ASYMMETRIC DIHYDROXYLATION APPROACH TO THE ENANTIOSELECTIVE SYNTHESES OF BIOACTIVE MOLECULES AND PCC MEDIATED OXIDATIVE ORGANIC TRANSFORMATION

A THESIS SUBMITTED TO THE

UNIVERSITY OF PUNE

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

BY

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JUNE 2002

CERTIFICATE

This is to certify that the work presented in the thesis entitled "**ASYMMETRIC DIHYDROXYLATION APPROACH TO THE ENANTIOSELECTIVE SYNTHESES OF BIOACTIVE MOLECULES AND PCC MEDIATED OXIDATIVE ORGANIC TRANSFORMATION"** submitted by **Rodney A. Fernandes** was carried out by the candidate at the National Chemical Laboratory, Pune, under my supervision. Such materials as obtained from other sources have been duly acknowledged in the thesis.

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CANDIDATE'S DECLARATION

I hereby declare that the thesis entitled "**ASYMMETRIC DIHYDROXYLATION APPROACH TO THE ENANTIOSELECTIVE SYNTHESES OF BIOACTIVE MOLECULES AND PCC MEDIATED OXIDATIVE ORGANIC TRANSFORMATION"** submitted for the degree of Doctor of Philosophy in Chemistry to the University of Pune has not been submitted by me to any other University or Institution. This work was carried out at the National Chemical Laboratory, Pune, India.

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DEDICATED

TO MY

PARENTS,
BROTHER AND SISTERS

ACKNOWLEDGEMENTS

It gives me great pleasure to place on record my deep sense of gratitude to my research supervisor, Dr. Pradeep Kumar for his encouragement and scientific temperament, which furthered my interest in synthetic organic chemistry. He has given me liberty to express my own views and ideas. He has taught me to be concise, systematic and correct in my approach from the formulation of ideas to the presentation of the results.

I take this opportunity to thank Prof. S. K. Paknikar, Dr. J. K. Kirtany and Dr. S. P. Kamat from Goa University, Goa for preliminary preparation to take up research work.

My sincere thanks goes to Dr. T. Ravindranathan (Former Head, OCT Division) and Dr. M. K. Gurjar, Head, OCT Division for support and encouragement. I extend my gratitude to Dr. V. H. Deshpande, Dr. U. R. Kalkote, Dr. K. V. Srinivasan, Dr. Ganesh Pandey and Dr. Borate for their help during the course of this work.

The kind help extended by the NMR facility fraternity Mr. Samuel, Dr. Rajmohan, Mr. Sathe and Miss Rupali, Mass Analysis by Mrs. Shantakumari and help by Analytical, Glass blowing and Library staff is greatly acknowledged.

This page would be incomplete without the mention of my lab mates who extended help throughout the tenure of my work in NCL. Thanks to Mandar, Subbarao, Priti, Ramalingam, Anis, Vasu, Puspesh and Pandey. I am also grateful to my colleagues and friends: Sushil Jha, Dr. Moneesha, Dr. C. Ramesh, Dr. Gorpade, Sambhaji, Ilyas, Yogesh, Vijay, Kale, Kapoor, Tiwari, Sanjay, Bidhan, Shivappa, Dr. Kharul, Dr. Bulbule, Joseph, Siddarth Rai, Sanki, Bennur, Dr. Sureshan, Dr. Pallan, Nagendra, Pallavi, Rajgopal, Dr. Gajare, Dr. Nabendu, Sadafulle, Anil, Agnel Fernandes and many more.

Support from OCT office staff: Babush, Catherine, Kulkarni, Vadrarajan, Rannowde and Ballan is also acknowledged.

I am equally indebted to the Director NCL for giving infrastructure facilities to work in a renowned institution like NCL. CSIR New Delhi is acknowledged for valuable support in the form of Junior and Senior Research Fellowships.

Finally I would like to thank in a special way my Parents, Brother, Sisters and Brothers-in-law who extended support, encouragement, love and appreciation throughout my research work to excel in whatever I did.

Rodney A. Fernandes

QUOTED

It gives me immense pleasure to compile my research work of the last few years, working in the Division of Organic Chemistry: Technology, National Chemical Laboratory, Pune, India in this thesis. I had the unique experience of the difference in framing schemes on paper and practically executing them. Research, I feel is a combination of lot of patience, a proper understanding of work, systematic execution of ideas, imagination and proper diagnosis of failures to hunt for a reasonable solution. I am obliged for the encouragement and appreciation from my research mentor, Dr. Pradeep Kumar who introduced me to one of the fascinating areas of the last decade, the "Sharpless Asymmetric Dihydroxylation". I remember here when I said in one of the group meetings- 'it is a fascinating reaction involving several reagents working collectively', my research mentor quoted "it is a fascinating reaction being carried

out in water".

Asymmetric Epoxidation Asymmetric Dihydroxylation

Prof. K. B. Sharpless

I wish to quote a few words on Prof. K. Barry Sharpless, Scripps Research Institute, of whom I am very much fond about. His pioneering work on "Chirally catalyzed oxidations" bagged him the Nobel Prize in part in Chemistry for the year 2001. The renowned reactions-'Sharpless Asymmetric Epoxidation' and 'Sharpless Asymmetric Dihydroxylation' (SAD) have opened the gateway to several complex natural product syntheses. I had an opportunity to employ the SAD reaction towards the asymmetric syntheses of a few bioactive molecules and compile it in this thesis for the award of the degree of Doctor of Philosophy in Chemistry.

While Mother Nature, an architect par excellence has her own ways of synthesizing several bioactive compounds, the synthetic organic chemist will always be bold to explore the hidden mysteries and work in parallel with Mother Nature.

--Rodney
June 2002

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ABBREVIATIONS

Ac	Acetyl
Ac_2O	Acetic anhydride
aq.	Aqueous
AD	Asymmetric dihydroxylation
Bn	Benzyl
Bu	Butyl
t-Bu	*tert*-Butyl
Bz	Benzoyl
ca.	Calculated
cat.	Catalytic/ Catalyst
$CDCl_3$	Deuterated chloroform
conc.	Concentrated
CPO	Choloroperoxidase
CSA	Camphorsulfonic acid
DET	Diethyltartrate
D_2O	Deuterium oxide
de	Diastereomeric excess
ds	Diastereoselectivity
DHP	Dihydropyran
$(DHQ)_2PHAL$	1,4-Bis(dihydroquinin-9-*O*-yl)phthalazine
$(DHQD)_2PHAL$	1,4-Bis(dihydroquinidin-9-*O*-yl)phthalazine
DIBAL-H	Diisobutyl aluminium hydride
DMAP	N,N-(Dimethylamino)pyridine
DMF	N,N-Dimethyl formamide
DMSO	Dimethyl sulfoxide
ee	Enantiomeric excess
EIMS	Electron impact mass spectrum
eq. or equiv	Equivalents
Et	Ethyl
EtOAc	Ethyl acetate
Et_3N	Triethyl amine
g	Grams
GLC	Gas liquid chromatography
h	Hours
HLADH	Horse liver alcohol dehydrogenase
Hz	Hertz
i-Pr	Isopropyl
IR	Infrared
M^+	Molecular ion
m-CPBA	*m*-Chloroperbenzoic acid
Me	Methyl
MeCN	Acetonitrile
mg	Milligram
min	Minutes
mL	Millilitre

mmol	Millimole
M.p.	Melting point
Ms	Methanesulfonyl
NBS	N-Bromosuccinimide
NIS	N-Iodosuccinimide
NMO	N-Methyl morpholine N-oxide
NMR	Nuclear magnetic resonance
PCC	Pyridinium chlorochromate
PFL	*Pseudomonas fluorescens* lipase
Piv	Pivaloyl
PhH	Benzene
PhMe	Toluene
PLE	Pig liver esterase
PMB	*p*-Methoxybenzyl
PPL	Porcine pancreatic lipase
ppm	Parts per million
PPTS	Pyridinium *p*-toluene sulfonate
p-TsOH	*p*-Toluene sulfonic acid
Pyr	Pyridine
rt	Room temperature
Rf	Retention factor
SAD	Sharpless asymmetric dihydroxylation
SAE	Sharpless asymmetric epoxidation
satd.	Saturated
TBAF	Tetrabutyl ammonium fluoride
TBAI	Tetrabutyl ammonium iodide
TBDMS	*tert*-Butyl dimethylsilyl
TBDPS	*tert*-Butyl diphenylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMS	Tetramethylsilyl
Tr	Trityl
Ts	*p*-Toluene sulfonyl

ABSTRACT

The Thesis entitled "**Asymmetric Dihydroxylation Approach to the Enantioselective Syntheses of Bioactive Molecules and PCC Mediated Oxidative Organic Transformation**" is divided into five chapters.

Chapter 1: describes a brief introduction to the Sharpless asymmetric dihydroxylation (SAD) and cyclic sulfites/sulfates as synthetic intermediates.

Chapter 2: deals with the enantioselective synthesis of β−hydroxy−δ−lactones and is divided into two sections.

Chapter 3: constitutes the asymmetric synthesis of vicinal amino alcohols and is divided into two sections.

Chapter 4: includes the enantioselective synthesis of chiral epoxides *via* asymmetric dihydroxylation and is divided into two sections.

Chapter 5: examines a new PCC-mediated unusual C-C bond cleavage reaction during oxidation of homobenzylic alcohols.

Chapter 1: Asymmetric Dihydroxylation and Cyclic Sulfites/Sulfates as Synthetic Intermediates.

This chapter gives a brief introduction to Sharpless asymmetric dihydroxylation (SAD) reaction and cyclic sulfites/sulfates as synthetic intermediates. Catalytic asymmetric reactions provide an especially practical entry into the chiral world due to their economical use of asymmetric inducing agents. Especially useful is the carbon-heteroatom bond forming reactions, since the resulting functionality can be readily manipulated to produce many important classes of compounds. The SAD reaction is one such reaction developed in early 1990.[1] It has evolved as one of the most powerful methods for enantioselective oxidation of olefins to optically active vicinal diols that are versatile and convenient building blocks in the synthesis of bioactive compounds.

In this chapter, the development of SAD reaction from stoichiometric to catalytic version, the mechanism, reaction conditions and varied ligands used along with recent applications will be covered. In our synthetic endeavors we have employed the chiral diol compounds obtained by SAD reaction towards the synthesis of β−hydroxy−δ−lactones,

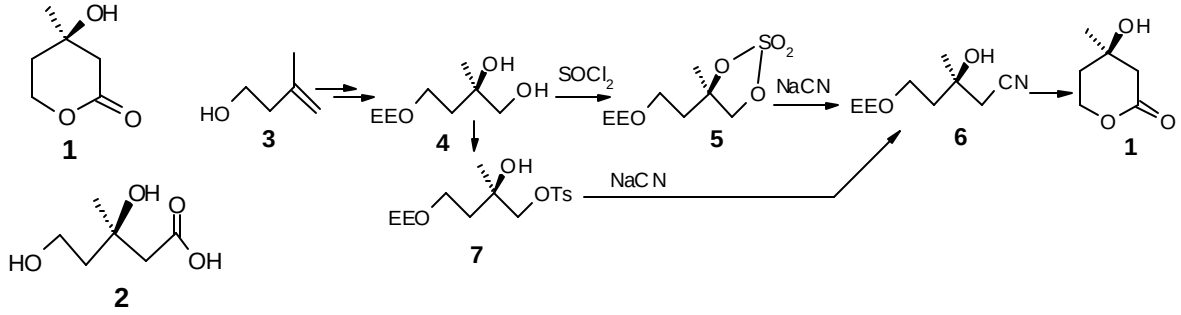
vicinal amino alcohols and chiral epoxides. To bring about the functional group changes we have also employed the chemistry of cyclic sulfites/sulfates as intermediates.[2] This chapter will also cover the synthesis, reactivity and applications of cyclic sulfites/sulfates as synthetic intermediates.

Chapter 2: Enantioselective Synthesis of b - Hydroxy - d - Lactones

This chapter deals with the asymmetric synthesis of β−hydroxy−δ−lactones and is divided into two sections.

Section A: Enantioselective Synthesis of (*R*)-Mevalonolactone

Mevalonolactone **1** or its open form, mevalonic acid **2** is the biosynthetic precursor of most terpenoids, steroids, carotenoids, isoprenoids and pentanoids.[3] Mevalonolactone was first discovered and synthesized by resolution method by Folkers and coworkers.[4] We have employed a five-step strategy for the synthesis of (*R*)-mevalonolactone (**Scheme 1**).



Scheme 1

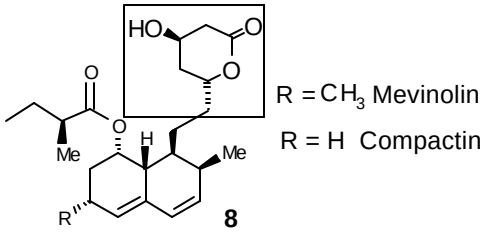
The hydroxyl protection of **3** and Sharpless asymmetric dihydroxylation to diol **4**, followed by regioselective nucleophilic opening of cyclic sulfate intermediate **5** with cyanide nucleophile to give **6** are the key steps in the synthesis. Basic hydrolysis of **6** followed by acidic hydrolysis resulted in deprotection of ethoxy ethyl ether and concomitant cyclization to give (*R*)-mevalonolactone **1**. The compound **6** was also synthesized from tosyl compound **7** by nucleophilic displacement with cyanide.

Thus, a short and efficient practical synthesis of (*R*)-mevalonolactone is achieved.

Section B: Enantioselective Synthesis of the Lactone Moiety of HMG-CoA Reductase Inhibitors-Compactin and Mevinolin

Cholesterol biosynthesis inhibition has become a powerful tool to lower plasma cholesterol high levels. 3-Hydroxy-3-methyl-glutaryl coenzyme reductase (HMGR) is a target of choice, because it is the early rate-limiting step in the biosynthesis of cholesterol.

Mevinolin and compactin **8** are specific inhibitors of HMGR and are effective in lowering blood plasma cholesterol levels.[5]



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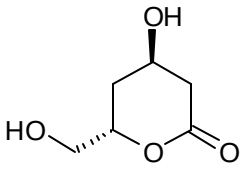

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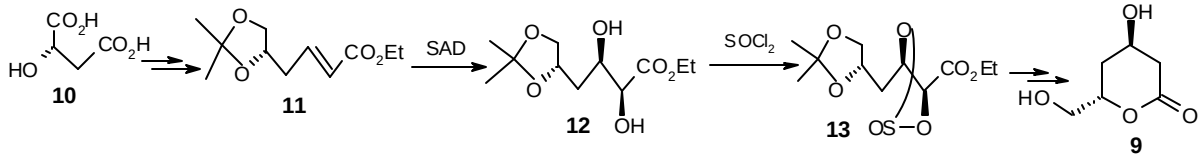
The key structural feature in HMGR inhibitors is the β−hydroxy−δ−lactone moiety **9** that is connected to a functionalized decalin unit *via* an ethylene bridge. In this section the asymmetric synthesis of the β−hydroxy−δ−lactone moiety **9**[6] is described. (*S*)-Malic acid **10** serves to establish the stereochemistry at C-6, while the C-4 hydroxyl is arrived at through the regioselective hydride opening of cyclic sulfite **13**. The synthetic route is depicted in **Scheme 2**.



Scheme 2

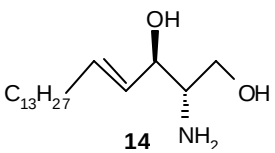
Thus, a short and efficient asymmetric synthesis of the β−hydroxy−δ−lactone moiety of mevinic acids-compactin and mevinolin, with requisite stereochemistry at C-4 and C-6 has been achieved.

Chapter 3: Asymmetric Synthesis of Vicinal Amino Alcohols: Dihydrosphingosine and Phytosphingosines

The vicinal amino alcohol moiety is the key structural feature in a variety of bioactive molecules.[7] This chapter summarizes our studies on the asymmetric synthesis of dihydrosphingosine and phytosphingosines and is divided into two sections.

Section A: Enantioselective Synthesis of D-(+)-*erythro*-Dihydrosphingosine

Sphingosine **14** and its biosynthetic precursor dihydrosphingosine (sphinganine, **15**) are long chain amino alcohols forming the backbone structures for complex molecules called sphingolipids. Dihydrosphingosine and related long chain bases display potent inhibiting properties of protein kinase C both *in vivo* and *in vitro* and thus play a pivotal role in cell recognition, cell growth modulation and signal transmission.[8]



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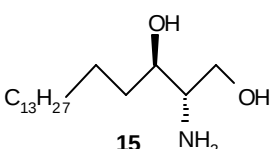

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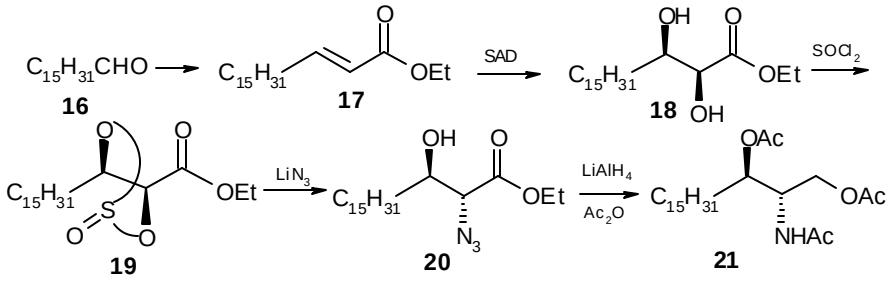
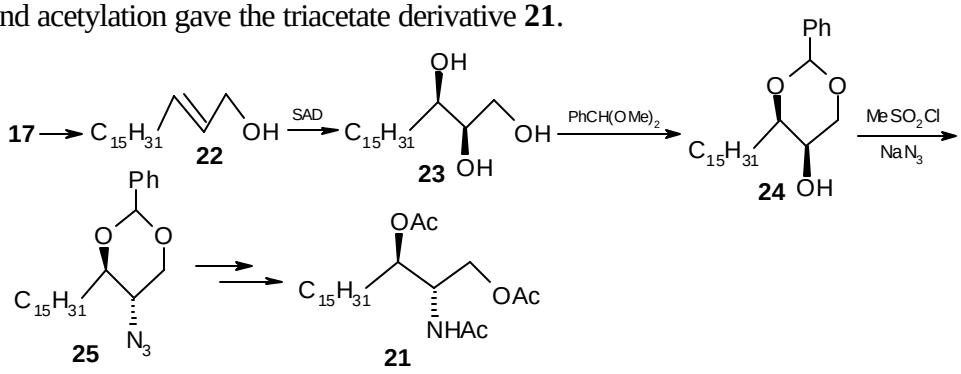
We have employed the asymmetric dihydroxylation process to convert prochiral olefin to chiral diol and regioselective opening of cyclic sulfite derived there from, towards the asymmetric synthesis of D-(+)-*erythro*-dihydrosphingosine **15** (**Scheme 3**).



Scheme 3

Asymmetric dihydroxylation of olefin **17** gave diol **18**. Diol **18** was converted into cyclic sulfite **19**, which was opened regioselectively with azide nucleophile to give **20**. Dual reduction of ester and azide functionality in **20** with $LiAlH_4$ gave D-(+)-*erythro*-dihydrosphingosine **15**, which was isolated by converting into triacetate derivative **21**.

Alternatively, the C-2 chirality of **15** was arrived by selective 1,3-benzylidene formation as shown in **Scheme 4**. Asymmetric dihydroxylation of allylic alcohol **22** gave triol **23**. Selective protection of 1,3-hydroxyls as cyclic benzylidene, followed by conversion of C-2 hydroxyl into the azido functionality gave **25**. Subsequent deprotection of benzylidene, reduction and acetylation gave the triacetate derivative **21**.

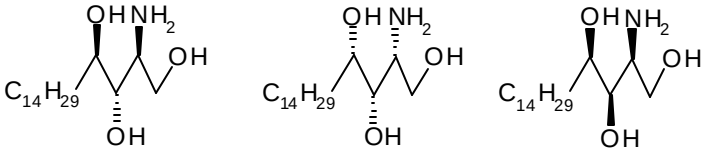


Scheme 4

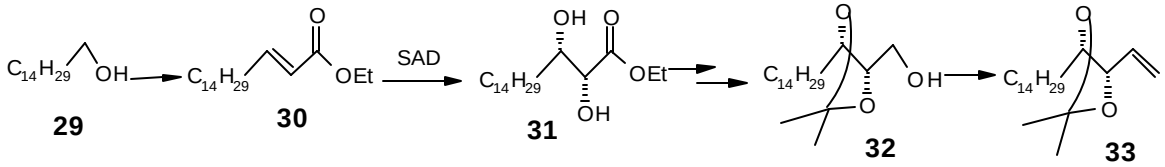
Thus, a short and practical asymmetric synthesis of dihydrosphingosine has been achieved through asymmetric dihydroxylation either by employing a cyclic sulfite intermediate or a cyclic benzylidene intermediate.

<u>Section B:</u> Double Diastereoselection in Asymmetric Dihydroxylation: Application to the Diastereoselective Synthesis of C_{18}-Phytosphingosines.

Phytosphingosine **26** exists abundantly as one of the molecular species of sphingolipids in microorganisms, plants and many mammalian tissues. In addition to its structural function as the long-chain base of sphingolipids in membranes, phytosphingosine itself is a bioactive lipid, a potential heat stress signal in yeast cells. Of the eight C_{18}-phytosphingosine isomers (*ribo*-, *arabino*-, *xylo*- and *lyxo*-series) most synthetic studies have been focused primarily on the preparation of *ribo*- or *arabino*-phytosphingosines. No report on the asymmetric synthesis of L-*xylo*-[2*R*,3*S*,4*S*]-C_{18}-phytosphingosine **27** was known until we arrived at its first synthesis.



Like many other reactions including the Sharpless asymmetric epoxidation and the Sharpless asymmetric dihydroxylation of olefins, the pre-existing chiral information in the substrate has a marked influence on the stereoselective outcome of the reaction. With a view to exploit the concept of double diastereoselection, we prepared the enantiomerically enriched terminal olefin **33** (and its enantiomer **34**) as shown in **Scheme 5**.



Scheme 5

Asymmetric dihydroxylation of olefin **30**, dihydroxyl protection, ester reduction followed by oxidation of alcohol **32** to aldehyde and subsequent Wittig olefination provided the terminal olefin **33**. Similarly **34** was prepared by β-dihydroxylation of olefin **30** and following the same reaction steps as described for **33**.

The olefins **33** and **34** have been subjected to asymmetric dihydroxylation by employing different ligands. The influence of existing chirality and ligand induction in matched and mismatched cases have been studied (**Table 1**).

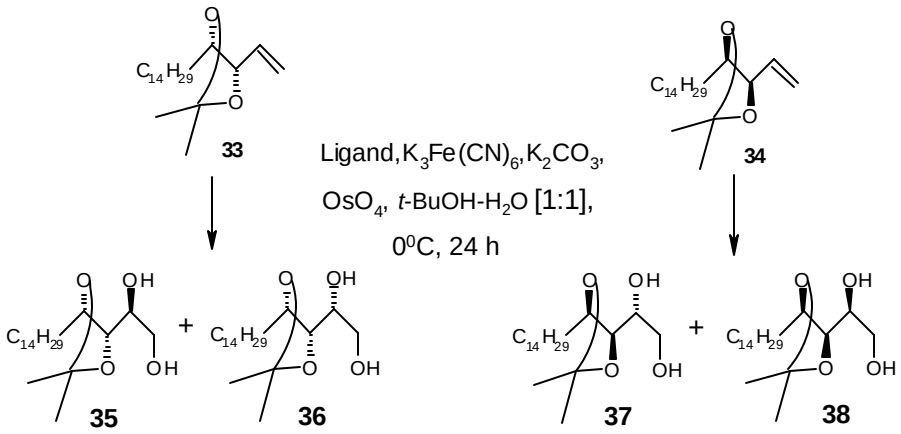
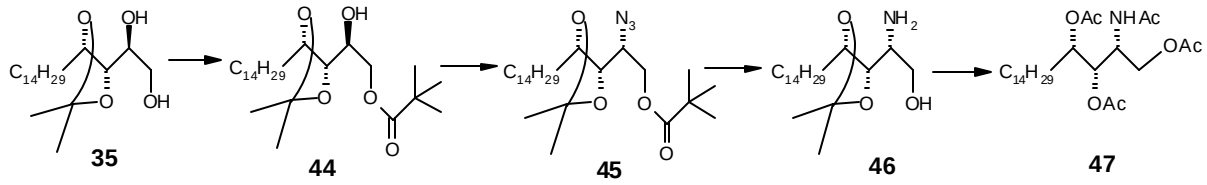


Table 1: Double diastereoselection in AD of olefins 33 and 34.

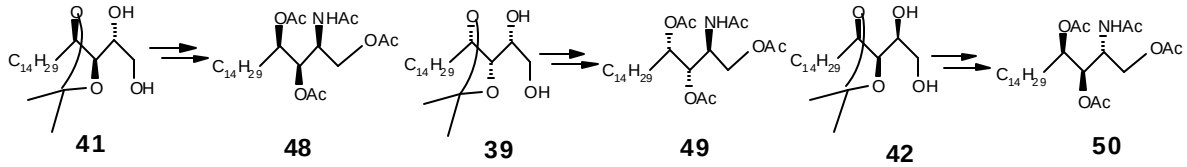
Substrate	Ligand	**35**	**36**	**37**	**38**	Yield %	Diastereomeric mixture
33	$(DHQ)_2PHAL$	1	2	-	-	89	**39** $[\alpha]_D^{20}$ – 17.3 (c = 1, $CHCl_3$)
33	$(DHQD)_2PHAL$	5	1	-	-	92	**40** $[\alpha]_D^{20}$ – 19.5 (c = 1, $CHCl_3$)
33	$(DHQD)_2AQN$	6	1	-	-	69	Pure diastereomer **35** $[\alpha]_D^{20}$ – 20.1 (c = 1, $CHCl_3$)
34	$(DHQ)_2PHAL$	-	-	5.45	1	93	**41** $[\alpha]_D^{20}$ + 20.3 (c = 1, $CHCl_3$)
34	$(DHQD)_2PHAL$	-	-	1	2	92	**42** $[\alpha]_D^{20}$ + 18.2 (c = 1, $CHCl_3$)
34	Pyridine	-	-	4.3	1	83	**43** $[\alpha]_D^{20}$ + 18.7 (c = 1, $CHCl_3$)

The diastereomeric mixture containing **35** and **36** (6:1) was separated by flash column chromatography and pure diastereomer **35** was employed in the total synthesis of L-*xylo*-[2*R*,3*S*,4*S*]-C_{18}-phytosphingosine **27** as shown in **Scheme 6** as the tetraacetate **47**.



Scheme 6

Selective mono-hydroxyl protection of **35** as pivaloate followed by conversion of C-2 hydroxyl into azido gave **45** with inversion at C-2 center. Reduction of **45** afforded **46**. In an attempt to make **46** directly from **33**, we tried aminohydroxylation, however it gave a complex mixture of unisolable products. Hydrolysis of acetonide in **46**, followed by acetylation furnished the target compound **27** as the tetraacetate **47**. Similarly **28** was prepared from **41** as the tetraacetate **48** obtained in 5.45:1 ratio, following the reaction steps as in **Scheme 6**. This was separated by flash column chromatography to give **48** in diastereomerically pure form. Similarly diastereomeric mixtures **39** and **42** were converted into **49** and **50** (33% de) respectively.



Thus, we have exploited the concept of double diastereoselection in SAD reaction and applied the results obtained toward the synthesis of four of the eight isomers of phytosphingosine.

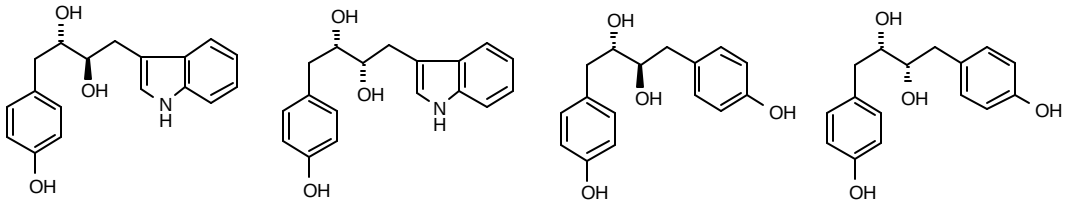
Chapter 4: Enantioselective Synthesis of Chiral Epoxides *via* Asymmetric Dihydroxylation: Synthesis of (+)-Diolmycin A2 and (+)- and (-)-Posticlure.

Epoxides are versatile intermediates in organic synthesis, while many bioactive molecules contain the epoxide function as well. This chapter describes methods to convert a chiral diol into epoxide intermediate which is further extrapolated towards the asymmetric synthesis of (+)-diolmycin A2 and both enantiomers of posticlure. This chapter is divided into two sections.

Section A: Enantioselective Synthesis of (+)-Diolmycin A2

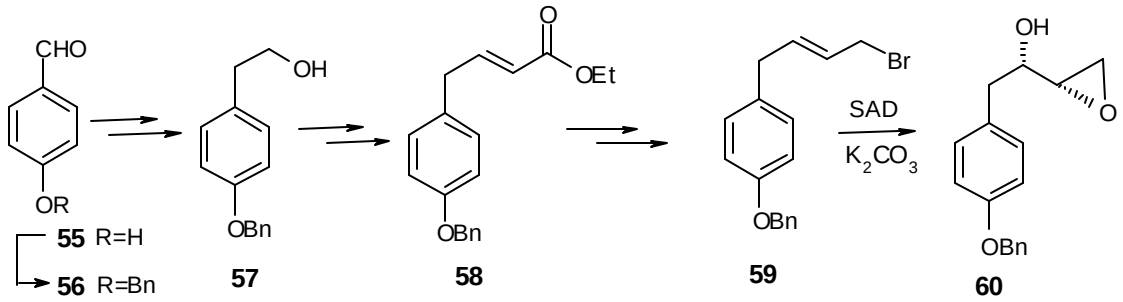
With a search for new anticoccidial agents, Omura and coworkers isolated diolmycin A1, A2, B1, and B2 (**51**-**54**) from a fermentation broth of *Streptomyces* sp.WK-2955.[9] Omura *et*

al.[10] reported the first total synthesis of Diolmycin A1 **51** as the racemate and then reported an asymmetric synthesis.[11]



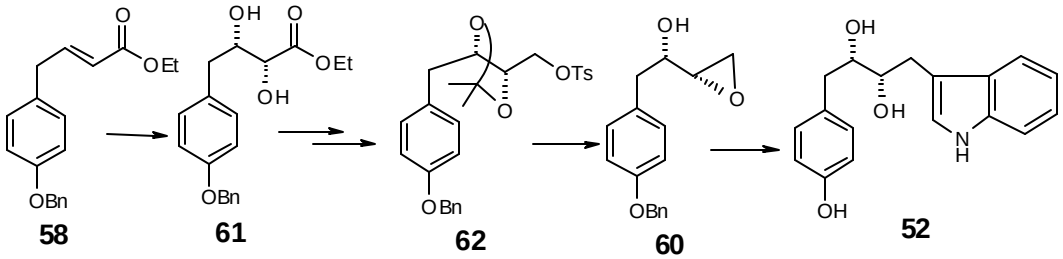
51 Diolmycin A1 **52** Diolmycin A2 **53** Diolmycin B1 **54** Diolmycin B2

The use of chiral pool materials, such as L-tartaric acid for the preparation of diolmycin A2 **52** has recently been reported by Kotsuki *et al.*[12] Diolmycin A2 **52** has *threo*-diol configuration which could easily be derived by asymmetric dihydroxylation. In view of this, an asymmetric synthesis of diolmycin A2 **52** was undertaken as shown in **Schemes 7** and **8**.



Scheme 7

Thus, in **Scheme 7**, the asymmetric dihydroxylation of **59** under buffered conditions gave the dihydroxybromide, which on subsequent base treatment gave the epoxide **60**.



Scheme 8

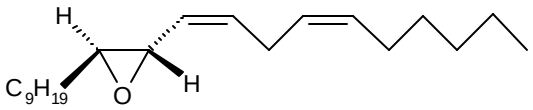
Alternatively, the epoxide **60** could be obtained from **58** following the reaction steps as shown in **Scheme 8**. The dihydroxylation of olefin **58** using the Sharpless asymmetric dihydroxylation procedure gave the diol **61**. The dihydroxyl protection, ester group reduction and tosylation furnished **62**. Deprotection of the acetonide and subsequent treatment with K_2CO_3 afforded the epoxide **60**. From here, we carried out the regioselective C-3 alkylation of indole, by employing a Lewis acid, $SnCl_4$ and a mixture of solvents like CH_2Cl_2 and CH_3NO_2. The solubility of the indole-Lewis acid complex has been greatly

increased by the use of CH_3NO_2 solvent thereby lowering the reaction time and raising the yields. The subsequent debenzylation afforded (+)-diolmycin A2 **52**.

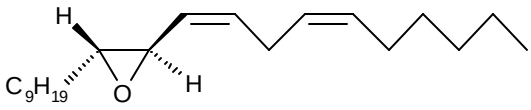
Thus, a short and efficient synthesis of (+)-diolmycin A2 **52** has been achieved, employing the SAD reaction and regioselective C-3 indole coupling routes.

Section B: Enantioselective Synthesis of (+)- and (-)-Posticlure

Wakamura *et al.*[13] isolated for the first time in the history of epoxide pheromones a novel *trans*-epoxide pheromone from the virgin females of the tussock moth, *Orgyia postica* and identified it as (6*Z*,9*Z*,11*S*,12*S*)-*trans*-11,12-epoxyhenicosa-6,9-diene **63a** and named it as posticlure after the species name. Wakamura *et al.*[13] also reported the first synthesis by employing Sharpless asymmetric epoxidation reaction and obtained the pheromone only in 59% ee. The pure sample was obtained by preparative HPLC.

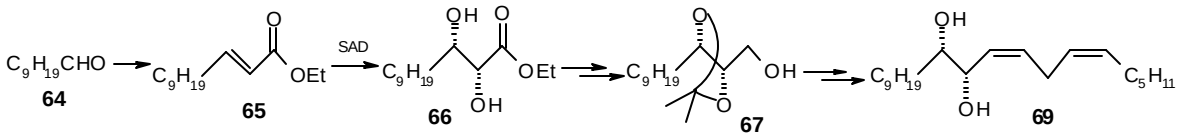


(-)-Posticlure **63a**



(+)-Posticlure **63b**

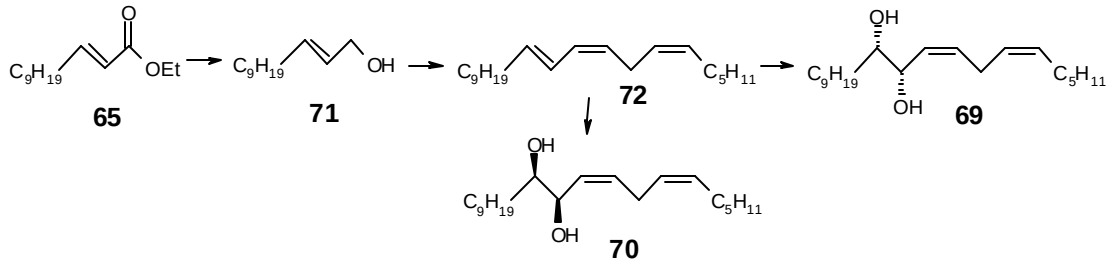
Since a chiral diol obtained by SAD reaction can be converted into an epoxide stereospecifically,[14] we designed an asymmetric synthesis of both enantiomers of posticlure by employing SAD reaction and one–pot epoxidation as shown in **Schemes 9-11**.



Scheme 9. (*Z*)-$C_5H_{11}CH{=}CHCH_2CH_2P^+Ph_3I^-$ **68**

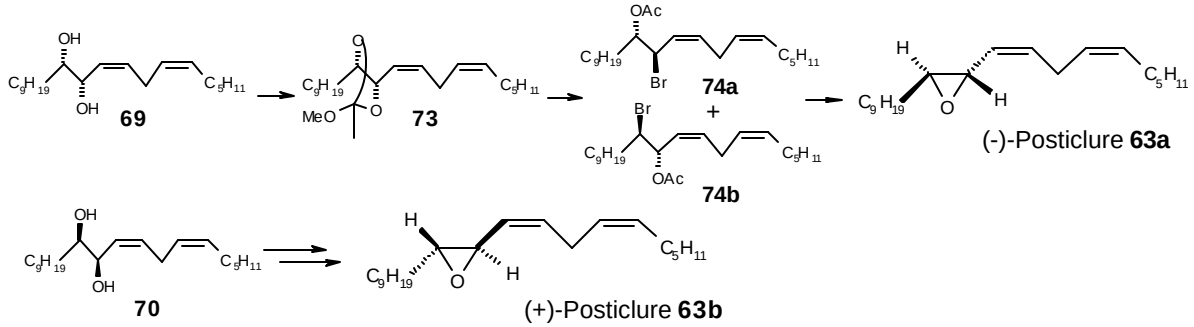
In **Scheme 9**, the intermediate diol **69** is synthesized. Asymmetric dihydroxylation of **65**, followed by dihydroxyl protection and reduction of ester gave **67**. Oxidation of alcohol and subsequent Wittig reaction with **68** followed by acetonide deprotection furnished **69**. Similarly the enantiomer of **69** i.e. **70** was synthesized by β-dihydroxylation of olefin **65** and following the same route as for **69**.

Alternatively, the diols **69** or **70** were synthesized by selective mono-dihydroxylation of a triene system like **72** as shown in **Scheme 10**. Selective mono-α-dihydroxylation of **72** gave **69**, while mono-β-dihydroxylation gave **70**.



Scheme 10

The diol **69** was converted into the epoxide pheromone (–)-posticlure **63a** *via* bromoester intermediates **74** as shown in **Scheme 11**. Similarly the diol **70** was converted into the enantiomer of **63a** i.e. **63b**.



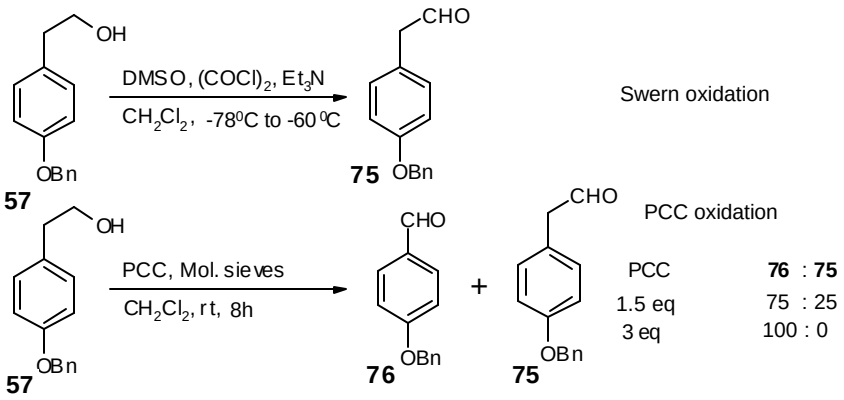
Scheme 11

Thus, a highly enantioselective synthesis of both enantiomers of a novel first *trans*-epoxide pheromone posticlure has been achieved.

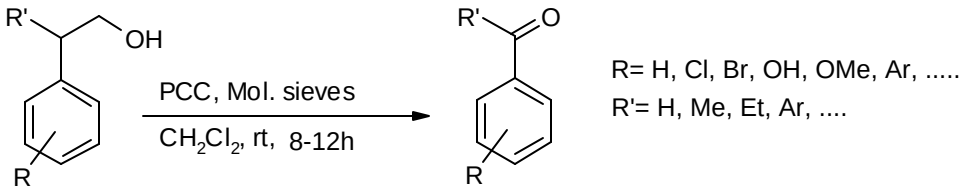
Chapter 5: A new PCC Mediated Unusual C-C Bond Cleavage During Oxidation of Homobenzylic Alcohols Leading to Benzylic Carbonyl Compounds.

Pyridinium chlorochromate (PCC) is a well-known oxidizing agent, converting alcohols to aldehydes or ketones with high efficiency.[15] Several rearrangements and useful conversions are known with PCC. All these make PCC a versatile oxidant in organic synthesis.[16]

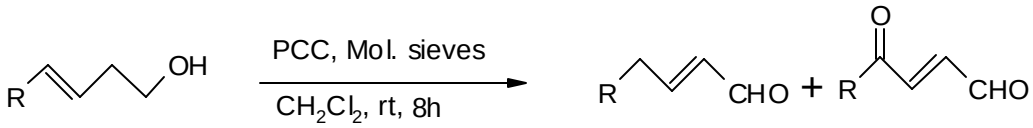
While working on the total synthesis of diolmycin A2, the oxidation of homobenzylic alcohol **57** under Swern oxidation conditions gave the expected aldehyde **75**. However when PCC was employed as an oxidant (1.5 equivalents), a mixture of **76** and **75** was obtained in 75:25 ratio. When PCC (3 equivalents) was used, the aldehyde **76** was the only product with no trace of **75**.



Thus, there is scission of C-C bond leading to the loss of one carbon atom and yet, to add to our enthusiasm the end product is an aldehyde without further oxidation. Several homobenzylic alcohols irrespective of aryl substituents and having no benzylic substitution on oxidation with PCC (3 equivalents), afforded the benzylic aldehydes in moderate to good yields. In order to understand better the scope of this oxidation, we elaborated the reaction on homobenzylic alcohols with substitution at benzylic position such that if degradation occurred, the end product would be a ketone. Indeed, this oxidation gave ketone as the only compound. Several such compounds are also covered in this chapter.



To elaborate further, when homoallylic alcohols were oxidized under similar conditions no degradation of carbon was observed. However the migration of double bond to α,β-position of carbonyl compound was observed. While in some cases 1,4-dicarbonyl-2*E*-ene products were formed from further allylic oxidation.



This kind of migration is not possible with homobenzylic alcohols, as it would destroy aromaticity. Both results are complementary and are new additions to the plethora of reactions brought about by PCC. This method should find widespread application in organic synthesis.

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Publications:

[1] 'Asymmetric Synthesis of (S)-Massoialactone'

Godwin, C. G. Pais, **Rodney A. Fernandes** and Pradeep Kumar

Tetrahedron **1999**, *55*, 13445-13450

[2] 'Enantioselective Synthesis of (*R*)-(−)-Mevalonolactone via Cylcic Sulfate Methodology'

Rodney A. Fernandes and Pradeep Kumar

Tetrahedron Asymmetry **1999**, *10*, 4349-4356

[3] 'A Short and Efficient Stereoselective Synthesis of Dihydrosphingosine Triacetate'

Rodney A. Fernandes and Pradeep Kumar

Tetrahedron Asymmetry **1999**, *10*, 4797-4802

[4] 'A Stereoselective Synthesis of Dihydrosphingosine'

Rodney A. Fernandes and Pradeep Kumar

Eur. J. Org. Chem. **2000**, 3447-3449

[5] 'Double Stereodifferentiation in Asymmetric Dihydroxylation: Application to the First Diastereoselective Synthesis of L-xylo-[2R,3S,4S]-C_{18}-Phytosphingosine'

Rodney A. Fernandes and Pradeep Kumar

Tetrahedron Lett. **2000**, *41*, 10309-10312

[6] 'Asymmetric Dihydroxylation and Regioselective C-3 Indole Coupling Routes to the Anticoccidial Antibiotic (+)-Diolmycin A2'

Rodney A. Fernandes, Mandar S. Bodas and Pradeep Kumar

Tetrahedron **2002**, 58, 1223

[7] 'An Asymmetric Dihydroxylation Route to Enantiomerically Pure Norfluoxetin and Fluoxetin'

Rajesh, K. Pandey, **Rodney A. Fernandes** and Pradeep Kumar

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[8] 'Asymmetric Dihydroxylation and One-Pot Epoxidation Routes to (+)- and (−)-Posticlure: a Novel *trans*-Epoxide as a Sex Pheromone Component of *Orgyia postica* (Walker)'

Rodney A. Fernandes and Pradeep Kumar

Tetrahedron **2002**, in press

[9] 'A Concise Synthesis of (+)-Compactin Lactone *via* Asymmetric Dihydroxylation and Regioselective Cyclic Sulfite Opening Reactions.

Rodney A. Fernandes and Pradeep Kumar

Eur. J. Org. Chem. **2002**, in press

[10] 'Double Stereodifferentiation in Asymmetric Dihydroxylation: Application to the Diastereoselective Syntheses of C_{18}-Phytosphingosines'

Rodney A. Fernandes and Pradeep Kumar

Communicated

[11] 'A New PCC Mediated Oxidation Reactions of Homobenzylic and Homoallylic Alcohols'

Rodney A. Fernandes and Pradeep Kumar

Communicated

[12] 'Enantioselective Synthesis of Oxybutynin *via* Asymmetric Dihydroxylation of α-Cyclohexyl Styrene'

Priti Gupta, **Rodney A. Fernandes** and Pradeep Kumar.

Manuscript in preparation.

[13] 'An Asymmetric Dihydroxylation Route to Denopamine, Tembamide and Aegeline'

Rodney A. Fernandes, Ramalingam, S. and Pradeep Kumar

Manuscript in preparation.

[14] An improved process for the preparation of (4*R*,6*S*)-4-Hydroxy-6-hydroxymethyl-tetrahydropyran-2-one, *US Patent*, Patent No. 6,376,683.

April 23, 2002.

Pradeep Kumar and **Rodney A. Fernandes**

Symposia/Conferences Attended:

[1] 'An Efficient Stereoselective Synthesis of Dihydrosphingosine: A Protein Kinase C Inhibitor'. 5th IUPAC International Symposium in Bioorganic Chemistry, ISBOC-5, NCL, Pune, India, Jan. 30-Feb. 4, 2000. Poster. No. 38.

[2] 'Enantioselective Synthesis of the Lactone Moiety of HMGR Inhibitors'. 5th IUPAC International Symposium in Bioorganic Chemistry, ISBOC-5, NCL, Pune, India, Jan. 30-Feb. 4, 2000. Poster. No. 39.

[3] 'Double Stereodifferentiation in Asymmetric Dihydroxylation: Application to the Diastereoselective Synthesis of Phytosphingosines'. Third National Symposium in Chemistry (NSC-3), Punjab University, Chandigarh, India, Feb. 2-4, 2001. Poster. No. 152.

[4] National Symposium on Recent Advances in Natural Product Chemistry, Garhwal University, Srinagar, Uttaranchal, India, Nov. 5-7, 2001 (Participated).

[5] National Bioorganic Symposium-7, GND University, Amritsar, Nov. 9-10, 2001 (Participated).

[6] Fourth National Symposium in Chemistry (NSC-4), National Chemical Laboratory, Pune, India, Feb. 1-3, 2002 (Participated).

Awards:

[1] The "**Dr. Rajappa Award**" to the Research Student for the Best Research Paper in Organic Chemistry, Year 2000, NCL Research Foundation.
Paper Entitled: "Double Stereodifferentiation in Asymmetric Dihydroxylation: Application to the First Diastereoselective Synthesis of L-xylo-[2R,3S,4S]-C_{18}-Phytosphingosine"
Rodney A. Fernandes and Pradeep Kumar, Tetrahedron Lett. **2000**, 41, 10309-*10312*
Awarded on 28th February 2001, National Science Day.

[2] The "**Keerti Sangoram Endowment Award**" for Best Research Scholar of the Year 2001 (Chemical Sciences), NCL Research Foundation. **Rodney A. Fernandes**
Awarded on 3rd January 2002, NCL Foundation Day.43

CHAPTER 1

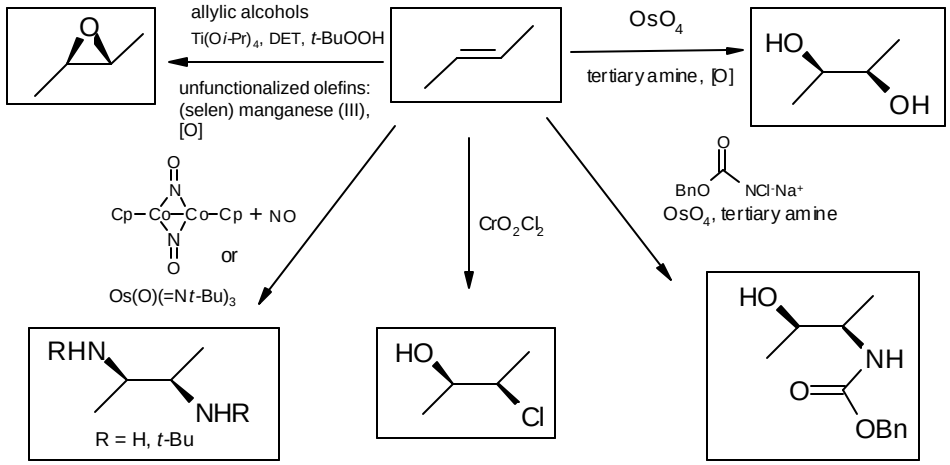
ASYMMETRIC DIHYDROXYLATION AND CYCLIC SULFITES/SULFATES AS SYNTHETIC INTERMEDIATES

1.1. ASYMMETRIC DIHYDROXYLATION (SAD)

1.1.1. Introduction

Nature, an architect par excellence, produces hundreds of compounds through a variety of biogenetic pathways and quite a few of them have attracted the synthetic organic chemist's attention due to their remarkable structural features and/or the conferred specific bioactivity. Asymmetric synthesis of bioactive molecules is in the forefront of synthetic organic chemistry due to its varied applications in drug and pharmaceutical industries and biotechnologies.

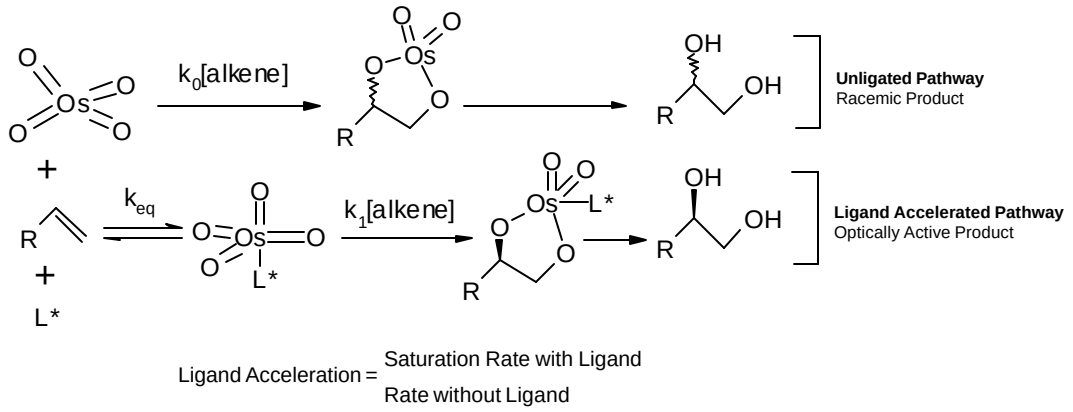
In the last two decades, many powerful asymmetric reactions have emerged as a result of the growing need to develop efficient and practical syntheses of biologically active compounds. Catalytic asymmetric reactions provide an especially practical entry into the chiral world due to their economical use of asymmetric inducing agents.[1] Especially useful is the carbon-heteroatom bond forming reaction, since the resulting functionality can be readily manipulated to produce many important classes of compounds. It is not surprising, therefore, that the oxidative addition of heteroatoms to olefins has been a fruitful area in recent years (**Scheme 1**).



Scheme 1. Transition metal mediated suprafacial 1,2-difunctionalization of olefins.

A number of transition metal-mediated methods for the epoxidation,[2] oxidative cyclization,[3] halohydrin formation,[4] dihydroxylation[5] and aminohydroxylation[6] have emerged. A common feature of most of these processes is the phenomenon of *ligand acceleration*,[7] wherein a metal-catalyzed process turns over faster in the presence of a co-ordinating ligand (**Scheme 2**). This causes the reaction to be funneled through the ligated pathway with the additional consequence

that the ligand may leave its 'imprint' on the selectivity determining step. Hence, the ligand can influence the chemo-, regio-, and stereoselectivity of the reaction in a profound way.



Scheme 2. Ligand accelerated catalysis-dihydroxylation of olefins.[7]

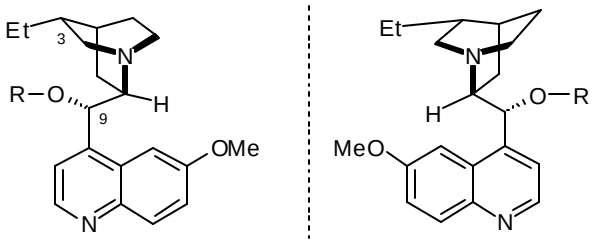
The osmium tetroxide-catalyzed asymmetric dihydroxylation (AD) of olefins, embedding two hydroxyl groups in a hydrocarbon framework is perhaps one of the most reliable and selective transformations in organic chemistry. In his pioneering work on the stoichiometric reaction of OsO_4 with olefins, Criegee[8] showed that pyridine accelerated the reaction considerably. However, cost considerations made the stoichiometric osmylation uneconomical. Not surprisingly, catalytic variants of the reaction, which employ relatively inexpensive reagents for the re-oxidation of the osmium (VI) glycolate products, greatly enhance its synthetic utility.[5b] Inorganic co-oxidants such as sodium or potassium chlorate[9a] or hydrogen peroxide,[9b,c] were among the first to be introduced, but in some cases diminished yields resulted due to over-oxidation. Much better results were obtained with alkaline *t*-BuOOH, introduced by Sharpless and Akashi,[10] or *N*-methylmorpholine *N*-oxide (NMO) (Upjohn Process).[11] Tsuji *et al.*[12] demonstrated that $K_3Fe(CN)_6$ in the presence of K_2CO_3 provides a powerful system for the osmium-catalyzed dihydroxylation of olefins.

Initial efforts by Sharpless and Hentges to induce enantioselectivity in the osmylation with chiral pyridine derivatives failed due to the low affinity of these ligands for OsO_4.[13] It was found that the binding constant of a ligand is extremely sensitive to the steric hindrance near the reacting center. Consequently, quinuclidine derivatives were used instead of pyridines for further investigations due to their intrinsically higher affinity for OsO_4.[14] Moderate to good enantiomeric excess using acetate esters of cinchona alkaloids as chiral ligands was obtained.[13]

Apart from the cinchona alkaloid catalyzed AD, there are a number of methods employing chiral monodentate[15] and bidentate diamine[16] ligands. Despite the good to excellent

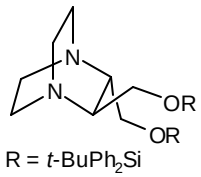
enantioselectivities that can be obtained with diamine ligands, a serious drawback results from their bidentate nature, that they form very stable chelate complexes with Os (VI) glycolate products and as a consequence prevent *in situ* recycling of the Os and the ligand. Thus, all the reactions involving bidentate ligands are stoichiometric in both OsO_4 and the chiral ligand[16] (**Figure 1**).

(a) Cinchona Alkaloid Ligands for AD under *Catalytic* Conditions[13,17,19,20]



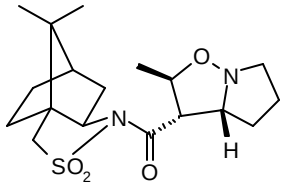
Dihydroquinidine (R = H) DHQD | Dihydroquinine (R = H) DHQ

(b) Monodentate Ligands for AD under *Catalytic* Conditions



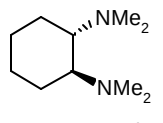
R = *t*-$BuPh_2Si$

Hirama *et al.*[15]

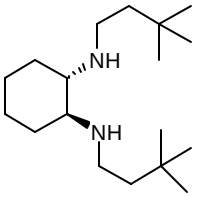


Murahashi *et al.*[16n]

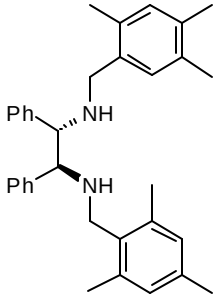
(c) Chiral Diamine Ligands for AD under *Stoichiometric* Conditions



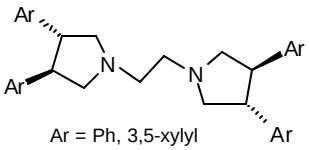
Snyder *et al.*[16m]



Hanessian *et al.*[16c]

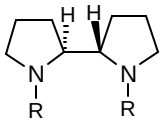


Corey *et al.*[16d]



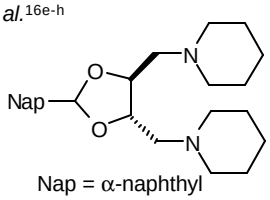
Ar = Ph, 3,5-xylyl

Tomioka *et al.*[16e-h]



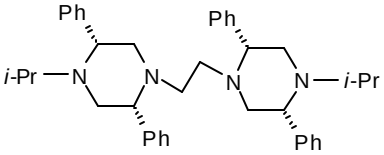
R = neohexyl

Hirama *et al.*[16j,k]



Nap = α-naphthyl

Narasaka *et al.*[16l]



Fuji *et al.*[16i]

Figure 1. Some ligands for AD reaction.[13,16]

Initially, the asymmetric dihydroxylation using the derivatives of cinchona alkaloids was performed under stoichiometric conditions, but in 1987 Marko and Sharpless[17] found that the process became catalytic when NMO was employed as the co-oxidant. However, the enantiomeric excess of the diol products obtained under these catalytic conditions was initially lower than that produced by the *stoichiometric* reaction. The origin of this discrepancy was found to be the presence of a second catalytic cycle,[18] (**Figure 2**) which exhibited only low or no enantioselectivity. Wai[18] discovered a partial remedy in slow addition of the olefin. Kwong[19] found that the participation of second catalytic cycle can be virtually eliminated by performing the reaction under two-phase conditions with $K_3Fe(CN)_6$ as the stoichiometric re-oxidant. Under these conditions there is no oxidant other than OsO_4 in the organic layer, in contrast to the homogeneous NMO conditions. Since the actual osmylation takes place in this layer, the resulting osmium (VI) monoglycolate ester undergoes hydrolysis, releasing the diol and the ligand to the organic layer and Os (VI) to the aqueous layer before its regeneration can occur, and consequently entry of the osmium glycolate into the second cycle is prevented (**Figure 3**).

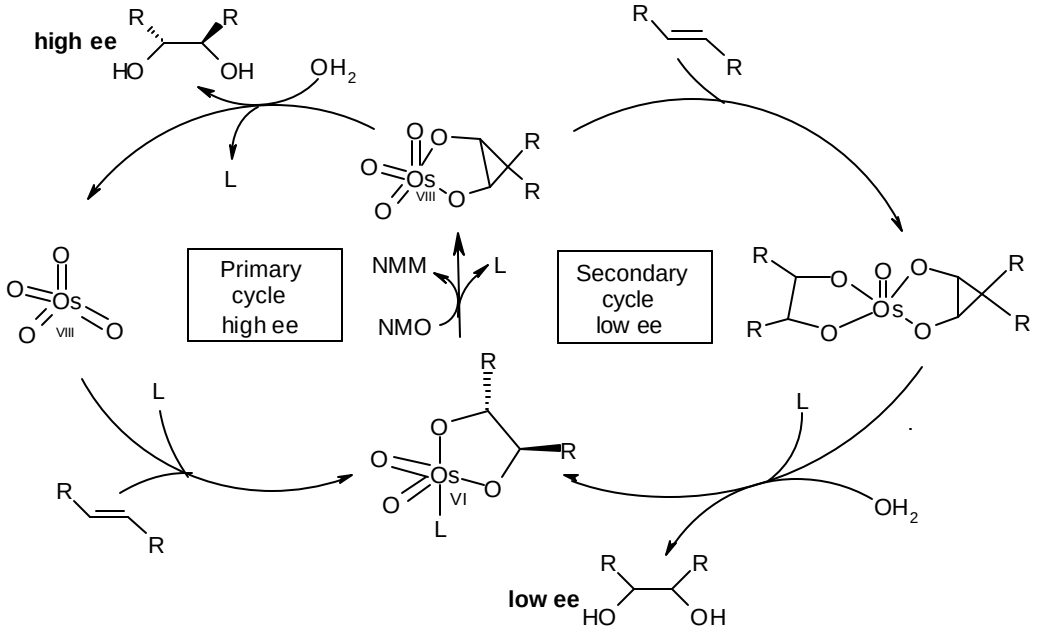


Figure 2. Two Catalytic Cycles for the AD Reaction using NMO as the Co-oxidant.[18]

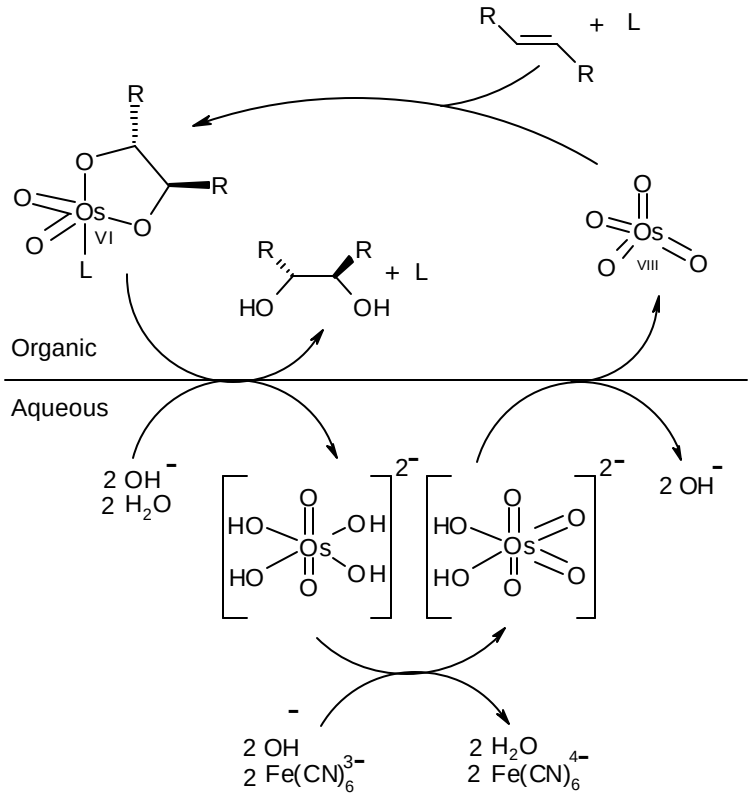


Figure 3. Catalytic Cycle of the AD Reaction with $K_3Fe(CN)_6$ as the Co-oxidant.[19]

Sharpless *et al*.[20] found that the hydrolysis of the osmium (VI) glycolate product could be accelerated considerably by using $MeSO_2NH_2$. The reaction time can be as much as 50 times shorter in the presence of this additive. This allows high catalytic turnover even with sterically encumbered substrates, and tetra substituted olefins are now within the scope of the reaction. Due to this "sulfonamide effect", most AD reactions can be carried out at 0°C rather than at room temperature, which may have beneficial influence on the selectivity.[21] For terminal olefins, $MeSO_2NH_2$ is not recommended. Surprisingly, terminal olefins actually react slower in the presence of $MeSO_2NH_2$. However this weak inhibitory effect is noticeable only if very small amount of OsO_4 (0.2 mol%) is employed.

The discovery of ligands with two independent cinchona alkaloid units by Hartung[20] (phthalazine core) and Crispino[22] (diphenylpyrimidine core) attached to a heterocylic spacer, has led to a considerable increase in both the enantioselectivity and the scope of the reaction (**Figure 4**).

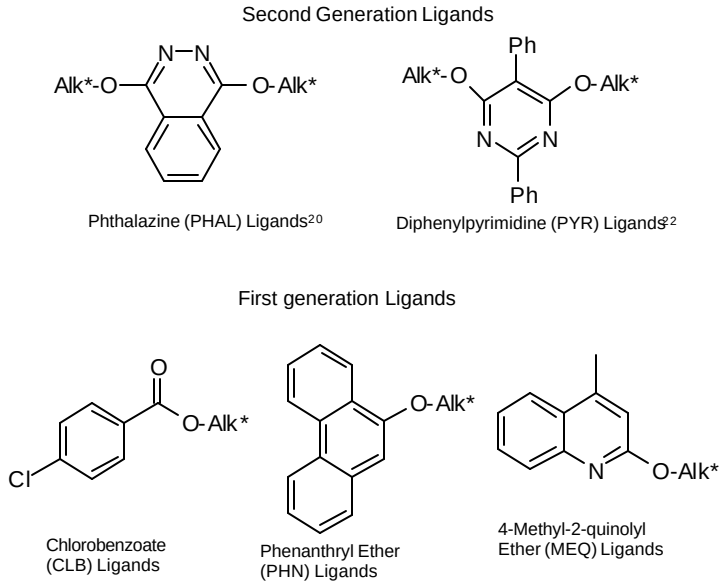
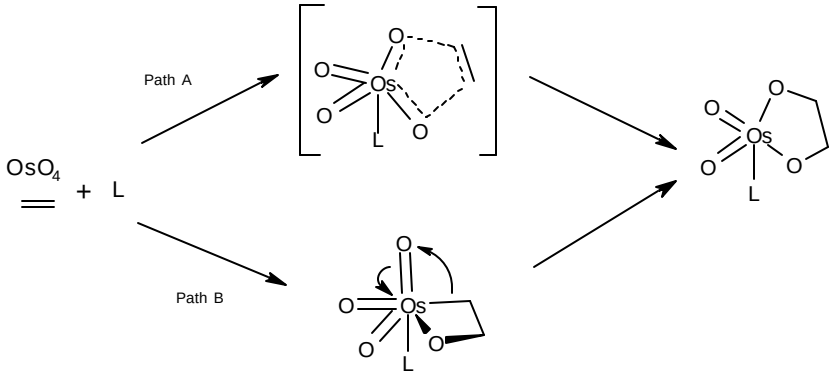


Figure 4. The latest generation of "dimeric" PHAL and PYR ligands and their predecessors (Alk* = DHQD or DHQ, see Fig. 1a)

1.1.2. The Mechanism of Asymmetric Dihydroxylation (AD)

The osmium-catalyzed dihydroxylation reaction has been the center of extensive mechanistic investigations and two different mechanisms have been suggested. Boseken[23a] and Criegee[8] originally proposed a concerted [3+2] pathway, (**Scheme 3**, **Path A**) while Sharpless *et al.*[23b] and Jorgensen *et al.*[23c] suggested a stepwise reaction which is initiated by a [2+2] like addition of the olefin across an Os=O bond (**Path B**), followed by rearrangement of the resulting osmaoxetane intermediate to the glycolate product.

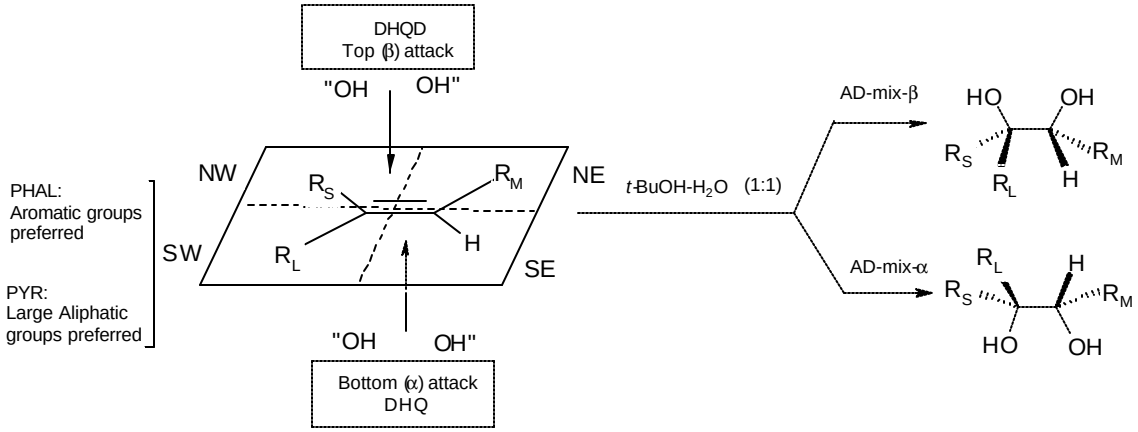


Scheme 3. Schematic presentation of the concerted [3+2] mechanism[23a] (Path A) and the stepwise osmaoxetane mechanism (Path B).[23b,c]

The recent observation of a nonlinear Erying relationship between enantiomeric excess and temperature[21] is consistent with Criegee's one-step [3+2] mechanism, but it can be explained by a reaction pathway with at least two selectivity determining steps which are weighted differently according to temperatures owing to their different activation parameters, ΔH and ΔS. Hence, this observation suggests that the stepwise [2+2]-like mechanism is operative. High level *ab initio* calculations have indeed shown that osmaoxetanes are energetically accessible minima on the potential energy surface.[24]

1.1.3. Empirical Rules for Predicting the Face Selectivity

Despite the mechanistic uncertainties, the face selectivity of the dihydroxylation can reliably be predicted using an empirical 'mnemonic device' (**Scheme 4**).[25] The plane of the olefin is divided into four quadrants and the substituents are placed into three quadrants according to a simple set of rules. The SE quadrant is sterically inaccessible and, with few exceptions, no substituent other than hydrogen can be placed here. The NW quadrant, lying diagonally across from the SE quadrant, is slightly more open and the NE quadrant appears to be quite spacious. The SW quadrant is special in that its preferences are ligand-dependent. Even though this SW quadrant normally accepts the largest group, especially in the case of PYR ligands, it is especially attractive for aromatic groups in the case of PHAL ligands.[25c] An olefin, which is placed into this plane according to the above constraints, receives the two OH groups from above, i.e. from the β-face, in the case of DHQD derived ligands and from the bottom, i.e. from the α-face, in the case of DHQ derivatives.



Scheme 4. The mnemonic device for predicting the face selectivity.

Predictions for 1,1-disubstituted olefins using the empirical mnemonic device are not always unambiguous,[26] since it may be difficult to judge which of the two substituents prefer the attractive, SW quadrant. Along with steric size, the properties of the substituents have also to be taken into account and compared with the ligand-specific preferences for the SW quadrant. PHAL ligands show the following preferences for the SW quadrant:[25c,26,27]

Aromatic groups >> *n*-alkyl > branched alkyl > oxygenated residues

Recent studies have revealed that oxygenated residues[26,28] have very small preferences for ligands binding pocket (SW quadrant). Studies with 1,1-disubstituted olefins have shown that pyrimidine (PYR) ligands have very different preferences for SW quadrant[25c,27] and the steric size of a substituent is much more important than in the PHAL system. Thus, the following preference is observed:

Branched alkyl > long *n*-alkyl (length ≥3) > aromatic residues > short *n*-alkyl

A few exceptions mostly for terminal olefins have appeared in recent years. The AD of certain *ortho*-substituted allyl benzenes in the presence of PHAL ligands have been shown to give facial selectivities opposite to those predicted by the mnemonic device.[29] Furthermore, *trans*-olefins in the same series react with the expected face selectivity even with the PHAL ligands; thereby demonstrating that exceptions are so far limited to the class of terminal olefins. Thus, the mnemonic device is a simple tool for predicting the facial selectivity of the AD reaction. However, reliable predictions require the intrinsic preference of each ligand to be taken into account. Thus, the SW quadrant is especially attractive for aromatic groups in the PHAL systems, while aliphatic groups are preferred in the PYR systems. PYR ligands are, therefore the ligands of choice for aliphatic and/or sterically congested olefins, while PHAL ligands are better for aromatic substrates. These simple rules allow the prediction of the face selectivities even in difficult cases and very few exceptions are known.

1.1.4. Reaction Conditions

Catalytic asymmetric dihydroxylation is performed in a 1:1 mixture of water and *t*-BuOH. The olefin concentration in the *t*-BuOH/water mixture is usually 0.1M.[20] While the reaction is normally run under basic conditions (K_2CO_3, pH 12.2, aq. layer),[30] it is possible to buffer the system with 3 equivalents of $NaHCO_3$ (pH 10.3, aq. layer). Buffering of the reaction has a beneficial effect on the yield when base-sensitive substrates are used or base-sensitive products are formed. Normally the reaction is performed with 3 equivalents of $K_3Fe(CN)_6$ as the re-

oxidant. The key reagents used are the Os reagent and the ligands. Only 0.2 to 0.4 mol% of Os reagent, either OsO_4 or the nonvolatile $K_2OsO_2(OH)_4$ is added. The ligand concentration is 1 mol%. However it can be dropped in some cases without much loss in enantioselectivity. For e.g. stilbene still gives 96% ee when 1/100 of 1 mol% of $(DHQD)_2$-PHAL is used as compared to the 99.8% ee obtained under normal conditions.[20] Alternatively, the amount of OsO_4 can be increased to 1 mol% for accelerating the reaction rate of relatively unreactive olefins. Additionally, the ligand can be recovered especially when large-scale reactions are carried out. For the PHAL ligands, the combined organic layers are extracted with 3% aq. H_2SO_4 saturated with K_2SO_4 (ca. 40 mL/1 g of ligand), followed by a second extraction of the organic solution with saturated K_2SO_4 (ca. 40 mL/1 g of ligand). The ligand enters the aqueous phase as the hydrogen sulfate salt and the solution can be reused directly for the subsequent AD reactions without further purification. However, the amount of K_2CO_3 in the subsequent reaction should be increased in order to neutralize excess H_2SO_4 and also to release the ligand salt as its free base. Additionally, the amount of water should be decreased by the volume of aqueous ligand solution added to the reaction mixture.

Since most substrates require very similar reaction condition, it is possible to use premix of all reactants. These are available commercially as 'AD-mixes' such as AD-mix-β [$(DHQD)_2$PHAL] and AD-mix-α [$(DHQ)_2$PHAL]. 1 kg of AD-mix contains $K_3Fe(CN)_6$ (699.6 g), K_2CO_3 (293.9 g), ligand (5.52 g) and $K_2OsO_2(OH)_4$ (1.04 g). The standard AD procedure calls for 1.4 g of this AD-mix per mmol of olefin. One equivalent of $MeSO_2NH_2$ should be added for all substrates other than terminal olefins to enhance hydrolysis of the osmate (VI) ester and hence the rate of catalytic turnover.

1.1.5. The Cinchona Alkaloid Ligands and their Substrate Preferences

Phthalazine (PHAL) ligands

The phthalazine ligands are most widely used, due to their ready availability and their broad substrate scope.[25b] This ligand class is used in the AD-mix formulation. PHAL ligands react especially well when aromatic groups are present, and remarkably high enantioselectivities are observed when the aromatic substituents appear in certain optimal locations/patterns.[25a] One such case is *trans*-stilbene for which the enantioselectivity is as high as 99.8%.[31] However, PHAL ligands give inferior results with aliphatic olefins, especially if they are branched near the double bond or if they have very small substituents.

Recent developments have provided ligands with even broader scope than that of the PHAL derivatives.

Anthraquinone (AQN) ligands

The anthraquinone ligands are especially well suited for almost all olefins having aliphatic substituents.[32] Even diols derived from allyl halides or allyl alcohols can now be obtained with satisfactory enantiomeric purity, thereby giving access to valuable chiral building blocks. The AQN derivatives are the ligands of choice for the AD reaction, except for olefins with aromatic or sterically demanding substituents.

Pyrimidine (PYR) ligands

The pyrimidine ligands are the ligands of choice for olefins with sterically demanding substituents.[22]

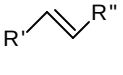
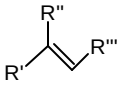
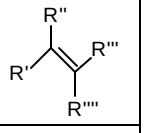
Diphenyl pyrazinopyridazine (DPP) and diphenyl phthalazine (DP-PHAL) ligands

These ligands give improved enantioselectivities for almost all olefins except for terminal alkyl olefins which are better served by the AQN or PYR ligands.[33] Even *cis*-1,2-disubstituted olefins give improved face selectivities with these ligands. The DPP ligand is normally slightly superior to the DP-PHAL ligand. The DPP derivatives are the optimal ligands for aromatic olefins and for certain *cis*-1,2-disubstituted olefins.

Indoline (IND) ligands

Cis-1,2-disubstituted olefins generally are poor substrates for the AD reaction and the IND derivatives are normally the ligands of choice.[34] However, in certain cases better results are obtained with the new second generation ligands.[32,33,35]

Table 1. Recommended ligands for each olefin class.

Olefin Class						
Preferred Ligand	R = Aromatic DPP, PHAL R = Aliphatic AQN R= Branched PYR	R′, R″ = Aromatic DPP, PHAL R′, R″ = Aliphatic AQN R′, R″ = Branched PYR	Acyclic IND Cyclic PYR, DPP, AQN	R′, R″ = Aromatic DPP, PHAL R′, R″ = Aliphatic AQN	PHAL, DPP, AQN	PYR, PHAL

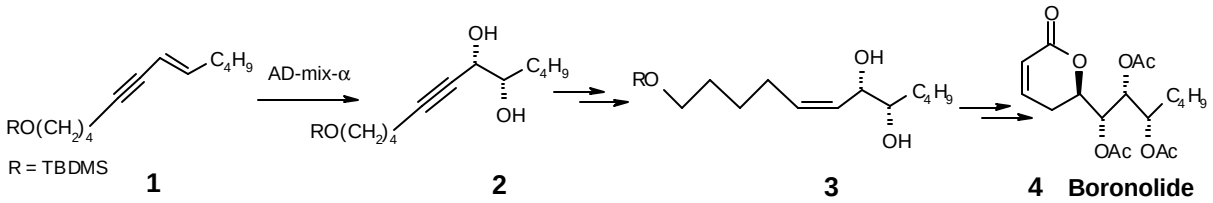
1.1.6. Recent Applications of Sharpless Asymmetric Dihydroxylation (SAD) Reaction in Organic Synthesis

Asymmetric dihydroxylation offers some important advantages over the use of chiral pool materials in enantioselective synthesis.

1] SAD, catalytic in both OsO_4 and the chiral ligand, provides either enantiomer of the product. 2] SAD is not limited to a certain number of standard starting materials (e.g. carbohydrates, tartrates, etc.), since virtually any olefin can be regarded as a substrate. 3] Third, most enantiospecific syntheses from the chiral pool require an elaborate protecting group strategy. However with SAD, the diol can be carried through the synthesis "masked" as an olefin, ready to be released at any point.

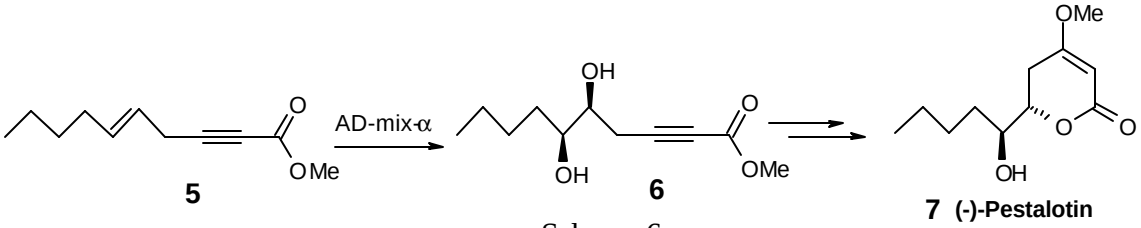
In most instances, diols are not the final products and their synthetic elaboration requires some further transformations. Commonly, these involve the selective manipulation of one of the two OH groups either by protecting it or by converting it into a leaving group, suitable for displacement by a nucleophile. Over the last decade, several applications of SAD reaction in the syntheses of bioactive molecules and natural products have been documented in the literature. While most synthetic applications of SAD are covered in the review article by Sharpless *et al.*,[5a] a few recent applications are documented below.

1. Boronolide **4**, [36] has been synthesized employing the SAD reaction on enyne **1**, followed by a second SAD reaction on *cis*-olefin **3** (**Scheme 5**).



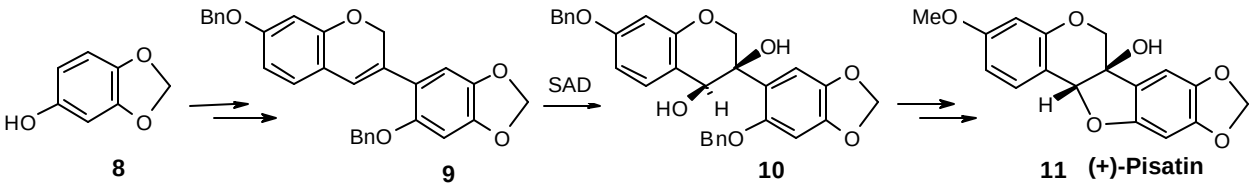
Scheme 5

2. A short synthesis of (−)-pestalotin **7**,[37] is achieved through the SAD of enyne **5** (**Scheme 6**).



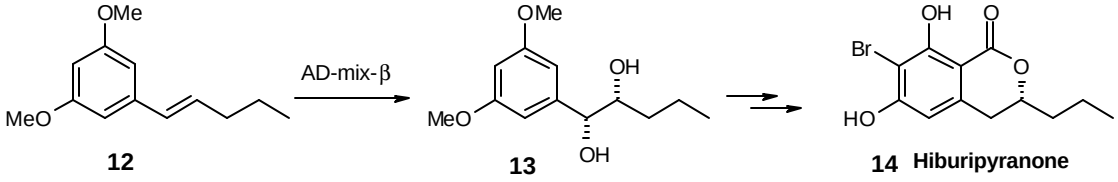
Scheme 6

3. The phytoalexin, (+)-pisatin **11**,[38] is synthesized by SAD reaction of cyclic olefin **9** (**Scheme 7**).



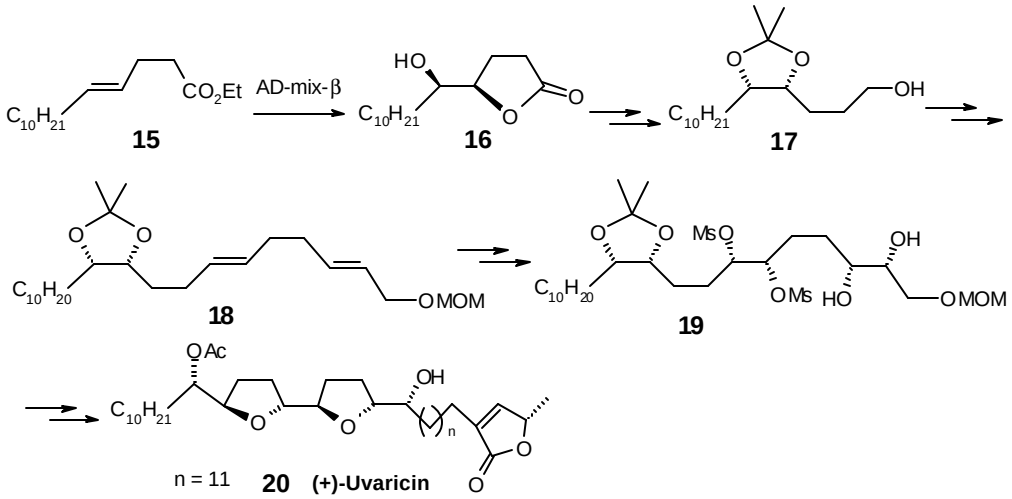
Scheme 7

4. Kitahara *et al.*[39] employed SAD of *trans*-olefin **12** in the asymmetric synthesis of both enantiomers of Hiburipyranone **14**, a cytotoxic metabolite of a marine sponge *Mycale adhaerens* (**Scheme 8**).



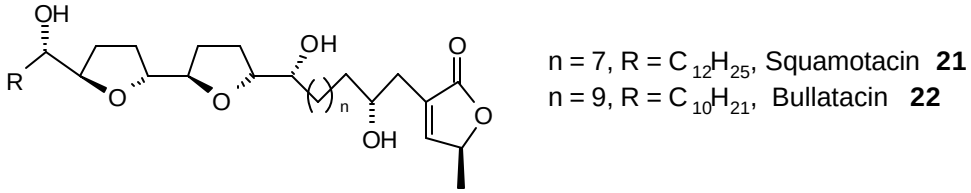
Scheme 8

5. The first total synthesis of naturally occurring (+)-Uvaricin **20**[40] is achieved using three consecutive SAD reactions to place the necessary oxygen functions on a naked carbon skeleton in a regio- and enantiocontrolled manner (**Scheme 9**).

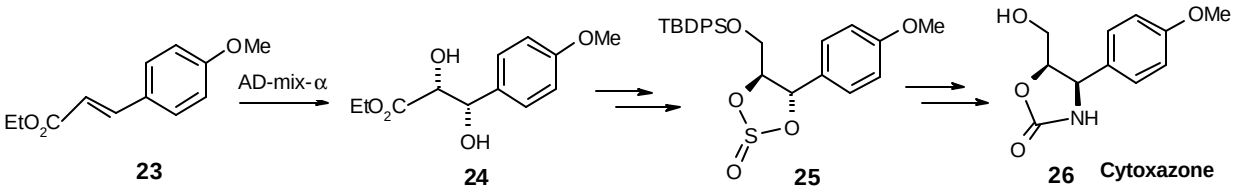


Scheme 9

6. Similarly, the analogs of Uvaricin, i.e. Squamotacin **21**[41] and Bullatacin **22**[41] are also synthesized employing the same strategy.

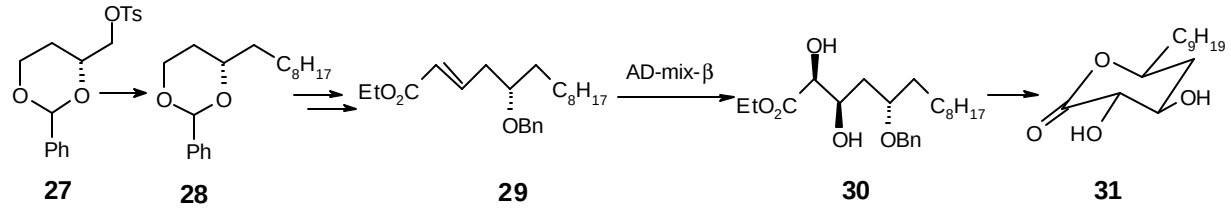


7. A novel cytokine modulator cytoxazone **26**[42] has been synthesized employing SAD and cyclic sulfite intermediate **25** (**Scheme 10**).



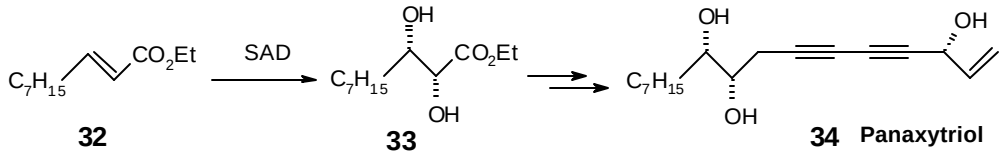
Scheme 10

8. The first synthesis of (2*S*,3*R*,5*S*)-(−)-2,3-dihydroxytetradecan-5-olide **31**,[43] a new biologically active δ-lactone produced by *Seiridium unicorne* is accomplished using (*R*)-malic acid and employing the SAD reaction (**Scheme 11**).



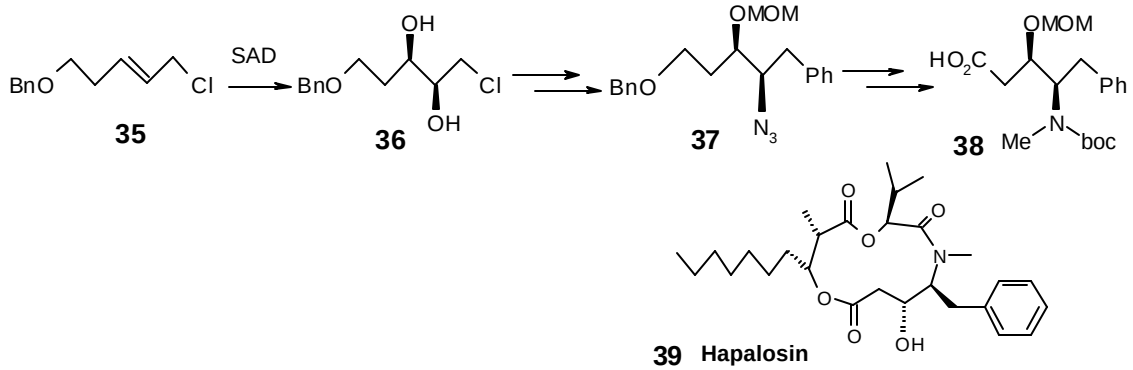
Scheme 11

9. SAD is successfully employed in the synthesis of antitumor agent panaxytriol **34** and its diastereomers[44] from olefin **32** (**Scheme 12**).



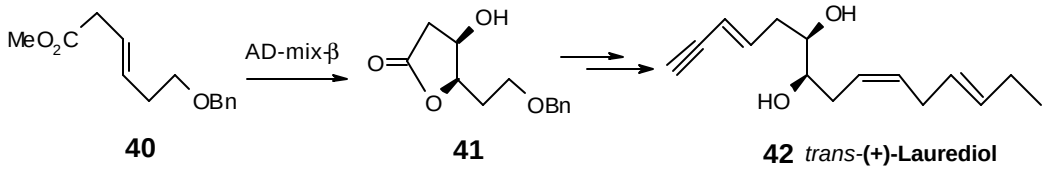
Scheme 12

10. The intermediate acid **38**[45] for the synthesis of depsipeptide hapalosin **39**, has been arrived at through SAD reaction of allylic chloride **35** (**Scheme 13**).



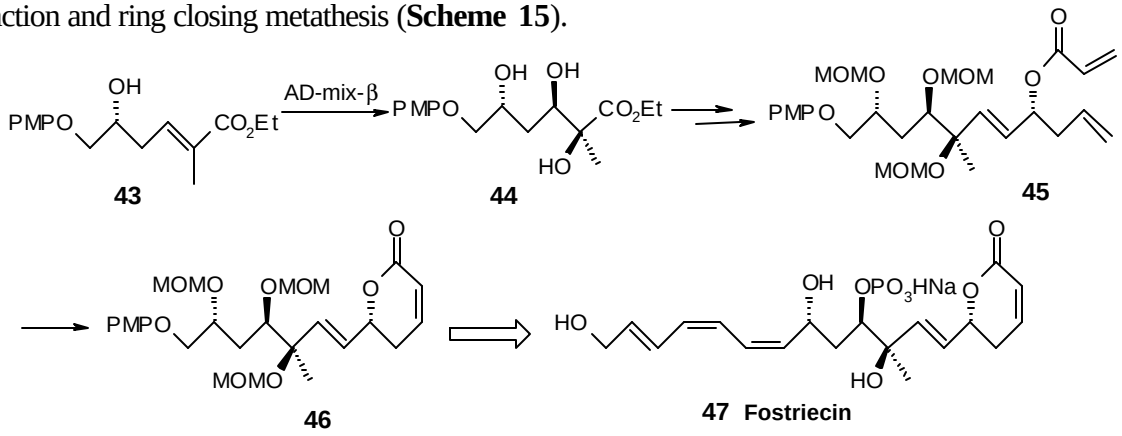
Scheme 13

11. An efficient synthesis of *trans*-(+)-laurediol **42**[46] has been achieved by SAD reaction of olefin **40** to give the intermediate β-hydroxy-γ-lactone **41** which is then extrapolated to **42** (**Scheme 14**).



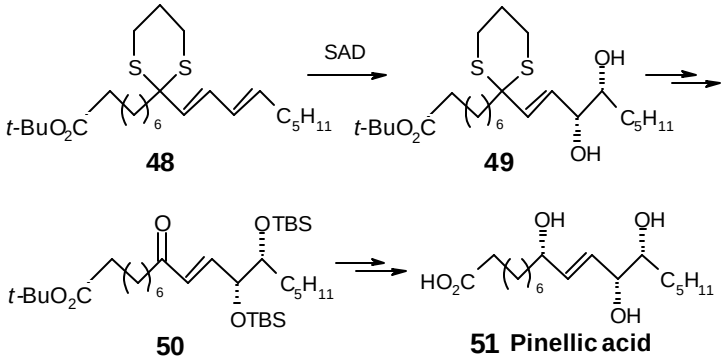
Scheme 14

12. The synthesis of C1-C12 fragment **46**[47] of fostriecin **47** has been achieved through SAD reaction and ring closing metathesis (**Scheme 15**).



Scheme 15

13. Regioselective SAD and stereoselective reduction routes have been applied towards the asymmetric synthesis of pinellic acid **51**,[48] a potent oral adjuvant for nasal influenza vaccine (**Scheme 16**).



Scheme 16

1.1.7. Conclusion

Thus, SAD reaction has become a powerful catalytic oxidation reaction. With the optimization of ligands and the amount of primary oxidant, this catalytic oxidation reaction of olefins to chiral diols is proving very promising in terms of both yields and enantioselectivities. It has contributed to rapid advances in synthetic organic chemistry giving access to new molecules needed to investigate hitherto unexplained and undiscovered phenomena in the molecular world.

1.2. CYCLIC SULFITES/SULFATES AS SYNTHETIC INTERMEDIATES

1.2.1. Introduction

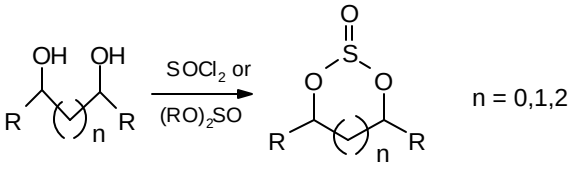
Cyclic sulfate esters have been known since 1932.[49] However, the lack of an efficient method for their preparation limited their applications in the repertoire of main line organic synthesis. But the improved process of converting the diol into cyclic sulfite with thionyl chloride, followed by oxidation of cyclic sulfite with $NaIO_4$ catalyzed by RuO_4[50] (generated *in situ*, using $RuCl_3.3H_2O$) represents an important development that broadened the use of cyclic sulfates as important synthetic intermediates. The advent of SAD reaction provided a route to chiral 1,2-diols from a wide spectrum of olefins, which can further be elaborated to cyclic sulfates.[51] Cyclic sulfites/sulfates have the following important features.

1] They have high reactivity toward various nucleophiles and are more reactive than epoxides.

2] They can activate nucleophilic attack at one position while serving as a protecting group at a second position; under vigorous conditions they can serve as an activator for two sequential reactions. 3] Reactions of five-membered cyclic sulfates with nucleophiles provide two contiguous stereocentres; moreover, a remote stereocenter can be controlled by cyclic sulfates of 1,3- and 1,4-diols. 4] The intermediate of substitution is generally a salt of monosulfate ester, probably enabling separation of the product from the non-salt by-product.

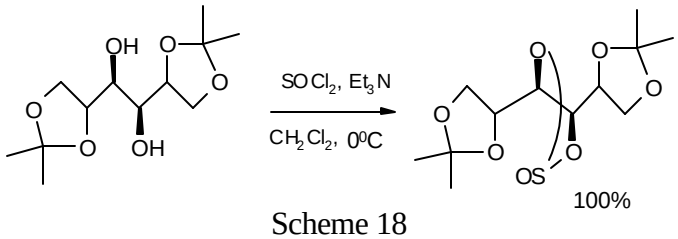
1.2.2. Preparation of Cyclic Sulfites/Sulfates

While several methods for preparation of cyclic sulfite are known, the most efficient synthesis involves the reaction of diol with thionyl chloride[52] or transesterification of a dialkyl sulfite with a diol[53] (**Scheme 17**).



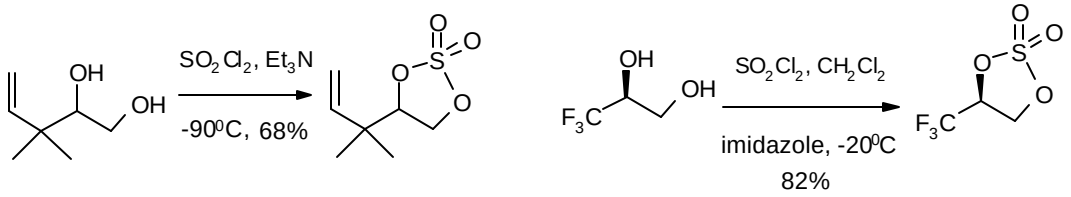
Scheme 17

In most reactions, expelling of hydrogen chloride by either refluxing[54] or using a stream of nitrogen improve the yield. In case of substrates with an acid-labile functionality, a base such as Et_3N, imidazole or pyridine is used to scavenge the hydrogen chloride generated during the reaction[55] (**Scheme 18**).



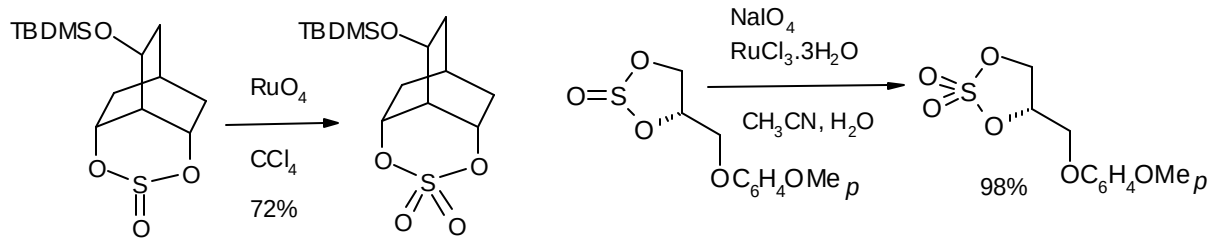
Scheme 18

Cyclic sulfate can be prepared directly by reaction of diol with sulfuryl chloride (SO_2Cl_2), but this gives only moderate yields due to the chlorinating nature of SO_2Cl_2[56] (**Scheme 19**).



Scheme 19

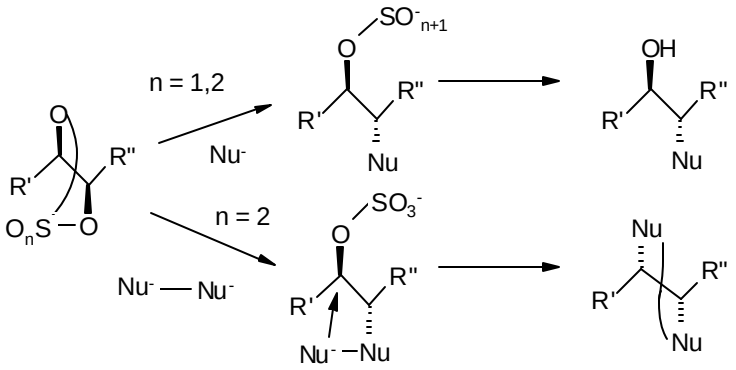
Oxidation of cyclic sulfites to sulfates is another alternative. Use of stoichiometric amount of RuO_4 gave cyclic sulfates in satisfactory yield.[57] However, this procedure is limited to small-scale preparations due to the expensive RuO_4. The discovery that a catalytic amount of RuO_4 is generated *in situ* by the reaction of $RuCl_3$ or RuO_2 with $NaIO_4$ made available an expedited route for the oxidation of cyclic sulfites to sulfates[50] (**Scheme 20**).



Scheme 20

1.2.3. Reactions of Cyclic Sulfites/Sulfates

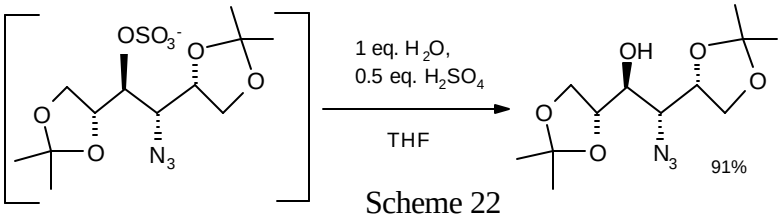
Analogous to epoxides, cyclic sulfites/sulfates can be opened by attack of a nucleophile at either carbon center giving a sulfite/sulfate monoester. These monoesters allow some interesting transformations, which make the chemistry of cyclic sulfites/sulfates more versatile than of epoxides. Hydrolysis of the monoesters leads to hydroxy compounds that parallel those obtained from oxiranes.[50] However, the sulfate monoester can function as a leaving group, leading to disubstitution products[50] (**Scheme 21**).



Scheme 21

Cyclic sulfites and especially sulfates react with a variety of nucleophiles and a few examples are Cl^- (LiCl),[58] Br^- (NH_4Br),[58] F^- ($Et_4NF.2H_2O$, *n*-Bu_4NF),[50,59] N_3^- (LiN_3, NaN_3),[50,55,59,60,61,62] RNH_2,[60,63] $PhCO_2^-$ ($PhCO_2NH_4$),[50,55,59] ROH,[64] NO_3^- (*n*-Bu_4NNO_3),[50] SCN^- (NH_4SCN),[50,58] PhS^- (PhSNa),[65] AcS^-,[66] H^- ($NaBH_4$, $NaBH_3CN$),[50] $PhCH_2^-$ ($PhCH_2MgBr$, Li_2CuCl_4),[50] $RC{\equiv}C^-$, ($RC{\equiv}CSiMe_3$ + MeLi),[67] $(RS)_2CH^-$ (with 1,4-cyclic sulfates).[68]

The hydrolysis of sulfate monoesters is carried out with an equal volume of 20% aq. H_2SO_4 and ether.[50] However, a chemoselective hydrolysis of sulfate ester in presence of acid-labile groups (acetonide and silyloxy) is carried out with a catalytic amount of H_2SO_4 and 0.5-1.0 equivalents of H_2O in THF[55] (**Scheme 22**). The use of a minimum of water is crucial to achieve the desired chemoselectivity.[55]

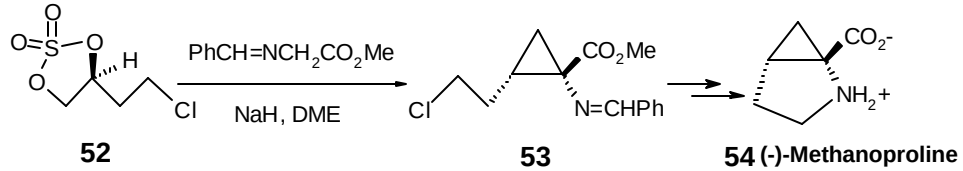


Scheme 22

1.2.4. Recent Applications of Cyclic Sulfites/Sulfates

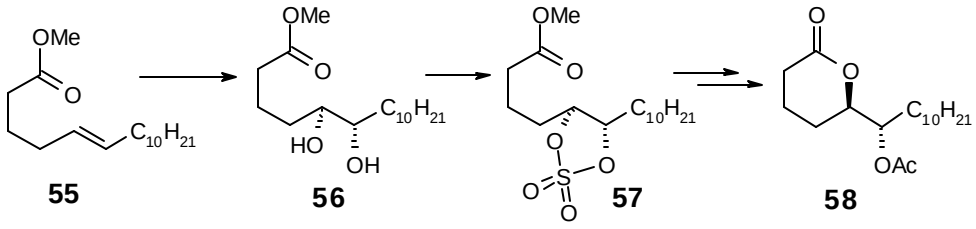
Several applications of cyclic sulfites/sulfates have been documented in the literature in the recent years. A few of them are described below.

1. The first asymmetric synthesis of (2*S*,3*R*)-(−)-methanoproline **54**[69] was achieved by condensation of cyclic sulfate **52** with methylbenzylidine glycinate (**Scheme 23**).



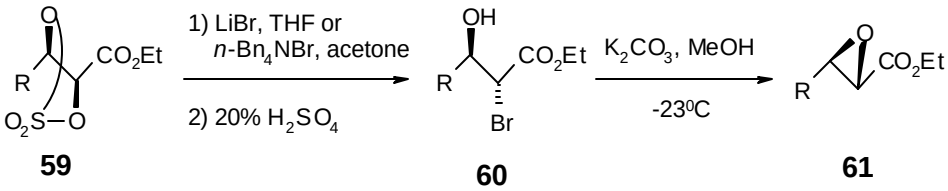
Scheme 23

2. Intramolecular S_N^2 ring opening of a cyclic sulfate **57** has been employed in the synthesis of *erythro*-(−)-6-acetoxy-5-hexadecanolide **58**,[70] a major component of mosquito oviposition attractant pheromone (**Scheme 24**).



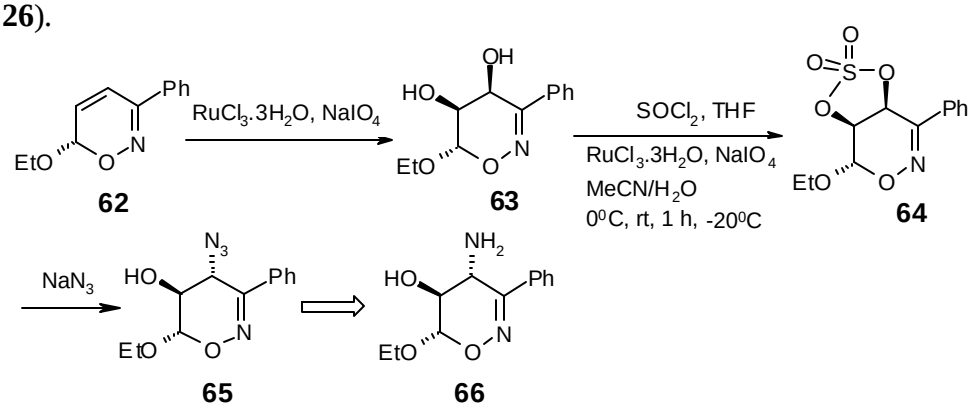
Scheme 24

3. α,β-Epoxyesters (**61**)[71] have been synthesized from cyclic sulfate (**59**) with the intermediate formation of 2-bromo-3-hydroxyesters (**60**) (**Scheme 25**).



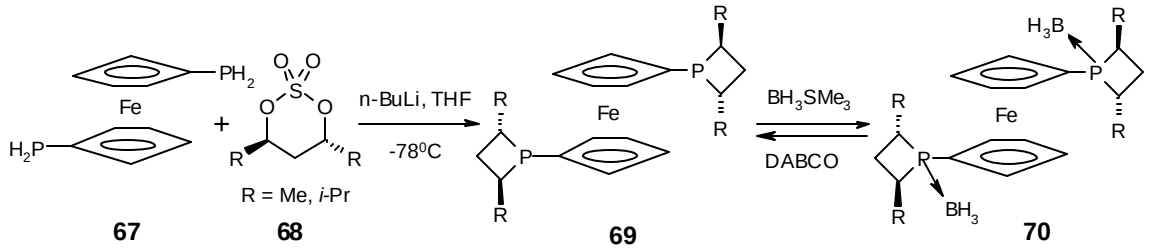
Scheme 25

4. 4-Amino-5-hydroxy substituted 1,2-oxazines **66**[72] are synthesized readily from 6*H*-1,2-oxizines **62** by *cis*-dihydroxylation and regioselective opening of cyclic sulfate **64** with azide (**Scheme 26**).



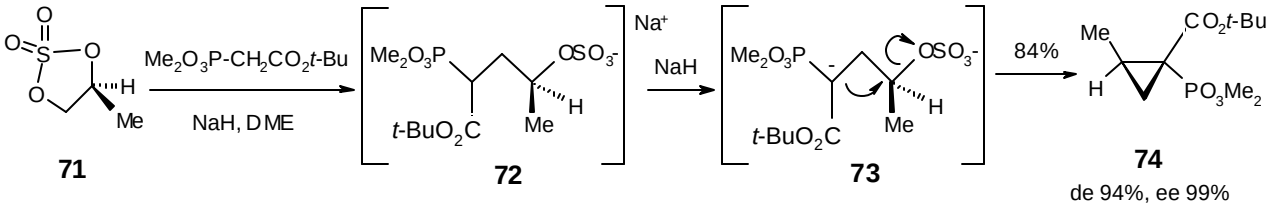
Scheme 26

5. The C_2-symmetric, chiral 1,1′-bis (phosphetano)ferrocenes **69**, **70**[73] have been prepared from the 1,3-diol cyclic sulfates **68** (**Scheme 27**). These have been tested in the rhodium-catalyzed hydrogenation of unsaturated substrates.



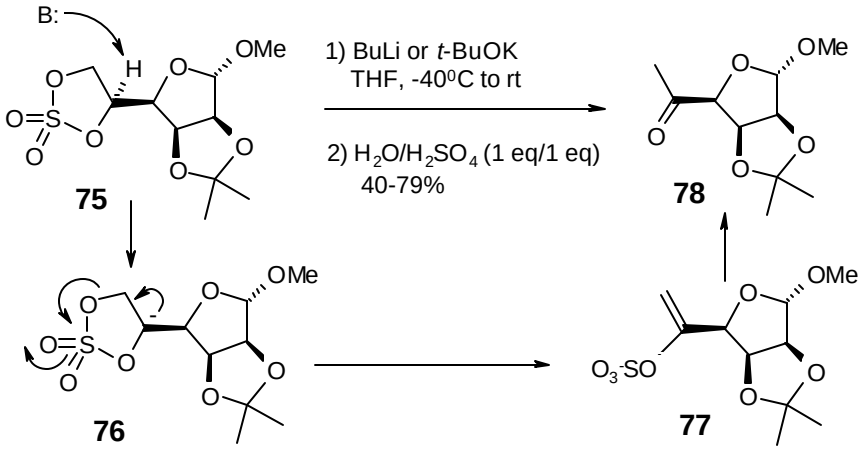
Scheme 27

6. (–)-(1*R*,2*R*)-1-Amino-2-methylcyclopropanephosphonic acid **74**[74] has been synthesized from (+)-(*S*)-1,2-propanediol cyclic sulfate **71** and dimethyl *t*-butoxycarbonyl methyl phosphonate (**Scheme 28**).



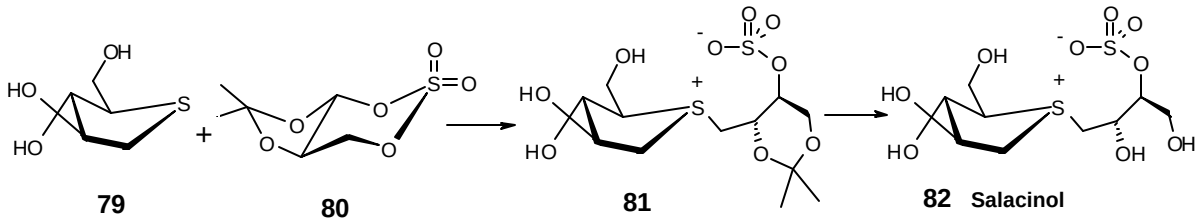
Scheme 28

7. Treatment of 5,6-cyclic sulfates **75** derived from glycofuranoses with strong bases resulted in 6-deoxy-hexofurano-5-ulose **78** derivatives[75] (**Scheme 29**).



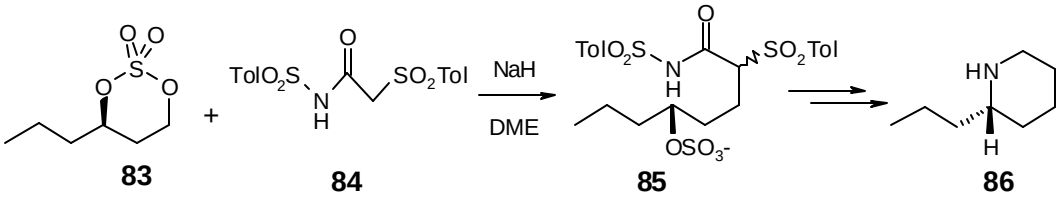
Scheme 29

8. Salacinol **82**[76] has been synthesized by using the cyclic sulfate of 1,3-*O*-isopropylidene-D-erythritol **80** and 1,4-epithio-D-arabinitol **79** (**Scheme 30**).



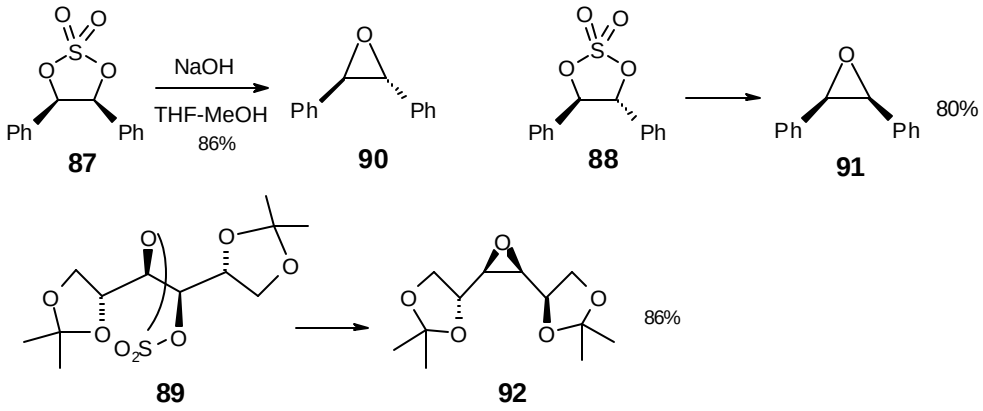
Scheme 30

9. Cyclic sulfate **83** undergoes double alkylation with stabilized C,N-dianions of **84** to provide the piperidine ring of (*S*)-coniine **86**[77] (**Scheme 31**).



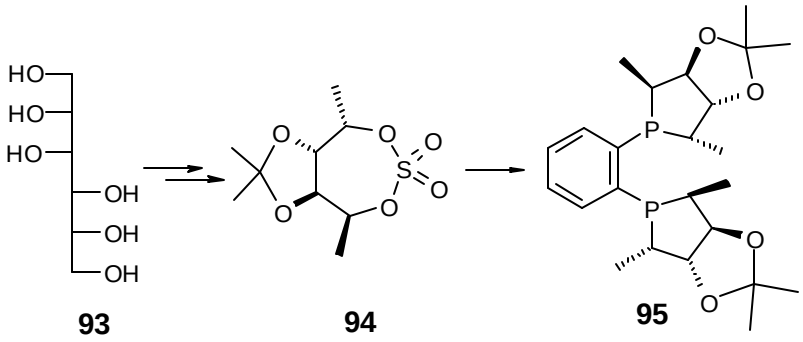
Scheme 31

10. Reaction of cyclic sulfates of *vic*-diols (**87**-**89**) with NaOH in THF-MeOH produced the corresponding epoxides (**90**-**92**) respectively in excellent yields[78] (**Scheme 32**).



