ENANTIOSELECTIVE TOTAL SYNTHESIS OF BIOLOGICALLY ACTIVE NATURAL PRODUCTS EMPLOYING HYDROLYTIC KINETIC RESOLUTION (HKR) AND ASYMMETRIC DIHYDROXYLATION

A THESIS SUBMITTED TO THE

UNIVERSITY OF PUNE

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

BY

SATYENDRA KUMAR PANDEY

DIVISION OF ORGANIC CHEMISTRY

NATIONAL CHEMICAL LABORATORY

PUNE-411008, INDIA

JUNE 2008

NATIONAL CHEMICAL LABORATORY

Dr. Homi Bhabha Road, PUNE. 411 008, INDIA.

Dr. Pradeep Kumar
Scientist F, FNASc
Division of Organic Chemistry

Telephone: + 91-20-25902050
Fax: + 91-20-25902629
E-mail: pk.tripathi@ncl.res.in
Website: http://www.ncl-india.org

CERTIFICATE

This is to certify that the work presented in the thesis entitled "**Enantioselective Total Synthesis of Biologically Active Natural Products Employing Hydrolytic Kinetic Resolution (HKR) and Asymmetric Dihydroxylation**" submitted by **Satyendra Kumar Pandey** was carried out by the candidate at National Chemical Laboratory, Pune under my supervision. Such materials as obtained from other sources have been duly acknowledged in the thesis.

(Dr. Pradeep Kumar)
Research Guide

June, 2008

CANDIDATE'S DECLARATION

I hereby declare that the thesis entitled "**Enantioselective Total Synthesis of Biologically Active Natural Products Employing Hydrolytic Kinetic Resolution (HKR) and Asymmetric Dihydroxylation**" 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 National Chemical Laboratory, Pune, India.

Satyendra Kumar Pandey
Senior Research Fellow
Division of Organic Chemistry
National Chemical Laboratory
Pune-411008, INDIA

June, 2008

Dedicated

To My

Beloved Parents

Acknowledgements

It gives me great pleasure to express my deep sense of gratitude to my research supervisor Dr. Pradeep Kumar for his guidance, support, encouragement and scientific temperament which furthered my interest in synthetic organic chemistry. I do sincerely acknowledge freedom rendered to me by him for independent thinking, planning and executing the research. He has taught me to be concise, systematic and correct in my approach from the formulation of ideas to the presentation of the results.

My sincere thanks goes to Dr. Ganesh Pandey, Head, Division of Organic Chemistry, for his support and encouragement. I extend my gratitude to Dr. M. K. Gurjar (Former Head, OCT Division), Dr. S. P. Chavan, Dr. C. V. Ramana, Dr. S. Hotha, Dr. H. V. Thulasiram, Dr. R. J. Lahoti, Dr. K. V. Srinivasan, Dr. M. Muthukrishnan and Dr. R. S. Vyas for their help during the course of this work.

Thanks to all my senior colleagues Dr. Rajesh Pandey, Dr. Mandar Bodas, Dr. K. V. Subbarao, Dr. S. Ramalingam, and S. Vasudeva Naidu for the preliminary training during my Ph.D program. I would like to thank my labmates Dr. Priti Gupta, Nagendra, Puspesh, Shijo, Abhishek, Divya, Menaka, Rajesh, Anis, Shinde, Sachin, Anand, Ankush, Partha, Rahul and Rajendra for maintaining a warm and cheerful atmosphere in the lab.

I would like to thank all my close friends Keshri, Anita, Subramnyam, Dharmendra, Sunil, Rahul, Manan, Sanjeev, Ashutosh, Sushil, Anuj, Ashish, Sudhir, Suresh, Kishor, Balaji, Ravi, Prasanna, Nishant, Swroop, Rajendra, Priyanka, Debasish, Namdev, Amol, Bapu, Pankaj, Sriram, Pandurang, Atul, Kulbhushan, Vinod, Venketesh, Indresh, Sahoo, Rosy, Shraeddha, Sonu, Soni, Raman, Patwa, Shreedhar, Ashwani, Roopa, Bibhash, Manaswani, Gitali, Sitaram, Sabita, Rahaman, Rita, Thakkar, Pallavi, Sambhaji, Pinak, Avinash and Smita for their cheerful company during my Ph.D. life.

No thanks can be enough to acknowledge the endless encouragement, care and long-distance support, which I had from my parents, and brothers Dr. Ravindra Pandey and Pankaj for their love and co-operation. Their constant encouragement helped me in pursuing the Ph. D. and made me achieve the goal. Thanks to my wife Rachana for her support and patience.

Help from the spectroscopy, micro-analysis and mass groups is gratefully acknowledged. I sincerely thank Dr. Rajmohan, Mrs. Phalgune, Mr. Sathe, Mrs. Rupali and Mrs. Shanta kumari for their kind co-operation.

Support from OCD office staff: Catherine, Kulkarni, Rannowde and Fernandes is also acknowledged.

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

Satyendra Kumar Pandey

CONTENTS

CHAPTER 1

A BRIEF ACCOUNT OF SHARPLESS ASYMMETRIC EPOXIDATION (AE), ASYMMETRIC DIHYDROXYLATION (AD) AND JACOBSEN'S HYDROLYTIC KINETIC RESOLUTION (HKR)

CHAPTER 2

ASYMMETRIC SYNTHESIS OF VICINAL DIOLS AND AMINO ALCOHOLS

CHAPTER 3

ENANTIOSELECTIVE SYNTHESIS OF HYDROXYORNITHINE AS A CORE UNIT OF BIOLOGICALLY ACTIVE NATURAL PRODUCTS

CHAPTER 4

EFFICIENT AND VERSATILE APPROACH TO ENANTIOPURE PIPERIDINE ALKALOIDS

CHAPTER 5

ENANTIOSELECTIVE SYNTHESES OF THE NATURALLY OCCURRING LACTONES

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
$(DHQ)_2PHAL$	-	1,4-Bis(dihydroquinin-9-*O*-yl)phthalazine
$(DHQD)_2PHAL$	-	1,4-Bis(dihydroquinindin-9-*O*-yl)phthalazine
DDQ	-	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	-	Diisobutylaluminium hydride
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
g	-	Grams
h	-	Hours
Hz	-	Hertz

Im	-	Imidazole
m-CPBA	-	*m*-Chloroperbenzoic acid
MeOH	-	Methanol
mg	-	Milligram
min	-	Minutes
mL	-	Millilitre
mmnol	-	Millimole
M. P.	-	Melting point
Ms	-	Methanesulfonyl
Me	-	Methyl
$NaBH_4$	-	Sodiumborohydride
NaH	-	Sodium hydride
Ph	-	Phenyl
Py	-	Pyridine
PMB	-	*para*-Methoxy benzyl
p-TSA	-	*par*a-Toluenesulfonic acid
RCM	-	Ring closing metathesis
TEA	-	Triethylamine
TBAI	-	Tetra-*n*-butylammonium iodide
TBAF	-	Tetra-*n*-butylammonium fluoride
TBDMS	-	*tert*-Butyldimethyl silyl
THF	-	Tetrahydrofuran
TPP	-	Triphenylphosphine
TsCl	-	*p*-Toluenesulphonyl chloride

GENERAL REMARKS

- ^{1}H NMR spectra were recorded on AC-200 MHz, MSL-300 MHz, and DRX-500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- ^{13}C NMR spectra were recorded on AC-50 MHz, MSL-75 MHz, and DRX-125 MHz spectrometer.
- Mass spectra were obtained with an API Q STARPULASAR using electron spray ionization [(ESI), solvent medium: a mixture of water, acetonitrile and ammonium acetate] technique and mass values are expressed as m/z.
- 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.
- Column chromatography were performed on silica gel (60-120, 100-200 and 230-400 mesh) using a mixture of petroleum ether/ethyl acetate and dichloromethane/methanol as eluent.

ABSTRACT

The thesis entitled **"Enantioselective Total Synthesis of Biologically Active Natural Products Employing Hydrolytic Kinetic Resolution (HKR) and Asymmetric Dihydroxylation"** is divided into five chapters.

Chapter 1: A brief account of Sharpless asymmetric epoxidation (AE), asymmetric dihydroxylation (AD) and Jacobsen's hydrolytic kinetic resolution (HKR).

Chapter 2: Asymmetric synthesis of vicinal diols and amino alcohols and is divided into two sections.

Chapter 3: Enantioselective synthesis of hydroxyornithine as a core unit of biologically active natural products and is divided into two sections.

Chapter 4: Efficient and versatile approach to enantiopure piperidine alkaloids and is divided into two sections.

Chapter 5: Enantioselective syntheses of three naturally occurring lactones and is further divided into two sections.

Chapter 1: A brief account of Sharpless asymmetric epoxidation (AE), asymmetric dihydroxylation (AD) and Jacobsen's hydrolytic kinetic resolution (HKR).

This chapter gives a brief introduction to the Sharpless asymmetric epoxidation (AE), asymmetric dihydroxylation (AD) and Jacobsen's hydrolytic kinetic resolution (HKR). Asymmetric synthesis of bioactive molecules is in the forefront of synthetic organic chemistry due to varied applications in drug and pharmaceutical industries. A large number of enantiomerically pure compounds have been obtained from nature, but quite a few of them are either not easily isolated or not available in useful amounts. However, an organic chemist can provide multi-gram biologically active compounds. The ultimate goal of an organic chemist is, how to assemble a given target molecule from readily available starting materials and reagents in highly efficient way. It is more elegant and economical to prepare just wanted isomer by asymmetric synthesis and through inexpensive catalytic processes.

The oxidation of olefins is considered as the single most versatile, powerful and reliable class of transformation in organic synthesis. The pioneering work of K. B. Sharpless on "Chirally

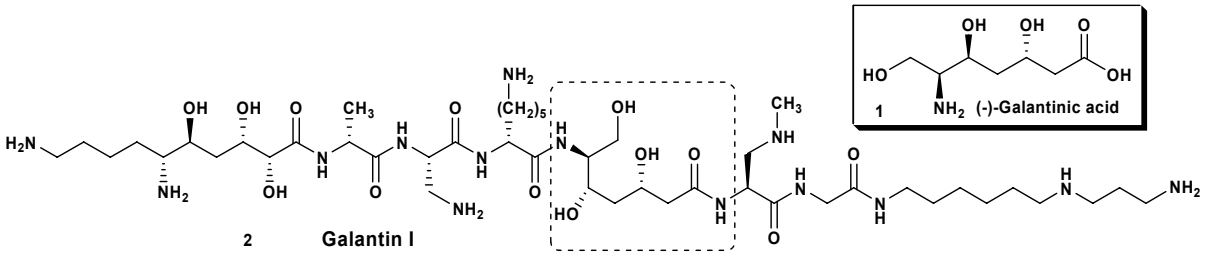
catalyzed oxidation reactions" viz. the asymmetric epoxidation (AE) developed in early 1980 and the asymmetric dihydroxylation (AD) in early 1990 and newly developed asymmetric aminohydroxylation (AA) in 1995, bagged him the 'Nobel Prize' in chemistry in the year 2001.

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

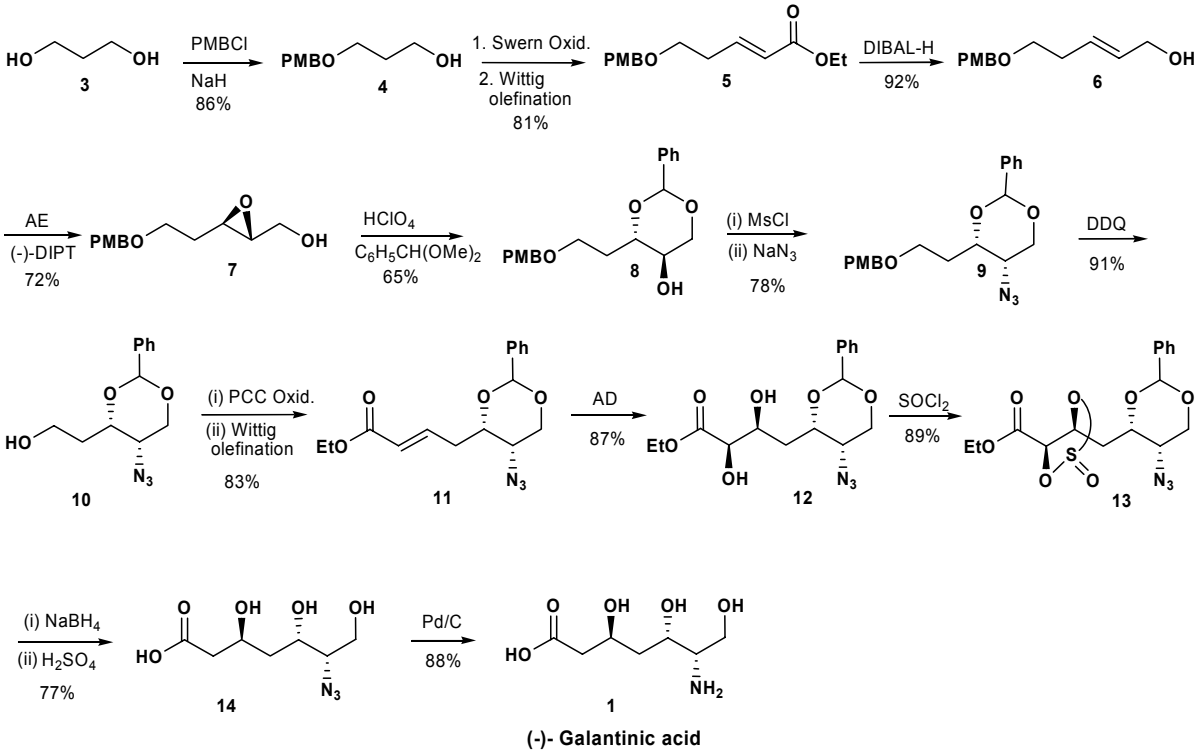
In this chapter, the development of HKR, development of AD and AE reaction from stoichiometric to catalytic version, the mechanism, reaction conditions, varied ligands used and its applications will be covered.

Chapter 2: Asymmetric synthesis of vicinal diols and amino alcohols and is divided into two sections.

Section A: Enantioselective synthesis of (-)-galantinic acid

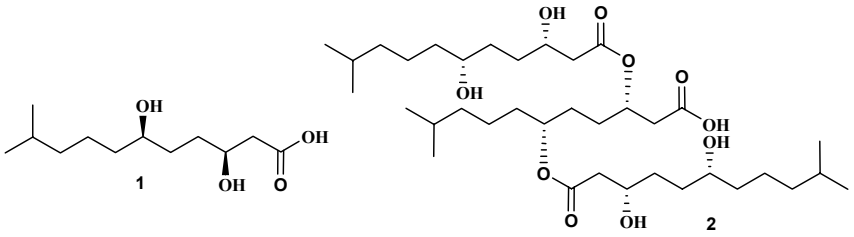


(-)-Galantinic acid **1** is a component of the peptide antibiotic galantin I **2**, isolated from a culture broth of *Bacillus pulvifaciens*.[1] Galantinic acid has been a synthetic target of considerable interest due to its potent biological activity and unique structure. We have accomplished enantioselective synthesis of (-)-galantinic acid **1**, using Sharpless asymmetric epoxidation, dihydroxylation and the regioselective nucleophilic opening of a cyclic sulfite as the key steps. The synthesis started from commercially available 1,3-propanediol **3** which on PMB protection, Swern oxidation[2] and Wittig olefination followed by DIBAL-H reduction and AE provided the epoxide **7**, which was further converted into triol and protected as 1,3-benzylidene compound **8**. The free alcohol was converted into azide and PMB protecting group was cleaved with DDQ to furnish the alcohol **10**.



Compound **10** on PCC oxidation and Wittig olefination followed by AD provided the diol **12**, which was further converted into cyclic sulfite **13**. For the synthesis of β-hydroxy compound **14**, the cyclic sulfite **13** was opened with hydride[3] followed by acid treatment to give the azido alcohol **14** which on hydrogenation led to the target compound (-)-galantinic acid **1**.

Section B: Efficient total synthesis of (−)-(3*S*,6*R*)-3,6-dihydroxy-10-methylundecanoic acid

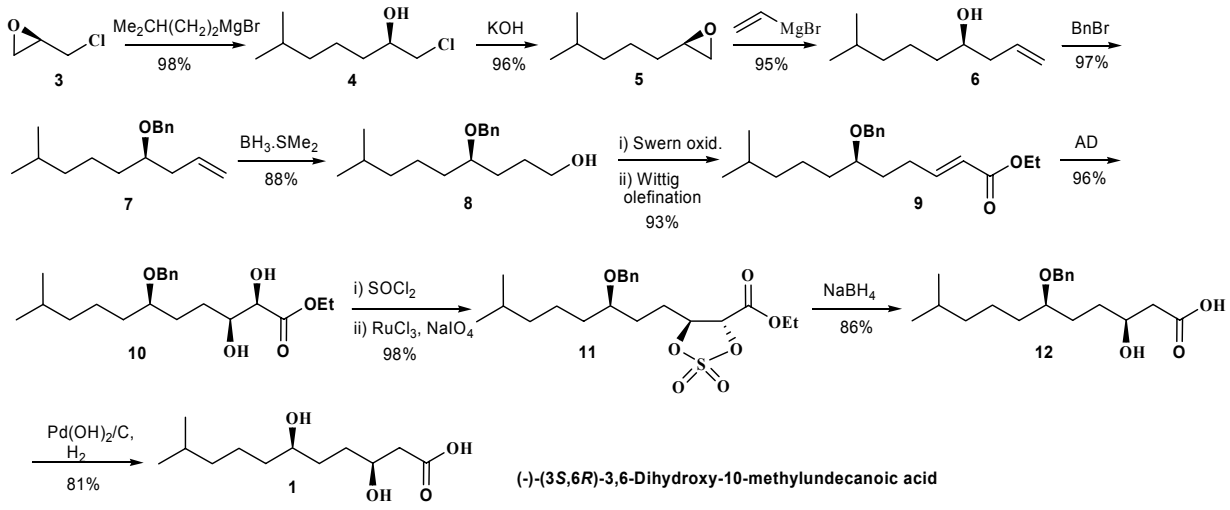


(-)-(3*S*,6*R*)-3,6-Dihydroxy-10-methylundecanoic acid **trimer**

(−)-(3*S*,6*R*)-3,6-Dihydroxy-10-methylundecanoic acid **1** and its trimer **2** were isolated from the aerial parts of *Lafuentea rotundifolia* Lag.[4] Compound **1** has been a synthetic target of considerable interest due to its β-hydroxyl acid skeleton and unique 1,4-dihydroxyl structure.

The synthesis of **1** started from (*R*)-epichlorohydrin **3** prepared from commercially available racemic epichlorohydrin by means of Jacobsen's HKR which was subjected to copper-

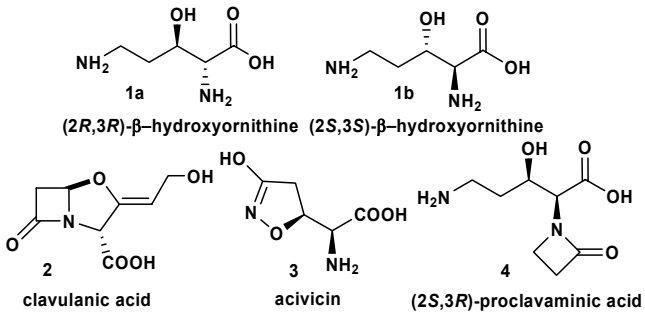
catalysed (CuI) regioselective ring-opening with *iso*-amylmagnesium bromide followed by base treatment to give the epoxide **5.** Subsequent ring opening with vinylmagnesium bromide followed by benzyl protection of free hydroxyl group furnished compound **7**.



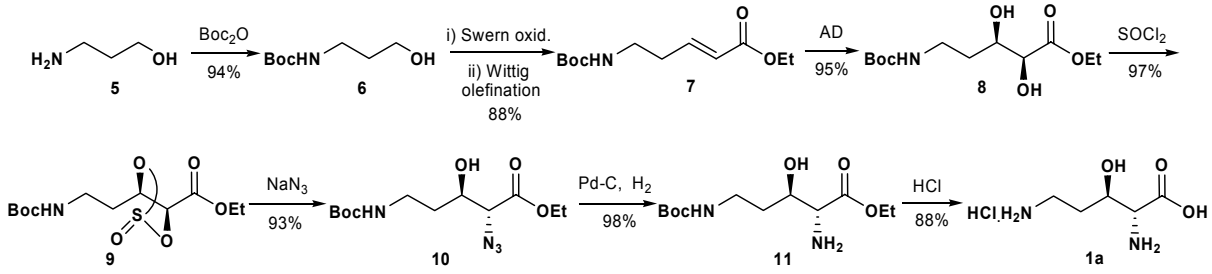
The compound **7** on hydroboration-oxidation, Swern oxidation and Wittig olefination followed by AD provided the diol **10**, which was further converted into cyclic sulfate **11**. The cyclic sulfate **11** was opened regioselectively at α-position with hydride followed by acid treatment to give the β-hydroxy compound **12**, which on hydrogenation led to target compound (−)-(3*S*,6*R*)-3,6-dihydroxy-10-methylundecanoic acid **1**.

Chapter 3: Enantioselective synthesis of hydroxyornithine as a core unit of biologically active natural products and is divided into two sections.

Section A: Enantioselective synthesis of (2*R*,3*R*)- and (2*S*,3*S*)-β-hydroxyornithine

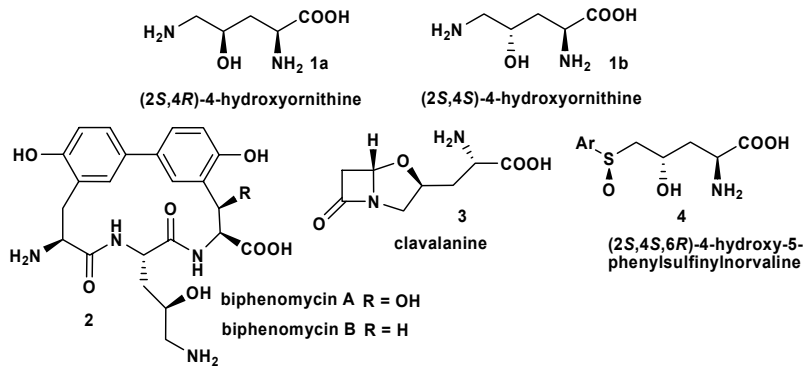


β-Hydroxyornithines **1a–b** serve as intermediates in the synthesis of important natural products like β-lactams and amino polyols[5] and as biosynthetic precursors to both the β-lactamase inhibitor clavulanic acid **2** and the anticancer agent, acivicin **3**.[6] Proclavaminic acid **4** has been recognized as the biosynthetic precursor of clavulanic acid **2**, a potent inhibitor of bacterial β-lactamase.



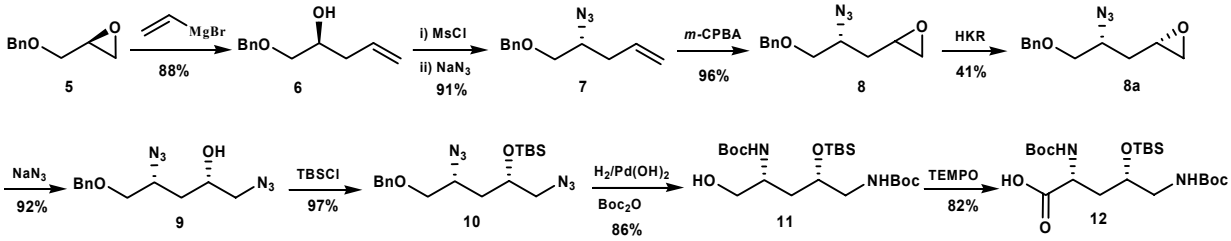
The synthesis of β-hydroxyornithine **1a-b** started from the commercially available 3-aminopropanol **5**, which on Boc protection, Swern oxidation and Wittig olefination followed by Sharpless AD provided the diol **8**, which was further converted into cyclic sulfite **9**.[7] For synthesis of target compound, cyclic sulfite **9** was opened with NaN_3 in regioselective manner at α-position to give azido alcohol **10** which was subjected to hydrogenation to give amino alcohol **11**. Finally, concomitant deprotections of the Boc group and ester hydrolysis were carried out with 6 N HCl to furnish **1a** as its hydrochloride salt. In a similar way, (2*S*,3*S*)-β-hydroxyornithine **1b** was synthesized using $(DHQ)_2PHAL$ in the Sharpless AD step.

Section B: An efficient and short synthesis of protected (2*S*,4*R*)-4-hydroxyornithine



4-Hydroxyornithine **1a-b** is a nonproteinogenic amino acid found abundantly in nature. It is a component of marine organism[8] and plants,[9] as well as a constituent of a number of peptide natural products, such as the antifungal lipopeptides echinocandin and pneumocandin,[10] the K

582 type antibiotics,[11] macrocyclic antibiotic such as biphenomycin A and B **2a-b**,[12] polyoxin M and anticancer agent clavalanine **3**.[13] The related 4-hydroxylated α-amino acids such as (2*S*,4*S*,6*R*)-4-hydroxy-5-phenylsulfinylnorvaline **4** has also been identified as a key component of ustiloxin A and B, a family of cyclic peptides with potent antimitotic activity.

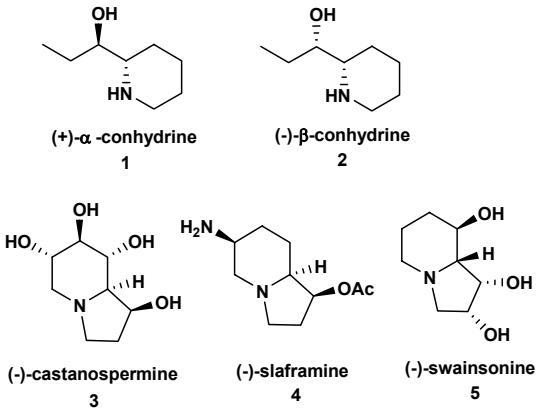


The synthesis of protected (2*S*,4*R*)-4-hydroxyornithine **12** started from the (*R*)-benzyl glycidol **5** prepared from commercially available racemic benzyl glycidol by means of Jacobsen's HKR. **5** was subjected to copper-catalysed (CuI) regioselective ring-opening with vinylmagnesium bromide followed by its conversion into homo allylic azide compound **7**. The compound **7** was subjected to *m*-CPBA epoxidation followed by Jacobsen' HKR to give **8a** as a single diastereoisomer. The epoxide **8a** was subjected to regioselective opening with NaN_3 to give the diazido alcohol **9** and free alcohol was protected with TBSCl. Concomitant one pot deprotection of benzyl group, reduction of both azide group to diamine and Boc protection were carried out with $H_2/Pd(OH)_2$ in the presence of Boc_2O to afford the alcohol **11**. Amino alcohol **11** was oxidised with TEMPO/NaOCl/$NaClO_2$ to give the desired carboxylic acid **12** in excellent yield.

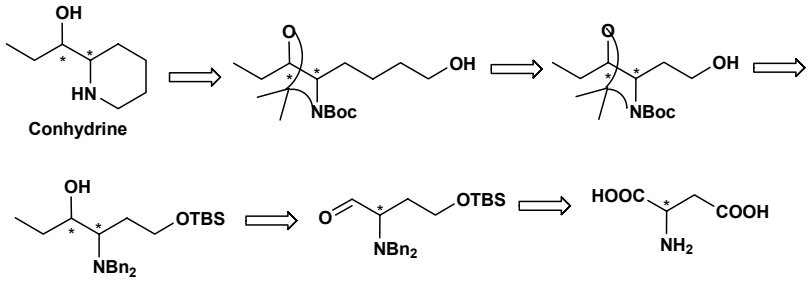
Chapter 4: Efficient and versatile approach to enantiopure piperidine alkaloids and is divided into two sections

Section A: Stereoselective syntheses of (+)-α- and (-)-β-conhydrine from L-aspartic acid

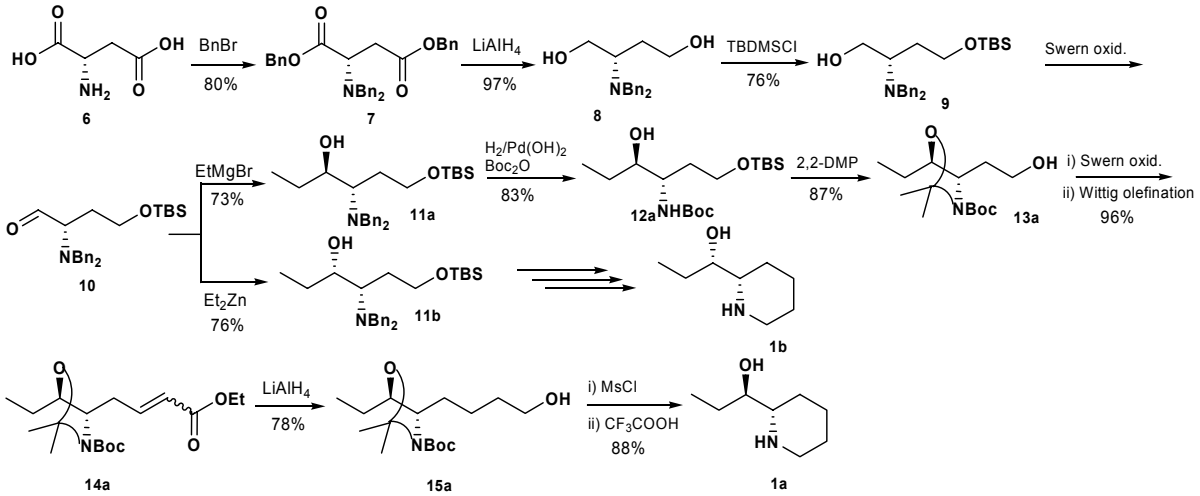
Biologically active alkaloids containing a 2-(1-hydroxyalkyl)piperidine unit are abundant in nature.[14] (+)-α-Conhydrine **1** and (-)-β-conhydrine **2**, are two such alkaloids isolated from the seeds and leaves of the poisonous plant *Conium maculatum*.[15] The indolizidine alkaloids such



as (-)-castanospermine **3**, (-)-slaframine **4** and (-)-swainsonine **5** contain a similar structural pattern and are known to exhibit potent glycosidase inhibitor, antiviral and antitumor properties.[16]

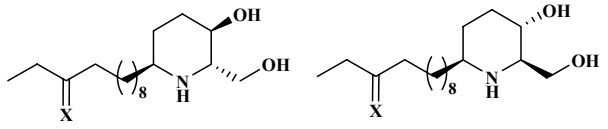


We have developed a general route for all isomer of conhydrine piperidine alkaloid. A stereocontrolled syntheses of (+)-α-conhydrine **1** and (-)-β-conhydrine **2** has been achieved by diastereoselective alkylation of an amino aldehyde derivative **10** with ethylmagnesium bromide or diethylzinc.



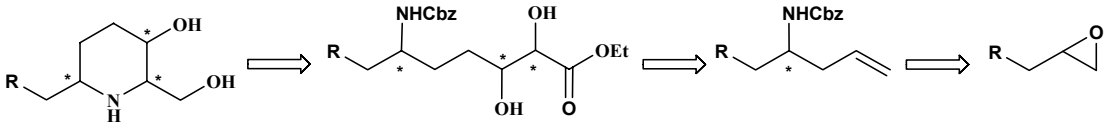
Further, in order to achieve the synthesis of target compound, compound **11a** was subjected to debenzylation by hydrogenation using $Pd(OH)_2$ followed by protection of the amino group with $(Boc)_2O$, acetonide protection and concomitant deprotection of the TBS group to afford **13a**. Compound **13a** on Swern oxidations, Wittig olefination and LAH reduction gave the alcohol **15a** in excellent yield which was subjected to cyclization using methanesulfonyl chloride and triethylamine followed by deprotection of the Boc group and base treatment to furnish (+)-α-conhydrine **1.** (-)-β-Conhydrine **2** was synthesized from **11b** following an analogous series of reactions as shown above.

Section B: An efficient and versatile approach to enantiopure 2,6-disubstituted piperidin-3-ol: Concise synthesis of (-)-deoxoprosopinine and (+)-deoxoprosophylline

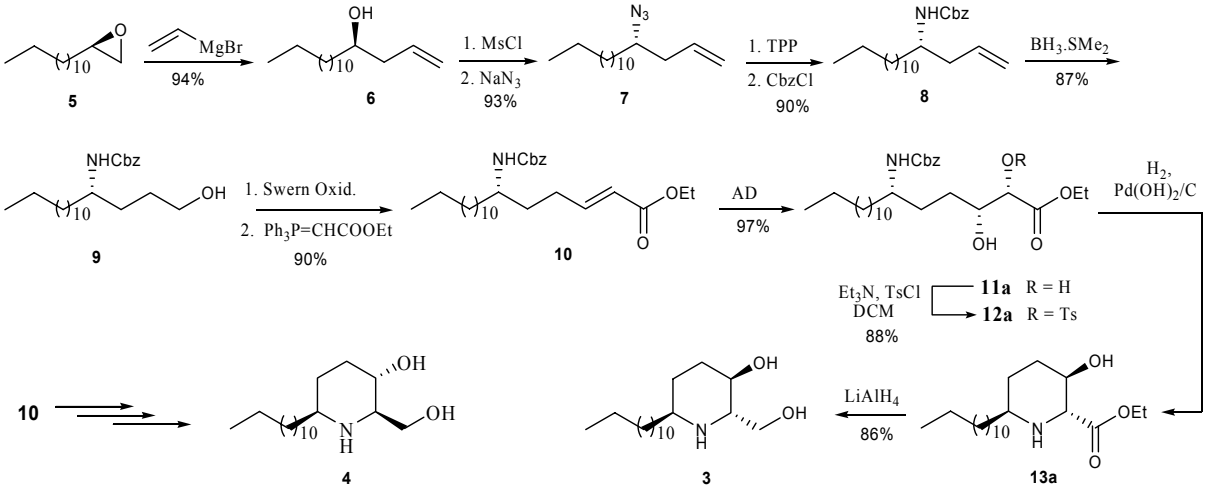


(-)-Prosopinine (1, X = O)
(-)-Deoxoprosopinine (3, X = H_2)
(+)-Prosophylline (2, X = O)
(+)-Deoxoprosophylline (4, X = H_2)

Naturally occurring alkaloids containing multi-functionalised piperidine rings are found abundantly in nature and many of them exhibit biological acitivity of medicinal interest.[17] Prosopis alkaloids, one of the sub groups of these piperidine alkaloids, were isolated from the leaves of *Prosopis afrikana* Taub, containing 2,6-disubstituted piperidin-3-ol piperidine framework such as prosopinine **1**, prosophylline **2** and their deoxo analogues deoxoprosopinine **3**, deoxoprosophylline **4**, respectively.[18] These alkaloids exhibit antibiotic, anesthetic, analgesic and CNS stimulating properties.



We have developed a simple and highly efficient approach to enantiopure 2,6-disubstituted piperidin-3-ol skeleton from racemic epoxide as a starting material and applied it to the total synthesis of (-)-deoxoprosopinine and (+)-deoxoprosophylline employing a Jacobsen's hydrolytic kinetic resolution (HKR) and Sharpless asymmetric dihydroxylation (AD) as key steps.



The synthesis of **3** and **4** started from the (*R*)-1,2-epoxytetradecane **5** prepared from commercially available racemic 1,2-epoxytetradecane by means of Jacobsen's HKR which was subjected to copper-catalysed (CuI) regioselective ring-opening with vinylmagnesium bromide to give **6** followed by its conversion into homoallylic azide **7** *via* mesylate.

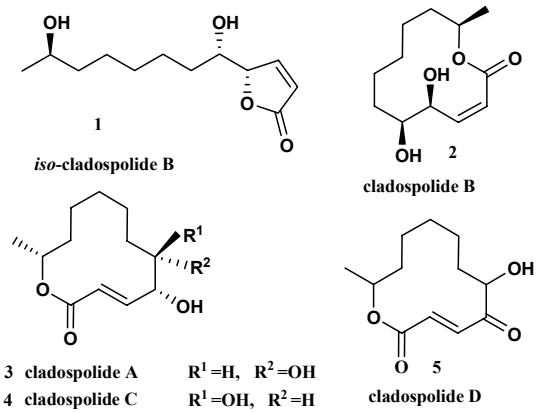
Compound **7** was subjected to Staudinger reaction[19] and converted into amine which on Cbz protection, hydroboration–oxidation reaction, Swern oxidation and Wittig olefination followed by AD provided the diol **11a**. Regioselective monotosylation[20] of diol **11a** with TsCl and concomitant deprotection of Cbz and nucleophilic displacement of α-tosylate on hydrogenation with $Pd(OH)_2$ led to the cyclized product **13a**. Finally, reduction of **13a** with LAH produced (-)-deoxoprosopinine **3** in excellent yield. In a similar way, (+)-deoxoprosophylline **4** was synthesized using $(DHQ)_2PHAL$ in the AD step and following same series of reactions.

Chapter 5: Enantioselective syntheses of three naturally occurring lactones and is further divided into two sections.

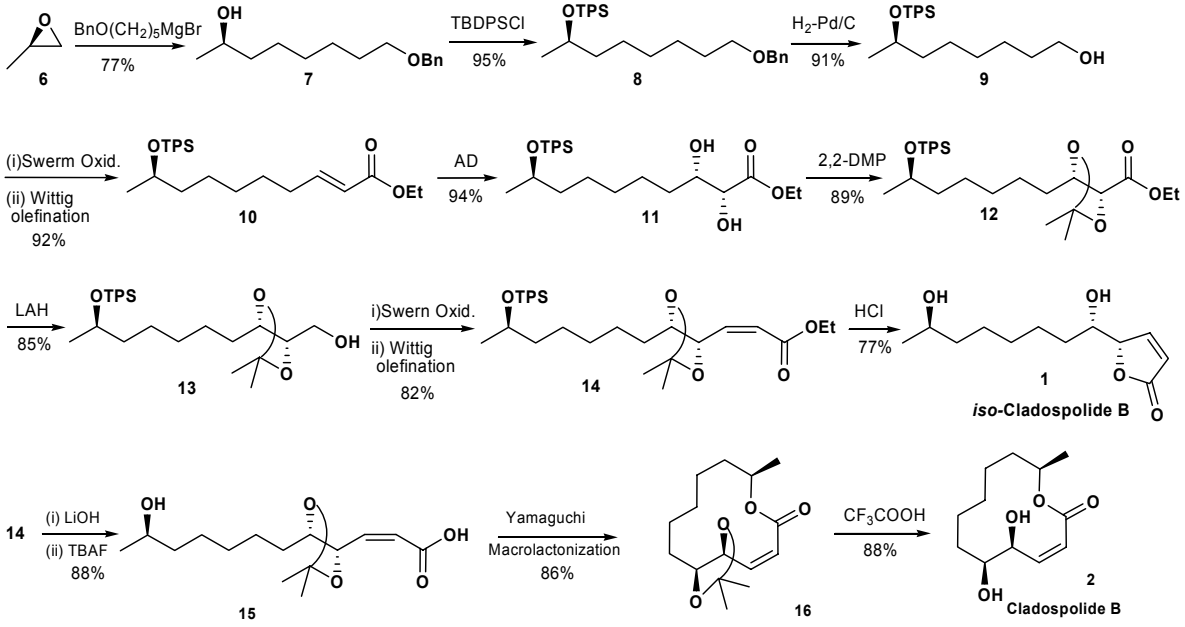
Section A: Total synthesis of *iso*-cladospolide B and cladospolide B

The novel hexaketide compounds *iso*-cladospolide B **1** and cladospolide B **2** were isolated from the fungal isolate I96S215.[21] Cladospolide A **3**, cladospolide B **2** along with cladospolide C **4** were also isolated from the soil fungi *Cladosporium tenuissimum*, whose culture filtrate showed plant growth retardant activity towards rice seedlings. Cladospolide B **2** is inhibitory to shoot elongation of rice seedlings (*Oryza sativa* L.) without damaging the cells.[22] Recently

cladospolide D **5** isolated from *Cladosporium sp.* FT-0012 whose configuration remains to be fully determined, was shown to exhibit antimicrobial activity against *Mucor racemosus* and *Pyricularia oryzae* with IC_{50} values of 0.15 and 29 μ g ml^{-1}, respectively.[23]



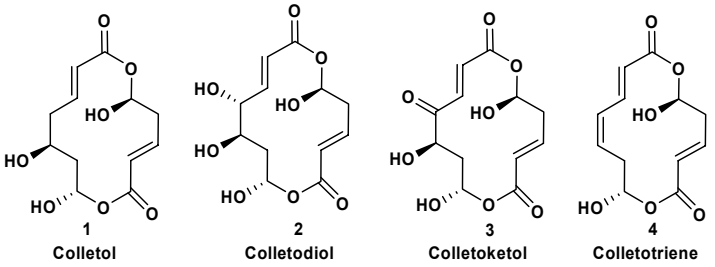
The synthesis of **1** and **2** started from (*R*)-propylene oxide **6** prepared from commercially available racemic propylene oxide by means of Jacobsen's HKR. **6** was subjected to regioselective opening with the Grignard reagent, derived from benzyl protected bromopentanol followed by protection of alcohol with TBDPS to give compound **8**. The compound **8** on benzyl deprotection, Swern oxidation and Wittig olefination followed by AD provided the diol **11** in excellent yield. The diol **11** on acetonide protection, LAH reduction of ester, Swern oxidation and Wittig olefination furnished **14** which served as common intermediate for synthesis of both *iso*-cladospolide B **1** and cladospolide B **2**.



