104** (0.41 g, 0.95 mmol) of *p*-benzyoxybenzyltriphenyl phosphonium chloride in THF (5 mL) under nitrogen was added (0.63 mL, of 1.6 M solution in hexane) of *n*-butyllithium. After stirring for 0.5 h, crude aldehyde **99** was added with THF (3 mL) and the reaction mixture stirred for an additional 1 h. The reaction mixture was quenched with saturated ammonium chloride, diluted with ether. Organic layer washed with water and brine and dried over sodium sulphate. Reaction mixture concentrated and crude product purified by column chromatography, eluting by ethyl acetate:light petroleum ether (3:97) offered product **100** (0.07 g)

Yield : 55 %

Mol. Formula : $C_{27}H_{28}O_3$

Optical Rotation $[\alpha]_D^{25}$: +15.0 (*c* 1.2, $CHCl_3$)

IR ($CHCl_3$) cm^{-1} : 3368, 2929, 2853, 1607, 1511, 1454, 1382, 1247, 1174, 1074, 1029, 834, 769.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.51-2.24 (m, 6H), 3.71 (s, 3H), 4.03-4.13 (m, 0.27H), 4.27-4.35 (m, 1.63H), 4.97 (s, 0.55H), 4.99 (s, 1.42H), 5.58 (dd, *J* = 8.7, 11.6 Hz, 0.68H), 6.06 (dd, *J* = 5.9, 16.0 Hz, 0.27H), 6.41 (d, *J* = 11.8 Hz, 0.8H), 6.63 (d, *J* = 16.0 Hz, 0.17H), 6.76-7.37 (m, 13H) ppm.

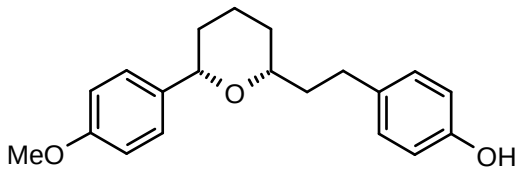
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 23.90, 24.09, 31.55, 31.77, 32.90, 33.43, 55.18, 69.94, 74.86, 78.79, 78.95, 79.57, 113.63, 114.54, 114.81, 127.24, 127.28, 127.41, 127.61, 127.90, 127.95, 128.53, 128.57, 128.95, 129.23, 129.90, 130.13, 130.81, 131.54, 135.43, 135.55, 136.95, 157.98, 158.26, 158.85 ppm.

ESI MS (*m/z*) : 423.5 $[M+ Na]^+$

Elemental Analysis **Calcd:** C; 80.97, H; 7.05.

Found: C; 80.78, H; 6.89.

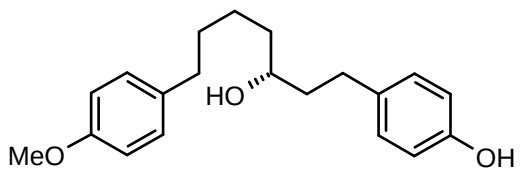
4-(2-((2*R*,6*S*)-6-(4-methoxyphenyl)tetrahydro-2*H*-pyran-2-yl)ethyl)phenol (14).



Compound **100** was hydrogenated by the same procedure used for the transformation of **96** to **98**. Product purified by column chromatography eluting at ethyl acetate: light petroleum ether (1: 10) to obtain (─)-centrolobine **14**.

Yield	: 89%
Mol. Formula	: $C_{20}H_{24}O_3$
Optical Rotation $[\alpha]_D^{25}$	: − 83.0 (c 0.6, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	: 3420, 2930, 1650, 1490, 1220, 1110.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.42-1.58 (m, 4H), 1.61-1.69 (m, 2H), 1.78-1.89 (m, 2H), 2.54-2.69 (m, 2H), 3.34-3.39 (m, 1H), 3.73 (s, 3H), 4.22 (dd, *J* = 1.9, 11.1 Hz, 1H), 6.67 (d, *J* = 8.4 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 6.98 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.6 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 24.04, 30.74, 31.25, 33.31, 38.28, 55.27, 77.12, 79.05, 113.6, 115.07, 127.06, 129.56, 134.70, 135.90, 153.46, 158.71 ppm.
ESI MS *(m/z)*	: 344.4 $[M+ Na]^+$
Elemental Analysis	**Calcd:** C; 76.89, H; 7.74.
	Found: C; 76.66, H; 7.67.

(*R*)-4-(3-hydroxy-7-(4-methoxyphenyl)heptyl)phenol (106).



Yield	: 97%
Mol. Formula	: $C_{20}H_{26}O_3$
Optical Rotation $[\alpha]_D^{25}$	: +3.75 (*c* 1.6, chloroform)
IR ($CHCl_3$) cm^{-1}	: 3369, 2931, 2856, 1612, 1512, 1454, 1244, 1176, 1035, 827.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.36-1.61 (m, 6H), 1.64-1.74 (m, 2H), 2.49-2.72 (m, 4H), 3.58-3.64 (m, 1H), 3.77 (s, 3H), 6.71 (d, *J* = 8.4 Hz, 2H), 6.80 (d, *J* = 8.6 Hz, 2H), 6.99 (d, *J* = 8.4 Hz, 2H), 7.05 (d, *J* = 8.6 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 25.14, 31.08, 31.65, 34.90, 37.24, 39.09, 55.19, 71.52, 113.71, 115.34, 129.22, 129.38, 133.62, 134.60, 154.01, 157.56 ppm.
ESI MS (*m/z*)	: 337.2 $[M+ Na]^+$

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CHAPTER 2

Towards the synthesis of superstolide A

Introduction

Marine natural products chemistry has experienced explosive growth over the past twenty years beginning with Werner Bergmann's[1] pioneer work in the 1950's. Ocean biodiversity began to be appreciated from the beginning of this century and estimates of the number of species range from 1.5 to 4.5 million species with the majority of these being, to date, undescribed. Thus, the potential of the oceans to provide new bioactive metabolites is enormous. The main interest in marine natural products and especially in sponge metabolites is the high incidence of anticancer and cytotoxic metabolites. Among marine invertebrates, demosponges originated the interest in marine chemistry for discovery of new drugs and remain the most prolific phylum concerning new and pharmacologically active compounds. However, some metabolites ascribed to sponges are now suspected to be actually biosynthesized by micro organisms frequently present in symbiotic association.

Sponges are able to biosynthesize original secondary metabolites, which present promising pharmacological activity especially in cancer chemotherapy. The role played by symbiotic microorganisms in the biosynthesis of sponge secondary metabolites is currently a subject of intensive studies in the hope that these structurally complex metabolites may be obtained by biotechnological processes.

Until the beginning of the century, only terrestrial plants were investigated for drug discovery. Interest in marine chemistry started with the work of W. Bergmann who isolated three nucleosides: spongouridine, spongothymidine and spongosine from the Caribbean sponge *Cryptotethya crypta*. The two pyrimidine nucleosides contained arabinose instead of the classical ribose and spongosine combined ribose with a novel base, methoxyadenine. Because of widespread interest in nucleosides at that period, due to the discovery of the anticancer activity of 5-fluorouracyl, the biological properties of these new nucleosides were widely studied. Antiviral properties of these nucleosides were demonstrated and initiated the synthesis of analogues which led to the first antiviral compound, Ara-A (Vidarabine)[2] active against Herpes viruses, and to an antitumor

compound, Ara-C (Cytarabine) effective in acute lymphoid leukemia. Currently these are the only marine related compounds in clinical use.

Since this pioneering work, a number of structurally original and biologically active compounds have been discovered from sponges, most of them with potential application as anticancer agents. The Japanese sponge *Halichondria okadai* provided the halichondrins, a new class of polyethers. Halichondrin B[3] (**1**) (Figure 1), the most potent in the series, are highly cytotoxic *in vitro* and *in vivo* towards P388 and B16 melanoma (ID_{50} 0.093 10^{-3} µg/mL). This is active *in vivo* against P388 leukemia (T/C: 323% at 10 µg/kg) and B16 melanoma (T/C 233 at 60 µg/kg). This is also potently active *in vivo* against lung tumor. Both inhibit microtubule assembly dependent on microtubule-associated proteins. Unfortunately, the development of halichondrins is hampered by limited supplies of material. Numerous synthetic approaches have been devoted to this class of compounds. However due to the complexity of the structures; these approaches are not economically profitable. Members of the halichondrins family were subsequently isolated from other sponges: *Axinella* sp. (Pettit *et al.* 1991),[4] *Phakellia sp*. (Pettit *et al.* 1993)[5] and *Lissodendoryx sp*. in New Zealand (Litaudon *et al.* 1997).[6]

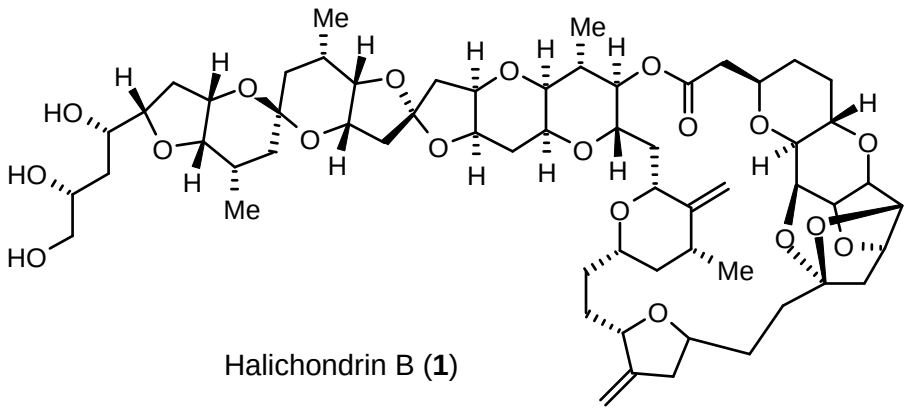


Figure 1

Alternative routes to obtain enough supply of halichondrins are investigated: the search for another original class of cytotoxic polyether derivatives are spongistatin **2,**[7] isolated from *Spongia sp*. and *Spirastrella spinispirulifera*. In addition, some presumably identical compounds, the altohyrtins (**4**, **5**, **6**)[8] have been isolated from the Okinawan sponge *Hyrtios altum* and cinachyrolide A[9] (**3**) (identical to spongistatin **2**) from a sponge of the genus *Cinachyra Sollas*.

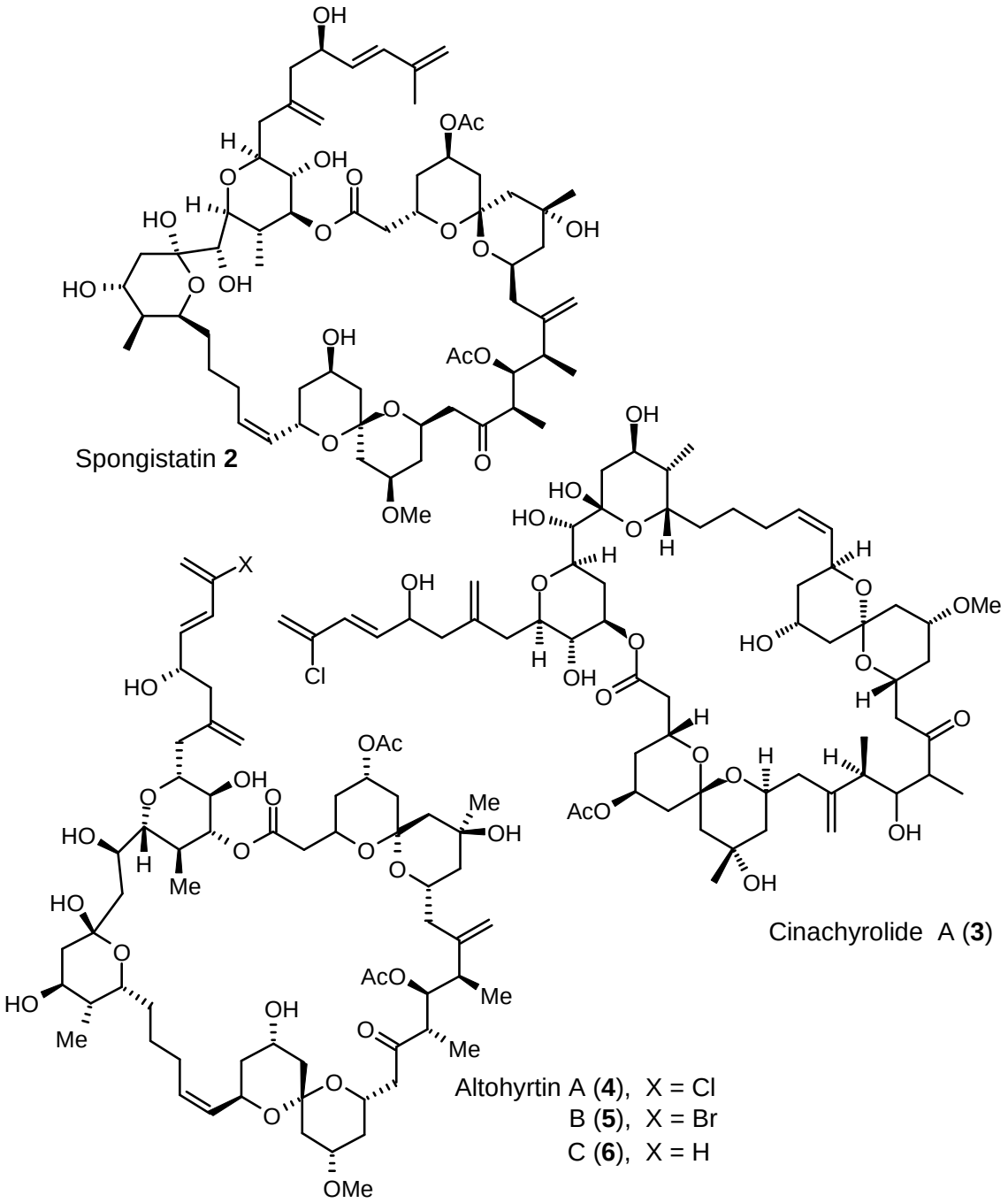
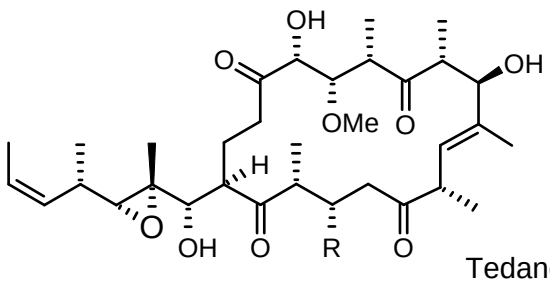


Figure 2

The most potent is spongistatin **2** (Figure 2), highly cytotoxic (ID_{50} 2.5-4 10^{-11} M) against a subset of highly chemoresistant tumor cells comprising the NCI panel of 60 human cancer cell lines (lung, brain, colon) and B16 melanoma. This is also inhibitor of tubulin polymerization and bind in a distinct region of the vinca domain. Cinchyrolide A

(**3**) (Figure 2) has been isolated from the marine sponge genous *cinachyra* in 1993. It was highly cytotoxic against L1210 murine leukemia cells with an IC_{50} <0.6 ng/mL.

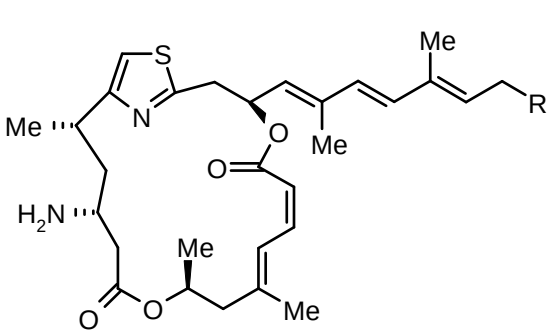
Since their isolation and characterization in the mid 1980's and early 1990's, the cytotoxic marine macrocycles tedanolide[10] **7** and 13-deoxitedanolide **8** (Figure 3) have attracted a great deal of synthetic interest due to strong biological activity and structural complexity. Tedanolide **7** has shown ED_{50}'s of 250 μg/mL (vs the KB human carcinoma cell line) and 16 μg/mL (vs PS lymphocytic leukemia). Preliminary data also suggest that tedanolide may induce terminal cell differentiation at the *S* phase at concentrations as low as 10 ng/mL, which offers the possibility of using it as a mechanism-based drug lead. 13-Deoxytedanolide **5**, on the other hand, has shown a T/C of 189% at a dose of 125 μg/kg vs P388 cell lines.



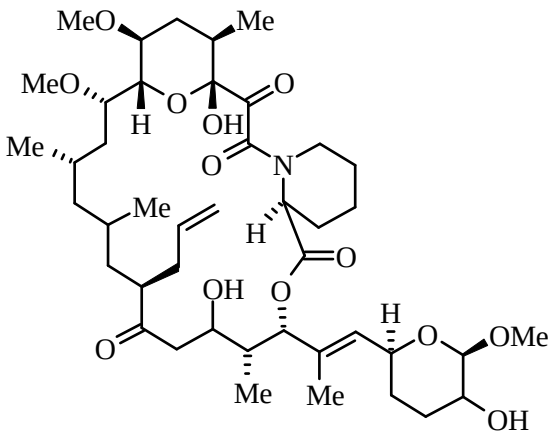
Tedanolide **7**, R = OH
Deoxytedanolide **8**, R = H

Figure 3

Peteamine[11] (**9**, **10**, **11**) (Figure 4) had been isolated from a New Zealand sponge *Mycale sp*. (Northcote *et al.* 1991). Total synthesis of pateamine A (**9**) (Romo *et al.* 1998) allowed to evaluate the biological activity of this promising immunosuppressive agent.



Peteamine A (**9**) R = NMe_2
B (**10**) R = NHMe
C (**11**) R = $N(O)Me_2$



FK 506 (**12**)

Figure 4

It showed great promise as a biological probe of complex intracellular signalling pathways involved in T-cell activation. Recent studies exhibited that **9** inhibits a specific intracellular signalling pathway involving in T-cell receptor-mediated IL-2 production, in addition to its effect on TCR signalling pathway, Pat A was found to induce apoptosis in certain mammalian cell lines. FK 506 (**12**)[12] was isolated from *Streptomyces tsukubaensis*. This unique 23-membered macrolide is an important new lead in the search for effective immunosuppressive agents. The exceptional activity of FK506 (**12**) is reportedly considerably greater, in several assays, than which is currently the drug of choice in bone marrow and organ transplantations.

Rapamycin[13] **13**, a naturally occurring 31 membered macrolide, was originally isolated from *Streptomyces hygroscopicus* as an antifungal agent. It shares some structural features with the natural product FK506 (**12**), an immunosuppressant, and as a result also binds to FKBP12 (FK506 binding protein) with high affinity. Like FK506 (**12**), rapamycin **13** exhibits potent immunosuppressive activity and has completed Phase III clinical evaluation for the prevention of organ transplant rejection (Figure 5).

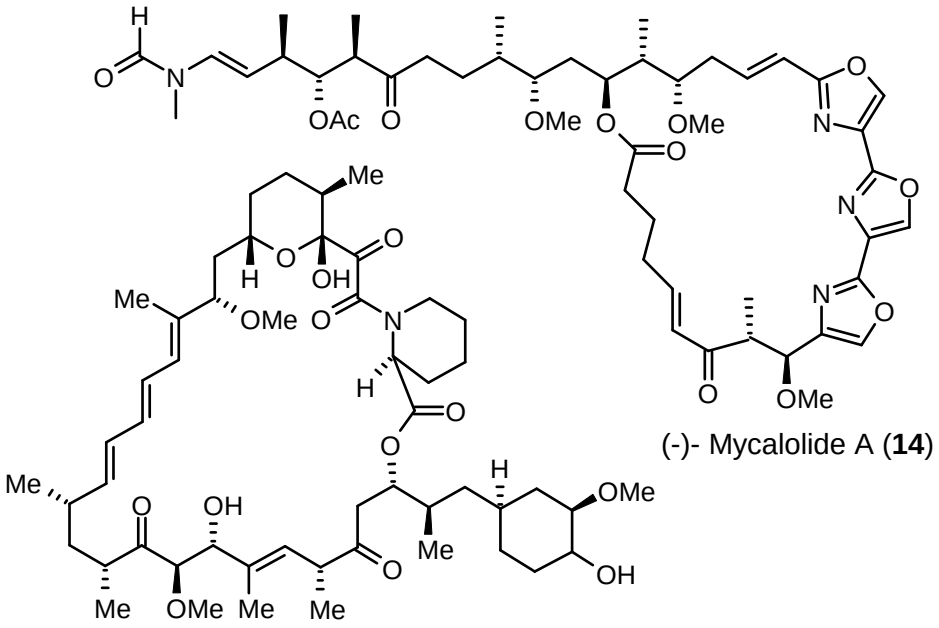
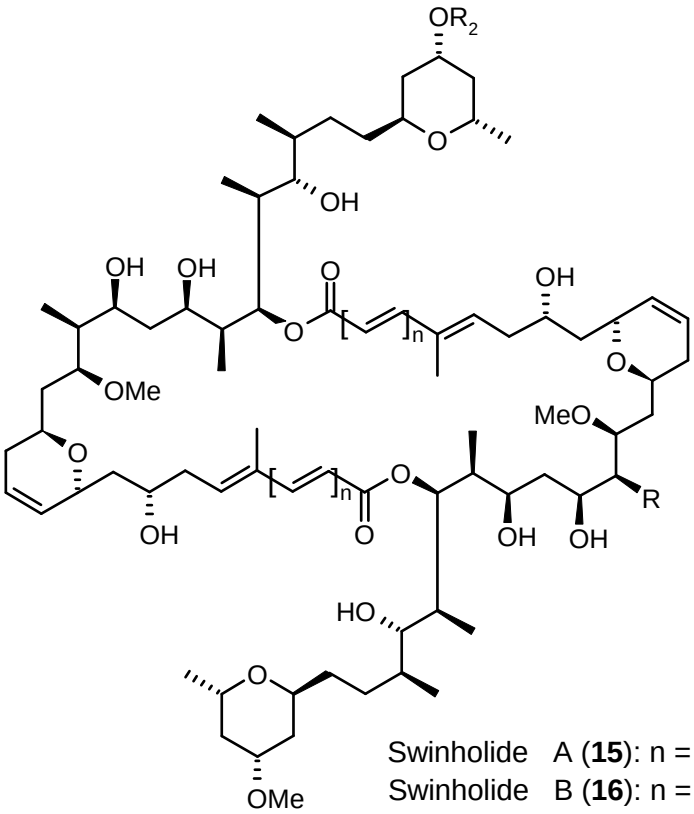


Figure 5

Macrolide belongs to a unique class of *tris*-oxazole containing natural products, display a range of potent biological activities. Foremost among these is mycalolide[14] A (**14**) (Figure 5), isolated by Fusetani and co-workers from sponge of genus *mycale sp*.,

which exhibits potent antifungal activity against a wide array of pathogenic fungi and cytotoxicity toward B-16 melanoma cells with IC_{50} values of 0.5-1.0 ng/mL. Mycalolide A (**14**) also specifically inhibits the actomyosin Mg^{2+}-ATPase, and serves as a novel actin depolymerizing agent which may find eventual applications in the pharmacological area for probing actin-mediated cell functions.

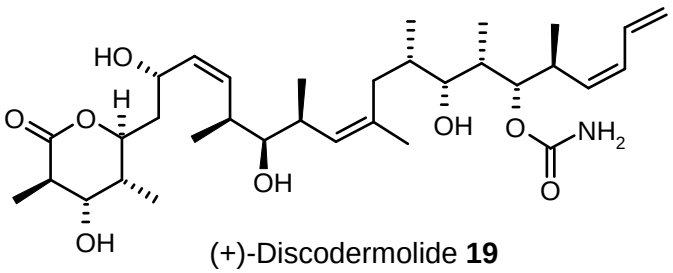


Swinholide A (**15**): n = 1, R1 = R2 = Me
Swinholide B (**16**): n = 1, R1 = H, R2 = Me
Swinholide C (**17**): n = 1, R1 = Me, R2 = H
Misakinolide A (**18**): n = 0, R1 = R2 = Me

Figure 6

Swinholide[15] A (**15**) (Figure 6), a complex polyketide metabolite and 22 membered macrolide has been isolated from a Red Sea sponge *Theonella swinhoei*, was first reported by Carmely and Kashman in 1985. Swinholide A (**15**) exhibits potent cytotoxic activity against a variety of human tumor cell lines (e.g., IC_{50} 0.03 μg mL^{-1} for L1210 cell, 0.04 μg mL^{-1} for KB cells). Several other dimeric macrolides have also been obtained from *Theonellu,* including swinholides B (**16**) and C (**17**) and the analogous 40-membered dilactone, misakinolide A (**18**). These marine macrolides have identical stereostructures and differ mainly in the ring size and the nature of the side-chain terminus.

Another promising candidate for immunosuppressive therapy is (+)-discodermolide **19**[16] (Figure 7) isolated from the sponge *Discodermia dissolute* (Schmidt, 1880) (Gunasekera *et al.* 1990) which shows cytotoxic and immunosuppressive activities. (+)-Discodermolide **19**, blocks cellular proliferation in lymphoid and non-lymphoid cells and this blocking action is not due to cytotoxicity (Longley *et al.* 1993). It also exhibits *in vivo* immunosuppressive properties, being effective in suppressing (93%) the graft-versus-host splenomegaly response of grafted mice at 1.25 mg/kg. More recently, it was demonstrated that (+)-discodermolide **19** competitively inhibits the binding of paclitaxel (Taxol) to tubulin polymers and inhibits the growth of paclitaxel-resistant cells.

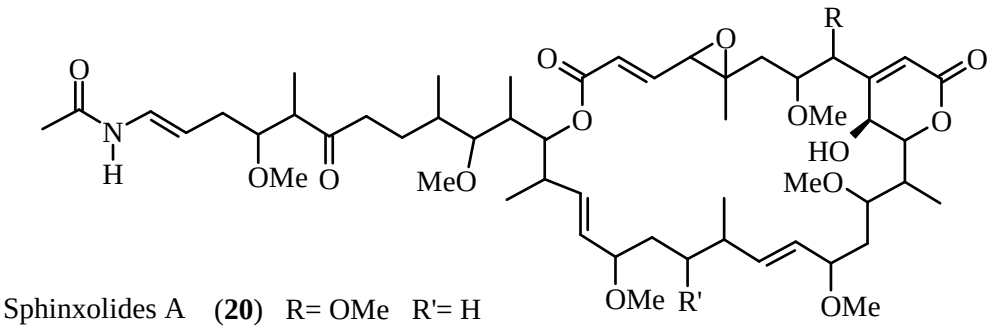


(+)-Discodermolide **19**

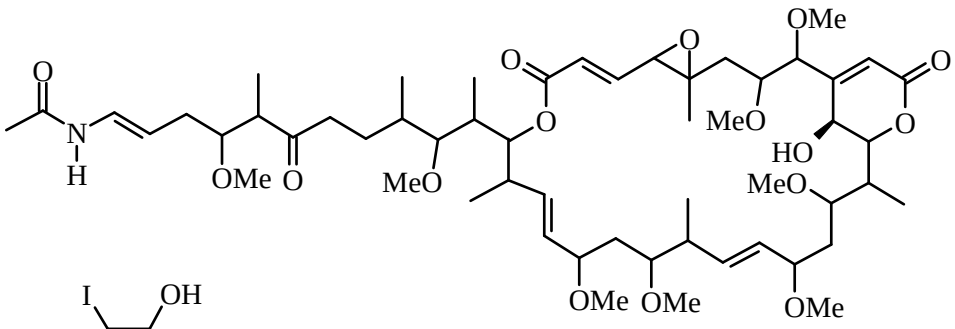
Figure 7

Bioactive natural products isolated from Neosiphonia superstes

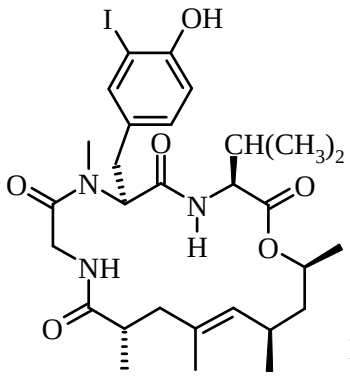
The first marine natural product research program in New Caledonia (*SNOM, Substances Naturelles d'Origine Marine*) was started by *Pierre Potier* in 1977. Nitrogenous compounds, macrolides, and steroids have been reported from eight lithistid sponges of New Caledonia, mostly from deeper waters (≥ 400 m depth), in the families Corallistidae, Phymatellidae, and Pleromidae. Macrolides of two types were isolated from deeper-water Phymatellidae lithistids. 26-membered polyoxygenated macrolides, such as sphinxolide[17] A (**20**) and sphinxolide D (**23**), first isolated from a *Hawaiian nudibranch*, as well as new sphinxolides B (**21**) and E (**24**) from *Neosiphonia superstes*, constitute one group. The other group comprises decalin-fused 16 membered macrolides, such as superstolide A (**26**) and B (**27**) isolated from *Neosiphonia superstes*.[18,19] Sphinxolides (**20, 21, 22, 23**) are the novel 26-membered macrolides, isolated from an unidentified Pacific Nudibranch, which, because of the difficulties in defining the source was named sphinxolide from the misterious Egyptian Sphinxg. Latter on from New Caledonian marine living fossil sponge *Neosiphonia superstes* again it was isolated and showed marked activity in antifungal and cytotoxic assays.



Sphinxolides A (**20**) R= OMe R'= H
B (**21**) R= H R'= H
C (**22**) R= OMe R'= Me
D (**23**) R= H R'= Me



Sphinxolides E (**24**)



Neosiphoniamolide A (**25**)

Figure 8

Sphinxolide A (**20**) and of three congeneric macrolides sphinxolide B (**21**)**,** C (**22**) and D (**23**) proved to be potent cytotoxins against various human carcinoma cells *in vitro*, NSCLC-N6: human bronchopulmunary non-small-cell-lungcarcinoma (IC_{50} = 0.027, 0.016, 0.03, 0.06 µg mL^{-1}). P388: murine leukaemia (IC_{50} = 0.33 10^{-3}, 0.02 10^{-3}, 30 10^{-3}, 8 10^{-3} µg mL^{-1}). P388DOX: murine leukaemia (IC_{50} = 4.1 10^{-3}, 3.1 10^{-3}, 40 10^{-3}, 3 10^{-3} µg mL^{-1}) expressing the multi-drug resistance gene mdr, expecially towards doxorubicine. KB: human nasopharyngeal carcinoma (IC_{50} = 7 10^{-3}, 0.03 10^{-3}, 40 10^{-3}, 3 10^{-3} µg mL^{-1}). HT29: human colon carcinoma (IC_{50} = 115 10^{-3}, 2.4 10^{-3}, 30 10^{-3}, 22 10^{-3} µg mL^{-1}).

Neosiphoniamolide[20] A (**25**) (Figure 8) has been isolated from the sponge *Neosiphonia superstes*. Neosiphoniamolide A (**25**) inhibited the growth of the fungi *Piricularia oryzae* and *Helminthosporium gramineum* with IC_{90}, values of *5* ppm, but exhibited weaker activity against a panel of fungi. More potent activities were exhibited by the co-occurring macrolides, the sphinxolides.

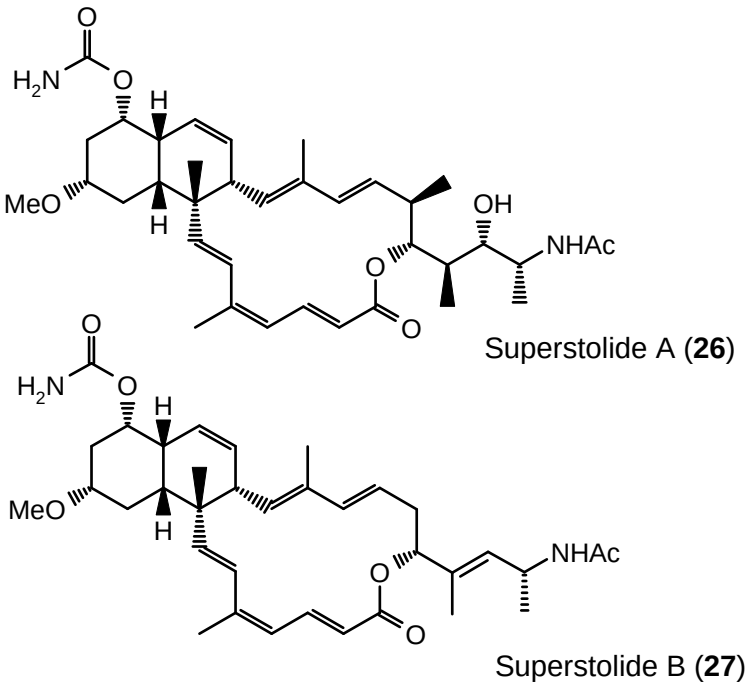


Figure 9

Isolation, structure elucidation of Superstolide A (26) and Superstolide B (27)

Superstolide A (**26**) and B (**27**) are member of a structurally unique family of cytotoxic macrolide, isolated by Minale and co-workers from the new Caledonian deep-water sponge *Neosiphonia superstes*. Superstolide A (**26**) and B (**27**) are highly cytotoxic against human bronchopulmunary non-small cell lung cercinoma NSCLC-N6-L16 cell with IC_{50} value of 0.04 and 0.039 μg /mL, respectively. Both Superstolide A (**26**) and B (**27**) exhibited potent cytotoxicity against murine leukemia P388 cells with IC_{50} of 0.03 μg /mL and human nasopharyngeal carcinoma KB cells with IC_{50} value 0.02 mg/mL and 0.005 μg /mL, respectively. In addition, superstolide A (**26**) is also highly cytotoxic against human colon carcinoma HT29 cell with an IC_{50} of 0.04 μg /mL and murine leukemia cells expressing resistance toward doxorubicine P388 DOX with IC_{50} of 0.02 μg /mL.

The structural novelty of these two molecules are characterized by a unique 16 membered macrolactone attached to a highly functionalized *cis*-decalin moiety. The gross structure was determined by extensive 2D NMR experiments on the lactone and on its opened-ring-derived methyl esters. The relative stereochemistry of the decaline moiety and the C22-C26 fragment were determined by a combination of NMR data and acetonide analysis. Absolute stereostructure of the decaline portion of **26** has been determined on the basis of GLC-modified Horeau's methodology**,** whereas the results of the application of the modified Mosher's method allowed to propose for the C22-C26 fragment the 22*R*, 23*R*, 24*R***,** 25*S***,** 26*R* configuration for superstolide A (**26**).

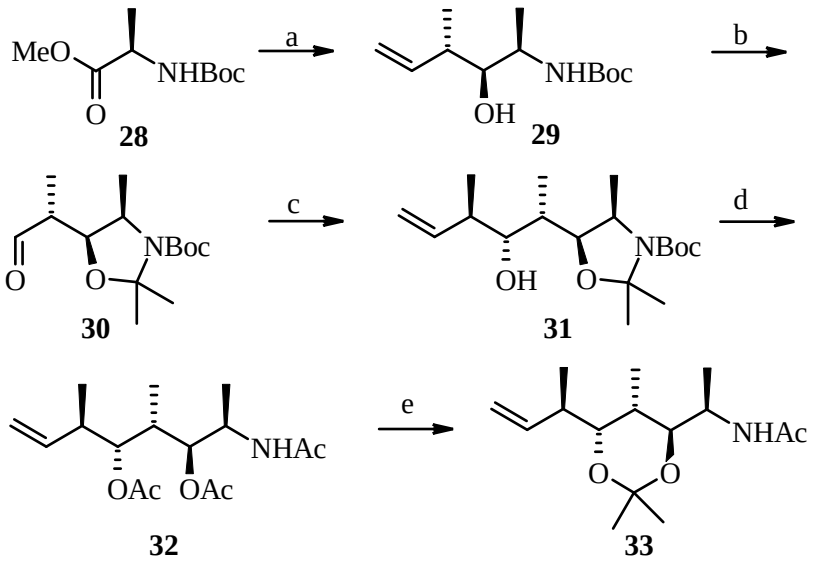
Previous work

Roush and co-worker[21] published a diastereoselective synthesis of *cis*-fused decalin using intramolecular Diels-Alder reaction in 1996. D' Auria and co-workers[22] reported a synthesis of C21-C26 polyketide segment of Superstolide A (**26**) in which Browns crotylborane reagent played a major part. They have generated four consecutive centers by this reagent. The group of Roush[23] and Jin[24] has reported an analogous route to the C20-C26 segment separately. Marshall group[25] has reported the C20-C26 segment, using chiral allenylmetal reagent. Urpi[26] *et al.* used an aldol type reaction to synthesize the polyketide fragment. Paterson group[27], in addition to C20-C26, reported the C1-C5 segment, where they used their own methodology boron-mediated aldol reaction. Very recently Roush group[28] have achieved the total synthesis of Superstolide A (**26**).

1. ***D Auria's approach (2001)***:

The dipropionate framework of superstolide A (**26**) was obtained by Auria's group with high stereoselectivity by two consecutive crotylborations using Brown's procedure starting from D-alanine. *N*-Boc-D-alaninal obtained by DIBAL-H reduction of the commercially available *N*-Boc-D-alanine methyl ester **28** was reacted with (*E*)-crotonyl-diisopinocampheylborane derived from (−)-*B*-methoxydiisopinocampheylborane to give the *anti*-homoallylic alcohol **29**. The concomitant protection of the hydroxyl group and *N*-Boc as the oxazolidine derivative, followed by oxidative cleavage of the double bond provided the aldehyde **30** required for the second crotylboration. Addition of the allylborane derived from (+)-B-methoxydiisopinocampheylborane and (*E*)-butene to

aldehyde **30** at −78 °C afforded the homoallylic alcohol **31**. To confirm the configuration of **31**, it was converted to acetonide **33** in four steps.

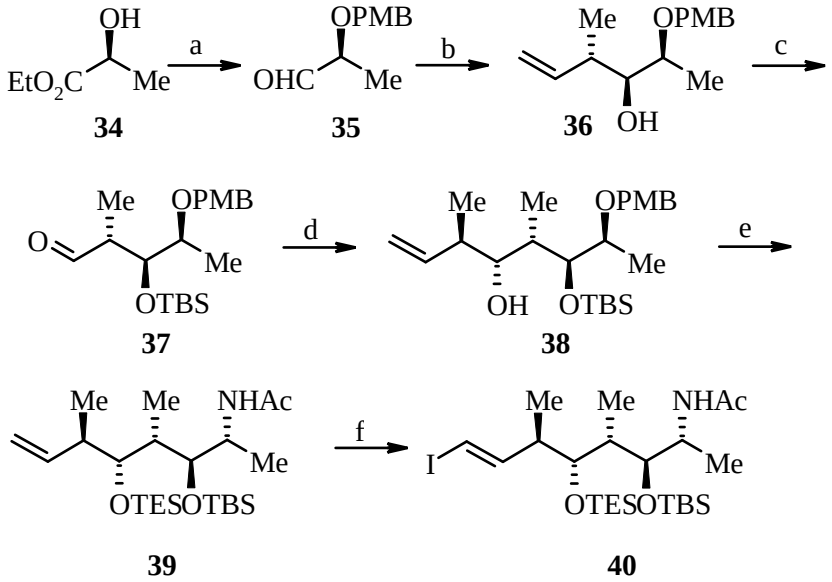


Scheme 1: ***Reagents and conditions:*** (a) i) DIBAL-H, CH_2Cl_2, −78 °C, 2 h; ii) *tert*-BuOK, (*E*)-but-2-ene, *n*-BuLi, −78 to −45 °C, (−)-B-methoxydiisopinocampheylborane, $BF_3{\cdot}OEt_2$, then aldehyde, −78 °C, 4 h, 81%, two steps; (b) i) 2,2-dimethoxypropane dry, *p*-TsOH (cat.), 25 °C, 14 h, 90%; ii) O_3, CH_2Cl_2, −78 °C, then DMS, 3 days, 90%; (c) *tert*-BuOK, (*E*)-but-2-ene, *n*-BuLi, −78 to −45 °C, (+) B-methoxydiisopinocampheylborane, $BF_3{\cdot}OEt_2$, aldehyde **29**, −78 °C, 4 h, 80%; (d) i) MeOH/HCl, 25 °C, 12 h; ii) Ac_2O, Pyr, Et_3N, 25 °C, 12 h; (e) i) K_2CO_3/MeOH, 12 h; ii) dimethoxypropane dry, *p*-TsOH (cat.).

2. ***Zhendong Jin's approach (2001***):

(*S*)-(−)-Ethyl lactate **34** was the point of departure for the synthesis of the polyketide fragment **40** (Scheme 2). The hydroxyl group was protected as PMB ether under acidic conditions and reduction of ester group with DIBAL-H provided (*S*)-2-(4-methoxy-benzyloxy)propionaldehyde **35**. Reaction of aldehyde **35** with (*d*)-(*E*)-crotyldiisopino-campheylborane under Brown's conditions afforded homoallylic alcohol **36**. Protection of the secondary alcohol by TBSOTf, followed by oxidative cleavage of the double bond gave the desired aldehyde **37**, which was reacted with (*l*)-(*E*) crotyldiisopinocampheyl-borane under Brown's conditions to provide homoallylic alcohol **38**. After alcohol **38** was protected by a TES group, the *p*-methoxybenzyl group

was removed by DDQ. The Mitsunobu reaction provided the desired azide. Reduction of the azide by Staudinger reaction followed by acylation provided amine **39**. Oxidative cleavage of the terminal double bond and by employing Takai's reaction, the aldehyde was homologated to the requisite *trans* vinyl iodide **40**.