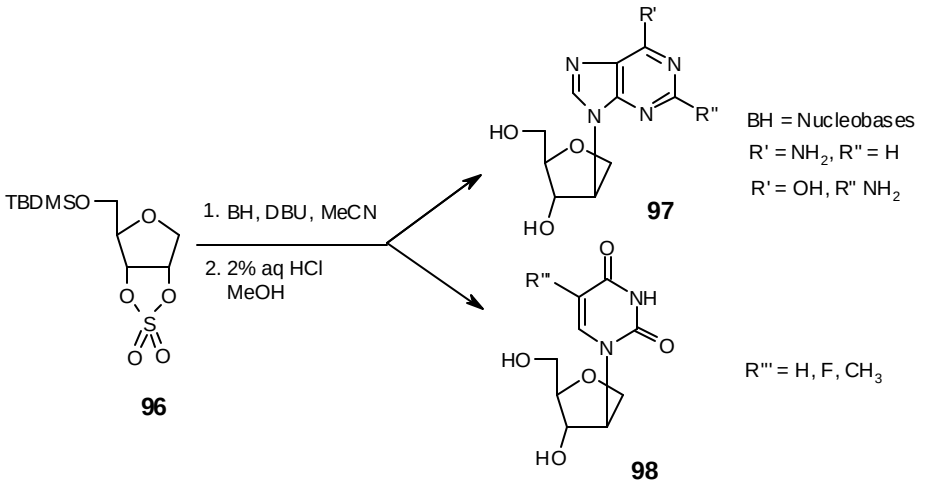
Scheme 32

11. Cyclic sulfate **94** derived from D-mannitol **93** has been employed in the synthesis of diphosphine ligands **95**[79] (**Scheme 33**).



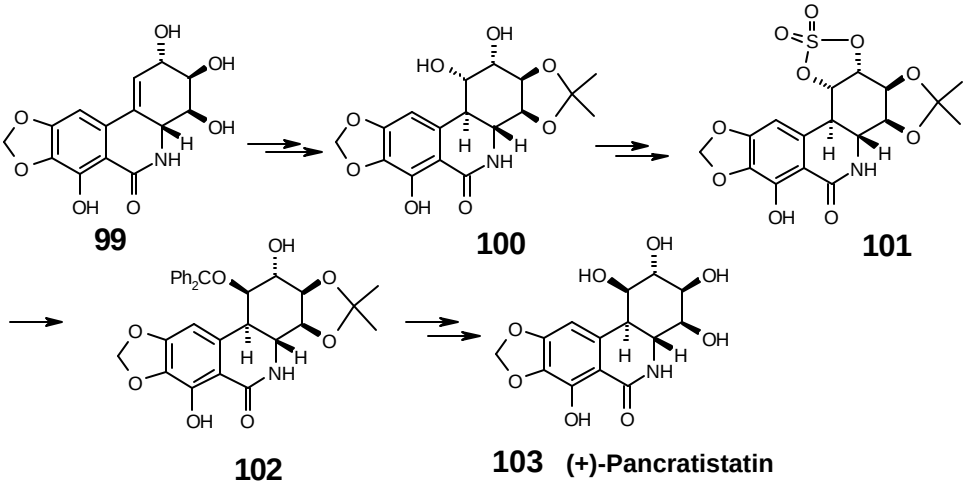
Scheme 33

12. Direct coupling of purine and pyrimidine bases with the cyclic sulfate **96** derived from carbohydrate intermediate gave access to isonucleosides (**97** and **98**)[80] as potential antiviral agents (**Scheme 34**).



Scheme 34

13. Synthesis of (+)-pancratistatin **103**[81] has been achieved from (+)-narciclasine **99** by employing the cyclic sulfate intermediate **101** (**Scheme 35**).



Scheme 35

1.1.1. Conclusion

Thus, given the vast chemistry associated with synthetic applications of epoxides, exploration of the chemistry of 1,2-cyclic sulfites/sulfates their hitherto neglected cousins in organic synthesis is proving fruitful today. The initial realization that these intermediates are epoxide-like, but generally much more reactive has given synthetic chemists many ideas as to where they might be useful.

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CHAPTER 2

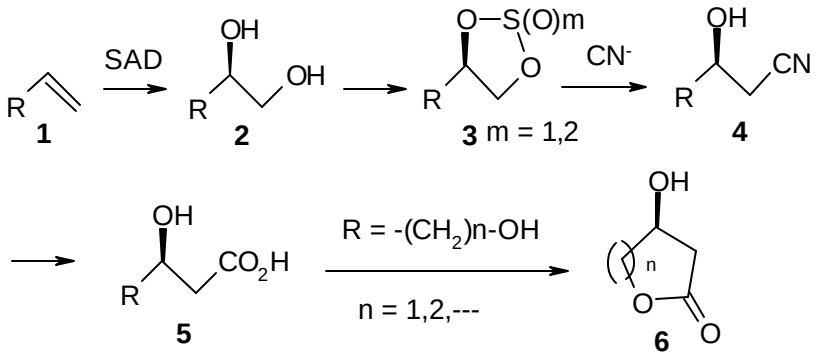
ENANTIOSELECTIVE SYNTHESIS OF b-HYDROXY-d-LACTONES

2.1. Introduction

The advent of Sharpless asymmetric dihydroxylation (SAD)[1] greatly facilitated the synthesis of optically active dihydroxy compounds that serve as important synthons to a vast array of natural products. The dihydroxy compounds provide varied opportunities for functional group changes to arrive at different functionalities present in the target molecules while many molecules contain the diol function as well. This chapter discloses a new approach from chiral dihydroxy compounds to β-hydroxy-δ-lactones. We have employed two different strategies depending on the substrate olefin chosen for the synthesis of β-hydroxy-δ-lactones. To carry out the above conversion, the cyclic sulfites/sulfates[2] are employed as one of the key intermediates.

Synthetic Strategy - 1 (Scheme 1):

Here, the substrate olefin employed is a terminal olefin. Asymmetric dihydroxylation of olefin **1** gives diol **2**, which is then converted into the cyclic sulfite/sulfate intermediate **3**. This activates the terminal position for regioselective nucleophilic opening. Towards this end, opening of the cyclic sulfite/sulfate **3** with CN^- nucleophile gives the cyano compound **4**, which on subsequent hydrolysis affords the key precursor β-hydroxy acid **5**. If the R group is HO–$(CH_2)_n$– where n = 1,2,---, the lactonization reaction can afford β-hydroxy lactones **6** of varied ring size depending on the value of n.

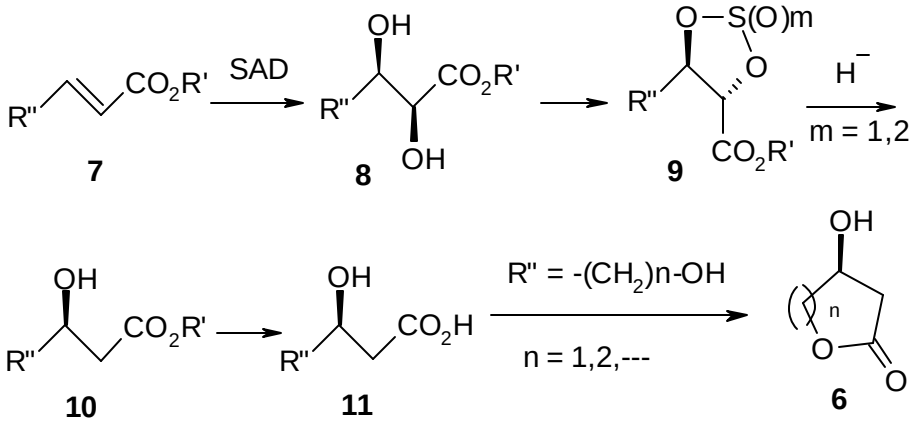


Scheme 1: Synthetic strategy-1

Synthetic Strategy - 2 (Scheme 2):

Here, α,β-unsaturated ester is used as a starting material. SAD of olefin **7** gives α,β-dihydroxy ester **8**, which is then converted into cyclic sulfite/sulfate **9**. This activates the α-position for regioselective nucleophilic opening. Towards this end, opening of **9** with H^-

nucleophile gives β-hydroxy ester **10**. Hydrolysis of ester affords β-hydroxy acid **11** (R″ = HO–$(CH_2)_n$–, where n = 1,2,----) which on subsequent lactonization would give β-hydroxy lactones **6** of varied ring size depending on the value of n.



Scheme 2: Synthetic strategy-2

Thus, the chiral dihydroxy compounds obtained by SAD reaction could be converted into β-hydroxy lactones of varied ring size depending on the value of n. When n = 1, a β-hydroxy-γ-lactone will be formed. Similarly, n = 2 will provide a β-hydroxy-δ-lactone. Other higher ring lactones could also be obtained with n = 3, 4, ---.

This chapter deals with the enantioselective synthesis of β-hydroxy-δ-lactones employing the Sharpless asymmetric dihydroxylation and cyclic sulfites/sulfates as intermediates.

Section A details the application of the **Synthetic strategy-1**, where n = 2. This gives the β-hydroxy-δ-lactone. Thus, the asymmetric synthesis of (*R*)-mevalonolactone has been achieved.

Section B details the application of the **Synthetic strategy-2** toward the synthesis of the lactone portion of compactin and mevinolin.

+ 2.2. SECTION A

ENANTIOSELECTIVE SYNTHESIS OF (*R*)-(-)-MEVALONOLACTONE

2.2.1. Introduction

(*R*)-(−)-mevalonic acid **12**, is a key intermediate in a broad spectrum of cellular biological processes and their regulation. Living systems precisely regulate the biosynthesis of mevalonate present as mevalonolactone **13** or mevalonic acid **12** (**Figure 1**), the essential precursor to a vast array of terpenoids, sterols, cytokines, carotenoids, isoprenoids and pentanoids.[3] The transformation of 3-hydroxy-3-methylglutaryl CoA into mevalonate catalyzed by HMG-CoA reductase, is a crucial step in the biosynthesis of cholesterol.[4] In medicine it is known that inhibition in the production of cellular **12** leads to lowering of plasma cholesterol.[5] This makes the biological formation of (*R*)-(−)-mevalonic acid **12** an important control site.[6a] The level of (*R*)-**12** in plasma and/or urine has been used to study the mechanisms and efficacy in the treatment of hyperlipidemias and the efficacy of lovastatin as an anticancer agent.[6] Thus, both for diagnostic and therapeutic reasons, simple and cheap access to natural mevalonic acid **12** is of significant value. As such **12**, or more particularly mevalonolactone **13**, have been a synthetic target of considerable interest.

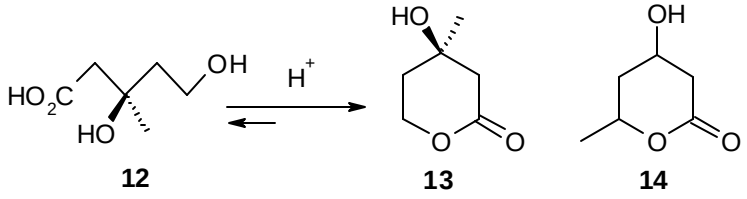


Figure 1.

Mevalonolactone **13**, was isolated from distiller's solubles as an acetate-replacing factor for *Lactobacilli* and identified by degradation and synthesis as 3-hydroxy-3-methyl-5-pentanolide **13** by Folkers *et al*.[7,8] Quite independently at the same time, Tamura[9] isolated from the broth of *Aspergillus oryzae* a growth factor for true hiochi bacteria, *Lactobacillus homohiochi* and *Lactobacillus heterohiochi*. He named it hiochic acid lactone and proposed **14** as its most probable structure. Later, Tamura revised the structure from **14** to **13** by synthesizing **13**.[10] The

identity of hiochic acid lactone with mevalonolactone was confirmed on the basis of identical IR spectra and biological activities.[11] Subsequently Arigoni[12] determined the absolute configuration of mevalonolactone **13** as (*R*)- by correlation with quinic acid.

The ubiquity of terpenes in nature together with the preeminent position of (*R*)-mevalonic acid in the biosynthetic pathway have prompted many research groups towards the development of asymmetric synthesis of (*R*)-mevalonolactone **13**.

2.2.2. Review of Literature

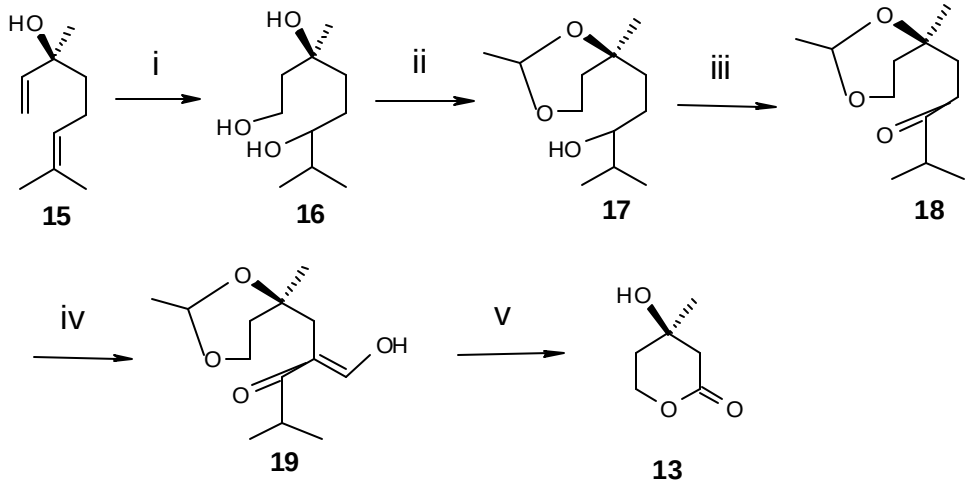
Cornforth and co-workers were the first to prepare both enantiomers of mevalonolactone in essentially 100% optically purity from (+)- and (−)-linalool.[13] Since then a number of asymmetric syntheses of (*R*)-(−)-mevalonolactone **13** have been documented in the literature. Among the chemical routes, the most important employ the Sharpless asymmetric epoxidation,[14] which is a stereodifferentiating reaction. There also exist routes exploiting starting materials from the chiral pool.[15] A different and highly enantioselective approach is based on chirality transcription from a chiral template.[16] Other interesting synthetic methodologies involve the use of chiral sulfoxides,[17] 1,3-oxathianes[18] and axially dissymmetric binaphthyldiamines.[19] Biocatalysts have also been used for the preparation of **13**, either by fermentation,[20] or procedures involving lipase-catalyzed kinetic resolution[21] or *via* hydrolysis of prochiral diesters employing esterases.[22]

More recent methods include a chloroperoxidase catalyzed epoxidation of 3-methylbut-3-enoate[23] and chemoenzymatic deracemization using lyophilized cells of *Nocardia* E H1.[24] Some of the interesting and important synthetic routes to (*R*)-(−)-mevalonolactone **13** are described below.

Cornforth *et al*. (1962)[13] Scheme 3

This report describes the first synthesis of both enantiomers in essentially 100% ee from (+)- and (−)-linalool. (+)-Linalool **15** is converted into dioxane **17** through hydroboration oxidation and 1,3-hydroxyl protection. Oxidation of the free hydroxyl of **17** into ketone **18** and condensation with methylformate and NaOMe gave **19**, which was immediately oxidized by

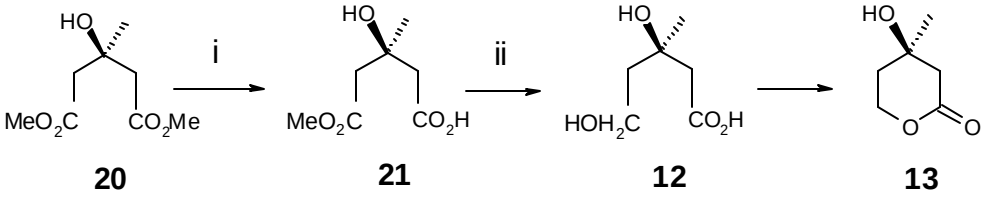
addition of aqueous methanolic $NaIO_4$. The acetal group was hydrolyzed during isolation of the product to afford (*R*)-(−)-mevalonolactone **13**.



Scheme 3. Reaction conditions: (i) $LiBH_4$, $BF_3.Et_2O$, THF, then MeOH, 3N NaOH, 30% H_2O_2, rt, 60%. (ii) CH_3CHO, *p*-TsOH, Et_2O, 2 d, 81%. (iii) CrO_3, pyridine 3 d, 88%. (iv) NaOMe, HCO_2Me, −15°C-rt, then CH_3CO_2H in Et_2O. (v) $NaIO_4$, H_2O, MeOH, 49%.

Sih *et al*. (1975)[22] Scheme 4

Sih and co-workers employed a chemoenzymatic route to (*R*)- and (*S*)-mevalonolactone. β-Hydroxy-β-methyl dimethylglutarate (**20**) was hydrolyzed with pig liver esterase to give the half ester **21**. Reduction of **21** with $LiBH_4$ or Na in liq. NH_3-EtOH afforded (*R*)-mevalonolactone **13**.

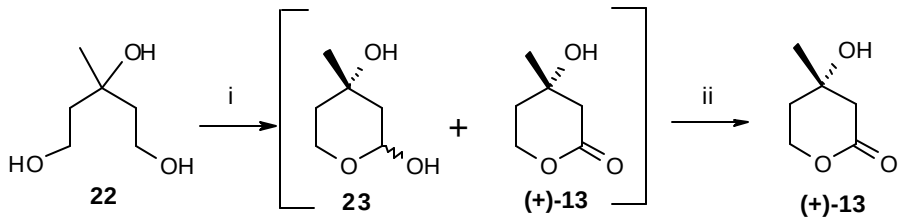


Scheme 4. Reaction conditions: (i) Pig liver esterase, 0.1M phosphate buffer, pH 8, 25°C, 62%. (ii) $LiBH_4$, 81% or Na in liq. NH_3-EtOH, 73%.

Jones *et al*. (1977)[25] Scheme 5

Jones and Irwin carried out oxidation of **22** with horse liver alcohol dehydrogenase (HLADH) for 23 h at pH 9 and NAD^+ co-enzyme recycling to give a mixture of hemiacetal **23** (82%), (*S*)-mevalonolactone (+)-**13** (4%) and residual **22** (7%) as determined by GLC. Silver oxide

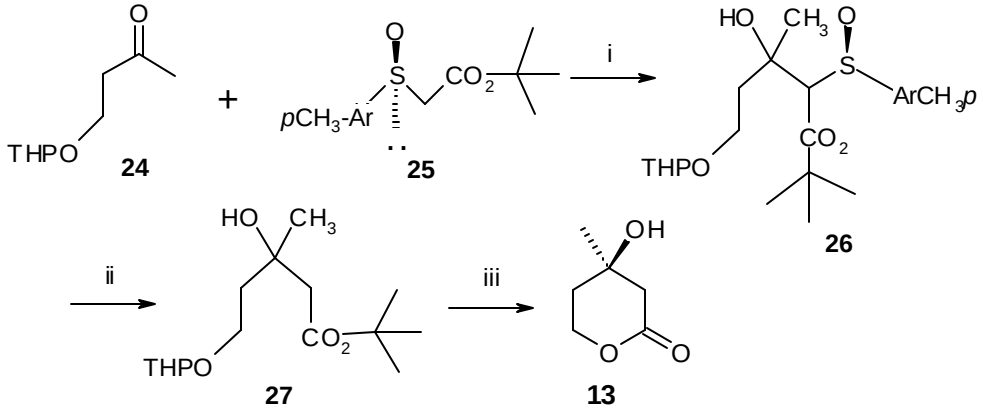
oxidation of the mixture gave (*S*)-mevalonolactone (+)-**13**. Thus, this synthesis involves the unnatural isomer of mevalonolactone.



Scheme 5. Reaction conditions: (i) HLADH, 20°C, pH 9, NAD^+ recycling, 23 h, (**23**, 82%; (+)-**13**, 4%; **22**, 7%). (ii) (a) Ag_2O, 20°C, 28 h, (b) 12N HCl, pH 3, 80%.

Sih *et al*. (1978)[17] **Scheme 6**

Sih and co-workers employed chiral sulfoxide **25** in the synthesis of (*R*)-mevalonolactone **13**. Reaction of the anion of **25** with ketone **24** gave the diastereomeric alcohol **26**. Removal of sulfoxide group afforded **27**. Deprotection of THP ether and lactonization gave **13**. However, the enantiomeric purity of **13** obtained was only 17%.

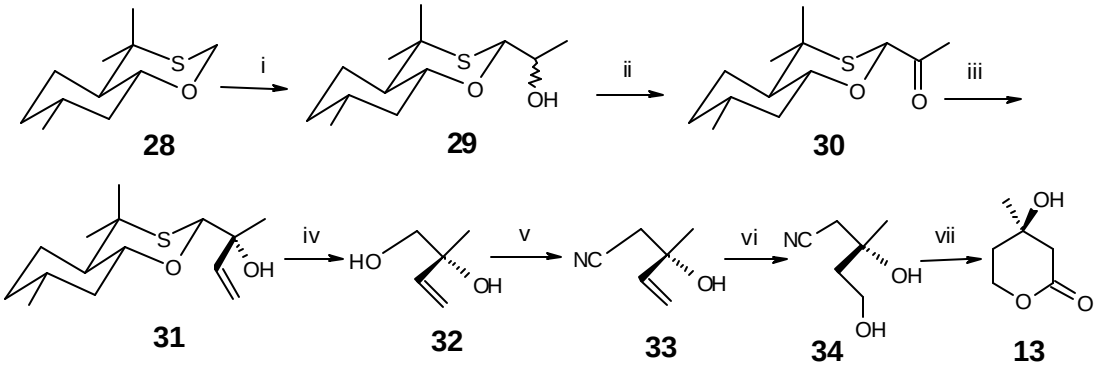


Scheme 6. Reaction conditions: (i) *t*-BuMgCl, THF-DME (2:1), −78°C, 75%. (ii) Al-foil, 3% aq. $HgCl_2$-THF (1:3), 60°C, 87%. (iii) (a) AcOH-H_2O-THF (1:1:1), 50°C, 98%, (b) 15% aq. NaOH, 100°C, 3 h, 61%.

Eliel *et al*. (1981)[26] **Scheme 7**

Eliel and co-workers utilized the anion of oxathiane **28** in reaction with acetaldehyde to give the diastereomeric alcohol **29**. Oxidation of **29** and Grignard reaction with vinyl magnesium bromide gave the alcohol **31** in 90% de. Cleavage of oxathiane and reduction of intermediate aldehyde produced diol **32**. The primary hydroxyl group was converted into cyanide **33**.

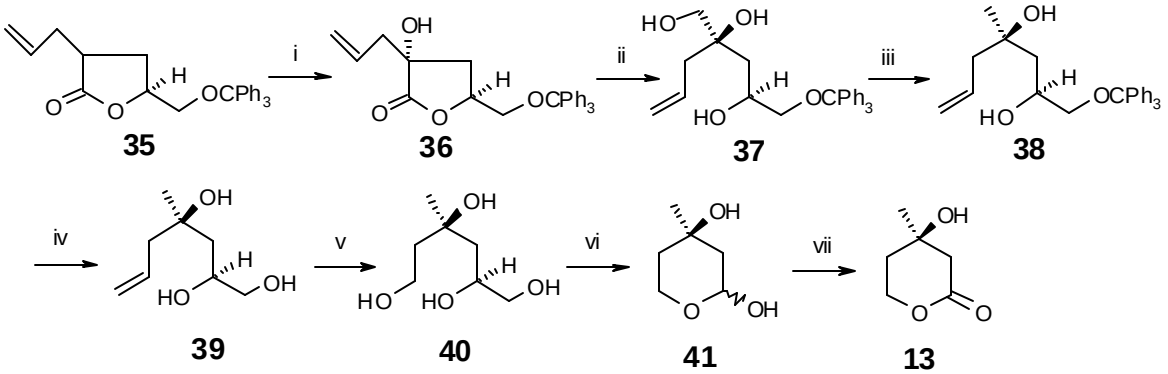
Hydroboration oxidation of **33**, cyano group hydrolysis and lactonization afforded (*R*)-mevalonolactone **13**.



Scheme 7. Reaction conditions: (i) *n*-BuLi, CH_3CHO, −78°C, 100%. (ii) Swern oxidation, 83%. (iii) $MgCl_2$, CH_2=CHMgBr, THF, −78°C, 100%. (iv) (a) NCS, $AgNO_3$, (b) $LiAlH_4$, 17%. (v) (a) *p*-TsCl, pyridine, 0°C, (b) KCN, EtOH-H_2O, rt, 60%. (vi) BH_3-THF, NaOH-H_2O_2. (vii) (a) 3N NaOH, 100°C, (b) 4N H_2SO_4, 30%.

Takano *et al.* (1984)[27] Scheme 8

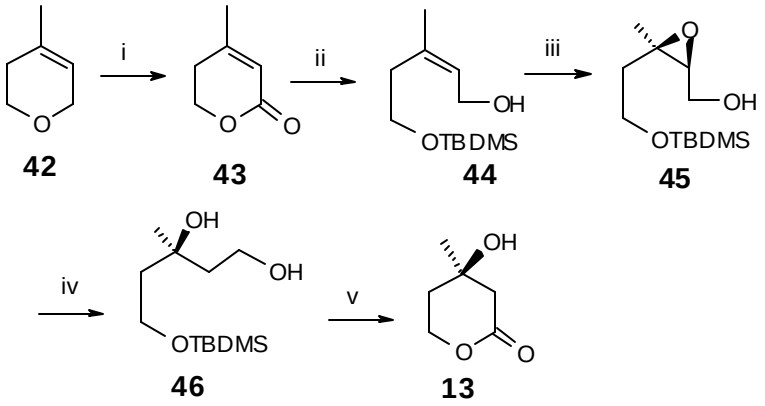
Takano and co-workers carried out the oxygenation of the lithium enolate generated from the known alkyl γ-lactone **35**[28a] (prepared from (*S*)-glutamic acid or D-mannitol) with 1.5 equivalents of MoOPH[28d] at −78°C to give **36** by diastereoselective reaction at the less hindered face of the molecule. Reduction of **36** with $LiAlH_4$, selective sulfonation of the primary hydroxyl and reduction of the tosylate produced the diol **38**. Detritylation of **38** to **39** and one-pot ozonolysis, reduction and cleavage of diol afforded the lactol **41**. PCC oxidation of **41** gave (*R*)-mevalonolactone **13**.



Scheme 8. Reaction conditions: (i) MoOPH, LDA, −78°C, 63%. (ii) $LiAlH_4$, THF, 0°C, 100%. (iii) (a) *p*-TsCl, pyridine, 0°C, 6 h, (b) $LiAlH_4$, THF, 0°C. (iv) cat. HCl, MeOH, 43% from **37**. (v) O_3, MeOH, −78°C, $NaBH_4$. (vi) aq. $NaIO_4$, 45%. (vii) PCC, CH_2Cl_2, rt, 89%.

Bonadies *et al*. (1984)[14a] Scheme 9

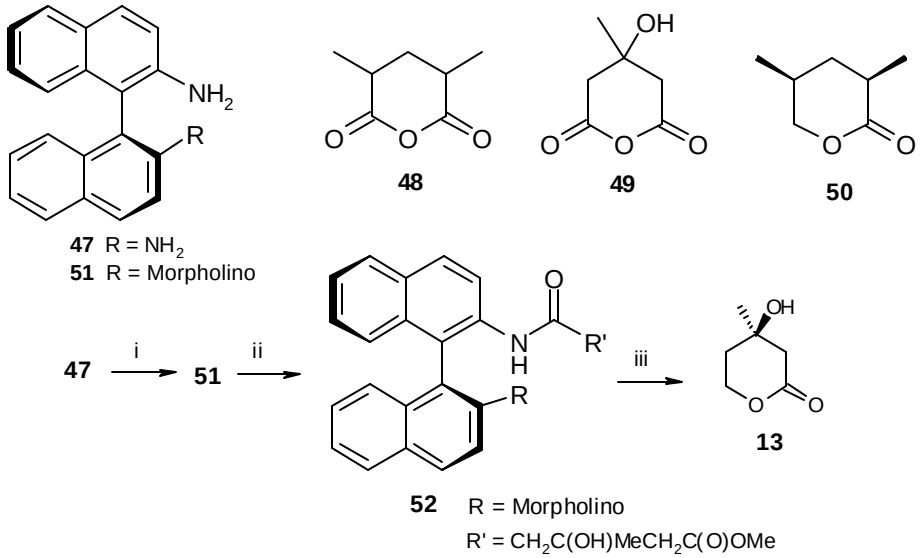
The Sharpless asymmetric epoxidation (SAE) reaction has been employed by Bonadies and co-workers in the synthesis of (*R*)-mevalonolactone. 4-Methyl-5,6-dihydropyran (**42**) is converted into the anhydromevalonolactone **43** by PCC oxidation. Sequential hydrolysis of lactone **43**, esterification followed by silylation of hydroxyl and ester reduction furnished allylic alcohol **44**. SAE of **44** using (+)-DET as the chiral catalyst gave **45**. Reductive opening of oxirane **45** produced **46**. Oxidation of primary hydroxyl to acid followed by deprotection of silyl group and lactonization gave **13**.



Scheme 9. Reaction conditions: (i) PCC, CH_2Cl_2, 70°C, 8 h, 85%. (ii) (a) 12N KOH, reflux, 15 min, CH_3I, DMF, rt, 24 h, (b) *t*-$BuMe_2Si$-Cl, DMAP, Et_3N, CH_2Cl_2, (c) DIBAL-H, $PhCH_3$, 0°C, 1 h, 55%. (iii) (+)-DET, *t*-BuOOH, $Ti(O\text{-}iPr)_4$, CH_2Cl_2, −30°C, 12 h, 98%. (iv) $LiBH_4$, THF, reflux, 2 h, 98%. (v) (a) $RuCl_3$, $NaIO_4$, CCl_4, CH_3CN, H_2O, rt, 1 h, (b) *p*-TsOH, CH_2Cl_2, 64%.

Oda *et al*. (1984)[19] Scheme 10

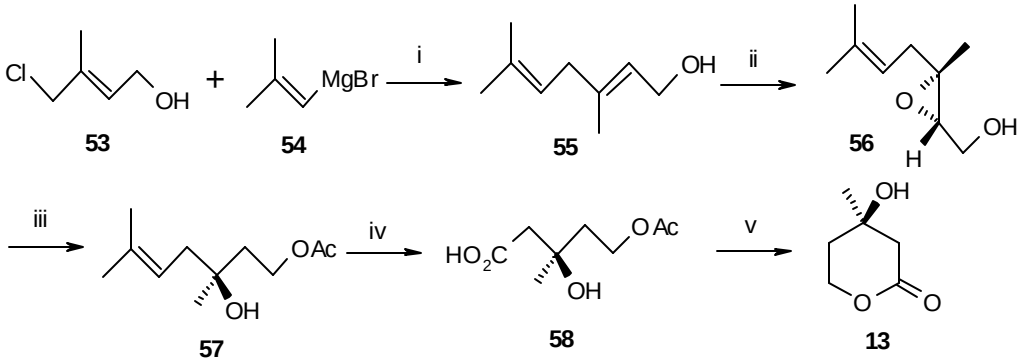
In Oda's approach, axially dissymmetric binaphthyldiamine derivatives formed by asymmetric ring opening of the cyclic anhydride **48** and **49** ring close on hydrolysis to give (–)-*cis* 2,4-dimethylvalerolactone **50** and (−)-mevalonolactone **13** in 92% and 58% enantiomeric excess respectively. Thus, the reductive alkylation of 1,1′-binaphthyl-2,2′-diamine [(−)-(*S*)-**47**] with 3-oxapentanedial using $NaCNBH_3$ gave the morpholino derivative **51**. An equimolar amount of 3-hydroxy-3-methyl anhydride **49** reacted with **51** to give after esterification the amide ester **52**. Selective reduction of the ester group and hydrolysis gave **13** in 58% ee.



Scheme 10. Reaction conditions: (i) $OHCCH_2$-O-CH_2CHO, $NaCNBH_3$. (ii) (a) **49**, (b) CH_2NH_2. (iii) $LiBH_4$, then hydrolysis, 44% from **51**.

Mori *et al*. (1985)[14b] **Scheme 11**

Mori and co-workers employed the SAE reaction on the allylic alcohol **55** to give **56**. Opening of epoxide **56** and monoacetylation produced **57**. Ozonolysis of **57** and oxidative workup gave the acid **58**. Acetate hydrolysis and subsequent lactonization afforded **13**.

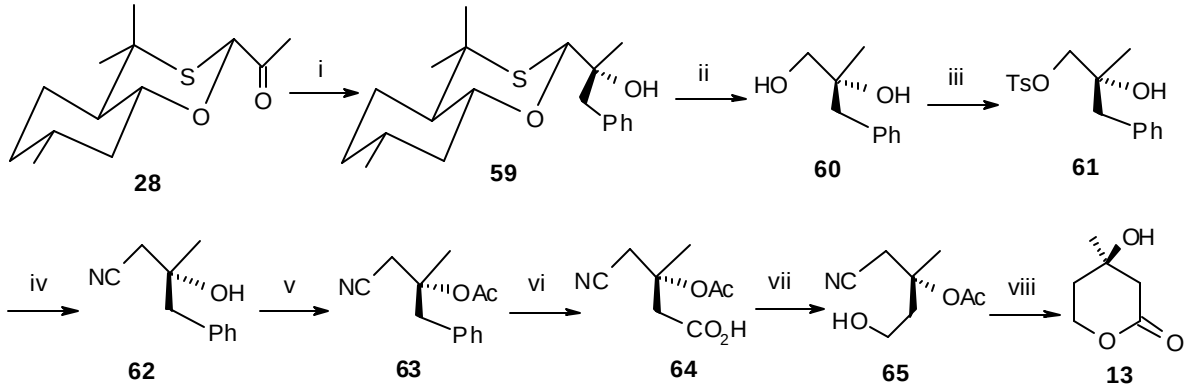


Scheme 11. Reaction conditions: (i) CuI, THF, −50°C, 88.3%. (ii) (+)-DET, Ti(O-*i*Pr)$_4$, *t*-BuOOH, CH_2Cl_2, −40°C to −30°C, 67.8%. (iii) (a) $LiAlH_4$, Et_2O, rt, 83.7%, (b) Ac_2O, pyridine, rt, 97%. (iv) O_3, −60°C, Jones oxidation, 100%. (v) (a) 2N NaOH, rt, (b) 4N H_2SO_4, 79.7%.

Eliel *et al*. (1985)[15a] **Scheme 12**

In an earlier synthesis, Eliel[26] carried out the reaction of vinyl magnesium bromide with ketone **28**. In this report, benzyl magnesium bromide was employed to give **59**. Cleavage of the oxathiane and reduction gave **60**. The primary hydroxyl group was converted into cyano

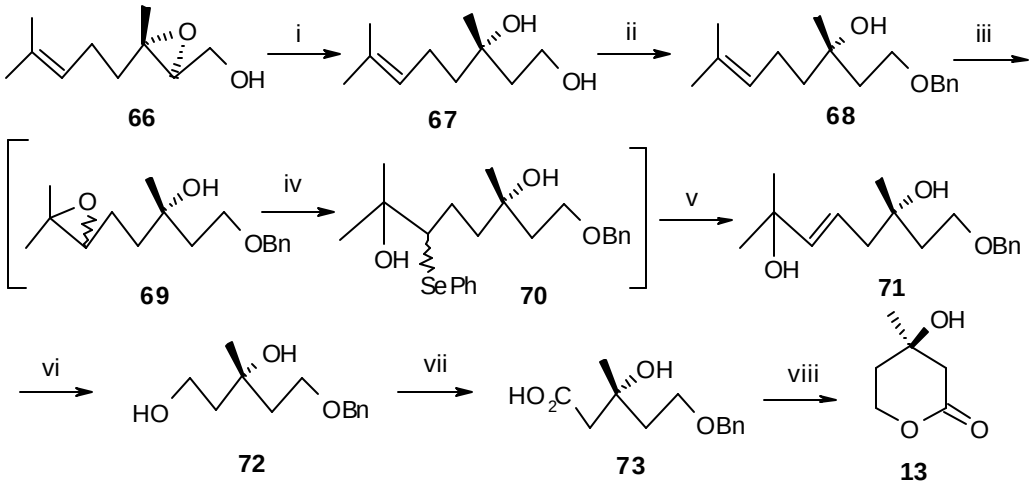
compound **62**. Acetylation of the hydroxyl group and oxidative degradation of the phenyl ring produced the carboxylic acid **64**. Reduction of acid **64** to alcohol **65**, cyanide hydrolysis and subsequent lactonization afforded **13** in 98% ee.



Scheme 12. Reaction conditions: (i) $PhCH_2MgBr$, −78°C, 98%. (ii) (a) NCS, $AgNO_3$, (b) $NaBH_4$, 80%. (iii) *p*-TsCl, pyridine, 0°C, 95%. (iv) KCN, EtOH, 0°C-rt, 95%. (v) Ac_2O, DMAP, 95°C, 6.5 h, 99%. (vi) $NaIO_4$, $RuCl_3$, CH_3CN, CCl_4, H_2O, 70°C, 14 h, 95%. (vii) BH_3-THF, THF, −50°C-rt, 20 h, 63%. (viii) (a) 3N NaOH, 30% aq. H_2O_2, 70°C, 6 h, (b) 6N HCl, 0.5 h, 58%.

Nozoe *et al.* (1989)[29] Scheme 13

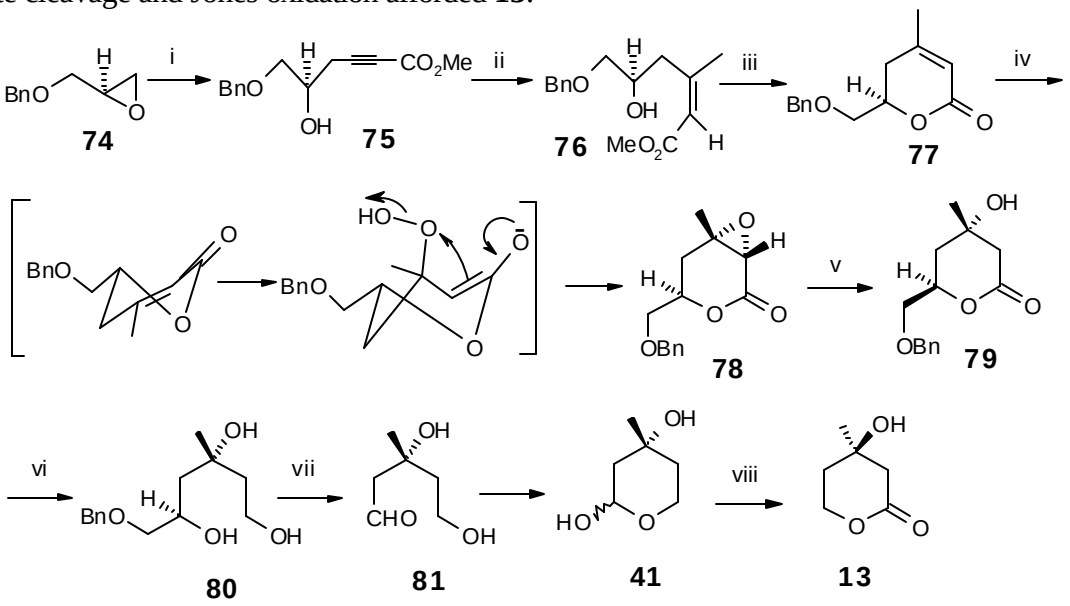
Nozoe and co-workers have utilized the geraniol epoxide **66**.[33] Ring opening of **66** gave 1,3-diol **67**. After benzylation, the 1-*O*-benzyl ether **68** is subjected to double bond migration according to the procedure by Sharpless and Laurer[30] to give the allylic alcohol **71**. Ozonolysis of **71** and reductive work-up produced **72**. Jones oxidation of **72** followed by hydrogenolysis, promoted lactonization to afford **13**.



Scheme 13. Reaction conditions: (i) $LiAlH_4$, Et_2O, reflux, 2 h, 78%. (ii) NaH, BnBr, DMF, 0°C, rt, overnight, 92%. (iii) *m*-CPBA, 7% aq. $NaHCO_3$, 0°C, 2 h. (iv) $(PhSe)_2$, $NaBH_4$, EtOH, reflux, 2 h. (v) Pyridine, 30% aq. H_2O_2, −15°C, 2 h, 0°C-rt, 3 h, 78%. (vi) O_3, MeOH, pyridine, −78°C, $NaBH_4$, rt, 36 h, 78%. (vii) Jones oxidation, 62%. (viii) 5% Pd-C, H_2, EtOH, 70%.

Takano *et al*. (1990)[31] Scheme 14

Takano and co-workers utilized (*S*)-*O*-benzylglycidol **74** as the chiral building block. Treatment of **74** with methyl lithiopropiolate followed by Michael addition with lithium dimethylcuprate gave the (*Z*)-olefin ester **76** which cyclized spontaneously to afford the α,β-unsaturated-δ-lactone **77**. Epoxidation of **77** gave rise **78** as a single epimer due to favorable streoelectronic effect of the α,β-unsaturated-δ-lactone system **77**. Regioselective cleavage of epoxide and reduction of lactone **79** furnished the triol **80**, which on sequential debenzylation, periodate cleavage and Jones oxidation afforded **13**.

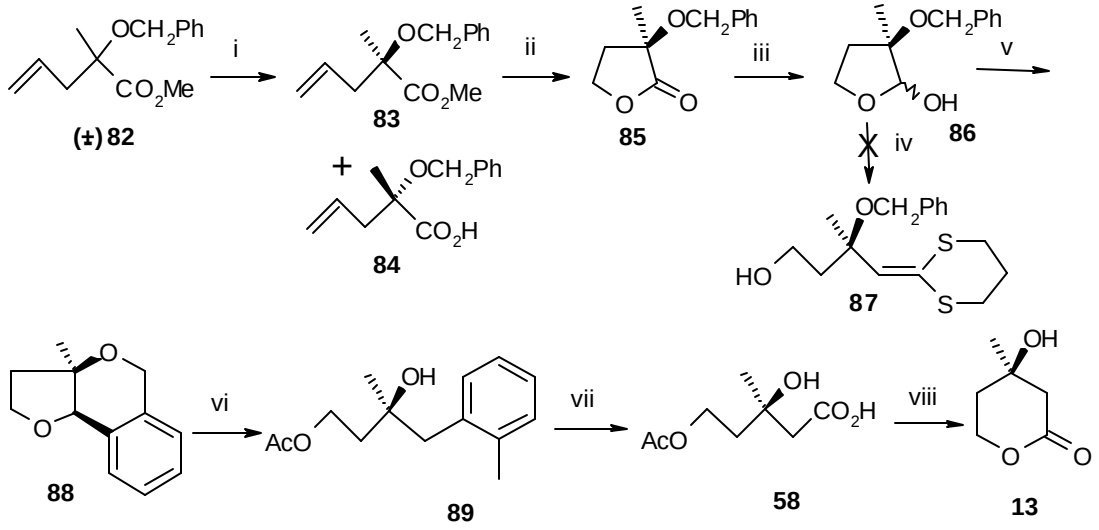


Scheme 14. Reaction conditions: (i) Methyl propiolate, *n*-BuLi, $BF_3.Et_2O$, THF, −90°C, 84%. (ii) Me_2CuLi, THF, −70°C. (iii) NH_4Cl, 91%. (iv) 30% H_2O_2, 6N NaOH, MeOH, 70%. (v) $(PhSe)_2$, $NaBH_4$, CH_3CO_2H, *i*-PrOH, 90%. (vi) $LiAlH_4$, THF, 100%. (vii) (a) H_2, $Pd(OH)_2$-C, MeOH, (b) HIO_4, H_2O. (viii) H_2SO_4, CrO_3, 79% from **80**.

Ohta *et al*. (1990)[21a] Scheme 15

Ohta and co-workers employed lipase OF in resolving the starting material (±)-**82** to give (*R*)-**83** and (*S*)-**84**. Ozonolysis of **83** and reductive work-up followed by DIBAL-H reduction gave

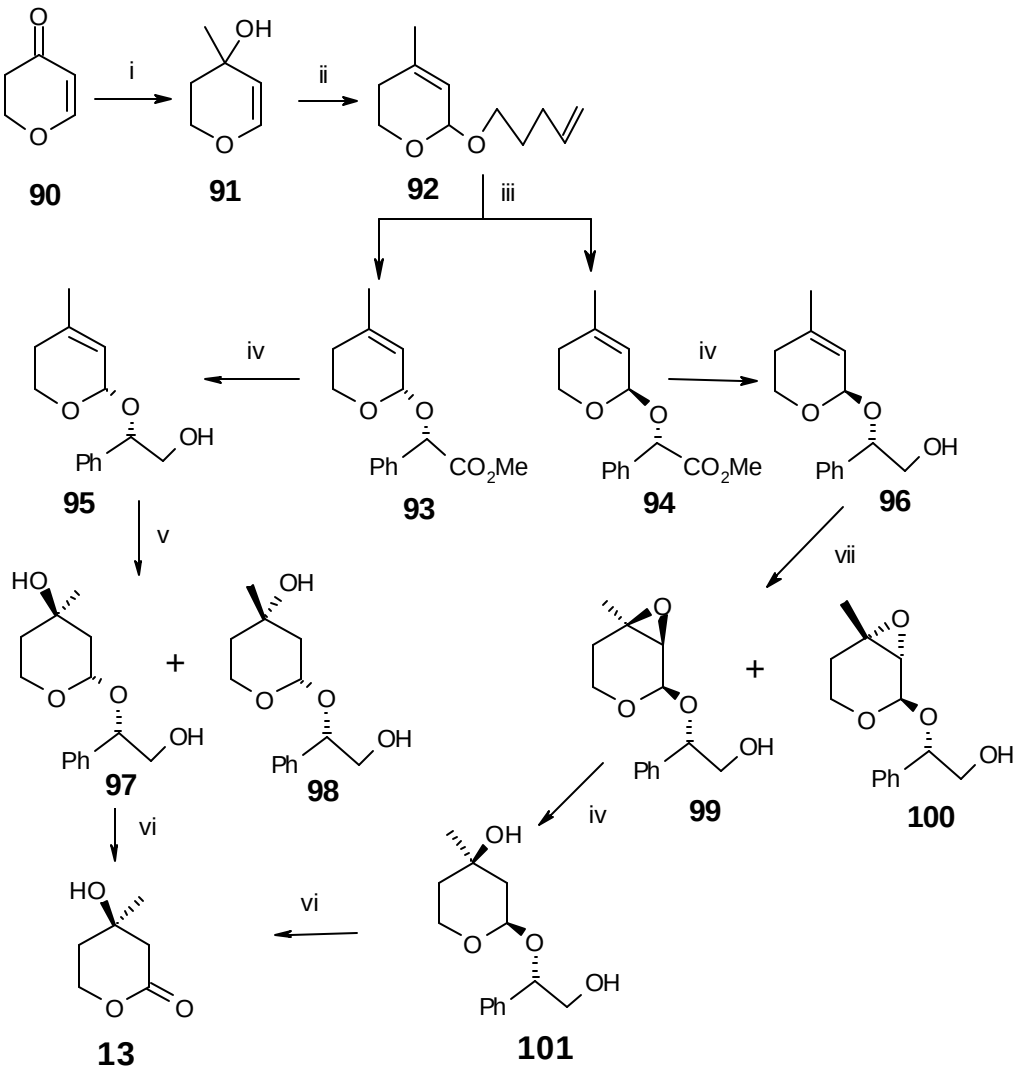
the lactol **86**. The lactol **86** on treatment with dithioacetal-stabilized phosphonate gave the unusual product **88** in presence of $BF_3.Et_2O$ instead of expected **87** probably *via* intramolecular Friedel-Craft type reaction. Compound **88** on hydrogenation followed by acetylation afforded **89**. Thus, a carbon chain elongation was achieved with the aid of protecting group without adding any special carbon source. Ozonolysis of **89** and oxidative work-up gave the acid **58**. Hydrolysis of acetate **58** and acidification afforded **13**.



Scheme 15. Reaction conditions: (i) Lipase OF. (ii) O_3, MeOH, $NaBH_4$, 86%. (iii) DIBAL-H, 84.8%. (iv) diethyl dithioacetalphosphonate. (v) $BF_3.Et_2O$, diethyl dithioacetalphosphonate. (vi) (a) H_2, Pd-C, AcOH, (b) Ac_2O, Pyridine, 94.4%. (vii) O_3, Acetone, H_2O_2. (viii) (a) aq. K_2CO_3, (b) H^+, 32.4% from **89**.

Mash *et al*. (1991)[15b] **Scheme 16**

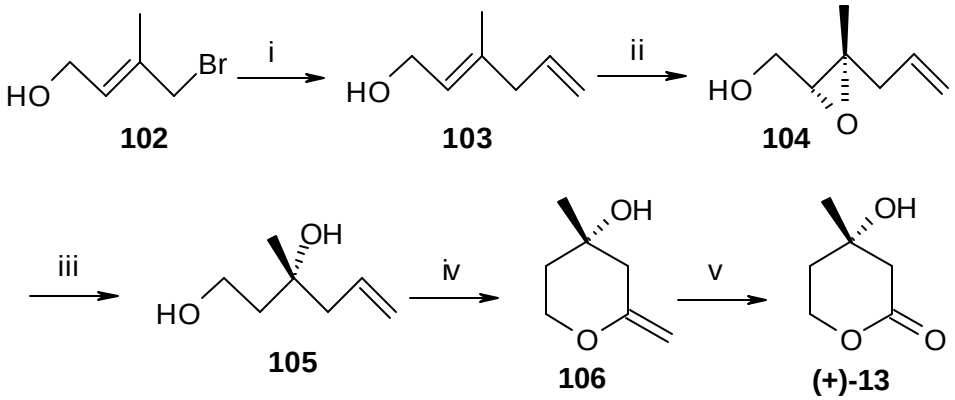
In Mash's approach, the reaction of pentenyl pyranoside **92** with iodonium bis-collidine perchlorate in the presence of (*S*)-(+)-methyl mandelate produced chromatographically separable diastereomers **93** and **94**. Both were reduced with $LiAlH_4$ to give **95** and **96** respectively. Oxymercuration-demercuration of **95** produced separable diastereomeric diols **97** and **98**. Hydrolysis of **97** gave the hemiacetal, which on subsequent oxidation afforded **13**. On the other hand, treatment of **96** with *m*-CPBA produced separable diastereomeric epoxides **99** and **100**. Reductive epoxide opening of **99** afforded **101**, which on subsequent hydrolysis and oxidation furnished **13**.



Scheme 16. Reaction conditions: (i) CH_3Li, Et_2O, −78°C, 0.25 h. (ii) 4-penten-1-ol, PPTS, 5 h, 91%. (iii) (*S*)-methyl mandelate, iodonium bis-collidine perchlorate, 0°C, 1 h, 36% (**93**), 35% (**94**). (iv) $LiAlH_4$, THF, 0°C, 100% (**95**), 97% (**96**). (v) (a) $Hg(OAc)_2$, 0°C, 18 h, (b) $NaBH_4$, 69% (**97**), 9% (**98**). (vi) (a) 10% aq. HCl, THF, 0.5 h, (b) PCC, 3A° molecular sieves, CH_2Cl_2, 7 h, rt, 76-74%. (vii) *m*-CPBA, CH_2Cl_2, 0°C, 18 h, 93% (**99**), 7% (**100**).

Mioskowski *et al*. (1991)[32] Scheme 17

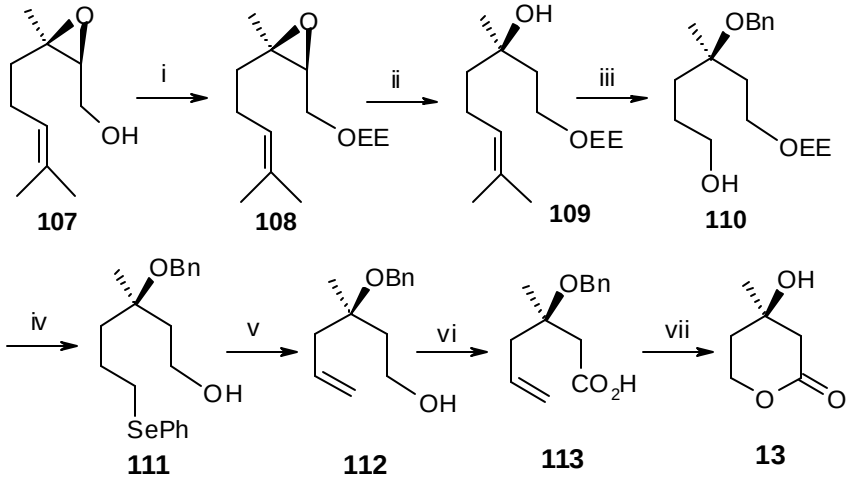
Mioskowski and co-workers employed the SAE of **103** to give the epoxide **104**. Reductive opening of epoxide **104** to diol **105** and iodoetherification followed by DBN-mediated dehydrohalogenation afforded **106**. Ozonolysis of **106** gave (+)-mevalonolactone (*S*)-**13**.



Scheme 17. Reaction conditions: (i) Vinyl magnesium bromide, CuI, THF, −50°C-rt, 10 h, 60%. (ii) Ti(O*i*-Pr)$_4$, *t*-BuOOH, (–)-DET, CH_2Cl_2, −40°C to −30°C, 20 h, 98%. (iii) $LiAlH_4$, Et_2O, 0°C, 10 h, 80%. (iv) I_2, $NaHCO_3$, DBN, 70%. (v) O_3, CH_2Cl_2:MeOH (4:1), −78°C, 84%.

Spencer *et al*. (1991)[14d] Scheme 18

Spencer and co-workers employed epoxide **107**[33] prepared by SAE of nerol. Hydroxyl group protection and reductive opening of epoxide gave **109**, which on hydroxyl group protection followed by ozonolysis and reductive work-up afforded **110**. Alcohol **110** is converted to olefin **112** *via* phenyl-selenoxide formation-elimination reaction and deprotection of ethoxy ethyl ether group. The primary hydroxyl group in **112** was oxidized to give the acid **113**, which on reductive ozonolysis followed by debenzylation furnished **13**.

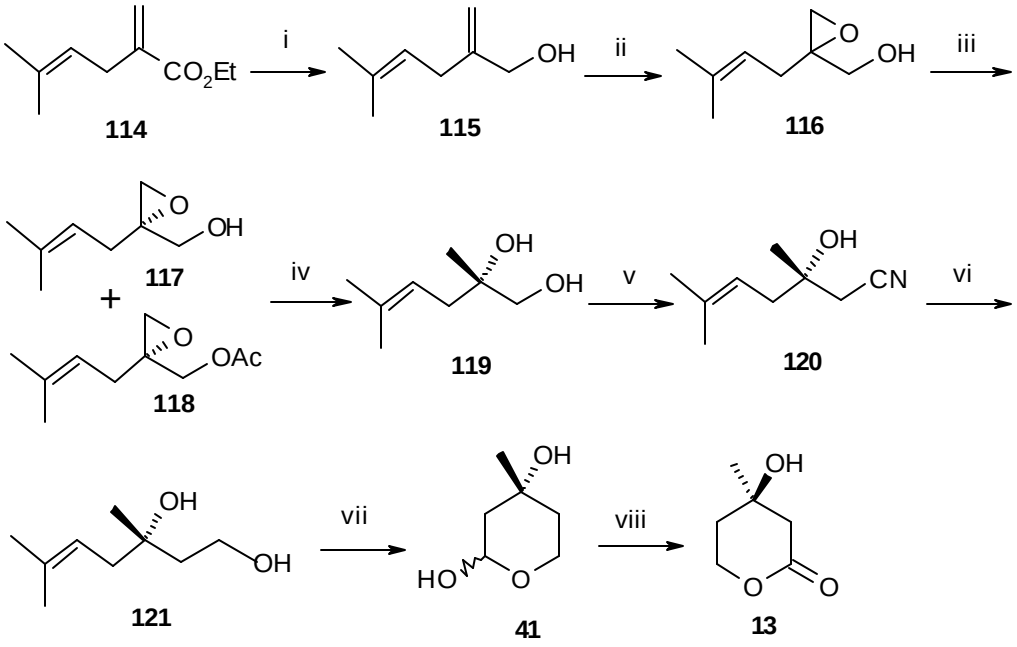


Scheme 18. Reaction conditions: (i) Ethyl vinyl ether, *p*-TsOH, 0°C-rt, 1 h, 95%. (ii) $LiAlH_4$, Et_2O, 0°C-rt, 16 h, 92%. (iii) (a) BnBr, KH, THF, 0°C-rt, 16 h, 97%. (b) O_3, CH_2Cl_2:pyridine (99:1), −78°C then $LiAlH_4$, Et_2O, 0°C, 80%. (iv) (a) N-(Phenylseleno) phthalimide, *n*-Bu_3P, CH_2Cl_2, 0°C, 87%, (b) 70-230 mesh silica gel–4M HCl, CH_2Cl_2, 0°C, 1 h. (v) N-(*p*-toluenesulfonyl)phenyloxaziridine, (*i*-Pr)$_2$NH, $CHCl_3$, 0°C, 15 h, rt, 20 h, reflux, 1 h, 100%. (vi)

PDC, DMF, rt, 36 h, 67%. (vii) (a) O_3, MeOH:CH_2Cl_2 (4:1), −78°C, $NaBH_4$, 71%, (b) 10% Pd/C, HCO_2NH_4, MeOH, 2 h, reflux, 88%.

Santaniello *et al*. (1994)[21b] Scheme 19

Santaniello *et al*. employed *Pseudomonas fluorescens* lipase (PFL) to resolve racemic 2-(3-methyl-2-butenyl)-oxirane methanol **116** to give (−)-epoxyalcohol **117** and (+)-acetate **118** in 98% ee. The epoxyalcohol on reduction gave the diol **119**. The primary hydroxyl is converted into cyanide **120**. Hydrolysis of cyanide **120** to acid and reduction produced the alcohol **121**. Ozonolysis of **121** followed by reduction of ozonide with polymeric triphenylphosphine furnished lactol **41**, which was directly oxidized with PCC to give **13**.

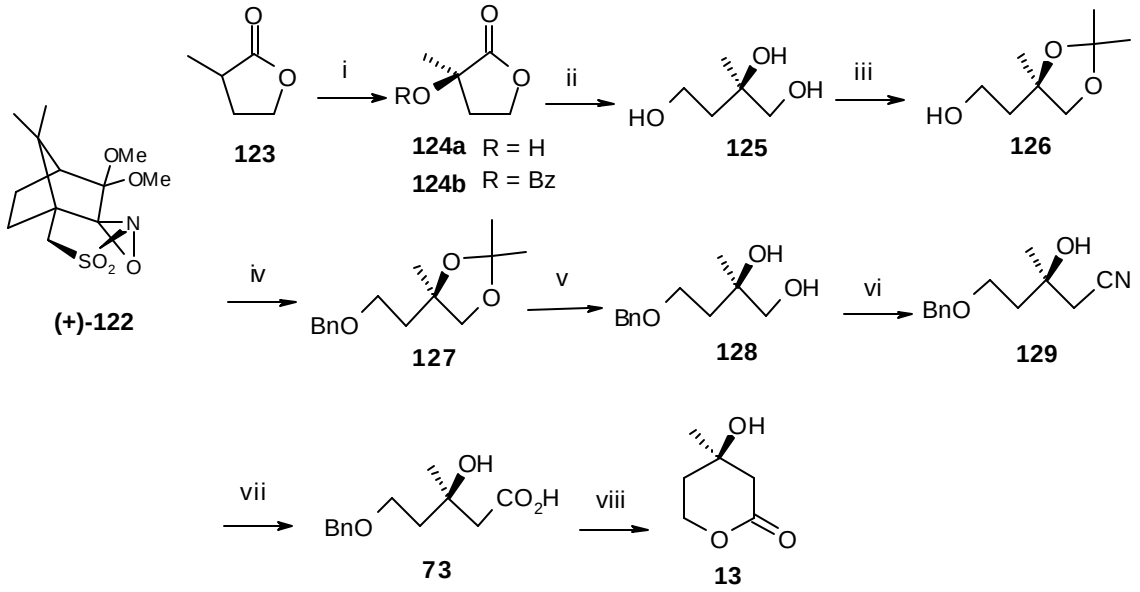


Scheme 19. Reaction conditions: (i) DIBAL-H, hexane. (ii) *t*-BuOOH, $VO(acac)_2$. (iii) PFL, vinyl acetate, $CHCl_3$. (iv) $LiAlH_4$. (v) (a) *p*-TsCl, pyridine, (b) KCN, EtOH:H_2O, rt. (vi) (a) NaOH, 100°C, 8 h then H_2SO_4, (b) $LiAlH_4$. (vii) O_3, $(PPh_3)_n$. (viii) PCC.

Davis *et al*. (1995)[34] Scheme 20

Davis and co-workers used [(8,8-dimethoxycamphoryl)sulfonyl] oxaziridine **122** to achieve asymmetric hydroxylation of the enolate of lactone **123** to give **124a**. Since it proved impossible to isolate **124a** from the reaction mixture, the alkoxide was trapped *in situ* with benzoylchloride to give the crystalline adduct **124b**. Reduction of **124b** and protection of 1,2-hydroxyl groups as

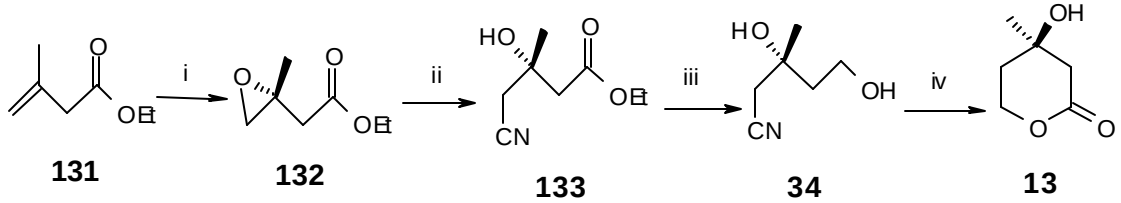
acetonide **126**, followed by protection of the third hydroxyl as benzyl ether gave **127**. Deprotection of acetonide and primary hydroxyl conversion into the cyanide afforded **129**. Hydrolysis of cyanide **129** and subsequent debenzylation furnished (*R*)-(−)-mevalonolactone **13**.



Scheme 20. Reaction conditions: (i) NaHMDS, −78°C, (+)-**122**, PhCOCl, 70%. (ii) $LiAlH_4$, THF, 0°C-rt, 5 h, 70%. (iii) 2,2-DMP, *p*-TsOH, rt, 2 h, 84 %. (iv) NaH, TBAI, BnBr, 90%. (v) H_2SO_4, H_2O, 5 h, 93%. (vi) (a) *p*-TsCl, pyridine, 89%, (b) KCN, EtOH/H_2O, 0°C-rt, 8 h, 94%. (vii) 3N NaOH, H_2O_2, 90°C, 1 h, 75%. (viii) Pd/C, H_2, THF, 8-10 h, 88%.

Hager *et al*. (1996)[23] Scheme 21

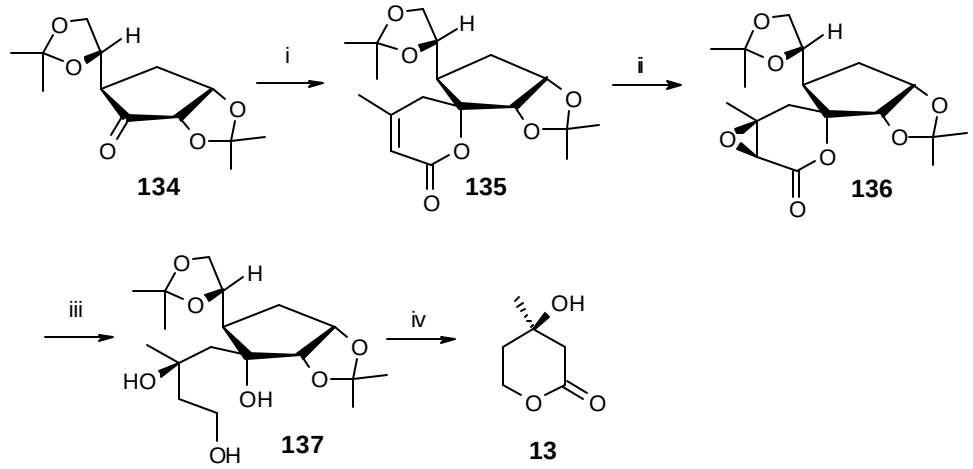
Hager *et al*. employed chloroperoxidase (CPO) in enantioselective epoxidation of ethyl-3-methyl-3-butenoate **131** to give **132** in 93% ee. Opening of epoxide **132** with cyanide and reduction of ester afforded **34**, which on hydrolysis and subsequent lactonization furnished **13**.



Scheme 21. Reaction conditions: (i) *t*-BuOOH, CPO, 0.01M Sodium citrate, pH 5.5, 1.5 h, 67%. (ii) KCN, CF_3CO_2H, EtOH, 50°C, 14 h, 90%. (iii) $NaBH_4$, EtOH, 16 h, 98%. (iv) (a) 2N NaOH, 100°C, 2 h, (b) 10% HCl, MeOH, CH_3SO_3H, THF, 3 h, 81%.

Kakinuma *et al*. (1997)[16] Scheme 22

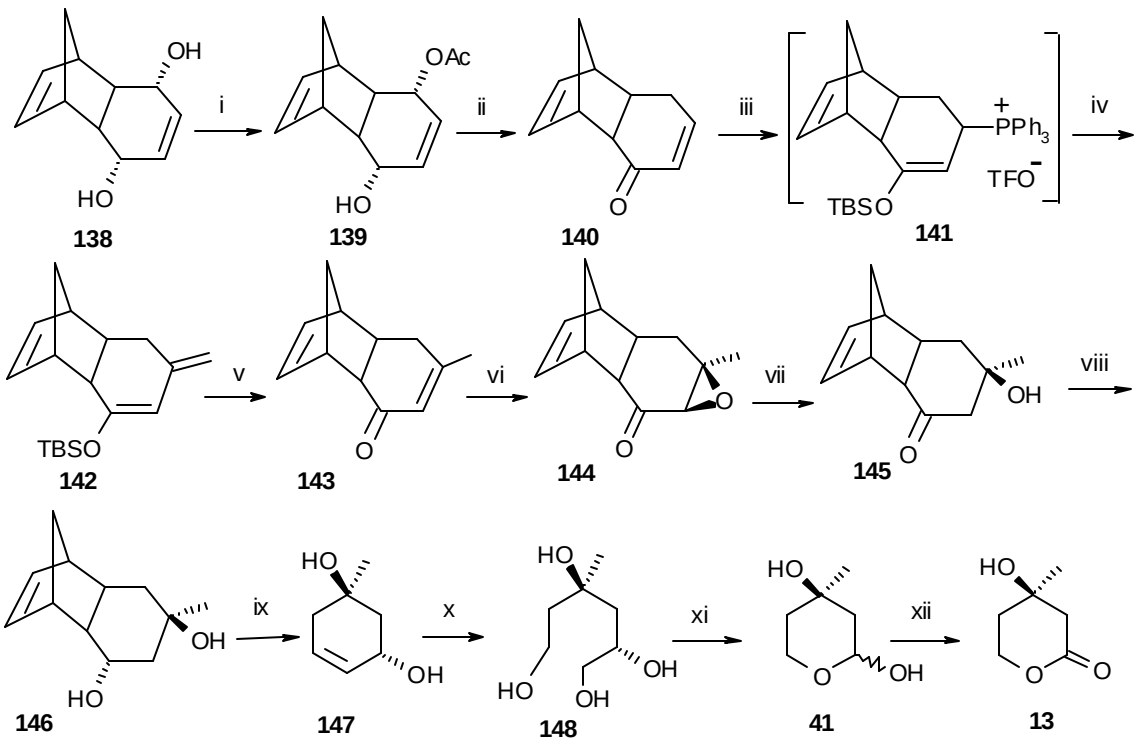
Kakinuma *et al*. employed the chirality transcription from chiral template ketone−diacetone-D-glucos-3-ulose **134** in the addition of an enolate of methyl senecioate to give **135**. The crucial step in the synthesis was subsequent epoxidation of **135** using alkaline H_2O_2 to give **136**. Simultaneous reduction of epoxide and lactone functionalities in **136** afforded the triol **137**. Deprotection of isopropylidene groups and subsequent exhaustive oxidation with $NaIO_4$ furnished (*R*)-(−)-mevalonolactone **13**.



Scheme 22. Reaction conditions: (i) $(CH_3)_2C{=}CHCO_2Me$, LDA, THF, −78°C, 20 min, 31%. (ii) 31% H_2O_2, NaOH, MeOH, 2.5 h, rt, 87%. (iii) $LiAlH_4$, THF, rt, 1 h, 87%. (iv) (a) CF_3CO_2H, 2 h, rt, (b) $NaIO_4$, H_2O, 8 h, rt, 47%.

Ogasawara *et al*. (1997)[35] Scheme 23

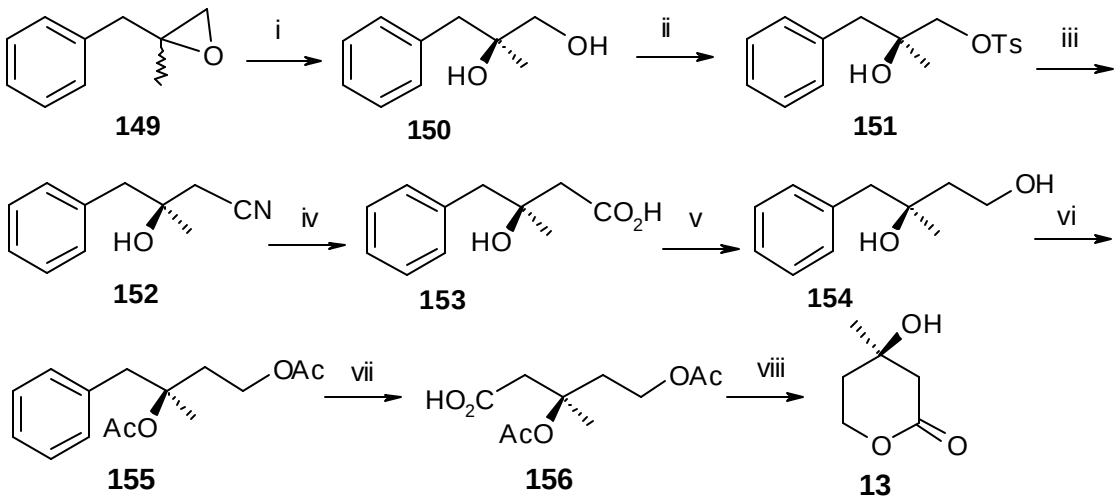
In Ogasawara's approach, the tricyclic meso-ene-1,4-diol **138** was enantiospecifically desymmetrized in the presence of a lipase to give the enantiomerically pure (+)-monoacetate **139** which on reflux with ammonium formate in the presence of $PdCl_2(PPh_3)_2$ (cat) furnished α,β-unsaturated ketone **140**. Ketone **140** was subjected to β-methylation procedure[36] to give β-methyl enone **143** followed by epoxidation to furnish *exo*-epoxide **144**. Regioselective epoxide cleavage and ketone reduction afforded 1,3-*trans*-diol **146** by hydride attack from the convex face. Thermolysis of **146** furnished cyclohexendiol **147** by retro-Diels-Alder reaction. Ozonolysis of **147** and reductive work-up followed by cleavage of glycol and cyclization afforded the lactol **41**, which was oxidized with Jones reagent to give **13**.



Scheme 23. Reaction conditions: (i) Lipase PS, vinyl acetate, THF, rt, 4 d, 85%, 99% ee. (ii) HCO_2NH_4, $PdCl_2(PPh_3)_2$ (cat), MeCN, reflux, 20 min, 80%. (iii) PPh_3, TBSOTf, THF, −78°C. (iv) *n*-BuLi, THF, −78°C, HCHO (gas). (v) 5% HCl, 78%. (vi) 30% H_2O_2, 0.5N NaOH, MeOH, 0°C, 88%. (vii) Al-Hg, *i*-PrOH, rt, 98%. (viii) DIBAL-H, CH_2Cl_2, −78°C, 89%. (ix) Ph_2O, $NaHCO_3$, reflux, 30 min, 82%. (x) O_3, MeOH, −78°C, and then $NaBH_4$. (xi) $NaIO_4$. (xii) Jones reagent, 40% from **147**.

Orru *et al*. (1998)[24] Scheme 24

Orru *et al*. employed an enantioconvergent chemoenzymatic route to deracemize 2-benzyl-2-methyloxirane **149** using lyophilized cells of *Nocardia* EH1 and sulphuric acid to get the (*S*)-diol **150** in 94% optical purity. Compound **150** was converted into the β-hydroxy acid **153** by tosylation of primary hydroxyl to **151**, cyanide displacement to **152** and hydrolysis. Reduction of acid **153** and acetylation gave the diacetate **155**. Oxidation of aryl group, saponification of acetates followed by lactonization afforded **13** in 99% ee.



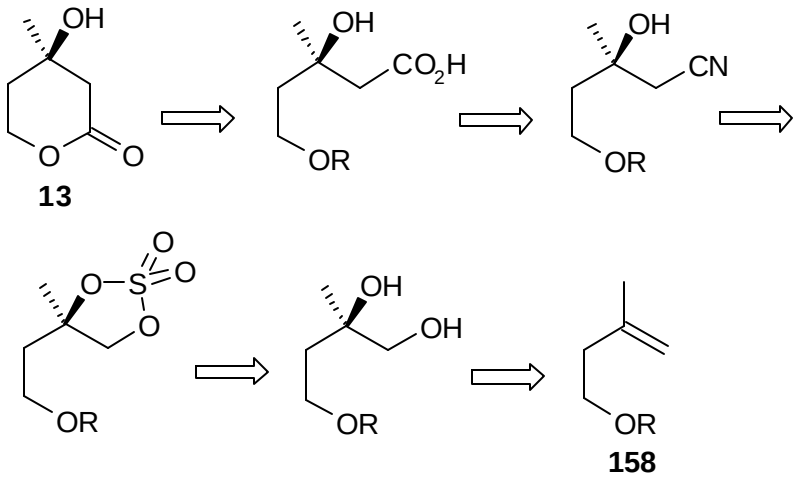
Scheme 24. Reaction conditions: (i) (a) *Nocardia* EH1, Tris, pH 7.5, 35°C, 48 h, (b) H_2SO_4 (cat), 0°C, rt, 15 min, dioxane-H_2O, 94%. (ii) *p*-TsCl, pyridine, rt, 18 h 95%. (iii) KCN, EtOH-H_2O, 0°C, rt, 18 h, 100%. (iv) (a) 30% H_2O_2, 3M NaOH, 65°C, 1 h, (b) 6M HCl, 96%. (v) $LiAlH_4$, THF, reflux, 1 h, 93%. (vi) Ac_2O, DMAP, 95°C, 4 h, 100%. (vii) (a) $NaIO_4$, $RuCl_3$-cat, CH_3CN-CCl_4-H_2O, (b) aq. HCl, 72%. (viii) (a) K_2CO_3, MeOH, reflux, (b) aq. HCl, pH 1, 97%.

2.2.3. Present Work

Objective:

Although several syntheses of both (+)- and (–)-mevalonolactone are documented in the literature through varied synthetic routes, most involve a large number of steps or costly chiral auxiliaries and resolving agents. Hence, interest in newer synthetic methods with fewer steps goes unabated.

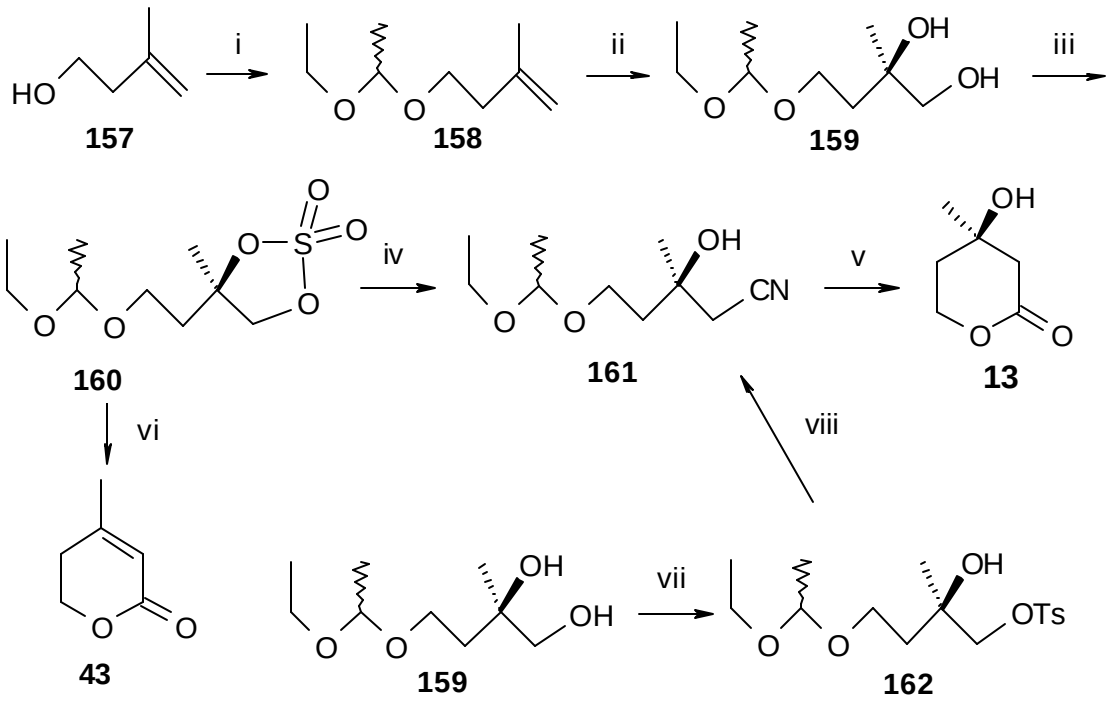
Since a cyclic sulfate derived from terminal diol could be converted into β-hydroxy-δ-lactone, we envisaged devising an asymmetric synthesis of (*R*)-(–)-mevalonolactone. The retrosynthetic analysis is shown below (**Scheme 25**). The β-hydroxy acid was visualized as an ultimate precursor to the target molecule. The essential feature of our retroanalysis was the regioselective opening of cyclic sulfate with cyanide at the terminal carbon and the chemoselective hydrolysis of the sulfate ester to give the desired β-hydroxy acid. Deprotection of the C-5 hydroxyl and lactonization would give (*R*)-(–)-mevalonolactone **13**.



Scheme 25: Retrosynthetic Analysis

2.2.4. Results and Discussion

The detailed synthetic strategy involving the SAD and regioselective opening of cyclic sulfate by cyanide nucleophile as key steps is given in **Scheme 26**. Commercially available 3-methyl-3-butene-1-ol (**157**) was protected with ethyl vinyl ether in the presence of catalytic *p*-TsOH at 0°C to give **158** in 93% yield. The IR spectrum of **158** showed C=C stretching at 1648 cm^{-1} and absence of hydroxyl absorption. In the ^1H NMR spectrum the terminal olefin protons gave a doublet at δ 4.76. The SAD of **158** using $(DHQD)_2$-PHAL as chiral ligand and OsO_4 (cat) gave the diol **159** in 97% yield. The IR spectrum of **159** showed hydroxyl absorption at 3430 cm^{-1} and absence of C=C stretching. The ^1H NMR spectrum showed absence of olefin peaks, while two



Scheme 26. Reaction conditions: (i) Ethyl vinyl ether, *p*-TsOH (cat), 0°C, 1 h, 93%. (ii) $(DHQD)_2$-PHAL, OsO_4 (cat), $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH:H_2O (1:1), 0°C, 24 h, 97%. (iii) (a) $SOCl_2$, Et_3N, CH_2Cl_2, 0°C, 20 min, (b) $RuCl_3.H_2O$, $NaIO_4$, CCl_4:CH_3CN:H_2O (1:1:1.5), 0°C, 2 h, 92%. (iv) NaCN, DMF, 80°C, 8 h, then THF, conc. H_2SO_4:H_2O (2:1), rt, 6 h (85%). (v) 3N NaOH, 70°C, 3 h, then MeOH, pH 2 (conc. HCl), acetone, *p*-TsOH (cat), rt, 8 h, 70%. (vi) NaCN, DMF, 80°C, 8 h, then conc. H_2SO_4 (2 eq.), EtOH:H_2O (1:2), reflux, 18 h, 60%. (vii) *p*-TsCl, pyridine, rt, 18 h, 96%. (viii) NaCN, EtOH:H_2O (3:2), rt, 18 h, 97%.

broad singlets for hydroxyl protons appeared at δ 2.17 and 2.97. Diol **159** was treated with $SOCl_2$ and Et_3N to produce the cyclic sulfite, which was further oxidized using $NaIO_4$ and a catalytic amount of $RuCl_3.H_2O$ to give the cyclic sulfate **160** in 92% yield. The IR spectrum of **160** showed the absence of hydroxyl absorption. A downfield shift in the ^1H NMR spectrum, of $-CH_2-SO_2-$ protons to δ 4.4-4.6 as multiplet was observed in comparison to the same protons of **159** at δ 3.43 (multiplet). The regioselective opening of cyclic sulfate **160** was presumed to occur at the terminal carbon in a nucleophilic attack. Hence, the cyclic sulfate was treated in DMF solvent with NaCN at 80°C followed by chemoselective hydrolysis[37] of the intermediate sulfate ester under mild conditions using H_2SO_4 and minimum water to give the β-hydroxy cyano compound **161** in 85% yield. Under these conditions the ethoxy ethyl ether group remained intact. The IR spectrum of **161** showed strong absorption at 3470 cm^{-1} for hydroxyl group and a weak C≡N stretching at 2250 cm^{-1}. The $-CH_2CN$ protons appeared as a doublet at δ 2.58 in the ^1H NMR spectrum of **161** and the cyanide carbon appeared at δ 117.54 in the ^{13}C NMR spectrum.

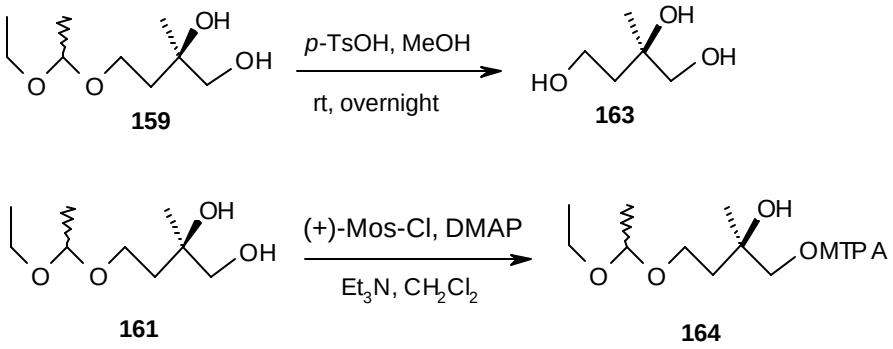
Alternatively, the cyano compound **161** was obtained from diol **159** *via* monotosylation and tosyl displacement with cyanide. Toward this end, treatment of diol **159** with *p*-TsCl and pyridine at room temperature afforded the mono-tosylate **162** in 96% yield. The ^1H NMR spectrum of **162** showed the aryl methyl as a singlet at δ 2.45 and two doublets at δ 7.36 and 7.80 with coupling constant J = 8 Hz for *ortho* coupled protons, indicating a tosyl group. The tosylate **162** was treated with NaCN in EtOH:H_2O (3:2, v/v) at 0°C to room temperature for 18 h to afford **161** in 97% yield. All data for **161** prepared *via* tosyl displacement matched well with the same prepared *via* cyclic sulfate opening.

The cyano compound **161** was hydrolyzed with aq. 3N NaOH at 70°C to give the corresponding acid which without isolation, was treated with *p*-TsOH in acetone to effect both ethoxy ethyl ether deprotection and lactonization to give (*R*)-mevalonolactone **13** in 70% yield. The $[\alpha]_D^{20}$ – 19.1 (c = 0.4, EtOH) matched with the literature value of $[\alpha]_D^{20}$ – 21.6 (c = 1.565, 95% EtOH)[15a] and $[\alpha]_D^{25}$ – 19.0 (c = 2.15, $CHCl_3$).[23] The lactone **13** was characterized by IR, ^1H NMR and EIMS spectral data. The IR spectrum of **13** showed strong hydroxyl absorption at 3400 cm^{-1} and the characteristic carbonyl of δ-lactone at 1732 cm^{-1}. In the ^1H NMR spectrum the methyl protons appeared as a singlet at δ 1.39 and the methylene protons α- to carbonyl as two doublets at δ 2.5 and 2.7 with a coupling constant of J = 18 Hz. The hydroxyl proton gave a

broad singlet at δ 2.6. The $-OCH_2-$ protons gave two multiplets at δ 4.36 and 4.62. The EIMS spectrum of **13** gave [M^+] peak at *m/z* 130 and other characteristic peaks at *m/z* 115, 85, 71 and 58. The IR, ^{1}H NMR and EIMS of **13** are in well accordance with the literature data.[24]

The attempt to achieve the one-pot cyclic sulfate opening with NaCN followed by hydrolysis of sulfate ester and cyano group to the corresponding β-hydroxy acid with concomitant deprotection of the ethoxy ethyl ether linkage and subsequent lactonization to the target lactone **13** in strong acid media failed. Thus, when the cyclic sulfate **160** was heated with NaCN in DMF solvent at 80°C, it gave the intermediate sulfate ester. Removal of solvent and treatment of residual sulfate ester with aq. ethanolic solution of conc. H_2SO_4 under reflux gave only the anhydromevalonolactone **43**. This indicates that in one-pot reaction, sulfate opening with cyanide is followed by acidic hydrolysis of cyanide to acid with simultaneous hydrolysis of sulfate ester as well as deprotection of ethoxy ethyl ether group to give the lactone **13**. However, under strong acidic conditions the anhydromevalonolactone **43** was formed presumably by facile dehydration of the β-hydroxyl group of **13** to give the stable α,β-unsaturated-δ-lactone. Lactone **43** was fully characterized by IR, ^{1}H NMR and EIMS spectral data, which matched well with reported data.[38] The IR spectrum of **43** showed carbonyl absorption at 1721 cm^{-1} and absence of hydroxyl absorption. The ^{1}H NMR spectrum exhibited a singlet at δ 1.99 for the methyl group, two triplets at δ 2.33 and 4.39 for methylene protons and a singlet at δ 5.79 for the olefin proton. The EIMS spectrum gave molecular ion peak at *m/z* 112.

To determine the enantiomeic purity, the diol **159** was converted into triol **163**. The enantiomeric excess of 89% for **163** was estimated by GLC using the chiral column Chirasil-Val-D (25m x 0.32mm I.D.) at 120°C for 5 min, 10°C/min to 220°C (**Figure 2**). The enantiomeric purity of **161** was determined by converting it into the (+)-MTPA[39] ester **164** and ^{1}H NMR analysis. The diastereomeric excess of 89% was indicated based on the integration of the characteristic methylene resonance α- to the cyano group, doublet in the δ 2.59-2.61 region due to the MTPA ester portion.



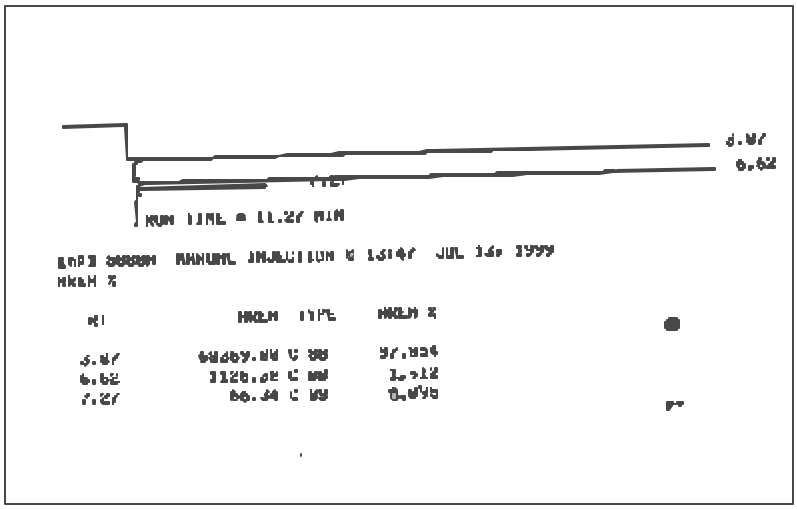


Figure 2. Chiral GLC profile for compound **163**.

2.2.5. Conclusion

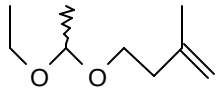
In conclusion, a short and high yielding asymmetric synthesis of (*R*)-mevalonolactone has been achieved through the Sharpless asymmetric dihydroxylation and regioselective cyanide opening of cyclic sulfate as the key steps for the first time.[40] Thus, the results described herein constitute a short and efficient synthesis of natural isomer of mevalonolactone. The unnatural (+)-isomer of mevalonolactone could also be synthesized *via* α-dihydroxylation using $(DHQ)_2$-PHAL instead of $(DHQD)_2$-PHAL as the chiral ligand. The synthetic strategy can be employed in general to make β-hydroxy lactones of varied ring size and also the chiral substituted β-hydroxy acids,[41] which serve as important synthons for several naturally occurring and bioactive molecules.

2.2.6. Experimental

General information

The solvents were purified and dried by standard procedures before use. Petroleum ether of boiling range 60-80°C was used. Optical rotations were measured using sodium D line on JASCO-181 digital polarimeter. Infrared spectra were recorded on ATI MATTSON RS-1 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR were recorded on Bruker AC-200 and MSL 300 NMR spectrometers respectively. Mass spectra were obtained with a Finnigan MAT-1020 B-70 eV mass spectrometer. Elemental analyses were carried out on a Carlo Erba CHNS-O analyzer. Enantiomeric excess was determined by ^{1}H NMR spectra and by Chirasil-Val-D gas chromatograph.

Synthesis of 4-(1-ethoxyethoxy)-2-methyl-1-butene, 158



158

To a stirred solution of ethyl vinyl ether (30 mL) containing *p*-TsOH (60 mg) was added 3-methyl-3-butene-1-ol **157** (8.6 g, 100 mmol) dropwise at 0°C. After stirring for 1 h, the reaction mixture was warmed to room temperature and diluted with petroleum ether (100 mL). Filtration through a short pad of neutral alumina and removal of solvent gave a yellowish liquid, which was distilled under *vacuo* to give **158** (14.65 g) as a colorless liquid.

Yield: 14.65 g, 93 %

B.p.: 60°C /10 torr

TLC: (silica gel, petroleum ether:EtOAc, 1:1) R_f = 0.89

IR (neat, cm^{-1}): n_{max} 3025, 2976, 1648, 1399, 1132, 1096, 830

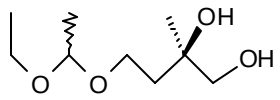
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.19 (t, *J* = 7 Hz, 3H), 1.30 (d, *J* = 6.5 Hz, 3H), 1.73 (s, 3H), 2.27 (t, *J* = 6.5 Hz, 2H), 3.3-3.65 (m, 4H), 4.69 (q, *J* = 6.5 Hz, 1H), 4.76 (d, *J* = 3 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 14.78. 19.27, 22.14, 37.64, 60.10, 63.18, 99.06, 110.9, 142.31

EIMS (*m/z* relative intensity, %): 158 [M^+] (0.8), 143 (3.8), 129 (4.3), 113 (40.6), 103 (32.5), 89 (22.7), 73 (97.4), 69 (100), 53 (29.5)

Analysis: $C_9H_{18}O_2$ (158.23) requires C, 68.31; H, 11.47. Found: C, 68.26; H, 11.62.

Synthesis of 4-(1-ethoxyethoxy)-2-methyl-(2*R*)-butane-1,2-diol, 159



159

To a mixture of $K_3Fe(CN)_6$ (4.8 g, 14.6 mmol), K_2CO_3 (2.02 g, 14.6 mmol) and $(DHQD)_2$-PHAL (38 mg, 0.0488 mmol) in *t*-BuOH-H_2O (1:1, 30 mL) cooled at 0°C was added osmium tetroxide (100 µL, 0.1M solution in toluene). After stirring for 5 min at 0°C, the olefin **158** (0.75 g, 4.74 mmol) was added in one portion. The reaction mixture was stirred at 0°C for 24 h and then quenched with solid sodium sulfite (7 g). The stirring was continued for an additional 45 min and then the solution was extracted with EtOAc (3 × 20 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether:EtOAc (3:2) as eluent gave **159** (0.884 g) as a colorless liquid.

Yield: 0.884 g, 97%

TLC: (silica gel, EtOAc) R_f = 0.62

$[\alpha]_D^{20}$: + 1.95 (c = 1, $CHCl_3$)

IR (neat, cm^{-1}): n_{max} 3430, 2977, 2931, 1451, 1381, 1343, 1132, 1089, 1054, 938

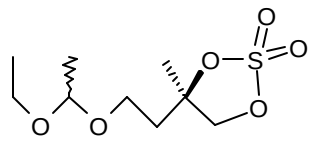
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.18 (t, *J* = 7 Hz, 3H), 1.28 (s, 3H), 1.30 (d, *J* = 6.5 Hz, 3H), 1.72 (m, 1H), 1.87 (m, 1H), 2.17 (brs, 1H), 2.97 (brs, 1H), 3.43 (m, 2H), 3.5-3.8 (m, 4H), 4.67 (q, *J* = 6.5 Hz, 1H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 15.00, 19.65, 23.86, 37.70, 61.09, 61.70, 69.70, 72.16, 99.78

EIMS (*m/z* relative intensity, %): 147 [M^+–OCH_2CH_3] (6), 115 (69), 103 (16.7), 89 (29), 85 (86.3), 73 (100), 57 (37)

Analysis: $C_9H_{20}O_4$ (192.25) requires C, 56.22; H, 10.48. Found: C, 56.19; H, 10.46.

Synthesis of 5-(1-ethoxyethoxy) ethyl-5-methyl-(5*R*)-1,3,2-dioxathiolane-2-dioxide, 160



160

To a stirred solution of the diol **159** (0.3 g, 1.56 mmol) in dry CH_2Cl_2 (10 mL) cooled at 0°C were added Et_3N (0.436 g, 0.6 mL, 4.3 mmol) and a solution of $SOCl_2$ (0.278 g, 0.17 mL, 2.34 mmol) in CH_2Cl_2 (5 mL) over a period of 10 min. Stirring was continued for 20 min at 0°C and

then the solution was quenched by adding water (5 mL) followed by addition of CH_2Cl_2 (30 mL). The organic layer was separated, washed with cold water (2 × 10 mL), brine (20 mL), dried (Na_2SO_4) and filtered through a pad of silica gel. The filtrate was concentrated to give a yellow liquid. To this was added a cold solution of CCl_4 (3 mL) and CH_3CN (3 mL). The reaction flask was cooled in an ice bath and cold water (4.5 mL) was added. $RuCl_3.H_2O$ (4.5 mg, 0.021 mmol) and $NaIO_4$ (0.535 g, 2.5 mmol) were added at once and the reaction mixture was stirred vigorously at 0°C. The progress of reaction was monitored by TLC. After 2 h, ether (20 mL) was added and the layers separated. The aqueous layer was extracted with ether (3 × 10 mL) and the combined organic layers were washed with brine (20 mL), dried (Na_2SO_4) and passed through a silica gel column. The filtrate was concentrated and the crude product was purified by silica gel column chromatography using petroleum ether:EtOAc (9:1) as eluent to give **160** (0.365 g) as a yellow liquid.

Yield: 0.365 g, 92 %

TLC: (silica gel, petroleum ether:EtOAc, 4:1) R_f = 0.51

[a]$_D^{20}$: – 1.3 (c = 0.3, MeOH)

IR (neat, cm^{-1}): n_{max} 3027, 2979, 1447, 1399, 1207, 1131, 1091, 1059, 955, 787

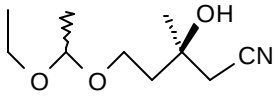
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.21 (t, *J* = 7 Hz, 3H), 1.26 (d, *J* = 6.5 Hz, 3H), 1.39 (s, 3H), 1.92 (m, 1H), 2.21 (m, 1H), 3.4-3.8 (m, 4H), 4.4 -4.6 (m, 2H), 4.65 (q, *J* = 6.5 Hz, 1H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 15.07, 19.68, 24.93, 38.87, 60.45, 60.76, 74.48, 87.1, 99.72

EIMS (*m/z* relative intensity, %): 208 [M^+–$HOCH_2CH_3$] (0.3), 165 (1), 100 (3), 85(67), 73 (100), 55 (4)

Analysis: $C_9H_{18}O_6S$ (254.29) requires C, 42.51; H, 7.14; S, 12.61. Found: C, 42.60; H, 7.20; S 12.58.

Synthesis of 4-(1-ethoxyethoxy)-2-hydroxy-2-methyl-(2*S*)-butylcyanide 161



161

To a solution of cyclic sulfate **160** (0.25 g, 0.983 mmol) in dry DMF (8 mL) was added NaCN (0.08 g, 1.63 mmol) and stirred under argon for 8 h at 80°C. The solvent was removed under reduced pressure. The residue was suspended in dry THF (5 mL) and conc. H_2SO_4 (0.05 mL) and water (0.025 mL) were added to the stirred suspension. The hydrolysis was monitored by TLC.

After 6 h, excess $NaHCO_3$ was added and stirred for 15 min. Filtration through celite and concentration of the filtrate under reduced pressure gave the crude product which was purified by silica gel column chromatography using petroleum ether:EtOAc (3:2) as eluent to give **161** (0.168 g) as a colorless oil.

Yield: 0.168 g, 85%

TLC: (silica gel, EtOAc) R_f = 0.825

[a]$_D^{20}$: + 1.3 (c = 0.8, EtOH)

IR (neat, cm^{-1}): n_{max} 3470, 2979, 2933, 2250, 1451, 1382, 1345, 1131, 1092, 1058, 950

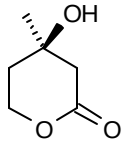
^{1}H NMR (200 MHz, CDCl$_3$): δ 1.21 (t, *J* = 7 Hz, 3H), 1.32 (d, *J* = 6.5 Hz, 3H), 1.40 (s, 3H), 1.92 (m, 2H), 2.58 (d, *J* = 2 Hz, 2H), 3.4-3.65 (m, 2H), 3.65-3.9 (m, 3H), 4.69 (dq, *J* = 3, 6.5 Hz, 1H)

^{13}C NMR (75 MHz, CDCl$_3$): δ 15.01, 19.62, 26.76, 31.13, 39.55, 61.24, 61.39, 70.32, 99.62, 117.54

EIMS (*m/z* relative intensity, %): 186 [M^+–15] (5.34), 156 [M^+–OCH_2CH_3] (13.24), 115 (13.9), 112 (21.36), 94 (27.35), 73 (100), 71 (53.84), 55 (3.84)

Analysis: $C_{10}H_{19}NO_3$ (201.25) C, 59.68; H, 9.52; N, 6.96. Found: C, 59.62; H, 9.56; N, 6.95.

Synthesis of (*R*)-(–)-Mevalonolactone 13



13

To the cyano compound **161** (100 mg, 0.497 mmol) was added aqueous solution of NaOH (3N, 1.2 mL) and the mixture was stirred at 70°C for 3 h. The suspension was cooled in an ice bath followed by addition of MeOH (4 mL). The solution was acidified to pH 2 with concentrated HCl. MeOH was stripped off and the residue was dissolved in acetone (5 mL). To this was added *p*-TsOH (100 mg) and the mixture stirred at room temperature for 8 h. Et_3N was added and the solvent removed under reduced pressure. The residue was purified by silica gel column chromatography using petroleum ether:EtOAc (1:4) as eluent to give **13** (0.045 g) as a pale yellow oil.

Yield: 0.045 g, 70%

TLC: (silica gel, EtOAc) R_f = 0.29

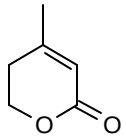
[a]$_D^{20}$: – 19.1 (c = 0.4, EtOH) [lit. $[\alpha]_D^{20}$ – 21.6 (c = 1.565, 95% EtOH),[15a] $[\alpha]_D^{25}$ – 19.0 (c = 2.15, $CHCl_3$)[23]]

IR (neat, cm^{-1}): n_{max} 3400, 3018, 2976, 1732, 1265, 1215, 1190, 754

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.39 (s, 3H), 1.91 (m, 2H), 2.5 (d, *J* = 18 Hz, 1H), 2.6 (brs, 1H), 2.7 (d, *J* = 18 Hz, 1H), 4.36 (m, 1H), 4.62 (m, 1H)

EIMS (*m/z* relative intensity, %): 131 [M^++1] (4.48), 130 [M^+] (2.56), 115 (4.9), 85 (14.95), 71 (100), 58 (16.66).

Synthesis of anhydromevalonolactone, 43



43

To a solution of cyclic sulfate **160** (0.225 g, 0.885 mmol) in dry DMF (8 mL) was added NaCN (0.087 g, 1.77 mmol) and stirred under argon for 8 h at 80°C. The reaction mixture was cooled to room temperature, washed with brine and extracted with ether (3 × 15 mL). The ether layer was dried (Na_2SO_4) and concentrated. To this was added an aqueous ethanolic solution of concentrated H_2SO_4 [conc. H_2SO_4 (0.1 mL, 2 eq.), EtOH (1 mL) and water (2 mL)] and refluxed for 18 h. The reaction mixture was cooled, neutralized ($NaHCO_3$) and extracted with CH_2Cl_2 (3 × 15 mL), dried ($NaSO_4$) and concentrated. Purification of the crude product by silica gel column chromatography using petroleum ether:EtOAc (1:1) as eluent gave **43** (0.06 g) as a colorless oil.

Yield: 0.06 g, 60%

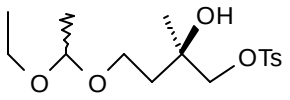
TLC: (silica gel, petroleum ether:EtOAc, 1:1) R_f = 0.57

IR (neat, cm^{-1}): n_{max} 2978, 2923, 1721, 1647, 1397, 1267, 1150, 1063, 998

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.99 (s, 3H), 2.33 (t, *J* = 6.5 Hz, 2H), 4.39 (t, *J* = 6.5 Hz, 2H), 5.79 (s, 1H)

EIMS (*m/z* relative intensity, %): 112 [M^+] (38.1), 99 (2.38), 82 (60.7), 67 (17.26), 54 (100).

Synthesis of 4-(1-ethoxyethoxy)-2-hydroxy-2-methyl-(2*R*)-butyl-(4-methyl)-1-benzene-sulfonate, 162



162

To a solution of diol **159** (0.25 g, 1.3 mmol) in dry pyridine (8 mL) was added *p*-TsCl (0.324 g, 1.7 mmol) at room temperature and stirred for 18 h. Then aqueous $CuSO_4$ solution (20%, w/v, 10 mL) and EtOAc (15 mL) were added and stirring continued for 45 min. The aqueous layer was extracted with EtOAc (4 × 20 mL) and combined organic layers were washed with water, brine and dried ($NaSO_4$). Removal of solvent gave a pale green liquid which was purified by silica gel column chromatography using petroleum ether:EtOAc (7:3) as eluent to give **162** (0.432 g) as a colorless oil.

Yield: 0.432 g, 96%

TLC: (silica gel, EtOAc) R_f = 0.92

[a]$_D^{20}$: – 0.83 (c = 0.8, EtOH)

IR (neat, cm^{-1}): n_{max} 3474, 2979, 2931, 1605, 1359, 1179, 1130, 1094, 1056, 979, 841

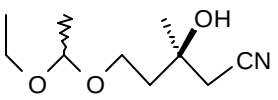
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.19 (t, *J* = 7 Hz, 3H), 1.26 (d, *J* = 6.5 Hz, 3H), 1.28 (s, 3H), 1.82 (m, 2H), 2.45 (s, 3H), 3.4-3.6 (m, 4H), 3.65-3.9 (m, 3H), 4.64 (dq, *J* = 3, 6.5 Hz, 1H), 7.36 (d, *J* = 8 Hz, 2H), 7.80 (d, *J* = 8 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 15.07, 19.62, 21.33, 24.41, 37.04, 61.24, 61.40, 70.74, 75.37, 99.78, 127.77, 129.72, 132.92, 144.71

EIMS (*m/z* relative intensity, %): 257 [M^+–89] (0.2), 172 (8.1), 155 (40), 115 (100), 107 (12.5), 91 (90.2), 71 (69.6), 65 (17.85), 57 (3.6)

Analysis: $C_{16}H_{26}O_6S$ (346.43) requires C, 55.47; H, 7.57; S, 9.25. Found: C, 55.48; H, 7.61; S, 9.23.

Synthesis of compound 161 *via* tosyl displacement



161

To a stirred solution of the tosylate **162** (0.35 g, 1.01 mmol) in EtOH:H_2O (3:2 v/v, 5 mL), cooled at 0°C was added NaCN (0.174 g, 3.55 mmol). The mixture was slowly allowed to warm to room temperature. After stirring for 18 h, it was diluted with water and extracted with CH_2Cl_2.

The organic layer was washed with brine, water, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether:EtOAc (7:3) gave **161** (0.198 g) as a colorless oil.

Yield: 0.198 g, 97 %

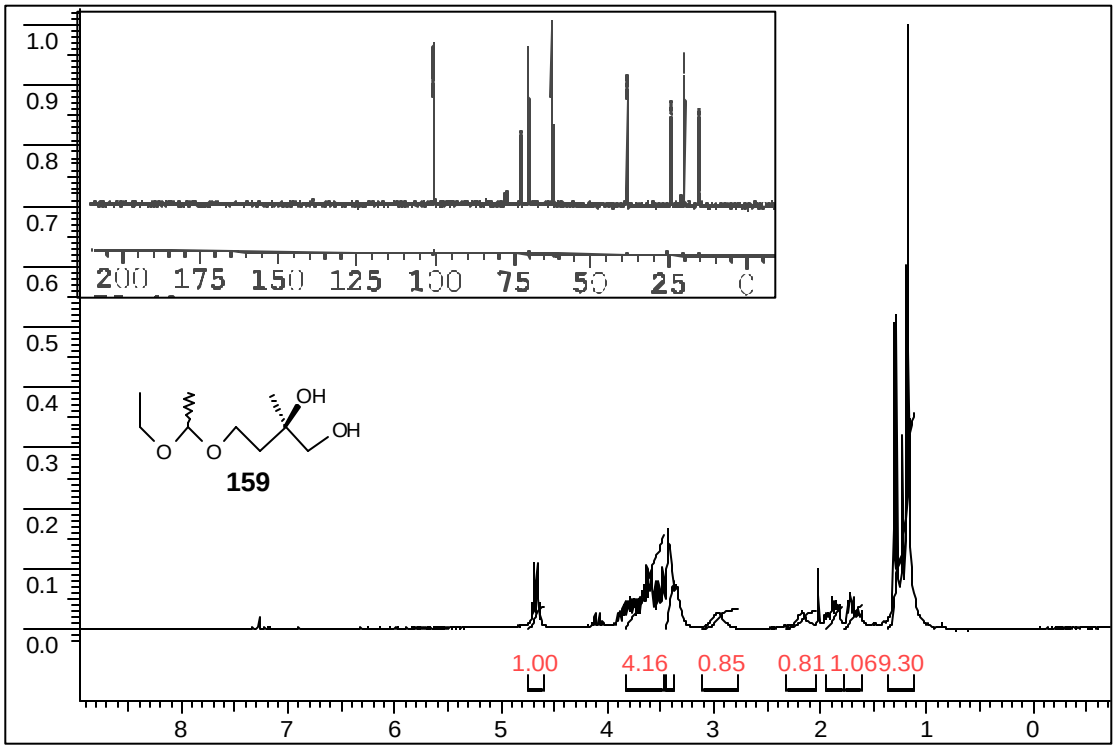
[a]$_D^{20}$: + 1.25 (c = 0.7, EtOH)

The spectroscopic data were in full agreement with the one prepared by the opening of cyclic sulfate **160** *via* step iv, **Scheme 26**.