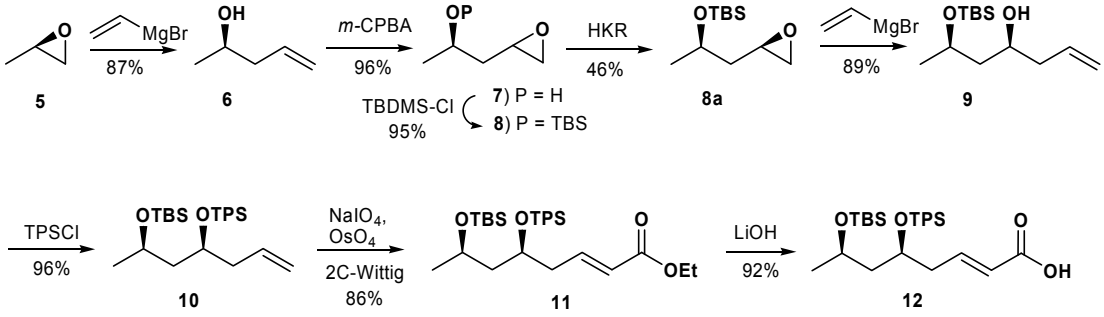
Deprotection of the acetonide and TPS groups and concomitant cyclization of the olefin **14** was achieved in one-pot using methanolic HCl to furnish the target molecule, *iso*-cladospolide B **1**.

The synthesis of cladospolide B **2** was also accomplished successfully from the intermediate olefin **14.** Thus, ester hydrolysis followed by TPS deprotection led to the *seco*-acid **15.** Subsequent macrolactonization under Yamaguchi conditions[24] (**15→16**) followed by cleavage of acetonide group furnished the target molecule **2** in excellent yield.

Section B: Formal total synthesis of (-)-colletol

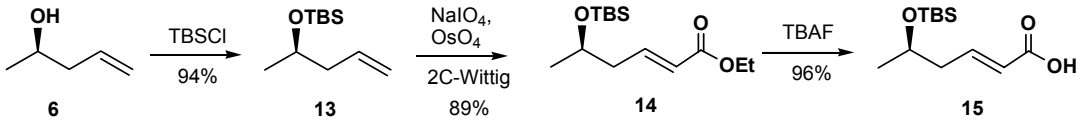


(-)-Colletol **1** is a 14-membered bis-macrolactone isolated from the fermentation broth of *Collectotrichum capsici* in 1973 along with related bis-lactones colletodiol **2**, colletoketol **3**.[25] Although no biological activity was reported for these macrolactones, interest in these compounds was stimulated when the isolation of grahamimycin A (colletoketol) **3**, which displayed potent activity against bacteria, algae, and fungi was reported.[26] These macrolactones can result from a biosynthesis *via* the macrodiolide colletotriene **4**.[27]

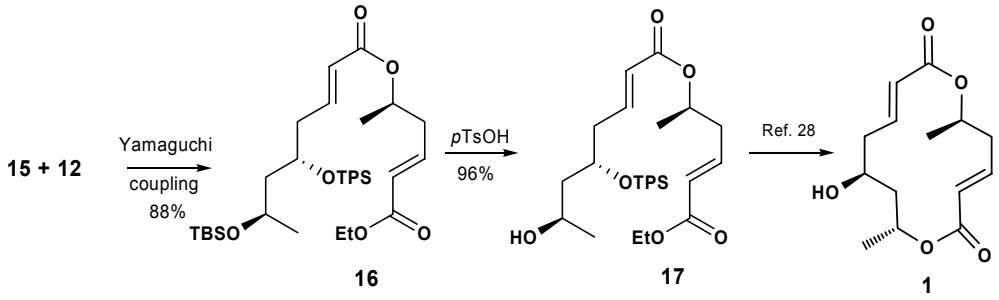


The synthesis started from the (*R*)-propylene oxide **5** prepared from Jacobsen's HKR. **5** was subjected to copper-catalyzed (CuI) regioselective ring-opening with vinylmagnesium bromide followed by epoxidation and TBS protection to give racemic epoxide **8**. In order to get diastereomerically pure epoxide, the racemic epoxide **8** was resolved using Jacobsen' HKR to

give compound **8a**. Opening of epoxide **8a** with vinyl Grignard followed by TPS protection, dihydroxylation, chopping, Wittig olefination and TBS deprotection furnished compound **12**.



Homoallylic compound **6** was subjected to TBS protection, dihydroxylation, chopping, Wittig olefination and hydrolysis to give the α,β-unsaturated acid **15.** Yamaguchi coupling of acid **12** and alcohol **15** led to the compound **16** which can be converted to the target compound **1** by known procedure.[28]



References:

1. Shoji, J.; Sakajaki, R.; Koizumi, K.; Matsurra, S. J. *J. Antibiot.* **1975**, *28*, 122.
2. For reviews on the Swern oxidation, see: (a) Tidwell, T. T. *Synthesis* **1990**, 857; (b) Tidwell, T. T. *Org. React*. **1990**, *39*, 297.
3. Gaw, Y.; Sharpless, K. B. *J. Am. Chem. Soc*. **1988**, *110*, 7538.
4. Barrero, A. F.; Herrador, M. M.; Haïdour, A.; Altarejos, J.; Arteaga, P.; Chahboun, R. *Tetrahedron Lett.* **1995**, *36*, 2649.
5. (a) Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis. Construction of Chiral Molecules Using Amino Acids*, J. Wiley and Sons, New York **1987**. (b) Miller, M. J. *Acc. Chem Res.* **1986**, *19*, 49 and references therein.
6. (a) Elson, S. W.; Baggaley, K. H.; Gillett, J.; Holland, S.; Nicholson, N. H.; Sime, J. T.; Woroniecki, S. R. *J. Chem. Soc., Chem. Commun.* **1987**, 1736. (b) Baldwin, J. E.; Adlington, R. M.; Bryans, J. S.; Bringhen, A. O.; Coates, J. B.; Crouch, N. P.; Lloyd, M. D.; Schofield, C. J.; Elson, S. W.; Baggaley, K. H.; Cassels, R.; Nicholson, N. *J. Chem. Soc., Chem. Commun.* **1990**, 617.

7. For reviews on cyclic sulfites/sulfates chemistry, see: (a) Lohray, B. B. *Synthesis* **1992**, 1035. (b) Byun, H.-S.; He, L.; Bittman, R. *Tetrahedron* **2000**, *56*, 7051.
8. (a) Fujita, Y. *Bull Chem. Soc. Jpn.* **1959**, *32*, 439. (b) Makisumi, S. *J. Biochem. (Tokyo)* **1961**, *49*, 284.
9. (a) Bell, E. A.; Tirimanna, A. S. L. *Nature (London)* **1963**, *197*, 901. (b) Bell, E. A.; Tirimanna, A. S. L. *Biochem. J.* **1964**, *91*, 356.
10. Denning, D. W. *J. Antimicrob. Chemother.* **1997**, *40*, 611.
11. Kondo, S.; Meguriya, N.; Mogi, H.; Aota, T.; Miura, K.; Fujii, T.; Hayashi, I.; Makino, K.; Yamamoto, M.; Nakajima, N. *J. Antibiot.* **1980**, *33*, 533.
12. Ezaki, M.; Iwami, M.; Yamashita, M.; Hashimoto, S.; Komori, T.; Umehara, K.; Mine, Y.; Kohsaka, M.; Aoki, H.; Imanaka, I. *J. Antibiot.* **1985**, *38*, 1453.
13. Shiro, Y.; Kato, K.; Fujii, M.; Idab, Y.; Akitaa, H.; *Tetrahedron* **2006**, *62*, 8687 and references therein.
14. Casiraghi, G.; Zanardi, F.; Rassu, G.; Spanu, P. *Chem. Rev*. **1995**, *95*, 1677.
15. Wertheim, T. *Liebigs Ann. Chem*. **1856**, *100*, 328.
16. (a) Elbein, A. D.; Molyneux, R. J.; Alkaloids: chemical and biological perspective: Pelletier, S.W., Ed.; Wiley:NewYork, **1986**; Vol. *5*, *pp* 1-54; (b) Comins, D. L.; Kuethe, J. T.; Hong, H.; Lakner, F. J. *J. Am. Chem. Soc.* **1999**, *121*, 2651; (c) Kuethe, J. T.; Comins, D. L. *Org. Lett*. **1999**, *1*, 1031.
17. For reviews that include piperidine alkaloids, see: (a) Ayer, W. A.; Habgood, T. E. In *The Alkaloids*; Manske, R. H., Ed.; Academic Press: London, **1968**; Vol. 11, p 492. (b) Strunz, G. M.; Findlay, J. A. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, **1985**; Vol. 26, pp 89. (c) Foder, G. B.; Colasanti, B. The Pyridine and Piperidine Alkaloids; Chemistry and Pharmacology. In *Alkaloids: Chemical and Biological Perspectives*: Pelletier, S. W., Ed.; Wiley: New York, **1985**; Vol. 3, pp 1. (d) Numata, A.; Ibuka, T. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, **1987**; Vol. 31, pp 193 and references therein. (e) Schneider, M. J. Pyridine and Piperidine Alkaloids: An Update. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: Oxford, **1996**; Vol. 10, pp 155. (f) Wang, C. J.; Wuonola, M. A. *Org. Prep. Proced. Int.* **1992**, *24*, 585. (g) Laschat, S.; Dickner, T.; *Synthesis* **2000**, 1781.

18. Prosopis alkaloids from the leaves, stems, and roots of *Prosopis africana*: (a) Ratle, G.; Monseur, X.; Das, B. C.; Yassi, J.; Khuong- Huu, Q.; Goutarel, R. *Bull. Soc. Chim. Fr*. **1966**, 2945. (b) Khuong-Huu, Q.; Ratle, G.; Monseur, X.; Goutarel, R. *Bull. Soc. Chim. Belg*. **1972**, *81*, 425, 443.
19. Staudinger, H.; Meyer, J. *Helv. Chim. Acta.* **1919**, *2*, 635.
20. Fleming, P. R.; Sharpless K. B. *J. Org. Chem.* **1991**, *56*, 2869.
21. Cameron, J. S.; Abbanat, D.; Bernan, V. S.; Maiese, W. M.; Greenstein, M.; Jompa, J.; Ireland, C. M. *J. Nat. Prod.* **2000**, *63*, 142.
22. (a) Hirota, H.; Hirota A.; Sakai, H.; Isogai A.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2147. (b) Hirota, A.; Sakai, H.; Isogai, A. *Agric. Biol. Chem*. **1985**, *49*, 731. (c) Fujii, Y. Fukuda, A.; Hamasaki, T.; Ichimoto, I.; Nakajima, H. *Phytochemistry* **1995**, *40*, 1443.
23. Zhang, H.; Tomoda, H.; Tabata N.; Miura H.; Namikoshi, M.; Yamaguchi, Y.; Masuma, R.; Omura S. *J. Antibiot.* **2001**, *54*, 635.
24. Inanaga, J.; Hirata, K.; Sacki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
25. (a) MacMillan, J.; Pryce, R. J. *Tetrahedron Lett.* **1968**, 5497; (b) MacMillan, J.; Simpson, T. J. *J. Chem. Soc., Perkin Trans.* **1973**, *1*, 1487.
26. (a) Gurusiddaiah, S.; Ronald, R. C. *Antimicrob. Agents Chemother.* **1981**, *19*, 153. (b) Keck, G. E.; Boden, E. P.; Wiley, M. R. *J. Org. Chem.* **1989**, *54*, 896.
27. Munoz, D. C.; Passey, S. C.; Simpson, T. J.; Willis, C. L.; Campbell, J. B.; Rosser, R. *Aust. J. Chem.* **2004**, *57*, 645.
28. Sharma, G. V. M.; Raja Rao, A. V. S.; Murthy, V. S. *Tetrahedron Lett.* **1995**, *36,* 4117.

PUBLICATIONS

1. A concise synthesis of protected (2*S*,4*R*)-4-hydroxyornithine
   Satyendra Kumar Pandey, Menaka Pandey and Pradeep Kumar*
   Tetrahedron Letters **2008**, *49*, 3297-3299
2. A Concise Synthesis of (-)-Deoxoprosopinine
   Satyendra Kumar Pandey and Pradeep Kumar*
   Synlett **2007**, *18*, 2894-2896
3. Efficient total synthesis of (-)-(3*S*,6*R*)-3,6-dihydroxy-10-methylundecanoic acid
   Satyendra Kumar Pandey and Pradeep Kumar*
   Eur. J. Org. Chem. **2007***, 2,* 369-373
4. Enantioselective synthesis of (2*R*,3*R*)- and (2*S*,3*S*)-β-hydroxyornithine
   Satyendra Kumar Pandey and Pradeep Kumar*
   Tetrahedron Letters **2006**, *47*, 4167-4169
5. BINOL: A versatile chiral reagent
   Satyendra Kumar Pandey*
   Synlett **2006**, *19*, 3366-3367
6. Efficient total synthesis of *iso*-cladospolide B and cladospolide B
   Satyendra Kumar Pandey and Pradeep Kumar*
   Tetrahedron Letters **2005**, *46*, 6625-6627
   (Appeared as *Tetrahedron Letters* top 25 Hottest Article in July-September 2005)
7. Stereoselective syntheses of (+)-α- and (-)-β-conhydrine from L-aspartic acid
   Satyendra Kumar Pandey and Pradeep Kumar*
   Tetrahedron Letters **2005**, *46*, 4091-4093
8. Enatioselective synthesis of (-)-galantinic acid
   Satyendra Kumar Pandey, Subbarao V. Kandula and Pradeep Kumar*
   Tetrahedron Letters **2004**, *45*, 5877-5879
9. An Efficient and Versatile Approach to Enantiopure 2,6-Disubstituted Piperidin-3-ol: Concise Synthesis of (-)-Deoxoprosopinine and (+)-Deoxoprosophylline
   Satyendra Kumar Pandey and Pradeep Kumar*
   (Manuscript under preparation)

10. Formal total synthesis of (-)-colletol
    Satyendra Kumar Pandey and Pradeep Kumar*
    (Manuscript under preparation)
11. Short asymmetric synthesis of (+)-*cis*-lauthisan
    Divya Tripathi, **Satyendra Kumar Pandey** and Pradeep Kumar*
    (Manuscript under preparation)
12. Enantioselective synthesis of (2*R*,3*S*)-2-amino-3,4-dihydroxybutyric acid
    Vishwajeet Jha, **Satyendra Kumar Pandey** and Pradeep Kumar*
    (Manuscript under preparation)

PRESENTATIONS / POSTERS

1. Oral Presentation in 3rd J -NOST Symposium 2007, G. N. D. University, Amritsar, Nov. 15-18, **2007,** India.
2. Participated in Second Junior National Organic Symposium Trust **2006**, I. C. G. College, Jaipur, India**.**
3. 2nd International Conference on Organic Synthesis and Process Chemistry (OSPC)- April 1-3, **2005**, IICT Hyderabad, India.
4. Sixth National Symposium in Chemistry (NSC-6), Feb **2004**, IIT Kanpur, (Poster presented) India.
5. Poster presentated in National Chemical Laboraotory on National Science Day, 28th February, **2004**.

AWARDS

- **Best poster award** on National Science Day Symposium NCL, **2004**, for the work of (-)-Galantinic acid.

CHAPTER 1

A BRIEF ACCOUNT OF SHARPLESS ASYMMETRIC EPOXIDATION (AE), ASYMMETRIC DIHYDROXYLATION (AD) AND JACOBSEN'S HYDROLYTIC KINETIC RESOLUTION (HKR)

1.1 ASYMMETRIC EPOXIDATION (AE)

1.1.1. Introduction

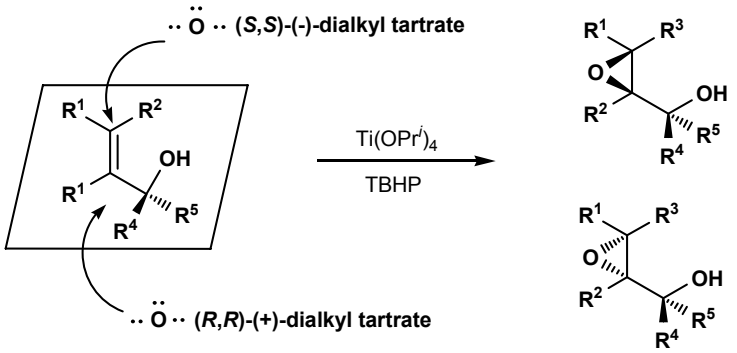
Asymmetric synthesis of bioactive molecules is in the forefront of synthetic organic chemistry due to varied applications in drug and pharmaceutical industries. A large number of enantiomerically pure compounds have been obtained from nature, but quite a few of them are either not easily isolated or not available in useful amounts. However, an organic chemist can provide multi-gram biologically active compounds. The ultimate goal of an organic chemist is, how to assemble a given target molecule from readily available starting materials and reagents in highly efficient way. It is more elegant and economical to prepare just wanted isomer by asymmetric synthesis and through inexpensive catalytic processes.

Nature provides thousands of enantiomerically pure compounds, but quite a few of them are either not easily isolated or not available in useful amounts. 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. Sharpless and katsuki discovered a system for the asymmetric epoxidation of primary and secondary allylic alcohols that utilizes titanium tetraisopropoxide, a diakyl tartrate as a chiral ligand, and *tert*-butyl hydroperoxide as the oxidant.[1] Notably, this reaction exhibits high levels of enantioselectivity. Like other metal catalyzed epoxidations, this reaction also proceeds under mild conditions with good chemical yield and with high regio-and chemoselectivity.

1.1.2. Asymmetric epoxidation with the titanium (IV) tartrate catalyst

The combination of $Ti(OPr^{i})_4$, a dialkyl tartrate, and *tert*-butyl hydroperoxide epoxidizes most allylic 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) 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 if an (*R*,*R*)-dialkyl tartrate is used as the chiral auxiliary. When an (*S*,*S*)-dialkyl 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.

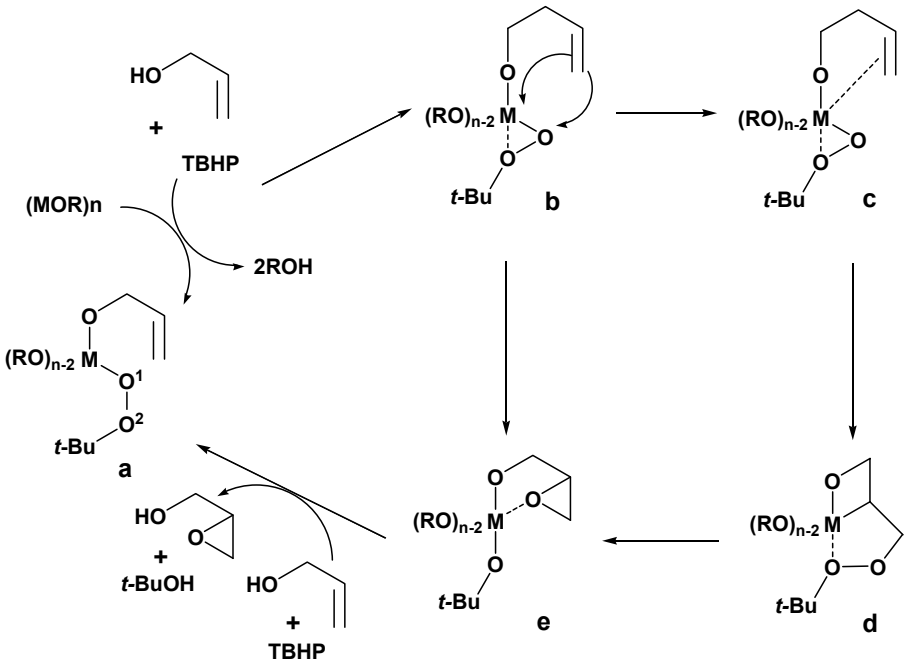
The enantioselectivity for substrate with unbranched R^3 substituents ranges from 80 to 94% ee, but that for substrates with branched substituent is lower.[2]



Scheme 1.

1.1.3 Mechanism

The reaction sequence proposed for the metal-catalyzed epoxidation of allylic alcohols is shown in **Scheme 2**.[3] 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 occurs in an intramolecular fashion is supported by comparison of the epoxidation rate of allylic alcohol with that of allyl methyl ether.[4] 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.[5] An alternative proposal is that the double bond attacks the distal oxygen along the axis of the O-O bond that is broken.[2,3d,5] Frontier molecular orbital treatment of peroxometal complexes also suggests that d-transition metal complexes of ROO- exhibit electrophilic behaviour.[6] Finally, exchange of *tert*-butoxide and the epoxy alkoxide so formed with allylic alcohol and alkyl hydroperoxide completes the reaction cycle.



Scheme 2.

The titanium tartrate mediated asymmetric epoxidation of allylic alcohols also follows the same basic reaction pathway of **Scheme 2**. Therefore the remaining mechanistic question is how oxygen is transferred enantioselectively to substrates. To answer this question, structures of titanium-dialkyl tartrate complexes,[7] as well as those prepared from Ti $(OPr^i)_4$ and (*R*,*R*)-N, N^1 dibenzyltartramide and from $Ti(OEt)_4$, (*R*,*R*)-diethyl tartrate, and Ph(CO)-N(OH)Ph were determined.[8] Based on the X-ray analysis of these complexes, the structure of the asymmetric epoxidation catalyst (**Fig. 1**) has been proposed.

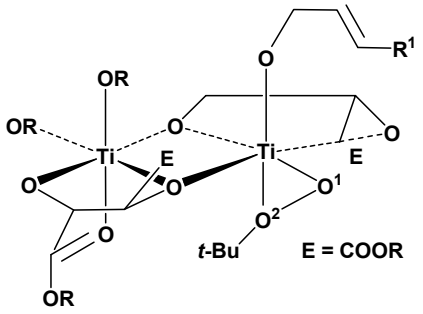


Figure 1.

When structure shown in Fig. 1 is viewed down the distal peroxide oxygen-titanium bond axis (O^1-Ti), the symmetry of the tartrate "windmill arms" becomes apparent. Within this model, conformer (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.[2]

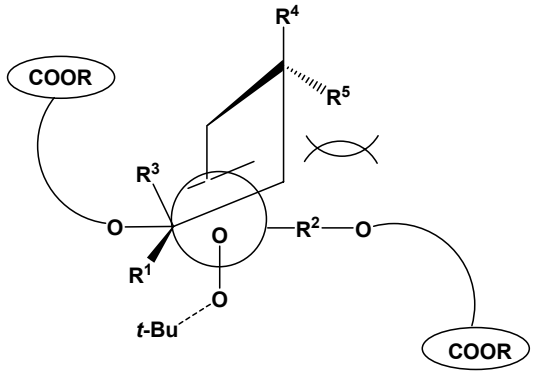


Figure 2.

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.[9] 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 (**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.

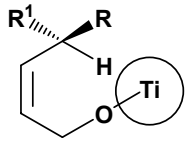


Figure 3.

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.[2] 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^1 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 $Ti(OPr^i)_4$- tartrate affects kinetic resolution.

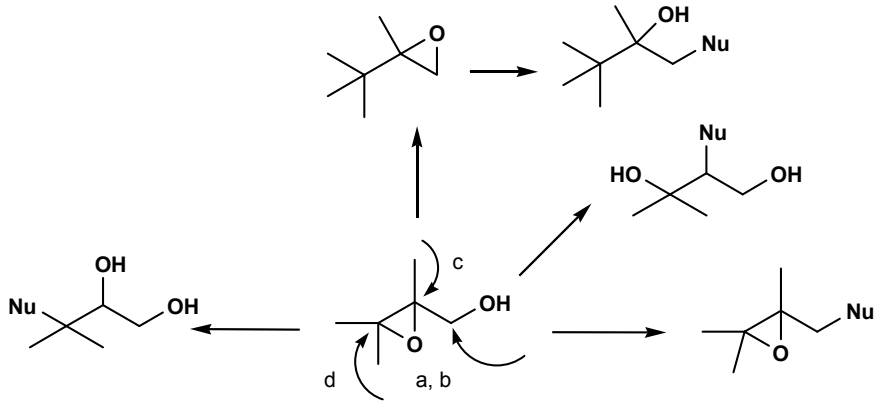
2. The C-2 substituent is near the Ti-tartrate moiety, its chirality also affects substrate reactivity. Thus enantiomers of a racemic substrate bearing a chiral C-2 substituent have different reactivities, and in some cases a good level of kinetic resolution is observed.

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.[10] 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 $Ti(OPr\text{-}i)_4$ and 6 mol% tartrate has been recommended as the most widely applicable system for asymmetric epoxidation.[11] 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).

1.1.4 Various synthetic manipulations of epoxide

The significant utility of the titanium mediated asymmetric epoxidation in organic synthesis is attributable to its enantioselectivity and to the numerous applications of epoxy alcohols as precursors to diversely functionalized compounds. However since epoxy alcohols have three reactive sites regio- and stereoselective reactions are essential for their use and many studies have been directed toward developing regioselective transformations

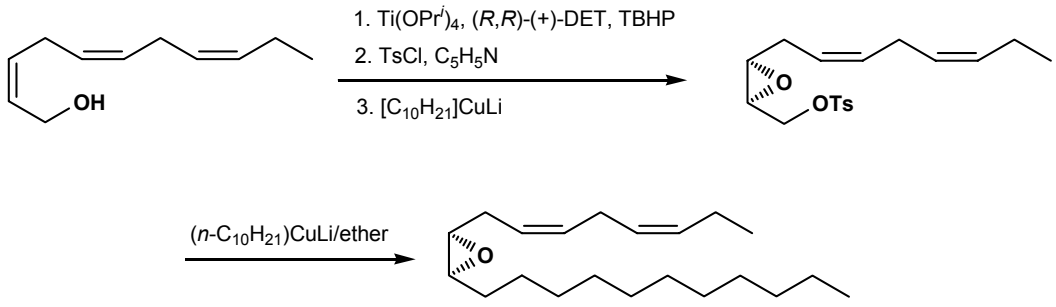
of epoxy alcohols. For convenience, these reactions are classified into three categories (**Scheme 3**).



Scheme 3.

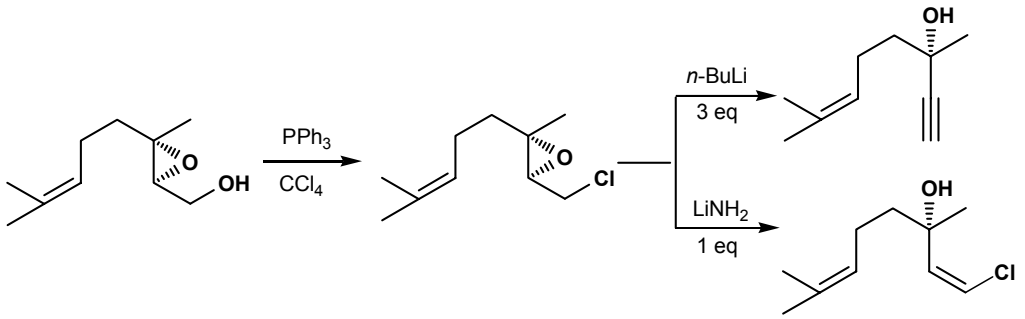
1. Transformations of the Hydroxy Group at C-1:

Epoxy alcohols can be converted directly into the corresponding epoxy ethers by using Mitsunobu procedures.[12] Activation of the hydroxy group as the corresponding mesylate or tosylate also provides a useful means of replacing it with various nucleophiles like organolithium or organocopper reagents[13] and hydride sources (**Scheme 4**).[1]



Scheme 4.

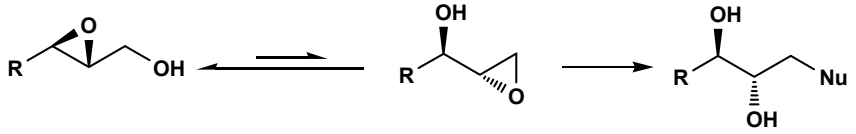
Treatment of epoxy alcohols with triphenyl phosphine-carbon tetrachloride, which are converted into propargylic alcohols by further treatment with 3 equivalents of an alkyl lithium or lithium diisopropyl amide.[14] On the other hand, treatment with 1 equivalent of an alkyl lithium instead of lithium amide gives a mixture of propargylic alcohol and vinyl chloride (**Scheme 5**).[15]



Scheme 5.

2. Payne rearrangement-Epoxide opening sequence:

2,3-Epoxy alcohols are rapidly equilibrated with 1,2-epoxy alcohols under alkaline conditions.[16] The equilibrium ratio of 1,2 to 2,3-epoxy alcohol is remarkably dependent on the substrate. However, as 1,2-epoxide is considerably more reactive than 2,3-epoxide, treatment of the equilibrium mixture with a nucleophile provides preferentially the product from the 1,2-epoxide (**Scheme 6**).[17]



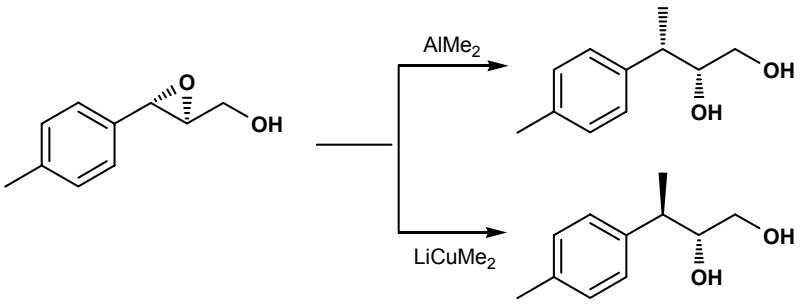
Scheme 6.

Thus, the Payne rearrangement-epoxide opening sequence is a useful alternative for activating C-1 for substitution[18] although this provides 2,3-diols while direct C-1 substitution provides 2,3-epoxides. For example, the Payne rearrangement epoxide-opening sequence has permitted the straightforward synthesis of sugars *via* iterative asymmetric epoxidation cycles,[19] other nucleophiles including OH- [20a] , TsHN- [20b] , CN- [20c], N_3 [20d] and R_2NH[20e] have also been used successfully.

3. Epoxide ring opening at C-2 or C-3:

The regio and stereo-chemistry in epoxide-opening reactions of 2,3-epoxy alcohols depend on the steric and electronic factors in the substrates and on reaction conditions. Nucleophilic substitution under neutral and basic conditions occurs preferentially from the less substituted side in an S_N2 manner, where the configuration of the attacked carbon is

inverted.[18] Nucleophilic attack under acidic conditions occurs at the more substituted side in an S_N2 manner.[19] With sterically unbiased epoxy alcohols or their *O*-protected derivatives, epoxide opening with nucleophiles occurs preferentially at C-3 (**Scheme 7**).[21] This regioselectivity is attributed to the presence of the electronegative hydroxy group at C-1, which retards S_N2 substitution at the vicinal carbon.

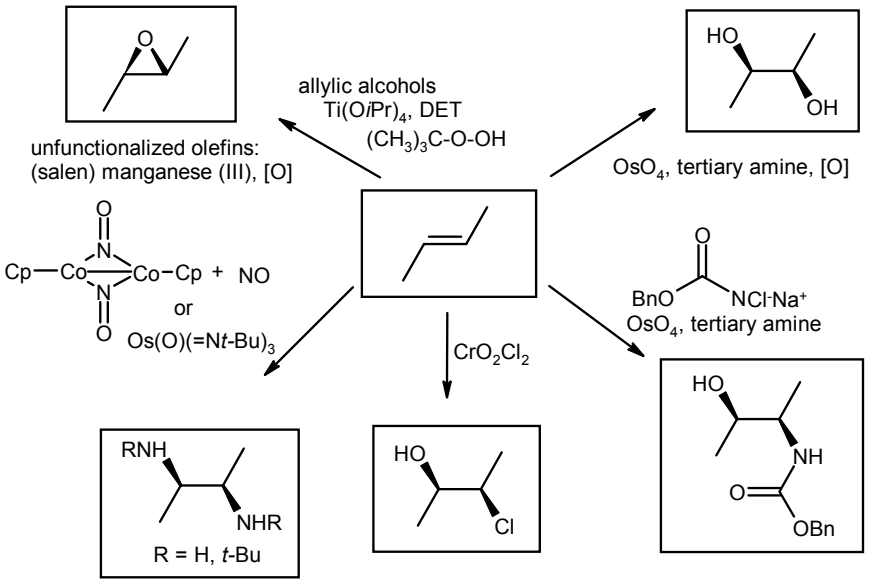


Scheme 7.

1.2 ASYMMETRIC DIHYDROXYLATION (AD)

1.2.1. Introduction

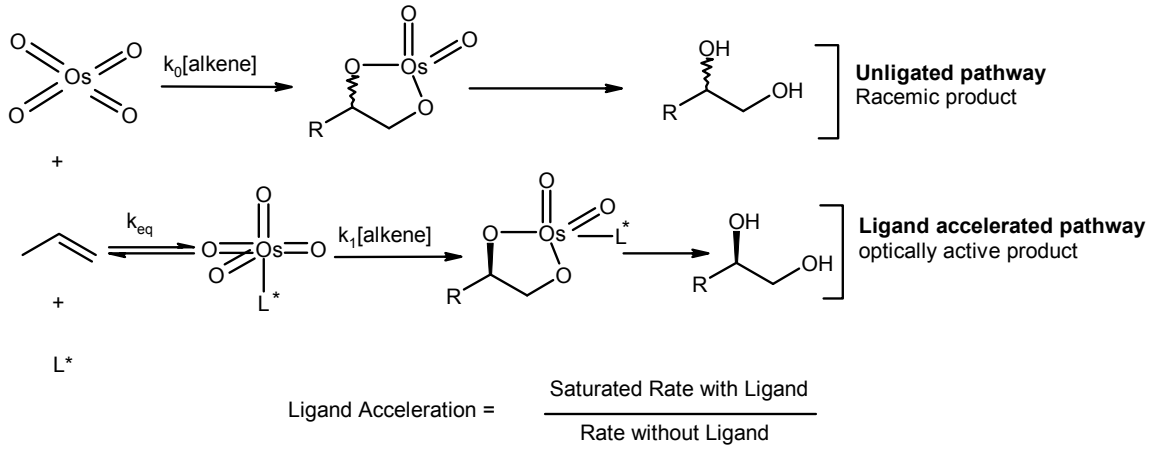
In the last two decades, many powerful asymmetric reactions have emerged as a result of the growing need to develop efficient and practical syntheses of biologically active compounds. Catalytic asymmetric reactions provide an especially practical entry into the chiral world due to their economical use of asymmetric inducing agents.[22] Especially useful is the carbon-heteroatom bond forming reaction, since the resulting functionality can be readily manipulated to produce many important classes of compounds. It is not surprising, therefore, that the oxidative addition of heteroatoms to olefins has been a fruitful area in recent years (**Scheme 8**).



Scheme 8. Transition metal mediated suprafacial 1,2-difunctionalization of olefins.

A number of transition metal-mediated methods for the epoxidation,[23] oxidative cyclization,[24] halohydrin formation,[25] dihydroxylation[26] and aminohydroxylation[27] have emerged. A common feature of most of these processes is the phenomenon of *ligand acceleration*,[28] wherein a metal catalyzed process turns over faster in the presence of a coordinating ligand (**Scheme 9**). This causes the reaction to be funneled through the ligated pathway with the additional consequence that the ligand may leave its 'imprint' on

the selectivity determining step. Hence, the ligand can influence the chemo-, regio-, and stereoselectivity of the reaction in a profound way.



Scheme 9. Ligand accelerated catalysis-dihydroxylation of olefins.[28]

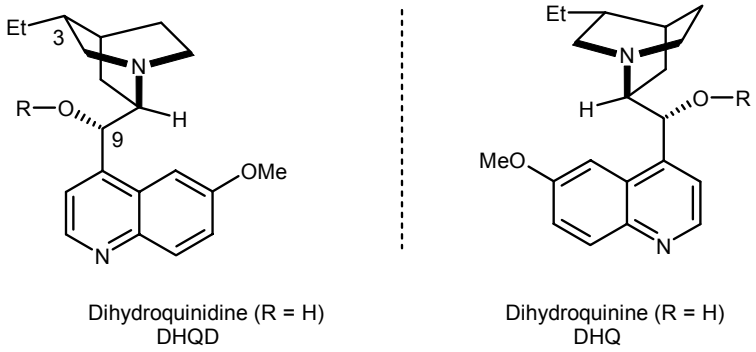
The osmium tetroxide-catalyzed asymmetric dihydroxylation (AD) of olefins, embedding two hydroxyl groups in a hydrocarbon framework is perhaps one of the most reliable and selective transformations in organic chemistry. In his pioneering work on the stoichiometric reaction of OsO_4 with olefins, Criegee[29] showed that pyridine accelerated the reaction considerably. However, cost considerations made the stoichiometric osmylation uneconomical. Not surprisingly, catalytic variants of the reaction, which employ relatively inexpensive reagents for the re-oxidation of the osmium (VI) glycolate products, greatly enhance its synthetic utility.[26b] Inorganic co-oxidants such as sodium or potassium chlorate[30a] or hydrogen peroxide,[30b,c] were among the first to be introduced, but in some cases diminished yields resulted due to over-oxidation. Much better results were obtained with alkaline *t*-BuOOH, introduced by Sharpless and Akashi,[31] or *N*-methylmorpholine *N*-oxide (NMO) (Upjohn Process).[32] Tsuji *et al*.[33] demonstrated that $K_3Fe(CN)_6$ in the presence of K_2CO_3 provides a powerful system for the osmium-catalyzed dihydroxylation of olefins.

Initial efforts by Sharpless and Hentges to induce enantioselectivity in the osmylation with chiral pyridine derivatives failed due to the low affinity of these ligands for OsO_4.[34] It was found that the binding constant of a ligand is extremely sensitive to the steric hindrance near the reacting center. Consequently, quinuclidine derivatives were used instead of

pyridines for further investigations due to their intrinsically higher affinity for OsO_4.[35] Moderate to good enantiomeric excess using acetate esters of cinchona alkaloids as chiral ligands was obtained.[34]

Apart from the cinchona alkaloid catalyzed AD, there are a number of methods employing chiral monodentate[36] and bidentate diamine[37] ligands. Despite the good to excellent enantioselectivities that can be obtained with diamine ligands, a serious drawback results from their bidentate nature, that they form very stable chelate complexes with Os (VI) glycolate products and as a consequence prevent *in situ* recycling of the Os and the ligand. Thus, all the reactions involving bidentate ligands are stoichiometric in both OsO_4 and the chiral ligand[37] (**Figure 4**).

Cinchona Alkaloid Ligands for AD under Catalytic Conditions



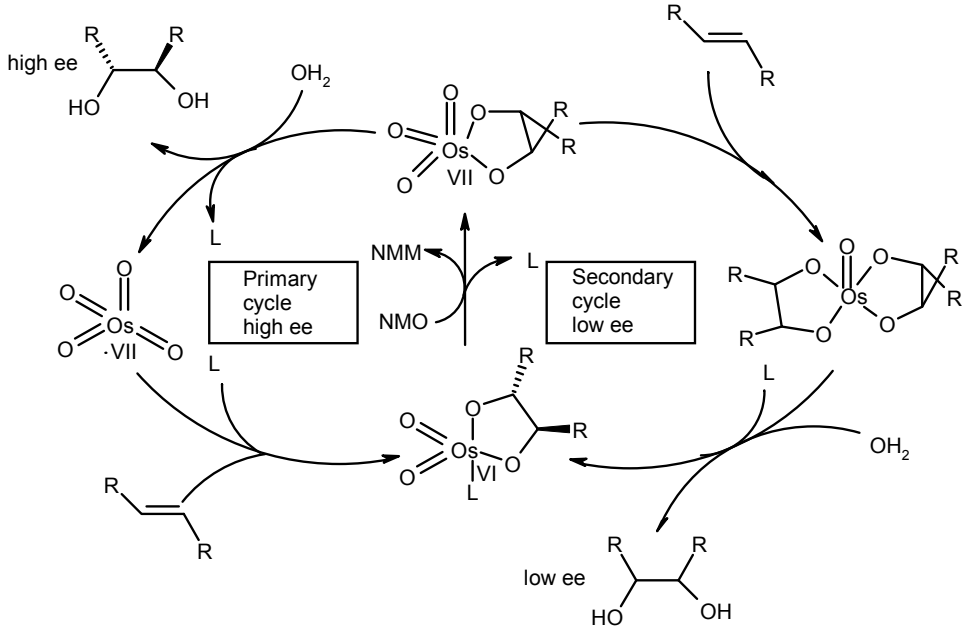
Dihydroquinidine (R = H)
DHQD

Dihydroquinine (R = H)
DHQ

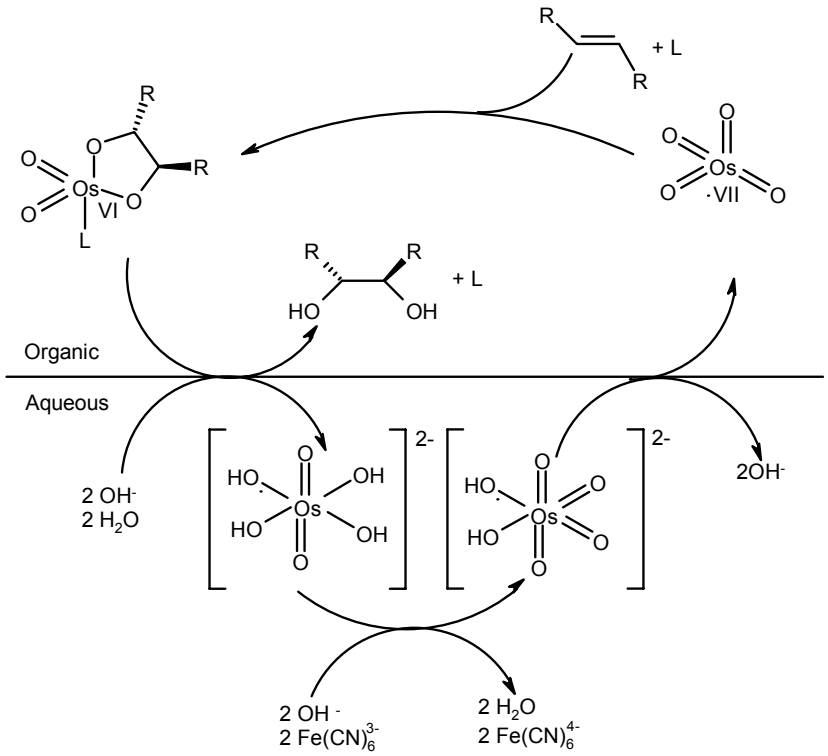
Figure 4. Ligands for AD reaction.

