STUDIES DIRECTED TOWARDS THE SYNTHESIS OF NATURALLY OCCURRING LACTONES, AMINO ALCOHOLS AND POLYOLS

A THESIS

SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)

TO

UNIVERSITY OF PUNE

BY

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RESEARCH GUIDE

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SEPTEMBER 2013

CANDIDATE'S DECLARATION

I hereby declare that the thesis entitled "**Studies Directed Towards the Synthesis of Naturally Occuring Lactones, Amino Alcohols and Polyols"** 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 CSIR-National Chemical Laboratory, Pune, India.

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CERTIFICATE

The research work presented in thesis entitled "**Studies Directed Towards the Synthesis of Naturally Occurring Lactones, Amino Alcohols and Polyols**" has been carried out under my supervision and is a bonafide work of **Mr. Ankushkumar D. Bhise**. This work is original and has not been submitted for any other degree or diploma of this or any other University.

Dr. Pradeep Kumar
(Research Guide)

September 2013

DEDICATED

TO MY BELOVED
FAMILY

Acknowledgements

It gives me great pleasure to express my deep sense of gratitude to my teacher and research guide Dr. Pradeep Kumar, who has helped me a lot to learn and think more about chemistry. I thank him for his excellent and inspiring guidance, constant encouragement, sincere advice and unstinted support during all the times of my Ph.D. work. Working with him was a great pleasure and learning experience.

I take this opportunity to specially thank Dr. R. A. Joshi, Dr. H. B. Borate, Mr. I. Shivakumar, Dr. S. P. Chavan, Dr. N. N. Joshi, Dr. S. Hotha, Dr. R. R. Joshi, Dr. Santosh Mhaske, Dr D. S. Reddy, Dr. Muthukrishnan, Dr. Ashish Bhattacharya, Dr. Jayant Gajbhiye, Dr. Kiran Sonawane, Dr. Borikar, Mr. Kalal, Mrs. Kunte, Dr. Ashish K. Tiwari and Late. Dr. D. D. Sawaikar for their helpful suggestions and encouragement.

Help from the NMR Division, Shrikant, Mayur, mass group are gratefully acknowledged. I sincerely thank Dr. Rajmohanan and Ganesh Jogdand for his helpful discussions and cooperation.

I extend thanks to the SAC office. I sincerely thank Mrs. Puranik, Mrs. Kohle, Mr. Pavitran and all other office staffs for their cooperation.

My sincere thanks to Mrs. C. Raphel, Mrs. P. Kulkarni, Mr. Iyer, Mr. K. Thangaraj, Mr. Babus, Mr. Ranade, Mr. Kakade, Mr. Damodar and all other office staffs for their cooperation.

My sincere thanks to Dr. G. Panday for his cooperation and support.

The warm and friendly attitude of my seniors Dr. Seetaram, Dr. Rahman, Dr. Sahoo, Dr. Rosy, Dr. Chinmoy, Dr. Sabita, Dr. Rita, Dr. Ramesh, Dr. Pradip, Dr. Debbrata, Dr. Ganesh, Dr. Anil, Dr. Ghorakh, Dr. Satyendra, Dr. Priti, Dr. Puspesh, Dr. Nagendra, Dr. Namarta, Mr. Shijo, Dr. Abhishek, Dr. Divya, Dr. Ruchi, Dr. Eeshwar, Dr. Satish is gratefully acknowledged. I take this opportunity to thank my colleagues Vishwajeet, Partha, Menaka, Mujaheed, Krishanu, Kiran, Shruti, Nookaraju, Brijesh, chandani and Shrikant for their help and cheerful atmosphere in the laboratory. I extend my deep sense of gratitude towards my friend Mr. Anand and

Mr. Abhijeet for helping me in all aspect of research and personal life. Also I heartedly thank friends at NCL and GJ hostel especially Abasaheb, Deepak, Manmath, Suleman, Prasad, Ganesh, Abhijeet, Bharat, Prakash, Ashif, Pankaj, Sachin, Mangesh, Ravennath, Dhanraj, Mangesh,, Majid, Atul, Chinmay, Pradeep, Bhausaheb, Shekhar, Nagesh. K, Nagesh, Digambar, Sharad, Giri, Sachin, Milind, Dyaneshwer, Sandeep, Kishor, Lalit, Pradeep, Prakash, Avinash, Dayanand, Shriram, Pandurang, Indra, Malvi, Deepika, Ajeet, Yogesh, Santosh, Yogesh, Harshada, Negi, Sunil, Ravi, Abhishek M., Krunal, Rahul, Pitamber, Gowri, Priyanka, Debashish, Sujit, Sumantra, Venu, Swaroop, Hemender Chand, Pankaj, Jyoti, Ranjeet, Sangmesh, Sandeep, Jeetendra, Shyamsundar, Shrinivas, Paresh, Satish, Tukaram, Sangram, Sanjeev……. the list goes on.

I extend my thanks to my friends Ganesh, Devidas, Vishal, Shivkumar, Abhijeet, Sushil, Harshad, Abrar, Firdos, Abbas, Balaji, Amol, Mahesh, Sachin, Sudhir, Santosh, Ramu, Uchit, Amol, Rahul, Vivek, Satish, Sandesh, shailesh, Sunil, Sandeep, Mohsin, Praveen, Sandy, Diksha, Mahendra, Shrikar and my roommates Sumanth, Prithviraj and Mohanraj who made the life memorable.

Special thanks to my M.Sc. teachers Dr. B. S. Dawane, Dr. Kuberkar, Dr. Vibhute, Dr. Gurav, Dr. Mali, Dr. Patel, Dr. Basheer, Dr. Kabeer, Dr. Kulkarni, Dr. Suryavanshi, Dr. Vartale for their constant encouragement and inspiration.

It is impossible to express my sense of gratitude for my parent, in mere words. Whatever I am and whatever I will be in future is because of their commitments to my ambitions and their selfless sacrifices. Words fall short to thank my brother Dr. Santosh, Sister Sulbha, Suvarna, Brother-in-law Ramdas, Devidas, Sister-in-law Rachana, Niece Anushka, nephew Arnav for their never ending encouragement, love and support which enable me to pursue my goal whole heartedly.

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

Ankush

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Abbreviations

Ac	-	Acetyl
AcOH	-	Acetic acid
Ac_2O	-	Acetic anhydride
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
Cat.	-	Catalytic
$CDCl_3$	-	Deuterated chloroform
DCM	-	Dichloromethane
DDQ	-	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	-	Diisobutylaluminiumhydride
DMP	-	2,2-Dimethoxypropane
DMF	-	*N, N'*-Dimethylformamide
DMAP	-	*N,N'*-Dimethylaminopyridine
DMSO	-	Dimethyl sulfoxide
ee	-	Enantiomeric excess
equiv.	-	Equivalents
EtOH	-	Ethanol
Et	-	Ethyl
Et_2O	-	Diethyl ether
EtOAc	-	Ethyl acetate
Et_3N	-	Triethylamine
Hz	-	Hertz
HPLC	-	High pressure liquid chromatography
IBX	-	Iodoxybenzoic Acid
Im	-	Imidazole
LiHMDS	-	Lithium hexamethyl disilazide

m-CPBA	-	*m*-Chloroperbenzoic acid
MeOH	-	Methanol
mg	-	Milligram
min	-	Minutes
mL	-	Millilitre
mmol	-	Millimole
M. p.	-	Melting point
Ms	-	Methanesulfonyl
Me	-	Methyl
MeI	-	Methyl iodide
$NaBH_4$	-	Sodiumborohydride
NaH	-	Sodium hydride
Ph	-	Phenyl
Py	-	Pyridine
PMB	-	*para*-Methoxy benzyl
p-TSA	-	*par*a-Toluenesulfonic acid
RCM	-	Ring closing metathesis
TEA	-	Triethylamine
TEMPO	-	(2,2,6,6-Tetramethylpiperidin-1-yl)oxy
TBAI	-	Tetra-*n*-butylammonium iodide
TBAF	-	Tetra-*n*-butylammonium fluoride
TBDMS	-	*tert*-Butyldimethyl silyl
TBSCl	-	*tert*-Butyldimethyl silyl chloride
THF	-	Tetrahydrofuran
TPP	-	Triphenylphosphine
p-TSA	-	*p*-Toluenesulphonic acid
TsCl	-	*p*-Toluenesulphonyl chloride

- ^{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 Finnigan 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, ninhydrin 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.
- All melting points and boiling points are uncorrected and the temperatures are in centigrade scale.
- The compounds, scheme and reference numbers given in each section of chapter refers to that particular section of the chapter only.

Abstract

The thesis entitled **"Studies Directed Towards The Synthesis of Naturally Occurring Lactones, Amino Alcohols and Polyols"** has been divided into three chapters.

Chapter I: Introduction to Sharpless asymmetric epoxidation, Jacobsen's hydrolytic kinetic resolution, Ring Closing Metathesis and proline catalyzed reactions.

Chapter II: Synthesis of naturally occurring lactones

Section A: Studies directed towards the synthesis of Stagonolide C & Modiolide A.

Section B: Studies directed towards the synthesis of Seimatopolide B.

Section C: Studies towards the synthesis of Dodoneine.

Chapter III: Studies directed towards the synthesis of Jaspine B and analogues

Chapter I: Introduction to Sharpless asymmetric epoxidation, Jacobsen's hydrolytic kinetic resolution, Ring closing metathesis and proline-catalyzed reactions.

This chapter gives a brief introduction to Sharpless asymmetric epoxidation, Jacobsen's hydrolytic kinetic resolution (HKR), ring closing metathesis (RCM) and proline-catalyzed organic transformations.

The Sharpless asymmetric epoxidation is an enantioselective chemical reaction to prepare 2,3-epoxyalcohols from primary and secondary allylic alcohols. This metal catalyzed epoxidation process was discovered by K. Barry Sharpless in 1980 and allows the transformation of a prochiral substrate into an optically active (or optically pure) product using a chiral catalyst.[1] The asymmetric induction is achieved by adding an enantiomerically enriched tartrate derivative. This epoxidation is arguably one of the most important reactions discovered in the last 30 years. This has been recognized by the award of the 2001 Nobel Prize to Professor Barry Sharpless.

In this epoxidation reaction, double bond of allylic alcohols is converted into epoxides using a transition metal catalyst titanium tetra-isopropoxide and a chiral additive (di-alkyltartrate, i.e., DET or DIPT used). The oxidant for the epoxidation is

tertbutylhydroperoxide. Notably, this reaction exhibits high levels of enantioselectivity (usually >90% *ee*) and proceeds under mild condition with good chemical yield.

The hydrolytic kinetic resolution (HKR)[2] of terminal epoxide catalyzed by chiral (salen)-Co(III)-OAc complex affords both recovered epoxide and 1,2-diol product in highly enantio-enriched form. In many cases there exist no practical alternatives for accessing these valuable chiral building blocks from inexpensive racemic materials.

Ring closing metathesis (RCM)[3] is a unique carbon skeleton redistribution in which unsaturated carbon-carbon bonds are rearranged to give cycloalkene. It utilizes no additional reagents beyond a catalytic amount of metal carbene. Various well-defined metathesis catalysts which are tolerant to many functional groups as well as reactive towards a diverse range of substrates have been developed.

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.[4] 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 Brönsted acid.

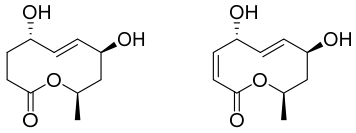
These methods have contributed to more advances in research not only in chemistry but also in material science, biology and medicine. This work gave access to new molecules needed to investigate hitherto undiscovered and unexplained phenomena in the molecular world.

Chapter 2: Section A: Studies directed towards the synthesis of Stagonolide C & Modiolide A.

Stagonolide C[5] was isolated by Antonio Evidente in 2008 from a fungal pathogen *Stagonospora Cirsii* isolated from *Cirsium arvense.* They were found weakly toxic to *Colpoda steinii, a protozoan, when tested at 0.05* mg/mL.

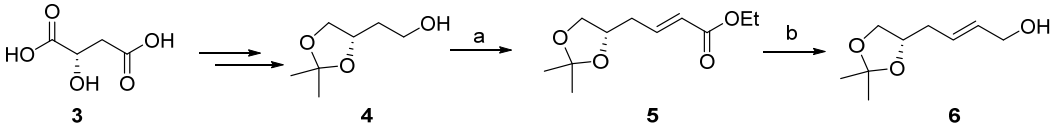
Modiolide A[6] was isolated from the cultured broth of a marine fungus *Paraphaeosphaeria* sp. (Strain N-119) which was separated from marine horse mussel. Modiolide A showed antibacterial activity against *Micrococcus luteus* (MIC value 16.7 µg/mL) and antifungal activity against *Neurospora crassa* (MIC value 33.3 µg/mL).

Total synthesis of stagonolide C and Modiolide A has been attempted using Ring closing metathesis and Yamaguchi esterification as key steps. The Steregenic centers were generated by Sharpless asymmetric epoxidation and hydrolytic kinetic resolution (HKR) of terminal epoxides.



Stagonolide C **1** Modiolide A **2**

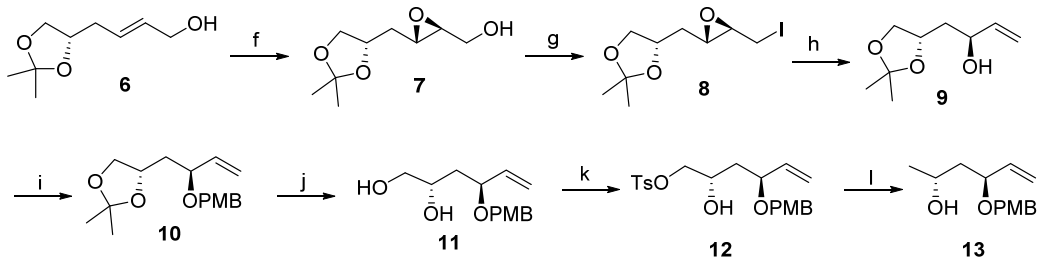
Our synthesis started with the conversion of L(+)-malic acid **3** to the known primary alcohol **6**. One pot conversion of the alcohol to the α,β-unsaturated ester **7** was achieved by IBX oxidation followed by treating the same reaction mixture with (ethoxycarbonylmethylene)triphenylphosphorane. The ester was selectively reduced to allylic alcohol **8** by DIBAL-H (Scheme-1).



3 **4** **5** **6**

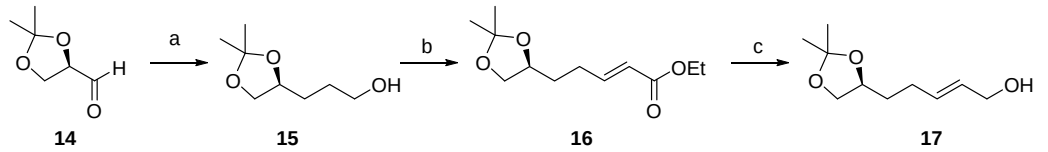
Scheme 1 : *Reagents and conditions:* (a) (i) IBX, DMSO, THF, (ii) $PPh_3CHCOOC_2H_5$, THF, reflux, 70 %; (b) DIBAL, CH_2Cl_2, -78 ^oC, 1 h, 75%.

Sharpless asymmetric epoxidation of the allylic alcohol **6** with (+)-DET gave the (*S*,*S*) epoxide **7**. The primary hydroxyl group of the epoxide **7** was transformed to its iodo derivative **8**. Opening of the epoxide of the iodo compound was achieved with Zn in refluxing EtOH. The secondary allylic alcohol **9** was protected as its *p*-methoxybenzyl ether **10**. Then the isopropylidine group was deprotected by treatment with *p*-TSA to give diol **11**. In order to secure the alcohol fragment **13**, we deoxygenated the primary hydroxyl group of diol. The diol **11** was selectively monoprotected with a tosyl group to give **12**. Then, **12** was treated with excess of lithium aluminium hydride (LAH) to give the required alcohol **13** in good yield (scheme-2).



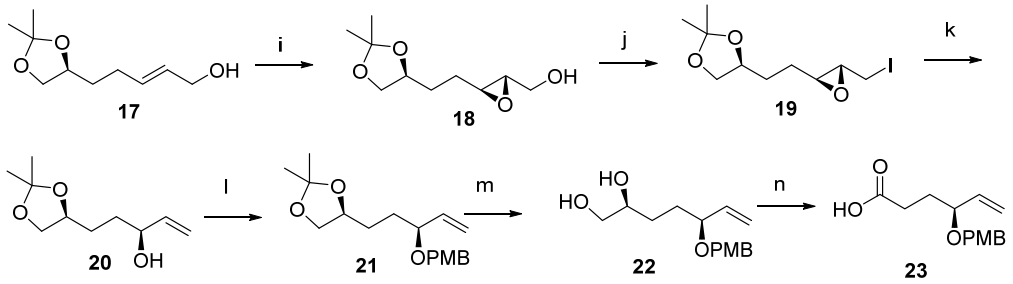
Scheme 2: *Reagents and conditions:* (f) (+)-DET, $Ti(O^iPr)_4$, TBHP, CH_2Cl_2,12 h, 80%; (g) TPP, imidazole, iodine, CH_2Cl_2, 75%; (h) Zn, Ethanol, reflux, 81%; (i) NaH, PMBCl, DMF, 0 ^oC to rt, 3 h, 81%; (j) MeOH, PTSA, 91%; (k) TsCl, Bu_2SnO, CH_2Cl_2, 12 h, 70%; (l) LAH, THF, 1 h, 77%.

A similar retrosynthetic strategy was planned for the acid fragment **23.** The D-glyceraldehyde derivative **(14)** when subjected to two-carbon Wittig olefination using (carbethoxymethylene)triphenylphosphorane gave α,β-unsaturated ester which on catalytic hydrogenation with Pd/C afforded saturated ester. This ester was reduced with lithium aluminium hydride (LAH) in anhydrous THF to furnish the alcohol **15.** In order to secure allyl alcohol **17**, the primary hydroxyl group of **15** was oxidized with IBX to afford an aldehyde which was treated with (carbethoxymethylene)triphenylphosphorane to furnish **16**. Hydride reduction of **23** with DIBAL afforded the key precursor allyl alcohol **17** (scheme 3)**.**



Scheme 3: *Reagents and conditions:* (a) (i) $PPh_3CHCOOC_2H_5$, Toluene, reflux, 78% (ii) Pd/c, ethyl acetate, 97% (iii) LAH, THF, 84% (iv) IBX, DMSO, 85% (b) $PPh_3CHCOOC_2H_5$, Toluene, reflux 75% (c) DIBAL, CH_2Cl_2, -78^oC 1h, 83%.

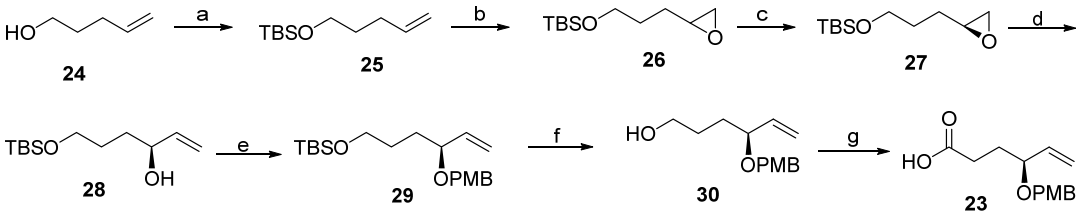
Generation of the second chiral centre relevant to the target was achieved by employing Sharpless asymmetric epoxidation on **17,** in a catalytic process using (-)-DET as chiral ligand, to furnish (2*R*,3*R*)-epoxide **18**. The next, epoxy alcohol was converted to epoxy iodide by iodination procedure to give **19**. Direct reduction with commercial zinc dust gave the diastereomerically pure terminal alkenic alcohol **20.** The terminal alkenic alcohol was protected as *p*-methoxybenzyl (PMB) ether **21**. The isopropylidene group of **21** was hydrolyzed under acidic conditions, to furnish diol **22**. The diol **22** was oxidatively cleaved with sodium metaperiodate to provide aldehyde which on further treatment with $NaClO_2$ in presence of NaH_2PO_4 and 2-methyl-2-butene as a scavenger gave required coupling partner acid **23** (Scheme 4).



Scheme 4: *Reagents and conditions:* (i) (-)-DET, $Ti(O^iPr)_4$, TBHP, 4Å MS powder, CH_2Cl_2, -20 ^oC,12 h, 82%; (j) TPP, imidazole, iodine, CH_2Cl_2, 72%; (k) Zn, Ethanol, reflux,70%; (l) NaH, PMBCl, DMF, 0 ^oC to r.t., 3 h, 85%; (m) 80% AcOH, r.t., 2 h, 90%; (n) (i) Silica Supported $NaIO_4$, 30 min. r.t.;(ii) $NaClO_2$, NaH_2PO_4, 2-Methyl-2-butene, *t*-BuOH:H_2O, r.t., 2 h, 54% (two steps).

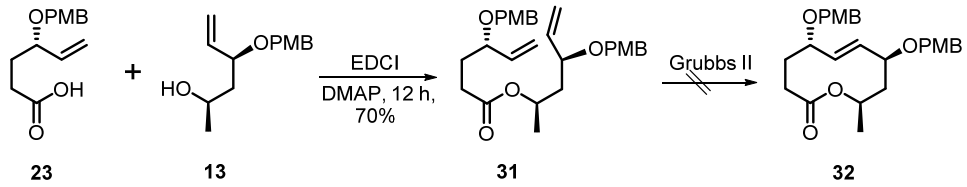
As synthesis of acid fragment was achieved in twelve steps, we were interested in the short and concise synthesis of acid fragment by applying the hydrolytic kinetic resolution.

Synthesis of acid fragment using Hydrolytic Kinetic Resolution: Our synthesis of acid fragment **23** started from 4-pentene-1-ol **(24)**. Protection of **24** with TBSCl in presence of imidazole afforded **25** in 90% yield, which was subjected to *m*-CPBA epoxidation followed by hydrolytic kinetic resolution using *S,S*-salen $Co^{(III)}$-OAc complex to furnish enantiopure epoxide **27** in 45% yield. The epoxide **27** was opened by dimethylsulfonium methylide to give allylic alcohol **28** which was then protected as its PMB ether to give compound **29.** This PMB ether was then treated with TBAF to give desilylated alcohol **30.** This alcohol **30** was then oxidized to aldehyde using IBX and then to acid by using $NaClO_2$ in presence of NaH_2PO_4 and 2-methyl-2-butene as a scavenger gave required coupling partner acid **23** (Scheme 5).



Scheme 5: *Reagents and conditions*: (a) TBSCl, imidazole, CH_2Cl_2, 0 ^oC- r.t., overnight, 90%; (b) *m*-CPBA, CH_2Cl_2, 0 ^oC to r.t., 5 h, 70%; (c) (*S,S*) Salen-Co^{III}-(OAc), H_2O, 16 h, 45%; (d) Trimethylsulphonium iodide, *n*-BuLi, THF, -23 ^oC, 8 h, 78%; (e) NaH, DMF, PMBCl, 0 ^oC-r.t., 6 h, 72%; (f) TBAF, THF, 0 ^oC, 90%; (g) (i) IBX, EtOAc, reflux (ii) $NaClO_2$, NaH_2PO_4, 2-Methyl-2-butene, *t*-BuOH:H_2O, rt, 2 h, 64% (two steps).

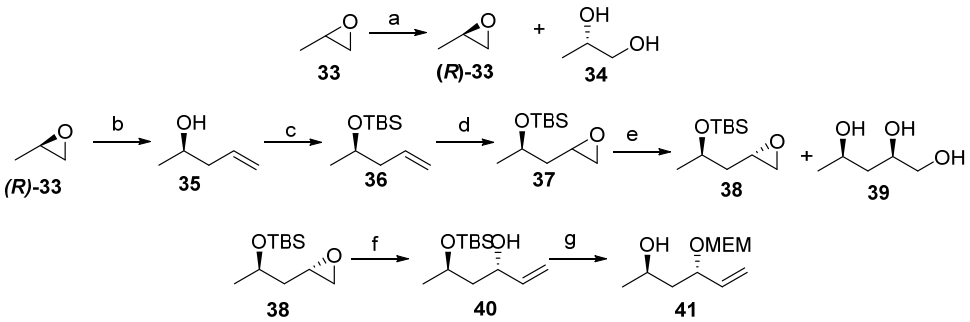
Coupling of alcohol and acid fragments: Alcohol **13** was coupled with acid **23** by using EDCI and catalytic amount of DMAP to give the diene ester **31**. The structure of **31** was proved by ^{1}H NMR and ^{13}C NMR spectra. The compound **31** was subjected for ring closing metathesis in CH_2Cl_2 with Grubbs' II generation catalyst under reflux conditions; we observed no reaction as we recovered the starting material even after 36 h (scheme 6).



Scheme 6: *Reagents and conditions*: (a) EDCI, DMAP, 12 h, 70%; (b) Grubbs II Gen. CH_2Cl_2.

Synthesis of Modiolide A:

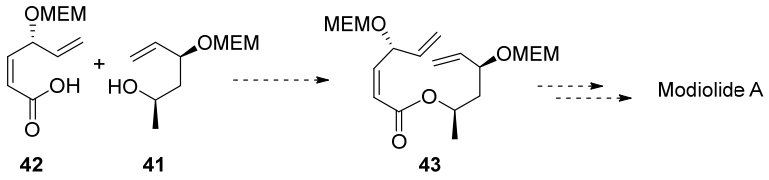
Synthesis of alcohol fragment using Hydrolytic Kinetic Resolution: Our synthesis of **41** requires iterative Jacobsen's hydrolytic kinetic resolution to install the stereogenic centers (Scheme 7). Thus racemic propylene oxide (±)**-33** was resolved by HKR method to give the enantiopure epoxide **(*R*)-33** and diol **(*S*)-34**. The epoxide **(*R*)-33** was opened with vinylmagnesium bromide followed by TBS protection and epoxidation to give the epoxide **37** as a mixture of *syn* and *anti* compounds. In order to get the diastereomerically pure epoxide, the epoxide **37** was resolved using (*S*,*S*)-salen $Co^{(III)}$-OAc and water in THF to give the diastereomerically pure epoxide **38** as well as diol **39**. With substantial amount of epoxide **38** in hand we further proceeded for the synthesis of **41** by opening of epoxide with trimethylsulfonium iodide to get the allylic alcohol followed by protection as its MEM ether and deprotection of TBS ether using TBAF.



Scheme 7: *Reagents and conditions:* (a) (*R,R)*-Salen-Co^{III}-(OAc) (0.5 mol%), dist. H_2O, (0.55 equiv), 0 ^{o}C, 14 h, (45% for 33 and 43% for 34); (b) vinylmagnesium bromide, CuI, THF, -20 ^{o}C, 12 h, 85%; (c) TBSCl, imidazole, CH_2Cl_2, 0 ^{o}C – r.t., 6 h, 80%; (d) *m*-CPBA, CH_2Cl_2, 0 ^{o}C- r.t., 72%; (e) *(S,S)*-Salen-

Co^{III}-(OAc) (0.5 mol%), dist. H_2O (0.55 equiv.), 45%; (f) Trimethylsulphonium iodide, *n*-BuLi, THF, -30 ^oC, 68%; (g) (i) MEMCl, DIEPA, CH_2Cl_2, 0 ^oC- r.t.; (ii) TBAF, THF, 0 ^oC – r.t., 72%.

Having synthesized alcohol fragment **41** and acid fragment **42** which is synthesized by another colleague, we proceeded for the coupling of compound **41** and **42** to achieve the diene ester. Further synthesis of Modiolide A is in progress (Scheme 8).

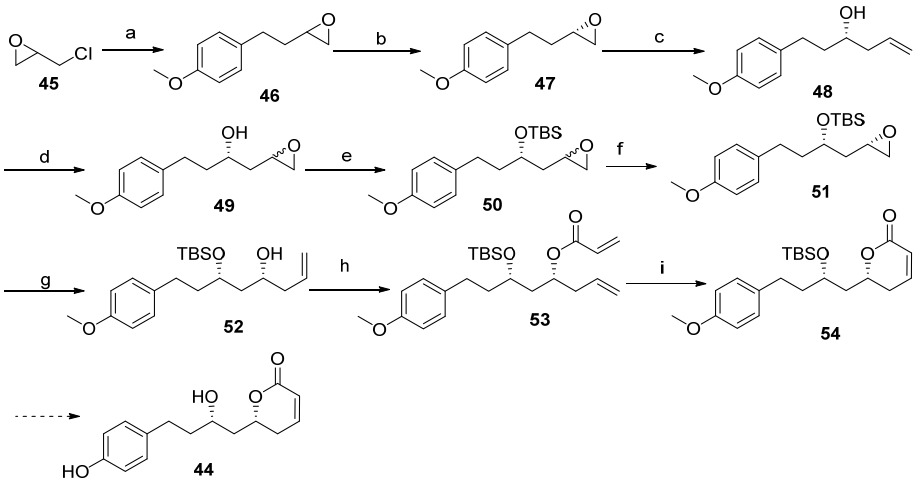


Scheme 8: Coupling acid and alcohol fragment for synthesis of modiolide A.

Chapter 2: Section B: Studies directed towards the synthesis of Dodoneine

Dodoneine **(44)** was isolated from the methanolic extract of a hemiplant parasite, *Tapinanthus dodoneifolius*[7]. *T. dodoneifolius* is known to be used as a remedy to treat cardiovascular and respiratory diseases, and also for cholera, diarrhoea, stomach ache and wounds. Dodoneine was found to exhibit relaxation effects on preconstricted rat aortic rings with an IC_{50} value of 81.4 ± 0.9 μM. Hence we planned to synthesize dodoneine and till date eight syntheses are reported in the literature.

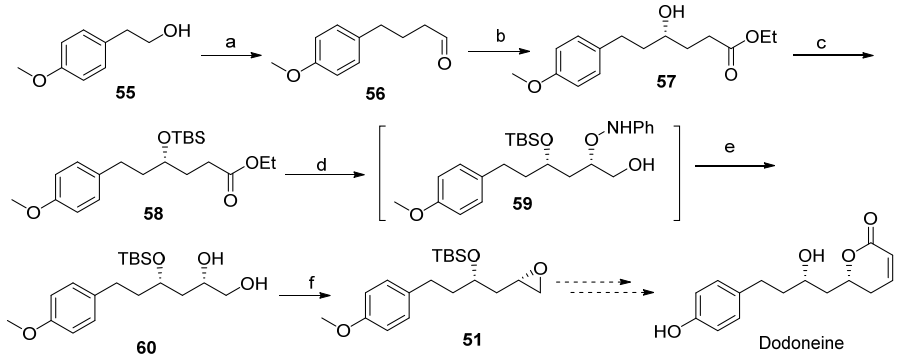
Synthesis of Dodoneine by hydrolytic Kinetic resolution: Synthesis of Dodoneine was started with reaction of p-methoxybenzyl magnesium chloride with epichlorohydrin **45** to give the chlorohydrin, which on potassium hydroxide treatment gave the epoxide **46**. The hydrolytic kinetic resolution of epoxide **46** using *S,S*-salen-Co catalyst gave the enantiopure epoxide **47** which was then opened with vinylmagnesium bromide in presence of copper iodide to give homoallylic alcohol **48**. This homoallylic alcohol **48** on epoxidation followed by TBS protection of alcohol group gave compound **50**. TBS protected epoxide **50** was then subjected for hydrolytic kinetic resolution using *S,S*-salen-Co-catalyst which gave the chiral epoxide **51**. This chiral epoxide **51** was then opened with vinylmagnesium bromide to give the homoallylic alcohol **52** which was then converted into its acrylate **53**. This acrylate **53** on ring closing metathesis with Grubbs 1^{St} Gen. catalyst gave the desired RCM product **54** in 85% yield. Further conversion of RCM product **54** to the natural product Dodoneine **44** is in progress (Scheme 9).



Scheme 9: *Reagents and Conditions:*(a) (i)PMB-MgCl, THF, CuI, -20 ^{o}C, 5 h; (ii) KOH , CH_2Cl_2, 73% (for two steps); (b) (*S*,*S*) Salen-Co^{III}-(OAc), H_2O, 16h, 45%; (c) vinylmagnesium bromide, CuI, THF, -23 ^{o}C, 5h, 85% (d) *m*-CPBA, CH_2Cl_2, 0 ^{o}C, 4 h, 72%; (e) TBSCl, imidazole, CH_2Cl_2, 0 ^{o}C- r.t., 24 h, 90%; (f) (*S*,*S*)- Salen-Co^{III}-(OAc), H_2O, THF, 16 h, 45%; (g) Vinylmagnesium bromide, CuI, THF, -23 ^{o}C, 12 h, 80%; (h) Acryloyl chloride, NEt_3, 0 ^{o}C, 1 h, 90%; (i) Grubbs 1St, CH_2Cl_2, 85%

Organocatalytic approach towards the synthesis of Dodoneine:

Oragnocatalytic route for the synthesis of Dodoneine started with 2-(4-methoxyphenyl) ethanol **55** which on oxidation-Wittig-reduction sequence gave aldehyde **56**.



Scheme 10: (a) (i) IBX, EtOAc, reflux, 7 h; (ii) $PPh_3CHCOOC_2H_5$, Toluene, reflux; (iii) $NiCl_2.6H_2O$, $NaBH_4$, MeOH, -30^{o}C; (iv) DIBAL-H, CH_2Cl_2, -78 ^{o}C, 60% (over four steps); (b) (i) D-proline, DMSO, Nitrosobenzene; HWE salt, DBU, LiCl, CH_3CN; (ii) H_2-Pd/C, EtOAc, 8 h, 65%(over two steps); (c) TBSCl, imidazole, DMF, Overnight, 87%; (d) DIBAL-H, CH_2Cl_2, -78^{o}C, 78%; (e) (i) D-Proline, Nitrosobenzene, DMSO (ii) $NaBH_4$, MeOH, 70%

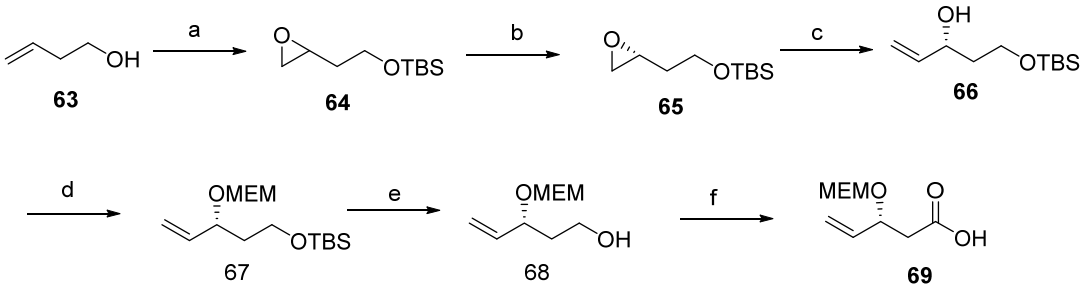
Aldehyde **56** on D-proline catalysed α-aminoxylation gave α-anilinoxy aldehyde which on in-situ HWE-olefination, and hydrogenation gave γ-hydroxy ester **63** which was then silylated with TBSCl. This O-silylated ester **58** was then reduced to aldehyde with DIBAL-H at -78^{o}C. This aldehyde was then aminoxylated using D-

proline to α-anilinoxy aldehyde which was *in situ* reduced to alcohol by using sodium borohydride in methanol. Further conversion of diol **60** into synthesized epoxide **51** is in progress (Scheme 10).

Chapter 2: Section C: Studies directed towards the synthesis of Seimatopolide B

Seimatopolides A (**61)** and B (**62**), two polyhydroxylated 10-membered macrolides, were recently isolated by Jang and Lee *et al*[8] from an ethyl acetate extract of *Seimatosporium discosioides* culture. Seimatopolides exhibited significant activity in a reporter gene assay for activation of peroxisome proliferator activated receptor c (PPAR-c) with EC_{50} values of 11.05 μM, which shows therapeutic potential in the treatment of type 2 diabetes, inflammatory disease and certain cancers.

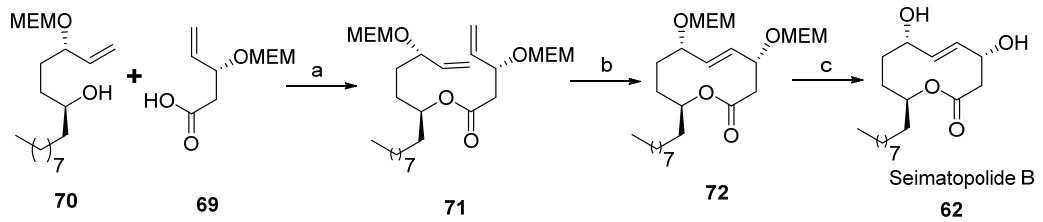
As depicted below (scheme 11), synthesis of acid fragment **69** commenced from commercially available 3-butene-1-ol which was protected as its TBS ether and then the double bond was epoxidised with *m*-CPBA to give epoxide. This epoxide was then resolved using *(R,R)*-salen-Co-complex to give enantiopure epoxide **65**. This chiral epoxide on ring opening with dimethylsulfonium methylide afforded one-carbon homologated allylic alcohol **66** which was protected as the MEM ether using MEMCl and DIPEA followed by removal of the TBS group to furnish alcohol **68**. TEMPO-catalysed oxidation of the alcohol with NaOCl resulted in the formation of acid **69** in excellent yield.



Scheme 11: Reagents and conditions: (a) TBDMSCl, imidazole, CH_2Cl_2, 0 ^oC to r.t., 4 h, 88%; (b) *m*-CPBA, CH_2Cl_2, 0 ^oC to r.t., 1 h, 90%; (c) (*R,R*)-salen-Co-(OAc) (0.5 mol %), dist. H_2O (0.55 equiv), isopropyl alcohol, 0 ^oC, 24 h, (46% for diol, 45% for **65**); (d) $(CH3)_3SI$, *n*-BuLi, THF, 4 h, 86%; (e) MEMCl, DIPEA, CH_2Cl_2, 16 h, 87%; (f) TBAF, THF, 1 h, 88%; (g) TEMPO, NaH_2PO_4, NaOCl, $NaClO_2$, CH_3CN, overnight, 95%.

With substantial amounts of acid **69** and alcohol fragment **70** which was synthesized by another colleague, the coupling of acid and alcohol was achieved by using

intermolecular DCC coupling to afford the diene ester **71** in 91% yield. This diene ester was then subjected to ring closing metathesis conditions using Grubbs' 2nd generation catalyst in CH_2Cl_2 under reflux conditions which led to the formation of cyclised product **72**, in only 50% yield. Subsequent deprotection of MEM ethers using TFA in CH_2Cl_2 afforded the natural product, seimotopolide B.



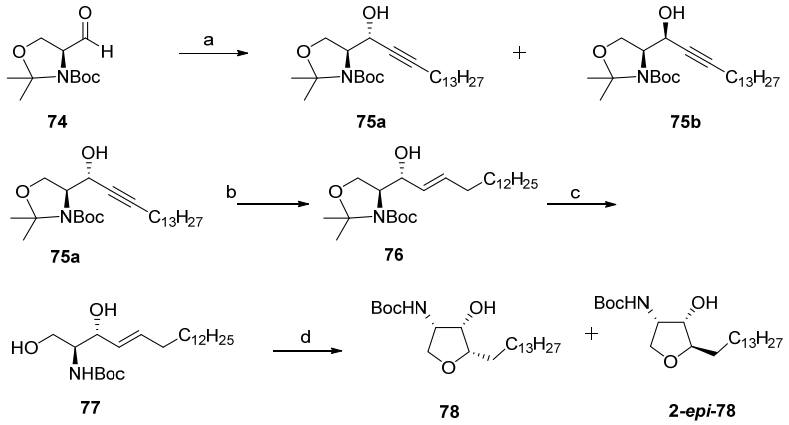
Scheme 12: (a) DCC, DMAP, CH_2Cl_2, 6 h, rt, 91%; (b) Grubbs II Gen. Catalyst, CH_2Cl_2, reflux, 16 h, 50%; (c) TFA, CH_2Cl_2, rt, 16 h, 70%.

Conclusion: We prepared the acid and alcohol fragments for the both Stagonolide C and modiolide A via different via different routes. Thus, the formal synthesis of Stagonolide C, synthesis of precursor for Dodoneine and total synthesis of seimatopolide B achieved.

Chapter III: Studies directed towards the synthesis of Jaspine B and analogues

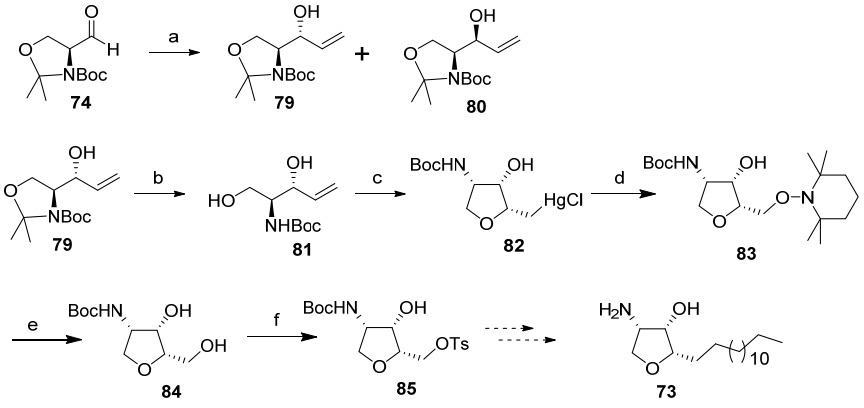
Pachastrissamine **(73)** is an anhydrophytosphingosine derivative, which was initially isolated from a marine sponge *Pachastrissa sp*. in 2002 by Higa and co- workers[9]. Soon after, the same compound was isolated from a different marine sponge *Jaspis* sp. and named Jaspine B by Debitus and co-workers. This marine natural product exhibits a high cytotoxic activity against various tumor cell lines in vitro.

Our synthesis began with the oxazolidine aldehyde known as Garner's Aldehyde **(74)**. The addition of lithium 1-pentadecyne to the Garner's aldehyde gave an 8:1 mixture of propargylic alcohols **75a** and **75b.**[10] The *erythro*-propargyl alcohol **75a** was converted to *trans*-allyl alcohol **76** using sodium bis(2-methoxyethoxy)aluminium hydride. The alcohol **76** was then treated with *p*-TSA and methanol to hydrolyse isopropylidene group to give the N-Boc protected amino alcohol **77**. Oxymercuration-demercuration sequence of the amino alcohol **77** afforded a mixture of Boc protected Jaspine B and 2-*epi*-jaspine B (scheme 13).



Scheme 13: *Reagents and conditions:* (a) Lithium-1-pentadecyne, -23 ^{o}C, 3 h, 63%; (b) Red-Al, ether, 0 ^{o}C-r.t., 60%; (c) *p*-TSA, Methanol, 4 h, 90%; (d) (i) $Hg(OCOCF_3)_2$, CH_2Cl_2, r.t., 2 h; (ii) alk. $NaBBH_4$, 0 ^{o}C, 15%.

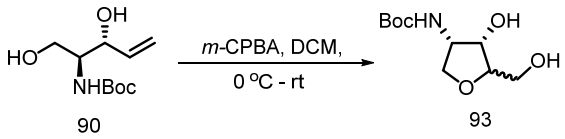
To improve the yield of the jaspine B we revised our strategy. Garner's aldehyde **74** (scheme 14), on reaction with vinylmagnesium bromide gave 6:1 mixture of **79** and **80.**[11] The allyl alcohol **79** was then treated with p-TSA and methanol to hydrolyse the isopropylidenegroup to give the diol **81**. The oxymercuration of **81** with $Hg(OAc)_2$ in CH_2Cl_2 gave the desired product **82** in 67% yield. The stereochemistry of which was determined by 2D NMR study. Oxidative demercuration[12] using six equivalents of TEMPO gave the mercury displaced product **83** in 80% yield. Reductive cleavage of the N-O bond using $Pd(OH)_2/C$ and H_2, at 70 *psi* gave the desired product **84** in 80% yield. The compound 84 was converted into its tosylate **85.** The study is under progress to functionalise **85** into Jaspine B and its analogues.



Scheme 14:*Reagents and conditions:* (a) vinyl magnesium bromide, THF, 0^{o}C- rt, 10h, 70% (b) p-TSA, Methanol, 6h, 90% (c) $Hg(OAc)_2$, CH_2Cl_2, 3h, 67% (d) DMF, O_2, $NaBH_4$, then **59,** TEMPO (6 equiv.), 30 min, 80% (e) $H_2/Pd(OH)_2/C$, 70*psi* 3d, 80%;(f) TsCl, Et_3N, CH_2Cl_2, 90%.

To improve the yield of the compound **84**, we modified our strategy. The allylic alcohol **81** was epoxidised with *m*-CPBA at 0 ^{o}C which gave a mixture of products.

This mixture was treated with tosyl chloride to get the monotosylated product **85** only in 40% yield.



90 93

In summary, we have synthesized 2-*epi* Jaspine B via oxymercuration method. Also we have synthesized the key intermediate for the synthesis of Jaspine B. Further functionalisation into various analogues of Jaspine B is in progress.

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Sharpless Asymmetric Epoxidation

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 last three decades. 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.

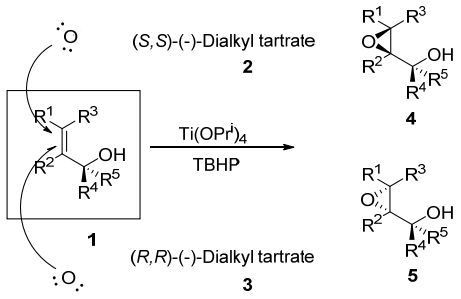
Epoxides are versatile and important intermediates in organic chemistry. The strain of three membered heterocyclic ring makes them accessible to a large variety of reagents. Metal catalyzed epoxidation process was discovered by K. Barry Sharpless & Katsuki in 1980 and allows the transformation of a prochiral substrate into an optically active (or optically pure) product using a chiral catalyst. The asymmetric induction is achieved by adding an enantiomerically enriched tartrate derivative. This epoxidation is arguably one of the most important reactions discovered in the last 30 years. This has been recognized by the award of the 2001 Nobel Prize to Professor Barry Sharpless.

In this epoxidation reaction, double bond of allylic alcohols is converted into epoxides using a transition metal catalyst ($Ti(O^iPr)_4$, titanium tetra-isopropoxide) and a chiral additive (dialkyltartrate, i.e., DET or DIPT used). The oxidant for the epoxidation is *tert*-butylhydroperoxide.[8] Notably, this reaction exhibits high levels of enantioselectivity (usually >90% *ee*) and proceeds under mild condition with good

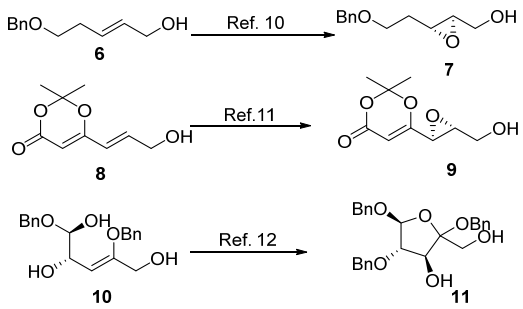
chemical yield. It is proposed that, coordination of the chiral ligand DET and the oxidant source TBHP to the metal center forms the catalytically active species.

Asymmetric epoxidation with the titanium (VI) tartrate Catalyst

The combination of $Ti(OPr^i)_4$, a dialkyl tartrate, and *tert*-butyl hydroperoxide epoxidizes most allyic alcohols in good chemical yield and with predictably high enantiofacial selectivity according to the empirical rule illustrated in **Scheme 1**. When an allylic alcohol (R^4, R^5 = H) **1** is drawn in a plane with the hydroxymethyl group positioned at the lower right, the delivery of oxygen occurs from the bottom side of the olefin to give the (2*S*)- epoxide **5** if an (*R*,*R*)-dialkyl tartrate **3** is used as the chiral auxiliary. When an (*S*,*S*)-dialkyl **2** tartrate is employed, oxygen is delivered from the top side. The enantiofacial selectivity of the reaction is > 90% *ee* for substrate without a Z-olefinic substituent (R^3 = H). The degree of facial selectivity for a Z-allylic alcohol depends on the nature of the Z substituent R^3. The enantioselectivity for substrate with unbranched R^3 substituents ranges from 80 to 94% *ee*, but that for substrates with branched substituent is lower.[9]



Scheme 1

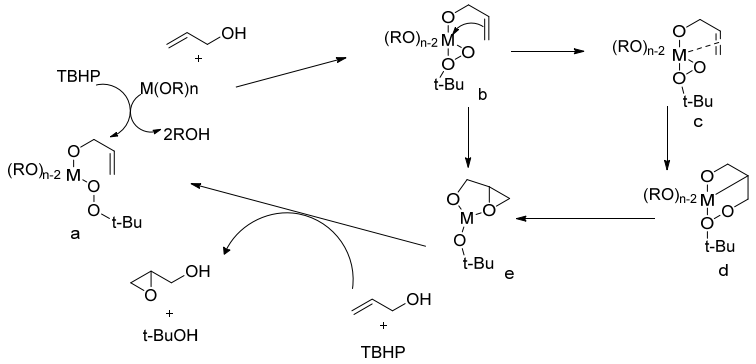


Scheme 2: Representative examples of epoxidation of allylic alcohols

Mechanism

The reaction sequence proposed for the metal-catalyzed epoxidation of allylic alcohols is shown in scheme 3.[13] Metal alkoxides generally undergo rapid ligand

exchange with alcohols. When a metal alkoxide, an allylic alcohol, and an alkyl hydroperoxide are mixed, ligand exchange occurs to afford a mixture of complexes M(OR)n-x-y-$(OCH_2CH{=}CH_2)_X$(OOR)y. Among them, only species such as '**a**', bearing both allylic alkoxide and alkyl hydroperoxide groups, are responsible for the epoxidation. The incorporated alkyl hydroperoxide is thought to be further activated by coordination of the second oxygen atom (O-2) to the metal center. The ensuing transfer of O-1 to the double bond of the allylic alcohol occurs in an intramolecular fashion is supported by comparison of the epoxidation rate of allylic alcohol with that of allyl methyl ether.[14] However controversy still surrounds the oxygen transfer process (**b-e**). One suggestion is that the double bond first coordinates to the metal center and then inserts into the μ2-alkyl hydroperoxide ligand to give an epoxide via the peroxometallocycle intermediate.[15] An alternative proposal is that the double bond attacks the distal oxygen along the axis of the O-O bond that is broken.[9,13d,15] Frontier molecular orbital treatment of peroxometal complexes also suggests that d-transition metal complexes of ROO- exhibit electrophilic behaviour.[16]



Scheme 3

Finally, exchange of *tert*-butoxide and the epoxy alkoxide so formed with allylic alcohol and alkyl hydroperoxide completes the reaction cycle. The titanium tartrate mediated asymmetric epoxidation of allylic alcohols also follows the same basic reaction pathway of **Scheme 3**. Therefore the remaining mechanistic question is how oxygen is transferred enantioselectively to substrates. To answer this question, structures of titanium-dialkyl tartrate complexes,[15,17] as well as those prepared from $Ti(O^iPr)_4$ and (*R*,*R*)-*N*,*N*'-dibenzyltartramide and from $Ti(OEt)_4$, (*R*,*R*)-diethyl tartrate, and Ph(CO)-N(OH)Ph were determined.[18] Based on the X-ray analysis of these complexes, the structure of the asymmetric epoxidation catalyst **12** (**Fig. 1**) has been proposed.

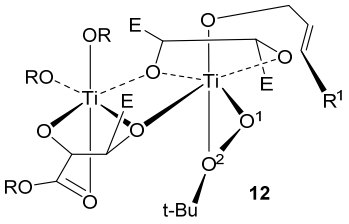


Figure 1

When structure shown in **Fig. 1** is viewed down the distal peroxide oxygen-titanium bond axis (O1-Ti), the symmetry of the tartrate "windmill arms" becomes apparent. Within this model, conformer **13** (**Fig 2**), in which the allylic alcohol and the TBHP-ligand align meridionally and the TiO-C-C=C dihedral angle is as small as 30°, has been suggested as a transition state.[9]

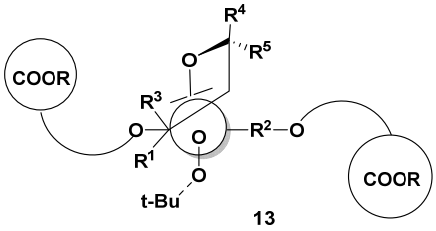


Figure 2

This conformer experiences severe steric interactions only when $R^5 \neq H$. This explains the high efficiency of kinetic resolution of racemic secondary allylic alcohols where one enantiomer (R^4 = alkyl, R^5 = H) reacts much faster than the other isomer (R^4 = H, R^5 = alkyl). The poor reactivity of *tertiary* allylic alcohols (R^4 and R^5 = alkyl) is rationalized analogously.[18] We also see that the Z olefinic substituent (R^3) is close to the hydroxymethyl group bound to titanium because of the small O-C-C=C dihedral angle. These interactions destabilize conformer **14** (**Fig. 3**) and lower the reactivity of this complex. The C-2 substituent (R^2) (**Fig. 2**) is also in the vicinity of the titanium complex, and only the E olefinic substituent (R^1) projects toward an open quadrant. This model explains following three observations.

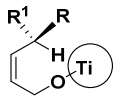


Figure 3

1. Bulky Z olefinic substituents retard epoxidation reactions, and substrate with branched Z substituents exhibit poor reactivity and decreased enantioselectivity. This may be rationalized by the conformational requirements for minimization of allylic strain due to the small C=C-C-OTi dihedral angle.[9] That is, the conformation in which H is in the plane of the olefin is energetically more accessible than the other two conformations (R and R' in-plane conformations). Thus the disposition of an alkyl group (R^1) to the bottom side raises the energy of the transition state depicted in **Fig. 3** [using (*R*,*R*) tartrate], causing retardation of the reaction and decreased enantioselectivity. When $R \neq R^1$, each enantiomer of a racemic substrate has different reactivity and treatment of such a racemic mixture with $Ti(O^iPr)_4$-tartrate affects kinetic resolution.
2. The C-2 substituent is near the Ti-tartrate moiety; its chirality also affects substrate reactivity. Thus enantiomers of a racemic substrate bearing a chiral C-2 substituent have different reactivities, and in some cases a good level of kinetic resolution is observed.
3. Except for a few examples, the E substituent, which is located in an open quadrant, has little effect on the stereoselectivity of the reaction. Therefore, the epoxidation of chiral *E*-allylic alcohols should proceed with same high level of enantioselectivity seen with achiral *E*-allylic alcohols.[19]

Since the principal difficulties (isolation of unstable and/or water soluble epoxy alcohols) with the stoichiometric reaction are mainly attributed to the mild Lewis acidity of titanium alkoxide and the aqueous workup required for hydrolysis of the stoichiometric catalyst, Sharpless discovered that addition of molecular sieves to the reaction mixture allows epoxidation to proceed to completion in the presence of only 5-10 mol% of the $Ti(OPr^i)_4$ and 6 mol% tartrate has been recommended as the most widely applicable system for asymmetric epoxidation.[20] Below the 5 mol% level, the enantioselectivity of the reaction decreases remarkably. The amount of tartrate ester must be carefully controlled, because a large excess of tartrate (>100 % excess) decreases the reaction rate while with too little tartrate (<10 % excess) the enantioselectivity may suffer.

Hydrolytic Kinetic Resolution (HKR)

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.[21] Different factors influence the practicality of an asymmetric reaction.[22] 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.[23]

Resolutions fall broadly into three classes. Classical resolutions involve the use of a stoichiometric amount of a chiral resolving agent.[24] 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.[25] 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.[26]

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[26] 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.[27] 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.[28] 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.[29] More recently, the epoxidation of unfunctionalized conjugated olefins by chiral (salen)Mn^{III} complexes has enabled the practical synthesis of certain classes of enantiomerically enriched epoxides.[30] 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.[31] Indirect routes to enantiopure epoxides involving asymmetric catalytic dihydroxylation or reduction reactions have also proven highly valuable in specific contexts.[32] 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.[33] 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[34] or by enzymatic kinetic resolution methods,[35] and these compounds have become widely used starting materials for target-oriented synthesis.[36] 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 **15** (Figure 4) catalyzed efficient hydrolytic kinetic resolution (HKR) of a variety of terminal epoxides (Scheme 4).[37-39] 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 **15** had previously been commercialized and manufactured on a ton scale in the context of (salen)Mn

epoxidation catalysts.[40] The cobalt analogues (*R*,*R*)-**15** and (*S*,*S*)-**15** proved equally accessible, and these are also now available in bulk.[41] 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.[42] 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.[43]

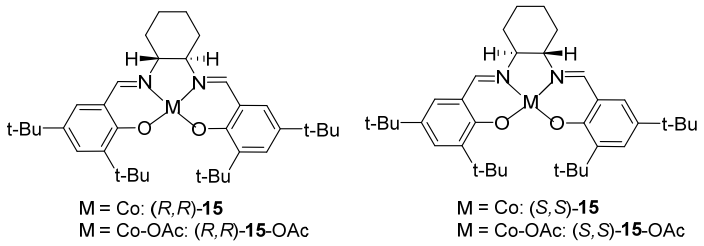
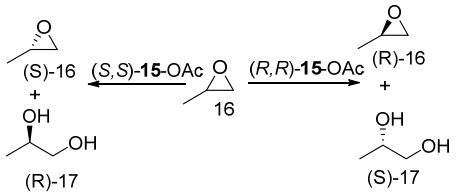


Figure 4: Jacobsen catalyst

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.[44] 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



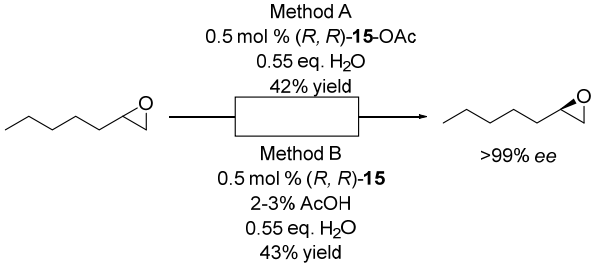
Scheme 4: Hydrolytic kinetic resolution reaction

useful chiral building blocks.[41] Jacobsen has discovered that the HKR is an extraordinarily general reaction, allowing efficient kinetic resolution of virtually any type of terminal epoxide.

Preparation of Catalyst and General Experimental Considerations

Both enantiomers of the (salen)Co^{II} complex **15** are available commercially on research or commercial scale,[41] or they can be prepared from the commercially

available ligands using $Co(OAc)_2$. The Co^{II} complex **15** is catalytically inactive, however, and it must be subjected to one-electron oxidation to produce a (salen)CoIII -X 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 **15**.OAc is convenient for use in HKR reactions both in terms of its preparation and reactivity. Two useful methods for the generation of complex **15**.OAc have been developed. Method A involves isolation of **15**.OAc as a crude solid prior to the HKR. The Co(II) complex **15** 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 **15**.OAc as a brown solid residue that can be used without further purification. Method B involves in situ generation of **15**.OAc under HKR conditions by suspension of the Co(II) complex **15** 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 5

Aside from the method of generation of **15**.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*)-15).

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*)-**15**) (11.6 g, 19.2 mmol, 96%).

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*)-**15** (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).

(b) Method B. (*R*)-1,2-Epoxy-5-hexene. A 100 mL flask equipped with a stir bar was charged with (*R,R*)-**15** (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).

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 **15** 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 **15**. Reoxidation to **15**.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.

Proline catalyzed asymmetric organic transformations

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'.[45] 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[46] introduced a system of classification based on the mechanism of catalysis (Figure 5). The four categories are Lewis base, Lewis acid, Brönsted base and Brönsted 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. Brönsted base and acid catalytic cycles are initiated via a (partial) deprotonation or protonation, respectively.

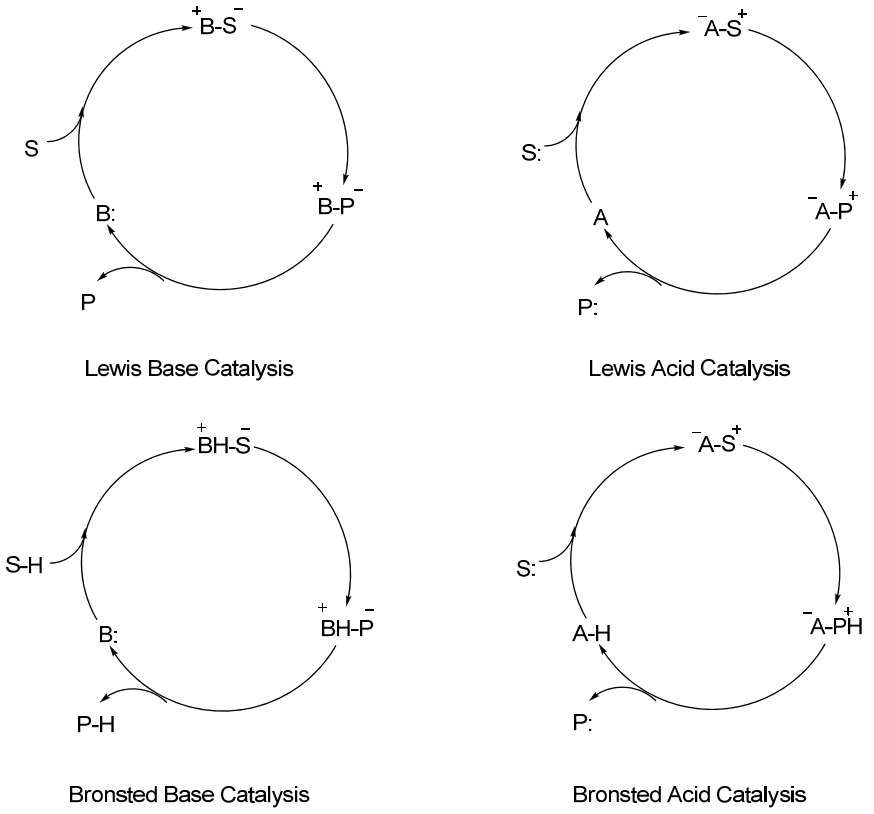


Figure 5: Organocatalytic cycles

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 Brönsted acid (Figure 6). 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.

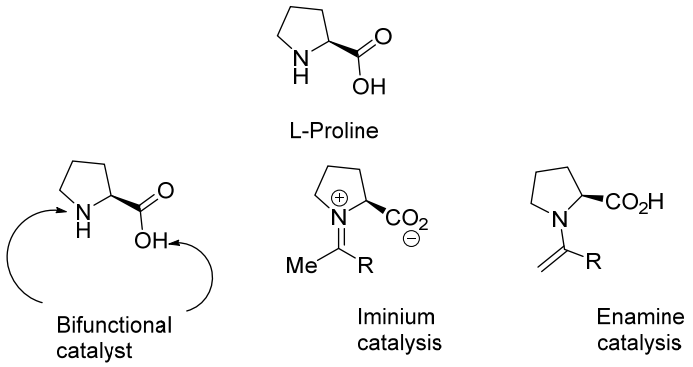


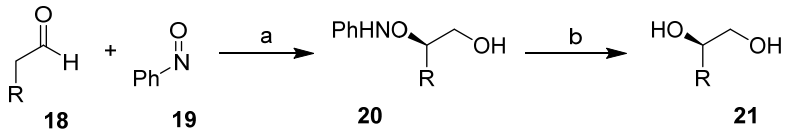
Figure 6: Modes of proline catalysis

It is known to catalyze aldol,[47] Diels-Alder,[48] Michael addition[49] and α-functionalization[50] among many other organic transformations.[51] Particularly proline-catalyzed α-aminoxylation[52] and α-amination[53] of carbonyl compounds have emerged as powerful methods because chiral building materials can be synthesized in effective manner starting from easily available materials.

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,[54a] Sharpless dihydroxylation of enol ethers,[54b] manganese–salen epoxidation of enol ethers,[54c] and Shi epoxidation of enol ethers.[54d] It is only rather recently that direct catalytic, asymmetric variants have been reported.[55] 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[52] of carbonyl compounds. When an aldehyde **18** without substitution at α-position was reacted with nitrosobenzene **19** 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 **21** in very high enantioselectivities (Scheme 6).



Scheme 6: *Reagents and conditions*: (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 7. The observed enantioselectivitiy of the catalytic α-aminoxylation of aldehydes can be rationalized by 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.

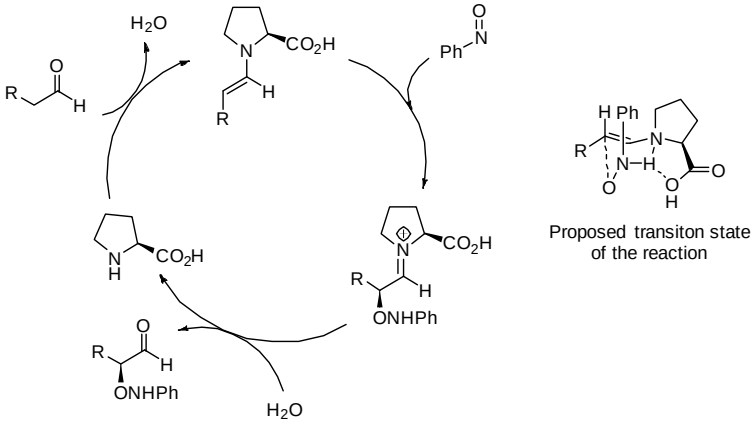
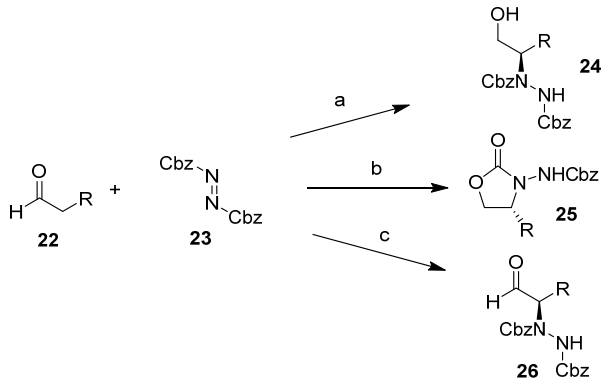


Figure 7: Proposed mechanism of the α-aminoxylation reaction

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.



Scheme 7: *Reagents 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.