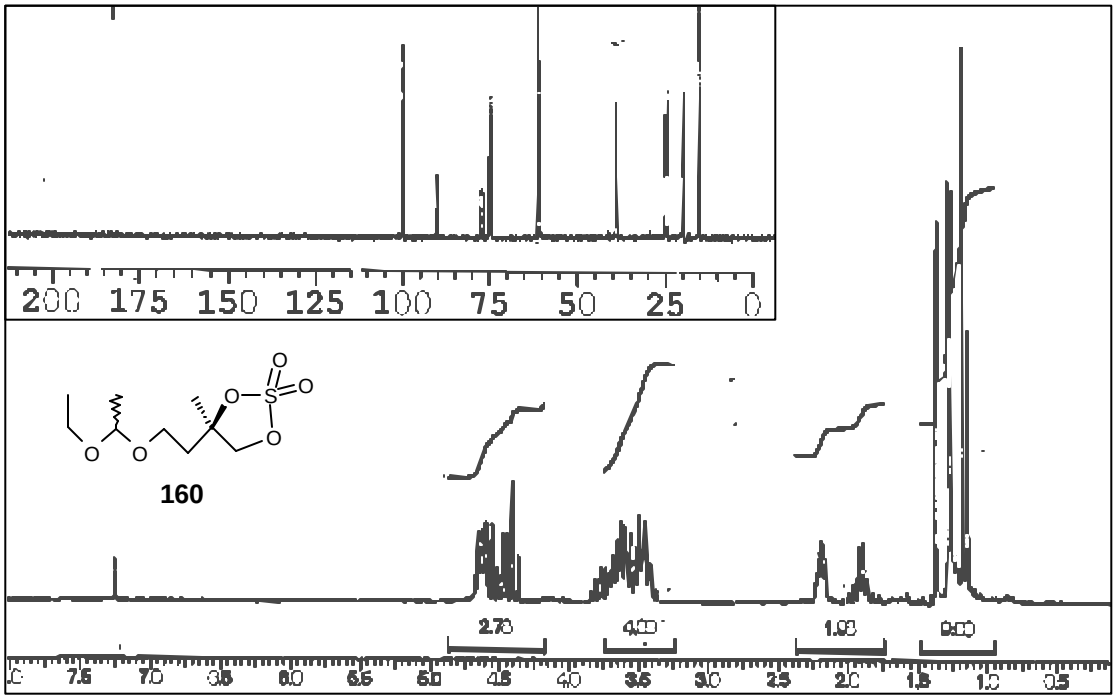
2.2.7. Spectra

+ 1] ^{1}H NMR and ^{13}C NMR Spectra of **159**
+ 2] ^{1}H NMR and ^{13}C NMR Spectra of **160**
+ 3] ^{1}H NMR Spectrum of **161**
+ 4] ^{13}C NMR Spectrum of **161**
+ 5] ^{1}H NMR Spectrum of **13**
+ 6] EIMS of **13**

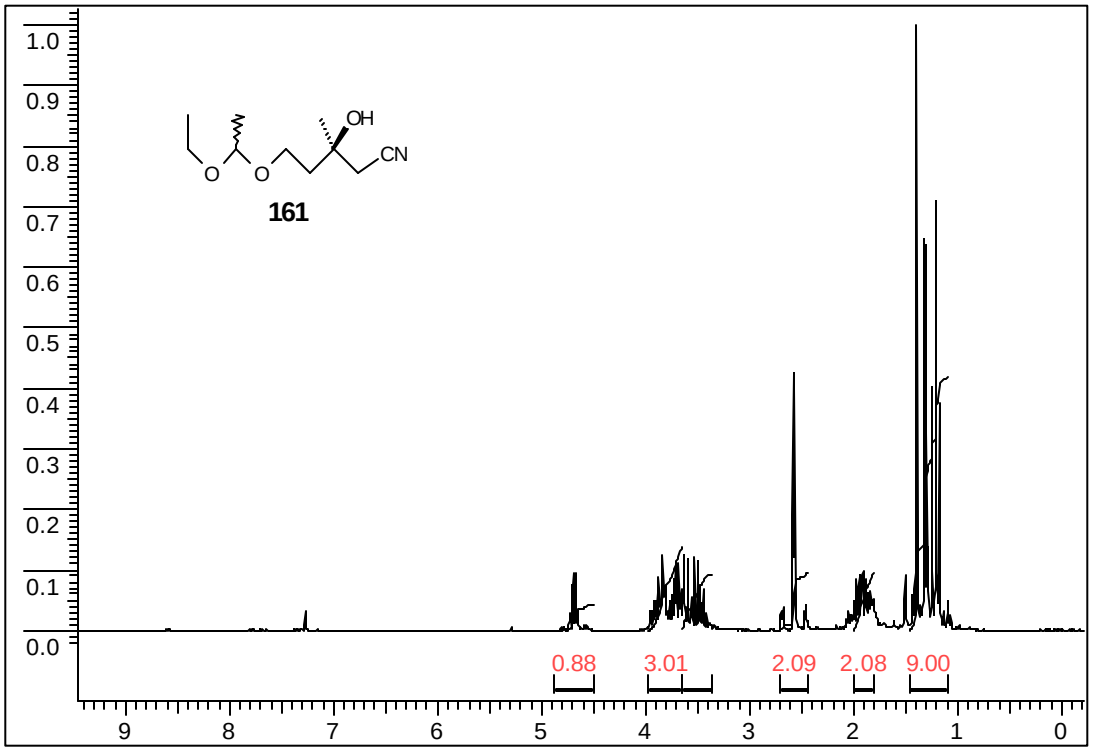
+ ^{1}H NMR and ^{13}C NMR Spectra of **159**



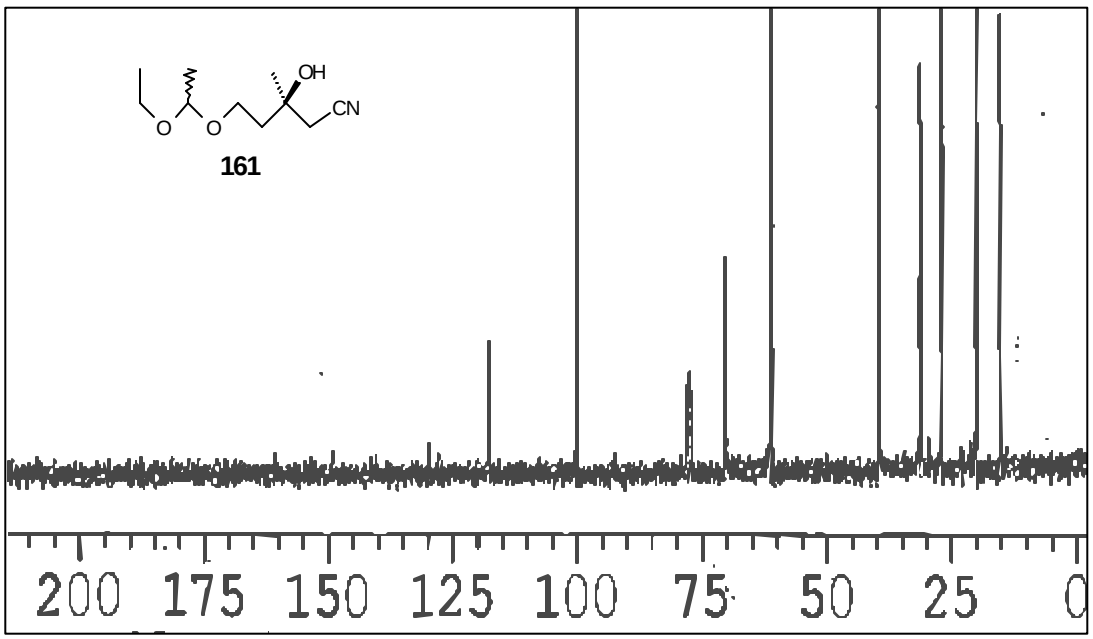
+ ^{1}H NMR and ^{13}C NMR Spectra of **160**



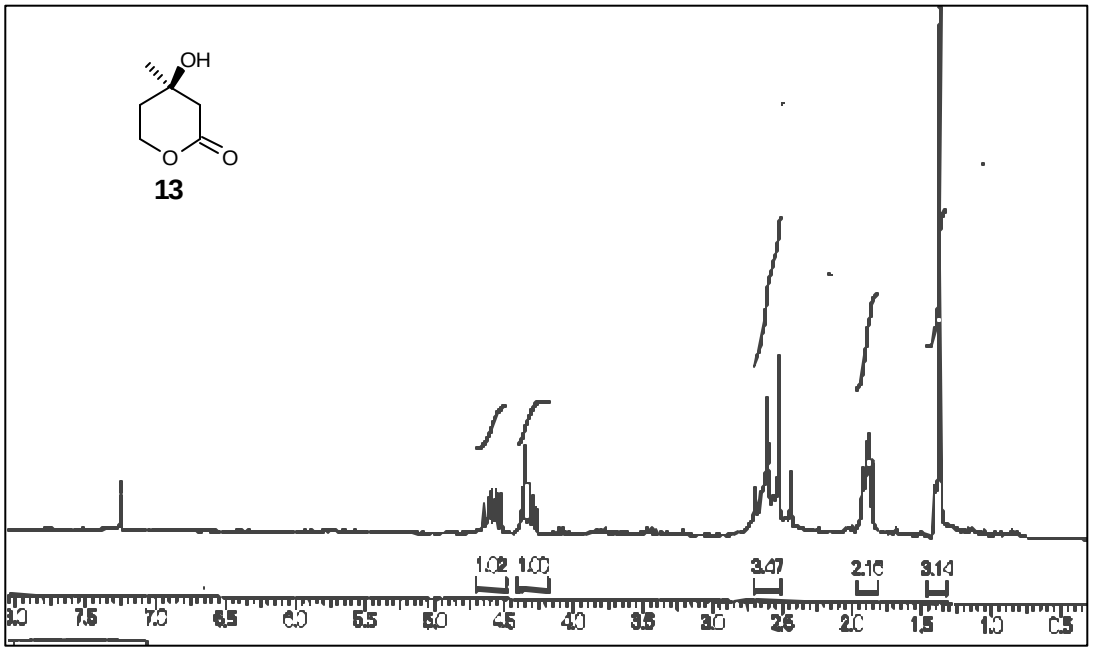
+ ^{1}H NMR Spectrum of **161**



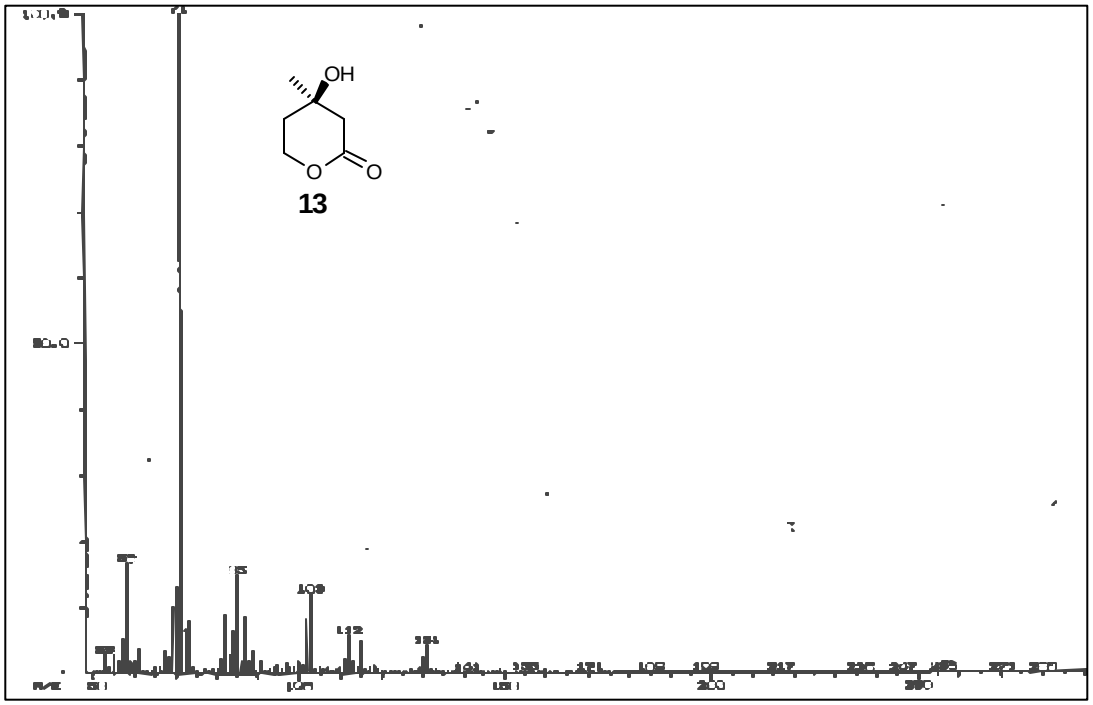
+ ^{13}C NMR Spectrum of **161**



+ ^{1}H NMR Spectrum of **13**



+ EIMS Spectrum of **13**



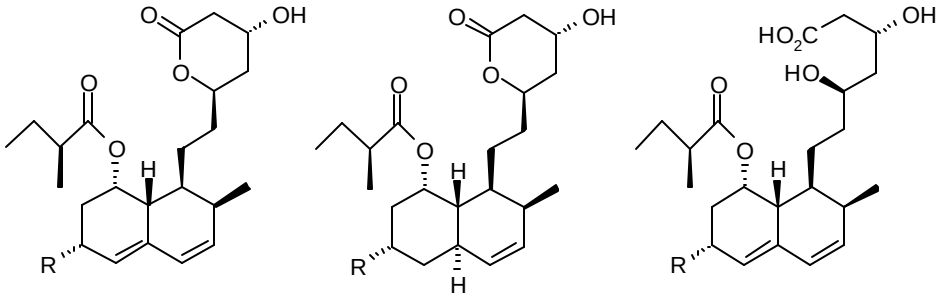
+ ^{1}H NMR Spectrum of **43**

2.3. SECTION B

ENANTIOSELECTIVE SYNTHESIS OF THE LACTONE MOIETY OF HMG-CoA REDUCTASE INHIBITORS: COMPACTIN AND MEVINOLIN

2.3.1. Introduction

In 1976, Endo *et al.*[42a-c] at the Sankyo Co. and Brown *et al.*[42d] at Beecham Pharmaceuticals isolated a potent competitive inhibitor of hydroxymethylglutaryl coenzyme A reductase (HMG-CoA reductase) from the metabolites of *Penicillium citrinum* and *Penicillium brevicompactum*, respectively. The new compound, shown to have structure **165**, was named ML 236B by the Japanese group and 'compactin' by the British workers. In 1980, Alberts *et al.*[43] at Merck, Sharp and Dohme, reported the isolation of a relative of compactin from *Aspergillus terrus*. The Merck compound was named 'mevinolin' and shown to have the absolute stereostructure **166**. The identical fungal metabolite was isolated from Monascus rubber and named monacolin K.[44] The Merck group also discovered that the active forms of compactin and mevinolin are the respective open-chain dihydroxy acids **169** and **170**.

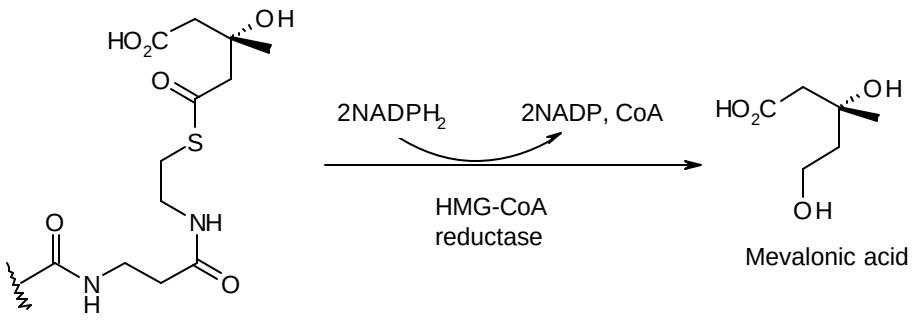


165 R = H Compactin
166 R = CH_3 Mevinolin

167 R = H
168 R = CH_3

169 R = H
170 R = CH_3

In humans, more than one-half of total body cholesterol is derived from *de novo* synthesis.[45] The rate-limiting step in cholesterol biosynthesis is the reduction of HMG-CoA to mevalonic acid.[46]



Because of their potent inhibitory activity on this key enzyme, there is the attractive possibility that compactin or some related compounds might be useful as hypocholesterolemic agents. Indeed, compactin has been shown to lower serum cholesterol levels in dogs,[47] cynomolgus monkeys,[48] and humans.[49] Compactin also has been used as a tool by biochemists in elegant studies which have provided insight into the mechanism by which mammalian cells regulate HMG-CoA reductase.[50] More recently the dihydro derivatives of compactin[51] and mevinolin,[52] **167** and **168**, respectively, have been isolated. The class of compounds, distinguished by a highly functionalized decalin unit and a β-hydroxy-δ-lactone portion linked by an ethylene bridge, are collectively referred to as mevinic acids.

Mechanism for HMG-CoA Reductase Inhibition

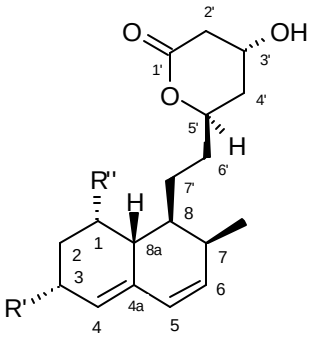
The inhibition of HMG-CoA reductase by compactin and related compounds is reversible.[42b,53] As can be expected from the structure of their acid forms, the inhibition by these compounds is competitive with respect to HMG-CoA. The K_i value for the acid form of compactin, which is determined from the partially purified rat liver enzyme, is ~10^{-9}M, while under the same conditions, the K_m value for HMG-CoA is 10^{-5}M.[53] Thus, the affinity of HMG-CoA reductase for compactin is 10,000-fold higher than its affinity for the natural substrate HMG-CoA, showing compactin to be a highly potent inhibitor.

Compactin does not affect other enzymes involved in cholesterol biosynthesis.[54] In addition, almost all studies on compactin with cultured cells and intact animals suggest that reductase is the only enzyme that is inhibited by compactin.

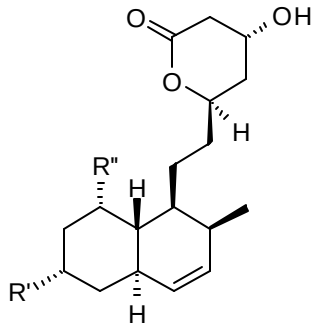
Structure Activity Relationship at Enzyme Level

Structural similarity between HMG-CoA and compactin-related compounds suggests that the active center of these agents in the inhibition of HMG-CoA reductase is at the δ-lactone moiety of the molecules. This hypothesis is supported by the data that inhibitory activity of compactin is reduced to 1/100 or less by acetylation of the hydroxyl group at either C-3′ or C-5′ and that 5′-phosphocompactin acid and 5′-phosphomonacolin K acid are 1/10 and 1/20 of compactin and monacolin K in the inhibitory activity, respectively.[55]

Other portions of the compactin molecule also seem to be involved in inhibitory activity (**Figure 3**). Among them, the α-methyl-butyrate ester plays a significant role, since analogues that lack such an ester (ML-236A and monacolin J) are 1/25 in the activity, as compared with their respective counterparts (compactin and monacolin K).



	R′	R″
ML-236A (2)	H	OH
ML-236B (compactin)(50)	H	
ML-236C (10)	H	H
Monacolin J (4)	CH_3	OH
Monacolin K (mevinolin)(100)	CH_3	
Monacolin L (15)	CH_3	H
Monacolin X (20)	CH_3	



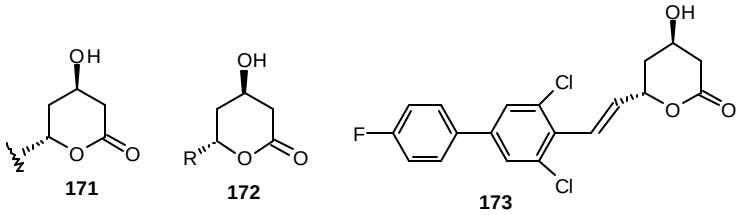
Dihydrocompactin (50)	H	
Dihydromevinolin (100)	CH_3	
Dihydromonacolin L (20)	CH_3	H

Figure 3: Compactin (ML-236B) related compounds of microbial origin. Numbers in parentheses represent relative activity to inhibit rat liver HMG-CoA reductase.

The decalin ring of compactin-related compounds is essential to the inhibitory activity. This is shown by the data that HMG is more than 10^6 fold less active than compactin.[56] Dihydrocompactin, dihydromevinolin, and dihydromonacolin L are comparable in the activity to compactin, monacolin K and monacolin L, respectively.[51,52]

Monacolin K analogs that have a methyl group at C-3 are twice as active as their respective compactin analogs (**Figure 3**), indicating a contribution of the methyl radical to potency. However, hydroxylation at C-8a, C-3, or C-6 has no significant effect.[57,58]

Since discovery, both compactin and mevinolin have attracted considerable world-wide attention due to their unique structural features and biological activities as inhibitors of HMG-CoA reductase which is a major rate limiting enzyme responsible for the reduction of HMG-CoA to mevalonic acid[55] which is a crucial intermediate in the biosynthesis of cholesterol. Mevinolin, presently marketed under the trade name 'Mevacor' by the Merck group is one of the most clinically useful hypocholesterolemic agents. It is manufactured by the fermentation process. Dihydromevinolin, which exhibits biological activity similar to mevinolin, is produced in small quantities during fermentation; it has, therefore not been developed as a clinical candidate. The lactone moiety of the mevinic acids is essential for the inhibition because in its open form, it closely mimics mevalonic acid. The role of the decalin unit is probably hydrophobic in nature.[59]



171 **172** **173**

The design of the synthetic analogs of mevinic acids[60] has been governed by two major considerations, namely the requirement for a lactone function **171** and the desirability of having a much simpler array of place of the complex decalin system present in the natural products. The resulting analogs **172** of mevinic acids were generally most active when the R group was arylethyl or (*E*)-arylethenyl;[61] an example being the material **173** which, in its dihydroxy acid form, displays 2.8 times the activity of the natural compactin **165** in HMG-CoA reductase inhibition.[62] This unique structure-activity relation has aroused the interest of synthetic organic chemists, resulting in an onslaught of activity directed at the stereocontrolled synthesis of lactone **172** with different R substituents.[63]

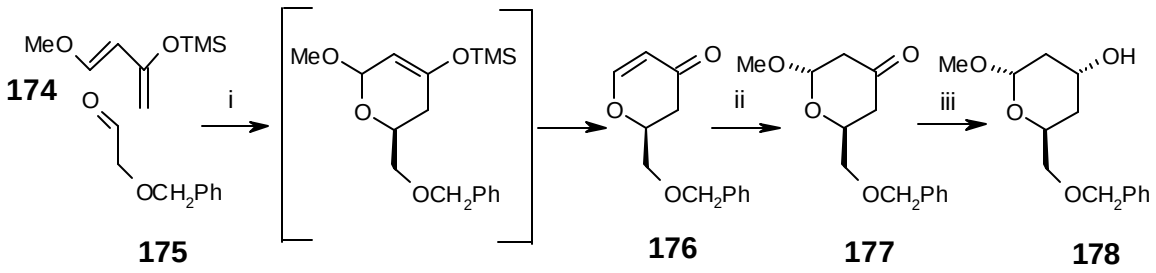
2.3.2. Review of Literature

Along with the interest generated by the biological properties of the mevinic acids, their unique structural features have aroused considerable global attention directed at the synthesis of these challenging targets. Synthetic studies in mevinic acids can be grouped into three primary sections: (1) total synthesis, (2) synthesis of the decalin units, and (3) synthesis of β-hydroxy-δ-lactone moiety.

The β-hydroxy-δ-lactone moiety in its open acid form closely mimics mevalonic acid and is of prime importance in inhibition. Hence, several research groups round the world have focused much attention in the synthesis of this δ-lactone portion.[60,63] Some of the important literature syntheses are given below.

Danishefsky *et al*. (1982)[64] Scheme 27

Danishefsky and co-workers have synthesized the masked pyranone segment **178** for the lactone moiety of compactin. The cyclocondensation of silyloxy diene **174** with benzyloxyacetaldehyde **175** gave adduct **176**. Treatment of **176** with methanolic HCl produced a methylglycoside **177** with concomitant ketalization; deketalization with acetone containing a trace of HCl. Stereoselective reduction of ketone **177** gave the racemic synthon **178**. By starting with an optically active acetonide of glyceraldehyde rather than with benzyloxyacetaldehyde, the synthesis has been manipulated to provide a 100% optically active version of **178**.[65]

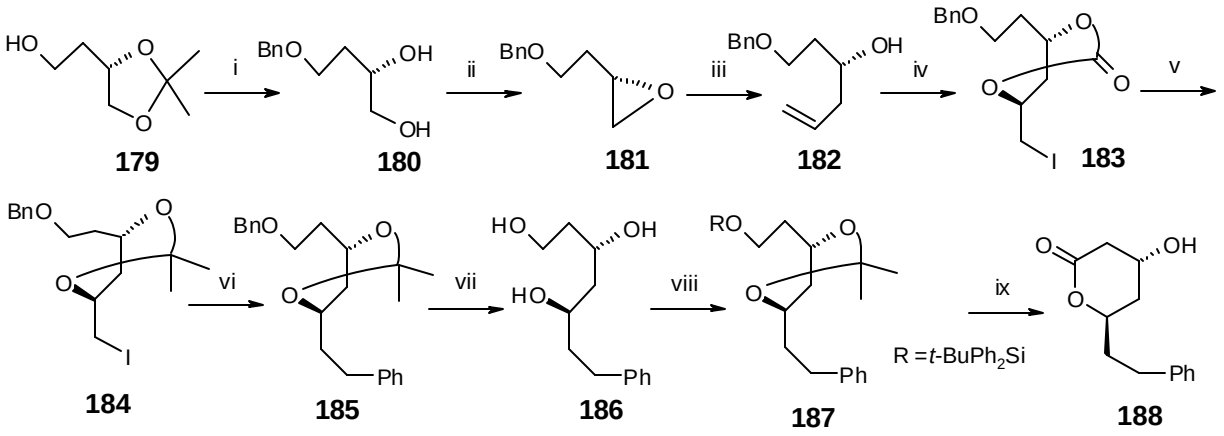


Scheme 27. Reaction conditions: (i) $ZnCl_2$, PhH, rt, 87%. (ii) (a) MeOH, HCl, 69%, (b) $(CH_3)_2CO$, HCl. (iii) L-Selectride, 88%.

Clive *et al*. (1984)[66] Scheme 28

Clive and co-workers utilized L-malic acid derivative **179** as a precursor. Sequential benzylation, acetonide deprotection, mono-mesylation and base treatment gave the epoxide **181**

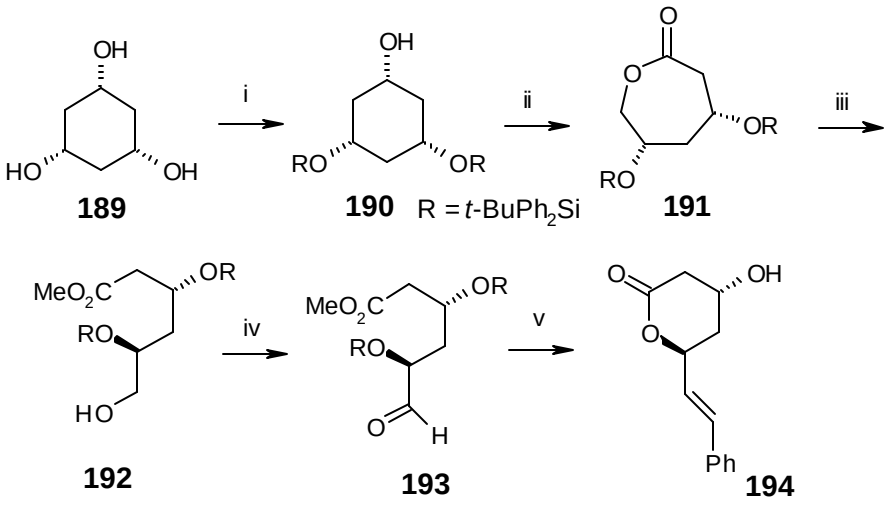
that was opened with vinyl magnesium bromide to obtain the hydroxy olefin **182**. Treatment of alkoxide of **182** sequentially with CO_2 and I_2 gave iodocarbonate which on hydrolysis and acetonide formation furnished pure acetal **184**. Benzyl coupling of **184** gave adduct **185**. Deprotection of acetonide and benzyl and oxidation with Fetizons's reagent afforded **188** in poor yield (20%). Alternatively, **186** on selective protection of primary alcohol and acetonide formation gave **187**. Desilylation, oxidation and subsequent lactonization led to the desired lactone **188** (33% yield).



Scheme 28. Reaction conditions: (i) (a) NaH, DMF, BnBr, (b) AcOH-H_2O, 50°C, 1 h, 86%. (ii) (a) MsCl, pyridine, (b) Triton B, 65%. (iii) H_2C=CHMgBr, 92%. (iv) *n*-BuLi, CO_2, I_2, 69%. (v) $(CH_3)_2CO$, *p*-TsOH. (vi) (a) *p*-$MeC_6H_4SO_2CH_2Ph$, KH, DMF, rt, 3 h, (b) 6% Na-Hg, MeOH, 78%. (vii) Me_3SiI, 73% (94% with one recycling of **185**). (viii) (a) *t*-$BuPh_2Si$-Cl, (b) $(CH_3)_2CO$, *p*-TsOH. (ix) (a) *n*-Bu_4NF, (b) Collins [O], (c) PDC, DMF, (d) HCl, CH_2Cl_2, 33% from **186**.

Prasad *et al*. (1984)[67] **Scheme 29**

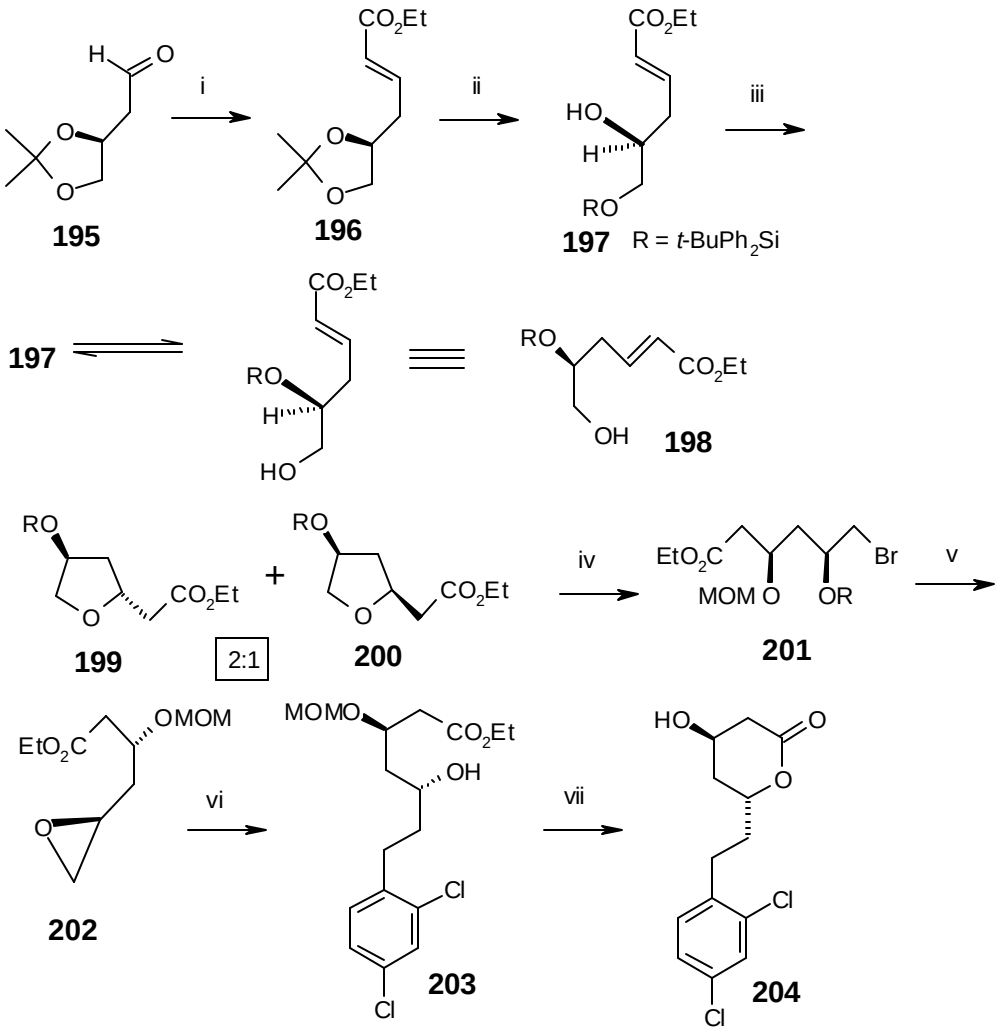
Prasad and Repic have synthesized the lactone moiety beginning with *cis*-cyclohexane-1,3,5-triol **189**. Conversion of **189** to bis silyl ether **190** followed by PCC and Baeyer-Villiger oxidations afforded the lactone **191**. Methanolysis and oxidation of the resulting hydroxyl gave the aldehyde **193**, which on Wittig coupling and desilylation furnished the unmasked lactone **194**.



Scheme 29. Reaction conditions: (i) *t*-$BuPh_2Si$-Cl, imidazole, DMF, 40%. (ii) (a) PCC, 4A° molecular sieves, CH_2Cl_2, 3 h, 93%, (b) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 18 h, 77%. (iii) MeOH, F_3CCO_2H, reflux, 20 min, 95%. (iv) PCC, 4A° molecular sieves, CH_2Cl_2, 4 h. (v) (a) $PhCH{=}PPh_3$, THF, –20°C, 3 h, 77%, (b) *n*-Bu_4NF, AcOH, THF, 20°C, 18 h, 60°C, 2 h, 45%.

Guindon *et al*. (1985)[68] **Scheme 30**

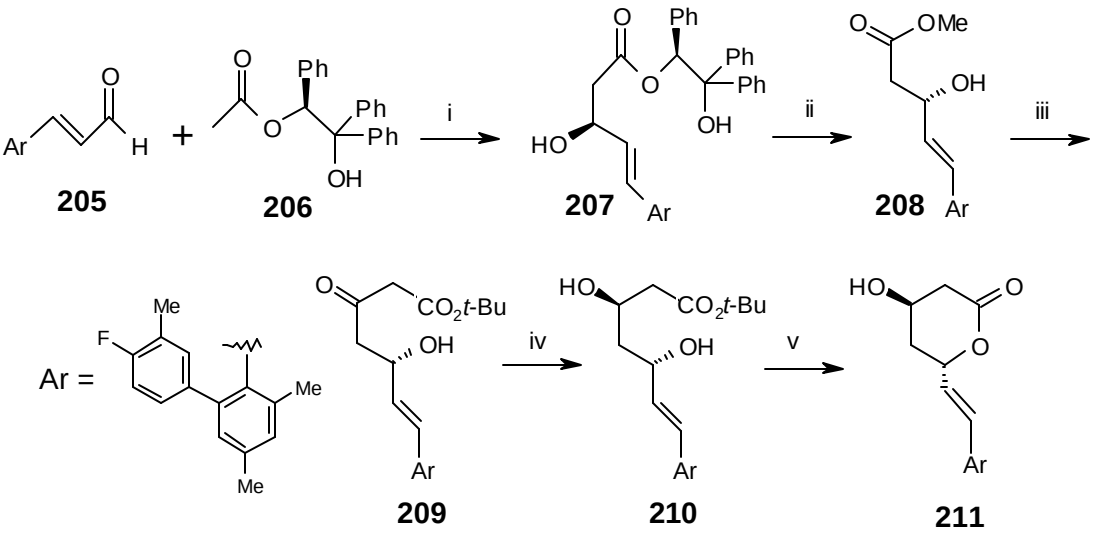
In Guidon's approach, the L-malic acid aldehyde **195** was converted into olefin ester **196**. Acetonide deprotection and selective silylation of the primary alcohol afforded the mono protected diol **197** that on treatment with catalytic NaOEt, establishes equilibrium with its isomer **198**. Ensuing intramolecular Michael reaction displaces the equilibrium and the tetrahydrofurans **199** and **200** are obtained in 2:1 ratio. Cleavage of **199** with dimethylboronbromide proceeds regiospecifically to produce, after protection, the bromide **201**. Cleavage of the silyl ether afforded the epoxide **202**, which was opened regioselectively to give **203**. Subsequent acid-catalyzed cyclization and unmasking of the hydroxyl group gave the lactone **204**.



Scheme 30. Reaction conditions: (i) $Ph_3P{=}CHCO_2Et$, 84%. (ii) (a) 1N HCl, THF, (b) *t*-$BuPh_2Si$-Cl, Et_3N, DMAP, CH_2Cl_2, rt. (iii) 10 mol% NaOEt, EtOH, 87%. (iv) (a) Me_2BBr, CH_2Cl_2, 82%, (b) MOMCl, *i*-Pr_2NEt, DMAP, CH_3CN, 94%. (v) *n*-Bu_4NF, THF, 80%. (vi) $R_2CuMgBr$, Et_2O, −78°C, then –23°C, 1 h, 100%. (vii) (a) *p*-TsOH, PhH, 90%, (b) Me_2BBr, CH_2Cl_2, 79%.

Lynch *et al*. (1987)[69] Scheme 31

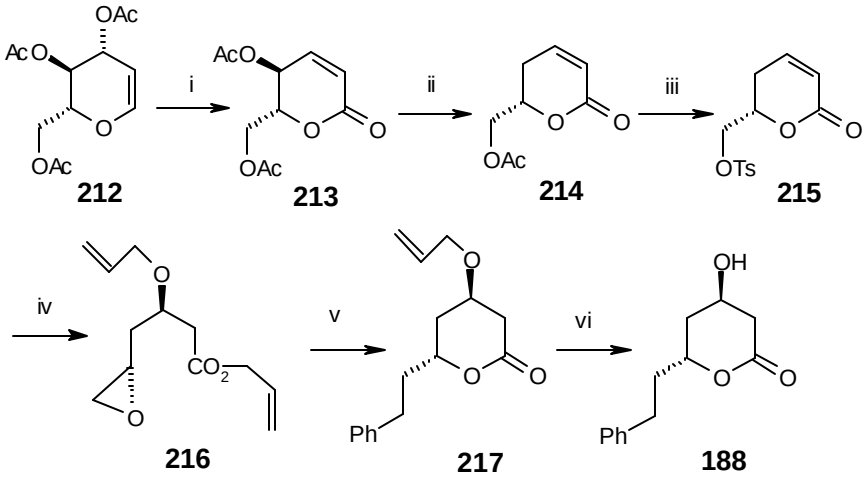
Lynch and co-workers have utilized the diastereoselective Aldol reaction of **205** with Mg (II) enolate of **206** following the procedure of Braun and Devant[70] to give the diastereoisomer **207** (*SS*:*SR* = 97:3). Transesterification of **207** followed by Claisen condensation furnished **209**. The 5-(*S*)-hydroxyl directed reduction of β-keto ester **209** gave diol **210**. Subsequent saponification and acidification afforded the lactone **211**.



Scheme 31. Reaction conditions: (i) (a) LDA, THF, (b) $MgBr_2$, 93%. (ii) NaOMe, MeOH, 95%. (iii) lithio *t*-butylacetate, THF, −40°C to −30°C, 90%. (iv) Et_3B, $NaBH_4$, THF-MeOH, −78°C, 93%. (v) H^+, pH 3.8, 85%.

Roth *et al*. (1988)[71] Scheme 32

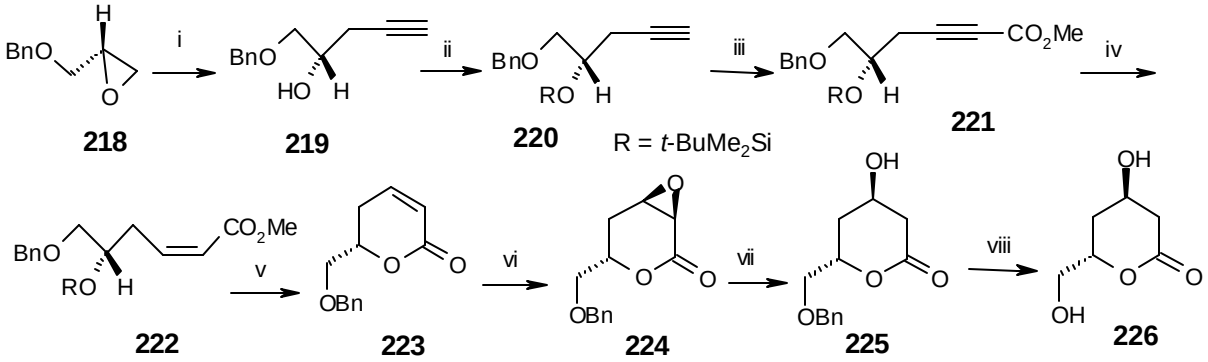
Roth and Roark have used the commercially available glucal **212**. PCC oxidation of **212** afforded the unsaturated lactone **213**. Reductive deconjugation with Zn-AcOH followed by reconjugation with Et_3N produced the 5-deoxygenated lactone **214**. Hydrolysis and tosylation gave **215**, which on reaction with sodium allyl alcoholate produced the epoxide **216**. Reaction of **216** with dibenzylcuprate followed by allyl deprotection gave the lactone **188**.



Scheme 32. Reaction conditions: (i) PCC, 85%. (ii) Zn-AcOH and then Et_3N, 92%. (iii) (a) 2N HCl, (b) *p*-TsCl, 92%. (iv) CH_2=$CHCH_2ONa$, allyl alcohol, 87%. (v) $PhCH_2MgCl$, CuBr-Me_2S, 73%. (vi) 10% Pd/C, dioxane:H_2O (2:1), 50%.

Takano *et al*. (1989)[72] Scheme 33

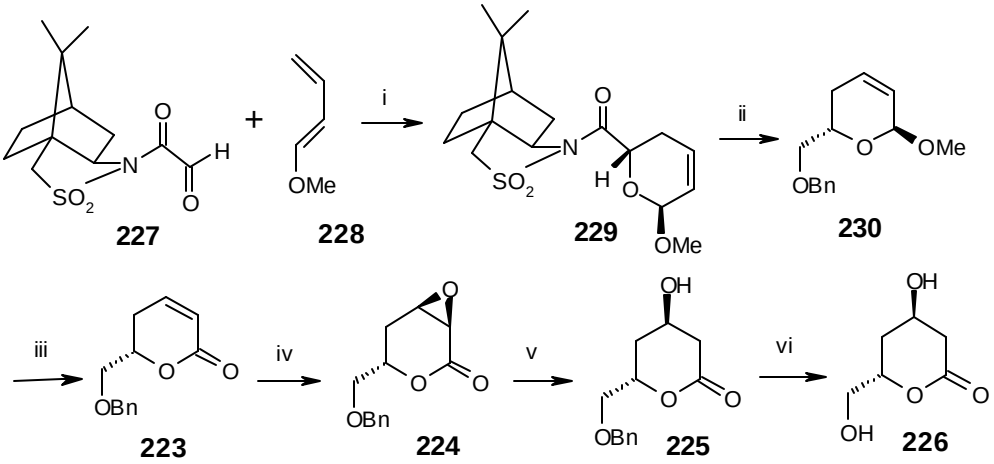
In Takano's approach, (*R*)-*O*-benzylglycidol **218** is opened with sodium acetylide to give **219**. Silyl protection of the hydroxyl group followed by sequential lithiation and methoxy carbonylation gave ester **221**. Alkyne reduction to (*Z*)-olefin and exposure to acid furnished the α,β-unsaturated lactone **223**. Epoxidation of **223** stereoselectively gave the epoxide **224**. Regioselective cleavage of the oxirane and debenzylation furnished the lactone **226**.



Scheme 33. Reaction conditions: (i) NaH, DMSO, acetylene, 87%. (ii) *t*-$BuMe_2Si$-Cl, imidazole, 99%. (iii) (a) *n*-BuLi, THF, −72°C, (b) $ClCO_2Me$, −50°C, 87%. (iv) H_2, Lindlar cat. PhH, quinoline, rt, 99%. (v) conc. HCl, MeOH, rt, 86%. (vi) 30% H_2O_2, 6N NaOH, MeOH, rt, 73%. (vii) $(PhSe)_2$, $NaBH_4$, AcOH, *i*-PrOH, rt, 87%. (viii) H_2, $Pd(OH)_2$, EtOAc, rt, 81%.

Jurczak *et al*. (1990)[73] Scheme 34

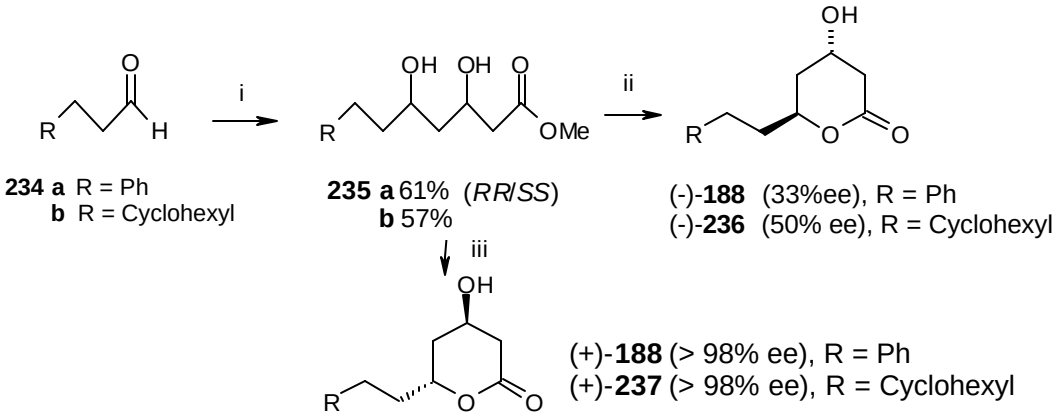
In Jurczak's approach the asymmetric hetero Diels-Alder reaction of 1-methoxybuta-1,3-diene **228** with (2*R*)-N-glyoxyloylbornane-10,2-sultam **227** furnished the adduct **229**. Reduction of **229** and benzylation of hydroxyl gave **230**. Anomeric oxidation[74] of **230** afforded **223**. Compound **223** is transformed into the lactone **226** as shown in **Scheme 33**.



Scheme 34. Reaction conditions: (i) (a) 2 mol% $Eu(fod)_3$, (b) PPTS. (ii) (a) $LiAlH_4$, (b) NaH, BnBr. (iii) (a) 30% H_2O_2, MoO_3 (cat), (b) Ac_2O, pyridine. (iv)-(vi) as in **Scheme 33**.

Bonini *et al*. (1991)[75] Scheme 35

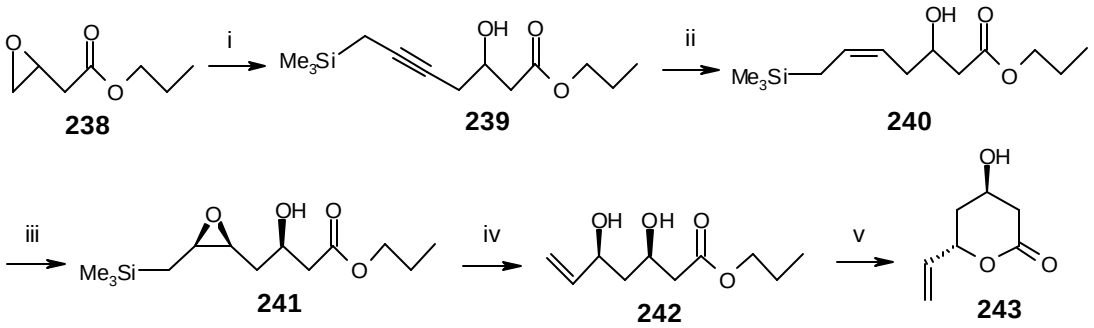
Bonini and co-workers employed biocatalytic lactonization of *syn*-3,5-dihydroxy esters **235** which were obtained by the diastereoselective reduction of the aldol derived from dianion of acetoacetate with an appropriate aldehyde **234**. Biocatalytic lactonization of **235a/b** with pig liver esterase (PLE) afforded the unnatural mevinic acid analogs (–)-**188** and (–)-**236** respectively. However, when porcine pancreatic lipase (PPL) is used to perform lactonization of the dihydroxy esters **235a/b**, natural analogs of the mevinic acid (+)-**188** and (+)-**237** are obtained in good yield and high enantiomeric excess.



Scheme 35. Reaction conditions: (i) (a) $H_3CCOCH_2CO_2Me$, 2LDA, (b) $Ti(O\textit{i}\text{-}Pr)_4$, $NaBH_4$. (ii) PLE, 80%. (iii) PPL, 70%.

Mohr *et al*. (1992)[76] Scheme 36

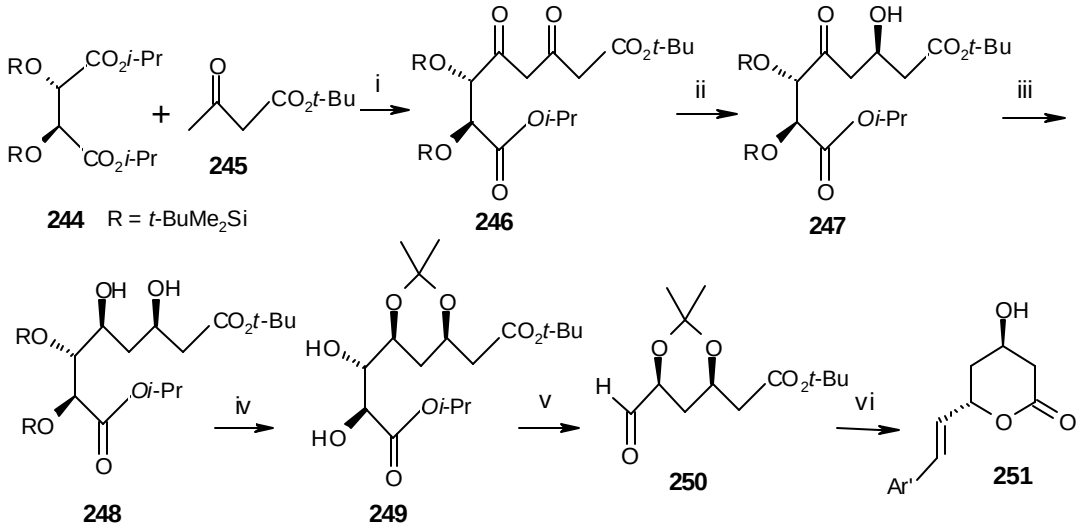
Mohr and co-workers employed the *Z*-allyl silane **240** in an epoxidation reaction with V^{5+}/*t*-BuOOH with high *erythro*-selectivity to give **241**. Subsequent HF or TBAF induced fragmentation afforded *syn*-1,3-diol **242** which is then transformed into the lactone **243**.



Scheme 36. Reaction conditions: (i) Propargyl trimethylsilane, *n*-BuLi, THF, $BF_3.Et_2O$. (ii) Lindlar catalyst, H_2. (iii) *t*-BuOOH (1.5 eq.), $VO(acac)_2$, −15°C-rt, 15 h, (iv) *n*-Bu_4NF, THF, 57% from **240**. (v) camphor sulfonic acid.

Hiyama *et al.* [77] **(1993) Scheme 37**

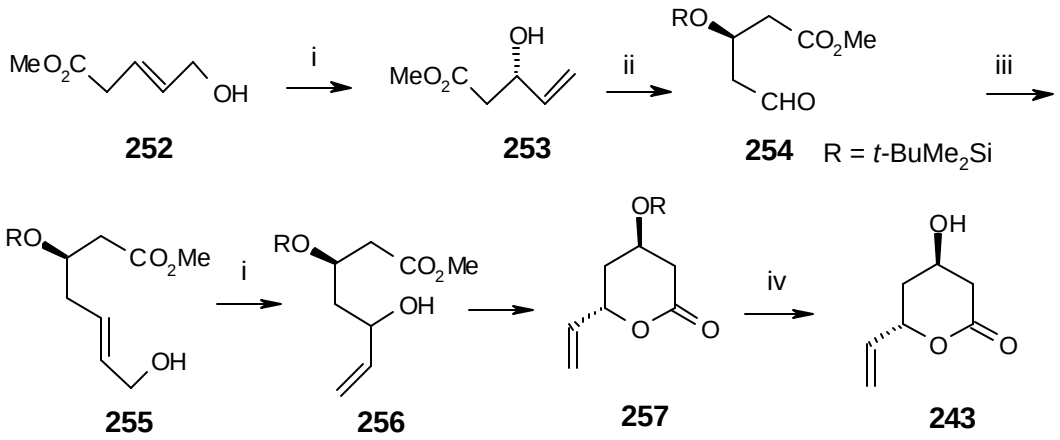
Hiyama and co-workers employed stereoselective reductions of a β,δ-diketo ester **246** derived from D-tartaric acid to give chiral β,δ-*syn* dihydroxyester **248**. Protection of 1,3-diol as acetonide and removal of silyl groups gave diol **249**. Oxidative cleavage of **249** afforded the desired aldehyde **250**. Wittig olefination with the carbanion of $Ar'CH_2P(O)Ph_2$ gave various types of HMG-CoA reductase inhibitors **251**.



Scheme 37. Reaction conditions: (i) NaH, *n*-BuLi, −78°C, 20 h, 74%. (ii) DIBAL-H, THF, hexane, 78°C, 4 h, 60%. (iii) Et_2BOMe, $NaBH_4$, THF, MeOH, −78°C-rt, 12 h, 76%. (iv) (a) 2,2-DMP, *p*-TsOH, rt, 2 h, 98%, (b) *n*-Bu_4NF, THF, rt, 3 h, 99%. (v) $NaIO_4$, Et_2O, H_2O, rt, 2 h, 85%. (vi) (a) $Ar'CH_2P(O)Ph_2$, lithium 2,2,6,6-tetramethylpiperazide, (b) CF_3CO_2H.

Dittmer *et al*.[78] **(1994) Scheme 38**

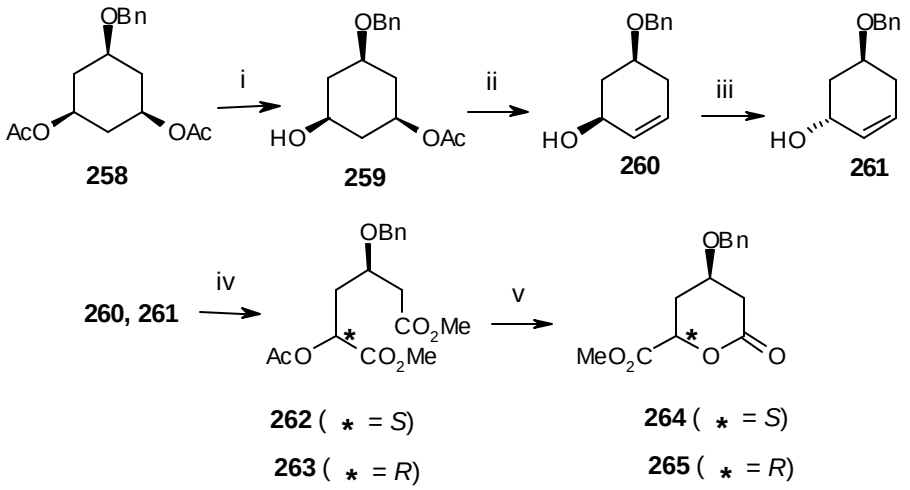
In Dittmer's approach the SAE of allylic alcohol **252** and conversion of hydroxyl into tosylate gave glycidyl sulfonate which on tellurium-induced nucleophilic reduction afforded allylic alcohol **253**. Sequential protection of hydroxyl, hydroboration and PCC oxidation gave aldehyde **254**. Subsequent Wittig reaction and borohydride reduction furnished the allylic alcohol **255**. The SAE-Te transposition sequence on **255** gave **256** which spontaneously lactonized to afford **257**. Silyl group deprotection gave **243**.



Scheme 38. Reaction conditions: (i) (a) *t*-BuOOH, (+)-DIPT, $Ti(O\textit{i}\text{-}Pr)_4$, (b) *p*-TsCl, Et_3N, CH_2Cl_2, (c) Te^{2-} (Te, $NaBH_4$, DMF). (ii) (a) *t*-$BuMe_2Si$-Cl, imidazole, DMF, (b) $(Me_2CHCHMe)_2BH$, THF, −12°C, (c) PCC, CH_2Cl_2, 63% from **253**. (iii) (a) Ph_3P=CHCHO, PhH, THF, (b) $NaBH_4$, MeOH, −50°C, 60% from **254**. (iv) *n*-Bu_4NF.

Suemune *et al*.[79] (1992) Scheme 39

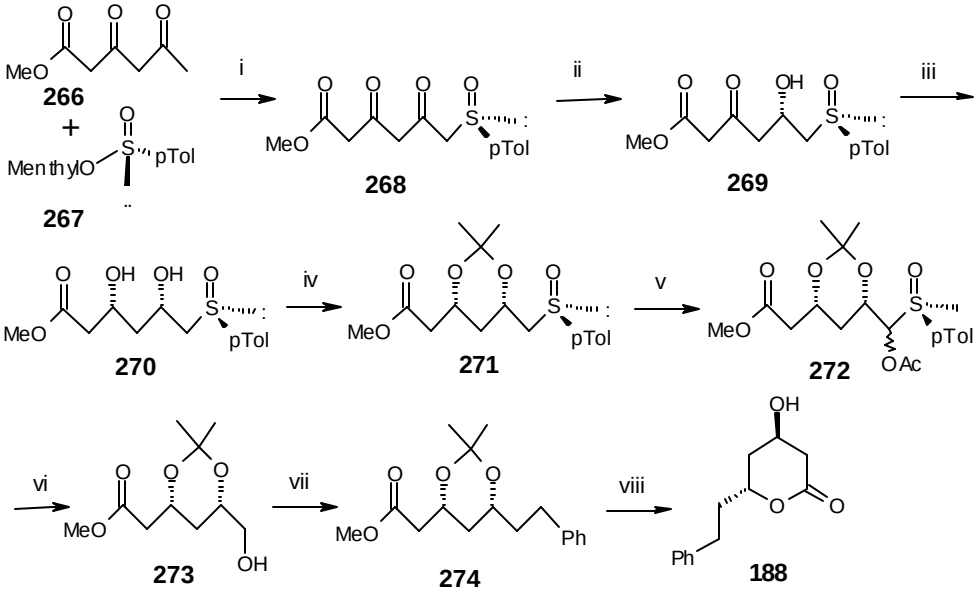
Suemune and co-workers used porcine liver esterase (PLE) in desymmetrization of **258** to give **259**. Subsequent oxidation and stereoselective reduction gave **260**. Mitsunobu's inversion of **260** gave the epimeric material **261**. Ozonolysis followed by Jones oxidation of **260**/**261** and subsequent esterification gave **262**/**263**. Solvolysis of **262**/**263** and subsequent lactonization afforded the lactone moiety of compactin **264** and its epimer at C-5, **265**.



Scheme 39. Reaction conditions: (i) PLE, pH 7, 62%. (ii) (a) Swern oxidation, 92%, (b) $NaBH_4$, $CeCl_3$, MeOH, 90%. (iii) (a) Ph_3P, DEAD, AcOH, THF, 87%, (b) K_2CO_3, MeOH, 82%. (iv) (a) O_3, (b) Jones oxidation, (c) CH_2N_2, 69%. (v) (a) K_2CO_3, MeOH, 78%, (b) *p*-TsOH, PhH, 65%.

Solladie *et al*.[80] **(1995) Scheme 40**

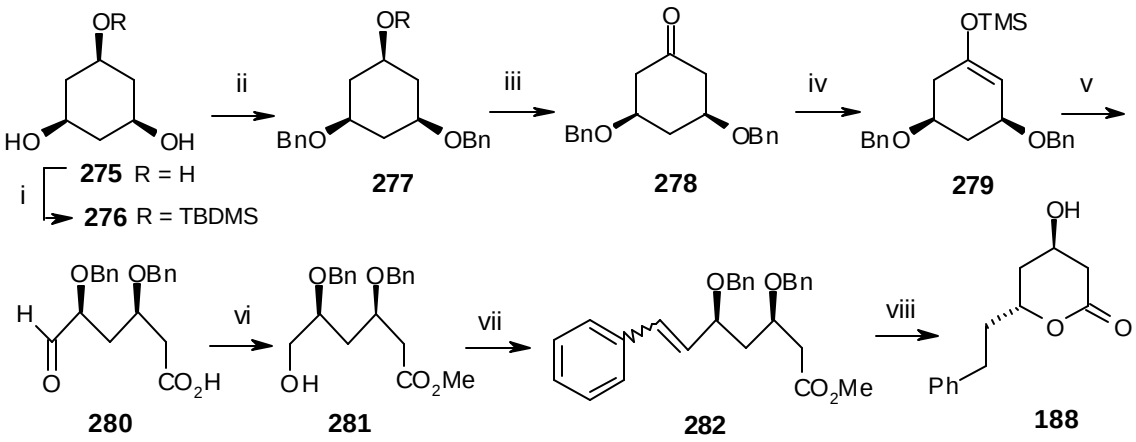
In Solladie's approach, reaction of the trianion of methyl-3,5-dioxahexanoate **266** with (–)-menthyl (*S*)-*p*-toluenesulfinate **267** gave the diketosulfoxide **268**. DIBAL-H reduction of **268** gave only one diastereomer **269**. Reduction of δ-keto group in **269** with $NaBH_4$ and Et_2BOMe gave the *syn*-diol **270** in greater than 98% diastereoselectivity. Protection of 1,3-dihydroxy function, Pummerer reaction, desulfurization and acetate hydrolysis furnished **273**. Oxidation of primary alcohol, Wittig olefination and subsequent reduction of olefin gave ester **274**. Acetic acid hydrolysis afforded the lactone **188**.



Scheme 40. Reaction conditions: (i) NaH, *t*-BuLi, 0°C, 68%. (ii) DIBAL-H, THF, 44%. (iii) $NaBH_4$, Et_2BOMe, 99%. (iv) 2,2-DMP, *p*-TsOH. (v) Pummerer, 97%. (vi) (a) Raney Ni, 73%, (b) K_2CO_3, 78%. (vii) (a) Swern oxidation, 81%, (b) Ph_3P=CHPh, 65%. (c) H_2, Pd/C, AcOEt, 96%. (viii) AcOH/H_2O, rt, 81%.

Honda *et al*. (1997)[81] **Scheme 41**

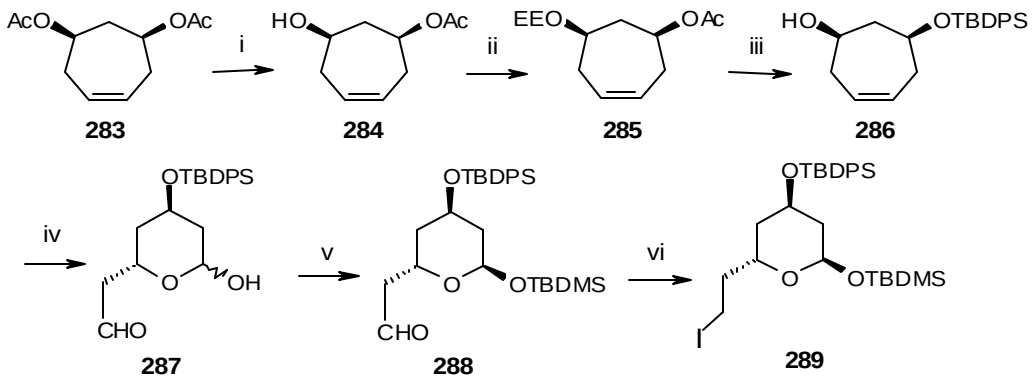
In Honda's approach, the reaction of mono-sodium salt derived from *cis*,*cis*-1,3,5-trihydroxy cyclohaxane **275** with 1 equivalent of *t*-$BuMe_2Si$-Cl gave **276**, which on further alkylation with BnBr furnished **277**. Desilylation, followed by oxidation afforded ketone **278**. Enantioselective deprotonation reaction of **278** with lithium (*S*,*S*)-α,α′-dimethyldibenzylamide as the chiral base and TMSCl gave the silyl ether **279**. Ozonolysis, aldehyde reduction and esterification of acid furnished **281**. Swern oxidation and Wittig reaction led to 1:4 mixture of *E*:*Z* isomers **282**. Benzyl ether deprotection, olefin reduction and lactonization eventually afforded **188**.



Scheme 41. Reaction conditions: (i) NaH, pyridine, rt, *t*-$BuMe_2Si$-Cl, THF, 0°C, 84%. (ii) NaH, BnBr, *n*-Bu_4NI, THF, rt, 100%. (iii) (a) *n*-Bu_4NF, THF, rt, (b) PCC, NaOAc, celite, CH_2Cl_2, rt, 76%. (iv) lithium (*S*,*S*′)-α,α′-dimethyldibenzylamide, TMSCl, THF, −100°C, 62%. (v) O_3, CH_2Cl_2, −78°C, then PPh_3, 71%. (vi) (a) $NaBH_4$, MeOH, rt, 68%, (b) MeI, K_2CO_3, DMF, rt, 90%. (vii) (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°C to −45°C, (b) $PhCH_2P^+Ph_3Cl^-$, *n*-BuLi, THF, 0°C-rt, 95%. (viii) (a) H_2, $Pd(OH)_2$, EtOH, rt, (b) *p*-TsOH, PhH, rt, 67%.

Suemune *et al*. (1997)[82] Scheme 42

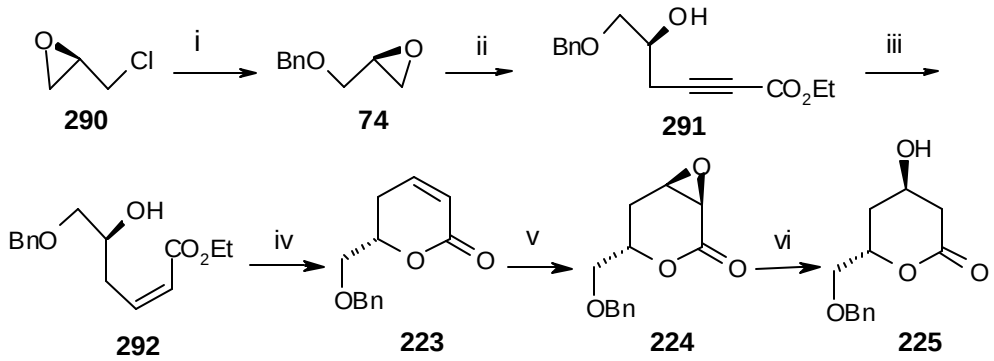
Suemune and co-workers desymmetrized meso-1,3-diacetoxy-5-cycloheptene **283** enzymatically using *Pseudomonas fluorescence* lipase (PFL) to afford the monoacetate **284**. Sequential protection of hydroxyl as ethoxy ethyl ether, solvolysis of acetate and protection as TBDPS followed by deprotection of ethoxy ethyl ether gave **286**. Reductive ozonolysis of **286** furnished the hemiacetal **287** as a 1:1 diastereomeric mixture at the C-2 position. Protection of the hemiacetal function as a TBDMS ether gave the sole product **288**. $NaBH_4$ reduction of **288** and iodination afforded **289**, a synthetic equivalent of the lactone moiety in mevinic acids.



Scheme 42. Reaction conditions: (i) PFL, phosphate buffer, pH 7, 44 h, 72%. (ii) Ethyl vinyl ether, PPTS, 79%. (iii) (a) K_2CO_3, MeOH, 82%, (b) *t*-$BuPh_2Si$-Cl, imidazole, 91%, (c) 5% aq. AcOH, $(CH_3)_2CO$, 89%. (iv) (a) O_3, CH_2Cl_2, (b) Zn, AcOH, 60%. (v) *t*-$BuMe_2Si$-Cl, imidazole, 70%. (vi) (a) $NaBH_4$, 74%, (b) I_2, Ph_3P, pyridine, 95%.

Ogasawara *et al*. (1997)[83] Scheme 43

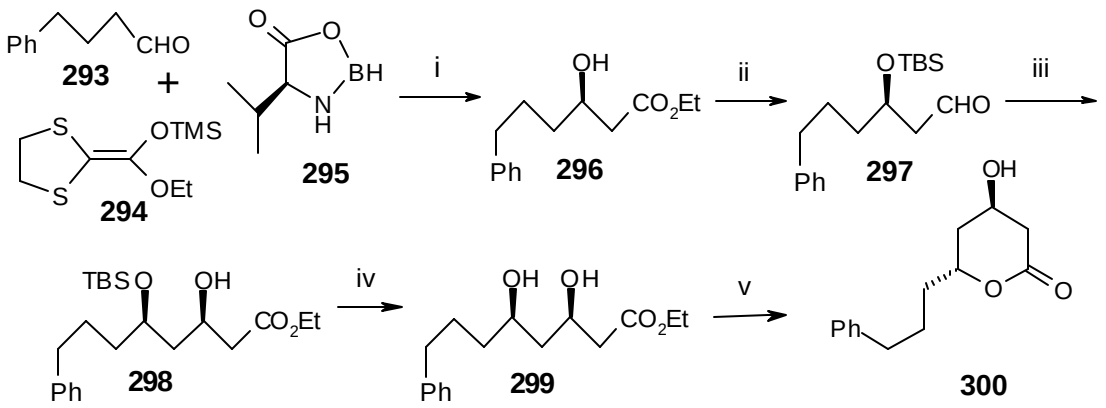
Ogasawara and co-workers have employed chiral epichlorohydrin **290**, which is transformed into (*S*)-*O*-benzylglycidol **74** by literature procedure.[84] Epoxide opening with ethyl 3-lithiopropiolate, partial hydrogenation of alkyne and acid-treatment gave the lactone **223** which on epoxidation with 30% H_2O_2 furnished single diastereomer **224**. Regioselective cleavage of the epoxide with aluminium amalgam gave **225**, the lactone equivalent of mevinic acid.



Scheme 43. Reaction conditions: (i) Ref. 84. (ii) Ethyl propiolate, *n*-BuLi, $BF_3.Et_2O$, THF, –78°C, 89%. (iii) H_2, Lindlar cat., $PhCH_3$, rt, 91%. (iv) *p*-TsOH, $PhCH_3$, reflux, 88%. (v) 30% H_2O_2, 6N NaOH, MeOH, 0°C, 89%. (vi) Al-Hg, Na_2HPO_4, *i*-PrOH, 70%.

Kiyooka *et al*. (1997)[85] Scheme 44

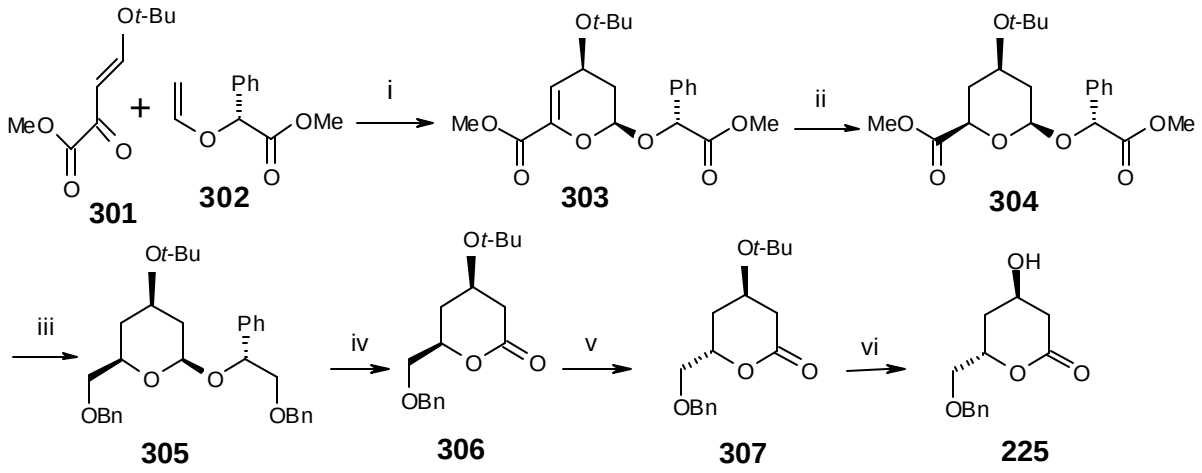
Kiyooka and coworkers employed the chiral oxazaborolidinone **295** catalyzed Aldol reaction of a silyl ketene involving a dithiolane moiety **294** with 4-phenylbutanal **293** to give **296**. Protection of hydroxyl and ester reduction afforded aldehyde **297**. A second Aldol reaction on **297** with **294** in the presence of **295** gave *syn*-1,3-diol **298**. Deprotection of TBS group and lactonization furnished the lactone **300**.



Scheme 44. Reaction conditions: (i) (a) Nitroethane, −78°C, 1 h, 86%, (b) Ni_2BH_2, 96%. (ii) (a) TBSCl, (b) DIBAL-H, 85%. (iii) (a) Nitroethane, **294**, **295**, −78°C, 1 h, (b) Ni_2BH_2, 77%. (iv) *n*-Bu_4NF. (v) *p*-TsOH, 70%.

Dujardin *et al*. (1998)[86] Scheme 45

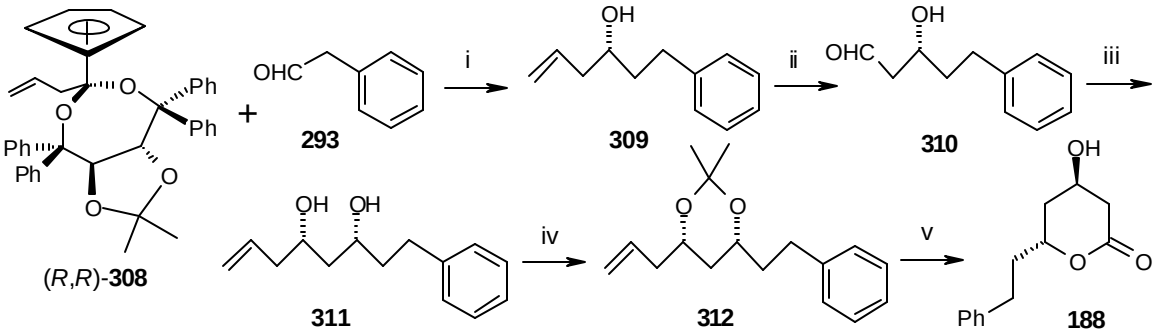
Dujardin and co-workers employed a hetero Diels-Alder reaction of oxabutadiene **301** with enolether **302** in the presence of $Eu(fod)_3$ to give the *endo*-heterocycloadduct **303** in 96% de. Catalytic hydrogenation of **303** and reduction of ester groups followed by benzylation gave **305**. Subsequent acidic hydrolysis and PCC oxidation afforded **306**. Hydrolysis of lactone and Mitsunobu inversion at C-5 center followed by *tert*-butyl deprotection furnished lactone **225**.



Scheme 45. Reaction conditions: (i) 5% $Eu(fod)_3$, hexane, reflux, 70%. (ii) H_2/Pd-C, EtOH, 88%. (iii) (a) $LiAlH_4$, Et_2O, 93%, (b) NaH, BnBr, DMF, 94%. (iv) (a) 3N HCl, THF, 96%, (b) PCC, 3A° molecular sieves, CH_2Cl_2, 89%. (v) (a) NaOH, THF, (b) NH_4Cl, (c) DIAD, Ph_3P, CH_2Cl_2, 42%. (vi) CF_3CO_2H, CH_2Cl_2, 72%.

Bouzbouz *et al*. (2000)[87] Scheme 46

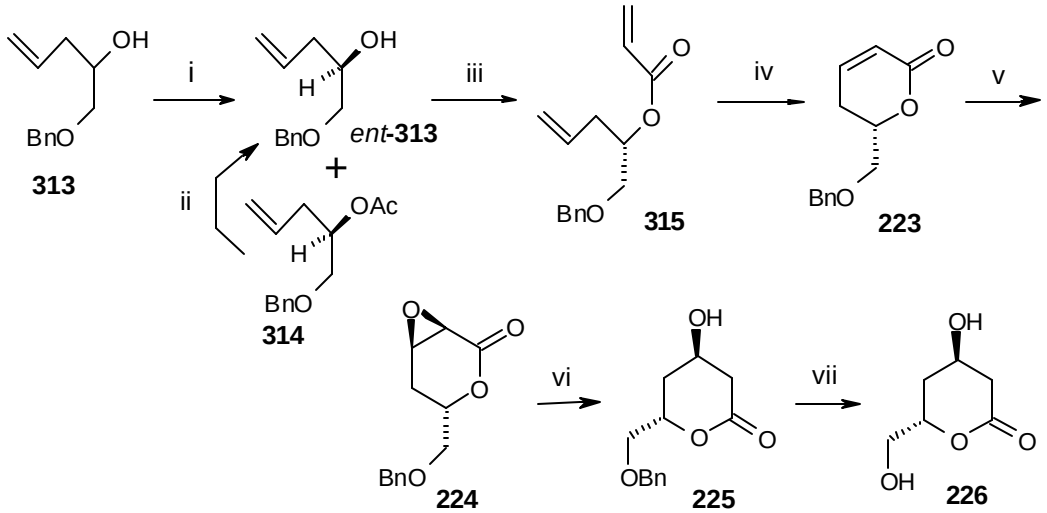
Bouzbouz and Cossy employed two consecutive enantioselective allytitanation with cyclopentadienyldial-ketoxyallytitanium complex (*R*,*R*)-**308**, first on **293** to give **309** and second on aldehyde **310** to give the *syn* 1,3-diol **311** in 95% diastereoselectivity. 1,3-Hydroxyl groups protection of **311** and $RuCl_3$ oxidation followed by acid treatment furnished the lactone **188**.



Scheme 46. Reaction conditions: (i) −78°C, 4 h, H_2O, 12 h, 90%. (ii) OsO_4, $NaIO_4$, Et_2O:H_2O, 90%. (iii) (*R*,*R*)-**308**, −78°C, 4 h, H_2O, 12 h, 80%. (iv) 2,2-DMP, $(CH_3)_2CO$, CSA, 0°C, 94%. (v) $RuCl_3.3H_2O$, AcOH, THF, 48%.

Ghosh *et al.* (2000)[88] Scheme 47

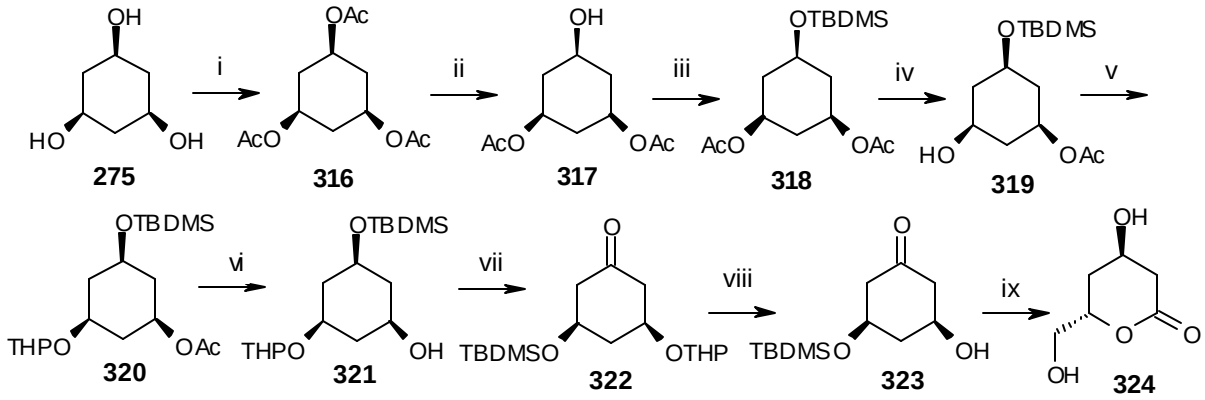
Ghosh and Lei carried out enzymatic acylation of racemic alcohol (±)-**313** with immobilized lipase PS-30 in presence of isopropenyl acetate to afford optically active *ent*-**313** and the acylated alcohol **314**. Compound **314** was converted to *ent*-**313** through saponification and Mitsunobu inversion. Reaction of *ent*-**313** with acryloyl chloride gave acrylate ester **315**. Olefin metathesis of **315** with Grubbs catalyst in the presence of Ti(O*i*-Pr)$_4$ furnished the α,β-unsaturated-δ-lactone **223**. Sequential epoxidation, reductive opening of epoxide and debenzylation produced the mevinic acid lactone **226**.



Scheme 47. Reaction conditions: (i) Immobilized lipase PS-30, CH_2=C(Me)OAc, DME, 37°C, 36 h. (ii) (a) LiOH, THF-H_2O, 23°C, 12 h, (b) *p*-NO_2PhCO_2H, Ph_3P, DEAD, 23°C, 12 h, 91%, (c) LiOH, THF-H_2O. (iii) CH_2=CHCOCl, Et_3N, DMAP (cat), −15°C, 30 min, 75%. (iv) Grubbs catalyst, Ti(O*i*-Pr)$_4$, CH_2Cl_2, 40°C, 15 h, 91%. (v) aq. NaOH, H_2O_2, MeOH, 23°C, 81%. (vi) $(PhSe)_2$, $NaBH_4$, *i*-PrOH, 0°C, 93%. (vii) H_2, Pearlman's cat., EtOAc, 5 h, 23°C, 70%.

Kalkote *et al*. (2001)[89] Scheme 48

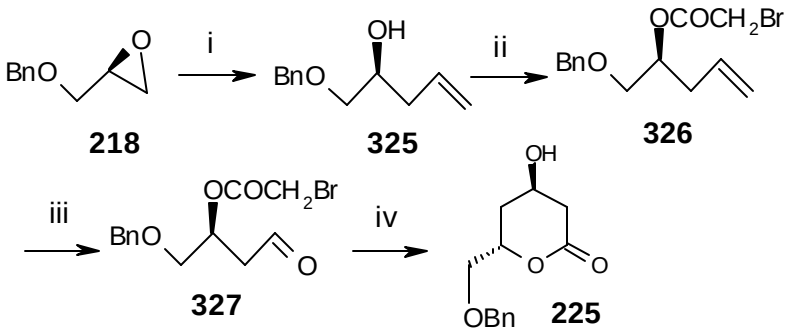
Kalkote and co-workers employed a chemoenzymatic deracemization of *cis*-phloroglucitol triacetate **316** with PLE to **317**. Hydroxyl protection as TBDMS ether gave **318**. Enzymatic desymmetrization employing PLE in hydrolysis of **318** afforded **319**. Subsequent hydroxyl protection as THP ether and acetate hydrolysis furnished **321**. PCC oxidation and magnesium bromide assisted selective deprotection of THP ether gave **323**. Baeyer-Villiger oxidation with neat *m*-CPBA afforded the lactone **324**.



Scheme 48. Reaction conditions: (i) Ac_2O, pyridine, 0°C-rt, 8 h, 100%. (ii) PLE, pH 7, 12 h, 90%. (iii) *t*-$BuMe_2Si$-Cl, Et_3N, DMAP, CH_2Cl_2, 0°C-rt, 90%. (iv) PLE, pH 8, *t*-BuOH, 30°C, 48 h, 70%. (v) DHP, *p*-TsOH, CH_2Cl_2, 0°C, 99%. (vi) K_2CO_3, MeOH, 96%. (vii) PCC, CH_2Cl_2, 80%. (viii) $MgBr_2.Et_2O$, Et_2O, 3 h, 90%. (ix) *m*-CPBA, rt, 45%.

Uang *et al*. (2002)[90] Scheme 49

Uang and co-workers employed the SmI_2 mediated intramolecular Reformatsky reaction in the synthesis of the lactone moiety of compactin. Vinyl magnesium bromide reaction on the glycidyl ether **218** furnished **325**. Reaction of **325** with bromoacetyl bromide gave **326**. Ozonolysis of **326** furnished the aldehyde **327** which on intramolecular Reformatsky reaction mediated by SmI_2 afforded the lactone **226** in >95:5 ratio.



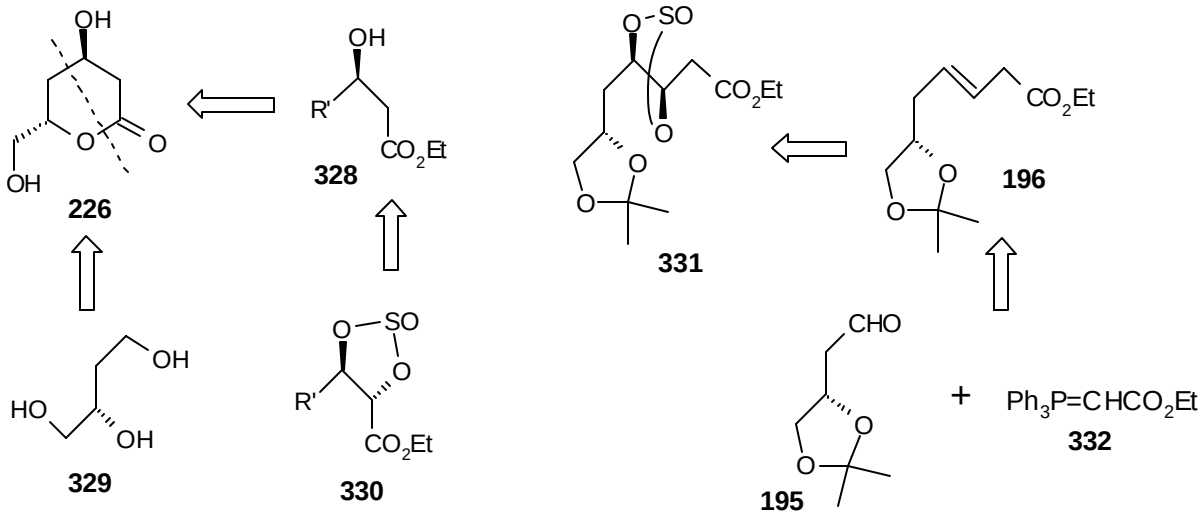
Scheme 49. Reaction conditions: (i) CH_2=CH-MgBr, CuCN, −10°C, 94%. (ii) $BrCOCH_2Br$, 2,6-lutidine, 0°C, 89%. (iii) O_3, CH_2Cl_2-MeOH, DMS. (iv) SmI_2, THF, 0°C, 2 h, 91% from **326**.

2.3.3. Present Work

Objective:

Efforts directed towards the synthesis of a key synthon representing the lactone portion **172** of mevinic acids with requisite C-4 and C-6 stereochemistry and a suitable linker group at the C-6 position for coupling with the lower decalin core continue unabated. Most of the reports described earlier have used chiral precursors, chiral auxiliaries or are limited in their flexibility of structural modification. Many involve a large number of steps or costly chiral materials and chiral auxiliaries. Hence, a practical route for the construction of the key synthon for mevinic acid lactone portion is still desirable. With the completion of the synthesis of (*R*)-(−)-mevalonolactone employing Sharpless asymmetric dihydroxylation and regioselective cyanide opening of chiral cyclic sulfate (**Synthetic strategy-1**) we planned to develop a new synthesis of the lactone portion of mevinic acids. Here we employed the **Synthetic strategy-2**, wherein the chiral cyclic sulfite derived from α,β-dihydroxy ester is opened regioselectively at α-carbon to give the β-hydroxy acid precursor, which on hydrolysis and lactonization gave the β-hydroxy-δ-lactone portion of compactin and mevinolin.

The retrosynthetic analysis for the asymmetric synthesis of lactone **226** is shown in **Scheme 50**. The left half of the lactone **226** is represented by the fragment **329**, which could be derived from (*S*)-(−)-malic acid. The right half is a β-hydroxy acid synthon **328**. In the asymmetric synthesis of (*R*)-(-)-mevalonolactone we have shown that β-hydroxy acid is obtained by regioselective cyanide opening of cyclic sulfate derived from terminal 1,2-diol. Herein **328** could be obtained by regioselective hydride opening of internal cyclic sulfite **330**. A common equivalent for both **329** and **330** is **331**. The cyclic sulfite **331** could be derived from olefin **196**, through asymmetric dihydroxylation and conversion of diol into cyclic sulfite. Olefin **196** could be obtained by Wittig reaction of stable phosphorane **332** with aldehyde **195** which in turn could be derived from **329**. Regioselective opening of cyclic sulfite **331** with hydride nucleophile followed by acidic hydrolysis of sulfite ester will also result in acetonide deprotection and subsequent lactonization to give the lactone **226**. Thus, the hydroxyl center in (*S*)-malic acid becomes the C-6 chiral center, while regiospecific hydride opening of cyclic sulfite generates the C-4 hydroxyl, which is the key step in the synthesis.

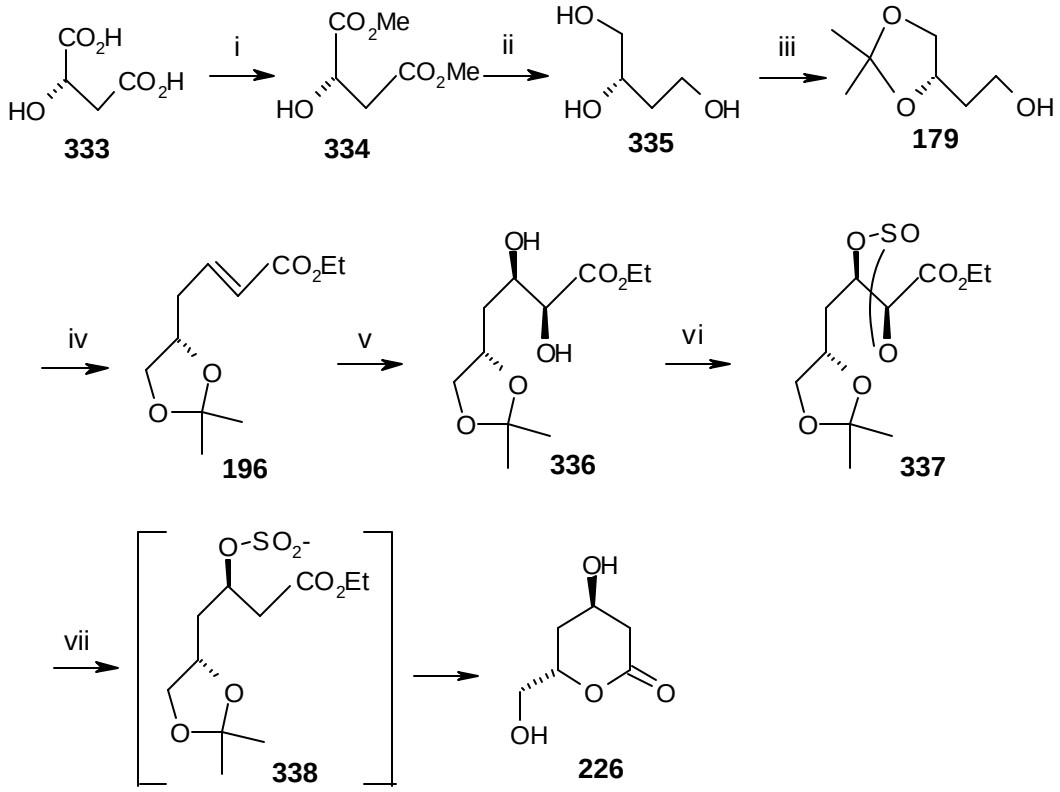


Scheme 50. Retrosynthetic analysis.

2.3.4. Results and Discussion

The detailed synthetic route with reaction conditions is given in **Scheme 51**. (*S*)-malic acid **333** was esterified with 5% HCl in MeOH at room temperature to furnish the diester **334** in 89% yield as a colorless liquid. The ^{1}H NMR spectrum of **334** showed two singlets for the two methoxy groups at δ 3.69 and 3.79 indicating formation of diester. The reduction of diester with lithium aluminium hydride gave the triol **335** as a thick syrupy liquid in 83% yield. The IR spectrum of **335** showed the absence of ester carbonyl. The protection of 1,2-dihydroxy with 2,2-dimethoxy propane gave the acetonide alcohol **179** in 88% yield as colorless oil. The minor 1,3-acetonide (5-10%) formed was not separated. The ^{1}H NMR spectrum of **179** showed acetonide methyls at δ 1.34 and 1.40 as singlets.[91] In the ^{13}C NMR spectrum, acetonide carbons appeared at δ 24.91, 26.09 (for two methyl) and δ 107.84 for tertiary carbon. Oxidation of primary hydroxyl group in **179** under normal Swern oxidation conditions gave the corresponding aldehyde (δ 9.78, singlet in ^{1}H NMR spectrum) which on subsequent Wittig reaction with (ethoxycarbonylmethylene)triphenylphosphorane gave the *trans*-olefin **196** in 83% yield. The IR spectrum of **196** gave a strong peak at 1713 cm^{-1} for ester carbonyl and a peak at 1650 cm^{-1} for olefinic bond. In the ^{1}H NMR spectrum of **196**, the olefinic peaks appeared at δ 5.85 (doublet of triplet) and δ 6.9 (doublet of triplet) with a coupling constant of J = 16 Hz indicating *trans*-

olefin. The $[\alpha]_D^{20}$ – 17.9 (c = 1, MeOH) matched well with that reported in the literature $[\alpha]_D^{20}$ – 18.0 (c = 2.48, MeOH).[68]



Scheme 51. Reaction conditions: (i) 5% HCl-MeOH, rt, 24 h, 89%. (ii) $LiAlH_4$, THF, reflux, 12 h, 83%. (iii) 2,2-DMP, acetone, *p*-TsOH, rt, 48 h, 88%. (iv) (a) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, –78°C, (b) $Ph_3P{=}CHCO_2Et$, THF, rt, 24 h, 83%. (v) $(DHQD)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, OsO_4 (cat), $MeSO_2NH_2$, *t*-BuOH:H_2O (1:1), 0°C, 24 h, 84%. (vi) $SOCl_2$, Et_3N, CH_2Cl_2, 0°C, 30 min, 90%. (vii) $NaBH_4$, THF, 12 h, rt, then 4N H_2SO_4, MeOH, overnight, 63%.

The Sharpless asymmetric dihydroxylation of olefin **196** using the $(DHQD)_2$-PHAL as chiral ligand and catalytic OsO_4 gave the diol **336** in 84% yield and 94% de. The IR spectrum of **336** showed hydroxyl absorption at 3436 cm^{-1}. In the ^1H NMR spectrum of **336**, the olefinic protons disappeared. In the ^{13}C NMR spectrum, the hydroxyl carbons appeared at δ 70.25 and 76.1. Treatment of diol **336** with thionyl chloride and Et_3N gave the cyclic sulfite **337** in 90% yield. The hydroxyl absorption disappeared in the IR spectrum of **337**. A downfeld shift of CH-OS- protons was found at δ 4.9 (multiplet) and 5.28 (doublet) in comparison to the same protons of dihydroxy compound **336**. With the cyclic sulfite in hand we proceeded to the regioselective

opening at α-carbon of the ester group. Opening of cyclic sulfite with hydride would give the intermediate sulfite ester **338** requiring acidic hydrolysis to free the hydroxyl group. Since the next two conversions involve acidic deprotection of acetonide and lactonization we carried out a one pot sequence of reactions involving a regioselective opening of cyclic sulfite, acidic hydrolysis of sulfite ester with simultaneous deprotection and lactonization. Toward this end, treatment of cyclic sulfite **337** with one equivalent of $NaBH_4$ gave the intermediate sulfite ester **338**, which without isolation was acidified with aq. 4N H_2SO_4 in MeOH to give the lactone **226** in the one pot reaction in 63% yield. The lactone **226** had $[\alpha]_D^{20}$ = + 1.89 (c = 0.5, MeOH), which matched well with literature value of $[\alpha]_D^{29}$ + 1.81 (c = 0.992, MeOH).[72] The IR spectrum of **226** showed hydroxyl absorption at 3477 cm^{-1} and carbonyl of δ-lactone at 1735 cm^{-1}. The ^1H NMR spectrum and EIMS data matched well with that reported in the literature.[72]

To determine the diastereomeric purity, the diol **336** was converted into dibenzoate with benzoyl chloride and pyridine. The diastereomeric purity of dibenzoate was estimated to be in excess of 94% by HPLC using Lichrocart 250-4 (4mm ID × 25cm) HPLC-Cartridge (R.R.-Whelk-01), 10% *i*-PrOH in hexane and also by ^1H NMR.

2.3.5. Conclusion

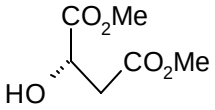
The Sharpless asymmetric dihydroxylation of α,β-unsaturated olefin **196** gave the diol **336** in high diastereoselectivity. The corresponding cyclic sulfite opening occurred regioselectively at the α-carbon giving the β-hydroxy acid which lactonized to **226**, representing the lactone portion of mevinic acid. Thus, a short, high yielding and efficient asymmetric synthesis of the lactone moiety of mevinic acids with desired stereochemistry at C-4 and C-6 has been achieved. The presence of hydroxylmethylene functionality at C-6 serves for easy coupling to the lower functionalized core of mevinic acids. The synthetic strategy could also be extended to the synthesis of all possible isomers of the lactone moiety either by using the unnatural (*R*)-(+)-malic acid and/or employing the $(DHQ)_2$-PHAL ligand in asymmetric dihydroxylation.

2.3.6. Experimental Section

General information

The solvents were purified and dried by standard procedures before use. Petroleum ether of boiling range 60-80°C was used. Optical rotations were measured using sodium D line on JASCO-181 digital polarimeter. Infrared spectra were recorded on ATI MATTSON RS-1 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR were recorded on Bruker AC-200 NMR and MSL 300 NMR spectrometers. Mass spectra were obtained with a Finnigan MAT-1020 B-70 eV mass spectrometer. Elemental analyses were carried out on a Carlo Erba CHNS-O analyzer

Preparation of (*S*)-dimethylmalate, 334



334

(*S*)-malic acid **333** (20 g, 149.15 mmol) was dissolved in 5% HCl in MeOH (120 mL) and stirred at room temperature for 24 h. The reaction mixture was concentrated and distilled (bath temp. 145-150°C/10 mm) to give (*S*)-dimethyl malate (17 g) as a colorless liquid. The residual material in the distillation flask was dissolved in 5% HCl in MeOH (60 mL) and processed as above. Distillation afforded additional 4.52 g of the diester, raising the total yield to 21.52 g.

Yield: 21.52 g, 89%.

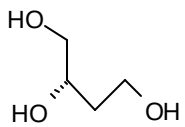
[a]$_D^{20}$: − 6.45 (c = 1, EtOH) [lit. $[\alpha]_D^{20}$ − 6.9 (neat),[92] lit. $[\alpha]_D^{25}$ + 6.4 (neat)[92b] for (*R*)-**334**]

IR (neat, cm^{-1}): n_{max} 3453, 3004, 2952, 1734, 1438, 1272, 1217, 1103, 922

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.81 (dd, *J* = 2, 4 Hz, 2H), 3.45 (brs, 1H), 3.69 (s, 3H), 3.79 (s, 3H), 4.48 (t, *J* = 4 Hz, 1H)

EIMS (*m/z* relative intensity, %): 163 [M^+] (1.8), 131 (25.1), 130 (25), 103 (100), 71 (91), 61 (50.3), 59 (36.5)

Preparation of (*S*)-1,2,4-butanetriol, 335



335

To a stirred suspension of $LiAlH_4$ (4.92 g, 129.5 mmol) in dry THF (150 mL) at 0°C was added a solution of **334** (10 g, 61.67 mmol) in dry THF (20 mL). The ice bath was removed and

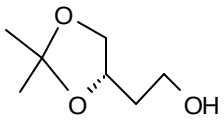
the reaction mixture was refluxed for 12 h. Excess $LiAlH_4$ was destroyed by adding water (50 mL). The white precipitate obtained was filtered and washed with MeOH (5 × 100 mL). The combined filtrate was concentrated to near dryness. The inorganic materials contained in the residual oil were removed by short column chromatography over 50 g of silica gel. Elution with $CHCl_3$:EtOH (550 mL, 3:1 v/v and 650 mL, 2:1 v/v) and concentration of the solvents gave (*S*)-1,2,4-butanetriol **335** (5.45 g) as a syrupy liquid.

Yield: 5.45 g, 83 %

[a]$_D^{20}$: – 28.2 (c = 1, MeOH) [lit. $[\alpha]_D^{25}$ – 28 (c = 1.07, MeOH)[91] lit. $[\alpha]_D^{25}$ – 29 (c = 1.03, MeOH)[92b]]

IR (neat, cm^{-1}): n_{max} 3389, 3339, 2936, 2883, 1414, 1052

Synthesis of 2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]ethanol, 179



179

To a solution of (*S*)-1,2,4-butanetriol **335** (5 g, 47.11 mmol) in dry acetone (250 mL) was added 2,2-dimethoxy propane (7.53 mL, 61.24 mmol) and *p*-TsOH (300 mg). The reaction mixture was stirred at room temperature for 48 h. A pinch of $NaHCO_3$ was added and stirred for 15 min. The reaction mixture was passed through a pad of silica gel. The filtrate was concentrated and distilled (bath temp. 120-125°C/10 mm) to give (*S*)-1,2,4-butanetriol 1,2-acetonide **179** (6.15 g) as a colorless liquid.

Yield: 6.15 g, 88%

[a]$_D^{20}$: – 3.89 (c = 1, MeOH) [lit. $[\alpha]_D^{20}$ – 2.23 (c = 9.8, MeOH)[93]]

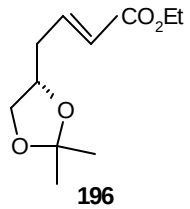
IR (neat, cm^{-1}): n_{max} 3395, 2972, 2930, 2873, 1367, 1212, 1148, 1048, 844

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.34 (s, 3H), 1.40 (s, 3H), 1.80 (q, *J* = 6 Hz, 2H), 2.65 (s, 1H), 3.57 (t, *J* = 8 Hz, 1H), 3.77 (t, *J* = 6 Hz, 2H), 4.07 (dd, *J* = 2, 6 Hz, 1H), 4.28 (m, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 24.91, 26.09, 35.57, 58.36, 68.69, 73.18, 107.84

EIMS (*m/z* relative intensity, %): 145 [M^+–1] (1.2), 131 (55.7), 115 (6.6), 85 (16.1), 71 (100), 59 (46.7)

Synthesis of ethyl (2*E*)-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4yl]but-2-enoate, 196



196

To a solution of oxalyl chloride (4.36 g, 3 mL, 34.34 mmol) in CH_2Cl_2 (80 mL) at –78°C was added dropwise dry DMSO (5.37 g, 4.9 mL, 68.70 mmol) in CH_2Cl_2 (20 mL). After 20 min, **179** (3.35 g, 22.9 mmol) in CH_2Cl_2 (20 mL) was added dropwise over 30 min giving a copious white precipitate. After stirring for 1 h at –60°C, Et_3N (14.4 mL, 103.02 mmol) was added slowly and stirred for 1 h allowing the reaction mixture to warm to room temperature. The reaction mixture was poured into 2N HCl (100 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL), brine (50 mL), dried (Na_2SO_4) and passed through a short pad of silica gel. The filtrate was concentrated to give the aldehyde (3.1 g) as pale yellow oil. This was used for the next step without further purification.

IR (neat, cm^{-1}): n_{max} 3035, 2957, 2805, 1717, 1631, 1374, 950

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (s, 3H), 1.40 (s, 3H), 2.6-2.8 (m, 2H), 3.57 (dd, *J* = 3, 6 Hz, 1H), 4.18 (dd, *J* = 3, 6 Hz, 1H), 4.52 (t, *J* = 7 Hz, 1H), 9.78 (s, 1H)

To a solution of (ethoxycarbonylmethylene)triphenylphosphorane (9.75 g, 28 mmol) in dry THF (30 mL) was added the solution of aldehyde (3 g, 20.8 mmol) in THF (5 mL) at 0°C. The ice-bath was removed and the reaction mixture was stirred for 24 h at room temperature and then concentrated to thick syrup. Column chromatography of the crude product on silica gel using petroleum ether:EtOAc (95:5) as eluent gave **196** (3.93 g) as a pale yellow oil.

Yield: 3.93 g, 83%

$[\alpha]_D^{20}$: − 17.9 (c = 1, MeOH) [lit. $[\alpha]_D^{20}$ − 18 (c = 2.48, MeOH)[68]]

IR (neat, cm^{-1}): n_{max} 2977, 2929, 2874, 1713, 1650, 1450, 1368, 1259, 1208, 1163, 1046, 975

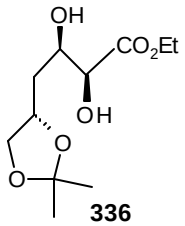
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.25 (t, *J* = 8 Hz, 3H), 1.32 (s, 3H), 1.39 (s, 3H), 2.4-2.5 (dq, *J* = 2, 6 Hz, 2H), 3.55 (dd, *J* = 2, 6 Hz, 1H), 4.03-4.21 (m, 4H), 5.85 (dt, *J* = 2, 16 Hz, 1H), 6.90 (dt, *J* = 6, 16 Hz, 1H)

^{13}C NMR (50MHz, $CDCl_3$): δ 14.04, 25.32, 26.65, 36.29, 59.82, 68.6, 74.11, 108.9, 123.61, 143.77, 165.53

EIMS (*m/z* relative intensity, %): 199 [M^+–15] (59.5), 169 (9.5), 139 (9.5), 111 (54.2), 101 (100), 83 (34), 67 (29.8), 55(16.7)

Analysis: $C_{11}H_{18}O_4$ (214.25) requires C, 61.66; H, 8.46. Found: C, 61.54; H, 8.53.

Synthesis of ethyl (2*S*,3*R*)-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,3-dihydroxy butanaote, 336



336

To a mixture of $K_3Fe(CN)_6$ (4.14 g, 12.6 mmol), K_2CO_3 (1.74 g, 12.6 mmol) and $(DHQD)_2$-PHAL (33 mg, 42.4 mmol, 1 mol%) in *t*-BuOH-H_2O (1:1, 50 mL) cooled at 0°C was added OsO_4 (340 µL, 0.1M soln in toluene, 0.8 mol%) followed by methanesulfonamide (0.4 g, 4.2 mmol). After stirring for 5 min at 0°C, the olefin **196** (0.9 g, 4.2 mmol) was added in one portion. The reaction mixture was stirred at 0°C for 24 h and then quenched with solid sodium sulfite (6 g). The stirring was continued for 45 min and the solution was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed (10% KOH, then brine), dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether:EtOAc (3:2) as eluent gave **336** (0.88 g) as a colorless syrupy liquid.

Yield: 0.88 g, 84%

[a]$_D^{20}$: + 9.9 (c = 1, MeOH)

IR (neat, cm^{-1}): n_{max} 3436, 2930, 2869, 1727, 1372, 1258, 1216, 1125, 1056

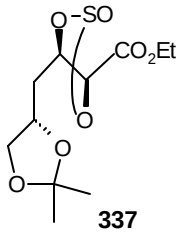
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.26 (t, *J* = 8 Hz, 3H), 1.34 (s, 3H), 1.40 (s, 3H), 1.8-1.9 (m, 2H), 3.4 (s, 2H), 3.6 (m, 1H), 4.0-4.14 (m, 4H), 4.28 (q, *J* = 8 Hz, 2H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 23.6, 25.7, 36.8, 62, 68.1, 69.5, 70.25, 76.1, 108.8, 168.1

EIMS (*m/z* relative intensity, %): 233 [M^+–15] (28), 191 (8.7), 173 (8), 145 (10.8), 117 (24.7), 99 (69.3), 87 (100), 71 (66.9), 59 (77.7)

Analysis: $C_{11}H_{20}O_6$ (248.27) requires C, 53.21; H, 8.12. Found: C, 52.98; H, 8.31.

Synthesis of compound, 337



337

To a stirred ice-cooled solution of **336** (0.4 g, 1.61 mmol) in dry CH_2Cl_2 (5 mL) was added Et_3N (0.9 mL, 6.45 mmol) followed by a solution of $SOCl_2$ (0.18 mL, 2.45 mmol) in dry CH_2Cl_2 (2 mL) over 5 min. The reaction mixture was stirred for 30 min and then quenched by addition of H_2O (5 mL) and CH_2Cl_2 (10 mL). The organic layer was separated and washed with brine (20 mL), dried (Na_2SO_4) and passed through a pad of neutral alumina. The filtrate was concentrated to give a yellow liquid. Column chromatography of the crude product on silica gel column using petroleum ether:EtOAc (95:5) as eluent gave **337** (0.427 g) as a pale yellow oil.

Yield: 0.427 g, 90%

$[\alpha]_D^{20}$: + 87.9 (c = 0.5, MeOH)

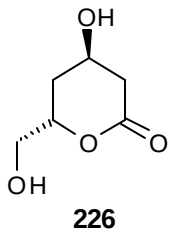
IR (neat, cm^{-1}): n_{max} 2977, 2877, 1744, 1449, 1370, 1204, 1035, 853

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33 (t, *J* = 8 Hz, 3H), 1.34 (s, 3H), 1.41 (s, 3H), 2.2-2.35 (m, 2H), 3.68 (dd, *J* = 2, 6 Hz, 1H), 4.11 (dd, *J* = 2, 6 Hz, 2H), 4.28 (q, *J* = 8 Hz, 2H), 4.82 (m, 1H), 5.28 (d, *J* = 8 Hz, 1H)

EIMS (*m/z* relative intensity, %): 295 [M^++1] (4.2), 279 [M^+–15] (100), 169 (34.5), 155 (71.4), 127 (85.7), 99 (74.4), 81 (75.6), 69 (37.7), 59 (9)

Analysis: $C_{11}H_{18}O_7S$ (294.32) requires C, 44.89; H, 6.16; S, 10.89. Found: C, 45.07; H, 6.39; S, 10.66.

Synthesis of (4*R*,6*S*)-4-hydroxy-6-hydroxymethyl-tetrahydro-pyran-2-one, 226



226

To a solution of cyclic sulfite **337** (175 mg, 0.594 mmol) in dry THF (8 mL) was added $NaBH_4$ (22.5 mg, 0.594 mmol) under argon. The reaction mixture was stirred under argon at

room temperature for 12 h. The solvent was removed under reduced pressure and MeOH (5 mL) was added to the residue. The reaction mixture was acidified with 4N H_2SO_4 (1 mL) and stirred at room temperature overnight. The solvent was stripped off under reduced pressure and the residue was purified by silica gel column chromatography using petroleum ether:EtOAc (1:4) as eluent to give **226** (0.054 g) as a colorless oil.

Yield: 0.054 g, 63%

[a]$_D^{20}$: + 1.89 (c = 0.5, MeOH) [lit. $[\alpha]_D^{29}$ + 1.81 (c = 0.992, MeOH)[72]

IR (neat, cm^{-1}): n_{max} 3477, 2952, 1735, 1438, 1270, 993

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.98 (m, 4H), 2.71 (d, *J* = 4 Hz, 2H), 4.0-4.07 (m, 2H), 4.48 (quint, *J* = 4 Hz, 1H), 4.7 (m, 1H)

EIMS (*m/z* relative intensity, %): 147 [M^++1] (4.2), 115 (60), 73 (100)

2.3.7. Spectra

+1] ^{1}H NMR Spectrum of **336**

+2] ^{13}C NMR Spectrum of **336**

+3] ^{1}H NMR Spectrum of **337**

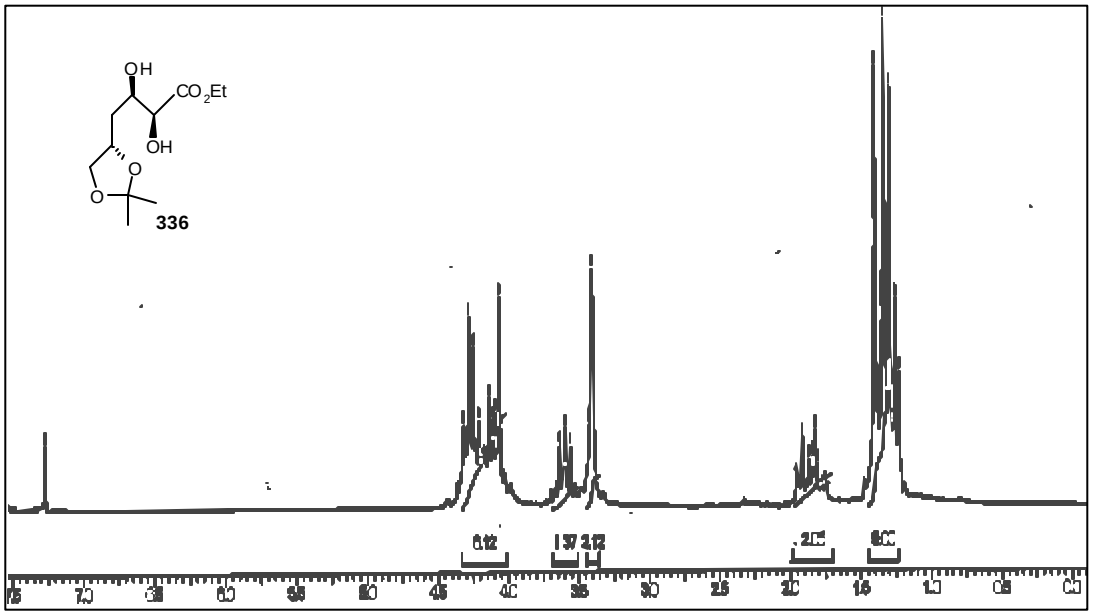
+4] ^{1}H NMR Spectrum of **226**

+5] EIMS of **226**

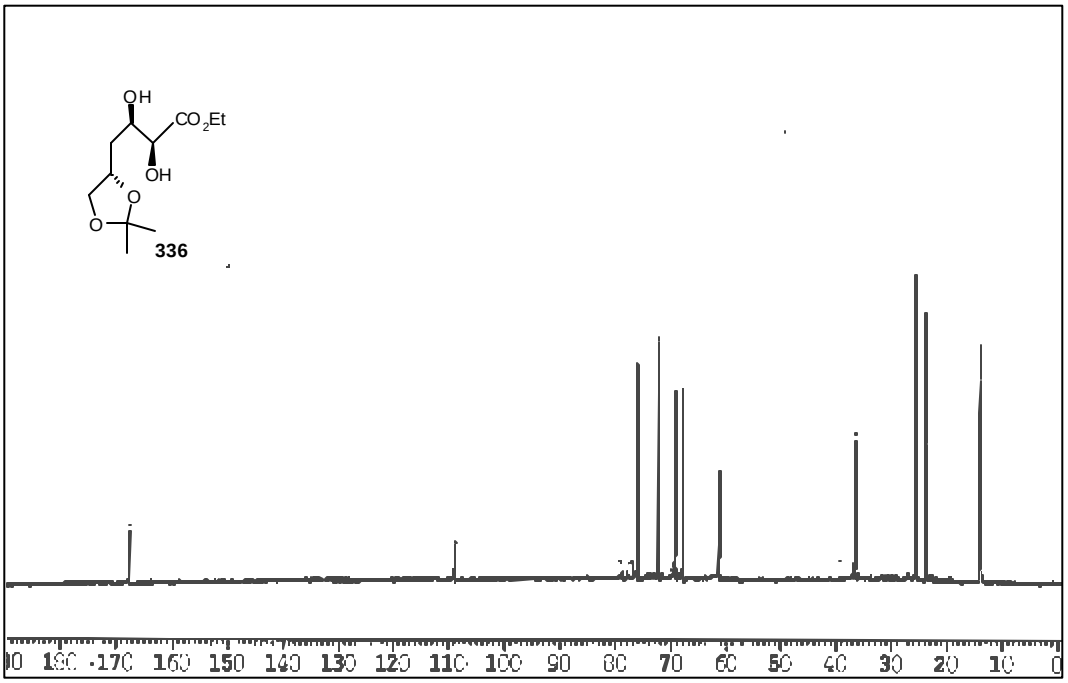
+6] ^{1}H NMR Spectrum of Mosher ester of dibenzoate of **336**

+7] ^{1}H NMR Spectrum of Mosher ester of **336** (racemic at C2,C3)

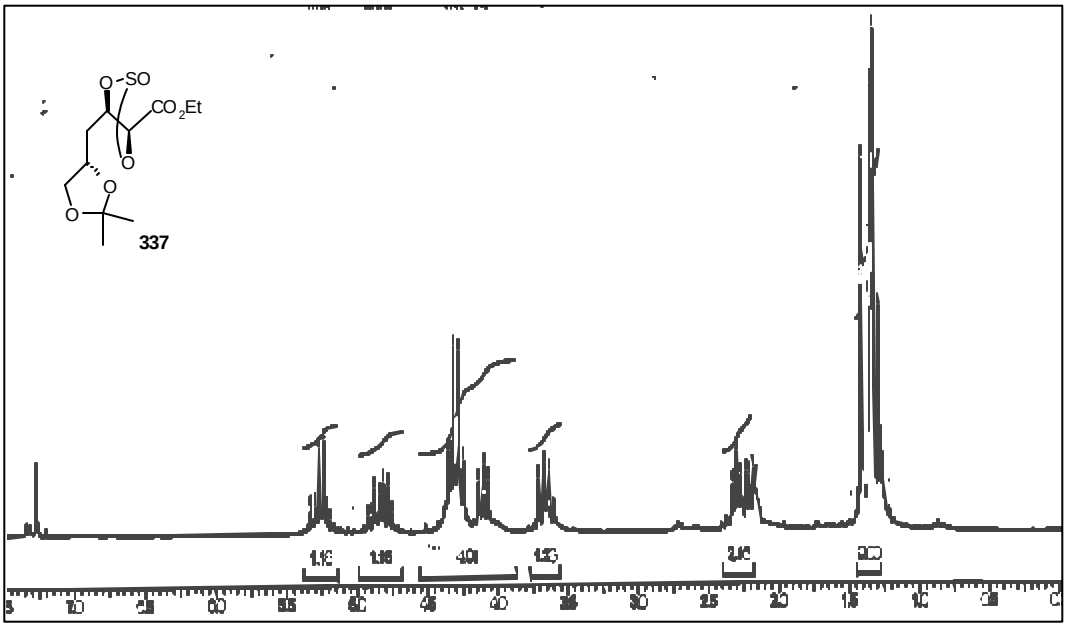
+ ^{1}H NMR Spectrum of **336**



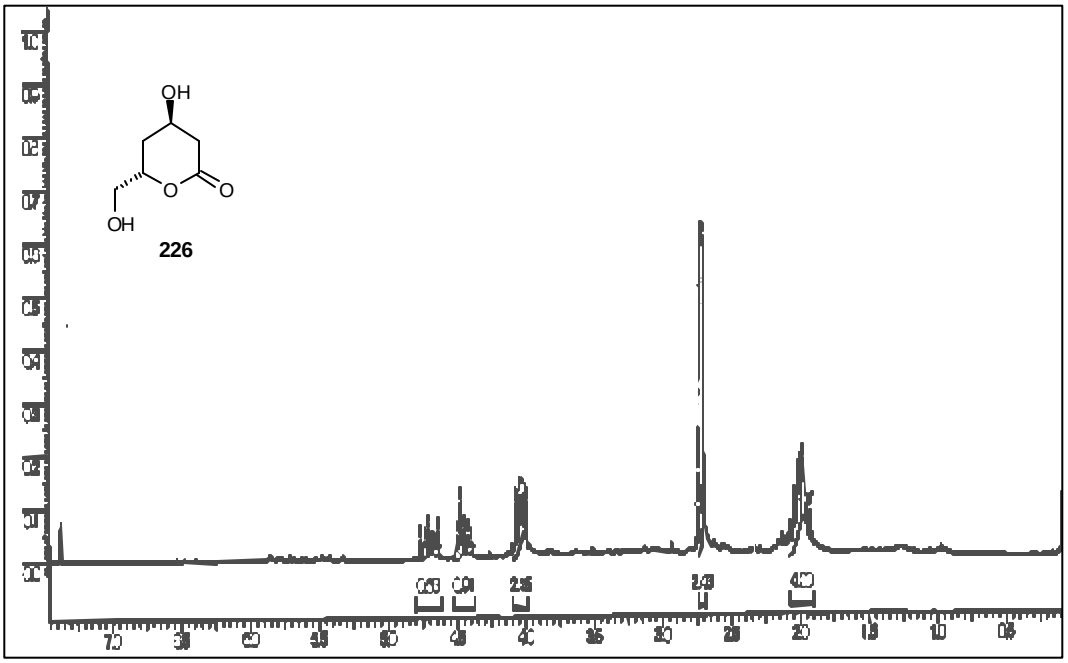
+ ^{13}C NMR Spectrum of **336**



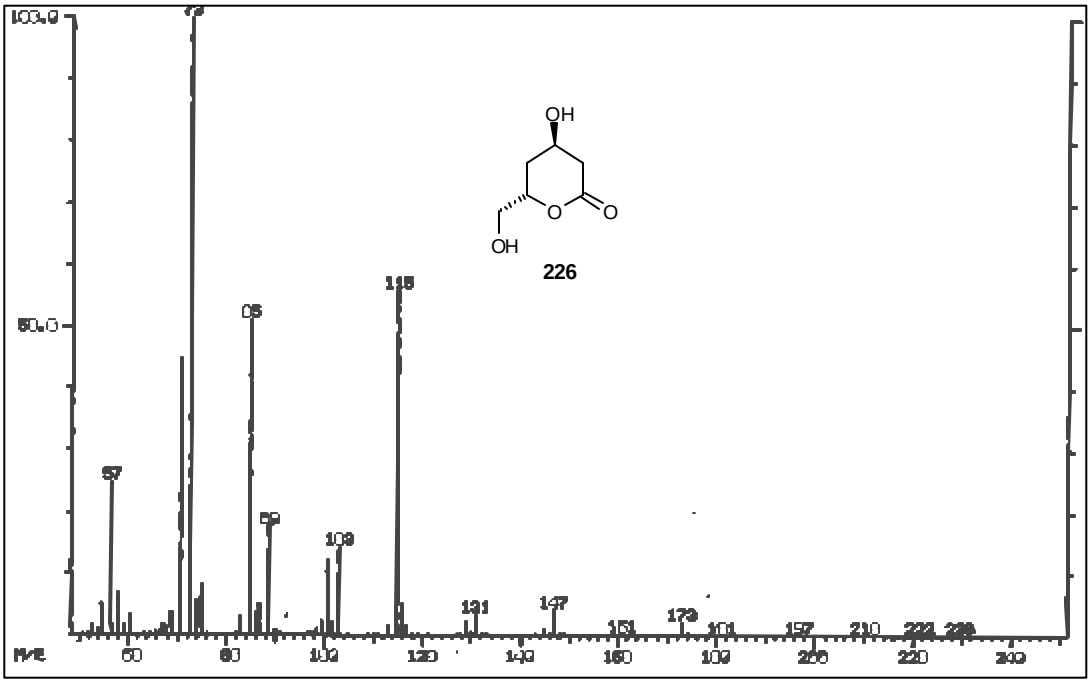
+ ^{1}H NMR Spectrum of **337**



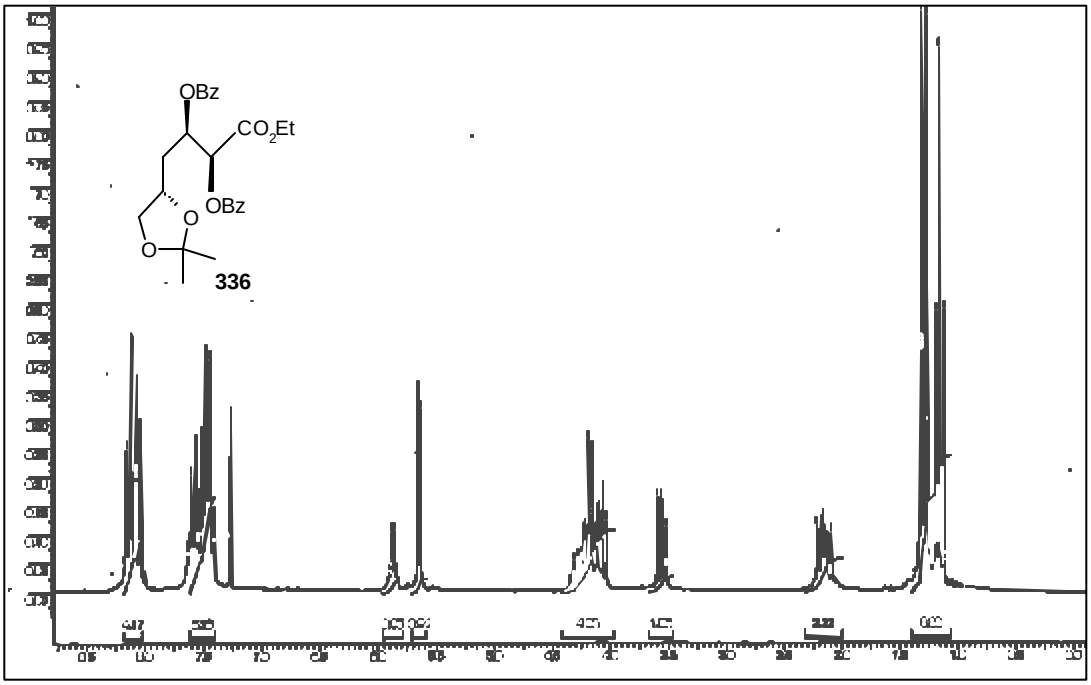
+ ^{1}H NMR Spectrum of **226**



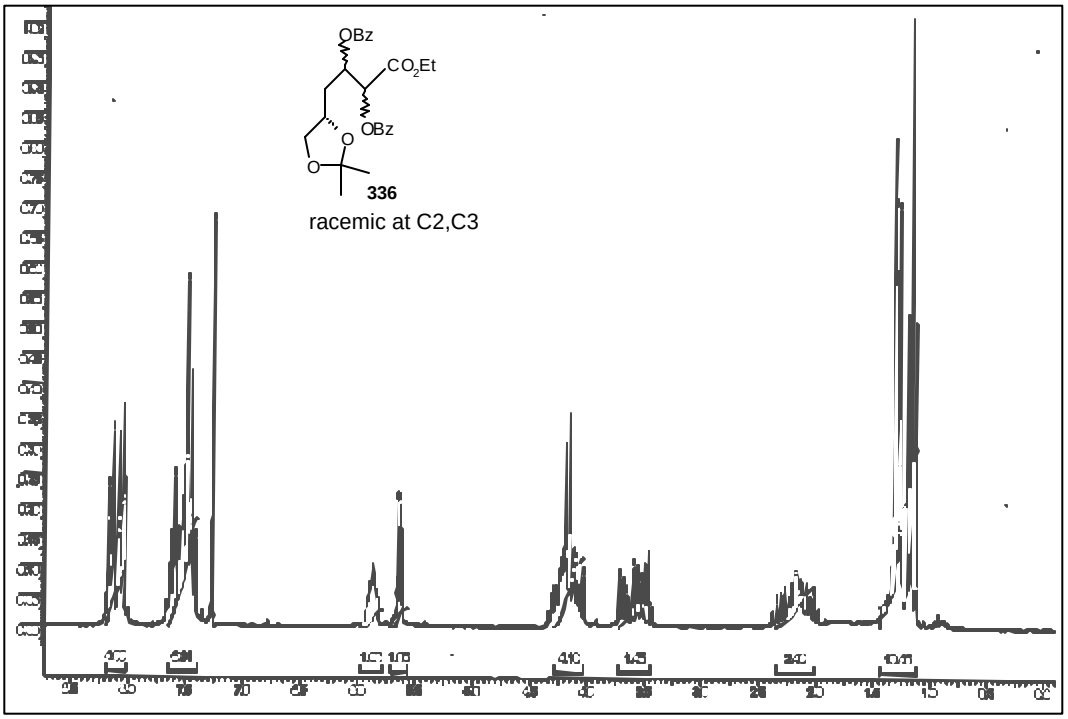
+ EIMS of **226**



+ ^{1}H NMR Spectrum of Mosher ester of dibenzoate of **336**



+ ^{1}H NMR Spectrum of Mosher ester of **336** (Racemic at C2,C3)



2.4. References

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CHAPTER 3

ASYMMETRIC SYNTHESIS OF VICINAL AMINO ALCOHOLS: DIHYDROSPHINGOSINE AND PHYTOSPHINGOSINES

3.1. Introduction

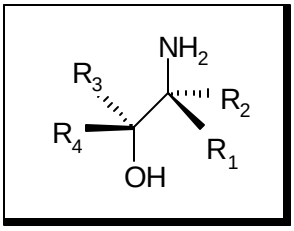
The vicinal amino alcohol moiety is a common structural component in a vast array of naturally occurring and synthetic molecules. The common name for this group varies from vicinal amino alcohol to β-amino alcohol to 1,2-amino alcohol. Either the amine or the alcohol can be acylated, alkylated or contained within rings. The presence of this moiety and the relative (as well as absolute) stereochemistry are generally important for the biological activity of molecules containing a vicinal amino alcohol. As such, a variety of stereoselective synthetic methods have been developed leading to vicinal amino alcohols.