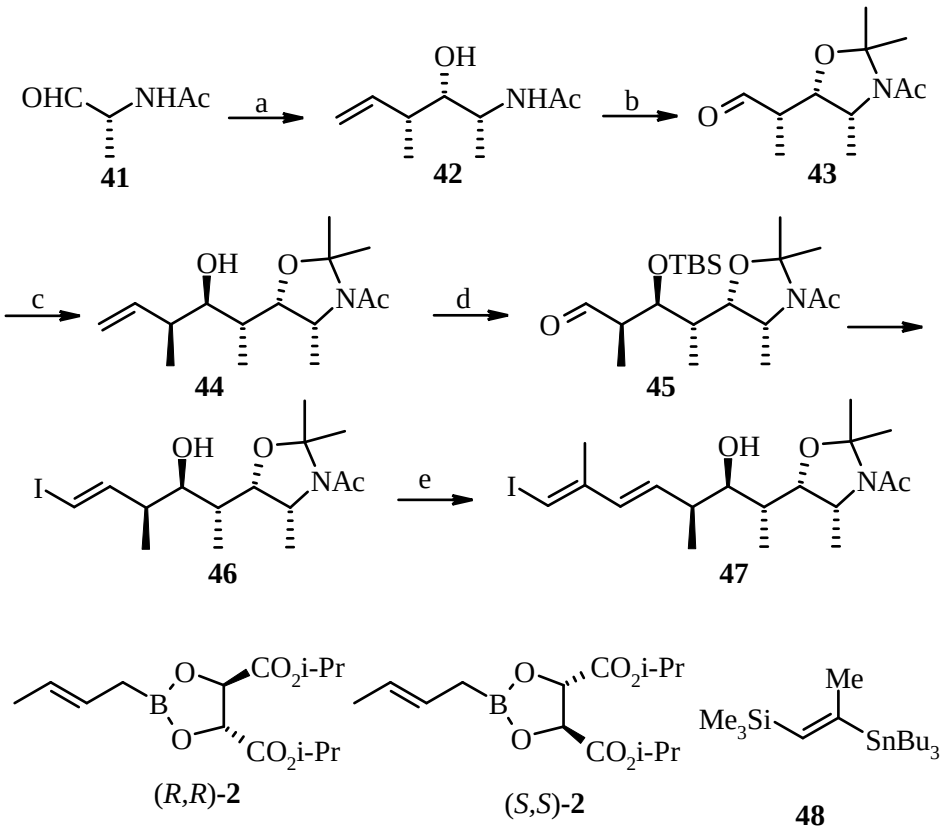


Scheme 2: ***Reagents and conditions:*** (a) i) *p*-methoxybenzyltrichloroacetimidate, CAS, CH_2Cl_2, 25 ^oC, 12 h, 91%; ii) DIBAL-H, CH_2Cl_2, –98 ^oC, 1 h, 89%; (b) i) (*d*)-(*E*)-crotyldiisopinocampheylborane, –78 ^oC, ether; ii) $NH_2CH_2CH_2OH$; (c) i) TBSOTf, Et_3N, CH_2Cl_2, –30 ^oC, 1 h, 64% over two steps; ii) OsO_4 (2%), $NaIO_4$, 2,6-Lutidine, Dioxane:H_2O, 25 ^oC, 4 h, 90%; (d) i) (*l*)-(E)-crotyldiisopinocampheylborane, –78 ^oC, ether; ii) aq. 10% NaOH, 30% H_2O_2, 71%; (e) i) Et_3SiOTf, NEt_3, CH_2Cl_2, –30 ^oC, 1 h, 95%; ii) DDQ, CH_2Cl_2, Buffer (pH 7), 94%; iii) DEAD, PPh_3, HN_3, THF, 6 h, 84%; iv) (v) PPh_3, H_2O, THF, reflux, 12 h; (vi) Ac_2O, Et_3N, 84% for two steps; (f) i) OsO_4, $NaIO_4$, 2,6-Lutidine, Dioxane:H_2O, 25 ^oC, 4 h, 71%; ii) $CrCl_2$, CHI_3, THF, 71%.

3. ***Roush's approach (2003):***

The synthesis started with the crotylboration of *N*-acetyl alaninal in presence of (*R*, *R*)-**2** to produce compound **42**. Acetonide protection, followed by oxidative cleavage of double bond released aldehyde **43**, which was required for 2nd crotylation reaction. In presence of (*S*,*S*)-**2** the aldehyde underwent to crotylboration reaction to release compound **44**. The newly generated hydroxyl group was sillylated by TBS ether and again oxidative cleavage of double bond provided aldehyde, which was converted to

vinyl iodide **46** under Takai olefination condition. The iodo compound **46** was coupled with tin compound **48** in presence of $Pd(PPh_3)_4$ catalyst and the product was immediately converted to iodo compound **47**.

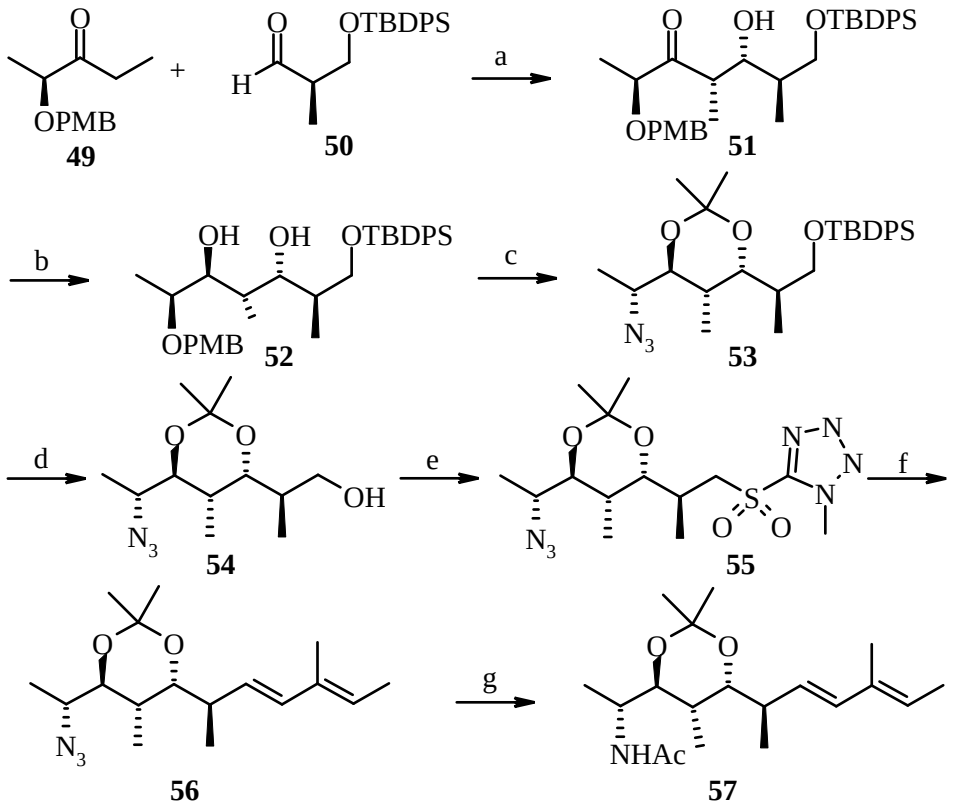


Scheme 3: ***Reagents and conditions:*** (a) (*R, R*)-**2**, 4Å M.S., tol., −78 ^oC, 67%; (b) i) 2,2-dimethoxypropane, PPTS (cat), tol., 98%; ii) O_3, CH_2Cl_2, −78 ^oC, then Me_2S, 23 ^oC; (c) (*S,S*)-**2**, 4Å M.S., tol, –78 ^oC, 76% in two step; (d) i) TBS-OTf, 2,6-lutidine, CH_2Cl_2, 86%; ii) O_3, CH_2Cl_2, –78 ^oC, then Ph_3P, 23 ^oC, 86%; iii) $CrCl_2$, CHI_3, THF, 76%; e) (i) **48**, *n*-BuLi, THF, –78 ^oC, then $ZnCl_2$, then $Pd(PPh_3)_4$ (cat), –10 ^oC, 87%; (ii) NIS, EtCN, –50 to 0 ^oC, 68%.

4. ***Urpi's approach (2003)***:

In their central transformation, titanium enolate of ketone **49** was reacted with aldehyde **50** to provide anti-Felkin adduct **51** as a single diastereomer. Next, diastereomerically pure anti-diol **52** was obtained after reduction of **51** with (Me_4N)-$HB(OAc)_3$. Diol **52** was then converted into the corresponding isopropylidene acetal **53**. Finally, a three-step sequence based on a DDQ mediated deprotection of the −*OPMB*

group, mesylation of the resulting alcohol, and introduction of the azido group with NaN_3 through an S_N2 protocol readily afforded the desired azido polyol **53**.

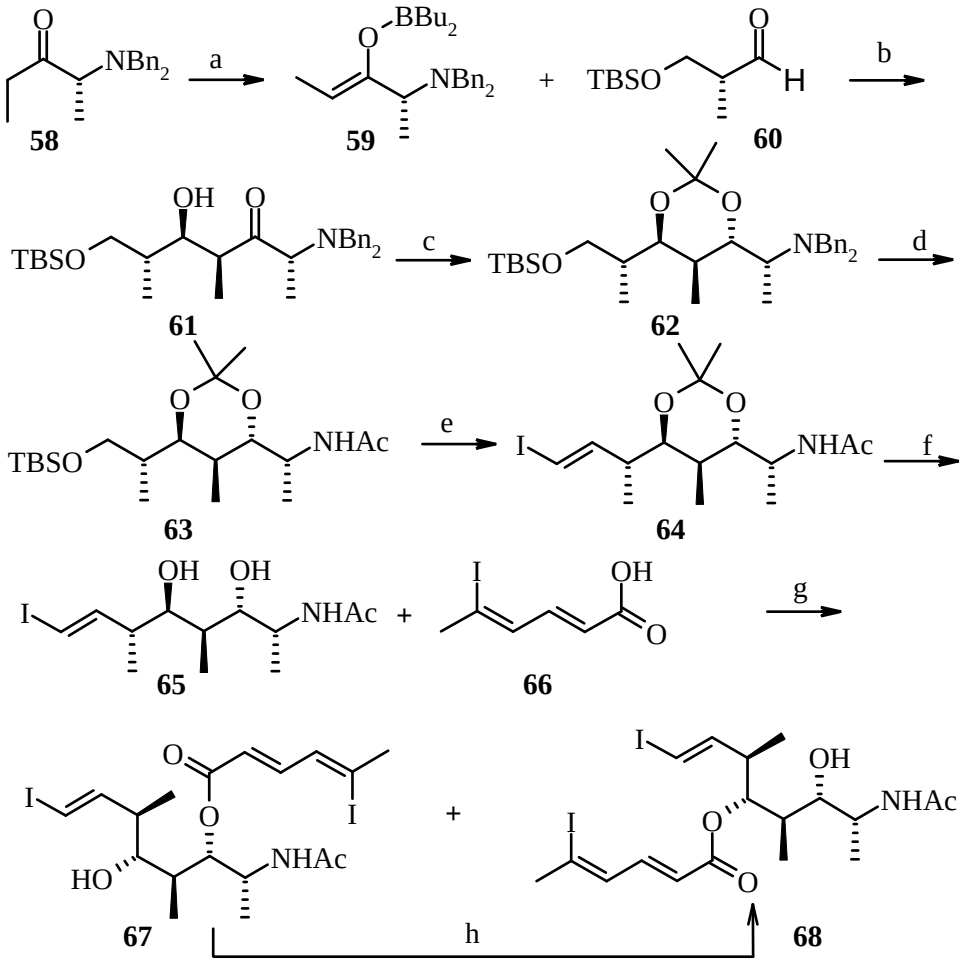


Scheme 4: ***Reagents and conditions:*** (a) (*i*-PrO)$TiCl_3$, *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 3.5 h, 82%; (b) $(Me_4N)HB(OAc)_3$, CH_3CN/AcOH (65:35), –40 to −25 °C, 12 h, 94:6 dr, 92%; (c) i) CH_2Cl_2/$Me_2C(OMe)_2$ (1:1), PPTS cat., rt, 24 h, 92%; ii) DDQ, CH_2Cl_2/ phosphate pH 7 (10:1), 0 °C, 2 h; iii) MsCl, Et_3N, CH_2Cl_2, 0 °C, 4 h; vi) NaN_3, DMF, 70 °C, 2 h, 80%; (d) TBAF.$3H_2O$, THF, rt, 30 h, 99%; (e) i) $Ph(CN_4)SH$, Ph_3P, DEAD, THF, rt, 4 h; (ii) $(NH_4)_2MoO_4$, H_2O_2, THF, rt, 24 h, 84%; (f) LHMDS, (*E*)-2-methyl-2-butenal, 1,2-dimethoxyethane, –65 °C to room temperature, (94:6) *EE*/*ZE*, 72%; (g) i) Me_3P, H_2O, THF, rt, 12 h; (ii) Ac_2O, Et_3N, CH_2Cl_2, rt, 1 h, 88%.

After removing the silicon protecting group of **53**, the azido sulfone **55** was obtained through a Mitsunobu reaction, followed by oxidation of the resulting thioether. Julia-Kocienski olefination involving tiglic aldehyde was carried out and in a straightforward manner with LHMDS in 1,2-dimethoxyethane, azido diene **56** was obtained. Finally, the azido group was converted into the corresponding acetamide **57** in a one pot reaction.

5. ***Paterson's approach (2004)***:

The synthesis of the C20–C26 fragment **65** of superstolide A (**26**) (Scheme 5) started out from the α-amino ethyl ketone **58**. The key *syn* boron aldol reaction of ketone **58** was carried out by first forming the (*Z*)-boron enolate **59**, followed by addition of the α-chiral aldehyde **60**.

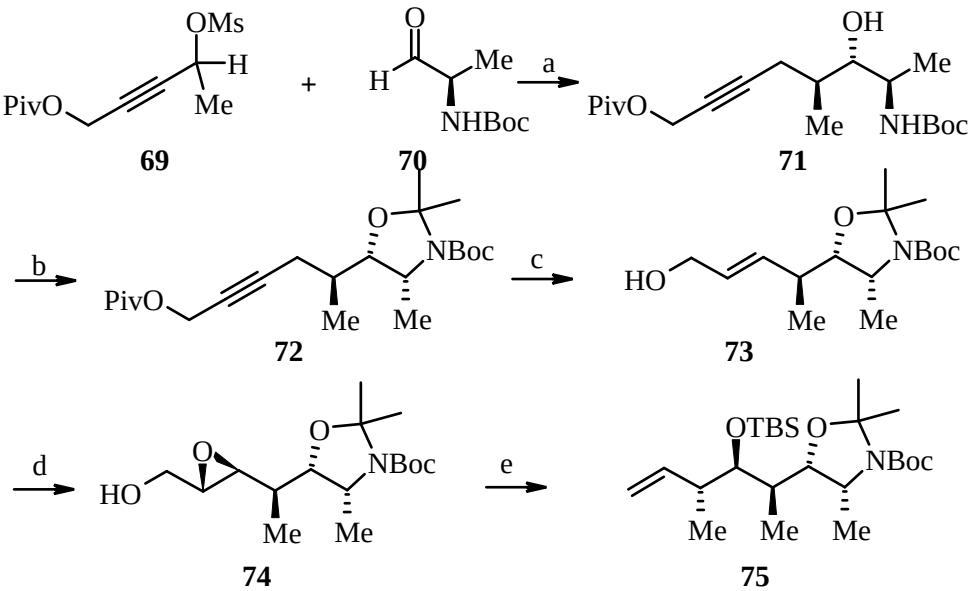


Scheme 5: ***Reagents and conditions*****:** (a) Bu_2BOTf, *i*-Pr_2NEt, CH_2Cl_2, –78 °C to 0 °C, 2 h; **60**, –78 °C to –20 °C, 18 h; (b) $Me_4NBH(OAc)_3$, MeCN, HOAc, –40 °C to –20 °C, 2.5 h; (c) $(MeO)_2CMe_2$, PPTS, CH_2Cl_2, reflux, 18 h; (d) (i) Pd/C, H_2, EtOAc, rt, 20 h; (ii) Ac_2O, Et_3N, CH_2Cl_2, rt, 18 h; (e) TBAF, THF, rt, 4 h; (f) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, rt., 2.5 h; (g)(i) $CrCl_2$, CHI_3, THF/dioxan (1:1), 0 °C, 18 h; (ii) PPTS, MeOH, r.t., 20 h; (iii) EDC, DMAP, CH_2Cl_2, –20 °C, 20 h; (h) $Ti(O^iPr)_4$, CH_2Cl_2, rt, 20 h.

To install the remaining C25 stereocenter required for the C20–C26 segment, reduction of the β-hydroxy ketone **61** provided the desired 1, 3-*anti* diol, which was

subjected to the treatment of PPTS, 2,2-dimethoxypropane in CH_2Cl_2 to give the corresponding acetonide **62**. Compound **62** was exposed to 10% Pd/C under a hydrogen atmosphere leading to debenzylation, followed by acetylation afforded the acetamide **63.** The TBS ether was first removed, followed by oxidation of the resulting alcohol furnished aldehyde, which was immediately subjected to Takai olefination providing the desired *E*-alkene **64.** The removal of acetonide accessesed the diol **65**. Finally, esterification of the diol **65** with acid **66** provided the mixture of two esters **67** and **68**. The undesired ester **67** was converted to the desired **68** by treating the mixture with titanium(IV) isopropoxide, which completed the synthesis of fragment.

6. ***Marshal's approach (2005)***:



Scheme 6: ***Reagents and conditions:*** (a) $Pd(OAc)_2{\cdot}PPh_3$, Et_2Zn, $InBr_3$, THF, 78%; (b) $(MeO)_2CMe_2$, *p*-TsOH, 100%; (c) Red-Al, THF, 0 ^oC, 85%; (d) $Ti(O^iPr)_4$, *t*-BuOOH, L-(+)-tartrate, THF, 85%: (e) i) $Li_2Cu(CN)Me_2$, THF, 98%; ii) TBSOTf, 2,6-lutidine, 85%; iii) HCl, MeOH, 94%; iv) Dess-Martin periodinane, 90%; v) (a) $Ph_3P{=}CH_2$, (b) TBAF, THF, 67%.

For the construction of C20-C26 polyketide segment of superstolide A (**26**), chiral allenylmetal reagents played a major role. Allenylindium reagents prepared *in situ* from propargylic mesylates **69**. In presence of Indium catalyst, it reacted with *N*-Boc alaninal **70** to provide compound **71**. Accordingly, acetonide formation followed by reduction with Red-Al afforded the unsaturated alcohol **73**. A matched Sharpless asymmetric

epoxidation led to the epoxide **74**. Regioselective addition of methyl cyanocuprate reagent provided the diol. Silylation and selective desilyation, followed by Dess-Martin periodinane oxidation afforded aldehyde, which was converted to alkene **75** on Wittig reaction**.**

CHAPTER 2

SECTION I

A chiral pool approach for the synthesis of C21-C26 segment of superstolide A

Present work

Over the decades, carbohydrates have been recognized as naturally occurring organic compounds endowed with wealth of stereochemical attributes. The bulk scale availability at low cost renders them ideal starting materials for organic preparative purposes. The acquisition of an enantiomerically homogeneous target molecule through sugar-based approach is a most attractive alternative for the construction of enantiopure target molecules by asymmetric synthesis.

The generation of enantiopure non-carbohydrate natural products from readily available sugars is of practical value only, if the individual reactions employed allow simple reagents, proceed uniformly, and avoid complex separations in work-up procedures to ultimately enable favourable overall yields. Such practical criteria entail the transformation of a sugar, over functionalized with chirality and hydroxyl groups, into an enantiopure building block with suitable functionalities.

Glucose, a simple monosaccharide sugar, is one of the most important carbohydrates and is used as a source of energy in animals and plants. The natural form, D-(+)-glucose is also referred as dextrose, especially in the food industry. D-(+)-Glucose has been the most popular starting material, due to its easy availability in large quantities, to the large number of its known derivatives and to the ease with which the *trans* relationship of its −*OH* groups can be preparatively exploited. In solutions, D-(+)-glucose exists preferably in pyranose form. The composition of D-(+)-glucose in aqueous solution is, α-pyranose: 38%, β-pyranose: 62%, β-furanose: 0.14% and acyclic carbonyl form: 0.02%.

1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose **77** is one of the most important and easily available D-glucose derivatives[29]. Because of the easy preparation from commercially available cheap starting material [(D-(+)-glucose], 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **77** has been employed as synthon for many synthetic sequences. The utilization of this compound is conditioned by the sequence in which synthetic transformations may most easily be accomplished. The free −*OH* group at C3 can immediately be transformed. Mild acid treatment cleaves the less substituted

dioxolane ring selectively exposing the 5,6-glycol group, which can in turn be elaborated in various ways. Further acid treatment cleaves the second dioxolane ring, exposing either both the C1 and C2 −*OH* groups.

The intriguing structure and biological activity of superstolide A (**26**) attracted us to develop a flexible strategy for its synthesis. A modern synthetic design demands better yielding sequences coupled with mild reaction conditions, high stereoselectivity and readily available starting materials. Keeping these features in mind, we have chosen D-(+)-glucose as starting material for our synthetic endeavour, because of its ready availability in enantiopure form, exceedingly cheap and most importantly, the flexibility of its functional groups for the required organic transformations.

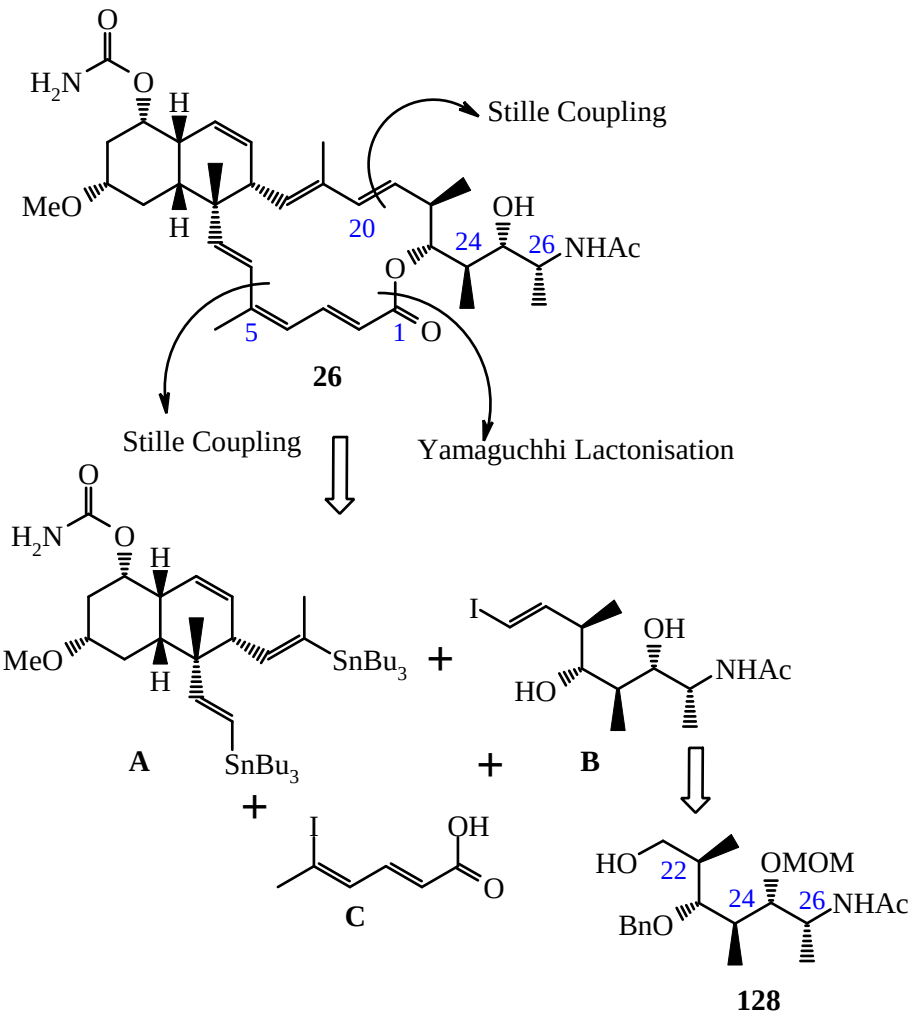
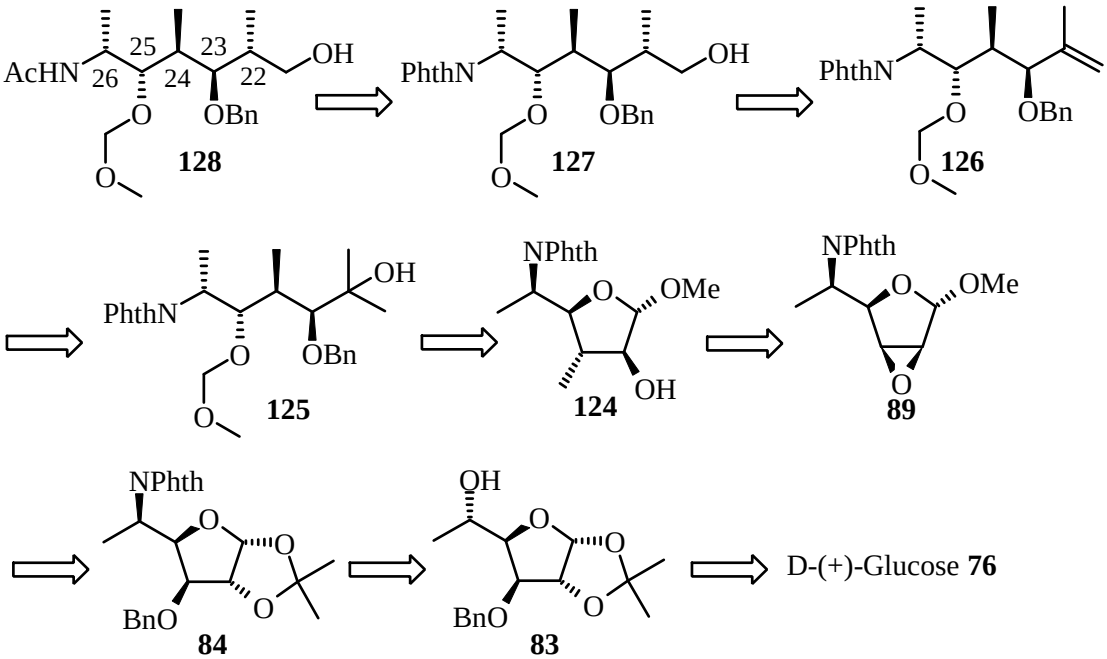


Figure 13

A number of synthetic approaches for the polyketide fragment have been reported in the literature. However, it continues to be a challenging endeavour to synthesize this molecule using inexpensive and readily available raw materials *via* shorter routes.

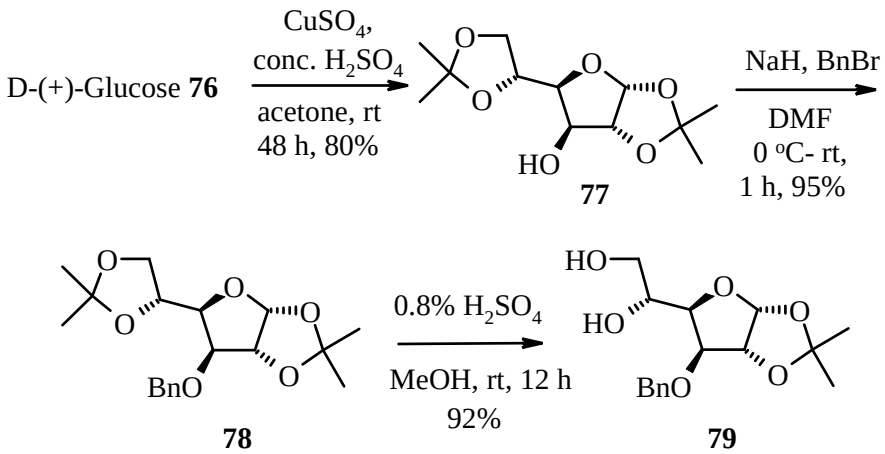
Gratifyingly, we adapted a chiral pool approach for the synthesis of the C21–C26 (**128**) fragment of Superstolide A (**26**). Our approach to **128** is illustrated in scheme 7 in which the key fragment **83** could be obtained from D-(+)-glucose **76** plays a central role, serving not only as the source of the C26, C25, C24 and C23 stereocenters (numbering based on **26**), but also sets the stage for introducing the C22 stereocenter through regio as well as stereospecific hydroboration oxidation. The olefin **126**, the precursor for hydroboration oxidation reaction could be obtained by elimination of the tertiary hydroxyl group of **125**, which in turn could be synthesized from **124** by cleavage of methyl glycoside followed by oxidation and Grignard reaction of the resulting lactone. The C24 methyl center and C23 hydroxyl group could be fixed by opening of epoxide **89** with methyl Grignard reagent. For the introduction of amine group, Mitsunobu reaction over alcohol **83** was envisaged.



Scheme 7

Thus, D-(+)-glucose **76** was transformed into 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **77** by combined action of acetone and anhydrous $CuSO_4$ in the presence of

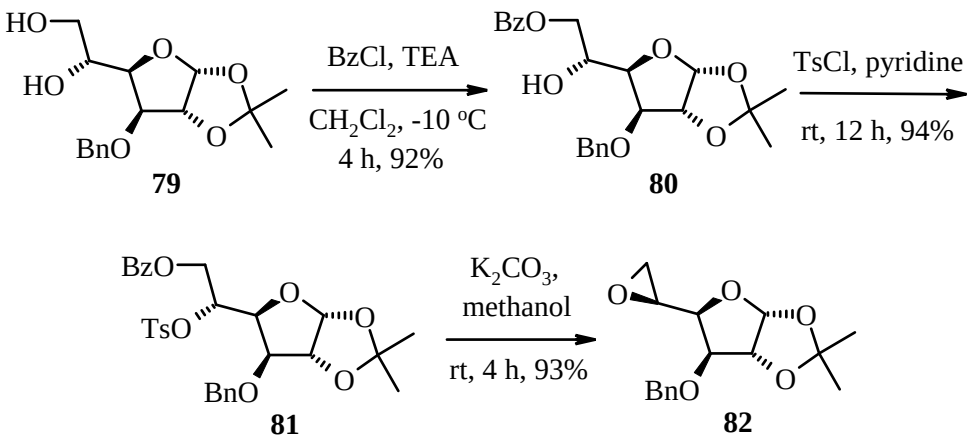
conc. H_2SO_4 (cat.). Subsequent protection of free hydroxyl group at C3 of **77** was carried out using benzyl bromide, sodium hydride in DMF to afford **78**.



Scheme 8

Selective hydrolysis of the 5,6-*O*-isopropylidene group of **78** was carried out by using 0.8% aqueous H_2SO_4 in methanol at ambient temperature for 12 h to afford diol[30] compound **79**, whose ^{1}H NMR spectrum indicated the absence of resonances related to 5,6-*O*-isopropylidene moiety.

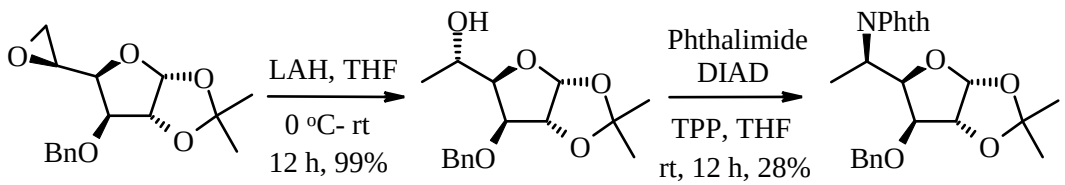
Our next endeavor was to apply the Mitsunobu reaction[31] to incorporate the amine functionality, so inversion of stereochemistry at C5 position of glucose system was required. Thus, diol **79** was selectively converted to its mono benzoate derivative **80** by treating with benzoyl chloride and triethylamine in dry CH_2Cl_2 at lower temperature (−10 ^{o}C). Treatment of **80** with tosyl chloride in pyridine at room temperature provided the tosyl derivative **81**, whose spectral data was in accordance with the assigned structure.



Scheme 9

When tosyl derivative **81** was subjected to the treatment of potassium carbonate in methanol, deprotection of benzoate group and concomitant substitution reaction afforded epoxide **82** with inverted stereocenter at C5. In the ^{1}H NMR spectrum, resonance due to protons corresponding to the tosyl group as well as benzoate group were absent, whereas the characteristic epoxide protons appeared at δ 2.53 (dd, *J* = 2.7, 4.9 Hz 1H), 2.75 (dd, *J* = 4.4, 4.8 Hz, 1H) and at δ 3.26 (ddd, *J* = 2.7, 4.2, 6.1 Hz, 1H) ppm. All the other resonances were at their expected chemical shift values. The structure was also supported by ^{13}C NMR and elemental analysis.

The epoxide **82** on reductive opening by LAH in THF at 0 ^{o}C afforded alcohol **83** as the only product. In ^{1}H NMR spectrum, the methyl group attached to the newly generated alcohol appeared as doublet at δ 1.13 (*J* = 6.4 Hz, 3H), methyl groups corresponding to 1,2-isopropylidene moiety were at δ 1.33 (3H) and 1.49 (3H) ppm as two singlet. ^{13}C NMR spectroscopy was also in accordance with the assigned structure. In IR spectrum, the absorbance corresponding to hydroxyl group was observed at 3455 cm.$^{-1}$ The alcohol **83** was treated with phthalimide in presence of DIAD and TPP in THF at room temperature to afford phthalimide derivative **84** with 28% yield. ^{1}H NMR spectrum was showing extra protons in aromatic region at δ 7.67-7.79 (4H) ppm as multiplet corresponding to phthalimide group. ^{13}C NMR spectrum was in accordance with the structure, where amide carbonyl of phthalimide appeared at δ 167.63 ppm. Further confirmation was obtained by IR spectrum, which showed absorbance for phthalimide group at 1775 and 1712 cm.$^{-1}$

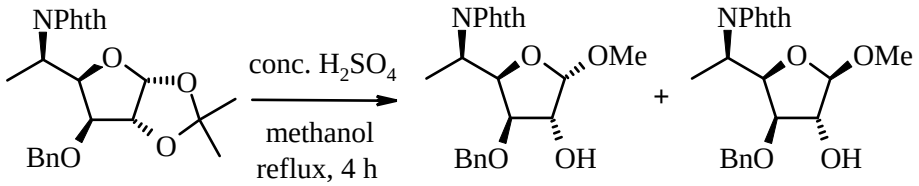


82 **83** **84**

Scheme 10

Deprotection of the 1,2-acetonide group and concomitant methyl glycosidation of **84** was accomplished using conc. H_2SO_4 (catalytic) in methanol to get a mixture of methyl acetal (α:β = 45:55) **85** and **86**, which were separated by silica gel column chromatography. The α-isomer (confirmed by the splitting pattern of anomeric proton) was used for next reaction. In ^{1}H NMR spectrum of compound **85**, anomeric proton was

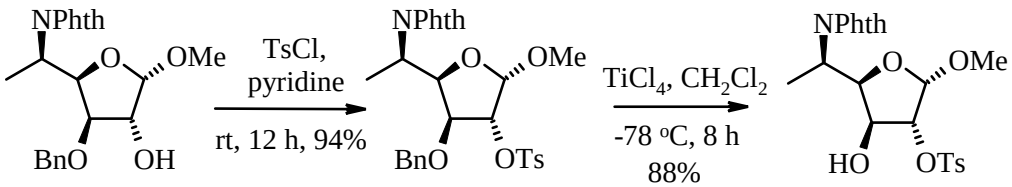
appeared at δ 5.05 (d, J = 4.7 Hz) ppm confirming the α-relationship with C2 proton, a singlet peak at δ 3.52 (3H) ppm was confirming the presence of methyl glycosidic linkage. In the ^{13}C NMR spectrum, the anomeric carbon resonated at δ 101.59 ppm confirming the α-isomer, peak at δ 167.65 ppm corresponded to amide carbonyl. IR spectrum showed absorbance for hydroxyl group and phthalimide group at 3436, 1774 and 1709 cm,$^{-1}$ respectively.



84 **85** **86**

Scheme 11

For achieving the appropriate functionality at C3 and C2 position with required streocenters, C2-C3 epoxide formation was needed. To fulfill this requirement, the hydroxyl group of compound **85** was treated with tosyl chloride in pyridine at room temperature to furnish the tosyl derivative **87**. In the ^{1}H NMR spectrum, resonance at δ 2.44 (s, 3H) ppm characteristic for tosyl group was appeared, and all the other protons were resonated at their expected position.

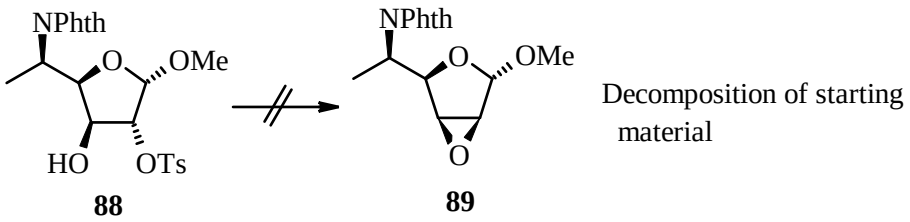


85 **87** **88**

Scheme 12

The cleavage of the benzyl ether (−*OBn*) present in **87** was found to be problematic. Catalytic hydrogenation of **87** was unsuccessful even at high pressure, and the system was not suitable for Birch reduction. However, the cleavage of benzyl ether proceeded smoothly with high yield (88%) using titanium tetrachloride[32] in dichloromethane at −78 ^{o}C to produce the alcohol **88**. The disappearance of resonance due to benzyl group was conspicuous in its ^{1}H NMR spectrum. In IR spectrum, absorbance at 3436 cm^{-1} was in accordance with the presence of hydroxyl group. Our next endeavor was to accomplish the epoxide **89**. Accordingly, the tosyl derivative **88** was treated with potassium

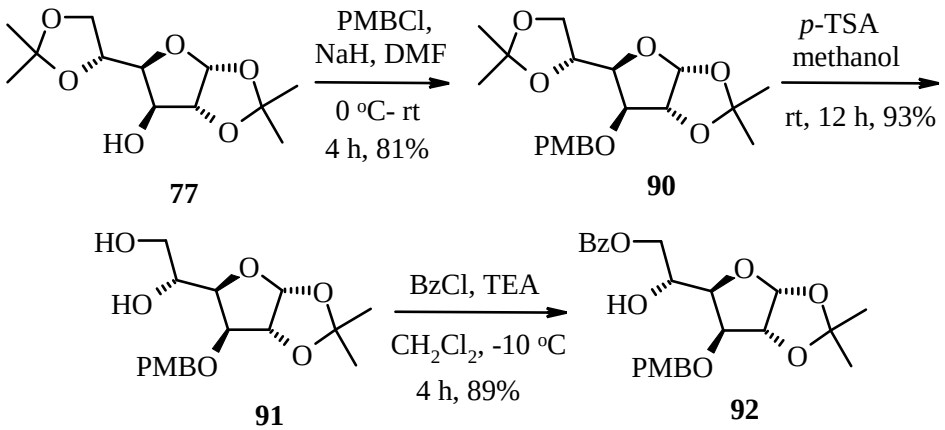
carbonate in methanol, unfortunately decomposition of starting material took place rapidly without getting traces of desired product.



Scheme 13

Having encountered the failure at this stage of our synthetic strategy, we decided to modify our synthetic pathway. Our explanation for this phenomenon was due to the presence of phthalimide group, which is highly base sensitive. Accordingly, instead of introducing phthalimide in the initial stage of our synthetic endeavor, we planned to install it in the later stage of synthetic sequence, there by avoiding the problem of epoxide formation.

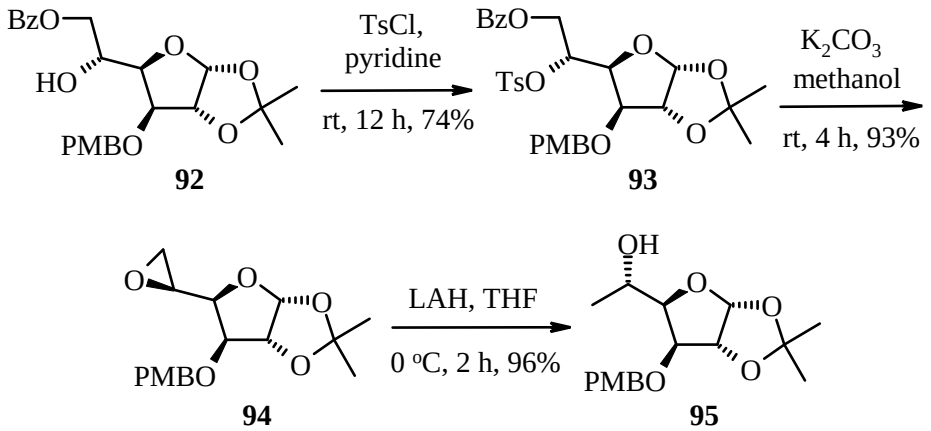
Thus, we started with 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose **77**, which was converted to diol **91** following literature procedure.[33] The free hydroxyl group of **77** was protected as *p*-methoxybenzyl ether using sodium hydride, PMBCl in DMF to obtain compound **90**. The 5,6-*O*-isopropyledene group of **90** was deketalised by catalytic *p*-TSA in methanol at room temperature to obtain compound **91** with 93% yield. Spectral and elemental data was in accordance with the reported value.