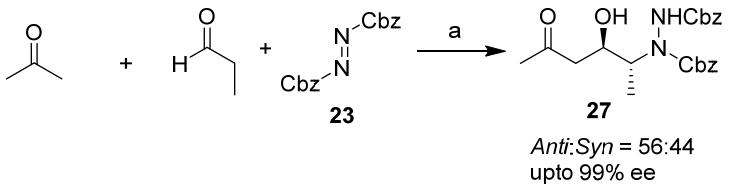
Asymmetric α-amination[53] of aldehydes using proline-catalyzed reactions represent a direct approach synthesizing chiral building blocks such as α-amino acids, α-amino aldehydes, and α-amino alcohols. The use of organocatalysis, in particular proline represents a drastic change in approach to asymmetric α-amination. Recently, both List[53a] and Jørgensen[53b] disclosed the asymmetric α-amination of aldehydes (Scheme 7) using catalytic quantities of proline. 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.

Proline-catalyzed sequential transformations

Proline-catalyzed sequential transformations,[56] 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[56a]

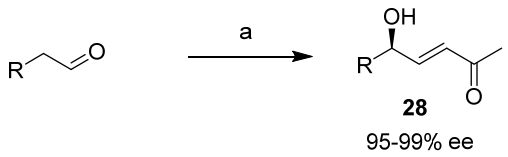
Barbas III *et al*. have developed a one-pot protocol for the synthesis of functionalized β-amino alcohols **27** from aldehydes, ketones and azodicarboxylates (Scheme 8).



Scheme 8: *Reagents and conditions*: (a) L-proline (20 mol%), CH_3CN, rt, 72 h, 80%.

Sequential aminoxylation-olefination[56b]

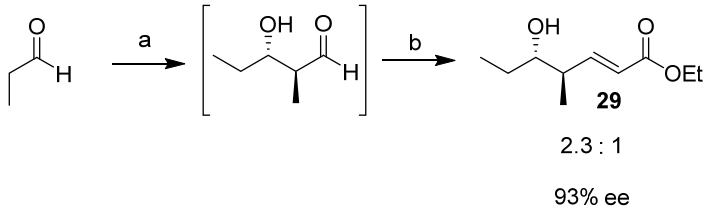
Zhong *et al*. have reported sequential asymmetric α-aminoxylation/Wadsworth-Emmons-Horner olefination of aldehydes for the synthesis of optically active *O*-amino-substituted allylic alcohols **28** in good enantioselectivities using cesium carbonate as base (Scheme 9).



Scheme 9: *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[56c]

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 10).

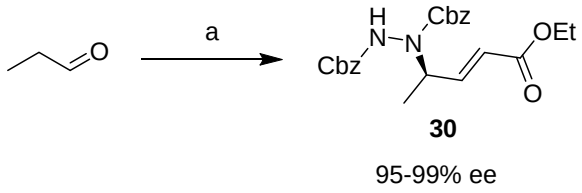


Scheme 10: *Reagents and conditions*: (a) L-proline (10 mol%), DMF; (b) Diethyl(2-oxopropyl)phosphonate, cesium carbonate (1.5 equiv.).

Apart from this transformation, Cordova *et al*. have also reported tandem Mannich olefination reaction.[56d]

Sequential α-amination-olefination[56e]

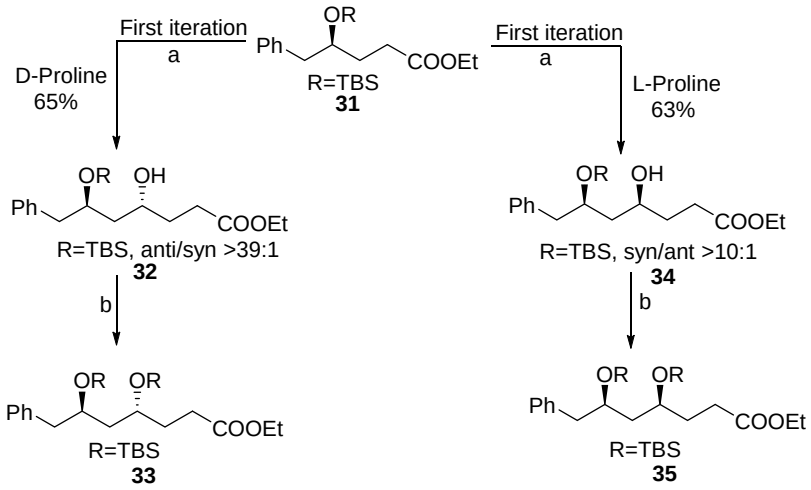
Sudalai *et al*. have reported sequential asymmetric α-amination/Wadsworth-Emmons-Horner olefination of aldehydes for the synthesis of optically active allylic amine in good enantioselectivities and yields (Scheme 11).



Scheme 11: *Reagents 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.).

An organocatalytic approach to *syn*- and *anti*-1,3-polyols[56f]

Recently, Zhong *et al*. have reported an α-aminoxylation directed tandem reaction catalyzed by proline which involves a sequential α-aminoxylation, HWE-olefination reaction at ambient temperature furnishing *O*-amino-substituted allylic alcohol from readily available achiral aldehydes. We envisioned that this reaction could give us stereocontrolled synthetic access to 1,3-polyol motifs. We have developed proline catalyzed new enantioselective approach to synthesize both syn/anti-1,3-polyols by tandem α-aminoxylation and HWE olefination of aldehyde.[56f] Our iterative strategy for the synthesis of polyols is outlined in Scheme 12.



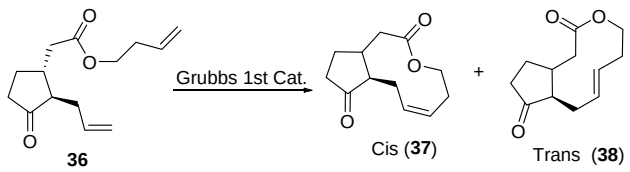
Scheme 12. *Reagents and Condition*s: (a) (i) DIBAL-H, -78 °C; (ii) Nitroso benzene, D/L Proline, DMSO, HWE salt, DBU, LiCl, CH_3CN; (iii) H_2/Pd-C, EtOAc; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2.

Ring closing metathesis (RCM)

Introduction

The ring closing metathesis has emerged as a powerful tool for organic synthesis and extensively employed in the construction of medium and large ring structures with multiple functionalities. The efficiency of this method is demonstrated by the syntheses of a large number of natural products including ten-membered lactones.

A typical example that illustrates the efficiency as well as the limitation of RCM in this area is a synthesis of jasmine ketolactone,[57] RCM reaction on diene with high dilution by using Grubbs first-generation catalyst affords the targeted ten-membered lactones as a mixture of *cis* and *trans* isomers (2.5:1) in remarkable yield.



36 Cis (**37**) Trans (**38**)

Over the past ten years, the area of olefin metathesis that has expanded most dramatically is the catalytic ring-closing metathesis (RCM).[58] RCM has developed into a versatile synthetic tool for carbon-carbon double bond construction. In particular, medium (5-8) to large (10-13 and higher) carbon or heterocyclic rings can be very effectively constructed, and thus RCM became a reliable tool for synthesis of the natural products and spurred the synthesis of even more varied structural variants.

The word metathesis is derived from Greek word meta (change) and thesis (position). Metathesis is the exchange of parts of two substances or interchange of covalent bonds between two molecules. In the generic reaction, AB + CD → AC + BD, B has changed position with C. An example is olefin metathesis. It refers to the redistribution of alkylidene moieties between two alkenes in the presence of a catalytic amount of a metal carbene. A compound with a C=C double bond, in which the strongest bond in an alkene is broken and remade. The 2005 Nobel Prize in Chemistry was awarded to Yves Chauvin, Robert H. Grubbs and Richard R. Schrock for development of the metathesis method in organic chemistry. History of transition metal-catalyzed olefin metathesis was discovered in the 1950's by industrial chemists at DuPont, Standard oil, and Phillips petroleum (H. S. Eleuterio, E. F. Peters, B. L.

Evering, R. L. Banks, and G. C. Bailey) who reported that propene reacted to form ethylene and 2-butenes when passed over molybdenum on alumina catalyst at high temperature. Olefin metathesis catalyzed by carbene complex has been known in polymer chemistry for 40 years. However, the reaction has been limited to simple, unfunctionalized olefin. After development of new catalyst by Schrock and Grubbs, chemists realized the potential utility of this methodology in organic synthesis.

Olefin metathesis has been utilized in three closely related types of reactions.

a) Ring opening metathesis polymerization (ROMP):

In which a cyclic olefin is the substrate and a polymer is the product. ROMP is the thermodynamically favored for strained ring system, such as 3-, 4-, 8-and large-membered compound (Figure-8).

Figure 8

b) Ring-closing metathesis (RCM):

Acyclic diene is converted into cyclic olefin, in which a loss of ethylene takes place (Figure-9).

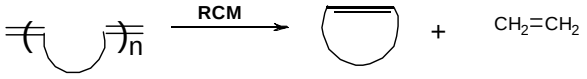


Figure 9

c) Cross metathesis

Two different olefins react to form a new product olefin and a by-product as a volatile olefin (usually ethylene).

Figure 10

Another variant of the reaction is the metathesis of an alkene and an alkyne, popularly known as enyne metathesis (EM).

Although a number of catalyst have been developed for metathesis and related reactions, the Schrock's catalyst, Hoveyda-Grubbs catalyst, Grubbs 1st and 2nd generation catalyst, the distinct catalysts shown in figure 8 and 9 have been used widely for olefin metathesis reaction.

Titanium and tungsten-based catalyst have been also developed but are less used. Schrock's alkoxy imidomolybdenum complex is highly reactive toward a broad range of substrate; however, this Mo-based has moderate to poor functional group tolerance, high sensitivity to air, moisture or even to trace impurities present in solvents and exhibits thermal instability.

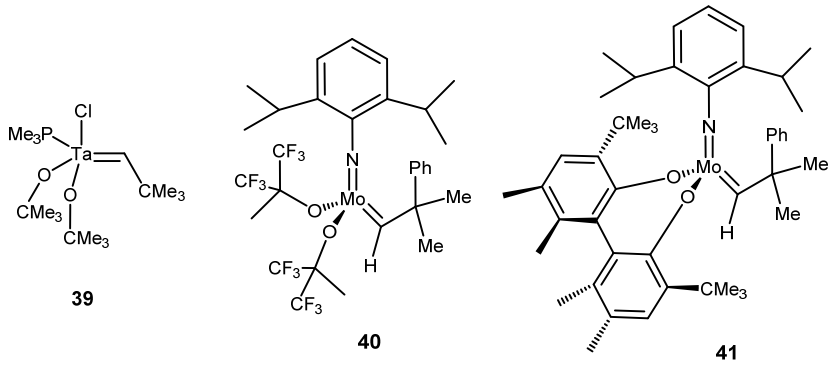


Figure 11: Tantalum and molybdenum metathesis catalyst

In particular, the ruthenium-based catalyst (Grubbs 1st and 2nd generation) have been used extensively in organic and polymeric chemistry due to its high reactivity with olefin substrate in presence of most common functional groups. Homogeneous Ruthenium catalysts are (generally) stable, more selective and highly active at mild condition. It has superior activity over other cyclization methods like macrocyclization, Diels-alder etc., and adaptable for both solution and solid phase reactions.

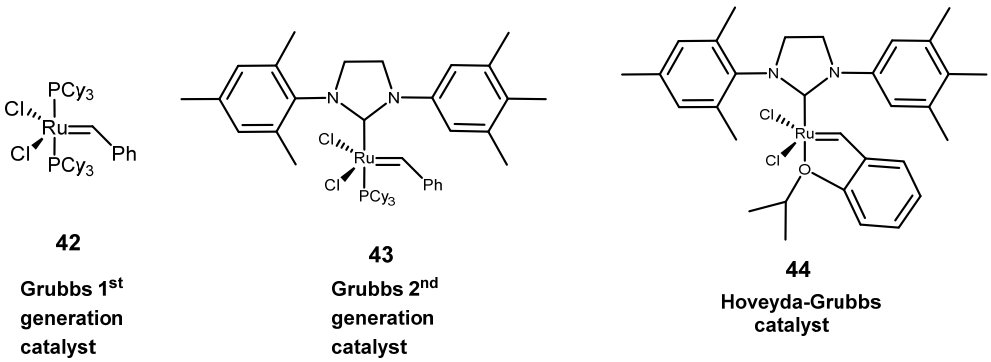


Figure 12: Ruthenium based metathesis catalyst

The construction of a 10-membered ring is by using RCM was first reported by Frustner and Muller in 1997 for the synthesis of Jasmine ketolactone (**37** & **38**). Frustner also synthesized herbarium I and herbarium II by RCM strategy.

RCM Mechanism:

The mechanism of the RCM reaction has been extensively studied both experimentally and theoretically. It is now well accepted that, during the reaction the

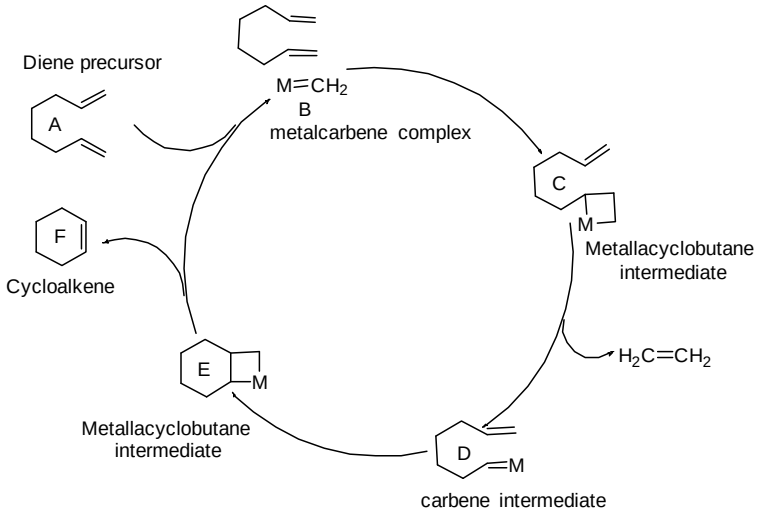


Figure 13: RCM mechanism

catalytically active metalacarbene complex such as [M] = CH_2 (**B**) is formed from the diene precursor (**A**) (figure-13) and the overall reaction mechanism involves, effectively, a series of alternating [2+2] cycloadditions. Metallacyclobutane intermediate such as (**C**) is formed, which opens in retro [2+2] fashion to form the carbene (**D**) as intermediate. The latter then undergoes re-cyclization to form the new metallacyclobutane (**E**), which analogously open to the product cycloalkene (**F**) and catalyst is regenerated. The mechanism is depicted schematically in figure-13. The equilibrium is continuously shifted towards the cycloalkene, due to the release of a volatile olefin (usually ethylene).

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42. While it may be assumed that an "ideal" resolution would involve no added reagents i.e., an enantiomer undergoing selective isomerization or polymerizations the rate of such transformation may be difficult to control because of the exothermicity ($\not{\epsilon}E$ > 30 kcal/mol) associated with epoxide ring opening. This is a special concern with reactions carried out on a large scale. The fact that the rate of nucleophile addition can be adjusted to control reaction rate therefore has significant practical advantages.
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Studies directed towards the synthesis of Stagonolide C and Modiolide A

Introduction

Weeds, diseases, and infestations by insects have always been major threats in the agricultural and environment, often giving rise to life-threatening periods of famine or causing serious food poisoning in vast parts of the world population. The effort to control weeds is as old as agriculture itself. Humans, however, were familiar with weeds even before the dawn of agriculture, as several aboriginal nomadic tribes suffered from allergies, hay fever, and other health problems caused by poisonous plants. The control of weed diffusion has been achieved with agrochemicals belonging to different class of organic compounds.

Extracts of plants containing chemicals of potential herbicidal activity have been used to different degrees over the years and often not in a systematic way. The first modern organic herbicides were introduced in the early 1943. The use of DDT[1] as an insecticide, the plant hormone-based phenoxy-acetic acid derivatives as herbicides,[2] organophosphates,[3] and some time later the carbamates as insecticides[4] and thiram as a fungicide[5] appeared in the market in the quantum progress.

Weeds are plants that are competitive, persistent, pernicious, and interfere negatively with the production and quality of crops and in certain situation with human activity. These are troublesome in many ways. Many plants of agricultural interest may dieback when the weed grows in the same field absorbing water, light, soil nutrients, space and carbon dioxide. Besides the agriculture field and roadside blockage, weeds are widespread through wetland habitats causing displacement of native plants, which are important for source of food and shelter for wildlife. Ecological process, such as oxygen production, may also change because invasive plants affect water chemistry and flow. Unrestricted invasion can block drainage pipe, impede navigation and hinder commercial and recreational fishing.

Since weeds are so prevalent in wide area of agricultural field, forest and wetland, and causing the damage of human resources, appropriate management techniques are required. The common methods to stop weeds include prevention, culture mechanical, biological and chemical means. Of these, chemically weed control is well-established technology to support sustainable production of crop and play a valuable role in agribusiness. The chemicals used effectively to kill weedy plant or interrupt the plant normal growth are commonly known as herbicides. They provide a convenient,

economical and efficient way to manage the crop production by selective destruction of noxious harmful plants.

Although a plethora of synthetic organic herbicides[6] are well established in the marketplace for long time to control different species of weeds, a number of serious disadvantages are associated with these. Conventional herbicides contain chemicals that contribute to a variety of adverse effects. These toxic chemicals are carcinogens that have been linked to health problems such as lymphoma, genetic damage, reproductive effects and heart-related issues. Chemical compounds are breathed in during or after spraying and can also be absorbed through the skin as a result of direct contact. Access must be restricted to areas treated with chemical herbicides. Furthermore, toxic chemicals from herbicides may seep into groundwater as a result of rain, runoff, watering the area or soil absorption. These herbicides also kill beneficial soil microbes; thus disrupting the normal condition of the soil.

So, considering the aforesaid limitations of synthetic organic chemicals as herbicides, alternative approaches are gaining increased platform to control weed in environmentally safe way. Plants produce hundreds of thousands of compounds that are not involved in the primary metabolism of the plants; the compounds involved in interspecific chemical interaction called allelopathy[7] with higher plants are often phytotoxic or herbicidal to other species or even to the species producing them. The importance of allelopathy in nature and in agroecosystem has attracted researcher's attention with the main goal of using the phenomenon in biological control of weeds. Currently, active involvement of scientist from different disciplines made allelopathy a multidisciplinary subject and transformed the research from basic to applied, enabling use of allelopathy in agriculture and forestry.

There are various examples of alleochemicals; these phytotoxic compounds released from plant are used as natural source of herbicides. Phytotoxic compounds from plants and microorganisms represent a wide range of chemistries and mechanism of action that have potential in the design and development of new herbicides. Some of light-activated compounds (photosensitizers)-naphtho and anthraquinones produced by fungi and higher plants, quinine and isoquinoline alkaloids are potentially useful for herbicides. Terpenoids, monoterpenes, sesquiterpenes lactones and triterpenes and fatty acids also show promising herbicidal activity.

Cyanobacterin **1**[8] produced by the filamentous, freshwater cyanobacterium Scytonema hofmanni inhibits photosynthesis and causes extensive damage to the thylakoid membranes of the chloroplasts. With a spectrum of activity encompassing species of cyanobacteria and eukaryotic algae as well as higher plants, cyanobacterin might be utilized as a commercial algicide. Bilanafos **2**[9], a tripeptide from Streptomyces hygroscopicus (Figure 1), which degrades to phosphinothricin in target plants, is the only commercial herbicide produced by biosynthesis.

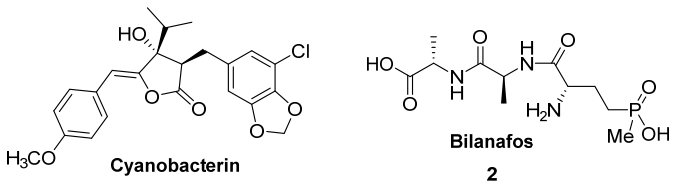


Figure 1

Similarly, rhizobitoxine,[10] a compound produced by the bacterium *Rhizobium japonicum* is an effective herbicide in amounts as low as 3 ounces/acre. Cinmethylin,[11] a potential herbicide is a product based on 1,8-cineole produced by *Salvia* species (sage). Like insects, weeds can develop resistance when continually selected by a single herbicide or group of herbicides having the same mechanism of toxic action. Weeds develop resistance in one of the two ways. Firstly, a few individuals in a population may possess a gene that enhances metabolic detoxification reactions, thereby breaking down the herbicides fast enough to avoid its phytotoxicity. The second and more prevalent method is the occurrence of some individuals with a gene that alters the biochemical target site of herbicides, making the plant resistant to injury. In either case, if these infrequent individuals escape control and successfully go to seed, comparatively more of these resistant individuals will occur in the population during the next growing cycle. Eventually, most of the population will be resistant to the herbicide.

So continuous searching and synthesis of natural products and their analogues with potent herbicidal activity, their mode of activity and their structure activity relationships is genuinely a new era of research for weed management.

Recently searching for herbicidal agent form fungus stagonospora cirsii isolated from Crisium arvense, main metabolite Stagonolide A with interesting phytotoxic properties was isolated[12a] form a liquid culture and characterised as a new nonenolide. Five new nonenolides named Stagonolide B-F[12b] and Modiolide A[12b,c]

were isolated and characterised using spectroscopic methods which showed varied phytotoxic properties (figure 2).

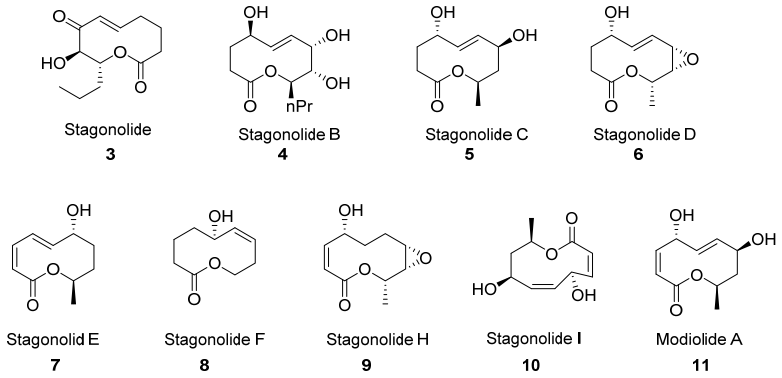


Figure 2: Stagonolide family

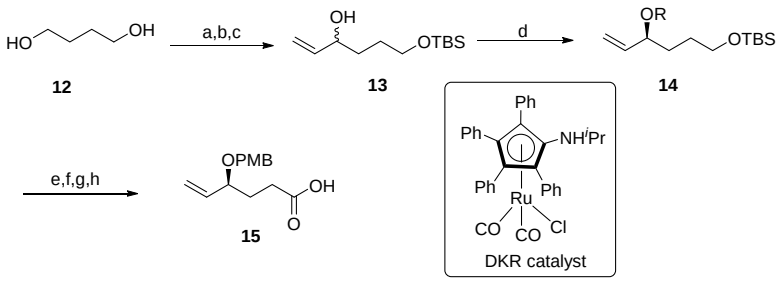
Tested by leaf disc-puncture assay at the concentration 1 mg/ml, stagonolides B–F show no toxicity to *C. arvense* and *S. arvensis* whereas stagonolide was highly toxic to both plants. Stagonolide and stagonolide C were low toxic to *Colpoda steinii* (*Protozoa*) tested at 0.05 mg/ml, other stagonolides were non-toxic. Stagonolides H-I and modiolide A, tested on *Cirsium arvense* in the same conditions reported above, had different phytotoxic activities. Stagonolide H was the most toxic to the leaves of *C. arvense*, stagonolide I and modiolide A were less active. Modiolide A exhibited strong phytotoxicity on radish leaves (necrotic lesion diameter ~ 7 mm, 72 h post application) whereas other plants tested were significantly less sensitive to the toxin (necrotic lesion diameter < 2.5 mm).

Review of literature

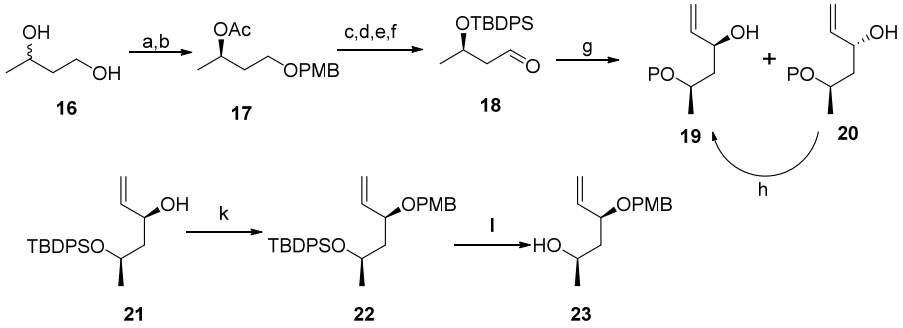
Many naturally occurring ten-membered lactones isolated from fungal metabolites, commonly known as decanolides, have attracted considerable attention from synthetic organic chemists as well as bioorganic chemists, because of their interesting structural features and various biological activities. A few interesting syntheses of stagonolide C are described below.

Nanda *et al.*[13]

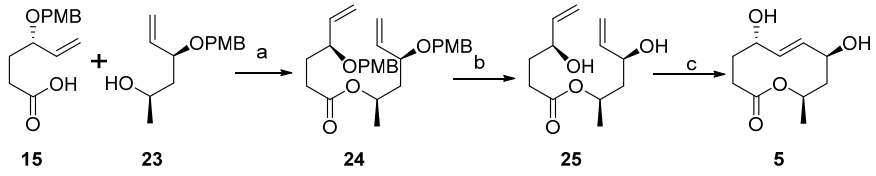
Nanda described the chemo-enzymatic asymmetric total synthesis of stagonolide C. A metal–enzyme combined DKR strategy was successfully applied to access two advanced intermediates **15** and **23**. Coupling of these two intermediates followed by ring-closing metathesis with Grubbs-second generation catalyst afforded the target molecule.



Scheme 1: *Reagents and conditions:* (a) NaH, TBSCl, 90%; (b) $(COCl)_2$, DMSO, Et_3N, -78 ^oC, 88%; (c) Vinylmagnesium bromide, -78 ^oC, 82%; (d) CAL-B, isopropenyl acetate, chlorodicarbonyl(1-(isopropylamino)-2,3,4,5-tetraphenylcyclopentadienyl) ruthenium(II), K_2CO_3, KO^{t}Bu 90%; (e) K_2CO_3, MeOH, 94%; (f) PMBO–(C=NH)–CCl_3, CSA, 85%; (g) PPTS, MeOH, 88%; (h) PDC, DMF, 72%.



Scheme 2: *Reagents and conditions*: (a) NaH, PMBBr, TBAI (cat), 80%; (b) CAL-B, isopropenyl acetate, chlorodicarbonyl(1-(isopropylamino)-2,3,4,5-tetraphenylcyclopentadienyl ruthenium (II), K_2CO_3, KO^{t}Bu, 92%; (c) K_2CO_3, MeOH, 90%; (d) imidazole, TBDPSCl, 95%; (e) DDQ, DCM/H_2O (19:1), 86%; (f) $(COCl)_2$, DMSO, Et_3N, -78 ^oC, 92%; (g) Vinyl MgBr, -78 ^oC, 80%; (h) TPP, DIAD, $PhCO_2H$, NaOH, 90% in two steps; (k) PMBO-(C=NH)-CCl_3, CSA, 82%; (l) TBAF, THF, 90%.

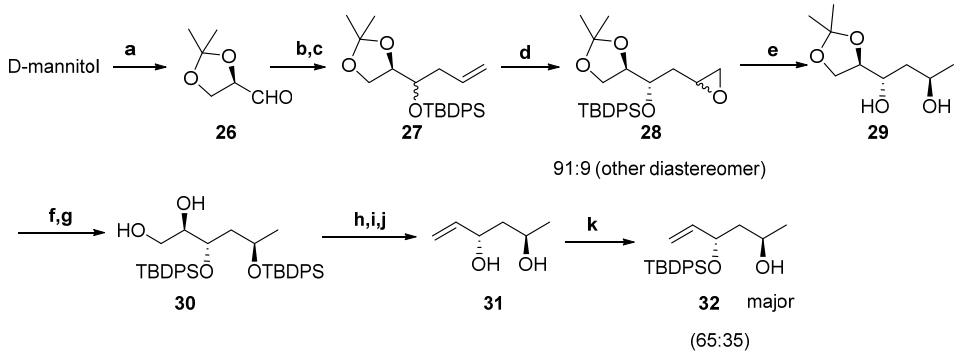


Scheme 3: Reagents and conditions: (a) EEDQ, THF, 92%; (b) DDQ, CH_2Cl_2/H_2O (19:1), 85%; (c) Grubbs-II, CH_2Cl_2, 66%.

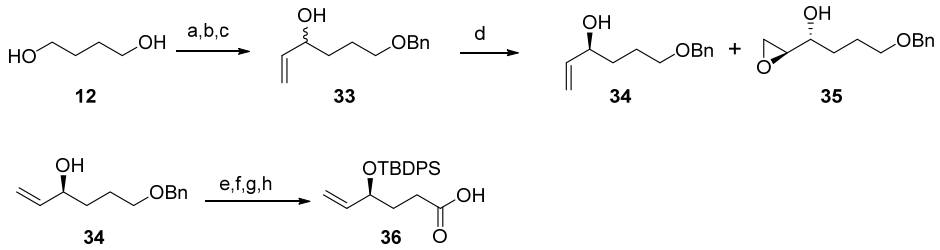
Nagaiah *et al.*[14]

Nagaiah reported the stereoselective synthesis of stagonolide C. The pivotal functionalities are derived from Barbier allylation, an epoxidation by m-CPBA, a

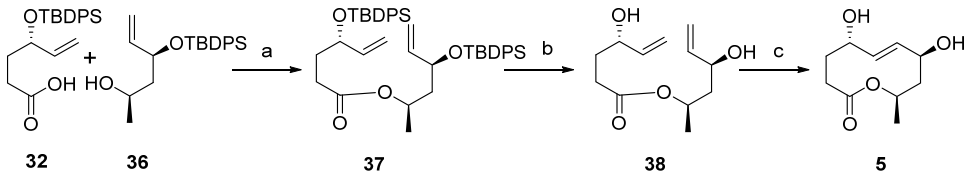
chiral-auxiliary mediated acetate aldol addition, a 1,3-*anti*-reduction, a Sharpless kinetic resolution, a Yamaguchi macrolactonization, and ring-closing metathesis.



Scheme 4: *Reagents and conditions* : (a) Ref. 15 (b) Zn, Allyl bromide, THF, 88% (c) TBDPSCl, imidazole, CH_2Cl_2, 95% (d) *m*-CPBA, CH_2Cl_2, 88% (e) DIBAL, -78 ^oC CH_2Cl_2, 82% (f) TBAF, THF, 92% (g) TBDPSCl, imidazole, CH_2Cl_2, 92% (h) PPTS, MeOH, 86% (i) (i)TPP, I_2, imidazole, toluene, Reflux, 10% (ii) Zn, DMF, Reflux, 86% (j) TBAF, THF, 91% (k) TBDPSCl, imidazole, 90%



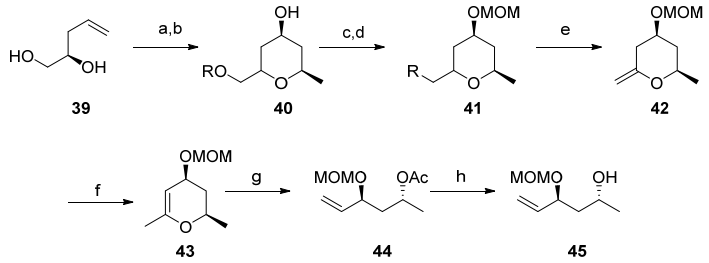
Scheme 5: *Reagents and conditions:* (a) NaH, BnBr, TBAI (Cat.), 90%; (b)PCC, CH_2Cl_2, 92%; (c) Vinylmagnesium bromide, THF, -78 ^oC, 88%; (d) (-)-DET, $Ti(O^iPr)_4$, TBHP, CH_2Cl_2, 4 Å, MS, -20 ^oC, 6 h, 46%; (e) TBDPSCl, imidazole, CH_2Cl_2, 95%; (f) DDQ, CH_2Cl_2:H_2O, reflux 90%; (g) PCC, NaOAc, CH_2Cl_2, 90%; (h) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O, 92%



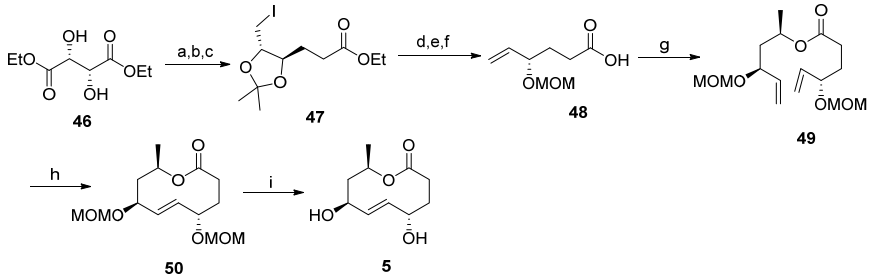
Scheme 6: *Reagents and conditions:* (a) 2,4,6-trichloro benzoyl chloride, Et_3N, THF, DMAP, 0 °C rt, 14 h, 86%; (b) HF/pyridine, Pyridine, THF, 0 °C to rt, 8 h, 84%; (c) Grubbs-II, CH_2Cl_2, reflux, 24 h, 68%

Yadav *et al.*[16]

Yadav described a flexible, efficient synthesis of stagonolide C, involving Prins cyclization and RCM as the key steps.



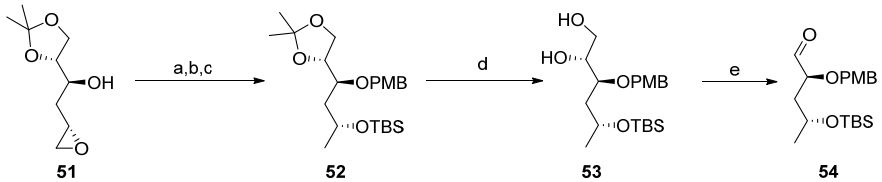
Scheme 7: *Reagents and conditions:* (a) MeCHO, CF_3COOH,CH_2Cl_2, then K_2CO_3, MeOH, r.t, 5 h, 55%; (b) TsCl, Et_3N, CH_2Cl_2, 0 ^oC to r.t., 3 h, 90%; (c) $MeOCH_2Cl$, $^iPr_2EtN$, CH_2Cl_2, 0 ^oC to r.t., 6 h, 94%; (d) NaI, acetone, reflux, 24 h, 95%; (e) NaH, DMF, r.t., 6 h; (f) SiO_2, 72%; (g) O_3, Ph_3P, CH_2Cl_2, then $Ph_3P{=}CH_2$, THF, -78 to 0 ^oC, 74%; (h) K_2CO_3, MeOH, r.t., 2 h 96%.



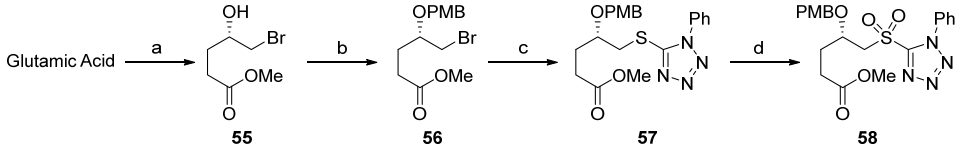
Scheme 8: *Reagents and conditions:* (a) Ref. 17; (b) H_2, Pd/C, AcOEt, reflux, 2 h, 90%; (c) I_2, Ph_3P, 1*H*-imidazole, THF, 0 ^oC to r.t., 4 h, 80%; (d) Zn, EtOH, reflux, 2 h 86%; (e) $MeOCH_2Cl$, $^iPr_2EtN$, DMAP (cat.), CH_2Cl_2, 0 ^oC to r.t., 3 h, 82%; (f) 2N NaOH, MeOH, r.t., 6 h, 85%; (g) **45**, DCC, DMAP, CH_2Cl_2, 0 ^oC to r.t., 2 h; 80%; (h) Grubbs II-gen. catalyst, CH_2Cl_2, reflux, 24 h, 60%; (i) Me_3SiBr, CH_2Cl_2, -40 ^oC, 15 min, 76%.

Qiao *et al.*[18]

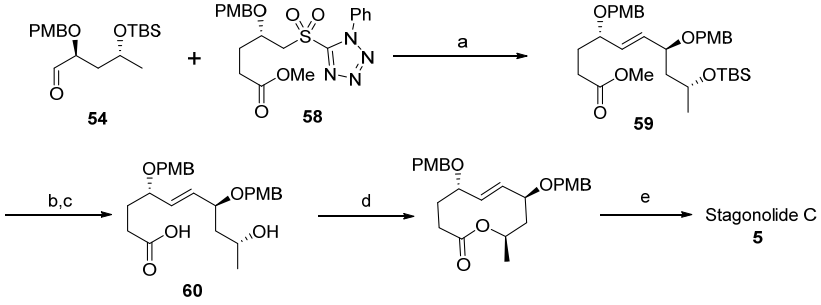
This protocol involved the utilization of previously developed chiral epoxide intermediate, Julia–Lythgoe coupling of two fragments and Yamaguchi esterification for intramolecular cyclization to achieve total synthesis of the target compound. This synthesis exemplified the usage of Mulzer epoxide as chiral building block.



Scheme 9: *Reagents and conditions*: (a) NaH, PMBCl, 86%; (b) $LiAlH_4$, 96%; (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 100%; (d) 50% TFA, CH_2Cl_2, 50%; (e) $NaIO_4$, THF/H_2O, quant.



Scheme 10: *Reagents and conditions*: (a) Ref.19; (b) PMBO-(C=NH)-CCl_3, PPTS, CH_2Cl_2, 70%; (c) 1-Phenyl-5-mercapto-tetrazole, K_2CO_3, Acetone, 84%; (d) *m*-CPBA, CH_2Cl_2, 82%



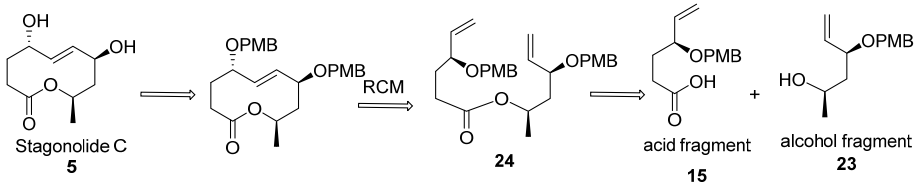
Scheme 11: *Reagents and conditions*: (a) NaHMDS, HMPA, -78 ^oC, 60%; (b) MeOH, CSA, 90%; (c) LiOH, 98% (d) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, then DMAP, Benzene, 63%; (e) CAN, $MeCN:H_2O$ (10:1), 100%

Studies towards the synthesis of Stagonolide C

Stagonolide C (**5**) and modiolide A (**11**) were isolated by Evidente *et al.* from the solid cultures of *Stagonospora cirsii* (a pathogen of *Cirsium arvense*) along with the four other new nonenolides.[12] The connectivity of the free hydroxyl groups and their relative orientations in stagonolides was proposed by correlating their spectral data with the previously reported natural products herbarumins data. Stagonolide C and modiolide A present a 2*E*-ene- 1,4-*trans*-diol unit which we have identified as one of the tough task to construct by employing ring closing metathesis based upon earlier observations.[20] As a part of our research programme aimed towards the synthesis of 10- or 12- membered macrocyclic lactones, we considered developing a new approach to the synthesis of stagonolide C. Now we describe our efforts towards the total synthesis of stagonolide C.

Retrosynthetic strategy for stagonolide C:

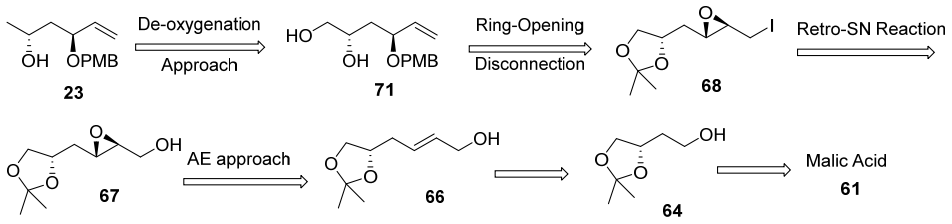
Our retrosynthetic approach and strategy is delineated in scheme 12, it involves a key disconnection of the double bond producing the diene ester synthon. Strategic bond disconnection in ester **24** leads to alcohol fragment **15** and acid fragment **23**.



Scheme 12: Retrosynthetic strategy

Retrosynthetic strategy for the alcohol fragment 23: The alcohol fragment **23** could be synthesized from the diol **71** through deoxygenation reaction. The diol **71** was envisaged to arise from epoxy methanol through base mediated ring opening of epoxymethyl iodide **68** and after simple functional group transformation. Appropriate oxidation/reduction reactions and C=C Wittig disconnections would imply the alcohol **64**, which could be conceivably synthesized from L(+)-malic acid through regioselective transformations. Our choice of chiral malic acid (**61**) over the racemic one (as the inherent chirality of the starting material has no relevant role in the synthetic sequence and is destroyed in the final step) was to ensure complete

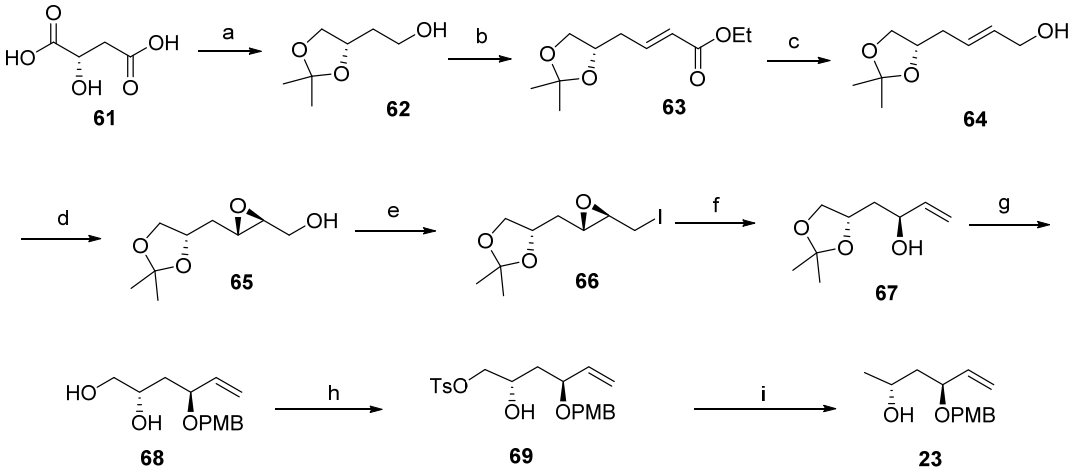
characterization of the intermediates and to avoid any misleading diastereomeric product in the Sharpless asymmetric epoxidation (Scheme 13).



Scheme 13: Retrosynthetic route to the alcohol fragment

Syntheses of alcohol fragment (23)

The synthesis of the alcohol fragment **23** began with conversion of L-(+)-malic acid (**61**) into alcohol **62** using known procedure.[21] Having the primary alcohol **62** in hand, two carbon extension to the carbon back bone was planned next. The hydroxyl group was oxidized by IBX, DMSO. The aldehyde thus obtained was quickly exposed to stable Wittig ylide (ethoxycarbonylmethylene)triphenylphosphorane in refluxing benzene for 2-3 h to furnish two chromatographically separable products. Reductive transformation of the *E* olefin **63** was next achieved selectively with DIBAL-H in CH_2Cl_2 at -78 °C. In PMR spectrum, resonances of olefinic protons moved upfield and were observed in the region 5.58-5.78 ppm as multiplets.



Scheme 14 : *Reagents and conditions:* (a) Ref. 21; (b) (i) IBX, DMSO, THF; (ii) $PPh_3CHCOOC_2H_5$, THF, reflux, 70 %; (c) DIBAL, CH_2Cl_2, -78^oC, 1 h,75%; (d) (+)-DET, $Ti(O^iPr)_4$, TBHP, CH_2Cl_2, 12 h, 80%; (e) TPP, imidazole, iodine, CH_2Cl_2, 75%; (f) Zn, Ethanol, reflux, 81%; (g) (i) NaH, PMBCl, DMF, 0 ^oC to rt, 3 h; (ii) MeOH, PTSA, 91% ; (h) TsCl, Bu_2SnO, CH_2Cl_2, 12 h, 70%; (i) LAH, THF, 1 h, 77%

Now the platform was set for a Sharpless asymmetric epoxidation[22] that would install the chiral center relevant to the target. Thus, catalytic asymmetric epoxidation of appropriate precursor **64** was conducted at -20 °C with *t*-butyl hydroperoxide as oxo donor and $Ti(O^iPr)_4$-[(+)-DET] complex as chiral adjuvant in anhydrous CH_2Cl_2 in presence of activated 4Å molecular sieves powder to afford (2*S*, 3*S*)-epoxide **65** in 80% yield. The epoxy alcohol **65** gave satisfactory spectral data with singular peaks indicating single diastereomer formation. The ^{1}H NMR spectrum illustrated new resonances attributed to methine protons of epoxide at 3.60 ppm (dd, 1H, J = 6.82, 8.0 Hz), and 3.67 ppm (dd, 1H, J = 12.1, 16.2 Hz), while the involved carbons resonated at 53.0 and 58.7 ppm in ^{13}C NMR spectrum. Conversion of epoxy methanol **65** to corresponding epoxy methyl iodide **66** was smooth as the exposure to triphenylphosphine, imidazole and iodine in toluene at room temperature resulted the desired iodo compound **66** in good yield. The epoxy methyl iodide compound **66** was converted to our next intermediate, the secondary allyl alcohol **67** with Zn/EtOH reflux conditions[23]. Both the products were reliably confirmed by the analysis of the ^{1}H NMR, ^{13}C NMR spectra. In the ^{1}H NMR spectrum of **66**, upfield shift of peaks belonging to methylene protons (CH_2I) compared to that of **65** was noticed. The ^{1}H NMR spectrum of the secondary alcohol **67** showed characteristic terminal olefin peaks at 5.12 ppm (dt, 1 H, J = 1.5, 10.4 Hz), 5.28 ppm (dt, 1 H, J = 1.5, 17.2 Hz), 5.90 ppm (ddd, 1 H, J = 5.4, 10.4, 17.2 Hz) and a broad singlet at 2.49 ppm for the hydroxyl proton.

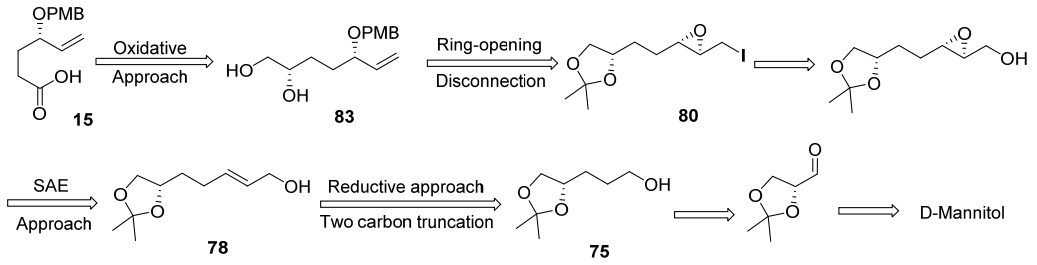
The secondary hydroxyl group was then protected as its PMB ether by reaction with PMBCl, being activated by NaH in DMF at room temperature in good yield. Close proximity of R_f values of the desired product and PMBCl made the purification and characterization of the new intermediate difficult. However, the next acid catalysed deketalization of the acetal moiety in protic solvent (MeOH) resulted in a highly polar diol intermediate **68**, which could be purified and characterized completely. The new A_2B_2 doublets at 6.87 and 7.25 ppm with J value 8.8 Hz (for aromatic ortho coupling) along with the singlet at 3.79 ppm for Ar-OCH_3 signals the introduction of the *p*-methoxybenzyl moiety.

In order to secure the alcohol fragment **23**, the diol **68** was selectively converted to its *p*-toluenesulphonate derivative **69** by reaction with TsCl, Et_3N, *n*-Bu_2SnO in CH_2Cl_2 at 0 °C to room temperature for 12 h in 70% yield.[24] The structure was confirmed by the presence of additional peaks in the ^{1}H NMR spectrum due to tosylate group. The

hydro-detosylation protocol was executed by treating compound **69** with excess of lithium aluminium hydride at 0 °C for 1 h in dry THF to provide requisite coupling partner **23** in 77% yield. New resonances due to methyl group at δ 1.08 (d, 3 H, J = 6.32 Hz) in PMR.

Retrosynthetic strategy for the acid fragment 15:

A similar retrosynthetic strategy was planned for the acid fragment **15** with the deployment of oxidative transformation of the diol instead of reduction and the starting material to start with. The acid fragment **15** could be prepared from the diol **83** through deoxygenation reaction. As depicted in scheme 15, the diol **83** can be generated from the allylic alcohol **78** by adapting a similar synthetic sequence as for the alcohol fragment. Twice retro Wittig reactions with prudent application of oxidation/reduction imply the three carbon synthon, *O*-isopropylidene-D-glyceraldehyde (**26**) as next synthon. Cheap and ready availability, high enantiomeric purity and equivalence to double unit of chiral building block due to C2 symmetry provided strong incentives for us to start with D(+)-mannitol.



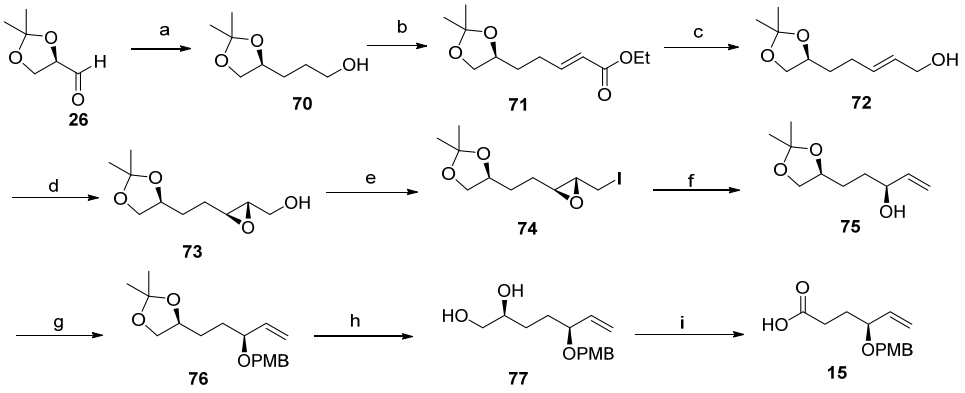
Scheme 15: Retosynthetic pathway for acid fragment **15**

Synthesis of acid fragment (15)

A similar retrosynthetic strategy was planned for the acid fragment **15** with the deployment of oxidative transformation of the diol using D-mannitol as starting material. D-mannitol was converted to 2,3-*O*-isopropylidene-D-glyceraldehyde **26**.[25] The D-glyceraldehyde derivative **26** when subjected to two-carbon Wittig olefination using (carbethoxymethylene)triphenylphosphorane to give α,β-unsaturated ester as a mixture of *trans* and *cis* isomer, the mixture was carried forward for catalytic hydrogenation with Pd/C followed by reduction with lithium aluminium hydride (LAH) in anhydrous THF to furnish the alcohol **70.** In order to secure allyl alcohol **72**, the primary hydroxyl group of **70** was oxidized with IBX to afford aldehyde which

was further subjected to two carbons Wittig olefination to furnish **71**. Hydride reduction of **71** with DIBAL-H afforded the key precursor allyl alcohol **72** (scheme 16).

Generation of the chiral centre relevant to the target was achieved by employing Sharpless asymmetric epoxidation in a catalytic procedure. Thus, **72** was treated with (+)-DET as chiral ligand, $Ti(O^iPr)_4$ and TBHP at −20 ^oC, in anhydrous CH_2Cl_2 in presence of freshly activated 4Å MS powder to furnish (2*S*,3*S*)-epoxide **73** in 82% yield. The NMR spectrum, elemental analysis and specific rotation data were in good agreement with the reported values.



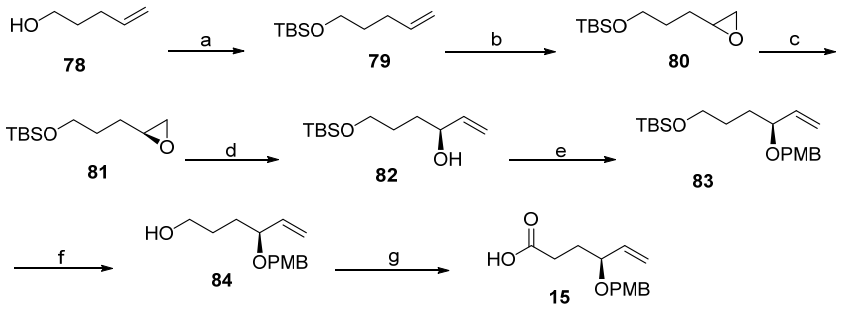
Scheme 16: *Reagents and conditions:* (a) (i) $PPh_3CHCOOC_2H_5$, toluene, reflux, 78%; (ii) Pd/C, ethyl acetate, 97%; (iii) LAH, THF, 84%; (b) (i) IBX, DMSO, 85%; (ii) $PPh_3CHCOOC_2H_5$, toluene, reflux 75%; (c) DIBAL-H, CH_2Cl_2, -78 ^oC 1 h, 83%; (d) (+)-DET, $Ti(O^iPr)_4$, TBHP, 4Å MS powder, CH_2Cl_2, -20 ^oC, 12 h, 82%; (e) TPP, imidazole, iodine, CH_2Cl_2, 72%; (f) Zn, Ethanol, reflux, 70%; (g) NaH, PMBCl, DMF, 0 ^oC to rt, 3 h, 85%; (h) 80% AcOH, r.t., 2 h, 90%; (i) Silica Supported $NaIO_4$, 30 min. r.t., then $NaClO_2$, NaH_2PO_4, 2-Methyl-2-butene, *t*-BuOH:H_2O, rt, 2 h, 54% (two steps).

Next, epoxide **73** was converted to acid **15** sequentially in six-steps. Deoxygenation of epoxide **73** to terminal alkenic alcohol **75** in high regioselectivity was achieved in two steps via epoxy iodide **74**. The terminal alkenic alcohol was protected by *p*-methoxy benzyl (PMB) ether to obtain **76** in 85% yield. Then, isopropylidene group of **76** was hydrolyzed with 80% AcOH to furnish diol **77** in 90% yield.

In order to secure the acid fragment **15**, the diol **77** was oxidatively cleaved using $NaIO_4$ supported on silica gel to afford aldehyde, which was subsequently

transformed to carboxylic acid *via* Pinnick oxidation[26] ($NaClO_2$ in presence of NaH_2PO_4 buffer and 2- methyl-2-butene as a scavenger) in 54% yield.

Synthesis of acid fragment using Hydrolytic Kinetic Resolution: As the synthesis of acid fragment **15** from chiral pool method took 14 steps to complete, we thought to make the same acid fragment using hydrolytic kinetic resolution. We started the synthesis of acid fragment **15** from 4-pentene-1-ol **(78)**. Protection of 7**8** with TBSCl in presence of imidazole afforded **79** in 90% yield, which was subjected to *m*-CPBA epoxidation followed by hydrolytic kinetic resolution using *S,S*-salen $Co^{(III)}$-OAc complex to furnish enantiopure epoxide **81** in 45% yield. The ring opening of epoxide **81** was performed by trimethyl sulphonium iodide to give allylic alcohol **82** which was then protected as its PMB ether to give compound **83.** This PMB ether was then treated with TBAF to give the alcohol **84**. Alcohol **84** was then oxidized to aldehyde using IBX and then to acid by using $NaClO_2$ in presence of NaH_2PO_4 and 2-methyl-2-butene as a scavenger to give the required coupling partner acid **15** (Scheme 17).

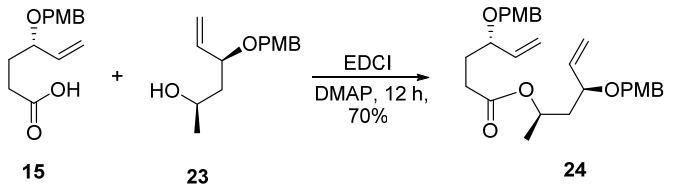


Scheme 17: *Reagents and conditions*: (a) TBSCl, imidazole, CH_2Cl_2, 0 ^oC - r.t., overnight, 90%; (b) *m*-CPBA, CH_2Cl_2, 0 ^oC to r.t., 5 h, 70%; (c) (*S,S*) Salen-Co^{III}-(OAc), H_2O, 16 h, 45%; (d) Trimethylsulphonium iodide, *n*-BuLi, THF, -23 ^oC, 8 h, 78%; (e) NaH, DMF, PMBCl, 0 ^oC- rt, 6 h, 72%; (f) TBAF, THF, 0 ^oC, 90%; (g) (i) IBX, EtOAc, reflux; (ii) $NaClO_2$, NaH_2PO_4, 2-Methyl-2-butene, *t*-BuOH:H_2O, rt, 2 h, 64% (two steps).

Coupling between the acid fragment and the alcohol fragment:

The two bifunctional coupling partners having functional groups at both end, may unite in two ways to form the cyclic lactone compounds. Either cross-metathesis followed by lactonization or esterification followed by ring-closing metathesis are the reaction sequences for the synthesis of these 10-membered lactones. So acid and

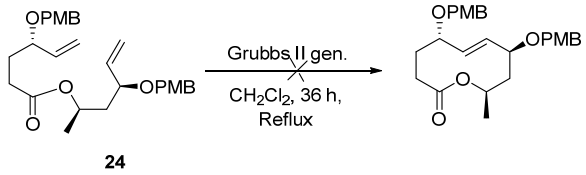
alcohol were coupled by EDCI coupling[27] to furnish the diolefinic ester **24** in 70% yield. The structure of which was confirmed by the ^{1}H and ^{13}C NMR spectrum.



Scheme 18

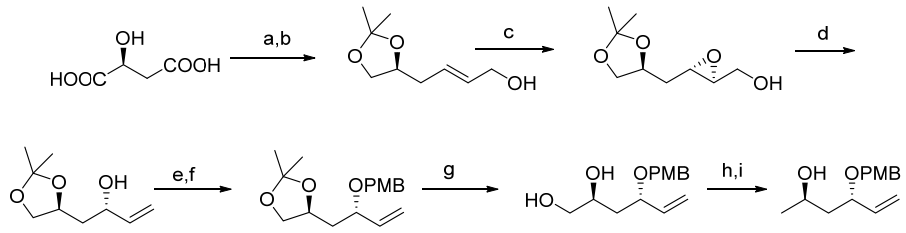
RCM reaction of the protected diolefinic ester 24:

The treatment of the diene ester with 10 mol% Grubbs second generation catalyst,[28] in dry, degassed CH_2Cl_2 even after 36 h under reflux condition was not successful to produce the RCM product.



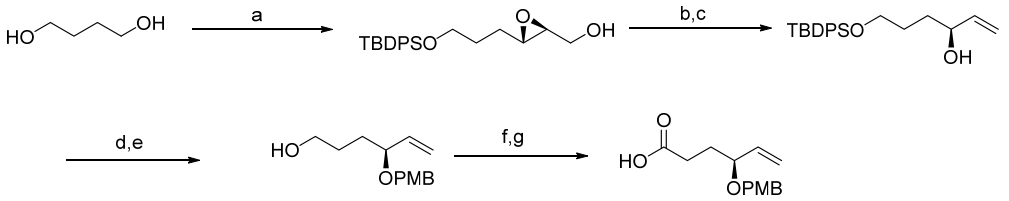
Scheme 19

While we were optimizing the RCM conditions for the diolefinic ester for stagonolide C, Mohapatra *et al* reported[29] the synthesis of stagonolide C starting from malic acid and 1,4-butane diol. The chiral centers were generated using Sharpless asymmetric epoxidation. The synthesis of alcohol fragment was achieved with same strategy as ours (Scheme 20).



Scheme 20: *Reagents and conditions* (a) Reference 30; (b) DIBAL-H, CH_2Cl_2, -78 ^{o}C, 15 min, 81%; (c) (+)-DIPT, $Ti(OPr^{i})_4$, TBHP, CH_2CL_2,12h, 85%; (d) TPP, imidazole, I_2 THF, 0 °C, 10 min; (e) Zn dust, NaI, MeOH, reflux, 3 h, 68% (for two steps); (f) NaH, PMBBr, THF, 0 °C to r.t. 4 h, 84%; (g) TsOH, MeOH, 0 °C to r.t., 3

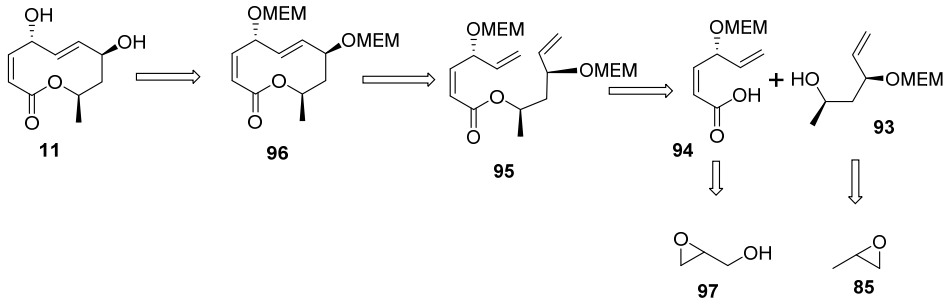
h, 90%; (h) TsCl, CH_2Cl_2, Et_3N, 0 °C to r.t., 6 h; (i) LAH, THF, 0 °C to r.t., 2 h, 76% for 2 steps.



Scheme 21: *Reagents and conditions* (a) Reference 31; (b) TPP, imidazole, I_2 THF, 0 °C, 15 min.; (c) Zn dust, NaI, MeOH, reflux, 4 h, 76% for 2 steps; (d) NaH, PMBBr, THF, 0 °C to r.t. 4 h, 84%; (d) TBAF, THF, 0 °C to r.t., 7 h 94%; (e) IBX, THF, DMSO, r.t., 3 h; (f) $NaClO_2$, $NaH_2PO_4.2H_2O$, 2-methyl-2-butene, *t*-BuOH–H_2O, 0 °C to r.t., 2 h, 84% over 2 steps.

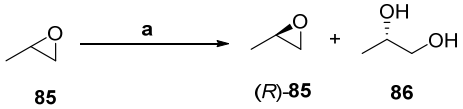
Studies towards the synthesis of Modiolide A

Our retrosynthetic analysis for the synthesis of modiolide A is based on convergent approach as outlined in Scheme 22. We envisioned that the ring-closing could be affected by ring-closing metathesis of diene **95** which could be prepared by intermolecular esterification of the alcohol **93** and acid **94**. Alcohol **93** could be obtained from (±)-propylene epoxide **85** *via* iterative HKR, while acid fragment **102** could be prepared from glycidol (**97**)



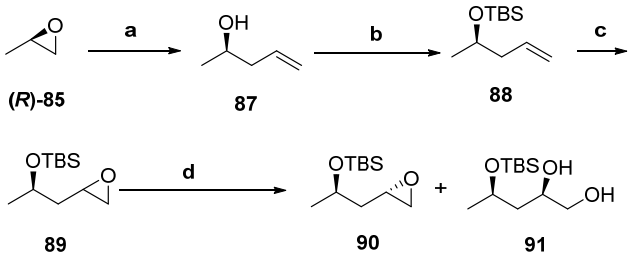
Scheme 22

As shown in Scheme 23, synthesis of alcohol fragment **93** started with Jacobsen's hydrolytic kinetic resolution of (±) propylene oxide **85** using (*R*,*R*)-salen-Co^{III}-(OAc) complex to give epoxide (*R*)-propylene oxide **85** as a single isomer which was easily isolated from diol **86** by distillation.[32b]



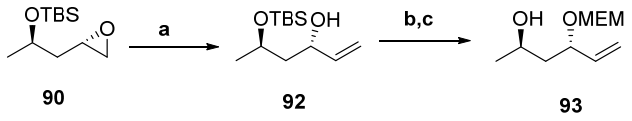
Scheme 23: *Reagents and conditions:* (a) (*R,R)*-Salen-Co^{III}-(OAc) (0.5 mol%), dist. H_2O, (0.55 equiv), 0 ^oC, 14 h, (45% for (*R*)-**85** and 43% for **86**);

Epoxide (*R*)-**85** was treated with vinylmagnesium bromide in the presence of cuprous iodide to give homoallylic alcohol **87** in 90% yield.[33] Protection of the hydroxy group of **93** as a TBDMS ether followed by epoxidation with *m*-CPBA afforded epoxide **89**. The epoxide thus obtained was found to be a mixture of two diastereomers. In order to improve the diastereoselectivity, we attempted the hydrolytic kinetic resolution method (HKR) as depicted in Scheme 24. Thus, the HKR was performed on epoxide **89** with (*S,S*)-salen-Co-(OAc) complex (0.5 mol %) and water (0.55eq) in THF (0.55 eq) to afford the diastereomerically pure epoxide **90** in 70% yield (>95% ee) and diol **91** in 22% yield (scheme 24).



Scheme 24: *Reagents and conditions:* (a) vinylmagnesium bromide, CuI, THF, -20 ^oC, 12 h, 85%; (b) TBSCl, Imidazole, CH_2Cl_2, 0 ^oC to r.t., 6 h, 80%; (c) *m*-CPBA, CH_2Cl_2, 0 ^oC- rt, 72%; (d) *(S,S)*-Salen-Co^{III}-(OAc) (0.5 mol%), dist. H_2O (0.55 equiv.), 70%

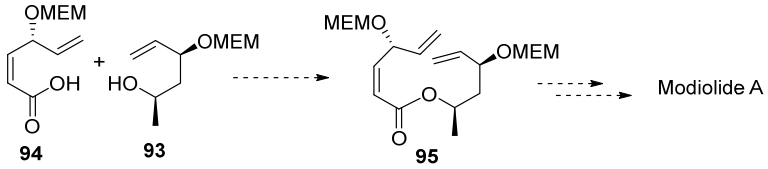
Epoxide **90** on reaction with dimethylsulfonium methylide afforded one-carbon homologated allylic alcohol **92** in 68% yield, which was protected as its MEM ether followed by TBDMS removal to furnish the alcohol fragment **93** in 80% yield (Scheme 25).



Scheme 25: *Reagents and conditions:* (a) Trimethylsulphonium iodide, *n*-butyl lithium, THF, -30 ^oC, 68%; (b) MEMCl, DIEPA, CH_2Cl_2, 0 ^oC – rt, 60%; (c) TBAF, THF, 0 ^oC – r.t., 72%

Having synthesized alcohol fragment **93** and acid fragment **94** which is synthesized by other member of our team, we proceeded for the coupling of compound **93** and **94**

to achieve the diene ester. Further synthesis of modiolide A is in progress in our group (Scheme 26).