There are three general groups of vicinal amino alcohols reported in the literature:

(1) Naturally occurring molecules

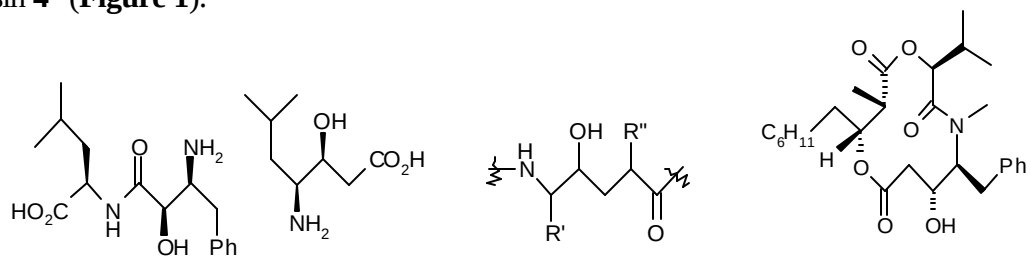
(2) Synthetic pharmacologically active molecules

(3) Catalysts containing vicinal amino alcohols



Naturally occurring molecules

Hydroxy amino acids are one of the most common naturally occurring molecules that contain the amino alcohol moiety. Serine and threonine are useful members of the chiral pool.[1] Other well known examples include bestatin **1**,[2] statine **2**,[3] hydroxy ethylene dipeptide isostere **3**[4] and hapalosin **4**[5] (**Figure 1**).



Bestatin **1** Statine **2** Hydroxy ethylene isostere **3** Hapalosin **4**

Figure 1.

Lipids and lipid-like molecules make up a large class of naturally occurring molecules containing the vicinal amino alcohol moiety. Possibly, sphingosine **5**,[6] is the most synthesized amino alcohol. Sphinganine **6**,[7] phytosphingosine **7**,[7] sulfobacin B **8**[8] and myriocin **9**[9] are related vicinal amino alcohols (**Figure 2**).

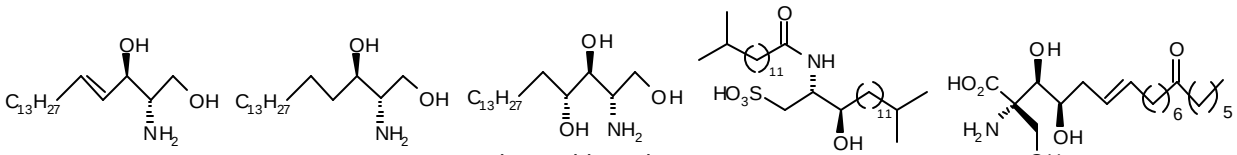


Figure 2

Cyclic amino alcohols constitute another larger class in which the amine N is contained within a ring. Penaresidin A **10**,[10] anisomysin **11**,[11] preussin **12**,[12] febrifugine **13**[13] and swainsonine **14**[14] (**Figure 3**) are well known examples.

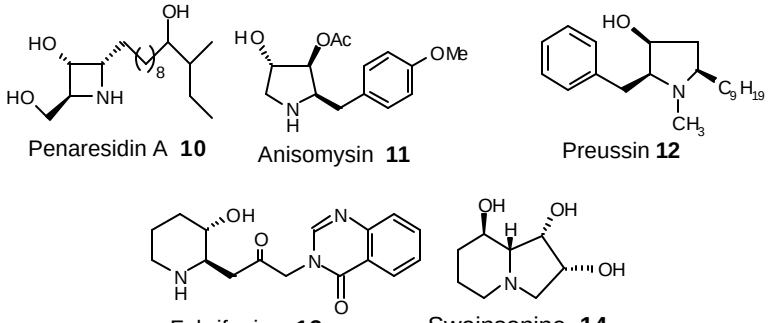


Figure 3

Sugars are yet another class, containing the amino alcohol moiety as components of larger molecules, either aglycones or other sugars. Daunomycin **15**,[15] elsamicin A **16**[16] and neomycin B **17**[17] are important examples (**Figure 4**).

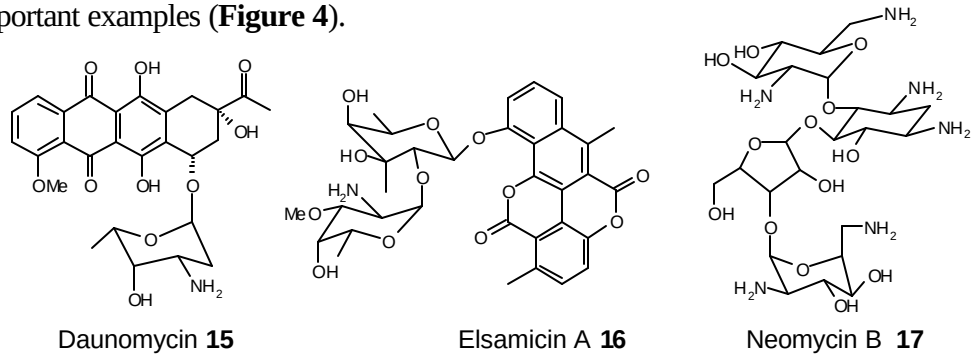


Figure 4

Miscellaneous examples like cytoxazone **18**[18] contain the amino alcohol moiety as oxazolidinone ring and balanol **19**[19] contains acylated amino and alcohol groups (**Figure 5**).

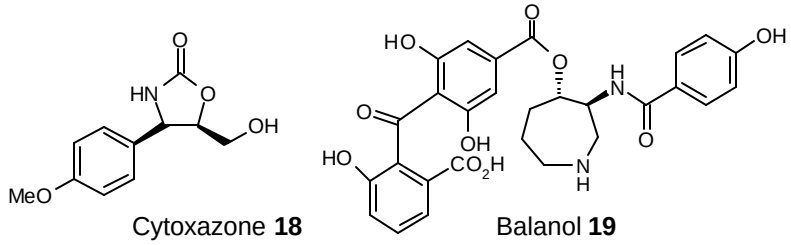
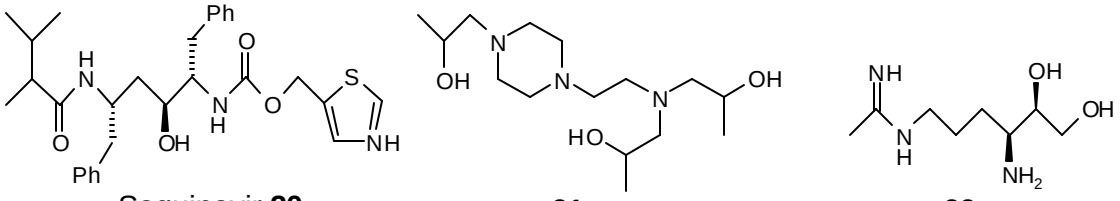


Figure 5

A variety of compounds containing the vicinal amino alcohol moiety have been isolated from natural sources. These compounds have a wide range of biological activities. It is the intriguing biological activity as well as the structural complexity of these molecules that have picked the interest of synthetic chemists and fueled extensive efforts to develop methods for the synthesis of vicinal amino alcohols.

Synthetic pharmacologically active molecules

A host of synthetic molecules used as drugs or pharmacological agents also contain the vicinal amino alcohol moiety. Often these compounds are analogs of natural products containing a vicinal amino alcohol. Saquinavir **20**[20] is an HIV protease inhibitor. Recently, the amino alcohol **21**[21] has been reported to selectively interact with RNA and has also been investigated as an anti-HIV agent. The amidine-containing molecule **22**[22] is reported to be an inhibitor of nitric oxide synthetase (NOS) (**Figure 6**).



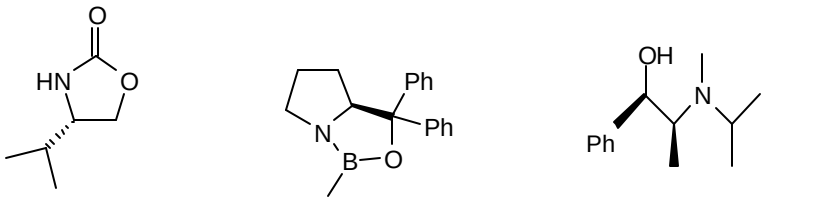
Saquinavir **20** **21** **22**

Figure 6

The presence of the vicinal amino alcohol moiety in these pharmacologically active molecules is essential for their biological activity. The need to prepare these compounds as well as analogs has dramatically increased the importance of the development of methods for the synthesis of vicinal amino alcohols.

Ligands and Chiral auxiliaries

A number of chiral reagents utilize enantiomerically pure amino alcohols as ligands or chiral auxiliaries.[23] The best known are the Evans auxiliaries **23**,[24] the oxaborolidines **24**[25] and the ephedrine derivatives **25**[26] (**Figure 7**). Most of the amino alcohols used as ligands or chiral auxiliaries are derived from natural sources such as amino acids. The amino acids are generally modified to improve their chelating ability or enhance their blocking effects.



Evans auxiliaries **23** Proline based **24** Ephedrine based **25**

Figure 7

From the listing above, it becomes quite obvious why synthetic organic chemists have devoted significant efforts to the development of methods for the synthesis of vicinal amino alcohols. This listing is by no means comprehensive, and many more examples exist in the literature. Nonetheless it does show the breadth and scope of molecular architectures that contain the vicinal amino alcohol moiety.

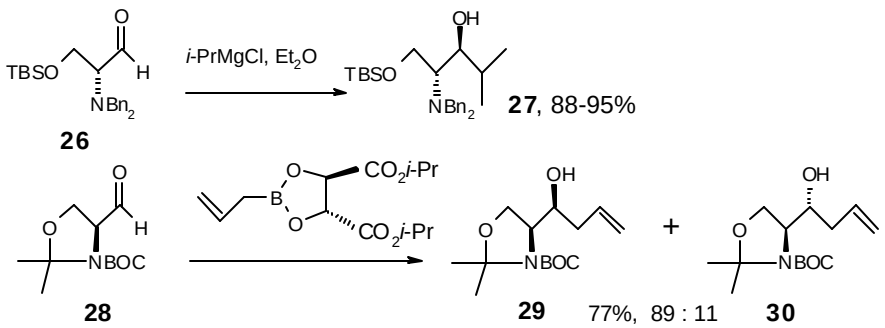
Synthetic routes to vicinal amino alcohols

Just as there are many examples of molecules containing the vicinal amino alcohol moiety, there are an equally large number of synthetic routes to these molecules. It is rather difficult to list every method, but several examples can be typified in the main disconnections used to prepare vicinal amino alcohols. Conceptually one can divide these syntheses into four different classes. (1) Functional group manipulation of a molecule containing both heteroatoms; (2) Addition of one heteroatom to a molecule which already contains the other; (3) Addition of both heteroatoms to a molecule which has neither; (4) Coupling of two molecules, each of which has one heteroatom.

Functional group manipulation

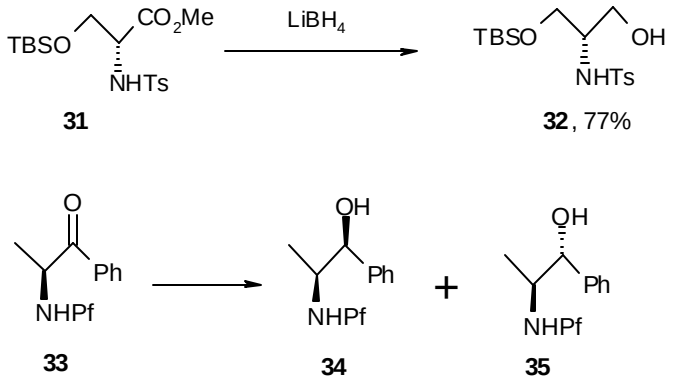
There are two general versions of this disconnection. One involves reduction or nucleophilic addition to an imine or carbonyl group. The second involves opening of an epoxide, aziridine, cyclic thiocarbonate or cyclic sulfite/sulfate.

(i) Addition of a nucleophile to an α-amino carbonyl (**Scheme 1**).[27-31]



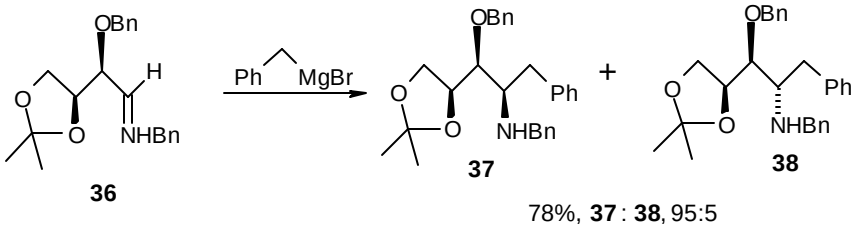
Scheme 1

(ii) Reduction of α-amino carbonyl compounds (**Scheme 2**).[32,33]



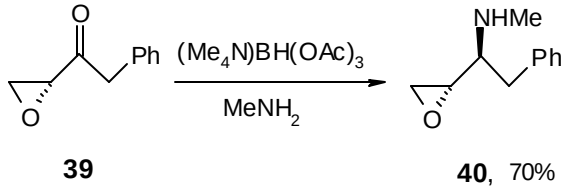
Scheme 2

(iii) Addition of a nucleophile to an α-hydroxy imine (**Scheme 3**).[34]



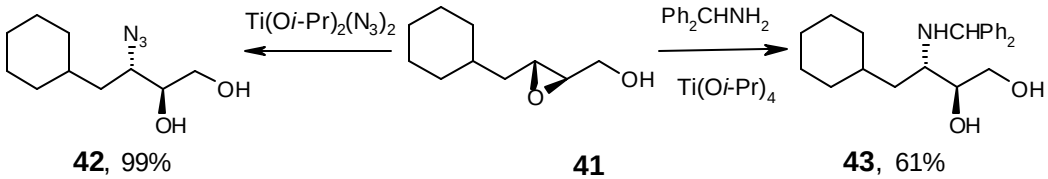
Scheme 3

(iv) Reductive amination (**Scheme 4**).[35]



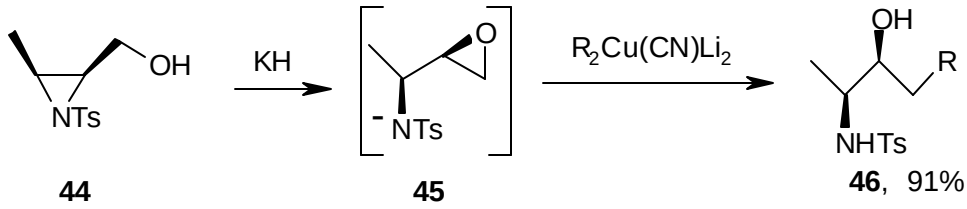
Scheme 4

(v) Ring opening reactions of epoxides (**Scheme 5**).[36,37,38]



Scheme 5

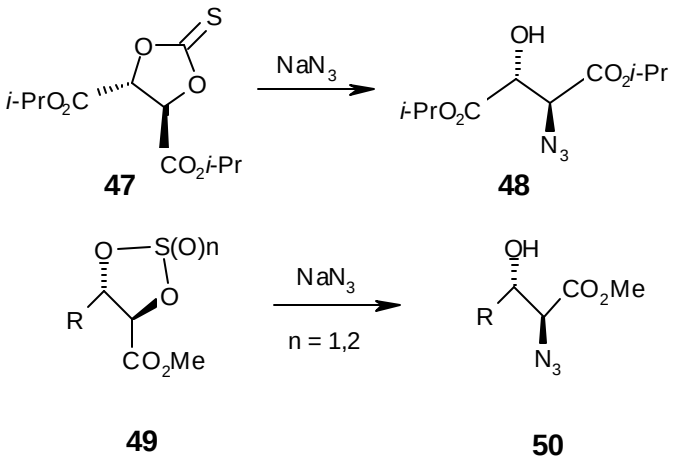
(vi) Ring opening reaction of aziridine (**Scheme 6**).[39,40]



44 **45** **46**, 91%

Scheme 6

(vii) Ring opening reactions of cyclic thiocarbonates[41,42] and cyclic sulfites/sulfates[43] (**Scheme 7**).



47 **48**

49 **50**

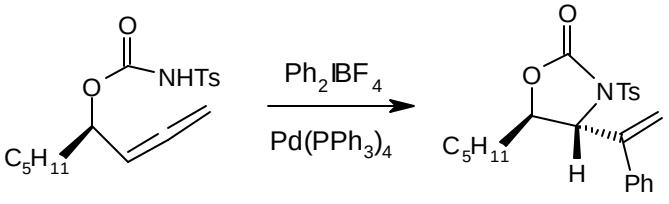
Scheme 7

Thus, a number of routes using functional group manipulations are available to prepare vicinal amino alcohols. Most of these methods rely upon the stereochemical information already contained within the molecule to control the stereochemistry of the new stereocenter. Thus, these methods generally rely upon some other method to ultimately control the stereochemistry of the vicinal amino alcohol.

Addition of one heteroatom

There are a number of methods by which one heteroatom can be added to a molecule already containing the other.

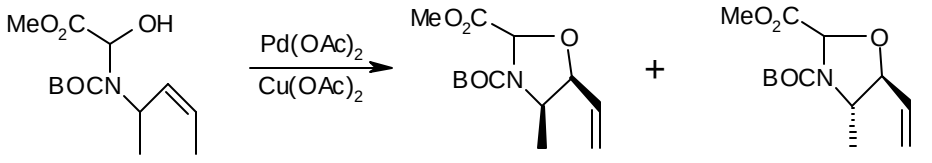
(i) Addition of nitrogen (**Scheme 8**).[44]



51 **52**, 71%

Scheme 8

(ii) Addition of oxygen (**Scheme 9**).[45]



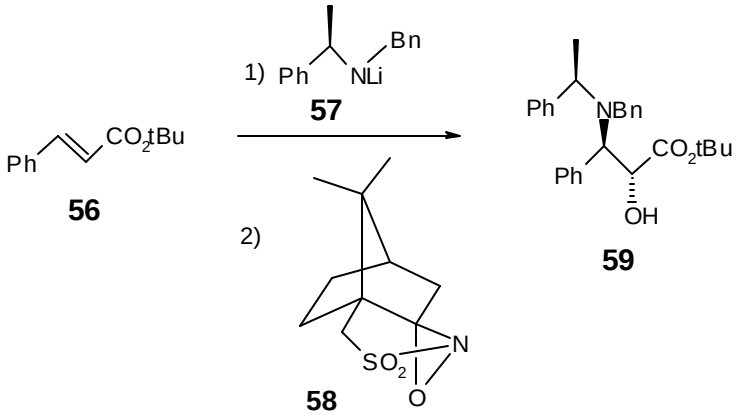
53 **54**, 32% **55**, 46%

Scheme 9

Aminohydroxylation

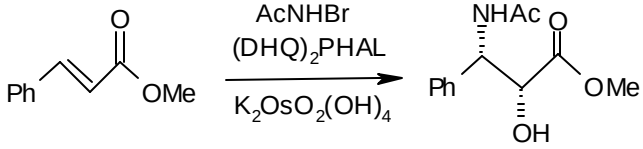
The hydroxyamination or aminohydroxylation reaction of an olefin is possibly the most basic route to vicinal amino alcohols. Two general methods are known and are listed below.

(i) The method of Davies, wherein a chiral amide anion is added to an α,β-unsaturated ester, followed by trapping of the enolate with an oxygen electrophile[46] (**Scheme 10**).



Scheme 10

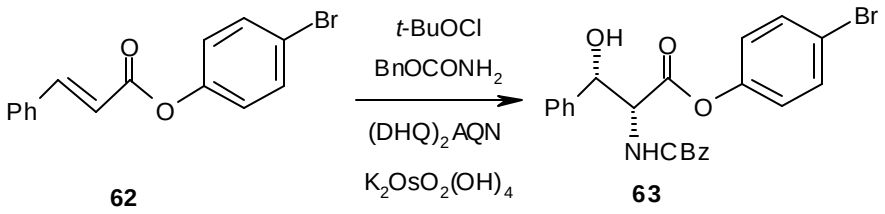
ii) The Sharpless method of metal catalyzed aminohydroxylation in presence of cinchona alkaloid ligands[47] (**Scheme 11**).



60 **61**, 81%

Scheme 11

The methods of Davies and Sharpless are complementary. The former gives *anti*-α-hydroxy-β-amino ester, while the latter gives *syn*-products. In the latter, the regioselectivity can be reversed as below[48] (**Scheme 12**).

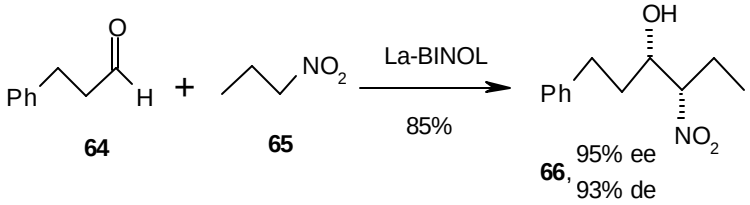


Scheme 12

Coupling Reactions

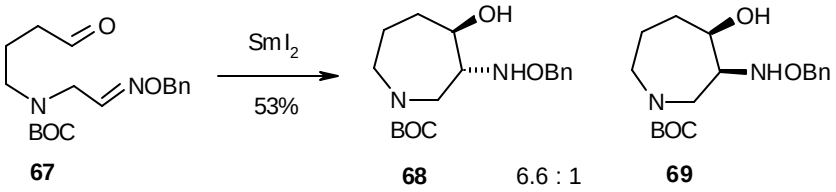
There are two general types of coupling reactions that have been used in the synthesis of vicinal amino alcohols.

(i) Aldol reaction in the presence of a chiral catalyst. The Henry reaction[49] is a typical example (**Scheme 13**).



Scheme 13

(ii) Pinacol-type reaction[50,51] (**Scheme 14**).



Scheme 14

Thus, there are numerous routes to the vicinal amino alcohol moiety. The choice of synthetic route for a given application will vary depending upon substitution, as well as the relative and/or absolute stereochemistry desired. A key theme in many of these methods is the generation of enantiomerically pure compounds. This can be achieved from enantiomerically pure starting material as well as *via* chiral catalysis. There are still many challenges in the area of vicinal amino alcohol synthesis. Limitations exist for most of the methods. For many, it is a question of substrate. Many of the methods work well for a fairly limited set of molecules. For others, it is an

issue of stereochemistry, both absolute and relative. While many of the methods do, or try to, prepare enantiomerically pure amino alcohols, many methods cannot. In summary, the synthesis of vicinal amino alcohols has seen much work in recent years, but much remains to be done.

In our synthetic endeavors, on the application of SAD reaction towards the synthesis of bioactive molecules, we envisaged to convert the chiral diols into the vicinal amino alcohols *via* varied functional group transformations.

This chapter consisting of two sections mainly focuses on the synthesis of

(i) D-*erythro*-dihydrosphingosine: a biosynthetic precursor to sphingolipids, which is a long chain amino alcohol, generally possessing 18 or 20 carbon atoms as the backbone structure. The amino alcohol moiety has been arrived at *via* the functional group transformation involving,

(a) the regioselective opening of cyclic sulfite prepared from the diol obtained by SAD reaction and

(b) the selective formation of 1,3-cyclic benzylidene from 1,2,3-triol and subsequent conversion of C-2 hydroxyl into an amino group.

These two synthetic routes are described in the first section of this chapter.

(ii) The second section of this chapter covers two aspects:

(a) the exploration of the concept of double diastereoselection in asymmetric dihydroxylation reaction. Here the diastereoselective outcome of SAD reaction under varied chiral ligands on a terminal olefin substrate with existing chirality in close proximity to the reacting olefin bond has been studied.

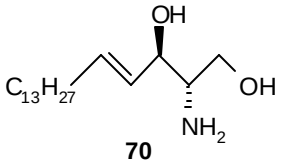
(b) the results of above double diastereoselection have been successfully applied toward the total synthesis of C_{18}-phytosphingosine isomers.

3.2. SECTION A

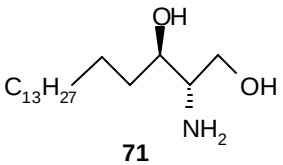
ENANTIOSELECTIVE SYNTHESIS OF D-(+)-*erythro*-DIHYDROSPHINGOSINE

3.2.1. Introduction:

Sphingosines constitute a group of related long-chain aliphatic 2-amino-1,3-diols, of which 2-amino-D-*erythro*-4(*E*)-octadecene-1,3-diol (commonly called sphingosine **70**) occurs most frequently in animal glycosphingolipids.[52] Sphingosines are known inhibitors of protein kinase C and are the backbone structures to glycosphingolipids. This larger family of biomolecules is involved in a plethora of processes related to cell growth, differentiation, adhesion, and neuronal repair.[53]



70



71

Glycosphingolipids contain two basic structural motifs: carbohydrate and ceramide (**Figure 8**). The ceramide portion consists of a sphingoid base and an amide-linked fatty acyl chain, e.g. stearoyl or palmitoyl. The structural variation in fatty acids (N-acyl portion, sphingosines and carbohydrates results in a great variety of chemically distinct glycosphingolipids.[52]

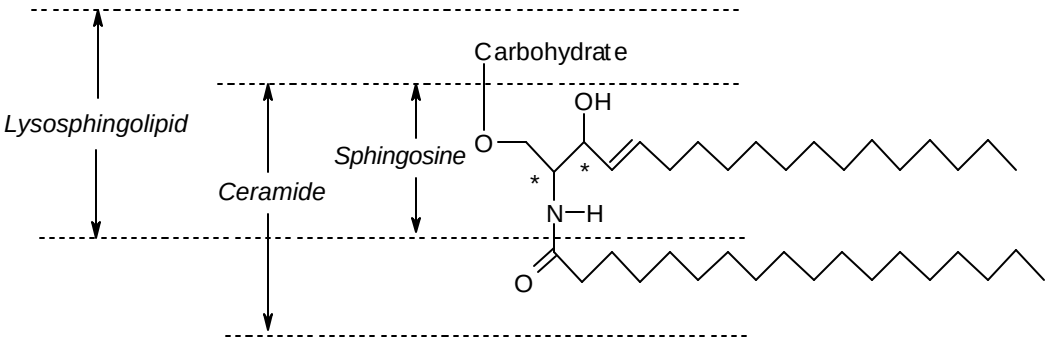


Figure 8. Glycosphingolipid structure

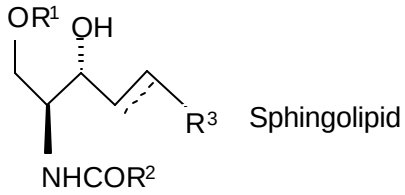
Glycosphingolipids are found in the cell membrane of all animal and many plant cells, where they serve as identifying markers and regulate cellular recognition, growth and development.[54a] They are thought to function by anchoring the hydrophobic ceramide portion (**Figure 8**) in the plasma membrane exposing the hydrophilic carbohydrate portion to the surrounding exterior which specifies the intended biological function.[54b] They are involved in several biological functions such as (i) HIV binding to galactosyl ceramide receptor sites in cells lacking the principal CD4 cellular receptor,[55] (ii) being unambiguous links between specific sphingolipids and malignant tumors which enables them to be used as 'biological markers' for possible early detection of cancer,[54a] and (iii) potent and reversible inhibition of protein kinase C by breakdown products of glycosphingolipids, e.g. sphingosine **70**, sphinganine **71** (dihydrosphingosine) and lysophingolipids (**Figure 8**).

Dihydrosphingosine **71** is a biosynthetic precursor to sphingosine **70** which is the most abundant long chain amino alcohol possessing generally 18 or 20 carbon atoms. Dihydrosphingosine is an intermediate in the biosynthesis of sphingolipids such as ceramides, sphingomyelin, cerebrosides and gangliosides, which play important roles in cell regulation and signal transduction.[56] Dihydrosphingosine is itself found to be an inhibitor of protein kinase C.[57]

The on-going recognition of glycosphingolipids as fundamental mediators of cellular interactions continues to sustain research in this field.

3.2.2. Review of Literature

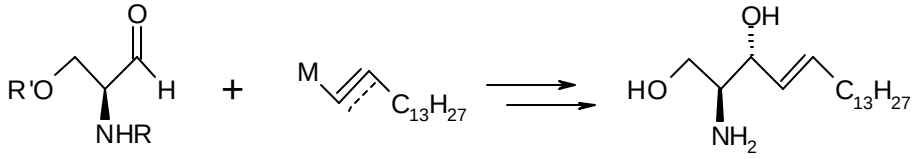
Although known for more than 100 years, the finding that defects in sphingolipid metabolism lead to several inherited human diseases and the findings that sphingolipids are involved in "essentially all aspects of cell regulation"[58] have led to an explosion of interest in sphingolipids.[56,58,59] Two problems make the utilization of sphingolipids from natural sources problematic. First, there are a large number of known sphingolipids which vary in the head group (R^1), N–acyl groups (R^2) and/or tail group (R^3) thus making the isolation of homogeneous material from natural sources difficult.[60] Second, the allylic alcohol function undergoes epimerization readily during isolation or manipulation to produce partially epimerized mixtures.[60] For these reasons, synthetic access to individual sphingosines is an attractive alternative.



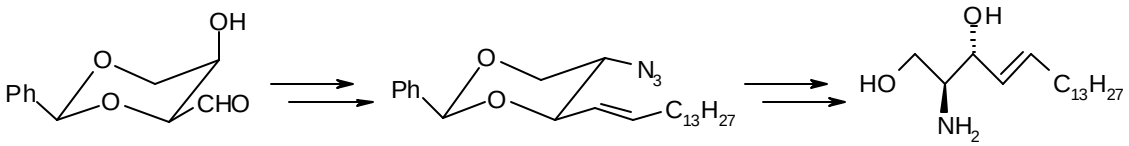
Sphingolipid

Quite a number of syntheses of sphingosine, dihydrosphingosine and their derivatives have been reported. In general, these can be grouped into three main catergories[61] as under:

(1) The first uses stereoselective addition of an organometallic reagent (often a lithium acetylide) to a protected serinal.[62] This approach forms the 3, 4 carbon-carbon bond and sets the stereochemistry of the C-3 hydroxyl group in one step.



(2) The second major strategy uses carbohydrate precursors as the source of stereochemistry at C-2 and C-3. The tail is often attached by an anionic addition of some type. [61,63]

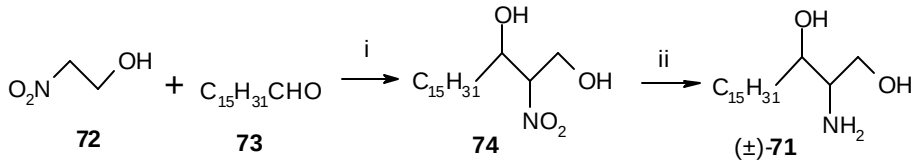


(3) The third major category uses a variety of chiral precursors to build up the structures by nucleophilic addition processes. [64]

All these approaches set the stereochemistry of the head groups early and attach the tail as a nucleophile. Most synthetic approaches describe the synthesis of sphingosine and its derivatives. However, saturation of the olefin bond in sphingosine gives sphinganine. Hence all syntheses leading to sphingosine could be elaborated to sphinganine syntheses. Some synthetic routes are developed to produce the dihydrosphingosine directly. A few interesting syntheses of sphinganine (dihydrosphingosine) are discussed below:

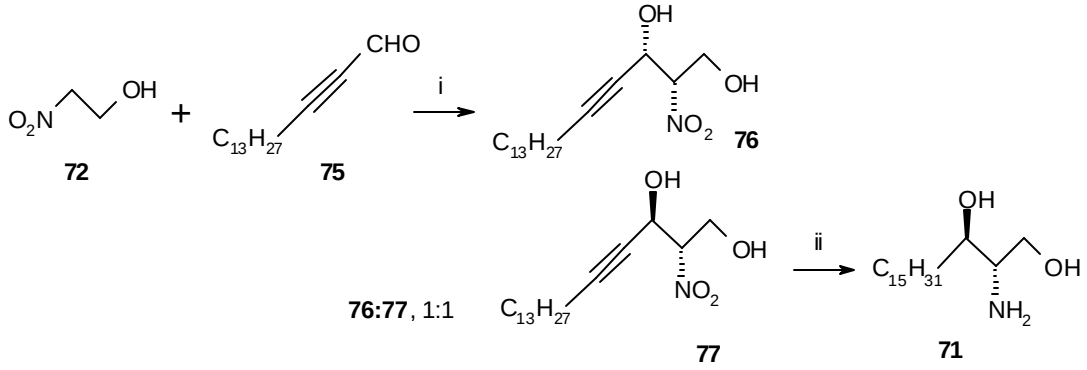
Grob *et al.* (1951)[65] Scheme 15

An early synthesis of racemic dihydrosphingosine (±)-**71** was reported by Grob and co-workers employing nitroaldol reaction. Condensation of nitroethanol **72** with palmitaldehyde **73** gave the aldol product **74**. Reduction of the nitro group in **74** afforded racemic dihydrosphingosine (±)-**71**.



Scheme 15. Reaction conditions: (i) OH^-. (ii) H_2/Ni.

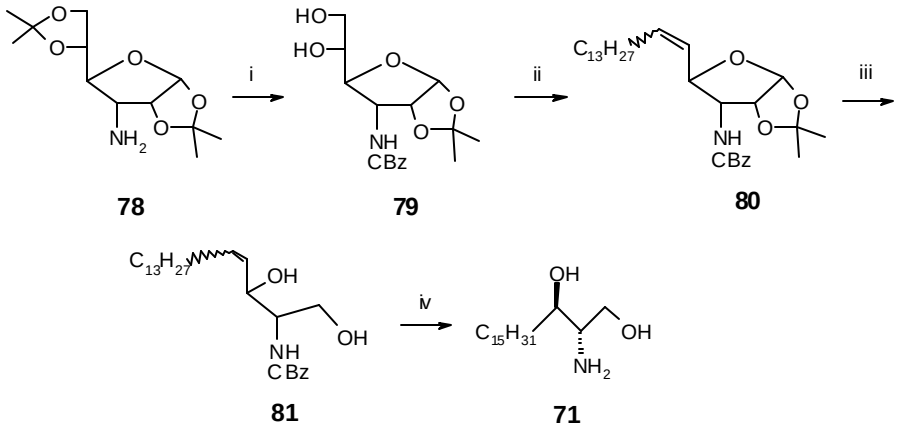
In another approach, Grob and Gadient[66] (**Scheme 16**) carried out nitroaldol reaction on hexadecynal **75** to give 1:1 mixture of *threo*- and *erythro*- products **76** and **77** respectively. Diastereomer **77** was separated by fractional crystallization. Sequential nitro group reduction followed by complete reduction of the triple bond furnished D-*erythro*-dihydrosphingosine **71**.



Scheme 16. Reaction conditions: (i) K_2CO_3, MeOH. (ii) (a) Zn, HCl, (b) H_2/Pd.

Reist *et al.* (1970)[67] Scheme 17

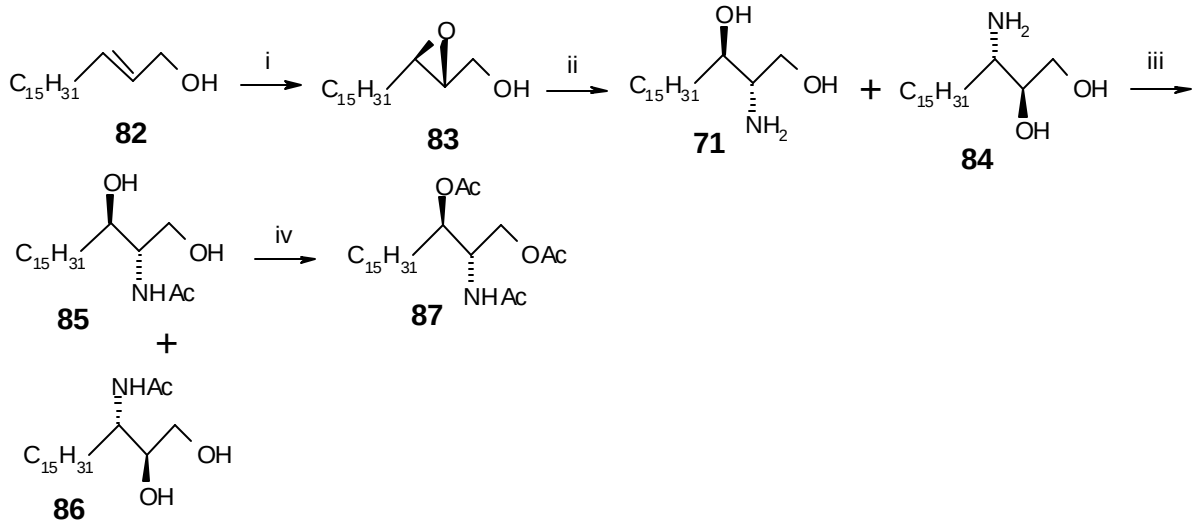
In Reist's approach, the readily available 3-amino-3-deoxy-1, 2:5,6-di-*O*-isopropylidene-α-D-allofuranose **78**[68] was protected at the amino group with benzylchloroformate and selective removal of the 5,6-isopropylidene group gave the diol **79**. Periodate cleavage of the diol and subsequent Wittig reaction on the aldehyde produced a mixture of *cis*- and *trans*-olefin **80**. Acetonide deprotection and periodate cleavage of the diol gave the aldehyde, which was subsequently reduced to afford **81**. Hydrogenation of **81** gave D-*erythro*-dihydrosphingosine **71**.



Scheme 17. Reaction conditions: (i) (a) CBzCl, pyridine, 0°C, 18 h, 64%, (b) 75% aq. AcOH, 60°C, 20 min, ~100%. (ii) (a) $NaIO_4$, MeOH:H_2O (1:1), 1 h, ~100%, (b) $C_{14}H_{29}P^{+}Ph_3Br^{-}$, PhLi, PhH, 21 h, 30%. (iii) (a) 80% aq. AcOH, reflux, 3 h, (b) $NaIO_4$, MeOH, 16 h, ~100%, (c) $NaBH_4$, MeOH, 16 h. (iv) 10% Pd/C, H_2, AcOH, 20 h.

Mori *et al.* (1981)[69] Scheme 18

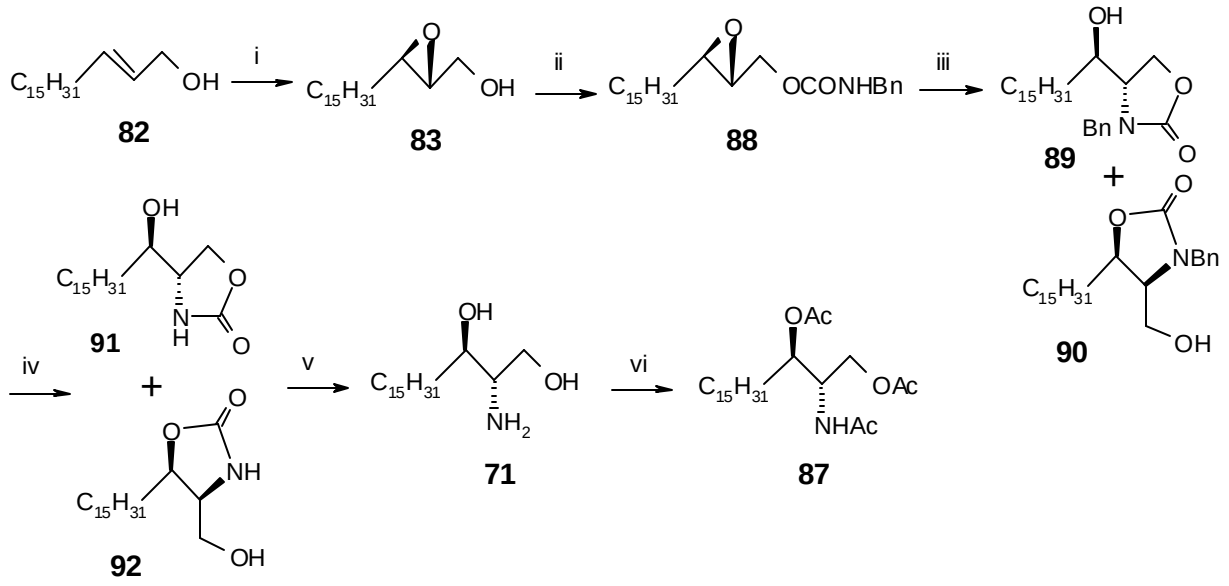
Mori and Umemura employed the asymmetric epoxidation approach towards the synthesis of D-*erythro*-dihydrosphingosine. Sharpless asymmetric epoxidation (SAE) of allylic alcohol **82** gave the epoxide **83**, which on opening with NH_3/MeOH afforded a mixture of regioisomers **71** and **84**. Acetylation of the mixture gave the corresponding N-acetates **85** and **86**. The unwanted isomer **86** was removed by HIO_4 treatment. Acetylation of **85** yielded the triacetate **87**.



Scheme 18. Reaction conditions: (i) (–)-DET, *t*-BuOOH, Ti(O*i*-Pr)$_4$, CH_2Cl_2, −20°C, 38 h, 75%. (ii) NH_3, MeOH, 100°C, 7 d, 99%. (iii) Ac_2O, MeOH, 98%. (iv) Ac_2O, pyridine, 73%.

Roush *et al*. (1985)[70] Scheme 19

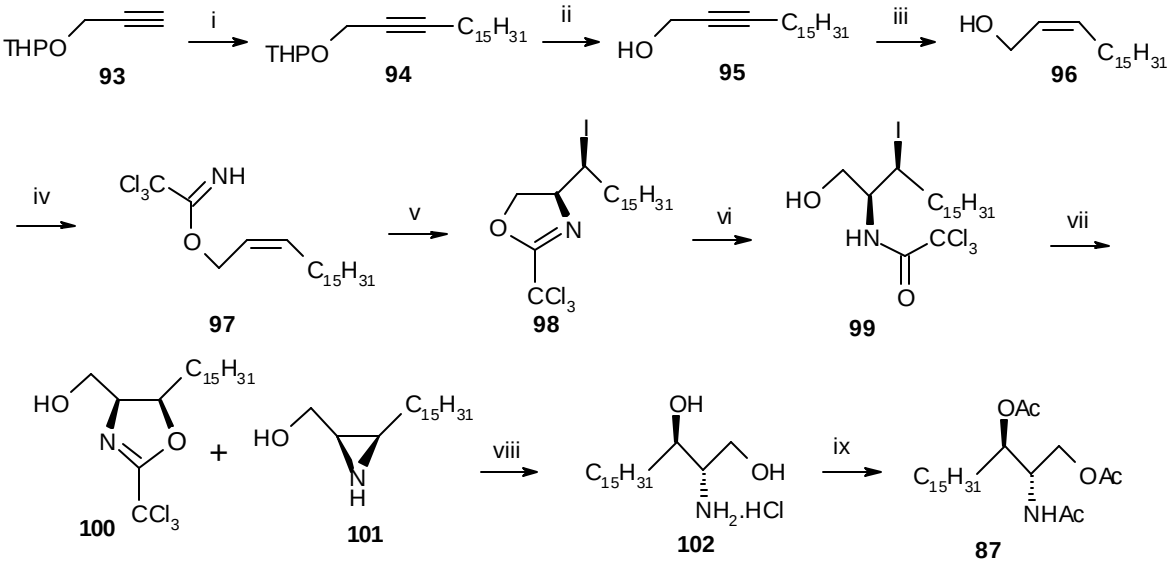
Roush and Adam employed the epoxyurethane intermediate in the synthesis of **71**. The allylic alcohol **82** on SAE gave epoxide **83**, which was converted into epoxyurethane **88**. Opening of the epoxyurethane **88** under basic conditions led to internal delivery of nitrogen to give a mixture of urethanes **89** and **90** which on debenzylation furnished **91** and **92**. The subsequent hydrolysis followed by acetylation furnished the desired compound **87**.



Scheme 19. Reaction conditions: (i) (−)-DET, *t*-BuOOH, CH_2Cl_2, −20°C, 24 h, 88%. (ii) $PhCH_2NCO$, Et_3N, overnight, 97%. (iii) NaH, THF, 23°C, 88%. (iv) Na, NH_3, THF, 1 h. (v) LiOH, EtOH-H_2O, reflux, overnight. (vi) Ac_2O, pyridine, 94% from **89**, **90**.

Cardillo *et al*. (1986)[71] **Scheme 20**

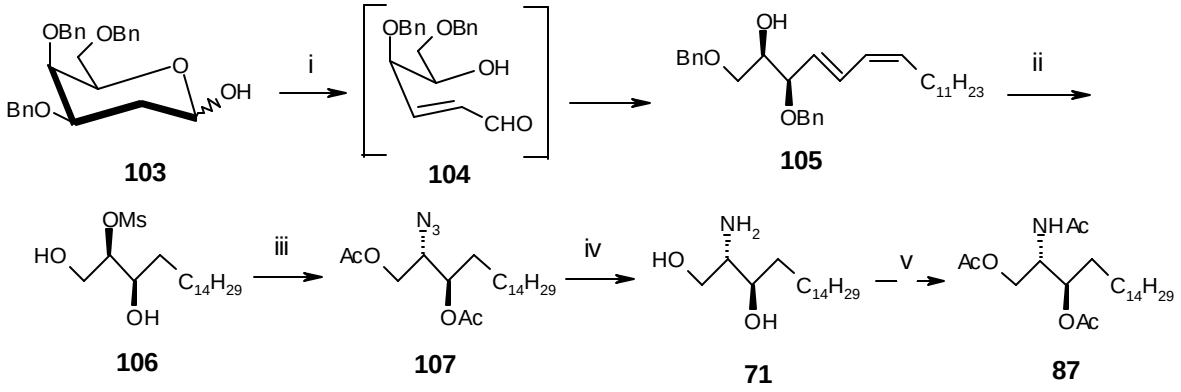
In Cardillo's approach, (*Z*)-1-trichloroacetimidoyloxyoctadec-2-ene **97** easily obtained from **96** was iodocyclized with NIS to give the 4,5-dihydro-oxazole **98**. The neutral cleavage of **98** gave the corresponding amide, which on treatment with Amberlyst A 26 afforded **100** together with a minor amount of aziridine **101**. After hydrolysis of the oxazole and acetylation, D-*erythro*-dihydrosphingosine **71** was obtained as triacetate **87**.



Scheme 20. Reaction conditions: (i) (a) LDA, THF, 3 h, rt, (b) $C_{15}H_{31}I$, THF, 12 h, 55°C, 75%. (ii) Amberlyst H 15, MeOH, 3 h, rt, 100%. (iii) H_2/Pd/$CaCO_3$, EtOAc, 6 h, rt, 80%. (iv) (a) NaH, THF, 1 h, 0°C, (b) CCl_3CN, THF, 1 h, 0°C. (v) NIS, $CHCl_3$, 12 h, rt. (vi) Acetone-water, 18 h, reflux. (vii) Amberlyst A 26 (CO_3^- form), C_6H_6, 1 h, reflux. (viii) 2M HCl, 2 h, rt. (ix) Ac_2O, pyridine, 18 h.

Schmidt *et al*. (1995)[72] Scheme 21

Schmidt *et al*. employed 2-deoxy-D-galactose **103** as the starting material which can be easily prepared from D-galactose.[73] Wittig reaction with dodecyltriphenylphosphoniumbromide and *t*-BuOK gave the (4*E*,6*Z*)-diene **105**, presumably first by base mediated β-elimination to **104** followed by (*Z*)-selective Wittig reaction. Mesylation of the C-2 hydroxyl and hydrogenation afforded **106**. Acetylation of the free hydroxyl and azide displacement of mesylate gave **107**. Removal of acetyl protection and reduction of azide followed by acetylation afforded **87**.

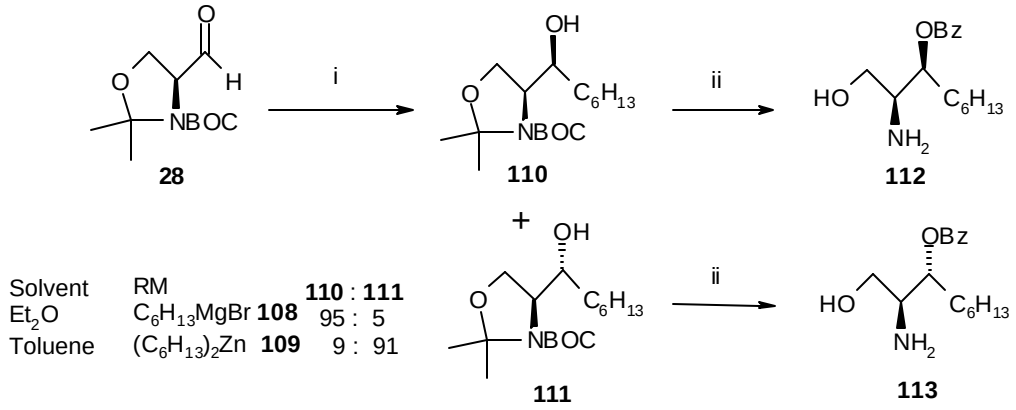


Scheme 21. Reaction conditions: (i) $C_{12}H_{25}P^+Ph_3Br^-$, *t*-BuOK, $PhCH_3$, 89%. (ii) (a) MsCl, pyridine, 70°C, 2 h, 81%, (b) Pd/C, H_2, MeOH/EtOAc, 24 h, 91%. (iii) (a) Ac_2O, pyridine, 4 h, 100%, (b) NaN_3, DMF, 100°C, 3 d, 84%. (iv) (a) MeOH, NaOMe, 2 h, (b) Amberlite IR 120, (c) Pyridine/water, H_2S, rt, 4 h, 70%. (v) Ac_2O, pyridine, rt, 12 h, 90%.

Buono *et al*. (1998)[74] Scheme 22

Buono synthesized analogs of dihydrosphingosine with a shortened alkyl chain *via* diastereoselective addition of hexyl magnesium bromide **108** or dihexylzinc **109** to a chiral aldehyde **28** (Garner aldehyde). Thus, reaction of **108** with **28** gave a diastereomeric mixture of **110** and **111** in 95:5 ratio, while addition of **109** to **28** afforded **110** and **111** in 9:91 ratio.

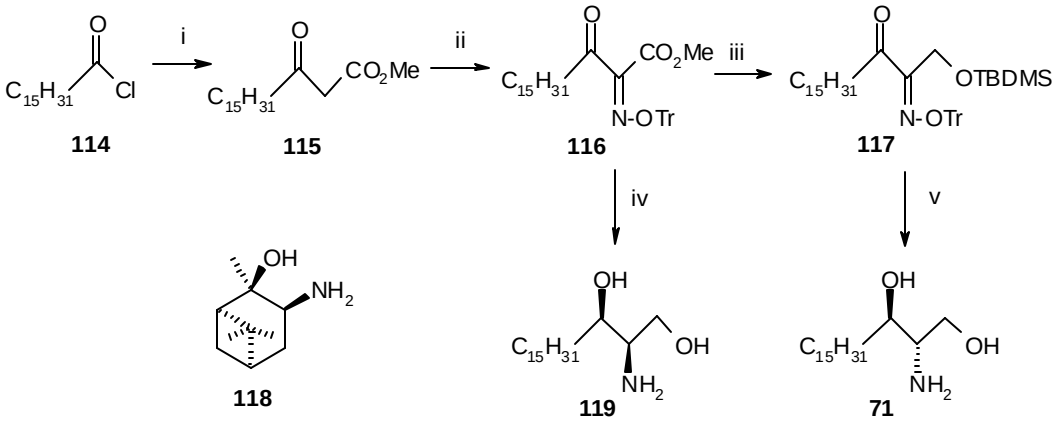
Treatment of pure alcohols **110** and **111** with benzoyl chloride followed by acidic hydrolysis led to amino alcohols **112** and **113** respectively.



Scheme 22. Reaction conditions: (i) RM, 25°C, solvent, 67-90%. (ii) (a) PhCOCl, DMAP, pyridine, $PhCH_3$, (b) 5N HCl, dioxane, reflux, 45 min, 71%.

Masui *et al*. (1998)[75] Scheme 23

Masui *et al*. employed asymmetric borane reduction of α-ketoxime trityl ether towards the synthesis of both *threo*- and *erythro*-dihydrosphingosine. Butylnitrite reaction with β-ketoester **115** and *O*-tritylation afforded α-ketoxime trityl ether **116**. Sequential reduction of **116**, protection of primary hydroxyl and Swern oxidation gave **117**. Asymmetric borane reduction of **116** with 0.2 eq. of **118** gave predominantly *threo*-isomer **119** (95%ee). On the other hand, reduction of **117** with 0.2 eq. of **118** afforded *erythro*-dihydrosphingosine **71** in 97%ee.

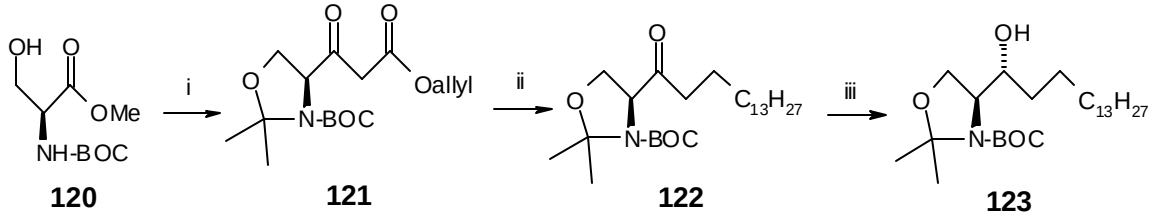


Scheme 23. Reaction conditions: (i) $KO_2CCH_2CO_2Me$, $MgCl_2$, Et_3N, CH_3CN, rt, 18 h, 52%. (ii) (a) BuONO, conc. H_2SO_4, Et_2O, rt, 1.5 h, 85%, (b) TrCl, Et_3N, CH_2Cl_2, rt, 2 h, 99%. (iii) (a) $NaBH_4$, EtOH, rt, 1 h, 99%, (b) *t*-$BuMe_2Si$-Cl, imidazole, DMF, rt, 24 h, 85%, (c) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C, 15 min, then Et_3N, rt, 1 h, 99%. (iv) Borane-N,N-diethylaniline

complex, 0.2 eq. **118**, reflux, 65 h, 90%. (v) (a) Borane-N,N-diethylaniline complex, 0.2 eq. **118**, 3 h, rt, 18 h, reflux, 94%, (b) 2N HCl.

Hoffman *et al.* (1998)[76] Scheme 24

Hoffman *et al*. employed L-serine-based synthesis of D-*erythro*-dihydrosphingosine *via* a 3-ketosphinganine intermediate. L-(N-BOC)-serine methyl ester **120** was protected as oxazolidine, followed by conversion to β-ketoester **121** with CDI and lithioallylacetate. β-Ketoester **121** was alkylated with tetradecyltriflate followed by deallylation and decarboxylation to give the 3-ketosphinganine **122**. Reduction of **122** furnished D-*erythro*-dihydrosphingosine derivative **123**.

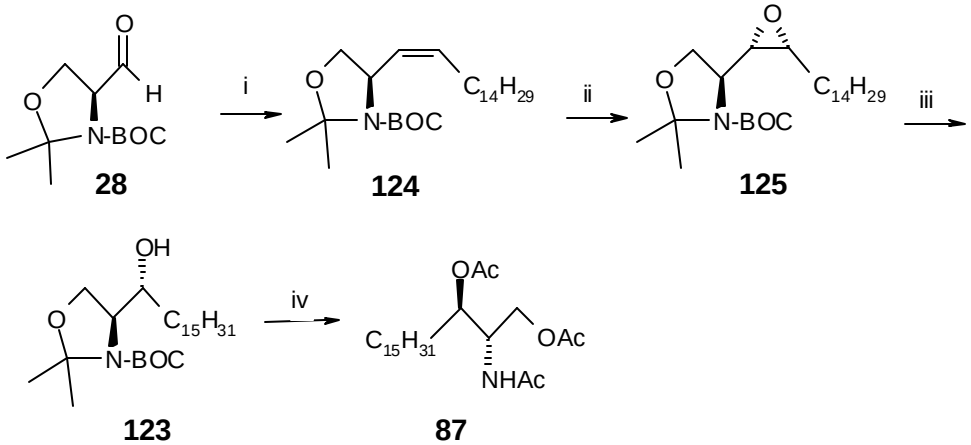


120 **121** **122** **123**

Scheme 24. Reaction conditions: (i) (a) 2,2-DMP, *p*-TsOH, (b) LiOH, (c) CDI, then $LiCH_2CO_2$allyl. (ii) (a) NaH, (b) $TfOCH_2C_{13}H_{27}$, (c) $Pd(PPh_3)_3$, morpholine. (iii) $NaBH_4$, CH_3OH, 90%, 91% de.

Ogino *et al*. (2000)[77] Scheme 25

Ogino *et al*. have used the Garner aldehyde **28** in Wittig reaction to give *cis*-olefin **124**. Epoxidation of **124** with *m*-CPBA in THF gave **125** along with its diastereomer (92:8). Regioselective epoxide opening afforded **123**. Removal of BOC and acetonide protections followed by acetylation eventually led to the desired compound **87**.

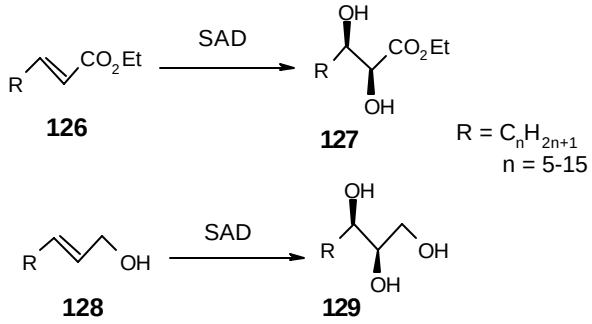


123 **87**

Scheme 25. Reaction conditions: (i) $C_{15}H_{31}P^+Ph_3Br^-$, LiHMDS, −78°C, 66%. (ii) *m*-CPBA, rt, 84%. (iii) $LiAlH_4$, 0°C, 86%. (iv) (a) CF_3CO_2H, rt, (b) Ac_2O, DMAP, rt, 83%.

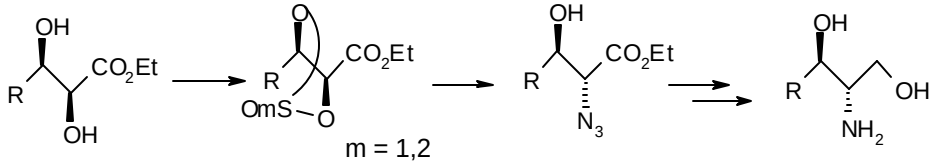
3.2.3. Present Work

The SAD reaction of *trans*-α,β-unsaturated esters[78a] (**126**) and long chain terminal *trans*-allylic alcohols[78b] (**128**) is reported to give the corresponding dihydroxy esters (**127**) and 1,2,3-trihydroxy compounds (**129**) respectively in high enantiomeric purity.



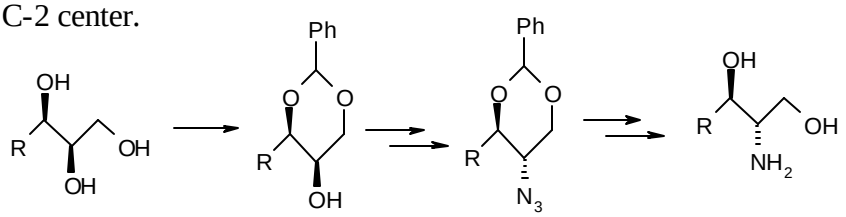
126 127 128 129

Thus, SAD reaction establishes the C-3 hydroxyl group of dihydrosphingosine, while the G-2 hydroxyl could be manipulated into amine functionality by standard synthetic transformation. We adopted two strategies towards the introduction of amino group. In the case of α,β-dihydroxy esters (**127**), cyclic sulfites/sulfates (**130**) proved to be promising intermediates for high reactivity in nucleophilic opening reactions and also provide high regioselectivity at the α-carbon with inversion at the C-2 center.[43]



127 130 131 132

In case of terminal triol (**129**) selective formation of cyclic benzylidene (**133**) gives 1,3-hydroxyl protection, leaving the C-2 hydroxyl free, which can be converted, into amino group with inversion at C-2 center.

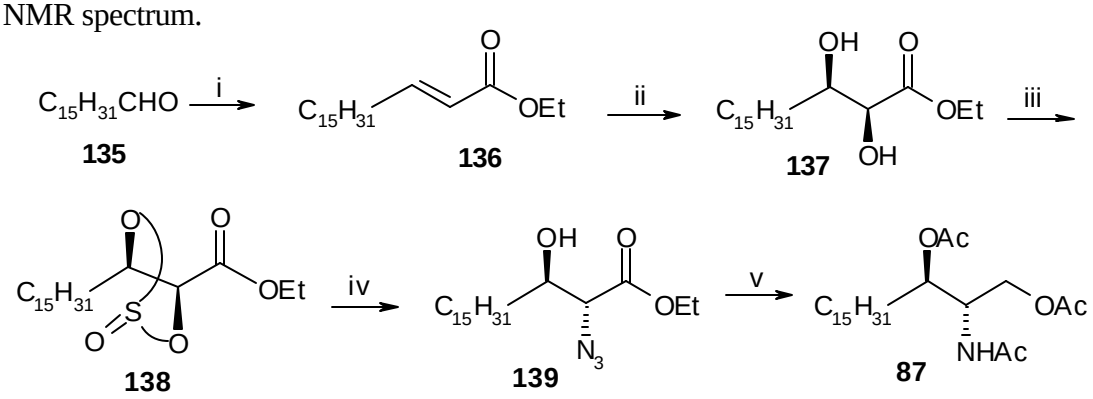


129 133 134 132

Thus, the objective of the present investigation is to employ the SAD reaction to fix the C-3 chirality and the chemistry of cyclic sulfites/sulfates or the selective 1,3-cyclic benzylidene formation to achieve the C-2 chirality of D-*erythro*-dihydrosphingosine. Thus, this synthetic strategy proves to be a short and practical approach to D-*erythro*-dihydrosphingosine in high enantiomeric purity.

3.2.4. Results and Discussion

The synthesis of D-*erythro*-dihydrosphingosine commences from hexadecanal **135** as shown in **Scheme 26**. Reaction of **135** with (ethoxycarbonylmethylene)triphenylphosphorane in THF under reflux gave the Wittig product **136** in 87% yield. The IR spectrum of **136** showed the ester carbonyl absorption at 1724 cm^{-1} and olefin C=C stretching at 1655 cm^{-1}. The ^1H NMR spectrum gave olefin protons at δ 5.8 (doublet of triplet) and 6.97 (doublet of triplet) with the coupling constant J = 15.63 Hz indicating *trans*-olefin. The SAD reaction of **136** using $(DHQD)_2$-PHAL as chiral ligand gave the diol **137** in excellent yield, having $[\alpha]_D^{20}$ + 8.6 (c = 2, $CHCl_3$).[79] The IR spectrum of **137** gave hydroxyl absorption at 3400-3300 cm^{-1} and ester carbonyl at 1732 cm^{-1}. The ^1H NMR spectrum indicated absence of olefin protons. The chiral protons appeared at δ 3.88 (multiplet) and 4.08 (doublet of doublet). The chiral carbons appeared at δ 72.5 and 73.2 in the ^{13}C NMR spectrum.

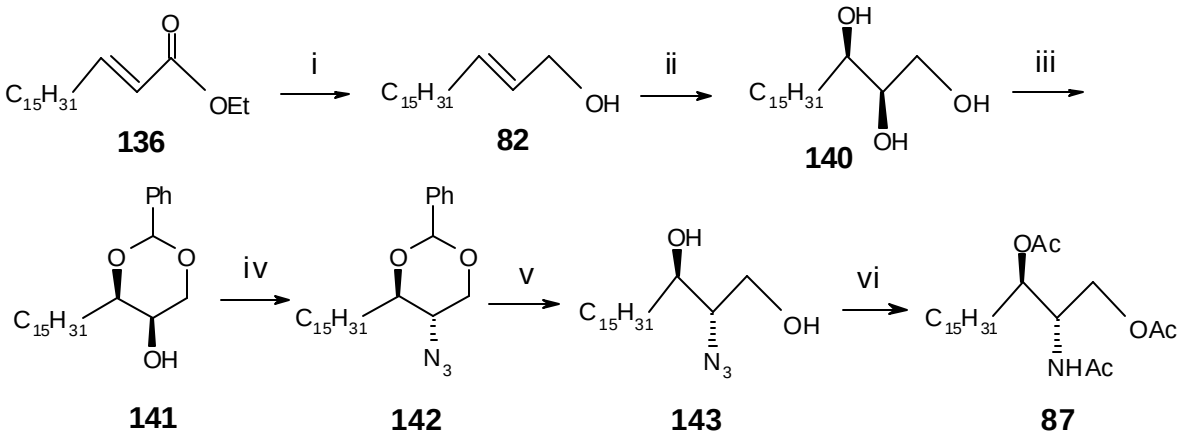


Scheme 26. Reaction conditions: (i) $Ph_3P{=}CHCO_2Et$, THF, reflux, 18 h, 87%. (ii) $(DHQD)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, OsO_4 (cat), $MeSO_2NH_2$, *t*-BuOH:H_2O (1:1), 0°C, 24 h, 94%. (iii) $SOCl_2$, CCl_4, reflux, 1.5 h, 96%. (iv) (a) LiN_3, DMF, 100°C, 18 h, (b) 20% H_2SO_4:Et_2O (1:1), rt, 12 h, 68%. (v) (a) $LiAlH_4$, Et_2O, 0°C to rt, overnight, (b) Ac_2O, pyridine, rt, 18 h, 76%.

The diol **137** was then treated with thionyl chloride to afford the cyclic sulfite **138** in 96% yield. The IR spectrum of **138** showed absence of hydroxyl absorption. The ^1H NMR spectrum showed diastereomeric peaks (for cyclic sulfite being diastereomeric at S atom) at δ 4.50 (doublet) 0.5 proton, 4.6-4.68 (multiplet) 0.5 proton, 5.05 (doublet) 0.5 proton and 5.09-5.17 (multiplet) 0.5 proton. The essential feature of our synthetic strategy shown in **Scheme 26** was based on the presumption that the nucleophilic opening of the cyclic sulfite **138** would occur in a

regioselective manner at the α-carbon. Indeed the cyclic sulfite **138** on treatment with lithium azide furnished the azido alcohol **139** in 68% yield. The IR spectrum of **139** showed hydroxyl absorption at 3476 cm^{-1} and strong azide absorption at 2109 cm^{-1}. Reduction of azido and ester functionality in **139** with lithium aluminium hydride and subsequent acetylation of the crude amino alcohol with acetic anhydride in pyridine gave the triacetate **87** of D-*erythro*-dihydrosphingosine **71** in 76% yield, having $[\alpha]_D^{20}$ + 17.2 (c = 0.2, $CHCl_3$) [lit. $[\alpha]_D^{23}$ + 16.8 (c = 1, $CHCl_3$),[72] $[\alpha]_D^{25}$ + 17.4 (c = 1, $CHCl_3$)[77]]. The triacetate **87** was fully characterized by IR, ^1H NMR and EIMS spectral data. The IR spectrum of **87** showed NH of amide at 3291 cm^{-1} and the carbonyls of acetates and amide at 1730 and 1646 cm^{-1} respectively. ^1H NMR spectrum gave acetyl methyl as three singlets at δ 1.97, 2.00 and 2.02. The chiral protons appeared at δ 4.33-4.37 (multiplet, one proton) and 4.98-5.01 (multiplet, one proton). The amide proton gave a doublet at δ 5.77-5.8 with coupling constant *J* = 8 Hz. The EIMS of **87** gave a molecular ion $[M^+]$ peak at *m/z* 427 and other characteristic peaks at *m/z* 308, 188 and 84. The physical constants for **87** obtained were in full agreement with the literature values.[72,77]

An alternative sequence of reactions to arrive at the target molecule **87** is depicted in **Scheme 27**. In this case the C-2 chirality is arrived at through selective 1,3-cyclic benzylidene formation. The α,β-unsaturated ester **136** was subjected to DIBAL-H reduction to furnish the corresponding allylic alcohol **82** in 92% yield. The IR spectrum of **82** showed hydroxyl absorption at 3330 cm^{-1} and absence of ester carbonyl. The dihydroxylation of olefin **82** with osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of 1,4-bis(9-*O*-dihydroquinidine)phthalazine [$(DHQD)_2$-PHAL] ligand under the Sharpless asymmetric dihydroxylation reaction condition gave the (2*R*,3*R*)-triol **140** in excellent yield, having $[\alpha]_D^{20}$ + 7.2 (c = 1.0, $CHCl_3$). The SAD of allylic alcohols with different long alkyl chains is reported to give the two stereogenic centers in 95-97% enantiomeric excess.[78b] Thus by analogy, the triol **140** prepared was assumed to be enantiomerically pure. The IR spectrum showed hydroxyl absorption at 3400-3200 cm^{-1} and absence of olefin C=C stretching. In the ^1H NMR spectrum the chiral protons appeared at δ 3.47-3.51 (multiplet) and 3.56-3.82 (multiplet). The EIMS gave the molecular ion $[M^+]$ peak at *m/z* 302. Further, in order to achieve the synthesis of azido sphinganine **143** from the triol **140**, we required the transformation of C-2 hydroxyl group to azido with concomitant reversal of stereochemistry. Towards this aim, the benzylidene protection of **140** was effected with benzaldehyde dimethylacetal in the presence of a catalytic amount of *p*-TsOH to afford a mixture of 1,3- and 1,2-benzylidene compounds in 9:1 ratio. The



Scheme 27. Reaction conditions: (i) DIBAL-H, Et_2O, 0°C, 92%. (ii) $(DHQD)_2$-PHAL, OsO_4, $MeSO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH:H_2O (1:1), 24 h, 0°C, 91%. (iii) $PhCH(OMe)_2$, *p*-TsOH, CH_2Cl_2, rt, overnight, 69%. (iv) (a) $MeSO_2Cl$, Et_3N, DMAP, CH_2Cl_2, rt, overnight, (b) NaN_3, DMF, 80°C, 24 h, 83%. (v) 3N HCl, MeOH, rt, overnight, 72%. (vi) (a) $LiAlH_4$, Et_2O, 0°C, rt, overnight, (ii) Ac_2O, pyridine, rt, 18 h, 71%.

desired major 1,3-benzylidene compound **141** was separated by silica gel column chromatography and obtained in 69% yield. Compound **141** showed acetal proton at δ 5.58 (singlet) in the ^1H NMR spectrum. Compound **141** was then converted into 5-*O*-mesylate with methanesulfonyl chloride using Et_3N and catalytic DMAP. The crude mesylate was treated with sodium azide in DMF to give the azido compound **142** with desired stereochemistry at 5-position. Compound **142** showed absence of hydroxyl absorption in the IR spectrum and strong azide absorption at 2097 cm^{-1}. The benzylidene protecting group was cleaved by treating **142** with 3N HCl to furnish the azido sphinganine **143** in 72% yield, which was identical in all respects with the reported compound.[72] The IR spectrum of **143** gave hydroxyl absorption at 3450-3400 cm^{-1} and azide absorption at 2100 cm^{-1}. The EIMS gave the molecular ion $[M^+]$ peak at *m/z* 327. Transformation of azido alcohol **143** into the target molecule **87** was readily performed by reduction with lithium aluminium hydride followed by subsequent acetylation with acetic anhydride in pyridine to give **87** in 71% yield, having m.p. 95–97°C (lit. 95–97°C)[72] and $[\alpha]_D^{20}$ + 17.0 (c = 0.2, $CHCl_3$) [lit. + 16.8 (c = 1, $CHCl_3$)[72]]. Spectroscopic data were in full agreement with **87** prepared according to **Scheme 26**.

3.2.5. Conclusion

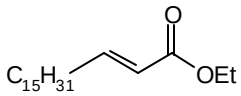
In conclusion, an asymmetric synthesis of D-*erythro*-dihydrosphingosine (sphinganine) as the triacetate has been realized using the Sharpless asymmetric dihydroxylation as the source of chirality for the first time.[80] We have successfully employed the chemistry of cyclic sulfites/sulfates or the cyclic 1,3-benzylidene to achieve the required stereochemistry of the C-2 centre of D-*erythro*-dihydrosphingosine. The merits of this synthesis are high-yielding reaction steps, high enantioselectivity and various possibilities available for structural modifications. The other enantiomer could be synthesized *via* α-dihydroxylation of olefin and following the reaction sequence as discussed above.

3.2.6. Experimental section

General information:

Solvents were purified and dried by standard procedures before use. Petroleum ether of boiling range 60-80°C was used. Melting points are uncorrected. Optical rotations were measured using sodium D line on JASCO-181 digital polarimeter. Infrared spectra were recorded on ATI MATTSON RS-1 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR were recorded on Bruker AC-200 and MSL 300 NMR spectrometers respectively. Mass spectra were obtained with a Finnigan MAT-1020 B-70 eV mass spectrometer. Elemental analyses were carried out on a Carlo Erba CHNS-O analyzer. Enantiomeric excess was determined by chiral HPLC or otherwise indicated.

Preparation of ethyl *trans*-octadec-2-enoate, 136



136

To a solution of (ethoxycarbonylmethylene)triphenylphosphorane (5.65 g, 16.22 mmol) in dry THF (35 mL) was added dropwise a solution of hexadecanal **135** (3 g, 12.47 mmol) in THF (5 mL) at room temperature. The reaction mixture was refluxed for 18 h. The solvent was removed

under reduced pressure and the crude product was purified on a silica gel column using petroleum ether:EtOAc (9:1) as eluent to give **136** (3.37 g) as a white solid.

Yield: 3.37 g, 87%

M.p.: 25-26°C

IR (neat, cm^{-1}): n_{max} 2926, 2854, 1724, 1655, 1466, 1367, 1310, 1178, 1128, 1045, 980, 721

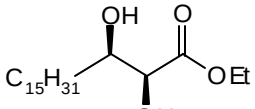
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.86 (t, J = 6.8 Hz, 3H), 1.15-1.30 (m, 24H), 1.35 (t, J = 7.2 Hz, 3H), 1.45 (m, 2H), 2.18 (ddt, J = 6.98, $J_{allylic}$ = 1.46 Hz, 2H), 4.18 (q, J = 7.2 Hz, 2H), 5.8 (dt, J_{trans} = 15.63, $J_{allylic}$ = 1.46 Hz, 1H), 6.97 (dt, J = 6.98, J_{trans} = 15.63 Hz, 1H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 14.4, 22.8, 28.3, 29.3, 29.5-29.9, 32.1, 32.4, 60.1, 121.6, 149.3, 166.7

EIMS (*m/z* relative intensity, %): 311 [M^++1] (18.58), 265 (46.15), 264 (48.71), 222 (12.82), 213 (37.6), 155 (21.36), 127 (60), 101 (64.53), 88 (47.43), 83 (56.4), 69 (60.25), 57 (86.32), 55 (100)

Analysis: $C_{20}H_{38}O_2$ (310.50) requires C, 77.36; H, 12.33. Found: C, 77.68; H, 11.99.

Synthesis of ethyl-(2*S*,3*R*)-2,3-dihydroxyoctadecanoate, 137



137

To a mixture of $K_3Fe(CN)_6$ (4.14 g, 12.6 mmol), K_2CO_3 (1.74 g, 12.6 mmol) and $(DHQD)_2$-PHAL (33 mg, 42.4 μmol, 1 mol%) in *t*-BuOH-H_2O (1:1, 50 mL) cooled at 0°C was added osmium tetroxide (170 μL, 0.1M solution in toluene, 0.4 mol%) followed by methanesulfonamide (0.4 g, 4.2 mmol). After stirring for 5 min at 0°C, the olefin **136** (1.3 g, 4.2 mmol) was added in one portion. The reaction mixture was stirred at 0°C for 24 h and then quenched with solid sodium sulfite (6 g). The stirring was continued for an additional 45 min and then the solution was extracted with EtOAc (3 × 20 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether:EtOAc (3:2) as eluent gave **137** (1.355 g) as a white solid.

Yield: 1.355 g, 94%

M.p.: 65-66°C

[a]$_D^{20}$: + 8.6 (c = 2, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): n_{max} 3400-3300, 3133, 3018, 2926, 2854, 1732, 1460, 1401, 1215, 760, 667

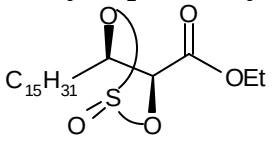
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, *J* = 7.5 Hz, 3H), 1.15-1.30 (m, 26H), 1.33 (t, *J* = 7.5 Hz, 3H), 1.60 (m, 2H), 1.95 (d, *J* = 8 Hz, 1H), 3.08 (d, *J* = 4 Hz, 1H), 3.88 (m, 1H), 4.08 (dd, *J* = 4, 2 Hz, 1H), 4.3 (q, *J* = 7.5 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 14.0, 22.5, 25.8, 29.2, 29.5, 31.8, 33.6, 61.9, 72.5, 73.2, 173.5

EIMS (*m/z* relative intensity, %): 299 [M^+–OCH_2CH_3] (0.5), 271 (0.9), 253 (1.3), 123 (3.6), 109 (7.6), 104 (100), 95 (15.20), 82 (17.85), 76 (32.14), 69 (14.3), 57 (14.20)

Analysis: $C_{20}H_{40}O_4$ (344.52) requires C, 69.72; H, 11.70. Found: C, 69.36; H, 12.08.

Synthesis of (4*S*,5*R*)-4-ethoxycarbonyl-5-pentadecyl-1,3,2-dioxathiolane-2-oxide, 138



138

A two necked round bottom flask equipped with a reflux condenser topped with a $CaCl_2$ guard tube and a rubber septum was charged with diol **137** (2.00 g, 5.8 mmol) and dry CCl_4 (15 mL). Thionyl chloride (1.043 g, 0.64 mL, 8.77 mmol) was added through a syringe and the reaction mixture was refluxed for 1.5 h. After completion of reaction, the reaction mixture was cooled and water (5 mL) and CH_2Cl_2 (20 mL) were added. The organic layer was separated and aqueous layer extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with saturated $NaHCO_3$ (20 mL), brine (30 mL), dried (Na_2SO_4) and passed through a pad of silica gel. The filtrate was concentrated and the crude product was purified on a silica gel column using petroleum ether:EtOAc (9:1) as eluent to give **138** (2.176 g) as a colorless oil.

Yield: 2.176 g, 96%

[a]$_D^{20}$: + 79.21 (c = 2, $CHCl_3$)

IR (neat, cm^{-1}): n_{max} 3131, 3024, 2925, 2854, 1741, 1461, 1397, 1278, 1215, 1032, 758

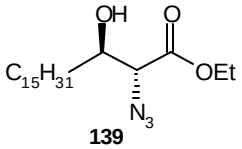
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7 Hz, 3H), 1.15-1.30 (m, 26H), 1.34 (t, *J* = 7 Hz, 3H), 1.8-1.95 (m, 2H), 4.30-4.34 (dq, *J* = 7, 2 Hz, 2H), 4.50 (d, *J* = 7.5 Hz, 0.5H), 4.6-4.68 (m, 0.5H), 5.05 (d, *J* = 7 Hz, 0.5H), 5.09 –5.17 (m, 0.5H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 13.73, 13.8, 22.43, 24.99, 25.39, 28.81, 29.11-29.15, 31.71, 32.29, 34.73, 62.13, 62.84 (diastereomeric), 80.08, 81.36 (diastereomeric), 82.41, 86.58 (diastereomeric), 167.00

EIMS (*m/z* relative intensity, %): 390 [M^+] (0.5), 345 [M^+–OCH_2CH_3] (1.28), 326 [M^+–SO_2] (3.85), 325 [M^+–HSO_2] (3.8), 317 (3.85), 2.53 (15.4), 233 (14.10), 157 (6.41), 130 (19.23), 109 (52.56), 95 (96), 83 (96), 69 (97.43), 57 (100), 55 (96)

Analysis: $C_{20}H_{38}O_5S$ (390.57) requires C, 61.50; H, 9.80; S, 8.20. Found: C, 61.42; H, 9.74; S, 8.12.

Synthesis of ethyl-(2*R*,3*R*)-2-azido-3-hydroxyoctadecanoate, 139



139

To a solution of cyclic sulfite **138** (0.5 g, 1.28 mmol) in dry DMF (10 mL) was added LiN_3 (0.125 g, 2.56 mmol) under argon. The reaction mixture was stirred at 100°C for 18 h under argon. The solvent was removed under reduced pressure and to the residue, was added 20% aq. H_2SO_4:Et_2O (1:1, 10 mL) and stirred at room temperature for 12 h. Excess $NaHCO_3$ was added to it and the reaction mixture was stirred for 20 min and then extracted with ether (3 × 20 mL). The organic layer was separated and passed through celite and silica gel bed. Removal of solvent afforded the crude product as a dark yellow oil which was purified on a silica gel column using petroleum ether:EtOAc (3:1) as eluent to give **139** (0.321 g) as a colorless low melting solid.

Yield: 0.321 g, 68%

$[\alpha]_D^{20}$: – 4.85 (c = 2, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): n_{max} 3476, 2922, 2853, 2109, 1741, 1460, 1373, 1263, 1191, 1119, 1095, 1028

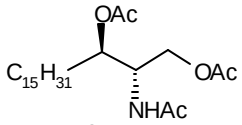
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7 Hz, 3H), 1.15-1.30 (m, 26H), 1.36 (t, *J* = 7 Hz, 3H), 1.62 (m, 2H), 2.23 (m, 1H), 3.22 (m, 1H), 4.14 (dd, *J* = 6, 8 Hz, 1H), 4.34 (q, *J* = 7 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 13.76, 13.80, 22.46, 29.18-29.51, 31.77, 61.20, 71.00, 72.5, 170.0

EIMS (*m/z* relative intensity, %): 369 [M^+] (2.6), 367 (10.52), 341 [M^+–N_2] (1.31), 268 (9.87), 253 (20), 241 (26.31), 167 (6.58), 154 (15.13), 111 (44.08), 104 (40.8), 97 (93.42), 83 (100), 71 (81.58), 57 (75.65), 55 (44.08)

Analysis: $C_{20}H_{39}N_3O_3$ (369.53) requires C, 65.00; H, 10.64; N, 11.37. Found: C, 64.89; H, 10.80; N, 11.65.

Synthesis of (2*S*,3*R*)-2-acetamido-1,3-diacetoxyoctadecane, 87



87

To a stirred suspension of $LiAlH_4$ (25 mg, 0.66 mmol) in dry Et_2O (8 mL) at 0°C was added dropwise a solution of **139** (100 mg, 0.27 mmol) in Et_2O (5 mL) through a syringe. The reaction mixture was subsequently warmed to room temperature and stirred overnight. It was next hydrolyzed with water (1 mL) and filtered through celite. The celite bed was washed with MeOH (3 × 20 mL). The total filtrate was concentrated to an off white solid, which was subsequently acetylated with Ac_2O (0.5 mL) and pyridine (1 mL). After stirring for 18 h, the solvent was stripped off under reduced pressure and the residue was purified on a silica gel column using petroleum ether:EtOAc (1:1) as eluent to give the triacetate **87** (0.088 g) as a white solid. It was further recrystallised from petroleum ether/EtOAc.

Yield: 0.088 g, 76%

M.p.: 96-98°C (lit. 97-98°C,[77] 95-97°C,[72] 89-91°C[71])

$[\alpha]_D^{20}$: + 17.2 (c = 0.2, $CHCl_3$), [lit. + 16.8 (c = 1, $CHCl_3$),[72] + 17.4 (c = 1, $CHCl_3$)[77]]

IR ($CHCl_3$, cm^{-1}): n_{max} 3291, 2913, 2847, 1730, 1646, 1537, 1368, 1233, 1036

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.84 (t, *J* = 6.5 Hz, 3H), 1.14-1.23 (m, 26H), 1.50-1.60 (m, 2H), 1.97 (s, 3H), 2.00 (s, 3H), 2.02 (s, 3H), 3.99-4.21 (m, 2H), 4.33- 4.37 (m, 1H), 4.98-5.01 (m, 1H), 5.77-5.80 (d, *J* = 8 Hz, 1H)

EIMS (*m/z* relative intensity, %): 427 [M^+] (1.31), 354 (3.94), 308 (2.63), 307 (5.26), 295 (6.58), 294 (35.53), 188 (6.58), 145 (7.9), 144 (56.58), 102 (27.63), 85 (81.6), 84 (100)

Analysis: $C_{24}H_{45}NO_5$ (427.62) requires C, 67.40; H, 10.60; N, 3.27. Found: C, 67.26; H, 10.68; N, 3.06.

Synthesis of *trans*-octadec-2-ene-1-ol, 82

82

To a solution of **136** (2.6 g, 8.37 mmol) in dry Et_2O (70 mL) at 0°C was added dropwise DIBAL-H (19 mL, 19 mmol, 1M in toluene) through a syringe. The reaction mixture was allowed to warm to room temperature over 0.5 h, then re-cooled to 0°C and treated with 1N HCl (50 mL). The resulting gel was dissolved by dropwise addition of 6N HCl. The ethereal phase

was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with sat $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. Silica gel column chromatography of the crude product using petroleum ether:EtOAc (8:2) as eluent gave **82** (2.07 g) as a white solid.

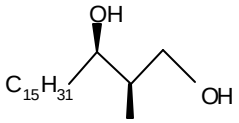
Yield: 2.07 g, 92%

M.p.: 47-48°C (lit. 46-48°C)[70]

IR ($CHCl_3$, cm^{-1}): n_{max} 3330, 2997, 2909, 2844, 1654, 1447, 1208, 967, 747

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6 Hz, 3H), 1.15-1.45 (m, 27H), 2.05 (bq, *J* = 6 Hz, 2H), 4.07 (d, *J* = 6 Hz, 2H), 5.65 (m, 2H).

Synthesis of (2*R*,3*R*)-octadecane-1,2,3-triol, 140



140

To a mixture of $K_3Fe(CN)_6$ (4.14 g, 12.6 mmol), K_2CO_3 (1.74 g, 12.6 mmol) and $(DHQD)_2$-PHAL (33 mg, 42.4 μmol, 1 mol%) in *t*-BuOH-H_2O (1:1, 50 mL) cooled at 0°C was added osmium tetroxide (170 μL, 0.1M solution in toluene, 0.4 mol%) followed by methanesulfonamide (0.4 g, 4.2 mmol). After stirring for 5 min at 0°C, the olefin **82** (1.13 g, 4.2 mmol) was added in one portion. The reaction mixture was stirred at 0°C for 24 h and then quenched with solid sodium sulfite (6 g). The stirring was continued for an additional 45 min and then the solution was extracted with EtOAc (5 × 30 mL). The combined organic phases were washed with 10% KOH, brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether:EtOAc (4:6) as eluent gave **140** (1.16 g) as a white solid.

Yield: 1.16 g, 91%

M.p.: 86-88°C

$[\alpha]_D^{20}$: + 8 (c = 1.0, $CHCl_3$ + MeOH [1:1])

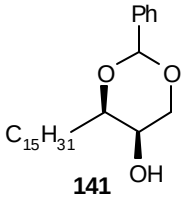
IR (nujol, cm^{-1}): n_{max} 3400-3200, 2919, 2851, 1458, 1375, 1074

^{1}H NMR (200 MHz, $CDCl_3$ + $[D_6]$DMSO): δ 0.9 (t, *J* = 6 Hz, 3H), 1.2-1.4 (m, 27H), 1.45-1.55 (m, 3H), 2.63 (brs, 1H), 3.47-3.51 (m, 1H), 3.56-3.82 (m, 3H)

EIMS (*m/z* relative intensity, %): 302 [M^+] (0.7), 279 (2.2), 167 (20.7), 149 (100)

Analysis: $C_{18}H_{38}O_3$ (302.5) requires C, 71.46; H, 12.66. Found: C, 71.09; H, 12.39.

Synthesis of (2*R*,3*R*)-1,3-*O*-benzylideneoctadecane-1,2,3-triol, 141



141

To a solution of **140** (1.00 g, 3.3 mmol) in dry CH_2Cl_2 (60 mL) was added *p*-TsOH (60 mg) and benzaldehyde dimethylacetal (0.61 g, 3.96 mmol). The reaction mixture was stirred at room temperature overnight. Subsequently it was neutralized with saturated aq. $NaHCO_3$ (10 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were washed with aq. $NaHCO_3$, brine, dried (Na_2SO_4) and concentrated. Column chromatography over silica gel using petroleum ether:acetone (9.2:0.8) as eluent furnished **141**, the major product (0.89 g) as a white solid.

Yield: 0.89 g, 69%

M.p.: 69-70°C

$[\alpha]_D^{20}$: + 7.2 (c = 1.0, $CHCl_3$)

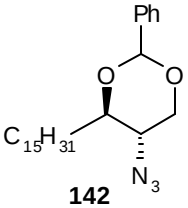
IR ($CHCl_3$, cm^{-1}): n_{max} 3423, 2917, 2849, 1605, 1451, 1377, 1276, 1215, 1079, 1026, 751

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.9 (t, *J* = 6 Hz, 3H), 1.15-1.45 (m, 26H), 1.71 (m, 2H), 2.40 (brs, 1H), 3.65-3.90 (m, 2H), 4.03-4.09 (dd, *J* = 2, 12 Hz, 1H), 4.21-4.28 (dd, *J* = 2, 12 Hz, 1H), 5.58 (s, 1H), 7.37-7.42 (m, 3H), 7.51- 7.55 (m, 2H)

EIMS (*m/z* relative intensity, %): 391 [M^++1] (21.5), 390 [M^+] (12.59), 389 (1.4), 285 (21.5), 107 (100), 79 (37.8)

Analysis: $C_{25}H_{42}O_3$ (390.6) requires C, 76.87; H, 10.84. Found: C, 76.53; H, 10.67.

Synthesis of (2*R*,3*R*)-2-azido-1,3-*O*-benzylideneoctadecane-1,3-diol, 142



142

To a solution of **141** (0.5 g, 1.28 mmol) in dry CH_2Cl_2 (20 mL) at 0°C was added methanesulfonylchloride (0.254 g, 2.2 mmol), Et_3N (0.5 mL) and DMAP (cat). The reaction

mixture was stirred at room temperature overnight and then poured into Et_2O-H_2O mixture. The organic phase was separated and the aqueous phase extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with water, brine, dried (Na_2SO_4) and concentrated to a yellow waxy solid, which was used as such in the next step.

To the solution of above mesylate in dry DMF (20 mL) was added sodium azide (0.42 g, 6.4 mmol) and the reaction mixture stirred at 80°C for 24 h. It was cooled and poured into water and extracted with petroleum ether:acetone (9.5:0.5, 4 × 20 mL). The organic extracts were washed with water, brine, dried (Na_2SO_4) and concentrated. Column chromatography on silica gel column using petroleum ether:acetone (9.5:0.5) as eluent gave **142** (0.44 g) as a white solid.

Yield: 0.44 g, 83%

M.p.: 109-110°C

[a]$_D^{20}$: – 6.6 (c = 1.0, $CHCl_3$)

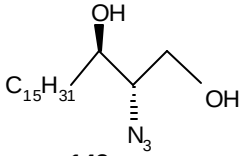
IR ($CHCl_3$, cm^{-1}): n_{max} 2919, 2851, 2097, 1600, 1452, 1372, 1109, 1074, 1029, 745, 693

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6 Hz, 3H), 1.15-1.4 (m, 26H), 1.71 (m, 2H), 3.96-3.99 (m, 2H), 4.11-4.17 (dd, *J* = 2, 12 Hz, 1H), 4.52-4.62 (dd, *J* = 2, 12 Hz, 1H), 5.60 (s, 1H), 7.36-7.42 (m, 3H), 7.50 –7.58 (m, 2H)

EIMS (*m/z* relative intensity, %): 415 [M^+] (3), 414 (10.4), 391 (66.7), 310 (100), 267 (38.5), 166 (98)

Analysis: $C_{25}H_{41}N_3O_2$ (415.6): requires C, 72.25; H, 9.94; N, 10.10. Found: C, 72.08; H, 10.03; N, 9.86.

Synthesis of (2*S*,3*R*)-2-azidooctadecane-1,3-diol, 143



143

To a solution of **142** (0.1 g, 0.24 mmol) in methanol (10 mL) was added 3N HCl (1 mL). The mixture was stirred for 24 h at room temperature. The reaction mixture was concentrated and co-evaporated with toluene (2 × 10 mL). The residue thus obtained was triturated with n-hexane to afford the crude product, which was recrystallized from EtOAc/n-hexane to give **143** (0.057 g) as a white solid.

Yield: 0.057 g, 72%

M.p.: 78–80°C (lit. 77–79°C)[72]

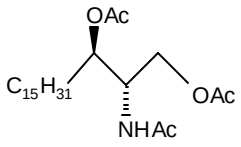
[a]$_D^{20}$: + 4.1 (c = 0.5, $CHCl_3$) [lit. + 4.2 (c = 0.5, $CHCl_3$/MeOH, 1:1)[72]]

IR ($CHCl_3$, cm^{-1}): n_{max} 3450-3400, 2925, 2854, 2100, 1465, 1338, 1215, 922, 699

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.5 Hz, 3H), 1.15-1.45 (m, 26H), 1.45-1.55 (m, 2H), 2.5 (brs, 1H), 3.17-3.30 (m, 2H), 3.82-3.98 (m, 2H), 4.59-4.71 (m, 1H)

EIMS (m/z relative intensity, %): 327 [M^+] (2.3), 285 (100), 267 (15.6), 239 (10.4), 167 (6.7).

Synthesis of (2*S*,3*R*)-2-acetamido-1,3-diacetoxyoctadecane, 87



87

To a suspension of $LiAlH_4$ (4.7 mg, 123 μmol) in Et_2O (10 mL) at 0°C was added a solution of **143** (20 mg, 61 μmol) in Et_2O (2 mL). The reaction mixture was subsequently warmed to room temperature and stirred overnight. Excess $LiAlH_4$ was destroyed by slow addition of 5% aq NaOH till effervescence ceased. EtOAc (10 mL) was added and the white cake was filtered and washed with EtOAc (3 × 10 mL). The organic layer was dried (K_2CO_3) and concentrated to an off white solid, which was subsequently acetylated with Ac_2O (0.15 mL) and pyridine (1 mL). After stirring for 24 h, the solvent was co-evaporated with toluene and the residue was purified on a silica gel column using petroleum ether:EtOAc (1:1) as eluent to give the triacetate **87** (0.0185 g) as a white solid. It was further recrystallized from hexane/EtOAc.

Yield: 0.0185 g, 71%

M..p.: 95–97°C (lit. 97-98°C,[72] 95-97°C,[72] 89-91°C[71])

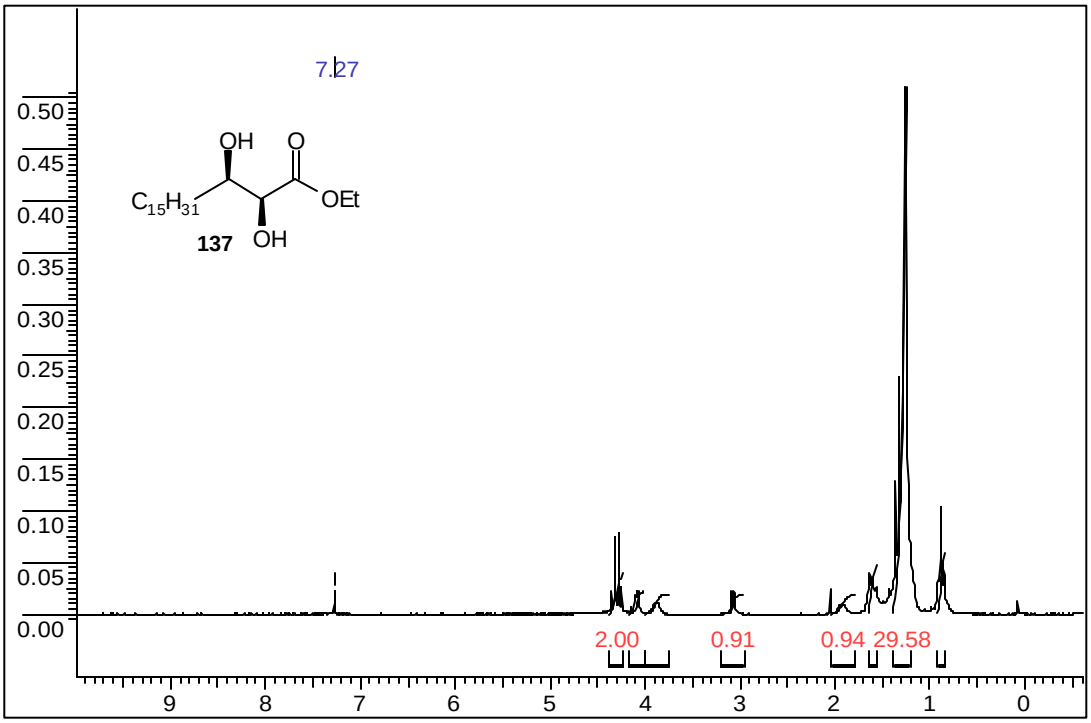
[a]$_D^{20}$: + 17.0 (c = 0.2, $CHCl_3$) [lit. + 16.8 (c = 1, $CHCl_3$),[72] + 17.4 (c = 1, $CHCl_3$)[77]]

The spectroscopic data were in full agreement with **87** prepared as per **Scheme 26**.