Initially, the asymmetric dihydroxylation using the derivatives of cinchona alkaloids was performed under stoichiometric conditions, but in 1987 Marko and Sharpless[38] found that the process became catalytic when NMO was employed as the co-oxidant. However, the enantiomeric excess of the diol products obtained under these catalytic conditions was initially lower than that produced by the *stoichiometric* reaction. The origin of this discrepancy was found to be the presence of a second catalytic cycle,[39] (**Scheme 10**) which exhibited only low or no enantioselectivity. Wai[39] discovered a partial remedy in slow addition of the olefin. Kwong[40] found that the participation of second catalytic cycle can be virtually eliminated by performing the reaction under two-phase conditions with

$K_3Fe(CN)_6$ as the stoichiometric re-oxidant. Under these conditions there is no oxidant other than OsO_4 in the organic layer, in contrast to the homogeneous NMO conditions.



Scheme 10. Two catalytic cycle for the AD reaction using NMO as the Co-oxidant



Scheme 11. Catalytic cycle of the AD reaction with $K_3Fe(CN)_6$ as the co-oxidant

Since the actual osmylation takes place in this layer, the resulting osmium (VI) monoglycolate ester undergoes hydrolysis, releasing the diol and the ligand to the organic layer and Os (VI) to the aqueous layer before its regeneration can occur, and consequently entry of the osmium glycolate into the second cycle is prevented (**Scheme 11**).

Sharpless *et al*.[41] found that the hydrolysis of the osmium (VI) glycolate product could be accelerated considerably by using $MeSO_2NH_2$. The reaction time can be as much as 50 times shorter in the presence of this additive. This allows high catalytic turnover even with sterically encumbered substrates, and tetra substituted olefins are now within the scope of the reaction. Due to this "sulfonamide effect", most AD reactions can be carried out at 0°C rather than at room temperature, which may have beneficial influence on the selectivity.[42] For terminal olefins, $MeSO_2NH_2$ is not recommended. Surprisingly, terminal olefins actually react slower in the presence of $MeSO_2NH_2$. However this weak inhibitory effect is noticeable only if very small amount of OsO_4 (0.2 mol%) is employed.

The discovery of ligands with two independent cinchona alkaloid units by Hartung[41] (phthalazine core) and Crispino[43] (diphenylpyrimidine core) attached to a heterocyclic spacer, has led to a considerable increase in both the enantioselectivity and the scope of the reaction (**Figure 5**).

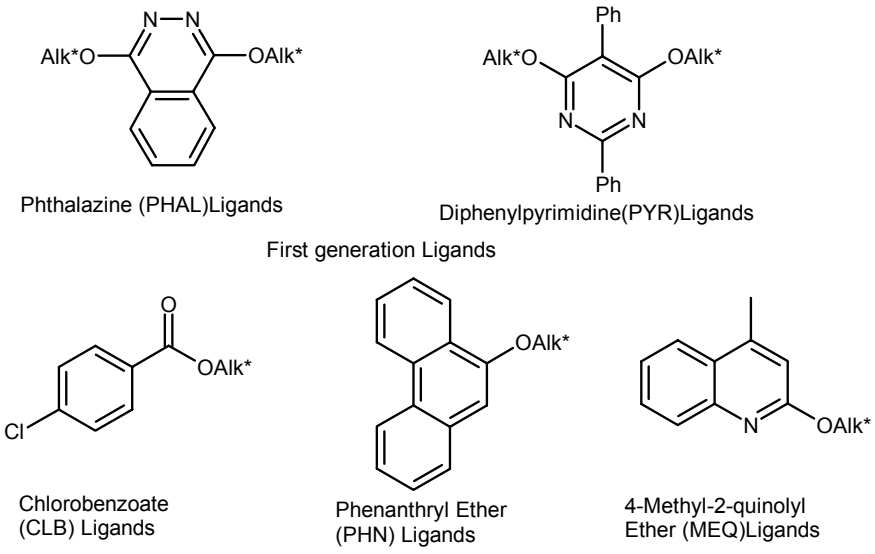
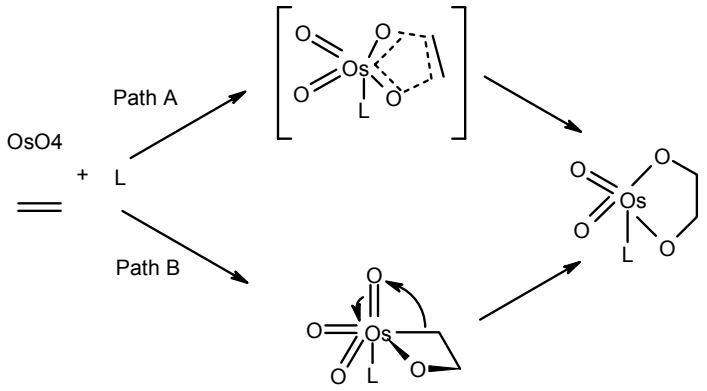


Figure 5. The latest generation of "dimeric" PHAL and PYR ligands and their predecessors (Alk* = DHQD or DHQ, see Fig. 4)

1.2.2. The Mechanism of Asymmetric Dihydroxylation (AD)

The osmium-catalyzed dihydroxylation reaction has been the center of extensive mechanistic investigations and two different mechanisms have been suggested. Boseken[44a] and Criegee[29] originally proposed a concerted [3+2] pathway, (**Scheme 12**, **Path A**) while Sharpless *et al*.[44b] and Jorgensen *et al*.[44c] suggested a stepwise reaction which is initiated by a [2+2] like addition of the olefin across an Os=O bond (**Path B**), followed by rearrangement of the resulting osmaoxetane intermediate to the glycolate product.



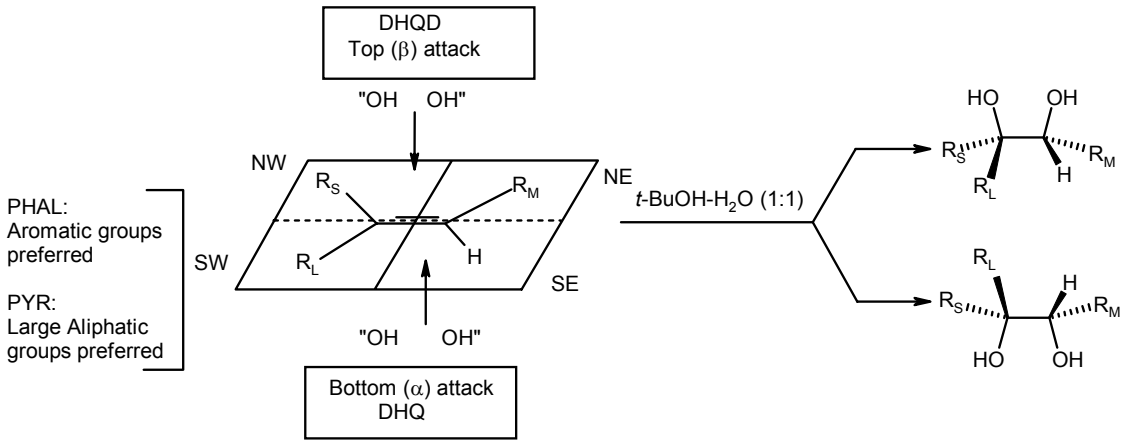
Scheme 12. Schematic presentation of the corrected [3+2] mechanism[44a] (Path A) and the stepwise osmaoxetane mechanism (Path B).[44b,c]

The recent observation of a nonlinear Erying relationship between enantiomeric excess and temperature is in consistent with Criegee's one-step [3+2] mechanism, but it can be explained by a reaction pathway with at least two selectivity determining steps which are weighed differently according to temperatures owing to their different activation parameters, ΔH and ΔS. Hence, this observation suggests that the stepwise [2+2]-like mechanism is operative. High level *ab initio* calculations have indeed shown that osmaoxetanes are energetically accessible minima on the potential energy surface.[45]

1.2.3 Empirical rules for predicting the face selectivity

Despite the mechanistic investigations, the face selectivity of the dihydroxylation can reliably be predicted using an empirical 'mnemonic device' (**Scheme 13**).[46] The plane of the olefin is divided into the four quadrants according to a simple set of rules. The SE quadrant is sterically inaccessible and, with few exceptions, no substituent other than

hydrogen can be placed here. The NW quadrant, lying diagonally across from the SE quadrant, is slightly more open and the NE quadrant appears to be quite spacious. The SW quadrant is special in that its preferences are ligand dependent. Even though this SW quadrant normally accepts the largest group, especially in the case of PYR ligands, it is especially attractive for aromatic groups in the case of PHAL ligands.[46c] An olefin which is placed into this olefin according to the above constraints receives the two OH groups from above, i.e. from the β-face, in the case of DHQD derived ligands and from the bottom, i.e. from the α-face, in the case of DHQ derivatives (**Scheme 13**).



Scheme 13. The mnemonic device for predicting the face selectivity

1.2.4 Reaction Conditions

The catalytic asymmetric dihydroxylation is performed in a 1:1 mixture of water and *t*-BuOH and the olefin concentration is usually 0.1 M.[41] The key reagents are 3 equivalents of $K_3Fe(CN)_6$ as the re-oxidant, 0.2-0.4 mol% osmium, 1 mol% of ligand, 3 equivalents of K_2CO_3 and 1 equivalent of $CH_3SO_2NH_2$. Additionally, the ligand can be recovered especially when large scale reactions are carried out. For PHAL ligand, the combined organic layers are extracted with 3% aq. H_2SO_4 satuarated with K_2SO_4 (ca. 40 mL/1g of ligand). The ligand enters the aqueous phase as the hydrogen sulphate salt and the solution can be reused directly for the subsequent AD reaction without further purification. However, the amount of K_2CO_3 in the subsequent reaction should be increased in order to neutralize excess H_2SO_4 and also to release the ligand salt as its free base, and the volume of aqueous ligand solution added to the reaction mixture.

1.2.5 The cinchona alkaloid ligands and their substrate preferences

Phthalazine (PHAL) ligands

Due to the ready availability of second generation ligands i.e. PHAL[47] (Phthalazine) ligands are widely used and this ligand class reacts especially when aromatic groups are present, and remarkably high enantioselectivities were observed when the aromatic substituents appear in certain optimal locations[48] like in *trans*-stilbene for which the enantioselectivity is as high as 99.8%.[49] However, PHAL ligands give inferior results with aliphatic olefins, especially if they are branched near the double bond or if they have very small substituents.

Anthraquinone (AQN) ligands

The anthraquinone ligands are well suited for almost all olefins having aliphatic substituents[50] and diols derived from allyl halides or allyl alcohols can be obtained with satisfactory enantiomeric purity, thereby giving access to valuable chiral building blocks. The AQN derivatives are the ligands of choice for the AD reaction, except for olefins with aromatic or sterically demanding substituents.

Pyrimidine (PYR) ligands

The pyrimidine ligands are the ligands of choice for olefins with sterically demanding substituents.[51]

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

These ligands give improved enantioselectivities for almost all olefins except for terminal alkyl olefins which are better served by the AQN or PRY ligands.[52] The DPP ligand is normally slightly superior to the DP-PHAL ligand. The DPP derivatives are the optimal ligands for aromatic olefins and for certain *cis*-1,2-disubstituted olefins.

Indoline (IND) ligands

Cis-1,2-disubstituted olefins generally are poor substrates for the AD reaction and the IND derivatives are normally the ligands of choice.[53] However, in certain cases better results are obtained with the new second generation ligands.[54]

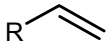
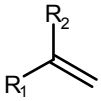
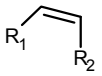
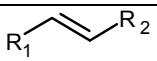
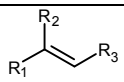
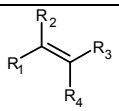
Olefin Class						
Preferred Ligands	<u>R=Aromatic</u> DPP, PHAL <u>R=Aliphatic</u> AQN <u>R=Branched</u> PYR	<u>R_1, R_2 =Aromatic</u> DPP, PHAL <u>R_1, R_2 =Aliphatic</u> AQN <u>R_1, R_2 = Branched</u> PYR	<u>Acyclic</u> IND <u>Cyclic</u> PYR, DPP, AQN	<u>R_1, R_2 = Aromatic</u> DPP, PHAL <u>R_1, R_2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

Table 1. Recommended ligands for each olefin class

1.3 HYDROLYTIC KINETIC RESOLUTION (HKR)

1.3.1. Introduction

The Sharpless epoxidation reaction has the most profound impact for asymmetric catalytic reaction, providing general access to highly enantio-enriched epoxy alcohols.[55] The Sharpless asymmetric epoxidation is limited for only allylic alcohol systems. Despite the considerable advances in asymmetric catalytic synthesis of epoxides, no general methods have been identified for the direct preparation of highly enantio-enriched terminal epoxides, arguably the most valuable class of epoxides for organic synthesis.[56]

Recently Jacobsen discovered the (salen)Co complex **1** (Fig. 6) catalyzed efficient hydrolytic kinetic resolution (HKR) of a variety of terminal epoxides (**Scheme 14**).[57-59] Since its discovery in the year 1997, HKR has got tremendous application for the synthesis of variety of compounds of biological interest.[60] Our group has recently compiled all the literature reports pertaining to the HKR application and published it in the form of a review article.[61] 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.

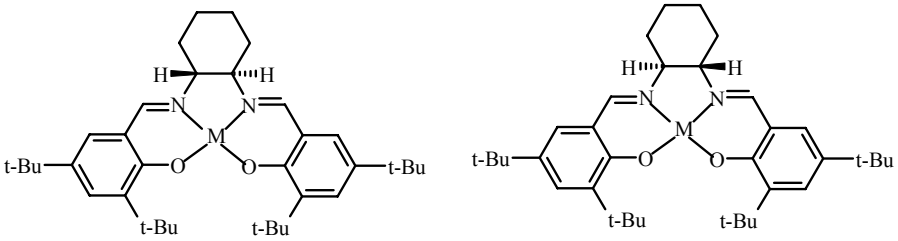
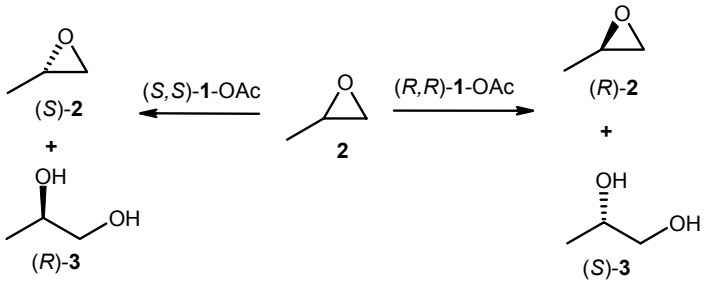


Figure 6. Jacobsen catalyst.

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

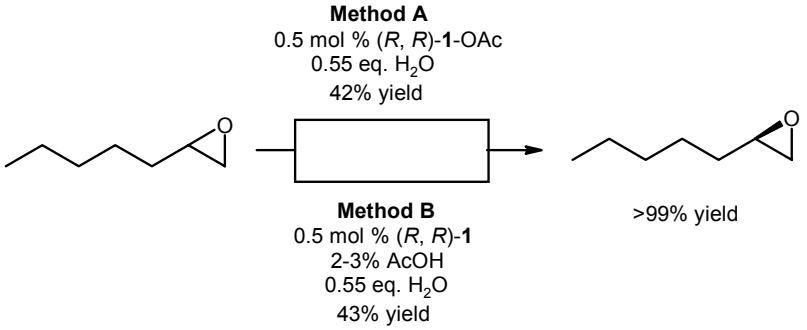


Scheme 14. Hydrolytic kinetic resolution reaction

1.3.2 Preparation of Catalyst and General Experimental Considerations

Both enantiomers of the (salen)CoII complex **1** are available commercially on research or commercial scale, or they can be prepared from the commercially available ligands using $Co(OAc)_2$. The Co(II) complex **1** (**Figure 6**) is catalytically inactive, however, and it must be subjected to one-electron oxidation to produce a (salen)CoIIIX complex (X) anionic ligand) prior to the HKR. This may be done conveniently by aerobic oxidation in the presence of a mild Brönsted acid. Water alone was found not to mediate the oxidation reaction, but a screen of additives revealed that acetic acid was effective and that the corresponding Co(III) precatalyst **1**.OAc (**Figure 6**) is convenient for use in HKR reactions both in terms of its preparation and reactivity. Two useful methods for the generation of complex **1**.OAc have been developed (**Scheme 15**). Method A involves isolation of **1**.OAc as a crude solid prior to the HKR. The Co(II) complex **1** is dissolved in toluene to generate a ca. 1 M solution, and acetic acid (2 equiv) is added. The resulting solution is stirred open to air at room temperature for 30 min, during which time the color of the mixture changes from orange to dark brown. All volatile materials are removed in vacuo, affording **1**.OAc as a brown solid residue that can be used without further purification. Method B involves in situ generation of **1**.OAc under HKR conditions by suspension of the Co(II) complex **1** in epoxide or epoxide/solvent and addition of HOAc under an aerobic atmosphere. Catalyst obtained by both methods was examined for each of the epoxides described in this study. For certain substrates such as 1-hexene oxide, catalyst prepared by either method leads to essentially identical results. In these situations, in situ catalyst generation (method B) is preferable since the procedure avoids an extra solvent removal step. On the other hand, catalyst prepared by method A was found to be more effective with less reactive substrates (vide infra) and was applicable to all substrates

examined. Therefore, if HKR did not afford epoxide in >99% ee with catalyst prepared by method B after optimization of solvent and catalyst loading, then catalyst prepared by method A was employed.



Scheme 15.

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

[(*R*,*R*)-*N*,*N*'-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminato(2-)]cobalt(II) ((*R*,*R*)-1). A solution of cobalt(II) acetate tetrahydrate (5.98 g, 24.0 mmol) in MeOH (80 mL was added to a solution of ligand [(*R,R*)-*N*,*N*'-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine] (10.9 g, 20.0 mmol) in CH_2Cl_2 (80 mL) *via* cannula under an atmosphere of N_2 with careful exclusion of air. A brick-red solid began to precipitate before addition was complete. The sides of the reaction flask were rinsed with MeOH (20 mL), and the mixture was allowed to stir for 15 min at room temperature and then 30 min

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

1.4 REFERENCES

1. Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.
2. (a) Wood, R. D.; Ganem, B. *Tetrahedron Lett.* **1982**, *23*, 707; (b) Erickson, T. J. *J. Org. Chem.* **1986**, *51*, 934.
3. (a) Parker, R. E.; Issacs, N. S. *Chem. Rev.* **1959**, *59*, 737; (b) Swern, D. *In Organic peroxides*, D. Swern, *Ed., Wiley-Interscience, New York,* **1971**, vol 2, ch. 5.; (c) Rao, A. S.; Paknikar, S. K.; Kirtane, J. G. *Tetrahedron* **1983**, *39*, 2323; (d) Sharpless, K. B.; Verhoeven, J. R. *Aldrichim*. *Acta* **1979**, *12*, 63.
4. Sharpless, K. B. Proceedings of the Robert A. *Welch Foundation Conferences on Chemical Reasearch XXVII*, Houston, Texas, **1983**, pp. 59.
5. (a) Chaumette, P.; Mimoun, H.; Sussine, L.; Fischer, J.; Mitschler, A. *J. Organomet. Chem.* **1983**, *250*, 291; (b) Mimoun, H.; Charpentier, R.; Mitschler, A.; Fische, J.; Weiss, R. *J. Am. Chem. Soc*. **1980**, *102*, 1047; (c) Mimoun, H. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 737 ; (d) Sharpless, K. B.; Woodard, S. S.; Finn, M. G. *Pure & Appl. Chem.* **1983**, *55*, 1823 ; (e) Woodard, S. S.; Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 106 ; (f) Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 106; (g) Mckee, B. H.; Kalantar, T. H.; Sharpless, K. B. *J. Org. Chem.* **1991**, *56*, 6966; (h) Narula, A. S. *Tetrahedron Lett.* **1982**, *23*, 5579.
6. Bach, R. D.; Wolber, G. J.; Coddens, B. A. *J. Am. Chem. Soc.* **1984**, *106*, 6098.
7. (a) Rossiter, B. E.; Sharpless, K. B. *The Scripps Research Institute*, La Jolla, CA, unpublished results ; (b) Puchot, C.; Samuel, O.; Dunach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc.* **1986**, *108*, 2353; (c) Woodward, S. S.; Ph.D Dissertation, *Stanford University*, California, **1981**; (d) Burgess, K.; Jennings, L. D. *J. Am. Chem. Soc.,* **1990**, *112*, 7434 ; (e) Carlier, P. R.; Sharpless, K. B. *J. Org. Chem.* **1989**, *54*, 4016.

8. (a) Williams, I. D.; Pedersen, S. F.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 1279; (b) Sharpless, K. B. *Chem. Scripta* **1987**, *27*, 521; (c) Pedersen, S. F.; Dewan, J. C.; Eckman, R. R.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 1279.
9. Katsuki, T.; Sharpless, K. B. *Kyushu University*, Unpublished results.
10. Masamune, S.; Choy, W.; Peterson, J. S.; Sita, L. R. *Angew. Chem. Int. Ed.* **1985**, *24*, 1.
11. (a) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922 ; (b) Gao, Y.; Hanson, R. M.; Kluder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
12. (a) Mitsunobu, O. *Synthesis* **1981**, 1 ; (b) Walba, D. M.; Vohra, R. T.; Clark, N. A.; Handschy, M. A.; Xue, J.; Parmar, D. S.; Langerwall, S. T. Skarp, K. *J. Am. Chem. Soc.* **1986**, *108*, 7424.
13. (a) Mori, K.; Ebata, T. *Tetrahedron Lett*. **1981**, *22*, 4281; (b) Mori, K.; Ebata, T. *Tetrahedron* **1986**, *42*, 3471.
14. (a) Takano, S.; Samizu, K.; Sigihara, T.; Ogasawara, K. *J. Chem. Soc., Chem*. *Commun*. **1989**, 1344; (b) Mhaskar, S. Y.; Lakshminarayana, G. *Tetrahedron Lett*. **1990**, *31*, 7227.
15. (a) Yadav, J. S.; Deshpande, P. K.; Sharma, G. V. M. *Pure & Appl. Chem.* **1990**, *62*, 1333; (b) Yadav, J. S.; Deshpande, P. K.; Sharma, G. V. M. *Tetrahedron* **1990**, *46*, 7033; (c) Marshall, J. A.; Luke, G. P. *Synlett* **1992**, 1007.
16. Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819.
17. Behrens, C. H.; Ko, S. Y.; Sharpless, K. B.; Walker, F. J. *J. Org. Chem.* **1985**, *50*, 5687.
18. (a) Behrens, C. H.; Sharpless, K. B. *Aldrichim*. *Acta* **1983**, 16, 67; (b) Katsuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.* **1982**, *47*, 1373; (c) Wrobel, J. E.; Ganem, B. *J. Org. Chem.* **1983**, *48*, 3761; (d) Behrens, C. H.; Ko, S. Y.; Sharpless, K. B.; Walker, F. J. *J. Org. Chem.* **1985**, *50*, 5687.
19. Lee, A. W. M.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Walker, F. J. *J. Am. Chem. Soc.* **1982**, *104*, 3515.
20. (a) Sharpless, K. B.; Behrens, C. H.; Katsuki, T.; Lee, A. W. M.; Martin, V. S.; Takatani, M.; Viti, S. M.; Walker, F. J.; Woodward, S. S. *Pure & Appl. Chem.* **1983**,

55, 589; (b) Wrobel, J. E.; Ganem, B. *J. Org. Chem.* **1983**, *48*, 3761; (c) Behrens, C. H.; Ko, S. Y.; Sharpless, K. B.; Walker, F. J. *J. Org. Chem.* **1985**, *50*, 5687; (d) Behrens, C. H.; Ko, S. Y.; Sharpless, K. B.; Walker, F. J. *J. Org. Chem.* **1983**, *50*, 5687. (e) Behrens, C. H.; Ko, S. Y.; Sharpless, K. B.; Walker, F. J. *J. Org. Chem.* **1985**, *50*, 5687; (f) Behrens, C. H.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 5696.

21. (a) Behrens, C. H.; Ko, S. Y.; Sharpless, K. B.; Walker, F. J. *J. Org. Chem.* **1985**, *50*, 5687; (b) Behrens, C. H.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 5696.
22. For recent reviews, see: *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, 1993.
23. (a) Katsuki, T.; Martin, V. S. *Org. React*. **1996**, *48*, 1; (b) Katsuki, T. *J. Mol. Catal. A: Chem*. **1996**, *113*, 87. For a recent review, see: Johnson, R. A.; Sharpless, K. B. *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, **1993**, pp. 101.
24. (a) McDonald, F. E.; Towne, T. B. *J. Org. Chem.* **1995***, 60*, 5750; (b) Kennedy, R. M.; Tang. S. *Tetrahedron Lett.* **1992***, 33*, 3729; (c) Tang, S.; Kennedy, R. M. *Tetrahedron Lett.* **1992***, 33*, 5299; (d) Tang, S.; Kennedy, R. M. *Tetrahedron Lett.* **1992***, 33*, 5303; (e) Boyce, R. S.; Kennedy, R. M. *Tetrahedron Lett*. **1994**, *35*, 5133.
25. Sharpless, K. B.; Teranishi, A. Y.; Backvall, J.-E. *J. Am. Chem. Soc*. **1977**, *99*, 3120.
26. (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev*. **1994**, *94*, 2483; (b) Schroder, M. *Chem*. *Rev*. **1980**, *80*, 187.
27. (a) Li, G.; Chang, H.-T.; Sharpless, K. B. *Angew*. *Chem*., *Int. Ed.* **1996**, *35*, 451; (b) Li, G.; Sharpless, K. B. *Acta Chem. Scand*. **1996**, *50*, 649; (c) Rudolph, J.; Sennhenn, P. C.; Vlaar, C. P.; Sharpless, K. B. *Angew*. *Chem*., *Int. Ed.* **1996**, *35*, 2810; (d) Li, G.; Angert, H. H.; Sharpless, K. B. *Angew*. *Chem*., Int. *Ed*. **1996**, *35*, 2813; (e) Angelaud, R.; Landais, Y.; Schenk, K. *Tetrahedron Lett*. **1997**, *38*, 1407.
28. Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1995**, *34*, 1059.
29. (a) Criegee, R. *Justus Liebigs Ann. Chem.* **1936***, 522*, 75; (b) Criegee, R. *Angew. Chem*. **1937***, 50,* 153; (c) Criegee, R. *Angew. Chem.* **1938**, *51*, 519; (d) Criegee, R.; Marchand, B.; Wannowias, H. *Justus Liebigs Ann*. *Chem*. **1942**, *550*, 99.
30. (a) Hofmann, K. A. *Chem. Ber*. **1912**, *45*, 3329; (b) Milas, N. A.; Sussman, S. *J. Am. Chem. Soc.* **1936***, 58,* 1302; (c) Milas, N. A.; Trepagnier, J. H.; Nolan, J. T., Jr.; Iliopulos, M. I. *J. Am. Chem. Soc*. **1959**, *81*, 4730.

31. Sharpless, K. B.; Akashi, K. *J. Am. Chem. Soc*. **1976**, *98*, 1986.
32. (a) Schneider, W. P.; McIntosh, A. V. US Patent 2,769,824 Nov. 6, 1956; (b) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett*. **1976**, 1973.
33. Minato, M.; Yamamoto, K.; Tsuji, J. *J. Org. Chem*. **1990**, *55*, 766.
34. Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980***, 102*, 4263.
35. (a) Cleare, M. J.; Hydes, P. C.; Griffith, W. P.; Wright, M. J. *J. Chem. Soc., Dalton Trans*. **1977**, 941; (b) Griffith, W. P.; Skapski, A. C.; Woode, K. A.; Wright, M. J. *Inorg. Chim. Acta.* **1978**, *31*, 413.
36. Oishi, T.; Hirama, M. *Tetrahedron Lett.* **1992***, 33*, 639.
37. (a) Johnson, R. A.; Sharpless, K. B. *Catalytic Asymmetric Dihydroxylation*. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, **1993**, pp. 227; (b) Lohray, B. B. *Tetrahedron: Asymmetry* **1992**, *3*, 1317; (c) Hanessian, S.; Meffre, P.; Girard, M.; Beaudoin, S.; Sanceau, J.-Y.; Bennani, Y. L. *J. Org. Chem*. **1993**, *58*, 1991; (d) Corey, E. J.; Jardine, P. D.; Virgil, S.; Yeun, P.-W.; Connell, R. D. *J. Am. Chem. Soc.* **1989***, 111*, 9243; (e) Tomioka, K.; Nakajima, M.; Koga, K. *J. Am. Chem. Soc.* **1987***, 109*, 6213; (f) Tomioka, K.; Nakajima, M.; Iitaka, Y.; Koga, K. *Tetrahedron Lett.* **1988***, 29*, 573; (g) Tomioka, K.; Nakajima, M.; Koga, K. *Tetrahedron Lett.* **1990***, 31*, 1741; (h) Nakajima, M. Tomioka, K.; Iitaka, Y.; Koga, K. *Tetrahedron Lett.* **1993***, 49*, 10793; (i) Fuji, K.; Tanaka, K.; Miyamoto, H. *Tetrahedron Lett.* **1992***, 33*, 4021; (j) Hirama, M.; Oishi, T.; Ito, S. *J. Chem. Soc., Chem. Commun.* **1989**, 665; (k) Oishi, T.; Hirama, M. *J. Org. Chem.* **1989***, 54*, 5834; (l) Yamada, T.; Narasaka, K. *Chem. Lett.* **1986**, 131; (m) Tokles, M.; Snyder, J. K. *Tetrahedron Lett*. **1986**, *27*, 3951; (n) Imada, Y.; Saito, T.; Kawakami, T.; Murahashi, S.-I. *Tetrahedron Lett.* **1992***, 33,* 5081.
38. Jacobsen, E. N.; Marko, I; Mungall, W. S.; Schroder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988***, 110*, 1968.
39. Wai, J. S. M.; Marko, I.; Svendsen, J. S.; Finn, M. G.; Jacobsen, E. N.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989***, 111*, 1123.
40. Kwong, H.-L.; Sorato, C.; Ogino, Y.; Chen, H.; Sharpless, K. B. *Tetrahedron Lett.* **1990***, 31*, 2999.

41. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768.
42. Gobel, T.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1993**, *32*, 1329.
43. Crispino, G. A.; Jeong, K.-S.; Kolb, H. C.; Wang, Z.-M.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785.
44. The [3+2] mechanism was originally proposed by Boseken: (a) Boseken, J. *Recl. Trav. Chim.* **1922**, *41*, 199. For the [2+2] mechanism, see: (b) Sharpless, K. B.; Teranishi, A. Y.; Backvall, J.-E. *J. Am. Chem. Soc.* **1977**, *99*, 3120; (c) Jorgensen, K. A.; Schiott, B. *Chem. Rev*. **1990**, *90*, 1483.
45. (a) Norrby, P.-O.; Kolb, H. C.; Sharpless, K. B. *Organometallics* **1994**, *13*, 344; (b) Veldkamp, A.; Frenking, G. *J. Am. Chem. Soc*. **1994**, *116*, 4937.
46. (a) Kolb, H. C.; Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 1278; (b) Sharpless, K. B.; Amberg, W; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768; (c) Vanhessche, K. P. M.; Sharpless, K. B. *J. Org. Chem.* **1996**, *61*, 7978.
47. Kolb, H. C.; Andersson, P. G.; Bennani, Y. L.; Crispino, G. A.; Jeong, K.-S.; Kwong, H.-L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 12226.
48. Becker, H.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **1996**, *35*, 448.
49. Crispino, G. A.; Jeong, K.-S.; Kolb, H. C.; Wang, Z.-M.; Xu, D.; Sharpless, K . B. *J. Org. Chem.* **1993**, *58*, 3785.
50. Becker, H.; King, S. B.; Taniguchi, M.; VanHessche, K. P. M.; Sharpless, K. B. *J. Org. Chem.* **1995**, *60*, 3940.
51. Wang, L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7568.
52. Wang, Z.-M.; Kakiuchi, K.; Sharpless, K. B. *J. Org. Chem*. **1994**, *59*, 6895.
53. (a) Baker, W.; Field, F.B. *J. Chem. Soc*. **1932**, 86 ; (b) Catlson, W. W.; Cretcher, L. H. *J. Am. Chem. Soc.* **1947**, *69*, 1952.
54. Gao. Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538.
55. (a) Katsuki, T. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Chapter 18.1; (b) Rossiter, B. E. in *Asymmetric Synthesis*, Vol. 5; Morrison, J. D., Ed.; Academic Press: New York, 1985;

Chapter 7; (c) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; Chapter 4.1; (d) Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1.

56. For the most enantioselective methods developed to date involving synthetic catalysts: (a) Palucki, M.; Pospisil, P. J.; Zhang, W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 9333; (b) Collman, J. P.; Wang, Z.; Straumanis, A.; Quelquejeu, M.; Rose, E. *J. Am. Chem. Soc.* **1999**, *121*, 460. For methods involving biocatalysts, see: (c) Botes, A. L.; Weijers, C. A. G. M.; Botes, P. J.; van Dyk, M. S. *Tetrahedron: Asymmetry* **1999**, *10*, 3327, and references therein; (d) Goswami, A.; Totleben, M. J.; Singh, A. K.; Patel, R. N. *Tetrahedron: Asymmetry* **1999**, *10*, 3167, and references therein.
57. (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936; (b) Furrow, M. E.; Schaus, S. E.; Jacobsen, E. N. *J. Org.Chem*. **1998**, *63*, 6776.
58. For earlier studies involving (salen) metal-catalyzed reactions of epoxides that served as a foundation for the discovery of the HKR, see: (a) Tekeichi, T.; Arihara, M.; Ishimori, M.; Tsuruta, T. *Tetrahedron* **1980**, *36*, 3391. (b) Maruyama, K.; Nakamura, T.; Nakamura, S.; Ogino, A.; Nishinaga, A. *React. Kinet. Catal. Lett.* **1991**, *45*, 165. (c) Larrow, J. F., Schaus, S. E., Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 7420.
59. The HKR is complementary to biocatalytic methods exploiting epoxide hydrolases. For a review, see: Archelas, A.; Furstoss, R. *Trends Biotechnol.* **1998**, *16*, 108.
60. (a) Liu, P.; Panek, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 1235; (b) Knölker, H.-J.; Baum, E.; Reddy, K. R. *Tetrahedron Lett.* **2000**, *41*, 1171; (c) Wroblewski, A. E.; Halajewska-Wosik, A. *Tetrahedron: Asymmetry* **2000**, *11*, 2053; (d) Liu, Z. Y.; Ji, J. X.; Li, B. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3519; (e) O'Neil, I. A.; Cleator, E.; Southern, J. M.; Hone, N.; Tapolczay, D. J. *Synlett* **2000**, 695; (f) Fürstner, A.; Thiel, O. R.; Ackermann, L. *Org. Lett.* **2001**, *3*, 449; (g) Chow, S.; Kitching, W. *Chem. Commun.* **2001**, 1040; (h) Rodriguez, A.; Nomen, M.; Spur, B. W.; Godfroid, J. J.; Lee, T. H. *Tetrahedron* **2001**, *57*, 25.
61. For review on Jacobsen's HKR, see; Kumar, P.; Naidu, S. V.; Gupta, P. *Tetrahedron* **2007**, *63*, 2745.

CHAPTER 2

ASYMMETRIC SYNTHESIS OF VICINAL DIOLS AND AMINO ALCOHOLS; (-)-GALANTINIC ACID & (−)-(3*S*,6*R*)-3,6-DIHYDROXY-10-METHYLUN-DECANOIC ACID

2.1 SECTION A

ENANTIOSELECTIVE SYNTHESIS OF (-)-GALANTINIC ACID

2.1.1. Introduction

(-)-Galantinic acid **1** is a component of the peptide antibiotic galantin I **2**, isolated from a culture broth of Bacillus pulvifaciens.[1] The original structure of galantin I **2** was assigned after the synthesis of its unusual constituent amino acids, galantinic acid **1** and galantinamic acid **4**. The originally proposed structure of (-)-galantinic acid **3** was later revised to **1** by Sakai and Ohfune[2] who also reported its first total synthesis (Fig. 1).[3] Galantinic acid has been a synthetic target of considerable interest due to its potent biological activity and unique structure with an array of functionalities.

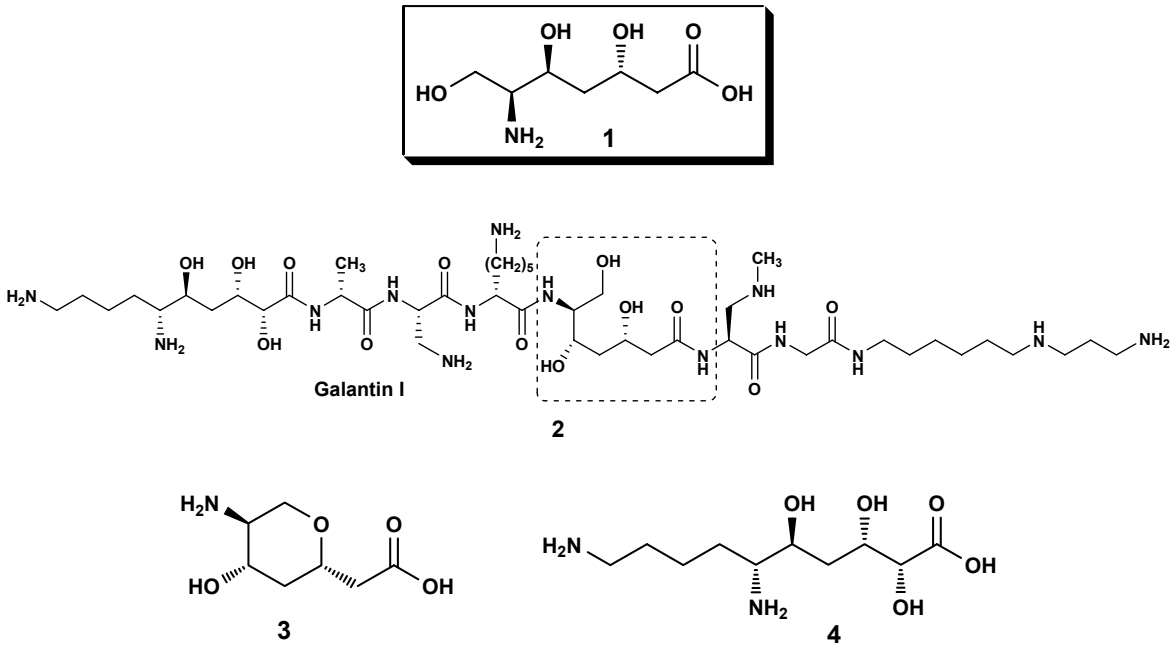


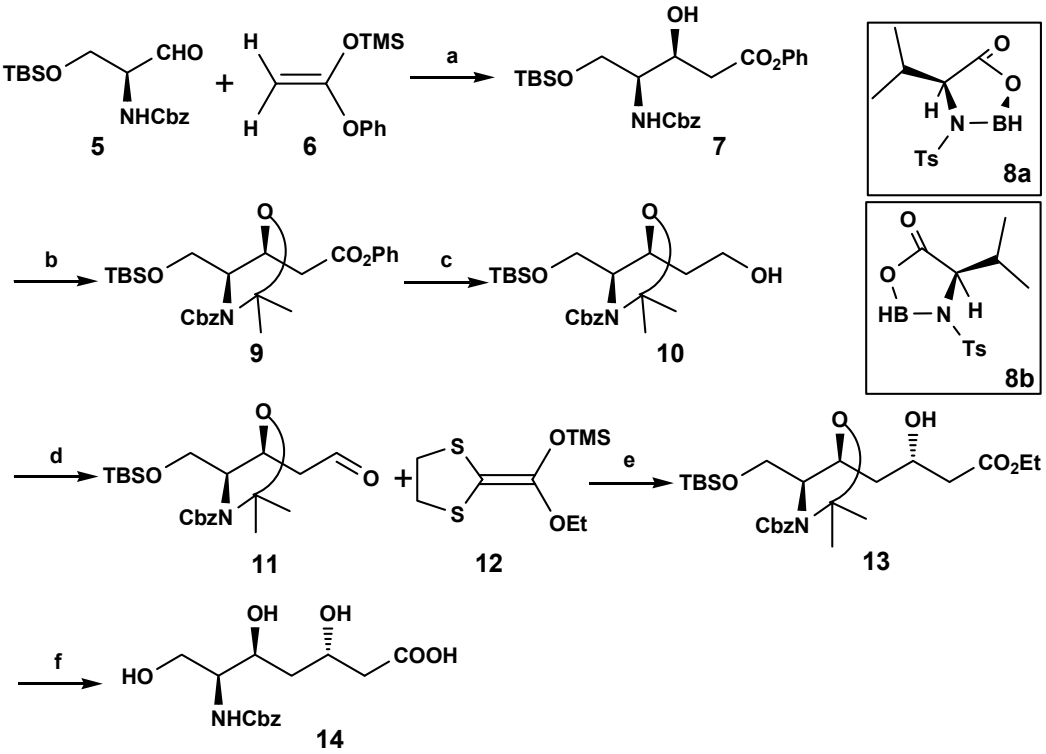
Figure 1.