Scheme 14

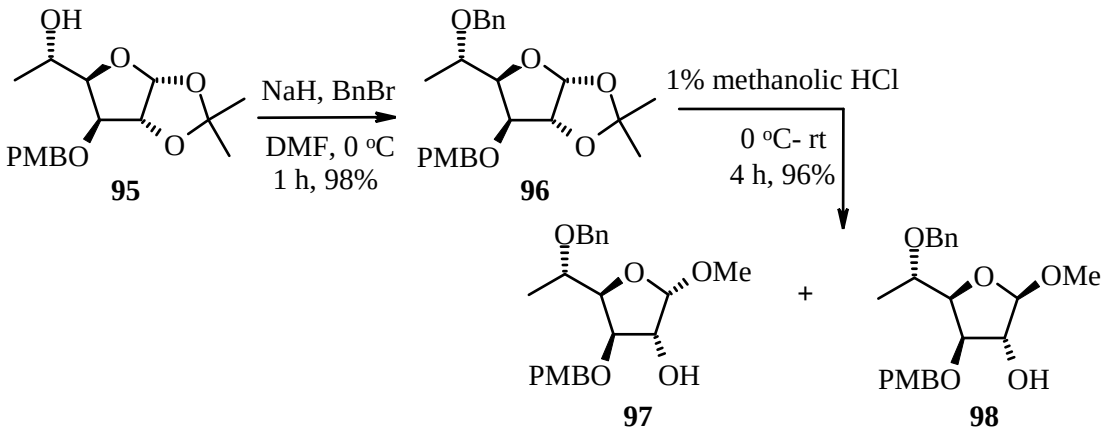
Since, we planned to perform Mitsunobu reaction for the introduction of amine functionality; inversion of stereocenter at C5 was required. Thus, compound **91** was

processed forward through benzyolation, tosylation, epoxidation and reduction to alcohol **95**. In ^{1}H NMR spectrum, newly generated methyl group appeared at δ 1.03 (J = 6.3 Hz) ppm as a doublet, methyl groups of acetonide moiety were at δ 1.25 (3H) and 1.40 (3H) ppm as two singlet. All the other protons were at their expected position. In IR spectrum, absorption due to hydroxyl group at 3403 cm^{-1} was observed.



Scheme 15

The secondary hydroxyl group in **95** was protected as its benzyl ether **96** (Scheme 16). In the ^{1}H NMR spectrum, peaks at aromatic region due to benzyl group were appeared at δ 7.11-7.30 ppm as multiplet, whereas benzylic −CH_2 was observed at δ 4.25 (1H) and 4.69 (1H) ppm as two doublets with coupling constant 11.4 Hz. The product was further confirmed by other spectral data and elemental analysis.

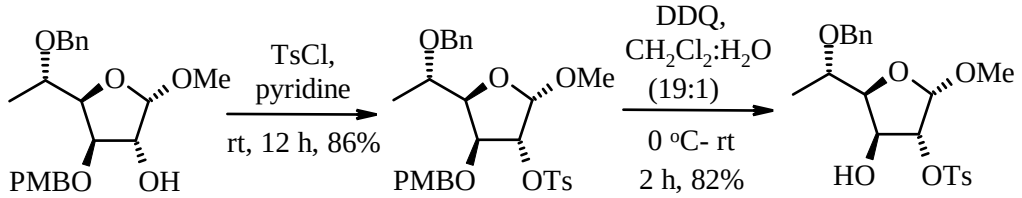


Scheme 16

Compound **96** on treatment with 1% methanolic HCl resulted in the cleavage[34] of isopropylidene moiety to furnish α and β-isomer **97** and **98** in 45:55 ratios, which were

separated by silica gel column chromatography. For the sake of selectivity in the epoxide opening reaction only *α*-isomer (confirmed by anomeric proton splitting in ^{1}H NMR) was taken for the next reaction. In the ^{1}H NMR spectrum of compound **97**, anomeric −*OMe* moiety resonated as a sharp singlet for three protons at δ 3.51 ppm. Anomeric proton resonated as a doublet at δ 5.05 ppm with coupling constant 4.8 Hz in evidence of the α-linkage of −*OMe* moiety. ^{13}C NMR spectrum and analytical data were in accordance with the assigned structure of compound **97**. In the IR spectrum, characteristic absorption for hydroxyl group was observed at 3422 cm.$^{-1}$

Alcohol **97** was treated with tosyl chloride in pyridine at room temperature to provide **99** in good yield. ^{1}H NMR spectrum showed three protons at δ 2.45 (s) ppm, which were the characteristic peak of tosyl group. The PMB ether was cleaved by DDQ[35] in CH_2Cl_2:H_2O (19:1) to obtain hydroxyl compound **100**. Disappearance of signal due to the PMB group was observed in ^{1}H NMR spectrum. In IR spectrum, absorption at 3468 cm^{-1} showed the presence of hydroxyl group. All the other spectral data and elemental analysis were in accordance with the assigned structure.

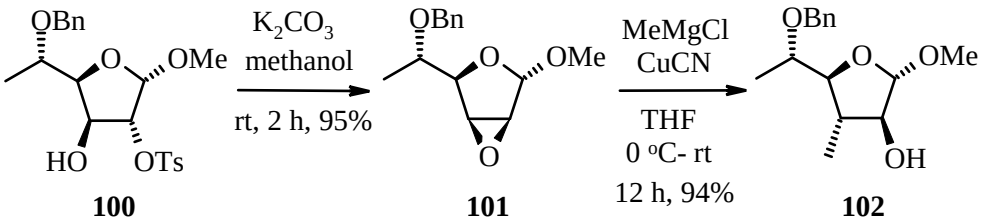


97 **99** **100**

Scheme 17

The hydroxyl compound **100** was subjected to the treatment of potassium carbonate in methanol at ambient temperature to obtain epoxide **101**. In ^{1}H NMR spectrum, disappearance of signal due to tosyl group was noted. Considering the stereochemistry of the epoxide (above the plane) and the −*OMe* group of glycoside (down the plane), we anticipated that the Grignard reaction would deliver the product with good regioselectivity. On treatment of MeMgCl and CuCN[36] in THF at 0 ^{o}C, epoxide **101** was converted to alcohol **102**. The ^{1}H NMR spectrum of **102** revealed one additional doublet at δ 1.36 (J = 7.5 Hz, 3H) ppm in accordance with the introduction of the methyl group at C3. The anomeric proton was resonated as singlet at δ 4.81 ppm in evidence of *trans*

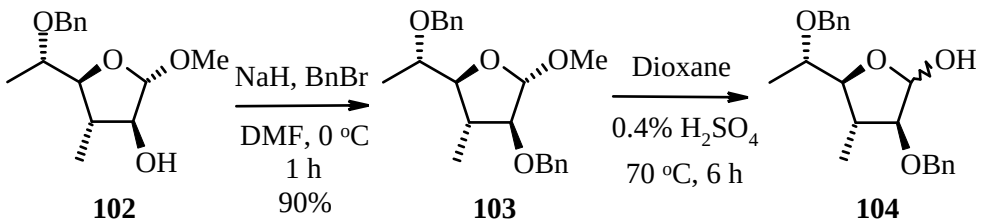
relationship with C2 proton. It was further supported by ^{13}C NMR information, mass and elemental analysis studies.



Scheme 18

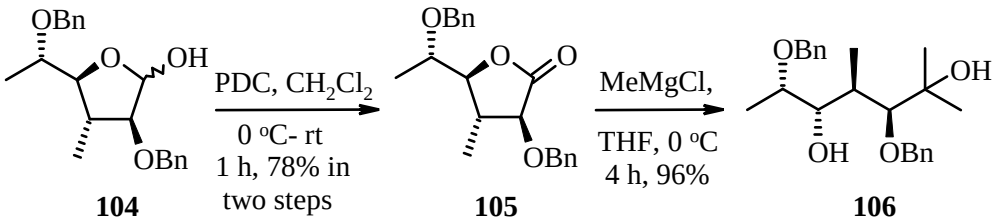
The newly generated hydroxyl group of **102** was protected as its benzyl ether **103** on treatment of benzyl bromide in presence of NaH in DMF. The compound **104** was thoroughly investigated with the spectral and analytical data.

Having the compound **103** in hand, our immediate concern was its transformation into the corresponding lactone derivative **105**. Thus, **103** was subjected to acidic hydrolysis using aq. 0.4% H_2SO_4 in dioxane[37] at 70 ^oC to afford the lactol **104**, which was oxidized to lactone **105** with PDC in dichloromethane without any further purification. The structure of lactone **105** was well supported by ^1H NMR, ^{13}C NMR studies together with elemental analysis. In ^{13}C NMR spectrum, characteristic resonance due to carbonyl carbon of lactone moiety appeared at δ 174.37 ppm. It was further supported by IR absorbance at 1783 cm^{-1} characteristic for lactone group.



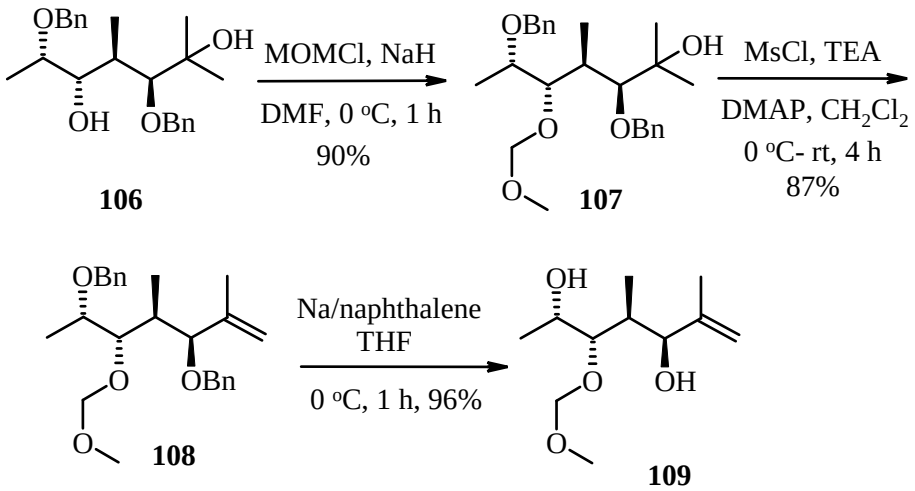
Scheme 19

Our next endeavor was the introduction of *exo*-methylene moiety in **108**. Accordingly, lactone **105** was treated with excess of MeMgCl in THF at 0 ^oC to obtain diol compound **106**. In ^1H NMR spectrum, two methyl groups attached with the tertiary carbon appeared at δ 1.19 (s) and 1.22 (s) ppm. The structure was further supported by ^{13}C NMR spectrum (the tertiary carbon at δ 73.58 ppm).



Scheme 20

The secondary hydroxyl group of **106** was selectively protected as its methoxy methyl ether by treating it with MOMCl in presence of sodium hydride in DMF. In the ^{1}H NMR spectrum, the −*OMe* moiety of MOM ether appeared as a sharp singlet at δ 3.34 ppm, whereas rest of the protons were appeared at their expected resonance position. Other spectral data as well as elemental analysis of **107** were in close agreement with the assigned structure.

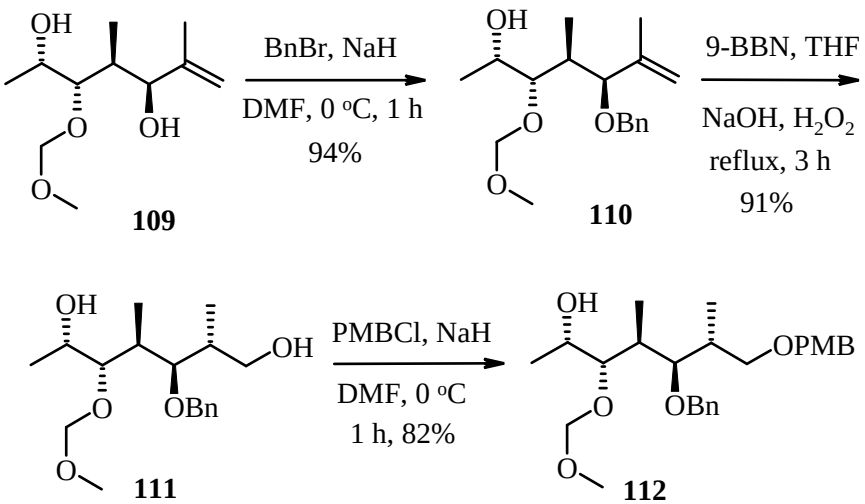


Scheme 21

Our next job was to generate the remaining stereocenter at C22 [numbering based on Superstolide A (**26**)] by employing regio and streoselective hydroboration oxidation reaction. Thus, the required double bond was generated by base catalyzed elimination of tertiary hydroxyl group. Accordingly, compound **107** was treated with excess triethylamine, methanesulphonyl chloride and DMAP in dichloromethane to obtain the substituted olefin[38] **108**. In ^{1}H NMR spectrum, two singlet at δ 4.86 and 4.94 ppm due to the *exo*-methylene moiety were observed. In addition, disappearance of two tertiary methyls and introduction of vinylic methyl at δ 1.64 (s) ppm was further secured the assigned structure. In the ^{13}C NMR spectrum, the two double bonded carbons appeared at

δ 142.79 and 112.31 ppm, respectively. In the following synthetic sequence, installation of ammine functionality was planned at C26 [numbering based on Superstolide A (**26**)]. For this endeavor, cleavage of benzyl ether was needed. Hence, **108** was treated with Na/naphthalene[39] in THF at 0 ^{o}C to produce diol **109** with 96% yield. Disappearance of aromatic protons corresponding to benzyl ring was observed in ^{1}H NMR spectrum, whereas rest of the protons resonated at their expected position. ^{13}C NMR spectrum was also in support of the structure. In IR spectrum, characteristic broad absorption peak due to hydroxyl group was appeared at 3439 cm.$^{-1}$

Keeping in mind, the higher reactivity of the allylic hydroxyl group, diol **109** was treated with 1 eq of benzyl bromide in presence of sodium hydride at 0 ^{o}C to accomplish the selective protection of the hydroxyl group at allylic position to provide compound **110**. In ^{1}H NMR spectrum, appearance of protons corresponding to benzylic $-CH_2$ moiety as two doublet at δ 4.45 and 4.67 (J = 11.8 Hz) ppm and aromatic protons as multiplets in the region of δ 7.27-7.34 (5H) ppm were traced. The structure was also supported by ^{13}C and elemental analysis.

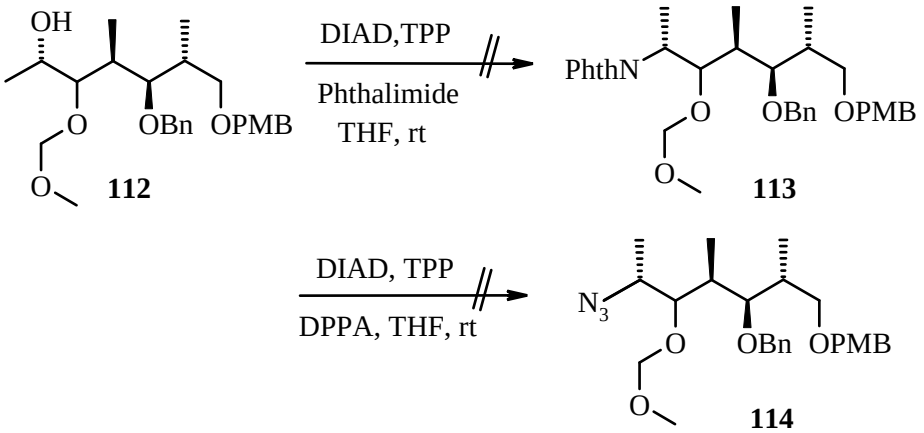


Scheme 22

We next envisaged to perform the sequential hydroboration oxidation reaction to generate the remaining stereocenter at C22 (numbering based on **26**). Thus, the olefin **110** was treated with 9-BBN[40] under refluxing condition in THF, followed by oxidation with hydrogen peroxide to obtain diol **111** with 91% yield. All spectral and analytical data were supported the assigned structure. The newly generated hydroxyl group was

selectively protected as PMB ether by using PMBCl in presence of sodium hydride in DMF. In the ^{1}H NMR spectrum, characteristic resonance due to PMB group appeared as sharp singlet at δ 3.79 (3H) ppm, whereas rest of the protons were resonated at their expected position.

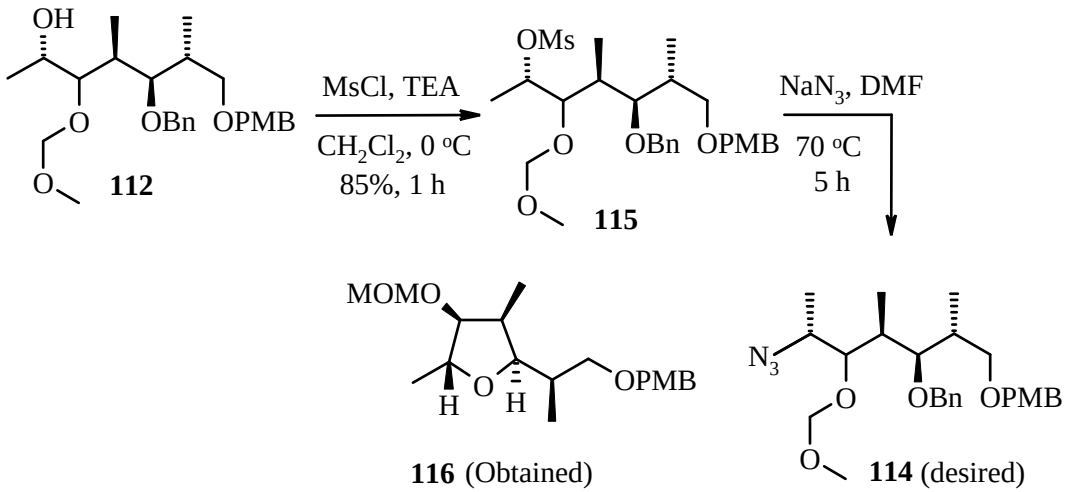
After successful installation of all the required streocenters, our next job was to introduce amine functionallty. Accordingly, **112** were treated with TPP, DIAD and phthalimide at room temperature, unfortunately only starting material was recovered. Same result was obtained when DPPA[41] was used instead of phthalimide under same reaction condition.



Scheme 23

Being unsuccessful in the introduction of the amine functionality in a single step, we opted for a two step sequence. Thus, the free hydroxyl group of compound **112** was converted to corresponding mesylate derivative **115** using MsCl and triethylamine in dichloromethane at 0 ^{o}C. The purpose behind the introduction of mesyl group at this stage was to use the leaving group character of mesyl group. In the ^{1}H NMR spectrum, methyl group characteristic of mesyl moiety appeared at δ 2.90 ppm as sharp singlet, whereas all other protons were well corresponding to the assigned structure. For the intended introduction of the azide group, **115** were treated with sodium azide in DMF at 70 ^{o}C to furnish **114**. However to our surprise, the product formed was not the desired azide derivative **114**, but the cyclized product **116**. In the ^{1}H NMR spectrum of **116**, the aromatic protons due to benzene ring and the benzylic $-CH_2$ moiety were absent, and there was some downfield shift of the methylene protons of the chain. In addition, mass

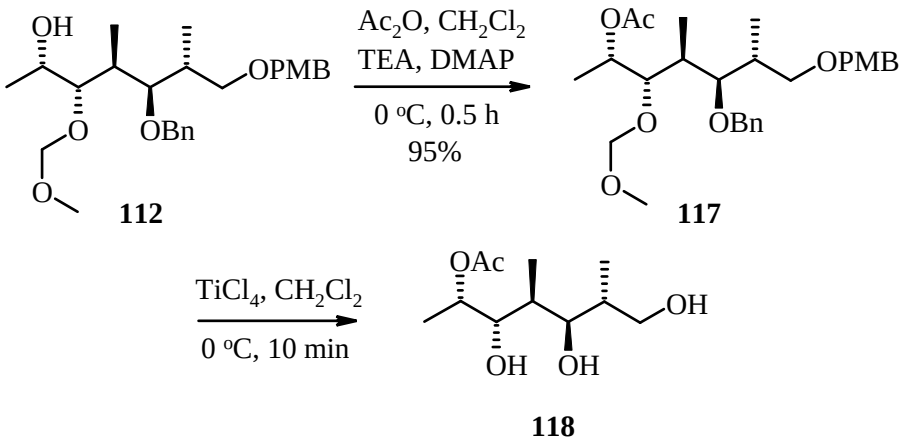
spectral analysis showed the peak at *m/z* 361 corresponds to $[M+ Na]^+$ further secured the structure of **116**.



Scheme 24

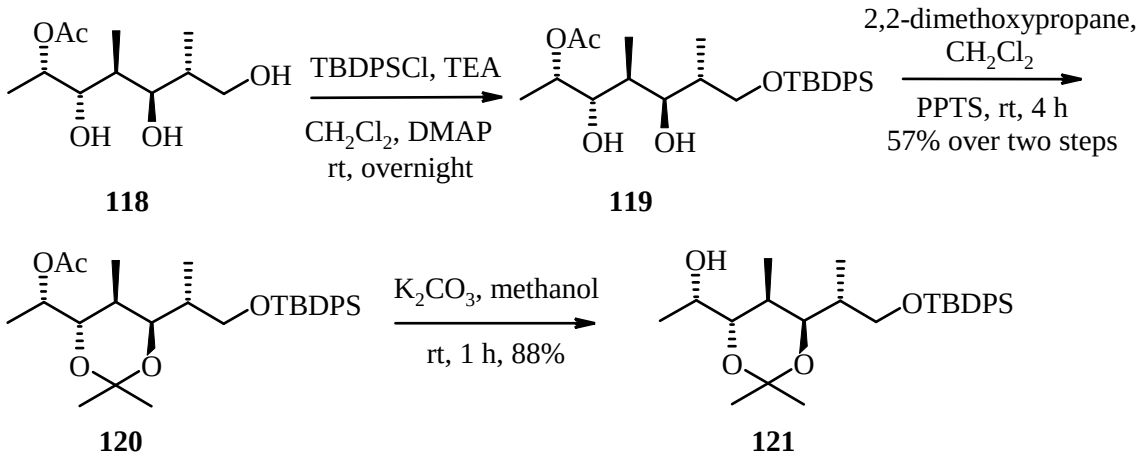
Since all the methods known to introduce amine functionality remained futile, because of undesired side reaction that is cyclization with benzyl ether cleavage, we thought of changing the protecting group from benzyl and MOM to isopropylidene derivative, thereby avoiding the cyclization problem. Thus, free hydroxyl group of **112** was converted to its acetate ester **117** by treatment with acetic anhydride, triethyl amine and DMAP in dichloromethane with quantitative yield. In the ^{1}H NMR spectrum, the characteristic methyl group of acetate moiety appeared at δ 2.05 ppm as sharp singlet and downfield migration of proton correspond to C26 [numbering based on **26**] at δ 5.08 ppm were observed. In ^{13}C NMR spectrum, carbonyl carbon corresponding to acetate moiety was appeared at δ 170.29 ppm. Absorption at 1733 cm^{-1} in IR spectrum was in evidence of ester moiety in the compound **117**. For the cleavage of PMB and benzyl ether, we followed cat. hydrogenation method, but only starting material was recovered, whereas Birch reduction with sodium or lithium in liquid ammonia or naphthalene provided decomposed starting material. Finally, we circumvented the aforesaid failure by treatment of acetate derivative **117** with titanium(IV) chloride at 0 ^{o}C for the cleavage of benzyl ether resulting in the simultaneous removal of all the ether linkage (benzyl, *p*-methoxybenzyl and methoxy methyl) affording **118**. The achievement of spectral data of compound **118** was a difficult tusk because of the acetate migration among the free

hydroxyl group on standing for a few second in spectroscopic solvent in NMR tube. So we proceeded further without taking any spectral characterization.



Scheme 25

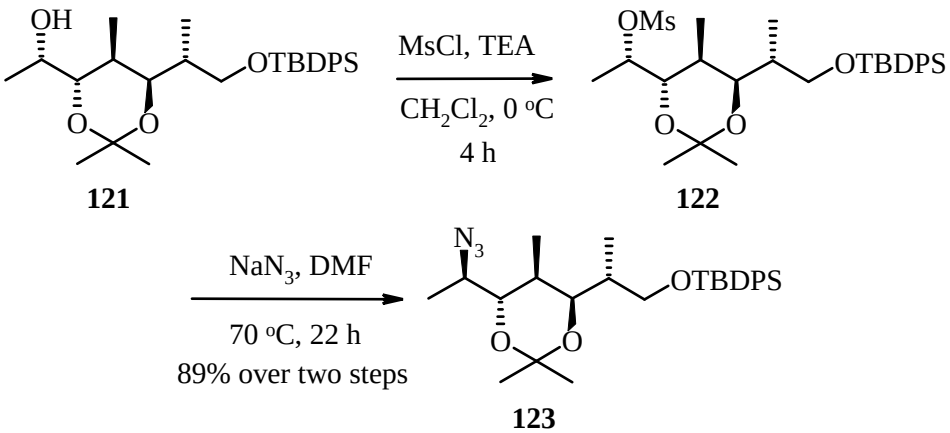
Selectively, the primary hydroxyl group of **118** was protected as TBDPS ether by treating it with TBDPSCl in presence of triethylamine and DMAP (cat) in dichloromethane at ambient temperature, followed by ketalisation of both the secondary hydroxyl group using 2,2-dimethoxypropane in presence of catalytic amount of PPTS in dichloromethane to afford **120**.



Scheme 26

In ^{1}H NMR spectrum, one sharp singlet at δ 1.08 (9H) ppm corresponding to three methyl group and at δ 7.37-7.70 (m, 10H) ppm for the aromatic moiety were secured the presence of TBDPS ether. Two singlet at δ 1.26 (3H) and 1.29 (3H) ppm corresponding to isopropylidene group and a sharp singlet at δ 2.10 (3H) ppm due to acetate methyl

were also indicated the product formation. The assigned structure was further supported by ^{13}C NMR spectrum, where carbonyl carbon of acetate at δ 170.95 ppm, methyl group of TBDPS at δ 27.0 ppm were present. IR spectrum showed a strong absorbance at 1739 cm^{-1} corresponding to acetate ester. Elemental analysis was also in support of the structure of **120**. Hydrolysis of the acetate ester of **120** was performed by using potassium carbonate in methanol to get alcohol **121**. Disappearance of signal due to acetate group was observed in ^{1}H NMR spectrum, whereas all other protons were at their expected chemical shift value. The structure was also supported by ^{13}C NMR and elemental analysis. In IR spectrum, absorbance due to ester group was absent and a broad brand for hydroxyl group appeared at 3447 $cm.^{-1}$



121 **122** **123**

Scheme 27

The hydroxyl compound **121** was treated with MsCl in presence of triethylamine and catalytic amount of DMAP in dichloromethane at 0 ^{o}C to obtain mesyl derivative **122**, which was used for next reaction without further purification. So the crude mesylate derivative **122** was heated at 70 ^{o}C in DMF with sodium azide for 22 h to get compound **123**, whose spectral data was well corresponded with the reported[27] value (Table 1).

Table 1: ^{1}H and ^{13}C NMR spectral data of Urpi's intermediate 53[27] and compound 123

^{1}H NMR (400 MHz, $CDCl_3$) Urpi's intermediate 53	**^{1}H NMR (400 MHz, $CDCl_3$) compound 123**	**^{13}C NMR (100MHz, $CDCl_3$) Urpi's intermediate 53**	**^{13}C NMR (100 MHz, $CDCl_3$) compound 123**
0.92 (d, *J* = 6.6 Hz, 3H)	0.92 (d, *J* = 6.8 Hz, 3H)	12.7	12.71
0.94 (d, *J* = 6.7 Hz,	0.95 (d, *J* = 6.7 Hz,	13.0	13.00

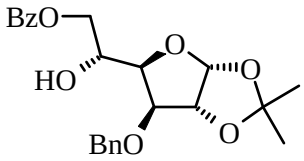
3H)	3H)		
1.07 (s 9H)	1.08 (s, 9H)	14.6	14.58
1.24 (s 3H)	1.24 (s, 3H)	19.4	19.37
1.25 (d, *J* = 6.7 Hz, 3H)	1.26 (d, *J* = 6.7 Hz, 3H)	23.6	23.63
1.30 (s, 3H)	1.31 (s, 3H)	25.3	25.34
1.76-1.62 (m, 1H)	1.74-1.67 (m, 1H)	27.0	26.99
1.89 (quinted, *J* = 6.6, 3.9 Hz)	1.86-1.90 (m, 1H)	34.0	33.97
3.35 (dd, *J* = 6.6, 4.2 Hz, 1H)	3.36 (dd, *J* = 6.6, 4.2 Hz, 1H)	35.4	35.46
3.50 (dq, *J* = 6.7, 4.2 Hz, 1H)	3.51 (dq, *J* = 6.7 4.2 Hz, 1H)	59.6	59.65
3.77-3.65 (m, 3H)	3.75-3.66 (m, 3H)	65.0	65.03
7.45-7.33 (m, 6H)	7.44-7.36 (m, 6H)	69.5	69.51
7.70-7.63 (m, 4H)	7.69-7.65 (m, 4H)	78.1	78.07
		100.7	100.74
		127.5	127.49
		129.4	129.46
		129.5	129.50
		133.9	133.90
		134.0	134.00
		135.7	135.70
		135.8	135.78

In conclusion, we have developed a novel route for the synthesis of C21-C26 fragment of Superstolide A (**26**) starting from readily available starting material D-(+)-glucose. The study involves CuCN coordinated regeioselective opening of C2-C3 (Numbering, according to **76**) epoxide **101** by MeMgCl. We have also demonstrated highly stereospecific hydroboration-oxidation of the *exo*-methylenic group.

EXPERIMENTAL

Experimental

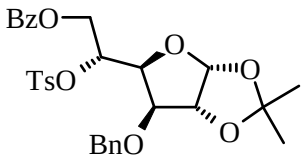
1,2-*O*-isopropylidene-3-*O*-Benzyl-6-*O*-benzoyl-α-D-glucofuranose (80):



To a solution of **79** (15.5 g, 50.0 mmol), Et_3N (10.5 mL, 75.0 mmol) in CH_2Cl_2 (400 mL) was added benzoyl chloride (6.44 mL, 55.0 mmol) at −10 ^oC. The reaction mixture was stirred for 4 h at 0 ^oC, diluted with CH_2Cl_2, washed with water, brine, dried (over Na_2SO_4) and concentrated. The residue was purified on silica gel by using EtOAc:hexane (1:4) to give **80** (19.01 g) as a yellow color liquid.

Yield	: 92%
Mol. Formula	: $C_{23}H_{26}O_7$
Optical Rotation $[\alpha]_D^{25}$	: −30.0 (*c* 1.8, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	: 3437, 2988, 2933, 1720, 1602, 1453, 1375, 1315, 1277, 1218, 1164, 1073, 1026, 769, 712.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.32 (s, 3H) 1.47 (s, 3H), 2.66 (bs, 1H), 4.13 (d, *J* = 3.0 Hz, 1H), 4.20 (dd, *J* = 8.1, 3.0 Hz, 1H), 4.26- 4.34 (m, 1H), 4.43 (dd, *J* = 5.8, 11.7 Hz, 1H), 4.59 (d, *J* = 11.7 Hz, 1H), 4.62- 4.68 (m, 2H), 4.74 (d, *J* = 11.7 Hz, 1H), 5.95 (d, *J* = 3.7 Hz, 1H), 7.30-7.60 (m, 8H), 8.03-8.07 (m, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 26.32, 26.79, 67.17, 67.91, 72.19, 79.49, 81.62, 82.11, 105.21, 111.81, 127.82, 128.16, 128.30, 128.64, 129.71, 129.86, 133.05, 137.16, 166.96 ppm.
ESI MS *(m/z)*	: 437.4 $[M+ Na]^+$
Elemental Analysis	**Calcd:** C, 66.65; H, 6.32. **Found:** C, 66.55; H, 6.20.

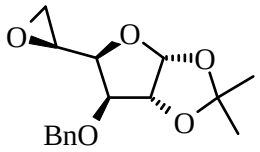
1,2-*O*-isopropylidene-3-*O*-Benzyl-6-*O*-benzoyl-5-*O*-*p*-toluene sulphonyl-α-D-glucofuranose (81):



Compound **80** (18.0 g, 43.47 mmol), TsCl (20.7 g, 108.69 mmol) and pyridine (100 mL) were stirred at room temperature for 24 h. Pyridine was removed under vacuo and the residue extracted with EtOAc, washed with 1 N HCl, water, brine, dried (Na_2SO_4) and evaporated. The residue was purified by silica gel column chromatography by eluting with light petroleum: EtOAc (10:1) to give **81** (23.2 g).

Yield	: 94%
Mol. Formula	: $C_{30}H_{32}O_9S$
Optical Rotation $[\alpha]_D^{25}$	: +1.8 (*c* 1.1, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	: 3021, 1723, 1600, 1453, 1374, 1274, 1216, 1116, 1177, 1026, 1076, 921, 757, 712.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.21 (s, 3H), 1.36 (s, 3H), 2.19 (s, 3H), 4.02 (d, *J* = 3.1 Hz, 1H), 4.28-4.39 (m, 2H), 4.49 (d, *J* = 3.7 Hz, 1H), 4.52-4.60 (m, 3H), 5.23 (ddd, *J* = 2.1, 6.0, 7.3 Hz, 1H), 5.79 (d, *J* = 3.7 Hz, 1H), 6.99 (d, *J* = 8.2 Hz, 2H), 7.22-7.46 (m, 8H), 7.58 (d, *J* = 8.3 Hz, 2H), 7.79-7.84 (m, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 21.30, 26.05, 26.56, 63.37, 71.87, 75.84, 78.48, 80.88, 81.24, 104.97, 111.93, 127.29, 127.73, 128.01, 128.27, 129.45, 129.50, 132.83, 133.81, 137.09, 144.50, 165.45 ppm.
ESI MS *(m/z)*	591 $[M+ Na]^+$
Elemental Analysis	**Calcd:** C, 63.37; H, 5.67.
	Found: C, 63.22; H, 5.59.

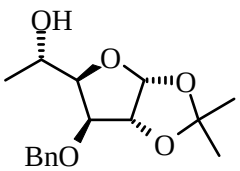
1,2-*O*-isopropylidene-3-*O*-Benzyl-5,6-anhydro-α-L-idofuranose (82):



Compound **81** (23.0 g, 40.49 mmol) was dissolved in MeOH (150 mL) and K_2CO_3 (11.17 g, 80.98 mmol) was added. The mixture was stirred at room temperature for 4 h and concentrated. The residue was dissolved in water and extracted with ethyl acetate, washed with water, dried (Na_2SO_4) and evaporated. Purification on silica gel using light petroleum: EtOAc (10:1) as an eluent afforded pure epoxide **82** (11.0 g).

Yield	: 93%
Mol. Formula	: $C_{16}H_{20}O_5$
Optical Rotation $[\alpha]_D^{25}$	: −71.1 (*c* 2.25, $CHCl_3$).
IR ($CHCl_3$) cm^{-1}	: 2988, 2933, 1598, 1454, 1383, 1216, 1164, 1075, 1027, 896, 856, 741, 699.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.32 (s, 3H), 1.45 (s, 3H), 2.53 (dd, *J* = 2.7, 4.9 Hz, 1H), 2.75 (dd, *J* = 4.4, 4.8 Hz, 1H), 3.26 (ddd, *J* = 2.7, 4.2, 6.1 Hz, 1H), 3.79 (dd, *J* = 3.6, 6.1 Hz, 1H), 3.95 (d, *J* = 3.6 Hz, 1H), 4.51 (d, *J* = 12.2 Hz, 1H), 4.63 (d, *J* = 3.8 Hz, 1H), 4.74 (d, *J* = 12.2 Hz, 1H), 5.99 (d, *J* = 3.8 Hz, 1H), 7.29-7.35 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 26.27, 26.80, 43.01, 50.07, 71.79, 81.97, 82.30, 82.58, 105.36, 111.80, 127.61, 127.99, 128.45, 137.17 ppm.
Elemental Analysis	**Calcd:** C, 65.74; H, 6.90.
	Found: C, 65.54; H, 6.79.

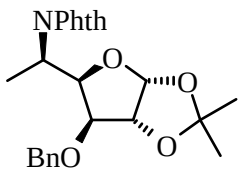
1,2-*O*-isopropylidene3-*O*-Benzyl-6-deoxy-α-L-idofuranose (83):



A suspension of LAH (1.95 g, 51.37 mmol), and **82** (10.0 g, 34.25 mmol) in THF (200 mL) was stirred at rt for 2 h at 0 ^{o}C. The excess LAH was quenched with saturated aq. solution of Na_2SO_4, filtered and the residue thoroughly washed with EtOAc. The filtrate was concentrated and purified on silica gel using EtOAc:light petroleum ether (1:4) to afford **83** (10.0 g) as a white solid.

Yield	: 99%
Mol. Formula	: $C_{16}H_{22}O_5$
Optical Rotation $[\alpha]_D^{25}$	: −61.4 (*c* 1.4, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	: 3455, 2979, 2931, 1602, 1454, 1384, 1217, 1165, 1075, 1028, 756, 697.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.13 (d, *J* = 6.3 Hz, 3H), 1.33 (s, 3H), 1.49 (s, 3H), 2.67 (bs, 1H), 3.91-3.98 (m, 2H), 4.12 (quin, *J* = 6.3 Hz, 1H), 4.45 (d, *J* = 11.8 Hz, 1H), 4.64 (d, *J* = 3.9 Hz, 1H), 4.71 (d, *J* = 11.8 Hz, 1H), 5.97 (d, *J* = 3.8 Hz, 1H), 7.26-7.41 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 18.44, 26.30, 26.77, 66.13, 71.79, 82.25, 84.24, 104.88, 111.75, 127.87, 128.19, 128.57, 136.77 ppm.
ESI MS (*m/z*)	: 317.3 $[M+ Na]^+$
Elemental Analysis	**Calcd:** C, 65.29; H, 7.53.
	Found: C, 65.01; H, 7.34.

1,2-*O*-isopropylidene-3-*O*-Benzyl-5,6-di-deoxy-5-phthalimido-α-D-glucofuranose (84):

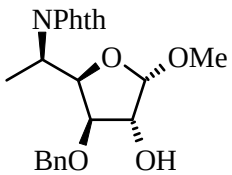


A 50 mL three necked round bottom flask charged with TPP (4.45 g, 17.0 mmol) phthalimide (2.5 g, 17.0 mmol) and THF (50 mL). The alcohol **83** (5.0 g, 17.0 mmol) in 2 mL THF and DIAD (2.9 mL, 18.7 mmol) in 2 mL THF was added to the flask simultaneously dropwise slowly over a period of 5 min, with stirring, the solution turned yellow. The reaction permitted to proceed at room temperature for 24 h, the solution then concentrated and product purified by column chromatography eluting with ethyl acetate:

hexane (1: 4) to obtain compound **84** (2.0 g) as yellow color solid (Melting point: 104.5 - 107.1 ^{o}C).

Yield	: 28%
Mol. Formula	: $C_{24}H_{25}NO_6$
Optical Rotation $[\alpha]_D^{25}$	: −25.2 (*c* 3.25, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	: 2987, 2935, 1775, 1712, 1455, 1384, 1210, 1190, 1072, 1060, 712.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.32 (s, 3H), 1.49 (d, *J* = 6.9 Hz, 3H), 1.55 (s, 3H), 3.73 (d, *J* = 3.1 Hz, 1H), 4.24 (d, *J* = 11.6 Hz, 1H), 4.45 (d, *J* = 11.6 Hz, 1H), 4.58 (d, *J* = 3.9 Hz, 1H), 4.61-4.73 (m, 1H), 5.02 (dd, *J* = 3.2, 10.0 Hz, 1H), 5.94 (d, *J* = 3.8 Hz, 1H), 7.04-7.21 (m, 5H), 7.67-7.79 (m, 4H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 17.05, 26.37, 26.84, 45.30, 71.45, 79.82, 80.26, 81.86, 105.03, 111.71, 123.11, 127.71, 128.16, 128.37, 131.89, 133.73, 136.40, 167.63 ppm.
ESI MS *(m/z)*	: 426 $[M+ Na]^+$
Elemental Analysis	**Calcd:** C, 68.07; H, 5.95.
	Found: C, 67.84; H, 5.69.

Methyl 5,6-di-deoxy-3-*O*-Benzyl-5-phthalimido-α-D-glucofuranoside (85):



A solution of **84** (2.0 g, 4.73 mmol) in MeOH (30 mL) with conc. H_2SO_4 (0.5 mL) was refluxed for 4 h. The reaction mixture was cooled to rt and neutralized with triethylamine, solvent evaporated and the residue was purified on silica gel using ethyl acetate and light petroleum (3:10) as eluent to provide **85** (0.68 g, 40%) and **86** (1.02 g, 60%) as pale yellow solid (mp; 117.6 ^{o}C – 119.2 ^{o}C).

Yield : 91%

Mol. Formula : $C_{22}H_{23}NO_6$

Optical Rotation $[\alpha]_D^{25}$: +56.0 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$) cm^{-1} : 3436, 2934, 1774, 1709, 1454, 1387, 1358, 1190, 1119, 1034, 721.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.48 (d, *J* = 6.8 Hz, 3H), 2.86 (d, *J* = 6.4 Hz, 1H), 3.52 (s, 3H), 3.75 (dd, *J* = 2.2, 4.7 Hz, 1H), 4.25 (bs, 1H), 4.26 (d, *J* = 11.7 Hz, 1H), 4.49-4.67 (m, 2H), 4.94 (dd, *J* = 4.8, 9.9 Hz, 1H), 5.05 (d, *J* = 4.7 Hz, 1H), 6.96-7.08 (m, 5H), 7.66-7.77 (m, 4H) ppm.

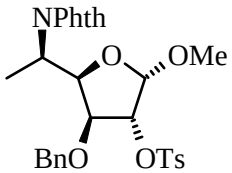
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 16.79, 45.67, 55.53, 71.04, 76.78, 77.65, 82.53, 101.59, 122.98, 127.43, 127.95, 128.29, 131.90, 133.58, 136.72, 167.65 ppm.

ESI MS *(m/z)* : 420 $[M+ Na]^+$

Elemental Analysis **Calcd:** C, 66.49; H, 5.38.

Found: C, 66.54; H, 5.49.

Methyl 5,6-di-deoxy-3-*O*-Benzyl-5-phthalimido-2-*O*-*p*-toluene sulphonyl-α-D-glucofuranoside (86):



Compound **85** (2.0 g, 5.03 mmol), TsCl (2.4 g, 12.59 mmol) and pyridine (15 mL) were stirred at room temperature for 24 h. Pyridine was removed under vacuo and the residue extracted with EtOAc, washed with 1 N HCl, water, brine, dried (Na_2SO_4) and evaporated. The residue was purified by silica gel column chromatography by eluting with light petroleum: EtOAc (17:3) to give **87** (2.6 g).