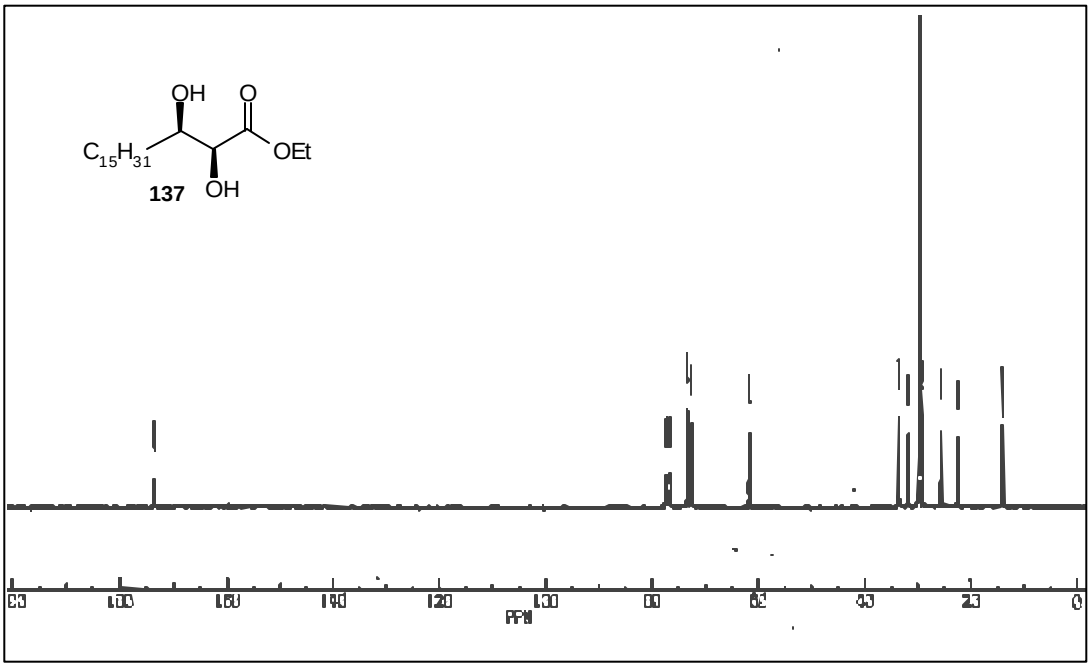
3.2.7. Spectra

+ 1] ^{1}H NMR Spectrum of **137**
+ 2] ^{13}C NMR Spectrum of **137**
+ 3] ^{1}H NMR Spectrum of **138**
+ 4] ^{13}C NMR Spectrum of **138**
+ 5] ^{1}H NMR Spectrum of **87**
+ 6] EIMS of **87**
+ 7] ^{1}H NMR Spectrum of **140**
+ 8] ^{1}H NMR Spectrum of **143**

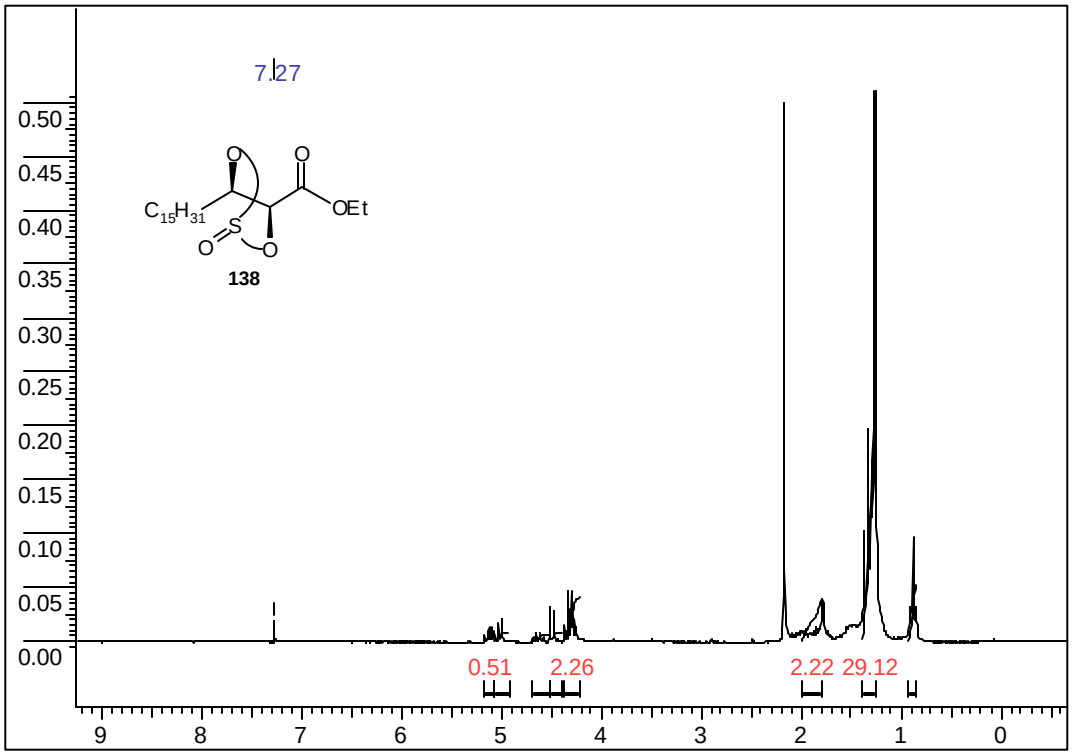
+ ^{1}H NMR Spectrum of **137**



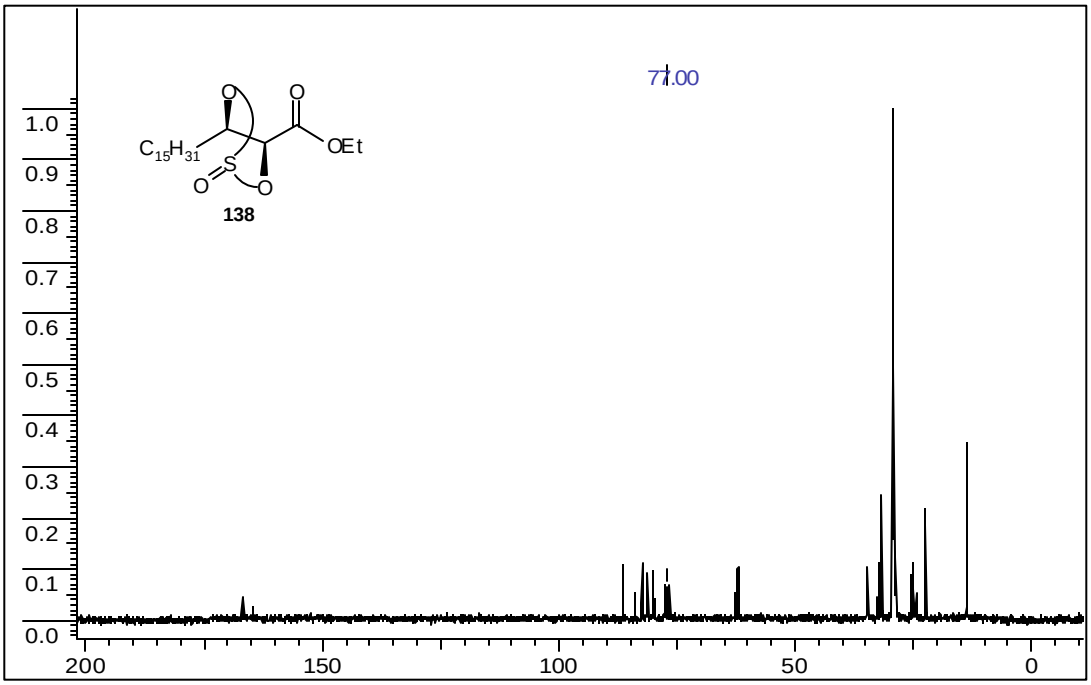
+ ^{13}C NMR Spectrum of **137**



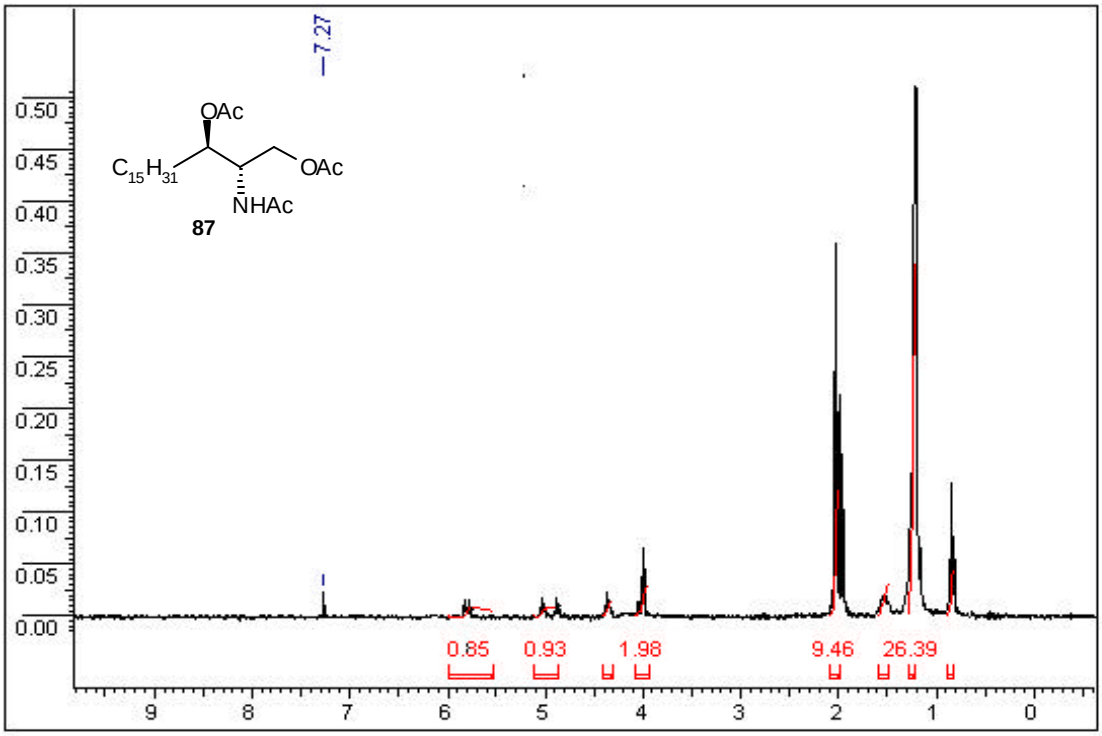
+ ^{1}H NMR Spectrum of **138**



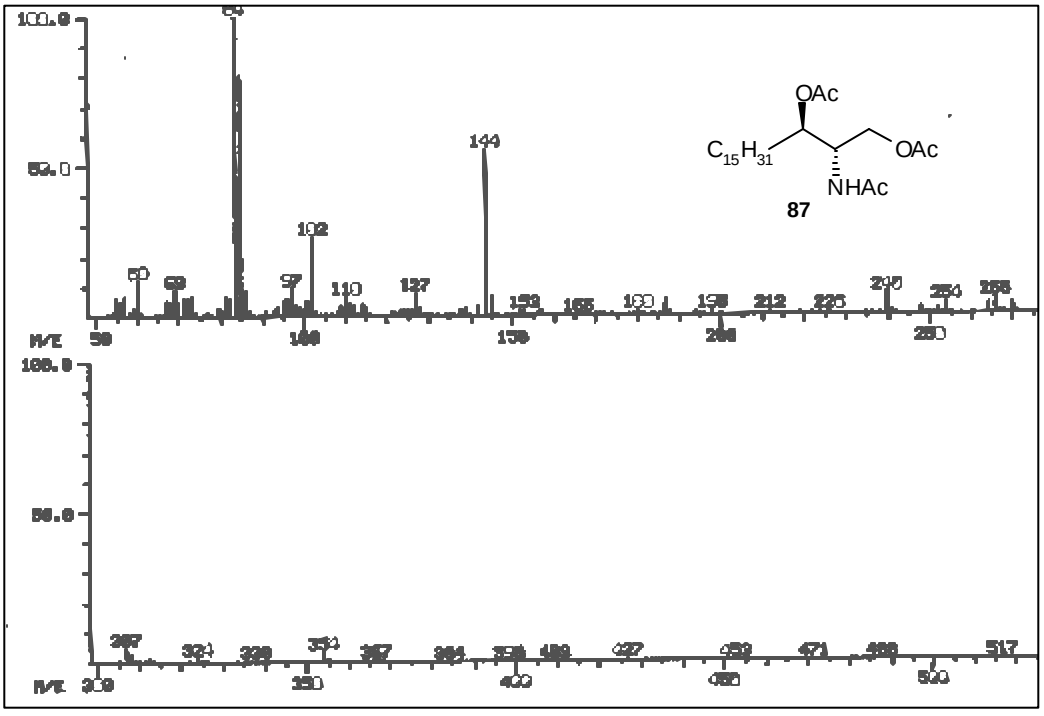
+ ^{13}C NMR Spectrum of **138**



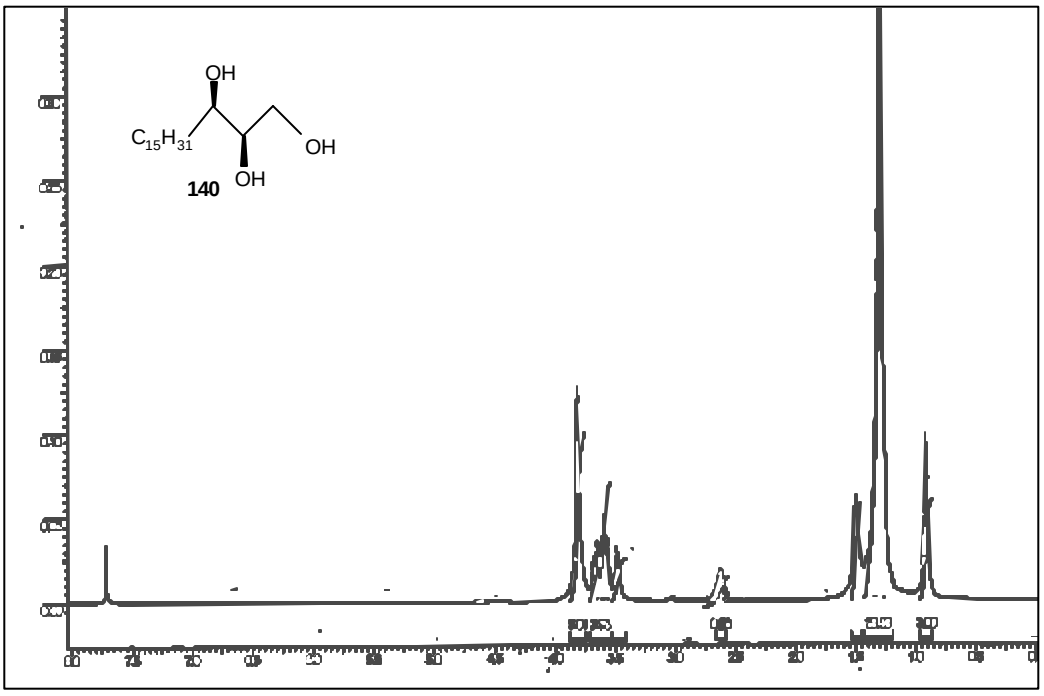
+ ^{1}H NMR Spectrum of **87**


7.27
OAc
C15H31
OAc
NHAc
87
0.85
0.93
1.98
9.46
26.39

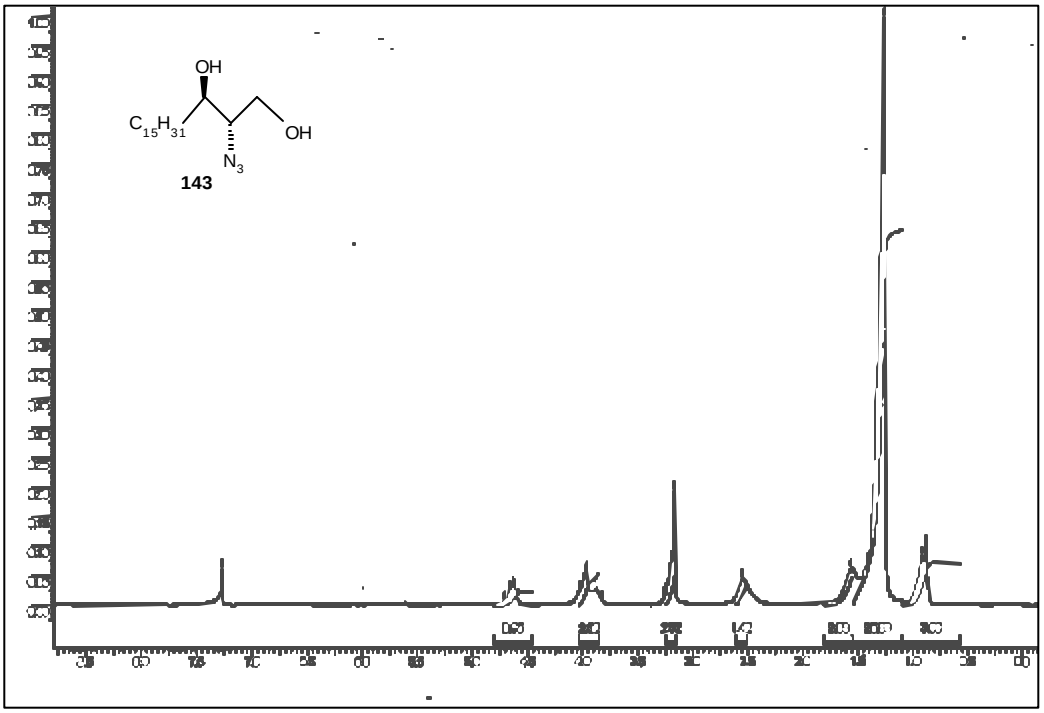
+ EIMS of **87**


OAc
C15H31
OAc
NHAc
87
144
102

+ ^{1}H NMR Spectrum of **140**



+ ^{1}H NMR Spectrum of **143**



3.3. SECTION B

DOUBLE DIASTEREOSELECTION IN ASYMMETRIC DIHYDROXYLATION: APPLICATION TO THE DIASTEREOSELECTIVE SYNTHESIS OF C_{18}-PHYTOSPHINGOSINES

3.3.1. Introduction

Double Diastereoselection in Asymmetric Dihydroxylation

Asymmetric dihydroxylation of prochiral olefins gives high levels of enantioselectivities with the recent developments in reaction conditions and ligands. But, what about asymmetric dihydroxylation of chiral olefins? For a given case, a determination of the intrinsic diastereofacial selectivity of a chiral substrate is helpful in order to estimate the likelihood of success, especially in the "mismatched" pairing.[81] This is most easily accomplished by carrying out the osmylation in the absence of chiral ligand. A few examples of matched and mismatched double diastereoselection in the asymmetric dihydroxylation of chiral olefins have been reported and are summarized in the following paragraphs.

In his studies on the stereoselective synthesis of amino sugars, Wade[82] investigated the asymmetric dihydroxylation of the 4,5-dihydroisoxazoles **144** and **145**, shown in **Table 1**. The reactions employing the phthalazine class of ligands displayed useful levels of matched and mismatched diastereoselectivity (entries 6-9). Thus, in the mismatched reaction (entries 7 and 9), the reagent was able to strongly override the intrinsic diastereofacial bias of the olefin substrate.

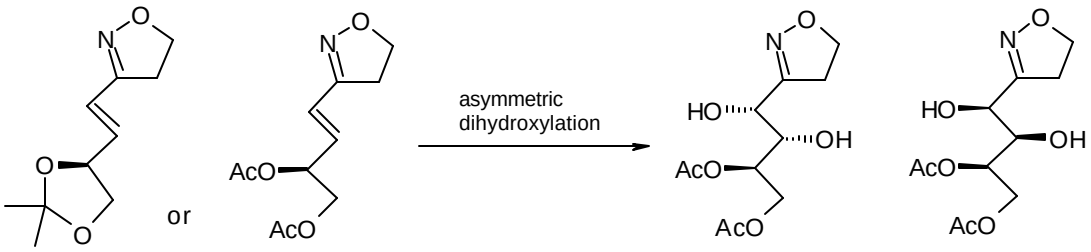
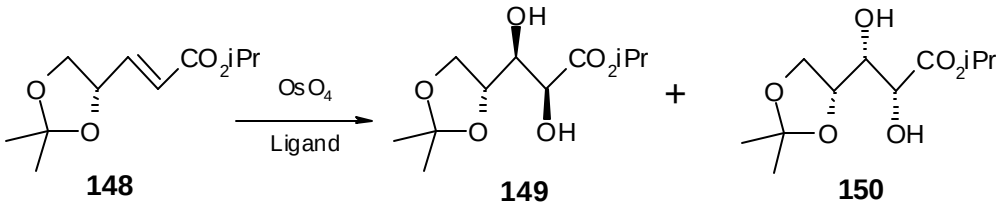


Table 1.

Entry	Substrate	Ligand	Conditions	*Anti*/*Syn*	Yield, %
1	**144**	None	cat. achiral[a]	77:23	85
2	**145**	None	cat. achiral[a]	76:24	83
3	**144**	DHQD-MEQ	cat. chiral[a,b]	89:11	52
4	**144**	DHQD-MEQ	stoich. chiral[c]	78:22	48
5	**145**	DHQ-MEQ	cat. chiral[d]	52:48	66
6	**144**	$(DHQD)_2$-PHAL	cat. chiral[d]	96:4	53
7	**144**	$(DHQ)_2$-PHAL	cat. chiral[d,e]	11:89	62
8	**145**	$(DHQD)_2$-PHAL	cat. chiral[d]	98:2	82
9	**145**	$(DHQ)_2$-PHAL	cat. chiral[d]	5:95	85

[a]0.1 eq. of OsO_4, 3 eq. NMO, THF/H_2O, 9:1, 20°C. [b]0.4 eq. of chiral aux, [c]3 eq. of chiral aux, 1 eq. OsO_4, $PhCH_3$, 20°C. [d]0.08 eq. of $K_2OsO_4.2H_2O$, 3 eq. $K_3Fe(CN)_6$, 3 eq. of K_2CO_3, 0.4 eq. of chiral aux, 1 eq. $MeSO_2NH_2$, *t*-BuOH/H_2O, 1:1, 20°C. [e]Use of AD-mix-α under recommended conditions gave only 20% reaction after 22 h.

Morikawa and Sharpless[83] carried out a similar set of experiments on carbohydrate-derived olefin **148** shown in **Table 2**. These experiments were performed to assess the relative ability of several different ligands in the context of matching and mismatching in the asymmetric dihydroxylation reaction. For this substrate, it was found that the phthalazine ligand $(DHQD)_2$-PHAL was the ligand of choice for the matched reaction (entry 4). Whereas, inspite of their poor performance in the matched reactions, the pyrimidine derivatives $(DHQ)_2$-PYR and $(DHQ)_2$-$PYR(OMe)_3$ gave the best results in the mismatched examples (entries 7 and 9).



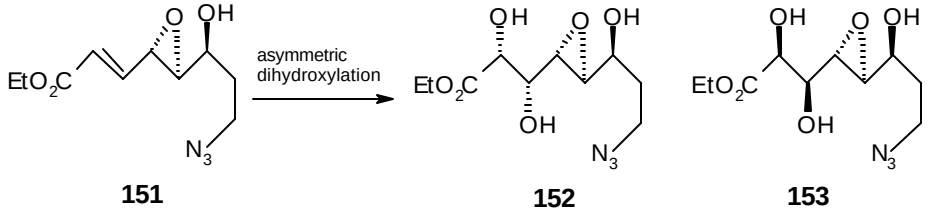
148 **149** **150**

Table 2.

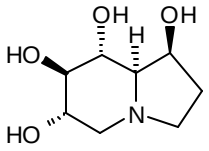
Entry	Ligand (mol%)	Ratio (**149**:**150**)	Yield, %
1	Quinuclidine (10)	2.6:1	85%
2	DHQD-CLB (10)	10:1	87%
3	DHQ-CLB (10)	1:10	85%

4	$(DHQD)_2$-PHAL (1)	39:1	84%
5	$(DHQ)_2$-PHAL (1)	1:1.3	52%
6	$(DHQD)_2$-PYR (5)	6.9:1	90%
7	$(DHQ)_2$-PYR (5)	1:4.1	86%
8	$(DHQD)_2$-PYR$(OMe)_3$ (5)	12:1	89%
9	$(DHQ)_2$-PYR$(OMe)_3$ (5)	1:7	90%

A mismatched double diastereoselective asymmetric dihydroxylation played a key role in the synthesis of polyhydroxylated indolizidine alkaloid castanospermine[84] (**Scheme 28**). In the asymmetric dihydroxylation of epoxy ester **151**, Cha[84] observed 10:1 preference for the *syn* diastereomer **152** in reactions employing the $(DHQ)_2$-PHAL ligand. A complete reversal of selectivity was observed in the matched case, as the *anti* product **153** was the major product with >20:1 diastereoselectivity. The major product **152** from the mismatched reaction was subsequently converted into (+)-castanospermine in what is one of the most concise syntheses of this target to date.



151 **152** **153**



(+)-castanospermine

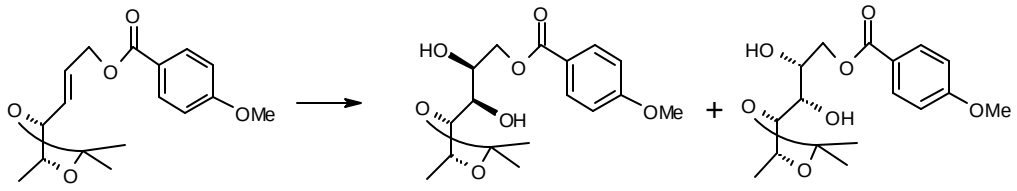
Ligand	Ratio (**152**:**153**)
none	1:2
$(DHQ)_2$-PHAL	10:1
$(DHQD)_2$-PHAL	1:20

Scheme 28

Several more examples of double diastereoselection in asymmetric dihydroxylation are reported in the literature. Among them are the synthesis of brassinosteroid analogs,[85] synthesis of immunosuppressant FK-506,[86] preparation of intermediates in the synthesis of mycalamide B,[87] insect juvenile hormone bisepoxide,[88] and the preparation of modified pyrimidine nucleobases.[89]

Corey *et al.*[90] have carried out the stereocontrolled total syntheses of several *vic*-polyols through double diastereoselective asymmetric dihydroxylation. Olefin **154** with the $(DHQ)_2$-PHAL ligand in the matched case gave excellent diastereoselectivity in favor of *anti* product

155, while use of $(DHQD)_2PYDZ$ ligand also resulted (mismatched case) in good diastereoselection in favor of *syn* product **156** (**Table 3**).

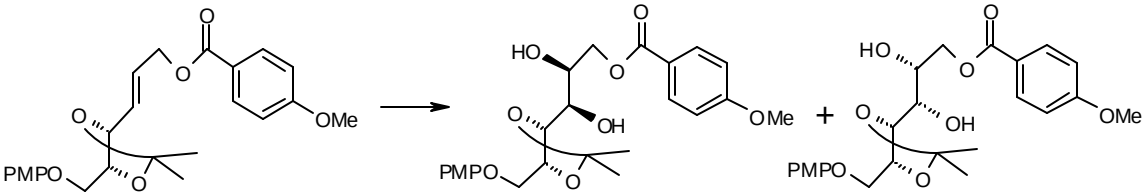


154 **155** *anti* **156** *syn*

Table 3.

Dihydroxylation conditions	Isolated Yield	Ratio of *anti*:*syn*
OsO_4, NMO, Acetone-H_2O (10:1)	88% of *anti* and *syn*	1.9:1
$(DHQ)_2$-PHAL (matched case)	86% of *anti*	54:1
$(DHQD)_2PYDZ$ (mismatched case)	86% of *syn*	1:35

Similarly, the asymmetric dihydroxylation of olefin **157** in the matched case with $(DHQ)_2$-PHAL ligand gave excellent diastereoselectivity in favor of *anti* product **158**, while the mismatched case with $(DHQD)_2$-PHAL ligand favored the *syn* product **159** (**Table 4**).



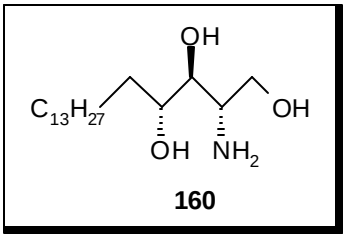
157 **158** *anti* **159** *syn*

Table 4.

Dihydroxylation conditions	Isolated Yield	Ratio of *anti*:*syn*
OsO_4, NMO, Acetone-H_2O (10:1)	96% of *anti* and *syn*	2.5:1
$(DHQ)_2$-PHAL (matched case)	93% of *anti*	200:1
$(DHQD)_2PYDZ$ (mismatched case)	90% of *syn*	1:90

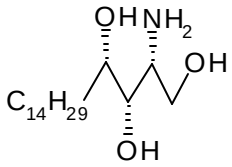
In our synthetic endeavors, after having achieved the synthesis of D-(+)-*erythro*-dihydrosphingosine *via* the asymmetric dihydroxylation approach, we further ventured into the synthesis of another target molecule of this class of compounds called phytosphingosine. The concept of double diastereoselection in asymmetric dihydroxylation on a terminal olefin with pre-existing chirality was utilized for the synthesis. This section highlights our work on double diastereoselection and also its application towards the synthesis of four of the eight isomers of C_{18}-phytosphingosine.

Phytosphingosine



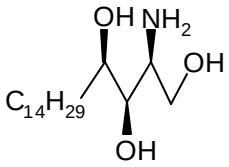
160

Phytosphingosine **160** exists abundantly as one of the molecular species of sphingolipids in microorganisms, plants and many mammalian tissues such as brain, hair, intestine,[91] uterus,[92] liver,[93] skin,[94] kidney[95] and in blood plasma.[96] It was first isolated from mushrooms in 1911[97] and its structure was elucidated by Oda[98a] and by Carter *et al*.[98b] In addition to its structural function as the long-chain base of sphingolipids in membranes, phytosphingosine itself is a bioactive lipid; for example, phytosphingosine **160** is a potential heat stress signal in yeast cells[99a,b] and some of its derivatives exhibit important physiological activities. α- and β-Galactosyl and glucosylphytoceramides possess very high tumor inhibitory potency.[99c]



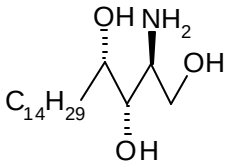
161

L-*xylo* [2*R*,3*S*,4*S*]



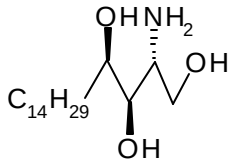
162

D-*xylo* [2*S*,3*R*,4*R*]



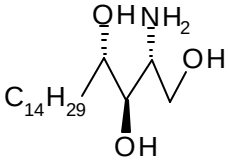
163

L-*lyxo* [2*S*,3*S*,4*S*]



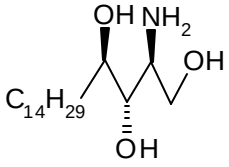
164

D-*lyxo* [2*R*,3*R*,4*R*]



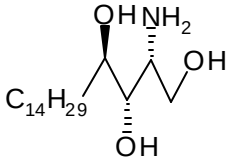
165

L-*ribo* [2*R*,3*R*,4*S*]



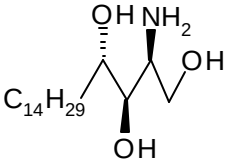
160

D-*ribo* [2*S*,3*S*,4*R*]



166

L-*arabino* [2*R*,3*S*,4*R*]



167

D-*arabino* [2*S*,3*R*,4*S*]

Figure 9

Of the eight C_{18}-phytosphingosine isomers (**Figure 9**) belonging to *ribo*-, *arabino*-, *xylo*-, and *lyxo*- series, most synthetic studies have been focused primarily on the preparation of *ribo*- or *arabino*-phytosphingosines, the stereochemistry of the C-2 position being either derived from the chiral pool materials, particularly serine, or by asymmetric synthesis.[100] To our knowledge, only eight syntheses of *lyxo*- or *xylo*-phytosphingosines, either racemic[101] or enantiomerically enriched,[102] have been described to date.

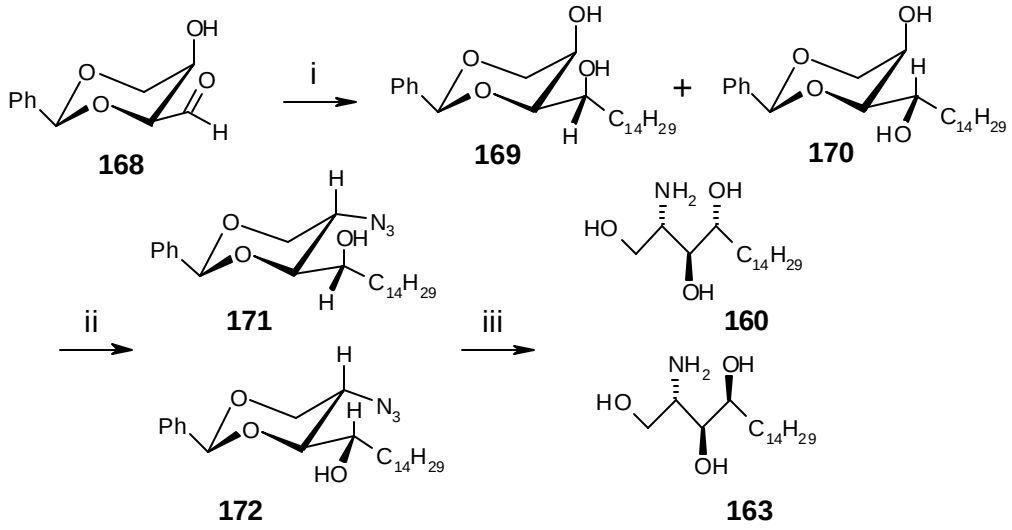
Although sphingolipids are known 100 years ago, no report on the asymmetric synthesis of L-*xylo*-(2*R*,3*S*,4*S*)-C_{18}-phytosphingosine **161** was known. In the present investigation, the first ever synthesis of this isomer and also the diastereoselective synthesis of D-*xylo*-(2*S*,3*R*,4*R*)-C_{18}, L-*lyxo*-(2*S*,3*S*,4*S*)-C_{18} and D-*lyxo*-(2*R*,3*R*,4*R*)-C_{18}-phytosphingosines have been achieved.

3.3.2. Review of Literature

Several syntheses of different isomers of phytosphingosine, predominantly in the *ribo*- and *arabino*-series have been documented. Most methods employ the chiral pool materials like carbohydrates and serine. A few interesting syntheses of phytosphingosine are described below.

Schmidt *et al*.[102a] (1988) Scheme 29

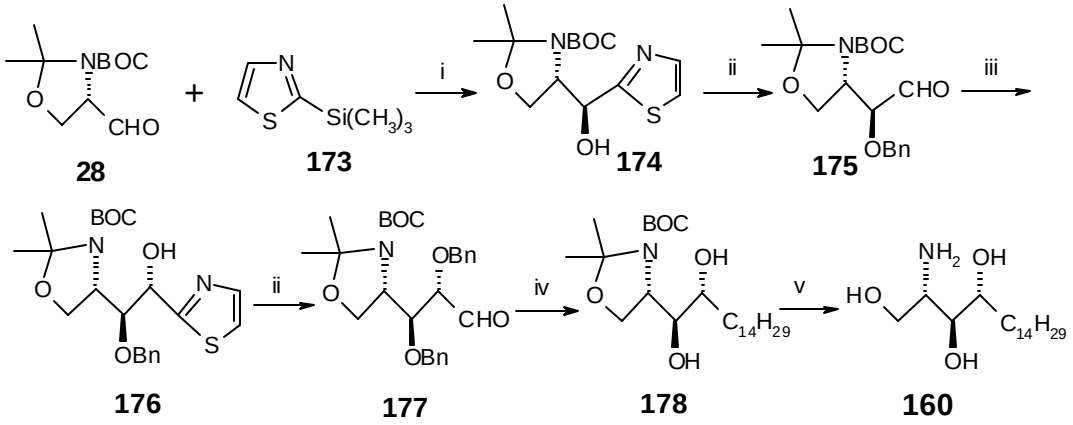
Schmidt *et al*. employed a D-threose-based synthesis of D-*ribo* and L-*lyxo*-phytosphingosine. Reaction of tetradecyl magnesium bromide with D-threose derivative **168** gave a separable 1:1 mixture of **169** and **170**. Conversion of HO-2 to mesylate and subsequent azide displacement furnished **171** and **172** respectively. Deprotection of benzylidene and reduction of azide afforded D-*ribo*- and L-*lyxo*-phytosphingosines **160** and **163** respectively.



Scheme 29. Reaction conditions: (i) $C_{14}H_{29}MgBr$, THF, 35% (**169**), 36% (**170**). (ii) (a) MsCl, pyridine, −30°C, 12 h, 75%, (b) DMF, NaN_3, 90°C, 2 d, 63%. (iii) (a) MeOH, conc. HCl, 15 h, 65%, (b) $LiAlH_4$, THF, rt, 30 min, 1 h, reflux, 95%.

Dondoni *et al*.[103] (1990) Scheme 30

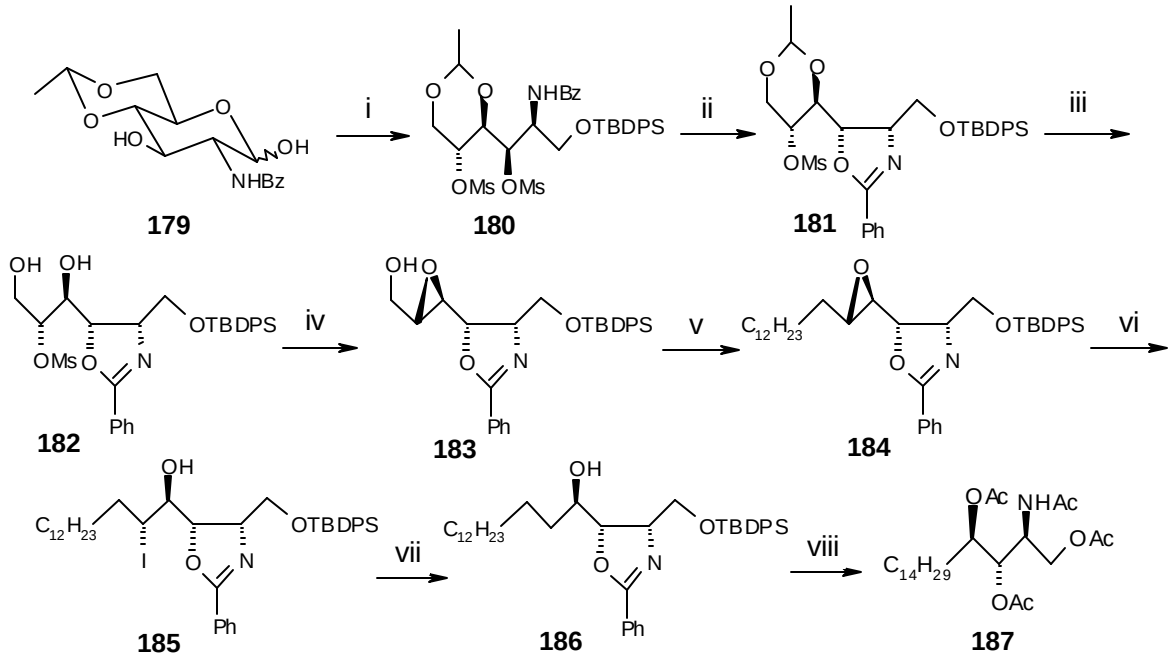
In Dondoni's approach, reaction of 2-(trimethylsilyl)thiazole (2-TST) **173** with Garner aldehyde **28** gave **174** (95% ds). Benzylation of the hydroxyl group and one-pot unmasking afforded the aldehyde **175**. Addition of 2-TST to aldehyde **175** furnished **176** in 85% ds. Protection of hydroxyl and unmasking gave aldehyde **177**, which on Wittig reaction and subsequent reduction of the resultant olefin and concomitant debenzylation produced **178**. Cleavage of acetonide and BOC deprotection afforded **160**.



Scheme 30. Reaction conditions: (i) CH_2Cl_2, rt, 20 h, then *n*-Bu_4NF, 1 h, 85%. (ii) (a) NaH, reflux, 20 min then BnBr, THF, *n*-Bu_4NI, 12 h, 73%, (b) MeI, CH_3CN, reflux, 12 h then $NaBH_4$, MeOH, −10°C, 30 min then $HgCl_2$, CH_3CN, H_2O, 15 min, 73%. (iii) 2-TST, THF, 0°C, 63%. (iv) (a) $C_{13}H_{27}P^+Ph_3Br^-$, *n*-BuLi, $PhCH_3$, rt, 2 h, 66%, (b) Raney Ni, EtOH, 8 h, reflux, 70%. (v) CF_3CO_2H, H_2O, 15 min, 95%.

Murakami *et al.*[104] (1994) Scheme 31

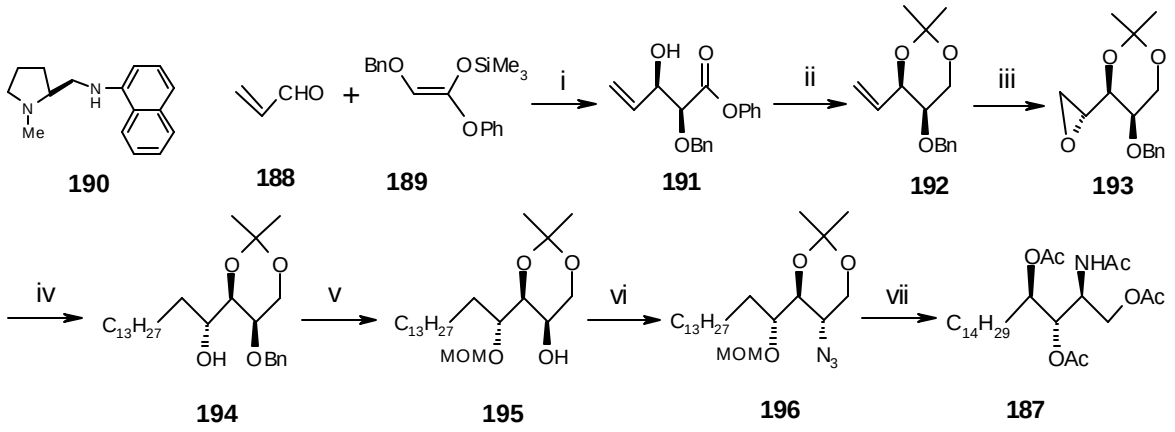
Murakami *et al*. synthesized D-*ribo*-phytosphingosine from D-glucosamine by utilizing its whole carbon skeleton and functional groups. 4,6-*O*-Ethylidene-N-benzoyl-D-glucosamine **179** (readily prepared from D-glucosamine[105]) was reduced to give the triol. Selective protection of the primary hydroxyl and mesylation gave the dimesylate **180**, which was further converted into phenyl oxazoline **181**. Deprotection of acetal followed by base treatment gave the epoxide **183**. Conversion of the free hydroxyl into tosylate and displacement with dodecyl magnesium bromide gave rise the epoxide **184**, which was subjected to ring opening with iodide to furnish **185**. Deiodination, hydrolysis of phenyloxazoline and TBDPS groups followed by acetylation afforded the tetraacetate derivative of D-*ribo*-phytosphingosine **187**.



Scheme 31. Reaction conditions: (i) (a) $NaBH_4$, *i*-PrOH, H_2O, 0°C, 1 h, 95%, (b) *t*-$BuPh_2Si$-Cl, pyridine, CH_2Cl_2, rt, 24 h then MsCl, Et_3N, CH_2Cl_2, 0°C, 2 h. (ii) Pyridine, Et_3N, toluene, 110°C, 24 h, 90%. (iii) $TiCl_4$, PhSH, CH_2Cl_2, 0°C, 2 h, 83%. (iv) K_2CO_3, MeOH, 0°C, 2 h. (v) (a) *p*-TsCl, DMAP, Et_3N, CH_2Cl_2, 0°C, 2 h, 88% from **182**, (b) $C_{12}H_{25}MgBr$, CuBr, THF, −30°C to 0°C, 4 h, 84%. (vi) NaI, Me_3SiCl, H_2O, CH_3CN, 0°C to 10°C, 2 h. (vii) *n*-Bu_3SnH, AIBN, $PhCH_3$, 60°C, 30 min, 88% from **184**. (viii) (a) 4N HCl, THF, rt, 24 h, (b) aq. NaOH, rt, (c) aq. NaOH, EtOH, 95°C, 12 h, (d) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 75%.

Kobayashi *et al*.[106] (1994) Scheme 32

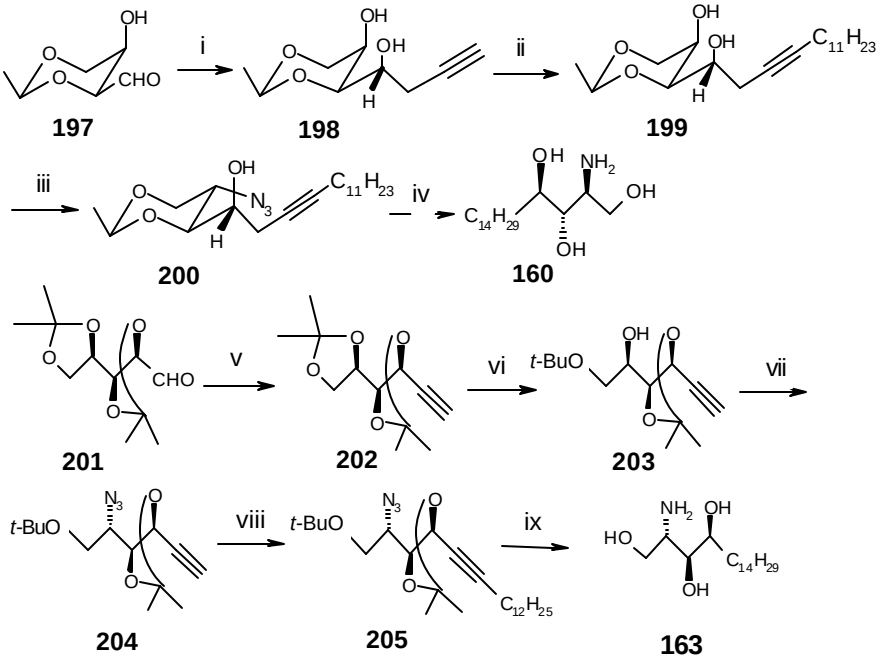
Kobayashi employed Lewis acid catalyzed asymmetric Aldol reaction of acrolein **188** with ketene silyl acetal **189** in presence of diamine **190** to give **191** (*syn*/*anti* = 98:2, 96% ee for *syn*). Reduction of **191** and diol protection gave **192**, which on epoxidation and subsequent alkylation with Grignard reagent furnished compound **194**. The subsequent protection/deprotection of hydroxyl groups followed by its conversion into azide eventually led to the formation of compound **196**. Removal of MOM and acetonide groups followed by azide reduction and subsequent acetylation gave the tetraacetate derivative of D-*ribo*-phytosphingosine **187**.



Scheme 32. Reaction conditions: (i) $Sn(OTf)_2$, SnO, **190**, propionitrile, 80%. (ii) (a) DIBAL-H, (b) *p*-TsOH, 2,2-DMP, 92%. (iii) *m*-CPBA, 96% (74/26). (iv) CuI, $C_{13}H_{27}MgBr$, 97%. (v) (a) MOMCl, *i*-Pr_2NEt, 93%, (b) H_2, Pd-C, 100%. (vi) (a) MsCl, pyridine, 96%, (b) NaN_3, 83%. (vii) (a) AcOH, H_2O, (b) Ph_3P/H_2O-pyridine, (c) Ac_2O, Et_3N, DMAP, 48% from **196**.

Wu *et al*.[102c] **(1995) Scheme 33**

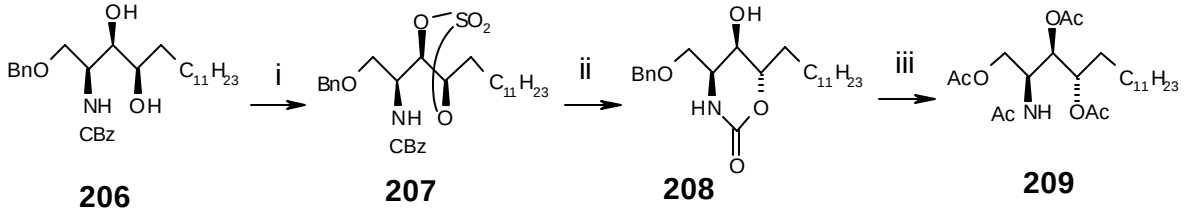
In Wu's approach, the reaction of 2,4-*O*-ethylidene-D-threose **197** (prepared from D-galactose[107]) with prop-2-ynyl bromide/Zn gave **198** (*erythro*:*threo*, 11.7:1). Alkyne substitution, triflation of 2-OH and azide displacement furnished **200**. Deprotection of acetal and hydrogenation of azide and alkyne gave D-*ribo*-phytosphingosine **160**. In order to synthesize L-*lyxo*-phytosphingosine, **201** (prepared from D-xylose[108]) was first converted into the alkyne **202**. Conversion of terminal acetonide into *t*-butyl ether gave **203**. Mesylation of hydroxyl and azide displacement followed by alkyne substitution furnished **205**. Deprotection of acetonide and hydrogenation afforded L-*lyxo*-phytosphingosine **163**.



Scheme 33. Reaction conditions: (i) prop-2-ynyl bromide, Zn, DMF-Et_2O, 85%. (ii) *n*-BuLi, $C_{11}H_{23}Br$, THF-HMPA, 74%. (iii) (a) Tf_2O, pyridine, CH_2Cl_2, −78°C to 0°C, (b) NaN_3, DMF, rt, 82%. (iv) (a) 90% CF_3CO_2H, (b) 10% Pd-C, MeOH. (v) (a) CBr_4, Ph_3P, Zn, CH_2Cl_2, 62%, (b) *n*-BuLi, THF, 89%. (vi) MeMgI, Et_2O-PhMe, reflux, 52%. (vii) (a) MsCl, pyridine, DMAP, CH_2Cl_2, (b) NaN_3, DMF, *n*-Bu_4NI, 110°C, 68%. (viii) LDA, $C_{12}H_{25}Br$, THF-HMPA, 82%. (ix) (a) CF_3CO_2H, 66%, (b) 10% Pd-C, MeOH, 77%.

Pedersen *et al*.[109] (1996) Scheme 34

In Pedersen's approach, the *syn*,*syn*-diol **206** obtained by Pinacol coupling[110] was converted into cyclic sulfate **207**. Compound **207** on heating in CH_3CN at reflux gave the cyclic carbonate **208**. Removal of benzyl protection, saponification of carbonate and acetylation afforded the D-*arabino*-phytosphingosine tetraacetate **209**.

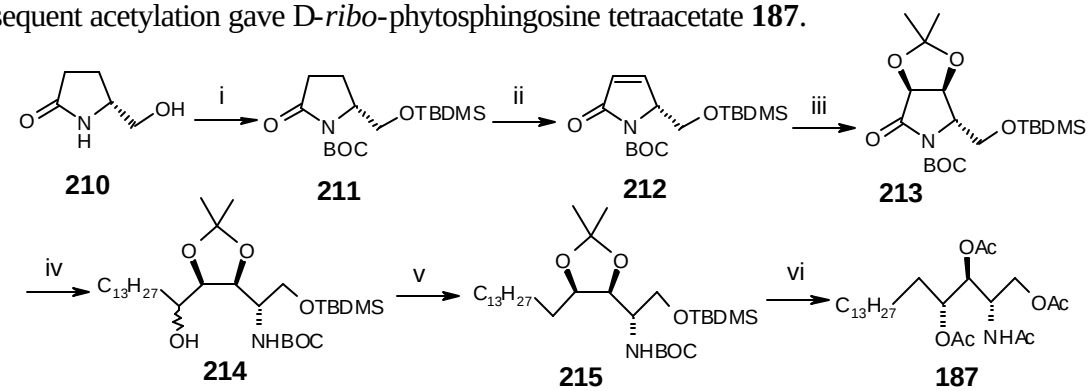


206 **207** **208** **209**

Scheme 34. Reaction conditions: (i) (a) $SOCl_2$, Et_3N, (b) $RuCl_3$, $NaIO_4$, 89%. (ii) (a) CH_3CN, reflux, (b) THF, 2% H_2SO_4. (iii) (a) HCO_2H, 10% Pd/C, (b) LiOH, EtOH, H_2O, (c) Ac_2O, pyridine.

Yoda *et al*.[111] (1996) Scheme 35

In Yoda's approach, the hydroxylactam **210**[112] on successive TBDMS and BOC protection followed by unsaturation gave **212**. Dihydroxylation and acetonide protection followed by treatment with tridecyl magnesium bromide and reduction afforded **214**, which on deoxygenation *via* thioimidazolide led to compound **215**. Deprotection of acetonide, BOC, TBDMS and subsequent acetylation gave D-*ribo*-phytosphingosine tetraacetate **187**.

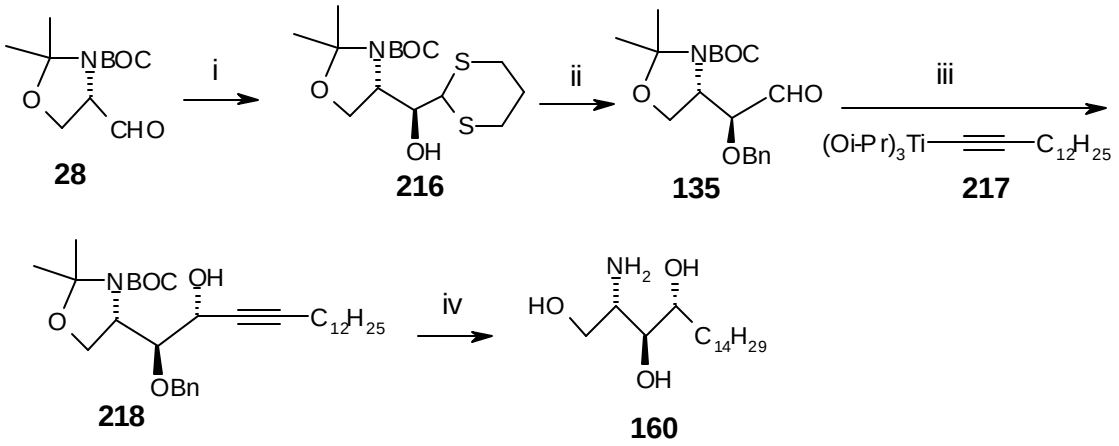


210 **211** **212** **213** **214** **215** **187**

Scheme 35. Reaction conditions: (i) (a) *t*-$BuMe_2Si$-Cl, imidazole, DMF, 88%, (b) $(BOC)_2O$, Et_3N, DMAP, CH_2Cl_2, 90%. (ii) (a) LDA, THF, PhSeBr, −78°C, (b) *m*-CPBA, −78°C. (iii) (a) OsO_4, NMO, acetone-H_2O, 55% from **211**, (b) 2,2-DMP, *p*-TsOH, 100%. (iv) (a) $C_{13}H_{27}MgBr$, −78°C, 60%. (b) $NaBH_4$, EtOH, 88%. (v) (a) (thiocarbonyl)diimidazole, 50°C, 98%, (b) *n*-Bu_3SnH, AIBN, toluene, 100°C, 87%. (vi) (a) CF_3CO_2H, H_2O then KOH, MeOH, 100%, (b) Ac_2O, pyridine, DMAP, 70%.

Fujisawa *et al.*[113] (1997) Scheme 36

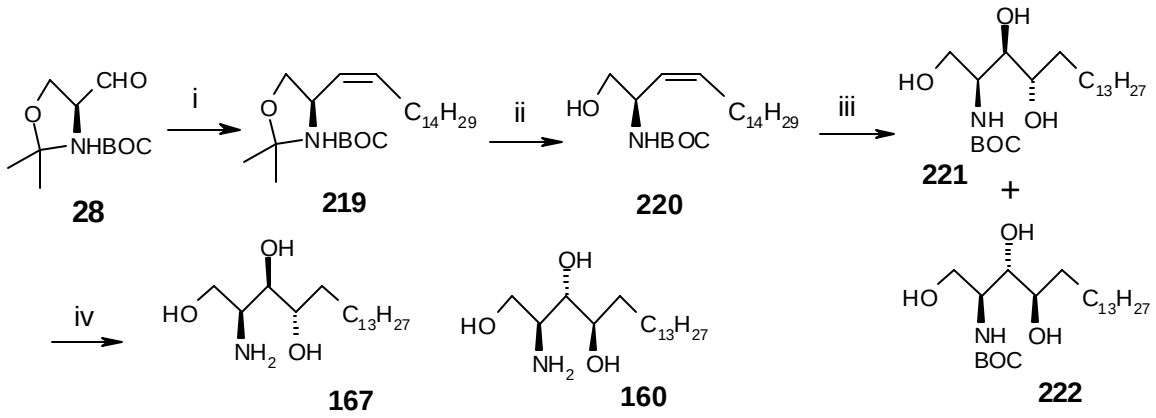
Fujisawa carried out the diastereoselective addition of dithianide to Garner aldehyde **28** with high *anti*-diastereoselectivity to give **216**. Protection of hydroxyl and selective dithiane hydrolysis furnished the aldehyde **135**. Dodecylacetylide **217** addition to aldehyde **135** at lower temperature gave **218** in high *anti*-diastereoselectivity (95% de). Hydrogenation of **218** followed by deprotection of acetonide and BOC groups eventually led to D-*ribo*-phytosphingosine **160**.



Scheme 36. Reaction conditions: (i) Li-dithianide, $BF_3.Et_2O$, CuI, −50°C-rt, THF, 70%. (ii) (a) KHMDS, BnBr, 92%, (b) NBS, 67%. (iii) **217**, −110°C to rt, THF. (iv) (a) 10% Pd-C, H_2, EtOH, 92%, (b) CF_3CO_2H, H_2O, 68%.

Horikawa *et al*.[114] (1998) Scheme 37

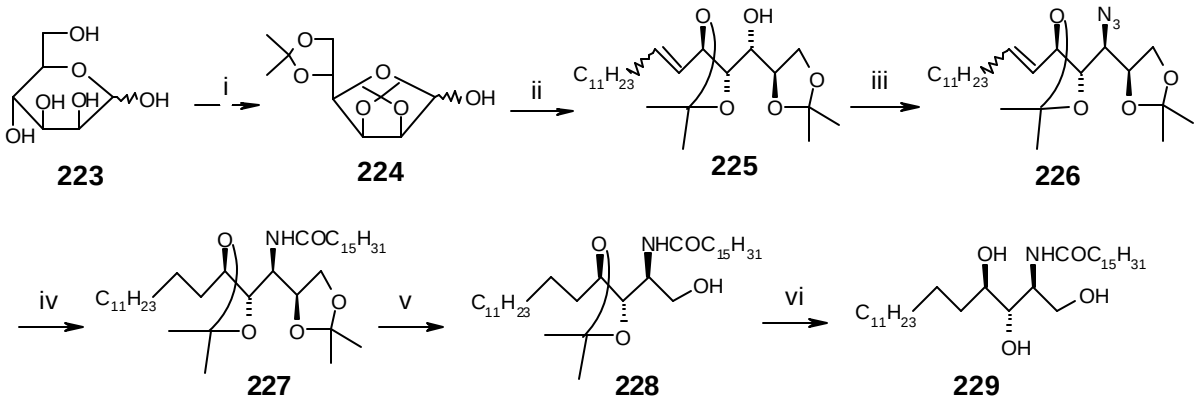
Horikawa carried out diastereoselective dihydroxylation on olefin **220** derived from Garner aldehyde **28**. When AD-mix-α was used in dihydroxylation, compound **221** was obtained in 83% ds; while use of AD-mix-β gave compound **222** in 83% ds. These two compounds on subsequent removal of BOC protecting group furnished D-*arabino* and D-*ribo*-phytosphingosines **167** and **160** respectively in quantitative yield.



Scheme 37. Reaction conditions: $C_{14}H_{29}CH{=}PPh_3$, 71%. (ii) Amberlite IR-120, 93%. (iii) AD-mix-α or AD-mix-β, 86-89%. (iv) (a) CF_3CO_2H, (b) aq. $NaHCO_3$, 96-100%.

Suryawanshi *et al*.[115] (1998) Scheme 38

Suryawanshi *et al*. employed diacetone mannose **224** in Wittig reaction to give the olefin **225**. Triflation of hydroxyl and azide displacement gave **226**, which on reduction followed by acylation furnished the palmitate **227**. Deprotection of terminal acetonide and periodic oxidation followed by reduction gave the alcohol **228**, which on subsequent deprotection of acetonide group led to D-*ribo*-ceramide **229**.

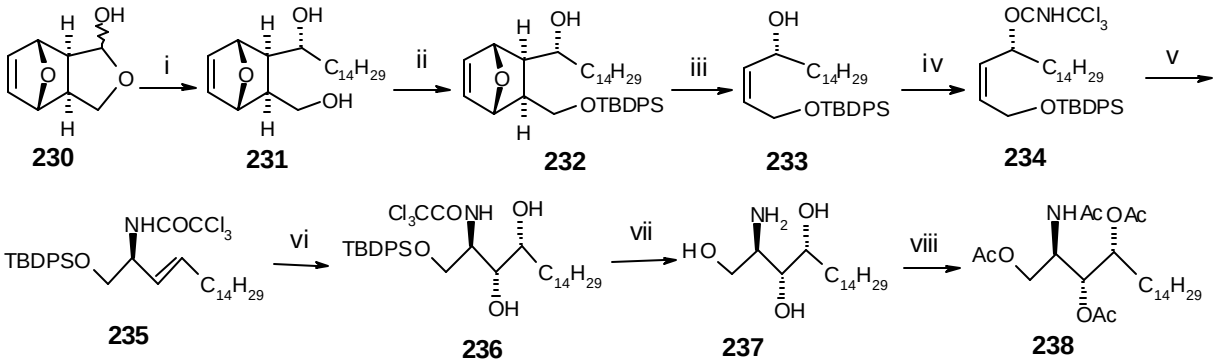


Scheme 38. Reaction conditions: (i) Acetone, H^+. (ii) $C_{12}H_{25}P^+Ph_3Br^-$, *t*-BuOK, $PhCH_3$, 80%. (iii) (a) Tf_2O, pyridine, (b) NaN_3, DMF, 80%. (iv) (a) 10% Pd-C, H_2, EtOAc, 65%, (b) $C_{15}H_{31}CO_2C_6H_4pNO2$, pyridine, 100%. (v) (a) H_5IO_6, EtOAc, (b) $NaBH_4$, EtOH, 60%. (vi) 70% CH_3CO_2H, 100%.

Martin *et al*.[116] (2000) Scheme 39

Martin *et al*. employed the lactol **230**[117] in Grignard reaction to give the diol **231** in 90% de. Primary hydroxyl protection and retro Diels-Alder reaction gave (*Z*)-allylic alcohol **233**, which

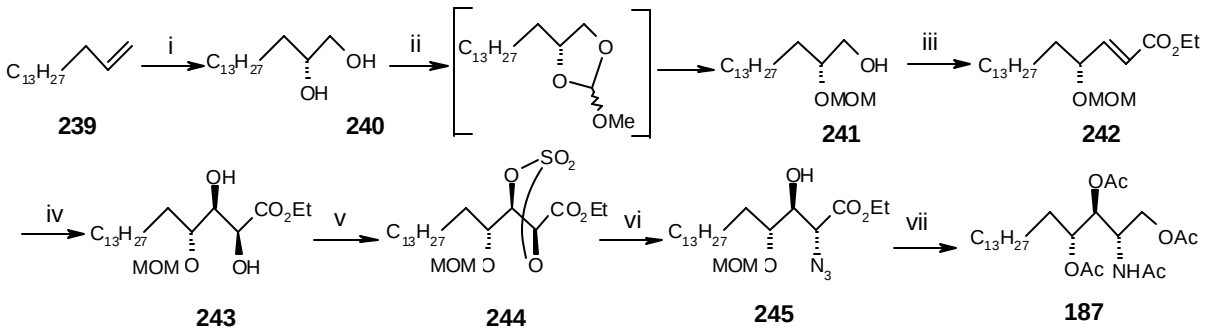
on reaction with trichloroacetonitrile in presence of DBU gave the unstable trichloroacetamide **234**. The subsequent thermal rearrangement afforded (*E*)-allylic trichloroacetamide **235**, which on asymmetric dihydroxylation with AD-mix-β gave **236** in 94% de. Deprotection of TBDPS and hydrolysis of trichloroacetamide, followed by acetylation eventually led to D-*lyxo*-phytosphingosine tetraacetate **238**.



Scheme 39. Reaction conditions: (i) $C_{14}H_{29}MgBr$, THF, 80%. (ii) *t*-$BuMe_2Si$-Cl, imidazole, DMF, 70%. (iii) Microwaves, 100%. (iv) CCl_3CN, DBU, CH_2Cl_2. (v) xylenes, 140°C, 7 h, 81% from **223**. (vi) AD-mix-β, 1% $K_2OsO_2(OH)_4$, $CH_3SO_2NH_2$, H_2O/*t*-BuOH, 4 h, 80%. (vii) (a) *n*-Bu_4NF, THF, 4 h, (b) NaOH, H_2O/C_2H_5OH, 100°C, 16 h, 67%. (viii) Ac_2O, pyridine, DMAP, CH_2Cl_2, 6h, 74%.

Bittman *et al*.[118] (2000) Scheme 40

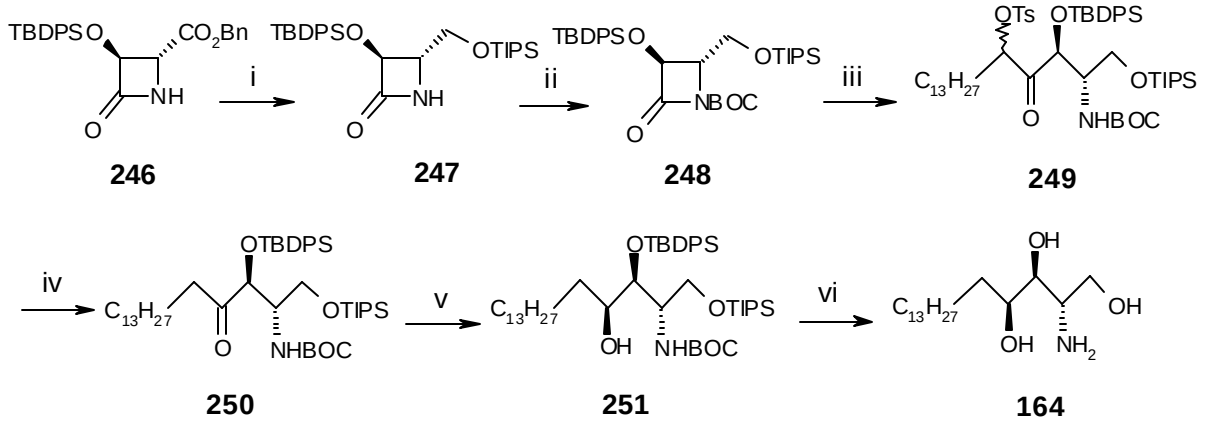
In Bittman's approach, asymmetric dihydroxylation and cyclic sulfate methodology was employed in the synthesis of **187**. Asymmetric dihydroxylation of terminal olefin **239** gave the diol **240**. Selective conversion of secondary hydroxyl into MOM ether *via* orthoacetate and DIBAL-H cleavage furnished **241**. Oxidation of alcohol **241** and Wittig reaction gave the olefin **242** that was subjected to a second asymmetric dihydroxylation to furnish the diol **243** in 91% de. The diol was converted into the cyclic sulfate **244**, which on opening with azide gave **245**. Removal of MOM protection, reduction of azide and ester followed by acetylation furnished D-*ribo*-phytosphingosine tetraacetate **187**.



Scheme 40. Reaction conditions: (i) AD-mix-β, *t*-BuOH, H_2O, 0°C, 95%. (ii) $CH(OMe)_3$, CH_2Cl_2, D-10-camphor sulfonic acid, rt, then DIBAL-H, −78°C, 96%, (iii) (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°C to −46°C, (b) $(i\text{-PrO})_2POCH_2CO_2Et$, LiBr, Et_3N, THF, rt, 86%. (iv) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH, H_2O, 0°C, 92%. (v) (a) $SOCl_2$, pyridine, CH_2Cl_2, 0°C, (b) $NaIO_4$, $RuCl_3$, MeCN, H_2O, rt, 88%. (vi) (a) NaN_3, Me_2CO, H_2O, rt, (b) 20% H_2SO_4, Et_2O, rt, 93%. (vii) (a) conc. HCl, MeOH, rt, 100%. (b) $LiAlH_4$, THF, 65°C, 78%, (c) Ac_2O, DMAP, pyridine, rt, 94%.

Shiozaki *et al*.[119] (2001) Scheme 41.

Shiozaki utilized the chiral β-lactam **246** obtained from D-tartaric acid.[120] Reduction of **246** and hydroxyl protection followed by BOC protection yielded **248**. Compound **248** was converted into α-sulfonyl ketone **249**. Removal of *p*-toluene sulfonyl moiety followed by diastereoselective reduction of ketone furnished **251** in 92% ds. The subsequent removal of silyl groups and BOC deprotection afforded L-*lyxo*-phytosphingosine **164**.

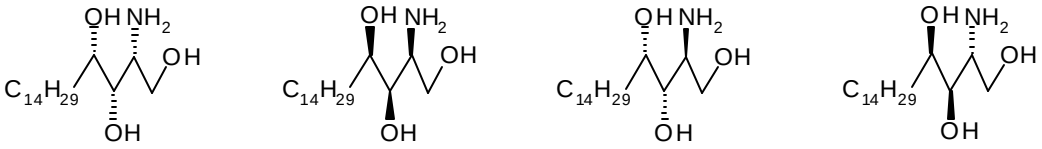


Scheme 41. Reaction conditions: (i) (a) $NaBH_4$, EtOH, rt, 1 h, 73%, (b) *i*-Pr_3Si-Cl, imidazole, DMF, rt, 4 h, 95%. (ii) $(BOC)_2O$, Et_3N, DMAP, CH_2Cl_2, rt, 1 h, 100%. (iii) $C_{14}H_{29}SO_2C_6H_4Me$, *n*-BuLi, THF, −78°C, 1 h, 88%. (iv) Li-naphthalenide, THF, −78°C, 20 min, 93%. (v) $LiEt_3BH$, THF, −78°C, 1 h, 86%. (vi) (a) *n*-Bu_4NF, THF, rt, 2 h, (b) 10% HCl in MeOH, 40°C, 9 h, 96%.

3.3.3. Present Work

Objective:

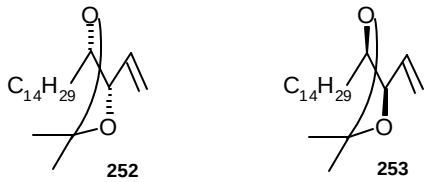
Given the vast chemistry, structural modifications and biological activities associated with the sphingolipids, the synthesis of this class of vicinal amino alcohols has aroused considerable interest among several research groups round the world. Although a few syntheses are reviewed above, several more are documented in the literature. This explains the importance of research work in sphingolipid chemistry. With the completion of synthesis of D-(+)-*erythro*-dihydrosphingosine[80] through asymmetric dihydroxylation coupled with the chemistry of cyclic sulfites/sulfates and cyclic benzylidene, our attention was further focused to extrapolate the above knowledge to the enantioselective total synthesis of C_{18}-phytosphingosines. Most syntheses in C_{18}-phytosphingosines are in the *arabino*- and *ribo*- series and only a few syntheses of *lyxo*- and *xylo*- isomers are known.



161 L-*xylo* [2*R*,3*S*,4*S*] **162** D-*xylo* [2*S*,3*R*,4*R*] **163** L-*lyxo* [2*S*,3*S*,4S] **164** D-*lyxo* [2*R*,3*R*,4*R*]

Figure 10

The *lyxo*- and *xylo*-isomers have the *syn*-placement of 3,4-hydroxyl groups (**Figure 10**). We envisaged therefore fixing these chiral centers first by asymmetric dihydroxylation. With a view to investigate the double diastereoselection in asymmetric dihydroxylation of chiral olefins, i.e. the influence of substrate chirality and the ligand induction, we synthesized the terminal olefins **252** and **253**. As it is well known that in the matched case, a good diastereoselection would result, we planned to elaborate the corresponding diol products from **252** and **253** towards the syntheses of *xylo*- and *lyxo*-isomers of C_{18}-phytosphingosines.



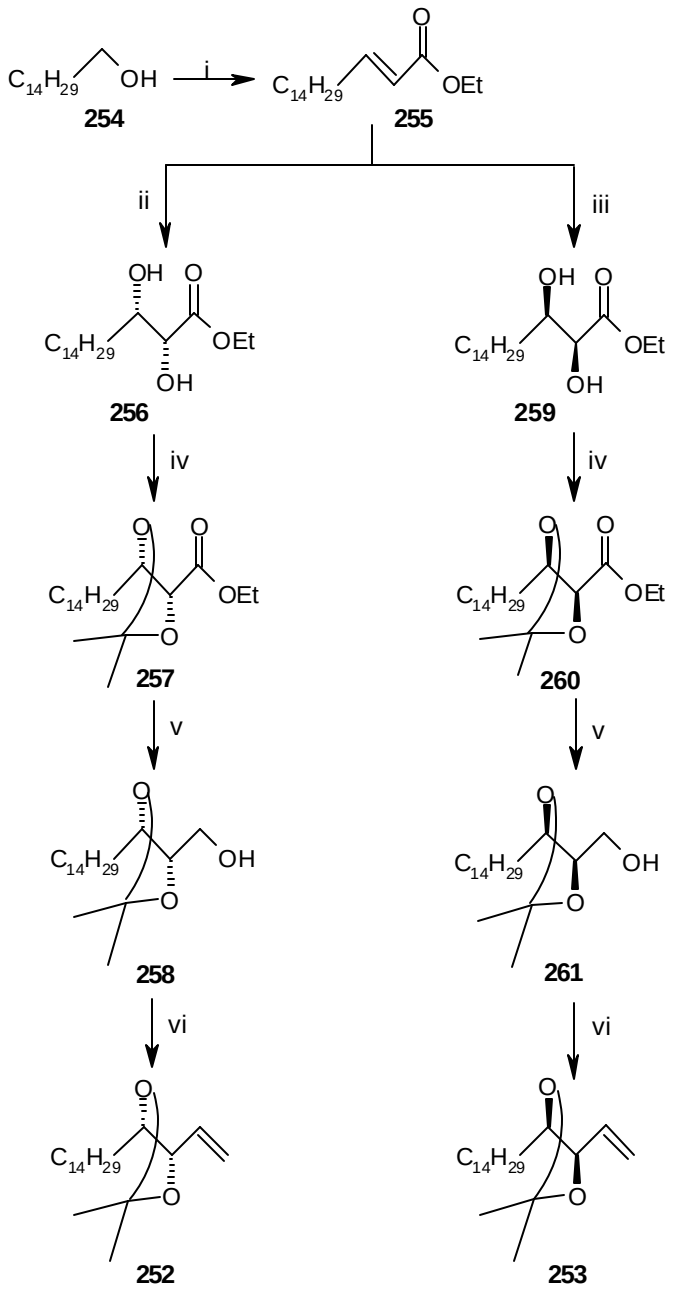
252 **253**

Thus, the objective of the present investigation is to study the double diastereoselection in asymmetric dihydroxylation and syntheses of *xylo*- and *lyxo*-C_{18}-phytosphingosines. In the present work we have undertaken the first synthesis of L-*xylo*-C_{18}-phytosphingosine. So far there has been no report of its synthesis in the literature.

3.3.4. Results and Discussion

With a view to explore the concept of double diastereoselection, we prepared the enantiomerically enriched terminal olefins **252** and **253** following the reaction steps as shown in **Scheme 42**. The commercially available pentadecanol **254** was oxidized to the aldehyde and subsequently treated with (ethoxycarbonylmethylene)triphenylphosphorane to give the Wittig product **255**. The IR spectrum of **255** gave carbonyl absorption at 1717 cm^{-1} and C=C stretching at 1653 cm^{-1}. The ^1H NMR spectrum gave olefin peaks at δ 5.8 (doublet of triplet) and 6.97 (doublet of triplet) with the coupling constant J = 16 Hz indicating *trans*-olefin. The asymmetric dihydroxylation of olefin **255** using $(DHQ)_2$-PHAL ligand under the Sharpless asymmetric dihydroxylation conditions gave the diol **256** in 94% yield and 99% ee.[121a] In the IR spectrum, the olefin absorption was absent and hydroxyl absorption appeared at 3372 cm^{-1}. The ^1H NMR spectrum showed chiral protons at δ 3.86 (multiplet) and 4.06 (multiplet). The corresponding chiral carbons appeared at δ 72.52 and 73.32 in the ^{13}C NMR spectrum. Protection of the diol **256** with 2,2-dimethoxypropane and catalytic *p*-TsOH gave the acetonide ester **257** in 98% yield. The IR spectrum of **257** indicated absence of hydroxyl groups. The acetonide methyl protons appeared at δ 1.43 (singlet) and 1.46 (singlet) in the ^1H NMR spectrum and the typical quaternary carbon of acetonide appeared at δ 110.82 in the ^{13}C NMR spectrum. The reduction of ester group in **256** with lithium aluminium hydride gave alcohol **258** in excellent yield. The IR spectrum of **258** gave hydroxyl absorption at 3440 cm^{-1} and the ester carbonyl group was absent. The primary alcohol was oxidized to the aldehyde under the normal Swern oxidation conditions. Subsequent Wittig reaction with ylide generated from methyltriphenylphosphoniumiodide and NaHMDS furnished the olefin **252** in 77% yield. The IR spectrum of **252** showed absence of hydroxyl absorption. The ^1H NMR spectrum of **252** gave olefin peaks at δ 5.2-5.4 (multiplet, two protons) and 5.7-5.9 (multiplet, one proton). Similarly the enantiomer of **252** i.e., **253** was prepared from **255** *via* β-dihydroxylation using $(DHQD)_2$-PHAL and following the reaction sequence as shown in **Scheme 42**.

In the SAD of olefins, the stereochemical outcome of the reaction may be influenced by the presence of pre-existing chirality in the substrate. In double diastereoselective SAD reactions of chiral olefins, the level of diastereoselectivity in both the matched and mismatched reactions varies with the chiral ligands.



Scheme 42. Reaction conditions: (i) (a) P_2O_5, DMSO, CH_2Cl_2, Et_3N, 0°C, (b) $Ph_3P{=}CHCO_2Et$, THF, reflux, 12 h, 90%. (ii) $(DHQ)_2$-PHAL, OsO_4, $MeSO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH:H_2O [1:1], 24 h, 0°C, 94%. (iii) $(DHQD)_2$-PHAL, OsO_4, $MeSO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH:H_2O [1:1], 24 h, 0°C, 94%. (iv) 2,2-DMP, $(CH_3)_2CO$, *p*-TsOH, rt, overnight, 98%. (v) $LiAlH_4$, Et_2O, 0°C to rt, overnight, 93%. (vi) (a) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78°C, (b) $Ph_3P^+CH_3I^-$, NaHMDS, THF, 0°C to rt, 12 h, 77%.

Having obtained the enantiomerically enriched terminal olefins **252** and **253**, we subjected them to the Sharpless asymmetric dihydroxylation reaction by varying the ligands employed. The results of double diastereoselection are given in **Table 5**.

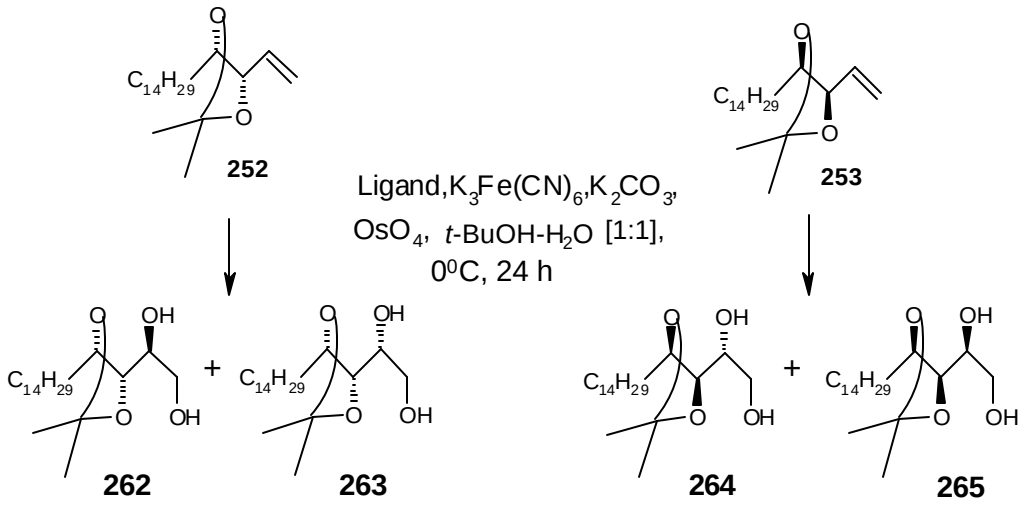


Table 5. Double diastereoselection in SAD reaction of **252** and **253**.[121b]

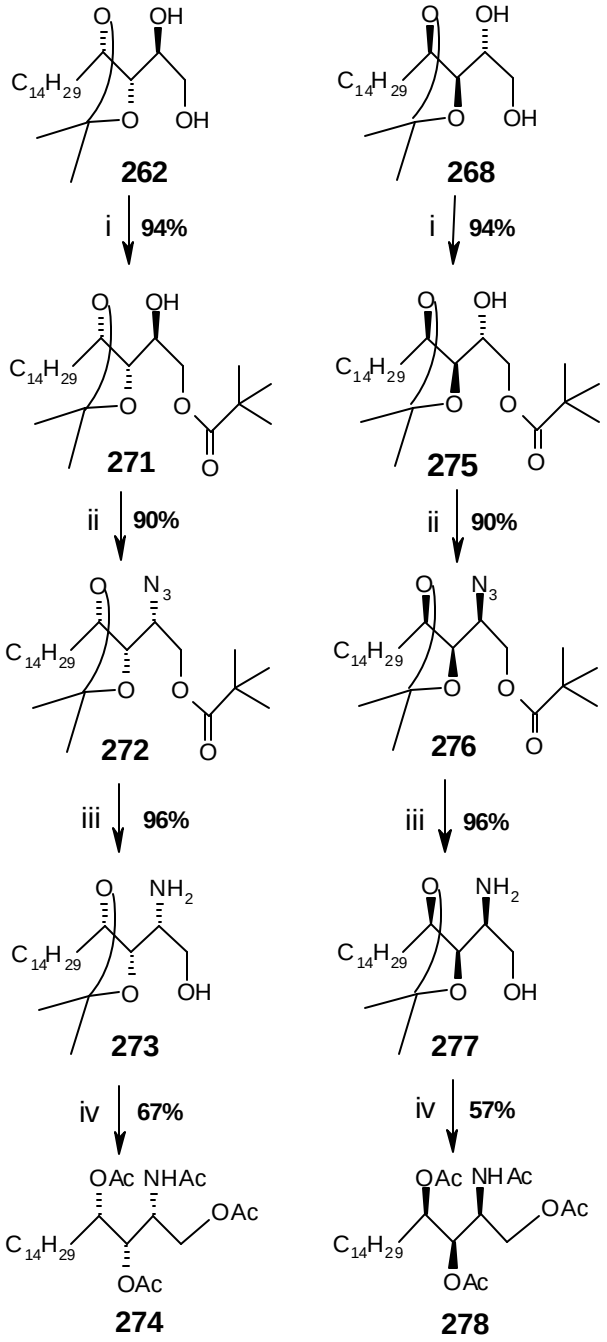
Olefin	Ligand	**262**	**263**	**264**	**265**	Yield%	Diastereomeric Mixture $[\alpha]_D^{20}$ (c = 1, $CHCl_3$)
252	$(DHQ)_2$PHAL	1	2	-	-	89	**266**, – 17.3
252	$(DHQD)_2$PHAL	5	1	-	-	92	**267**, – 19.5
252	$(DHQD)_2$AQN	6	1	-	-	69	**262**, – 20.1 Pure diastereomer
253	$(DHQ)_2$PHAL	-	-	5.45	1	93	**268**, + 20.3
253	$(DHQD)_2$PHAL	-	-	1	2	92	**269**, + 18.2
253	Pyridine	-	-	4.3	1	83	**270**, + 18.7

Thus, when the olefin **252** was subjected to the Sharpless asymmetric dihydroxylation using $(DHQ)_2$-PHAL ligand, the diastereomers **262** and **263** were obtained in 1:2 ratio, whereas a considerable enhancement in the diastereomeric ratio of **262**:**263** (5:1) was observed with the use of $(DHQD)_2$-PHAL ligand (**Table 1**). The poor diastereoselectivity observed in the former case may be because of opposite influences of the chiral reagent and substrate (mismatched case) while the latter could be regarded as matched case where the chirality information of the reagent

and the substrate probably act synergistically and therefore, a high degree of diastereoselection was obtained. The use of $(DHQD)_2$-AQN ligand showing a marginal improvement in the diastereomeric ratio of **262**:**263** (6:1) could be regarded as another example of matched case (**Table 5**). Similar results were obtained with olefin **253** giving diastereomers **264** and **265** in 5.45:1 ratio with the use of $(DHQ)_2$-PHAL ligand and in 1:2 ratio with $(DHQD)_2$-PHAL ligand (**Table 5**). Interestingly, when the olefin **253** was subjected to the Sharpless asymmetric dihydroxylation reaction conditions using pyridine instead of cinchona alkaloid as ligand, the diastereomers **264** and **265** were obtained in 4.3:1 ratio showing relatively a good diastereoselection (**Table 5**). This could be explained on the basis of the chirality present in the substrate, which has significant influence on diastereoselection and the stereochemical course of the reaction. It may be pertinent to mention here that although a few examples of matched and mismatched double diastereoselection in the SAD of chiral olefins have been reported, the levels of diastereoselection observed in the SAD of chiral monosubstituted olefin are not as high as those observed for the other olefin substitution classes.[122]

Further, we extended the above results towards the synthesis of L-*xylo*-(2*R*,3*S*,4*S*)-C_{18}-, D-*xylo*-(2*S*,3*R*,4*R*)-C_{18}-, L-*lyxo*-(2*S*,3*S*,4*S*)-C_{18}-, and D-*lyxo*-(2*R*,3*R*,4*R*)-C_{18}–phytosphingosines. The diastereomeric mixture of **262**:**263** in 6:1 ratio was separated by flash column chromatography on a TLC mesh silica gel[123] to give **262** in diastereomerically pure form in 69% yield. The pure diastereomer **262** was converted into L-*xylo*-(2*R*,3*S*,4*S*)-C_{18}-phytosphingosine **161** as its tetraacetate derivative **274** as shown in **Scheme 43**.

Compound **262** had $[\alpha]_D^{20}$ – 20.1 (c = 1, $CHCl_3$). The IR spectrum of **262** gave broad hydroxyl absorption at 3358-3250 cm^{-1}. The hydroxyl protons appeared at δ 2.62 (broad singlet) and the chiral protons at δ 3.55-3.76 (multiplet, two protons) and 3.8-4.0 (multiplet, one proton) in the ^1H NMR spectrum. Protection of the primary hydroxyl group of **262** was carried out using pivaloyl chloride and pyridine at 0°C to give **271**. The pivaloate carbonyl appeared at 1725 cm^{-1} in the IR spectrum of **271** and the *t*-butyl protons appeared at δ 1.23 (singlet, 9 protons) in the ^1H NMR spectrum. The carbonyl carbon appeared at δ 178.67 in the ^{13}C NMR spectrum. The C-2 hydroxyl was then converted into the azido functionality through mesylation with methanesulfonyl chloride, pyridine and catalytic DMAP, followed by the nucleophilic displacement with LiN_3 to give **272** in 88% yield, with inversion of configuration at C-2. The IR spectrum of **272** gave prominent azide absorption at 2116 cm^{-1}. The protection of the primary

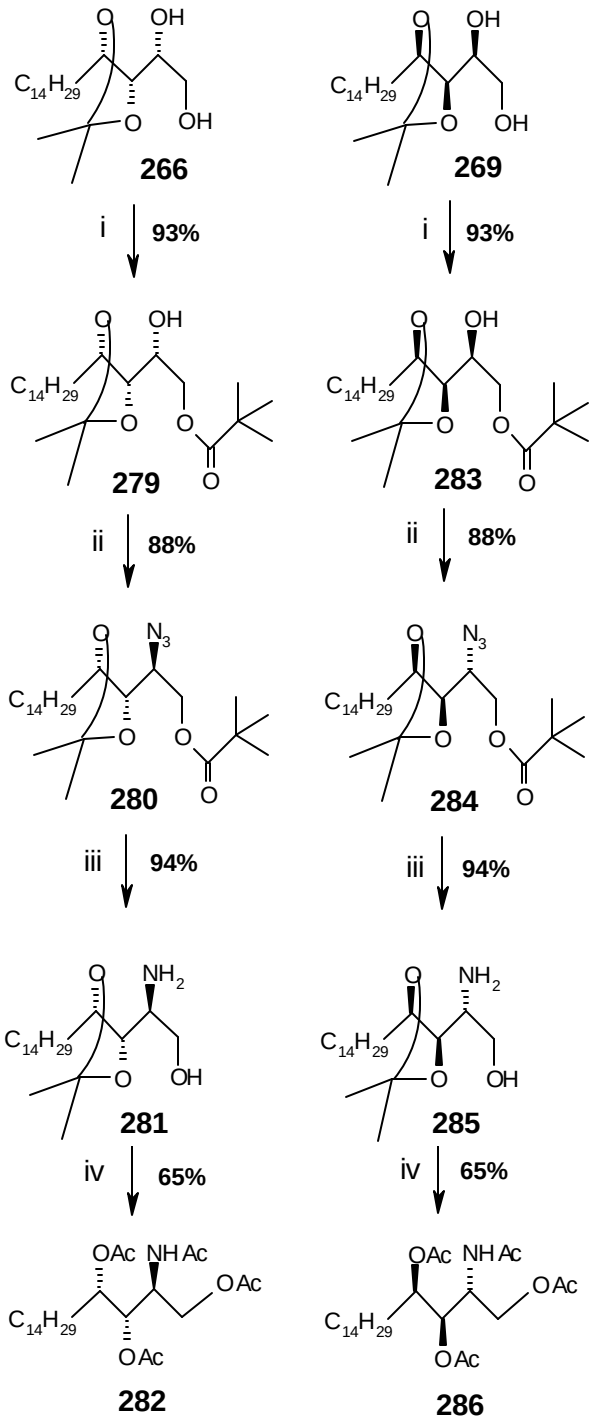


Scheme 43. Reaction conditions: (i) Pivaloyl chloride, pyridine, CH_2Cl_2, 0°C to rt, overnight. (ii) (a) $MeSO_2Cl$, pyridine, DMAP (cat), CH_2Cl_2, 60°C, overnight, (b) LiN_3, DMF, 80°C, 12 h. (iii) $LiAlH_4$, Et_2O, 0°C to rt, overnight. (iv) (a) 6N HCl, MeOH, rt, overnight, (b) Ac_2O, pyridine, DMAP (cat), CH_2Cl_2, rt, 12 h.

hydroxyl group as a pivaloate was advantageous over other protecting groups since both pivaloate deprotection and azide reduction could be accomplished together under the same conditions. Thus, the lithium aluminium hydride reduction of **272** gave the amino alcohol **273** in

excellent yield of 96%. The IR spectrum of **273** gave hydroxyl and amine absorptions at 3370 and 3357 cm^{-1} and absence of pivaloate carbonyl. In an attempt to obtain amino alcohol **273** by an alternative approach, the terminal olefin **252** was subjected to the Sharpless asymmetric aminohydroxylation reaction using $(DHQD)_2$-PHAL ligand. However, it gave a complex mixture of compounds, which could not be isolated. Deprotection of the acetonide in **273** was effected with 6N HCl in MeOH to give the hydrochloride salt of (2*R*,3*S*,4*S*)-2-amino-1,3,4-trihydroxyoctadecane. This was subsequently acetylated using Ac_2O, pyridine and catalytic amount of DMAP to give the tetraacetate **274** of L-*xylo*-(2*R*,3*S*,4*S*)-C_{18}-phytosphingosine **161** in diastereomerically pure form (**Figure 11A**), having $[\alpha]_D^{20}$ – 7.2 (c = 1.2, $CHCl_3$) [lit $[\alpha]_D^{21}$ + 7.0 (c = 0.86, $CHCl_3$)[124] for enantiomer of **274**]. The IR spectrum of **274** gave amine absorption at 3297-3290 cm^{-1}, acetyl carbonyls at 1744 cm^{-1} and amide carbonyl at 1662 cm^{-1}. The ^1H NMR spectrum of **274** gave acetyl methyl protons at δ 2.03 (singlet, one methyl), 2.04 (singlet, two methyl) and 2.07 (singlet, one methyl), the chiral protons at δ 4.5 (multiplet, one proton), 5.02-5.18 (multiplet, two potons) and the amide proton at δ 5.92 (doublet with *J* =10 Hz). The ^{13}C NMR spectrum gave the chiral carbons at δ 48.00, 71.26 and 71.93 and four carbonyl carbons at δ 169.45, 169.52, 169.78, 169.85. The EIMS of **274** gave $[M^+]$ peak at *m/z* 486 and other characteristic peaks at 292, 144 and 84.

Following the similar reaction sequence, the diastereomeric mixture **268** was converted into the tetraacetate **278** of D-*xylo*-(2*S*,3*R*,4*R*)-C_{18}-phytosphingosine **162** (69% de, **Scheme 43**). Pure diastereomer **278** was further separated from the mixture by column chromatography on TLC mesh silica gel[123] (**Figure 11C**). Similarly diastereomeric mixture **266** was converted into the tetraacetate **282** of L-*lyxo*-(2*S*,3*S*,4*S*)-C_{18}-phytosphingosine **163** (33% de) and **269** into the tetraacetate **286** of D-*lyxo*-(2*R*,3*R*,4*R*)-C_{18}-phytosphingosine **164** (33% de, **Scheme 44**).



Scheme 44. Reaction conditions: (i) Pivaloyl chloride, pyridine, CH_2Cl_2, 0°C to rt, overnight. (ii) (a) $MeSO_2Cl$, pyridine, DMAP (cat), CH_2Cl_2, 60°C, overnight. (b) LiN_3, DMF, 80°C, 12 h. (iii) $LiAlH_4$, Et_2O, 0°C to rt, overnight. (iv) (a) 6N HCl, MeOH, rt, overnight, (b) Ac_2O, pyridine, DMAP (cat), CH_2Cl_2, rt, 12 h.

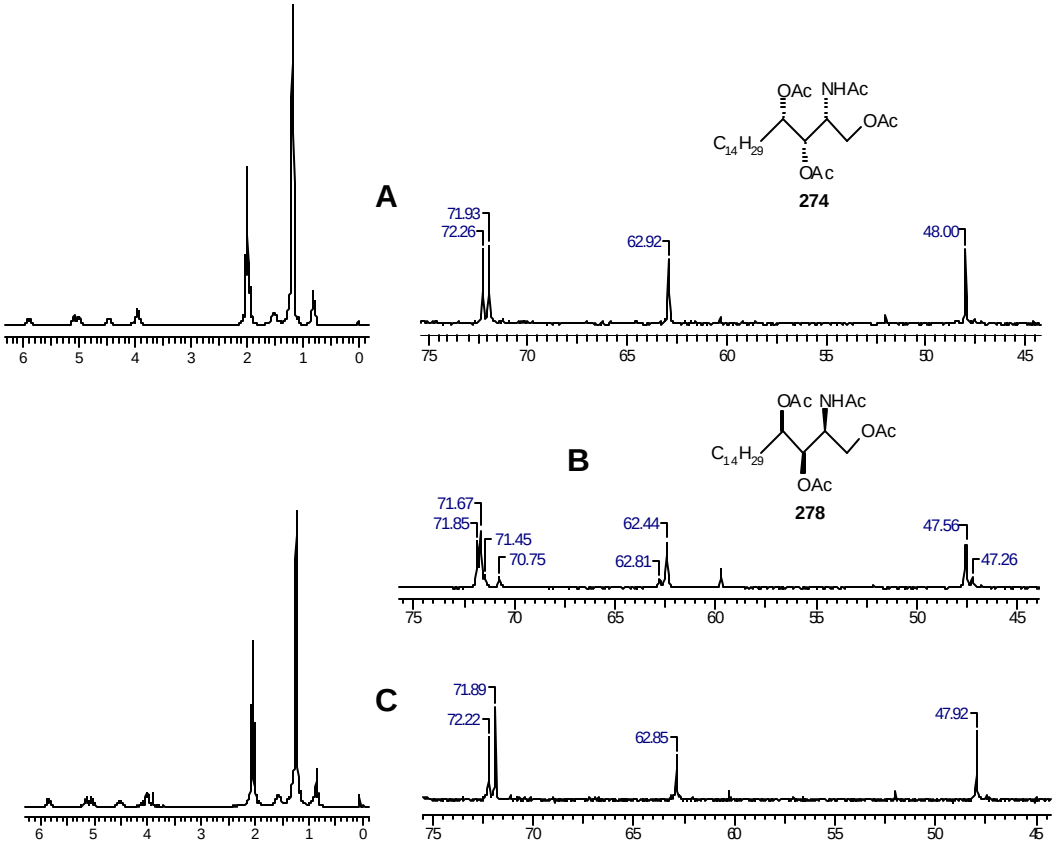


Figure 11: (**A**) ^{1}H NMR and partial ^{13}C NMR spectra of pure diastereomer **274**. (**B**) Partial ^{13}C NMR spectrum of diastereomeric mixture **278** (69% de) before separation showing diastereomeric peaks. (**C**) ^{1}H NMR and partial ^{13}C NMR spectra of pure diastereomer **278** after separation.

3.3.5. Conclusion

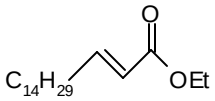
We have exploited the concept of double diastereoselection in Sharpless asymmetric dihydroxylation reaction and applied the results obtained toward the diastereoselective synthesis of four of the eight isomers of C_{18}-phytosphingosine.[125] The diastereomeric mixture obtained could be separated by TLC mesh silica gel column chromatography. Thus, the L-*xylo*-(2*R*,3*S*,4*S*)-C_{18}- and D-*xylo*-(2*S*,3*R*,4*R*)-C_{18}-phytosphingosines were synthesized in diastereomerically pure form. The synthetic strategy employed can be further extended toward the synthesis of the *arabino*- and *ribo*- isomers by employing the *cis*-olefin for step (ii and iii) in **Scheme 42**. Thus, the diastereoselective synthesis of all the eight isomers of C_{18}-phytosphingosine can be achieved through a single synthetic strategy.

3.3.6. Experimental Section

General information

Solvents were purified and dried by standard procedures before use. Petroleum ether of boiling range 60-80°C was used. Melting points are uncorrected. Optical rotations were measured using sodium D line on a JASCO P-1020 microprocessor based polarimeter. Infrared spectra were recorded on ATI MATTSON RS-1 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC-200 spectrometer. In the ^{13}C NMR data, peaks of only the major diastereomer (in case of a mixture) are given. Mass spectra were obtained with a TSQ 70, Finningen MAT mass spectrometer. Elemental analyses were carried out on a Carlo Erba CHNS-O analyzer.

Synthesis of ethyl *trans*-heptadec-2-enoate, 255



255

A two-necked round bottom flask was charged with pentadecanol **254** (8 g, 35 mmol) in CH_2Cl_2 (200 mL) under nitrogen and then ice cooled. DMSO (5 mL, 70.42 mmol) and P_2O_5 (10 g, 70.42 mmol) were added sequentially. The reaction mixture was stirred and allowed to warm to room temperature until the TLC showed complete disappearance of the starting material (45 min). The flask was cooled to 0°C and Et_3N (17 mL) was added dropwise over one minute. Stirring was continued for 45 min in ice bath and another 45 min at room temperature. The reaction mixture was quenched with 10% aq. HCl (150 mL) and the solution extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuum to give pentadecanal as pale yellow oil, which was used in the next step without further purification.

To a solution of (ethoxycarbonylmethylene)triphenylphosphorane (14 g, 40.33 mmol) in dry THF (100 mL) was added dropwise a solution of pentadecanal in THF (10 mL) at room temperature. The reaction mixture was refluxed for 12 h. The solvent was removed under reduced pressure and the crude product was purified on a silica gel column using petroleum ether:EtOAc (9:1) as eluent to give **255** (9.34 g) as a colorless oil.

Yield: 9.34 g, 90%

IR (neat, cm^{-1}): n_{max} 2926, 1717, 1653, 1461, 1269, 1183, 1043, 758, 420

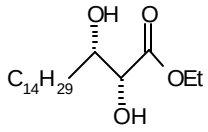
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88, (t, *J* = 7 Hz, 3H), 1.23-1.3 (m, 22H), 1.32 (t, *J* = 8 Hz, 3H), 1.45 (m, 2H), 2.2 (dd, $J_{allylic}$ = 6 Hz, 2H), 4.20 (q, *J* = 8 Hz, 2H), 5.8 (dt, J_{trans} = 16 Hz, 1H), 6.97 (dt, J_{trans} = 16 Hz, $J_{allylic}$= 6 Hz, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.63, 13.81, 22.34, 27.74, 28.85, 29.07, 29.36, 31.60, 59.4, 121, 148.46, 165.8

EIMS (*m/z* relative intensity, %): 296 [M^+] (14.9), 251 (35), 250 (36.3), 199 (28.6), 155 (40), 127 (99), 101 (100), 83 (25), 69 (7.1), 55 (5.9)

Analysis: $C_{19}H_{36}O_2$ (296.5) requires C, 76.97; H, 12.24. Found: C, 77.01; H, 12.16.

Synthesis of (2*R*,3*S*) ethyl-2,3-dihydroxyheptadecanoate, 256



256

To a mixture of $K_3Fe(CN)_6$ (9.98 g, 30.35 mmol), K_2CO_3 (4.2 g, 30.35 mmol) and $(DHQ)_2$-PHAL (79 mg, 102 μmol, 1 mol%) in *t*-BuOH-H_2O (1:1, 120 mL) cooled at 0°C was added osmium tetroxide (410 μL, 0.1M solution in toluene, 0.4 mol%) followed by methane-sulfonamide (0.964 g, 10.12 mmol). After stirring for 5 min at 0°C, the olefin **255** (3 g, 10.12 mmol) was added in one portion. The reaction mixture was stirred at 0°C for 24 h and then quenched with solid sodium sulfite (5 g). The stirring was continued for an additional 45 min and then the solution was extracted with EtOAc (5 × 30 mL). The combined organic phases were washed with 10% KOH, brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether:EtOAc (3:2) as eluent gave **256** (3.15 g) as a white solid.

Yield: 3.15 g, 94%

M.p.: 77-78°C

[a]$_D^{20}$: – 10.13 (c = 1, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): n_{max} 3372, 2916, 1712, 1463, 1293, 1088, 491

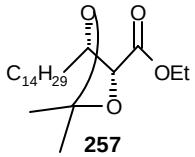
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.85 (t, *J* = 6 Hz, 3H), 1.2-1.3 (m, 24H), 1.31 (t, *J* = 8 Hz, 3H), 1.56 (m, 2H), 3.1 (brs, 2H), 3.86 (m, 1H), 4.06 (m, 1H), 4.24 (q, *J* = 8 Hz, 2H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.89, 13.9, 22.5, 25.61, 29.18, 29.51, 31.75, 33.33, 61.49, 72.52, 73.32, 173.53

EIMS (*m/z* relative intensity, %): 329 [M^+–1] (0.64), 312 (0.7), 257 (4.12), 239 (1.5), 104 (100), 76 (8.5), 57 (2.5)

Analysis: $C_{19}H_{38}O_4$ (330.5) requires C, 69.05; H, 11.58. Found: C, 68.94; H, 11.67.

Synthesis of ethyl (2*R*,3*S*)-2,3-*O*-isopropylideneheptadecanoate-2,3-diol, 257



257

To a solution of the diol **256** (8 g, 24.2 mmol), *p*-TsOH (200 mg) in acetone (200 mL) was added 2,2-dimethoxypropane (3.53 g, 33.9 mmol) and stirred overnight. Solid $NaHCO_3$ (1 g) was added and stirred for 30 min. The reaction mixture was filtered through a pad of neutral alumina and concentrated. Silica gel column chromatography using petroleum ether:EtOAc (24:1) gave **257** (8.79 g) as a colorless liquid.

Yield: 8.79 g, 98%

$[\alpha]_D^{20}$: – 10.87 (c = 1, $CHCl_3$)

IR (neat, cm^{-1}): n_{max} 2927, 1746, 1214, 1097, 462

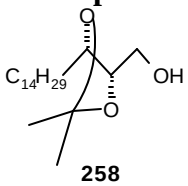
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6 Hz, 3H), 1.2-1.3 (m, 24H), 1.31 (t, *J* = 8 Hz, 3H), 1.43 (s, 3H), 1.46 (s, 3H), 1.70 (m, 2H), 4.10-4.19 (m, 2H), 4.25 (q, *J* = 8 Hz, 2H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.22, 14.28, 22.86, 25.79, 27.34, 29.7, 29.88, 32.14, 33.75, 61.22, 79.39, 79.41, 110.82, 171.06

EIMS (*m/z* relative intensity, %): 369 [M^+–1] (1.3), 355 [M^+–15] (100), 341 (7.7), 297 (34.6), 239 (10.2), 144 (21.8), 109 (43.6), 59 (11.5)

Analysis: $C_{22}H_{42}O_4$ (370.6) requires C, 71.3; H, 11.42. Found: C, 71.44; H, 11.38.

Synthesis of (2*S*,3*S*)-2,3-*O*-isopropylideneheptadecane-1,2,3-triol, 258



258

To a stirred suspension of $LiAlH_4$ (0.615 g, 16.2 mmol) in dry Et_2O (100 mL) at 0°C was added the solution of **257** (4 g, 10.8 mmol) in Et_2O (10 mL) dropwise. The reaction mixture was

allowed to warm to room temperature and stirred overnight. Excess $LiAlH_4$ was destroyed by slow addition of 10% aq NaOH (2 mL) and EtOAc (20 mL). The white precipitate was filtered through a pad of neutral alumina and washed with MeOH (3 × 100 mL). The filtrate was concentrated and the residue was purified by silica gel column chromatography using petroleum ether:EtOAc (4:1) as eluent to give **258** (3.3 g) as a white solid.

Yield: 3.3 g, 93%

M.p.: 45-46°C

$[\alpha]_D^{20}$: − 16.50 (c = 1, MeOH)

IR ($CHCl_3$, cm^{-1}): n_{max} 3440, 2926, 1460, 1361, 1216, 764, 667

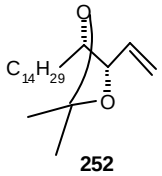
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7 Hz, 3H), 1.2-1.3 (m, 24H), 1.4 (s, 3H), 1.41 (s, 3H), 1.54 (m, 2H), 2.17 (brs, 1H), 3.55-3.63 (m, 1H), 3.7-3.85 (m, 2H), 3.93 (m, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.89, 22.56, 25.24, 25.43, 25.83, 26.53, 26.97, 27.27, 29.21, 29.54, 31.82, 33.11, 62.26, 77.15, 81.67, 108.47

EIMS (*m/z* relative intensity, %): 329 [M^++1] (1.3), 314 [M^+−15] (100), 297 (27), 231 (2.6), 109 (12.8), 95 (14.1), 59 (1.3)

Analysis: $C_{20}H_{40}O_3$ (328.5) requires C, 73.12; H, 12.27. Found: C, 72.96; H, 12.36.

Synthesis of (3*S*,4*S*)-3,4-*O*-isopropylideneoctadec-1-ene-3,4-diol, 252



252

To a solution of oxalyl chloride (1.74 g, 1.2 mL, 13.7 mmol) in dry CH_2Cl_2 (75 mL) cooled at −78°C was added dropwise DMSO (1.95 mL, 27.4 mmol) in CH_2Cl_2 (5 mL) over 20 min. The reaction mixture was stirred for 30 min at −78°C and the solution of alcohol **258** (3 g, 9.13 mmol) in CH_2Cl_2 (10 mL) was added dropwise at −60°C over 20 min. The reaction mixture was stirred for 30 min when a copious white precipitate was obtained. Et_3N (5.8 mL, 41 mmol) was added dropwise and stirred for 1 h allowing the temperature to rise to room temperature. The reaction mixture was quenched with 5% aq. HCl (100 mL) and the new phase extracted with EtOAc. The combined organic phases were washed (brine), dried (Na_2SO_4) and concentrated to give the crude aldehyde, which was used in the next step without further purification.

To a suspension of methyltriphenylphosphoniumiodide (5 g, 12.37 mmol) in dry THF (10 mL) was added NaHMDS (14 mL, 14 mmol, 1M in THF) and stirred overnight at room

temperature. The precipitated solids were allowed to settle and the supernatant liquid was added through a syringe to the solution of the aldehyde in dry THF (15 mL). The reaction mixture was stirred at room temperature for 18 h and then quenched with saturated aq. NH_4Cl. The aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed (brine), dried (Na_2SO_4) and concentrated. Purification of the residue by silica gel column chromatography using petroleum ether:EtOAc (24:1) gave **252** (2.28 g) as a pale yellow oil.

Yield: 2.28 g, 77%

[a]$_D^{20}$: – 4.62 (c = 1, $CHCl_3$]

IR (neat, cm^{-1}): n_{max} 2926, 2855, 1460, 1361, 1217, 1048, 764, 639

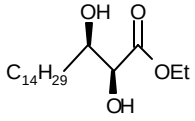
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7 Hz, 3H), 1.2-1.3 (m, 24H), 1.41 (s, 6H), 1.53 (m, 2H), 3.6-3.7 (m, 1H), 3.98 (t, *J* = 8 Hz, 1H), 5.2-5.4 (m, 2H), 5.7-5.9 (m, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.59, 23.22, 26.57, 27.45, 27.82, 29.91, 30.06, 30.24, 32.49, 81.26, 83.29, 108.94, 118.79, 136.29

EIMS (*m/z* relative intensity, %): 324 [M^+] (1.3), 309 [M^+–15] (50), 225 (21.8), 123 (9), 109 (15.4), 98 (100), 83 (7.7), 57 (1.3)

Analysis: $C_{21}H_{40}O_2$ (324.6) requires C, 77.7; H, 12.42. Found: C, 77.50; H, 12.48.

Synthesis of ethyl (2*S*,3*R*)-2,3-dihydroxyheptadecanoate, 259



259

Compound **259** was prepared following the procedure as described for compound **256**. In this case the ligand used was $(DHQD)_2$-PHAL in place of $(DHQ)_2$-PHAL. White solid.

M.p.: 74-75°C

[a]$_D^{20}$: + 10.41 (c = 1, $CHCl_3$)

IR (CHCl3, cm^{-1}): n_{max} 3485, 2927, 1732, 1462, 1216, 1098, 464

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6 Hz, 3H), 1.2-1.3 (m, 24H), 1.31 (t, *J* = 8 Hz, 3H), 1.59 (m, 2H), 2.78 (brs, 2H), 3.87 (m, 1H), 4.07 (m, 1H), 4.26 (q, *J* = 8 Hz, 2H)

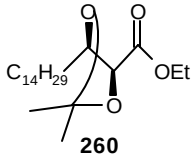
^{13}C NMR (50 MHz, $CDCl_3$): δ 13.7, 13.99, 22.59, 25.71, 29.28, 29.61, 31.85, 33.43, 61.6, 72.62, 73.42, 173.63

EIMS (*m/z* relative intensity, %): 329 [M^+–1] (0.3), 312 (0.6), 257 (5), 239 (4.5), 104 (100), 76 (8.4), 57 (2)

Analysis: $C_{19}H_{38}O_4$ (330.5) requires C, 69.05; H, 11.58. Found: C, 69.09; H, 11.66.

Compounds **260, 261** and **253** were prepared by the procedures as described for compounds **257**, **258** and **252** respectively.

Ethyl (2*S*,3*R*)-2,3-*O*-isopropylideneheptadecanoate-2,3-diol, 260



260

Colorless liquid.

[a]$_D^{20}$: + 11.33 (c = 1.5, $CHCl_3$)

IR (neat, cm^{-1}): n_{max} 2925, 1757, 1264, 1098, 451

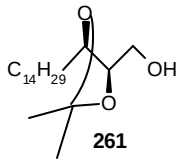
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6 Hz, 3H), 1.2-1.3 (m, 24H), 1.29 (t, *J* = 8 Hz, 3H), 1.44 (s, 3H), 1.46 (s, 3H) 1.70 (m, 2H), 4.1-4.2 (m, 2H), 4.29 (q, *J* = 8 Hz, 2H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.80, 13.86, 22.43, 25.36, 26.92, 29.27, 29.45, 31.71, 33.33, 60.79, 78.96, 78.98, 110.39, 170.63

EIMS (*m/z* relative intensity, %): 370 [M^+] (1.3), 356 (100), 342 (4.5), 297 (24.4), 239 (8.4), 144 (34.6), 109 (19.3), 59 (9.0)

Analysis: $C_{22}H_{42}O_4$ (370.6) requires C, 71.3; H, 11.42. Found: C, 71.20; H, 11.38.

(2*R*,3*R*)-2,3-*O*-isopropylideneheptadecane-1,2,3-triol, 261



261

White solid.

M.p.: 46-47°C

[a]$_D^{20}$: + 18.23 (c = 1.2, MeOH)

IR ($CHCl_3$, cm^{-1}): n_{max} 3445, 2927, 1458, 1370, 1215, 763, 668 cm^{-1}

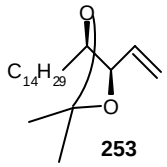
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7 Hz, 3H), 1.2-1.3 (m, 24H), 1.41 (s, 6H), 1.54 (m, 2H), 2.04 (brs, 1H), 3.5-3.63 (m, 1H), 3.70-3.9 (m, 3H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.89, 22.56, 25.83, 26.97, 27.27, 29.21, 29.54, 31.82, 33.11, 62.26, 77.15, 81.67, 108.47

EIMS (*m/z* relative intensity, %): 329 [M^++1] (1.2), 314 [M^+–15] (25.6), 313 (100), 297 (29.5), 109 (30.8), 95 (54), 59 (6.4)

Analysis: $C_{20}H_{40}O_3$ (328.5) requires C, 73.12; H, 12.27. Found: C, 73.02; H, 12.47.

(3*R*,4*R*)-3,4-*O*-isopropylideneoctadec-1-ene-3,4-diol, 253



253

Pale yellow oil.

[a]$_D^{20}$: + 4.7 (c = 1, $CHCl_3$)

IR (neat, cm-1): n_{max} 2927, 2855, 1466, 1372, 1216, 1049, 761, 669

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6 Hz, 3H), 1.22-1.3 (m, 24H), 1.41 (s, 3H), 1.42 (s, 3H), 1.54 (m, 2H), 3.63-3.72 (m, 1H), 4.0 (t, *J* = 8 Hz, 1H), 5.21-5.4 (m, 2H), 5.73-5.9 (m, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.85, 22.49, 25.87, 26.68, 27.08, 29.18, 29.51, 31.75, 80.53, 82.51, 108.13, 117.84, 135.63

EIMS (*m/z* relative intensity, %): 324 [M^+] (1.2), 309 [M^+–15] (26.3), 225 (9.61), 123 (3.8), 109 (6.4), 98 (100), 83 (11.6), 57 (1.3)

Analysis: $C_{21}H_{40}O_2$ (324.6) requires C, 77.7; H, 12.42. Found: C, 77.97; H, 12.31.

General procedure for asymmetric dihydroxylation of olefins 252 and 253

To a mixture of $K_3Fe(CN)_6$ (7.6 g, 23.1 mmol), K_2CO_3 (3.2 g, 23.1 mmol) and the ligand (72 mg, 92.4 μmol, 1.2 mol%) in *t*-BuOH-H_2O (1:1, 90 mL) cooled at 0°C was added osmium tetroxide (468 μL, 0.1M solution in toluene, 0.6 mol%). After stirring for 5 min at 0°C, the olefin **252** or **253** (2.5 g, 7.7 mmol) was added in one portion. The reaction mixture was stirred at 0°C for 24 h and then quenched with solid sodium sulfite (3 g). The stirring was continued for an additional 45 min and then the solution was extracted with EtOAc (5 × 30 mL). The combined organic phases were washed (brine), dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether:acetone (7:3) as eluent gave the diols (**266**-**269**) as white solids in 89 -93% yields.

Compound 266

M.p.: 53-55°C

[a]$_D^{20}$: – 17.3 (c = 1, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): n_{max} 3420-3300, 2923, 1465, 1378, 1245, 861, 487

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.86 (t, *J* = 6 Hz, 3H), 1.2-1.3 (m, 24H), 1.37 (s, 6H), 1.52 (m, 2H), 3.18 (brs, 2H), 3.61-3.76 (m, 2H), 3.85-4.09 (m, 3H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.37, 22.05, 25.36, 25.47, 26.42, 26.83, 28.77, 29.07, 29.58, 29.95, 31.35, 33.15, 67.04, 76.74, 79.98, 80.82, 108.06

EIMS (*m/z* relative intensity, %): 359 [M^++1] (1.2), 343 [M^+–15] (100), 297 (91), 269 (28.2), 109 (38.46), 95 (65.4), 83 (38.46), 59 (21.8)

Analysis: $C_{21}H_{42}O_4$ (358.6) requires C, 70.34; H, 11.8. Found: C, 70.23; H, 11.78.

Compound 267

M.p.: 51-52°C

[a]$_D^{20}$: – 19.5 (c = $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): n_{max} 3355-3253, 2923, 1460, 1375, 1215, 755, 481

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6 Hz, 3H), 1.2-1.3 (m, 24H), 1.38 (s, 3H), 1.40 (s, 3H), 1.52 (m, 2H), 2.94 (brs, 2H), 3.6-3.8 (m, 4H), 3.9-4.12 (m, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.20, 21.95, 25.48, 26.39, 26.84, 28.27, 28.64, 29.0, 29.41, 29.81, 31.25, 33.67, 63.52, 72.71, 79.33, 80.47, 107.78

EIMS (*m/z* relative intensity, %): 359 [M^++1] (1.2), 343 [M^+–15] (100), 297 (87.2), 269 (29.5), 109 (25.6), 95 (36.0), 83 (42.3), 59 (32.0)

Analysis: $C_{21}H_{42}O_4$ (358.6) requires C, 70.34; H, 11.8. Found: C, 70.18; H, 11.92.

Compound 268

M.p.: 49-50°C

[a]$_D^{20}$: + 20.3 (c = 1, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): n_{max} 3353-3253, 2922, 1463, 1380, 1215, 759, 479

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6 Hz, 3H), 1.23-1.3 (m, 24H), 1.36 (s, 3H), 1.38 (s, 3H), 1.51 (m, 2H), 3.10 (brs, 2H), 3.55-3.74 (m, 2H), 3.8-4.1 (m, 3H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.63, 22.3, 25.61, 25.72, 26.49, 26.68, 27.08, 29.03, 29.33, 29.84, 30.21, 33.41, 67.30, 77.26, 80.23, 81.08, 108.32

EIMS (*m/z* relative intensity, %): 359 [M^++1] (1.2), 343 [M^+–15] (100), 297 (84.6), 269 (21.8), 109 (27), 95 (51.3), 83 (41.0), 59 (18.0)

Analysis: $C_{21}H_{42}O_4$ (358.6) requires C, 70.34; H, 11.8. Found: C, 70.46; H, 11.75.

Compound 269

M.p.: 48-50°C

$[\alpha]_D^{20}$: + 18.2 (c = 1, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): n_{max} 3354-3252, 2924, 1467, 1377, 1216, 756, 478, 454 cm^{-1}

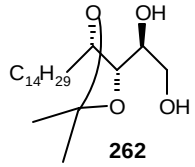
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6 Hz, 3H), 1.2-1.3 (m, 24H), 1.38 (s, 3H), 1.41 (s, 3H), 1.53 (m, 2H), 2.01 (brs, 1H), 2.62 (brs, 1H), 3.55-3.81 (m, 3H), 3.9-4.2 (m, 2H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.34, 22.05, 25.32, 25.58, 26.42, 26.83, 28.74, 29.07, 29.51, 29.88, 31.35, 33.15, 33.77, 63.58, 76.74, 79.98, 80.86, 108.06

EIMS (*m/z* relative intensity, %): 343 [M^+–15] (7.7), 297 (100), 265 (16.7), 107 (66.7), 95 (27.0), 83 (28.2), 59 (2.5)

Analysis: $C_{21}H_{42}O_4$ (358.6) requires C, 70.34; H, 11.8. Found: C, 70.50; H, 12.06.

Synthesis of compound 262



262

To a mixture of $K_3Fe(CN)_6$ (3.043 g, 9.24 mmol), K_2CO_3 (1.28 g, 9.24 mmol) and $(DHQD)_2AQN$ (40 mg, 46.6 μmol, 1.5 mol%) in *t*-BuOH-H_2O (1:1, 40 mL) cooled at 0°C was added osmium tetroxide (250 μL, 0.1M solution in toluene, 0.8 mol%). After stirring for 5 min at 0°C, the olefin **252** (1 g, 3.08 mmol) was added in one portion. The reaction mixture was stirred at 0°C for 24 h and then quenched with solid sodium sulfite (2 g). The stirring was continued for an additional 45 min and then the solution was extracted with EtOAc (5 × 30 mL). The combined organic phases were washed (brine), dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether:EtOAc (7:3) as eluent gave a diastereomeric mixture of **262** and **263** (1.016 g, 92%) in 6:1 ratio. Diastereomereric mixture **262**

and **263** was separated by flash column chromatography on TLC mesh silica gel using petroleum ether:EtOAc (7:3) as eluent to give **262** (0.763 g) as a white solid.

Yield: 0.763 g, 69%

M.p.: 54-56°C

[a]$_D^{20}$: – 20.1 (c = 1, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): n_{max} 3358-3250, 2924, 1465, 1382, 1220, 760, 479

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6 Hz, 3H), 1.23-1.3 (m, 24H), 1.38 (s, 3H), 1.40 (s, 3H), 1.53 (m, 2H), 2.62 (brs, 2H), 3.55-3.76 (m, 4H), 3.8-4.0 (m, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.03, 22.64, 26.13, 27.05, 27.34, 29.29, 29.66, 31.90, 34.18, 63.88, 72.74, 79.35, 81.23, 108.72

EIMS (*m/z* relative intensity, %): 359 [M^++1] (1.2), 343 [M^+–15] (100), 297 (84.6), 269 (21.8), 109 (28), 95 (55.3), 83 (42.2), 59 (17.0)

Analysis: $C_{21}H_{42}O_4$ (358.6) requires C, 70.34; H, 11.8. Found: C, 70.36; H, 11.73.

