ASYMMETRIC SYNTHESIS OF BIOLOGICALLY ACTIVE CYCLIC ETHERS AND POLYOLS EMPLOYING PROLINE CATALYZED REACTIONS AND HYDROLYTIC KINETIC RESOLUTION (HKR)

A THESIS SUBMITTED **TO**

UNIVERSITY OF PUNE

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)

BY

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UNDER THE GUIDANCE OF

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MARCH 2012

CANDIDATE'S DECLARATION

I hereby declare that the thesis entitled "**Asymmetric synthesis of biologically active cyclic ethers and polyols employing proline catalyzed reactions and hydrolytic kinetic resolution (HKR)"** 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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CERTIFICATE

The research work presented in thesis entitled "**Asymmetric synthesis of biologically active cyclic ethers and polyols employing proline catalyzed reactions and hydrolytic kinetic resolution (HKR)**" has been carried out under my supervision and is a bonafide work of **Ms. Divya Tripathi**. This work is original and has not been submitted for any other degree or diploma of this or any other University.

(Dr. Pradeep Kumar)

March 2012 **Research Guide**

DEDICATED

TO MY BELOVED

GRANDFATHER

AND MY FAMILY

Acknowledgements

Synthetic chemists often define their achievements in terms of the number of natural products they have synthesized or the number of novel reactions they have developed. Yet, I realize that my greatest achievements have been the professional and personal relationships I have developed that have got me to this stage in life. So it is with tremendous gratitude that I write these acknowledgements to show my appreciation to some of the people who have helped me throughout the years. I am grateful to my guide, *Dr. Pradeep Kumar* not only for the unwavering support and freedom in the choice of my research and the execution of my own ideas, but also for his competent guidance and advice when my ideas failed. I will never forget his encouraging words and patience when my motivation was at a low. I preserve an everlasting gratitude for him. I have been fortunate to have had *Dr. S. B. Katti* as mentor in my early days in *Central Drug Research Institute*, Lucknow. Not only is he a remarkable chemist, but also a competent and patient teacher. His help and guidance were crucial to the completion of the project. I have fond memories of those two years. My sincere thanks goes to *Dr. Ganesh Pandey*, Head, OCT Division for support and encouragement. I extend my gratitude to *Dr. C. V. Ramana, Dr. N. N. Joshi, Dr. D. S. Reddy, Dr. D. H Dethe Dr. M. Sashidhar* and *Dr. S.P. Chavan* for their help during the course of this work. I extend my thanks to the technical and official staff of NCL for their assistance.

I have been fortunate to have had *Dr. David Charles* as mentor in my early days in post-graduation. Not only is he a remarkable chemist, but also a competent and patient teacher. His teaching style, both in the classroom and the laboratory, motivated me to join the organic group. I would also like to thank *Mr. Rashmirathi Dinger*, who helped me fall in love with organic chemistry. He has an amazing ability to think beyond the traditional boundaries of our field, and I feel fortunate to have had the opportunity to learn from him. My undergraduate science teachers also deserve special thanks. My roots as a science student come from *Mrs. K. Sen.* She was always full of sound advice and was able to foster a great learning environment for us. I always feel what I do today is simply an extension of what she taught me. I would like to thank my undergraduate advisor *Dr. A. Aggarwal*, for his enthusiasm and energy, inspired in me the desire to study organic chemistry. His love for organic chemistry and teaching

were truly inspiring. I would like to take this opportunity to thank all my childhood teachers and nuns. I had the pleasure of attending *Loreto Convent* from kindergarten through twelfth grade. During this time, I was guided by the most inspiring people.

I have had the privilege of working with a number of interesting and exceptional people and I would like to take the opportunity to thank them individually. Early days of my project were carried out in conjunction with *Dr. Vasudeva Naidu*, and I am indebted to him for his diligence and commitment to the project. In addition, I am indebted to *Dr. Nagendra B. Kondekar* for being my honorable unofficial adviser. I will always be grateful to him for the P. S. Baran stories over lunch, the D. A. Evans series over the breakfast, and in general for the support he has given me. I would like to thank *Dr. Priti Gupta*, for her generosity with food and discussions. She deserves special recognition for providing helpful and critical discussions. I am also grateful to her for proofreading sections of this thesis as well as my papers. And of course, I must thank our humble *Dr. Namrata Dwivedi*, my "partner in crime" for many of my projects. She has been incredibly supportive and has provided me with scientific insight numerous times. She taught me how to perform chemistry in lab and how to emotionally survive chemistry outside of lab. I am sure she will continue to be an important influence in my life for many years to come.

NCL has been an amazing place and my lab has been like a second home to me. I had the good fortune to work with some outstanding labmates, *Rahul Jha*, *Shruti Vandana Kauloorkar* and *Krishanu Show*. *Rahul's* desire to seek answers for unanswered questions, must have eventually driven him to pursue graduate studies in chemistry. I am indebted to *Shruti* for her generosity with various reagents and glassware. Besides being a fun lab-mate, *Krishanu* brought a lot of great ideas and discoveries to the project, which made working together exciting at all times. *Shijo Cherian* is known for being the computer guru of the group, but to me he is so much more. I could not have made it through without his advice and sense of humor. I look forward to staying in touch with them.

I would like to collectively thank *Menaka, Partho* and *Kiran* for creating a peaceful and pleasurable work atmosphere. Everyone in 205 for keeping things exciting on a daily basis which includes, *Dr. Puspesh Upadhyay*, *Dr. Satyendra Pandey* and *Dr. Abhisheik Dubey*. I would like to thank my labmates *Dr. Ruchi, Ankush, Anand, U.*

Nookaraju and *Brijesh* for maintaining a warm and cheerful atmosphere in the lab. I have been fortunate to have friendship with people like *Tanaya, Jhumur, Shyamsundar, Animesh, Arun, Alok, Madhuri, Tanpreet, Rajesh, Mujahid, Prashant, Yadagiri, Pitamber, Sutar, Bharat, Santosh, Priyanka, Sujit Pal, Deepak, Ravindra, Dharmendra, Naidu, Richa, Aparna, Dr. Neha, Dr. Upasana, Dr. Rajendra, Dr. Swaroop, Binoy, Dr. Ashwani, Deepti, Dr. Debu, Dr. Bibhas, Dr. Prasanna, Dr. Keshri, Dr. Monisha Fernandes, Dr. Sahoo and Dr. Sriram.*

There are also a number of people whom I would like to acknowledge individually: the original members of my group: *Suman Sahoo* and *Manaswini Nanda* for being a part of the lab in the early days–especially *Roopa Mitra* and *Ashish Tripathi* whom I have stayed close friends with over the years; *Shraeddha Tiwari* for her sound advice and for good times at the NCL hostel. Her skills as a critical thinker are outstanding. I've learned so much from her, and I really miss her.

I am indebted to all my school friends *Dr. Nidhi Chaturvedi, Dr. Nimisha Singh, Dr. Garima Goel, Himali Joshi, Dr. Surabhi Prakash, Dr. Chhaya Shadra, Pallavi Singh, Dr. Naumi Nautiyal, Priyanka Chaturvedi, Esha Srivastav, Dr. Neha Chandra* and *Dr. Chhavi Bhatnagar* for their emotional support, but more importantly, for their friendship over the past few years. I was fortunate enough to develop some amazing friendships that have withstood the test of time. I would like to thank all my *Central Drug Research Institute* friends, *Dr. Tumul Srivastava, Dr. Ajay Srivastava, Dr. Ajay Sharma, Dr. Nidhi Sethi, Dr. Ramsagar Misra, Dr. Shilpi Pandey* and *Dr. Vandana Varshney*. Over the years, they have always been there to support me, and they have taught me the true meaning of friendship.

I must thank the most important people in my life, my family. I would like to thank my grandfather *Late Mr. Diwakar Shastri* who has done everything in his power to make sure that I succeed in life. I am what I am because of his enormous blessings. His memories will always be with me. My mother, *Snigdha Tripathi*, is the backbone of our family. She has sacrificed everything to ensure that all of us would always be able to strive for our goals. She deserves this Ph.D. as much as I do. My father, *Dr. C.K.M. Tripathi*, is my role model in life. I need to thank him for developing my insatiable passion for pursuing knowledge and Science. He has also taught me the value of hard work and humility. I am nothing without them. My sister, *Richa Tripathi*, is my best

friend, my mentor, and my biggest pillar of support. I could not imagine living a single day of my life without her support. My brother, *Pranav M. Tripathi*, is an amazing person. He has always been willing to support me with his crazy ideas. Our family would not be complete without his mischiefs. His very existence is a source of inspiration. No thanks can be enough to acknowledge for the endless encouragement, care and long-distance support, which I had from my father-in-law. Finally, I must thank the only person in this world who seems to fit in all of these categories. I am thankful to my husband, *Ravi Alok Sharma*, for his care, encouragement, support and sacrifice. He has been my constant source of strength and has brought a great deal of happiness to my life.

This page would be incomplete without the mention of our humble Director, *Dr. Sourav Pal, National Chemical Laboratory*, Pune for providing infrastructural facilities to complete my work successfully. I am also thankful to UGC, New Delhi for the financial assistance in the form of fellowship. At last but not the least, I thank whole heartedly, the omnipotent God, the illimitable superior spirit, who revels himself in the slight details I am able to perceive with my frail and feeble mind.

Divya Tripathi

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ABBREVIATIONS

Ac	-	Acetyl
AcOH	-	Acetic acid
Ac_2O	-	Acetic anhydride
AIBN	-	2,2'-Azobisisobutyronitrile
Bn	-	Benzyl
BnBr	-	Benzyl bromide
$BH_3 \cdot Me_2S$	-	Boron dimethyl sulfide complex
Boc	-	*tert*-Butoxy carbonyl
$(Boc)_2O$	-	Di-*tert*-butyl dicarbonate
BuLi	-	Butyl Lithium
DCM	-	Dichloromethane
DDQ	-	2,3-Dichloro-5,6-dicyano-1,4-nzoquinone
de	-	Diastereomeric excess
ds	-	Diastereoselectivity
DIBAL-H	-	Diisobutylaluminiumhydride
DHP	-	Dihydropyran
$(DHQ)_2PHAL$	-	1,4-Bis(dihydroquinin-9-*O*-yl)phthalazine
$(DHQD)_2PHAL$	-	1,4-Bis(dihydroquinidin-9-*O*-)phthalazine
DMP	-	Dess–Martin periodinane
DMP	-	2,2-Dimethoxypropane
DMF	-	*N, N*′-Dimethylformamide
DMAP	-	*N,N*′-Dimethylaminopyridine
DMSO	-	Dimethyl sulfoxide
ee	-	Enantiomeric excess
eq. or equiv	-	Equivalents
EtOH	-	Ethanol
Et	-	Ethyl
Et_2O	-	Diethyl ether
EtOAc	-	Ethyl acetate
Et_3N	-	Triethylamine
h	-	Hours
Hz	-	Hertz

IBS	-	Iodoxybenzoic Acid
Im	-	Imidazole
i-Pr	-	Isopropyl
IR	-	Infrared
LDA	-	Lithium diisopropylamide
m-CPBA	-	*m*-Chloroperbenzoic acid
MeOH	-	Methanol
MsCl	-	Methanesulfonyl chloride
Ms	-	Methanesulfonyl
Me	-	Methyl
MeI	-	Methyl iodide
$NaBH_4$	-	Sodiumborohydride
NaH	-	Sodium hydride
NOE	-	Neuclear Overhauser Effect
Ph	-	Phenyl
Py	-	Pyridine
PDC	-	Pyridiniumdichromate
p-TSA	-	*par*a-Toluenesulfonic acid
RCM	-	Ring closing metathesis
TEA	-	Triethylamine
TBAI	-	Tetra-*n*-butylammonium iodide
TBAF	-	Tetra-*n*-butylammonium fluoride
TBDMSCl	-	*tert*-Butyldimethyl chlorosilane
TBDMS	-	*tert*-Butyldimethyl silyl
THF	-	Tetrahydrofuran
TPP	-	Triphenylphosphine
*P*TSA	-	*p*-Toluenesulphonic acid
TsCl	-	*p*-Toluenesulphonyl chloride

GENERAL REMARKS

- ^{1}H NMR spectra were recorded on AC-200 MHz, MSL-300 MHz, and DRX-500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- ^{13}C NMR spectra were recorded on AC-50 MHz, MSL-75 MHz, and DRX-125 MHz spectrometer
- EI Mass spectra were recorded on Finngan MAT-1020 spectrometer at 70 *eV* using a direct inlet system.
- Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}.
- Optical rotations were measured with a JASCO DIP 370 digital polarimeter.
- Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected.
- All reactions are monitored by Thin Layer chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV light, I_2 and anisaldehyde in ethanol as development reagents.
- All solvents and reagents were purified and dried by according to procedures given in Vogel's Text Book of Practical Organic Chemistry. All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.
- All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 40 °C.
- Silica gel (60–120) used for column chromatography was purchased from ACME Chemical Company, Mumbai, India.

ABSTRACT

Asymmetric synthesis of biologically active cyclic ethers and polyols employing proline catalyzed reactions and hydrolytic kinetic resolution (HKR)

Chapter 1: A brief introduction to the Asymmetric Dihydroxylation, Jacobsen's Hydrolytic Kinetic resolution (HKR) and proline catalyzed organic transformations.

Chapter 2: Asymmetric synthesis of medium sized ring ethers lauthisan and isolaurepan.

Chapter 3: An organocatalytic route to the synthesis of (6S)-5,6-dihydro-6-[(2R)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one and ravensara lactones.

Chapter 4: An efficient and versatile general approach to β-hydroxy lactones and its application to the formal synthesis of two anti-obesity agents, tetrahydrolipstatin and tetrahydroesterastin.

Chapter 5: The attempted synthesis of naturally occuring lactones pectinolide A,B and C.

Chapter 1: A brief introduction to the Asymmetric Dihydroxylation, Jacobsen's Hydrolytic Kinetic resolution (HKR) and proline catalyzed organic transformations.

This chapter gives a brief introduction to Asymmetric Dihydroxylation,[1] Jacobsen's Hydrolytic Kinetic resolution[2] (HKR) and proline catalyzed organic transformations.[3]

The osmium tetroxide-catalyzed asymmetric dihydroxylation[1] (AD) of olefins, embedding two hydroxyl groups in a hydrocarbon framework is perhaps one of the most

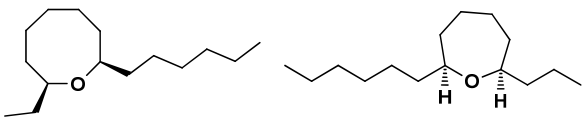
reliable and selective transformations in organic chemistry. $K_3Fe(CN)_6$ in the presence of K_2CO_3 provides a powerful system for the osmium-catalyzed dihydroxylation of olefins. The hydrolytic kinetic resolution (HKR)[2] of terminal epoxides catalyzed by chiral (salen) Co(III)OAc complex affords both recovered epoxides and 1,2-diol products in highly enantio-enriched form. In many cases there exist no practical alternatives for accessing these valuable chiral building blocks from inexpensive racemic materials.

In recent years, area of organocatalysis has emerged as a promising strategy and as an alternative to expensive protein catalysis and toxic metal catalysis, thus becoming a fundamental tool in the catalysis toolbox available for asymmetric synthesis.[3]

These methods have contributed to more advances in research not only in chemistry but also in material science, biology and medicine. This work gave access to new molecules needed to investigate hitherto undiscovered and unexplained phenomena in the molecular world.

Chapter 2: Asymmetric synthesis of medium sized ring ethers lauthisan and isolaurepan

Red algae of the genus *Laurencia* are unique in terms of producing C_{15} acetogenins along with many other biologically active marine natural products, particularly medium-ring ethers. Among them, are (-)-lauthisan **1**, and (+)-isolaurepan **2** (Figure **1**) which have been isolated from a sample of sea alga[4] *Laurencia obtuse* and are used as a target to check the validity of a particular synthetic methodology for efficient oxocane construction.



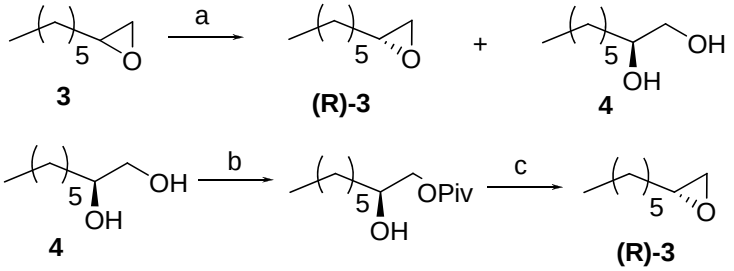
(-)- lauthisan 1 (+)-isolaurepan 2

Figure 1

An asymmetric synthesis of Lauthisan

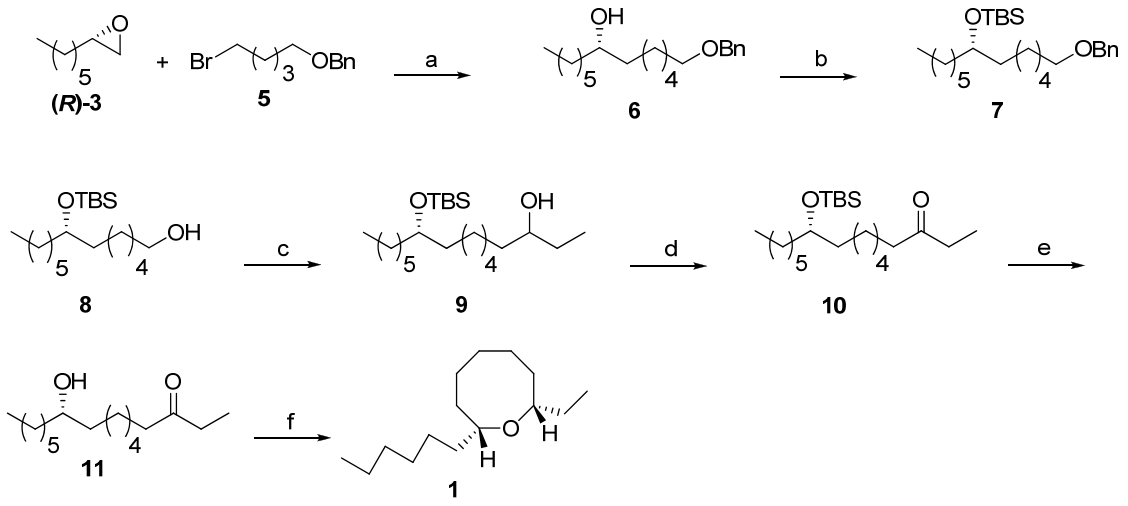
The synthesis of (-)-*cis*-lauthisan **1** started from racemic epoxide **3**, which was subjected to Jacobsen's HKR by using (*R,R*)-Salen-Co^{III}OAc catalyst to give chiral epoxide (*R*)-**3** along with chiral (*S*)-diol **4** (Scheme **1**). The conversion of diol **4** into (*R*)-**3** was achieved by the chemoselective pivalation of diol **4**, followed by mesylation

of the secondary hydroxyl and treatment of the crude mesylate product with K_2CO_3 resulting in concomitant ring closure by intramolecular S_N2 displacement of the mesylate to furnish the epoxide (*R*)-**3** (Scheme **1**).



Scheme 1. *Reagents and conditions:* (a) (*R,R*)-Salen-Co-(OAc) (0.5 mol%), dist. H_2O (0.55 equiv), 0 ^oC, 14 h, 45% for (*R*)-**3**, 43% for **4**; (b) i) PivCl, Et_3N, cat. DMAP, rt, 2 h; ii) MsCl, Et_3N, DMAP, 0 ^oC to rt, 1 h; c) K_2CO_3, MeOH, rt, overnight (61% for three steps).

Epoxide (*R*)-**3** was subjected to Grignard reagent, derived from benzyl protected bromopentanol **5** and Mg in THF at -78 ^oC to furnish the alcohol **6** (Scheme **2**). Silyl protection of the secondary alcohol **6** with *tert*-butyldimethylsilyl chloride afforded **7**. Subsequently the terminal benzyl group was deprotected using 20% $Pd(OH)_2/H_2$ which led to alcohol **8**. The alcohol **8** was then subjected to Swern oxidation[5] to give aldehyde which on Grignard reaction with EtMgBr furnished compound **9**. Oxidation of free hydroxyl group with IBX afforded ketone **10**. Silyl deprotection of **10** with *p*-TSA gave the keto-hydroxy precursor **11** which was treated with Et_3SiH and TMSOTf to give exclusively the *cis*-disubstituted cyclic 8-membered ether, (-)-lauthisan **1**.

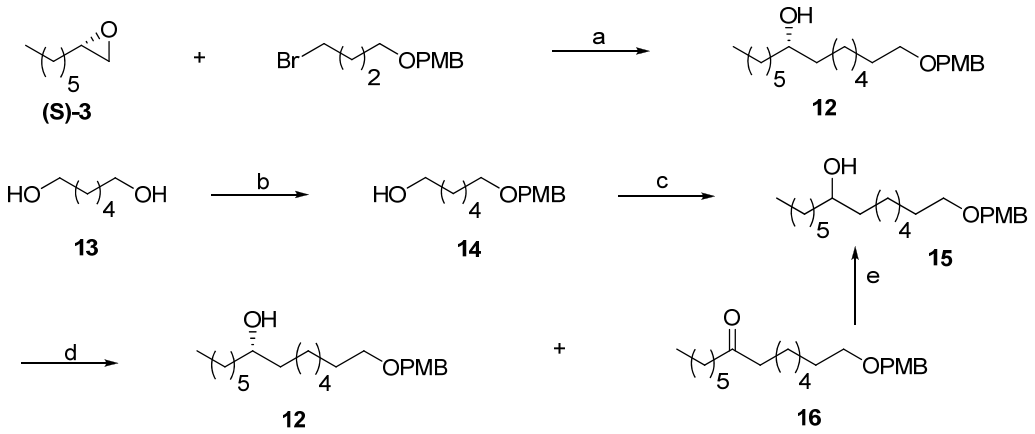


Scheme 2. *Reagents and conditions*: (a) $C_6H_5CH_2O$-$(CH_2)_5MgBr$, CuI, THF, -78 ^oC, 2 h, 72%; (b) TBSCl, 2,6-lutidine, cat. DMAP, dry CH_2Cl_2, 8 h, 0 ^oC, 94%; (c) 20% $Pd(OH)_2/H_2$, EtOAc , 1 atm, 12 h, 89%; (d) (i) $(COCl)_2$, DMSO, Et_3N, dry CH_2Cl_2, -78 ^oC, 2 h; (ii) *n*-C_2H_5MgBr, THF, 0 °C to rt, 1 h, 87%; (e) IBX, EtOAc, 80 ^oC, 90%; (f) *p*-TSA, MeOH, rt, 30 min; 96% (g) Et_3SiH, TMSOTf, CH_2Cl_2, 0 ^oC, 1 h, 42%.

Total synthesis of Isolaurepan

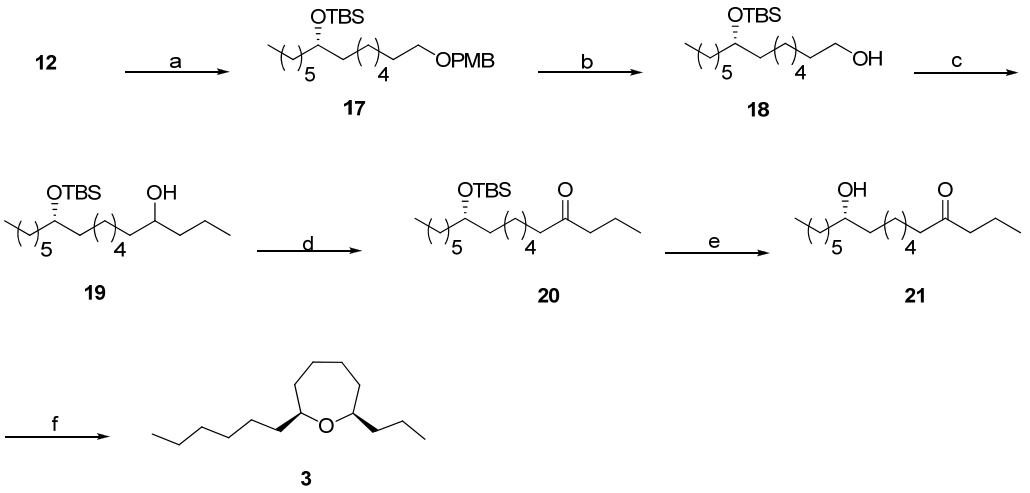
The synthesis of isolaurepan as shown in scheme **3** started from chiral epoxide (*S*)-**3** prepared from Jacobsen's hydrolytic kinetic resolution (HKR) of the racemic epoxide **3** using (*S,S*)-Salen-Co^{III}Ac complex. The regioselective opening of chiral epoxide (*S*)-**3** with Grignard reagent derived from *p*-methoxybenzyl protected bromobutanol and Mg in THF gave rise to the required alcohol fragment (*S*)-**12**, albeit in low yield (30%). To overcome the problem of low yield, this fragment was resynthesized starting with 1,6-hexanediol **13**. The selective mono hydroxyl protection of **13** with *p*-methoxybenzyl bromide gave the monoprotected diol **14** which was oxidized to the corresponding aldehyde under Swern conditions and subsequently treated with the Grignard reagent derived from 1-bromohexane and Mg in THF at 0 ^oC to furnish the racemic alcohol **15**. The racemic alcohol **15** was subjected to oxidative resolution using (*S,S*)-Salen $Mn^{III}Cl$ as catalyst to give the required optically active alcohol **12** along with the oxidized compound

16. Ketone **16** was recycled by conversion into the racemic alcohol **15** by reduction with $NaBH_4$.



Scheme 3. *Reagents and conditions*: a) *p*-$CH_3OC_6H_4CH_2O(CH_2)_4MgBr$, CuI, THF, -38 ^oC, 2 h, 30%; (b) *p*-$CH_3OC_6H_4CH_2Br$, NaH, dry DMF, cat. TBAI, 0 °C to rt, 1 h, 85%; (c) (i) $(COCl)_2$, DMSO, Et_3N, dry CH_2Cl_2, -78 ^oC, 2 h; (ii) *n*-$C_6H_{13}MgBr$, THF, 0°C to rt, 1 h, 91%. (d) (*S,S*)-Salen-Mn ^{III}(Cl) (0.02 eq), KBr (0.8 eq), $PhI(OAC)_2$ (0.7 eq), H_2O:CH_2Cl_2 2:1, rt, 30 min., 45% for **12** and 43% for **16**; (e) $NaBH_4$, MeOH, 4 h, 89%.

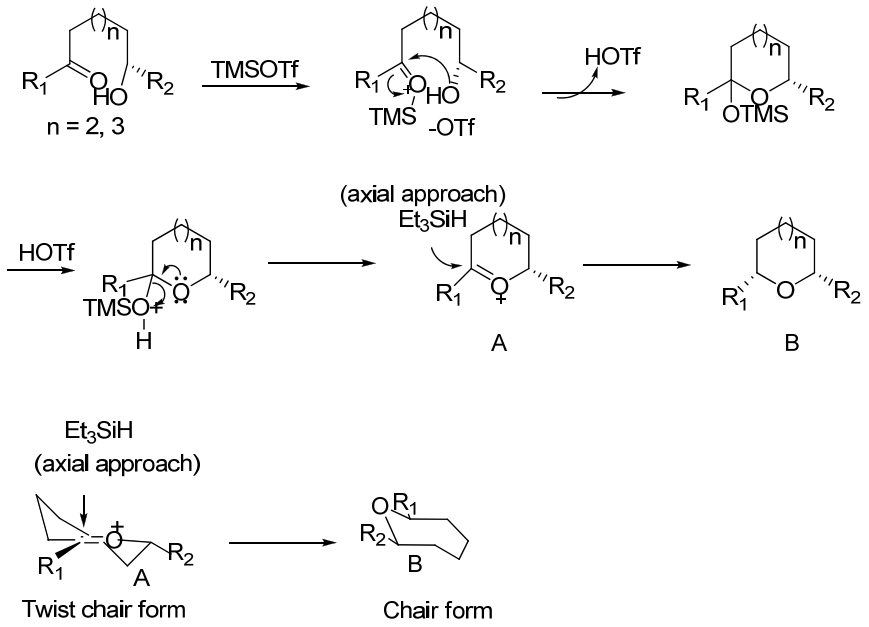
As shown in Scheme **4**, hydroxyl protection of **12** with *tert*-butyldimethylsilyl triflate afforded the silyl ether 1**7**. Subsequent *p*-methoxybenzyl deprotection of the primary alcohol was carried out with DDQ to give the required alcohol **18**. Alcohol **18** was oxidized to the aldehyde by Swern oxidation followed by Grignard reaction with 1-bromopropane and Mg in THF at 0 ^oC to give the desired compound **19**. The newly formed secondary alcohol was oxidized using IBX to give ketone **20** which on treatment with *p*-TSA in methanol afforded the required deprotected hydroxy-keto precursor **21**. Ketone **21** was treated with Et_3SiH and TMSOTf which promoted reductive cyclization to give exclusively, the *cis*-disubstituted cyclic 7-membered ether, (+)-isolaurepan **3**.



Scheme 4. *Reagents and conditions*: (a) TBS-OTf, 2,6-lutidine, cat. DMAP, dry CH_2Cl_2, 3 h, 0 ^oC, 85%; (b) DDQ, CH_2Cl_2/H_2O (18:1), rt, 1 h, 94%; (c) i) $(COCl)_2$, DMSO, Et_3N, dry CH_2Cl_2, -78 ^oC, 2 h, 90%; ii) *n*-C_3H_7MgBr, THF, 0°C to rt, 1 h, 62%; (d) IBX, EtOAc, 80 ^oC; 92% (e) *p*-TSA, MeOH, rt, 30 min; (f) Et_3SiH, TMSOTf, CH_2Cl_2, 0 ^oC, 1 h, 84%.

Mechanistic and Stereochemical pathway for the reductive cyclization process

A general possible mechanistic pathway explaining the formation of major *cis* diastereomer in the cyclization step is shown in scheme **5**. Activation of carbonyl group of the hydroxyl-ketone by TMSOTf favors the intramolecular nucleophilic addition of the hydroxyl group which eventually leads to the carboxonium intermediate **A** through an acetal precursor. The axial approach of Et_3SiH[6] to **A**, a seven membered twist-chair-like transition state, affording cis diastereomer **B**, is certainly favoured because of the higher stability of the resulting chair like transition state. Similar reasons could explain the major formation of the *cis* isomer in case of eight-membered cyclic ether (-)-lauthisan **1**



Scheme 5. Pathway for the reductive cyclization process

<u>Chapter 3:</u> An organocatalytic route to the synthesis of (6S)-5,6- dihydro-6-[(2R)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one and ravensara lactones

The 5,6-dihydro-2*H*-pyran-2-one with an integrated 1,3-skipped polyol system are ubiquitous structural motifs of several biologically active compounds. α,β-Unsaturated δ-lactone functionality is presumed to be responsible for wide range of biological properties, such as antifungal activity,[7] cytotoxicity against human tumor cells, [8] and inducing apoptosis. [9] The 1,3,5-polyol/pyrones **22a** and **22b** have been isolated from *Ravensara anisata*[10a] and **23a** and **23b** were isolated from *Ravensara crassifolia*. [10b] (Figure **2**).

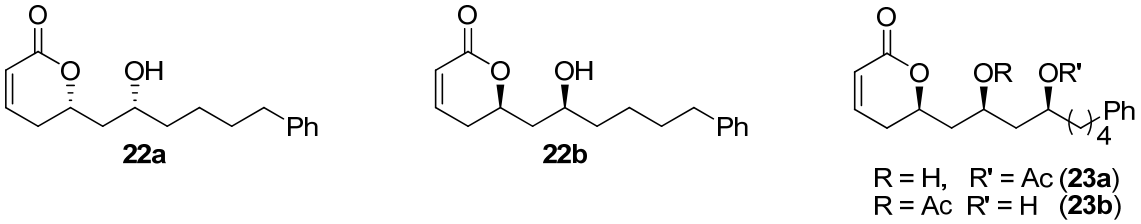
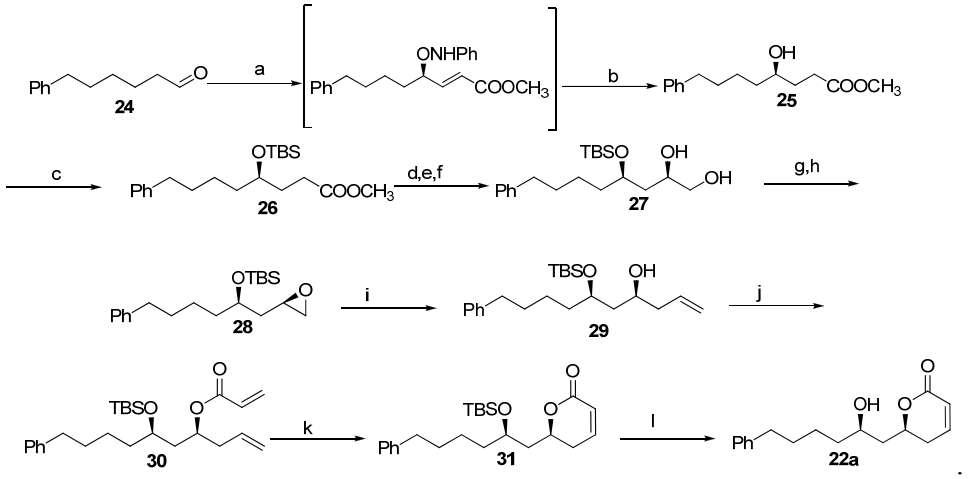


Figure 2

An asymmetric synthesis of (6*S*)-5,6-dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one (22a)

Our synthesis as shown in scheme **6**, commenced with phenyl hexanal **24** which was subjected to sequential α-aminoxylation (L-proline) followed by HWE-olefination reaction, to furnish *O*-amino-substituted allylic alcohol. The crude product obtained after workup was directly subjected to hydrogenation conditions using Pd/C to furnish the *γ*-hydroxy ester **25**. The TBS protection of the hydroxy group followed by reduction of ester **26** with DIBAL-H at -78 ^{o}C furnished the corresponding aldehyde, which was furthur subjected to α-aminoxylation catalyzed by L-proline, followed by in situ reduction using $NaBH_4$ to furnish the required *α*-amino-substituted diol. The *α*-amino-substituted diol thus obtained was subsequently subjected to reductive hydrogenation to afford the required diol **27**. Diol **27** on selective monotosylation and base treatment furnished epoxide **28**. Ring opening of epoxide **28** with vinylmagnesium bromide gave the homoallylic alcohol **29**. The alcohol **29** was esterified with acryloyl chloride to afford the acryloyl ester **30**. Subsequent ring-closing metathesis [3] of ester **30** with Grubbs' 1st generation catalyst afforded the α,β-unsaturated δ-lactone **31**. Finally desilylation was achieved by treatment of **31** with *p*-TSA to give the target molecule **22a**.

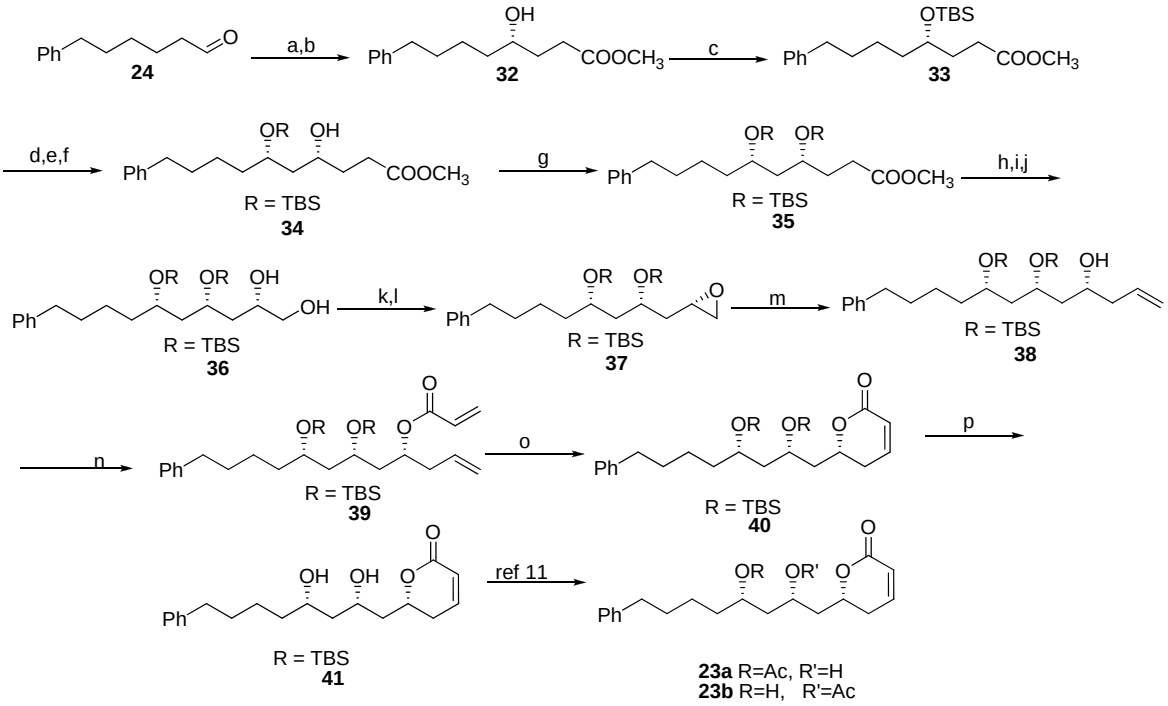


Scheme 6. *Reagents and conditions*: (a) Nitrosobenzene, L-Proline, DMSO; trimethyl phosphonoacetate, DBU, LiCl, CH_3CN; (b) H_2/Pd–C, EtOAc, 8 h, 65% (overall two steps); (c) TBSCl, imidazole, DCM, overnight, 92%; (d) DIBAL-H, DCM, -78 ^{o}C; (e) L-Proline, nitrosobenzene, DMSO, 60 min then $NaBH_4$, MeOH, 10 min; (f) H_2/Pd–C,

EtOAc, 12 h, 78% (over three steps); (g) TsCl, Bu_2SnO, Et_3N, DCM 2 h; (h) K_2CO_3, MeOH, rt, 1 h, 82% (over two steps); (i) vinylmagnesium bromide, THF, CuI, -20 ^oC, 12 h, 85%; (j) Acryloyl chloride, *i*-Pr_2NEt, DCM, -78 ^oC, 75%; (k) $(PCy_3)_2Ru(Cl)_2$=CH-Ph (20 mol%), CH_2Cl_2, reflux, 24 h, 92%; (l) PTSA, methanol 20 min, 90%.

An enantioselective synthesis of ravensara lactones (23a & 23b)

The synthesis of target compound as shown in scheme **7** commenced with aldehyde **24**, which was subjected to α-aminoxylation using D-proline followed by HWE-olefination reaction to furnish *O*-amino-substituted allylic alcohol and subsequently subjected to hydrogenation conditions using Pd/C to furnish the *γ*-hydroxy ester **32**. The free hydroxy group of *γ*-hydroxy ester **32** was protected as TBS ether using TBSCl to furnish compound **33**. The DIBAL-H reduction of ester **33** furnished the corresponding aldehyde which on α-aminoxylation using D-proline followed by HWE olefination and subsequent Pd/C reduction gave the *syn*-diol **34**. Further TBS protection of free hydroxy group afforded TBS ether **35**. The DIBAL-H reduction of compound **35** at -78 ^oC furnished aldehyde, which was again subjected to α-aminoxylation catalyzed by D-proline, followed by in situ reduction using $NaBH_4$ to furnish the required *α*-amino-substituted diol, which on reductive hydrogenation afforded the diol **36**. Diol **36** on selective monotosylation and base treatment afforded epoxide **37** which was treated with vinylmagnesium bromide to get the homoallylic alcohol **38**. The, alcohol **38** was esterified with acryloyl chloride to afford the acryloyl ester **39**. Ring-closing metathesis of ester **39** with Grubbs' 1st generation catalyst gave **40**. Finally global deprotection of TBS group was achieved by treatment of lactone **40** with TFA to give diol **41** which can be converted into the target compounds by the reported methods.[11] This constitutes the formal synthesis of **23a** and **23b**.

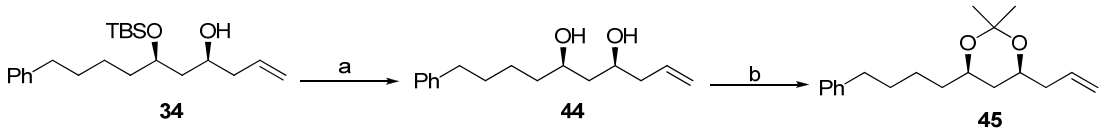


Scheme 7. *Reagents and conditions:* (a) Nitrosobenzene, D-Proline, DMSO; HWE salt, DBU, LiCl, CH_3CN; (b) H_2/Pd–C, EtOAc, 8 h, 60% (overall two steps); (c) TBSCl, imidazole, DCM, overnight, 90%; (d) DIBAL-H, DCM, -78 ^oC; (e) Nitrosobenzene, D-Proline, DMSO; HWE salt, DBU, LiCl, CH_3CN; (f) H_2/Pd–C, EtOAc, 8 h, 65%; (g) TBSCl, imidazole, DCM, overnight, 50% (overall four steps); (h) DIBAL-H, DCM, -78 ^oC; (i) D-Proline, Nitrosobenzene, DMSO, after 30 mins $NaBH_4$, MeOH, 0.5 h; (j) H_2/Pd–C, EtOAc, 8 h, 75% (over three steps); (k) TsCl, Bu_2SnO, Et_3N, 2 h; (l) K_2CO_3, MeOH, rt, 1 h, 80% (over two steps); (m) vinylmagnesium bromide, THF, CuI, -20 ^oC, 12 h, 80 %; (n) Acryloyl chloride, i-Pr_2NEt, DCM, -78 ^0C, 4 h, 85%; (o) $(PCy_3)_2Ru(Cl)_2$=CH-Ph (20 mol%), CH_2Cl_2, reflux, 88 %; (p) TFA, DCM, 30 min, rt, 90%

Relative stereochemistry determination

The relative stereochemistry of 1,3-diol **34** was determined *via* Rychnovsky's acetonide method[12] (Scheme **8**). The TBS deprotection of compound **34** furnished diol **44** which on treatment with 2,2-DMP gave the *syn* acetonide **45**. The appearance of methyl resonance

peaks at δ 18.78 and 30.44 ppm and acetal carbon resonating at δ 99.18 ppm confirmed the presence of *syn* acetonide.

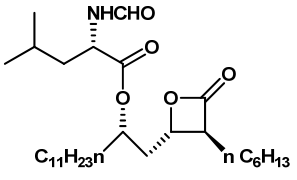


34 44 45

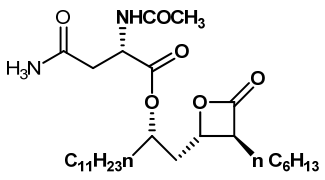
Scheme 8. *Reagents and conditions*: (a) TFA, DCM, overnight, rt, 92%; (b) 2,2-DMP, *p*-TSA, DCM, 8 h, 82%

<u>Chapter 4:</u> An efficient and versatile general approach to β-hydroxy lactones and its application to the formal synthesis of two anti-obesity agents, tetrahydrolipstatin and tetrahydroesterastin.

It is well-documented that tetrahydrolipstatin **46a** (Figure **3**) marketed under the trade name Orlistat, or Xenical belonging to trans-3,4-dialkyl-β-lactone class of compound, is an approved drug for treating obesity, tetrahydroesterastin **46b** is also a potent inhibitor of thioesterase domain of fatty acid synthase (FAS).We have developed a versatile and efficient method for the formal synthesis of **46a** and **46b** using both hydrolytic kinetic resolution (HKR) and proline catalyzed sequential a-aminoxylation, followed by HWE-olefination reaction.



Tetrahydrolipstatin 46a

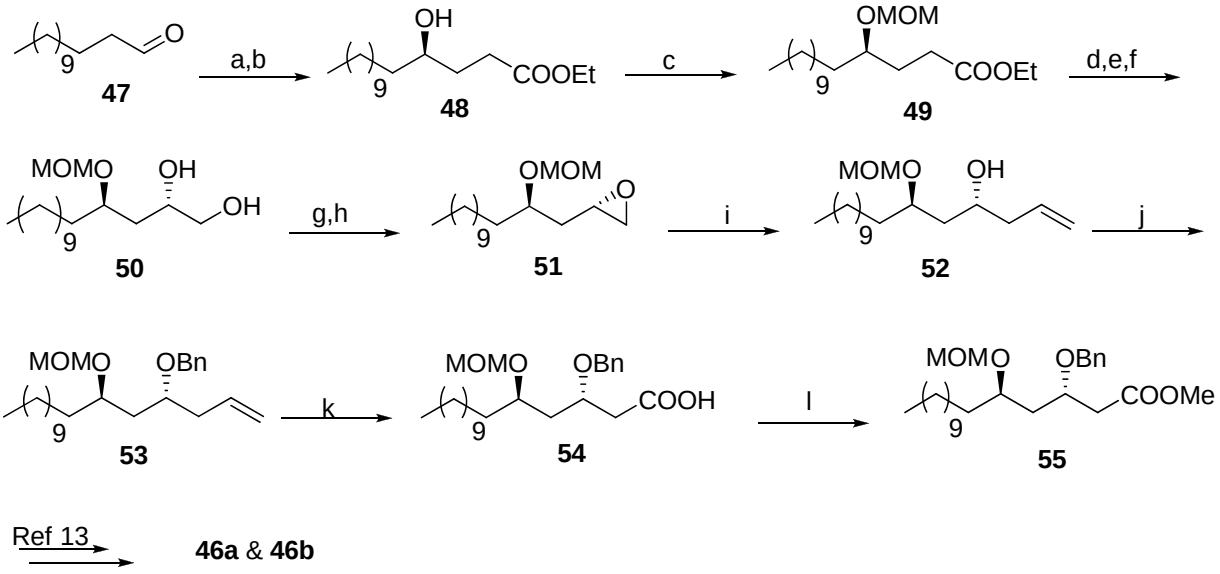


Tetrahydroesterastin 46b

Figure 3

As illustrated in Scheme **9**, the synthesis of target compounds commenced from aldehyde **47** which was subjected to α-aminoxylation using L-proline and subsequently Horner-Wadsworth-Emmons olefination followed by Pd/C reduction of double bond to furnish the ester **48**. The hydroxyl protection of **48** with methoxymethyl

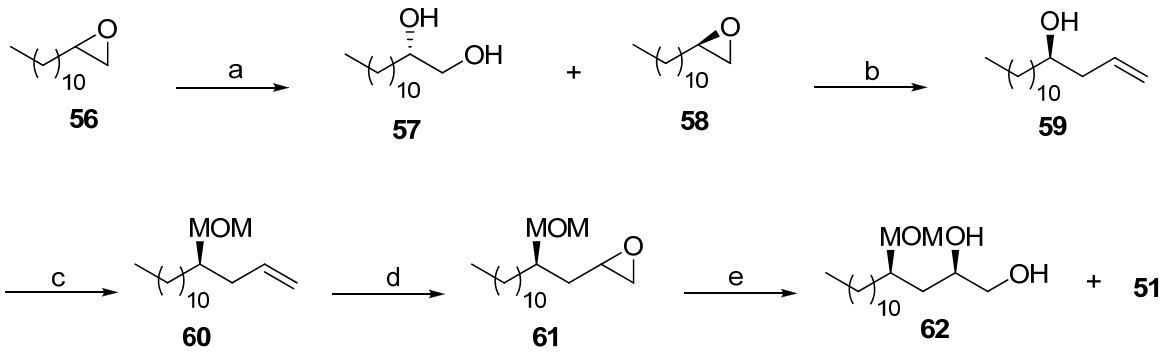
chloride afforded ester **49**. DIBAL-H reduction of ester **49** furnished the corresponding aldehyde which on aminoxylation, using D-proline followed by *in-situ* reduction with $NaBH_4$ gave diol **50**. The selective primary hydroxyl tosylation of **50** and its subsequent treatment with K_2CO_3 in methanol led to enantiomerically pure epoxide **51**. Ring-opening of epoxide **51** with Grignard reagent, derived from vinyl bromide and Mg in THF at -30 ^oC furnished the homoallylic alcohol **52**. Benzyl protection of the newly generated homoallylic alcohol **52** was accomplished by its reaction with benzyl bromide to afford the protected homoallylic alcohol **53**. Oxidative cleavage of terminal olefin **53** furnished the corresponding aldehyde which was converted to acid **54** using $RuCl_3.3H_2O$ and $NaIO_4$ protocol. Finally the acid **54** was esterified using MeI to give methyl ester **55**. The final stage of the synthesis could be achieved through the known procedure[13] of incorporation of the C8 side chain, cyclization to β-lactone and coupling of either *(S)*-N-formylleucine group to give tetrahydrolipstatin **46a** or *(S)*-N-acetylasparagine group to give tetrahydroesterastin **46b**.



Scheme 9. *Reagents and conditions:* (a) Nitroso benzene, L-proline, DMSO, 30 min, then trimethyl phosphonoacetate, DBU, LiCl, CH_3CN, 1h; (b) Pd/C, EtOAc, overnight, 62%; (c) MOMCl, DIPA, DCM, 8h, 89%; (d) DIBAL-H, DCM, -78 ^oC, 1h; (e) Nitroso benzene, D-proline, DMSO, 30 min, then $NaBH_4$, EtOAc; (f) Pd/C, EtOAc, 12h, 72%;

(g) TsCl, Et_3N, DCM, Bu_2SnO, 6h; (h) K_2CO_3, MeOH, 1h, 85%; (i) Vinylmagnesium bromide, CuI, dry THF, -30 ^oC, 12h, 92%; (j) BnBr, NaH, DMF, 4h, 95%; (k) $RuCl_3.3H_2O$, $NaIO_4$ CCl_4−CH_3CN−H_2O, 2:2:3, 3h, 85%; (l) MeI, K_2CO_3, MeOH, 30 min, 85%.

Alternatively, epoxide **51** could be prepared from racemic epoxide **56**, (Scheme **10**) which was subjected to Jacobsen's HKR by using (*R,R*)-Salen-Co^{III}OAc catalyst to give chiral (*S*)-diol **57** along with chiral (*R*) epoxide **58**. The chiral epoxide **58** was treated with vinylmagnesium bromide to give the homoallylic alcohol **59**. The hydroxyl group of homoallylic alcohol **59** was protected as the MOM ether to afford **60**, followed by epoxidation with *m*CPBA to give the racemic epoxide **61**. The epoxide **61** was treated with (*S,S*)-Salen-Co-OAc complex to afford the epoxide **51** and the diol **62**.

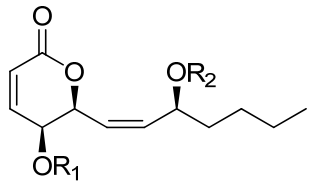


Scheme 10. *Reagents and conditions:* (a) *R,R*-Salen-Co^{III}(OAc) (0.5 mol%), dist. H_2O (0.55 equiv), isopropanol, 24 h, (45% for **57**, 43% for **58**); (b) C_2H_3MgBr, CuI, THF, -78 ^oC, 12 h, 91%; (c) MOMCl, DIPA, DCM, overnight, 89%; (d) *m*-CPBA, CH_2Cl_2, 10 h, 96%; (e) *S,S*-Salen-Co^{III}(OAc) (0.5 mol%), dist. H_2O (0.55 equiv), THF, 24 h, (34% for **62**, 56% for **51**).

Chapter 5: The attempted synthesis of naturally occuring lactones pectinolide A,B and C

Pectinolides (Figure **4**) have been isolated from *Hyptis pectinata*, [14] a plant of Mexican origin. Formulations of the plant are used in popular medicine as a multipurpose remedy

in the treatment of fevers, certain skin diseases, gastric disturbances, [15] rhinopharyngitis, and lung congestion. [16]

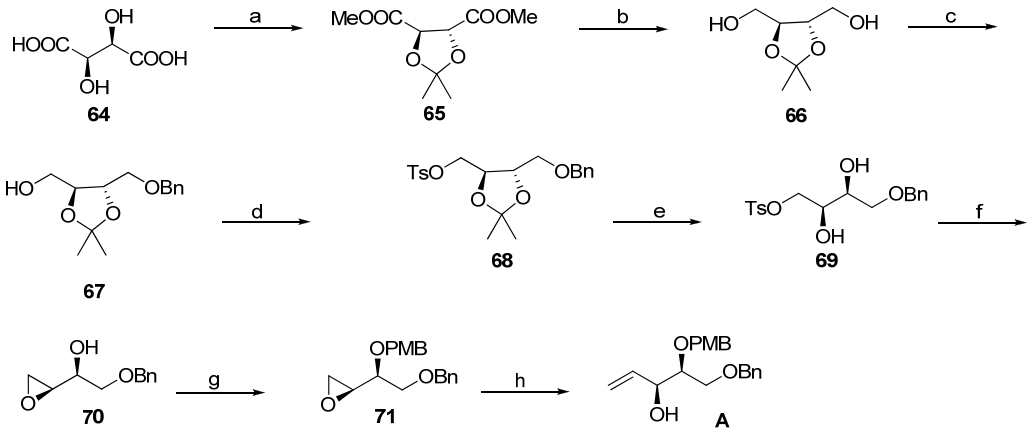


63a $R_1 = R_2 = Ac$
63b $R_1 = Ac, R_2 = H$
63c $R_1 = H, R_2 = Ac$

Figure 4

A divergent approach which relies on the coupling of two different olefin fragments via silicon tethering, has been devised.

Synthesis of fragment A: The synthesis of olefin fragment A started from L-tartaric acid **64**. Protection of the two alcohols and esterification was achieved in a single step using dimethoxy propane and methanol to afford diester **65**. Reduction of the diester **65** with $LiAlH_4$ afforded the diol **66** which on mono protection with benzyl bromide gave alcohol **67**. Tosylation of the alcohol furnished compound **68** which on deprotection of the acetonide group using camphor sulphonic acid rendered diol **69**. Treatment of tosylated diol **69** with K_2CO_3 furnished epoxide **70**. Epoxy-alcohol **70** on mono protection with para-methoxybenzyl alcohol afforded epoxide **71** which on one carbon homologation afforded fragment **A**.

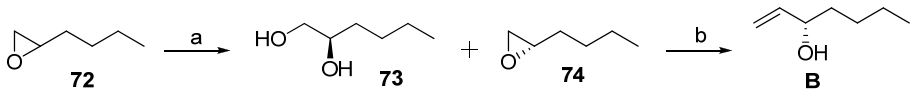


Scheme 11. *Reagents and conditions:* (a) MeOH, 2,2-DMP, *p*-TSA, 50 ^oC, 2 h then dry cyclohexane, 2,2 DMP, 24 h, 78 ^oC, 95%; (b) $LiAlH_4$, dry THF, 0 ^oC to reflux, overnight,

85%; (c) $C_6H_5CH_2Br$, NaH, dry THF, rt, 10 h, 82%; (d) TsCl, Et_3N, DCM, DMAP, 5 h; (e) CSA, MeOH/DCM (1:1), 3 h; (f) K_2CO_3, MeOH, rt, 4 h, 71% (over three steps); (g) *p*-$CH_3OC_6H_4CH_2Br$, NaH, dry DMF, rt, 6 h, 95%; (h) *n*-BuLi, $(CH_3)_3{}^+SI^-$, -20 ^oC dry THF, 4 h, 60%.

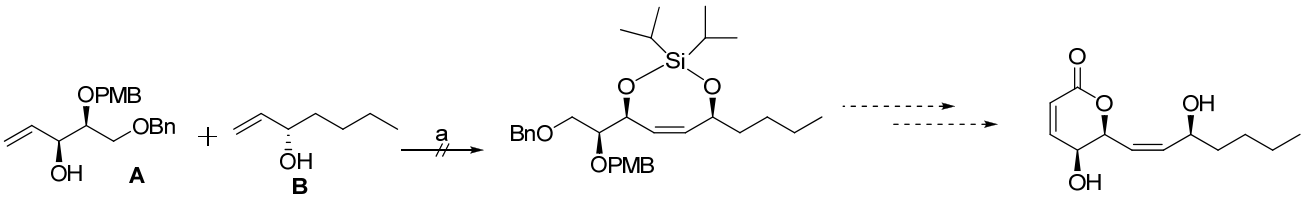
.

Synthesis of fragment B: The synthesis of fragment **B** commenced from epoxide **72**. which on HKR gave (*S*)-epoxide **74** along with (*R*)-diol **73**. One carbon homologation of epoxide **74** with trimethyl sulphonium iodide gave the desired fragment **B**.



Scheme 12. *Reagents and conditions:* (a) *R,R*-Salen-Co^{III}(OAc) (0.5 mol%), dist. H_2O (0.55 equiv), Isopropanol, 24 , (45% for **73**, 43% for **74**); (b) *n*-BuLi, $(CH_3)_3{}^+SI^-$, dry THF, 4 h, -20 ^oC, 70%.

Coupling of both the fragments: Both the fragment **A** and **B** were tried to be coupled using silicon tethering protocol . A complex reaction mixture was spotted on TLC due to which we were unable to isolate the product.



Scheme 13. *Reagents and conditions:* (a) *n*-BuLi, THF, $(Me)_2SiCl_2$, 3 h then Grubb's II, DCM.

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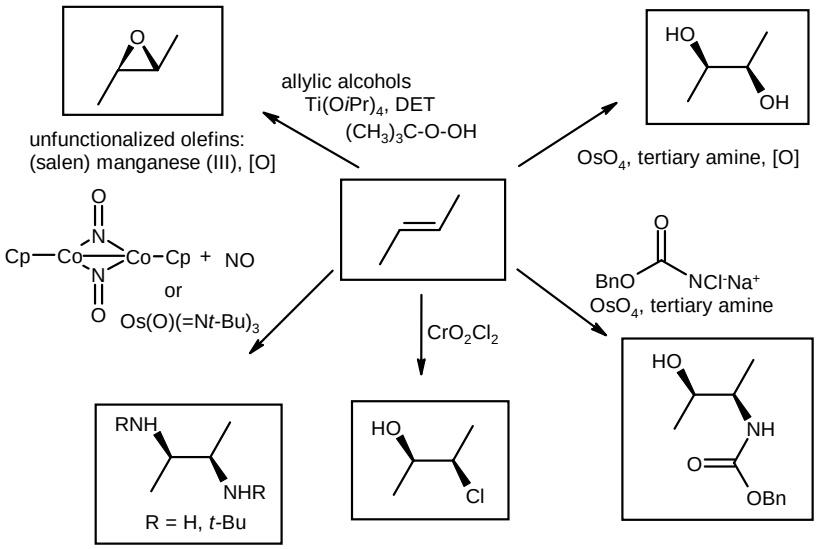
Chapter 1
Introduction to, Asymmetric Dihydroxylation, Jacobsen's Hydrolytic Kinetic resolution and proline catalyzed organic transformations

1.1. ASYMMETRIC DIHYDROXYLATION (AD)

1.1.1. Introduction

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. The goal of asymmetric synthesis-whether it is done in an academic or an industrial setting-is to prepare stereochemically-enriched compounds in the most efficient and practical manner possible.

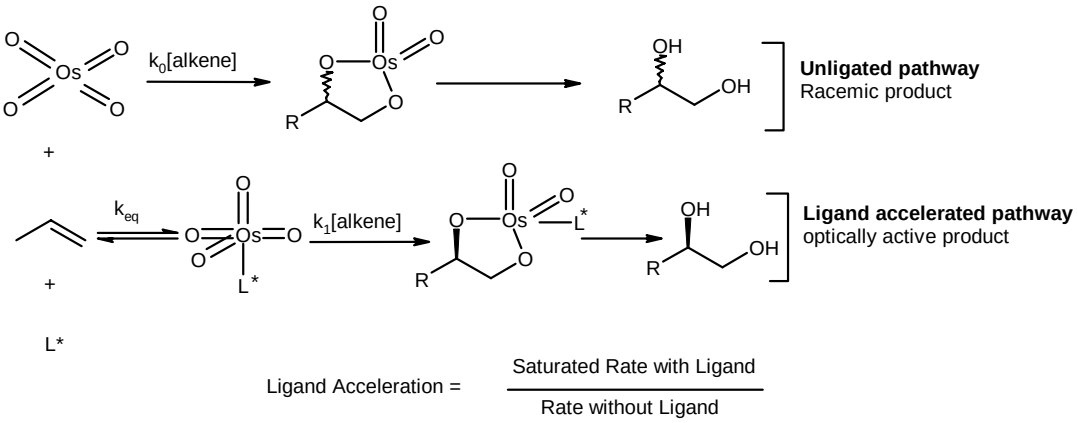
In the last two decades, many powerful asymmetric reactions have emerged as a result of the growing need to develop efficient and practical syntheses of biologically active compounds. Catalytic asymmetric reactions provide an especially practical entry into the chiral world due to their economical use 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 coordinating 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.



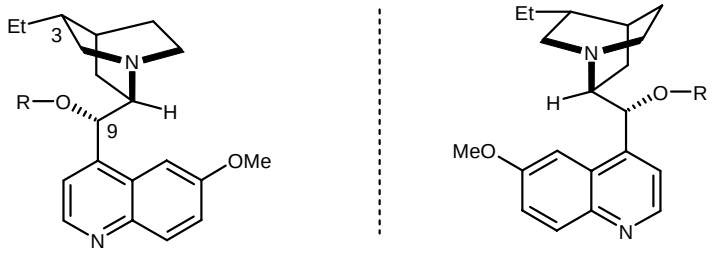
Scheme 2. Ligand accelerated catalysis-dihydroxylation of olefins.[7]

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**).

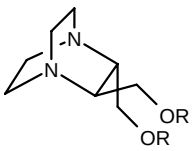
(a) Cinchona Alkaloid Ligands for AD under Catalytic Conditions



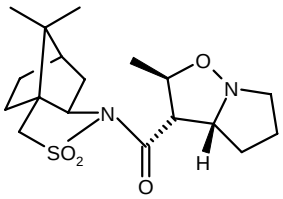
Dihydroquinidine (R = H)
DHQD

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

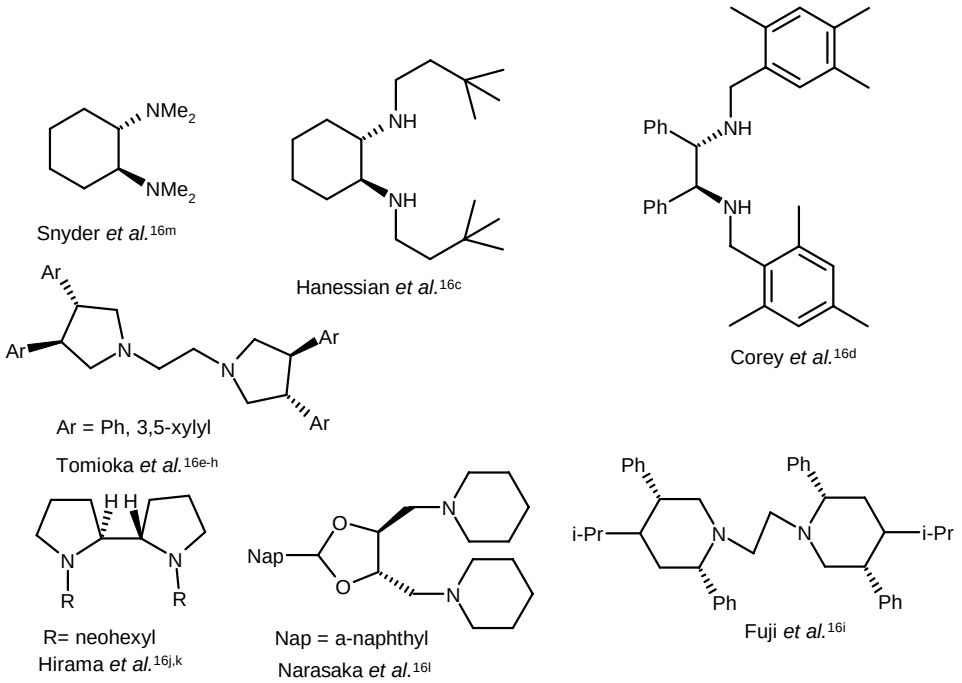


Figure 1. Some ligands for AD reaction.[13,16]

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**).

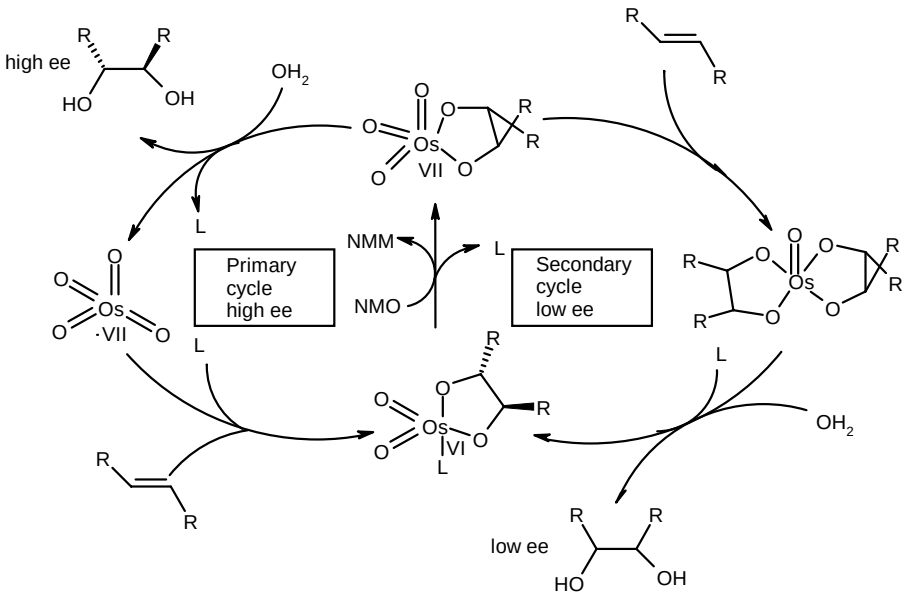


Figure 2. Two catalytic cycle for the AD reaction using NMO as the Co-oxidant

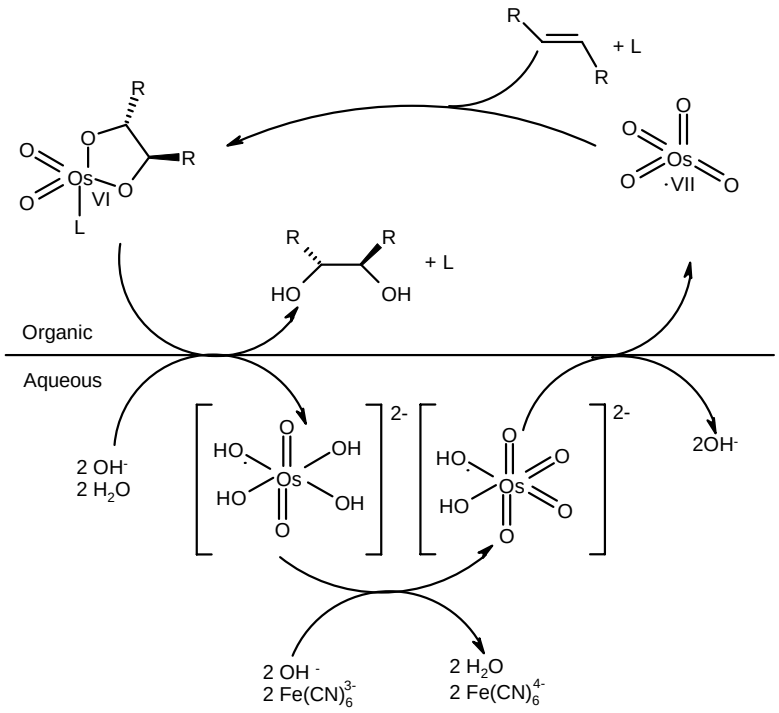


Figure 3. Catalytic cycle of the AD reaction with $K_3Fe(CN)_6$ as the Co-oxidant

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 heterocyclic spacer, has led to a considerable increase in both the enantioselectivity and the scope of the reaction (**Figure 4**).

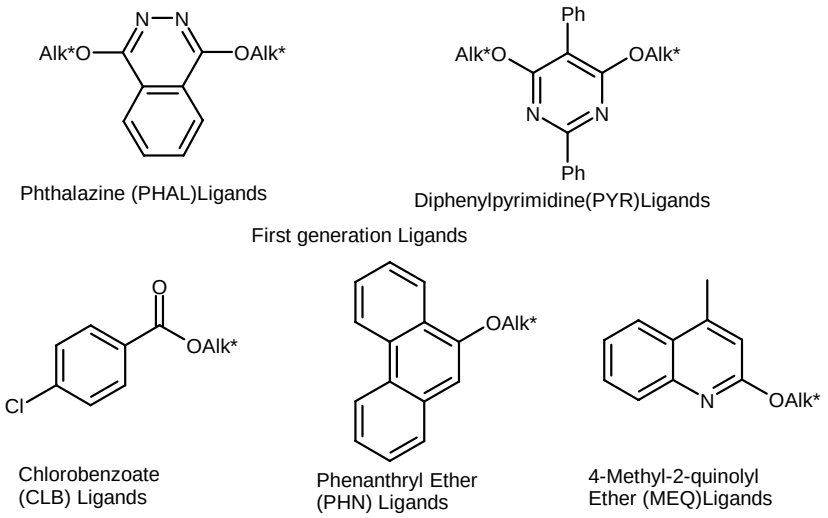
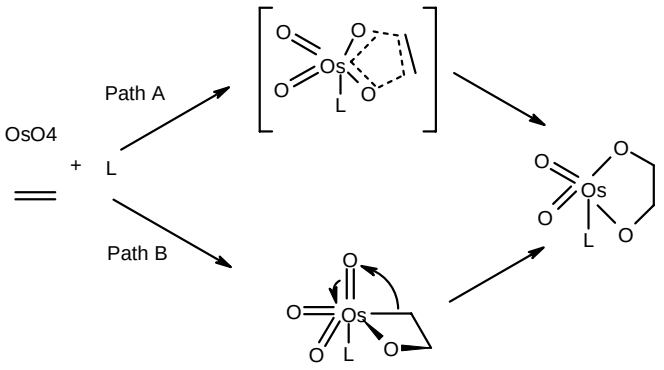


Figure 4. The latest generation of "dimeric" PHAL and PYR ligands and their predecessors (Alk* = DHQD or DHQ, see Fig. 1)

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.

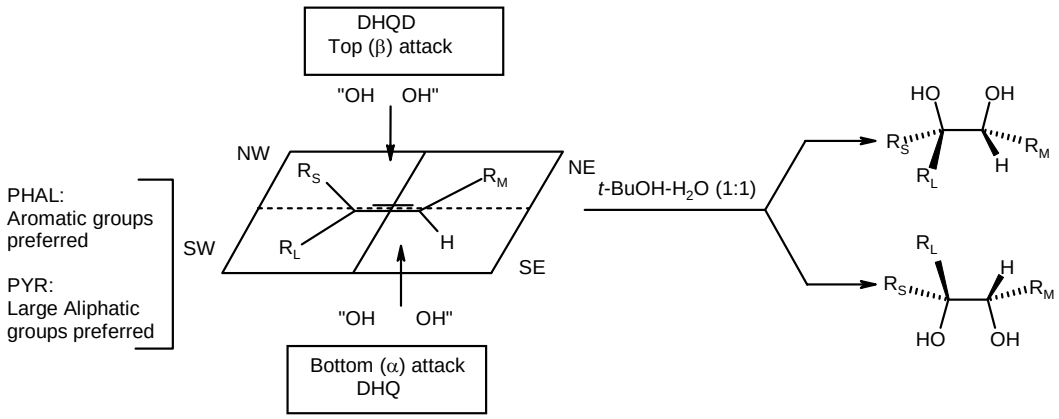


Scheme 3. Schematic presentation of the corrected [3+2] mechanism[23a] (Path A) and the stepwise osmaoxetane mechanism (Path B).[23b,c]

The recent observation of a nonlinear Erying relationship between enantiomeric excess and temperature[21] is in 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 investigations, 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 the four 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 quadrant 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**).



Scheme 4. The mnemonic device for predicting the face selectivity

1.1.4 Reaction Conditions

The catalytic asymmetric dihydroxylation is performed in a 1:1 mixture of water and *t*-BuOH and the olefin concentration is usually 0.1 M.[20] The key reagents are 3 equivalents of $K_3Fe(CN)_6$ as the re-oxidant, 0.2-0.4 mol% osmium, 1 mol% of ligand, 3 equivalents of K_2CO_3 and 1 equivalent of $CH_3SO_2NH_2$. Additionally, the ligand can be recovered especially when large scale reactions are carried out. For PHAL ligand, the combined organic layers are extracted with 3% aq. H_2SO_4 saturated with K_2SO_4 (ca. 40 mL/1g of ligand). The ligand enters the aqueous phase as the hydrogen sulphate salt and the solution can be reused directly for the subsequent AD reaction 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, and the volume of aqueous ligand solution added to the reaction mixture.

1.1.5 The cinchona alkaloid ligands and their substrate preferences

Phthalazine (PHAL) ligands

Due to the ready availability of second generation ligands i.e. PHAL[26] (Phthalazine) ligands are widely used and this ligand class reacts especially when aromatic groups are present, and remarkably high enantioselectivities were observed when the aromatic substituents appear in certain optimal locations[27] like in *trans*-stilbene for which the enantioselectivity is as high as 99.8%.[28] 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.

Anthraquinone (AQN) ligands

The anthraquinone ligands are well suited for almost all olefins having aliphatic substituents[29] and diols derived from allyl halides or allyl alcohols can 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.[30]

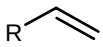
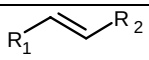
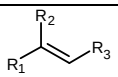
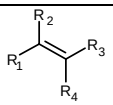
Diphenyl pyrazinopyridazine (DPP) and diphenyl phthalazine (DP-PHAL) ligands

These ligands give improved enantioselectivities for almost all olefins except for terminal alkyl olefins which are better served by the AQN or PRY ligands.[31] 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.[32] However, in certain cases better results are obtained with the new second generation ligands.[33]

Table 1. Recommended ligands for each olefin class

Olefin Class						
Preferred Ligands	<u>R=Aromatic</u> DPP, PHAL <u>R=Aliphatic</u> AQN <u>R=Branched</u> PYR	<u>R_1, R_2 =Aromatic</u> DPP, PHAL <u>R_1, R_2 =Aliphatic</u> AQN <u>R_1, R_2 = Branched</u> PYR	<u>Acyclic</u> IND <u>Cyclic</u> PYR, DPP, AQN	<u>R_1, R_2 = Aromatic</u> DPP, PHAL <u>R_1, R_2 = Aliphatic</u> AQN	PHAL, DPP, AQN	PYR, PHAL

1.2. HYDROLYTIC KINETIC RESOLUTION (HKR)

1.2.1. Introduction

Enormous advances have been made over the past several years in asymmetric synthesis, with particular emphasis having been placed on the development of enantioselective catalytic reactions.[34] Different factors influence the practicality of an asymmetric reaction.[35] A list of the features that would describe the ideal enantioselective transformation is necessarily subjective, but it could include:

· Products are obtained in quantitative yield.

· Reaction provides product in 100% enantiomeric excess (ee).

· Starting materials are inexpensive.

· Reaction times are short.

· Large amounts of product can be obtained with available glassware/equipment (high volumetric throughput).

· The chiral catalyst, reagent, or auxiliary is inexpensive and available, and does not contribute to the overall cost.

· Products are easily isolated, with little-or-no purification necessary.

· There is minimal generation of byproducts and waste.

· The reaction can be applied reliably and reproducibly on any scale.

· The reaction displays broad substrate scope, including high functional group compatibility.

· There is no better way to make the product in question.

Arguably no reactions discovered to date meet all of these criteria. To the extent that no enantioselective process is perfect, it is interesting to compare asymmetric reactions to the best methods for synthesizing the corresponding products in racemic form. In a few cases, e. g., for the laboratory synthesis of 1,2-diols, epoxy alcohols, and certain

hydrogenation products, asymmetric catalytic methodologies do in fact exist that make it as easy to prepare highly enantio-enriched materials as it is to prepare racemic mixtures. However, in a far greater number of cases, it is still much easier and less expensive to access racemates. As a result, despite what they might lack in "elegance", resolution strategies must always be evaluated carefully against any asymmetric process.[36]

Resolutions fall broadly into three classes. Classical resolutions involve the use of a stoichiometric amount of a chiral resolving agent.[37] The resolving agent is associated to the substrate, either covalently or non-covalently, to generate a pair of diastereomers. The diastereomers are separated and, through a separate chemical transformation, the substrate is released from the resolving agent. This approach has proven to be especially useful if salt formation is straightforward, as in the case of amines and carboxylic acids.[38] Chiral chromatography generally relies on the use of a chiral stationary phase to resolve enantiomers contained in a mobile phase, and in principle it can be carried out on analytical or preparative scale. In reality, the large solvent volumes, long separation times, and relatively high costs of chiral chromatography supports often limit the scale at which chromatographic separations can be carried out. Kinetic resolution involves using a chiral catalyst or reagent to promote selective reaction of one enantiomer over the other giving a mixture of enantio-enriched starting material and product, and the desired component is then isolated.[39]

As noted above, the theoretical yields for such resolutions are usually 50%. If the "undesired" resolution byproduct can be racemized or otherwise converted back to the desired enantiomer, then this can improve the yield, and therefore the practicality, of the resolution process, provided the additional cost in time and materials does not eclipse the cost of the initial resolution. In some special circumstances, it is possible to induce substrate racemization under the conditions of resolution. It then becomes possible in principle to convert essentially 100% of the racemate to the desired product. Such processes constitute a very special subclass of kinetic resolution reactions known as dynamic kinetic resolutions.

For the most part, however, racemization is not readily effected and the issue of a maximum yield of 50% holds. This applies equally to parallel kinetic resolutions, an additional subclass of kinetic resolution reactions. However, given that racemates can

often be much less than half as expensive than their enantiopure counterparts, it is clearly simplistic to consider resolutions as being inherently inelegant or impractical. Indeed, the fact that resolution remains so widely used is probably the best evidence that it can in fact be the most attractive option for accessing enantioenriched compounds. Catalytic kinetic resolutions are particularly attractive, at least in principle, because of the need for only small amounts of chiral "resolving agent". However, kinetic resolution has been used very little in a commercial context compared to classical or even chromatographic resolution. The following conditions must be met in order for kinetic resolution to be practical:

· The racemate is cheap and no good enantioselective, chiral pool, or classical resolution route to the product exists.