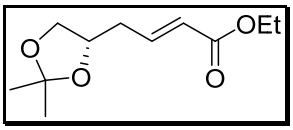


Scheme 26: Synthesis of modiolide A

Conclusion

In summary, We have successfully synthesized the key precursors for the synthesis of stagonolide C and modiolide A by employing a convergent synthetic route with ring-closing metathesis as the key step. This route exemplifies coupling of two different fragments, coupled via esterification and ring closing metathesis sequentially. Both the fragments have been synthesized in a similar fashion: Sharpless asymmetric epoxidation and hydrolytic kinetic resolution to introduce chirality. We believe that this synthetic sequence can be a stepping stone for synthesis of 10-membered lactones in general and other stagonolides in particular.

(*S*,*E*)-Ethyl 4-(2,2-dimethyl-1,3-dioxolan-4-yl)but-2-enoate (**63**):



The alcohol **62** (11.2g, 84.85 mmol) was dissolved in DMSO (100 mL) and to this IBX (26.9 g, 101.82 mmol) was added slowly while cooling the reaction mixture in cold water. The reaction mixture was stirred at rt for 2 h. After completion of the oxidation reaction, two carbon Wittig ylide (ethoxycarbonylmethylene)triphenylphosphorane (35.43 g, 101.82 mmol) in 75 mL DMSO was added and the reaction mixture was stirred at room temperature for 5 h. Then the reaction mixture was quenched with aqueous $NaHCO_3$ solution and the colloidal solution was filtered with a sintered funnel. The filtrate was extracted with ethyl acetate. The combined organic layer was washed with water and brine solution. Then the organic portion was dried over Na_2SO_4, concentrated and purified by column chromatography using EtOAc: petroleum ether (1:9) as eluent to give *E* olefin **63** (11.4 g, 70%) as a colorless liquid.

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

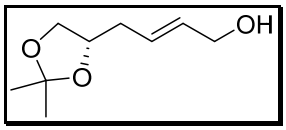
Mol. Weight : 214.26

ESI-MS *m/z* : 237.15 $[M+Na]^+$

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.29 (t, 3H, *J* = 7.15 Hz), 1.35 (s, 3H), 1.42 (s, 3H), 2.34-2.60 (m, 2H), 3.57 (dd, 1H, *J* = 6.6, 8.1 Hz), 4.05 (dd, 1H, *J* = 6.1, 8.1 Hz), 4.18 (q, 2H, *J* = 7.2 Hz), 4.21 (m, 1H), 5.89 (dt, 1H, *J* = 1.5, 15.7 Hz), 6.91 (dt, 1H, *J* = 7.2, 15.7 Hz)

^{13}C NMR (50 MHz, $CDCl_3$) : δ 14.3, 25.6, 26.9, 36.5, 60.2, 68.8, 74.2, 109.3, 123.9, 143.6, 166.0.

(*S*,*E*)-4-(2,2-Dimethyl-1,3-dioxolan-4-yl)but-2-en-1-ol (**64**):



The *E* olefin **63** (12.5 g, 58.41 mmol) was dissolved in CH_2Cl_2 (50 mL) and cooled to -78 °C. To it DIBAL-H (73 mL of 2M solution in toluene, 146 mmol) was added

dropwise and the reaction mixture was stirred at -78 °C for 1 h. After the completion of the reaction, it was quenched with aqueous sodium potassium tartrate solution and stirred at room temperature for 30 min. Then the two layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over Na_2SO_4, concentrated and purified by column chromatography using EtOAc: petroleum ether (4:6) as eluent to yield the trans allylic alcohol **64** (7.27 g, 75%) as a viscous liquid.

Mol. Formula : $C_9H_{16}O_3$

Mol. Weight : 172.23

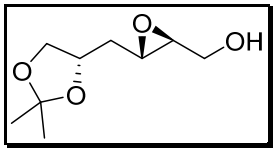
ESI-MS *m/z* : 195.12 $[M+Na]^+$

[α**]D25** : +8.2 (*c* 1, MeOH)

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.35 (s, 3H), 1.41 (s, 3H), 2.21-2.45 (m, 3H), 3.56 (dd, 1H, *J* = 6.7, 7.8 Hz), 4.02 (dd, 1H, *J* = 6.1, 7.8 Hz), 4.08 (m, 2H), 4.16 (dd, 1H, *J* = 6.3, 12.8 Hz), 5.58-5.8 (m, 2H)

^{13}C NMR (50 MHz, $CDCl_3$) : δ 25.5, 26.8, 36.4, 63.1, 68.7, 75.2, 108.9, 127.0, 132.2

((2*S*,3*S*)-3-(((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)methyl)oxiran-2-yl)methanol (**65**):



Flame dried powdered 4 Å molecular sieves (5 g) were taken with dry CH_2Cl_2 (50 mL) in a dry clean two neck round bottom flask. To it (+) DET (1.9 mL, 8.7 mmol) was added and cooled to -20 °C followed by $Ti(O^iPr)_4$ (1.7 mL, 5.8 mmol). After 10 min, *t*- BuOOH (10 mL 5-6 M solution in decane, 58 mmol) was added to the reaction mixture and stirred at -20 °C for 30 min. Then a CH_2Cl_2 (15 mL) solution of the allylic alcohol **64** (5g, 29 mmol) was added slowly and the stirring was continued for 12 h. After completion of the reaction, it was quenched with 2 mL of saturated aqueous solution of NaOH and NaCl (1:9). The mixture was filtered through a small pad of celite and concentrated. The crude product was purified by column chromatography using EtOAc: petroleum ether (1:1) as eluent to get the (*S*,*S*) epoxide **65** (4.13 g, 80%) as a viscous liquid.

Mol. Formula : $C_9H_{16}O_4$

Mol. Weight : 188.23

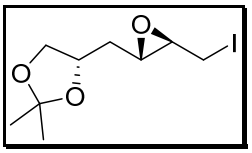
ESI-MS *m/z* : 211.15 $[M+Na]^+$

[α]D 25 : -33.3 (*c* 1, $CHCl_3$)

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.37 (s, 3H), 1.42 (s, 3H), 1.62 (ddd, 1H, *J* = 5.1, 7.6, 13.9 Hz), 1.98 (ddd, 1H, *J* = 4.1, 7.6, 13.9 Hz), 2.14 (bs, 1H), 2.96 (m, 1H), 3.11 (m, 1H), 3.60 (dd, 1H, *J* = 6.82, 8.0 Hz), 3.67 (dd, 1H, *J* = 12.1, 16.2 Hz), 3.90 (dd, 1H, *J* = 3.5, 12.6 Hz), 4.11 (dd, 1H, *J* = 8.1, 6.1 Hz), 4.30 (m, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 25.5 (q), 26.8 (q), 36.2 (t), 53.0 (d), 58.7 (d), 61.5 (t), 69.2 (t), 73.4 (d), 109.0 (s)

(*S*)-4-(((2*S*,3*R*)-3-(Iodomethyl)oxiran-2-yl)methyl)-2,2-dimethyl-1,3-dioxolane (**66**):



The alcohol **65** (2.4 g, 12.77 mmol) was dissolved in toluene (30 mL). To it imidazole (1.074 g, 25.53 mmol), triphenyl phosphine (4.02 g, 15.32 mmol) and iodine (3.89 g, 15.32 mmol) was added sequentially keeping the reaction temperature at 25 °C and the reaction mixture was stirred at room temperature for 15 min. As TLC showed the completion of the reaction, it was concentrated in vacuo and purified by column chromatography using EtOAc: petroleum ether (1:9) as eluent to get the iodo compound **66** (2.89 g, 75%) as a yellow liquid.

Mol. Formula : $C_9H_{15}IO_3$

Mol. Weight : 298.12

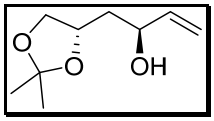
ESI-MS *m/z* : 321.09 $[M+Na]^+$

[α]D25 : -8.9 (*c* 1.4, $CHCl_3$)

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.36 (s, 3H), 1.42 (s, 3H), 1.62 (m, 1H), 1.98 (m, 1H), 2.95 (ddd, 1H, *J* = 1.5, 3.3, 7.4 Hz), 3.04 (m, 1H), 3.09 (dd, 1H, *J* = 1.5, 6.3 Hz), 3.20 (dd, 1H, *J* = 2.2, 8.8 Hz), 3.57 (dd, 1H, *J* = 2.2, 7.4, 8.1 Hz), 4.08 (ddd, 1H, *J* = 2.7, 6.0, 8.0 Hz), 4.25 (m, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 4.3 (t), 25.6 (q), 27.0 (q), 36.2 (t), 58.4 (d), 59.4 (d), 69.2 (t), 73.1 (d), 109.9 (s)

(*S*)-1-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)but-3-en-2-ol (**67**):



The iodo compound **66** (2.6 g, 8.7 mmol) in ethanol was mixed with activated Zn dust (2.85 g, 43.62 mmol). The resulting suspension was refluxed for 2 h. The suspension was filtered through a small pad of celite and the filtrate was concentrated and purified by column chromatography using EtOAc: petroleum ether (3:7) as eluent to obtain terminal olefin **67** (1.21 g, 81%) as colorless liquid.

Mol. Formula : $C_9H_{16}O_3$

Mol. Weight : 172.23

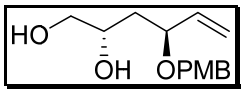
ESI-MS *m/z* : 195.18 $[M+Na]^+$

[α**]D25** : +7.3 (*c* 1, $CHCl_3$)

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.36 (s, 3H), 1.42 (s, 3H), 1.79 (ddABq, 2H, *J* = 3.5, 3.7, 4.7, 4.6, 7.7, 7.8, 8.2, 8.1, 14.2 Hz), 2.49 (br s, 1H), 3.57 (t, 1H, *J* = 7.7 Hz), 4.07 (dd, 1H, *J* = 6.0, 8.1 Hz), 4.33 (m, 2H), 5.12 (dt, 1H, *J* = 1.5, 10.4 Hz), 5.28 (dt, 1H, *J* = 1.5, 17.2 Hz), 5.90 (ddd, 1H, *J* = 5.4, 10.4, 17.2 Hz)

^{13}C NMR (50 MHz, $CDCl_3$) : δ 25.7 (q), 27.0 (q), 39.8 (t), 69.5 (t), 70.0 (d), 73.8 (d), 108.9 (s), 114.5 (t), 140.6 (d)

(2*S*,4*S*)-4-(4-Methoxybenzyloxy)hex-5-ene-1,2-diol (**68**):



NaH (0.419 g of 60% suspension in paraffin oil, 10.47 mmol) was added to a DMF solution (10mL) of the alcohol **67** (0.9 g, 5.23 mmol) at 0 °C. After stirring the reaction mixture for 15 min, PMBCl (1.42 mL, 10.47 mmol) was added slowly and the reaction mixture was stirred at room temperature for 3 h. Then it was quenched by water and the layers were separated. The aqueous layer was washed with ethyl acetate and the combined organic layer was dried over Na_2SO_4, concentrated and purified by column chromatography. The resulting compound was dissolved in MeOH (8 mL) and to it catalytic amount of *p*-TSA was added. The mixture was stirred at room temperature for 10 h. Then it was quenched with Et_3N. The reaction mixture was

concentrated and purified by column chromatography using EtOAc: petroleum ether (7:3) as eluent to get the pure diol **68** (1.2g, 91%) as a highly viscous liquid.

Mol. Formula : $C_{14}H_{20}O_4$

Mol. Weight : 252.31

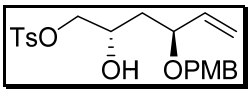
ESI-MS *m/z* : 275.19 $[M+Na]^+$

[α]D 25 : -34.1 (*c* 1, $CHCl_3$)

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.58-1.78 (m, 2H), 2.82 (bs, 2H), 2.91 (d, 1H, *J* = 14.7 Hz), 3.42 (dd, 1H, *J* = 7.1, 10.1 Hz), 3.48 (dd, 1H, *J* = 3.1, 10.1 Hz), 3.79 (s, 3H), 4.08 (m, 1H), 4.28 (d, 1H, *J* = 11.3 Hz), 4.55 (d, 1H, *J* = 11.3 Hz), 5.29 (m, 2H), 5.81 (ddd, 1H, *J* = 7.3, 10.2, 17.2 Hz), 6.87 (d, 2H, *J* = 8.8 Hz), 7.25 (d, 2H, *J* = 8.8 Hz)

^{13}C NMR (50 MHz, $CDCl_3$): δ 38.3 (t), 55.2 (q), 66.6 (t), 69.0 (d), 70.0 (t), 77.2 (d), 113.8 (d), 117.2 (t), 129.4 (d), 130.1 (s), 138.0 (d), 159.1 (s)

(2*S*,4*S*)-2-Hydroxy-4-((4-methoxybenzyl)oxy)hex-5-en-1-yl 4-methylbenzenesulfonate (69)



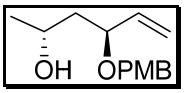
To a solution of **68** (1.0 g, 3.96 mmol) in dry CH_2Cl_2 (30 mL), were added Et_3N (0.44 g, 4.27 mmol), *n*-Bu_2SnO (0.47 g, 1.89 mmol), DMAP (catalytic) and TsCl (0.76 g, 3.96 mmol) at 0 °C. The reaction mixture was stirred for 12 h at room temperature, quenched with saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with EtOAc, and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography using EtOAc:petroleum ether (1:5) as eluent to afford **69** as a colorless liquid (1.12 g, 70%).

Molecular Formula: $C_{21}H_{26}O_6S$

Molecular Weight: 406.49

^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 1.68 (t, *J*=1.00 Hz, 2 H) 2.45 (s, 3 H) 2.65 (br. s, 1 H) 3.81 (s, 3 H) 3.83 - 4.00 (m, 2 H) 4.00 - 4.13 (m, 2 H) 4.39 (dd, *J*=1.00 Hz, 2 H) 5.18 - 5.35 (m, 2 H) 5.64 - 5.85 (m, 1 H) 6.88 (d, *J*=1.00 Hz, 2 H) 7.18 (d, *J*=1.00 Hz, 2 H) 7.33 (d, *J*=1.00 Hz, 2 H) 7.75 (d, *J*=1.00 Hz, 2 H)

(2*R*,4*S*)-4-((4-Methoxybenzyl)oxy)hex-5-en-2-ol (23)



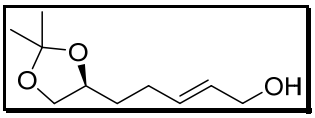
To a solution of compound **69** (0.210 g, 0.5 mmol) in dry THF (10 mL) at 0 ^{o}C was added LAH (0.076 g, 2.0 mmol) and stirred for 1 h. Excess of LAH was quenched by addition of a saturated Na_2SO_4 solution (1 mL). The solid formed was filtered, washed with ethyl acetate and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography using EtOAc: petroleum ether (1:4) as eluent to afford **23** as a colorless liquid (0.091 g, 77%).

Molecular Formula: $C_{14}H_{20}O_3$

Molecular Weight: 236.31

^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 1.06 (d, *J*=1.00 Hz, 3 H) 1.61 (ddd, *J*=7.10 Hz, 2 H) 2.62 (br. s., 1 H) 3.72 (s, 3 H) 3.99 (m, *J*=17.80 Hz, 2 H) 4.21 (d, *J*=11.37 Hz, 1 H) 4.47 (d, *J*=1.00 Hz, 1 H) 5.09 - 5.29 (m, 2 H) 5.74 (ddd, *J*=1.00 Hz, 1 H) 6.81 (d, *J*=1.00 Hz, 2 H) 7.17 (d, *J*=8.97 Hz, 2 H)

(*S*,*E*)-5-(2,2-Dimethyl-1,3-dioxolan-4-yl)pent-2-en-1-ol (**72**):



DIBAL-H (48.3 mL, 96.5 mmol, 2M in toluene) was added to a stirred solution of **71** (10.0 g, 43.8 mmol) in dry CH_2Cl_2 (100 mL) at -20 °C drop wise in 30 min. After 2 h, the reaction mixture was warmed to 0 °C and quenched with MeOH (5 mL) to obtain a gelatinous cake. The mixture was diluted with CH_2Cl_2 (100 mL) and stirred for 15 min. A saturated solution of Na-K tartrate (10 mL) was added dropwise and stirred for an additional 45 min. the reaction mixture was filtered through celite and washed with CH_2Cl_2. The organic layer was washed with water, brine, dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography using EtOAc: petroleum ether (3:7) as eluent to afford **72** as a colorless liquid (6.9 g, 83%).

Mol. Formula : $C_{10}H_{18}O_3$

Mol. Weight : 186.25

ESI-MS *m/z* : 209.18 $[M+Na]^+$

IR (CHCl3, cm-1) : 3422, 2986, 2935, 2868, 1670, 1455, 1379, 1216, 1157, 1062, 752

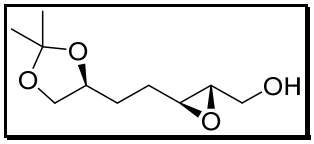
$[\alpha]_D^{25}$: +15.6 (*c* 1.0, $CHCl_3$)

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.35 (s, 3H), 1.40 (s, 3H), 1.58-1.72 (m, 3H), 2.07-2.21

(m, 2H), 3.51 (t, 1H, *J* = 6.6 Hz), 3.99-4.08 (m, 4H), 5.66- 5.71 (m, 2H)

^{13}C NMR (50 MHz, $CDCl_3$) : δ 25.6, 26.8, 28.3, 32.9, 63.1, 69.1, 75.3, 108.6, 129.7, 131.3

((2*S*,3*S*)-3-(2-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)ethyl)oxiran-2-yl)methanol (73):



To a stirred and cooled (-20 °C) suspension of molecular sieves (4 Å, 2.0 g) in CH_2Cl_2 (50 mL) under N_2 atmosphere, (+)-DET (2.0 g, 9.7 mmol) in CH_2Cl_2 (25 mL), $Ti(O^iPr)_4$ (2.30 g, 8.1 mmol) and TBHP (9.75 mL, 5.0-6.0 M solution in decane, 53.8 mmol) were added sequentially. After 20 min, the resulting mixture was treated with a solution of **72** (5.0 g, 26.85 mmol) in CH_2Cl_2 (25 mL). After 12 h, the reaction mixture was quenched with 10% NaOH solution in saturated with NaCl (10 mL) and filtered through celite. Evaporation of the solvent and purification of the residue by column chromatography using EtOAc: petroleum ether (1:1) as eluent afforded **73** as a colorless liquid (4.5 g, 82%).

Mol. Formula : $C_{10}H_{18}O_4$

Mol. Weight : 202.25

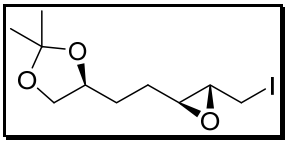
ESI-MS *m/z* : 225.17 $[M+Na]^+$

$[\alpha]_D^{25}$: -22.6 (*c* 1.0, $CHCl_3$)

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.34 (s, 3H), 1.40 (s, 3H), 1.67-1.74 (m, 3H), 1.83 (m, 1H), 2.06 (br s, 1H), 2.94 (dt, 1H, *J* = 2.5, 4.2 Hz), 3.00 (m, 1H), 3.52 (dd, 1H, *J* = 6.9, 7.5 Hz), 3.65 (m, 1H), 3.89 (m, 1H), 4.03 (dd, 1H, *J* = 6.0, 7.6), 4.15 (m, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 25.4, 26.7, 27.4, 29.4, 55.2, 58.4, 61.5, 68.9, 74.9, 108.6

(*S*)-4-(2-((2*S*,3*R*)-3-(Iodomethyl)oxiran-2-yl)ethyl)-2,2-dimethyl-1,3-dioxolane (74):



To a solution of **73** (2.02 g, 10.0 mmol) in dry toluene (30 mL) were added imidazole (2.04 g, 30.0 mmol), triphenylphosphine (3.93 g, 15.0 mmol) and iodine (3.02 g, 12.0 mmol) at room temperature. The reaction mixture was stirred for 30 min. at same temperature (monitored by TLC) and quenched the reaction mixture by saturated $NaHCO_3$ solution. The aqueous layer was washed with EtOAc, and the combined organic layer was dried over Na_2SO_4, and evaporated in vacuo. Purification of the residue by column chromatography using EtOAc: petroleum ether (1:9) as eluent afforded iodo compound **74** (2.23 g, 72%) as a light yellowish liquid.

Mol. Formula : $C_{10}H_{16}IO_3$

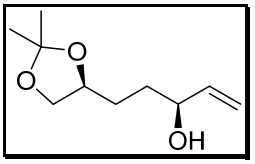
Mol. Weight : 312.15

ESI-MS *m/z* : 335.05 $[M+Na]^+$

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.35 (s, 3H), 1.40 (s, 3H), 1.63-1.72 (m, 4H), 2.84 (m, 1H), 2.96-3.06 (m, 2H), 3.27 (dd, 1H, *J* = 8.7, 13.0 Hz), 3.52 (dd, 1H, *J* = 7.0, 7.6 Hz), 4.04 (dd, 1H, *J* = 6.0, 7.6 Hz), 4.15 (m, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 4.6, 25.6, 26.9, 27.8, 29.6, 58.2, 61.8, 69.1, 75.0, 108.9

(*S*)-5-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)pent-1-en-3-ol (**75**):



A solution of the iodo compound **74** (2.23 g, 7.13 mmol) and Zn dust (4.64 g, 71.3 mmol) in absolute EtOH (30 mL) was heated to reflux for 3 h. The reaction mixture was filtered through a small celite pad and the filtrate was evaporated, and purification of the residue by column chromatography using EtOAc: petroleum ether (1:3) as eluent afforded **75** as a colorless liquid (0.98 g, 70%).

Mol. Formula : $C_{10}H_{18}O_3$

Mol. Weight : 186.25

ESI-MS *m/z* : 209.17 $[M+Na]^+$

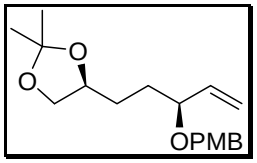
IR ($CHCl_3$, cm^{-1}) : 3436, 3079, 2986, 2871, 1644, 1455, 1379, 1216, 1058, 922, 757.

[α]$_D^{25}$: +22.0 (*c* 1.0, $CHCl_3$)

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.35 (s, 3H), 1.41 (s, 3H), 1.61-1.69 (m, 4H), 2.68 (br s, 1H), 3.52 (t, 1H, *J* = 7.2 Hz), 4.01-4.18 (m, 3H), 5.11 (dt, 1H, *J* = 1.3, 10.4 Hz), 5.24 (dt, 1H, *J* = 1.5, 17.2 Hz), 5.87 (ddd, 1H, *J* = 5.9, 10.4, 17.2 Hz)

^{13}C NMR (50 MHz, $CDCl_3$) : δ 25.6, 26.8, 29.4, 33.1, 69.2, 72.5, 75.8, 108.8, 114.5, 140.9

(*S*)-4-((*S*)-3(4-Methoxybenzyloxy)pent-4-enyl)-2,2-dimethyl-1,3-dioxolane (**76**):



To a solution of **75** (2.5 g, 13.4 mmol) in dry DMF (40 mL) was added NaH (0.80 g, 33.5 mmol, 60% dispersion in mineral oil) at 0 °C, stirred for 30 min. Then *p*-methoxy benzyl chloride (2.5 g, 16.0 mmol) was added and the reaction mixture was stirred for additional 3 h at room temperature. The reaction mixture was quenched by cold water and aqueous layer washed with EtOAc, dried over Na_2SO_4, The solvent was evaporated in vacuo and the residue was purified by column chromatography using EtOAc: petroleum ether (1:9) as eluent to afford **76** (3.5 g, 85%) as a yellow liquid.

Mol. Formula: $C_{18}H_{26}O_4$

Mol. Weight: 306.41

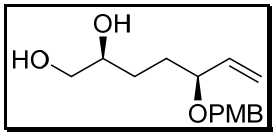
ESI-MS *m/z* : 329.35 $[M+Na]^+$

[α]$_D^{25}$: -23.3 (*c* 0.8, $CHCl_3$)

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.33 (s, 3H), 1.39 (s, 3H), 1.50-1.59 (m, 2H), 1.65-1.75 (m, 2H), 3.48 (m, 1H), 3.62-3.78 (m, 2H), 3.81 (s, 3H), 3.98 (m, 1H) 4.27 (d, 1H, *J* = 11.5 Hz), 4.53 (d, 1H, *J* = 11.5 Hz), 5.18-5.28 (m, 2H), 5.73 (m, 1H), 6.86 (d, 2H, *J* = 8.6 Hz), 7.24 (d, 2H, *J* = 8.6 Hz)

^{13}C NMR (50 MHz, $CDCl_3$) : δ 25.7, 26.9, 29.1, 31.3, 55.1, 69.2, 69.6, 75.7, 79.5, 108.6, 113.6, 117.3, 129.2, 130.6, 138.7, 159.0

(2*S*,5*S*)-5-(4-Methoxybenzyloxy)hept-6-ene-1,2-diol (**77**):



A solution of **76** (1.53 g, 5.0 mmol) in 80% AcOH (20 mL) was stirred for 2 h at room temperature and quenched the reaction mixture with saturated $NaHCO_3$ solution. The aqueous layer was washed with EtOAc and the organic layer was dried over Na_2SO_4, concentrated and purified by column chromatography using EtOAc: petroleum ether (1:1) as eluent to afford **77** as a colorless liquid (1.02 g, 90%).

Mol. Formula: $C_{15}H_{22}O_4$

Mol. Weight: 266.34

ESI-MS *m/z*: 289.29 $[M+Na]^+$

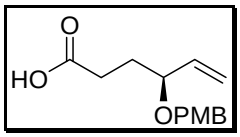
IR ($CHCl_3$, cm^{-1}): 3409, 3076, 3000, 2936, 2868, 1612, 1514, 1442, 1302, 1248, 1174, 1072, 995, 821.

$[\alpha]_D^{25}$: -37.5 (*c* 1.2, $CHCl_3$)

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.44-1.56 (m, 2H), 1.61-1.76 (m, 2H), 2.41 (br s, 1H), 3.04 (br s, 1H), 3.37 (dd, 1H, *J* = 7.2, 11.0 Hz), 3.53-3.65 (m, 2H), 3.73 (m, 1H), 3.80 (s, 3H), 4.26 (d, 1H, *J* = 11.4 Hz), 4.54 (d, 1H, *J* = 11.4 Hz), 5.23 (m, 2H), 5.75 (m, 1H), 6.86 (d, 2H, *J* = 8.7 Hz), 7.23 (d, 2H, *J* = 8.7 Hz)

^{13}C NMR (50 MHz, $CDCl_3$) : δ 28.9, 31.6, 55.1, 66.5, 69.7, 71.9, 80.0, 113.7, 117.3, 129.4, 130.2, 138.6, 159.1

(*S*)-4-((4-Methoxybenzyl)oxy)hex-5-enoic acid (15)



The diol **83** (1.05 g, 4.17 mmol) was dissolved in CH_2Cl_2 (15 mL) and silica supported $NaIO_4$ (1.34 g, 6.25 mmol) was added to it. The reaction mixture was stirred at room temperature for 30 min. The suspension was then filtered and the filtrate was concentrated to give the crude aldehyde. The crude aldehyde and 2-methyl-2- butene (0.8 mL, 8.33 mmol) was dissolved in *t*-BuOH: H_2O (9:3 mL) solvent mixture. To it NaH_2PO_4 (1.0 g, 8.33 mmol) was added followed by $NaClO_2$ (0.753 g, 8.33 mmol). The reaction mixture was stirred at room temperature for 2 h. Then the reaction mixture was concentrated in vacuo and partitioned between ethyl acetate and water. The aqueous layer was washed with ethyl acetate. The combine organic layer was dried over Na_2SO_4, concentrated and purified by flash column

chromatography using EtOAc:petroleum ether (2:8) as eluent to give the pure acid **15** (0.54 g, 54%) as a colorless liquid.

Molecular Formula: $C_{14}H_{18}O_4$

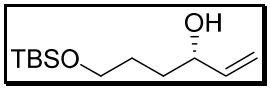
Molecular Weight: 250.29

$[\alpha]_D^{25}$ = −27.4 (*c* 1.0, $CHCl_3$)

^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 1.91 (m, *J*=17.68 Hz, 2 H) 2.49 (t, *J*=1.00 Hz, 2 H) 3.76 - 3.89 (m, 4 H) 4.28 (d, *J*=1.00 Hz, 1 H) 4.54 (d, *J*=1.00 Hz, 1 H) 5.23 - 5.36 (m, 2 H) 5.67 - 5.88 (m, 1 H) 6.87 (d, *J*=1.00 Hz, 2 H) 7.25 (d, *J*=1.00 Hz, 2 H)

^{13}C NMR (50 MHz, $CDCl_3$) δ ppm 30.0, 30.1 55.1, 69.7, 78.6, 96.1, 113.7, 117.7, 138.19, 159.0,179.6

(*S*)-6-((tert-Butyldimethylsilyl)oxy)hex-1-en-3-ol (82)



A solution of trimethyl sulphonium iodide (3.75 g, 18.35 mmol) in THF (50 mL) was cooled to –78 °C and treated with *n*-BuLi (6.9 ml, 16.2 mmol) and stirred for 20 min. To this, a solution of **81** (1.0 g, 4.6 mmol) in THF (10 mL) was added slowly and stirred at –78 °C for 1 h and at rt for 6 h. The reaction mixture was partitioned between water and EtOAc. The aqueous phase was extracted with EtOAc.The combined organic phase was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The purification of residue by silica gel column chromatography (5% ethyl acetate in petroleum ether) gave **82** (0.84 g, 78%) as colorless oil.

$[\alpha]_D^{25}$ = + 1.8 (*c* 1, $CHCl_3$)

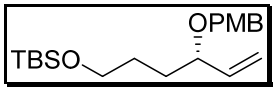
IR ($CHCl_3$) ν_{max}**:** 3370, 2930, 2858, 1472, 1256, 835 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.88 (s, 9H), 1.57–1.67 (m, 4H), 2.77 (br. s, 1H), 3.63 (br. t, *J* = 5.8 Hz, 2H), 4.11 (dd, *J* = 5.8, 11.0 Hz, 1H), 5.06 (ddd , *J* = 1.2, 1.7, 10.4 Hz, 1H), 5.21 (dt, *J* = 1.6, 17.2 Hz, 1H), 5.85 (ddd, *J* = 5.9, 10.4, 17.2 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ −5.4, 18.3, 25.9, 28.7, 34.3, 63.3, 72.6, 114.2, 141.2 ppm.

ESI-MS *m/z*: 253.4 $[M+Na]^+$

(*S*)-tert-Butyl((4-((4-methoxybenzyl)oxy)hex-5-en-1-yl)oxy)dimethylsilane (83)



To a cooled solution of **82** (1.7 g, 7.35 mmol) in anhydrous DMF (20 mL), NaH (60% dispersion in mineral oil, 310 mg, 7.75 mmol) was added slowly and stirred for 5 min. Then PMB-Cl (1.1 mL, 8.1 mmol) was added and continued at room temperature for 4 h. The reaction mixture was partitioned between water and EtOAc and the aqueous layer was extracted with EtOAc. The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The purification of residue by silica gel column chromatography (2% ethyl acetate in petroleum ether) afforded **83** (1.55 g, 72%) as colorless oil.

$[\alpha]_D^{25}$ = - 17.5 (*c* 1, $CHCl_3$).

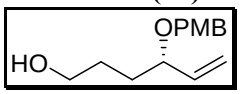
IR ($CHCl_3$) ν: 2954, 2857, 1613, 1514, 1250, 1097, 835 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.03 (s, 6H), 0.89 (s, 9H), 1.50−1.68 (m, 4H), 3.59 (br. t, *J* = 5.8 Hz, 2H), 3.67−3.77 (m, 1H), 3.79 (s, 3H), 4.28 (d, *J* = 11.5 Hz, 1H), 4.53 (d, *J* = 11.5 Hz, 1H), 5.19 (br. ddd, *J* = 0.8, 1.9, 16.2 Hz , 1H), 5.22 (br. ddd, *J* = 0.7, 1.9, 11.2 Hz, 1H), 5.65 (br. ddd, *J* = 7.6, 11.2, 16.2 Hz 1H), 6.86 (br. d, *J* = 8.6 Hz, 2H), 7.25 (br. d, *J* = 8.6 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ −5.35, 18.3, 25.9, 28.6, 31.8, 55.1, 63.0, 69.6, 80.0, 113.7, 116.9, 129.2, 130.8, 139.2, 159.0 ppm.

ESI−MS *m/z*: 351.0 $[M+H]^+$

(*S*)-4-((4-methoxybenzyl)oxy)hex-5-en-1-ol (84)



To a cooled solution of **83** (1.5 g, 4.25 mmol) in dry THF (20 mL) was added TBAF (1.34 g, 5.1 mmol) and stirred at room temperature for 4 h. The reaction mixture was partitioned in sat. ammonium chloride and ethyl acetate and the aqueous layer was extracted with ethyl acetate. The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The purification of residue by silica gel column chromatography (25% ethyl acetate in petroleum ether) gave **84** (0.9 g, 90% yield) as a colorless oil.

$[\alpha]_D^{25}$ = −23.6 (*c* 1, $CHCl_3$)

IR ($CHCl_3$) ν_{max}: 3020, 2928, 2855, 1612, 1514, 1215, 1035, 758 cm^{-1}.

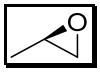
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.59−1.67 (m, 4H), 1.96 (br. s, 1H), 3.57−3.63 (m,

2H), 3.71−3.79 (m, 4H), 4.27 (d, *J* = 11.4 Hz, 1H), 4.53 (d, *J* = 11.4 Hz, 1H), 5.21 (br. ddd, *J* = 0.9, 1.8, 16.2 Hz, 1H), 5.23 (br. ddd, *J* = 0.7, 1.8, 11.3 Hz, 1H), 5.76−5.83 (m, 1H), 6.86 (br. d, *J* = 8.6 Hz, 2H), 7.25 (br. d, *J* = 8.6 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 28.8, 32.3, 55.2, 62.8, 69.8, 80.1, 113.8, 117.2, 129.4, 130.4, 138.7, 159.1.

ESI−MS *m/z*: 259.4 $[M+Na]^+$

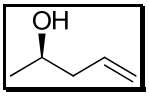
(*R*)-Propylene oxide (*R*-85).



The racemic propylene oxide **85** was resolved to chiral epoxide *R*-**85** in high enantiomeric excess (>99% *ee*) by the HKR method following a literature procedure.[32b]

Yield: 14.71 g, 45%

(*R*)-Pent-4-en-2-ol (87)



A round bottomed flask was charged with copper (I) iodide (1.64 g, 8.6 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, 172 mL, 172.4 mmol) was injected to it. A solution of propylene oxide (*R*)-**85** (5 g, 86.09 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 organic layer was washed with brine, dried (Na_2SO_4) and concentrated to afford the crude homoallylic alcohol which on distillation provided alcohol **87** (5.9 g, 85%) as a colorless liquid.

B.P.: 115 ^oC,

Mol. Formula: $C_5H_{10}O$

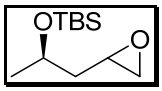
$[\alpha]_D^{25}$: –10.86 (*c* 3.2 in Et_2O).

IR ($CHCl_3$, cm^{-1}): ν_{max} 3400, 3078, 2931, 2975, 1562, 1457, 1432, 1243, 1071, 914.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.85-5.77 (m, 1H), 5.12 (d, *J* = 6.6 Hz, 1H), 5.09 (d, *J* = 2.4 Hz, 1H), 3.86-3.80 (m, 1H), 2.38-2.22 (m, 2H), 1.82 (s, 1H), 1.18 (d, *J* = 6.1, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 134.6, 116.6, 66.5, 43.2, 22.1.

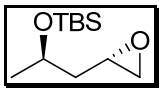
***tert*-Butyldimethyl(((2R)-1-(oxiran-2-yl)propan-2-yl)oxy)silane (88)**



To a stirred soluion of alcohol **87** (3.0 g, 34.83 mmol) in CH_2Cl_2 (25 mL), imidazole (3.57, 52.24 mmol) was added. To this solution *t*-butylchlorodimethyl silane (5.77 g, 38.31 mmol) was added at 0 ^oC and reaction was stirred at room temperature for 6 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2 (3 X 50 mL). The extract was washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using pet ether/EtOAc (49:1) as eluent provided **88 (**5.76 g, 80%).

To a stirred solution of olefin **88** (6 g, 30.0 mmol) in CH_2Cl_2 (50 mL) at 0 ^oC was added *m*-CPBA (50%) (12.42 g, 36.0 mmol). The reaction mixture was stirred at room temperature for 10 h and quenched by saturated $NaHCO_3$ solution, extracted with CH_2Cl_2, washed with sat. $NaHCO_3$ and brine, dried (Na_2SO_4), concentrated and purified by silica gel column chromatography using pet ether/EtOAc (9:1) as eluent to yield the epoxide **89** (4.1 g, 72%.)as a colorless liquid in diastereomeric mixture (3:1).

***tert*-Butyldimethyl(((*R*)-1-((*S*)-oxiran-2-yl)propan-2-yl)oxy)silane (90)**



A solution of epoxide **89** (5 g, 23.1 mmol) and (*S,S*)-Salen-Co(III)-OAc (0.076 g, 0.11 mmol) in THF (0.23 mL) was stirred at 0 ^oC for 5 min, and then distilled water (230 μL, 12.6 mmol) was added. After stirring for 24 h, it was concentrated and purified by silica gel column chromatography using pet ether/EtOAc (9:1) to afford **90 (**3.5g, 70%) as a yellow color liquid. Continued chromatography with pet ether/EtOAc (3:2) provided the diol **91 (**3.5g, 70%) as a brown color liquid as a single diastereomer.

Mol. Formula: $C_{11}H_{24}O_2Si$

$[\alpha]_D^{25}$: –11.4 (*c* 0.67, $CHCl_3$).

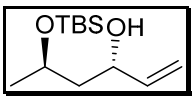
IR (CHCl3, cm^{-1}): ν_{max} 3018, 2958, 2930, 1858, 1472, 1463, 1377, 1256, 1216, 1101, 1005, 938, 878, 760.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.96-3.83 (m, 1H), 3.13-3.01 (m, 1H), 2.81-2.69 (m, 1H), 2.52-2.43 (m, 1H), 1.95-1.76 (m,1H), 1.69-1.60 (m, 1H), 1.18 (d, *J* = 6.53 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 70.5, 50.1, 47.8, 47.0, 25.6, 19.6, 17.9, –4.4, –4.7

ESI–MS: m/z =239 $[M+Na]^+$

(3*S*, 5*R*)-5-((*tert*-Butyldimethylsilyl)oxy)hex-1-en-3-ol (92)



To a suspension of trimethylsulfonium iodide (5.76 g, 28.2 mmol) in dry THF (10 mL) at −20 ^oC was added *n*-BuLi (14.3 mL, 2.1 M solution in hexane, 30.0 mmol) dropwise over 20 min and stirred for 30 min. Then the epoxide **90** (1 g, 4.6 mmol) in dry THF (10 mL) was added to the above reaction mixture and stirred for 3 h. After consumption of the starting material the reaction mixture was quenched with H_2O (15 mL) and extracted with EtOAc (4 × 15 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated. The column chromatography of crude product using pet ether:ethyl acetate (85:15) gave **92** (0.74 g, 70%).

Mol. Formula: $C_{12}H_{26}O_2Si$

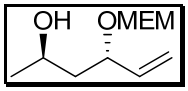
$[\alpha]_D^{25}$: –29.18 (*c* 1.04, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 3430, 3018, 2957, 2931, 2859, 1652, 1471, 1379, 1256, 1212, 1101, 1036, 971, 869, 758.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.83-5.67 (m, 1H), 5.18-5.01 (m, 2H), 4.54-4.41 (m, 1H), 4.27-4.18 (m, 1H), 1.74-1.59 (m, 2H), 1.08 (d, *J* = 6.44 Hz, 3H), 0.82 (s, 9H), –0.01 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 140.8, 114.2, 71.3, 70.6, 40.1, 25.8, 18.9, –4.6, –4.7.

(2*R*, 4*S*)-4-((2-Methoxyethoxy)methoxy)hex-5-en-2-ol (93).



A mixture of compound **92** (0.5 g, 2.17 mmol), diisopropylethylamine (0.84 g, 1.13 mL, 6.5 mmol), MEM-Cl (0.32 g, 0.30 mL, 2.60 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature for 8 h. The reaction mixture was quenched with water and extracted with CH_2Cl_2, washed with water, brine, dried (Na_2SO_4) and evaporated to afford crude product, which was used as such for the next step without purification. To a solution of olefin (0.69 g, 2.17 mmol) in THF (10 mL) was added TBAF (3.25 mL, 3.25 mmol, 1.0 M solution in THF) at room temperature. The reaction mixture was stirred for 6 h and then diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (7:3) as eluent gave alcohol **93 (**0.31 g, 72%) as a colorless liquid.

Mol. Formula: $C_{10}H_{20}O_4$

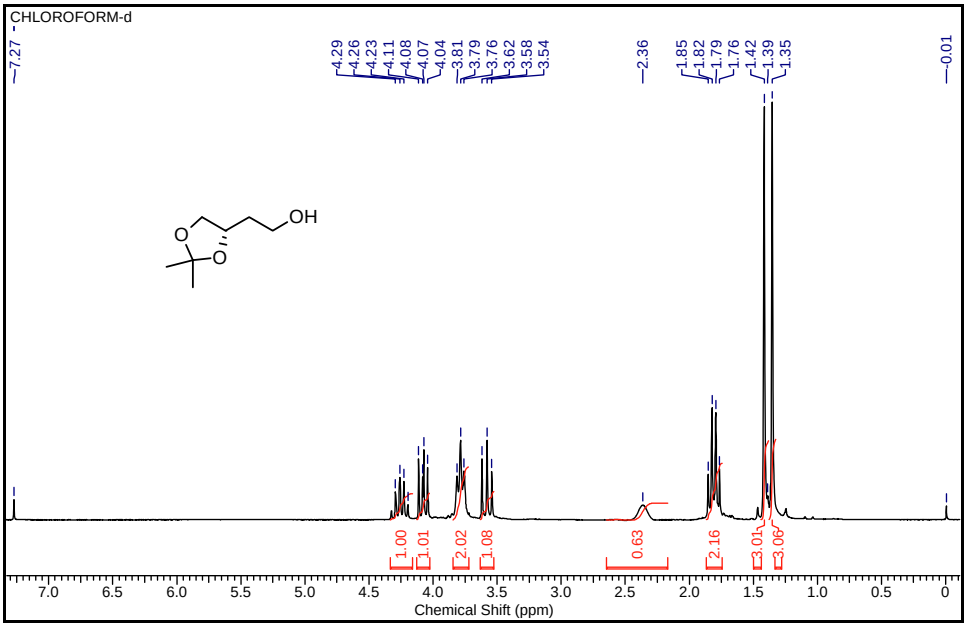
$[\alpha]_D^{25}$: –95.88 (*c* 1.22, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 3462, 3016, 2968, 2893, 2448, 1645, 1456, 1422, 1367, 1241, 1216, 1133, 1098, 993.

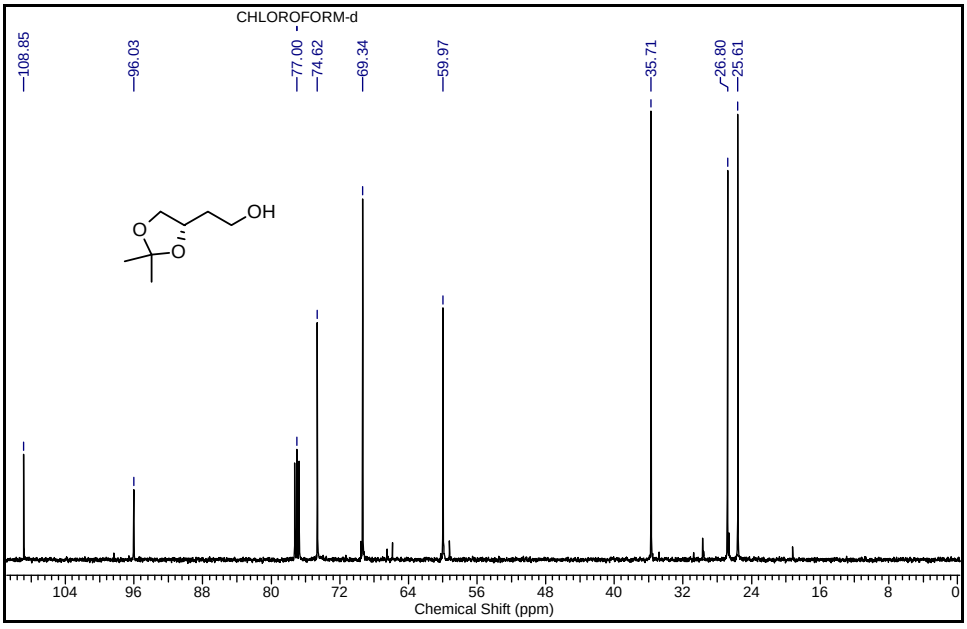
^{1}H NMR (200 MHz, $CDCl_3$): δ 5.79-5.61 (m, 1H), 5.27-5.14 (m, 2H), 4.81-4.73 (m, 2H), 4.11- 4.01 (m, 1H), 3.73-3.68 (m, 1H), 3.62-3.53 (m, 4H), 3.39 (s, 3H). 2.36 (brs, 1H), 1.64-1.55 (m, 2H), 1.17 (d, *J* = 6.2 Hz, 3H).

Spectra

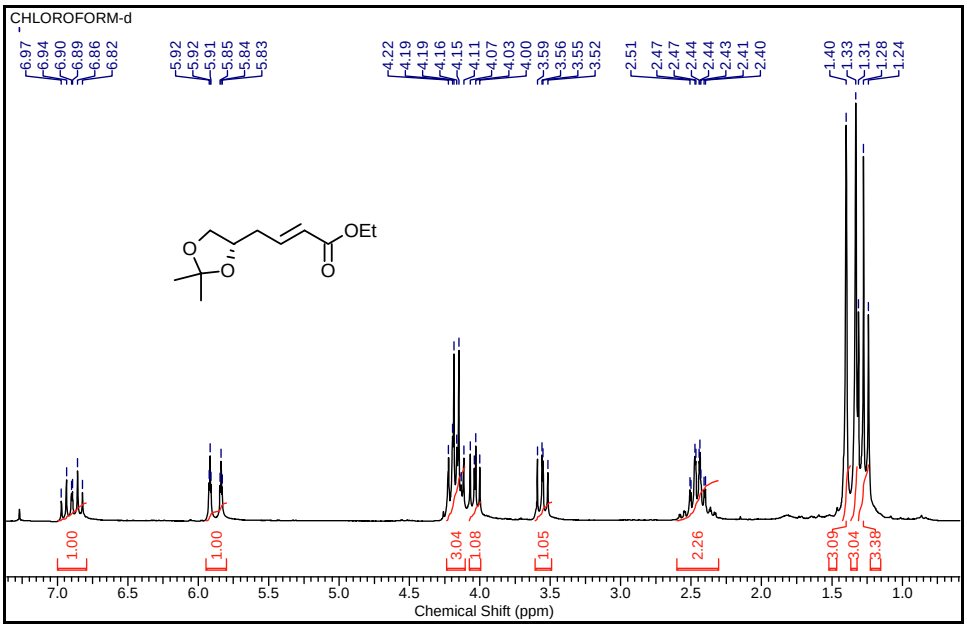
1. ^{1}H and ^{13}C NMR spectra of **62**
2. ^{1}H and ^{13}C NMR spectra of **63**
3. ^{1}H and ^{13}C NMR spectra of **64**
4. ^{1}H and ^{13}C NMR spectra of **65**
5. ^{1}H and ^{13}C NMR spectra of **66**
6. ^{1}H and ^{13}C NMR spectra of **67**
7. ^{1}H and ^{13}C NMR spectra of **68**
8. ^{1}H NMR spectra of **69**
9. ^{1}H NMR spectra of **23**
10. ^{1}H and ^{13}C NMR spectra of **72**
11. ^{1}H and ^{13}C NMR spectra of **73**
12. ^{1}H and ^{13}C NMR spectra of **74**
13. ^{1}H and ^{13}C NMR spectra of **75**
14. ^{1}H and ^{13}C NMR spectra of **76**
15. ^{1}H and ^{13}C NMR spectra of **77**
16. ^{1}H and ^{13}C NMR spectra of **82**
17. ^{1}H and ^{13}C NMR spectra of **83**
18. ^{1}H and ^{13}C NMR spectra of **84**
19. ^{1}H and ^{13}C NMR spectra of **15**
20. ^{1}H and ^{13}C NMR spectra of **24**
21. ^{1}H and ^{13}C NMR spectra of **88**
22. ^{1}H and ^{13}C NMR spectra of **89**
23. ^{1}H and ^{13}C NMR spectra of **90**
24. ^{1}H and ^{13}C NMR spectra of **92**
25. ^{1}H NMR spectra of **93**



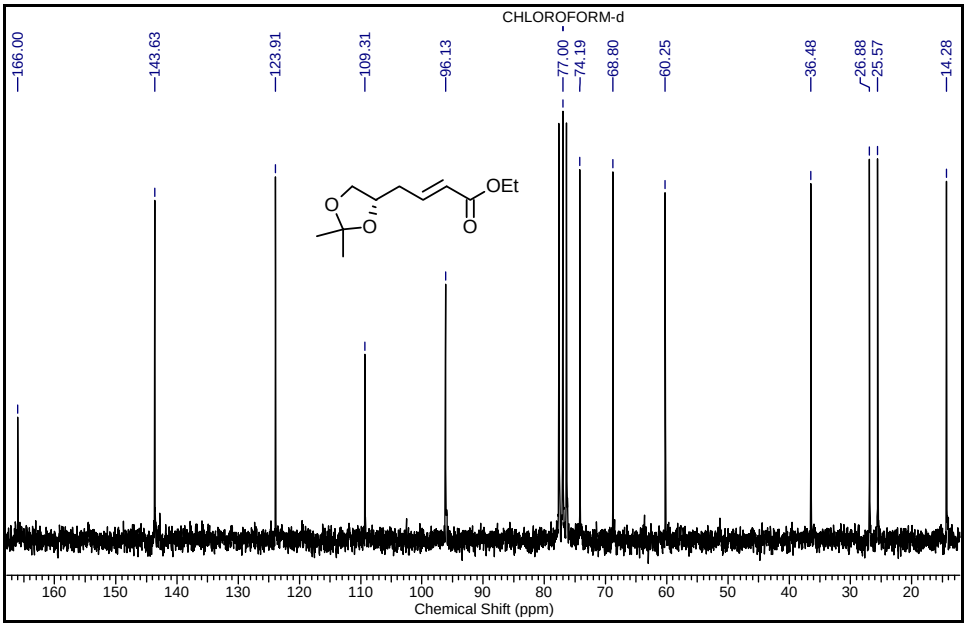
^{1}H NMR spectrum of Compound 62 in $CDCl_3$



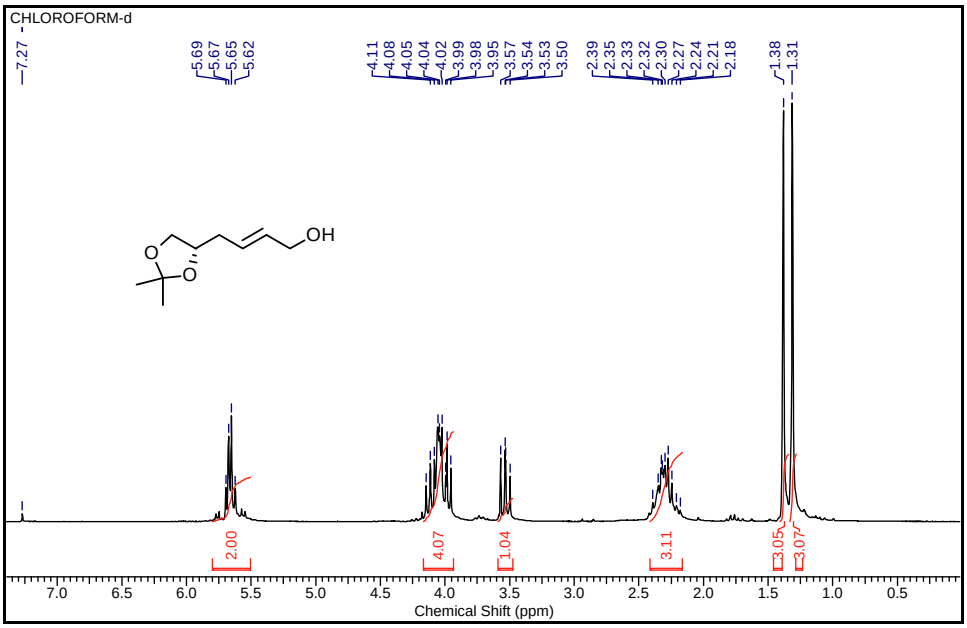
^{13}C NMR spectrum of Compound 62 in $CDCl_3$



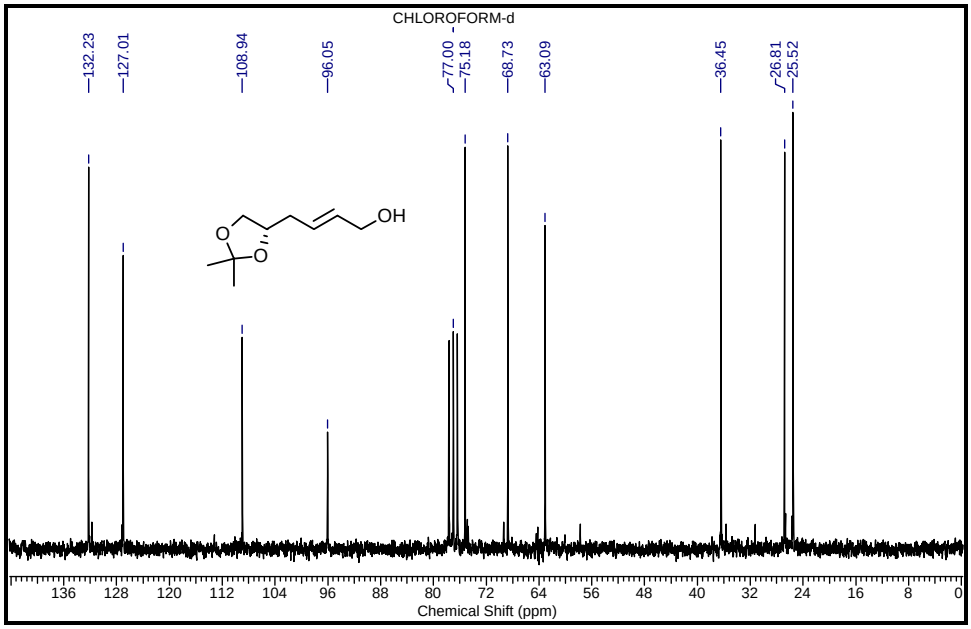
^{1}H NMR spectrum of Compound 63 in $CDCl_3$



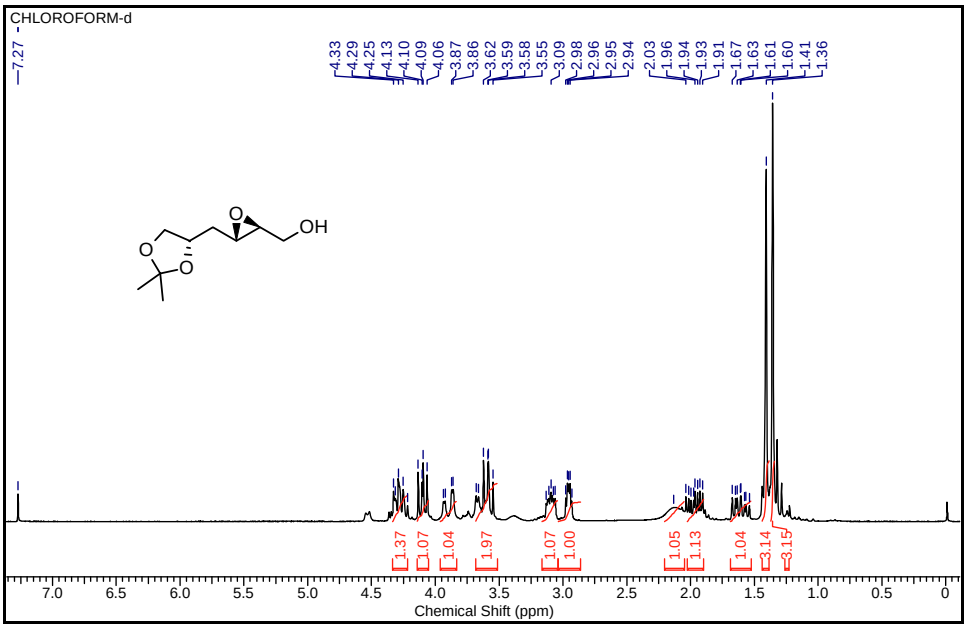
^{13}C NMR spectrum of Compound 63 in $CDCl_3$



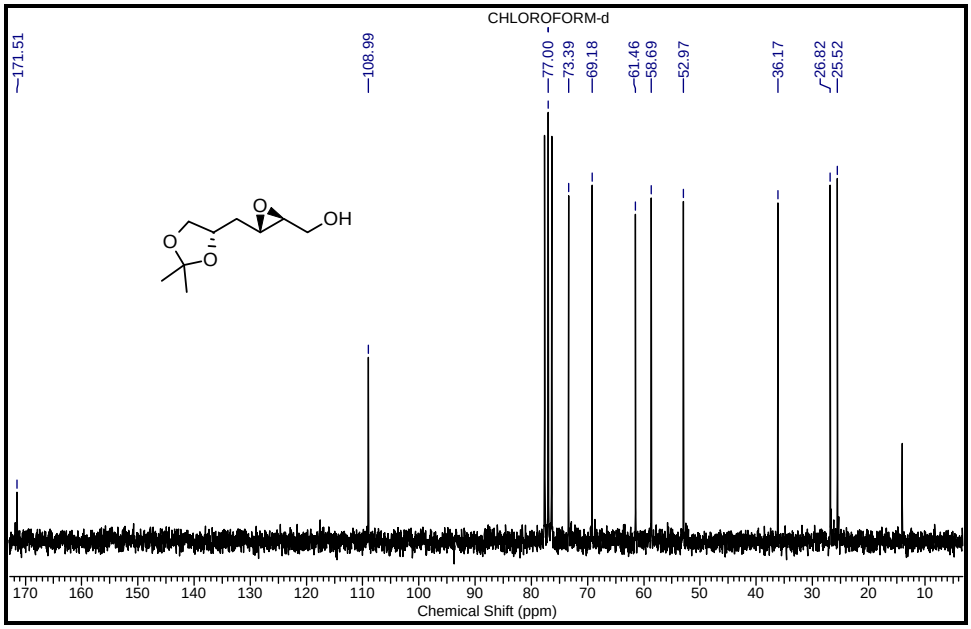
^{1}H NMR spectrum of Compound 64 in $CDCl_3$



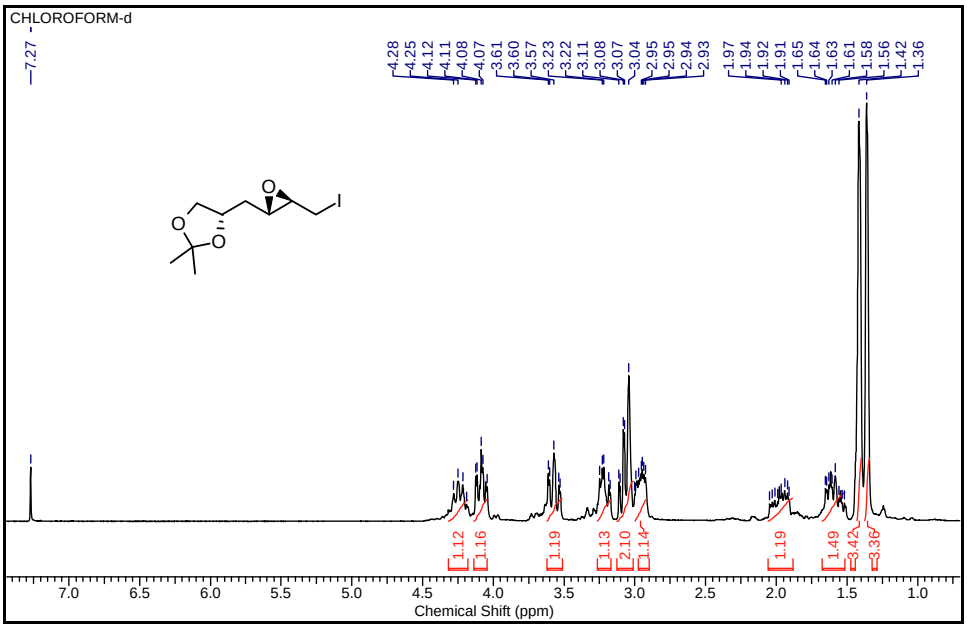
^{13}C NMR spectrum of Compound 64 in $CDCl_3$



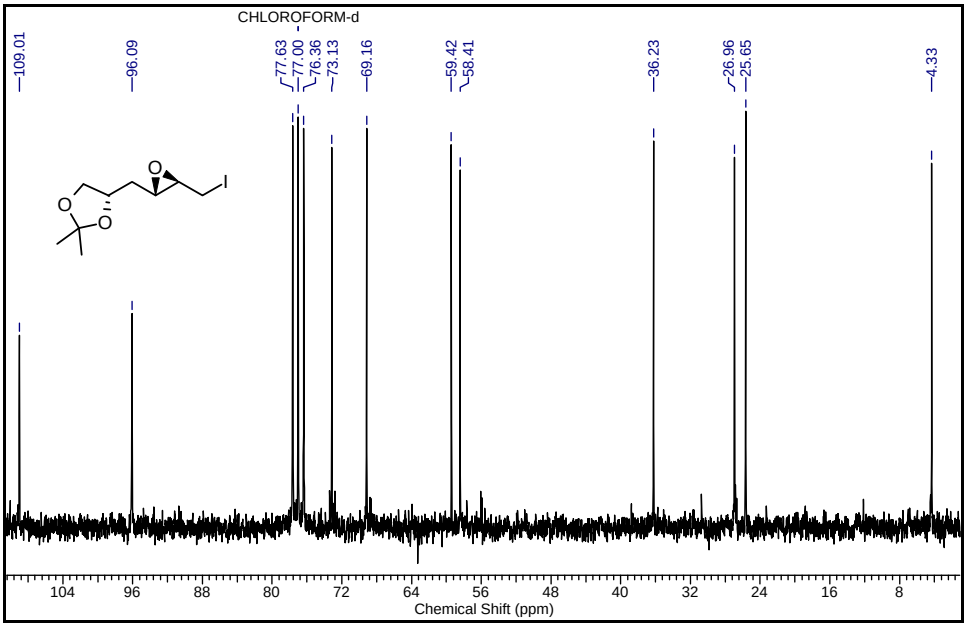
^{1}H NMR spectrum of Compound 65 in $CDCl_3$



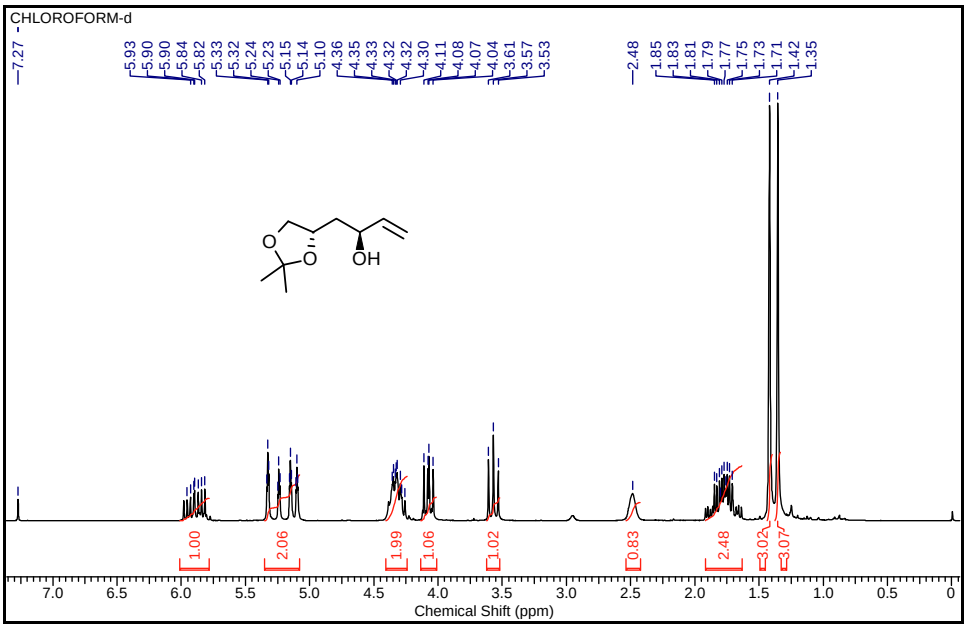
^{13}C NMR spectrum of Compound 65 in $CDCl_3$



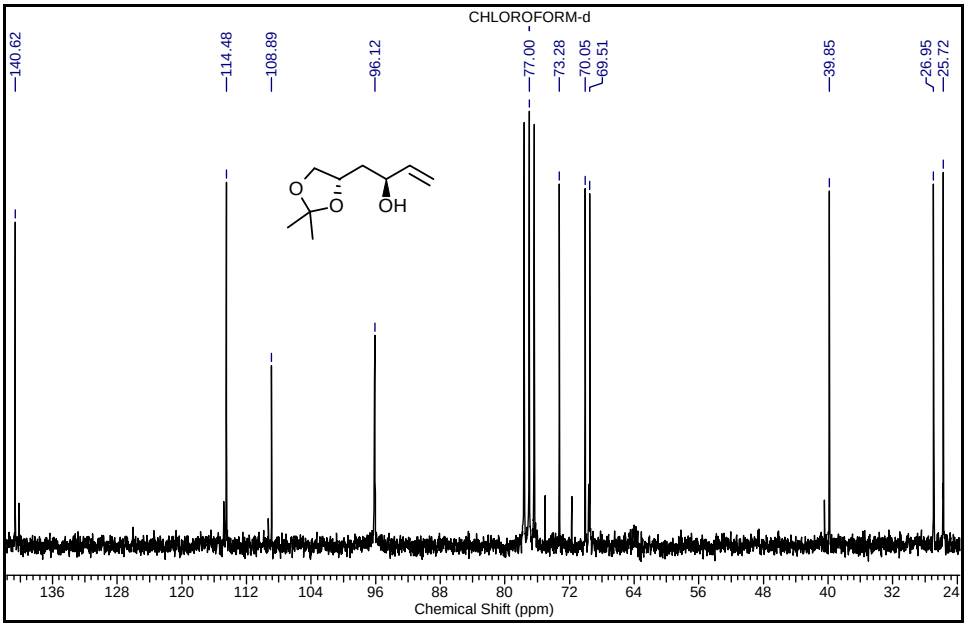
^{1}H NMR spectrum of Compound 66 in $CDCl_3$