2.1.2. Review of Literature

Various methods for the synthesis of (-)-Galantinic acid have been documented in the literature.[4] Most of these approaches employ chiral pool starting materials. Some of the recent syntheses of (-)-Galantinic acid **1** are described below.

Kiyooka, S. *et al* . (2000).[4c]

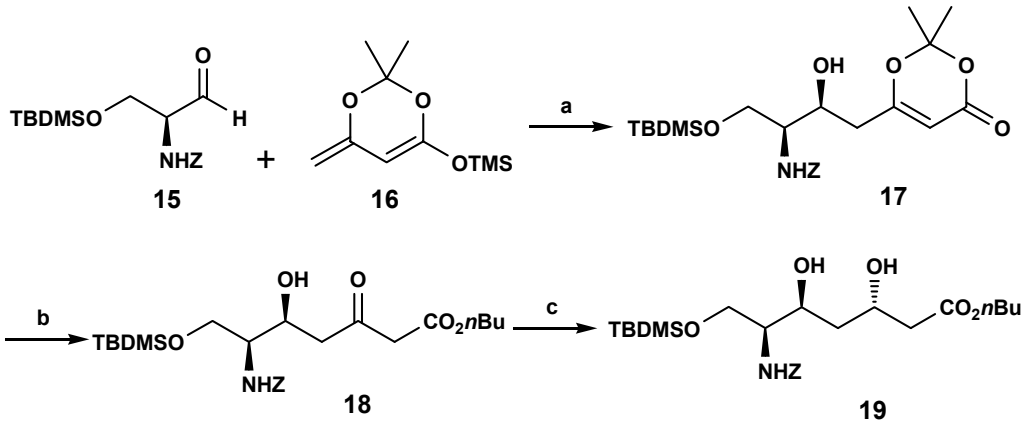
Syun-ichi Kiyooka and co-workers accomplished the synthesis of *N*-Cbz-galantinic acid **14** under promoter control on enantioselective acyclic stereoselection based on chiral oxazaborolidinone-promoted aldol reactions. The aldol reaction of **5** with silyl nucleophile **6** in the presence of (*S*)-**8a** furnished the desired *syn*-aldol product (*syn*-**7**) in a ratio of 10:1, which was converted into acetonide **9** followed by reduction with DIBAL-H to give the corresponding alcohol **10** in 94% yield. The second aldol reaction of aldehyde **11**, with silyl nucleophile **12**, in the presence of (*R*)-**8b** afforded the desired 1,3-*anti* diol as a single isomer in 76% yield. Desulfurization with *n*-Bu_3SnH and AIBN quantitatively gave *anti*-aldol product **13**. The protected groups of **13** were cleaved upon treatment with 80% AcOH at room temperature for 2 days to give *N*-Cbz-galantinic acid **14** in 75% yield (Scheme 1).



Scheme 1. *Reagents and conditions*: (a) **8a**, CH_2Cl_2, -78 ^oC, 2 h, 74%; (b) 2,2-DMP, acetone, CSA, 68%; (c) DIBAL-H, CH_2Cl_2, -78 ^oC, 2 h, 94%; (d) Swern oxidation, 88%; (e) i) **8b**, $C_2H_5N_2$, -78 ^oC, 15 h, 76%; ii) *n*-BuSnH, AIBN, 95%; (f) 80% AcOH, rt, 2 d, 75%.

Campagne, J.-M. *et al* . (2001).[4d]

Jean-Marc Campagne and co-workers reported the synthesis of *N-(Z)*-galantinic butyl ester **19** using two highly diastereoselective reactions, namely a vinylogous Mukaiyama reaction and a 1,3-hydroxy directed Evans reduction. The reaction of known serinal aldehyde **15** with dienolate **16**, in the presence of 10% of $Eu(fod)_3$ led to the formation of the vinylogous aldol product **17** with a good (9:1) diastereoselectivity. The dioxinone ring was opened-up by refluxing **17** in butanol at 120°C, to give the keto-alcohol **18** which on reduction under Evans conditions led to galantinic butyl ester **19** in 56% yield (over two steps) and 98:2 diastereoselectivity (Scheme 2).

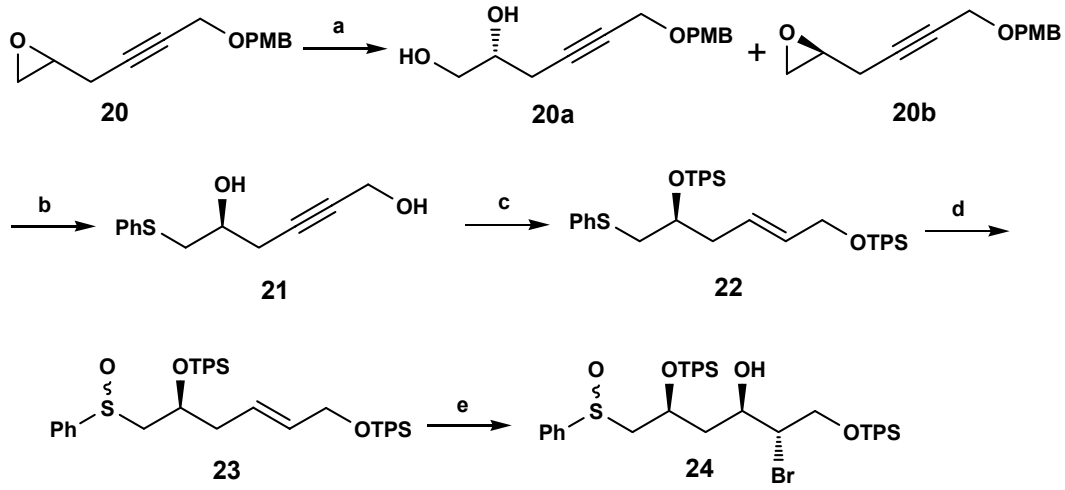


Scheme 2. *Reagents and conditions*: (a) 10% $Eu(fod)_3$, DCM, 0 ^oC to room temperature, 60%; (b) n-butanol, reflux; (c) $NaHB(OAc)_3$, CH_3CN/AcOH, 56% (two steps).

Raghavan, S. *et al* . (2003).[5]

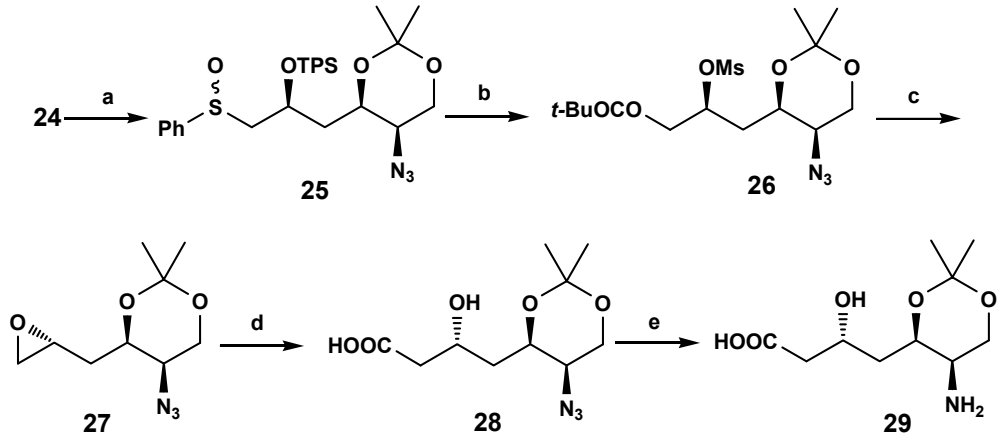
Sadagopan Raghavan and co-workers reported the stereoselective synthesis of protected (-)-galantinic **30** acid using a sulfinyl moiety as an internal nucleophile through 1,3-asymmetric induction. Triethylamine-promoted opening of epoxide **20b** by thiophenol

afforded the homopropargyl alcohol **21** which on *p*-methoxybenzyl group deprotection and subsequent reduction of the resulting propargyl alcohol with $LiAlH_4$ and silyl ether protection afforded **22**. Oxidation of sulfide **22** with $NaIO_4$ yielded an equimolar, inseparable mixture of sulfoxides **23** which on treatment with *N*-bromosuccinimide (NBS) furnished bromohydrin **24.**



Scheme 3. *Reagents and conditions*: (a) (*S*,*S*)-Salen.Co(III)OAc catalyst, H_2O, THF, rt, 42.5% of **20a** and 49% of **20b**; (b) i) PhSH, Et_3N, CH_3CN, rt, 85%; (c) i) DDQ, CH_2Cl_2/H_2O (19:1), rt, 80%; ii) $LiAlH_4$, THF, 60 °C, 78%; iii) TBDPS-Cl, Imd., CH_2Cl_2, rt, 96%; (d) $NaIO_4$, THF, MeOH, H_2O, rt, 85%; (e) NBS, toluene, H_2O, rt, 75%;

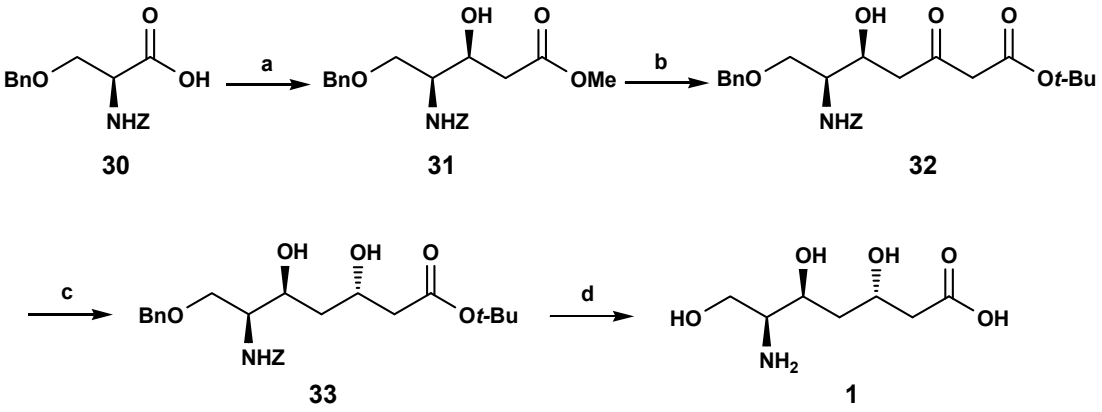
Selective deprotection of the primary silyl ether in **24,** acetonide protection and displacement of the bromide by an azide afforded acetonide **25**. The compound **25** was subjected to Pummerer rearrangement and reduction of the resulting aldehyde to alcohol and TPS deprotection afforded diol, which on selective pivalation and mesylation furnished **26**. Hydrolysis of the pivalate ester led to concomitant displacement of the mesyl group to afford epoxide **27** with an inversion of configuration. The epoxide was opened with sodium cyanide, using Sharpless protocol to yield the β-hydroxy cyano compound which on hydrolysis with aq. alkaline hydrogen peroxide yielded the β-hydroxy acid **28** which on reduction with 5% Pd/C under an atmosphere of hydrogen afforded the protected galantinic acid derivative **29**.



Scheme 4. *Reagents and conditions*: (a) i) CSA, CH_2Cl_2/MeOH (1:1), rt, 78%; ii) 2.2-DMP, acetone, CSA, rt, 90%; iii) NaN_3, DMSO, 80 °C, 75%; (b) i) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, rt, ii) aq. $NaHCO_3$, $NaBH_4$, 0 °C, 70%; iii) *n*-Bu_4NF, AcOH, THF, rt, 70%; iv) pivaloyl-Cl, Et_3N, DMAP, CH_2Cl_2, 0 °C; v) MsCl, Et_3N, CH_2Cl_2, 0 °C; (c) 0.2 N NaOH, MeOH, 0 °C to rt, 65% overall yield for 3 steps; (d) i) NaCN, Ti(O*i*Pr)$_4$, *n*-Bu_4NI, DMSO, 70 °C, 80%; ii) 3 N NaOH, 30% H_2O_2, 70 °C, 1 h, 90 °C, 1 h, 70%; (e) H_2, Pd/C, MeOH, 80%.

Gademann, K. *et al* . (2006).[6]

Karl Gademann and co-workers accomplished the synthesis of (–)-galantinic acid **1** *via* Heathcock–Claisen condensation, Evans reduction and deprotection in 10% overall yield from protected serine. The synthesis started from the β-hydroxy-γ-amino acid **31**, which was prepared from protected serine **30** (Scheme 5). A Claisen condensation using the procedure of Heathcock gave the hydroxyketoester **32** in 75% yield. The keto ester **32** was reduced by directed hydride delivery following the method of Evans to give the *anti* 3,5-diol **33** in stereoselectivity (>95:5). The diol **33** was then deprotected first by hydrogenolysis and short treatment with trifluoroacetic acid to afford a sample of (–)-galantinic acid **1**.



Scheme 5. *Reagents and conditions*: (a) i) carbonyldiimidazole, KO_2CCH_2COOMe, $MgCl_2$, 74%; ii) $NaBH_4$, Et_2O, (90%, dr, 1.2:1), 42% after recryst.; (b) $C_6H_{11}O_2Li$ (6eq.), THF, 75%; (c) $Me_4NB(OAc)_3H$, MeCN, AcOH, 81%; (d) i) H_2, Pd/C, MeOH, AcOH; ii) CH_2Cl_2, CF_3CO_2H, 50 %.

2.1.3 Present work:

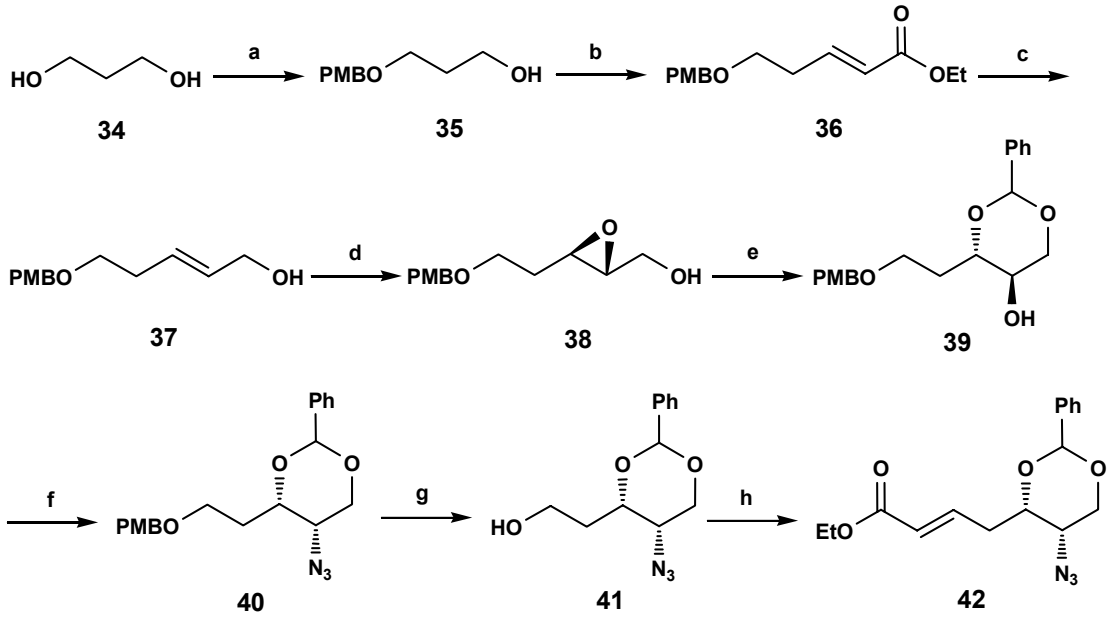
Objective:

Various methods for the synthesis of (-)-galantinic acid **1** have been documented in the literature. Most of these approaches employ chiral pool starting materials. As part of our research programme aimed at developing enatioselective synthesis of naturally occurring amino alcohols[7] and lactones,[8] we became interested to develop a new and highly enantioselective synthesis of (-)-galantinic acid employing Sharpless asymmetric epoxidation and dihydroxylation procedures as the source of chirality.

2.1.4. Results and Discussion:

The synthesis of (-)-galantinic acid **1** started from commercially available 1,3-propanediol **34** as illustrated in Scheme 6. The mono hydroxyl protection of **34** with *p*-methoxybenzyl chloride in the presence of NaH gave **35** in 86% yield. Compound **35** was oxidized to the aldehyde and subsequently treated with (ethoxycarbonylmethylene) triphenylphosphorane in THF at room temperature to furnish the Wittig product **36** in 81% yield. The IR spectrum of **36** showed the ester carbonyl absorption at 1718 cm^{-1} and olefin C=C stretching at 1654 cm^{-1}. The ^1H NMR spectrum gave olefin protons at δ 5.91 (doublet, one

proton) with the coupling constant J = 15.66 Hz and at δ 6.96-7.02 (multiplet, one proton) indicating *trans*-olefin. The reduction of olefinic ester **36** to the corresponding allylic alcohol **37** was achieved with DIBAL-H at 0 ^{o}C-rt in excellent yield. Compound **37** was then treated with titanium tetraisopropoxide and *t*-butyl hydroperoxide in the presence of (-)-DIPT under the Sharpless asymmetric epoxidation reaction conditions[9] to give the epoxide **38** in good

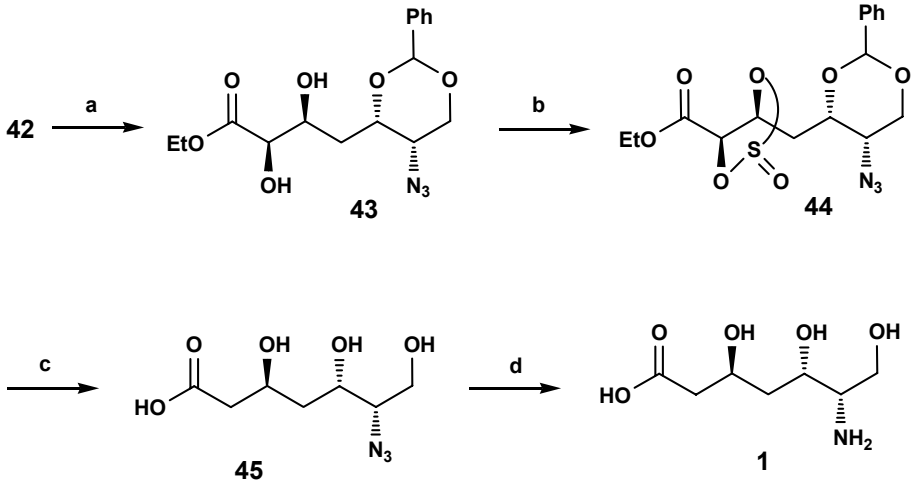


Scheme 6. *Reagents and conditions*: (a) *p*-$CH_3OC_6H_5CH_2Cl$, NaH, dry DMF, rt, 6 h, 86%; (b) (i) PCC, anhyd. CH_3COONa, dry CH_2Cl_2, 0 ^{o}C- rt, 6 h; (ii) Ph_3P=CHCOOEt, dry THF, rt, 24 h, 81%; (c) DIBAL-H, dry CH_2Cl_2, 0 ^{o}C-rt, 2 h, 92%; (d) $Ti(OPr^{i})_4$, (-)-DIPT, *t*-BuOOH, dry CH_2Cl_2, -25 ^{o}C, 36 h, 72%; (e) (i) 60% DMSO, $HClO_4$, 0 ^{o}C, 3 h, 89%; (ii) $C_6H_5CH(OMe)_2$, *p*-TSA (cat.), DMAP (cat.), dry CH_2Cl_2, rt, overnight, 65%; (f) (i) MsCl, Et_3N, dry CH_2Cl_2, 5 h, 83%; (ii) NaN_3, dry DMF, 78%; (g) DDQ, CH_2Cl_2, H_2O, rt, 3 h, 91%; (h) (i) PCC, anhyd. CH_3COONa, dry CH_2Cl_2, rt, 6 h; (ii) Ph_3P=CHCOOEt, dry THF, rt, 24 h, 83%.

yield. The *trans*-selective opening of the epoxide **38**[10] was accomplished using perchloric acid and 60% DMSO to afford the triol, which was subsequently protected with benzaldehyde dimethyl acetal in the presence of a catalytic amount of *p*-TSA and DMAP to afford a mixture of 1,3- and 1,2-benzylidene derivatives in a 9:1 ratio. The desired major

1,3-benzylidene compound **39** was separated by silica gel column chromatography. Compound **39** showed acetal proton at δ 5.46 (singlet) and aromatic protons appeared at δ 7.27 (t, J = 5.68, 3H) and 7.34-7.38 (m, 2H) in the ^{1}H NMR spectrum.

At this stage an attempt to convert the free hydroxyl group of **39** to azide under Mitsunobu conditions was not very satisfactory. Accordingly the free hydroxyl group of **39** was converted into *O*-mesylate, which on nucleophilic displacement with sodium azide in dry DMF afforded compound **40** in 78% yield. Compound **40** showed absence of hydroxyl absorption in the IR spectrum and strong azide absorption at 2104 cm^{-1}. The *p*-methoxy benzyl protecting group was cleaved by treating **40** with DDQ to furnish the alcohol **41** in excellent yield. The PCC oxidation of **41** to the aldehyde and subsequent reaction with (ethoxycarbonylmethylene)triphenylphosphorane gave the olefin **42** in 83% yield. The IR -



Scheme 7. *Reagents and conditions*: (a) $(DHQ)_2PHAL$, OsO_4, $CH_3SO_2NH_2$, K_3FeCN_6, K_2CO_3, *t*-BuOH/H_2O (1:1), 24 h, 0 ^oC, 87%; (b) $SOCl_2$, Et_3N, 30 min, 89%; (c) (i) $NaBH_4$, dry THF, MeOH; (ii) 4N H_2SO_4, 2 h, rt, 77%; (d) 10% Pd/C, H_2, MeOH, rt, 88%.

spectrum of **42** showed the ester carbonyl absorption at 1724 cm^{-1} and olefin C=C stretching at 1656 cm^{-1}. The ^{1}H NMR spectrum gave olefin protons at δ 6.01 (doublet) with the coupling constant J = 15.89 Hz and δ 6.99-7.07 (multiplet) indicating *trans*-olefin. The dihydroxylation of olefin **42** with osmium tetroxide and $K_3Fe(CN)_6$ as co-oxidant in the presence of $(DHQ)_2PHAL$ as the chiral ligand under the Sharpless asymmetric dihydroxylation conditions[11] furnished the diol **43** in excellent yield. The diastereomeric excess was found to be 91% using ^{13}C NMR analysis. The IR spectrum of **92** showed

hydroxyl absorption at 3561 cm^{-1}, ester carbonyl at 1716 cm^{-1} and azide absorption at 2112 cm^{-1}. The ^1H NMR indicated absence of olefin protons. The diol **43** was then treated with thionyl chloride and Et_3N to give the cyclic sulfite **44** in 89% yield.

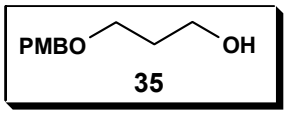
The essential feature of the synthetic strategy shown in Scheme 7 was based on the presumption that the nucleophilic opening of the cyclic sulfite **44** would occur in a regiospecific manner at the α-carbon atom.[12] Indeed, the cyclic sulfite **44** reacted with one equivalent of $NaBH_4$ with apparent complete selectivity for attack at C-2, the α-position, to furnish the intermediate sulfite ester which, without further isolation was subjected to acidic hydrolysis using 4N H_2SO_4 to give **45** in good yield. Due to high polar nature of the resulted acid **45,** it was subjected directly to reduce the azide under hydrogenation conditions using 10% Pd/C in methanol to afford (-)-galantinic acid **1** in 88% yield, $[\alpha]_D^{25}$ -29.7 (lit.[3] $[\alpha]_D^{25}$ -29.4). The physical and spectroscopic data of **1** are in full agreement with the literature data.[3]

2.1.5. Conclusion

In conclusion, a practical and enantioselective synthesis of (-)-galantinic acid **1** has been achieved using Sharpless asymmetric epoxidation and dihydroxylation and through regioselective nucleophilic opening of a cyclic sulfite. The synthetic strategy described has significant potential for further extension to other isomers and related analogues including galantinamic acid **4**, the other component of galantin I **2**.

2.1.6. Experimental Section

3-(4-Methoxybenzyloxy)propan-1-ol (35):



To a solution of 1,3-propanediol **34** (5.0 g, 65.71 mmol) in dry DMF (200 mL) was added sodium hydride (60%, 2.90 g, 72.28 mmol) at 0 ^{o}C. The reaction mixture was then stirred at room temperature for 30 min after which it was again cooled to 0 ^{o}C. To this was added slowly *p*-methoxybenzyl chloride (11.32 g, 10.75 mL, 72.28 mmol) with further stirring for 6 h at the same temperature. The reaction mixture was quenched with addition of cold water at 0 ^{o}C. The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with water (3 x 100 mL), brine, dried (Na_2SO_4) and concentrated. The residual oil was purified by silica gel column chromatography using petroleum ether/EtOAc (8:2) as eluent to furnish the mono-PMB protected alcohol **35** as colorless oil.

Yield: 11.09 g, 86%

Mol. Formula: $C_{11}H_{16}O_3$

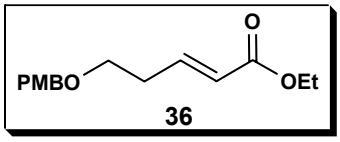
IR (neat, cm^{-1}): ν_{max}3410, 2940, 2863, 1612, 1513, 1249, 1175, 1098.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.22-2.27 (m, 2 H), 2.82 (brs, 1 H), 4.02 (t, *J* = 5.27 Hz, 2 H), 4.15 (t, *J* = 5.67 Hz, 2 H), 4.20 (s, 3 H), 4.85 (s, 2, H), 7.28 (d, *J* = 10 Hz, 2H), 7.65 (d, *J* = 9.8 Hz, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 32.2, 55.2, 61.5, 68.7, 72.8, 113.8, 129.2, 130.2, 159.2, ppm.

Analysis: Calcd.: C, 67.32; H, 8.22%; **Found:** C, 67.41; H, 8.19%.

(*E*)-Ethyl 5-(4-methoxybenzyloxy)pent-2-enoate (36):



(a) PCC oxidation. To a mixture of PCC (16.48 g, 76.43 mmol) and powdered molecular sieves (3A°, ½ the wt of PCC) in dry CH_2Cl_2 was added the mono-PMB protected alcohol **35** (10 g, 50.95 mmol) at 0°C. The reaction mixture was stirred for 6 h at room temperature and then CH_2Cl_2 was evaporated and, to the residue was added Et_2O. The slurry was stirred and filtered through a pad of celite. The residue was washed 4 times and filtered. The filtrate was concentrated to give the aldehyde as pale yellow oil, which was used as such for the next step without purification.

(b) Wittig olefination. To a solution of (ethoxycarbonylmethylene)triphenylphosphorane (19.49 g, 56.01 mmol) in dry THF (150 mL) was added a solution of the above aldehyde in dry THF (50 mL). The reaction mixture was stirred for 24 h at room temperature. It was then concentrated and purified by silica gel column chromatography using petroleum ether/EtOAc (8.5:1.5) as eluent to afford the α,β-unsaturated olefin **36** as a colorless liquid.

Yield: 10.91 g, 81%

Mol. Formula: $C_{15}H_{20}O_4$

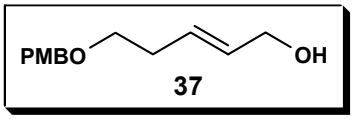
IR ($CHCl_3$, cm^{-1}): ν_{max}2955, 2858, 1718, 1654, 1038, 1300, 1216.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.31(t, *J* = 8 Hz, 3 H), 2.52 (q, *J* = 8.21, 15.86 Hz, 2 H), 3.58 (t, *J* = 6.01 Hz, 2 H), 3.83 (s, 3H), 4.21 (q, *J* = 5.0, 15.20 Hz, 2 H), 4.48 (s, 2 H), 5.91 (d, *J* = 15.66 Hz, 1H), 6.90 (d, , *J* = 10 Hz, 2 H), 6.96-7.02 (m, 1H), 7.28 (d, *J* = 9 Hz, 2 H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 32.2, 55.0, 60.2, 68.4, 72.3, 96.2, 113.5, 146.6, 158.9, 166.4 ppm.

Analysis: Calcd.: C, 68.16; H, 7.63 %; **Found:** C, 68.09; H, 7.69 %.

(*E*)-5-(4-Methoxybenzyloxy)pent-2-en-1-ol (37):



37

To a solution of **36** (8.0 g, 30.27 mmol) in dry CH_2Cl_2 (100 mL) at 0 ^oC was added dropwise DIBAL-H (68.14 mL, 45.40 mmol, 1M in toluene) through a syringe. The reaction mixture was allowed to warm to room temperature over 2 h, then re-cooled to 0 ^oC and treated with saturated solution of sodium/potassium tartrate. The solid material was

filtered through a pad of celite and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (7:3) as eluent gave **37** as a colorless oil.

Yield: 6.19 g, 92%

Mol. Formula: $C_{13}H_{18}O_3$

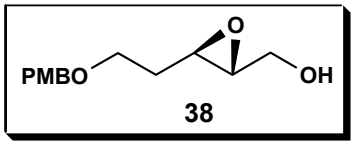
IR ($CHCl_3$, cm^{-1}): ν_{max} 3440, 2938, 2860, 1640, 1204

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.83 (brs, 1H), 2.36 (q, *J* = 5.04, 12.61 Hz, 2H), 3.50 (t, *J* = 9.6 Hz, 2H), 3.81 (s, 3H), 4.08 (s, 2H), 4.45 (s, 2H), 5.71 (s, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 32.2, 55.7, 64.3, 69.8, 72.3, 114.7, 128.3, 129.1, 130.3, 131.3, 158.9 ppm.

Analysis: Calcd.: C, 70.24; H, 8.16 %; **Found:** C, 70.19; H, 8.21 %.

((2*R*,3*R*)-3-(2-(4-Methoxybenzyloxy)ethyl)oxiran-2-yl)methanol (38):



To a solution of Ti(O*i*-Pr)$_4$ (5.75 g, 6.03 mL, 20.24 mmol) in CH_2Cl_2 (40 mL) at -25 ^oC was added (-) DIPT (5.22 g, 4.73 mL, 22.27 mmol). After stirring for 10 min., the allylic alcohol **37** (4.5 g, 20.24 mmol) was added. After stirring for 20 min. at -25 ^oC, *t*-BuOOH (5.0 M in decane, 7.36 mL, 3.65 g, 40.49 mmol) was added and the reaction mixture was stirred for 36 h at -25 ^oC. The resultant mixture was then quenched by addition of sat. aq. $NaHCO_3$ (40 mL) and Et_2O (80 mL), and stirred for 1 h at room temperature after which it was filtered through a pad of celite. The filtrate was diluted with Et_2O (80 mL) and stirred for 20 min. with 1 M NaOH (50 mL). The phases were separated and the aqueous phase was extracted twice with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography using petroleum ether :EtOAc (1:1) as eluent afforded the epoxide **38** as a pale yellow color oil.

Yield: 3.47 g, 72%

Mol. Formula: $C_{13}H_{18}O_4$

$[\alpha]_D^{25}$: +4.65 (*c* 0.4, $CHCl_3$).

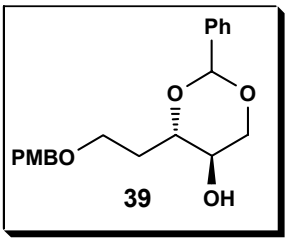
IR ($CHCl_3$, cm^{-1}): ν_{max} 3431, 2938, 2860, 1695, 1362, 1210.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.74 (brs, 1 H), 1.80-1.84 (m, 1 H), 1.85-1.93 (m, 1H), 2.97 (t, *J* = 5.30 Hz, 1 H), 3.10 (t, *J* = 5.80 Hz, 1 H), 3.59 (t, *J* = 5.0 Hz, 3 H), 3.81 (s, 3 H), 3.89 (d, *J* = 9.8 Hz, 1 H), 4.46 (s, 2 H), 6.89 (d, *J* = 9.89 Hz, 2 H), 7.26 (d, *J* = 10.0 Hz, 2 H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ31.7, 52.1, 55.0, 58.6, 62.9, 66.2, 72.3, 113.5, 129.05, 130.3, 158.9 ppm.

Analysis: Calcd.: C, 65.53; H, 7.61%; **Found:** C, 65.43; H, 7.59%.

(4*S*,5*R*)-4-(2-(4-Methoxybenzyloxy)ethyl)-2-phenyl-1,3-dioxan-5-ol (39):



To a solution of **38** (3.1 g, 13.00 mmol) in 60% DMSO (20 mL) was added $HClO_4$ (0.16 mL, 2.60 mmol) and reaction mixture was stirred at 0 ^oC for 3 h. The reaction mixture was diluted with EtOAc (50 mL), washed with $NaHCO_3$ and water dried over Na_2SO_4 and concentrated to give crude triol 2.97 g (89%). To the solution of triol (2.97 g, 11.58 mmol) in dry CH_2Cl_2 (40 mL) were added benzaldehyde dimethyl acetal (1.94 g, 1.91 mL, 12.75 mmol) *p*-TsOH (cat.) and DMAP (cat.). The reaction mixture was stirred at room temperature for overnight. Subsequently, it was neutralized with saturated aq. $NaHCO_3$. The organic phase was separated and the aqueous phase extracted with CH_2Cl_2. The combined organic extracts were washed with aq. $NaHCO_3$, brine, dried (Na_2SO_4) and concentrated. Column chromatography over silica gel using EtOAc/pet ether (1:9) as eluent furnished the major product **39** as a colorless liquid.

Yield: 2.59 g, 65%

Mol. Formula: $C_{20}H_{24}O_5$

$[\alpha]_D^{25}$: -8.89 (*c* 1.0, $CHCl_3$).

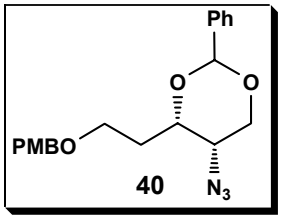
IR ($CHCl_3$, cm^{-1}): ν_{max} 3390, 2948, 2831, 1680, 1204.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.03-2.18 (m, 2 H), 3.59-3.72 (m, 5H), 3.81 (s, 3H), 4.32 (d, *J* = 5.08 Hz, 1H), 4.51 (q, *J* = 8.02, 13.56 Hz, 2H), 5.46 (s, 1 H), 6.90 (d, *J* = 10 Hz, 2 H), 7.27 (t, *J* = 5.68, 3 H), 7.34-7.38 (m, 2 H), 7.47 (d, *J* = 5.80 Hz, 2 H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 30.3, 52.7, 67.7, 70.3, 75.3, 76.7, 113.7, 127.3, 128.3, 128.9, 129.7, 130.2, 159.2 ppm.

Analysis: Calcd.: C, 69.75; H, 7.02%; **Found:** C, 69.80; H, 7.11%.

(4*S*,5*S*)-4-(2-(4-Methoxybenzyloxy)ethyl)-5-azido-2-phenyl-1,3-dioxane (40):



To a solution of **39** (2.0 g, 5.81 mmol) in dry CH_2Cl_2 (20 mL) at 0 ^oC was added methanesulfonyl chloride (0.73 g, 0.50 mL, 6.38 mmol), Et_3N (0.97 mL, 6.97 mmol). The reaction mixture was stirred at room temperature for 5 h and then poured into Et_2O-H_2O mixture. The organic phase was separated and the aqueous phase extracted with Et_2O. The combined organic phases were washed with water, brine, dried (Na_2SO_4) and concentrated which was dissolved in dry DMF (20 mL). Sodium azide (940 mg, 14.41 mmol) was added and the reaction mixture stirred at 80 ^oC for 24 h. It was then cooled and poured into water and extracted with ethyl acetate. The organic extracts were washed with water, brine and dried (Na_2SO_4) and concentrated. Column chromatography on silica gel using EtOAc/pet ether (0.7:9.3) as eluent gave **40** as a pale yellow liquid.

Yield: 1.38 g, 78%

Mol. Formula: $C_{20}H_{23}N_3O_4$

$[\alpha]_D^{25}$: -4.39 (*c* 0.22, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 2938, 2104, 1612, 1513, 1465, 1362, 1248, 1216.

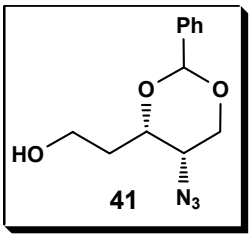
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.76–1.83 (m, 2 H), 3.70 (s, 3 H), 3.73 (t, *J* = 3.67 Hz, 2 H), 3.88 (td, *J* = 8.71, 3.21, 1 H), 4.32-4.34 (m, 1 H), 4.40–4.52 (m, 2 H), 4.54 (s, 2 H), 5.50 (s, 1H), 6.87 (d, *J* = 10 Hz, 2 H), 7.29 (d, *J* = 10 Hz, 2 H), 7.37-7:42 (m, 5 H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 29:67, 31.58, 38.26, 55.22, 64.62, 69.00, 72.25, 72.74, 75.63, 101.13, 113.77, 126.04, 128.24, 129.19, 129.49, 159.22.

GC–MS: 369 (M+), 357.05, 331.05, 279.05, 261.05, 241.05, 200.05, 172.04.

Analysis: Calcd.: C, 65.03; H, 6.28; N, 11.37%; **Found:** C, 64.98; H, 6.31; N, 11.29%.

2-((4*S*,5*S*)-5-Azido-2-phenyl-1,3-dioxan-4-yl)ethanol (41):



To a solution of **40** (1.2 g, 3.25 mmol) in CH_2Cl_2 (20 mL) and H_2O (1.0 mL) at 0 ^oC was added DDQ (1.11 g, 4.87 mmol) in portions. The resultant mixture was stirred at room temperature for 3 h and then sat. aq. $NaHCO_3$ (10 mL) was added. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 60 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the residue by using petroleum ether:EtOAc (3:1) furnished alcohol **41** as a pale yellow oil.

Yield: 745 mg, 91%

Mol. Formula: $C_{12}H_{15}N_3O_3$

$[\alpha]_D^{25}$: -13.21 (*c* 0.5, $CHCl_3$)

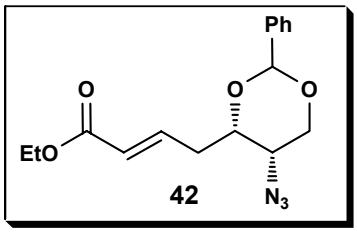
IR ($CHCl_3$, cm^{-1}): ν_{max} 3441, 2938, 2101, 1680, 1515, 1470, 1362, 1216.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.77-1.91 (m, 2 H), 3.67 (t, *J* = 6.0 Hz, 2 H), 3.79-4.07 (m, 5 H), 5.51 (s, 1 H), 7.28-7.41 (m, 5 H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 32.6, 55.3, 62.6, 70.2, 72.6, 101.92, 128.31, 129.19, 129.5, 134.2 ppm.

Analysis: Calcd.: C, 57.82; H, 6.07; N, 16.86%; **Found:** C, 57.79; H, 6.11; N, 16.95%.

(*E*)-Ethyl 4-((4*S*,5*S*)-5-azido-2-phenyl-1,3-dioxan-4-yl)but-2-enoate (42):



(a) PCC oxidation. To a mixture of PCC (130 mg, 0.60 mmol) and powdered molecular sieves (3A°, ½ the wt of PCC) in dry CH_2Cl_2 was added the alcohol **41** (100 mg, 0.40 mmol) at 0 °C. The reaction mixture was stirred for the 6 h at room temperature and then CH_2Cl_2 was evaporated and, to the residue was added Et_2O. The slurry was stirred and filtered through a pad of celite. The residue was washed 5 times and filtered. The filtrate was concentrated to give the aldehyde as pale yellow oil, which was used as such for the next step without purification.

(b) Wittig olefination. To a solution of (ethoxycarbonylmethylene)triphenylphosphorane (167 mg, 0.50 mmol) in dry THF (5 mL) was added a solution of the above aldehyde in dry THF (1 mL). The reaction mixture was stirred at room temperature for 24 h. It was then concentrated and purified by silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluent to afford the α,β-unsaturated olefin **42** as a pale yellow liquid.

