# Synthetic Studies toward Microcarpalide, *C*-Disaccharide and Dicerandrols

A THESIS

SUBMITTED FOR THE DEGREE OF

**DOCTOR OF PHILOSOPHY**

**(IN CHEMISTRY)**

TO

**UNIVERSITY OF PUNE**

BY

**Ravi Naga Prasad**

ORGANIC CHEMISTRY: TECHNOLOGY

NATIONAL CHEMICAL LABORATORY

PUNE-411008

NOVEMBER 2004

*DEDICATED*

*TO*

*MY FAMILY*

# 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-8 **(Ravi Naga Prasad)**

November 2004 **Candidate**

# NATIONAL CHEMICAL LABORATORY

Dr. Homi Bhabha Road, PUNE - 411 008 (INDIA)

**Dr. M. K. Gurjar**

**Head & Deputy Director**

**Division of Organic Chemistry: Technology**

Telephone and Fax: + 91-20-25893614

+ 91-20-25882456

E-mail: gurjar@dalton.ncl.res.in

Website: http://www.ncl-india.org


## CERTIFICATE

The research work presented in thesis entitled " **Synthetic studies toward microcarpalide, C-disaccharide and Dicerandrols**" has been carried out under my supervision and is a bonafide work of **Mr. Ravi**. **Naga Prasad** This work is original and has not been submitted for any other degree or diploma of this or any other University.

Pune-8

November 2004

**(Dr. M. K. Gurjar)**

**Research Guide**

## *Acknowledgements*

*It gives me great pleasure to express my deep sense of esteem and gratitude to my research guide, Dr. M. K. Gurjar, Deputy Director, N. C. L., Head, Division of Organic Chemistry (Tech.), for his inspiring guidance, never diminishing encouragement, support and his complete dedication during the progress of my work.*

*I am equally thankful to Dr. C. V. Ramana for his deep interest and valuable suggestions. The help of Dr. D. K. Mahapatra, Dr. R. A. Joshi, Dr. R. R. Joshi, Mr. I. Shivakumar, Dr. M. N. Deshmukh, Dr. Kalkote, Dr. S. P. Chavan, Dr. Muthukrishnan and Dr. A. Murugan, is greatly acknowledged.*

*I gratefully acknowledge the guidance, training and support extended by my senior colleagues Dr. Hotha, Dr. A. M. S. Murugaiah, Dr. Kishore, Dr. Ranga Reddy, Dr. K. K. Reddy, Dr. S. V. R. Nadh, Dr. Arindam, Dr. Murali Krishna and Dr. Baquer during formative period of my Ph.D life. I would like to thank all my colleagues B. S. Reddy, Joseph, Eku, Mahesh, D. P. S. Reddy, Sankar, Siddhartha, Bhargav, Ramesh, Raghupathi, Tushar, Smriti, Ramdas, Sukhen, Dhananjoy, Manjusha, Seetaram, Bhagwat, Sabita, Gorakh, Kulbhushan, Kiran, Srinivas, Nageshwar, Sahoo, Pradip, Chinmoy, Bhaskar, Sumanth, Rosy, Rehaman, Rita, Abhijit, Anuj, Sharad, Indu, Susheel, Soumitra, Ganesh, Debabrata and Mondal for their cooperation and friendly attitude.*

*Help from the spectroscopy and mass groups is gratefully acknowledged. I sincerely thank Dr. Rajmohan, Mrs. U. D. Phalgune and Mr. Sathe for the helpful discussions and cooperation.*

*I sincerely acknowledge the help of Mrs. C. Raphel, Mrs. Kulkarni and all other office staff.*

*I wholeheartedly thank my colleagues at NCL and GJ hostel for their cheerful company, which made my stay at NCL memorable one. My regards to my friends and all well wishers.*

*I would like to thank my friends Bhoje, Rama Krishna, Praveen, Raghu, Malli, Vasu, Subbu and all my M. Sc. classmates for their Cheerful Company.*

*Whatever I am and whatever I will be in future is because of the goodwill and unstinted support that I have received from my parents. Their kind cooperation helped me in pursuing my PhD and no words are enough to acknowledge them. Their constant encouragement, support and sacrifice made me achieve the goal. My special thanks to my brother Srinu and sister in-law who stood by me during all difficult times.*

*Finally I thank Director, National Chemical Laboratory, Pune for providing infrastructural facilities to complete my work successfully. I am also thankful to CSIR, New Delhi for the financial assistance in the form of fellowship.*

***R. Naga Prasad***

## ABBREVIATIONS

| | | |
|---|---|---|
| AcOH | - | Acetic acid |
| $Ac_2O$ | - | Acetic anhydride |
| AIBN | - | 2,2'-Azobisisobutyronitrile |
| Bn | - | Benzyl |
| BnBr | - | Benzyl bromide |
| BzCl | - | Benzoyl chloride |
| Bz | - | Benzoate |
| *n*-BuLi | - | *n*-Butyl lithium |
| $Cu(OAc)_2$ | - | Copper (II) Acetate |
| DCC | - | Dicyclohexylcarbodiimide |
| DIBAL-H | - | Diisobutylaluminium hydride |
| DIPEA | - | Diisopropyl ethylamine |
| DMA | - | *N*,*N'*-Dimethylacetamide |
| DMF | - | *N*,*N'*-Dimethylformamide |
| DMAP | - | *N*,*N'*-Dimethylaminopyridine |
| DMSO | - | Dimethyl sulfoxide |
| EtOH | - | Ethanol |
| Et | - | Ethyl |
| EtOAc | - | Ethyl acetate |
| HMDS | - | Hexamethyldisilazane |
| HMPA | - | Hexamethylphosphoramide |
| $H_2SO_4$ | - | Sulphuric acid |
| Im | - | Imidazole |
| KOH | - | Potassium hydroxide |
| LiHMDS | - | Lithium hexamethyl disiloxane |
| $Li/Liq.NH_3$ | - | Lithium/liquid ammonia |
| LDA | - | Lithium diisopropylamide |
| MeOH | - | Methanol |
| Me | - | Methyl |

| | | |
|---|---|---|
| MeI | - | Methyl iodide |
| *m*-CPBA | - | *meta*-Chloroperbenzoic acid |
| MEM | - | Methoxyethoxy methoxyl |
| NaOH | - | Sodium hydroxide |
| NaOMe | - | Sodium methoxide |
| $O_2$ | - | Oxygen |
| PPTS | - | Pyridine *p*-toluene sulphonate |
| PhSH | - | Thiophenol |
| Piv | - | Pivolyl |
| Pd/C | - | Palladium on Carbon |
| $PdCl_2$ | - | Palladium (II) Chloride |
| $Pd(OH)_2/C$ | - | Palladium hydroxide on Carbon |
| Ph | - | Phenyl |
| py | - | Pyridine |
| PCC | - | Pyridinium chlorochromate |
| PDC | - | Pyridiniumdichromate |
| $TiCl_4$ | - | Titanium tetrachloride |
| *p*-TSA | - | *para*-Toluenesulfonic acid |
| TsCl | - | Tosyl chloride |
| TBAI | - | Tetra-*n*-butylammonium iodide |
| TBAF | - | Tetra-*n*-butylammonium fluoride |
| TBDMS | - | *tert*-Butyldimethyl silyl |
| THF | - | Tetrahydrofuran |
| Tr | - | Trityl |
| TrCl | - | Trityl chloride |

## GENERAL REMARKS

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

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

❋ 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.

❋ 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, Bombay, India.

# CONTENTS

# Abstract

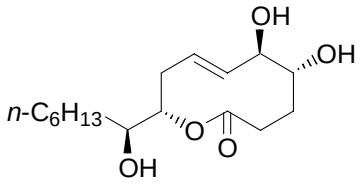
**Abstract**

The thesis entitled "Synthetic Studies Toward Microcarpalide, *C*-Disaccharide and Dicerandrols" consists of three chapters and each chapter is further sub-divided into following sections: Introduction, Present Work, Experimental, References and Spectroscopic data. Chapter I deal with the total synthesis of microcarpalide using a combination of chiral pool approach and Sharpless asymmetric dihydroxylation. Utilization of henry reaction for the synthesis of *C*-disaccharide analogue of motif *C* of cell wall AG complex of *mycobacterium tuberculosis* constitutes the Chapter II. Chapter III incorporates the chiral pool synthesis of an advanced cyclohexenone intermediate in the process of total synthesis of dicerandrol.

## Chapter I:

### Total synthesis of microcarpalide

Microcarpalide (**1**), a ten-membered cyclic lactone (a $C_{16}$ -nonenolide) recently isolated and characterized by Hemscheidt and co-workers from the fermentation broths of an unidentified endophytic fungus growing on the bark of *Ficus microcarp*a, has been shown to be a promising microfilament disrupting agent. Microcarpalide represents a novel alkyl substituted nonelide structurally related to a family of phytotoxins such as achaetolide, pinolidoxin, lethalotoxin, putaminotoxins and herbarumins, from which it differs in the hydroxylation pattern and double bond position within the 10-memberedlactones, as well as in the longer side chain at C-10.

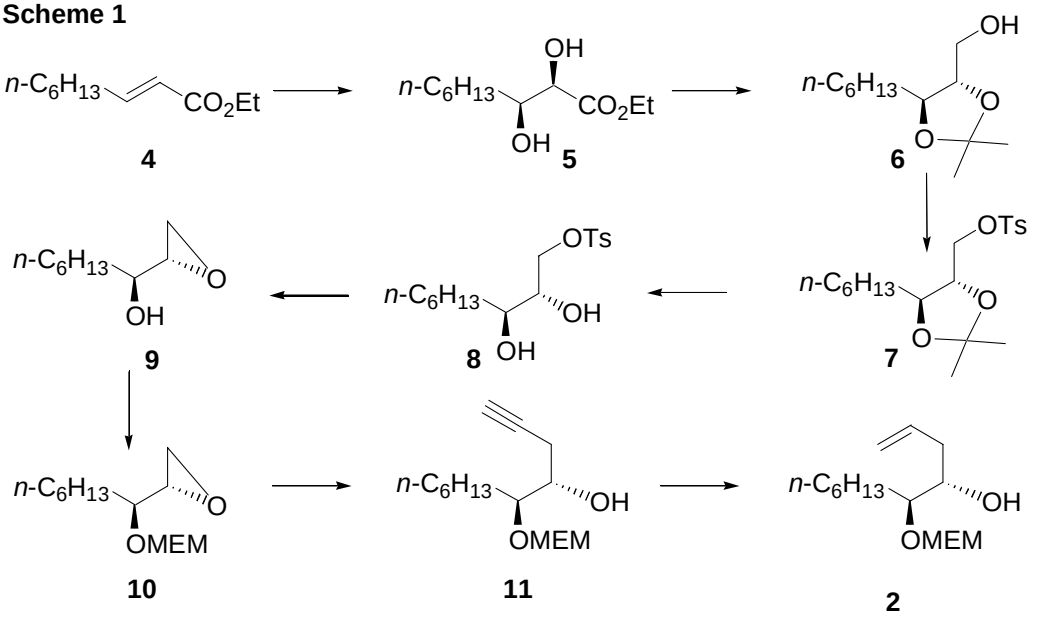



Microcarpalide (**1**)

Our synthetic strategy towards the total synthesis of microcarpalide relies on the enantioselective preparation of the key fragment **2** via a Sharpless asymmetric dihydroxylation, and D-mannose as a chiral pool source with a zinc-mediated elimination of an α-iodo acetonide derivative for the preparation of the other coupling partner **3**.

Synthesis of the olefinic alcohol **2** (Scheme 1) was initiated by the Sharpless asymmetric dihydroxylation of the unsaturated ester **4** with commercially available AD-mix-α. Isopropylidenation of the resulting diol **5** and subsequent reduction using DIBAL-H provided the alcohol **6**. The tosylate **7** obtained upon treating **6** with *p*-TsCl in pyridine, following acid catalyzed deiso-propylidenation, was reacted with $K_2CO_3$ in methanol to give **9** and the free hydroxyl group of resulting epoxide **9** was protected as its methoxyethoxymethyl (MEM) ether to furnish **10**. Opening the epoxide **10** with an excess of lithium acetylide and partial hydrogenation of the resulting acetylene **11** with Lindlar catalyst achieved the olefinic alcohol.

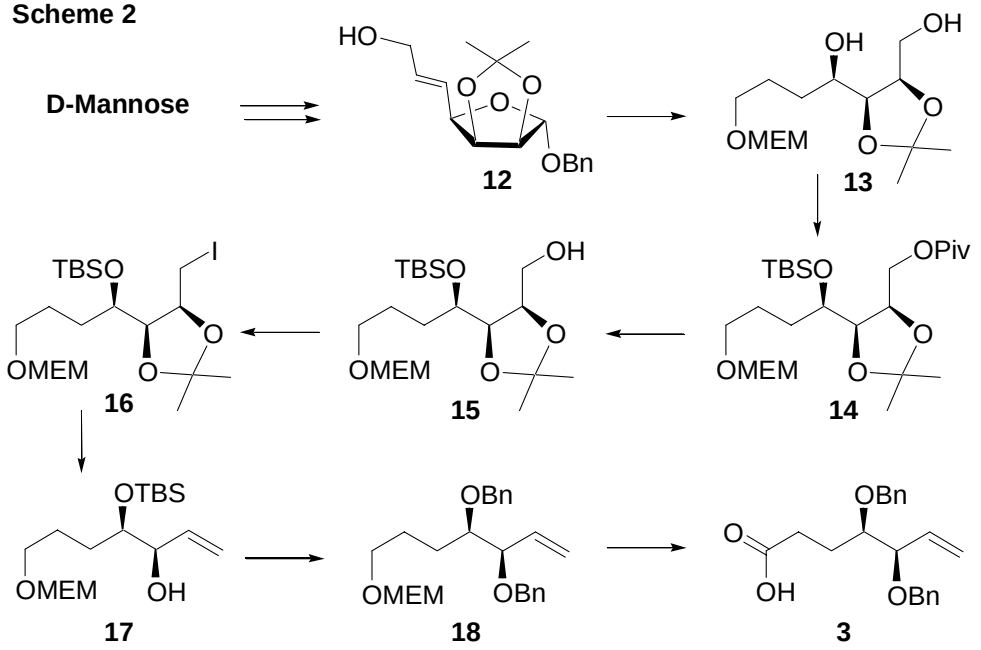
**Scheme 1**




The synthesis of acid component **3** commenced with **12**, which was synthesized according to the literature procedure from D-mannose (Scheme 2). Protection of the hydroxyl group of **12** as its MEM-ether, hydrogenation using 10% Pd–carbon, and subsequent reduction with lithium aluminum hydride gave the diol **13**. The TBS-ether **15** was obtained in 73% overall yield following selective pivaloylation of the $C_1$ -OH, protection of the $C_4$ -OH as its TBS ether, and reductive depivaloylation using DIBAL-H. Primary alcohol in **15** was converted to its iodo derivative, **16** in good yield. A facile elimination of **16** resulting in the corresponding allylic alcohol **17** was then accomplished using freshly activated Zn in refluxing ethanol. Removal of the TBS-protection and benzylation gave **18**. The synthesis of

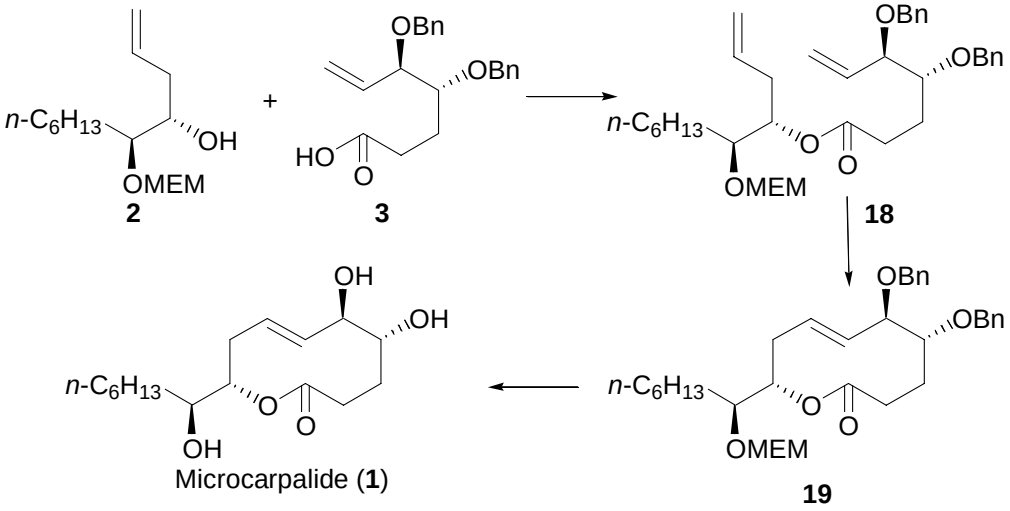
the second key fragment, the olefinic acid **3** was completed by deprotection of the MEM-ether, oxidation of the resulting primary alcohol to the corresponding aldehyde using Swern conditions and further oxidation using sodium chlorite in DMSO under buffered conditions.

**Scheme 2**




Having completed the synthesis of both fragments **2** and **3**, it remained to couple the two fragments and achieve subsequent ring closing metathesis reaction. The coupling reaction of **2** and **3** was carried out via DCC mediated esterification reaction to give di olefinic ester **18.** RCM of **18** with the first generation Grubbs' catalyst (Scheme 3) under high dilution conditions gave the *E*-and *Z*-isomers of **19** in a 10:1 ratio. The attempted deprotection of MEM with $TiCl_4$ lead to the global deprotection, yielding the target molecule microcarpalide (**1**).

**Scheme 3**

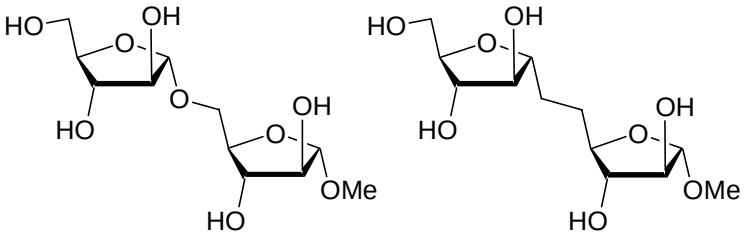



# Chapter II:

**First synthesis of methyl α-*C*-D-arabinofuranosyl-(1→5)-α -D-arabinofuranoside: the *C*-disaccharide segment of motif *C* of *Mycobacterium tuberculosis***

The mycolic arabino-galactan (AG) complex present on the cell wall surface of *Mycobacterium tuberculosis* has unique structural features unknown in actinomycetes. The furanoside rings of AG complex are conformation-ally more mobile (than pyranosides) and are largely linked through primary hydroxyl groups. These characteristics enable the crowded AG complex to adopt a structure in which mycolic acids are closely arranged in parallel arrays. The AG complex is critical for the survival of M. *tuberculosi*s. The hydrophobic AG complex acts as a strong barrier for the passage of antibiotics into the cell and therefore, plays an important role in developing resistance of *Mycobacteria* to many antibiotics. The drug ethambutol blocks the biosynthetic pathway of arabinose. The inhibition of biosynthetic pathway, involved in development of M. *tuberculosis* cells, is considered as an attractive strategy for drug develop-ment against M. *tuberculosi*s. The *C*-linked glycosides of glycosyl compounds are stable to both chemical and metabolic degradation. The conformational features of *C*-glycosides to a large extent resemble those of naturally occurring *O*-glycosides. The *C*-glycosides serve as glycosyl regulators and as synthetic ligands for probing cellular interactions. In continua tion of our interest in AG complex, we undertook the first synthesis

of α-*C*-D-ar*af*-(1→5) α-D-ar*af* as a methyl glycoside **2** which constitutes the *C*-analogue of motif *C* oligosaccharide (Fig. 1).



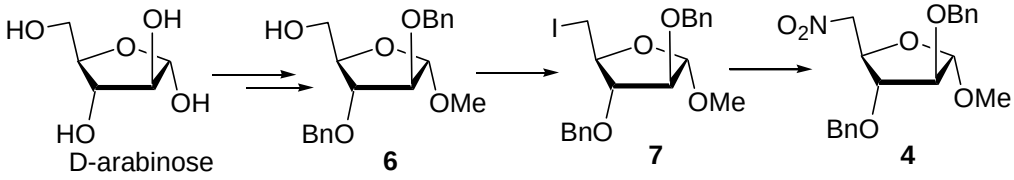

*a*-Ara*f*-(1–>5)-ara*f* **Motif C (1)**

*a*-*C*-Ara*f*-(1–>5)-ara*f* **2**

**Figure 1.**

The synthetic scheme for **2** was based on the C–C coupling reaction between two partners **4** and **5** via the nitro-aldol condensation reaction. The synthesis of **4** was initiated from methyl 2,3-di-*O*-benzyl-α-D-arabinofuranoside **6**, which was converted into the 5-deoxy-5-iodo derivative **7**. Replacement of the iodine with a nitro group was accomplished with $NaNO_2$, phloroglucinol.monohydrate in DMSO (Scheme 1).

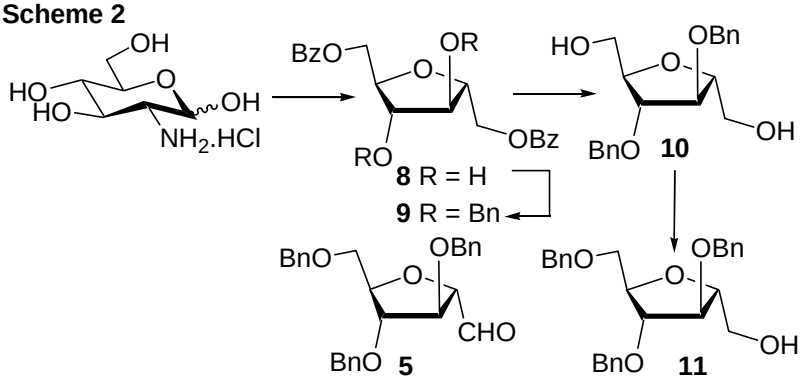
**Scheme 1**




The second component **5** was obtained from D-glucosaminehydrochloride, which was subjected to a diazotization mediated ring contraction reaction, subsequent reduction and selective benzoylation to afford the known dibenzoate derivative **8**. The free hydroxyl group of **8** was protected as benzyl ethers by treatment with BnBr, $Ag_2$ O in $CH_2$ $Cl_2$ followed by debenzoylation with NaOMe in methanol to give the dibenzyl derivative **10**. The selective protection of one of the hydroxy methyl groups was performed with 1 equiv. of each NaH and BnBr in DMF. Compound **10** being $C_2$ -symmetric, afforded only one diastereomer **11**. The free hydroxy-methyl functionality in **11** was oxidized under Swern conditions and the

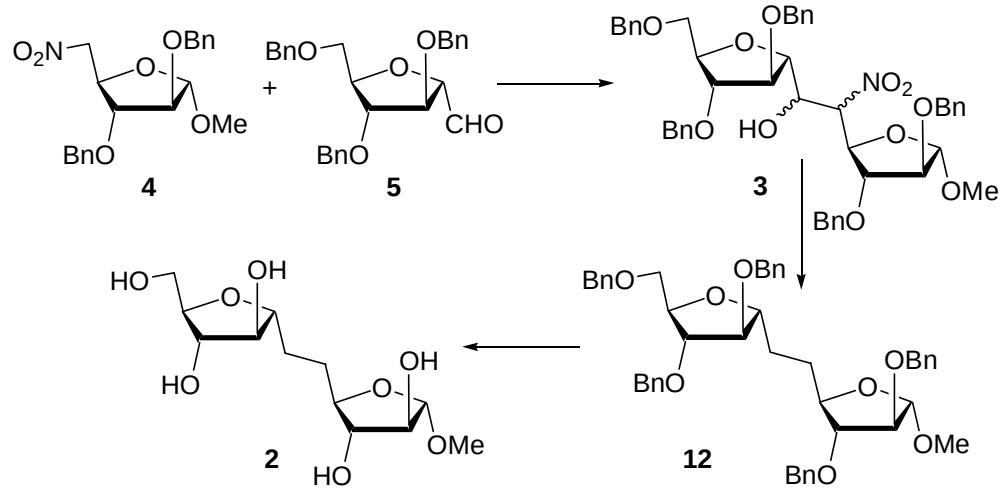
resulting aldehyde **5**, being unstable, was utilized for the next step without any delay (Scheme 2).

**Scheme 2**




The coupling reaction between **4** and **5** occurred in the presence of catalytic KF in $CH_3$ CN to give a diastereomeric mixture of **3** which was subjected to three successive steps, i.e. dehydration, selective reduction of conjugated olefin and denitration with n-$Bu_3SnH$ to give the penta-*O*-benzyl *C*-disaccharide **12**. Finally hydrogenolysis of **12** in presence of $Pd(OH)_2$ at normal temperature and pressure gave the *C*-disaccharide **2** (Scheme 3).

**Scheme 3**




In summary, we achieved the first successful synthesis of the C-oligosaccharide of motif C of M. *tuberculosi*s. The biological and structural implications of this C-analogue will not be only interesting but significant from a drug development point of view.

## Chapter III:

**Synthetic studies toward dicerandrol:**

Dicerandrol (Fig.1) is a symmetrical dimer isolated from a fungus *phomopsis longicolla* grown in an endangered mint plant, shows antibacterial and cytotoxic activity. Molecule is characterized by the presence of tetra substituted aromatic ring, an enol, two methylene groups, two methines and one quaternary carbon in each isomer, whose absolute structure is not known, but the NMR studies shown that the methyl and hydroxy functionalities were arranged in syn manner to each other. This molecule structurally resembles with that of secalonic acid family, from which it differs by the presence of hydroxymethyl functionality in the place of ethoxy carbonyl.

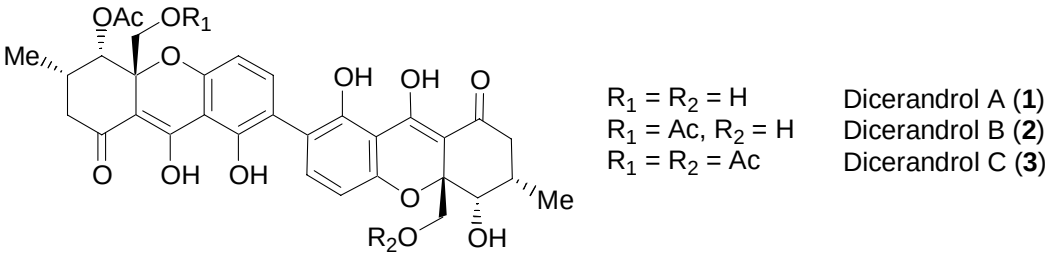



**Figure 1.** *Structures of the dicerandrols*

We have designed a intramolecular-Micheal addition reaction for the formation of monomer **8** (Fig 2) for the synthesis of the key intermediate **5** we have intended to to use chiral pool approach.

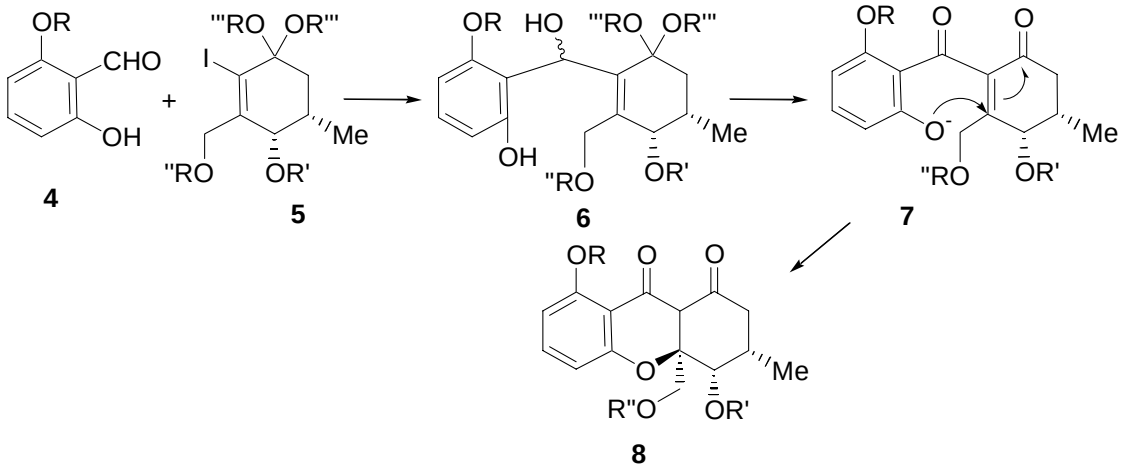
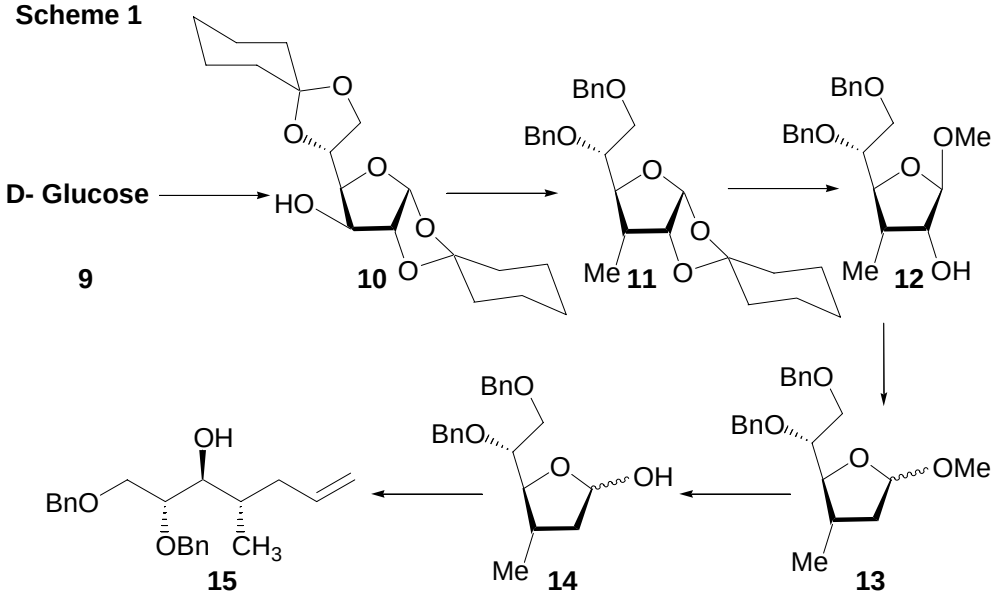



**Figure 2.** *Intramolecular Micheal addition protocol*

**Synthesis of fragment 5**.

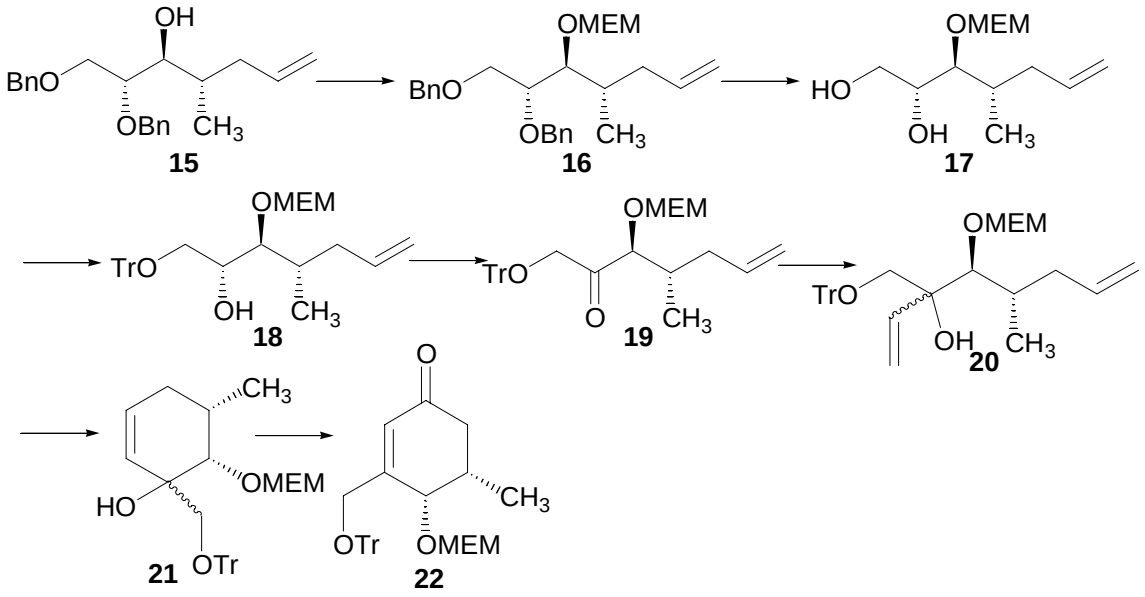
Our synthetic endeavor begins with **13**, which can be obtained from 1,2;5,6-di-*O*-cyclohexylidene-$\alpha$ -D-glucofuranose **9**, Following a sequence of reactions starting with the compound 5 like a) selective 5,6-cyclohexylidine deprotection b) the protection of the resulting diol as its dibenzyl ether c) 1,2-cyclohexylidene deprotection and d) radical deoxygenation of C-2 hydroxyl group in **12** led to the formation of derivative **13**. The acid catalyzed anomeric demethylation and subsequent one carbon Wittig homologation on the resulting lactol **14** to gave hydroxy olefin derivative **15** (Scheme 1).

**Scheme 1**



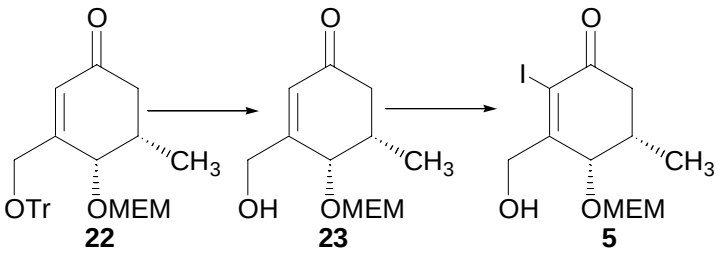

The C-5 hydroxy group in **15** was protected as its MEM-ether and debenzylation was achieved under birch condition to give **17**. Selective protection of primary-OH of **16** as its trityl ether **18**, and subsequent oxidation of the secondary-OH using PDC condition gave keto derivative **19**. The ketone **19** was subjected to Grignard reaction using vinyl magnesium bromide to obtain diolefinic compound **20**, which up on treatment with Grubbs' I$^{st}$ generation catalyst yielded the substituted cyclohexene derivative **21**. Compound **21** was converted to the key cyclohexenone derivative **22** by employing PCC mediated oxidative rearrangement (Scheme 2).

**Scheme 2**




The trityl group of **22** was deprotected by the treatment with HCOOH in ether and the resulting alcohol **23** was subjected to the direct α –iodination by treating with iodine in the presence of pyridine the key intermediate **5**(Scheme 3).

**Scheme 3**



# Chapter I

## Total synthesis of Microcarpalide

# Introduction

## Introduction

Cancer[1] is the ability of some of the cells in a person's body to divide uncontrollably, form a tumor and often spread to other parts of the body through the blood stream. Cancerous cells are often significantly mixed up in their DNA structure. An entire chromosome may be linked with another, broken at odd locations or strands maybe linked together incorrectly. These mutated cells often have many genetic defects. It is these defects that generally lead to uncontrolled cell growth. Over time some cells in one's body, for various reasons (may be age, environment, smoking, probably lots of things), lose the p53 gene. The p53 gene automatically commands cells to die if there is a mutation during the division process. Without the control of the p53 gene these cells are much more susceptible to further mutations later on. Over more time some cells further mutate again and begin producing growth factors such as EGF or PSA. Growth factors are simply small molecules that mutated cells are producing on a regular basis. Over even more time some of the p53 defective cells may further mutate on the Ras gene. These cells are very dangerous as Ras controls whether a cell reacts to a growth signal like EGF or PSA based on other conditions in the cell. Because of the high motility rated involved with this disease it is very much warranted to look for new anti cancer agents, in this regard recently many new chemical entities have been isolated from one of the most abundant species Fungi.

Fungi[2] produce a fascinating range of structurally diverse secondary metabolites, which often possess unusual and sometimes unexpected biological activities. This structural diversity makes these marine natural products excellent molecular probes for the investigation of biochemical pathways. Recently, a number of novel and stereo chemically complex macrolides, having a large macrolactone (22-to 44-membered) ring that interacts with the actin cytoskeleton have been isolated from different fungal and marine sources. Many molecules, which are of fungal as well as marine origin shown promising effect on the disruption of microfilaments of carcinomal cells, which consists mainly a protein actin.

Actin[3], like tubulin, is a major component of the cytoskeleton and has important cellular functions. Although the details of these interactions are still under investigation, these macrolides are becoming increasingly important as novel molecular probes to help elucidate the cellular functions of actin. Owing to their potent anti tumor activities, these compounds,

for example the aplyronines, also have potential for preclinical development in cancer chemotherapy. Their appealing molecular structures, with an abundance of stereochemistry, and biological significance, coupled with the extremely limited availability from the fungal sources, have stimulated enormous interest in the synthesis of these compounds. Actin is one of the two major components of the cytoskeleton in eukaryotic cells.[3] The other major component, tubulin, is more familiar to the chemistry community, primarily due to the success of paclitaxel in the treatment of cancer[4] and the subsequent discovery of a number of other natural products (the epothilones, discodermolide, laulimalide,the eleutherobins, and sarcodictyins) that share paclitaxel's microtubule-stabilizing properties.[5] The actin cytoskeleton plays a critical role in the determination of cell shape, and in a variety of cellular processes, including cell motility, division, adhesion, and intracellular transportation. Actin also interacts with tubulin, although the two-cytoskeleton systems more often operate independently. Very recently, an actin dependent cell cycle checkpoint that ensures the proper orientation of microtubule spindles during metaphase has been uncovered by Gachet and Hyams *et al*[6] Furthermore, certain bacterial and viral (e.g. HIV) pathogens have been found to exploit the actin cytoskeleton during their lifecycle of infection.[7] As a consequence, the implications of the actin cytoskeleton and the release of actin filaments into extracellular space in numerous disease states are now being recognized.[8]

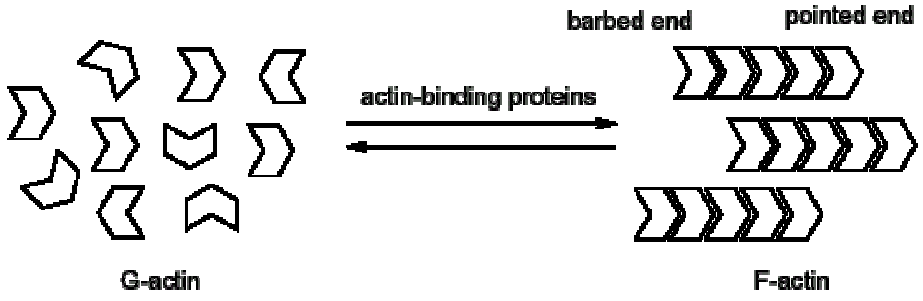
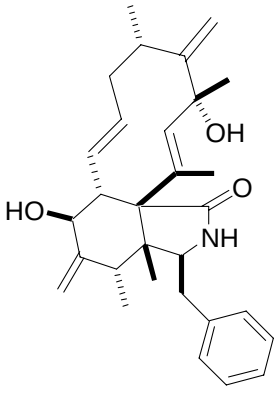



**Figure 1**. A simplified schematic representation

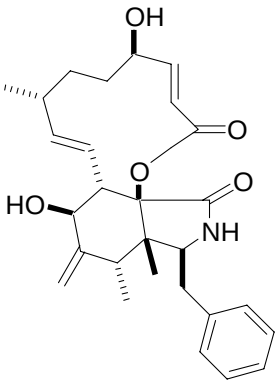
In cells, actin structures are assembled and disassembled constantly in a reversible process. The dynamic polymerization/ depolymerization equilibrium between monomeric soluble globular actin (G-actin; about 43 kDa) and helical filamentous actin (F-actin), and the organization of the three dimensional architecture of actin filaments in response to intracellular and extra cellular stimulations is regulated and performed by a panoply of actin-

binding proteins[9] (e.g.profilin, cofilin, gelsolin, filamin, actinin and Arp2/3 complex) (Figure 1).

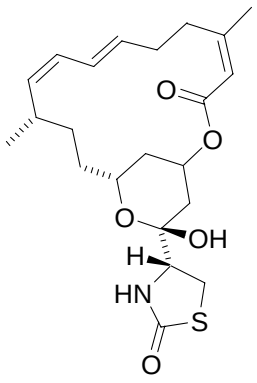
These proteins act through a number of mechanisms, including the sequestering of G-actin, severing of F-actin, control of nucleation, and capping of the barbed or pointed ends of F-actin.[10] G-actin itself is an ATPase and this activity affects the polymerization kinetics. The ATP- and ADP-bound actin monomers dissociate from actin filaments at different rates, and are recognized by different sets of actin binding proteins. Genetic approaches are often used to study the highly complex and dynamic actin cytoskeleton and its associated cellular functions. However, new and versatile molecular probe agents[11] are becoming increasingly valuable in advancing the understanding of actin organization and by unveiling important cellular functions of actin. The fungal secondary metabolites, cytochalasins (e.g. cytochalasin B (**1**) and cytochalasin D (**2**), are the earliest agents that were widely adopted as molecular probes to study the actin cytoskeleton.[12a] However, these agents exhibit nonspecific modes of actions, often complicating experiments performed with them. Latrunculin A (**3**) and latrunculin B (**4**) were the first marine macrolides identified to have well-defined actin-binding properties[12b] These 2-thiazolidinone-containing macrocycles form a 1:1 complex with G-actin, inhibiting its polymerization. They also induce F-actin depolymerization. Latrunculin B (**4**) was used in the seminal work of Gachet and Hyams *et al*[6] that established the very important and previously unknown role of the actin cytoskeleton in spindle orientation.



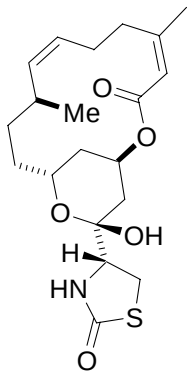
Cytochalasin B (**1**)



Cytochalasin D (**2**)



Latrunculin A (**3**)



Latrunculin B (**4**)

In recent years the secondary metabolites from endophytic fungi have been receiving great deal of attention, because of peculiar structures with specific biological activities. Along this line, microcarpalide[12c] a nonenolide has been recently characterized as a new secondary metabolite produced by an endophytic fungus growing on the bark of *Ficus microcarpa* L. Bio-assay guided purification of fermentation broths using immunofluorescence microscopy to test anticytoskeletal activity led to the isolation of a new substance displaying a remarkable microfilament disrupting activity[12c], which mainly consists of protein called actin, which was first identified in non-muscle cells only about three decades ago, and at about the same time, it was found that actin filaments were disrupted in the malignant transformed cells. The actin network is a rather complex, yet important structural and functional system of all eukaryotic cells. Actin filaments provide the basic infrastructure for maintaining cell morphology and functions such as adhesion, motility, exocytosis, endocytosis, and cell division. Growing evidence from this laboratory and others shows that alterations of actin polymerization, or actin remodeling, plays a pivotal role in regulating the morphologic and phenotypic events of a malignant cell. Actin remodeling is the result of activation of oncogenic actin signaling pathways (e.g., Ras and Src), or inactivation of several important actin-binding proteins that have tumor suppressor functions (e.g., gelsolin). Distinctive protein expression patterns of some of these genes in cancer and progressive carcinogenic processes have been observed. It has become evident that actin dynamics are regulated by a complex interplay of the small GTPase proteins of Ras superfamily Rac, Rho, and Cdc42, and efforts to develop specific inhibitors for these small G proteins as anticancer drug are underway. In the present context similar to the cytochalacins[12a], microcarpalide[12c], which was isolated from the fermentation broths of the un identified endophytic fungus growing on the bark of *Ficus microcarpa* L. was proved to disrupt actin microfilaments in approximately 50% of A-10 cells (from rat smooth muscles) at a concentration of 0.5 μg $mL^{-1}$, by binding to the (+) end of the F-actin and prevents the subunit addition. Depolymeriztion at the (-) end led to the loss of the filament, moreover, it displayed a weak cytotoxicity in mammalian cells, thus making at the attractive tool for studying cell motility and cell metastasis, and a potential tool for the development of anti-cancer drugs.[12c]

**Medium ring compounds in general**

Medium ring compounds (those having a ring size in the range (8 to 11)[13] are becoming increasingly important in organic chemistry, as they are contained in an ever-growing number of natural products. Hydrocarbons, as well as heterocyclic compounds (ethers, lactones, amines, amides) have been isolated, and a number of reviews have already been published.[14] These compounds have specific characteristics which had been recognized by at the beginning of this century,[15] and it was soon observed that they were much more difficult to synthesize by cyclization methods than other cyclic compounds including macrocyclic compounds (ring sizes >12). These difficulties are caused by the fact that the formation of these cyclic compounds are disfavoured by entropy as well as enthalpy[15] (vide infra). The entropic factor is disfavoured by the carbon chain becoming too long, and thus the probability of a reaction taking place between the two chain termini decreases. The enthalpic factor is mainly created by steric interactions. There are three different interactions:

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

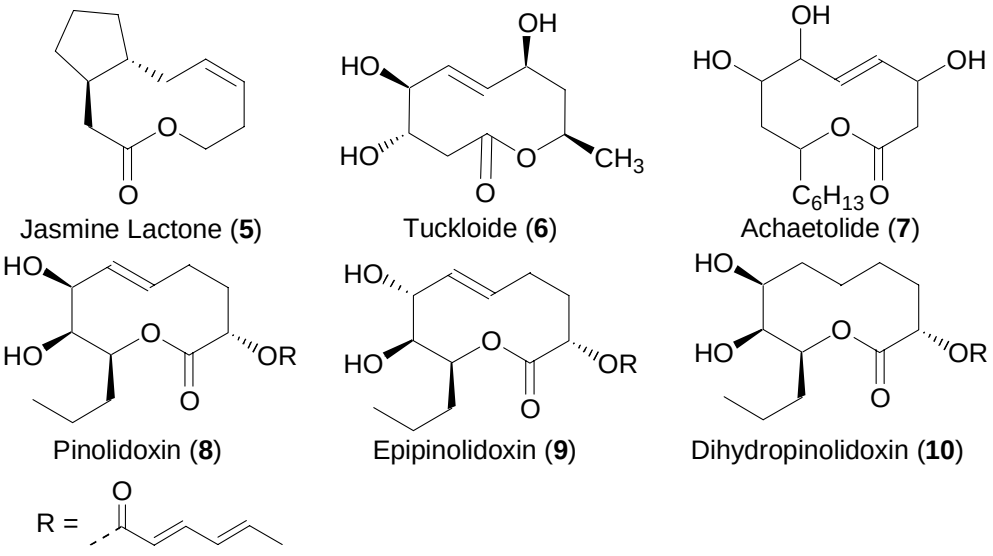
The pioneering work of Hunsdiecker and Erlbach reported the yields obtained in the reaction of ω-bromo alkanoic acids with potassium carbonate to give the corresponding lactones.[16] Good yields were observed in the preparation of five- to eight- and twelve- to eighteen-membered ring lactones. The yield of the nine-membered ring lactone was almost zero. This work was subsequently reinvestigated and developed by the Illuminati group.[17] They measured with great precision the rate of lactone formation in the ring sizes 3 to 23 by reaction of ω-bromoalkanoic acids with a base (KOH or diisopropylethylamine) in 21% aqueous DMSO. A maximum rate of cyclisation was observed for the formation of γ-butyrolactone and then the rate decreased dramatically to the 8-membered ring lactone, which was formed more than 106 times less rapidly than the 5-membered ring lactone. A slow increase of the cyclisation rate was then observed, the cyclisation rate constant of the 18-membered ring lactone being close to that of the intermolecular reaction rate constant (formation of esters). From a synthetic point of view, these constant rate values mean that

good yields (intramolecular reactions) should be obtained for the formation of 3- to 7- and 13- to 18-membered ring lactones, while polymerization (intermolecular reactions) should be the major pathway for 8- to 12-atom chains.[18]

In medium ring lactones, stereoelectronic factors can, however decrease the strain energy slightly. Lactones can exist in Z (or *syn)* and *E* (or *anti)* forms. The *syn* form is in general more stable than the *anti* form (2-8 kcal/mole). For lactones with a ring sizes of at least 7 the rings are forced into the disfavored *anti* conformation. In 8- and 9-membered ring lactones, an equilibrium *syn anti* conformation was observed, while in 10- and 11-membered ring lactones (and macrolactones), the *syn* form is normal.[19]

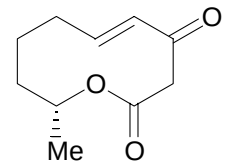
**Naturally occuring medium ring lactones: 10-membered ring lactones (2-oxecanones)**

Natural products containing a medium ring lactone framework are found in plants, insects (pheromones) and bacteria (antibiotics); they can have a terrestrial, fungal or a marine origin. In the present context the emphasis was made only on 10-membered lactones. The oldest natural product possessing an oxecan-2-one framework would appear to be the jasmine ketolactone (**5**), a component of the essential oil of *Jasminum grandiflorium* isolated in 1942,[20] whose structure was confirmed twenty years later.[21]

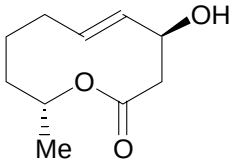


More recently, tuckolide (**6**) was isolated as metabolite of the Canadian tuckahoe, the sclerotium of *Polyporus tuberaster,* a subterranean fungus.[22] Achaetolide (**7**), a compound with a very similar structure, was also isolated from the fungus, *Achaetomium cristalliferum*.[23a] Pinolidoxin (**8**), a phytotoxin (anthraenose of pea) was produced by the fungus *Aschochyta pinodes.*[23b] Subsequently, three new metabolites of this fungus were found: epi-(**9**),and dihydropinolidoxins (**10**).[23c]

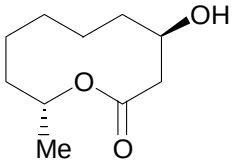
Diplodialides A, B, C and D (**11-14**), the metabolites of the phytopathogenic fungus *Diplodia pinea,* have more simple structures than pinolidoxine derivatives.[24] Diplodialide A (**11**) has been reported to be a steroid hydroxylase inhibitor. Another phytopathogenic fungus, *Pyrenophora teres,* produces metabolites, pyrenolides A, B and C (**15-17**), which have similar structures to the diplodialides.[25a] These compounds show inhibitory activity against fungi.[25b]



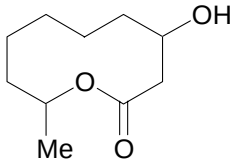
Diplodialide A (**11**)



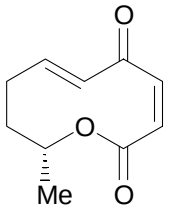
DiplodialideB (**12**)



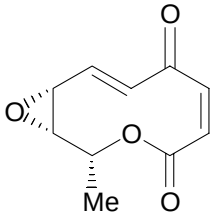
Diplodialide C (**13**)



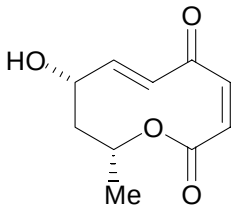
Diplodialide D (**14**)



Pyrenolide A (**15**)

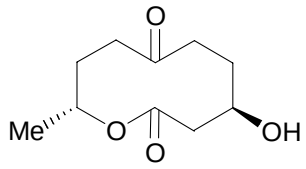


Pyrenolide B (**16**)

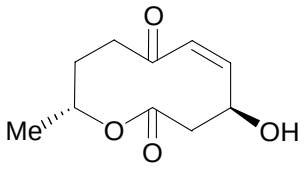


Pyrenolide C (**17**)

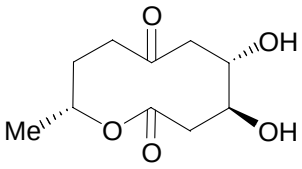
Two other similar structures, cephalosporolides B and C (**19-20**), are metabolites of the fungus *Cephalosporium aphidicola.*[26a] Another interesting metabolite, thiobiscephalosporolide A (**21**), was isolated during the fermentation of *Cephalosporium a.* and found to be a dimeric 10-membered ring lactone.[26b] On degradation, it led to a compound which is a regioisomer of diplodialide D (**14**). The biogenesis of these different compounds has been discussed recently.[26c]



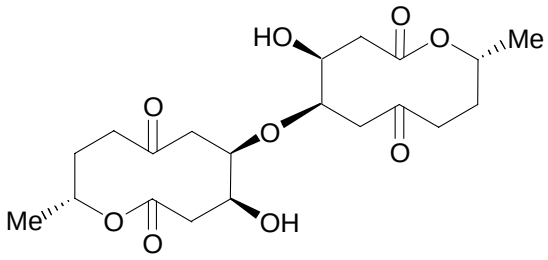

Cephalosporolide A (**18**)




Cephalosporolide B (**19**)

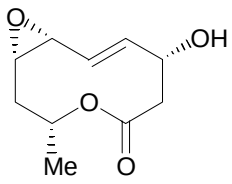



Cephalosporolide C (**20**)

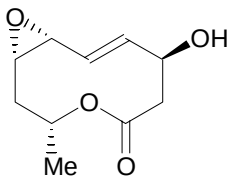



Thiobiscephalosporolide A (**21**)

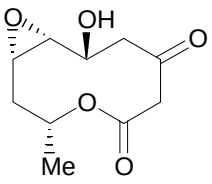
Various oxygenated oxecan-2-ones, decarestrictines A-J (**22-33**), were formed during the fermentation of *Penicillium simplicissimum*.[27] These compounds show important inhibitory effects on cholesterol biosynthesis.[28] Decarestritine D (**27**) is identical to tuckolide, and its isolation was published simultaneously.[22]



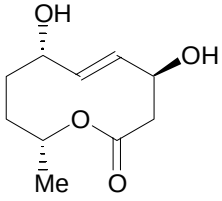

$A_1$ (**22**)



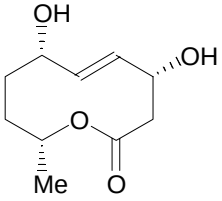

$A_2$ (**23**)



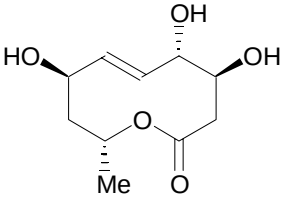

B (**24**)



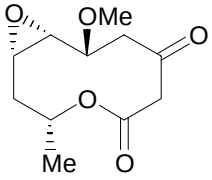

$C_1$ (**25**)



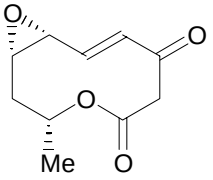

$C_2$ (**26**)



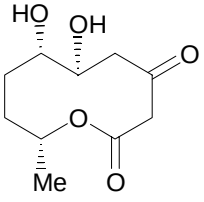

D (**27**)



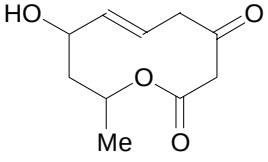

E (**28**)



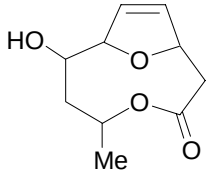

F (**29**)



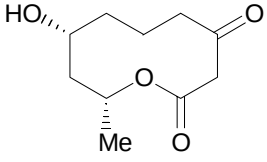

G (**30**)




H (**31**)

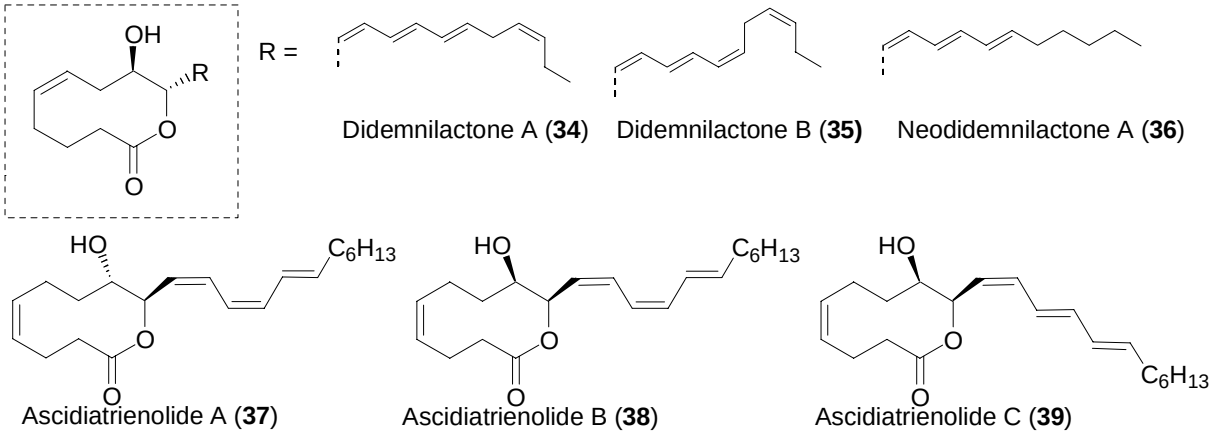



I (**32**)

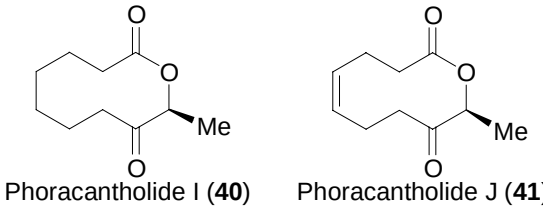



J (**33**)

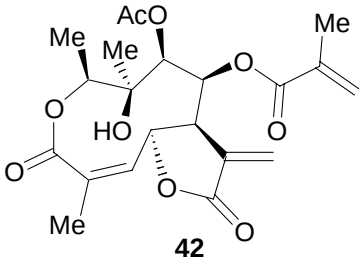
Metabolites of *Didenmum moseleyi* (Herdman), a tunicate living in the sea in Japan, didemnilactones A and B (**34, 35**), and neodidemnilactone, were also found to be 10-membered ring lactones.[29] These compounds exhibit weak binding activity to leukotriene $B_4$ receptors in human polymorphonuclear leukocyte membrane fractions. Ascidiatrienolides A, B, and C,[30a] (**37-39**) whose structures were recently reinvestigated,[30b] were found in marine ascidian *(Didemnum candidum)* and corresponded to oxidation products of C20 fatty acid.