· The catalyst is highly selective for one enantiomer and is effective at low loadings.

· The catalyst is inexpensive or it can be recycled efficiently.

· The reaction is economical and safe (i. e., inexpensive stoichiometric reagents, no undue dangers associated with the reagents, high volumetric throughput, and a minimum of waste generated).

· The resolved starting material and converted product are easily separated.

· In the ideal case, both the product and the resolved substrate are valuable and recoverable in highly enantio-enriched form.

The importance of epoxides in organic synthesis arises partly from the occurrence of the strained three-membered ring unit in a number of interesting natural products[39] but more so because the ring opening of epoxides allows straightforward elaboration to useful new functionality, often with generation of new carbon-carbon bonds. Indeed, reactions of epoxides with nucleophiles, Lewis acids, radicals, reducing agents, oxidizing agents, acids, and bases have all been well documented and utilized in synthesis.[40] Further, the stereospecific manner in which epoxides generally react renders these compounds attractive chiral building blocks for asymmetric synthesis.

Since those epoxides that are produced naturally are typically complex compounds available only in limited amounts, Nature's chiral pool has not proven to be a useful

direct source of optically active epoxides for use in organic synthesis. Instead, enantio-enriched epoxides have been accessed indirectly from the chiral pool via multistep procedures.[41] These, however, tend to be inherently inefficient, and the range of epoxides available by this approach is also quite limited. As a consequence, the preparation of enantio-enriched epoxides has long stood as a most significant target for asymmetric synthesis. In particular, the identification of catalytic asymmetric olefin oxidation methods has been an area of active research for several decades, and the advances made in this field have increased greatly the number of enantiomerically enriched epoxides available for use in organic synthesis.

Among available methods for the preparation of enantio-enriched epoxides, the Sharpless epoxidation reaction has arguably had the most profound impact of any asymmetric catalytic reaction discovered thus far, providing general access to highly enantio-enriched epoxyalcohols.[42] More recently, the epoxidation of unfunctionalized conjugated olefins by chiral (salen)MnIII complexes has enabled the practical synthesis of certain classes of enantiomerically enriched epoxides.[43] A highly complementary strategy for epoxidation of simple olefins involving chiral dioxirane intermediates has expanded the range of chiral epoxides now accessible in enantio-enriched form to a significant extent.[44] Indirect routes to enantiopure epoxides involving asymmetric catalytic dihydroxylation or reduction reactions have also proven highly valuable in specific contexts.[45] Despite these considerable advances in asymmetric catalytic synthesis of epoxides, no general methods have been identified for the direct preparation of highly enantio-enriched 1-oxiranes, arguably the most valuable class of epoxides for organic synthesis.[46] The utility of terminal epoxides as chiral building blocks is perhaps best illustrated by the fact that the few examples for which effective catalytic approaches exist have found extensive use in asymmetric synthesis. In particular, glycidol and a number of its derivatives are available in enantiomerically enriched form using the Sharpless epoxidation technology[47] or by enzymatic kinetic resolution methods,[48] and these compounds have become widely used starting materials for target-oriented synthesis.[49] Epichlorohydrin has been rendered commercially available in bulk by microbial resolution of ((±)-2,3-dichloro-1-propanol, and it, too, has found widespread application.

Recently Jacobsen had discovered the (salen)Co complex **1** catalyzed efficient hydrolytic kinetic resolution (HKR) of a variety of terminal epoxides (Scheme 1).[50-52] This new method appeared to hold considerable promise with regard to meeting all of the criteria outlined above for kinetic resolution to be practical. Racemic 1,2-epoxides are generally available directly from commercial suppliers at low cost or are obtainable in one step from inexpensive olefins or aldehydes. In fact, certain racemic epoxides, such as propylene oxide, epichlorohydrin, styrene oxide, and butadiene monoepoxide, are commodity chemicals and are no more expensive than common organic solvents. Second, the ligands for catalyst **1** had previously been commercialized and manufactured on a ton scale in the context of (salen)Mn epoxidation catalysts.[53] The cobalt analogues (*R*,*R*)-**1** and (*S*,*S*)-**1** proved equally accessible, and these are also now available in bulk.[54] Third, water is perhaps the ideal reagent for effecting the resolution reaction: it is inexpensive and safe, and the rate of the ring-opening reaction can be controlled simply by modulating the rate of addition of water to the epoxide-catalyst mixture.[55] Fourth, for those examples that were described in the preliminary report, highly enantio-enriched epoxides were recovered from the HKR. Finally, the HKR provided useful enantio-enriched 1,2-diols, including many that are otherwise not readily accessible using existing asymmetric dihydroxylation methods.[56]

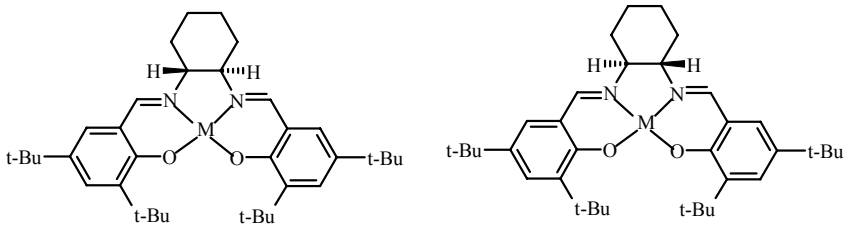
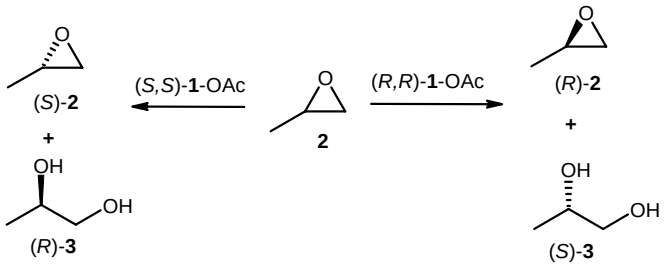


Figure 5. Jacobsen catalyst



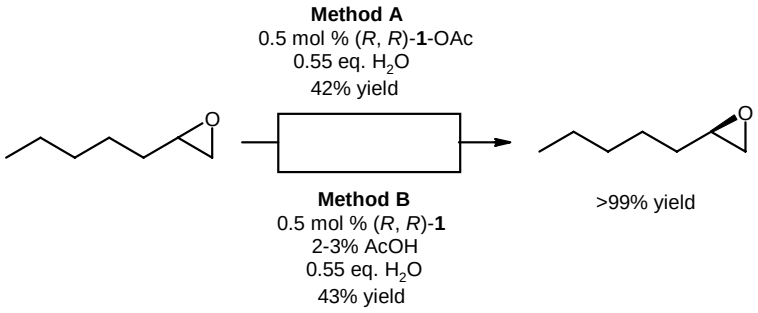
Scheme 5. Hydrolytic kinetic resolution reaction

The HKR has seen rapid adoption as the method of choice for the preparation of a variety of terminal epoxides in enantio-enriched form, and a number of applications in target oriented synthesis have been reported already.[57] In addition, the commercial manufacture of enantio-enriched propylene oxide, epichlorohydrin, and styrene oxide using HKR methodology has been implemented, thereby reducing the cost of these useful chiral building blocks.[54] Jacobsen has discovered that the HKR is an extraordinarily general reaction, allowing efficient kinetic resolution of virtually any type of terminal epoxide.

1.2.2 Preparation of Catalyst and General Experimental Considerations

Both enantiomers of the (salen)CoII complex **1** are available commercially on research or commercial scale,[54] or they can be prepared from the commercially available ligands using $Co(OAc)_2$. The Co(II) complex **1** is catalytically inactive, however, and it must be subjected to one-electron oxidation to produce a (salen)CoIIIX complex (X) anionic ligand) prior to the HKR. This may be done conveniently by aerobic oxidation in the presence of a mild Brönsted acid. Water alone was found not to mediate the oxidation reaction, but a screen of additives revealed that acetic acid was effective and that the corresponding Co(III) precatalyst **1**.OAc is convenient for use in HKR reactions both in terms of its preparation and reactivity (eq 1). Two useful methods for the generation of complex **1**.OAc have been developed. Method A involves isolation of **1**.OAc as a crude solid prior to the HKR. The Co(II) complex **1** is dissolved in toluene to generate a ca. 1 M solution, and acetic acid (2 equiv) is added. The resulting solution is stirred open to air at room temperature for 30 min, during which time the color of the mixture changes from orange to dark brown. All volatile materials are removed in vacuo, affording **1**.OAc as a brown solid residue that can be used without further purification. Method B involves in situ generation of **1**.OAc under HKR conditions by suspension of the Co(II) complex **1** in epoxide or epoxide/solvent and addition of HOAc under an aerobic atmosphere. Catalyst obtained by both methods was examined for each of the epoxides described in this study. For certain substrates such as 1-hexene oxide, catalyst prepared by either method leads to essentially identical results. In these situations, in situ catalyst generation (method B) is preferable since the procedure avoids an extra solvent removal step. On the other hand, catalyst prepared by method A was found to

be more effective with less reactive substrates (vide infra) and was applicable to all substrates examined. Therefore, if HKR did not afford epoxide in >99% ee with catalyst prepared by method B after optimization of solvent and catalyst loading, then catalyst prepared by method A was employed.



Scheme 6.

Aside from the method of generation of **1**.OAc, the only reaction parameters in the HKR that required optimization for individual substrates were catalyst loading and choice of solvent. With few exceptions, epoxide of >99% ee could be obtained using 0.55 equiv of water relative to racemate. Relatively small epoxides with some degree of water solubility could be resolved effectively without added solvent. However, the HKR of more lipophilic substrates did benefit from inclusion of a water miscible organic solvent such as tetrahydrofuran (THF), 2-propanol, or 1,2-hexanediol. In general, one volume of solvent relative to racemic epoxides was sufficient to allow efficient HKR. Catalyst loadings of 0.5 mol % or lower relative to racemic epoxide were effective for many substrates, but epoxides bearing sterically hindered or unsaturated substituents often required more catalyst (up to 2 mol %) to attain complete resolution. Reactions were initiated at 0 °C and then allowed to warm to room temperature with continued stirring for 12- 18 h.

[(*R*,*R*)-*N*,*N*'-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminato(2-)]cobalt(II) ((*R*,*R*)-1). A solution of cobalt(II) acetate tetrahydrate (5.98 g, 24.0 mmol) in MeOH (80 mL was added to a solution of ligand [(*R*,*R*)-*N*,*N*'-bis(3,5-di-*tert*-butylsalicylidene)-1,2- cyclohexanediamine] (10.9 g, 20.0 mmol) in CH_2Cl_2 (80 mL) via cannula under an atmosphere of N_2 with careful exclusion of air. A brick-red solid began to precipitate before addition was complete. The sides of the reaction flask were rinsed with MeOH (20 mL), and the mixture was allowed to stir for 15 min at room

temperature and then 30 min at 0 °C. Precipitated solids were isolated by vacuum filtration and rinsed with cold (0 °C) MeOH (2 x 75 mL). The red solid was collected and dried in vacuo to yield [(*R*,*R*)-*N*,*N*'-bis(3,5-di-*tert*butylsalicylidene)-1,2-cyclohexanediaminato(2-)]cobalt(II) ((*R*,*R*)-**1**) (11.6 g, 19.2 mmol, 96%).

1.2.3. Representative Procedures for the HKR of Terminal Epoxides

(a) Method A. (*S*)-Propylene Oxide. A 100 mL flask equipped with a stir bar was charged with (*S*,*S*)-**1** (242 mg, 400 μmol, 0.002 equiv). The catalyst was dissolved in 5 mL of PhMe and treated with AcOH (240 μL, 4.2 mmol). The solution was allowed to stir at room temperature open to air for 30 min over which time the color changed from orange-red to a dark brown. The solution was concentrated in vacuo to leave a crude brown solid. The resulting catalyst residue was dissolved in propylene oxide (14.0 mL, 11.6 g, 200 mmol) at room temperature, the reaction flask was cooled to 0 °C, and H_2O (1.98 mL, 110 mmol, 0.55 equiv) was added dropwise over 5 min. The reaction was allowed to warm to room temperature and stir for 14 h at which time (*S*)-propylene oxide (5.35 g, 92.1 mmol, 46%) was isolated by distillation from the reaction mixture at atmospheric pressure and 36 °C. Propylene diol was removed by vacuum distillation (65 °C, 0.25 Torr). The catalyst was recovered by suspension in MeOH and collection by vacuum filtration. The ee of the propylene oxide was determined to be 99.7% by chiral GC analysis of the 1-azido-2- trimethylsiloxypropane derivative obtained by opening the epoxide with $TMSN_3$ (Cyclodex-B, 55 °C, isothermal, *t*R(minor)) 12.29 min, *t*R(major)) 12.57 min). $[R]_{23}{}^{D}$ -11.6° (neat).

(b) Method B. (*R*)-1,2-Epoxy-5-hexene. A 100 mL flask equipped with a stir bar was charged with (*R*,*R*)-**1** (302 mg, 500 μmol, 0.005 equiv). The catalyst was treated with ((±)-1,2-epoxy-5-hexene (11.3 mL, 9.81 g, 100 mmol), AcOH (120 μL, 2.1 mmol, 0.02 equiv), and 1 mL of THF. The reaction flask was cooled to 0 °C, and H_2O (1.0 mL, 55 mmol, 0.55 equiv) was added in one portion. The reaction was allowed to warm to room temperature and stir 16 h at which time the volatile materials were isolated by vacuum transfer at 0.25 Torr into a cooled (-78 °C) receiving flask. The recovered epoxide was filtered through a silica plug to remove residual water, and the THF was removed by rotary evaporation to yield (*R*)-1,2-epoxy-5-hexene (4.23 g, 43.1 mmol). The diol was distilled under reduced pressure (56 °C, 0.25 Torr). The catalyst was recovered by suspension in MeOH and vacuum filtration. The ee of the recovered

epoxide was determined to be 99.5% by chiral GC analysis of the 1-azido-2-trimethylsiloxy-5-hexene derivative obtained by opening the epoxide with $TMSN_3$ (Cyclodex-B, 70 °C, isothermal, *t*R(minor), 38.00 min, *t*R(major), 39.06 min). $[\alpha]_D^{25}$ +9.36° (neat)

1.2.4. Catalyst Recycling

The possibility of recycling a catalyst has obvious practical appeal, particularly in cases where the catalyst is precious due to cost or limited availability. Catalyst **1** is prepared in bulk from low-cost components, and as a result it is quite inexpensive relative to most chiral catalysts. On the other hand, the HKR employs reactants (racemic epoxide, water, minimal if any solvent) that impact the cost of the overall process to an almost negligible extent in many cases, and as a result the catalyst is a significant contributor to the material costs. Accordingly, efforts were directed toward identifying practical methods for effecting catalyst recovery and recycling. The HKR reaction of propylene oxide presents an especially straightforward scenario with respect to catalyst recovery because both the epoxide and the diol are relatively volatile and can be removed by distillation. The solid residue remaining in the reaction vessel after product separation was found to have the characteristic red-brick color of the reduced (salen)CoII complex **1**. Reoxidation to **1**.OAc with air and AcOH led to catalyst with undiminished levels of reactivity and selectivity.

Thus the HKR provides a straightforward method for the preparation of a wide assortment of terminal epoxides in highly enantio-enriched form. Given that in many cases there exist no practical alternatives for accessing the valuable chiral building blocks, it is hoped that the HKR will have a beneficial and enabling effect on the field of organic synthesis.

1.3 PROLINE CATALYZED ASYMMETRIC ORGANIC TRANSFORMATIONS

1.3.1. Introduction to organocatalysis

The broad utility of synthetic chiral molecules as single-enantiomer pharmaceuticals, in electronic and optical devices, as components in polymers with novel properties, and as probes of biological function, has made asymmetric catalysis a prominent area of investigation. Organocatalysis, or the use of small organic molecules to catalyse organic transformations, is a relatively new and popular field within the domain of chiral molecule (or enantioselective) synthesis. Although chemical transformations that use organic catalysts, or organocatalysts, have been documented sporadically over the past century, it was not until the late 1990s that the field of organocatalysis was 'born'.[58] It is now widely accepted that organocatalysis is one of the main branches of enantioselective synthesis (the other, previously accepted, branches being enzymatic catalysis and organometallic catalysis), and those who are involved in the synthesis of chiral molecules consider organocatalysis to be a fundamental tool in their catalysis toolbox.

This rediscovery has initiated an explosive growth of research activities in organocatalysis both in industry and in academia. The 1970s brought a milestone in the area of asymmetric organocatalysis, when two industrial groups led by Hajos and Wiechert published the first and highly enantioselective catalytic aldol reactions using simple amino acid proline as the catalyst. Organocatalysis is the catalysis of chemical transformations using a purely organic molecule, which is composed of mainly carbon, hydrogen, nitrogen, sulfur, and phosphorus, and does not contain any metals. The advent of organocatalysis brought the prospect of a complementary mode of catalysis, with the potential for savings in cost, time and energy, an easier experimental procedure, and reductions in chemical waste, which confers a huge direct benefit in the production of pharmaceutical intermediates when compared with transition metal catalysts. Organic molecules not only have ease of manipulation and a "green" advantage but also can be very efficient catalysts. Several aspects of organocatalysis will undoubtedly attract researchers' attention. Tremendous efforts will continue to be directed towards the discovery and design of catalysts with better efficiency, new reactivities and greater turnover numbers. And in near future asymmetric

organocatalysis may begin to catch up with the spectacular advancements of enantioselective transition metal catalysis.

Recently, List[59] introduced a system of classification based on the mechanism of catalysis (Figure **6**). The four categories are Lewis base, Lewis acid, Bronsted base and Bronsted acid catalysis. Accordingly, Lewis base catalysts (B:) initiate the catalytic cycle via nucleophilic addition to the substrate (S). The resulting complex undergoes a reaction and then releases the product (P) and the catalyst for further turnover. Lewis acid catalysts (A) activate nucleophilic substrates (S:) in a similar manner. Brønsted base and acid catalytic cycles are initiated via a (partial) deprotonation or protonation, respectively.

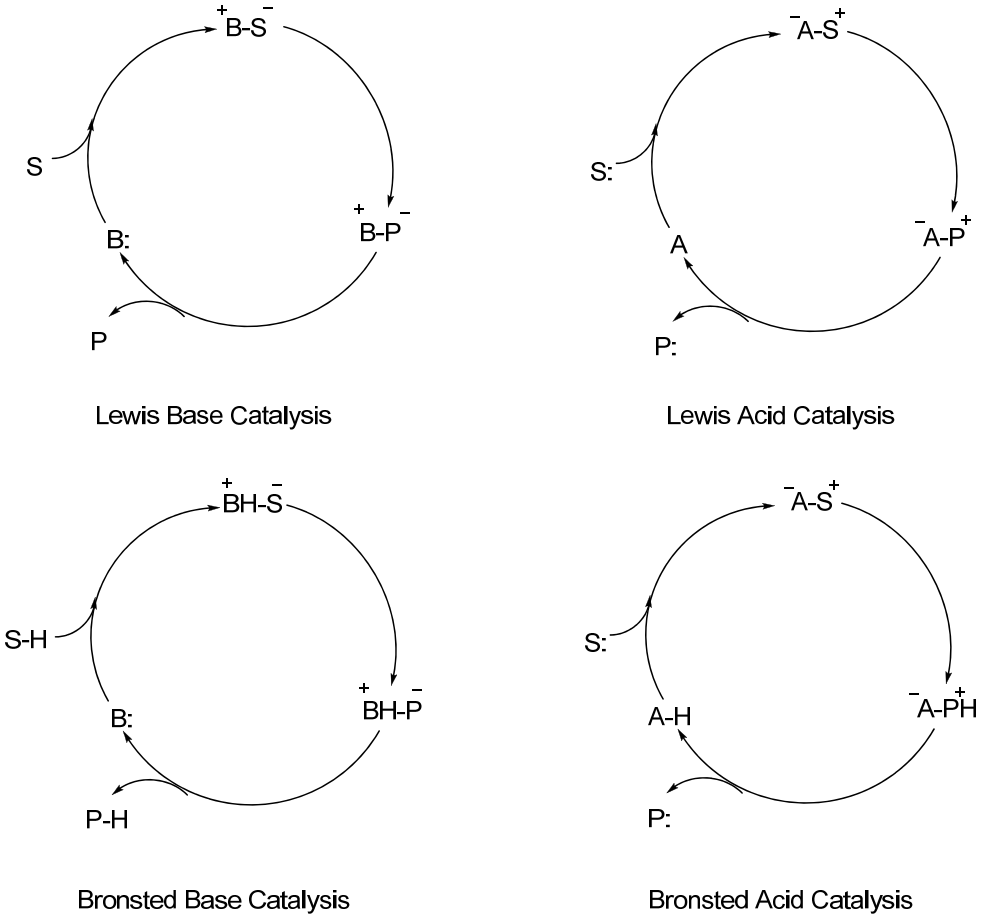


Figure 6. Organocatalytic cycles

1.3.2. Proline a "Universal catalyst"

Proline has been defined as a "universal catalyst" because of its high utility in variety of asymmetric organic transformations. Proline is the only natural amino acid with a secondary amine functionality, which raises the pKa value and better nucleophilicity as compared to other amino acids. It can act as a nucleophile to carbonyl groups (iminium intermediate) or Michael acceptors (enamines). It can be regarded as a bifunctional catalyst as the secondary amine acts as Lewis base and the acid group acts as Bronsted acid (Figure **7**). The high stereoselectivity in the proline-catalyzed reactions is possibly due to its formation of organized transition states with many hydrogen bonding frameworks. Proline is not the only molecule to promote catalysis, but it still seems to be one of the best in the diversity of transformations.

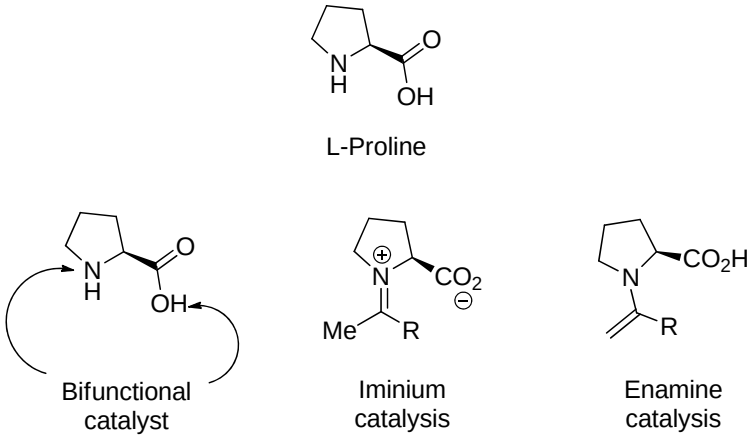


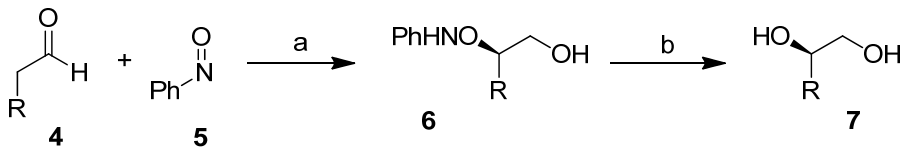
Figure 7. Modes of proline catalysis

It is known to catalyze aldol,[60] Diels-Alder,[61] Michael addition[62] and α-functionalization[63] among many other organic transformations.[64] Particularly proline-catalyzed α-aminoxylation[65] and α-amination[66] of carbonyl compounds have emerged as powerful methods because chiral building materials can be synthesized in effective manner starting from easily available materials.

1.3.3. Proline-catalyzed α-aminoxylation

Optically active α-hydroxyaldehydes and ketones are important intermediates in organic synthesis as they are direct precursors to 1,2-diols. Because of this utility many methods have been developed for their preparation. The more prominent, well-established

methods of enantioselective α-oxygenations include the use of Davis oxaziridine,[67a] Sharpless dihydroxylation of enol ethers,[67b] manganese–salen epoxidation of enol ethers,[67c] and Shi epoxidation of enol ethers.[67d] It is only rather recently that direct catalytic, asymmetric variants have been reported.[68] Most of these methods, however, require multiple manipulations and there is no direct method, nor catalytic asymmetric method for their synthesis from the corresponding aldehyde. Recently, proline has been found to be an excellent asymmetric catalyst for α-aminoxylation[65] of carbonyl compounds. When an aldehyde **4** without substitution at α-position was reacted with nitrosobenzene **5** in presence of L-proline in DMSO at ambient temperature, aminoxylation of the aldehyde takes place at the α-position. Aldehyde can be reduced *in situ* with sodium borohydride and the aminoxyl moiety undergoes hydrogenolysis with Pd/C, H_2 or $CuSO_4$ to give the corresponding diols **7** in very high enantioselectivities (Scheme **7**).



Scheme 7. *Reaction and reagents*: (a) (i) S-proline (20 mol%), DMSO, 25 °C; (ii) $NaBH_4$, MeOH; (b) Pd/C, H_2 or 30 mol% $CuSO_4$. R = Ph, *i*-Pr, *n*-Bu, CH_2Ph etc. > 99% ee

The mechanism of the α-aminoxylation reaction is shown in figure **8**. The observed enantioselectivitiy of the catalytic α-aminoxylation of aldehydes can be rationalized by

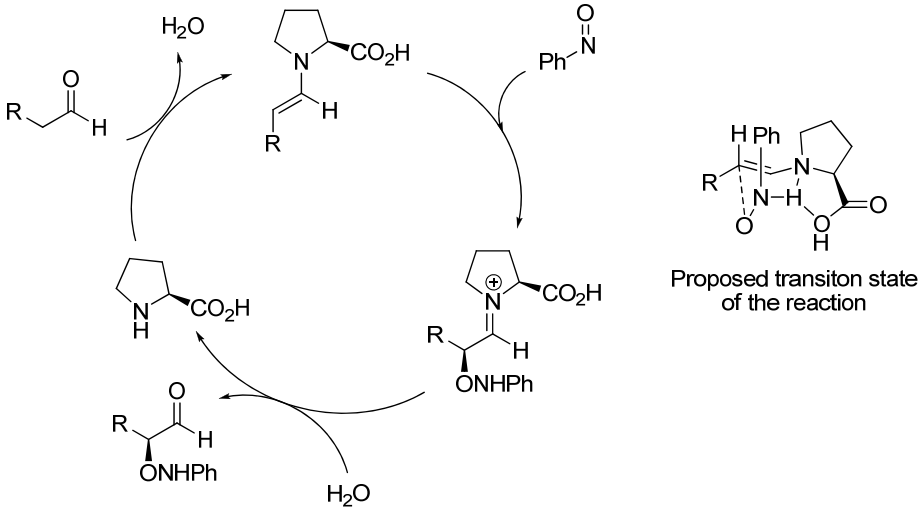


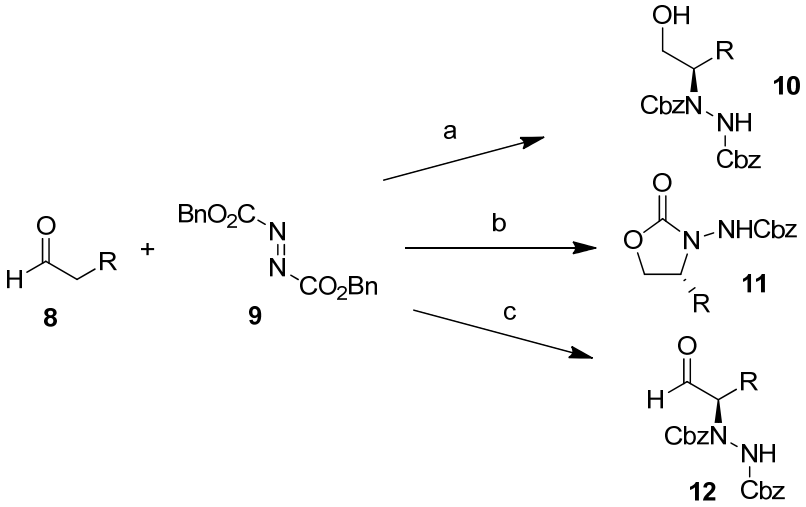
Figure 8. Proposed mechanism of the α-aminoxylation reaction

invoking an enamine mechanism operating through a chair transition state where the *Si* face of an α-enamine formed from the aldehyde and L-proline approaches the less hindered oxygen atom of nitrosobenzene to provide a chiral α-aminoxyaldehyde with *R* configuration. Since proline is commercially available in both enantiopure forms, a one pot sequential catalytic α-aminoxylation of aldehydes followed by *in situ* reduction with $NaBH_4$ affords *R*- or *S*- configured 1,2-diol units (the secondary alcohol "protected" by an *O*-amino group) with excellent enantioselectivities and in good yields.

1.3.4. Proline-catalyzed α-amination

The importance of optically active α-amino acids, α-amino aldehydes, and α-amino alcohols, formed by asymmetric catalysis, has stimulated an enormous development in synthetic strategies, and two different catalytic, enantioselective approaches are attractive: the *C-C* and the *C-N* bond-forming reactions.

Asymmetric α-amination[66] of aldehydes using proline-catalyzed reactions represent a direct approach synthesizing chiral building blocks such as α-amino acids, α-amino aldehydes, and α-amino alcohols. The use of organocatalysis, in particular proline represents a drastic change in approach to asymmetric α-amination. Recently, both List[66a] and Jørgensen[66b] disclosed the asymmetric α-amination of aldehydes (Scheme **8**) using catalytic quantities of proline.



Scheme 8.*Reactions and conditions*: (a) L-proline (10 mol%), CH_3CN, 0 °C, 3 h; $NaBH_4$, EtOH; (b) L-proline (10 mol%), CH_2Cl_2, 25 °C; $NaBH_4$, MeOH; 0.5 N NaOH; (c) L-proline (10 mol%), CH_2Cl_2, 25 °C; H_2O.

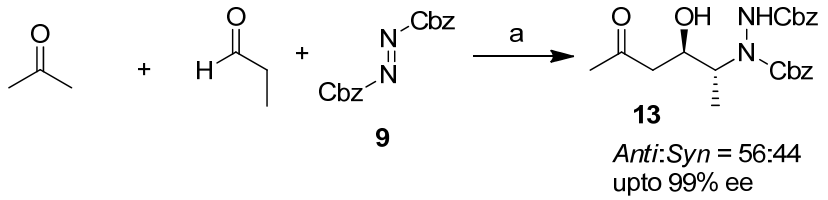
While both transition structures lead to identical products directed by the hydrogen bond from the carboxylic acid of proline, they presumably possess unique energies, so one transition state should be favored. However, the operative transition state has yet to be established.

1.3.5. Proline-catalyzed sequential transformations

Proline-catalyzed sequential transformations,[69] is a emerging research field in organic synthesis as synthesis of complex organic molecules could be accessible in one-pot procedure. Recently a variety of such transformations has been developed by different research groups, some of them are described below.

Sequential amination-aldol[69a]

Barbas III *et al*. have developed a one-pot protocol for the synthesis of functionalized β-amino alcohols **30** from aldehydes, ketones and azodicarboxylates (Scheme **9**).



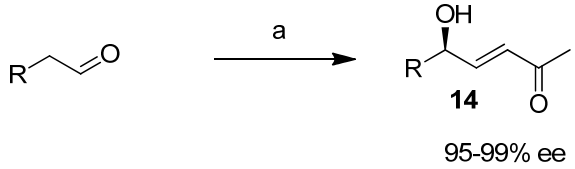
Scheme 9. *Reactions and conditions*: (a) L-proline (20 mol%), CH_3CN, rt, 72 h, 80%.

Sequential aminoxylation-olefination[69b]

Zhong *et al*. have reported sequential asymmetric α-aminoxylation/Wadsworth-Emmons-

Horner olefination of aldehydes for the synthesis of optically active *O*-amino-substituted

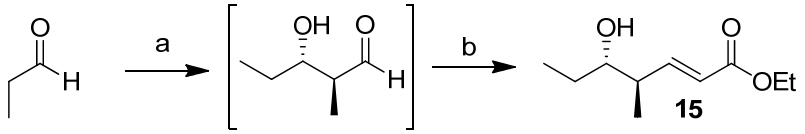
allylic alcohols **14** in good enantioselectivities using cesium carbonate as base (Scheme **10**).



Scheme 10. *Reactions and conditions*: (a) L-proline (20 mol%), nitrosobenzene (1.0 equiv.), DMSO, rt, 10-20 min then diethyl(2-oxopropyl)phosphonate, cesium carbonate (1.5 equiv.).

Sequential aldol-olefination[69c]

Cordova *et al*. have reported one-pot organocatalytic asymmetric tandem cross-aldol/Horner-Wittig-Emmons olefination for the synthesis of polyketide and carbohydrate
derivatives (Scheme **11**).



15

2.3 : 1

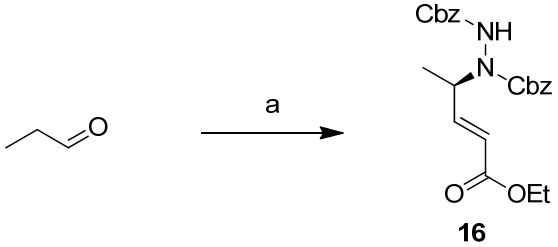
93% ee

Scheme 11. *Reactions and conditions*: (a) L-proline (10 mol%), DMF; (b) Diethyl(2-oxopropyl)phosphonate, cesium carbonate (1.5 equiv.).

Apart from this transformation, Cordova *et al*. have also reported tandem Mannich olefination reaction.[69c]

Sequential α-amination-olefination[69e]

Sudalai *et al*. have reported sequential asymmetric α-amination/Wadsworth-Emmons-Horner olefination of aldehydes for the synthesis of optically active allylic amine in good enantioselectivities and yields (Scheme **12**).



16

95-99% ee

Scheme 12. *Reactions and conditions*: (a) L-proline (20 mol%), DBAD (1.0 equiv.), CH_3CN, rt, 10-20 min then diethyl(2-oxopropyl)phosphonate, cesium carbonate (1.5 equiv.).

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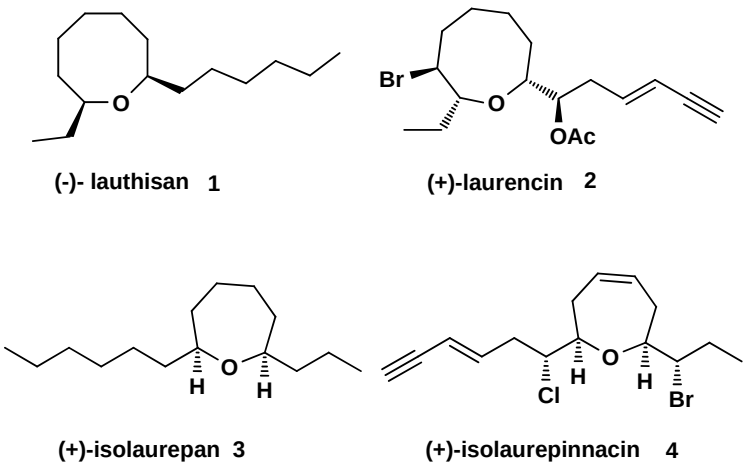
Chapter2
Asymmetric synthesis of medium sized ring ethers lauthisan and isolaurepan

TOTAL SYNTHESIS OF LAUTHISAN AND ISOLAUREPAN

2.1. Introduction

Red algae of the genus *Laurencia* are unique in terms of producing C_{15} acetogenins along with many other biologically active marine natural products, particularly medium-ring ethers. Medium sized ring ethers may bear an enyne or allenic side chain moiety and halogen groups. Most of these compounds possess alkyl substituents with *cis* or *trans* orientations at the α and ω positions on the cyclic ethereal skeleton. Many compounds of this class contain an eight-membered oxocane or oxocene ring usually with cis stereochemistry in the alkyl substituents at C-2 and C-8. Among them, (-)-lauthisan **1**, (Figure 1) isolated from a sample of sea alga *Laurencia obtuse* is a fully saturated core of the natural derivative (+)-laurencin **2**, and has often been used as a target to check the validity of a particular synthetic methodology for efficient oxocane construction. (+)-Laurencin **2**, isolated from the extracts of *Laurencia glandulifera* by Irie and Masamune in 1965,[1] is a representative example that has been the subject of significant synthetic efforts within the past decade.[2] The difficulty of the eight-membered ring construction from acyclic precursors, due to entropy factors and developing transannular repulsions as the ring is formed, is well-known.[2c,d] Several strategies have been employed for the stereoselective preparation of racemic[3] and enantioriched[4] *cis*-lauthisan, most of them require multistep synthesis or take place with moderate *cis*-selectivities. Thus, the development of efficient and stereoselective approaches to cis-2,8-disubstituted oxocenes and oxocanes has been an important challenge to synthetic organic chemists. (+)-Isolaurepan **3** (Figure **1**), a representative members of the *Laurencia*-derived C15 acetogenins containing an α,α'-cis-disubstituted oxepane ring is a fully saturated analogue of the core of (+)-isolaurepinnacin **4** and other chiral oxepane derivatives.[5] Kotsuki *et al.* reported the first total synthesis of (+)-isolaurepan via *cis* selective reduction mediated by triethylsilane/$TiCl_4$.[6] A few more groups have described its formal synthesis by different approaches.[7] Although there have been a number of reports on the stereoselective construction of racemic *cis*-2,7-disubstituted oxepanes, literature describing synthetic strategies for its non racemic derivatives is rather scarce. Therefore, a general strategy for the enantioselective synthesis of functionalised

medium ring ether skeleton present in many *Laurencia* non-terpenoid metabolites is highly desirable.



(-)- lauthisan **1** (+)-laurencin **2**

(+)-isolaurepan **3** (+)-isolaurepinnacin **4**

Figure 1

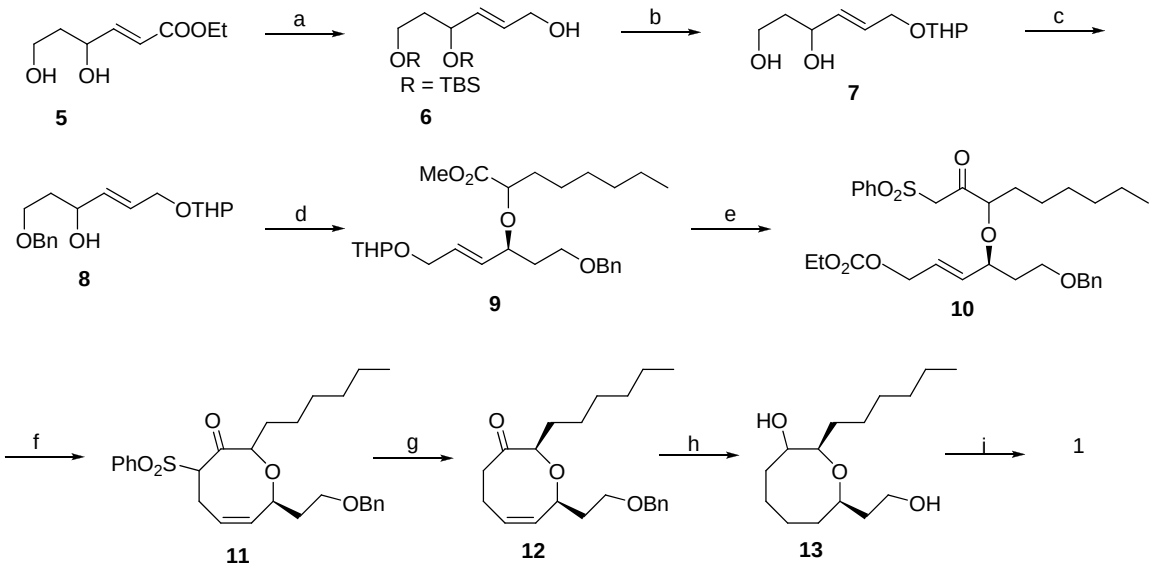
2. 2. Review of Literature

The syntheses of ring ethers have been achieved through a wide range of methods that have been recently reviewed.[8] One of them, the trimethylsilyl triflate catalyzed synthesis of ethers by reductive condensation of carbonyl compounds and alkoxysilanes originally reported by Olah,[9] was later modified by Nicolaou[10] and applied to the intramolecular preparation of cis-2,7-disubstituted oxepane rings from hydroxy ketones. Although this approach to cyclic ethers is stereoselective and high-yielding method, it has been scarcely used in the asymmetric synthesis of tetrahydrofuran and tetrahydropyran derivatives,[11] despite the accessibility of γ- or δ-hydroxyketones necessary as starting materials.

Suh *et al*.[12] (1995)

Suh *et al*. employed chiral allylic carbonate **10**, as a cyclization precursor, which was derived from the conjugated ester **5** as outlined in scheme **1**. The dihydroxy conjugated ester **5** was protected with TBS and reduced to allylic alcohol **6**. THP protection of allylic alcohol **6** followed by desilylation furnished diol **7** which on selective monobenzylation of primary alcohol afforded alcohol **8**. Transformation of alcohol **8** into the cyclization precursor **10** was achieved by sequential O-alkylation of alcohol **8** followed by esterification, conversion of ester **9** to benzenesulfonyl methyl ketone and then allylic carbonate. Regioselective cyclization of allylic carbonate **10** was carried

out with 10 mol % of $Pd(dppe)_2$ catalyst to give **11**. Desulfonation followed by reduction of keto group to alcohol led to compound **13**. Finally removal of hydroxyl group afforded lauthisan **1**.

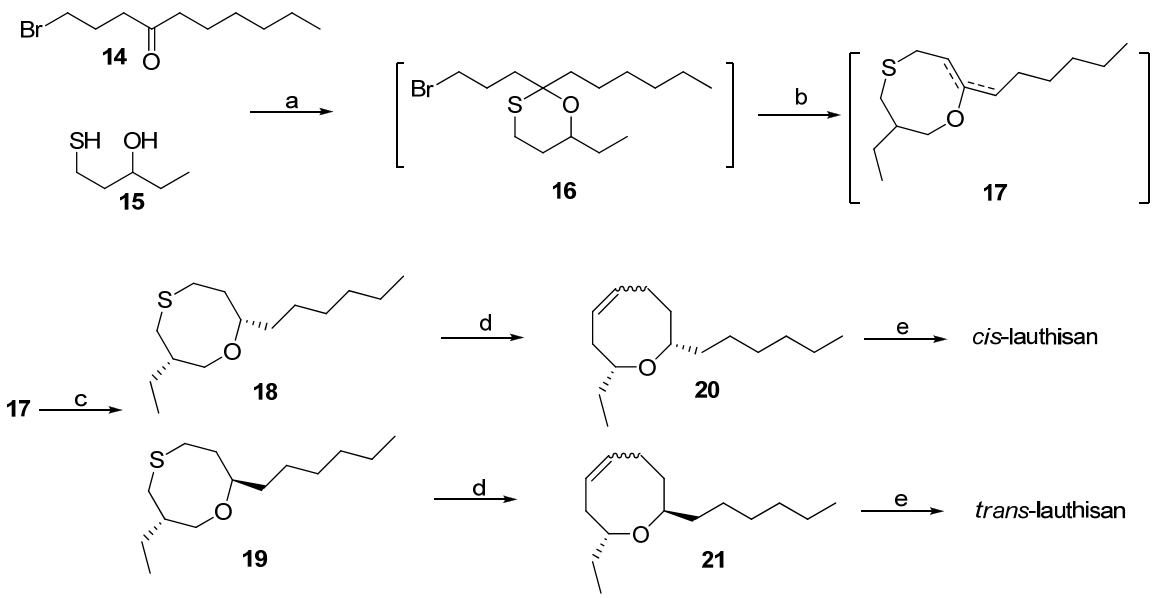


Scheme 1. *Reagents and conditions*: (a) (i) TBSCl, imidazole, DMF, 78% (ii) DIBAL-H, CH_2Cl_2, 86% (b) (i) DHP, PPTS, CH_2Cl_2 (ii) n-Bu_4NF, THF (c) BnBr NaH, n-Bu_4NI, THF, 89% (d) (i) NaH, 2-bromooctanoic acid, THF (ii) MeOH, DCC, DMAP, CH_2Cl_2, 72% (e) (i) $PhSO_2CH_2Li$, THF, 70% (ii) PPTS, EtOH. (iii) $ClCO_2Et$, Pyridine, benzene, 96% (f) 10 mol % of $Pd(dppe)_2$, DMSO, 70% (g) (i) Chromatography(EtOAc: *n*-Hexane = l:5) (ii) 6% Na-Hg, AcOH (iii) K_2CO_3, MeOH, 65% (h) (i) $NaBH_4$, MeOH ii) 5% Pd/C, H_2, EtOH, 95% (i) (i) DMAP, ClC(S)OPh, CH_3CN (ii) n-Bu_3SnH, AIBN, benzene, 71%.

Voss *et al*.[13] (2002)

Voss *et al*. investigated a one-pot procedure for the in situ ring expansion of bromo oxathiane **16** (scheme **2**). Thus, treatment of **14** and **15** with $BF_3.OEt_2$ gave the ring-expanded enol ether **17** in situ. Reduction of enol ether **17** with $NaBH_3CN$ led to the corresponding saturated ethers as mixture (2.3:1) of **18** and **19** in 49% yield, which were readily separated by column chromatography. The relative stereochemistry of **18**

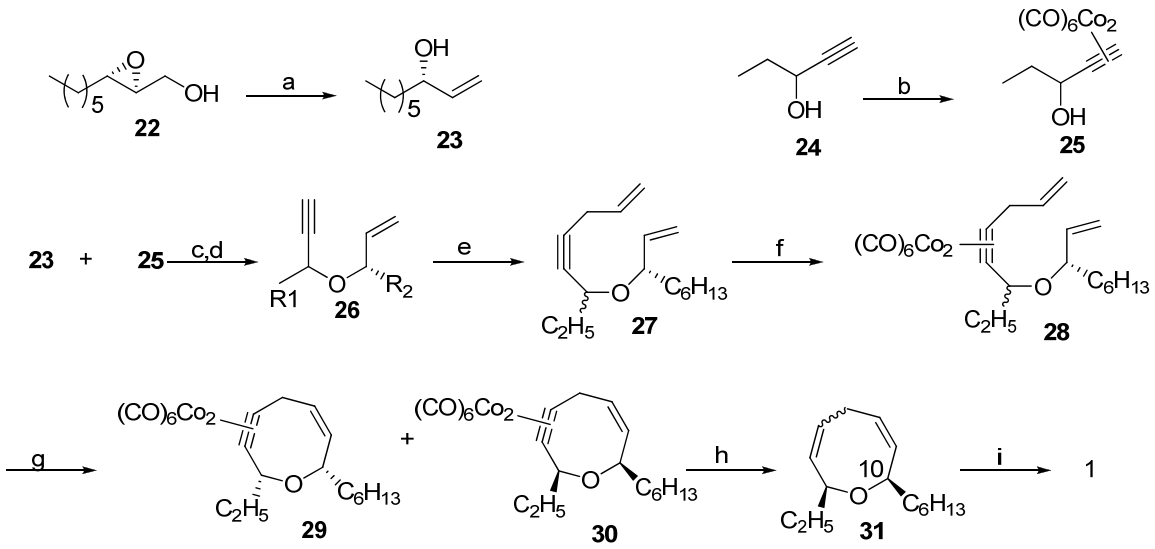
and **19** was assigned after separate conversion of these compounds to the corresponding lauthisan and comparison with literature spectroscopic data.



Scheme 2. *Reagents and conditions*: (a) $BF_3.OEt_2$, 3 Å molecular sieves, CH_2Cl_2, 2 h. then Et_3N, 1 h. (b) $NaBH_3CN$, TFA, THF, 15 min. (c) NCS, CCl_4, 4-6 h. (d) *m*-CPBA, CH_2Cl_2, 16 h. (e) *t*-BuOK, THF, 4-16 h. (f) H_2, Pd/C, THF, 1-3 h.

Ortega *et al*.[14] (2006)

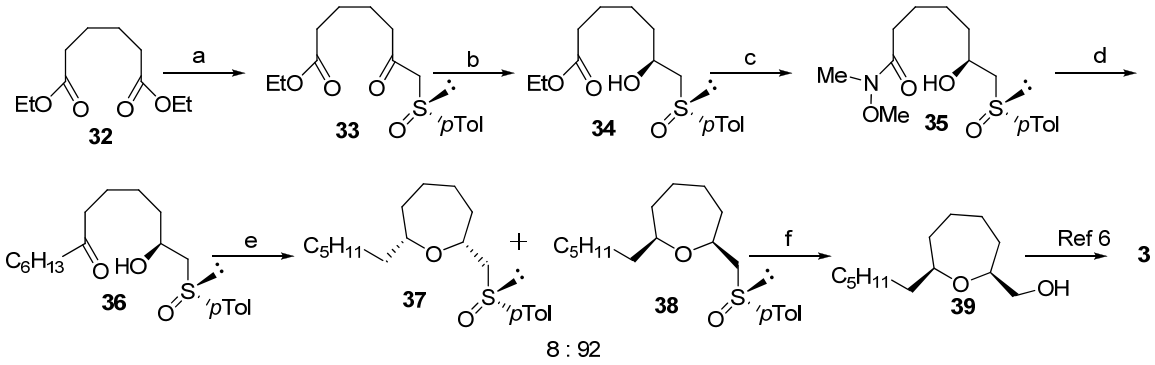
Ortega *et al*. prepared *cis*-2,8-disubstituted oxocanes (scheme **3**) and the parent unsaturated precursors from the corresponding $Co_2(CO)_6$-cycloalkynic ethers. The synthesis of ether **26** was brought about by intermolecular Nicholas reaction of alcohols **23** and **25**. Copper-catalyzed homologation of **26** with allylbromide provided the dienyl derivative **27** in excellent yield. To avoid the participation of the triple bond in the metathesis process, **27** was subjected to $Co_2(CO)_8$ to afford the cobalt complex **28** in quantitative yield. RCM of **28** with Grubbs' second generation catalyst yielded both diastereomers **29** and **30**. Reductive cleavage of $Co_2(CO)_6$-cycloalkynic ethers furnished **31** which on hydrogenation afforded lauthisan **1**.



Scheme 3. *Reagents and conditions*: (a) Cp_2TiCl_2, $ZnCl_2$, Zn, THF, 64%. (b) $Co(CO)_8$, CH_2Cl_2, 95%. (c) $BF_3.OEt_2$, CH_2Cl_2, 0 °C. (d) CAN, acetone, 0 °C, 63%. (e) TBAB, CH_2=$CHCH_2Br$, Cu_2I_2, K_2CO_3, DMF, rt, 94%. (f) $Co(CO)_8$, CH_2Cl_2, rt, 95%. (g) Grubbs II, CH_2Cl_2, 35 °C, 83%. (h) *n*-Bu_3SnH, Benzene, 60 °C, 94%. (i) H_2, Pd(C), EtOAc, 87%.

Carreno *et al*.[7a] (2004)

Carreno *et al*. employed highly diastereoselective Et_3SiH/TMSOTf-promoted reductive cyclization of enantiopure hydroxyl sulfinyl alkyl ketone (scheme **4**). Commercially available diester diethyl pimelate **32** was converted to *β*-keto sulfoxide **33** which on stereoselective reduction of the ketone using DIBAL-H in the presence of $ZnBr_2$ afforded *β*-hydroxy sulfoxide **34** (de >98%). Sulfoxide **34** was then converted into Weinreb's amide **35** to introduce the aliphatic *n*-hexyl chain in compound **36**. The reductive cyclization of **36** using Et_3SiH/TMSOTf afforded 8:92 diastereomeric ratio of the *cis* cyclic ethers **37** and **38**. The major isomer **38** was subjected to Pummerer conditions to yield free hydroxyl compound which was converted into isolaurepan **3**.[6]



Scheme 4. *Reagents and conditions*: (a) methyl-*p*-tolylsulfoxide, LDA, THF, -78 °C, 79%. (b) DIBAL-H, THF, -78 °C, 1 h, 88%. (c) *N*-methyl methylhydroxylamine, $AlMe_3$, DCM, 86%. (d) *n*-HexMgBr, THF, 50 °C, 1 h, 78%. (e) Et_3SiH, TMSOTf, CH_2Cl_2, 0 ^oC, 1 h, 85%. (f) (i) TFAA, 2,4,6-collidine, CH_3CN, 0 ^oC, 10 min. (ii) K_2CO_3, H_2O, rt, 30 min. (iii) $NaBH_4$, rt, 1.5 h, 79%.

2.3. PRESENT WORK

Objective

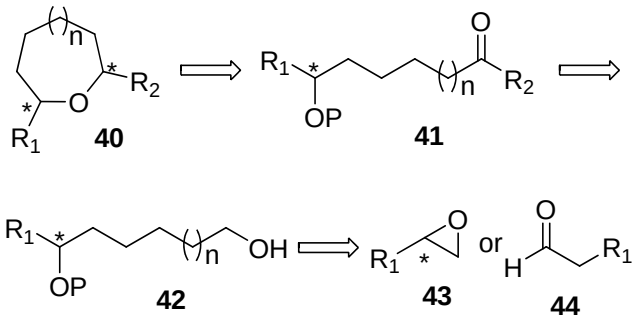
Polyfunctionalized medium sized cyclic ethers have attracted much attention from synthetic and medicinal chemists due to a wide range of biologically active natural products, including ladder marine toxins, lauroxanes, antibiotic etc.[15] These units can be found in monocyclic and polycyclic structures, fused with carbocyclic or other cyclic ethers, or as spiroketals. These ethers constitute important structural features present in a number of biologically active marine natural products, particularly from *Laurencia* red algae.[16] Many compounds of this class contain a seven or eight-membered cyclic ether ring usually with *cis* stereochemistry in the alkyl substituents.

In view of the increasing number of biologically active marine natural products containing medium and large sized cyclic ether derivatives, much attention has been focused on efficient approaches towards these systems. However, their synthesis is generally difficult *via* standard cyclization methodologies.[17] Nevertheless, the challenge in their efficient construction has led to the development of several strategies for their synthesis,[18] mainly in racemic form. Thus a general strategy for these ethers is highly desirable. A general route to *cis*-disubstituted cyclic ether-based molecules and its application to the synthesis of (-)-*cis*-lauthisan **1** and (+)-isolaurepan **3** using HKR, hydrolytic kinetic resolution of epoxides, oxidative kinetic resolution of secondary alcohol and *cis*-selective reduction with triethylsilane as the key steps has been described.

2.4. Results and Discussion

In connection with a program devoted to asymmetric synthesis of biologically active compounds we became interested in the preparation of enantiomerically pure 2,7 and 2,8-disubstituted medium sized ring ether derivatives. The key reaction in our synthesis was the kinetic resolution to obtain the first stereocentre and reductive cyclization of the corresponding enantiopure hydroxy ketones to obtain the second stereocentre. Our retrosynthetic approach for the synthesis of *cis*-disubstituted cyclic ether-based molecule **40** was envisioned *via* the synthetic route as shown in scheme **5**. The hydroxy-keto derivative **41** was visualized as a synthetic intermediate from which (-)-*cis*-lauthisan **1** and (+)-isolaurepan **3** could be synthesized. The hydroxy-keto

derivative **41** could be obtained from the alcohol **42** which in turn could be easily synthesized from the enantiomerically pure terminal epoxide **43** or aldehyde **44**.



Scheme 5. Retrosynthetic route to medium-sized ring ethers.

Synthesis of (-)-*cis*-lauthisan

The synthesis of (-)-*cis*-lauthisan **1** started from racemic epoxide **45**, which was subjected to Jacobsen's HKR by using (*R,R*)-Salen-Co^{III}OAc catalyst (Figure **2a**) to give chiral epoxide (*R*)-**45** along with chiral (*S*)-diol **46** as single isomer (scheme **6**).[19] ^{1}H NMR spectrum of (*R*)-**45** showed epoxide protons at δ 2.92-2.44 (multiplet, 1 H), 2.77 (doublet of doublet, 1 H, with coupling constant *J* = 4.9, 1.2 Hz) and 2.44 (doublet of doublet, with coupling constant *J* = 4.9, 2.4 Hz). The ^{13}C NMR spectrum of (*R*)-**45** showed upfield carbons characteristic of epoxide at δ 52.3 and 47.1. The chiral epoxide (*R*)-**45** was easily isolated from the more polar chiral diol **46** by silica gel column chromatography.

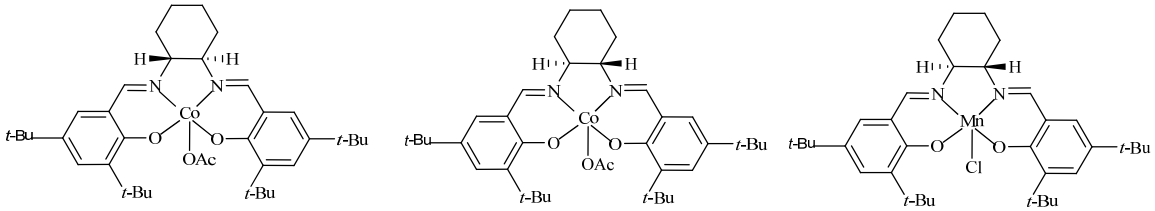
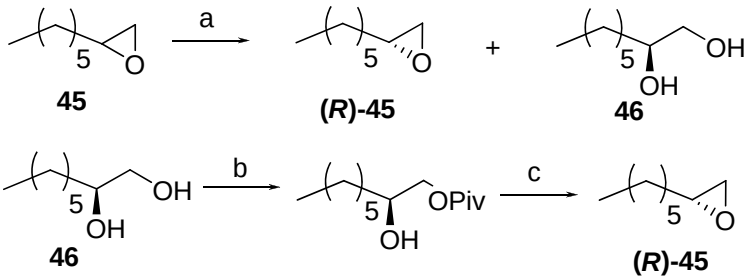


Figure 2

We thought it would be appropriate to convert diol **46** into the required epoxide (*R*)-**45** by means of an internal nucleophilic substitution of a secondary mesylate. Accordingly, the chemoselective pivalation of diol **46** with pivaloyl chloride, followed by mesylation of the secondary hydroxyl and treatment of the crude mesylate product with K_2CO_3 in methanol led to the deprotection of the pivaloyl ester. Concomitant ring

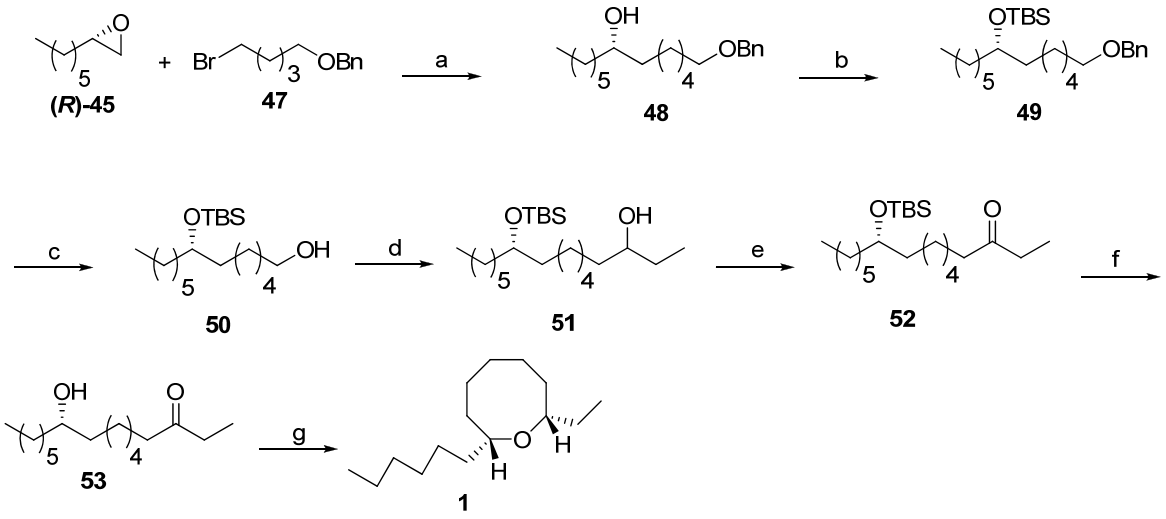
closure by intramolecular S_N2 displacement of the mesylate furnished the epoxide (*R*)-**45** in 61% overall yield (scheme **6**).



Scheme 6. *Reagents and conditions:* (a) (*R,R*)-Salen-Co-(OAc) (0.5 mol%), dist. H_2O (0.55 equiv), 0 ^oC, 14 h, 45% for **(*R*)-45**, 43% for **46**; (b) i) PivCl, Et_3N, cat. DMAP, rt, 2 h; ii) MsCl, Et_3N, DMAP, 0 ^oC to rt, 1 h; c) K_2CO_3, MeOH, rt, overnight (61% for three steps).

With enantiomerically pure epoxide **(*R*)-45** in hand, we subjected it to copper-catalyzed (CuI) regioselective opening with the Grignard reagent, derived from benzyl protected bromopentanol **47** and Mg in THF at -78 ^oC to furnish the alcohol **48** in 72% yield (scheme **7**). The IR spectrum of **48** showed broad hydroxyl absorption at 3426 cm^{-1}. Silyl protection of the newly generated secondary alcohol **48** with *tert*-butyldimethylsilyl chloride in presence of 2,6-lutidine and catalytic amount of DMAP afforded **49** in 94% yield. The IR spectra of **49** showed absence of hydroxyl absorption. Subsequently the terminal benzyl group was deprotected using 20% $Pd(OH)_2/H_2$ which led to alcohol **50** in excellent yield. The IR spectrum of **50** showed broad hydroxyl absorption at 3440 cm^{-1} The alcohol **50** was then subjected to Swern oxidation[20] to give aldehyde followed by Grignard reaction with EtMgBr in dry THF at 0 ^oC to furnish compound **51** in 87% yield. Oxidation of free hydroxyl group **51** with IBX (**51**→**52**) afforded ketone **52.** The IR spectra of **52** showed absence of hydroxyl absorption. Instead, a characteristic absorbtion peak of ketone is seen at 1710 cm^{-1}. ^{13}C NMR showed carbonyl peak at δ 211.9. Silyl deprotection of **52** was carried out by its treatment with *p*-TSA in methanol to afford the keto-hydroxy precursor **53** in excellent yield. In order to generate *cis*-disubstituted cyclic ether, **53** was treated with Et_3SiH and TMSOTf in the next step which promoted reductive cyclization to give exclusively the *cis*-disubstituted cyclic 8-membered ether, (-)-lauthisan **1** as the target compound in

42% yield. The physical and spectroscopic data of **1** were identical with those reported in the literature.[21]

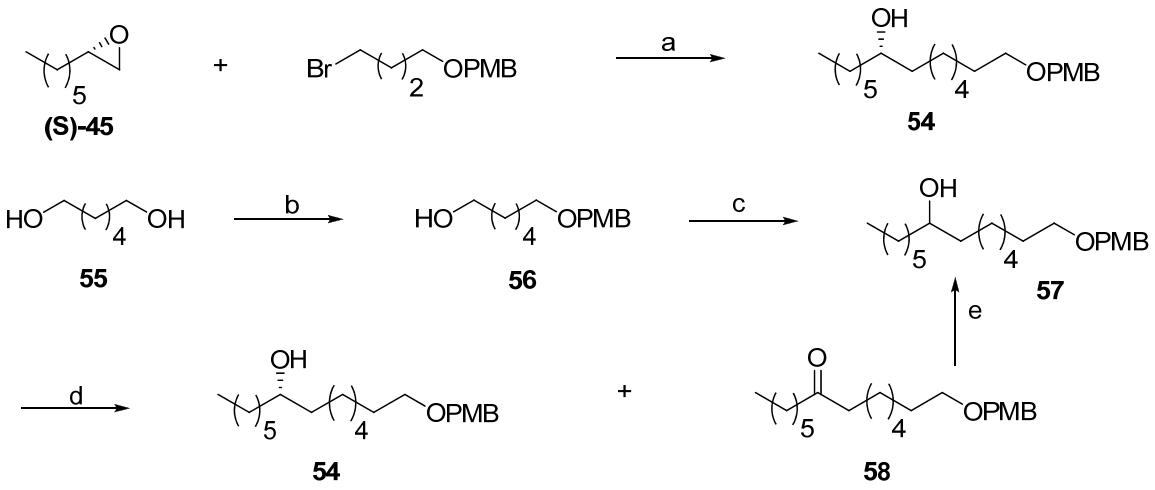


Scheme 7. *Reagents and conditions*: (a) $C_6H_5CH_2O$-$(CH_2)_5MgBr$, CuI, THF, -78 ^oC, 2 h, 72%. (b) TBSCl, 2,6-lutidine, cat. DMAP, dry CH_2Cl_2, 8 h, 0 ^oC, 94%. (c) 20% $Pd(OH)_2/H_2$, EtOAc , 1 atm, 12 h, 89%. (d) (i) $(COCl)_2$, DMSO, Et_3N, dry CH_2Cl_2, -78 ^oC, 2 h. (ii) *n*-C_2H_5MgBr, THF, 0 °C to rt, 1 h, 87%. (e) IBX, EtOAc, 80 ^oC, 90%. (f) *p*-TSA, MeOH, rt, 30 min; 96%. (g) Et_3SiH, TMSOTf, CH_2Cl_2, 0 ^oC, 1 h, 42%.

Synthesis of (+)-isolaurepan

Our synthetic strategy for the synthesis of (+)-isolaurepan **3** is shown in scheme **8**. The synthesis started from chiral epoxide (*S*)-**45** prepared from Jacobsen's hydrolytic kinetic resolution (HKR) of the racemic epoxide **45** by using (*S,S*)-Salen-Co^{III}Ac complex (Figure **2b**). The ^1H NMR spectrum of (*S*)-**45** showed epoxide protons at δ 2.92-2.44 (multiplet, 1 H), 2.77 (doublet of doublet, 1 H, with coupling constant J = 4.9, 1.2 Hz) and 2.47 (doublet of doublet, with coupling constant J = 4.9, 2.4 Hz). The ^{13}C NMR spectrum of (*S*)-**45** showed upfield carbons characteristic of epoxide at δ 52.3 and 47.0. The copper catalyzed (CuI) regioselective opening of chiral epoxide (*S*)-**45** with Grignard reagent derived from *p*-methoxybenzyl protected bromobutanol and Mg in THF gave rise to the required alcohol fragment (*S*)-**54**, albeit in low yield (30%). The IR spectrum of (*S*)-**54** showed broad hydroxyl absorption at 3426 cm^{-1}. Prompted by low yield, we thought it appropriate to find another suitable route to this fragment with an improved yield. Thus, the synthesis of this fragment commenced with

commercially available 1,6-hexanediol **55** as illustrated in scheme **8**. Thus selective mono hydroxyl protection of **55** with *p*-methoxybenzyl bromide in the presence of NaH gave the monoprotected diol **56** in 85% yield. The ^{1}H NMR spectrum of **56** showed benzylic protons at δ 4.46 (singlet, 2 H) and aromatic protons at δ 7.29 (doublet) and 6.89 (doublet) with coupling constant J = 8.8 Hz. This was then oxidized to the corresponding aldehyde under Swern conditions and subsequently treated with the Grignard reagent derived from 1-bromohexane and Mg in THF at 0 ^{o}C to furnish the racemic alcohol **57** in 91% yield. The IR spectrum of **57** showed broad hydroxyl absorption at 3426 cm^{-1}.



Scheme 8. *Reagents and conditions*: a) *p*-$CH_3OC_6H_4.CH_2O(CH_2)_4MgBr$, CuI, THF, -38 ^{o}C, 2 h, 30%. (b) *p*-$CH_3OC_6H_4CH_2Br$, NaH, dry DMF, cat. TBAI, 0 °C to rt, 1 h, 85%. (c) (i) $(COCl)_2$, DMSO, Et_3N, dry CH_2Cl_2, -78 ^{o}C, 2 h. (ii) *n*-$C_6H_{13}MgBr$, THF, 0°C to rt, 1 h, 91%. (d) (*S,S*)-Salen-Mn ^{III}(Cl) (0.02 eq), KBr (0.8 eq), $PhI(OAC)_2$ (0.7 eq), H_2O:CH_2Cl_2 2:1, rt, 30 min., 45% for **54** and 43% for **58**. (e) $NaBH_4$, MeOH, 4 h, 89%.

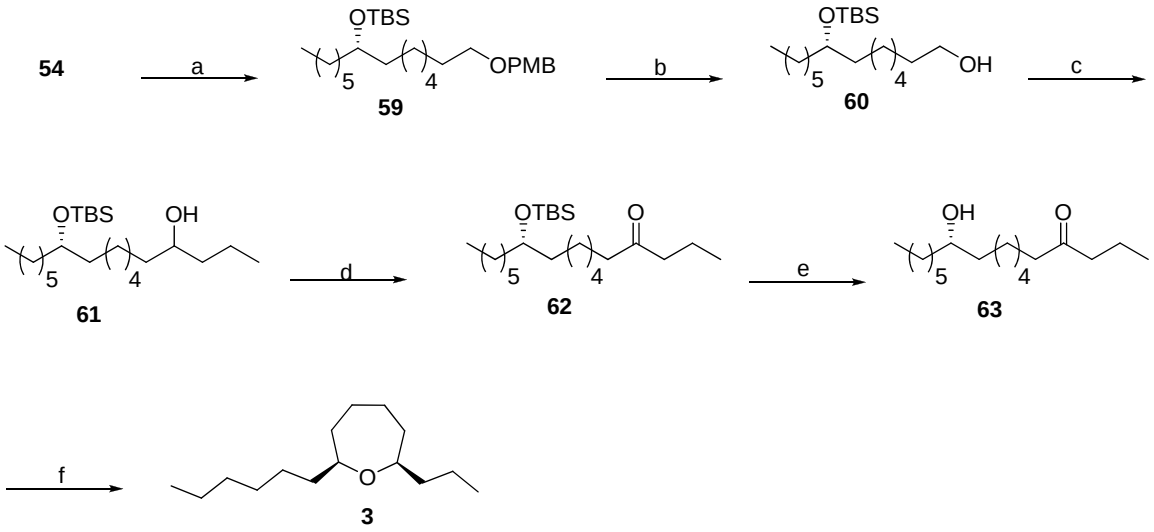
With substantial amounts of racemic alcohol **57** in hand, our next aim was to resolve this alcohol to obtain enantiomerically pure **54**. As illustrated in scheme **8**, the racemic alcohol **57** was subjected to oxidative resolution[22] using (*S,S*)-Salen $Mn^{III}Cl$ as catalyst (Figure **2c**) to give the required optically active alcohol **54** in 45% yield and 93% ee along with the oxidized compound **58** in 43% yield which was easily isolated from the polar alcohol **54** using silica gel chromatography. The IR spectra of **58** showed absence of hydroxyl absorption. The characteristic absorption peak of ketone is seen at 1710

cm^{-1}. ^{13}C NMR showed carbonyl peak at δ 210.8. Ketone **58** was recycled by conversion into the racemic alcohol **57** in 89% yield by reduction with $NaBH_4$ in MeOH.

As shown in scheme **9**, hydroxyl protection of **54** with *tert*-butyldimethylsilyl triflate in the presence of a catalytic amount of DMAP and 2,6-lutidine afforded the silyl ether **59** in 85% yield. The IR spectra of **59** showed absence of hydroxyl absorption. Subsequent *p*-methoxybenzyl deprotection of the primary alcohol was carried out with DDQ in DCM: H_2O (18:1) to give the required alcohol **60** in 94% yield. The IR spectrum of **60** showed broad hydroxyl absorption at 3430 cm^{-1}.

Alcohol **60** was oxidized to the aldehyde by Swern oxidation followed by Grignard reaction with 1-bromopropane and Mg in THF at 0 ^oC to give the desired compound **61** in 62% yield. The newly formed secondary alcohol was oxidized using IBX to give ketone **62.** The IR spectra of **62** showed absence of hydroxyl absorption. The characteristic absorption peak of ketone is seen at 1710 cm^{-1}. ^{13}C NMR showed carbonyl peak at δ 211.4. Ketone **62** on treatment with *p*-TSA in methanol afforded the required deprotected hydroxy-keto precursor **63**. The IR spectrum of **63** showed broad hydroxyl absorption at 3420 cm^{-1}.

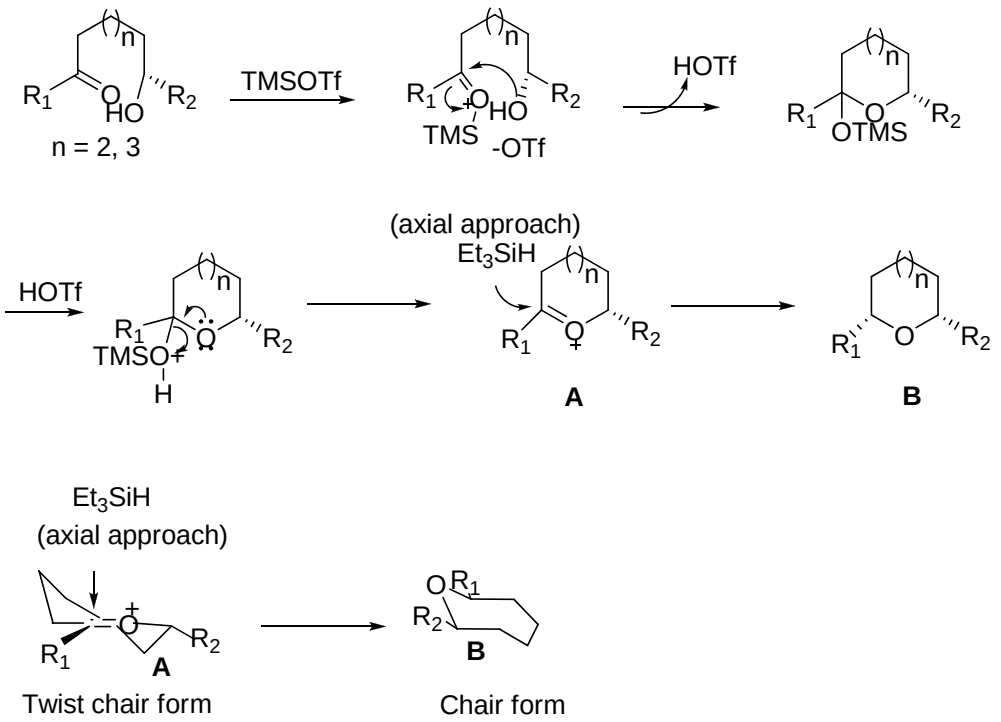
In order to generate the *cis*-disubstituted cyclic ether, ketone **63** was treated with Et_3SiH and TMSOTf which promoted reductive cyclization to give exclusively, the *cis* disubstituted cyclic 7-membered ether, (+)-isolaurepan **3** in 84% yield. The configuration of the newly generated centres in **3** can be deduced by ^1H-NMR and NOE experiments.[23] The physical and spectroscopic data of **3** were identical with those reported in the literature.[23]



Scheme 9. *Reagents and conditions*: (a) TBS-OTf, 2,6-lutidine, cat. DMAP, dry CH_2Cl_2, 3 h, 0 ^oC, 85%. (b) DDQ, CH_2Cl_2/H_2O (18:1), rt, 1 h, 94%. (c) (i) $(COCl)_2$, DMSO, Et_3N, dry CH_2Cl_2, -78 ^oC, 2 h, 90%. (ii) *n*-C_3H_7MgBr, THF, 0°C to rt, 1 h, 62%. (d) IBX, EtOAc, 80 ^oC; 92%. (e) *p*-TSA, MeOH, rt, 30 min. (f) Et_3SiH, TMSOTf, CH_2Cl_2, 0 ^oC, 1 h, 84%.

Mechanistic and Stereochemical pathway for the reductive cyclization process

A general possible mechanistic pathway explaining the formation of major *cis* diastereomer in the cyclization step is shown in scheme **10**. Activation of carbonyl group of the hydroxyl-ketone by TMSOTf favors the intramolecular nucleophilic addition of hydroxyl group which eventually leads to the carboxonium intermediate **A** through an acetal precursor. The axial approach of Et_3SiH[24] to **A**, a seven membered twist-chair-like transition state, affording *cis* diastereomer **B**, is certainly favoured because of the higher stability of the resulting chair like transition state. Similar reasons could explain the major formation of the *cis* isomer in case of eight-membered cyclic ether (-)-lauthisan **1**



Scheme 10. pathway for the reductive cyclization process

2.5. Conclusion

In summary, we have developed a new and short approach to *cis*-disubstituted oxepanes in high enantiomeric excess using Jacobsen Co and Mn and (*R,R*)- and (*S,S*)-based Salen catalysts. The *R* and *S* configurations of the *cis* ring can be manipulated simply by changing the catalyst in the resolution step. The reductive cyclization of hydroxysulfinyl ketones is a short and efficient protocol to enantiopure tetrahydrofuran and tetrahydropyran derivatives. High yielding reaction steps have been employed. The synthetic strategy described here has significant potential for stereochemical variations and further extension to other stereoisomers and analogues.

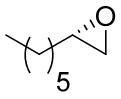
2.6. Experimental Section

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. 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 CHNSO analyzer.

2-Hexyloxirane ((*R*)-45)



The racemic 2-hexyloxirane **45** was resolved to (*R*)-2-hexyloxirane (***R***)-**45** in high enantiomeric excess by the HKR method following a literature procedure.[19]

Yield: 4.82 g, 45%

Mol. Formula: $C_8H_{16}O$

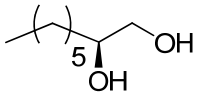
$[\alpha]_D^{25}$ +13.46 (neat); lit.[19] $[\alpha]_D^{24}$ +14.0 (neat)

IR ($CHCl_3$, cm^{-1}) ν_{max} = 3018, 2952, 2929, 2862, 1472, 1466, 1379,1260, 1022, 916, 828.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.8 Hz, 3H), 1.26-1.51 (m, 10H), 2.44-2.48 (m, 1H), 2.72-2.77 (m, 1H), 2.87-2.93 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.9, 22.5, 25.9, 29.1, 31.7, 32.5, 47.1, 52.3.

(*S*)-Octane-1,2-diol (46)



Yield: 4.61 g, 43%

Mol. Formula: $C_8H_{18}O_2$

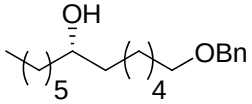
$[\alpha]_D^{25}$ -15.9 (*c* 1.67, EtOH)

IR ($CHCl_3$, cm^{-1}) ν_{max} = 3391, 2957, 2932, 2861, 1466, 1216, 1069, 869

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.69-3.65 (m, 2H), 3.46-3.40 (m, 1H), 2.97 (brs, 2H), 1.42-1.30 (m, 10H), 0.89 (t, J = 7 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 71.7, 63.5,45.7,31.7, 25.2, 22.5, 21.3,13.9

(*R*)-1-(Benzyloxy)tridecan-7-ol (48).