Yield: 106 mg, 83%

Mol. Formula: $C_{16}H_{19}N_3O_4$

$[\alpha]_D^{25}$: -9.62 (*c* 0.8, $CHCl_3$)

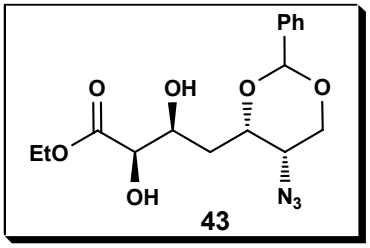
IR ($CHCl_3$, cm^{-1}): ν_{max}2956, 2858, 2103, 1724, 1656, 1038, 1300, 1204, 1100.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.30 (t, *J* = 7.2 Hz, 3 H), 2.64-2.88 (m, 2 H), 3.79-3.89 (m, 4 H), 4.21 (q, *J* = 6.69, 13.77 Hz, 2 H), 5.52 (s, 1 H), 6.01 (d, *J* = 15.89 Hz, 1 H), 6.99-7.07 (m, 1 H), 7.36-7.46 (m, 5 H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ14.1, 31.8, 55.1, 60.0, 69.4, 72.4, 101.9, 121.4, 128.2, 129.1, 130.5, 133.5, 148.8, 166.5 ppm..

Analysis: Calcd.: C, 60.56; H, 6.03; N, 13.24%; **Found:** C, 60.61; H, 6.11; N, 13.31%.

(2*R*,3*S*)-Ethyl 4-((4*S*,5*S*)-5-azido-2-phenyl-1,3-dioxan-4-yl)-2,3-dihydroxybutanoate (43):



43

To a mixture of $K_3Fe(CN)_6$ (280 mg, 0.85 mmol), K_2CO_3 (118 mg, 0.85 mmol) and $(DHQ)_2PHAL$ (3 mg, 1 mol%), in *t*-BuOH-H_2O (1:1, 5 mL) cooled at 0 ^oC was added OsO_4 (0.01 mL, 0.1 M solution in toluene, 0.4 mol%) followed by methanesulfonamide (27 mg, 0.28 mmol). After being stirred for 5 min at 0 ^oC, the olefin **42** (90 mg, 0.28 mmol) was added in one portion. The reaction mixture was stirred at 0 ^oC form 24 h and then quenched with solid sodium sulfite (180 mg). The stirring was continued for an additional 45 min, and then the solution was extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with 10% KOH, and brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (3:2) as eluent gave the diol **43** as a colorless syrupy liquid.

Yield: 86 mg, 87%

Mol. Formula: $C_{16}H_{21}N_3O_6$

$[\alpha]_D^{25}$: -3.28 (c 0.80, $CHCl_3$)

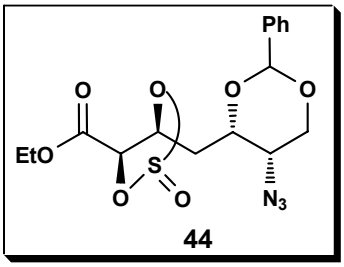
IR (neat, cm^{-1}): ν_{max} 3561, 2112, 1716, 1522, 1343, 1218, 1210

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.93 (t, *J* = 9 Hz, 3 H), 2.06 (br, 2 H), 3.06 (t, *J* = 4 Hz, 2 H), 3.54-3.56 (m, 1 H), 3.62-3.74 (m, 2 H), 4.22 (q, *J* = 8 Hz, 1 H), 4.06 (q, *J* = 6 Hz, 2 H), 4.13 (d, *J* = 8 Hz, 1 H), 4.21-4.25 (m, 1 H), 5.51 (s, 1 H), 7.25–7.32 (m, 5 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.75, 22.02, 25.26, 29.23, 32.94, 54.85, 60.91, 69.40, 72.20, 78.67, 113.37, 128.84, 158.73, 170.56 ppm.

Analysis: Calcd.: C, 54.70; H, 6.03; N, 11.96%; **Found:** C, 54.62; H, 5.98; N, 11.99%.

Cyclic sulfite (44):



To a stirred solution of diol **43** (75 mg, 0.21 mmol) in dry CH_2Cl_2 (4 mL) cooled at 0 ^oC were added Et_3N (0.05 mL, 0.03 g, 0.32 mmol) and a solution of $SOCl_2$ (0.03 g, 0.02 mL, 0.24 mmol) in CH_2Cl_2 (1 mL) over a period of 10 min. Stirring was continued for 20 min at 0 ^oC and then the solution was quenched by adding water and extracted with CH_2Cl_2. The organic layer was separated, washed with water followed by brine, dried (Na_2SO_4) and filtered through a pad of silica gel. The filtrate was concentrated to give cyclic sulfite **44** as a yellow liquid.

Yield: 76 mg, 89%

Mol. Formula: $C_{16}H_{19}N_3O_7S$

$[\alpha]_D^{25}$: -18.62 (*c* 0.46, $CHCl_3$).

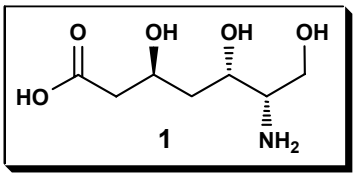
IR (neat, cm^{-1}): ν_{max} 3010, 2964, 1712, 1680, 1512, 1248, 1230, 1032.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (t, *J* = 7.0 Hz, 3 H), 2.59-3.18 (m, 2 H), 3.59-3.66 (m, 5 H), 3.80 (d, *J* = 5.01 Hz, 1 H), 4.22 (q, *J* = 7.20, 14.27 Hz, 2 H), 5.46 (s, 1 H), 7.29-7.49 (m, 5 H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 26.3, 52.7, 55.2, 57.7, 61.9, 74.3, 103.7, 127.3, 128.3, 129.7, 130.2, 170.03 ppm.

Analysis: Calcd.: C, 48.36; H, 4.82; N, 10.57%; **Found:** C, 48.44; H, 4.79; N, 10.68%.

(3*S*,5*S*,6*S*)-6-Amino-3,5,7-trihydroxyheptanoic acid; (-)-Galantinic acid (1):



To a solution of cyclic sulfite **44** (70 mg, 0.18 mmol) in dry THF (4 mL) was added $NaBH_4$ (7 mg, 0.18 mmol) under argon. The reaction mixture was stirred under argon at

room temperature for 12 h. The solvent was removed under reduced pressure and MeOH (3 mL) was added to the residue. The intermediate sulfite ester which, without further isolation was subjected to acidic hydrolysis using 4N H_2SO_4 to give crude azido-acid **45,** 30 mg (77% yield). Due to high polar nature of the resulted azido acid **45,** it was subjected directly to reduce the azide under hydrogenation conditions using 10% Pd/C in methanol to afford crude crystals of **1**. These were recrystallized from H_2O/MeOH to give pure (-)-galantinic acid **1.**

Yield: 16 mg, 88%

M.P. : 128 ^oC (lit.[3] 125 -130 ^oC).

Mol. Formula: $C_7H_{15}NO_5$

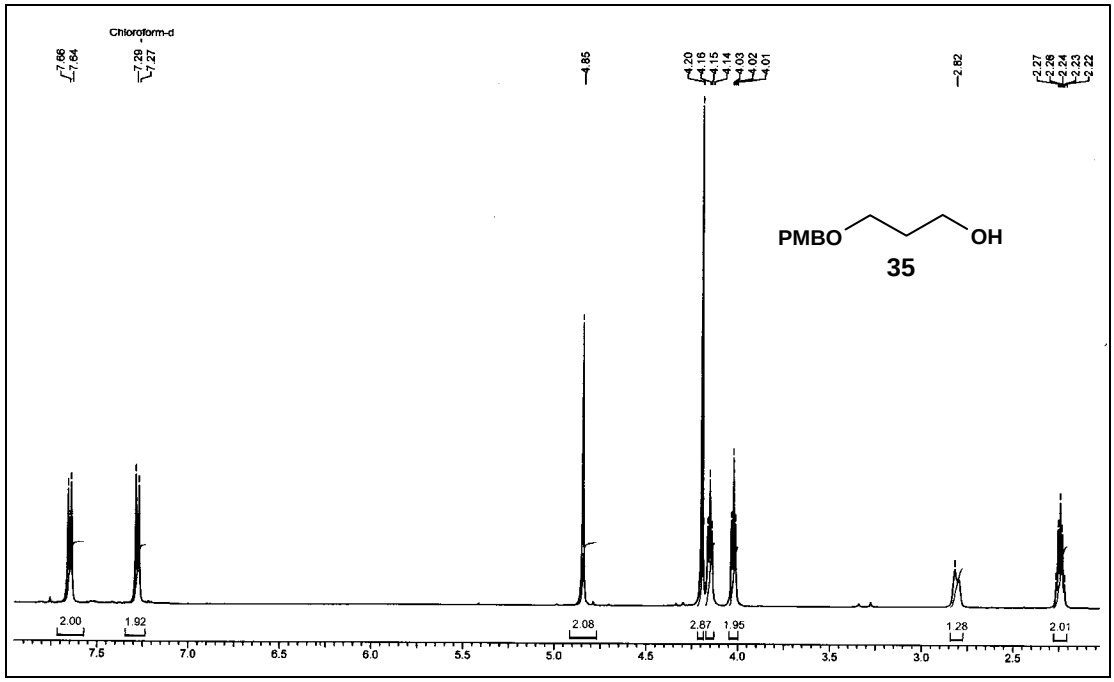
$[\alpha]_D^{25}$: $[\alpha]_D^{25}$ -29.7 (lit.[3] $[\alpha]_D^{25}$ -29.4).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.51-1.83 (m, 2 H), 2.37 (dd, *J* = 5.8, 13.65 Hz, 1 H), 2.49 (dd, *J* = 6.5, 13.86 Hz, 1 H), 3.132.37 (dt, *J* = 7.0, 12.25 Hz, 1 H), 3.61 (q, *J* = 8.32, 14.91 Hz, 1 H), 3.91-4.21 (m, 3 H) ppm.

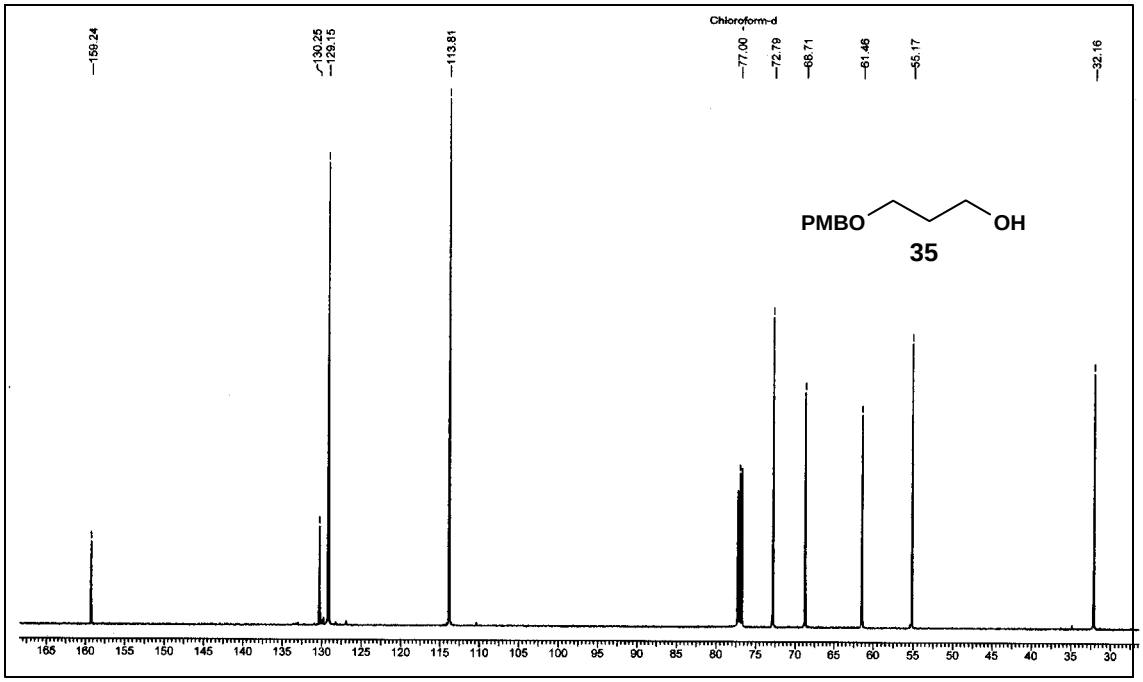
MS (ESI) *m/z*: 194 $[M + H]^+$

2.1.7 Spectra

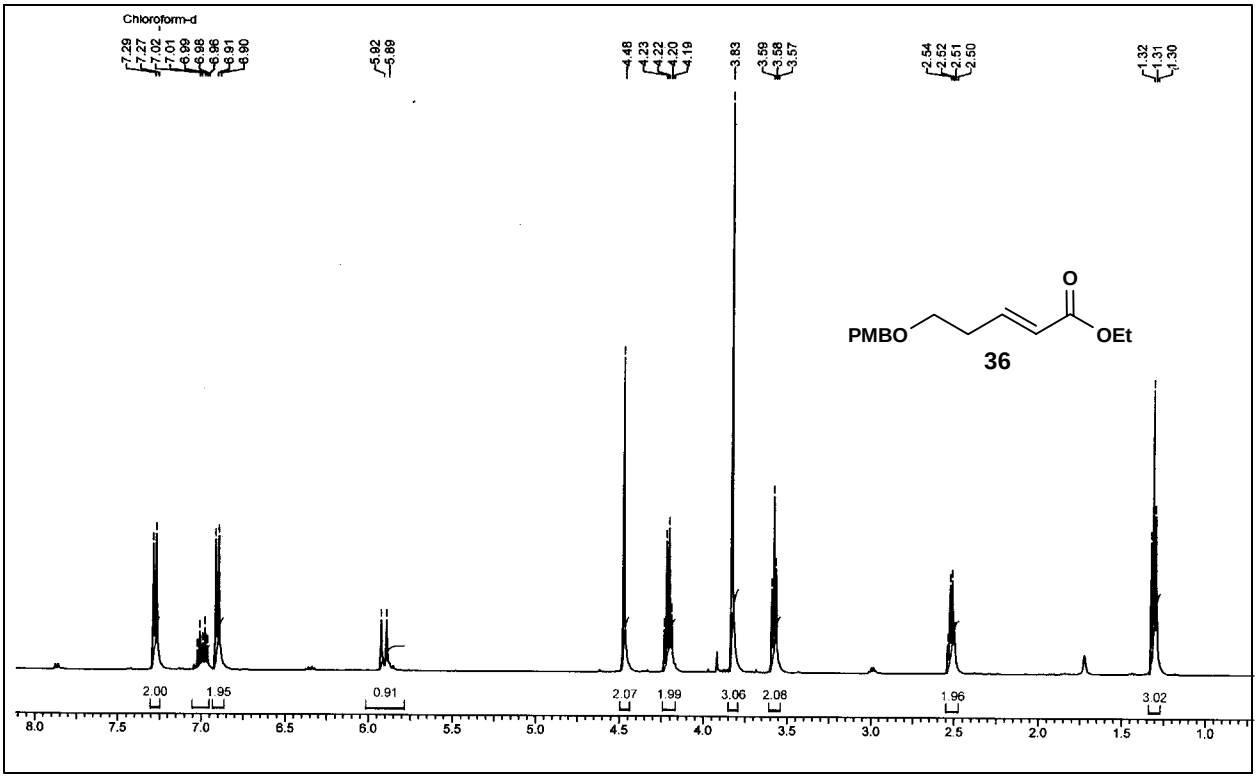
1. ^{1}H and ^{13}C NMR spectra of **35**
2. ^{1}H and ^{13}C NMR spectra of **36**
3. ^{1}H and ^{13}C NMR spectra of **37**
4. ^{1}H and ^{13}C NMR spectra of **38**
5. ^{1}H and ^{13}C NMR spectra of **39**
6. ^{1}H and ^{13}C NMR spectra of **40**
7. ^{1}H and ^{13}C NMR spectra of **41**
8. ^{1}H and ^{13}C NMR spectra of **42**
9. ^{1}H and ^{13}C NMR spectra of **43**
10. ^{1}H and ^{13}C NMR spectra of **44**
11. ^{1}H and Mass spectra of **1**



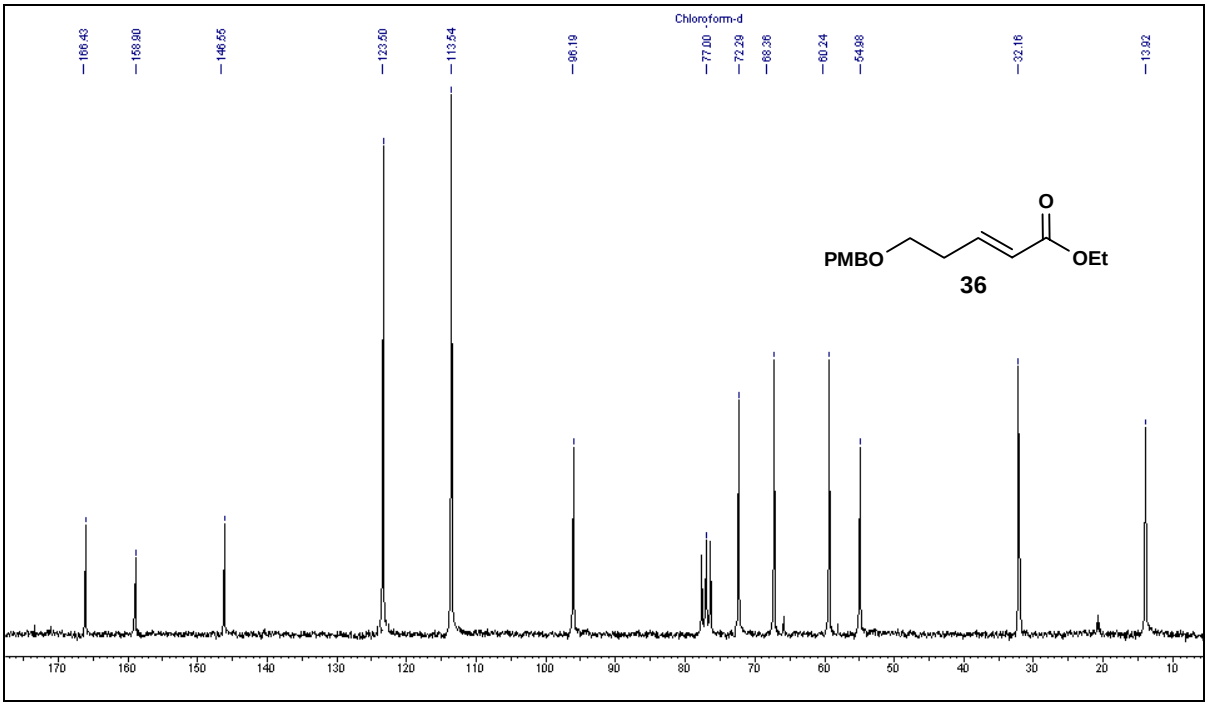
☞ **^{1}H NMR of the compound 35 in $CDCl_3$**



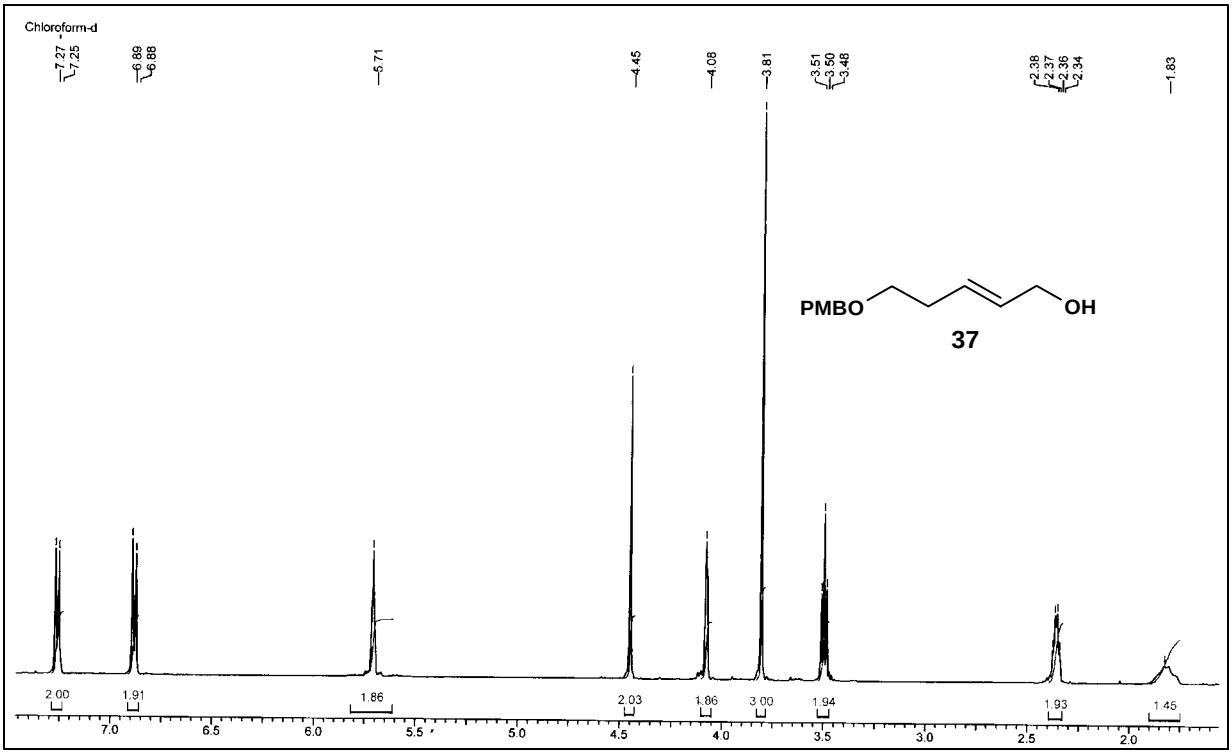
☞ **^{13}C NMR of the compound 35 in $CDCl_3$**



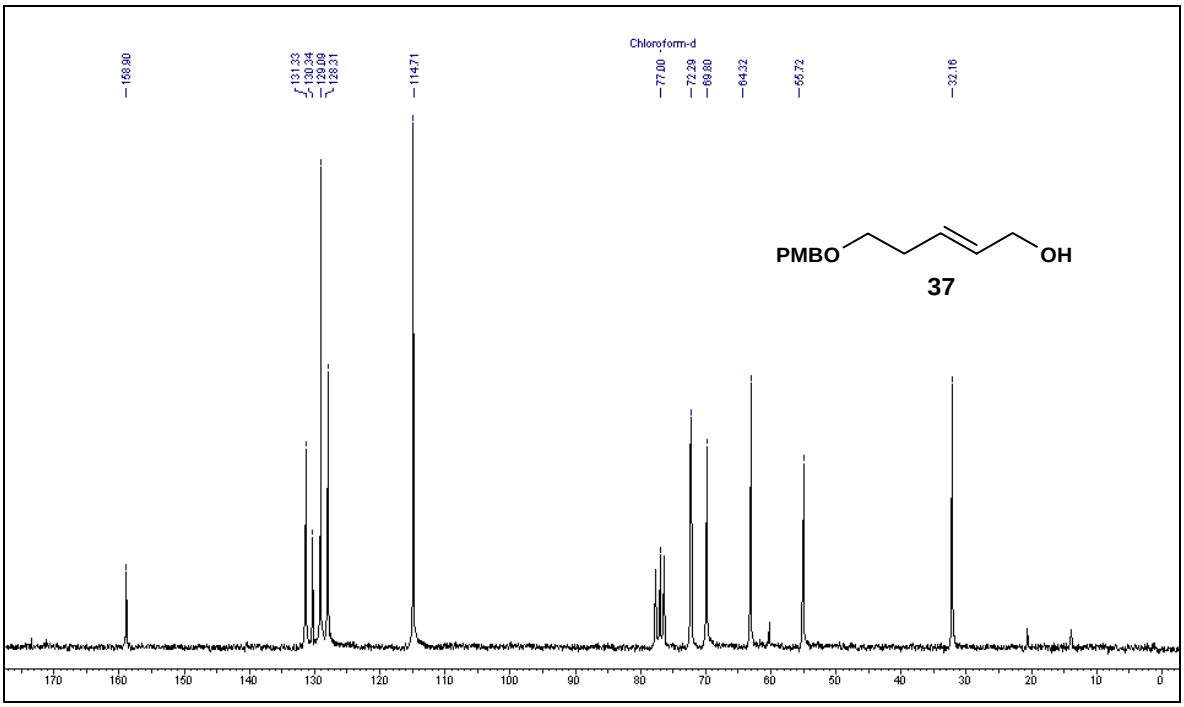
☞ **^{1}H NMR of the compound 36 in $CDCl_3$**



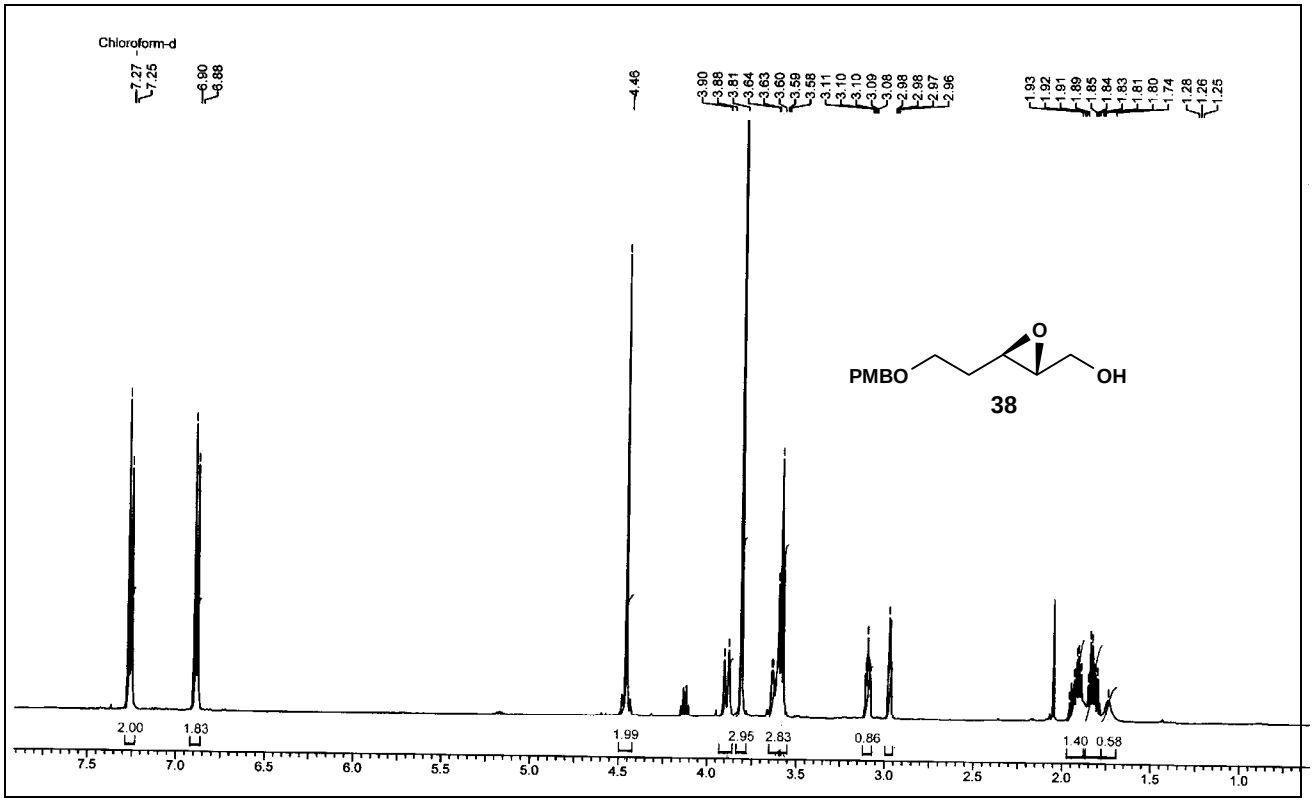
☞ **^{13}C NMR of the compound 36 in $CDCl_3$**



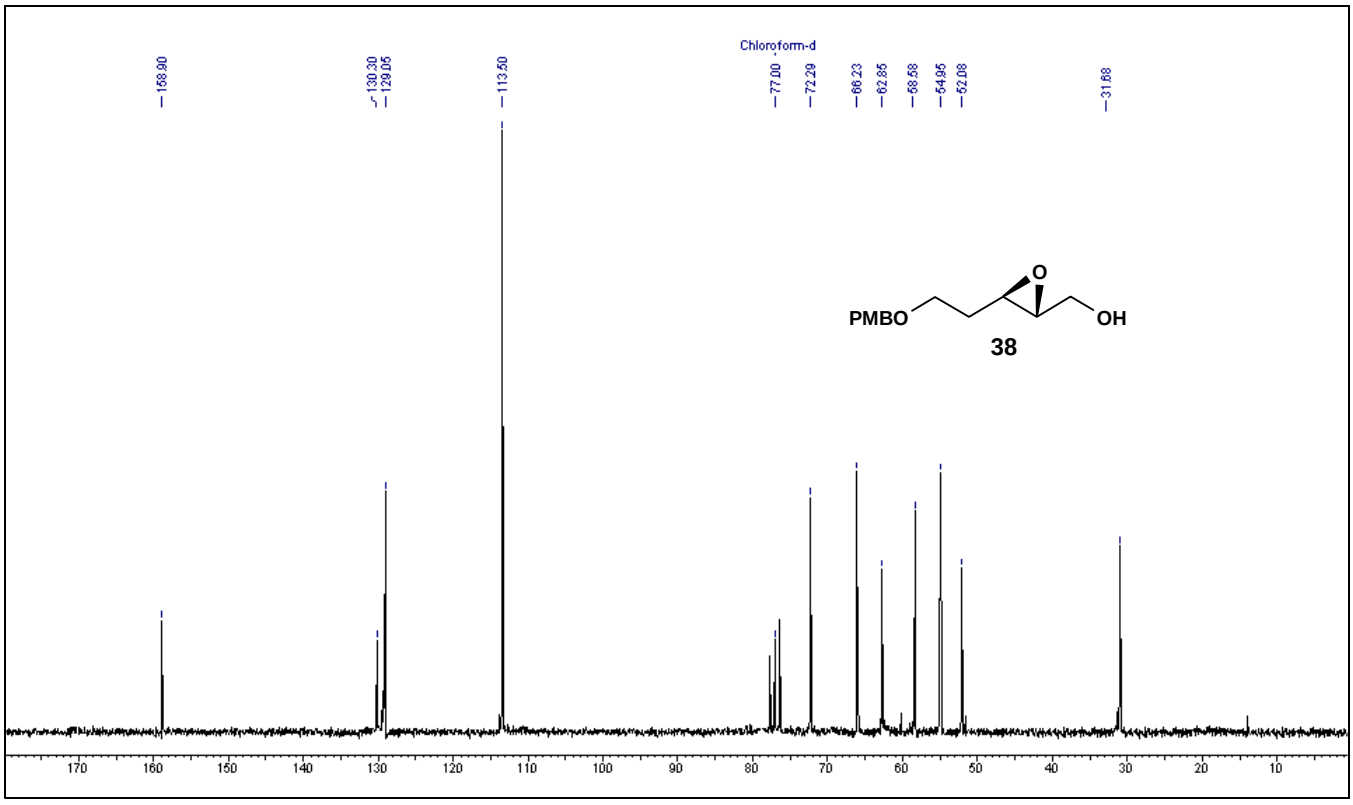
☞ **^{1}H NMR of the compound 37 in $CDCl_3$**



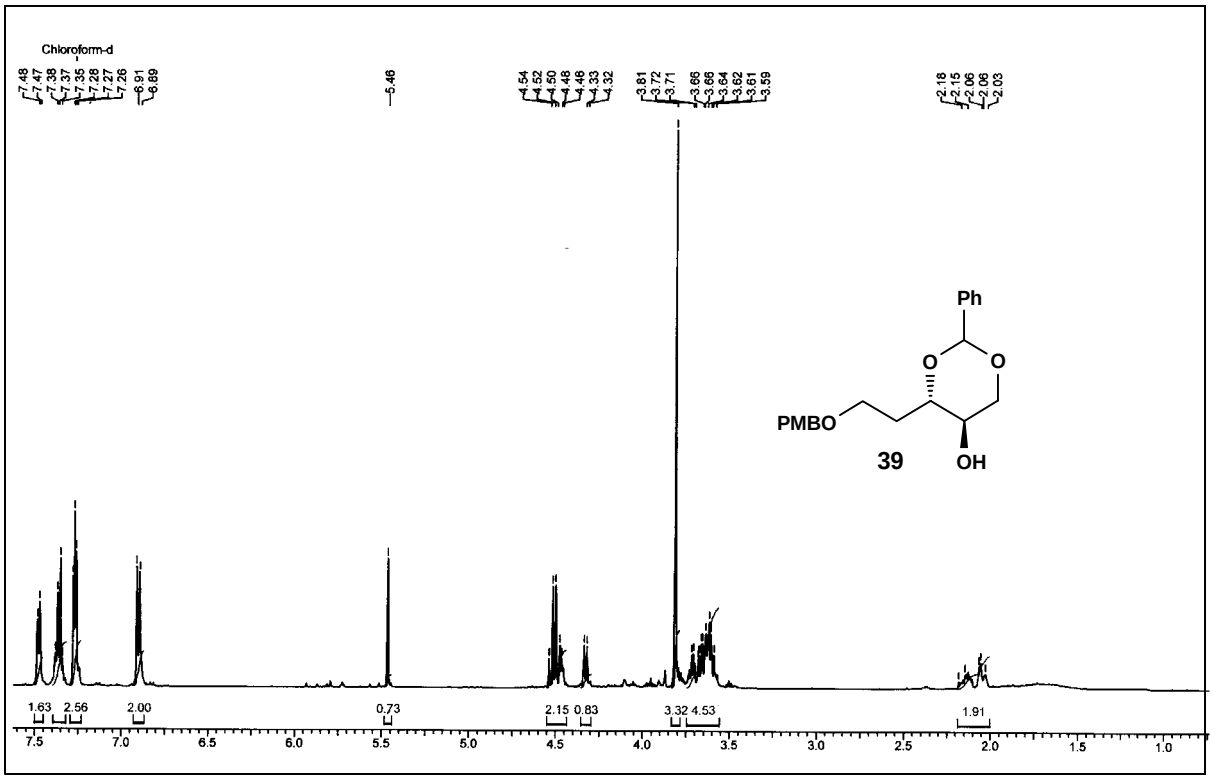
☞ **^{13}C NMR of the compound 37 in $CDCl_3$**



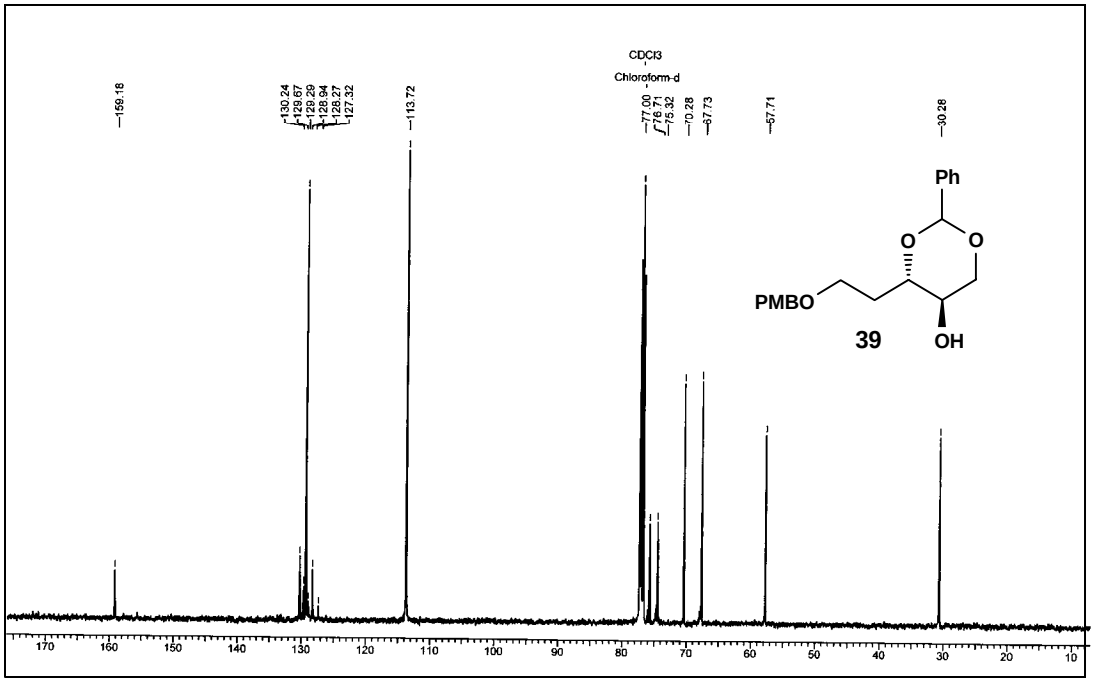
☞ **^{1}H NMR of the compound 38 in $CDCl_3$**



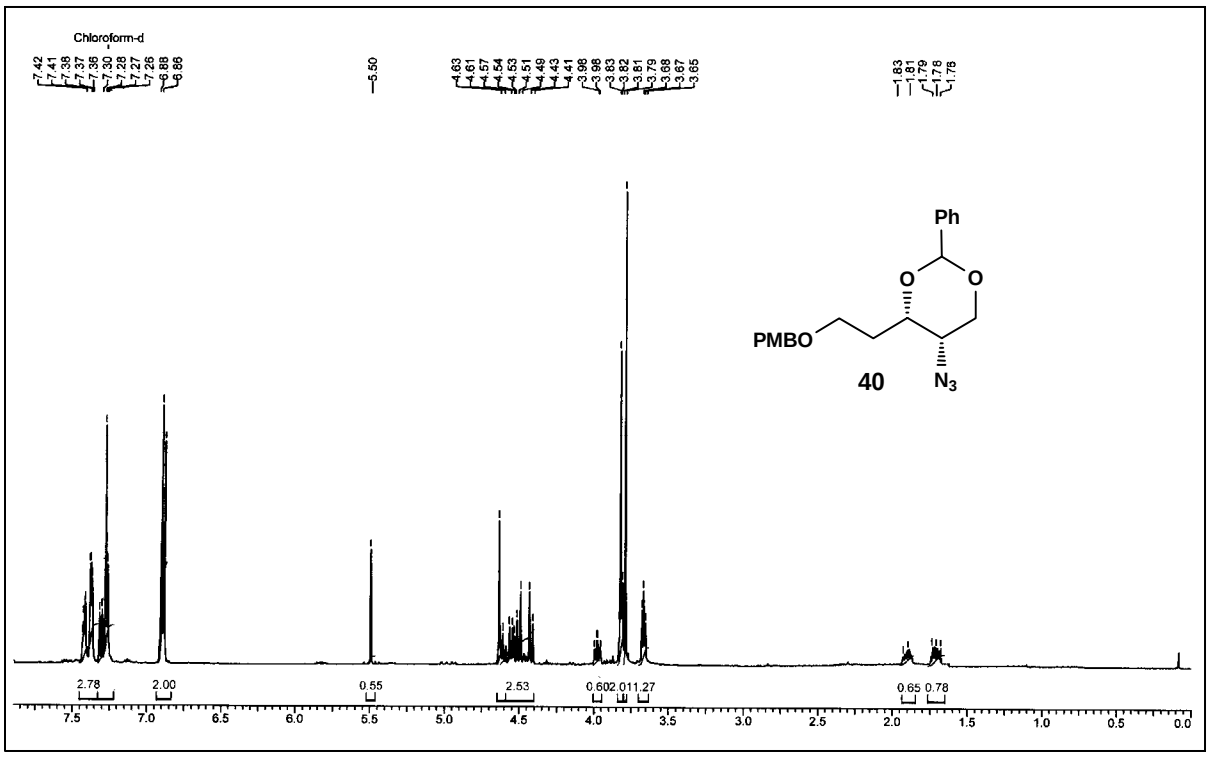
☞ **^{13}C NMR of the compound 38 in $CDCl_3$**