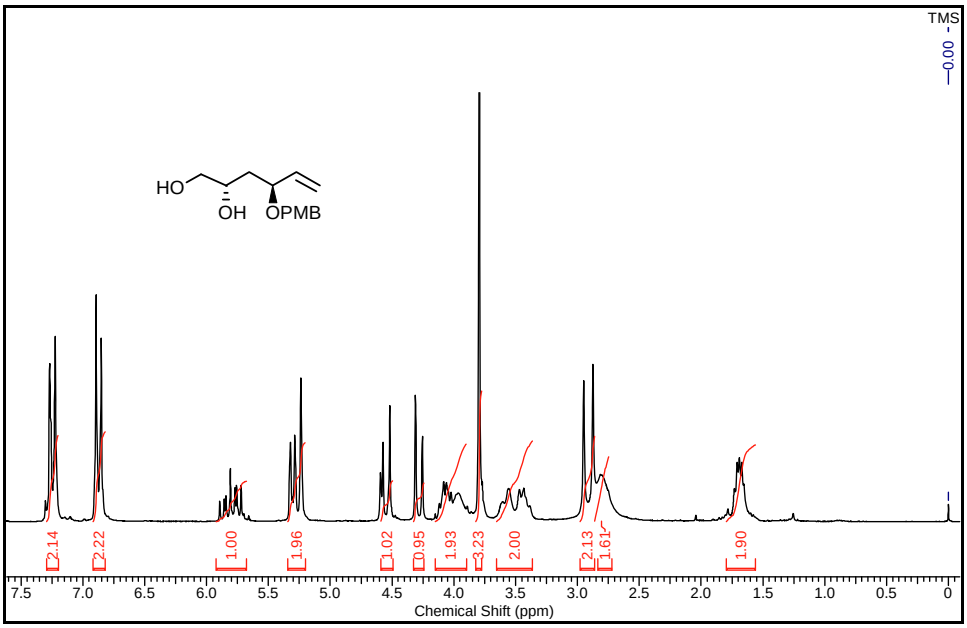
^{13}C NMR spectrum of Compound 66 in $CDCl_3$



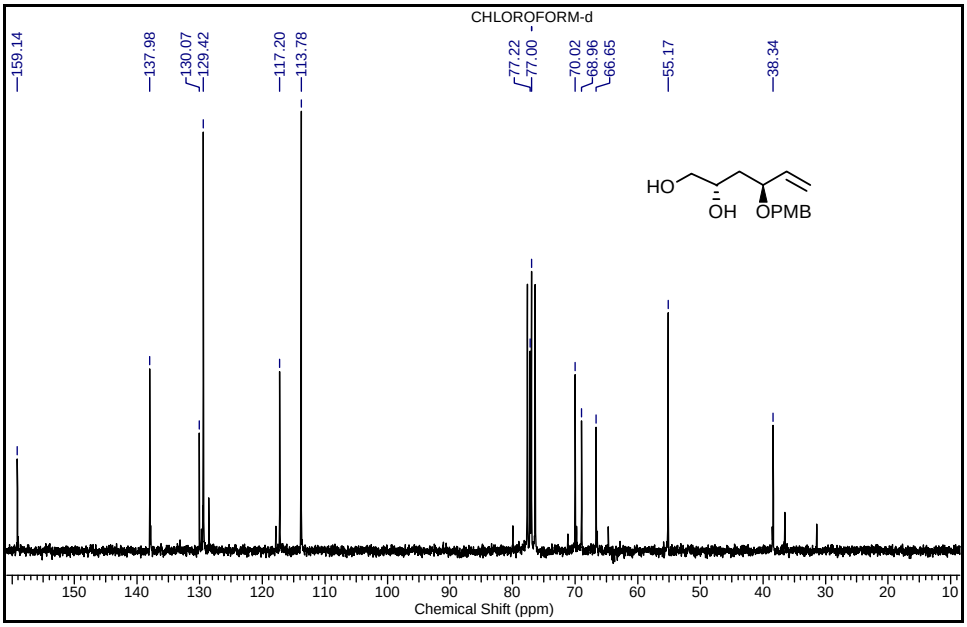
^{1}H NMR spectrum of Compound 67 in $CDCl_3$



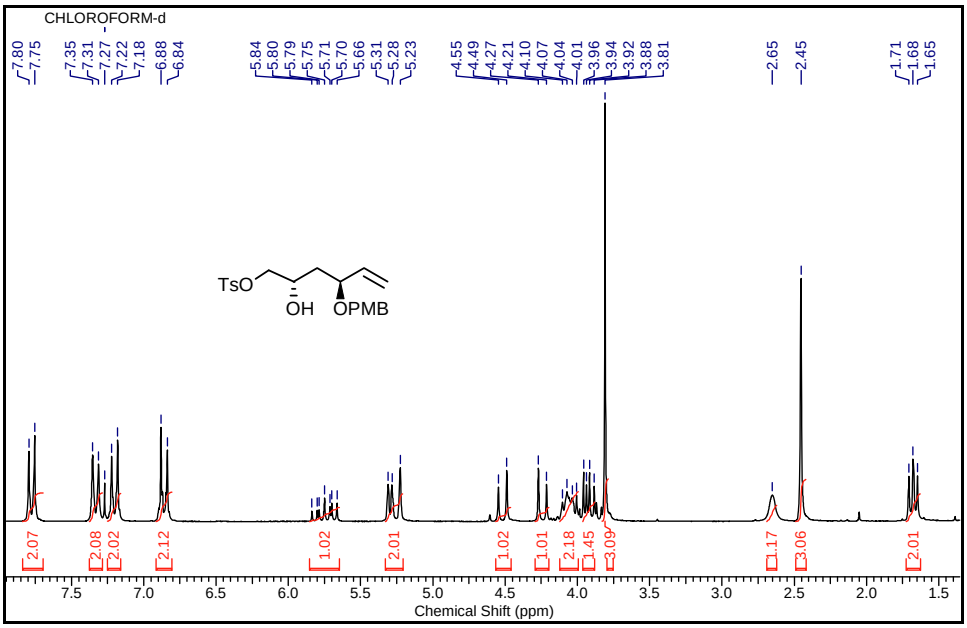
^{13}C NMR spectrum of Compound 67 in $CDCl_3$



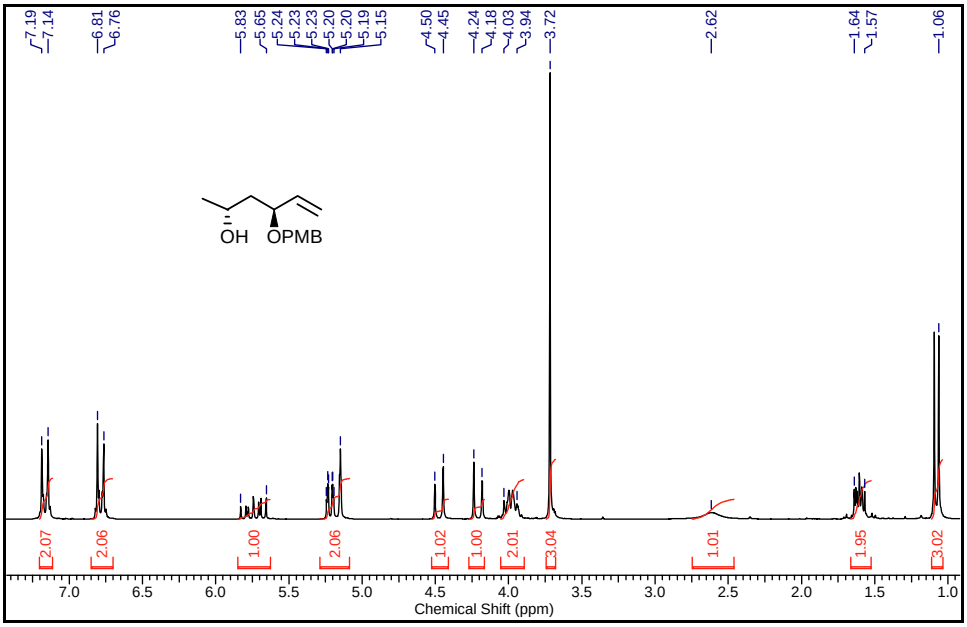
^{1}H NMR spectrum of Compound 68 in $CDCl_3$



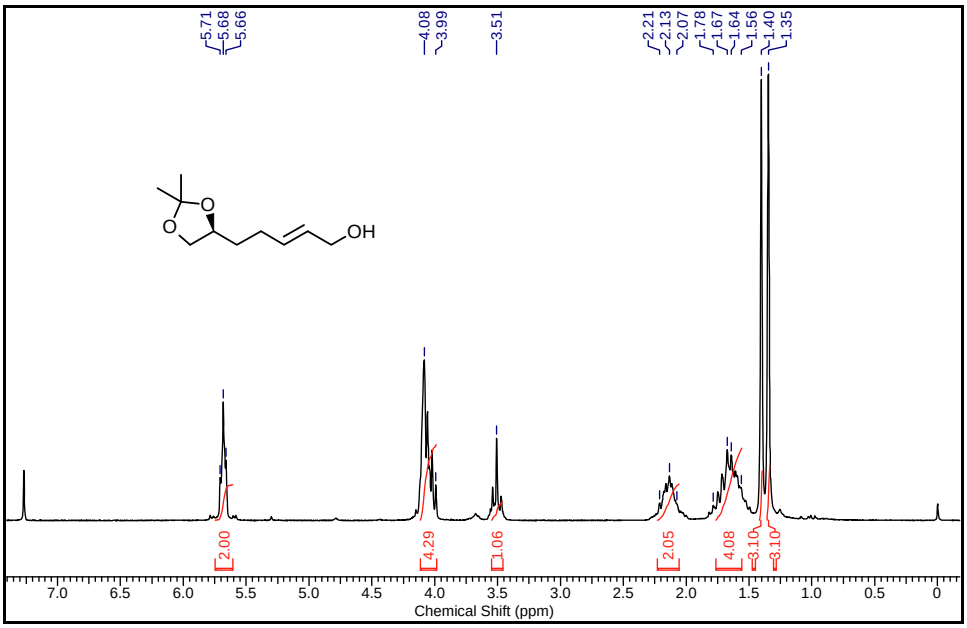
^{13}C NMR spectrum of Compound 68 in $CDCl_3$



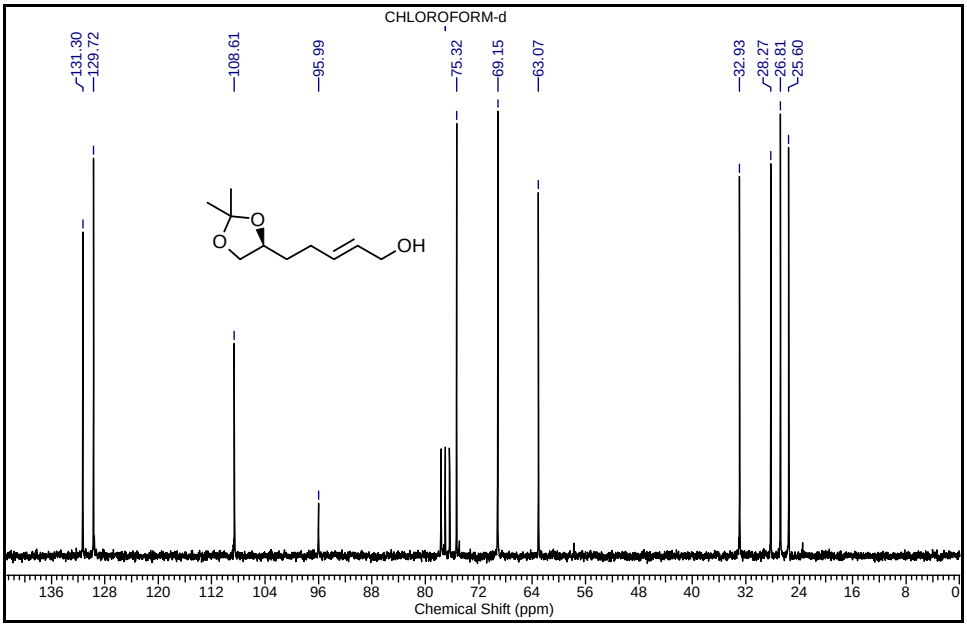
^{1}H NMR spectrum of Compound 69 in $CDCl_3$



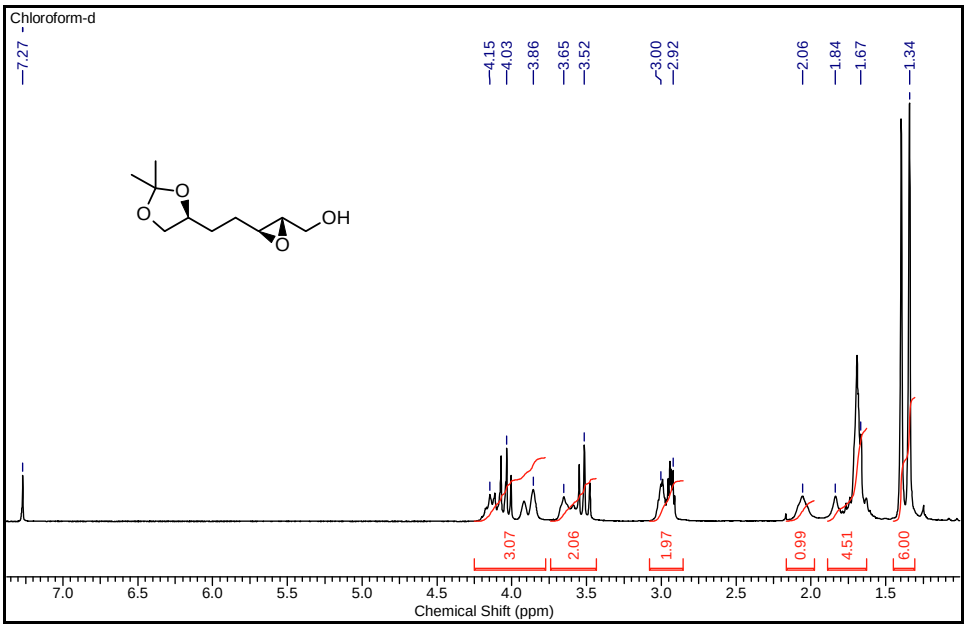
^{1}H NMR spectrum of Compound 23 in $CDCl_3$



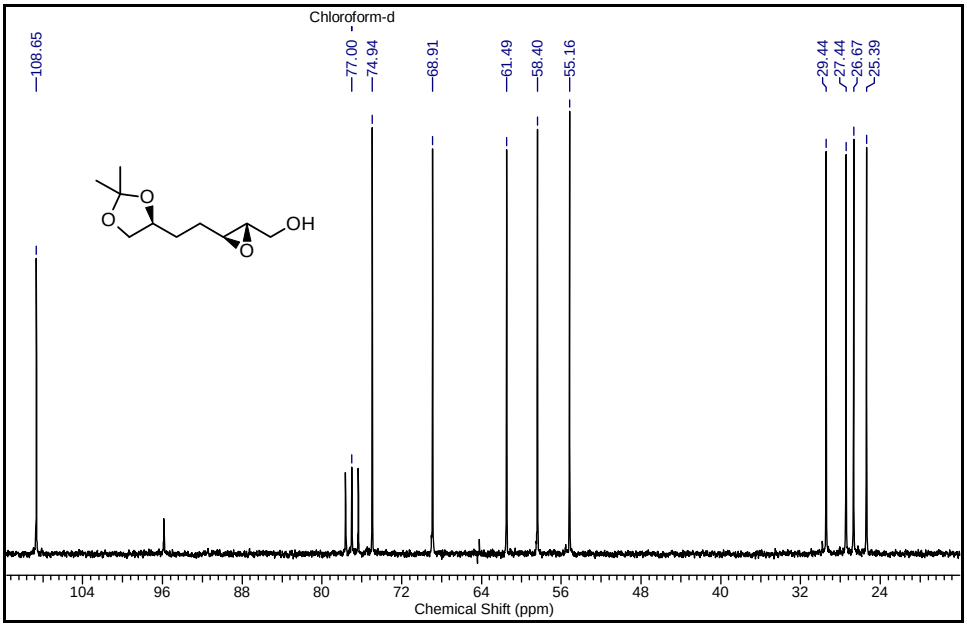
^{1}H NMR spectrum of Compound 72 in $CDCl_3$



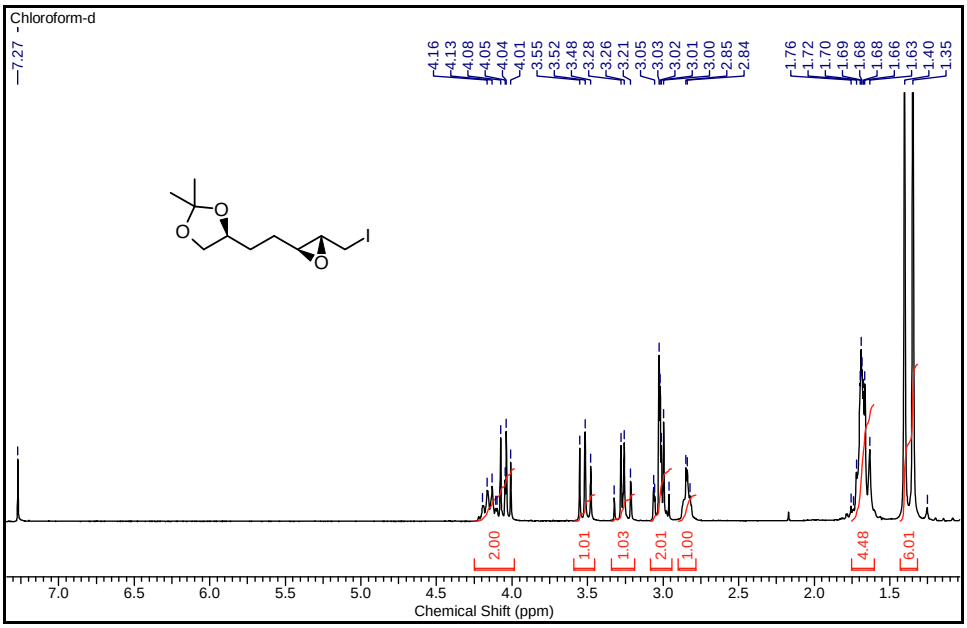
^{13}C NMR spectrum of Compound 72 in $CDCl_3$



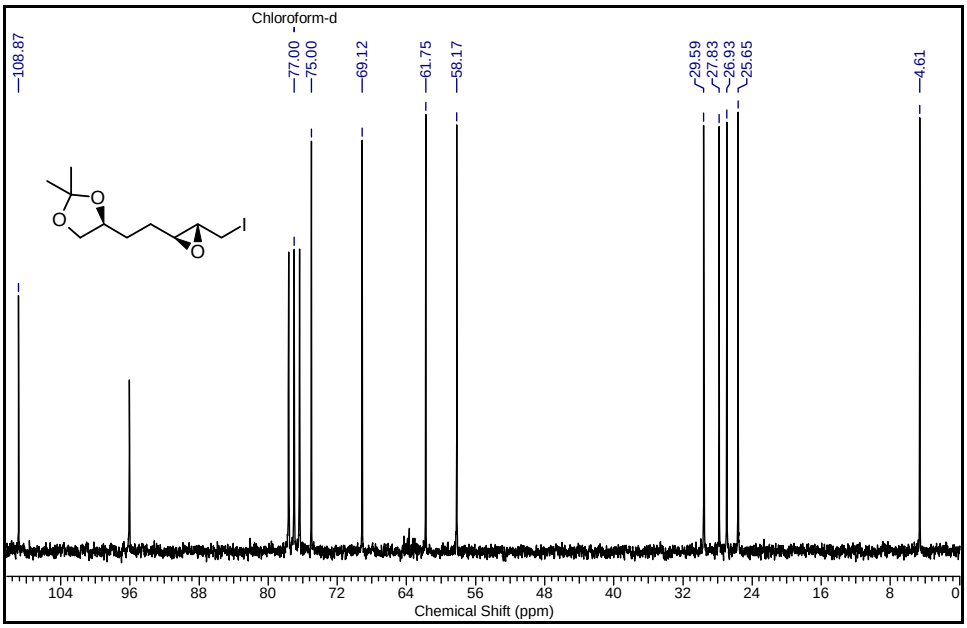
^{1}H NMR spectrum of Compound 73 in $CDCl_3$



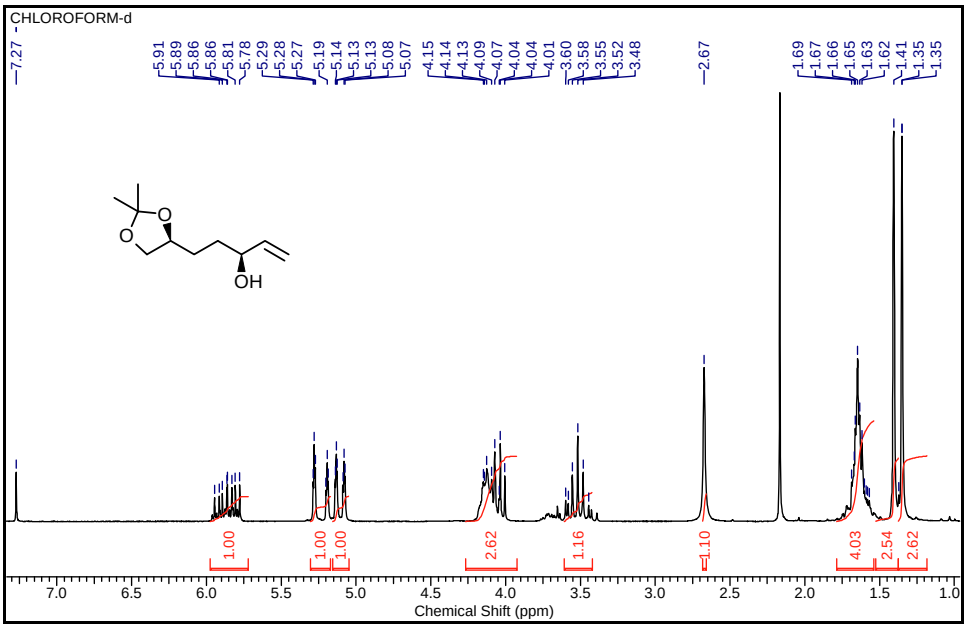
^{13}C NMR spectrum of Compound 73 in $CDCl_3$



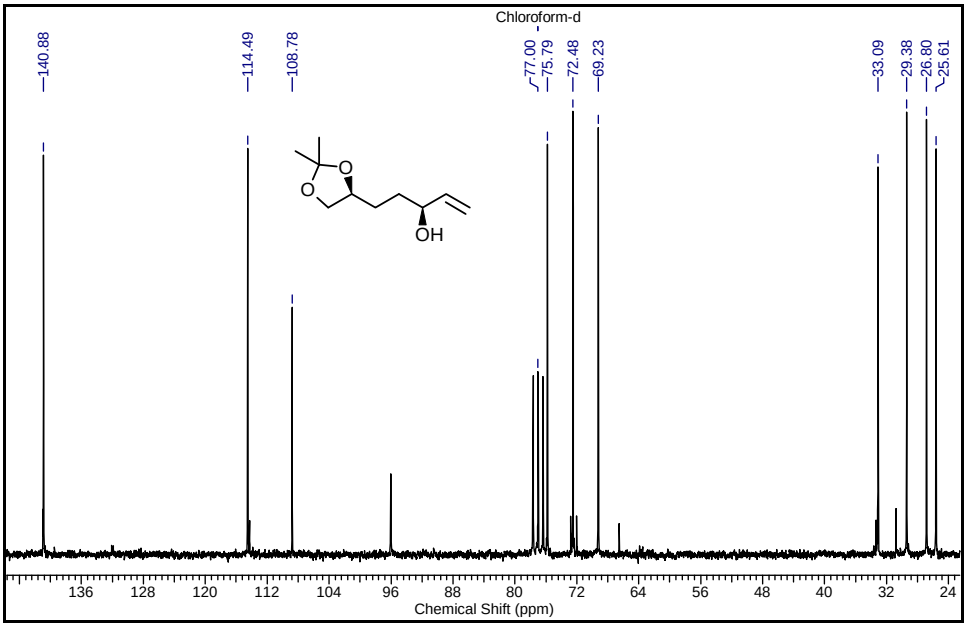
^{1}H NMR spectrum of Compound 74 in $CDCl_3$



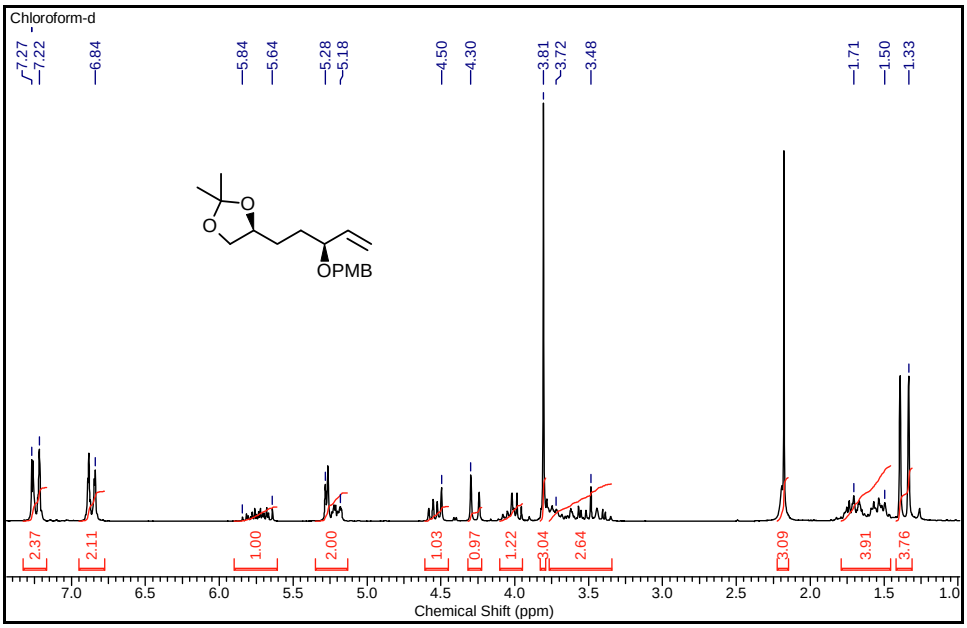
^{13}C NMR spectrum of Compound 74 in $CDCl_3$



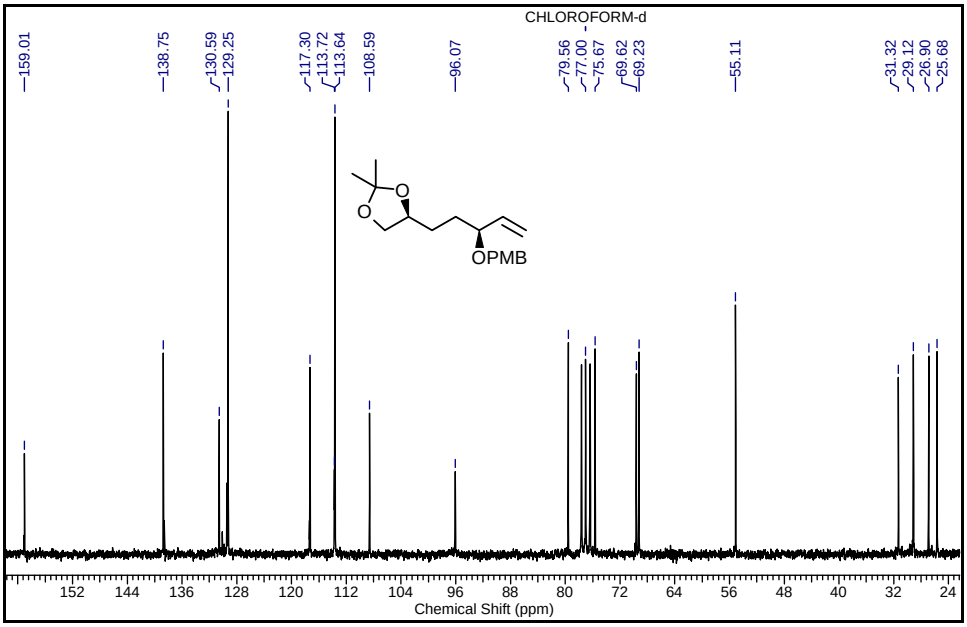
^{1}H NMR spectrum of Compound 75 in $CDCl_3$



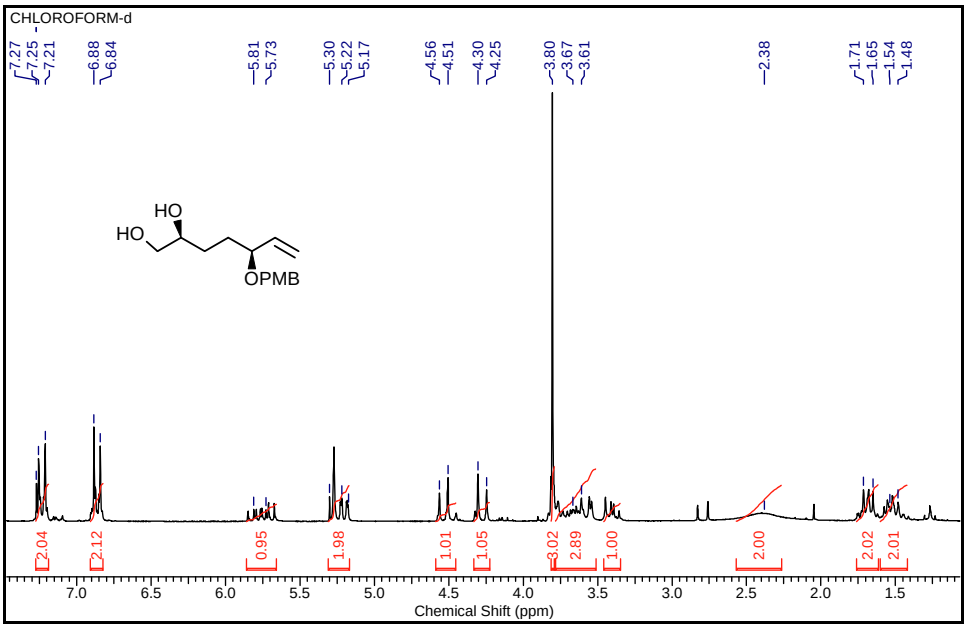
^{13}C NMR spectrum of Compound 75 in $CDCl_3$



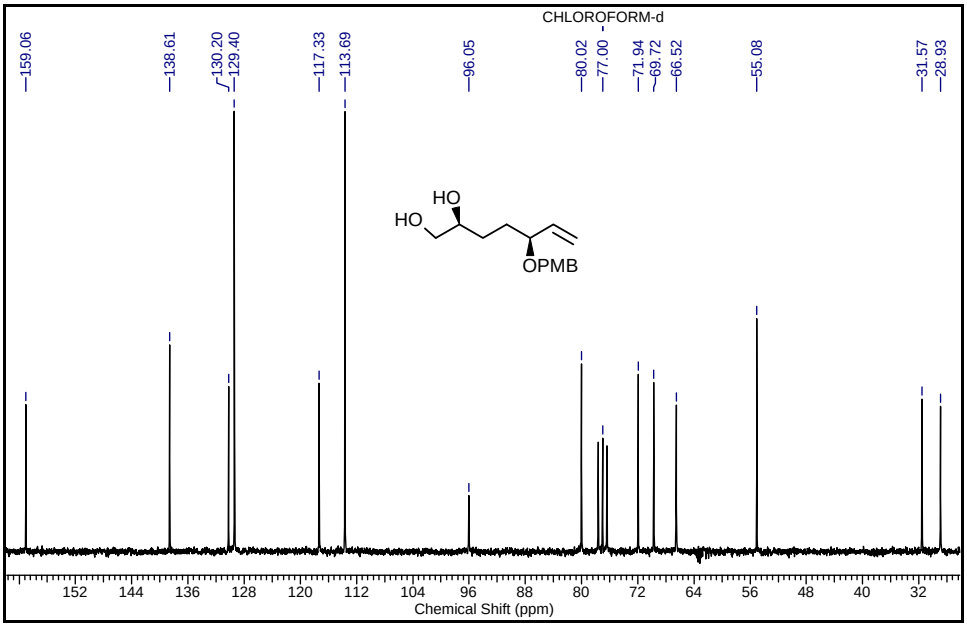
^{1}H NMR spectrum of Compound 76 in $CDCl_3$



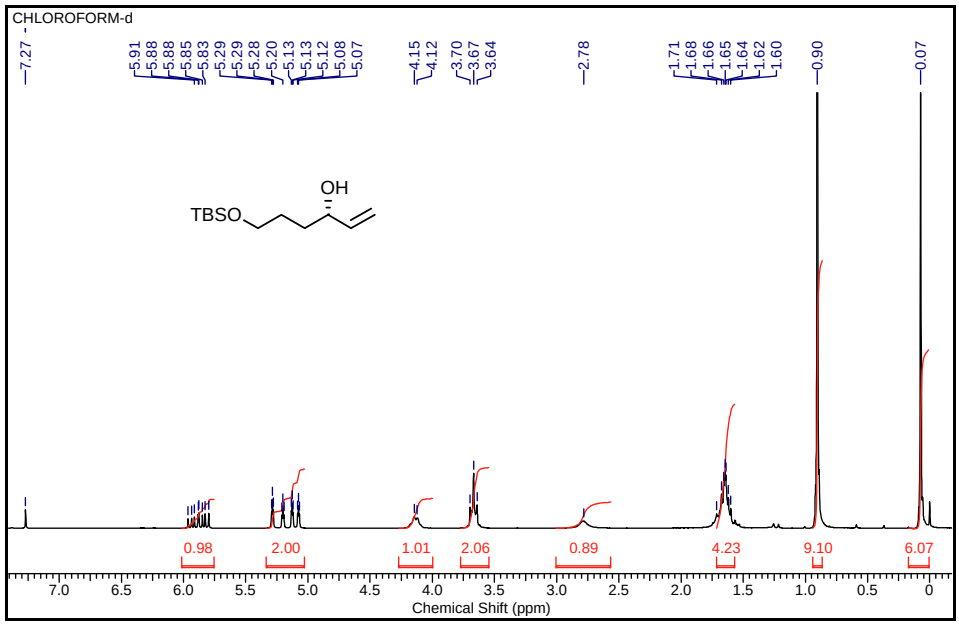
^{13}C NMR spectrum of Compound 76 in $CDCl_3$



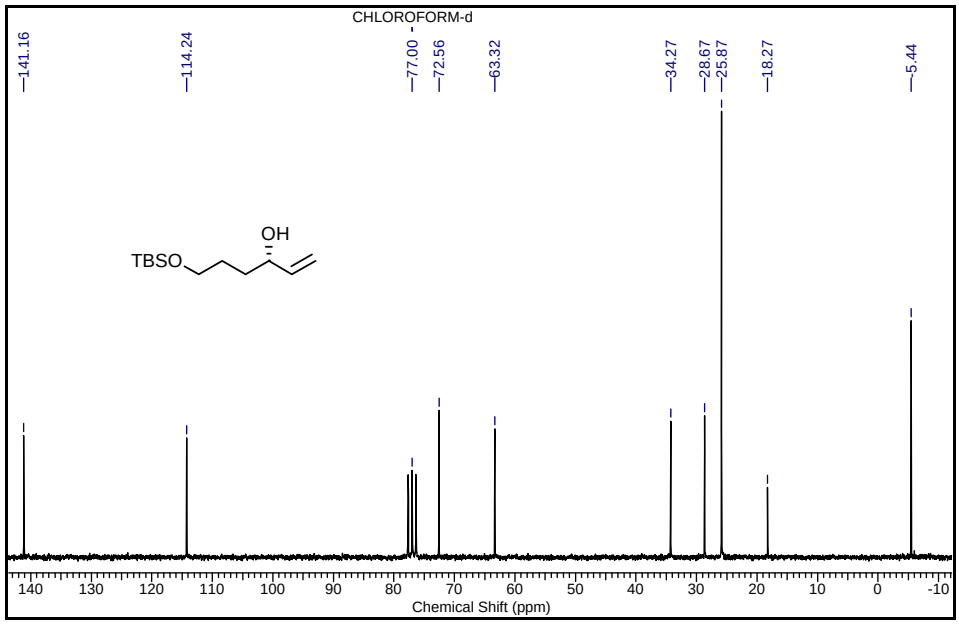
^{1}H NMR spectrum of Compound 77 in $CDCl_3$



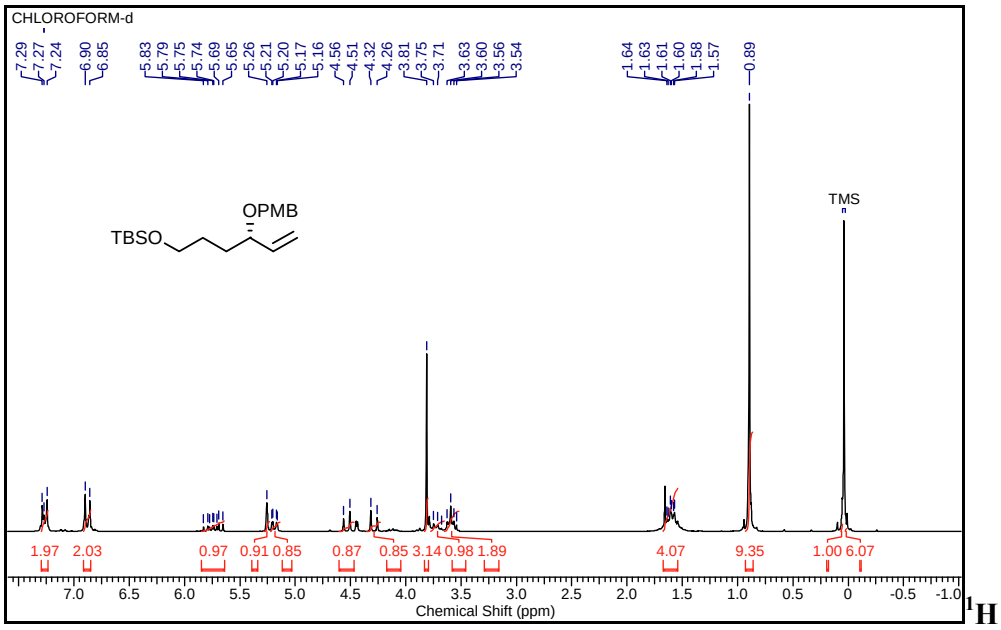
^{13}C NMR spectrum of Compound 77 in $CDCl_3$



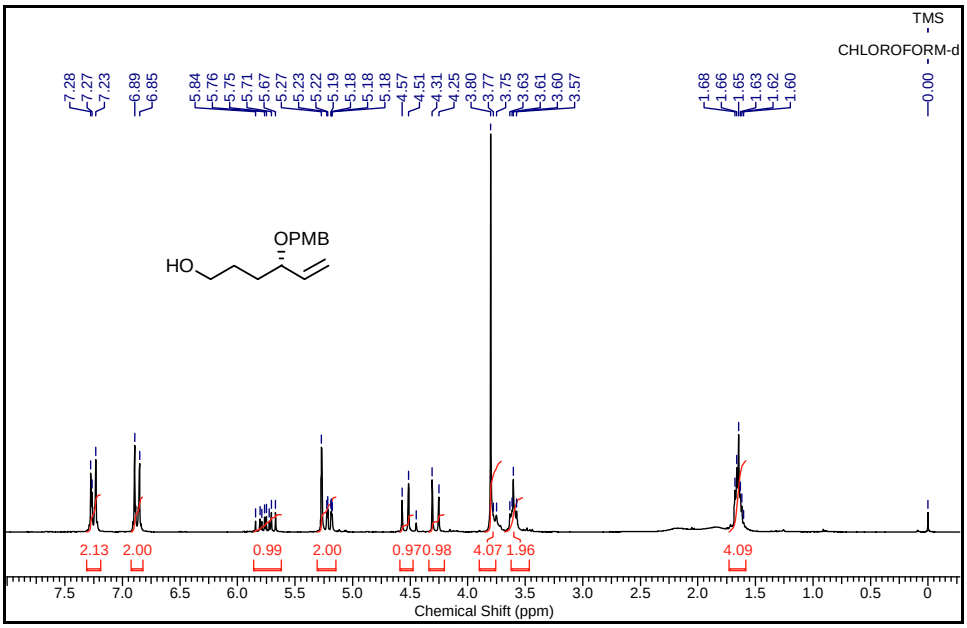
^{1}H NMR spectrum of Compound 82 in $CDCl_3$



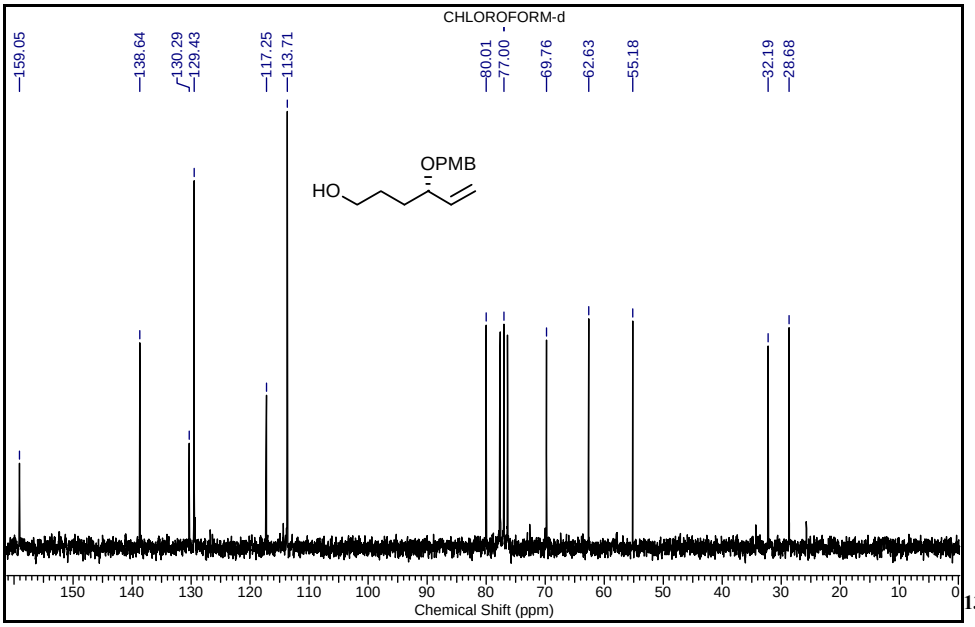
^{13}C NMR spectrum of Compound 82 in $CDCl_3$



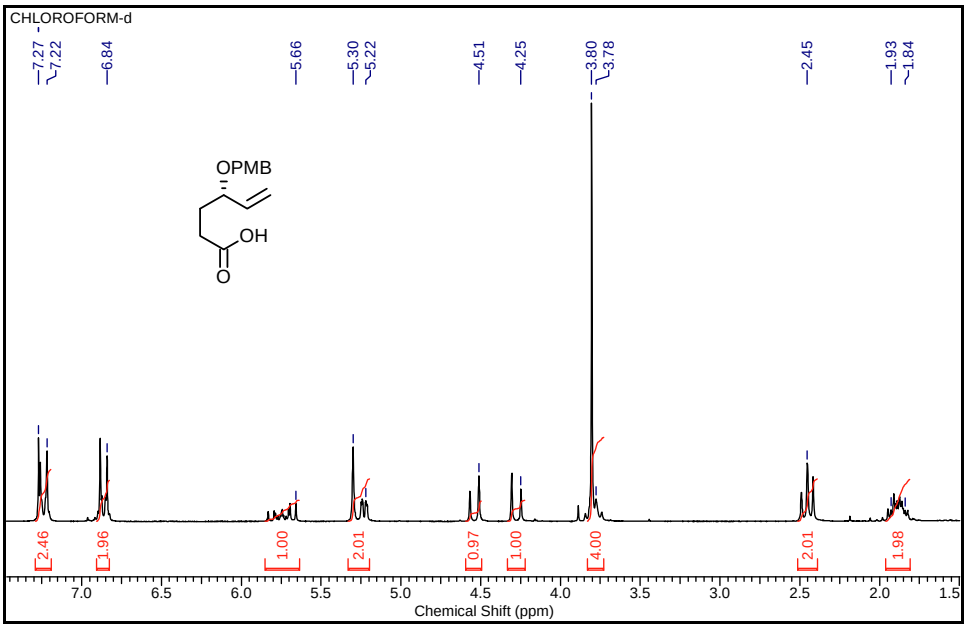
NMR spectrum of Compound 83 in $CDCl_3$



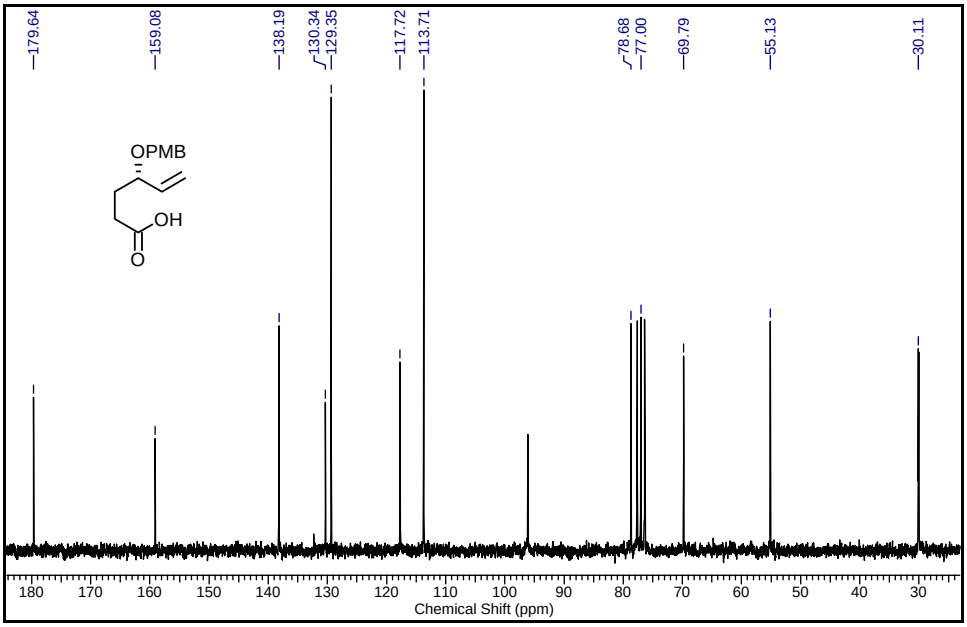
^{1}H NMR spectrum of Compound 84 in $CDCl_3$



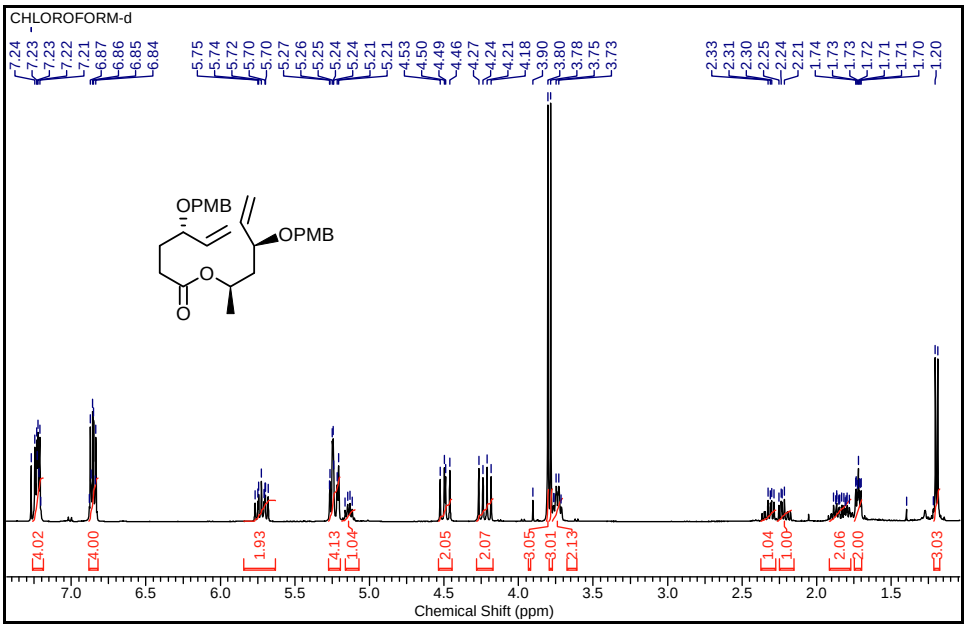
^{13}C NMR spectrum of Compound 84 in $CDCl_3$



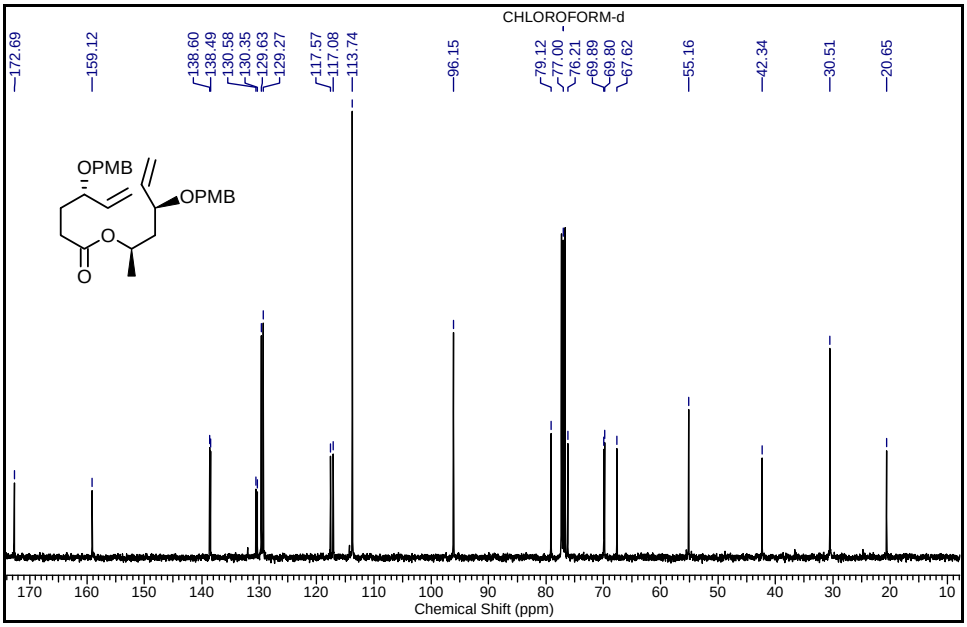
^{1}H NMR spectrum of Compound 15 in $CDCl_3$



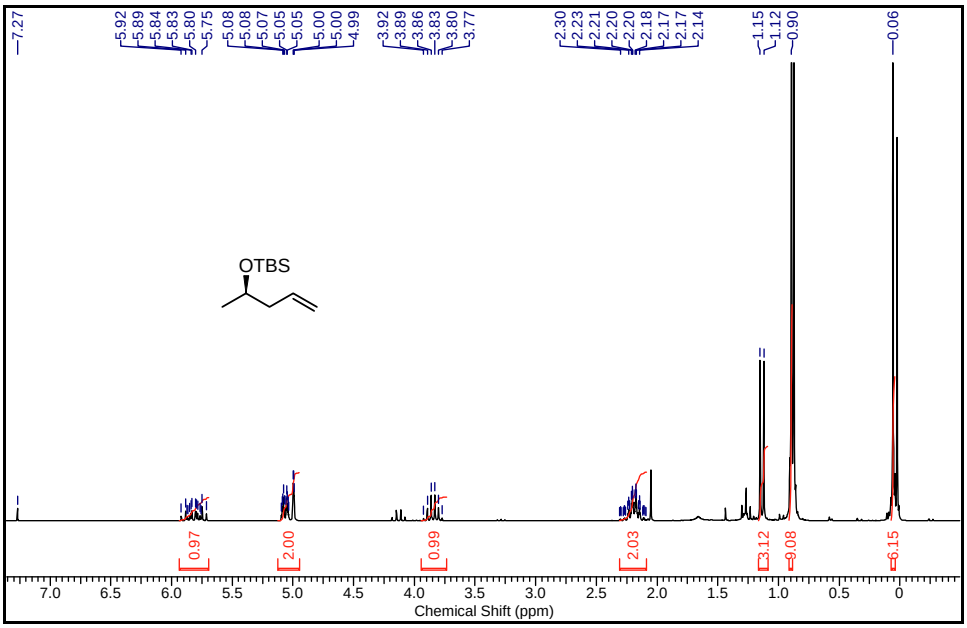
^{13}C NMR spectrum of Compound 15 in $CDCl_3$



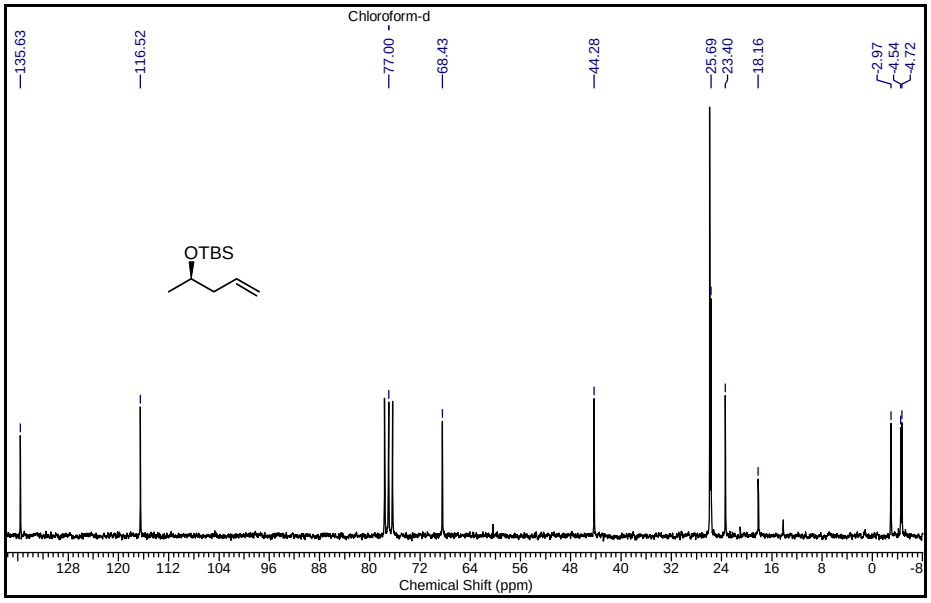
^{1}H NMR spectrum of Compound 24 in $CDCl_3$



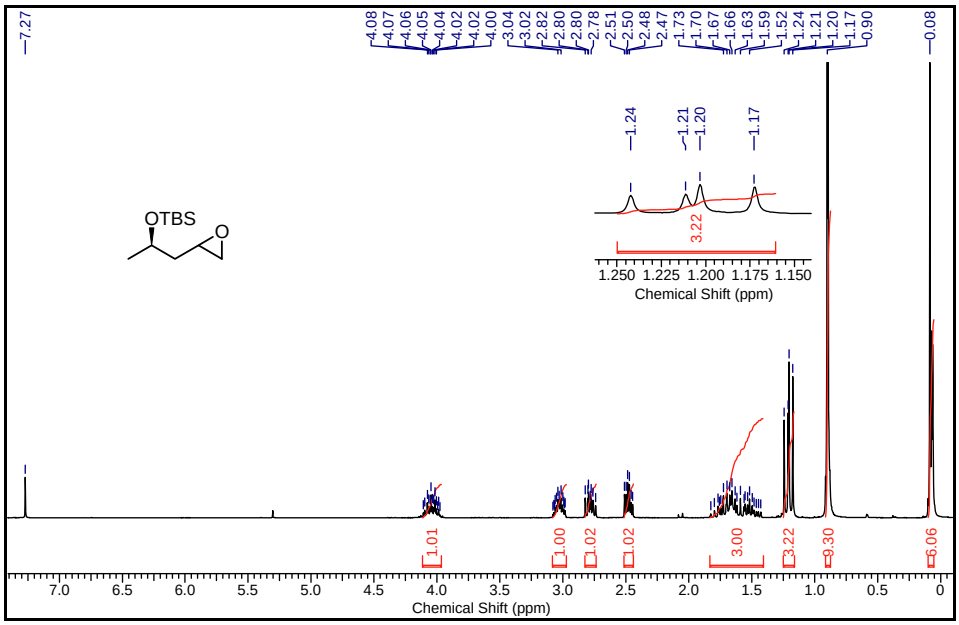
^{13}C NMR spectrum of Compound 24 in $CDCl_3$



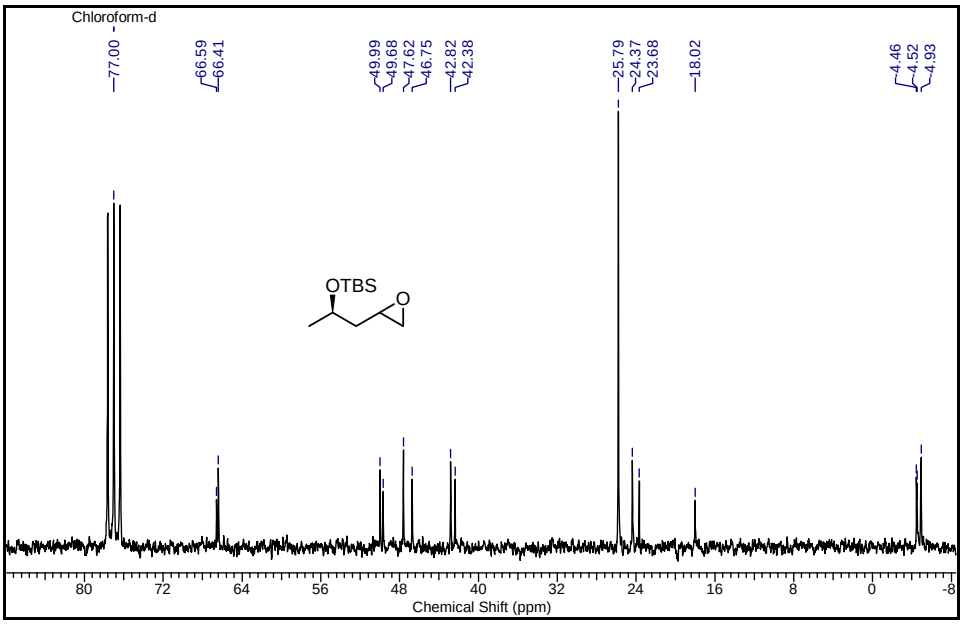
^{1}H NMR spectrum of Compound 88 in $CDCl_3$



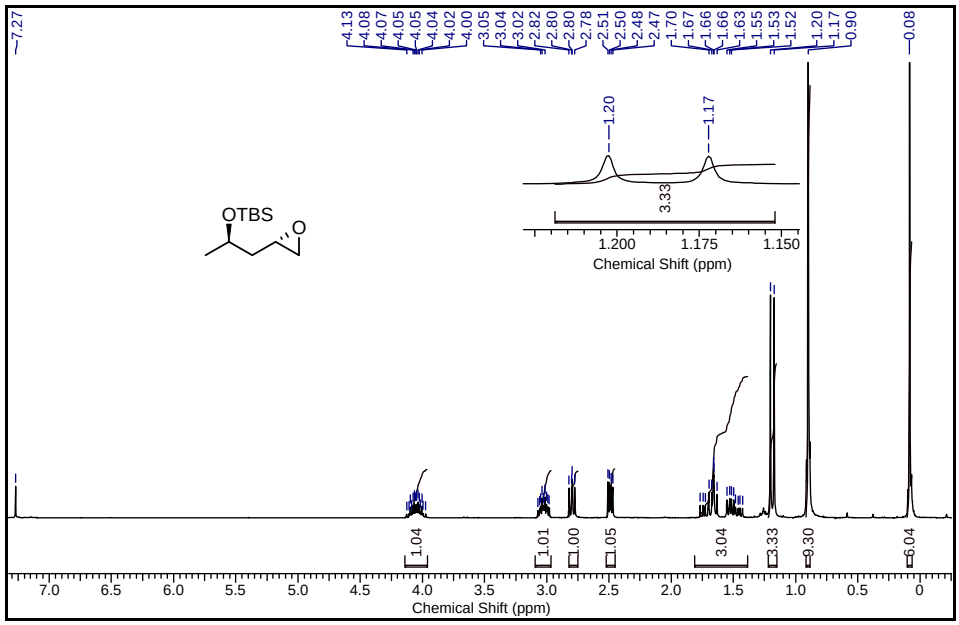
^{13}C NMR spectrum of Compound 88 in $CDCl_3$



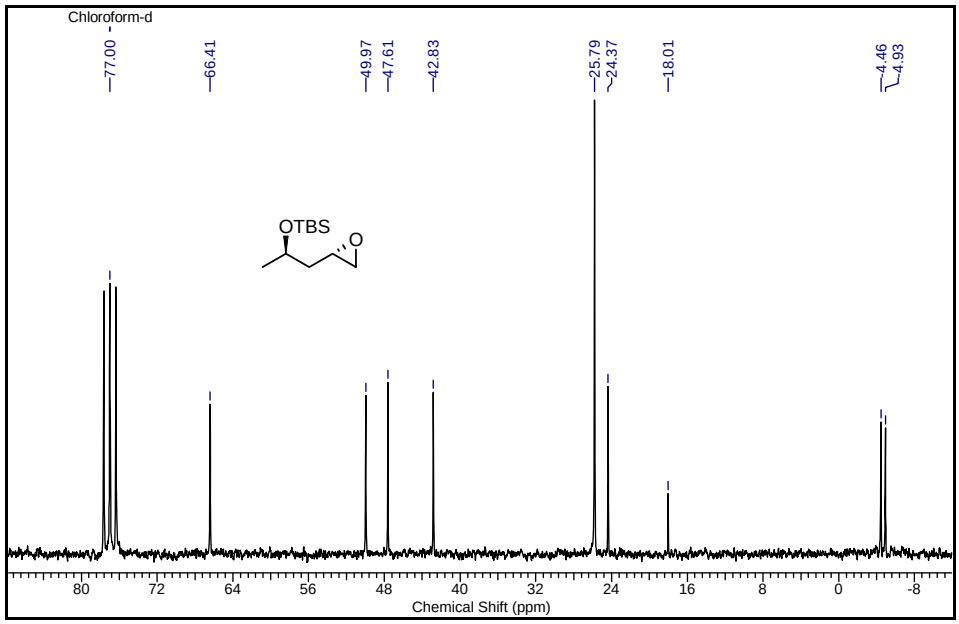
^{1}H NMR spectrum of Compound 89 in $CDCl_3$



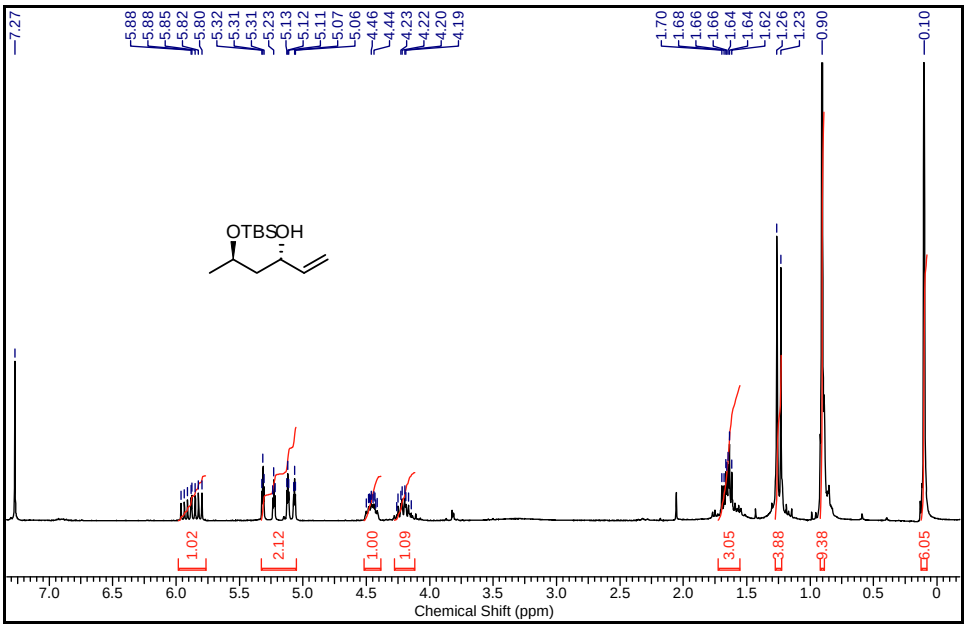
^{13}C NMR spectrum of Compound 89 in $CDCl_3$



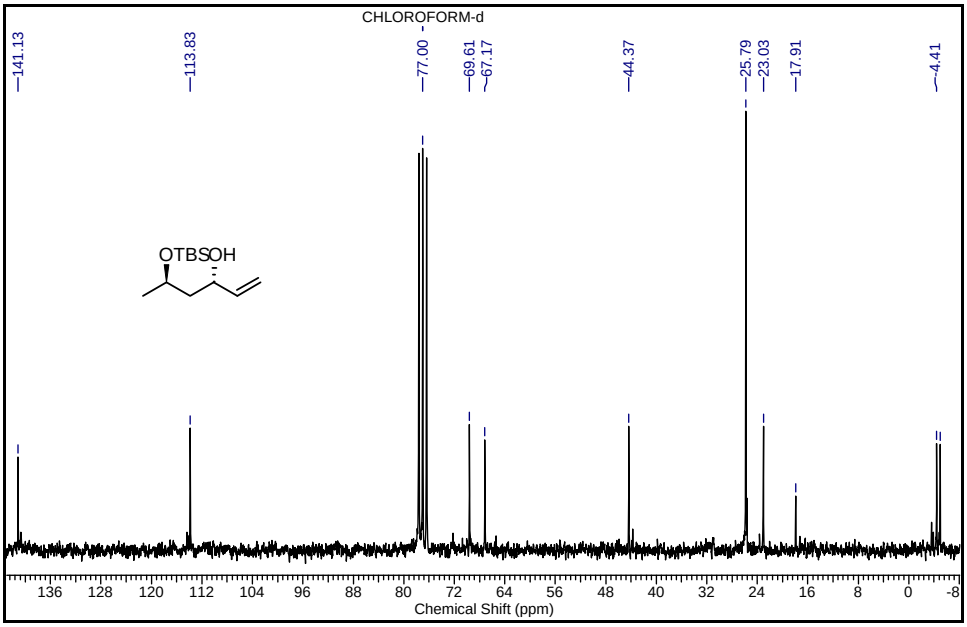
^{1}H NMR spectrum of Compound 90 in $CDCl_3$



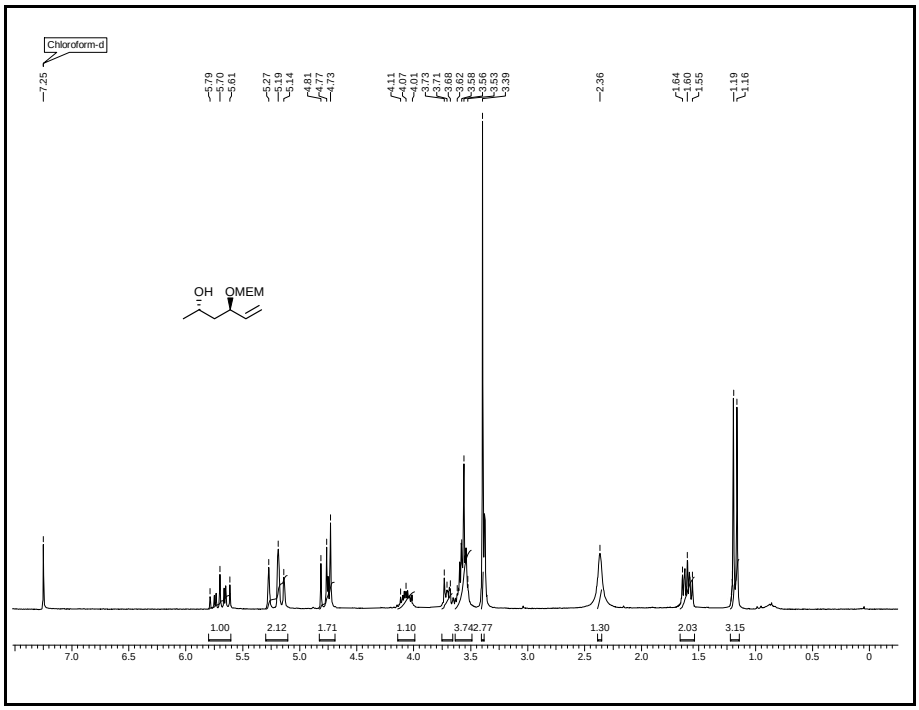
^{13}C NMR spectrum of Compound 90 in $CDCl_3$



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



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



^{1}H NMR spectra of **93**

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Studies directed towards the synthesis of Dodoneine

Introduction

Today, in the 21st century, when science and technology have reached great heights, some diseases like hypertension, cardiovascular events such as stroke, heart attack etc. remain a big concern for the human being. Cardiovascular disease refers to the class of diseases that involve the heart or blood vessels (arteries and veins). While the term technically means any disease that affects the cardiovascular system, it is usually used to refer to those related to atherosclerosis (arterial disease).