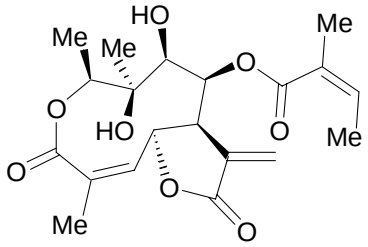

The metastemal gland secretion of the common eucalypt longicom, *Phoracantha semipunctata* contains two lactones as major components, phoracantholide I (**40**) and phoracantholide J (**41**).[31]



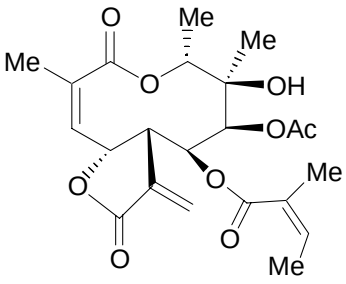

Much more complex lactones have been also isolated. Trichlogoniolide lactones (**42-45**) were also observed among the metabolites isolated in the aerial parts of *Trichogonia* species *(vide supra)*.[32]



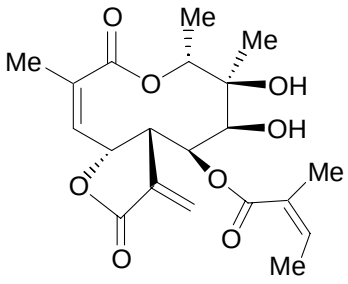

**42**




**43**

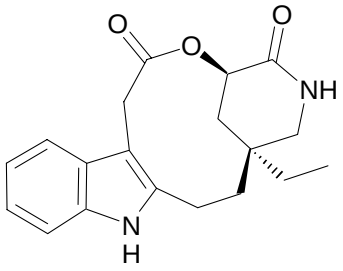



**44**

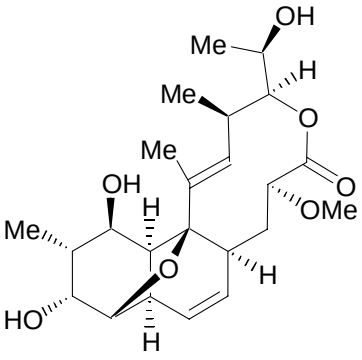



**45**

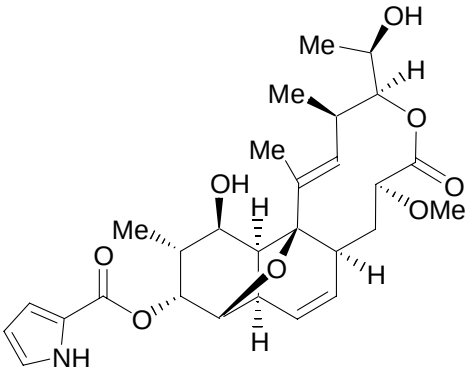
A new alkaloid, aspidochibine (**46**), was isolated from the bark of the tree, *Aspidosperma quebracho blanco* Schlecht, which is used for the treatment of bronchial asthma and dyspnoe in South America.[33] Nargenicin A[1](**48**)[34] and nodusmicin (**47**)[35] are antibiotics produced by *Nocardia argentinensis* and *Saccharopolyspora hirsuta* respectively. Their biosynthesis was recently investigated.[36] 18-Deoxynargenicin $A_1$ was prepared, and showed more potent activity against *streptococci* than Nargenicin $A_1$.[37]




Aspidochibine (**46**)

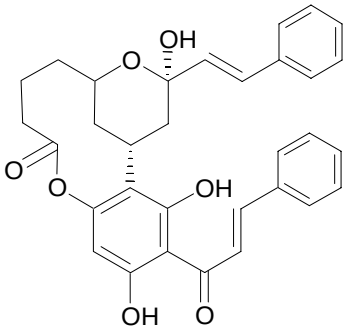



Nodusmicin (**47**)

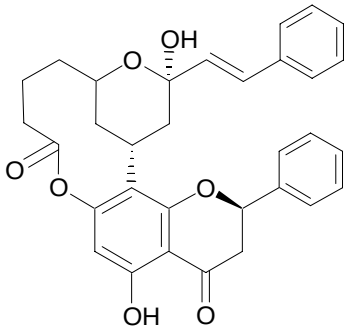



Nargenicin $A_1$ (**48**)

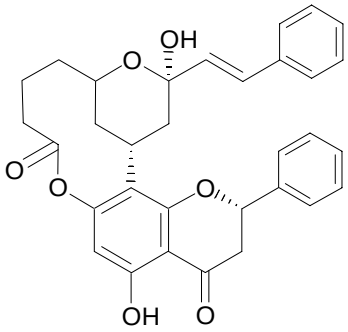
Four flavanones, kurziflavolactones A, B, C and D, (**50-53**) and a chalcone, kurzichalcolactone, have been found recently in the leaves of a Malaysian plant, *Cryptocarya kurzeii* (Lauracae) and have a weak cytotoxicity against KB cells.[38]



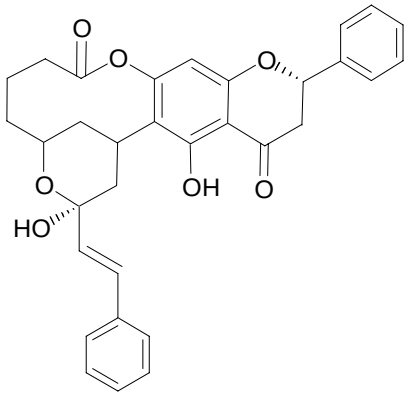

Kurzichalcolactone (**49**)



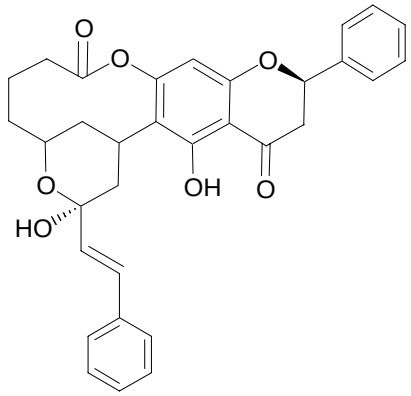

Kurziflavolactone A (**50**)




Kurziflavolactone B (**51**)

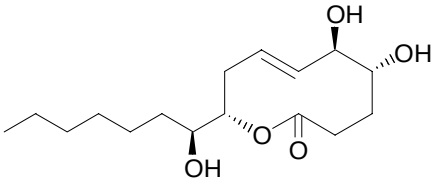



Kurziflavolactone C (**52**)

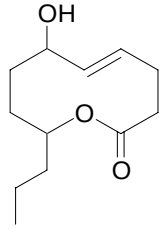



Kurziflavolactone D (**53**)

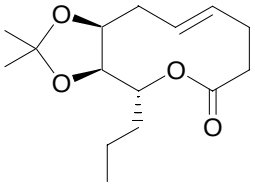
Microcarpalide[12c] (**54**) represents novel alkyl-substituted nonenolide structurally related to a family of phytotoxins such as achaetolide[23a] (**7**), pinolidoxin[23b] (**8**), putaminotoxins[39a] (**55**) and herbarumins[39b] (**56**), from which it differs in the hydroxylation pattern and the double bond position within the 10-membered lactones, as well as in the length of the side chain at C-10.




Microcarpalide (**54**)




Putaminoxin (**55**)



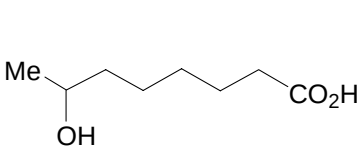

Herbarumin (**56**)

**Preparation of medium ring lactones**

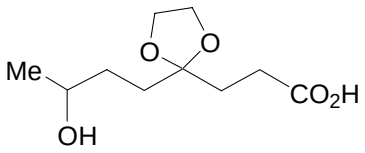
**Lactonisation of ω-hydroxyalkanoic acids: Direct cyclisation**

A number of reviews have been published on the subject of cyclisation methods and the synthesis of macrolides. However, only a few containing information about medium ring lactones are available.[40] The first attempt to prepare medium ring lactones by cyclisation of ω-hydroxyalkanoic acids was reported by Stoll and Rouvé.[41] They showed that of oligomer was the major product and the yields of monolide were very low (for example 1% for the formation of nonanolide). An attempts to improve the yield by using boron trifluoride etherate in the presence of un functionalized polystyrene beads as catalyst was not successful.[42] Stoll and Rouvé's procedure was, however applied successfully to the synthesis of phoracantholide I **40** (60%yield).[43]

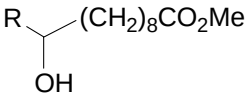
The cyclisation of ω-hydroxyalkanoic acids and alkanoates by means of enzyme-catalysed lactonisations has also been studied. No reaction was observed between hydroxy acid **58** and the lipase of *Pseudomonas sp.,* while hydroxy acid **59** led to a mixture of two diastereoisomeric diolides.[44a] Similarly, lactonisation of ω-hydroxydecanoic acid was studied with different lipases, and only a mixture of di-, tri-, tetra-and pentanolides was obtained, and macrolactones could also be formed.[44b]




**58**




**59**




**60**

Lactonisation of racemic methyl 10-hydroxyundecanoate (**60**: R = $CH_3$) with the lipase of *Pseudomonas* sp was reported to give a mixture of mono- and diolide.[45a] Recently, this study was reinvestigated with PPL as lipase. With methyl 10-hydroxydecanoate (**60**: R = H), di- and triolides were the major products, while with methyl 10-hydroxyundecanoate (**60**: R = Me) the monolide was the major product. With 10-hydroxydodecanoate (**60**: R = Et), the tendency to favour of the monolide becomes more marked (the ratio was 81:19 in favor of the monolide), although the reactivity of the substrate was very low.[45b] Using vinyl esters did not give much better results. With vinyl 10-hydroxyundekanoate, only 11% of the corresponding (*R*)-8-membered ring lactone was formed. For the other ring sizes, no monolides were seen.[45c]

***Activation methods***

The activation methods of ω-hydroxy acids that have been developed to synthesize macrolactones have already been reviewed.[40] This section will focus on results obtained in the lactonisation of 8-hydroxyoctanoic acid (as an example) using some of these methods (see Table 1).

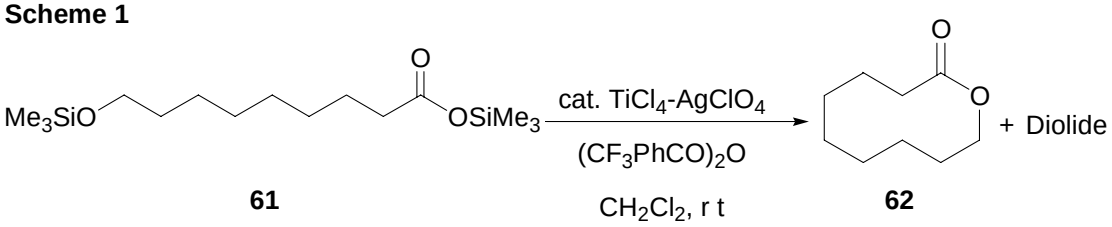
Table 1

| Method | Ref. | Yield in nonalactone (diolide) (%) |
|---|---|---|
| Corey | 85 | 8a (41) |
| Mitsunobu | 86 | 0.8 (70) |
| Mukaiyama | 87 | 13 (34) |
| Steliou | 88 | 0 (36) |
| Yamaguchi | 90 | 18 (41) |

In all cases, unsatisfactory yields of nonanolide were observed; comparable results should be obtained for other medium-ring lactone sizes. In a recent study, Bartra and Vilarrasa[46] have reinvestigated different activation methods for the cyclisation of 9-hydroxydecanoic acid to give phoracantholide I (**40**) using the same reaction conditions. The best results were observed using the method developed by Gerlach[47] (50% yield), while very low yields were obtained using some of the methods reported in Table 3. However, in their review, Batra and Vilarrasa[56d] have collected examples, which show that the cyclization leading to natural products can occur if a double bond is present in the carbon chain.

Recently, Mukaiyama and coworkers[48] have reported a new activation method based on the lactonisation of silyl ω-siloxyalkanoate using p-trifluoromethylbenzoic anhydride and a catalytic amount of a mixture of $TiCI_4$ and $AgC1O_4$. In the specific case of medium ring lactones, low yields were obtained (0% for the 8 and 9-membered ring lactones; 33% for the decanolide) except for the formation of the undecanolide (70%).

**Scheme 1**

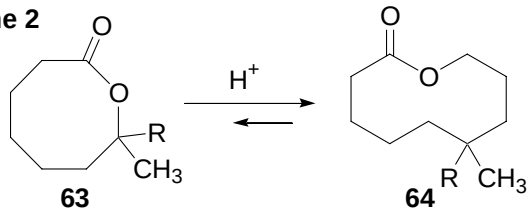



**61** **62**

***Translactonisation method***

In this method, first introduced by Corey and coworkers,[49] a hydroxy lactone is subjected to the action of a catalytic amount of acid to give a thermodynamically more stable hydroxylactone.

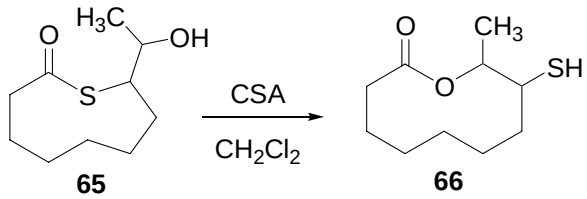
**Scheme 2**




**63** **64**

Since medium ring lactones are less stable than other lactones, it should be*, a priori,* difficult to obtain medium ring lactones by this technique. Corey showed that an 8-membered ring lactone can be transformed to a 11-membered ring lactone. In a subsequent work, Vedejs and coworkers[50] have shown that, starting with thiolactones, such an isomerisation can indeed take place. For example, a seven-membered ring thiolactone was transformed in good yield to a 8-membered ring lactone (70% yield) even though equilibrium between these two lactones was observed.

**Scheme 3**




**65** **66**

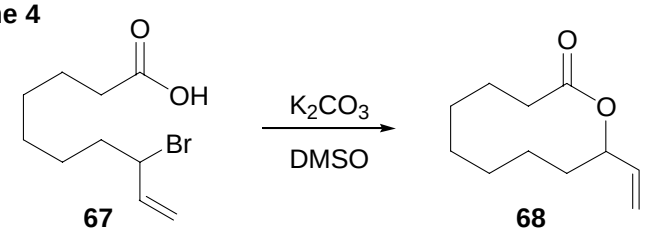
The transformation 6→8 was much less favourable (20% yield) and diolide was obtained (30%). The transformations 9→10 and 10→11 were accomplished in high yields (70 - 91%). The former reaction was applied to the preparation of phoracantholide I **40**.[50]

Isomerisation of 7-membered ring lactone to a 10-membered ring lactone was observed by Corey during the synthesis of erythronolides,[51] and transformation of macrolides to 10 and 11-membered ring lactones were also described.[52] These examples are, however specific, and can probably be explained by strain relief favoured by the conformations of the resulting medium ring lactones.

***Cyclisation of ω-haloalkanoic acids and related compounds***

The cyclisation of ω-haloalkanoic acids induced by a base such as $K_2CO_3$ or NaOH is one of the oldest methods available for the preparation of medium ring lactones. Hunsdiecker reported the formation 10-and 11-membered ring lactones in good yields by the reaction of the corresponding bromoalkanoic acids with potassium carbonate.[16] The kinetic study of Illuminati and coworkers showed the limitation of this method and the necessity of high dilution conditions if medium ring lactones are to be formed in satisfactory yields *(videsupra),*[17] These chemists also examined the kinetic influence on the cyclization of a *gem-dimethyl* substituent fixed in the 3-position of the carbon chain. Formation of 3,3-dimethyl nonanolactone occurred.6 times faster than nonanolactone; however, in the other ring sizes examined (10 and 11), no such effect was observed,[53a] Using the optimal cyclisation conditions necessary for the synthesis of 11-undecanolide described by Galli and Mandolini[53b] (reaction at 100 °C in DMSO in the presence of $K_2CO_3$), Cameron and Knight obtained an 11-membered ring lactone in 60% yield.[53c]

**Scheme 4**



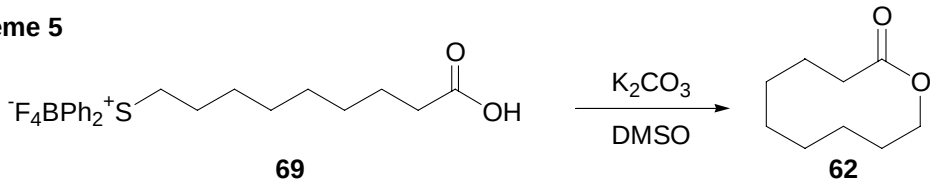

**67** **68**

Kellog reported that ω-halo acids led, when treated with caesium carbonate, to macrolides in good yields.[54a] For 8- to 10-membered ring lactones, this cyclization did not work as diolides were formed and only the undecalactone was obtained in 23% yield. However employing *O*-methanesulfonyl derivatives in this cyclisation was found to be favourable, and 10- and 11-membered ring lactones were obtained in approximately 50%

yields.[54b] The superiority of *O*-methanesulfonyl derivatives was also recognised by Vedejs in the syntheses of fulvine,[55] crispatine,[55] and monocrotaline.[56]

Another possible improvement was proposed by Matsuyama and coworkers[57] who studied the cyclisation of sulfonium salts. For macrolides, the replacement of bromide (X = Br) by a sulfonium salt (X = $^{+}SPh_2$, $BF4^{-}$) led to improved yields.

**Scheme 5**

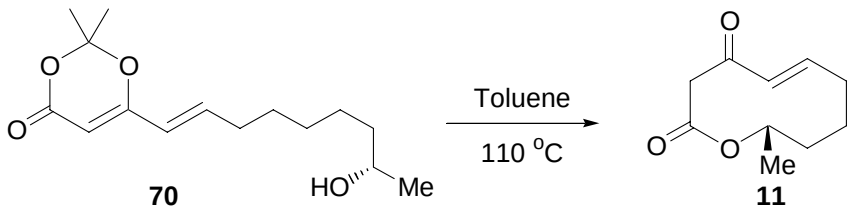



**69** **62**

***Intramolecular alcohol-ketene reactions***

It would appear that the activation of an acid generates under some conditions, a ketene which then reacts intramolecularly with a free alcohol to give the lactone. This was demonstrated in the Mukaiyama method by Funk and coworkers.[58] However as has already been shown, the efficiency of this approach is not obvious for the preparation of medium ring lactones. Two research groups have shown independently that the thermal generation of ketches from dioxolenones is much more efficient. Boeckman obtained (+)-diplodialide A (**11**) in 68% yield using this method.[59]

**Scheme 6**

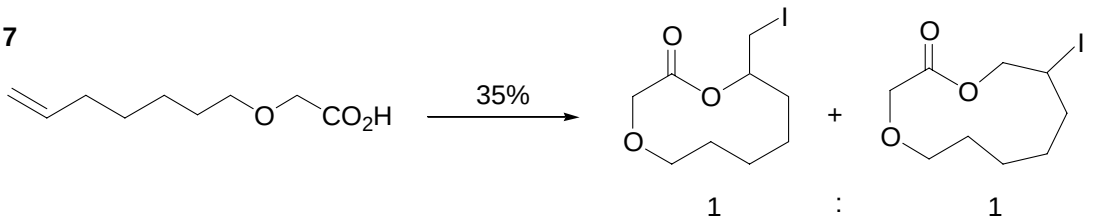



**70** **11**

***Electrophilic heteroatom cyclisations***

Electrophilic heteroatom cyclisations have been widely used in organic synthesis, most common electrophilic reagents are $I_2$, $Br_2$, PhSeC1, $Hg(OAc)_2$, $Pd(OAc)_2$, bis(sym-collidine)iodine(I) hexafluorophosphate[60] and $AgNO_3$.

**Scheme 7**



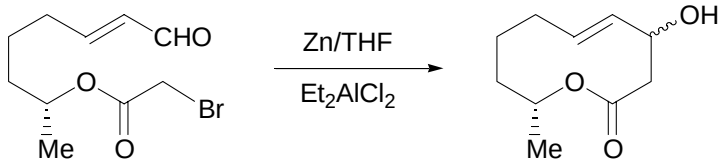

**71** **72** **73**

**<u>Cyclisation via carbon-carbon formation</u>**

**(i)** ***Electrophile-induced cyclisation***

Intramolecular Reformatsky reaction promoted by $Et_2A1C1$ was found to induce the ring closure and give an unsaturated 10-membered ring lactone, of which one diastereoisomer was diplodialide A[61a] (**11**).

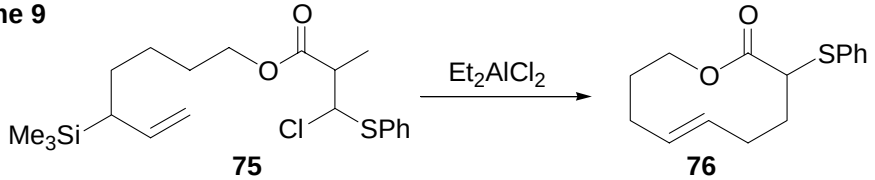
**Scheme 8**




**74** **11**

Intramolecular additions of allylsilanes to α-chlorosulfides promoted by $EtA1C1_2$ furnished, in moderate yields, 8- to 11-membered ring lactones.[61b] A formal synthesis of phoracantholide I (**40**) was also reported (42% yield for the cyclisation step).

**Scheme 9**

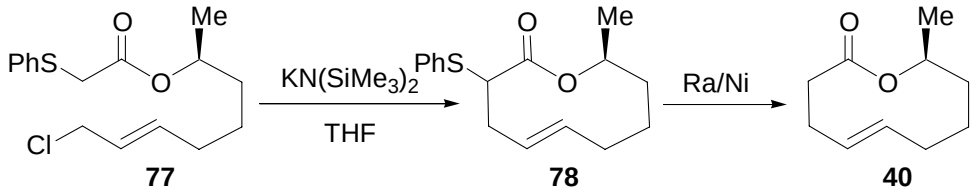



**75** **76**

**(ii)** ***Nucleophile-induced cyclisation***

Tsuji and coworkers have shown that lactone formation could take place by carbon-carbon bond formation via the intramolecular alkylation of a carbanion generated from phenylthioacetate.[62a] This strategy was applied to the preparation of a ten-membered ring lactone, which could be transformed into phoracantholide I (**40**).

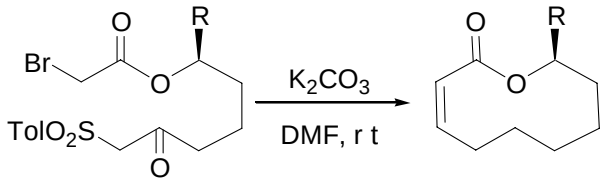
**Scheme 10**




**77** **78** **40**

A very similar method was employed by Lygo and O'Connor who studied the intramolecular cyclisation of 13-ketosulphone anions with bromoacetates. Moderate yields were obtained for 8 to10-membered ring lactones.[62b]

**Scheme 11**



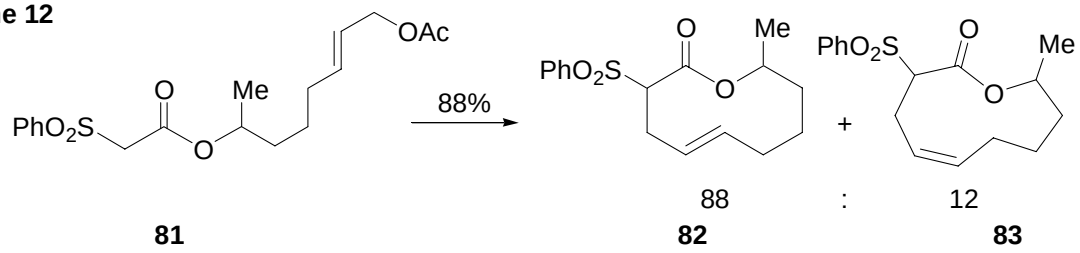

**79** **80**

## Metal-induced Coupling Reactions

***Palladium-induced reactions***

Work in this field was pioneered by Trost who observed that stabilized anions react intramolecularly with acylic acetates in the presence of $Pd(PPh_3)_4$ and 1,2-diphenylphosphinoethane to give medium ring lactones.[63a] Examples are given below. Interestingly, the higher ring size lactones were always the only or major products. In cases where either a *cis* or *trans* double bond could be formed, the trans (*E*) was always the major. Cyclisation of ethyl carbonates instead of acetates was reported to give improved yields.[63b]

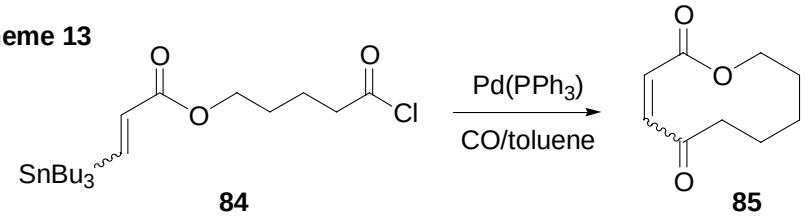
**Scheme 12**




**81** **82** **83**

Recently, Baldwin and coworkers reported the intramolecular Pd(0)-catalysed coupling of acid chloride and β-stannylalkenoate in the presence of CO as a new route to 10-20-membered ring lactones. For the medium lactones, low yields were observed.[63c]

**Scheme 13**



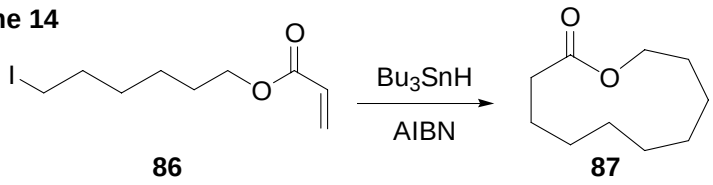

**84** **85**

## Radical-induced cyclisations

### *Chemical generation*

Porter reported that treatment of 10-iodoalkyl acrylate with tributyltin hydride and AIBN in benzene led to the formation of a 11-membered ring lactone in low yield (15-25%).[64a]

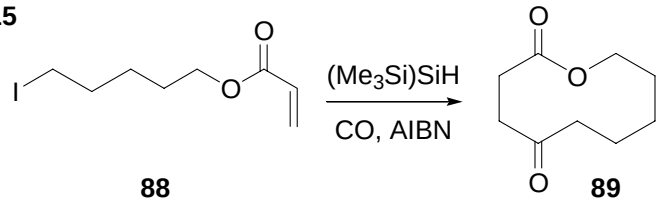
**Scheme 14**




**86** **87**

The yields of this cyclisation was subsequently improved (77-95%) and extended to the 10-membered ring lactone, by modification of the reaction procedure. [64b] However, the corresponding propiolate could not be used.[65a] When these substrates were treated with tris(trimethylsilyl)silane and AIBN under 30 atmospheres of CO γ-ketolactones were formed. This reaction was applied to the preparation of 10- to 17-membered ring lactones.[65b]

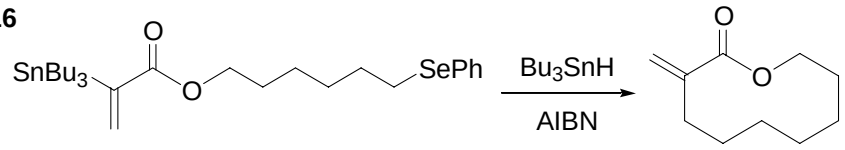
**Scheme 15**




**88** **89**

Baldwin showed that (ω-phenylselenoalkyl α-tributyltinacrylates also lead to 10- and 11-membered ring lactones when treated with tributyltin hydride and AIBN. This cyclisation did not work for the smaller medium ring lactones.[65c]

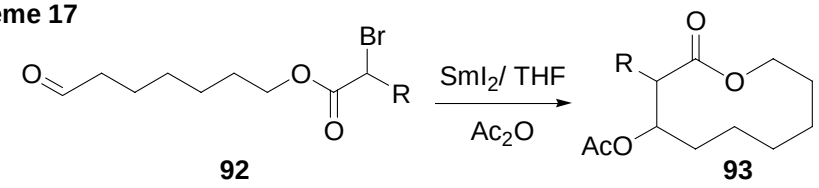
**Scheme 16**




**90** **91**

Finally, the cyclisation of ω-oxoalkenyl α-bromoalkanoates induced by $SmI_2$ has been reported to lead in high yields (76-92%) to 9-11-membered ring lactones.[66a] Macrolides were also formed with the same efficiency. This method was applied to the preparation of ferrulactone .[66b]

**Scheme 17**



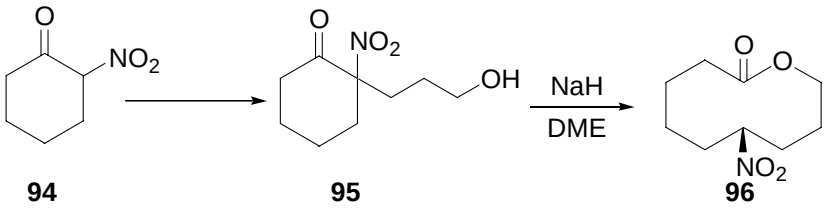

**92** **93**

## Ring Expansion Methods

### *Hesse-Cookson approach*

In this strategy, the chain bearing the alcohol is on the same carbon as the electron with drawing group. It was soon determined[67] that the best electron withdrawing group for this reaction was $NO_2$. Cookson[67b] and Hesse[68] reported their results simultaneously. Cookson showed that this method could be applied to the preparation of 10- and 11-membered ring lactones with excellent yields (76-78%), while Hesse applied this approach to the synthesis of phoracantholide I (**40**).

**Scheme 18**



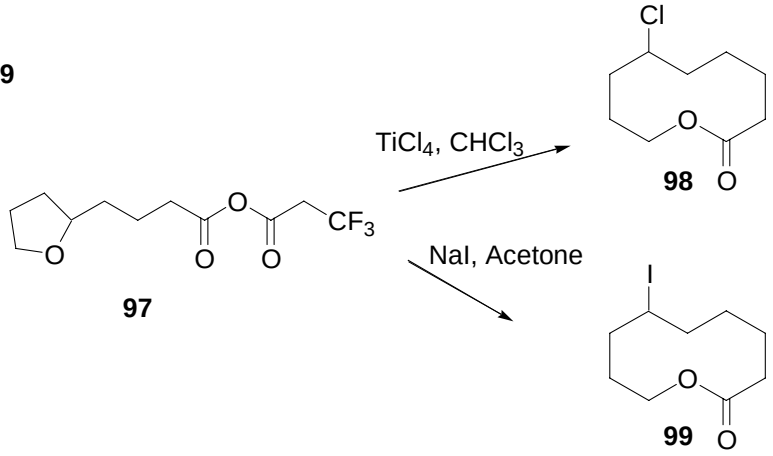

**94** **95** **96**

## Heterocycle-ring expansion

### *Oxa compound rearrangement*

Recently, Grayson and Roycroft reported that reaction of 5-(tetrahydro-2-furyl)pentanoic tdfluoroacefic anhydride with a Lewis acid ($TiCl_4$) or NaI in acetone leads to the formation of halolactones.[69]

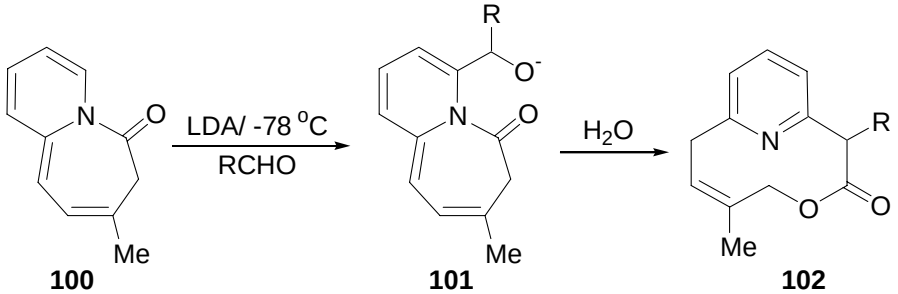
**Scheme 19**




### *Lactam rearrangement*

Eberbach and coworkers found that the carbanion formed from pyrido[1,2a] azepinone reacts with aldehydes and gives by ring expansion, 10-membered ring lactones.[70]

**Scheme 21**

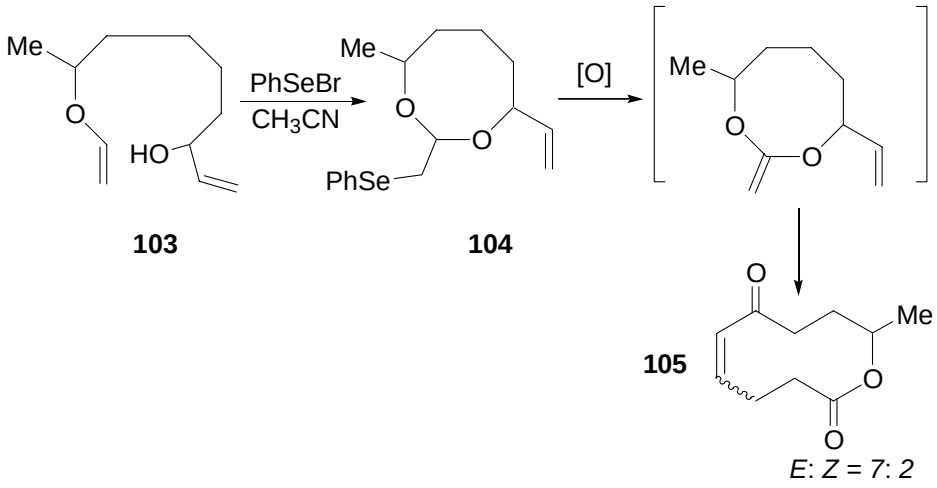


## Thermal reactions

### *[3,3] Sigmatropic rearrangement*

An interesting 10-membered ring lactone synthesis was reported by Petrzilka, based on a Claisen rearrangement.[71a] The desired cyclic intermediate was formed by an unusual phenylselenoetherification. The [3.3] sigmatropic rearrangement of allylic thiocarbonate to medium ring thiocarbonate has been studied extensively by Kurihara and coworkers. Highly stereoselective formation of medium ring compounds was observed, leading to an E or Z carbon-carbon double bond, depending on the ring size.[71b]

**Scheme 22**



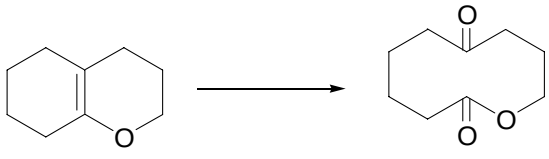

**103** **104** **105**

*E*: *Z* = *7*: *2*

### *Activated carbon-carbon double bond*

This reaction was first investigated by Borowitz, who showed that it is general for the formation of 10-and 11-membered ring lactones.[72] The mixture of ruthenium tetraoxide-sodium metaperiodate[73a] and Corey's reagents, PCC, and PDC,[73b] were also found to be effective for this oxidative cleavage; Corey's reagents seem, however, to give better yields.

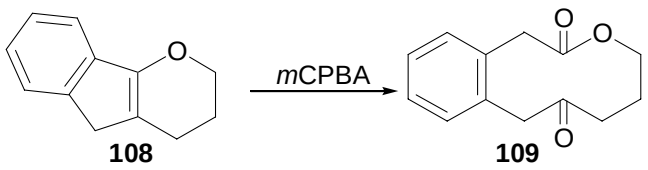
**Scheme 23**




**106** **107**

*meta*-Chloroperbenzoic acid was the reagent of choice for this cleavage, although ozone could be also used.[72d] Benzo-medium ring lactones have been prepared in good yields using this procedure.[74a]

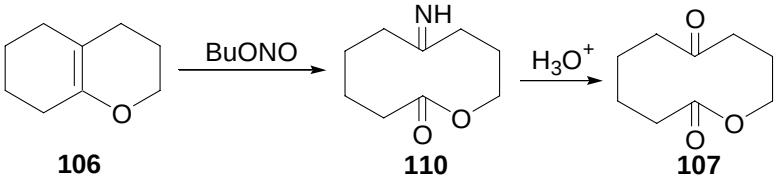
**Scheme 25**




**108** **109**

Mahajan showed some years later that n-butylnitrite was an excellent alternative reagent for this cleavage.[74b]

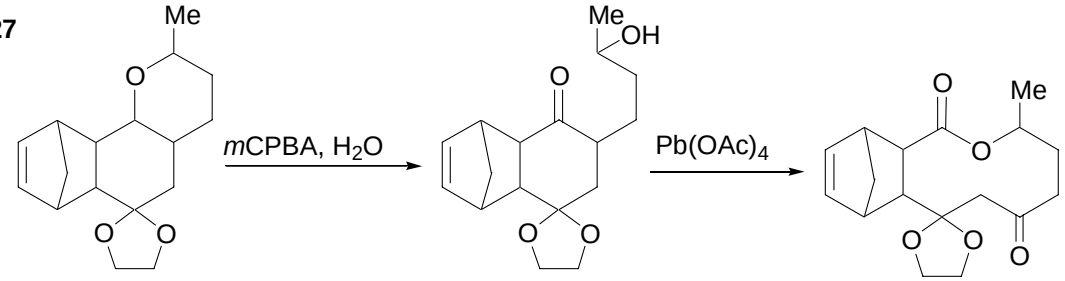
**Scheme 26**




**106** **110** **107**

In the synthesis of pyrenolide B (**16**), a Japanese group found that it was not possible to cleave a bicyclic enol ether in satisfactory yield. Instead it was opened to give an α-hydroxyketone which, after reaction with lead tetraacetate, gave the desired 10-membered ring lactone in 65% yield.[75a]

**Scheme 27**

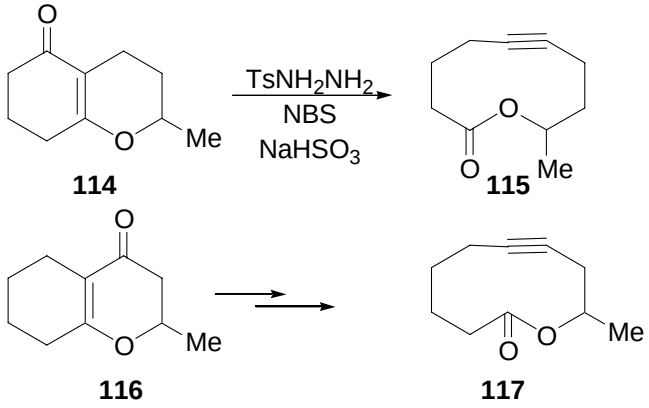



**111** **112** **113**

***Fragmentation reactions***

Mahajan reported recently that the fragmentation of keto enol ethers leads to 9- and 10-membered ring acetylenic lactones.[75b]

**Scheme 28**

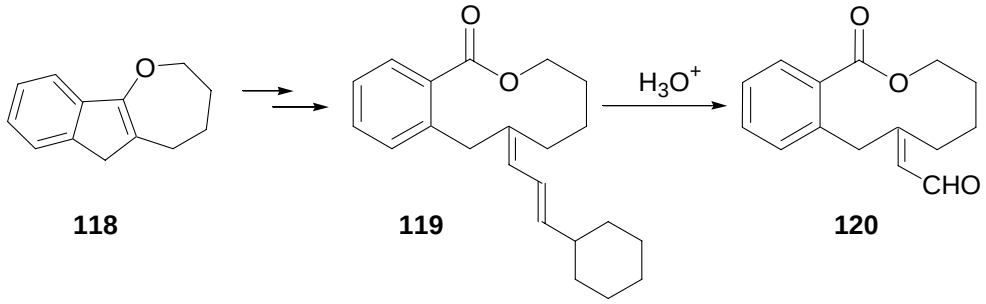



**114** **115** **116** **117**

***1,2-Oxazine cleavage***

Shatzmiller and coworkers reported that cyclic enol ethers react with α-chloronitrone to give an adduct which, after reaction with potassium carbonate and heating, give to medium ring lactones in excellent yields.[76]

**Scheme 29**



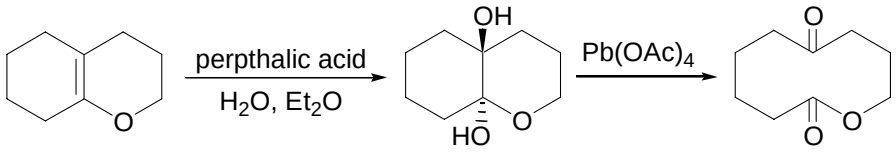

**118** **119** **120**

**<u>Cleavage of saturated bicyclic compounds</u>**

***Ionic cleavage of bicyclic hemiketals***

The first approach using this method was published by Borowitz, who reported the cleavage of a bicyclic *trans* 1,2-diol with lead tetra acetate[77a]

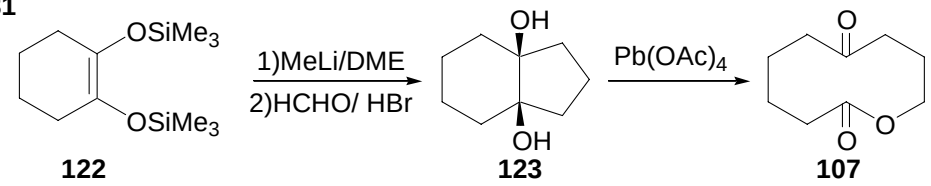
**Scheme 30**




**106** **121** **107**

Wakamatsu and coworkers showed that bicyclic *cis* 1,2-diols, formed by alkylation of 1,2-enediolates with m-bromo-l-alkanols, can also undergo to the same fragmentation.[77b] The application of this to the synthesis of diplodialides A and C (**11**, **13**) was reported.[77c]

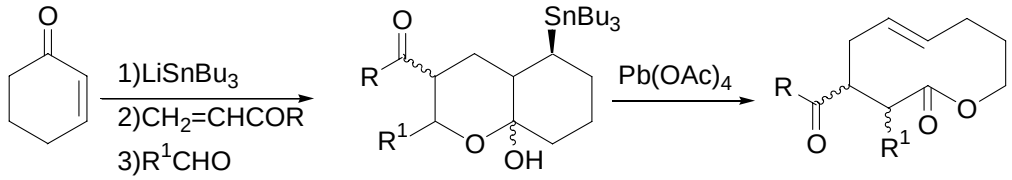
**Scheme 31**




**122** **123** **107**

Posner used the same strategy to cleave bicyclic hemiketals, which were formed by sequential Michael reaction of enals or enones. Application of the reaction to the preparation of phoracantholide (**40**) was reported.[78]

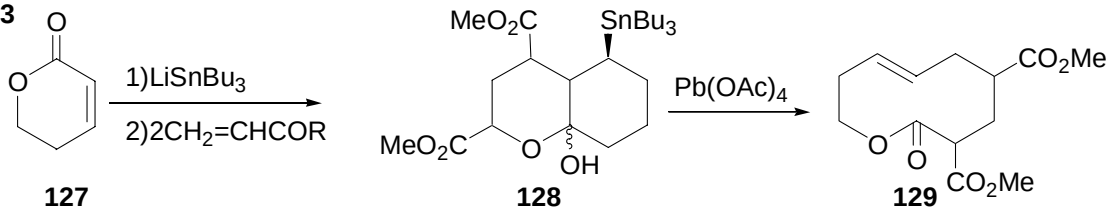
**Scheme 32**




**124** **125** **126**

The same sequential Michael addition and cleavage were also performed using methyl acrylate.[79]

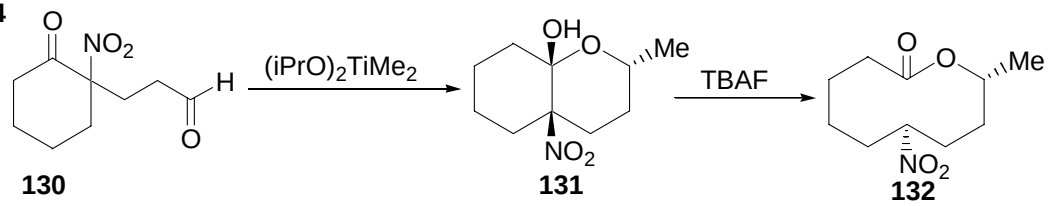
**Scheme 33**




**127** **128** **129**

The anionic cleavage of hemiketals was also successfully investigated; however, the presence of an anion-stabilising group appears to be necessary. Mahajan used a keto group,[80] and Hess a nitro group.[81]

**Scheme 34**

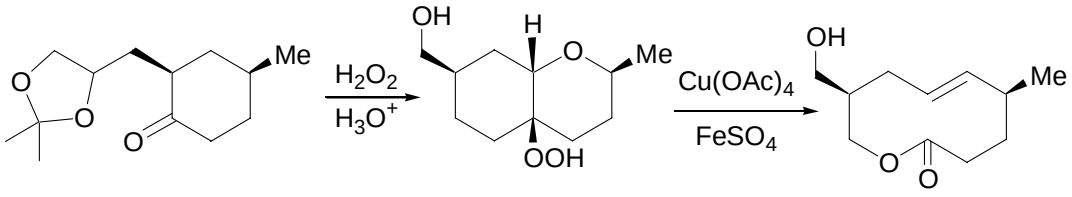



**130** **131** **132**

***Radical cleavage of bicyclic hemiketals***

Schreiber and coworkers have reported the preparation of perhemiacetals which, when treated with a mixture of $FeSO_4$ and $Cu(OAc)_2$, give the corresponding lactones.[82]

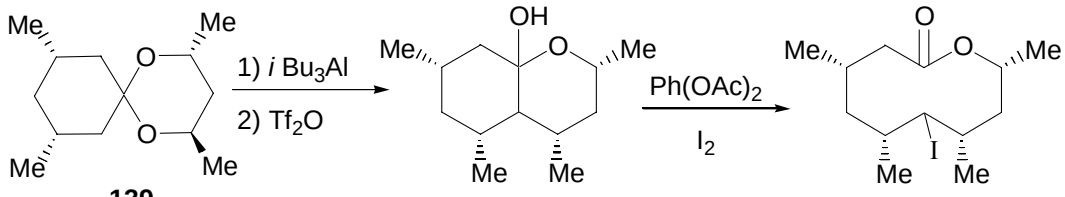
**Scheme 35**




**133** **134** **135**

When this cleavage was applied to manool derivatives, bicyclic 10-membered ring lactones resulted.[83] Using this procedure, Yamamoto has reported the preparation of a ten-membered ring lactone which is a key intermediate for the synthesis of (-)-lardoline.[83c]

**Scheme 36**



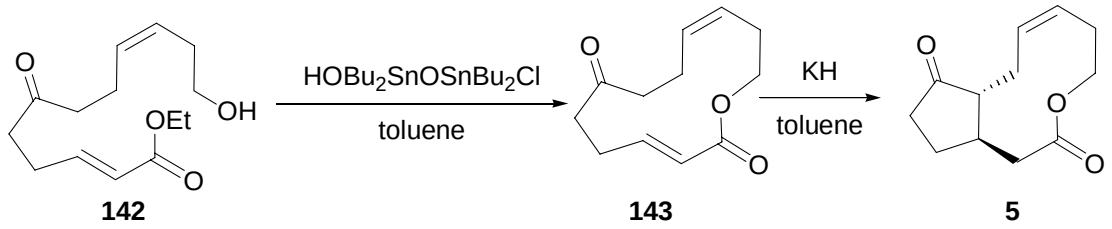

**139** **140** **141**

## Other approaches

***Transannular Michael reaction***

In the studies directed towards the synthesis of (+)-jasmine lactone (**5**), Shimizu and Nakayawa showed that a 13-membered ring lactone could be made first, and then the 10-membered ring lactone could be obtained by an intramolecular Michael reaction.[84]

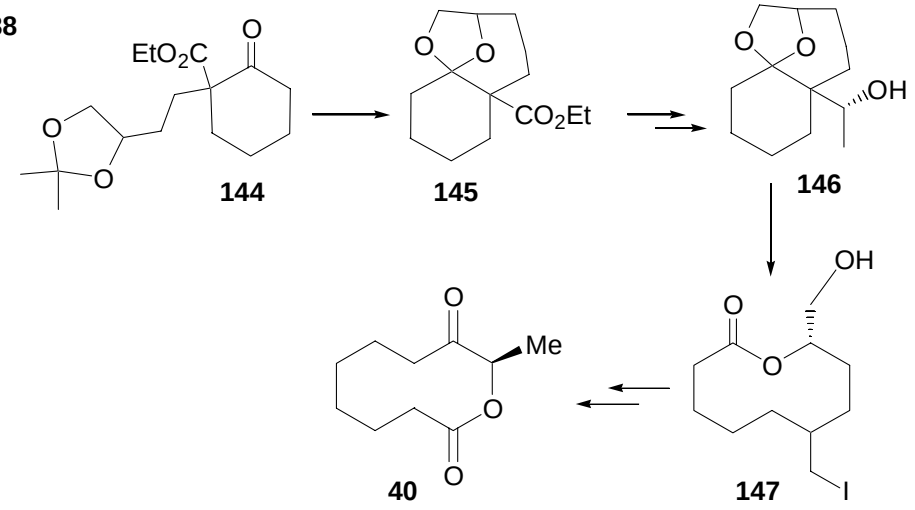
**Scheme 37**




***Fragmentation reactions***

Sakai and coworkers have explored the possibility of preparing medium ring lactones by a Grob fragmentation of tricyclic acetals.[85] This strategy was applied to a fairly lengthy synthesis of phoracantholide I (**40**).

**Scheme 38**

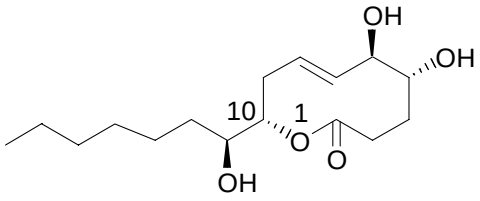



Recently ring-closing olefin metathesis (RCM) has received a great deal of attention for the synthesis of medium or large sized rings from acyclic diene precursors. One of the major considerations for RCM in the synthesis of highly flexible large (≥9) ring systems is the conformational predisposition of starting material for favorable intramolecular cyclization.[86] However, it has been demonstrated that macrocyclization metathesis is highly efficient not only with substrates having suitable restrictions but also with substrates devoid of any rigorous conformational constraints by modification of the reaction conditions (usually by slow addition). Therefore, RCM is becoming recognized as one of the most straightforward and reliable methods for the formation of large ring systems and compares favorably to all current synthetic alternatives. (+) Jasmine lactone[87] (**5**) was the first 10-membered lactone

synthesized by applying the RCM protocol, later on the molecules like herbarumin[88a] (**55**), pinolidoxin[88b](**8**) and microcarpalide[88c](**54**) were synthesized by applying the RCM reaction as the key macrocyclization step.

# Present Work

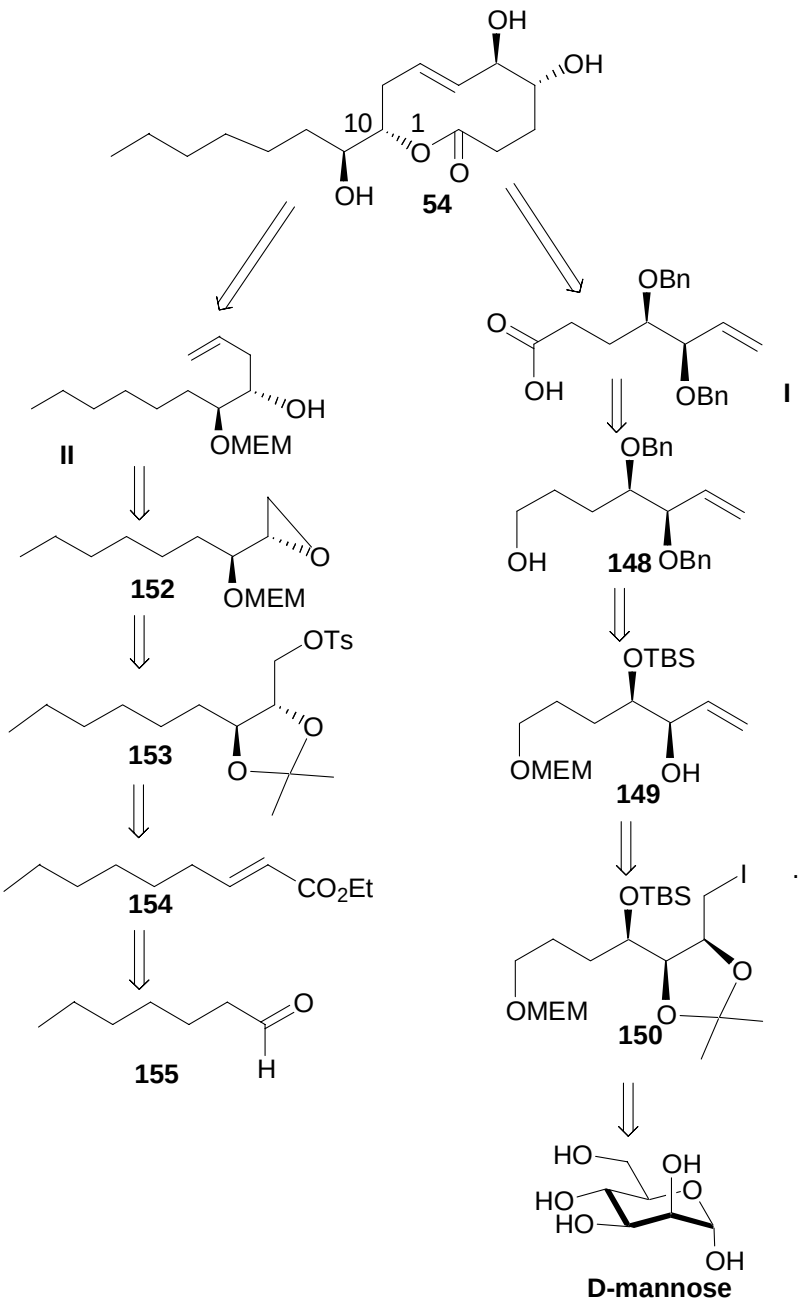
Secondary metabolites from endophytic fungi have been receiving a great deal of attention in recent years, and a number of peculiar structures with specific bioactivities have been discovered so far. Along this line, microcarpalide[12c] (**54**) has been recently characterized as a new secondary metabolite produced by an endophytic fungus (so far unidentified) isolated from the bark of the tropical tree *Ficus microcarpa* L. Bioassay-guided purification[12c] of fermentation broths using immunofluorescence microscopy to test anticytoskeletal activity led to the isolation of microcarpalide displaying a remarkable disrupting action on actin microfilaments,[12c] to which the structure **54** was assigned.




Microcarpalide (**54**)

Microcarpalide (**54**) represents a novel alkyl-substituted nonenolide structurally related to a family of phytotoxins such as achaetolide,[23a] pinolidoxin,[23b,23c] putaminoxins[39a] and herbarumins,[39b] from which it differs in the hydroxylation pattern and the double bond position within the 10-membered lactone, as well as in the length of the side chain at C-10. At concentrations of 0.5–1 μg $mL^{-1}$, microcarpalide (**54**) was found to disrupt actin microfilaments in approximately 50% of A-10 cells (from rat smooth muscle); moreover, it displayed a weak cytotoxicity to mammalian cells, thus making it an attractive tool for studying cell motility and metastasis, and a potential lead structure to develop new anticancer drugs.[12c]

Owing to such a peculiar biological activity and structural similarity with the other natural products prompted us to take up the synthesis of microcarplide (**54**). Flexible Scheme with this in mind, the retrosynthetic approach outlined in Scheme 39 was devised.




**Scheme 39.** *Retrosynthetic analysis for* **54**

The macrocyclic framework of microcarpalide was retrosynthetically disassembled into fragments **I** and **II** (Scheme 39) by means of two key disconnections, namely a ring-closing metathesis reaction (RCM)[86] for the construction of the oxecin ring, and an esterification reaction[89] for assembling the two alkene fragments. Both fragments contain two

stereogenic carbon atoms and bear a terminal alkene group that is required for the RCM macrocyclization.

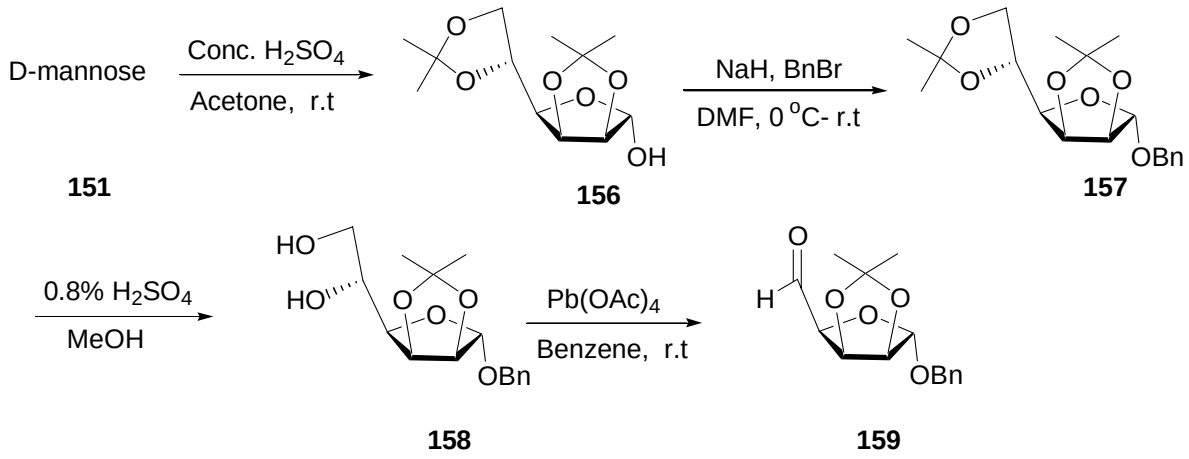
Fragment **I** represents a 4,5-disubstituted 6-heptenoic acid consisting of two contiguous stereocentres arranged in *threo* fashion with *R* absolute configurations. **I** could be obtained from **148** by means of two step oxidation, which in turn can be obtained from **149** by performing suitable functional group manipulations. It was envisaged that compound **149** could be obtained from **150** by means of Zinc mediated facile elimination reaction.[90] Compound **150** could be easily obtained starting from commercially available D-mannose (**151**).

Fragment **II** represents a dihydroxy substituted 1-undecene with *S* as absolute configuration at both adjacent stereocenters (C-10 and C-$1^1$ in **1**) and can be ultimately disconnected to the C-6 alkyl epoxide **152** which could be obtained from **153** by the judicious combinaton of functional group manipulations. A careful observation revealed that compound **153** could be obtained from **154** by employing Sharpless asymmetric dihydroxylation[91] and a series of transformation, which can be traced back to the commercially available 1-heptanal (**155**).

**Synthesis of fragment I**

Retrosynthetic analysis outlined in (Scheme 39) identified compound **150** as one of the potential synthetic intermediate and the construction of **150**, which would mark the first synthetic objective in the construction of, fragment **I**. As it turned out, the synthesis of **150** began with commercially available D-mannose (**151**), which was converted to 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose[92] (**156**) (Scheme 40) by the action of conc. $H_2SO_4$ and acetone. Subsequent protection of anomeric hydroxy group with BnBr and NaH in anhydrous DMF afforded the benzyl mannofuranoside **157**. Selective deprotection of the 5,6-*O*-isopropylidene group in **157** with 0.8% $H_2SO_4$ in MeOH followed by oxidative cleavage[93]of resulting diol **158** using $Pb(OAc)_4$ in anhydrous benzene furnished the aldehyde **159,** which was used without further purfication.

**Scheme 40**



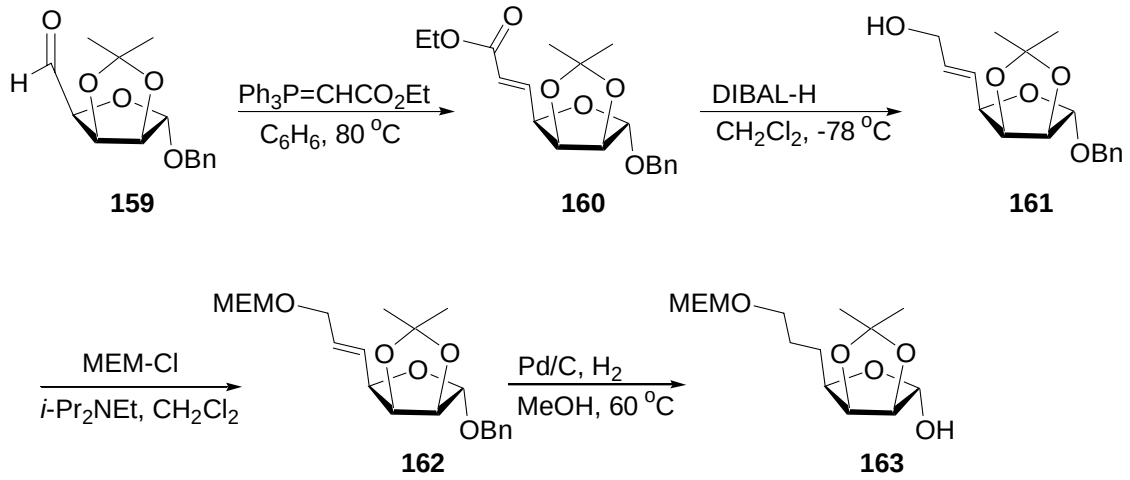

**151** **156** **157** **158** **159**

The aldehyde **159** was subjected to two-carbon Wittig homologation using (ethoxycarbonylmethylene) triphenylphosphorane (Scheme 41) in benzene at 80 $^{o}$C for 3 h to furnish **160** as a inseparable 1:1 mixture of *cis* and *trans* isomers in 83% from **158**. Since the geometry of double bond in **160** was of no consequence, as it would be hydrogenated at a later stage, the mixture was carried forward for subsequent reactions. The structure of **160** was assigned based on its $^{1}$H NMR and $^{13}$C NMR spectral data. In the $^{1}$H NMR spectrum the characteristic olefinic signals appeared in the region of 5.45–6.96 ppm, H-1 was observed as two singlets at $\delta$ 5.10 and 5.12 ppm (corresponding to *E, Z*- isomers), while H-2 and H-3 resonated as a multiplet between 4.40 – 4.80 ppm. In the aromatic region a multiplet integrating for five protons was observed at 7.26–7.32 ppm. The $^{13}$C spectrum displayed resonances at 165.2 and 164.9 (*E, Z* isomers) for C=O group. The IR spectrum showed a strong band at 1783 cm$^{-1}$ corresponding to $\alpha$, $\beta$ unsaturated ester. Treatment of **160** with DIBAL-H in anhydrous $CH_2Cl_2$ at –78 °C for 1 h afforded the allyl alcohol **161** in 83 % yield. The structure was confirmed by its $^{1}$H NMR, $^{13}$C NMR spectra and elemental analysis. In the $^{1}$H NMR spectrum, protons specify for $CO_2Et$ were absent. The olefinic protons moved upfield and located between 5.82–5.95 ppm.