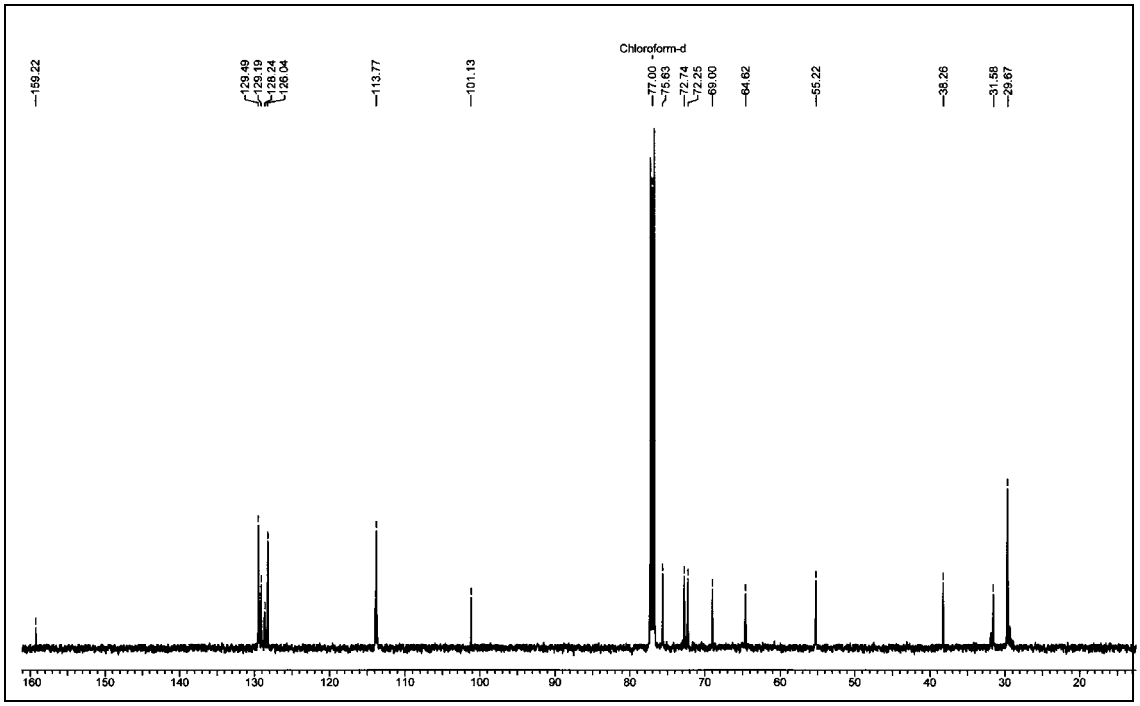
☞ ^{1}H NMR of the compound 39 in $CDCl_3$



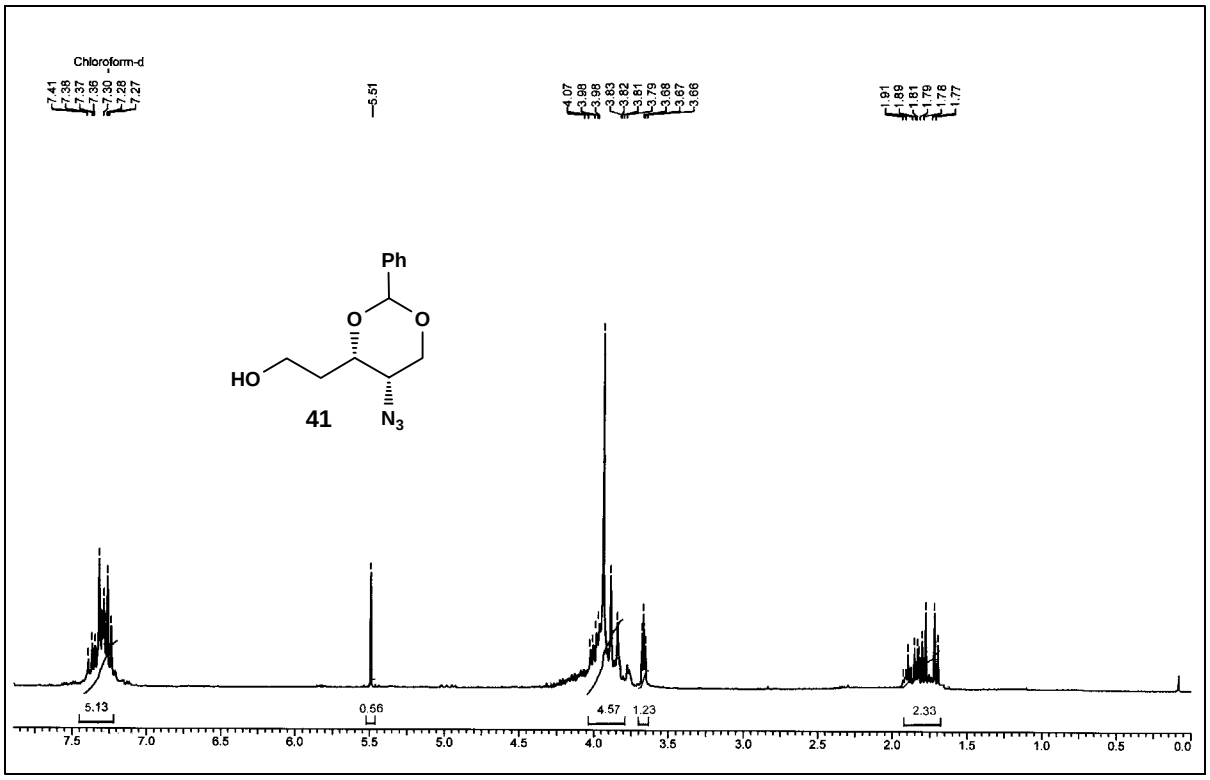
☞ ^{13}C NMR of the compound 39 in $CDCl_3$



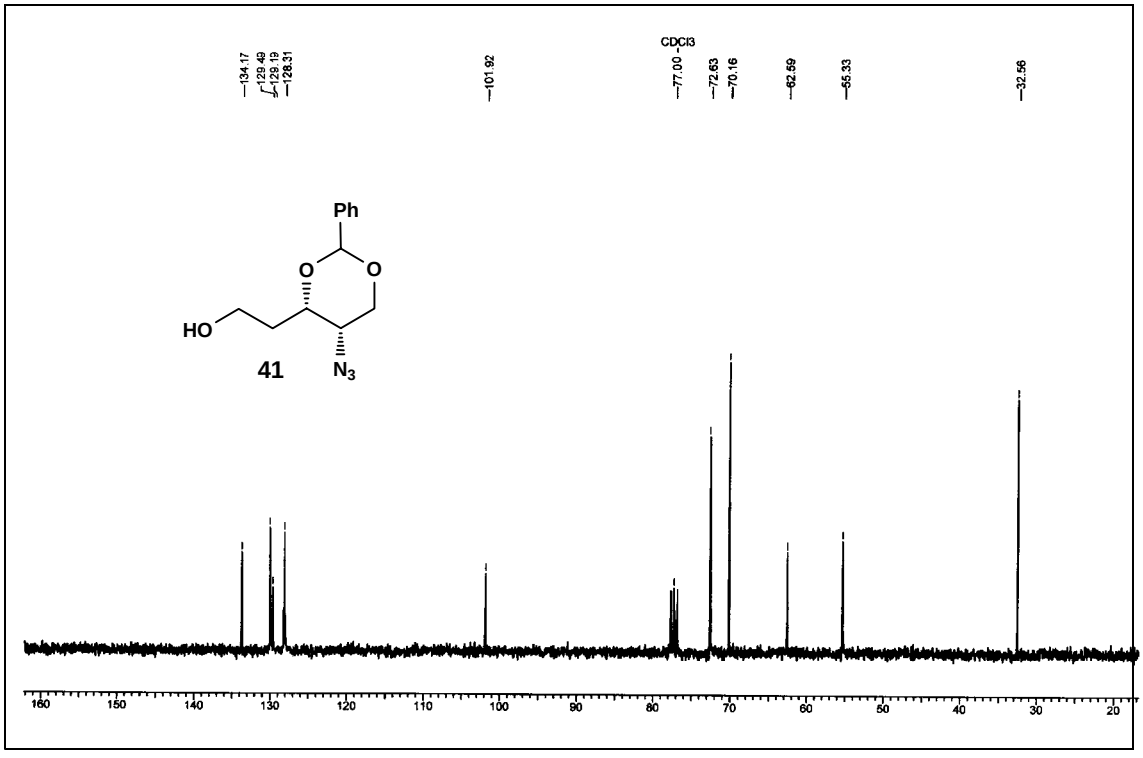
☞ **^{1}H NMR of the compound 40 in $CDCl_3$**



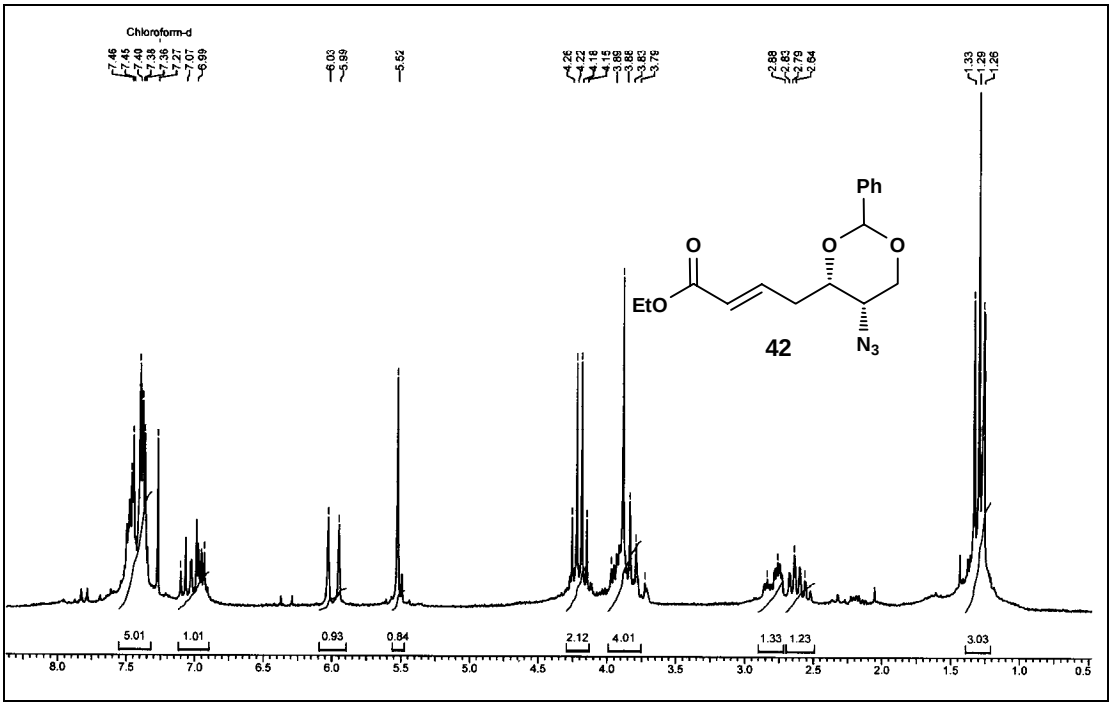
☞ **^{13}C NMR of the compound 40 in $CDCl_3$**



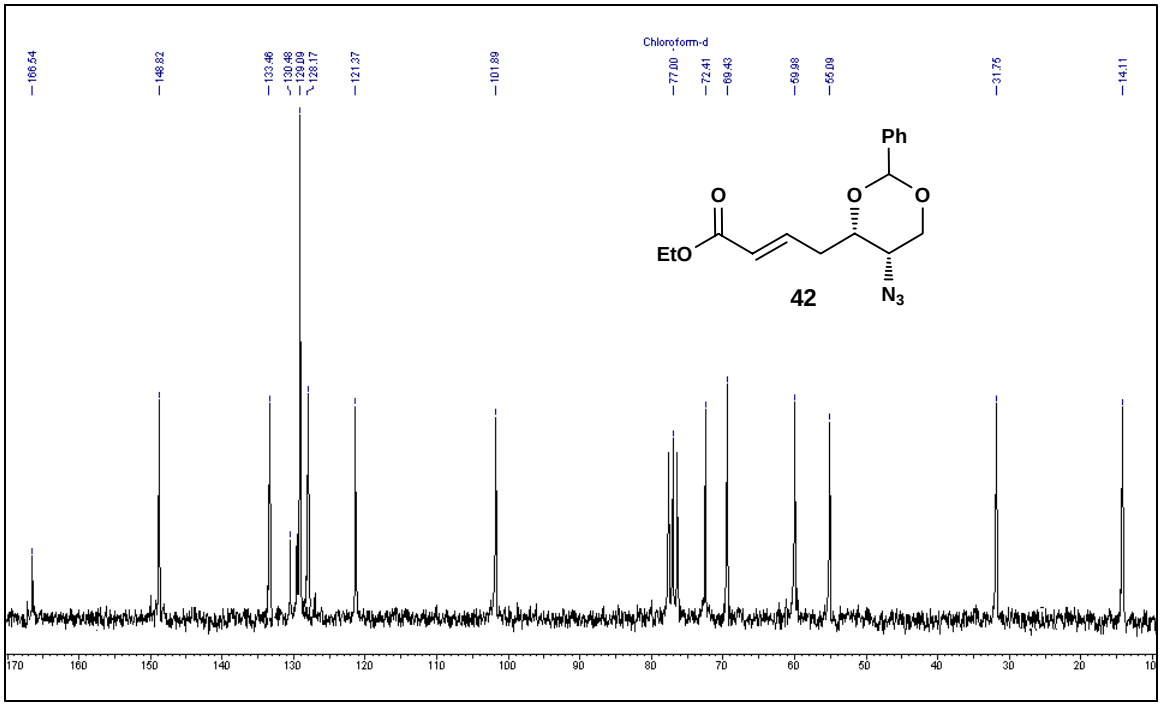
☞ **^{1}H NMR of the compound 41 in $CDCl_3$**



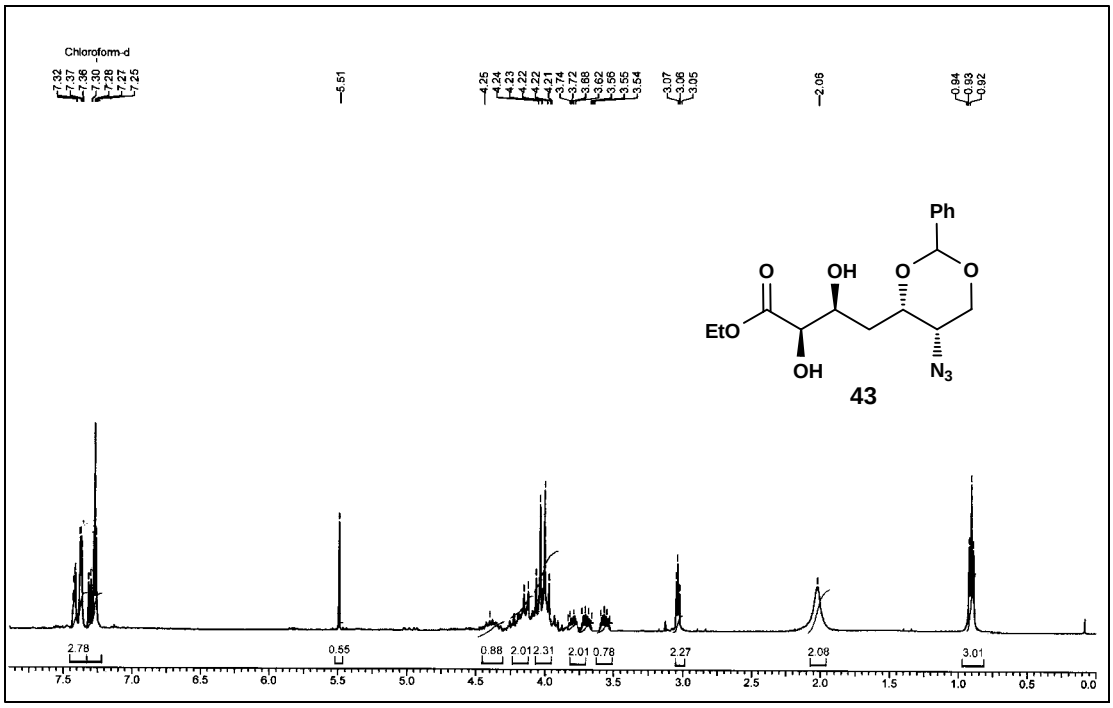
☞ **^{13}C NMR of the compound 41 in $CDCl_3$**



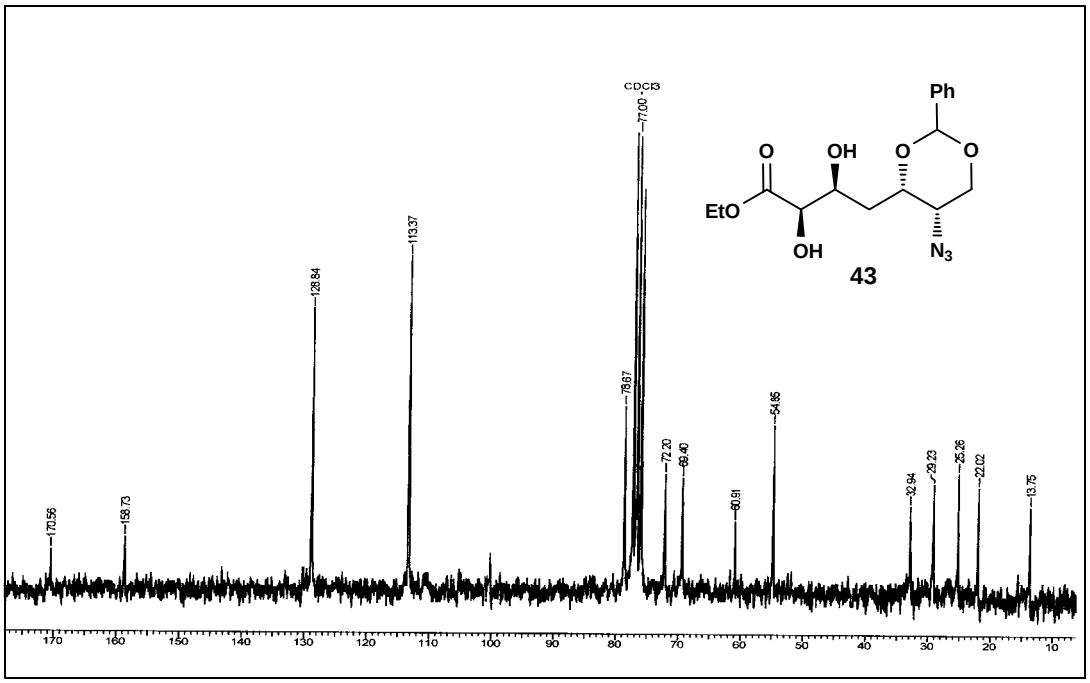
☞ ^{1}H NMR of the compound 42 in $CDCl_3$



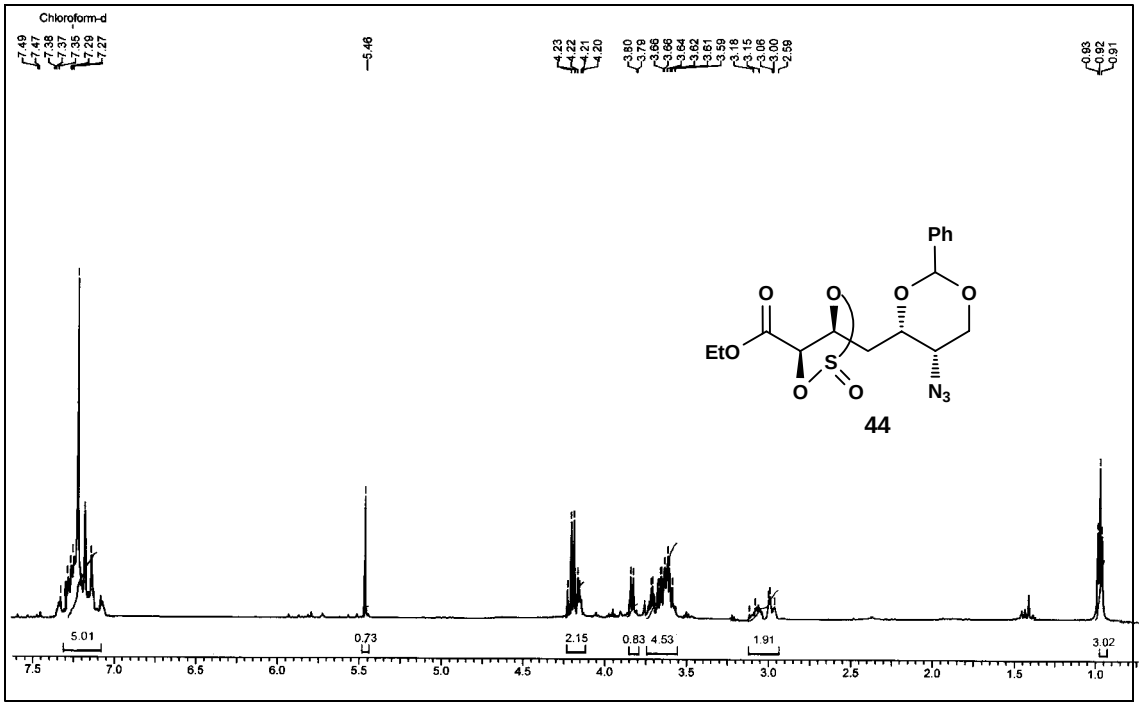
☞ ^{13}C NMR of the compound 42 in $CDCl_3$



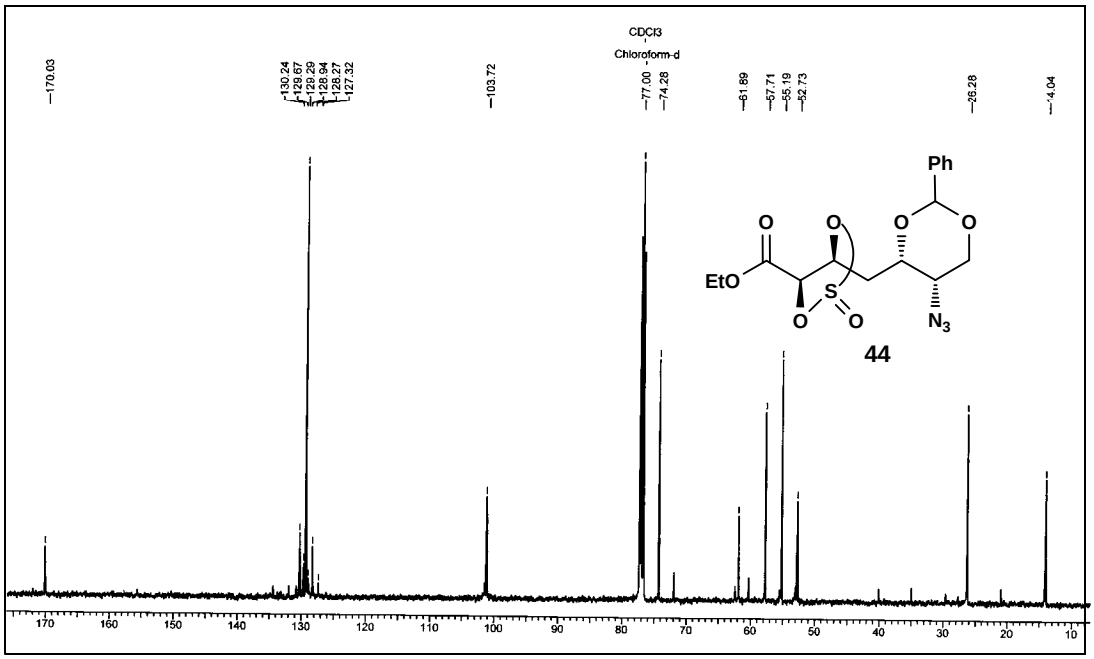
☞ ^{1}H NMR of the compound 43 in $CDCl_3$



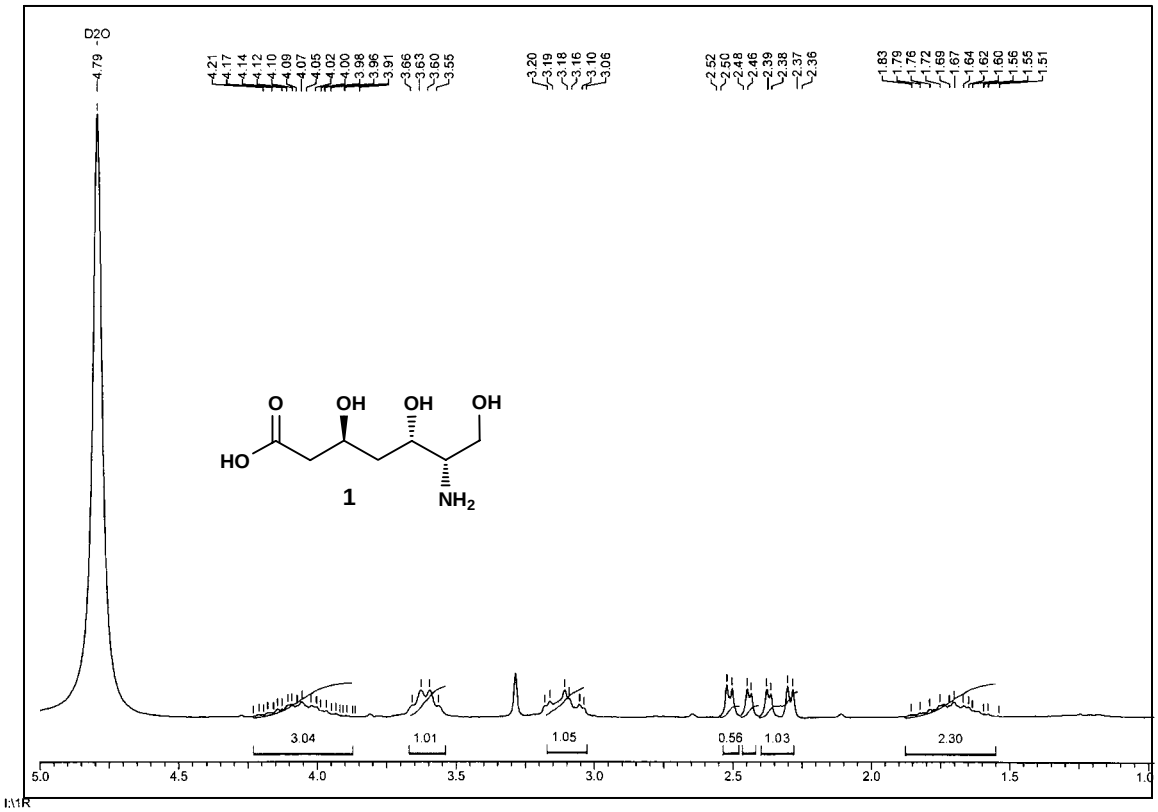
☞ ^{13}C NMR of the compound 43 in $CDCl_3$



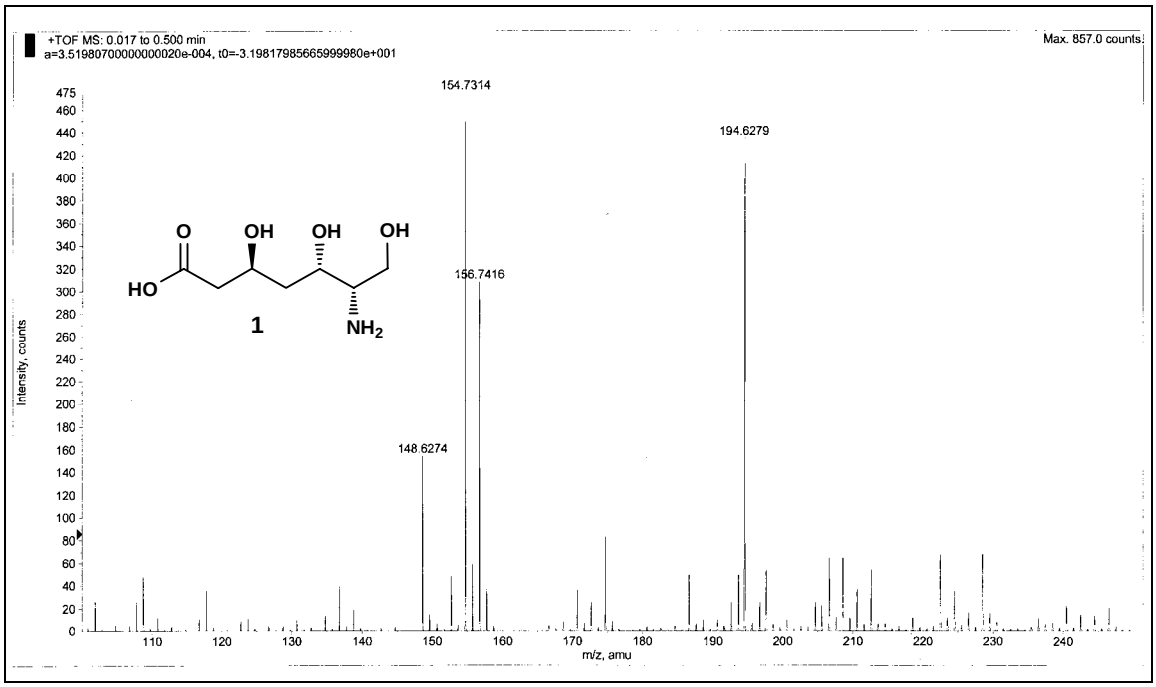
☞ **^{1}H NMR of the compound 44 in $CDCl_3$**



☞ **^{13}C NMR of the compound 44 in $CDCl_3$**



☞ **^{1}H NMR of the compound 1 in D_2O**



☞ **Mass spectra of compound 1**

2.2 SECTION B

EFFICIENT TOTAL SYNTHESIS OF (−)-(3*S*,6*R*)-3,6-DIHYDROXY-10-METHYLUNDECANOIC ACID

2.2.1. Introduction

(−)-(3*S*,6*R*)-3,6-Dihydroxy-10-methylundecanoic acid **46** and its trimer **47** were isolated from the aerial parts of *Lafuentea rotundifolia* Lag.[13] The original structure of **46** was assigned based on the spectroscopic methods and absolute configuration of chiral center *via* Mosher's analysis (Figure 2).[14] Compound **46** has been a synthetic target of considerable interest due to its β-hydroxyl acid skeleton and unique 1,4-dihydroxyl structure.

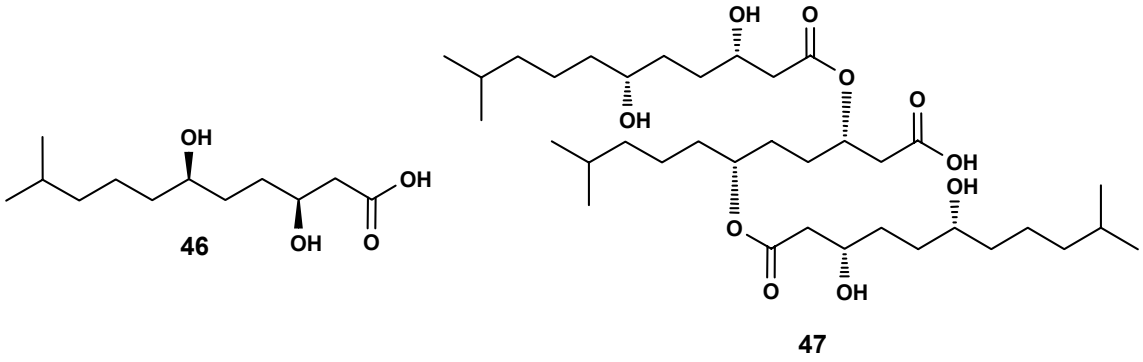


Figure 2. (−)-(3*S*,6*R*)-3,6-dihydroxy-10-methylundecanoic acid **46** and its trimer **47.**

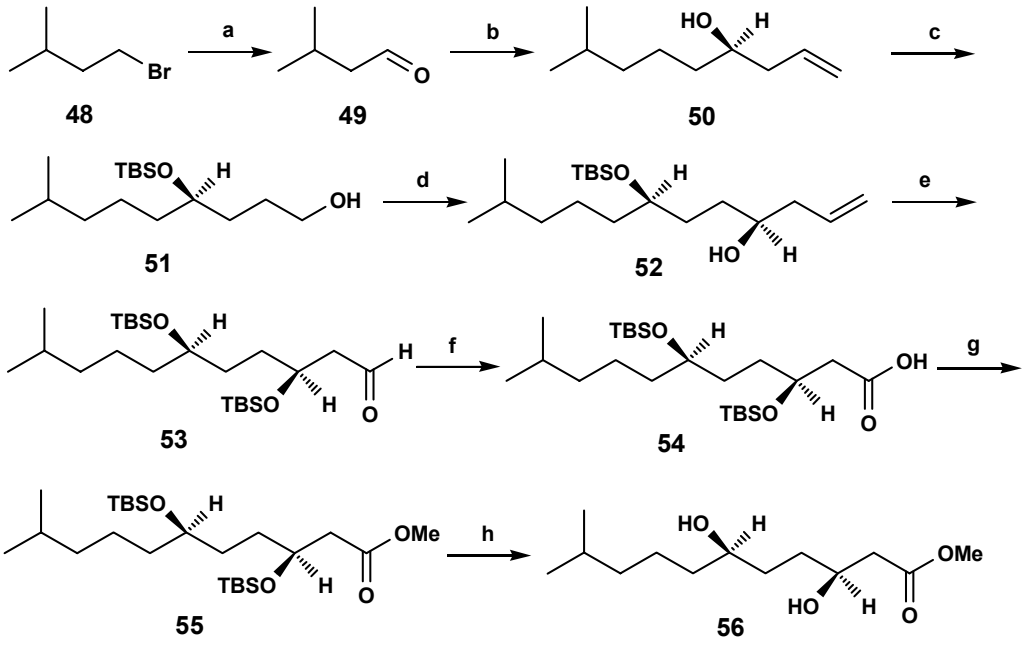
2.2.2. Review of Literature

In the literature, so far only one approach has been reported for (−)-(3*S*,6*R*)-3,6-dihydroxy-10-methylundecanoic acid recently by Zhixiang Xie *et al*.

Xie, Z. *et al*. (2006).[15]

Zhixiang Xie and co-workers accomplished the first total synthesis of (3*S*,6*R*)-3,6-dihydroxy-10-methylundecanoic acid from commercially available 1-bromo-3-methylbutane in 11 steps and 25.8% overall yield. The key steps were asymmetric allylic

alkylations *via* allyldiisopinocampheylborane and hydroboration-oxidation. The Grignard reaction of isopentylmagnesium bromide prepared from isopentyl bromide **48** to the 5-methylhexanal **49** with $dIpc_2B$(allyl) reagent under Brown's conditions afforded homoallylic alcohol **50** in 90.3% ee, which was protected as its corresponding TBS ether followed by hydroboration-oxidation reaction to furnish alcohol **51**. The alcohol **51** was oxidized by Dess–Martin reagent followed by reaction with $lIpc_2B$(allyl) reagent under Brown's conditions to afford homoallylic alcohol **52** in 92.6% de which was protected as its corresponding TBS ether followed by ozonolysis to give the aldehyde **53**. The oxidation of aldehyde **53** with $KMnO_4$ in 5% *t*-BuOH–aqueous NaH_2PO_4 afforded acid **54.** The acid **54** was treated with diazomethane in ethyl ether to afford methyl ester **55** and two TBS groups were removed with TBAF in THF leading to the methyl ester derivative **56**.



Scheme 8. *Reagents and conditions:* (a) i) Mg, Et_2O; ii. ethylene oxide, Et_2O, 0 ^oC-reflux, 3 h, 90%; ii) DMSO, $(COCl)_2$, CH_2Cl_2, -78 to 0 ^oC, 30 min, 88%; (b) Ipc_2B(allyl), Et_2O, -100 to 23 ^oC, 5 h; ii. 3M NaOH, H_2O_2, reflux, 1 h, 80%; (c) i) TBDMSCl, imidazole, DMF, 30 ^oC, 24 h, 95%; ii) $BH_3.SMe_2$, THF, -78 to 0 ^oC, 2.5 h, then 3M NaOH, H_2O_2, 3.5 h, 20 ^oC, 85%; (d) i) Dess–Martin reagent, CH_2Cl_2, rt, 2 h, 95%; ii) Ipc_2B(allyl), Et_2O, -100 to 23 ^oC, 5 h, then 3M NaOH, H_2O_2, reflux, 1 h, 72%; (e) TBDMSCl, imidazole, DMF, 30 ^oC, 24 h, 98%; ii) O_3, CH_2Cl_2, -78 ^oC; ii. PPh_3, rt, 4 h, 90%; (f) 5% NaH_2PO_4,

2M $KMnO_4$, aq. *t*-BuOH, rt, 30 min, 90%; (g) diazomethane, Et_2O, rt, 5 min, 98%; (h) TBAF, THF, rt, 12 h, 90%.

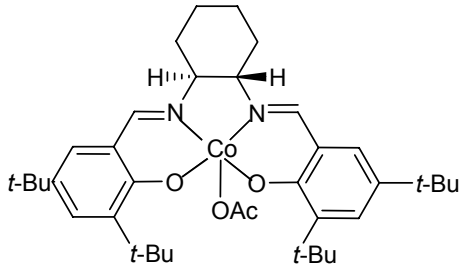
2.2.3. Present work:

Objective:

(−)-(3*S*,6*R*)-3,6-Dihydroxy-10-methylundecanoic acid **46** has been a synthetic target of considerable interest due to its β-hydroxyl acid skeleton and unique 1,4-dihydroxyl structure. As part of our continuing interest towards asymmetric synthesis of naturally occurring compounds, we further aimed towards the efficient total synthesis of **46** from commercially available epichlorohydrin using Jacobsen's HKR, Sharpless asymmetric dihydroxylation and regioselective opening of epoxide and cyclic sulfate as the key steps.

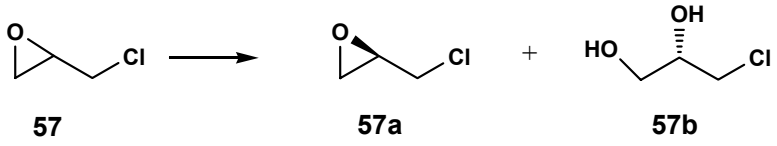
2.2.4. Results and Discussion:

The synthesis of (−)-(3*S*,6*R*)-3,6-dihydroxy-10-methylundecanoic acid **46** started from the commercially available epichlorohydrin **57** as shown in the Scheme 9. Epichlorohydrin **57** was subjected to Jacobsen's HKR using (*S*,*S*)-Salan-Co-(OAc) (Figure 3) catalyst to give (*R*)-epichlorohydrin **57a** as a single isomer $[\alpha]_D^{25}$ –32.5° (*c* 1.25, MeOH); {lit[16]. $[\alpha]_D^{26}$ –32.8° (*c* 1.27, MeOH)}, which was easily isolated from the more polar diol **57b** by distillation (Scheme 9).



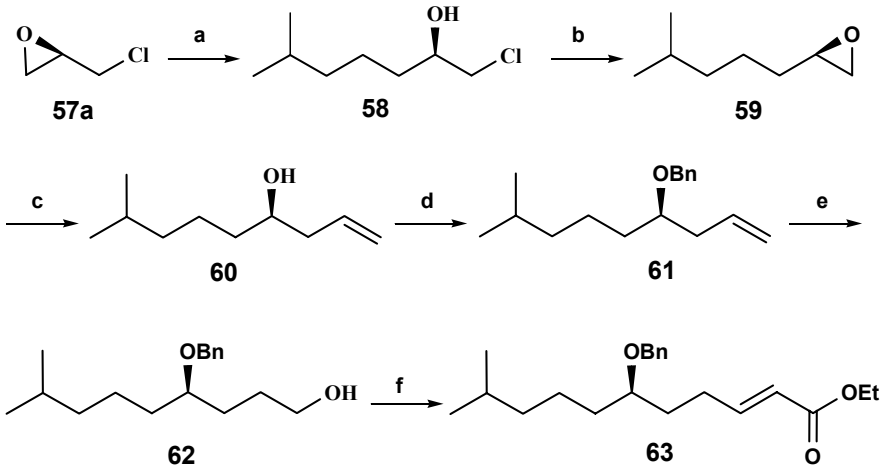
(*S*,*S*)-SalenCo (III) OAc complex

Figure 3.



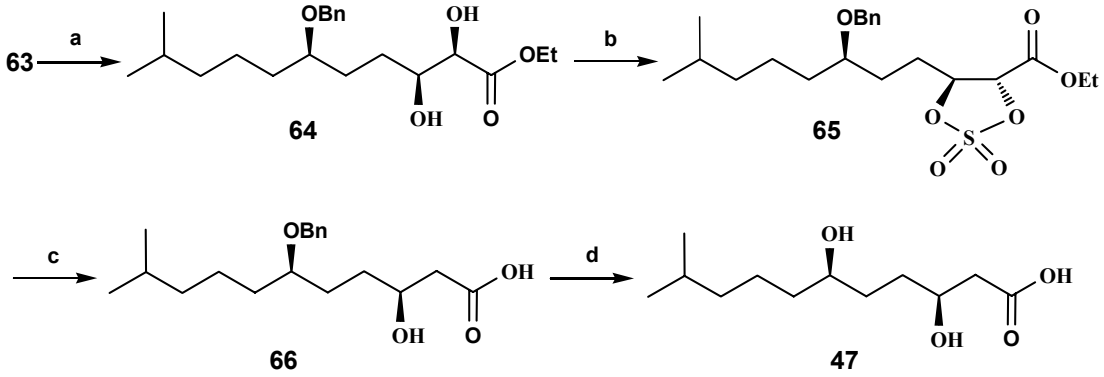
Scheme 9. ***Reagents and conditions:*** (i) (*S*,*S*)-Salen-Co-(OAc) (0.5 mol%), dist. H_2O (0.55 eq), 0 ^oC, 14 h, (46% for **57a**, 45% for **57b**).