Among the various types of cardiovascular diseases, the most common and important one is high blood pressure (hypertension). In this prologue we would focus mainly on the pros and cons of this particular cause. Hypertension, most commonly referred to as "high blood pressure", is a medical condition in which the blood pressure is chronically elevated. It was previously referred as nonarterial hypertension, but in current usage, the word "*hypertension*" without a qualifier normally refers to arterial hypertension (high blood pressure of the arteries).[1] Persistent hypertension is one of the risk factors for strokes, heart attacks, heart failure and arterial aneurysm, and is a leading cause of chronic renal failure. Even moderate elevation of arterial blood pressure leads to shortened life expectancy. At severely high pressures, defined as mean arterial pressures 50% or more above average, a person can expect to live no more than a few years unless appropriately treated.[2] Hypertension is considered to be present when a person's systolic blood pressure is consistently 140 mmHg or greater, and/or their diastolic blood pressure is consistently 90 mmHg or greater. Recently, as of 2003, the *Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure*[3] has defined blood pressure 120/80 mmHg to 139/89 mmHg as "prehypertension". Prehypertension is not a disease category; rather, it is a designation chosen to identify individuals at high risk of developing hypertension. The Mayo Clinic website specifies blood pressure is "normal if it's below 120/80" but that "some data indicate that 115/75 mm Hg should be the gold standard." Studies have shown that in patients with diabetes mellitus or kidney disease, blood pressure over 130/80 mmHg should be considered high and warrants further treatment.

Based on the nature and symptoms of a patient, hypertension can be classified as follow:

1) Primary or essential hypertension

2) Secondary hypertension

1) Primary hypertension: Nearly 95% of all hypertensives suffer from this type of hypertension. In these cases, despite all investigations, one cannot attribute any direct cause for the problem of hypertension. There could be a whole lot of contributory factors, like the patient's lifestyle or various hereditary factors.

2) Secondary hypertension: Approximately 4-5% of all patients with hypertension have specific causes. In particular, patients in whom hypertension develops at an early age, those who first exhibit hypertension when over age 50 years, or those previously well controlled who become refractory to treatment are more likely to have secondary hypertension. Causes include renal disease, genetic causes, renal vascular hypertension, primary hyperaldosteronism, Cushing's syndrome, pheochromocytoma, coarctation of the aorta, hypertension associated with pregnancy, estrogen use, as well as other causes (eg. hypercalcemia and medications).

Factors of primary/essential hypertension: Although no specific medical cause can be determined in essential hypertension, the most common form has several contributing factors. These include salt sensitivity, renin homeostasis, insulin resistance, genetics, and age to name a few**.**

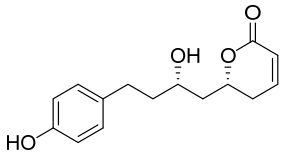
Etiology of secondary hypertension: Only in a small minority of patients with elevated arterial pressure, a specific cause can be identified. This is probably due to an endocrine or renal defect that, if corrected, could bring blood pressure back to normal values.

Coarctation of the aorta: Coarctation of the aorta accounts for approximately 5% of all heart diseases and is found at necropsy in up to 1:1550 patients.[4] It is approximately three times more common in males.[5] The traditional classification into infantile (preductal) and (postductal) types is now regarded as too simplistic, since many patients with preductal lesions do not present until adulthood.[6] Coarctation of the aorta was not regularly diagnosed clinically until after 1933.[7] Details of the natural history of aortic coarctation are therefore incomplete, being largely derived from hospital post-mortem records and selected case series prior to 1945, at which time operative repair was introduced. As hypertension is a multiparametric pathology, its treatment generally involves a large panel of drugs.

The development of new, cost-effective, non-toxic drugs is required to contribute to the world-wide control of these diseases. In some developing countries where it also

affects a significant part of people hypertension is usually treated by plant decoctions or extracts.

In 2007, Coustard and co-workers isolated a new dihydropyranone, (*R*)-6-[(*S*)-2-hydroxy-4-(4-hydroxyphenyl)butyl]-5,6-dihydropyran-2-one (named as Dodoneine) **1**, from well studied mistletoe already known for its various remedies,[8] *Tapinanthus dodoneifolius* (synonym = *Agelanthus dodoneifolius*). The structure was determined from spectroscopic and X-ray crystallographic analysis. Dodoneine showed a relaxing effect on preconstricted rat aortic rings (IC_{50} of 81.4 ± 0.9 μM).

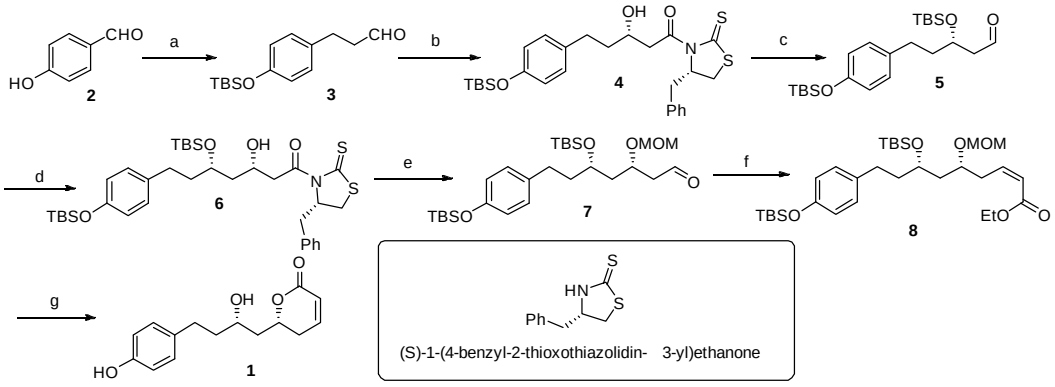


Dodoneine 1

Literature review

Srihari *et al.*[9]

Srihari and co workers reported the first stereoselective total synthesis of (+)-dodoneine which involves a Crimmins aldol reaction and a Horner–Wadsworth–Emmons olefination as the key steps.

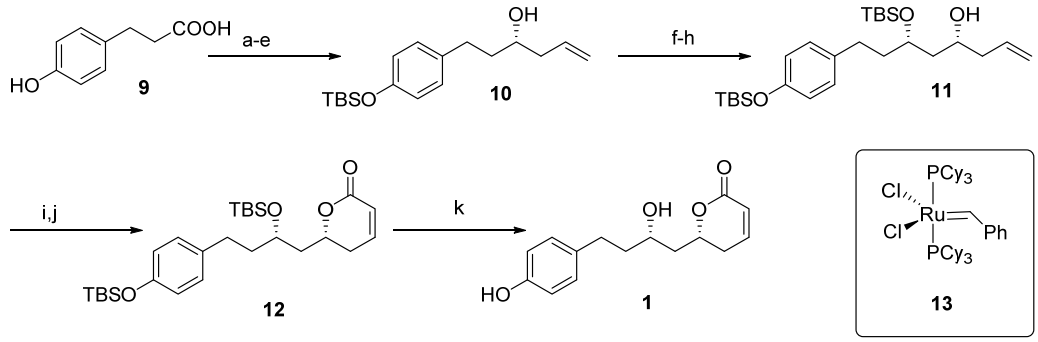


Scheme 1: *Reagents and conditions*: (a) (i) Ph_3PCHCO_2Et, CH_2Cl_2, 12 h; (ii) TBSCl, imidazole, 2 h, rt, 98%; (iii) LAH, THF, reflux, 30 min.; (iv) PCC, CH_2Cl_2, 0 ^oC-rt, 1 h 86%; (b) (i) (S)-1-(4-benzyl-2-thioxothiazolidin- 3-yl)ethanone, $TiCl_4$, DIPEA CH_2Cl_2, -78 ^oC 85%; (ii) TBSCl, 2,6-lutidine DMF, rt, 4 h, 98%; (c) DIBAL-H, CH_2Cl_2, -78 ^oC, 5 min, 93%; (d) (S)-1-(4-benzyl-2-thioxothiazolidin- 3-yl)ethanone, $TiCl_4$, DIPEA CH_2Cl_2, -78 ^oC 81%; (e) (i) MOMCl, DIPEA CH_2Cl_2, -78 ^oC 76% (ii) DIBAL-H CH_2Cl_2, -78 ^oC, 5 min, 93%; (f) $(CF_3CH_2O)_2P(O)CH_2CO_2CH_3$, NaH, THF, -78 ^oC, 82% (g) 3 M HCl, THF (1:1), 18 h, rt 70%

The synthesis started with 2C-Wittig homologation of 4-hydroxybenzaldehyde **2,** protection of the resulting product with TBSCl, $LiAlH_4$ reduction and PCC oxidation gave aldehyde **3**. The aldehyde **3** was treated with (S)-1-(4-benzyl-2-thioxothiazolidin- 3-yl)ethanone in the presence of titanium chloride using the Crimmins protocol to give the easily separable diastereomers of β-hydroxy amide **4**. The hydroxyl group in **4** was protected as TBS ether and then treated with DIBAL-H to give aldehyde **5**. The aldehyde **5** was subjected to the Crimmins aldol reaction with (S)-1-(4-benzyl-2-thioxothiazolidin-3-yl)ethanone to give compound **6**. The free hydroxyl group in compound **6** was masked as MOM ether and treated with DIBAL-H to provide aldehyde **7** which was further subjected to a Horner–Wadsworth–Emmons olefination reaction to give the cis-olefinic ester **8**. The global deprotection of the silyl and MOM groups and simultaneous cyclization of the ester and alcohol functionalities with 3 mol % HCl solution acid gave Dodoneine **1**.

Marco *et al.*[10]

Another asymmetric synthesis of **1** was reported by Marco and co workers in 2008. Homoallyl alcohol **10** was prepared from commercial dihydro-*p*-coumaric acid **9** according to previously described procedures, which included asymmetric Keck allylation of an intermediate silylated dihydro-*p*-coumaraldehyde. Homoallyl alcohol **10** was also prepared by Brown's asymmetric allylboration of the same intermediate (scheme 2).

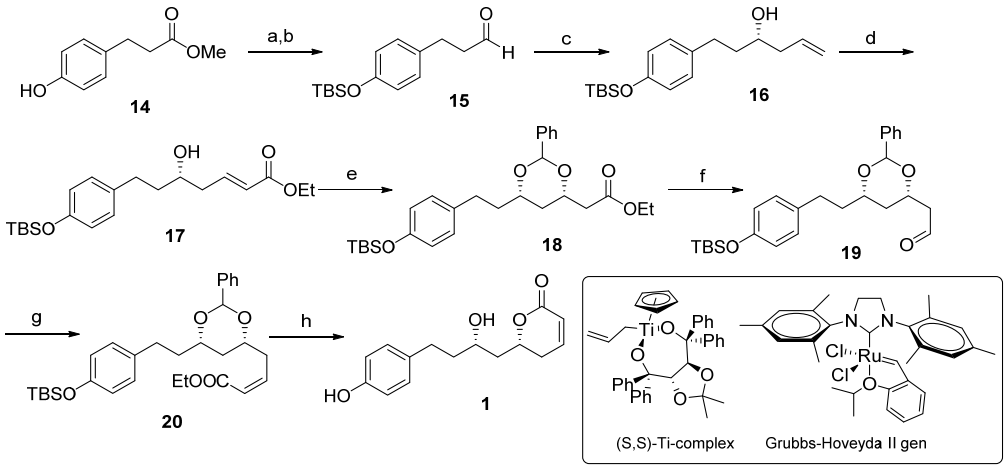


Scheme 2: *Reagents and conditions*: (a) MeOH/H+, Δ; (b) TBSCl, imidazole, 12 h, r.t.; (c) DIBAL-H, 0 ^{o}C,; (d) Swern oxidation; (e) allyltri-*n*-butyltin, (*R*)-BINOL, (~60% overall); (f) TBSOTf, base, rt, 2 h, 85%; (g) ozonolysis; (h) (+)- Ipc_2BCl, allylMgBr, -90 ^{o}C, 2 h (65% over two steps); (i) Acryloyl chloride, $^{i}Pr_2NEt$, -78 ^{o}C 62%; (j) 10% Grubbs Ru-I, CH_2Cl_2, Δ, 4 h, 84%; (k) aq. HF, MeCN, r.t., 16 h, 89%.

Silylation of **10** and ozonolytic cleavage of the olefinic bond yielded an aldehyde, which on asymmetric allylboration with (+)-Ipc_2BCl/allylmagnesium bromide provided homoallyl alcohol **11**, which was isolated as a single diastereomer. Sequential acylation with acryloyl chloride and ring-closing olefin metathesis of the resulting acrylate using Grubbs' first-generation catalyst Ru-I **13** furnished pyranone **12**. Cleavage of the two silyl groups in **12** was achieved with aqueous HF in MeCN to yield dodoneine **1**.

Cossy *et al.*[11]

The synthesis of (+)-dodoneine starts with the TBS protection of commercially available ester **14** followed by a DIBAL-H reduction to give the aldehyde **15**. The allylation with the highly face-selective allyltitanium complex furnished the optically active homoallylic alcohol **16** which was transformed to the unsaturated ester **17** by using a cross-metathesis. The δ-hydroxy α,β-unsaturated ester **17** was transformed into the protected 1,3-diol **18** by treatment with benzaldehyde under basic conditions. The compound **18** was reduced to the corresponding aldehyde **19**, which on Horner–Wadsworth–Emmons reaction by using the Still–Gennari reagent gave unsaturated ester **20** with a *Z*/*E* ratio of 90:10. Treatment of **20** with 80% aqueous AcOH, at 60 °C for 24 hours, gave (+)-dodoneine **1** (Scheme 3).

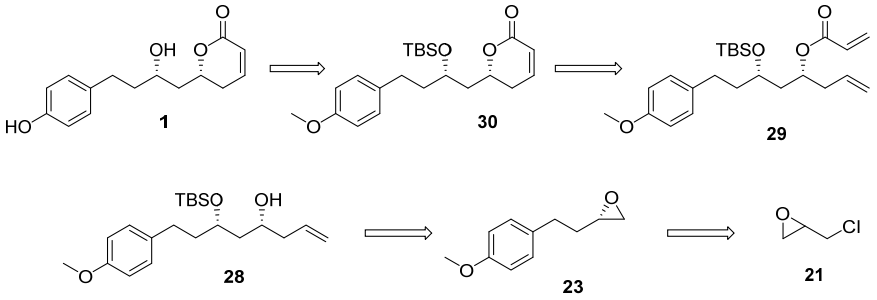


Scheme 3: *Reagents and conditions*: (a) TBSCl imidazole CH_2Cl_2; (b) DIBAL-H toluene, −78 °C 88%; (c) (S,S)-Ti-complex, Et_2O -78 °C, 3 h 97%; (d) Ethyl acrylate, Grubbs-Hoveyda **II** gen (5 mol%) CH_2Cl_2, rt, 2 d 80%; (e) PhCHO *t*-BuOK THF 0 °C, 2 h 68%; (f) DIBAL-H toluene, −78 °C 94%; (g) KHMDS, 18-C-6 THF, -78 °C, 2 h 70%; (h) aq. AcOH 60 °C, 24 h 70%.

As alluded to in the preceding prologue isolation of Dodoneine from *Tapinanthus dodoneifolius* (DC) Dancer (Lorenthaceae) was reported in 2007 by Coustard and co-workers.[8] *T. dodoneifolius* is used as a remedy to treat wounds, stomachache, diarrhea, cholera, nervous confusion, and cardiovascular and respiratory diseases. Experiments using dodoneine performed on rat aortic rings mounted in an organ bath apparatus displayed the vasodilator activity. Dodoneine (**1**) relaxed preconstricted aortic rings with half-maximal relaxation IC_{50} value of 81.4 ± 0.9 μM. This interesting biological activity and 5,6-dihydro-2*H*-pyran-2-one with an integrated 1,3-*syn* polyol system of dodoneine has been responsible for stimulating synthetic efforts targeted at this scaffold. As a part of our research programme[12] aimed at developing enantioselective synthesis of biologically active 5,6-dihydro-2*H*-pyran-2-one natural products, we became interested in designing a concise route to Dodoneine. Herein we describe our studies towards synthesis of Dodoneine employing hydrolytic kinetic resolution (HKR) and ring closing metathesis as key steps.

Result and Discussion

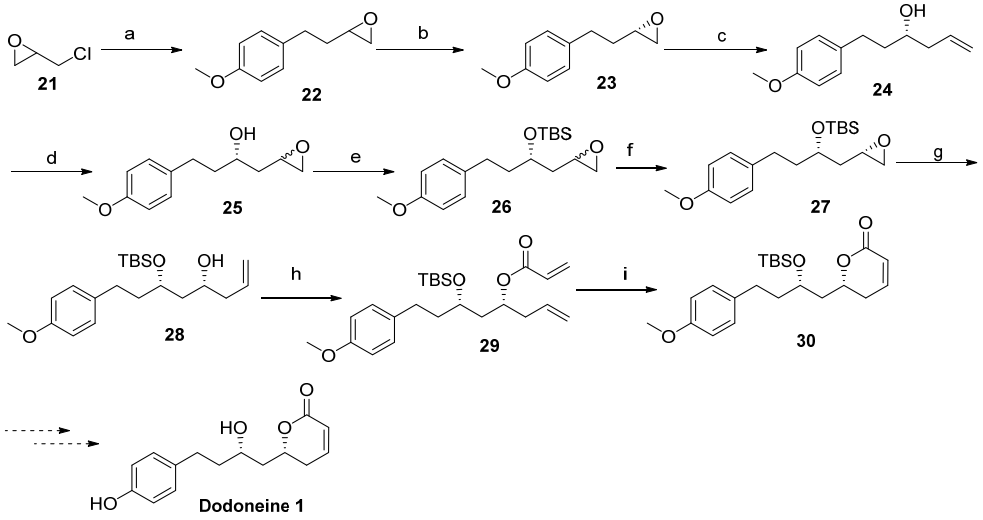
Our retrosynthetic analysis for Dodoneine is as outlined in Scheme 4. We envisioned that the natural product **1** could be prepared from **30** which in turn could be obtained by ring-closing metathesis of diene precursor **29,** The acrylate **29** could be prepared by acryloyl protection of homoallylic alcohol **28.** This homoallylic alcohol in turn could be obtained by iterative hydrolytic kinetic resolution of epoxide **23**.



Scheme 4: Retrosynthetic strategy

Synthesis of Dodoneine by hydrolytic Kinetic resolution (HKR): Synthesis of Dodoneine started with reaction of p-methoxybenzyl magnesium chloride with epichlorohydrin **21**, to give the chlorohydrin, which on potassium hydroxide treatment

gave the epoxide **22**.The ^{1}H NMR of compound showed characteristic peaks at δ 2.48, 2.2.75 and 2..93. The hydrolytic kinetic resolution of epoxide **22** using S,S-salen-Co^{III}-(OAc) complex gave the enantiopure (*S*)-epoxide **23**. The epoxide **23** was treated with vinylmagnesium bromide in presence of copper iodide to give homoallylic alcohol **24**. The ^{1}H NMR spectrum of the homoallylic alcohol **24** showed characteristic terminal olefin peaks at 5.15 (dd, J= 13.96,1.33 Hz) and 5.85 (m, 1H) ppm.

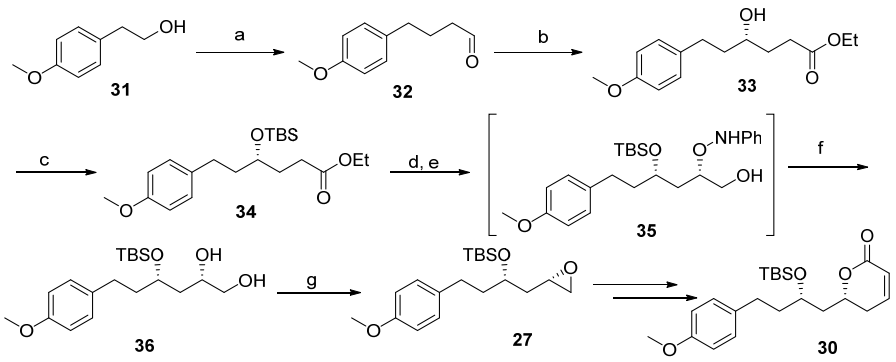


Scheme 5: *Reagents and Conditions:*(a) (i)PMB-MgCl, THF, CuI, -20^{o}C, 5 h (ii) KOH , CH_2Cl_2, 73% (for two steps) (b) (*S,S*) Salen-Co^{III}-(OAc), H_2O, 16 h, 45%; (c) vinylmagnesium bromide, CuI, THF, -23^{o}C, 5 h, 85% (d) *m*-CPBA, CH_2Cl_2, 0 ^{o}C, 4 h, 72% (e) TBSCl, Imidazole, CH_2Cl_2, 0 ^{o}C- rt, 24 h, 90%; (f) (*S,S*)- Salen-Co^{III}-(OAc), H_2O, THF, 16 h, 45%; (g) Vinylmagnesium bromide, CuI, THF, -23^{o}C, 12 h, 80%; (h) Acryloyl chloride, NEt_3, 0 ^{o}C 1 h, 90% (i) Grubbs 1st, CH_2Cl_2, 85%

This homoallylic alcohol **24** on epoxidation with *m*-CPBA followed by TBS protection of alcohol group gave compound **26**. The TBS protected epoxide **26** was then subjected for hydrolytic kinetic resolution using *S,S*-salen-Co-catalyst which gave the chiral epoxide **27**. The ring opening of the chiral epoxide **27** with vinylmagnesium bromide gave homoallylic alcohol **28** which was then derivatised as its acrylate **29**. The acrylate **29** on ring closing metathesis with Grubbs 1st Gen. catalyst gave the desired RCM product **30** in 85% yield (Scheme 5).

Organocatalytic approach towards the synthesis of Dodoneine:

Recently, we have developed an iterative approach to enantiopure synthesis of *syn/anti*-1,3-polyols, which is based on proline-catalysed sequential α-aminoxylation and Horner-Wadsworth-Emmons (HWE) olefination of aldehydes. In continuation of our interest in organocatalysis and asymmetric synthesis of biologically active compounds, we have devised a simple and concise route to dodoneine via our recently developed organocatalytic methodology.

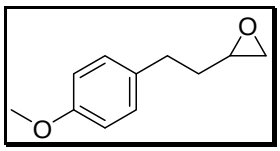


Scheme 6: *Reagents and conditions*: (a) (i) IBX, DMSO, 0 ^{o}C- rt, 6 h; (ii) $PPh_3CHCOOC_2H_5$, Toluene, reflux; (iii) $NaBH_4$. $NiCl_2.6H_2O$, -30 ^{o}C; (iv) DIBAL-H, CH_2Cl_2, -78 ^{o}C, 1 h; (b) Nitrosobenzene, D-Proline, DMSO; trimethyl phosphonoacetate, DBU, LiCl, CH_3CN; (b) H_2/Pd–C, EtOAc, 8 h, 65% (overall two steps); (c) TBSCl, imidazole, CH_2Cl_2, overnight, 92%; (d) DIBAL-H, CH_2Cl_2, -78 ^{o}C; (e) D-Proline, nitrosobenzene, DMSO, 60 min then $NaBH_4$, MeOH, 10 min; (f) H_2/Pd–C, EtOAc, 12 h, 78% (over three steps); (g) (i) TsCl, Bu_2SnO, Et_3N, CH_2Cl_2, 2 h; (ii) K_2CO_3, MeOH, rt, 1 h, 82% (over two steps)

As illustrated in scheme 6, our synthesis commenced with p-methoxy phenyl ethanol **31** which on IBX oxidation, 2-C Wittig olefination, double bond reduction followed by DIBAL reduction of ester gave aldehyde **32**. The aldehyde **32** was subjected to sequential α-aminoxylation (D-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 **33** in good yield. Thus, in two steps and one column purification, γ-hydroxy ester **33** was obtained in 65% yield. Appearance of peak at 3486 cm^{-1}in IR spectrum confirmed the formation of compound **33**. The TBS protection of the hydroxy group eventually furnished the TBS protected γ-hydroxy ester **34** 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 **34**. Ester **34** was then reduced with DIBAL-H at -78 ^{o}C to furnish aldehyde, which was further subjected to α-aminoxylation catalyzed by D-proline, followed by *in situ* reduction using $NaBH_4$ to furnish the required *α*-amino-substituted diol **35** in 73% 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 subjected to Pd/C reduction and purified by column chromatography to get a single diastereomer **36**. The IR spectrum of **36** showed broad hydroxyl absorption at 3412 cm^{-1}. Diol **36** on selective monotosylation and base treatment furnished epoxide, which was compared with our earlier synthesised epoxide **27** and was eventually converted to compound **30** as per the reaction sequence mentioned in scheme 5. Further demethylation and desilylation is in progress to complete the total synthesis of Dodoneine **1.**

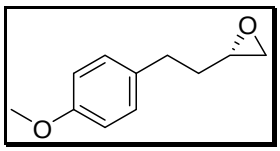
2-(4-Methoxyphenethyl)oxirane (22)



A round bottom flask was charged with copper (I) iodide (1.02 g, 5.40 mmol), gently heated under vaccum, and slowly cooled with a flow of argon after which dry THF (25 mL) was added. This suspension was cooled to -30 ^{o}C and vigorously stirred after which p-methoxy benzyl magnesium chloride solution (prepared from p-methoxy benzyl chloride (50.78 g, 324.24 mmol) and Mg turnings (7.88 g, 324.24 mmol) in dry THF (200 mL) was injected to it. A solution of (±)-epichlorohydrin **21** (10 g, 108.08 mmol) in THF (30 mL) was added slowly to the above reagent and the mixture was stirred at -20 ^{o}C for 5 h. The reaction mixture was quenched with a saturated solution of NH_4Cl. The layers were separated. Aqueous layer was extracted with EtOAc. The combined organic layers was washed with brine, dried over Na_2SO_4 and concentrated to dryness.

To a solution of crude compound (61.23 g, 285.20 mmol) in CH_2Cl_2 (500 mL) was added finely powdered KOH (32 g, 570.4 mmol). The mixture was stirred vigorously for 16 h and poured into 500mL water. After separation of the layers, the aqueous layer was extracted with CH_2Cl_2 (3 x 200mL) and the combined organic layers were dried over Na_2SO_4. Evaporation of the solvent and silica gel column chromatographic purification (petroleum ether :EtOAc, 98: 2) of the crude product gave **22** (42.5 g, 73 %) as a colorless liquid.

(*S*)-2-(4-Methoxyphenethyl)oxirane (23)



A solution of epoxide **22** (25 g, 140.26 mmol) and (*S,S*)-Salen-Co(III)-OAc (464 mg, 0.701 mmol) in isopropyl alcohol (5 mL) was stirred at 0 ^{o}C for 5 min and then distilled water (1.4 mL, 77.143 mmol) was added. After stirring for 16 h, it was concentrated and purified by silica gel column chromatography using pet ether to

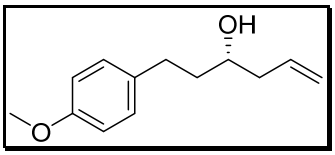
afford **23 (**11.2 g, 45%) as a yellow color liquid. Continued chromatography with petroleum ether: EtOAc (60: 40), provided the diol as a brown color solid.

$[\alpha]_D^{25}$: + 23.7 (c 1, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.74 - 1.92 (m, 2 H) 2.48 (dd, *J*=5.04, 2.75 Hz, 1 H) 2.66 - 2.83 (m, 3 H) 2.93 - 2.99 (m, 1 H) 3.80 (s, 3 H) 7.13 (d, *J*=8.70 Hz, 2 H)

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 31.3, 34.4, 47.2, 51.7, 55.2, 113.7, 129.2, 133.2, 157.8.

(*S*)-1-(4-Methoxyphenyl)hex-5-en-3-ol (24)



To a stirred solution of **23** (10 g, 56.10 mmol) and CuI (0.534 g, 2.80 mmol) in dry THF (150 mL), was added , 1 M solution of vinyl magnesium bromide in THF (22.09 g, 168.32 mmol, 168 ml, 1M solution in THF) drop-wise over a period of 30 min. at -23 °C and stirred for 5 h. The mixture was allowed to warm up to 0 °C, before it was quenched with a saturated NH_4Cl solution. The layers were separated, the aqueous layer extracted with EtOAc, the combined organic extracts were washed with brine (100 mL) and dried over Na_2SO_4,evaporated to dryness and silica gel column chromatographic purification (petroleum ether : EtOAc, 96: 4) of the crude product gave **24** as a colorless oil (9.84 g, 85%).

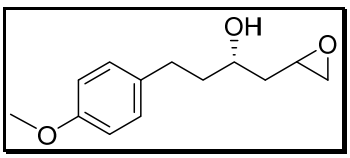
$[\alpha]_D^{25}$= □ 18.6 (c 1, $CHCl_3$)

IR: (neat): 3441, 2924, 2856, 1610, 1509, 1457, 1378, 1236, 1174, 1020 cm^{-1} .

^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 1.64 (s, 1 H) 1.80 (t, *J*=7.83 Hz, 1 H) 2.09 - 2.42 (m, 2 H) 2.55 - 2.86 (m, 2 H) 3.58 - 3.76 (m, 1 H) 3.80 (s, 3 H) 5.15 (dd, *J*=13.96, 1.33 Hz, 2 H) 5.71 - 5.96 (m, 1 H) 6.84 (d, *J*=8.59 Hz, 2 H) 7.13 (d, *J*=8.59 Hz, 2 H)

^{13}C NMR (50 MHz, $CDCl_3$) δ ppm 31.0, 38.6, 42.0, 55.2, 69.8, 113.8, 118.2, 129.2, 134.6, 157.7.

(2*S*)-4-(4-Methoxyphenyl)-1-(oxiran-2-yl)butan-2-ol (25)



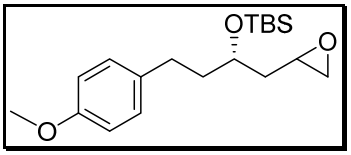
To a stirred solution of alcohol **24** (4 g, 19.39 mmol) in CH_2Cl_2 (50 mL) at 0 ^oC was added *m*-CPBA (50%) (13.38 g, 38.78 mmol). The reaction mixture was stirred at 0 ^oC for 4 h and quenched by saturated Na_2CO_3 solution, extracted with CH_2Cl_2, washed with sat.$NaHCO_3$ and brine, dried over Na_2SO_4, concentrated and purified by silica gel column chromatography using (petroleum ether : EtOAc, 96: 4) as eluent to yield the epoxide **25** (3.2 g, 72%) as a yellow liquid.

$[\alpha]_D^{25}$= □ 13 $CHCl_3$).

IR (neat): 3429, 2927, 2856, 1611, 1510, 1460, 1379, 1244, 1174, 1076 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) □ ppm 1.72 - 1.92 (m, 3 H) 2.29 (br. s., 1 H) 2.51 (dd, *J*=4.93, 2.78 Hz, 1 H) 2.56 - 2.91 (m, 4 H) 3.04 - 3.21 (m, 1 H) 3.80 (s, 3 H) 3.85 - 3.99 (m, 1 H) 6.84 (d, *J*=1.00 Hz, 2 H) 7.13 (d, *J*=1.00 Hz, 2 H)

***tert*-Butyl(((2*S*)-4-(4-methoxyphenyl)-1-(oxiran-2-yl)butan-2-yl)oxy)dimethylsilane (26)**

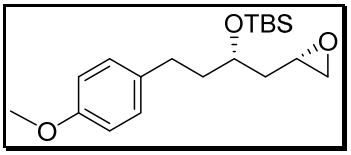


To a stirred solution of alcohol **25** (3 g, 13.49 mmol) in CH_2Cl_2 (50 mL) was added imidazole (1.84 g, 26.98 mmol). To this solution *t*-butyl dimethylchlorosilane (2.65 g, 17.53 mmol) was added at 0 ^oC and reaction was stirred at room temperature for 24 h. The reaction mixture was quenched with a saturated solution of NH_4Cl and extracted with CH_2Cl_2 (2 x 100mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Silica gel column chromatography of the crude product using (petroleum ether : EtOAc, 98: 2) as eluent provided **26** as a colorless liquid (4 g, 90%).

^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 0.03 - 0.15 (m, 6 H) 0.92 (d, *J*=1.14 Hz, 9 H) 1.65 - 1.88 (m, 4 H) 2.44 - 2.54 (m, 1 H) 2.54 - 2.72 (m, 2 H) 2.74 - 2.86 (m, 1 H) 2.99 - 3.12 (m, 1 H) 3.80 (s, 3 H) 3.87 - 4.03 (m, 1 H) 6.84 (d, *J*=8.72 Hz, 2 H) 7.11 (dd, *J*=8.72, 2.27 Hz, 2 H)

^{13}C NMR (50 MHz, $CDCl_3$) δ ppm -4.7, -4.3, 18.0, 25.8, 30.4, 30.9, 39.2, 39.8 - 40.2, 46.8, 47.7, 49.4, 49.8, 55.2, 69.7, 69.9, 113.7, 129.1, 133.7 - 134.9, 157.7.

tert-Butyl(((*S*)-4-(4-methoxyphenyl)-1-((*S*)-oxiran-2-yl)butan-2-yl)oxy)dimethylsilane (27)



A solution of epoxide **26** (4 g, 11.88 mmol) and (*S,S*)-Salen-Co(III)-OAc (39 mg, 0.06 mmol) in isopropyl alcohol (1 mL) was stirred at 0 ^{o}C for 5 min, and then distilled water (0.12 mL, 6.53 mmol) was added. After stirring for 16 h, it was concentrated and purified by silica gel column chromatography using (petroleum ether : EtOAc, 98:2) to afford **27 (**1.8 g, 45%) as a yellow color liquid. Continued chromatography with pet ether:EtOAc (60:40) provided the diol as a brown color solid.

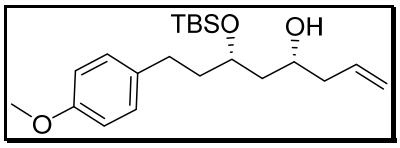
$[\alpha]_D^{25}$= □ 11.3 (C = 1, $CHCl_3$).

IR (neat): 3429, 2969, 2854, 1641, 1511, 1465, 1250, 1169, 1075 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 0.09 (s, 6 H) 0.92 (s, 9 H) 1.66 - 1.93 (m, 4 H) 2.42 - 2.51 (m, 1 H) 2.60 (dd, *J*=9.16, 7.01 Hz, 2 H) 2.74 - 2.86 (m, 1 H) 3.06 (tq, *J*=6.28, 3.14 Hz, 1 H) 3.93 (dq, *J*=11.07, 5.36 Hz, 1 H) 6.84 (d, *J*=8.72 Hz, 2 H) 7.11 (d, *J*=8.72 Hz, 2 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm -4.6, -4.5, 18.0, 25.8, 30.9, 39.2, 40.0, 46.8, 49.4, 55.2, 69.9, 113.7, 129.1, 134.3, 157.7

(4*R*,6*S*)-6-((tert-Butyldimethylsilyl)oxy)-8-(4-methoxyphenyl)oct-1-en-4-ol (**28**)



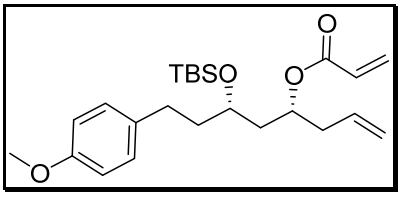
To a stirred solution of **27** (1.8 g, 53.05 mmol) and CuI (50 mg, 2.17 mmol) in dry THF (10 mL), was added, 1 M solution of vinyl magnesium bromide in THF (2.1 g, 16.09 mmol, 16 mL 1M solution in THF) drop-wise over a period of 30 min. at -23 °C and stirred for 2 h. The mixture was allowed to warm up to 0°C, before it was quenched with a saturated NH_4Cl solution (20 mL). The layers were separated, the aqueous layer extracted with EtOAc (3 x 100 mL), the combined organic extracts were washed with brine (50 mL) and dried over Na_2SO_4, evaporated to dryness and silica gel column chromatographic purification (petroleum ether : EtOAc, 96: 4) of the crude product gave **28** as a colorless oil (1.56 g, 80%).

$[\alpha]_D^{25}$ = □ 0.8 (c 1, $CHCl_3$)

IR (neat): 1710, 1612, 1510, 1455, 1238.

^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 0.11 (s, 6 H), 0.91 (s, 9 H) 1.59 - 1.71 (m, 2 H) 1.72 - 1.95 (m, 2 H) 2.16 - 2.32 (m, 2 H) 2.46 - 2.68 (m, 2 H) 3.80 (s, 3 H) 3.91 - 4.12 (m, 1 H) 5.03 - 5.20 (m, 2 H) 5.70 - 5.99 (m, 1 H) 6.84 (d, *J*=8.46 Hz, 2 H) 7.09 (d, *J*=8.21 Hz, 2 H)

(4*R*,6*S*)-6-((tert-Butyldimethylsilyl)oxy)-8-(4-methoxyphenyl)oct-1-en-4-yl acrylate (29)



Acryloyl chloride (0.5 mL, 6.17 mmol) was added dropwise under N_2 to a solution of compound **27** (1.5 g, 4.11 mmol), Et_3N (1.7 mL, 12.33 mmol), and DMAP (0.05 mmol) in anhyd CH_2Cl_2 (10 mL). The mixture was stirred at r.t. for 1 h. After completion of reaction, the mixture was poured into brine (15 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases were washed with aq 1 M HCl (6 mL) and brine (2 × 50 mL), dried (Na_2SO_4), and evaporated under reducer pressure. The crude product was purified by column chromatography on silica gel (PE– EtOAc, 8:2) to give **29** as a liquid; (1.55 g, 90%);

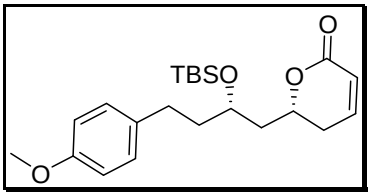
$[\alpha]_D^{25}$ = □ 7.3 (c 1, $CHCl_3$)

IR (neat): 2923, 2854, 1746, 1610, 1510, 1238, 1106 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 0.04 (s, 6 H) 0.92 (s, 9 H) 1.71 - 1.84 (m, 4 H) 2.37 (br. s., 2 H) 2.52 - 2.70 (m, 2 H) 3.79 (s, 4 H) 4.98 - 5.20 (m, 2 H) 5.64 - 5.88 (m, 2 H) 6.01 - 6.20 (m, 1 H) 6.32 - 6.48 (m, 1 H) 6.82 (d, *J*=8.46 Hz, 2 H) 7.09 (d, *J*=8.59 Hz, 2 H)

13C NMR (100MHZ, $CDCl_3$) δ ppm -4.5, 18.0, 22.6, 25.8, 29.3, 29.6, 30.5, 31.9, 38.7, 38.9, 41, 55.2, 68.8, 70.9, 113.7, 118, 129.7, 130.5, 133.3, 134.3, 157.6, 165.6

(R)-6-((S)-2-((tert-Butyldimethylsilyl)oxy)-4-(4-methoxyphenyl)butyl)-5,6-dihydro-2H-pyran-2-one (30)

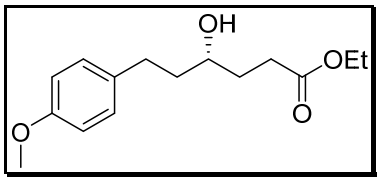


To a solution of **29** (0.10 g, 0.238 mmol, 0.001M) in freshly distilled degassed anhydrous CH_2Cl_2 (276mL) was added Grubb's 1st generation catalyst (38 mg, 0.047 mmol, 20 mol%) and heated at reflux for 4 h under an argon atmosphere. The solvent was evaporated to a brown residue, which was purified by column chromatography using (petroleum ether : EtOAc, 70: 30) as eluent to afford **30** (80 mg, 85%) as a yellow colour liquid.

IR (neat): 2923, 2854, 1736, 1636, 1510, 1459, 1238, 1165, 916 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 0.03 - 0.15 (m, 6 H) 0.91 (s, 10 H) 1.71 - 1.91 (m, 3 H) 1.99 - 2.22 (m, 1 H) 2.28 - 2.42 (m, 2 H) 2.51 - 2.74 (m, 2 H) 3.79 (s, 3 H) 3.98 (quin, *J*=11.70 Hz, 1 H) 4.51 - 4.72 (m, 1 H) 6.04 (dd, *J*=9.79, 1.45 Hz, 1 H) 6.79 - 6.98 (m, 3 H) 7.10 (m, *J*=8.59 Hz, 2 H)

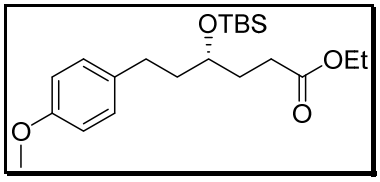
Ethyl (*S*)-4-hydroxy-6-(4-methoxyphenyl)hexanoate (33)



To a solution of phenyl hexanal **32** (2.0 g, 11.36 mmol) and nitrosobenzene (1.21 g, 11.36 mmol) in anhydrous DMSO (20 mL) was added D-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 ^{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 used for the next step.

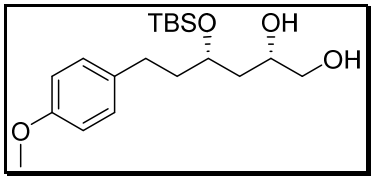
(2S,4S)-4-((tert-Butyldimethylsilyl)oxy)-6-(4-methoxyphenyl)hexane-1,2-diol (34)



To an ice-cold stirred solution of **33** (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. (1.8 g, 92%)

^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 0.06 (s, 6 H) 0.91 (s, 9 H) 1.25 (t, *J*=1.00 Hz, 3 H) 1.59 - 1.91 (m, 3 H) 2.29 - 2.47 (m, 2 H) 2.50 - 2.69 (m, 2 H) 3.80 (s, 4 H) 4.13 (q, *J*=1.00 Hz, 2 H) 6.81 (d, *J*=1.00 Hz, 2 H) 7.08 (d, *J*=1.00 Hz, 2 H)
13C NMR (100MHZ, $CDCl_3$) δ ppm -4.6, -4.4, 14.1, 25.8, 29.9, 30.5, 31.6, 39.0, 55.1, 60.1, 70.6, 113.7, 129.0, 134.3, 157.6, 173.7.

(2*S*,4*S*)-4-((tert-Butyldimethylsilyl)oxy)-6-(4-methoxyphenyl)hexane-1,2-diol (36)



To a solution of ester **34** (1.0 g, 2.74 mmol) in dry CH_2Cl_2 (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 D-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 anhydrous 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 **36** yellow solid. (400 mg, 63%)

^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 0.11 (s, 6 H) 0.93 (s, 9 H) 1.68 - 1.95 (m, 4 H) 2.50 - 2.68 (m, 2 H) 3.50 - 3.58 (m, 2 H) 3.80 (s, 3 H) 3.91 - 4.18 (m, 2 H) 6.85 (d, *J*=8.59 Hz, 2 H) 7.10 (d, *J*=8.59 Hz, 2 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm -4.7, -4.5, 25.7, 30.1, 30.7, 39.5, 40.0, 49.5, 55.1, 68.5, 70.2, 71.3, 113.8, 129.0, 133.8, 157.7.

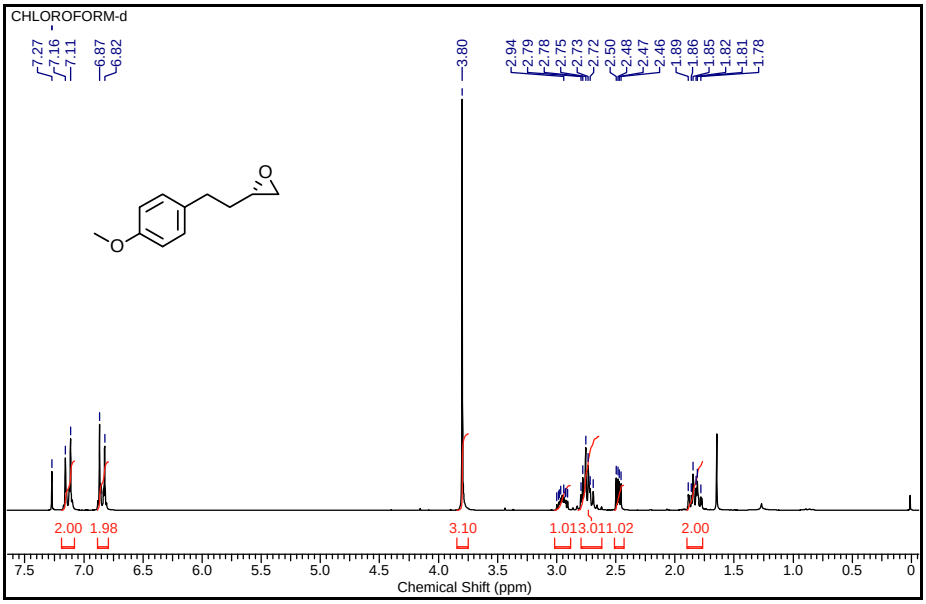
tert-Butyl(((*S*)-4-(4-methoxyphenyl)-1-((*S*)-oxiran-2-yl)butan-2-yl)oxy)dimethylsilane (27)

To a mixture of diol **36** (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

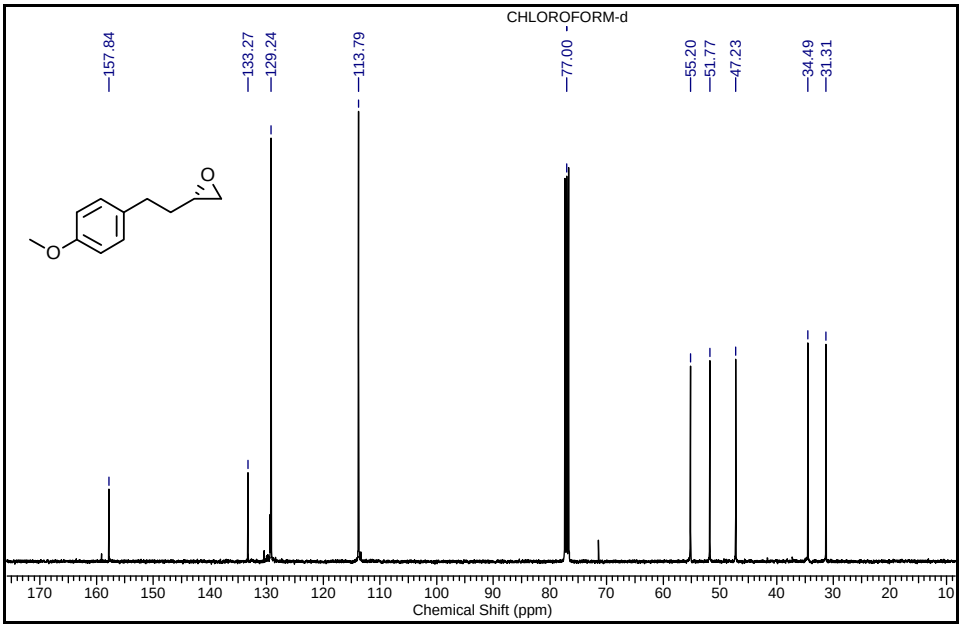
stirred at room temperature under nitrogen. The reaction was monitored by TLC, after completion of reaction the mixture was quenched by adding water. The solution was extracted with CH_2Cl_2 (3 X 10 mL) and then combined organic phase was washed with water, dried (Na_2SO_4) and concentrated. To this 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 **27** (120 mg, 82%) as a colorless liquid.

Spectra

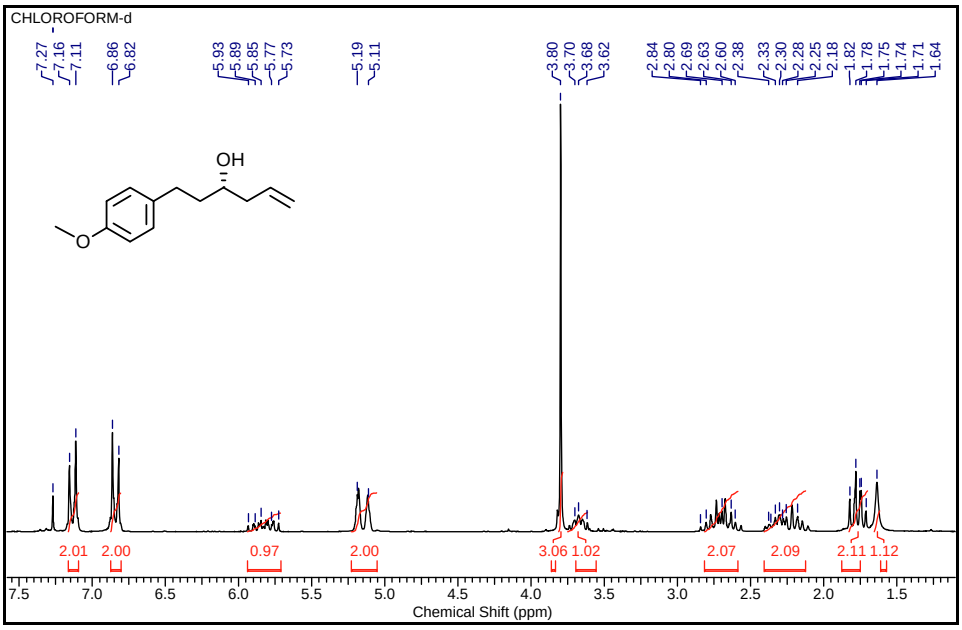
1. ^{1}H and ^{13}C NMR spectra of **23**
2. ^{1}H and ^{13}C NMR spectra of **24**
3. ^{1}H and ^{13}C NMR spectra of **26**
4. ^{1}H and ^{13}C NMR spectra of **27**
5. ^{1}H and ^{13}C NMR spectra of **29**
6. ^{1}H and ^{13}C NMR spectra of **30**
7. ^{1}H and ^{13}C NMR spectra of **34**
8. ^{1}H and ^{13}C NMR spectra of **36**



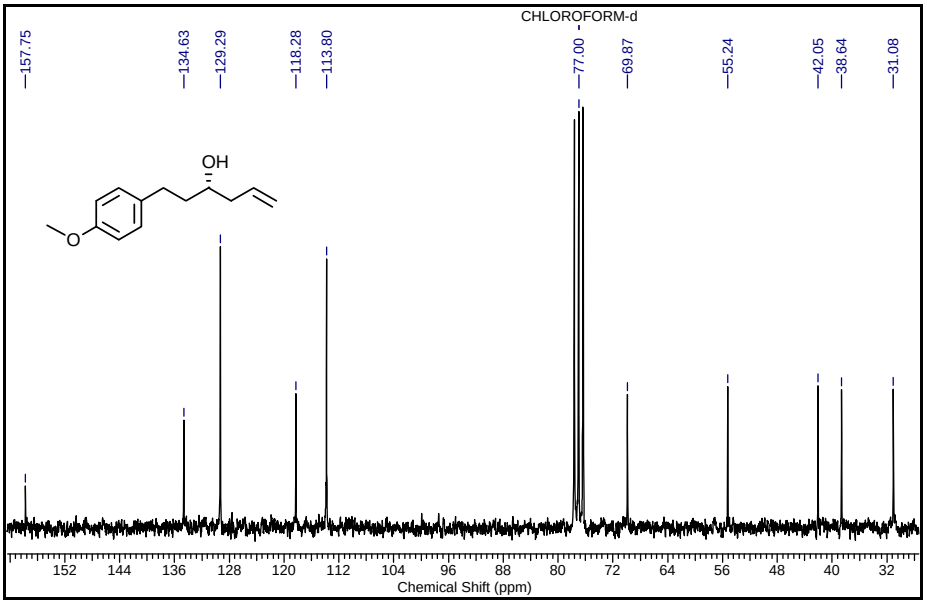
^{1}H NMR spectrum of Compound 23 in $CDCl_3$



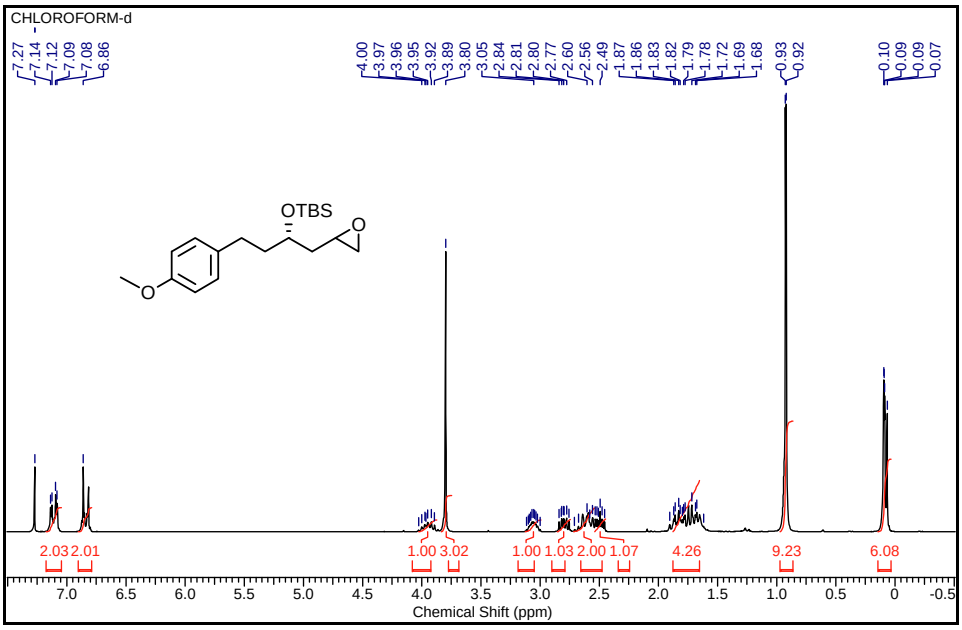
^{13}C NMR spectrum of Compound 23 in $CDCl_3$



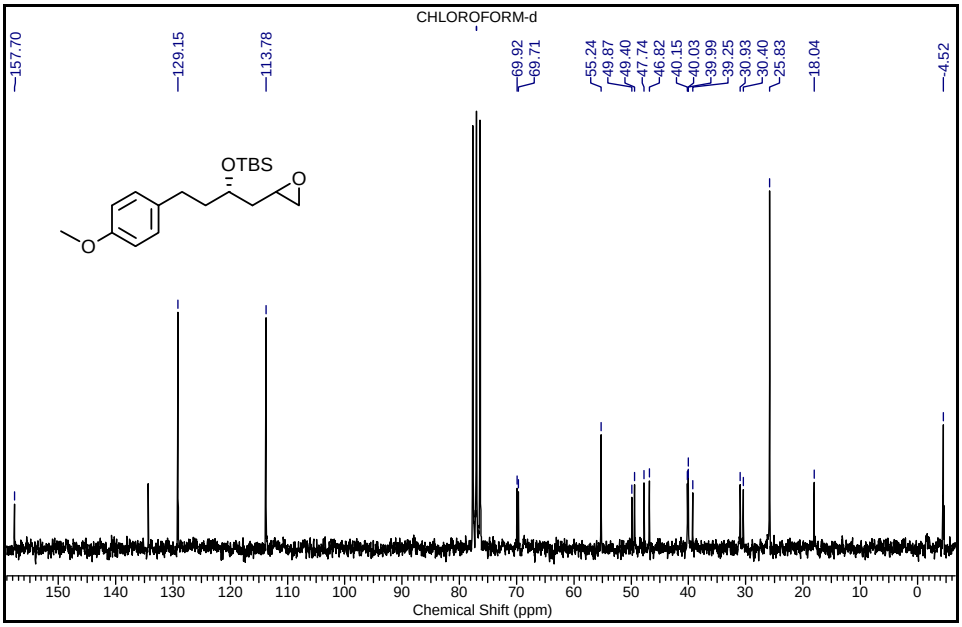
^{1}H NMR spectrum of Compound 24 in $CDCl_3$



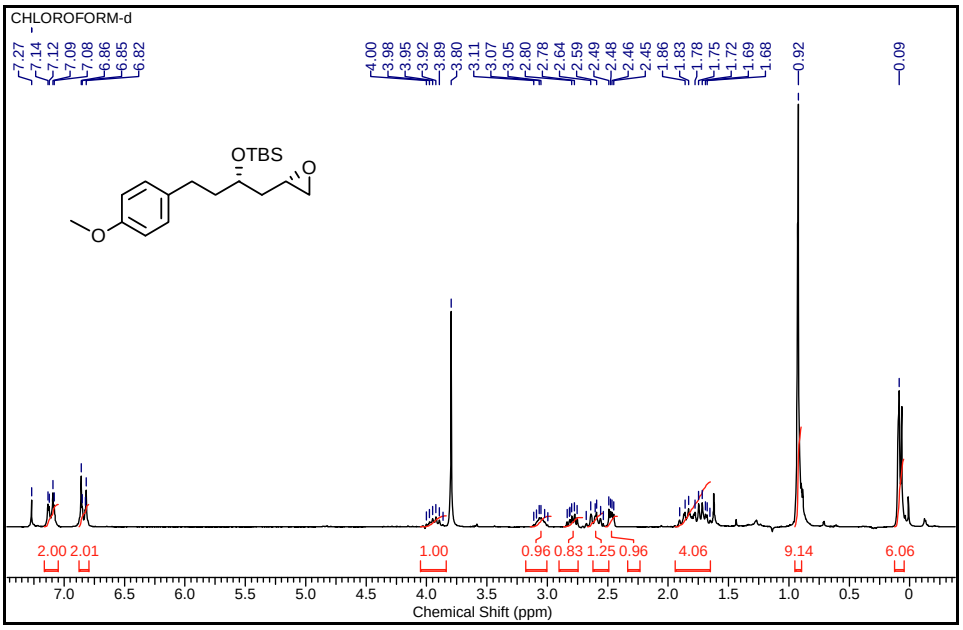
^{13}C NMR spectrum of Compound 24 in $CDCl_3$



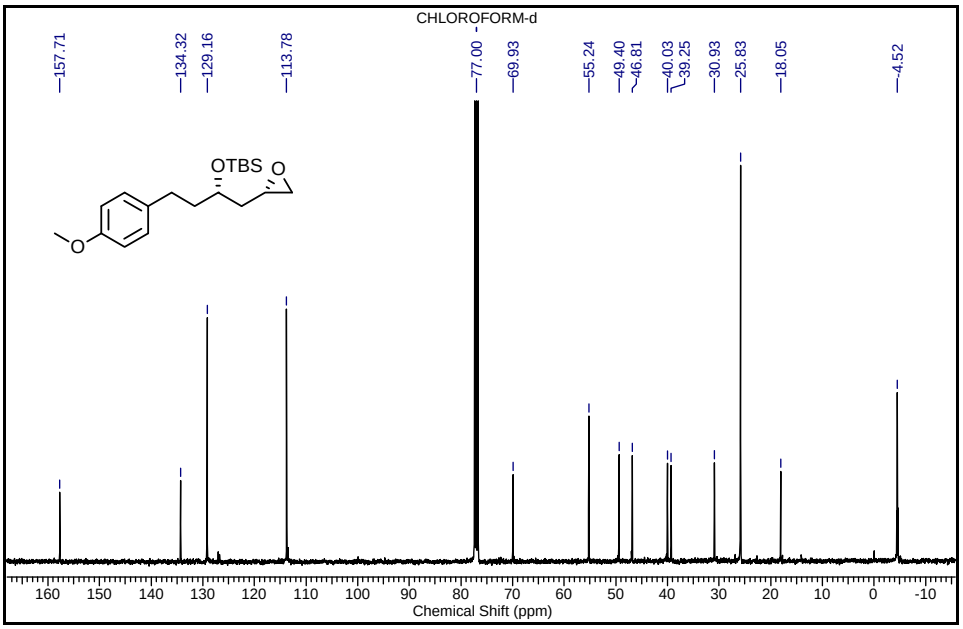
^{1}H NMR spectrum of Compound 26 in $CDCl_3$



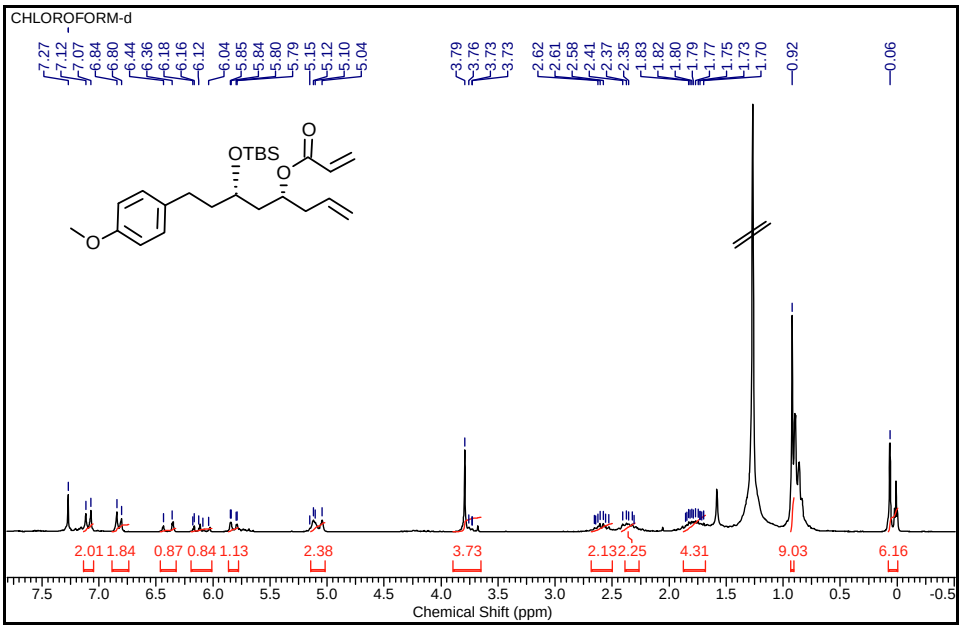
^{13}C NMR spectrum of Compound 26 in $CDCl_3$



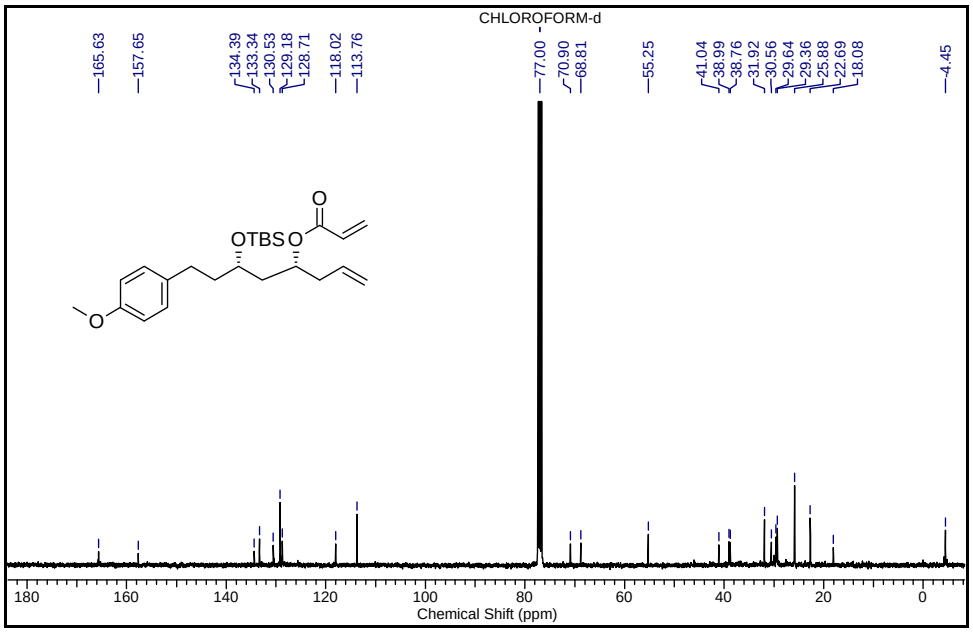
^{1}H NMR spectrum of Compound 27 in $CDCl_3$