The primary hydroxyl group of compound **161** was protected as the MEM-ether[94] by using MEM-Cl, DIPEA in anhydrous $CH_2Cl_2$ at ambient temperature to provide MEM-ether **162** in 84% yield. The structural identity was secured by the interpretation of the $^{1}$H NMR and $^{13}$C NMR spectra. The characteristic signals for MEM group were observed. For example, a

singlet resonated at $\delta$ 4.67 ($OCH_2O$), $\delta$ 3.4 ($OCH_3$), and a multiplet at 3.55–3.70 ($OCH_2CH_2O$) corresponding with MEM group while rest of the protons appeared at expected chemical shifts. The $^{13}C$ NMR spectrum showed resonances at 58.8, 66.7, 68.8, 94.7 for newly introduced MEM group. Compound **162** was subjected to reduction over Pd/C under hydrogen atmosphere at 6 bar and at 60 °C in methanol for 4 h to give the lactol **163**, whose structure was characterized by the spectral data. The loss of benzyl group also occurred during this step (Scheme 41).

**Scheme 41**

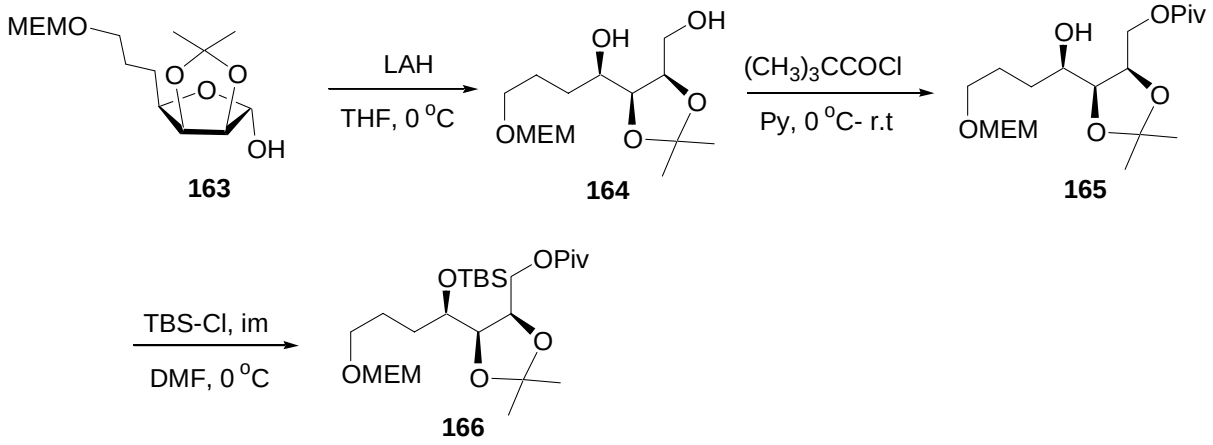



Compound **163** on exposure to LAH in anhydrous THF at 0 °C for 1 h resulted in the formation of the diol derivative **164** in 75 % yield. In its $^1H$ NMR spectrum, H-1, H-4 and H-8 appeared as multiplet in the region 3.63–3.77, a broad singlet at 2.24 was assigned to OH while H-2 appeared as double-doublet ($J$ = 6.8, 3.4 Hz) at 4.01 ppm. H-3 appeared as double-triplet ($J$ = 6.8, 6.6, 5.1 Hz) at 4.17 ppm.

The next task in the synthetic endeavor dwells up on the conversion of the newly generated primary hydroxyl to the corresponding iodide. However, methodologies for selective iodination are scarce and thus protection of secondary hydroxyl group is warranted. So, compound **165** was attained by the selective masking of primary hydroxyl group of **164** as the pivolate derivative[95] by treating with pivolyl chloride in pyridine at room temperature for 6 h in 91% yield. The $^1H$ NMR spectrum of **165** revealed a distinct singlet at $\delta$ 1.21 attributed to trimethyl acetyl group. The remaining hydroxy group at C-4 was protected as silyl ether[96]

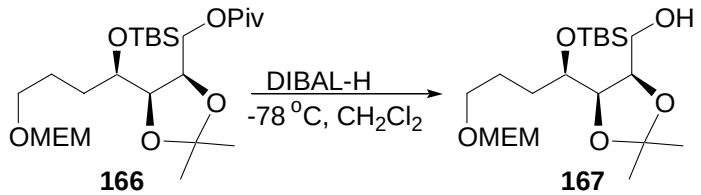
by using TBS-Cl and imidazole in anhydrous DMF at room temperature for 4 h to afford **166** in 90% yield (Scheme 42). The structure of product **166** was confirmed beyond doubt by it's $^{1}H$ NMR and $^{13}C$ spectra. In the $^{1}H$ NMR spectrum two singlets at 0.05 for $Me_2Si$ and at 0.87 for $C(CH_3)_3$ of TBS-group were accounted. The peaks at –4.8, -4.3, 25.1 and 25.6 ppm in the $^{13}C$ NMR spectrum were in support of **166**.

**Scheme 42**




Compound **167** was obtained by subjecting the pivolate derivative **166** to reductive depivolylation[97] using DIBAL-H in anhydrous $CH_2Cl_2$ at –78 °C for 1 h in 89% yield (Scheme 43). The structure was readily confirmed by its $^{1}H$ NMR and $^{13}C$ spectral data. The $^{1}H$ NMR spectrum indicated the absence of signals due to pivolyl group.

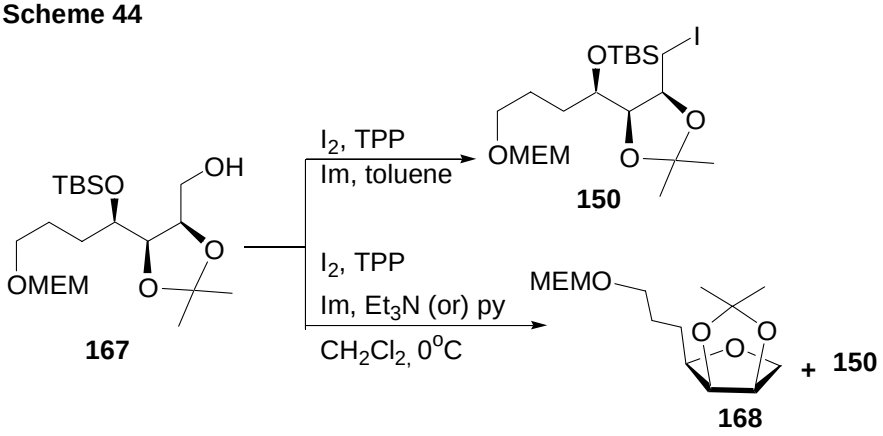
**Scheme 43**




Having had the compound **167** in hand, our next concern was to transform **167** in to the corresponding $\alpha$-iodo derivative **150**. Thus, compound **167** was subjected to Corey's deoxyhalogenation protocol[98a] by treating with $I_2$, TPP and imidazole in toluene at room

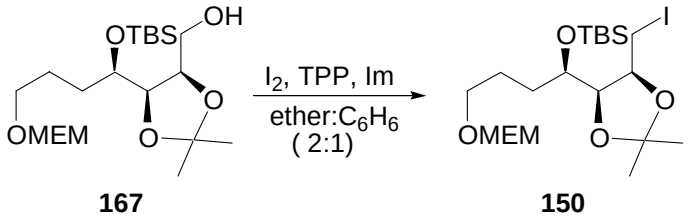
temperature, which led to the formation of **150** moderate 40% yield. Efforts toward improving yield by the addition of bases like $Et_3N$ or pyridine were proved to be ineffective. In addition under these conditions, we observed the formation of the cyclized product **168** in 15% yield along with desired product **150** (45%)(Scheme 44). In the $^1H$ NMR spectrum of **168** the down field shift of resonances due to H-1 were observed, rest of the protons resonanced at the expected positions.

**Scheme 44**




In order to circumvent the iodination problem with respect to yield and side products the modified Corey's protocol developed by Smith *et al*[98b] was envisaged. Treatment of compound **167** with $I_2$, TPP and imidazole in ether-benzene (2:1) for 1.5 h at room temperature furnished **150** in 86% yield. In the $^1H$ NMR spectrum of **150** the resonances due to $CH_2I$ were located at 3.12 as a triplet ($J$ = 10.4 Hz), and at 3.27 as a doublet of doublet ($J$ = 10.4, 3.3 Hz) (Scheme 45).

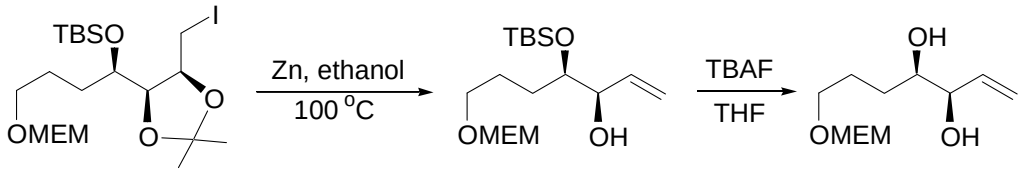
**Scheme 45**




Compound **149** was accomplished from **150** through Zinc mediated elimination[90] reaction in refluxing ethanol for 1.5 h in 96% yield. In the $^1H$ NMR spectrum of **149** peaks

owing to $CH_2I$ and isopropylidene group were absent. The terminal olefinic group showed peaks at $\delta$ 5.19 and 5.31 (double–triplets, $J$ = 1.5,10.2) and at $\delta$ 5.84 (double–double–doublet. The OH signal ($D_2O$ exchangeable) was found at $\delta$ 2.37 as a doublet ($J$ = 6.3 Hz). All other protons resonated at the expected chemical shift. The $^{13}C$ spectrum displayed peaks at 114.7, 137.8 corresponding to olefinic carbons at C-2 and C-1. Compound **149** was desilylated[96] with TBAF in anhydrous THF at 0 °C to give the diol **169**. The $^1H$ NMR, $^{13}C$ NMR spectra and elemental analysis were in support of the structure **169** (Scheme 46).

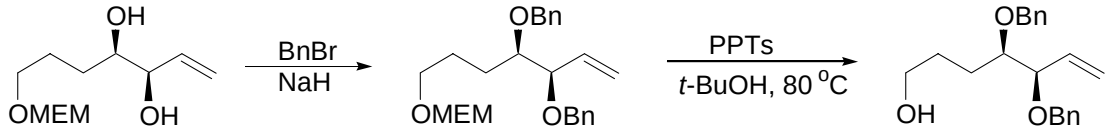
**Scheme 46**




**150** **149** **169**

The diol **169** was converted in to the dibenzyl ether derivative **170** by using BnBr and NaH in anhydrous DMF at 0 °C – rt for 1 h in 88% yield. In the $^1H$ NMR spectrum, the benzylic protons appeared at $\delta$ 4.25 ($J$ = 12.1 Hz), 4.55 ($J$ = 11.4 Hz), 4.65 ($J$ = 12.1 Hz) and 4.76 ($J$ = 11.4 Hz). Compound **148** was obtained from **170** by acid mediated deprotection[99] of MEM, using PPTs in *t*-BuOH at 80 °C for 1.5 h in 85% yield. The resonances relevant to MEM group were absent in the $^1H$ NMR and $^{13}C$ NMR spectra (Scheme 47).

**Scheme 47**

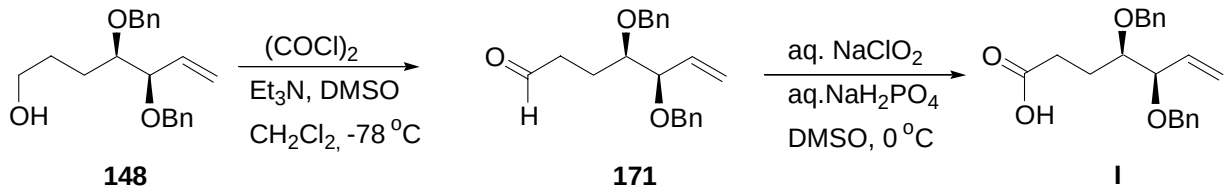



**169** **170** **148**

**148** was first subjected to Swern oxidation[100a] by using $(COCl)_2$, DMSO and $Et_3N$ in $CH_2Cl_2$ at –78 °C to furnish the aldehyde **171** which was immediately transformed in to the corresponding acid fragment **I** by treating with aq. $NaClO_2$ solution in DMSO in the presence

of phosphate buffer[100b]. The $^{1}H$ NMR and $^{13}C$ spectra of **I** were compatible with the assigned structure (Scheme 48).

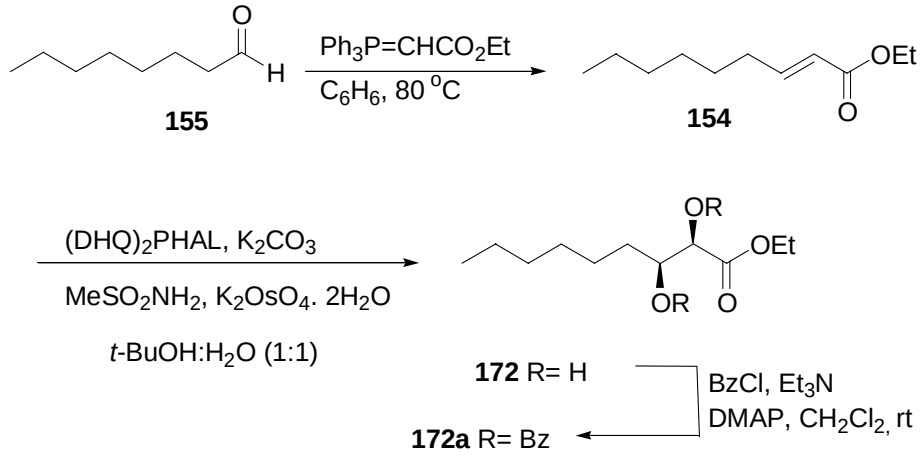
**Scheme 48**




**Synthesis of fragment II**

The journey toward the synthesis of **II** began with commercially available 1-heptanal (**155**), which was subjected to two-carbon Wittig homologation by using $Ph_3P{=}CHCO_2Et$ in anhydrous benzene at 80 °C to give **154** as a mixture of *trans* and *cis* isomers in the ratio of 85:15. They separated by silica gel chromatography and the major *trans* isomer was obtained in 78% yield.[101]

**Scheme 49**

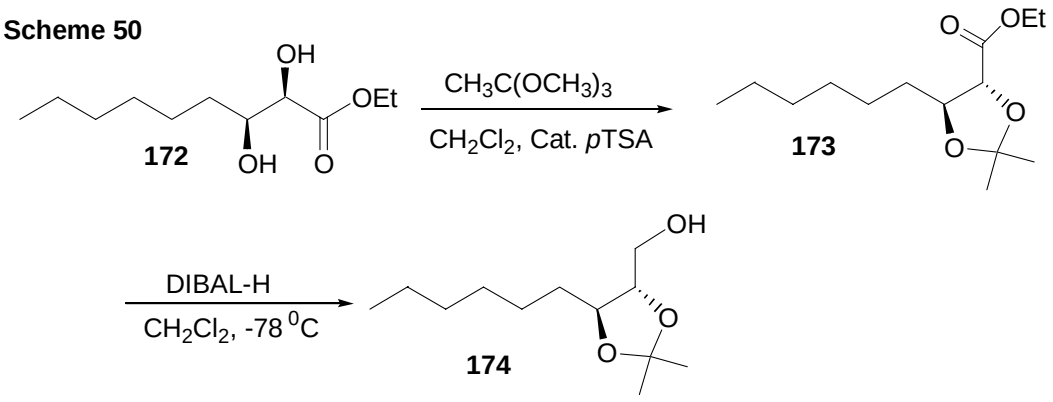



The next task was to generate stereo-centers at C-2 and C-3, which was carried out by employing Sharpless asymmetric dihydroxylation procedure.[91] Thus, compound **154** was treated with ligand $(DHQ)_2PHAL$, $K_2Fe(CN)_6$, $K_2CO_3$, $MeSONH_2$ and $K_2OsO_4$; $2H_2O$ in *t*-BuOH- $H_2O$ (1:1) at 0 °C for 10 h to afford the diol **172**.The compound was thoroughly investigated by the $^{1}H$ NMR and $^{13}C$ NMR spectra and elemental analysis. In the $^{1}H$ NMR

spectrum, the H-2 and H-3 protons were resonated as double triplet at $\delta$ 3.88 ($J$ = 6.4, 2.1 Hz) and as doublet at 4.08 ($J$ = 2.1 Hz) respectively. In the $^{13}$C spectrum, peaks at 73.2, 72.4 correspond to C-2 and C-3 (Scheme51). Enatiomeric purity of (**172**) was estimated to be 97.5% ee, by HPLC analysis of the corresponding dibenzoate (**172a**) using a chiracel OD (semiprep) column (1% i-propanol/n-hexane, flow rate 2.0 mL/min, $\lambda$ = 225 nm).

The diol **172** was ketalized under acidic condition using 2,2-dimethoxy propane in $CH_2Cl_2$ in the presence of catalytic *p*-TSA to furnish **173**. The structure was assigned by $^1$H NMR and $^{13}$C NMR spectra. Reduction of carboxylate group of **173** was performed by using DIBAL-H in anhydrous $CH_2Cl_2$ at –78 °C to obtain **174** in 97% yield. The structure was suggested by the $^1$H NMR spectrum in which resonances at $\delta$ 3.67 as a multiplet due to $CH_2OH$, the acetonide methyl peaks at 1.39 and 1.40 ppm (Scheme 50).

**Scheme 50**




***A short account of Sharpless asymmetric dihydroxylation (AD)***

*The stereospecific cis-dihydroxylation of olefins achieved by $OsO_4$ is one of the most valued transformations for introducing functionality into organic molecules. Initially the AD using derivatives of cinchona alkaloids was performed under stoichiometric conditions. Lateron, with the advent of: i) use of two phase conditions with $K_3Fe(CN)_6$ as reoxidant; ii) $MeSO_2NH_2$ for rate acceleration and iii) second generation ligands (phthalazine and diphenylpyrimidine, with two independent cinchona alkaloid units) by Sharpless et al., catalytic AD came into focus. The enantioselectivity in the AD reaction is due to the enzyme-like binding pocket*

*present in the dimeric cinchona alkaloid ligands. The Cinchona alkaloid backbone is ideally suited for providing high ligand acceleration and enantioselectivity. The reaction rates are influenced by the nature of O-9 substituent of the Cinchona alkaloid. The rate enhancement is caused by a stabilization of the transition state due to aromatic stacking interactions. Although this kind of stabilization is operative even in monomeric first generation ligand, it is most effective in the dimeric second-generation ligands due to the presence of a binding pocket. Thus the almost perfect match between the phthalazine ligands and aromatic olefins with respect to rates and enantioselectivities can be readily explained by an especially good transition state stabilization resulting from offset-parallel interactions between the aromatic substituent of the olefin and the phthalazine floor of the ligand, as well as favorable edge-to-face interactions with the bystander methoxyquinoline ring.*

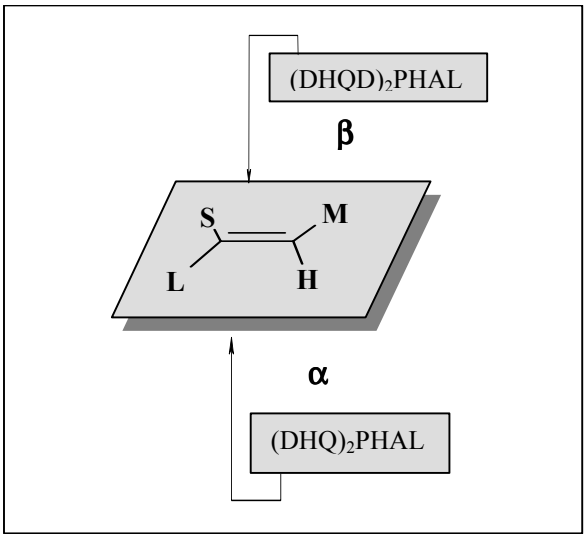



**Fig. 2** ***Mnemonic diagram*** *(S = small group, L = large group, M = medium group, H = proton).*

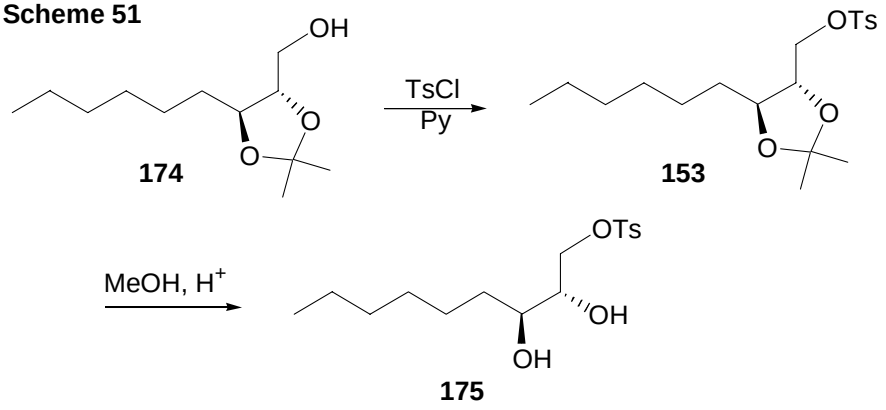
*The above observations have led to a revised mnemonic device for predicting the enantiofacial selectivity in the reaction. An olefin positioned accordingly will be attacked either from the top face (β face) in the case of dihdroquinidine derivatives or from the bottom face (α face) in the case of dihydroquinine derived ligands.*

---

The primary hydroxyl group of **174** was converted to the sulphonate derivative **153** by using *p*-TsCl in pyridine[102a, 102b] at room temperature for 7 h. In the $^{1}$H NMR spectrum of **153**,

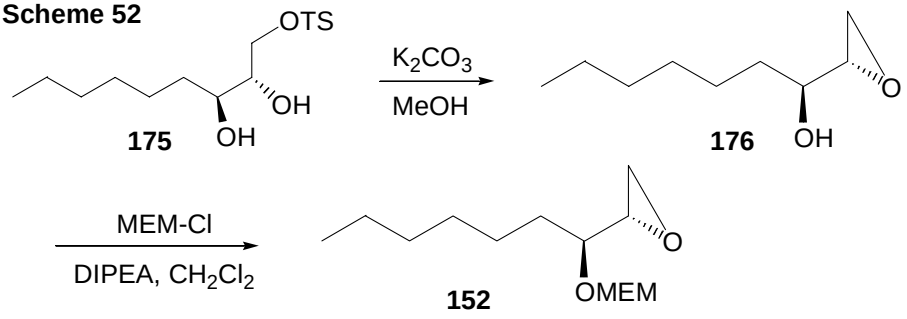
the characteristic resonances for the aromatic ring protons of tosyl group were observed as two doublets at $\delta$ 7.36 and 7.81 ($J$ = 8.4 Hz), while the methyl group appeared as a singlet at $\delta$ 2.46. Deketalization[103] was performed by treating **153** with catalytic amount of HCl in MeOH for 3 h to provide **175** in 87% yield (Scheme 51). The structure **175** supported from the $^1$H NMR and $^{13}$C NMR spectral analysis.

**Scheme 51**



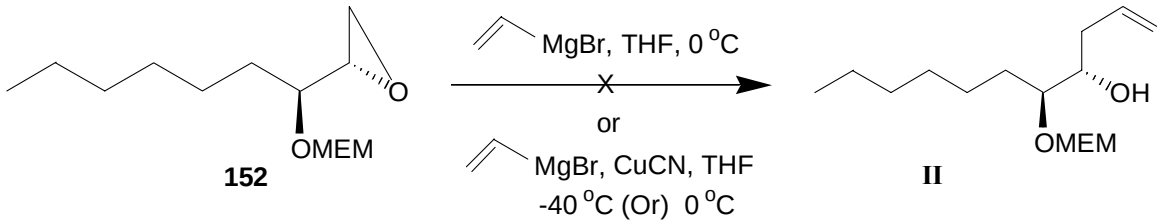

The next step involved the oxirane derivatisation for which, compound **175** was treated with $K_2CO_3$ in MeOH to furnish the terminal epoxide **176** in 85% yield. The $^1$H NMR spectrum of **176** showed characteristic resonances due to terminal epoxy protons at $\delta$ 2.72 (double-doublet, $J$ = 4.8, 2.5 Hz), 2.82 (triplet, $J$ = 4.8 Hz), and at $\delta$ 2.97 as a double-triplet ($J$ = 6.8, 2.5 Hz). The hydroxyl group of **176** was protected as the MEM ether **152** using MEM-Cl and DIPEA in $CH_2Cl_2$. The $^1$H NMR, $^{13}$C NMR spectra and elemental analysis were in accordance with the structure of **152** (Scheme 52).

**Scheme 52**



The ring opening reaction of the oxirane **152** with vinyl magnesium bromide to get the key synthetic intermediate **II**. Thus, compound **152** on exposure to vinyl magnesium bromide in THF at 0 °C led to a mixture of products in which the require product **II** was minor. This was partly attributed to many side reactions particularly opening of the oxirane ring with iodide (Scheme 53).

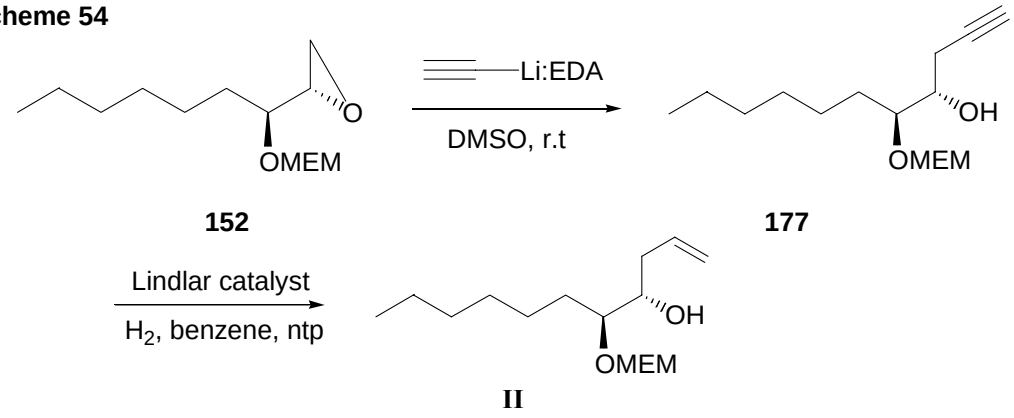
**Scheme 53**




**152** **II**

Based on this failure we decided to make **II** by two step process in which **152** was treated with lithium acetylide-EDA complex [104] in DMSO at room temperature for 12 h to afford **177** in 86% yield. In the $^1$H NMR spectrum of **177** a triplet at $\delta$ 1.99 ($J$ = 3.6 Hz) was attributed to acetylenic proton while propargylic methylene resonated as doublet of a double-doublet at $\delta$ 2.43 ($J$ = 11.9, 10.7, 2.4 Hz). Partial reduction of the triple bond of **177** was carried out by hydrogenation over Lindlar's catalyst[105] at normal temperature and pressure for 0.5 h to release the key intermediate **II** in excellent yield (Scheme 54). The $^1$H NMR spectrum of **II** showed resonances for olefinic protons at $\delta$ 5.06-5.17 as a multiplet, and a broad doublet of a double- triplet at $\delta$ 5.88 ($J$ = 17.6, 10.6, 7.0 Hz). The $^{13}$C NMR spectrum indicated peaks at 117.1, 134.9 for olefinic carbons.

**Scheme 54**

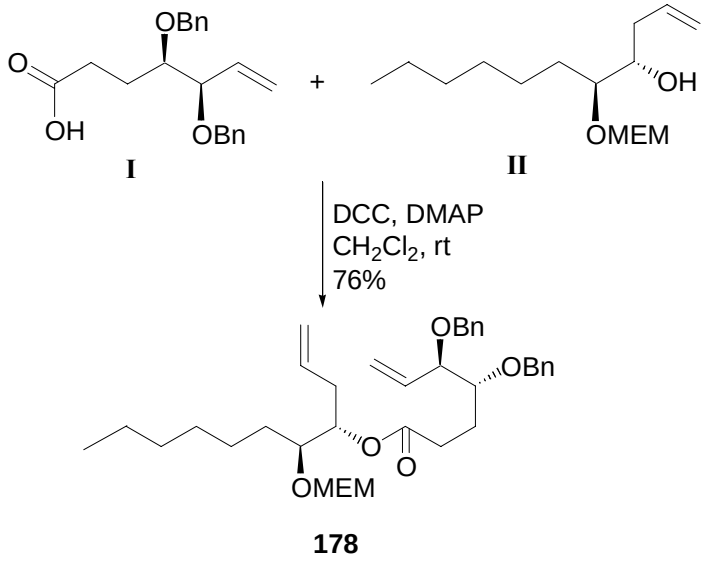



**152** **177** **II**

**Coupling reaction between I and II.**

With the key intermediates **I** and **II** in hand, then the stage was set to couple both the olefinic partners. Coupling reaction of fragments **I** and **II** was performed by using DCC[89] in presence of catalytic DMAP in anhydrous $CH_2Cl_2$ for 18 h to give ester **178** in 76% yield. The structure of **178** was proven by the $^1H$ NMR and $^{13}C$ NMR spectra (Scheme 55). In the $^1H$ NMR spectrum, a clear cut down field shift of H-10 signals (numbering based on fig.1), was observed, which indicates that the ester formation indeed occurred.

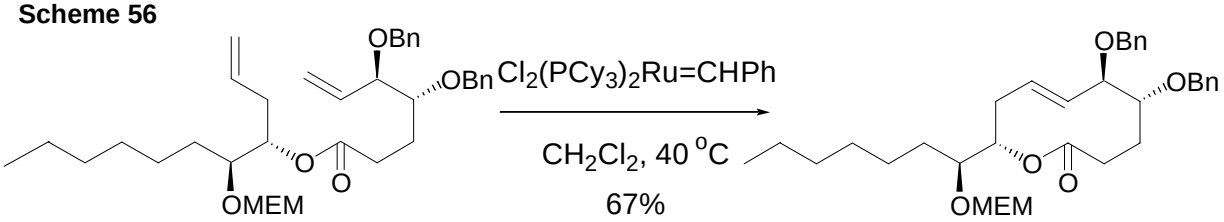
**Scheme 55**




**178**

Ring closing metathesis reaction[86] of **178** with Grubbs' first generation catalyst ($Cl_2(PCy_3)_2Ru$=CHPh) in degassed $CH_2Cl_2$ under reflux for 28 h afforded the ten- membered lactone **179** in 67% yield as a mixture of two geometric isomers in 9:1 ratio favoring *E*-isomer. Chromatographic purification on silicagel gave pure *E*–isomer but the minor *Z* isomer (*Z*–33) couldn't be isolated in its pure form as it was always contaminated with *E*-compound. The major *E*-oxecin was isolated and *E*–configuration was confirmed by large $J_{7\text{-}8}$ coupling constants (17.3 Hz) at 5.71 and 5.88 ppm (Scheme 56).

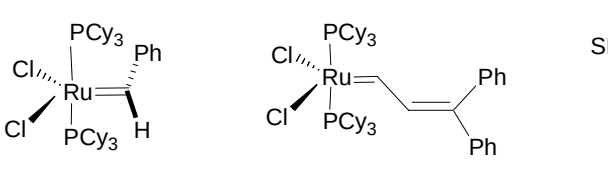
**Scheme 56**



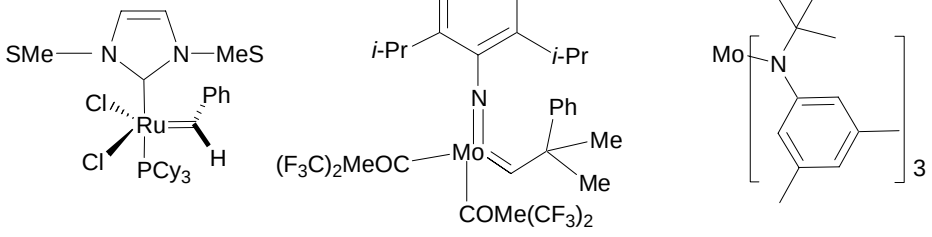

**178** **179**

***A brief account on stereo selectivity in RCM cyclization (Ten– membered lactones):***

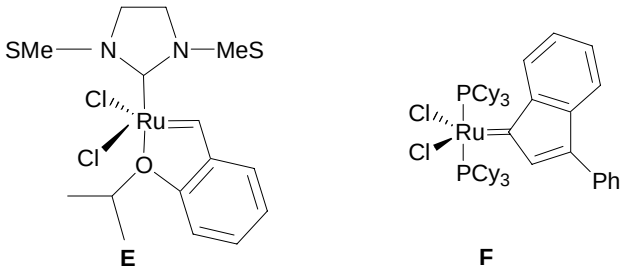
In the recent past ring closing metathesis reaction has emerged as an effective tool for the generation of C=C bond. The pioneering efforts by Grubbs[86] and Schorck[86] led to the introduction of catalyst I and II respectively which find wide spread use now-a-days, although the discovery and development of new variants for these catalysts is warranted in terms of improving yields and stereo control of the newly formed double bond. Presently to meet the needs of synthetic chemists various catalysts were available at disposal. (Complete account of mechanism of RCM reaction will be presented in Chap.3)



**A** **A'** **B**



**B'** **C** **D**

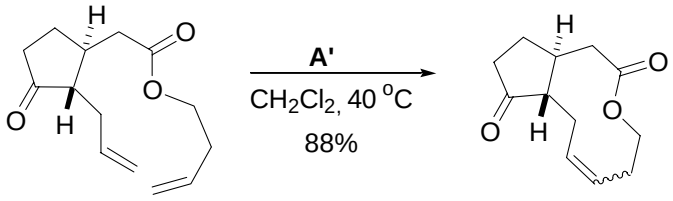


**E** **F**

In relation to the present context, there have been numerous applications of RCM reaction for the synthesis of macrocyclic lactones. The formation of medium-size lactones by RCM constitutes a considerable challenge, since the inherent ring strain predisposes cycloalkenes containing 8-11 atoms toward ring-opening metathesis (ROM) or ring-opening metathesis polymerization (ROMP). Particularly in the synthesis of medium- size rings (8-11) by RCM reaction lead to the formation of mixture of *E*, *Z* cycloalkenes. Therefore, a reliable and general method of controlling the geometry of newly formed double bond in RCM macro cyclizations has been called for. In this respect, second generation Grubbs' catalyst is known to favor the formation of the thermodynamically more stable *Z* isomers.

The first construction of a 10-membered lactone using a RCM was reported by Fűrstner and Muller in 1997 in the synthesis of jasmine ketolactone[87] (**5**), a minor component of the essential oil of jasmine. Heating a dilute solution of **180** in the presence of **A'** then furnished **5** as a mixture (1.4:1) of *E*/*Z* isomers.

**Scheme 57**

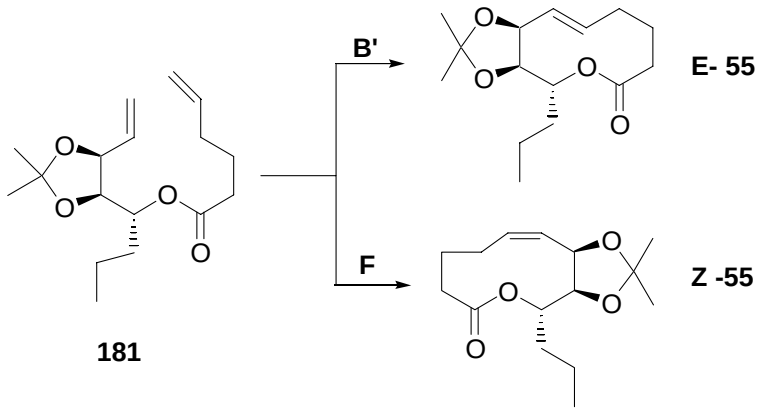



**180**

*E*/*Z* = 1.4:1
**5**

Fűrstner[88a] first reported the synthesis of the herbarumin I and II through key RCM ring closure. The isopropylidene group adjacent to the alkene is expected to stabilize the conformation of **181** that would affect the ring closure. Semi empirical calculations for **181** suggested that *Z*-isomer is about 3.5 Kcal/mol more stable than the *E*-isomer.

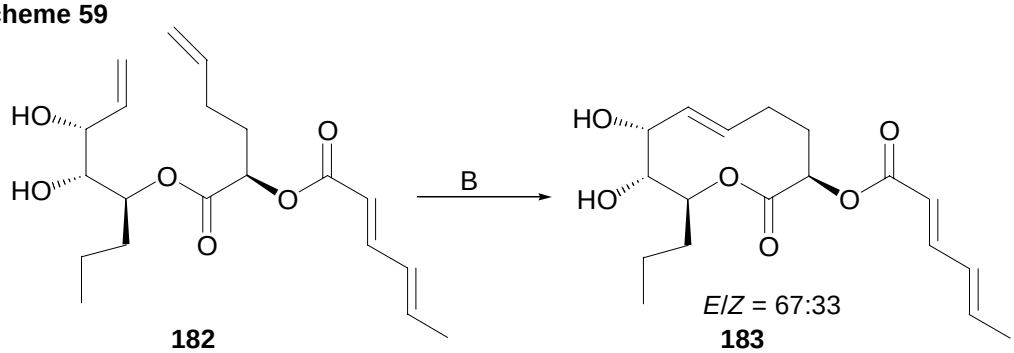
**Scheme 58**




Thus, conducting the RCM reaction under the thermodynamic control would be expected to be counterproductive for obtaining *E*-alkenes. This prediction suggested that RCM catalysts known to equilibrate the initial products should not be employed. Cyclization of **181** with second generation catalyst B' led to the selective formation of Z-**55**. In contrast, exposure of the diene **181** to catalytic amounts of ruthenium indenylidene complex **F**, whose properties are very similar to those of **A**, afforded the desired lactone *E*-**55** as major product. The *E*/*Z* ratio didn't altered with reaction time suggesting that the product formation occurs under kinetic control.

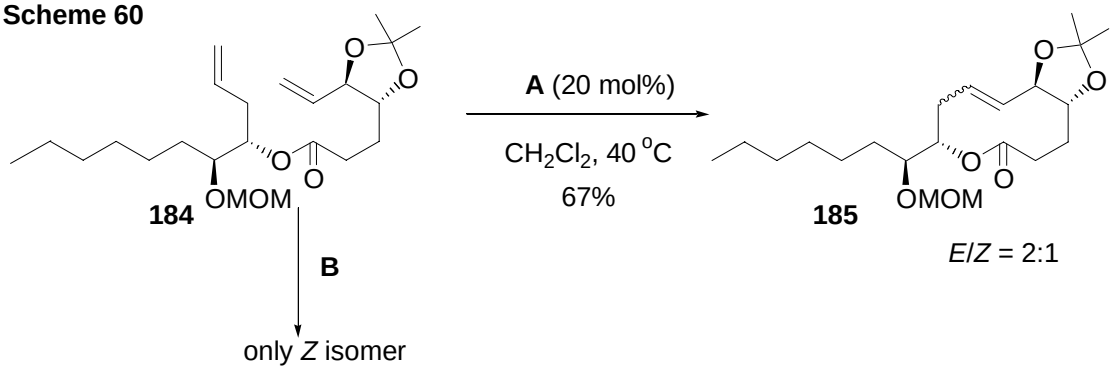
Kozmin *et al* [88b] reported similar reverse of selectivity results in the synthesis of pinolidoxin. Treating compound **182** with catalyst **A** in $CH_2Cl_2$ led to the mixture of *E* and *Z* in a ratio of 1:1. Subjecting the compound **182** to RCM reaction using catalyst **B** proceeded to exclusive formation of **183** as a mixture of *E*: *Z* in a ratio 67:33. When the hydroxyls were protected as it's isopropylidene ketal, with catalyst **B** led to the exclusive formation of *Z* - isomer.

**Scheme 59**



Marco[88c] recently reported the synthesis of the microcarpalide employing RCM reaction. When compound **184** was treated with catalyst **A** led to the mixture of *E*: *Z* isomers in 2:1 ratio, alternatively when treated with second generation catalyst **B** gave thermodynamically favourable *Z*-isomer. This observation is in agreement with those reported by grubbs, who found that *E*/*Z*-ratio in ring closures using **B** catalyst is not kinetically controlled but is rather the result of an equilibration of the products.

**Scheme 60**

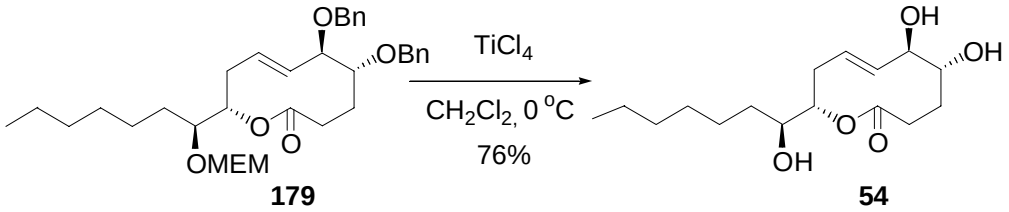



Thus on the outset the outcome of ring closure by RCM reaction particularly in the formation of ten-membered lactones depends on the type of catalyst, stability of the conformer implying the desired product could be obtained only by trail and error method.

**Removal of protecting groups**

Treatment of *E*–(**179**) with titanium tetrachloride[94,105] at 0 °C (Scheme 61) for the deprotection of MEM-group, resulted in the simultaneous removal of both the protective group, affording a single product whose spectral data matched with those reported by Hemscheidt *et al*[12c] for the natural product. Like the natural microcarpalide (**54**), in deuterated acetonitrile, the NMR spectrum of synthetic **54** revealed two slowly inter converting conformers in a 76:24 ratio. The resonances due to H-10 were seen at 4.84 ppm for the major conformer and at 4.63 ppm for the minor. This conformer ratio is identical to the 3.5:1 value reported for natural product in the in the same solvent.

**Scheme 61**




**179** **54**

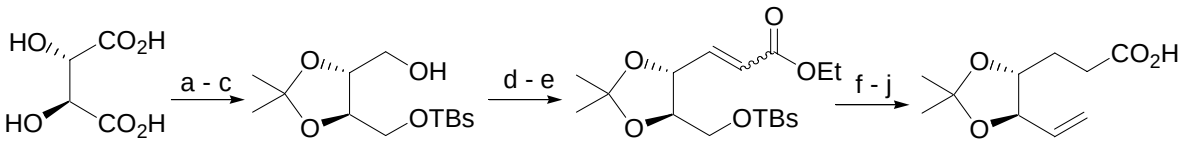
## Conclusion

In summary, total synthesis of the microfilament disrupting agent microcarpalide (**54**), a secondary metabolite produced by an endophytic fungus, has been accomplished. Formation of the required 10-membered lactone was achieved by using both chiral pool approach and an asymmetric dihydroxylation in an efficient manner. Finally global deprotection of protective groups was achieved by employing $TiCl_4$ condition, thus completing the total synthesis of microcarpalide.

**Post Work:** After the report of our total synthesis of microcarpalide, there are three more total syntheses reported. A brief description of these total syntheses follows.

**A) Prati's Synthesis of Microcarpalide:** Prati *et al* [106a] in 2003 accomplished the synthesis of microcarpalide by using the RCM reaction as the key step for the ring closure. The diene ester required for the macrocyclization reaction was assembled via DCC mediated esterification of suitable parners, each bearing the terminal alkene group. The acid fragment was synthesized stating from the D-tartaric acid as shown in below.

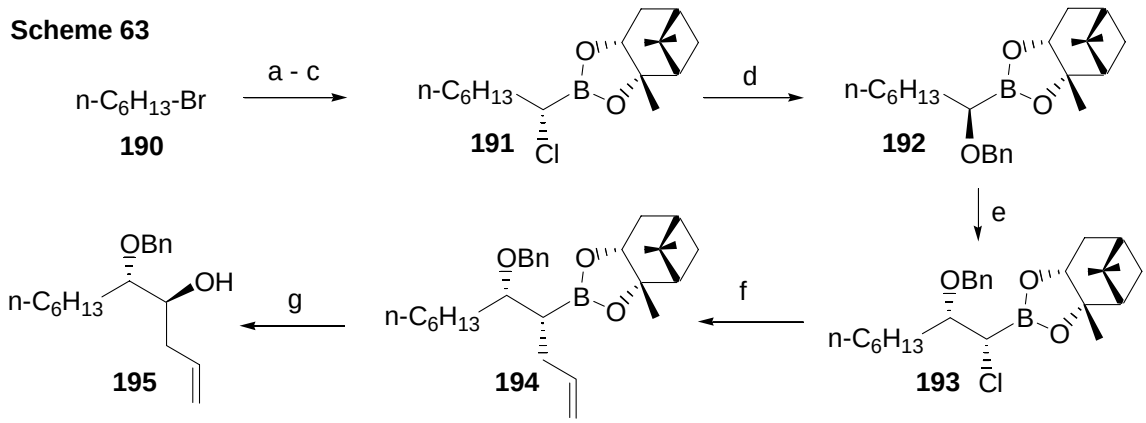
**Scheme 62**




**186** **187** **188** **189**

*Reagents and conditions*: a) 2,2-Dimethoxy propane, *p*-TSOH; b) LAH, $Et_2O$, reflux; c) TBDMSCl, NaH, THF; d) $(COCl)_2$, DMSO, $Et_3N$, -70 °C; e) $Ph_3P{=}CHCO_2Et$, DMF, rt; f) $H_2$, Pd/C, EtOH, rt; g)TBAF, THF, rt; h) $(COCl)_2$, DMSO, $Et_3N$, -72 °C; i) $Ph_3P{=}CH_2$, n-BuLi, THF, -20 °C - rt; j) KOH-MeOH-$H_2O$, rt.

**Scheme 63**

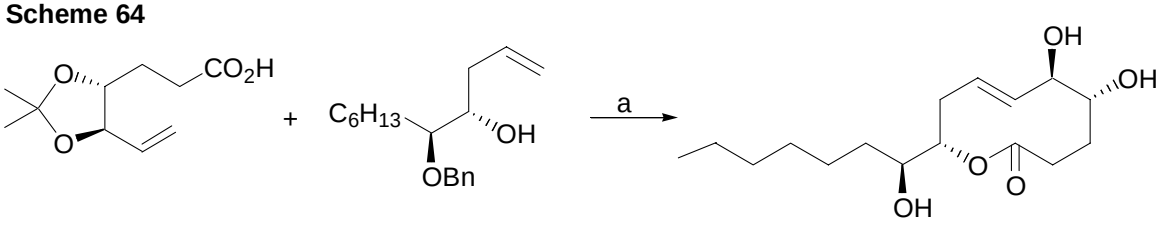



**190** **191** **192** **193** **194** **195**

*Reagents and conditions*: a) Mg, $Et_2O$, $(MeO)_3B$, reflux; b) (1*S*,2*S*,3*R*,5*S*)-(+)-pinanediol, $Et_2O$, rt; c) $Cl_2MeLi$, THF, -100 °C; d) $C_6H_5OH$, n-BuLi, THF, -78 °C; e) $Cl_2MeLi$, $ZnCl_2$,THF, -100 °C; f) allylMgBr, THF, -78 °C; g) $H_2O_2$, NaOH, THF, 0 °C.

As shown in Scheme 63, the alcohol fragment was synthesized from n-bromohexane utilizing the stereo selective homologations of chiral boronic esters as strategic transformation for the sequential insertion of two stereo centers having *S*-configuration, using the (+)-pinanediol as the chiral director.

**Scheme 64**

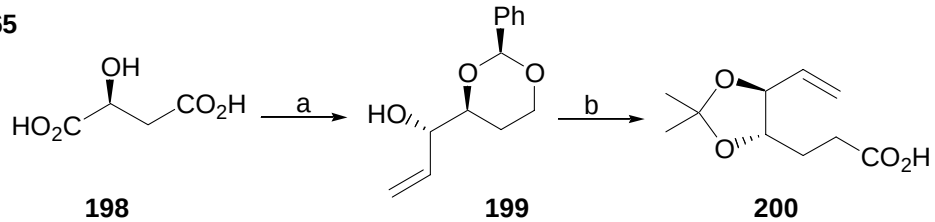



**196** **197** **54**

*Reagents and conditions*: a) (i) DCC, DMAP, $Et_2O$; (ii) ($Cl_2(PCy_3)_2Ru$=CHPh), $CH_2Cl_2$, reflux; (iii) $TiCl_4$, $CH_2Cl_2$, 0 °C.

**B) Banwell's Synthesis of Microcarpalide:** Banwell *et al*[106b] in 2004 reported the synthesis of enatiomer of (-) microcarpalide, once again using RCM as the key reaction. A chiral pool approach for the preparation of the acid component from (*S*)-malic acid (**198**) was executed using well established reactions.

**Scheme 65**

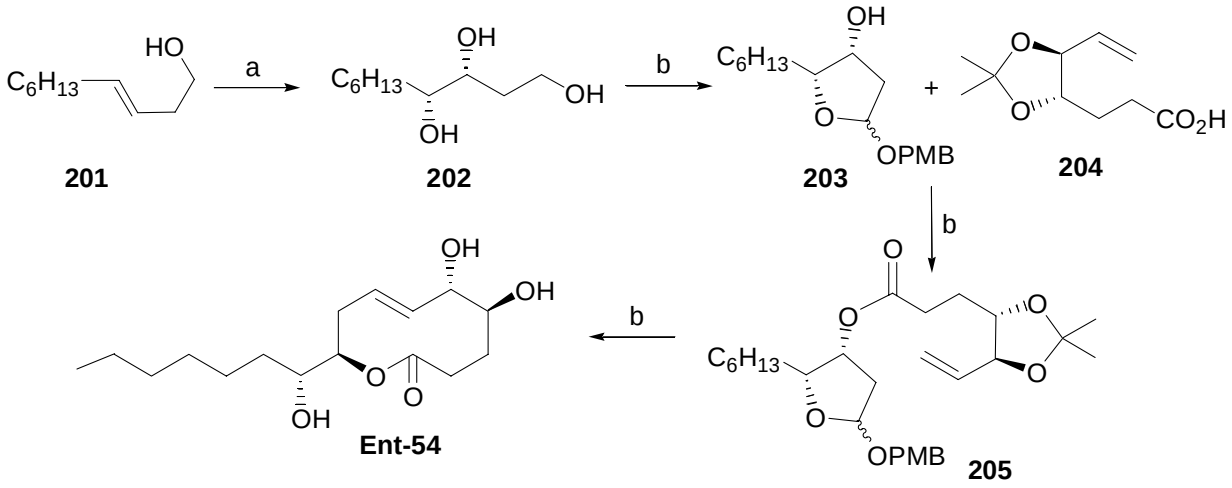



**198** **199** **200**

*Reagents and conditions*: a) (i) $BH_3$-DMS, $B(OMe)_3$, THF; (ii) PhCHO, $(MeO)_3CH$, TFA, $CH_2Cl_2$; (iii) 4-AcN-TEMPO, $PhI(OAc)_2$, $CH_2Cl_2$; (iv) $(CH_2{=}CH)_2Zn$, THF, -50 °C; (b) (i) 1 M aq. HCl, THF; (ii) *p*-TSCl, Py, DMAP; (iii) KCN, DMF, 60 °C; (iv) KOH, MeOH-$H_2O$.

Sharpless dihydroxylation of a homoallyl alcohol **201** has been used in the preparation of the second fragment. One of the difference in the approach of Banwell is they have coupled both the fragment in advance before constructing the olefin of the alcohol fragment.

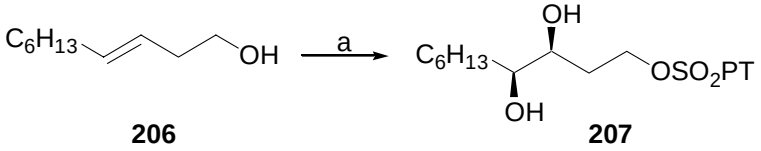
**Scheme 66**




*Reagents and conditions*: a) AD-mix-β, $MeSONH_2$, t-BuOH-$H_2O$, 0 °C; b) 2,2-DMP, *p*-TSOH, $CH_2Cl_2$; c) 4-AcN-TEMPO, $PhI(OAc)_2$, $CH_2Cl_2$; d) AcOH-$H_2O$-THF, 50 °C; e) PMB-OH, *p*-TSOH, $CH_2Cl_2$; f) DCC, DMAP, $CH_2Cl_2$; g) DDQ, THF; h) $Ph_3P{=}CHCO_2Me$, toluene, 0 °C; i) MOM-Cl, DIPEA, $CH_2Cl_2$; j) Grubbs 2$^{nd}$ gen. Cat., $CH_2{=}CH_2$, $CH_2Cl_2$; k) ($Cl_2(PCy_3)_2Ru{=}CHPh$), $CH_2Cl_2$, 40 °C; l) $(CH_2SH)_2$, $BF_3.Et_2O$, $CH_2Cl_2$.

**C) Kitahara's Synthesis of Microcarpalide:** Kitahara *et al*[106c] accomplished the synthesis of microcarpalide employing the Julia olefination and macrolactonization. Synthesis of sulphone fragment required for the Julia olefination reaction was obtained starting from 3-decenol **206** as shown in the Scheme 68.

**Scheme 68**

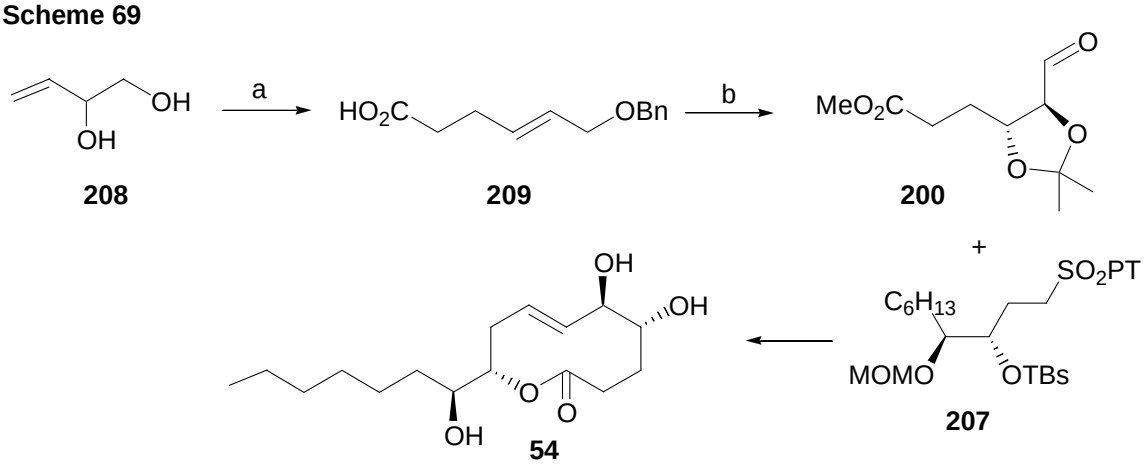



*Reagents and conditions:* a) (i) PMBCl, NaH, TBAB, THF, reflux; (ii) AD-mix-α, t-BuOH, $H_2O$; (iii) DDQ, $CH_2Cl_2$; (iv) MOMCl, DIPEA, $CH_2Cl_2$; (v) AcOH, $H_2O$, THF; (v) PTSH, $PPh_3$, DIAD; (vi) $(NH_4)Mo_7O_{24}.4H_2O$, EtOH; (vii) TBSOTf, 2,6-lutidine, $CH_2Cl_2$.

As depicted in the Scheme 69, the synthesis of aldehyde fragment started from diol **208**. After having the key coupling partners **207** and **200** in hand the authors employed the

Julia olefination reaction for the formation of trans olefin, followed by Yamaguchi protocol for the ring closure and the deprotection led to the formation of microcarpalide **54.**

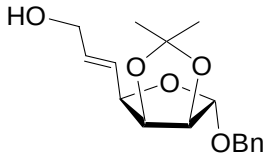
**Scheme 69**




*Reagents and conditions*: a) (i) BnBr, NaH, TBAI, THF; b) $MeC(OMe)_3$, $EtCO_2H$, 140 °C; c) LiOH, THF, $H_2O$; d) AD-mix-β, t-BuOH, $H_2O$; e) 2,2-DMP, HCl, acetone; f) $H_2$, Pd/C, *i*-PrOH; g) 4-MeO-TEMPO, KBr, NaOCl, $NaHCO_3$, $CH_2Cl_2$; g) KHMDS, 18-C-6, -108 °C; h) TBAF, THF; i) LiOH, THF; j) 2,4,6-trichlorobenzoyl chloride, $Et_3N$, THF, DMAP, $C_6H_6$; k) $BF_3.Et_2O$, $(CH_2SH)_2$, $CH_2Cl_2$.

# Experimental Section

**Benzyl 5,6-Dideoxy-2,3-*O*-(isopropylidene)- α-D-*lyxo*-hept-5(*E/Z*)-en-furanoside (161)**




A mixture of **159** (5.2 g, 18.7 mmol) and $PPh_3$=$CHCO_2Et$ in anhydrous $C_6H_6$ under nitrogen atmosphere were stirred under refluxing for 2 h. Removal of solvent followed by chromatographic purification on silica gel by eluting with light petroleum: EtOAc (4:1) afforded **160** (5.3 g, 82 %) as a mixture of *cis*: *trans* isomers (1:1).

**IR** 1783, 1652 $cm^{-1}$

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 1.27–1.35 (m, 6 H), 1.43 (2s, 3 H), 4.15 (dq, 2 H, *J* = 13.6, 7.3 Hz), 4.45 (d, 0.5 H, *J* = 4.9 Hz), 4.51 (d, 0.5 H, *J* = 4.9 Hz), 4.58–4.80 (m, 3 H), 5.11 (2s, 1 H), 5.45–5.51 (m, 0.5 H), 5.97 (dd, 0.5 H, *J* = 11.7, 1.4 Hz), 6.13 (dd, 0.5 H, *J* = 15.6, 1.4 Hz), 6.33 (dd, 0.5 H, *J* = 11.7, 6.8 Hz), 6.96 (dd, 0.5 H, *J* = 15.6, 5.4 Hz), 7.31–7.39 (m, 5 H);

**$^{13}$C NMR** (50 MHz): $\delta$ 13.8, 24.3, 24.6, 25.7, 59.7, 59.8, 68.2, 68.5, 76.2, 77.0, 78.8, 80.7, 81.2, 84.8, 84.9, 104.9, 111.8, 112.5, 120.5, 122.8, 127.3, 127.6, 128.0, 136.8, 137.0, 140.7, 144.5, 164.9, 165.2.