Yield : 94%

Mol. Formula : $C_{29}H_{29}NO_8S$

Optical Rotation $[\alpha]_D^{25}$: +36.4 (*c* 6.26, $CHCl_3$)

IR ($CHCl_3$) cm^{-1} : 3022, 2936, 1775, 1711, 1597, 1454, 1386, 1217, 1190, 1047, 770, 720.

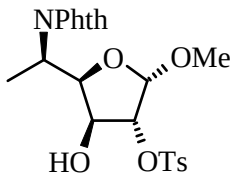
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.42 (d, *J* = 6.8 Hz, 3H), 2.44 (s, 3H), 3.29 (s, 3H), 4.07 (d, *J* = 11.6 Hz, 1H), 4.12 (dd, *J* = 3.1, 6.0 Hz, 1H), 4.33 (d, *J* = 11.6 Hz, 1H), 4.43-4.58 (m, 1H), 4.81-4.87 (m, 2H), 4.94 (dd, *J* = 6.1, 9.8 Hz, 1H), 6.81-7.04 (m, 5H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.63-7.72 (m, 4H), 7.84 (d, *J* = 8.1 Hz, 2H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 16.61, 21.48, 45.67, 55.19, 71.25, 75.65, 79.25, 83.13, 99.80, 122.87, 127.47, 127.84, 127.98, 128.10, 129.62, 131.73, 133.21, 133.54, 135.84, 144.92, 167.42 ppm.

Elemental Analysis **Calcd:** C, 63.15; H, 5.30.

Found: C, 62.92; H, 5.11.

Methyl 5,6-di-deoxy-5-phthalimido-2-*O*-p-toluene sulphonyl-α-D-glucofuranoside (88):



To a solution of **87** (1.1 g, 1.99 mmol), in anhydrous CH_2Cl_2 (10 mL) under nitrogen atmosphere at −78 ^{o}C, $TiCl_4$ (0.44 mL, 3.99 mmol) was added. The reaction mixture stirred for 8 h, at the same temperature. Excess reagent was quenched by saturated aq. sodium bicarbonate, extracted with CH_2Cl_2, dried over sodium sulphate, evaporated. The reaction mixture was purified on silica gel column chromatography by eluting with light petroleum: ethyl acetate (4:1) to obtain **88** (0.8 g) as colourless liquid.

Yield : 88%

Mol. Formula : $C_{22}H_{23}NO_8S$

Optical Rotation $[\alpha]_D^{25}$: −7.4 (*c* 2.45, $CHCl_3$)

IR ($CHCl_3$) cm^{-1} : 3436, 2930, 1775, 1709, 1598, 1451, 1385, 1191, 1178, 1094, 1052, 979, 722.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.57 (d, *J* = 6.8 Hz, 3H), 2.42 (s, 3H), 2.87-2.96 (m, 1H), 3.40 (s, 3H), 3.88 (d, *J* = 4.6 Hz, 1H), 4.34-4.50 (m, 1H), 4.65 (s, 1H), 4.93 (dd, *J* = 10.3, 4.0 Hz, 1H), 4.97 (s, 1H) 7.34 (d, *J* = 7.9 Hz, 2H), 7.68-7.82 (m, 6H) ppm.

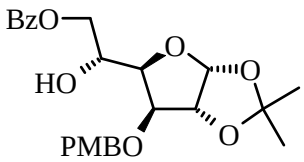
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 16.69, 21.63, 46.46, 55.57, 73.35, 82.73, 84.96, 106.22, 123.22, 127.94, 130.02, 131.78, 132.82, 133.92, 133.99, 145.30, 167.85 ppm.

ESI MS *(m/z)* : 484.2 $[M+ Na]^+$

Elemental Analysis **Calcd:** C, 57.26; H, 5.02.

Found: C, 57.12; H, 5.10.

1,2-*O*-isopropylidene-3-*O*-(4-methoxybenzyl)-6-*O*-benzoyl-α-D-glucofuranose (92):



To a solution of **91** (15.0 g, 44.12 mmol), Et_3N (12.3 mL, 88.23 mmol) in CH_2Cl_2 (400 mL) was added benzoyl chloride (5.68 mL, 48.53 mmol) at −10 ^{o}C. The reaction mixture was stirred for 4 h at 0 ^{o}C, diluted with CH_2Cl_2, washed with water, brine, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel by using EtOAc-hexane (1:4) to give **92** (17.5 g), as a yellow color liquid.

Yield : 89%

Mol. Formula : $C_{24}H_{28}O_8$

Optical Rotation $[\alpha]_D^{25}$: −29.7 (*c* 0.9, $CHCl_3$)

IR ($CHCl_3$) cm^{-1} : 3498, 2989, 2936, 1720, 1612, 1585, 1514, 1452, 1315, 1277, 1250, 1217, 1113, 1073, 1027, 831, 755, 712.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.23 (s, 3H), 1.37 (s, 3H), 3.70 (s, 3H), 4.01 (d, *J* = 3.0 Hz, 1H), 4.07-4.22 (m, 2H), 4.28-4.43 (m, 2H), 4.43-4.61 (m, 3H), 5.85 (d, *J* = 3.7 Hz, 1H), 6.79 (d, *J*

= 8.0 Hz, 2H), 7.16-7.20 (m, 2H), 7.29-7.46 (m, 3H), 7.93-7.98 (m, 2H) ppm.

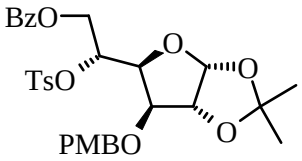
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 26.32, 26.78, 55.12, 67.06, 67.91, 71.79, 79.42, 81.16, 82.13, 105.21, 111.76, 114.03, 128.27, 129.09, 129.55, 129.70, 129.88, 133.01, 159.53, 166.88 ppm.

ESI MS *(m/z)* : 467 $[M+ Na]^+$

Elemental Analysis **Calcd:** C, 64.85; H, 6.35.

Found: C, 64.67; H, 6.29.

1,2-*O*-isopropylidene-3-*O*-(4-methoxybenzyl)-6-*O*-benzoyl-5-*O*-*p*-toluene sulphonyl-α-D-glucofuranose (93):



Compound **92** (17.0 g, 38.28 mmol), TsCl (14.6 g, 76.57 mmol) and pyridine (50 mL) were stirred at room temperature for 24 h. Pyridine was removed under vacuo and the residue extracted with EtOAc, washed with 1 N HCl, water, brine, dried (Na_2SO_4) and evaporated. The residue was purified by silica gel column chromatography by eluting with light petroleum: EtOAc (17:3) to give **93** (17.0 g).

Yield : 74%

Mol. Formula : $C_{31}H_{34}O_{10}S$

Optical Rotation $[\alpha]_D^{25}$: −4.4 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$) cm^{-1} : 3022, 2990, 2935, 2837, 1724, 1612, 1601, 1514, 1452, 1373, 1217, 1190, 1114, 1075, 1027, 918, 815, 712, 667.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.31 (s, 3H), 1.46 (s, 3H), 2.30 (s, 3H), 3.81 (s, 3H), 4.10 (d, *J* = 3.1 Hz, 1H), 4.41 (dd, *J* = 12.7, 6.1 Hz, 1H), 4.45 (dd, *J* = 7.0, 3.1 Hz, 1H), 4.56 (d, *J* = 10.8 Hz, 1H), 4.58 (d, *J* = 3.8 Hz, 1H), 4.60 (d, *J* = 10.8, 1H), 4.65 (dd, *J* = 12.7, 2.1 Hz, 1H), 5.30 (dt, *J* = 2.1, 6.7 Hz, 1H), 5.87 (d, *J* = 3.7 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.90-7.92 (m, 2H) ppm.

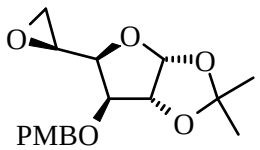
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 21.50, 26.28, 26.77, 55.13, 63.47, 71.95, 75.95, 78.64, 80.77, 81.60, 105.17, 112.07, 113.83, 127.49, 128.13, 129.32, 129.61, 129.65, 129.71, 132.89, 134.24, 144.49, 159.42, 165.52 ppm.

ESI MS *(m/z)* : 612 $[M+ Na]^+$

Elemental Analysis **Calcd:** C, 62.19; H, 5.72.

Found: C, 61.98; H, 5.69.

1,2-*O*-isopropylidene-3-*O*-(4-methoxybenzyl)-5,6-anhydro-α-L-idofuranose (94):



Compound **93** (16.0 g, 26.75 mmol) was dissolved in MeOH (80 mL) and K_2CO_3 (7.4 g, 53.5 mmol) was added. The mixture was stirred at room temperature for 4 h and then concentrated. The residue was dissolved in water and extracted with ethyl acetate, washed with water, dried (Na_2SO_4) and evaporated. Purification on silica gel using light petroleum: EtOAc (17:3) as an eluent afforded pure epoxide **94** (8.0 g).

Yield : 93%

Mol. Formula : $C_{17}H_{22}O_6$

Optical Rotation $[\alpha]_D^{25}$: −65.4 (*c* 1.65, $CHCl_3$)

IR ($CHCl_3$) cm^{-1} : 2991, 2936, 2838, 1721, 1612, 1513, 1455, 1374,

1280, 1250, 1217, 1110, 1030, 891, 833, 755, 715.

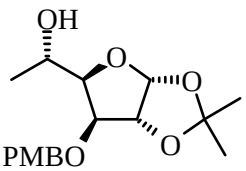
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.30 (s, 3H), 1.43 (s, 3H), 2.49 (dd, *J* = 4.9, 2.7 Hz, 1H), 2.72 (t, *J* = 4.6 Hz, 1H), 3.21 (dq, *J* = 4.3, 2.7 Hz, 1H), 3.75 (dd, *J* = 3.6, 6.1 Hz, 1H), 3.79 (s, 3H), 3.91 (d, *J* = 3.4 Hz, 1H), 4.41 (d, *J* = 11.9 Hz, 1H), 4.59 (d, *J* = 3.8 Hz, 1H), 4.65 (d, *J* = 11.9 Hz, 1H), 5.96 (d, *J* = 3.8 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 26.27, 26.80, 42.97, 50.09, 55.11, 71.47, 82.00, 82.11, 83.37, 105.36, 111.74, 113.80, 128.24, 129.28, 159.42 ppm

Elemental Analysis **Calcd:** C, 63.34; H, 6.88.

Found: C, 63.50; H, 6.90.

1,2-*O*-isopropylidene-6-deoxy-3-*O*-(4-methoxybenzyl)-α-L-idofuranose (95):



A suspension of LAH (1.88 g, 49.68 mmol), and **94** (8.0 g, 24.84 mmol) in THF (100 mL) was stirred for 2 h at 0 ^{o}C. The excess reagent was quenched with saturated solution of Na_2SO_4 and filtered and the residue thoroughly washed with EtOAc. The filtrate was concentrated and purified on silica gel using EtOAc-light petroleum ether (3:7) to afford **95** (8.0 g) as a colourless liquid.

Yield : 99%

Mol. Formula : $C_{17}H_{24}O_6$

Optical Rotation $[\alpha]_D^{25}$: −55.9 (*c* 0.8, $CHCl_3$)

IR ($CHCl_3$) cm^{-1} : 3403, 2982, 2935, 2838, 1613, 1586, 1513, 1457, 1375, 1247, 1169, 964, 832, 755, 638.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.03 (d, *J* = 6.3 Hz, 3H), 1.25 (s, 3H), 1.40 (s, 3H), 2.67 (bs, 1H), 3.72 (s, 3H), 3.80-3.87 (m, 2H), 3.99 (quin, *J* = 6.3 Hz, 1H), 4.28 (d, *J* = 11.5 Hz, 1H), 4.54 (d, *J* = 4.2 Hz, 1H), 4.55 (d, *J* = 11.5 Hz, 1H), 5.87 (d, *J* = 3.8 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 2H), 7.15 (d, *J* = 7.8 Hz, 2H) ppm.

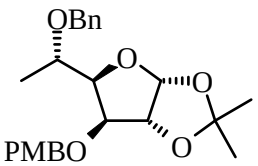
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 18.41, 26.26, 26.72, 55.12, 66.06, 71.35, 81.72, 82.19, 84.13, 104.84, 111.64, 113.87, 128.72, 129.57, 159.50 ppm.

ESI MS *(m/z)* : 347 $[M+ Na]^+$

Elemental Analysis **Calcd:** C, 62.95; H, 7.46.

Found: C, 62.74; H, 7.31.

1,2-*O*-isopropylidene-5-*O*-Benzyl-6-deoxy-3-*O*-(4-methoxybenzyl)-α-L-idofuranose (96):



To a solution of 95 (8.0 g, 24.69 mmol) in DMF (50 mL) at 0 °C was added NaH (60 % dispersion in mineral oil, 1.97 g, 49.38 mmol). After 15 min, benzyl bromide (4.4 mL, 37.03 mmol) was introduced and the reaction further stirred for 1 h at room temperature. Water was carefully added to the reaction mixture, extracted with ether, washed with water and dried (Na_2SO_4). On evaporation of solvent, the residue was purified by silica gel chromatography by eluting with light petroleum: EtOAc (1:19) to afford **96** (10.0 g).

Yield : 98%

Mol. Formula : $C_{24}H_{30}O_6$

Optical Rotation $[\alpha]_D^{25}$: −38.1 (*c* 2.0, $CHCl_3$).

IR ($CHCl_3$) cm^{-1} : 2990, 2935, 1613, 1586, 1514, 1454, 1374, 1251, 1216, 1171, 1074, 1028, 830, 698, 666.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.98 (d, *J* = 6.3 Hz, 3H), 1.24 (s, 3H), 1.42 (s, 3H), 3.71 (s, 3H), 3.72-3.83 (m, 2H), 4.03 (dd, *J* = 8.2, 3.4 Hz, 1H), 4.25 (d, *J* = 11.4 Hz, 1H), 4.47-4.54 (m, 3H), 4.69 (d, *J* = 11.4 Hz, 1H), 5.90 (d, *J* = 3.9 Hz, 1H), 6.66 (d, *J* = 8.5 Hz, 2H), 7.11-7.30 (m, 7H) ppm.

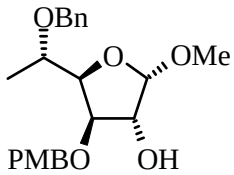
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 16.67, 26.35, 26.74, 55.12, 71.20, 72.11, 74.08, 81.29, 81.87, 84.82, 105.16, 111.45, 113.79, 127.16, 127.60, 128.13, 128.99, 129.61, 139.20, 159.43 ppm.

ESI MS *(m/z)* : 437 $[M+ Na]^+$

Elemental Analysis **Calcd:** C, 69.55; H, 7.30.

Found: C, 69.34; H, 7.20.

Methyl 6-deoxy-5-*O*-Benzyl-3-*O*-(4-methoxybenzyl)-α-L-idofuranoside (97):



1% methanolic HCl (470 mL) was added to **96** (10.0 g, 24.15 mmol) at 0 ^oC and stirred it for 8 h at room temperature, cool it to 0 ^oC, quenched by triethylamine concentrated under reduced pressure. Residue was purified by column chromatography using ethyl acetate: light petroleum ether (3:7) to obtain **97** (4.0 g) and **98** (5.0 g).

Yield : 96%

Mol. Formula : $C_{22}H_{28}O_6$

Optical Rotation $[\alpha]_D^{25}$: +25.5 (*c* 0.85, $CHCl_3$).

IR ($CHCl_3$) cm^{-1} : 3422, 3004, 2933, 2837, 1613, 1514, 1464, 1455, 1303, 1249, 1212, 1179, 1111, 821, 755, 697.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.12 (d, *J* = 6.4 Hz, 3H), 2.86 (d, *J* = 6.7 Hz, 1H), 3.51 (s, 3H), 3.73-3.87 (m, 2H), 3.80 (s, 3H), 4.04 (dd, *J* = 5.0, 6.3 Hz, 1H), 4.28-4.35 (m, 1H), 4.42 (d, *J* = 11.4 Hz, 1H), 4.57 (d, *J* = 11.6 Hz, 1H), 4.68 (d, *J* = 11.4 Hz, 2H), 5.05 (d, *J* = 4.8 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 2H), 7.22-7.36 (m, 7H) ppm.

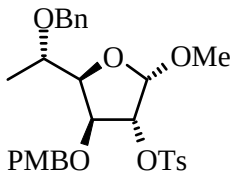
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 16.57, 55.08, 55.64, 71.23, 71.84, 73.85, 75.57, 82.60, 83.65, 101.79, 113.69, 127.17, 127.61, 128.10, 129.48, 129.69, 139.17, 159.24 ppm.

ESI MS *(m/z)* : 411 $[M+ Na]^+$

Elemental Analysis **Calcd:** C, 68.02; H, 7.27.

Found: C, 67.84; H, 7.11.

Methyl 6-deoxy-5-*O*-Benzyl-3-*O*-(4-methoxybenzyl)-2-*O*-*p*-toluene sulphonyl-α-L-idofuranoside (99):



Compound **97** (4.0 g, 10.3 mmol), TsCl (4.9 g, 25.77 mmol) and pyridine (20 mL) were stirred at room temperature for 24 h. Pyridine was removed under vacuo and the residue extracted with EtOAc, washed with 1 N HCl, water, brine, dried (Na_2SO_4) and evaporated. The residue was purified by silica gel column chromatography by eluting with light petroleum: EtOAc (17:1) to give **99** (4.8 g).

Yield : 86%

Mol. Formula : $C_{29}H_{34}O_8S$

Optical Rotation $[\alpha]_D^{25}$: +55.9 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$) cm^{-1} : 2932, 2837, 1613, 1598, 1514, 1455, 1370, 1303, 1249, 1190, 1177, 1127, 1097, 1027, 851, 756, 668.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.18 (d, *J* = 6.5 Hz, 3H), 2.45 (s, 3H), 3.29 (s, 3H), 3.71 (dq, *J* = 6.6, 3.4 Hz, 1H), 3.84 (s, 3H), 3.98 (dd, *J* = 3.4, 7.2 Hz, 1H), 4.33 (d, *J* = 7.2 Hz, 1H), 4.40 (d, *J* = 5.5 Hz, 1H), 4.46-4.61 (m, 3H), 4.71 (d, *J* = 4.67 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.2 Hz, 2H), 7.32-7.43 (m, 5H), 7.76 (d, *J* = 8.2 Hz, 2H) ppm.

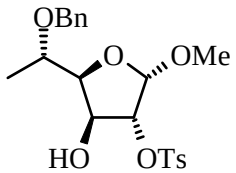
^{13}C NMR ($CDCl_3$, 50 MHz) : 16.10, 21.59, 55.11, 55.43, 71.46, 72.16, 72.70, 79.01 79.55, 82.15, 99.59, 113.64, 127.33, 127.92, 128.08,

128.18, 129.40, 129.50, 129.60, 133.37, 138.71, 144.68, 159.25 ppm.

Elemental Analysis **Calcd:** C, 64.19; H, 6.32.

Found: C, 63.94; H, 6.19.

Methyl 6-deoxy-5-*O*-Benzyl-2-*O*-*p*-toluene sulphonyl-α-L-idofuranoside (100):



DDQ (1.36 g, 5.99 mmol) was added to a solution of **99** (2.5 g, 4.61 mmol) in CH_2Cl_2:H_2O (19:1), (40 mL) at 0 ^oC. The reaction mixture stirred for 2 h at room temperature, diluted with excess CH_2Cl_2, and washed by saturated sodium bicarbonate. Organic layer dried, concentrated under vacuum and purified on silica gel by eluting with ethyl acetate: light petroleum ether (1:4) to get alcohol **100** (1.6 g).

Yield : 82%

Mol. Formula : $C_{21}H_{26}O_7S$

Optical Rotation $[\alpha]_D^{25}$: + 231.1 (*c* 0.7, $CHCl_3$)

IR ($CHCl_3$) cm^{-1} : 3468, 2931, 1597, 1454, 1364, 1190, 1124, 1097, 1013, 855, 814, 756, 669.

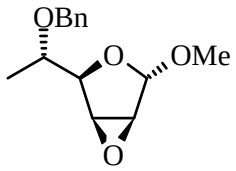
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.22 (d, *J* = 6.5 Hz, 3H), 1.64 (bs, 1H), 2.33 (s, 3H), 3.21 (s, 3H), 3.75 (dq, *J* = 6.4, 2.2 Hz, 1H), 3.91 (dd, *J* = 2.2, 7.5 Hz, 1H), 4.30 (d, *J* = 11.3 Hz, 1H), 4.40 (t, *J* = 7.2 Hz, 1H), 4.52-4.61 (m, 2H), 4.68 (d, *J* = 4.4 Hz, 1H), 7.14-7.28 (m, 7H), 7.64 (d, *J* = 8.1 Hz, 2H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 15.11, 21.57, 55.38, 70.44, 72.80, 73.59, 78.61, 83.60, 99.34, 127.84, 127.91, 128.02, 128.50, 129.58, 133.17, 137.59, 144.65 ppm.

Elemental Analysis **Calcd:** C, 61.93; H, 7.09.

Found: C, 61.54; H, 7.29.

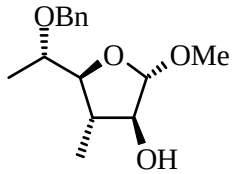
Methyl 6-deoxy-5-*O*-Benzyl-2,3-anhydro-α-D-gulofuranoside (101):



Compound **100** (1.5 g, 3.55 mmol) was dissolved in MeOH (20 mL) and K_2CO_3 (0.981 g 7.11 mmol) was added. The mixture was stirred at room temperature for 2.5 h and concentrated. To the reaction mixture, water was added and extracted with ethyl acetate, washed with water, dried (Na_2SO_4) and evaporated. Purification on silica gel using light petroleum:EtOAc (10:1) as an eluent afforded pure epoxide **101** (0.89 g).

Yield	: 95%
Mol. Formula	: $C_{14}H_{18}O_4$
Optical Rotation $[\alpha]_D^{25}$	: +41.0 (*c* 1.15, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	: 2977, 2908, 1601, 1496, 1454, 1354, 1216, 1193, 1113, 1047, 973, 879, 754, 698.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.22 (d, *J* = 6.4 Hz, 3H), 3.34 (s, 3H), 3.51 (d, *J* = 2.9 Hz, 1H), 3.57 (dd, *J* = 0.6, 2.8 Hz, 1H), 3.66 (quin, *J* = 6.5 Hz, 1H), 3.94 (d, *J* = 6.7 Hz, 1H), 4.54 (d, *J* = 11.9 Hz, 1H), 4.62 (d, *J* = 11.9 Hz, 1H), 4.88 (s, 1H), 7.14-7.30 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 16.99, 53.78, 55.21, 55.35, 71.73, 74.83, 79.92, 102.15, 127.38, 127.54, 128.22, 138.77 ppm.
ESI MS (*m/z*)	: 273 $[M+ Na]^+$
Elemental Analysis	**Calcd:** C, 67.18; H, 7.25.
	Found: C, 66.94; H, 7.01.

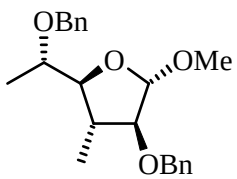
Methyl 5-*O*-Benzyl-3,6-di-deoxy-3-C-methyl-α-L-galactofuranoside (102):



A solution of 3 M CH_3MgC1 (Aldrich) in THF (10.6 mL, 32.0 mmol) was added to a stirred suspension of CuCN (0.351 g, 3.84 mmol) in 10 mL of dry THF under argon at 0 ^oC. After ca. 10 min a clear yellow solution was observed and a solution of **101** (0.8 g, 3.2 mmol) in 5 mL of THF was slowly added. The solution was stirred for 1 h, and then quenched by saturated aqueous NH_4C1. The reaction mixture was partitioned between ethyl acetate and water. Organic layer separated, dried over sodium sulphate and purified through column chromatography, eluting by ethyl acetate: pet ether (1:4) to obtain compound **102** (0.8 g).

Yield	: 94 %
Mol. Formula	: $C_{15}H_{22}O_4$
Optical Rotation $[\alpha]_D^{25}$	: +92.0 (*c* 0.8, $CHCl_3$).
IR ($CHCl_3$) cm^{-1}	: 3436, 2963, 2930, 1496, 1455, 1375, 1191, 1106, 1073, 1028, 962, 739, 698.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.16 (d, *J* = 7.5 Hz, 3H) 1.36 (d, *J* = 6.4 Hz, 3H), 1.95-2.08 (m, 1H), 3.34 (s, 3H), 3.53 (dq, *J* = 2.0, 6.4 Hz, 1H), 3.69 (bs, 1H), 3.71 (dd, *J* = 2.0, 4.0 Hz, 1H), 4.43 (d, *J* = 11.4 Hz, 1H), 4.71 (d, *J* = 11.4 Hz, 1H), 4.81 (s, 1H), 7.28-7.37 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 15.62, 17.76, 43.24, 54.64, 71.15, 74.54, 80.89, 89.05, 110.69, 128.03, 128.28, 128.49, 137.28 ppm.
ESI MS (*m/z*)	: 289 $[M+ Na]^+$
Elemental Analysis	**Calcd:** C, 67.64; H, 8.33.
	Found: C, 67.33; H, 8.12.

Methyl 2,5-di-*O*-Benzyl-3,6-di-deoxy-3-C-methyl-α-L-galactofuranoside (103):

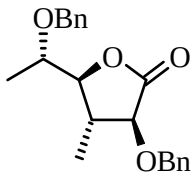


To a solution of **102** (0.9 g, 3.38 mmol) in DMF (15 mL) at 0 °C was added NaH (60 % dispersion in mineral oil, 0.203 g, 5.07 mmol). After 15 min, benzyl bromide (0.6

mL, 5.07 mmol) was introduced and the reaction further stirred for 1 h at room temperature. Water was carefully added to the reaction mixture, extracted with ether, washed with water and dried (Na_2SO_4). On evaporation of solvent, the residue was purified by silica gel chromatography by eluting with light petroleum: EtOAc (1:19) to afford **103** (1.2 g).

Yield	: 90%
Mol. Formula	: $C_{22}H_{28}O_4$
Optical Rotation $[\alpha]_D^{25}$	: +23.2 (*c* 1.1, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	: 2970, 2932, 2877, 1496, 1454, 1373, 1217, 1192, 1108, 1027, 959, 756, 698.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.96 (d, *J* = 7.0 Hz, 3H), 1.17 (d, *J* = 6.2 Hz, 3H), 2.03-2.20 (m, 1H), 3.27 (s, 3H), 3.50 (dd, *J* = 1.4, 4.9 Hz, 1H), 3.54-3.63 (m, 2H), 4.41-4.53 (m, 3H), 4.61 (d, *J* = 12.2 Hz, 1H), 4.86 (d, *J* = 1.1 Hz, 1H), 7.14-7.29 (m, 10H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 15.77, 16.14, 40.21, 54.71, 71.17, 71.76, 73.97, 86.53, 90.91, 107.50, 127.39, 127.58, 127.62, 127.70, 128.23, 128.31, 138.06, 138.76 ppm.
ESI MS (*m/z*)	: 379.5 $[M+ Na]^+$
Elemental Analysis	**Calcd:** C, 74.13; H, 7.92.
	Found: C, 73.94; H, 7.79.

(3*S*, 4*R*, 5*S*)-3-(benzyloxy)-5((*S*)-1-(benzyloxy)ethyl)-4-methyldihydrofuran-2(3H)-one (105):



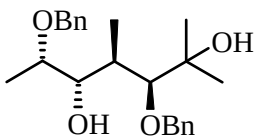
A stirred solution of compound **103** (400 mg, 1.12 mmol) and aq. 0.4% H_2SO_4 (9.7 mL) in 1,4-dioxane (30 mL) was heated at 70 ^oC for 6 h. Reaction mixture was neutralized by addition of solid $NaHCO_3$, filtered, concentrated and the residue partitioned between EtOAc and water. Combined organic layer was washed with brine,

dried (Na_2SO_4), concentrated and residue purified on silica gel column chromatography using EtOAc:light petroleum ether (6:4) to obtain lactol **104**, which was used for the next reaction without further purification.

To a mixture of lactol **104** and 4 Å molecular sieves powder (0.8 g) in anhydrous dichloromethane (10 mL), PDC (0.845 g, 2.25 mmol) was added at 0 ^oC. The reaction mixture was stirred at room temperature for 1 h. Dichloromethane was removed under reduced pressure and ethyl acetate was added. Solid was filtered, the filtrate evaporated and silica gel column chromatography purification using light petroleum: EtOAc (10:1) offered **105** (0.3 g).

Yield	: 78%, in two steps
Mol. Formula	: $C_{21}H_{24}O_4$
Optical Rotation $[\alpha]_D^{25}$	: +14.9 (*c* 1.95, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	: 3019, 2975, 2934, 2875, 1783, 1496, 1455, 1378, 1311, 1216, 1142, 1117, 1092, 1065, 698, 667.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.04 (d, *J* = 6.6 Hz, 3H), 1.27 (d, *J* = 6.5 Hz, 3H), 2.44-2.63 (m, 1H), 3.66 (dq, *J* = 3.9, 6.4 Hz, 1H), 3.79 (d, *J* = 10.4 Hz, 1H), 3.87 (dd, *J* = 3.9, 9.4 Hz, 1H), 4.49 (d, *J* = 11.9 Hz, 1H), 4.66 (d, *J* = 11.9 Hz, 1H), 4.76 (d, *J* = 11.8 Hz, 1H), 5.07 (d, *J* = 11.8 Hz, 1H), 7.18- 7.37 (m, 10H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 14.90, 15.25, 37.62, 71.16, 72.19, 72.40, 79.47, 84.32, 127.77, 127.81, 128.08, 128.27, 128.42, 128.48, 137.24, 137.96, 174.37 ppm.
ESI MS (*m/z*)	: 363.4 $[M+ Na]^+$
Elemental Analysis	**Calcd:** C, 74.09; H, 7.11.
	Found: C, 73.84; H, 7.01.

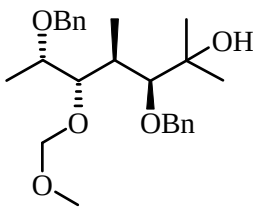
(3*S*,4*R*,5*S*,6*S*)-3,6-bis(benzyloxy)-2,4-dimethylheptane-2,5-diol (106):



A solution of MeMgCl (1.5 mL, 4.47 mmol) in THF was added to a solution of lactone **105** (0.38 g, 1.12 mmol) in THF (5 mL) at 0 ^{o}C. It was stirred at the same temperature for 4 h, then quenched by saturated aq. ammonium chloride and extracted by ethyl acetate. The reaction mixture concentrated and product purified by column chromatography, eluting with ethyl acetate:light petroleum ether (3:7) to get diol **106** (0.39 g) as a colourless liquid.

Yield	: 96%
Mol. Formula	: $C_{23}H_{32}O_4$
Optical Rotation $[\alpha]_D^{25}$	: +46.7 (*c* 3.0, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	: 3563, 3015, 2976, 2934, 1497, 1454, 1386, 1374, 1216, 1090, 1070, 757, 698.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.88 (d, *J* = 6.9 Hz, 3H), 1.19 (s, 3H), 1.22 (s, 3H), 1.28 (d, *J* = 6.2 Hz 3H), 1.94-2.06 (m, 1H), 2.27 (bs, 2H), 3.14 (dd, *J* = 2.4, 8.9 Hz, 1H), 3.66 (dq, *J* = 2.4, 6.2 Hz, 1H), 3.76 (d, *J* = 1.6 Hz, 1H), 4.39 (d, *J* = 11.7 Hz, 1H), 4.60 (d, *J* = 11.5 Hz, 1H), 4.67 (d, *J* = 11.7 Hz, 1H), 4.78 (d, *J* = 11.5 Hz, 1H), 7.24-7.34 (m, 10H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 11.68, 16.52, 25.89, 27.51, 36.91, 70.62, 73.10, 73.58, 74.87, 77.85, 83.58, 127.37, 127.76, 127.87, 128.23, 128.35, 138.14, 138.99 ppm.
ESI MS (*m/z*)	: 395.5 $[M+ Na]^+$
Elemental Analysis	**Calcd:** C, 74.16; H, 8.66.
	Found: C, 74.24; H, 8.49.

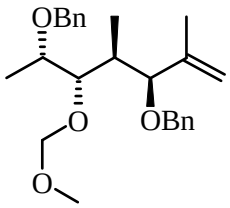
(3*S*,4*R*,5*S*,6*S*)-3,6-bis(benzyloxy)-5-(methoxymethoxy)-2,4-dimethylheptan-2-ol (107):



To a solution of **106** (1.3 g, 3.49 mmol) in DMF (30 mL) at 0 °C was added NaH (60 % dispersion in mineral oil, 0.279 g, 6.98 mmol). After 15 min, methoxymethyl chloride (0.3 mL, 4.19 mmol) was introduced and the reaction further stirred for 1 h at same temperature. Water was carefully added to the reaction mixture, extracted with ethyl acetate, washed with water and dried (Na_2SO_4). On evaporation of solvent, the residue was purified by silica gel column chromatography by eluting with light petroleum: EtOAc (1:17) to afford **107** (1.3 g) as a yellow colour liquid.

Yield	: 90%
Mol. Formula	: $C_{25}H_{36}O_5$
Optical Rotation $[\alpha]_D^{25}$	: −14.4 (*c* 1.15, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	: 3467, 3030, 2976, 2931, 1717, 1496, 1453, 1372, 1275, 1214, 1148, 1097, 919, 754, 698.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.94 (d, *J* = 7.1 Hz, 3H), 1.14 (s, 3H), 1.15 (s, 3H), 1.17 (d, *J* = 6.5 Hz, 3H), 2.06-2.13 (m, 1H), 3.29 (dd, *J* = 3.8, 8.1 Hz, 1H), 3.34 (s, 3H), 3.63 (dq, *J* = 3.9, 6.4 Hz, 1H), 3.56 (d, *J* = 1.4 Hz, 1H), 4.38 (d, *J* = 11.8 Hz, 1H), 4.53 (d, *J* = 11.6 Hz, 1H), 4.57 (d, *J* = 11.8 Hz, 1H), 4.64 (d, *J* = 6.9 Hz, 1H), 4.67 (d, *J* = 6.9 Hz, 1H), 4.73 (d, *J* = 11.6 Hz, 1H), 7.19-7.29 (m, 10H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 12.28, 15.68, 25.97, 26.75, 35.26, 56.33, 71.03, 73.81, 74.48, 75.12, 84.02, 85.51, 98.41, 127.31, 127.43, 127.54, 127.71, 128.32, 138.58, 139.14 ppm.
ESI MS (*m/z*)	: 439.5 $[M+ Na]^+$
Elemental Analysis	**Calcd:** C, 72.08; H, 8.71.
	Found: C, 71.89; H, 8.69.

((2*S*,3*S*,4*S*,5*S*)-3-(methoxymethoxy)-4,6-dimethylhept-6-ene-2,5-diyl)bis(oxy)bis(methylene)dibenzene (108).



To a solution of **107** (1.2 g, 2.88 mmol) in CH_2Cl_2 (20 mL) DMAP (1.4 g, 11.53 mmol), triethylamine (1.6 mL, 11.53 mmol), and MsCl (1.13 mL, 11.53 mmol) were added and the reaction mixture was stirred for 2 h at room temperature (monitored by TLC). After completion of the reaction, the mixture was partitioned between dichloromethane (30 mL) and water (10 mL). The organic layer was washed with brine and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure and the crude was purified by silica gel column chromatography using ethyl acetate and light petroleum (1:4) to offer **108** (1.0 g) as a colorless liquid.

Yield : 87%

Mol. Formula : $C_{25}H_{34}O_4$

Optical Rotation $[\alpha]_D^{25}$: +7.5 (*c* 0.8, $CHCl_3$)

IR ($CHCl_3$) cm^{-1} : 2973, 2930, 1660, 1497, 1454, 1371, 1092, 1037, 907, 734, 697.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.81 (d, *J* = 7.0 Hz, 3H), 1.17 (d, *J* = 6.4 Hz, 3H), 1.64 (s, 3H), 1.93-2.03 (m, 1H), 3.31 (s, 3H), 3.38 (dd, *J* = 2.6, 8.2 Hz, 1H), 3.61 (dq, *J* = 2.7, 6.4 Hz, 1H), 3.85 (d, *J* = 3.8 Hz, 1H), 4.15 (d, *J* = 11.6 Hz, 1H), 4.35 (d, *J* = 11.9 Hz, 1H), 4.46-4.58 (m, 4H), 4.86 (s, 1H), 4.94 (s, 1H), 7.17-7.26 (m, 10H) ppm.

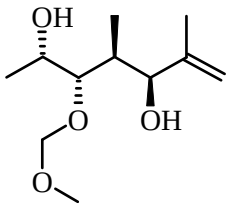
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 9.96, 15.83, 19.42, 37.44, 55.88, 70.03, 70.74, 74.44, 81.91, 83.26, 98.35, 112.31, 127.17, 127.31, 127.44, 127.55, 128.01, 128.17, 138.52, 139.07, 142.79 ppm.

ESI MS (*m/z*) : 421.5 $[M+ Na]^+$

Elemental Analysis **Calcd:** C, 75.34; H, 8.60.

Found: C, 75.14; H, 8.49.

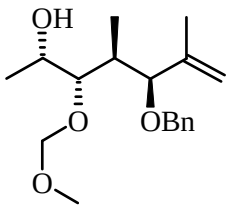
(2*S*,3*S*,4*S*,5*S*)-3-(methoxymethoxy)-4,6-dimethylhept-6-ene-2,5-diol (109).



To a solution of naphthalene (530 mg, 4.14 mmol) in THF (15 mL) sodium metal (95 mg, 4.14 mmol) was added at room temperature under N_2. The mixture was stirred at room temperature until a dark green solution was formed. Then it was cooled to −20 °C and a solution of olefin **108** (550 mg, 1.38 mmol) in THF (5 mL) was added. The mixture was stirred at 0 °C for 1 h. The reaction mixture was then partitioned between ether and saturated aqueous NH_4Cl. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel column (Ethyl acetate:light petroleum ether, 2:3) to give diol **109** as a colorless oil (290 mg).

Yield	: 96%
Mol. Formula	: $C_{11}H_{22}O_4$
Optical Rotation $[\alpha]_D^{25}$	: +4.6 (*c* 0.6, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	: 3439, 2925, 2853, 1714, 1463, 1455, 1378, 1182, 1215, 1096, 698, 666.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.87 (d, *J* = 7.0 Hz, 3H), 1.22 (d, *J* = 6.4 Hz, 3H), 1.68 (s, 3H), 1.94-2.08 (m, 1H), 2.94 (d, *J* = 2.6 Hz, 1H), 3.19 (bs, 1H), 3.32 (t, *J* = 5.4 Hz, 1H), 3.47 (s, 3H), 3.96 (m, 1H), 4.34 (bs, 1H), 4.73 (d, *J* = 6.6 Hz, 1H), 4.81 (d, *J* = 6.6 Hz, 1H), 4.93 (s, 1H), 5.09 (s, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 9.79, 19.92, 20.04, 36.00, 56.36, 67.74, 72.75, 90.34, 99.51, 110.51, 144.88 ppm.
ESI MS (*m/z*)	: 241.3 $[M+ Na]^+$
Elemental Analysis	**Calcd:** C, 60.52; H, 10.16.
	Found: C, 60.37; H, 10.00.

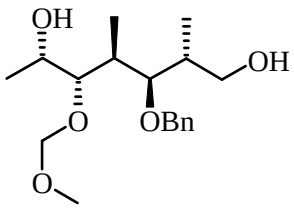
(2*S*,3*S*,4*S*,5*S*)-5-(benzyloxy)-3-(methoxymethoxy)-4,6-dimethylhept-6-en-2-ol (110).



To a solution of **109** (0.3 g, 1.38 mmol) in DMF (13 mL) at 0 °C was added NaH (60 % dispersion in mineral oil, 0.66 g, 1.65 mmol). After 15 min, benzyl bromide (0.18 mL, 1.51 mmol) was introduced and the reaction further stirred for 1 h at the same temperature. Water was carefully added to the reaction mixture, extracted with ether, washed with water and dried (Na_2SO_4). On evaporation of solvent, the residue was purified by silica gel column chromatography by eluting with light petroleum:EtOAc (10:1) to afford **110** (0.4 g) as yellow colour liquid.

Yield	: 94%
Mol. Formula	: $C_{18}H_{28}O_4$
Optical Rotation $[\alpha]_D^{25}$	: −13.3 (*c* 0.9, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	: 3435, 2925, 2854, 1619, 1454, 1377, 1218, 1028, 770, 697.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.72 (d, *J* = 7.0 Hz, 3H), 1.24 (d, *J* = 6.3 Hz, 3H), 1.67 (s, 3H), 2.00-2.08 (m, 1H), 3.27 (d, *J* = 2.0 Hz, 1H), 3.43 (s, 3H), 3.40-3.47 (m, 1H), 3.73 (dq, *J* = 4.4, 6.3 Hz, 1H), 4.37 (bs, 1H), 4.45 (d, *J* = 11.8 Hz, 1H), 4.67 (d, *J* = 11.8 Hz, 1H), 4.78 (s, 2H), 4.92 (s, 1H), 5.08 (s, 1H), 7.27-7.34 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 14.10, 16.15, 22.68, 29.35, 35.61, 45.82, 56.53, 71.17, 72.64, 75.22. 85.92, 99.28, 110.13, 127.65, 127.95, 128.32, 138.40, 145.37 ppm.
ESI MS (*m/z*)	: 331.4 $[M+ Na]^+$
Elemental Analysis	**Calcd:** C, 70.10; H, 9.15.
	Found: C, 70.02; H, 8.98.