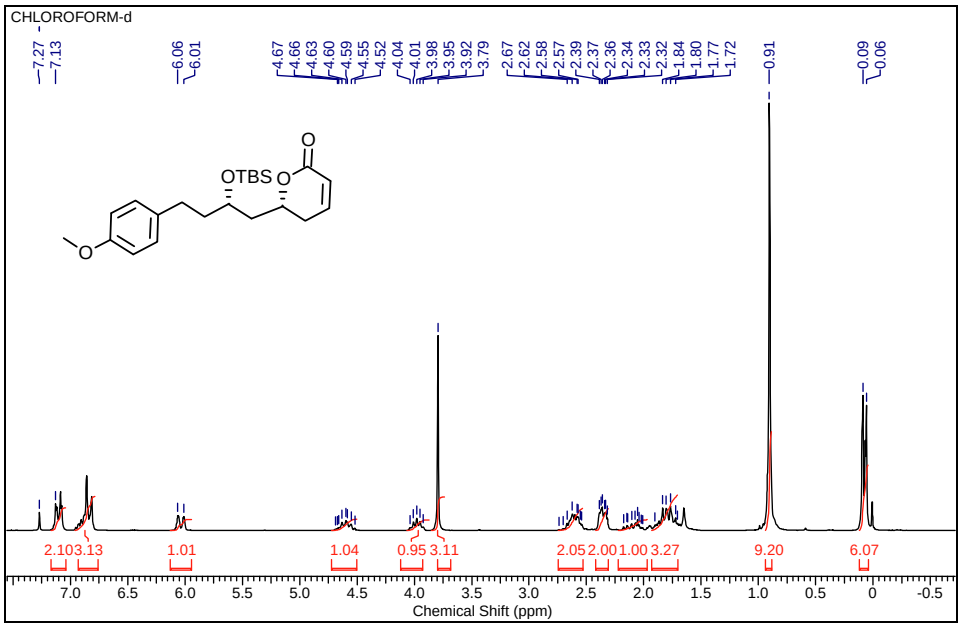
^{13}C NMR spectrum of Compound 27 in $CDCl_3$



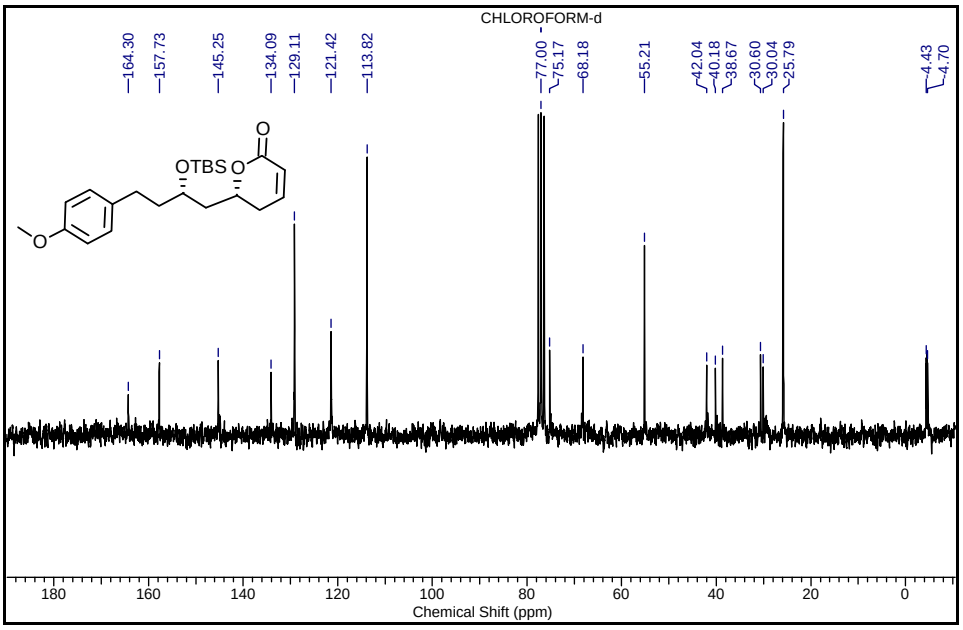
^{1}H NMR spectrum of Compound 29 in $CDCl_3$



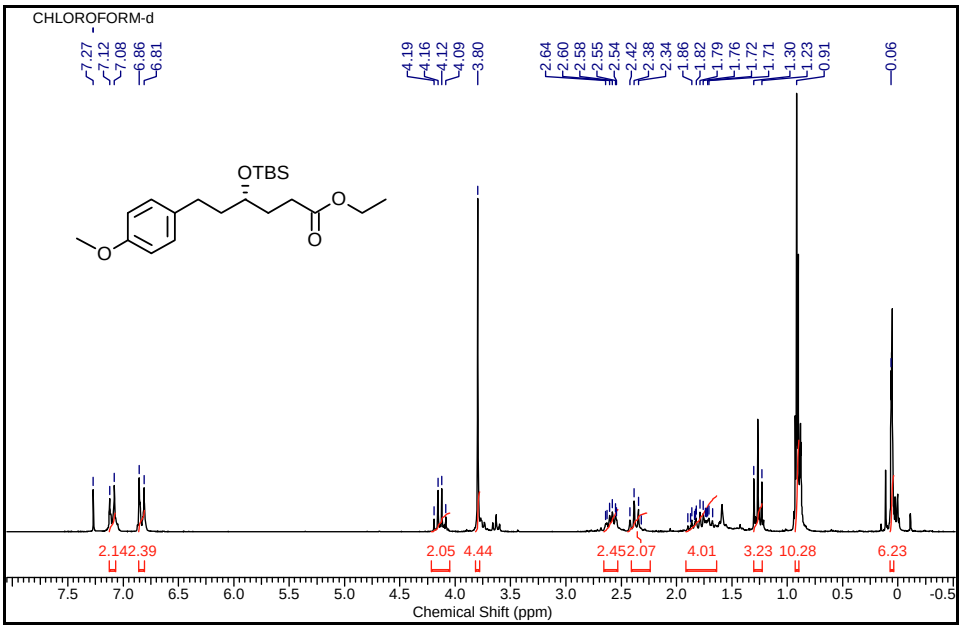
^{13}C NMR spectrum of Compound 29 in $CDCl_3$



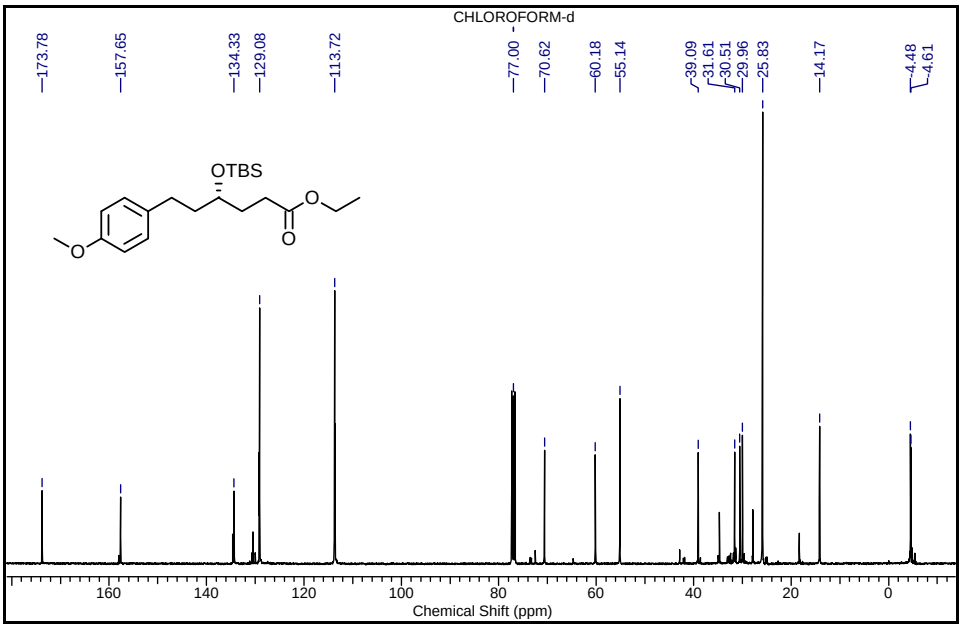
^{1}H NMR spectrum of Compound 30 in $CDCl_3$



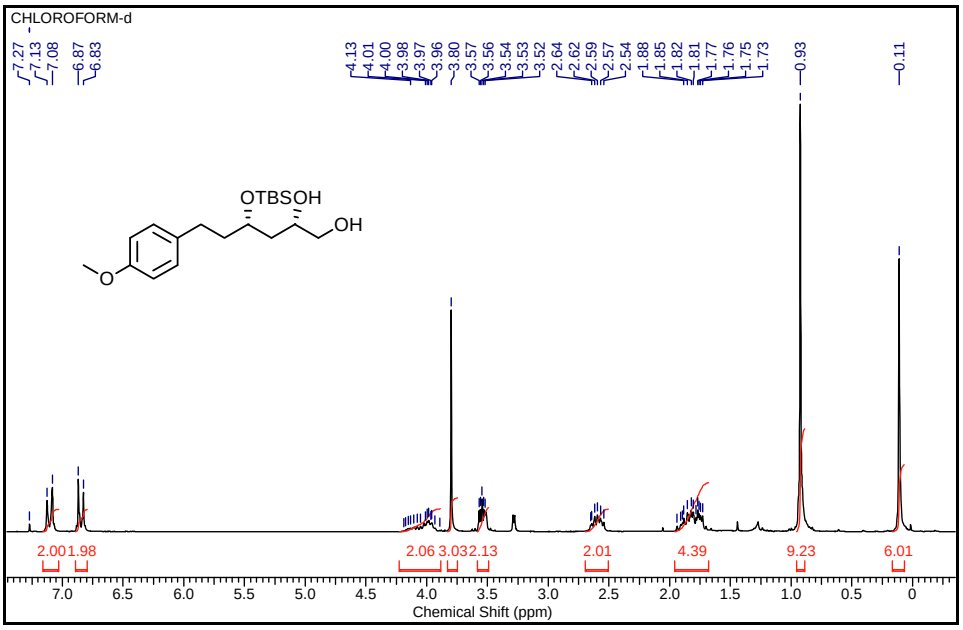
^{13}C NMR spectrum of Compound 30 in $CDCl_3$



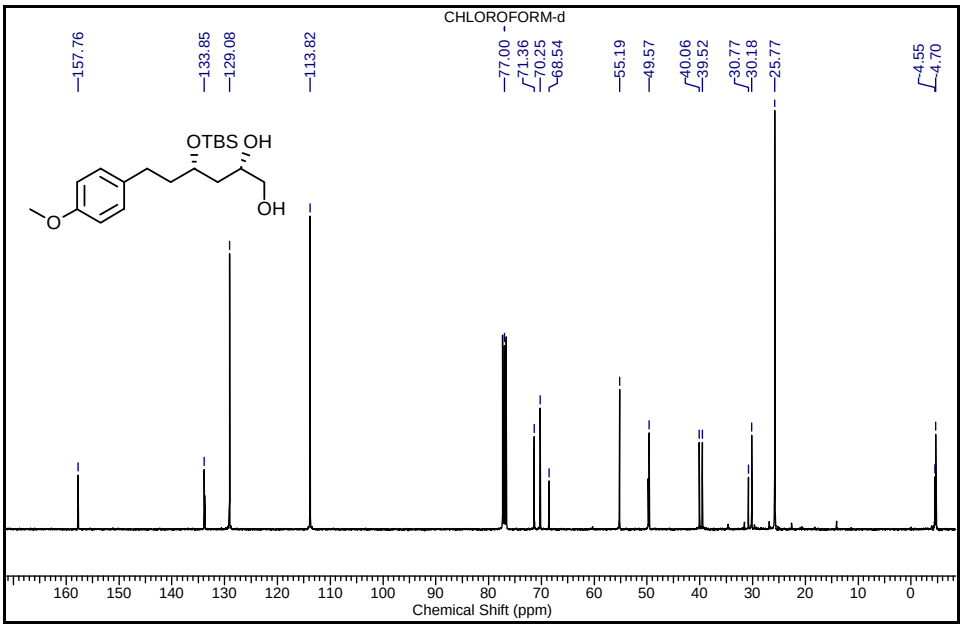
^{1}H NMR spectrum of Compound 34 in $CDCl_3$



^{13}C NMR spectrum of Compound 34 in $CDCl_3$



^{1}H NMR spectrum of Compound 36 in $CDCl_3$



^{13}C NMR spectrum of Compound 36 in $CDCl_3$

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Introduction

Diabetes is one of the major health and development challenges of the 21st century. Diabetes mellitus, or simply diabetes, is a group of metabolic diseases in which a person has high blood sugar, either because the pancreas does not produce enough insulin, or because cells do not respond to the insulin that is produced.[1] This high blood sugar produces the classical symptoms of polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger). There are three main types of diabetes mellitus (DM).

- Type 1 DM results from the body's failure to produce insulin, and currently requires the person to inject insulin or wear an insulin pump. This form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes".
- Type 2 DM results from insulin resistance, a condition in which cells fail to use insulin properly, sometimes combined with an absolute insulin deficiency. This form was previously referred to as non insulin-dependent diabetes mellitus (NIDDM) or "adult-onset diabetes".
- The third main form, gestational diabetes occurs when pregnant women without a previous diagnosis of diabetes develop a high blood glucose level. It may precede development of type 2 DM.

Type 2 diabetes, also known as non-insulin dependent diabetes mellitus (NIDDM), is a chronic disease that affects 5-10% of adults over the age of 30 in most populations.[2] Type 2 diabetes is characterized by resistance to the effects of insulin in peripheral tissues, which is manifested as reduced insulin-stimulated glucose uptake into skeletal muscle (which normally disposes of 90% of post-prandial plasma glucose) and adipose tissue, defective insulin-dependent suppression of hepatic glucose output and reduced insulin secretion from pancreatic B-cells.[3] A new class of drugs, the thiazolidinediones (TZDs), has been developed recently that directly targets insulin resistance, a primary defect of type 2 diabetes, and potentially represents a major therapeutic advance in the treatment of this disease.[4] The peroxisome proliferator activated receptor g (PPAR-γ), an orphan nuclear receptor, has a central role in the insulin-sensitizing actions of TZDs.

Over the past few years, a dramatic increase in our understanding of the physiological role of PPAR-γ has resulted from its identification as the major factor involved in differentiation of adipocytes and as the cellular target of the TZDs.[5] The synthetic TZDs were the first class of compounds to be identified as PPAR-γ ligands. (Fig.1)

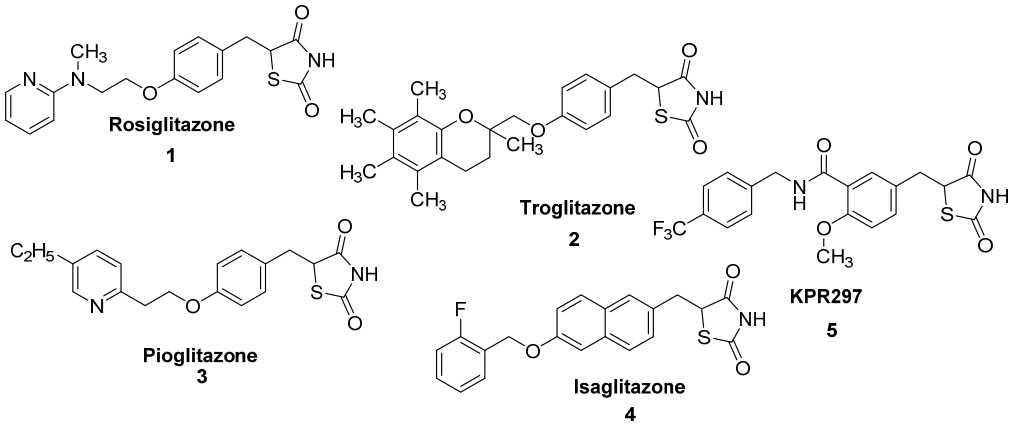


Figure 1: Thiazolidinedione PPAR-g agonists

Furthermore, selective non-TZD agonists of PPAR-γ have been developed that also improve insulin sensitivity in animal models of NIDDM[6] (Fig. 2).

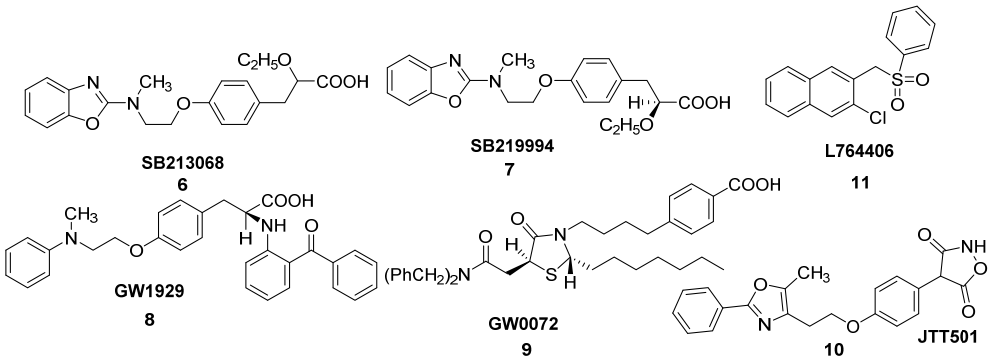


Figure 2: Nonthiazolidinedione PPAR-γ agonists

In 1992, a collaborative work by Wink, J. *et al.* from Hoechst AG, Germany {currently named as *Industriepark Höchst* (*Industrial Park Höchst*)}and Zeeck, A. *et al.*[7] from institute of Gottingen, Germany has reported the isolation of Decarestrictine A-D (**12-17**) from soil samples collected in Bryce Canyon (Utah, U.S.A.), Oak Greek Canyon (Arizona, U.S.A.), and Portugal (Aljezun). Their regular effort and vivid research[8] in isolation and characterization of microorganisms from various natural sources, *e.g.* soil samples, plant materials, and food stuff etc. by extracting the strains, cultivated on the culture broths, resulted many natural products of biological interest. In this continued effort, they found that different *pencillium* species (strains FH-A

6090, FH-A 6099, FH-A 6530, and FH-A 6360) exhibit a similar but unusual secondary metabolite pattern. By taxonomic investigations the strains have been classified to be the members of the species *penicillium simplicissimum* and *penicillium corylophilum*, which can be combined in the subgenus *Furcatum*. Later, in the same year the same group reported[9] the addition to this decarestrictine family i.e. Decarestrictine E-M (**18-26**). A more detailed examination of the culture broth of *penicillium simplicissimum* (strain FHA6090) resulted in the detection of these minor components of decarestrictine family (Fig. 3)

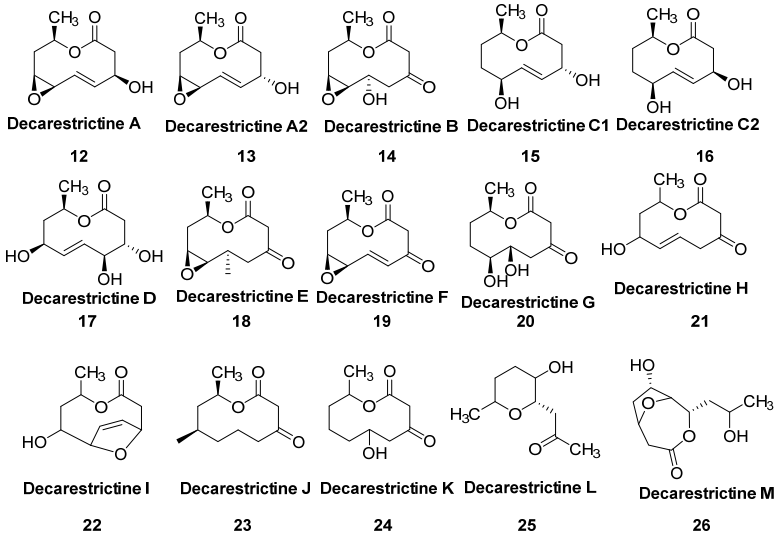


Figure 3: Novel decarestrictine family

Pinolidoxin (**29**), a phytotoxin was produced from the fungus of *Aschochyta pinodes*, subsequently new metabolites of this fungus were found as epipinolidoxins (**27**) and dihydropinolidoxins (**28**) (Figure 4).

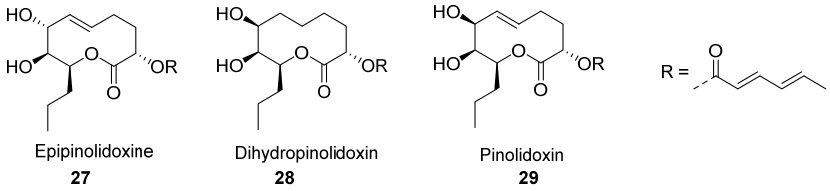


Fig. 4: Phinolodoxin family

Structural features: These metabolites were characterized spectroscopically, their molecular formulae were determined by high resolution mass spectra, and their structures were elucidated by ^{1}H, ^{13}C, IR, ^{1}H-^{1}H-correlation and ^{1}H-^{13}C-shift-correlation data etc. Additional information concerning the stereochemistry was obtained from X-ray analysis. The structural features of these fungal metabolites are the presence of:

- 10-membered lactone ring,
- ii) an exocyclic methyl appendage,
- iii) oxygen appendages at positions varying from C3 to C7.

With the exception, lack of 10-membered lactone ring was observed for decarestrictine L and M. Decarestrictine I (**22**) possesses a bicyclic ring system, in which the 10-membered lactone is bridged forming an ether linkage between C3 and C6 (Figure 3).

Biological activities: It is considered that these metabolites are structurally related to each other based on their physico-chemical properties. Pharmacological interest is based on the biological activities of decarestrictines, especially on component D. This metabolite appears to resemble a potent inhibition of the cholesterol biosynthesis, which yields favorable effects on lipid metabolism *in vivo*. The decarestrictines show interesting activity in cell line tests with HEP-G2 liver cells due to an inhibitory effect on cholesterol biosynthesis. Due to the lack of pathologic changes of defined safety parameters, decarestrictine D revealed a good tolerability. These decarestrictines are selective in drug parameters as they exhibit no significant antibacterial, antifungal, antiprotozoal, and antiviral activity.

Earlier synthetic reports of 10-membered lactone natural products from our group:

Our research group has reported[10] the synthesis of a few 10-memebered lactone natural products recently (Figure 5). These include microcarpalide, herbarumin III, decarestrictine D, decarestrictine J, aspinolide A. The striking common strategy has been the esterification of alcohol and acid fragments with terminal olefin functionality, followed by ring closing or cross metathesis followed by lactonization.

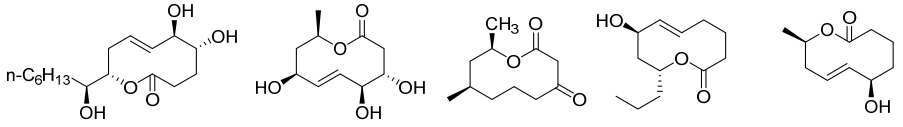


Fig. 5

Seimatopolide A and B belong to a novel class of 10-membered lactones, as well as members of the deacarestrictine,[12] microcarpalide[13] and pinolidoxin[14] families. These compounds are structurally related to each other based on their physico-chemical properties.

Recently seimatopolides A and B, two polyhydroxylated 10-membered macrolides, were isolated by Jang and Lee *et al*[11] from an ethyl acetate extract of *Seimatosporium discosioides* culture medium, along with three known compounds: monosporascone, arthrinone and 3a,9a-deoxy-3a-hydroxy-1-dehydroxyarthrinone. Seimatopolides belong to a novel class of 10-membered lactones, as well as members of the deacarestrictine,[12] microcarpalide[13] and pinolidoxin[14] families. These compounds are structurally related to each other based on their physico-chemical properties. Owing to their interesting biological properties, including inhibition of cholesterol biosynthesis,[15] antimalarial and antibacterial activities,[16] and microfilament formation,[13] these compounds have attracted a great deal of interest among synthetic organic chemists worldwide as attractive synthetic targets towards developing new therapeutic agents. Seimatopolides exhibited significant activity in a reporter gene assay for activation of peroxisome proliferator activated receptor c (PPAR-c)[17a] with EC_{50} values of 11.05 μM, which shows therapeutic potential in the treatment of type 2 diabetes, inflammatory disease and certain cancers.[17b]

As a part of our research programme aimed at developing enantioselective syntheses of biologically active natural products[10] based on hydrolytic kinetic resolution (HKR),[18] we considered attempting at the first total asymmetric synthesis seimatopolide B.

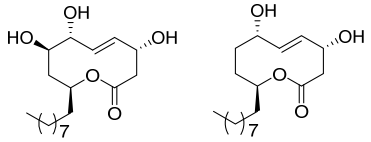
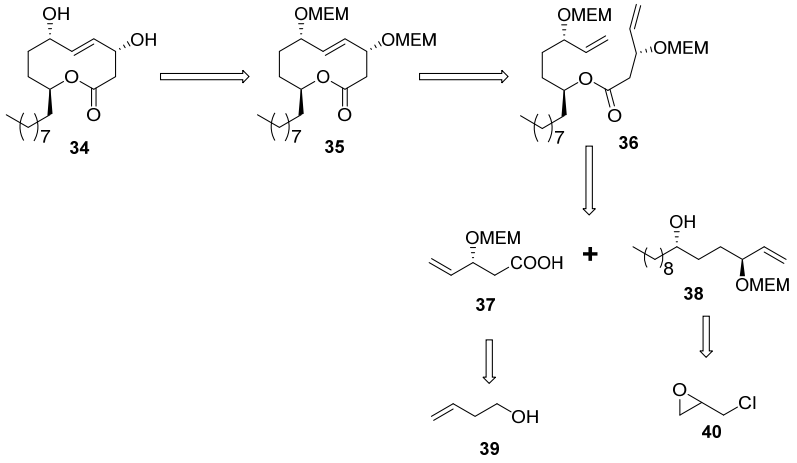


Figure 6: Proposed structures of seimatopolide A and seimatopolide B

Retrosynthetic analysis:

Our retrosynthetic analysis for seimatopolide B is based on the convergent approach as outlined in Scheme 1. We envisioned that the natural product **34** could be obtained by ring-closing metathesis (RCM)[19] of diene precursor **36**, which in turn could be prepared by intermolecular DCC coupling of acid **37** and alcohol **38**. The acid

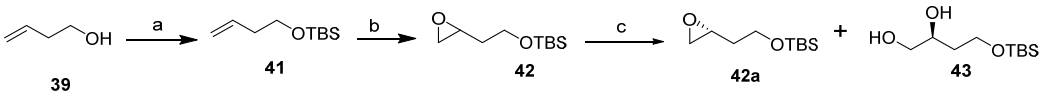
fragment **37** could be obtained from 3-butene-1-ol **39** while the alcohol fragment could be prepared from rac-epichlorohydrin **40** via iterative HKR.



Scheme 1: Retrosynthetic analysis

Result and discussion

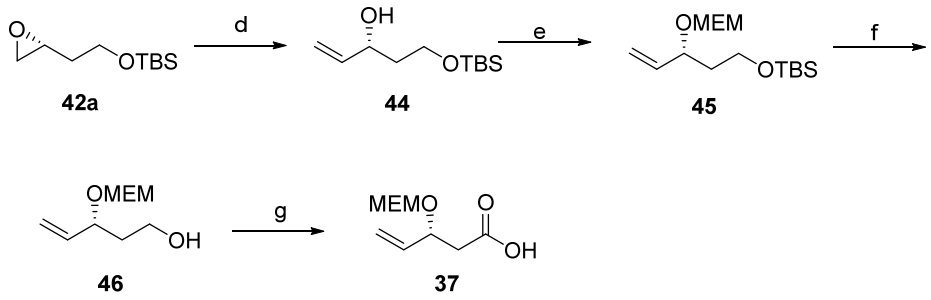
The synthesis of acid fragment began with the TBS protection of the commercially available 3-butene-1-ol **39** with TBS chloride, imidazole in dichloromethane at 0 ^{o}C to give TBS olefin **41**. This TBS protected olefin **41** was then converted to the chiral epoxide in two steps. In the first step, oxidation of double bond with *m*CPBA gave epoxide **42** in 90% yield. The epoxidation was confirmed by the analysis of ^{1}H NMR data which showed three characteristic peaks at 2.46, 2.74, 2.90 ppm. This racemic epoxide was subjected to Jacobsen's Hydrolytic kinetic resolution using (R,R)-salen-Co^{III}(OAc) catalyst to give the enantiopure epoxide (*R*)-**42a** in 46% yield along with diol **43** in 45% yield.



Scheme 2: Synthesis of chiral epoxide **42a**: *Reagents and conditions:* (a) TBDMSCl, imidazole, CH_2Cl_2, 0 ^{o}C to r.t., 4 h, 88%; (b) *m*-CPBA, CH_2Cl_2, 0 ^{o}C to rt, 1 h, 90%; (c) (*R,R*)-salen-Co^{III}-(OAc) (0.5 mol%), dist. H_2O (0.55 equiv), isopropyl alcohol, 0 ^{o}C, 24 h (46% for **42a**, 45% for **43**)

Epoxide (*R*)-**42a**, on ring opening with dimethylsulfonium methylide,[20] afforded one-carbon homologated allylic alcohol **44** in 86% yield. The ^{1}H NMR spectrum of the secondary alcohol **44** showed characteristic terminal peaks at 5.80-5.96 (ddd, *J*= 5.31, 10.36, 17.18 Hz, 1H), 5.31 (dt, *J*= 1.65, 17.18 Hz, 1H), 5.13 (dt, *J*= 1.65, 10.49 Hz,

1H). The secondary hydroxy group was then protected as the MEM ether by reaction with MEM chloride, being activated by DIPEA in dichloromethane at 0 ^{o}C to room temperature to give **45** in good yield. The TBS protecting group was then cleaved using TBAF to furnish primary alcohol **46** in 88% yield. TEMPO-catalyzed oxidation of the alcohol with NaOCl resulted in the formation of acid **37** in excellent yield.

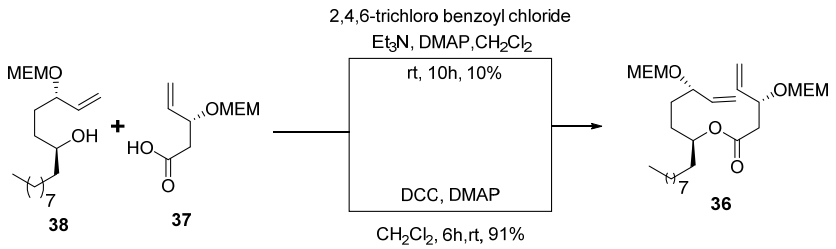


Scheme 3: *Reagents and conditions:* (d) Me_3SI, *n*-BuLi, THF, □20 ^{o}C, 4 h, 86%; (e) MEMCl, DIPEA, CH_2Cl_2, 16 h, 87%; (f) TBAF, THF, 1 h, 88%; (g) TEMPO, NaH_2PO_4, NaOCl, $NaClO_2$, CH_3CN, overnight, 95%.

The alcohol fragment **38** was synthesised by another colleague in our group starting from commercially available epichlorohydrin **40** in 10 steps.

Coupling between the acid fragment and the alcohol fragment:

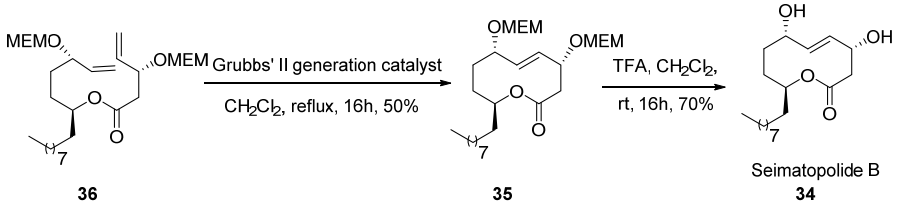
The two bifunctional coupling partners having functional groups at both end, may unite in two ways to form the cyclic lactone compounds. Either cross-metathesis followed by lactonization or esterification followed by ring-closing metathesis are the reaction sequences for the synthesis of these 10-membered lactones. In our protocol, we adopted the later sequence so as to observe and generalize the outcome of RCM reaction of the protected ester and the naked ester. Thus, Yamaguchi's protocol was then employed to unite both the fragments to furnish the diolefinic ester in poor yield. Then the coupling of acid and alcohol was achieved by using intermolecular DCC coupling to afford the diene ester **36** in 91% yield. The product was confirmed for its structure by the ^{1}H NMR spectrum and also by ^{13}C NMR.



Scheme 4

RCM reaction of the protected diolefinic ester:

The Key precursor **36** was then subjected to ring-closing metathesis conditions using Grubbs' 2nd generation catalyst in dry degassed CH_2Cl_2 under reflux for 16 h which led to the formation of desired 10-membered lactone **35**, in only 50% yield. The exclusive *E* isomer, showed distinct coupling constant (J = 16.32) for olefinic protons in the PMR spectrum. The other protons resonated at routine positions. The synthesis of seimatopolide B **34** was culminated by deprotection of the MEM ethers using TFA in CH_2Cl_2. The product obtained was unambiguously supported by its ^{1}H NMR, ^{13}C NMR spectral data except specific rotation $[\alpha]_D^{25}$ = -212.60 (c 0.035, MeOH). {lit.[11] $[\alpha]_D^{25}$= - 125.3 (c 0.03, MeOH)}.



Scheme 5

Table 1: Comparison of 1H and 13C NMR data of both natural and synthetic *E*-seimatopolide B

E-Seimatopolide B (natural) spectroscopic data (500 MHz, pyridine-d5)		E-Seimatopolide B (synthetic) spectroscopic data (500 MHz, pyridine-d5)	
^{1}H NMR (J in Hz)	^{13}C NMR	^{1}NMR (J in Hz)	^{13}C NMR
6.56, dd (8.5, 16.0)	170.5	6.56, dd (8.54,16.17)	170.6
5.98, dd (3.0, 16.0)	133.4	5.98, dd (3.05,16.17)	133.4
5.06, ddd (7.0, 7.0, 13.0)	133.4	5.09, m	133.4
4.96, m	76.5	4.99, m	76.5
4.62, dd (7.5, 7.5)	74.9	4.64, m	74.9
2.89, dd (3.0, 11.5)	67.8	2.90, dd (3.4,11.6)	67.8
2.72, dd (3.0, 11.5)	45.7	2.74, dd (3.9,11.6)	45.8
2.30,m	38.5	2.32, m	38.6
2.00,m	36.3	2.00, m	36.4
2.00,m	32.4	2.00, m	32.4
1.72,m	31.0	1.72, m	31.2
1.62,m	30.2	1.63, m	30.3
1.51,m	30.2	1.51, m	30.2
1.22, m	30.1	1.23 (brs)	30.1
1.22, m	29.9	0.88,t (7.0)	29.9
1.22, m	26.0		26.1
1.22, m	23.2		23.3
1.22, m	14.6		14.6
1.22, m			
1.22, m			
0.86,dd (7.0,7.0)			

Conclusion

In conclusion, a convergent and efficient first total synthesis of proposed structure of seimatopolide B **34** was accomplished with high enantioselectivity, in which the stereocentres were generated by means of iterative Jacobsen's hydrolytic kinetic resolution, and cyclization was achieved by ring-closing metathesis. This approach could be used for the synthesis of other members of this class of macrolides for structure-activity relationship studies. Work in this direction is currently under progress in our group.

Post work and structure correction

After this work was published, the Hiep *et al.*[11] corrected the originally proposed structures (fig. 7).

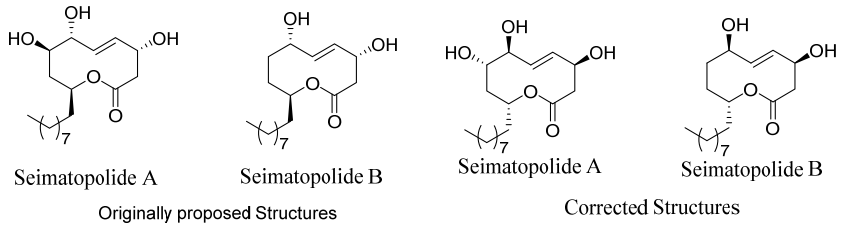
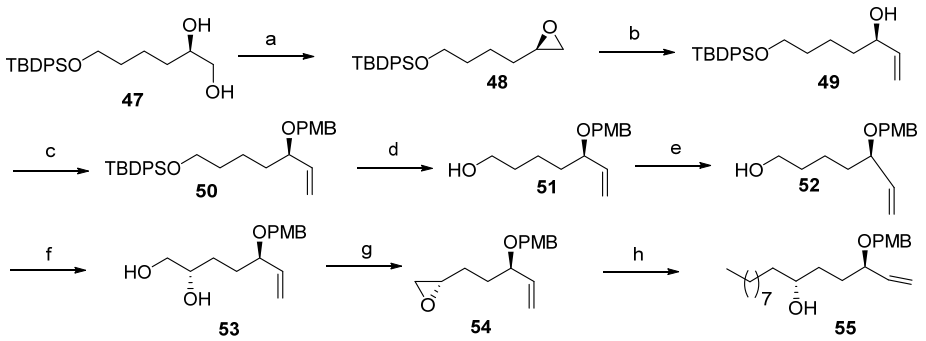
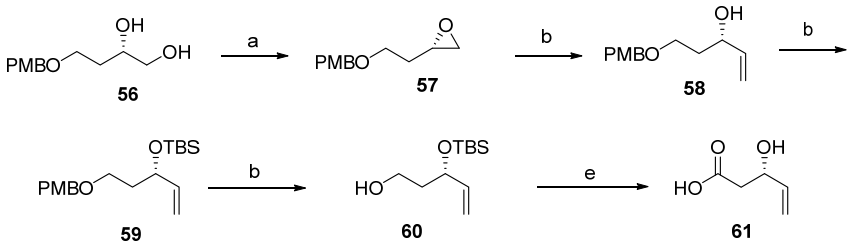


Figure 7

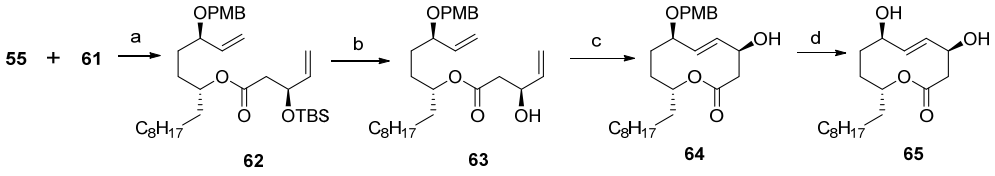
It is worth mentioning here that after publishing our work of seimatopolide B, another report came soon from Reddy[22] in 2012. Their synthetic strategy was also based on the Yamaguchi esterification of acid and alcohol fragments and ring-closing metathesis to get access to natural product. The alcohol and acid fragments were synthesised using hydrolytic kinetic resolution as a key step. The chiral epoxide resulting from HKR was used for the synthesis of one isomer while the diol was converted into epoxide with opposite stereochemistry to get the other isomer. Based on the spectroscopic data of both the isomers, Reddy and co-workers also suggested that the stereochemistry of the natural product should be (3*S*, 6*R*, 9*R*) instead of (3*R*, 6*S*, 9*S*), which confirms the revised stereochemistry corrected by Heip *et al.*



Scheme 6: *Reagents and conditions:* (a) tosylimidazole, NaH, 0 °C to r.t., 2 h, 83%; (b) Me_3SI, *n*-BuLi, THF, -20 °C, 2 h, 93%; (c) $PMBOC(NH)CCl_3$, $Sc(OTf)_3$, -20 °C, toluene, 15 min, 76%; (d) TBAF (1 M in THF), THF, 0 °C to r.t., 2 h, 92%; (e) Dess-Martin periodinane, CH_2Cl_2, r.t., 1 h, 87%; (f) PhNO, L-proline, $CHCl_3$, 0 °C, 2 h then $NaBH_4$, EtOH, 0 °C, 2 h then AcOH, Zn, 12 h, 70%; (g) tosylimidazole, NaH, THF, 0 °C to r.t., 2 h, 89%; (h) 1-bromooctane, Mg, THF, 0 °C to reflux, 2 h, Li_2CuCl_4, -78 °C to -20 °C, 2 h, 77%.



Scheme 7: *Reagents and conditions:* (a) tosylimidazole, NaH, 0 °C to r.t., 2 h, 86% (b) Me_3SI, *n*-BuLi, THF, -20 °C, 2 h, 90%; (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 30 min, 88%; (d) DDQ, CH_2Cl_2 : pH 7 buffer (9:1), 0 °C, 30 min, 93%; (e) TEMPO, BAIB, CH_2Cl_2:H_2O (1:1), 0 °C to r.t., 2 h, 86%.

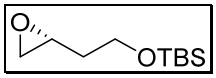


Scheme 8: *Reagents and conditions:* (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 0 °C to r.t., 2 h, **55**, DMAP, toluene, 0 °C, 1 h, 82%; (b) TBAF (1 M in THF), THF, 0 °C to r.t., 2 h, 91%; (c) Grubbs II gen. (10 mol%), CH_2Cl_2, reflux, 8 h, 62%; (f) DDQ, CH_2Cl_2 : H_2O (9:1), 0 °C, 30 min, 73%.

***tert*-Butyldimethyl(2-(oxiran-2-yl)ethoxy)silane (42)**

To a stirred solution of but-3-en-1-ol **39** (10.0 g, 138.67 mmol) in CH_2Cl_2 (100 mL) was added imidazole (18.8 g, 277.35 mmol).To this solution *t*-butyl dimethylchlorosilane (22.99 g, 152.54 mmol) was added at 0 ^oC and reaction was stirred at room temperature for 4 h. The reaction mixture was quenched with water and extracted with CH_2Cl_2 (3 x 150 mL).The extract was washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using (petroleum ether :EtOAc, 99: 1)as eluent provided the TBS protected compound, (But-3-en-1-yloxy)(tert-butyl)dimethylsilane (22.7 g, 88%) yield as a colorless liquid. To a stirred solution of above compound (21 g, 112.81mmol) in CH_2Cl_2 (200 mL) at 0 ^oC was added *m*-CPBA (50%) (58.40g, 169.22 mmol). The reaction mixture was stirred at room temperature for 1 h and quenched by saturated Na_2CO_3 solution, extracted with CH_2Cl_2, washed with sat. $NaHCO_3$ and brine, dried (Na_2SO_4), concentrated and purified by silica gel column chromatography using petroleum ether: EtOAc (97:3) as eluent to yield the epoxide **42** (20.5 g, 90%) as a colorless liquid.

(*R*)-*tert*-Butyldimethyl(2-(oxiran-2-yl)ethoxy)silane (42a)



A solution of epoxide **42** (14 g, 69.26 mmol) and (*R,R*)-Salen-Co(III)-OAc (0.229 g, 0.346 mmol) in isopropyl alcohol (3 mL) was stirred at 0 ^oC for 5 min. and then distilled water (0.68 mL, 38.09 mmol) was added. After stirring for 24 h, it was concentrated and purified by silica gel column chromatography using petroleum ether : EtOAc : (97:3) as eluent to afford **42a (**6.44 g, 46%) as a yellow color liquid. Continued chromatography with eluent (petroleum ether: EtOAc, 60:40) provided the diol **43** (6.3 g, 45%) as a brown color liquid.

$[\alpha]_D^{25}$: +10.85 (c 2, $CHCl_3$) lit.[21] $[\alpha]_D^{24}$: +11.0 (c 2, $CHCl_3$);

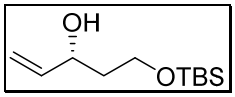
IR (neat, cm^{-1}): ν_{max} 3434, 1630, 728, 515;

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.77 (dd, *J*= 5.69, 6.44 Hz, 2H), 3.0-3.09 (m, 1H), 2.78 (m, 1H), 2.51(dd, *J*=2.77, 5.05 Hz, 1H), 1.67-1.84 (m, 2H), 0.89 (brs, 9H), 0.06 (brs, 6H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 60.1, 50.2, 47.3, 36.0, 26.0, 18.4, -5.3;

ESI-MS: m/z = 242.16 $[M + Na + H_2O]^+$.

(*R*)-5-((*Tert*-butyldimethylsilyl)oxy)pent-1-en-3-ol (44)



To a -20 ^oC suspension of trimethylsulfonium iodide (25.23 g, 123.69 mmol) in dry THF (80 mL) was added *n*-BuLi (77.29 mL, 1.6 M, 123.69 mmol). After 40 min, epoxide **42a** (5 g, 24.73 mmol) in THF was added drop-wise. The reaction mixture was stirred at -20 ^oC for 4 h and quenched by saturated solution of ammonium chloride. 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 (3 x 50 mL), brine, dried over Na_2SO_4 and concentrated. The residual oil was purified by silica gel column chromatography using petroleum ether: EtOAc, (9:1) as eluent to furnish the allylic alcohol **44** (4.59 g, 86%) as colorless oil.

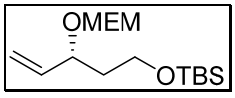
$[\alpha]_D^{25}$: -0.10 (c 1.0, $CHCl_3$);

IR (neat,cm^{-1}): ν_{max} 3419, 2929, 1635, 1255, 1097, 1017, 835, 776;

^{1}HNMR (200MHz, $CDCl_3$): δ 5.80-5.96 (ddd, *J*= 5.31, 10.36, 17.18 Hz, 1H), 5.31 (dt, *J*= 1.65, 17.18 Hz, 1H), 5.13 (dt, *J*= 1.65, 10.49 Hz, 1H), 4.36 (m, 1H), 3.75-3.93(m, 2H), 3.36 (d, 1H), 1.69-1.80 (m, 2H), 0.90 (s, 9H), 0.08 (s, 6H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 140.7, 114.2, 72.6, 62.0, 38.3, 25.9, 18.2, -5.4.

(*R*)-3-((2-Methoxyethoxy)methoxy)-5-((*Tert*-butyldimethylsilyl)oxy)pent-1-en-3-ol (45)



To a solution of **44** (4.5 g, 20.81mmol) in dry CH_2Cl_2 (35 mL) was added DIPEA (7.56 mL, 45.80 mmol) at 0 ^oC. To this mixture MEM chloride (5.18 mL, 41.63 mmol) was added slowly with further stirring for 16 h at the room temperature. The reaction mixture was quenched with addition of cold water at 0 ^oC. 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 (3 x 100 mL), brine, dried over Na_2SO_4 and concentrated. The residual oil was purified by silica gel column

chromatography using (petroleum ether: EtOAc, 98:2) as eluent to furnish the MEM ether **45** (5.5g, 87%) as colorless oil.

$[\alpha]_D^{25}$: +0.22 (c 1.0, $CHCl_3$).

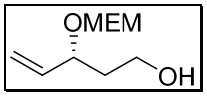
IR (neat,cm^{-1}): ν_{max} 3344, 2928, 1619, 1254, 1094, 1034, 928, 835, 775, 492.

^{1}H NMR (200 MHz, $CDCl_3$): δ 5.60-5.77 (ddd, *J*= 7.58, 10.11, 17.43 Hz, 1H), 5.15-5.26 (m, 2H), 4.76 (q, 2*J*ab = 6.82, 6.82 Hz, 2H), 4.19 (m,1H), 3.52-3.58 (m, 2H), 3.62-3.83 (m, 4H), 3.39 (s, 3H), 1.63-1.89 (m, 2H), 0.89 (s, 9H),0.02 (s, 6H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 138.3, 117.4, 93.0, 74.6, 71.9, 66.9, 59.5, 59.1, 38.7, 26.0, 18.4, -5.2;

ESI-MS: m/z = 327.13 $[M+Na]^+$.

(*R*)-3-((2-Methoxyethoxy)methoxy)pent-4-en-1-ol (46)



A solution of TBAF (24.65 mL, 1M in THF, 24.65mmol) was added to a stirred solution of MEM ether **45** (5.0 g, 16.43 mmol) in THF. The mixture was stirred at room temperature for 1 h and then diluted with water and extracted with EtOAc. The organic layer was washed with water dried over $Na_2SO_4$and concentrated. The crude product was purified by silica gel column chromatography using petroleum ether : EtOAc (60:40) to provide compound **46** (2.75 g, 88%)as a yellow color liquid.

$[\alpha]_D^{25}$: +0.97 (c 1.0, $CHCl_3$);

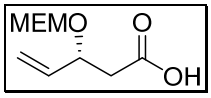
IR (neat, cm^{-1}): ν_{max} 3409, 2933, 2883, 1033, 928, 483;

^{1}H NMR (200 MHz, $CDCl_3$): δ 5.63-5.80 (ddd, *J* = 7.20, 10.11, 17.30 Hz, 1H), 5.17-5.30 (m, 2H), 4.65 (q, 2*J*ab = 6.90, 7.08 Hz, 2H), 4.29-4.40 (m, 1H), 3.80-3.95 (m, 2H), 3.54-3.75 (m,4H), 3.40 (s, 3H), 2.86 (brs, 1H), 1.71-1.83 (m, 2H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 137.9, 117.4, 92.5, 74.9, 71.9, 67.2, 59.2, 38.1;

ESI-MS: m/z = 213.02 $[M+Na]^+$.

(*R*)-3-((2-Methoxyethoxy)methoxy)pent-4-enoic acid (37)



Round-bottomed flask equipped with a mechanical stirrer was charged with alcohol **46** (2.0g, 10.51 mmol), TEMPO (0.164 g, 1.051 mmol), 15 mL of acetonitrile and 15 mL of 0.67 M sodiumphosphate buffer (pH 6.7). A solution of sodium chlorite was

prepared by dissolving 80% $NaClO_2$ (1.90 g, 21.03 mmol) in 2.4 mL of water and a solution of dilute sodium hypochlorite (NaOCl) was prepared by diluting household bleach (5.25% NaOCl, 16 mg, ca. 2.0 mol%) with 0.3 mL of water. The reaction mixture is heated to 35 °C with stirring and approximately 20% of the $NaClO_2$ solution is added via one addition funnel followed by 20% of dilute bleach solution via the other funnel. The remaining portions of both reagents are then added simultaneously over 2 h. The resulting mixture is stirred at 35 °C for 16 h.The reaction mixture is then poured into ice-cold 10% sodium sulfite solution maintained below 20 °C with an ice-water bath. The mixture is acidified with 0.2 N HCl. The organic layer is separated and the aqueous layer is extracted with two 100-mL portions of EtOAc. The combined organic phases are washed with 20 mL of brine and dried over Na_2SO_4, concentrated and purified by silica gel column chromatography using petroleum ether:EtOAc (20:80) to give **37** (2.0g, 95%) as a yellow liquid.

$[\alpha]_D^{25}$:+93.25 (c 0.4, $CHCl_3$);

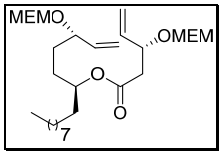
IR (neat ,cm^{-1}): ν_{max} 2926, 1735, 1409, 1108, 933, 848, 499;

^{1}H NMR (200 MHz, $CDCl_3$): δ 5.65-5.82 (ddd, *J*= 7.45, 10.23, 17.43 Hz, 1H), 5.23-5.37(m, 2H), 4.72 (q, 2*J*ab = 7.20, 7.07 Hz, 2H), 4.49-4.59 (m, 1H), 3.53-3.65 (m, 3H), 3.73-3.85 (m, 1H),3.39 (s, 3H), 2.50-2.73 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 175.5, 136.4, 118.72, 93.1, 73.8, 71.9, 67.2, 59.1, 40.8.

ESI-MS: m/z = 242.17 [M +K]+; HRMS (ESI) for C9H17O5(M + H)+ found 205.1066, calcd. 205.1071.

(*R*)-(3*S*,6*S*)-3-((2-Methoxyethoxy)methoxy)tetradec-1-en-6-yl-3-((2-methoxyethoxy) methoxy)-pent-4-enoate (36)



To a stirred solution of **37** (0.54 g, 2.67 mmol) in dry CH_2Cl_2 (5 mL) at 0^{o}C, DCC (0.66 g, 3.175 mmol) was added portion-wise and white precipitate was formed. Then DMAP (catalytic) was added followed by addition of solution of **38** (0.400 g, 1.27 mmol) in dry CH_2Cl_2 (5mL) stirred for 6 h at room temperature. The reaction mixture was evaporated to dryness. The crude product was purified by column

chromatography using petroleum ether : EtOAc (80:20) as an eluent to afford **36** (0.6 g,91%) as a colorless liquid.

$[\alpha]_D^{25}$:-5.37(c 0.8, $CHCl_3$);

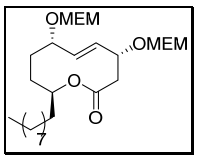
IR (neat, cm^{-1}): ν_{max} 3418, 2926, 1732, 1455, 1190, 1108, 1036, 930,850;

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.69-5.77 (ddd, *J* = 7.58, 10.27, 17.61 Hz, 1H), 5.59-5.68 (ddd, *J* = 7.58, 10.27, 17.61 Hz, 1H), 5.17-5.33 (m, 4H), 4.85-4.92 (m, 1H), 4.75 (dd, *J* = 2.93, 6.85 Hz, 2H), 4.65 (dd, *J* = 7.09, 9.29 Hz, 2H), 4.50 (m, 1H), 3.98 (m, 1H), 3.73-3.80 (m, 2H), 3.51-3.64 (m, 6H), 3.39 (s,6H), 2.62 (dd, *J*= 8.07, 15.16 Hz, 1H), 2.47 (dd, *J*= 5.62, 15.16 Hz, 1H), 1.63-1.70 (m, 1H), 1.49-1.55 (m, 4H), 1.25 (s, 15H), 0.88 (t, *J* = 6.60, 7.10, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 138.0, 136.8, 118.5, 117.72, 93.1, 92.9, 74.6, 74.0, 71.93, 71.90, 67.1, 59.1, 41.2, 34.3, 32.0, 31.28, 30.10, 29.85, 29.68, 29.65, 29.46, 25.4, 22.2, 14.2;

ESI-MS: m/z = 539.39 [M +Na]+. **HRMS (ESI)** for $C_{28}H_{52}O_8$ (M + Na)+ found 539.3535, calcd 539.3554.

(4*R*,7*S*,10*S*,*E*)-4,7-bis((2-Methoxyethoxy)methoxy)-10-octyl-3,4,7,8,9,10-hexahydro-2H-oxecin-2-one (35)



To a solution of **36** (0.10 g, 0.193 mmol, 0.001M) in freshly distilled degassed anhydrous CH_2Cl_2 (276mL) was added Grubb's second generation catalyst (0.033 g, 0.038 mmol, 20 mol%) and heated at reflux for 16h under an argon atmosphere. The solvent was evaporated to a brown residue, which was purified by column chromatography using petroleum ether: EtOAc, (70:30) as eluent to afford **35** (0.048 g, 50% based on recovery of starting material) as a colorless liquid.

$[\alpha]_D^{25}$: +3.289 (c= 0.733, $CHCl_3$).

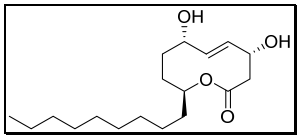
IR (δneat, cm^{-1}): ν_{max} 2926, 2855, 1735, 1109, 1042, 850;

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.70 (dd, *J* = 3.01, 16.32 Hz, 1H), 5.58 (dd, *J* = 8.29, 16.57 Hz, 1H), 4.70-4.81 (m, 4H), 4.63 (m, 1H), 4.10-4.18 (m, 1H), 3.60-3.68 (m, 1H), 3.60-3.78 (m, 4H), 3.53-3.56 (m, 4H), 3.39 (s, 6H), 2.68 (dd, *J* = 3.01, 12.05 Hz, 1H), 2.48 (dd, *J* = 3.76, 12.05 Hz, 1H), 2.25-2.38 (m, 1H), 1.72-2.02 (m, 4H), 1.25 (s, 15H), 0.86 (dd, *J* = 7.02, 7.28 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.71, 141.4, 132.5, 93.7, 92.7, 71.9, 71.8, 71.0, 67.3, 67.0, 59.1, 42.6, 35.75, 32.0, 29.85, 29.82, 29.76, 29.67, 29.59, 29.44, 25.3, 22.8, 14.2;

ESI-MS: m/z = 511.336 $[M+Na]^+$; **HRMS (ESI)** for $C_{26}H_{48}O_8$ (M+Na)+ found 511.3289, calcd 511.3241.

(4*R*,7*S*,10*S*,*E*)-4,7-Dihydroxy-10-nonyl-3,4,7,8,9,10-hexadihydro-2*H*-oxecin-2-one (34)



To a solution of compound **35** (0.040 g, 0.082 mmol) in CH_2Cl_2, was added TFA (0.062 mL, 0.82 mmol) and the mixture stirred at room temperature for 16 h. The reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$, extracted with EtOAc and the organic layer was separated, washed with brine, dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography using EtOAc : petroleum ether (1:1) as eluent to afford E-seimatopolide B (0.018 g, 70%) as a white amorphous solid.

$[a]_D^{25}$: -212.60 (c 0.035, MeOH).{lit.[11] $[\alpha]_D^{25}$= -125.3 (c 0.03, MeOH)};

IR (neat, cm^{-1}): ν_{max} 3242, 2912, 2853, 1721;

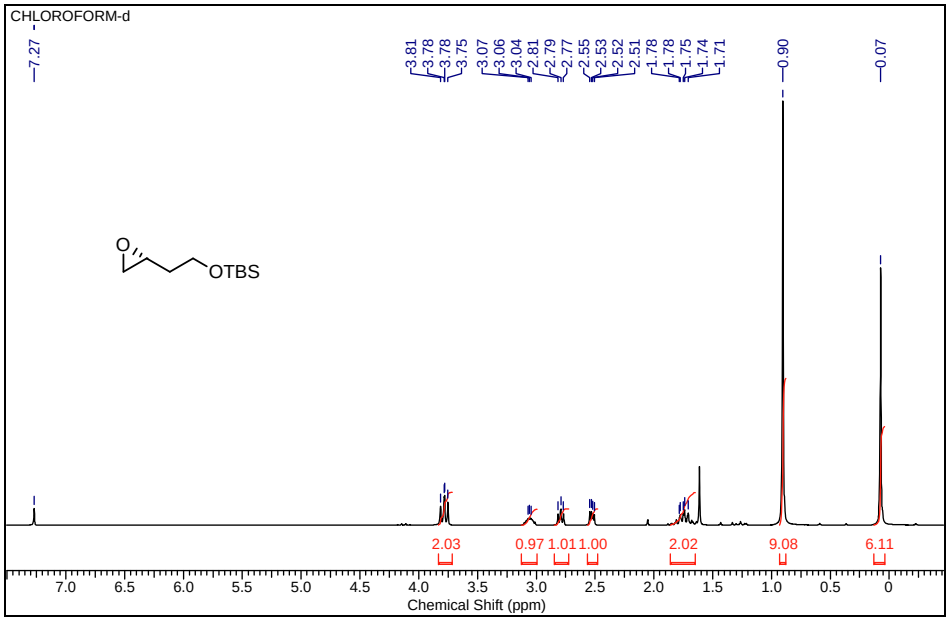
^{1}H NMR (500 MHz, pyridine-d_5): d 6.56 (dd, J = 8.54, 16.17 Hz 1H), 5.98 (dd, J = 3.05, 16.17 Hz 1H), 5.09 (m, 2H), 4.99 (m, 1H), 4.64 (m, 1H), 2.90 (dd, J = 3.36, 11.60 Hz, 1H), 2.74 (dd, J = 3.97, 11.60 Hz, 1H), 2.32 (m, 1H), 2.00 (m, 2H), 1.72 (m, 1H), 1.63 (m, 1H), 1.51 (m, 1H), 1.23 (m, 14H), 0.88 (t, J = 7.02 Hz, 3H);

^{13}C NMR (125 MHz, pyridine-d_5): d 170.6, 133.4, 76.5, 74.9, 67.8, 45.8, 38.6, 36.4, 32.4, 31.2, 30.3, 30.2, 30.1, 29.9, 26.1, 23.3, 14.6;

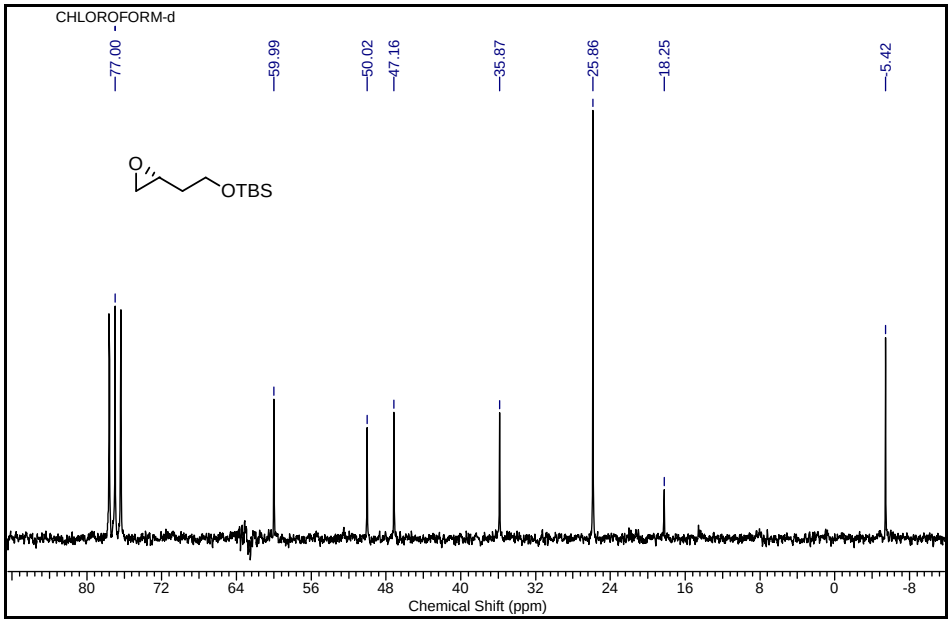
ESI-MS: m/z = 335.17 $[M+Na]^+$. **HRMS (ESI)** for $C_{18}H_{32}O_4$ $(M+Na)^+$ found 335.2187, calcd. 335.2193.