To a stirred solution of (***R***)-**45** (4.8 g, 37.38 mmol) and CuI (0.306 g, 3.73 mmol) in dry THF (30 mL), was added Grignard reagent prepared from benzyl protected bromopentanol (19.23 g, 74.76 mmol) and Mg-turning (2.72 g, 112.14 mmol) in dry THF, drop wise at -78 °C. The mixture was warmed to -78 °C over 2 h and poured into a saturated NH_4Cl solution. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined EtOAc extracts were dried over Na_2SO_4. The extracts were concentrated to near dryness and purified on silica gel column chromatography (EtOAc/petroleum ether, 1:9) to give **48** as colorless oil.

Yield: 8.26 g, 72%.

Mol. Formula: $C_{20}H_{34}O_2$

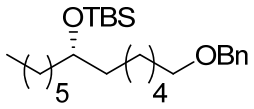
$[\alpha]_D^{25}$ +1.85 (*c* 1.08, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}) ν_{max} = 3426, 3011, 2857, 2930, 1712, 1454, 1364, 1277, 1216, 1099, 755 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 6.9 Hz, 3H), 1.29-1.43 (m, 16H), 1.61-1.63 (m, 4H), 3.47 (t, *J* = 6.9 Hz, 2H), 3.60-3.63 (m, 1H), 4.51 (s, 2H), 7.27-7.37 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0, 22.5, 25.5, 26.1, 29.3, 29.4, 29.6, 31.7, 70.4, 71.8, 72.8, 127.4, 127.5, 128.3, 138.5.

(*R*)-(1-(Benzyloxy)tridecan-7-yloxy)(*tert*-butyl)di-methylsilane (49).



Imidazole (1.59 g, 23.49 mmol) was added to a stirred solution of alcohol **48** (3.2 g, 10.44 mmol) in CH_2Cl_2 (25 mL). *tert*-butyl dimethylchlorosilane (2.04 g, 13.57 mmol) was then added to this solution at 0 ^oC, and reaction was stirred at room temperature for 8 h. After this time, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (3 x 30 mL). The organic extracts were washed with brine, dried (Na_2SO_4), and then concentrated. Silica-gel column chromatography of the crude product (petroleum ether/EtOAc 19:1) provided **49** as a colorless liquid.

Yield: 4.13 g, 94%

Mol. Formula: $C_{26}H_{48}O_2Si$

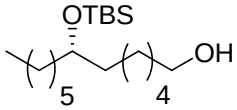
$[\alpha]_D^{25}$ +1.35 (*c* 0.92, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}) ν_{max} = 3018, 2932, 1463, 1361, 1255, 1215, 1092, 1028.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.04 (s, 6H), 0.88-0.92 (m, 12H), 1.27-1.49 (m, 20H), 3.60-3.63 (m, 1H), 3.65 (t, *J* = 6.5 Hz, 2H), 4.51 (s, 2H), 7.31-7.37 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = -4.4, 14.1, 18.1, 22.6, 25.3, 25.9, 26.2, 26.9, 29.5, 29.7, 31.9, 37.1, 70.5, 72.3, 72.8, 127.4, 127.6, 128.2, 138.6.

(*R*)-7-(*tert*-Butyldimethylsilyloxy)tridecan-1-ol (50).



Compound **49** (4 g) was dissolved in dry EtOAc (10 mL) and 20% $Pd(OH)_2$ (70 mg) was added carefully. The reaction mixture was stirred under an atmosphere of H_2 filled in a balloon for 12 h at room temperature. The mixture was filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc/pet ether (18:2) as eluent to give **50**.

Yield: 2.8 g, 89%.

Mol. Formula: $C_{19}H_{42}O_2Si$

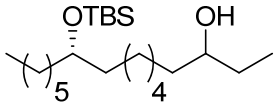
$[\alpha]_D^{25}$ +2.92 (*c* 1.02, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}) ν_{max} = 3440, 3018, 2931, 1471, 1361, 1255, 1215, 1049.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.04 (s, 6H), 0.85-0.92 (m, 12H), 1.27-1.49 (m, 20H), 3.65 (t, *J* = 6.5 Hz, 2H), 3.60 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = -5.4, -4.5, 14.0, 18.1, 22.6, 25.3, 25.6, 25.8, 25.9, 29.4, 31.8, 32.7, 37.1, 62.8, 72.3.

(9*R*)-9-(*tert*-Butyldimethylsilyloxy)pentadecan-3-ol (51).



To a solution of oxalyl chloride (1.13 mL, 12.7 mmol) in dry CH_2Cl_2 (100 mL) at -78 ^oC was added dropwise dry DMSO (5.4 mL, 76.22 mmol) in CH_2Cl_2 (20 mL). After 30 min, alcohol **50** (2.8 g, 8.46 mmol) in CH_2Cl_2 (20 mL) was added over 10 min giving a copious white precipitate. After stirring for 1 h at -78 ^oC the reaction mixture was

brought to -60 ^{o}C and Et_3N (5.31 mL, 38.11 mmol) was added slowly and stirred for 30 min allowing the reaction mixture to warm to room temperature. The reaction mixture was then diluted with water (50 mL) and CH_2Cl_2. The organic layer was separated and washed with water and brine, dried (Na_2SO_4) and passed through short pad of celite. The filtrate was concentrated to give the crude aldehyde as pale yellow oil, which was used as such for the next step without purification.

To a stirred solution of above crude aldehyde was added a solution of Grignard reagent dropwise at 0 °C, prepared from ethyl bromide (1.18 mL, 15.82 mmol) and Mg-turning (0.72 g, 23.73 mmol) in dry THF. The mixture was warmed to rt over 1 h and poured into a saturated NH_4Cl solution. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined EtOAc extracts were dried over Na_2SO_4. The extracts were concentrated to near dryness and purified on silica gel column chromatography (EtOAc/petroleum ether, 1:9) to give **51** as colorless oil.

Yield: 2.64 g, 87%

Mol. Formula: $C_{19}H_{42}O_2Si$

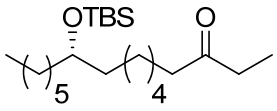
$[\alpha]_D^{25}$ +3.16 (*c* 0.98, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}) ν_{max} = 3616, 3443, 3019, 2932, 2400, 1463, 1377, 1215, 1049

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.04 (s, 6H), 0.87-0.92 (m, 15H), 1.27-1.52 (m, 22H), 3.50-3.66 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = -4.5, 9.8, 14.1, 18.1, 22.6, 25.3, 25.7, 26.0, 29.5, 29.5, 29.9, 30.1, 31.9, 36.9, 37.1, 37.2.

(*R*)-9-(*tert*-Butyldimethylsilyloxy)pentadecan-3-one (52).



To a solution of **51** (2 g, 5.57 mmol) in EtOAc (5 mL) in 25 mL R.B. flask was added IBX (4.68 g, 16.72 mmol) in one portion and the reaction mixture was refluxed for 3 h. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated to give the crude ketone **52** which was used without any further purification.

Yield: 1.78 g, 90%

Mol. Formula: $C_{21}H_{44}O_2Si$

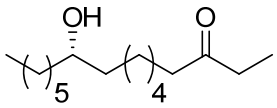
$[\alpha]_D^{25}$ -2.39 (*c* 1.06, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}) ν_{max} = 2932, 1710, 1462, 1255, 1215, 1051

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.03 (s, 6H), 0.88-0.92 (m, 12H), 1.05 (t, *J* =7.3 Hz, 3H), 1.27-1.38 (m, 18H), 2.40-2.44 (m, 4H) 3.52-3.64 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = -4.5, 7.9, 14.1, 18.1, 22.6, 23.9, 25.1, 25.3, 25.9, 29.5, 31.9, 35.8, 36.8, 37.1, 42.34, 72.2, 211.9.

(*R*)-9-Hydroxypentadecan-3-one (53).



To a stirred solution of compound **52** (999 mg) in MeOH was added a catalytic amount of *p*-TSA at room temperature and the reaction mixture stirred for 30 min at the same temperature. The mixture was filtered through a celite pad, washed with MeOH and concentrated to give **53**.

Yield: 651.8 mg, 96%.

Mol. Formula: $C_{15}H_{30}O_2$

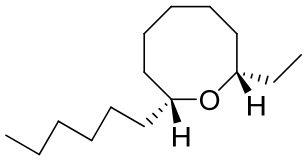
$[\alpha]_D^{25}$ -4.92 (*c* 1.06, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}) ν_{max} = 3421, 3019, 2932, 2858, 2400, 1709, 1461, 1215, 1047.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.7 Hz, 3H), 1.05 (t, *J* = 7.4 Hz, 3H), 1.28-1.42 (m, 12H), 1.55-1.63 (m, 6H), 2.37-2.48 (m, 4H) 3.56-3.58 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 7.8, 14.0, 22.5, 23.7, 25.3, 25.5, 29.3, 31.7, 35.8, 37.1, 37.4, 42.2, 71.7, 211.9.

(2*S*,8*R*)-2-Ethyl-8-hexyloxocane: (+)-*cis*-Lauthisan (1).



To a solution of the hydroxy ketone **53** (400 mg, 1.65 mmol) in dry CH_2Cl_2 (4 mL), TMSOTf (0.328mL, 1.81 mmol), followed by Et_3SiH (0.58 mL, 3.63 mmol) were added dropwise at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and quenched with a saturated aqueous solution of NH_4Cl. After workup and flash chromatography

(eluent EtOAc/hexane 1:40), pure (–)-*cis*-Lauthisan **1** was obtained as a colorless oil, (EtOAc/petroleum ether 1:19)

Yield: 157mg, 42%.

Mol. Formula: $C_{15}H_{30}O$

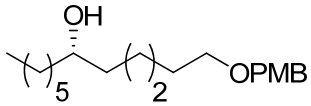
$[\alpha]_D^{24}$ -3.92 (*c* 0.15, $CHCl_3$); lit.[15] $[\alpha]^{20}{}_D$ –4.0 (*c* 0.15, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}) ν_{max} = 2910, 2860, 1460, 1090.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.5 Hz, 3H), 0.93 (t, *J* = 7.5 Hz, 3H), 1.8-1.2 (m, 22H), 3.35-3.57 (m, 1H), 3.43-3.45 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.9, 14.2, 22.7, 24.2, 26.4, 27.2, 29.6, 30.0, 32.0, 33.5, 33.7, 37.1, 79.6, 81.1.

(*S*)-1-(4-Methoxybenzyloxy)dodecan-6-ol (54)



A mixture of the substrate **57** (7.0 g, 21.70 mmol), catalyst (*S,S*)-Salen-Mn^{III} (Cl) (276 mg, 0.43 mmol), additive, KBr (207 mg, 1.73 mmol), CH_2Cl_2 (5 mL), and water (10 mL) were stirred in a 5 mL tube for a few minutes at room temperature. The oxidant $PhI(OAc)_2$ (4.89 g, 15.19 mmol) was then added and the system was stirred for 30 min until the completion of reaction. The products were extracted by using diethyl ether giving yields as 45% for **54** (3.15 g) and 43% for **58** (3 g). The conversion and ee values were determined by chiral HPLC. The ee was measured by HPLC using a Chiralcel OD column (isopropyl alcohol/ petroleum ether = 1:99); flow, 1.0 ml/min.

Yield: 3.15g , 45%

Mol. Formula: $C_{20}H_{34}O_3$

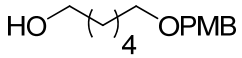
$[\alpha]_D^{25}$ +2.35 (*c* 1.7, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}) ν_{max} = 3426, 3011, 2857, 2930, 1712, 1454, 1364, 1277, 1216.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.7 Hz, 3H), 1.22–1.61 (m, 18H), 3.44 (t, *J* = 6.4 Hz, 2H), 3.57 (m, 1H) 3.80 (s, 3H), 4.43 (s, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 7.29 (d, *J* = 8.7 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0, 22.5, 25.4, 25.6, 26.2, 29.3, 29.6, 31.8, 37.4, 55.2, 55.2, 69.9, 71.8, 72.4, 113.6, 127.1, 129.2, 130.6, 158.9.

6-(4-Methoxybenzyloxy) hexan-1-ol (56).



To a solution of 1,5-hexanediol **55** (8.0 g, 67.79 mmol) in dry DMF (200 mL) was added sodium hydride (60%, 2.44 g, 45.76 mmol) at 0 ^{o}C. The reaction mixture was then stirred at room temperature for 30 min after which it was again cooled to 0 ^{o}C. To this was added slowly *p*-methoxybenzyl bromide (9.55 g, 61.01 mmol) and *tetra* N-butylammonium iodide (cat.) with further stirring for 1 h at the same temperature. The reaction mixture was quenched with addition of cold water at 0 ^{o}C. The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated. The residual oil was purified by silica gel column chromatography using petroleum ether/EtOAc (8:2) as eluent to furnish the mono-PMB protected alcohol **56** as colorless oil.

Yield: (13.54 g, 85%)

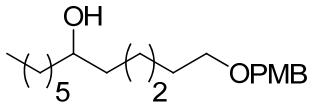
Mol. Formula: $C_{13}H_{20}O_3$

IR ($CHCl_3$, cm^{-1}) ν_{max} = 3402, 3009, 2938, 1718, 1496, 1454, 1216, 1096.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.32-1.60 (m, 6H), 3.43 (t, J = 6.5 Hz, 2H), 3.62 (t, J = 6.4 Hz, 2H), 3.79 (d, 3H), 4.05-4.13 (m, 1H), 4.42 (s, 1H), 4.61 (s, 1H), 6.84-6.90 (m, 2H), 7.23-7.31 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.4, 20.2, 24.8, 25.2, 28.9, 31.8, 54.5, 113.1, 127.86, 129.9, 132.5, 158.4.

7-(4-Methoxybenzyloxy)heptan-3-ol (57)



To a solution of oxalyl chloride (5.60 g, 29.4 mmol) in dry CH_2Cl_2 (100 mL) at -78 ^{o}C was added dropwise dry DMSO (6.88 g, 6.2 mL, 88.21 mmol) in CH_2Cl_2 (20 mL). After 30 min, alcohol **56** (7.0 g, 29.40 mmol) in CH_2Cl_2 (20 mL) was added over 10 min giving a copious white precipitate. After stirring for 1 h at -78 ^{o}C the reaction mixture was brought to -60 ^{o}C and Et_3N (5.72 g, 7.88 mL, 132.32 mmol) was added slowly and stirred for 30 min allowing the reaction mixture to warm to room

temperature. The reaction mixture was then diluted with water (150 mL) and CH_2Cl_2. The organic layer was separated and washed with water and brine, dried (Na_2SO_4) and passed through short pad of celite. The filtrate was concentrated to give the aldehyde as pale yellow oil, which was used as such for the next step without purification.

To a stirred solution of the above crude aldehyde in dry THF (50 mL), was added Grignard reagent prepared from a solution of 1-bromohexane (6.08 g, 36.84 mmol) and Mg-turning (0.78 g, 31.93 mmol), dropwise at 0 °C. The mixture was warmed to rt over 1 h and poured into a saturated NH_4Cl solution. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined EtOAc extracts were dried over Na_2SO_4. The extracts were concentrated to near dryness and purified on silica gel column chromatography (EtOAc/petroleum ether, 1:9) to give **57** as colorless oil.

Yield: 7.2g, 91%.

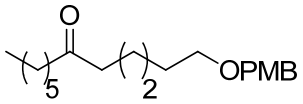
Mol. Formula: $C_{20}H_{34}O_3$

IR ($CHCl_3$, cm^{-1}) ν_{max} = 3426, 3011, 2857, 2930, 1712, 1454, 1364, 1277, 1216.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.89 (t, J = 6.7 Hz, 3H), 1.22–1.61 (m, 18H), 3.44 (t, J = 6.4 Hz, 2H), 3.57 (m, 1H) 3.80 (s, 3H), 4.43 (s, 2H), 6.90 (d, J = 8.7 Hz, 2H), 7.29 (d, J = 8.7 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0, 22.5, 25.4, 25.6, 26.2, 29.3, 29.6, 31.8, 37.4, 55.2, 55.2, 69.9, 71.8, 72.4, 113.6, 127.1, 129.2, 130.6, 158.9.

7-(4-Methoxybenzyloxy) heptan -3-one (58).



Yield: (3.29 g, 47%)

Mol. Formula: $C_{20}H_{32}O_3$

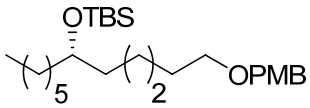
IR ($CHCl_3$, cm^{-1}) ν_{max} = 2932, 2400, 1710, 1215, 1051, 759.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.89 (t, J = 6.7 Hz, 3H), 1.22–1.61 (m, 18H), 3.44 (t, J = 6.4 Hz, 2H), 3.80 (s, 3H), 4.43 (s, 2H), 6.90 (d, J = 8.7 Hz, 2H), 7.29 (d, J = 8.7 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 22.6, 23.5, 28.8, 25.3, 25.9, 29.5, 30.8, 37.9, 39.1, 55.2, 72.3, 72.5, 114.2, 113.7, 129.2, 129.8 130.7, 159.1, 210.8.

Conversion of compound 58 to 57: To a solution of **58** (3 g, 10.79 mmol) in EtOH (10 ml) was added $NaBH_4$ (1.22 g, 32.37 mmol). After stirring for 4 h at room temperature, the reaction mixture was quenched with 10% AcOH aqueous solution. After the removal of solvents under reduced pressure, the mixture was added to water (20 ml) and extracted with ether (250 ml). The organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated to give a residue which was purified by silica gel column chromatography to give **57** (2.68 g) in 89% yield.

(*S*)-*tert*-Butyl(1-(4-methoxybenzyloxy)dodecan-6-yloxy)dimethylsilane (59).



Compound **59** was prepared following the procedure described for compound **49** in 85% yield as a yellow syrup.

Yield: (1.54 g, 85%)

Mol. Formula: $C_{26}H_{48}O_3Si$

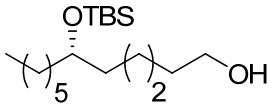
$[\alpha]_D^{25}$ +2.85 (*c* 1.4, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}) ν_{max} = 3018, 2857, 2932, 1463, 1361, 1255, 1215, 1092, 1028, 836, 759.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.04 (s, 6H), 0.87-0.92 (m, 12H), 1.27-1.37 (m, 12H), 1.55-1.60 (m, 6H), 3.44, (t, *J* = 6.7 Hz, 2H), 3.59-3.64 (m, 1H), 3.81 (s, 3H), 4.44 (s, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 7.29 (d, *J* = 8.8 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = -4.4, 14.1, 18.1, 22.6, 25.2, 25.3, 25.9, 26.4, 29.5, 29.8, 31.9, 37.1, 55.2, 70.1, 72.3, 72.5, 113.7, 129.2, 130.7, 159.1.

(*S*)-6-(*tert*-Butyldimethylsilyloxy)dodecan-1-ol (60).



To a stirring solution of PMB ether **59** (4.8 g, 2.77 mmol) in CH_2Cl_2/H_2O (18:1) was added DDQ (756 mg, 3.33 mmol). The resulting mixture was stirred for 1 h at rt. The mixture was poured into saturated aqueous $NaHCO_3$ and further diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 30

mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was then filtered through a pad of celite and washed with 50% EtOAc/hexane (20 mL). The solvents were removed under reduced pressure to give the crude product mixture as yellow oil. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (7:3) as eluent afforded **60** as colorless oil.

Yield: 3.27 g, 94%

Mol. Formula: $C_{18}H_{40}O_2Si$

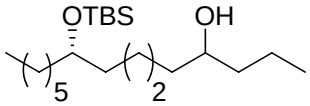
$[\alpha]_D^{25}$ +5.24 (*c* 1.62, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}) ν_{max} = 3430, 3018, 2857, 2931, 1471, 1361, 1255, 1215, 1049.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.04 (s, 6H), 0.87-0.92 (m, 12H), 1.27-1.37 (m, 12H), 1.55-1.60 (m, 6H), 3.44 (t, *J* = 6.7 Hz, 2H), 3.59–3.64 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = -4.4, 14.1, 22.7, 25.4, 25.9, 29.6, 30.92, 31.8, 32.2, 37.1, 37.2, 62.8, 72.4.

(9*S*)-9-(*tert*-Butyldimethylsilyloxy)pentadecan-4-ol (61).



Compound **61** was prepared following the procedure described for compound **51** as a yellow syrup.

Yield: 2.37 g, 62%

Mol. Formula: $C_{21}H_{46}O_2Si$

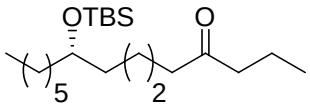
$[\alpha]_D^{25}$ +2.08 (*c* 0.96, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}) ν_{max} = 3616, 3443, 3019, 2932, 2400, 1463, 1377, 1215, 1049.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.04 (s, 6H), 0.89 (s, 9H), 0.88 (t, *J* = 6.8 Hz, 3H), 0.94 (t, *J* = 6.6 Hz, 3H), 1.27-1.32 (m, 14H), 1.39-1.44 (m, 8H), 3.61 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 0.5, 18.6, 18.9, 22.2, 23.0, 27.5, 28.9, 29.9, 30.1, 30.8, 34.4, 36.8, 41.7, 41.9, 47.7, 49.6, 81.6, 81.8, 82.1.

(*S*)-9-(*tert*-Butyldimethylsilyloxy)pentadecan-4-one (62).



Compound **62** was prepared following the procedure described for compound **52** as a yellow syrup.

Yield: 2.22 g, 92%

Mol. Formula: $C_{21}H_{44}O_2Si$

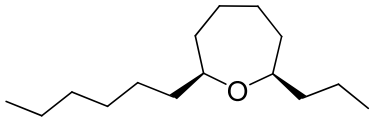
$[\alpha]_D^{25}$ +4.0 (*c* 1.02, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}) ν_{max} = 2932, 2400, 1710, 1215, 1051, 759.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.03 (s, 3H), 0.04 (s, 3H), 0.88 (s, 9H), 0.92 (t, *J* = 7.4 Hz, 6H), 1.27-1.30 (m, 10H), 1.39-1.41 (m, 4H), 1.59-1.61 (m, 4H), 2.36-2.39 (m, 4H), 3.60, (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 0.5, 18.6, 18.9, 22.2, 23.0, 27.5, 28.9, 29.9, 30.1, 30.8, 34.4, 36.8, 41.7, 41.9, 47.7, 49.6, 81.6, 81.8, 82.1, 216.3.

(2*S*,7*R*)-2-Pentyl-7-propyloxepane:(+)Isolaurepan (3).



Compound **3** was prepared following the procedure described for compound **1** as a yellow syrup.

Yield: 300 mg, 84%

Mol. Formula: $C_{21}H_{44}O_2Si$

$[\alpha]_D^{25}$ +1.5 (*c* 0.97, $CHCl_3$); lit.[7a] $[\alpha]_D^{24}$ +1.5 (*c* 0.97, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}) ν_{max} = 2950, 2920, 2850, 1465, 1455, 1375, 1340,1140, 1100.

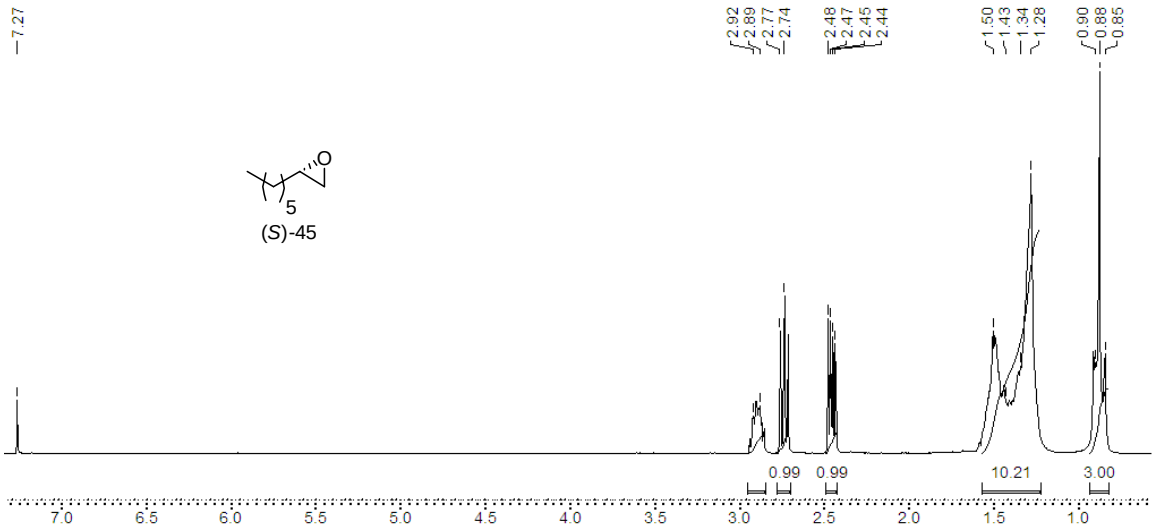
^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.03 (s, 3H), 0.04 (s, 3H), 0.88 (s, 9H), 0.92 (t, *J* = 7.4 Hz, 6H), 1.27-1.30 (m, 10H), 1.39-1.41 (m, 4H), 1.59-1.61 (m, 4H), 2.36-2.39 (m, 4H), 3.60, (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.8 Hz, 3H), 0.90 (t, *J* = 7.0 Hz, 3H), 1.26-1.44 (m, 10H), 1.47-1.55 (m, 8H), 1.65-1.73 (m, 4H), 3.37-3.39 (m, 2 H).

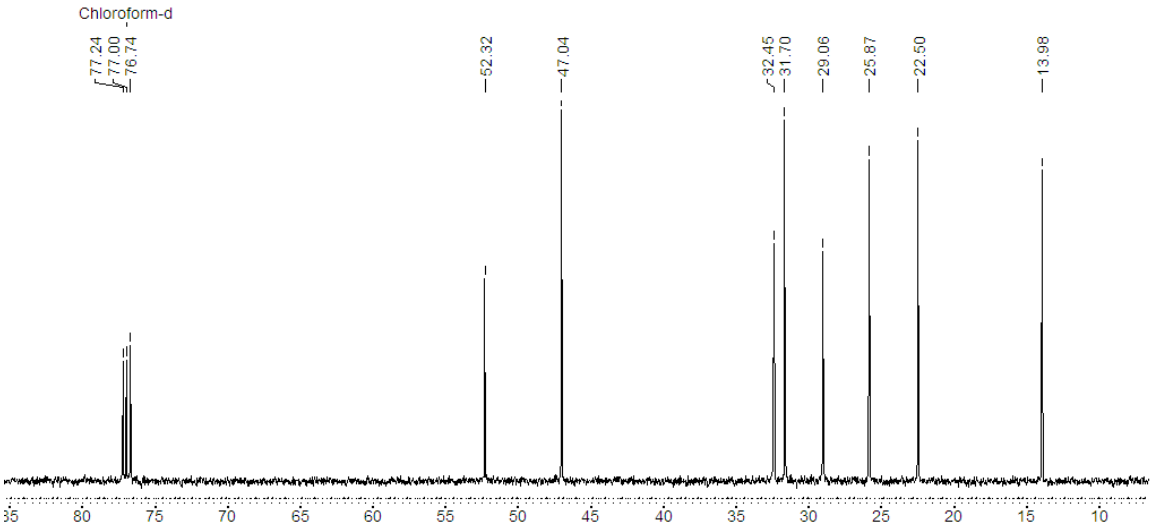
2.7 Spectra

1. ^{1}H and ^{13}C NMR spectra of **(*S*)-45**
2. ^{1}H and ^{13}C NMR spectra of **47**
3. ^{1}H and ^{13}C NMR spectra of **48**
4. ^{1}H and ^{13}C NMR spectra of **50**
5. ^{1}H and ^{13}C NMR spectra of **51**
6. ^{1}H and ^{13}C NMR spectra of **52**

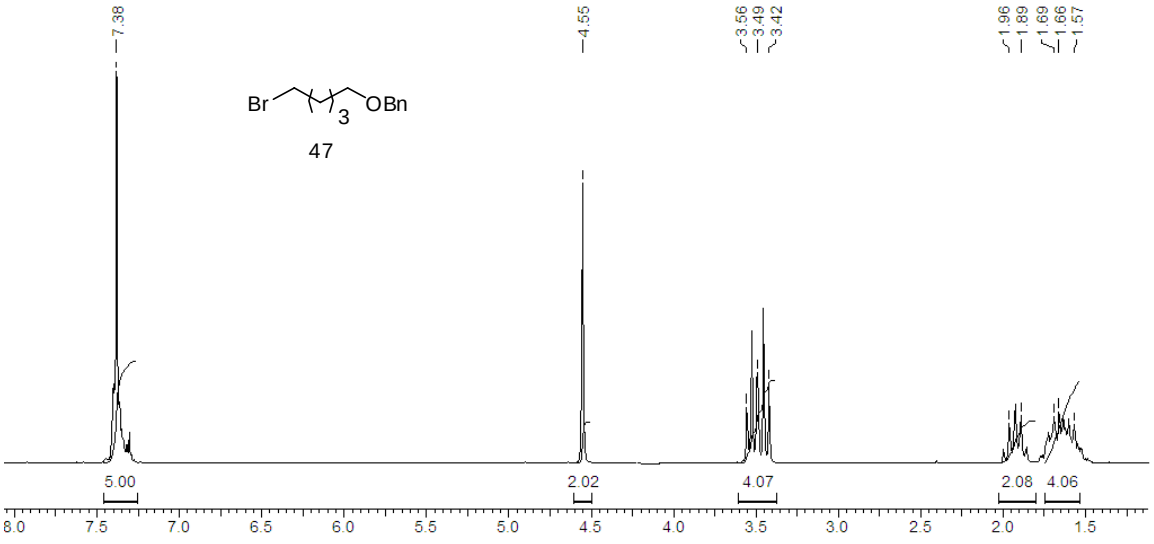
7. ^{1}H and ^{13}C NMR spectra of **53**
8. ^{1}H and ^{13}C NMR spectra of **1**
9. ^{1}H and ^{13}C NMR spectra of **56**
10. ^{1}H and ^{13}C NMR spectra of **57**
11. ^{1}H and ^{13}C NMR spectra of **59**
12. ^{1}H and ^{13}C NMR spectra of **60**
13. ^{1}H and ^{13}C NMR spectra of **61**
14. ^{1}H and ^{13}C NMR spectra of **62**
15. ^{1}H and ^{13}C NMR spectra of **3**



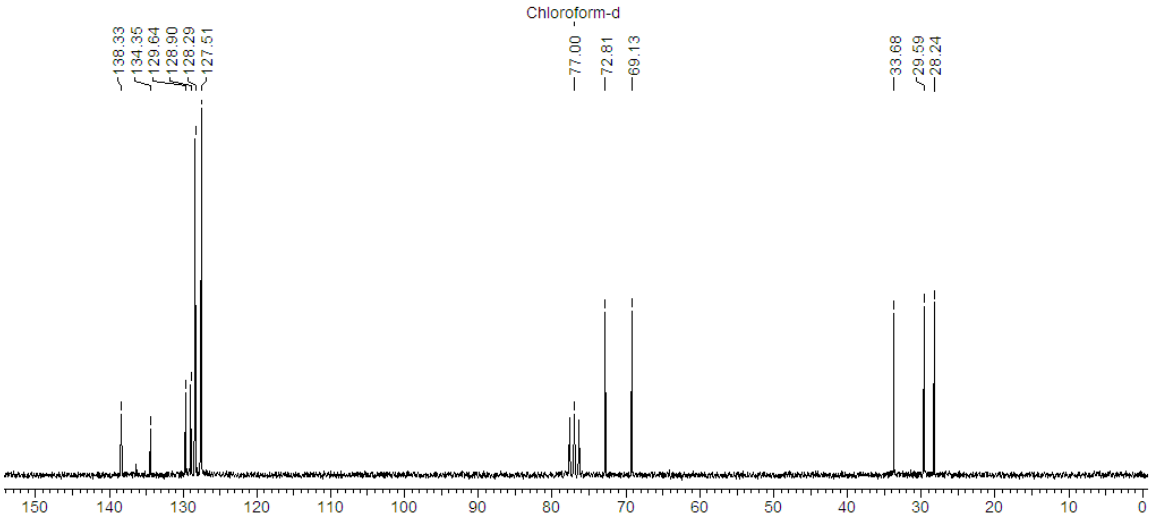
^{1}H-NMR spectrum of compound (*S*)-45 in $CDCl_3$



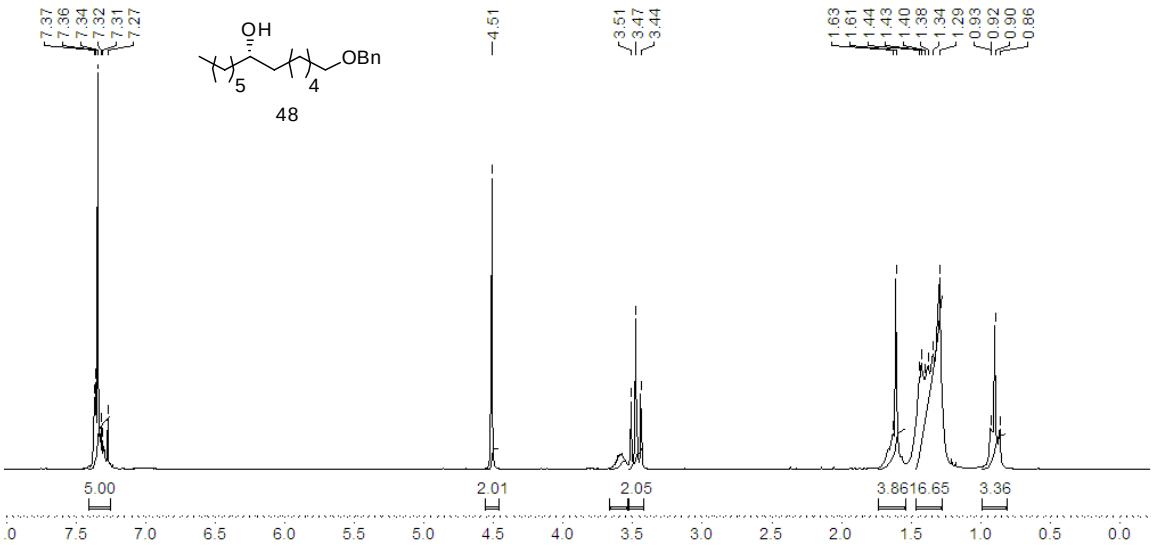
^{13}C-NMR spectrum of compound (*S*)-45 in $CDCl_3$



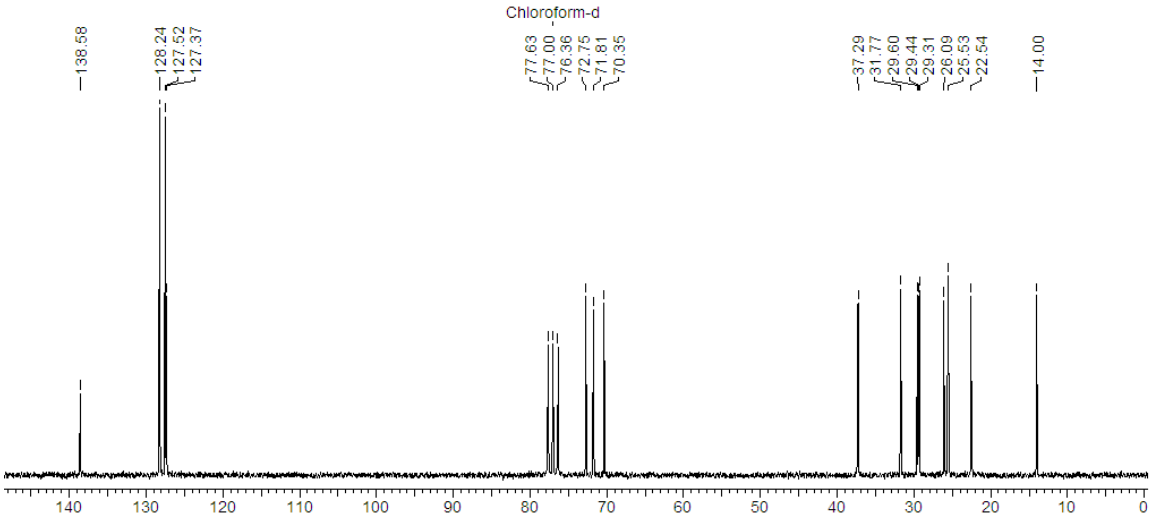
^{1}H-NMR spectrum of compound 47 in $CDCl_3$



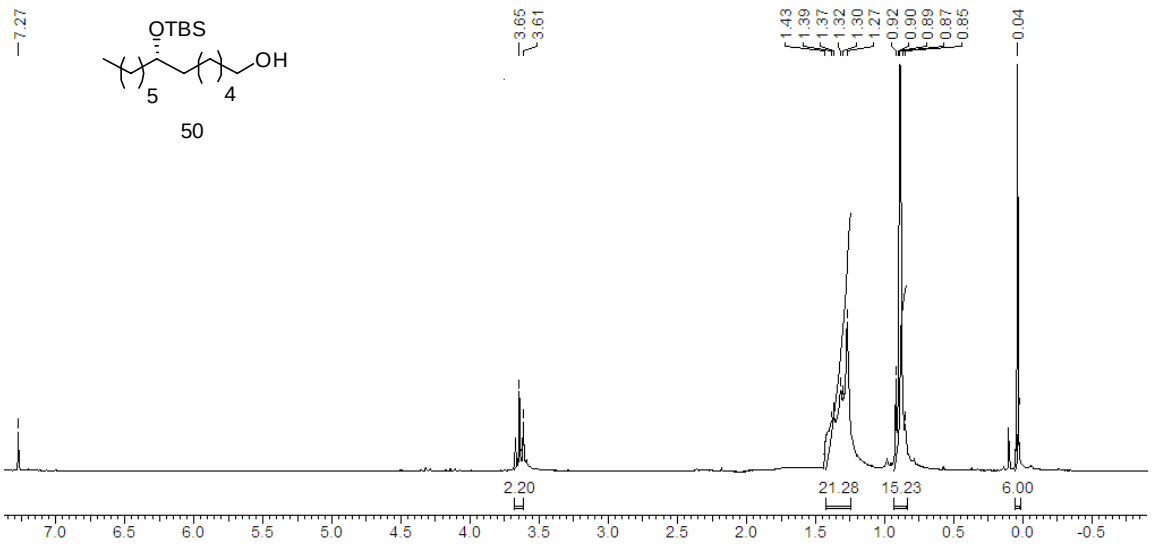
^{13}C-NMR spectrum of compound 47 in $CDCl_3$



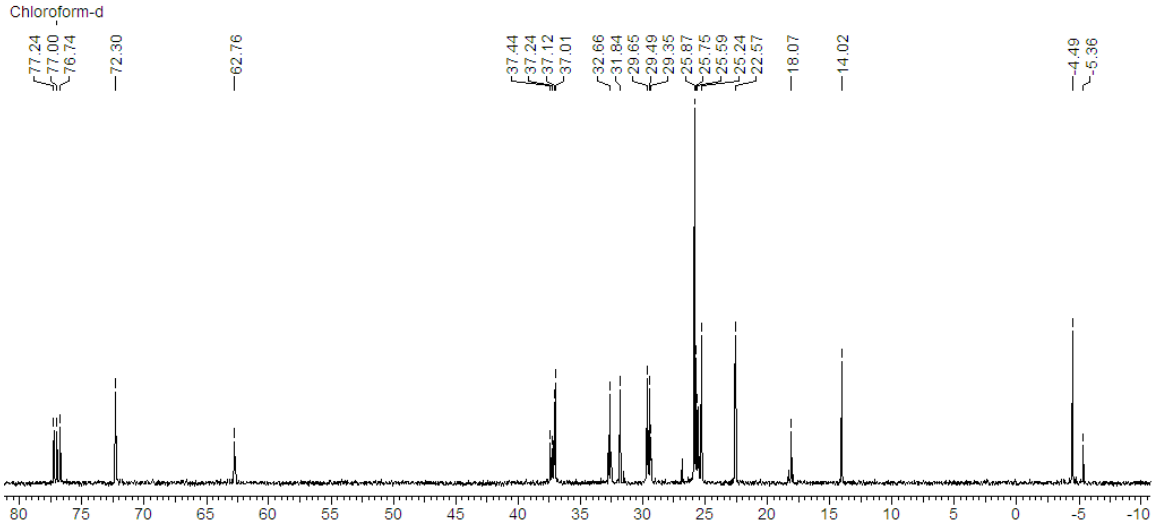
^{1}H-NMR spectrum of compound 48 in $CDCl_3$



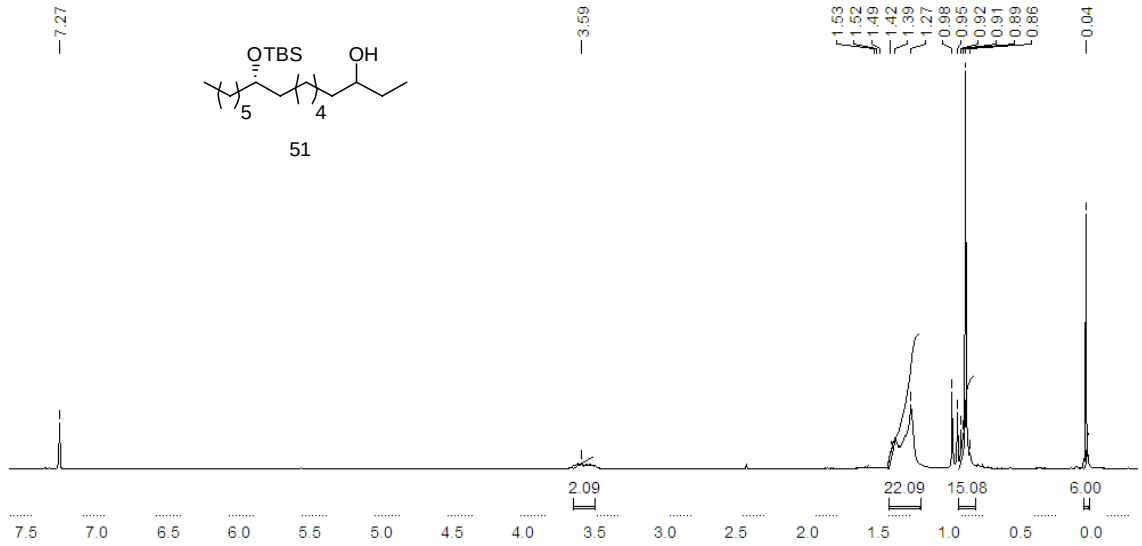
^{13}C-NMR spectrum of compound 48 in $CDCl_3$



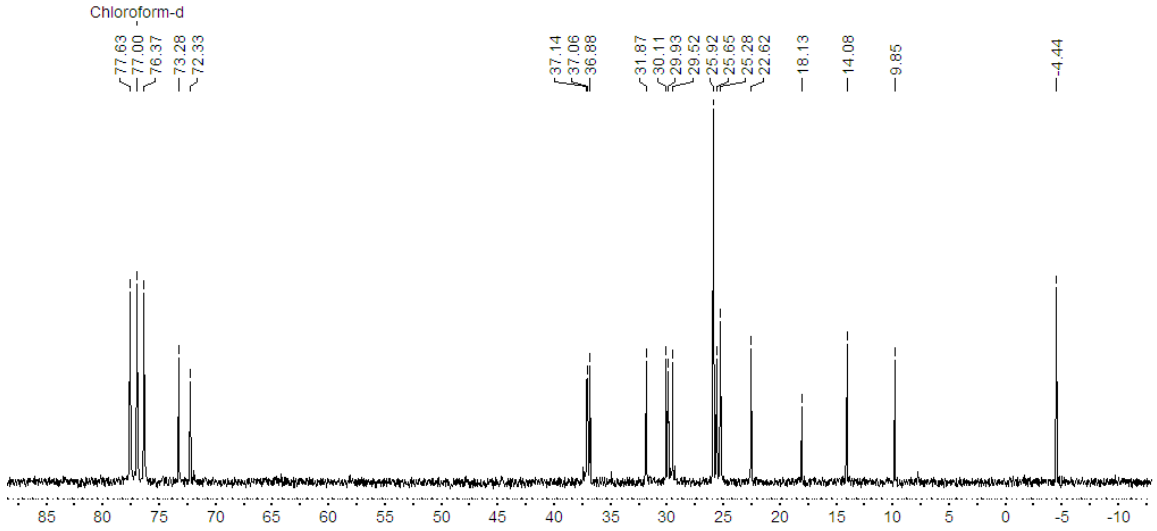
^{1}H-NMR spectrum of compound 50 in $CDCl_3$



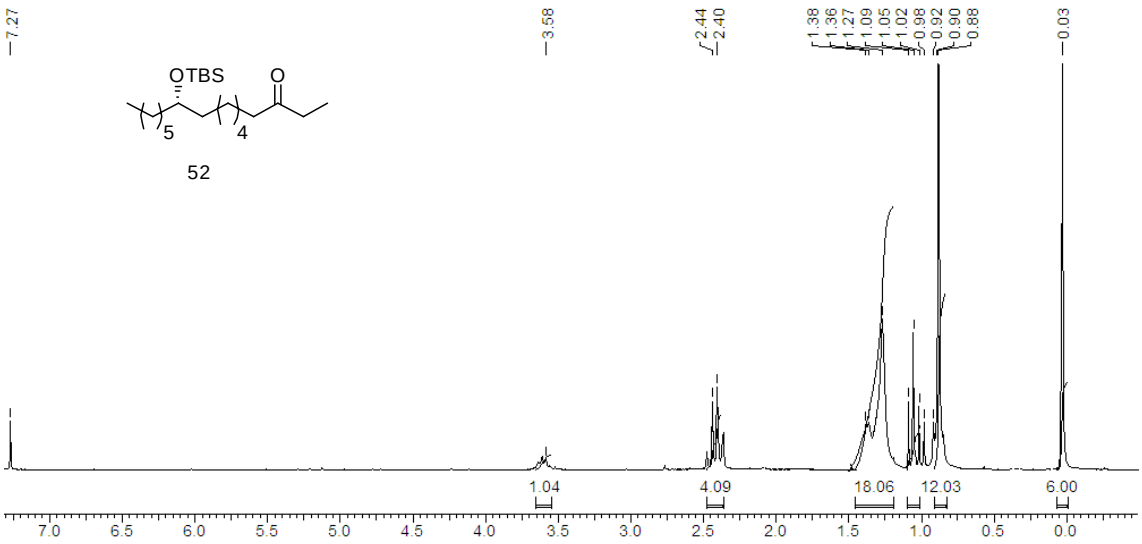
^{13}C-NMR spectrum of compound 50 in $CDCl_3$



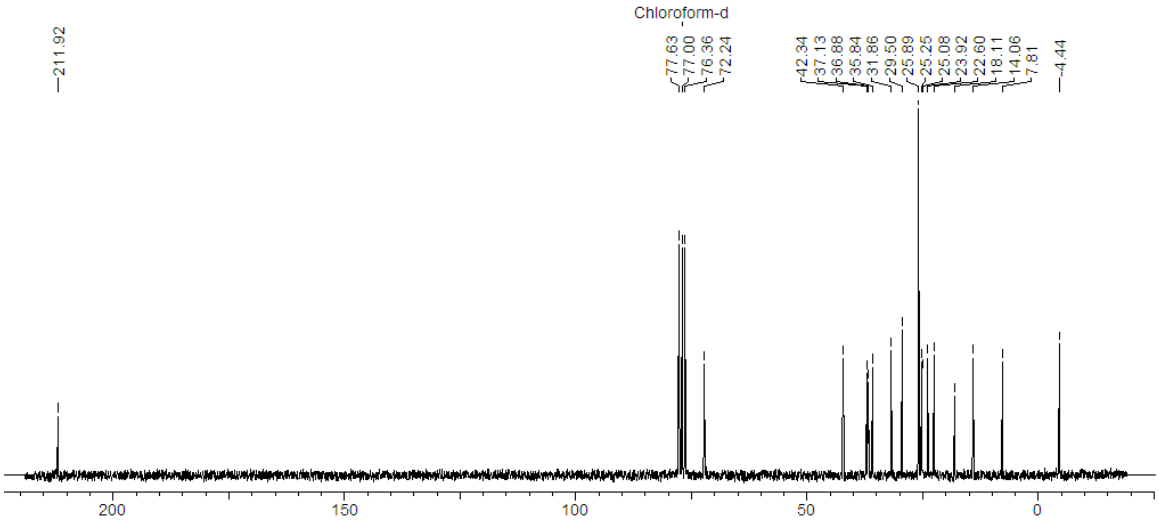
^{1}H-NMR spectrum of compound 51 in $CDCl_3$



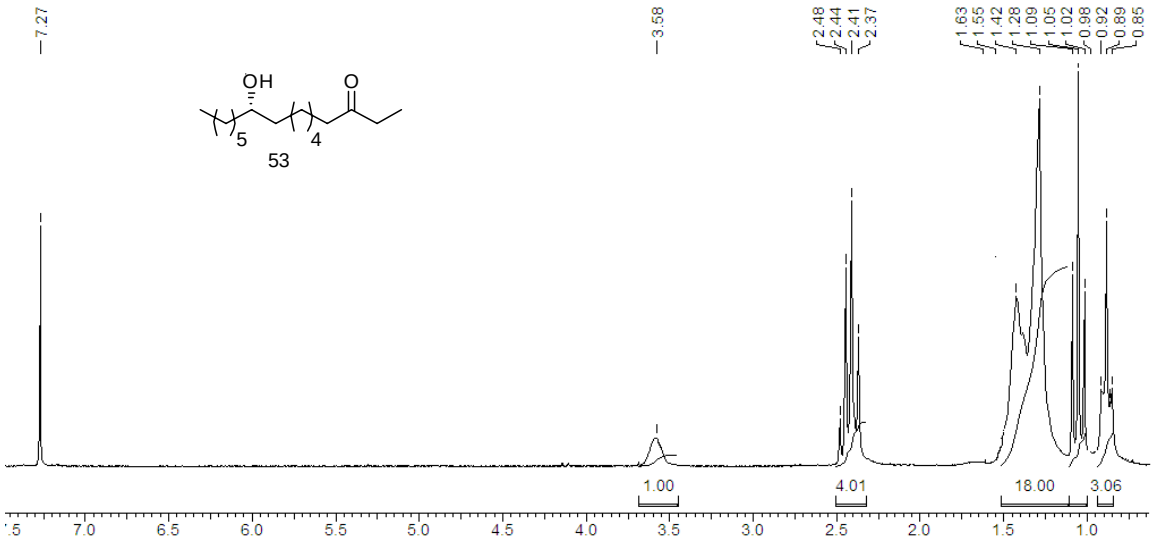
^{13}C-NMR spectrum of compound 51 in $CDCl_3$



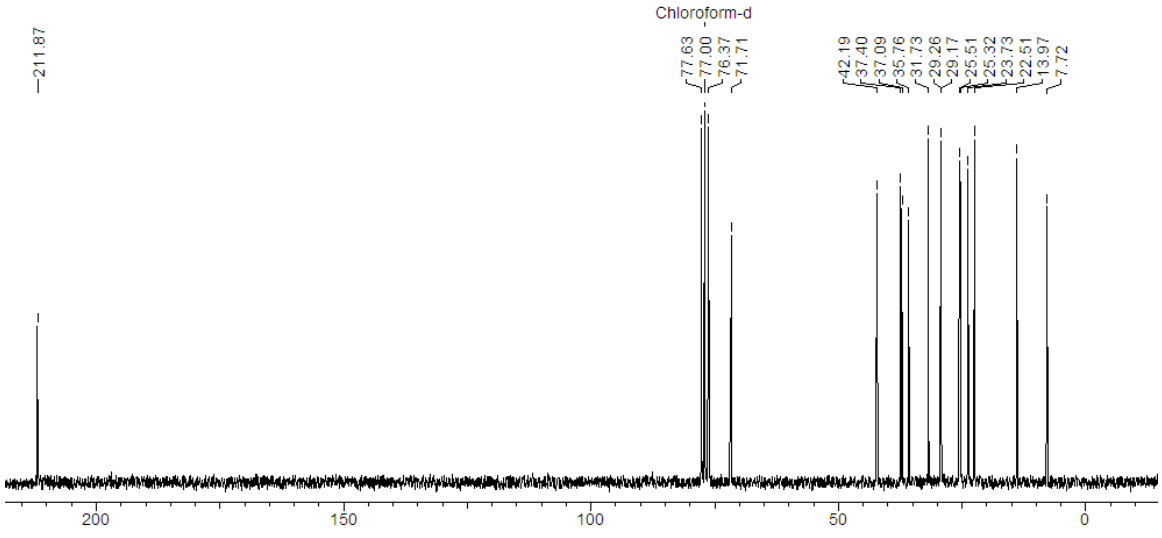
^{1}H-NMR spectrum of compound 52 in $CDCl_3$



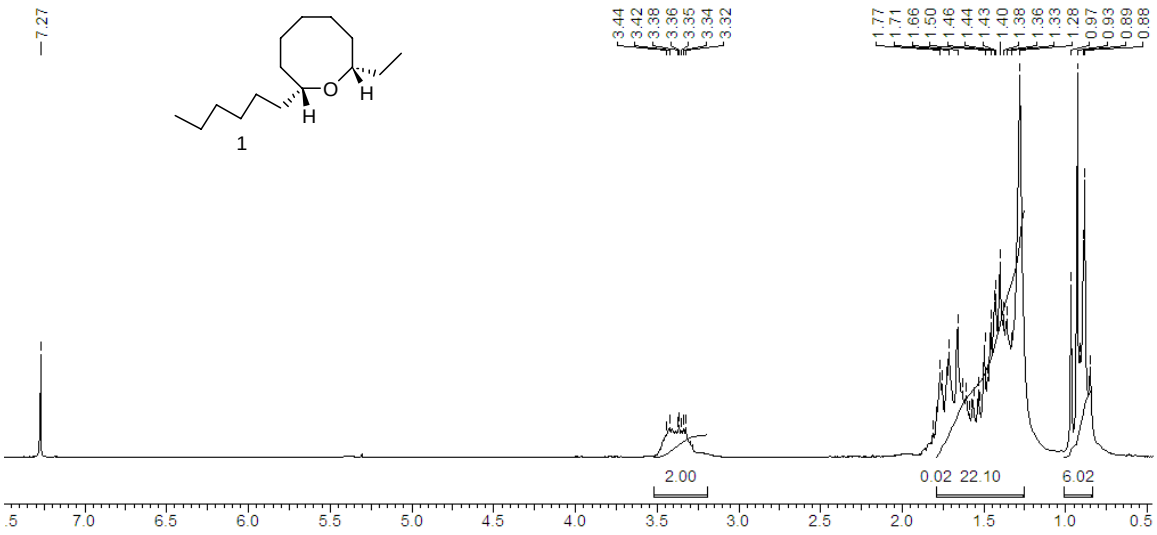
^{13}C-NMR spectrum of compound 52 in $CDCl_3$



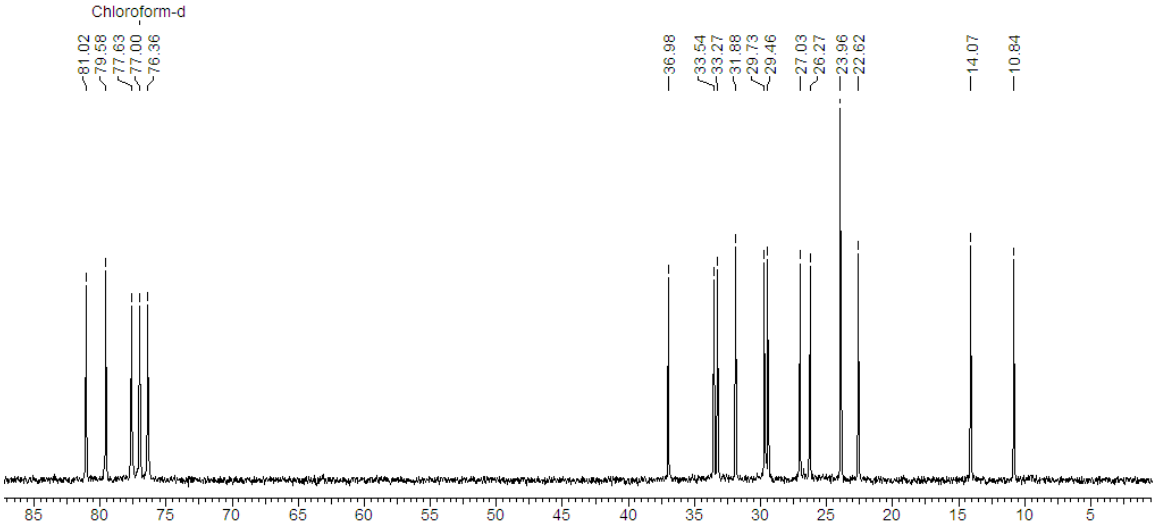
^{1}H-NMR spectrum of compound 53 in $CDCl_3$



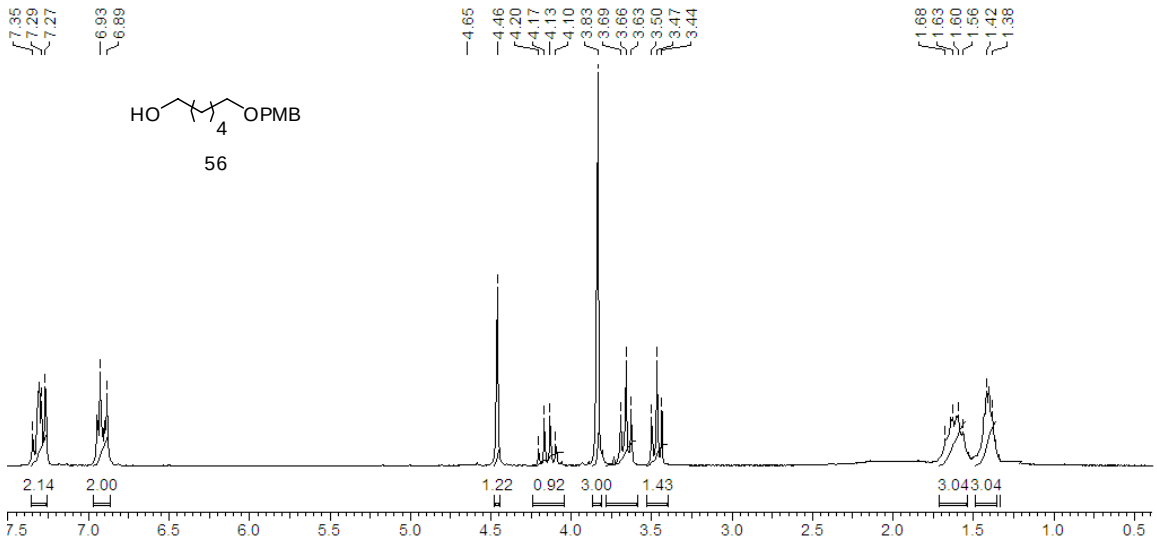
^{13}C-NMR spectrum of compound 53 in $CDCl_3$



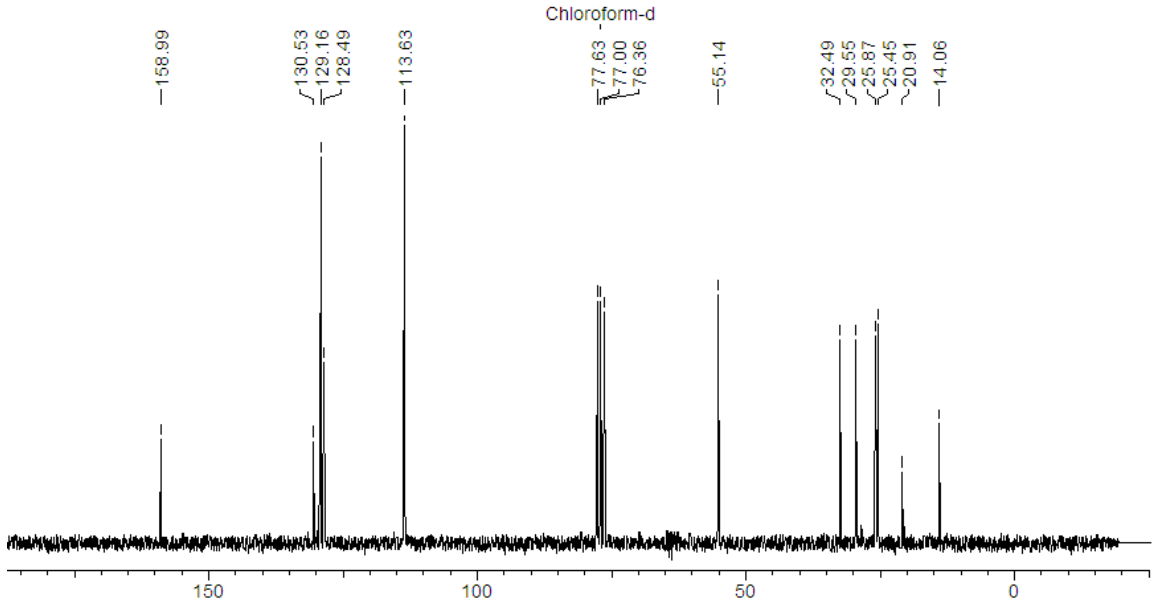
^{1}H-NMR spectrum of compound 1 in $CDCl_3$



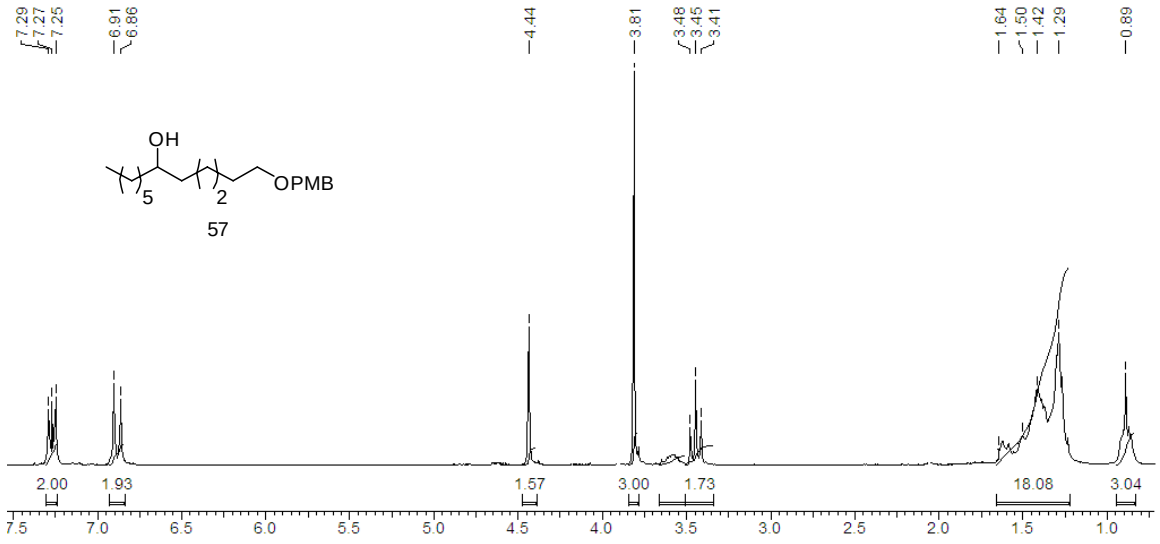
^{13}C-NMR spectrum of compound 1 in $CDCl_3$



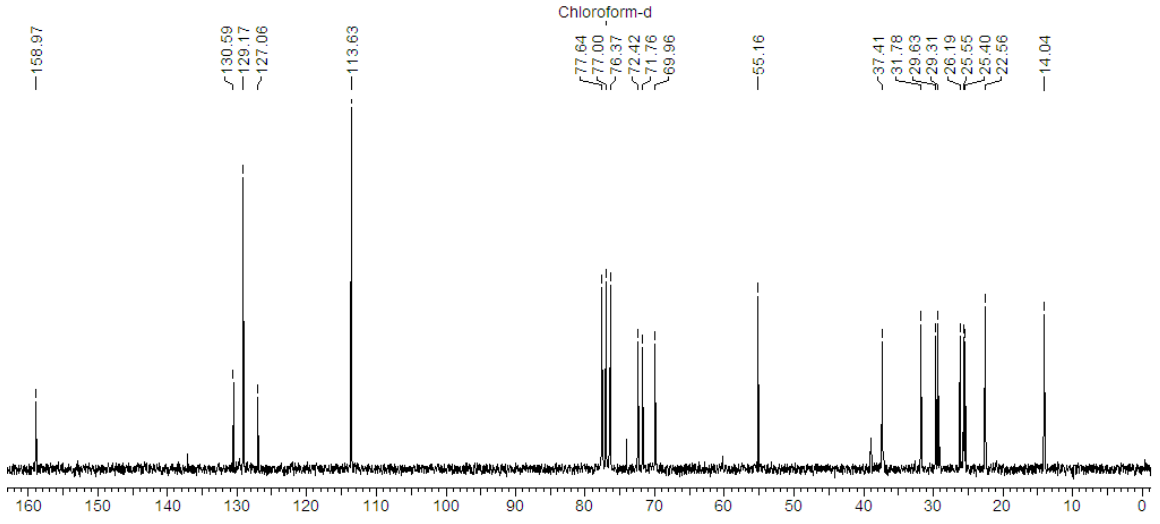
^{1}H-NMR spectrum of compound 56 in $CDCl_3$



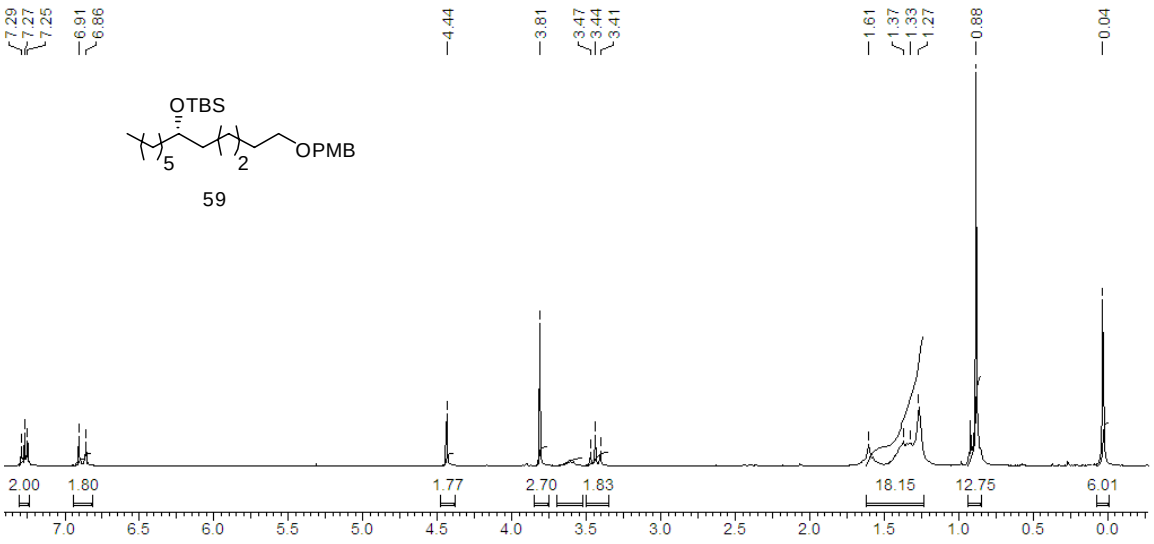
^{13}C-NMR spectrum of compound 56 in $CDCl_3$



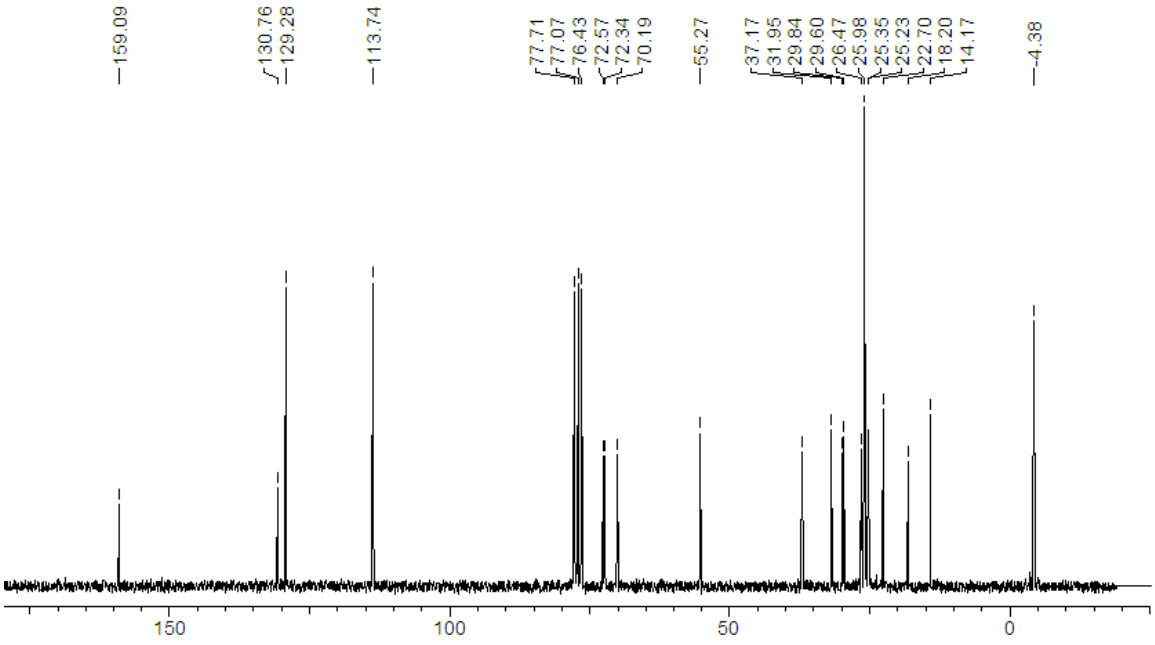
^{1}H-NMR spectrum of compound 57 in $CDCl_3$



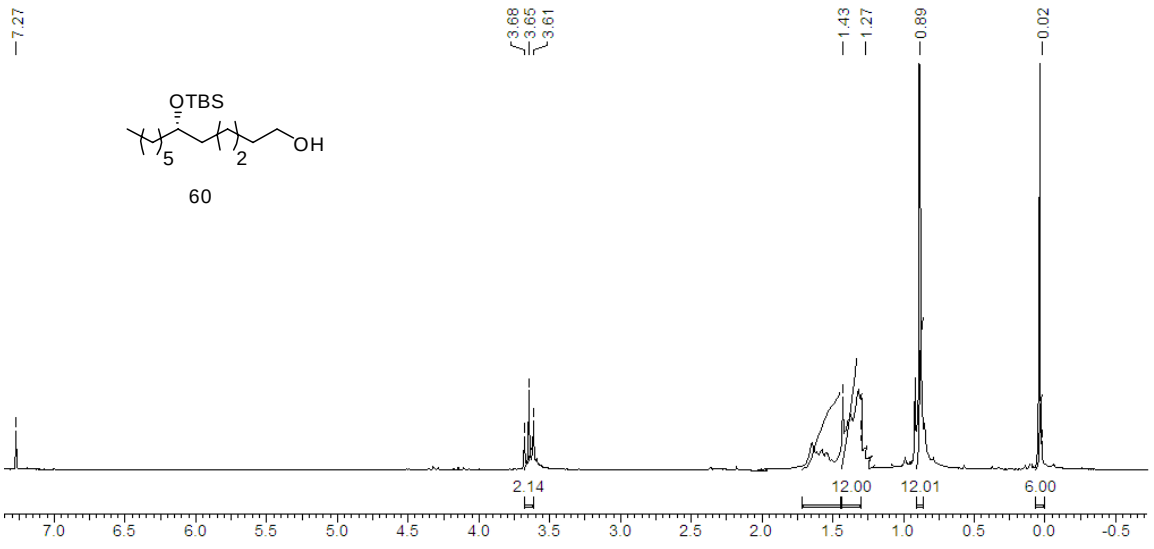
^{13}C-NMR spectrum of compound 57 in $CDCl_3$



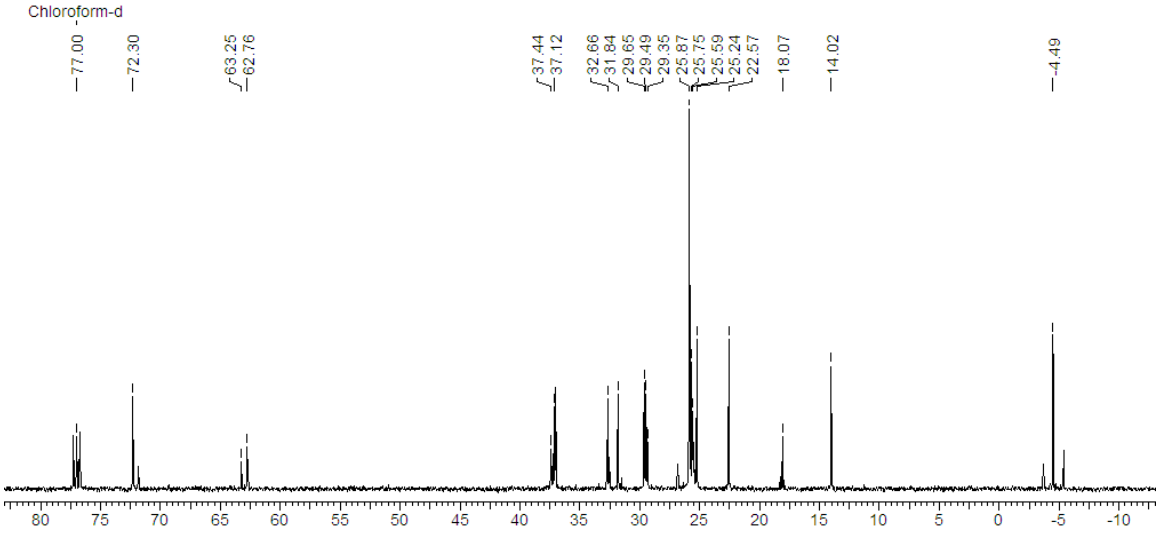
^{1}H-NMR spectrum of compound 59 in $CDCl_3$



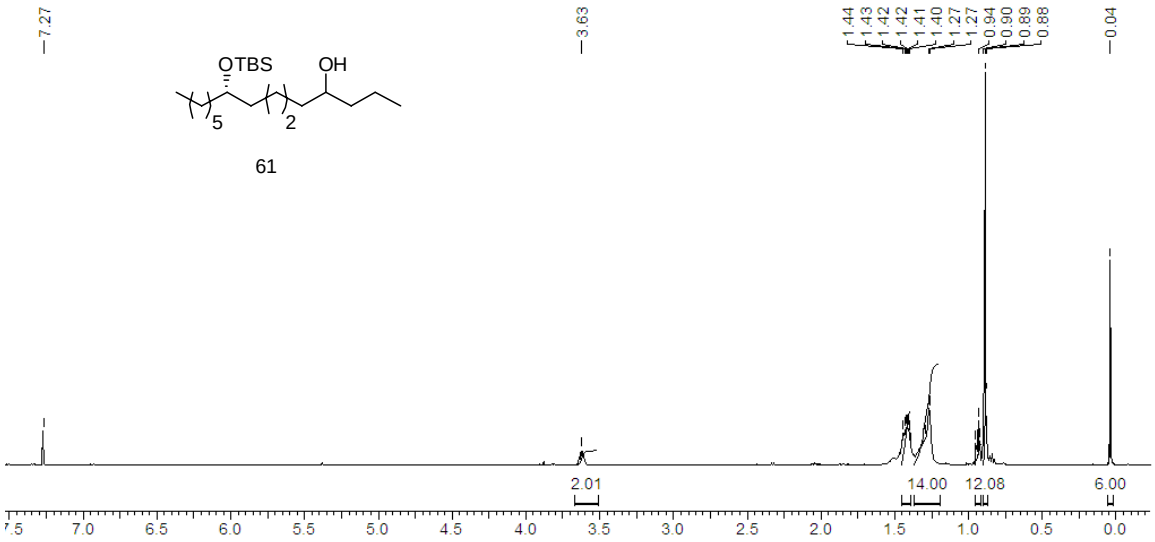
^{13}C-NMR spectrum of compound 59 in $CDCl_3$



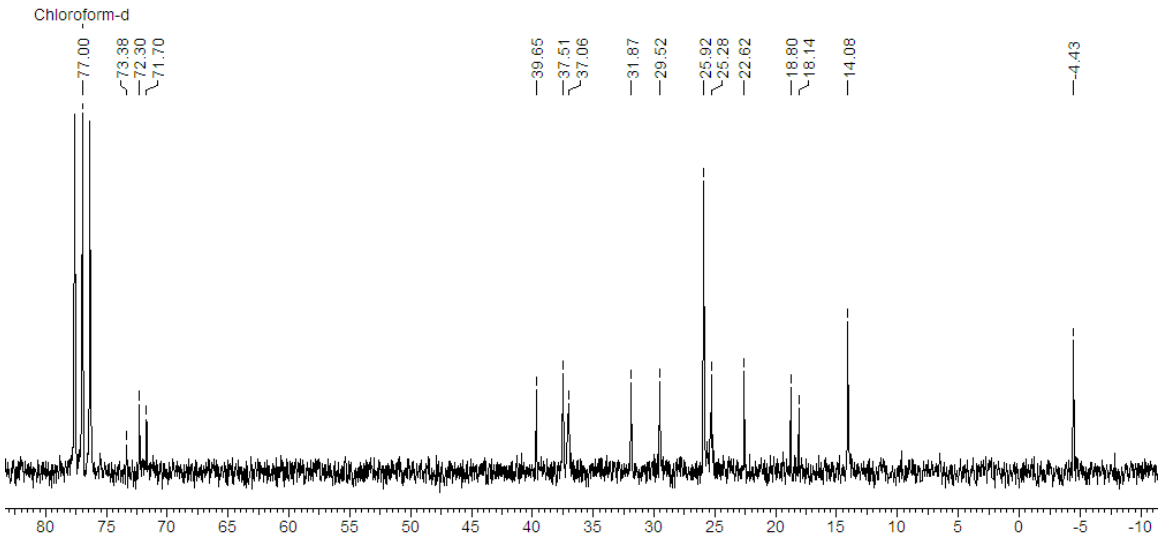
^{1}H-NMR spectrum of compound 60 in $CDCl_3$



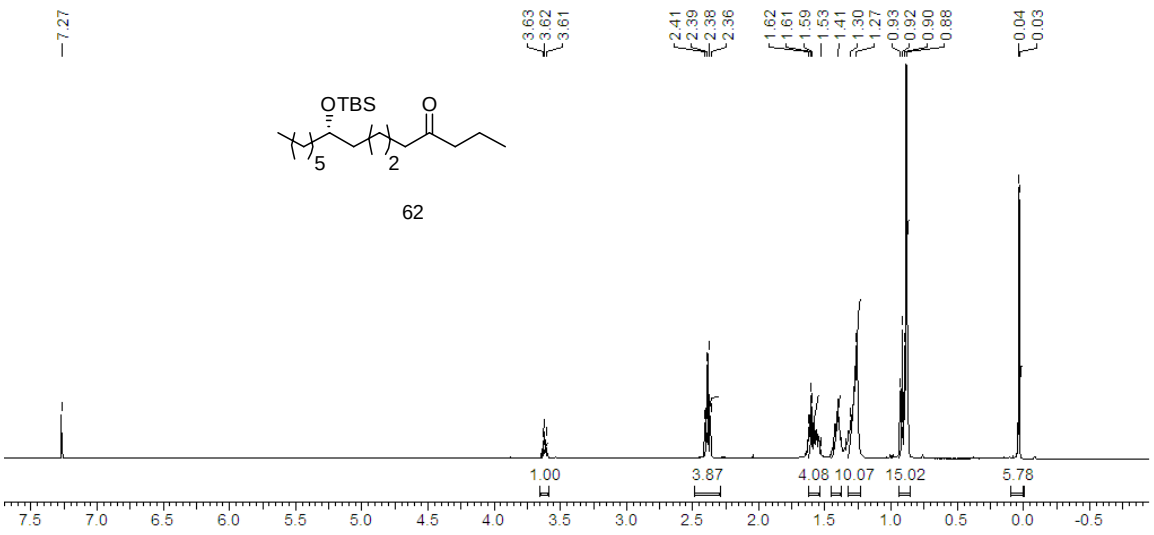
^{13}C-NMR spectrum of compound 60 in $CDCl_3$



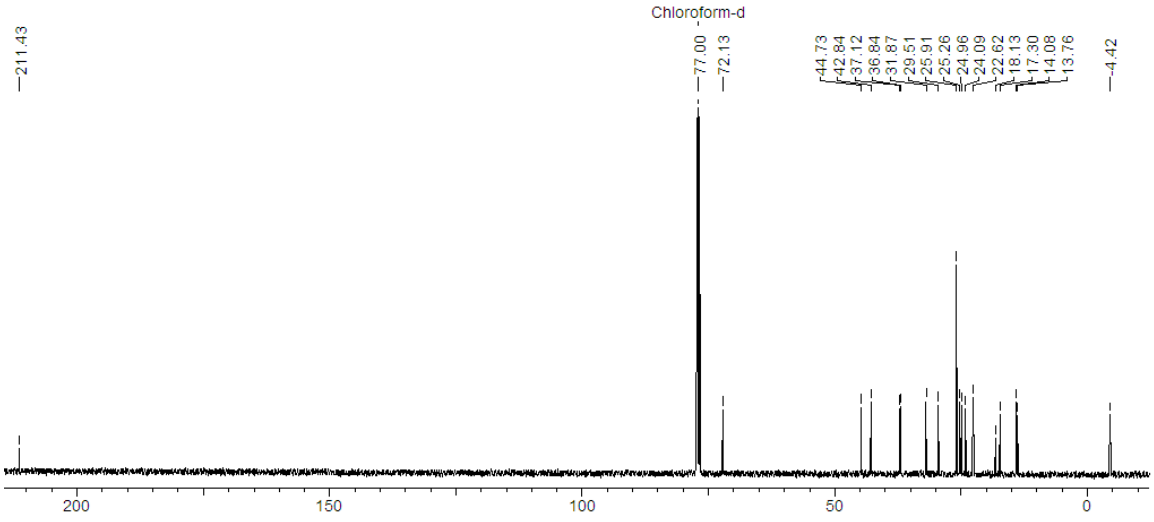
^{1}H-NMR spectrum of compound 61 in $CDCl_3$



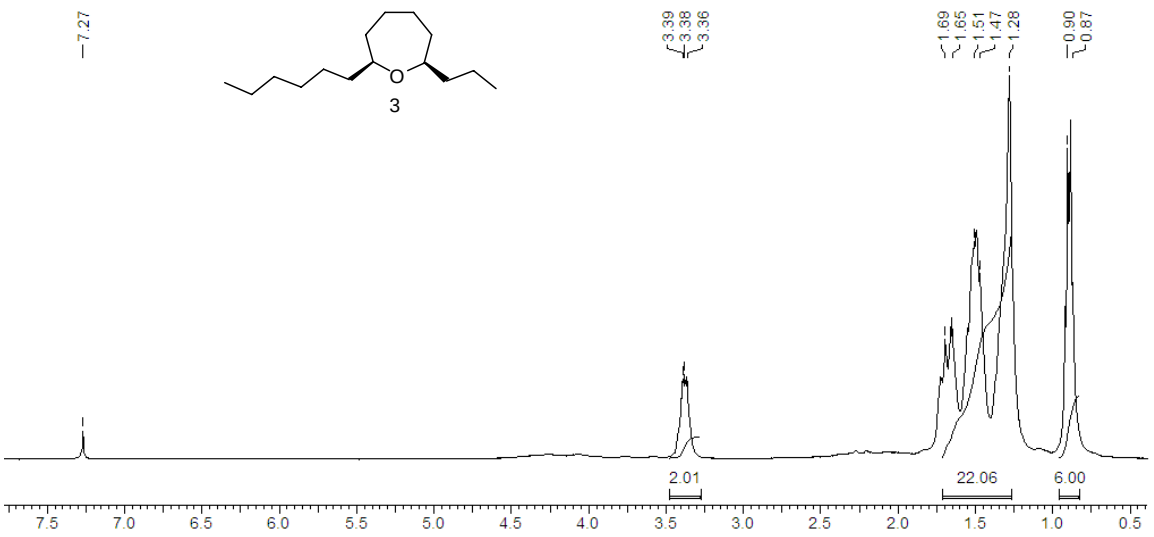
^{13}C-NMR spectrum of compound 61 in $CDCl_3$



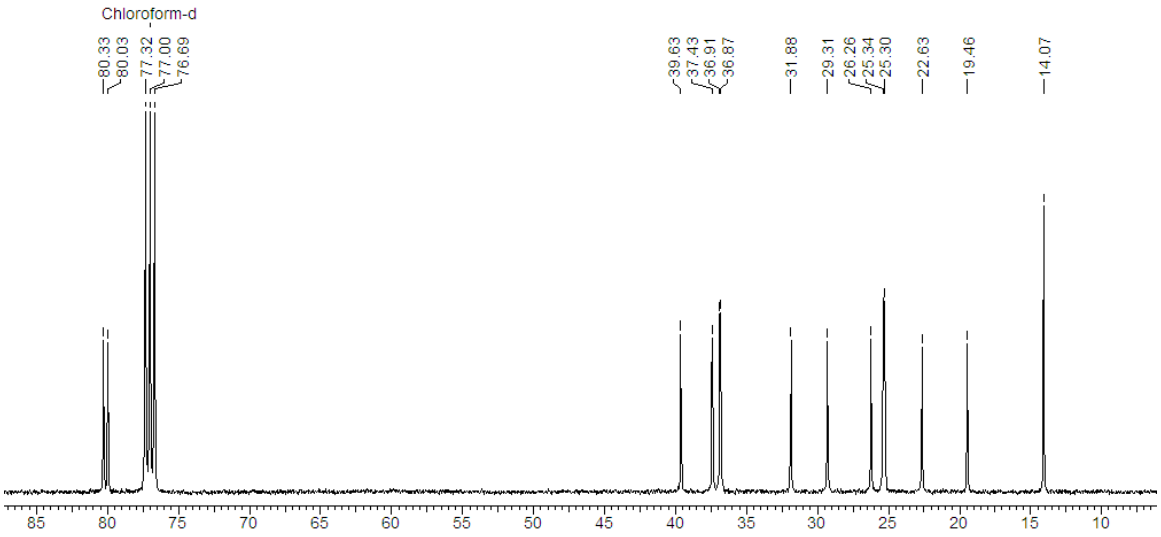
^{1}H-NMR spectrum of compound 62 in $CDCl_3$



^{13}C-NMR spectrum of compound 62 in $CDCl_3$



^{1}H-NMR spectrum of compound 3 in $CDCl_3$



^{13}C-NMR spectrum of compound 3 in $CDCl_3$

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Chapter 3
An organocatalytic route to the synthesis of (6S)-5,6-dihydro-6-[(2R)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one and ravensara lactones

TOTAL SYNTHESIS OF α-PYRONES: (6S)-5,6-DIHYDRO-6- [(2R)-2-HYDROXY-6-PHENYLHEXYL]-2H-PYRAN-2-ONE AND RAVENSARA LACTONES

3.1. Introduction

The 5,6-dihydro-2*H*-pyran-2-one with an integrated 1,3-skipped polyol[1] system are ubiquitous structural motifs of several biologically active compounds like cryptocarya diacetate **1**,[2] passifloricin **2,**[3] strictifolione **3,** [4] 1,3-polyol/α-pyrones **4a** and **4b**,[5] and (6*S*)-5,6-dihydro-6- [(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one (**5a** and **5b**).[6] The main structural features of these compounds are *syn*-1,3-diol and a 6-substituted 5,6-dihydro-α-pyrone. A broad range of biological activities associated with these natural products include plant growth inhibition, antifeedant, cytotoxicity against human tumor cells,[7] antifungal activity[8] and inducing apoptosis.[9] Therefore these class of compounds are of marked interest not only from a chemical, but also from a pharmacological perspective. The 1,3,5-polyol/pyrones **4a** and **4b** [5] have been isolated from *Ravensara anisata* and **5a** and **5b**[6] viz 5,6-dihydro-α–pyrone derivatives having an alkyl side chain at the C6 position were isolated from *Ravensara crassifolia.* [6] Due to their distribution, strong and selective biological profile, as well as their interesting structure, extensive efforts have been focused by the synthetic organic chemists worldwide on the development of an efficient synthetic method for stereoselective construction of these attractive synthetic targets.