(2*R*,3*R*,4*S*,5*S*,6*S*)-3-(benzyloxy)-5-(methoxymethoxy)-2,4-dimethylheptane-1,6-diol (111):

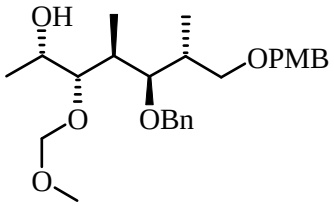


To a solution of **110** (300 mg, 0.97 mmol) in THF (5 mL) was added 9-BBN (356 mg 2.92 mmol) at 0 ^{o}C. The reaction mixture was warmed up to room temperature and heated to reflux for 3 h. It was cooled to 0 ^{o}C, NaOH (3 M, 0.7 mL) and H_2O_2 (30%, 0.2 mL) were added. After 2.5 h, the reaction mixture was diluted with H_2O. The mixture was extracted with diethyl ether, washed with brine. The organic layer dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified on a silica gel column chromatography using petroleum ether /EtOAc (1/1) as the eluent to afford **111** as colorless oil (290 mg).

Yield	: 91%
Mol. Formula	: $C_{18}H_{30}O_5$
Optical Rotation $[\alpha]_D^{25}$	: −3.3 (*c* 1.2, $CHCl_3$).
IR ($CHCl_3$) cm^{-1}	: 3435, 2934, 1618, 1454, 1383, 1217, 1144, 1029, 768.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.74 (d, *J* = 6.9 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H), 1.21 (d, *J* = 6.4 Hz, 3H), 1.86-1.92 (m, 1H), 1.95-2.02 (m, 1H), 3.39 (dd, *J* = 5.1, 6.2 Hz, 1H), 3.44 (s, 3H), 3.62 (m, 1H), 3.66 (d, *J* = 8.3 Hz, 1H), 3.69-3.75 (m, 1H), 3.84 (d, *J* = 9.9 Hz, 1H), 4.04 (bs, 1H), 4.45 (d, *J* = 11.8 Hz 1H), 4.66 (d, *J* = 11.8 Hz, 1H), 4.75 (d, *J* = 6.7 Hz, 1H), 4.78 (d, *J* = 6.7 Hz, 1H), 7.28-7.36 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 9.74, 13.35, 16.15, 35.22, 36.93, 56.53, 69.66, 71.28, 75.37, 77.20, 86.42, 99.31, 127.72, 127.93, 128.38, 138.32 ppm.
ESI MS (*m/z*)	: 349.4 $[M+ Na]^+$
Elemental Analysis	**Calcd:** C, 66.23; H, 9.26.

Found: C, 66.04; H, 9.10.

(2*S*,3*S*,4*S*,5*R*,6*R*)-5-(benzyloxy)-7-(4-methoxybenzyloxy)-3-(methoxymethoxy)-4,6-dimethylheptan-2-ol (112).



To a solution of **111** (0.250 g, 0.77 mmol) in DMF (7 mL) at 0 °C was added NaH (60 % dispersion in mineral oil, 0.37 g, 0.92 mmol). After 15 min, *p*-methoxybenzyl chloride (0.12 mL, 0.84 mmol) was introduced and the reaction further stirred for 1 h at the same temperature. Water was carefully added to the reaction mixture, extracted with ethyl acetate, washed with water and dried (Na_2SO_4). On evaporation of solvent, the residue was purified by silica gel column chromatography by eluting with light petroleum: EtOAc (10:1) to afford **112** (0.28 g).

Yield : 82%

Mol. Formula : $C_{26}H_{38}O_6$

Optical Rotation $[\alpha]_D^{25}$: +11.1 (*c* 0.85, $CHCl_3$).

IR ($CHCl_3$) cm^{-1} : 3445, 3010, 2971, 2936, 1612, 1586, 1513, 1454, 1302, 1248, 1216, 1142, 1069, 1033, 757, 698, 667.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.99 (d, *J* = 7.0 Hz, 3H), 1.00 (d, *J* = 7.0 Hz, 3H), 1.17 (d, *J* = 6.4 Hz, 3H), 1.95-2.08 (m, 2H), 2.70 (d, *J* = 5.7 Hz, 1H), 3.24 (dd, *J* = 3.9, 6.5 Hz, 1H), 3.37 (s, 3H), 3.48-3.52 (m, 2H), 3.62 (dd, *J* = 1.8, 8.2 Hz, 1H), 3.79 (s, 3H), 3.88 (bs, 1H), 4.41 (s, 2H), 4.51 (d, *J* = 11.6 Hz, 1H), 4.61-4.70 (m, 3H), 6.84 (d, *J* = 8.7 Hz, 2H), 7.22-7.31 (m, 7H) ppm.

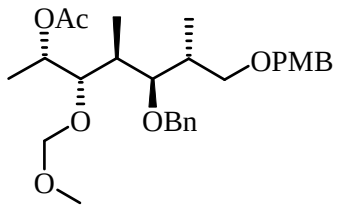
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 11.21, 15.04, 20.56, 36.52, 37.28, 55.13, 55.89, 67.26, 72.20, 72.73, 73.37, 79.70, 87.67, 98.15, 113.64, 127.08, 128.14, 129.18, 130.69, 139.58, 159.04 ppm.

ESI MS (*m/z*) : 469 $[M+ Na]^+$

Elemental Analysis **Calcd:** C, 69.93; H, 8.58.

Found: C, 69.74; H, 8.39.

(2*S*,3*S*,4*S*,5*R*,6*R*)-5-(benzyloxy)-7-(4-methoxybenzyloxy)-3-(methoxymethoxy)-4,6-dimethylheptan-yl acetate (117).



A mixture of **112** (0.25 g, 0.56 mmol), triethylamine (0.1 mL, 0.84 mmol), acetic anhydride (0.06 mL, 0.67 mmol) and catalytic amount of DMAP in dichloromethane was stirred for 30 min at 0 ^oC. The mixture diluted with dichloromethane, washed with brine dried over sodium sulphate. After evaporation under reduced pressure, the residue purified by column chromatography using light petroleum:ethyl acetate (19:1) to obtain **117** (260 mg).

Yield : 95%

Mol. Formula : $C_{28}H_{40}O_7$

Optical Rotation $[\alpha]_D^{25}$: −1.9, (*c* 0.7, $CHCl_3$)

IR ($CHCl_3$) cm^{-1} : 3064, 2937, 1733, 1608, 1585, 1513, 1455, 1372, 1301, 1170, 1093, 1030, 960, 821, 755, 698.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.91 (d, *J* = 7.0 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 1.23 (d, *J* = 6.5 Hz, 3H), 1.86-2.02 (m, 2H).2.05 (s, 3H), 3.37 (s, 3H), 3.42 (dd, *J* = 3.1, 8.2 Hz, 1H), 3.50-3.55 (m, 2H), 3.72 (dd, *J* = 1.6, 8.5 Hz, 1H), 3.79 (s, 3H), 4.41 (s, 2H), 4.55 (d, *J* = 11.8 Hz, 1H), 4.64 (d, *J* = 11.8 Hz, 1H), 4.68 (s, 2H), 5.08 (dq, *J* = 3.1, 6.5 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 2H), 7.22-7.31 (m, 7H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 10.22, 15.21, 16.38, 21.33, 37.04, 37.14, 55.17, 56.09, 70.80, 72.35, 72.78, 73.58, 79.68, 83.17, 98.13, 113.65, 127.09, 128.19, 129.20, 130.77, 139.62,

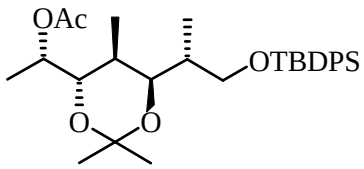
159.05, 170.29 ppm.

ESI MS (*m/z*) : 511 $[M+ Na]^+$

Elemental Analysis **Calcd:** C, 68.83; H, 8.25.

Found: C, 68.64; H, 8.10.

(*S*)-1-((4*S*,5*S*,6*R*)-6-((*R*)-1-(*tert*-butyldiphenylsilyloxy)propan-2-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl)ethylacetate (120):



To a solution of **117** (250 mg, 0.5 mmol) in anhydrous CH_2Cl_2 (5 mL) under nitrogen at 0 °C was added $TiCl_4$ (0.5 mL, 5.1 mmol). After 30 min, excess of reagent was quenched with saturated aq. $NaHCO_3$ solution, extracted with CH_2Cl_2, washed with brine, dried (Na_2SO_4), evaporated. The resulting triol **118** was taken on to the next reaction without further purification.

To a solution of **118**, Et_3N (0.1 mL, 0.77 mmol) and DMAP (5.0 mg) in CH_2Cl_2 (5 mL) was added TBDPS chloride (0.1 mL, 0.56 mmol) at room temperature. The reaction mixture was stirred for overnight, diluted with CH_2Cl_2, washed with brine, dried (over Na_2SO_4) and concentrated. The crude mass was eluted through a pad of silica gel (hexanes/EtOAc 1:1) and the colourless liquid remaining after evaporation of the volatiles was taken on to the next reaction without further purification.

A solution of **119** and a catalytic amount of PPTS in 1:1 CH_2Cl_2/2,2-dimethoxy-propane (5 mL) was stirred for one day at rt under N_2. It was concentrated *in vacuo* and the residue was purified by flash column chromatography using hexanes/EtOAc (97:3), which afforded 150 mg of **120** as colourless liquid.

Yield 57% over three steps

Mol. Formula : $C_{30}H_{44}O_5Si$

Optical Rotation $[\alpha]_D^{25}$: −16.7 (*c* 0.6, $CHCl_3$)

IR ($CHCl_3$) cm^{-1} : 3049, 2931, 2962, 2857, 1739, 1589, 1472, 1462, 1428, 1377, 1240, 1112, 1048, 999, 823, 702, 690, 667 ppm.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.89 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H), 1.08 (s, 9H), 1.27 (d, *J* = 6.3 Hz, 3H), 1.26 (s, 3H), 1.29 (s, 3H), 1.71-1.84 (m, 2H), 2.10 (s, 3H), 3.28 (dd, *J* = 3.9, 7.3 Hz, 1H), 3.64-3.72 (m, 3H), 4.94-5.06 (m, 1H), 7.37-7.43 (m, 6H), 7.63-7.70 (m, 4H) ppm.

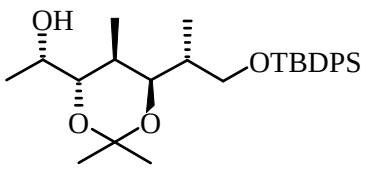
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 12.11, 13.05, 15.98, 19.36, 23.43, 25.23, 27.00, 33.62, 35.43, 65.06, 69.70, 70.53, 76.56, 77.43, 100.88, 127.49, 127.89, 129.46, 129.48, 135.70, 135.78, 170.95 ppm.

ESI MS (*m/z*) : 535 $[M+ Na]^+$

Elemental Analysis **Calcd:** C, 70.27; H, 8.65.

Found: C, 70.09; H, 8.54.

(*S*)-1-((4*S*,5*S*,6*R*)-6-((*R*)-1-(*tert*-butyldiphenylsilyloxy)propan-2-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl)ethanol (121):



Compound **120** (100 mg, 0.19 mmol) was dissolved in MeOH (5 mL) and K_2CO_3 (40 mg, 0.29 mmol) was added. The mixture was stirred at room temperature for 2 h and concentrated. The residue was dissolved in water and extracted with ethyl acetate, washed with water, dried (Na_2SO_4) and evaporated. Purification on silica gel using light petroleum:EtOAc (10:1) as an eluent afforded pure alcohol **121** (80 mg).

Yield 88%

Mol. Formula : $C_{28}H_{42}O_4Si$

Optical Rotation $[\alpha]_D^{25}$: −19.3 (*c* 1.4, $CHCl_3$)

IR ($CHCl_3$) cm^{-1} : 3447, 3050, 3071, 2960, 2855, 1462, 1428, 1379, 1222, 1187, 1112, 1057, 822, 758, 666 ppm.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.92 (d, *J* = 6.7 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H), 1.09 (s, 9H), 1.22 (d, *J* = 6.3 Hz, 3H), 1.26 (s, 3H), 1.32 (s, 3H), 1.69-1.75 (m, 1H), 1,79-1.87 (m, 1H),

3.09 (t, *J* = 6.4 Hz, 1H), 3.68-3.77 (m, 4H), 7.37-7.44 (m, 6H), 7.67-7.70 (m, 4H) ppm.

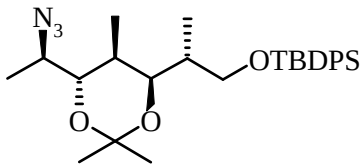
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 12.27, 13.00, 18.46, 19.35, 23.76, 25.33, 27.00, 34.12, 35.42, 65.02, 69.56, 69.61, 79.48, 100.82, 127.49, 129.45, 129.48, 133.85, 134.00, 135.69, 135.78 ppm.

ESI MS (*m/z*) : 493 $[M+ Na]^+$

Elemental Analysis **Calcd:** C, 71.44; H, 8.99.

Found: C, 71.34; H, 8.84.

((*R*)-2-((4*R*,5*S*,6*S*)-6-((*R*)-1-azidoethyl)-2,2,5-trimethyl-1,3-dioxan-4yl)propoxy)(*tert*-butyl)diphenylsilane (123).



Compound **121** (80 mg, 0.17 mmol) was dissolved in CH_2Cl_2 (2.5 mL), cooled to 0 °C under N_2, then Et_3N (0.03 mL, 0.25 mmol) and MsCl (0.01 mL, 0.2 mmol) were added dropwise. The reaction was stirred for 4 h at 0 °C, diluted with CH_2Cl_2 (20 mL), and washed with H_2O, saturated $NaHCO_3$, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The resulting liquid was taken on to the next reaction without further purification.

It was diluted with DMF (1 mL) and NaN_3 (77 mg, 1.19 mmol) was added. The resulting suspension was stirred for 22 h at 70 °C. The mixture was diluted with Et_2O (25 mL) and washed with H_2O, brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash column chromatography (hexanes/EtOAc 97:3) affording 75 mg of **123** as colorless liquid.

Yield 89%, over two steps.

Mol. Formula : $C_{28}H_{41}N_3O_3Si$

Optical Rotation $[\alpha]_D^{25}$: −24.0 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$) cm^{-1} : 3072, 2931, 2109, 1725, 1471, 1428, 1380, 1223, 1112, 1025, 822, 759, 667.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.92 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H), 1.08 (s, 9H), 1.24 (s, 3H), 1.26 (d, *J* = 6.7 Hz, 3H), 1.31 (s, 3H), 1.67-1.74 (m, 1H), 1.86-1.90 (m, 1H), 3.36 (dd, *J* = 4.2, 6.6 Hz, 1H), 3.51 (dq, *J* = 4.2, 6.7 Hz, 1H), 3.66-3.75 (m, 3H), 7.36-7.44 (m, 6H), 7.65-7.69 (m, 4H) ppm.

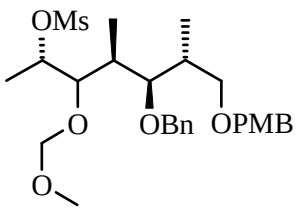
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 12.71, 13.00, 14.58, 19.37, 23.63, 25.34, 26.99, 33.97, 35.46, 59.65, 65.03, 69.51, 78.07, 100.74, 127.49, 129.46, 133.90, 134.00, 135.70, 135.78 ppm.

ESI MS (*m/z*) : 518 $[M+ Na]^+$

Elemental Analysis **Calcd:** C, 67.84; H, 8.34.

Found: C, 67.75; H, 8.29.

(2*S*,3*S*,4*R*,5*R*,6*R*)-5-(benzyloxy)-3-(methoxymethoxy)-7-(4-methoxybenzyloxy)-4,6-dimethylheptan-2-yl methanesulfonate (115):



Compound **112** (250 mg, 0.56 mmol) was dissolved in CH_2Cl_2 (5 mL), cooled to 0 °C under N_2, Et_3N (0.1 mL, 0.84 mmol), MsCl (0.05 mL, 0.67 mmol) and DMAP (catalytic) were added. The reaction was stirred for 1 h at 0 °C, diluted with CH_2Cl_2 (20 mL), and washed with H_2O, saturated aq. $NaHCO_3$, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The reaction mixture purified by column chromatography using light petroleum ether:ethyl acetate (6:1) to obtain **115** (250 mg).

Yield 85%

Mol. Formula : $C_{27}H_{40}O_8S$

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.92 (d, *J* = 7.1 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 1.38 (d, *J* = 7.5 Hz, 3H), 1.67-1.75 (m, 1H), 1.95-2.07 (m, 1H), 2.90 (s, 3H), 3.37 (s, 3H), 3.48-3.57 (m, 2H), 3.66-3.79 (m, 2H), 3.79 (s, 3H), 4.42 (s, 2H), 4.60-

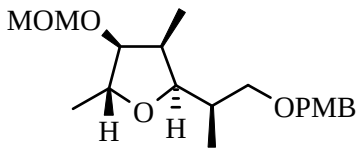
4.74 (m, 4H), 4.95 (dq, *J* = 1.8, 8.4 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 2H), 7.22-7.31 (m, 7H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 10.13, 14.68, 15.06, 36.98, 37.88, 38.70, 55.20, 56.15, 72.82, 73.84, 79.57, 80.75, 81.94, 98.02, 113.70, 127.19, 127.23, 128.27, 129.19, 139.48, 159.12 ppm.

Elemental Analysis **Calcd:** C, 61.81; H, 7.68.

Found: C, 61.62; H, 7.49.

(2*R*,3*S*,4*S*,5*R*)-2-((*R*)-1-(4-methoxybenzyloxy)propan-2-yl)-4-(methoxymethoxy)-3,5-dimethyltetrahydrofuran (116):



Compound **115** (100 mg, 0.2 mmol) was dissolved in DMF (2 mL) and NaN_3 (37 mg, 0.6 mmol) was added. The resulting suspension was stirred for 5 h at 70 °C. The mixture was diluted with Et_2O (25 mL) and washed with H_2O, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The reaction mixture was purified by flash column chromatography (hexanes/EtOAc 97:3) affording 50 mg of **116**, as yellow colour liquid.

Yield 78%

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

IR ($CHCl_3$) cm^{-1} : 2934, 1613, 1586, 1513, 1464, 1301, 1248, 1217, 1172, 1154, 1094, 1041, 920, 822, 756, 666.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.91 (d, *J* = 7.2 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 1.18 (d, *J* = 6.6 Hz, 3H), 1.90-2.04 (m, 1H), 2.24-2.35 (m, 1H), 3.38 (s, 3H), 3.30-3.44 (m, 2H), 3.65 (dd, *J* = 3.3, 8.9 Hz, 1H), 3.80 (s, 3H), 3.94-4.08 (m, 1H), 4.40 (d, *J* = 11.6 Hz, 1H), 4.47 (d, *J* = 11.6 Hz, 1H), 4.61 (s, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 7.24 (d, *J* = 8.7 Hz, 2H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 8.12, 14.21, 17.09, 34.43, 37.92, 55.21, 55.69, 72.80, 72.86, 75.24, 79.20, 80.57, 96.35, 113.68, 129.08, 131.13, 159.04 ppm.
ESI MS (*m/z*)	361 $[M+ Na]^+$
Elemental Analysis	**Calcd:**
	C, 67.43; H, 8.93.
	Found: C, 67.34; H, 8.79.

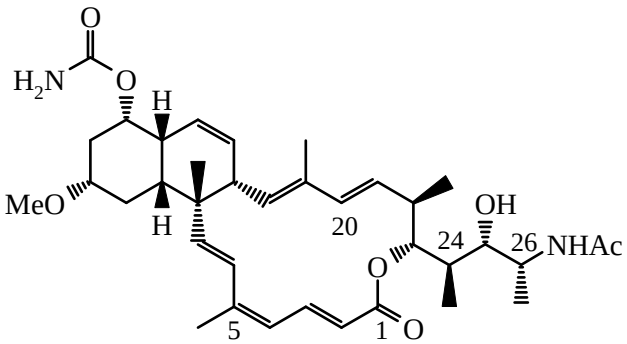
CHAPTER 2

SECTION II

Stereoselective synthesis of C21-C26 fragment of superstolide A

Present Work

In the previous section, we have accomplished the synthesis of C21-C26 segment of Superstolide A (**26**) (Figure 13). While the earlier work was in progress, an alternative stereoselective route leading to C21-C26 segment of superstolide A (**26**) was also in progress. This section deals with new studies on C21-C26 fragment. We planned a new concise synthetic strategy for polyketide region of **26** with lesser transformations and stereoselective reactions.



Superstolide A (**26**)

Figure 13

Closely examination of the structure of **26** revealed that the molecule was comprised of two distinctive *trans*-hydroxymethyl isoster moieties and one amine moiety with (*R*)-stereocenter, represented by C23-C22, C25-C24, and C26 segments (Figure 14).

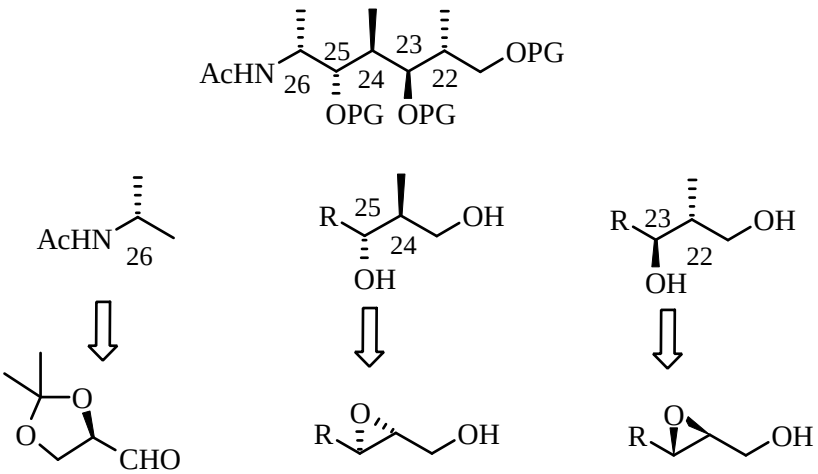
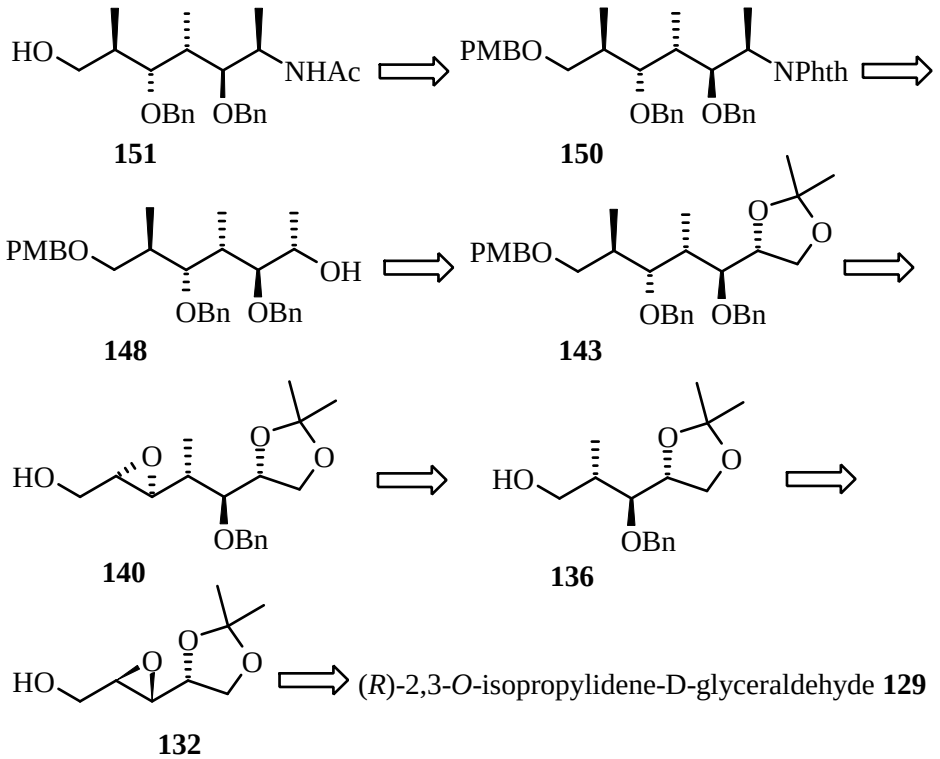


Figure 14

In order to assemble these units, the adaptation of stereocontrolled reactions has been envisaged. We believed that hydroxymethyl units could be furnished by stereospecific epoxide opening with MeMgCl, whereas the remaining center could be obtained from (*R*)-2,3-*O*-isopropylidene-D-glyceraldehyde **129**.

A linear strategy was opted in which starting material derived from common and inexpensive compound, namely, (*R*)-2,3-*O*-isopropylidene-D-glyceraldehyde **129**. The retrosynthetic analysis is depicted below (Scheme 28).

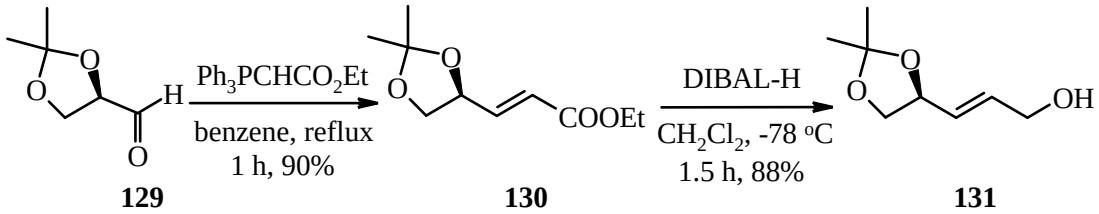


Scheme 28: Retrosynthetic analysis of C21-C26 segment of **26**

The Sharpless asymmetric epoxidation followed by regioselective opening by methyl Grignard reagent was explored to install the required four chiral centers in the targeted segment as depicted in scheme 28. Alcohol **136** could be obtained by Grignard reaction on **132**, followed by some protecting group manipulation. By the same sequence of reactions **143** could be accomplished from epoxide **140**. The phthalimide derivative **150** could be furnished by Mitsonobu reaction on alcohol **148**. Finally, reduction of phthalimide group would give rise to the target segment **151**.

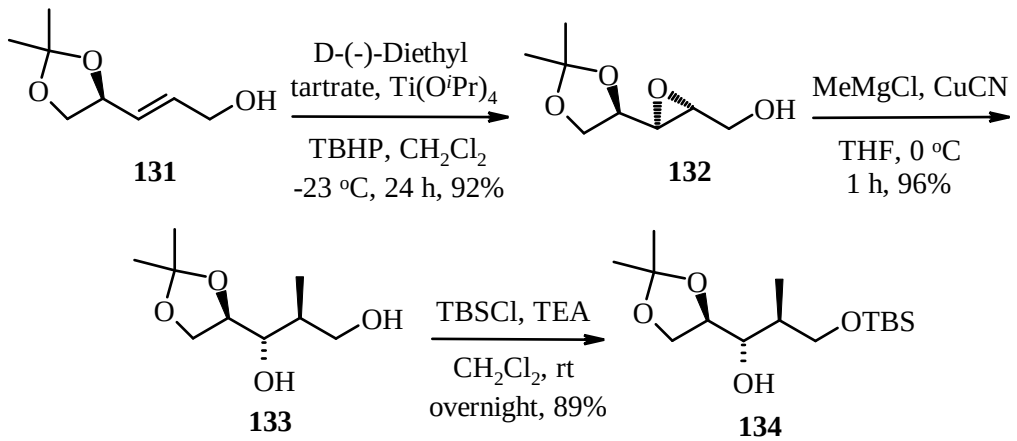
Accordingly, the journey began with (*R*)-2,3-*O*-isopropylidene-D-glyceraldehyde **129**, which was subjected to Wittig reaction with Ph_3P=CHCOOEt in benzene under

refluxing condition to provide *cis*:*trans* (1:9)[42] mixture of compound. These were separated by column chromatography, and the major *trans* product **130** (confirmed by coupling constant value of double bond) was used for the next reaction.



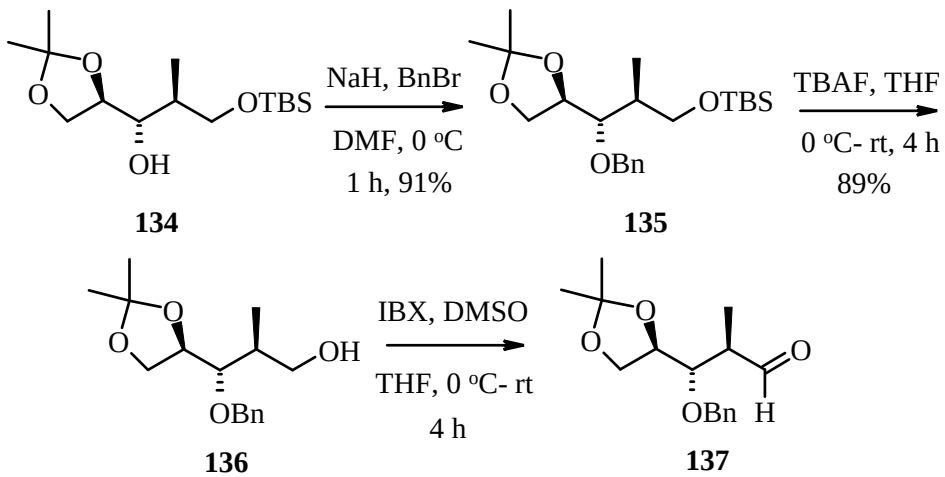
Scheme 29

The α,β-unsaturated ester **130** was then reduced with DIBAL-H in CH_2Cl_2 at −78 ^oC to give the *E*-allyl alcohol **131** in 88% yield. Our next objective was the diastereoselective epoxidation of **131**. Accordingly, the substituted allyl alcohol **131** was treated with D-(−)-diethyltartrate, TBHP, and titanium(IV) isopropoxide in CH_2Cl_2 at −23 ^oC to furnish the epoxy alcohol **132** in 92% yield. The spectral data of **132** was well corresponded with the reported one. Formation of a single diastereomer was adjudged by the analysis of its ^1H and ^{13}C NMR spectral data. The ^1H NMR spectrum displayed characteristic signals due to epoxy protons as multiplet at δ 3.05-3.11 (2H) and 3.67 (dd, *J* = 3.3, 12.5 Hz, 1H) ppm, all other protons resonated in accordance with the assigned structure of **132**. The structure was further supported by ^{13}C NMR spectrum as well as elemental analysis. The rotation value of this compound was closely coordinated with the reported one {Lit[43] $[\alpha]_D^{21}$ +32.4 (c, 1.85 ethanol), observed $[\alpha]_D^{25}$ +30.3 (c, 1.5 ethanol)}.



Scheme 30

Our next concern was the nucleophilic ring opening of epoxide **132** with Grignard reaction to produce the 1,3-diol **133**, which correlated with the stereogenic centers of C25-C24 of **26**. The epoxy alcohol **132** was subjected to the treatment of MeMgCl in presence of CuCN in THF at 0 ^{o}C to accomplish exclusively 1,3-diol **133** in good yield. From ^{1}H NMR and ^{13}C NMR spectrum, it was confirmed that only one product was formed. For our satisfaction, since 1,2-diol was of no consequence to us, the mixture was subjected to periodate oxidation. This treatment provided no faster moving spot in TLC indicating the absence of 1,2-diol formation. In the ^{1}H NMR spectrum, the characteristic resonances due to newly added methyl group was located at δ 0.96 (d, J = 7.1 Hz) ppm, two singlet of acetonide methyls appeared at δ 1.37 and 1.42 ppm, and all other protons resonated at their expected chemical shift value. The structure was further supported by ^{13}C NMR spectrum and analytical data. In IR spectrum, absorption at 3433 cm^{-1} was present in evidence of hydroxyl group.

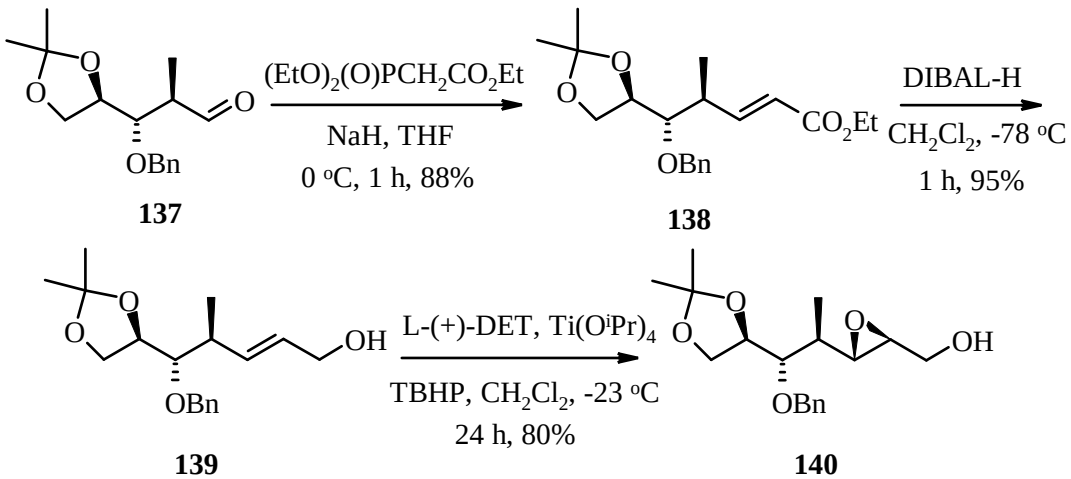


134 **135** **136** **137**

Scheme 31

With compound **133** in hand, the protection of the secondary hydroxyl group was needed prior to the extension from the primary hydroxyl side. Thus, a straight forward protection-deprotection sequence was planed. Accordingly, the diol **133** was converted to TBS ether[44] **134** using TBDMSCl in presence of triethylamine and catalytic amount of DMAP in CH_2Cl_2 at room temperature in 89% yield. In ^{1}H NMR spectrum, the characteristic peak appeared at δ 0.08 (s, 6H), 0.9 (s, 9H) ppm in favor of TBDMS group introduction, whereas isopropylidene methyl groups were at their expected position at δ 1.36 (3H) and 1.39 (3H) ppm. The structure was further supported by ^{13}C NMR, where

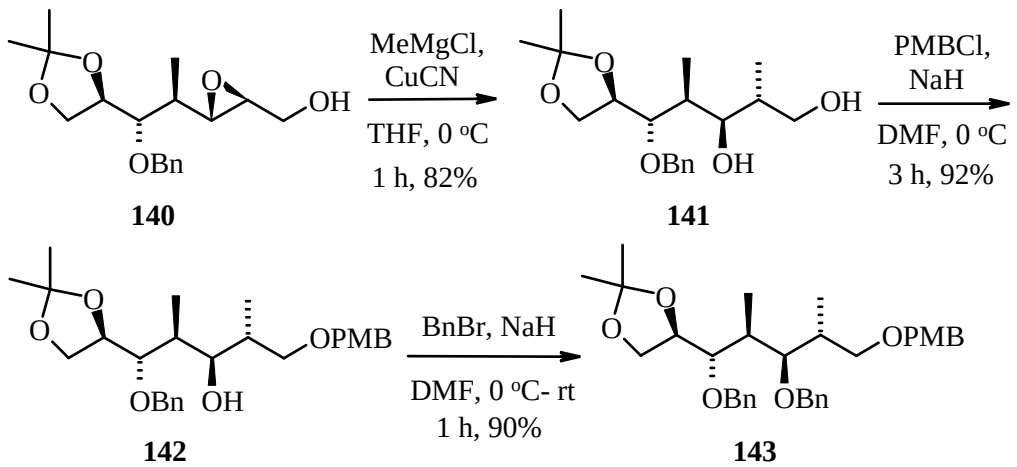
peaks at δ (−) 5.66, (−) 5.61 ppm corresponding to TBDMS group was noted. The secondary hydroxyl group of **134** was converted to benzyl ether **135** by treatment of benzyl bromide in presence of NaH in DMF. The ^{1}H NMR spectrum showed resonances as two doublet at δ 4.59 (*J* = 11.3 Hz, 1H) and 4.73 (*J* = 11.3 Hz, 1H) ppm characteristic of benzylic $-CH_2$ group, and multiplets at δ 7.29-7.34 (5H) ppm in evidence of benzyl group introduction. The structure was also supported by ^{13}C NMR and elemental analysis. On exposure of compound **135** to TBAF in anhydrous THF at room temperature offered hydroxyl compound **136** with 89% yield. Disappearance of resonance due to TBDMS group was observed both in ^{1}H and ^{13}C NMR spectrum. In IR spectrum, absorbance at 3463 cm^{-1} was appeared due to hydroxyl group. Structure was further supported by elemental analysis. Now the primary hydroxyl group was oxidized by using IBX to provide aldehyde **137**. The crude aldehyde **137** obtained was used for the next reaction without further purification. The aldehyde **137** was treated with a suspension of triethylphosphonoacetate, sodium hydride in THF at 0 ^{o}C to get selectively *trans* olefin **138** in 88% yield over two steps. In ^{1}H NMR spectrum, double bonded protons appeared as two double doublet at δ 5.73 (*J* = 15.8, 1.1 Hz) and 6.91 (*J* = 8.3, 15.8 Hz) ppm and all other protons were at their expected resonance position. In the ^{13}C NMR Spectrum, carbonyl carbon of ester moiety resonated at δ 166.30 ppm and the double bonded carbons at δ 121.62 and 150.05 ppm were noticed. The assigned structure was also supported by IR spectrum, where the carbonyl stretching at 1712 cm^{-1} characteristic of α,β unsaturated ester was observed.



Scheme 32

The substituted allyl alcohol **139** was accomplished in excellent yield through the reduction of conjugated ester **138** with DIBAL-H at –78 ^{o}C in advance of installing the other chiral centres. The structural identity was supported by interpretation of ^{1}H NMR, ^{13}C NMR, IR, and mass spectral data. Disappearance of resonances due to ethyl moiety of ester **138** in ^{1}H NMR spectrum was observed. The rest of the protons were resonated at the expected chemical shift regions. IR spectrum was showing absorbance at 3434 cm^{-1} in accordance of the hydroxyl group.

The next phase of endeavor was Sharpless asymmetric epoxidation (SAE) of the unsaturated alcohol **139**. The epoxidation was performed by using Ti(O^{i}Pr)$_4$-(+)-DET chiral complex and *tert*-butyl hydroperoxide to afford **140** in 80% yield. The spectral information from ^{1}H NMR, ^{13}C NMR, IR, and mass spectral studies proved the structure of **140** beyond doubt. In ^{1}H NMR spectrum, disappearance of resonance due to double bonded protons was observed. By ^{1}H and ^{13}C NMR spectrums, it was proved to be a single diastereomer. Analytical data was matched with the expected structure of compound **140**. No quantitative study was undertaken to estimate the enantioselection in the epoxidation step, as it was thought that the enantiopurity could be determined at later stage.



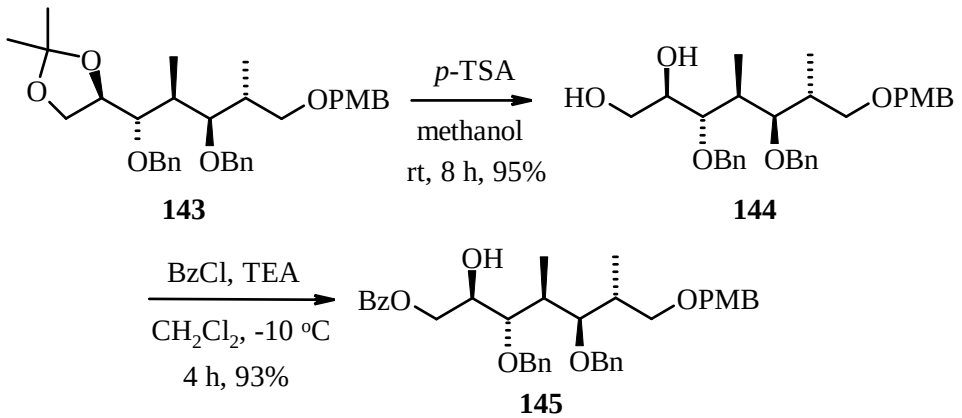
140 **141** **142** **143**

Scheme 33

The epoxide **140** was subjected to CuCN coordinated regioselective nucleophilic opening with methylmagnesium chloride to provide the diol **141** in 82% yields, which was adequately substantiated by spectral studies. Though ^{1}H and ^{13}C NMR spectroscopy was in favor of single compound, we decided to prove it unambiguously by chemical

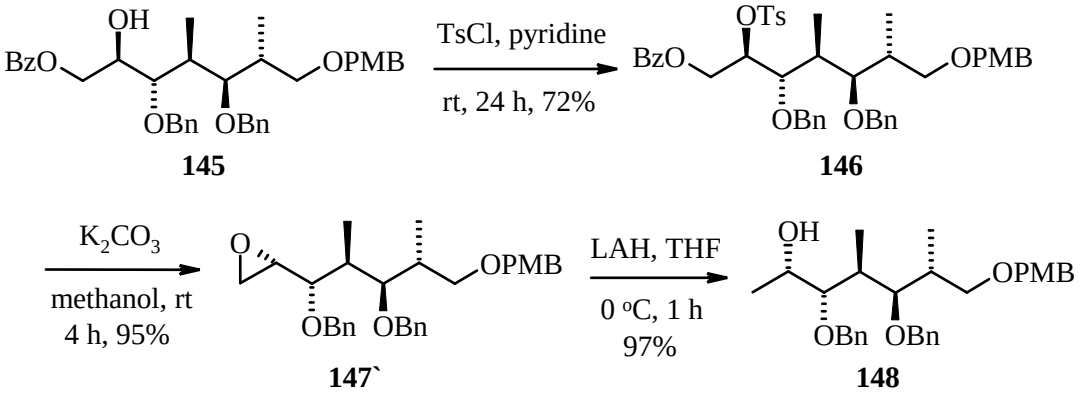
modification. Accordingly, compound **141** was treated with sodium metaperiodate but no faster moving spot was observed. In ^{1}H NMR spectroscopy, one additional doublet at δ 0.76 (J = 6.9 Hz) ppm for three protons confirmed the incorporation of methyl group. In IR spectrum, absorption at 3400 cm^{-1} was in accordance with the presence of hydroxyl group in the system.