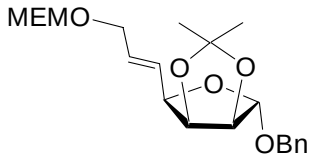
To a solution of compound **160** (5.0 g, 14.36 mmol) in $CH_2Cl_2$ at –78 °C was added DIBAL-H (2.5 M toluene solution) (17.8 mL, 35.7 mmol). After stirring for 1.5 h at –78 °C, excess DIBAL-H was quenched with sat. sodium potassium tartarate solution. The solid formed was filtered and the filtrate was concentrated and the residue purified on silica gel eluting with light petroleum: EtOAc (1:1) to give **161** (4.03 g, 92 %).

**$^1$H NMR** (200 MHz, $CDCl_3$):$\delta$ 1.30 (s, 3 H), 1.45 (s, 3 H), 1.91 (br. s, OH), 4.09–4.23 (m, 3 H), 4.45–4.53 (m, 1 H), 4.58–4.80 (m, 3 H), 5.07 (m, 1 H), 5.71–6.00 (m, 2 H), 7.26–7.37 (m, 5 H);

**$^{13}$C NMR** (50 MHz): $\delta$ 24.5, 25.8, 58.2, 62.0, 68.5, 68.6, 75.3, 80.1, 81.0, 85.0, 104.8, 111.8, 124.4, 125.2, 127.5, 128.1, 133.3,134.4.

Analysis calcd. for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.17; H, 7.09.

**Benzyl 5,6-Dideoxy-2,3-*O*-(isopropylidene)-7-[(2-methoxyethoxy)methoxy]-hept-5(*E/Z*)-en-α-D-*lyxo*-furanoside (162)**



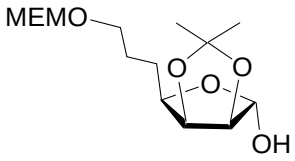

A mixture of compound **161** (3.5 g, 11.43 mmol), diisopropylethylamine (3.0 mL), MEM-Cl (1.6 mL, 13.68 mmol) in $CH_2Cl_2$ (20 mL) was stirred at room temperature for 8 h. The solvent was removed and the residue extracted with ethyl acetate, washed with water, brine, dried ($Na_2SO_4$), evaporated and purified by silica gel column chromatography by eluting with light petroleum: EtOAc (3:2) to afford **162** (3.51 g, 78 %).

**$^1$H NMR** (200 MHz, $CDCl_3$):$\delta$ 1.30 (s, 3 H), 1.46 (s, 3 H), 3.36–3.40 (m, 4 H), 3.50–3.62 (m, 3 H), 3.68–3.75 (m, 2 H), 4.15–4.23 (m, 1 H), 4.46–4.53 (m, 1 H), 4.67 (s, 2 H), 4.74–4.76 (m, 2 H), 5.10 (s, 2 H), 5.82–5.95 (m, 2 H), 7.26–7.32 (m, 5 H);

**$^{13}$C NMR** (50 MHz): $\delta$ 24.9, 26.0, 58.7, 63.2, 66.8, 67.7, 68.7, 71.7, 75.6, 80.3, 81.4, 85.4, 94.5, 94.7, 105.2, 112.4, 126.8, 127.1, 127.6, 127.9, 128.3, 130.1, 131.0, 137.4.

Analysis calcd. for $C_{21}H_{30}O_7$: C, 63.94; H, 7.67. Found: C, 64.10; H, 7.19.

**2,3-*O*-(Isopropylidene)-5,6–dideoxy-7-[(2-methoxyethoxy)methoxy]-α-D-*lyxo*-heptofuranose (163)**

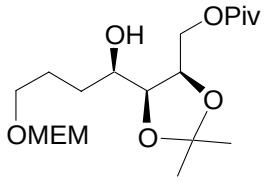



A mixture of compound **162** (3.5 g, 8.88 mmol), cat. Pd/C (100 mg), in MeOH was stirred under hydrogen atmosphere at 6 bar and at 60 °C for 3 h. Catalyst was filtered off and the filtrate was concentrated to give **163** (2.6 g, 96 %).

**$^1$H NMR** (200 MHz, $CDCl_3$):$\delta$ 1.30 (s, 3 H), 1.43 (s, 3 H), 1.69–1.75 (m, 4 H), 2.87 (br. s, OH), 3.38 (s, 3 H), 3.52–3.61 (m, 4 H), 3.65–3.68 (m, 2 H), 4.01–4.17 (m, 2 H), 4.54–4.65 (m, 2 H), 4.69 (s, 2 H);

Analysis calcd. for $C_{14}H_{26}O_7$: C, 54.89; H, 8.55. Found: C, 54.43; H, 8.71.

**(2*R*,3*S*,4*R*)-1-(Trimethylacetyl)-2,3-isopropylidenedioxy-4-hydroxy-7-[(2-methoxyethoxy)methoxy]heptanol (165)**




To a solution of compound **163** (2.5 g, 8.16 mmol) in THF (20 mL) at 0 °C was added $LiAlH_4$ (0.31 g, 8.07 mmol) and stirred at 0 °C for 3 h. Excess of $LiAlH_4$ was quenched by the addition of ethyl acetate. The solid formed was filtered, and the filtrate was concentrated, purified by silicagel column chromatography eluting with light petroleum ether: EtOAc (1:4) to afford **164** (2.3 g, 92 %).

$[\alpha]_D$ + 18.2 (*c* 2.8, $CHCl_3$)

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 1.35–1.48 (2s, 6 H), 1.57–1.84 (m, 4 H), 2.25 (br s, OH), 3.37 (s, 3 H), 3.51–3.57 (m, 4 H), 3.63–3.77 (m, 5 H), 4.01 (dd, 1H, *J* = 6.8, 3.4 Hz), 4.17 (dt, 1 H, *J* = 6.8, 5.1 Hz), 4.68 (s, 2 H);

**$^{13}$C NMR** (50 MHz): $\delta$ 24.6, 25.6, 26.8, 31.0, 58.4, 60.3, 66.2, 68.25, 71.3, 77.0, 94.9,107.7.

To a solution of **164** (2.0 g, 6.5 mmol) in pyridine (10 mL) under nitrogen at 0 °C was added pivolyl chloride (1.2 mL, 9.74 mmol) drop wise. After stirring for 1 h at room temperature, solvent was evaporated, the residue extracted with ethyl acetate, washed with 1N HCl, brine, dried ($Na_2SO_4$) and evaporated. The residue was purified on silica gel by eluting with light petroleum: EtOAc (7:3) to give **165** (2.31 g, 91 %).

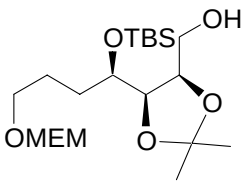
$[\alpha]_D$ + 24.2 (*c* 2.5, $CHCl_3$)

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 1.21 (s, 9 H), 1.36-1.48 (2s, 6 H), 1.56–1.83 (m, 4 H), 3.39 (s, 3 H), 3.52–3.61 (m, 5 H), 3.64–3.70 (m, 2 H), 4.03 (t, 1 H, *J* = 4.8 Hz), 4.22–4.30 (m, 3 H), 4.7 (s, 2 H);

**$^{13}$C NMR** (50 MHz): $\delta$ 23.5, 24.6, 26.6, 26.9, 30.1, 58.2, 62.9, 66.2, 66.9, 68.0, 71.2, 74.5, 79.1, 94.8, 107.8.

Analysis calcd. for $C_{19}H_{36}O_8$: C, 58.14; H, 9.25. Found: C, 57.91; H, 9.18.

**(2*R*,3*R*,4*R*)-2,3-(Isopropylidenedioxy)-4-(*tert*-butyldimethylsilyloxy)-7-[(2-methoxyethoxy)methoxy]hept-1-ol (167)**




A solution of **165** (2.3 g, 58.88 mmol), imidazole (0.8 g, 11.7 mmol) and TBS-Cl (1.33 g, 8.82 mmol) in DMF (10 mL) under nitrogen was stirred at room temperature for 4 h. Reaction mixture was diluted with ether, washed with water, dried ($Na_2SO_4$), residue purified on silica gel by eluting with light petroleum: EtOAc (4:1) to afford **166** (2.6 g, 90 %).

$[\alpha]_D$ + 41.1 (*c* 3.6, $CHCl_3$)

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ -0.05 (s, 6 H), 0.87 (s, 9 H), 1.31–1.43 (2s, 6 H), 1.51–1.85 (m, 4 H), 3.37 (s, 3 H), 3.49–3.55 (m, 4 H), 3.62–3.76 (m, 3 H), 3.99 (dd, 4 H, *J* = 8.1, 5.4 Hz), 4.67 (s, 2 H);

**$^{13}$C NMR** (50 MHz): $\delta$ -4.8, -4.3,18.0, 25.2, 25.7, 26.8, 27.58, 30.46, 38.29, 58.4, 62.9, 66.3, 67.0, 70.0, 71.4, 74.6, 80.2, 95.0, 107.9,177.4.

To the above product **166** (2.5 g, 6.39 mmol) in DCM (20 mL) under nitrogen and at -78 °C was added DIBAL-H (2.6 M toluene solution) (6.2 mL, 62.62 mmol) drop wise. After1 h, excess of DIBAL-H was quenched by using aq. sodium potassium tartarate solution. The solid was filtered and filtrate concentrated, and the residue purified on silica gel by using light petroleum: EtOAc (1:1) to give **167** (1.88 g, 89 %).

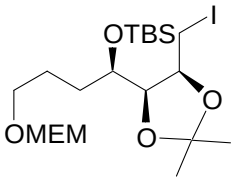
$[\alpha]_D$ + 56.3 (*c* 3.1, $CHCl_3$)

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ -0.05 (s, 6 H), 0.87 (s, 9 H), 1.31–1.43 (2s, 6 H), 1.51–1.72 (m, 4 H), 2.25 (br s, OH), 3.37 (s, 3 H), 3.48–3.76 (m, 9 H), 3.98–4.18 (m, 2 H), 4.67 (s, 2 H);

**$^{13}$C NMR** (50 MHz): $\delta$ –4.8, –4.3,18.0, 25.0, 25.7, 27.8, 30.5, 58.4, 60.9, 66.3, 67.1, 70.0, 71.4, 77.4, 80.2, 95.0,107.8.

Analysis calcd. for $C_{20}H_{42}O_7Si$: C, 56.84; H, 10.02. Found: C, 56.79; H, 9.98.

**(2*S*,3*R*,4*R*)-1-Iodo-2,3-isopropylidenedioxy-4-(*tert*-butyldimethylsilyloxy)-7-[(2-methoxyethoxy)methoxy]heptane (150) and (2*S*,3*R*)-1,4-Anhydro-2,3-(isopropylidenedioxy)-7-[(2-methoxyethoxy)methoxy]-D-*lyxo*-heptitol (168)**



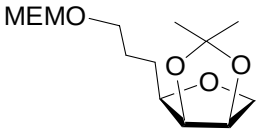

**Procedure A**: A mixture of compound **167** (0.5 g, 2.82 mol), $PPh_3$ (0.46 g, 1.76 mmol), imidazole (0.12 g, 1.76 mmol) and $Et_3N$ (0.25 mL) in $CH_2Cl_2$ was stirred at room temperature under nitrogen atmosphere for 2.5 h. The reaction mixture was diluted with $CH_2Cl_2$, washed with 20% aq. $Na_2S_2O_3$ solution, brine, dried ($Na_2SO_4$), evaporated. The residue was purified on silica gel by eluting with light petroleum: EtOAc (4:1) to obtain **150** (0.28 g, 45%), Further elution gave **168** (0.015 g, 15%).

$[\alpha]_D$ + 84.8 (*c* 2.2, $CHCl_3$)

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ -0.07 (s, 6H), 0.88 (s, 9 H), 1.34–1.49 (2s, 6 H), 1.53–1.83 (m, 4 H), 3.12 (t, 1 H, *J* = 10.4 Hz), 3.27 (dd, 1 H, *J* = 10.4, 3.3 Hz), 3.4 (s, 3 H), 3.52–3.58 (m, 4 H), 3.65–3.70 (m, 2 H), 3.78–3.81 (m, 1 H), 3.93 (dd, 1 H, *J* = 8.2, 5.3 Hz), 4.22 (m, 1 H), 4.7(s, 2 H);

**$^{13}$C NMR** (50 MHz): $\delta$ -4.9, -4.4, 5.6,18.0, 25.2, 25.6, 27.8, 30.2, 58.4, 66.3, 66.8, 70.0, 71.3, 77.0, 80.2, 94.9.

Analysis calcd. for $C_{20}H_{41}IO_6Si$: C, 45.11; H, 7.76. Found: C, 44.98; H, 7.58.



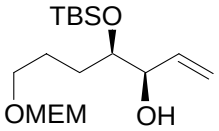

$[\alpha]_D$ + 32.2 (*c* 1, $CHCl_3$)

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 1.30 (s, 3 H), 1.46 (s, 3 H), 1.65–1.81 (m, 4 H), 3.38 (s, 3 H), 3.43–3.47 (m, 2 H), 3.52–3.60 (m, 4 H), 3.64–3.70 (m, 2 H), 3.96 (d, 1 H, *J* = 10.6 Hz), 4.5 (dd, 1 H, *J* = 6.3, 3.7 Hz), 4.7 (s, 2 H), 4.73 (dd, 1 H, *J* = 6.3, 3.7 Hz);

Analysis calcd. for $C_{14}H_{26}O_6$: C, 57.91; H, 9.03. Found: C, 57.79; H, 9.12.

**Procedure B:** A mixture of **167** (1.5 g, 3.54 mmol), $PPh_3$ (1.4 g, 5.33 mmol), imidazole (0.36 g, 5.28 mmol) and $I_2$ (1.34 g, 5.29 mmol) was stirred under nitrogen in ether-benzene (2:1) (10 mL) at room temperature for 1.5 h. the reaction mixture was diluted with ether, washed with 20% aq. $Na_2S_2O_3$ solution, water, brine, dried ($Na_2SO_4$) and evaporated. The residue was purified on silica gel by eluting with light petroleum: EtOAc (4:1) to get exclusively **150** (1.6 g, 86%).

**(3*R*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)-7-[(2-methoxyethoxy)methoxy]hept-1-en-3-ol (149)**




A mixture of **150** (1.5 g, 2.82 mmol), Zinc (0.36 g, 5.64 g. eq) in refluxing ethanol (15 mL) under nitrogen was stirred for 1.5 h. The zinc was filtered, filtrate concentrated, and the residue purified by silica gel chromatography by using light petroleum: EtOAc (7:3) to obtain **149** (0.94 g, 94 %).

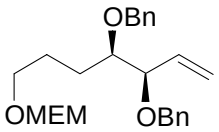
$[\alpha]_D$ + 72.7 (*c* 0.75, $CHCl_3$)

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ -0.65 (s, 6 H), 0.89 (s, 9 H), 1.56–1.69 (m, 4 H), 2.38 (d, OH, *J* = 6.3 Hz), 3.40 (s, 3 H), 3.51–3.61 (m, 5 H), 3.70 (ddd, 2 H, *J* = 5.4, 3.5, 1.1 Hz), 3.95–4.04 (m, 1 H), 4.71 (s, 2H), 5.19 (dt, 1 H, *J* = 10.2, 1.5 Hz), 5.31 (dt, 1 H, *J* = 17.3, 1.5 Hz), 5.84 (ddd, 1 H, *J* = 17.3, 10.2, 5.3 Hz);

**$^{13}$C NMR** (50 MHz): $\delta$ -4.9,17.5, 25.0, 25.4, 58.2, 66.0, 67.2, 71.2, 73.8, 74.5, 94.7,114.7, 137.8.

Analysis calcd. for $C_{17}H_{36}O_5Si$: C, 58.58; H, 10.41. Found: C, 58.23; H, 10.15.

**(4*R*,5*R*)-4,5-Bis(benzyloxy)-7-[(2-methoxyethoxy)methoxy]hept-1-ene (170)**




A solution of **149** (2.0 g, 5.7 mmol) and 1 M solution of TBAF (5.7 mL, 5.7 mmol) in THF (10 mL) was stirred at room temperature for 1 h and evaporated. The residue was purified by silica gel by using light petroleum: EtOAc (3:7) to give **169** (1.31 g, 85%).

$[\alpha]_D$ + 24.5 (*c* 0.9, $CHCl_3$)

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 1.52–1.81 (m, 4 H), 3.39 (s, 3 H), 3.44–3.62 (m, 5 H), 3.65–3.71 (m, 2 H), 3.89 (t, 1 H, *J* = 1.3 Hz), 4.71 (s, 2 H), 5.22 (dt, 1 H, *J* = 10.2, 1.4 Hz), 5.34 (dt, 1 H, *J* = 17.2, 1.4 Hz), 5.84 (ddd, 1 H, *J* = 17.2, 10.5, 6.5 Hz);

**$^{13}$C NMR** (50 MHz): $\delta$ 25.5, 29.9, 58.5, 66.4, 67.5, 71.4, 73.8, 75.9, 95.0,116.5, 137.6.

To the above product **169** (1.5 g, 6.41 mmol) in DMF (10 mL) at 0 °C was added NaH (60 % dispersion in mineral oil, 0.56 g, 14 mmol). After 15 min, benzylbromide (1.7 mL, 14 mmol) was introduced and the reaction further stirred for 2 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 (1:9) to afford **170** (2.34 g, 88 %).

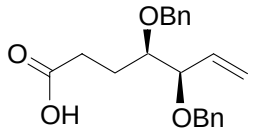
$[\alpha]_D$ + 8.9 (*c* 1.4, $CHCl_3$)

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 1.44–1.76 (m, 4 H), 3.39 (s, 3 H), 3.47–3.55 (m, 5 H), 3.63–3.68 (m, 2 H), 3.9 (t, 1 H, *J* = 6.4 Hz), 4.25 (d, 1 H, *J* = 12.1 Hz), 4.55 (d, 1 H, *J* = 11.4 Hz), 4.65 (d, 1 H, *J* = 12.1 Hz), 4.68 (s, 2 H), 4.76 (d, 1 H, *J* = 11.4 Hz), 5.25–5.35 (m, 2 H), 5.82 (ddd, 1 H, *J* = 18.5, 10.9, 7.6 Hz), 7.23-7.32 (m, 10 H);

**$^{13}$C NMR** (50 MHz): $\delta$ 25.5, 27.2, 58.4, 66.3, 70.2, 71.5, 72.7, 80.6, 82.2, 95.0, 118.0,127.0, 127.3, 127.5, 127.9, 135.1, 138.3, 138.6.

Analysis calcd. for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27. Found: C, 72.18; H, 8.13.

**(4*R*,5*R*)-4,5-Bis(benzyloxy)hept-6-enoic acid (I)**




A solution of **170** (0.9 g, 2.1 mmol) and PPTs (5.27 g, 21 mmol) in *t*-BuOH (20 mL) was heated at 80 °C for 1.5 h. Solvent was removed, residue extracted with ethyl acetate, washed with water, brine, dried ($Na_2SO_4$), evaporated. The residue was purified by silica gel column chromatography by eluting with EtOAc: light petroleum (2:3) to give **148** (0.59 g, 85 %).

$[\alpha]_D$ + 10.4 (*c* 1.3, $CHCl_3$)

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 1.43–1.70 (m, 4 H), 1.83 (s, OH), 3.46–3.57 (m, 3 H), 3.93 (t, 1 H, *J* = 6.4 Hz), 4.38 (d, 1 H, *J* = 11.9 Hz), 4.54 (d, 1 H, *J* = 11.4 Hz), 4.63 (d, 1 H, *J* = 11.9 Hz), 4.75 (d, 1 H, *J* = 11.4 Hz), 5.25–5.35 (m, 2 H), 5.8 (ddd, 1H, *J* = 16.6, 10.8, 7.5 Hz), 7.22-7.31 (m, 10 H);

**$^{13}$C NMR** (50 MHz): $\delta$ 27.1, 28.7, 62.3, 70.4, 73.0, 80.9, 82.2, 118.6,121.7-128.1 (m), 135.1, 138.3, 138.4.

A solution of DMSO (0.34 mL, 4.76 mmol) in anhydrous $CH_2Cl_2$ was added drop wise to a solution of $(COCl)_2$ (0.17 mL, 1.98 mmol) in anhydrous $CH_2Cl_2$ (5 mL) under nitrogen atmosphere at –78 °C. The mixture was stirred for 5 min and then a solution of **148** (0.52 g, 1.59 mmol) in anhydrous $CH_2Cl_2$ was added drop wise. After 30 min $Et_3N$ (0.9 mL) was slowly introduced. After 1 h at room temperature, the reaction mixture was diluted with water, extracted with $CH_2Cl_2$, washed with brine, dried ($Na_2SO_4$) and evaporated to give aldehyde **171** (0.46 g, 89 %) used as such for the next reaction.

A solution of $NaClO_2$ (0.19 g, 2.08 mmol) in water (2 mL) was added drop wise in to **171** (0.46 g, 1.41 mmol), DMSO (2 mL), $NaH_2PO_4$ (0.16 g, 1.05 mmol) and 2 mL water. After 2 h the reaction mixture was then diluted with water, extracted with EtOAc, dried ($Na_2SO_4$) concentrated, followed by silica gel chromatography by eluting with light petroleum: EtOAc (9:1) to give **I** (0.33 g, 69 %).

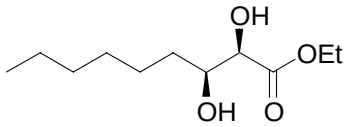
$[\alpha]_D$ + 16.8 (*c* 0.7, $CHCl_3$)

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 1.61-1.80 (m, 1 H), 1.83-1.99 (m, 1 H), 2.33-2.44 (m, 2 H), 3.52 (ddd, 1 H, *J* = 9.3, 6.0, 3.7 Hz), 3.90 (t, 1 H, *J* = 6.5 Hz), 4.38 (d, 1 H, *J* = 12.2 Hz), 4.52 (d, 1 H, *J* = 11.3 Hz), 4.64 (d, 1 H, *J* = 12.1 Hz), 4.76 (d, 1 H, *J* = 11.3 Hz), 5.32 (br. dd, 1 H, *J* = 18.4, 1.7 Hz), 5.36 (br. dd, 1 H, *J* = 9.1, 1.8 Hz), 5.81 (br. ddd, 1 H, *J* = 18.3, 10.9, 7.5 Hz), 7.25-7.33 (m, 10 H);

**$^{13}$C NMR** (50 MHz, $CDCl_3$): $\delta$ 26.3, 30.9, 70.5, 73.3, 80.2, 82.7, 96.1, 118.8, 127.4, 127.6, 127.9, 135.1, 138.6, 178.7.

Anal. calcd for $C_{15}H_{30}O_4$: C, 65.66; H, 11.02. Found: C, 65.07; H, 10.83.

**Ethyl (2*R*,3*S*)-2,3-Dihydroxy nonoate (172)**




To a mixture of $K_3[Fe(CN)_6]$ (26.67 g, 81.2 mmol), $K_2CO_3$ (11.2 g, 81.2 mmol), $(DHQ)_2$ PHAL (0.211 g, 0.27 mmol), $MeSO_2NH_2$ (2.57 g, 27.1 mmol) and $K_2OsO_4.2H_2O$ (0.211 g, 0.1 mmol) in *t*-BuOH:$H_2O$ (200 mL total volume, 1:1 mixture) at 0 °C was added olefin **154** (5 g, 27.1 mmol) and stirred at 0 °C. After 10 h, sodium sulphite (10.2 g) was added, solvent removed under vacuo. The residue was extracted with ethyl acetate, washed with 2N KOH, water, brine, dried ($Na_2SO_4$) and evaporated. The residue on purification by silica gel chromatography by eluting with light petroleum: EtOAc (4:1) to afford the diol **172** (5.56 g, 94 %)

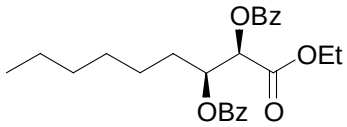
$[\alpha]_D$ – 10.7 (*c* 1.0, $CHCl_3$)

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 0.87 (t, 3 H, *J* = 6.6 Hz), 1.21–1.38 (m, 8 H), 1.44–1.51 (m, 2 H), 1.56 (t, 3 H, *J* = 7.4 Hz), 2.50 (br.s, OH), 3.88 (dt, 1 H, *J* = 6.4, 2.1 Hz), 4.08 (d, 1 H, *J* = 2.1 Hz), 4.28 (q, 2 H, *J* = 7.4 Hz);

**$^{13}$C NMR** (50 MHz, $CDCl_3$): $\delta$ 13.8, 22.3, 25.5, 29.0, 31.5, 33.2, 61.5, 72.4, 73.3, 173.5.

Anal. calcd for $C_{11}H_{22}O_4$: C, 60.52; H, 10.16. Found: C, 60.27; H, 10.43.

**Ethyl (2*R*,3*S*)-2,3-di-*O*-benzoyl nonoate (172a)**

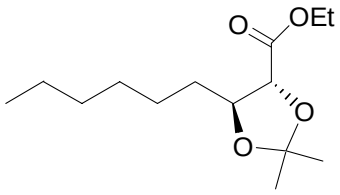



A solution of **172** (0.1 g, 0.46 mmol) and benzoyl chloride (0.64 mL, 0.55 mmol), $Et_3N$ (0.96 mL, 0.68 mmol) in anhydrous $CH_2Cl_2$ were stirred at room temperature for 3 h. the reaction mixture was diluted with $CH_2Cl_2$ and washed with water, dried ($Na_2SO_4$) and concentrated. The residue was purified by silica gel chromatography by using light petroleum ether: EtOAc (85:15) to give **172a** (0.16 g, 86%).

$[\alpha]_D$ – 33.4 (*c* 1.1, $CHCl_3$)

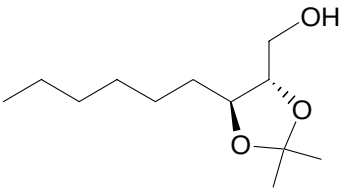
**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 0.87 (t, 3 H, $J$ = 6.8 Hz), 1.24–1.34 (m, 11 H), 1.56 (t, $J$ = 7.3 Hz), 4.18 (q, 2 H, $J$ = 7.3 Hz), 5.50 (dt, 1 H, $J$ = 1.9 Hz), 5.74 (dt, 1 H, $J$ = 6.6, 1.9 Hz), 7.46-7.63 (m, 6 H), 8.07 (d, 2 H, $J$ = 6.65 Hz), 8.16 (d, 2 H, $J$ = 6.65 Hz);
Anal. calcd for $C_{25}H_{30}O_6$: C, 70.40; H, 7.09. Found: C, 70.57; H, 7.66.

**Ethyl (2*R*,3*S*)-2,3-(Isopropilidenedioxy)nonoate (173)**




A solution of **172** (5.5 g, 25.2 mmol), 2,2-dimethoxypropane (3.7 mL, 30.27 mmol) and catalytic *p*-TSA in $CH_2Cl_2$ (50 mL) was stirred at room temperature for 4 h. It was diluted with $CH_2Cl_2$, washed with $NaHCO_3$, water, brine, concentrated and purified by silica gel chromatography by using light petroleum: EtOAc (9:1) to afford **173** (6.26 g, 96%).
$[\alpha]_D$ – 17.6 (*c* 1.4, $CHCl_3$)
**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 0.89 (t, 3 H, $J$ = 6.4 Hz), 1.21–1.42 (m, 10 H), 1.40–1.43 (2s, 6 H), 1.57 (t, 3 H, $J$ = 7.4 Hz), 4.05–4.12 (m, 2 H), 4.25 (q, 2 H, $J$ = 7.4 Hz);
**$^{13}$C NMR** (50 MHz, $CDCl_3$): $\delta$ 13.6, 22.2, 25.2, 28.8, 31.3, 33.2, 61.0, 78.9, 110.3,170.5.
Anal. calcd for $C_{14}H_{26}O_4$: C, 65.09; H, 10.14. Found: C, 64.87; H, 10.37.

**(2*R*,3*S*)-2,3-(Isopropilidenedioxy)-nonane-1-ol (174)**



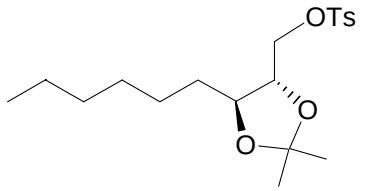

To a solution of **173** (5.2 g, 20.1 mmol) in $CH_2Cl_2$ (50 mL) at –78 °C was added DIBAL-H (2.5 M solution in toluene, 20 mL, 50 mmol). After stirring at –78 °C for 1 h, excess of DIBAL-H was quenched by the addition of saturated aq. sodium potassium tartarate. The solid was filtered, filtrate concentrated and the residue purified on silica gel eluting with light petroleum: EtOAc (3:2) to give **174** (4.2 g, 97 %).
$[\alpha]_D$ – 24.5 (*c* 1.1, $CHCl_3$)

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 0.86 (t, 3 H, $J$ = 6.2 Hz), 1.26–1.37 (m, 8 H), 1.39–1.40 (2 s, 6 H), 1.46–1.59 (m, 2 H), 1.8 (br s, OH), 3.53 (dd, 1 H, $J$ = 11.3, 3.8 Hz), 3.67 (m, 2 H), 3.81–3.91 (m, 1 H);

**$^{13}$C NMR** (50 MHz): $\delta$ 13.8, 22.4, 25.8, 26.9, 27.2, 29.2, 31.6, 33.0, 62.2, 77.2, 81.9, 108.4.27.1, 28.7, 62.3, 70.4, 73.0, 80.9.

Analysis calcd. for $C_{12}H_{24}O_3$: C, 66.63; H, 11.18. Found: C, 66.81; H, 10.98.

**(2*R*,3*S*)-2,3-(Isopropilidenedioxy)-1-(*p*-toluene sulphonyl) nonane (153)**




Compound **174** (4.1 g, 19.0 mmol), TsCl (4.43 g, 22.76 mmol) and pyridine (20 mL) were stirred at room temperature for 7 h. Pyridine was removed under vacuo and the residue extracted with EtOAc, washed with 1N HCl, water, brine, dried ($Na_2SO_4$) and evaporated. The residue was purified by silica gel column chromatography by eluting with light petroleum: EtOAc (4:1) to give **153** (6.74 g, 96%).

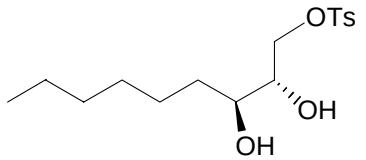
$[\alpha]_D$ – 16.4 (*c* 3.6, $CHCl_3$), Lit.[102b] $[\alpha]_D$ – 16.2 (*c* 1.17, $CHCl_3$)

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 0.89 (t, 3 H, $J$ = 6.9 Hz), 1.27-1.31 (m, 11 H), 1.37 (s, 3 H), 1.46–1.58 (m, 2 H), 2.46 (s, 3 H), 3.77–3.81 (m, 2 H), 4.07–4.11 (m, 2 H), 7.35 (d, 2 H, $J$ = 8.2 Hz), 7.81 (d, 2 H, $J$ = 8.2 Hz);

**$^{13}$C NMR** (50 MHz): $\delta$ 13.3, 20.7, 21.7, 25.0, 25.6, 26.5, 28.4, 30.9, 32.3, 68.6, 76.0, 77.5, 108.3, 127.2, 129.1, 132.4,144.2.

Analysis calcd. for $C_{21}H_{34}O_5S$: C, 61.59; H, 8.16, S, 8.65. Found: C, 61.86; H, 8.03, S, 8.32.

**(2*R*,3*S*)-1-(*p*-Toluene sulphonyl)-2,3-dihydroxy nonane (175)**




To a solution of **153** (6.5 g, 17.56 mmol) in MeOH (30 mL) was added HCl (cat.) and the mixture was stirred at room temperature for 3 h. Solvent was removed in vacuo and the

residue extracted with EtOAc, washed with water, brine, dried ($Na_2SO_4$) and evaporated. The residue was purified by silica gel chromatography eluting with light petroleum: EtOAc (3:2) to afford diol **175** (5.1 g, 87 %)

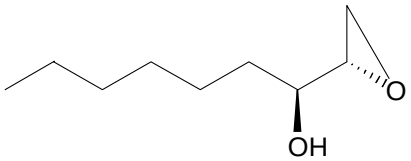
$[\alpha]_D$ – 23.41 (*c* 1.6, $CHCl_3$)

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 0.88 (t, 3 H, *J* = 6.5 Hz), 1.27 (m, 8 H), 1.41–1.53 (m, 2 H), 2.05 (br s, OH), 2.46 (s, 3 H), 3.55–3.63 (m, 1 H), 3.70–3.76 (m, 1 H), 4.09 (dd, 2 H, *J* = 4.9, 3.3 Hz), 7.36 (d, 2 H, *J* = 8.4 Hz), 7.81 (d, 2 H, *J* = 8.4 Hz);

**$^{13}$C NMR** (50 MHz): $\delta$ 13.8, 21.4, 22.3, 25.3, 29.0, 29.2, 31.5, 33.1, 70.6, 71.3, 128.0, 129.8, 132.4, 144.9.

Analysis calcd. for $C_{16}H_{26}O_5S$: C, 60.31; H, 8.43, S, 8.94. Found: C, 60.1; H, 8.58; S, 8.68.

**(3*S*,4*S*)-2,3-Epoxy-4-hydroxy nonane (176)**




Compound **175** (5 g, 15.13 mmol) was dissolved in MeOH (30 mL) and $K_2CO_3$ (3.13 g, 22.68 mmol) was added. The mixture was stirred at room temperature for 3.5 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 **176** (2.03 g, 85 %).

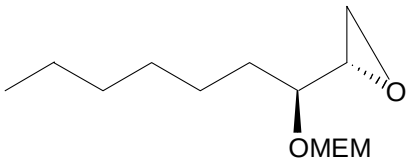
$[\alpha]_D$ – 5.0 (*c* 1.2, $CHCl_3$)

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 0.96 (t, 3 H, *J* = 6.4 Hz), 1.24–1.41 (m, 8 H), 1.56–1.64 (m, 2 H), 2.72 (dd, 1 H, *J* = 4.9, 2.5 Hz), 2.82 (t, 1 H, *J* = 4.9 Hz), 2.97 (dt, 1H, *J* = 6.8, 2.5 Hz), 3.43 (br m, 1H);

**$^{13}$C NMR** (50 MHz): $\delta$ 13.8, 22.4, 25.1, 29.1, 29.2, 31.6, 34.1, 45.0, 55.5, 71.7.

Analysis calcd. for $C_9H_{18}O_2$: C, 68.31; H, 11.47. Found: C, 68.08; H, 11.73.

**(3*S*,4*S*)-2,3-Epoxy-4-[(2-methoxyethoxy)methoxy]nonane (152)**




A mixture of compound **176** (2.0 g, 12.6 mmol), MEM-Cl (1.73 mL, 15.17 mmol) and DIPEA (3.28 mL, 18.97 mmol) in $CH_2Cl_2$ (15 mL) were stirred at room temperature for 6 h and concentrated. The residue was extracted with ethyl acetate, washed with water, dried ($Na_2SO_4$), evaporated and was purified by silica gel chromatography using light petroleum: EtOAc (4:1) to afford **152** (2.55 g, 82 %)

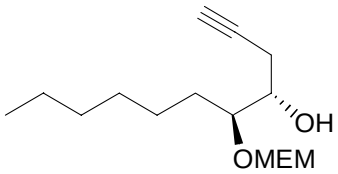
$[\alpha]_D$ – 41.06 (*c* 1.7, $CHCl_3$)

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 0.87 (t, 3 H, *J* = 6.4 Hz), 1.2–1.36 (m, 8 H), 1.55–1.62 (m, 2 H), 2.5 (dd, 1 H, *J* = 4.9, 2.6 Hz), 2.74 (dd, 1 H, *J* = 4.9, 3.9 Hz), 2.93 (ddd, 1 H, *J* = 7.0, 4.2, 2.7 Hz), 3.22-3.32 (m, 1 H), 3.37 (s, 3 H), 3.51–3.77 (m, 4 H), 4.73 (d, 1 H, *J* = 6.9 Hz), 4.92 (d, 1 H, *J* = 6.9 Hz);

**$^{13}$C NMR** (50 MHz): $\delta$ 13.3, 21.8, 24.6, 28.6, 31.0, 42.6, 53.7, 57.9, 66.2, 71.0, 77.0, 93.5.

Analysis calcd. for $C_{13}H_{26}O_4$: C, 63.38; H, 10.64. Found: C, 63.28; H, 10.23.

**(4*S*,5*S*)-4-Hydroxy-5-[(2-methoxyethoxy)methoxy]-undeca-1-yne (177)**




To a solution of **152** (1.5 g, 6.08 mmol) in DMSO (5 mL) at 0 °C was added lithium acetylide-EDA complex (0.82 g, 8.87 mmol) in one portion. The reaction mixture was stirred at 0 °C for 30 min and over night at room temperature. The excess of reagent was quenched with sat. ammonium chloride and extracted with EtOAc, washed with water, brine, dried ($Na_2SO_4$), concentrated. The residue was purified by silica gel chromatography by eluting with light petroleum ether: EtOAc (7:3) to afford **177** (1.42 g, 86 %).

$[\alpha]_D$ + 10.1 (*c* 1.05, $CHCl_3$)

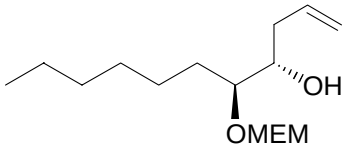
**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 0.87 (t, 3 H, *J* = 6.4 Hz), 1.21–1.27 (m, 8 H), 1.47–1.65 (m, 2 H), 1.99 (t, 1 H, *J* = 3.6 Hz), 2.05 (s, OH), 2.43 (ddd, 2 H, *J* = 11.9, 10.7, 2.4 Hz), 3.42 (s, 3

H), 3.56 (t, 2 H, *J* = 3.6 Hz), 3.62-3.86 (m, 4 H), 4.82 (d, 2 H, *J* = 3.6 Hz), 4.92 (d, 1 H, *J* = 6.9 Hz);

**$^{13}$C NMR** (50 MHz): $\delta$ 13.8, 22.3, 23.3, 24.9, 29.1, 30.5, 31.5, 58.6, 67.3, 70.0, 70.7, 71.5, 80.4, 80.6,95.4.

Analysis calcd. for $C_{15}H_{28}O_4$: C, 66.14; H, 10.36. Found: C, 66.28; H, 10.21.

**(4*S*,5*S*)-4-Hydroxy-5-[(2-methoxyethoxy)methoxy]-undeca-1-ene (II)**




Compound **177** (1 g, 3.67 mmol), Lindlar catalyst (20 mg) and quinoline (5 mg) in benzene (10 mL) were stirred under hydrogen atmosphere at ntp for 30 min. 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 (7:3) to give **II** (0.93 g, 91 %).

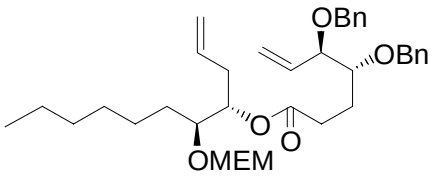
$[\alpha]_D$ + 38 (*c* 0.9, $CHCl_3$)

**$^1$H NMR** (200MHz, $CDCl_3$): $\delta$ 0.90 (t, 3 H, *J* = 6.6 Hz), 1.21–1.38 (m, 8 H), 1.44–1.61 (m, 2 H), 2.1–2.39 (m, 2 H), 2.81 (s, OH), 3.37–3.49 (m, 1 H), 3.39 (s, 3 H), 3.52–3.84 (m, 5 H), 4.7–4.87 (m, 2 H), 5.06–5.17 (m, 2 H), 5.88 (br. ddt, 1 H, *J* = 17.4, 10.6, 7.0 Hz);

**$^{13}$C NMR** (50 MHz): $\delta$ 14.1, 22.6, 25.1, 29.4, 30.8, 31.7, 37.8, 58.9, 67.6, 71.7, 72.0, 82.4, 95.9, 117.1,134.9.

Analysis calcd. for $C_{15}H_{30}O_4$: C, 66.66; H, 11.02. Found: C, 65.07; H, 10.83.

**(4*R*,5*R*)-4,5-(Isopropylidenedioxy)hept-6-enoicacid,**
**(1'*S*,1''*S*)-1'-(1''-[(2-methoxyethoxy)methoxy]-3'-butenyl ester (178)**




To a solution of compounds **I** (0.07 g, 0.25 mmol), **II** (0.08 g, 0.25 mmol) and DMAP (5 mg) in $CH_2Cl_2$ (2mL) was added DCC (0.057 g, 0.27 mmol). The reaction mixture was

stirred at room temperature for 15 h, filtered and evaporated to afford a residue, which on purification by silica gel column chromatography eluting with light petroleum: EtOAc (7:3) afforded **178** (0.11 g, 76 %).

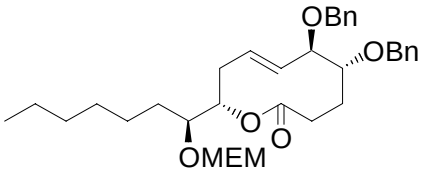
$[\alpha]_D$ + 10.7 (*c* 1.0, $CHCl_3$)

**$^1$H NMR** (500 MHz, $CDCl_3$): $\delta$ 0.87 (t, 3H, *J* = 6.9 Hz), 1.21–1.34 (m, 8 H), 1.46–1.54 (m, 2 H), 1.67–1.74 (m, 1 H), 1.88–1.95 (m, 1 H), 2.25–2.46 (m, 4 H), 3.37 (s, 3 H), 3.49–3.54 (m, 3 H), 3.58 (br. ddd, 1 H, *J* = 6.2, 5.6, 4.3 Hz), 3.66–3.73 (m, 2 H), 3.87 (t, 1 H, *J* = 6.7 Hz), 4.38 (d, 1 H, *J* = 11.9 Hz), 4.52 (d, 1 H, *J* = 11.4 Hz), 4.62 (d, 1 H, *J* = 11.9 Hz), 4.71–4.77 (m, 3 H), 4.99–5.07 (m, 3 H), 5.27–5.33 (m, 2 H), 5.71 (dddd, 1 H, *J* = 17.1, 10.1, 7.6, 6.6 Hz), 5.80 (ddd, 1 H, *J* = 17.3, 10.6, 7.6 Hz), 7.25–7.30 (m, 10 H);

**$^{13}$C NMR** (125 MHz, $CDCl_3$): $\delta$ 14.1, 22.6, 25.4, 26.3, 29.4, 30.5, 31.8, 34.7, 59.0, 67.5, 70.6, 71.8, 73.4, 78.1, 80.2, 82.60, 96.2, 117.6, 118.8, 127.5, 127.5, 127.7, 127.9, 128.33, 134.08, 135.2, 138.6, 138.7, 172.8.

Anal. calcd for $C_{36}H_{52}O_7$: C, 72.45; H, 8.78. Found: C, 72.08; H, 9.13.

**(5*R*,6*R*,7*E*,10*S*)-10-[(1'*S*)-1'-[(2-methoxyethoxy)methoxy]-5,6-isopropylidenedioxy-3,4,5,6,9,10-hexahydro-2*H*-oxecin-2-one (179)**




A mixture of compound **178** (0.1 g, 0.16 mmol) and Grubbs' catalyst (0.03 g, 0.0034 mmol) in degassed $CH_2Cl_2$ (100 mL) was stirred under reflux for 28 h. The reaction mixture evaporated and then purified on silica gel by eluting with light petroleum: EtOAc (7:3) to afford *E*-**179** (0.063 g, 67 %)

$[\alpha]_D$ – 41.1 (*c* 0.52, $CHCl_3$)

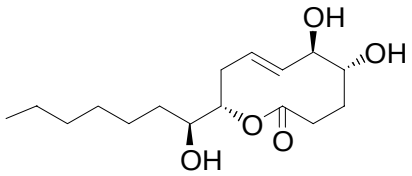
**$^1$H NMR** (500 MHz, $CDCl_3$): $\delta$ 0.87 (t, 3 H, *J* = 6.9 Hz), 1.26–1.32 (m, 8 H), 1.54–1.59 (m, 3 H), 2.02 (ddd, 1 H, *J* = 15.2, 10.6, 6.2 Hz), 2.17 (ddd, 1 H, *J* = 14.7, 10.6, 1.4), 2.24–2.30 (m, 2 H), 2.61 (dd, 1 H, *J* = 14.7, 9.2 Hz), 3.38 (s, 3 H), 3.54–3.56 (m, 2 H), 3.67–3.78 (m, 4 H), 4.07 (br. d, 1 H, *J* = 4.5 Hz), 4.47 (d, 1 H, *J* = 11.9 Hz), 4.48 (d, 1 H, *J* = 12.5 Hz), 4.54 (d, 1

H, $J$ = 11.9 Hz), 4.65 (d, 1 H, $J$ = 12.5 Hz), 4.78–4.81 (m, 2 H), 5.15 (dt, 1 H, $J$ = 9.2, 4.6 Hz), 5.64 (dd, 1 H, $J$ = 15.8, 2.1 Hz), 5.64–5.73 (m, 1 H), 7.28–7.35 (m, 10 H).

**$^{13}$C NMR** (125 MHz, $CDCl_3$): $\delta$ 14.0, 22.6, 25.0, 29.4, 31.2, 31.7, 36.1, 59.0, 67.4, 71.3, 71.5, 71.8, 78.2, 95.4, 126.5, 127.2, 127.5, 127.6, 128.3, 128.4, 131.7, 138.5, 138.8, 175.17.

Anal calcd. for $C_{34}H_{48}O_7$: C, 71.80; H, 8.51. Found C, 71.97; H, 8.98.

**MICROCARPALIDE (54)**




To a solution of **179** (0.053 g, 0.1 mmol) in anhydrous $CH_2Cl_2$ (2 mL) under nitrogen at 0 °C was added $TiCl_4$ (0.1 mL, 1 mmol). After 30 min, excess of reagent was quenched with water, extracted with $CH_2Cl_2$, washed with water, dried ($Na_2SO_4$), evaporated. The reaction mixture was purified on silica gel by eluting with light petroleum: EtOAc (2:3) to afford **54**, which existed as atwo slowly intercinverting conformers in a 76: 24 ratio (0.022 g, 76 %).

$[\alpha]_D$ – 23.2 (*c* 0.7, MeOH); lit.,[12c] $[\alpha]_D$ – 22 (*c* 0.67, MeOH)

**$^1$H NMR** (500 MHz, $CD_3CN$): $\delta$ 0.92 (t, 3 H, $J$ = 6.8 Hz), 1.28–1.38 (m, 8 H), 1.42–1.48 (m, 2 H), 1.72–1.83 (m, 1 H), 2.01 (br ddd,1 H, minor conformer) 2.12–2.23 (m, 3 H), 2.28–2.34 (br m, 1 H), 2.37 (ddd, 1 H, $J$ = 5.2, 2.6, 1.1 Hz), 2.51 (br m, 1 H), 2.88 (br s, OH), 3.12 (br s, OH), 3.28 (br dt, 1 H, minor conformer), 3.58 (br m, 1 H), 3.64 (dt, 1 H, $J$ = 9.1, 3.1 Hz), 3.81 (br m, 1 H), 4.14 (br m, 1 H), 4.64 (ddd, $J$ = 8.3, 4.6, 2.7 Hz), 4.85 (ddd, 1 H, $J$ = 7.9, 4.7, 3.4 Hz), 5.08 (dd, $J$ = 15.7, 9.4 Hz), 5.53 (dddd, 1 H, $J$ = 15.8, 7.2, 5.0, 2.1 Hz), 5.68 (m, 1 H, minor conformer), 5.73 (dd, 1 H, $J$ = 15.8, 2.2 Hz);

**$^{13}$C NMR** (125 MHz, $CD_3CN$): $\delta$ 14.4, 23.3, 26.1, 26.4, 29.9, 32.5, 34.2, 36.7, 72.3, 72.8, 73.5, 79.7, 126.6, 134.5, 174.1, 176.3.

Anal calcd. for $C_{16}H_{28}O_7$: C, 63.96; H, 9.40. Found C, 64.17; H, 9.75.

# References

**References**


1. www.cancer.org.
2. www.helios.bto.ed.ac.uk.
3. Sheterline, P.; Clayton, J.; Sparrow, J. C. 4th ed., Oxford University Press, New York, **1999**.
4. Kingston, D. G. I. *Chem. Commun*. **2001**, *10*, 867.
5. He, L.; Orr, G. A.; Horwitz S. B. *Drug Discovery Today* **2001**, *6*, 1153.
6. Gachet, Y.; Tournier, S.; Millar, J. B. A.; Hyams, J. S. *Nature*. **2001**, *412*, 352.
7. a) Cameron, L. A.; Giardini, P. A.; Soo, F. S.; Theriot, J. A. *Nat. Rev. Mol. Cell Biol.* **2000**, *1*, 110. b) Ploubidou, A.; Way, M. *Curr. Opin. Cell Biol.* **2001**, *13*, 97.
8. a) Jordan, M. A.; Wilson, L. *Curr. Opin. Cell Biol.* **1998**, *10*, 123. b) Janmey, P. A.; Chaponnier, C. *Curr. Opin. Cell Biol.* **1995**, *7*, 111.
9. a) Stossel, T. P.; Hartwig, J.; Kwiatkowski, D.; Allen, P. *The Cell Biology and Cytoskeleton Group Home Page,* http://zk.bwh.harvard.edu; b) Stossel, T. P.; *J. Biol. Chem.* **1989**, *264*, 18261.
10. Pollard, T. D.; Blanchoin, L.; Mullins, R. D. *Annu. Rev. Biophys. Biomol. Struct.* **2000**, *29*, 545.
11. a) Spector, I.; Braet, F.; Shochet, N. R.; Bubb, M. *Microsc. Res. Tech.* **1999**, *47*, 18. b) Saito, S-y.; Karaki, H.; *Clin. Exp. Pharmacol. Physiol.* **1996**, *23*, 743.
12. a) Cooper, J. A.; *J. Cell Biol.* **1987**, *105*, 1473. b) Spector, I.; Shochet, N. R.; Kashman, Y.; Groweiss, A. *Science* **1983**, *219*, 493. c) Ratnayake, A.S.; Yoshida, W.Y.; Moobery, S.L.; Hemscheidt, T. *Org. Lett.* **2001**, *3*, 3479.
13. Brown, H.C.; Fletcher, R.S.; Johansen, R.B. *J. Am. Chem. Soc.* 1951, *73,* 214. b) Eliel, E. in *"Stereochemistry of Carbon Compounds"* Mc Graw-Hill Edit. New York, 1962, p. 189.
14. a) Roxburgh, C.J. *Tetrahedron* **1993**, *49*, 10749. b) Evans, P.A.; Holmes, A.B. *Tetrahedron,* **1991**, *47,* 9131. c) Smalley, R.K. in *"Comprehensive Heterocyclic Chemistry"*; Katritzky, A.R.; Rees, C.W. *Eds, Pergamon: Oxford*, **1984**, Vol. *7*, ch. *5*, p. 491. d) Moore, J.A.; Anet, F.A. *ibid,* **1984**, Vol. *7*, ch. *5*, p. 653. e) Anastassiou,

A.G. *ibid,* **1984**, Vol. *7*, ch. *5*, p. 709. f) Petasis, N.A.; Patane, M.A. *Tetrahedron* **1992**, *48,* 5757.

15. Sicher, J. *Progr. Stereochem.* **1962**, *3*, 202.
16. Hunsdiecker, H.; Erlbach, H. *Chem. Ber.* **1947**, *80,* 129.
17. a) Galli, C.; Illuminati, G.; Mandolini, *L. J. Am. Chem. Soc.* **1973**, *95,* 8374. b) Galli, C.; Illuminati, G.; Mandolini, L.; Tamborra, *P. J. Am. Chem. Soc.* **1977**, *99,* 2591. c) IllUuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14,* 95.
18. Galli, C.; Mandolini, L. J. *Chem. Soc., Chem. Commun.* **1982**, 252.
19. a) Huisgen, R.; Ott, H. *Tetrahedron,* **1959**, *6*, 253. b) Wiberg, K.B.; Waldron, R.F.; Schulte, G.; Saunders, *M. J. Am. Chert Soc.* **1991**, *113,* 971.
20. Naves, Y.R.; Grampoloff, A.V. *Helv. Chim. Acta* **1942**, *25,* 1500.
21. Demole, E.; Willhalm, B.; Stoll, M. *Helv. Chim. Acta* **1964**, *47,* 1152.
22. Ayer, W.A.; Sun, M.; Bowne, L.M.; Brinen, L.S.; Clardy, J. J. *Nat. Prod.* **1992**, *55,* 649.
23. a) Bodo, B.; Molho, L.; Davoust, D.; Molho, D. *Phytochemistry* **1983**, *22*, 447. b) Evidente, A.; Lanzetta, R.; Capasso, R.; Vurro, M.; Bottalico, A. *Phytochemistry* **1993**, *34,* 999. c) Evidente, A.; Capasso, R.; Abouzeid, M.A.; Lanzetta, R.; Vurro, M.; Bottalico, A. *J. Nat. Prod.***1993**, *56,* 1937.
24. Wada, K.; Ishida, T. J. *Chem. Soc., Perkin Trans. 1* **1979**, 1155.
25. a) Nukina, M.; Sassa, T.; Ikeda, M. *Tetrahedron Lett.* 1980, *21,301.* Nukina, M.; Ikeda, M.; Sassa, *Agric. Biol. Chem.* **1980**, *44,* 2761. b) Suzuki, S.; Tanaka, A.; Yamashita, K. *Agric. Biol. Chem.* **1987**, *51,* 3095.
26. a) Ackland, M.J.; Hanson, J.R.; Hitchcock, P.B.; Ratcliffe, A.H. *J. Chem- Soc., Perkin Trans.1* **1985**, 843. b) Ackland, M.J.; Hanson, J.R.; Hitchcock, P.B.; Mabelis, R.P.; Ratcliffe, A.H. *J. Chem. Soc., Perkin Trans. l* **1984**, 2755. c) Mayer, M.; Thiericke, R., *J. Chem. Soc., Perkin Trans. 1* **1993**, 495.
27. a) GÖhrt, A.; Zeeck, A.; Hiitter, K.; Kirsch, R.; Kiuge, H.; Thiericke, R. J. *Antibiotics* **1992**, *45,*66. b) Grabley, S.; Hammann, P.; Hiatter, K.; Kirsch, R.; Kluge, H.; Thiericke, R.; Mayer, M.; Zeeck, *A. J. Antibiotics* **1992**, *45,* 1176.

28. a) Granzer, E.; Hamman, P.; Wink, J.; Grabley, S. *Eur. Pat. Appl.* EP 477,552; *Chem. Abstr.* **1992**, *117,* 922. b) Granzer, E.; Hamman, P.; Kirsch, R. *Eur. Pat. Appl.* EP 516015.; *Chem. Abstr.* **1993**, *119,* 8597.
29. a) Niwa, H.; Inagaki, H.; Yamada, K. *Tetrahedron Lett.* **1991**, *32,* 5127. b) Niwa, H.; Watanabe, M.; Inagaki, H.; Yamada, K. *Tetrahedron.* **1994**, *50,* 7385.
30. a) Lindquist, N.; Fenical, W. *Tetrahedron Lett.* **1989**, *30,* 2735. b) Congreve, M.S.; Holmes, A.B.; Hughes, A.B.; Looney, M.G. *J. Am. Chem. Soc.* **1993**, *115,*5815.
31. Moore, B.P.; Brown, W.V. *Aust. J. Chem.* **1976**, *29,* 1365.
32. a) Bohlmann, F.; Zdero, C.; Pickard, J.; Robinson, H.; King, R.M. *Phytochemistry* **1981**, *20,*1323. b) Bohlmann, F.; Zdero, C.; Jakupovic, J.; Gerke, T.; Wallmeyer, M.; King, R.M.; Robinson, H. *Liebigs Ann. Chem.* **1984**, 162.
33. Aimi, N.; Uchida, N.; Ohya, N.; Hosokawa, H.; Takayama, H.; Sakai, S.-i.; Mendonza, L.A.; Polz, L.; StOckigt, J. *Tetrahedron Lett.* **1991**, *32,* 4949.
34. Celmer, W.D.; Chmurny, G.N.; Moppett, C.E.; Ware, R.S.; Watts, P.C.; Whipple, E.B. *J. Chem. Soc.* **1980**, *102,* 4203.
35. Whaley, H.A.; Chidester, C.G.; Mizsak, S.A.; Wnuk, R.J. *Tetrahedron Lett.* **1980**, *21,* 3659.
36. a) Cane, D.E.; Yang, C.-C. *J. Antibiotics* **1985**, *38,* 423. b) Cane, D.E.; Yang, C.-C. *J. Am. Chem. Soc.* **1984**, *106,* 784. c) Snyder, W.C.; Rinehart, K.L. *J. Am. Chem. Soc.* **1984**, *106,* 787. d) Cane, D.E.; Tan, W.; Ott, W.R. *J. Am. Chem. Soc.* **1993**, *115,* 1527.
37. Magerlein, B.J.; Reid, R.J. *J. Antibiotics,* **1982**, *35,* 254.
38. Fu, X.; Sévenet, T.; Remy, F.; País, M.; Hadi, A.H.A.; Zeng, L.M. *J. Nat. Prod.* **1993**, *56,* 1153.
39. a) Evidante, A.; Lanzetta, R.; Capasso, R.; Andolfi, A.; Botallico, A.; Vurro, M.; Zonno, M.C. *Phytochemistry*, **1997**, *40*, 1637. b) Rivero-Cruz, J.F.; Garcia-Aguirre, G.; Cerda-Gracias-Rojas.; Mata, R. *Tetrahedron*, **2000**, *56*, 5337. (ii) Rivero-Cruz, J.F.; Macias, M.; Garcia-Aguirre, G.; Cerda-Gracias-Rojas.; Mata, R. *J. Nat. Pro.*, **2003**, *66*, 511.

40. a) Masamune, S.; Gates, G.S.; Corcoran, J.W. *Angew. Chem. Int. Ed. Engl.* **1977**, *16,* 585. b) Nicolaou, K.C. *Tetrahedron* **1977**, *33,* 683. c) Back, T.G. *Tetrahedron* **1977**, *33,* 3041.
41. Stoll, M.; Rouvé, A. *Helv. Chiat Acta* **1935**, *18,* 1087.
42. Scott, L.T.; Naples, J.O. *Synthesis* **1976**, 738.
43. Cossy, J.; Pete, J.P. *Bull. Soc. Chiat Fr.* **1988**, 989.
44. a) Ngooi, T.K.; Scilimati, A.; Guo, Z.-w.; Sih, C.J. *J. Org. Chem.* **1989**, *54,* 911. b) Guo, Z.-w.; Ngooi, T.K.; Scilimati, A.; Fijlling, G.; Sih, C.J. *Tetrahedron Lett.* **1988**, *29,*5583.
45. a) Makita, A.; Nihira, T.; Yamada, Y. *Tetrahedron Lett.* **1987**, *28,* 805. b) Xu, J.W.; Li, Z.Y. *Chinese Chem. Lett.,* **1992**, *3*, 251. c) Lobell, M.; Schneider, M.P. *Tetrahedron: Asymmetry* **1993**, *4*, 1027.
46. Bartra, M.; Vilarrasa, J. *J. Org. Chem.* **1991**, *56,* 5132.
47. Gerlach, H.; Thalman, A. *Helv. Chim. Acta* **1974**, *57,* 2661.
48. Mukaiyama, T.; Izumi, J.; Miyashita, M.; Shiina, I. *Chem. Lett.* **1993**, 907.
49. Corey, E.J.; Brunelle, D.J.; Nicolaou, K.C. *J. Am. Chem. Soc.* **1977**, *99,* 7359.
50. a) Vedejs, E.; Powell, D.W. *J. Am. Chem. Soc.* **1982**, *104,* 2046. b) Vedejs, E.; Buchanan, R.A. *J. Org. Chem.* **1984**, 49, 1840.
51. a) Corey, E.J.; Kim, S.; Yoo, S.-e.; Nicolaou, K.C.; Melvin, L.S.; Brunelle, D.J.; Falck, J.R.; Trybulski, E.J.; Lett. R.; Sheldrake, P.W. *J. Am. Chem. Soc.* **1978**, *100,* 4620. b) Corey, E.J.; Hopkins, P.B.; Kim, S.; Yoo, S-e.; Nambiar, K.P.; Falck, J.R. *J. Am. Chem. Soc.* **1979**, *101,* 7131.
52. a) Nagel, A.A.; Celmer, N.D.; Jefferson, M.T.; Vincent, L.A.; Whipple, E.B.; Schulte, G. *J. Org.Chem.* **1986**, *51,* 5397. b) Kibwage, I.O.; Busson, R.; Janssen, G.; Hoogmartens, J.; Vanderhaeghe, H.; Bracke, J. *J. Org. Chem.* **1987**, *52,* 990. c) Kirst, H.A.; Wind, J.A.; Paschal, J.W. *J. Org. Chem.* **1987**, *52,* 4359.
53. a) Galli, C.; Giovannelli, G.; Illuminati, G.; Mandolini, *L. J. Org. Chem.* **1979**, *44,* 1258. b) Galli, C.; Mandolini, L. *Org. Syntheses* **1978**, *58,* 98. c) Cameron, A.G.; Knight, D.W. *Tetrahedron Lett.* **1982**, *23,* 5455.
54. a) Kruizinga, W.H.; Kellog, R.M. *J. Chem. Soc., Chem. Commun.* **1979**, 286. b) Barbier, *M. J. Chem. Soc., Chem. Commun.,* **1982**, 668.