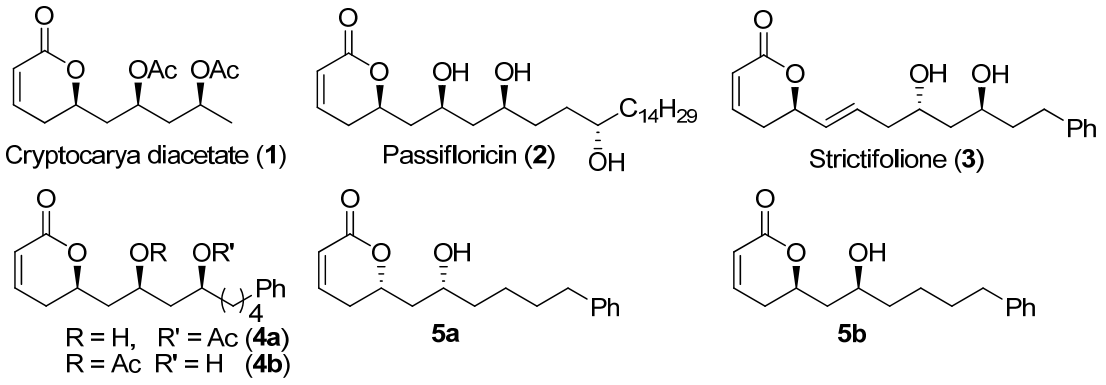


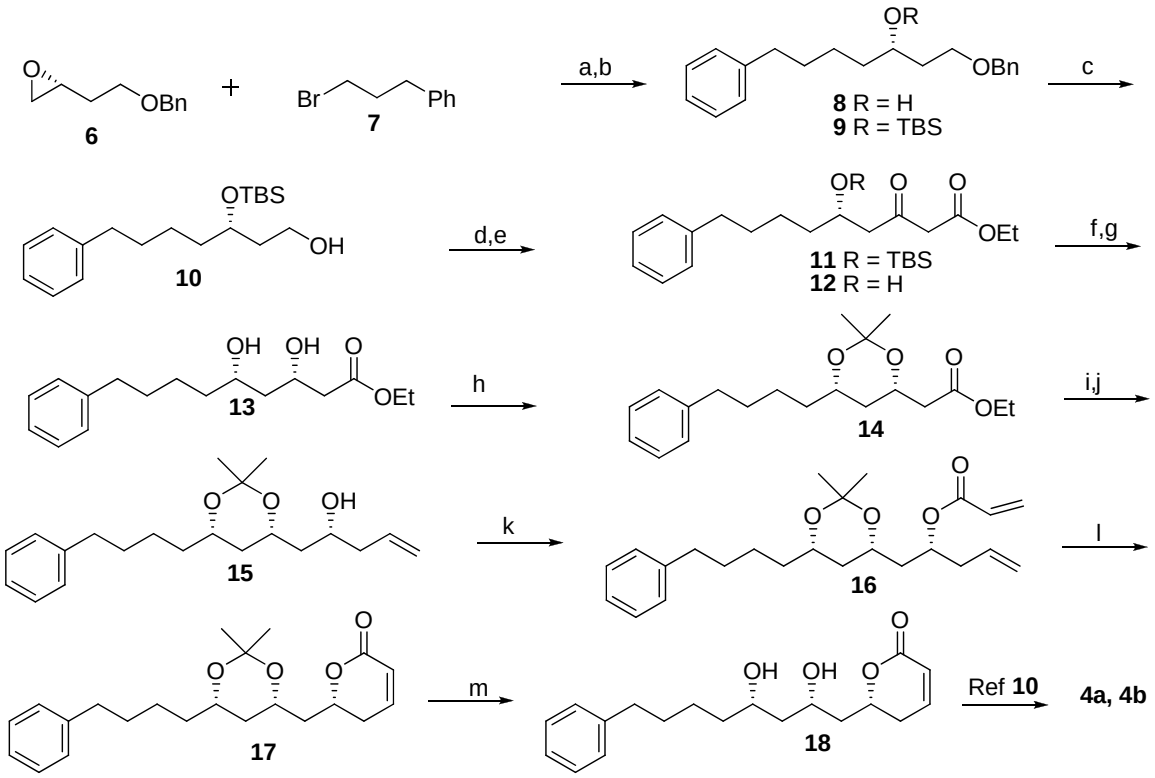
Figure 1. Representative skipped polyol natural products

3.2. Review of Literature

Various methods are available in literature for the synthesis of these compounds. Shibasaki and co-workers[10] reported the enantioselective synthesis of these pyrones, which relies upon catalytic asymmetric epoxidation of α,*β*-unsaturated imidazolides and amides, using lanthanide-BINOL complexes, and diastereoselective reduction of ketones. Keck allylation has very often been reported for the formation of the stereocentres. Carbohydrate based approach has also been reported starting from α-D-glucoheptonic-*γ*-lactone for the synthesis of **4a** and **4b.** [11a] Mostly all the strategies rely upon RCM to form the α,β unsaturated lactone moiety.

Yadav *et al*.[11b] (2008)

Yadav *et al*. employed RCM and Keck allylation to synthesize the target compounds **4a** and **4b**. The synthesis of the target compound **4a** and **4b** (Scheme**1**) started from the known epoxide **6** which on treatment with the Grignard reagent prepared from (3-bromopropyl)benzene **7** afforded the alcohol **8**. The alcohol **8** was protected as TBS ether and subsequently debenzylated using Li in liquid NH_3 to afford primary alcohol **10**. Alcohol **10** was oxidized to the aldehyde which on treatment with ethyl diazoacetate furnished hydroxy protected β-ketoester **11**. Removal of the TBS group followed by enantioselective reduction of the keto group with catecholborane furnished 1,3-syn-diol **13**. Acetonide protection of the diol **13** and subsequent DIBAL-H reduction afforded aldehyde which on Keck allylation furnished the chiral homoallylic alcohol **15**. Acrylation of the alcohol **15** was carried out efficiently with acryloyl chloride to yield a diene **16**, a precursor for the ring closing metathesis. The diene **16** was reacted with the Grubbs' catalyst to furnish lactone **17**. Cleavage of the acetonide with PPTS in MeOH yielded dihydroxylactone **18** which was converted to **4a** and **4b** using known literature procedure. [10]

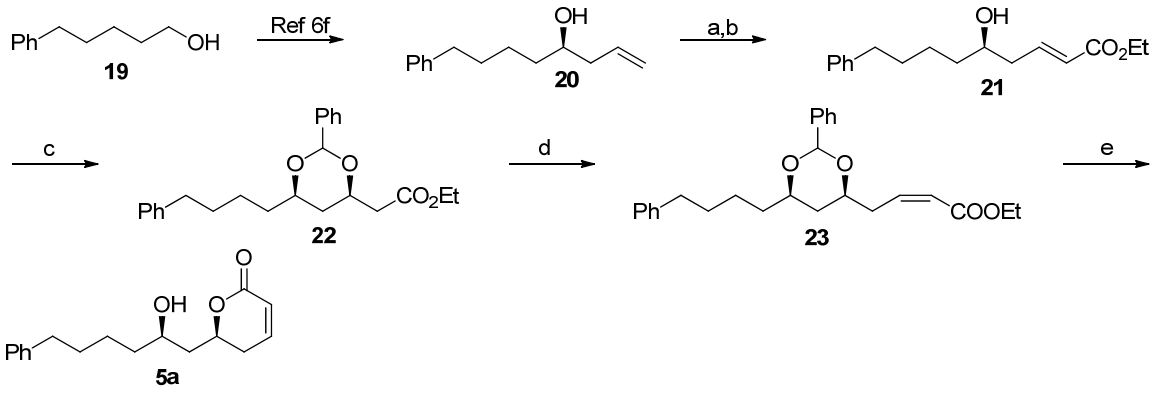


Scheme 1. *Reagents and conditions*: (a) Mg, THF, CuI, 0 °C, 2 h, 86%. (b) Imidazole, TBSCl, CH_2Cl_2, 2 h, 95%. (c) Li/liq.NH_3 , 87%. (d) IBX, DMSO, CH_2Cl_2, 2 h, 94%. (e) Ethyl diazoacetate, $SnCl_2$, CH_2Cl_2, 30 min, 83%. (f) THF, TBAF, 0.5 h, 85%. (g) Catecholborane, THF, 5 h, 70%. (h) DMP, CH_2Cl_2, PPTS, 12 h, 90%. (i) DIBAL-H, CH_2Cl_2, -78 °C, 70%. (j) (*R*)-(+)-1,1'-Binaphthalene-2,2'-diol, (*i*-PrO)$_4$Ti, 0 °C, CH_2Cl_2, 3 h. (k) Acryloyl chloride, EtN(*i*-Pr)$_2$, 0 °C, 3 h, 89%. (l) Grubbs' generation I, CH_2Cl_2, 0 °C, 6 h, 95%. (m) PPTS, MeOH, r.t., 4 h, 81%.

Radha Krishna *et al*.[6a] (2007)

Radha Krishna *et al*. investigated the olefin cross-metathesis with ethyl acrylate and RCM to synthesize the target molecule **5a**. The synthesis of **5a** (Scheme **2**) began from commercially available 5-phenylpentan-1-ol **19**. The homoallylic alcohol olefin **20** on cross-metathesis with ethyl acrylate using second generation Grubbs' catalyst led to unsaturated ester **21**. Later, homoallylic alcohol **21** was treated with benzaldehyde to afford benzylidene acetal **22**. The ester **22** was reduced with DIBAL–H to afford the aldehyde, which was then chain-elongated via a Wittig reaction to give the corresponding α,β-unsaturated ester **23** predominantly as the Z-isomer. Finally acid

catalyzed deprotection of the benzylidene acetal **23** followed by concomitant lactone cyclization with *p*-toluene sulfonic acid yielded target compound **5a**.

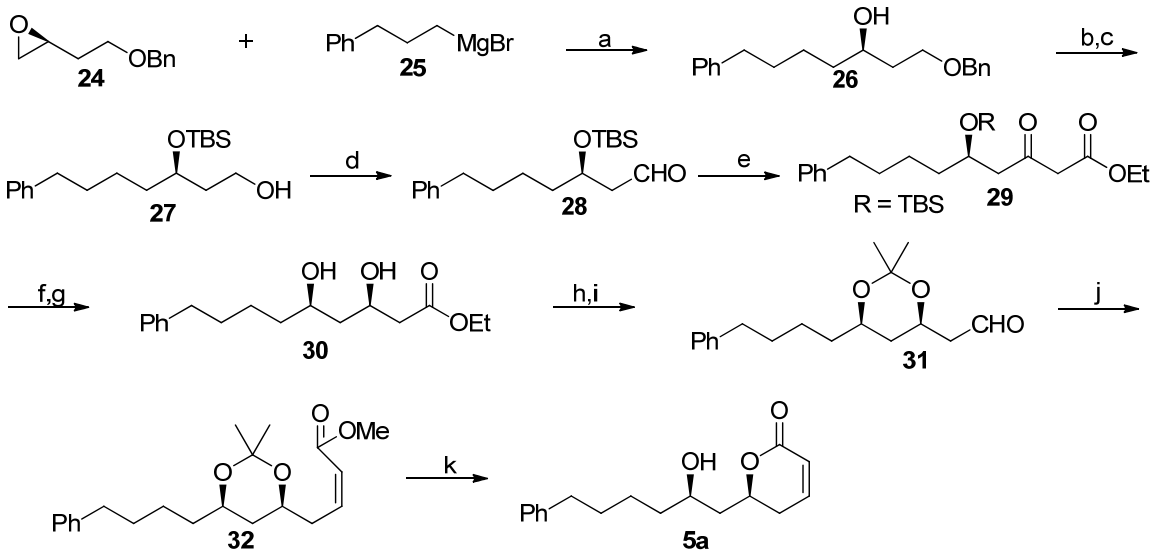


Scheme 2. *Reagents and conditions*: (a) Ethyl acrylate, Grubbs'-II, CH_2Cl_2, 40 °C, 12 h, 85% (b) (i) OsO_4, NMO, THF:H_2O, rt, 8 h (ii) $NaIO_4$, $NaHCO_3$, CH_2Cl_2, rt, 6 h (iii) Ph_3P=CHCOOEt, benzene, reflux, 1 h (65% over three steps) (c) Benzaldehyde, *t*-BuOK, THF, pH 7 buffer; 1 h, 57% (d) (i) DIBAL-H, CH_2Cl_2, -78 °C, 30 min (ii) $(F_3CCH_2O)_2POCH_2CO_2Me$, KHMDS, 18-crown-6, -78 °C, 1 h (76% over two steps) (e) (i) 80% aq AcOH, 60 °C, 3 h (ii) *p*-TSA, benzene, 4 h, 61%.

Sabitha *et al*.[6b] (2007)

Sabitha *et al*. employed catecholborane and Still–Gennari condensation to afford the target molecule **5a**. The synthesis of **5a** began with the known epoxide **24** (Scheme **3**) which on treatment with (3-phenylpropyl)magnesium bromide **25** furnished the secondary alcohol **26**. The secondary hydroxy group of **26** was protected as its *tert*-butyldimethylsilyl ether followed by the removal of benzyl group to afford the free primary hydroxy compound **27**. Oxidation of alcohol **27** provided the corresponding aldehyde **28** which was converted to the δ-silyloxy-β-oxo ester **29** on treatment with ethyl diazoacetate. The second stereogenic center with the required stereochemistry was established using catecholborane. Accordingly, the silyl group was deprotected and stereoselective reduction of the resulting acyclic β-hydroxy ketone employing catecholborane resulted in the *syn*-1,3-dihydroxy ester **30**. The 1,3-diol moiety of **30** was protected as acetonide, converted into aldehyde **31** and subsequently subjected to Still–Gennari condensation with bis (2,2,2-trifluoroethyl) (methoxycarbonylmethyl)

phosphonate to afford the *Z*-olefinic ester **32**. Treatment of **32** with *p*-toluenesulfonic acid finally afforded the target molecule **5a**

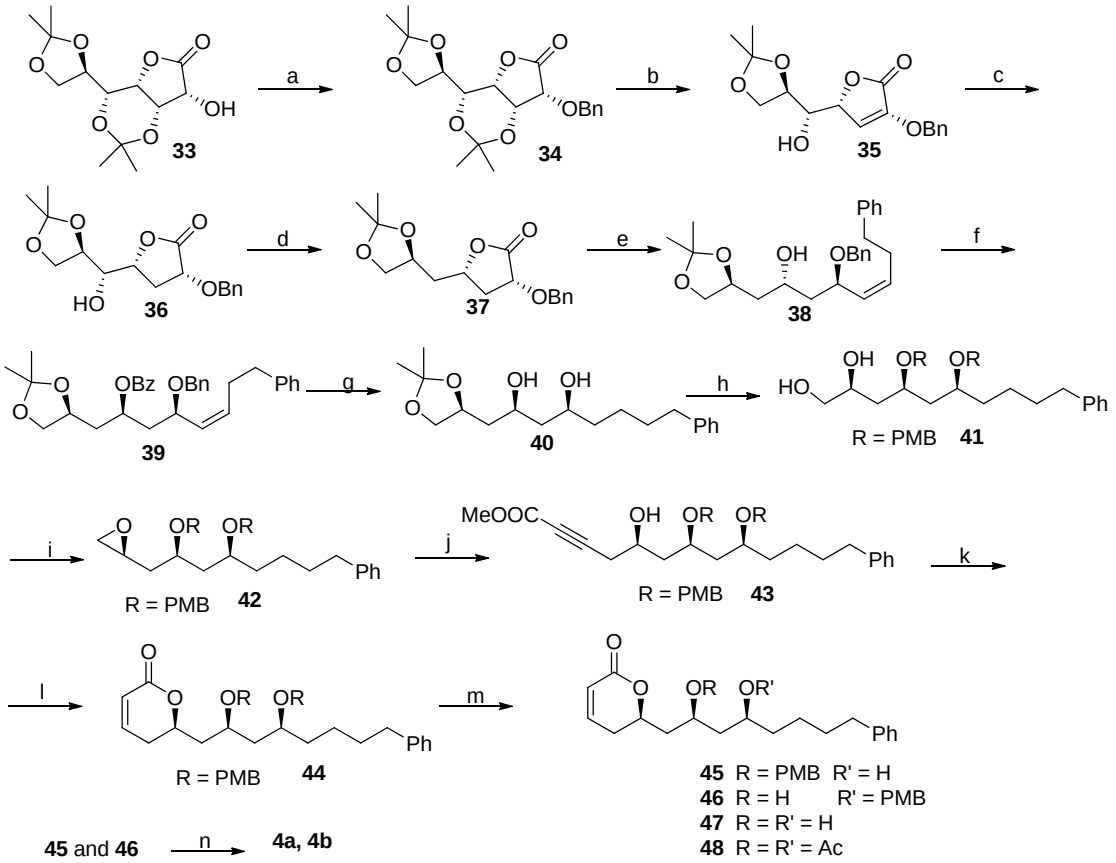


Scheme 3. *Reagents and conditions*: a) CuI, THF, 0 °C to rt, 2 h, 86% b) TBDMSCl, imidazole, CH_2Cl_2, DMAP, 0 °C, 2 h, 95% c) H_2, Pd/C, EtOAc, rt, 6 h, 87% d) IBX, DMSO, 0 °C to rt, 2 h, 94% e) N_2CHCO_2Et, anhyd $SnCl_2$, CH_2Cl_2, 0 °C to rt, 40 min, 83% f) TBAF, THF, 2 h, 85% g) catecholborane, THF, –10 °C, 5 h, 96% h) 2,2-dimethoxypropane, PPTS, 90% i) DIBAL-H, CH_2Cl_2, –78 °C, 1 h, 70% j) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, NaH, THF, –78 °C, 2 h, 80% k) *p*-TSA, benzene, rt, 1 h, 73%.

Ramana *et al.*[11a] (2005)

Ramana *et al.* investigated the deoxygenation by base mediated elimination and stereocontrolled reduction and Barton-McCombie radical deoxygenation for the synthesis of **4a** and **4b**. Benzyl protection of the C-2 hydroxyl group of R-D-glucoheptonic-γ-lactone diacetonide **33** gave the benzyl ether **34** (Scheme **4**) which was subjected to elimination followed by selective conjugate reduction to give lactone **35**. Subsequent reduction of **35** with DIBAL-H followed by Wittig olefination with 3-phenylpropyltriphenylphosphorane furnished **38**. Mitsunobu reaction of **38** furnished the benzoate derivative **39** which on hydrogenation followed by saponification gave the diol **40**. The diol **40** was protected with *p*-methoxybenzyl chloride and subsequently the 1,2-isopropylidene group was hydrolyzed to obtain the terminal diol **41**. Selective tosylation of primary hydroxyl group followed by cyclization afforded the epoxide **42**. Lithium methyl propiolate was reacted with epoxide **42** to furnish the β-hydroxy

alkyne derivative **43** which was successively subjected to partial reduction and lactonization resulting in the formation of the α-pyrone intermediate **44**. Deprotection of PMB ethers of **44** provided a (1:1) regiomeric mixture of mono-PMB ethers **45** and **46** along with the diol **47**. The diol **47** was converted to the diacetate **48**. The acetylation of **45**/**46** followed by treatment with TFA gave a mixture of **4a** and **4b** (3:1), separated by preparative HPLC.

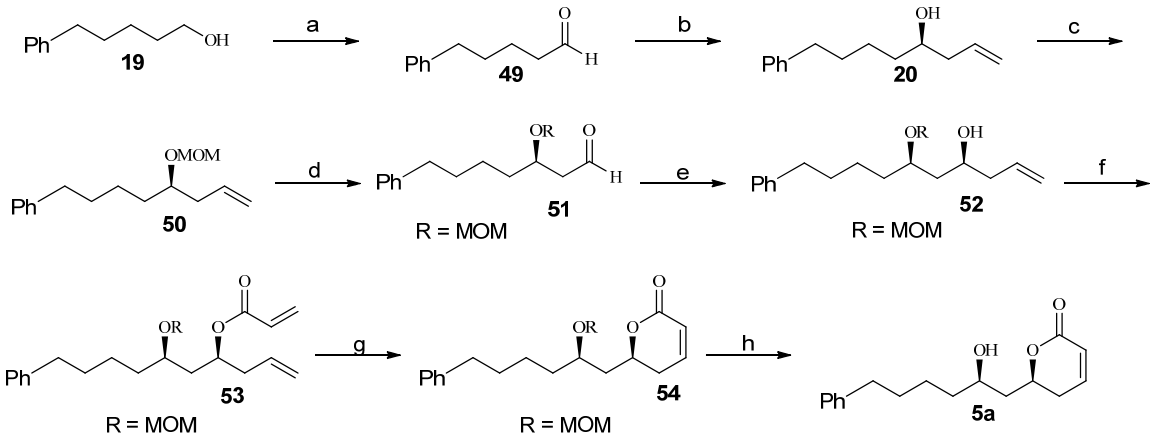


Scheme 4. *Reagents and conditions*: (a) Ag_2O, BnBr, CH_2Cl_2, reflux, 6 h, 84% (b) KO^{t}Bu, THF, -78 °C, 0.25 h, 81% (c) $NaBH_4$, $NiCl_2.6H_2O$, methanol, 0 °C, 1.5 h, 61% (d) NaH, CS_2, MeI, THF, -15 °C to rt, 12 h, 93%, followed by *n*-Bu_3SnH, AIBN, toluene, reflux, 5 h, 71% (e) DIBAL-H, CH_2Cl_2, -78 °C, 0.5 h, followed by $[C_6H_5CH_2CH_2CH_2PPh_3]$+I-, *n*-BuLi, THF, 0 °C to rt, 12 h, 93% (f) DEAD, TPP, benzoic acid, THF, 0 °C, 2 h, 69% (g) H_2-Raney-Ni, ethanol, 20 psi, 12 h, followed by NaOMe, MeOH, rt, 2 h, 91% (h) NaH, PMBCl, DMF, 0°C rt, 6 h, followed by PPTS, methanol, 24 h, 85% (i) (i) TsCl, Bu_2SnO (cat.), triethylamine, DMAP, CH_2Cl_2, rt, 1 h (ii) K_2CO_3, MeOH, 0 °C to rt, 0.5 h, 78%. (j) methyl propiolate, *n*-BuLi, $BF_3.Et_2O$, THF, -78 °C, 1 h, 93% (k) H_2, $Pd/CaCO_3$, quinoline, benzene, 1 NTP, 0.5-1 h, 72%,

followed by PPTS, $CHCl_3$, reflux, 6 h, 95% (l) TFA, DCM, 0 °C, 0.5 h, 78% (**45**/**46** and **47**) and 90% (**4a**/**4b**) (m) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 6 h, 94%.

Chandrasekhar *et al*.[11c] (2004)

Chandrasekhar *et al*. employed the asymmetric Keck allylation , Maruoka allylation and RCM to achieve the target molecule **5a**. The enantioselective synthesis of compound **5a** commenced from commercially available 5-phenyl-1-pentanol **19** as shown in (Scheme **5**) which on oxidation followed by Keck allylation afforded homoallylic alcohol **20**. The free hydroxyl group of homoallylic alcohol was protected with MOMCl followed by dihydroxylation–oxidative cleavage of olefin to give the required aldehyde **51**. Aldehyde **51** was once again subjected to asymmetric Keck allylation to furnish the homoallyl alcohol **52** which was treated with acryolyl chloride to yield acryloyl ester **53**. Acryloyl ester **53** was subsequently subjected to RCM employing Grubbs' catalyst to furnish lactone **54** which on MOM deprotection afforded **5a**.



Scheme 5. *Reagents and conditions*: (a) IBX, DMSO–THF, rt, 4 h, 88% (b) $TiCl_4$ (5 mol%), $Ti(O^iPr)_4$ (15 mol%), rt, 1 h, Ag_2O (10 mol%), rt, 5h, *S*-BINOL (20 mol%), rt, 2 h, CH_2Cl_2, allyltri^{n}butyltin, 0 ^oC, 12 h, 82% (c) MOMCl, DIPEA, CH_2Cl_2, 3 h, 0 ^oC, 90% (d) (i) OsO_4 (0.5 mol%), NMO, acetone–H_2O, rt, 4 h (ii) $NaIO_4$, rt, 2 h (e) $Ti(O^iPr)$ (10 mol%) *S*-BINOL (20 mol%), rt, 1 h, allyltri^{n}butyltin, CH_2Cl_2, rt, 12 h, 72% (f) acryolyl chloride, DIPEA, CH_2Cl_2, rt, 3 h, 85% (g) Grubbs' catalyst, (5 mol%), DCM, rt, 18 h, 80% (h) 6N HCl–THF–H (1:2:1), rt, 24 h, 90%.

3.3. PRESENT WORK

Objective

The 6-substituted 5,6-dihydro-2*H*-pyran-2-ones (α,β-unsaturated-δ-lactones) are important structural subunits in many biologically active natural products. These structural units are important for a wide variety of biological activities such as plant growth inhibition as well as antifungal,[8] antifeedant, antibacterial, and antitumour properties.[7] α,β-Unsaturated δ-lactone functionality is presumed to be responsible for biological activities as a result of its ability to act as a Michael acceptor, enabling these molecules to bind to a specific target enzyme. Because of their wide range of biological properties,[7,8,9] such as antifungal activity, cytotoxicity against human tumor cells,[7] and inducing apoptosis [9], these compounds are of marked interest not only from a chemical, but also from a pharmacological perspective. The 1,3,5-polyol/pyrones **4a** and **4b**[5] belong to this class of compounds. They have been isolated from Ravensara anisata and possess inhibitory activity against C. Cucumerinum. (*6S*)-5,6-Dihydro-6-[(*2R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one **5a**, an example of this class of natural product, is also a leading antifungal compound and was isolated by Hostettmann and co-workers, from Ravensara crassifolia.[6] They showed that **5a** exhibited antifungal activity against the phytopathogenic fungus Cladosporium cucumarinum in a bioautographic TLC assay. Considering its strong and selective biological profile, ravensara has attracted a great deal of interest among synthetic organic chemists worldwide as an attractive synthetic target. Biological activity, structural uniqueness and the challenge to synthesize them in optically pure form have made them attractive targets for many total syntheses.

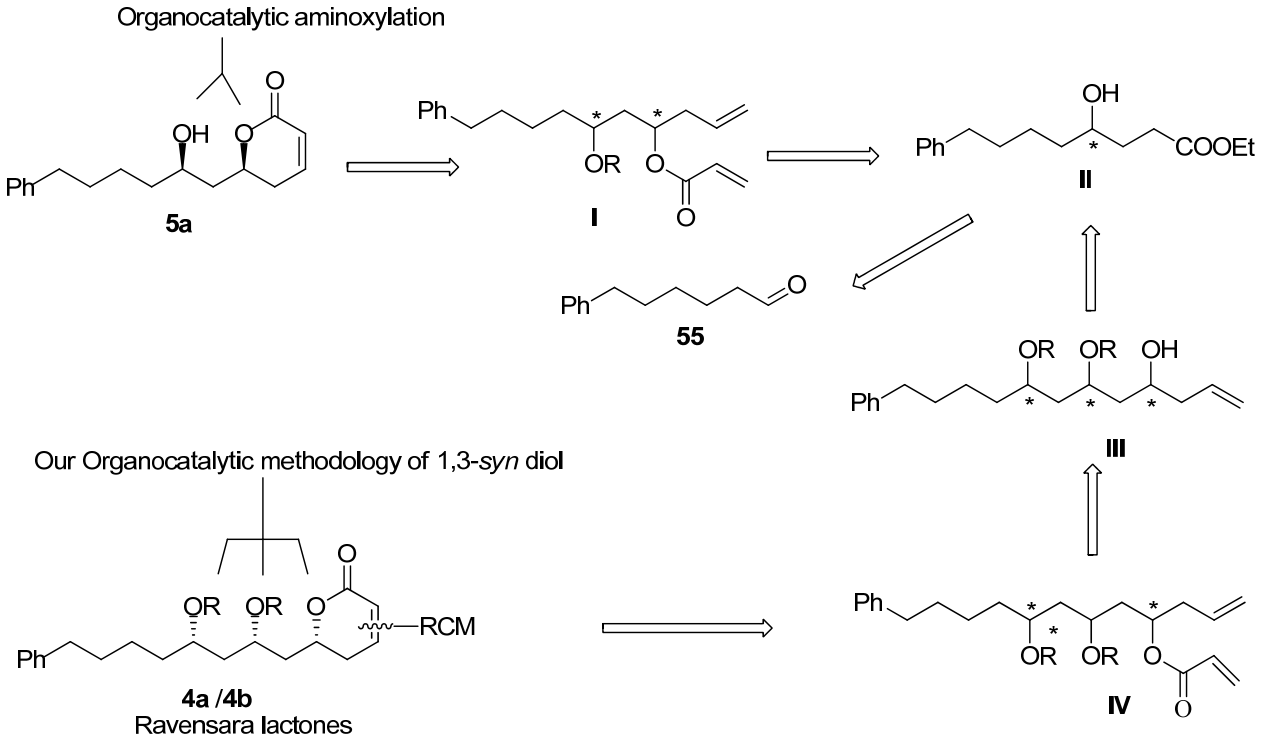
3.4. Results and Discussion

Last decade has witnessed an upsurge of interest in using small organic molecules as a highly selective and effective catalyst. [12] As a result the area of organocatalysis has now emerged as powerful tool available for asymmetric synthesis.[13] Proline in the recent past has been defined as a 'universal catalyst' because of its utility in different reactions providing rapid, catalytic, atom-economical access to enantiomerically pure products.[14,15]

In continuation of our interest in organocatalysis[16] and asymmetric synthesis of biologically active compounds,[17]we became interested in proline-catalyzed sequential α-aminoxylation, Horner-Wadsworth-Emmons (HWE) olefination approach[18] for the synthesis of (6*S*)-5,6-dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one and ravensara lactones.

As retrosynthetically delineated in Scheme **6**, the target molecules, **4a**/**4b** and **5a** could be

obtained by the ring-closing metathesis (RCM) of the respective acryloyl esters **I** and **IV**. We envisioned that acryloyl esters **I** and **IV** could be derived by proline-catalyzed α-aminoxylation and subsequent synthetic manipulation of **II**, which in turn could be obtained from iterative sequential α-aminoxylation and Horner-Wadsworth-Emmons olefination of aldehyde **55** which is based on method developed by us to prepare both *syn* and *anti*-1,3 polyols in a stereo-and enantioselective manner.[16a]

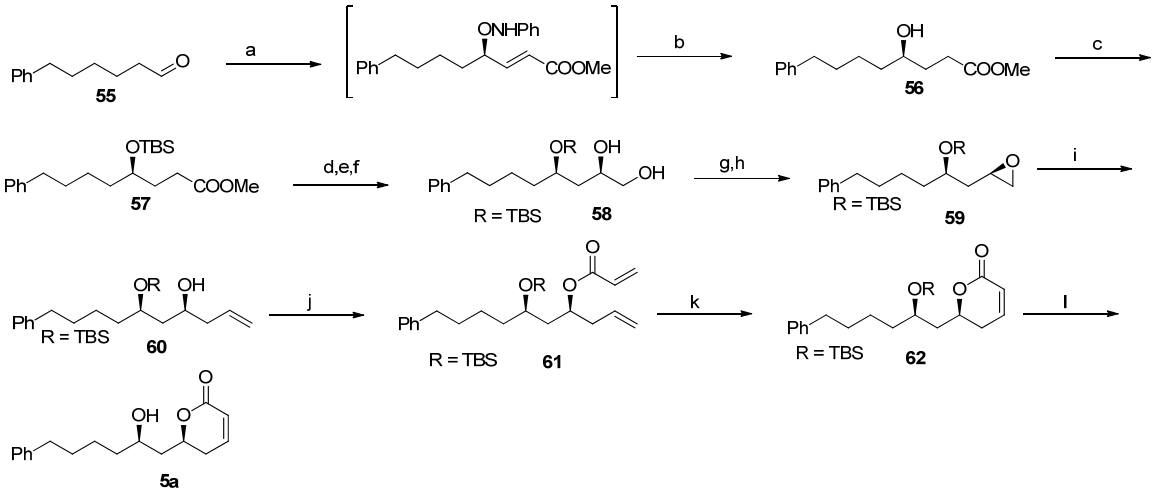


Scheme 6. Retrosynthetic route to **5a** and Ravensara lactones **4a**/**4b**

Synthesis of (6*S*)-5,6-dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one

As illustrated in scheme **7**, our synthesis commenced with phenyl hexanal **55** which was subjected to sequential α-aminoxylation (L-proline as a catalyst) followed by HWE olefination reaction, to furnish *O*-amino-substituted allylic alcohol. In an effort to minimize handling of intermediates and its time-consuming purification, the crude product obtained after workup was directly subjected to hydrogenation conditions using catalytic amount of Pd/C to furnish the *γ*-hydroxy ester **56** in good yield. Thus, in two steps and one column purification, *γ*-hydroxy ester **56** was obtained in 65% yield and 98% ee. Appearance of peak at 3486 cm^{-1}in IR spectrum confirmed the formation of compound **56**. The TBS protection of the hydroxy group eventually furnished the TBS protected γ-hydroxy ester **57** in 92% yield. The appearance of singlets at δ -0.02, 0.00, 0.85 in ^{1}H NMR and disappearance of peak at 3486 cm^{-1} in IR spectrum confirmed the formation of compound **57**. Ester **57** was then reduced with DIBAL-H at -78 ^{o}C to furnish aldehyde, which was further subjected to α-aminoxylation catalyzed by L-proline, followed by in situ reduction using $NaBH_4$ to furnish the required *α*-amino-substituted diol in 78% yield and > 95% de (determined from the ^{1}H and ^{13}C NMR spectral analysis of crude reaction mixture). The crude product which was a mixture of diastereoisomers was purified by column chromatography to get a single diastereomer **58**. The IR spectrum of **58** showed broad hydroxyl absorption at 3412 cm^{-1}. Diol **58** on selective monotosylation and base treatment furnished epoxide **59** in 82% yield. ^{1}H NMR spectrum of **59** showed epoxide protons at δ 2.92-2.74 (multiplet, 1 H), 2.71 (doublet of doublet, 1 H, with coupling constant J = 4.9, 1.2 Hz) and 2.42 (doublet of doublet, with coupling constant J = 4.9, 2.4 Hz). The ^{13}C NMR spectrum of **59** showed upfield carbons characteristic of epoxide at δ 50 and 47.7. Ring opening of epoxide **59** with vinylmagnesium bromide in the presence of CuI gave the homoallylic alcohol **60** in 85% yield. The IR spectrum of **60** gave broad hydroxyl absorption at 3400 cm^{-1}. The ^{1}H NMR spectrum of **60** gave olefin peaks at 5.69-5.78 (multiplet, one proton), 5.07 (doublet, one proton), 5.05 (doublet, one proton). With the desired homoallylic alcohol **60** in hand, our next task was to construct the pyranone moiety by ring-closing metathesis. Thus alcohol **60** was esterified with acryloyl chloride in the presence of $i Pr_2NEt$ in DCM at -78 ^{o}C to afford the acryloyl ester **61**. The IR spectrum of **61** indicated absence of hydroxyl group; acryloyl carbonyl appeared at 1726 cm^{-1}. The carbonyl carbon appeared at δ 164.6 in the ^{13}C NMR spectrum. Subsequent ring-

closing metathesis[19] of ester **61** with commercially available Grubbs' 1st generation catalyst in refluxing CH_2Cl_2 for 24 h afforded the α,β-unsaturated δ-lactone **62** in 92% yield. The IR spectrum of **62** showed characteristic carbonyl group absorption of α,β-unsaturated δ-lactone at 1721 cm^{-1}. The olefin protons appeared at 6.83 (doublet of doublet of doublet) with J = 9.6, 5.8, 2.1 Hz, 6.01 (doublet of doublet of doublet) with J = 9.6, 1.9, 1.6 Hz, in the ^{1}H NMR spectrum. The olefinic carbons appeared at δ 145.8 and 121.5 in ^{13}C NMR spectrum. Finally desilylation was achieved by treatment of **62** with PTSA in methanol to give the target molecule **5a** in 90% yield. $[\alpha]^D_{25}$ -63.8 (c = 0.5, $CHCl_3$); lit.[20] $[\alpha]^D_{25}$ -58.85 (c = 0.65, $CHCl_3$); lit.[21] $[\alpha]^D_{25}$ -53.1 (c 0.40, $CHCl_3$). The physical and spectroscopic data of **5a** were in full agreement with the literature data.[20,21]



Scheme 7. *Reagents and conditions:* (a) Nitrosobenzene, L-Proline, DMSO; trimethyl phosphonoacetate, DBU, LiCl, CH_3CN (b) H_2/Pd–C, EtOAc, 8 h, 65% (overall two steps) (c) TBSCl, imidazole, DCM, overnight, 92% (d) DIBAL-H, DCM, -78 ^oC (e) L-Proline, nitrosobenzene, DMSO, 60 min then $NaBH_4$, MeOH, 10 min (f) H_2/Pd–C, EtOAc, 12 h, 78% (over three steps) (g) TsCl, Bu_2SnO, Et_3N, DCM 2 h (h) K_2CO_3, MeOH, rt, 1 h, 82% (over two steps) (i) vinylmagnesium bromide, THF, CuI, -20 ^oC, 12 h, 85% (j) Acryloyl chloride, i-Pr_2NEt, DCM, -78 ^oC, 75% (k) $(PCy_3)_2Ru(Cl)_2$=CH-Ph (20 mol%), CH_2Cl_2, reflux, 24 h, 92% (l) p-TSA, methanol, 20 min, 90%.

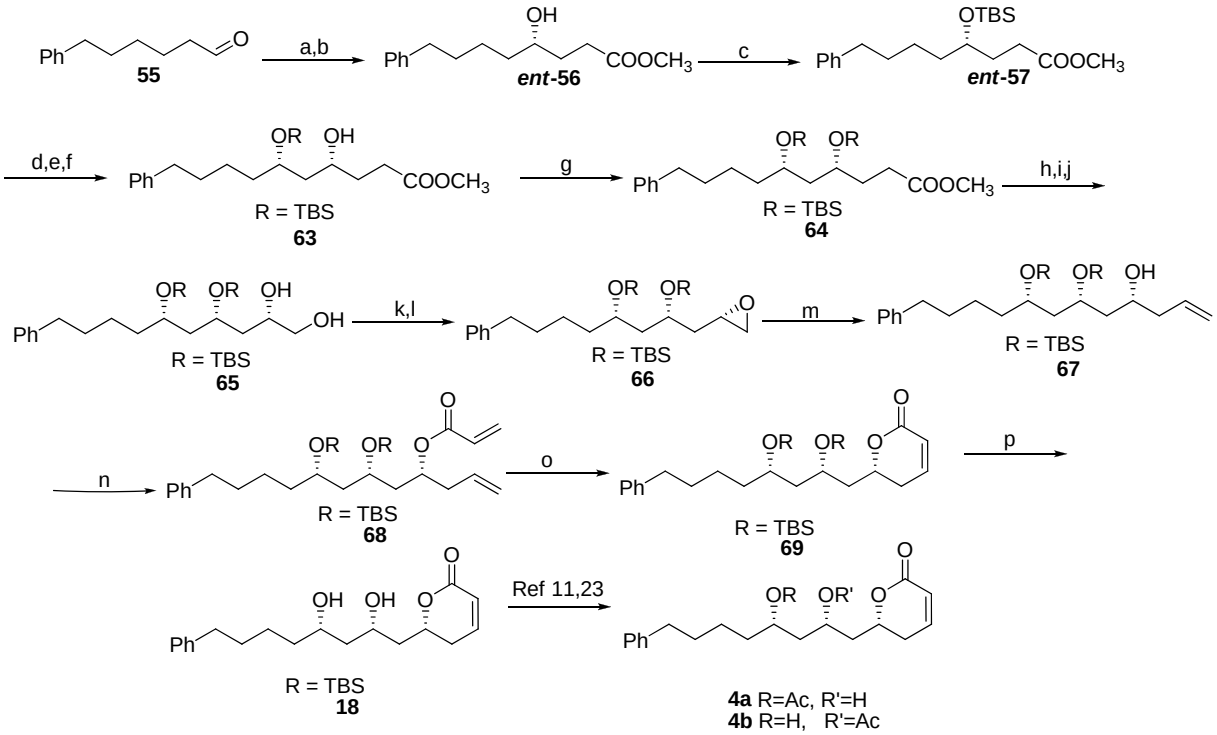
Synthesis of Ravensara lactones

We further extended this approach for the synthesis of a ravensara lactones **4a** and **4b** containing *syn*/*syn*-1,3,5-triol (Scheme **8**). The synthesis of target compound

commenced with commercially available aldehyde **55**, which was subjected to α-aminoxylation using D-proline as catalyst followed by HWE-olefination reaction to furnish *O*-amino-substituted allylic alcohol which was directly subjected to hydrogenation conditions using catalytic amount of Pd/C to furnish the γ-hydroxy ester ***ent*-56** in 60% yield and 95% ee. The free hydroxy group of γ-hydroxy ester ***ent*-56** was protected as TBS ether using TBSCl to furnish compound ***ent*-57** in 90% yield. The appearance of singlets at δ -0.02, 0.00, 0.85 in ^{1}H NMR and disappearance of peak at 3368 cm^{-1}in IR spectrum confirmed the formation of compound ***ent*-57**. With a substantial amount of the TBS ether ***ent*-57** in hand, we then proceeded toward the first cycle of iteration. The DIBAL-H reduction of ester ***ent*-57** furnished the corresponding aldehyde which on α-aminoxylation using D-proline as a catalyst followed by HWE olefination and subsequent Pd/C reduction gave γ-hydroxy ester **63**. Further TBS protection of free hydroxy group afforded TBS ether **64** in overall 50% yield. The ^{1}H NMR analysis revealed the diastereomeric purity (de) of the reaction to be >95%. The crude product which was a mixture of diastereoisomers was purified by column chromatography to get a single diastereomer **64**. Appearance of the peaks in the range of δ 3.83-4.01 in ^{1}H NMR confirmed the formation of compound **64**. The DIBAL-H reduction of compound **64** at -78 ^{o}C furnished aldehyde, which was again subjected to α-aminoxylation catalyzed by D-proline, followed by in situ reduction using $NaBH_4$ to furnish the required α-amino-substituted diol, which on reductive hydrogenation afforded the diol **65** in 75% yield and >85% de ratio. Again the diastereomeric ratio was calculated by ^{1}H and ^{13}C NMR analysis of crude reaction mixture. The crude product thus obtained was subjected to column chromatography to get a single diastereomer **65**. The IR spectrum of **65** showed broad hydroxyl absorption at 3411 cm^{-1}. Diol **65** on selective monotosylation and base treatment afforded epoxide **66** in 80% yield. ^{1}H NMR spectrum of **66** showed epoxide protons at δ 3.05-2.99 (multiplet, 1 H), 2.73 (doublet of doublet, 1 H, with coupling constant J = 4.9, 1.2 Hz) and 2.59 (doublet of doublet, with coupling constant J = 4.9, 2.4 Hz). The ^{13}C NMR spectrum of **66** showed upfield carbons characteristic of epoxide at δ 54.9 and 44.3. Epoxide **66** was opened with vinylmagnesium bromide to get the homoallylic alcohol **67** in 80% yield. The ^{1}H NMR analysis revealed the diastereomeric purity (de) of the reaction to be >95%. The IR spectrum of **67** gave broad hydroxyl absorption at 3400 cm^{-1}. The ^{1}H NMR spectrum of **67** gave olefin peaks at 5.82-5.61 (multiplet, one

proton), 5.04 (doublet, one proton), 4.96 (doublet, one proton). With the desired homo allylic alcohol **67** in hand, our next task was to construct the pyranone moiety by ring-closing metathesis. Thus, alcohol **67** was esterified with acryloyl chloride in the presence of iPr$_2$NEt in DCM at -78 ^{o}C to afford the acryloyl ester **68** in 85% yield. The IR spectrum of **68** indicated absence of hydroxyl group; acryloyl carbonyl appeared at 1716 cm^{-1}. The carbonyl carbon appeared at δ 165.4 in the ^{13}C NMR spectrum. Subsequent ring-closing metathesis[19] of ester **68** with commercially available Grubbs' 1st generation catalyst gave **69** in 88% yield. The IR spectrum of **69** showed characteristic carbonyl group absorption of α,β-unsaturated δ-lactone at 1721 cm^{-1}. The olefin protons appeared at 6.13 (doublet of doublet of doublet) with J = 9.6, 5.8, 2.1 Hz, 5.85 (doublet of doublet of doublet) with J = 9.6, 1.9, 1.6 Hz, in the ^{1}H NMR spectrum. The olefinic carbons appeared at δ 142.6 and 128.8 in ^{13}C NMR spectrum.

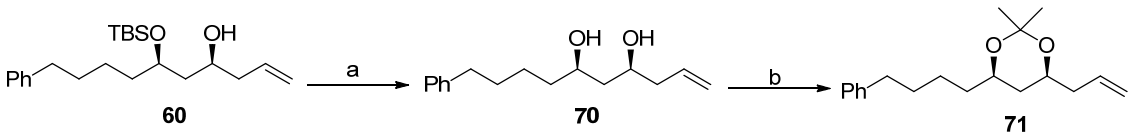
Finally global deprotection of TBS group was achieved by treatment of lactone **69** with TFA to give diol **18** in 90% yield. $[\alpha]^{D}_{25}$ +62.1 (c = 1, $CHCl_3$); lit. [11b] $[\alpha]^{D}_{25}$ + 61.9 (c = 1, $CHCl_3$) The physical and spectroscopic data of **18** were in full agreement with the literature data.[10,11] Since the monoacetylation of lactone **18** to the target molecules has already been reported,[11b] this constitutes the formal synthesis of **4a** and **4b**.



Scheme 8. Reagents and conditions: (a) Nitrosobenzene, D-Proline, DMSO; HWE salt, DBU, LiCl, CH_3CN (b) H_2/Pd–C, EtOAc, 8 h, 60% (overall two steps) (c) TBSCl, imidazole, DCM, overnight, 90% (d) DIBAL-H, DCM, -78 ^oC (e) Nitrosobenzene, D-Proline, DMSO; HWE salt, DBU, LiCl, CH_3CN (f) H_2/Pd–C, EtOAc, 8 h, 65% (g) TBSCl, imidazole, DCM, overnight, 50% (overall four steps) (h) DIBAL-H, DCM, -78 ^oC (i) D-Proline, Nitrosobenzene, DMSO, after 30 mins $NaBH_4$, MeOH, 0.5 h (j) H_2/Pd–C, EtOAc, 8 h, 75% (over three steps) (k) TsCl, Bu_2SnO, Et_3N, 2 h; (l) K_2CO_3, MeOH, rt, 1 h, 80% (over two steps) (m) vinylmagnesium bromide, THF, CuI, -20 ^oC, 12 h, 80 % (n) Acryloyl chloride, i-Pr_2NEt, DCM, -78 ^oC, 4 h, 85% (o) $(PCy_3)_2Ru(Cl)_2$=CH-Ph (20 mol%), CH_2Cl_2, reflux, 88% (p) TFA, DCM, 30 min, rt, 90%.

Relative stereochemistry determination

The relative stereochemistry of 1,3-diols **60** was determined *via* Rychnovsky's acetonide method[22] (Scheme **9**). The TBS deprotection of compound **60** furnished the diol **70** in 92% yield. Diol **70** on treatment with 2,2-DMP gave the *syn* acetonide **71** in 82% yield . The appearance of methyl resonance peaks at δ 18.78 and 30.44 ppm and acetal carbon resonating at δ 99.18 ppm confirmed the presence of *syn* acetonide. (Scheme **9**).



60 **70** **71**

Scheme 9. *Reagents and conditions*: (a) TFA, DCM, overnight, rt, 92% (b) 2,2-DMP, *p*-TSA, DCM, 8 h, 82%.

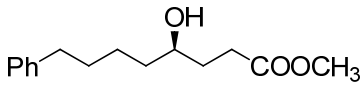
3.5. Conclusion

In conclusion, the stereoselective synthesis of **4a**/**4b** and **5a** has been achieved by using a concise and efficient organocatalytic strategy with a high degree of enantio- and diastereoselectivities. The desired stereocentres can simply be achieved by changing the catalyst. We believe that this approach would permit maximum variability in product structure with regard to stereochemical diversity which is particularly

important for making of various synthetic analogues required for screening of biological activity.

3.6. Experimental Section

(*R*)-Methyl-4-hydroxy-6-phenyloctanoate (56)



To a solution of phenyl hexanal **55** (2.0 g, 11.36 mmol) and nitrosobenzene (1.21 g, 11.36 mmol) in anhydrous DMSO (20 mL) was added L-proline (0.52 g, 4.54 mmol) at 20 °C. The mixture was vigorously stirred for 25 min under argon (the color of the reaction changed from green to yellow during this time), then cooled to 0 °C. Thereafter, a pre-mixed and cooled (0 °C) solution of trimethylphosphonoacetate (4.92 mL, 34.09 mmol), DBU (5.1 mL, 34.09 mmol) and LiCl (1.43 g, 34.09 mmol) in CH_3CN (29 mL) was added quickly (1–2 min) at 0 °C. The resulting mixture was warmed to room temperature over 1 h, the reaction was quenched by addition of ice pieces. The acetonitrile was evaporated under vacuum. The reaction mixture was then poured into water (100 mL) and extracted with Et_2O (5x100 mL). The combined organic layer was washed with water, brine, dried (Na_2SO_4) and concentrated in vacuo to give the crude product which was directly subjected to the next step without purification. To the crude allylic alcohol in ethyl acetate was added Pd-C (10%) under hydrogenation conditions and the reaction mixture was allowed to stir overnight. After completion of the reaction (until ^1H NMR analysis of the crude mixture indicated complete conversion), the mixture was filtered through a pad of Celite and concentrated in vacuo to give the γ-hydroxy ester. The crude product was then purified by using flash column chromatography using petroleum ether/EtOAc (85:15) as eluent to give **56** as a colorless liquid.

Yield: 1.95 g, 65%

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

$[\alpha]_D^{25}$: -12.38 (*c* 1, $CHCl_3$).

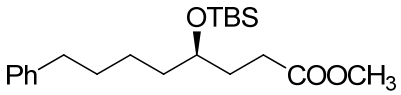
IR ($CHCl_3$, cm^{-1}) ν_{max} = 3486, 1730, 1602, 1491, 1023, 931.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.22-7.24 (m, 5H), 3.51-3.64 (m, 4H), 2.62 (t, J = 7.7 Hz, 2H), 2.30 (t, J = 7.3 Hz, 2H), 1.55-1.32 (m, 6H), 1.67–1.71 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.2, 141.3, 127.1, 124.3, 69.7, 35.6, 34.7, 30.4, 23.6, 28.5.

LC–MS m/z =273 $[M + Na]^+$.

(*R*)-Methyl 4-((*tert*-butyldimethylsilyloxy)-8-phenyloctanoate (57)



To an ice-cold stirred solution of **56** (1.5 g, 5.99 mmol) in CH_2Cl_2 (10 mL) were added imidazole (0.81 g, 11.91mmol) and TBSCl (1.358 g, 8.99 mmol) at 0 °C. The resulting mixture was stirred overnight at room temp before H_2O (20 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Silica gel column chromatography of the crude product using petroleum ether/ethyl acetate (99:1) gave TBS ether **57** as a colorless liquid.

Yield: 1.99 g, 92%

Mol. Formula: $C_{21}H_{36}O_3Si$

$[\alpha]_D^{25}$: -17.0 (*c* 0.8, $CHCl_3$).

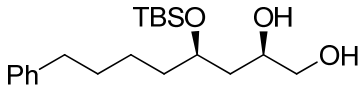
IR ($CHCl_3$, cm^{-1}) ν_{max} = 2955, 1736, 1684, 1454.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.16-7.22 (m, 5H), 3.60-3.72 (m, 4H), 2.58 (t, J = 8.0 Hz, 2H), 2.34 (t, J = 8.0 Hz, 2H), 1.69–1.78 (m, 2H) 1.38–1.67 (m, 6H), 0.85 (s, 9H), -0.02 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.4, 142.6, 128.4, 125.6, 71.0, 51.5, 36.8, 35.9, 31.7, 29.7, 25.8, 24.9, 18.0, 4.4.

Elemental Analysis: calculated for $C_{21}H_{36}O_3Si$ C, 69.18, H, 9.95 % ; Found C, 69.11, H, 9.91% .

(2*R*,4*R*)-4-((*tert*-Butyldimethylsilyloxy)-8-phenyloctane-1,2-diol (58).



To a solution of ester **57** (1.0 g, 2.74 mmol) in dry DCM (10 mL) at 0 °C was added dropwise DIBAL-*H* (5.49 mL, 5.49 mmol, 1 M in toluene) through a syringe. The reaction mixture was warmed to room temperature over 1 h, then recooled to 0 °C and treated with satd. aqueous solution of sodium potassium tartrate (50 mL). The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3X50 mL). The combined organic extracts were washed with water, brine, dried (Na_2SO_4), filtered and concentrated to give the crude aldehyde, which was used for the next step without purification. To a stirred solution of aldehyde (0.50 g, 1.49 mmol) and nitrosobenzene (0.160 g, 1.49 mmol) in DMSO (9 mL) was added L-proline (0.034 g, 0.29 mmol, 20 mol %) in one portion at 25 °C. After 60 min, the temperature was lowered to 0 °C, followed by dilution with anhyd. MeOH (10 mL) and careful addition of exces $NaBH_4$ (0.199 g, 5.2 mmol). The reaction was quenched after 10 min by pouring the reaction mixture into a vigorously stirred biphasic solution of Et_2O and aqueous HCl (1 M). The organic layer was separated, and the aqueous phase was extracted with EtOAc (3X20 mL). The combined organic phase was dried with anhyd Na_2SO_4, concentrated, and purified by column chromatography over silica gel using EtOAc/petroleum ether (40:60) as eluent to give pure aminoxy alcohol. The aminoxy alcohol (0.30 g, 0.85 mmol) was dissolved in EtOAc (10 mL) and to the solution was added 10% Pd/C (0.050 g) and the reaction mixture was stirred in a hydrogen atmosphere (1 atm, balloon pressure) for 12 h. After completion of the reaction (monitored by TLC), the reaction mixture was filtered through a Celite pad, concentrated, and the crude product was then purified by silica gel chromatography using petroleum ether/ethyl acetate (3:2) as eluent to give pure diol **58** yellow liquid.

Yield: 0.75 g, 78%

Mol. Formula: $C_{20}H_{36}O_3Si$

$[\alpha]_D^{25}$: + 6.4, (*c* 0.5, $CHCl_3$).

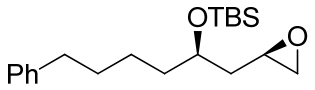
IR ($CHCl_3$, cm^{-1}) ν_{max} = 3412, 3018, 2938, 1612, 1513, 1248, 1215.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.08–7.15 (m, 5H), 4.00–4.03 (m, 2 H), 3.81 (dd, *J* = 4.0, 7.4 Hz, 1H), 3.48 (dd, *J* = 3.5, 7.25 Hz, 1H), 2.46–2.54 (m, 2H), 2.11 (brs, 2H), 1.15–1.53 (m, 8H), 0.79 (s, 9 H), 0.01 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 142.4, 138.1, 128.2, 125.7, 72.7, 70.8, 66.4, 37.7, 35.8, 31.5, 25.8, 25.1, 24.4, 17.9, –4.0, –4.7.

LC–MS: m/z =375 $[M + Na]^+$.

***Tert*-Butyldimethyl((*R*)-1-((*R*)-oxiran-2-yl)-6-phenylhexan-2-yloxy)silane (59).**



To a mixture of diol **58** (0.2 g, 0.56 mmol), in dry DCM (5 mL) was added dibutyltin oxide (2.82 mg, 0.011 mol) followed by the addition of *p*-toluenesulfonyl chloride (0.108 g, 0.56 mmol) and triethylamine (0.07 mL, 0.56 mmol) and reaction was stirred at room temperature under nitrogen. The reaction was monitored by TLC, after completion of reaction the mixture was quenched by adding water. The solution was extracted with DCM (3 X 10 mL) and then combined organic phase was washed with water, dried (Na_2SO_4) and concentrated. To this crude mixture in MeOH at 0 °C was added K_2CO_3 (117 mg, 0.85 mmol) and the resultant mixture was allowed to stir for 1 h at same temp. After completion of reaction as indicated by TLC, the reaction was quenched by addition of ice pieces and methanol was evaporated. The concentrated reaction mixture was then extracted with ethyl acetate (3 X 20 mL), the combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The column chromatography of crude product using petroleum ether: ethyl acetate (9:1) gave the epoxide **59** yield as a colorless liquid.

Yield: 0.15 g, 82%

Mol. Formula: $C_{20}H_{34}O_2Si$

$[\alpha]_D^{25}$ +4.8 (*c* 1.0, $CHCl_3$).

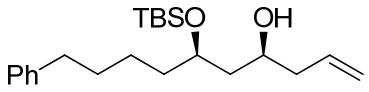
IR ($CHCl_3$, cm^{-1}) ν_{max} = 2934, 2858, 1612, 1586, 1513, 1463, 1248.

^{1}H NMR (200 MHz, $CDCl_3$): δ = δ 7.12–7.19 (m, 5H), 3.75–3.84 (m, 1H), 2.89–2.95 (m, 1 H), 2.71 (t, *J* = 4.12 Hz, 1H), 2.58 (t, *J* = 7.9 Hz, 2H), 2.38–2.42 (m, 1H), 1.26–1.57 (m, 8H),) 0.82 (s, 9H), –0.01 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 142.5, 128.2, 125.6, 70.0, 49.9, 47.7, 40.2, 37.7, 35.9, 31.6, 25.8, 24.7, 18.0, – 4.4.

LC–MS: m/z =357 $[M + Na]^+$.

(4*S*,6*R*)-6-(*tert*-Butyldimethylsilyloxy)-10-phenyldec-1-en-4-ol (60).



A round bottom flask was charged with copper (I) iodide (8 mg, 0.044 mmol), gently heated under vacuum, and slowly cooled with a flow of argon, and dry THF (2 mL) was added. This suspension was cooled to –20 ^{o}C and vigorously stirred, and vinylmagnesium bromide (1M in THF, 0.898 mL, 0.898 mmol) was injected to it. A solution of compound **59** (150 mg, 0.449 mmol) in THF (1 mL) was added slowly to the above reagent, and the mixture was stirred at –20 ^{o}C for 12 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl. The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum to get the crude residue, which was purified by silica gel column chromatography (PE/EtOAc, 4:1) to afford the pure product **60** as colorless oil.

Yield: 138 mg, 85%

Mol. Formula: $C_{22}H_{38}O_2Si$

$[\alpha]_D^{25}$ -7.1 (*c* 0.65, $CHCl_3$).

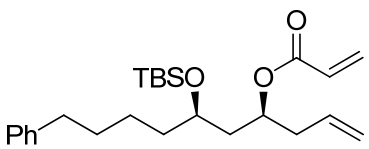
IR ($CHCl_3$, cm^{-1}) ν_{max} = 3400, 3071, 2927, 2560, 1726, 1629, 1411, 1261, 1195, 1055.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.07–7.21 (m, 5H), 5.69-5.78 (m, 1H), 5.05-5.07 (m, 2H) 3.70-3.87 (m, 2H), 2.57 (t, *J* = 7.59 Hz, 2H), 2.14–2.17 (dd, *J* = 7.41, 12.72 Hz, 2H), 1.18–1.51 (m, 8H), 0.81 (s, 9H), 0.00 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 142.5, 135, 128.3, 128.4, 128.3, 125.6, 117.5, 71.1, 69.2, 67.8, 42.9, 40.1, 37.7, 36.0, 31.6, 25.8, 24.6, 17.9, -4.1, -4.6.

Elemental Analysis: calculated for $C_{22}H_{38}O_2Si$ C, 72.87, H, 8.82%; found C, 72.91, H, 8.86%.

(4*S*,6*R*)-6-(*tert*-Butyl dimethylsilyloxy)-10-phenyldec-1-en-4-yl acrylate (61):



To a stirred solution of compound **60** (130 mg, 0.358 mmol) in dichloromethane (10 mL) were added acryloyl chloride (0.067 mL, 0.716 mmol) and *i*-Pr_2NEt (0.25 mL, 1.43 mmol) at -78 ^oC. The mixture was allowed to warm to room temperature and stirred for 4 h. The reaction mixture was diluted with water (8 mL) and extracted with dichloromethane (2X10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum to get the crude residue, which was purified by silica gel column chromatography (PE/EtOAc, 9:1) to afford the pure product **61** as colorless oil.

Yield: 112 mg, 75%

Mol. Formula: $C_{25}H_{40}O_3Si$

$[\alpha]_D^{25}$ +4.7 (*c* 1.0, $CHCl_3$).

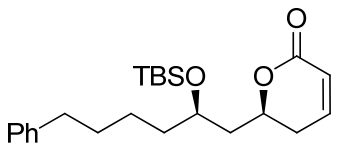
IR ($CHCl_3$, cm^{-1}) ν_{max} = 3071, 2927, 2560, 1726, 1629, 1411, 1261, 1195, 1055.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.25–7.17 (m, 5H), 6.41 (dd, *J* = 2.0 and 16.0 Hz, 1H), 6.09 (dd, *J* = 10.0, 18.0 Hz 1H), 5.70–5.76 (m, 2H), 5.02–5.08 (m, 3H), 3.64-3.75 (m, 1H), 2.58 (t, *J* = 7.5 Hz, 2H), 2.33–2.39 (m, 2H), 1.24–1.87 (m, 8H), 0.85 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 164.6, 141.6, 129.4, 127.7, 124.5, 116.9, 70.7, 69.8, 68.0, 40.1, 38.0, 35.5, 34.8, 30.5, 28.6, 24.8, 23.7, 23.3, 17.0, -0.01, -5.7.

Elemental Analysis: calculated for $C_{25}H_{40}O_3Si$ C, 72.06, H, 9.68%; Found C, 72.01, H, 9.71%.

(6*S*)-5,6-Dihydro-6-[(2*R*)-2-(*tert*-butyl dimethyl silanyloxy)-6-phenylhexyl]-2*H*-pyran-2-one (62):



To a stirred solution of bis(tricyclohexyl phosphine)benzylidine ruthenium(IV) dichloride (Grubbs catalyst, 10.4 mg, 5 mol %) in dichloromethane (50 mL) at 55 ^oC was added compound **61** (100 mg, 0.24 mmol) dissolved in dichloromethane (25 mL). The resulting mixture was heated for 24 h. After completion of the reaction, the

contents were cooled and solvent was removed under reduced pressure to yield crude product, which was purified on silica gel column eluting with petroleum ether/EtOAc (7:3) as eluent to afford the pure compound **62** as colorless oil.

Yield: 81.6 mg, 92%

Mol. Formula: $C_{23}H_{36}O_3Si$

$[\alpha]_D^{25}$ 10.4 (*c* = 0.5 $CHCl_3$).

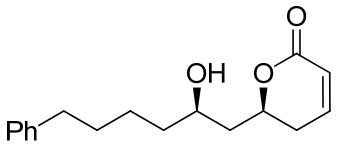
IR ($CHCl_3$, cm^{-1}) ν_{max} = 2938, 1719, 1638, 1399, 777.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.15-7.22 (m, 5H), 6.83–6.88 (m, 1H), 6.01 (d, *J* = 10 Hz, 1H), 4.48–4.59 (m, 1H), 3.83–3.89 (m, 2H), 2.54 (t, *J* = 8.0 Hz, 2H), 2.27–2.33 (m, 1H), 1.96–2.06 (m, 2H), 1.22-1.81 (m, 6H), 0.82 (s, 9H), 0.02 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 164.4, 145.0, 142.5, 128.4, 125.6, 121.5, 75.3, 67.4, 41.9, 36.4, 35.9, 31.5, 29.7, 25.8 24.8, 18.0, -4.2, -4.6.

Elemental Analysis: calculated for $C_{23}H_{36}O_3Si$ C, 71.08, H, 9.34%; Found C, 71.10, H, 9.39%

(6*S*)-5,6-Dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one (5a).



To a stirred solution of compound **62** (50 mg, 0.128 mmol) in methanol, catalytic amount of *p*-toluene sulfonic acid (5 mol %) was added and stirred for 20 min. Then the reaction mixture was treated with solid $NaHCO_3$. The methanol was removed and extracted with ethyl acetate (3 x 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and solvent was removed under reduced pressure to yield product, which was purified on silica gel column eluting with PE/EtOAc (6:4) to afford the pure product **5a** as a pale yellow solid. m.p. 32–35 °C; lit [20] 34–36 °C.

Yield: 62 mg, 90%

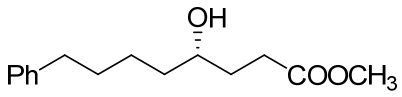
Mol. Formula: $C_{17}H_{22}O_3$

$[\alpha]^D_{25}$ -63.8 (*c* = 0.5, $CHCl_3$); lit. [20] $[\alpha]^D_{25}$ -58.85 (*c* 0.65, $CHCl_3$); lit. [21] $[\alpha]^D_{25}$ -53.1 (*c* 0.40, $CHCl_3$).

IR (KBr, cm^{-1}) ν_{max} = 3441, 2922, 2845, 1690, 1478, 1390, 1259.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.15–7.28 (m, 5H). 6.84–6.87 (m, 1H), 6.02 (dd, , *J* = 1.7 and 9.72 Hz, 1H), 4.45–4.50 (m, 1H), 3.70–3.75 (m, 1H), 3.45 (brs, 1H), 2.60 (t, *J* = 7.5 Hz, 2H), 2.41–2.46 (m, 2H), 2.10-2.16 (m, 2H), 1.57–1.64 (m, 6H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.5, 146.6, 144.4, 128.3, 128.8, 129.4, 128.3, 122.3, 75.0, 68.5, 44.3, 37.1, 35.0, 31.9, 29.7, 24.1.

(*S*)-Methyl 4-hydroxy-8-phenyloctanoate (*ent* 56):



To a solution of phenyl hexanal **55** (6.0 g, 34.08 mmol) and nitrosobenzene (3.63 g, 34.08 mmol) in anhydrous DMSO (520 mL) was added D-proline (1.56 g, 13.62 mmol) at 20 °C. The mixture was vigorously stirred for 25 min under argon (the color of the reaction changed from green to yellow during this time), then cooled to 0 °C. Thereafter, a pre-mixed and cooled (0°C) solution of trimethylphosphonoacetate (14.78 mL, 102.27 mmol), DBU (15.3 mL, 102.27 mmol) and LiCl (4.293 g, 102.27 mmol) in CH_3CN (80 mL) was added quickly (1–2 min) at 0°C. The resulting mixture was warmed to room temperature over 1 h, the reaction was quenched by addition of ice pieces. The solvent acetonitrile was evaporated under vacuum. The reaction mixture was then poured into water (100 mL) and extracted with Et_2O (5x100 mL). The combined organic layer was washed with water, brine, dried (Na_2SO_4) and concentrated in vacuo to give the crude product which was directly subjected to the next step without purification. To the crude allylic alcohol in ethyl acetate was added Pd-C (10%) under hydrogenation conditions and the reaction mixture was allowed to stir for 8 h. After completion of the reaction (until ^{1}H NMR analysis of the crude mixture indicated complete conversion), the mixture was filtered through a pad of Celite and concentrated in vacuo to give the γ-hydroxy ester. The crude product was then purified by using flash column chromatography using petroleum ether/EtOAc (85:15) as eluent to give ***ent* 56** as a colorless liquid.

Yield: 5.11 g, 60 %

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

$[\alpha]^{D}_{25}$= +12.55 (*c* 0.8, $CHCl_3$).

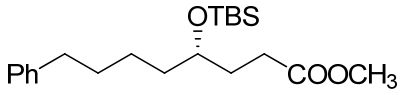
IR ($CHCl_3$, cm^{-1}) ν_{max} = 3368, 3022, 1728, 1602, 1496, 1454, 1217

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.11-7.40 (m, 5H), 3.63-3.75 (m, 4H), 2.61 (t, *J* = 7.7 Hz, 2H), *2*.40 (t, *J* = 7.3 Hz, 2H), 1.58-1.87(m, 2H), 1.20-1.47 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.3, 142.4, 128.2, 128.0, 125.5, 70.7, 36.6, 35.7, 31.4, 29.6, 24.7.

LC–MS: m/z =273 $[M + Na]^+$.