After successful installation of all the required stereocenters, our next concern was the introduction of the amine functionality. Before proceeded further, it was necessary to protect the hydroxyl groups. Thus, the primary hydroxyl group was selectively protected as PMB ether by treating the diol **141** with PMBCl in presence of NaH in DMF. In ^{1}H NMR spectrum, characteristic resonance due to PMB group was observed, i.e. the aromatic methyl ether (−*OMe*) appeared as a sharp singlet at δ 3.80 ppm. The structure was also supported by ^{13}C NMR spectrum and elemental analysis. The remaining secondary hydroxyl group was converted to its benzyl ether using benzyl bromide in presence of NaH to obtain compound **143**. All spectral data were in good agreement with the assigned structure.



Scheme 34

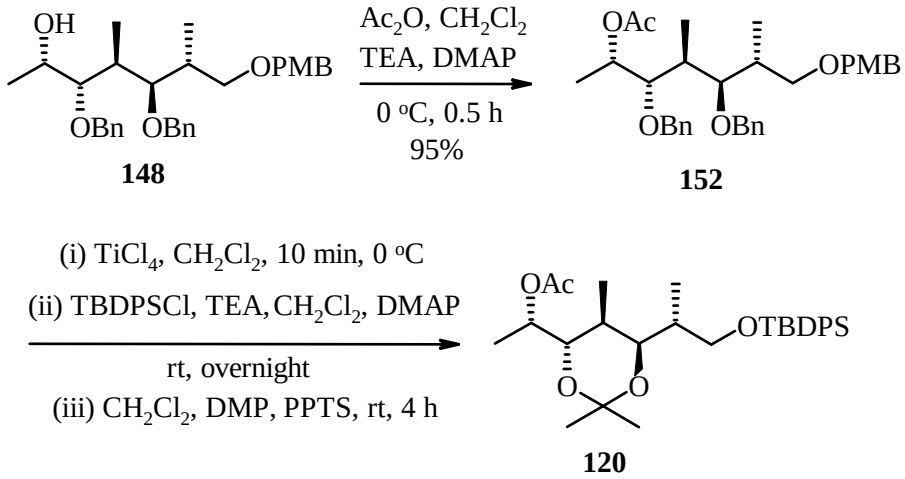
By the treatment of catalytic amount of *p*-TSA in methanol, compound **143** was deketalised to diol **144**. Disappearance of methyl protons due to isopropylidene group was noted in ^{1}H NMR spectrum. The structure was also supported by ^{13}C NMR spectroscopy and elemental analysis. In IR spectrum, absorption due to hydroxyl group at 3411 cm^{-1} was present. The diol **144** was processed forward through benzoylation, tosylation, epoxidation and LAH reduction to get the required alcohol **148**. The product was adequately substantiated by spectral as well as combustion data.



145 **146** **147`** **148**

Scheme 35

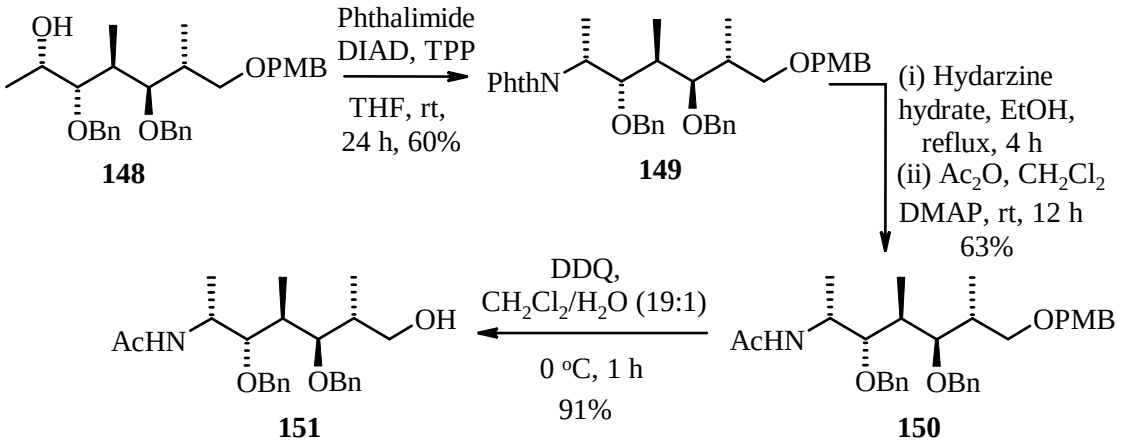
For the inspection of optical purity, alcohol **148** was converted to intermediate **120**, which was already synthesize in previous section (chapter 2; section I), by following standard synthetic sequence. All spectral and analytical data of both the compound was identical, thereby secured the optical purity of compound **148**.



148 **152** **120**

Scheme 36

According to our plan, hydroxyl compound **148** was treated with phthalimide, DIAD and TPP in THF to obtain the phthalimide derivative **149** in 60% yield. Appearance of extra protons in ^{1}H NMR spectrum in the region δ 7.68-7.83 (m, 4H) ppm characteristics for phthalimide group were noted and rest of the protons had the expected chemical shifts. In IR spectrum, characteristic absorptions due to phthalimide group were appeared at 1773 cm^{-1}, 1709 cm.$^{-1}$



Scheme 37

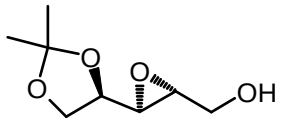
Phthalimide **149** was reduced to amine by refluxing in ethanol in presence of catalytic amount of hydrazine hydrate,[45] the solid byproduct was separated out by filtration. The crude product was used for immediate protection of amine group without further purification. Thus, the crude amine was subjected to the treatment of acetic anhydride in presence of triethylamine in dichloromethane to get **150**. ^{1}H NMR spectrum showed peak at δ 1.59 (3H) ppm as singlet characteristic for *N*-acetate, whereas characteristic protons for phthalimide was disappeared. ^{13}C NMR spectrum was also in good agreement with the structure, for example, peak at δ 168.8 ppm for amide carbonyl was present. IR spectrum showed absorbance at 1651 cm^{-1} for amide group. Finally, oxidative cleavage of PMB ether with DDQ in CH_2Cl_2/water at 0 ^{o}C completed the target fragment **151** with 91% yield. In ^{1}H and ^{13}C NMR spectrum, absence of resonance due to PMB group was observed. IR spectrum showed absorption at 3413 cm^{-1} in evidence of hydroxyl group. Mass and elemental analysis were also supported the structure.

In conclusion, fragment C21-C26 (**151)** was successfully synthesized using Sharpless asymmetric epoxidation followed by regeioselective opening with MeMgCl in a linear fashion. Following our developed protocol, it is possible to make other diastereomers of this fragment in gram quantities, which will be helpful during the total synthesis of the target molecule and its isomers.

EXPERIMENTAL

Experimental

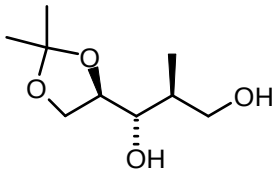
((2*R*,3*S*)-3-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)oxiran-2-yl)methanol (132).



To a solution of (+)-DET (1.5 mL, 8.85 mmol) and 4Å molecular sieves powder (10.0 g) in CH_2Cl_2 (400 mL) was added titanium(IV) isopropoxide (1.8 mL, 6.32 mmol) at −20 °C. After 15 minutes, a solution of allylic alcohol **131** (10.0 g, 63.21 mmol) in CH_2Cl_2 (100 mL) was introduced and stirred for 45 min. Then reaction mixture was charged with TBHP (5 M solution in toluene, 37.9 mL, 189.64 mmol) slowly over period of 15 min at the same. After 24 h, the reaction was quenched with 30% aq. NaOH solution saturated with sodium chloride. After stirring for ½ h reaction mixture was filtered through celite, two layers are separated and aqueous layer 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 (2:3) as an eluent to obtain **132** (10.1 g).

Yield	: 92%
Mol. Formula	: $C_8H_{14}O_4$
Optical Rotation $[\alpha]_D^{25}$	: +36.1 (*c* 1.15, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	: 3447, 3019, 2991, 1383, 1374, 1215, 1062, 758, 668.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.36 (s, 3H), 1.44 (s, 3H), 2.04 (bs, 1H), 3.05-3.11 (m, 2H), 3.67 (dd, *J* = 3.3, 12.5 Hz, 1H), 3.86-3.99 (m, 3H), 4.07-4.17 (m, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 25.16, 26.40, 55.14, 57.20, 60.96, 66.75, 75.28, 109.77 ppm.
Elemental Analysis	**Calcd:** C, 55.16; H, 8.10.
	Found: C, 55.34; H, 8.29.

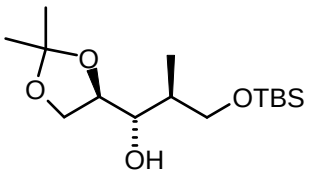
(1*S*,2*S*)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylpropane-1,3-diol (133).



A solution of 3 M CH_3MgC1 (Aldrich) in THF (76.54 mL, 229.63 mmol) was added to a stirred suspension of CuCN (4.94 g, 55.11 mmol) in 100 mL of dry THF under argon at 0 ^oC. After ca. 10 min, a clear yellow solution was obtained. To this reaction mixture a solution of **132** (8.0 g, 45.93 mmol) in 100 mL of THF was slowly added. The solution was stirred for 1 h, and then quenched by saturated aqueous NH_4C1. The mixture was partitioned between ethyl acetate and water. Organic layer separated, dried over sodium sulphate and purified through column chromatography, eluting by ethyl acetate: light petroleum ether (1:1) to obtain compound **133** (8.4 g).

Yield	: 96%
Mol. Formula	: $C_9H_{18}O_4$
IR ($CHCl_3$) cm^{-1}	: 3433, 3019, 2926, 2854, 1465, 1215, 1026, 759, 669.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.96 (d, *J* = 7.1 Hz, 3H), 1.37 (s, 3H), 1.42 (s, 3H), 1.68-1.80 (m, 1H), 3.10 (bs, 2H), 3.62-3.78 (m, 3H), 3.89-4.06 (m, 2H), 4.15-4.24 (m, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 13.61, 25.31, 26.48, 36.75, 65.08, 66.74, 75.72, 76.75, 109.00 ppm.
ESI MS (*m/z*)	: 213.2 $[M+ Na]^+$
Elemental Analysis	**Calcd:** C, 56.82; H, 9.54.
	Found: C, 56.64; H, 9.40.

(1*S*,2*S*)-3-(tert-butyldimethylsilyloxy)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylpropan-1-ol (134):



To a solution of **133** (8.0 g, 42.05 mmol), Et_3N (7.04 mL, 50.46 mmol) and DMAP (206 mg) in CH_2Cl_2 (210 mL) was added TBDMSCl (6.9 g, 46.26 mmol) at room

temperature. The reaction mixture was stirred for over night, diluted with CH_2Cl_2, washed with water, brine, dried (over Na_2SO_4) and concentrated. The residue was purified on silica gel column chromatography by using EtOAc:hexane (1:9) to obtain **134** (11.4 g).

Yield : 89%

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

Optical Rotation $[\alpha]_D^{25}$: +9.8 (*c* 0.75, $CHCl_3$)

IR ($CHCl_3$) cm^{-1} : 3480, 2956, 2931, 1463, 1471, 1381, 1371, 1216, 1255, 1070, 1017, 839, 813, 667.

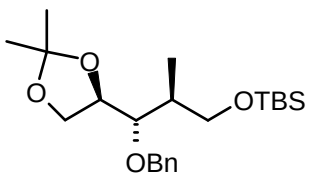
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.08 (s, 6H), 0.90 (s, 9H), 1.07 (d, *J* = 7.1 Hz, 3H), 1.36 (s, 3H), 1.39 (s, 3H), 1.75-1.90 (m, 1H), 3.46-3.54 (m, 2H), 3.63 (dd, *J* = 3.9, 10.1 Hz, 1H), 3.95-4.19 (m, 4H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ −5.66, −5.61, 14.40, 18.13, 25.52, 25.84, 26.76, 35.81, 66.22, 66.83, 76.09, 77.31, 108.99 ppm.

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

Found: C, 59.24; H, 10.50.

((2*S*,3*S*)-3-(benzyloxy)-3-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-ethylpropoxy)(tert-butyl)dimethylsilane (135):



Compound **134** (11.0 g, 36.12 mmol) in DMF (100 mL) at 0 °C was added NaH (60 % dispersion in mineral oil, 2.2 g, 54.19 mmol). After 15 min, benzyl bromide (4.7 mL, 39.74 mmol) was introduced and the reaction further stirred for 1 h at room temperature. Water was carefully added to the reaction mixture, extracted with ethyl acetate, washed with water and dried (Na_2SO_4). On evaporation of solvent, the residue was purified by silica gel column chromatography by eluting with light petroleum:EtOAc (1:9) to afford **135** (13.04 g) as colourless liquid.

Yield : 91%

Mol. Formula : $C_{22}H_{38}O_4Si$

Optical Rotation $[\alpha]_D^{25}$: +8.6 (*c* 1.35, $CHCl_3$)

IR ($CHCl_3$) cm^{-1} : 3019, 2957, 2930, 1471, 1382, 1372, 1253, 1215, 1071, 837, 758, 668.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.05 (s, 6H), 0.91 (s, 9H), 0.98 (d, *J* = 7.0 Hz, 3H), 1.37 (s, 3H), 1.42 (s, 3H), 1.78-1.90 (m, 1H), 3.62 (d, *J* = 5.5 Hz, 2H), 3.67 (dd, *J* = 4.6, 6.1 Hz, 1H), 3.88-4.04 (m, 2H), 4.22-4.31 (m, 1H), 4.59 (d, *J* = 11.3 Hz, 1H), 4.73 (d, *J* = 11.3 Hz, 1H), 7.29-7.34 (m, 5H) ppm.

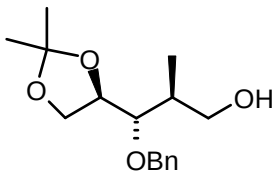
^{13}C NMR ($CDCl_3$, 50 MHz) : δ −5.42, −5.34, 13.53, 18.30, 25.49, 25.97, 26.53, 38.49, 64.82, 65.77, 73.97, 76.91, 79.53, 108.55, 127.47, 127.71, 128.27, 138.83 ppm.

ESI MS *(m/z)* : 417 $[M+ Na]^+$

Elemental Analysis **Calcd:** C, 66.69; H, 9.71.

Found: C, 66.54; H, 9.57.

(2*S*,3*S*)-3-(benzyloxy)-3-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylpropan-1-ol (136):



A solution of **135** (12.5 g, 31.7 mmol) and 1 M solution of *n*-Bu_4NF (47.55 mL, 47.5 mmol) in THF (50 mL) were stirred for 4 h and concentrated. The crude was extracted with EtOAc, washed with water, dried (Na_2SO_4), concentrated. The residue was chromatographed on silica gel using EtOAc:light petroleum ether (1:4) to provide **136** as colorless thick syrup (6.5 g).

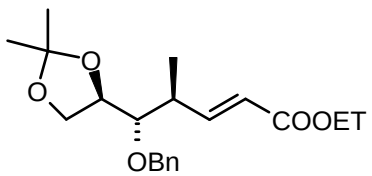
Yield : 89%

Mol. Formula : $C_{16}H_{24}O_4$

Optical Rotation $[\alpha]_D^{25}$: +25.6 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$) cm^{-1}	: 3463, 2935, 2987, 2883, 1455, 1381, 1372, 1216, 1158, 1068, 1028, 756, 699, 667.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.94 (d, *J* = 7.1 Hz, 3H), 1.27 (s, 3H), 1.34 (s, 3H), 1.79-1.97 (m, 1H), 2.56 (bs, 1H), 3.46-3.63 (m, 3H), 3.82 (dd, *J* = 7.1, 8.1 Hz, 1H), 3.99 (dd, *J* = 6.2, 8.1 Hz, 1H), 4.14 (dd, *J* = 6.5, 12.6 Hz, 1H), 4.53 (d, *J* = 11.2 Hz, 1H), 4.60 (d, *J* = 11.2 Hz, 1H), 7.17-7.27 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 13.06, 25.31, 26.51, 37.09, 65.39, 66.55, 73.89, 75.93, 82.75, 109.10, 127.91, 128.48, 137.92 ppm.
ESI MS *(m/z)*	: 303 $[M+ Na]^+$
Elemental Analysis	**Calcd:** C, 68.54; H, 8.63.
	Found: C, 68.64; H, 8.79.

(4*S*,5*S*,*E*)-ethyl 5-(benzyloxy)-5-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-methylpent-2-enoate (138).



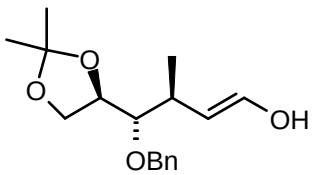
To a solution of IBX (15.0 g, 53.54 mmol) in DMSO (30 mL) at room temperature, was added pyridine (10 mL), followed by alcohol **136** (3.0 g, 15.46 mmol) in dry THF (25 mL). After 3.5 h of stirring, water (H_2O) (60 mL) was added, diluted with ether (250 mL) and stirred it for additional 30 min. The solid was filtered off and from the filtrate organic layer was isolated, washed with brine, dried over Na_2SO_4, concentrated to give aldehyde **137** (2.9 g, crude product) the crude aldehyde was used immediately for the next reaction.

To a solution of phosphonate (8.5 mL, 42.83 mmol) in THF (75 mL) at 0 ^oC, was added NaH (1.3 g, 60% dispersion in minerals oil, 32.12 mmol) portion wise. After 1 h stirring at the same temperature, the crude aldehyde in THF was added slowly. After 2 h, reaction was quenched with saturated aq. solution of NH_4Cl, and extracted with ethyl

acetate. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. Purification was done by silica gel (60-120 mesh) column chromatography using ethyl acetate: hexane (1: 10) to afford unsaturated ester **138** as colorless oil (6.58 g).

Yield	: 88% in two steps.
Mol. Formula	: $C_{20}H_{28}O_5$
Optical Rotation $[\alpha]_D^{25}$	: +7.8 (*c* 0.75, $CHCl_3$).
IR ($CHCl_3$) cm^{-1}	: 3018, 2986, 2937, 1712, 1651, 1583, 1455, 1381, 1371, 1216, 1187, 1072, 758, 699, 668.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.07 (d, *J* = 7.0 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.23 (s, 3H), 1.30 (s, 3H), 2.51-2.67 (m, 1H), 3.44 (dd, *J* = 3.6, 5.7 Hz, 1H), 3.75 (dd, *J* = 6.3, 7.9 Hz, 1H), 3.85-3.99 (m, 2H), 4.09 (q, *J* = 7.1 Hz, 2H), 4.52 (d, *J* = 11.4 Hz, 1H), 4.59 (d, *J* = 11.4 Hz, 1H), 5.73 (dd, *J* = 15.8, 1.1 Hz, 1H), 6.91 (dd, *J* = 8.2, 15.8 Hz, 1H), 7.17-7.26 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 14.27, 16.08, 25.26, 26.62, 39.15, 60.09, 66.29, 74.37, 76.66, 82.85, 108.70, 121.62, 127.71, 128.33, 138.06, 150.05, 166.30 ppm.
ESI MS *(m/z)*	: 371 $[M= Na]^+$; 387 $[M+ K]^+$
Elemental Analysis	**Calcd:** C, 68.94; H, 8.10.
	Found: C, 69.04; H, 8.29.

(3*S*,4*S*,*E*)-4-(benzyloxy)-4-(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-methylbut-1-en-1-ol (139):

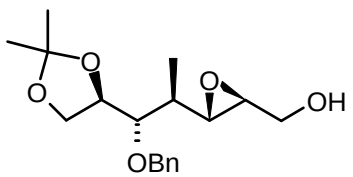


To a solution of **138** (6.0 g, 17.23 mmol) in CH_2Cl_2 (60 mL) was added DIBAL-H (1.46 M solution in toluene, 29.5 mL, 43.08 mmol) dropwise over a period of 5 min at

−78 °C. After stirring for 1 h, the reaction was quenched with saturated aq. sodium potassium tartrate solution, stirred for overnight. The organic layer separated, aqueous layer was washed with CH_2Cl_2, combined organic layer was dried over Na_2SO_4 and concentrated. The residue was purified on silica gel column chromatography using EtOAc: light petroleum ether (3:7) as an eluent to afford **139** (5.0 g).

Yield	: 95%
Mol. Formula	: $C_{18}H_{26}O_4$
Optical Rotation $[\alpha]_D^{25}$	: +20.9 (*c* 1.0, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	: 3434, 3013, 2987, 2935, 1665, 1607, 1454, 1381, 1372, 1216, 1071, 757, 699, 667.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.01 (d, *J* = 7.0 Hz, 3H), 1.24 (s, 3H), 1.32 (s, 3H), 2.35-2.46 (m, 1H), 3.44 (dd, *J* = 3.7, 5.1 Hz, 1H), 3.75-3.91 (m, 2H), 3.91-4.03 (m, 3H), 4.52 (d, *J* = 11.4 Hz, 1H), 4.62 (d, *J* = 11.4 Hz, 1H), 5.56-5.60 (m, 2H), 7.17-7.25 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 17.30, 25.27, 26.56, 39.16, 63.26, 65.89, 74.50, 77.14, 83.14, 108.31, 127.55, 127.66, 128.23, 129.84, 133.52, 138.42 ppm.
ESI MS *(m/z)*	: 329 $[M+ Na]^+$
Elemental Analysis	**Calcd:** C, 70.56; H, 8.55.
	Found: C, 70.44; H, 8.38.

((2*S*,3*S*)-3-((1*S*,2*R*)-1-(benzyloxy)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)propan-2-yl)oxiran-2-yl)methanol (140):

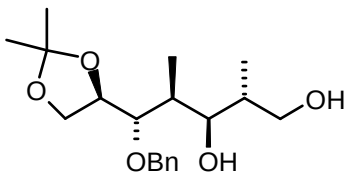


To a solution of (+)-DET (0.3 mL, 1.96 mmol) and 4Å molecular sieves powder (5.0 g) in CH_2Cl_2 (100 mL) was added titanium tetraisopropoxide (0.4 mL, 1.4 mmol) at −20 °C. After 15 minutes, a solution of allylic alcohol **139** (4.3 g, 14.03 mmol) in CH_2Cl_2

(20 mL) was introduced and stirred for 45 min. Then reaction mixture was charged with TBHP [5 M solution in toluene, 8.4 mL, 42.10 mmol] slowly over period of 15 min at the same temperature. After 24 h, the reaction was quenched with 30% aq. NaOH solution saturated with sodium chloride. After stirring for ½ h, reaction mixture was filtered through celite, two layers are separated and aqueous layer extracted with CH_2Cl_2. Combined organic layer was dried (Na_2SO_4), concentrated and the residue purified on silica gel column chromatography using EtOAc:light petroleum ether (3:7) as an eluent to obtain **140** (3.6 g).

Yield	: 80%
Mol. Formula	: $C_{18}H_{26}O_5$
Optical Rotation $[\alpha]_D^{25}$	: +4.85 (*c* 0.55, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	: 3430, 2984, 2934, 2877, 1497, 1455, 1381, 1371, 1252, 1212, 1028, 897, 855, 749, 700.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.17 (d, *J* = 7.0 Hz, 3H), 1.35 (s, 3H), 1.40 (s, 3H), 2.95-3.03 (m, 2H), 3.05-3.18 (m, 1H), 3.49-3.60 (m, 2H), 3.73-3.89 (m, 2H), 4.05 (dd, *J* = 6.2, 8.0 Hz, 1H), 4.19 (q, *J* = 6.4 Hz, 1H), 4.60 (d, *J* = 11.4 Hz, 1H), 4.67 (d, *J* = 11.4 Hz, 1H), 7.29-7.35 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 13.67, 25.22, 26.51, 38.51, 57.57, 58.82, 61.70, 66.53, 74.13, 76.08, 81.78, 108.85, 127.62, 127.72, 128.32, 137.97 ppm.
Elemental Analysis	**Calcd:** C, 67.06; H, 8.13. **Found:** C, 67.14; H, 8.20.

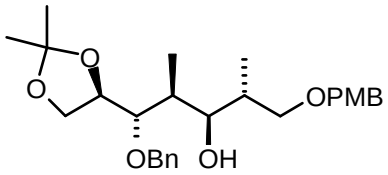
(2*R*,3*R*,4*S*,5*S*)-5-(benzyloxy)-5-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,4-dimethylpentane-1,3-diol (141):



A solution of 3 M CH_3MgC1 (Aldrich) in THF (18.1 mL, 54.32 mmol) was added to a stirred suspension of CuCN (1.16 g, 13.04 mmol) in 30 mL of dry THF under argon at 0 ^oC. After ca. 10 min, a clear yellow solution was obtained. To this reaction mixture, a solution of **140** (3.5 g, 10.86 mmol) in 20 mL of THF was slowly added. The solution was stirred for 1 h, before quenched by saturated aqueous NH_4C1 solution. The mixture was partitioned between water and ethyl acetate. Organic layer washed with brine, concentrated and product **141** (3.0 g) was purified by silica gel column chromatography eluting with ethyl acetate:hexane (45:55).

Yield	: 82%
Mol. Formula	: $C_{19}H_{30}O_5$
Optical Rotation $[\alpha]_D^{25}$	: +8.1 (*c* 0.85, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	: 3400, 2973, 2934, 1455, 1382, 1215, 1068, 1028, 754, 699, 665.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.76 (d, *J* = 6.9 Hz, 3H), 1.05 (d, *J* = 7.2 Hz, 3H), 1.36 (s, 3H), 1.41 (s, 3H), 1.65 (bs, 1H), 1.82-1.91 (m, 1H), 2.04-2.17 (m, 1H), 3.47 (dd, *J* = 2.8, 7.3 Hz, 1H), 3.60-3.68 (m, 3H), 3.78-3.88 (m, 1H), 3.95 (bs, 1H), 4.10-4.20 (m, 2H), 4.55 (d, *J* = 11.3 Hz, 1H), 4.63 (d, *J* = 11.3 Hz, 1H), 7.28-7.39 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 8.76, 13.79, 25.29, 26.55, 36.38, 37.45, 67.57, 68.91, 73.95, 75.11, 77.87, 85.11, 109.26, 127.88, 128.09, 128.56, 137.49 ppm.
ESI MS (*m/z*)	: 361 $[M+ Na]^+$
Elemental Analysis	**Calcd:** C, 67.43; H, 8.93.
	Found: C, 67.54; H, 9.15.

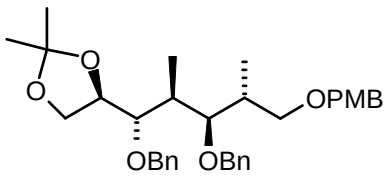
(1*S*,2*S*,3*R*,4*R*)-1-(benzyloxy)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-5-(4-methoxybenzyloxy)-2,4-dimethylpentan-3-ol (142):



The dihydroxy compound **141** (2.8 g, 8.27 mmol) in DMF (65 mL) at 0 °C was added NaH (60 % dispersion in mineral oil, 0.4 g, 10.75 mmol). After 15 min, para-methoxybenzyl chloride (1.3 mL, 9.1 mmol) was introduced and the reaction was further stirred for 3 h at the same temperature. Water was carefully added to the reaction mixture, extracted with ether, washed with water and dried (Na_2SO_4). On evaporation of solvent, the residue was purified by silica gel chromatography by eluting with light petroleum:EtOAc (1:5) to afford **142** (3.5 g).

Yield	: 92%
Mol. Formula	: $C_{27}H_{38}O_6$
Optical Rotation $[\alpha]_D^{25}$	: +0.5 (*c* 1.0, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	: 3492, 2933, 1612, 1513, 1455, 1379, 1248, 1071, 753, 699.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.84 (d, *J* = 6.9 Hz, 3H), 0.98 (d, *J* = 7.1 Hz, 3H), 1.37 (s, 3H), 1.42 (s, 3H), 1.83-1.94 (m, 2H), 3.47-3.70 (m, 4H), 3.80 (s, 3H), 3.91 (t, *J* = 7.7 Hz, 1H), 4.03-4.11 (m, 1H), 4.21-4.30 (m, 1H), 4.45 (s, 2H), 4.63 (d, *J* = 11.1 Hz, 1H), 4.70 (d, *J* = 11.1 Hz, 1H), 6.85 (d, *J* = 8.5 Hz, 2H), 7.23-7.33 (m, 7H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 8.98, 13.80, 25.41, 26.46, 36.35, 36.85, 55.08, 66.21, 72.89, 73.85, 74.24, 74.37, 76.37, 82.70, 108.79, 113.69, 127.65, 127.81, 128.33, 129.12, 130.34, 138.29, 159.09 ppm.
Elemental Analysis	**Calcd:** C; 70.71, H; 8.35.
	Found: C; 70.63, H; 8.25.

(*R*)-4-((1*S*,2*S*,3*R*,4*R*)-1,3-bis(benzyloxy)-5-(4-methoxybenzyloxy)-2,4-dimethylpentyl)-2,2-dimethyl-1,3-dioxolane (143).



To a solution of **142** (3.5 g, 7.63 mmol) in DMF (25 mL) at 0 °C was added NaH (60 % dispersion in mineral oil, 0.458 g, 11.45 mmol). After 15 min, benzyl bromide (1.54 mL, 12.97 mmol) was introduced and the reaction mixture further stirred for 1 h at room temperature. Water was carefully added to the reaction mixture, extracted with ether, washed with water and dried (Na_2SO_4). On evaporation of solvent, the residue was purified by silica gel column chromatography by eluting with light petroleum:EtOAc (3:97) to afford **143** (3.76 g) as yellow colour liquid.

Yield : 90%

Mol. Formula : $C_{34}H_{44}O_6$

Optical Rotation $[\alpha]_D^{25}$: −5.3 (*c* 1.85, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.05 (d, *J* = 6.9 Hz, 3H), 1.07 (d, *J* = 7.1 Hz, 3H), 1.41 (s, 3H), 1.47 (s, 3H), 1.92-2.02 (m, 1H), 2.09-2.21 (m, 1H), 3.49 (dd, *J* = 5.9, 8.9 Hz, 1H), 3.59 (dd, *J* = 6.7, 8.9 Hz, 1H), 3.81 (s, 3H), 3.73-3.81 (m, 2H), 3.96-4.11 (m, 2H), 4.31-4.40 (m, 1H), 4.45-4.59 (m, 5H), 4.77 (d, *J* = 11.6 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 2H), 7.26-7.40 (m, 12H) ppm.

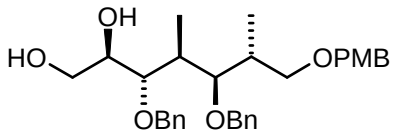
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 11.01, 15.25, 25.34, 26.44, 36.72, 37.99, 55.08, 65.57, 72.03, 72.72, 73.41, 74.13, 76.88, 80.27, 80.98, 108.57, 113.66, 127.12, 127.32, 127.49, 128.20, 128.23, 129.17, 130.69, 138.87, 139.24, 159.02 ppm.

ESI MS *(m/z)* : 607 $[M+ Na]^+$; 623 $[M+ K]^+$

Elemental Analysis **Calcd:** C, 74.42; H, 8.08.

Found: C, 74.34; H, 8.19.

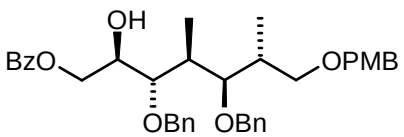
(2*R*,3*S*,4*S*,5*R*,6*R*)-3,5-bis(benzyloxy)-7-(4-methoxybenzyloxy)-4,6-dimethylheptane-1,2-diol (144).



A mixture of **143** (3.5 g, 6.38 mmol) and *p*-TSA (0.1 g) in MeOH (50 mL) were stirred at rt for 8 h. Solvent was removed *in vacuo* and the residue extracted with EtOAc, washed with water, dried (Na_2SO_4) and evaporated. The residue was purified by silica gel column chromatography with light petroleum:EtOAc (1:1) as an eluent to afford diol **144** (3.0 g).

Yield	: 95 %
Mol. Formula	: $C_{31}H_{40}O_6$
Optical Rotation $[\alpha]_D^{25}$	: −5.0 (*c* 1.05, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	: 3411, 2933, 1612, 1513, 1454, 1302, 1247, 1173, 1069, 735, 697.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.06 (d, *J* = 7.0 Hz, 3H), 1.11 (d, *J* = 7.2 Hz, 3H), 1.70 (bs, 1H), 2.10-2.33 (m, 3H), 3.52-3.60 (m, 3H), 3.82 (s, 3H), 3.76-3.85 (m, 4H), 4.46-4.65 (m, 6H), 6.89 (d, *J* = 8.5 Hz, 2H), 7.26-7.37 (m, 12H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 10.72, 14.33, 36.47, 36.70, 55.13, 63.69, 71.48, 72.30, 72.85, 72.96, 73.65, 80.59, 83.73, 113.77, 127.37, 127.45, 127.63, 127.71, 128.31, 128.40, 129.28, 130.36, 138.41, 138.59, 159.20 ppm.
ESI MS *(m/z)*	: 531 $[M+ Na]^+$
Elemental Analysis	**Calcd:** C, 73.20; H, 7.93.
	Found: C, 73.12; H, 7.80.

(2*R*,3*S*,4*S*,5*R*,6*R*)-3,5-bis(benzyloxy)-2-hydroxy-7-(4-methoxybenzyloxy)-4,6-dimethylheptyl benzoate (145):

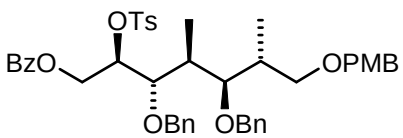


To a solution of **144** (2.0 g, 3.93 mmol), Et_3N (0.8 mL, 5.89 mmol) in CH_2Cl_2 (40 mL) was added benzoyl chloride (0.5 mL, 4.32 mmol) at −10 ^oC. The reaction mixture

was stirred for 4 h at 0 ^{o}C, diluted with CH_2Cl_2, washed with water, brine, dried (over Na_2SO_4) and concentrated. The residue was purified on silica gel column chromatography by using EtOAc-hexane (1:9) to give **145** (2.23 g), as a colorless liquid.

Yield	: 93%
Mol. Formula	: $C_{38}H_{44}O_7$
Optical Rotation $[\alpha]_D^{25}$	: +7.8 (*c* 1.1, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	: 3494, 3358, 2964, 1715, 1584, 1556, 1513, 1453, 1365, 1274, 1248, 1093, 1070, 861, 755, 698, 666.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.08 (d, *J* = 6.9 Hz, 3H), 1.17 (d, *J* = 7.1 Hz, 3H), 2.20-2.31 (m, 2H), 3.56 (dd, *J* = 1.1, 5.3 Hz, 2H), 3.67 (t, *J* = 5.8 Hz, 1H), 3.79-3.87 (m, 1H), 3.82 (s, 3H), 4.15-4.24 (m, 1H), 4.47-4.73 (m, 8H), 6.87 (d, *J* = 8.7 Hz, 2H), 7.30-7.36 (m, 12H), 7.46-7.53 (m, 2H), 7.60-7.67 (m, 1H), 8.08-8.13 (m, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 10.85, 14.51, 36.55, 36.66, 55.03, 66.82, 70.99, 72.16, 72.70, 73.21, 73.47, 80.33, 82.63, 113.65, 127.25, 127.44, 127.61, 128.19, 128.27, 128.30, 129.19, 129.64, 130.38, 132.98, 129.97, 138.42, 138.79, 159.03, 166.88 ppm.
ESI MS *(m/z)*	: 635 $[M+ Na]^+$
Elemental Analysis	**Calcd:** C, 74.48; H, 7.24.
	Found: C, 74.64; H, 7.35.

(2*R*,3*S*,4*S*,5*R*,6*R*)-3,5-bis(benzyloxy)-7-(4-methoxybenzyloxy)-4,6-dimethyl-2-(tosyloxy)heptyl benzoate (146):

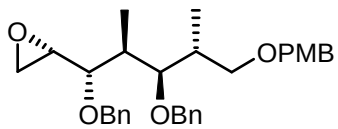


Compound **145** (2.0 g, 3.26 mmol), TsCl (2.18 g, 11.42 mmol) and pyridine (10 mL) were stirred at room temperature for 24 h. Pyridine was removed under vacuo and the residue extracted with EtOAc, washed with 1 N HCl, water, brine, dried (Na_2SO_4)

and evaporated. The residue was purified by silica gel column chromatography by eluting with light petroleum:EtOAc (19:5) to give **146** (1.8 g).

Yield	: 72%
Mol. Formula	: $C_{45}H_{50}O_9S$
Optical Rotation $[\alpha]_D^{25}$	: +17.2 (*c* 2.25, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	: 3031, 2926, 1718, 1601, 1512, 1453, 1366, 1271, 1189, 1177, 1095, 1069, 913, 815, 754, 698, 668.
^{1}H NMR ($CDCl_3$, 200 MHz)	:δ 0.86 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 1.73-1.81 (m, 1H), 1.85-1.98 (m, 1H), 2.06 (s, 3H), 3.36 (d, *J* = 4.4 Hz, 1H), 3.63-3.68 (m, 1H), 3.68 (s, 3H), 3.82 (d, *J* = 9.8 Hz, 1H), 4.15-4.57 (m, 8H), 4.83 (d, *J* = 11.6 Hz, 1H), 5.01 (m, 1H), 6.72 (d, *J* = 8.5 Hz, 2H), 6.92 (d, *J* = 8.1 Hz, 2H), 7.09-7.23 (m, 12H), 7.26-7.33 (m, 2H), 7.44 (m, 1H), 7.61 (d, *J* = 8.1 Hz, 2H), 7.71-7.75 (m, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 10.08, 14.83, 21.43, 36.85, 37.93, 55.06, 62.42, 72.21, 72.61, 73.67, 73.85, 79.03, 81.86, 82.71, 113.61, 127.14, 127.23, 127.50, 127.60, 127.70, 128.13128.26, 128.27, 129.00, 129.38, 129.69, 130.66, 133.01, 133.55, 138.08, 139.01, 144.54, 158.95, 166.05 ppm.
ESI MS *(m/z)*	: 789 $[M+ Na]^+$
Elemental Analysis	**Calcd:** C, 70.47; H, 6.57.
	Found: C, 70.64; H, 6.69.

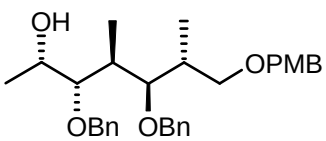
(*S*)-2-((1*S*,2*S*,3*R*,4*R*)-1,3-bis(benzyloxy)-5-(4-methoxybenzyloxy)-2,4-dimethylpentyl)oxirane (147).



Compound **146** (1.8 g, 2.35 mmol) was dissolved in MeOH (10 mL) and K_2CO_3 (0.8 g, 5.86 mmol) was added. The mixture was stirred at room temperature for 4 h before it was concentrated. The residue was dissolved in water and extracted with ethyl acetate, washed with water, dried (Na_2SO_4) and evaporated. Purification on silica gel using light petroleum:EtOAc (19:1) as an eluent afforded pure epoxide **147** (1.09 g).

Yield	: 95%
Mol. Formula	: $C_{31}H_{38}O_5$
Optical Rotation $[\alpha]_D^{25}$	: −14.5 (*c* 1.05, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	: 3063, 2974, 2935, 1612, 1513, 1454, 1248, 1173, 1092, 1071, 821, 755, 698, 666.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.87 (d, *J* = 7.1 Hz, 3H), 0.91 (d, *J* = 7.0 Hz, 3H), 1.90-1.97 (m, 2H), 2.47 (dd, *J* = 2.4, 4.9 Hz, 1H), 2.73-2.77 (m, 1H), 2.89-2.93 (m, 2H), 3.42 (d, *J* = 4.6 Hz, 2H), 3.72 (s, 3H), 3.78 (dd, *J* = 1.6, 9.4 Hz, 1H), 4.15-4.39 (m, 5H), 4.86 (d, *J* = 11.9 Hz, 1H), 6.76(d, *J* = 8.8, 2H), 7.05-7.33 (m, 12H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 9.85, 14.85, 36.98, 38.42, 44.08, 54.71, 55.18, 71.55, 72.44, 72.67, 74.08, 78.93, 82.10, 113.69, 127.13, 127.23, 127.39, 127.68, 128.21, 128.32, 129.09, 130.82, 138.77, 139.26, 159.02 ppm.
ESI MS (*m/z*)	: 513 $[M+ Na]^+$
Elemental Analysis	**Calcd:** C, 75.89; H, 7.81.
	Found: C, 75.64; H, 7.79.

(2*S*,3*S*,4*S*,5*R*,6*R*)-3,5-bis(benzyloxy)-7-(4-methoxybenzyloxy)-4,6-dimethylheptan-2-ol (148):

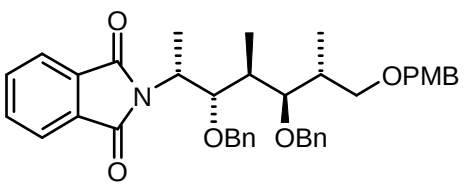


A suspension of LAH (1.0 g, 4.08 mmol), and **147** (1.0 g, 2.04 mmol) in THF (10 mL) was stirred at rt for 3 h at 0 ^oC. The excess reagent was quenched with saturated aq.

solution of Na_2SO_4, filtered and the residue thoroughly washed with EtOAc. The filtrate was concentrated and purified on silica gel using EtOAc:light petroleum ether (1:5) to afford **148** (1.0 g) as thick oil.