Synthesis of compound 270

To a mixture of $K_3Fe(CN)_6$ (7.6 g, 23.1 mmol), K_2CO_3 (3.2 g, 23.1 mmol) and pyridine (31 μL, 385 μmol, 5 mol%) in *t*-BuOH-H_2O (1:1, 90 mL) cooled at 0°C was added osmium tetroxide (468 μL, 0.1M solution in toluene, 0.6 mol%). After stirring for 5 min at 0°C, the olefin **253** (2.5 g, 7.7 mmol) was added in one portion. The reaction mixture was stirred at 0°C for 24 h and then quenched with solid sodium sulfite (3 g). The stirring was continued for an additional 45 min and then the solution was extracted with EtOAc (4 × 30 mL). The combined organic phases were washed (brine), dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether:acetone (7:3) as eluent gave **270** (2.3 g) as a white solid.

Yield: 2.3 g, 83%

M..p.: 50-52°C

[a]$_D^{20}$: + 18.7 (c = 1, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): n_{max} 3350-3245, 2928, 1465, 1378, 1210, 766, 474

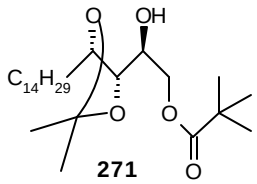
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6 Hz, 3H), 1.2-1.33 (m, 24H), 1.36 (s, 3H), 1.40 (s, 3H), 1.53 (m, 2H), 2.94 (brs, 2H), 3.55-3.75 (m, 4H), 3.97 (m, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.85, 22.49, 25.91, 26.72, 27.05, 27.30, 29.18, 31.79, 34.14, 66.19, 71.52, 79.35, 80.46, 108.69

EIMS (*m/z* relative intensity, %): 343 [M^+−15] (7.9), 297 (100), 265 (17.9), 107 (66.7), 95 (32.0), 83 (28.2), 59 (3.5)

Analysis: $C_{21}H_{42}O_4$ (358.6) requires C, 70.34; H, 11.8. Found: C, 70.44; H, 11.96.

Synthesis of (2*S*,3*R*,4*S*)-1-*O*-pivaloyl-3,4-*O*-isopropylideneoctadecane-1,2,3,4-tetrol, 271



271

To a solution of **262** (1.25 g, 3.48 mmol) in CH_2Cl_2 (5 mL) and pyridine (3 mL) at 0°C was added pivaloyl chloride (0.45 mL, 3.65 mmol) in CH_2Cl_2 (2 mL) dropwise over 30 min. The reaction mixture was allowed to warm to room temperature and stirred overnight. Water (15 mL) was added and the aqueous layer extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed (water and then brine), dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using petroleum ether:acetone (9:1) to give **271** (1.43 g) as a colorless oil.

Yield: 1.43 g, 93%

[a]$_D^{20}$: – 17.2 (c =1, $CHCl_3$)

IR (neat, cm^{-1}): n_{max} 3484, 2925, 1725, 1480, 1371, 1164, 1064, 458

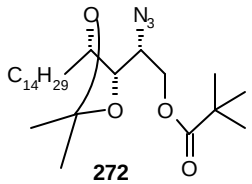
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6 Hz, 3H), 1.23 (s, 9H), 1.22-1.3 (m, 25H), 1.37 (s, 3H), 1.40 (s, 3H), 1.57 (m, 2H), 3.6 (t, *J* = 6 Hz, 1H), 3.89 (m, 1H), 4.01 (m, 1H) 4.17 (m, 1H), 4.29 (m, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.81, 22.45, 25.87, 26.83, 26.94, 27.19, 29.14, 31.71, 34.07, 38.62, 66.01, 71.30, 79.32, 80.27, 108.54, 178.67

EIMS (*m/z* relative intensity, %): 427 [M^+−15] (84.6), 367 (3.8), 340 (1.0), 297 (100), 158 (24.3), 109 (11.5), 85 (43.6), 57 (21.8)

Analysis: $C_{26}H_{50}O_5$ (442.7) requires C, 70.54; H, 11.38. Found: C, 70.42; H, 11.25.

Synthesis of (2*R*,3*S*,4*S*)-1-*O*-pivaloyl-2-azido-3,4-*O*-isopropylideneoctadecane-1,3,4-triol, 272



272

To a solution of **271** (1.2 g, 2.7 mmol) in dry pyridine (3 mL) and CH_2Cl_2 (4 mL) was added DMAP (cat), followed by $MeSO_2Cl$ (0.42 mL, 5.4 mmol) and the reaction mixture was heated to 60°C for 5 h. It was then cooled and quenched with water (10 mL). The aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed (water and then brine), dried (Na_2SO_4) and concentrated to give the crude mesylate, which was used for the next step without further purification.

To the solution of mesylate in dry DMF (15 mL) was added LiN_3 (0.53 g, 10.8 mmol) and stirred at 80°C for 12 h. The reaction mixture was cooled and treated with acetone. The solid material was filtered and washed with acetone. The filtrate was concentrated and the residue was purified by silica gel column chromatography using petrol ether:EtOAc (24:1) to give **272** (1.11 g) as a colorless oil.

Yield: 1.11 g, 88%

[a]$_D^{20}$: – 22.81 (c = 1, $CHCl_3$)

IR (neat, cm^{-1}): n_{max} 2926, 2855, 2116, 1738, 1463, 1371, 1281, 1149, 1100, 487

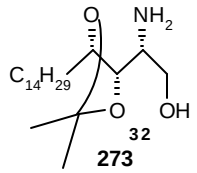
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6 Hz, 3H), 1.24 (s, 9H), 1.25-1.3 (m, 24H), 1.39 (s, 3H), 1.44 (s, 3H), 1.53 (m, 2H), 3.47 (t, *J* = 6 Hz, 1H), 3.67 (m, 1H), 4.05 (m, 1H), 4.34 (m, 2H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.81, 22.45, 25.72, 26.31, 26.86, 27.16, 29.14, 29.44, 31.71, 32.74, 38.55, 59.39, 64.02, 77.26, 80.20, 109.13, 177.39

EIMS (*m/z* relative intensity, %): 469 [M^++2] (1.0), 452 [M^+–15] (3.9), 297 (100), 280 (30.8), 214 (30.7), 109 (14.1), 85 (20.5), 57 (2.5)

Analysis: $C_{26}H_{49}N_3O_4$ (467.7) requires C, 66.77; H, 10.56; N, 8.98. Found: C, 66.55; H, 10.66; N, 8.89.

Synthesis of (2*R*,3*S*,4*S*)-2-amino-3,4-*O*-isopropylideneoctadecane-1,3,4-triol, 273



273

To a stirred suspension of $LiAlH_4$ (0.244 g, 6.41 mmol) in dry Et_2O (20 mL) at 0°C was added the solution of **272** (1 g, 2.14 mmol) in Et_2O (5 mL) dropwise. The reaction mixture was allowed to warm to room temperature and stirred overnight. Excess $LiAlH_4$ was destroyed by slow addition of 10% aq. NaOH (2 mL) and EtOAc (15 mL). The white precipitate was filtered through a pad of neutral alumina and washed with MeOH (3 × 50 mL). The filtrate was concentrated and the residue was purified by silica gel column chromatography using $CHCl_3$:MeOH (9:1) as eluent to give **273** (0.72 g) as a white solid.

Yield: 0.72 g, 94%

M.p.: 55-57°C

$[\alpha]_D^{20}$: – 24.32 (c = 1, MeOH)

IR ($CHCl_3$, cm^{-1}): n_{max} 3370, 3357, 2925, 1380, 758, 468 cm^{-1}

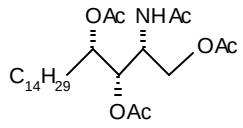
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6 Hz, 3H), 1.2 -1.3 (m, 24H), 1.40 (s, 6H), 1.54 (m, 2H), 2.9-3.3 (m, 4H), 3.5-3.6 (m, 3H), 3.93 (m, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.00, 22.60, 26.05, 27.01, 27.34, 29.25, 29.58, 31.82, 33.44, 53.66, 63.91, 78.00, 81.12, 108.69

EIMS (*m/z* relative intensity, %): 357 [M^+] (1.0), 342 [M^+–15] (14.0), 326 (16.7), 297 (16.6), 282 (16.8), 268 (37.1), 167 (1.3), 149 (1.4), 100 (100), 60 (99.0)

Analysis: $C_{21}H_{43}NO_3$ (357.6) requires C, 70.53; H, 12.12; N, 3.91. Found: C, 70.62; H 12.08; N, 3.85.

Synthesis of (2*R*,3*S*,4*S*)-2-acetamido-1,3,4-triacetoxyoctadecane, 274



274

To the solution of **273** (0.78 g, 2.18 mmol) in MeOH (15 mL) was added 6N HCl (3 mL) at room temperature and stirred overnight. Solid $NaHCO_3$ (1 g) was added and the reaction mixture was filtered through a pad of neutral alumina and further eluted with MeOH (3 × 20 mL). The

combined filtrate was concentrated to a white powder of hydrochloride salt, which was subsequently acetylated with pyridine (5 mL), DMAP (cat) and Ac_2O (3 mL) in CH_2Cl_2 (5 mL). After stirring for 12 h at room temperature the reaction mixture was quenched with water (10 mL). The aqueous layer was extracted with EtOAc (4 × 20 mL). The combined organic extracts were washed (water and then brine), dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petrol ether:EtOAc (3:2) as eluent gave **274** (0.69 g) as a waxy white solid.

Yield: 0.69 g, 67%

M.p.: 51-52°C

[a]$_D^{20}$: – 7.2 (c = 1.2, $CHCl_3$) [lit $[\alpha]_D^{21}$ + 7.0 (c = 0.86, $CHCl_3$), for enantiomer of **274**][124]

IR ($CHCl_3$, cm^{-1}): n_{max} 3297, 3290, 2925, 1744, 1662, 1226, 479

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.86 (t, *J* = 6 Hz, 3H), 1.2-1.3 (m, 24H), 1.55 (m, 2H), 2.03 (s, 3H), 2.04 (s, 6H), 2.07 (s, 3H), 3.95-4.05 (m, 2H), 4.5 (m, 1H), 5.02 -5.18 (m, 2H), 5.92 (d, *J* = 10 Hz, 1H)

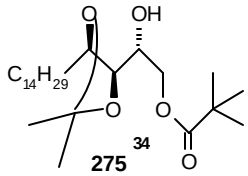
^{13}C NMR (50 MHz, $CDCl_3$): δ 13.45, 19.92, 20.14, 22.08, 22.19, 24.29, 28.77, 29.07, 29.99, 31.35, 48.00, 62.92, 71.26, 71.93, 169.45,169.52, 169.78, 169.85

EIMS (*m/z* relative intensity, %): 486 [M^++1] (2.5), 426 (2.4), 292 (32.0), 144 (86.0), 102 (60.0), 84 (100)

Analysis: $C_{26}H_{47}NO_7$ (485.67) requires C, 64.3; H, 9.8; N, 2.88. Found: C, 64.57; H, 9.86; N, 2.95.

Compounds 275-278 were prepared by the same procedures as described for compounds 271-274 respectively.

Compound 275



275

Colorless oil.

[a]$_D^{20}$: + 15.47 (c = 1.2, $CHCl_3$)

IR (neat, cm^{-1}): n_{max} 3485, 2933, 1725, 1285, 1162, 1064, 472

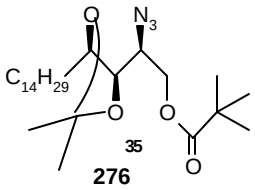
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6 Hz, 3H), 1.21 (s, 9H), 1.22-1.3 (m, 24H), 1.36 (s, 3H), 1.39 (s, 3H), 1.55 (m, 2H), 2.64 (brs, 1H), 3.6 (t, *J* = 6.5 Hz, 1H), 3.82-3.94 (m, 2H), 3.99-4.26 (m, 2H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.74, 22.34, 25.80, 26.83, 27.08, 29.03, 29.36, 31.6, 33.96, 38.48, 65.97, 71.16, 79.24, 80.12, 108.32, 178.41

EIMS (*m/z* relative intensity, %): 428 (80.0), 340 (2.0), 297 (95.0), 158 (32.0), 109 (27.0), 85 (100.0), 57 (45.0)

Analysis: $C_{26}H_{50}O_5$ (442.7) requires C, 70.54; H, 11.38. Found: C, 70.48; H, 11.36.

Compound 276.



35

276

Colorless oil.

$[\alpha]_D^{20}$: + 24.38 (c = 1, $CHCl_3$)

IR (neat, cm^{-1}): n_{max} 2956, 2855, 2105, 1729, 1281, 1154, 482

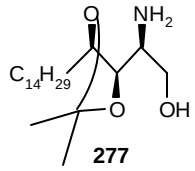
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6 Hz, 3H), 1.23 (s, 9H), 1.24-1.3 (m, 24H), 1.38 (s, 3H), 1.43 (s, 3H), 1.52 (m, 2H), 3.43-3.5 (t, *J* = 6 Hz, 1H), 3.66 (m, 1H), 4.0 (m, 1H), 4.25-4.45 (m, 2H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.85, 22.49, 25.80, 26.31, 26.86, 27.16, 29.18, 29.47, 31.75, 32.71, 38.55, 59.28, 64.10, 77.22, 80.12, 109.13, 177.50

EIMS (*m/z* relative intensity, %): 469 [M^++ 2] (1.0), 453 (1.2), 297 (100.0), 280 (27.0), 214 (64.0), 109 (38.5), 85 (15.4), 57 (16.6)

Analysis: $C_{26}H_{49}N_3O_4$ (467.7) requires C, 66.77; H, 10.56; N, 8.98. Found: C, 66.65; H, 10.58; N, 9.05.

Compound 277



277

White solid.

M.p.: 56-58°C

$[\alpha]_D^{20}$: + 24.01 (c = 1.2, MeOH)

IR ($CHCl_3$, cm^{-1}): n_{max} 3374, 3383, 2924, 1379, 455

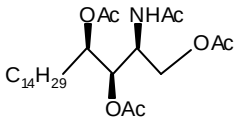
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6 Hz, 3H), 1.2 -1.3 (m, 24H), 1.40 (s, 6H), 1.54 (m, 2H), 3.0-3.5 (m, 4H), 3.51-3.6 (m, 3H), 3.92 (m, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.59, 22.23, 25.72, 26.68, 27.05, 28.92, 29.25, 31.53, 33.18, 53.40, 64.25, 77.55, 81.34, 107.95

EIMS (*m/z* relative intensity, %): 357 [M^+] (1.2), 342 [M^+–15] (12.1), 326 (14.1), 297 (15.4), 282 (10.9), 268 (23.0), 167 (30.8), 149 (100.0), 100 (51.3), 60 (19.3)

Analysis: $C_{21}H_{43}NO_3$ (357.6) requires C, 70.53; H, 12.12; N, 3.91. Found: C, 70.63; H, 12.05; N, 4.01.

Compound 278



278

Waxy white solid.

M.p.: 53-55°C

[a]$_D^{20}$: + 7.16 (c = 1, $CHCl_3$) [lit $[\alpha]_D^{21}$ + 7.0 (c = 0.86, $CHCl_3$)[124]

IR ($CHCl_3$, cm^{-1}): n_{max} 3356, 3317, 2926, 1740, 1667, 1239, 468

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.86 (t, *J* = 6 Hz, 3H), 1.2-1.3 (24H), 1.57 (m, 2H), 2.01 (s, 3H), 2.05 (s, 6H), 2.08 (s, 3H), 3.96-4.02 (m, 2H), 4.47-4.54 (m, 1H), 4.9-5.17 (m, 2H), 5.88 (d, *J* = 10 Hz, 1H).

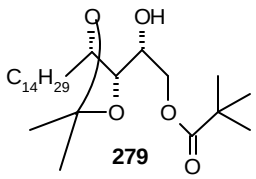
^{13}C NMR (50 MHz, $CDCl_3$): δ 14.03, 20.54, 20.80, 22.64, 23.11, 24.77, 29.29, 29.47, 29.62, 30.50, 31.86, 47.92, 62.85, 71.89, 72.22, 169.89, 169.6, 170.07, 170.5

EIMS (*m/z* relative intensity, %): 486 [M^++1] (1.0), 426 (1.2), 292 (15.4), 144 (100.0), 102 (63.0), 84 (83.4)

Analysis: $C_{26}H_{47}NO_7$ (485.67) requires C, 64.3; H, 9.8; N, 2.88. Found: C, 64.31; H, 9.77; N, 2.79.

Compounds 279-282 were prepared by the same procedures as described for compounds 271-274 respectively.

Compound 279



279

Colorless oil.

[a]$_D^{20}$: – 15.5 (c = 1, $CHCl_3$)

IR (neat, cm^{-1}): n_{max} 3483, 2925, 1734, 1458, 1360, 1163, 1064, 491

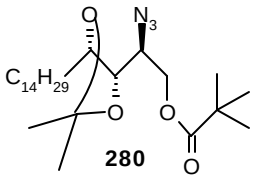
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6 Hz, 3H), 1.22 (s, 9H), 1.24-1.3 (m, 24H), 1.37 (s, 3H), 1.39 (s, 3H), 1.53 (m, 2H), 2.3 (brs, 1H), 3.6 (t, *J* = 6.5 Hz, 1H), 3.85-4.0 (m, 2H), 4.05-4.29 (m, 2H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.74, 22.34, 25.69, 25.80, 27.08, 29.03, 29.36, 31.6, 32.67, 33.96, 38.44, 65.94, 71.12, 79.24, 80.12, 108.28, 178.34

EIMS (*m/z* relative intensity, %): 427 [M^+–15] (100), 383 (1.2), 340 (1.0), 297 (39.7), 158 (10.3), 110 (4.5), 85 (4.5), 57 (5.13)

Analysis: $C_{26}H_{50}O_5$ (442.7) requires C, 70.54; H, 11.38. Found: C, 70.63; H, 11.31.

Compound 280



280

Colorless oil.

[a]$_D^{20}$: – 19.12 (c = 1, $CHCl_3$)

IR (neat, cm^{-1}): n_{max} 2955, 2855, 2102, 1738, 1463, 1371, 1280, 1149, 1099, 477

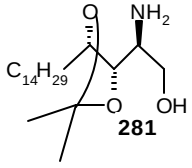
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6 Hz, 3H), 1.24 (s, 9H), 1.25-1.3 (m, 24H), 1.4 (s, 3H), 1.44 (s, 3H), 1.53 (m, 2H), 3.44-3.7 (m, 2H), 4.01-4.46 (m, 3H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.89, 22.52, 25.83, 26.35, 26.9, 27.19, 29.21, 29.51, 31.79, 32.78, 33.85, 38.62, 59.32, 64.13, 77.26, 80.16, 109.16, 177.61

EIMS (*m/z* relative intensity, %): 469 [M^++2] (2.56), 452 [M^+–15] (46.15), 297 (100), 280 (19.23), 214 (12), 109 (18), 85 (9), 57 (6.4)

Analysis: $C_{26}H_{49}N_3O_4$ (467.7) requires C, 66.77; H, 10.56; N 8.98. Found: C, 66.61; H, 10.62; N, 8.84.

Compound 281



281

White solid.

M.p.: 61-63°C

[a]$_D^{20}$: – 23.16 (c = 1, MeOH)

IR ($CHCl_3$, cm^{-1}): n_{max} 3362, 3330, 2926, 1370, 768, 442

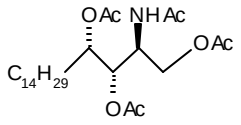
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7 Hz, 3H), 1.2 -1.3 (m, 24H), 1.39 (s, 6H), 1.54 (m, 2H), 3.0-3.15 (m, 4H), 3.5-3.56 (m, 3H), 3.93 (m, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.79, 22.35, 25.81, 26.62, 26.95, 27.02, 29.04, 29.37, 31.61, 33.27, 33.45, 54.63, 60.47, 78.15, 78.66, 109.03

EIMS (*m/z* relative intensity, %): 359 [M^++2] (1.3), 357 [M^+] (1.2), 343 (15.4), 327 (18), 298 (15.4), 283 (12.8), 269 (20.5), 167 (30.8), 149 (79.5), 100 (100), 60 (21.8)

Analysis: $C_{21}H_{43}NO_3$ (357.6) requires C, 70.53; H, 12.12; N, 3.91. Found: C, 70.69; H, 11.96; N, 3.94.

Compound 282



282

White solid.

M.p.: 53-54°C

[a]$_D^{20}$: – 6.62 (c = 1, $CHCl_3$) [lit $[\alpha]_D^{20}$ + 4.3 (c = 0.5, $CHCl_3$) for the enantiomer of **282**][100]

IR ($CHCl_3$, cm^{-1}): n_{max} 3430, 3020, 2927, 1740, 1681, 1218, 429

^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85 (t, *J* = 7 Hz, 3H), 1.2-1.3 (24H), 1.54 (m, 2H), 1.99 (s, 3H), 2.03 (s, 3H), 2.06 (s, 3H), 2.1 (s, 3H), 3.92-4.17 (m, 2H), 4.4-4.56 (m, 1H), 4.9-5.17 (m, 2H), 5.96 (d, *J* = 10 Hz, 1H)

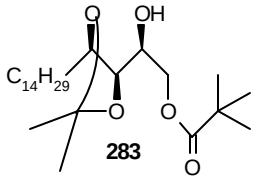
^{13}C NMR (50 MHz, $CDCl_3$): δ 13.25, 19.7, 19.92, 20.03, 21.9, 24.11, 24.44, 28.59, 28.92, 29.80, 30.21, 31.16, 47.41, 62.26, 71.49, 71.63, 169.12, 169.52, 169.6, 169.7

EIMS (*m/z* relative intensity, %): 485 [M^+] (1.3), 426 (1.2), 292 (12.82), 144 (100), 102 (27), 84 (11.53)

Analysis: $C_{26}H_{47}NO_7$ (485.67) C, 64.3; H, 9.8; N, 2.88. Found: C, 64.19; H, 9.71; N, 2.78.

Compounds 283-286 were prepared by the same procedures as described for compounds 271-274 respectively.

Compound 283



283

Colorless oil.

[a]$_D^{20}$: + 15.8 (c = 1, $CHCl_3$)

IR (neat, cm^{-1}): n_{max} 3486, 2924, 1735, 1460, 1360, 1161, 1065, 490

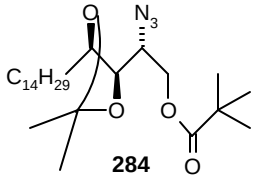
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6 Hz, 3H), 1.21 (s, 9H), 1.24-1.32 (m, 24H), 1.37 (s, 3H), 1.4 (s, 3H), 1.53 (m, 2H), 2.32 (brs, 1H), 3.61 (t, *J* = 6.5 Hz, 1H), 3.85-4.0 (m, 2H), 4.05-4.29 (m, 2H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.76, 22.38, 25.71, 25.82, 27.10, 29.05, 29.38, 31.8, 32.69, 33.98, 38.46, 65.96, 71.14, 79.26, 80.14, 108.30, 178.36

EIMS (*m/z* relative intensity, %): 427 [M^+–15] (100), 383 (1.5), 340 (1.7), 297 (32.6), 158 (10.8), 110 (4.9), 85 (4.8), 57 (7.43)

Analysis: $C_{26}H_{50}O_5$ (442.7) requires C, 70.54; H, 11.38. Found: C, 70.58; H, 11.41

Compound 284



284

Colorless oil.

[a]$_D^{20}$: + 19.32 (c = 1, $CHCl_3$)

IR (neat, cm^{-1}): n_{max} 2960, 2855, 2108, 1740, 1471, 1375, 1280, 1155, 1095, 868, 477

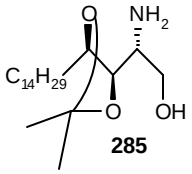
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6 Hz, 3H), 1.25 (s, 9H), 1.25-1.32 (m, 24H), 1.42 (s, 3H), 1.44 (s, 3H), 1.55 (m, 2H), 3.44-3.7 (m, 2H), 4.01-4.48 (m, 3H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.90, 22.54, 25.88, 26.39, 26.96, 27.22, 29.21, 29.51, 31.82, 32.82, 33.87, 38.64, 59.36, 64.17, 77.27, 80.17, 109.18, 177.62

EIMS (*m/z* relative intensity, %): 469 [M^++2] (3.56), 452 [M^+–15] (48.18), 297 (100), 280 (29.23), 214 (12.4), 109 (18.8), 85 (9.6), 57 (8.4)

Analysis: $C_{26}H_{49}N_3O_4$ (467.7) requires C, 66.77; H, 10.56; N 8.98. Found: C, 66.71; H, 10.42; N, 8.94.

Compound 285



285

White solid.

M.p.: 62-64°C

[a]$_D^{20}$: + 23.56 (c = 1, MeOH)

IR ($CHCl_3$, cm^{-1}): n_{max} 3366, 3340, 2928, 1376, 775, 439

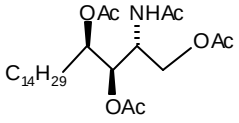
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7 Hz, 3H), 1.2-1.3 (m, 24H), 1.41 (s, 6H), 1.56 (m, 2H), 3.0-3.15 (m, 4H), 3.5-3.58 (m, 3H), 3.96 (m, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.82, 22.36, 25.81, 26.65, 26.96, 27.04, 29.06, 29.38, 31.66, 33.29, 33.44, 54.66, 60.49, 78.21, 78.69, 109.06

EIMS (*m/z* relative intensity, %): 359 [M^++2] (2.3), 357 [M^+] (1.8), 343 (15.8), 327 (19.4), 298 (16.4), 283 (10.8), 269 (20.4), 167 (33.8), 149 (79.8), 100 (100), 60 (11.8)

Analysis: $C_{21}H_{43}NO_3$ (357.6) requires C, 70.53; H, 12.12; N, 3.91. Found: C, 70.59; H, 12.06; N, 3.84.

Compound 286



286

White solid.

M.p.: 51-52°C

[a]$_D^{20}$: + 6.68 (c = 1, $CHCl_3$) [lit $[\alpha]_D^{20}$ + 4.3 (c = 0.5, $CHCl_3$)]^{100}

IR ($CHCl_3$, cm^{-1}): n_{max} 3432, 3028, 2928, 1735, 1680, 1220, 432

^{1}H NMR (200 MHz, $CDCl_3$): 0.86 (t, *J* = 7 Hz, 3H), 1.2-1.32 (m, 24H), 1.56 (m, 2H), 2.02 (s, 3H), 2.04 (s, 3H), 2.08 (s, 3H), 2.15 (s, 3H), 3.92-4.22 (m, 2H), 4.4-4.58 (m, 1H), 4.9-5.19 (m, 2H), 5.98 (d, *J* = 10 Hz, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.28, 19.74, 19.98, 20.05, 21.93, 24.16, 24.46, 28.62, 28.94, 29.85, 30.23, 31.176, 47.43, 62.27, 70.52, 71.48, 169.15, 169.53, 169.7, 169.9

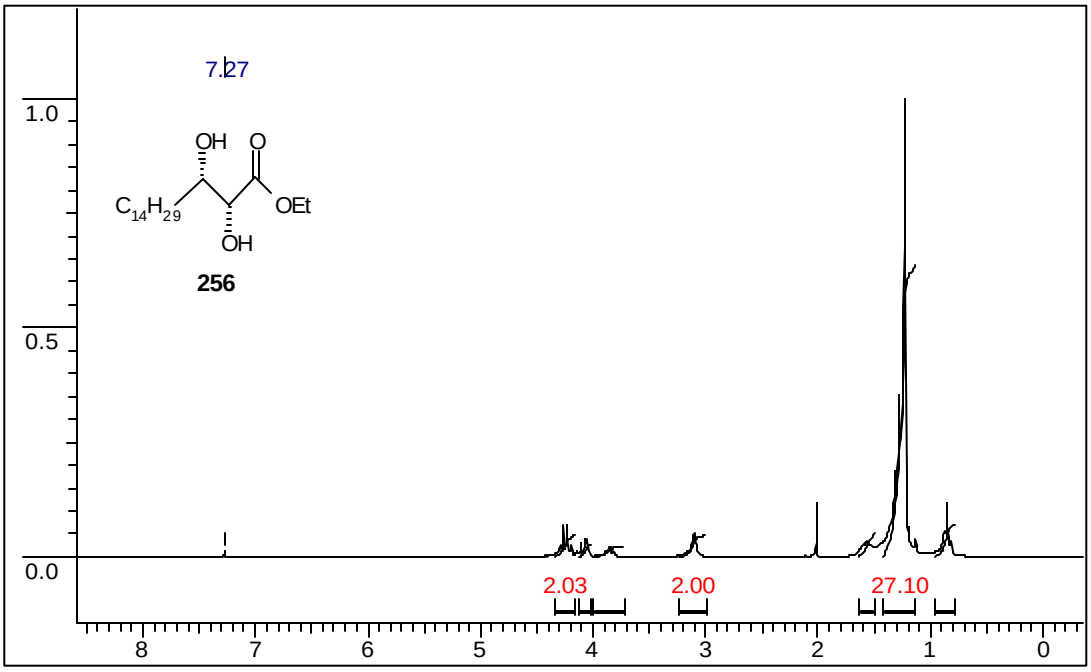
EIMS (*m/z* relative intensity, %): 485 [M^+] (1.8), 426 (1.5), 292 (18.85), 144 (100), 102 (29), 84 (11.67)

Analysis: $C_{26}H_{47}NO_7$ (485.67) requires C, 64.3; H, 9.8; N, 2.88. Found: C, 64.24; H, 9.66; N, 2.82.

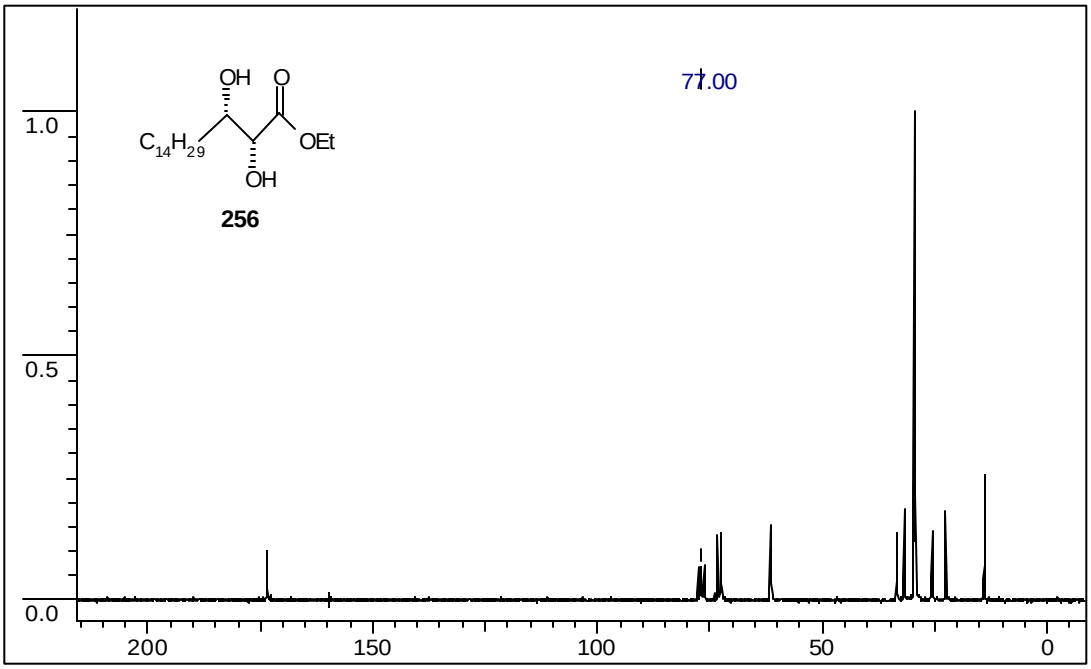
3.3.7. Spectra

+ 1] ^{1}H NMR Spectrum of **256**
+ 2] ^{13}C NMR Spectrum of **256**
+ 3] ^{1}H NMR Spectrum of **252**
+ 4] ^{13}C NMR Spectrum of **252**
+ 5] ^{1}H NMR Spectrum of **262**
+ 6] ^{13}C NMR Spectrum of **262**
+ 7] ^{1}H NMR Spectrum of **272**
+ 8] ^{13}C NMR Spectrum of **272**
+ 9] ^{1}H NMR Spectrum of **274**
+ 10] ^{13}C NMR Spectrum of **274**

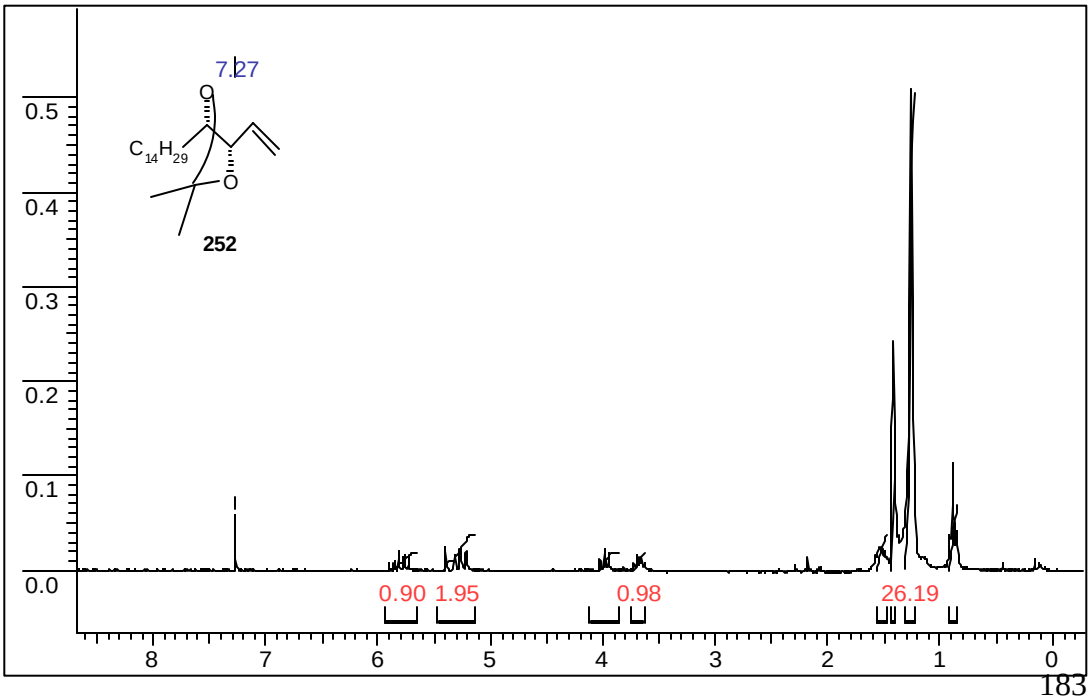
+ ^{1}H NMR Spectrum of **256**



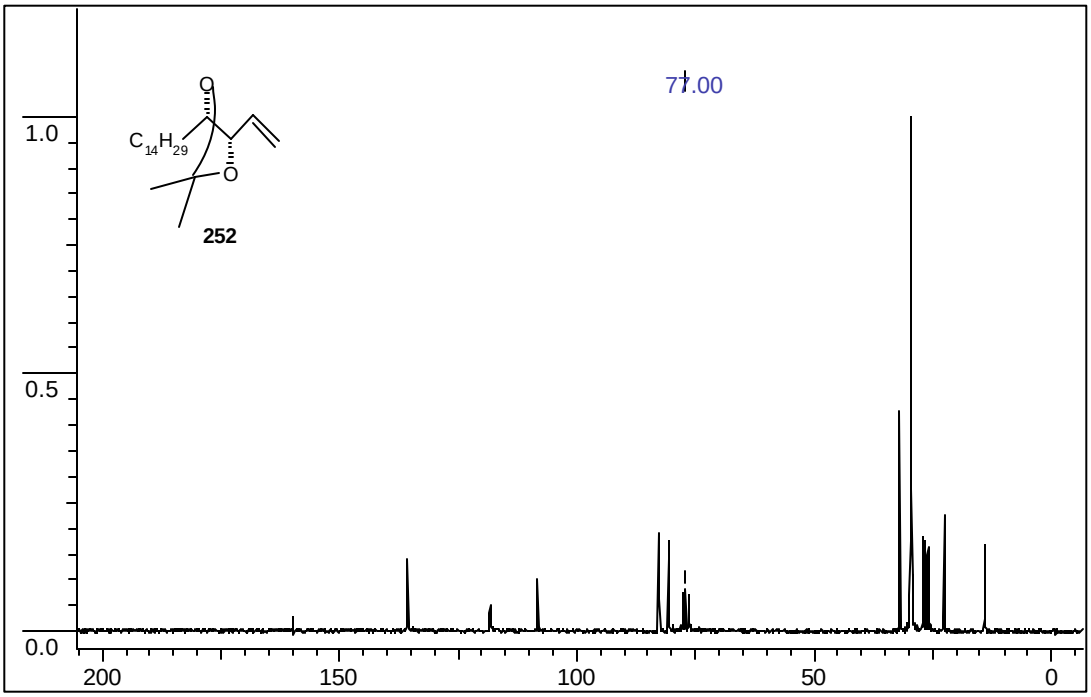
+ ^{13}C NMR Spectrum of **256**



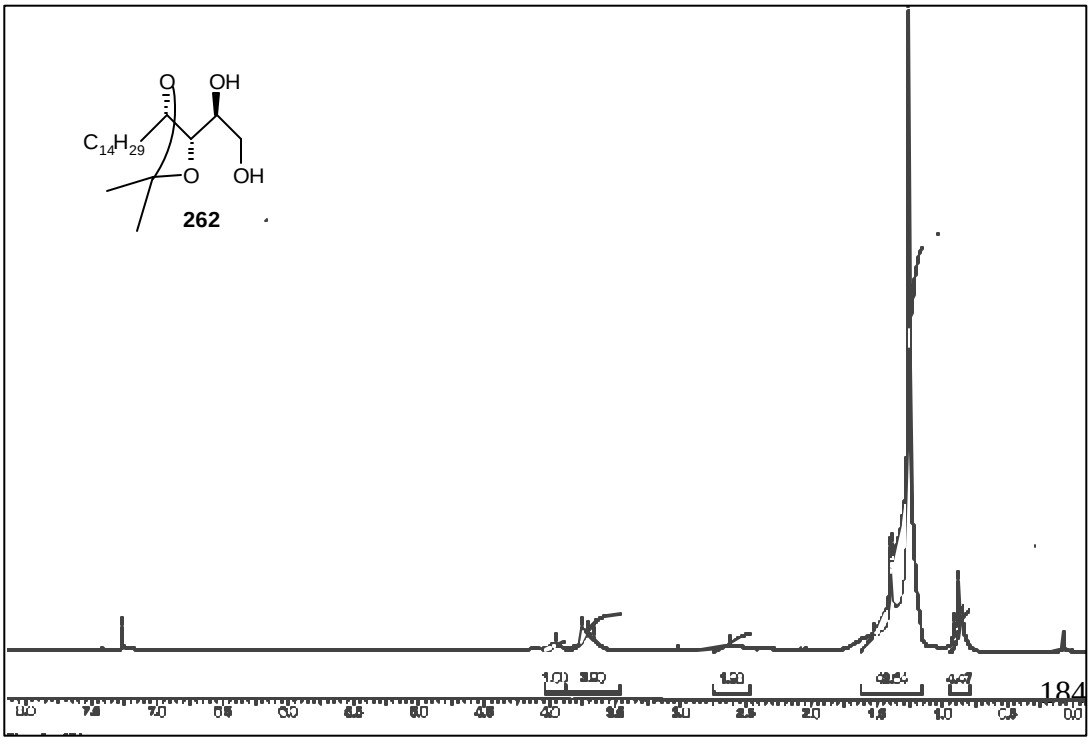
+ ^{1}H NMR Spectrum of **252**



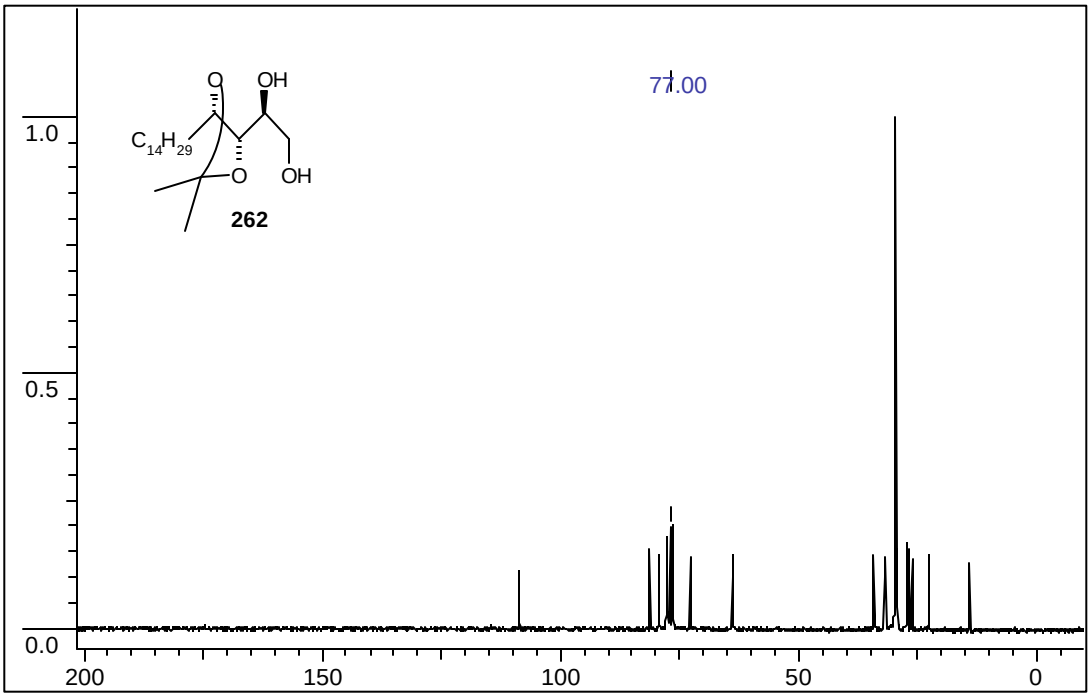
+ ^{13}C NMR Spectrum of **252**



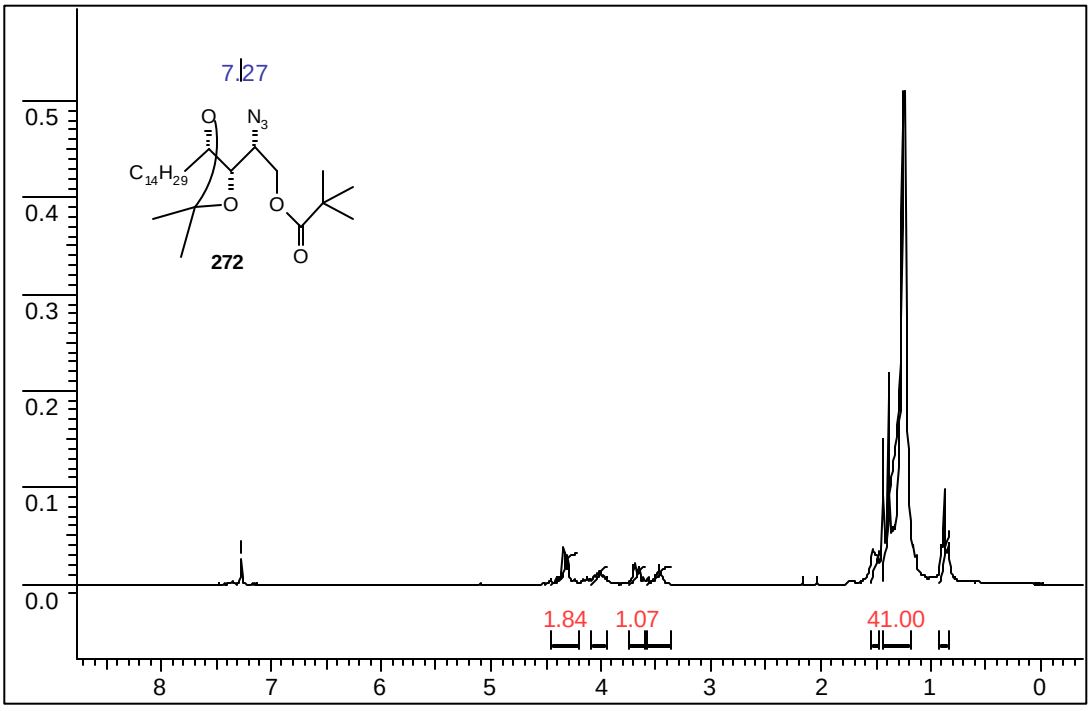
+ ^{1}H NMR Spectrum of **262**



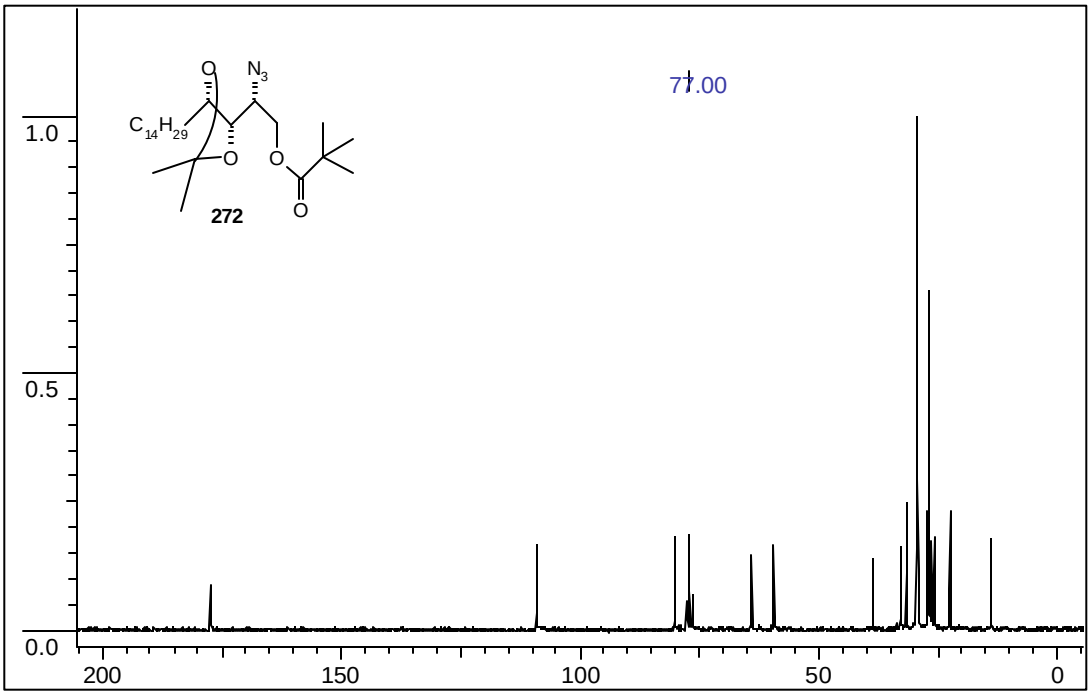
+ ^{13}C NMR Spectrum of **262**



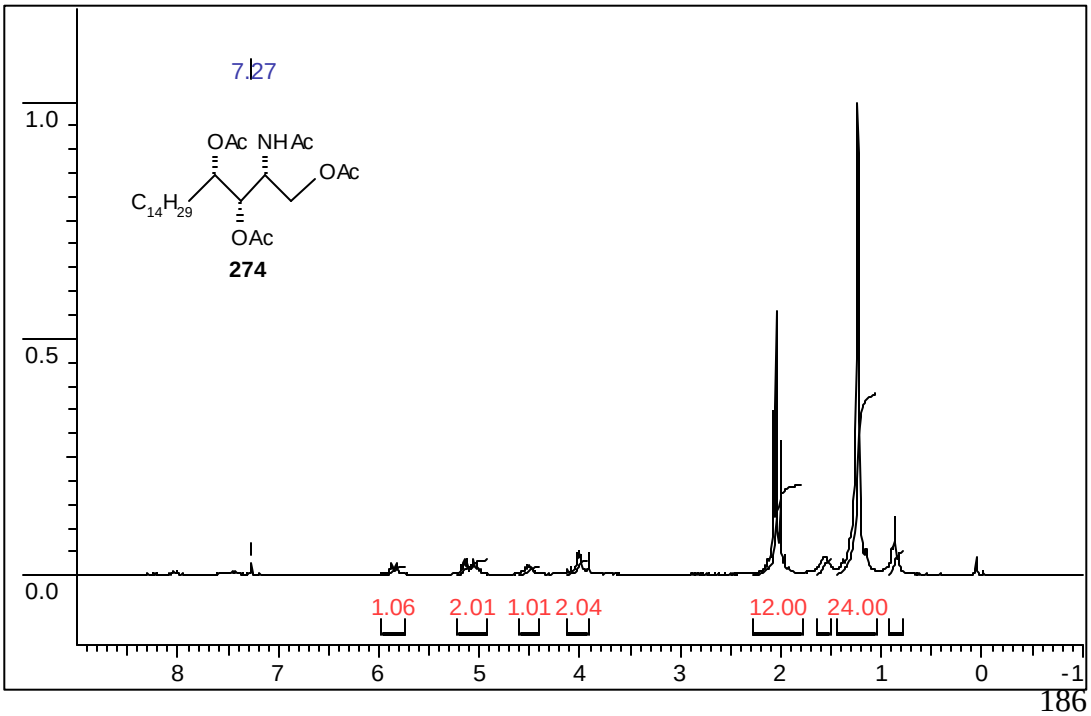
+ ^{1}H NMR Spectrum of **272**



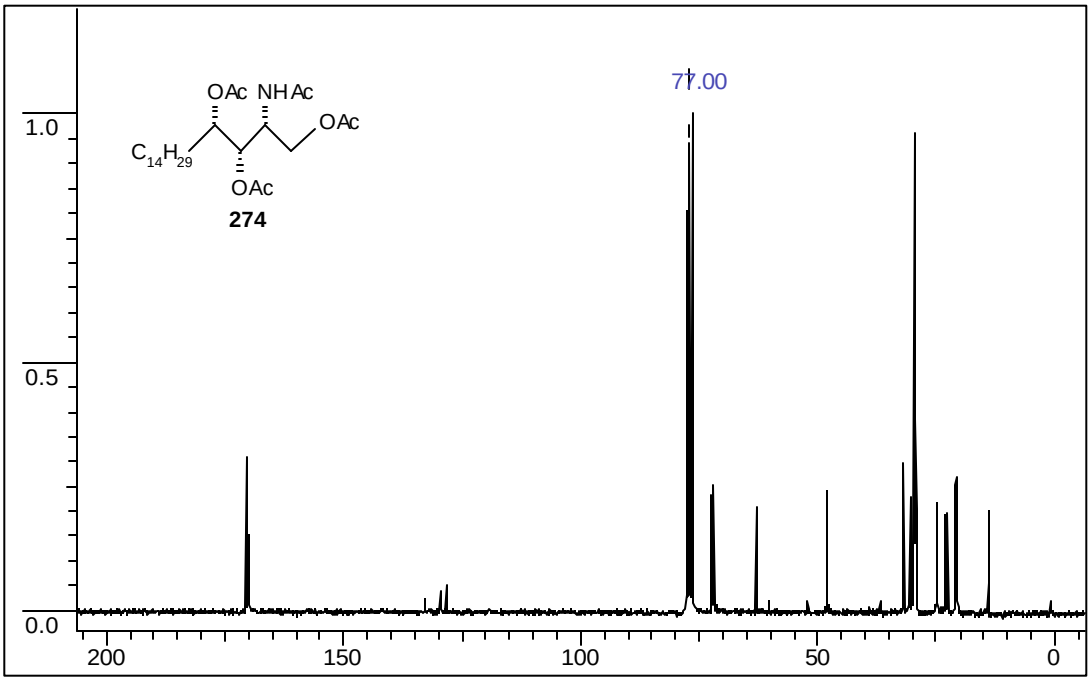
+ ^{13}C NMR Spectrum of **272**



+ ^{1}H NMR Spectrum of **274**



+ ^{13}C NMR Spectrum of **274**



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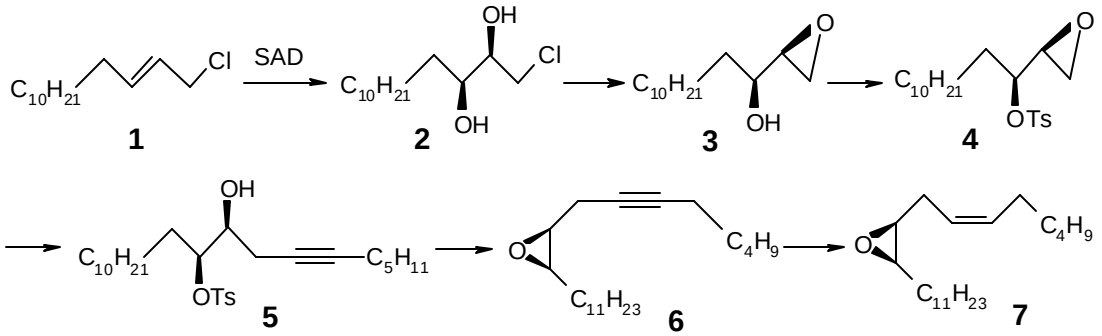
CHAPTER 4

ENANTIOSELECTIVE SYNTHESIS OF CHIRAL EPOXIDES *via* ASYMMETRIC DIHYDROXYLATION: SYNTHESIS OF (+)-DIOLMYCIN A2 AND (+)- AND (-)-POSTICLURE

4.1. Introduction

Enantiomerically pure epoxides have found widespread applications as chiral building blocks in organic synthesis,[1] while many bioactive molecules contain the epoxide function as well. The advent of Sharpless asymmetric epoxidation in 1980[2] dramatically facilitated the synthesis of optically active epoxides.[3] Despite its venerability, an astonishing number of total syntheses of complex natural products rely on this transformation in a pivotal step. While the need of an allylic alcohol system limits the generality of this method, it can be a beneficial feature, since selective and directed epoxidation of only one double bond within a polyene can be achieved.

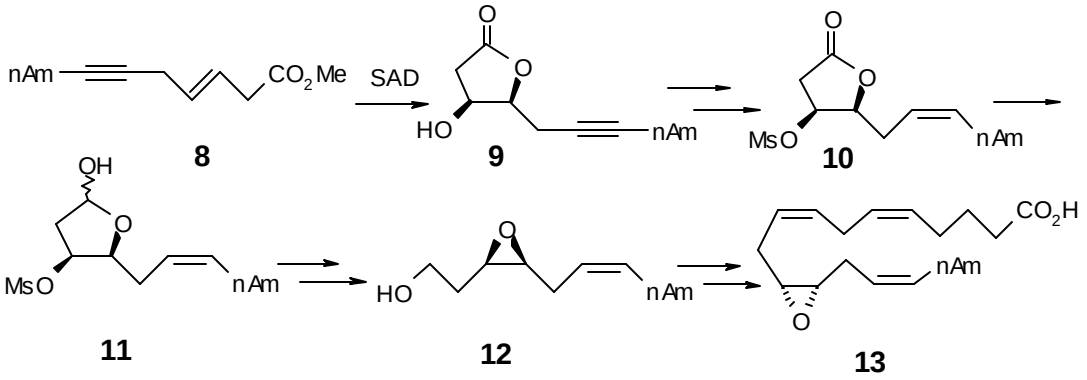
There are currently only few methods for the direct enantioselective epoxidation of olefins bearing no directing functional groups in close proximity to the double bond.[4] In contrast, the Sharpless asymmetric dihydroxylation (SAD) of olefins, needless of directing groups has reached a high level of efficiency due to recent advances in reaction conditions and ligands[5] employed. Thus, enantiomeric excess of greater than 90% can now be achieved with a number of olefins representing four of the six olefin substitution classes. The chiral 1,2-diol provides varied opportunities to achieve different functionality in asymmetric synthesis. One among them is stereospecific conversion of diol into epoxide. One way of achieving this conversion is by carrying out SAD of allylic halides. For example, the SAD of olefin **1** gives diol **2**, which is then converted into the terminal epoxide **3**. To get an internal epoxide, the free hydroxyl is converted into a leaving group and the terminal epoxide opened regioselectively to give **5**. Second epoxidation gave internal epoxide **6**. This strategy has been employed in the synthesis of the insect pheromone (6*Z*,9*S*,10*R*)-9,10-epoxyhenicos-6-ene **7**[6] (**Scheme 1**).



Scheme 1

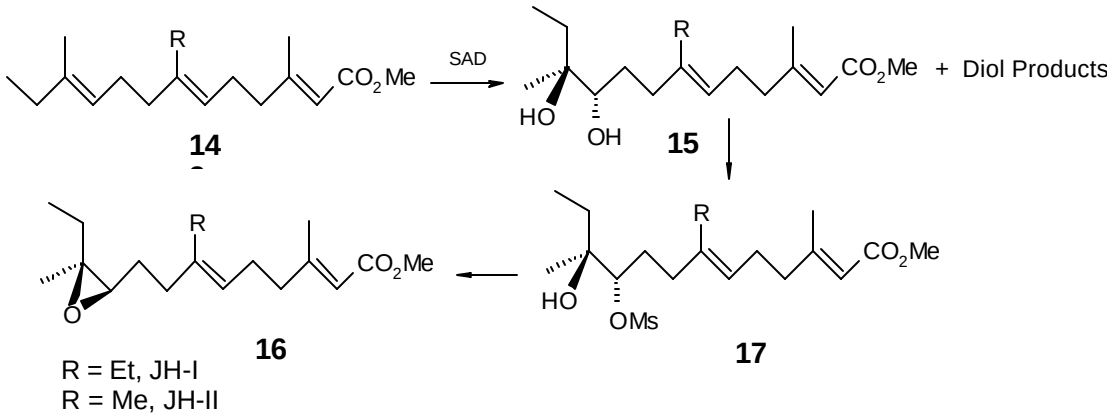
Another method employed to make an epoxide *via* dihydroxylation, is to involve one hydroxyl in an intramolecular reaction (compound **9**) and convert the other hydroxyl into a leaving group (compound **10**), followed by releasing the first hydroxyl and epoxidation. This

strategy has been employed in the synthesis of vascular anti-inflammatory eicosanoid (11*R*,12*S*)-oxidoarachidonic acid **13**[7] (**Scheme 2**).



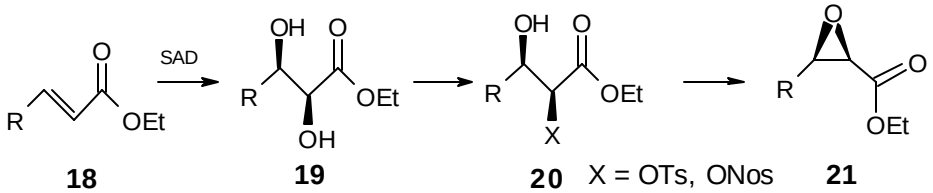
Scheme 2

When two hydroxyl groups differ in reactivity, one hydroxyl can be converted into a leaving group (compound **17**) and displaced by the second hydroxyl to give the epoxide. For example, Mori *et al.*[8] synthesized the (10*R*,11*S*)-(+)-Juvenile Hormone I and II by employing the above strategy (**Scheme 3**).



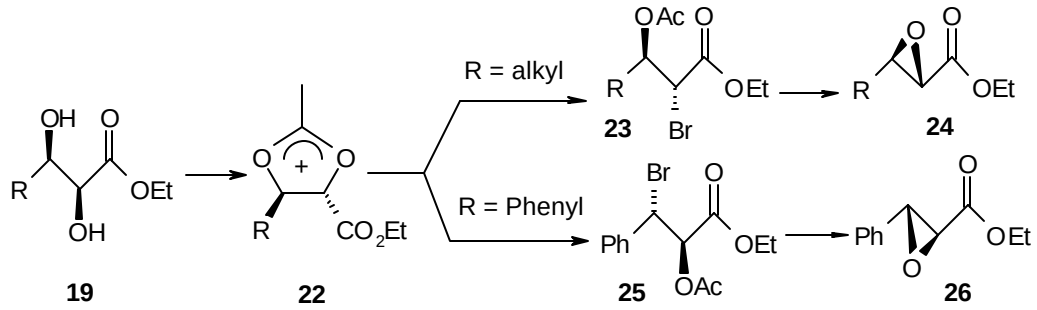
Scheme 3

α,β-Epoxy esters have been conveniently synthesized from corresponding α,β-dihydroxy esters (**19**) *via* conversion of α-hydroxyl into a leaving group, either tosylate or nosylate (**20**). This gives the *cis*-epoxide (**21**) (**Scheme 4**).[9]



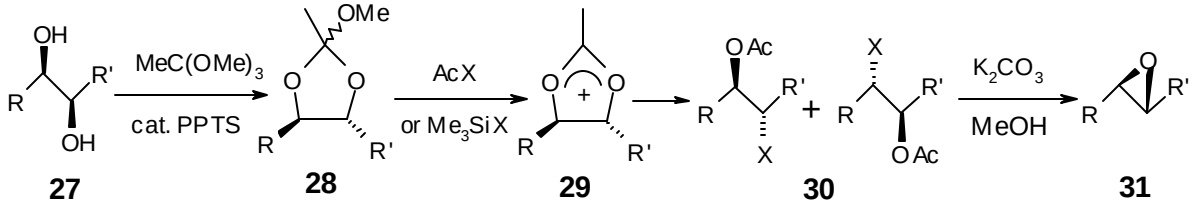
Scheme 4

However, treatment of α,β-dihydroxy ester with HBr in acetic acid gave acetoxy bromide ester (**23**) or (**25**), which on basic methanolysis afforded *trans*-epoxide (**24**) or (**26**) respectively (**Scheme 5**).[9]



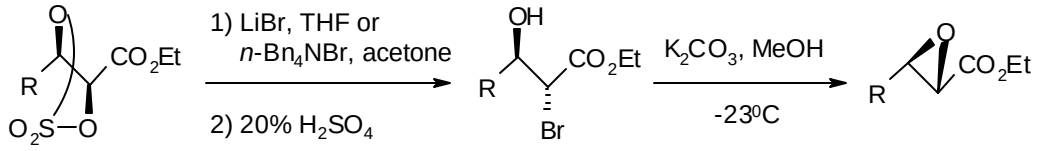
Scheme 5

Sharpless *et al*.[10] have developed a one-pot conversion of diol into epoxide *via* a halohydrin ester intermediate. This involves conversion of diol (**27**) into cyclic orthoacetate (**28**) followed by opening of a cyclic acetoxonium intermediate (**29**), generated from the orthoacetate (**28**) and Me_3SiCl, AcBr or AcCl/NaI giving 1-acetoxy-2-halide intermediate (**30**). Subsequent base mediated methanolysis gives epoxide (**31**) (**Scheme 6**).



Scheme 6

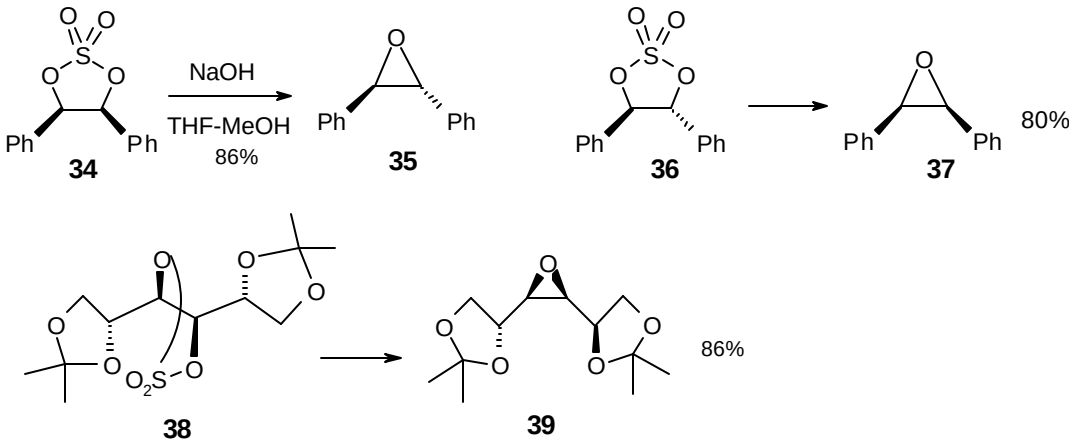
α,β-Epoxyesters (**24**) have also been synthesized from cyclic sulfates (**32**) obtained from chiral diol with the intermediate formation of 2-bromo-3-hydroxyesters (**33**) (**Scheme 7**).[11]



R = *t*-Bu, -CO_2*i*Pr, -CH_2OPMP, $C_{15}H_{31}$, Ph, *c*-C_6H_{11}

Scheme 7

On the other hand cyclic sulfates obtained from chiral diol on treatment with NaOH in THF-MeOH give epoxides directly (**Scheme 8**).[12]



Scheme 8

Thus, varied approaches from a chiral diol compound to chiral epoxide are available. Although this involves one-pot or more than one-step conversions, many a time it is much more compatible in terms of both, yields and enantioselectivities, to that of direct epoxidation. In our work on the synthesis of bioactive molecules like (+)-diolmycin A2 and (+)- and (–)-posticlure, we have converted the chiral diols obtained *via* asymmetric dihydroxylation into chiral epoxides and extrapolated them to achieve the synthesis of target molecules.

ENANTIOSELECTIVE SYNTHESIS OF (+)-DIOLMYCIN A2

4.2.1. Introduction

Omura and coworkers, in a search for new anticoccidial agents, recently isolated four active compounds designated diolmycins A1, A2, B1 and B2 (**40**-**43**, **Figure 1**) from the fermentation broth of *Streptomyces* sp. WK-2955.[13] Diolmycin A1 showed anticoccidial activity at concentrations ranging above 0.02 μg/mL and diolmycin A2 at 0.2 μg/mL. Diolmycins B1 and B2 showed poor anticoccidial activity at concentrations above 20 μg/mL.[14] The structures of diolmycins were determined by spectroscopic analysis.[14] The coupling constants between the vicinal protons of the two chiral carbons of **40** and **41** were 5.4 and 2.2 Hz respectively, suggesting an *erythro*-configuration for **40** and a *threo*-configuration for **41**. Diolmycins A1 and A2 are stereoisomers with the structure of 1-(3-indoyl)-4-(*p*-hydroxyphenyl)-2,3-butanediol. From the chemical synthesis, the relative configurations of diolmycins A1 and A2 were confirmed to be *erythro*- and *threo*-isomers, respectively. The structures of diolmycins B1 and B2 were also deduced to be *erythro*- and *threo*-1,4-di(*p*-hydroxyphenyl)-2,3-butanediol respectively.

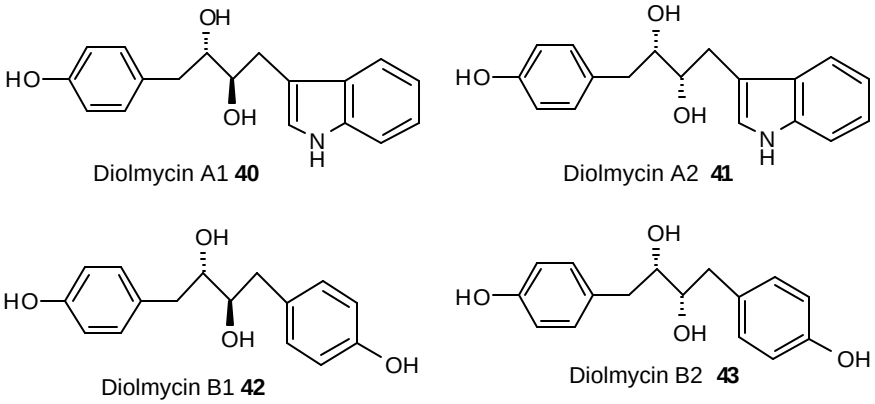


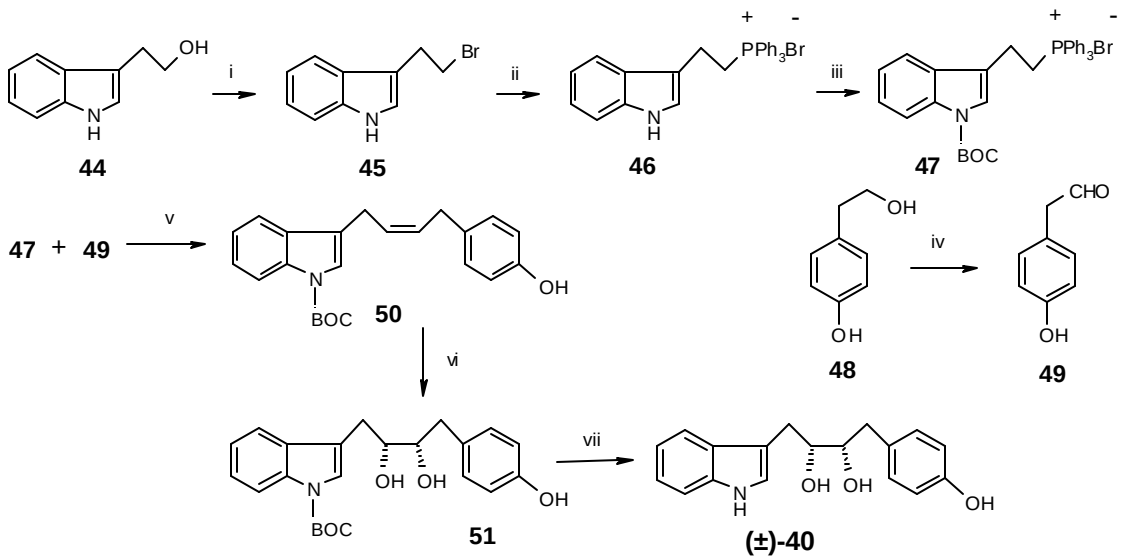
Figure 1. Diolmycins

4.2.2. Review of Literature

With the structure elucidation of all diolmycins, the first total synthesis of (±)-diolmycin A1 was reported by Omura and coworkers,[14] which confirmed the deduced structure and the relative stereochemistry. Subsequently an asymmetric synthesis of diolmycin A1 **40**, was also reported by Omura and coworkers[15] by exploiting the principle of kinetic resolution of an allylic alcohol *via* the Sharpless asymmetric epoxidation. The first asymmetric synthesis of diolmycin A2 **41** from L-tartaric acid is recently reported by Kotsuki and coworkers[16] through the ytterbium(III) trifluoromethanesulfonate catalyzed high-pressure ring opening of an intermediate epoxide with indole as the key step. All these syntheses are described below in fair details.

Omura *et al.*[14] (1993) Scheme 9

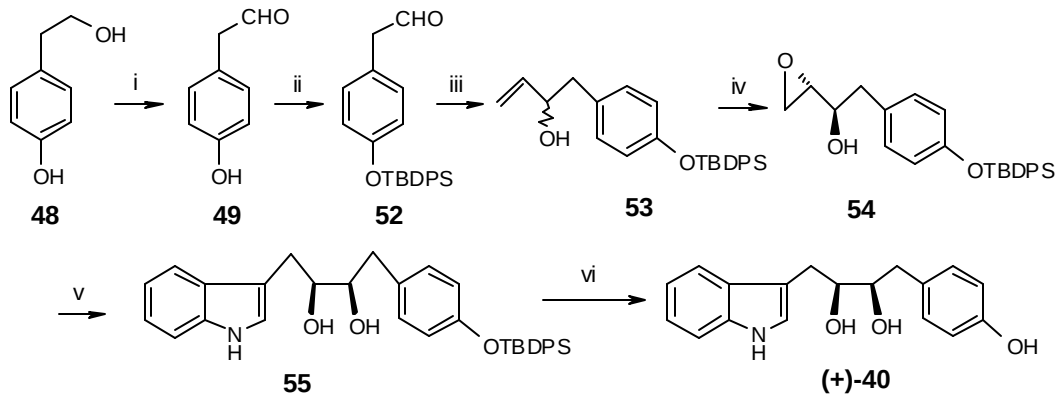
In this report the synthesis of (±)-diolmycin A1 **40** is described *via* stereoselective Wittig reaction of 3-(1-*tert*-butoxycarbonyl)indoleethyltriphenylphosphoniumbromide **47** and 4-hydroxyphenylacetaldehyde **49**. The resulting *cis*-olefin **50** is oxidized by osmium tetroxide (cat) and NMO to yield *erythro*-diol **51**. Removal of BOC-protection gave (±)-diolmycin A1 **40**.



Scheme 9. Reaction conditions: (i) CBr_4, Ph_3P, THF, rt, 15 min, 100%. (ii) Ph_3P, $PhCH_3$, reflux, 18 h, 99%. (iii) $(BOC)_2O$, DMAP, CH_3CN, rt, 5 h, 72%. (iv) SO_3-pyridine, DMSO, Et_3N, rt, 1 h, 71%. (v) LiHMDS, THF, 0°C, 60%. (vi) OsO_4 (cat), NMO, THF-H_2O (10:1), rt, 3 h, 55%. (vii) CF_3CO_2H, CH_2Cl_2, 0°C, 1.3 h, 91%.

Omura *et al.*[15] (1993) Scheme 10

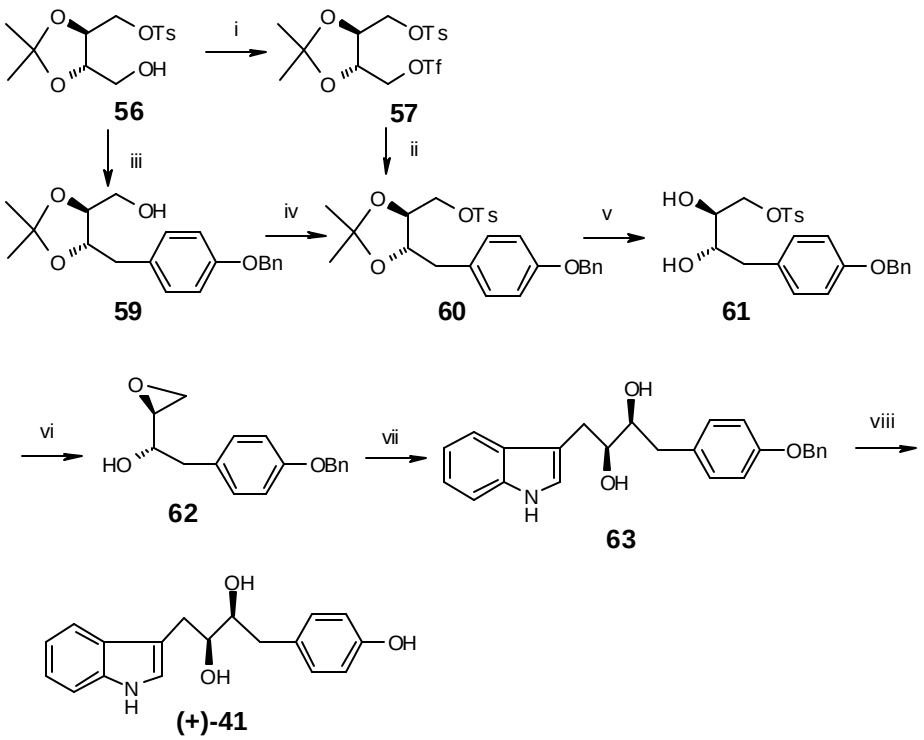
Omura and coworkers reported the asymmetric synthesis of (+)-diolmycin A1 **40** from commercially available 2-(*p*-hydroxyphenyl)ethanol **48**. Alcohol **48** was oxidized to aldehyde **49** followed by phenolic hydroxyl protection as TBDPS ether to give **52**. Grignard reaction of vinyl magnesium bromide on **52** gave the allylic alcohol **53**. Kinetic resolution of (±)-**53** *via* Sharpless asymmetric epoxidation furnished the desired epoxy alcohol (−)-**54** in 90% ee. Stereospecific alkylation of indole with epoxide **54** in the presence of Lewis acid $SnCl_4$ afforded the diol **55**, which on subsequent deprotection of TBDPS group gave (+)-diolmycin A1 **40**.



Scheme 10. Reaction conditions: (i) SO_3-pyridine, DMSO, Et_3N, 71%. (ii) *t*-$BuPh_2Si$-Cl, imidazole, 95%. (iii) CH_2=CHMgBr, THF, 51%. (iv) (−)-DIPT, Ti(O-*i*Pr)$_4$, cumene-hydroperoxide, −20°C, 2 d, 45%. (v) Indole, $SnCl_4$, CCl_4, 0°C, 32%. (vi) TBAF, 89%.

Kotsuki *et al.*[16] (1996) Scheme 11

Kotsuki and coworkers have employed the ytterbium(III) trifluoromethanesulfonate catalyzed high-pressure ring opening of epoxide **62** with indole as the key step in the synthesis of (+)-diolmycin A2 **41**. The required epoxy alcohol **62** is successfully assembled from monotosylate **56** readily available from L-tartaric acid.[17] Triflation of **56** to **57**, followed by Grignard reaction with **58** gave the tosylate **60**. Alternatively, **60** is prepared by adding excess Grignard reagent to **56** to give **59**, followed by tosylation. Deprotection of acetonide group in **60** followed by base treatment afforded the epoxy alcohol **62**. The epoxide **62** is opened with indole in CH_2Cl_2 containing 5 mol% Yb(OTf)$_3$ and 5 mol% H_2O, by subjecting to a high pressure of 10 kbar and 60°C for 42 h to give the adduct **63**. Catalytic debenzylation of **63** provided (+)-diolmycin A2 **41.**



Scheme 11. Reaction conditions: (i) Tf_2O, Et_3N. (ii) *p*-benzyloxy phenyl magnesium bromide **58**, CuBr, Et_2O, 0°C, 75% from **56**. (iii) Excess **58**, CuBr, Et_2O, 0°C. (iv) *p*-TsCl, pyridine, 28% from **56**. (v) 60% $HClO_4$, rt, 2 h. (vi) K_2CO_3, MeOH, rt, 1 h, 88% from **60**. (vii) Indole, 5 mol% $Yb(OTf)_3$, 5 mol% H_2O, CH_2Cl_2, 10 kbar, 60°C, 42 h, 51%. (viii) H_2, $Pd(OH)_2/C$, 100%.

4.2.3. Present Work

Objective

A very few syntheses of diolmycins are documented in the literature either by kinetic resolution or from chiral material like L-tartaric acid. Hence, a general strategy with fewer steps and higher optical purity to achieve the synthesis of all diolmycins is still desirable. The SAD of α,β-unsaturated esters with *trans*-olefinic bond provides an excellent approach to *threo*-diol in high enantiomeric purity. Since (+)-diolmycin A2 **41** has a *threo*-diol configuration, it can easily be derived through the asymmetric dihydroxylation method.

In a recent report, it has been shown that acylation of indole in the presence of Lewis acid is greatly enhanced if CH_3NO_2 is employed as cosolvent,[18] since it greatly increases the solubility of solid indole-Lewis acid complex. This prompted us to explore the possibility of regioselective C-3 alkylation of indole with epoxide in the presence of Lewis acid and the reaction being assisted by CH_3NO_2 cosolvent. The SAD reaction of allylic halides[6] or α,β-unsaturated esters[10] can be extended to make terminal or internal epoxides.[6,10] Thus, the objective of present work is,

(i) to employ SAD reaction in the synthesis of an intermediate epoxide for alkylation of indole and

(ii) to explore the possibility of regioselective C-3 coupling of indole with the intermediate epoxide in the presence of a Lewis acid and employing CH_3NO_2 as cosolvent to assist the alkylation reaction towards the synthesis of (+)-diolmycin A2 **41** (**Figure 2**).

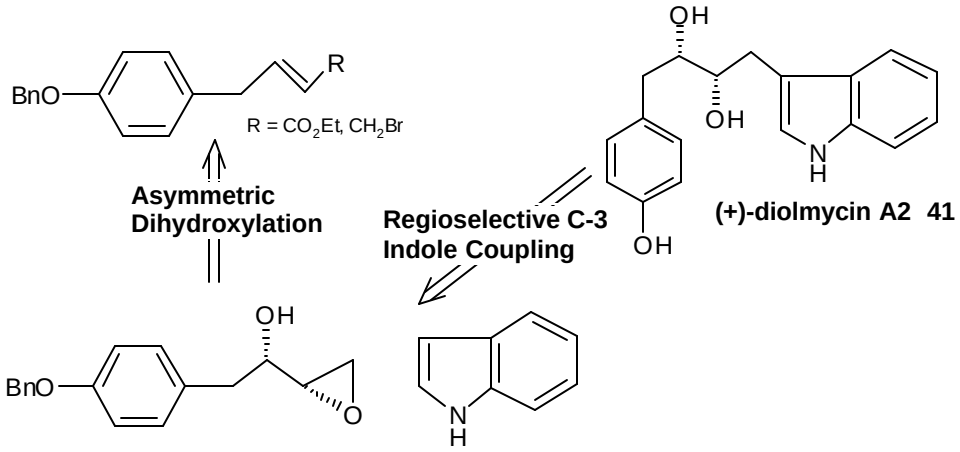
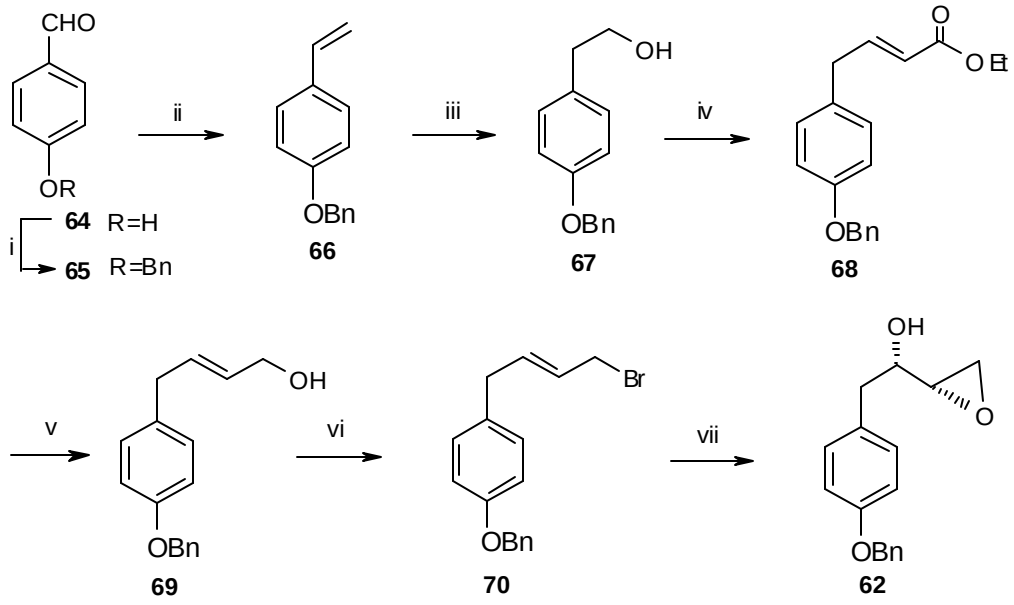


Figure 2. Synthetic Strategy

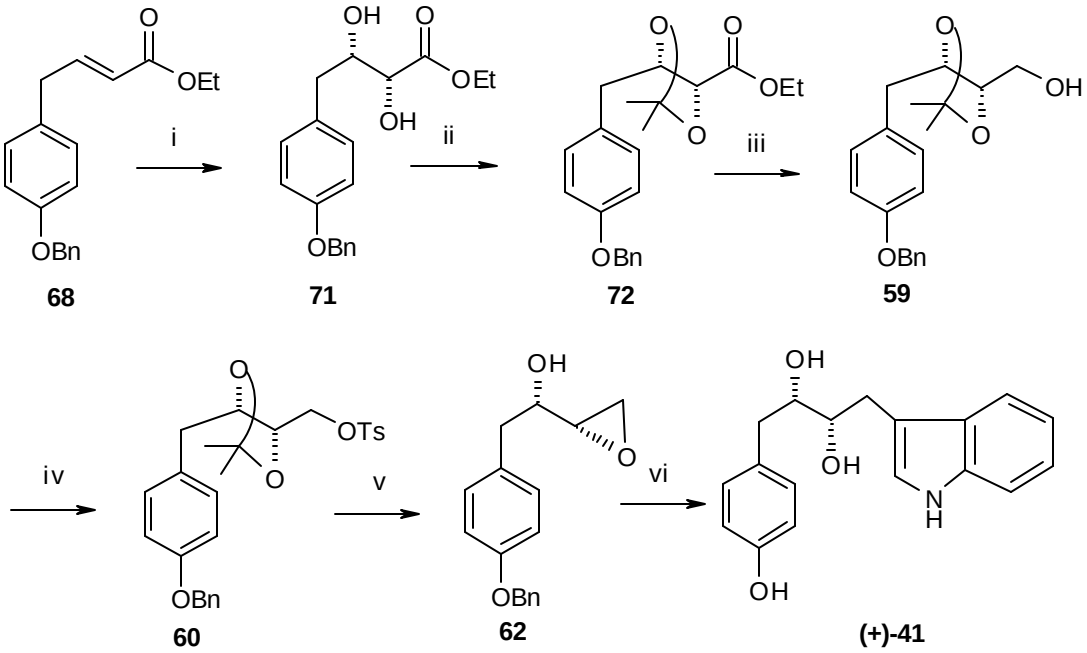
4.2.4. Results and Discussion

Schemes 12 and **13** depict the synthetic route to (+)-diolmycin A2 **41** by employing the Sharpless asymmetric dihydroxylation to get the *threo*-diol functionality and its elongation to chiral epoxy alcohol intermediate **62**, which is then used for regioselective C-3 coupling of indole. The synthesis of intermediate epoxy alcohol **62** commences from commercially available 4-hydroxy benzaldehyde **64** as shown in **Scheme 12**. The protection of hydroxyl group of **64** with benzyl bromide in DMF gave 4-benzyloxybenzaldehyde **65** in 99% yield. The benzylic methylene of **65** appeared as singlet at δ 5.16 in the ^{1}H NMR spectrum. The subsequent Wittig olefination of **65** with the one carbon ylide generated from methyltriphenylphosphoniumiodide and sodium amide gave the styrene compound **66** in 78% yield. The ^{1}H NMR spectrum of **66** showed olefinic signals of styrene at δ 5.59 (singlet), 5.68 (singlet) and 6.7 (multiplet). 4-Benzyloxy styrene **66** was subjected to hydroboration oxidation using $BH_3.Me_2S$ complex in THF and alkaline 30% H_2O_2 oxidation to afford the primary alcohol **67** in 88% yield. The IR spectrum of **67** showed hydroxyl absorption at 3402 cm^{-1} and the ^{1}H NMR spectrum gave two triplets at δ 2.82 for benzylic methylene and δ 3.83 for hydroxyl methylene. This indicates as expected, the formation of only the primary alcohol in the hydroboration oxidation and not the regioisomeric secondary alcohol. Swern oxidation of alcohol **67** with oxalyl chloride and DMSO at –78°C to – 60°C and work-up with Et_3N gave the corresponding aldehyde, which was virtually pure by ^{1}H NMR spectrum, showing δ 9.8 singlet for aldehyde proton. The aldehyde was used for subsequent Wittig reaction with (ethoxycarbonylmethylene)triphenylphosphorane in THF at room temperature to give the *trans*-olefin **68** in 72% yield. The IR spectrum of **68** showed strong absorption at 1713 cm^{-1} for ester carbonyl and a moderate absorption at 1651 cm^{-1} for C=C stretching of olefin. The olefin proton (α- to carbonyl) appeared at δ 5.85 (doublet of triplet) and the other, one proton peak merged with aryl protons at δ 7.14 as multiplet. The coupling constant of J = 16 Hz for olefinic peak indicated *trans*-olefin. DIBAL-H reduction of the ester group in **68** in Et_2O at 0°C gave the allylic alcohol **69** in 93% yield. The IR spectrum of **69** showed hydroxyl absorption at 3339 cm^{-1} and C=C stretching of olefin at 1611 cm^{-1}. The ^{1}H NMR spectrum showed absence of ethyl ester peaks and presence of hydroxyl proton, which appeared as broad singlet at δ 2.15. The hydroxyl methylene protons appeared at δ 4.15 (multiplet) in the ^{1}H NMR spectrum and the corresponding carbon appeared at δ 62.96 in the ^{13}C NMR spectrum. The allylic alcohol **69** was converted into allylic bromide **70** with NBS and

triphenylphosphine in CH_2Cl_2 at −30°C in 83% yield. Both IR and ^1H NMR spectra indicated the absence of hydroxyl group. Asymmetric dihydroxylation of allylic bromide **70** in the presence of $(DHQ)_2$-PHAL as chiral ligand gave the diol, which on subsequent treatment with K_2CO_3 in dry methanol afforded the epoxide **62** in 73% yield, having m.p. 67-69°C and $[\alpha]_D^{20}$ + 11.07 (c = 1, $CHCl_3$) which are in accordance with the literature data, m.p. 68-69°C and $[\alpha]_D^{20}$ + 11.2 (c = 0.98, $CHCl_3$)[16] respectively. The IR spectrum of **62** showed strong absorption at 3443 cm^{-1} for hydroxyl group. The ^1H NMR spectrum of **62** showed epoxide protons appearing upfield at δ 2.62-2.65 (doublet of doublet, one proton), 2.77 (triplet, one proton) and 3.04 (multiplet, one proton). The ^{13}C NMR spectrum of **62** showed upfield carbons characteristic of epoxide at δ 44.87 and 54.61.



Scheme 12. Reaction conditions: (i) BnBr, K_2CO_3, DMF, TBAI (cat), rt, 24 h, 99%. (ii) $Ph_3P{=}CH_2$, THF, rt, 24 h, 78%. (iii) (a) $BH_3.Me_2S$, THF, rt, 4 h, (b) NaOH in EtOH:H_2O (2:1), then 30% aq. H_2O_2, 0°C, 3 h, 88%. (iv) (a) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C, Et_3N, −60°C, 1 h, (b) $Ph_3P{=}CHCO_2Et$, THF, rt, 24 h, 72%. (v) DIBAL-H, Et_2O, 0°C, 1 h–rt, 30 min, 93%. (vi) NBS, Ph_3P, CH_2Cl_2, −30°C, 4 h, 83%. (vii) (a) $K_3Fe(CN)_6$, K_2CO_3, $(DHQ)_2PHAL$, OsO_4 (cat), $NaHCO_3$, $MeSO_2NH_2$, *t*-BuOH:H_2O (1:1), 0°C, 18 h, (b) MeOH, K_2CO_3, rt, 10 h, 73%.

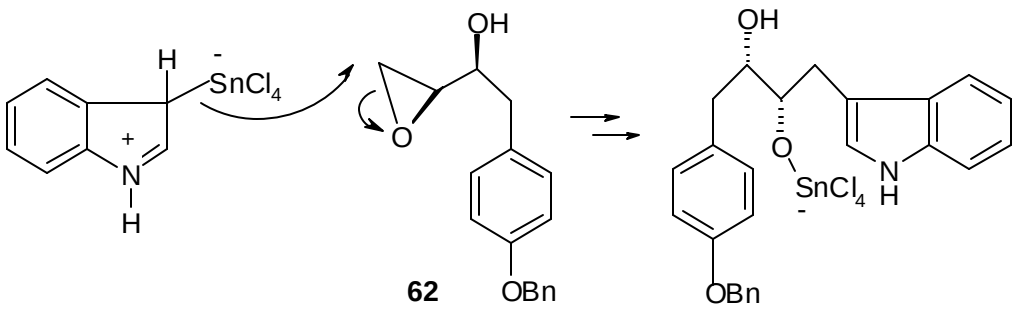


Scheme 13. Reaction conditions: (i) $K_3Fe(CN)_6$, K_2CO_3, $(DHQ)_2PHAL$, OsO_4 (cat), $MeSO_2NH_2$, *t*-BuOH:H_2O (1:1), 0°C, 24 h, 91%. (ii) 2,2-DMP, *p*-TsOH (cat), $(CH_3)_2CO$, rt, overnight, 99%. (iii) $LiAlH_4$, Et_2O, 0°C to rt, overnight, 97%. (iv) *p*-TsCl, pyridine, CH_2Cl_2, rt, 12 h, 90%. (v) (a) 3N HCl, MeOH, rt, 12 h, (b) K_2CO_3, MeOH, rt, 10 h, 85%. (vi) (a) Indole, $SnCl_4$, CH_2Cl_2:CH_3NO_2 (4:3), 0°C-rt, 12 h, (b) 10% Pd-C, EtOH, H_2, rt, 18 h, 53%.

Alternatively, the epoxide **62** was prepared from compound **68** following the reaction sequence shown in **Scheme 13**. The dihydroxylation of olefin **68** using the $(DHQ)_2$-PHAL ligand gave the diol **71** in 91% yield, having $[\alpha]_D^{20}$ – 29.8 (c = 1, $CHCl_3$) and m.p. 104-106°C. The IR spectrum showed absence of olefin peak, while strong hydroxyl absorption appeared at 3488 cm^{-1} and ester carbonyl at 1732 cm^{-1}. The ^1H NMR spectrum of **71** showed absence of olefin protons. The chiral carbons appeared at δ 71.9 and 73.5 in the ^{13}C NMR spectrum of **71**. The dihydroxyl protection of **71** with 2,2-dimethoxypropane in the presence of catalytic *p*-TsOH in acetone gave the acetonide **72** in 99% yield. The hydroxyl absorption was absent in the IR spectrum of **72**. Two singlets at δ 1.44 and 1.48 in the ^1H NMR spectrum and a peak at δ 110.49 (acetonide carbon) in the ^{13}C NMR spectrum indicated presence of isopropylidene group in **72**. Reduction of ester group in **72** with $LiAlH_4$ at 0°C in Et_2O gave the alcohol **59** in 97% yield. The IR spectrum of **59** showed absence of ester carbonyl, while hydroxyl absorption appeared at 3468 cm^{-1}. In the ^1H NMR spectrum of **59** the characteristic triplet and quartet of the ethyl ester disappeared indicating ester group reduction. The free hydroxyl in **59** was converted into the

tosylate **60** with *p*-TsCl and pyridine in CH_2Cl_2 at room temperature in 90% yield. The m.p. 83-84°C and $[\alpha]_D^{20}$ – 19.62 (c = 1, $CHCl_3$) obtained for **60** are in accordance with the reported values of m.p. 83.5-84°C and $[\alpha]_D^{20}$ – 19.7 (c = 1.07, $CHCl_3$)[16] respectively. The hydroxyl absorption in the IR spectrum disappeared. The ^{1}H NMR spectrum of **60** showed aryl methyl at δ 2.44 (singlet) for tosyl group. The deprotection of acetonide in **60** was effected with 3N HCl in MeOH to give the diol which was immediately treated with K_2CO_3 in dry MeOH at room temperature to afford the epoxide **62** in 85% yield, having $[\alpha]_D^{20}$ + 11.12 (c = 1, $CHCl_3$) and m.p. 67-69°C. All spectroscopic data matched well with that of **62** prepared as per **Scheme 12**.

With the enantiomerically pure epoxide **62** in hand the next step involved an efficient coupling with indole at the C-3 position. Although, the 3-position is the most reactive site for electrophilic attack, low yields are usually encountered due to the competitive formation of 1-alkylated and/or 1,3-dialkylated products often associated with self polymerization of indole as side product.[19] However the recent report about an improved synthesis of 3-acylindoles by Ottoni *et al.*[18] prompted us to explore the Lewis acid catalyzed regioselective C-3 coupling of indole with epoxide **62** for diolmycin synthesis. It has been observed that in C-3 acylation of indole using Lewis acid, the addition of CH_3NO_2 as co-solvent greatly increases the solubility of the solid indole-Lewis acid complex in the reaction media, shortening the reaction time and raising the yields significantly.[18] Indeed, following the above procedure, the treatment of epoxide **62** with indole in a mixture of CH_2Cl_2 and CH_3NO_2 (4:3) in the presence of $SnCl_4$ as the Lewis acid gave the C-3 coupled product in good yield. A probable mechanism of this reaction is depicted in **Scheme 14**. Presumably the Lewis acid $SnCl_4$ complexes at 3-position of indole, it being the most reactive site for electrophilic attack. The intermediate thus formed would then collapse in a nucleophilic attack toward the epoxide, eventually leading to the C-3 coupled indole. The subsequent deprotection of benzyl group with 10% Pd-C in EtOH under H_2 atmosphere furnished (+)-diolmycin A2 **41** in 53% yield. The $[\alpha]_D^{20}$ + 46.32 (c = 0.2, MeOH) obtained for (+)-**41** is in accordance with reported value of $[\alpha]_D^{27}$ + 49.2 (c = 0.24, MeOH).[16] The structure of (+)-**41** was confirmed by IR, ^{1}H NMR, and EIMS analysis. The IR spectrum of (+)-**41** showed hydroxyl and NH- absorptions at 3417 cm^{-1}. The protons of chiral carbons appeared in the ^{1}H NMR spectrum of (+)-**41** at δ 3.66 and 3.9 (doublet of doublet of doublet each) with a coupling constant of J = 2 Hz, indicating the expected *threo*-configuration. The EIMS showed a molecular ion peak at *m/z* 297 and a peak at *m/z* 130, characteristic of the indole moiety.



Scheme 14. Alkylation of the Complex Indole-$SnCl_4$

To determine the enantiomeric purity, the compounds **62** (**Scheme 12**) and **59** were converted into their corresponding Mosher esters with (*S*)-(+)-2-methoxy-α-trifluoromethyl-acetylchloride, pyridine and DMAP (cat) in CH_2Cl_2 solvent. The diastereomers formed were analyzed by ^1H NMR and ^{19}F NMR spectra. Analysis indicated an enantiomeric purity of greater than 95% ee.

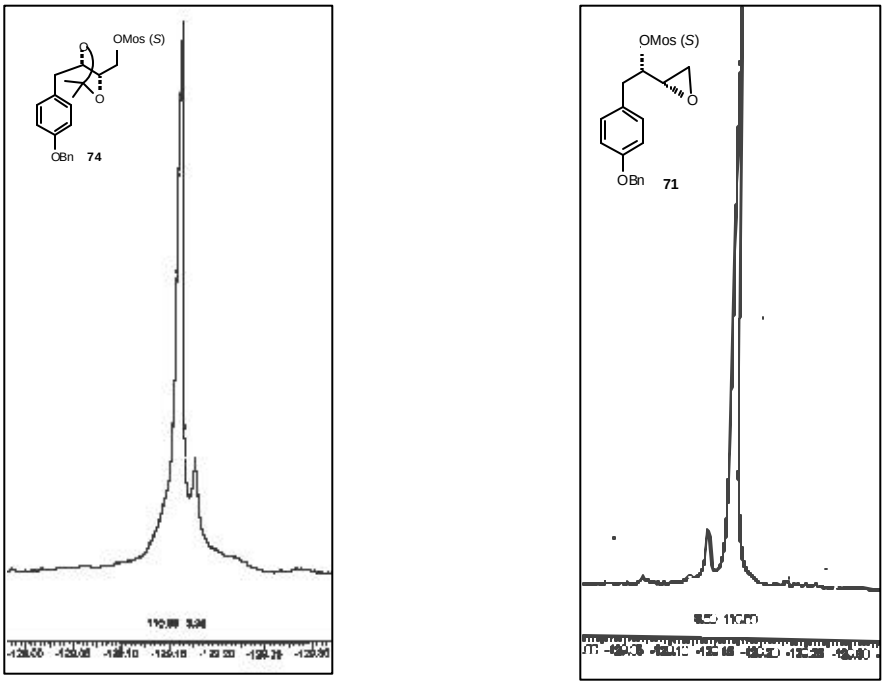


Figure 3. ^{19}F NMR Spectra of Mosher esters of **59** and **62**.

4.2.5. Conclusion

In summary, a highly enantioselective synthesis of (+)-diolmycin A2 **41**, a recently discovered anticoccidial antibiotic has been achieved from readily accessible starting material, 4-hydroxybenzaldehyde by a simple and operationally feasible synthetic strategy.[20]

There are two noteworthy features in the synthetic strategy employed.

(i) the application of SAD reaction to produce a chiral diol and subsequent conversion of the diol into epoxide intermediate **62** in high enantiomeric purity.

(ii) the intermolecular highly regioselective C-3 coupling of indole, assisted by CH_3NO_2 as cosolvent, which greatly assists the reaction by increasing the solubility of the solid indole-lewis acid complex. A probable mechanism for this reaction is also proposed.

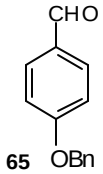
The synthetic strategy employed has significant potential for further extension to the asymmetric synthesis of other analogues of diolmycin A2 by either changing the chiral ligand employed in the SAD reaction or using the *cis*-olefin in place of the *trans*-olefin to get the *erythro*-diol functionality (present in diolmycin A1 **40** and B1 **42**). While quite a few synthetic approaches towards diolmycins are known, this new route with high yielding steps and enantiomeric purity will provide an alternative to diolmycin synthesis for biological evaluations.

4.2.6. Experimental section

General Information

Solvents were purified and dried by standard procedures before use. Petroleum ether of boiling range 60-80°C was used. Melting points are uncorrected. Optical rotations were measured using sodium D line on a JASCO P-1020 microprocessor based polarimeter. Infrared spectra were recorded on ATI MATTSON RS-1 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC-200 spectrometer with residual $CHCl_3$ as internal standard (δ 7.27 ^{1}H NMR and δ 77.00 ^{13}C NMR). Mass spectra were obtained with a TSQ 70, Finningen MAT mass spectrometer. Elemental analyses were carried out on a Carlo Erba CHNS-O analyzer.

Preparation of 4-benzyloxybenzaldehyde, 65



65

To a stirred suspension of K_2CO_3 (34 g, 246 mmol) in dry DMF (200 mL) at room temperature was added 4-hydroxybenzaldehyde **64** (20 g, 163.93 mmol) and TBAI (cat). The mixture was stirred for 30 min and then benzylbromide (28.5 g, 166.6 mmol) was added. The reaction mixture was stirred at room temperature for 24 h and then quenched with water and extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with water (2 × 100 mL), brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether:EtOAc (85:15) as eluent gave **65** (34.41 g) as a white solid.

Yield: 34.41 g, 99%

Mp.: 78-79°C

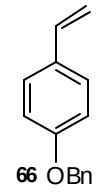
IR ($CHCl_3$, cm^{-1}): n_{max} 2728, 1690, 1601, 1578, 832, 758

^{1}H NMR (200 MHz, $CDCl_3$): δ 5.16 (s, 2H), 7.1 (d, *J* = 8 Hz, 2H), 7.3 (m, 5H), 7.85 (d, *J* = 8 Hz, 2H), 9.9 (s, 1H)

EIMS *m/z* (relative intensity, %): 212 [M^+] (4.3), 91 (100), 65 (9.5)

Analysis: $C_{14}H_{12}O_2$ (212.3) requires C, 79.23; H, 5.69. Found: C, 79.18; H, 5.74.

Preparation of 4-benzyloxystyrene, 66



66

To a mixture of methyltriphenylphosphoniumiodide (24 g, 59.35 mmol) and sodium amide (3.48 g, 89.23 mmol) was added dry THF (150 mL) and stirred for 12 h at room temperature. The yellow supernatant liquid was added through a syringe to the solution of **65** (10 g, 47.11 mmol) in dry THF (20 mL). The reaction mixture was stirred for 24 h at room temperature and then quenched with 2% aq. HCl and extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with water (2 × 100 mL), brine, dried (Na_2SO_4) and concentrated. Silica

gel column chromatography of the crude product using petroleum ether:EtOAc (95:5) as eluent gave **66** (7.72 g) as a white solid.

Yield: 7.72 g, 78%

Mp.: 71-72°C (lit. 68-69°C) [16]

IR ($CHCl_3$, cm^{-1}): n_{max} 1606, 1510, 836, 759

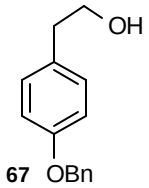
^{1}H NMR (200 MHz, $CDCl_3$): δ 5.09 (s, 2H), 5.59 (s, 1H), 5.68 (s, 1H), 6.7 (m, 1H), 6.95 (d, *J* = 8 Hz, 2H), 7.35-7.44 (m, 7H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 69.94, 111.6, 114.9, 127.36, 127.84, 128.46, 130.7, 136.18, 136.95, 158.57

EIMS *m/z* (relative intensity, %): 210 [M^+] (38), 91 (100), 65 (3.6)

Analysis: $C_{15}H_{14}O$ (210.26) requires C, 85.67; H, 6.71. Found: C, 85.49; H, 6.86.

Preparation of 2-(*p*-benzyloxyphenyl) ethanol, 67



67

To a solution of **66** (10 g, 47.56 mmol) in dry THF (100 mL) at 0°C under argon atmosphere was added $BH_3.Me_2S$ (24 mL, 48 mmol, 2M solution in THF) and the reaction mixture was allowed to warm to room temperature and stirred for 4 h. The reaction flask was cooled to 0°C and then a solution of NaOH (24 g, 96 mmol) in EtOH:H_2O (2:1, 60 mL), followed by H_2O_2 (16.4 mL, 144 mmol, 30% w/v solution in water) were added dropwise over 30 min. It was then allowed to stir at room temperature for 3 h. The product was taken up in EtOAc and the aqueous layer extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine, water, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether:EtOAc (8:2) as eluent gave **67** (9.55 g) as a white solid.

Yield: 9.55 g, 88%

Mp.: 85-86°C

IR ($CHCl_3$, cm^{-1}): n_{max} 3402, 1611, 1511, 824, 757

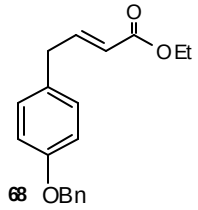
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.72 (br s, 1H), 2.82 (t, *J* = 6 Hz, 2H), 3.83 (t, *J* = 6 Hz, 2H), 5.07 (s, 2H), 6.95 (d, *J* = 8 Hz, 2H), 7.2 (d, *J* = 8 Hz, 2H), 7.3-7.4 (m, 5H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 38.12, 63.45, 69.95, 114.91, 127.26, 127.70, 128.36, 129.79, 130.86, 137.07, 157.36

EIMS *m/z* (relative intensity, %): 228 [M^+] (29), 210 (1.2), 107 (6.6), 91 (100), 65 (5.4)

Analysis: $C_{15}H_{16}O_2$ (228.28) requires C, 78.91; H, 7.06. Found: C, 79.12; H, 6.95.

Synthesis of ethyl *trans*-4-(*p*-benzyloxyphenyl)but-2-enoate, 68



To a solution of oxalyl chloride (5.48 g, 46 mmol) in dry CH_2Cl_2 (50 mL) at −78°C was added dropwise DMSO (6.53 mL, 91.98 mmol) in CH_2Cl_2 (5 mL) over 15 min. The reaction mixture was stirred for 30 min and a solution of **67** (7 g, 30.66 mmol) in CH_2Cl_2 (20 mL) was added dropwise over 15 min. The reaction mixture was stirred for 30 min at −78°C and 30 min at −60°C and then Et_3N (15 mL) in CH_2Cl_2 (10 mL) was added dropwise and stirred for 1 h. The reaction mixture was poured into 10% aq. HCl (100 mL) and the organic layer separated. The aqueous layer was extracted with EtOAc (3 × 50 mL) and the combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated to give the crude aldehyde. This was used for the next step without further purification.

To a solution of (ethoxycarbonylmethylene)triphenylphosphorane (10.5 g, 30.14 mmol) in dry THF (30 mL) was added a solution of the above aldehyde in dry THF (10 mL). The reaction mixture was stirred at room temperature for 24 h. It was then concentrated and the residue purified by silica gel column chromatography using petroleum ether:EtOAc (9:1) as eluent to give **68** (6.54 g) as a pale yellow oil.

Yield: 6.54 g, 72%

IR (neat, cm^{-1}): n_{max} 1713, 1651, 1609, 1509, 910, 733

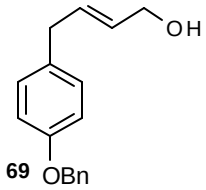
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (t, *J* = 8 Hz, 3H), 3.50 (d, *J* = 6 Hz, 2H), 4.23 (q, *J* = 8 Hz, 2H), 5.07 (s, 2H), 5.85 (dt, *J* = 16, 2 Hz, 1H), 6.98 (d, *J* = 8 Hz, 2H), 7.14 (m, 3H), 7.4 (m, 5H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.07, 37.41, 59.98, 70.02, 115.12, 122.10, 127.25, 127.73, 128.39, 129.64, 130.00, 137.10, 147.35, 157.65, 159.52, 166.25

EIMS *m/z* (relative intensity, %): 296 [M^+] (13.7), 251 (1.8), 127 (10.7), 91 (100), 65 (2.9)

Analysis: $C_{19}H_{20}O_3$ (296.35) requires C, 77.00; H, 6.80. Found: C, 77.02; H, 6.72.

Synthesis of *trans*-4-(*p*-benzyloxyphenyl)-but-2-ene-1-ol, 69



To a stirred solution of **68** (1.5 g, 5.06 mmol) in dry ether (75 mL) at 0°C was added DIBAL-H (12.7 mL, 12.7 mmol, 1M solution in toluene) dropwise over 15 min. The reaction mixture was stirred for 1 h at 0°C and 30 min at room temperature. It was cooled again to 0°C and quenched with 2N HCl. The resulting gel was dissolved by adding 6N HCl. The organic layer was separated and aqueous layer extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether:EtOAc (9:1) as eluent gave **69** (1.2 g) as a colorless liquid.

Yield: 1.2 g, 93%

IR (neat, cm^{-1}): n_{max} 3339, 1611, 1600, 1510, 811, 755

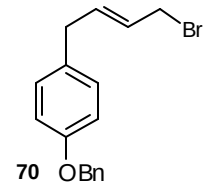
^{1}H NMR (200 MHz, $CDCl_3$): δ 2.15 (brs, 1H), 3.35 (d, *J* = 6 Hz, 2H), 4.15 (m, 2H), 5.06 (s, 2H), 5.62-5.93 (m, 2H), 6.95 (d, *J* = 8 Hz, 2H), 7.31 (d, *J* = 8 Hz, 2H), 7.4-7.48 (m, 5H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 37.52, 62.96, 69.98, 114.90, 127.17, 127.62, 128.28, 128.31, 130.08, 131.29, 132.36, 137.14, 157.17

EIMS *m/z* (relative intensity, %): 254 [M^+] (7.4), 228 (1.9), 91 (100), 77 (6.0), 65 (20.7)

Analysis: $C_{17}H_{18}O_2$ (254.3) requires C, 80.29; H, 7.13. Found: C, 80.52; H, 7.01.

Synthesis of *trans*-4-(*p*-benzyloxyphenyl)-1-bromo-but-2-ene, 70



To a solution of **69** (1 g, 3.93 mmol) in dry CH_2Cl_2 (15 mL) cooled at –30°C was added Ph_3P (1.237 g, 4.72 mmol) followed by NBS (0.84 g, 4.72 mmol). After 4 h of stirring, the reaction mixture was diluted with water (10 mL). The organic layer was separated and aqueous layer extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were washed with brine, dried

(Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether:EtOAc (24:1) gave **70** (1.03 g) as a pale yellow liquid.

Yield: 1.03, 83%

IR (neat, cm^{-1}): n_{max} 1608, 1508, 1454, 825, 736, 695

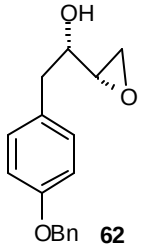
^{1}H NMR (200 MHz, $CDCl_3$): δ 3.39 (d, *J* = 7 Hz, 2H), 4.00 (d, *J* = 8 Hz, 2H), 5.07 (s, 2H), 5.8-5.97 (m, 2H), 6.95 (d, *J* = 8 Hz, 2H), 7.14 (d, *J* = 8 Hz, 2H), 7.38-7.48 (m, 5H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 37.46, 53.45, 70.03, 115.05, 127.37, 127.77, 128.47, 129.24, 129.5, 131.63, 134.10, 135.01, 137.26, 157.47

EIMS *m/z* (relative intensity, %): 318 [M^++1] (6.0), 317 [M^+] (5.0), 292 (1.5), 236 (5.0), 196 (1.6), 91 (100), 77 (5.0), 65 (24.4), 57 (8.8)

Analysis: $C_{17}H_{17}BrO$ (317.3) requires C, 64.35; H, 5.40. Found: C, 64.50; H, 5.72.

Synthesis of (2*S*,3*S*)-4-(*p*-benzyloxyphenyl)-1,2-epoxy-3-hydroxybutane, 62



62

To a mixture of $K_3Fe(CN)_6$ (1.55 g, 4.727 mmol), K_2CO_3 (0.653 g, 4.727 mmol), $(DHQ)_2PHAL$ (12.27 mg, 15.75 μmol, 1 mol%) and $NaHCO_3$ (0.4 g, 4.727 mmol) in *t*-BuOH/H_2O (1:1, 20 mL) at 0°C was added osmium tetroxide (79 μL, 0.1M solution in toluene, 0.5 mol %), followed by methanesulfonamide (0.150 g, 1.575 mmol). After stirring for 2 min at 0°C, the allylic bromide **70** (0.5 g, 1.575 mmol) was added in one portion. The reaction mixture was stirred at 0°C for 18 h and then quenched with solid sodium sulfite (1 g). The stirring was continued for additional 15 min and then the solution was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with 10% aq. KOH and brine, dried (Na_2SO_4) and concentrated. To the residue was added dry MeOH (10 mL) and K_2CO_3 (0.262 g, 1.9 mmol) and the mixture stirred at room temperature for 10 h. Water (20 mL) and EtOAc (20 mL) were added. The organic layer was separated and aqueous layer extracted with EtOAc (2 × 20 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether:EtOAc (4:1) as eluent gave **62** (0.310 g) as a white solid.

Yield: 0.310 g, 73%

Mp.: 67-69°C (lit. 68-69°C)[16]

[a]$_D^{20}$: + 11.07 (c = 1, $CHCl_3$) [lit. + 11.2 (c = 0.98, $CHCl_3$)][16]

IR ($CHCl_3$, cm^{-1}): n_{max} 3443, 1611, 1511, 1177, 1025, 759, 697, 668

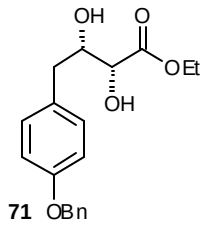
^{1}H NMR (200 MHz, $CDCl_3$): δ 2.09 (s, 1H), 2.62-2.65 (dd, *J* = 2, 4 Hz, 1H), 2.77 (t, *J* = 4 Hz, 1H), 2.86-2.89 (dd, *J* = 4, 2 Hz, 2H), 3.04 (m, 1H), 3.66 (m, 1H), 5.06 (s, 2H), 6.96 (d, *J* = 8 Hz, 2H), 7.18 (d, *J* = 8 Hz, 2H), 7.37-7.48 (m, 5H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 40.02, 44.87, 54.61, 70.09, 72.41, 115.04, 127.32, 127.80, 128.42, 129.60, 130.26, 137.14, 157.68

EIMS (*m/z* relative intensity, %): 270 [M^+] (10.8), 197 (10.2), 107 (3.4), 91 (100), 77 (5.4), 65 (21.6)

Analysis: $C_{17}H_{18}O_3$ (270.3) requires C, 75.53; H, 6.71. Found: C, 75.63; H, 6.98.