Spectra

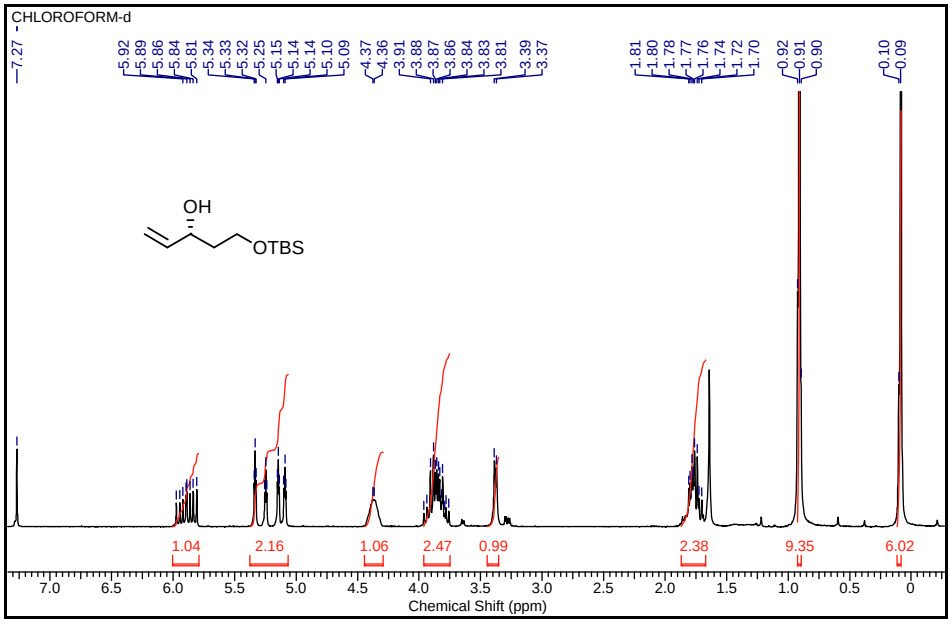
1. ^{1}H and ^{13}C NMR spectra of **42a**
2. ^{1}H and ^{13}C NMR spectra of **44**
3. ^{1}H and ^{13}C NMR spectra of **45**
4. ^{1}H and ^{13}C NMR spectra of **46**
5. ^{1}H and ^{13}C NMR spectra of **37**
6. ^{1}H and ^{13}C NMR spectra of **36**
7. ^{1}H and ^{13}C NMR spectra of **35**
8. ^{1}H and ^{13}C NMR spectra of **34**



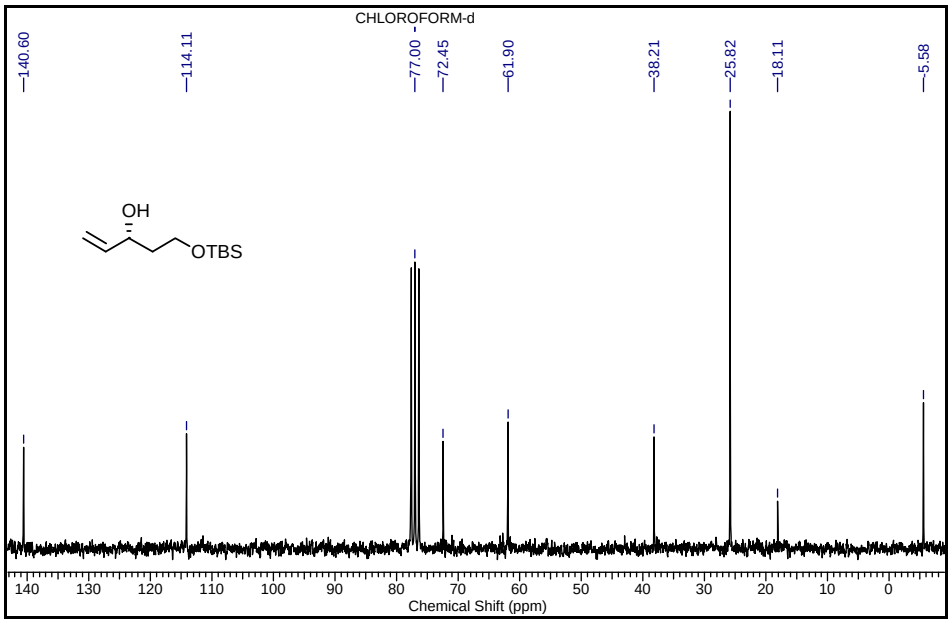
^{1}H NMR spectrum of Compound 42a in $CDCl_3$



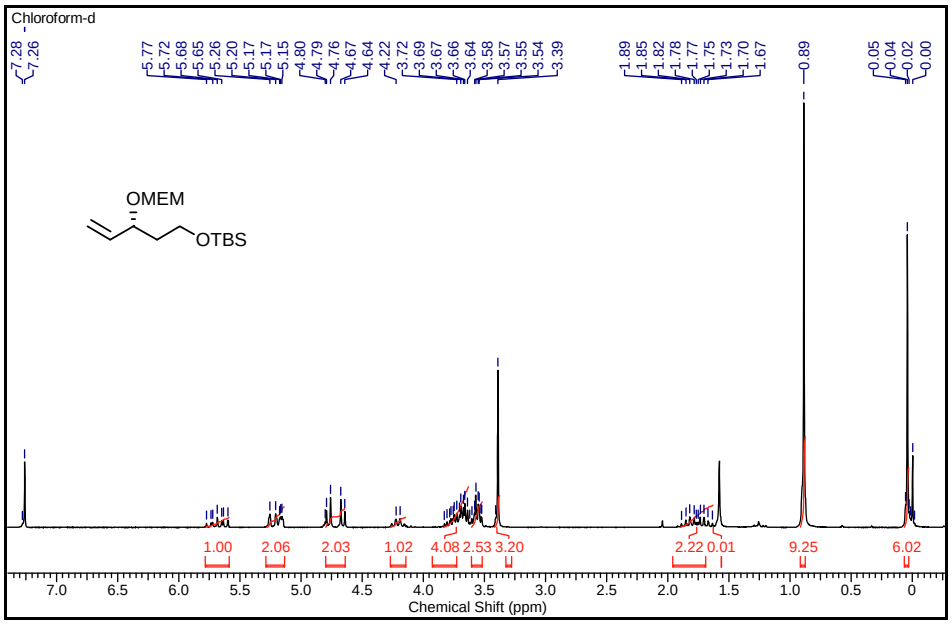
^{13}C NMR spectrum of Compound 42a in $CDCl_3$



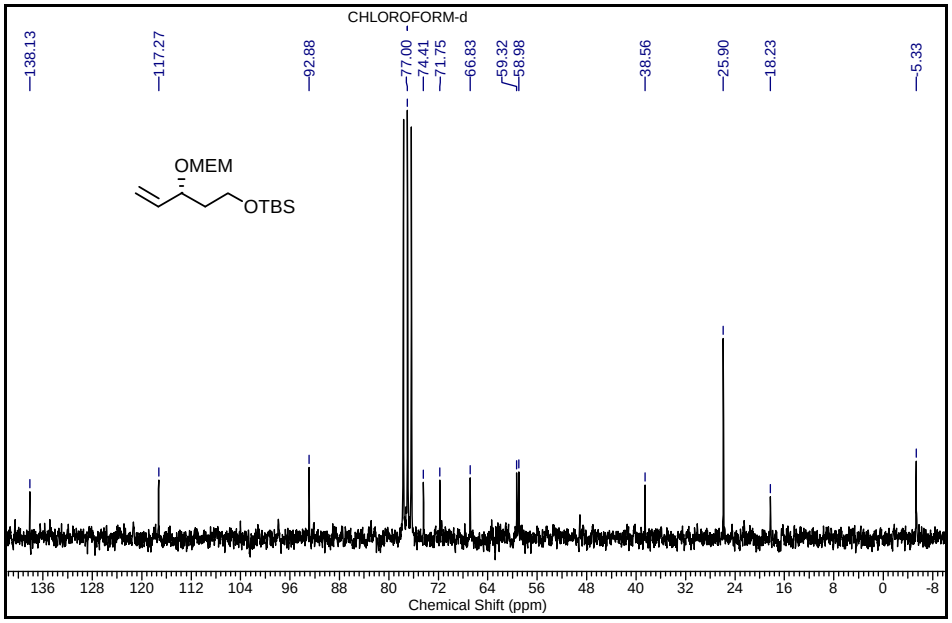
^{1}H NMR spectrum of Compound 44 in $CDCl_3$



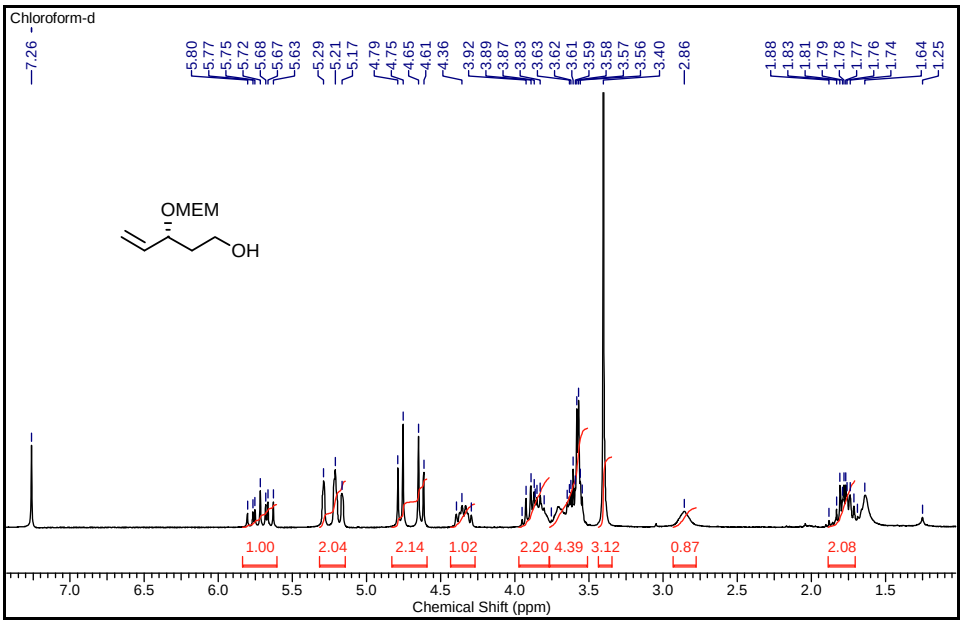
^{13}C NMR spectrum of Compound 44 in $CDCl_3$



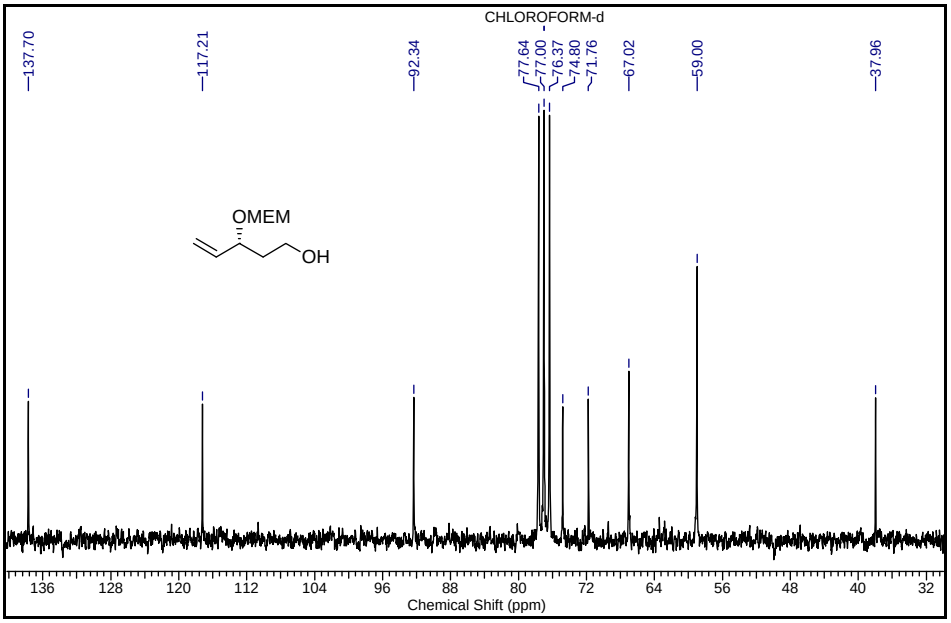
^{1}H NMR spectrum of Compound 45 in $CDCl_3$



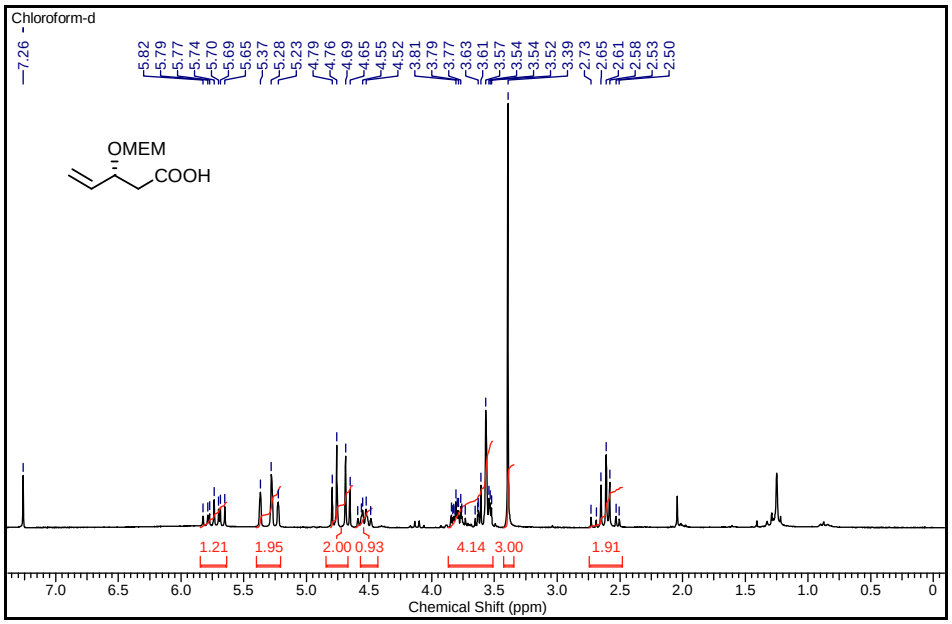
^{13}C NMR spectrum of Compound 45 in $CDCl_3$



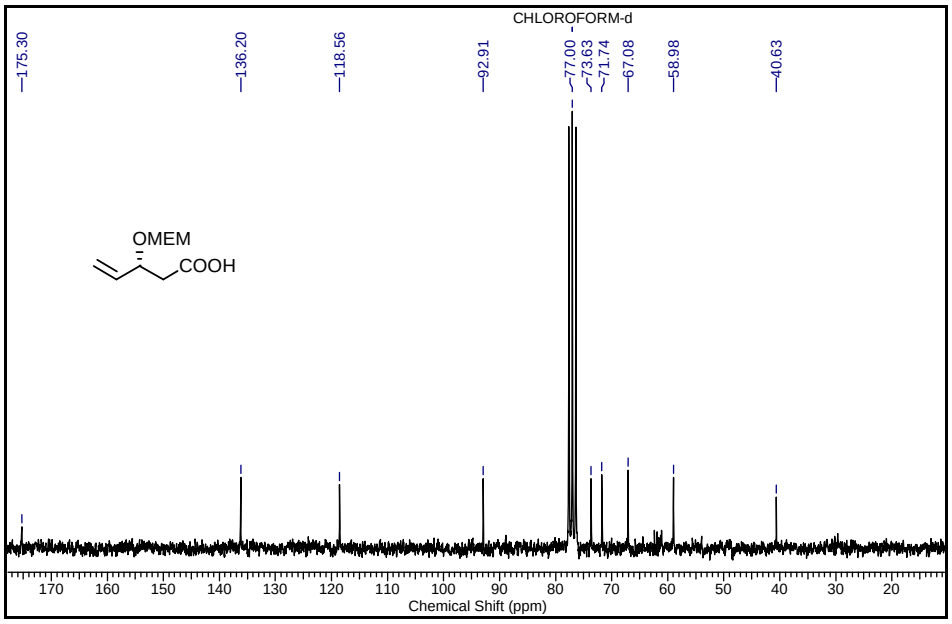
^{1}H NMR spectrum of Compound 46 in $CDCl_3$



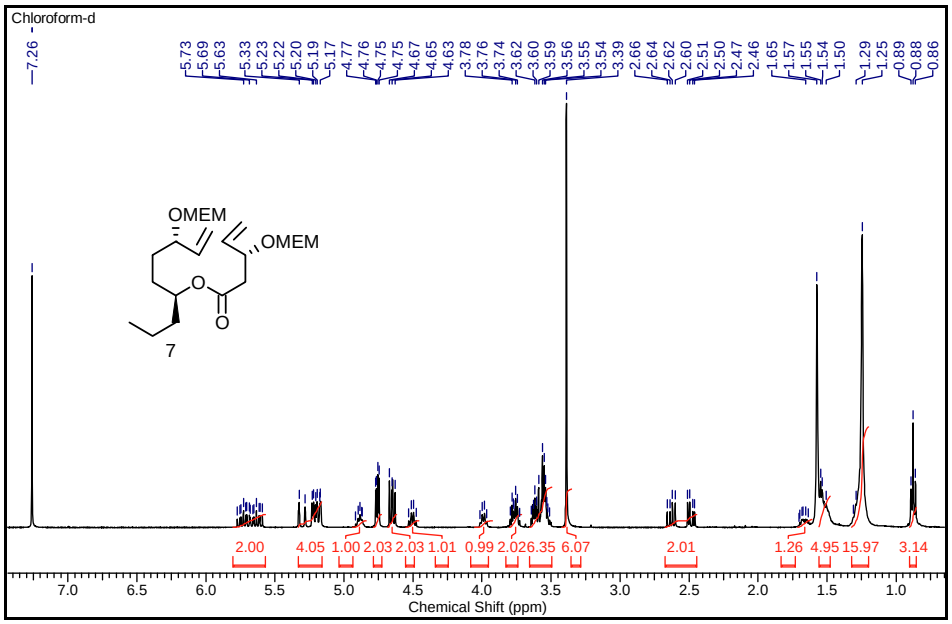
^{13}C NMR spectrum of Compound 46 in $CDCl_3$



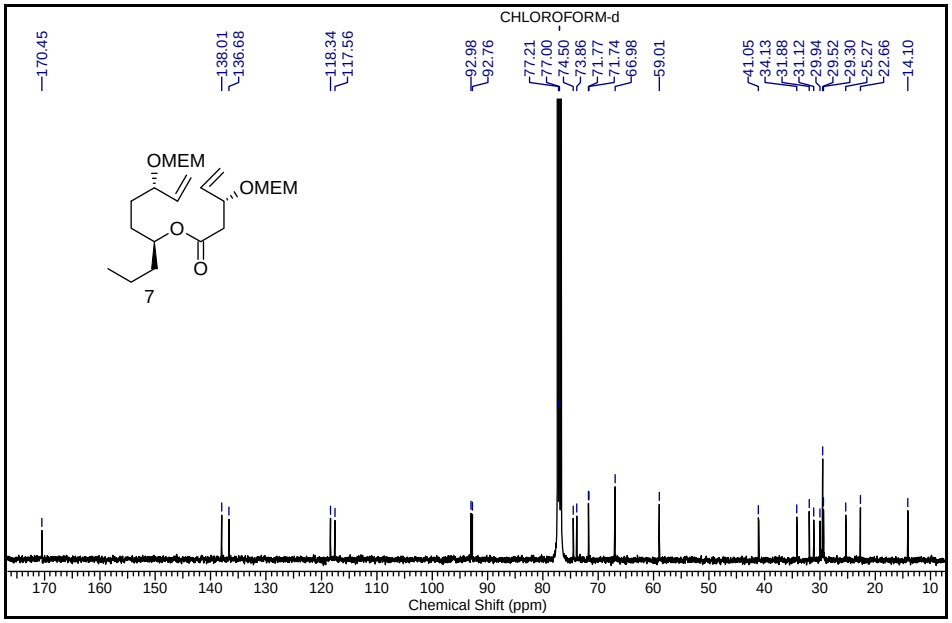
^{1}H NMR spectrum of Compound 37 in $CDCl_3$



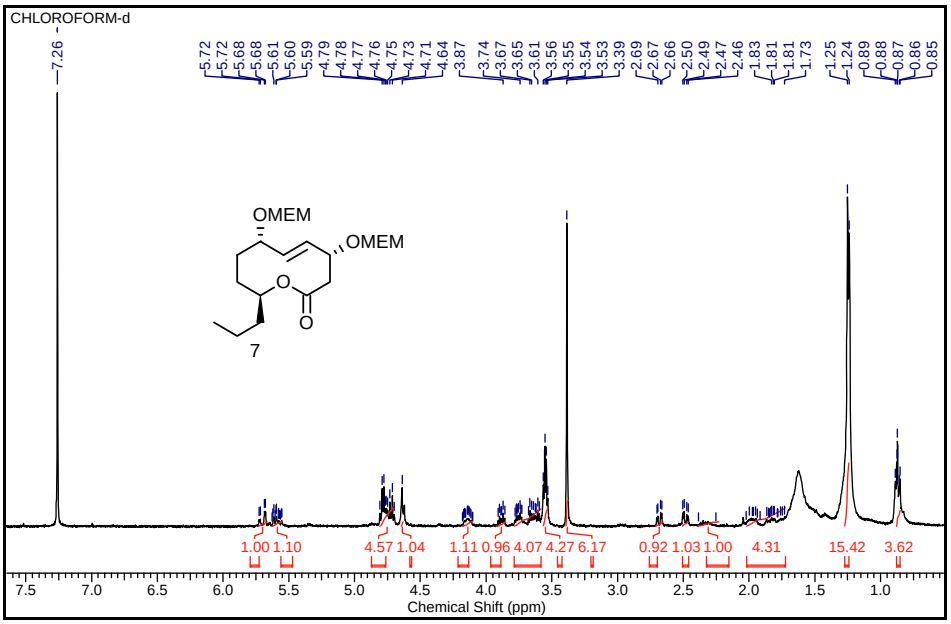
^{13}C NMR spectrum of Compound 37 in $CDCl_3$



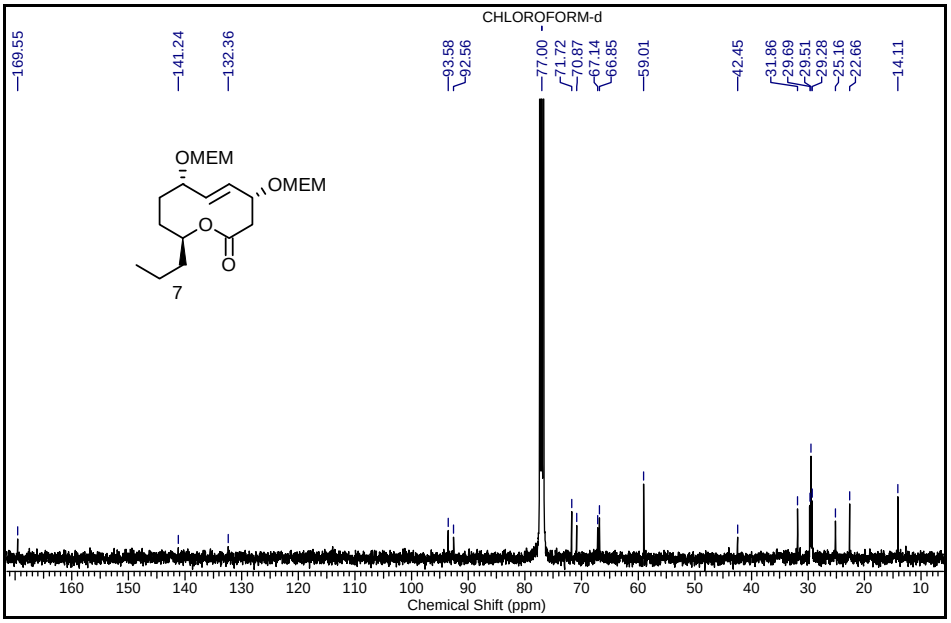
^{1}H NMR spectrum of Compound 36 in $CDCl_3$



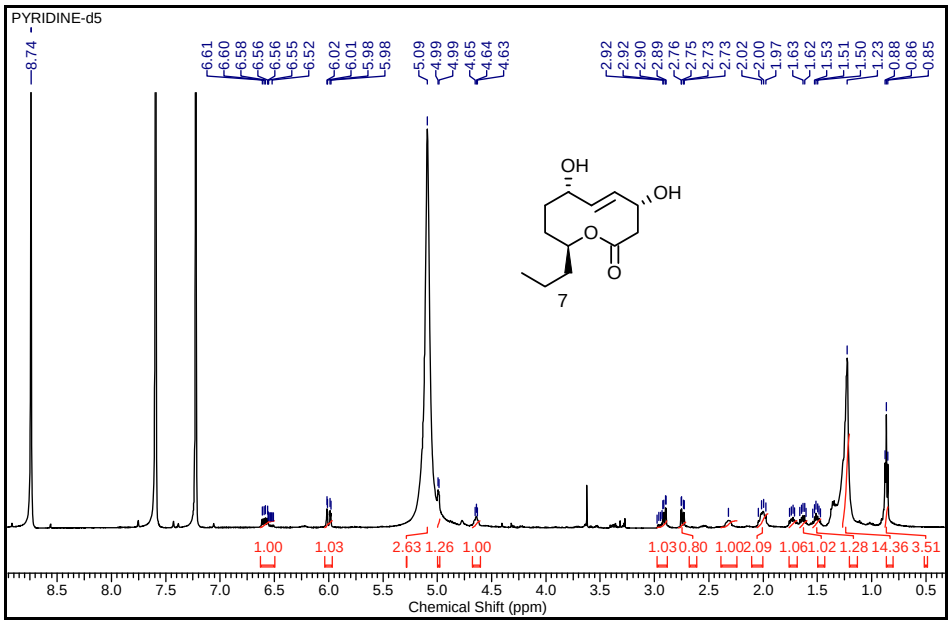
^{13}C NMR spectrum of Compound 36 in $CDCl_3$



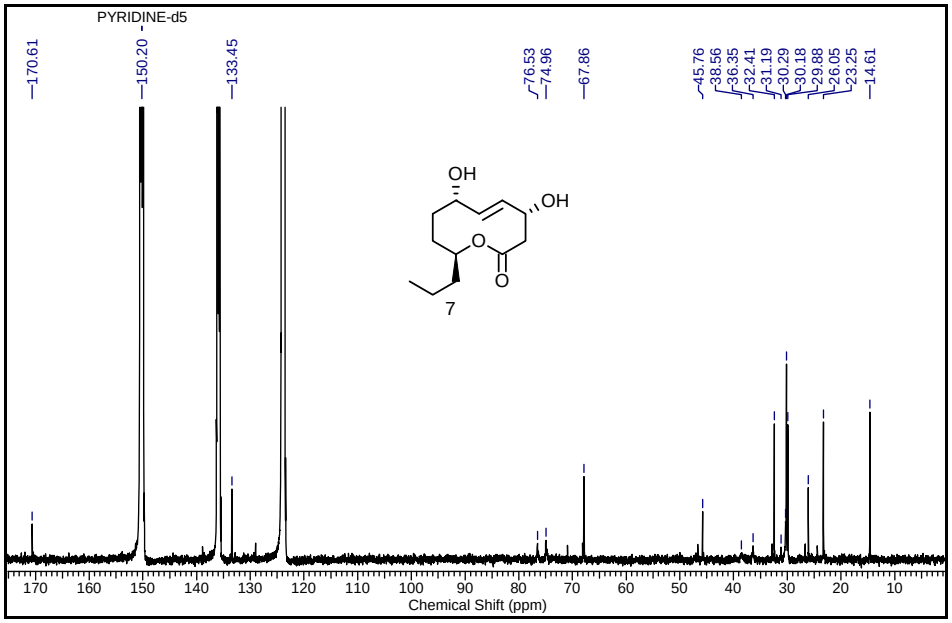
^{1}H NMR spectrum of Compound 35 in $CDCl_3$



^{13}C NMR spectrum of Compound 35 in $CDCl_3$



^{1}H NMR spectrum of Compound 34 in $CDCl_3$



^{13}C NMR spectrum of Compound 34 in $CDCl_3$

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Studies directed towards the synthesis of Jaspine B and its analogues

Introduction

Sphingolipids are structurally diverse constituents of membranes in mammals, plants, fungi, yeast and in some prokaryotic organism and viruses.[1] Sphingolipids and some of their metabolites exhibit essentially all type of cell regulation such as cell proliferation, differentiation, immune response, cell recognition, apoptosis, adhesion and signal transduction.[2] The most important sphingolipids are sphingosine and phytosphingosine. Phytosphingosines constitute a group of related long chain aliphatic 2-amino-1,3,4-triols of which D-*ribo*-C18-phytosphingosine is the most predominant. D-*ribo*-Phytosphingosine was first isolated from the mushroom *Amanita muscaria* in 1911 by Zellner as a nitrogen-containing substance "fungus cerebrin" and it is very important for, keratinocytes and constitutes 40% of the membrane content. Due to its plant origin and its structural similarity to sphingosine, the name "phytosphingosine" was coined for this base. Because of the additional free hydroxy group in phytosphingosine, additional hydrogen bonds can be formed, which may enhance the rigidity of the multicellular lipid layer. This in turn leads to a decrease in transepidermal water loss. Ceramides and glycosphingolipids are *N*-acyl derivatives of these compounds. The structural variation in fatty acids (*N*-acyl portion) sphingosines and carbohydrates results in a great variety of chemically distinct glycosphingolipids. Glycospingolipids are involved in several biological functions such as (i) HIV binding to galactosyl ceramide receptor sites in cells lacking the principal CD4 cellular receptor,[3] (ii) being unambiguous links between specific sphingolipids and malignant tumors which enables them to be used as 'biological markers' for possible early detection of cancer,[4] and (iii) potent and reversible inhibition of protein kinase C by breakdown products of glycosphingolipids, e.g. sphingosine, dihydrosphingosine and lysosphingolipids.

Pachastrissamine also known as Jaspine B was the first naturally occurring anhydrophytosphingosine isolated,[5] which also displays potent biological activity. Since its isolation in 2002, there has been a great deal of interest from synthetic chemists concerning the total synthesis of Pachastrissamine **5**, its C(2)-epimer (2-*epi*-jaspine B **6**) and their analogues (Figure 1).

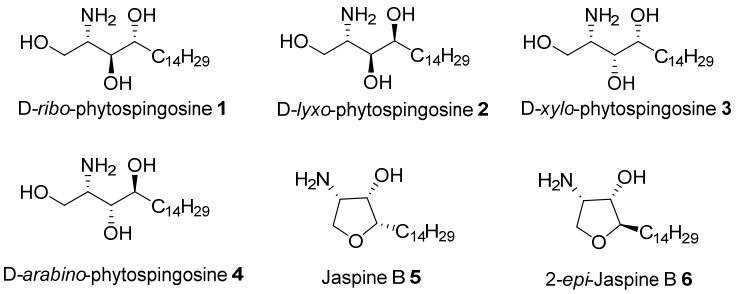
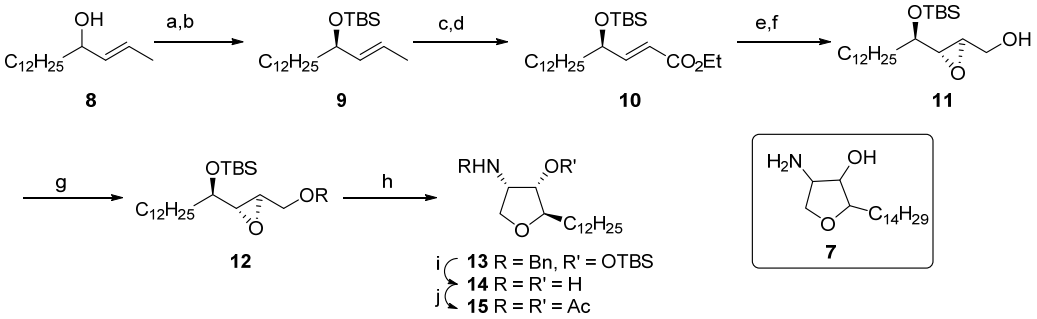


Figure 1

Synthesis of anhydrophytosphingosines prior to the isolation of jaspine B:

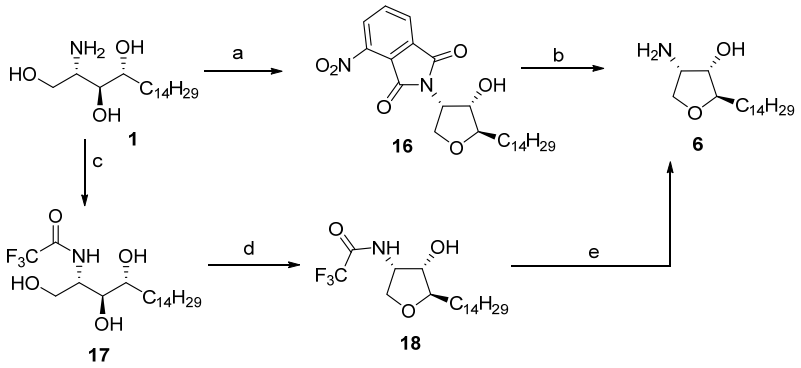
In 1959 the first report of an anhydrophytosphingosine **7** appeared, although a stereochemical assignment was not given.[6] Subsequently, its structure and relative configuration were assigned by analogy with the 'truncated' analogue **14**, bearing a $C_{12}H_{25}$ side chain. In this synthesis, allylic alcohol **8** was kinetically resolved under Sharpless asymmetric epoxidation conditions with (+)-DIPT to afford an enantioenriched sample,[7] which upon *O*-silylation afforded (*R*)-**9** of 97% ee. Ozonolysis of (*R*)-**9** followed by Horner-Wadsworth-Emmons olefination gave **10**. Reduction of the ester functionality of **10** was achieved with DIBAL-H, which was oxidised under Sharpless asymmetric epoxidation conditions with (–)-DIPT to give epoxide **11**. Treatment of **11** with benzylisocyanate gave urethane **12**, and subsequent base-mediated epoxide opening gave tetrahydrofuran derivative **13**. The configuration of **13** (2*R*,3*S*,4*S*) was determined by ^{1}H NMR NOE studies on *N*,*O*-diacetyl derivative **15** (Scheme 1).[8]



Scheme 1. *Reagents and conditions*: (a) $Ti(O^iPr)_4$, (+)-DIPT, *t*-BuO_2H, CH_2Cl_2, -20 ^oC, 15 h; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 ^oC, 12 h; (c) O_3, CH_2Cl_2, -78 ^oC then Me_2S, -78 ^oC to rt; (d) $(EtO)_2P(O)CH_2CO_2Et$, NaH, C_6H_6, 60 ^oC to rt, 15 min; (e) DIBAL-H, hexane, 0 ^oC to rt, 12 h; (f) $Ti(O^iPr)_4$, (-)-DIPT, $tBuO_2H$, CH_2Cl_2, -20 ^oC, 21 h; (g) BnNCO, Et_3N, CH_2Cl_2, rt, 12 h; (h) NaH, THF, rt, 12 h; (i) HF, H_2O,

MeCN, 70 ^{o}C, 2 h then Pd/C, cyclohexene, HCl (1 M, aq), MeOH, reflux, 2 h; (j) Ac_2O, pyridine, 70 ^{o}C, 1.5 h.

Recently (in 2001), the synthesis of an authentic sample of 2-*epi*-jaspine B **6** was reported by Kim *et al*., starting from D-*ribo*-phytosphingosine **1**. Initial treatment of **1** with 3-nitrophthalic acid at reflux under Dean-Stark conditions is reported to give tetrahydrofuran derivative **16**, which on hydrazine mediated *N*-deprotection afforded **6**. Kim *et al*. also report that treatment of *N*-trifluoroacetyl D-*ribo*-phytosphingosine **17** with TsCl in pyridine effected cyclisation to tetrahydrofuran derivative **18**, which upon deprotection also gave **6**, with identical spectroscopic data (Scheme 2).[9]



Scheme 2. *Reagents and conditions:* (i) 3-nitrophthalic acid, PhMe, reflux, 3 h; (ii) NH_2NH_2, H_2O, EtOH reflux, 2 h; (iii) NaH, HS(*p*-MeC_6H_4), DMF, 25 ^{o}C, 2 h; (iv) F_3CCO_2Et, EtOH, 25 ^{o}C, 16 h; (v) TsCl, pyridine, 25 ^{o}C, 16 h; (vi) K_2CO_3, MeOH, 25 ^{o}C, 16 h.

Isolation of pachastrissamine (Jaspine B):

In 2002, studies on the marine sponge *Pachastrissa* sp. by Higa and coworkers[5a] led to the isolation of an anhydrophytosphingosine derivative which they named pachastrissamine (**5**) (Figure 2). Shortly after, in an independent study, Debitus and co-workers reported the isolation of two anhydrophytosphingosines from the marine sponge *Jaspis* sp.,[5b] which they named jaspine A (**19**) and B (**5**); pachastrissamine and jaspine B being identical (Figure 2). Both jaspines A (**19**) and B (**5**) display biological activity;[5a] jaspine B (**5**) in particular being the most potent compound isolated from the *Jaspis* genus to date against the A549 human lung carcinoma cell line.

Stereochemical assignment:

Higa *et al*. determined the relative configuration of pachastrissamine (**5**) after the conversion of **5** by ^{1}H NMR NOE analysis of the *N*,*O*-diacetyl derivative **21**, which indicated the all-*cis* relationship of the substituents around the tetrahydrofuran ring.

The (2*S*,3*S*,4*S*)–absolute configuration of the natural product was then established using the Mosher method, by conversion of *N*-acetyl pachastrissamine (**20**) to the corresponding (*R*)- and (*S*)-2-methoxy-2-trifluoromethylphenyl acetyl (MTPA) derivatives.[10] In their independent study, Debitus *et al*. also converted jaspine B (**5**) to the corresponding *N*-acetyl and *N*,*O*-diacetyl derivatives **20** and **21**, and compared the ^{1}H and ^{13}C NMR data with that of the known $C_{12}H_{25}$ side-chain *N*,*O*-diacetyl derivative **15**[9] which also indicated an all-*cis* relationship of the substituents around the tetrahydrofuran ring. The absolute configuration of the natural product was then determined, also by the Mosher method, as (2*S*,3*S*,4*S*) (Figure 2).

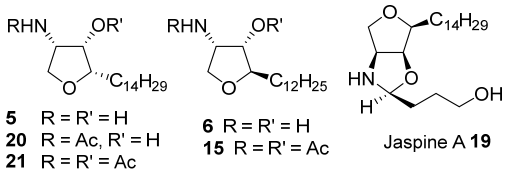


Figure 2

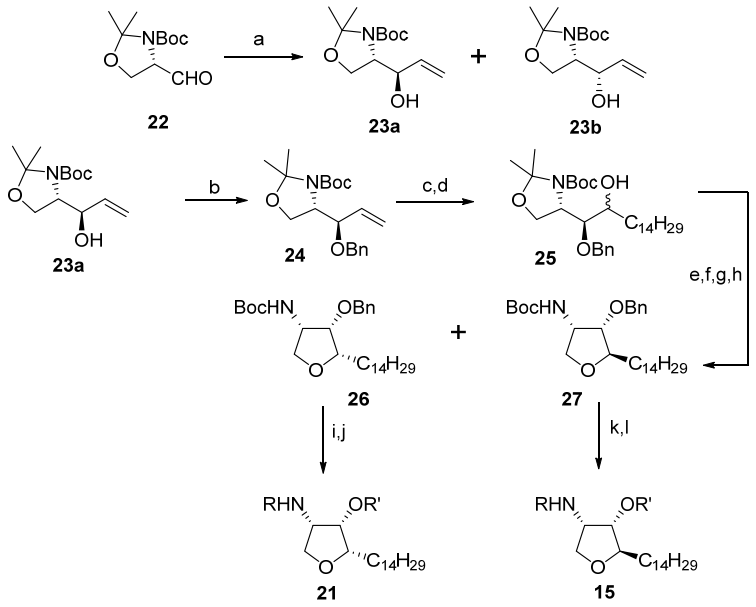
Literature Review

Due to the variety of their simple structure and promising cytotoxicity in the nanomolar range against P388, A549, HT29 and MEL28 (IC50 = 0.001 μg/mL) cancer cell lines, it has become important synthetic target. Chiral pool synthesis is one of the simplest approaches for enantioselective synthesis. Garner's aldehyde **22** is perhaps one of the most valuable chiral building blocks in recent times. Although there are numerous total synthesis of jaspine B starting from different chiral starting materials, a few simple, interesting synthesis in which Garner aldehyde is used as the starting material are described below.

B. Venkateswara Rao *et al.*[11]

The first total synthesis of Jaspine B was reported by Rao and co-workers by using L-serine derived Garner's aldehyde. Addition of vinylmagnesium bromide to Garner's aldehyde gave a separable 86:14 mixture of diastereoisomeric alcohols **23a** and **23b** in accordance with the well-known modified Felkin-Ahn selectivity for addition. The major diastereoisomer **23a** was protected as the corresponding benzyl ether to give **24**. Ozonolysis of **24** was followed by addition of tetradecylmagnesium bromide to give an inseparable 70:30 mixture of the diastereoisomeric alcohols **25**. Protection and deprotection manipulations followed by mesylation and treatment of the mesylates with TBAF promoted desilylation and concomitant cyc1isation to a separable 70:30 mixture of tetrahydrofurans, from which the all-*cis* diastereoisomer **26** and its C(2)-

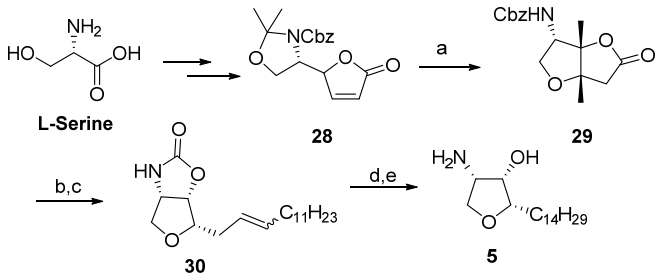
epimer **27** was isolated. Subsequent debenzylation and diacetylation of **26** and **27** gave *N*,*O*-diacetyl jaspine B (**21**) and *N*,*O*-diacetyl 2-*epi*-jaspine B (**15**) respectively (Scheme 3).



Scheme 3: *Reagents and conditions*: (a) vinylmagnesium bromide, THF, 0 °C to rt, 12 h; (b) BnBr, THF, NaH, 0 °C to rt, 12 h, 92%; (c) O_3, CH_2Cl_2, -78 °C, 1 h, Me_2S; (d) $C_{14}H_{29}MgBr$, THF, 12 h, rt, 83% for two steps; (e) 80% AcOH, 0 °C to rt, 12 h, 91%; (f) TBSCl, imidazole, CH_2Cl_2, DMAP, 0 °C to rt, 12 h, 86%; (g) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt 2 h; (h) TBAF, THF, rt, 2 h, 88% for two steps; (i) Na, NH_3, THF, -78 °C, 30 min, 96%; (j) TFA:CH_2Cl_2 (1:1), rt, 6 h, 87%; (k) Et_3N, AC_2O, CH_2Cl_2, 0 °C to rt, 4h, 94%.

Apurba Datta *et al.* [12]

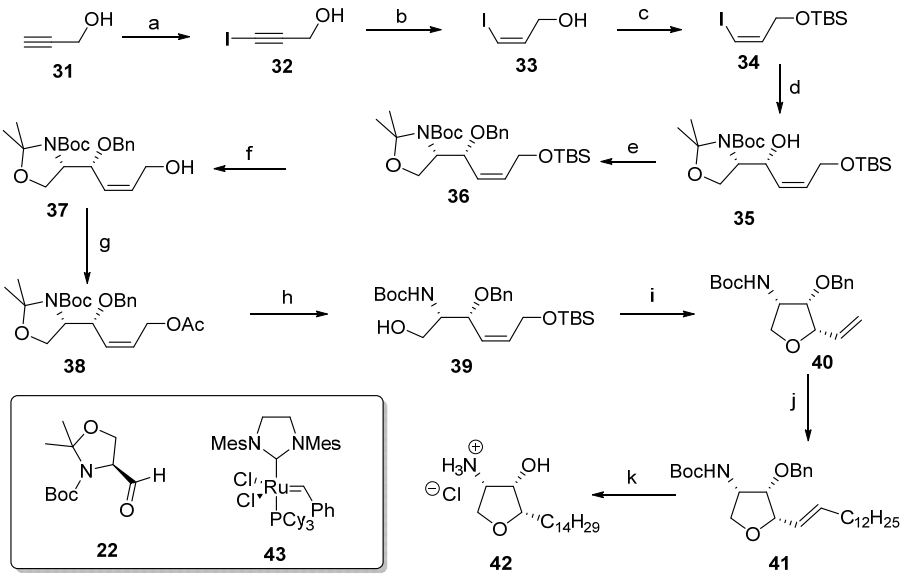
Datta and co workers reported the synthesis of jaspine B (**5**) starting from L-serine, which was converted into butenolide **28**. Formic acid treatment enabled the deprotection of the acetonide, with subsequent Michael addition of the free hydroxyl group giving *cis*-fused bicycle **29**. DIBAL-H reduction of the resulting lactone to lactol and subsequent Wittig olefination gave **30**. Hydrogenation and cleavage of the resultant oxazolidinone of **30** afforded jaspine B (**5**) (Scheme 4).



Scheme 4: *Reagents and conditions*: (i) HCO_2H, CH_2Cl_2, 0 °C then EtOAc, satd. aq $NaHCO_3$, 79%; (ii) DIBAL-H, −78 °C, 83%; (iii) $C_{12}H_{25}Ph_3P^+Br^-$, *n*-BuLi, THF, −78 °C to rt, 81%; (iv) H_2, Pd/C, EtOAc, rt, 90%; (v) aq KOH, EtOH, reflux, 77%.

Koskinen *et al.*[13]

Koskinen *et al.* reported the synthesis of jaspine B hydrochloride **42** using L- Serine-derived Garner's aldehyde **22** as the source of chirality, with Pd(0)-mediated cyclisation and Ru-mediated cross-metathesis reactions as the key steps in the synthesis. Iodide **34** was coupled with Garner's aldehyde **22** by treatment with BuLi and *N,N*'-dimethyl-*N,N'*-propylene urea (DMPU) to give a separable 92:8 mixture of diastereoisomers, with the major isomer **35**. Subsequent benzylation, O-TBS deprotection and acetylation gave acetate. Hydrolysis of the *N,O*-acetal followed by Pd(0)-mediated intramolecular 1,5-cyclisation[14] gave a separable 67:33 mixture of diastereoisomeric tetrahydrofuran derivatives in 95% combined yield. The all-cis isomer **40** was then coupled with 1-tetradecene (10 equiv) via a cross-metathesis reaction with Grubbs II **43** to give **41** as the only diastereoisomer in 87% yield. Tandem hydrogenation/ hydrogenolysis of **41** with $Pd(OH)_2/C$ under H_2, followed by treatment with HCl gas was reported to afford jaspine B hydrochloride **42** (Scheme 5).

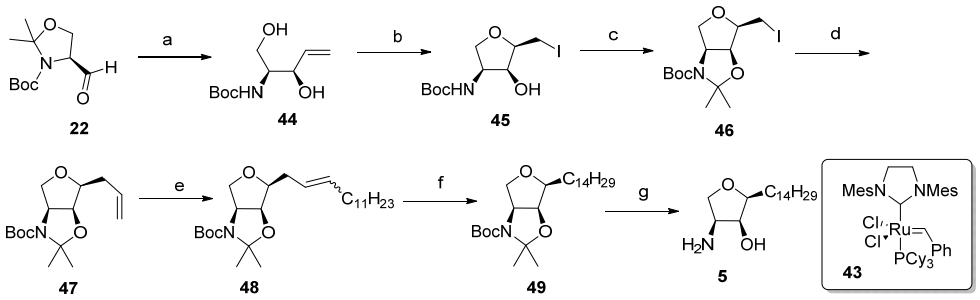


Scheme 5. *Reagents and conditions:* (a) I_2, KOH, MeOH; (b) $KO_2CN{=}NCO_2K$, AcOH, MeOH; (c) TBSCl, imidazole, DMF; (d) BuLi, DMPU, PhMe, -78 ^oC then **22**, PhMe, -95 ^oC; (e) BnBr, TBAI, NaH, THF, 0 ^oC then Δ; (f) TBAF, CH_2Cl_2, rt; (g) Ac_2O, DMAP, Et_3N, CH_2Cl_2, rt; (h) $FeCl_3$–SiO_2, $CHCl_3$, rt; (i) $Pd(PPh_3)_4$, PPh_3, THF, 55 ^oC; (j) Grubbs II **43**, 1-tetradecene, CH_2Cl_2, 40 ^oC; (k) H_2, $Pd(OH)_2$, MeOH/EtOAc (1:1), rt then HCl, MeOH/EtOAc (1:1).

Gautam Panda *et al.*[15]

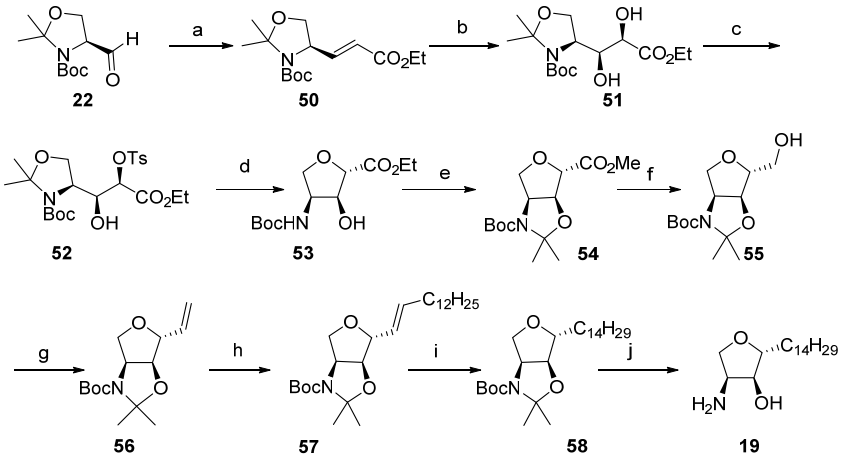
Panda and co-workers reported the stereoselective synthesis of Jaspine B and its C2 epimer from Garner aldehyde by diastereoselective nucleophilic addition[16] of vinylmagnesium bromide followed by separation of the major anti product (dr 6:1) through column chromatography, and acetonide ring opening using PTSA in methanol. The iodocyclization of the allylic alcohol **44** gave the tetrahydrofuran derivative **45**. Compound **45** on acetonide protection and treatment with vinyl magnesium solution gave the olefin compound **47**. Compound **48** was obtained by the cross metathesis reaction between **47** and 1-tridecene in presence of Grubbs' catalyst. Hydrogenation of **48** under Pd/C–H_2 conditions and acetonide, Boc deprotection gave jaspine B (scheme 6).

For the synthesis of C(2) epimer of jaspine B from Garner aldehyde, Panda *et al* have used HWE olefination, Sharpless asymmetric dihydroxylation, selective α-tosylation and acid catalysed cyclisation to get a cyclised product **53**.



Scheme 6: *Reagents and conditions:* (a) 1) vinylmagnesium bromide, THF, -78 ^{o}C, 2 h; 2) PTSA, methanol, 0 ^{o}C to rt, 1 h, 70% (over two steps); (b) I_2/K_2CO_3, CH_3CN, 0 ^{o}C, 30 min. 90%; (c) 2,2-DMP/(±)-CSA, dry CH_2Cl_2, 0 ^{o}C to rt, 4 h, 95%; (d) Vinyl magnesium bromide/CuI/HMPA, THF, -30 ^{o}C, 1 h, 80%; (e) **47**, Grubbs II Gen (8 mol%), dry CH_2Cl_2, 45 ^{o}C, 8 h, 82%; (f) H_2–Pd/C, EtOAc, 50 *psi*, rt, 0.5 h, 95%; (g) 6 N HCl in MeOH, 0 ^{o}C to rt, 5 h, 79%.

This cyclised ester was then acetonide protected which underwent transesterification with MeOH formed in situ, in the reaction. This ester was then reduced, oxidised to aldehyde and one carbon Wittig gave the olefin which on cross-metathesis with 1-tridecene produced the **57**. Hydrogenation, acetonide and Boc deprotection of **57** gave the C2 epimer of Jaspine B (scheme 7).



Scheme 7: *Reagents and conditions:* (a) $Ph_3P{=}CHCO_2Et$, C_6H_6, 0 ^{o}C to rt, 4 h, 90%; (b) AD-mix-α, $MeSO_2NH_2$, *t*-BuOH/H_2O (1 : 1), 0 ^{o}C, 36 h, 95%; (c) TsCl, Et_3N, CH_2Cl_2, 0 ^{o}C, 24 h, 85%; (d) PPTS, MeOH, 0 ^{o}C, 24 h, 70%; (e) 2,2-DMP, BF_3–OEt_2, dry acetone, 0 ^{o}C to rt, 4 h, 85%; (f) $LiBH_4$, dry THF, 0 ^{o}C to rt, 1 h, 80%; (g) 1) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^{o}C, 2 h; 2) Ph_3PCH_3Br, KHMDS, THF, -78 ^{o}C, 2 h (70% over two steps); (h) 1-tetradecene, **43** (8 mol%), dry CH_2Cl_2, 45 ^{o}C, 8 h, 80%; (i) H_2–Pd/C, EtOAc, 50 psi, 0.5 h, 95%; (j) 6 N HCl in MeOH, 0 ^{o}C to rt, 5 h, 85%.

Present Work

Sphingolipids are ubiquitous as components of cell membranes. Some unusual sphingolipids have been described from marine organisms. An example is a series of α- galactoceramides, agelasphins exhibiting potent in *vivo* antitumor activity but no in *vitro* cytotoxicity, from the sponge *Agelas mauritianus*.[17] This discovery led Natori and co-workers to the development of a synthetic anticancer agent (coded KRN7000), which is now under clinical trial.[18] Studies on the marine sponge *Pachastrissa* sp. by Higa and co-workers in 2002, led to the isolation of a cyclic anhydrophytosphingosine, which they named as pachastrissamine (**5**).[5a] Shortly after (in 2003), Debitus and co-workers[5b] reported the isolation of two anhydrophytosphighosines from the marine sponge *Jaspis* sp. and named as jaspine A (**19**) and jaspine B ; pachastrissamine and jaspine B being identical. Jaspine B was reported to exhibit promising cytotoxic activity in the submicromolar range against P388, A549, HT29 and MEL28 (IC50 = 0.001 μg/mL) cancer cell lines. An analogous anhydrophytosphingosine 2-*epi*-jaspine B (**6**) has been reported without stereochemistry as derivative of a plant metabolite.[6] Later its absolute structure was assigned by asymmetric synthesis of a compound **7** having a shorter side chain.[8] In a recent report on the early synthesis of jaspine B has indeed revealed that the synthetic samples data given was matching with **15**. This proposed an unwarranted synthesis of anhydrosphytosphingosine **5**.[9]

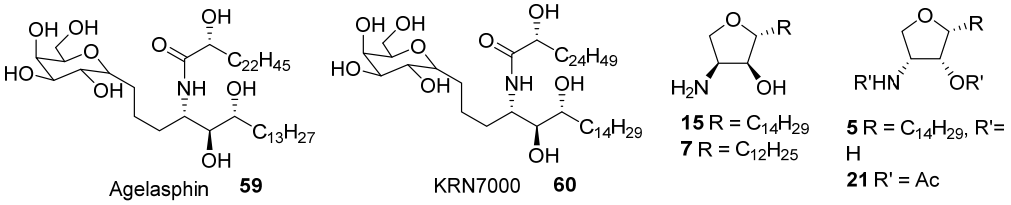
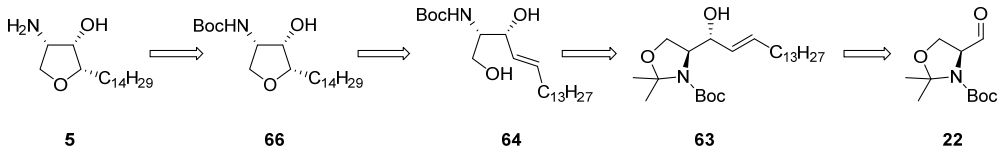


Figure 3

The novel structural features and interesting biological activities of pachastrissamine have prompted extensive synthetic efforts from a number of laboratories. As a part of our interest in the synthetic studies of sphingosines phytospingosines and related compounds, we considered exploring the coordination-controlled intramolecular mercuriocyclization for the synthesis of Jaspine B.

Retrosynthetic analysis of Jaspine B:

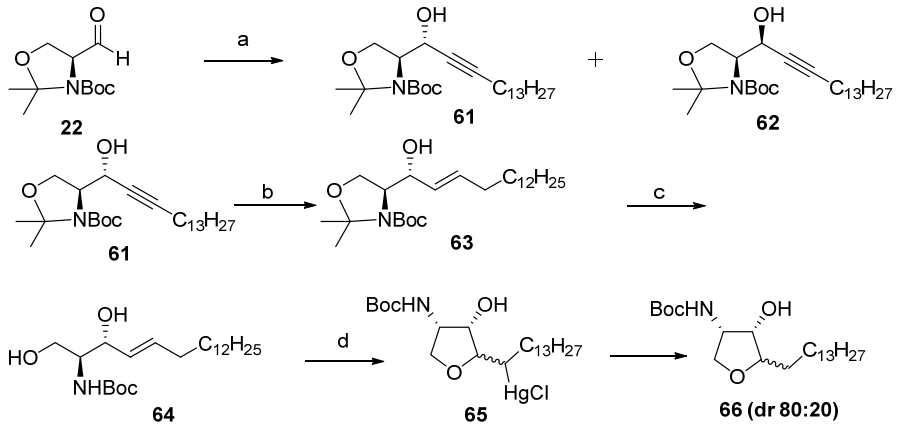
Our retrosynthetic analysis for the target compound is based on convergent approach delineated in scheme 8. We envisioned that the target compound could be synthesised by oxymercuration-demercuration sequence from olefin **64**. This olefin could in turn be obtained from nucleophilic addition of alkyne on Garner's aldehyde **22**.



Scheme 8: Retrosynthetic analysis for jaspine B

Synthesis of Jaspine B:

Our synthesis began with the oxazolidine aldehyde known as Garner's Aldehyde **(22)** available in >60% yield from L-serine in 4 steps. The stereoselective addition of lithium 1-pentadecyne[19] to the Garner's aldehyde gave chromatographically seperable mixture (8:1) of propargylic alcohols **61** and **62.** The ^{1}H NMR spectrum of **61** displayed signal for CH_2 adjacent to C-C triple bond as doublet of triplet at δ 1.96 (J = 6.95 Hz). The ^{13}C spectrum of **61** displayed signal due to acetylinic carbons at δ 94.8 and 96.1. The IR spectrum and specific rotations were in accordance with the literature reports. The *erythro*-isomer **61** was then converted to *trans*-allyl alcohol **63** exclusively using sodium bis(2-methoxyethoxy)aluminium hydride. The ^{1}H and ^{13}C spectroscopic data confirmed the structure of **63** by displaying characteristic olefin signals. This allyl alcohol **63** was then treated with *p*-TSA and methanol to hydrolyse isopropylidene group to give the *N*-Boc protected amino alcohol **64** (D-erythro-sphingosine). The spectral data for compound **64** was in complete agreement with the known structure. Now the stage was set for the crucial mercuriocyclisation reaction to obtain substituted tetrahydrofuran derivative. The oxymercuration reaction of the allylic alcohol **64** was carried out in the presence of mercury trifiuoroacetate (3 equiv.)/$NaHCO_3$ (3 equiv.), and subsequent demercuration with alkaline sodium borohydride in THF delivering the poor yield (15%) of the tetrahydrofuran derivative (dr 80:20 determined by ^{1}H NMR).

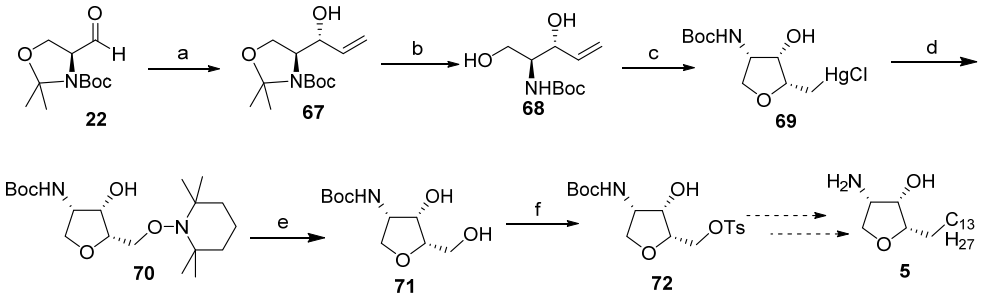


Scheme 9: *Reagents and conditions:* (a) Lithium-1-pentadecyne, -23 ^{o}C, 3 h, 63%; (b) Red-Al, ether, 0 ^{o}C –rt, 60%;(c) *p*-TSA, Methanol, 6 h, 90%; (d) (i) $Hg(OCOCF_3)_2$, CH_2Cl_2, rt, 2 h, (ii) alk. $NaBH_4$, THF, rt, 1 h 15%

As the substrates with internal alkene and long chain alkyl group gave the low yields of desired product, and the free C3-hydroxy group gave a ratio of diastereomers (80:20), so we now changed our strategy to use the terminal alkene for mercuriocyclisation which will give flexibility in placing the side chain, so as to synthesize a collection of the jaspine like small molecules.

In order to synthesize jaspine B, we started our synthesis with Garner's aldehyde **22** (scheme 10), which on reaction with vinyl magnesium bromide gave 6:1 diastereomeric mixture of **67.**[16] The ^{1}H and ^{13}C NMR spectrum displayed the signals for olefin. This mixture was then treated with p-TSA and methanol to hydrolyse the isopropylidine group to give the diol **68**. The oxymercuration of **68** with $Hg(OCOCF_3)_2$ in CH_2Cl_2 at -78 ^{o}C gave the mixture of two products in 77% yield, which were difficult to separate. The compound **69** was purified by using repeated column chromatography (R_f = 0.7 in 50% EtOAc:petroleum ether twice run) from the mixture. This compound was characterised by ^{1}H, ^{13}C NMR spectrum and 2D NMR. In the n*O*e experiment, the protons at δ 4.07 shows n*O*e correlations with the one at δ 3.63 indicating that these two protons are close in space. Also the proton at 4.07 shows n*O*e correlations with proton at 4.47 indicating the close proximity of these two protons. This confirms the all syn stereochemistry of compound **69**. Still the correlations between the proton at δ 3.63 and the proton at δ 4.47 do not appear. Oxidative demercuration using 6 equivalents of TEMPO gave the mercury displaced product **70** in 80% yield. The spectral data was in accordance with the derived

structure. Reductive cleavage of the N-O bond using $Pd(OH)_2/C$ and H_2, at 70 *psi* gave the desired product **71** in 80% yield. The alcohol **71** was then converted to its primary tosyl derivative with tosyl chloride, Et_3N in CH_2Cl_2. The postion of tosyl group and the absolute stereochemistry of compound **72** was confirmed by single crystal X-ray crystallography.



Scheme-10:*Reagents and conditions:* (a) vinyl magnesium bromide, THF, 0°C- rt, 10h, 70% (b) p-TSA, Methanol, 6 h, 90% (c) $Hg(OCOCF_3)_2$, CH_2Cl_2, 0 °C, 3h, 67% (d) DMF, O_2, $NaBH_4$, then **69,** TEMPO (6 equiv.), 30 min, 80% (e) $H_2/Pd(OH)_2/C$, 70 *psi*, 80% (f) TsCl, Et_3N, CH_2Cl_2, 90%.

The ORTEP diagram for the tosyl derivative **72** is given in Figure 4.

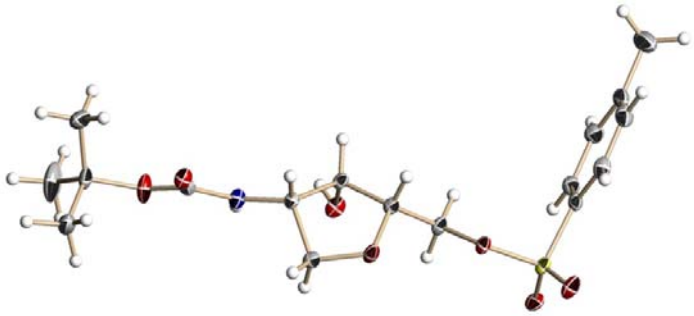
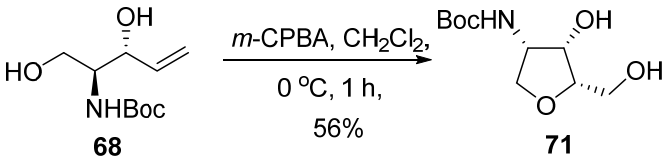


Figure 4: The ORTEP diagram for compound **72**

In order to explore the synthesis of the intermediate **71** in various stereoselective manner, the diol **68** was epoxidised with *m*-CPBA to give epoxide which *in situ* cyclised to give a mixture of products.



This mixture was treated with tosyl chloride to get the monotosylated product **72** only in 40% yield over two steps. The stereochemistry of this product was confirmed using

^{1}H, ^{13}C NMR and specific rotation values. Now the stage was set to displace the tosyl group with C13-alkyl chain to get jaspine B.

Further manipulation of compound **72** to ge**t** jaspine B and its analogues is in progress in our lab.

In conclusion we have synthesised the C2-epimer of jaspine B and a key intermediate which will be explored for the synthesis of jaspine B and its analogues.