55. Vedejs, E.; Larsen, S.D. *J. Am. Chem. Soc.* **1984**, *106,* 3030.

56. a) Vedejs, E.; Ahmad, S.; Larsen, S.D.; Westwood, S. *J. Org. Chem.* **1987**, *52,* 3937. b) Niwa, H.; Okamoto, O.; Yamada, K.; *Tetrahedron Lett.* **1988**, *29,* 5139. c) Niwa, H.; Ogawa, T.; Okamoto, O.; Yamada, K. *Tetrahedron* **1992**, *48,* 10531.

57. Nakamura, T.; Matsuyama, H.; Kamigata, N.; Iyoda, *M. J. Org. Chem.* **1992**, *57,* 3783.

58. Funk, R.L.; Abelman, M.M.; JeUison, K.M. *Synlett* **1989**, 36.

59. Boeckman, R.K.; Pruitt, J.R. *J. Am. Chem. Soc.* **1989**, *111,* 8286.

60. a) Simonot, B.; Rousseau, *G. J. Org. Chem.* **1993**, *58,* 4. b) Simonot, B.; Rousseau, G. *J. Org. Chem.* **1994**, *59,* 5912.

61. a) Tsuji, J.; Mandai, T. *Tetrahedron Lett.* **1978**, 1817. b) Wada, M.; Shigheshisa, T.; Akiba, K.-y. *Tetrahedron Lett.* **1985**, *26,* 5191.

62. a) Takahashi, T.; Hashiguchi, S.; Kasuga, K.; Tsuji, *J. J. Am. Chem. Soc.* **1978**, *100,* 7424. b) Lygo, B.; O'Connor, N. *Synlett.* **1990**, 282.

63. a) Trost, B.M.; Verhoeven, T.R. *J. Am. Chem. Soc.* **1980**, *102,* 4743. b) Suh, Y.G.; Koo, B.A.; Cho, Y.S. *Yakhah. Hoechi* **1990**, *34, 166; Chem. Abstr.* **1991**, *114,*122013. c) Baldwin, J.E.; Adlington, R.M.; Ramcharitar, S.H. *Tetrahedron.* **1992**, *48,* 2957.

64. a) Porter, N.A.; Chang, V.H.-T. *J. Am. Chem. Soc.* **1987**, *109,* 4977. b) Kurata, T.; Narita, K. *Yukagaku* **1991**, *40,* 39. *Chem. Abstr.* **1991**, *114,* 163967.

65. a) Baldwin, J.E.; Adlington, R.M.; Ramcharitar, S.H. *Tetrahedron* **1992**, *48,* 3413. b) Ryu, I.; Nagahara, K.; Tsunoi, S.; Sonoda, N. *Synlett* **1994**, 643. c) Baldwin, J.E.; Adlington, R.M.; Mitchell, M.B.; Robertson, J. *Tetrahedron* **1991**, *47,* 5901.

66. a) Tabuchi, T.; Kawamura, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27,* 3889. b) Moriya, T.; Handa, Y.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1988**, *29,* 6947.

67. a) Bhat, V.; Cookson, R.C. *J. Chem. Soc., Chem. Commun.* **1981**, 1123. b) Cookson, R.C.; Ray, P.S. *Tetrahedron Lett.* **1982**, *23,* 3521.

68. a) Kostova, K.; Lorenzi-Riatsch, A.; Nakashita, Y.; Hesse, M. *Helv. Chim. Acta* **1982**, *65,* 249. b) Kostova, K.; Hesse, M. *Helv. Chim. Acta* **1984**, *67,* 1713.

69. Grayson, D.H.; Roycroft, E.D. *J. Chem. Soc., Chem. Commun.* **1993**, 269.

70. Maier, W.; Keller, M.; Eberbach, W., *Heterocycles* **1993**, *35,* 817.

71. a) Petrzilka, M. *Helv. Chim. Acta* **1978**, *61,* 3075. b) Harusawa, S.; Osaki, H.; Fujii, H.; Yoneda, R.; Kurihara, T. *Tetrahedron* **1992**, *48,* 9433.

72. a) Borowitz, I.J.; Gonis, G. *Tetrahedron Lett.* **1964**, 1151. b) Borowitz, I.J.; Williams, G.J. *Tetrahedron Lett.* **1965**, 3813. c) Borowitz, I.J.; Williams, G.J.; Gross, L.; Rapp, R. *J. Org. Chem.* **1968***, 33,* 2013. d) Borowitz, I.J.; Rapp, R. *J. Org. Chem.* **1969**, *34,* 1370.

73. a) Torri, S.; Inokuchi, T.; Kondo, K. *J. Org. Chem.* **1985**, *50,* 4980. b) Baskaran, S.; Islam, I.; Raghavan, M.; Chandrasekaran, S. *Chem. Lett.* **1987**, 1175.

74. a) Mahajan, J.R.; Ferreira, G.A.L.; Arafjo, H.C. *J. Chem. Soc., Chem. Commun.* **1972**, 1078. b) Mahajan, J.R.; De Aratljo, H.C. *Synthesis* **1981**, 49.

75. a) Asaoka, M.; Naito, S.; Takei, H. *Tetrahedron Lett.* **1985**, *26,* 2103. b) Mahajan, J.R.; Resck, I.S. *J. Chem. Soc., Chem. Commun.* **1993**, 1748.

76. Shalom, E.; Zenou, J.L.; Shatzmiller, S. *J. Org. Chem.* **1977**, *42,* 4213.

77. a) Borowitz, I.J.; Gonis, G.; Kelsey, R.; Rapp, R.; Williams, G.J. *J. Org. Chem.* **1966**, *31,* 3032. b) Wakamatsu, T.; Akasaka, K.; Ban, Y. *Tetrahedron Lett.* **1977**, 2751. c) Wakamatsu, T.; Akasaka, K.; Ban, Y. *J. Org. Chem.* **1979**, *44,* 2008.

78. a) Posner, G.H.; Asirvatham, E.; Webb, K.S.; Jew, S.-s. *Tetrahedron Lett.* **1987**, *28,* 5071. b) Webb, K.S.; Asirvatham, E.; Posner, G.H. *Org. Syntheses* **1990**, *69,* 188.

79. Posner, G.H.; Webb, K.S.; Asirvatham, E.; Jew, S.-s. Degl'Innocenti, A. *J. Am. Chem. Soc.* **1988**, *110,* 4754.

80. a) Mahajan, J.R.; Resck, I.S. *Synthesis* **1980**, 998. b) Mahajan, J.R.; DaSilva, C. R. *J. Braz. Chem. Soc.* **1990**, *1*, 87.

81. a) Kostova, K.; Hesse, M. *Helv. Chim. Acta* **1984**, *67,* 1713. b) Stanchev, S.; Hesse, M. *Helv. Chim. Acta* **1990**, *73,460.*

82. a) Schreiber, S.L.; Sammakia, T.; Hulin, B.; Schulte, G. *J. Am. Chem. Soc.* **1986**, *108,* 2106. b) Schreiber, S.L.; Hulin, B.; Liew, W.F. *Tetrahedron* **1986**, *42,* 2945. c) Schreiber, S.L.; Hulin, B. *Tetrahedron Lett.* **1986**, *27,* 4561.

83. a) Grant, P.K.; Lai, C.K.; Prasad, J.S.; Yap, T.M. *Aust. J. Chem.* **1988**, *41,711.* b) Grant, P.K.; Hanton, L.R.; Lynch, G.P.; Simpson, J.; Slim, G.C. *Aust. J. Chem.* **1991**,

*44,* 897. c) Kaino, M.; Naruse, Y.; Ishihara, K.; Yamamoto, H. *J. Org. Chem.* **1990**, *55,* 5814.

84. Shimizu, I.; Nakagawa, H. *Tetrahedron Lett.* **1992**, *33,* 4957.

85. Nagumo, S.; Suemune, H.; Sakai, K. *Tetrahedron Lett.* **1991**, 32, 5585 and *Tetrahedron* **1992**, *48,* 8667.

86. Reviews: (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res*. **2001**, *34*, 18. b) Fűrstner, A. *Angew. Chem*. **2000**, *112*, 3140; *Angew. Chem., Int. Ed*. **2000**, *39*, 3012. (c) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. d) Fu¨rstner, A. *Top. Catal*. **1997**, *4*, 285. (e) Schuster, M.; Blechert, S. *Angew. Chem.* **1997**, *109*, 2124; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2037. (f) Schrock, R. R. *Top. Organomet. Chem*. **1998**, *1*, 1. (g) Maier, M. E. *Angew. Chem*. **2000**, *112*, 2153; *Angew. Chem., Int. Ed*. **2000**, *39*, 2073. For syntheses of 10-membered rings by RCM, see: (h) Fűrstner, A.; Műller, *Synlett* **1997**, 1010. (i) Chang, S.; Grubbs, R. H. *Tetrahedron Lett*. **1997**, *38*, 4757. (j) Gerlach, K.; Quitschalle, M.; Kalesse, M. *Synlett* **1998**, 1108. (k) Fink, B. E.; Kym, P. R.; Katzenellenbogen, J. A. *J. Am. Chem. Soc*. **1998**, *120*, 4334. (l) Oishi, T.; Nagumo, Y.; Hirama, M. *Chem. Commun.***1998**, 1041. (m) Quitschalle, M.; Kalesse, M. *Tetrahedron Lett*. **1999**, *40*, 7765. (n) Delgado, M.; Martin, J. D. *J. Org. Chem*. **1999**, *64*, 4798. (o) Bamford, S. J.; Goubitz, K.; van Lingen, H. L.; Luker, T.; Schenk, H.; Hiemstra, H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 345. (p) Nakashima, K.; Ito, R.; Sono, M.; Tori, M. *Heterocycles* **2000**, *53*, 301. (q) Cho, S. C.; Dussault, P. H.; Lisec, A. D.; Jensen, E. C.; Nickerson, K. W. *J. Chem. Soc., Perkin Trans. 1* **1999**, 193. (r) Nevalainen, M.; Koskinen, A. M. P. *Angew. Chem*. **2001**, *113*, 4184; *Angew. Chem., Int. Ed.* **2001**, *40*, 4060. Heinrich, M. R.; Steglich, W. *Tetrahedron Lett*. **2001**, *42*, 3287. (s) Banwell, M. G.; Bray, A. M.; Edwards, A. J.; Wong, D. J. *New J. Chem*. **2001**, *25*, 1347. (t) Telser, J.; Beumer, R.; Bell, A. A.; Ceccarelli, S. M.; Montio, D.; Gennari, C. *Tetrahedron Lett*. **2001**, *42*, 9187.

87. Fűrstner, A.; Műller, T. *Synlett* **1997**, 1010.

88. a) Fűrstner, A.; Radkowski, K.; Wirtz, C.; Goddard, R.; Lehmann, C. W.; Mynott, R. *J. Am. Chem. Soc.* **2002**, *124*, 7061. b) Kozmin, A. S.; Liu, D. *Org. Lett.* **2002**, 3005. c) Murga, J.; Falomir, E.; Garcia-Fortanet, J.; Carda, M.; Marco, J. A. *Org. Lett.* **2002**, *4*, 3447.

89. Keck, E.G.; Boden, P.E. *J. Org. Chem.* **1985**, *50*, 2394.

90. Rama Rao, A. V.; Reddy, E. R.; Joshi, B. V.; Yadav, J. S. *Tetrahedron Lett*. **1987**, 28, 6497.

91. (a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem*. **1992**, *57*, 2768. (b) Kolb, H. C.; Van-Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev*. **1994**, *94*, 2483.

92. a) Moore, B. S.; Cho, H.; Casati, R.; Kennedy, E.; Reynolds, K. A.; Mocek, U.; Beale, J. M.; Floss, H. G. *J. Am. Chem. Soc*. **1993**, *115*, 5254. (b) Coutrot, P.; Grison, C.; Lecouvey, M. *Bull. Soc. Chim. Fr.* **1997**, *134*, 27.

93. Criegee, R. *Ber.* **1931**, *64*, 260.

94. Corey, E.J.; Gras, J.-L.; Ulrich, P. *Tetrahedron. Lett.* **1976**, 809.

95. Robins, M.J.; Hawrelak, S.D.; Kanai, T.; Siefert, J.-M.; mengel. R. *J.Org. Chem.* **1979**, *44*, 1317.

96. Corey, E. J.; Venkateswarulu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

97. Nicaolou, K. C.; Webber, S. E. *Synthesis.* **1986**, 453.

98. a) Corey, E. J.; Pyne, S.G. *Tetrahedron. Lett.* **1983**, *24*, 4833. b) Smith, A. B., III; Qiu, Y.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc*. **1995**, *117*, 12011.

99. Monti, H.; Leandri, G.; Klos-Ringuet, M.; Corriol, C. *Synth. Commun*. **1983**, *13*, 1021.

100. a) Mancuo, A.J.; Swern, D. *Synthesis* **1981**, 165. b) Dalcanale, E.; Montanari, F. *J. Org. Chem*. **1986**, *51*, 567.

101. Liav, A.; Goren, M. B. *Carbohydr. Res.* **1984**, *131*, C8.

102. a) Angyal, S. J.; Beveridge, R. J. *Carbohydr. Res.* **1978**, *65*, 279. b) Liu, G.; Wang, Z. *Synthesis*, **2001**, *1*, 119.

103. Hanack, M.; Kunzmann, E.; Schumacher, W. *Synthesis* **1978**, 26.

104. Lindlar, h.; Dubuis, R. *Organic Syntheses*, *Wiley: Newyork*. **1973**, *Collect. Vol. V*, 880.

105. Bhatt, M. V.; Kulkarni, S. V. *Synthesis* **1983**, 249.

106. a) Davoli, P.; Spaggiai, A.; Castagnetti, L.; Prati, F. *Org. Biomol. Chem.* **2004**, *2*, 38. b) Banwell, G. M.; Loong, J. T. D.; *Heterocycles*, **2004**, *62*, 713. c) Ishigami, K.; Kitahara, T. *Heterocycles*. **2003**, *63*, 765.

# Chapter II

---

## First synthesis of Methyl α-*C*- D-arabinofuranosyl-(1→5)- arabinofuranoside: the *C*- disaccharide segment of *Mycobacterium tuberculosis*

# Introduction

Unlike the monosaccharides, the pentose arabinose exists in nature in all possible absolute and ring configurations, namely, D-arabinose (D-Ara*f*), L-arabinofuranose (L-Ara*f*), L-arabinopyranose (L-Ara*p*), and D-arabinopyaranose (D-Ara*p*). The pyranose forms are more rare and are found primarly in protozoan parasites or as constituents of plant saponins. Oligo- and polysaccharides comprised of L-arabinofuranose are also widely spread in plant kingdom, where they are present as constituents of arabinoxylans, pectins, and hydroxyproline rich glucoproteins (HPRGS). This chapter mainly focuses in polysaccharides containing D-arabinofuranose and in particular the most prominent examples of members of these polymers, which are found as important components of members of Actinomycetes family including the genera *Mycobacteria*, *Corneybacteria*, *Nocardia*, and *Rhodococcus*.

The social and economical burden due to mycobacterial diseases such as leprosy and tuberculosis are of unprecedented nature particularly as it relates to developing countries.[1] In spite of enormous efforts to develop anti-infective drug molecules, tuberculosis still constitutes the leading killer disease.[2] Seven million new cases and three million deaths occur every year due to tuberculosis, and with AIDS becoming epidemic in many developing countries; this mortality figure is bound to increase at an alarming rate.[3] After antibiotics to treat tuberculosis became widely available in the 1950s, it was believed that the disease would eventually be eliminated. But *M. tuberculosis*, the organism that causes the disease, has proven to be very resilient. The specter of a worldwide resurgence of tuberculosis (TB) and its drug resistant forms has generated an intense effort to develop new and more effective therapeutic agents. Following lines highlight a brief view to this growing public health threat in a chemist's perspective with little insight into biology.

**Introduction to *Mycobacteria***

The genus mycobacterium contains three important bacterial pathogens *Mycobacterium* (*M.*) *tuberculosis*, *M. leprae*, *M. avium*, and an important fast growing non-pathogenic research species *M. smegmatis*. Mycobacteria, although strictly speaking gram-positive, are readily distinguished from other bacteria by their unique cell wall, which confirms neither to the classical gram-positive nor gram-negative cell wall but includes features of both.[4] *M. tuberculosis* has a very slow growth cycle (dividing every 24 hours,

compared with every 20 minutes for *Escherichia coli*), a complex cell envelope, the ability to colonize macrophages and the ability to remain quiescent and then reactivate decades later.[5]

*M. tuberculosis* is transmitted almost exclusively by air-borne route and infectious unit is a small bacillus-containing particle called a droplet nucleus. When a droplet nucleus containing one or two viable bacilli is inhaled by an immuno compromised person, it is deposited in the alveolar surface where the bacilli begin to multiply. Initially, the infecting organism meets only limited resistance from the host, as phagocytosis by alveolar macrophages has little effect on the bacilli, which continue to multiply intracellularly in the human host. After several weeks of infection, the number of leukocytes in the area decreases and the mononuclear cells predominate; these crowd together and contain pale, foamy, cytoplasmic material that is rich in lipid. The resulting unit is called a tubercle, the fundamental lesion of tuberculosis.[4]

**Tuberculosis research highlights**

The first milestone in tuberculosis research came way back in 1882 from a German microbiologist Robert Koch who announced that the disease TB is caused by a rod shaped bacteria when he managed to make the bacteria visible only through a staining procedure that was complicated to perform.[6] Since then, tuberculosis has claimed at least 200 million lives while scientists have been struggling to explain why *M. tuberculosis* is such a successful pathogen. Also, Koch attributed the complication to the "covering of the bacterium" and the likelihood that "the tubercle bacillus is surrounded with a special wall of unusual properties". After about 90 years, a group led by Patrick J. Brennan in a seminal work showed[7] the importance of the unique cell wall of *M. tuberculosis* and unraveled the complete fine structure of its cell wall.

**The primary structure of the cell wall**

The basic cell wall structure of *M. tuberculosis* does not differ from that of other nonpathogenic mycobacteria. It consists of three interconnected "macromolecules".[8] The outermost of these are mycolic acids, unique 70-90 carbon branched fatty acids, which form outer lipid layer similar to, but differing from, the classical outer membrane of gram-negative bacteria. The mycolic acids are esterified to the middle component, arabinogalactan (AG), a polymer composed primarily of D-galactofuranosyl and D-arabinofuranosyl residues. AG is connected *via* a linker disaccharide phosphate to the

6-position of a muramic acid residue of the peptidoglycan. The peptidoglycan is the inner most of the three cell wall core macromolecules. The major polysaccharide components are arabinoglactan (AG) and a lipoarabinomannan (LAM) in which all of the galactose and arabinose residues are present in the furanose form.

**Structural features of Lipoarabinomannan (LAM)**

The LAM, which is an antigenic polymer, contains about 120 sugar residues 71 of which are arabinoses and 49 of which are mannoses. Distinct features are:

1. Within LAM, all *ara* are in furanose form and *man* are in pyranosyl form
2. The terminal end is a branched hexaarabinofuranoside with the structure [β-D-ara*f*-(1→2)-α-D-ara*f*)] $_2$-3,5-α-D-ara*f*- (1→5)-α-D-ara*f*, similar to that in AG
3. A linear β-D-ara*f*- (1→2)-α-D-ara*f*- (1→5)-α-D-ara*f*
4. *Ara* termini are extensively capped with man*p* residues
5. Mycolic acids are not present in LAM

**Structural features of Arabinogalactan (AG):**

Partial depolymerisation of the per-*O*-alkylated polysaccharide and analysis of the generated oligomers by GC-MS and FAB MS has established[7a] the fine structure of Arabinogalactan as depicted in figure 1. The AG, which is a structural polymer, contains approximately 100 sugar residues, 69 of which are arabinofuranoses and 31 of which are galactofuranoses. Salient features are:

1. Within AG, all *ara* and *gal* are in the furanose form[9]
2. The non-reducing termini of arabinan consist of a branched pentaarabinofuranosyl structure [β-D-ara*f*- (1→2)-α-D-ara*f*] $_2$-3,5-α-D-ara*f*- (1→5)-
3. The majority of the arabinan consists of 5-linked α-D-ara*f* residues with branching introduced by 3,5-α-D-ara*f* residues replaced at both branched positions with 5-α-D-ara*f*
4. The arabinan chains are attached to the galactan core through the C-5 of some of the 6-linked alternating 5- and 6- linked β-D-gal*f* moieties.
5. The galactan of AG is linked to the C-6 of some muramyl residues of peptidoglycan *via* the glycophosphoryl bridge L-Rha*p*- (1→3)-D-GlcNAc- (1→*p*)
6. The mycolic acids are located in clusters of four on the terminal pentaarabinofuranosyl units.

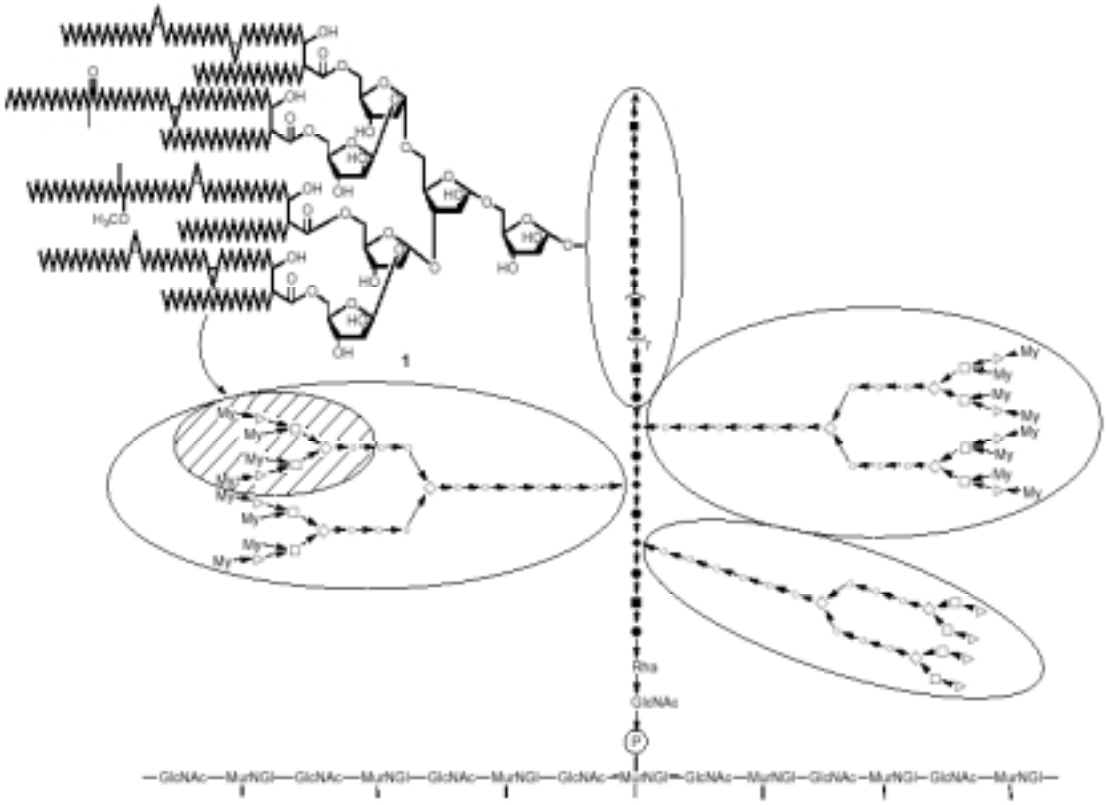



**Fig. 1** Schematic diagram of the proposed illustration of the macro structural motifs of the cell wall arabinogalactan. My, Mycolic acid; (▼) t-β-D-Araf; (□) 2-α-D-Araf; (◇) 3, 5-α-D-Araf; (▲) t-β-D-Galf; (■) 6-β-D-Galf; (●) 5-β-D-Galf; (◆) 5,6-β-D-Galf; GlcNAc, *N*-acetylglucosamine; Rha, rhamnose; MurNGl, *N*-glycolylmuramic acid.

The major *ara*- containing degradation products were the hexaarabinofuranoside and linear disaccharide, α-D-ara*f*-(1→5)-D-ara*f*. Oligosaccharide fragments containing up to 23 *ara* residues were obtained by gentle acid hydrolysis of the per-*O*-methylated AG and all the major structural motifs of AG, namely motifs A-E were as represented in figure 2.

Structural motif A is significant due to the presence of two 1→2 *cis* linkages,[7d] whereas structural motifs B and C account for the bulk of internal portions of the arabinan segments of the arabinogalactan and structural motif D, composed of alternating 6-linked and 5-linked galactofuranosyl residues, is supported by the presence of the disaccharide, 6-*O*-*β*-D-galactofuranosyl-D-galactose, among the products of the degradation of AG. Motif E is unique in that it contains both arabinofuranose and galactofuranose residues and both 5- and 6- positions of the galactofuranose component are linked with arabinofuranosyl and galactofuranosyl residues, respectively.

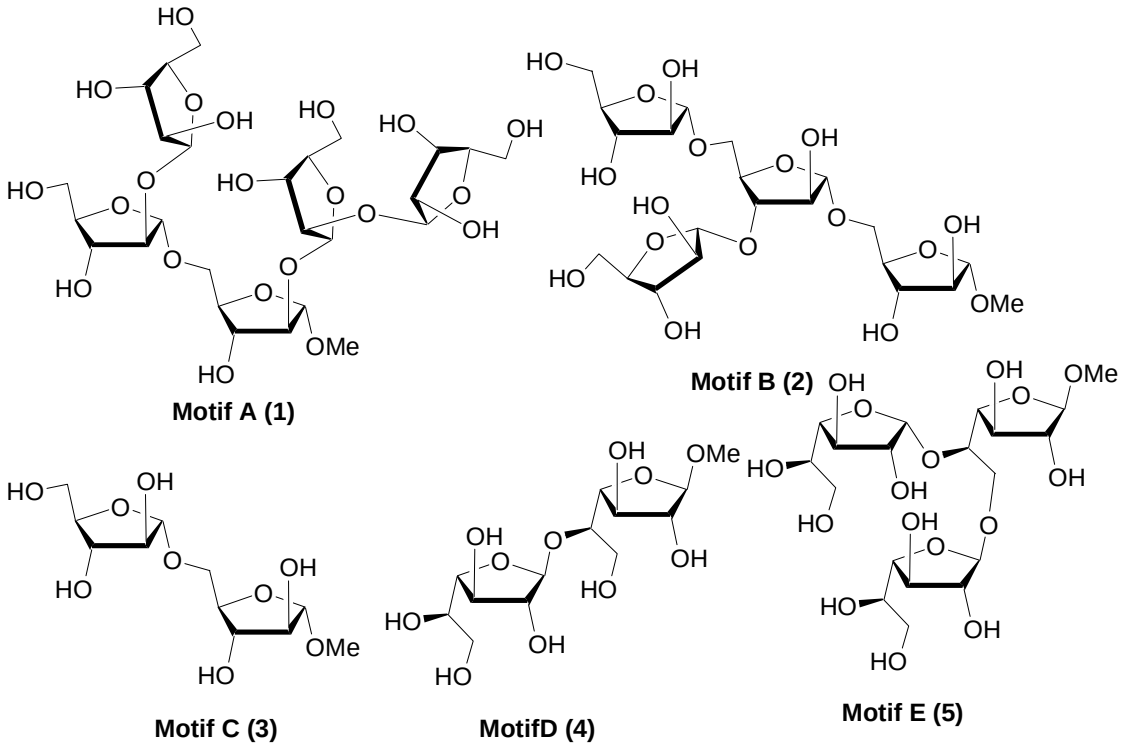



**Figure 2: Five Structural motifs A-E of AG**

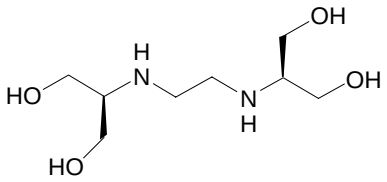
Synthesis of these motifs provides tremendous opportunities to understand their role in the survival and pathogenicity of these organisms. The structural analysis revealed that motifs A, B, and C are composed of arabinofuranose units having subtle differences between them with respective *O*-glycosidic linkage.

A major impetus for the study of the cell wall core molecule AG arises from the need for new drugs against *M. tuberculosis* and *M. avium*.[10] AG of *M. tuberculosis* has special interest for two fundamental reasons, 1) it appears to be essential for viability[11] and 2) three out of the four sugars of which it is composed, D-Ara*f*, D-Gal*f* and L-Rha*p* are not found in humans. Thus any of a score or more of enzymes involved in the formation of sugar donors and their polymerization are potential drug targets. The isolation and expression of the genes for these enzymes is a high research priority. Inhibitors of the resultant enzymes can be obtained by using "high through put" screens and by enzyme characterization (ultimately X-ray analysis) and the subsequent design of "rational" inhibitors.

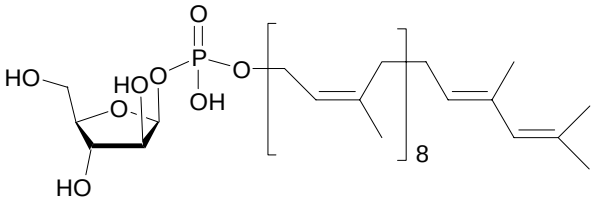
The terminal ends of both AG and LAM are capped with a penta arabinofuranosyl motif A, which is linked to the remainder of the polymer *via* a α-(1→5)-linked linear chain of arabinofuranosyl residues. This motif A serves as an attachment site for other functionalities present in the cell wall. These groups are located at the periphery of the cell wall complex and are therefore interface between the microorganisms and the environment.[2a] In LAM, the primary hydroxyl groups in motif A are often substituted with mannopyranosyl oligosaccharides, which have been implicated in the initial stages of infection through their interaction with human mannose binding proteins.[12] In the AG, the same hydroxyl groups are esterified with mycolic acids, branched, long chain fatty acids.[8] Through the tight packing of the alkyl chains, the mycolic acids form a protective hydrophobic façade that in some cases is nearly crystalline.[13]

The peptidoglycan-bound arabinogalactan of a virulent strain of *M. tuberculosis* was per-*O*-methylated, partially hydrolyzed with acid and the resulting oligosaccharides were separated by high pressure liquid chromatography and the structures of all those 43 constituent oligosaccharide fragments were identified by exhaustive NMR studies.[7d] Based on availability of sugars and number of glycosyl linkages, the fine structure of AG polymer has been characterized.[7a] It has been proven that arabinosyl residues are responsible for the antigenicity of AG, and that serological activity resides largely in fraction containing 2-linked arabinosyl residues.[14] Thus it is logical to speculate that part, or all, of structural motif A is the major humoral immunological epitope of arabinogalactan and, consequently, of whole mycobacteria.[15] Monoclonal antibodies raised against lipoarabinomannan also react with purified cell walls,[16] suggesting an arabinose-containing epitope common to lipoarabinomannan and arabinogalactan.

As the distal ends of both polymers (AG and LAM) are terminated with motif A, this motif is believed to play critical role in both infection by and survival of the organism in the human host.[8,13b] Ethambutol (**6**), one of the drugs currently used to treat tuberculosis, has recently been shown to be an arabinosyltransferase inhibitor.[17] Thus, new compounds that act, as does Ethambutol (**6**), in preventing complete arabinan biosynthesis are likely to be potent antimycobacterial agents. Furanosyl oligo- and polysaccharides are not found in mammalian glycoconjugates and therefore inhibitors of the biosynthetic pathways leading to their formation are particularly attractive drug candidates.




**Ethambutol (6)**




**β-D-Arabinofuranosyl-1-monphophoryl -decaprenol (7)**

Attention is now being focused on understanding mycobacterial cell wall biosynthesis[18] but there is still much to be learned concerning the details of this process, especially the assembly of the arabinan component. Decaprenol arabinofuranosyl phosphate (**7**) has been identified as the source of the arabinose in mycobacteria[7b,19] and there is presumably an array of glycosyl transferases that use **7** and various oligosaccharide acceptors to produce the glycan. None of these putative arabinosyltransferases have yet been isolated or purified,[18] however, an assay for their activity using mycobacterial membrane preparations as the enzyme source has been developed.[17a] The transfer of arabinose from **7** to an arabinofuranosyl dimer and trimer has been evaluated using this assay; the effect of the aglyconic group (*e.g.* methyl *vs*. octyl) was also investigated.[20] However, a major limiting factor in these studies is the lack of availability of discrete oligosaccharide structures that can be used for unraveling the biosynthetic pathways, including the isolation and purification of the enzymes and the development of individual assays for their activity. Such compounds are most easily obtained *via* chemical synthesis but synthetic studies are rare. Thus the current endeavor stands as a pivotal point in this direction.

**Biosynthesis of arabinan**

Arabinan is pivotal to the integrity of the mycobacterial cell wall. Attached via galactan to the peptidoglycan, arabinan provides the fulcrum for the impermeable mycolyl layer. In the context of LAM, however, it mediates the interaction with host macrophages. The common terminal penta arabinosyl motif in both AG and LAM suggests that similar sets of arabinosyl transferases are involved in their assembly, however, the overall arabinan ensemble must either be compartmentalized, or sufficiently distinct in structure, to allow divergent processing. Searches for sugar nucleotides of Araf have not been successful. However, isolation, characterization and preliminary studies of a β-D-Araf-

monophosphodecaprenol (DPA) by Wolucka and co-workers[21] have shown DPA to be an Araf donor. Furthermore, using synthetically derived DPA, they developed a basic arabinosyl transfer assay and DPA incorporation into wall material was assayed.[22] The DPA assay has been refined through the use of simple synthetic disaccharide and trisaccharide hydrophobic acceptors, and new results have shown that DPA is indeed the donor of 2-linked and 5-linked Araf residues present in both AG and LAM. [$^{14}$C] Arabinan was shown to be formed by the particulate enzymes of *M. smegmatis,* using synthetic polyprenylphosphate. [$^{14}$C] arabinose.[23] The arabinan was further characterized biochemically,[24] and digestion of the product with arabinanases produced. [$^{14}$C] hexaarabinoside and [$^{14}$C] diarabinoside oligomers. These oligomers represent the widely distributed structural motifs present in LAM as well as AG. Detection of [$^{14}$C] arabinose in both external and internal arrangements of the arabinan suggests that polyprenylphosphate-arabinose is perhaps the major arabinosyl donor in mycobacteria. It is not clear how the donor substrate DPA is derived biosynthetically. One hypothesis is that it is ultimately derived from 5'-phosphoribosyl-1-pyrophosphate (pRpp) by way of 5'-phosphoarabinosyl-1-pyrophosphate (pApp), although the latter does not accumulate to a significant extent.

**Importance and synthesis of C-saccharides**

*C*-saccharides are stable mimics of the naturally occurring *O*-saccharides in which interglycosidic oxygen has been replaced by a methylene groups. As potential inhibitors of glycolase inhibitors such as the disaccharides of the digestive tract,[25] and as the probes of the stereo electronic effects which may control the confirmation of oligosaccharides,[26] these pseudo disaccharides are of considerable interest and have stared to attract a great deal of attention. The first example of *C*-disaccharide, methyl *C*-gentobioside, was reported in 1983 by Sinay and Rouzad,[27] this compound is also first of its kind to have been submitted to X-ray crystal structure analysis.[28] Since then, several other chain extended[29] and branched-chain[30] *C*-disaccharides have been described; Kishi's extensive contributions in this field have recently culminated with the synthesis of a *C*,*C*-trisaccharide,[31] the bis-carba analog of a blood group antigenic determinant. With the exception of *C*-sucrose[32] and a few related anlogs,[33] no other examples of the challenging carba-analogs of non-reducing disaccharides have been reported. Because of the intrinsic properties associated with the *C*-saccharides in terms of non-hydrolizability, stability to enzymes, and conformational rigidity prompted the

scientific community in terms developing the new methods for the synthesis of *C*-saccharide analogs. In this much of the emphasis was given to synthesis of the *C*-saccharides having one or two methylenic linkers between the two sugar moieties.

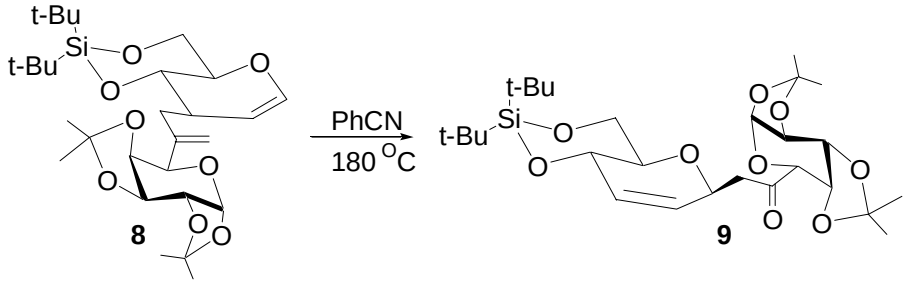
**Chemical synthesis of *C*-saccharides**

**SIGMATROPIC APPROACHES**

**[3,3]-Rearrangements**

Fairbanks and Godage[34] began with esterification of the partially protected glycal with acid to provide ester, followed by methylenation of the ester to the acyclic enol ether **8** was affected with Tebbe reagent and heating of **8** to 180 °C furnished the keto-β-*C*-disaccharide **9**, Scheme1. The methodology should also be applicable to a *C*-disaccharide synthesis and is well suited for the preparation of 1,6-linked-*C*-oligosaccharides *via* an iterative-based approach. It should be noted that the methodology delivers a compound that contains a ketone in the linking chain as well as an *endo*cyclic 3,4-double bond. Work directed at the preparation of *C*-glycopeptides that relies on the Claisen rearrangement has also been reported[35] (Scheme 1).

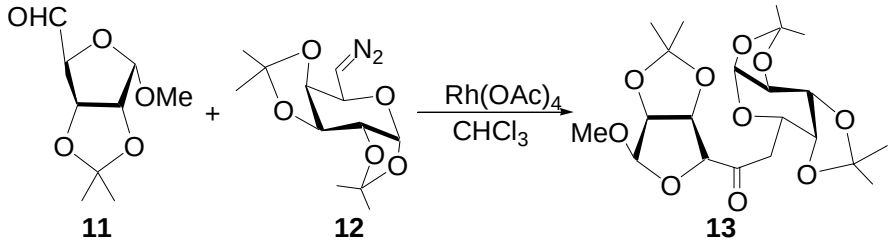
**Scheme 1**




**Carbenoid Chemistry**

Although the chemistry shown in Scheme 2 does not use transition metals in the strictest sense, it involves the use of carbenes, which are often generated from the reaction of diazo compounds with rhodium diacetate. This is the reason that this work is included in this section. Reaction of the aldehyde **11** with diazo compound **12** gave ketone **13** as the major compound.[36]

**Scheme 2**




**11** **12** **13**

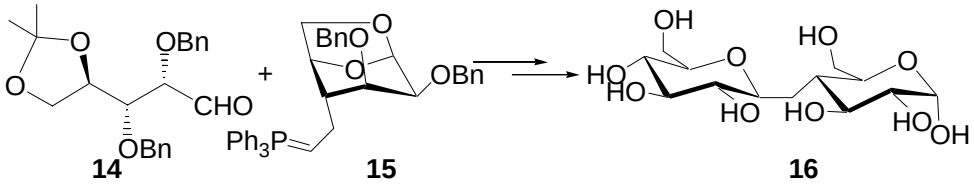
## CYCLIZATION APPROACHES

Another approach to *C*-glycosides relies on the coupling of an open chain fragment with an intact monosaccharide to give a product that is then cyclized to deliver the *C*saccharide target.

### Wittig Reaction-Cyclization

The Kishi group was the first to use a Wittig-cyclization approach for the synthesis of *C*-disaccharides.[37] Their synthesis started with Wittig reaction between **14** and **15**, followed by a series of reactions to give the corresponding *C*-disaccharide 16, (Scheme 3).

**Scheme 3**

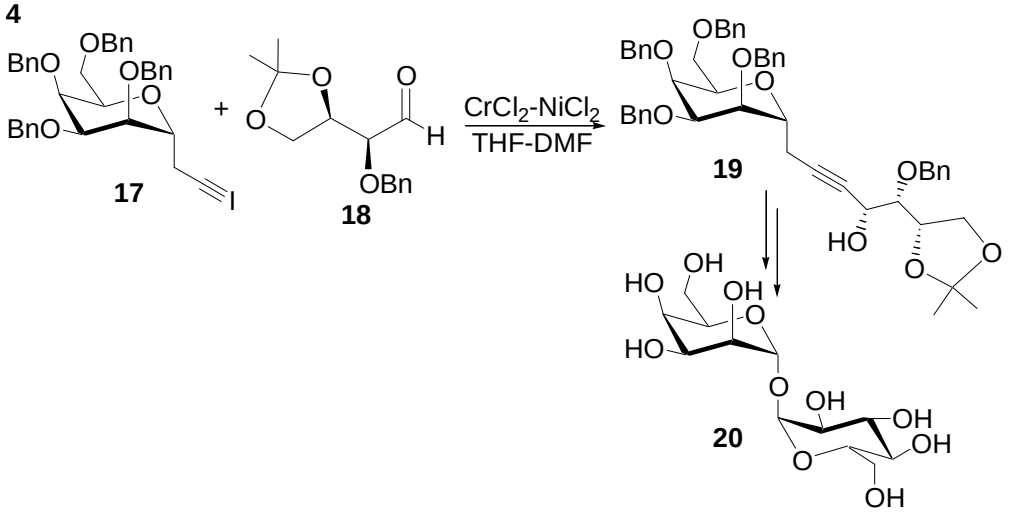



**14** **15** **16**

### Anionic Addition-Cyclization

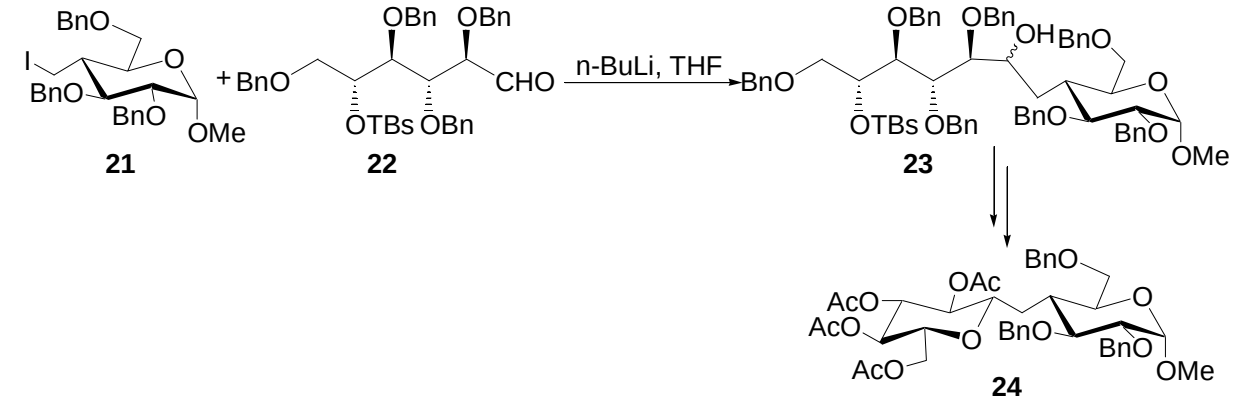
It is appropriate to point out that not only has Kishi been a pioneer in the area of *C*-saccharide synthesis, but has also developed several fundamental reactions in the area of *C*glycoside synthesis[38] Kishi-Nozaki reaction to couple **17** and an aldehyde **18** to give **19**. The triple bond was partially reduced and osmylation was followed by selective protection to give **20**. Which up on exposure to a series of functional group manipulations gave α,α –*C* trehalose[39] (**20**) Scheme (4).

**Scheme 4**




Schmidt[40] added the anionic sugar lithium reagent derived from **21** to aldehyde **22** to give **23** as a mixture of isomers. Mesylation, desilylation, sodium hydride treatment followed by hydrogenation of the benzyl groups and peracetylation gave the 1,4- linked-*C*-disaccharide **24**, Scheme (5).

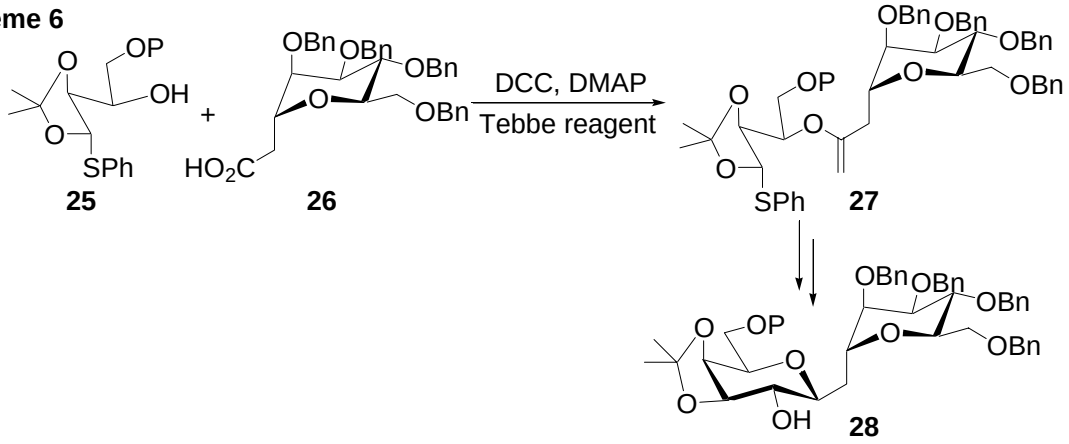
**Scheme 5**




**Esterification-Cyclization**

Mootoo and co-workers used electrophilic cyclization chemistry to assemble *C*-disaccharide structures[41] Alcohol **25** was coupled with acid **26** to give ester, which up on methylenation furnished enol ether **27**, which up a series of reactions gave *C*-Disaccharides **28** Scheme (6).

**Scheme 6**

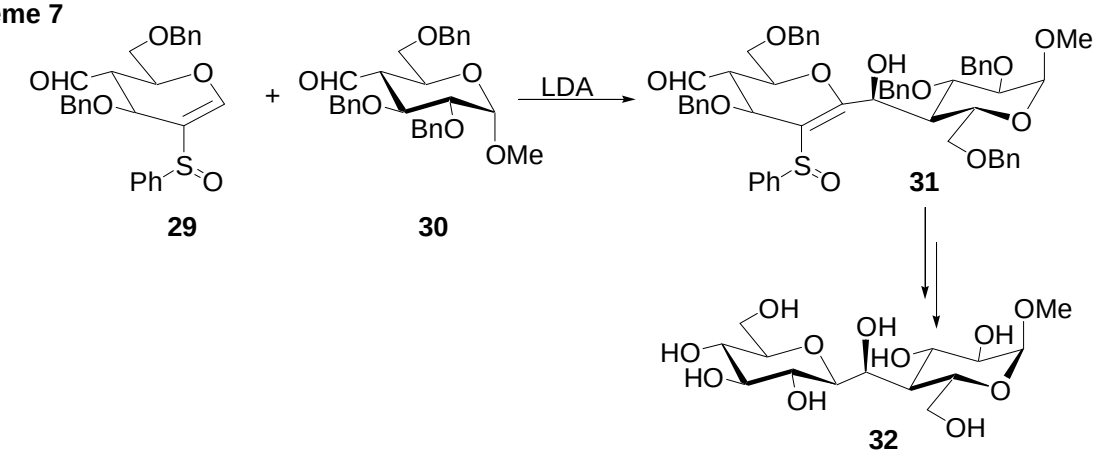



## ANIONIC APPROACHES

*C-1 Vinyl Anions*

Schmidt was the first to explore the addition of sulfoxide stabilized vinyl *C*-1-anions to carbohydrate-based carbonyl compounds[42] The vinyl sulfoxide **29** (prepared from Dglucal in three steps) was deprotonated with LDA, and addition of anion to aldehyde **30** gave a mixture of diastereoisomers of which the major **31**, was formed in a 10:1 ratio. Desulfurization, hydroboration and removal of the benzyl groups gave the (1→4)-β-*C*-disaccharide **32**, Scheme (7).

**Scheme 7**

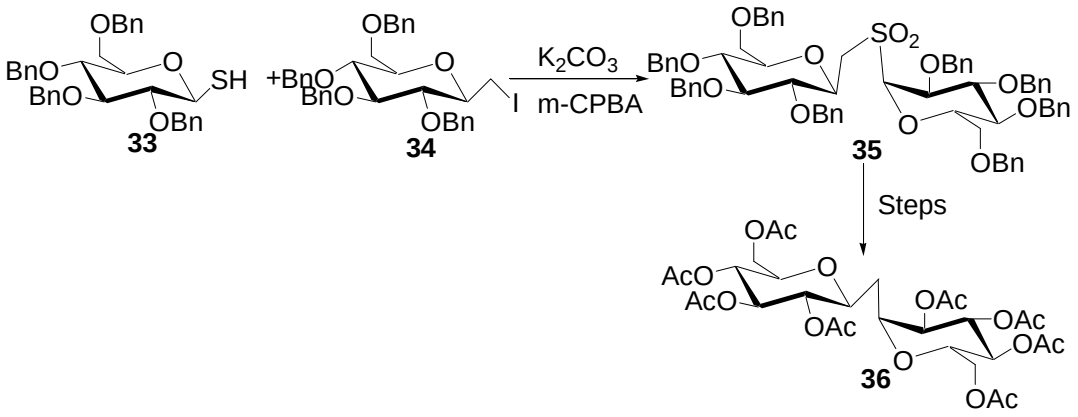



### Sulfur Stabilized Anions

The Taylor group relied upon the Meyers variant of the Ramberg-Backlund reaction for the synthesis of *C* disaccharides[43] The protected thioglucose derivative **33** was coupled

with iodide **34** and oxidation of the formed sulfide gave sulfone **35**. Exposure of **35** to the Meyers variant[44] of the Ramberg-Backlund reaction then furnished enol ether, as a mixture of isomers, which up on hydrogenation of this mixture stereoselectively reduced the enol ether

**Scheme 8**

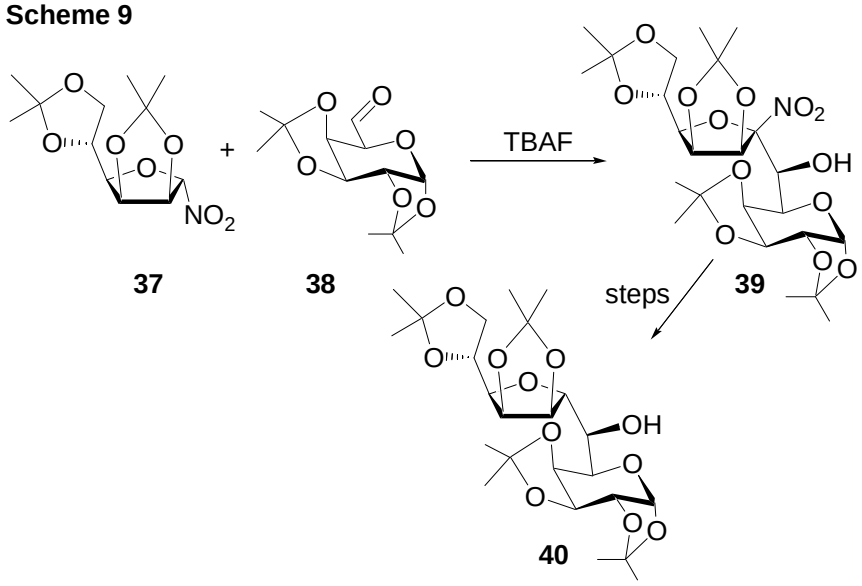



double bond and cleaved the benzyl groups, followed by peracetylation of the free sugar gave acetylated *C*-trehalose **36**, Scheme (8).

**Nitro Stabilized Anions**

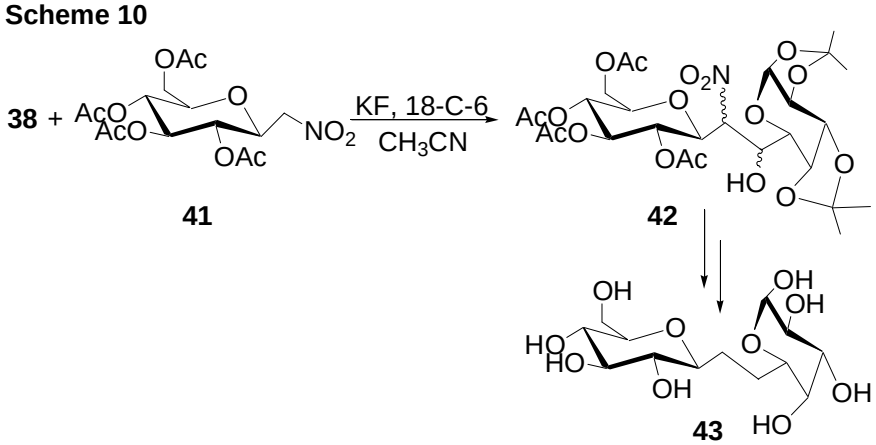
Vasella and Martin are both pioneers in the use of nitrobased anions for *C*-saccharide synthesis. The anomeric nitro derivative **37** was treated with TBAF and exposed to aldehyde **38** to give a 78% yield of adduct **39**[45] Reductive denitration of **39** then gave **40**, Scheme (9).[46]

**Scheme 9**



Martin's work relied upon the Henry reaction. Henry aldol condensation of nitro sugar **41** with aldehyde **38** gave **42**. Dehydration conjugate reduction radical-based removal of nitro group **42** and the sequence was completed by removal of the protecting groups to give the (1→6)-β-*C*-disaccharide **43**, Scheme (58).[47]

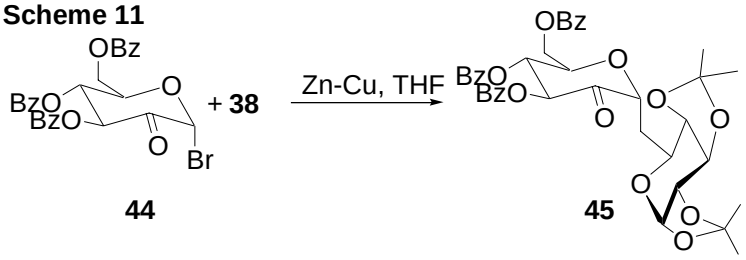
**Scheme 10**




**Enolate Anions**

The enolate, generated from bromide **44**, was condensed with aldehyde **38** and gave an 8:1 mixture of aldol products with **45** as the major, Scheme (11).[48]

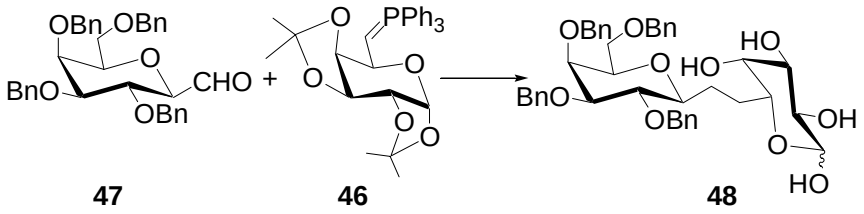
**Scheme 11**




**Phosphorous Stabilized Anions**

The synthesis of (1→6)-*C*-disaccharides is perfectly suited for this methodology, since one sugar can hold the aldehyde and the other the ylide or phosphonate anion. Dondoni has prepared a wide variety of (1→6)-*C* disaccharides by this approach,[49] Coupling of ylide **46** with aldehyde **47** gave a 76% yield of a single alkene, followed by deprotection furnished the free (1→6)-*C*-disaccharide **48**, Scheme (12).

**Scheme 12**

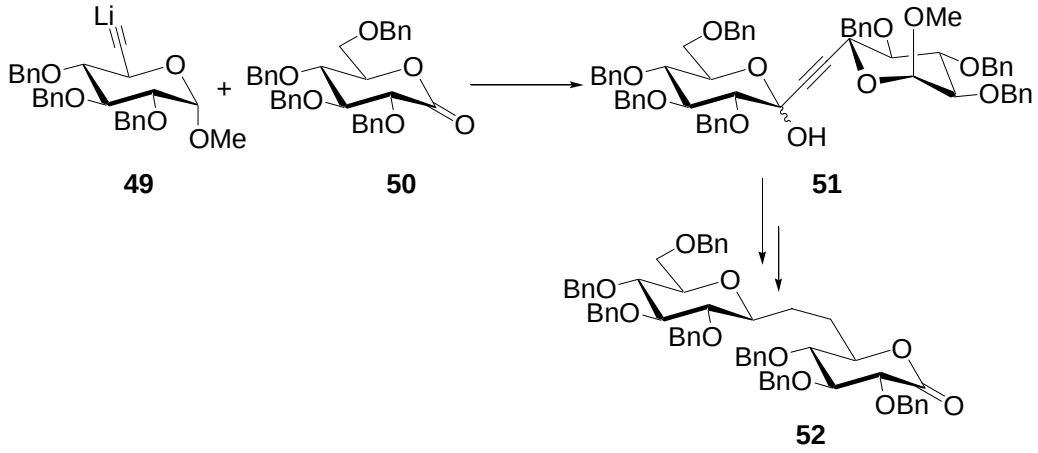



47 46 48

**Acetylide-Based Anions**

It is appropriate to point out that Sinaÿ was the first to prepare a *C*-disaccharide.[27] His approach involved the coupling of a *C*-6 alkyne with an anomeric lactone followed by reduction of the formed hemiacetal. Accordingly, nucleophilic addition of acetylide **49**, to lactone **50**, gave a mixture of lactols **51** in excellent yield. Stereoselective reduction of lactol **51** was followed by hydrogenation of the benzyl groups and the triple bond to deliver the (1→6)-β-*C*-disaccharide **52**, Scheme (13).