Yield	: 99%
Mol. Formula	: $C_{31}H_{40}O_5$
Optical Rotation $[\alpha]_D^{25}$	: +32.9 (*c* 0.6, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	: 3438, 3018, 2975, 2936, 1612, 1513, 1454, 1247, 1215, 1089, 1067, 1036, 758, 699, 668.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.01 (d, *J* = 6.9 Hz, 3H), 1.04 (d, *J* = 6.9 Hz, 3H), 1.25 (d, *J* = 6.5 Hz, 3H), 2.02-2.18 (m, 2H), 3.20 (dd, *J* = 3.1, 7.3 Hz, 1H), 3.47 (d, *J* = 5.1 Hz, 2H), 3.68 (dd, *J* = 2.3, 7.4 Hz, 1H), 3.76 (s, 3H), 3.82-3.95 (m, 1H), 4.38 (s, 2H), 4.48-4.60 (m, 4H), 4.67 (bs, 1H), 6.81 (d, *J* = 8.7 Hz, 2H), 7.18-7.36 (m, 12H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 11.33, 14.99, 21.33, 37.06, 55.10, 65.13, 67.51, 72.30, 72.71, 73.25, 74.46, 80.30, 85.56, 113.68, 126.89, 127.00, 127.14, 127.50, 127.59, 128.19, 128.37, 128.45, 129.11, 130.70, 138.43, 139.42, 159.04 ppm.
ESI MS (*m/z*)	: 515 $[M+ Na]^+$
Elemental Analysis	**Calcd:** C, 75.58; H, 8.18.
	Found: C, 75.45; H, 8.19.

2-((2*R*,3*S*,4*S*,5*R*,6*R*)-3,5-bis(benzyloxy)-7-(4-methoxybenzyloxy)-4,6-dimethylheptan-2-yl)isoindoline-1,3-dione (149):

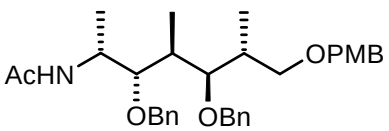


A 50 mL three necked round bottom flask charged with TPP (0.532 g, 2.03 mmol) phthalimide (0.298 g, 2.03 mmol) and THF (10 mL). The alcohol **148** (1.0 g, 2.03 mmol,

in 2 mL THF) and DIAD (0.4 mL, 2.03 mmol) in 2 mL THF are added to the flask simultaneously dropwise over a period of 5 min with stirring, the solution turned yellow. The reaction permitted to proceed at room temperature for 24 h, the solution then concentrated and purified by silica gel column chromatography eluting with ethyl acetate:hexane (1:10) to obtain **148** (402 mg).

Yield	: 60%
Mol. Formula	: $C_{39}H_{43}NO_6$
Optical Rotation $[\alpha]_D^{25}$	: +6.0 (*c* 1.1, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	: 3029, 2964, 2935, 1773, 1709, 1612, 1513, 1454, 1384, 1353, 1247, 1089, 754, 722, 698, 665.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.70 (d, *J* = 6.9 Hz, 3H), 1.12 (d, *J* = 7.1 Hz, 3H), 1.57 (d, *J* = 6.8 Hz, 3H), 1.85-2.01 (m, 2H), 3.31 (dd, *J* = 6.5, 8.9 Hz, 1H), 3.44-3.54 (m, 2H), 3.76 (s, 3H), 4.13 (dd, *J* = 4.1, 8.5 Hz, 1H), 4.30-4.35 (m, 3H), 4.52-4.68 (m, 4H), 6.80 (d, *J* = 8.6 Hz, 2H), 7.09-7.29 (m, 12H), 7.68-7.83 (m, 4H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 12.12, 15.18, 15.88, 37.62, 37.92, 49.10, 55.13, 72.02, 72.52, 73.26, 75.06, 79.94, 83.26, 113.65, 123.18, 126.90, 127.26, 127.38, 127.78, 128.02, 128.19, 129.02, 130.88, 131.98, 133.95, 138.55, 139.44, 158.97, 168.17 ppm.
ESI MS (*m/z*)	: 644 $[M+ Na]^+$
Elemental Analysis	**Calcd:** C, 75.34; H, 6.97.
	Found: C, 75.16; H, 7.15.

N-((2*R*,3*S*,4*S*,5*R*,6*R*)-3,5-bis(benzyloxy)-7-(4-methoxybenzyloxy)-4,6-dimethylheptan-2-yl)acetamide (150):

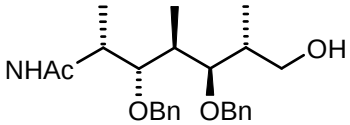


A solution of compound **149** (0.45 g, 0.724 mmol) in ethanol (5 mL) with catalytic amount (two drops) of hydrazine hydrate was heated to reflux for 4 h. The solid byproduct was filtered off. Organic layer concentrated and directly carried forward to the next reaction.

To a solution of the crude product in CH_2Cl_2 (5 mL), Ac_2O (0.14 mL, 1.45 mmol) triethylamine (0.2 mL, 1.81 mmol) and DMAP (2 mg, 0.01 mmol) was added at 0 ^oC. After stirring for 8 h at room temperature, the reaction mixture was diluted with CH_2Cl_2, washed with brine, dried over sodium sulphate, concentrated and residue purified on silica gel using EtOAc:light petroleum ether (2:3) as an eluent to obtain **150** (188 mg).

Yield	: 63% in two steps
Mol. Formula	: $C_{33}H_{43}NO_5$
Optical Rotation $[\alpha]_D^{25}$	: +45.4 (*c* 1.5, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	: 3290, 3030, 2974, 2935, 1651, 1547, 1513, 1454, 1372, 1247, 1172, 1091, 754, 698, 666.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.94 (d, *J* = 6.9 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 1.02 (d, *J* = 6.9 Hz, 3H), 1.59 (s, 3H), 2.04-2.17 (m, 2H), 3.40-3.47 (m, 3H), 3.73 (s, 3H), 3.66-3.73 (m, 1H), 4.09-4.25 (m, 2H), 4.37 (s, 2H), 4.45-4.71 (m, 3H), 5.32 (d, *J* = 8.6 Hz, 1H), 6.78 (d, *J* = 8.5 Hz, 2H), 7.16-7.30 (m, 12H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 10.65, 14.19, 14.91, 23.15, 36.77, 37.95, 46.30, 55.11, 72.43, 72.72, 73.07, 74.75, 79.88, 84.75, 113.64, 127.15, 127.23, 127.28, 127.67, 128.27, 128.61, 129.14, 130.60, 139.17, 139.19, 159.02, 168.80 ppm.
ESI MS (*m/z*)	: 556 $[M+ Na]^+$
Elemental Analysis	**Calcd:** C, 74.27; H, 8.12.
	Found: C, 74.45; H, 8.28.

***N*-((2*R*,3*S*,4*S*,5*R*,6*R*)-3,5-bis(benzyloxy)-7-hydroxy-4,6-dimethylheptan-2-yl)acetamide (151)**:



A mixture of compound **150** (0.1 g, 0.187 mmol) and DDQ (51 mg, 0.225 mmol) in CH_2Cl_2:H_2O (9.5:0.5) was stirred at 0 ^oC for 2 h. After completion of reaction, the reaction mixture was diluted with excess of CH_2Cl_2 and washed with saturated aq. $NaHCO_3$ solution followed by brine. The organic layer dried over Na_2SO_4 and concentrated. The product was purified by silica gel column chromatography by eluting with ethyl acetate:hexane (1:1) to obtain **151** (77 mg).

Yield : 91%

Mol. Formula : $C_{25}H_{35}NO_4$

Optical Rotation $[\alpha]_D^{25}$: +33.0 (*c* 0.75, $CHCl_3$)

IR ($CHCl_3$) cm^{-1} : 3413, 3031, 2975, 2931, 2878, 1652, 1549, 1454, 1373, 1065, 1093, 1028, 977, 754, 698.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.94 (d, *J* = 6.9 Hz, 3H), 1.05 (d, *J* = 7.1 Hz, 3H), 1.10 (d, *J* = 6.8 Hz, 3H), 1.73 (s, 3H), 1.81-1.89 (m, 1H), 1.99-2.06 (m, 1H), 2.55 (bs, 1H), 3.53 (dd, *J* = 2.6, 9.2 Hz, 1H), 3.63 (d, *J* = 5.5 Hz, 2H), 3.69 (dd, *J* = 1.9, 7.3 Hz, 1H), 4.18-4.26 (m, 1H), 4.42 (d, *J* = 12.2 Hz, 1H), 4.60 (d, *J* = 11.3 Hz, 1H), 4.65 (d, *J* = 11.3 Hz, 1H), 4.73 (d, *J* = 12.2 Hz, 1H), 5.31 (d, *J* = 8.5 Hz, 1H), 7.26-7.39 (m, 10H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 10.99, 14.01, 14.47, 23.33, 38.60, 38.77, 46.55, 66.29, 73.99, 75.18, 82.54, 85.10, 127.28, 127.60, 127.72, 127.89, 128.51, 128.71, 138.45, 138.82, 168.87 ppm.

ESI MS (*m/z*) : 436 $[M+ Na]^+$

Elemental Analysis **Calcd:** C, 72.61; H, 8.53.

Found: C, 72.50; H, 8.49.

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CHAPTER 3

Studies of Some Useful Radical Rearrangement, Extensive Ueno Reaction

INTRODUCTION

Introduction

The use of radicals in organic synthesis has increased dramatically within the last decade. At the beginning of the 1980's, the place of radical reaction in natural products synthesis was limited to a few important functional group transformations (such as the Barton-McCombie reaction[1]). However, during the past decade, radical carbon-carbon bond-forming reactions have grown in importance to the point where they are now routinely considered in strategy level planning of complex targets.[2]

Radical reactions have a number of synthetic advantages, which are:

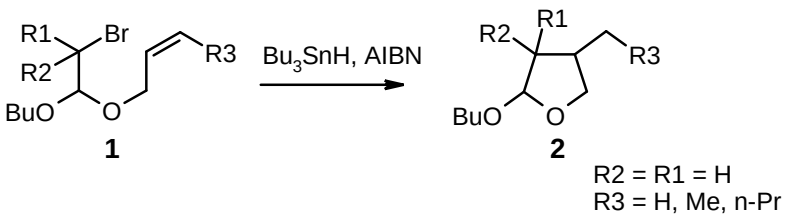
1. Carbon-centred radicals are extremely reactive. Nevertheless, radical addition reactions proceed under mild, neutral conditions, and the reactivity of radicals does not compromise a high level of chemo-, regio-, and stereoselectivity. Conformational restrictions often increase the rates and intensify the stereoselectivity of radical cyclizations in complex natural product syntheses. By contrast, problems of reactivity and especially chemo selectivity are often magnified by molecular complexity for ionic reactions.
2. Radical additions to C=C bonds are usually exothermic and irreversible, with early, reactant-like transition states. Reactions under kinetic control with early transition states often afford unique products that are unavailable by traditional ionic methods.
3. Because radicals are highly reactive and their reactions have early transition states, radical intermediates are ideally suited for the synthesis of crowded bonds.
4. Carbon-centred radicals are inert toward $-OH$ or $-NH$ groups. Radical reactions do not need to be dry, and the protection of alcohols, amines, and related functional groups often unnecessary. The same is rarely true for reactions involving carbanion or carbocations due to their respective basicity and electrophilicity.
5. In contrast to carbanion, carbon radicals are not subjected to β elimination of $-OR$ or $-NR_2$ groups. In contrast to carbocations, carbon radicals are subjected neither to capture by β-OR or $-NR_2$ groups nor migration or elimination of β-H or $-CR_3$ group.

6. Most alkyl and alkenyl radicals have negligible barriers to inversion, such that radical centeres do not usually retain stereochemistry. Stereochemical lability is not all bad, however, because it simplified the synthesis of radical precursors.

One of the most powerful methods in today's synthetic arsenal is radical cyclization and/or radical rearrangement-cyclization. Tri-*n*-butyltin hydride is the reagent most commonly used to conduct free radical reaction. Although the tin hydride method was first applied in natural product synthesis to the construction of a 6-membered ring, radical cyclization reactions[3] are most often applied to the synthesis of 5-membered rings because; cyclizations are usually faster for the formation of 5-membered ring than any other ring size[4,5] and the regioselectivity[4,5,3] for 5-exo cyclization is often outstanding, as well as it is stereoselective[4,5,6,7] too.

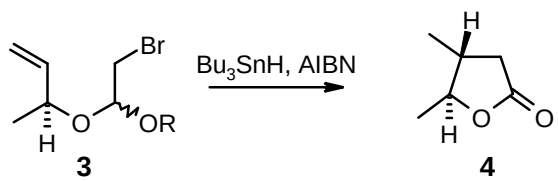
Ueno and Stork Rearrangement

Ueno[8] had reported a method for preparation of *γ*-butyrolactone *via* 2-alkoxytetrahydrofuran (Scheme 1) in which the key step consists of the homolytic carbo-cyclization. The cyclization method was particularly useful for the C-C bond formation at the sterically bulky carbon, since such bond formation in polar reaction involving carbocations or carboanions are often accompanying the elimination reaction or skeletal rearrangement, are well-known to be strongly affected by the steric hindrance and generally gave very poor result.



Scheme 1

Stork[9] had reported a similar type of rearrangement for the construction of *cis*-bicyclic system (Scheme 2).



Scheme 2

Cyclopropylmethyl radicals

From the literature, it is evident that the cyclopropyl ring can undergo several kinds of ring opening reactions like electrophilic, nucleophilic and radical ring opening.[10-12] Carbon-carbon bond cleavages of strained ring systems like cyclopropane triggered by cyclopropylmethyl radical have been studied as a method for preparing alkenyl compounds[13] (Figure 1).

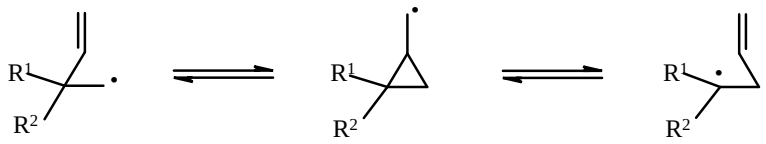
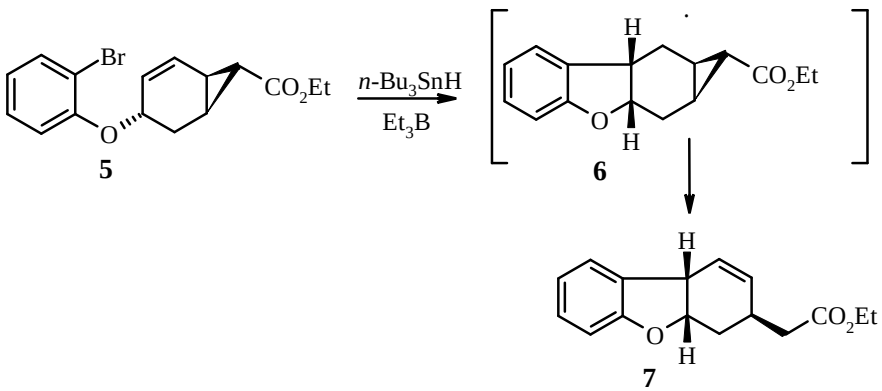


Figure 1

The rapidity of the ring opening of cyclopropylmethyl radical has resulted in the widespread use of cyclopropane rings as a probe of reaction mechanism both in chemical and enzyme catalysed reactions. Formation of ring-opened products from substrates containing the cyclopropylmethyl group has been widely used as an indication that a particular reaction proceeds *via* a radical intermediate.[12,14]

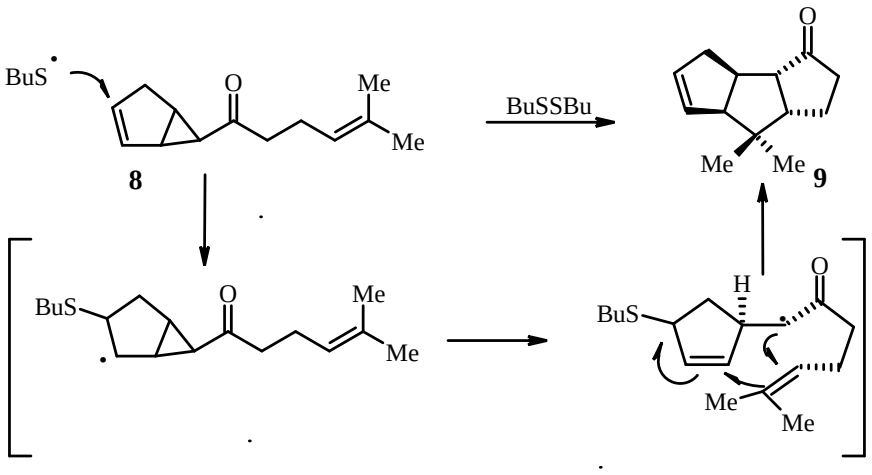
While extensive work on radical rearrangement has focused, a few examples of reactions from the synthetic point of view have thus far been reported. A tandem radical ring closing-radical ring opening strategy has been developed by Clive and co-workers for the synthesis of several benzofuran derivatives **7** for the evaluation of inhibitors of leukotriene biosynthesis, through the intermediate of cyclopropylmethyl radical (Scheme 3).[15]



Scheme 3

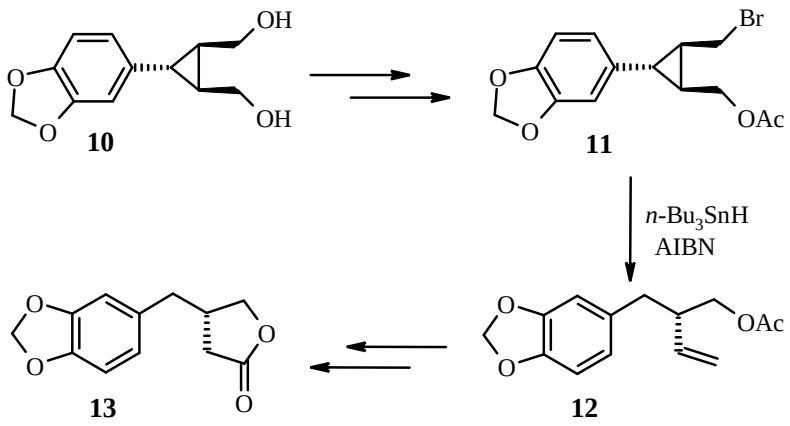
Initiation of radical cyclizations by fragmentation of a strained cyclopropyl ring system **8** beginning with the addition of a sulfur centered radical (generated by photolysis of alkyl disulfide) to an alkene was studied by Jung *et al.* for the synthesis

of linear triquinanes **9** through the radical intermediate using suitably placed intramolecular radical acceptor (Scheme 4).[16]



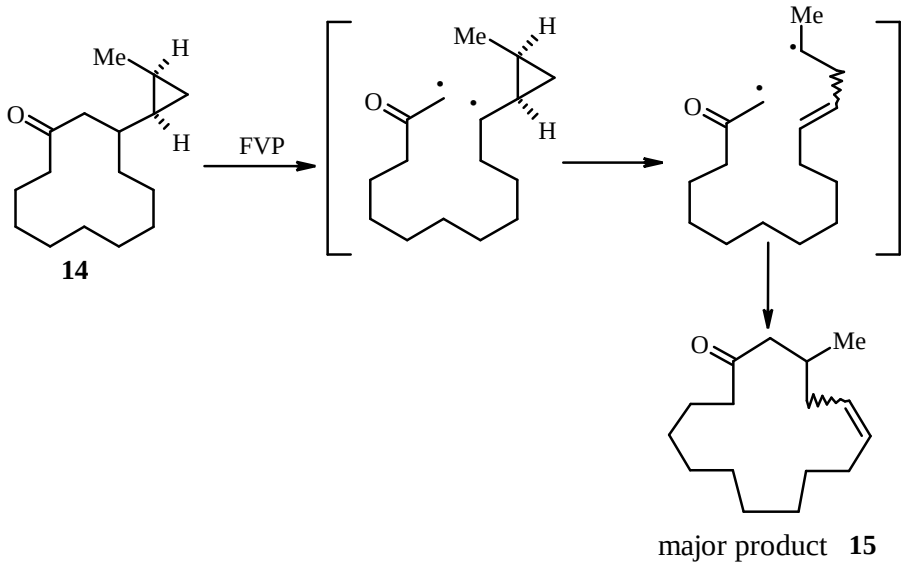
Scheme 4

Takekawa *et al*. achieved a regeioselective cleavage of C-C bond of optically active cyclopropanes initiated by cyclopropyl methyl radicals and enantioselective synthesis of suitably functionalized alkenes that would serve as versatile chiral building blocks for the construction of a wide variety of biologically active compounds. Here the optically active bromide **11** obtained from *meso*-diol **10** by enzymatic desymmetrization, was converted to enantiopure homoallylic acetate **12** using the cyclopropylcarbinyl-homoallylic radical rearrangement. This acetate was converted to a key intermediate **13** for the synthesis of biologically active lignanes (Scheme 5).[17]



Scheme 5

Recently, Ruedi *et al.* developed a three-carbon ring expansion strategy for the synthesis of *rac*-muscone **15** from inexpensive C12 starting materials, in which cyclopropyl ketone **14** cleaved homolytically under flash vacuum pyrolysis. Cyclopropylmethyl radical has been proposed as an intermediate in this rearrangement (Scheme 6).[18]

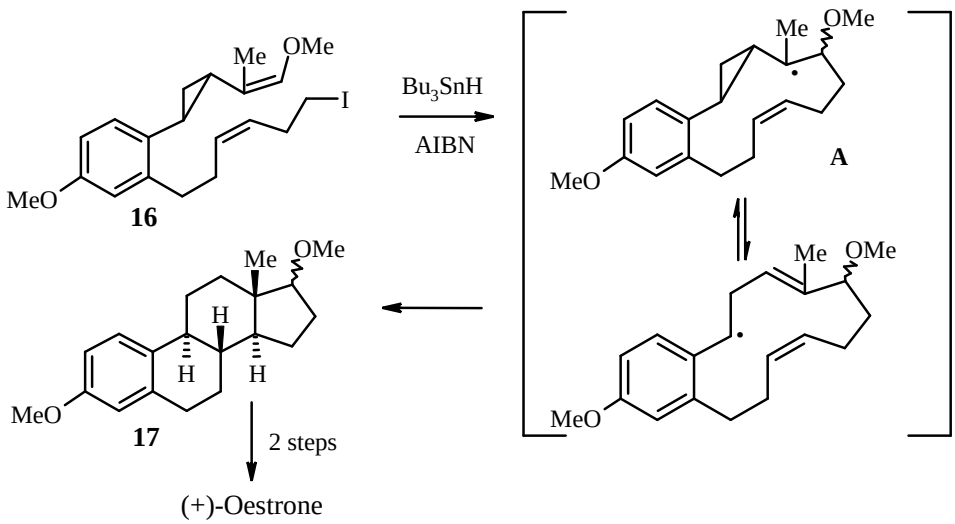


14

major product **15**

Scheme-6

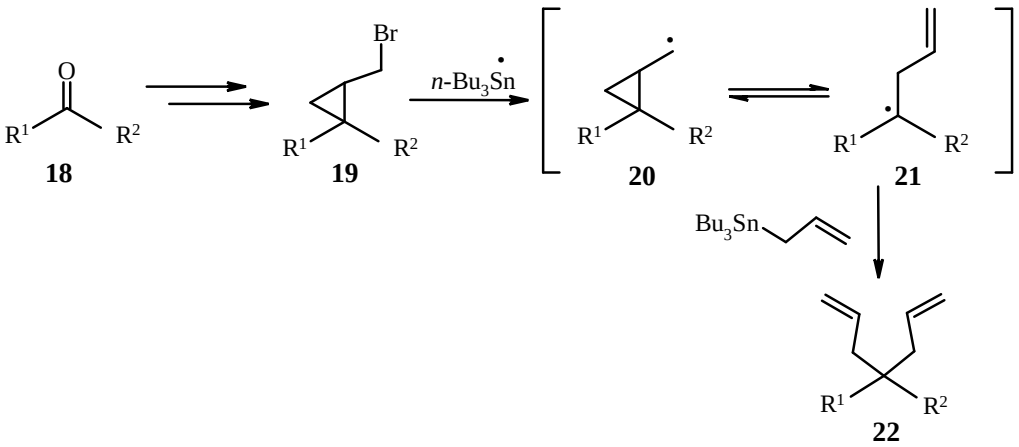
Pattenden and co-workers have disclosed a new total synthesis of *rac*-oestrone recently, in which three carbocycles were formed in a single step through a radical cascade. Cyclopropylmethyl radical **A** was an intermediate in that synthesis (Scheme 7).[19]



Scheme 7

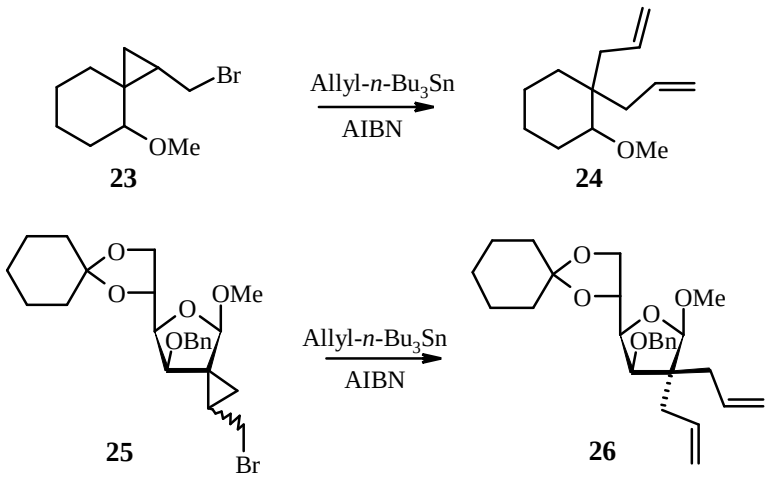
Radical mediated gem-diallylation

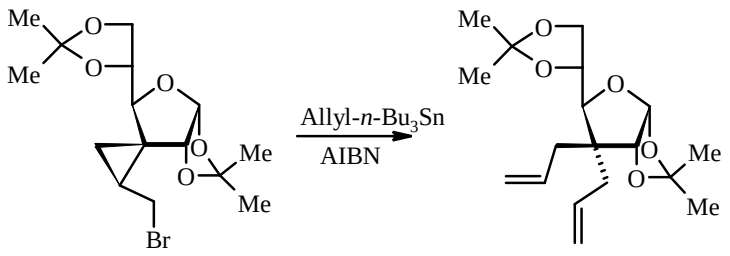
Introduction of *gem*-diallyl functionality in a molecule is usually achieved either by direct base mediated diallylation using allyl halides[20] or by Pd-catalyzed allylation using allyl acetates.[21] But these methods are limited only to compounds having active methylene groups. To overcome this problem a new method has been developed in our laboratory (Gurjar *et al.*),[22] in which a aldehyde/ketone carbonyl group was converted to *gem*-diallyl group. Key transformation in this strategy was trapping the allylcarbinyl radical **21** (formed by the rearrangement of cyclopropylcarbinyl radical **20**) with allyltri-*n*-butylstannane (Keck allylation)[23] as given in scheme 8.



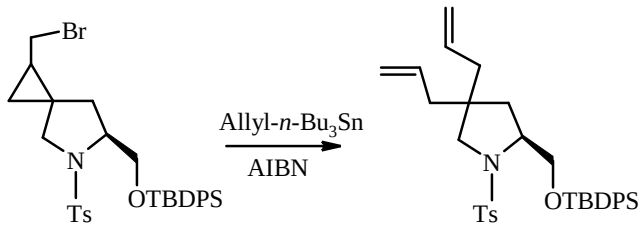
Scheme 8

This *gem*-diallylation method has been successfully used in aliphatic **23**, carbohydrate (**25**, **27**) and amino acid **29** systems as given below (Scheme 9).[22, 24]





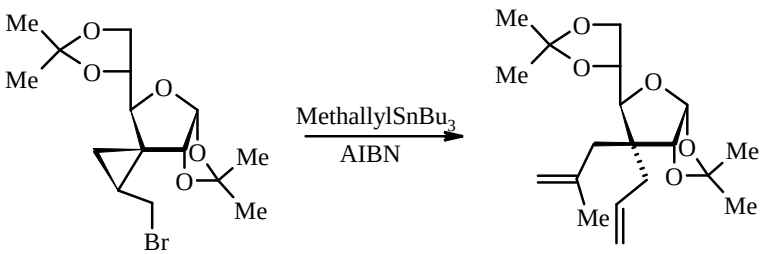
27 **28**



29 **30**

Scheme 9

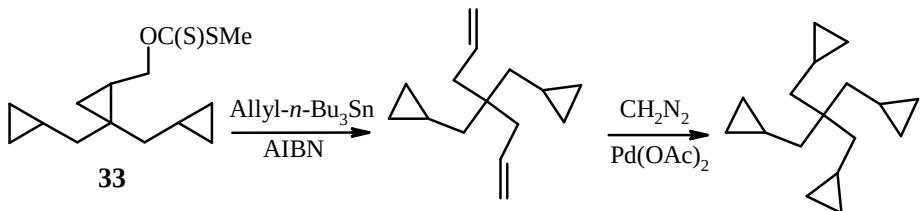
Similarly, methallyltri-*n*-butylstannane was used to generate differentially substituted *gem*-diallyl system **31** as a single diastereomer. Exclusive formation of the compound **32** was a result of steric hindrance from the 1,2-*O*-isopropylidene group for the approach of methallyl tin reagent (Scheme 10).[24]



31 **32**

Scheme 10

By using this radical mediated *gem*-diallylation strategy an expedient synthesis of tetrakis(cyclopropylmethyl)methane **35**, a symmetric molecule was achieved for its conformational studies in solid and solution phase (Scheme 11).[25]



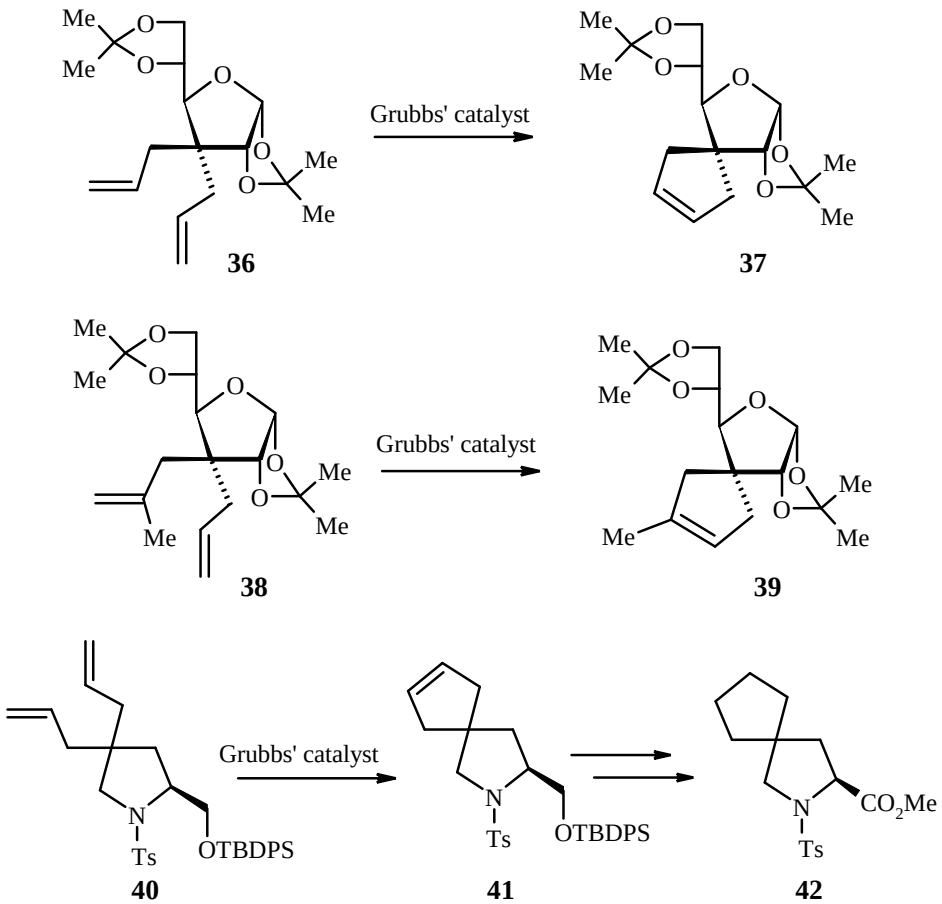
33 **34** **35**

Scheme 11

Spirocycles by gem-diallylation/RCM strategy

Molecules containing spirocycles find innumerable applications particularly in peptides,[26] nucleosides[27] and carbohydrates.[28] Synthesis of spirocycles was difficult until the advent of novel catalysts by Schrock[29] and Grubbs' used in ring closing olefin metathesis (RCM) though there are a number of methods available like, intramolecular alkylation, cycloaddition and rearrangements.[30] The RCM based approaches have made the introduction of a spiro group in the structural framework of an organic molecule an easy proposition.[31] For instance, *gem*-diallyl containing substrates undergo RCM to produce spirocyclopentenyl derivatives.[32]

A new strategy has been developed in our laboratory by the combination of radical mediated *gem*-diallylation and RCM to synthesis spirocyclopentenyl derivatives. Accordingly, carbohydrates and amino acids having diallyl functionality were cyclized by RCM to generate spirocyclopentenyl derivatives **37**, **39** and **41** (Scheme 12).[24]



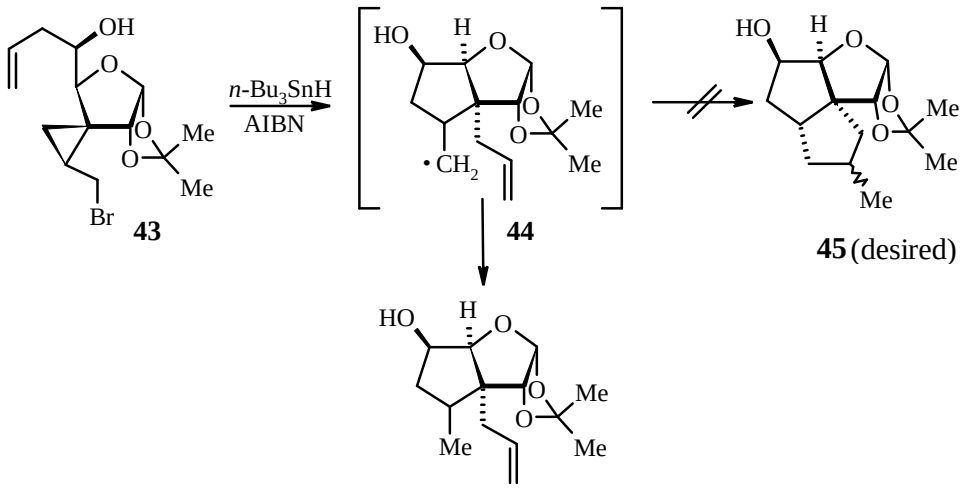
36 **37** **38** **39** **40** **41** **42**

Scheme 12

Triquinanes from cyclopropylcarbinyl radicals

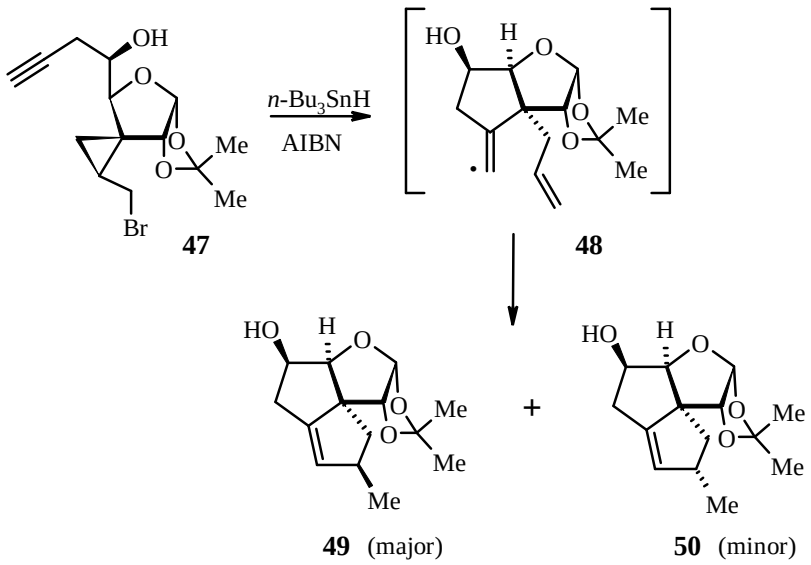
Angularly fused triquinanes have attracted intense attention of synthetic organic chemists as challenging targets.[33] Structural complexity associated with significant biological activity has necessitated development of many approaches for their synthesis.[34] Among them, radical cascade reactions are by far the most elegant and efficient approaches as significantly demonstrated by the work of Curran and others.[35] Fraser-Reid[36] and co-workers have performed some novel transformations mediated by serial radical cyclization on carbohydrate substrates to synthesize naturally occurring triquinanes.

A novel approach has been disclosed for the synthesis of carbohydrate based oxa- and dioxa-triquinanes from our group using a radical cascade initiated by the cyclopropylcarbinyl radical. In this approach, the olefin initially formed from the rearrangement of cyclopropylcarbinyl radical acts as an intramolecular radical acceptor to complete the radical cascade with the formation of triquinanes.[37] Substrate **43** on treatment with *n*-Bu_3SnH produced a fused bicyclic compound **46** instead of the expected angularly fused tricyclic compound **45**. This premature termination of radical cascade could be attributed to the poor reactivity of the methyl radical **44** (Scheme 13).



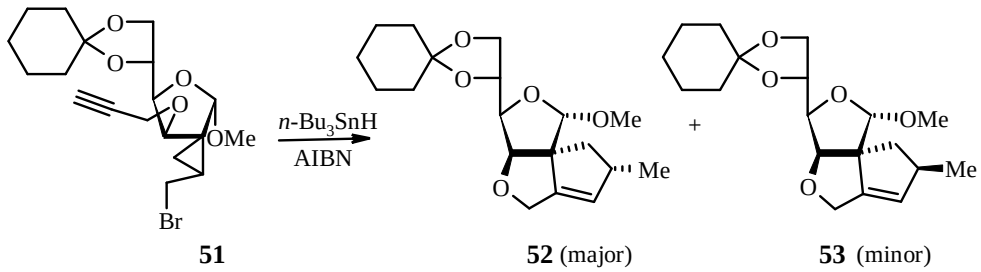
Scheme 13

In order to circumvent this problem a homopropargyl alcohol substrate **47** was used to generate the desired triquinanes (**49** and **50**) as a mixture of epimers at the newly formed methyl center (Scheme 14).



Scheme 14

Similarly, dioxa-triquinanes were also synthesized by following the same strategy, as a mixture of epimers, **52** and **53** (Scheme 15).

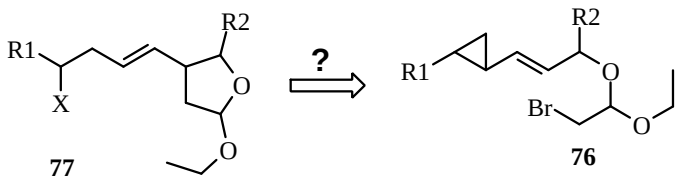


Scheme 15

PRESENT WORK

Present Work

The usual procedure for the synthesis of organic compounds is the stepwise formation of the individual bonds in the target molecule. However, it would be much more efficient if one could form several bonds in one sequence without isolating the intermediates, changing reaction conditions, or adding reagents. It is obvious that this type of reaction would allow the minimization of waste and thus making the waste management unnecessary since compared to stepwise reactions the amount of solvent reagents, absorbents and energy would be dramatically decreased. Thus, these reactions would allow an ecologically and economically favourable production. This type of reactions is called domino reaction. In particular, the homo radical domino reaction is useful tool for the construction of complex molecules[38]. Ueno reaction is very useful for construction of those rings especially sterically hindered systems. Unfortunately, in Ueno substrates there were no such functional groups for further manipulation to the natural products. In our laboratory cyclopropyl methyl radical was utilized to generate diallyl compounds, which was very constructive to incorporate allyl group where active methylene group was not present. In continuation of our work, based on Ueno reaction and our approach, we intended to utilize and couple these two approaches as a radical mediated domino reaction wherein the rearrangement is triggered by allyltri-*n*-butylstannane. The radical generated in bromo acetal **76** would form a tetrahydrofuran ring followed by opening of Cyclopropane ring and finally trapping of the radical by allyl functionality would lead to **77**. The underlying concept is depicted in scheme 16.

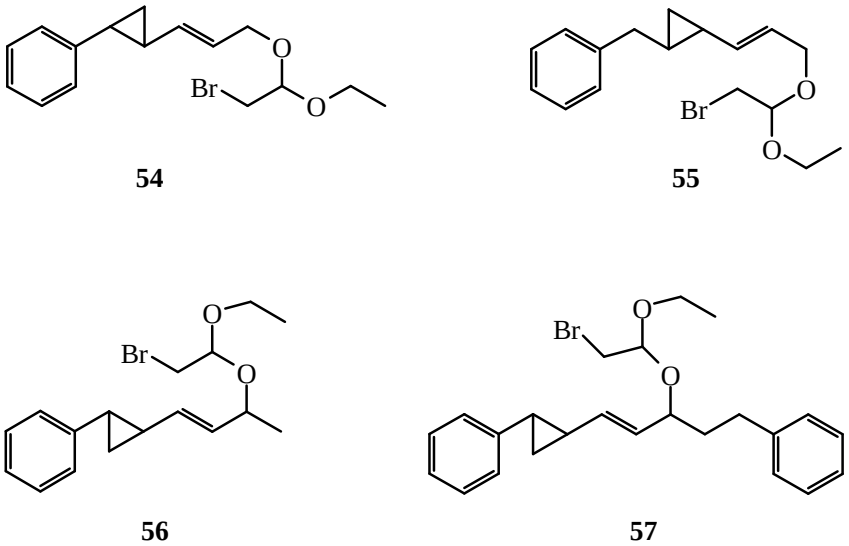


77 **76**

X= H or allyl

Scheme 16

In order to establish the versatility of this reaction, a number of mixed bromo acetal derivatives (**54**, **55**, **56** and **57**) were synthesized.