(*S*)-Methyl 4-(*tert*-Butyldimethylsilyloxy)-8-phenyloctanoate (*ent* 57):



To an ice-cold stirred solution of ***ent* 56** (3.0 g, 11.98 mmol) in CH_2Cl_2 (10 mL) were added imidazole (1.63 g, 23.96 mmol) and TBSCl (2.70 g, 17.97 mmol) at 0 °C. The resulting mixture was stirred overnight at room temp before H_2O (20 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Silica gel column chromatography of the crude product using petroleum ether/ethyl acetate (99:1) gave TBS ether ***ent* 57** as a colorless liquid.

Yield: 3.93 g, 90%

Mol. Formula: $C_{21}H_{36}O_3Si$

$[\alpha]^{D}_{25}$ = +17.01 (*c* 1.5, $CHCl_3$).

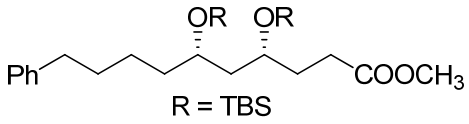
IR ($CHCl_3$, cm^{-1}) ν_{max} = 2955, 1736, 1684, 1454.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.17-7.35 (m, 5H), 3.71-3.75 (m, 4H), 2.65 (t, *J* = 8.0 Hz, 2H), 2.40 (t, *J* = 8.0 Hz, 2H), 1.39–1.62 (m, 6H), 1.74–1.77 (m, 2H), 0.9 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.5, 142.5, 128.4, 128.2, 125.7, 70.9, 51.6, 36.8, 35.9, 31.6, 29.8, 25.8, 24.9, 18.0, –4.5.

Elemental Analysis: calculated for $C_{21}H_{36}O_3Si$ C, 69.18, H, 9.95%; found C, 69.11, H, 9.91%.

(4*S*,6*R*)-Ethyl 4,6-bis(*tert*-butyldimethylsilyloxy)-10-phenyldecanoate (64):



To a solution of compound **63** (2.0 g, 5.49 mmol) and nitrosobenzene (5.87 g, 5.49 mmol) in anhydrous DMSO (20 mL) was added D-proline (0.063 g, 0.590 mmol) at 20 °C. The mixture was vigorously stirred for 25 min under argon (the color of the reaction changed from green to yellow during this time), then cooled to 0 °C. Thereafter, a pre-mixed and cooled (0 °C) solution of trimethylphosphonoacetate (1.55 mL, 16.47 mmol), DBU (2.50 mL, 16.47 mmol) and LiCl (0.698 g, 16.47 mmol) in CH_3CN (40 mL) was added quickly (1–2 min) at 0 °C. The resulting mixture was warmed to room temperature over 1 h, the reaction was quenched by addition of ice pieces. The acetonitrile was evaporated under vacuum. The reaction mixture was then poured into water (100 mL) and extracted with Et_2O (5x100 mL). The combined organic layer was washed with water, brine, dried (Na_2SO_4) and concentrated in vacuo to give the crude product which was directly subjected to the next step without purification. To the crude allylic alcohol in ethyl acetate was added Pd-C (10%) under hydrogenation conditions and the reaction mixture was allowed to stir overnight. After completion of the reaction (until ^1H NMR analysis of the crude mixture indicated complete conversion), the mixture was filtered through a pad of Celite and concentrated in vacuo to give the γ-alcohol. The crude product was then carried to the next step without further purification. To an ice-cold stirred solution of crude product CH_2Cl_2 (10 mL) were added imidazole (1.120 g, 16.47 mmol) and TBSCl 2.43 g, 16.47 mmol) at 0 °C. The resulting mixture was stirred overnight at room temp before H_2O (20 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Silica gel column chromatography of the crude product using petroleum ether/ethyl acetate (99:1) gave TBS ether **64** as a colorless liquid.

Yield: 1.43 g, 50%

Mol. Formula: $C_{29}H_{54}O_4Si_2$

$[\alpha]^D_{25}$= +22.18 (*c* 1, $CHCl_3$)

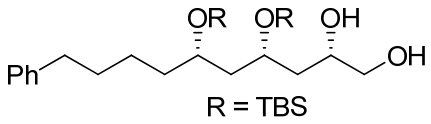
IR ($CHCl_3$, cm^{-1}) ν_{max} = 2955, 1736, 1684, 1454.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.10-7.17 (m, 5 H), 3.40-4.15 (m, 5H), 2.54 (t, J = 7.7 Hz, 2H), 2.24 (t, J = 7.3 Hz, 2H), 1.95–1.98 (m, 2H), 1.34-1.51 (m, 8H), 0.78 (s, 18H), 0.01 (s, 6H), -0.03 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.4, 142.6, 128.4, 125.6, 75.5, 71.0, 51.5, 36.8, 35.9, 31.7, 29.7, 25.8, 24.9, 18.0, -4.4, -5.0.

LC–MS: m/z =545 $[M + Na]^+$.

(2*R*,4*S*,6*R*)-4,6-bis(*tert*-Butyldimethylsilyloxy)-10-phenyldecane-1,2-diol (65):



To a solution of ester **64** (2.0 g, 3.82 mmol) in dry DCM (100 mL) at 0 °C was added dropwise DIBAL-H (7.65 mL,7.65 mmol, 1 M in toluene) through a syringe. The reaction mixture was warmed to room temperature over 1 h, then recooled to 0 °C and treated with satd. aqueous solution of sodium potassium tartrate (50 mL). The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3 X 50 mL). The combined organic extracts were washed with water, brine, dried (Na_2SO_4), filtered and concentrated to give the crude aldehyde, which was used for the next step without purification. To a stirred solution of aldehyde (1.2 g, 2.43 mmol) and nitrosobenzene (0.26 g, 2.43 mmol) in DMSO (9 mL) was added D-proline (0.056 g, 0.48 mmol, 20 mol %) in one portion at 25 °C. After 1 h, the temperature was lowered to 0 °C, followed by dilution with anhyd. MeOH (10 mL) and careful addition of excess $NaBH_4$ (0.185 g, 4.86 mmol). The reaction was quenched after 10 min by pouring the reaction mixture into a vigorously stirred biphasic solution of Et_2O and aqueous HCl (1 m). The organic layer was separated, and the aqueous phase was extracted with EtOAc (3X20 mL). The combined organic phase was dried with anhyd Na_2SO_4, concentrated, and purified by column chromatography over silica gel using EtOAc/petroleum ether (40:60) as eluent to give pure aminoxy alcohol . The aminoxy alcohol (1.02 g, 1.69 mmol) was dissolved in EtOAc (10 mL) and to the solution was added 10% Pd/C (0.1 g) and the reaction mixture was stirred in a hydrogen atmosphere (1 atm, balloon pressure) for 12 h. After completion of the reaction (monitored by TLC) the reaction mixture was filtered through a Celite pad, concentrated, and the crude product was then

purified by silica gel chromatography using petroleum ether/ethyl acetate (3:2) as eluent to give pure diol **65** as a colorless liquid.

Yield: 0.93 g, 75%

Mol. Formula: $C_{28}H_{54}O_4Si_2$

$[\alpha]_D^{25}$ -7.8, (*c* 1.0, $CHCl_3$)

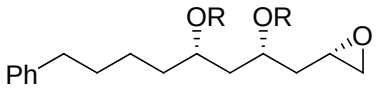
IR ($CHCl_3$, cm^{-1}) ν_{max} = 3411, 3012, 2923, 1634, 1523, 1249, 1211.

^{1}H NMR (200 MHz, $CDCl_3$): $\delta = \delta$ 7.12–7.19 (m, 5H), 3.97-4.08 (m, 1H), 3.75–3.83 (m, 1H), 3.62-3,64 (m, 1H), 3.52-3.57 (m, 1H), 3.35-3.41 (m, 1H), 2.54 (t, *J* = 7.33, 2H) 1.18–1.69 (m, 10H), 0.80 (s, 18H), 0.05 (s, 6H), -0.06 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 144.2, 128.3, 128.2, 125.6, 70.3, 69.3, 52.1, 45.3, 37.8, 36.3, 35.9, 29.6, 25.8, 24.3, 17.9, -3.9, -4.6.

Elemental Analysis: calculated for $C_{24}H_{54}O_4Si_2$ C, 65.83, H, 10.65%; found C, 65.93, H, 10.61%

((5*R*,7*S*)-2,2,3,3,9,9,10,10-Octamethyl-5-((*S*)-oxiran-2-ylmethyl)-7-(4-phenylbutyl)-4,8-dioxa-3,9-disilaundecane (66):



R = TBS

To a mixture of diol **65** (0.75 g, 1.46 mmol), in dry DCM (5 mL) was added dibutyltin oxide (3.65 mg, 0.014 mol) followed by the addition of p-toluenesulfonyl chloride (0.28 g, 1.46 mmol) and triethylamine (0.1 mL, 1.46 mmol) and reaction was stirred at room temperature for 2 h under nitrogen. The reaction was monitored by TLC, after completion of reaction the mixture was quenched by adding water. The solution was extracted with DCM (3X10 mL) and then combined organic phase was washed with water, dried (Na_2SO_4) and concentrated. To this crude mixture in MeOH at 0 °C was added K_2CO_3 (303 mg, 2.20 mmol) and the resultant mixture was allowed to stir for 2 h at same temp. After completion of reaction as indicated by TLC the reaction was quenched by addition of ice pieces and methanol was evaporated. The concentrated reaction mixture was then extracted with ethyl acetate (3 X 20 mL), the combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The

column chromatography of crude product using petroleum ether: ethyl acetate (9:1) gave the epoxide **66** as a light yellow colored liquid.

Yield: 0.57 mg, 80%

Mol. Formula: $C_{28}H_{52}O_3Si_2$

$[\alpha]_D^{25}$ - 2.5 (*c* 1.5, $CHCl_3$).

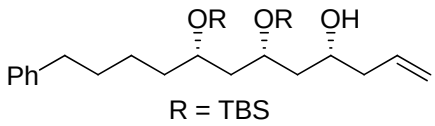
IR (neat, cm^{-1}) ν_{max} = 2929, 2858, 1608, 1578, 1523, 1476, 1254.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.09–7.25 (m, 5H) 3.92–3.99 (m, 1H), 3.60–3.76 (m, 1H), 2.99-3.08 (m, 1H), 2.71–2.78 (dd, , *J* = 4.00 and 4.80 Hz, 1H), 2.55 (t, *J* = 7.7 Hz, 2H), 2.40–2.46 (dd, *J* = 4.40, 4.80 Hz, 1H), 1.20–1.71 (m, 10H), 0.87 (s, 18 H), 0.04 (s, 6H), -0.02 (s, 6 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 143.2, 127.3, 127.2, 69.6, 68.3, 44.3, 51.1, 39.1, 36.8, 34.9, 28.6, 24.8, 23.3, 21.6, 16.8, –4.9,-5.5.

LC–MS: m/z =515 $[M + Na]^+$.

(4*R*,6*R*,8*S*)-6,8-bis(*tert*-Butyldimethylsilyloxy)-12-phenyldodec-1-en-4-ol (67) :



A round bottom flask was charged with copper (I) iodide (5.78 mg, 0.030 mmol), gently heated under vacuum, and slowly cooled with a flow of argon, and dry THF (20 mL) was added. This suspension was cooled to –20 ^oC and vigorously stirred, and vinylmagnesium bromide (1M in THF, 0.609 mL, 0.609 mmol) was injected to it. A solution of compound **66** (150 mg, 0.3046 mmol) in THF (10 mL) was added slowly to the above reagent, and the mixture was stirred at –20 ^oC for 12 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl. The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum to get the crude residue, which was purified by silica gel column chromatography (PE/EtOAc, 4:1) to afford the pure product **67** as colorless oil.

Yield: 129 mg, 80%

Mol. Formula: $C_{30}H_{56}O_3Si_2$

$[\alpha]_D^{25}$ +8.7 (*c* 1,$CHCl_3$)

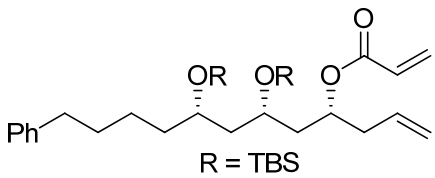
IR ($CHCl_3$, cm^{-1}) ν_{max} = 3400, 3071, 2929, 2559, 1726, 1621, 1409, 1255, 1195, 1055.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.05–7.22 (m, 5H), 5.61–5.82 (m, 1H), 4.96-5.04 (m, 2H), 3.47-4.13 (m, 3H), 2.55 (t, *J* = 7.70 Hz, 2H), 2.02–2.25 (dd, , *J* = 6.19, 11.88 Hz, 2H), 1.16–1.67 (m, 10H), 0.79 (s, 18H), 0.02 (s, 6H), -0.07 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 142.5 135.0, 128.3, 125.6, 117.5, 71.1 69.9, 67.8, 46.4, 42.3, 40.1, 37.7, 36.0, 31.6, 25.8, 24.6, 17.9, -4.5, -4.0.

Elemental Analysis: calculated for $C_{30}H_{56}O_3Si$ C, 69.17, H, 10.84%; found C, 69.11, H, 10.89%

(4*R*,6*R*,8*S*)-6,8-bis(*tert*-Butyldimethylsilyloxy)-12-phenyldodec-1-en-4-yl acrylate (68):



To a stirred solution of compound **67** (110 mg, 0.211 mmol) in dichloromethane (5 mL) were added acryloyl chloride (0.034 mL, 0.422 mmol) and *i*-Pr_2NEt (0.146 mL, 0.841 mmol) at -78 ^oC. The mixture was allowed to warm to room temperature and stirred for 4 h. The reaction mixture was diluted with water (5 mL) and extracted into dichloromethane (2X6 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum to get the crude residue, which was purified by silica gel column chromatography (PE/EtOAc, 9:1) to afford the pure product **68** as colorless oil.

Yield: 103 mg, 85%

Mol. Formula: $C_{33}H_{58}O_4Si_2$

$[\alpha]_D^{25}$ +4.7 (*c* 1 $CHCl_3$).

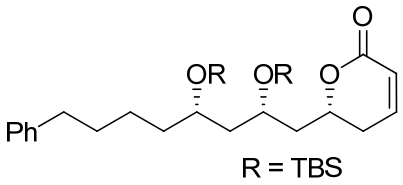
IR (KBr, cm^{-1}) ν_{max} = 3045, 2921, 2556, 1716, 1622, 1415, 1267, 1199, 1051.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.13–7.29 (m, 5H), 6.41 (dd, *J* =11.64, 15.54 Hz, 1H), 6.08 (dd, *J* = 11.75, 17.18 Hz, 1H), 5.63-5.84 (m, 2H), 5.01-5.09 (m, 2H), 3.59–4.21 (m, 3H), 2.59. (t, *J* = 7.57 Hz, 2H), 2.29–2.39 (m, 2H), 1.24-1.36 (m, 10H), 0.85 (s, 18H), 0.05 (s, 6H), 0.03 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.9, 142.6, 133.4, 130.3, 128.8, 128.4, 128.2, 125.6, 117.9, 71.0, 69.2, 67.1, 41.0, 39.1, 36.0, 31.6, 29.7, 25.9, 24.6, 18.0, -4.6, -4.9.

Elemental Analysis: calculated for $C_{33}H_{58}O_4Si_2$ C, 68.93, H, 10.17%; found C, 68.99 H, 10.19%

(*R*)-6-((2*R*,4*S*)-2,4-bis(*tert*-Butyldimethylsilyloxy)-8-phenyloctyl)-5,6-dihydro-2*H*-pyran-2-one (69):



To a stirred solution of bis(tricyclohexyl phosphine)benzylidine ruthenium(IV) dichloride (Grubbs catalyst, 14.3 mg, 10 mol %) in dichloromethane (50 mL) at 55 ^oC was added compound **68** (100 mg, 0.17 mmol) dissolved in dichloromethane (25 mL). The resulting mixture was heated for 12 h. After completion of the reaction, the contents were cooled and solvent was removed under reduced pressure to yield crude product, which was purified on silica gel column eluting with petroleum ether/EtOAc as (7:3) as eluent to afford the pure compound **69**.

Yield: 83.7 mg, 88%.

Mol. Formula: $C_{31}H_{54}O_4Si_2$

$[\alpha]_D^{25}$ -10.2 (*c* 0.45, $CHCl_3$).

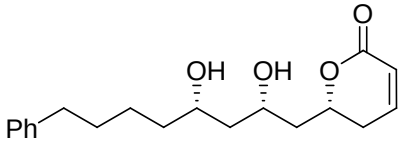
IR ($CHCl_3$, cm^{-1}) ν_{max} = 2930, 1721, 1493, 1389, 1254, 1149, 1052, 746, 700.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.13–7.29 (m, 5H), 5.67–6.13(m, 1H), 5.94-5.99 (d, *J* = 9.73 Hz, 1H), 3.56-4.16 (m, 3H), 2.59 (t, *J* = 7.33 Hz, 2H), 2.33–2.44 (m, 2H), 1.24–1.32 (m, 10H), 0.85 (s, 18H), 0.05 (s, 6H), -0.2 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 163.0, 142.6, 128.8, 128.6, 125.6, 117.9, 70.9, 69.2, 67.1, 41.0, 39.1, 39.7, 35.9, 31.6, 29.6, 25.9, 24.6, 17.9.

Elemental Analysis: calculated for $C_{31}H_{54}O_4Si_2$ C, 68.08; H, 9.95%; found C, 68.10, H, 9.99%.

(*R*)-6-((2*S*,4*S*)-2,4-Dihydroxy-8-phenyloctyl)-5,6-dihydro-2*H*-pyran-2-one (18):



A solution of compound **69** (80 mg, 0.146 mmol) in DCM (5 mL) at 0 °C, was treated with TFA (40 µl) and stirred for 30 min at 0 °C. The reaction was quenched by addition of saturated bicarbonate solution and the aqueous layer was extracted with DCM. Combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated, which was purified on silica gel column eluting with petroleum ether/EtOAc as (1:1) as eluent to afford the pure compound **18** .

Yield: 41.1 mg, 90%.

Mol. Formula: $C_{19}H_{26}O_4$

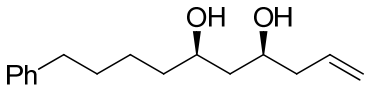
$[\alpha]_D^{25}$ +62.1 (*c* 1, $CHCl_3$); lit. [11, 23] $[\alpha]_D^{25}$ +61.9 (*c* 0.55, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}) ν_{max} = 3684, 3020, 2934, 1725, 1522, 1476, 1215, 1055, 759, 669.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.14-7.26 (m, 5H), 6.81 (dt, *J* = 9.95, 4.10, 3.98 Hz, 1H) 5.99 (dd, *J* = 9.50, 1.90 Hz, 1H), 4.51-4.55 (m, 1H,) 4.15 -4.18 (m, 1H), 3.61-3.70 (m, 1H), 2.56 (t, *J* = 7.33 Hz, 2H) 2.23–2.31 (m, 2H), 1.31–1.43 (m, 10H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 164.1, 142.4, 134.4, 128.2, 125.6, 122.6, 117.6, 69.1, 65.8, 51.8, 35.9, 31.9,29.7, 25.9, 22.7, 18.0, 14.1.

(4*S*,6*R*)-10-Phenyldec-1-ene-4,6-diol (70):



A solution of compound **60** (100 mg, 0.2760 mmol) in DCM (5 mL) at 0 °C, was treated with TFA (50 µl) and stirred for 30 min at 0 °C. The reaction was quenched by addition of saturated bicarbonate solution and the aqueous layer was extracted with DCM. Combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to yield crude product, which was purified with petroleum ether/EtOAc as (1:1) as eluent to afford the pure compound **70** as a foam.

Yield: 0.062 g, 91%

Mol. Formula: $C_{16}H_{24}O_2$

$[\alpha]^D_{25}$ -32.6 (*c* 1.0, $CHCl_3$)

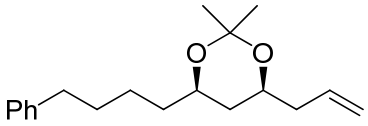
IR (neat, cm^{-1}) ν_{max} = 3675, 3121, 2934, 1522, 1476, 1215, 1055, 765, 650.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.11-7.30 (m, 5H), 6.89 (dt, *J* = 9.8, 3.8 Hz, 1H), 6.02 (d, *J* = 9.8, 1.8 Hz, 1 H), 4.03-4.15 (m, 1H),), 3.79-3.90 (m, 2H), 2.62 (t, *J* = 7.33 Hz, 2H), 2.39–2.45 (m, 2H), 1.32–1.81 (m, 8H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 142.4. 128.3, 128.2, 125.7, 114.2, 71.2, 69.5, 42.3, 38.1, 35.8, 31.4, 29.4, 24.9.

Elemental Analysis: calculated for $C_{16}H_{24}O_2$ C, 77.38; H, 9.74%. found: C, 77.33; H, 9.79%.

(4*S*,6*R*)-4-Allyl-2,2-dimethyl-6-(4-phenylbutyl)-1,3-dioxane (71) :



To a solution of the diol **70** (0.30 g, 1.20 mmol), in dry DCM (2 mL) was added 2,2-dimethoxypropane (1 mL), *p*-TsOH (0.020 g) and stirred overnight. Solid $NaHCO_3$ (0.05g) 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: ethyl acetate (24:1) gave **71** as a colorless liquid.

Yield: 0.028 g, 82%.

Mol. Formula: $C_{19}H_{28}O_2$

$[\alpha]_D^{25}$ - 11.7 (*c* 0.6, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}) ν_{max} = 2926, 2856, 1604, 1454, 1262, 1118.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.08-7.35 (m, 5H), 5.80- 5.87 (s, 1H), 4.96-5.05 (m, 2H), 3.74-3.78 (m, 2H), 2.54 (t, *J* =7.2 Hz, 2H), 2.00-2.20 (m, 2H), 1.30-1.55 (m, 8H), 1.27 (s, 6H).

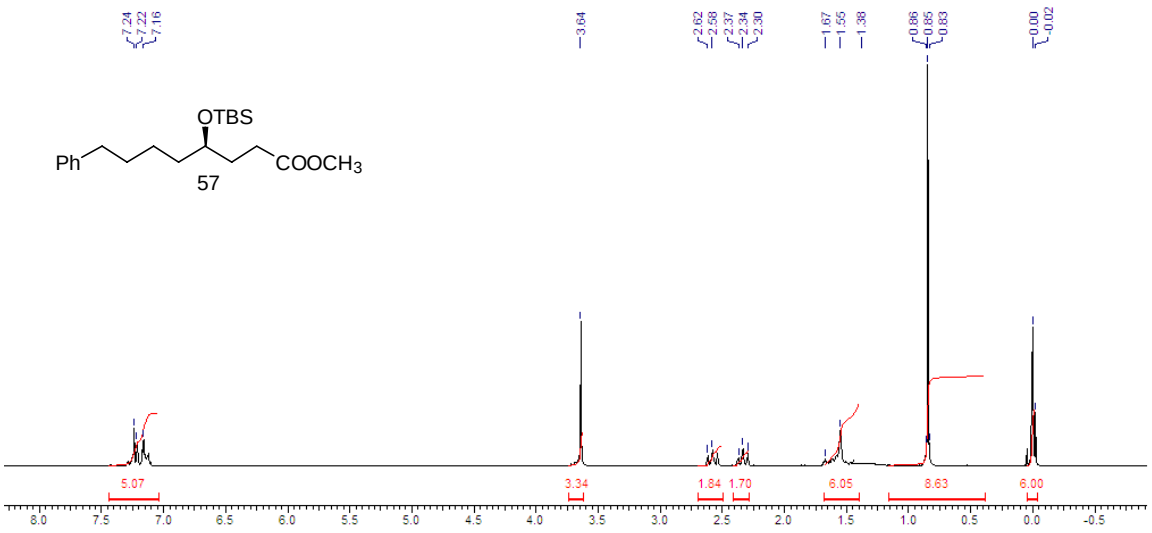
^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.6, 133.4, 127.3, 127.2, 124.5, 115.5, 99.1, 67.6, 65.5, 39.1, 37.1, 34.8, 30.4, 24.0, 23.7, 18.7.

LC–MS: m/z =311 $[M + Na]^+$.

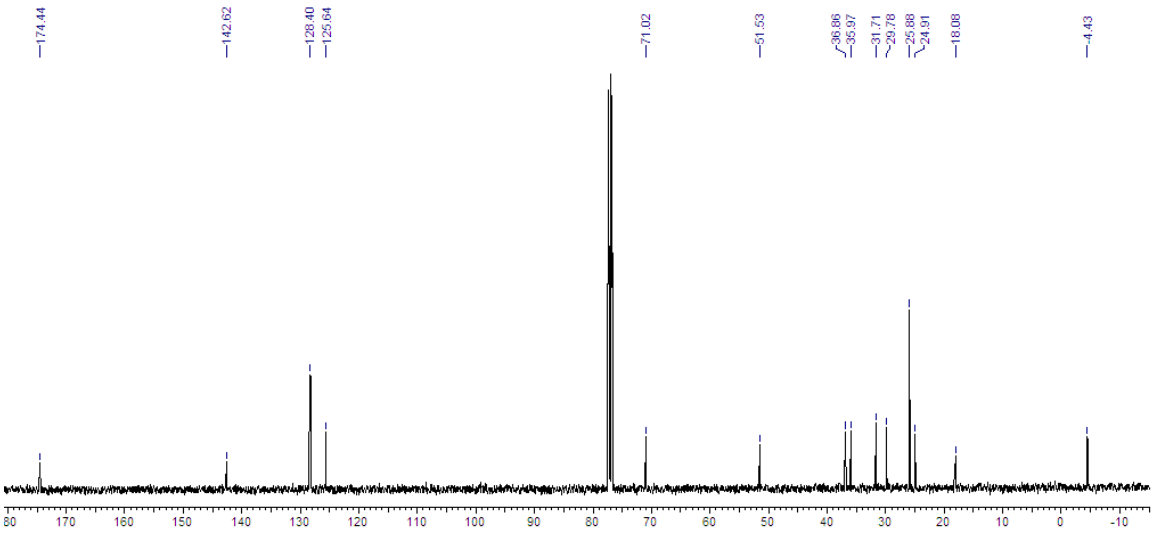
3.7. Spectra

1. ^{1}H and ^{13}C NMR spectra of **57**
2. ^{1}H and ^{13}C NMR spectra of **58**
3. ^{1}H and ^{13}C NMR spectra of **59**
4. ^{1}H and ^{13}C NMR spectra of **60**
5. ^{1}H and ^{13}C NMR spectra of **61**
6. ^{1}H and ^{13}C NMR spectra of **5a**
7. ^{1}H and ^{13}C NMR spectra of ***ent* 57**

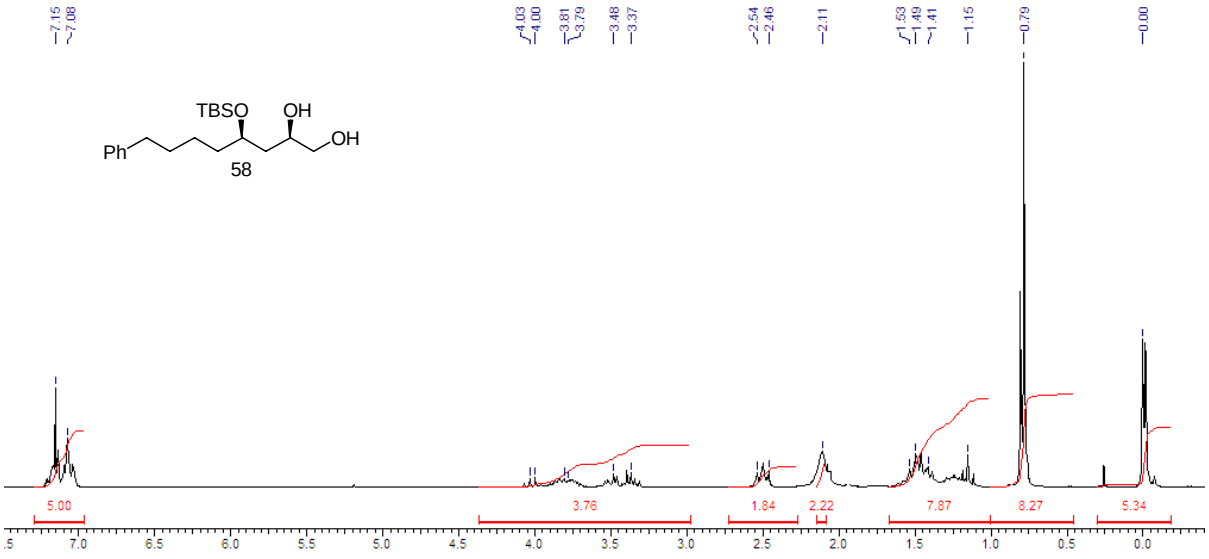
8. ^{1}H and ^{13}C NMR spectra of **63**
9. ^{1}H and ^{13}C NMR spectra of **64**
10. ^{1}H and ^{13}C NMR spectra of **65**
11. ^{1}H and ^{13}C NMR spectra of **66**
12. ^{1}H and ^{13}C NMR spectra of **67**
13. ^{1}H and ^{13}C NMR spectra of **68**
14. ^{1}H and ^{13}C NMR spectra of **69**
15. ^{1}H and ^{13}C NMR spectra of **18**



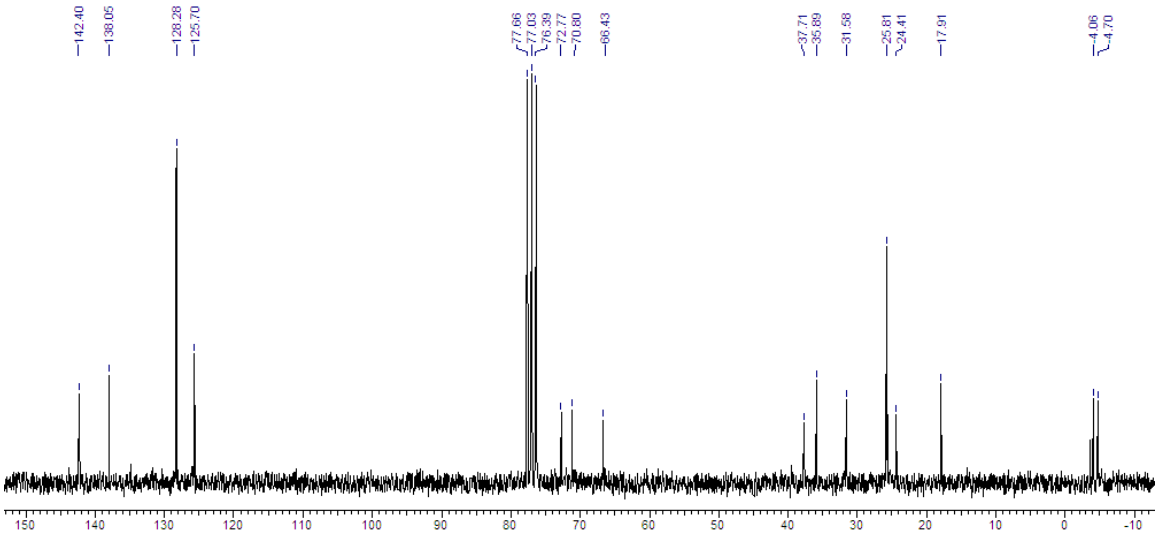
^{1}H-NMR spectrum of compound 57 in $CDCl_3$



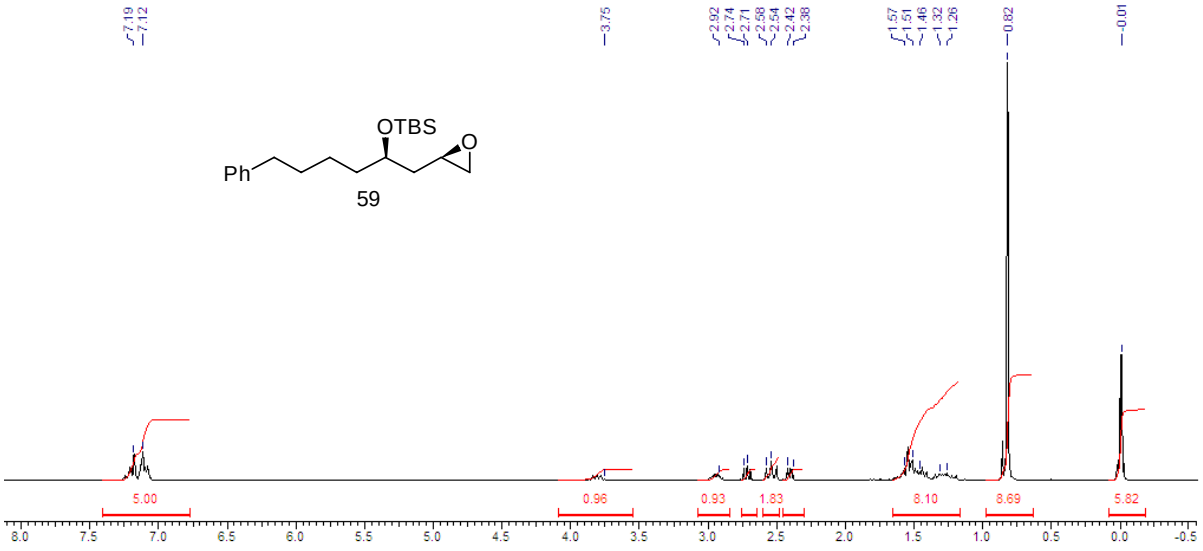
^{13}C-NMR spectrum of compound 57 in $CDCl_3$



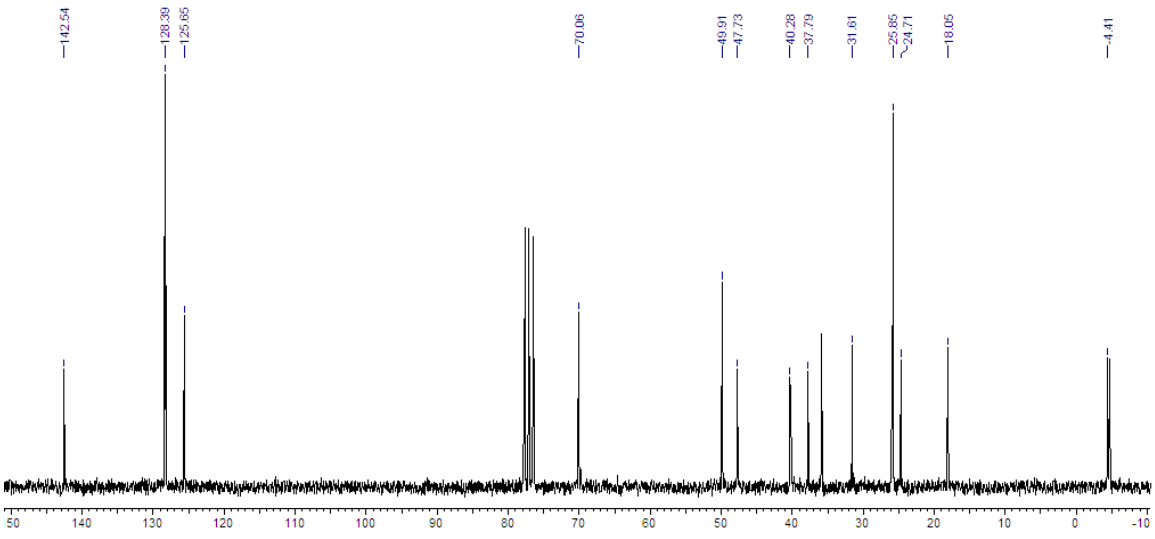
^{1}H-NMR spectrum of compound 58 in $CDCl_3$



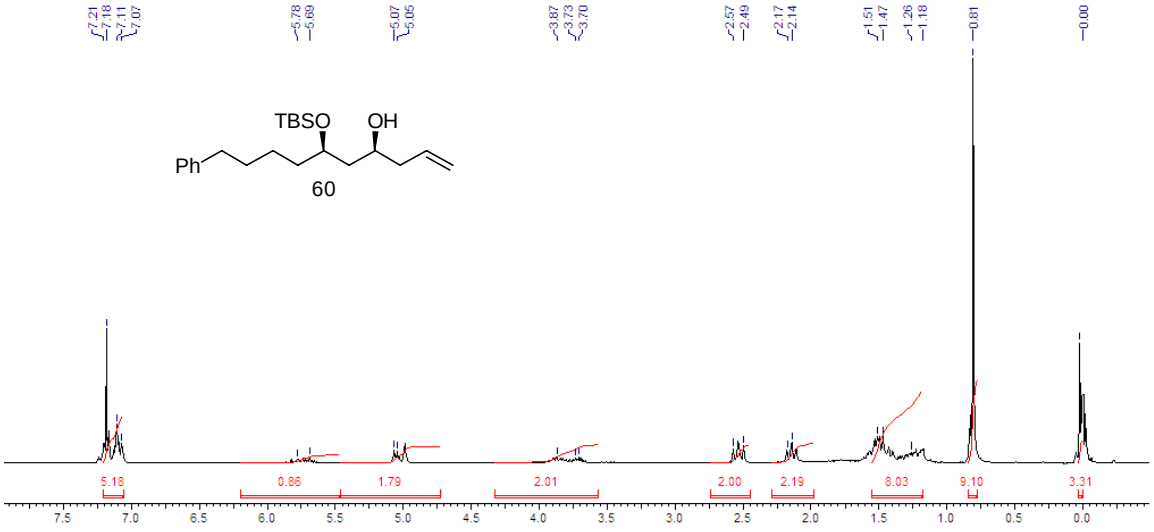
^{13}C-NMR spectrum of compound 58 in $CDCl_3$



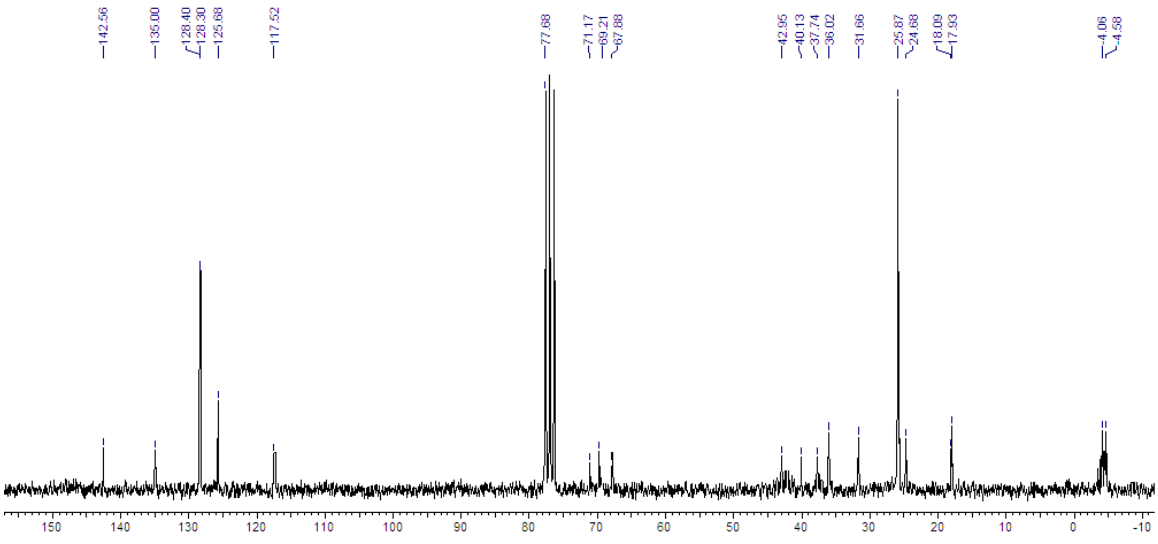
^{1}H-NMR spectrum of compound 59 in $CDCl_3$



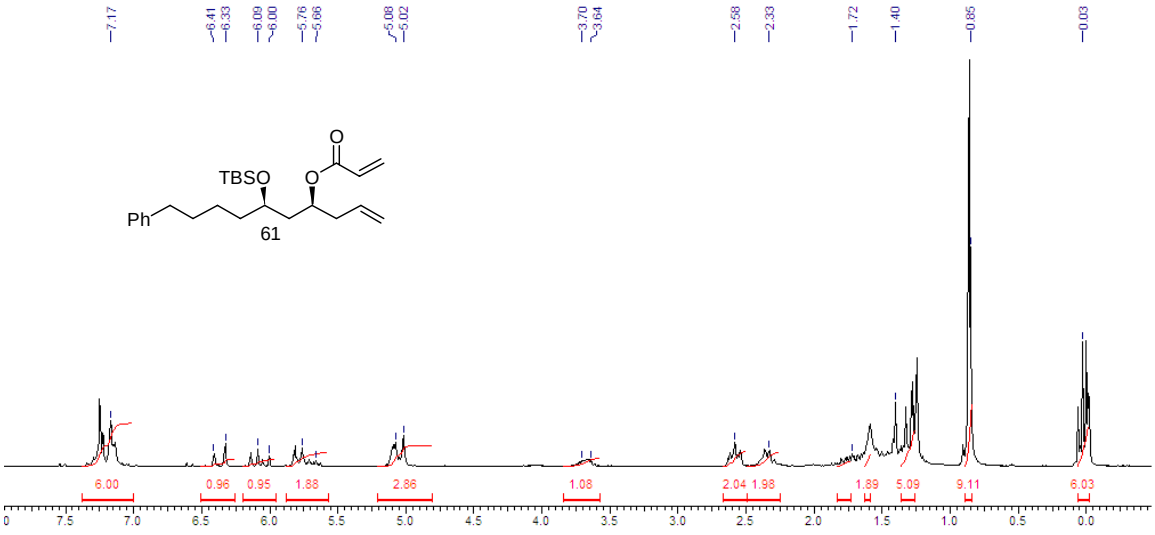
^{13}C-NMR spectrum of compound 59 in $CDCl_3$



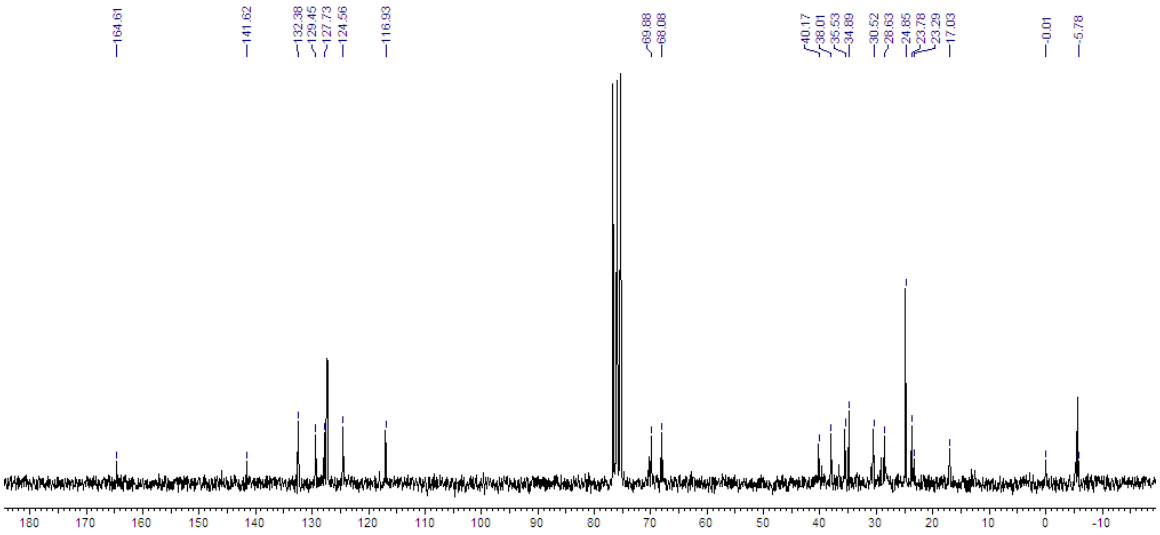
^{1}H-NMR spectrum of compound 60 in $CDCl_3$



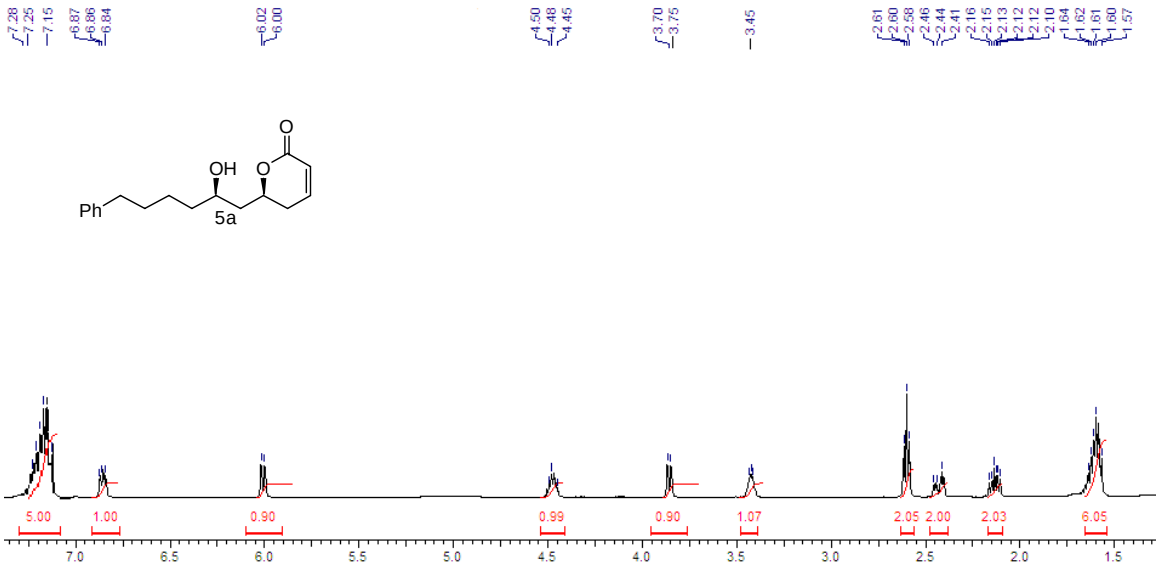
^{13}C-NMR spectrum of compound 60 in $CDCl_3$



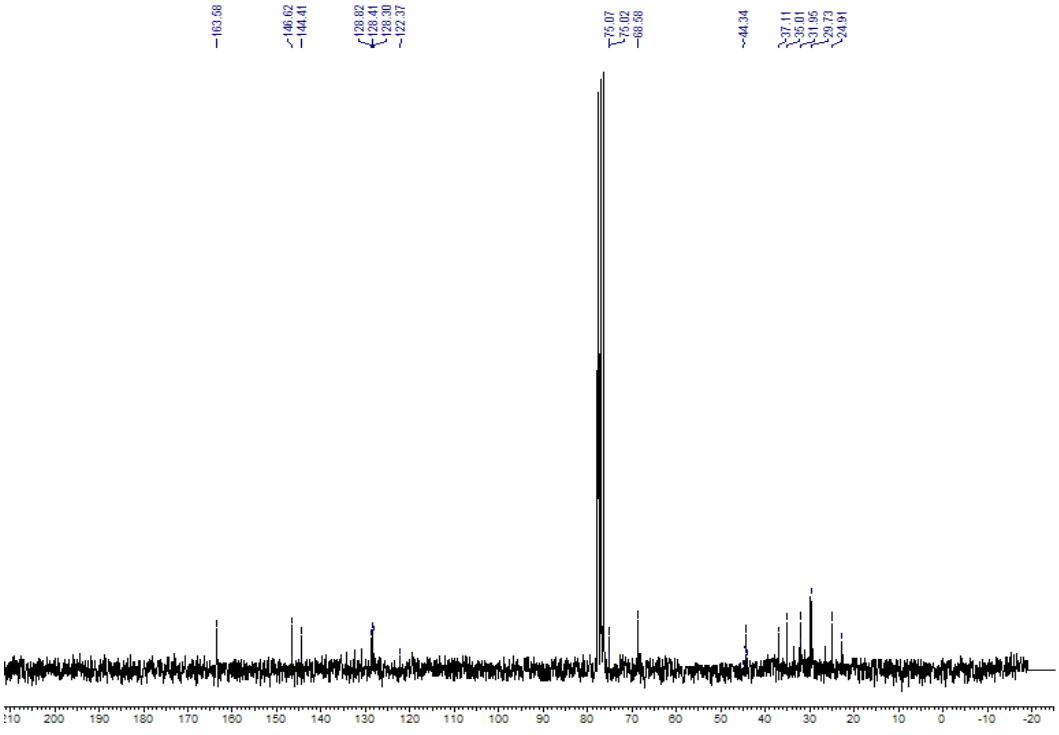
^{1}H-NMR spectrum of compound 61 in $CDCl_3$



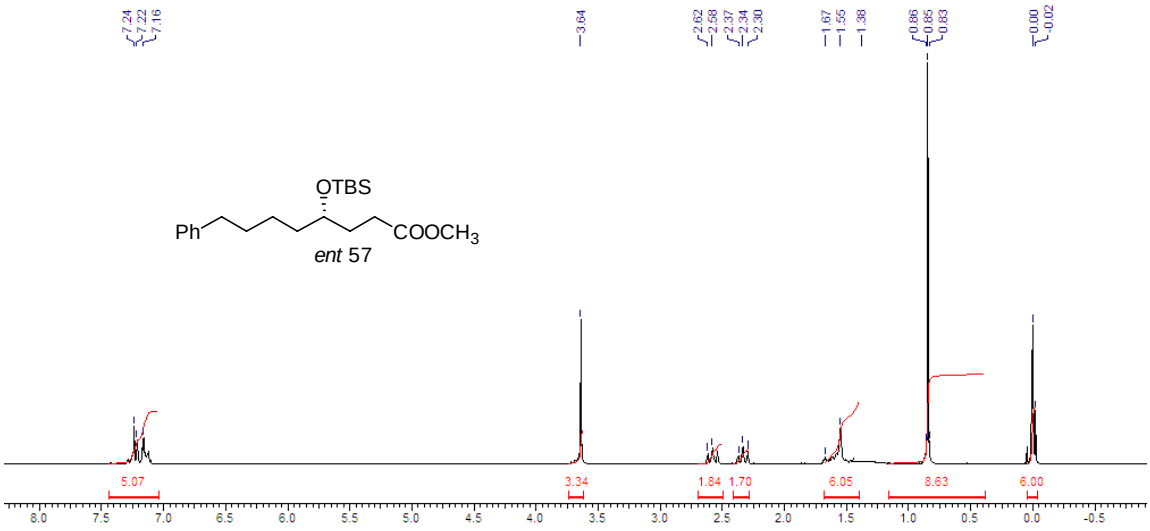
^{13}C-NMR spectrum of compound 61 in $CDCl_3$



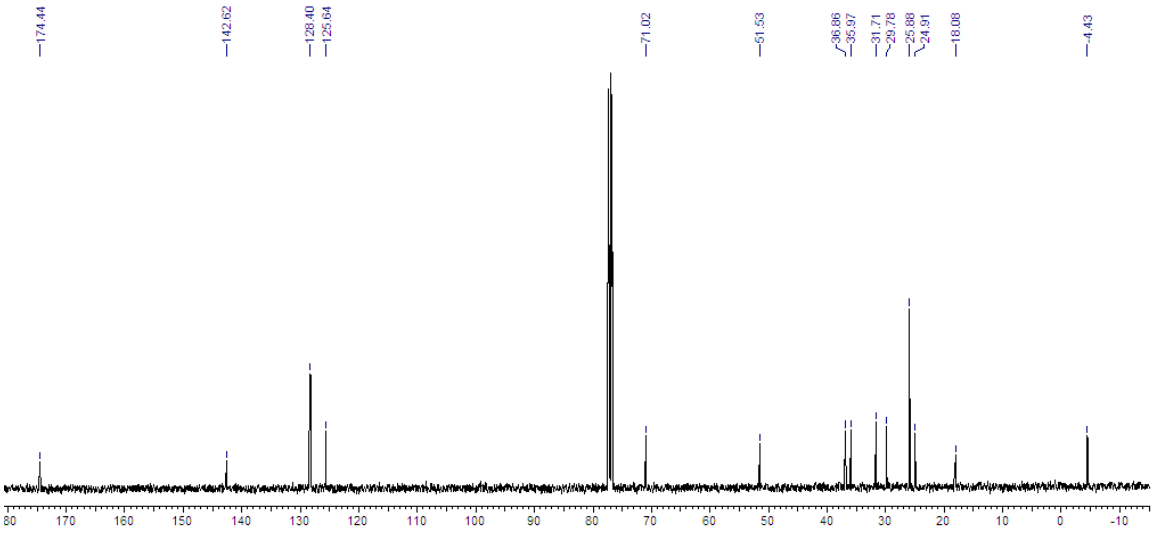
^{1}H-NMR spectrum of compound 5a in $CDCl_3$



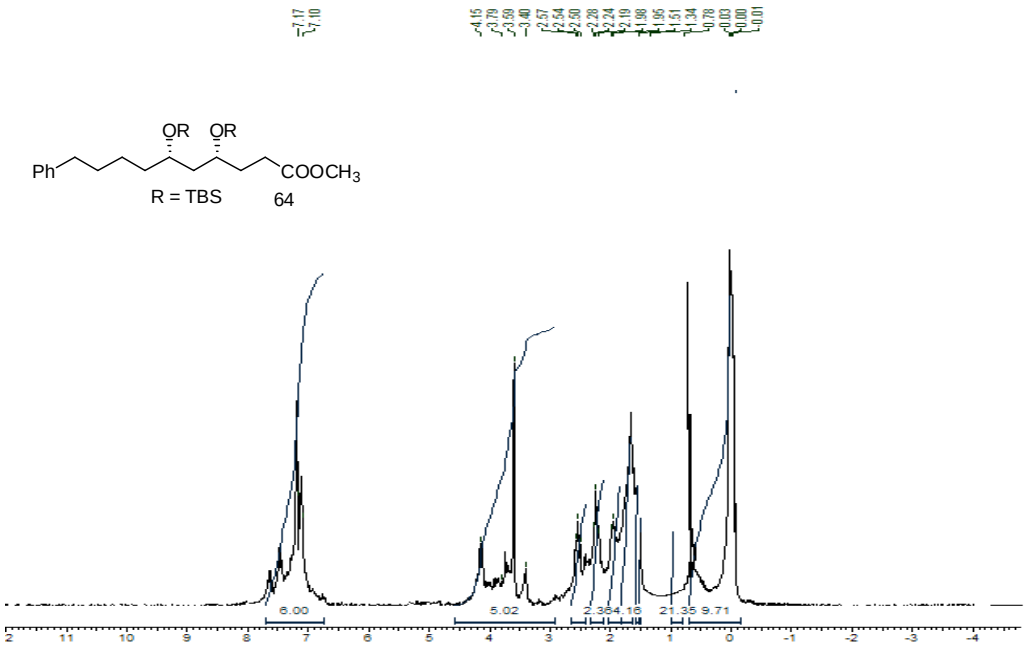
^{13}C-NMR spectrum of compound 5a in $CDCl_3$



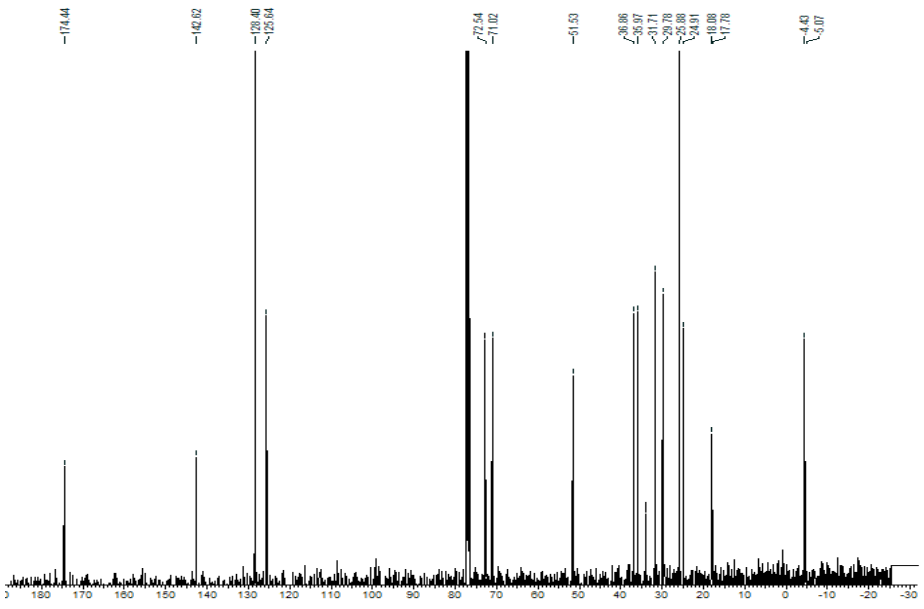
^{1}H-NMR spectrum of compound *ent* 57 in $CDCl_3$



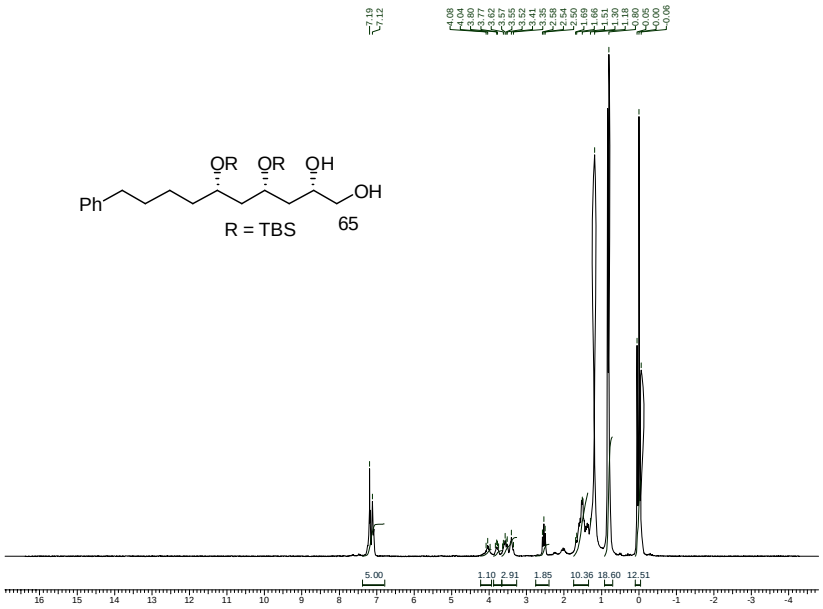
^{13}C-NMR spectrum of compound *ent* 57 in $CDCl_3$



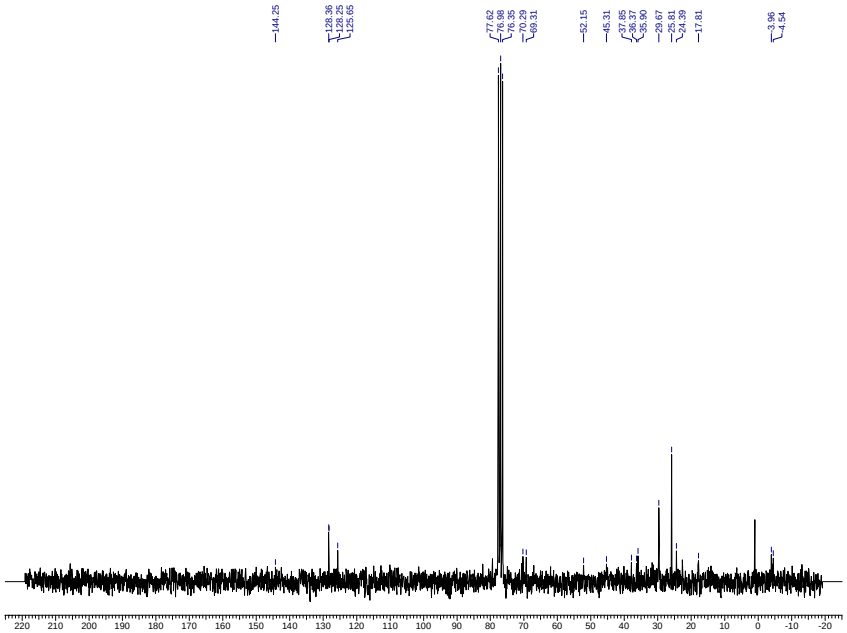
^{1}H-NMR spectrum of compound 64 in $CDCl_3$



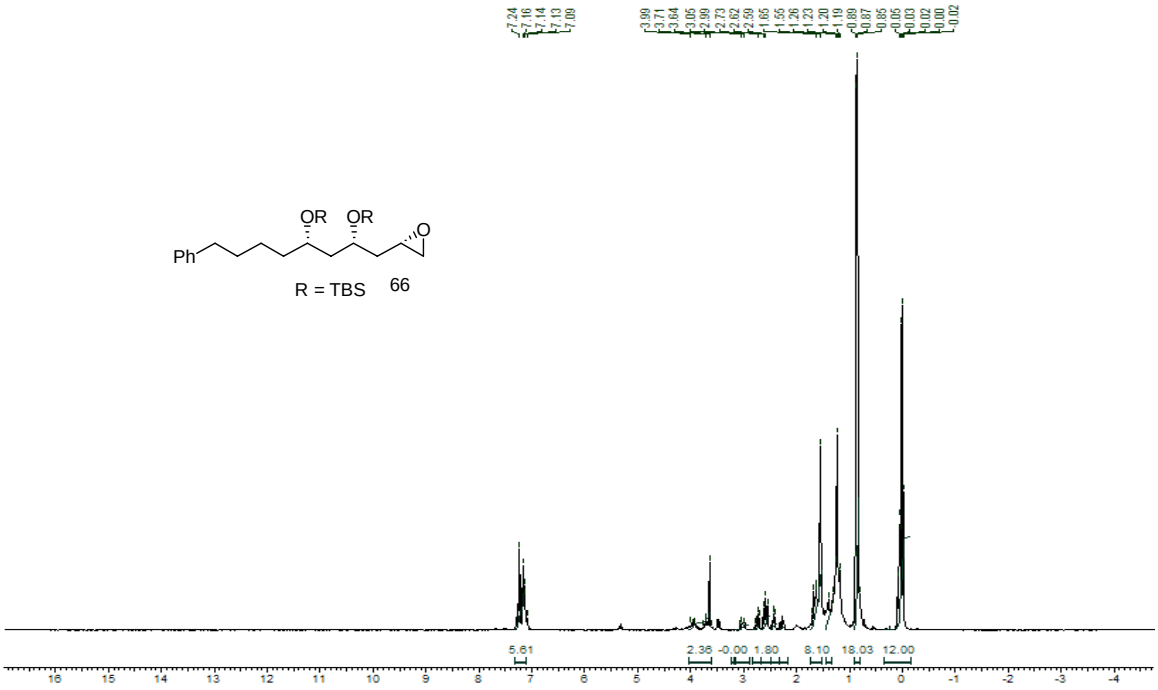
^{13}C-NMR spectrum of compound 64 in $CDCl_3$



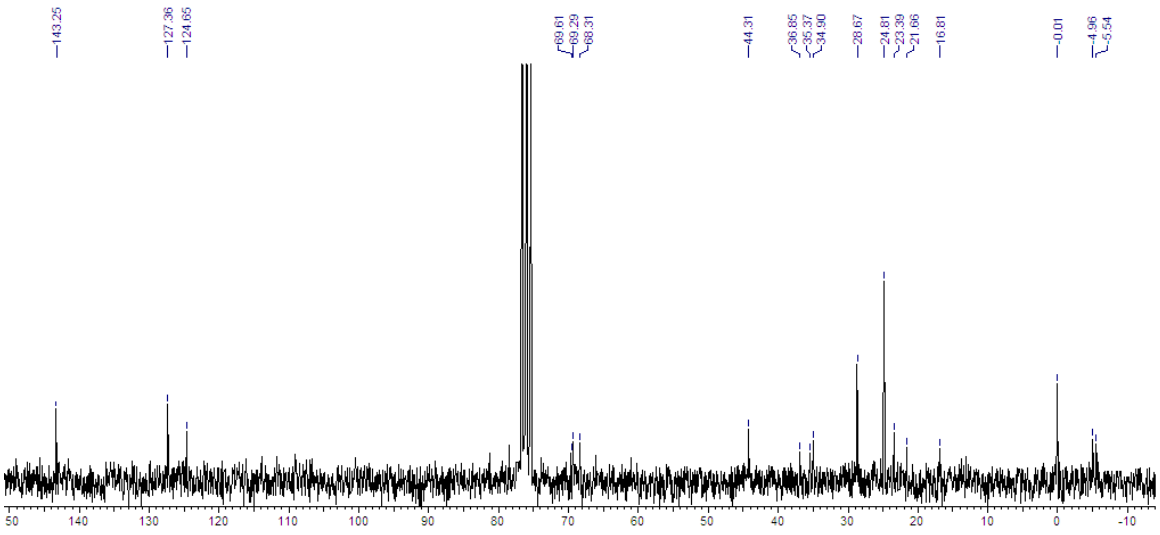
^{1}H-NMR spectrum of compound 65 in $CDCl_3$



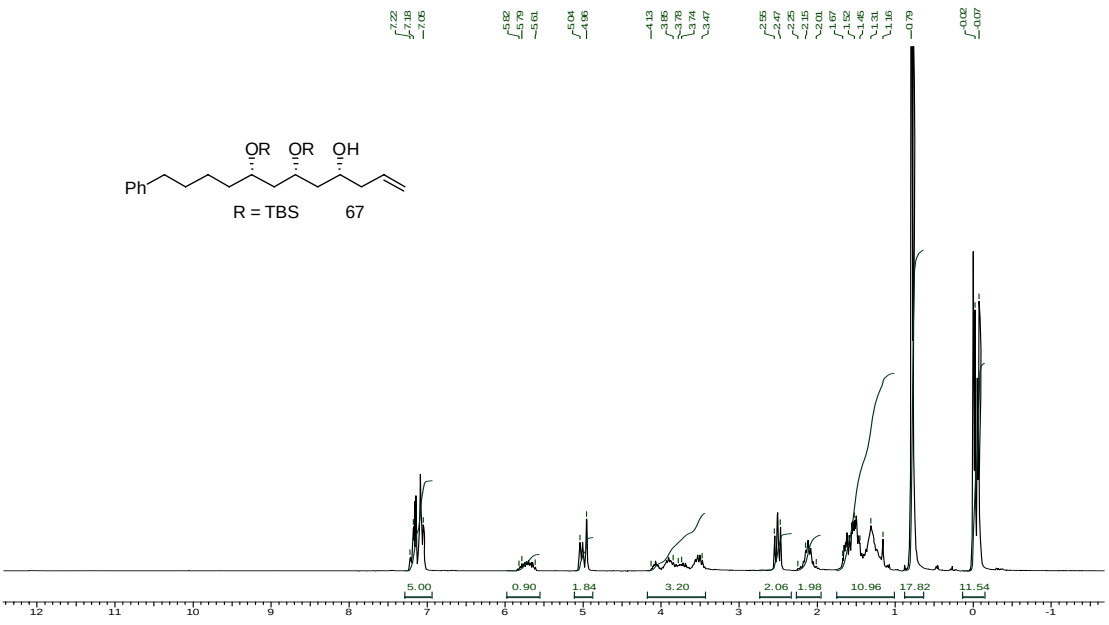
^{13}C-NMR spectrum of compound 65 in $CDCl_3$



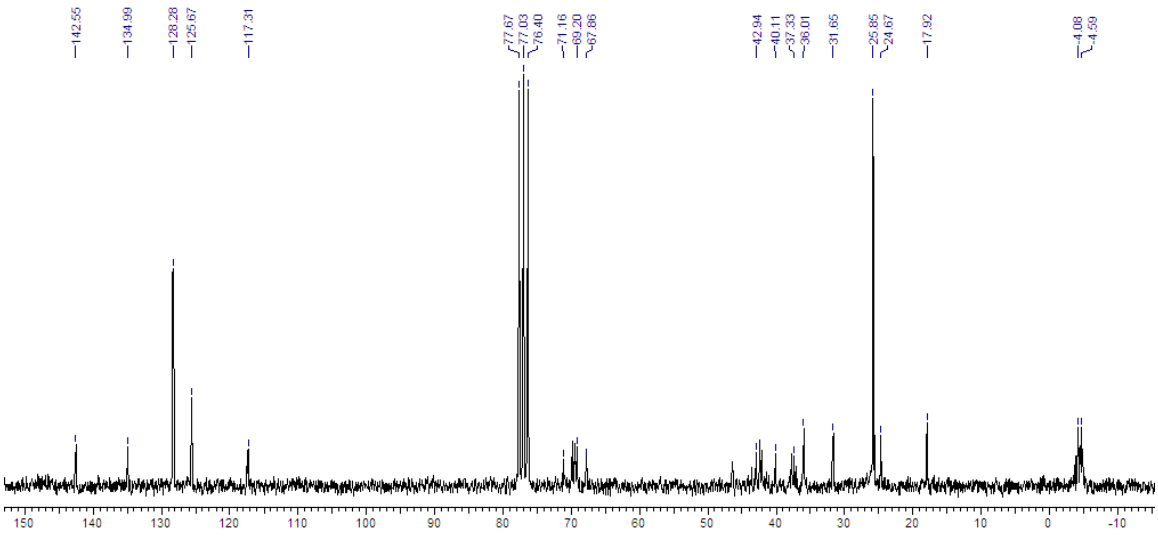
^{1}H-NMR spectrum of compound 66 in $CDCl_3$



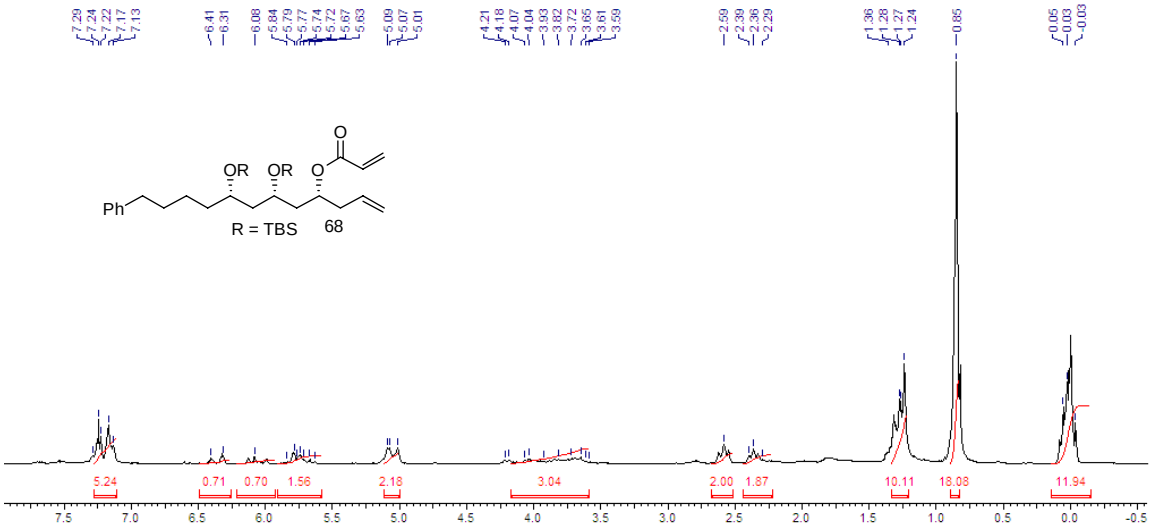
^{13}C-NMR spectrum of compound 66 in $CDCl_3$



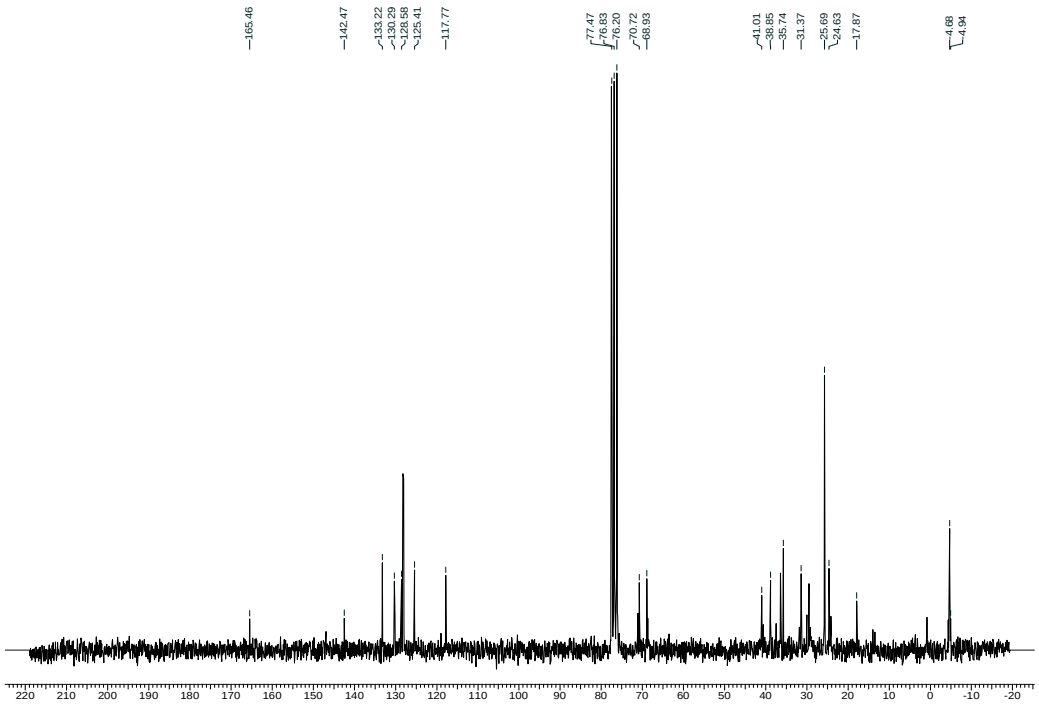
^{1}H-NMR spectrum of compound 67 in $CDCl_3$



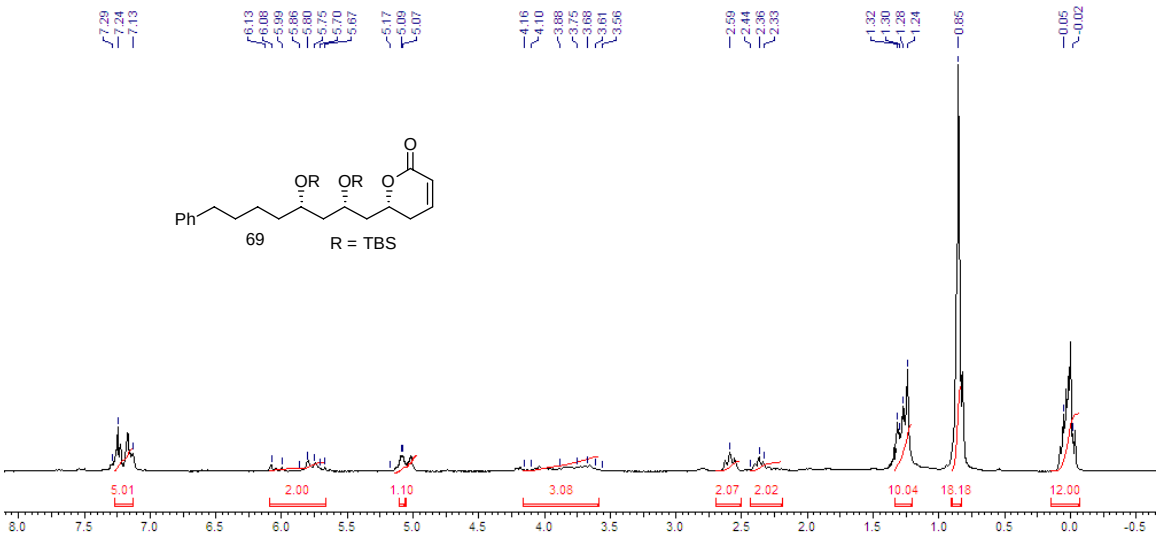
^{13}C-NMR spectrum of compound 67 in $CDCl_3$



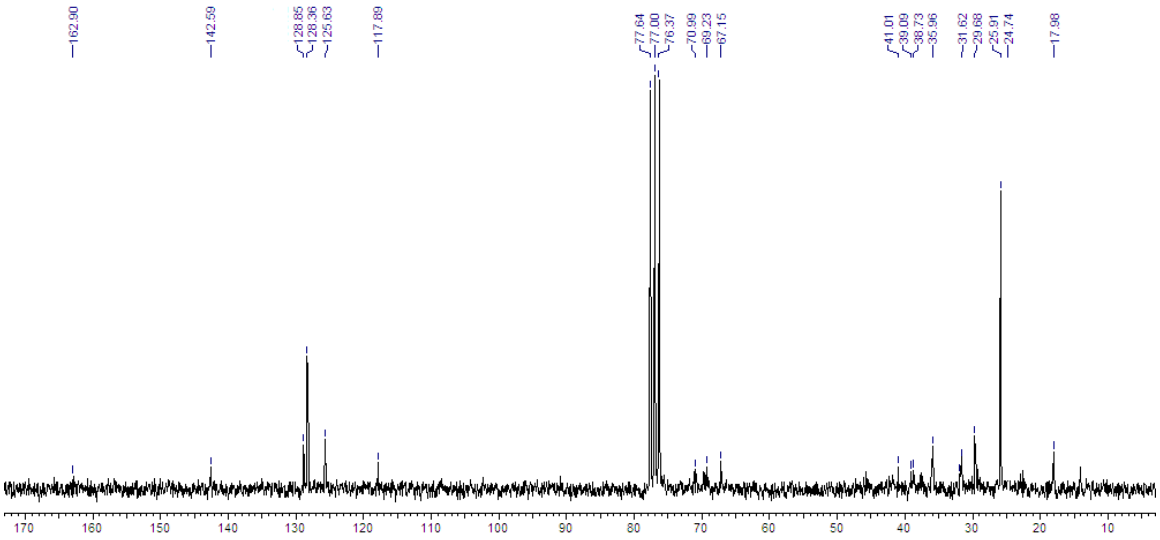
^{1}H-NMR spectrum of compound 68 in $CDCl_3$



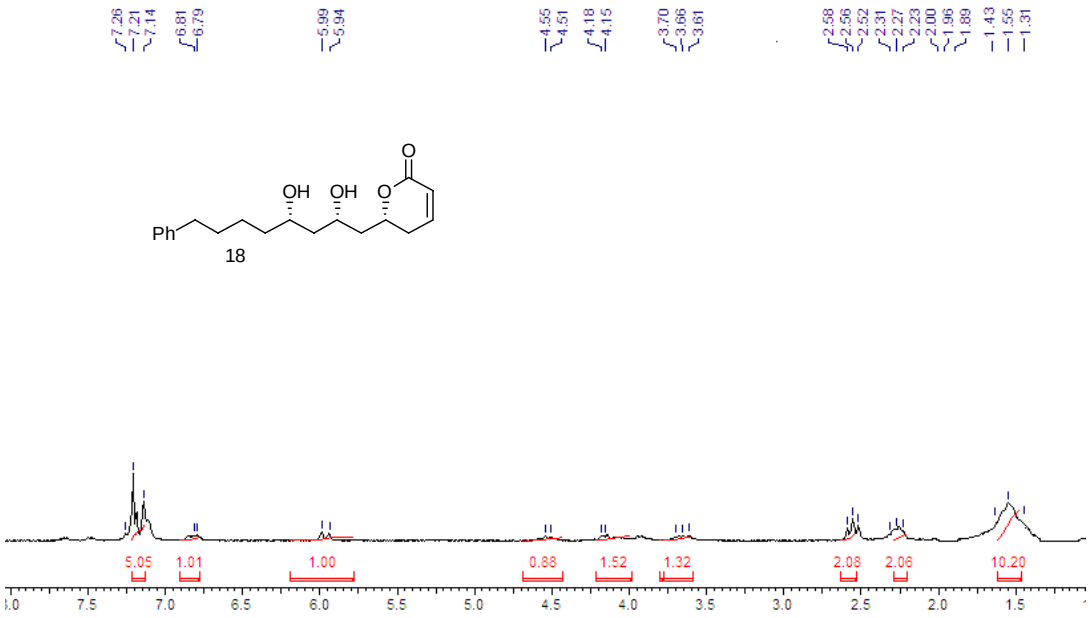
^{13}C-NMR spectrum of compound 68 in $CDCl_3$



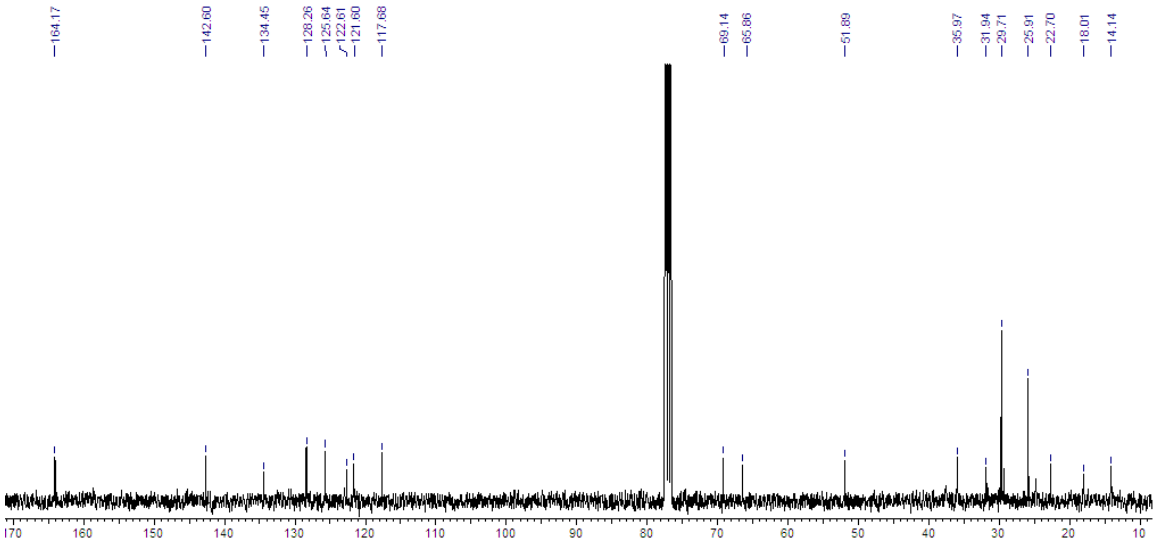
^{1}H-NMR spectrum of compound 69 in $CDCl_3$



^{13}C-NMR spectrum of compound 69 in $CDCl_3$



^{1}H-NMR spectrum of compound 18 in $CDCl_3$



^{13}C-NMR spectrum of compound 18 in $CDCl_3$

3.8. References

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Chapter 4

An efficient and versatile general approach to β-hydroxy lactones and its application to the formal synthesis of two anti-obesity agents, tetrahydrolipstatin and tetrahydroesterastin

ASYMMETRIC SYNTHESIS OF A KEY CHIRAL BUILDING BLOCK FOR TRANS DIALKYL-β-LACTONE VIA HKR AND ORGANOCATALYSIS: APPLICATION TO THE FORMAL SYNTHESIS OF ANTI-TUMOR AND ANTI-OBESITY AGENTS TETRAHYDROLIPSTATIN AND TETRAHYDROESTERASTIN

4.1. Introduction

Lipstatin **1a**,[1a] esterastin **1b**[1b] valilactone **1e**[1c] and panclicin D, **1f**[1d] are analogous 3,4-disubstituted 2-oxetanones isolated from *Streptomyces* species[1] differing only in the structure of C-4 side chain and the nature of amino acid attached to it. These compounds are unique examples of fatty acid derived oxetanones linked to an *N*-acyl amino acid by an ester bond. Lipstatin **1a** known since 1978 was isolated from *Streptomyces toxytricini* and its structure and absolute configuration were established in 1987 by scientists at Hoffmann-La Roche. Esterastin **1b** isolated from *Streptomyces lavendulae* MD4-C1 is a 2-oxetanone closely related to lipstatin **1a**. It inhibits pancreatic lipase but is less efficient than lipase and has therefore attracted less attention. These compounds **1a** and **1b** along with their tetrahydro derivatives, tetrahydrolipstatin **1c**[1e] and tetrahydroesterastin **1d**[1f] are esterase inhibitor. As pancreatic lipase is responsible for the cleavage of free fatty acids from their triglyceride precursors and for their subsequent absorption by the organism, the inhibition of this enzyme should enable dietary fat to pass into the gut without being absorbed. The structure of valilactone **1e**, isolated from *Streptomyces albolongus* MG147-CF2 was established by X-ray analysis. (-)-Panclicin D, **1f** is also a pancreatic lipase inhibitor with twice the inhibitory activity of the approved antiobesity agent tetrahydrolipstatin (Orlistat) **1c**.