Synthesis of ethyl-(2*R*,3*S*)-4-(*p*-benzyloxyphenyl)-2,3-dihydroxybutanoate, 71



To a mixture of $K_3Fe(CN)_6$ (9.93 g, 30.4 mmol), K_2CO_3 (4.2 g, 30.4 mmol) and $(DHQ)_2PHAL$ (78.9 mg, 101 μmol, 1 mol%) in *t*-BuOH/H_2O (1:1, 120 mL) at 0°C was added osmium tetroxide (411 μL, 0.1M solution in toluene, 0.4 mol%), followed by methanesulfonamide (0.964 g, 10.12 mmol). After stirring for 5 min at 0°C, the olefin **68** (3 g, 10.13 mmol) was added in one portion. The reaction mixture was stirred at 0°C for 24 h and then quenched with solid Na_2SO_3 (5 g). The stirring was continued for an additional 45 min and then the solution was extracted with EtOAc (5 × 30 mL). The combined organic layers were washed with 10% KOH, brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether:EtOAc (9:3) as eluent gave **71** (3.05 g) as a white solid.

Yield: 3.05 g, 91%

Mp.: 104-106°C

[a]$_D^{20}$: – 29.8 (c = 1, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): n_{max} 3488, 1732, 1611, 1514, 757

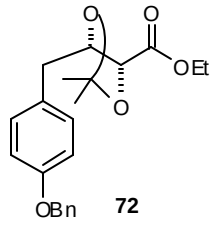
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (t, *J* = 7 Hz, 3H), 2.70 (brs, 2H), 2.90 (d, *J* = 8 Hz, 2H), 4.12 (m, 2H), 4.3 (q, *J* = 7 Hz, 2H), 5.06 (s, 2H), 6.95 (d, *J* = 8 Hz, 2H), 7.22 (d, *J* = 8 Hz, 2H), 7.4 (m, 5H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9, 38.9, 61.6, 69.8, 71.9, 73.5, 114.86, 127.17, 127.65, 128.28, 129.89, 130.23, 136.99, 157.43, 159.41, 173.38

EIMS *m/z* (relative intensity, %): 330 [M^+] (14), 312 (9), 239 (25.6), 197 (14), 107 (16.6), 91 (100), 65 (2.5)

Analysis: $C_{19}H_{22}O_5$ (330.36) requires C, 69.07; H, 6.71. Found: C, 68.85; H, 6.82.

Synthesis of ethyl-(2*R*,3*S*)-4-(*p*-benzyloxyphenyl)-2,3-*O*-isopropylidenedioxybutanoate, 72



72

To a solution of **71** (2.5 g, 7.56 mmol) and *p*-TsOH (cat) in dry acetone (75 mL) was added 2,2-dimethoxypropane (1.2 g, 1.4 mL, 11.35 mmol) and stirred overnight. A pinch of $NaHCO_3$ was added and stirred for 10 min. The reaction mixture was filtered through a short pad of neutral alumina and concentrated. Column chromatography of the crude product using petroleum ether:EtOAc as eluent (9:1) gave **72** (2.77 g) as a colorless oil.

Yield: 2.77 g, 99%

$[\alpha]_D^{20}$: − 17.74 (c = 1, $CHCl_3$)

IR (neat, cm^{-1}): n_{max} 1752, 1611, 1512, 1382, 1297, 1024, 757

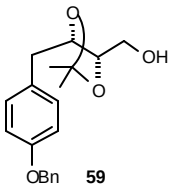
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.27 (t, *J* = 7 Hz, 3H), 1.44 (s, 3H), 1.48 (s, 3H), 2.98-3.10 (m, 2H), 4.15-4.22 (m, 3H), 4.38 (m, 1H), 5.06 (s, 2H), 6.95 (d, *J* = 8 Hz, 2H), 7.30 (d, *J* = 8 Hz, 2H), 7.47 (m, 5H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.7, 25.47, 26.8, 38.0, 60.6, 69.65, 77.5, 79.35, 110.49, 114.5, 126.95, 127.39, 128.06, 128.9, 130.26, 136.95, 137.03, 157.43, 170

EIMS *m/z* (relative intensity, %): 370 [M^+] (9), 312 (6.4), 239 (12.8), 173 (23), 155 (15.4), 91(100), 65 (3.8)

Analysis: $C_{22}H_{26}O_5$ (370.42) requires C, 71.33; H, 7.07. Found: C, 71.52; H, 6.97.

Synthesis of (2*S*,3*S*)-4-(*p*-benzyloxyphenyl)-2,3-*O*-isopropylidenedioxy-butan-1-ol, 59



59

To a stirred suspension of $LiAlH_4$ (307 mg, 8.1 mmol) in dry ether (100 mL) at 0ºC was added **72** (2 g, 5.4 mmol) in ether (10 mL) dropwise. The reaction mixture was warmed to room temperature and stirred overnight. Excess $LiAlH_4$ was destroyed by slow addition of 5% aq. NaOH followed by addition of EtOAc (100 mL). The white cake was filtered and washed with EtOAc (3 × 50 mL) and MeOH (2 × 20 mL). The filtrate was dried (K_2CO_3) and concentrated. Column chromatography of the crude product using petroleum ether:EtOAc (4:1) gave **59** (1.72 g) as a white solid.

Yield: 1.72 g, 97%

Mp.: 58-59°C

$[\alpha]_D^{20}$: − 11.00 (c = 1.2, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): n_{max} 3468, 1610, 1510, 1216, 1038, 763

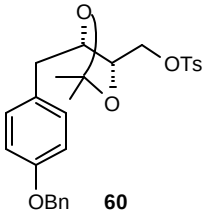
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.43 (s, 6H), 2.8 (m, 1H), 2.99 (m, 1H), 3.15 (brs, 1H), 3.35 (m, 1H), 3.5 (m, 1H), 3.83 (m, 1H), 4.12 (m, 1H), 5.05 (s, 2H), 6.95 (d, *J* = 8 Hz, 2H), 7.18 (d, *J* = 8 Hz, 2H), 7.4 (m, 5H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.72, 26.94, 38.15, 61.86, 69.69, 77.34, 80.90, 108.35, 114.64, 126.99, 127.43, 128.09, 129.31, 129.37, 136.92, 157.32

EIMS *m/z* (relative intensity, %): 328 [M^+] (6.6), 313 [M^+−15] (2.4), 198 (4.2), 131 (55.4), 91 (100), 65 (3.0), 58 (10.2)

Analysis: $C_{20}H_{24}O_4$ (328.4) requires C, 73.14; H, 7.36. Found: C, 73.18; H, 7.45.

Synthesis of (2*S*,3*S*)-4-(*p*-benzyloxyphenyl)-2,3-*O*-isopropylidenedioxy-1-*p*-toluenesulfony-loxybutane, 60



60

To a solution of **59** (0.5 g, 1.52 mmol) in dry CH_2Cl_2 (10 mL) was added pyridine (1 mL) followed by *p*-TsCl (435 mg, 2.28 mmol) and stirred at room temperature for 12 h. The reaction

mixture was diluted with EtOAc (50 mL) and washed with water (2 × 20 mL), brine, dried (Na_2SO_4) and concentrated. Column chromatography of the crude product using petroleum ether:EtOAc (9:1) gave **60** (0.66 g) as a white solid.

Yield: 0.66 g, 90%

Mp.: 83-84°C (lit. 83.5-84°C)[16]

[a]$_D^{20}$: – 19.62 (c = 1, $CHCl_3$) [lit. – 19.7 (c = 1.07, $CHCl_3$)] [16]

IR ($CHCl_3$, cm^{-1}): n_{max} 1611, 1512, 1370, 1241, 1217, 1177, 1020, 982, 830, 815, 757, 668

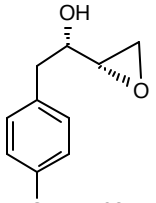
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33 (s, 3H), 1.37 (s, 3H), 2.44 (s, 3H), 2.7-3.01 (m, 2H), 3.8-4.06 (m, 4 H), 5.07 (s, 2H), 6.9 (d, *J* = 8 Hz, 2H), 7.10 (d, *J* = 8 Hz, 2H), 7.3-7.45 (m, 7H), 7.75 (d, *J* = 8 Hz, 2H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 20.91, 26.31, 26.8, 37.82, 68.88, 69.57, 77.40, 77.62, 108.91, 114.6, 126.88, 127.36, 128.02, 128.72, 129.38, 129.93, 132.76, 136.88, 144.34, 157.35

EIMS *m/z* (relative intensity, %): 482 [M^+] (12.7), 467 [M^+–15] (4.0), 285 (8.7), 227 (27.0), 91 (100), 65 (12.7)

Analysis: $C_{27}H_{30}O_6S$ (482.51) requires C, 67.21; H, 6.27. Found: C, 67.52; H, 6.05.

Synthesis of epoxide 62 from tosylate 60



62

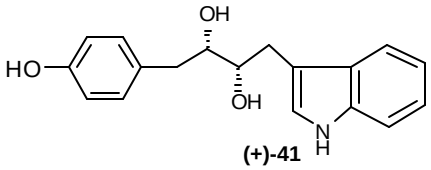
To a solution of tosylate **60** (0.5 g, 1.03 mmol) in MeOH (15 mL) was added 3N HCl (4 mL) and stirred at room temperature for 12 h. A pinch of $NaHCO_3$ was added and stirred for 10 min. The reaction mixture was filtered through a pad of neutral alumina and concentrated. The residue was dissolved in dry MeOH and K_2CO_3 (0.151 g, 1.1 mmol) was added and stirred for 10 h at room temperature. Water (20 mL) and EtOAc (20 mL) were added, the organic layer was separated and the aqueous layer extracted with EtOAc (2 × 20 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether:EtOAc (4:1) as eluent gave **62** (0.238 g) as a white solid.

Yield: 0.238 g, 85%

Mp.: 67-69°C

[a]$_D^{20}$: + 11.12 (c = 1, $CHCl_3$)

Synthesis of diolmycin A2, 41



(+)-41

To a stirring solution of indole (21 mg, 179 μmol) in dry CH_2Cl_2 (4 mL) under argon atmosphere at 0°C was added $SnCl_4$ (25 μL, 207 μmol). The ice bath was removed and the reaction mixture was stirred for 45 min at room temperature. The epoxide **62** (40 mg, 148 μmol) in CH_2Cl_2 (1 mL) was added in small portions to the suspension, followed by CH_3NO_2 (3 mL). The mixture was stirred for 10 h at room temperature and then quenched with cold water (10 mL) and EtOAc (20 mL). The mixture was filtered and the organic layer was separated. The aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated to a syrupy liquid. This was dissolved in dry EtOH (10 mL) and 10% Pd-C (25 mg) was added carefully. The reaction mixture was stirred under an atmosphere of H_2 filled in a balloon for 18 h at room temperature. The mixture was filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using $CHCl_3$:MeOH (5:1) as eluent to give diolmycin A2 **41** (21 mg) as a thick syrupy liquid.

Yield: 21 mg, 53%

$[\alpha]_D^{20}$: + 46.32 (c = 0.2, MeOH) [lit. + 49.2 (c = 0.24, MeOH)][16]

IR ($CHCl_3$, cm^{-1}): ν_{max} 3417, 1611, 1511, 1455, 824

^{1}H NMR (200 MHz, CD_3OD + $CDCl_3$, 4:1): δ 2.8 (dd, *J* = 14, 7 Hz, 1H), 2.9 (dd, *J* = 14, 6 Hz, 1H), 3.06 (dd, *J* = 14, 8 Hz, 1H), 3.1 (dd, *J* = 14, 7 Hz, 1H), 3.66 (ddd, *J* = 8, 4, 2 Hz, 1H), 3.9 (ddd, *J* = 8, 6, 2 Hz, 1H), 6.9 (d, *J* = 8 Hz, 2H), 7.1 (d, *J* = 8 Hz, 2H), 7.2-7.48 (m, 5H)

EIMS m/z (relative intensity, %): 297 [M^+] (2), 296 [M^+–1] (7), 190 (35), 173 (21.3), 160 (12.4), 130 (22.8), 117 (55), 107 (100).

4.2.7. Spectra

+1] ^{1}H NMR Spectrum of **71**

+2] ^{13}C NMR Spectrum of **71**

+3] ^{1}H NMR Spectrum of **59**

+4] ^{13}C NMR Spectrum of **59**

+5] ^{1}H NMR Spectrum of **62**

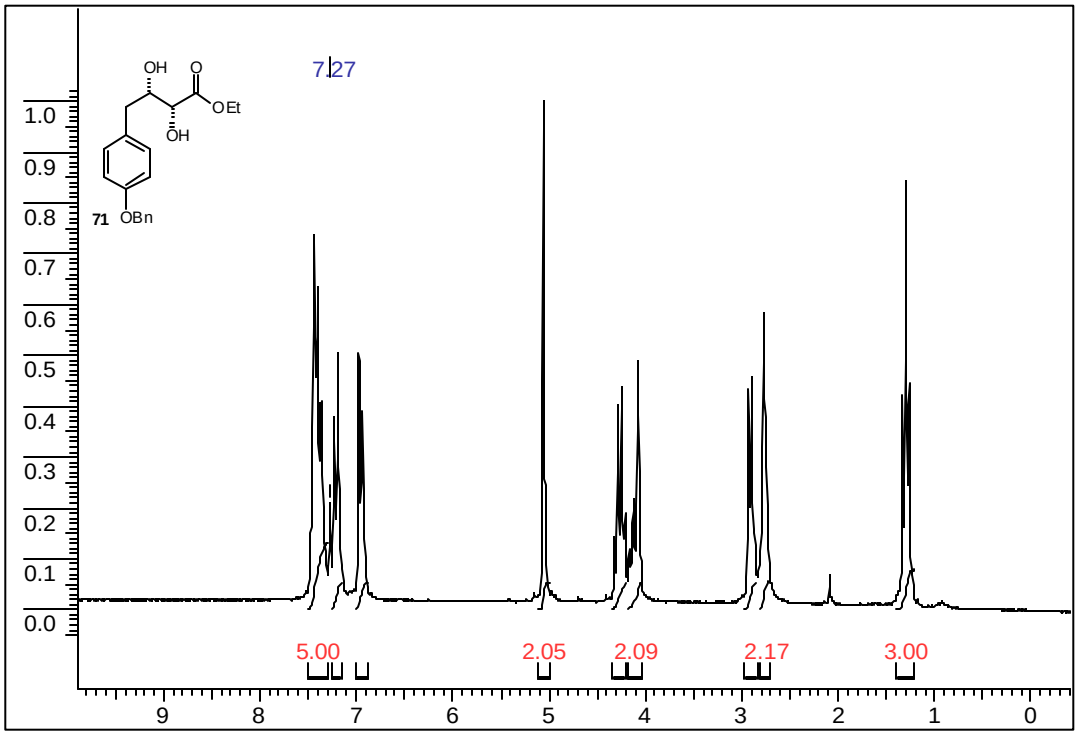
+6] ^{13}C NMR Spectrum of **62**

+7] EIMS of **62**

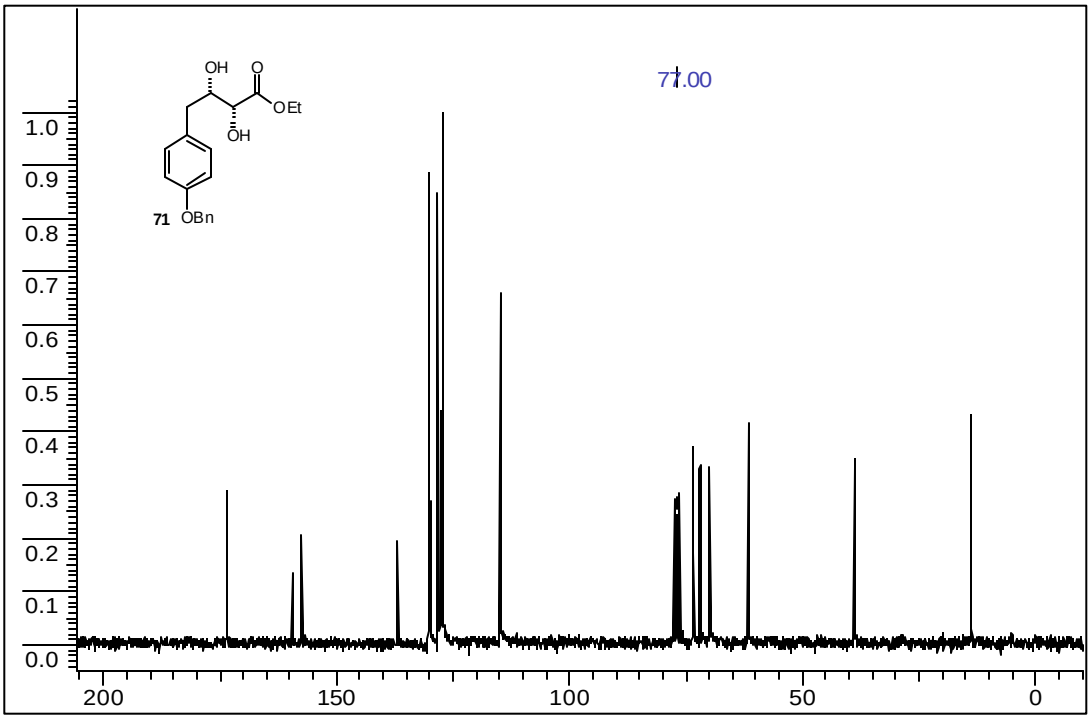
+8] IR spectrum of (+)-**41**

+9**]** ^{1}H NMR Spectrum of (+)-**41**

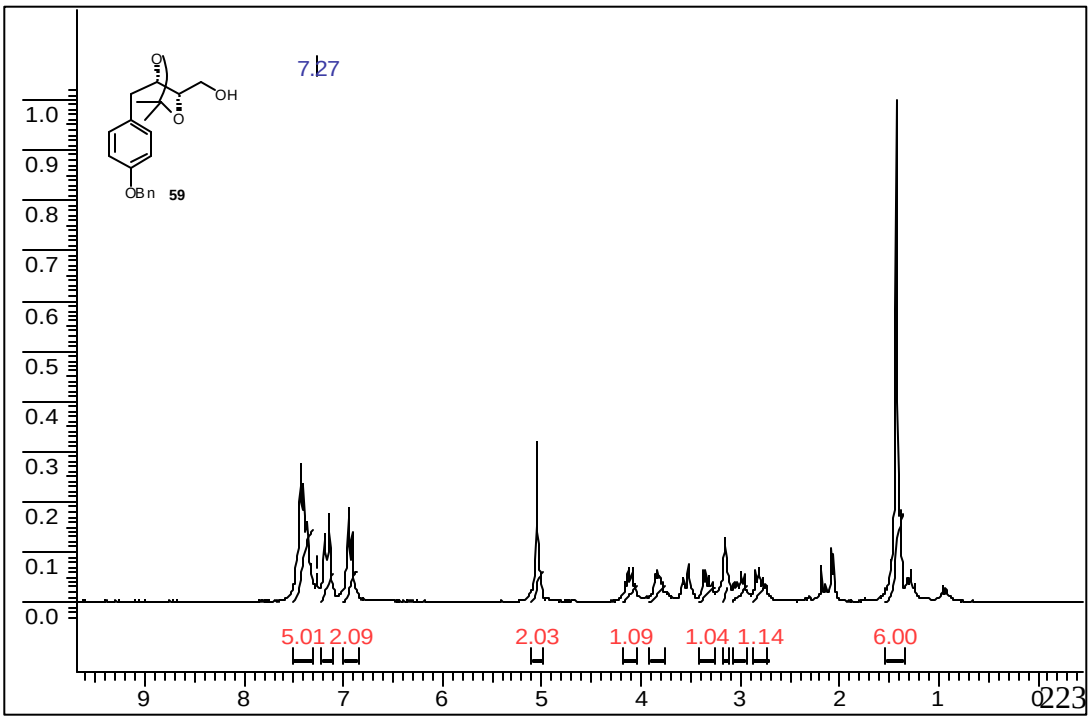
\+ ^{1}H NMR Spectrum of **71**



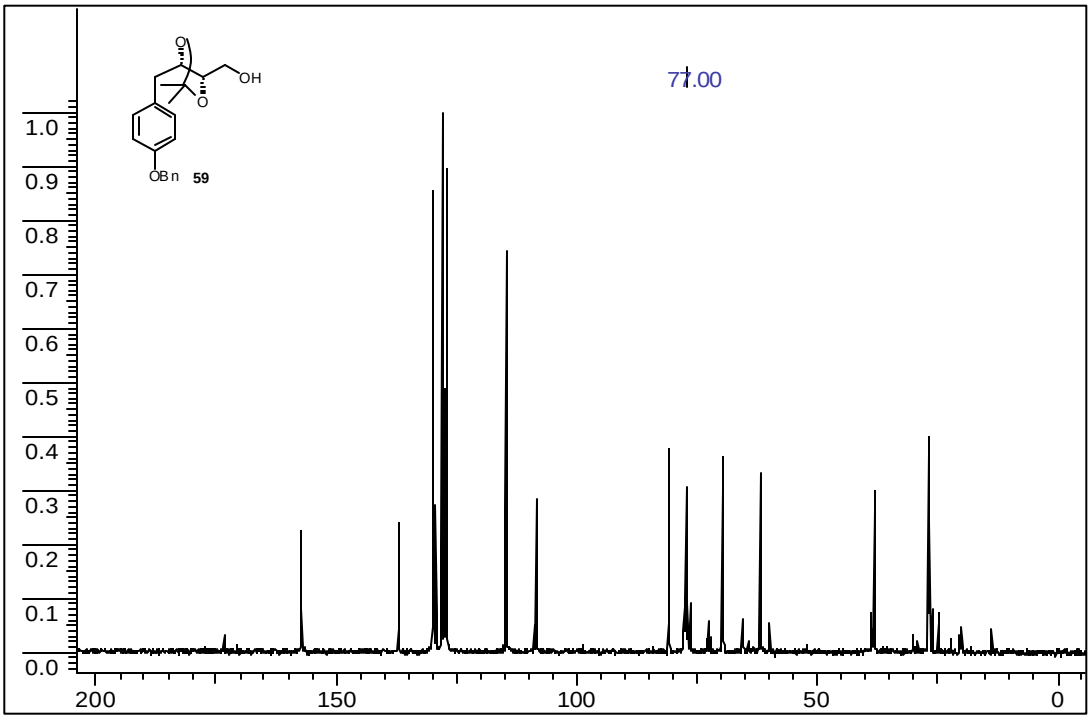
+ ^{13}C NMR Spectrum of **71**



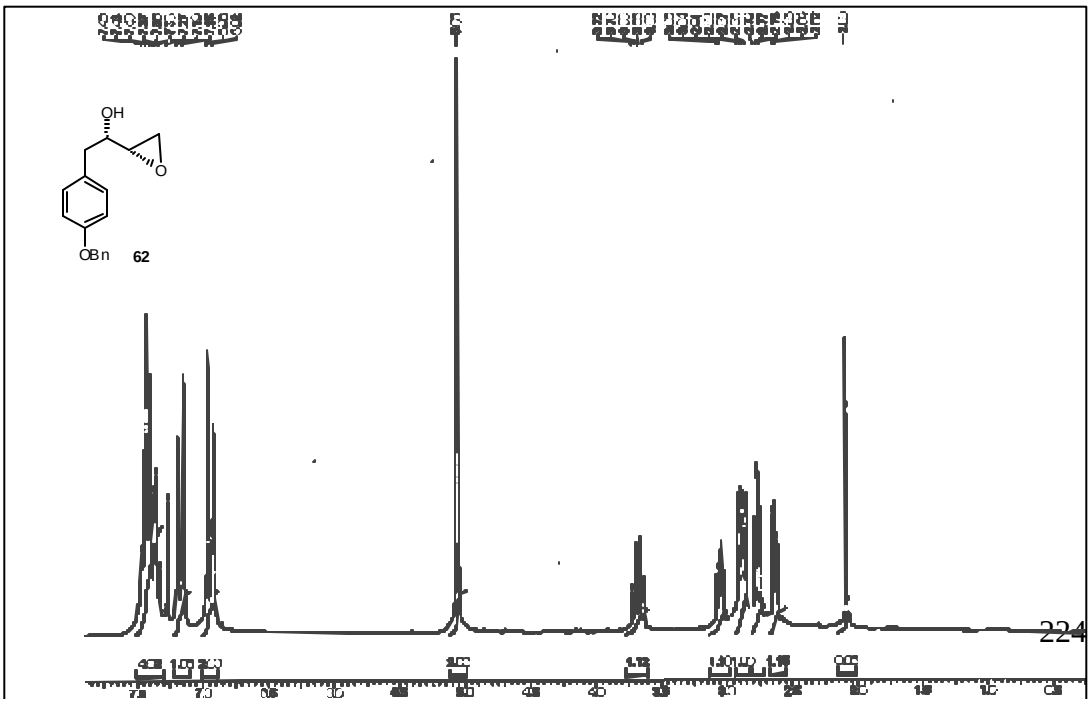
+ ^{1}H NMR Spectrum of **59**



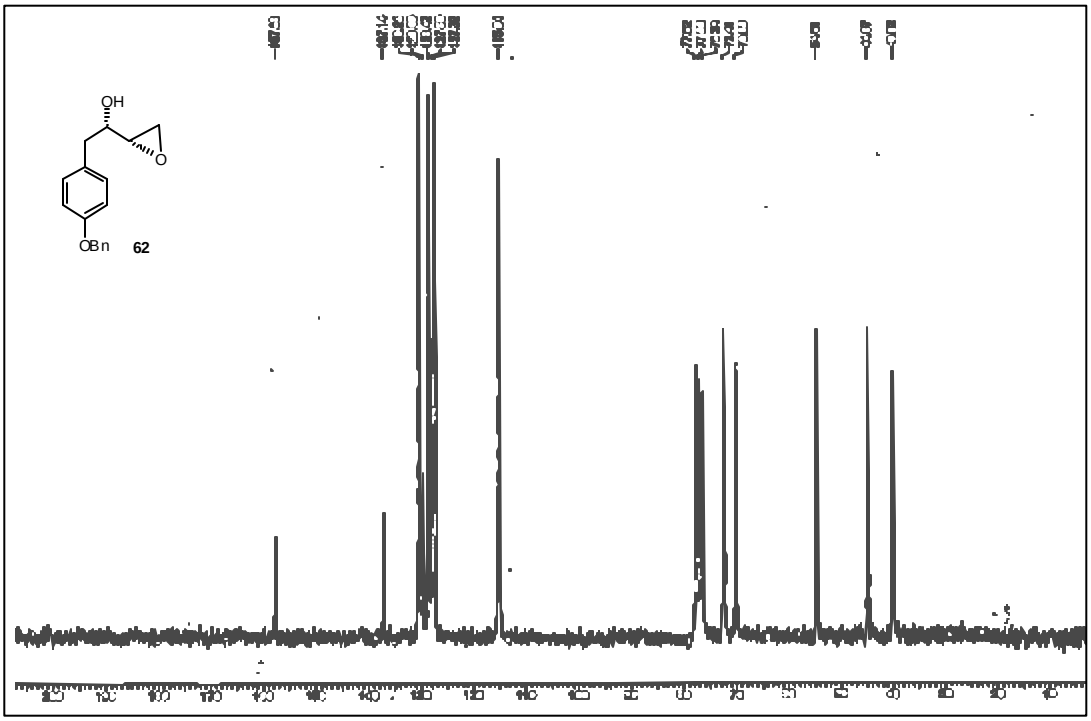
+ ^{13}C NMR Spectrum of **59**



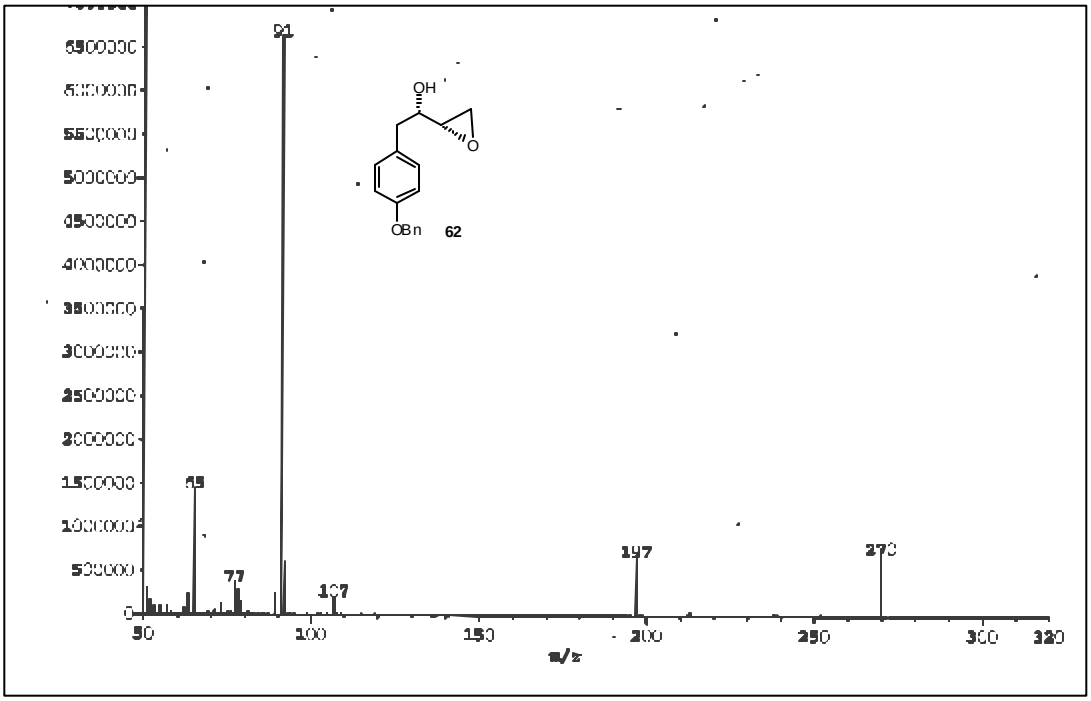
+ ^{1}H NMR Spectrum of **62**



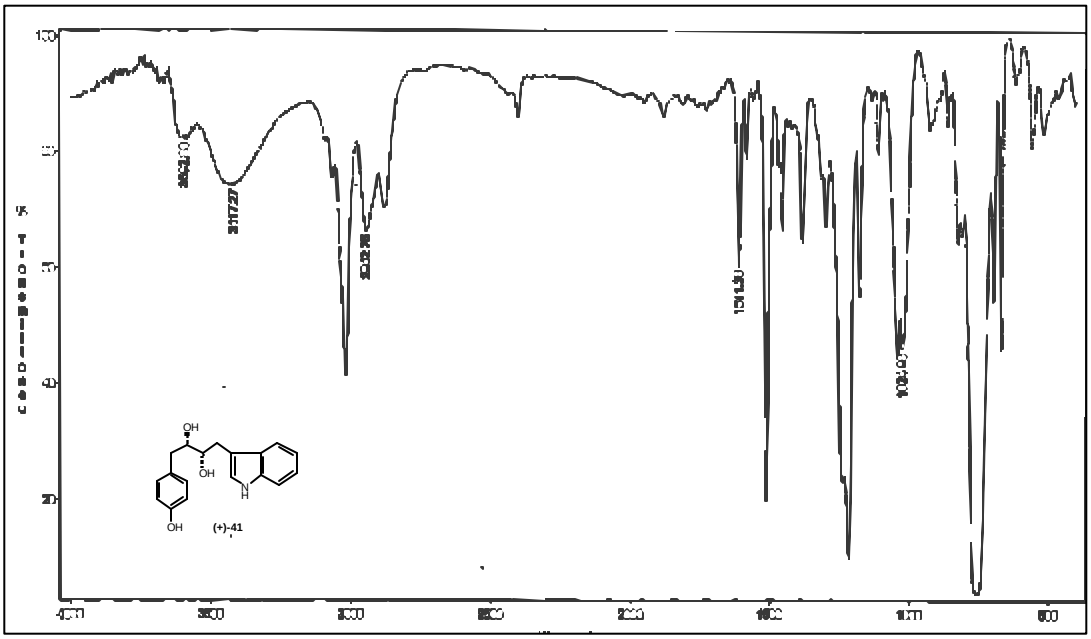
+ ^{13}C NMR Spectrum of **62**



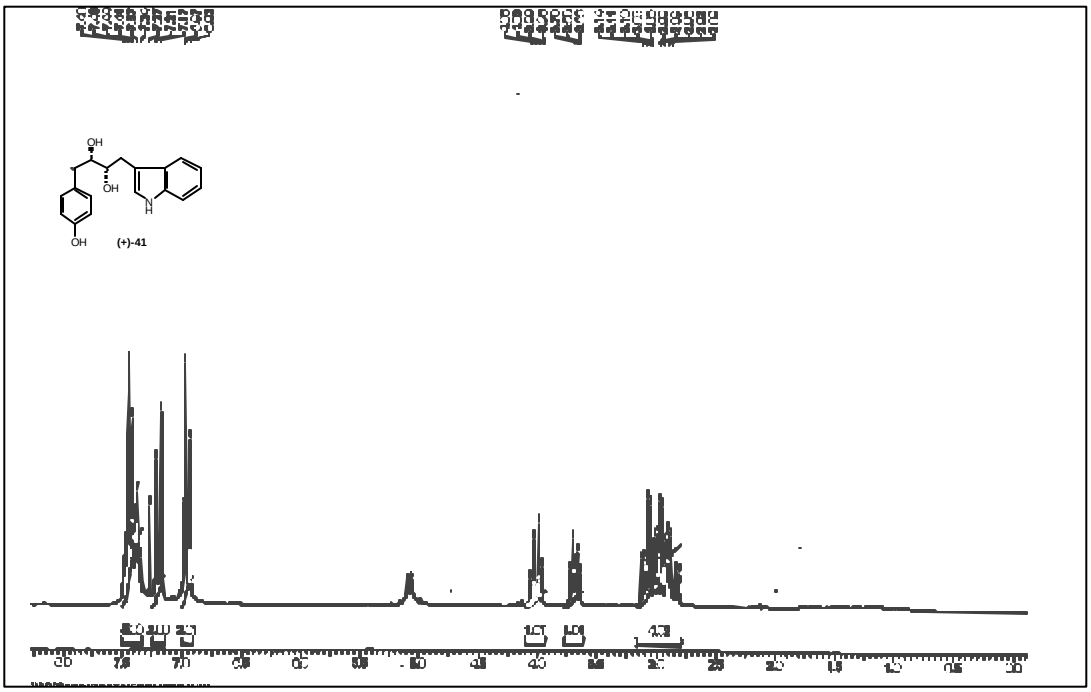
+ EIMS of **62**



+ IR spectrum of (+)-**41**



+ ^{1}H NMR Spectrum of (+)-**41**

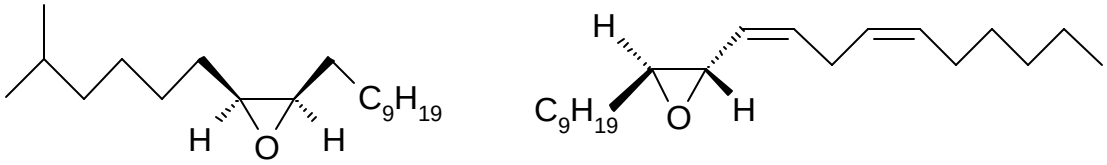


4.3. SECTION B

ENANTIOSELECTIVE SYNTHESIS OF (+)- AND (-)-POSTICLURE.

4.3.1. Introduction:

The need for pure enantiomers is particularly apparent in the field of insect pheromone chemistry, since insect chemoreception can be highly stereoselective.[21-23] Optically active epoxides are an important class of natural products commonly encountered as sex attractants of Lepidopteran pests,[24] and self defensive substances against rice blast disease.[25] Many mono-epoxy compounds with *Z*-ene, *Z,Z*-diene and *Z,Z,Z*-triene and saturated analogues, common being (+)-dispalure **73**, identified as attractant pheromones, have a unique and common feature i.e. ***cis*-epoxide** functionality.[26] No *trans*-epoxide pheromone was known in the literature until Wakamura *et al.*[27] (2001) isolated for the first time in the history of epoxide pheromones, a novel *trans*-oxirane pheromone from the virgin females of the tussock moth, *Orgyia postica* and identified it as (6*Z*,9*Z*,11*S*,12*S*)-*trans*-11,12-epoxyhenicosa-6,9-diene **74**. This novel *trans*-oxirane pheromone was named '**posticlure'** in reference to the species name (**Figure 4**).



(+)-Dispalure **73** (-)-Posticlure **74**

Figure 4.

The larvae of *Orgyia postica* were collected in mango fields and reared on an artificial diet. A solvent extract of the sex pheromone glands was obtained from ca. 600 virgin females and analyzed with a capillary GC linked directly to electroantennographic (EAG) recording[28] from the antenna of a male *O. postica*. Single EAG response was observed at Kovat's Index (KI) 2548 on a polar HP-INNOWAX column, and KI 2200 on a non-polar HP-1 column. The EAG active compound was eluted gas chromatographically as an almost pure material with 5% ether in *n*-hexane from column chromatography using 200 mg of Florisil. The EAG response coincided

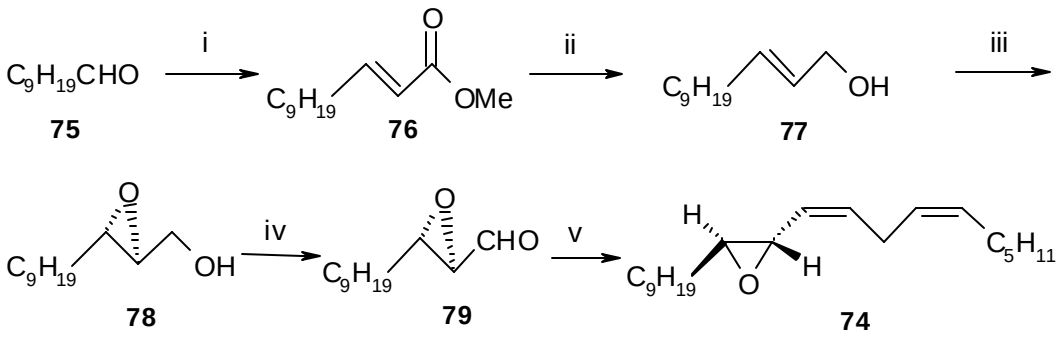
well with an FID peak on the GC, which was predominant in the fraction that represented approximately 17 ng per female abdominal tip.

The EAG active compound was fully characterized by GC-MS, ^{1}H NMR, chiral HPLC analysis and chemical derivation and further by chemical synthesis. In the ^{1}H NMR spectrum, the two epoxide protons at δ 2.82 (doublet of triplet) and 3.36 (doublet of doublet) had a coupling constant of J = 2.2 Hz which confirmed the *trans*-epoxide structure. The stereoisomerism possible for posticlure was (11*S*,12*S*) or (11*R*,12*R*). Both isomers were synthesized separately and analyzed by chiral HPLC. The natural pheromone showed only one peak with the same retention time of synthetic (11*S*,12*S*)-posticlure. Furthermore males were captured by this (11*S*,12*S*)-isomer but not by the (11*R*,12*R*)-isomer. Hence, the (11*S*,12*S*)-configuration was assigned to the natural sex pheromone of *Orgyia postica* females.

4.3.2. Review of Literature

Wakamura *et al*.[27] (2001) Scheme 14

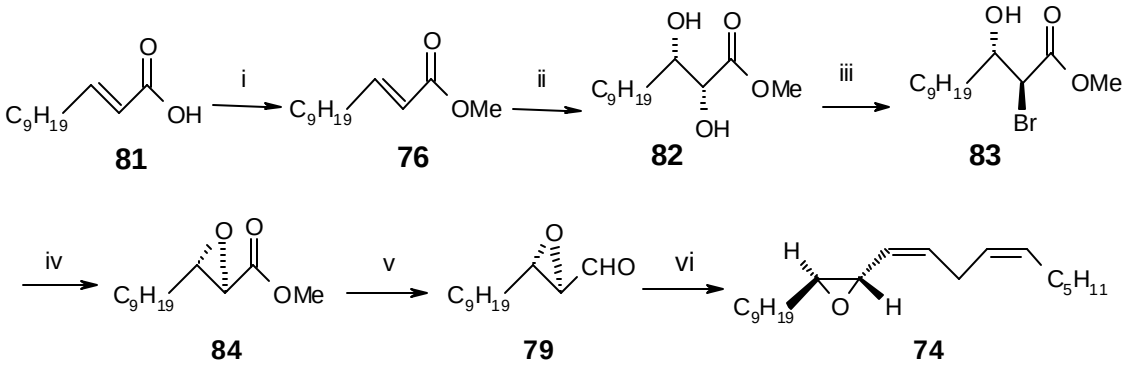
Wakamura *et al.*[27], besides isolation and structure elucidation, in the same report have arrived at the synthesis of both enantiomers of posticlure by employing the Sharpless asymmetric epoxidation[2] as the key step (**Scheme 14**). Decanal **75** on Wittig reaction with stable phosphorane gave methyl *trans*-dodec-2-enoate **76**. Reduction of ester **76** gave the allylic alcohol **77**. The Sharpless asymmetric epoxidation of **77** using (+)-DET gave the epoxide **78**. The free hydroxyl in **78** was oxidized with PCC to the corresponding aldehyde **79**. Reaction of aldehyde **79** with the Wittig ylide **80** gave the natural posticlure **74**. The enantiomeric purity was only 59% and pure material was obtained by preparative HPLC with a chiral column (Chiral-Pak AD).



Scheme 14. Reaction conditions: (i) $Ph_3P{=}CHCO_2Me$. (ii) $LiAlH_2(OEt)_2$. (iii) (+)-DET, Ti(O*i*-Pr)$_4$, *t*-BuOOH. (iv) PCC. (v) (*Z*)-$Ph_3P{=}CH\text{-}CH_2\text{-}CH{=}CH\text{-}(CH_2)_4CH_3$ **80**.

Mori *et al*.[29a] (2001) Scheme 15

Mori *et al*. synthesized the intermediate aldehyde **79** (also prepared by Wakamura *et al.*[27]). The SAD of olefin **76** gave diol **82**. The α-hydroxyl was converted into α-bromide **83** *via* the acetoxonium ion chemistry. Base mediated methanolysis of **83** gave the epoxide **84**, which on DIBAL-H reduction of ester furnished the aldehyde **79**. The subsequent Wittig reaction with **80** afforded the natural pheromone epoxide posticlure **74**.



Scheme 15. Reaction conditions: (i) K_2CO_3, MeI, DMF, overnight, 92%. (ii) AD-mix-α, $MeSO_2NH_2$, *t*-BuOH, H_2O, 0°C, overnight, 71%. (iii) HBr, AcOH, then MeOH, overnight, 84%. (iv) K_2CO_3, MeOH, rt , 2 h, 71%. (v) DIBAL-H, toluene, −78°C, 2 h, 85%. (vi) **80**, THF, −100°C, overnight, 76%.

4.3.3. Present Work[29b]

Objective:

With the advent of Sharpless asymmetric epoxidation (SAE)[2] several synthesis of pheromone epoxides such as (+)-dispalure **73**,[30,31] (3*Z*,6*Z*)-*cis*-9,10-epoxy-3,6-henicosadiene **85**,[31] (3*Z*,6*Z*)-*cis*-9,10-epoxy-1,3,6-henicosatriene **86**,[32] (6*Z*,9*Z*,3*S*,4*R*)-*cis*-3,4-epoxynonadecadiene **87** and (3*Z*,6*Z*)-*cis*-9,10-epoxy-1,3,6-icosatriene **88**[33] (**Figure 5**) were reported by employing SAE reaction. Current literature documents a very few methods for preparing chiral epoxides of olefins bearing no directing functional groups in close proximity to the double bond.[4] The Sharpless asymmetric dihydroxylation has been envisaged as an alternative way for conversion of diol into an epoxide function.[6-12]

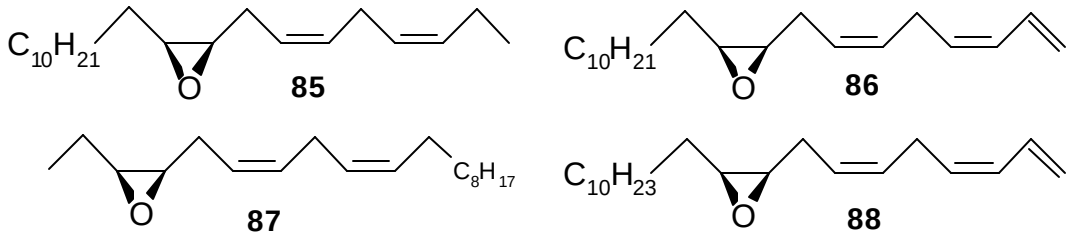


Figure 5. Some epoxide pheromones synthesized *via* SAE reaction.

The Sharpless method[10] of one-pot conversion of vicinal diols into epoxides *via* halohydrin ester intermediates seemed to be an easy alternative. This method tolerates a wide range of functionality including acid-sensitive functional groups and the transformation proceeds without epimerisation even with benzylic substrates in high yields and stereospecificity.

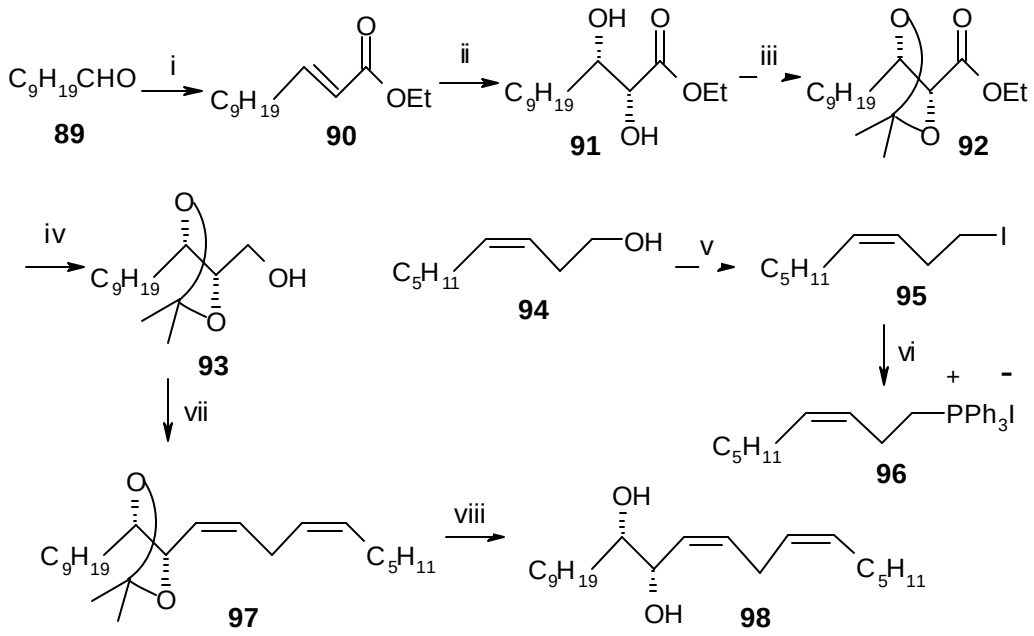
Since Wakamura[27] synthesized both enantiomers of posticlure by SAE reaction with 59% ee and obtained pure samples by preparative HPLC, an upsurge of interest in the asymmetric synthesis of such a novel first *trans*-epoxide pheromone in both large scale and high optical purity led us to employ the SAD reaction towards the synthesis of posticlure. Enormous opportunities are available for synthetic manipulation by the SAD of internal activated olefins like α,β-unsaturated esters, allylic alcohols or allylic halides to produce chiral diols followed by their conversion into epoxide by a one-pot sequence in high yields and stereospecificity.

4.3.4. Results and Discussion:

The synthetic strategy for both (+)- and (–)-posticlure is depicted in **Schemes 16-19**. The key steps involve the Sharpless asymmetric dihydroxylation and one-pot conversion of diol into epoxide. In **Scheme 16**, the synthesis of intermediate diol **98** is depicted. The commercially available decanal **89** was chosen as starting material, which on Wittig reaction with (ethoxycarbonylmethylene)triphenylphosphorane in THF at room temperature afforded the *trans*-olefin **90** in 86% yield. The IR spectrum of **90** showed strong carbonyl absorption at 1724 cm^{-1} and C=C stretching of olefin at 1656 cm^{-1}. In the ^1H NMR spectrum, the olefin peaks appeared at δ 5.76 and 6.95, both as doublet of triplet with the coupling constant of J = 16 Hz, indicating *trans*-olefin. The SAD reaction of olefin **90** using $(DHQ)_2$-PHAL ligand and catalytic OsO_4 gave the diol **91** in 94% yield. The IR spectrum of **91** showed hydroxyl absorption at 3377 cm^{-1} and ester carbonyl absorption at 1736 cm^{-1}. The protons of the chiral carbons appeared at δ 3.84 (broad triplet) and 4.05 (multiplet) in the ^1H NMR spectrum and the corresponding carbons appeared at δ 72.44 and 73.25 in the ^{13}C NMR spectrum. The hydroxyl group protection of **91** with 2,2-dimethoxypropane in presence of catalytic amount of *p*-TsOH at room temperature furnished **92** in almost quantitative yield. The characteristic acetonide group appeared at δ 1.41 (singlet) and 1.43 (singlet) for two methyl protons in the ^1H NMR spectrum and the acetonide carbon at δ 109.97 in the ^{13}C NMR spectrum. Reduction of the ester group of **92** with $LiAlH_4$ in Et_2O at 0°C to room temperature gave the alcohol **93** in 97% yield. Compound **93** showed hydroxyl absorption at 3460 cm^{-1} and absence of ester carbonyl in the IR spectrum.

The further reaction involved the treatment of aldehyde derived from alcohol **93** with the ylide derived from Wittig salt **96**. The Wittig salt **96** was prepared from commercially available *cis*-3-nonen-1-ol (**94**) in two steps. The hydroxyl group of **94** was converted into iodide **95** with triphenylphosphine, iodine and imidazole followed by reaction of iodide **95** with triphenylphosphine in benzene under reflux to give **96** as a sticky white solid. This was used immediately after preparation. The alcohol **93** was oxidized under Swern oxidation conditions using DMSO and $(COCl)_2$ at –78°C to –60°C and workup with Et_3N to give the corresponding aldehyde. The aldehyde prepared from **93** was treated with the ylide generated from **96** and *n*-BuLi at –80°C to give the *Z,Z*-olefin **97** in 76% yield. The IR spectrum of **97** showed C=C stretching at 1723 cm^{-1}. In the ^1H NMR spectrum of **97** the olefin protons appeared at δ 5.3-5.5 as multiplet (three protons) and 5.7 as doublet of triplet (one proton) with the coupling constant

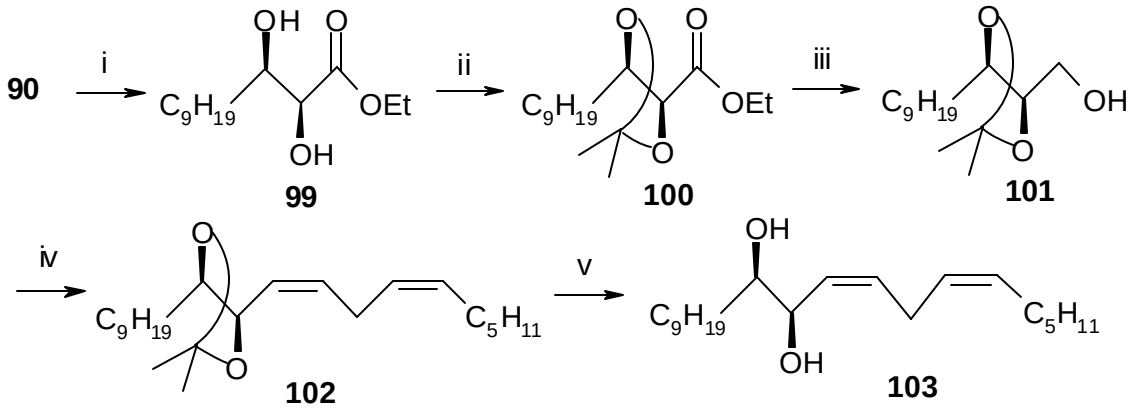
of J = 8 Hz indicating *cis*-olefin. The ^{13}C NMR showed four olefinic carbons at δ 126.45, 126.51, 130.63 and 133.57 indicating diene formation. The acetonide deprotection of **97** was effected with aq. 3N HCl in MeOH at room temperature to give the diol-diene **98** in 90% yield. The hydroxyl absorption in the IR spectrum appeared at 3384 cm^{-1}. The ^1H NMR and ^{13}C NMR spectra showed the absence of characteristic acetonide group peaks.



Scheme 16. Reaction conditions: (i) $Ph_3P{=}CHCO_2Et$, THF, rt, 12 h, 86%. (ii) $(DHQ)_2$-PHAL, OsO_4, $MeSO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH:H_2O (1:1), 24 h, 0°C, 94%. (iii) 2,2-DMP, $(CH_3)_2CO$, *p*-TsOH, rt, 8 h, 99%. (iv) $LiAlH_4$, Et_2O, 0°C to rt, overnight, 97%. (v) Ph_3P, I_2, imidazole, rt, CH_2Cl_2, 2 h, 98%. (vi) Ph_3P, PhH, reflux, 24 h, 95%. (vii) (a) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78°C, (b) **96**, *n*-BuLi, THF, −80°C, 8 h, 76%. (viii) aq. 3N HCl, MeOH, rt, 12 h, 90%.

The *ent*-**103** (**Scheme 17**) was synthesized by employing the $(DHQD)_2$-PHAL ligand in the SAD reaction of **90** and following the same reaction sequence as in **Scheme 16**.

It is known that in the SAD reaction under the heterogeneous ferricyanide conditions, the asymmetric dihydroxylation may be controlled to selectively produce enediols from conjugated polyenes.[34] The regioselectivity of monodihydroxylation is determined both by electronic and steric effects. It has been shown that the rate constants for dihydroxylation of isolated double

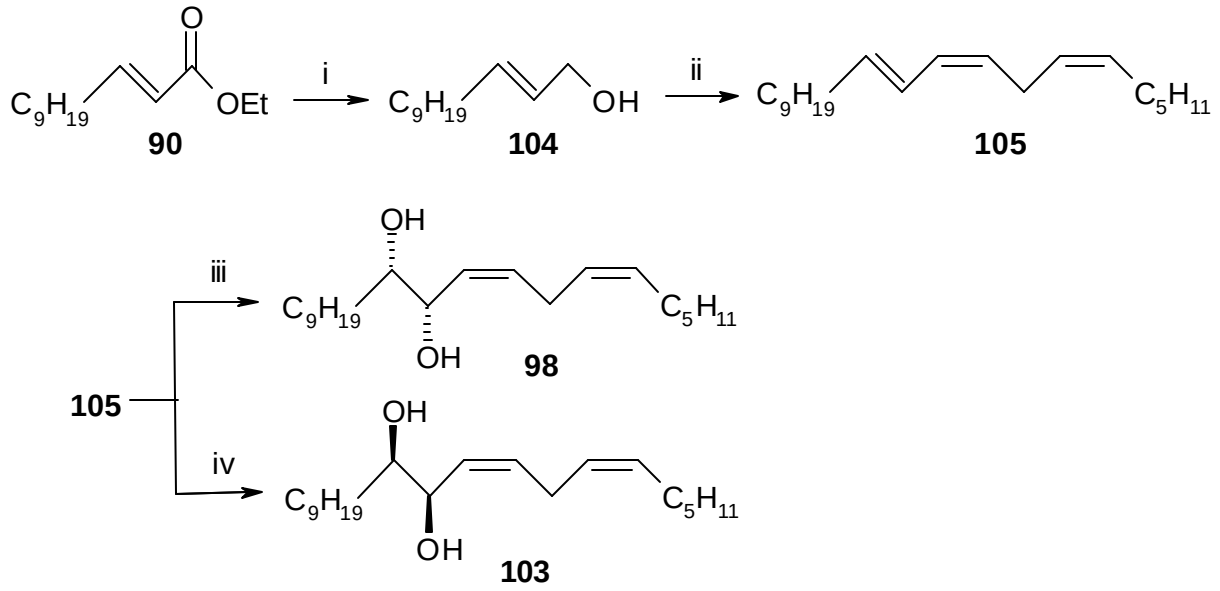


Scheme 17. Reaction conditions: (i) $(DHQD)_2$-PHAL, OsO_4, $MeSO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH:H_2O (1:1), 24 h, 0°C, 94%. (ii) 2,2-DMP, $(CH_3)_2CO$, *p*-TsOH, rt, 8 h, 99%. (iii) $LiAlH_4$, Et_2O, 0°C to rt, overnight, 97%. (iv) (a) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78°C, (b) **96**, *n*-BuLi, THF, −80°C, 8 h, 76%. (v) aq. 3N HCl, MeOH, rt, 12 h, 90%.

bonds is much larger with *trans*-1,2-disubstituted and trisubstituted olefins than with *cis*-1,2-disubstituted and terminal olefins.[35]

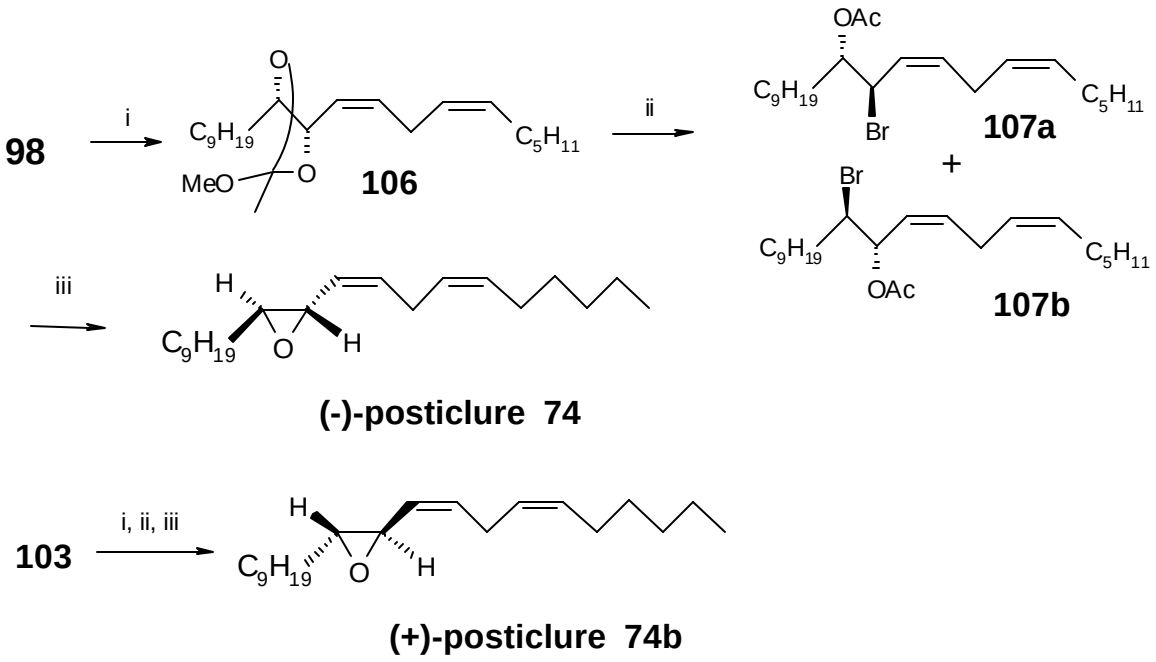
Taking advantage of *trans*-olefin dihydroxylation to be faster than the *cis*-olefin, we thought of preparing compound **98** or **103** by selective monodihydroxylation of the *trans*-olefin of a (*Z*,*Z*,*E*)-triene system like **105**. To explore the possibility of selective monodihydroxylation, the triene **105** was prepared as shown in **Scheme 18**. DIBAL-H reduction of **90** in Et_2O at 0°C gave the allylic alcohol **104** in 90% yield. The IR spectrum of **104** showed hydroxyl absorption at 3393 cm^{-1} and absence of carbonyl function. The allylic hydroxyl was oxidized with PCC in CH_2Cl_2 at room temperature to give the corresponding aldehyde in virtually pure form. Wittig olefination of the above aldehyde with the ylide generated from **96** and *n*-BuLi at –80°C gave the (6*Z*,9*Z*,11*E*)-triene **105** in 74% yield. The triene **105** showed olefinic C=C stretching at 1680 and 1642 cm^{-1} in the IR spectrum. In the ^1H NMR spectrum, the olefinic protons appeared at δ 5.38-5.63 (multiplet, 4 protons), 5.99 (multiplet, 1 proton), 6.24 (doublet of doublet, 1 proton) with the coupling constant of J = 15 Hz indicating one *trans*-olefin bond. In the ^{13}C NMR spectrum, the six olefinic carbons appeared at δ 125.81, 128.98, 129.49, 130.48, 130.81 and 134.53. Chemoselective dihydroxylation of triene **105** with $(DHQ)_2$-PHAL ligand (1 mol%) and slightly lower concentration of OsO_4 (0.2 mol%) gave the monodihydroxylated product **98** in 78% yield. Similarly **103** was obtained from triene **105** by SAD reaction using $(DHQD)_2$-PHAL ligand in 79% yield. The $[\alpha]_D^{20}$ values and other spectral characteristics of **98** and **103** matched well with the same prepared through **Schemes 16** and **17** respectively. The enantiomeric excess of >97%

ee was determined by comparison of optical rotations of **98** and **103** with that prepared by **Schemes 16** and **17** respectively.



Scheme 18. Reaction conditions: (i) DIBAL-H, Et_2O, 0°C, 2 h, 90%. (ii) (a) PCC, CH_2Cl_2, rt, 8 h, (b) **96**, *n*-BuLi, THF, –80°C, 8 h, 74%. (iii) $(DHQ)_2$-PHAL, OsO_4, $MeSO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH:H_2O (1:1), 12 h, 0°C, 78%. (iv) $(DHQD)_2$-PHAL, OsO_4, $MeSO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH:H_2O (1:1), 12 h, 0°C, 79%.

With the enantiomerically pure diols **98** and **103** in hand, the next crucial step was to convert them into the epoxides *via* a one-pot reaction sequence (**Scheme 19**). Treatment of diol **98** with trimethylorthoacetate and catalytic *p*-TsOH in CH_2Cl_2 at room temperature and subsequent removal of the volatiles gave the cyclic ortho ester **106**. Subsequent treatment of **106** in the same reaction flask with 1.3 equivalents of acetyl bromide in CH_2Cl_2 for 4 h at room temperature gave the mixture of virtually pure acetoxy bromides **107a** and **107b**. The ^1H NMR spectrum of a fraction of the reaction mixture after filtration and concentration showed protons of the chiral carbons at δ 4.96 (multiplet) and 5.09 (multiplet) and acetyl methyl at 2.09 (singlet) indicating formation of acetoxy bromide. Concentration of the reaction mixture containing **107a** and **107b** and saponification with K_2CO_3 in dry MeOH resulted in deacetylation followed by concomitant cyclization to furnish the *trans*-epoxide **74** (posticlure) in 88% yield. This stereospecific one-pot epoxidation sequence involved the first inversion at the bromide-receiving center followed by a second inversion at the bromide-leaving center to give the *trans*-epoxide. Thus, this transformation resulted in overall retention of configuration and therefore the regioselectivity of the acetyl bromide formation is immaterial.



Scheme 19. Reaction conditions: (i) $CH_3C(OMe)_3$, *p*-TsOH (cat), CH_2Cl_2, rt, 30 min. (ii) CH_3COBr, CH_2Cl_2, rt, 4 h. (iii) K_2CO_3, MeOH, rt, 8 h, 86-88% overall.

Posticlure **74** had $[\alpha]_D^{20}$ – 11.1 (c = 1, $CHCl_3$) which is in accordance to literature value of $[\alpha]_D^{24}$ – 10.8 (c = 1.07, $CHCl_3$).[29a] (–)-Posticlure **74** was fully characterized by IR, ^1H NMR, ^{13}C NMR, EIMS and elemental analysis. The IR spectrum of (–)-**74** showed olefin peaks at 1725 and 1708 cm^{-1}. In the ^1H NMR spectrum of (–)-**74** the epoxide protons appeared at δ 2.82 (doublet of triplet) with coupling constant of J = 2.1 Hz, 3.36 (doublet of doublet) with J = 2.1, 8.7 Hz. The coupling constant of J = 2.1 Hz indicates the *trans*-epoxide functionality. The olefinic protons appeared at δ 5.08 (doublet of doublet of doublet, 1 proton), 5.37 (doublet of triplet of triplet, 1 proton), 5.44 (doublet of triplet of triplet, 1 proton), and 5.67 (doublet of triplet, 1 proton). The chemical shifts and coupling constants for epoxide protons and olefin protons matched well with the reported data[27] (**Figure 6**). The EIMS showed a distinct molecular ion peak at *m/z* 306. Also diagnostic peaks at *m/z* 209, 195, 179, 155 and 136 matched well with the reported data of natural posticlure[27] (**Figure 7**).

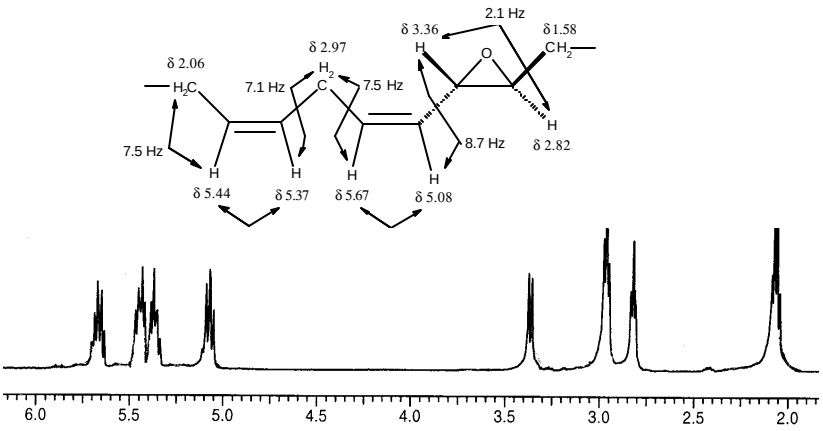


Figure 6. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of synthetic (–)-posticlure **74**. For ^{1}H NMR spectrum of natural posticlure **74**, see ref. 27.

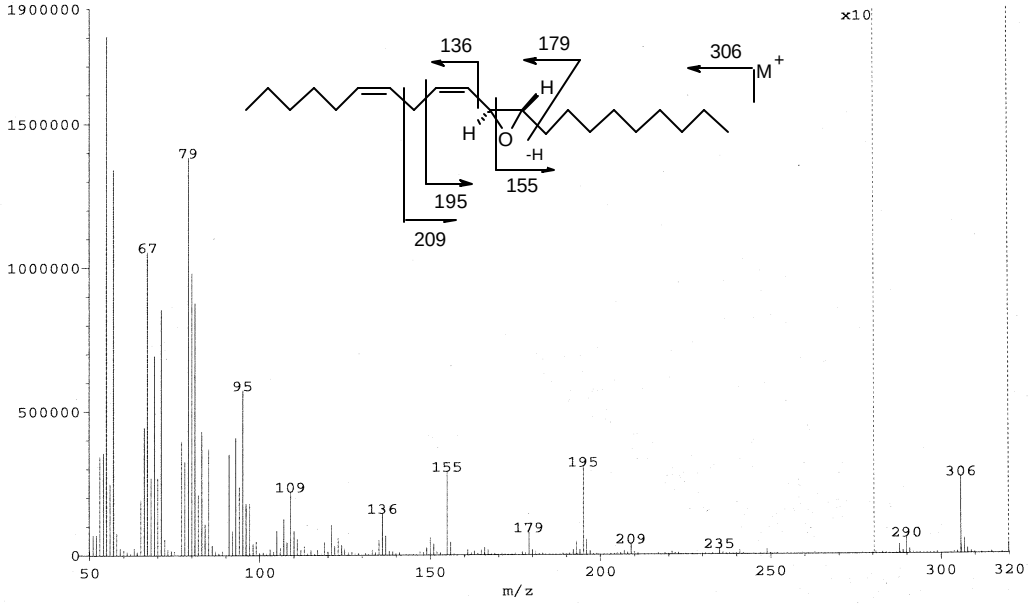


Figure 7. EIMS of synthetic (–)-posticlure **74**. For EIMS of natural posticlure **74** see ref. 27.

In a similar way, the diol **103** was converted into the unnatural antipode (+)-posticlure **74b** in 86% yield, having (11*R*,12*R*) configuration and $[\alpha]_D^{20}$ + 11.33 (c = 2, $CHCl_3$) [lit. $[\alpha]_D^{24}$ + 10.9 (c = 1.09, $CHCl_3$)].[29a] The spectral details are the same as described for (–)-**74**.

Determination of enantiomeric purity:

To determine the enantiomeric purity of both natural and unnatural posticlure prepared by the above synthetic strategy, the compounds **93** and **101** having free hydroxyl groups were chosen for analysis. The free hydroxyl group of **93** and **101** were converted into their Mosher esters with (*S*)-(+)-2-methoxy-α-trifluoromethylphenylacetylchloride and DMAP in CH_2Cl_2 solvent to give **108** and **109** respectively. The diastereomers **108** and **109** were analyzed by ^{19}F NMR separately.

For comparison, both **108** and **109** were mixed in equal amounts and analyzed for separation in ^{19}F NMR spectrum. The ^{19}F NMR spectra for **108**, mixture and **109** are given in **Figure 8**. Analysis of these ^{19}F NMR spectra indicated an enantiomeric excess of >99%.

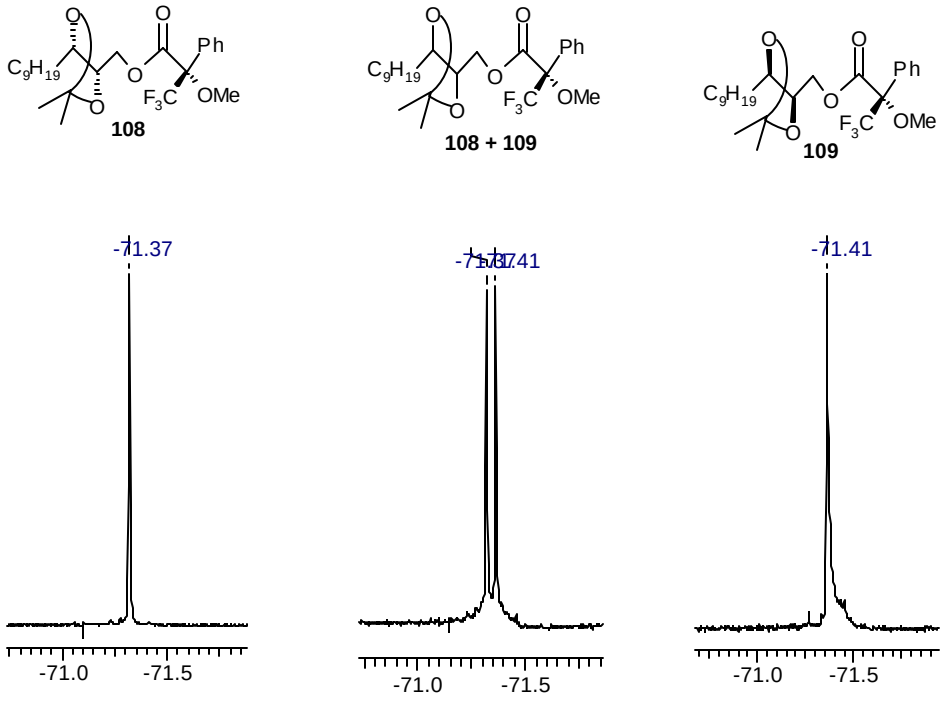


Figure 8. ^{19}F NMR spectra of Mosher esters **108**, racemate (**108** + **109**) and **109**

4.3.5. Conclusion

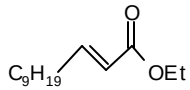
Posticlure is a novel first *trans*-epoxide pheromone in the class of epoxides identified as attractant pheromones. Wakamura *et al.* have synthesized both isomers in 59% ee by employing the SAE reaction and obtained the pure material by preparative HPLC. However, we have employed an alternative sequence of reactions to SAE involving a two-step process, SAD and stereospecific one-pot epoxidation. Although two steps, it is much more compatible in terms of both yields and enantioselectivity. Thus, a highly enantioselective synthesis of the first novel *trans*-epoxide pheromone posticlure has been achieved on a large-scale.[36] The natural posticlure having (11*S*,12*S*) configuration has been identified to possess the negative optical rotation. The unnatural isomer (+)-posticlure has also been synthesized. This alternative route will provide an easy excess to large-scale synthesis of both (–)- and (+)-posticlure for biological studies and pest control.

4.3.6. Experimental

General information

Solvents were purified and dried by standard procedures before use. Petroleum ether of boiling range 60-80°C was used. Melting points are uncorrected. Optical rotations were measured using sodium D line on a JASCO P-1020 microprocessor based polarimeter. Infrared spectra were recorded on ATI MATTSON RS-1 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC-200 spectrometer or Bruker 500 MHz spectrometer as indicated with residual $CHCl_3$ as internal standard (δ 7.27 ^{1}H NMR and δ 77.00 ^{13}C NMR). Mass spectra were obtained with a TSQ 70, Finningen MAT mass spectrometer. Elemental analyses were carried out on a Carlo Erba CHNS-O analyzer.

Preparation of ethyl *trans*-dodec-2-enoate, 90



90

To a solution of (ethoxycarbonylmethylene)triphenylphosphorane (12.2 g, 35 mmol) in dry THF (100 mL) was added decanal **89** (5 g, 32 mmol) in THF (10 mL). The reaction mixture was stirred at room temperature for 12 h and then concentrated. To the residue was added ether and the precipitated solids of triphenylphosphine oxide were filtered off and washed with ether. The filtrate was concentrated and the residue was purified by silica gel column chromatography using petroleum ether:EtOAc (9:1) to give **90** (6.23 g) as a colorless oil.

Yield: 6.23 g, 86%

IR (neat, cm^{-1}): n_{max} 1724, 1656, 1465

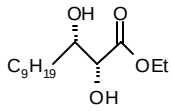
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.86, (t, J = 6.5 Hz, 3H), 1.2-1.26 (m, 12H), 1.3 (t, J = 8 Hz, 3H), 1.5 (m, 2H), 2.19 (brq, $J_{allylic}$ = 7, 2 Hz, 2H), 4.18 (q, J = 8 Hz, 2H), 5.76 (dt, J_{trans} = 16 Hz, 2 Hz, 1H), 6.95 (dt, J_{trans} = 16 Hz, $J_{allylic}$= 7 Hz, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.38, 13.56, 22.23, 27.67, 28.48, 28.77, 29.03, 31.49, 31.75, 59.4, 120.93, 148.53, 165.84

EIMS *m/z* (relative intensity, %): 226 [M^+] (2.4), 197 (1.4), 181 (19.7). 155 (5.8), 127 (20.4), 101 (36), 81 (45.6), 68 (36.7), 55 (100).

Analysis: $C_{14}H_{26}O_2$ (226.35) requires C, 74.28; H, 11.57. Found: C, 74.46; H, 11.32.

Synthesis of (2*R*,3*S*)-ethyl-2,3-dihydroxydodecanoate, 91



91

To a mixture of $K_3Fe(CN)_6$ (13.06 g, 39.76 mmol), K_2CO_3 (5.49 g, 39.76 mmol) and $(DHQ)_2$-PHAL (104 mg, 0.133 mmol, 1 mol%) in *t*-BuOH:H_2O (1:1, 140 mL) cooled at 0°C was added osmium tetroxide (536 µL, 0.1M solution in toluene, 0.4 mol%) followed by methanesulfonamide (1.26 g, 13.25 mmol). After stirring for 5 min at 0°C, the olefin **90** (3 g, 13.25 mmol) was added in one portion. The reaction mixture was stirred at 0°C for 24 h and then quenched with solid sodium sulfite (5 g). The stirring was continued for an additional 45 min and then the solution was extracted with EtOAc (5 × 30 mL). The combined organic phases were washed with 10% aq KOH, brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether:EtOAc (3:2) as eluent gave **91** (3.24 g) as a white solid.

Yield: 3.24 g, 94%

Mp.: 52-53°C

$[\alpha]_D^{20}$: − 10.54 (c = 1, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3377, 1736, 1460

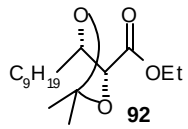
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.85 (t, *J* = 7 Hz, 3H), 1.2-1.3 (m, 14H), 1.31 (t, *J* = 8 Hz, 3H), 1.56 (m, 2H), 3.06 (brs, 2H), 3.84 (brt, *J* = 6 Hz, 1H), 4.05 (m, 1H), 4.24 (q, *J* = 8 Hz, 2H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.81, 13.82, 22.38, 25.54, 29.07, 29.33, 31.64, 33.29, 61.41, 72.44, 73.25, 173.45;

EIMS *m/z* (relative intensity, %): 187 [M^+–CO_2Et] (3.3), 157 (1.4), 133 (2.4), 104 (100), 95 (4.7), 76 (88.4), 55 (23.1).

Analysis: $C_{14}H_{28}O_4$ (260.37) requires C, 64.58; H, 10.84. Found: C, 64.66; H, 10.71.

Synthesis of (2*R*,3*S*)-ethyl-2,3-*O*-isopropylidenedodecanoate-2,3-diol, 92



92

To a solution of the diol **91** (5 g, 19.2 mmol), *p*-TsOH (cat) in acetone (100 mL) was added 2,2-dimethoxy propane (4 g, 38.4 mmol) and stirred at room temperature for 8 h. Solid $NaHCO_3$

(1 g) was added and stirred for 30 mins. The reaction mixture was filtered through a pad of neutral alumina and concentrated. Silica gel column chromatography of the residue using petroleum ether:EtOAc (24:1) gave **92** (5.71 g) as a colorless liquid.

Yield: 5.71 g, 99%

[a]$_D^{20}$: – 15 (c = 1, $CHCl_3$)

IR (neat, cm^{-1}): n_{max} 1758, 1460, 1376, 1097

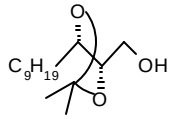
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.85 (t, *J* = 7 Hz, 3H), 1.2-1.26 (m, 14H), 1.30 (t, *J* = 7.5 Hz, 3H), 1.41 (s, 3H), 1.43 (s, 3H), 1.67 (m, 2H), 4.08 (m, 2H), 4.23 (q, *J* = 7.5 Hz, 2H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.5, 13.52, 22.08, 25.02, 26.57, 28.74, 28.96, 31.35, 33.04, 60.31, 78.69, 78.7, 109.97, 170.18

EIMS *m/z* (relative intensity, %): 285 [M^+–15] (100), 271 (4.8), 227 (29.3), 197 (2.7), 144 (17), 109 (15), 95 (38.1) 69 (22.4), 59 (59.2), 55 (40.8)

Analysis: $C_{17}H_{32}O_4$ (300.43) requires C, 67.96; H, 10.73. Found: C, 67.88; H, 10.93.

Synthesis of (2*S*,3*S*)-2,3-*O*-isopropylidenedodecane-1,2,3-triol, 93



93

To a stirred suspension of $LiAlH_4$ (0.615 g, 16.2 mmol) in dry Et_2O (100 mL) at 0°C was added a solution of **92** (3.25 g, 10.81 mmol) in Et_2O (10 mL) dropwise. The reaction mixture was allowed to warm to room temperature and stirred overnight. Excess $LiAlH_4$ was destroyed by slow addition of 10% aq NaOH (2 mL) and EtOAc (20 mL). The white precipitate was filtered through a pad of neutral alumina and washed with MeOH (3 × 100 mL). The filtrate was concentrated and the residue was purified by silica gel column chromatography using petroleum ether:EtOAc (4:1) as eluent to give **93** (2.71 g) as colorless oil.

Yield: 2.71 g, 97%

[a]$_D^{20}$: – 21.16 (c = 1, $CHCl_3$)

IR (neat, cm^{-1}): n_{max} 3460, 1462, 1378, 1246

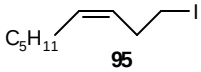
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.85 (t, *J* = 7.5 Hz, 3H), 1.2-1.35 (m, 14H), 1.38 (s, 6H), 1.52 (m, 2H), 2.58 (s, 1H), 3.58 (m, 1H), 3.72 (m, 2H), 3.82 (m, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.52, 22.16, 25.5, 26.53, 26.86, 28.85, 29.07, 29.25, 31.42, 32.82, 61.89, 77, 81.45, 107.95

EIMS *m/z* (relative intensity, %): 243 [M^+–15] (97.4), 227 (21.7), 155 (1.6), 109 (17.8), 95 (28.3), 81 (19), 69 (19), 59 (100), 55 (44).

Analysis: $C_{15}H_{30}O_3$ (258.4) requires C, 69.72; H, 11.70. Found: C, 69.63; H, 11.82.

Preparation of *cis*-3-nonen-1-iodide, 95



95

To a solution of triphenylphosphine (13.72, 52.3 mmol) in dry CH_2Cl_2 (50 mL) was added iodine (13.27, 52.3 mmol). The orange precipitate was stirred for 30 min and a solution of *cis*-3-nonen-1-ol **94** (6.2 g, 43.58) and imidazole (3.56, 52.3 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 1.5 h and then CH_2Cl_2 was evaporated. The residue was diluted with water and the solution was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with 20% aq. $Na_2S_2O_3$, brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using petroleum ether:ether (9.8:0.2) to give *cis*-3-nonen-1-iodide **95** (10.77 g) as colorless oil.

Yield: 10.77, 98%

IR (neat, cm^{-1}): n_{max} 1648, 1457

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7 Hz, 3H), 1.25-1.35 (m, 6H), 2.0 (m, 2H), 2.65 (dd, *J* = 8, 6 Hz, 2H), 3.14 (t, *J* = 7 Hz, 2H), 5.34 (dt, *J* = 11, 6 Hz, 1H), 5.55 (dt, *J* = 11, 6 Hz, 1H)

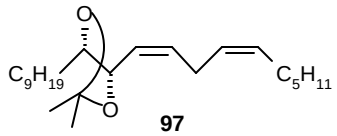
^{13}C NMR (50 MHz, $CDCl_3$): δ 5.18, 13.96, 22.41, 27.30, 29.07, 31.35, 127.62, 132.47

EIMS *m/z* (relative intensity, %): 252 [M^+] (1.6), 155 (2.6), 127 (5.9), 83 (29.4), 69 (71.2), 55 (100).

Preparation of *cis*-3-nonenetriphenylphosphoniumiodide, 96

To a solution of triphenylphosphine (10.4 g, 39.65 mmol) in dry benzene (50 mL) was added the iodide **95** (10 g, 39.65 mmol) and the solution refluxed for 24 h. The reaction mixture was cooled to room temperature and benzene removed under reduced pressure. The sticky solid was triturated with dry Et_2O to remove unreacted starting materials. The residue was dried under high vacuum to a white sticky solid of *cis*-3-nonenetriphenylphosphoniumiodide **96** (19.4 g, 95%) and was used as such immediately.

Synthesis of (6*Z*,9*Z*,11*S*,12*S*)-11,12-*O*-isopropylidenehenicosa-6,9-diene, 97



97

To a solution of oxalyl chloride (5.89 g, 4.05 mL, 46.42 mmol) in dry CH_2Cl_2 (250 mL) cooled at −78°C was added dropwise DMSO (6.6 mL, 92.84 mmol) in CH_2Cl_2 (15 mL) over 20 min. The reaction mixture was stirred for 30 min at −78°C and the solution of alcohol **93** (8 g, 30.95 mmol) in CH_2Cl_2 (15 mL) was added dropwise at −60°C over 20 min. The reaction mixture was stirred for 30 min when a copious white precipitate was obtained. Et_3N (16 mL) was added dropwise and stirred for 1 h allowing the temperature to rise to room temperature. The reaction mixture was quenched with 2% aq. HCl (200 mL) and the new phase extracted with EtOAc. The combined organic phases were washed (brine), dried (Na_2SO_4) and concentrated to give the crude aldehyde, which was used in the next step without further purification.

To a stirred suspension of the Wittig salt **96** (19.4 g, 37.7 mmol) in dry THF (100 mL) was added *n*-BuLi (20 mL, 40 mmol, 2M in hexane) dropwise at 0°C. The reaction mixture was stirred till all solids dissolved (30 min). To the dark red solution was added the above aldehyde in dry THF (20 mL) dropwise at −80°C. The reaction was stirred for 8 h at −80°C and then allowed to warm to room temperature. It was quenched with saturated aq. NH_4Cl and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using petroleum ether:EtOAc (9:1) as eluent to give **97** (8.58 g) as colorless oil.

Yield: 8.58 g, 76%

$[\alpha]_D^{20}$: − 8.37 (c = 1, $CHCl_3$)

IR (neat, cm^{-1}): ν_{max} 1723, 1464, 1378, 1221, 1052

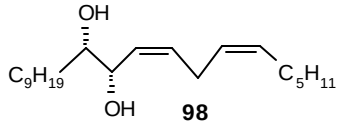
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (m, 6H), 1.2-1.35 (m, 20H), 1.42 (s, 3H), 1.43 (s, 3H), 1.52 (m, 2H), 2.04 (m, 2H), 2.89 (m, 2H), 3.68 (m, 1H), 4.4 (t, *J* = 8 Hz, 1H), 5.3-5.5 (m, 3H), 5.7 (dt, *J* = 8, 4 Hz, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.8, 13.81, 22.3, 22.45, 25.83, 25.98, 26.83, 27.01, 29.1, 29.33, 29.55, 31.27, 31.68, 76.38, 80.68, 107.91, 126.45, 126.51, 130.63, 133.57

EIMS *m/z* (relative intensity, %): 364 [M^+] (1.3), 349 [M^+−15] (11), 289 (2.6), 208 (11.3), 155 (9.7), 97 (92.3), 80 (51.6), 69 (40.3), 55 (100)

Analysis: $C_{24}H_{44}O_2$ (364.61) requires C, 79.06; H, 12.16. Found: C, 79.32; H, 11.88.

Synthesis of (6*Z*,9*Z*,11*S*,12*S*)-11,12-dihydroxyhenicosa-6,9-diene, 98



98

To a solution of **97** (2.6 g, 7.13 mmol) in MeOH (50 mL) was added 3N HCl (6 mL) and stirred at room temperature for 12 h. Excess HCl was quenched by adding solid $NaHCO_3$ and the reaction mixture diluted with water (50 mL). The solution was extracted with EtOAc (4 × 50 mL), washed (brine), dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the residue with petroleum ether:EtOAc (3:2) as eluent gave **98** (2.09 g) as a colorless syrup.

Yield: 2.09 g, 90%

[a]$_D^{20}$: – 5.93 (c = 1, $CHCl_3$)

IR (neat, cm^{-1}): n_{max} 3384, 1723, 1714, 1465, 1067

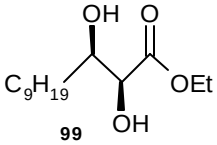
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (m, 6H), 1.2-1.35 (m, 22H), 2.03 (m, 2H), 2.34 (br s, 2H), 2.87 (m, 2H), 3.45 (m, 1H), 4.23 (t, *J* = 8 Hz, 1H), 5.34-5.46 (m, 3H), 5.61 (dt, *J* = 8, 4 Hz, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.81, 13.82, 22.49, 25.69, 26.16, 27.05, 29.1, 29.51, 31.31, 31.75, 32.67, 70.9, 74.79, 126.66, 129.12, 130.63, 131.84

EIMS *m/z* (relative intensity, %): 324 [M^+] (1.7), 306 (8.7), 290 (3.3), 213 (11.4), 157 (17.4), 97 (27.5), 83 (65.7), 69 (53.7), 57 (100)

Analysis: $C_{21}H_{40}O_2$ (324.54) requires C, 77.72; H, 12.42. Found: C, 77.98; H, 12.26.

Synthesis of (2*S*,3*R*)-ethyl-2,3-dihydroxydodecanoate, 99



99

Compound **99** was prepared following the procedure as described for compound **91**. In this case the ligand used was $(DHQD)_2$-PHAL in place of $(DHQ)_2$-PHAL. White solid.

Yield: 94%

Mp.: 53-54°C

[a]$_D^{20}$: + 11.41 (c = 0.6, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): n_{max} 3507, 1730, 1467

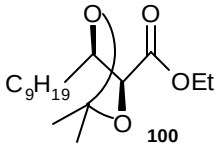
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6.5 Hz, 3H), 1.2-1.3 (m, 14H), 1.31 (t, *J* = 8 Hz, 3H), 1.59 (m, 2H), 2.75 (br s, 2H), 3.88 (br t, *J* = 6 Hz, 1H), 4.07 (m, 1H), 4.26 (q, *J* = 8 Hz, 2H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.84, 13.91, 22.48, 25.64, 29.17, 29.43, 31.74, 33.39, 61.51, 72.54, 73.35, 173.55

EIMS *m/z* (relative intensity, %): 187 [M^+–CO_2Et] (1.93), 157 (1.2), 133 (1.9), 104 (100), 95 (3.8), 76 (60.6), 55 (21.3)

Analysis: $C_{14}H_{28}O_4$ (260.37) requires C, 64.58; H, 10.84. Found: C, 64.38; H, 11.02.

Synthesis of (2*S*,3*R*)-ethyl-2,3-*O*-isopropylidenedodecanoate-2,3-diol, 100



100

Compound **100** was prepared by following the same procedure as described for compound **92**. Colorless liquid.

Yield: 99%

[a]$_D^{20}$: + 15.52 (c = 1, $CHCl_3$)

IR (neat, cm^{-1}): n_{max} 1758, 1464, 1380, 1098

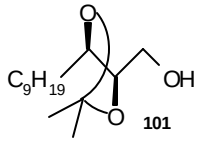
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.86 (t, *J* = 6.5 Hz, 3H), 1.2-1.26 (m, 14H), 1.31 (t, *J* = 7.5 Hz, 3H), 1.42 (s, 3H), 1.44 (s, 3H), 1.68 (m, 2H), 4.09 (m, 2H), 4.24 (q, *J* = 7.5 Hz, 2H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.6, 13.62, 22.18, 25.12, 26.67, 28.84, 29.06, 31.45, 33.14, 60.41, 78.79, 78.8, 110.07, 170.28

EIMS *m/z* (relative intensity, %): 285 [M^+–15] (46.4), 271 (2.6), 227 (15.5), 197 (1.9), 144 (13.5), 109 (14.2), 95 (52.9) 69 (34.8), 59 (100), 55 (65.1)

Analysis: $C_{17}H_{32}O_4$ (300.43): C, 67.96; H, 10.73. Found: C, 68.13; H, 10.55.

Synthesis of (2*R*,3*R*)-2,3-*O*-isopropylidenedodecane-1,2,3-triol, 101



101

Compound **101** was prepared by following the same procedure as described for compound **93**. Colorless oil.

Yield: 97%

[a]$_D^{20}$: + 22.07 (c = 1, $CHCl_3$)

IR (neat, cm^{-1}): n_{max} 3441, 1459, 1374, 1244

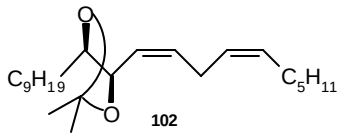
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.84 (t, *J* = 6.5 Hz, 3H), 1.2-1.35 (m, 14H), 1.38 (s, 6H), 1.51 (m, 2H), 2.64 (br s, 1H), 3.59 (m, 1H), 3.73 (m, 2H), 3.81 (m, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.57, 22.21, 25.55, 26.58, 26.91, 28.90, 29.12, 29.30, 31.47, 32.87, 61.94, 77.05, 81.50, 108

EIMS *m/z* (relative intensity, %): 243 [M^+–15] (38), 227 (7.7), 155 (0.96), 109 (13.5), 95 (27.1), 81 (18), 69 (15.5), 59 (100) 55 (31)

Analysis: $C_{15}H_{30}O_3$ (258.4): C, 69.72; H, 11.70. Found: C, 69.77; H, 11.63

Synthesis of (6*Z*,9*Z*,11*R*,12*R*)-11,12-*O*-isopropylidenehenicosa-6,9-diene, 102



102

Compound **102** was prepared by following the same procedure as described for compound **97**. Colorless oil.

Yield: 76%

$[\alpha]_D^{20}$: + 8.54 (c = 1, $CHCl_3$)

IR (neat, cm^{-1}): n_{max} 1723, 1464, 1378, 1220, 1054

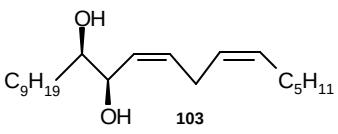
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.86 (m, 6H), 1.2-1.35 (m, 20H), 1.41 (s, 3H), 1.42 (s, 3H), 1.52 (m, 2H), 2.04 (m, 2H), 2.89 (m, 2H), 3.64 (m, 1H), 4.39 (t, *J* = 8 Hz, 1H), 5.3-5.5 (m, 3H), 5.68 (dt, *J* = 8, 4 Hz, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.81, 13.82, 22.3, 22.45, 25.98, 26.83, 27.01, 29.03, 29.10, 29.33, 29.55, 31.68, 76.49, 80.68, 107.91, 126.45, 126.51, 130.63, 133.57

EIMS *m/z* (relative intensity, %): 349 [M^+–15] (0.7), 207 (1.3), 155 (4.7), 95 (16.7), 81 (27.5), 69 (44.3), 55 (100)

Analysis: $C_{24}H_{44}O_2$ (364.61) requires C, 79.06; H, 12.16. Found: C, 78.97; H, 12.28

Synthesis of (6*Z*,9*Z*,11*R*,12*R*)-11,12-dihydroxyhenicosa-6,9-diene, 103



103

Compound **103** was prepared by following the same procedure as described for compound **98**. Colorless syrup.

Yield: 90%

[a]$_D^{20}$: + 6.04 (c = 1, $CHCl_3$)

IR (neat, cm^{-1}): n_{max} 3367, 1724, 1712, 1465, 1048

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.87 (m, 6H), 1.2-1.35 (m, 22H), 2.02 (m, 2H), 2.79-2.89 (m, 4H), 3.41 (m, 1H), 4.21 (t, *J* = 8 Hz, 1H), 5.33-5.48 (m, 3H), 5.60 (dt, *J* = 8, 4 Hz, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.90, 13.92, 22.58, 25.78, 26.25, 27.14, 29.19, 29.60, 31.40, 31.84, 32.76, 70.99, 74.88, 126.75, 129.21, 130.72, 131.93

EIMS *m/z* (relative intensity, %): 324 [M^+] (0.5), 306 (0.4), 195 (2.8), 155 (23.4), 97 (49.3), 83 (100), 69 (44.7), 55 (50)

Analysis: $C_{21}H_{40}O_2$ (324.54): C, 77.72; H, 12.42. Found: C, 77.58; H, 12.46.

Preparation of *trans* dodec-2-ene-1-ol, 104

104

To a solution of **90** (2 g, 8.83 mmol) in dry Et_2O (70 mL) at 0°C was added dropwise DIBAL-H (19.5 mL, 19.5 mmol, 1M in toluene) through a syringe. The reaction mixture was allowed to warm to room temperature over 0.5 h, then recooled to 0°C and treated with 1N HCl (50 mL). The resulting gel was dissolved by dropwise addition of 6N HCl. The ethereal phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. Silica gel column chromatography of the crude product using petroleum ether:EtOAc (8:2) as eluent gave **104** (1.47 g) as colorless oil.

Yield: 1.47 g, 90%

IR (neat, cm^{-1}): n_{max} 3393,1694,1460

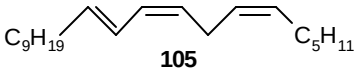
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7 Hz, 3H), 1.2-1.45 (m, 14H), 1.71 (br s, 1H), 2.05 (br q, *J* = 6 Hz, 2H), 4.09 (d, *J* = 4 Hz, 2H), 5.67 (m, 2H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.92, 22.56, 29.25, 29.47, 31.82, 32.12, 63.22, 129.01, 133.2

EIMS *m/z* (relative intensity, %): 184 [M^+] (0.65), 169 (2.6), 155 (5.2), 110 (14.4), 97 (59.5), 83 (100), 71 (68.6), 55 (63.4).

Analysis: $C_{12}H_{24}O$ (184.32) requires C, 78.19; H, 13.12. Found: C, 78.40; H, 12.98

Synthesis of (6*Z*,9*Z*,11*E*)-henicosatriene, 105



105

To a stirred suspension of PCC (11.76, 54.55 mmol) and powdered molecular sieves (3A°, 4 g) in dry CH_2Cl_2 (200 mL) was added **104** (6.7 g, 36.35 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature for 8 h and then concentrated. The residue was triturated with ether, filtered through a pad of celite and washed with ether (3 × 50 mL). The filtrate was concentrated to give virtually pure aldehyde (5.62 g, 85%) as colorless oil. This was used as such in subsequent reaction.

To a suspension of the Wittig salt **96** (19.4 g, 37.7 mmol) in dry THF (100 mL) was added LiHMDS (45 mL, 45 mmol, 1M soln. In THF) dropwise at 0°C. The reaction mixture was stirred till all solids dissolved (30 min). To the dark red solution was added the above aldehyde in dry THF (20 mL) dropwise at −80°C. The reaction was stirred for 8 h at −80°C and then allowed to warm to room temperature. It was quenched with saturated aq. NH_4Cl and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using petroleum ether:ether (99:1) as eluent to give **105** (7.81 g) as a colorless oil.

Yield: 7.81 g, 74%

IR (neat, cm^{-1}): n_{max} 1680, 1642, 1465 cm^{-1}

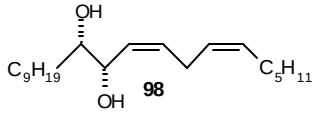
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (m, 6H), 1.25-1.3 (m, 20H), 2.01-2.22 (m, 6H), 5.38-5.63 (m, 4H), 5.99 (m, 1H), 6.24 (dd, *J* = 15, 4 Hz, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.96, 14.07, 22.27, 22.78, 29.36, 29.47, 29.66, 31.53, 32.01, 32.34, 32.71, 33, 34.8, 125.81, 128.98, 129.49, 130.48, 130.81, 134.53.

EIMS *m/z* (relative intensity, %): 290 [M^+] (3.3), 247 (1.3), 193 (2.6), 109 (14.4), 95 (34.6), 81 (56.2), 67 (100), 55 (78.4)

Analysis: $C_{21}H_{38}$ (290.53) requires C, 86.81; H, 13.18 Found: C, 87.01; H, 12.98

Monodihydroxylation of triene 105 to 98



98

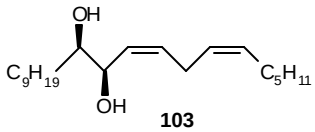
To a mixture of $K_3Fe(CN)_6$ (3.4 g, 10.33 mmol), K_2CO_3 (1.43 g, 10.33 mmol) and $(DHQ)_2$-PHAL (27 mg, 0.0344 mmol, 1 mol%) in *t*-BuOH-H_2O (1:1, 40 mL) cooled at 0°C was

added osmium tetroxide (68 µL, 0.1M solution in toluene, 0.2 mol%) followed by methanesulfonamide (0.327 g, 3.44 mmol). After stirring for 5 min at 0°C, the triene **105** (1 g, 3.44 mmol) was added in one portion. The reaction mixture was stirred at 0°C for 10 h and then quenched with solid sodium sulfite (5 g). The stirring was continued for an additional 45 min and then the solution was extracted with EtOAc (5 × 30 mL). The combined organic phases were washed with 10% aq. KOH, brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether:EtOAc (3:2) as eluent gave **98** (0.87 g) as colorless syrup.

Yield: 0.87 g, 78%

$[\alpha]_D^{20}$: – 5.69 (c = 1, $CHCl_3$).

Monodihydroxylation of triene 105 to 103



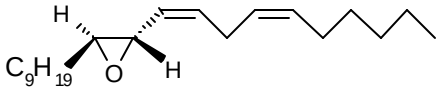
103

In this case $(DHQD)_2$-PHAL ligand was used. Following the above procedure, **105** gave **103** as colorless syrup.

Yield: 0.89 g, 79%

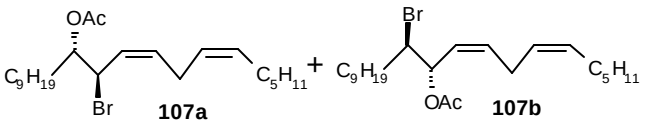
$[\alpha]_D^{20}$: + 5.81 (c = 1, $CHCl_3$)

Synthesis of (-)-posticlure, 74



74

To solution of diol **98** (0.8 g, 2.46 mmol), and *p*-TsOH (8 mg) in dry CH_2Cl_2 (5 mL) was added trimethylorthoacetate (0.385 g, 3.2 mmol) and stirred at room temperature for 30 min. The solvent was evaporated and the residual methanol was removed under high vacuum. The residue was taken in CH_2Cl_2 (5 mL) and acetyl bromide (0.237 mL, 3.2 mmol) was added dropwise at room temperature. The reaction mixture was stirred for 4 h and concentrated to give a mixture of virtually pure acetoxy bromides **107a** and **107b**.



^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (m, 6H), 1.2-1.35 (m, 20H), 1.67 (m, 2H), 2.06 (m, 2H), 2.09 (s, 3H), 2.87 (br t, *J* = 7 Hz, 2H), 4.96 (m, 1H), 5.09 (m, 1H), 5.4-5.75 (m, 4H)

EIMS *m/z* (relative intensity, %): 429 [M^+] (0.3), 369 (0.7), 349 (0.5), 307 (6.6), 289 (11.9), 195 (4.6), 155 (15.5), 109 (13.2), 95 (29.8), 81 (47.7), 67 (56.3), 55 (100)

To the mixture of **107a** and **107b** was added dry MeOH (4 mL) and powdered K_2CO_3 (0.443 g, 3.2 mmol) and stirred for 4 h at room temperature. The reaction mixture was filtered through a pad of neutral alumina and the pad washed with Et_2O (3 × 50 mL). The filtrate was concentrated and the residue purified by silica gel column chromatography using petroleum ether:ether (9:1) as eluent to give (−)-**74** (0.665 g) as colorless oil.

Yield: 0.665 g, 88%

[a]$_D^{20}$: − 11.1 (c = 1, $CHCl_3$) [lit. $[\alpha]_D^{24}$ − 10.8 (c = 1.07, $CHCl_3$)][29a]

IR (neat, cm^{-1}): n_{max} 2956, 1725, 1708, 1465, 1389

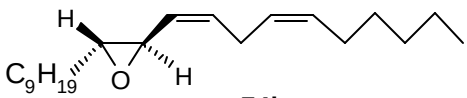
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89 (m, 6H), 1.2-1.45 (m, 20H), 1.58 (m, 2H), 2.06 (m, 2H), 2.82 (dt, *J* = 2.1 Hz, 1H), 2.97 (dd, *J* = 7.1, 7.5 Hz, 2H), 3.36 (dd, *J* = 2.1, 8.7 Hz, 1H), 5.08 (ddd, *J* = 8.7, 10.8 Hz 1H), 5.37 (dtt, *J* = 7.1, 10.7 Hz, 1H), 5.44 (dtt, *J* = 7.5, 10.7 Hz, 1H), 5.67 (dt, *J* = 7.5, 10.8 Hz, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.74, 13.75, 22.3, 22.41, 25.76, 26.94, 29.07, 29.21, 29.33, 31.24, 31.64, 31.82, 53.77, 59.5, 126.59, 127.28, 130.59, 133.53

EIMS *m/z* (relative intensity, %): 306 [M^+] (15), 290 (3.4), 235 (1.4), 209 (2), 195 (17), 179 (4.1), 155 (16.3), 136 (8.1), 109 (12.2), 95 (32), 79 (76.8), 71 (47.6), 67 (58.5), 55 (100)

Analysis: $C_{21}H_{38}O$ (306.53) requires C, 82.28; H, 12.49. Found: C, 82.32; H, 12.43

Synthesis of (+)-posticlure, 74 b



74b

(+)-Posticlure **74b** was prepared by following the same procedure as described for compound **74.** Colorless oil.

Yield: 86%

[a]$_D^{20}$: + 11.33 (c = 2, $CHCl_3$) [lit. $[\alpha]_D^{24}$ + 10.9 (c = 1.09, $CHCl_3$)][29a]

IR (neat, cm^{-1}): n_{max} 2955, 1723, 1705, 1465, 1378

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (m, 6H), 1.2-1.45 (m, 20H), 1.57 (m, 2H), 2.05 (m, 2H), 2.82 (dt, *J* = 2.1 Hz, 1H), 2.96 (dd, *J* = 7.1, 7.6 Hz, 2H), 3.39 (dd, *J* = 2.1, 8.8 Hz, 1H), 5.07 (ddd, *J* = 8.7, 10.8 Hz 1H), 5.3-5.5 (m, 2H), 5.69 (dt, *J* = 7.5, 10.8 Hz, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.8, 13.82, 22.38, 22.49, 25.84, 27.02, 29.15, 29.41, 31.72, 31.90, 53.85, 59.58, 126.67, 127.36, 130.67, 133.61

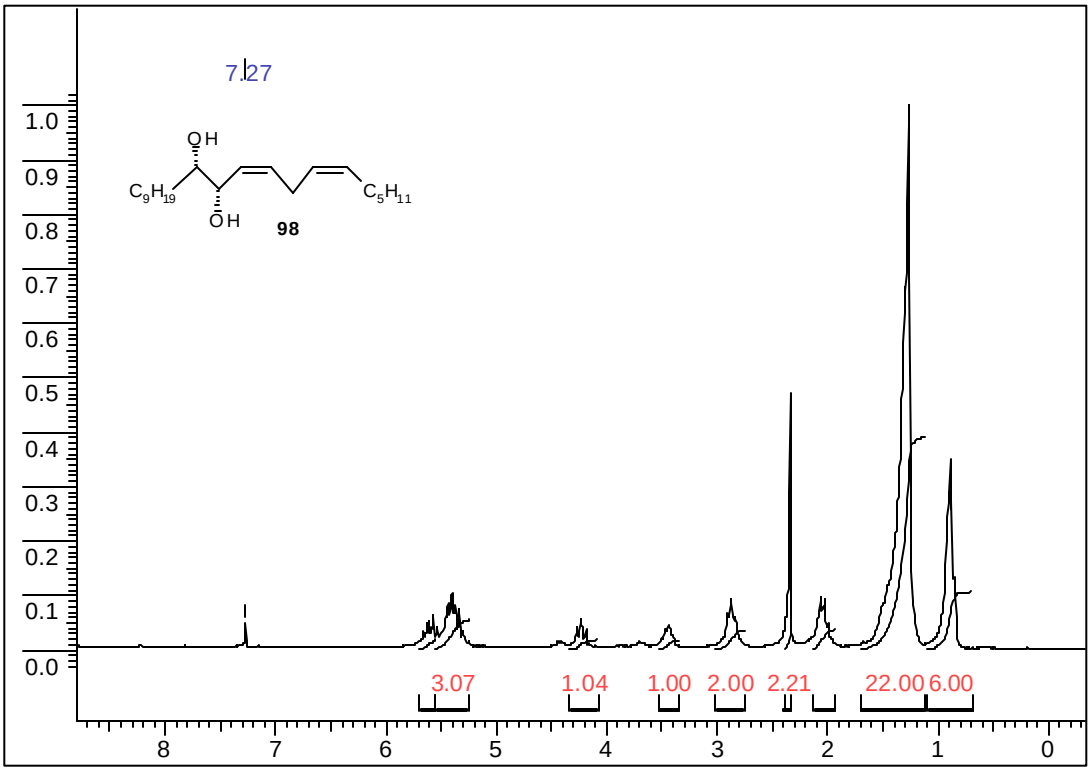
EIMS *m/z* (relative intensity, %): 306 [M] (2.6), 290 (0.7), 235 (1.3), 209 (3.3), 195 (25.5), 179 (4.6), 155 (18.3), 136 (9.2), 109 (15), 95 (32), 79 (79.7), 71 (36.6), 67 (52.3), 55 (100).

Analysis: $C_{21}H_{38}O$ (306.53): C, 82.28; H, 12.49. Found: C, 82.39; H, 12.36.