**Scheme 13**

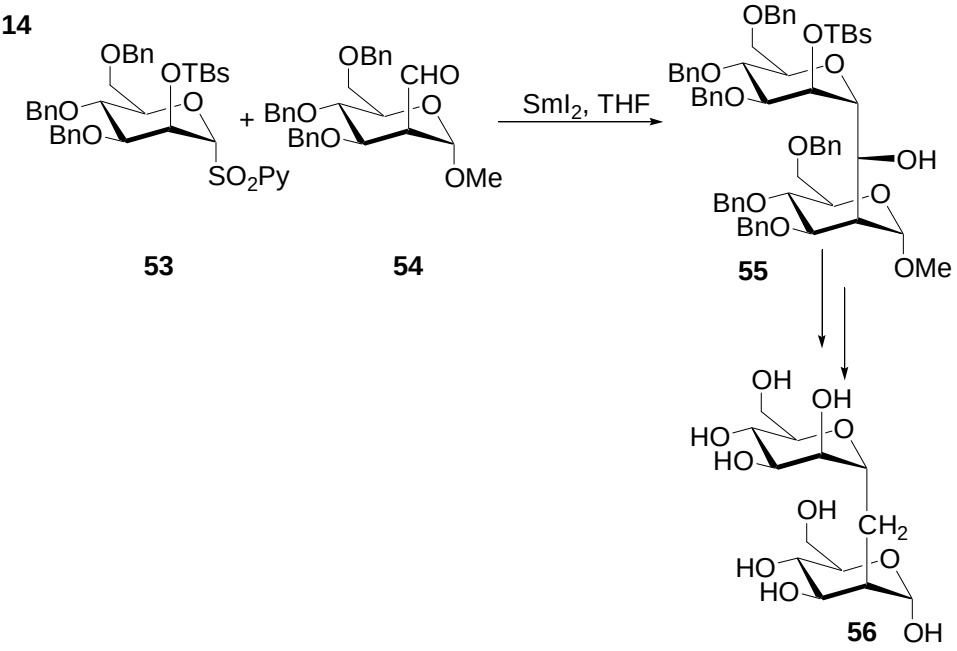



49 50 51 52

**Glycosyl Samarium Species**

Beau and Skrydstrup were the first to realize the potential of anomeric organosamarium intermediates as precursors to *C*-glycosides and *C*-saccharides,[50] then they used their methodology to prepare an a-*C*-mannobioside which may be an inhibitor of *M.tuberculosis*.[51]

**Scheme 14**




Aldehyde **54** was prepared by the use Jung's radical-based methodology.[52] Condensation of the formed organosamarium species derived from **53** with aldehyde **54** gave a single diastereoisomer assigned the structure **55**. Radical deoxygenation of **55** was followed by deprotection to give the target compound **56**, Scheme (14).

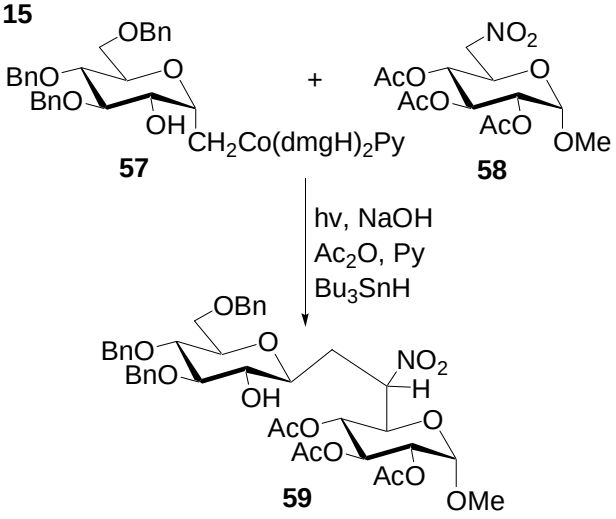
**Free Radical Approaches**

The use of free radical chemistry in the realm of carbohydrates is not a new concept. Deoxygenation of carbohydrate derivatives by free radical methods has been known for sometime. There is also a large body of published work dealing with free radical-mediated approaches to the synthesis of *C*-glycosides.

**Intermolecular Approaches III, Radical and SRN1 Coupling**

There are only a handful of papers that describe the preparation of *C*-disaccharides by radical coupling-based methods. Martin photolyzed the cobalt complex **57** in the presence of the nitro sugar **58** to give a mixture of adducts, which up on denitration gave the protected *C*-disaccharide **59**, Scheme (15).[53]

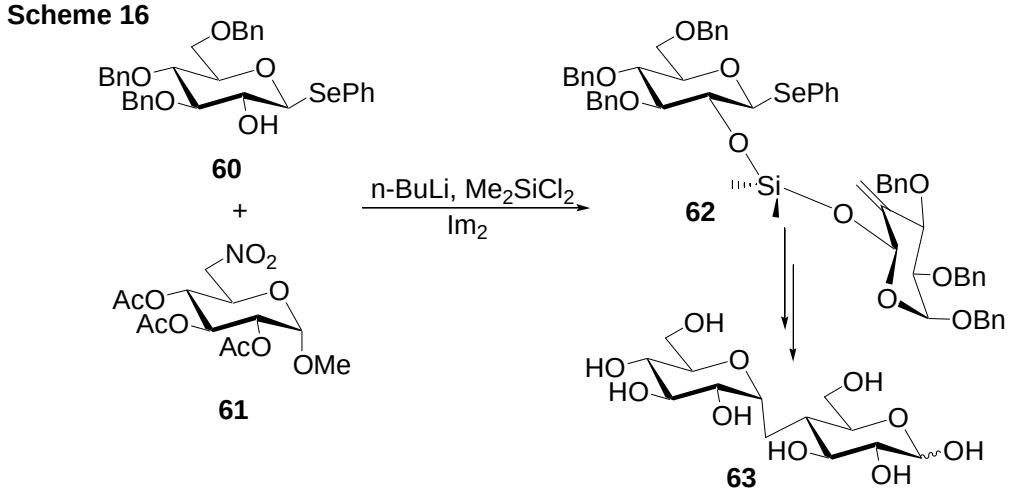
**Scheme 15**




**Intramolecular Approaches**

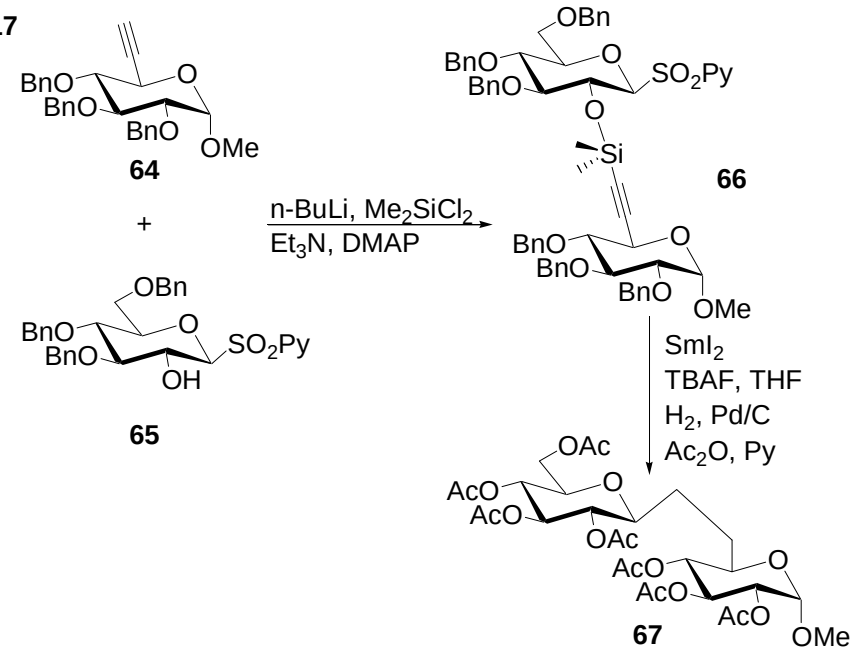
Sinaÿ has been a leader in this area and his work is based on a tether-radical cyclization approach. His work has been overviewed,[54] In their first generation approach,[55] they chose to link alcohols **60** and **61** via a dimethylsilyl tether. To that end, the anion of **60** was mixed with chlorodimethylsilane at low temperature. The temperature was raised and imidazole and compound **61** were added to the reaction to deliver the tethered compound **62**. Exposure to tin hydride and AIBN, removal of the silyl tether followed by debenzylation afforded *C* maltoside (**63**), Scheme (16).

**Scheme 16**



Beau and Skrydstrup joined the acetylene derivative **64** to the pyridyl sulfone **65** to obtain **66**. Samarium mediated radical cyclization gave the product of 5-*exo* cyclization which was desilylated, hydrogenated and acetylated to give the (1→6)-α-*C*-disaccharide **67**, Scheme (17).[56]

**Scheme 17**

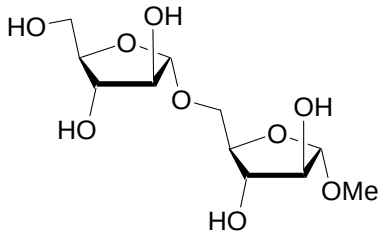



Because of the interesting properties associated with the *C*-saccharides in terms of their stability towards enzymes and hydrophobicity prompted us to synthesize for the first time the *C*-analogue of motif *C* of *M. tuberculosis*.

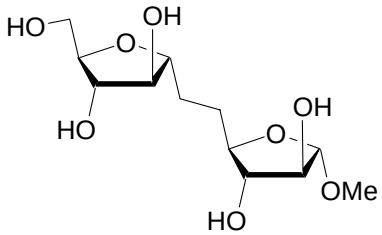
The mycolic arabino-galactan (AG) complex present on the cell wall surface of *mycobacterium tuberculosis* has unique structural features unknown in actinomycetes.[7a,8] The furonoside rings of AG complex are conformationally more mobile (than pyranosides) and are largely linked through primary hydroxyl groups.[9] These characteristics enable the crowded AG complex to adopt a structure in which mycolic acids are closely arranged in parallel arrays.[57] The AG complex is critical for the survival of M. tuberculosis. The hydrophobic AG complex acts as a strong barrier for the passage of antibiotics into the cell and therefore, plays an important role in developing the resistance of mycobacteria to many antibiotics.

The drug ethambutol[17a] blocks the biosynthetic pathway of arabinose. The inhibition of biosynthetic pathway, involved in displacement of *M. tuberculosis* cells, is considered as an attractive strategy for drug development against *M. tuberculosis*. The oligosaccharides present on various motifs of AG complex are structurally elucidated and their synthesis has dominated the area in recent times.

The C-linked glycosides[58] are generated by the replacement of interglycosidic oxygen atom by the methylene group, which differ from natural substrate, being stable to both chemical and metabolic degradations and more over the confirmational features[59] of *C*-glycosides to a large extent resemble those of naturally occurring *O*-glycosides. The *C*-glycosides serve as glycosyl regulators and as synthetic ligands for probing cellular interactions. Because of the intrinsic properties associated with the *C*-glycosides interms of stability and confirmational aspects prompted us to take up the synthesis of *C*-saccharides of the AG complex and this chapter provides our initial success in the synthesis of a *C*-disaccharide corresponding to the motif-C of *M. tuberculosis*.

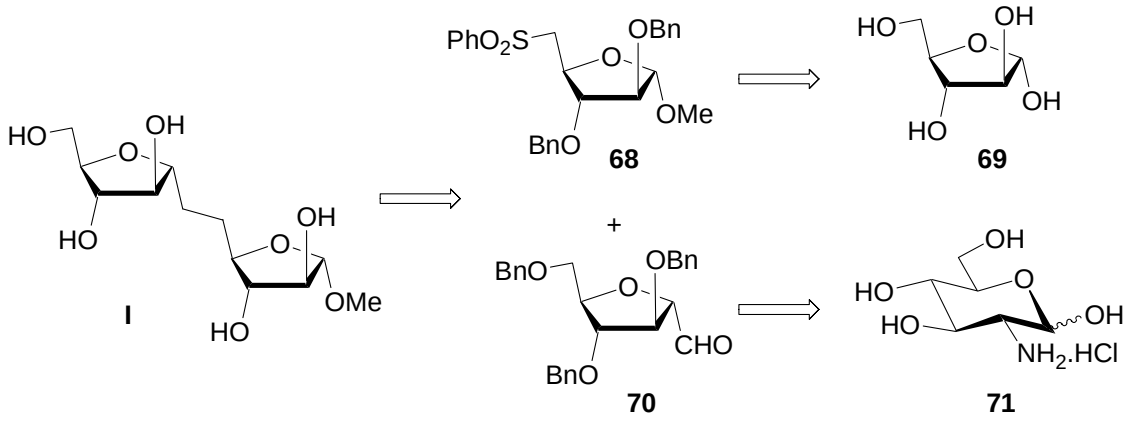



Motif C (**3**)




C-Glycosidic Motif C (**I**)

We envisioned the replacement of interglycosidic oxygen atom by a methylene group could be achieved, employing a base promoted reaction between the suitably substituted coupling partners **68** and **70**. The coupling partner **68** could be obtained from the commercially available D-arabinose (**69**). The other coupling partner **70** was envisioned from D-glucosamine hydrochloride (**71**) (scheme 1).



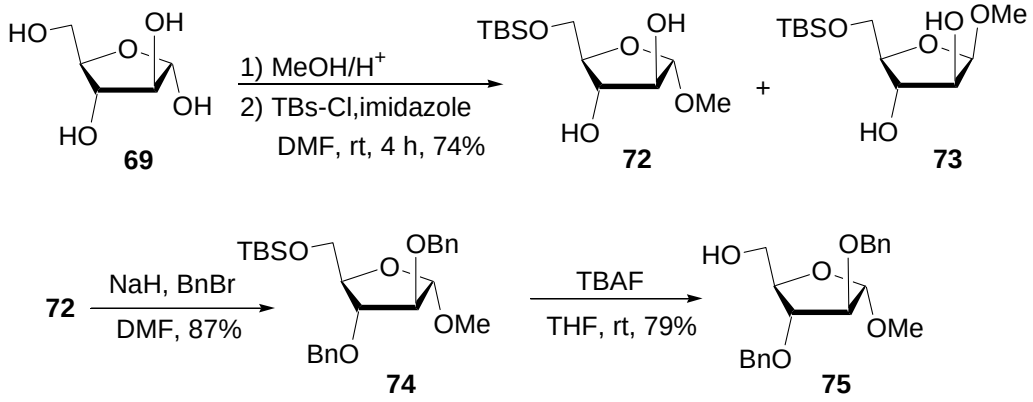

**Scheme 18:** *Retrosynthetic analysis for* ***I***

**Synthesis of the Sulphone derivative (68)**

The alcohol **75**[60] was synthesized starting from D-arabinose (**69**) following a literature procedure. D-arabinose (**69**) was treated with methanolic HCl to obtain the corresponding methyl arabinofuranoside as a mixture of $\alpha$- and $\beta$- anomers[60], which were used for further reactions without separation of $\alpha$- and $\beta$- glycosides. Selective protection of the primary hydroxyl group was achieved by treating with TBS-Cl, imidazole in anhydrous DMF at room temperature for 4 h to give **72** and **73**, which were separated by silica gel chromatography. The major $\alpha$ anomer **72**, was scrutinized by the $^{1}$H NMR and $^{13}$C NMR spectra. In the $^{1}$H NMR spectrum of **72** two-singlets due to methyl groups of TBS group were observed at $\delta$ -0.05 and 0.88. The H-1 proton resonated as a singlet at 4.89 ppm. In the case of the $\beta$ anomer (**73**), H-1 resonated as a doublet ($J$ = 4.15 Hz) at $\delta$ 4.75. The dibenzylate **74** was prepared from **72** by using NaH-BnBr in anhydrous DMF at room temperature for 1.5 h in 87% yield. The structure was assigned based on the $^{1}$H NMR and $^{13}$C NMR spectra. Compound **74** was

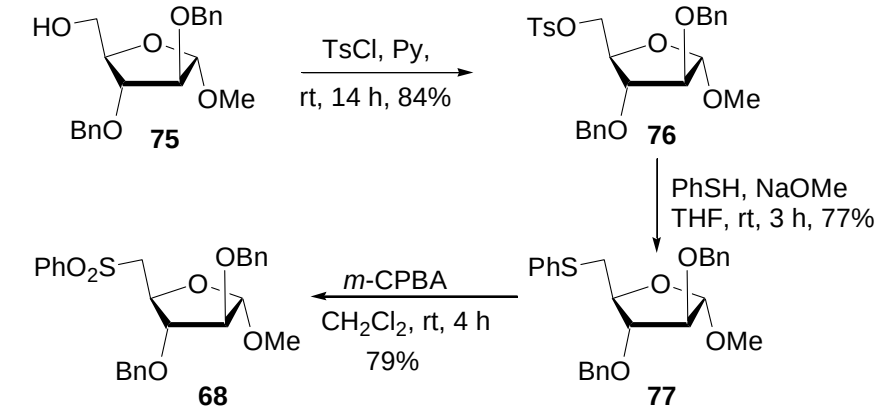
desilylated-using TBAF in THF at room temperature for 1 h to give the alcohol **75** (Scheme 18).

**Scheme 18**




Our next concern was to convert **75** in to the sulphone derivative (**68**). Thus, the primary hydroxyl group of **75** was converted in to the tosylate **76** by treating with TsCl and pyridine at room temperature. The structure of tosyl ether **76** was confirmed by the $^{1}H$ NMR, $^{13}C$ NMR spectra and the elemental analysis. In the $^{1}H$ NMR spectrum of **76**, the characteristic singlet at 2.39 ppm due to Me group was observed. As expected resonances due to $CH_2$-5 showed down field shift of 0.3 ppm when compared with resonances of corresponding protons of **75**.

**Scheme 19**

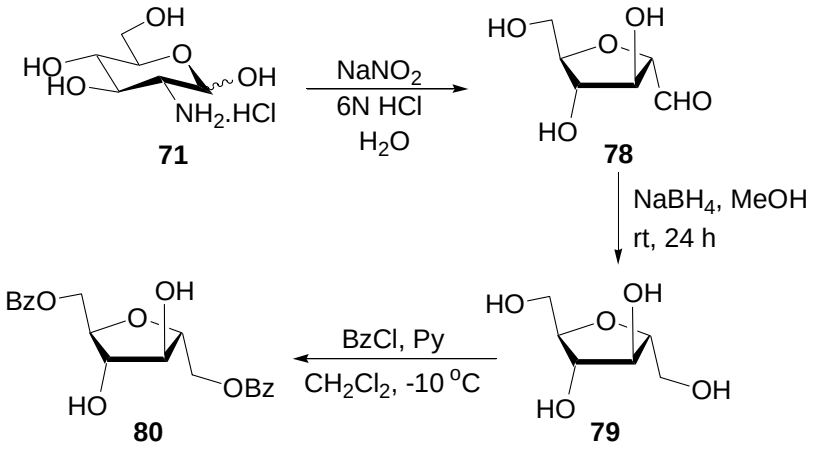


The nucleophilic displacement of OTs group using sodium thiophenolate (generated *insitu* from thiophenol and NaOMe) in anhydrous THF at room temperature furnished **77**. The structure was proved by the $^{1}$H NMR and $^{13}$C NMR spectral analysis. In the $^{1}$H NMR spectrum of **77**, an upfield shift of $CH_2$-5 resonances was noticed. Oxidation of **77** using *m*-CPBA in $CH_2Cl_2$ at room temperature for 4 h resulted in the formation of sulphone **68** in 79% yield. The structure was confirmed based on its $^{1}$H NMR, $^{13}$C NMR and IR spectra. In the $^{1}$H spectrum of **68**, a distinctive down field shift (0.2 ppm) of $CH_2$-5 protons was observed compared to **77**. In the IR spectrum a strong absorption due to $SO_2$ group was observed at 1384 $cm^{-1}$ (Scheme 19).

**Synthesis of the aldehyde derivative (70)**

The aldehyde **70** was synthesized starting from commercially available D-glucosamine hydrochloride (**71**). By subjecting **71** to diazotization-mediated ring contraction reaction in aqueous solution at 0 ºC using $NaNO_2$, and conc.HCl for 5 h, the furanoaldehyde **78**, was

**Scheme 20**

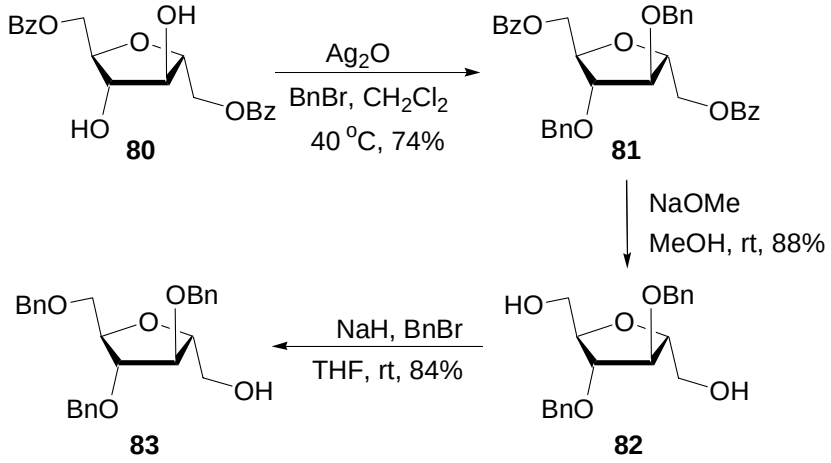



reduced with $NaBH_4$ at room temperature for 24 h to give the 2,5-anhydro-D-mannitol derivative **79**. The selective protection of the primary hydroxyl groups of **79** with benzoyl chloride (BzCl) in pyridine at –10 ºC gave the dibenzoate **80**[61] in 35% yield starting from **71**. Having $C_2$-axis of symmetry, the $^{1}$H NMR spectrum of **80** exhibited resonances for half the molecule as expected (Scheme 20).

Transformation of **80** in to the dibenzyl ether **81** was accomplished by using BnBr, $Ag_2O$ and anhydrous $CH_2Cl_2$ under reflux for 8 h. In the $^{1}$H NMR spectrum of **81**, half signals

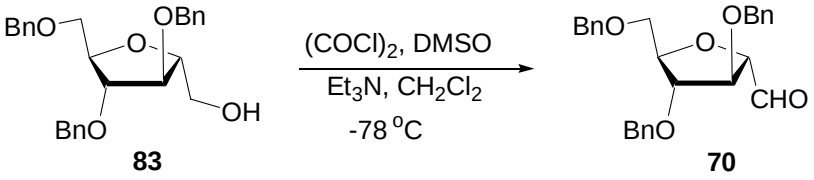
were observed including for benzylic protons. Zemplen deacetylation[62] of **81** gave **82** with NaOMe in methanol. The structure was characterized by the $^{1}H$ NMR and $^{13}C$ NMR spectra. The mono benzylation of **82** was achieved by using NaH, BnBr (1.1 eq) and anhydrous DMF at 0 ºC to provide **83** in 84% yield. The $^{1}H$ NMR and $^{13}C$ NMR spectra were in support of the structure of **83** (Scheme 21).

**Scheme 21**




Oxidation of **83** to the corresponding aldehyde derivative **70** was carried out under Swern oxidation[63] conditions and the resulting aldehyde **70** was immediately used for next reaction.

**Scheme 22**




**Julia olefination reaction:**

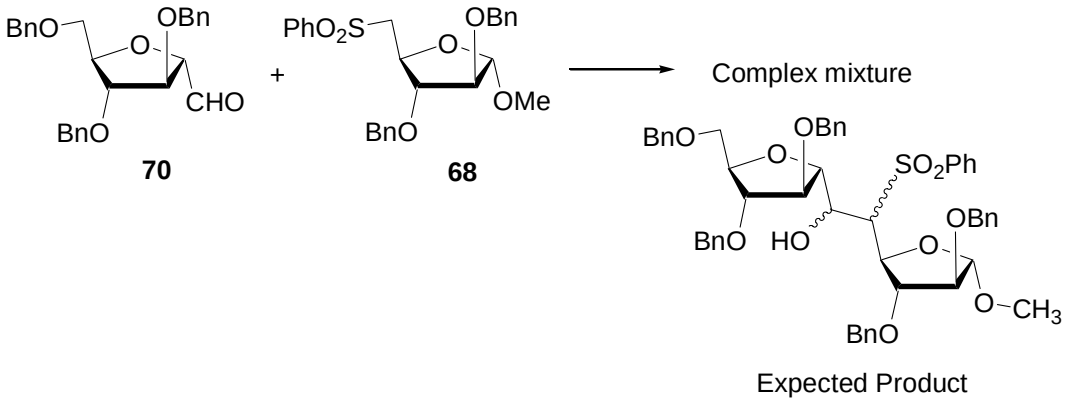
The two coupling partners **68** and **70** have now been obtained, the objective was to evaluate the feasibility of Julia olefination reaction.[64] The attempted coupling reaction by treating the sulphone **68** with n-BuLi in THF at -78 ºC for 15 min followed by addition of the **70** gave a complex mixture. Modifications such as the use of HMPA to stabilize the anion, or

lowering-increasing the temperatures had no success. Change of base such as LDA was not very fruitful (Table 1). The failure was partly attributed to the incompatibility of the substrates. The possibility of ring opening of anion derived from **68** resulting with a vinylsulphone could not be ruled out for failure.

Table 1:

| **S.No** | **Reaction Conditions** | **Result** |
|---|---|---|
| 1. | n-BuLi, THF, -78 ºC | Complex mixture |
| 2. | n-BuLi, HMPA, THF, -78 ºC | Complex mixture |
| 3. | LDA, THF, -78 ºC | Complex mixture |

**Scheme 23**



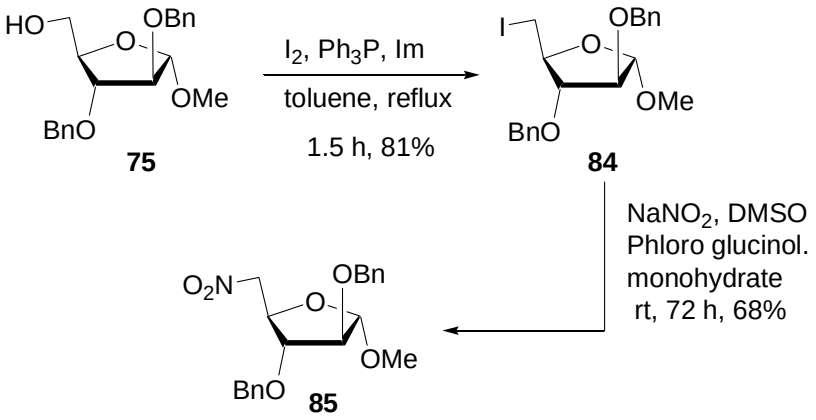

Owing to the failure with the phenyl sulphone strategy, the fluoride ion mediated nitro-aldol reaction (Henry reaction) as the key reaction for the construction of the key C-C linkage was envisaged.

**Synthesis of the Nitro Precursor (85)**

The iodo derivative **84**[65] was formed by treating **75** with $I_2$, $Ph_3P$ and imidazole in toluene under reflux for 1.5 h. The structure of **84** was confirmed by the $^1H$ NMR and $^{13}C$ NMR spectral analysis. As expected, in the $^{13}C$ NMR spectrum of **84**, 5-carbon was revealed at 6.1 ppm. An upfiled shift (0.5 ppm) of $CH_2$-5 protons was noticed in the $^1H$ NMR spectrum while the rest of the protons appeared at expected chemical shifts. Displacement of the iodo

group of **84** with nitrite was accomplished by employing a modified Kornblum reaction[66]. Thus, treatment of **84** with $NaNO_2$, in DMSO and phloroglucinol.monohydrate at room temperature for 72 h gave the nitro derivative **85** in 68% yield. In the IR spectrum of **85** $NO_2$ showed strong absorption at 1342 $cm^{-}1$. In the $^1H$ NMR spectrum of **85** C-5 methylene resonated as a doublet ($J$ = 5.7, 2.9 Hz) at 3.77 and as a multiplet located in the region 3.96–4.01 ppm (Scheme 24).

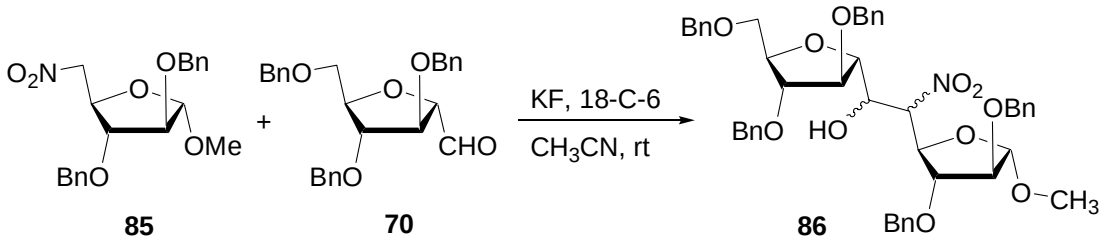
**Scheme 24**




**Coupling reaction**

The treatment of compound **85** with the aldehyde **70**, in the presence of 18-crown-6 and anhydrous KF[67] in $CH_3CN$ with at room temperature gave the required nitroalcohols as a diastereomeric mixture (Scheme 25). Because of the complex overlapping of the signals due to streoisomeric mixture, the structural assignment was done at a later stage.

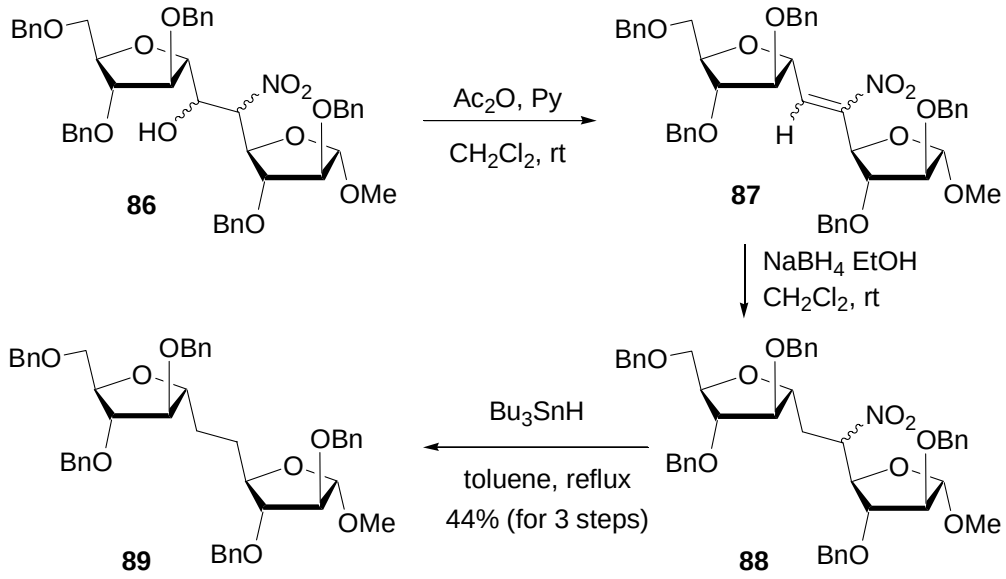
**Scheme 25**




The auxiliary functional groups of **86** were then removed in three successive steps (Scheme 10).

1) Acetylation followed by elimination of AcOH in **86** by using $Ac_2O$/Py in anhydrous $CH_2Cl_2$ at room temperature gave nitroalkene **87** (existed as a mixture of *E*: *Z* isomers. In the IR spectrum of **87** the absorptions corresponding to nitro, and alkene were noticed at 1368, 1525 $cm^{-1}$ respectively).
2) Selective C=C reduction of **87** was carried out by $NaBH_4$ in EtOH at room temperature for 2.5 h, to give the nitro derivative **88**.
3) Reductive denitration of **88** by using $Bu_3SnH$ and cat. AIBN in refluxing toluene led to the formation of penta-*O*-benzyl-*C*-disaccharide **89** in 44% yield.

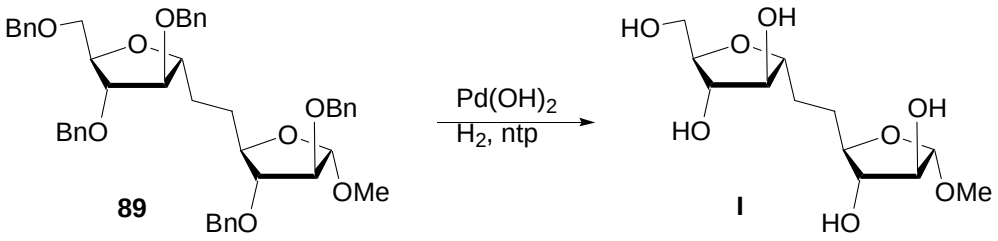
**Scheme 25**




The structure of **89** was fully scrutinized by $^1H$ NMR, $^{13}C$ NMR and elemental analysis. For example, in the $^1H$ NMR spectrum of **89**, characteristic signals due to two bridge methylene groups, were observed between 2.57 as a triplet ($J$ = 5.9 Hz), and at 3.61 as a multiplet. The anomeric protons were located at 4.89 (H-1, s) and 3.77 (H-$1^1$, dd, $J$ = 5.9, 2.9 Hz). The observed resonances due to the two methylenic carbons at $\delta$ 28.1 and 28.8 in the $^{13}C$ NMR spectrum of **89**.

Finally, hydrogenolysis of **89** in presence of $Pd(OH)_2$ at room temperature and normal pressure gave the *C*-disaccharide **I**. The $^1H$ NMR and $^{13}C$ NMR spectra are in complete agreement with the structure of **I**

**Scheme 26**




## Conclusion

Herein we described the first synthesis of *C*-oligosacchride of *M. tuberculosis* in an efficient manner employing the fluoride ion mediated nitro aldol reaction. The biological and structural implications of this analogue will not only be interesting but also significant from the drug development point of view.

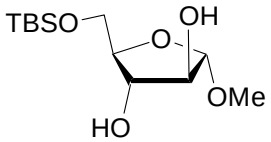
# Experimental Section

**Methyl 5-*O*-(tertiarybutyldimethylsilyl)-D-arabinofuranoside**

A suspension of D-arabinose (**69**) (10.0 g, 66.7 mmol) in 2% methanolic HCl (100 mL) was stirred at room temperature for 4 h. The reaction mixture was neutralized with solid $BaCO_3$ and the solid was filtered, washed with methanol. Combined filtrates were concentrated to give a syrup (10.5 g), which was used for the next step with out any purification.

To a solution of the above syrup in anhydrous DMF (50 mL) was added TBS-Cl (10.59 g, 70.2 mmol) and imidazole (8.70 g, 127.7 mmol) at room temperature and the reaction mixture was allowed to stir for 3 h. The reaction mixture was diluted with ethyl acetate washed with water, brine, dried ($Na_2SO_4$) and evaporated. The residue was purified by silica gel column chromatography by eluting with light petroleum:EtOAc (7:3) to afford *α*-anomer (9.25 g, 52%) and the *β*-anomer (3.91 g, 22%).

**α-anomer (72)**

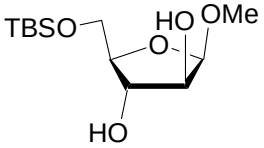



$[\alpha]_D$ + 63.4 (*c* 1.5, $CHCl_3$)

**$^1$H NMR** (200 MHz, $CDCl_3$): *δ* –0.05 (s, 6 H), 0.88 (s, 9 H), 3.36 (s, 3 H), 3.57–3.61 (m, 1 H), 3.65–3.70 (m, 1 H), 3.79–3.81 (m, 2 H), 3.9 (br s, OH), 4.08–4.12 (m, 1 H), 4.83 (s, 1 H).

**$^{13}$C NMR** (125 MHz, $CDCl_3$): *δ* –5.9, -5.8, 17.9, 25.4, 54.3, 63.0, 63.9, 79.7, 84.7, 108.7.

**β-anomer (73)**

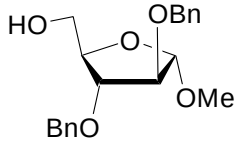



$[\alpha]_D$ + 42. 8 (*c* 1.3, $CHCl_3$)

**$^1$H NMR** (200 MHz, $CDCl_3$): *δ* –0.05 (s, 6 H), 0.87 (s, 9 H), 3.38 (s, 3 H), 3.65–3.68 (m, 3 H), 3.73–3.82 (m, 2 H), 3.99–4.01 (m, 1 H), 4.75 (d, 1 H, *J* = 4.1 Hz);

**$^{13}$C NMR** (125 MHz, $CDCl_3$): *δ* –5.6, 18.1, 26.0, 54.8, 64.8, 75.6, 77.5, 82.1, 101.8.

**Methyl 2,3-di-*O*-benzyl-α-D-arabinofuranoside (75)**




To a solution of **72** (5.0 g, 17.9 mmol) in anhydrous DMF (30 mL) was added NaH (60% dispersion in mineral oil) (1.51 g, 39.3 mmol). After 15 min, benzyl bromide (4.7 mL, 39.3 mmol) was introduced and the reaction mixture stirred for 2 h at 0 ºC. Water was added to the reaction mixture, extracted with ether, washed with water, brine, dried ($Na_2SO_4$) and concentrated. The residue was purified on silica gel by using light petroleum: EtOAc (9:1) as an eluant to afford **74** (6.91 g, 84%).

$[\alpha]_D$ + 45.3 (*c* 1.8, $CHCl_3$)

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 0.07 (s, 6 H), 0.90 (s, 9 H), 3.37 (s, 3 H), 3.74 (d, 2 H, $J$ = 4.7 Hz), 3.89–3.93 (m, 1 H), 3.96–3.98 (m, 1 H), 4.02–4.10 (m, 1 H), 4.49 (d, 2 H, $J$ = 5.4 Hz), 4.55 (s, 2 H), 4.89 (s, 1 H), 7.28–7.32 (m, 10 H);

**$^{13}$C NMR** (125 MHz, $CDCl_3$): $\delta$ –5.5, 18.2, 25.8, 54.5, 63.0, 71.6, 71.8, 82.3, 83.0, 88.1, 107.0, 127.4, 127.5, 128.1, 137.5, 137.9.

A solution of **74** (5.4 g, 11.77 mmol) and 1M solution of TBAF (13 mL) in anhydrous THF (50 mL) was stirred at room temperature for 1 h. The reaction mixture was diluted with water and extracted with ethyl acetate washed with water, dried ($Na_2SO_4$) and concentrated. The residue was purified by silica gel column chromatography eluting with light petroleum:EtOAc (3:2) to give **75** (3.15 g, 78%).

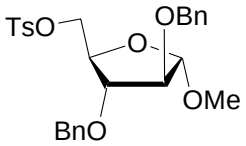
$[\alpha]_D$ + 82.4 (*c* 1.1, $CHCl_3$); lit.[60] $[\alpha]_D$ + 83.2 (*c* 1.14, $CHCl_3$)

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 1.63 (br s, OH), 3.37 (s, 3 H), 3.57–3.61 (m, 1 H), 3.78–3.86 (m, 1 H), 3.94–3.97 (m, 2 H), 4.08–4.14 (m, 1 H), 4.43–4.86 (m, 4 H), 4.90 (s, 1 H), 7.30–7.38 (m, 10 H);

**$^{13}$C NMR** (50 MHz, $CDCl_3$): $\delta$ 54.6, 61.8, 71.7, 72.2, 82.1, 82.5, 87.8, 107.2, 127.7, 127.8, 128.3, 137.2, 137.6.

Analysis calcd. for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.43; H, 7.31.

**Methyl 2,3-di-*O*-benzyl-5-*O*-*p*-toluenesulphonyl-α-D-arabinofuranoside (76)**




A mixture of **75** (3.0 g, 8.71 mmol) and *p*-TsCl (2.0 g, 10.43 mmol) in anhydrous pyridine (15 mL) were stirred at room temperature for 14 h. The reaction mixture was diluted with ether, washed with 1N HCl, water, dried ($Na_2SO_4$) and evaporated. The residue was purified on silica gel by eluting with light petroleum: EtOAc (7:3) to provide **76** (3.21 g, 74%).

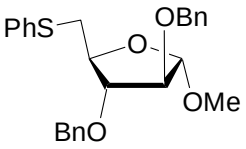
$[\alpha]_D$ + 31.3 (*c* 0.9, $CHCl_3$)

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 2.39 (s, 3 H), 3.35 (s, 3 H), 3.76 (dd, 1 H, *J* = 5.8, 2.8 Hz), 3.88–3.91 (m, 1 H), 4.03–4.19 (m, 3 H), 4.35–4.55 (m, 4 H), 4.85 (s, 1 H), 7.23–7.39 (m, 12 H), 7.75 (d, 2 H, *J* = 8.42 Hz);

**$^{13}$C NMR** (50 MHz, $CDCl_3$): $\delta$ 21.2,54.5, 68.5, 71.5, 71.8, 78.8, 82.6, 87.2, 107.1, 127.5, 128.1, 129.4, 132.6, 137.0, 137.2, 144.3.

Analysis calcd. for $C_{27}H_{30}O_7S$: C, 65.04; H, 6.06; S, 6.43. Found: C, 65.34; H, 6.11; S, 6.68.

**Methyl 2,3-di-*O*-benzyl-5-deoxy-5-(thio-phenyl)-α-D-arabinofuranoside (77)**




A mixture of **76** (2.0 g, 4.01 mmol), PhSH (0.5 mL, 4.81 mmol) and NaOMe (0.26 g, 4.81 mmol) were stirred in anhydrous THF (10 mL) at room temperature for 4 h. The reaction mixture was diluted with water, extracted with ethyl acetate, washed with sat. $NaHCO_3$, water, dried ($Na_2SO_4$) and concentrated. The residue was purified on silica gel by eluting with light petroleum: EtOAc (4:1) to give **77** (1.26 g, 72%).

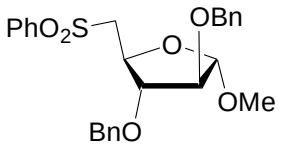
$[\alpha]_D$ + 22.5 (*c* 1, $CHCl_3$)

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 3.13-3.16 (m, 2 H), 3.35 (s, 3 H), 3.86 (dd, 1 H, *J* = 5.8, 2.6 Hz), 3.93–3.95 (m, 1 H), 4.2 (dd, 1 H, *J* = 11.8, 5.9 Hz), 4.43–4.55 (m, 4 H), 4.92 (s, 1 H), 7.25–7.38 (m, 15 H);

**$^{13}$C NMR** (50 MHz, $CDCl_3$): $\delta$ 36.0, 54.2, 71.4, 71.5, 80.0, 85.4, 87.5, 106.7, 125.5, 127.8, 127.9, 135.9, 137.1, 137.4.

Analysis calcd. for $C_{26}H_{28}O_4S$: C, 71.53; H, 6.46; S, 7.35. Found: C, 71.67; H, 6.71; S, 7.08.

**Methyl 2,3-di-*O*-benzyl-5-deoxy-5-phenylsulphonyl-α-D-arabinofuranoside (68)**




To a solution of **77** (1.5 g, 3.43 mmol) in $CH_2Cl_2$ (15 mL) was added *m*-CPBA (3.0 g, 8.68 mmol) slowly at 0 ºC. After 2.5 h, the reaction mixture was neutralized with sat. $NaHCO_3$ solution and extracted with ethyl acetate, dried ($Na_2SO_4$) and evaporated. The residue was purified by silica gel column chromatography eluting with light petroleum: EtOAc (7:3) to afford **68** (1.24 g, 78%).

$[\alpha]_D$ + 23.4 (*c* 1, $CHCl_3$)

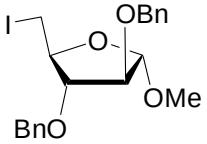
IR ($CHCl_3$): 1384 $cm^{-1}$

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 3.23 (s, 3 H), 3.31–3.36 (m, 2 H), 3.76 (dd, 1 H, *J* = 6.4, 2.5 Hz), 3.86–3.88 (m, 1 H), 4.31–4.38 (m, 1 H), 4.42–4.51 (m, 3 H), 4.58 (d, 1 H, *J* = 12.0 Hz), 4.72 (s, 1 H), 7.25–7.34 (m, 10 H), 7.48–7.62 (m, 3 H), 7.88–7.93 (m, 2 H);

**$^{13}$C NMR** (50 MHz, $CDCl_3$): $\delta$ 54.8, 59.4, 72.1, 72.3, 75.7, 86.1, 87.3, 107.3, 127.8, 127.9, 128.3, 128.4, 128.9, 133.4, 137.2, 137.5, 140.0.

Analysis calcd. for $C_{26}H_{28}O_6S$: C, 66.65; H, 6.02; S, 6.84. Found: C, 66.43; H, 6.41; S, 6.48.

**Methyl 2,3-di-*O*-benzyl-5-deoxy-5-iodo-α-D-arabinofuranoside (84)**




A mixture of **75** (2.0 g, 5.8 mmol), $I_2$ (2.2 g, 8.66 mmol), $Ph_3P$ (2.3 g, 8.69 mmol) and imidazole (0.6 g, 8.66 mmol) in toluene (25 mL) were refluxed for 1.5 h. The reaction mixture was cooled to room temperature, diluted with ether, washed with 20% $Na_2S_2O_3$ solution, water, brine, dried ($Na_2SO_4$) and concentrated. The residue was purified on silica gel using light petroleum: EtOAc (9:1) as an eluent to give **84** (2.13 g, 81%).

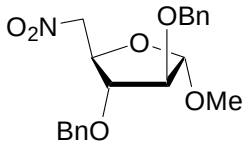
$[\alpha]_D$ + 57.6 (*c* 2, $CHCl_3$)

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 3.20–3.32 (m, 2 H), 3.37 (s, 3 H), 3.78 (dd, 1 H, *J* = 5.9, 2.7 Hz), 3.97–4.02 (m, 2 H), 4.48–4.57 (m, 4 H), 4.96 (s, 1 H), 7.28–7.33 (m, 10 H);

**$^{13}$C NMR** (50 MHz, $CDCl_3$): $\delta$ 6.1, 54.7, 71.9, 72.1, 80.5, 86.5, 88.1, 107.1, 127.7, 128.2, 137.2, 137.4.

Analysis calcd. for $C_{20}H_{23}IO_4$: C, 52.88; H, 5.10. Found: C, 52.67; H, 5.34.

**Methyl 2,3-di-*O*-benzyl-5-deoxy-5-nitro-α-D-arabinofuranoside (85)**




A mixture of **84** (1.5 g, 3.3 mmol), phloroglucinol.monohydrate (0.90 g, 6.24 mmol) and sodium nitrite (0.46 g, 6.60 mmol) was stirred for 72 h at room temperature. Water was added to the reaction mixture and extracted with ethyl acetate and washed with sat. $NaHCO_3$ solution, dried ($Na_2SO_4$) and evaporated. The residue was purified by silica gel column chromatography eluting with light petroleum: EtOAc (4:1) to provide **85** (0.83 g, 68%).

IR ($CHCl_3$): 1342 $cm^{-1}$

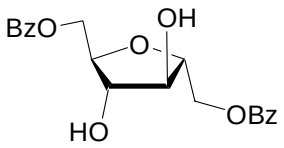
$[\alpha]_D$ + 67.8 (*c* 0.4, $CHCl_3$)

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 3.37 (s, 3 H), 3.77 (d, 1 H, *J* = 5.7, 2.9 Hz), 3.96–4.01 (m, 1 H), 4.31–4.69 (m, 7 H), 4.9 (s, 1 H), 7.23–7.48 (m, 10 H);

**$^{13}$C NMR** (50 MHz, $CDCl_3$): $\delta$ 54.2, 71.6, 71.7, 76.2, 77.2, 83.7, 86.9, 106.9, 127.4, 128.0, 137.0.

Analysis calcd. for $C_{20}H_{23}NO_6$: C, 64.33; H, 6.21; N, 3.75. Found: C, 64.49; H, 6.38; N, 3.97.

**1,6-Di-*O*-benzoyl-2,5-anhydro-D-mannitol (80)**




A solution of D-glucosamine hydrochloride **71** (25.0 g, 115.7 mmol) in water (250 mL) was added sodium nitrite (23.72 g, 115.7 mmol) by portion wise at 0 ºC over a period of 0.5 h. Conc. HCl (19.6 mL), was then added drop wise maintaining the temperature below 2

ºC. The reaction mixture was stirred for 5 h at room temperature. Nitrogen was bubbled through the reaction mixture for 0.5 h to remove the excess of nitrous acid, and then neutralized with 10N NaOH to $P^H$ 7 to give aldehyde **78**.

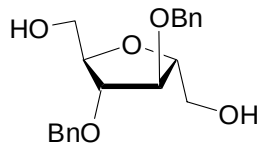
The crude aldehyde **78** was cooled to 0 ºC, $NaBH_4$ (4.4 g, 115.4 mmol) was added portion wise and stirred at room temperature for 24 h. the solution was neutralized with 6N HCl and the aqueous solution was concentrated under reduced pressure. The semisolid material was treated with MeOH and evaporated. The residue was extracted with MeOH and extracts were stirred with ion-exchange resin (Dowex-50, H+, 20 g). After 1 h and the resin was filtered, concentrated to give **79** (11.57 g).

To a solution of crude **79** (11.57 g, 70.4 mmol) in pyridine (25 mL) and $CH_2Cl_2$ (250 mL) at –10 ºC was added benzoyl chloride (7.5 mL, 64.8 mmol). After 2 h additional benzoyl chloride (7.5 mL, 64.8 mmol) was introduced. After 24 h, the reaction mixture was extracted with ethyl acetate and the organic layer was washed with ice-cooled solution of 2N HCl, sat. $NaHCO_3$, dried ($Na_2SO_4$) and evaporated. The residue was chromatographed on silica gel by eluting with light petroleum: EtOAc (7:3) to give **80** (9.18 g, 35%).

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 4.17 (br m, 2 H), 4.47 (br m, 2 H), 7.32–7.39 (m, 2 H), 7.45–7.52 (m, 2 H), 7.97–8.01(m, 2 H);

Analysis calcd. for $C_{20}H_{20}O_7$: C, 64.51; H, 5.41. Found: C, 64.82; H, 5.68.

**3,4-Di-*O*-benzyl-2,5-anhydro-D-mannitol (82)**




A mixture of **80** (3.5 g, 9.39 mmol), $Ag_2O$ (5.44 g, 23.47 mmol) and benzyl bromide (2.5 mL, 20.63 mmol) in anhydrous $CH_2Cl_2$ was stirred at room temperature for 10 h. The solid was filtered and the filtrate was concentrated, and the residue was purified by silica gel chromatography eluting with light petroleum: EtOAc (9:1) to provide **81** (4.46 g, 86%).

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 4.15 (br m, 1 H), 4.45 (br m, 4 H), 4.57 (br m, 2 H) 7.28–7.31 (m, 5 H), 7.37–7.41 (m, 2 H), 7.50–7.57 (m, 2 H), 8.01–8.05 (m, 2 H);

**$^{13}$C NMR** (50 MHz, $CDCl_3$): $\delta$ 64.2, 71.6, 81.0, 84.4, 127.4, 127.6, 128.0, 128.2, 129.4, 129.6, 132.6, 137.1, 165.7.

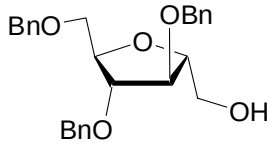
A mixture of **81** (2.5 g, 4.52 mmol), NaOMe (0.48 g, 9.03 mmol) in MeOH (10 mL) was stirred at room temperature for 0.5 h. The reaction mixture was quenched with dry ice, solvent evaporated and the residue purified on silica gel by eluting with light petroleum: EtOAc (3:2) to give **82** (1.37 g, 88%).

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 2.75 (br s, OH), 3.64 (d, 2 H, $J$ = 5.0 Hz), 3.96–3.98 (m, 1 H), 4.09–4.12 (m, 1 H), 4.52 (br m, 2 H), 7.28–7.32 (m, 5 H);

**$^{13}$C NMR** (50 MHz, $CDCl_3$): $\delta$ 62.6, 72.0, 83.3, 84.0, 127.7, 127.9, 128.4, 129.8, 137.4.

Analysis calcd. for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 70.13; H, 6.87.

**1,3,4-tri-*O*-benzyl-2,5-anhydro-D-mannitol (83)**




To a solution of **82** (1.0 g, 2.9 mmol) in anhydrous DMF (15 mL) was added NaH (60% dispersion in mineral oil) (0.10 g, 2.58 mmol). After 20 min, BnBr (0.4 mL, 3.18 mmol) was added followed by stirring for 1 h at which time water was added, extracted with ethyl acetate, washed with water, brine, brine, dried ($Na_2SO_4$) and evaporated. The residue was chromatographed on silica gel by using light petroleum: EtOAc (4:1) as a eluant to obtain **83** (1.05 g, 84%).

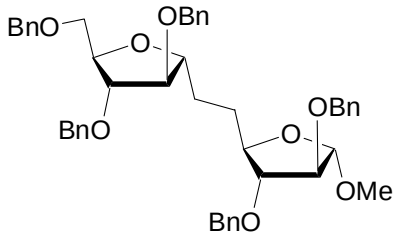
$[\alpha]_D$ + 22 (*c* 1.8, $CHCl_3$)

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 2.32 (br s, OH), 3.49–3.61 (m, 2 H), 3.62–3.64 (m, 2 H), 4.01–4.18 (m, 3 H), 4.29–4.32 (m, 2 H), 4.48–4.69 (m, 6 H), 7.24–7.49 (m, 15 H);

**$^{13}$C NMR** (50 MHz, $CDCl_3$): $\delta$ 64.2, 69.9, 71.6, 73.2, 81.5, 83.1, 84.5, 126.2, 127.5, 137.6, 137.9.

Analysis calcd. for $C_{27}H_{30}O_5$: C, 74.63; H, 6.96. Found: C, 74.97; H, 6.59.

**Methyl 7,10-anhydro-5,6-dideoxy-2,3,8,9,11-pentakis-*O*-(benzyl)-D-arabino-β-L-galacto-undecafuranoside (89)**




A solution of DMSO (0.48 mL, 6.78 mmol) in anhydrous $CH_2Cl_2$ was added drop wise to a solution of $(COCl)_2$ (0.25 mL, 2.86 mmol) in anhydrous $CH_2Cl_2$ (5 mL) under nitrogen atmosphere at –78 °C. The mixture was stirred for 5 min and then a solution of **70** (1.0 g, 2.30 mmol) in anhydrous $CH_2Cl_2$ was added drop wise. After 30 min $Et_3N$ (1.28 mL) was slowly introduced. After 1 h at room temperature, the reaction mixture was diluted with water, extracted with $CH_2Cl_2$, washed with brine, dried ($Na_2SO_4$) and evaporated to give aldehyde **25** (0.86 g, 86 %) used as such for the next reaction.

A solution of **70** (0.86 g, 1.99 mmol), **85** (0.5 g, 1.33 mmol), KF (0.12 g, 2.08 mmol), and 18-crown-6 (0.05 g) in $CH_3CN$ (5 mL), was vigorously stirred for 2.5 h at room temperature. The reaction mixture was diluted with ether (10 mL) and washed with water, dried ($Na_2SO_4$) concentrate to give **86**, which was taken for the next reaction.

The above product **86**, $Ac_2O$ (0.2 mL, 2.0 mmol), pyridine (3 mL), and a catalytic DMAP (3 mg) were stirred at room temperature for 24 h. the reaction mixture was then diluted with ethyl acetate, washed with 1N HCl, water, dried ($Na_2SO_4$) and evaporated to give **87**. Which was dissolved in EtOH (1 mL) and then $NaBH_4$ (0.025 g, 0.66 mmol) was added, stirred at room temperature for 3 h The reaction mixture was extracted with ethyl acetate washed with water, brine, dried ($Na_2SO_4$) and concentrated to afford **88**, which was dissolved in toluene (5 mL) and then AIBN (10 mg) and $Bu_3SnH$ (0.4 mL, 1.59 mmol) were introduced. After 1 h of refluxing, solvent was evaporated and the residue purified by silica gel column chromatography eluting with light petroleum: EtOAc (4:1) afforded **89** (0.43 g, 44% in 3 steps).

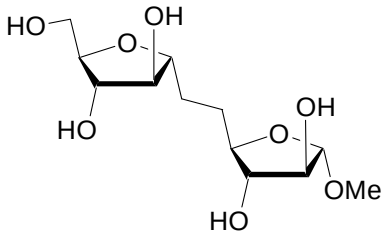
$[\alpha]_D$ + 26.8 (*c* 0.5, $CHCl_3$)

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 2.57 (t, 2 H, $J$ = 5.9 Hz), 3.33 (s, 3 H), 3.61 (m, 2 H), 3.77 (dd, 1 H, $J$ = 5.9, 2.9 Hz), 3.94 (m, 1 H), 4.01 (t, 1 H, $J$ = 2.9 Hz), 4.11 (q, 1 H, $J$ = 5.9 Hz), 4.27 (br s, 1 H), 4.35–4.70 (m, 14 H), 4.89 (s, 1 H), 7.30 (m, 25 H);

**$^{13}$C NMR** (50 MHz, $CDCl_3$): $\delta$ 28.1, 28.8, 54.4, 70.1, 71.2, 71.8, 71.9, 73.6, 80.8, 81.2, 82.3, 83.7, 86.1, 88.5, 91.2, 107.0, 127.6-128.2, 134.1-135.0.

Analysis calcd. for $C_{47}H_{52}O_8$: C, 75.78; H, 6.97. Found: C, 75.43; H, 6.97.

**Methyl 7,10-anhydro-5,6-dideoxy-D-arabino-β-L-galacto-undecafuranoside (I)**




A solution of compound **89** (0.2 g, 0.26 mmol), 10% $Pd(OH)_2$ (50 mg) in methanol (5 mL) was stirred under the atmosphere of hydrogen, normal temperature and pressure. After 8 h, the catalyst was filtered and the filtrate concentrated to give **I** (0.065 g, 83%).

$[\alpha]_D$ + 46.2 (*c* 0.6, $CHCl_3$)

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 1.80–2.11 (m, 4 H), 3.70 (s, 3 H), 3.66–4.25 (m, 9 H), 4.81 (s, 1 H);

**$^{13}$C NMR** (50 MHz, $CDCl_3$): $\delta$ 27.3, 29.1, 53.2, 62.5, 77.4, 77.5, 78.9, 81.8, 83.2, 84.2, 84.7, 107.1.

Analysis calcd. for $C_{12}H_{22}O_8$: C, 48.97; H, 7.53. Found: C, 48.93; H, 7.92.

# References

**References**


1. (a) Opravil, M. *Infection* **1997**, *25*, 56. (b) Millard, F. J. *J. Royal Soc. Med.* **1996**, 89, 497. (c) Efferen, L. S.; Hyman, C. L. *Curr. Opin. Pulm. Med.* **1996**, *2*, 236. (d) Sudre, P.; ten Dam G.; Kochi, A. *Bulletin of the World Health Organization* **1992***, 70*, 149. (e) Huebner, R. E.; Castro, K. G. *Annu. Rev. Med.* **1995**, *46*, 47.
2. (a) Lee, R. E.; Brennan, P. J.; Besra, G. S. Tuberculosis. In *Current Topics in Microbiology and Immunology*; Shinnick, T. M., Ed.; Springer-Verlag: Berlin, **1996**; Chapter 1, p 215. (b) Bloom, B. R.; Murray, C. J. *Science* **1992**, *257*, 1055. (c) Fischl, M. A. *Ann. Int. Med*. **1992**, *117*, 184.
3. (a) Valainis, G. T.; Cardona, I. M.; Greer, D. L. *JAIDS, J. Acquired Immune Defic. Syndr.* **1991**, *4*, 516. (b) Spinney, L. *New Sci.* **1996**, 8. (c) Gilbert, G. L. *Med. J. Aust.* ***1996****, 154*, 121. (d) Dye, C.; Scheele, S.; Dolin, P.; Pathania, V.; Raviglione, M. C. *J. Am. Med. Ass*. **1999**, *282*, 677.
4. McNeil, M.; Brennan, P.J. *Res. Microbiol*. **1991**, *142*, 451.
5. Kaneda, K.; Imaizumi, S.; Mizuno, S.; Baba, T.; Tsukamura, M.; Yano, I. *J. Gen. Microbiol.* **1988**, *134*, 2213.
6. Rouhi, A. M. *Chem.& Engg. News* **1999**, *May 17*, 52.
7. (a) Besra, G. S.; Khoo, K.-H.; McNeil, M. R.; Dell, A.; Morris, H. R.; Brennan, P. J. *Biochemistry* **1995**, *34*, 4257. (b) Wolucka, B. A.; McNeil, M. R.; de Hoffman, E.; Chojnacki, T.; Brennan, P. J. *J. Biol. Chem.* **1994**, *269*, 23328. (c) McNeil, M. R.; Daffe, M.; Brennan, P. J. *J. Biol. Chem.* **1990**, *265*, 18200. (d) Daffe, M.; Brennan, P. J.; McNeil, M. *J. Biol. Chem.* **1990**, *265*, 6734. (e) McNeil, M. R.; Robuck, K. G.; Harter M.; Brennan, P. J. *Glycobiology* **1994**, *4*, 165.
8. Brennan, P. J.; Nikaido, H. *Annu. Rev. Biochem.* **1995**, *64*, 29.
9. McNeil, M.; Wallner, S. J.; Hunter, S. W.; Brennan, P. J. *Carbohydr. Res.* **1987**, *166*, 299.
10. (a). Cohen, M. L. *Science*, **1992**, *257*, 1050. (b) Moran, N. *Nature Medicine* **1996**, *2,* 377.
11. McNeil, M. In *Mycobacterium avium*-Complex Infection, Ed. Korvick, J. A.; Benxon, C. A. Marcel Dekker, Inc.; New York, **1996**.