Although lipstatin **1a** is more efficient than THL **1c**, most biological studies available were performed on THL **1c** which is still very active, easier to synthesize and more stable. The Hoffmann-La Roche company patented a number of synthetic THL 2-

oxetanones analogues which are useful agents in the treatment of obesity, hyperlipaemia, atherosclerosis and arteriosclerosis.

Orlistat, or tetrahydrolipstatin (THL) **1c**, is an FDA-approved antiobesity drug, which works primarily on pancreatic and gastric lipases within the gastrointestinal (GI) tract.[2a] Recently, Orlistat was found to inhibit the thioesterase domain of fatty acid synthase (FAS), an enzyme essential for the growth of cancer cells but not normal cells.[3a] By effectively blocking the cellular FAS activity, Orlistat induces endoplasmic reticulum stress in tumor cells, inhibits endothelial cell proliferation and angiogenesis, and consequently delays tumor progression on a variety of cancer cells, including prostate, breast, ovary, and melanoma cancer cells.[3a] As a result, this compound (as well as other Orlistat-like analogues with improved potency and bioavailability[4]) has been proposed as a promising anticancer drug.

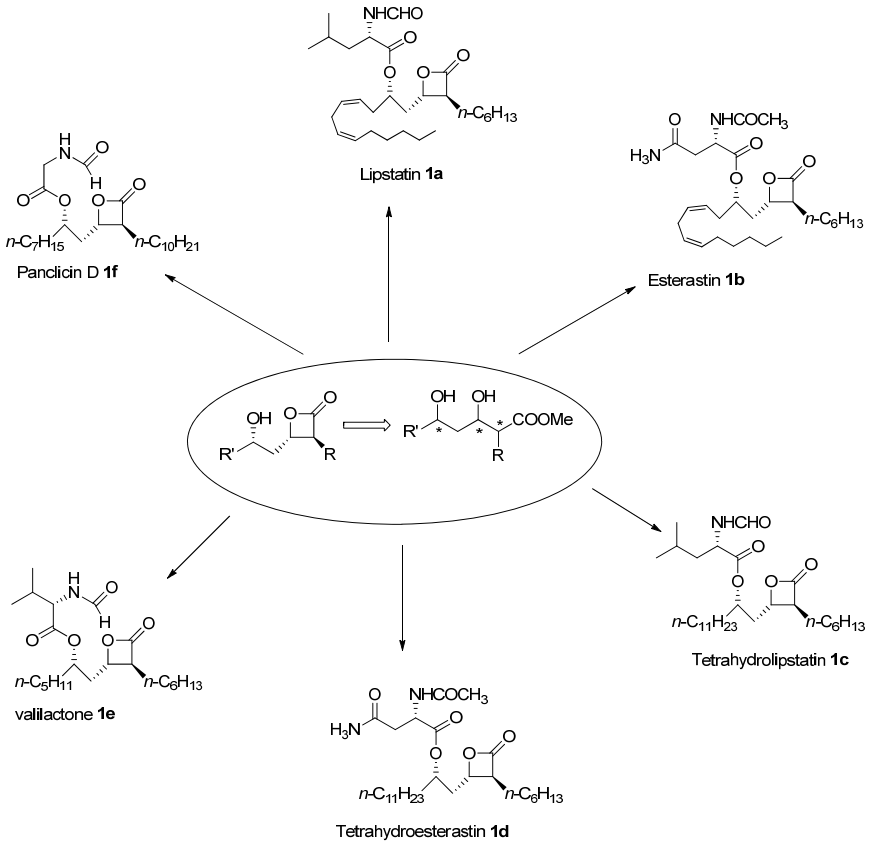


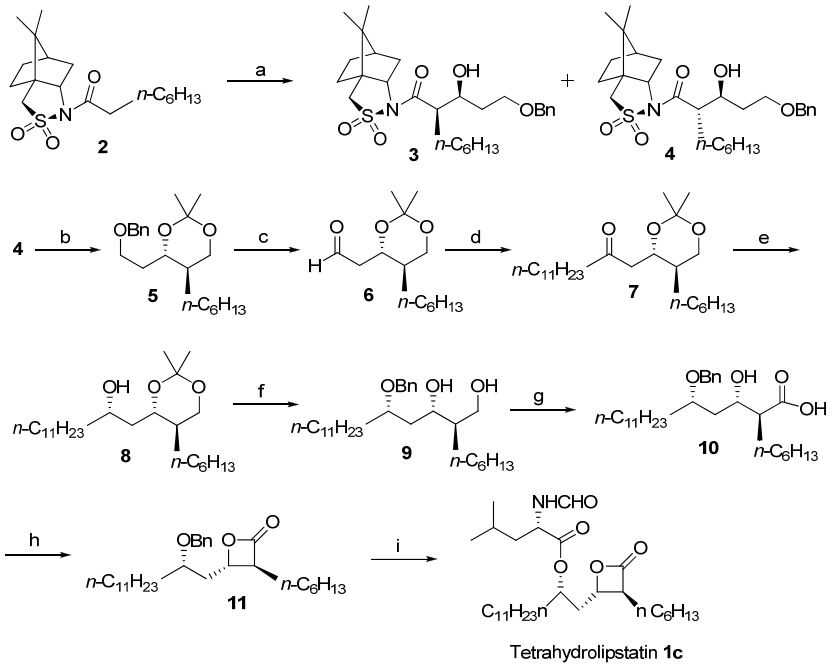
Figure 1. Structures of various esterase inhibitors

4.2. Review of Literature

The synthesis of *trans*-3,4-dialkyl-β-lactone has been achieved through a wide range of methods.[5] Yadav[5a] *et al*. reported Prins cyclization and Cu-mediated regioselective ring opening for the synthesis of THL **1c**. Barbier[5b] *et al*. employed condensation of aldehyde with the anion of lithium while Yadav[5c] *et al*. relied on Barton–McCombie reaction to synthesize **1c**. Several of these naturally occurring *trans*-3,4-dialkyl-β-lactone have been synthesized, and the utility of β-lactones as anti-cancer agents has also been studied extensively. Thus developing novel chemical strategies that enable large-scale studies of *trans*-3,4-dialkyl-β-lactones are still in high demand.

Kumaraswamy *et al*.[5d] (2008)

Kumaraswamy *et al*. prepared acylsultam **2** which was treated with $TiCl_4$ and benzyloxypropanal to give *syn* and *anti* aldol adducts **3** and **4** respectively (Scheme **1**). Reductive cleavage of anti-aldol adduct **4** with LAH gave 1,3-diol which was protected with 2,2-DMP to afford **5**. Debenzylation of **5** furnished the corresponding alcohol, which was oxidized with IBX to give the aldehyde **6**. The Grignard reagent generated using undecyl bromide and Mg in THF was added to aldehyde **6** to furnish the corresponding alcohol as a diastereomeric mixture. This was further subjected to oxidation with IBX to give the corresponding ketone **7**. A highly *syn* stereoselective 1,3-asymmetric reduction was carried out using LiI–LAH to provide the desired 1,3-syn product **8**. The hydroxy group was protected as its benzyl ether and the acetonide cleaved to give the corresponding diol **9**. Chemoselective oxidation of **9** with TEMPO followed by further oxidation of the resulting aldehyde furnished the β-hydroxy acid **10**. The acid **10** was lactonized to furnish β-lactone **11**. Debenzylation of β-lactone **11** provided the corresponding alcohol which was coupled with (*S*)-N-formylleucine to give (-)-tetrahydrolipstatin **1c**.

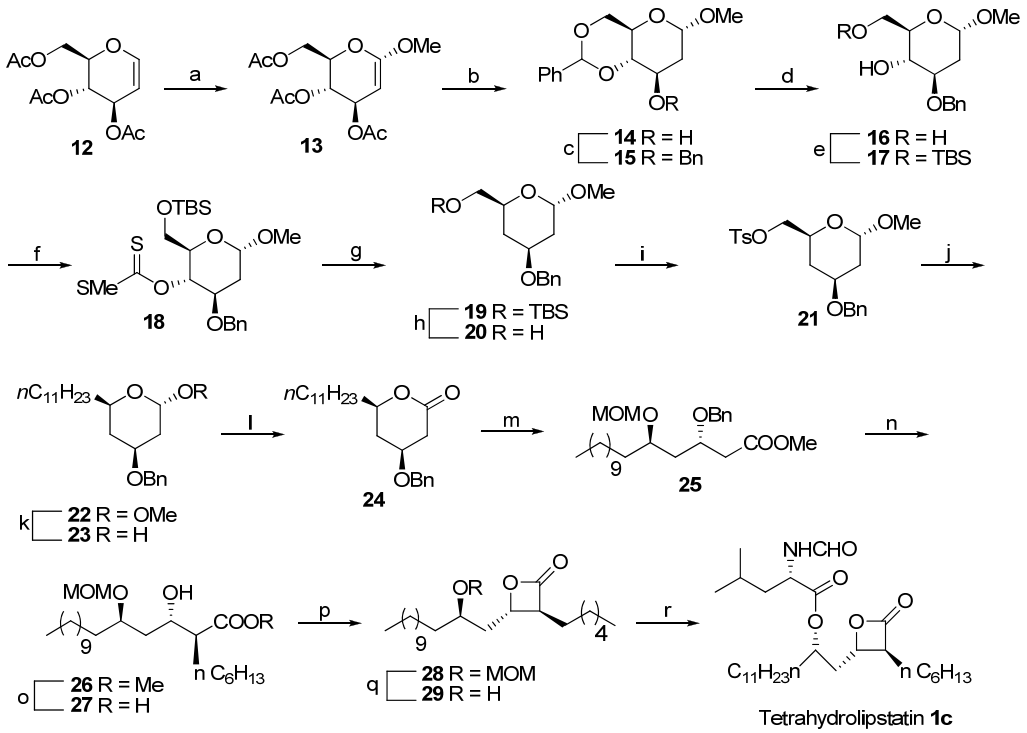


Scheme 1. *Reagents and conditions*: (a) $TiCl_4$, *i*Pr_2NEt, 3-(benzyloxy)propanal, CH_2Cl_2, -78 ^oC. (b) (i) LAH, ether, 0 ^oC to rt, 3 h, 75%. (ii) CSA, 2,2-DMP, CH_2Cl_2, 0 ^oC, 6 h, 90%. (c) (i) Li, NH_3, THF, 1 h, 82%. (ii) IBX, DMSO, CH_2Cl_2, rt, 4 h, 90%. (d) (i) Mg, undecyl bromide, THF, 0 ^oC to rt, 12 h, 70%. (ii) IBX, DMSO, CH_2Cl_2, rt, 4 h, 90%. (e) LiI, LAH, ether, -100 ^oC, 30 min, 80%. (f) (i) BnBr, NaH, THF, 0 ^oC to reflux, 6 h, 80%. (ii) 1 N HCl, THF (1:1) 0–60 ^oC, 3 h, 88%. (g) TEMPO, BAIB, CH_2Cl_2, rt, 2 h; then $NaClO_2$, 20% $NaH_2PO_4.2H_2O$, *t*-BuOH, 0 ^oC to rt, 4 h, 90%. (h) BOPCl, Et_3N, CH_2Cl_2, 23 ^oC, 1 h, 75%. (i) (i) $Pd(OH)_2/C$, H_2, EtOAc/EtOH (9:1), 12 h, 92%. (ii) DCC, DMAP, (*S*)-N-formyl leucine, CH_2Cl_2, rt, 24 h, 80%.

Yadav *et al*.[5c] (2006)

Yadav *et al*. employed C-glycosidation of tri-*O*-acetyl- D-glucal **12** (Scheme **2**) to afford methyl acetal **13** which was subjected to methanolysis and subsequently selective protection of the 1,3-diol part to furnish **14**. Compound **14** was protected as benzyl ether **15** and then subjected to benzylidene acetal cleavage to afford 1,3-diol **16**, which was selectively protected with a TBS group at the primary hydroxy group and the secondary hydroxy group as xanthate ester to afford **18**. Compound **18** was subjected to Barton–McCombie deoxygenation to afford **19**. The TBS deprotection of **19** followed by its treatment with tosyl chloride afforded the corresponding tosylate **21**, which was treated with *n*-decylmagnesium bromide to obtain the coupled product **22**. The methyl acetal of **22** was converted into lactol **23** which in turn was subjected to

oxidation with Dess–Martin periodinane to yield lactone **24**. The β-lactone **24** was opened to yield the corresponding δ-hydroxy ester, which was protected as its methoxymethyl ether **25**. The methyl ester **25** was hydrogenated to afford a β-hydroxy ester. The key step, stereocontrolled alkylation, was effected by treating the β-hydroxy ester with lithium diisopropylamide followed by addition of *n*-hexyl iodide to the dianion to give **26** as the major diastereomer. Hydroxy ester **26** was converted to β-lactone **28** by hydrolysis of ester group. Deprotection of the methoxymethyl ether of β-lactone **28** furnished alcohol **29** which on esterification with (*S*)-*N*-formyl-L leucine under Mitsunobu conditions furnished (–)-tetrahydrolipstatin **1c**.

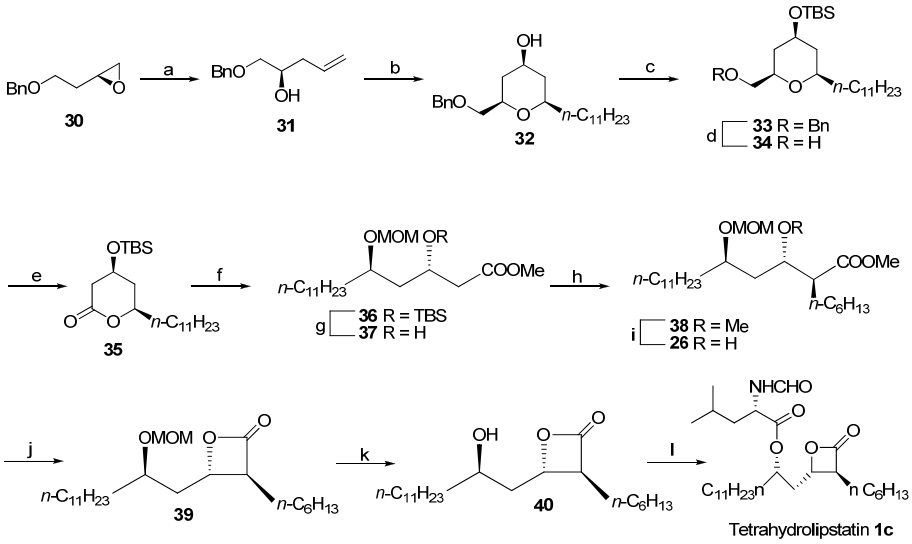


Scheme 2. *Reagents and conditions*: (a) $CeCl_3$-NaI, MeCN, MeOH, reflux, 3 h, 87%. (b) (i) NaOMe, MeOH, rt, 2 h. (ii) $PhCH(OMe)_2$, PTSA (cat.), toluene, reflux, 2 h, 66% for 2 steps. (c) NaH, BnBr, TBAI (cat.), THF, reflux, 6 h, 78%. (d) *p*-TSA (cat.), MeOH, overnight, 79%. (e) TBSCl, imidazole, CH_2Cl_2, 0 °C to rt, 4 h, 83%. (f) NaH, CS_2, MeI, 0 °C to rt, overnight, 78%. (g) *n*-Bu_3SnH, AIBN (cat.), toluene, reflux, 6 h, 79%. (h) TBAF, THF, 0 °C to rt, 2 h, 98%. (i) TsCl, Et_3N, DMAP (cat.), CH_2Cl_2, 0 °C to rt, 2 h, 92%. (j) *n*-$C_{10}H_{21}MgBr$, CuBr (cat.), THF, 0 °C to rt, 5 h, 76%. (k) 80% aq AcOH, reflux, 6 h, 72%. (l) Dess–Martin periodinane, CH_2Cl_2, 0 °C to rt, 2 h, 84%. (m) Et_3N, MeOH, 0 °C to rt, 12 h, then MOMCl, DIPEA, CH_2Cl_2, 0 °C to rt, 12 h, 71%. (n) (i) $Pd(OH)_2$/C, EtOAc, 12 h, 94%. (ii) LDA, *n*-$C_6H_{13}I$, HMPA, THF, –78 °C,

3 h, 75%. (o) LiOH, THF–H_2O, (4:1), 0 °C to rt, 12 h, 88%. (p) $PhSO_2Cl$, pyridine, 12 h, 0 °C, 76%. (q) $BF_3.OEt_2$, $(CH_2SH)_2$, 0 °C to rt, 1 h, 88%. (r) DIAD, TPP, *N*-formyl-L-leucine, 0 °C to rt, 2 h, 90%.

Yadav *et al*.[5a] (2006)

Prasad *et al*. investigated Prins cyclization for the synthesis of THL (Scheme **3**). Cu mediated regioselective ring opening of (*R*)-benzyl glycidyl ether **30** with vinyl magnesium bromide resulted in homoallylic alcohol **31**. Prins cyclisation of **31** with dodecanal followed by hydrolysis of the resulting trifluoroacetate gave trisubstituted pyran **32**. Protection of the secondary alcohol as the TBS ether **33** followed by cleavage of the primary benzyl ether furnished pyranyl methanol **34**. PCC mediated oxidative cleavage of **34** provided triketide δ-lactone **35**. Methanol addition to the lactone **35** resulted in the corresponding δ-hydroxy ester which was protected as its MOM ether **36**. Cleavage of the silyl ether **36** yielded β-hydroxy ester **37**. The dianion of **37**, formed on treatment with LDA, was alkylated with hexyl iodide to give **38** as the predominant diastereomer. Hydroxy ester **38** was transformed into β-lactone **39** by hydrolysis of the ester group followed by treatment of acid **26** with $PhSO_2Cl$. β-Lactone **39** on cleavage of MOM ether afforded alcohol **40** which on esterification with (*S*)-*N*-formyl leucine under Mitsunobu conditions furnished (-)-THL **1c**.

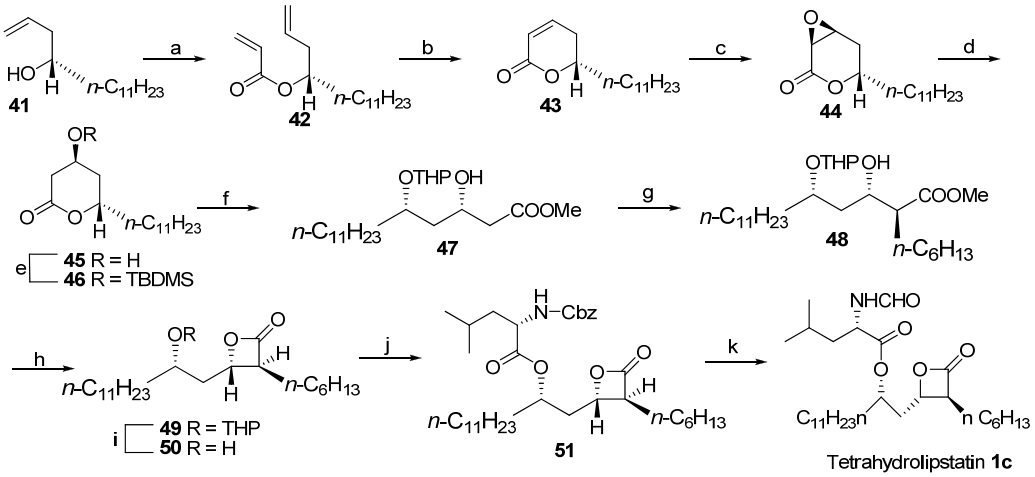


Scheme 3. *Reagents and conditions*: (a) vinylmagnesium bromide, CuCN, THF, -78 ^oC-rt, 4 h, 84%. (b) dodecanal, TFA, DCM then K_2CO_3, MeOH rt, 2 h, 64%. (c)

TBSCl, imidazole DMAP, DCM, 0 ^{o}C-rt, 6 h, 96%. (d) Na, NH_3, THF, -33 ^{o}C, 5 min, 92%. (e) PCC, benzene, reflux, 6 h, 65%. (f) TEA, MeOH, rt, 12 h then DIPEA, MOMCl, DMAP, DCM, 0 ^{o}C-rt, 2 h, 90%. (g) TBAF, THF, 0 ^{o}C-rt, 6 h, 98%. (h) LDA, *n*-$C_6H_{13}I$, THF, -78 to -20 ^{o}C, 3 h, 75%. (i) LiOH, THF, H_2O, rt, 12 h, 88%. (j) $PhSO_2Cl$, Py, THF, 0 ^{o}C, 12 h, 76%. (k) $BF_3.OEt_2$, $(CH_2SH)_2$, 0 ^{o}C-rt, 1 h, 88%. (l) (*S*)-*N*-formyl leucine, DIAD, TPP, THF, 0 ^{o}C-rt, 3 h, 90%.

Ghosh *et al*.[5e] (2009)

Ghosh *et al*. employed homoallylic alcohol **41** which was reacted with acryloyl chloride to furnish the acrylate ester **42** (Scheme **4**). Olefin metathesis of **42** with Grubbs' catalyst afforded the α,β-unsaturated δ-lactone **43**. Epoxidation of lactone **43** was carried out with alkaline H_2O_2 which furnished the epoxide **44** stereoselectively from the less hindered β-face. Exposure of epoxide **44** to PhSeSePh resulted in the β-hydroxy-δ-lactone **45**. Introduction of the C-2 alkyl chain, was carried out by Seebach's asymmetric alkylation of β-hydroxy esters.[5f] The β-hydroxy lactone **45** was first protected as a TBDMS ether **46** and then converted to β-hydroxy ester **47** in a three step sequence involving opening of the lactone ring by exposure to Et_3N, protection of the resulting δ-hydroxy methyl ester as THP ether, and finally removal of the TBDMS group . The C-2 hexyl side chain was then introduced by an asymmetric alkylation of the β-hydroxy ester **47** which was reacted with hexyl iodide to afford the alkylated product **48**. The removal of the THP ether group in **48** followed by saponification of ester **48** with aqueous LiOH and exposure of the resulting acid to $PhSO_2Cl$ afforded the β-lactone **49**. Removal of the THP group furnished the β-lactone **50**. *N*-formylleucine was introduced by an alternate protocol as described by Uskokovic *et al.*[5g] Esterification of **50** with Cbz-leu provided the Cbz derivative **51**. Catalytic hydrogenation of **51** followed by *N*-formylation of the resulting amine with formic acetic anhydride furnished the synthetic (-)-tetrahydrolipstatin **1c**.

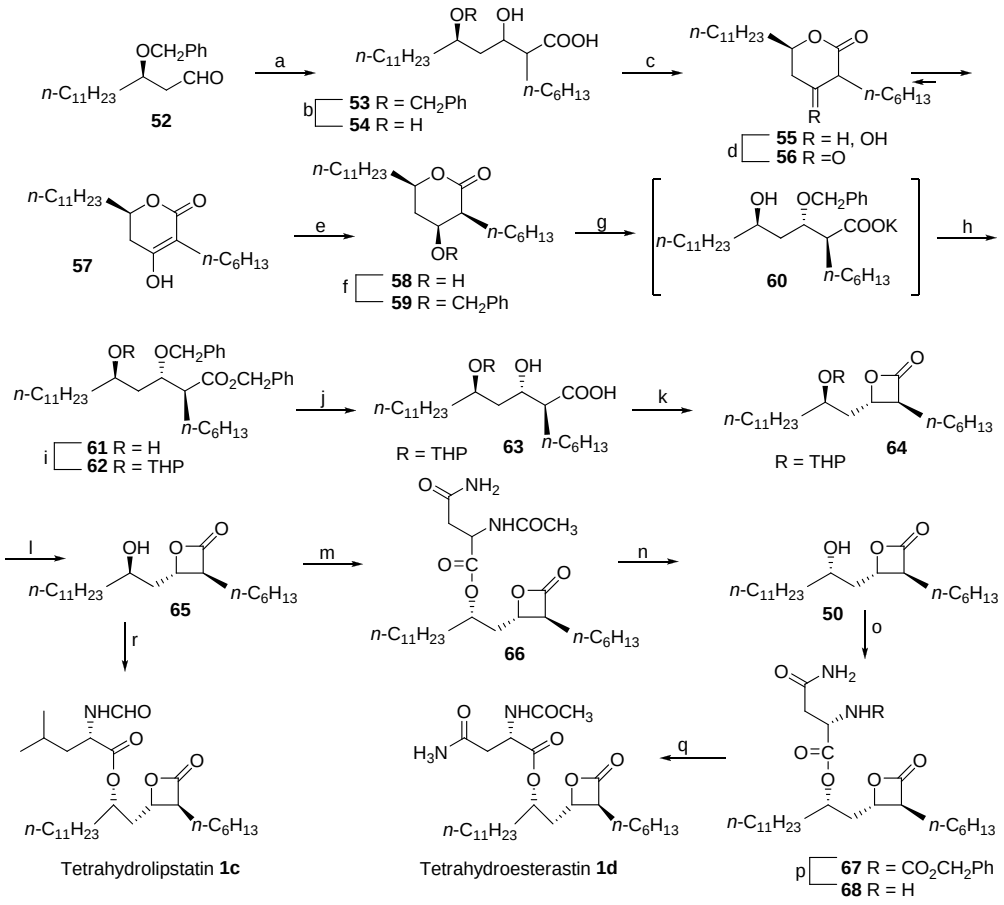


Scheme 4. *Reagents and conditions*: (a) CH_2=CHCOCl, Et_3N, DMAP, 23 °C, 91%. (b) $(PCy_3)_2Cl_2Ru$=CHPh, 10 mol%, $Ti(O^iPr)_4$, 0.3 equiv, CH_2Cl_2, 40 °C, 93%. (c) aq. NaOH, H_2O_2, 23 °C. (d) PhSeSePh, $NaBH_4$, Pr^iOH, AcOH, 0 °C 83%. (e) TBDMSCl, Pr^i_2NEt, DMF, 25 °C, 98%. (f) (i) Et_3N, MeOH, 23 °C, 12 h, 75%. (ii) DHP, PPTS, 8 h. (iii) Bu_4NF, THF, AcOH, 25 °C, 5 h, 60%. (g) LDA, HMPA, $C_6H_{13}I$, THF, -78 to 0 °C, 6 h, 85%. (h) (i) aq. LiOH, 25 °C, 12 h, H^+. (ii) $PhSO_2Cl$, Py, 0 °C, 8 h, 84%. (i) PPTS, EtOH, reflux, 3 h, 90%. (i) Cbz-Leu, DCC, DMAP, 95%. (k) (i) H_2, Pd-C, 12 h. (ii) AcOCHO, THF, 25 °C, 87%.

Barbier *et al*.[5b] (1988)

Barbier *et al*. employed aldehyde **52** which was condensed with the anion of lithium octanoate to yield hydroxy acid **53** as a mixture of diastereomers, (scheme **5**) which by deprotection furnished hydroxy acid **54.** Cyclization of **54** gave β-hydroxy δ-lactone **55** as a mixture of diastereomers, which were oxidized to β-keto δ-lactone **56**, present in chloroform solution under its enol form **57**. Hydrogenation of **57** yielded the crucial β-hydroxy-δ-lactone **58** which was protected as its benzyl ether **59**. Ring opening of **59** occurred on treatment with KOH to give the potassium salt of hydroxy acid **60**, which on immediate treatment with benzyl bromide afforded benzyl ester **61**. THP protection of **61** followed by benzyl deprotection furnished hydroxy acid **63** which was treated with benzenesulfonyl chloride and pyridine to give β-lactone **64**. THP deprotection yielded β-lactone **65** which on esterification under Mitsunobu's conditions with (*S*)-*N*-formylleucine gave tetrahydrolipstatin **1c**. In order to synthesize tetrahydroesterastin **1d**, compound **66** was saponified to furnish β-hydroxy lactone **50** which could also be obtained from tetrahydrolipstatin **1c** under the same conditions, the β-lactone ring

being cleaved under the reaction conditions. Esterification of **50** with the mixed anhydride prepared from pivaloyl chloride and *(S)-N-*Zasparagine afforded ester **67,** and cleavage of the Z protecting group by hydrogenolysis and acetylation of **68** with acetyl chloride gave pure tetrahydroesterastin **1d**.



Scheme 5. *Reagents and conditions*: (a) Octanoic acid, LDA. (b) H_2, Pd/C, 10%. (c) *p*-TsOH, $CHCl_3$. (d) Jones' CrO_3, acetone. (e) H_2, Pt, 50 bars. (f) Benzyl trichloroacetimidate, CF_3SO_3H, CH_2Cl_2. (g) 1N aq KOH. (h) benzyl bromide, THF, HMPA. (i) dihydropyran, *p*-TsOH, CH_2Cl_2. (j) H_2, Pd/C, 10%, THF. (k) benzenesulfonyl chloride, pyridine. (l) pyridinium *p*-toluenesulfonate, EtOH. (m) (*S*)-*N*-acetylasparagine, PPh_3, diethyl azodicarboxylate, THF. (n) 0.02 N aq NaOH, dioxane. (o) (*S*)-*N*-(benzyloxycarbonyl) asparagine, pivaloyl chloride, Et_3N, DMF. (p) H_2, Pd/C, 10%, THF. (q) CH_3COCl, Et_3N, THF. (r) (*S*)-*N*-Formylleucine, PPh_3, diethyl azodicarboxylate, THF.

4.3. PRESENT WORK

Objective

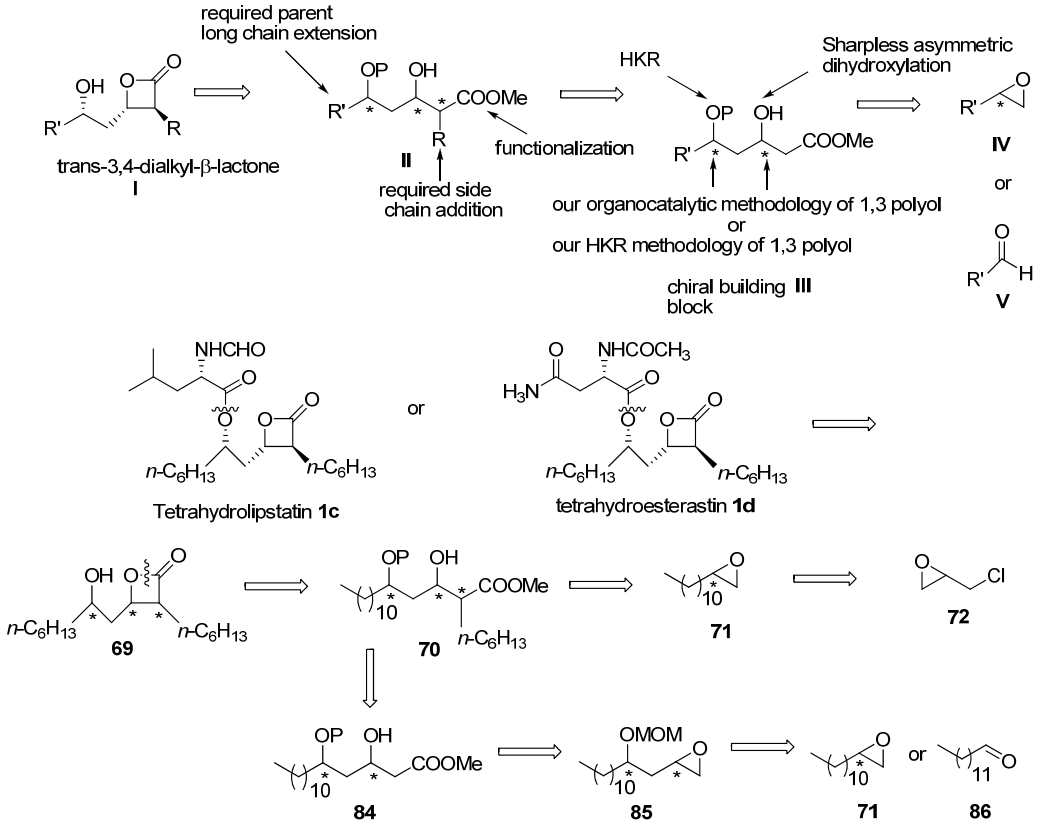
It is well-documented that tetrahydrolipstatin (THL) marketed under the trade name Orlistat, or Xenical belonging to *trans*-3,4-dialkyl-β-lactone class of compound, is an approved drug for treating obesity, and a potent inhibitor of thioesterase domain of fatty acid synthase (FAS). Recent findings have important implications in the consideration of Orlistat as a potential anticancer drug at its early stages of development for cancer therapy. THL is cytotoxic and cytostatic to tumor cells in vitro and can inhibit tumor growth in vivo.[3b] FAS is generating a great deal of excitement as an interesting drug target in oncology because by effectively blocking the cellular FAS activity, orlistat induces endoplasmic reticulum stress in tumor cells, inhibiting endothelial cell proliferation and angiogenesis, and consequently delays tumor progression on a variety of cancer cells, including breast, [2b,c] prostate, [2d,e] ovary, [2f] and melanoma cancer cells.[3a]

Lipstatin **1a** esterastin **1b**, valilactone **1e** and panclicin D **1f** (Fig **1**) are β-lactone analogous 3,4-disubstituted 2-oxetanones isolated from Streptomyces species[1] differing only in the structure of C-4 side chain and the nature of the amino acid linked to it. The saturated derivatives of **1a** and **1b**, tetrahydrolipstatin **1c**[1e] and tetrahydroesterastin **1d**[1f] exhibit comparable pharmacological properties, but are more stable than the parent compounds. The unique structural features of these trans β-lactone class of drugs, and their potential applications as thioesterase inhibitors has resulted in an onslaught of activities directed at the synthesis of these challenging target molecules.[5] Despite the numerous strategies to synthesize polyols through substrate-controlled asymmetric induction, the interest in the new methods of its synthesis continues unabated.[6]

4.4. Results and Discussion

As part of our research interest in the asymmetric synthesis of bioactive molecules,[7] we became interested in devising a general route to a key chiral building block which will eventually lead to all of the above stated *trans*-3,4-dialkyl-β-lactones. As a synthetic application, we have applied this strategy to a common fragment which would inevitably lead to both (-)-tetrahydrolipstatin **1c** and tetrahydroesterastin **1d**. Herein

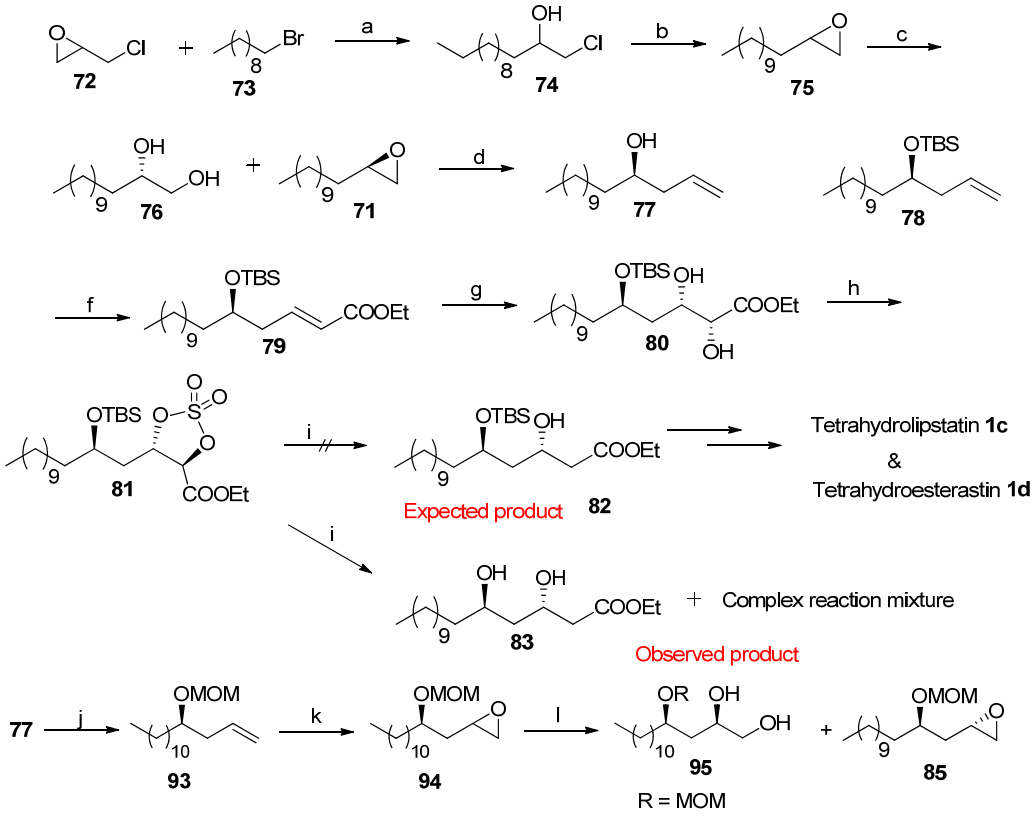
we describe our synthetic endeavor towards the target molecules **1c** and **1d** employing HKR of epoxides and proline-catalyzed sequential α-aminoxylation, and HWE olefination of aldehyde as the key steps.



Scheme 6. Retrosynthetic route to tetrahydrolipstatin **1c** and tetrahydroesterastin **1d**

As retrosynthetically delineated in scheme **6**, 2-oxetanone (β-lactone) **I** can have variations at C-3 and C-6 side chains as well as it can have any amino acid linked to β-hydroxy group, thus it can be considered as common structure for all the *trans*-3,4-dialkyl-β-lactones. β-Lactone **I** in turn can be obtained from its open chain structure **II** which can have a required parent C-6 long chain, a C-2 side chain as well as amino acid attached to it. Functionalization of ester group is possible *via* coupling with the β-hydroxy group. **II** in turn, can be obtained from chiral building block **III**, which can have the chiral centres derived from HKR as well as Sharpless asymmetric dihydroxylation. Building block **III** can be synthesized from chiral epoxide **IV**. Alternatively chiral building block **III**, can be synthesized either from epoxide **IV** or from aldehyde **V** and can have the chiral centres derived from our iterative approach to

the synthesis of *syn* and *anti*-1,3 polyols *via* HRK[9a] as well as *via* organocatalysis which is based on proline-catalyzed sequential α-aminoxylation, followed by Horner-Wadsworth- Emmons (HWE) olefination of aldehydes.[9b] Coupling of *(S)*-N-formylleucine group in tetrahydrolipstatin **1c** or *(S)*-N-acetylasparagine group in tetrahydroesterastin **1d** could be effected by esterification with the respective β-lactone moietiy **69**. We envisioned that β-lactone **69** in turn could be derived from C-2 alkylated β-hydroxy ester **70**, which in turn could be derived from 1,3-polyol system **84**. Ester **84** in turn can be obtained from chiral epoxide **85** which can be procured either by iterative hydrolytic kinetic resolution (HKR) of epoxide **71** or by iterative proline catalyzed α-aminoxylation and Horner-Wadsworth-Emmons olefination of aldehyde **86**. Epoxide **71** can be prepared from commercially available epichlorohydrin **72**.



Scheme 7. *Reagents and conditions:* (a) Mg, **73**, CuI, dry Et_2O, -78 ^oC, 12 h. (b) KOH, Et_2O, 0 ^oC-rt, 6 h, 86%. (c) *R,R*-Salen-Co^{III}(OAc) (0.5 mol%), dist. H_2O (0.55 equiv), isopropanol, 24 h, (45% for **76**, 43% for **71**). (d) C_2H_3MgBr, CuI, THF, -78 ^oC, 12 h, 91%. (e) TBSCl, imidazole, DCM, overnight, 92%. (f) (i) OsO_4, $NaIO_4$, 2,6-Lutidine,

1,4-Dioxane: H_2O (3:1), 0 ^oC, 30 min. (ii) $Ph_3P{=}CHCO_2Et$, THF, rt, 24 h, 87%. (g) $(DHQ)_2PHAL$ (1 mol%), 0.1 M OsO_4 (0.5 mol%), K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, *t*-BuOH/H_2O 1:1, 0 ^oC, 24 h, 96%. (h) (i) $SOCl_2$, Et_3N, CH_2Cl_2, 0 ^oC, 30 min. (ii) $RuCl_3.3H_2O$, $NaIO_4$, CCl_4–MeCN–H_2O; 2:2:3, 0 ^oC, 1 h, 87%. (i)$NaBH_4$, DMAC, 25 ^oC, 30 min, then 20% aq. H_2SO_4, overnight. (j) MOMCl, DIPA, DCM, overnight, 89%. (k) *m*-CPBA, CH_2Cl_2, 10 h, 96%. (l) *S,S*-Salen-Co^{III}(OAc) (0.5 mol%), dist. H_2O (0.55 equiv), THF, 24 h, (34% for **95**, 56% for **85**).

Synthesis of tetrahydrolipstatin and tetrahydroesterastin

The synthesis of tetrahydrolipstatin (**1c**) and tetrahydroesterastin (**1d**) commenced from commercially available epichlorohydrin **72** (Scheme **7**) which was subjected to the copper-catalyzed (CuI) regioselective ring-opening with Grignard reagent, derived from decanyl bromide **73** and Mg in ether at -78 ^oC to furnish the chloro alcohol **74**. Appearance of peak at 3488 cm^{-1}in IR spectrum confirmed the formation of compound **74**. Subsequent treatment with KOH in ether led to racemic epoxide **75** in 86% yield. ^1H NMR spectrum of **75** showed epoxide protons at δ 2.91-2.85 (multiplet, 1H), 2.76 (doublet of doublet, 1H, with coupling constant J = 4.9, 1.2 Hz) and 2.46 (doublet of doublet, with coupling constant J = 4.9, 2.4 Hz). The ^{13}C NMR spectrum of **75** showed upfield carbons characteristic of epoxide at δ 52.3 and 47.0. Racemic epoxide **75** was subjected to Jacobsen's HKR by using (*R,R*)-Salen-Co^{III}OAc catalyst to give chiral (*S*)-diol **76** along with chiral (*R*)-epoxide **71** as single isomer in 95% ee. To establish the second stereogenic center with required stereochemistry, the chiral epoxide **71** was treated with vinylmagnesium bromide in the presence of CuI to give the homoallylic alcohol **77** in 91% yield. The IR spectrum of **77** gave broad hydroxyl absorption at 3360 cm^{-1}. The ^1H NMR spectrum of **77** gave olefin peaks at 5.94 - 5.82 (multiplet, 1H), 5.20 (doublet, 1H), 5.09 (doublet, 1H). The newly generated hydroxyl group of homoallylic alcohol **77** was protected using TBSCl in presence of imidazole to afford **78** as silyl ether in 92% yield. One-pot oxidative cleavage was effected employing osmium tetroxide and sodium meta periodate to furnish the corresponding aldehyde which was subsequently treated with (ethoxycarbonylmethylene) triphenylphosphorane in benzene under reflux conditions to furnish the *trans*-olefin **79** in 87% yield. The IR spectrum of **79** showed the ester carbonyl absorption at 1721 cm^{-1} and olefin C=C stretching at 1654 cm^{-1}. The ^1H NMR spectrum gave olefin protons at δ 5.83 (doublet

of triplet) with the coupling constant J = 1.70, 15.7 Hz and δ 6.89 - 7.04 (multiplet) indicating *trans*-olefin. The olefin **79** was treated with osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of $(DHQ)_2PHAL$ ligand under AD conditions[8] to give the diol **80** in 96% yield with 95% ee (as determined from ^1H and ^{13}C NMR spectral analysis of the crude reaction mixture).The IR spectrum gave hydroxyl absorption at 3444 cm^{-1} and ester carbonyl at 1736 cm^{-1}. The ^1H NMR indicated absence of olefin protons. The chiral protons appeared at δ 4.28 (multiplet) and 3.94 (doublet). The chiral carbons appeared at δ 74.1 and 69.4 in the ^{13}C NMR spectrum. Treatment of diol **80** with thionyl chloride and excess triethylamine in CH_2Cl_2 gave the cyclic sulfite, which was further oxidised using $NaIO_4$ and a catalytic amount of ruthenium trichloride to furnish the corresponding cyclic sulfate **81** in quantitative yield. The synthetic strategy shown in scheme **7** was based on the presumption that the nucleophilic opening of the cyclic sulfate **81** would occur in a regiospecific manner at α-carbon. Indeed, the cyclic sulfate **81** reacted with one equivalent of $NaBH_4$ with apparent complete selectivity for attack at C-2 position to furnish the intermediate sulfate ester which, without further isolation was subjected to acidic hydrolysis using 4N H_2SO_4 in anticipation of obtaining β-OH ester **82** but unfortunately the product obtained was TBS deprotected compound **83** along with a complex reaction mixture.

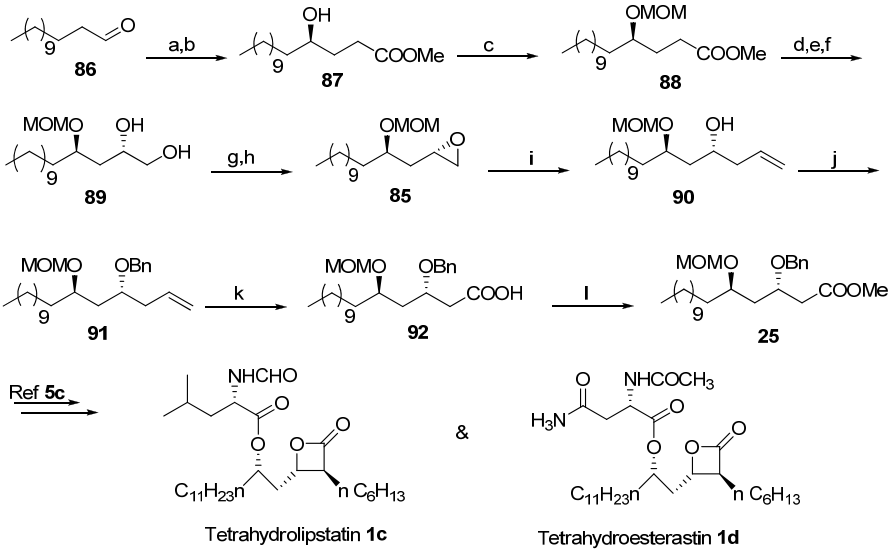
The route to this synthesis was revised and we resorted to HKR approach to generate the next stereocenter. Accordingly, the hydroxyl group of homoallylic alcohol **77** was protected using methoxy methyl chloride in presence of di-isopropyl amine to afford **93** as MOM ether in 89% yield. Epoxidation of **93** with *m*CPBA furnished the epoxide **94** in 3:2 diastereomeric ratio (as determined from ^1H and ^{13}C NMR spectral analysis of the crude reaction mixture) in 96% yield. ^1H NMR spectrum of **94** showed epoxide protons at δ 3.03 – 3.10 (multiplet, 1 H), 2.80 (doublet of doublet, 1 H, with coupling constant J = 4.9, 1.2 Hz) and 2.51 (doublet of doublet, with coupling constant J = 4.9, 2.4 Hz). The ^{13}C NMR spectrum of **94** showed upfield carbons characteristic of epoxide at δ 55.5 and 44.9. The next step in the synthesis was to construct the diastereomerically pure epoxide by means of Jacobsen's hydrolytic kinetic resolution (HKR). To this end, the epoxide **94** was treated with (S,S)-Salen-Co-OAc complex and water in THF to afford the epoxide **85** as a single stereoisomer (as determined by ^1H and ^{13}C NMR spectral analysis of crude reaction mixture) in 56% yield and the diol **95**

in 34% yield. The conversion of epoxide **85** to the target molecules **1c** and **1d** can be accomplished as per the synthetic sequences illustrated in scheme **8.**

Synthesis of tetrahydrolipstatin and tetrahydroesterastin *via* organocatalysis

As illustrated in scheme **8**, the synthesis of target compounds commenced from aldehyde **86** which was subjected to α-aminoxylation using L-proline as a catalyst and subsequently Horner-Wadsworth-Emmons olefination followed by Pd/C reduction to furnish the ester **87** in 62% yield and 97% ee. Appearance of peak at 3444 cm^{-1}in IR spectrum confirmed the formation of compound **87**. The enantiomeric excess was determined by converting the alcohol **87** into Mosher ester and analyzing the ^{19}F spectrum. The hydroxyl protection of **87** with methoxymethyl chloride in the presence of di-isopropyl amine as base afforded ester **88** in 89% yield. Temperature controlled DIBAL-H reduction of ester **88** furnished the corresponding aldehyde which on aminoxylation, using D-proline as catalyst followed by *in-situ* reduction with $NaBH_4$ furnished the required α-amino substituted diol which was subsequently subjected to reductive hydrogenation to afford the required diol **89** as a single diastereomer (as determined from ^1H and ^{13}C NMR spectral analysis of the crude reaction mixture) in 72% yield. The IR spectrum of **89** showed broad hydroxyl absorption at 3392 cm^{-1}.The selective primary hydroxyl tosylation of **89** and its subsequent treatment with K_2CO_3 in methanol led to enantiomerically pure epoxide **85** in 85% yield. ^1H NMR spectrum of **85** showed epoxide protons at δ 3.03 – 3.10 (multiplet, 1 H), 2.80 (doublet of doublet, 1 H, with coupling constant J = 4.9, 1.2 Hz) and 2.51 (doublet of doublet, with coupling constant J = 4.9, 2.4 Hz). The ^{13}C NMR spectrum of **85** showed upfield carbons characteristic of epoxide at δ 55.5 and 44.9. With required framework in hand we then proceeded with the copper-catalyzed (CuI) regioselective ring-opening of epoxide **85** with Grignard reagent, derived from vinyl bromide and Mg in THF at -30 ^oC to furnish the homoallylic alcohol **90** in 92% yield. The IR spectrum of **90** gave broad hydroxyl absorption at 3342 cm^{-1}. The ^1H NMR spectrum of **90** gave olefin peaks at 5.79 - 5.96 (multiplet, one proton), 5.16 (doublet, one proton), 5.08 (doublet, one proton). Benzyl protection of the newly generated homoallylic alcohol **90** was accomplished by its reaction with benzyl bromide in the presence of sodium hydride to afford the protected homoallylic alcohol **91** in 95% yield. One-pot oxidative cleavage and conversion to acid, of terminal olefin **91** was effected employing ruthenium trichloride and sodium

meta periodate to furnish the corresponding acid **92** in 85% yield. Finally the acid **92** was esterified using MeI and K_2CO_3 to give methyl ester **25** in 85% yield. $[\alpha]_D^{25}$ = -24.44 (*c* = 3.3, $CHCl_3$); lit.[5c] $[\alpha]_D^{25}$ = -24.46 (*c* = 3.3, $CHCl_3$). The physical and spectroscopic data of **25** were compared with those reported earlier and were found to be similar[5c] in all respects. The final stage of the synthesis could be achieved through the known procedure[5c,f] of alkylation of the C-2 side chain, cyclization to β-lactone and coupling of either *(S)*-N- formylleucine group[5g] to give tetrahydrolipstatin **1c** or *(S)*-N-acetylasparagine group[5b] to give tetrahydroesterastin **1d**.



Scheme 8. *Reagents and conditions:* (a) Nitroso benzene, L-proline, DMSO, 30 min, then trimethyl phosphonoacetate, DBU, LiCl, CH_3CN, 1h. (b) Pd/C, EtOAc, overnight, 62%. (c) MOMCl, DIPA, DCM, 8h, 89%. (d) DIBAL-H, DCM, -78 ^oC, 1h. (e) Nitroso benzene, D-proline, DMSO, 30 min, then $NaBH_4$, EtOAc. (f) Pd/C, EtOAc, 12h, 72%. (g) TsCl, Et_3N, DCM, Bu_2SnO, 6h. (h) K_2CO_3, MeOH, 1h, 85%. (i) Vinylmagnesium bromide, CuI, dry THF, -30 ^oC, 12h, 92%. (j) BnBr, NaH, DMF, 4h, 95%. (k) $RuCl_3.3H_2O$, $NaIO_4$ CCl_4−CH_3CN−H_2O, 2:2:3, 3h, 85%. (l) MeI, K_2CO_3, MeOH, 30 min, 85%.

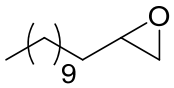
4.5. Conclusion

In conclusion we have devised a general route to a key chiral building block which will eventually lead to all of the above stated *trans*-3,4-dialkyl-β-lactones. As a

synthetic application, we have applied this strategy to a common fragment which would inevitably lead to both (-)-tetrahydrolipstatin **1c** and tetrahydroesterastin **1d**. While the parent C-6 long chain of β-lactone can be varied by changing the aldehyde or the epoxide, the *R* and *S* configurations of the polyol can be manipulated simply by changing the catalyst in the aminoxylation step or the HKR step. The C-2 side chain as well as the nature of the amino acid attached to it can be varied. For the above mentioned reasons, our strategy should be broadly useful for significant stereochemical and structural variations in the synthesis of a wide variety of β-lactone analogues (as well as other orlistat-like analogues with improved potency and bioavailability). It will also help in identification against quite a number of potential leads or drug candidates which can be explored as various potential drug targets.

4.6. Experimental Section

Tridecane-1,2-diol (75)



To a stirred solution of epichlorohydrin **72** (5.00 g, 54.05 mmol) and CuI (0.21 g, 1.08 mmol) in dry Et_2O (20 mL), was added a solution of magnesium bromodecane prepared from 1-bromodecane **73** (23.89 g, 108.10 mmol) and Mg-turning (3.94 g, 162.16 mmol) in dry Et_2O, dropwise at -78 °C. The mixture was stirred to this temperature over 12 h and poured into a saturated NH_4Cl solution. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined ethereal extracts were dried over Na_2SO_4. The combined organic layer was washed with brine and dried (Na_2SO_4) to give crude chloro alcohol **74** which was used as such for the next step without further purification. To a crude solution of **74** in Et_2O (50 mL) was added finely powdered KOH (4.30 g, 76.76 mmol). The mixture was stirred vigorously for 6 h and poured into 50 mL water. After separation of the layers, the aqueous layer was extracted with Et_2O (3 x 50 mL) and the combined organic layers were dried over Na_2SO_4. Evaporation of the solvent and silica gel column chromatographic purification (EtOAc/petroleum ether, 1:49) of the crude product gave **75** as a colorless liquid.

Yield: 9.26 g, 86%

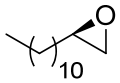
Mol. Formula: $C_{13}H_{26}O$

IR ($CHCl_3$, cm^{-1}) ν_{max} = 3050, 910, 830, 720

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.2 Hz, 3H), 1.25 (brs, 18H), 1.33 - 1.50 (m, 2H), 2.43 - 2.47 (m, 1H), 2.71 - 2.76 (m, 1H), 2.85 - 2.91 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 22.7, 25.9, 29.4, 29.5, 29.6, 29.7,31.9, 32.5, 47.1, 52.3.

(*S*)-Tridecane-1,2-diol (76) and **(*R*)-2-undecyloxirane (71)**



A solution of epoxide **75** (5 g, 25.25 mmol) and (*R*,*R*)-Salen-CoIII-OAc (0.10 g, 0.15 mmol) in isopropanol (0.3 mL) was stirred at 0 ^oC for 5 min and then distilled water (454 mL, 25.25 mmol) was added. After stirring for 24 h, this mixture was concentrated and purified by silica-gel column chromatography (petroleum ether/EtOAc 19:1) to afford **71** as a yellow liquid. Continued chromatography with petroleum ether/EtOAc 3:2) provided the diol **76** as a brown liquid and as a single diastereomer.

Yield: 2.15 g, 43%

Mol. Formula: $C_{13}H_{26}O$

$[\alpha]_D^{25}$ + 10.8 ^oC (*c* = 1.1, Et_2O); Lit^{10} $[\alpha]_D^{20.1}$ + 11.8 (*c* = 1.09, ether).

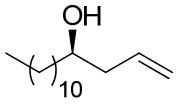
IR ($CHCl_3$, cm^{-1}) ν_{max} = 3050, 910, 830, 720

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.2 Hz, 3H), 1.25 (brs, 18H), 1.33 - 1.50 (m, 2H), 2.43 - 2.47 (m, 1H), 2.71 - 2.76 (m, 1H), 2.85 - 2.91 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 22.7, 25.9, 29.4, 29.5, 29.6, 29.7, 31.9, 32.5, 47.1, 52.3.

Elemental Analysis: Calcd for $C_{13}H_{26}O$ C, 78.72; H, 13.21; Found: C, 78.68; H, 13.25.

(*R*)-Pentadec-1-en-4-ol (77)



A round bottom flask was charged with copper (I) iodide (0.20 g, 1.06 mmol), gently heated under vacuum, and slowly cooled with a flow of argon, and dry THF (20 mL) was added. This suspension was cooled to –78 ^oC, vigorously stirred and

vinylmagnesium bromide (5.5 M in THF, 4.8 mL, 26.51 mmol) was injected to it. A solution of epoxide **71** (2.1 g, 10.60 mmol) in THF (10 mL) was added slowly to the above reagent, and the mixture was stirred at –20 ^{o}C for 4 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl. The organic layer was washed with brine, dried (Na_2SO_4), concentrated and purified by silica-gel column chromatography (petroleum ether/EtOAc 9:1) to afford **77** as a yellow liquid.

Yield: 2.1 g, 91%

Mol. Formula: $C_{15}H_{30}O$

$[\alpha]_D^{25}$ +6.0 (*c* 1.7, $CHCl_3$).

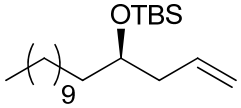
IR ($CHCl_3$, cm^{-1}) ν_{max} = 3360, 2920, 2840, 1700, 1455, 1115, 1075, 1018, 985, 900.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.7 Hz, 3H), 1.26 (brs, 18H), 1.38 - 1.54 (m, 2H), 2.10 -2.35 (m, 2H), 3.59 - 3.71 (m, 1H), 5.09 - 5.20 (m, 2H), 5.74 - 5.94 (m,1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 22.7, 25.7, 29.3, 29.6, 29.7, 31.9, 36.8, 41.9, 70.7, 117.9, 134.9.

Elemental Analysis: Calcd for $C_{15}H_{30}O$ C, 79.58; H, 13.36;Found: C, 79.63; H, 13.31..

(*R*)-*tert*-Butyldimethyl(pentadec-1-en-4-yloxy)silane (78)



Imidazole (1.70 g, 24.97 mmol) was added to a stirred solution of alcohol **77** (3.7 g, 16.65 mmol) in CH_2Cl_2 (15 mL). *tert*-Butyldimethylchlorosilane (3.76 g, 24.97 mmol) was then added to this solution at 0 ^{o}C, and reaction was stirred at room temperature overnight. After this time, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (3 x 30 mL). The organic extracts were washed with brine, dried (Na_2SO_4), and then concentrated. Silica-gel column chromatography of the crude product (petroleum ether/EtOAc 19:1) provided **78** as a colorless liquid.

Yield: 5.12 g, 92%

Mol. Formula: $C_{21}H_{44}OSi$

$[\alpha]_D^{25}$ +10.04 (*c* 0.96, $CHCl_3$)

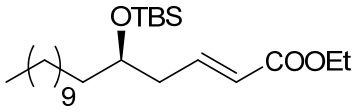
IR ($CHCl_3$, cm^{-1}) ν_{max} = 2910, 2830, 1720, 1455, 1110, 1075, 1012, 985.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.05 (s, 6H), 0.87 (t, *J* = 6.7 Hz, 3H), 0.90 (s, 9H), 1.27 – 1.42 (m, 20H), 2.18 – 2.25 (m, 2H), 3.66 - 3.71 (m, 1H), 4.99 - 5.07 (m, 2H), 5.76 - 5.90 (m,1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = -4.5, -2.9, 14.1, 18.2, 22.7, 25.3, 25.7, 25.9, 29.3, 29.6, 31.9, 36.8, 41.9, 72.1, 116.5, 135.5.

Elemental Analysis: Calcd for $C_{21}H_{44}OSi$ C, 74.04; H, 13.02; Found: C, 74.08; H, 13.06.

(*R*,*E*)-Ethyl 5-(*tert*-butyldimethylsilyloxy)hexadec-2-enoate (79)



To a solution of compound **78** (2 g, 8.83 mmol) in dioxane-water (3:1, 20 mL) were added 2,6-lutidine (2.07 mL, 17.66 mmol), OsO_4 (0.1M solution in toluene, 2.17 mL, 0.22 mmol) and $NaIO_4$ (7.5 g, 35.33 mmol). The reaction was stirred at 25 ^oC for 30 mins. After the reaction was complete, water (10 mL) and CH_2Cl_2 (20 mL) were added. The organic layer was separated, and the water layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layer was washed with brine and dried (Na_2SO_4) to give crude aldehyde which was used as such for the next step without further purification.

To a solution of (ethoxycarbonylmethylene)triphenylphosphorane (3.19 g, 8.78 mmol) in dry THF (20 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 purified by silica gel column chromatography (EtOAc/petroleum ether, 1:9) to give olefin **79** as a pale yellow oil.

Yield: 2.09 g, 87 %

Mol. Formula: $C_{24}H_{48}O_3Si$

$[\alpha]_D^{25}$ -4.76 (*c* 1.68, $CHCl_3$)

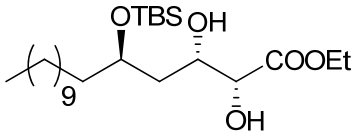
IR ($CHCl_3$, cm^{-1}) ν_{max} = 2953, 1721, 1654, 1268, 1046.

^{1}H NMR (200 MHz, $CDCl_3$): *δ* = 0.04 (s, 6H), 0.85 (t, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 1.20 - 1.29 (m, 18H), 1.32 – 1.37 (m, 3H), 1.39 – 1.43 (m, 2H), 2.30 - 2.37 (m, 2H), 3.73 - 3.79 (m, 1H), 4.19 (q, *J* = 7.6, 14.4 Hz, 2H), 5.83 (dt, *J* =1.70, 15.7 Hz, 1 H), 6.89 – 7.04 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): *δ* = -4.6, 14.0, 14.2, 17.9, 22.6, 25.2, 25.7, 29.3, 29.6, 31.8, 37.2, 40.1, 59.9, 71.3, 123.1, 146.04, 166.3.

Elemental Analysis: Calcd for $C_{24}H_{48}O_3Si$ C, 69.84; H, 11.72; Found: C, 69.88; H, 11.67.

(2*R*,3*S*,5*R*)-Ethyl 5-(*tert*-butyldimethylsilyloxy)-2,3-dihydroxyhexadecanoate (80)



To a mixture of $K_3Fe(CN)_6$ (10.07 g, 30.62 mmol), K_2CO_3 (4.22 g, 30.62 mmol) and $(DHQ)_2PHAL$ (11 mg, 1 mol%), in *t*-BuOH-H_2O (1:1, 50 mL) cooled at 0 ^oC was added OsO_4 (0.4 mL, 0.1 M solution in toluene, 0.4 mol%) followed by methanesulfonamide (97 mg, 10.20 mmol). After being stirred for 5 min at 0 ^oC, the olefin **79** (4.2 g, 10.20 mmol) was added in one portion. The reaction mixture was stirred at 0 ^oC form 24 h and then quenched with solid sodium sulfite (6.2 g). The stirring was continued for an additional 45 min, and then the solution was extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with 10% KOH, and brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (3:2) as eluent gave the diol **80** as a colorless syrupy liquid.

Yield: 4.26 g, 96%

Mol. Formula: $C_{24}H_{50}O_5Si$

$[\alpha]_D^{25}$ +5.45 (*c* 0.82, $CHCl_3$)

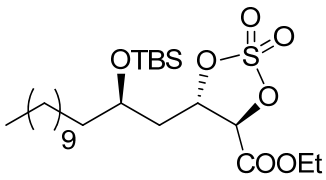
IR ($CHCl_3$, cm^{-1}) ν_{max} = 3444, 2867, 1737, 1454, 1275, 1206.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.10 (s, 6H), 0.85 (t, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 1.21 - 1.35 (m, 18H), 1.54 – 1.64 (m, 7H), 2.86 (s, 2H), 4.34 – 3.94 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = -4.6, -4.1, 14.0, 22.6, 24.6, 25.4, 25.7, 29.2, 29.5, 29.6, 31.8, 37.7, 38.4, 61.6, 69.4, 73.4, 74.1, 173.25.

Elemental Analysis: Calcd for $C_{24}H_{50}O_5Si$ C, 64.53; H, 11.28; Found: C, 64.47; H, 11.36.

Cyclic sulfate (81)



To a solution of diol **80** (2.45 mg, 5.5 mmol) in dry CH_2Cl_2 (15 mL) was added Et_3N (3.98 mL, 33.0 mmol). The mixture was cooled in an ice bath and thionyl chloride (0.48 mL, 6.6 mmol) added dropwise. The reaction mixture was stirred for 30 min and then quenched by adding water (10 mL). The phases were separated and aqueous phase extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated. Then the solution was cooled with an ice-water bath and diluted with CH_3CN (10 mL) and CCl_4 (10 mL). $RuCl_3.5H_2O$ (67 mg, 5.12 mmol) and $NaIO_4$ (903 mg, 84.66 mmol) were added followed by water (15 mL). The resulting orange mixture was stirred at room temperature for 1 h. The mixture was then diluted with ether (20 mL), and the two phases separated. The organic layer was washed with water (20 mL), saturated with aq. $NaHCO_3$ (20 mL), brine, dried Na_2SO_4, and concentrated. Silica gel column chromatography purification (EtOAc/petroleum ether, 1:5) of the crude product gave cyclic sulfate **81** as a colorless liquid.

Yield: 2.42 g, 87%

Mol. Formula: $C_{24}H_{48}O_7SSi$

$[\alpha]_D^{25}$ +4.08 (*c* 0.54, $CHCl_3$)

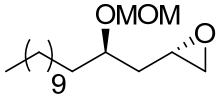
IR ($CHCl_3$, cm^{-1}) ν_{max} = 2954, 1765, 1739, 1454, 1217.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.4 (s, 6H), 0.85 (t, *J* = 6.5 Hz, 3H), 0.90 (s, 9H), 1.21 - 1.32 (m, 21H), 1.44 – 1.59 (m, 4H), 3.21 – 3.25 (m, 1H), 4.21 (q, *J* = 7.6, 14.4 Hz, 2H), 5.31- 5.50 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = -4.4, 14.1, 22.6, 25.3, 25.9, 29.3, 29.5, 29.7, 31.9, 37.1, 40.3, 61.3, 66.2, 73.2, 82.9, 172.8.

Elemental Analysis: Calcd for $C_{24}H_{48}O_7SSi$ C, 56.66; H, 9.51; Found: C, 56.71; H, 9.46.

(*S*)-2-((*R*)-2-(Methoxymethoxy)tridecyl)oxirane (85)



To a mixture of diol **89** (2.8 g, 9.19 mmol), in dry DCM (5 mL) was added dibutyltin oxide (45.7 mg, 0.18 mol) followed by the addition of *p*-toluenesulfonyl chloride (1.74 g, 9.19 mmol) and triethylamine (1.27 mL, 9.19 mmol) and reaction was stirred at room temperature under nitrogen. The reaction was monitored by TLC, after

completion of reaction the mixture was quenched by adding water. The solution was extracted with DCM (3 x 20 ml) and then combined organic phase was washed with water, dried (Na_2SO_4) and concentrated. To this crude mixture in MeOH at 0 °C was added K_2CO_3 (1.52 g, 11.0 mmol) and the resultant mixture was allowed to stir for 1 h at same temp. After completion of reaction as indicated by TLC, the reaction was quenched by addition of ice pieces and methanol was evaporated. The concentrated reaction mixture was then extracted with ethyl acetate (3 x 20 mL), the combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The column chromatography of crude product using pet ether : ethyl acetate (9:1) gave the epoxide **85** as a colorless liquid.

Yield: 2.24 g, 85%

Mol. Formula: $C_{17}H_{34}O_3$

$[\alpha]_D^{25}$ – 7.9 (*c* 1.04, $CHCl_3$).

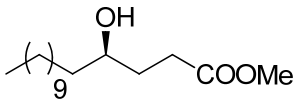
IR (neat, cm^{-1}) ν_{max} = 2954, 2932, 2893, 2859, 1471, 1376, 1361, 1252, 1215, 1102, 1042, 919.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7 Hz, 3H), 1.26 (brs, 18H), 1.50 - 1.70 (m, 4H), 2.50 - 2.52 (m, 1H), 2.80 - 2.84 (m, 1H), 3.03 - 3.10 (m, 1H) 3.41 (s, 3H), 3.79 - 3.82 (m, 1H), 4.70 - 4.72 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 22.7, 29.3, 29.6, 29.7, 31.9, 34.5, 44.7, 44.8, 55.6, 83.1, 95.6.

Elemental Analysis: Calcd for $C_{17}H_{34}O_3$ C, 71.28; H, 11.96; Found: C, 71.32; H, 11.91.

(*R*)-Methyl 4-hydroxypentadecanoate (87)



To a solution of tridecanal **86** (10.0 g, 50.4 mmol) and nitroso benzene (3.41 g, 50.4 mmol) in anhydrous DMSO (100 mL) was added L-proline (1.46 g, 12.7 mmol) at rt. The mixture was vigorously stirred for 30 min under argon (the color of the reaction changed from green to orange during this time), then cooled to 0 °C. Thereafter, a premixed and cooled (0 °C) solution of trimethylphosphonoacetate (20 mL,100.8 mmol), DBU (15.4 mL,100.8 mmol) and LiCl (4.3g, 100.8 mmol) in CH_3CN (100 mL) was added quickly (1-2 min) at 0 °C. The resulting mixture was allowed to warm to

room temperature over 1 h, and quenched by addition of ice pieces. The acetonitrile was evaporated under vacuum. This reaction mixture was then poured into water (50 mL) and extracted with Et_2O (5×50 mL). The combined organic layer was washed with water, brine, dried (Na_2SO_4) and concentrated in vacuo to give crude product which was directly subjected to next step without purification. To the crude allylic alcohol in ethyl acetate was added Pd-C (10%) under hydrogenation conditions and the reaction mixture was allowed to stir overnight. On completion of reaction (until ^1H NMR analysis of the crude mixture indicated complete conversion), the mixture was filtered through a pad of celite and concentrated in vacuo to give γ-hydroxy ester. The crude product was then purified by flash column chromatography using pet ether: EtOAc (85:15) as eluent to give **87** as a colorless liquid.

Yield: 8.5 g, 62%

Mol. Formula: $C_{16}H_{32}O_3$

$[\alpha]_D^{25}$ +11.8 (*c* 0.05).

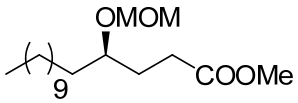
IR ($CHCl_3$, cm^{-1}) ν_{max} = 3444, 2840, 1737, 1455, 1275, 1075.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.9 Hz, 3H), 1.26 (brs, 18H), 1.48 - 1.65 (m, 4H), 2.40 - 2.46 (m, 2H), 3.65 - 3.73 (m, 4H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.7, 23.3, 25.9, 29.9, 30.1, 30.2, 32.5, 35.0, 37.9, 52.0, 70.1, 175.1;

Elemental Analysis: Calcd for $C_{16}H_{32}O_3$ C, 70.54; H, 11.84; Found: C, 70.48; H, 11.78.

(*R*)-Methyl 4-(methoxymethoxy)pentadecanoate (88)



To a solution of the alcohol **87** (6.0 g, 22.02 mmol) and diisopropylethylamine (11.51 mL, 44.04 mmol) in dry CH_2Cl_2 (30 mL) was added MOMCl (2.0 mL, 26.42 mmol) under argon over 5 min at 0 °C, and the mixture was allowed to warm to room temperature and stirred for 8 h. After cooling to 0 °C, the reaction mixture was quenched with water and extracted with CH_2Cl_2 (3 X 30 mL). The combined organic extracts were washed with water (3 X 50 mL) and brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) gave **88** as a colorless liquid.

Yield: 6.20 g, 89%

Mol. Formula: $C_{18}H_{36}O_4$

$[\alpha]_D^{25}$ +1.4 (*c* 0.8, $CHCl_3$).

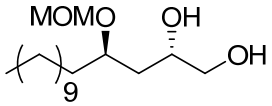
IR ($CHCl_3$, cm^{-1}) ν_{max} = 2928, 2856, 1742, 1216, 1038.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.8 Hz, 3H), 1.26 (brs, 18H), 1.48 - 1.65 (m, 4H), 2.40 - 2.46 (m, 2H), 3.37 (s, 3H), 3.65 - 3.73 (m, 4H), 4.66 (s, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 22.6, 25.3, 29.3, 29.5, 29.6, 31.9, 34.4, 37.3, 51.4, 55.5, 79.7, 95.4, 174.5.

Elemental Analysis: Calcd for $C_{18}H_{36}O_4$ C, 68.31; H, 11.47; Found: C, 68.38; H, 11.39.