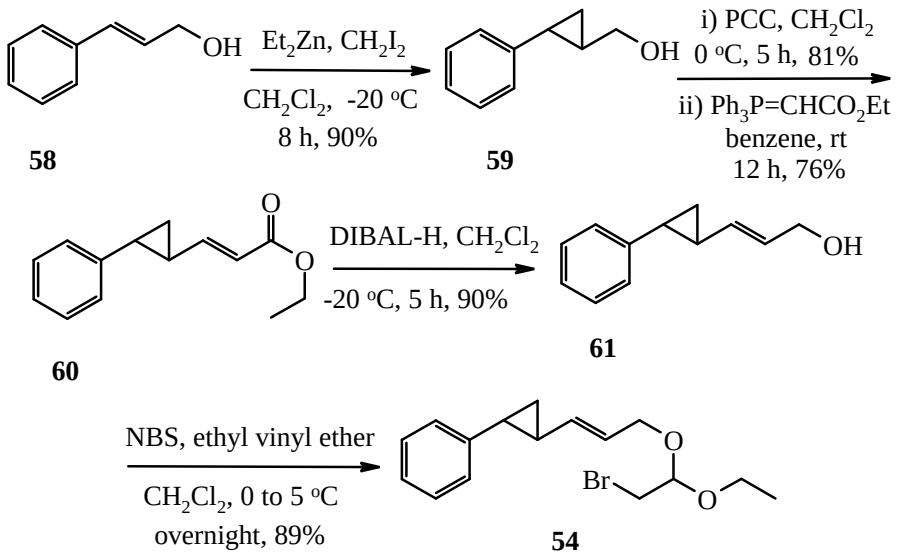
54 **55**

56 **57**

Figure 2

Synthesis of radical precursor 54

Accordingly, the journey started with a reported cyclopropyl alcohol **59**, which was synthesized from commercially available cinnamyl alcohol **58** by modified Simmons-Smith[39] method using diethyl zinc and diiodomethane in dichloromethane at −20 ^{o}C. ^{1}H NMR spectrum of **59** revealed the resonance at δ 0.86-0.97 (m, 2H), 1.35-1.46 (m, 1H) and 1.73-1.82 (m, 1H) ppm in accordance with the cyclopropyl system. Other spectral data was in good agreement with the reported value.



58 **59** **60** **61** **54**

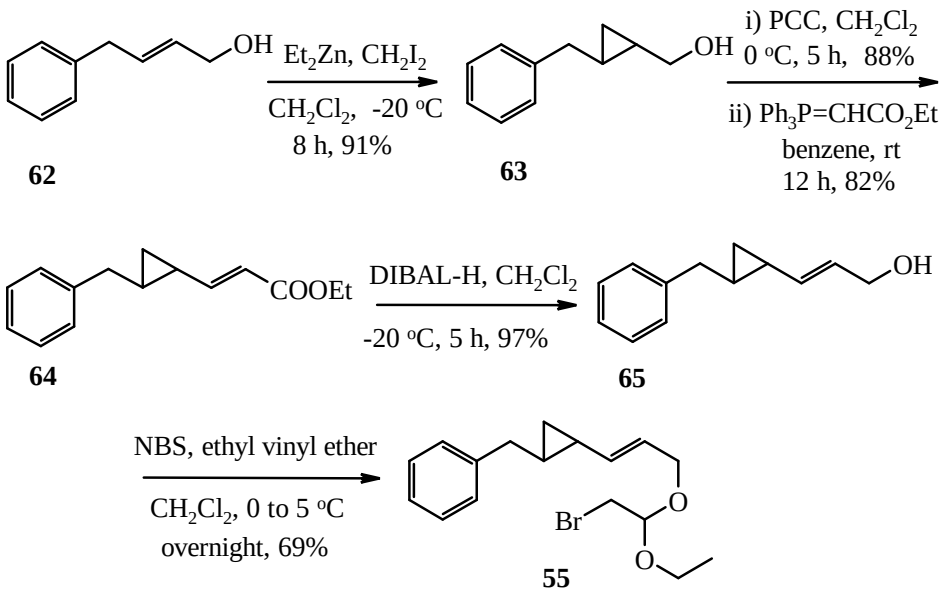
Scheme 17

On treatment of PCC in dichloromethane at 0 ^{o}C, cyclopropyl alcohol **59** was converted to the corresponding aldehyde, which on Wittig reaction with

ethoxycarbonylmethylenetriphenylphosphorane ($Ph_3P{=}CHCO_2Et$) in dry benzene provided *E*-enoate **60**. In ^1H NMR spectrum, the double bonded protons resonated at δ 5.88 (d, *J* = 15.5 Hz, 1H) and 6.58 (dd, *J* = 9.8, 15.5 Hz, 1H) ppm, whereas rest of the protons were resonated at their expected position. IR spectrum showed absorption at 1709 cm^{-1} corresponding to unsaturated ester. ^{13}C NMR spectrum and all other analytical data were in full agreement with the structure of compound **60**. The ester group of compound **60** was reduced to unsaturated alcohol **61** with DIBAL-H at −20 ^oC in dichloromethane. Absence of resonance due to ester moiety was noticed in all the spectral data. Elemental analysis was in good agreement with the structure. In the IR spectrum, absorption at 3402 cm^{-1} supported the presence of hydroxyl group. Derivatisation to cyclopropyl bromoacetal[40] **54** from **61** was affected with NBS and ethyl vinyl ether in dichloromethane with 89% yield. All the other spectral data was in accordance with the assigned structure.

Synthesis of radical precursor 55

Similarly, unsaturated alcohol **62** was converted to the bromo ether derivative **55** (Scheme 18) following the same sequence of reactions described above. Accordingly, alcohol **62** was subjected to the treatment of diethyl zinc and diiodomethane in dichloromethane to furnish cyclopropyl alcohol **63**. Alcohol **63** was transformed into the substituted allyl alcohol **65** through PCC oxidation, 2-carbon Wittig olefination and subsequent reduction of the ester **64** using DIBAL-H.

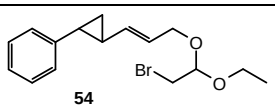
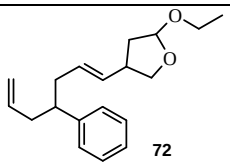
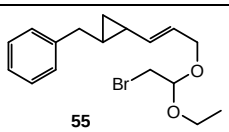
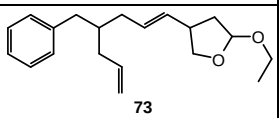


Scheme 18

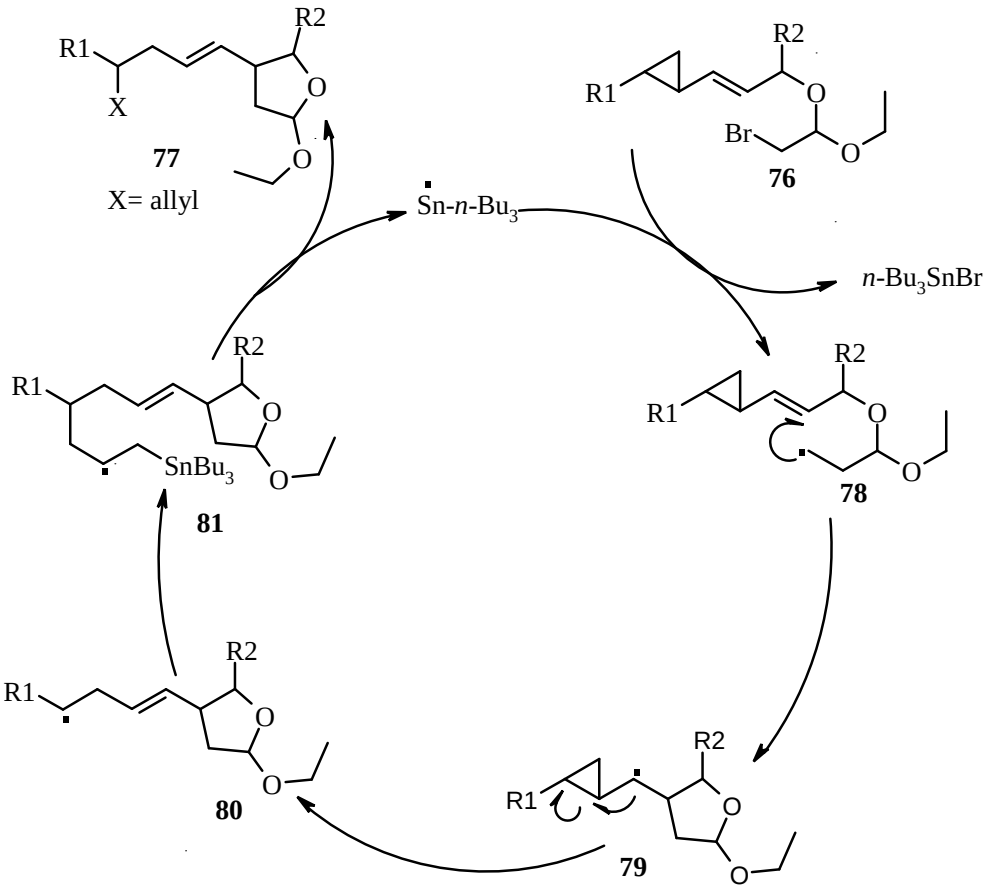
In the ^{1}H NMR spectrum of unsaturated alcohol **65**, signals at δ 5.28 (dd, *J* = 8.6, 15.2 Hz, 1H) and 5.68 (dt, *J* = 6.1, 15.2 Hz, 1H) ppm were confirming the presence of *trans* double bond in the system, whereas rest of the protons were observed at their expected positions. In the ^{13}C NMR spectrum, the double bonded carbons were resonated at δ 125.91 and 141.17 ppm. All the other spectral data were consistent with the structure of compound **65**. Finally, reaction of alcohol **65** with NBS and ethyl vinyl ether in dichloromethane provided the bromoacetal **55** with 69% yield. The assigned structure was substantiated by ^{1}H, ^{13}C NMR spectrum and elemental analysis.

Our initial investigation on the viability of free radical rearrangement followed by allyl transfer *via* reaction of allyltri-*n*-butylstannane with carbon centred radicals began with very simple bromo-acetals **54** and **55**. These reactions were conducted using azobisisobutyronitrile (AIBN) as initiator in refluxing toluene. It was found that good yields of expected rearrangement products were obtained which are tabulated in Table 1. However, it proved very difficult to initiate the reaction in this case, and a large amount of initiator was required to consume the starting material. Further, isolation of tin containing materials from the desired products was found to be tedious job. A number of procedures such as stirring with aqueous KF, followed by filtration etc. provided the **72** as a pure compound but the same was unsuccessful with **73**. Only by GC-mass, the product formation was confirmed.

Table 1

Sr No	**Substrate**	**Reagents**	**Time**	**Product**	**Yield**
1	 **54**	Allyltri-*n*-butylstannane	2 days	 **72**	50%
2	 **55**	Allyltri-*n*-butylstannane	4 days	 **73**	45%

The plausible mechanism for the rearrangement starting from bromoacetal in presence of allyltri-*n*-butylstannane has been shown in scheme 19.



Scheme 19

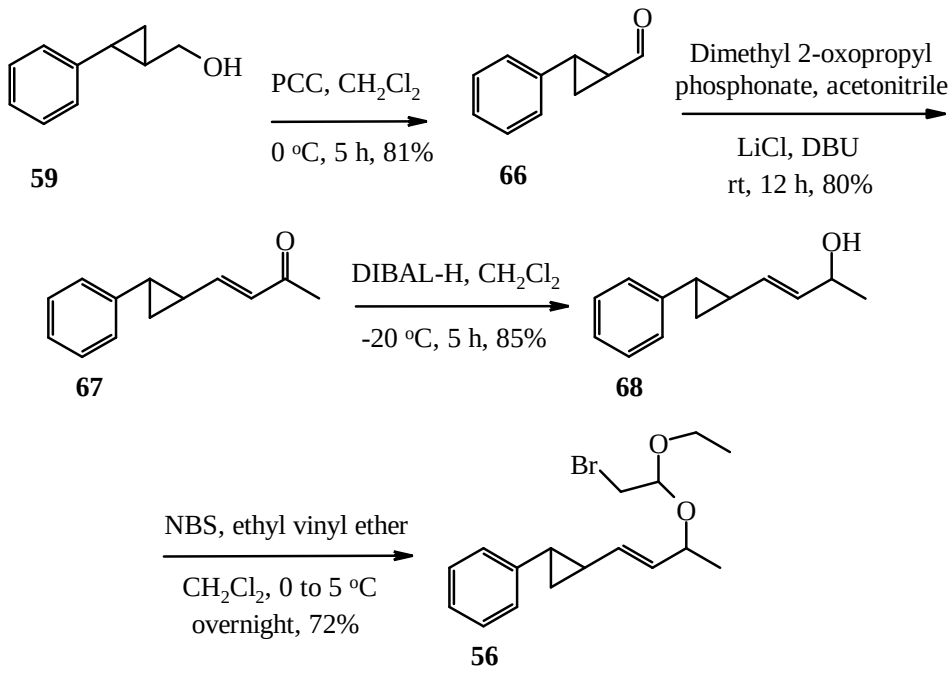
The rearrangement initiated by the fragmentation of the carbon-halide bond under refluxing condition in toluene in presence of allyltri-*n*-butylstannane. The radical **78** generated in the reaction from the corresponding bromoacetal derivative, rapidly cyclizes to **79** under Uno cyclization conditions without yielding any appreciable amount of the allyl (or hydride) trapping product **79**. The newly generated cyclopropyl methyl radical rapidly isomerises to the corresponding tertiary allyl radical. In the propagation step, the tertiary allyl radical generated adds to the allyl (hydride) tri-*n*-butyltin leading to adduct radical. Under refluxing condition this undergoes fragmentation reaction releasing the diolefinic compound **77** and tri-*n*-butyltin radical, which propagates the cycle.

Having established that the expected reaction process could be realised in satisfactory yields with such simple substrates, attention was then turned to investigation in more complex system. Of particular interest in this regard, bromoacetal radical precursor derived from secondary alcohol, compound **56** and **57**

was chosen whose synthesis from cyclopropyl alcohol **58** is described in scheme 20 and 21.

Synthesis of radical precursor 56

Accordingly, cyclopropyl alcohol **59** was oxidized to aldehydes **66** with PCC, followed by Wadsworth Horner Emmons olefination with commercially available dimethyl-2-oxopropyl phosphonate (Scheme 20) provided unsaturated keto compound **67**.

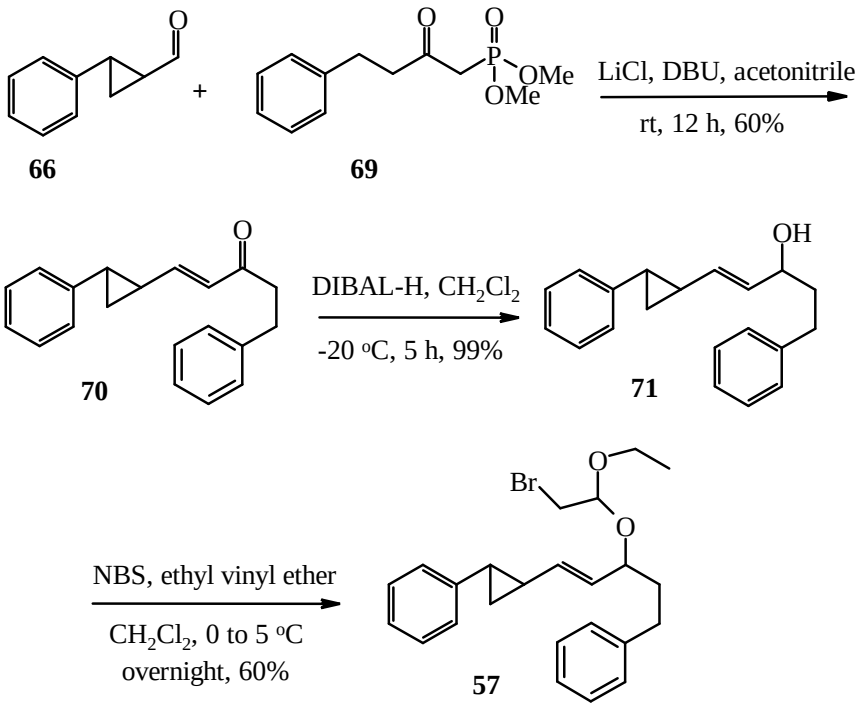


Scheme 20

In ^{1}H NMR spectrum, the olefinic protons were appeared at δ 6.18 (d, *J* = 15.7 Hz, 1H) and 6.44 (dd, *J* = 9.4, 15.7 Hz 1H) ppm, confirming the presence of *trans* olefin in the system, rest of the protons resonated at their expected position. ^{13}C NMR spectrum showed resonance at δ 197.03 ppm, which indicated the presence of keto moiety in the system. The structure was further supported by IR spectrum where absorption at 1688 cm,$^{-1}$ characteristics of unsaturated keto moiety was noticed. Reduction of keto group was performed using DIBAL-H to obtain secondary alcohol **68**. By applying the same protocol (as done for **55**), the hydroxyl group of compound **68** was converted to the bromo acetal **56**. Structure of **56** was thoroughly examined by all the spectral and analytical data.

Synthesis of radical precursor 57

Synthesis of bromoacetal **57** (Scheme 21) was commenced with aldehyde **66**. The compound **66** was forwarded to the target bromo acetal **57** following the same synthetic pathway as it was in the previous entry.



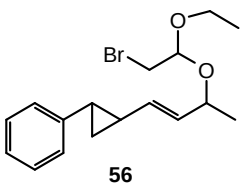
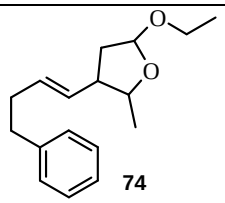
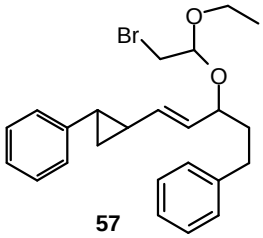
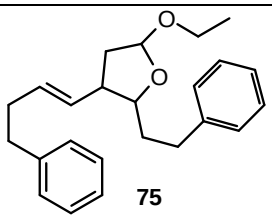
Scheme 21

The cyclopropyl aldehyde **66** was converted to the unsaturated keto compound **70** with *trans* selectivity under Wadsworth-Horner-Emmons olefination condition in presence of phosphonate **69**. Compound **70** was fully characterized by spectral data. When the keto compound was subjected to reduction with DIBAL-H, it was converted to hydroxyl compound **71**. Transformation from alcohol **71** to bromoacetal **57** was accomplished with NBS and ethyl vinyl ether. Spectral and analytical data was in accordance with the assigned structure of **57**.

With substrate **56** and **57**, no product corresponding to rearrangement and subsequent allylation were obtained using the thermal (toluene, 120 ^{o}C and AIBN initiation) protocol previously described, after several attempts only starting material was recovered. Considerably more forcing conditions e.g. xylene or chlorobenzene at reflux, using di-^{t}butylperoxide as initiator was used in these cases but, starting materials were decomposed in that condition. Surprisingly, on treatment of tri-*n*-butyltin hydride, we obtained the furan derivative as well as cyclopropyl ring opening product with excellent yield (Table-2).

The aforesaid failure could be attributed to the steric hindrance posed by the methyl and phenyl ethyl moiety present in **56** and **57** or that other effects, presently unknown.

Table-2

Sr No	**Substrate**	**Reagents**	**Time**	**Product**	**Yield**
1	 **56**	Tri-*n*-butyltin hydride	4 h	 **74**	90%
2	 **57**	Tri-*n*-butyltin hydride	4 h	 **75**	87%

In conclusion, a useful extension of Ueno reaction has been developed as an alternative for the incorporation of allyl units in systems where active methylene group are not present. It is noteworthy that the requisite stannane is readily available from inexpensive starting materials. A good streochemical control could be achieved in the introduction of such substitutions. The observed products may in general be predicted by assuming preferential addition of allyltri-*n*-butylstannane to the less hindered face of an intermediate radical, and good streoselectivity in such reactions appears to require a significant steric bias in the substrate. Unfortunately, the scope of the reaction with respect to substitution patterns of the stannane is much more restricted, as mentioned above. Further progress quite obviously requires a greater understanding of the factors, which control such rearrangement. Efforts in these regards are in progress in our laboratory.

EXPERIMENTAL

Experimental

HWE reaction. General Procedure:

Anhydrous LiCl (1.2 equiv.), weighed in a glove bag and transferred under a stream of argon to the flask. Acetonitrile and phosphonate (2 equiv.) was added and the mixture stirred for 5 min. DBU (1.2 eq) was added and the mixture stirred an additional 10 min. The carbonyl compound was then added dropwise and the reaction mixture was stirred overnight. After being quenched with dilute aqueous HC1, the reaction mixture was extracted with ether. The organic extracts were combined and dried over Mg_2SO_4, and the solvent was removed under vacuum. The crude product was purified by silica gel column chromatography.

General procedure for reduction:

To a solution of unsaturated carbonyl compound (1 equiv.) in CH_2Cl_2 was added DIBAL-H (2.5 eq) dropwise over a period of 5 min at −20 °C. After completion of reaction, the reaction was quenched with saturated aq. sodium potassium tartrate solution, stirred for overnight. The organic layer separated, aqueous layer was washed with CH_2Cl_2, combined organic layer was dried over Na_2SO_4 and concentrated. The residue was purified on silica gel column chromatography to afford the corresponding alcohol.

General procedure for bromo acetal preparation:

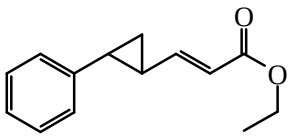
To a solution of alcohol (1 eq) in dichloromethane, NBS (1.1 eq) and ethyl vinyl ether (1.5 eq) was added at 0 ^oC. The reaction mixture was stirred for overnight at 5 ^oC. It was diluted with dichloromethane and washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel column cromatogaphy using EtOAc-light petroleum to afford the corresponding bromo acetals.

General procedure for rearrengement:

A solution of bromo acetal (1 eq), allyltri-n-butylstannane (or tri-*n*-butyltin hydride) (2 eq), and AIBN (catalytic) in toluene was degassed with argon for 0.5 h and then heated to reflux under argon. TLC analysis revealed complete consumption of the starting material. Toluene was removed and the reaction mixture was stirred with 15% aqueous solution of KF and diethyl ether as solvent at ambient temperature for overnight. Solid was filtered, dried (Na_2SO_4) and organic layer concentrated. The

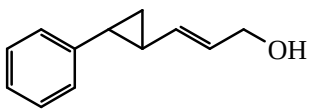
mixture was chromatographed over silica gel column using Hexane:EtOAc to obtain the corresponding rearranged products.

(*E*)-ethyl 3-(2-phenylcyclopropyl)acrylate (60):



Yield	: 67%
Mol. Formula	: $C_{14}H_{16}O_2$
IR ($CHCl_3$) cm^{-1}	3023, 2982, 1709, 1644, 1605, 1498, 1460, 1364, 1258, 1175, 1094, 978, 925, 755.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.29 (t, *J* = 7.12 Hz, 3H), 1.39-1.48 (m, 2H), 1.74-1.87 (m, 1H), 2.12-2.21 (m, 1H), 4.18 (q, *J* = 7.15 Hz, 2H), 5.88 (d, *J* = 15.46 Hz, 1H), 6.58 (dd, *J* = 9.83, 15.46 Hz, 1H), 7.04-7.08 (m, 2H), 7.16-7.31 (m, 3H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 14.27, 17.65, 26.69, 26.76, 59.96, 118.82, 125.79, 126.11, 128.39, 140.61, 151.40, 166.39 ppm.
Elemental Analysis	**Calcd:** C, 77.75; H, 7.46. **Found:** C, 77.59; H, 7.32.

(*E*)-ethyl 3-(2-phenylcyclopropyl)prop-2-en-1-ol (61):



Yield	: 90%
Mol. Formula	: $C_{12}H_{14}O$
IR ($CHCl_3$) cm^{-1}	3402, 3014, 2871, 1665, 1604, 1497, 1459, 1216, 1082, 964, 697.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.03-1.13 (m, 1H), 1.16-1.26 (m, 1H), 1.43 (bs, 1H), 1.61-1.74 (m, 1H), 1.86-1.96 (m, 1H), 4.09 (d, *J* = 5.9, 2H), 5.39 (dd, *J* = 8.5, 15.3 Hz, 1H), 5.73

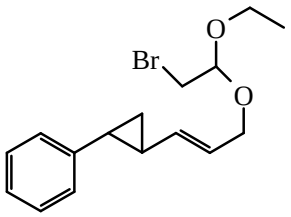
(dt, *J* = 6.9, 15.3 Hz, 1H), 7.02-7.07 (m, 2H), 7.12-7.29 (m, 3H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 16.67, 25.17, 26.00, 63.26, 125.60, 127.39, 128.27, 134.96, 142.01 ppm.

Elemental Analysis **Calcd:** C, 82.72; H, 8.10.

Found: C, 82.59; H, 7.90.

(*E*)-(2-(3-(2-bromo-1-ethoxy)prop-1-enyl)cyclopropyl)benzene (54):



Yield : 89%

Mol. Formula : $C_{16}H_{21}BrO_2$

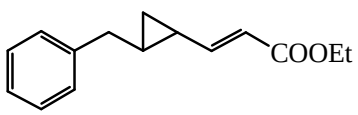
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.05-1.21 (m, 2H), 1.24 (t, *J* = 6.96 Hz, 3H), 1.61-1.75 (m, 1H), 1.88-1.97 (m, 1H), 3.36 (d, *J* = 5.50 Hz, 2H), 3.54-3.73 (m, 2H), 3.97-4.17 (m, 2H), 4.70 (t, *J* = 5.49 Hz, 1H), 5.44 (dd, *J* = 8.22, 15.35 Hz, 1H) 5.66 (dt, *J* = 6.05, 15.35 Hz, 1H), 7.03-7.29 (m, 5H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 15.25, 16.78, 25.29, 26.11, 31.68, 62.19, 67.23, 100.79, 124.04, 125.71, 128.35, 136.95, 142.01 ppm.

Elemental Analysis **Calcd:** C, 59.09; H, 6.51.

Found: C, 58.90; H, 6.38.

(*E*)-ethyl 3-(2-benzylcyclopropyl)acrylate (64):

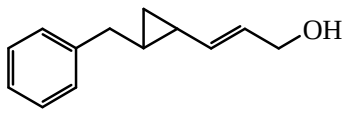


Yield : 82%

Mol. Formula : $C_{15}H_{18}O_2$

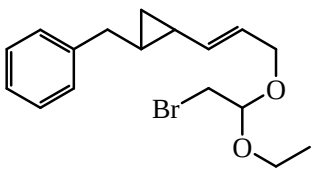
IR ($CHCl_3$) cm^{-1}	3023, 1710, 1644, 1496, 1453, 1303, 1264, 1217, 1046, 757, 698.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.87-0.94 (m, 2H), 1.27 (t, *J* = 7.13 Hz, 3H), 1.25-1.36 (m, 1H), 1.40-1.54 (m, 1H), 2.66 (d, *J* = 6.8 Hz, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 5.84 (d, *J* = 15.5 Hz, 1H), 6.48 (dd, *J* = 9.9, 15.5 Hz, 1H), 716-7.31 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 15.25, 16.78, 25.29, 26.11, 31.68, 62.19, 67.23, 100.79, 124.04, 125.71, 128.35, 136.95, 142.01 ppm.
Elemental Analysis	**Calcd:** C, 59.09; H, 6.51. **Found:** C, 58.90; H, 6.38.

(*E*)-ethyl 3-(2-benzylylcyclopropyl)prop-2-en-1-ol (65):



Yield	: 97%
Mol. Formula	: $C_{13}H_{16}O$
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.63-0.74 (m, 2H), 0.99-1.10 (m, 1H), 1.25-1.38 (m, 1H), 1.61 (bs, 1H), 2.51-2.74 (m, 2H), 4.04 (d, *J* = 6.2 Hz, 2H), 5.28 (dd, *J* = 8.6, 15.2 Hz, 1H), 5.68 (dt, *J* = 6.1, 15.2 Hz, 1H), 7.18-7.37 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 13.82, 21.20, 21.44, 39.29, 63.41, 125.91, 126.48, 128.19, 128.24, 136.05, 141.17 ppm.
Elemental Analysis	**Calcd:** C, 82.94; H, 8.57. **Found:** C, 82.79; H, 8.41.

(*E*)-((2-(3-(2-bromo-1-ethoxyethoxy)prop-1-enyl)cyclopropyl)methyl)benzene (55):



Yield : 69%

Mol. Formula : $C_{17}H_{23}BrO_2$

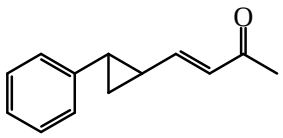
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.42-0.72 (m, 2H), 1.02-1.09 (m, 1H), 1.17-1.35 (m, 5H), 2.50-2.75 (m, 2H) 3.35 (d, *J* = 5.51 Hz, 1.5H), 3.40 (d, *J* = 5.51 Hz, 0.5H), 3.52-3.74 (m, 2H), 3.94-4.30 (m, 2H), 4.56-5.71 (m, 3H), 7.18-7.36 (m, 5H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 13.86, 15.09, 21.23, 21.44, 31.71, 39.19, 62.09, 67.35, 100.55, 123.02, 125.86, 128.19, 137.96, 141.09 ppm.

Elemental Analysis **Calcd:** C, 60.18; H, 6.83.

Found: C, 60.06; H, 6.71.

(*E*)-4-(2-phenylcyclopropyl)but-3-en-2-one (67):



Yield : 80%

Mol. Formula : $C_{13}H_{14}O$

IR ($CHCl_3$) cm^{-1} 3017, 1688, 1663, 1612, 1498, 1360, 1260, 1064, 972, 757, 667.

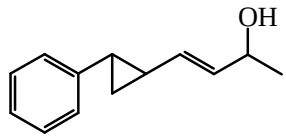
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.27-1.37 (m, 1H), 1.43-1.53 (m, 1H), 1.74-1.86 (m, 1H), 2.22 (s, 3H), 2.14-2.22 (m, 1H), 6.18 (d, *J* = 15.7 Hz, 1H), 6.44 (dd, *J* = 9.5, 15.7 Hz, 1H), 7.05-7.09 (m, 2H), 7.18-7.28 (m, 3H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 17.91, 26.67, 27.22, 125.89, 126.16, 128.39, 140.48, 150.40, 197.03 ppm.

Elemental Analysis **Calcd:** C, 83.83; H, 7.58.

Found: C, 83.66; H, 7.39.

(*E*)-4-(2-phenylcyclopropyl)but-3-en-2-ol (68):



Yield : 85%

Mol. Formula : $C_{13}H_{16}O$

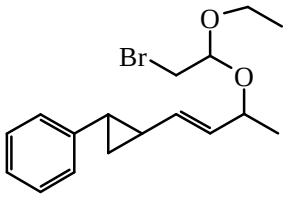
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.02-1.12 (m, 1H), 1.15-1.22 (m, 1H), 1.26 (d, J = 6.4 Hz, 3H), 1.46 (bs, 1H), 1.58-1.71 (m, 1H), 1.85-1.94 (m, 1H), 4.27 (q, J = 6.4 Hz, 1H), 5.33 (dd, J= 8.4, 15.3 Hz, 1H), 5.62 (dd, J = 6.5, 15.3 Hz, 1H), 7.02-7.28 (m, 5H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 16.78, 23.41, 25.15, 25.98, 68.57, 125.59, 128.28, 132.66, 132.78, 142.06 ppm.

Elemental Analysis **Calcd:** C, 82.94; H, 8.57.

Found: C, 82.80; H, 8.31.

(E)-(2-(3-(2-bromo-1-ethoxyethoxy)but-1-enyl)cyclopropyl)benzene (56):



Yield : 72%

Mol. Formula : $C_{17}H_{23}BrO_2$

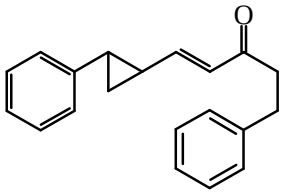
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.10-1.92 (m, 8H), 1.61-1.73 (m, 1H), 1.85-1.97 (m, 1H), 3.31-3.42 (m, 2H), 3.50-3.71 (m, 2H), 4.08-4.19 (m, 1H), 4.66-4.73 (m, 1H), 5.28-5.61 (m, 2H), 7.02-7.29 (m, 5H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 15.13, 15.37, 16.88, 17.04, 21.45, 21.99, 25.36, 17.04, 21.45, 21.99, 25.36, 25.97, 32.12, 32.56, 60.78, 62.17, 73.74, 74.35, 98.76, 100.05, 125.64, 128.35, 129.60, 130.45, 134.28, 134.32, 135.61, 135.72, 141.99 ppm.

Elemental Analysis **Calcd:** C, 60.18; H, 6.83.

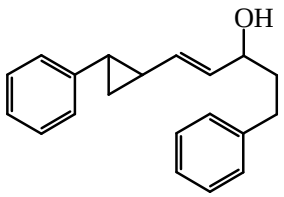
Found: C, 60.01; H, 6.70.

(*E*)-5-phenyl-1-(2-phenylcyclopropyl)pent-1-en-3-one (70):



Yield	: 60%
Mol. Formula	: $C_{20}H_{20}O$
IR ($CHCl_3$) cm^{-1}	3025, 3063, 1689, 1661, 1614, 1496, 1454, 1217, 1191, 1089, 972, 753, 697.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.25 (m, 1H), 1.48 (m, 1H), 1.77 (m, 1H), 2.15 (m, 1H), 2.75-3.0 (m, 4H), 6.22-6.5 (m, 2H), 7.00-7.30 (m, 10H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 17.88, 26.80, 27.16, 30.12, 42.06, 125.86, 128.30, 128.43, 140.48, 141.24, 149.82, 198.04 ppm.
Elemental Analysis	**Calcd:** C, 86.92; H, 7.29.
	Found: C, 86.74; H, 7.11.

(*E*)-5-phenyl-1-(2-phenylcyclopropyl)pent-1-en-3-ol (71):



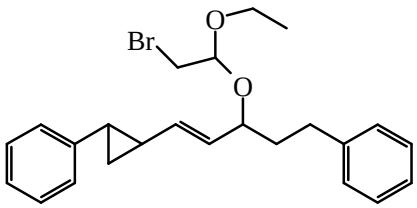
Yield	: 99%
Mol. Formula	: $C_{20}H_{22}O$
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.95-1.04 (m, 1H), 1.11-1.18 (m, 1H), 1.46 (bs, 1H), 1.56-1.65 (m, 1H), 1.70-1.86 (m, 3H), 2.59-2.67 (m, 2H), 3.99 (q, *J* = 6.6 Hz, 1H), 5.27 (dd, *J* = 8.5, 15.4 Hz, 1H), 5.53 (dd, *J* = 6.8, 15.4 Hz, 1H), 6.95-7.29 (m, 10H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 16.87, 25.25, 26.09, 31.76, 38.79, 72.02, 125.60, 125.77, 128.32, 128.42, 131.27, 134.13, 141.83, 142.02 ppm.

Elemental Analysis **Calcd:** C, 86.29; H, 7.97.

Found: C, 86.11; H, 7.80.

(E)-(3-(2-bromo-1-ethoxyethoxy)-5-(2-phenylcyclopropyl)pent-4-enyl)benzene (57):



Yield : 70%

Mol. Formula : $C_{24}H_{29}BrO_2$

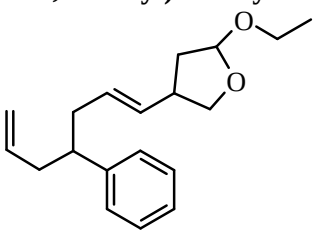
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.08-1.11 (m, 1H), 1.14-1.19 (m, 1H), 1.20-1.26 (m, 3H), 1.66-1.70 (m, 1H), 1.79-1.84 (m, 1H), 1.90-1.97 (m, 2H), 2.66-2.73 (m, 2H), 3.33-3.42 (m, 2H), 3.46-3.71 (m, 2H), 3.86-4.02 (m, 1H), 4.64-4.91 (m, 1H), 5.33-5.56 (m, 2H), 7.03-7.28 (m, 10H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 15.09, 15.37, 16.70, 16.92, 17.11, 25.26, 25.44, 25.90, 26.01, 31.50, 31.64, 32.20, 32.29, 32.61, 37.24, 37.41, 61.13, 61.22, 62.58, 77.09, 78.43, 78.48, 98.61, 100.44, 125.67, 125.70, 125.78, 125.87, 128.16, 128.33, 128.41, 128.47, 129.14, 135.72, 137.03, 137.09, 141.87 ppm.

Elemental Analysis **Calcd:** C, 67.13; H, 6.81.

Found: C, 67.01; H, 6.70.

(*E*)-2-ethoxy-4-(4-phenylhepta-1,6-dienyl)tetrahydrofuran(72):



Yield : 50%

Mol. Formula : $C_{19}H_{26}O_2$

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.15-1.21 (m, 3H), 1.48-1.65 (m, 1.6H), 1.89-1.96 (m, 0.4H), 2.15-2.40 (m, 4H), 2.61-2.68 (m, 1.38H), 2.89-2.97 (m, 0.46H), 3.28-3.46 (m, 2H), 3.65-3.99 (m, 2H), 4.90-5.08 (m, 3H), 5.16-5.35 (m, 2H), 5.60-5.67 (m, 1H), 7.08-7.27 (m, 5H) ppm.

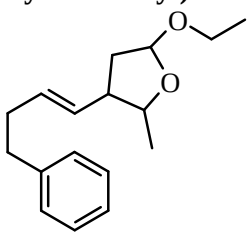
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 15.35, 15.31, 39.03, 39.64, 39.93, 40.23, 42.18, 45.89, 62.56, 63.02, 71.14, 72.13, 103.89, 104.38, 116.18, 126.13, 127.77, 128.22, 129.34, 132.22, 132.59, 136.77, 144.55 ppm.

GC MS (*m/z*) : 286 $[M]^+$

Elemental Analysis **Calcd:** C, 79.68; H, 9.15.

Found: C, 79.55; H, 9.02.

(E)-5-ethoxy-2-methyl-3-(4-phenylbut-1-enyl)tetrahydrofuran(74):



Yield : 90%

Mol. Formula : $C_{17}H_{24}O_2$

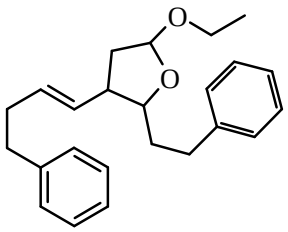
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.13-1.23 (m, 6H), 1.65-1.78 (m, 1H), 1.93-2.03 (m, 0.5H), 2.13-2.23 (m, 0.5H), 2.29-2.37 (m, 2H), 2.39-2.57 (m, 1H), 2.66 (m, 2H), 3.37-3.44 (m, 1H), 3.66-3.76 (m, 2H), 4.97-5.08 (m, 1H), 5.19-5.34 (m, 1H), 5.45-5.55 (m, 1H), 7.12-7.26 (m, 5H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 15.35, 18.15, 18.42, 20.68, 20.94, 34.29, 34.39, 40.46, 40.70, 40.86, 41.16, 48.18, 50.21, 62.24, 63.08, 77.72, 78.11, 80.80, 81.33, 103.04, 103.30, 125.84, 125.93, 128.27, 128.35, 128.50, 130.62, 130.73, 131.34, 141.69, 141.72 ppm.

GC MS (*m/z*) : 260 $[M]^+$

Elemental Analysis	**Calcd:** C, 78.42; H, 9.29.
	Found: C, 78.35; H, 9.20.

(E)-5-ethoxy-2-phenethyl-3-(4-phenylbut-1-enyl)tetrahydrofuran(75):



Yield	: 87%
Mol. Formula	: $C_{24}H_{30}O_2$
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.17-1.33 (m, 3H), 1.59-199 (m, 4H), 2.17-2.40 (m, 3H), 2.61-2.79 (m, 4H), 3.39-3.50 (m, 1H), 3.59-3.66 (m, 1H), 3.73-3.81 (m, 1H), 5.03-5.12 (m, 1H), 5.19-5.59 (m, 2H), 7.12-7.27 (m, 10H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 15.31, 32.69, 34.19, 34.28, 45.06, 35.77, 40.26, 40.73, 46.36, 48.26, 62.26, 63.02, 80.90, 83.95, 103.03, 103.21, 125.68, 125.74, 128.21, 128.26, 128.42, 130.43, 130.75, 130.85, 131.33, 131.42, 141.71, 142.24 ppm.
ESI MS (*m/z*)	: 373.5 $[M+ Na]^+$
Elemental Analysis	**Calcd:** C, 82.24; H, 8.63.
	Found: C, 82.18; H, 8.55.

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List of Publications

1. Total Synthesis of (S)-(−)-Curvularin: A Ring-Closing Metathesis Based Construction of the Macrocyclic Framework. Debendra K. Mohapatra, Hasibur Rahaman, **Rita Pal** and Mukund K. Gurjar. *Synlett* **2008** (*Accepted)*.
2. Stereoselective formal synthesis of novel antibiotic (−)-centrolobine. Debendra K. Mohapatra, **Rita Pal** and Mukund K. Gurjar, *Communicated*.
3. Toward a synthesis of the anti cancer macrolide superstolide A: a chiral pool approach for the C21-C26 segment. Mukund K. Gurjar; **Rita Pal**; Debendra K. Mohapatra, *Cmmunicated*.
4. A streoselective synthesis of the C21-C26 fragment of superstolide A. Mukund K. Gurjar; **Rita Pal**; Debendra K. Mohapatra (*Under manuscripts*).