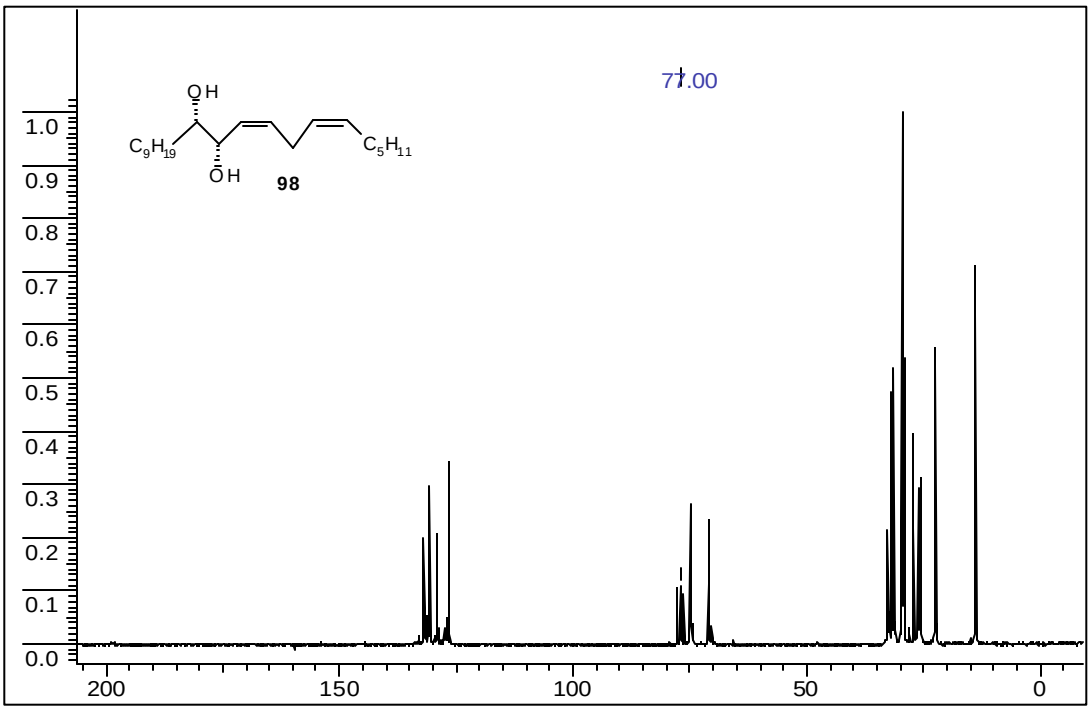
4.3.7. Spectra

+ 1] ^{1}H NMR Spectrum of **98**
+ 2] ^{13}C NMR Spectrum of **98**
+ 3] ^{1}H NMR Spectrum of **105**
+ 4] ^{13}C NMR Spectrum of **105**
+ 5] ^{1}H NMR Spectrum of **107a** + **107b**
+ 6] ^{1}H NMR Spectrum of (–)**74**
+ 7] ^{13}C NMR Spectrum of (–)**74**

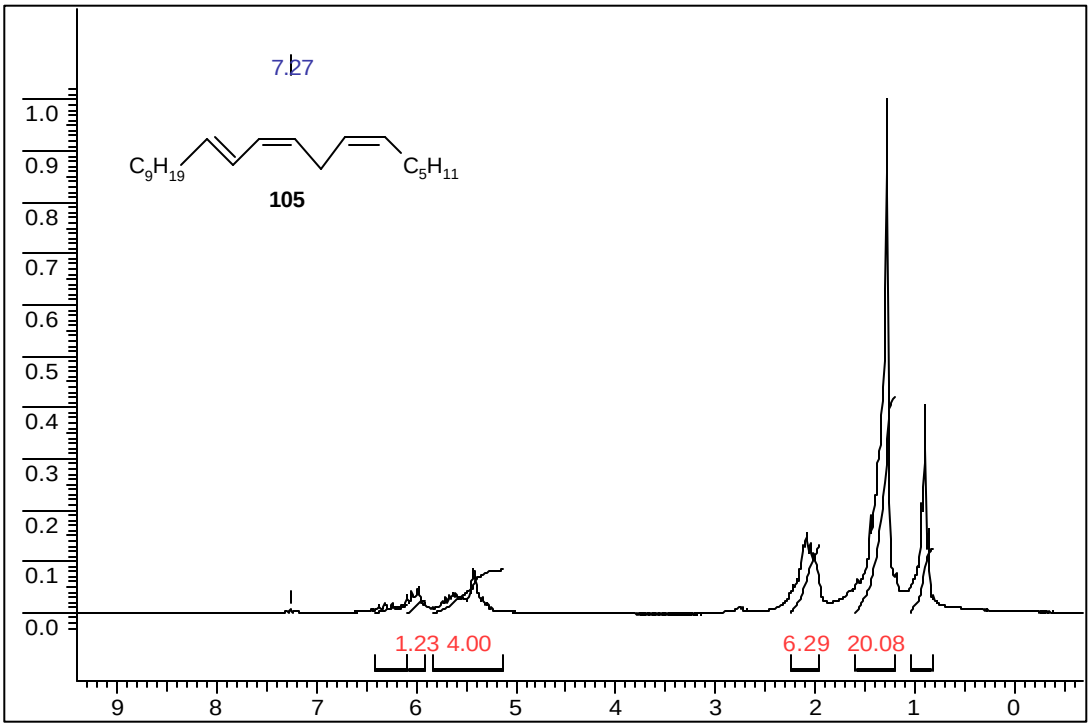
+ ^{1}H NMR Spectrum of **98**



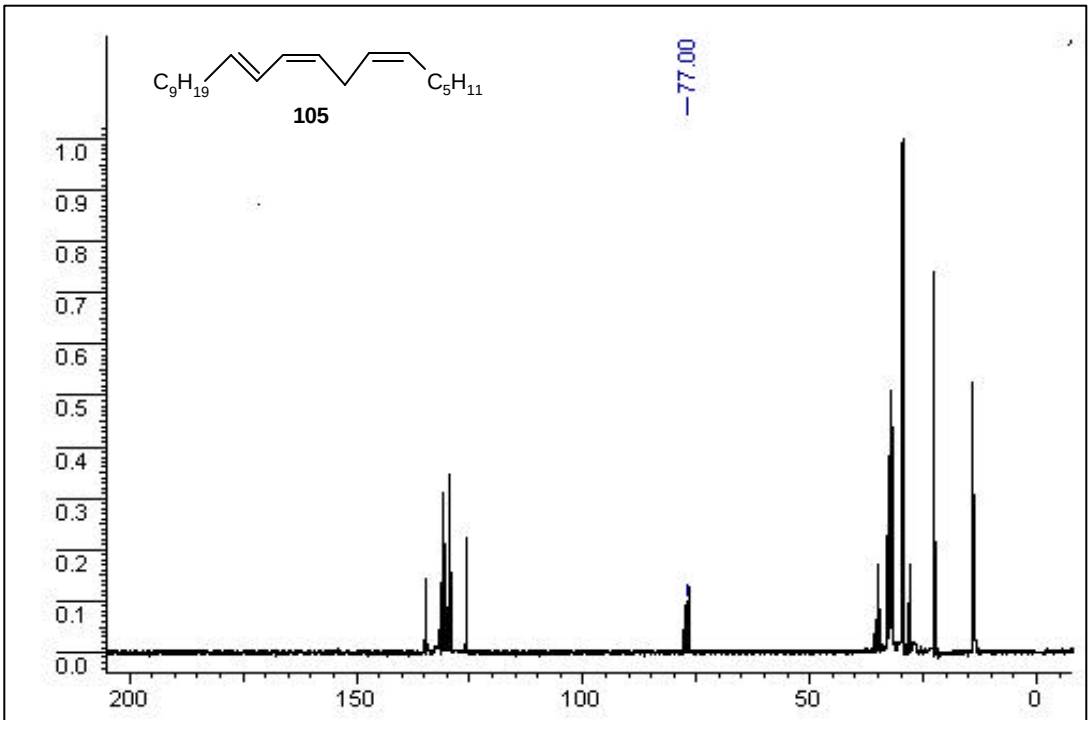
+ ^{13}C NMR Spectrum of **98**



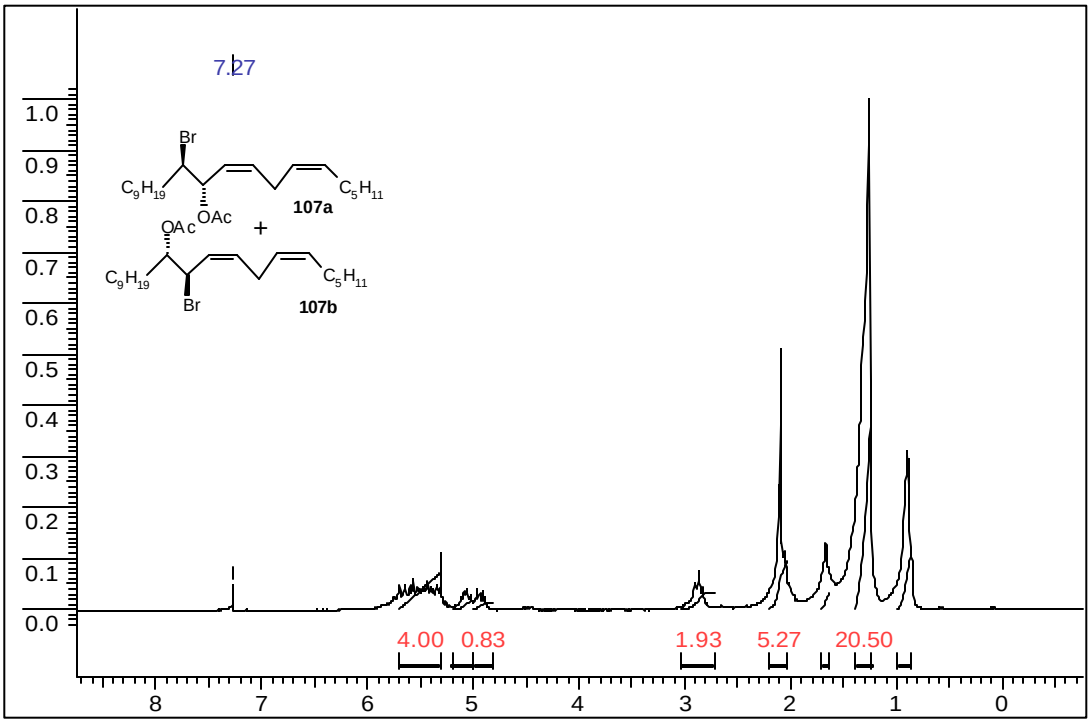
+ ^{1}H NMR Spectrum of **105**



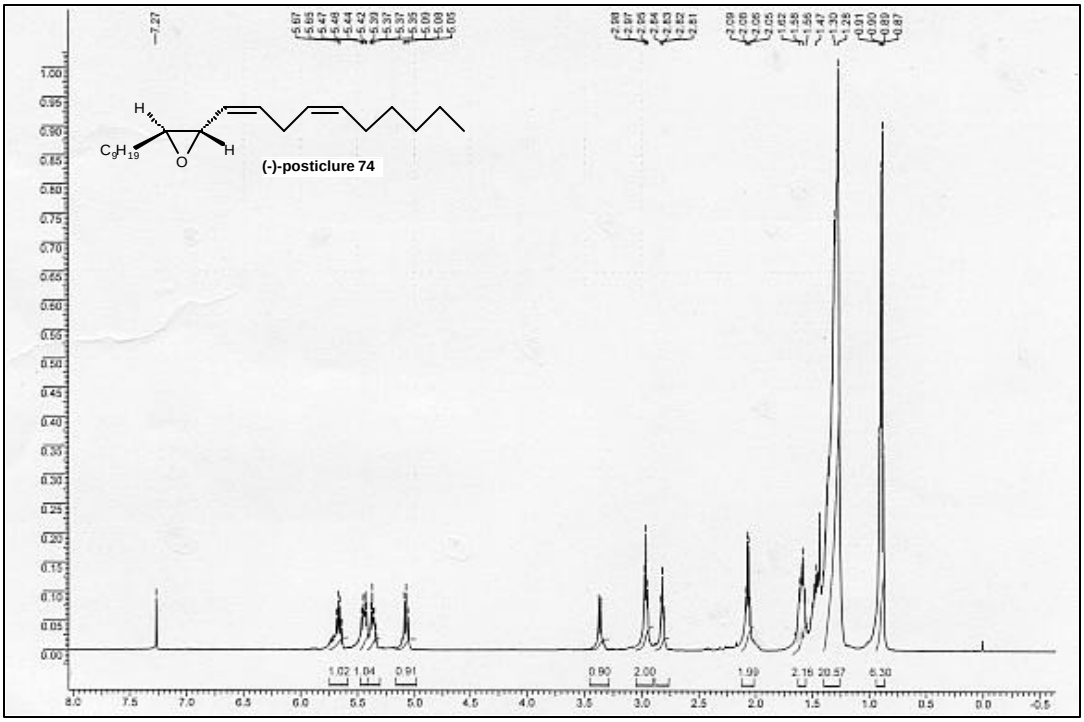
+ ^{13}C NMR Spectrum of **105**



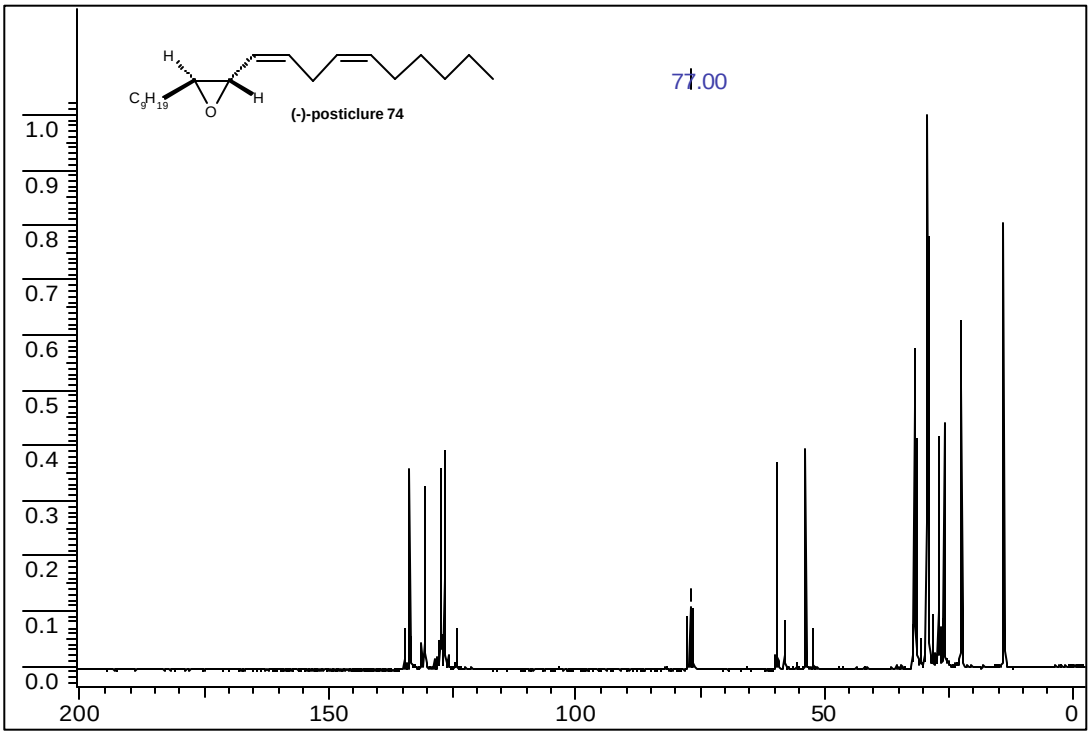
+ ^{1}H NMR Spectrum of **107a** + **107b**



+ ^{1}H NMR Spectrum of (–)**74**



+ ^{13}C NMR Spectrum of (–)**74**



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CHAPTER 5

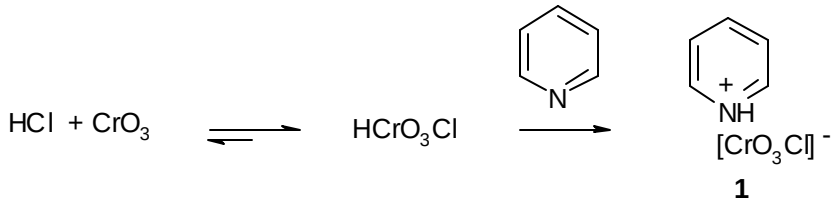
A NEW PCC MEDIATED UNUSUAL C-C BOND CLEAVAGE DURING OXIDATION OF HOMOBENZYLIC ALCOHOLS LEADING TO BENZYLIC CARBONYL COMPOUNDS

5.1. Introduction

Until the studies of Corey and co-workers, the reactivity of pyridinium chlorochromate (PCC **1**) had little been investigated; therefore little data is available in the literature before 1975. The first report on the chlorochromate anion dates back to 1833, when the preparation of potassium chlorochromate was described by Peligot.[1,2] Subsequently only two modified versions of this method have been reported,[3,4] and in 1899, the first synthesis of PCC was achieved.[5]

The search for mild, versatile and selective reagents for the operationally simple oxidation of alcohols to carbonyl compounds has long been the objective of many research laboratories. Many reagents containing the chromium (VI) ion have been studied,[6] but a large number of them cannot be conveniently used in the modern organic synthesis, especially for the oxidation or preparation of complex or highly sensitive substances. The most popular of them, the Collins reagent, showed several difficulties. The CrO_3/pyridine complex must be used in large excess (5 or 6 mol-equivalents), it is unstable, hygroscopic, and it is prepared by a dangerous procedure, during which it can ignite spontaneously. Finally, it shows a poor selectivity in the oxidation of primary alcohols to aldehydes.[7] The studies of Corey and co-workers[8] arose both from the foregoing remarks and from the need to improve the selectivity and effectiveness of the oxidant species.

The first advantage of PCC is that it is prepared easily and safely.[8] The addition of CrO_3 to 6N HCl furnishes the unstable chlorochromic acid and subsequent addition of pyridine at 0°C immediately gives PCC **1** (**Scheme 1**) as a yellow-orange solid which is not appreciably hygroscopic.



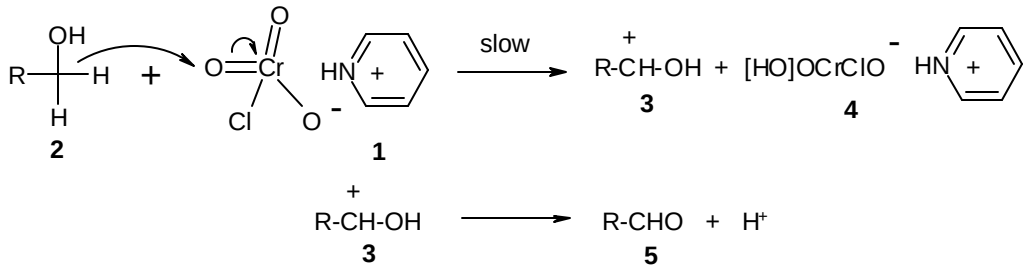
Scheme 1. Preparation of PCC.

The second advantage is that it shows a high capability to convert primary alcohols exclusively to aldehydes with greater efficiency. PCC shows a slightly acidic character and for acid-labile groups the reaction could be buffered with NaOAc.

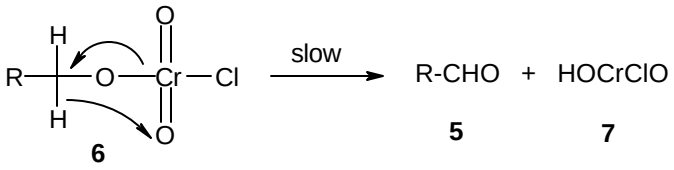
Mechanism of the reaction:

There are only a very few, non-homogeneous reports on the reaction mechanism of pyridinium chlorochromate.[9-14] Banerji[9,10,11] has studied the kinetics of the oxidation by pyridinium chlorochromate of several primary aliphatic and aromatic alcohols. On the basis of experimental data, two different pathways (**A** and **B**) can be proposed.[9,10]

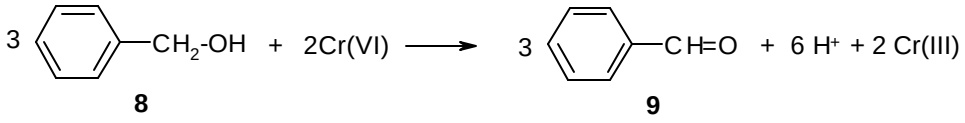
Path A:



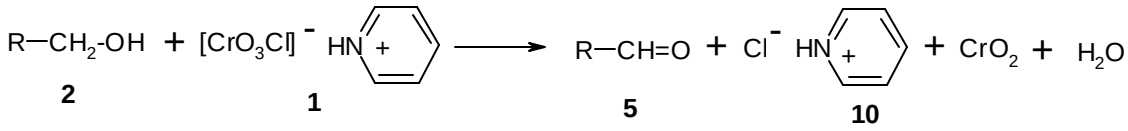
Path B:



Furthermore, a stoichiometry in which a three-electron change is involved was proposed, whereby the oxidant, Cr (VI), is reduced to Cr (III).



More recently, Brown *et al.*[14] have also examined the stoichiometry of this oxidation. The alcohols were oxidized by the Corey[8] procedure utilizing the theoretical amount of PCC and it was proposed that the reaction could involve the transfer of only two electrons.



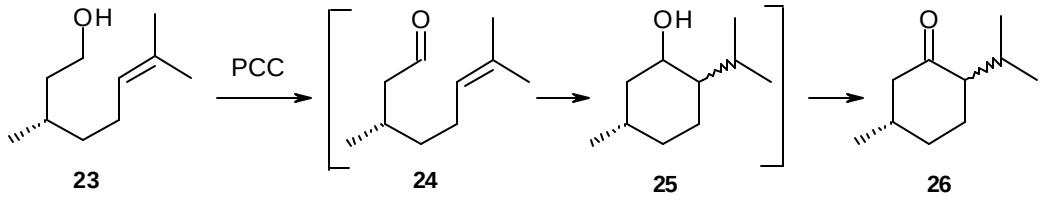
5.2. Review of Literature

PCC is a well-known reagent for oxidation of primary and secondary alcohols to carbonyl compounds with high efficiency.[7] Corey *et al*.[8] carried out oxidations of several primary and secondary alcohols to carbonyl compounds in high yields (**Table 1**).

Table 1.

Alcohol	Product	Yield %
1-Decanol **11**	Decanal **17**	92
1,6-Hexanediol **12**	Hexanedial **18**	68
Benzhydrol **13**	Benzophenone **19**	100
Oct-2-yn-1-ol **14**	Oct-2-ynal **20**	84
Citronellol **15**	Citronellal **21**	82
(*Z*) $HOCH_2CH=CHCH_2OTHP$ **16**	(*E*) $OHCCH=CHCH_2OTHP$ **22**	81

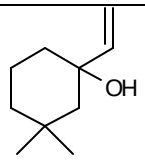
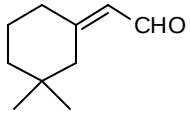
Corey[15] took advantage of both the oxidant power and the acidic nature of PCC to bring about an essentially one-step conversion of (−)-citronellol **23** to (−)-pulegone **26**,[15] an important intermediate in the asymmetric synthesis of prostaglandins[16,17] (**Scheme 2**).

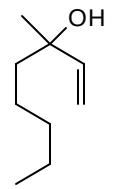
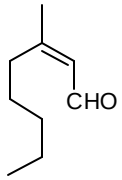
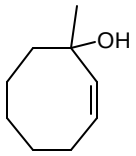
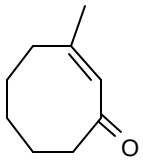
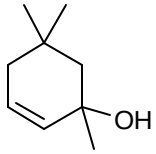
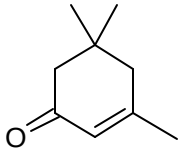
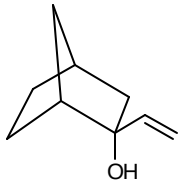
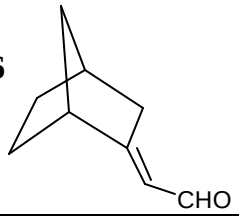


Scheme 2

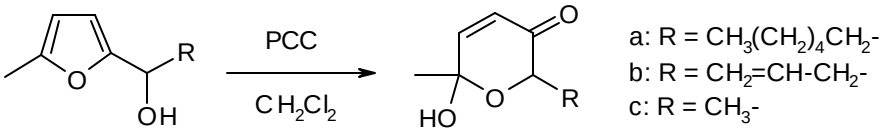
Babler and Coghlan[18] and Sundararaman and Herz[19] have shown that the oxidant and slightly acidic character of PCC is able to convert allylic tertiary alcohols into α,β-unsaturated aldehydes (**Table 2**). Similarly, Dauben *et al*.[20] have shown that tertiary vinyl alcohols can be oxidized by PCC to transposed 3-alkyl α,β-unsaturated carbonyl compounds in excellent yields (**Table 2**).

Table 2.

Substrate	Product	Yield %	Reference
27 	**28** 	85	18

29 	**30** 	72	20
31 	**32** 	88	20
33 	**34** 	94	20
35 	**36** 	79	19

Piancatelli and co-workers[21] used PCC in the oxidation of 5-methyl-2-(α-hydroxyalkyl)-furans (**37**) to 6-hydroxy-2*H*-pyran-3-(6*H*)-ones (**38**). Thus, PCC showed an unusual behavior as dienophile and oxidant in the ring enlargement of 2-furylcarbinols to pyran derivatives (**Scheme 3**).



37 **38**

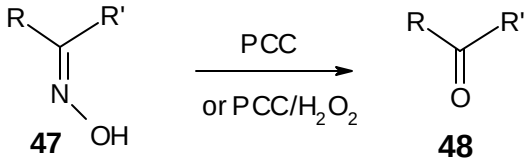
Scheme 3

Piancatelli *et al*.[22] subsequently reported oxidation of linear and cyclic enol-ethers to esters and lactones by using PCC (**Table 3**). The reagent behaves as an oxidizing, weakly electrophilic species, capable of attacking particularly nucleophilic olefins, such as olefin ethers.

Table 3.

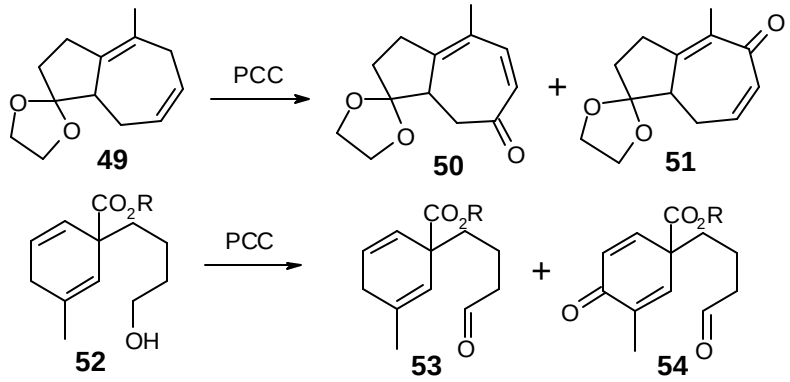
Enol-ether	**Product**	**Yield %**
5-cholesten-3β-vinyl-ether **39**	Cholesteryl-3β-acetate **40**	95
Ethyl-vinyl-ether **41**	Ethylacetate **42**	75
2,3-dihydro-4H-pyran **43**	δ-valerolactone **44**	90
2,3-dihydrofuran **45**	γ-butyrolactone **46**	85

Maloney *et al.*[23] have achieved the deoxamination of oximes to regenerate the carbonyl compound by using PCC. In contrast, Drabowicz[24] found that the PCC/H_2O_2 system was more effective as a deblocking agent and the reactions proceeded within 10 min at 0-10°C when 30% H_2O_2 was added to an acetone solution of the oxime and PCC (**Scheme 4**).



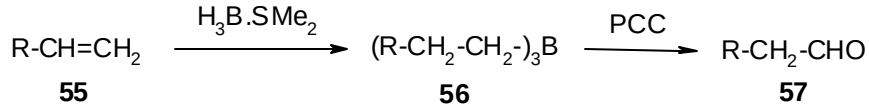
Scheme 4

Wender *et al.*[25] have found that PCC can oxidize 1,4-dienes to dienones. The chemoselectivity is noteworthy, as it does not affect oxidation of isolated double bonds or more reactive systems such as diphenylmethane and allyl benzene. Thus, oxidation of **49** gave **50** and **51** in 9:1 ratio. Similarly, Marshall and Wuts[26] reported the oxidation of **52** with PCC to ester aldehyde **53** along with the product of allylic oxidation, the dienone aldehyde **54** (**Scheme 5**).



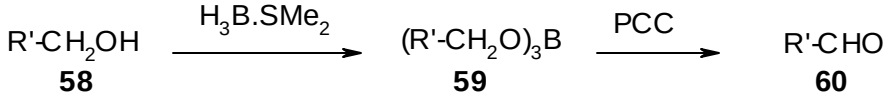
Scheme 5

Brown *et al.*[27] have reported the synthesis of aldehydes by PCC oxidation of trialkylboranes (**56**), derived by the hydroboration of 1-alkenes (**Scheme 6**).



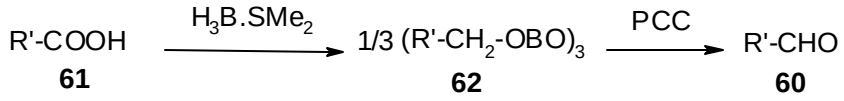
Scheme 6

Subsequently, Brown and co-workers[28] reported the synthesis of carbonyl compounds by PCC oxidation of borate esters (**59**) (**Scheme 7**).



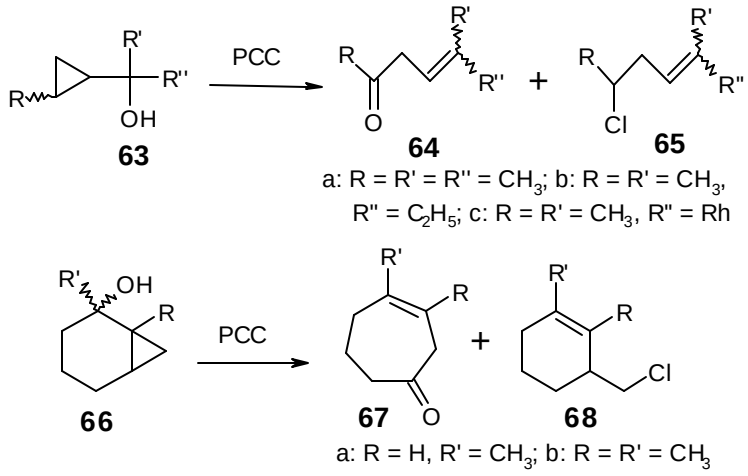
Scheme 7

In a subsequent report by the same authors,[29] the efficient conversion of carboxylic acids into aldehydes was described *via* oxidation of intermediate boroxines (**62**) obtained by the reaction of carboxylic acids with diborane (**Scheme 8**).



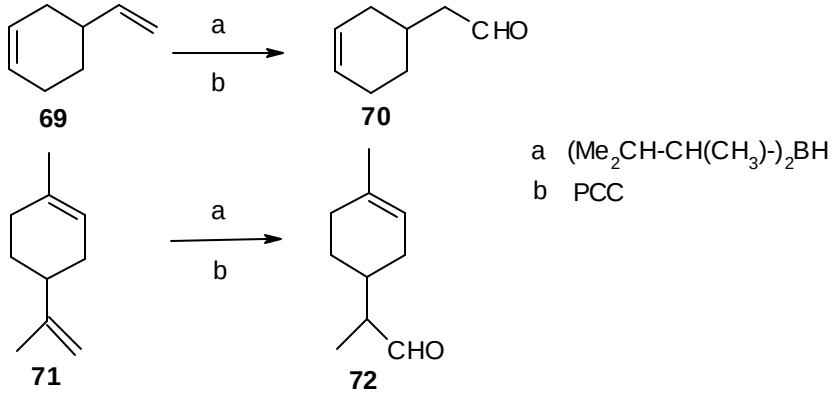
Scheme 8

Nakai *et al.*[30] carried out PCC oxidation of tertiary 2-alkyl cyclopropylcarbinols to the transposed β,γ-enones *via* homoallylic rearrangement, making the overall process a synthetically useful method for 1,4-carbonyl transposition (**Scheme 9**).



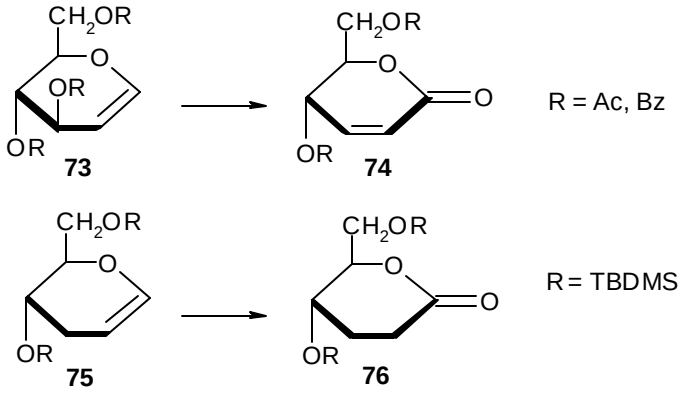
Scheme 9

Brown *et al.*[31] reported highly selective conversion of terminal olefins into aldehydes. The selectivity is achieved *via* selective hydroboration of the terminal olefin with disiamyl borane (**Scheme 10**).



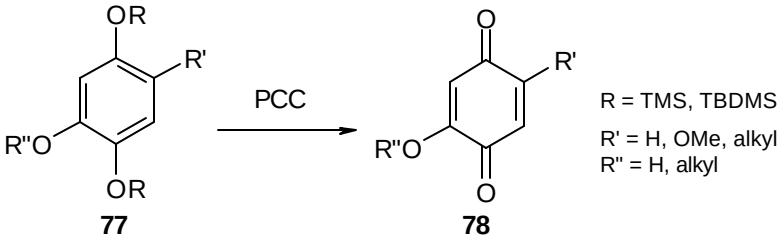
Scheme 10

Rollin and Sinay[32] demonstrated a convenient one-step oxidation of glycals to lactones using PCC (**Scheme 11**).



Scheme 11

Miller and co-workers[33] showed the high capability of PCC to release quinone from hydroquinone silyl ethers by a simple and efficient procedure (**Scheme 12**).



Scheme 12

A number of vicinal diols have been oxidatively cleaved by PCC to give good yields of the corresponding aldehydes or ketones under mild conditions (**Table 4**).[34]

Table 4.

Substrate	**Product**	**Yield %**
PhCH(OH)CH(OH)Ph **79**	Benzaldehyde **9**	98
PhC(OH)(CH_3)CH(OH)Ph **80**	Benzaldehyde **9** Acetophenone **81**	90 85
cis-1,2-cyclohexanediol **82**	Hexanedial **18**	79
3,17,20-trihydroxypregnane **83**	3,17-androstandione **84**	70

Chandrasekaran *et al*.[35] reported a highly selective oxidative cleavage of aryl substituted olefins with PCC to the corresponding carbonyl compounds (**Table 5**).

Table 5.

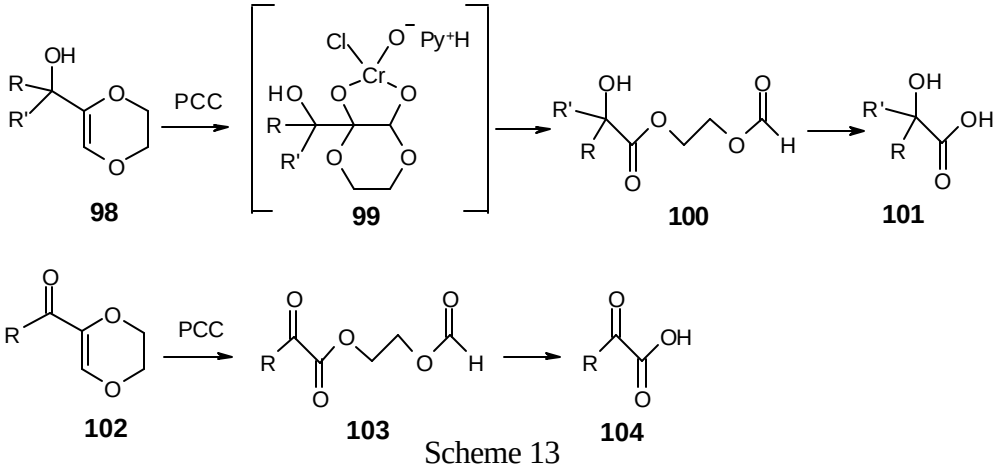
Substrate	Product	Yield %
trans-Stilbene **85**	Benzaldehyde **9**	90
1,1-Diphenylethylene **86**	Benzophenone **19**	84
1,1-Diphenylpropene **87**	Benzophenone **19**	92
Tetraphenyl ethylene **88**	Benzophenone **19**	90
9-Benzylidenefluorene **89**	Benzaldehyde **9** + Fluorenone **90**	85 86

A convenient method of benzylic oxidation with PCC to carbonyl compounds was also reported by Chandrasekaran[36] (**Table 6**).

Table 6.

Substrate	Product	Yield %
$PhCH_2CH_3$ **91**	Acetophenone **81**	71
$PhCH_2Ph$ **92**	Benzophenone **19**	88
$PhCH_2COPh$ **93**	PhCOCOPh **94**	86
Tetralin **95**	1-Tetralone **96**	83
Fluorene **97**	Fluorenone **90**	89

Fetizon *et al.*[37] reported that the allylic alcohols (**98**) obtained from lithiated 1,4-dioxene and ketones or aldehydes undergo regiospecific oxidative cleavage with PCC at the dioxene double bond to give, after saponification, α-hydroxy acids (**101**). Extension of this reaction to α,β-unsaturated ketones (**102**) afforded α-keto acids (**104**) (**Scheme 13**).

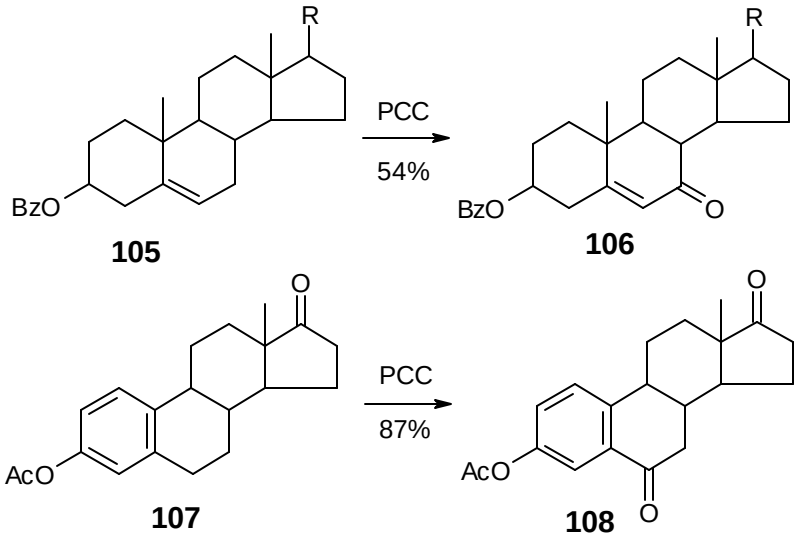


98 **99** **100** **101**

102 **103** **104**

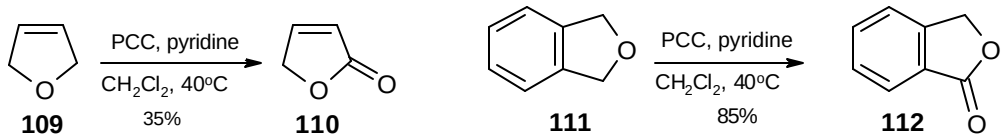
Scheme 13

PCC in refluxing CH_2Cl_2 has been found to be an effective reagent for allylic and benzylic oxidations of activated methylene groups to yield the corresponding unsaturated ketones[38] (**Scheme 14**).



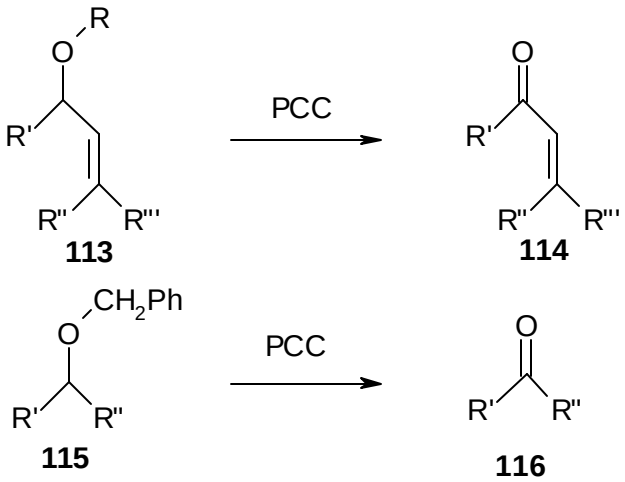
Scheme 14

Similarly, butenolide and benzofuranone are conveniently prepared by PCC oxidation of active methylene compounds in the presence of pyridine in CH_2Cl_2 (**Scheme 15**). [39]



Scheme 15

Cossy *et al*.[40] carried out specific oxidative cleavage of allylic and benzylic ethers by using PCC (**Scheme 16**).



Scheme 16.

5.3. Present Work

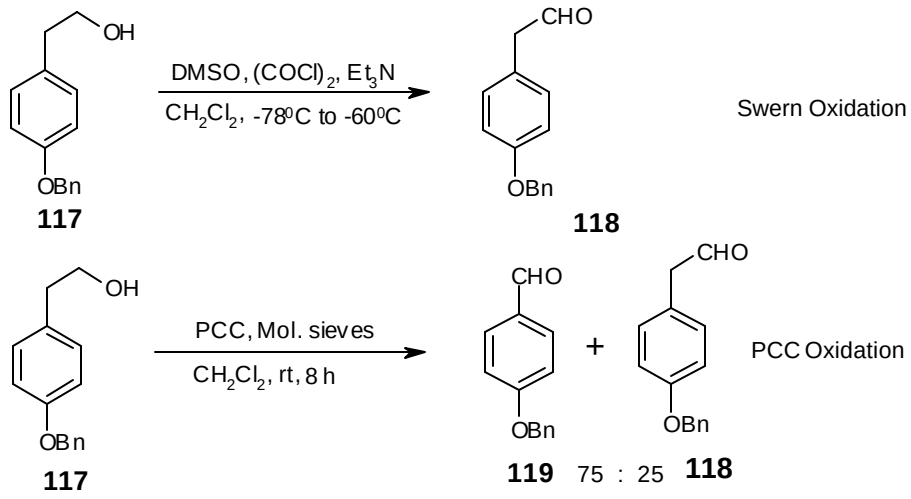
objective

PCC is a well-known oxidizing agent, for conversion of alcohols to aldehydes and ketones with high efficiency. Several rearrangements and useful conversions are mediated by PCC. This makes PCC a versatile oxidant (reagent) in organic synthesis. The present work in our laboratory is an accidental finding that PCC in excess oxidizes the homobenzylic alcohols to benzylic carbonyl compounds. Thus, the objective of the present investigation is to explore the following possibilities.

1. To generalize the C-C bond breaking reaction on several homobenzylic alcohols with no benzylic substitution, such that the end product of this oxidation would be a benzylic aldehyde.
2. To generalize this C-C bond breaking reaction on several homobenzylic alcohols with benzylic substitution, such that the end product of this oxidation would be an aryl ketone.
3. To explore the similar reaction on homoallylic alcohols, in order to investigate the course of reaction as there could be ample opportunity of double bond migration and/or allylic oxidation.

5.4. Results and Discussion

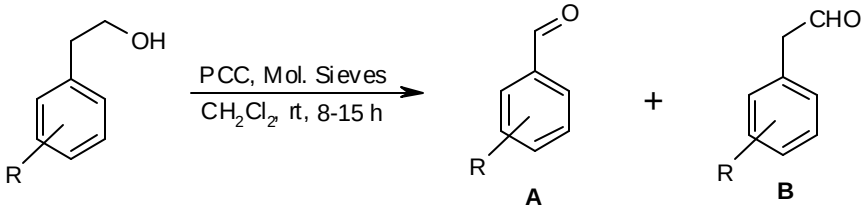
In our synthetic endeavor on the total synthesis of anticcocidial antibiotic (+)-Diolmycin A2,[41] we were in need of 2-(4-benzyloxyphenyl)acetaldehyde **118**. Swern oxidation of 2-(4-benzyloxyphenyl)ethanol **117** gave 2-(4-benzyloxyphenyl)acetaldehyde **118**. To ease the work-up procedure involving odorous dimethylsulfide, we carried out PCC oxidation. Surprisingly, this oxidation with 1.5 equivalents of PCC gave a 75:25 mixture of 4-benzyloxybenzaldehyde **119** and the expected 2-(4-benzyloxyphenyl)acetaldehyde **118** respectively (**Scheme 17**).



Scheme 17.

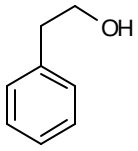
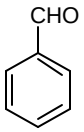
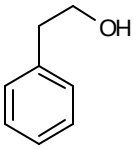
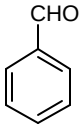
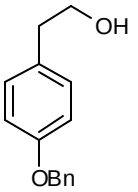
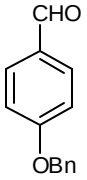
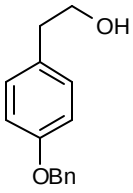
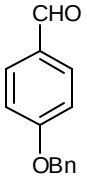
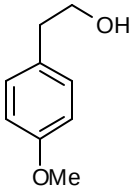
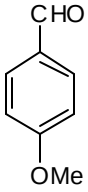
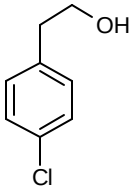
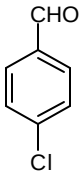
Thus, there is scission of C-C bond leading to loss of one carbon atom and yet, to add to our enthusiasm, the end product is still a benzylic aldehyde without further oxidation. The product mixture was confirmed by ^{1}H NMR spectrum where the benzylic methylene of **118** was rudimentary. The aldehyde proton of **119** was a sharp singlet above δ 10.00 indicating a benzylic aldehyde, while a rudimentary triplet was obtained below δ 10.00 indicating a small amount of homobenzylic aldehyde **118**. Thus, this degradative oxidation involving C-C bond cleavage adds to one of the novel and new oxidation reactions of PCC.

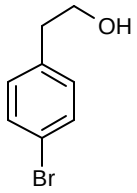
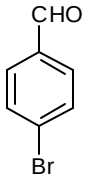
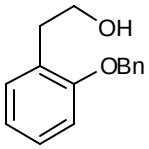
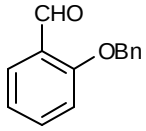
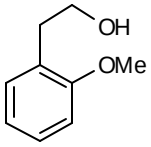
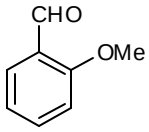
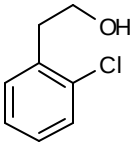
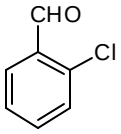
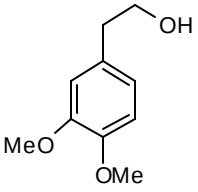
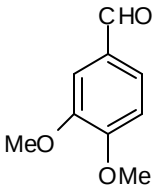
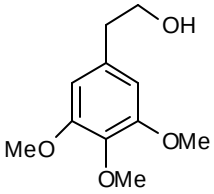
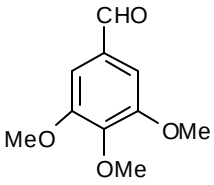
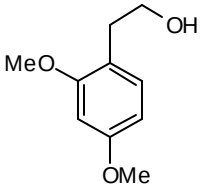
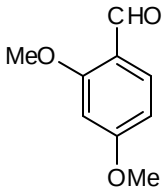
Aimed at achieving a better understanding of this new oxidation reaction of PCC, we subjected varied homobenzylic alcohols with no benzylic substitution (**Table 7**) to PCC oxidation. Initial experiments with 1.5 equivalents of PCC gave a small amount of homobenzylic aldehyde, but the major product was benzylic aldehyde (entry 1 and 3, **Table 7**). However when the oxidation was carried out with 3 equivalents of PCC, only benzylic aldehyde was obtained. Thus, varied homobenzylic alcohols with no benzylic substitution, irrespective of aryl ring substituents, on oxidation with 3 equivalents of PCC gave the benzylic aldehydes in moderate to good yields. The novelty lies in the fact that although one carbon is lost, still an aldehyde is obtained without further oxidation to an acid. The product was isolated in pure form without the need for further purification beyond mere filtration and concentration.

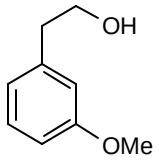
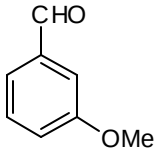
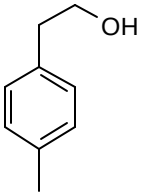
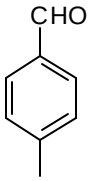


R = H, Cl, Br, OMe, OCH_2Ph, Ar, ...

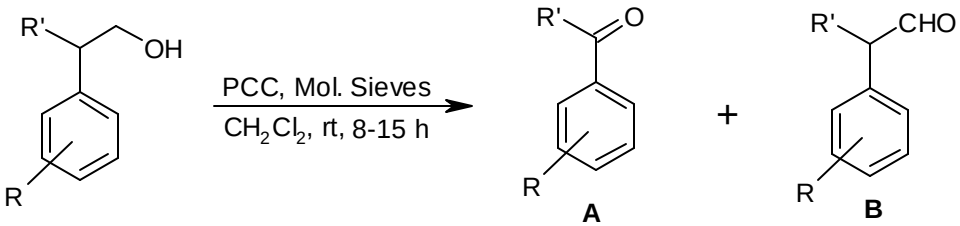
Table 7: Oxidation of homobenzylic alcohols with no benzylic substitution to benzylic aldehydes.

Entry	Substrate	Equivalents of PCC	Reaction time/h	Major Product	Ratio of A:B	Isolated Yield %
1	 **120**	1.5	8	 **121**	80:20	65
2	 **120**	3	8	 **121**	100:0	71
3	 **117**	1.5	8	 **119**	75:25	68
4	 **117**	3	8	 **119**	100:0	70
5	 **122**	3	8	 **123**	100:0	69
6	 **124**	3	8	 **125**	100:0	63

7	 **126**	3	8	 **127**	100:0	64
8	 **128**	3	8	 **129**	100:0	66
9	 **130**	3	8	 **131**	100:0	64
10	 **132**	3	8	 **133**	100:0	70
11	 **134**	3	8	 **135**	100:0	72
12	 **136**	3	8	 **137**	100:0	73
13	 **138**	3	8	 **139**	100:0	73

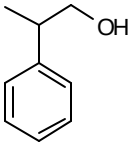
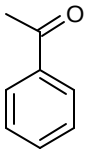
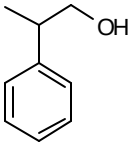
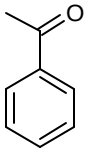
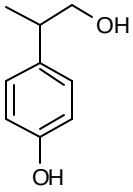
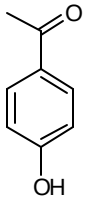
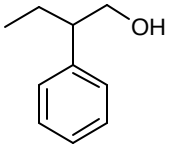
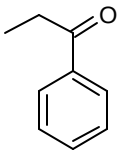
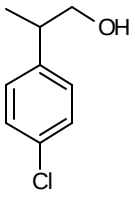
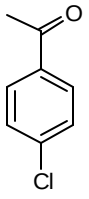
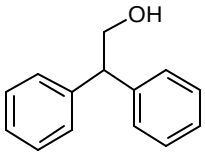
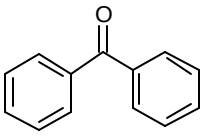
14	 **140**	3	8	 **141**	100:0	65
15	 **142**	3	8	 **143**	100:0	66

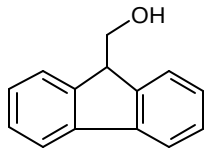
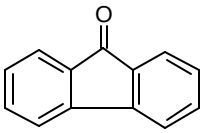
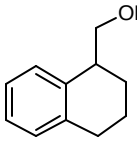
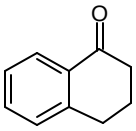
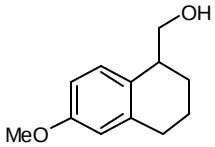
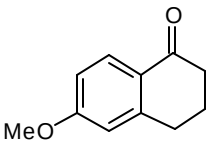
To understand better the scope of this oxidation reaction, we extended the reaction to homobenzylic alcohols with benzylic substitution such that the end product could be a aryl ketone. The simplest substrate available was 2-phenyl-1-propanol (obtained by hydroboration reaction on α-methylstyrene) where the reaction should yield acetophenone as an expected product. Indeed the PCC oxidation of 2-phenyl-1-propanol initially with 1.5 equivalents of PCC gave a 9:1 mixture of acetophenone and 2-phenyl-1-propanal respectively (entry 1, **Table 8**). However, with 3 equivalents of PCC only acetophenone was obtained (entry 2, **Table 8**). Thus, varied homobenzylic alcohols with benzylic alkyl/aryl substitution, on oxidation with 3 to 4 equivalents of PCC gave only the aryl ketones in good yields (**Table 8**). Another noteworthy observation is that although PCC is known for oxidation of benzylic and active methylene compounds, no oxidation of benzylic methylene was observed for entry 8 and 9, indicating the need of reflux conditions as reported in the literature.[38]



R = H, Cl, OH, OCH_2Ph, Ar, ...
R' = Me, Et, Ar,....

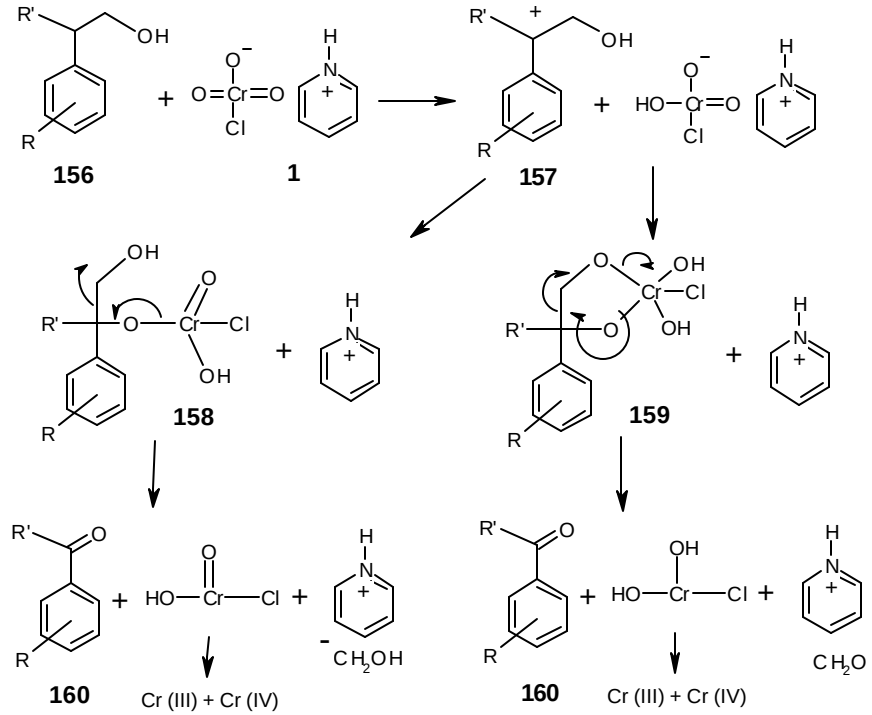
Table 8: Oxidation of homobenzylic alcohols with benzylic alkyl/aryl substitution to give aryl ketones.

Entry	Substrate	Equivalents of PCC	Reaction time/h	Major Product	Ratio of A:B	Isolated yields %
1	 **144**	1.5	8	 **81**	9:1	70
2	 **144**	3	8	 **81**	100:0	71
3	 **145**	3	12	 **146**	100:0	63
4	 **147**	3	10	 **148**	100:0	68
5	 **149**	3	8	 **150**	100:0	63
6	 **151**	4	12	 **19**	100:0	75

7	 **152**	4	12	 **90**	100:0	63
8	 **153**	4	15	 **96**	100:0	66
9	 **154**	4	15	 **155**	100:0	67

Mechanism of the reaction

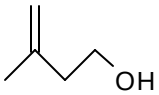
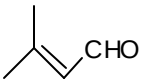
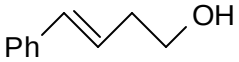
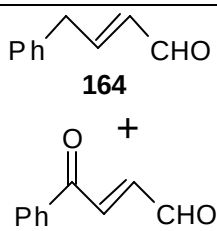
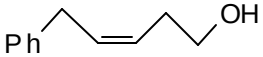
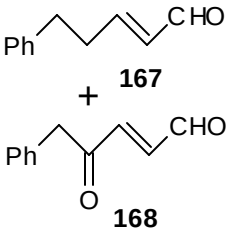
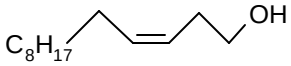
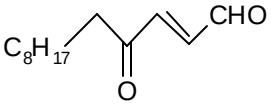
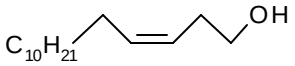
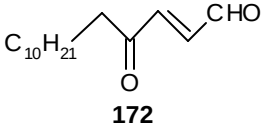
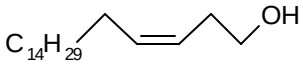
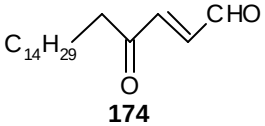
A probable mechanism may involve a benzylic hydride abstraction from **156** leading to the formation of carbocation **157**, which is then trapped by the chlorochromate anion to produce **158** or **159**, which breaks off to product **160** and Cr (VI), which in turn dismutates into Cr (III) and Cr (IV) species (**Scheme 18**). However proving such a mechanism is beyond the scope of this investigation.

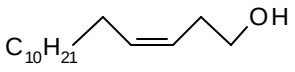
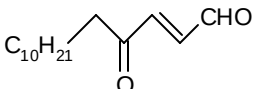
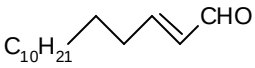


Scheme 18. Hypothetical mechanism for homobenzylic alcohol oxidation.

Encouraged by the results of C-C bond cleavage during oxidation reaction mediated by PCC on homobenzylic alcohols, we aimed to study the same reaction on homoallylic alcohols. While allylic oxidation to α,β-unsaturated carbonyl compounds is well known with PCC, the oxidation of homoallylic alcohols, where there is ample opportunity for double bond migration and/or allylic oxidation still remains to be explored. In order to investigate the course of reaction we carried out a detailed study of PCC oxidation on homoallylic alcohols. The results of this investigation are shown in **Table 9**.

Table 9. PCC oxidation of homoallylic alcohols.

Entry	**Substrate**	**Equiv. of PCC**	**React. time/h**	**Product**	**Isolated Yield**
1	 **161**	3	4	 **162**	68%
2	 **163**	3	8	 **164** + **165**	**164:165** 1:1 60%
3	 **166**	3	8	 **167** + **168**	**167:168** 1:1 58%
4	 **169**	3	8	 **170**	58%
5	 **171**	3	8	 **172**	59%
6	 **173**	3	8	 **174**	60%

7	 **171**	1.5	8	 **172** +  **175**	30% 28%

As shown in **Table 9** (entry 1), PCC (3 equivalents) oxidation of 3-methyl-3-butene-1-ol (**161**) gave 3-methyl-2-butenal (**162**) in 68% yield as a result of alcohol oxidation and subsequent double bond migration. However oxidation of homoallylic alcohol **163** with PCC (3 equivalents) afforded a 1:1 mixture of **164** and **165** in 60% yield. Probably the oxidation of alcohol occurred first followed by double bond migration to give **164** and subsequent allylic/benzylic oxidation furnished **165**. Similarly the oxidation of **166** gave a 1:1 mixture of **167** and **168**. The isomerization of *cis*- to *trans*-olefin was observed in this case. The oxidation of long chain aliphatic *cis*-homoallylic alcohols gave clearly the products arising from alcohol oxidation, double bond migration with isomerization from *cis*- to *trans*- and allylic oxidation (entry 4-7). When the concentration of PCC was lowered from 3 equivalents to 1.5 equivalents (entry 7), a mixture of **172** and **175** was obtained. Thus, a one-pot conversion of homoallylic alcohols to 1,4-dicarbonyl-2*E*-ene compounds is achieved with PCC.

5.5. Conclusion

To summarize, we have exploited a new and novel oxidation reaction by PCC involving C-C bond cleavage during oxidation of homobenzylic alcohol to benzylic aldehyde or aryl ketone. This is one of the rare reactions of PCC where a degradation of one carbon occurs, and yet the end-product remains an aldehyde or ketone without further oxidation. Such a reaction will be very useful in analyzing functional group compatibilities in the design of oxidation reactions involving PCC. On the other hand, the homoallylic alcohols gave interesting results due to the double bond migration and concomitant *cis*- to *trans*-isomerization and/or allylic oxidation. Thus, this is a very useful conversion of homoallylic alcohols to 1,4-dicarbonyl-2*E*-ene compounds that may have a lot of potential as intermediates in organic synthesis.

5.6. Experimental

General information:

The solvents were purified and dried by standard procedures before use. Petroleum ether of boiling range 60-80°C was used. Melting points are uncorrected. Infrared spectra were recorded on ATI MATTSON RS-1 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR were recorded on Bruker AC-200 NMR spectrometer. Mass spectra were obtained with a Finnigan MAT- 1020 B-70 eV mass spectrometer. Elemental analyses were carried out on a Carlo Erba CHNS-O analyzer.

Preparation of homobenzylic alcohols.

2-Phenyl ethanol (**120**) and most homoallylic alcohols were procured from commercial sources.

Most homobenzylic alcohols were prepared by either of the following process.

1. A two-step process, involving Wittig reaction on benzylic aldehydes or ketones to give the corresponding styrene compounds followed by hydroboration oxidation to the corresponding alcohols.
2. Some commercially available styrene compounds were directly subjected to hydroboration oxidation to give homobenzylic alcohols.

General procedure for styrene preparation:

To a solution of the benzylic aldehyde or ketone (1 equivalent) in dry THF (1 mL/2 mmol) was added the ylide generated from methyltriphenylphosphoniumiodide (1.2 equivalent) and NaHMDS (1M soln in THF) or *n*-BuLi (2M soln in hexane) (1.4 equivalents) in THF (3 mL/mmol) at 0°C. The reaction mixture was stirred at room temperature for 4-8 h and then quenched with aqueous NH_4Cl solution. The resulting solution was extracted with EtOAc. The EtOAc extracts were washed with brine, dried (Na_2SO_4) and concentrated. Column chromatography on silica gel using petroleum ether:EtOAc (95:5) gave the corresponding styrene compounds in 70-80% yields.

General procedure for hydroboration oxidation of styrenes:

To a solution of styrene (1 equivalent) in dry THF (2 mL/mmol) was added $BH_3.SMe_2$ (2M solution in THF) (1.1 equivalents) at 0°C. The reaction mixture was stirred at room temperature

for 4 h. It was cooled to 0°C and a solution of NaOH (2 equivalents) in EtOH/H_2O (2:1, 2 mL/mmol) was added followed by addition of H_2O_2 (30% w/v solution in water, 3 equivalents). It was then allowed to stir at room temperature for 4 h. The product was taken in EtOAc and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Column chromatography on silica gel using petroleum ether:EtOAc (4:1) as eluent gave the corresponding homobenzylic alcohol in 75-90% yields.

4-Benzyloxy styrene:

White solid

Yield: 78%

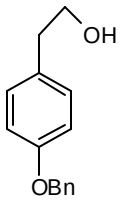
M.p.: 71-72°C

IR ($CHCl_3$, cm^{-1}): n_{max} 1606, 1510, 836, 759

^{1}H NMR (200 MHz, $CDCl_3$): δ 5.09 (s, 2H), 5.59 (s, 1H), 5.68 (s, 1H), 6.7 (m, 1H), 6.95 (d, *J* = 8 Hz, 2H), 7.35-7.44 (m, 7H)

EIMS (*m/z* relative intensity, %): 210 [M^+] (38), 91 (100), 65 (3.6).

2-(4-Benzyloxyphenyl) ethanol, 117



117

White solid

Yield: 88%

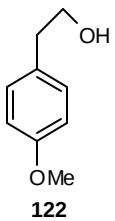
M.p.: 85-86°C

IR ($CHCl_3$, cm^{-1}): n_{max} 3402, 1611, 1511, 824, 757

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.72 (brs, 1H), 2.82 (t, *J* = 6 Hz, 2H), 3.83 (t, *J* = 6 Hz, 2H), 5.07 (s, 2H), 6.95 (d, *J* = 8 Hz, 2H), 7.2 (d, *J* = 8 Hz, 2H), 7.3-7.4 (m, 5H)

EIMS (*m/z* relative intensity, %): 228 [M^+] (29), 210 (1.2), 107 (6.6), 99 (100), 65 (5.4).

2-(4-Methoxyphenyl) ethanol, 122



122

Colorless oil

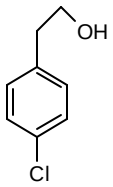
Yield: 86%

IR ($CHCl_3$, cm^{-1}): n_{max} 3382, 1612, 1513, 822, 583

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.9 (brs, 1H), 2.69 (t, *J* = 6 Hz, 2H), 3.66 (t, *J* = 6 Hz, 2H), 3.69 (s, 3H), 6.78 (d, *J* = 8 Hz, 2H), 7.07 (d, *J* = 8 Hz, 2H)

EIMS (*m/z* relative intensity, %): 152 [M^+] (24), 121 (100), 105 (4.0), 91 (6.7), 77 (11.3), 65 (4.1).

2-(4-Chlorophenyl) ethanol, 124



124

Colorless oil

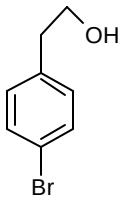
Yield: 85%

IR ($CHCl_3$, cm^{-1}): n_{max} 3361, 1598, 1492, 1047, 813, 540

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.04 (s, 1H), 2.82 (t, *J* = 7 Hz, 2H), 3.81 (t, *J* = 7 Hz, 2H), 7.18 (d, *J* = 10 Hz, 2H), 7.31 (d, *J* = 10 Hz, 2H)

EIMS (*m/z* relative intensity, %): 156 [M^+] (39), 141 (39), 125 (100), 91 (33.3), 77 (39.7), 63 (13.5).

2-(4-Bromophenyl) ethanol, 126



126

Colorless oil

Yield: 75%

IR ($CHCl_3$, cm^{-1}): n_{max} 3386, 1600, 1498, 1057, 815, 570

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.1 (s, 1H), 2.83 (t, *J* = 7 Hz, 2H), 3.82 (t, *J* = 7 Hz, 2H), 7.19 (d, *J* = 10 Hz, 2H), 7.33 (d, *J* = 10 Hz, 2H)

EIMS (*m/z* relative intensity, %): 201 [M^+] (40.5), 186 (32), 170 (100), 91 (33.8), 77 (49.7), 63 (14.5).

2-Benzyloxy styrene:

Colorless liquid

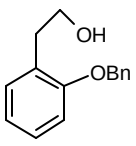
Yield: 75%

IR ($CHCl_3$, cm^{-1}): n_{max} 1616, 1518, 846, 753

^{1}H NMR (200 MHz, $CDCl_3$): δ 5.04 (s, 2H), 5.60 (s, 1H), 5.7 (s, 1H), 6.9 (m, 2H), 7.2 (m, 1H), 7.35-7.5 (m, 7H)

EIMS (*m/z* relative intensity, %): 210 [M^+] (13.8), 91 (100), 65 (21.7).

2-(2-Benzyloxyphenyl) ethanol, 128



128

Colorless oil

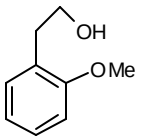
Yield: 78%

IR ($CHCl_3$, cm^{-1}): n_{max} 3379, 1596, 1500, 1025, 752, 697

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.3 (s, 1H), 2.95 (t, *J* = 7 Hz, 2H), 3.83 (t, *J* = 7 Hz, 2H), 5.1 (s, 2H), 6.95 (m, 2H), 7.25 (m, 2H), 7.45 (m, 5H).

EIMS (*m/z* relative intensity, %): 228 [M^+] (8.0), 120 (11.33), 107 (6.7), 91 (100), 77 (8), 65 (13.33).

2-(2-Methoxyphenyl) ethanol, 130



130

Colorless oil

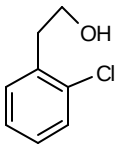
Yield: 75%

IR (neat, cm^{-1}): n_{max} 3443, 1625, 1597, 1015, 910, 748, 695,

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.40 (s, 1H), 2.92 (t, *J* = 6 Hz, 2H), 3.8 (t, *J* = 6 Hz, 2H), 3.83 (s, 3H), 6.92 (m, 2H), 7.24 (m, 2H)

EIMS (*m/z* relative intensity, %): 152 [M^+] (43.4), 121 (86.8), 107 (10.5), 91 (100), 77 (19.0), 65 (19.7), 57 (9.8).

2-(2-Chlorophenyl) ethanol, 132



132

Colorless oil

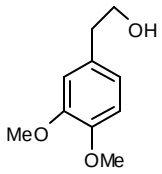
Yield: 75%

IR (neat, cm^{-1}): n_{max} 3362, 1589, 1492, 1047, 1015, 813, 540

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.47 (s, 1H), 2.98 (t, *J* = 6 Hz, 2H), 3.96 (t, *J* = 6 Hz, 2H), 7.30 (m, 2H), 7.48 (m, 2H)

EIMS (*m/z* relative intensity, %): 156 [M^+] (54.2), 125 (100), 91 (99.0), 77 (15.7), 63 (35.9).

2-(3,4-Dimethoxyphenyl) ethanol, 134



134

White solid

Yield: 78%

M.p.: 47-48°C

IR (neat, cm^{-1}): n_{max} 3400, 1608, 1591, 1523, 1141, 1027, 765,

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.15 (s, 1H), 2.77 (t, *J* = 7 Hz, 2H), 3.78 (t, *J* = 7 Hz, 2H), 3.82 (s, 3H), 3.84 (s, 3H), 6.77 (m, 3H)

EIMS (*m/z* relative intensity, %): 182 [M^+] (21.0), 151 (100), 135 (4.6), 107 (28.9), 91 (20.4), 77 (33.5), 65 (46.0).

3,4,5-Trimethoxystyrene:

Colorless liquid

Yield: 74%

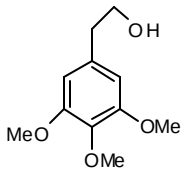
IR (neat, cm^{-1}): n_{max} 1581, 1503, 1325, 1183, 906, 835

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.85 (s, 3H), 3.87 (s, 6H), 5.23 (d, *J* = 10 Hz, 1H), 5.7 (d, *J* = 18 Hz, 1H), 6.62 (m, 1H), 6.65 (s, 2H)

EIMS (*m/z* relative intensity, %): 194 [M^+] (100), 179 (90.3), 151 (37.9), 136 (26.6), 121 (19.3), 91 (26.2), 77 (17.2), 65 (22.0).

2-(3,4,5-Trimethoxyphenyl) ethanol, 136

White solid



136

Yield: 80%

M.p.: 76-78°C

IR (neat, cm^{-1}): n_{max} 3463, 1590, 1506, 1044, 1008, 825, 732

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.36 (s, 1H), 2.75 (t, *J* = 6 Hz, 2H), 3.8 (t, *J* = 6 Hz, 2H), 3.84 (s, 9H), 6.45 (s, 2H)

EIMS (*m/z* relative intensity, %): 212 [M^+] (34.5), 197 (8.1), 181 (100), 167 (20.3), 148 (19.6), 109 (7.4), 95 (9.5), 77 (16.9), 65 (15.5).

2,4-Dimethoxystyrene:

Colorless liquid

Yield: 72%

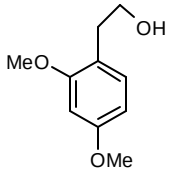
IR (neat, cm^{-1}): n_{max} 1608, 1577, 1505, 1045, 999, 827

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.78 (s, 6H), 5.22 (d, *J* = 9 Hz, 1H), 5.88 (d, *J* = 17 Hz, 1H), 6.5 (m, 2H), 7.01 (m, 1H), 7.45 (m, 1H)

EIMS (*m/z* relative intensity, %): 164 [M^+] (67.7), 149 (74.2), 121 (100), 105 (7.7), 91 (43.8), 77 (35.5), 63 (22.6).

2-(2,4-Dimethoxyphenyl) ethanol, 138

Colorless oil



138

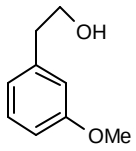
Yield: 78%

IR (neat, cm^{-1}): n_{max} 3400, 1592, 1514, 1027, 807, 750

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.82 (t, *J* = 6 Hz, 2H), 3.05 (s, 1H), 3.76 (t, *J* = 6 Hz, 2H), 3.78 (s, 6H), 6.41 (m, 2H), 7.07 (d, *J* = 8 Hz, 1H)

EIMS (*m/z* relative intensity, %): 182 [M^+] (19.7), 151 (100), 137 (3.4), 121 (44.2), 108 (4.7), 91 (28), 77 (30.6), 65 (20.4).

2-(3-Methoxyphenyl) ethanol, 140



140

Colorless oil

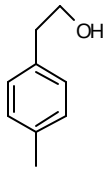
Yield: 78%

IR (neat, cm^{-1}): n_{max} 3354, 1596, 1599, 1290, 1117, 1037, 753

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.4 (s, 1H), 2.92 (t, *J* = 6 Hz, 2H), 3.83 (t, *J* = 6 Hz, 2H), 3.84 (s, 3H), 6.93 (m, 2H), 7.25 (m, 2H)

EIMS (*m/z* relative intensity, %): 152 [M^+] (62.7), 121 (98.7), 107 (16.0), 91 (100), 77 (26.0), 65 (33.3).

2-(4-Methylphenyl) ethanol, 142



142

Colorless oil

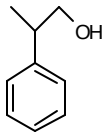
Yield: 76%

IR (neat, cm^{-1}): n_{max} 3359, 1642, 1513, 1042, 808, 494

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.15 (s, 1H), 2.36 (s, 3H), 2.84 (t, *J* = 6 Hz, 2H), 3.83 (t, *J* = 6 Hz, 2H), 7.15 (m, 4H)

EIMS (*m/z* relative intensity, %): 136 [M^+] (30.7), 121 (18.3), 105 (100), 91 (36.0), 77 (44.4), 65 (20.2).

2-Phenyl-1-propanol, 144



144

Colorless oil

Yield: 78%

IR (neat, cm^{-1}): n_{max} 3382, 1603, 1494, 1397, 1014, 761, 700

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.29 (d, *J* = 6 Hz, 3H), 2.04 (s, 1H), 2.94 (m, 1H), 3.72 (d, *J* = 8 Hz, 2H), 7.29 (m, 5H)

EIMS (*m/z* relative intensity, %): 136 [M^+] (13.5), 105 (100), 91 (14.2), 71 (25.0), 63 (4.7).

4-Hydroxy-a **-methylstyrene:**

Colorless liquid

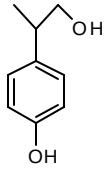
Yield: 70%

IR (neat, cm^{-1}): n_{max} 3380, 1607, 1511, 1443, 1177, 830, 755

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.28 (brs, 1H), 2.13 (s, 3H), 5.0 (s, 1H), 5.29 (s, 1H), 6.84 (d, *J* = 8 Hz, 2H), 7.36 (d, *J* = 8 Hz, 2H)

EIMS (*m/z* relative intensity, %): 135 [M^++1] (100), 134 (31.8), 119 (32.5), 107 (25.3), 91 (24.7), 65 (31.1), 55 (39.6).

2-(4-Hydroxyphenyl)-1-propanol, 145



145

Colorless solid

Yield: 75%

M.p.: 68-72°C

IR (neat, cm^{-1}): n_{max} 3556, 1610, 1514, 1222, 805

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.23 (d, *J* = 6 Hz, 3H), 1.26 (s, 1H), 2.88 (m, 1H), 2.97 (s, 1H), 3.71 (m, 2H), 6.79 (d, *J* = 8 Hz, 2H), 7.08 (d, *J* = 8 Hz, 2H)

EIMS (*m/z* relative intensity, %): 152 [M^+] (10.1), 136 (12.1), 121 (100), 107 (9.5), 103 (73.5), 91 (21.0), 77 (24.3), 65 (10.1).

2-Phenyl-1-butene:

Colorless oil

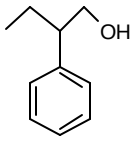
Yield: 76%

IR (neat, cm^{-1}): n_{max} 1610, 1462, 1222, 758, 669

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.2 (t, *J* = 8 Hz, 3H), 2.63 (q, *J* = 8 Hz, 2H), 5.16 (s, 1H), 5.37 (s, 1H), 7.28-7.54 (m, 5H)

EIMS (*m/z* relative intensity, %): 132 [M^+] (69.3), 117 (100), 103 (46.6), 91 (40.0), 77 (45.3), 63 (17.3).

2-Phenyl-1-butanol, 147



147

Colorless oil

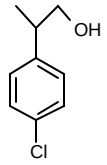
Yield: 90%

IR (neat, cm^{-1}): n_{max} 3384, 1640, 1454, 1055, 625

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.85 (t, *J* = 7 Hz, 3H), 1.5-1.7 (m, 2H), 1.95 (s, 1H), 2.68 (m, 1H), 3.73 (dd, *J* = 2, 4 Hz, 2H), 7.2-7.4 (m, 5H)

EIMS (*m/z* relative intensity, %): 150 [M^+] (16.3), 119 (30.0), 103 (11.1), 91 (100), 77 (13.0), 65 (7.8).

2-(4-Chlorophenyl)-1-propanol, 149



149

Colorless oil

Yield: 75%

IR (neat, cm^{-1}): n_{max} 3340, 1602, 1492, 1396, 1012, 748, 700

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.3 (d, *J* = 6 Hz, 3H), 2.08 (s, 1H), 2.96 (m, 1H), 3.76 (d, *J* = 7.5 Hz, 2H), 7.18 (d, *J* = 8 Hz, 2H), 7.32 (d, *J* = 8 Hz, 2H)

EIMS (*m/z* relative intensity, %): 170 [M^+] (40.0), 155 (39.0), 139 (100), 91 (25.0), 77 (28.3), 63 (12.0).

1,1-Diphenylethylene:

Colorless liquid

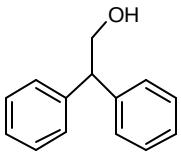
Yield: 74%

IR (neat, cm^{-1}): n_{max} 1658, 1598, 1574, 1153, 917, 696, 589

^{1}H NMR (200 MHz, $CDCl_3$): δ 5.6 (s, 2H), 7.47 (m, 10H)

EIMS (*m/z* relative intensity, %): 180 [M^+] (100), 165 (84.9), 152 (13.1), 125 (47.7), 105 (13.1), 89 (47), 77 (34), 63 (17.6).

2,2-Diphenyl ethanol, 151



151

White solid

Yield: 76%

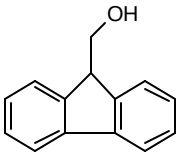
M.p.: 52-54°C

IR (neat, cm^{-1}): n_{max} 3381, 1600, 1494, 1056, 754, 740, 699, 536.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.89 (s, 1H), 4.18-4.24 (m, 3H), 7.34 (m, 10H)

EIMS (*m/z* relative intensity, %): 198 [M^+] (8.0), 184 (4.6), 167 (100), 152 (21.3), 128 (3.3), 105 (21.3), 91 (6.7), 77 (21.3), 63 (7.3).

9-Fluorenylmethanol, 152



152

Pale yellow solid

Yield: 76%

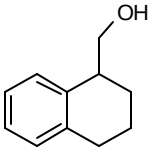
M.p.: 98-100°C

IR (neat, cm^{-1}): n_{max} 3355, 1585, 1449, 1087, 759, 737

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.89 (s, 1H), 4.2-4.27 (m, 3H), 7.35 (m, 8H)

EIMS (*m/z* relative intensity, %): 196 [M^+] (10.5), 165 (100), 77 (21.0), 63 (10.1).

Alcohol 153



153

Colorless syrup

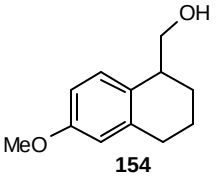
Yield: 78%

IR (neat, cm^{-1}): n_{max} 3353, 1671, 1489, 1034, 759, 738

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.7-2.0 (m, 4H), 2.5 (s, 1H), 2.8 (m, 2H), 3.2 (m, 1H), 3.85 (d, *J* = 6.5 Hz, 2H), 7.3 (m, 4H)

EIMS (*m/z* relative intensity, %): 162 [M^+] (13.6), 131 (100), 115 (21.4), 103 (5.2), 91 (35.7), 77 (10.4), 63 (7.1).

Alcohol 154



154

Colorless syrup

Yield: 80%

IR (neat, cm^{-1}): n_{max} 3381, 1609, 1579, 1330, 1041, 814

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (d, *J* = 8 Hz, 2H), 1.6-2.0 (m, 2H), 2.34 (s, 1H), 2.7-3.0 (m, 3H), 3.77 (m, 2H), 3.79 (s, 3H), 6.7-6.9 (m, 2H), 7.2 (m, 1H)

EIMS (*m/z* relative intensity, %): 192 [M^+] (58.8), 177 (22.8), 161 (100), 148 (98.7), 135 (16.9), 115 (24.0), 105 (19.6), 91 (24.8), 77 (18.9), 65 (8.5).

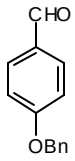
PCC oxidation of homobenzylic and homoallylic alcohols:

General Procedure:

To a mixture of PCC (1.5 or 3-4 equivalents) and powdered molecular sieves (3A°, ½ the wt of PCC) in dry CH_2Cl_2 was added the homobenzylic or homoallylic alcohol (1 equivalent) at 0°C. The reaction mixture was stirred for the specified time (4-12 h) at room temperature. CH_2Cl_2 was evaporated and, to the residue was added Et_2O. The slurry was stirred and filtered

through a pad of celite. The residue was washed 3 to 4 times and filtered. The filtrate was concentrated to give virtually pure carbonyl compounds.

4-Benzyloxybenzaldehyde, 119



119

White solid

Yield: 70%

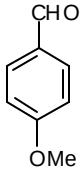
M.p.: 78-79°C

IR ($CHCl_3$, cm^{-1}): n_{max} 2728, 1690, 1601, 1578, 832, 758

^{1}H NMR (200 MHz, $CDCl_3$): δ 5.16 (s, 2H), 7.1 (d, *J* = 8 Hz, 2H), 7.3 (m, 5H), 7.85 (d, *J* = 8 Hz, 2H), 9.9 (s, 1H)

EIMS (*m/z* relative intensity, %): 212 [M^+] (4.3), 91 (100), 65 (9.5).

***p*-Anisaldehyde, 123**



123

Pale yellow oil

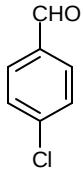
Yield: 69%

IR ($CHCl_3$, cm^{-1}): n_{max} 2740, 1685, 1600, 1578, 1026, 834

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.85 (s, 3H), 6.99 (d, *J* = 8 Hz, 2H), 7.83 (d, *J* = 8 Hz, 2H), 9.85 (s, 1H)

EIMS (*m/z* relative intensity, %): 136 [M^+] (100), 119 (30.2), 104 (23.5), 92 (28.2), 77 (75.2), 65 (32.2).

4-Chlorobenzaldehyde, 125



125

Pale yellow solid

Yield: 63%

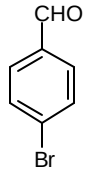
M.P.: 44-46°C

IR ($CHCl_3$, cm^{-1}): n_{max} 2840, 1695, 1589, 1094, 839, 816, 541

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.53 (d, *J* = 10 Hz, 2H), 7.84 (d, *J* = 10 Hz, 2H), 9.98 (s, 1H)

EIMS (*m/z* relative intensity, %): 140 [M^+] (76.8), 139 (100), 111 (53.6), 85 (7.9), 75 (37.1), 57 (6.0).

4-Bromobenzaldehyde, 127



127

Colorless solid

Yield: 64%

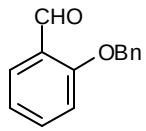
M.P.: 65-67°C

IR ($CHCl_3$, cm^{-1}): n_{max} 2836, 1686, 1581, 1085, 841, 812, 545

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.54 (d, *J* = 10 Hz, 2H), 7.85 (d, *J* = 10 Hz, 2H), 9.99 (s, 1H)

EIMS (*m/z* relative intensity, %): 185 [M^+] (72.8), 184 (100), 156 (23.8), 130 (17.9), 75 (37.5), 57 (16.0).

2-Benzyloxybenzaldehyde, 129



129

Colorless solid

Yield: 66%

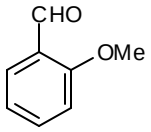
M.p.: 45-46°C

IR (neat, cm^{-1}): n_{max} 2862, 1684, 1598, 1303, 1013, 855, 736, 697

^{1}H NMR (200 MHz, $CDCl_3$): δ 5.01 (s, 2H), 6.90 (d, *J* = 8 Hz, 2H), 7.31 (m, 6H), 7.71 (d, *J* = 8 Hz, 1H), 10.4 (s, 1H)

EIMS (*m/z* relative intensity, %): 212 [M^+] (6.5), 183 (6.5), 152 (3.2), 121 (13.0), 91 (100), 77 (6.5), 65 (28.7).

***o*-Anisaldehyde, 131**



131

Colorless oil

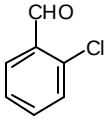
Yield: 64%

IR (neat, cm^{-1}): n_{max} 2845, 1688, 1600, 1439, 1104, 835, 759

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.95 (s, 3H), 7.1 (m, 2H), 7.62 (m, 1H), 7.85 (d, *J* = 8 Hz, 1H), 10.45 (s, 1H)

EIMS (*m/z* relative intensity, %): 136 [M^+] (100), 119 (29.6), 104 (22.3), 92 (31.0), 71 (69.7), 65 (34.8).

***o*-Chlorobenzaldehyde, 133**



133

Colorless oil

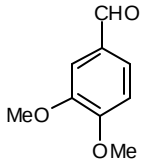
Yield: 70%

IR (neat, cm^{-1}): n_{max} 2753, 1696, 1650, 1591, 1053, 825, 758, 633

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.42 (m, 3H), 7.89 (d, *J* = 7 Hz, 1H), 10.44 (s, 1H)

EIMS (*m/z* relative intensity, %): 140 [M^+] (69.3), 139 (100), 111 (53.6), 104 (10.4), 85 (13.0), 75 (79.0), 61 (17.0), 55 (7.8).

3,4-Dimethoxybenzaldehyde, 135



135

Colorless solid

Yield: 72%

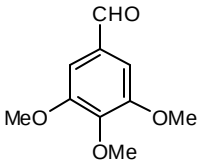
M.p.: 41–42°C

IR (neat, cm^{-1}): n_{max} 2839, 1681, 1590, 1022, 812, 733, 642

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.90 (s, 3H), 3.93 (s, 3H), 6.96 (d, *J* = 8 Hz, 1H), 7.42 (m, 2H), 9.81 (s, 1H)

EIMS (*m/z* relative intensity, %): 166 [M^+] (100), 165 (70), 151 (1.2), 119 (10.7), 105 (9.3), 95 (56), 77 (32.0), 65 (14.6).

3,4,5-Trimethoxy benzaldehyde, 137



137

Pale yellow solid

Yield: 73%

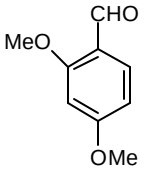
M.p.: 72–74°C

IR (neat, cm^{-1}): n_{max} 2737, 1692, 1588, 1232, 1001, 834, 755, 628

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.90 (s, 9H), 7.1 (s, 2H), 9.83 (s, 1H)

EIMS (*m/z* relative intensity, %): 196 [M^+] (100), 181 (55.8), 175 (5.8), 153 (9.0), 135 (10.4), 7.5 (48.7), 110 (42.8), 95 (34.4), 77 (19.5), 67 (19.5), 57 (19.6).

2,4-Dimethoxybenzaldehyde, 139



139

Pale yellow solid

Yield: 73%

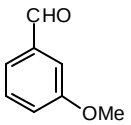
M.p.: 68–70°C

IR (neat, cm^{-1}): n_{max} 2847, 1673, 1602, 1440, 1105, 828, 763, 668

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.82 (s, 3H), 3.9 (s, 3H), 6.48-6.6 (m, 2H), 7.76 (d, *J* = 8 Hz, 1H), 10.3 (s, 1H)

EIMS (*m/z* relative intensity, %): 166 [M^+] (100), 165 (65.6), 149 (53.9), 135 (28.6), 120 (24.7), 106 (22.7), 92 (9.7), 77 (11.7), 63 (7.1).

***m*-Anisaldehyde, 141**



141

Colorless solid

Yield: 65%

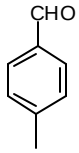
M.p.: 33°C

IR (neat, cm^{-1}): n_{max} 2730, 1701, 1593, 1263, 1038, 898, 772, 681, 644

^{1}H NMR (200 MHz, CDCl$_3$): δ 3.8 (s, 3H), 7.23 (m, 1H), 7.48 (m, 3H), 9.98 (s, 1H)

EIMS (*m/z* relative intensity, %): 136 [M$^+$] (100), 135 (92.81), 107 (43.8), 92 (24.8), 77 (64.0), 65 (39.2).

***p*-Tolualdehyde, 143**



143

Colorless oil

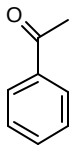
Yield: 66%

IR (neat, cm^{-1}): n_{max} 2733, 1698, 1605, 1222, 805, 750

^{1}H NMR (200 MHz, CDCl$_3$): δ 2.42 (s, 3H), 7.3 (d, *J* = 8 Hz, 2H), 7.9 (d, *J* = 8 Hz, 2H), 9.95 (s, 1H)

EIMS (*m/z* relative intensity, %): 120 [M$^+$] (80), 119 (100), 105 (8.3), 91 (92), 77 (12.7), 65 (43.1).

Acetophenone, 81



81

Colorless oil

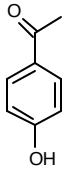
Yield: 71%

IR (neat, cm^{-1}): n_{max} 1684, 1596, 1278, 1076, 760, 690, 588

^{1}H NMR (200 MHz, CDCl$_3$): δ 2.62 (s, 3H), 7.47 (m, 3H), 7.95 (d, *J* = 10 Hz, 2H)

EIMS (*m/z* relative intensity, %): 120 [M$^+$] (52), 105 (100), 77 (98.7), 74 (8.7), 63 (6.0).

4-Hydroxyacetophenone, 146



146

Pale yellow solid

Yield: 63%

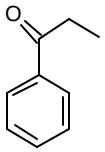
M.p.: 105-106°C

IR (neat, cm^{-1}): n_{max} 3380, 1661, 1604, 1362, 840, 768, 699

^{1}H NMR (200 MHz, CDCl$_3$): δ 2.6 (s, 3H), 6.99 (d, *J* = 8 Hz, 2H), 7.94 (d, *J* = 8 Hz, 2H), 8.44 (s, 1H).

EIMS (*m/z* relative intensity, %): 136 [M^+] (36.7), 121 (100), 107 (2.7), 93 (28.7), 77 (12.0), 65 (26.7).

Propiophenone, **148**



148

Colorless oil

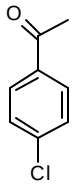
Yield: 68%

IR (neat, cm^{-1}): n_{max} 1685, 1594, 1222, 750,

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.22 (t, *J* = 8 Hz, 3H), 2.98 (q, *J* = 8 Hz, 2H), 7.45 (m, 3H), 7.95 (d, *J* = 7 Hz, 2H)

EIMS (*m/z* relative intensity, %): 134 [M^+] (21.7), 119 (5.8), 105 (100), 91 (19.5), 77 (47.0), 71 (5.8), 65 (4.3), 57 (7.2).

4-Chloroacetophenone, 150



150

Pale yellow oil

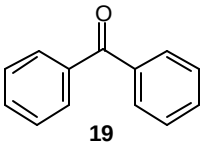
Yield: 63%

IR (neat, cm^{-1}): n_{max} 1660, 1608, 1352, 840, 765, 698

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.57 (s, 3H), 7.43 (d, *J* = 8 Hz, 2H), 7.90 (d, *J* = 8 Hz, 2H)

EIMS (*m/z* relative intensity, %): 154 [M^+] (29.0), 139 (100), 111 (49.3), 104 (2.0), 85 (3.8), 75 (31.6), 63 (5.3).

Benzophenone, 19



19

White solid

Yield: 75%

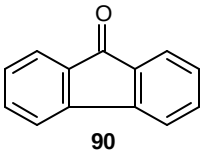
M.p.: 47-48°C

IR (neat, cm^{-1}): n_{max} 1659, 1619, 1599, 1217, 1074, 920, 710, 667, 639

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.31 (m, 6H) 7.59 (d, *J* = 7 Hz, 4H)

EIMS (*m/z* relative intensity, %): 182 [M^+] (68.8), 171 (5.7), 152 (5.7), 105 (100), 91 (3.5), 77 (75.9), 63 (3.5).

Fluorenone, 90



90

Pale yellow solid

Yield: 63%

M.p.: 82-84°C

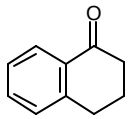
IR (neat, cm^{-1}): n_{max} 1712, 1610, 1598, 1300, 1263, 1222, 813, 735, 670

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.34 (m, 2H), 7.5 (m, 4H), 7.68 (d, *J* = 7 Hz, 2H)

EIMS (*m/z* relative intensity, %): 180 [M^+] (100), 152 (36.8), 126 (8.5), 98 (78.4), 76 (37.5), 63 (23.0).

1-Tetralone, 96

Colorless oil



96

Yield: 66%

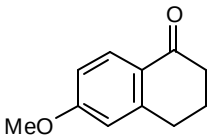
IR (neat, cm^{-1}): n_{max} 1683, 1600, 1191, 1025, 905, 765, 553

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.04-2.17 (m, 2H), 2.63 (t, *J* = 7 Hz, 2H), 2.94 (t, *J* = 7 Hz, 2H), 7.24 (m, 2H), 7.45 (m, 1H), 8.0 (d, *J* = 8 Hz, 1H)

EIMS (*m/z* relative intensity, %): 146 [M^+] (61.3), 131 (14.0), 118 (100), 104 (8.0), 90 (96.7), 77 (13.3), 63 (36.0).

6-Methoxy-1-tetralone, 155

Pale yellow solid



155

Yield: 67%

M.p.: 76-77°C

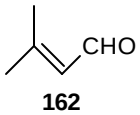
IR (neat, cm^{-1}): n_{max} 1673, 1599, 1570, 1445, 1157, 1035, 829, 755, 666

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.2 (m, 2H), 2.59 (t, *J* = 6.5 Hz, 2H), 2.91 (t, *J* = 6.5 Hz, 2H), 3.84 (s, 3H), 6.68-6.77 (m, 2H), 7.96-8.01 (d, *J* = 8 Hz, 1H)

EIMS (*m/z* relative intensity, %): 176 [M^+] (48.3), 161 (7.2), 148 (100), 120 (26.5), 105 (12.6), 91 (15.9), 77 (19.2), 63 (9.9).

3-Methyl-2-butenal, 162

Colorless liquid



162

Yield: 68%

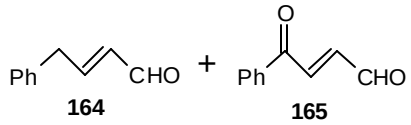
IR (neat, cm^{-1}): n_{max} 2738, 1688, 1609, 1438, 786

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.93 (s, 3H), 2.12 (s, 3H), 5.85 (d, *J* = 8 Hz, 1H), 9.92 (d, *J* = 8 Hz, 1H)

EIMS (*m/z* relative intensity, %): 84 [M^+] (59), 55 (100), 42 (23)

Compound mixture 164 and 165 (1:1)

Colorless oil



164 **165**

Yield: 60%

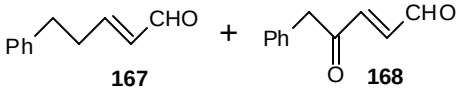
IR (neat, cm^{-1}): n_{max} 2742, 1705, 1660, 1612, 1450, 1220, 786

^{1}H NMR (200 MHz, CDCl$_3$): δ 3.67 (d, *J* = 6 Hz, 2H, **164**), 6.18 (dd, *J* = 8 Hz, 1H, **164**), 6.79 (dd, *J* = 8 Hz, 1H), 6.93 (dt, *J* = 16, 2 Hz, 1H, **164**), 7.2-7.7 (m, 11H), 9.56 (d, *J* = 8 Hz, 1H), 9.73 (d, *J* = 8 Hz, 1H)

EIMS (*m/z* relative intensity, %): 162 [**165**, M^++2] (3.3), 160 [**165**, M^+] (1.9), 146 [**164**, M^+] (75), 131 (**165**, M^+–CHO] (83.5), 117 [**164**, M^+–CHO] (100), 103 (42.1), 91 (55.9), 77 (33.5), 65 (21.1), 55 (11.8).

Compound mixture 167 and 168 (1:1)

Colorless oil



167 **168**

Yield: 58%

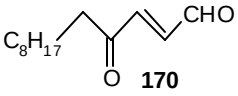
IR (neat, cm^{-1}): n_{max} 2738, 1712, 1654, 1609, 1463, 1230, 789

^{1}H NMR (200 MHz, CDCl$_3$): δ 2.71 (m, 2H), 2.83 (m, 2H), 3.69 (d, *J* = 6 Hz, 2H, **168**), 6.1 (m, 1H), 6.95 (m, 1H), 7.13 (m, 1H), 7.2-7.5 (m, 11H), 9.53 (d, *J* = 8 Hz, 1H), 9.58 (d, *J* = 8 Hz, 1H)

EIMS (*m/z* relative intensity, %): 174 [**168**, M^+] (0.7), 160 [**167**, M^+] (4.7), 145 [**168**, M^+–CHO] (4.8), 131 [**167**, M^+–CHO] (6.6), 115 (16.6), 105 (8.0), 91 (100), 84 (36.6), 77 (12.6), 65 (13.3).

4-Keto-tridec-2*E*-enal, 170

Colorless oil



170

Yield: 58%

IR (neat, cm^{-1}): n_{max} 2750, 1698, 1692, 1611, 1468, 1218, 769, 478

^{1}H NMR (200 MHz, CDCl$_3$): δ 0.88 (t, *J* = 6 Hz, 3H), 1.2-1.3 (m, 12H) 1.65 (m, 2H), 2.69 (t, *J* = 8 Hz, 2H), 6.82 (m, 2H), 9.78 (d, *J* = 6 Hz, 1H)

^{13}C NMR (50 MHz, CDCl$_3$): δ 14.01, 22.5, 23.6, 29.2, 29.54, 31.54, 31.8, 41.3, 136.9, 143.8, 192.9, 200.09

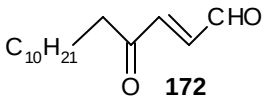
EIMS (*m/z* relative intensity, %): 210 [M^+] (12.3), 181 (M^+–CHO] (66.2), 168 (9.3), 139 (23.4), 125 (25.3), 98 (58.7), 83 (85.2), 55 (100)

Analysis: $C_{13}H_{22}O_2$ (210.31) requires C, 74.24; H, 10.54. Found: C, 74.29; H, 10. 46.

4-Keto-pentadec-2*E*-enal, 172

White solid

Yield: 59%



172

M.p.: 78-80°C

IR (neat, cm^{-1}): n_{max} 2736, 1696, 1694, 1612, 1216, 759, 477

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6 Hz, 3H), 1.2-1.3 (m, 16H) 1.69 (m, 2H), 2.7 (t, *J* = 8 Hz, 2H), 6.83 (m, 2H), 9.8 (d, *J* = 6 Hz, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.03, 22.64, 23.66, 29.07, 29.29, 29.55, 31.86, 41.20, 137.28, 144.89, 193.34, 200.14

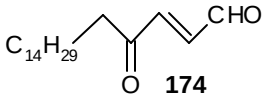
EIMS (*m/z* relative intensity, %): 238 [M^+] (9.1), 209 [M^+–CHO] (68.2), 195 (3.2), 183 (4.5), 153 (5.8), 139 (28.6), 125 (43.5), 111 (15.6), 98 (56.5), 83 (76.6), 70 (40.2), 55 (100)

Analysis: $C_{15}H_{26}O_2$ (238.37) requires C, 75.58; H, 10.99. Found: C, 75.39; H, 10.76.

4-Keto-nonadec-2*E*-enal, 174

Pale yellow solid

Yield: 60%



174

M.p.: 85-88°C

IR (neat, cm^{-1}): n_{max} 2736, 1696, 1695, 1610, 1468, 1216, 758, 669, 502

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6 Hz, 3H), 1.2-1.3 (m, 24H) 1.71 (m, 2H), 2.69 (t, *J* = 8 Hz, 2H), 6.84 (m, 2H), 9.81 (d, *J* = 6 Hz, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 22.6, 23.63, 29.03, 29.29, 29.58, 31.86, 41.16, 137.21, 144.82, 193.26, 200.03

EIMS (*m/z* relative intensity, %): 294 [M^+] (2.6), 265 [M^+–CHO] (5.9), 139 (9.9), 125 (13.2), 98 (42.7), 83 (82.2), 70 (46.0), 55 (100).

Analysis: $C_{19}H_{34}O_2$ (294.47) requires C, 77.5; H, 11.63. Found: C, 77.39; H, 11.44.

Pentadec-2*E*-enal, 175

Colorless syrup

Yield: 28%

175

IR (neat, cm^{-1}): n_{max} 1696, 1611, 1459, 1220, 768, 649, 501

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6 Hz, 3H), 1.19-1.25 (m, 18H) 1.55 (m, 2H), 2.24 (m, 2H), 6.01 (dt, *J* = 16 Hz, 1H), 6.81 (dt, *J* = 16, Hz, 1H), 9.44 (d, *J* = 8 Hz, 1H)

EIMS (*m/z* relative intensity, %): 224 [M^+] (10.5), 195 [68.0] 182 (5.4), 169 (12.5), 70 (40.2), 55 (100).

Analysis: $C_{15}H_{28}O$ (224.38) requires C, 80.29; H, 12.57. Found: C, 80.35; H, 12.32.

5.6. Spectra

+1] ^{1}H NMR Spectrum of **136**

+2] ^{1}H NMR Spectrum of **154**

+3] ^{1}H NMR Spectrum of **164** + **165**

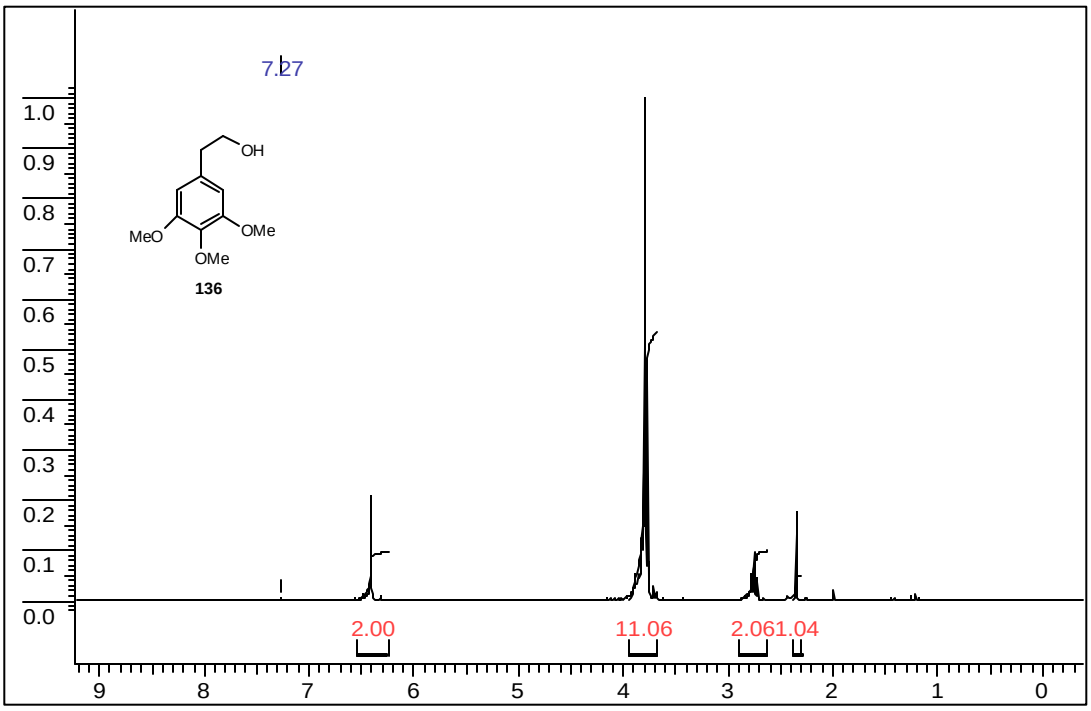
+4] EIMS of **164** + **165**

+5] ^{1}H NMR Spectrum of **172**

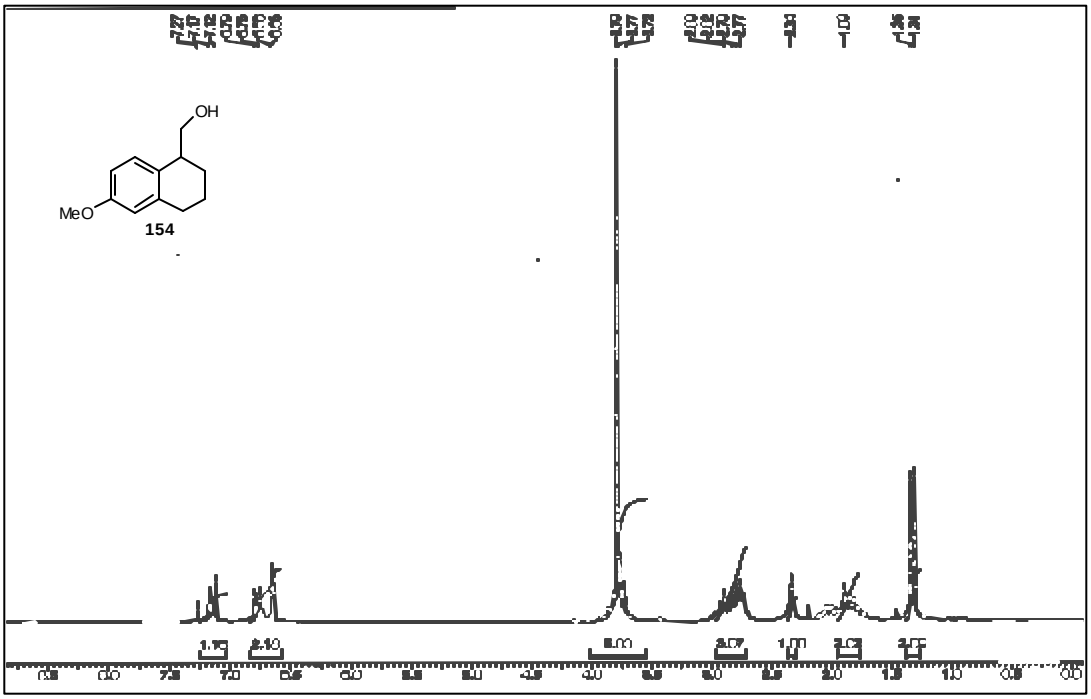
+6] ^{13}C NMR Spectrum of **172**

+7] EIMS of **172**

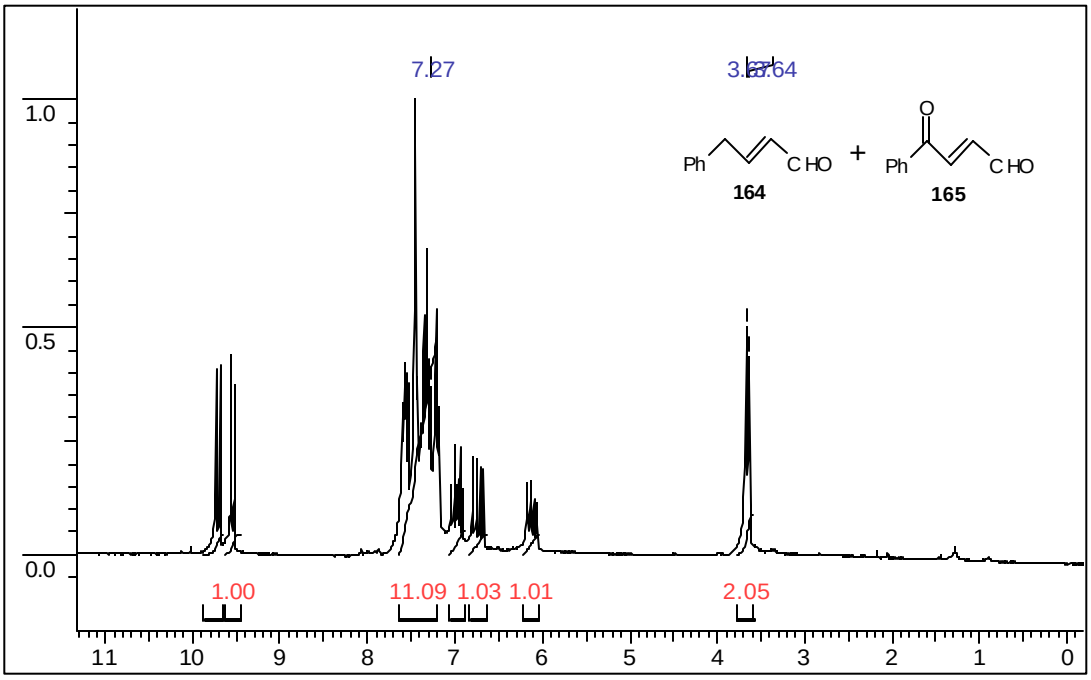
+ ^{1}H NMR Spectrum of **136**



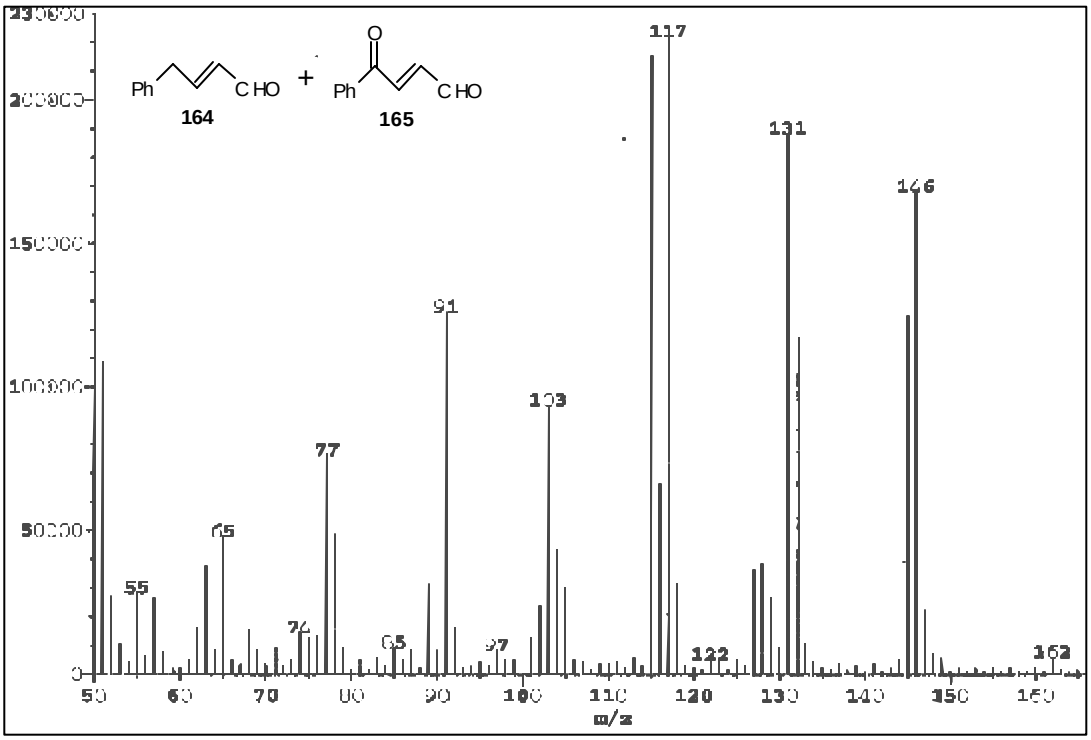
+ ^{1}H NMR Spectrum of **154**



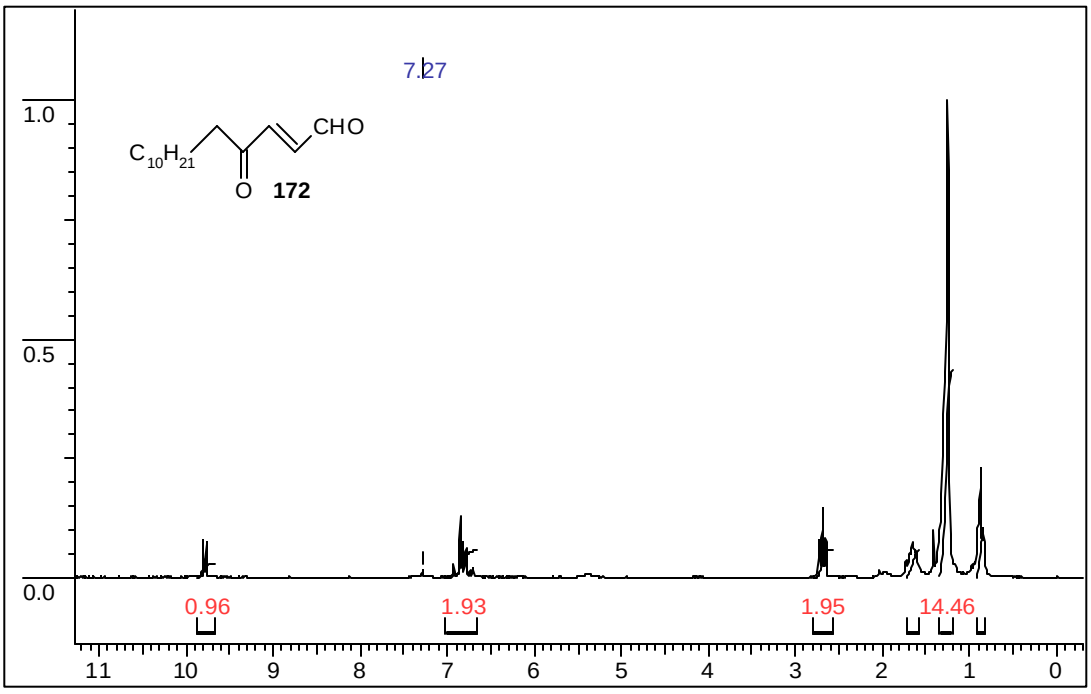
+ ^{1}H NMR Spectrum of **164** + **165**



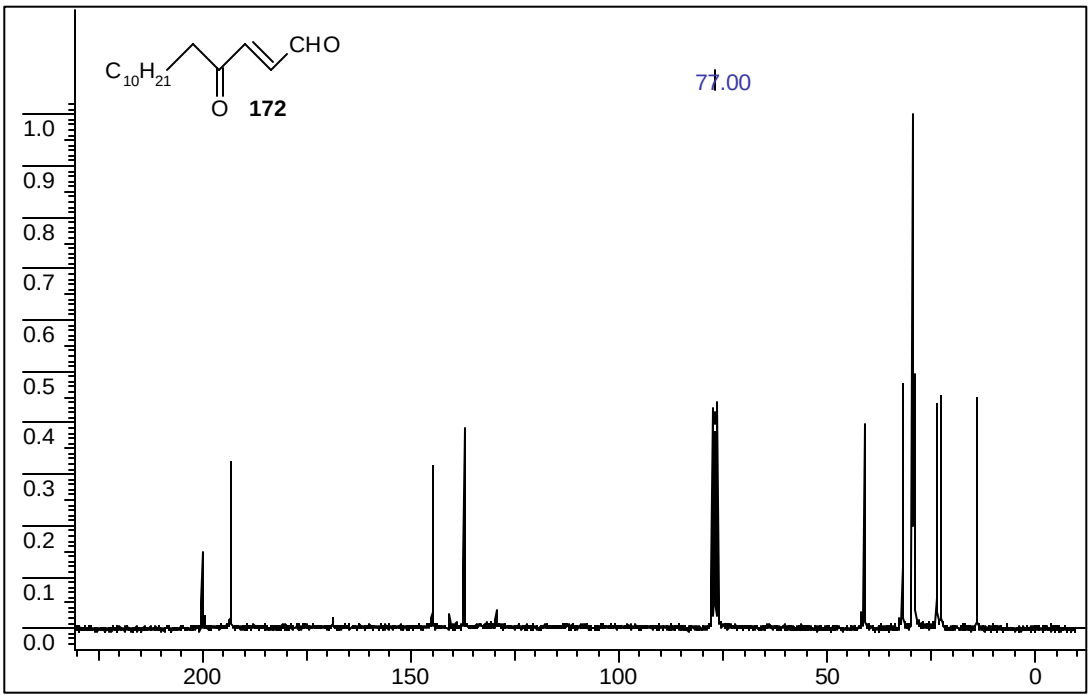
+ EIMS of **164** + **165**



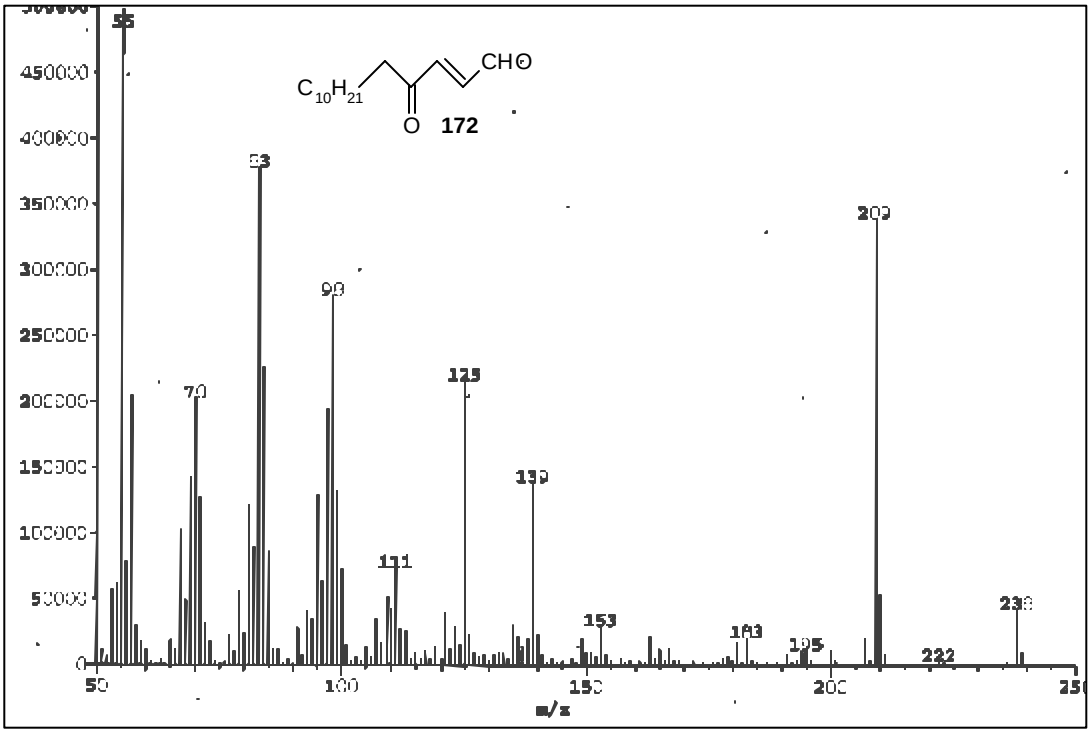
+ ^{1}H NMR Spectrum of **172**



+ ^{13}C NMR Spectrum of **172**



+ EIMS of **172**


55
450000
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350000
300000
250000
200000
150000
100000
50000
0
50
100
150
200
m/z
C10H21
CHO
O
172
93
99
70
125
139
111
153
193
195
209
222
238

5.7. References

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