(2*S*,4*R*)-4-(Methoxymethoxy)pentadecane-1,2-diol (89)



To a solution of ester **88** (5.0 g, 183.6 mmol) in dry DCM (30 mL) at -78 °C was added dropwise DIBAL-*H* (18.35 mL, 183.6 mmol, 1 M in toluene). The reaction mixture was stirred for 1 h, then treated with sat. aqueous solution of sodium potassium tartrate (50 mL). The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with water, brine, dried (Na_2SO_4), filtered and concentrated to give the crude aldehyde, which was used for the next step without purification. To a stirred solution of aldehyde (5.0g, 20.94 mmol) and nitrosobenzene (2.24 g, 20.94 mmol) in DMSO (42 mL) was added D-proline (0.9 g, 8.3 mmol, 20 mol %) in one portion at 25 °C. After 30 min, the temperature was lowered to 0 °C, followed by dilution with anhydrous EtOAc (10 mL) and careful addition of excess $NaBH_4$ (2.78 g, 73.3 mmol). The reaction was quenched after 20 min by pouring the reaction mixture into a vigorously stirred biphasic solution of Et_2O and aqueous HCl (1M). The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phase was dried over anhyd Na_2SO_4, concentrated, and purified by column chromatography over silica gel using EtOAc/Pet. Ether (40:60) as eluent to give pure aminoxy alcohol. The aminoxy alcohol was dissolved in EtOAc (10 mL) and to the solution was added 10% Pd/C (0.050 g) and the reaction mixture was stirred in a hydrogen atmosphere (1 atm, balloon pressure) for 12 h. After completion of reaction (monitored by TLC), the

reaction mixture was filtered through a celite pad, concentrated, and the crude product was then purified by silica gel chromatography using petroleum ether : ethyl acetate (2:3) as eluent to give pure diol **89** as a colorless liquid.

Yield: 2.9 g, 72%)

Mol. Formula: $C_{17}H_{36}O_4$

$[\alpha]_D^{25}$ – 6.68 (*c* 1.92, $CHCl_3$)

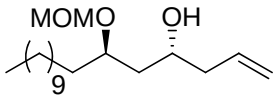
IR ($CHCl_3$, cm^{-1}) ν_{max} = 3392, 3018, 2854, 1458, 1263, 1099, 759.

^{1}H NMR (200 MHz, $CDCl_3$): 0.88 (t, *J* = 6.7 Hz, 3H), 1.26 (brs, 18H), 1.56 - 1.74 (m, 4H), 3.42 (s, 3H), 3.59 - 3.70 (m, 1H), 3.81 - 3.87 (m, 1H), 4.07 - 4.18 (m, 2H), 4.64 - 4.77 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): 14.1, 22.6, 29.3, 29.5, 29.6, 31.8, 34.3, 37.8, 45.7, 55.7, 60.4, 70.4, 80.1, 96.3.

Elemental Analysis: Calcd for $C_{17}H_{36}O_4$ C, 67.06; H, 11.92; Found: C, 67.11; H, 11.98.

(4*R*,6*R*)-6-(Methoxymethoxy)heptadec-1-en-4-ol (90)



A round bottom flask was charged with copper (I) iodide (0.19 g, 1.04 mmol), gently heated under vacuum, and slowly cooled with a flow of argon, and dry DMF (25 mL) was added. This suspension was cooled to –30 ^oC and vigorously stirred, and vinylmagnesium bromide (1.6 M in THF, 16.3 mL, 26.18 mmol) was injected to it. A solution of epoxide **85** (3 g, 10.47 mmol) in THF (10 mL) was added slowly to the above reagent, and the mixture was stirred at –30 ^oC for 12 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated to afford the crude homoallylic alcohol which on silica gel column chromatography of the crude product using petroleum ether/EtOAc (8:2) as eluent furnished **90** as colorless liquid.

Yield: 3.03 g, 92%

Mol. Formula: $C_{19}H_{38}O_3$

$[\alpha]_D^{25}$ – 14.35 (*c* 1.06, $CHCl_3$)

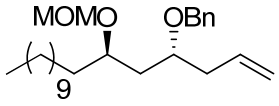
IR ($CHCl_3$, cm^{-1}) ν_{max} = 3342, 3018, 1610, 1556, 1492, 1284, 1089, 759.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7 Hz, 3H), 1.26 (brs, 18H), 1.51 - 1.68 (m, 4H), 1.96 - 2.10 (m, 2H), 3.40 (s, 3H), 3.77 - 3.88 (m, 2H), 4.62 - 4.77 (m, 2H), 5.08 - 5.16 (m, 2H), 5.79 - 5.96 (m,1H).

^{13}C NMR (50 MHz, $CDCl_3$): *δ* = 14.2, 22.7, 29.4, 29.6, 29.8, 31.9, 34.8, 40.7, 42.0, 55.8, 67.2, 76.0, 96.3, 117.5, 135.1.

Elemental Analysis: Calcd for $C_{19}H_{38}O_3$ C, 72.56; H, 12.18; Found: C, 72.52; H, 12.12.

(((4*R*,6*R*)-6-(Methoxymethoxy)heptadec-1-en-4-yloxy)methyl)benzene (91)



To a solution of alcohol **90** (2.0 g, 6.36 mmol) in dry THF (50 mL) was added sodium hydride (50%, 0.30 g, 7.63 mmol) at 0 °C. The reaction mixture was then stirred at room temperature for 30 min after which it was again cooled to 0 °C. To this was added slowly benzyl bromide (0.9 mL, 7.63 mmol) with further stirring for 4 h at room temperature. The reaction mixture was quenched with addition of cold water at 0 °C. The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with water (3 x 25 mL), brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) as eluent furnished **91** as colorless liquid.

Yield: 2.44 g, 95%

Mol. Formula: $C_{26}H_{44}O_3$

$[\alpha]_D^{25}$ – 20.3 (*c* 1.04, $CHCl_3$).

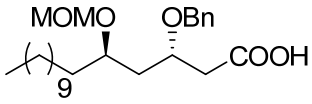
IR ($CHCl_3$, cm^{-1}) ν_{max} = 2867, 1455, 1115, 1075, 985, 900.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.9 Hz, 3H), 1.26 (brs, 18H), 1.39 - 1.57 (m, 4H), 2.35 - 2.42 (m, 2H), 3.37 (s, 3H), 3.57 - 3.80 (m, 2H), 4.45 - 4.65 (m, 4H), 5.08 - 5.16 (m, 2H), 5.76 - 5.94 (m,1H) 7.32 - 7.37 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.2, 22.7, 29.4, 29.7, 29.8, 29.9, 31.9, 35.4, 38.5, 40.1, 55.6, 70.9, 74.9, 75.4, 96.1, 117.3, 127.6, 127.9, 128.4, 134.5, 138.8.

Elemental Analysis: Calcd for $C_{26}H_{44}O_3$ C, 77.18; H, 10.96; Found: C, 77.11; H, 10.92.

(3*S*,5*R*)-3-(Benzyloxy)-5-(methoxymethoxy)hexadecanoic acid (92)



Compound **91** (300 mg, 0.74 mmol) was dissolved in 7 ml of 2:2:3 CCl_4−CH_3CN−H_2O, $NaIO_4$ (318 mg, 1.48 mol) and $RuCl_3.3H_2O$ (10 mg, 0.003 mmol) was then added. The resulting mixture was stirred vigorously at room temperature for 3 h. The mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using pet ether/EtOAc (8:2) as eluent provided **92** as a brown color syrupy liquid.

Yield: 266 mg, 85%

Mol. Formula: $C_{25}H_{42}O_5$

$[\alpha]_D^{25}$ – 2.07 (*c* 1.9, $CHCl_3$)

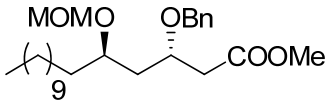
IR ($CHCl_3$, cm^{-1}) ν_{max} = 3392, 1714, 1482, 1258, 1054, 837, 759.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.7 Hz, 3H), 1.26 - 130 (m, 18H), 1.43 - 1.55 (m, 4H), 2.33 - 2.38 (m, 2H), 3.37 (s, 3H), 3.64 - 3.68 (m, 1H), 3.71 - 3.80 (m, 1H), 4.03 - 4.28 (m, 1H), 4.51 - 4.65 (m, 4H), 7.30 – 7.35 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.4, 22.0, 24.3, 28.6, 28.9, 29.2, 31.3, 34.7, 37.8, 41.9, 54.9, 70.3, 74.8, 80.0, 95.4, 126.8, 127.2, 127.7, 138.1, 178.6.

Elemental Analysis: Calcd for $C_{25}H_{42}O_5$ C, 71.05; H, 10.02; Found: C, 71.09; H, 10.08.

(3*S*, 5*R*)-Methyl 3-(benzyloxy)-5-(methoxymethoxy)hexadecanoate (25)



To an ice cold solution of **92** (225 mg, 0.53 mmol) in MeOH (2 mL) is added solid K_2CO_3 (0.29 g, 1.06 mmol). After stirring for 10 min in an ice bath, methyl iodide (0.09 g, 0.64mmol) is added to the white suspension and stirring continued at 0 ^oC for 30 min. where upon the mixture solidifies. The reaction was warmed to room temperature and stirred for additional 1 h or at point when TLC analysis indicates complete formation of the methyl ester. The reaction mixture was filtered by suction and the filtrate partitioned between EtOAc and water. The organic phase was washed

with brine, dried, filtered and concentrated. Silica gel column chromatography of the crude product using petroleum ether / EtOAc (9:1) as eluent gave methyl ester **25** as a yellow colour thick liquid.

Yield: 185 mg, 85%

Mol. Formula: $C_{26}H_{44}O_5$

$[\alpha]_D^{25}$ -24.44 (*c* = 3.3, $CHCl_3$); lit.[5c] $[\alpha]_D^{25}$ = -24.46 (*c* = 3.3, $CHCl_3$).

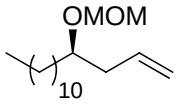
IR ($CHCl_3$, cm^{-1}) ν_{max} = 2926, 2854, 1740, 1459, 1038, 740.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.9 Hz, 3H), 1.26 (brs, 18H), 1.48 - 1.57 (m, 4H), 2.35 - 2.42 (m, 2H), 3.37 (s, 3H), 3.64 - 3.80 (m, 4H), 4.03 - 4.05 (m, 1H) 4.45 - 4.57 (m, 4H), 7.30 - 7.37 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 22.7, 24.9, 29.6, 29.9, 31.9, 35.4, 38.5, 40.1, 52.2, 55.5, 70.9, 74.8, 75.4, 96.1, 127.5, 127.8, 128.4, 134.5, 174.7.

Elemental Analysis: Calcd for $C_{26}H_{44}O_5$ C, 71.52; H, 10.16; Found: C, 71.48; H, 10.12.

(*R*)-4-(Methoxymethoxy)pentadec-1-ene (93)



To a solution of the alcohol **77** (2.0 g, 8.84 mmol) and diisopropylethylamine (4.62 mL , 26.54 mmol) in dry CH_2Cl_2 (20 mL) was added MOMCl (0.8 mL, 10.61 mmol) under argon over 5 min at 0 °C, and the mixture was allowed to warm to room temperature overnight. After cooling to 0 °C, the reaction mixture was quenched with water and extracted with CH_2Cl_2 (3 X 20 mL). The combined organic extracts were washed with water (3 X 20 mL) and brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (19:1) gave **93** as a colorless liquid.

Yield: 2.12 g, 89%

Mol. Formula: $C_{17}H_{34}O_2$

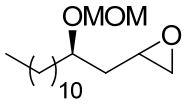
$[\alpha]_D^{25}$ +5.3 (*c* 1.5, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}) ν_{max} = 2932, 2859, 1471, 1378, 1284, 1234, 1128, 1068, 910

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.9 Hz, 3H), 1.26 (brs, 18H), 1.42 - 1.56 (m, 2H), 2.26 - 2.32 (m, 2H), 3.39 (s, 3H), 3.58 - 3.67 (m, 1H), 4.63 - 4.71 (m, 2H), 5.04 - 5.12 (m, 2H), 5.73 - 5.93 (m,1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 22.7, 25.3, 29.3, 29.6, 31.9, 34.1, 38.9, 55.4, 76.4, 95.3, 116.9, 134.9.

2-((*R*)-2-(Methoxymethoxy)tridecyl)oxirane (94)



To a stirred solution of olefin **93** (1.0 g, 3.69 mmol) in CH_2Cl_2 (25 mL) at 0 ^oC was added *m*CPBA (50%, 7.65 g, 4.43 mmol). The reaction mixture was stirred at room temperature for 10 h and then quenched with saturated $NaHCO_3$ solution. The resulting mixture was extracted with CH_2Cl_2, washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), concentrated, and then purified by silica-gel column chromatography (petroleum ether/EtOAc 9:1) to yield the epoxide **94** as a colorless liquid and as a diastereomeric mixture (3:2).

Yield: 1.0 g, 96%

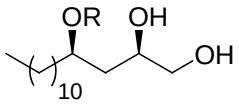
Mol. Formula: $C_{17}H_{34}O_3$

IR (neat, cm^{-1}) ν_{max} = 2954, 2932, 2893, 2859, 1471, 1376, 1361, 1252, 1215, 1102, 1042, 919.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7 Hz, 3H), 1.26 (brs, 18H), 1.50 - 1.70 (m, 4H), 2.50 - 2.52 (m, 1H), 2.80 - 2.84 (m, 1H), 3.03 - 3.10 (m, 1H) 3.41 (s, 3H), 3.79 - 3.82 (m, 1H), 4.70 - 4.72 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 22.7, 29.3, 29.6, 29.7, 31.9, 34.5, 44.7, 44.8, 55.6, 83.1, 95.6.

(2*R*,4*R*)-4-(Methoxymethoxy) pentadecane-1,2-diol (95) and **(*S*)-2-((*R*)-2-(methoxymethoxy) tridecyl) oxirane (85)**



A solution of epoxide **94** (0.6g, 2.09mmol) and (S,S)-Salen-CoIII-OAc (9 mg, 0.01 mmol) in THF (0.3 mL) was stirred at 0 ^oC for 5 min and then distilled water (0.021 mL, 1.15 mmol) was added. After stirring for 24 h, this mixture was concentrated and purified by silica-gel column chromatography (petroleum ether/EtOAc 19:1) to afford **85** (336 mg, 56%) as a yellow liquid. Continued chromatography with petroleum ether/EtOAc 3:2) provided the diol **95** as a brown liquid and as a single diastereomer.

Yield: 216 mg, 34%

Mol. Formula: $C_{17}H_{36}O_4$

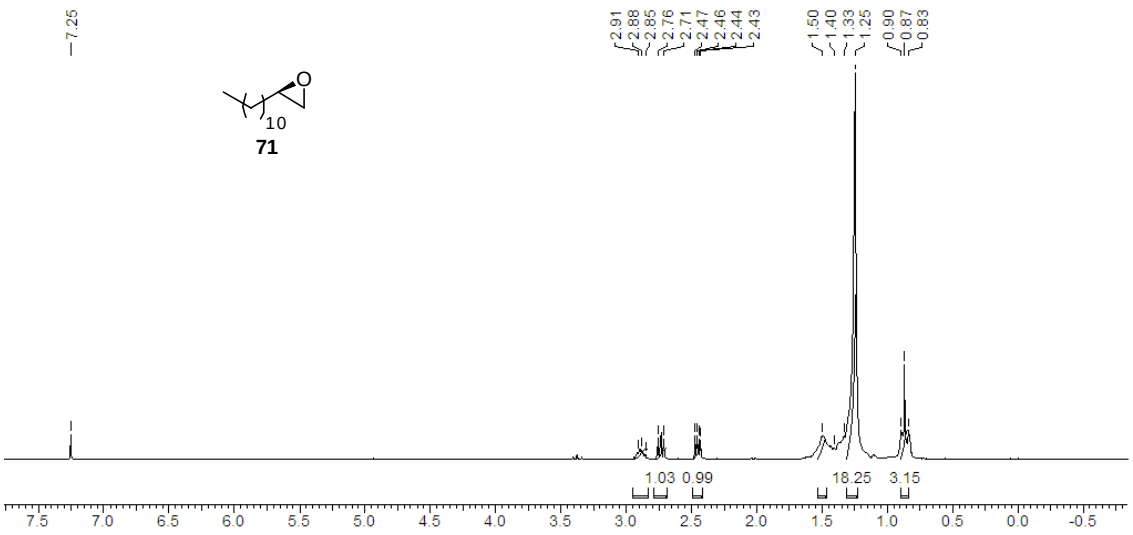
IR ($CHCl_3$, cm^{-1}) ν_{max} = 3392, 3018, 2854, 1458, 1263, 1099, 759.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.7 Hz, 3H), 1.26 (brs, 18H), 1.56 - 1.74 (m, 4H), 3.42 (s, 3H), 3.59 - 3.70 (m, 1H), 3.81 - 3.87 (m, 1H), 4.07 - 4.18 (m, 2H), 4.64 - 4.77 (m, 2H).

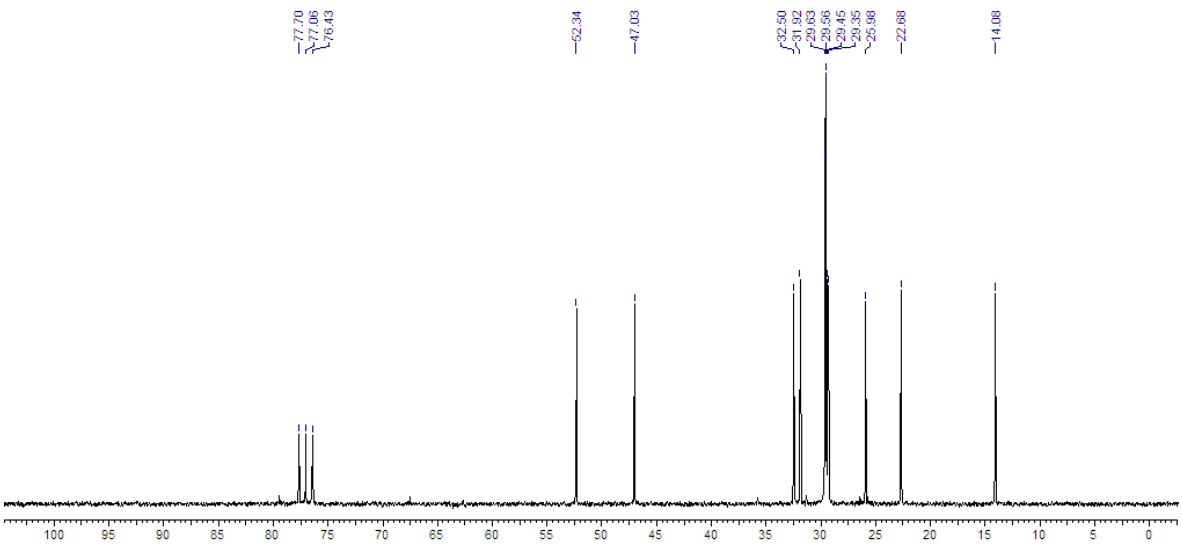
^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 22.6, 29.3, 29.5, 29.6, 31.8, 34.3, 37.8, 55.7, 60.4, 70.4, 80.1, 95.1.

4.7. Spectra

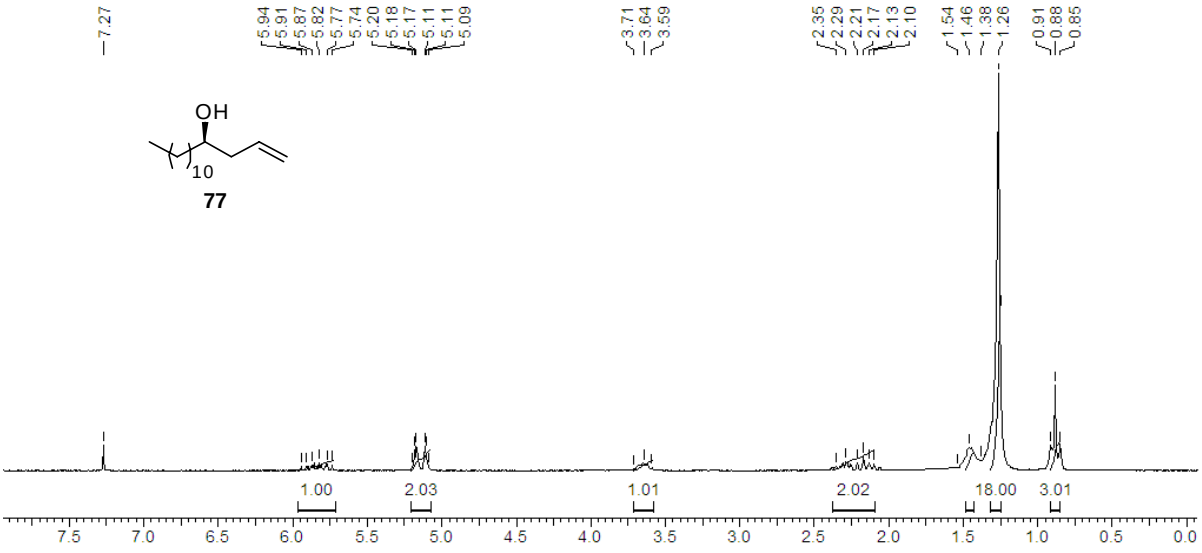
1. ^{1}H and ^{13}C NMR spectra of **71**
2. ^{1}H and ^{13}C NMR spectra of **77**
3. ^{1}H and ^{13}C NMR spectra of **78**
4. ^{1}H and ^{13}C NMR spectra of **79**
5. ^{1}H and ^{13}C NMR spectra of **80**
6. ^{1}H and ^{13}C NMR spectra of **85**
7. ^{1}H and ^{13}C NMR spectra of **87**
8. ^{1}H and ^{13}C NMR spectra of **88**
9. ^{1}H and ^{13}C NMR spectra of **89**
10. ^{1}H and ^{13}C NMR spectra of **90**
11. ^{1}H and ^{13}C NMR spectra of **91**
12. ^{1}H and ^{13}C NMR spectra of **92**
13. ^{1}H and ^{13}C NMR spectra of **25**
14. ^{1}H and ^{13}C NMR spectra of **93**



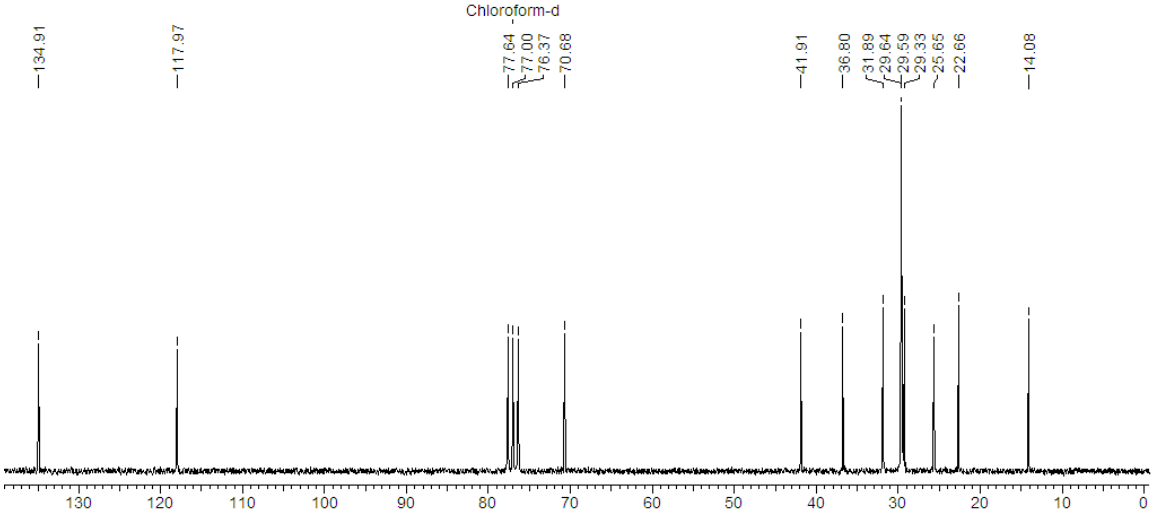
^{1}H-NMR spectrum of compound 71 in $CDCl_3$



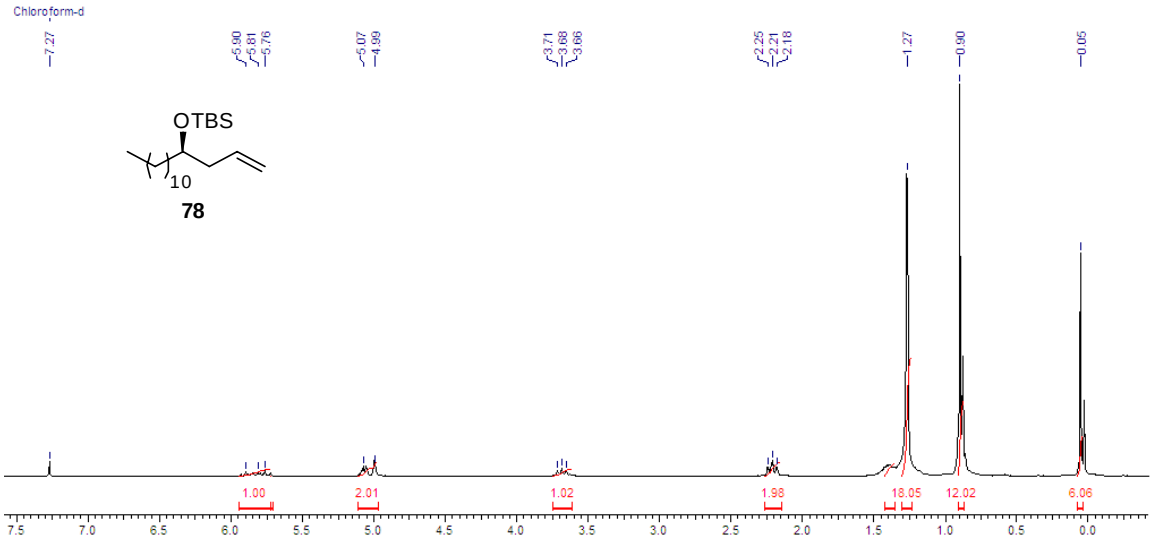
^{13}C-NMR spectrum of compound 71 in $CDCl_3$



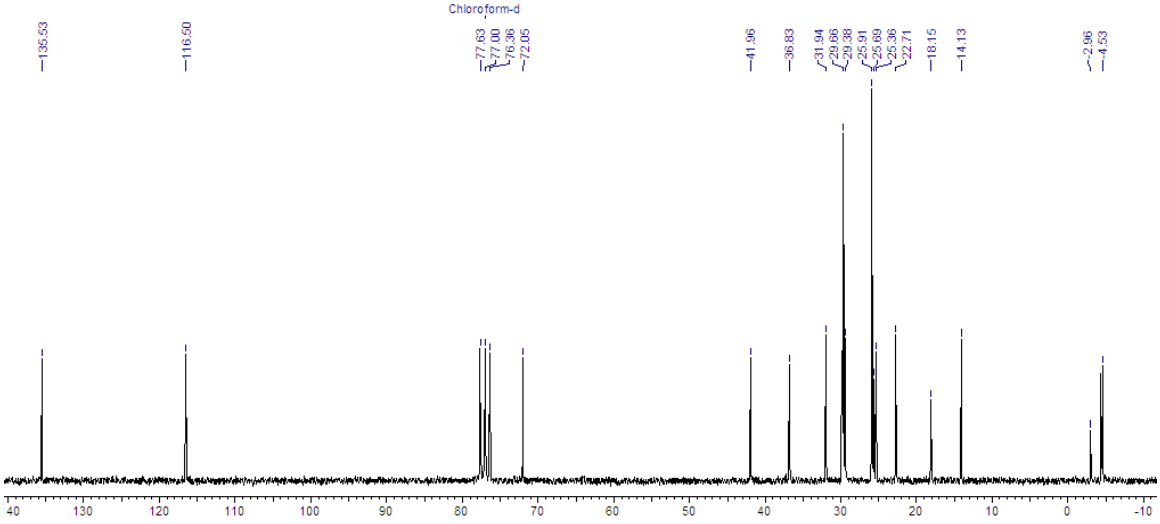
^{1}H-NMR spectrum of compound 77 in $CDCl_3$



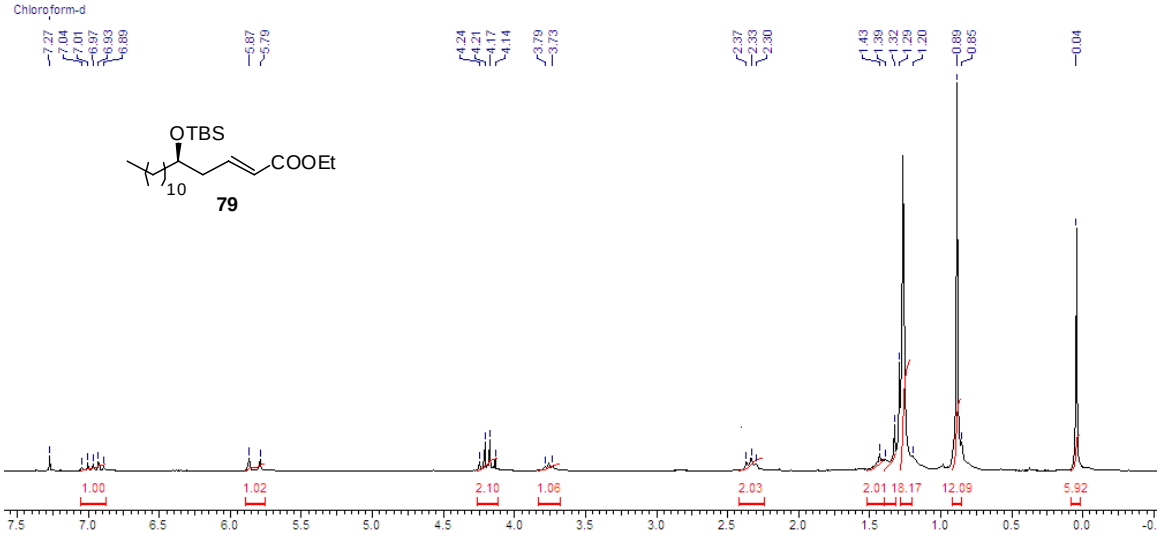
^{13}C-NMR spectrum of compound 77 in $CDCl_3$



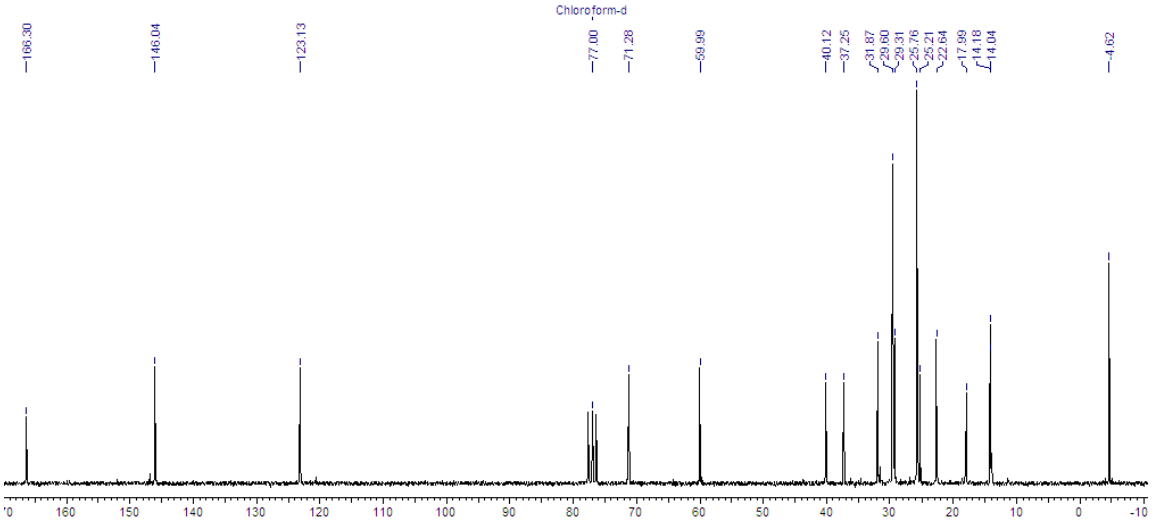
^{1}H-NMR spectrum of compound 78 in $CDCl_3$



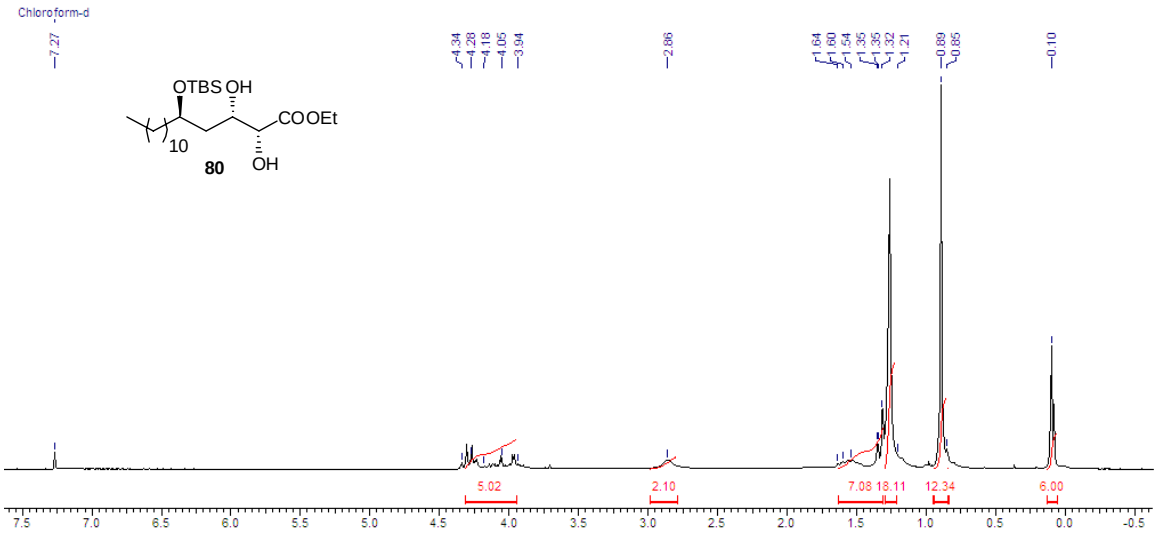
^{13}C-NMR spectrum of compound 78 in $CDCl_3$



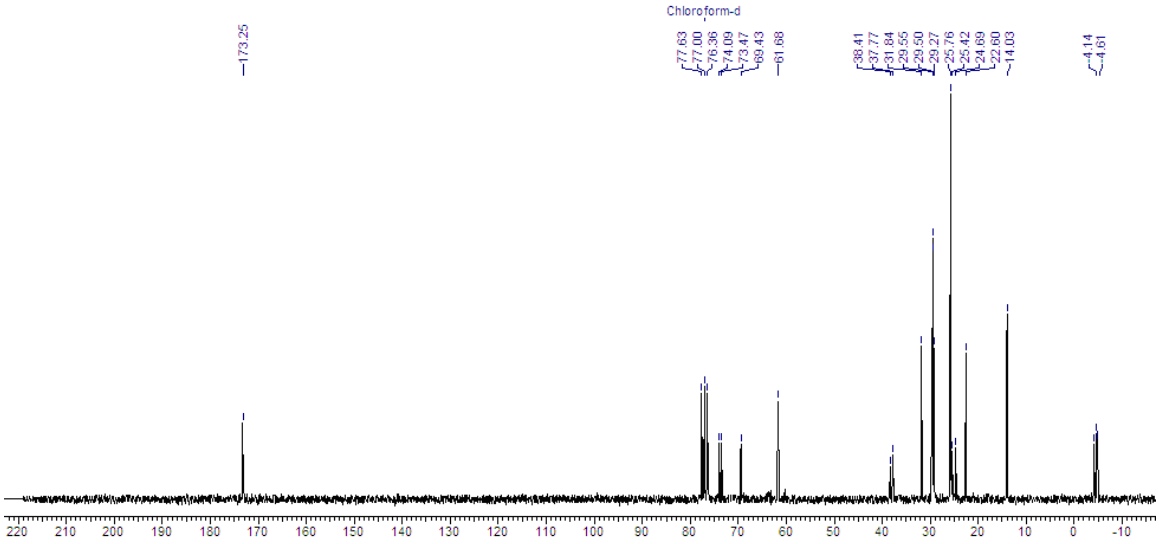
^{1}H-NMR spectrum of compound 79 in $CDCl_3$



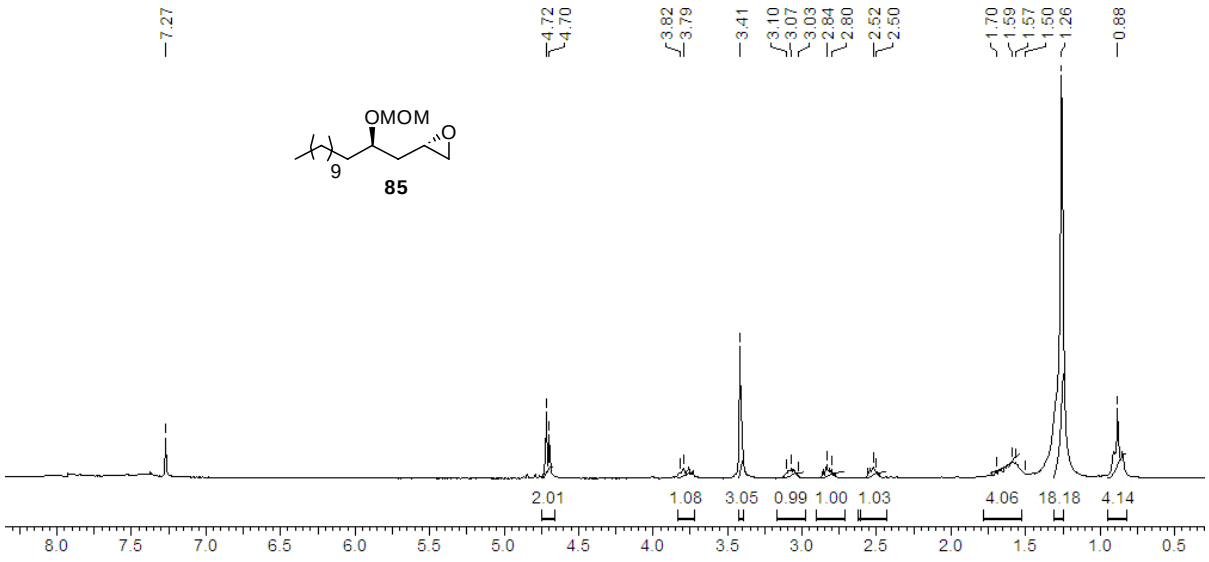
^{13}C-NMR spectrum of compound 79 in $CDCl_3$



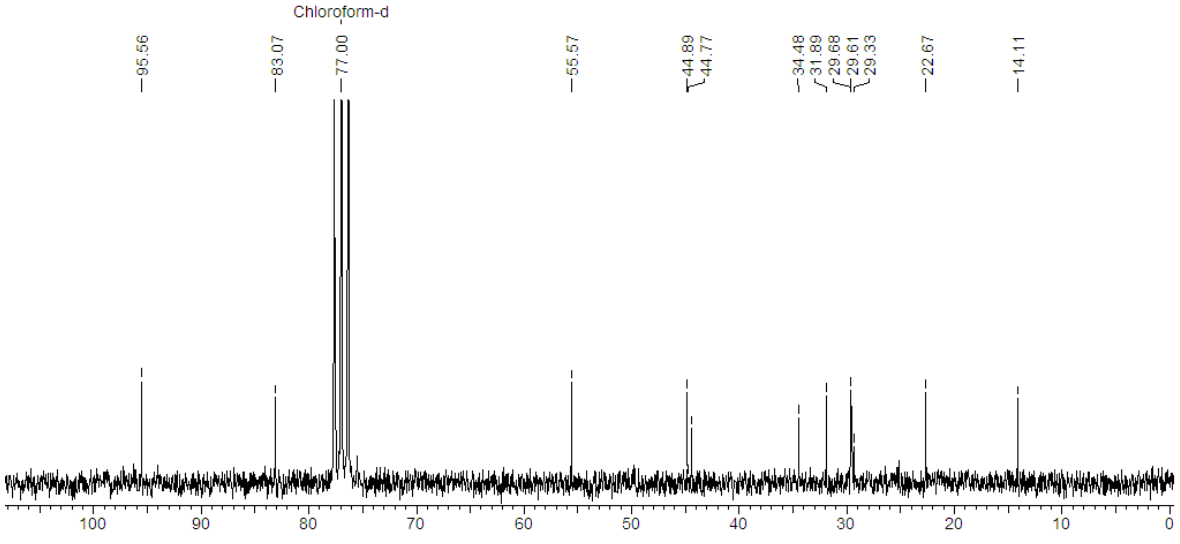
^{1}H-NMR spectrum of compound 80 in $CDCl_3$



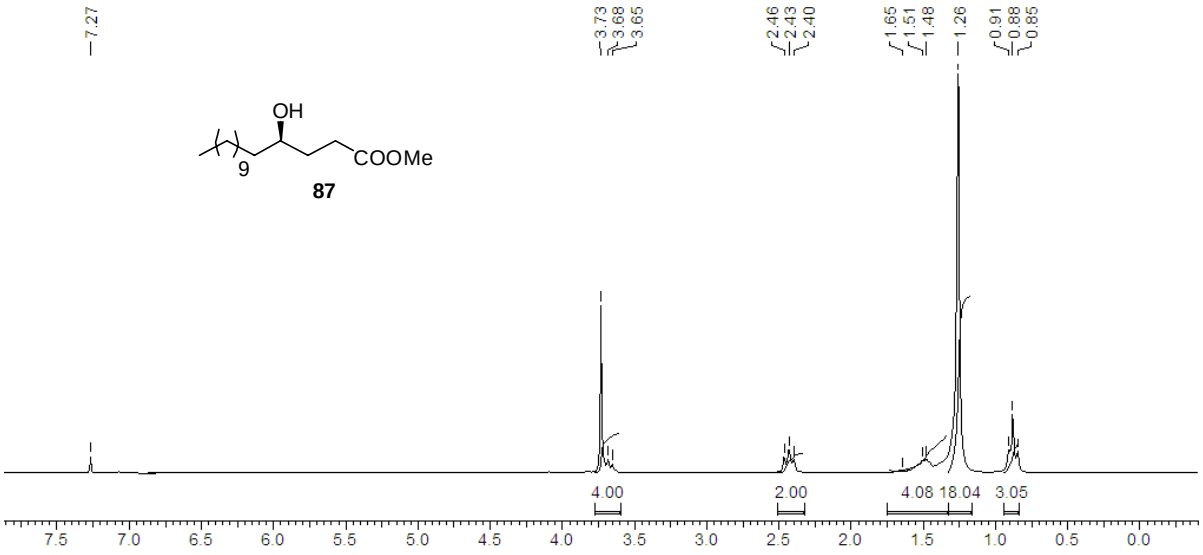
^{13}C-NMR spectrum of compound 80 in $CDCl_3$



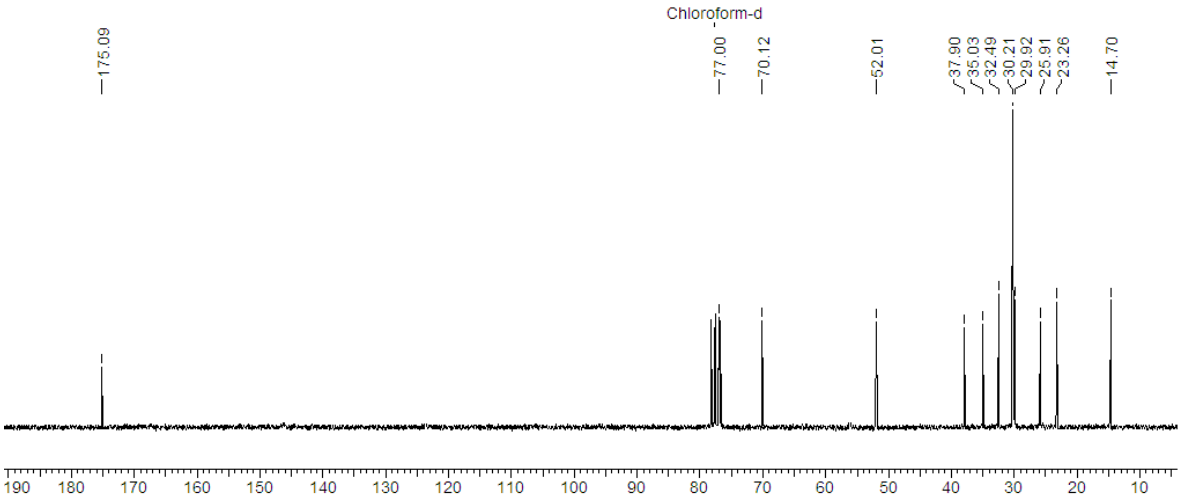
^{1}H-NMR spectrum of compound 85 in $CDCl_3$



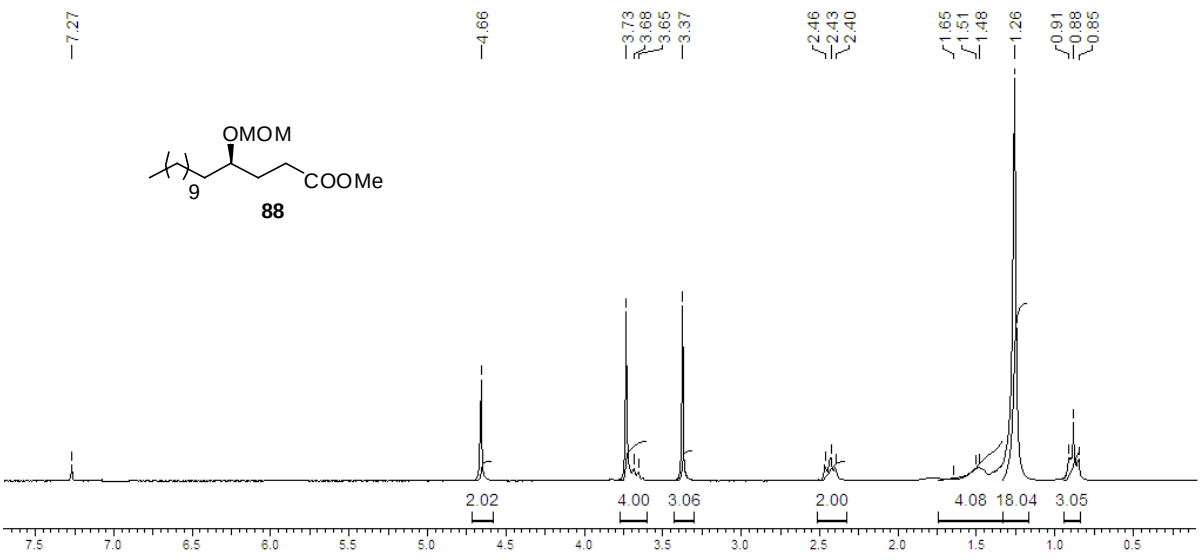
^{13}C-NMR spectrum of compound 85 in $CDCl_3$



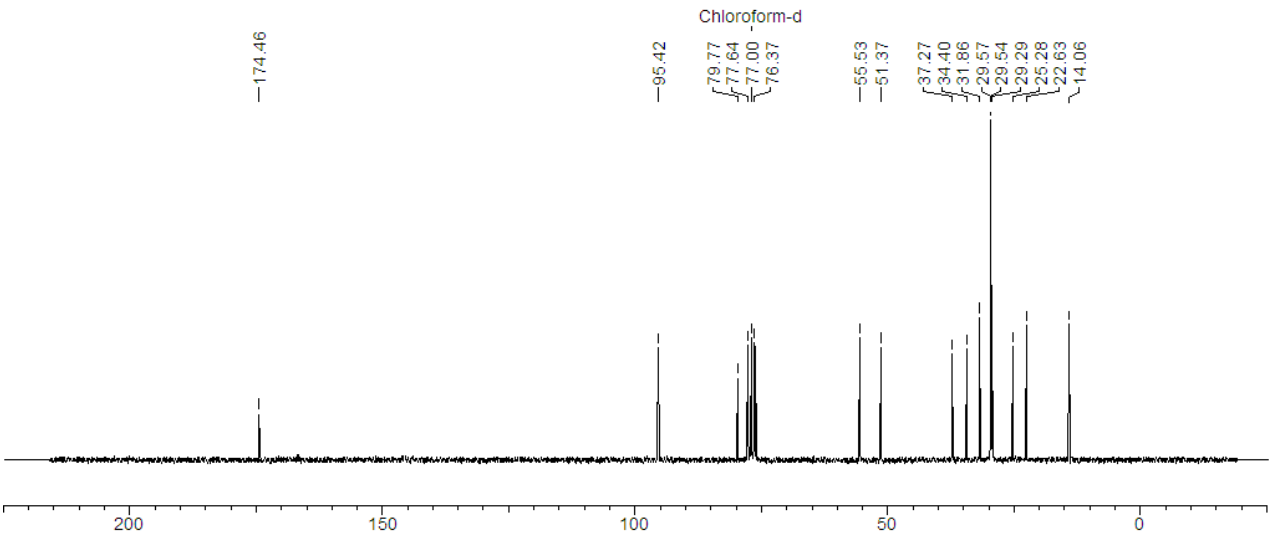
^{1}H-NMR spectrum of compound 87 in $CDCl_3$



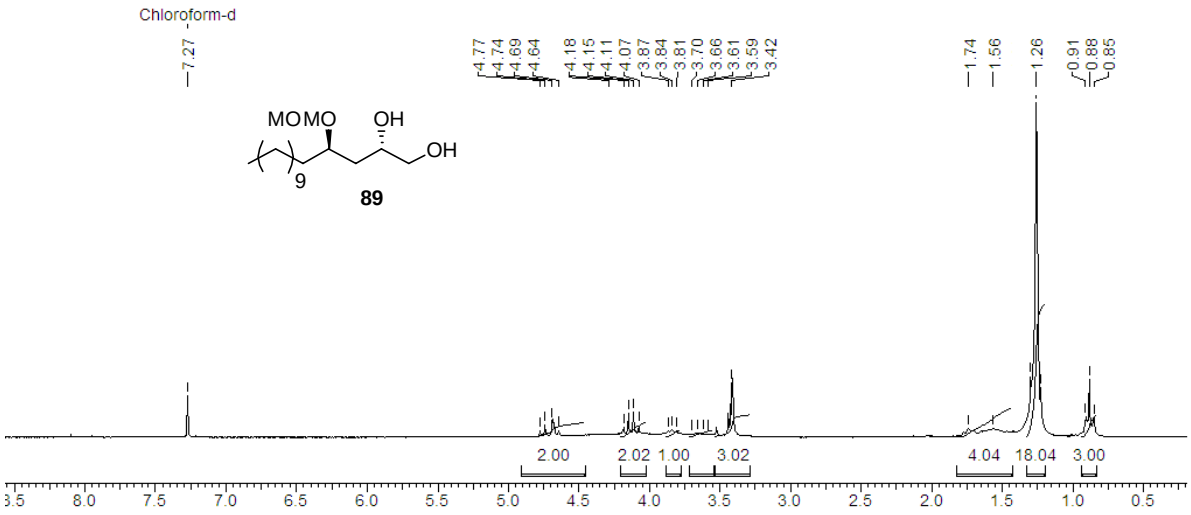
^{13}C-NMR spectrum of compound 87 in $CDCl_3$



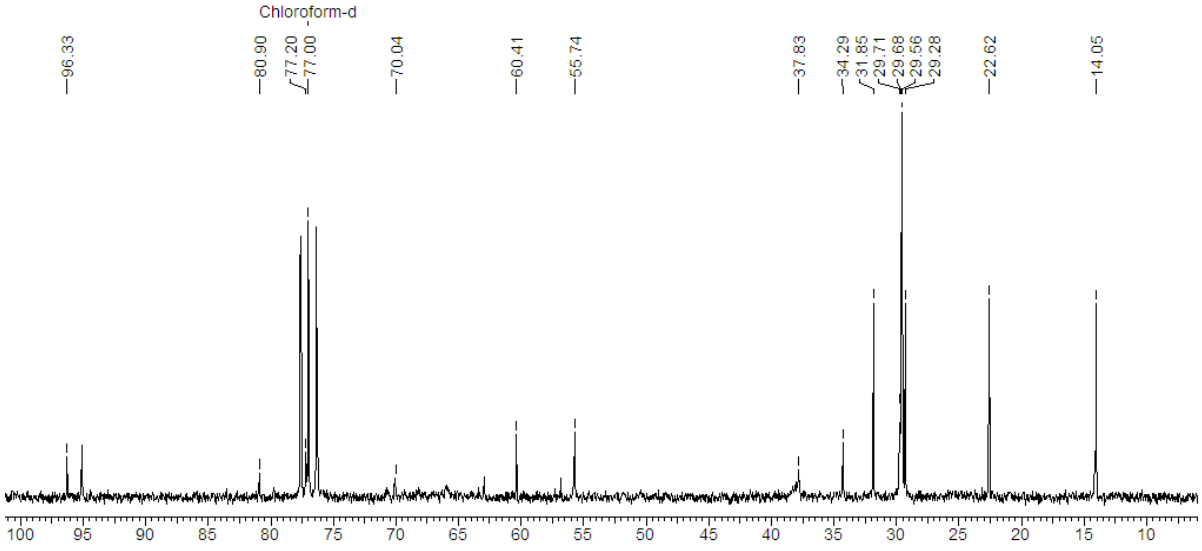
^{1}H-NMR spectrum of compound 88 in $CDCl_3$



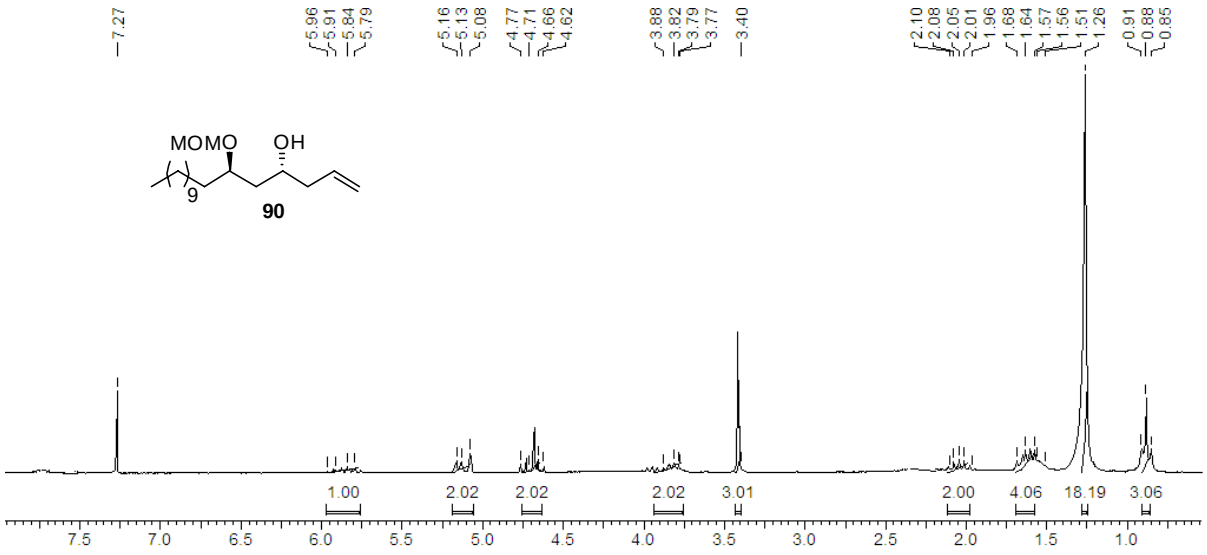
^{13}C-NMR spectrum of compound 88 in $CDCl_3$



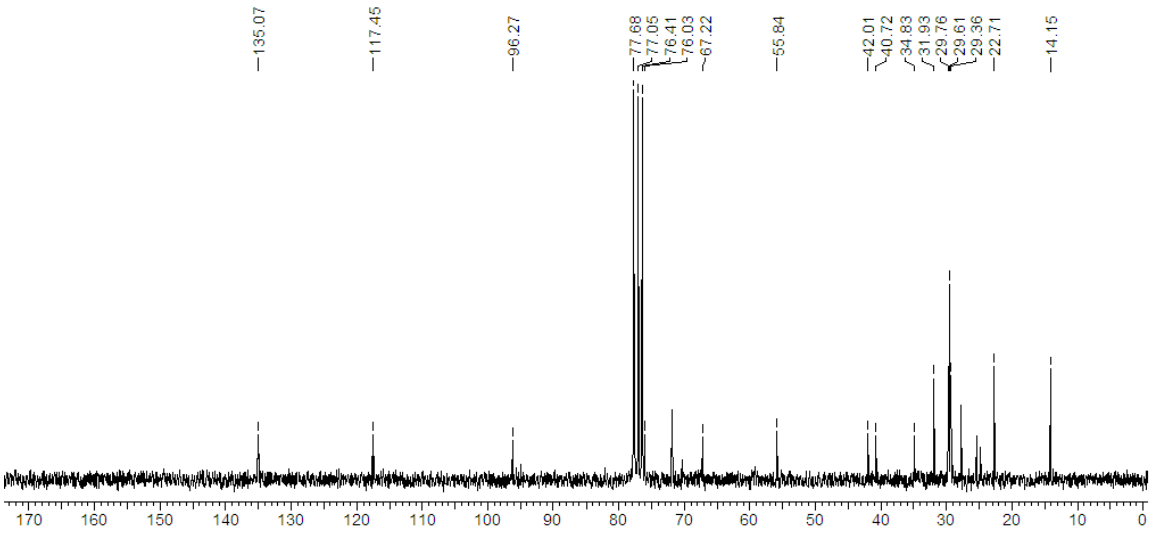
^{1}H-NMR spectrum of compound 89 in $CDCl_3$



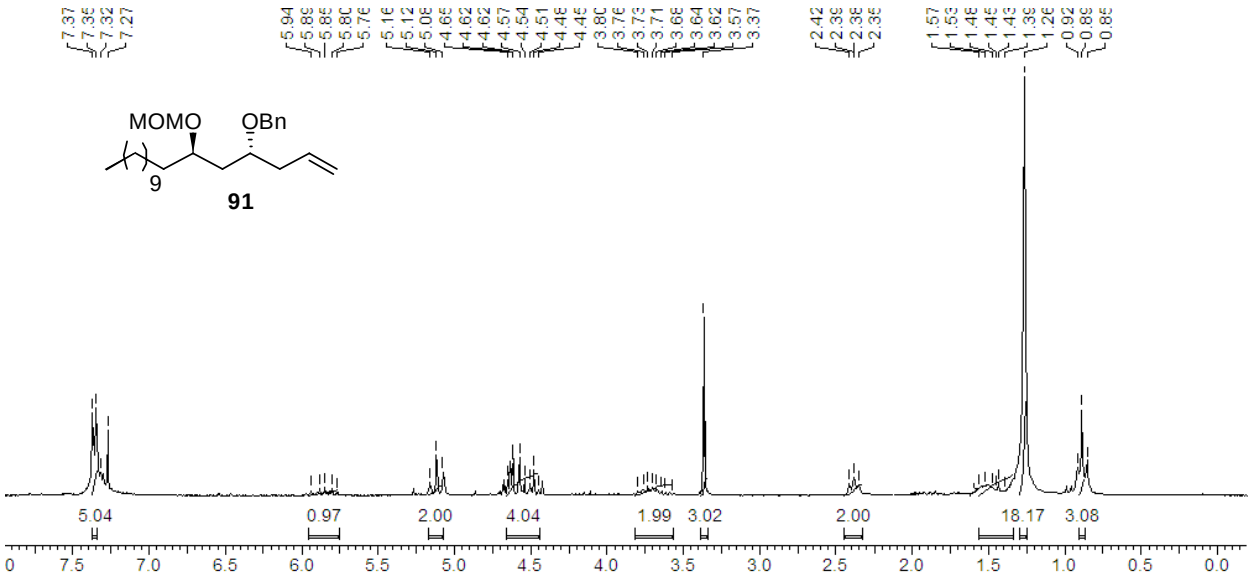
^{13}C-NMR spectrum of compound 89 in $CDCl_3$



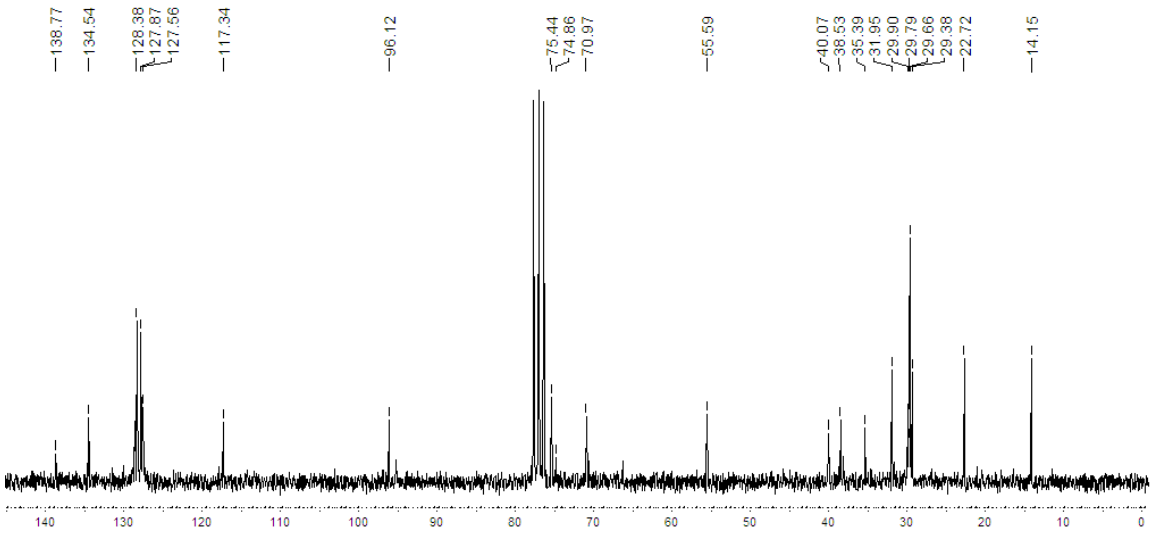
^{1}H-NMR spectrum of compound 90 in $CDCl_3$



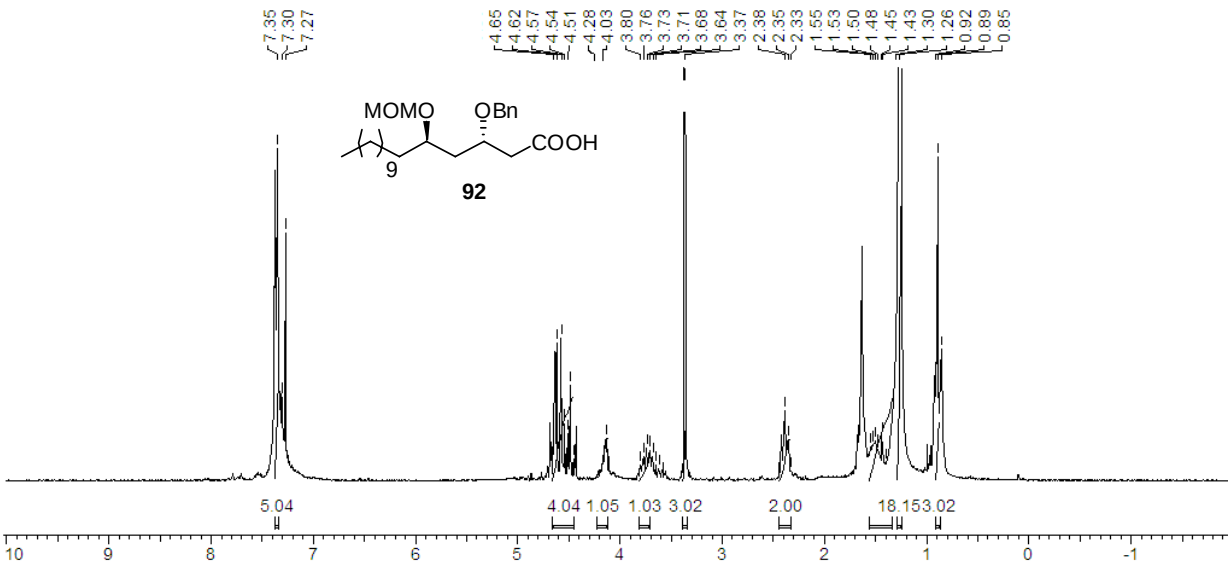
^{13}C-NMR spectrum of compound 90 in $CDCl_3$



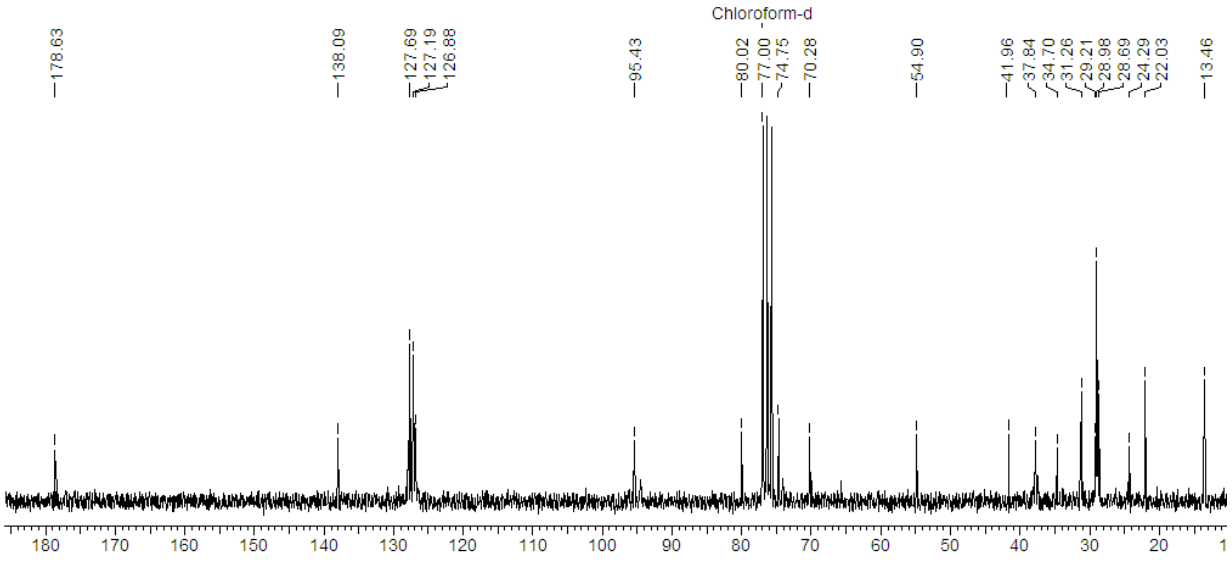
^{1}H-NMR spectrum of compound 91 in $CDCl_3$



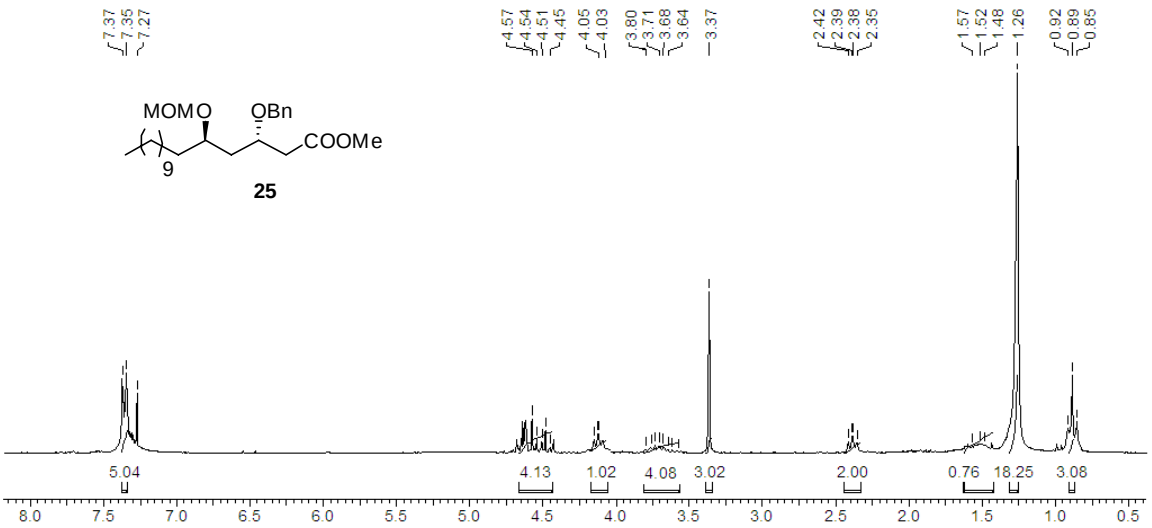
^{13}C-NMR spectrum of compound 91 in $CDCl_3$



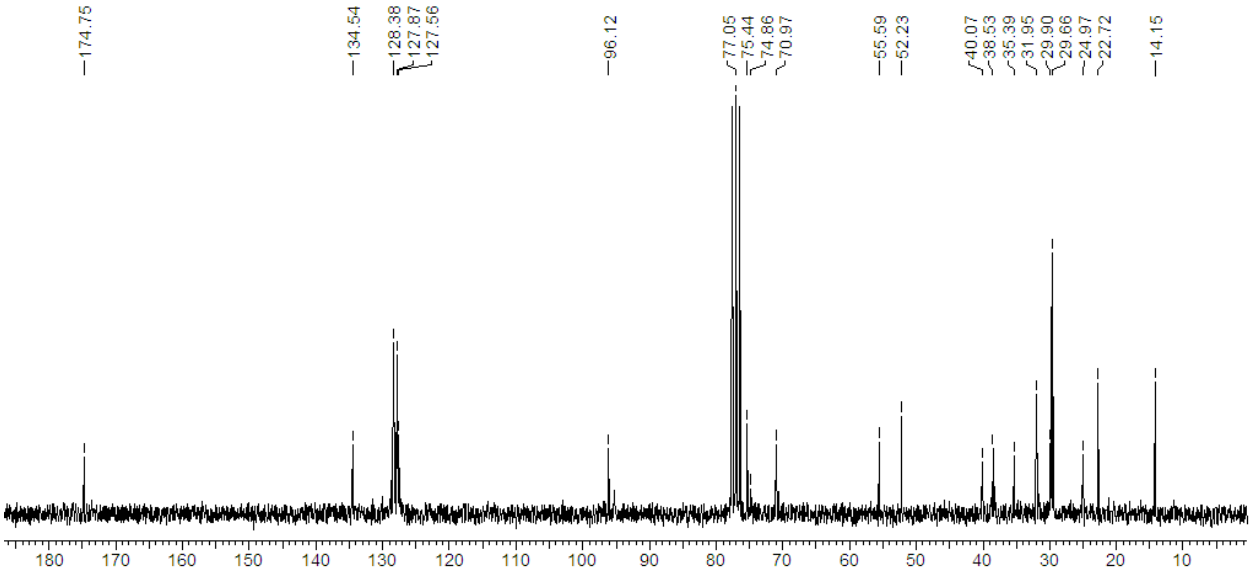
^{1}H-NMR spectrum of compound 92 in $CDCl_3$



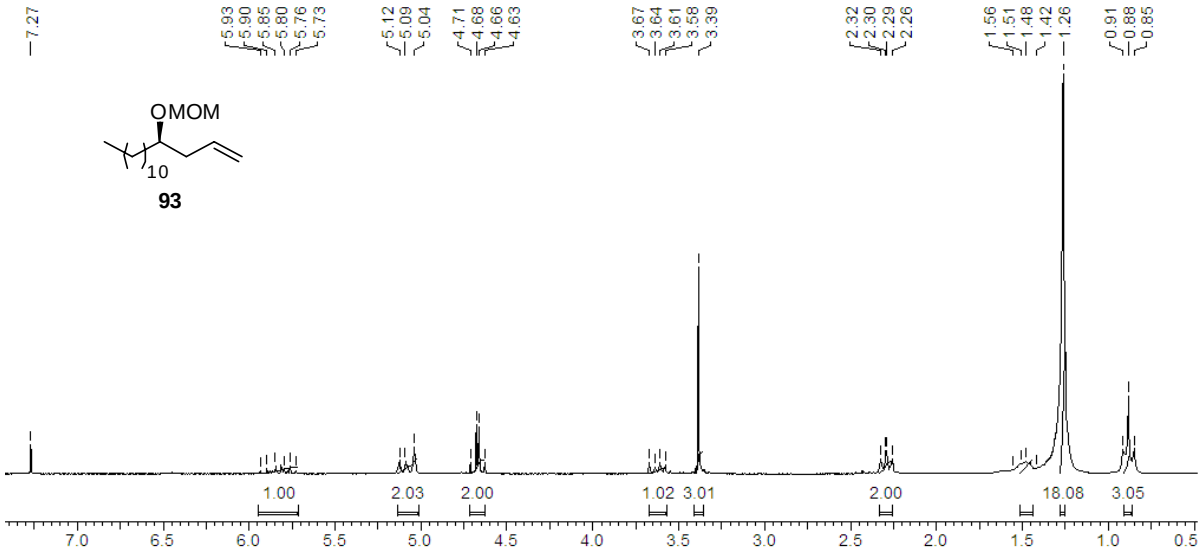
^{13}C-NMR spectrum of compound 92 in $CDCl_3$



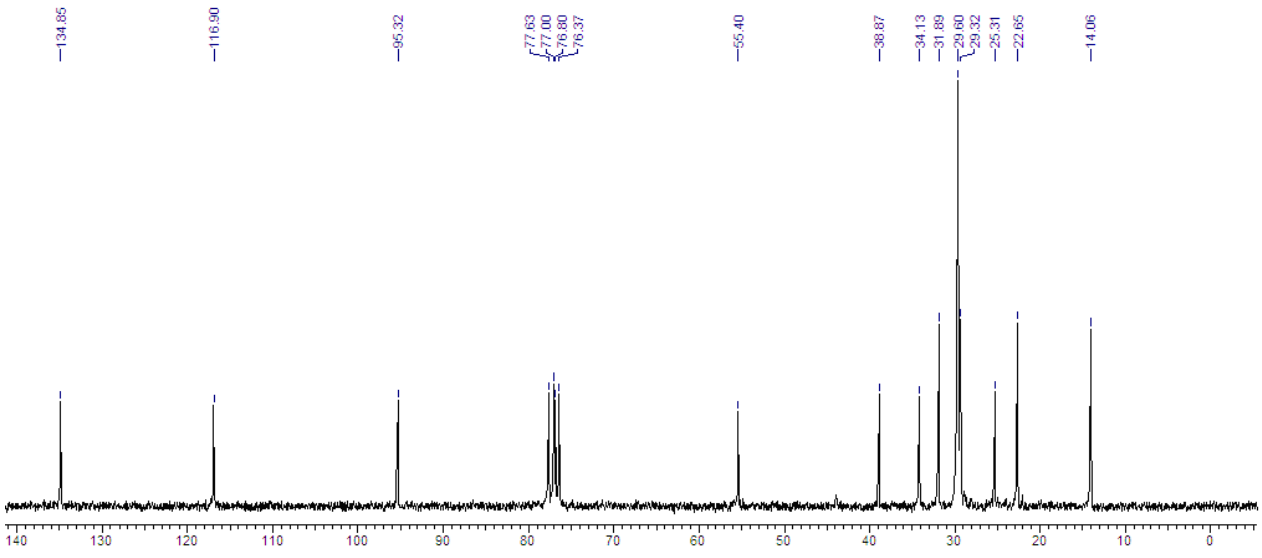
^{1}H-NMR spectrum of compound 25 in $CDCl_3$



^{13}C-NMR spectrum of compound 25 in $CDCl_3$



^{1}H-NMR spectrum of compound 93 in $CDCl_3$



^{13}C-NMR spectrum of compound 93 in $CDCl_3$

4.8. References

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Chapter 5
The attempted synthesis of naturally occuring lactones pectinolide A,B and C.