12. (a) Schlesinger, L. S. *Curr. Topics. Microbiol. Immunol.* **1996**, *215*, 71. (b) Schlesinger, L. S.; Hull, S. R.; Kaufman, T. M. *J. Immunol*. **1994**, *152*, 4070.
13. (a) Jarlier, V.; Nikaido, H. *FEMS Microbiol. Lett*. **1994**, *123*, 11. (b) Liu, J.; Barry, C. E.;III; Besra, G. S.; Nikaido, H. *J. Biol. Chem.* **1996**, *271*, 29545.
14. Misaki, A.; Seto, N.; Azuma, I. *J. Biochem. (Tokyo)* **1974**, *76*, 15.
15. Brennan, P. J. *Rev. Infect Dis.* 11 (Suppl. 2) **1989**, S240.
16. Melancon-Kaplan, J.; Hunter, S. W.; McNeil, M.; Srewart, C.; Modlin, R. L.; Rea, T. H.; Convit, J.; Salgame, P.; Mehra, V.; Bloom, B. R.; Brennan, P. J. *Proc. Natl. Acad. Sci. U. S. A*. **1988**, *85*, 1917.
17. (a) Lee, R. E.; Mikušová, K.; Brennan, P. J.; Besra, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 11829. (b) Deng, L.; Mikušová, K.; Robuck, K.G.; Scherman, M.; Brennan, P. J.; McNeil, M. R. *Antimicrob. Agents Chemother*. **1995**, *39*, 694. (c) Mikušová, K.; Slayden, R. A.; Besra, G. S.; Brennan, P. J. *Antimicrob. Agents Chemother*. **1995**, *39*, 2484.
18. Brennan, P. J.; Besra, G. S. *Biochem. Soc. Trans.* **1997**, *25*, 188.
19. Scherman, M. S.; Kalbe-Bournonville, L.; Bush, D.; Xin, Y.; Deng, L.; McNeil, M. *J. Biol. Chem.* **1996**, *271*, 29652.
20. Lee, R. E.; Brennan, P. J.; Besra, G. S. *Glycobiology* **1997**, *7*, 1121.
21. Woluka, B. A.; McNeil, M. R.; de Hoffmann, E.; Chojnacki, T.; Brennan, P.J. *J. Biol. Chem.* **1994**, *269*, 23328.
22. Lee, R. E.; Mikusova, K.; Brennan, P.J.; Besra, G.S. *J. Am. Chem. Soc.* **1995**, *117*,11829.
23. Yi Xin, Lee, R.E.; Scherman, M.S.; Khoo, K.H.; Besra, G.S.; Brennan, P.J.; McNeil M. *Biochim Biophys Acta* **1997**, *1335*, 231.
24. Scherman, M.S.; Bournonville, L.K.; Bush, D.; Xin, Y.; Deng, L.; McNeil, M. *J. Biol. Chem.* **1996**, *271*, 29652.
25. Truscheit, E.; Frommer, W.; Junge, B.; Muller, L.; Schimdt, D.D.; Wingender, W. *Angew. Chem.,Int. Ed. Engl.* **1981**, *20*, 744.
26. Tvaroska, L.; Bleha, T. *Adv. Carbohydr. Chem. Biochem*. **1989**, *47*, 45.
27. Rouzaud, D.; Sinay, P. *J. Chem. Soc., Chem.Commun*. **1983**, 1353.

28. Neuman, A.; Longchambon, F.; Abbes, O.; Gillier-Pandraud, H.; Perez, S.; Rouzaud, D.; Sinay, P. *Carbohydr. Res.* **1990**, *195*, 187.
29. Goekijan, P. G.; Wu, T. C.; Kang, H. Y.; Kishi, Y. *J. Org. Chem.* **1991**, *56*, 6422.
30. (a) Giese, B.; Witzel, T. *Angew. Chem.,Int. Ed. Engl.* **1986**, *25*, 450. (b) Giese, B.;Hoch, M.; Lamberth, C.; Schimdt, R. R. *Tetrahedron Lett.* **1988**, *29*, 1375. (c) Babirad, S.A.; wang, Y.; Kishi, Y. *J. Org. Chem.* **1987**, *52*, 1370. (d) Preuss, R.; Schmidt, R. R. *J. Carbohydr. Chem.* **1991**, *10*, 887. (e) Bimwala, R. M.; Vogel, P. *Tetrahedron Lett.* **1991**, *32*, 1429. (f) Wang, Y.; Babiard, S. A.; Kishi, Y. *J. Org. Chem.* **1992**, *57*, 468. (g) Bimwala, R. M.; Vogel, P. *J. Org. Chem.* **1992**, *57*, 2076.
31. Haneda, T.; goekijian, P. G.; Kim, S. H.; Kishi, Y. *J. Org. Chem.* **1992**, *57*, 490.
32. Dyer, U. C.; Kishi, Y. *J. Org. Chem.* **1988**, *53*, 3384.
33. (a) carcano, M.; Nictora, F.; Panza, L.; Russo, G. *J. Chem. Soc., Chem.Commun*. **1989**, 642. (b) Lay, L.; Nictora, F.; Panza, L.; Russo, G.; Caneva, E. *J. Org. Chem.* **1992**, *57*, 1304.
34. Godage, H. Y.; Fairbanks, A. J. *Tetrahedron Lett.* **2000**, *41*, 7589.
35. Vidal, T.; Haudrehcy, A.; Langlois, Y. *Tetrahedron Lett.* **1999**, *40*, 5677.
36. Sarabia-García, F.; López-Herrera, F. J.; González, M. S. P. *Tetrahedron* **1995**, *51*, 5491.
37. Babirad, S. A.; Wang, Y.; Kishi, Y. *J. Org. Chem.* **1987**, *52*, 1370.
38. Cha, J. K.; Kim, N.-S. *Chem. Rev.* **1995**, *95*, 1761.
39. Wei, A.; Kishi, Y. *J. Org. Chem.* **1994**, *59*, 88.
40. Khan, A. T.; Sharma, P.; Schmidt, R. R. *J. Carbohydr. Chem.* **1995**, *14*, 1353.
41. Khan, N.; Cheng, X.; Mootoo, D. R. *J. Am. Chem. Soc.* **1999**, *121*, 4918.
42. Schmidt, R. R.; Preuss, R. *Tetrahedron Lett.* **1989**, *30*, 3409.
43. Griffin, F. K.; Paterson, D. E.; Taylor, R. J. K. *Angew. Chem. Int. Engl.* **1999**, *38*, 2939.
44. Meyers, C. Y.; Malte, A. M.; Matthews, W. S. *J. Am. Chem. Soc.* **1969**, *91*, 7510.
45. Aebischer, B.; Bieri, J. H.; Vasella, A. *Helv. Chim. Acta* **1982**, *65*, 2251.
46. Baumberger, F.; Vasella, A. *Helv. Chim. Acta* **1983**, *66*, 2210.
47. Martin, O. R.; Lai, W. *J. Org. Chem.* **1993**, *58*, 176.

48. Binch, H. M.; Griffin, A. M.; Schwidetzky, S.; Ramsay, M. V. J.; Gallagher, T.; Lichtentaler, F. W. *J. Chem. Soc. Chem. Commun.* **1995**, 967.
49. Dondoni, A.; Zuurmond, H. M.; Boscarato, A. *J. Org. Chem.* **1997**, *62*, 8114.
50. Mazéas, D.; Skrydstrup, T.; Beau, J.-M. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 909.
51. Jarreton, O.; Skrydstrup, T.; Beau, J.-M. *J. Chem. Soc. Chem. Commun.* **1996**, 1661.
52. Jung, M. E.; Choe, S. W. T. *Tetrahedron Lett.* **1993**, *34*, 6247.
53. Martin, O. R.; Xie, F.; Kakarla, R.; Benhamza, R. *Synlett* **1993**, 165.
54. (a) Sinaÿ, P. *Pure Appl. Chem.* **1997**, *69*, 459. (b) Sinaÿ, P. *Pure Appl. Chem.* **1998**, *70*, 407. (c) Sinaÿ, P. *Pure Appl. Chem.* **1998**, *70*, 1495.
55. Xin, Y. C.; Mallet, J.-M.; Sinaÿ, P. *J. Chem. Soc. Chem. Commun.* **1993**, 864.
56. Skrydstrup, T.; Mazéas, D.; Elmouchir, M.; Doisneau, G.; Riche, C.; Chiaroni, A.; Beau, J.-M. *Chem. Eur. J.* **1997**, *3*, 1342.
57. Connell, N. D.; Nikaido, H. M. In *Tuberculosi*s: *Patho-genesi*s, *Protection and Contro*l; Bloom, B. R., Ed.; American Chemical Society for Microbiology: Washington, DC, 1994; p. 333.
58. Dondoni, A.; Marra, A.; Mizuno, M.; Giovannini, P. P. *J. Org. Chem.* **2002**, *67*, 4186.
59. Wen, L.; Martin, O. R. *J. Org. Chem.* **1993**, *58*, 176.
60. (a) Glaudemans, C. P. I.; Fletcher, H. G., Jr. *J. Am. Chem. Soc.* **1965**, *87*, 4636; (b) Mikhailopulo, I. A.; Sivets, G. G. *Helv. Chim. Acta* **1999**, *82*, 2052; (c) Yin, H.; Lowary, T. L. *Tetrahedron Lett.* **2001**, *42*, 5829. (d) Cuzzupe, A.N.; Di Florio, R.; Rizzacasa, M.A. *J. Org. Chem.* **2002**, *67*, 4392.
61. Lei, Z.; Min, J. M.; Zhang, L. H. *Tetrahedron*: *Asymmetry*. **2000**, 11, 2899.
62. Zemplen, G.; Kunz, A. *Ber.* **1981**, *114*, 1256.
63. Mancuo, A.J.; Swern, D. *Synthesis* **1981**, 165.
64. Baudin, J.-B.; Julia, S. A. *Tetra hedron. Lett.* **1988**, *29*, 3255.
65. Corey, E. J.; Ptne, S. G. *Tetrahedron. Lett.* **1983**, *24*, 4883.
66. Kornblum, N.; Larson, H. O.; Blackwood, R. K.; Mooberry, D. D.; Oliveto, E. P.; Graham, G. E. *J. Am. Chem. Soc.* **1956**, *78*, 1497.
67. (a) Suami, T.; Sasai, H.; Matsuno, K. *Chem. Lett.* **1983**, 819; (b) Kozaki, S.; Sakananka, O.; Yasuda, T.; Shimizu, T.; Ogawa, S.; Suami, T. *J. Org. Chem.* **1988**, *53*, 281.

# Chapter III

## Synthetic Studies toward Dicerandrols

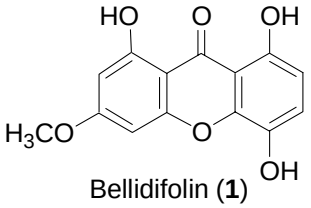
# Introduction

## Introduction

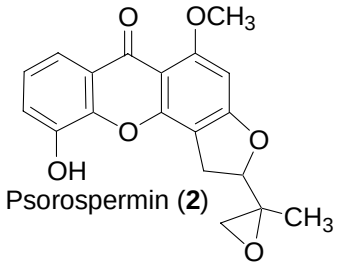
The search for biologically active natural products for the development of new drugs has a long tradition.[1] Most such compounds were isolated from plants, animals, fungi, and microorganisms like bacteria, which exist in great variety on earth. Total synthesis is playing a major role in the drug discovery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

In continuation of our interest in the total synthesis of natural products, we have selected the recently isolated decerandrols as targets.[3] Diceradrols belongs to class of natural products, known with their integral aromatic skeleton *i.e.*, xanthones. Xanthones are a small class of natural products which are isolated as plant, fungal and lichen metabolites.[4] A brief introduction about various natural products belonging to this class in the order of increasing complexity preceded by the total synthetic effort towards secalonic acid A, which is closed related to dicerandrols will be exemplified.

Xanthones are secondary metabolites commonly occurring in a few higher plant families, and in fungi and lichens.[4] Their taxonomic importance in such families and their pharmacological properties has aroused great interest.[5] The broad spectrum activity of xanthones for various biological actions and tuning of activity by glycosidation of aromatic-OH has lead to study xanthones not only from a chemo systematic viewpoint, but also from a pharmacological point of view. Xanthones posses antidepressant action and antitubercular activity, while xanthone glycosides exhibit depressant action.[6] The choleretic, diuretic, antimicrobial, antiviral and cardiotonic action of some xanthones has also been established.[7] The inhibition of type A and type B monoamine oxidases by a number of xanthones has also been observed.[8] And in spite of their restricted occurrence in the plant kingdom, some xanthones are reported to possess antileukaemic, antitumour, antiulcer, antimicrobial, antihepatotoxic and CNS-depressant activities. For example, bellidifolin (**1**), a 1,5,8-trihydroxy-3-methoxy- xanthone was found to be a selective inhibitor of MAO A,[9] where as psorospermin (**2**),[10] a dihydrofuranoxanthone epoxide, exhibits significant activity against leukemia and in colon and mammary tumor models. In general, xanthones and their derivatives have also been shown to be effective as allergy inhibitors and bronchodilators in the treatment of asthma.[11]



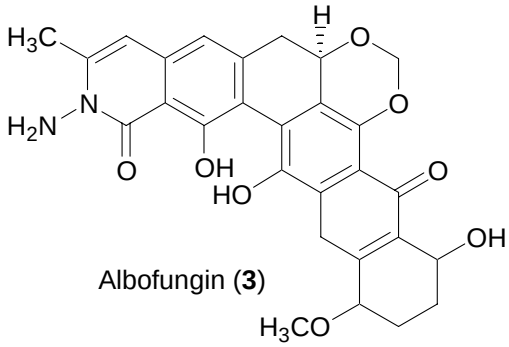

Bellidifolin (**1**)




Psorospermin (**2**)

**Figure 1**

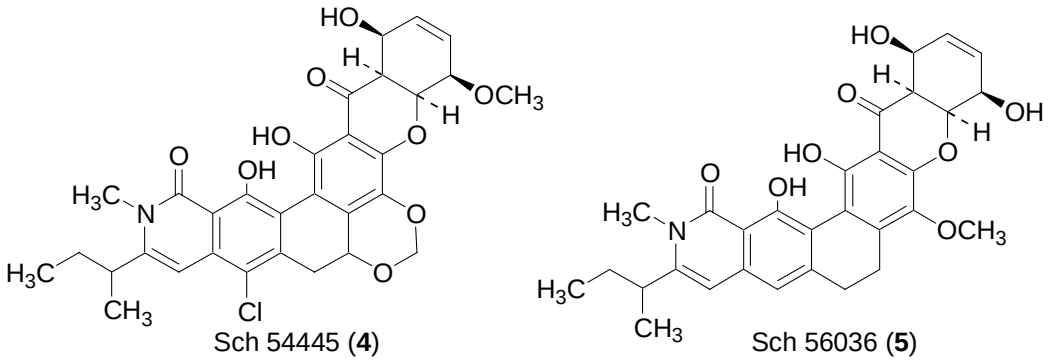
Albofungin (**3**)[12] is a well known natural anti-fungal medicine. Albofungin was isolated about a half century ago, belongs to the class of xanthones, however, contains a novel hexa cyclic aromatic ring system in which a tetrahydroxanthone makes the right hand side of the molecule. Albofungin is a metabolite of *Actinomyces albus var.* fungatus, is highly active against Gram-positive bacteria and yeasts. The following structure has been assigned based on degradation studies and with the help of CD-excitation studies the absolute configuration was confirmed.[13]




Albofungin (**3**)

**Figure 2**

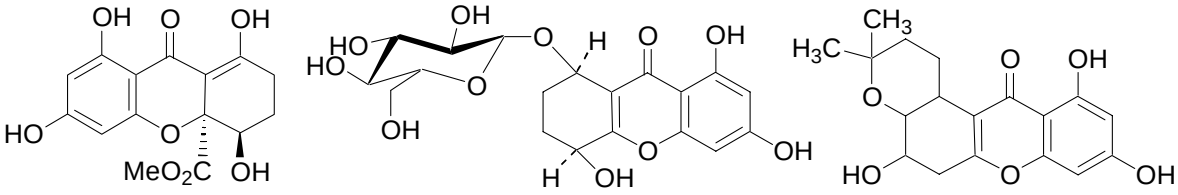
In the course of searching for novel antifungal antibiotics, recently researchers at *Schering-Plough Research Institute* isolated a variety of novel polycyclic xanthones namely, Sch 54445[14] and Sch 56036[15] from the culture broth of an *Actinoplanes* sp. (SCC 2314, ATCC 55600), which were collected at Tarlac on the Philippine Island. Compound **5**, **6** related to the albofungin family of compounds, displays potent broad-spectrum antifungal activities against a range of fungal pathogens, such as yeasts, dermatophytes and *Aspergillus.*




Sch 54445 (**4**) Sch 56036 (**5**)

**Figure 3**

The xanthones, which have more than 600 members, over 100 of which display a tetrahydroxanthone moiety, are among these privileged structures. Diversonolic acids and their esters,[16] toxylxanthones[17] are the basic monomeric units belonging to the class of these tetrahydroxanthones.




α-diversonilic acid methyl ester (**6**) Tetrahydroxanthone glucloside (**7**) Toxylxanthone B (**8**)

**Figure 4**

Secalonic acids, ergo chromes are members of this group of natural products, however are symmetrical dimers. Secalonic acid A, the oldest one in this series which was isolated in 1906.[18] The secalonic acids exhibit toxic, antibacterial, and mutagenic properties, along with fetotoxic and teratogenic actions. Some derivatives of the secalonic acids were tested as cytostatics. Secalonic acid D inhibits HIV protease and several protein kinases,[19] while secalonic acid F[20] is phytotoxic. Coming to the total synthesis of secalonic acids, despite their proven diverse biological activity, so far only successful total synthesis of a member of this group is known, that of 10- methyl-10-demethoxycarbonylhemisecalonic acid A.[21] And a few additional reports concerning the synthesis of basic tetrahydroxanthone moiety.[22]

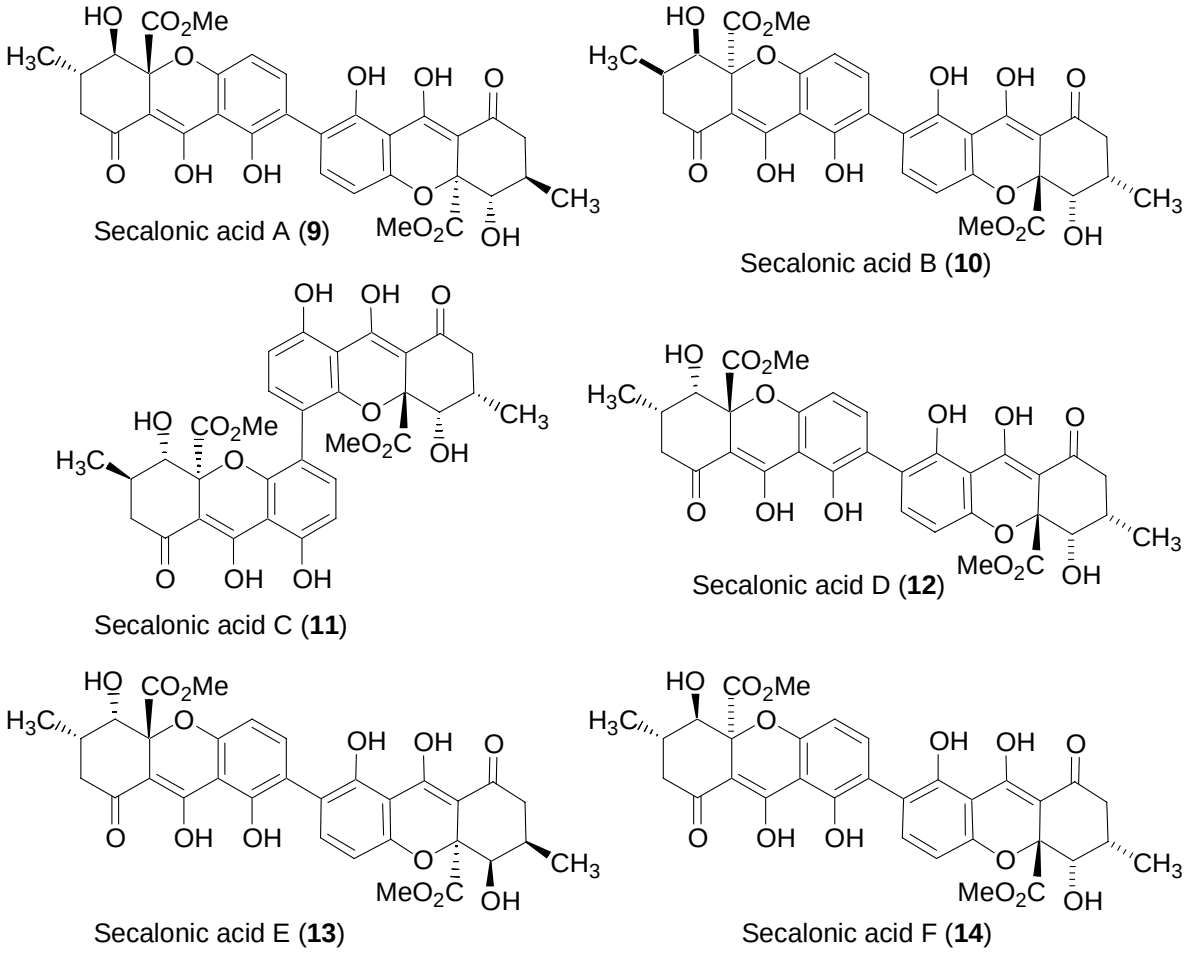



**Figure 5**

Sturdikov *et al* isolated two unsymmetrical tetrahydroxanthone dimmers neosartorin (**15**), Eumitrin A1 (**16**) from *Neosartorya fischeri* which are phylogenetically related to *Asperigillus fumigatus* having antifungal activity.[23] Very recently, two new unsymmetrical xanthone dimers, rugulotrosin A (**17**) and B (**18**) having promising antibacterial activity were obtained from cultures of a *Penicillium* sp. isolated from soil samples acquired near Sussex Inlet, New South Wales, Australia.[24] Although the basic skeleton of **15** – **18** was similar to secalonic acids, the difference is the positioning of methyl group. In secalonic acids it was present on the cyclohexene ring systems where as in the case of **15** – **18**, it is present on one of the aromatic ring system.

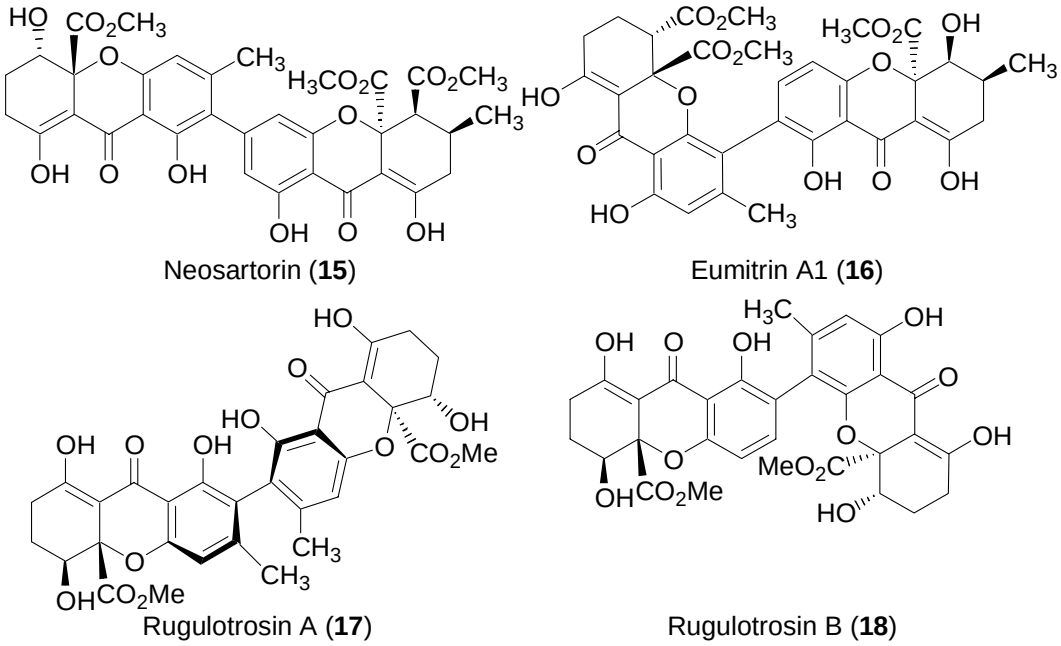



**Figure 6**

Endophytic fungi, fungi that grow in the intercellular spaces of higher plants, are recognized as one of the most chemically promising groups of fungi in terms of diversity and pharmaceutical potential. A very recent analysis of the magnitude of fungal species suggests that fungal endophytes alone are a hyper diverse group of fungi with an estimated range of 30-150 species per host. Furthermore, it has been noted that a subset of the endophytic fungi may be host-species specific. Therefore, the entire plant community likely harbors a major portion of fungal diversity, and the extinction of even one plant species could result in the loss of several host-specific fungal endophytes.

One fungus, MMW29, isolated from the stem of a *D.frutescens* plant, exhibited activity against *Staphylococcus aureus* and *Bacillus subtilis* when grown in shake culture in potato dextrose broth (PDB). *Dicerandra frutescens* (Labiatae), a rare mint plant on the Federal Endangered Species List, is found at about a dozen sites within an area of only a few hundred acres in central Florida. The fungus was identified as *Phomopsis longicolla* by isolation of DNA from the fungal mycelium, PCR amplification of the internal transcribed spacer regions ITS1 and ITS2, and comparison of the resulting ITS1 and ITS2 sequence with deposited sequences using a BLAST search. Using bioassay-guided fractionation, three closely related yellow antibiotics trivially named dicerandrols were isolated.[3]

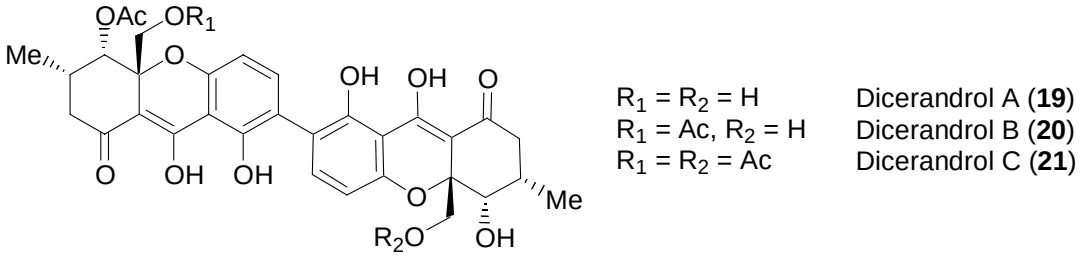
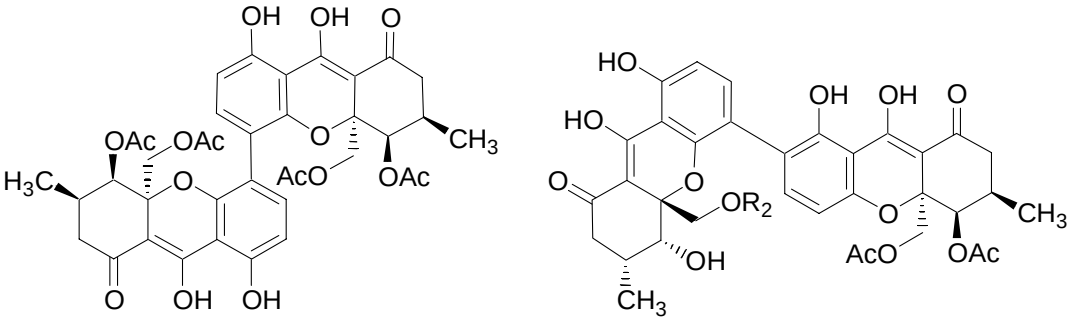



**Figure 7**

Dicerandrols A, B, and C (**19**, **20**, and **21**) are a symmetrical dimers, which structurally related to the ergochromes and secalonic acids in that they contain the same tricyclic C15 system with similar arrangement of substituents. Dicerandrols A, B, and C (**19** - **21**) exhibit antibacterial activity against both *Staphylococcus aureus* and *Bacillus subtilis,* out of these particularly *Bacillus subtilis* had developed resistance against vancomycin type antibiotics, thus making the need to look for the new antibiotics which can actively arrest the bacteria, further these compounds also possess modest activity in two human cancer cell lines, A549 and HCT-116.

In the subsequent paper, professor Isaka and co-workers reported the isolation of two similar xanthone dimers namely, Phomoxanthones A (**22**) and B (**23**) which are structurally related to dicerandrols (except the position of biaryl bond) from the endophytic fungus *Phomopsis* sp. BCC 1323.[25] Structures and the relative configuration of **22** and **23** were elucidated by exhaustive spectroscopic methods. These compounds exhibited significant activity against *Plasmodium falciparum* (K1, multi drug-resistant strain) and against *Mycobacterium tuberculosis* (H37Ra strain), although weaker than standard drugs. However, these compounds are also cytotoxic to two cancer cell lines (KB, BC-1) and to Vero cells. Phomoxanthones also belong to the family of dimeric tetrahydroxanthones and the key monomeric unit has a similar skeleton and substitution pattern present in secalonic acids, albeit the ester functionality has been reduced to the corresponding alcohol.

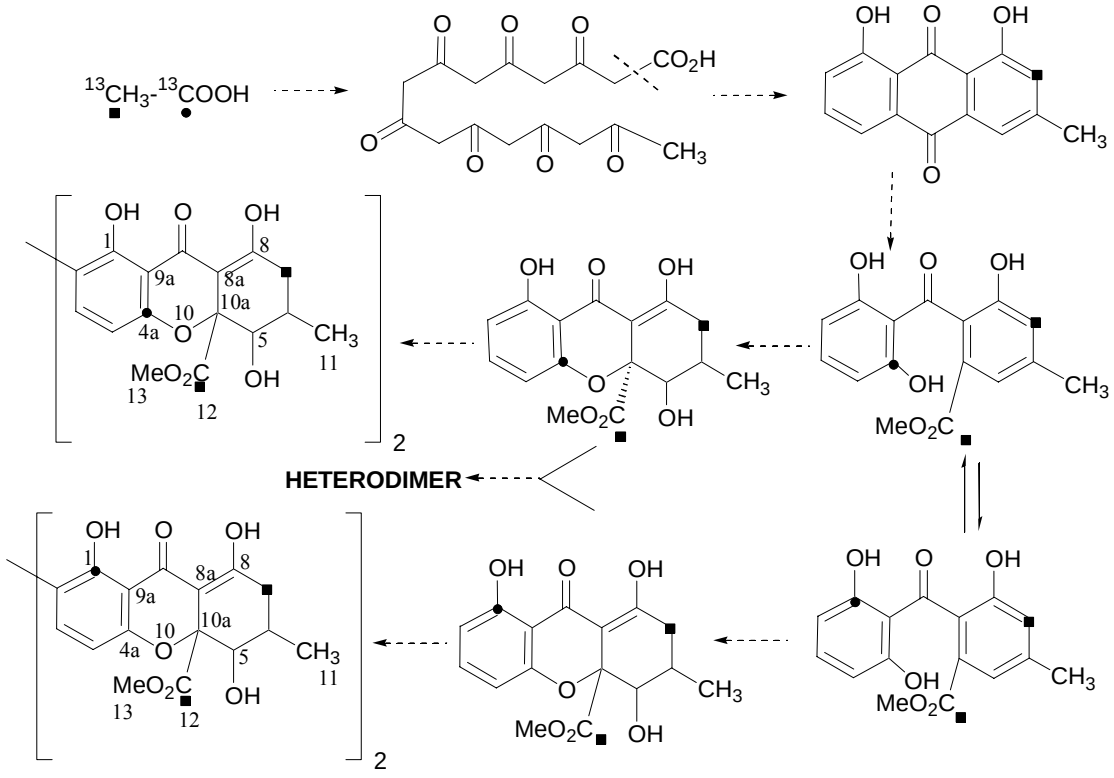


Phomaxanthone A (**22**) Phomaxanthone B (**23**)

**Figure 8**

**Biosynthesis of Tetrahydroxanthones:**

After an exhaustive labeling study, Vining *et al* have successfully elucidated the biosynthetic path of Secalonic acid A. The biosynthetic path way of secalonic acid A by administering the sodium acetate (90% $^{13}C$- enriched) to *Pyrenochaeta* has been depicted in Scheme 1.[26] One of the final steps in the formation of the secalonic acids is methylation of the carboxylic acid to give the C-10a carbomethoxy functionality.

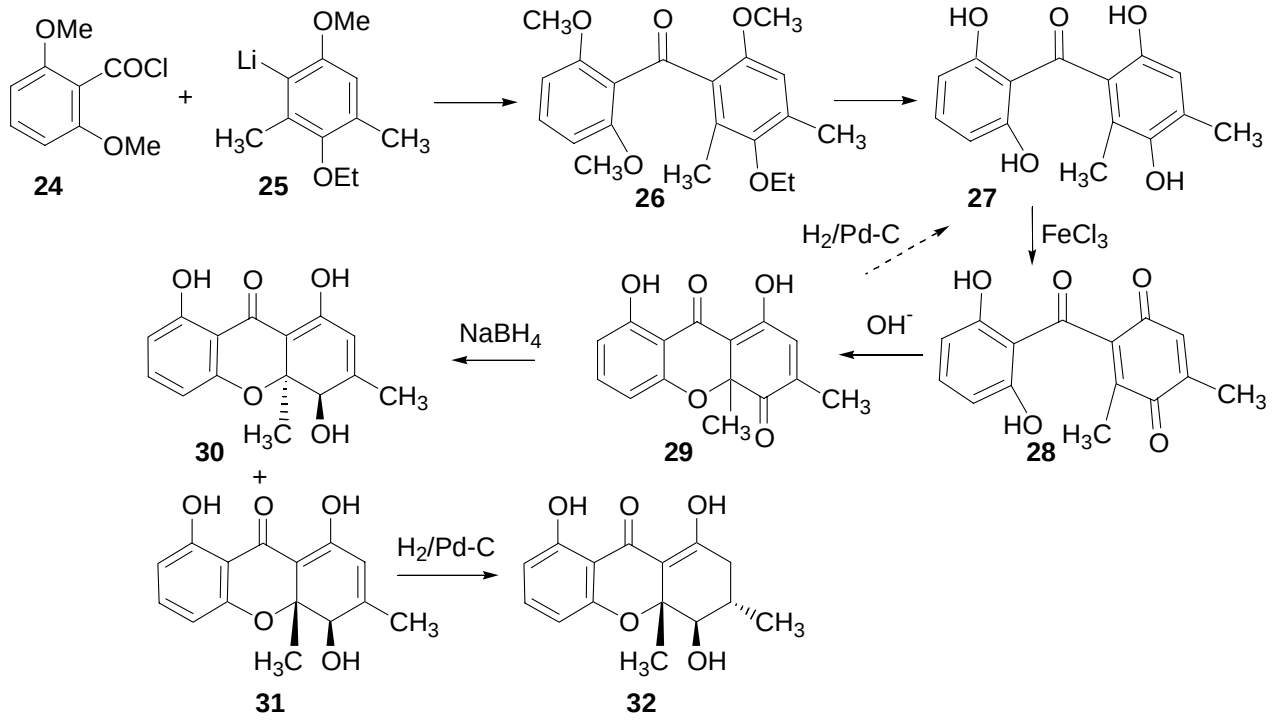



**Scheme 1.** *Biosynthesis of Secalonic Acid A*

The dicerandrols (**19** – **21**) are the first reported compounds with this tricyclic C15 skeleton with a reduced C-12 functionality. As Vining has indicated it, the final step in the biosynthesis of Secalonic acids is the methylation of a carboxylic acid. It has been presumed by the Clardy and co-workers that before the esterification, the reduction of the carboxylic acid takes place to provide hydroxymethyl functionality.

**Franck's approach for the Synthesis of monomer of the Secalonic Acid A:**

As it has been indicated earlier, only one synthesis has been reported so far dealing with the tetrahydroxanthone monomer of Secalonic acid A. On very few occasions the construction of the tetrahydroxanthone skeleton has been reported using some model substrates. So far none of the dimer of a secalonic acids synthesis has been reported. Franck and Zeidler reported the synthesis of the monomer of the secalonic acid A. The executed synthesis utilizes an intramolecular nucleophilic ring closure of a suitably fictionalized benzoquinone.




**Scheme 2.** *Franck's Approach for the Synthesis of Monomeric Unit of Secalonic Acid A*

As shown in Scheme 2, the synthesis of the key benzoquinone derivative **28** started with ortho lithiation and benzoylation to prepare the benzophenone **26**. Deprotection of the phenolic methyl/ethyl ethers followed by $FeCl_3$ mediated oxidation gave the key benzoquinone **28**. The benzopyranone ring was constructed by using key intramolecular nucleophilic addition to the benzoquinone. Initial attempts to hydrogenate **28** were resulted with the isolation of **27**. This problem has been over come by a two stage reduction protocol, first reduction of the non-enolised ketone with sodium borohydride followed by hydrogenation.

Because of the scarcity and extinction of the natural sources gives an alarm for the synthesis of active compounds chemically. The broad spectrum activity taken together with the fact that only a few efforts towards the synthesis of tetrahydroxanthones are reported, we devised a project dealing with the synthesis of these tetrahydroxanthones. Our basic strategy is funded upon the construction of the C ring (a cyclohexenone ring with the required functionality) and then execution of either acylation or a Baylis-Hilmann reaction for the coupling of the A (aromatic ring) followed by an intramolecular dihydropyranone ring formation. The lack of information about the absolute stereochemistry of either dicerandrols or phomoxanthones attracted out attention to synthesize the key cyclohexenone intermediate with known absolute stereochemistry. Herein we report the synthesis of the key cyclohexenone intermediate having the required relative stereochemistry and also with known absolute stereochemistry by using chiral pool approach.

# Present Work

Endophytic fungi, fungi that grow in the intercellular spaces of higher plants, are recognized as one of the most chemically promising groups of fungi in terms of diversity and pharmaceutical potential. A very recent analysis of the magnitude of fungal species suggests that fungal endophytes alone are a hyper diverse group of fungi with an estimated range of 30-150 species per host.[27] Further more, it has been noted that a subset of the endophytic fungi may be host-species specific. Therefore, the entire plant community likely harbors a major portion of fungal diversity, and the extinction of even one plant species could result in the loss of several host-specific fungal endophytes.

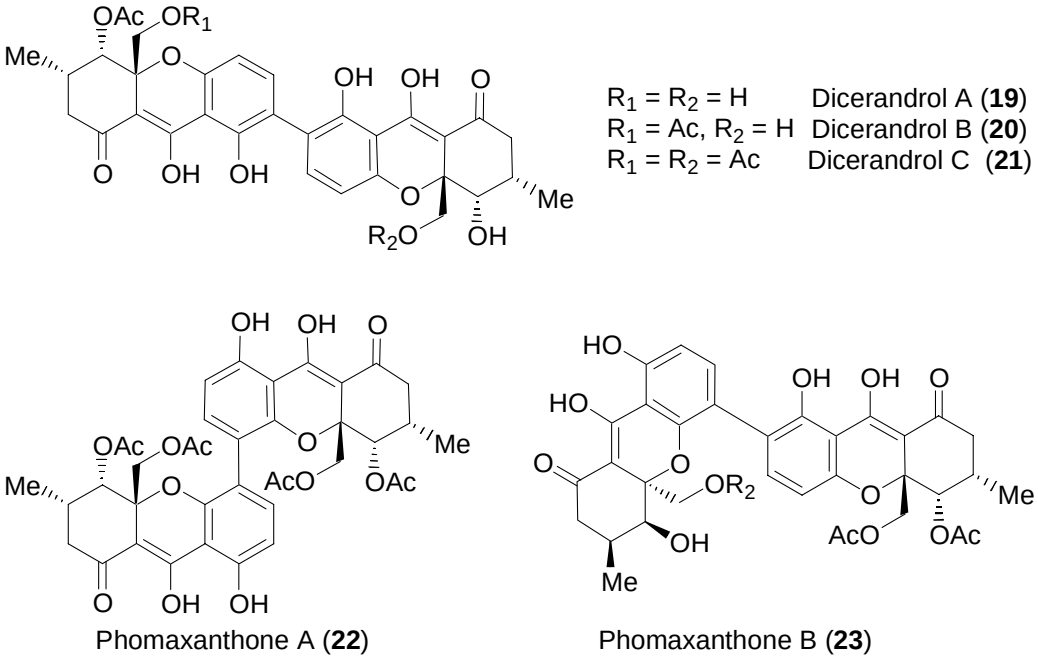



**Figure 9.** *Structures of the xanthone dimers isolated from different fungus*

*Dicerandra frutescens* (Labiatae), a rare mint plant on the Federal Endangered Species List, is found at about a dozen sites within an area of only a few hundred acres in central Florida, USA. One fungus, MMW29, isolated from the stem of a *D. frutescens* plant, exhibited activity against *Staphylococcus aureus* and *Bacillus subtilis*.[3] Later which has identified as *Phomopsis longicolla*. Using bioassay-guided fractionation, Clardy and co-workers isolated three closely related yellow antibiotics trivially named dicerandrols and their

relative stereochemistry has been assigned as given in Figure 1, based on extensive NMR studies.[3] During the same period, in an independent endeavour, Isaka *et. al.* isolated two novel xanthone dimers phomoxanthones A and B from the fungus *Phomopsis* sp. BCC 1323,[25] a teak endophyte collected from northern Thailand. Phomoxanthones posse's substantial antimalarial activity. The structural elucidation of phomoxanthones revealed a similar substitution with same relative orientation on their xanthone monomer, however they vary only at the position of biarylbond.

After a careful structural analysis, we have identified **33** as a common monomer, which can be transformed to dicernadrol/ phomoxanthones by oxidative dimerisation.[28] An intended retrosynthetic analysis for the synthesis of these biaryl xanthones by taking Diceradrol A as an example has been given in Figure 10.

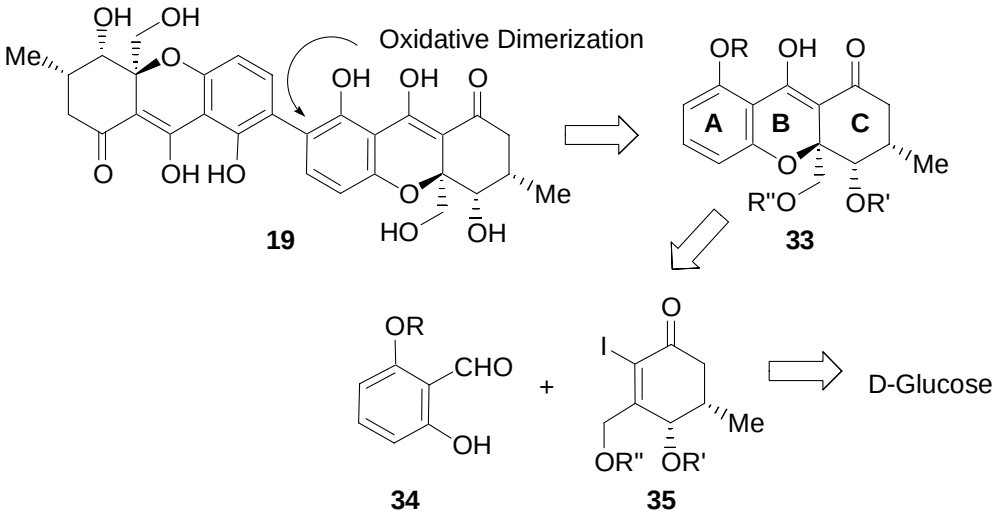



**Figure 10.** *Retrosynthetic strategy for the synthesis of Dicerandrol 1.*

One of the important aspect in the synthesis of xanthone derivative **33** will be construction of the central pyranone ring. Keeping a intramolecular oxa-Micheal addition reaction as the key transformation in mind (Figure 11), the molecule was further fragmented in to a key iodo cyclohexenone derivative **35** corresponding to the ring **C.** The objective of present investigation is to provide a stereo selective route for the synthesis **C**-ring of the Dicerandrol of having the substituents with established relative and absolute stereochemistry. A chiral pool approach starting from D-glucose has been intended in this context.

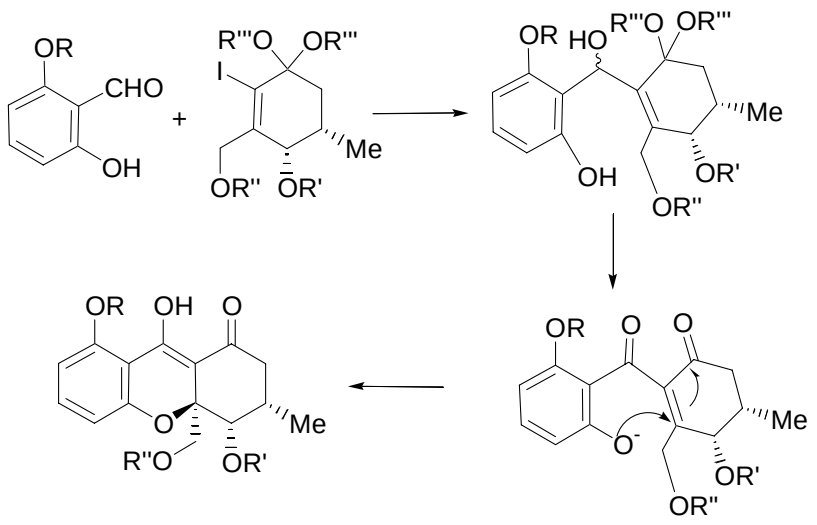



**Figure 11.** *Intramolecular Oxa-Micheal Addition Protocol*

After analysing the relative stereochemistry of the hydroxyl and methyl substituents of α-iodo cyclohexenone **35**, an iterative regression analysis led to identify D-glucose derived intermediated **37** as one of the key intermediate in the synthesis of α-iodo cyclohexenone **35**, using intramolecular aldol as the key reaction.

After designing a potential retrosynthetic strategy for the synthesis of xanthone dimers, we have started our synthetic endeavor by targeting the key α-iodo cyclohexenone **35** (Figure 12).

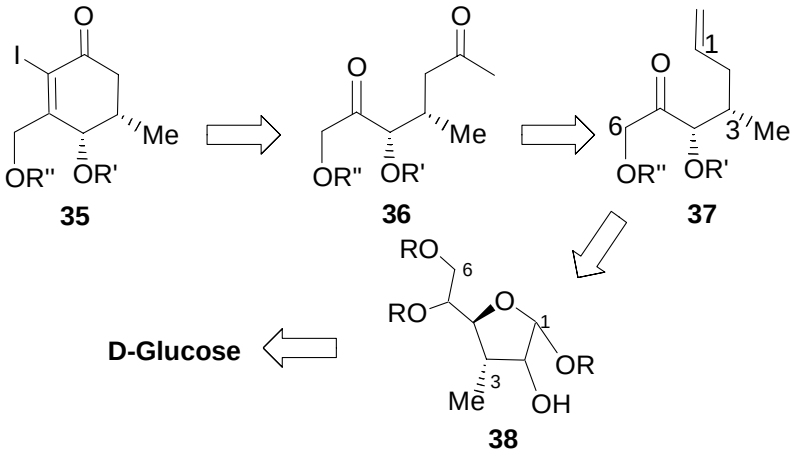
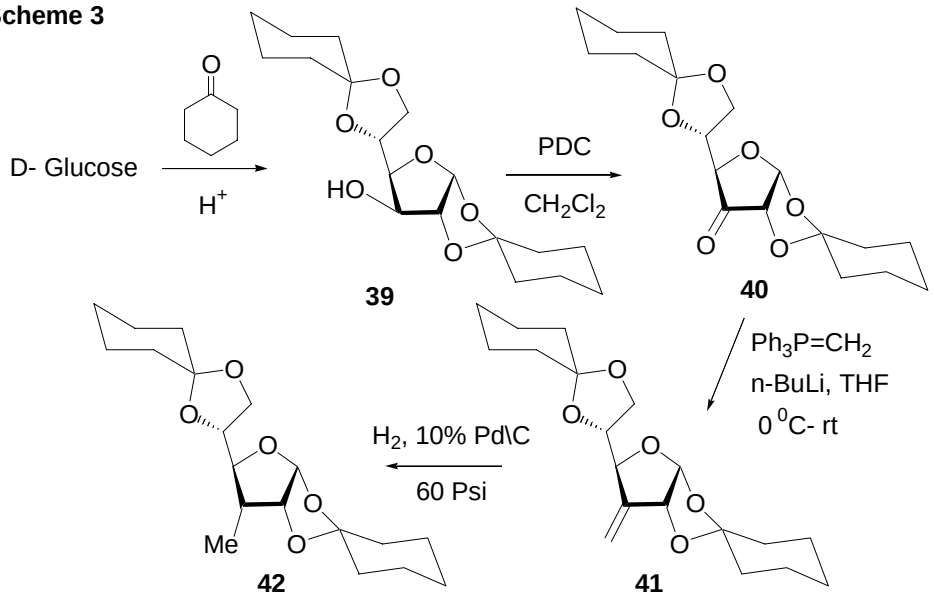



**Figure 12**: *Retro synthetic analysis for α- iodo cyclohexenone* **35**

The synthetic endeavor began with 1,2;5,6-di-*O*-cyclohexylidene-α-D-ribohexofuranos-3-ulose, which can be prepared from D-glucose in two steps by employing literature procedure. Thus, D-glucose was converted in to 1,2;5,6-di-*O*-cyclohexylidene-α -D-glucofuranose[29] (**39**) by the combined action of cyclohexanone and catalytic $H_2SO_4$. Subsequent oxidation[29] at C-3 with PDC in the presence of 4 Å molecular sieve powdered and cat. $Ac_2O$ in anhydrous $CH_2Cl_2$ at room temperature afforded the corresponding 3-ulose derivative **40**. One carbon homologation of the ulose **40** using methylenetriphenylphosphorane in THF at 0 °C, gave the *exo*-methylene derivative **41**[30] in moderate yield. The compound **41** was characterized by its $^1$H NMR and $^{13}$C NMR spectral analysis. In the $^1$H spectrum of **41**, the olefinic protons resonated as singlets at $\delta$ 5.43 and 5.53, anomeric proton (H-1) resonated as a doublet at $\delta$ 5.76 ($J$ = 4.0 Hz), and H-2 appeared as a doublet of doublet at 4.84 ppm ($J$ = 4.0, 1.2 Hz). The proton H-5 was located between 4.55-4.57 ppm as a multiplet. The resonaces due to H-6, H'-6 were observed as a doublet of doublet at $\delta$ 3.90 and 4.04 ($J$ = 8.1, 6.0 Hz). The resonances at 104.2 (d), 113.2 (t), 147 (s) ppm corresponding to anomeric and olefinic carbons respectively in the $^{13}$C NMR spectrum of **41**.

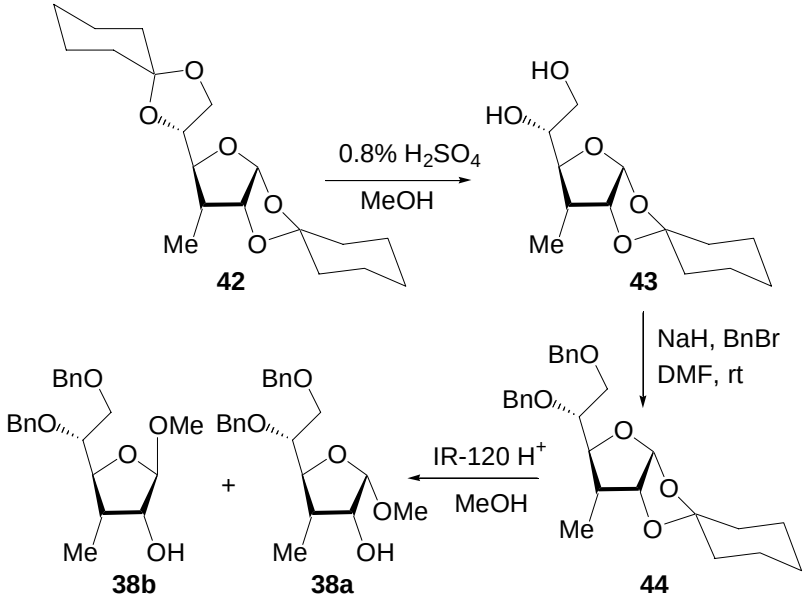
**Scheme 3**



As expected [30] the hydrogenation of *exo*-methylene derivative **41** over Pd/C at 60 psi and at room temperature was found to be diastereospecific resulting with a single product **42** in quantitative yield. In the $^{1}$H NMR spectrum of **42**, H-2 appeared as a triplet at 4.50 ppm ($J$ = 4.2 Hz) clearly indicated a *cis*-relation between H-1 – H-2 and between H-2 – H-3 thus confirming the assigned relative stereochemistry. The newly formed methyl group was resonated as a doublet at $\delta$ 0.87 ($J$ = 6.8 Hz) and H-3 resonated as a doublet of a double doublet ($J$ = 4.8, 6.8, 9.8 Hz). Further, in the $^{13}$C spectrum, methyl at C-3 was located at 10.2 ppm (Scheme 3).

The selective deprotection of the 5,6-*O*-cyclohexylidene group of **42** to afford the diol **43** was accomplished with 0.8% $H_2SO_4$ in MeOH at ambient temperature for 24 h. The $^{1}$H NMR and $^{13}$C NMR spectra were in conformity with the assigned structure of **43**. The diol **43** was protected as its di-benzyl ether derivative **44** by treating with NaH, BnBr in anhydrous DMF at 0 ºC in 97% yield. In the $^{1}$H spectrum of **44**, the characteristic four benzylic doublets appeared at $\delta$ 4.79, 4.57, 4.55, 4.52 ($J$ = 11.6 Hz), H-2 and H-1 resonated as a broad triplet at 4.50 ($J$ = 4.3 Hz) and a doublet ($J$ = 3.7 Hz) at $\delta$ 5.72 respectively. Further confirmation for **44** came from its $^{13}$C NMR spectrum.

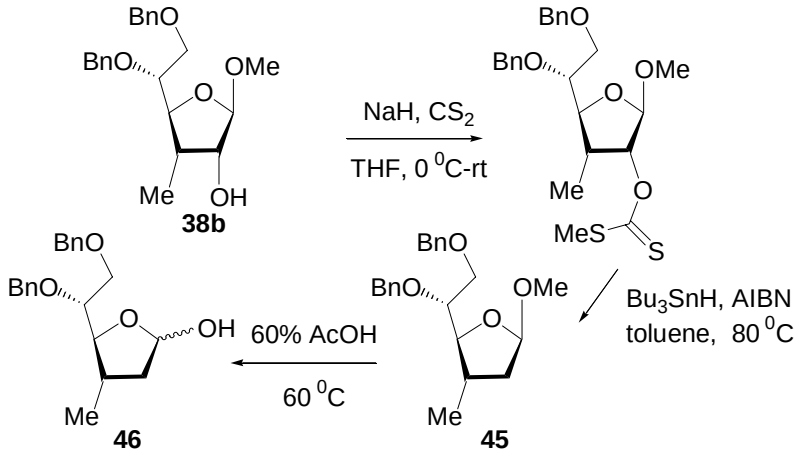
**Scheme 4**



Having compound **44** in hand, our next task was to deoxygenate OH group at C-2 by using Barton-McCombie deoxygenation protocol.[31] Thus, compound **44** was treated with IR-120 ($H^+$) resin in MeOH at refluxing temperature to afford α,β-anomeric methylglycosides **38a** and **38b**. The major β-isomer **38b** could be separated in pure form by silica gel chromatography and used for further transformations. In the $^1$H NMR spectrum of **38b**, anomeric H-1 resonated as a singlet at 4.73 ppm. H-2 resonated as a doublet at $\delta$ 3.95 ($J$ = 4.5 Hz) while the rest of the protons appeared at the expected chemical shifts (Scheme 4).

For the execution of Barton-McCombi reaction,[31] the compound **38b** was first converted into the corresponding xanthate derivative, by treating with NaH, $CS_2$, MeI at 0 ºC followed by treatment with n-$Bu_3SnH$ and cat. AIBN in refluxing toluene to obtain the 2-deoxy derivative **45** in 82% yield. The structure of **45** was well supported by the $^1$H NMR, $^{13}$C NMR spectra and elemental analysis. In the $^1$H NMR spectrum of **45**, a multiplet for C-2 methylene was located in the region of 1.97-2.34 ppm. The peak at $\delta$ 35.0 in $^{13}$C spectrum further was assigned to C-2. The demethylation of **45** was achieved by using 60% AcOH at 60 ºC to obtain **46** as a mixture of α,β- anomers (Scheme 5).

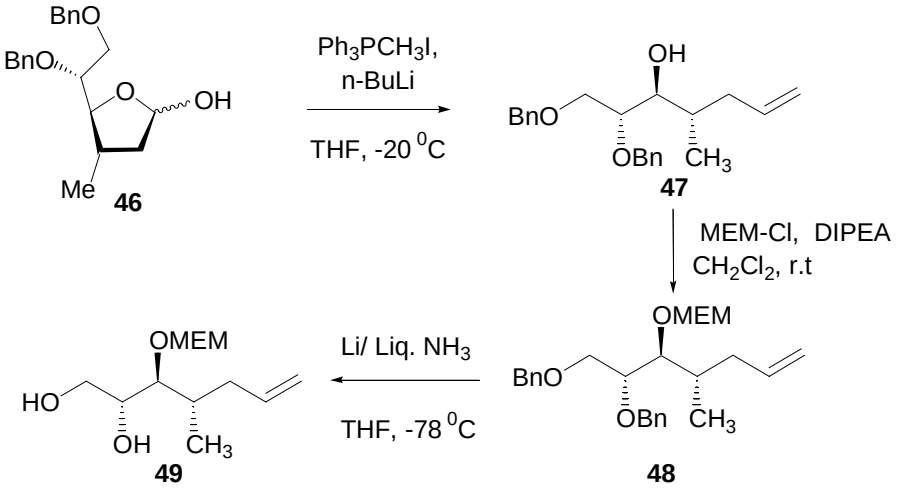
**Scheme 5**




One carbon Wittig homologation of **46** by treating with methyltriphenylphosphorane in THF gave **47** in 84% yield. In the $^1$H NMR spectrum of **47**, the internal olefinic protons resonated at 5.75 ppm (dddd, $J$ = 16.2, 10.4, 8.0, 6.1 Hz) and terminal olefinic protons appeared as a multiplet spanning between 4.98-5.01 ppm. In the $^{13}$C NMR spectrum of **47**

peaks for olefinic carbons were observed at $\delta$ 115.7 (t), 137.0 (d) and were in support of the assigned structure of **47**. The free hydroxy of **47** was protected as its MEM ether by using MEM-Cl, DIPEA in anhydrous $CH_2Cl_2$ at room temperature to give **48** in 82% yield. The $^1H$ NMR and $^{13}C$ NMR spectra were in accordance with the assigned structure of **48**. Debenzylation[32] of **48** was carried out by using Lithium in Liq. $NH_3$ at –78 ºC to get **49** in good yield. The structure was confirmed by its $^1H$ NMR and $^{13}C$ NMR spectral analysis. In the $^1H$ NMR spectrum of **49**, resonances for MEM as well as olefinic carbons were seen at the expected positions (Scheme 6).