With enantiomercially pure epichlorohydrin **57a** in hand, we then subjected it to copper-catalysed (CuI) regioselective ring-opening with *iso*-amylmagnesium bromide (**57a→58**) followed by treatment with base to give the epoxide **59**. In the ^1H NMR spectrum peaks owing to epoxide were present at 2.47 (doublet of doublet, J = 3.1, 5.3 Hz, 1H), 2.76 (triplet, J = 4.5 Hz, 1H), and 2.87-2.96 (multiplet, 1H). Subsequent reaction with vinylmagnesium bromide furnished **60** in overall 89% yield. The IR spectrum of **60** gave broad hydroxyl absorption at 3421 cm^{-1}. The ^1H NMR spectrum of **60** showed olefin peaks at 5.08-5.12 (multiplet, one proton), 5.16-5.20 (multiplet, one proton) and 5.74-5.94 (multiplet, one proton). The hydoxyl protection of **60** with benzyl bromide in the presence of NaH gave **61** in 97% yield, which was then subjected to hydroboration-oxidation reaction to afford the alcohol **62** in 88% yield.



Scheme 10. ***Reagents and conditions:*** (a) $Me_2CH(CH_2)_2MgBr$, CuI, dry Et_2O, -78 ^oC, 12 h, 98%; (b) KOH, Et_2O, 0 ^oC-rt, 6 h, 96%; (c) C_2H_3MgBr, CuI, THF, -78 ^oC, 12 h, 95%; (d) BnBr, TBAI, NaH, THF, 0 ^oC-rt, 97%; (e) (i) $BH_3.SMe_2$, THF, 0 ^oC, 4 h; (ii) 3N NaOH, H_2O_2, 6 h, 88%; (f) $(COCl)_2$, DMSO, CH_2Cl_2, -78 ^oC, Et_3N, -65 ^oC, 1 h (ii) $Ph_3P{=}CHCO_2Et$, THF, rt, 24 h, 93%.

Our next aim was to carry out the two carbon homologation of **62** *via* Wittig reaction. To this end, compound **62** was oxidised to the aldehyde under Swern conditions[17] and subsequently treated with (ethoxycarbonylmethylene)triphenylphosphorane in dry THF at room temperature to furnish the *trans*-Wittig product **63** in 93% yield. The IR spectrum of **63** showed the ester carbonyl absorption at 1721 cm^{-1} and olefin C=C stretching at 1654 cm^{-1}. The ^1H NMR spectrum gave olefin protons at δ 5.82 (doublet of triplet) with the coupling constant J = 1.70, 15.7 Hz and δ 6.86-7.05 (multiplet) indicating *trans*-olefin. The dihydroxylation of olefin **63** with osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of $(DHQ)_2PHAL$ under the Sharpless asymmetric conditions[11] gave the diol **64** in 96% yield with 94% de. The diastereomeric excess was found to be 94% using ^1H NMR and ^{13}C NMR analysis. The IR spectrum of **64** showed hydroxyl absorption at 3444 cm^{-1} and ester carbonyl at 1737 cm^{-1}. The ^1H NMR indicated absence of olefin protons. Treatment of diol **64** with thionyl chloride and triethylamine in CH_2Cl_2 gave the cyclic sulfite, which was further oxidised using $NaIO_4$ and a catalytic



Scheme 11. ***Reagents and conditions:*** (a) $(DHQ)_2PHAL$ (1 mol%), 0.1 M OsO_4 (0.5 mol%), K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, *t*-BuOH/H_2O 1:1, 0 ^oC, 24 h, 96%; (b) (i) $SOCl_2$, Et_3N, CH_2Cl_2, 0 ^oC, 30 min; (ii) $RuCl_3$, $NaIO_4$, CCl_4–MeCN–H_2O; 2:2:3, 0^o C, 1 h, 98%; (c) $NaBH_4$, DMAC, 25 ^oC, 30 min, then 20% aq. H_2SO_4, overnight, 86%; (d) 20% $Pd(OH)_2/C$, H_2, EtOAc, rt, 10 h, 81%.

amount of ruthenium trichloride to furnish the corresponding cyclic sulfate **65** in quantitative yield.[12] The synthetic strategy shown in Scheme 11 was based on the

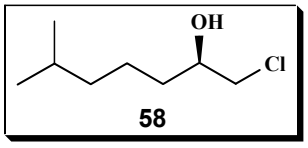
presumption that the nucleophilic opening of the cyclic sulfate **65** would occur in a regiospecific manner at α-carbon.[12] Indeed, the cyclic sulfate **65** reacted with one equivalent of $NaBH_4$ with apparent complete selectivity for attack at C-2 position to furnish the intermediate sulfate ester which, without further isolation was subjected to acidic hydrolysis using 4N H_2SO_4 to give **66** in excellent yield. Finally, benzyl deprotection with 20% $Pd(OH)_2/H_2$ led to **47** as a white powder in 81% yield.

2.2.5. Conclusion

In conclusion, a practical and enantioselective synthesis of (−)-(3*S*,6*R*)-3,6-dihydroxy-10-methylundecanoic acid has been achieved from epichlorohydrin in 10 steps and 46.5% overall yield, employing Jacobsen's HKR, Sharpless asymmetric dihydroxylation, regioselective opening of epoxide and cyclic sulfate as the key steps. The merits of this synthesis are high diastereoselectivity and high yielding reaction steps. The synthetic strategy described has significant potential for further extension to other analogues of β-hydroxy carboxylic acid with no substituents at Cα.

2.2.6. Experimental Section

(*R*)-1-Chloro-6-methylheptan-2-ol (58):



58

To a stirred solution of (*R*)-epichlorohydrin **57a** (>99% *ee*, 3.00 g, 32.43 mmol) and CuI (1.24 g, 6.49 mmol) in dry Et_2O (50 mL), was added a solution of *iso*-amylmagnesium bromide prepared form *iso*-amyl bromide (9.8 g, 64.85 mmol) and Mg-turning (1.58 g, 64.85 mmol) in dry Et_2O, dropwise at –78 °C. The mixture was warmed to -20 °C over 12 h and poured into a saturated NH_4Cl solution. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined ethereal extracts were dried over

Na_2SO_4. The extracts were concentrated to near dryness and purified on silica gel column chromatography (EtOAc/petroleum ether, 1:9) to give **58** as colorless oil.

Yield: 5.23 g, 98%

Mol. Formula: $C_8H_{17}ClO$

$[\alpha]_D^{25}$ = +6.07 (*c* 1, $CHCl_3$)

IR (neat, cm^{-1}): ν_{max} 3409, 2955, 1467, 1216

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (d, *J* = 6.6 Hz, 6 H), 1.14-1.64 (m, 7 H), 2.09 (brs, 1 H), 3.57 (ddd, *J* = 3.3, 8.0, 18.0 Hz, 2 H), 3.76-3.87 (m, 1 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 22.4, 23.2, 27.8, 34.4, 38.7, 50.3, 71.4 ppm.

Analysis: Calcd.: C, 58.35; H, 10.41%; **Found:** C, 58.40; H, 10.39%.

(*R*)-2-(4-Methylpentyl)oxirane (59):

59

To a solution of **58** (5.10 g, 30.97 mmol) in Et_2O (50 mL) was added finely powdered KOH (5.21 g, 92.91 mmol). The mixture was stirred vigorously for 6 h and poured into 20 mL water. After separation of the layers, the aqueous layer was extracted with Et_2O (3 x 50 mL) and the combined organic layers were dried over Na_2SO_4. Evaporation of the solvent and silica gel column chromatographic purification (EtOAc/petroleum ether, 1:49) of the crude product gave **59** as a colorless liquid.

Yield: 3.81 g, 96%

Mol. Formula: $C_8H_{16}O$

$[\alpha]_D^{25}$: +5.96 (*c* 1, $CHCl_3$).

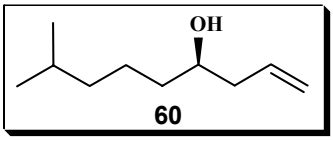
IR (neat, cm^{-1}): ν_{max} 3018, 2869, 1736, 1467, 1216

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (d, *J* = 6.7 Hz, 6 H), 1.16-1.63 (m, 7 H), 2.47 (dd, *J* = 3.1, 5.3 Hz, 1 H), 2.76 (t, *J* = 4.5 Hz, 1 H), 2.87-2.96 (m, 1 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 22.4, 23.2, 27.8, 34.4, 38.7, 50.3, 71.4 ppm.

Analysis: Calcd.: C, 74.94; H, 12.58%; **Found:** C, 74.84; H, 12.49%.

(*R*)-8-Methylnon-1-en-4-ol (60):



To a stirred solution of **59** (2.00 g, 15.60 mmol) and CuI (594 mg, 3.12 mmol) in dry THF (30 mL), was added over 30 min a 1 M solution of vinylmagnesium bromide in THF (3.07 g, 23.40 mmol, 23.40 ml, 1M solution in THF) dropwise at -78 °C and stirred for 12 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 Et_2O (3 x 30 mL), the combined ethereal extracts were washed with brine (20 mL) and dried (Na_2SO_4). Evaporation of the solvent and silica gel column chromatographic purification (EtOAc/ petroleum ether 1:20) of the crude product gave **60** as a colorless oil.

Yield: 2.32 g, 95%

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

$[\alpha]_D^{25}$: + 2.80 (*c* 1.0, $CHCl_3$).

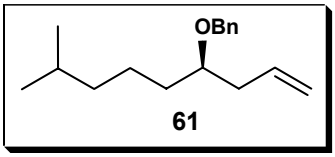
IR (neat, cm^{-1}): ν_{max} 3421, 2955, 1640, 1467, 1216

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (d, *J* = 6.6 Hz, 6 H), 1.13-1.61 (m, 7 H), 2.06-2.38 (m, 2 H), 3.59-3.71 (m, 1 H), 5.08-5.12 (m, 1 H), 5.16-5.20 (m, 1 H), 5.74-5.94 (m, 1 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 22.5, 23.4, 27.9, 37.0, 38.9, 41.9, 70.6, 117.8, 134.9 ppm.

Analysis: Calcd.: C, 76.86; H, 12.90%; **Found:** C, 76.51; H, 12.93%.

(*R*)-((8-Methylnon-1-en-4-yloxy)methyl)benzene (61):



To a solution of **60** (2.2 g, 14.07 mmol) in dry DMF (50 mL) was added sodium hydride (60%, 0.85 g, 21.12 mmol) at 0 ^oC. The reaction mixture was then stirred at room temperature for 30 min after which it was again cooled to 0 ^oC. To this was added slowly benzyl bromide (2.49 g, 15.49 mmol) and tetra *n*-butylammonium iodide (262 mg, 0.71 mmol) with further stirring for 1 h at the same temperature. The reaction mixture was

quenched with addition of cold water at 0 ^{o}C. The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with water (3 x 20 mL), brine, dried (Na_2SO_4) and concentrated. The residual oil was purified by silica gel column chromatography (EtOAc/petroleum ether, 1:50) to furnish the protected alcohol **61** as a colorless oil.

Yield: 3.36 g, 97%

Mol. Formula: $C_{17}H_{26}O$

$[\alpha]_D^{25}$: + 9.44 (*c* 1.0, $CHCl_3$).

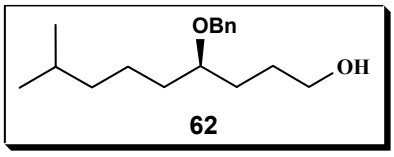
IR (neat, cm^{-1}): ν_{max} 2867, 1640, 1454, 1095

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (d, *J* = 6.82 Hz, 6 H), 1.11-1.60 (m, 7 H), 2.34 (t, *J* = 6.37 Hz , 2 H), 3.40-3.51 (qn, 1 H), 4.54 (d, *J* = 7.26 Hz, 2 H), 5.04-5.06 (m, 1 H) 5.09-5.16 (m, 1 H), 5.77-5.98 (m, 1 H), 7.30-7.41 (m, 5 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 22.6, 23.1, 27.9, 34.0, 38.3, 39.0, 70.9, 78.5, 116.7, 127.4, 127.7, 128.2, 135.1, 138.9 ppm.

Analysis: Calcd.: C, 82.87; H, 10.64%; **Found:** C, 82.91; H, 10.59%.

(*R*)-4-(Benzyloxy)-8-methylnonan-1-ol (62):



62

To a solution of **61** (3.2 g, 12.99 mmol) in dry THF (35 mL) at 0°C under argon atmosphere was added BH_3.DMS (1.09 g, 6.58 mL, 14.29 mmol, 2 M solution in THF) and the reaction mixture was allowed to warm to room temperature and stirred for 4 h. The reaction flask was cooled to 0 °C and then a solution of NaOH (1.04 g, 25.98 mmol) in EtOH/H_2O (2:1, 15 mL), followed by H_2O_2 (4.41 mL, 38.96 mmol, 30% w/v solution in water) were added dropwise over 30 min. It was then allowed to stir at room temperature for 6 h. The product was taken up in EtOAc and the aqueous layer extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine, water, dried (Na_2SO_4) and concentrated. Silica gel column chromatography purification (EtOAc/petroleum ether, 2:8) of the crude product gave alcohol **62** as a colorless liquid.

Yield: 3.02 g, 88%

Mol. Formula: $C_{17}H_{28}O_2$

$[\alpha]_D^{25}$: -6.37 (*c* 1.0, $CHCl_3$).

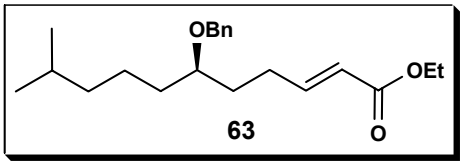
IR (neat, cm^{-1}): ν_{max} 3388, 2867, 1726, 1454, 1063

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (d, *J* = 7.0 Hz, 6 H), 1.11-1.74 (m, 11 H), 1.94 (brs, 1 H), 3.39-3.50 (qn, 1 H), 3.64 (t, *J* = 6.9 Hz, 2 H), 4.53 (d, *J* = 2.8 Hz, 2 H), 7.30-7.37 (m, 5 H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 22.5, 22.9, 27.8, 28.4, 30.1, 33.7, 38.9, 62.7, 70.7, 78.8, 127.4, 127.7, 128.2, 138.6 ppm.

Analysis: Calcd.: C, 77.22; H, 10.67%; **Found:** C, 77.15; H, 10.70%.

(*R*,*E*)-Ethyl 6-(benzyloxy)-10-methylundec-2-enoate (63) :



63

To a solution of oxalyl chloride (2.02 g, 15.89 mmol) in dry CH_2Cl_2 (30 mL) at −78°C was added dropwise DMSO (2.56 g, 2.33 mL, 32.83 mmol) in CH_2Cl_2 (5 mL) over 15 min. The reaction mixture was stirred for 30 min and a solution of **62** (2.8 g, 10.59 mmol) in CH_2Cl_2 (20 mL) was added dropwise over 15 min. The reaction mixture was stirred for 30 min at −78°C and 30 min at −60°C and then Et_3N (4.72 g, 6.50 mL, 46.60 mmol) in CH_2Cl_2 (5.00 mL) was added dropwise and stirred for 1 h. The reaction mixture was poured into saturated solution of $NaHCO_3$ (50 mL) and the organic layer separated. The aqueous layer was extracted with ether (3 x 20 mL) and the combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated to give the crude aldehyde. This was used for the next step without further purification.

To a solution of (ethoxycarbonylmethylene)triphenyl phosphorane (4.06 g, 11.65 mmol) in dry THF (20 mL) was added a solution of the above aldehyde in dry THF (10 mL). The reaction mixture was stirred at room temperature for 24 h. It was then concentrated and purified by silica gel column chromatography (EtOAc/petroleum ether, 1:9) to give olefin **63** as a pale yellow oil.

Yield: 3.27 g, 93%

Mol. Formula: $C_{21}H_{32}O_3$

$[\alpha]_D^{25}$: -11.45 (*c* 1.0, $CHCl_3$).

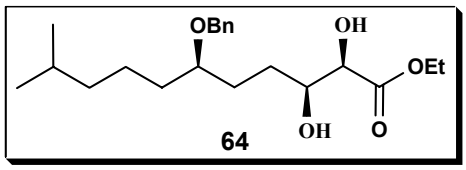
IR (neat, cm^{-1}): ν_{max} 2953, 1721, 1654, 1268, 1046

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (d, *J* = 6.4 Hz, 6 H), 1.15-1.74 (m, 12 H), 2.20-2.41 (m, 2 H), 3.36-3.47 (qn, 1 H), 4.19 (q, *J* =7.6, 14.5 Hz, 2 H), 4.51 (d, *J* = 5.9 Hz, 2 H), 5.82 (dt, *J* =1.70, 15.7 Hz, 1 H) 6.86-7.05 (m, 1 H), 7.29-7.37 (m, 5 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.2, 22.5, 27.8, 28.0, 32.1, 33.8, 39.0, 60.0, 70.8, 77.9, 121.3, 127.4, 127.7, 128.2, 138.7, 149.0, 166.5 ppm.

Analysis: Calcd.: C, 75.86; H, 9.70%; **Found:** C, 75.88; H, 9.69%.

(2*R*,3*S*,6*R*)-Ethyl 6-(benzyloxy)-2,3-dihydroxy-10-methylundecanoate (64):



64

To a mixture of $K_3Fe(CN)_6$ (4.46 g, 13.53 mmol), K_2CO_3 (1.87 g, 13.53 mmol), $(DHQ)_2PHAL$ (35 mg, 1 mol%) in *t*-BuOH/H_2O (1:1, 20 mL) at 0°C was added osmium tetroxide (0.22 mL, 0.1 M solution in toluene, 0.5 mol%), followed by methanesulfonamide (428 mg, 4.50 mmol). After stirring for 2 min at 0°C, the olefin **63** (1.5 g, 4.51 mmol) was added in one portion. The reaction mixture was stirred at 0°C for 24 h and then quenched with solid sodium sulfite (3 g). The stirring was continued for additional 15 min and then the solution was extracted with EtOAc (3 x 20 mL). The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography purification (EtOAc/petroleum ether, 1:4) of the crude product gave **64** as a colorless syrupy liquid (94% de).

Yield: 1.59 g, 96%

Mol. Formula: $C_{21}H_{34}O_5$

$[\alpha]_D^{25}$: -15.08 (*c* 1.0, $CHCl_3$).

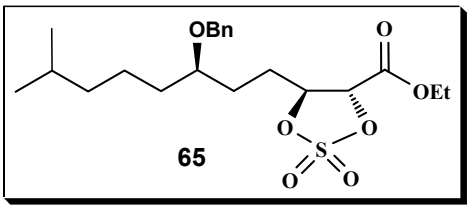
IR (neat, cm^{-1}): ν_{max} 3444, 2867, 1737, 1454, 1275, 1206

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.86 (d, *J* = 6.5 Hz, 6 H), 1.14-1.79 (m, 14 H), 2.54 (brs, 2 H), 3.38-3.50 (m, 1 H), 3.89 (dt, *J* = 1.77, 5.68 Hz, 1 H), 4.06 (dd, *J* = 2.0, 4.1 Hz, 1 H), 4.30 (q, *J* = 7.1 Hz, 2 H), 4.53 (d, *J* = 3.9 Hz, 2 H), 7.30-7.36 (m, 5 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 22.5, 22.9, 27.8, 29.3, 29.7, 33.7, 38.9, 61.7, 70.6, 72.5, 73.3, 78.6, 127.4, 127.7, 128.2, 138.6, 173.4 ppm.

Analysis: Calcd.: C, 68.82; H, 9.35%; **Found:** C, 68.64; H, 9.43%.

(2*R*,3*S*,6*R*)-5-(3-Benzyloxy-7-methyl-octyl)-2,2-dioxo-[1,3,2]dioxathiolane-4-carboxylic acid ethyl ester (65):



To a solution of diol **64** (500 mg, 13.65 mmol) in dry CH_2Cl_2 (15 mL) was added Et_3N (290 mg, 0.4 mL, 2.87 mmol). The mixture was cooled in an ice bath and thionyl chloride (180 g, 0.11 mL, 15.02 mmol) added dropwise. The reaction mixture was stirred for 30 min and then quenched by adding water (10 mL). The phases were separated and aqueous phase extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated. Then the solution was cooled with an ice-water bath and diluted with CH_3CN (10 mL) and CCl_4 (10 mL). $RuCl_3/H_2O$ (15 mg, 0.07 mmol) and $NaIO_4$ (518 mg, 2.43 mmol) were added followed by water (15 mL). The resulting orange mixture was stirred at room temperature for 1 h. The mixture was then diluted with ether (20 mL), and the two phases separated. The organic layer was washed with water (20 mL), saturated with aq. $NaHCO_3$ (20 mL), brine, dried Na_2SO_4, and concentrated. Silica gel column chromatography purification (EtOAc/petroleum ether, 1:5) of the crude product gave sulfate **65** as a colorless liquid.

Yield: 573 mg, 98%

Mol. Formula: $C_{21}H_{32}O_7S$

$[\alpha]_D^{25}$: -1.27 (*c* 1.0, $CHCl_3$)

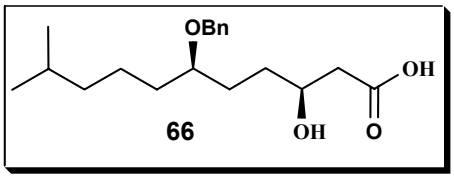
IR (neat, cm^{-1}): ν_{max} 2954, 1765, 1739, 1454, 1217

^{1}H NMR (20 MHz, $CDCl_3$): δ 0.89 (d, *J* = 6.3 Hz, 6 H), 1.16-2.23 (m, 14 H), 3.40-3.51 (qn, 1 H), 4.30 (q, *J* = 7.6, 11.4 Hz, 2 H), 4.51 (d, *J* = 7.89 Hz, 2H), 4.59-4.73 (m, 1 H), 5.00-5.20 (m, 1 H), 7.30-7.36 (m, 5 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9, 22.5, 27.8, 29.5, 30.2, 33.7, 38.9, 62.4, 70.8, 81.3, 82.5, 86.64, 127.5, 127.7, 128.3, 138.6, 166.8 ppm.

Analysis: Calcd.: C, 58.86; H, 7.53%; **Found:** C, 58.79; H, 7.55%.

(3*S*,6*R*)-6-(Benzyloxy)-3-hydroxy-10-methylundecanoic acid (66):



$NaBH_4$ (26 mg, 0.70 mmol) was added under argon to a solution of cyclic sulfate **65** (300 mg, 0.70 mmol) in dry DMAC (8 mL). The reaction mixture was stirred under argon at room temperature for 12 h. The solvent was removed under reduced pressure and reaction mixture was acidified with 4 N H_2SO_4 (6 mL) and stirred at room temperature overnight. The solvent was stripped off under reduced pressure and the residue was purified by silica gel column chromatography purification (EtOAc/petroleum ether 1:1.5) to give **66** as a colorless syrup.

Yield: 190 mg, 86%

Mol. Formula: $C_{19}H_{30}O_4$

$[\alpha]_D^{25}$: +4.01 (*c* 1.0, $CHCl_3$).

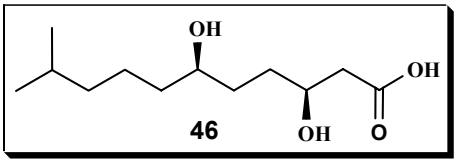
IR (neat, cm^{-1}): ν_{max} 3425, 2916, 1651, 1265

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.86 (d, *J* = 6.6 Hz, 6 H), 1.18-1.85 (m, 11 H), 2.33-2.56 (m, 3 H), 3.99-4.09 (m, 1 H), 4.16 (d, *J* = 7.2 Hz, 2 H), 5.12-5.24 (qn, 1 H), 7.33-7.61 (m, 3 H), 8.05 (d, *J* = 7.0 Hz, 2 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.7, 19.2, 19.7, 22.5, 22.6, 27.9, 30.5, 38.0, 65.5, 71.7, 72.5, 128.3, 128.8, 130.9, 132.3, 167.7 ppm.

Analysis: Calcd.: C, 70.77; H, 9.38%; **Found:** C, 70.84; H, 9.41%.

(3*S*,6*R*)-3,6-Dihydroxy-10-methylundecanoic acid (46):



To a solution of **66** (51 mg, 0.16 mmol) in EtOAc (8 mL) was added the catalytic amount of 20% $Pd(OH)_2/C$. The reaction mixture was hydrogenated using a H_2 balloon for 10 h. After this time the reaction mixture was filtered through a pad of Celite and the pad was washed with additional EtOAc (30 mL). Silica gel column chromatography purification (EtOAc/pet ether 8:2) of the crude product gave **46** as a white solid powder.

Yield: 30 mg, 81%

M.P.: 150-151 ^{o}C.

$[\alpha]_D^{25}$: -9.66 (*c* 0.9 $CHCl_3$)

IR (neat, cm^{-1}): ν_{max} 3386, 2957, 1685

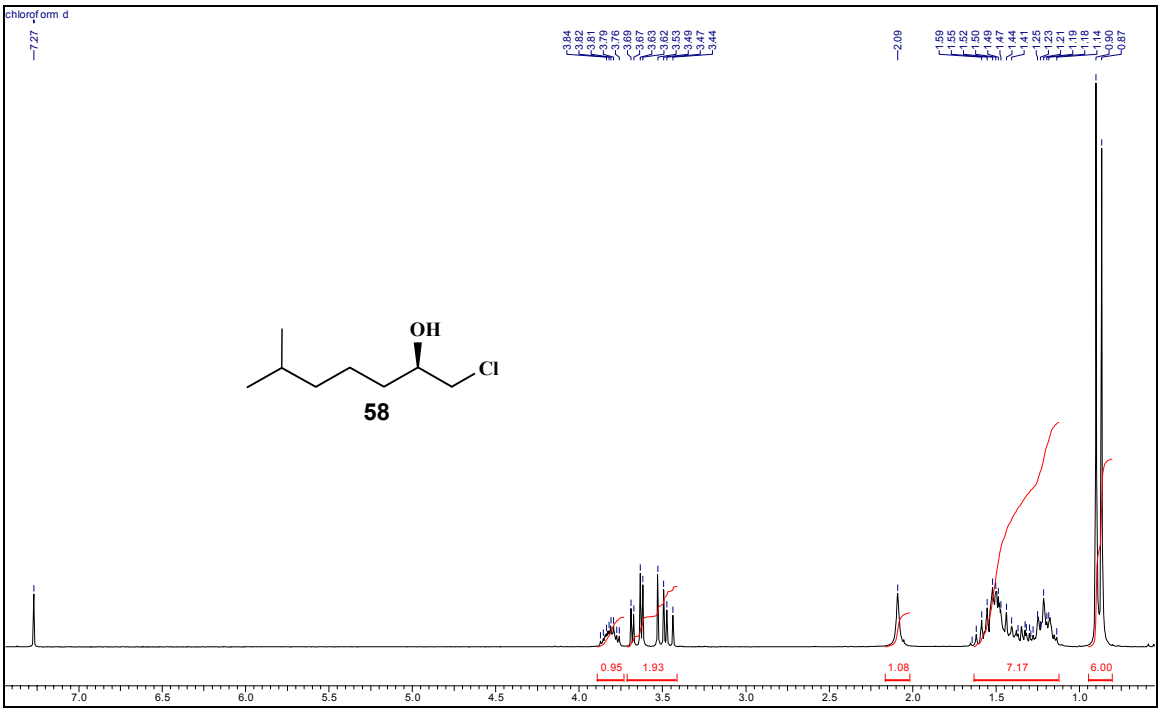
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (d, *J* = 6.8 Hz, 6 H), 1.16-1.67 (m, 11 H), 1.84 (brs, 2 H), 2.47-2.50 (m, 2 H), 3.60-3.69 (m, 1 H), 4.01-4.10 (m, 1 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 19.7, 22.6, 28.3, 31.9, 38.2, 40.4, 44.3, 68.8, 72.9, 176.7 ppm.

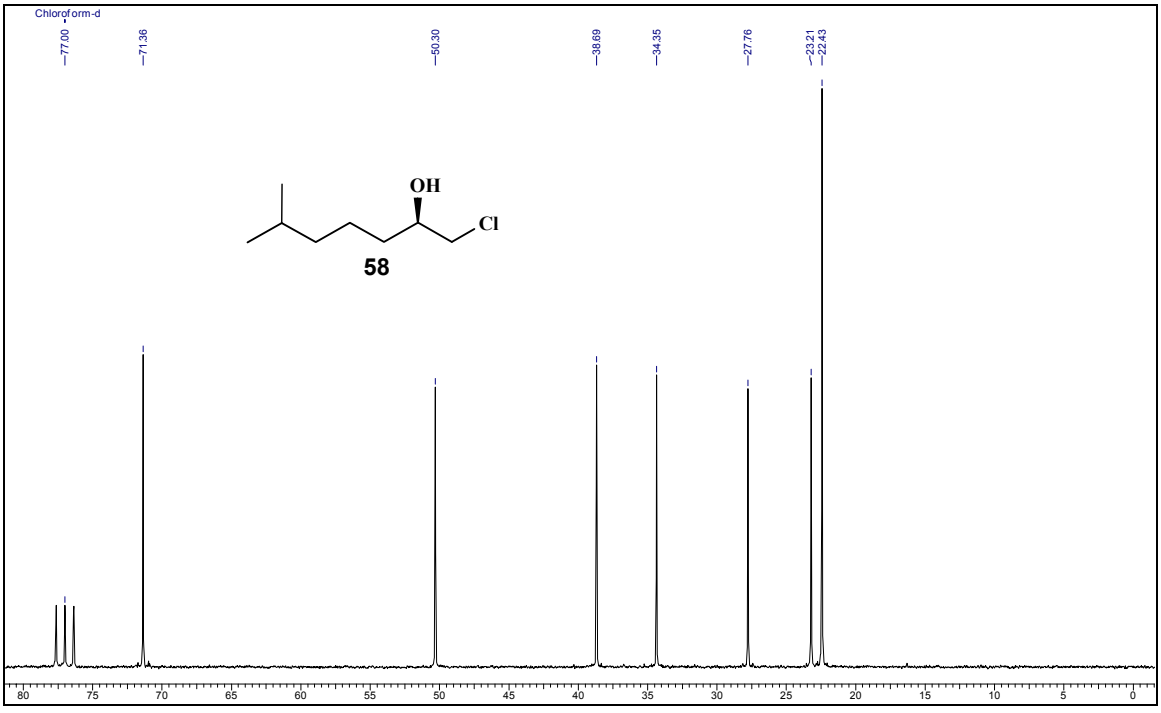
MS (ESI) m/z = 232 $[M]^+$.

2.2.7 Spectra

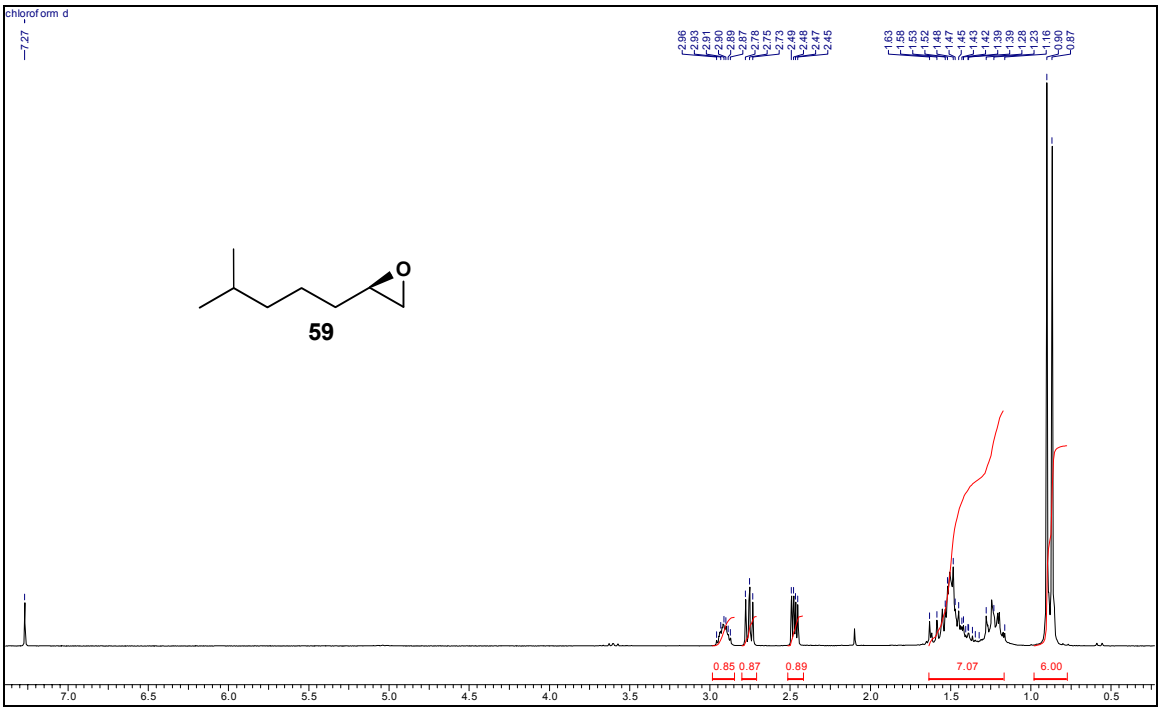
1. ^{1}H and ^{13}C NMR spectra of **58**
2. ^{1}H and ^{13}C NMR spectra of **59**
3. ^{1}H and ^{13}C NMR spectra of **60**
4. ^{1}H and ^{13}C NMR spectra of **61**
5. ^{1}H and ^{13}C NMR spectra of **62**
6. ^{1}H and ^{13}C NMR spectra of **63**
7. ^{1}H and ^{13}C NMR spectra of **64**
8. ^{1}H and ^{13}C NMR spectra of **65**
9. ^{1}H and ^{13}C NMR spectra of **66**
10. ^{1}H and ^{13}C NMR spectra of **46**



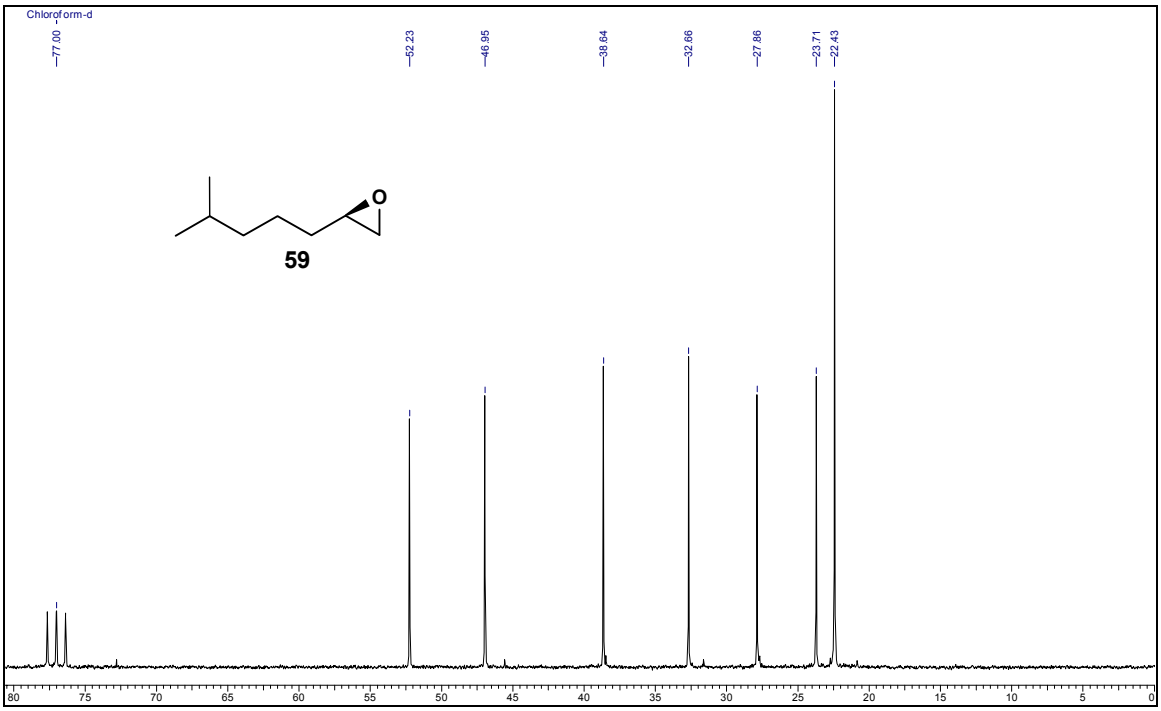
☞ ^{1}H NMR of the compound 58 in $CDCl_3$



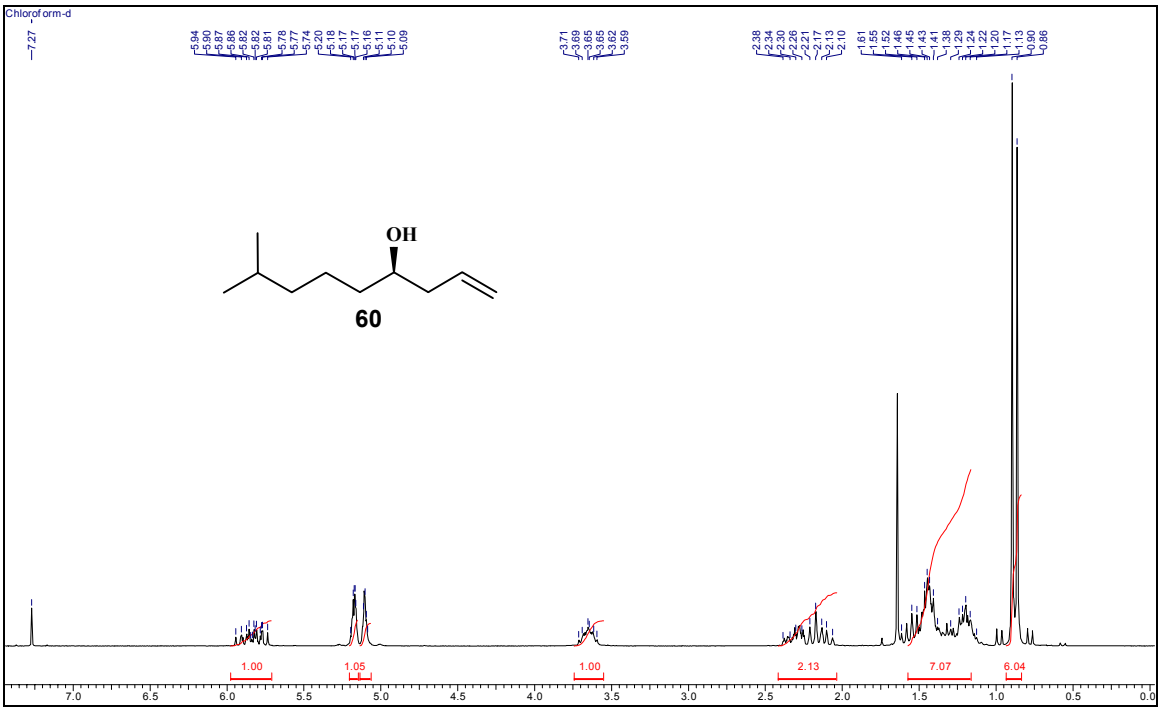
☞ ^{13}C NMR of the compound 58 in $CDCl_3$



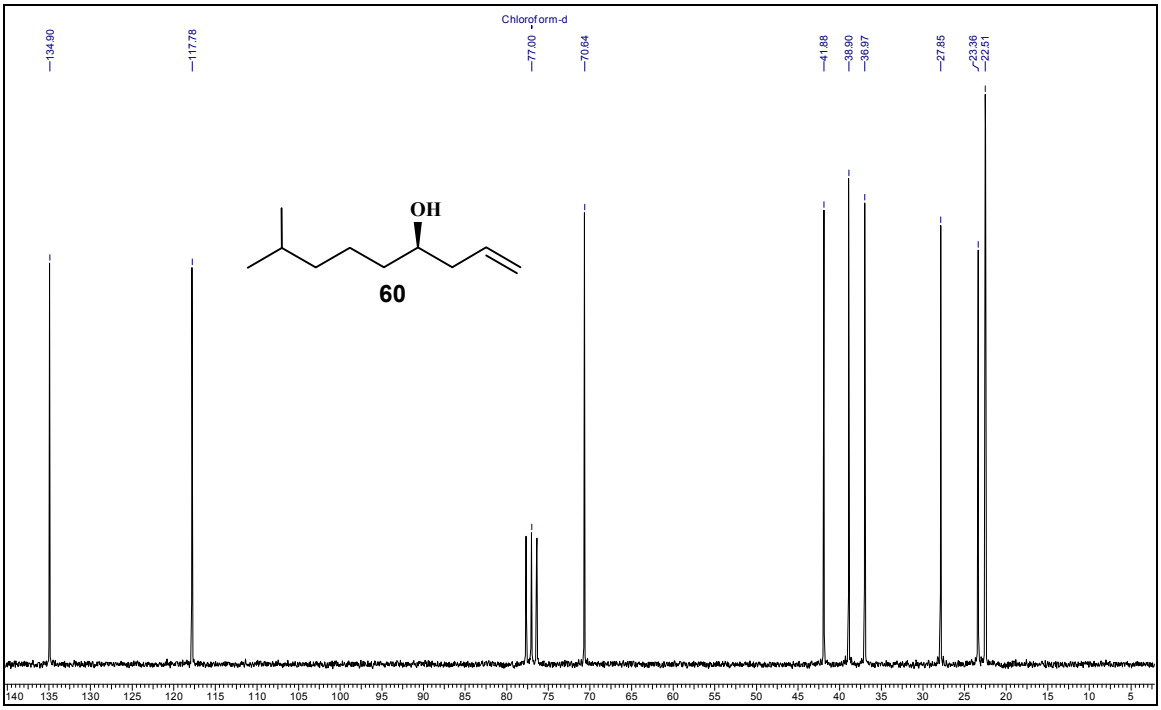
☞ ^{1}H NMR of the compound 59 in $CDCl_3$