ATTEMPTED SYNTHESIS OF PECTINOLIDES A,B AND C

5.1. Introduction

Five membered lactone having a substitution at the γ-position is an important structural subunit in many bio-active compounds.[1] γ-Lactone containing natural products are known to exhibit various biological activities,[2] including anti-fungal, anti-bacterial,[3] anti- tumor,[4] cytotoxic,[5] cyclo-oxygenase or phospholipase A2 inihibition.[6] Antimicrobial and cytotoxic 5,6-dihydro-α-pyrones, pectinolides A, **1a**, B, **1b** and C **1c** have been isolated from *Hyptis pectinata*[7] of family Lamiaceae. *Hyptis pectinata* is a very common herbaceous plant valued for its medicinal qualities and for its smell and taste in the regional cuisine of the southeastern region of Mexico. Formulations of the plant are used in popular medicine as a multipurpose remedy in the treatment of fevers, certain skin diseases, gastric disturbances,[8] rhinopharyngitis, and lung congestion.[9] The absolute stereochemistry of pectinolide A was established as *6S*-[(3*S*-acetyloxy)-lZ-heptenyl)-5*S*-(acetyloxy)-5,6-dihydro-2*H*-pyran-2-one, on the basis of spectral, chiroptical, and chemical evidence. The structures of pectinolides B, **1b** and C, **1c** were determined as the monodeacetylated forms of pectinolide A, **1a** by comparison of their spectral data and chemical correlation with the prototype compound. *Staphylococcus aureus* and *Bacillus subtilis* were sensitive to pectinolide A in the concentration range of 6.25-12.5 μg/ml. Compounds A, B and C exhibited significant cytotoxic activity (ED_{50},<4 μg/ml) against a variety of tumor cell lines. Pectinolide H, **1d**, a structurally distinctive γ-lactone having three stereogenic centers has also been isolated from the chloroform extract of the aerial parts of the same Mexican terrestrial plant *Hyptis pectinata*.[7] It shows cytotoxic and antimicrobial properties.[10] The β-lactone hypurticin **1e** has been isolated[11] from Hyptis urticoides as its main secondary metabolite. The structure of hypurticin was established mainly on spectroscopic grounds. (+)-Asperlin **1f**, isolated from Aspergillus nidulans and Aspergillus caespiyosus, has been shown to exhibit antitumor and antibacterial activity. Its structure, including the absolute configuration, was determined by spectroscopic and chemical studies,[12–14]

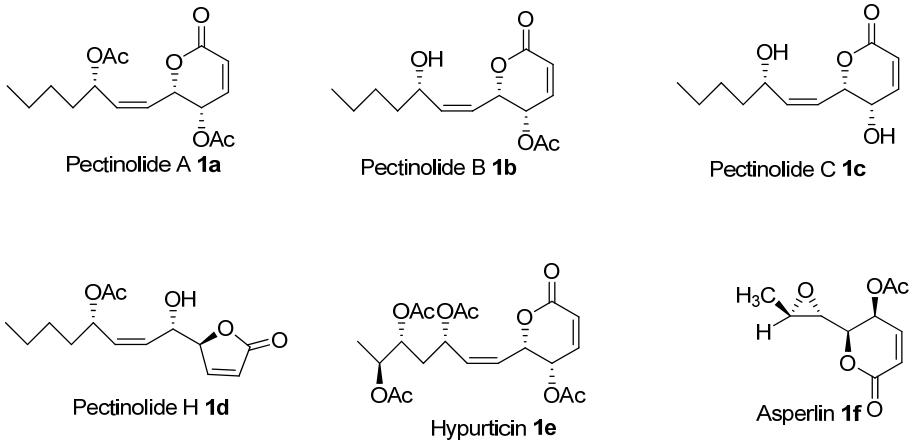


Figure 1

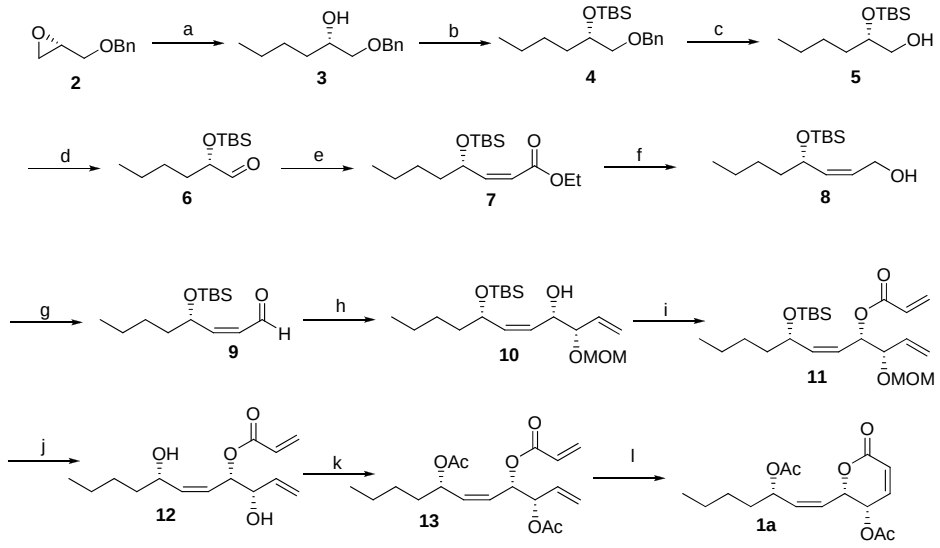
5.2. Review of Literature

Only two total syntheses have been achieved so far for pectinolides. The first total synthesis of pectinolide A has been accomplished by Yadav[15] *et al*. and pectinolide H has been successfully first synthesized by Venkateswarlu[16] *et al.*

Yadav *et al*.[15] (2011)

Yadav *et al*. employed the chiral epoxide **2** which was regioselectively opened with *n*-propylmagnesium bromide to afford secondary alcohol **3** (Scheme **1**). Alcohol **3** was protected as corresponding TBS ether **4** followed by debenzylation to afford the primary alcohol **5**. The primary alcohol **5** was oxidized under Swern oxidation conditions to furnish the corresponding aldehyde **6** which was subjected to a Still–Gennari reaction[17] in the presence of NaH in THF to provide the α,β-unsaturated ester **7**. The chemoselective reduction of α,β-unsaturated ester **7** with DIBAL-H was achieved at -20 ^{o}C to afford the allyl alcohol **8**. The allyl alcohol **8** was oxidized under Swern oxidation conditions to the corresponding aldehyde **9** which was treated with in-situ generated [(Z)-γ-(methoxy methoxy)allyl]-diisopinocampheylborane, in a regioselective and stereoselective manner to yield the corresponding threo-β-methoxymethylhomoallyl alcohol **10** in 99% diastereoselectivity and >95% enantioselectivity. The esterification of the secondary alcohol in **10** with acryloyl chloride afforded compound **11**. Deprotection of TBS and

MOM groups using 6 N HCl afforded the diol **12**. Acetylation of the diol **12** was achieved with acetic anhydride to furnish compound **13**. Finally, ring-closing metathesis of the compound **13** was accomplished using Grubbs 2nd generation[18] catalyst to afford the required 5,6 dihydro-2*H*-pyran-2-one, pectinolide A **1a**.

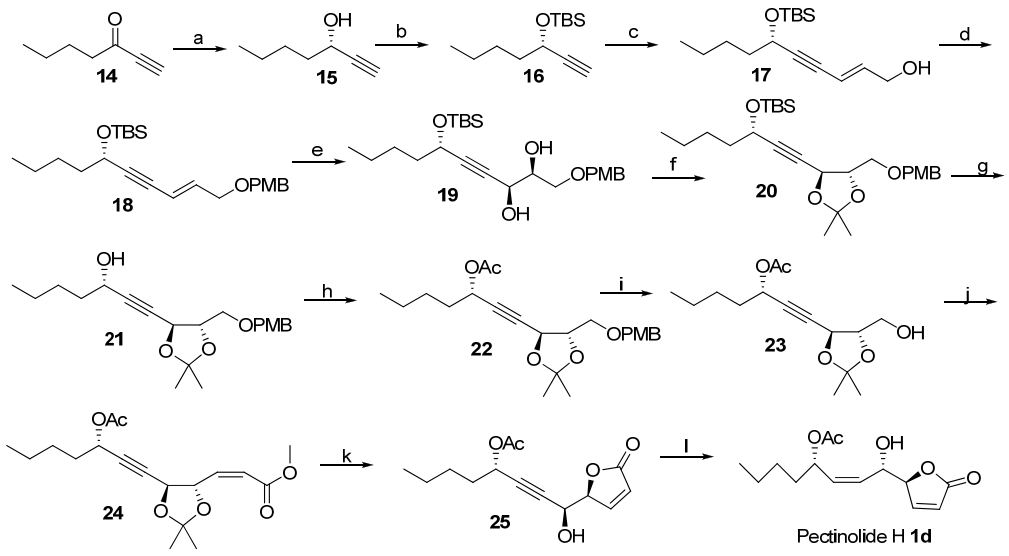


Scheme 1. *Reagents and conditions*: (a) propyl bromide, Mg, CuI, THF, -30 ^{o}C, 3 h, 85%. (b) TBS-OTf, 2,6-lutidine, CH_2Cl_2, rt, 3 h, 92%. (c) 20% $Pd(OH)_2$/C, H_2, THF, 89%. (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, rt, 3 h, 92%. (e) NaH, THF, -78 ^{o}C, 1 h, $EtO_2CCH_2P(O)(OCH_2CF_3)_2$, 90%. (f) DIBAL-H, CH_2Cl_2, -20 ^{o}C, 3 h, 95%. (g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, rt, 3 h, 90%. (h) (i) 3-(methoxymethoxy)prop-1-ene, *sec*-BuLi, β-methoxy diisopinocamphenyl borane. (ii) $BF_3.Et_2O$, -78 ^{o}C. (iii) $NaOH/H_2O_2$, THF, 3 h, 62%. (i) Acryloyl chloride, DIPEA, DMAP, CH_2Cl_2, rt, 3 h, 92%. (j) 6N HCl, THF, rt, 3 h, 85%. (k) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 1 h, 89%. (l) Grubbs' 2nd generation (10 mol%) CH_2Cl_2, 40 ^{o}C, 3 h, 90%.

Venkateswarlu *et al*.[16] (2012)

Venkateswarlu *et al.* relied on the acetylenic ketone **14** (Scheme **2**). The first stereogenic centre was generated by the enantioselective reduction of **14** with (*S*)-alpine borane to

furnish the chiral propargyl alcohol **15**. The alcohol **15** was protected as corresponding TBS ether **16** which was subjected to Sonogashira[19] cross coupling with (*E*)-3-iodoprop-2-en-1-ol to afford allylic alcohol **17**. The primary alcohol **17** was protected with *p*-methoxybenzyl chloride to afford compound **18**. Sharpless dihydroxylation of **18** with AD-mix-α furnished diol **19** which was protected with 2,2-dimethoxy propane to yield compound **20**. The silyl deprotection of **20** afforded secondary alcohol **21** which was acetylated using acetic anhydride in pyridine to afford compound **22**. The *p*-methoxybenzyl deprotection of **22** gave primary alcohol **23**. The alcohol **23** was oxidized with Dess-Martin periodinane to afford aldehyde, which was further subjected to *Z*-selective Still-Gennari olefination[17] by employing bis((2,2,2-trifluoroethyl) (methoxy carbonylmethyl phosphonate)) to afford *cis*-olefinic ester **24**. Deprotection of acetonide group and lactonization were achieved in one-pot using 80% AcOH to give acetylenic lactone **25**. Finally, partial hydrogenation of triple bond **25** with Lindlar's catalyst furnished the target natural product, pectinolide H **1d**.



Scheme 2. *Reagents and conditions*: (a) (*S*)-alpine borane, THF, 8 h, rt, 75% (b) imidazole, TBDMSCl, DCM, rt, 3 h. (c) (E)-3-iodoprop-2-en-1-ol, *i*Pr_2NH, $Pd(PPh_3)_4$, CuI, dry benzene, rt, 2 h, 88%. (d) NaH, PMBCl, dry THF, 0 ^oC to rt, 4 h, 93%. (e) AD-mix-α, $MeSO_2NH_2$, *t*-BuOH/H_2O (1:1), 0 ^oC, 24 h, 82%. (f) 2,2-dimethoxypropane, PTSA, dry DCM, rt, 12 h, 90%. (g) TBAF, THF, rt, 2 h, 97%. (h) Ac_2O, pyridine, rt, 4 h, 96%. (i)

DDQ, DCM/H_2O (10:1), rt, 2 h, 95%. (j) (i) Dess-Martin periodinane, DCM, 0 ^oC to rt, 2 h, 94%. (ii) $(F_3CCH_2O)_2POCH_2COOMe$, 18-crown ether, KHMDS, dry THF, -78 ^oC, 4 h, 86%. (k) 80% AcOH, 0 ^oC to rt, 20 h, 96%. (l) Lindlar's catalyst, quinoline, ethyl acetate, rt, 2 h, 88%.

5.3. PRESENT WORK

Objective

Many natural products with different biological activities such as insect growth inhibition, antitumor,[20] antibacterial, antifungal or immunosuppressive properties, possess α,β-unsaturated δ-lactone moiety as an important structural feature. α,β-Unsaturated δ-lactone functionality is presumed to be responsible for biological activities due to its ability to act as a Michael acceptor enabling these molecules to bind to a target enzyme. The pyrone units are widely distributed in all parts of plants (Lamiaceae, Piperaceae, Lauraceae, and Annonaceae families) including leaves, stems, flowers and fruits. α-Pyrones possessing polyhydroxy or polyacetoxy side chains have attracted much attention from synthetic and medicinal chemists due to their broad range of biological activities such as plant-growth inhibition, as well as antifeedant, antifungal, antibacterial, and antitumor properties.[20] Examples of such compounds include pectinolides A-C (Fig. **1**) which are isolated from *Hyptis pectinata* and known to show cytotoxic and antimicrobial properties.[10] In particular, pectinolide H (**1d**) displayed significant antimicrobial activity against a panel of multidrug-resistant strains of *Staphylococcus aureus*.[7] The structure and stereochemistry of **1d** was established on the basis of spectral, chiroptical data and chemical evidence. The β-lactone hypurticin **1e** has been isolated from Hyptis urticoides[11] as its main secondary metabolite. The structure of hypurticin was established mainly on spectroscopic grounds. (+)-Asperlin **1f**, isolated from Aspergillus nidulans and Aspergillus caespiyosus, has been shown to exhibit antitumor and antibacterial activity. Its structure, including the absolute configuration, was determined by spectroscopic and chemical studies.[12–14]

As these natural products are available in scarce amounts, the synthesis of pectinolides is an attractive goal for further biological activity studies. Intrigued by the biological properties of this class of pyrones as well as, in continuation of our work on the synthesis of lactone containing natural products,[21] we have taken up the total synthesis of pectinolides A, B and C. Herein, we report the attempted total synthesis of pectinolides A, B and C.

5.4. Results and Discussion

As part of our research interest in the asymmetric synthesis of bioactive molecules,[21] we became interested in devising a general route to all the pectinolides A **1a**, B **1b**, C **1c** and H **1d** as well as hypurticin **1e**. Thus as a divergent approach, (Figure **2**) two common fragments allylic alcohol **A** and allylic alcohol **B** were synthesized which could be coupled by silicon mediated temporary tethered olefin metathesis to give the target molecule pectinolide.[22] Structurally related molecules such as hypurticin could also be synthesized using similar strategy and by the use of fragment **C** instead of fragment **B** in the tethering step. Thus by variation in the fragments and protecting group modifications different molecules can be synthesized.

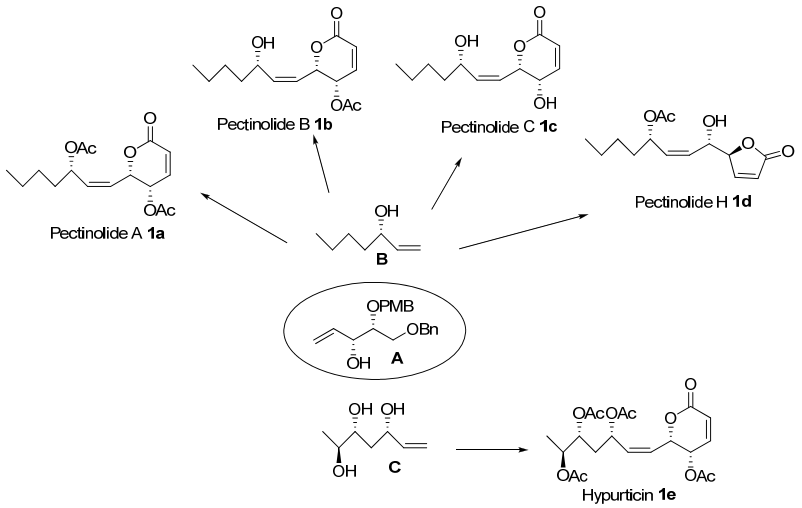
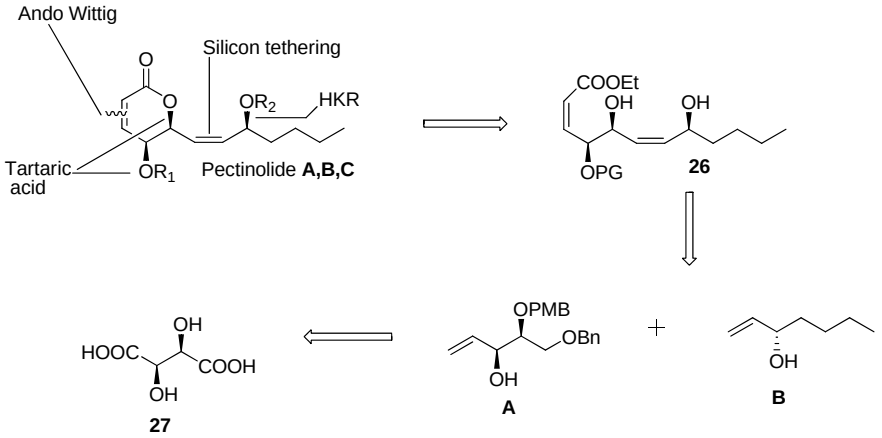


Figure 2

Our retrosynthetic approach for the synthesis of pectinolides and all pectinolide-based molecules (Figure **2**) was envisioned *via* the synthetic route as shown in Scheme **3**. The key reaction in our synthesis was silicon mediated temporary tethered olefin metathesis[22] to obtain the *cis* double bond in the side chain. The *cis* double bond of lactone **26** would be obtained from the *cis*-Ando Wittig reaction. The first stereocentre was obtained by HKR and rest of the two stereocentres were obtained from the chiral pool starting material, L-tartaric acid **27**. Our divergent synthesis consists of two different fragments allylic

alcohol **A**, and **B**. The chiral centres in allylic alcohol **A** could be obtained from the chiral pool starting material, L-tartaric acid **27**. The chiral centre in allylic alcohol **B** could be obtained from HKR.

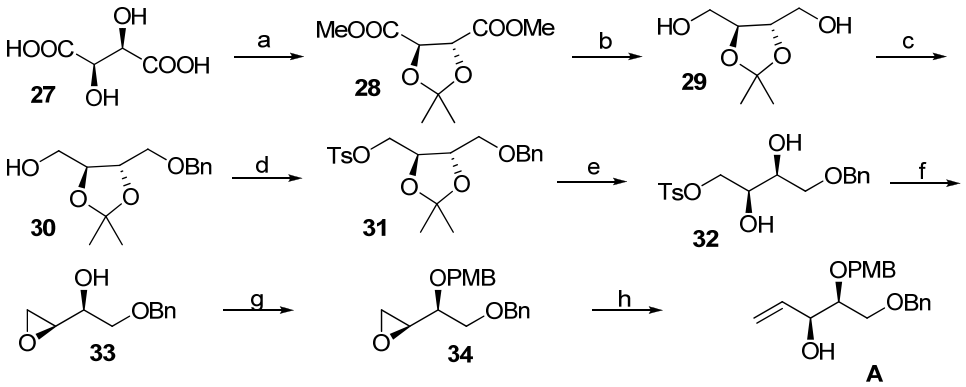


Scheme 3. Retrosynthetic route to pectinolides.

Synthesis of Fragment A

As illustrated in scheme **4**, the synthesis of fragment **A** commenced with commercially available L-tartaric acid **27** which was subjected to combined esterification and 1,2 diol protection with 2,2-dimethoxy propane in presence of dry cyclohexane and *p*-toluene sulfonic acid under reflux conditions to furnish DMP protected diester **28** in 95% yield. The diester **28** was subjected to LAH reduction under reflux conditions in presence of THF to afford diol **29** in 85% yield. The IR spectrum of **29** showed broad hydroxyl absorption at 3450 cm^{-1}. The mono- hydoxyl protection of **29** with benzyl bromide in the presence of NaH gave benzyl ether **30** in 82% yield. The ^{1}H NMR spectrum of **30** showed benzylic protons at δ 4.60 (singlet, 2 H) and aromatic protons at δ 7.34 (multiplet, 5 H). Tosylation was carried out with tosyl chloride in presence of triethyl amine and DMAP to furnish the tosylate **31**. The IR spectrum of **31** showed absence of broad hydroxyl absorption at 3450 cm^{-1}. The tosylate **31** was further subjected to acetonide deprotection using camphor sulphonic acid in MeOH and DCM (1:1) to afford diol **32**. The IR spectrum of **32** gave hydroxyl absorption at 3444 cm^{-1}. It is worth

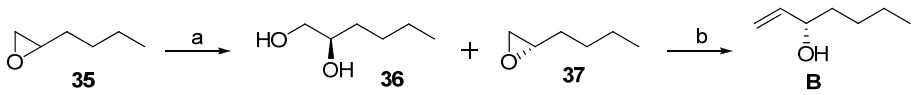
mentioning here that when *p*-TSA is used instead of CSA, a complex reaction mixture can be seen on TLC. Tosylate **32** on subsequent treatment with K_2CO_3 in MeOH afforded epoxy alcohol **33** in 71% yield. The IR spectrum of **33** gave hydroxyl absorption at 3440 cm^{-1}. ^1H NMR spectrum of **33** showed epoxide protons at δ 3.03 – 3.10 (multiplet, 1H), 2.80 (doublet of doublet, 1H, with coupling constant J = 4.9, 1.2 Hz) and 2.50 (doublet of doublet, with coupling constant J = 4.9, 2.4 Hz). The ^{13}C NMR spectrum of **33** showed upfield carbons characteristic of epoxide at δ 55.7 and 43.2. Alcohol **33** was protected using PMBBr in presence of NaH to furnish epoxide **34** in 95% yield. The IR spectrum of **34** showed absence of broad hydroxyl absorption at 3440 cm^{-1}. Ring opening and one carbon Corey-Chezkovsky homologation of epoxide **34** afforded allylic alcohol **A** in 60% yield. The IR spectrum of **31** showed absence of broad hydroxyl absorption at 3443 cm^{-1}. The ^1H NMR spectrum of **A** gave olefin peaks at 5.73 - 5.93 (multiplet, 1H), 5.04 (doublet, 1H), 5.09 (doublet, 1H).



Scheme 4. *Reagents and conditions:* (a) MeOH, 2,2-DMP, *p*-TSA, 50 ^oC, 2 h then dry cyclohexane, 2,2 DMP, 24 h, 78 ^oC, 95%. (b) $LiAlH_4$, dry THF, 0 ^oC to reflux, overnight, 85%. (c) $C_6H_5CH_2Br$, NaH, dry THF, rt, 10 h, 82% (d) TsCl, Et_3N, DCM, DMAP, 5 h. (e) CSA, MeOH/DCM (1:1), 3 h. (f) K_2CO_3, MeOH, rt, 4 h, 71% (over three steps). (g) *p*-$CH_3OC_6H_4CH_2Br$, NaH, dry DMF, rt, 6 h, 95%. (h) *n*-BuLi, $(CH_3)_3{}^+SI^-$, -20 ^oC dry THF, 4 h, 60%.

Synthesis of Fragment B

The synthesis of fragment **B** as shown in scheme **5**, began with racemic C-6 epoxide **35** which was subjected to Jacobsen's HKR by using (*R,R*)-Salen-Co^{III}OAc catalyst to give chiral (*S*)-diol **36** along with chiral (*R*) epoxide **37** as single isomer in <95% ee. Ring opening and one carbon Corey-Chezkovsky homologation of epoxide afforded allylic alcohol **B** in 70% yield. The IR spectrum of **31** showed absence of broad hydroxyl absorption at 3421 cm^{-1}.The ^1H NMR spectrum of **B** gave olefin peaks at 5.74 - 5.94 (multiplet, 1H), 5.18 (doublet, 1H), 5.11 (doublet, 1H).



Scheme 5. *Reagents and conditions*: (a) *R,R*-Salen-Co^{III}(OAc) (0.5 mol%), dist. H_2O (0.55 equiv), Isopropanol, 24 , (45% for **36**, 43% for **37**). (b) *n*-BuLi, $(CH_3)_3{}^+SI^-$, dry THF, 4 h, -20 ^oC, 70%.

Silicon mediated temporary tethered olefin metathesis

With both the required fragments in hand we then proceeded with the silicon mediated temporary tethered olefin metathesis to get the required *cis*-double bond. Three different tethering reagents as illustrated in figure **3**; diisopropyl dichloro-silane **38a**, dimethyl dichloro-silane **38b** and diphenyl dichlorosilane **38c** were used for temporary tethering.

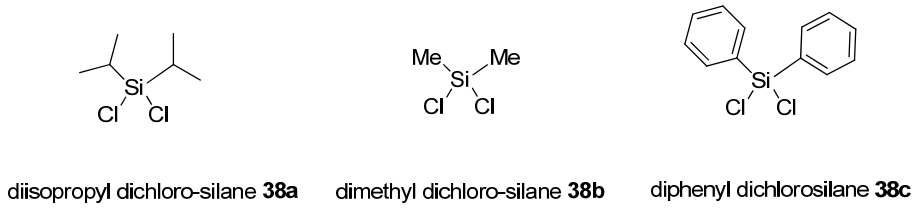
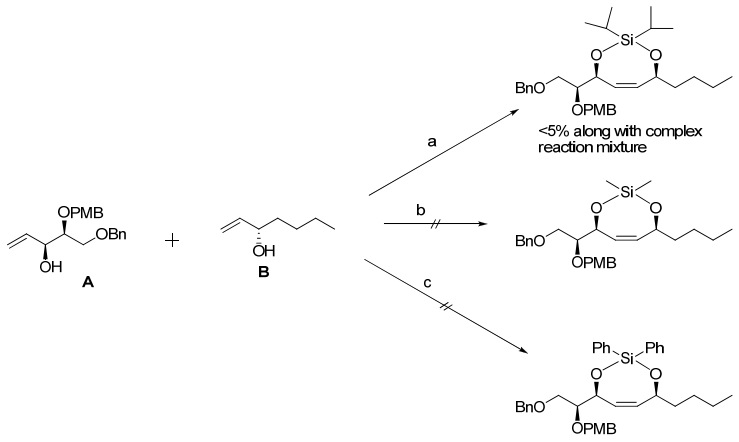


Figure 3: Different tethering reagents

The order of addition in the tethering reaction was allylic alcohol **B** followed by reagent and then **A,** but due to volatile nature of allylic alcohol **B,** during work-up problems were

encountered thus, it was decided that the addition sequence would be reversed, that is first the addition of allylic alcohol **A** followed by the reagent and then addition of allylic alcohol **B**. Unfortunately, the tethering of dimethyl dichlorosilane and diphenyl dichlorosilane resulted in non-isolable complex reaction mixture. Diisopropyl dichlorosilane was the only reagent to give us the required product albeit in low yield (>5%). To overcome the low yield, we thought it appropriate to optimize the reaction conditions for the improved yields.



Scheme 8. *Reagents and conditions*: (a) *n*-BuLi, THF, $(i\text{Pr})_2SiCl_2$, 3 h then Grubb's II, DCM, 5%. (b) *n*-BuLi, THF, $(Me)_2SiCl_2$, 3 h then Grubb's II, DCM. (b) *n*-BuLi, THF, $(Ph)_2SiCl_2$, 3 h then Grubb's II, DCM.

Attempted optimization of the tethering reaction conditions

As illustrated in table **1** entries 1,5 and 9 show that imidazole in DCM gives no to negligible yield with any of the silicon reagents (**38a**, **38b** or **38c**) whereas entries 2,6 and 10 show that with pyridine as base as well solvent there is no reaction in presence of any of the silicon reagents (**38a**, **38b** or **38c**). Entries 1, 3 and 4 indicate that with greater equivalent of reagent **38a** used there is some increase in yield. Entries 8 and 12 indicate that with 2,6-lutidine as base there is no reaction in presence of any of the silicon reagents (**38a**, **38b** or **38c**). Entries 3,4,7 and 11 indicate that only a combination of imidazole and *n*-BuLi as base, yield negligible amount of product which could not be optimized.

Optimization of coupling reaction of A and B *via* silicon mediated tethered olefin metathesis

S.No	Reagent	Eq of reagent	Base 1	Base 2	Solvent	Time (h)	Yield
1.	diisopropyl dichloro-silane	6	Imidazole	Imidazole	DCM	16	<2%
2.	diisopropyl dichloro-silane	8	pyridine	pyridine	pyridine	72	_
3.	diisopropyl dichloro-silane	8	*n*-BuLi	Imidazole	THF	24	<5%
4.	diisopropyl dichloro-silane	10	*n*-BuLi	Imidazole	THF	24	<8%
5.	38b	10	Imidazole	Imidazole	DCM	48	_
6.	38b	10	pyridine	pyridine	pyridine	72	_
7.	38b	10	*n*-BuLi	Imidazole	THF	24	_
8.	38b	10	2,6-lutidine	2,6-lutidine	DMF	24	_
9.	38c	10	Imidazole	Imidazole	DCM	48	_
10.	38c	10	pyridine	pyridine	pyridine	72	_
11.	38c	10	*n*-BuLi	Imidazole	THF	24	_
12.	38c	10	2,6-lutidine	2,6-lutidine	DMF	24	_

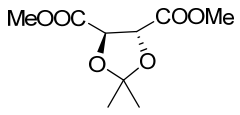
Table 1

5.5. Conclusion

In conclusion, an efficient strategy has been developed for the syntheses of pectinolides and hypurticin. The synthetic protocol has been utilized for the synthesis of pectinolides A,B and C (**1a**, **1b** and **1c**) in which two stereocenters were established by chiral pool naturally occuring starting material L-tartaric acid and one stereocenter was achieved using hydrolytic kinetic resolution. The introduction of *cis*-double bond was to be brought about by silicon mediated temporary tethering. Various tethering reagents were tried and also an effort was made to optimize the reaction conditions by changing the base as well as the solvent used. Nonetheless, we could not make an appreciable change in the yield of the reaction. Thus completion of the synthesis of pectinolides could not be achieved.

5.6. Experimental Section

Dimethyl (4*S*,5*S*)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (28).



28

To a suspension of D-(-)-tartaric acid (5.0 g, 33.3 mmol) in dry methanol (2.0 mL), was added 2,2-dimethoxypropane (9.4 mL, 76.8 mmol) and *p*-toluene sulfonic acid (0.010 g). The resulting mixture was warmed for about two hours, on an oil bath at 50 ºC, till a dark orange color developed. Dry cyclohexane (22.5 mL) and a further quantity of 2,2-dimethoxy propane (3.9 mL, 38.2 mmol) were added to the cooled reaction mixture. The reflux condenser was replaced with a long distillation head and the resulting two-layered reaction mixture was heated to afford a slow removal of azeotropes of cyclohexane-methanol (bp 53.0 ºC) and cyclohexaneacetone (bp 54.5 ºC) over a period of 24 h. When the vapor temperature fell below 50 ºC, 2,2-dimethoxypropane (1 mL) was added and the oil bath temperature was increased till the vapor temperature reached 78 ºC. The reaction mixture was cooled; the solvent and excess 2,2-dimethoxy propane were removed at the rotary evaporator. The resulting thick liquid was then distilled under vacuum (bp = 90 ºC/

0.5 mm, lit.[23] bp = 82-90 ºC/ 0.02 mm) to afford **28** as a pale yellow liquid.

Yield: 6.90 g, 95%

Mol. Formula: $C_9H_{14}O_6$

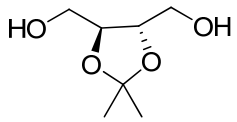
$[\alpha]_D^{25}$ -54 (neat)

IR ($CHCl_3$, cm^{-1}) ν_{max} = 3018, 2952, 1716,1472, 1379,1260, 1022, 916, 828.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.50 (s, 6H), 3.83 (s, 6H), 4.82 (s, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.8, 52.5, 78.3, 109.2, 167.

[(4*R*,5*R*)-5-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]methanol (29).



29

A solution of **28** (30.0 g, 121.82 mmol) in dry THF (50 mL) was added to a stirring suspension of lithium aluminium hydride (11.56 g, 304.6 mmol) in dry THF (400 mL) at 0 ºC, over a period of 15 min. After stirring for about an hour at rt, the reaction mixture was refluxed overnight. Upon cooling to 0 ºC, it was quenched by a slow addition of an aqueous solution of NaOH (20%). To the resulting white suspension was added anhydrous Na_2SO_4 and the slurry was filtered at the suction pump. The solid residue was washed with distilled THF (100 mL) and the combined filtrate was concentrated under vacuum. This crude mixture upon column chromatography (silica, pet ether-ethyl acetate, 2:3) afforded **29** as a syrupy mass.

Yield: 18.9 g, 85%

Mol. Formula: $C_7H_{14}O_4$

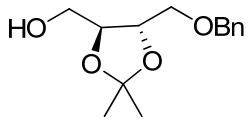
$[\alpha]_D^{25}$ +5.1 (*c*, 1.67, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}) ν_{max} = 3450, 2988, 2935, 1457, 1377, 1251, 1219, 1166, 1109.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.43 (s, 6H), 2.72 (bs, 2H), 3.68 - 3.81 (m, 4H), 3.98 - 4.0 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.8, 109.2, 78.3, 62.1.

((4*S*,5*S*)-5-(Benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (30).



30

To a solution of diol **29** (10.0 g, 61.41 mmol) in dry THF (100 mL) was added sodium hydride (60%, 2.44 g, 61.41 mmol) at 0 °C. The reaction mixture was then stirred at room temperature for 30 min after which it was again cooled to 0 °C. To this was added slowly benzyl bromide (6.57 mL, 55.27 mmol) with further stirring for 4 h at room temperature. The reaction mixture was quenched with addition of cold water at 0 °C. The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with water (3 x 25 mL), brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) as eluent furnished **30** as colorless liquid.

Yield: 12.74 g, 82%

Mol. Formula: $C_{14}H_{20}O_4$

$[\alpha]_D^{25}$ +9 (*c* 1.08, $CHCl_3$)

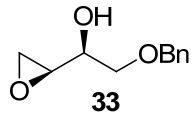
IR ($CHCl_3$, cm^{-1}) ν_{max} = 3426, 3011, 2857, 2930, 1454, 1099, 755 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.43 (s, 6H), 3.51 - 3.77 (m, 5H), 3.91 - 4.18 (m, 2H), 4.60 (s, 2H), 7.26 - 7.34 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.8, 62.3, 70.2, 73.6, 79.5, 109.3, 127.7, 128.4, 137.4

Elemental Analysis: Calcd for $C_{14}H_{20}O_4$ C, 66.65; H, 7.99; Found: C, 66.61; H, 7.92.

(*S*)-2-(Benzyloxy)-1-((*S*)-oxiran-2-yl)ethanol (33).



33

To a mixture of alcohol **30** (11.8 g, 46.67 mmol), in dry DCM (50 mL) was added *p*-toluenesulfonyl chloride (10.64 g, 56.0 mmol), triethylamine (7.81 mL, 56.0 mmol) and DMAP. Reaction was stirred at room temperature under nitrogen. The reaction was

monitored by TLC, after completion of reaction the mixture was quenched by adding water. The solution was extracted with DCM (3 x 20 mL) and then combined organic phase was washed with water, dried (Na_2SO_4) and concentrated to give **31**.

To this crude mixture of **31** in MeOH (50 mL) at 0 °C was added CSA (cat.) and DCM (50 mL). The mixture was stirred for 4 h at rt and then quenched with saturated aqueous $NaHCO_3$ (10 mL) and the solvent removed on rotavapour followed by extraction with EtOAc. The extract was washed with water and brine, dried and concentrated to give **32**.

To this crude mixture of **32** in MeOH at 0 °C was added K_2CO_3 (1.52 g, 11.0 mmol) and the resultant mixture was allowed to stir for 4 h at same temp. After completion of reaction as indicated by TLC the reaction was quenched by addition of ice pieces and methanol was evaporated. The concentrated reaction mixture was then extracted with ethyl acetate (3 x 20 mL), the combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The column chromatography of crude product using pet ether : ethyl acetate (9:1) gave the epoxide **33** as a colorless liquid.

Yield: 9.07 g, 71%

Mol. Formula: $C_{11}H_{14}O_3$

$[\alpha]_D^{25}$ +1.35 (*c* 0.92, $CHCl_3$)

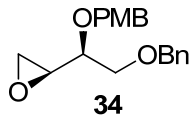
IR ($CHCl_3$, cm^{-1}) ν_{max} = 3440, 2932, 1463, 1361, 1255, 1215, 1092, 1028.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.50 – 2.52 (m, 1H), 2.80 – 2.84 (m, 1H), 3.03 – 3.10 (m, 1H), 3.77 - 4.08 (m, 3H), 4.60 (s, 2H), 7.26 - 7.34 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 43.1, 55.7, 70.2, 73.6, 127.1, 128.4, 129.1, 133.1.

Elemental Analysis: Calcd for $C_{11}H_{14}O_3$ C, 68.02; H, 7.27; Found: C, 68.06; H, 7.22.

(*S*)-2-((*S*)-2-(Benzyloxy)-1-(4-methoxybenzyloxy)ethyl)oxirane (34)



34

To a solution of **33** (7.0 g, 67.79 mmol) in dry DMF (200 mL) was added sodium hydride (60%, 1.73 g, 43.27 mmol) at 0 ^oC. The reaction mixture was then stirred at room temperature for 30 min after which it was again cooled to 0 ^oC. To this was added slowly

p-methoxybenzyl bromide (8.69 g, 43.27 mmol) and *tetra N*-butylammonium iodide (cat.) with further stirring for 6 h at the same temperature. The reaction mixture was quenched with addition of cold water at 0 ^{o}C. The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated. The residual oil was purified by silica gel column chromatography using petroleum ether/EtOAc (8:2) as eluent to furnish the PMB protected alcohol **34** as a colorless oil.

Yield: 10.76 g, 95%

Mol. Formula: $C_{19}H_{22}O_4$

$[\alpha]_D^{25}$ +2.92 (*c* 1.02, $CHCl_3$)

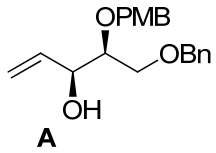
IR ($CHCl_3$, cm^{-1}) ν_{max} = 3018, 2931, 1471, 1361, 1255, 1215, 1049.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.50 – 2.52 (m, 1H), 2.80 – 2.84 (m, 1H), 2.97 – 3.07 (m, 1H), 3.41 – 3.77 (m, 3H), 3.91 (s, 3H), 4.60 (s, 2H), 6.89 – 6.93 (m, 2H), 7.29 - 7.35 (m, 7H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 43.1, 51.4, 55.7, 70.2, 73.6, 84.6, 115.7, 127.1, 128.4, 129.1, 130.5, 133.1, 158.9.

Elemental Analysis: Calcd for $C_{19}H_{22}O_4$ C, 72.59; H, 7.05; Found: C, 72.52; H, 7.09.

(3*S*,4*S*)-5-(Benzyloxy)-4-(4-methoxybenzyloxy)pent-1-en-3-ol (A)



A

To a suspension of trimethylsulfonium iodide (317 mg, 1.55 mmol) in dry THF (5 mL) at –20 ^{o}C was added *n*-BuLi (1.0 mL, 1.6 M solution in hexane, 1.55 mmol) dropwise over 20 min and stirred for 30 min. Then the epoxide **34** (80 mg, 0.25 mmol) in dry THF (1 mL) was added to the above reaction mixture and slowly allowed to warm to 0 ^{o}C over 1 h. The reaction mixture was then stirred at ambient temperature for 2 h. After completion of the starting material the reaction mixture was quenched with H_2O (2 mL) and extracted with EtOAc (4 x 10 mL). The combined extracts were washed with brine (10 mL), dried

over Na_2SO_4, filtered and concentrated to near dryness. The residue was purified by flash silica gel column chromatography using petroleum ether/EtOAc (94:6) as eluent to give **A** as a colorless liquid.

Yield: 50 mg, 60%

Mol. Formula: $C_{20}H_{24}O_4$

$[\alpha]_D^{25}$ +3.16 (*c* 0.98, $CHCl_3$)

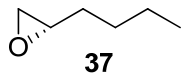
IR ($CHCl_3$, cm^{-1}) ν_{max} = 3443, 3019, 2932, 2400, 1463, 1377, 1215, 1049

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.41 – 3.77 (m, 3H), 3.91 (s, 3H), 4.21 (m, 1H), 4.60 (s, 2H), 5.03 – 5.12 (m, 2H), 5.73 – 5.93 (m, 1H), 6.89 – 6.93 (m, 2H), 7.29 - 7.35 (m, 7H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 55.1, 62.6, 64.6, 69.9, 72.3, 73.2, 73.6, 89.7, 113.6, 115.7, 127.1, 128.4, 129.1, 130.5, 133.1, 158.9.

Elemental Analysis: Calcd for $C_{20}H_{24}O_4$ C, 73.15; H, 7.37; Found: C, 73.11; H, 7.42.

(*R*)-Hexane-1,2-diol (36) and (*S*)-2-butyloxirane (37)



37

A solution of epoxide **35** (10 g, 138.88 mmol) and (*R*,*R*)-Salen-CoIII-OAc (645 mg, 0.97 mmol) in isopropanol (5 mL) was stirred at 0 ^oC for 5 min and then distilled water (1.37 mL, 76.38 mmol) was added. After stirring for 24 h, this mixture was concentrated and purified by silica-gel column chromatography (petroleum ether/EtOAc 19:1) to afford **37** as a yellow liquid. Continued chromatography with petroleum ether/EtOAc 3:2) provided the diol **36** as a brown liquid and as a single diastereomer.

Yield: 4.3 g, 43%

Mol. Formula: $C_6H_{12}O$

$[\alpha]_D^{25}$ -2.39 (*c* 1.06, $CHCl_3$)

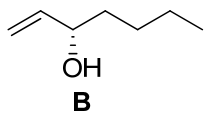
IR ($CHCl_3$, cm^{-1}) ν_{max} = 2932, 1462, 1255, 1215, 1051

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.7 Hz, 3H), 1.25 – 1.33 (brs, 4H), 1.40 – 1.50 (brs, 2H), 2.43 - 2.47 (m, 1H), 2.71 - 2.76 (m, 1H), 2.85 – 2.91 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 22.6, 29.3, 33.1, 46.9, 54.5.

Elemental Analysis: Calcd for $C_6H_{12}O$ C, 71.95; H, 12.08; Found: C, 71.89; H, 12.12.

(*S*)-Hept-1-en-3-ol (B)



B

To a suspension of trimethylsulfonium iodide (48.96 g, 0.24 mmol) in dry THF (20 mL) at –20 ^oC was added *n*-BuLi (150 mL, 1.6 M solution in hexane, 0.24 mmol) dropwise over 20 min and stirred for 30 min. Then the epoxide **37** (4.0 g, 0.04 mmol) in dry THF (100 mL) was added to the above reaction mixture and slowly allowed to warm to 0 ^oC over 1 h. The reaction mixture was then stirred at ambient temperature for 2 h. After completion of the starting material the reaction mixture was quenched with H_2O (20 mL) and distilled (bp = 48-50 ºC/ 4 mm) to give **B** as a colorless liquid.

Yield: (3.50 g) 70%

Mol. Formula: $C_7H_{14}O$

$[\alpha]_D^{25}$ +10.3 (*c* 1.45, pentane)

IR ($CHCl_3$, cm^{-1}) ν_{max} = 3421, 3019, 2932, 1461, 1215, 1047.

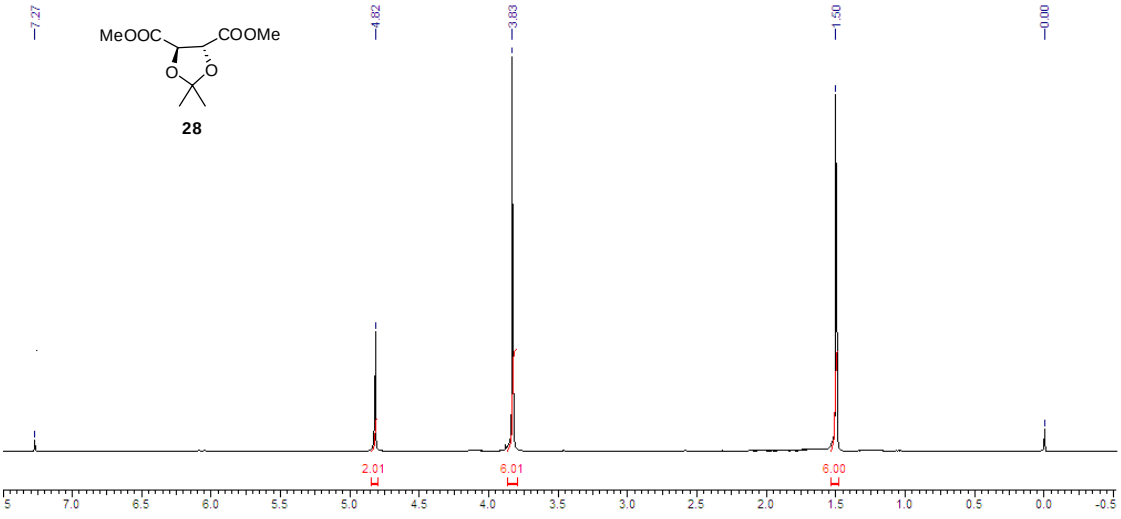
^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.7 Hz, 3H), 1.26 – 1.38 (brs, 4H), 1.46 – 1.54 (brs, 2H), 3.59 – 3.71 (m, 1H), 5.09 – 5.20 (m, 2H), 5.74 – 5.94 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.8, 22.6, 25.6, 36.8, 73.2, 117.9, 138.9.

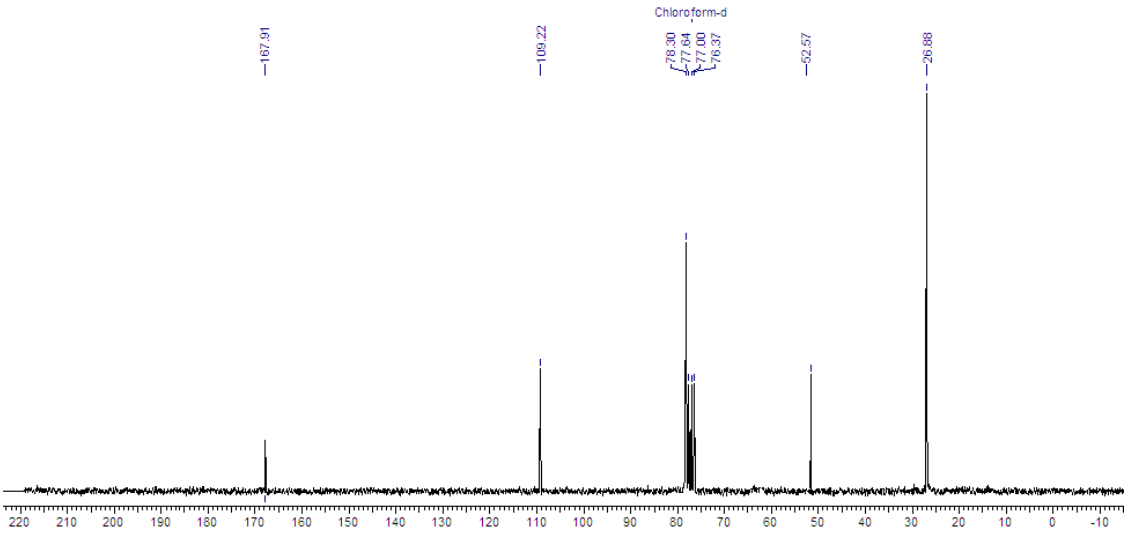
Elemental Analysis: Calcd for $C_7H_{14}O$ C, 73.63; H, 12.36; Found: C, 73.56; H, 12.41;.

5.7. Spectra

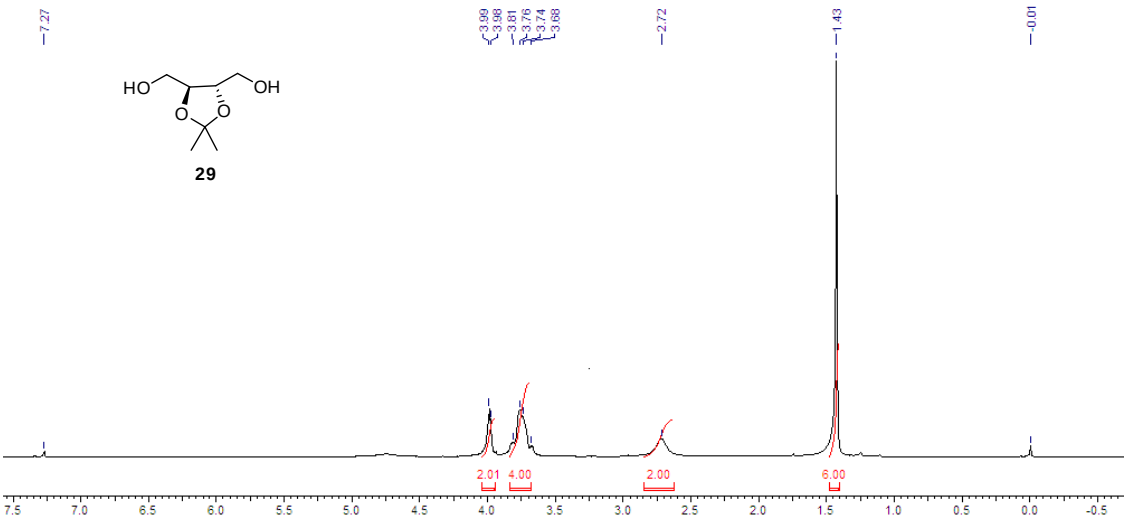
1. ^{1}H and ^{13}C NMR spectra of **28**
2. ^{1}H and ^{13}C NMR spectra of **29**
3. ^{1}H and ^{13}C NMR spectra of **30**
4. ^{1}H and ^{13}C NMR spectra of **33**
5. ^{1}H and ^{13}C NMR spectra of **34**
6. ^{1}H and ^{13}C NMR spectra of **A**
7. ^{1}H and ^{13}C NMR spectra of **37**
8. ^{1}H and ^{13}C NMR spectra of **B**



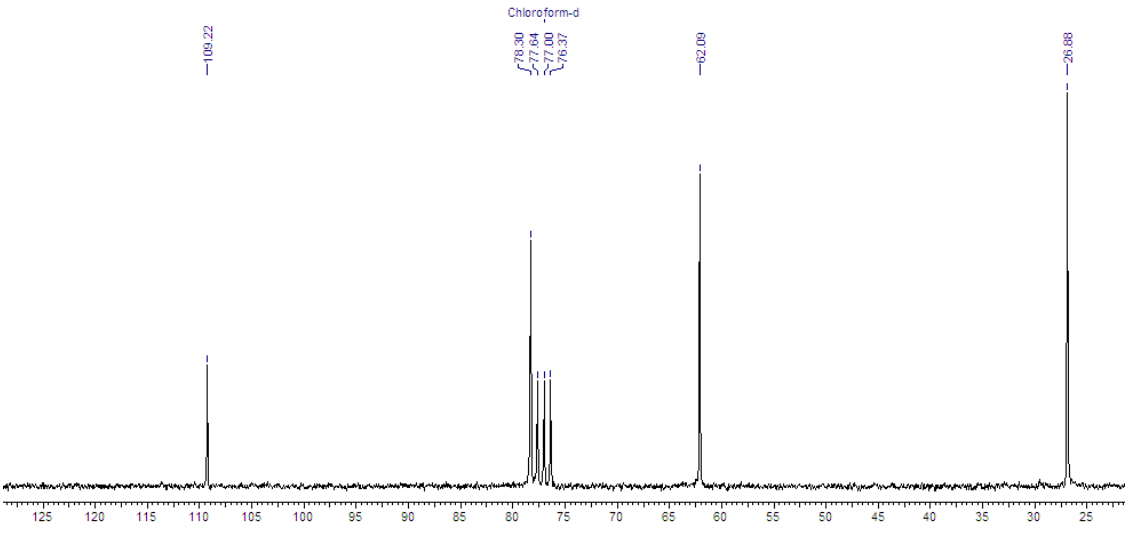
^{1}H-NMR spectrum of compound 28 in $CDCl_3$



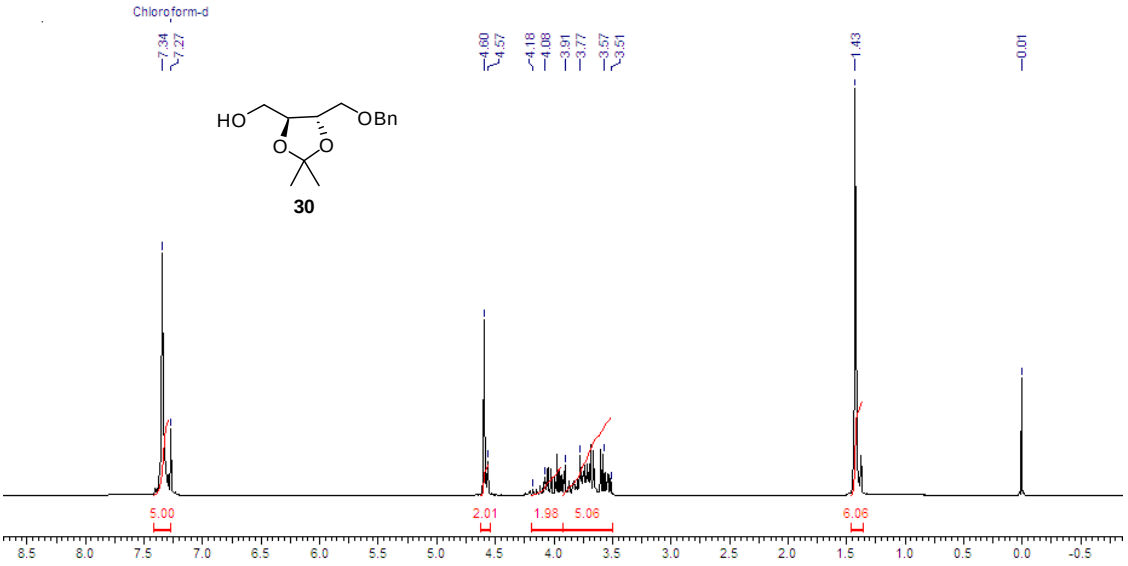
^{13}C-NMR spectrum of compound 28 in $CDCl_3$



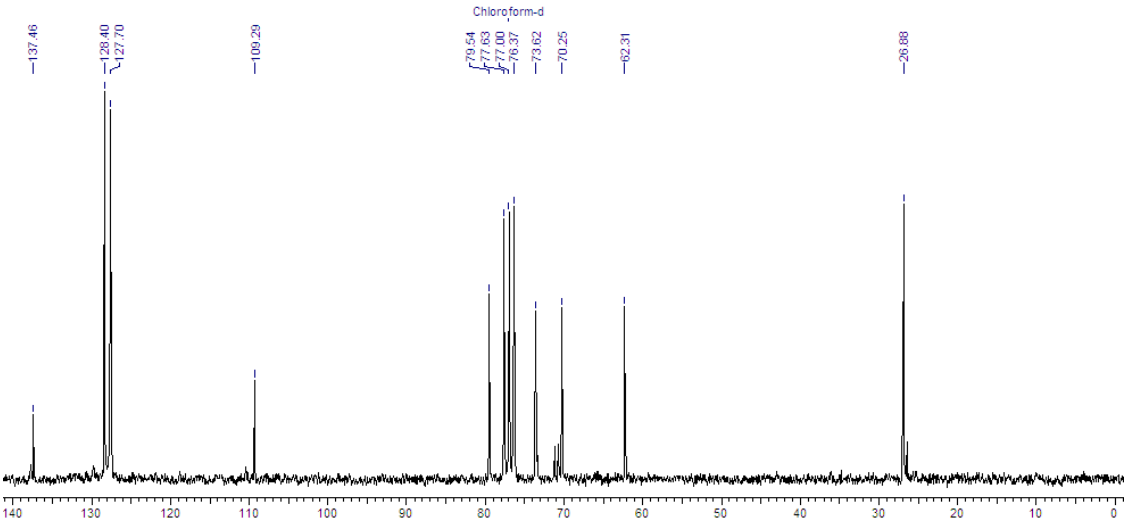
^{1}H-NMR spectrum of compound 29 in $CDCl_3$



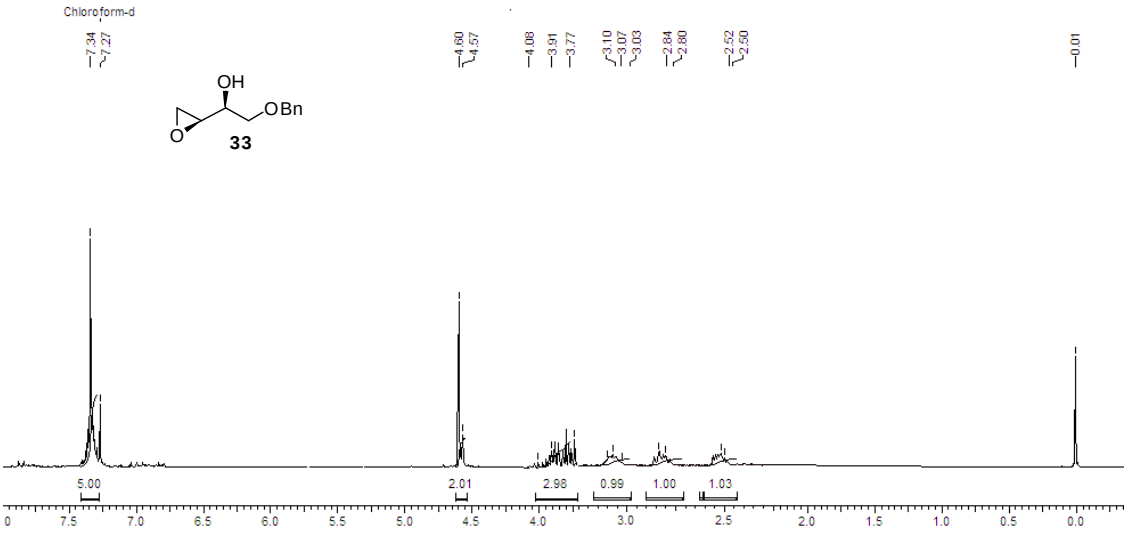
^{13}C-NMR spectrum of compound 29 in $CDCl_3$



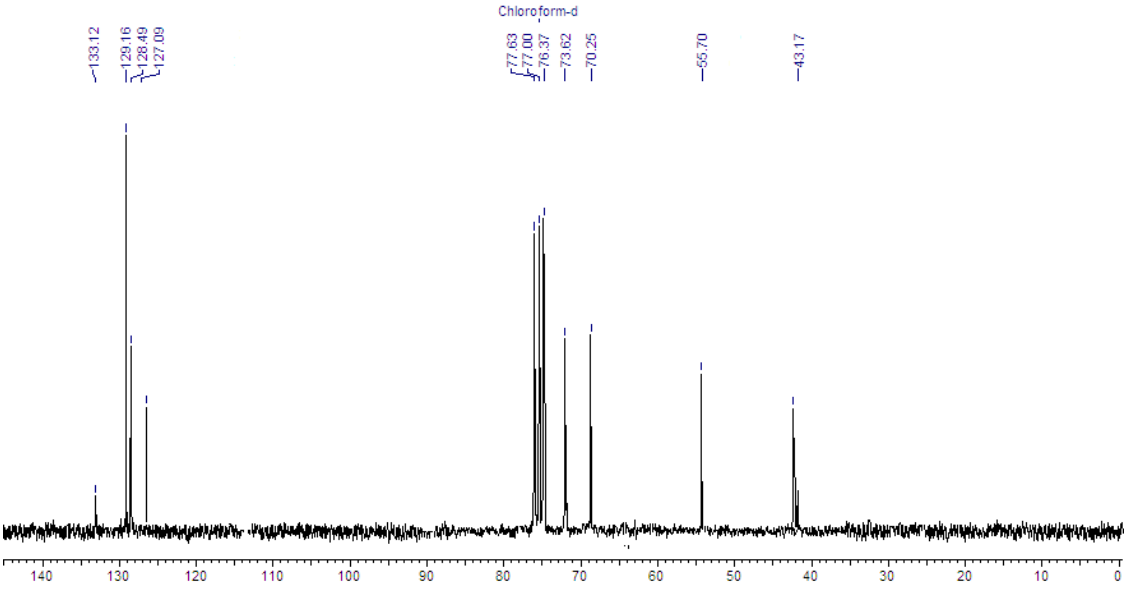
^{1}H-NMR spectrum of compound 30 in $CDCl_3$



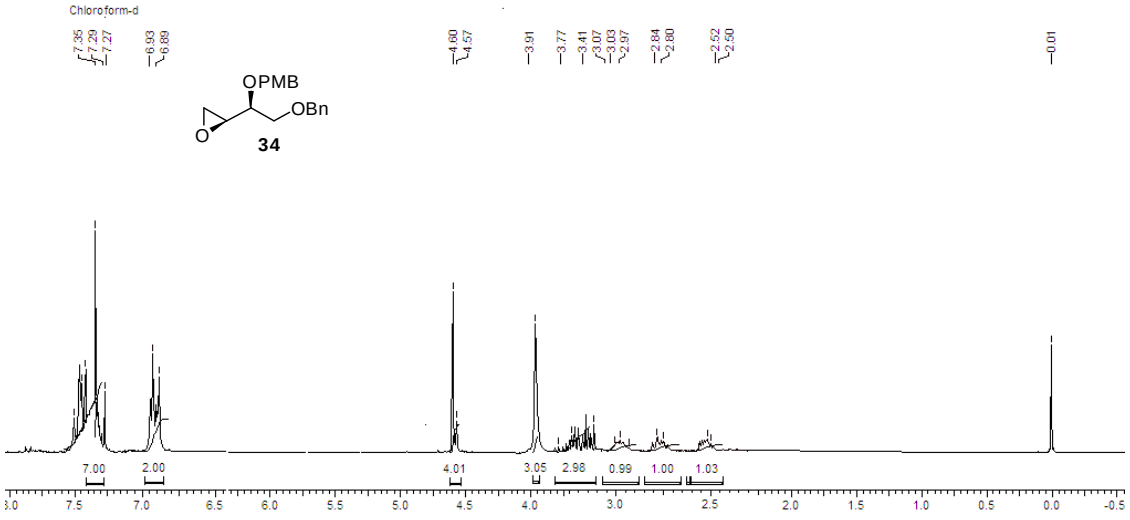
^{13}C-NMR spectrum of compound 30 in $CDCl_3$



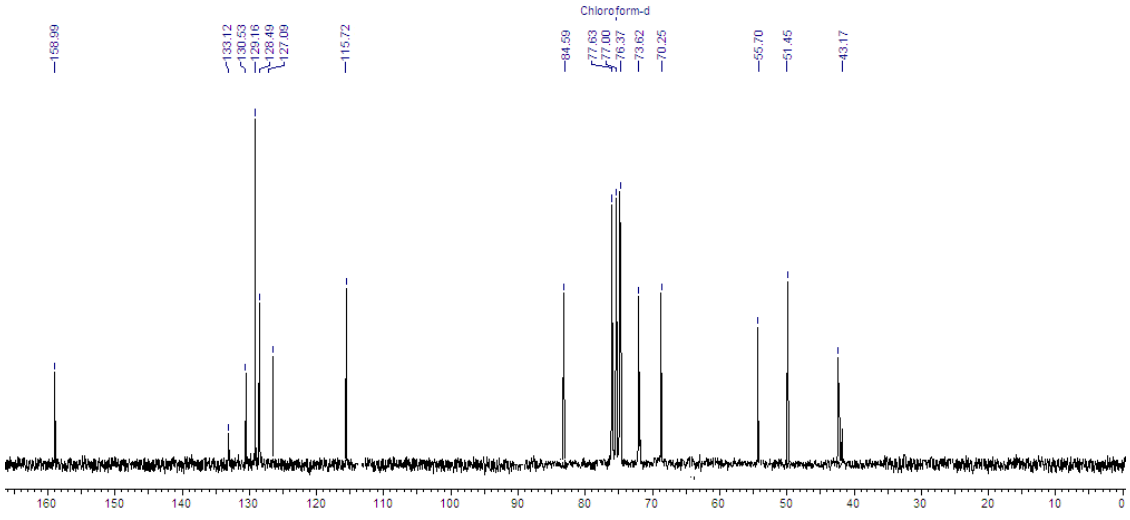
^{1}H-NMR spectrum of compound 33 in $CDCl_3$



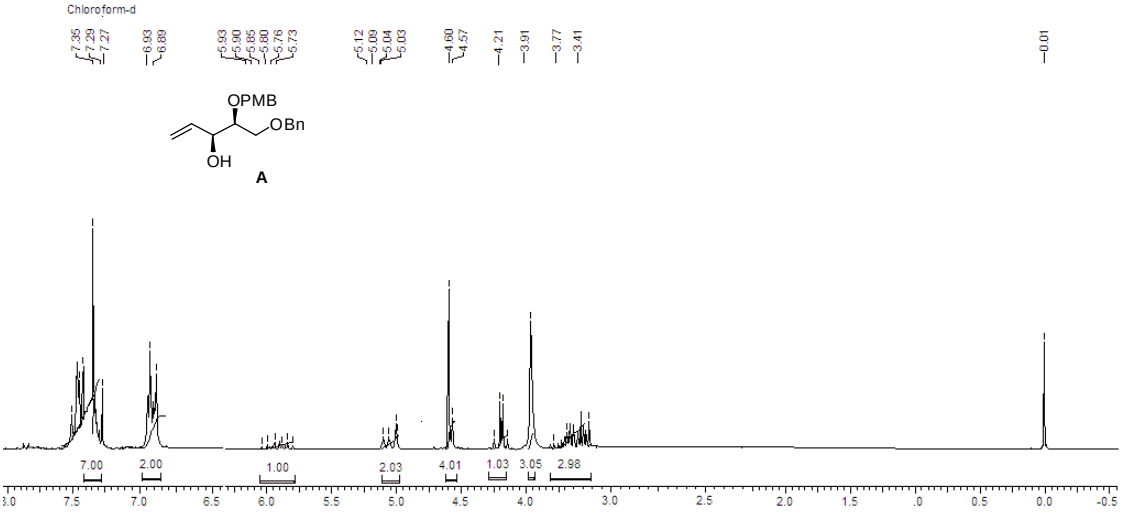
^{13}C-NMR spectrum of compound 33 in $CDCl_3$



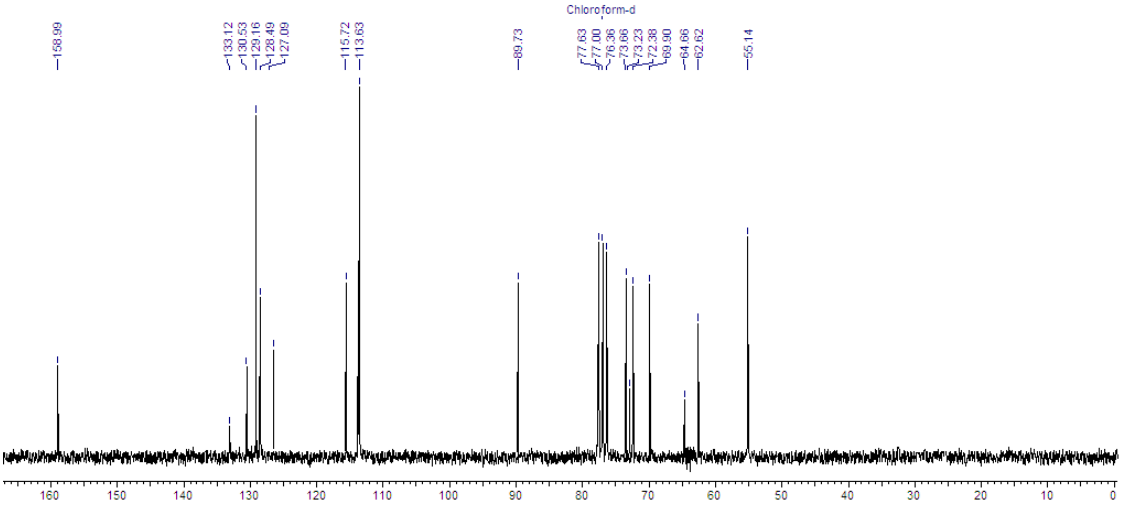
^{1}H-NMR spectrum of compound 34 in $CDCl_3$



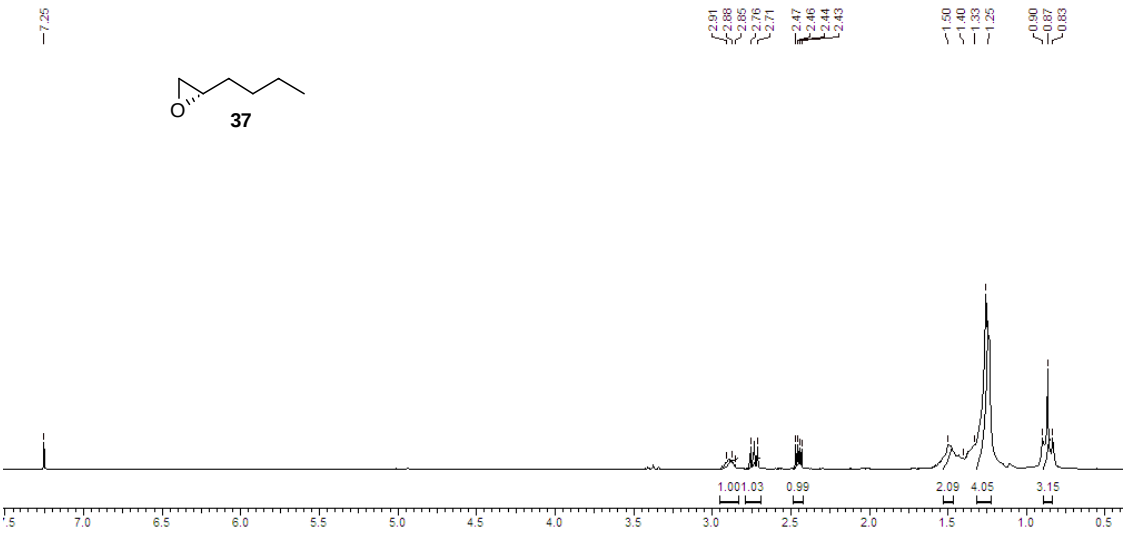
^{13}C-NMR spectrum of compound 34 in $CDCl_3$



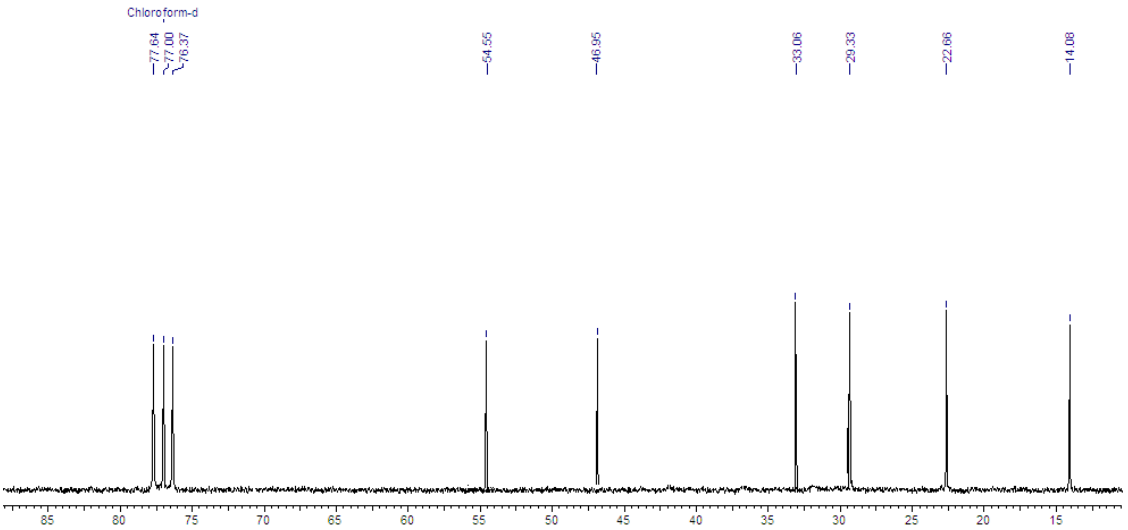
^{1}H-NMR spectrum of compound A in $CDCl_3$



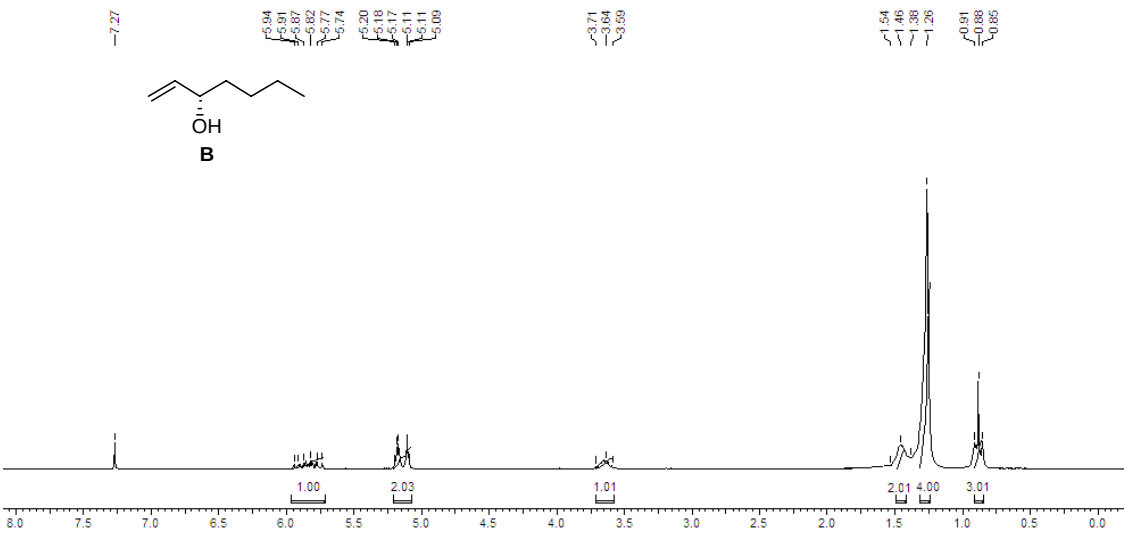
^{13}C-NMR spectrum of compound A in $CDCl_3$



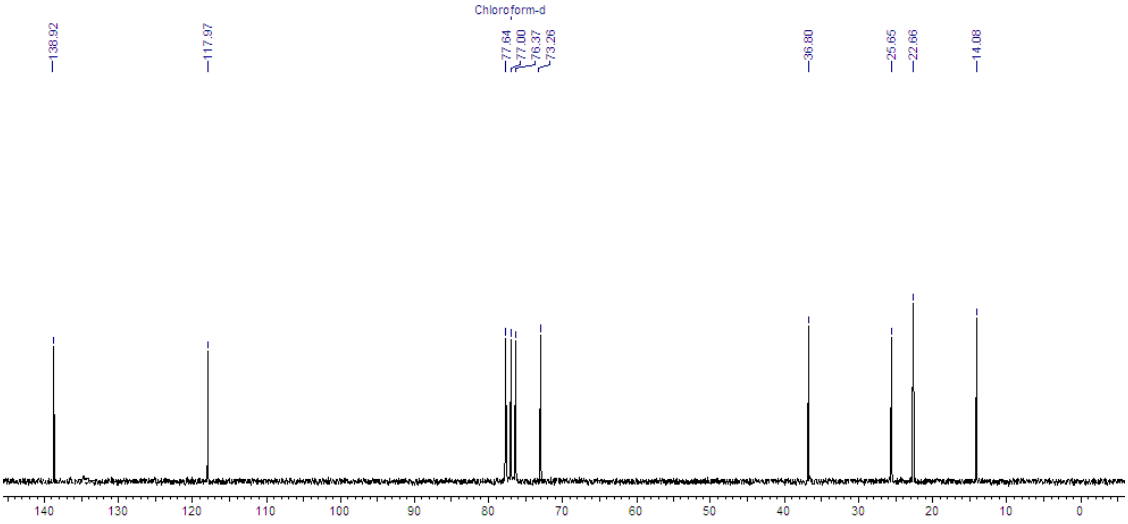
^{1}H-NMR spectrum of compound 37 in $CDCl_3$



^{13}C-NMR spectrum of compound 37 in $CDCl_3$



^{1}H-NMR spectrum of compound B in $CDCl_3$



^{13}C-NMR spectrum of compound B in $CDCl_3$

5.8. Refrences

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Curriculum Vitae

Educational Qualifications

M.Sc. (Master of Science)	**Organic Chemistry** Luknow Christian College, Lucknow University, Uttar Pradesh, India. **2003**.
B.Sc. (Bachelor of Science)	**Chemistry**, Zoology, Botany Isabella Thoburn, Lucknow University Uttar Pradesh, India. **2001**.

Fellowships

2005-2007: Junior Research Fellowship awarded by University Grants Commission (UGC), India

2007-2010: Senior Research Fellowship awarded by University Grants Commission (UGC), India

Examinations Qualified

- **July 2003**, qualified the *Central drug Research Institute entrance examination* for the research scholars
- **December 2003,** Qualified *National Eligibility Test*, Eligibility (NET) test for the lectureship at the University
- **Feb 2004**, Qualified *Graduate Aptitude Test* in Engineering (GATE) conducted by Indian Institute of Technology (IIT) Delhi, India with 82% score.
- **June 2004,** qualified *Joint CSIR-UGC Junior Research Fellowship (JRF) and Eligibility for Lectureship- National Eligibility Test (NET)*

Awards

1. The "**Keerthi Sangoram Memorial Endowment Award**" for Best Research Scholar of the Year **2011** (*Chemical Sciences*), NCL Research Foundation.
2. Secured **Second Place** in Lucknow Christian College, Lucknow (India) in Master of Science (Chemistry) **2003**.

Experience

Joined as research scholar in *Central Drug Research Institute (CSIR-CDRI)* in *Medicinal Chemistry Division,* Lucknow and worked on ***"Isolation purification and characterization of biologically active metabolites from microbial source"*** from **September 2003** to **April 2005.**

Publications

1. An organocatalytic route to the synthesis of (6*S*)-5,6-dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one and ravensara lactones.
   Namrata Dwivedi, **Divya Tripathi** and Pradeep Kumar*
   ***Tetrahedron Asymmetry,* 2011**, *22,* 1749-1756.
2. A general approach to medium-sized ring ethers *via* hydrolytic and oxidative kinetic resolutions: Stereoselective syntheses of (-)-*cis*-lauthisan and (+)-isolaurepan
   Divya Tripathi, Satyendra Kumar Pandey and Pradeep Kumar*
   ***Tetrahedron,* 2009,** *65,* 2226-2231.
3. A total synthesis of (+)-isolaurepan
   Divya Tripathi and Pradeep Kumar*
   ***Tetrahedron Letters,* 2008,** *49,* 7012-7014.
   (Most downloaded article in first 3 months)
4. Asymmetric synthesis of a key chiral building block for *trans* dialkyl-β-lactone *via* HKR and organocatalysis: Application to the formal synthesis of anti-tumor and anti-obesity agents tetrahydrolipstatin and tetrahydroesterastin.
   Divya Tripathi and Pradeep Kumar*
   (Communicated to ***Tetrahedron Asymmetry***).

5. An An Organocatalytic Proline calalysed α-aminoxylation reaction: Its application for the synthesis of biologically active compounds

   Divya Tripathi, Namrata Dwivedi and Pradeep Kumar*

   (To be Communicated for publication).

Oral Presentation

Total Synthesis of Biologically Active Natural Products, in *J-NOST* (Junior-National Organic Symposium Trust) held at Indian Institute of Technology (IIT-Kanpur), India in **December 2009** organized by National organic symposium trust (*NOST*) India.

Posters presented at symposia / conferences attended

1. Isolation of biologically active natural products of fungal origin. Presented at International Conference on chemistry biology interface: Synergistic new frontiers (CBISNF 2004) at Delhi University, India in **November 2004**.

2. Participated in the 12^{th} CRSI National Symposium in Chemistry 2010 held at Indian Institute of Chemical Technology (IICT), Hyderabad in **February 2010**.

Research Interests

- Development of new asymmetric synthetic methodologies and its applications to the synthesis of bioactive molecules with special emphasis on organocatalysis.

- Total synthesis of bioactive molecules and there application to the medicinal chemistry and material chemistry.