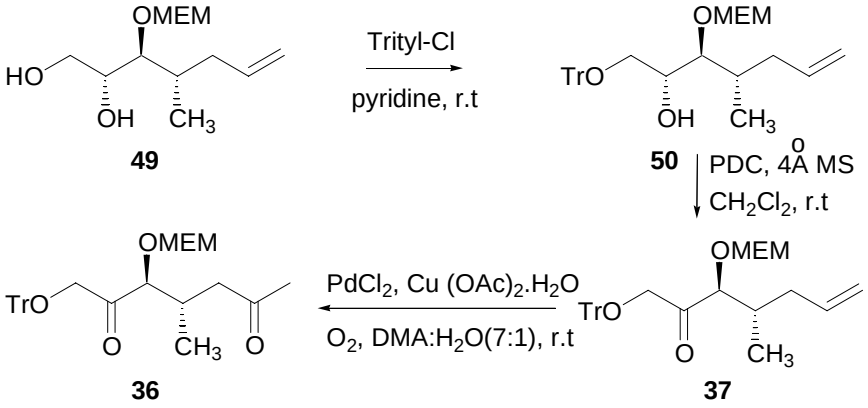
**Scheme 6**




Treatment of **49** with trityl chloride in pyridine at room temperature resulted in selective primary hydroxyl group protection[33] and gave the trityl ether **50** in 87% yield. The oxidation at C-2 of **50** using PDC in presence of 4Å molecular sieves powder in anhydrous $CH_2Cl_2$ furnished the ketone **37**. The structure of **37** was readily confirmed by its $^1H$ NMR and $^{13}C$ NMR and IR spectra. The $^1H$ NMR spectrum of **37** clearly indicated a down field shift and diminished multiplicity of methylene protons C-5 and C-7. The protons H-7 and H´-7 resonated together as a broad singlet at 3.89 ppm while H-5 appeared as a doublet at 4.09 ppm ($J$ = 5.1 Hz). In the $^{13}C$ NMR spectrum, the carbonyl carbon was located at $\delta$ 206.9.these spectral properties appeared to substantiate the assigned structure of **37**. Compound **37** was subjected to modified Wacker oxidation protocol[34] to introduce carbonyl group. Thus, to introduce carbonyl group **37** was treated with Cu $(OAc)_2$. $H_2O$ (0.2 eq), 10 mol% of $PdCl_2$ in

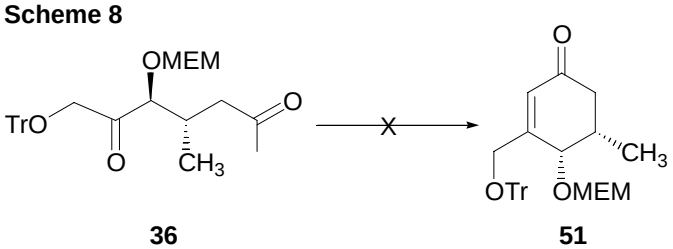
a mixture of DMA: $H_2O$ (7:1) under oxygen atmosphere at ambient temperature for 16 h to afford **36** in 76% yield. In the $^1H$ NMR spectrum of **36** the distinct absence of olefinic protons was noticed. A sharp singlet at 2.09 ppm corresponding to the methyl group adjacent to the carbonyl group confirmed the structure of **36**. Further, the presence of two carbonyl signals at 206.8 and 206.9 ppm in the $^{13}C$ NMR spectrum of **36** substantiated the assigned structure of **36** (Scheme 7).

**Scheme 7**




Our next objective was to effect the key intra-molecular aldol reaction[35] of **36**, which should construct derivative **51**. Attempted intra-molecular aldol reaction of compound **36** under thermodynamic[35] (NaOH, NaOMe) as well as kinetic controlled[35] (BuLi, LDA, LiHMDS) conditions were proved to be futile and led to complex mixture of products. The failure was partly attributed to the presence of many reactive sites present in the substrate **36** (Scheme 8).

**Scheme 8**




The intended intra-molecular aldol reaction unsuccessful, we modified our retrosynthetic strategy for the cyclohexenone **51** (Figure 13) based on the RCM reaction of the diene precursor.

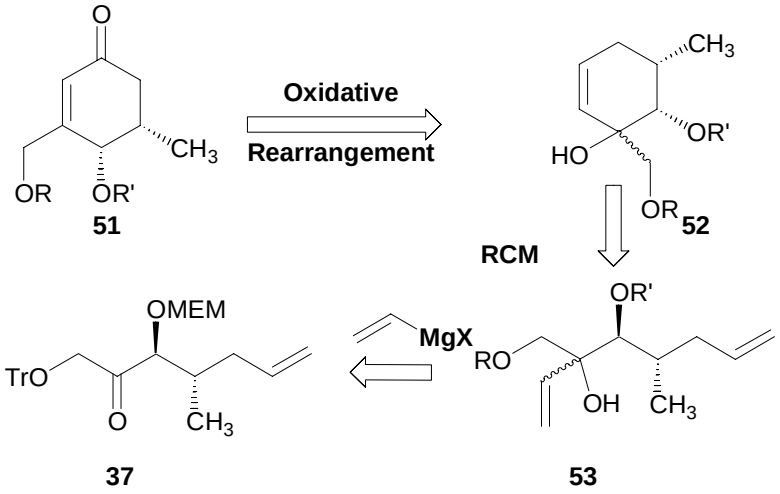
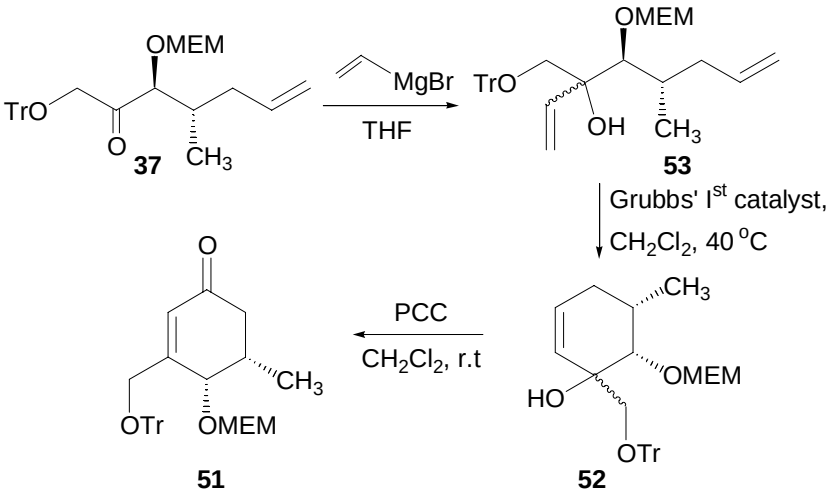



**Figure 13.** *RCM Based Approach for the Key Cyclohexenone* **51**

Accordingly, the previously synthesized ketone **37** was treated with vinylmagnesium bromide in THF at -40 ºC to provide the diene **53** as an inseparable mixture of diastereomers (85:15). Since the newly formed center would be destroyed at a later stage of synthetic sequence, we have proceeded further. The structural integrity of compound **53** was established by $^{1}$H NMR and $^{13}$C NMR spectra. In the $^{1}$H NMR spectrum of **53**, signals for vinylic group appeared at expected chemical shifts.

Gratifyingly, the ring closing metathesis (RCM) reaction[36] of **53** using Grubbs' first generation catalyst in anhydrous $CH_2Cl_2$ was found to be facile and afforded the cyclohexene derivative **52** in 82% yield. The $^{1}$H NMR spectrum of **52** showed the resonances due to the ring olefinic protons at $\delta$ 5.48 (dd, $J$ = 10.2, 1.3 Hz) and at $\delta$ 5.92 (dddd, $J$ = 9.9, 6.9, 4.5, 2.3 Hz). Finally, the oxidative rearrangement [37] of the cyclohexenol precursor **52** by using PCC in anhydrous $CH_2Cl_2$ afforded **51** in good yield. In the $^{1}$H NMR spectrum of **51**, olefinic proton appeared as a singlet at $\delta$ 6.48. In the $^{13}$C NMR spectrum the resonances for olefinic carbons and carbonyl carbon appeared at 143.6, 159.2, 198.5 respectively (Scheme 9).

**Scheme 9**




## Ring Closing Metathesis: A Brief Review

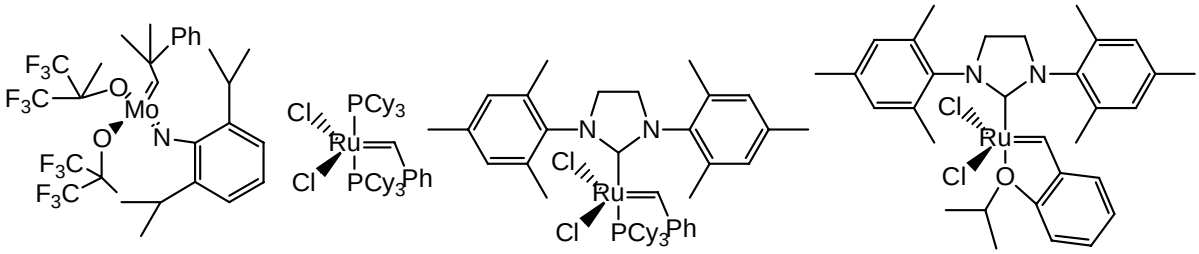
Olefin metathesis is a unique carbon skeleton redistribution in which unsaturated C–C bonds are rearranged in the presence of metal carbene complexes.[36] This can be utilized in three closely related types of reactions such as ring-opening metathesis polymerization (ROMP), ring-closing metathesis (RCM) and acyclic cross metathesis (CM). Ring closing metathesis (RCM), 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 sized ring systems from acyclic diene precursors.[38] The reasons being:

1) Well designed, stable and highly active catalysts.
2) Very high turnover number was observed in the catalytic process.
3) Its efficacy in medium to macro-ring cyclization.
4) Its superiority over other cyclization methods like macrocyclization, Diels-Alder etc., because of favorable 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.

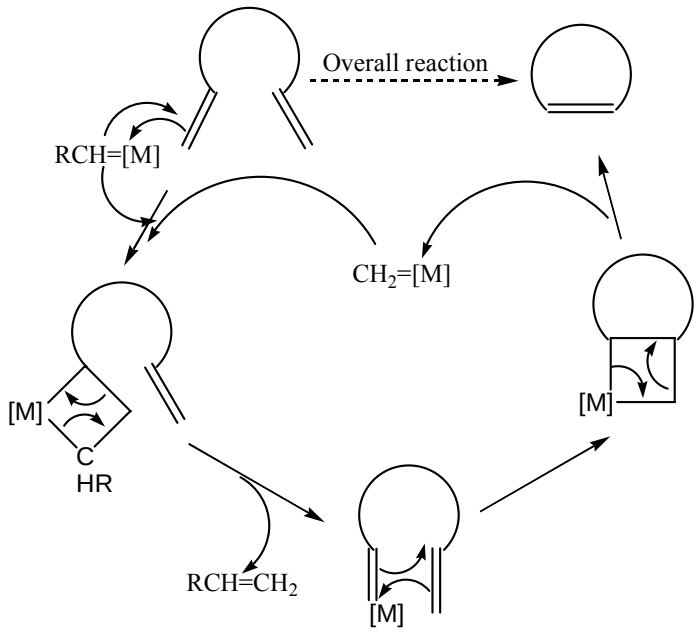
Although a number of titanium and tungsten catalysts have been developed for metathesis and related reactions, the Schrock's catalyst (**A**), Grubbs' 1st and 2nd generation catalysts (**B** and **C**), and Hoveyda-Grubbs catalyst (**D**) have greatly attracted the attention of synthetic chemists because of their high reactivity and commercial availability. This reaction has changed the strategy of synthetic chemists and it is very common to find RCM as key transformation in the recent total syntheses of natural products, esp., for ring construction.



**A** **B** **C** **D**

The postulated mechanism involves an iterative process of [2+2] cycloaddition and

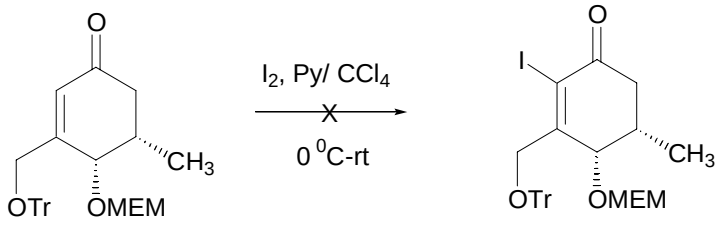
**Scheme 10: Ring closing metathesis Mechanism**



cycloreversion between the olefins, metal alkylidene and metallocyclobutane species (Scheme 12).[39] The initial retro-type intermolecular [2+2] cycloaddition between the catalyst and one of the olefins of diene leads to the incorporation of the metal alkylidene in the substrate. The second cycloaddition takes place in a facile intramolecular fashion and ring opening of resulting metallocyclobutane leads to the cycloalkene and regeneration of the metal carbene, which takes up another diene molecule and acts in same fashion. In the first turn of the cycle, the volatile nature of the alkene by-product (the gaseous ethene in most cases) tends the reaction to proceed forward thermodynamically (Scheme 10).

The next objective of our synthetic endeavor needed introduction of iodo group α to the carbonyl carbon. One of the simple and generally followed method[40] for the iodination of cyclohexenones is by treating with elemental iodine in an appropriate solvent and the presence of a amine as base. Accordingly, the iodination of cyclohexenone **32** was attempted in a mixture of pyridine and $CCl_4$ at room temperature using elemental iodine. To our dismay, even after a prolonged period or the use of excess $I_2$ didn't resulted the iodo derivative **14**, this may be probably due to the steric hindrance created by the bulky trityl group (Scheme 11).

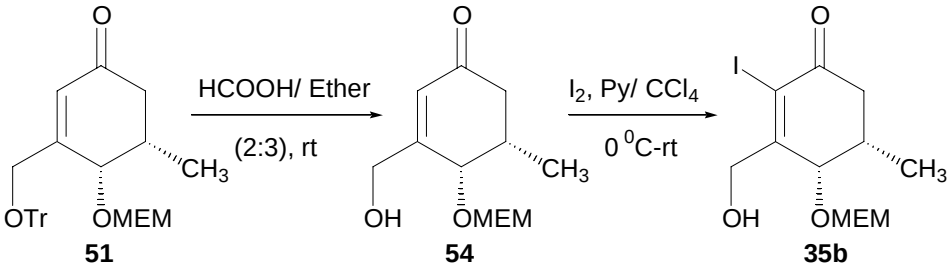
**Scheme 11**




**51** **35**

As expected replacement of trityl protection of **51** followed by iodination was found to be facile. Thus the compound **51** was subjected to selective deprotection[41] of trityl in presence of MEM-group by treating with formic acid in ether (2:3) and the alcohol **54** was obtained in 81% yield. The structure was confirmed by its $^1$H NMR and $^{13}$C NMR spectral analysis. The α-iodination[40] of enone **54** with $I_2$ dissolved in anhydrous $CCl_4$ at 0 ºC in the presence of pyridine and $CCl_4$ furnished **35** in 67% yield. The structure of **35** was derived out unambiguously from the $^1$H NMR and $^{13}$C NMR spectra. The $^{13}$C spectrum of **35** showed the peaks at 107.6, 165.9 corresponding to disubstituted olefinic carbons (Scheme 12).

**Scheme 12**

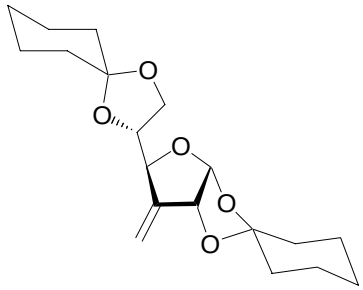



## Conclusion

Thus, a sugar based approach for the synthesis of a cyclohexenone intermediate **35** which can be used in the total synthesis of natural xanthone dimers like dicerandrol, phomoxanthone and secalonic acids was described. A strategy consisting Ring Closing Metathesis followed by oxidative rearrangement forms the core of our approach. Further studies toward the applicability of the iodocyclohexenone derivative **35** in executing the total synthesis of the dicerandrols is in progress.

# Experimental Section

**1,2:5,6-Di-*O*-cyclohexylidene-3-deoxy-3-methylene-α-D-*ribo*-hexofuranose (41)**



A 1.6 M solution of n- Butyl lithium (24.7 mL, 39.5 mmol) was added dropwise to a ice cooled solution of methyltriphenylphosphoniumiodide (17.98 g, 44.3 mmol) in anhydrous THF (60 mL). After 30 min, the mixture was cooled to –20 °C, **40**[30] (6.0 g, 17.8 mmol) in THF (20 mL) was added. The reaction mixture was allowed to attain 0 °C, and quenched with saturated aq. $NH_4Cl$ solution. The reaction mixture was extracted with ether, dried, evaporated, chromatographed on silica gel by using EtOAc: light petroleum (1:9) as eluant to give **41** (3.34 g, 56%).

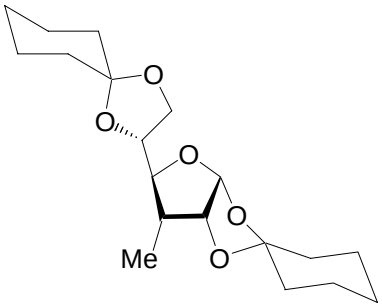
$[\alpha]_D$ + 105.7 (*c* 1.2, $CHCl_3$); lit.[30] $[\alpha]_D$ + 106.0 (*c* 2.0, $CHCl_3$)

**$^1$H NMR** (500 MHz, $CDCl_3$): $\delta$ 1.38–1.41 (m, 4 H), 1.52–1.58 (m, 8 H), 1.60–1.64 (m, 6 H), 1.69–1.73 (m, 2 H), 3.91 (dd, 1 H, *J* = 8.1, 6.0 Hz), 3.96–4.00 (m, 1 H), 4.04 (dd, 1 H, *J* = 8.1, 6.0 Hz), 4.55–4.57 (m, 1 H), 4.84 (dd, 1 H, *J* = 4.0, 1.2 Hz), 5.43 (s, 1 H), 5.52 (s, 1 H), 5.76 (d, 1 H, *J* = 4.0 Hz);

$^{13}$C NMR (125 MHz): $\delta$ 23.8, 24.0, 25.3, 35.2, 36.5, 36.8, 37.1, 66.9, 79.6, 81.8, 104.3, 110.4, 113.2.

Analysis calcd. for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 67.58; H, 8.47.

**1,2:5,6-Di-*O*-cyclohexylidene-3-deoxy-3-*C*-methyl-α-D-allofuranose (42)**




A mixture of compound **41** (6.5 g, 19.32 mmol), Pd/C (0.2 g) in MeOH was stirred under hydrogen at 60 psi, and at room temperature for 1 h. Catalyst was filtered and the filtrate concentrated, purified on silica gel by eluting with light petroleum: EtOAc (9:1) to afford **42** (6.33 g, 97%).

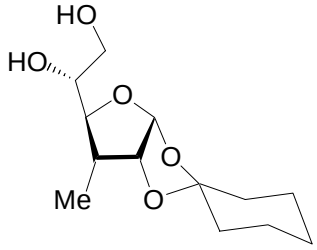
$[\alpha]_D$ + 36.3 (*c* 2.0, $CHCl_3$); lit.[30] $[\alpha]_D$ + 36 (*c* 2.0, $CHCl_3$).

**$^1$H NMR** (500 MHz, $CDCl_3$): $\delta$ 1.19 (d, 3 H, *J* = 6.8 Hz), 1.39 (br m, 4 H), 1.54–1.61 (m, 11 H), 1.65–1.72 (m, 4 H), 1.88–1.95 (ddq, 1 H, *J* = 9.8, 6.8, 4.8 Hz), 3.78 (dd, 1 H, *J* = 9.7, 7.2 Hz), 3.88 (dd, 1 H, *J* = 8.3, 5.8 Hz), 3.95 (br.q, 1 H, *J* = 12.6, 6.2 Hz), 4.05 (dd, 1 H, *J* = 8.3, 6.3 Hz), 4.5 (t, 1 H, *J* = 4.3 Hz), 5.72 (d, 1 H, *J* = 3.6 Hz).

**$^{13}$C NMR** (50 MHz): $\delta$ 10.2, 23.7, 23.9, 24.0, 25.1, 25.2, 35.0, 36.1, 36.3, 36.5, 43.1, 67.4, 77.7, 83.0, 104.6, 111.0, 112.1.

Analysis calcd. for $C_{19}H_{30}O_5$: C, 67.43; H, 8.93. Found: C, 67.63; H, 9.01.

**1,2-*O*-Cyclohexylidene-3-deoxy-3-*C*-methyl-α-D-allofuranose (43)**




A mixture of compound **42** (4.5 g, 13.29 mmol), 0.8% $H_2SO_4$ and MeOH (50 mL) was stirred at room temperature for 24 h. Reaction mixture was neutralized with $Et_3N$, concentrated. The residue was dissolved in ethyl acetate and washed with water, brine, dried ($Na_2SO_4$) and purified on silica gel by eluting with light petroleum: EtOAc (3:7) to give **43** (2.88 g, 84%).

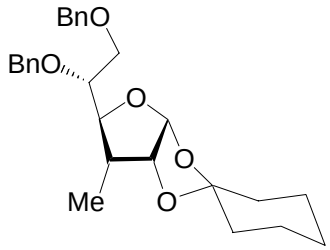
$[\alpha]_D$ + 34.3 (*c* 1.8, $CHCl_3$); lit.[30] $[\alpha]_D$ + 34.5 (*c* 2.0, $CHCl_3$).

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 1.15 (d, 3 H, *J* = 6.9 Hz), 1.39-1.41 (m, 2 H), 1.51–1.57 (m, 3 H), 1.65–1.70 (m, 5 H), 1.96–2.04 (m, 1 H), 2.37 (br s, OH), 2.66 (br s, OH), 3.70-3.76 (m, 3 H), 3.82 (dd, 1 H, *J* = 10.2, 4.4 Hz), 4.52 (t, 1 H, *J* = 4.3 Hz), 5.75 (d, 1 H, *J* = 3.6 Hz);

**$^{13}$C NMR** (50 MHz): $\delta$ 10.3, 23.6, 23.9, 25.1, 36.0, 36.4, 40.5, 63.5, 73.2, 83.0, 83.4, 104.3, 112.2.

Analysis calcd. for $C_{13}H_{22}O_5$: C, 60.45; H, 8.58. Found: C, 60.09; H, 8.78.

**1,2-*O*-Cyclohexylidene-3-deoxy-3-*C*-methyl-5,6-di-*O*-benzyl-α-D-allofuranose (44)**




To a solution of compound **43** (3.0 g, 11.61 mmol) in DMF (15 mL) at 0 °C was added NaH (60% dispersion in mineral oil, (1.02 g, 25.54 mmol). After 15 min, benzyl bromide was introduced. After 2 h. at 0 °C, water was added, extracted with ether, washed with water and dried ($Na_2SO_4$). Solvent was evaporated and the residue was purified on silica gel by eluting with light petroleum: EtOAc (9:1) to furnish **44** (4.68 g, 92%).

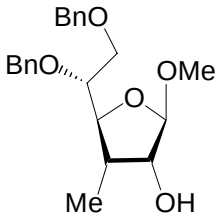
$[\alpha]_D$ + 13.2 (*c* 0.9, $CHCl_3$)

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 1.15 (d, 3 H, *J* = 6.7 Hz), 1.39–1.41 (m, 2 H), 1.51–1.57 (m, 3 H), 1.65–1.70 (m, 5 H), 2.04–2.16 (m, 1 H), 3.05-3.58 (m, 3 H), 3.62 (dd, 1 H, *J* = 10.2, 6.5 Hz), 3.71 (dd, 1 H, *J* = 10.2, 3.9 Hz), 3.79 (ddd, 1 H, *J* = 9.9, 6.5, 3.9 Hz), 3.93 (dd, 1 H, *J* = 9.9, 4.5 Hz), 4.5 (br t, 1 H, *J* = 4.3 Hz), 4.52 (d, 1 H, *J* = 11.6 Hz), 4.55 (d, 1 H, *J* = 11.6 Hz), 4.57 (d, 1 H, *J* = 11.6 Hz), 4.79 (d, 1 H, *J* = 11.6 Hz), 5.72 (d, 1 H, *J* = 3.7 Hz);

**$^{13}$C NMR** (125 MHz): $\delta$ 10.6, 23.7, 23.9, 25.1, 36.2, 36.6, 40.3, 70.9, 73.0, 73.3, 79.5, 82.5, 83.1, 104.4, 111.9, 127.4, 127.5, 127.8, 128.2, 128.3, 138.3, 138.7.

Analysis calcd. for $C_{27}H_{34}O_5$: C, 73.94; H, 7.81. Found: C, 73.59; H, 7.43.

**Methyl 5,6-di-*O*-benzyl-3-deoxy-3-*C*-methyl-β-D-allofuranose (38b)**




A mixture of compound **44** (3.5 g, 7.98 mmol), IR-120 ($H^+$) resin (10.0 g), in MeOH (40 mL) was heated under reflux for 4 h, filtered, concentrated to give anomeric mixture of **38**, which on further purification by silica gel column chromatography with light petroleum: EtOAc (2: 3) afforded **38b** (2.16 g, 73%).

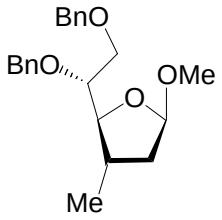
$[\alpha]_D$ – 46.1 (*c* 1.0, $CHCl_3$)

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 1.12 (d, 3 H, *J* = 6.6 Hz), 1.58 (br s, OH), 2.30–2.36 (m, 1 H), 3.28 (s, 3 H), 3.55 (ddd, 1 H, *J* = 8.6, 6.1, 2.4 Hz), 3.64 (dd, 2 H, *J* = 10.2, 5.8 Hz), 3.86–3.89 (m, 2 H), 3.95 (d, 1 H, *J* = 4.5 Hz), 4.54 (d, 1 H, *J* = 11.8 Hz), 4.60 (d, 2 H, *J* = 11.8 Hz), 4.73 (s, 1 H), 4.78 (d, 1 H, *J* = 11.8 Hz), 7.25-7.33 (m, 10 H);

**$^{13}$C NMR** (50 MHz): $\delta$ 10.9, 15.0, 39.1, 62.5, 71.0, 72.5, 73.2, 78.0, 81.7, 83.2, 107.6, 127.7, 128.1, 128.2, 138.3,138.4.

Analysis calcd. for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 70.58; H, 7.77.

**Methyl 5,6-Di-*O*-benzyl-2,3-dideoxy-3-*C*-methyl-β-D-allofuranoside (45)**




A mixture of **38b** (3.0 g, 80.5 mmol), NaH (0.36 g, 88.5 mmol), $CS_2$ (0.6 mL, 96.5 mmol), MeI (0.6 mL, 96.5 mmol) in anhydrous THF (10 mL) were stirred at 0 °C for 30 min. Excess of NaH was quenched by the careful addition of water and then extracted with ethyl acetate. It was washed with water, brine, dried ($Na_2SO_4$) and concentrated to afford the xanthate derivative (3.7 g), which was dissolved in toluene (25 mL), containing AIBN (10 mg) and $Bu_3SnH$ (2.3 mL, 87.6 mmol). After 2 h of refluxing, solvent was evaporated and the

residue purified on silica gel by eluting with light petroleum ether: EtOAc (9:1) to give **45** (2.7 g, 77%, 2 steps).

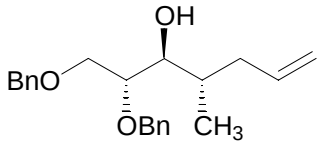
$[\alpha]_D$ – 36.4 (*c* 0.8, $CHCl_3$)

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 1.09 (d, 3 H, *J* = 6.7 Hz), 1.54–1.60 (m, 1 H), 1.97–2.08 (m, 1 H), 2.31–2.34 (m, 1 H), 3.25 (s, 3 H), 3.54 (d, 1 H, *J* = 5.8 Hz), 3.60-3.73 (m, 2 H), 3.80 (dd, 1 H, *J* = 11.8, 4.5 Hz), 4.55 (d, 1 H, *J* = 11.8 Hz), 4.60 (d, 2 H, *J* = 11.8 Hz), 4.84 (d, 1 H, *J* = 11.8 Hz), 4.88 (d, 1 H, *J* = 5.3 Hz);

**$^{13}$C NMR** (50 MHz): $\delta$ 18.6, 35.0, 41.6, 54.6, 71.2, 72.8, 73.3, 78.0, 81.9, 85.3, 105.1, 127.6, 127.8, 128.3, 138.5,138.8.

Analysis calcd. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 73.87; H, 7.66.

**(2*R*,3*S*,4*S*)-1,2-Dibenzyloxy-4-methyl-hept-6-en-3-ol (47)**




A 1.6 M solution of n-butyl lithium (14.4 mL, 22.9 mmol) was added dropwise to a ice cooled solution of methyl triphenylphosphoniumiodide (10.33 g, 25.6 mmol) in THF (40 mL) at –20 °C. Compound **46** (3.5 g, 10.0 mmol) in THF (10 mL) was added and then stirred at 0 °C for 1 h. It was quenched with saturated aq. $NH_4Cl$ solution, extracted with ether, dried and evaporated. The residue was chromatographed on silica gel by using light petroleum: EtOAc (4:1) to afford **47** (2.88 g, 83%).

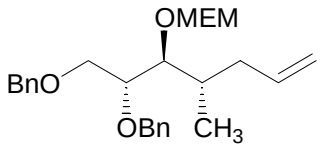
$[\alpha]_D$ = – 9.4 (*c* 1.1, $CHCl_3$)

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 0.86 (d, 3 H, *J* = 6.8 Hz), 1.69–1.78 (m, 1 H), 1.84–1.94 (m, 1 H), 2.34–2.41 (m, 1 H), 2.46 (d, OH, *J* = 3.21 Hz), 3.56–3.68 (br m, 2 H), 3.72–3.78 (br m, 2 H), 4.02–4.55 (br m, 2 H), 4.58 (d, 1 H, *J* = 11.7 Hz), 4.70 (d, 1 H, *J* = 11.7 Hz), 4.97–5.03 (m, 2 H), 5.75 (dddd, 1 H, *J* = 16.2, 10.4, 8.0, 6.1 Hz), 7.25–7.37 (m, 10 H);

**$^{13}$C NMR** (50 MHz): $\delta$ 15.6, 34.3, 36.0, 69.9, 71.8, 73.2, 75.4, 78.5, 115.8, 127.3, 127.5, 128.0, 137.0,137.9, 138.2.

Analysis calcd. for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.72; H, 8.16.

**(2*R*,3*S*,4*S*)-1,2-Dibenzyloxy-3-[(2-methoxyethoxy)methoxy]-4-methyl-hept-6-ene (48)**




A mixture of **47** (3.0 g, 8.81 mmol), diisopropylethyl amine (2.3 mL, 13.2 mmol), MEM-Cl (1.2 mL, 10.5 mmol) in dry $CH_2Cl_2$ (10 mL) at room temperature was stirred for 10 h, evaporated to give a residue, which was extracted with EtOAc, washed with water, brine, dried ($Na_2SO_4$). The product was and purified by silica gel chromatography by eluting with light petroleum: EtOAc (9:1) to give **48** (3.1 g, 82%).

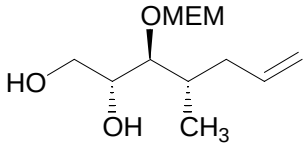
$[\alpha]_D$ − 15.9 (*c* 0.8, $CHCl_3$)

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 0.89 (d, 3 H, *J* = 6.7 Hz), 1.77–1.91 (m, 2 H), 2.28– 2.37 (m, 1 H), 3.36 (s, 3 H), 3.47–3.50 (m, 2 H), 3.58–3.66 (m, 3 H), 3.69–3.78 (m, 3 H), 4.51 (d, 1 H, *J* = 11.8 Hz), 4.57 (d, 1 H, *J* = 11.8 Hz), 4.58 (d, 1 H, *J* = 11.8 Hz), 4.69 (d, 1 H, *J* = 6.6 Hz), 4.72 (s, 1 H), 4.87 (d, 1 H, *J* = 6.6 Hz), 4.98–5.03 (br m, 2 H), 5.68-5.79 (m, 1 H), 7.26–7.36 (m, 10 H);

**$^{13}$C NMR** (50 MHz): $\delta$ 16.1, 34.4, 36.5, 58.6, 67.4, 70.3, 71.6, 72.0, 73.1, 79.3, 81.7, 96.5, 115.7, 127.3, 127.5, 128.1, 137.2,138.2.

Analysis calcd. for $C_{26}H_{36}O_5$: C, 72.87; H, 8.47. Found: C, 72.74; H, 8.31.

**(2*R*,3*S*,4*S*)-3-[(2-methoxyethoxy)methoxy]-4-methyl-hept-6-en-1,2-diol (49)**




A solution of **48** (4.5 g, 10.5 mmol) in anhydrous THF (10 mL) was added to a solution of lithium (0.74 g, 105.0 mmol) in liq. $NH_3$ (50 mL) maintained at –78 °C. The reaction mixture was stirred for 1 h and quenched with solid $NH_4Cl$. $NH_3$ was allowed to evaporate and then the resulting residue was taken in ethyl acetate washed with water, brine, dried ($Na_2SO_4$) and evaporated. The residue was purified on silica gel by using light petroleum: EtOAc (1:9) to obtain **49** (2.36 g, 91%).

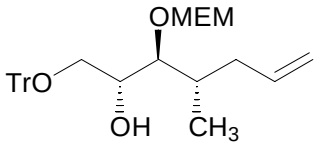
$[\alpha]_D$ + 73.5 (*c* 1.1, $CHCl_3$)

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 0.94 (d, 3 H, $J$ = 6.9 Hz), 1.71–1.80 (m, 1 H), 1.90– 2.05 (m, 1 H), 2.36–2.49 (m, 1 H), 2.62 (br s, OH), 3.40 (s, 3 H), 3.53–3.58 (m, 2 H), 3.64–3.68 (m, 2 H), 3.80–3.90 (m, 1 H), 4.67 (d, 1 H, $J$ = 6.9 Hz), 4.86 (d, 1 H, $J$ = 6.9 Hz), 5.04 (br dd, 2 H), 5.72–5.87 (m, 1 H);

**$^{13}$C NMR** (50 MHz): $\delta$ 15.6, 36.5, 37.5, 58.6, 62.7, 67.4, 71.3, 71.5, 76.6, 86.1, 97.1, 115.8, 136.7,136.8.

Analysis calcd. for $C_{12}H_{24}O_5$: C, 58.04; H, 9.74. Found: C, 58.16; H, 9.67.

**(2*R*,3*S*,4*S*)-3-[(2-methoxyethoxy)methoxy]-4-methyl-1-triphenylmethoxy-hept-6-en-2-ol (50)**




To a solution of compound **49** (2.0 g, 8.05 mmol), trityl chloride (3.36 g, 12.05 mmol) in pyridine (10 mL) was stirred for 12 h at room temperature. After usual work up, followed by evaporation gave a residue, which was purified on silica gel by eluting with light petroleum: EtOAc (4:1) to afford **50** (3.43 g, 87%).

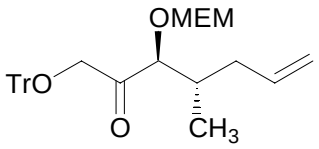
$[\alpha]_D$ + 13.4 (*c* 2.1, $CHCl_3$)

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 0.85 (d, 3 H, $J$ = 6.9 Hz), 1.86–1.88 (m, 2 H), 2.24–2.34 (m, 1 H), 3.14–3.49 (m, 10 H), 4.53 (d, 1 H, $J$ = 6.8 Hz), 4.69 (d, 1 H, $J$ = 6.8 Hz), 4.93–4.99 (br m, 2H), 5.57–5.74 (m, 1 H), 7.20–7.31 (m, 10 H), 7.41–7.45 (m, 5 H);

**$^{13}$C NMR** (50 MHz): $\delta$ 15.8, 34.5, 36.9, 58.7, 64.7, 67.4, 70.7, 71.4, 86.6, 86.7, 97.1, 116.0, 126.8, 137.0,143.9.

Analysis calcd. for $C_{31}H_{38}O_5$: C, 75.89; H, 7.81. Found: C, 76.13; H, 7.67.

**(3*S*,4*S*)-3-(2-Methoxyethoxymethoxy)-4-methyl-1-triphenylmethoxy-hept-6-en-2-one (37)**




A mixture of compound **50** (2.5 g, 5.09 mmol), PDC (2.87 g, 7.62 mmol), 4 ºA molecular sieves powder (5 g) in anhydrous $CH_2Cl_2$ (15 mL) were stirred at room temperature for 1 h. Solid was filtered, the filtrate evaporated and silica gel purification (light petroleum: EtOAc (4:1)) to gave **16** (2.18 g, 88%).

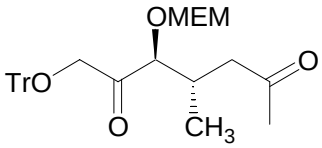
$[\alpha]_D$ − 41.3 (*c* 1.6, $CHCl_3$)

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 0.87 (d, 3 H, *J* = 6.5 Hz), 1.84–1.97 (m, 1 H), 2.04–2.16 (m, 1 H), 3.31 (s, 3 H), 3.36–3.41 (m, 2 H), 3.51–3.58 (m, 2 H), 3.89 (d, 1 H, *J* = 10.8 Hz), 4.09 (d, 1 H, *J* = 5.1 Hz), 4.62 (s, 2 H), 4.91–5.05 (m, 2H), 5.53–5.73 (m, 1 H), 7.23–7.33 (m, 10 H), 7.43-7.48 (m, 5 H);

**$^{13}$C NMR** (50 MHz): $\delta$ 15.5, 35.6, 35.8, 58.8, 67.7, 71.6, 73.2, 73.6, 84.5, 96.2, 116.8, 127.8, 128.4, 136.0, 137.2, 207.9.

Analysis calcd. for $C_{31}H_{36}O_5$: C, 76.20; H, 7.43. Found: C, 76.61; H, 7.28.

**(3*S*,4*S*)-3-[(2-Methoxyethoxy)methoxy]-4-methyl-1-triphenylmethoxy-heptan-2,6-dione (36)**




A solution of compound **37** (1.2 g, 2.45 mmol), Cu $(OAc)_2$. $H_2O$ (0.097 g, 0.48 mmol), $PdCl_2$ (0.043 g, 0.24 mmol) in DMA: $H_2O$ (7:1) (total volume 5 mL) were stirred under oxygen atmosphere at ntp for 14 h. The reaction was filtered, extracted with ether, washed with water, brine, dried ($Na_2SO_4$) and evaporated. The residue was purified on silica gel by eluting with light petroleum: EtOAc (3:1) to afford **36** (0.94 g, 76%).

$[\alpha]_D$ − 73.3 (*c* 0.7, $CHCl_3$)

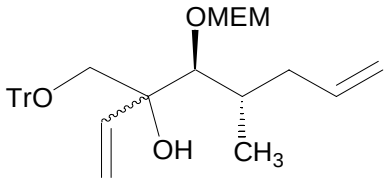
**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 0.96 (d, 3 H, *J* = 6.8 Hz), 2.06 (s, 3 H), 2.23–2.32 (m, 1 H), 2.50–2.62 (m, 2 H), 3.31 (s, 3 H), 3.36–3.43 (m, 2 H), 3.54–3.60 (m, 2 H), 3.89 (d, 2 H, *J* =

1.4 Hz), 4.23 (d, 1 H, *J* = 3.9 Hz), 4.56 (d, 1 H, *J* = 6.8 Hz), 4.63 (d, 1 H, *J* = 6.8 Hz), 4.63 (d, 1 H, *J* = 6.8 Hz), 7.23-7.35 (m, 10 H), 7.43-7.48 (m, 5 H);

**$^{13}$C NMR** (50 MHz): $\delta$ 17.0, 30.1, 30.6, 44.6, 58.7, 67.3, 68.6, 71.4, 82.7, 87.2, 96.0, 127.1, 127.8, 128.4, 143.0, 206.8,206.9.

Analysis calcd. for $C_{31}H_{36}O_6$: C, 73.79; H, 7.19. Found: C, 73.58; H, 7.28.

**(3*S*/*R*,4*S*,5*S*)-4-[(2-Methoxyethoxy)methoxy]-5-methyl-3-triphenylmethoxymethyl-octa-1,7-dien-3-ol (53)**



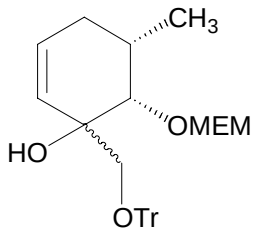

To a solution of compound **37** (0.82 g, 1.62 mmol) in anhydrous THF at –40 °C was added vinyl magnesium bromide (1.0 M solution in THF) (0.43 mL, 3.23 mmol). After 1 h., saturated $NH_4Cl$ solution was added, extracted with ethyl acetate. The organic layer was washed with water, brine, dried ($Na_2SO_4$) and concentrated. The residue was purified on silica gel by eluting with light petroleum: EtOAc (4:1) to give **53** as diastereomers (85:15) (0.69 g, 83 %).

**$^{1}$H NMR** (200 MHz, $CDCl_3$): $\delta$ 0.92 (d, 3 H, *J* = 6.6 Hz), 1.61–1.77 (m, 2 H), 2.27–2.32 (m, 1 H), 2.63 (s, OH), 3.17 (d, 1 H, *J* = 8.2 Hz), 3.22 (d, 1 H, *J* = 8.2 Hz), 3.35 (s, 3 H), 3.42–3.48 (m, 3 H), 3.50–3.53 (m, 2 H), 3.61–3.68 (m, 1 H), 4.53 (d, 1 H, *J* = 6.6 Hz), 4.64 (d, 1 H, *J* = 6.6 Hz), 4.81–4.87 (m, 2 H), 5.24 (dd, 1 H, *J* = 17.4, 1.4 Hz), 5.45 (dd, 1 H, *J* = 17.4, 1.4 Hz), 6.08 (dd, *J* = 17.4,10.8 Hz) 7.20–7.31 (m, 10 H), 7.38–7.40 (m, 5 H);

**$^{13}$C NMR** (50 MHz): $\delta$ 18.7, 33.0, 36.1, 58.7, 67.4, 71.3, 76.2, 71.4, 86.5, 97.4, 114.4, 114.9, 126.6, 127.5, 128.5, 137.8, 139.9,143.2.

Analysis calcd. for $C_{33}H_{40}O_5$: C, 76.71; H, 7.80. Found: C, 76.88; H, 7.49.

**(1*S*/*R*,5*S*,6*S*)-6-[(2-Methoxyethoxy)methoxy]-5-methyl-1-triphenylmethoxymethyl-cyclohex-2-enol (52)**



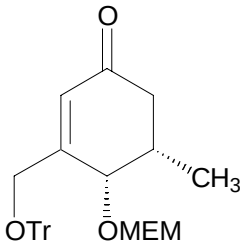

A mixture of **53** (0.5 g, 0.96 mmol) and Grubbs' Ist generation catalyst ($Cl_2(PCy_3)_2Ru$=CHPh) (79 mg, 0.096 mmol) in anhydrous $CH_2Cl_2$ (300 mL) was stirred at reflux for 6 h. The solvent was evaporated and chromatographed on silica gel by eluting with light petroleum: EtOAc (3:1) to yield **52** (0.40 g, 86%).

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 1.05 (d, 3 H, $J$ = 6.7 Hz), 1.76–2.01 (m, 2 H), 2.21–2.33 (m, 1 H), 2.74 (br s, OH), 3.20–3.42 (m, 7 H), 3.62–3.69 (m, 2 H), 4.19 (d, 1 H, $J$ = 7.1 Hz), 4.58 (d, 1 H, $J$ = 7.1 Hz), 5.48 (dd, 1 H, $J$ = 10.2, 1.3 Hz), 5.92 (dddd, 1H, $J$ = 9.9, 6.9, 4.5, 2.3 Hz), 7.21–7.33 (m, 10 H), 7.39–7.44 (m, 5 H);

**$^{13}$C NMR** (50 MHz): $\delta$ 18.1, 28.4, 30.2, 59.0, 67.4, 71.5, 71.9, 83.2, 86.8, 97.4, 126.2, 127.2,128.9,128.8,133.0,143.3.

Analysis calcd. for $C_{31}H_{36}O_5$: C, 76.20; H, 7.43. Found: C, 76.48; H, 7.89.

**(4*S*,5*S*)-4-[(2-Methoxyethoxy)methoxy]-5-methyl-3-triphenylmethoxymethyl-cyclohex-2-enone (51)**




A mixture of **52** (0.67 g, 1.37 mmol), PCC (0.44 g, 2.04 mmol) in anhydrous $CH_2Cl_2$ (5 mL) was stirred at room temperature for 20 h. The reaction mixture was concentrated and then diluted with diethyl ether (15 mL), which was washed with 1.0 M NaOH solution, water, brine, dried ($Na_2SO_4$) and evaporated. The residue was purified on silica gel by eluting with light petroleum: EtOAc (7:3) to afford **51** (0.53 g, 77%).

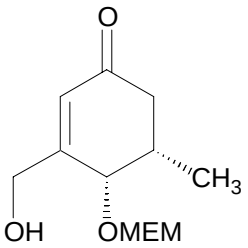
$[\alpha]_D$ – 34.4 (*c* 1.0, $CHCl_3$)

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 0.99 (d, 3 H, $J$ = 6.2 Hz), 2.33–2.51 (m, 3 H), 3.19–3.43 (m, 7 H), 3.72 (br. d, 1 H, $J$ = 17.2 Hz), 4.06 (br dd, 1 H, $J$ = 17.2 Hz), 4.13 (br.d, 1 H, $J$ = 3.2 Hz), 4.57 (d, 1 H, $J$ = 7.2 Hz), 4.63 (d, 1 H, $J$ = 7.2 Hz), 6.48 (s, 1 H), 7.22–7.34 (m, 10 H), 7.41-7.45 (m, 5 H);

**$^{13}$C NMR** (50 MHz): $\delta$ 15.0, 33.7, 41.9, 58.9, 64.0, 67.3, 71.4, 74.6, 87.2, 96.1, 124.2, 127.2, 127.9, 128.5, 143.6,159.2, 198.5.

Analysis calcd. for $C_{31}H_{34}O_5$: C, 76.52; H, 7.04. Found: C, 76.26; H, 6.91.

**(4*S*,5*S*)-3-Hydroxymethyl-4-[(2-methoxyethoxy)methoxy]-5-methyl-cyclohex-2-enone (54)**




A mixture of compound **51** (0.5 g, 1.0 mmol) was stirred with a mixture of HCOOH and ether (2:3, 2 mL) at room temperature for 45 min. The reaction mixture was diluted with ether, washed with sat. $NaHCO_3$ solution, water, brine, dried ($Na_2SO_4$) and evaporated. The residue was purified by silica gel column chromatography with light petroleum: EtOAc (1:4) to give **54** (0.20 g, 81%).

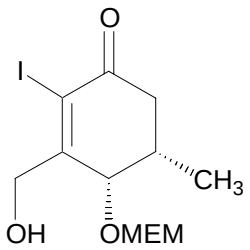
$[\alpha]_D$ – 39.9 (*c* 1.1, $CHCl_3$)

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 1.07 (d, 3 H, $J$ = 6.5 Hz), 2.30–2.43 (m, 3 H), 3.39 (s, 3 H), 3.51–3.64 (m, 4 H), 3.76–3.88 (m, 1 H), 4.25 (d, 1 H, $J$ = 2.9 Hz), 4.39 (d, 1 H, $J$ = 1.4 Hz), 4.80 (d, 1 H, $J$ = 7.2 Hz), 4.85 (d, 1 H, $J$ = 7.2 Hz), 6.04 (s, 1 H);

**$^{13}$C NMR** (50 MHz): $\delta$ 15.2, 33.7, 41.2, 58.6, 62.3, 67.1, 71.3, 74.4, 95.6, 123.7, 162.4,198.9.

Analysis calcd. for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 59.28; H, 8.61.

**(4*S*,5*S*)-3-Hydroxymethyl-2-iodo-4-[(2-methoxyethoxy)methoxy]-5-methyl-cyclohex-2-enone (35)**




A solution of compound **54** (0.25 g, 1.02 mmol), iodine (0.517 g, 2.04 mmol) in dry $CCl_4$, pyridine in (1:1, 5 mL) were stirred at room temperature for 6 h, diluted with ether and washed with 20% $Na_2S_2O_3$, 1 N HCl, water, dried ($Na_2SO_4$) and concentrated. The residue was purified on silica gel by eluting with light petroleum: EtOAc (2:3) to obtain **35** (0.25 g, 67%).

$[\alpha]_D$ − 54.5 (*c* 0.6, $CHCl_3$)

**$^1$H NMR** (200 MHz, $CDCl_3$): $\delta$ 1.12 (d, 3 H, *J* = 6.8 Hz), 1.25 (s, OH), 2.16–2.33 (m, 1 H), 2.49–2.80 (m, 2 H), 3.41 (s, 3 H), 3.53–3.63 (m, 4 H), 3.76–3.88 (m, 1 H), 4.43–4.59 (br m, 2 H), 4.78 (d, 1 H, *J* = 7.1 Hz), 4.89 (d, 1 H, *J* = 7.1 Hz);

**$^{13}$C NMR** (50 MHz): $\delta$ 16.7, 29.7, 34.2, 39.3, 59.0, 67.5, 69.9, 71.4, 75.1, 96.9, 107.7,165.9, 191.5.

Analysis calcd. for $C_{12}H_{19}IO5$: C, 38.93; H, 5.17. Found: C, 39.18; H, 5.26.

# References

## References


1. "Moving Beyond Natural Products" *C & E News* **2003**, *81*, 104-107.
2. Nicolaou, K. C., Vourloumis, D.; Winssinger, N.; Baran, P. S. *Angew. Chem. Int. Ed.* **2000**, *39*, 44.
3. Clardy, J.; Wagenaar, M. M. *J. Nat. Prod.* **2001**, *64*, 1006.
4. Sultanbawa, M. U. S. *Tetrahedron* **1980**, *36*, 1465.
5. Cardona, M. L., Fernandez, M. I., Pedro, J. R. and Serrano, A. *Phytochemistry* **1990**, *29*, 3003.
6. Peres, V.; Nagem T. J. *Phytochemistry,* **1997**, *44*, 191. b) Peres, V.; Nagem T. J.; de Oliveira, F. F. *Phytochemistry,* **2000**, *55*, 683.
7. a) Kitanov, G. M. and Blinova, K. F. *Chem.Nat.Compds* **1987**, *2*, 151. b) Hostettmann, K. and Wagner, H. *Phytochemistry* **1977**, *16*, 821.
8. a) Suzuki, O.; Katsumata, Y.; Oya, M.; Chari, V.M.; Klapfenberger, R.; Wagner, H.; Hostettmann, K. *Planta Med.* **1980**, *39*, 19. b) Suzuki, O.; Katsumata, Y.; Oya, M.; Chari, V.M.; Vermes, B.; Wagner, H.; Hostettmann, K. *Planta Med.* **1981**, *42*, 17.
9. Terreaux, C.; Maillard, M.; Gupta, M.P.; Hostettmann, K. *Phytochemistry*, **1995**, *40*, 1791.
10. Beerhues, L.; Berger, U.; *Phytochemistry* **1994**, *35*, 1227.
11. Balasubramanian, K.; Rajagopalan, K. *Phytochemistry* **1988**, *27*, 1552.
12. Gurevich, A.I.; Karapetyan, Y.G.; Kolosov, M. N.; Omelchenko, V. N.; Onoprienko, V. V.; Petrenko, G. I.; Popravko, S. A. *Tetrahedron. Lett.* **1972**, *18*, 1751.
13. Gurevich, A.I.; Deshko, T. N.; Kogan, G. A.; Kolsov, M. N.; Kudryashova, V. V.; Onoprienko, V. V. *Tetrahedron. Lett.* **1974**, *33*, 2801.
14. Chu, M.; Truumees, I.; Mierzwa, R.; Terracciano, J.; Patel, M.; Loebenberg, D.; Kaminski, J J.; Das, P.; Puar, M. S. *J. Nat. Prod.* **1997,** *60,* 525.
15. Chu, M.; Truumees, I.; Mierzwa, R.; Terracciano, J.; Patel, M.; Loebenberg, D.; Kaminski, J J.; Das, P.; Puar, M. S.; Chan, T-M. *Tetrahedron. Lett.* **1998,** *39,*7649.
16. Holker, J. S. E.; O'Brien, E.; Simpson, T. J. *J. Chem. Soc., Perkin Trans. 1* **1983**, *7*, 1365.

17. Deshplande, V. H.; Rama Rao, A. V.; Varadan M.; Venkataraman, K. *Indian J. Chem* **1973**, *11*, 518. b) Kirtany, J. K.; Paknik, S. K. *Indian J. Chem* **1975**, *13*, 104. c) Cotterill P. J.; Scheinmann, F. *Chem. Comm.* **1975**, 664.
18. Kraft, F. *Arch. Pharm.* (*Weinheim*), **1906**, 79.
19. a) McPhee, F.; Caldera, P. S.; Bemis, G.W.; McDonagh, A. F.; Kuntz, I. D.; Craik, C. S. *Biochem. J.* **1996**, *320*, 681. b) Wang, B. H.; Polya, G. M.; *Planta Med.* **1996**, *62*, 111.
20. Zeng, R. S.; Luo, S. M.; Shi, Y. H.; Shi, M. B.; Tu, C. Y. *Agron. J.* **2001**, *93*, 72.
21. a) Franck, B.; Zeidler, U. Chem. Ber. **1973**, *106*, 1182. b) Franck, B.; Zeidler, U. Chem. Ber. **1973**, *106*, 1198.
22. a) Gabbutt, C. D.; Hepworth, J. D.; Urquhart, M.W. J.; Vazquez de Miguel, L. M.; *J. Chem. Soc. Perkin Trans. 1* **1997**, 1819. b) Klutchko, M.S.; Strandtmann, V.; Shavel, J. R.US Pat. 3862141, **1975**. c) Ghosh, C. K.; Bhattacharyya, S.; Ghosh, C.; Patra, A. *J. Chem. Soc. Perkin Trans. 1* **1999**, 3005. d) Letcher, R. M.; Yue, T.-Y.; Chiu, K.-F.; Kelkar, A. S.; Cheung, K.-K. *J. Chem. Soc. Perkin Trans. 1* **1998**, 3267.
23. Proksa, B.; Uhrin Ĭ. D.; Liptaj, T.; Strudikova, M. *Phytochemistry*, **1998**, *48*, 1161.
24. Stewart, M.; Capon, R. J.; White, J. M.; Lacey, E.; Tennant, S.; Gill, J. H.; Shaddock M. P. *J. Nat. Prod.* **2004,** *67,*728.
25. Isaka, M.; Jaturapat, A.; Rukseree, K.; Danwisetkanjana, K.; Tanticharoen, M.; Thebtaranonth, Y. *J. Nat. Prod.* **2001**, *64*, 1015.
26. Vining, C. L.; Kurbone, I.; Mc Innes, G. A.; Walter, A. J.; Wright, L. J. *Tetrahedron. Lett.* **1978**, *19*, 1379.
27. Arnold, A. E.; Maynard, Z.; Gilbert, G. S.; Coley, P. D.; Kursar, T. A. *Ecol. Lett.* **2000**, *3*, 267.
28. a) Taylor, W. L.; Battersby, A. R. *Oxidative Coupling of phenols*, M. Dekker, New York. **1967**. b) Anjali, P.; Pal, T. *Current Science.* **1996**, *71*, 106. c) Moussa, G. E. *Acta. Chem Scand.* **1968**, *22*, 3329. d) Majumdar, P. L.; Kundu, A. J.; *Indian Chem Soc.* **1984**, *61*, 142. e) Ikekawa, T. *Chem Pharma Bull*. **1963**, *11*, 749. e) Hewgill, F. R.; Stewart, J. M.; *J. Chem. Soc. Perkin Trans 1*, **1988**, 1305.
29. Corey, E. J.; Shibasaki, M.; Knolle, J. *Tetrahedron Lett.* **1977**, 1625.

30. Gurjar, M. K.; Tushar, K.; Ramdas, G. B.; Murugan, A. *Tetrahedron Lett*. **2003**, *44*, 5183.
31. Barton, D. H. R.; Mc Combi, S. W. *J. Chem. Soc. Perkin Trans 1*, **1975**, 1574.
32. McCloskey, C. M. *Adv. Carbohydr. Chem.* **1957**, *12*, 137. b) Philips, K. D.; Zemlicka, J.; Horowitz, J. P. *Carbohydr. Res*. **1973**, *30*, 281. c) Schon, I. *Chem Rev.* **1984**, *84*, 287. d) Reist, E. J.; Bartuska, V. J.; Goodman, L. *J. Org. Chem*. **1964**, *29*, 3725.
33. Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett*. **1979**, 95.
34. Smith, A. B.; Cho, Y. S.; Friestad, G. K. *Tetrahedron Lett.* **1998**, *39*, 8765.
35. a) Evans, D. A. *Asymmetric Synthesis*. Ed. Morrison, J. D. Acadamic Press, New York, **1984**, *Vol. 3*, Chap. 1, p. 1. b) Heathcock, C. H. *Asymmetric Synthesis*. Ed. Morrison, J. D. Acadamic Press, New York, **1984**, *Vol. 3*, Chap. 2, p. 111. c) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1.
36. a) Grubbs, R. H.; Pine, S. H. *In Comprehensive Organic Synthesis*, Trost, B. M.; Flemming, I.; Paqueet, L. A. Eds.; Pergamon: New York, **1991**, *Vol. 5*, Chap. 9.3. b) Schrock, R. R. In *The Srem Chemiker*, Vol. XIV, Strem Chemicals, Newburgport, 1992, No. 1, p 1. c) Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Metathesis Polymerization*, Acadamic Press, San Diego, 1997.
37. Dauben, W.; Micheno, D. *J. Org. Chem.* **1977**, *42*, 682.
38. For recent reviews, see: Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. b) Tranka, T. M.; Grubbs, R. H. *Acc. Chem. Res*. **2001**, *34*, 18. c) Fürsther, A. *Angew. Chem. Int. Ed*. **2000**, *39*, 3012. d) kotha, S.; Sreenivasachary, N. *Ind. J. Chem. B.* **2001**, *40*, 763.
39. a) Herdson, J. L.; Chauvin, Y. *Makromol. Chem*, **1971**, *141*, 161. b) Sehrer, J. C.; Gundaiah, S. J. *Sci. Ind. Res*. **1983**, *55*, 250. c) Kress, J.; Osborn, J. A.; Green, R. M. E.; Ivin, K. J.; Rooney, J. J. *J. Am. Chem. Soc*. **1987**, *109*, 899.
40. Johnson, C. R.; Adams, J. P.; Braun, P. B.; Senanayake, C. B. W. *Tetrahedron Lett.* **1992**, *33*, 917.
41. Bessodes, M.; Komiotis, D.; Antonakis, K. *Tetrahedron Lett.* **1986**, *27*, 579.

## **List of Publications**:

1. Total synthesis of microcarpalide. Gurjar, M. K.; **Naga Prasad, R.**; Ramana, C. V. *Tetrahedron Lett*. **2002**, *43*, 7557.

2. First synthesis of methyl-α-*C*-D-arabinofuranosyl-(1→5)-α-D-arabinofuranoside: the *C*-disaccharide segment of motif C of *Mycobacterium tuberculosis.* Gurjar, M. K.; **Naga Prasad, R.**; Ramana, C. V. *Tetrahedron Lett*. **2003**, *44*, 2873.