Table 1: Crystal data and structure refinement for compound **72**

Empirical formula	$C_{17}H_{25}NO_7S$	
Formula weight	387.44	
Temperature	297(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 5.4823(3) Å	α= 90°.
	b = 29.7850(14) Å	β= 98.952(2)°.
	c = 5.8176(3) Å	γ = 90°.
Volume	938.39(8) $Å^3$	
Z	2	
Density (calculated)	1.371 Mg/m^3	
Absorption coefficient	0.211 mm^{-1}	
F(000)	412	
Crystal size	0.56 x 0.47 x 0.13 mm^3	
Theta range for data collection	2.74 to 28.32°.	
Index ranges	-7<=h<=6, -31<=k<=39, -7<=l<=7	
Reflections collected	8805	
Independent reflections	3657 [R(int) = 0.0204]	
Completeness to theta = 28.32°	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9731 and 0.8910	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3657 / 1 / 240	
Goodness-of-fit on F^2	1.188	
Final R indices [I>2sigma(I)]	R1 = 0.0434, wR2 = 0.0957	
R indices (all data)	R1 = 0.0442, wR2 = 0.0960	
Absolute structure parameter	0.01(8)	
Largest diff. peak and hole	0.414 and -0.333 $e.Å^{-3}$	

Table 2: Bond Lengths [Å] and angles [deg] for compound **72**

O(1)-C(5)	1.427(3)	N(18)-H(18N)	0.8600
O(1)-C(2)	1.444(3)	O(20)-C(21)	1.476(3)
C(2)-C(6)	1.513(3)	C(21)-C(23)	1.504(5)
C(2)-C(3)	1.525(4)	C(21)-C(22)	1.514(5)
C(2)-H(2)	0.9800	C(21)-C(24)	1.515(5)
C(3)-O(25)	1.416(3)	C(22)-H(22A)	0.9600
C(3)-C(4)	1.536(4)	C(22)-H(22B)	0.9600
C(3)-H(3)	0.9800	C(22)-H(22C)	0.9600
C(4)-N(18)	1.443(3)	C(23)-H(23A)	0.9600
C(4)-C(5)	1.521(4)	C(23)-H(23B)	0.9600
C(4)-H(9)	0.9800	C(23)-H(23C)	0.9600
C(5)-H(5A)	0.9700	C(24)-H(24A)	0.9600
C(5)-H(5B)	0.9700	C(24)-H(24B)	0.9600
C(6)-O(7)	1.461(3)	C(24)-H(24C)	0.9600
C(6)-H(6A)	0.9700	O(25)-H(25)	0.8200
C(6)-H(6B)	0.9700		
O(7)-S(8)	1.5785(18)	C(5)-O(1)-C(2)	108.51(19)
S(8)-O(10)	1.427(2)	O(1)-C(2)-C(6)	108.5(2)
S(8)-O(9)	1.431(2)	O(1)-C(2)-C(3)	107.8(2)
S(8)-C(11)	1.758(3)	C(6)-C(2)-C(3)	114.6(2)
C(10)-O(19)	1.212(3)	O(1)-C(2)-H(2)	108.6
C(10)-O(20)	1.346(3)	C(6)-C(2)-H(2)	108.6
C(10)-N(18)	1.348(3)	C(3)-C(2)-H(2)	108.6
C(11)-C(12)	1.382(4)	O(25)-C(3)-C(2)	109.7(2)
C(11)-C(16)	1.386(4)	O(25)-C(3)-C(4)	109.6(2)
C(12)-C(13)	1.391(4)	C(2)-C(3)-C(4)	100.4(2)
C(12)-H(14)	0.9300	O(25)-C(3)-H(3)	112.2
C(13)-C(14)	1.386(4)	C(2)-C(3)-H(3)	112.2
C(13)-H(13)	0.9300	C(4)-C(3)-H(3)	112.2
C(14)-C(15)	1.394(5)	N(18)-C(4)-C(5)	114.6(2)
C(14)-C(17)	1.507(5)	N(18)-C(4)-C(3)	112.5(2)
C(15)-C(16)	1.392(4)	C(5)-C(4)-C(3)	101.3(2)
C(15)-H(15)	0.9300	N(18)-C(4)-H(9)	109.4
C(16)-H(16)	0.9300	C(5)-C(4)-H(9)	109.4
C(17)-H(17A)	0.9600	C(3)-C(4)-H(9)	109.4
C(17)-H(17B)	0.9600	O(1)-C(5)-C(4)	104.4(2)
C(17)-H(17C)	0.9600	O(1)-C(5)-H(5A)	110.9

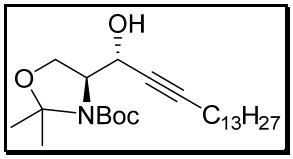
C(4)-C(5)-H(5A)	110.9	C(14)-C(17)-H(17A)	109.5
O(1)-C(5)-H(5B)	110.9	C(14)-C(17)-H(17B)	109.5
C(4)-C(5)-H(5B)	110.9	H(17A)-C(17)-H(17B)	109.5
H(5A)-C(5)-H(5B)	108.9	C(14)-C(17)-H(17C)	109.5
O(7)-C(6)-C(2)	104.0(2)	H(17A)-C(17)-H(17C)	109.5
O(7)-C(6)-H(6A)	111.0	H(17B)-C(17)-H(17C)	109.5
C(2)-C(6)-H(6A)	111.0	C(10)-N(18)-C(4)	123.5(2)
O(7)-C(6)-H(6B)	111.0	C(10)-N(18)-H(18N)	118.3
C(2)-C(6)-H(6B)	111.0	C(4)-N(18)-H(18N)	118.3
H(6A)-C(6)-H(6B)	109.0	C(10)-O(20)-C(21)	120.8(2)
C(6)-O(7)-S(8)	120.33(15)	O(20)-C(21)-C(23)	110.1(2)
O(10)-S(8)-O(9)	120.17(13)	O(20)-C(21)-C(22)	102.1(2)
O(10)-S(8)-O(7)	104.16(11)	C(23)-C(21)-C(22)	110.3(3)
O(9)-S(8)-O(7)	108.97(11)	O(20)-C(21)-C(24)	110.7(3)
O(10)-S(8)-C(11)	109.97(13)	C(23)-C(21)-C(24)	111.5(3)
O(9)-S(8)-C(11)	109.24(13)	C(22)-C(21)-C(24)	111.8(3)
O(7)-S(8)-C(11)	102.86(12)	C(21)-C(22)-H(22A)	109.5
O(19)-C(10)-O(20)	125.1(3)	C(21)-C(22)-H(22B)	109.5
O(19)-C(10)-N(18)	125.1(3)	H(22A)-C(22)-H(22B)	109.5
O(20)-C(10)-N(18)	109.8(2)	C(21)-C(22)-H(22C)	109.5
C(12)-C(11)-C(16)	122.0(3)	H(22A)-C(22)-H(22C)	109.5
C(12)-C(11)-S(8)	118.9(2)	H(22B)-C(22)-H(22C)	109.5
C(16)-C(11)-S(8)	119.0(2)	C(21)-C(23)-H(23A)	109.5
C(11)-C(12)-C(13)	118.7(3)	C(21)-C(23)-H(23B)	109.5
C(11)-C(12)-H(14)	120.6	H(23A)-C(23)-H(23B)	109.5
C(13)-C(12)-H(14)	120.6	C(21)-C(23)-H(23C)	109.5
C(14)-C(13)-C(12)	121.3(3)	H(23A)-C(23)-H(23C)	109.5
C(14)-C(13)-H(13)	119.3	H(23B)-C(23)-H(23C)	109.5
C(12)-C(13)-H(13)	119.3	C(21)-C(24)-H(24A)	109.5
C(13)-C(14)-C(15)	118.3(3)	C(21)-C(24)-H(24B)	109.5
C(13)-C(14)-C(17)	120.6(3)	H(24A)-C(24)-H(24B)	109.5
C(15)-C(14)-C(17)	121.1(3)	C(21)-C(24)-H(24C)	109.5
C(16)-C(15)-C(14)	121.8(3)	H(24A)-C(24)-H(24C)	109.5
C(16)-C(15)-H(15)	119.1	H(24B)-C(24)-H(24C)	109.5
C(14)-C(15)-H(15)	119.1	C(3)-O(25)-H(25)	109.5
C(11)-C(16)-C(15)	117.9(3)		
C(11)-C(16)-H(16)	121.1		
C(15)-C(16)-H(16)	121.1		

Table 3: Torsion angles [deg] for compound 72

C(5)-O(1)-C(2)-C(6)	-124.3(2)
C(5)-O(1)-C(2)-C(3)	0.4(3)
O(1)-C(2)-C(3)-O(25)	-90.8(2)
C(6)-C(2)-C(3)-O(25)	30.1(3)
O(1)-C(2)-C(3)-C(4)	24.6(3)
C(6)-C(2)-C(3)-C(4)	145.5(2)
O(25)-C(3)-C(4)-N(18)	-46.0(3)
C(2)-C(3)-C(4)-N(18)	-161.4(2)
O(25)-C(3)-C(4)-C(5)	76.9(3)
C(2)-C(3)-C(4)-C(5)	-38.6(3)
C(2)-O(1)-C(5)-C(4)	-25.8(3)
N(18)-C(4)-C(5)-O(1)	162.0(2)
C(3)-C(4)-C(5)-O(1)	40.6(2)
O(1)-C(2)-C(6)-O(7)	-62.0(3)
C(3)-C(2)-C(6)-O(7)	177.5(2)
C(2)-C(6)-O(7)-S(8)	-175.68(17)
C(6)-O(7)-S(8)-O(10)	-172.9(2)
C(6)-O(7)-S(8)-O(9)	-43.5(2)
C(6)-O(7)-S(8)-C(11)	72.3(2)
O(10)-S(8)-C(11)-C(12)	155.4(2)
O(9)-S(8)-C(11)-C(12)	21.6(3)
O(7)-S(8)-C(11)-C(12)	-94.1(2)
O(10)-S(8)-C(11)-C(16)	-28.0(3)
O(9)-S(8)-C(11)-C(16)	-161.9(2)
O(7)-S(8)-C(11)-C(16)	82.4(2)
C(16)-C(11)-C(12)-C(13)	0.2(4)
S(8)-C(11)-C(12)-C(13)	176.6(2)
C(11)-C(12)-C(13)-C(14)	-0.4(4)
C(12)-C(13)-C(14)-C(15)	0.0(4)
C(12)-C(13)-C(14)-C(17)	-179.2(3)
C(13)-C(14)-C(15)-C(16)	0.6(4)
C(17)-C(14)-C(15)-C(16)	179.7(3)
C(12)-C(11)-C(16)-C(15)	0.3(4)
S(8)-C(11)-C(16)-C(15)	-176.1(2)
C(14)-C(15)-C(16)-C(11)	-0.7(4)

O(19)-C(10)-N(18)-C(4)	-1.6(4)
O(20)-C(10)-N(18)-C(4)	179.4(2)
C(5)-C(4)-N(18)-C(10)	97.3(3)
C(3)-C(4)-N(18)-C(10)	-147.6(3)
O(19)-C(10)-O(20)-C(21)	0.1(4)
N(18)-C(10)-O(20)-C(21)	179.2(2)
C(10)-O(20)-C(21)-C(23)	-64.2(4)
C(10)-O(20)-C(21)-C(22)	178.7(3)
C(10)-O(20)-C(21)-C(24)	59.6(4)

1,1-Dimethylethyl*[R-(R,S)]*-2,2-Dimethyl-4-1(-hydroxy-2-hexadecyny1)-3-oxazolidinecarboxylate (61).



To a -23 ^{o}C solution of 1-pentadecyne (4.762 g, 22.894 mmol) in dry THF (150 mL) was added 1.6 M *n*-BuLi (14.3 mL, 22.894 mmol) under N_2 atmosphere. The resulting suspension of lithium 1-pentadecyne was stirred at this temperature for 30 min when a -23 ^{o}C solution of aldehyde **22** (3.5 g, 15.263 mmol) in dry THF (75 mL) was added via cannula using positive N_2 pressure. The colorless solution was stirred at -23 ^{o}C for 3 h when the TLC in EtOAc: Petroleum ether (2:8) showed the clean formation of two products. At this point pure **61** could be obtained in 63% yield as a colorless oil after flash chromatography on silica gel, eluting with EtOAc: petroleum ether.

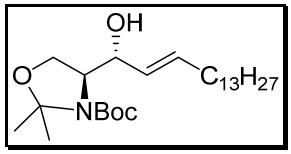
$[\alpha]_D^{25}$ = -36.7^{o} (c = 0.9 $CHCl_3$);

IR (neat) 3440, 2220, 1700 cm^{-1}

^{1}HNMR (200 MHz): δ 0.88 (t, 3H), 1.25 (br s, 22H), 1.50 (br s, 15H), 2.15-2.22 (dt, 2H, J= 6.95 Hz), 3.90-4.10 (br m, 3H), 4.50-4.72 (m, 2H)

^{13}C NMR (50 MHz): 14.1, 18.7, 22.6, 25.7, 28.4, 28.5, 28.8, 29.1, 29.3, 29.5, 29.6, 31.9, 62.7, 64.0, 65.0, 94.8, 96.1

1,1-Dimethylethyl [*R*-[*R,S*-(*E*)]]-2,2-Dimethyl-4-(1-hydroxy-2-hexadeceny1)-3-oxazolidinecarboxylate (63).



To a solution of **61** (700 mg, 1.6 mmol) in anhydrous Et_2O (20 mL)at 0 ^{o}C was added a solution of Red-Al (0.6 mL, 2.4 mmol) dropwise. After 10 min, the cooling bath was removed, and the reaction mixture was stirred at room temperature for 6 h. An aqueous saturated solution of NH_4Cl (2 mL) was slowly added. The resulting white slurry was diluted with Et_2O (10 mL), 1 N NaOH (5 mL) and water (5 mL), and the layers were separated. Aqueous phase was re-extracted with Et_2O (3 x 5 mL), and the combined

organic phase was dried and concentrated. The residue was purified by chromatography with EtOAc:petroleum ether (1:9), to afford (420 mg, 60%) of allyl alcohol **63** as colourless oil.

Molecular Formula: $C_{26}H_{49}NO_4$

Molcular weight: 439.37

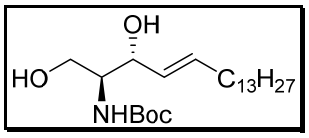
ESI-MS: 462.25 $[M+Na]^+$

$[\alpha]_D^{25}$= -28^o (c 0.65, $CHCl_3$);

IR (neat) 3400, 1700 cm^{-1};

^{1}HNMR (200 MHz): δ 0.89 (t, 3H), 1.26 (br s, 22H), 1.49 (br s, 15H), 2.00-2.09(dt, 2H, J= 6.95 Hz), 3.9-4.17(br m, 5H), 5.39-5.48 (dd, 1H, J = X,X), 5.66-5.81(dt, 1H, J= 15.69)

***tert*-Butyl ((2*S*,3*R*,*E*)-1,3-dihydroxyoctadec-4-en-2-yl)carbamate**

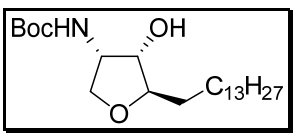


The compound **63** (400 mg, 0.9 mmol) was dissolved in MeOH (15 mL) and to it catalytic amount of *p*-TSA was added. The mixture was stirred at room temperature for 6 h. Then it was quenched with Et_3N. The reaction mixture was concentrated and purified by column chromatography using EtOAc: petroleum ether (7:3) as eluent to get the pure diol **64** (320 mg, 90 %) as a white solid.

IR (neat): ν_{max} 3460, 2900, 1670 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, *J*=6.65 Hz, 3 H) 1.26 (s, 20 H) 1.35 - 1.41 (m, 2 H) 1.46 (s, 9 H) 2.06 (q, *J*=7.03 Hz, 2 H) 3.58 (br. s., 1 H) 3.70 (dd, *J*=11.29, 3.51 Hz, 1 H) 3.93 (dd, *J*=11.42, 3.64 Hz, 1 H) 4.31 (t, *J*=4.77 Hz, 1 H) 5.30 (d, *J*=7.03 Hz, 1 H) 5.53 (dd, *J*=15.56, 6.27 Hz, 1 H) 5.78 (dt, *J*=1.00 Hz, 1 H)

***tert*-Butyl ((3*S*,4*S*,5*S*)-4-hydroxy-5-tetradecyltetrahydrofuran-3-yl)carbamate (66)**



Mercury trifluoroacetate (400 mg, 0.937 mmol) was dissolved in CH_2Cl_2 (40 mL) and cooled to -78 ^{o}C. To this cooled solution, compound **64** (250 mg, 0.625 mmol) in CH_2Cl_2 (10 mL) was added dropwise, the solution becomes yellow. Reaction mixture

was allowed to stir for 30 min. Then reaction was quenched with saturated sodium chloride, and allowed to stir for another 30 min. the reaction mixture was filtered through a pad of celite and concentrated. This crude product was then treated with alk. $NaBH_4$. The precipitated mercury was filtered off and the filtrate was concentrated, and purified by flash column chromatography using EtOAc: petroleum ether (4:6) to give **66** (37 mg, 15%) as colourless solid.

Molecular Formula: $C_{23}H_{45}NO_4$

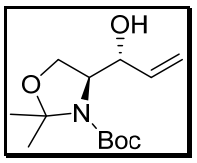
Molcular weight: 399.62

ESI-MS: 422.34 $[M+Na]^+$

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (t, *J*=1.00 Hz, 3 H) 1.25 (s, 22 H) 1.45 (s, 9 H) 1.51 - 1.58 (m, 2 H) 2.48 (s, 1 H) 3.48 - 3.54 (m, 1 H) 3.71 (q, *J*=1.00 Hz, 1 H) 3.93 (br. s., 1 H) 4.13 (m, *J*=1.00, 1.00, 1.00 Hz, 2 H) 5.05 (br. s., 1 H)

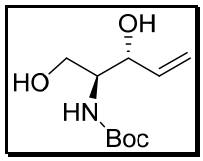
^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1, 22.6, 25.7, 28.3, 29.3, 29.5, 29.5, 29.6, 29.6, 31.9, 33.5, 52.9, 70.2, 71.8, 74.8, 76.7, 77.2 80, 82.1, 85.1, 156.

***tert*-Butyl (*S*)-4-((*R*)-1-hydroxyallyl)-2,2-dimethyloxazolidine-3-carboxylate (67)**



To a solution of Garner aldehyde 10 (8 g, 34.89 mmol) in dry THF (60 mL) at 0 ^oC, vinyl magnesium bromide solution 41.8 mL, 1 M solution in THF) was added and stirred at the same temperature for 10 h. After the completion of the reaction, it was quenched by saturated NH_4Cl solution and diluted with ethyl acetate and water followed by brine. The organic layer was dried over sodium sulphate. The solvent was evaporated and the residue was purified by flash column chromatography furnish the major anti product (6.2 g, 70%)

***tert*-Butyl ((2*S*,3*R*)-1,3-dihydroxypent-4-en-2-yl)carbamate (68)**



To a solution of **67** (3 g, 243 mmol) in methanol, a catalytic amount of PTSA was added at 0 ^oC and stirred at room temperature for 6 h. The reaction mixture was neutralized by

saturated $NaHCO_3$ solution, and extracted with EtOAc. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified using column chromatography to furnish 68 (2.3 g, 90%).

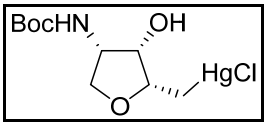
$[\alpha]_D^{25}$ = - 8.3 (c 0.5, CH_3OH)

IR = 3433, 3015, 2980, 2935, 1691, 1257, 1164, 668 cm^{-1}.

^{1}H NMR (200 MHz, $CDCL_3$): δ 1.46 (s, 9 H) 2.25 (br. s., 2 H) 3.60 - 3.71 (m, 1 H) 3.73 - 4.01 (m, 2 H) 4.35 - 4.48 (m, 1 H) 5.28 (dq, *J*=10.23, 1.39 Hz, 1 H) 5.33 - 5.46 (m, 1 H) 5.35 - 5.46 (m, 1 H) 5.82 - 6.05 (m, 1 H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 28.3, 62.3, 63.7, 74.5, 79.9, 116.5, 137.4, 156.2.

(((2*R*,3*S*,4*S*)-4-((tert-Butoxycarbonyl)amino)-3-hydroxytetrahydrofuran-2-yl)methyl)mercury(II) chloride (69)



To an ice cooled solution of alcohol **68** (1.7 g, 7.82 mmol) in CH_2Cl_2 was added $Hg(OCOCF_3)$ (5 g, 11.72 mmol). The reaction mixture was stirred at the same temperature for 30 min. After completion of the reaction, it was quenched by addition of saturated NaCl solution, and extracted with ethyl acetate the mixture was washed with brine. The organic layer was dried over sodium sulfate. The solvent was evaporated and the residue was purified with carefully with flash column chromatography to furnish **69** (2.3 g, 67%) as colourless solid.

Molecular formula: $C_{10}H_{18}ClHgNO_4$

Molecular weight: 452.3

ESI-MS: 475.36 $[M+Na]^+$

$[\alpha]_D^{25}$ = +18.43 (c 0.5, EtOH)

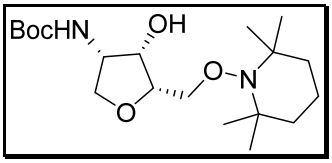
IR = 3433, 3015, 2980, 2935, 1691, 1257, 1164, 668 cm^{-1}.

Melting Point: Decomposes at 188 ^oC

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.46 (s, 9 H) 1.94 (dd, *J*=12.10, 3.50 Hz, 1 H) 2.09 (dd, *J*=11.80, 6.78 Hz, 1 H) 3.47 (dd, *J*=9.54, 5.02 Hz, 1 H) 3.61 (br. s., 1 H) 3.97 (d, *J*=3.26 Hz, 1 H) 4.07 (br. s., 1 H) 4.28 (dd, *J*=9.29, 6.78 Hz, 1 H) 4.42 - 4.50 (m, 1 H) 4.70 (br. s., 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 27.5, 28.3, 60.4, 69.6, 77.08, 79.4.

***tert*-butyl ((3*S*,4*S*,5*S*)-4-hydroxy-5-(((2,2,6,6-tetramethylpiperidin-1-yl)oxy)methyl)tetrahydrofuran-3-yl)carbamate (70)**



To a solution of **69** (1.5 g 3.31 mmol) in dry DMF (10 mL) was added TEMPO (1.55 g 9.94 mmol). This solution was then added dropwise to an oxygen-saturated solution of $NaBH_4$ (13.26 mmol) in dry DMF (8 mL) cooled to 0 ^oC. 30 min. after the addition, the precipitated mercury was filtered off through a pad of celite and the solution was diluted with ether and washed with water. The organic phase was dried (MgSO4), filtered and concentrated. The residue was purifieded by column chromatography using hexane as eluent to afford the pure TEMPO adduct **70** (1.4 g, 80%)

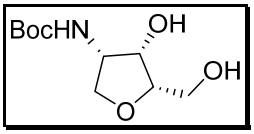
Molecular formula:$C_{19}H_{36}N_2O_5$

$[\alpha]_D^{25}$ = -1.46 (c 1.1, $CHCl_3$)

IR = 2966, 2365, 1659, 693 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) δ 1.11 (br. s., 6 H) 1.18 - 1.24 (m, 6 H) 1.44 (s, 15 H) 3.38 (dd, *J*=1.00 Hz, 1 H) 3.65 (dd, *J*=1.00 Hz, 1 H) 3.99 (dd, *J*=8.40, 6.63 Hz, 1 H) 4.04 - 4.08 (m, 1 H) 4.09 - 4.14 (m, 2 H) 4.25 - 4.42 (m, 2 H) 5.38 (d, *J*=8.00 Hz, 1 H)

***tert*-Butyl((3*S*,4*S*,5*S*)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-3-yl)carbamate (71)**



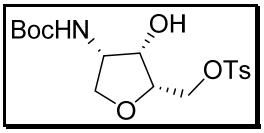
To compound **70** (200 mg, mmol) in ethyl acetate was added $Pd(OH)_2/C$ (10%) and stirred under hydrogen atmosphere at 600 *psi* in parr reactor for 24 h. On completion of reaction, the mixture was filtered through a pad of celite and concentrated in vacuo. Silica gel column chromatography of the crude product using EtOAc:petroleum ether (1:1) as eluent afforded compound **71** as a colourless Solid.(140 mg, 80%)

Molecular formula: $C_{10}H_{19}NO_5$

^{1}H NMR (200 MHz, $CDCl_3$) δ 1.45 (s, 9 H) 3.66 (t, *J*=1.00 Hz, 1 H) 3.86 - 4.14 (m, 6 H) 4.16 - 4.42 (m, 3 H) 5.35 (d, *J*=7.83 Hz, 1 H)

^{13}C NMR (50 MHz, $CDCl_3$) δ 28.3, 54.0, 61.6, 70.4, 72.6, 78.1, 79.9, 155.8.

((2*S*,3*S*,4*S*)-4-((tert-Butoxycarbonyl)amino)-3-hydroxytetrahydrofuran-2-yl)methyl 4-methylbenzenesulfonate(72)



To a solution of **71** (400 mg, 1.71 mmol) in dry CH_2Cl_2 (10 mL), were added Et_3N (0.44 g, 4.27 mmol), DMAP (catalytic) and TsCl (326 mg, 1.71 mmol) at 0 °C. The reaction mixture was stirred for 12 h at room temperature, quenched with saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with EtOAc, and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography using EtOAc:petroleum ether (1:5) as eluent to afford **72** as a colorless solid.(590 mg, 90%).

Molecular Formula: $C_{17}H_{25}NO_7S$

$[\alpha]_D^{25}$ = -26.74 (c 0.75, $CHCl_3$)

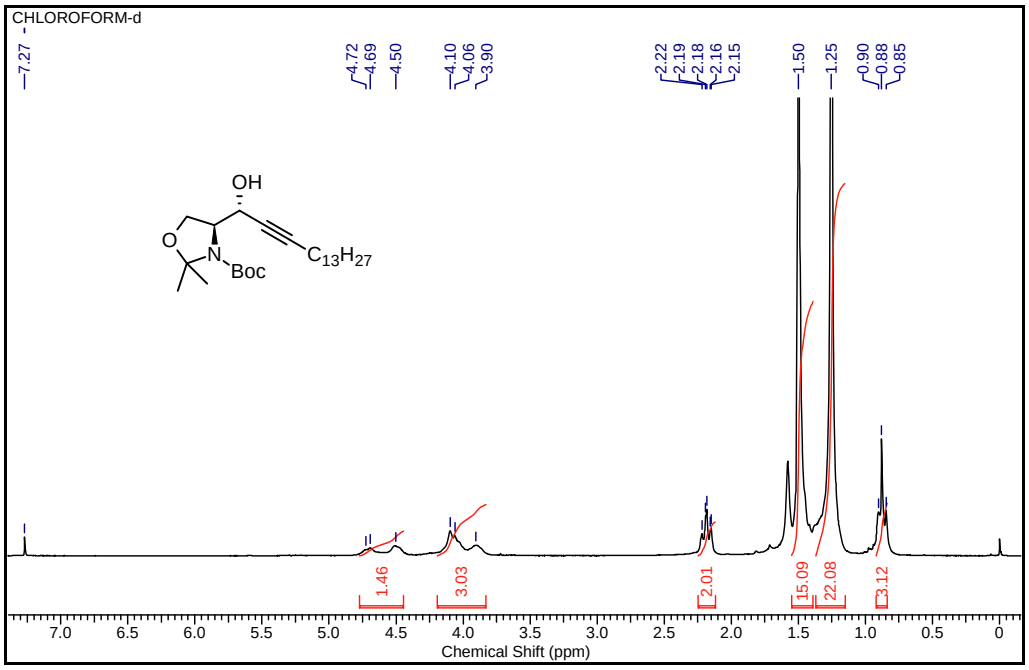
Melting Point: 125-126 ^oC

^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9 H) 2.47 (s, 3 H) 2.72 (br. s., 1 H) 3.55 (t, *J*=8.31 Hz, 1 H) 4.00 - 4.08 (m, 2 H) 4.10 - 4.16 (m, 1 H) 4.27 - 4.39 (m, 3 H) 5.06 (br. s., 1 H) 7.37 (d, *J*=8.07 Hz, 2 H) 7.81 (d, *J*=8.31 Hz, 2 H)

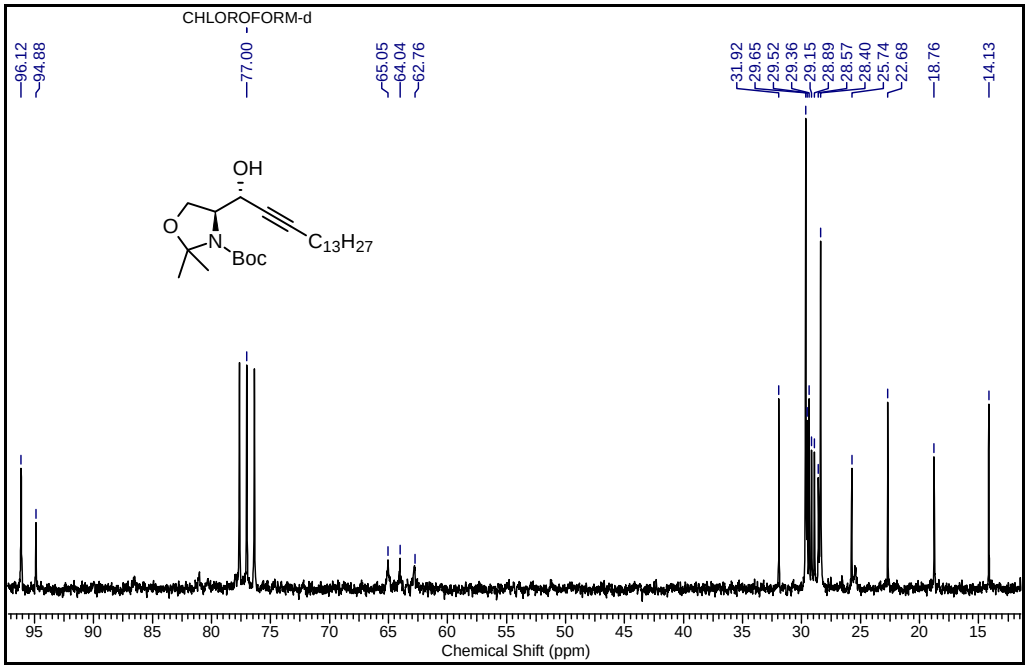
^{13}C NMR (100 MHz): δ 21.6, 28.3, 53.3, 67.0, 69.9, 70.5, 78.7, 80.0, 127.9, 129.9, 132.3, 145.2, 155.5.

Spectra

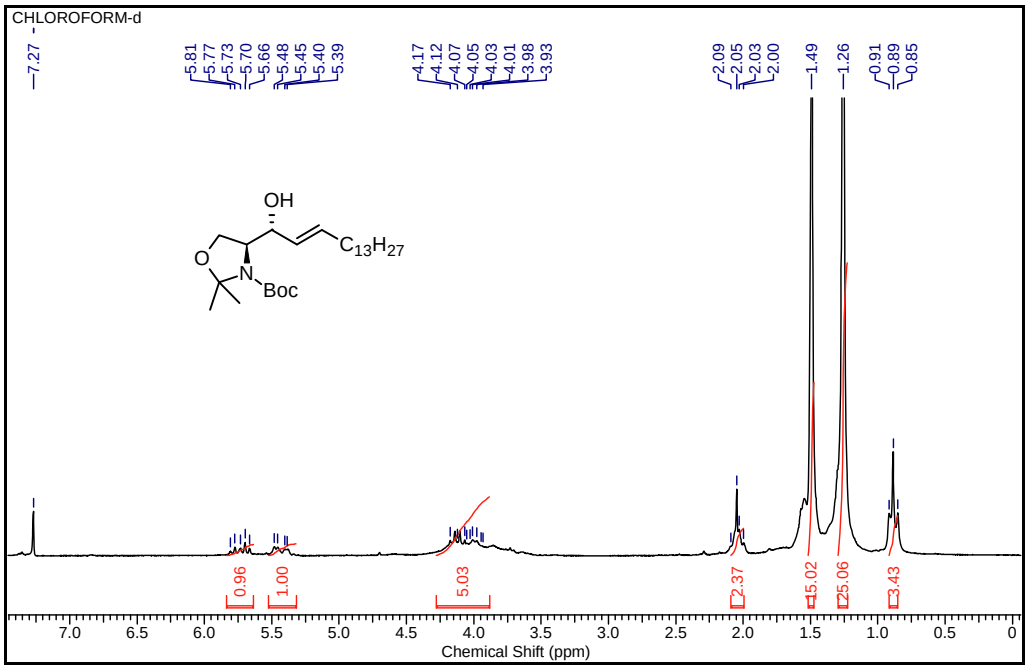
1. ^{1}H and ^{13}C NMR spectra of **61**
2. ^{1}H spectra of **63,** and **64**
3. ^{1}H and ^{13}C NMR spectra of **66**
4. ^{1}H and ^{13}C NMR spectra of **67**
5. ^{1}H and ^{13}C NMR spectra of **69**
6. COSY and NOSEY Spectra of compound **69**
7. ^{1}H and ^{13}C NMR spectra of **70**
8. ^{1}H and ^{13}C NMR spectra of **71**
9. ^{1}H and ^{13}C NMR spectra of **72**



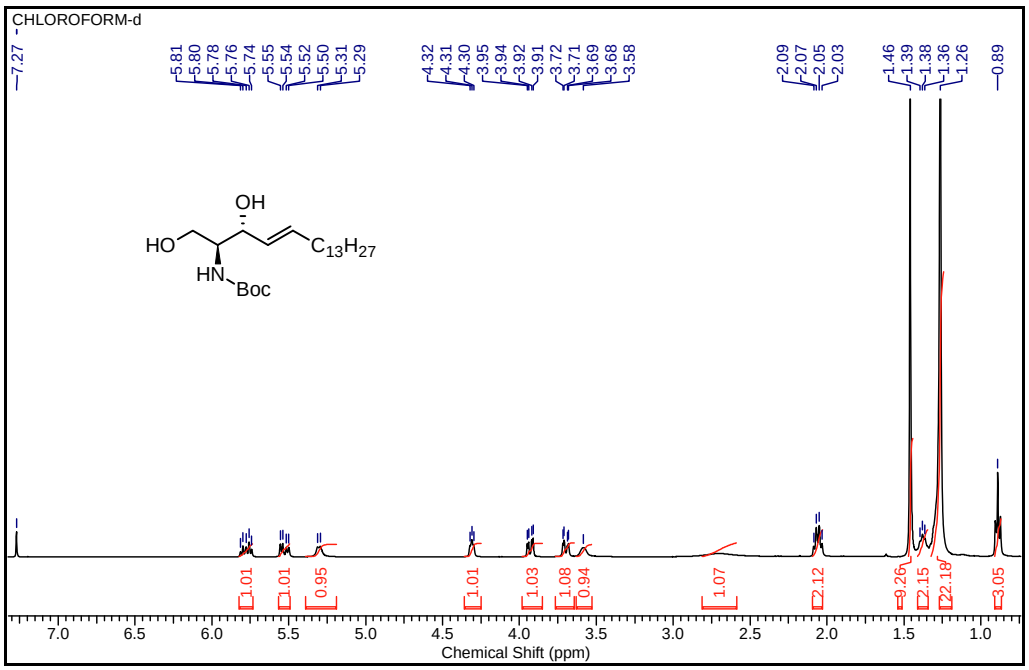
^{1}H NMR spectrum of compound 61 in $CDCl_3$



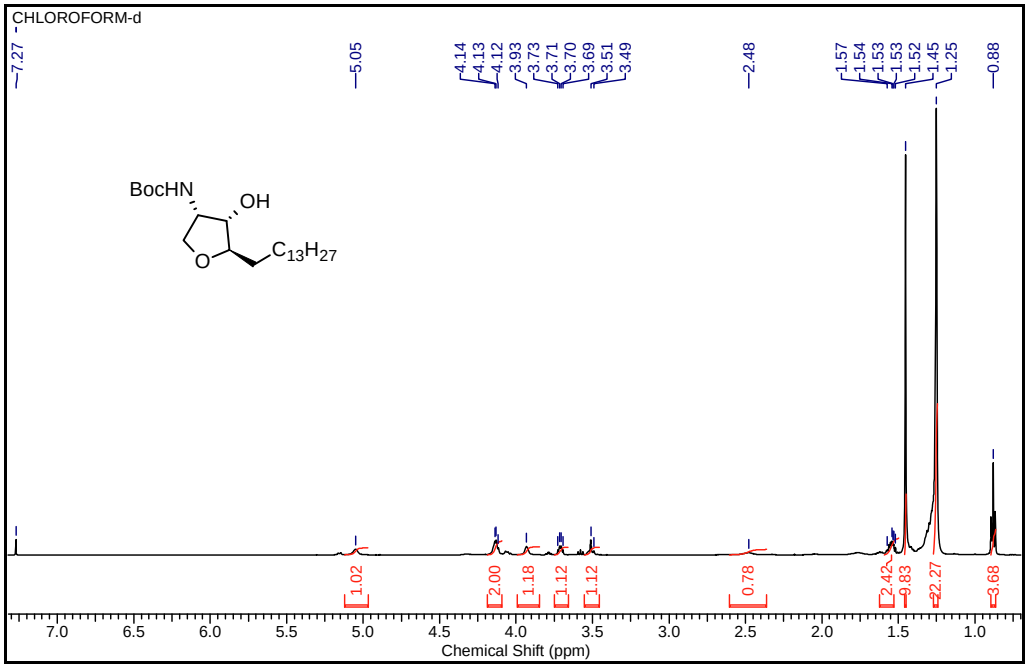
^{13}C NMR spectrum of compound 61 in $CDCl_3$



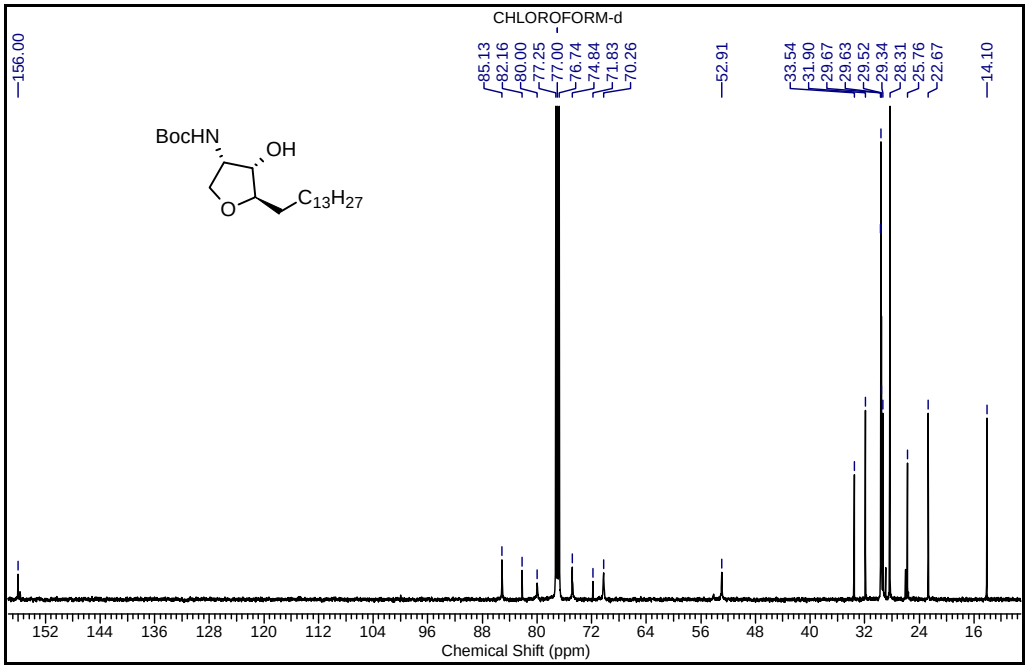
^{1}H NMR spectrum of compound 63 in $CDCl_3$



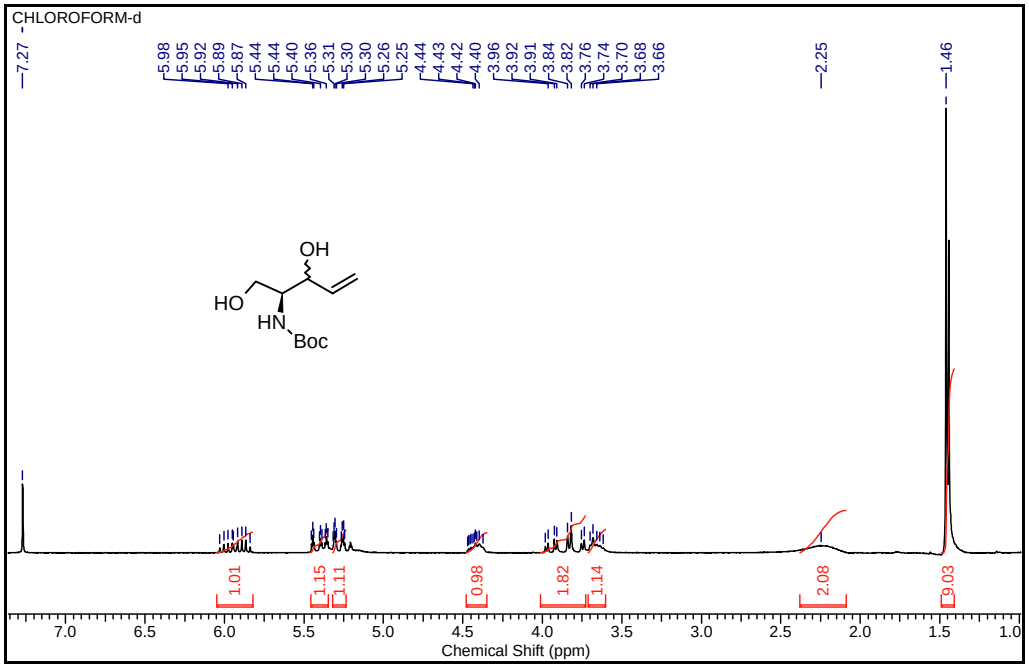
^{1}H NMR spectrum of compound 64 in $CDCl_3$



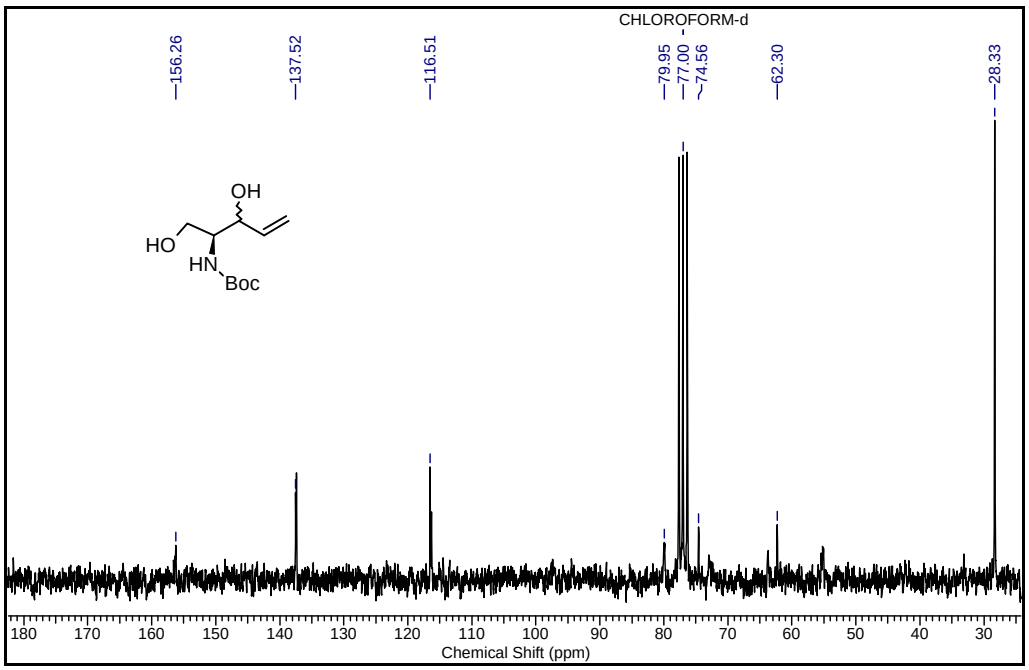
^{1}H NMR spectrum of compound 66 in $CDCl_3$



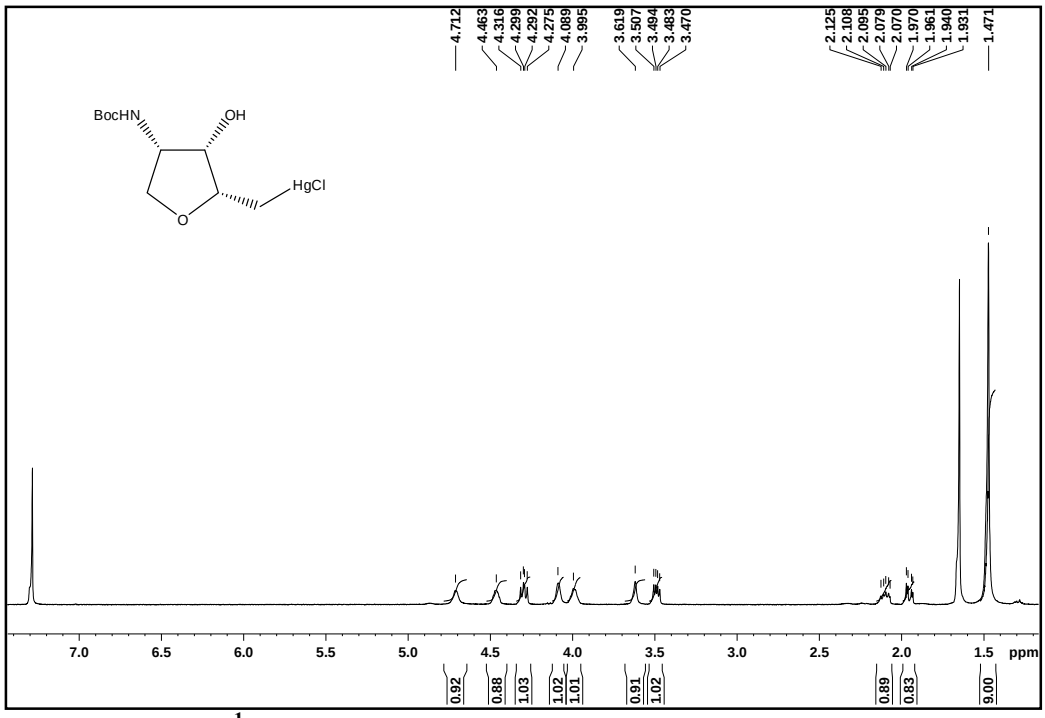
^{13}C NMR spectrum of compound 66 in $CDCl_3$



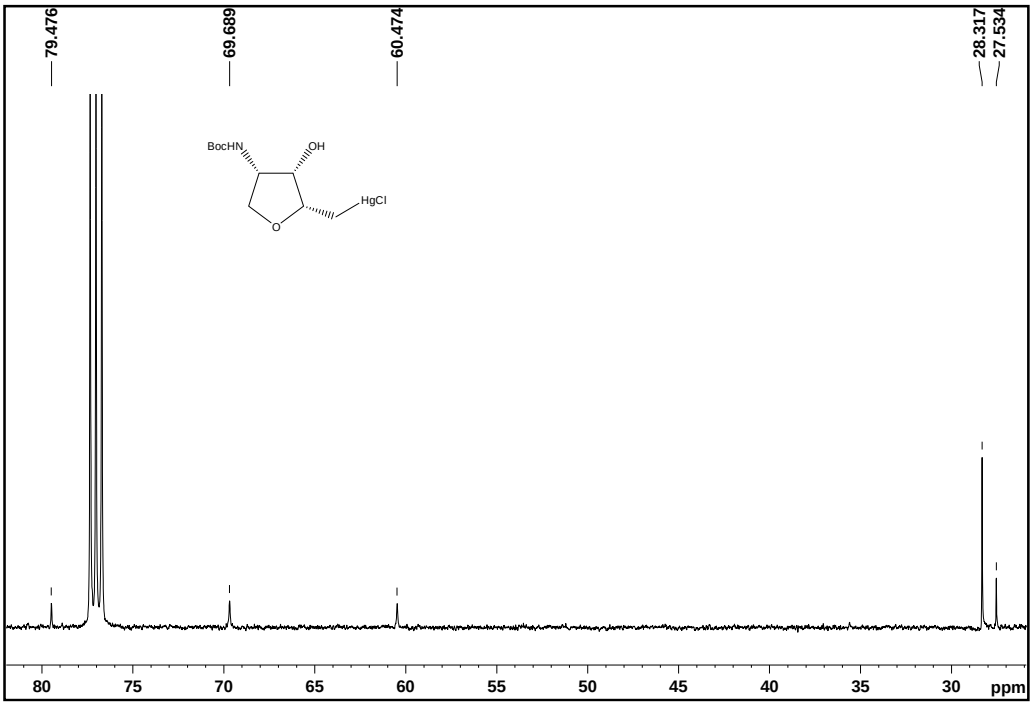
^{1}H NMR spectrum of compound 67 in $CDCl_3$



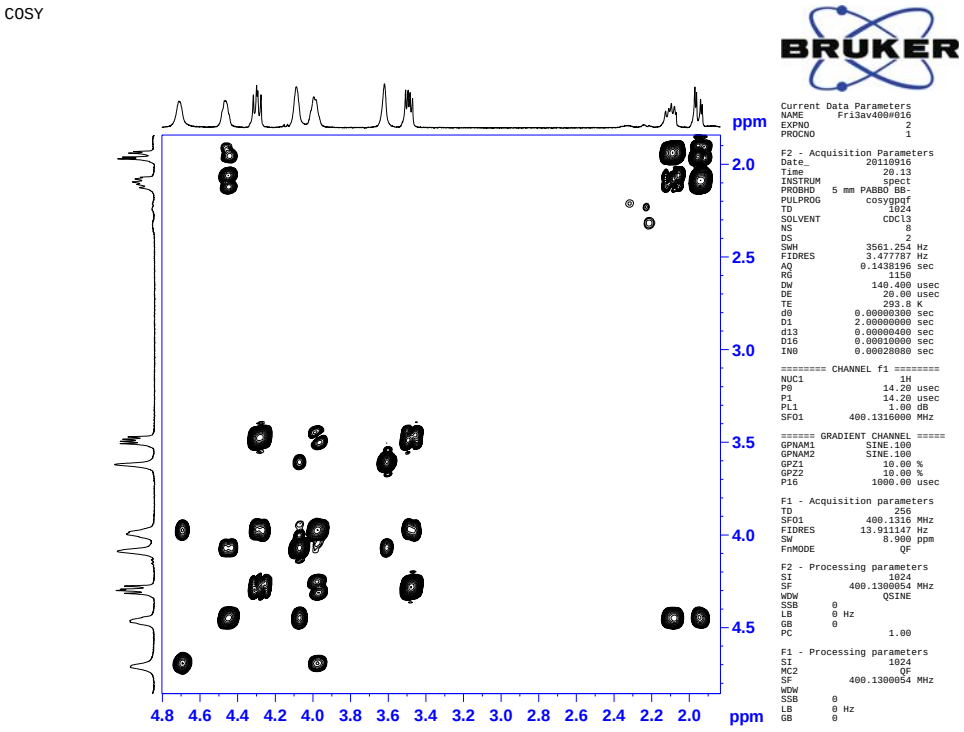
^{13}C NMR spectrum of compound 67 in $CDCl_3$



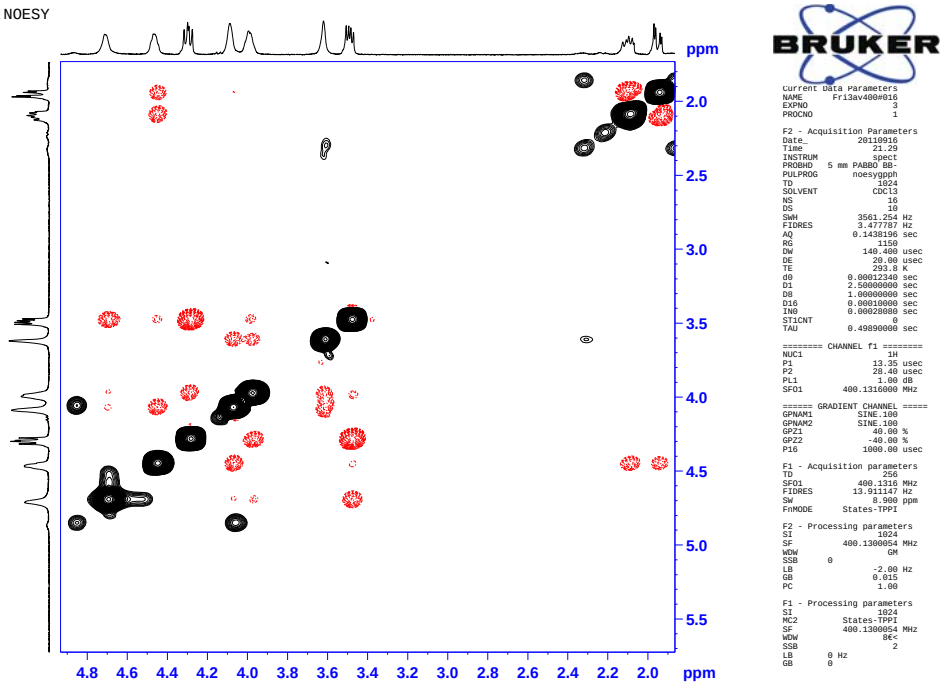
^{1}H NMR spectrum of compound 69 in $CDCl_3$



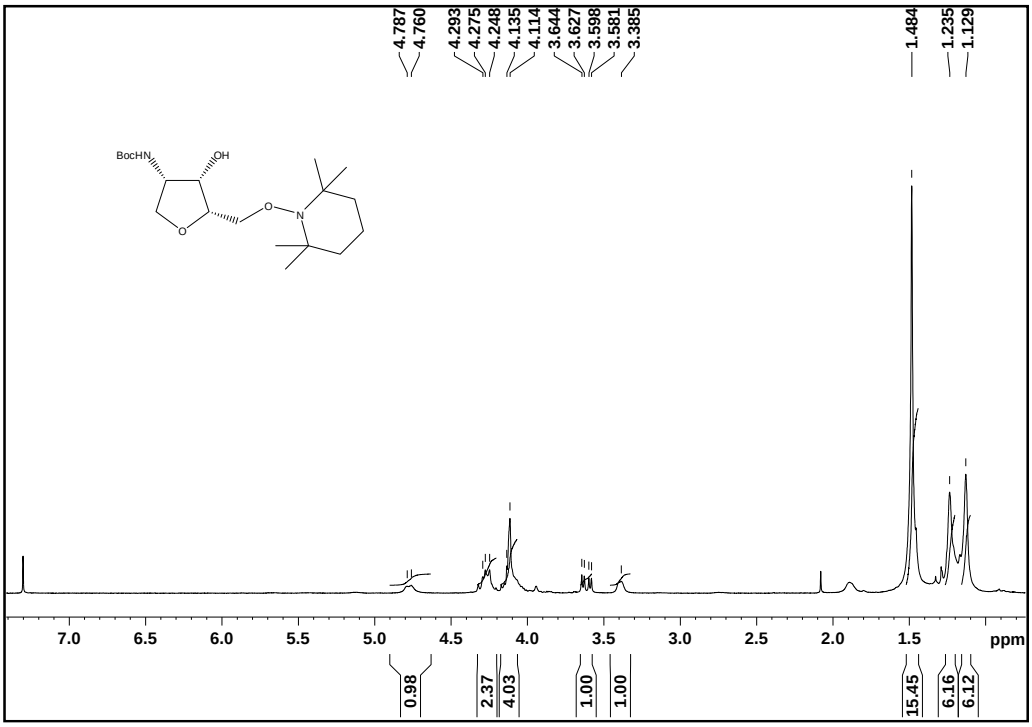
^{13}C NMR spectrum of compound 69 in $CDCl_3$



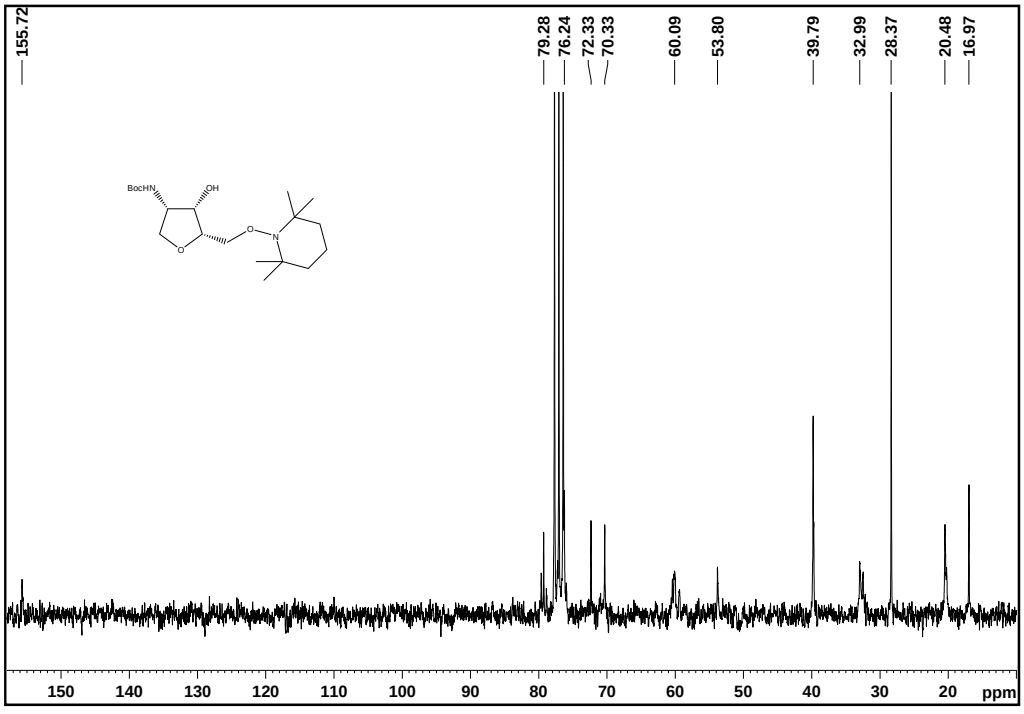
COSY spectrum of compound 69 in $CDCl_3$



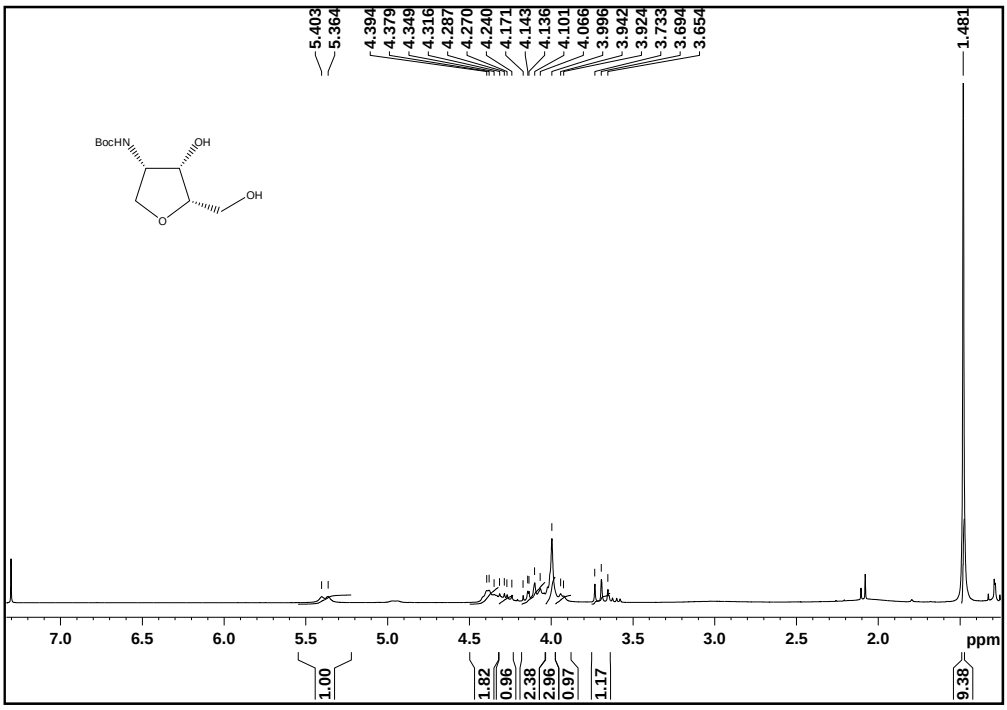
NOESY spectrum of compound 69 in $CDCl_3$



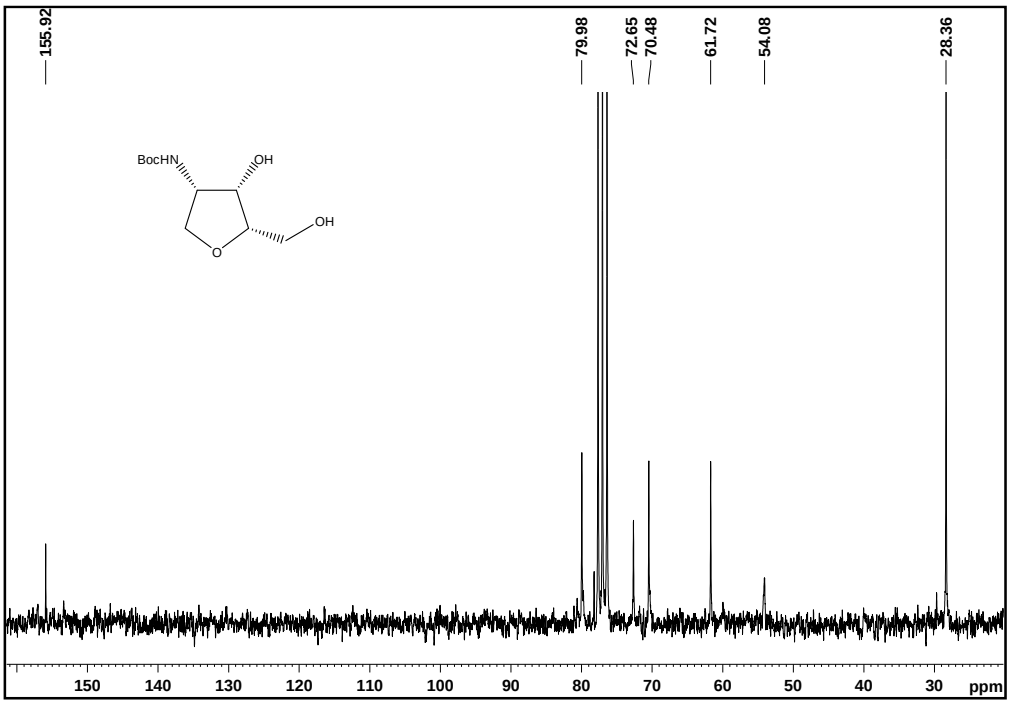
^{1}H NMR spectrum of compound 70 in $CDCl_3$



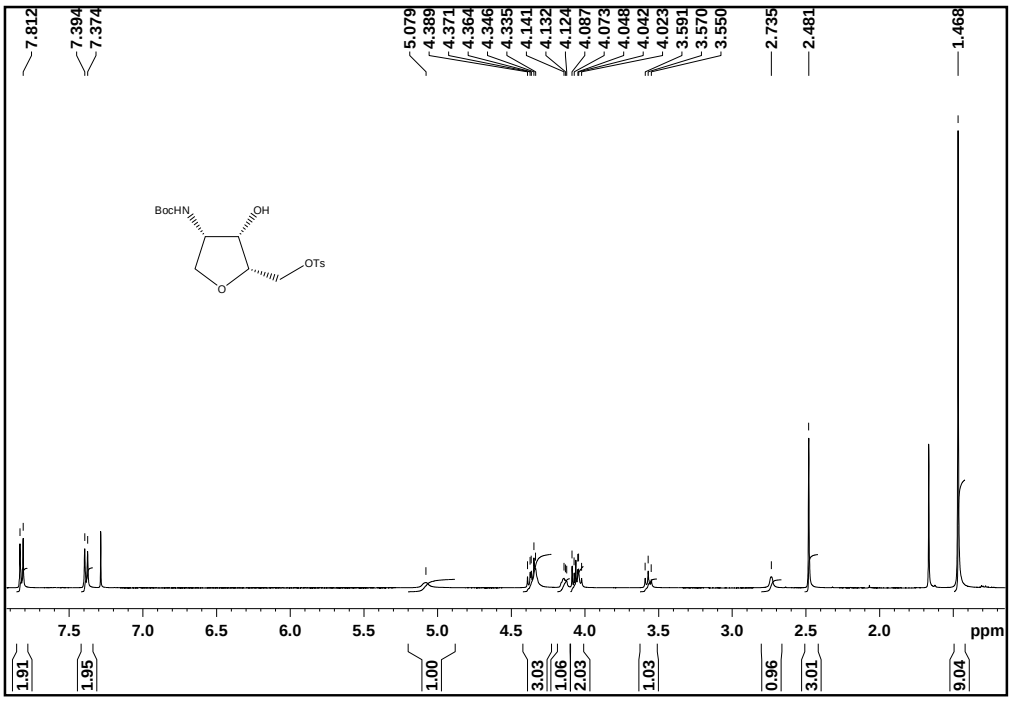
^{13}C NMR spectrum of compound 70 in $CDCl_3$



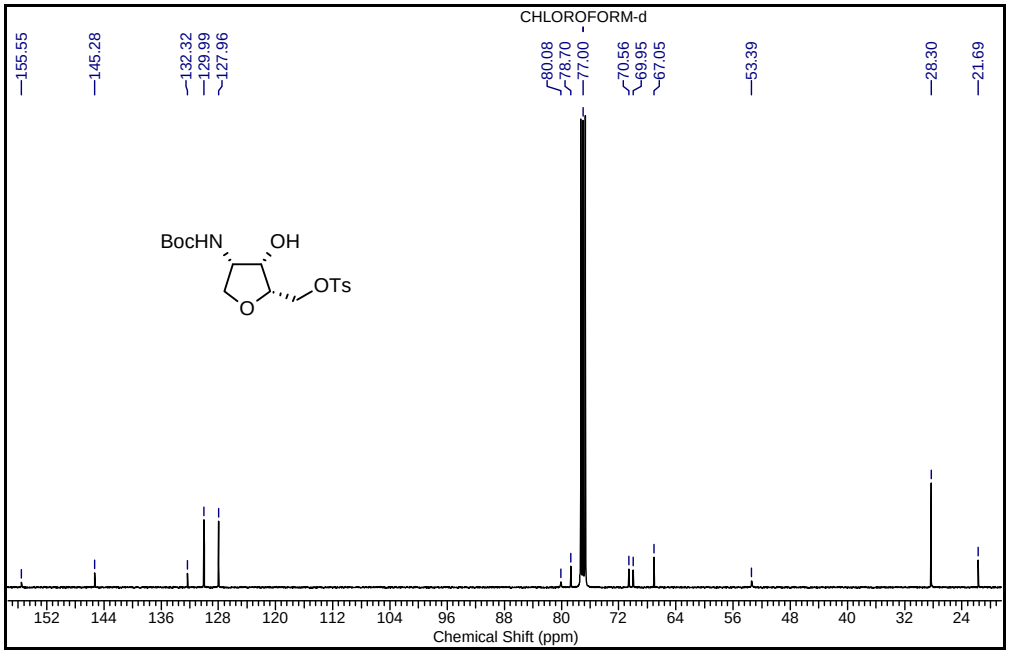
^{1}H NMR spectrum of compound 71 in $CDCl_3$



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



^{1}H NMR spectrum of compound 72 in $CDCl_3$



^{13}C NMR spectrum of compound 72 in $CDCl_3$

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Publications

1. "First total synthesis of Seimatopolide B" U. Nookaraju, Anand Harbindu, **Ankushkumar D. Bhise,** Brijesh M. Sharma, Pradeep Kumar* *RSC Advances*, **2012**, *2*, 11231-11234.
2. "A concise synthesis of (5*R*,6*S*)-*tert*-butyl 5-acetoxy- 6-(hydroxymethyl)-5,6-dihydropyridine-1(2*H*)-carboxylate" S. Ramalingam, **Ankushkumar D. Bhise,** Krishanu Show, Pradeep Kumar* ***ARKIVOC*** **2013** *(ii)*, 220-227.
3. "Stereoselective synthesis of Modiolide A and Stagonolide C" **Ankushkumar D. Bhise,** Brijesh M. Sharma, Anand Harbindu, Pradeep Kumar* (Manuscript under preparation).
4. "Stereoselective synthesis of jaspine B and its C2 epimer" **Ankushkumar D. Bhise,** Pradeep Kumar* (Manuscript under preparation).

Curriculum Vitae

Educational Qualifications

M.Sc. (Master of Science)	**Organic Chemistry (First Division)** S. R. T. M. U. Nanded. Maharashtra, India. **2005**.
B.Sc. (Bachelor of Science)	**Chemistry**, Zoology, Envi. Sci. **(First Division)** S. R. T. M. U. Nanded. Maharashtra, India **2003**.

Examinations Qualified

- Qualified *National Eligibility Test* (NET), Eligibility test for the lecturership/JRF Conducted by Council of Scientific and Industrial Research (CSIR) and University Grant Commission , **June 2006**

Award and Fellowships

- Junior Research Fellowship Awarded by Council of Scientific and Industrial Research (CSIR), India (www.csir.res.in) **2007-2009**
- Senior Research Fellowship Awarded by Council of Scientific and Industrial Research (CSIR), India (www.csir.res.in) **2009-2013**

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 their application to the medicinal chemistry and material chemistry.

Publications

1. "First total synthesis of Seimatopolide B" U. Nookaraju, Anand Harbindu, **Ankushkumar D. Bhise,** Brijesh M. Sharma, Pradeep Kumar* *RSC Advances*, **2012**, *2*, 11231-11234.
2. "A concise synthesis of (5*R*,6*S*)-*tert*-butyl 5-acetoxy- 6-(hydroxymethyl)-5,6-dihydropyridine-1(2*H*)-carboxylate" S. Ramalingam, **Ankushkumar D. Bhise,** Krishanu Show, Pradeep Kumar* ***ARKIVOC*** **2013** *(ii)*, 220-227.
3. "Stereoselective synthesis of Modiolide A and Stagonolide C" Ankushkumar D. Bhise, Brijesh M. Sharma, Anand Harbindu, Pradeep Kumar* (Manuscript under preparation).
4. "Stereoselective synthesis of jaspine B and its C2 epimer" Ankushkumar D. Bhise, Pradeep Kumar* (Manuscript under preparation).

Symposia / conferences attended

- Attended 4th INSA-KOSEF symposium in Organic Chemistry: Contemporary Organic Chemistry and its Future directions, **Jan 12−13, 2009** conducted at National Chemical Laboratory, Pune, India.
- Attended 11th CRSI National Symposium in Chemistry 2010 held at National Chemical Laboratory (NCL), Pune in **February 2009**.
- Attended 12th CRSI National Symposium in Chemistry 2010 held at Indian Institute of Chemical Technology (IICT), Hyderabad in **February 2010**.
- Attended 8th Indo-French International Symposium in Chemistry, **Jan 6–8, 2012** conducted at National Chemical Laboratory, Pune, India.
- Attended ACS on Campus event, **October 1–12, 2012** conducted at National Chemical Laboratory, Pune, India.

Ankushkumar D. Bhise