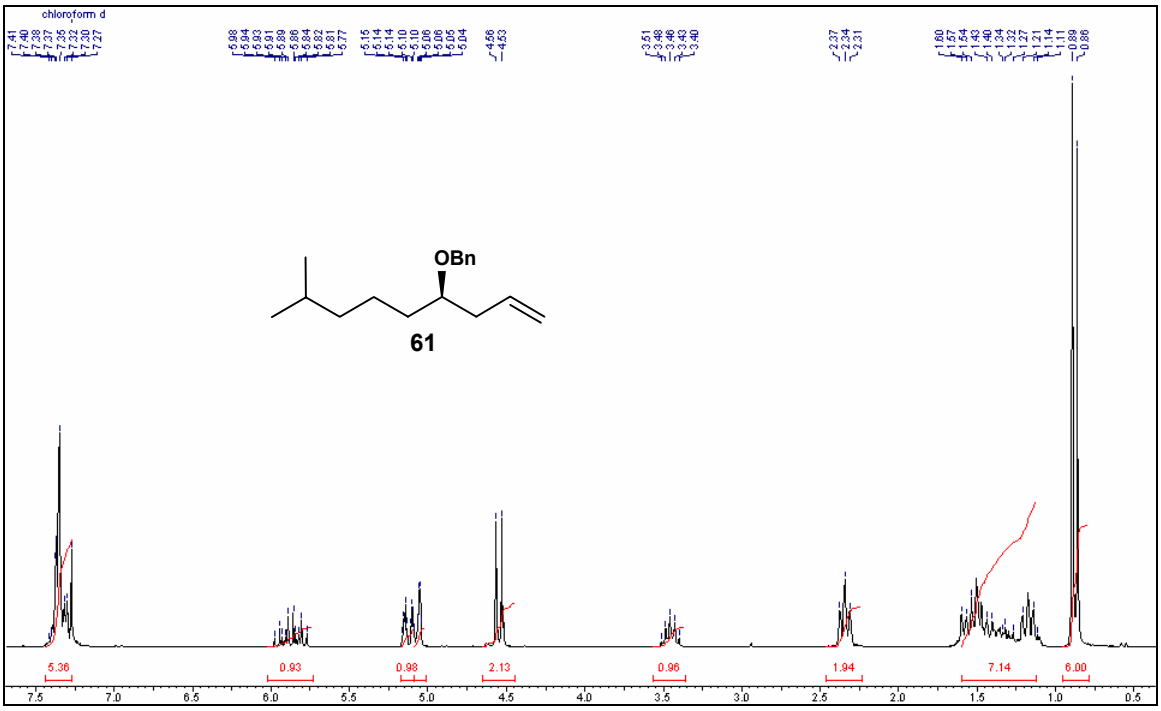
☞ ^{13}C NMR of the compound 59 in $CDCl_3$



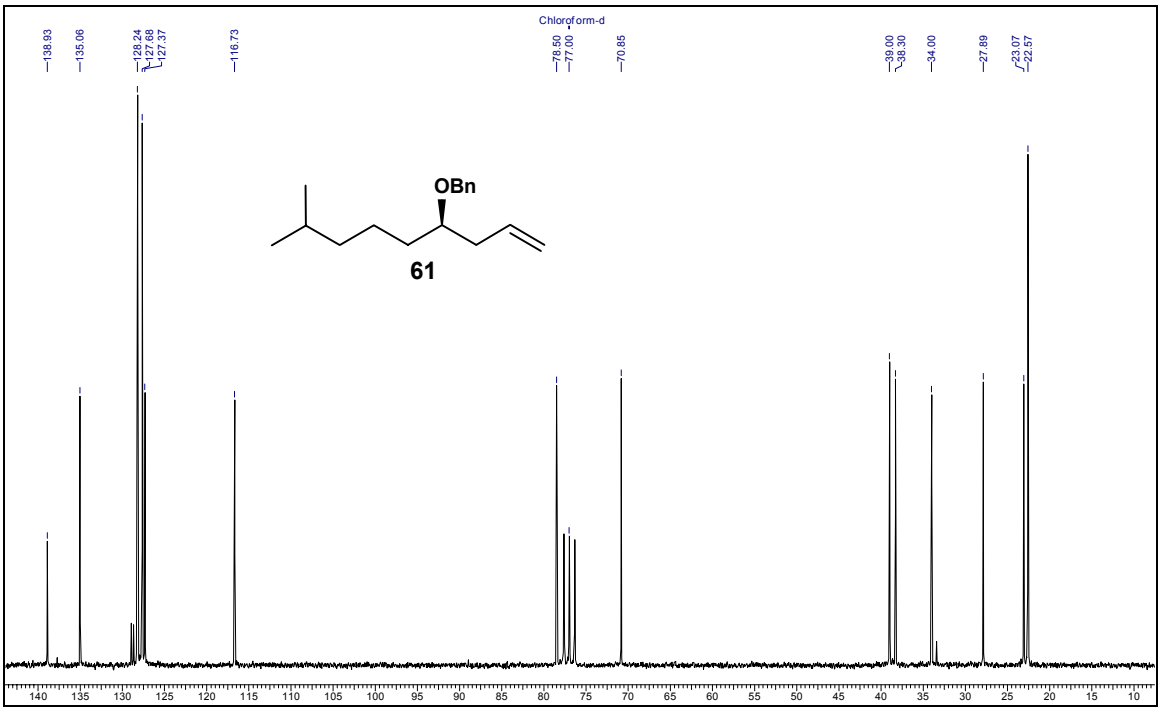
☞ ^{1}H NMR of the compound 60 in $CDCl_3$



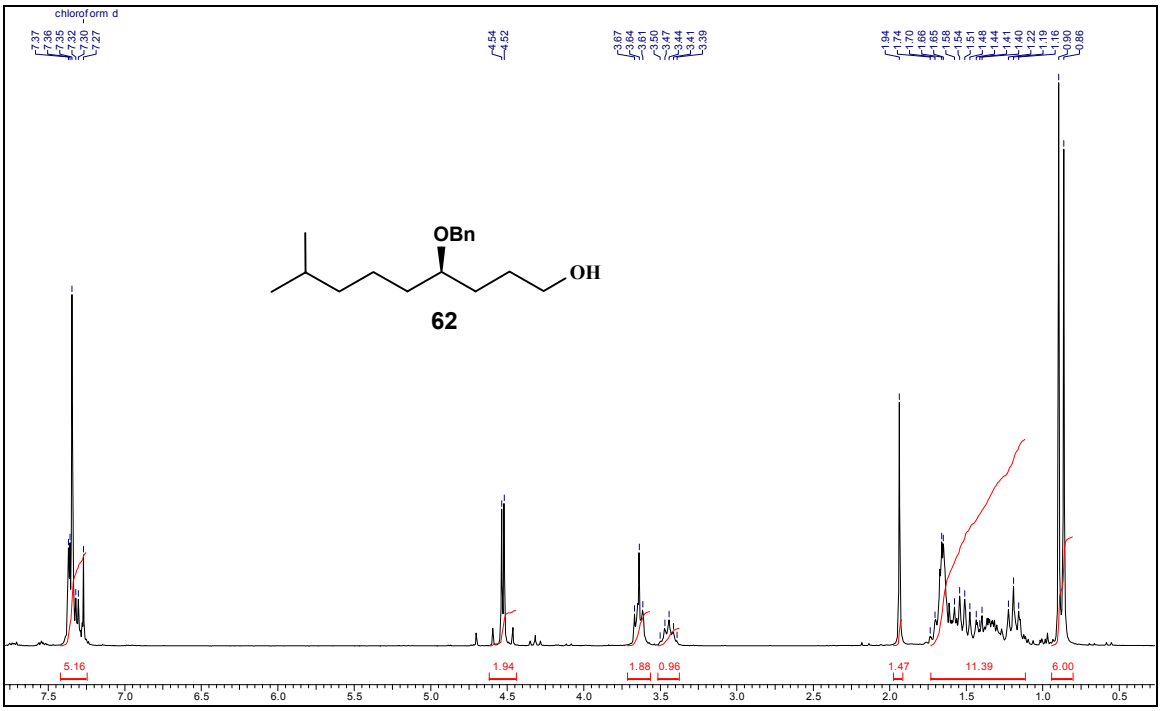
☞ ^{13}C NMR of the compound 60 in $CDCl_3$



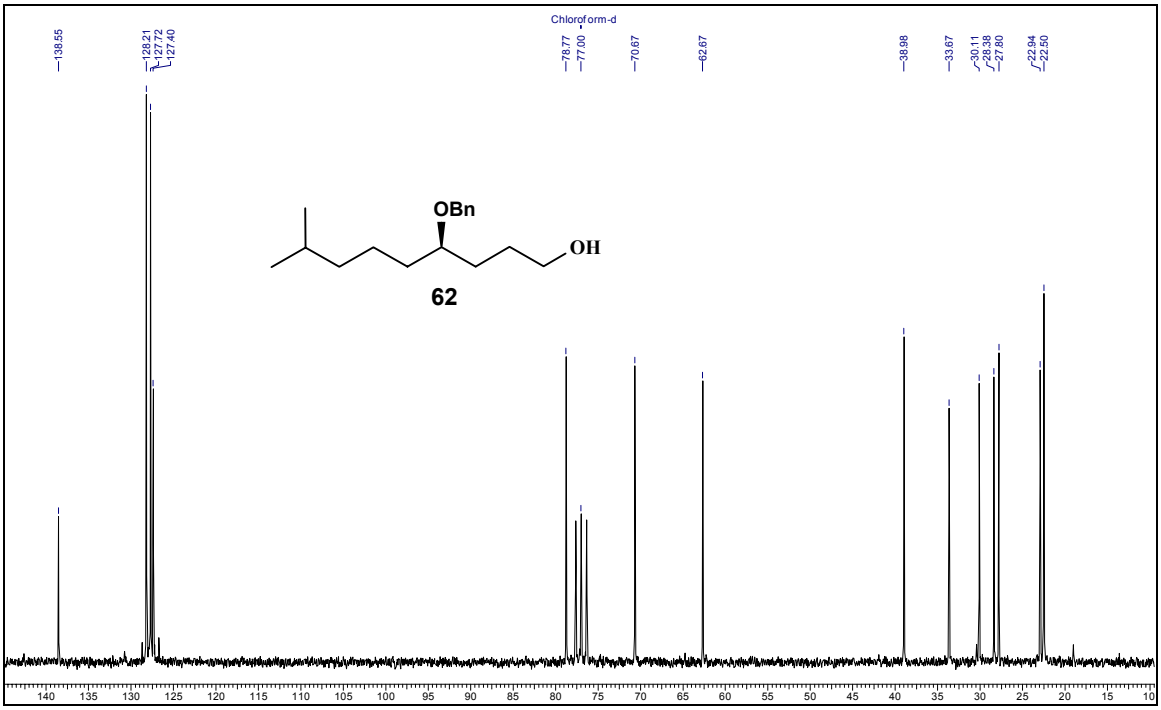
☞ ^{1}H NMR of the compound 61 in $CDCl_3$



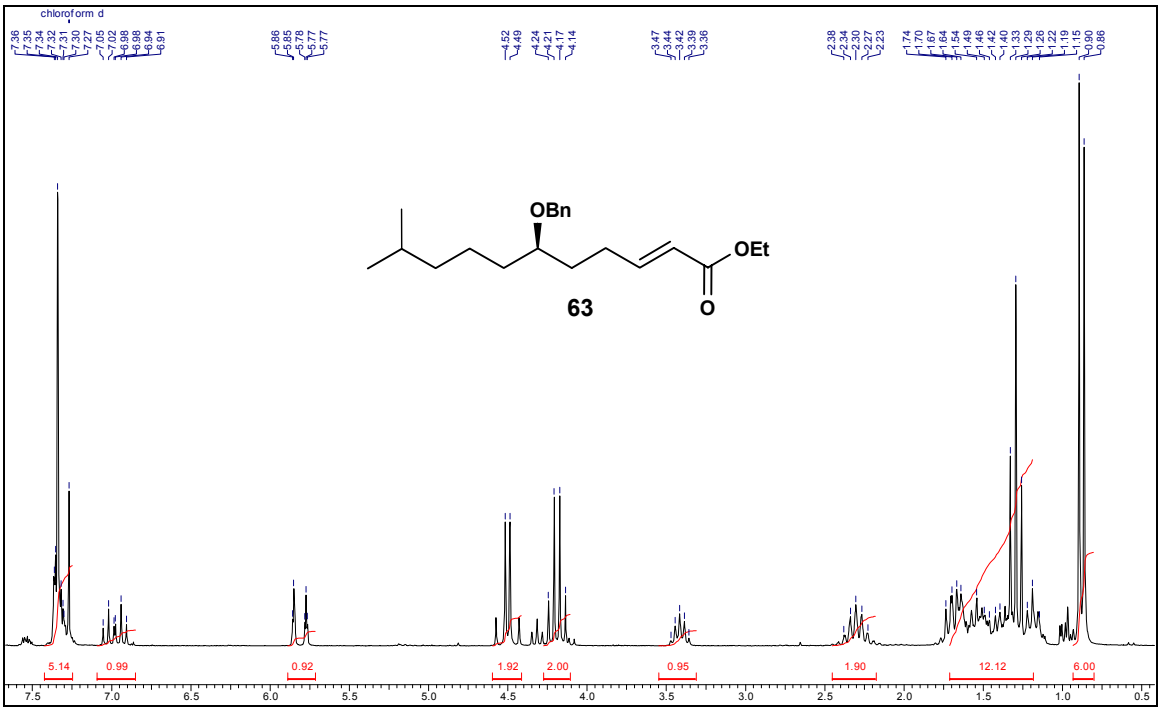
☞ ^{13}C NMR of the compound 61 in $CDCl_3$



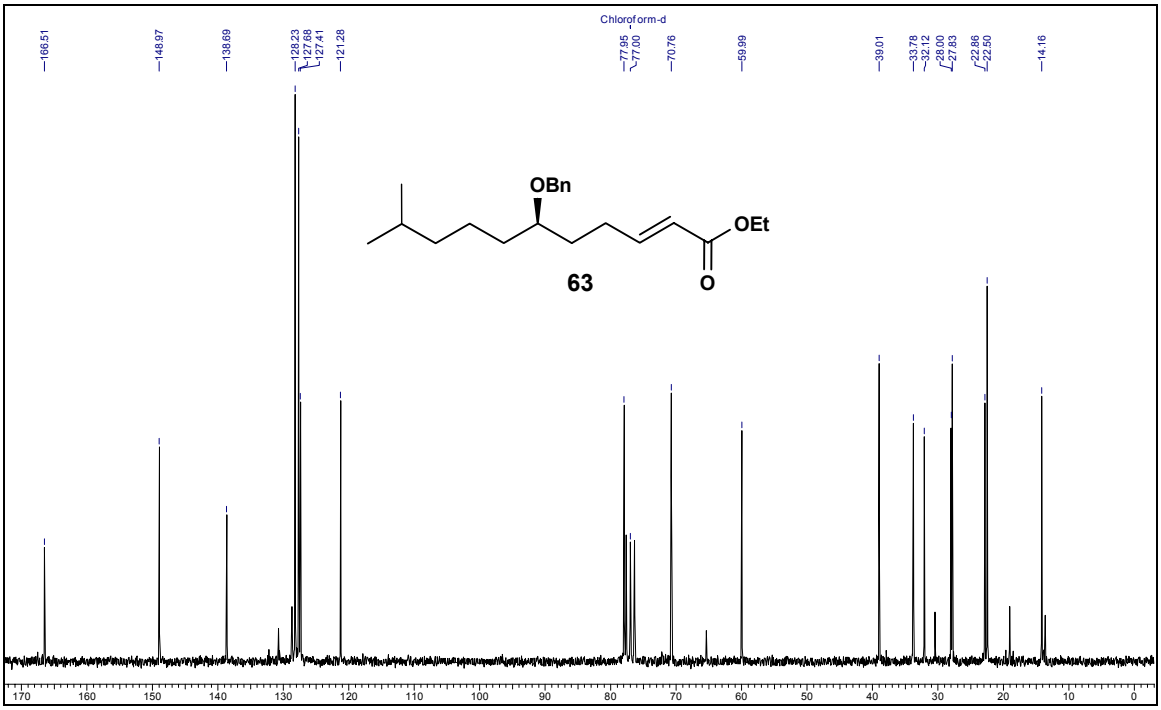
☞ ^{1}H NMR of the compound 62 in $CDCl_3$



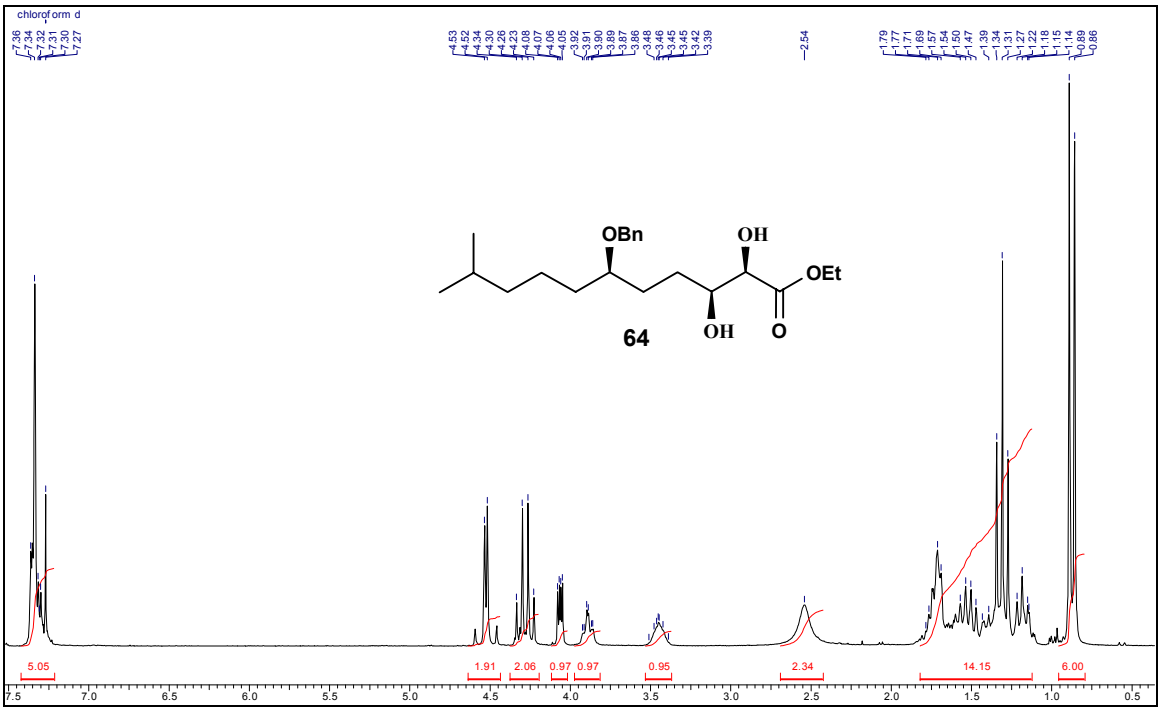
☞ ^{13}C NMR of the compound 62 in $CDCl_3$



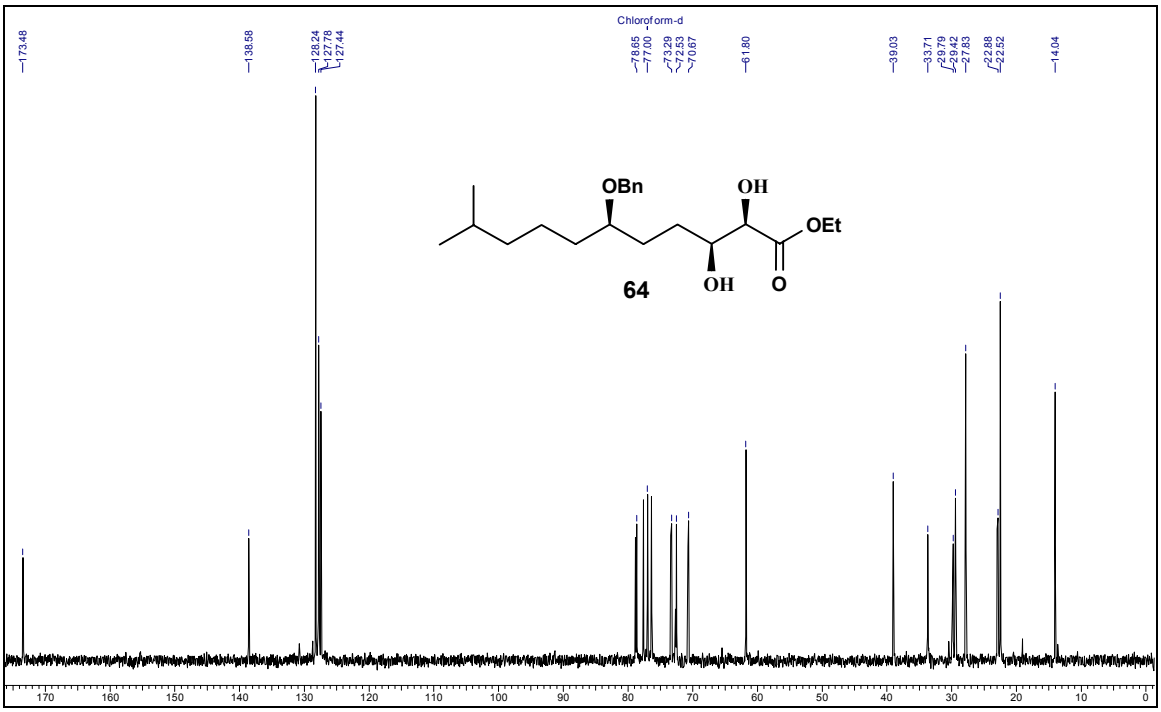
☞ ^{1}H NMR of the compound 63 in $CDCl_3$



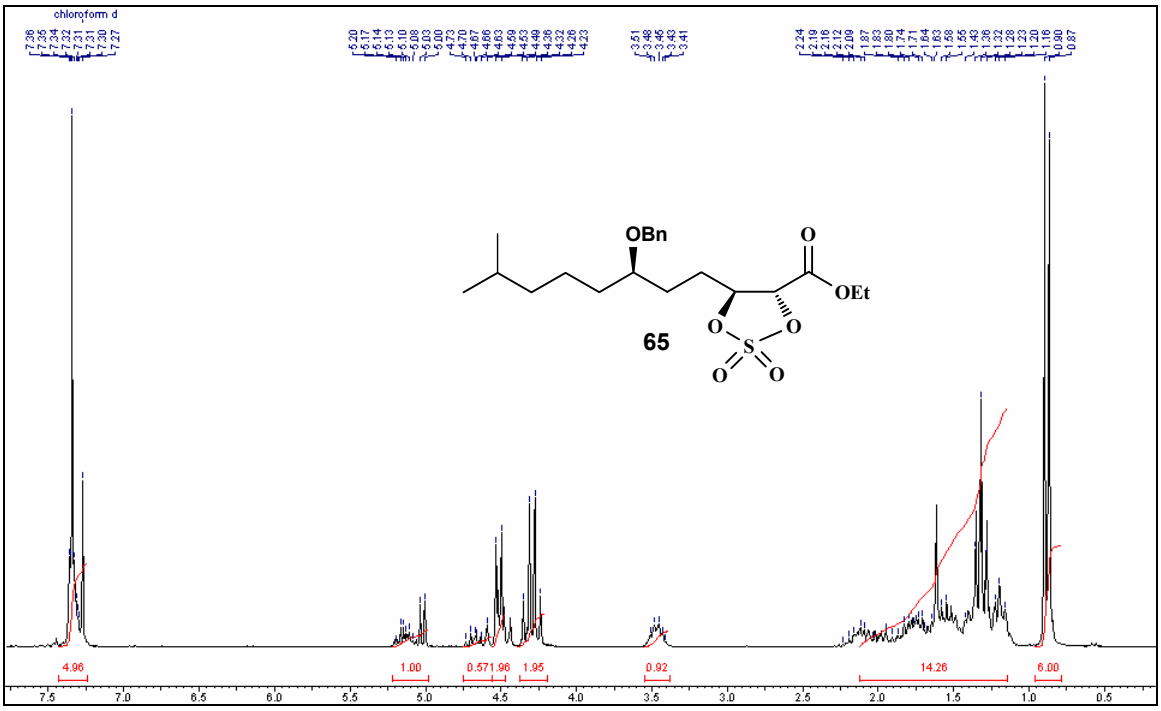
☞ ^{13}C NMR of the compound 63 in $CDCl_3$



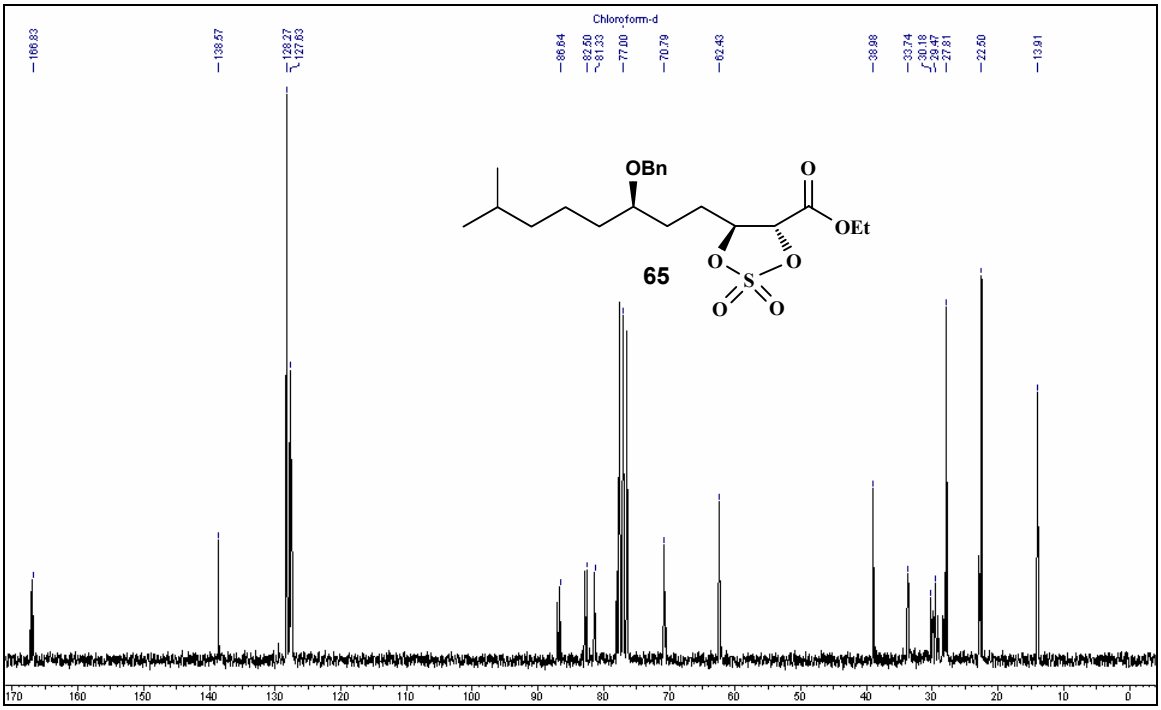
☞ ^{1}H NMR of the compound 64 in $CDCl_3$



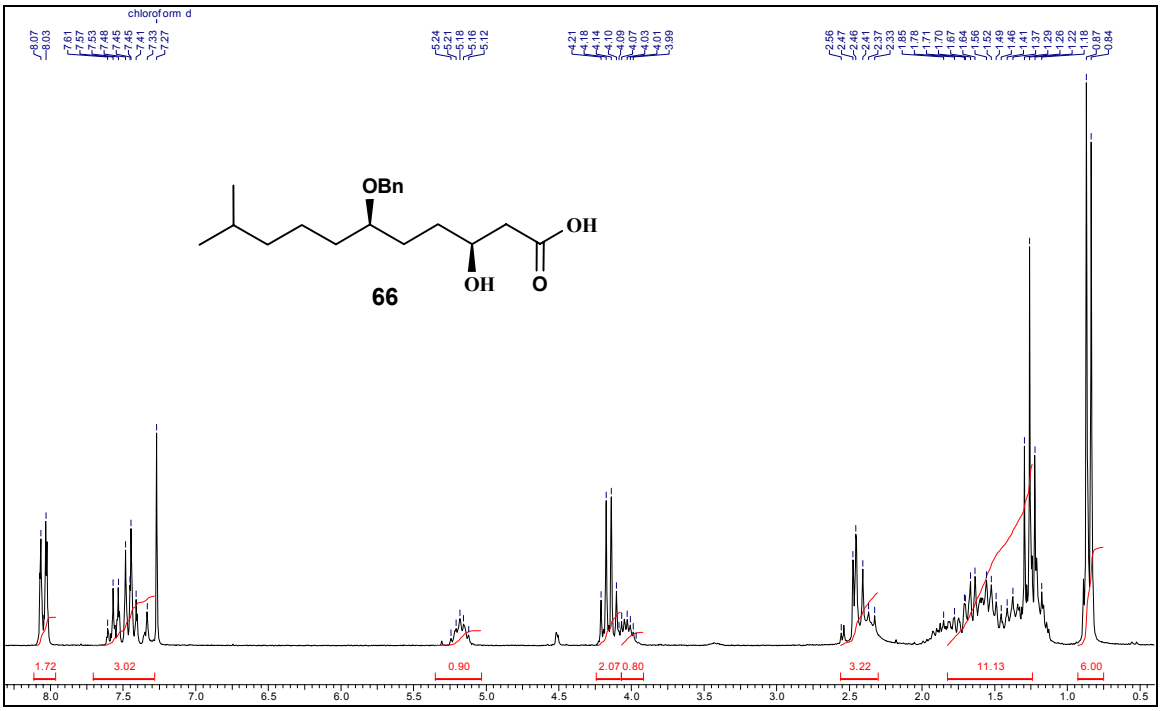
☞ ^{13}C NMR of the compound 64 in $CDCl_3$



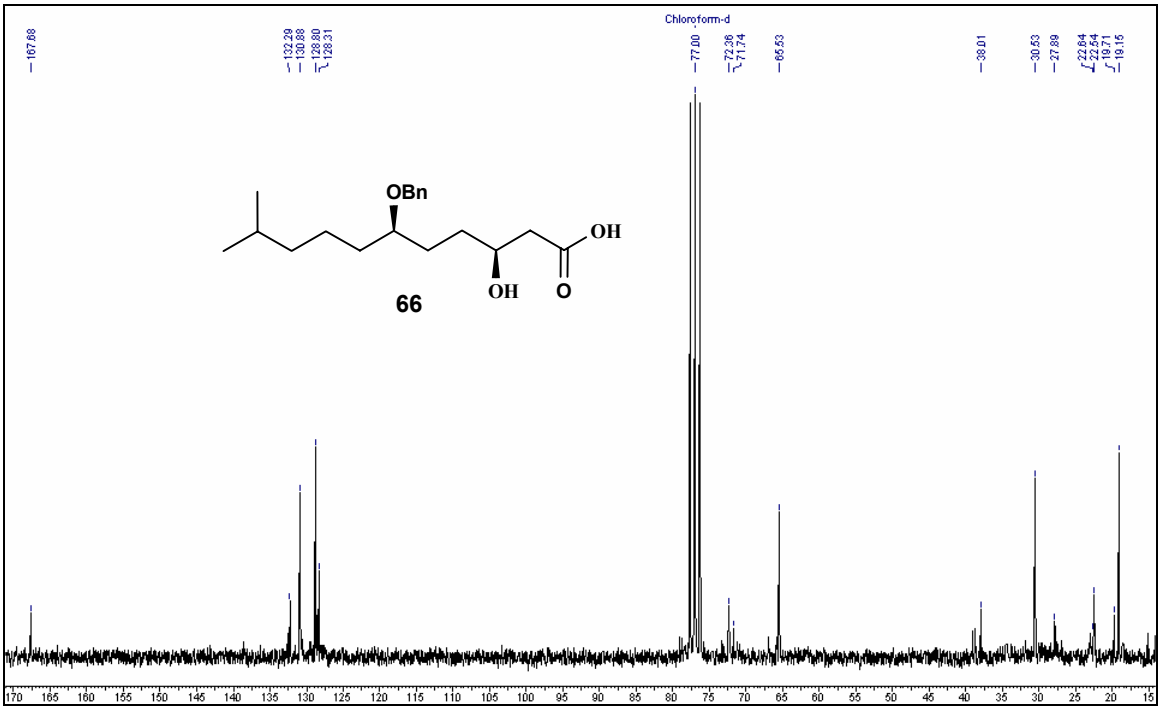
☞ ^{1}H NMR of the compound 65 in $CDCl_3$



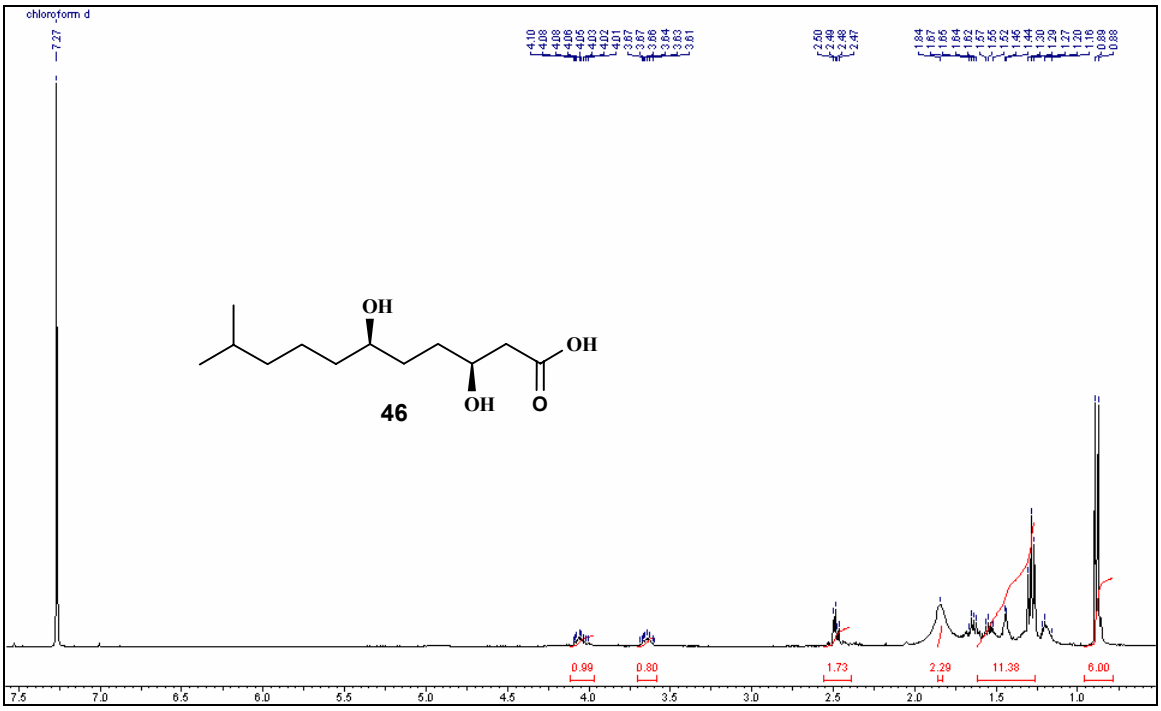
☞ ^{13}C NMR of the compound 65 in $CDCl_3$



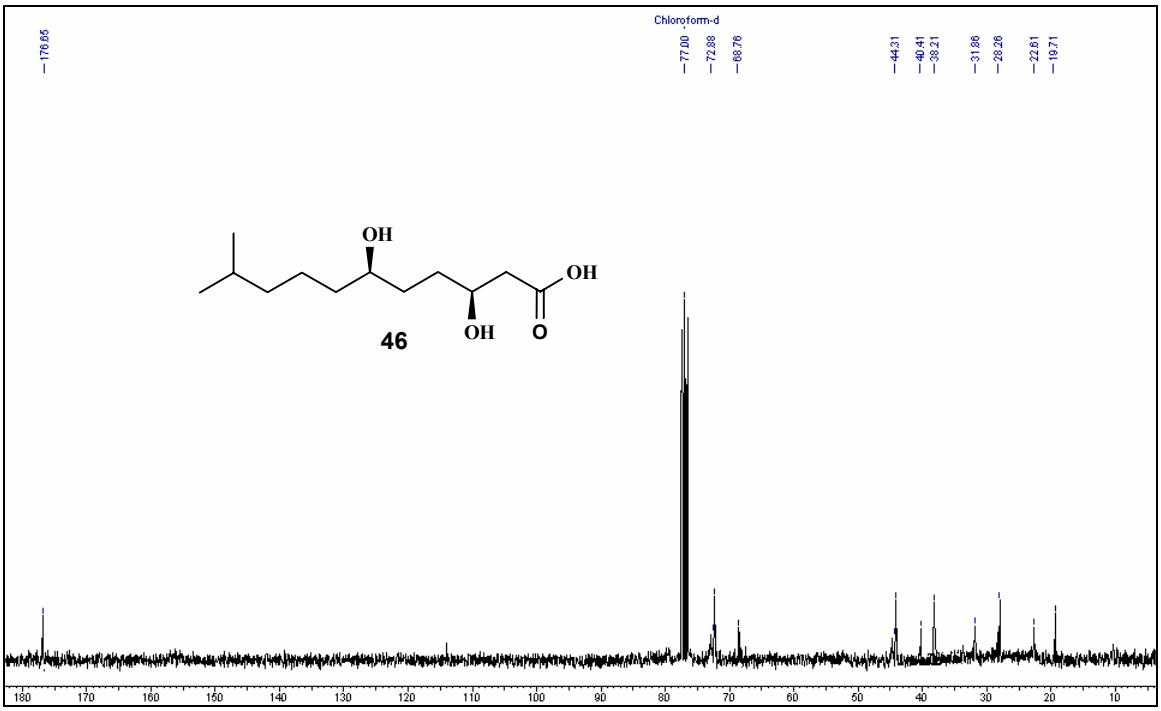
☞ ^{1}H NMR of the compound 66 in $CDCl_3$



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



☞ ^{1}H NMR of the compound 46 in $CDCl_3$



☞ ^{13}H NMR of the compound 64 in $CDCl_3$

2.3 REFERENCES:

1. Shoji, J.; Sakajaki, R.; Koizumi, K.; Matsurra, S. J. *J. Antibiot.* **1975**, *28*, 122.
2. Sakai, N.; Ohfune, Y. *Tetrahedron Lett.* **1990**, *31*, 4151.
3. Sakai, N.; Ohfune, Y. *J. Am. Chem. Soc.* **1992**, *114*, 998.
4. (a) Ikota, N. *Heterocycles* **1991**, *32*, 521; (b) Kumar, J. S. R.; Datta, A. *Tetrahedron Lett.* **1999**, *40*, 1381; (c) Kiyooka, S.; Goh, K.; Nakamura, Y.; Takesue, H.; Hena, M. A. *Tetrahedron Lett.* **2000**, *41*, 6599; (d) Moreau, X.; Campagne, J. *Tetrahedron Lett.* **2001**, *42*, 4467.
5. Raghavan, S.; Ramakrishna Reddy, S. *J. Org. Chem.* **2003**, *68*, 5754.
6. Bethuel, Y.; Gademann, K. *Synlett* **2006**, 1580.
7. (a) Fernandes, R. A.; Kumar, P. *Eur. J. Org. Chem*. **2000**, 3447; (b) Fernandes, R. A.; Kumar, P. *Tetrahedron Lett.* **2000**, *41*, 10309; (c) Subba Rao V. Kandula.; Kumar, P. *Tetrahedron Lett*. **2003**, *44*, 1957; (d) Pandey, R. K.; Fernandes, R. A.; Kumar, P. *Tetrahedron Lett*. **2002**, *43*, 4425; (e) Fernandes, R. A.; Kumar, P. *Synthesis* **2003**, 129; (e) Naidu S. V., Kumar, P. *Tetrahedron Lett*. **2003**, *44*, 1035.
8. (a) Pais, G. C. G.; Fernandes, R. A.; Kumar, P. *Tetrahedron* **1999**, *55*, 13445; (b) Fernandes, R. A.; Kumar, P. *Tetrahedron: Asymmetry* **1999**, *10*, 4349; (c) Fernandes, R. A.; Kumar, P. *Eur. J. Org. Chem*. **2002**, 2921.
9. (a) Katsuki, T.; Sharpless K. B. *J. Am. Chem. Soc*. **1980***, 102,* 5974; (b) Pfenninger, A. *Synthesis* **1986**, 89; (c) Baker, S. R.; Boot, J. R.; Molgan, S. E.; Osborne, D. T.; Ross, W.J.; Shrubsall, P. R. *Tetrahedron Lett.* **1983**, *24,* 4469.
10. (a) Behrens, C. H.; Ko, S. Y.; Sharpless, K. B.; Walker, F. J. *J. Org. Chem.* **1985**, *50*, 5687; (b) Behrens, C. H.; Sharpless K. B. *J. Org. Chem.* **1985**, *50*, 5696; (c) Katsuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.* **1982**, *47*, 1373.
11. Becker, H.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **1996**, *35*, 448; (b) Torri, S.; Liu, P.; Bhuvaneswari, N.; Amatore, C.; Jutand, A. *J. Org. Chem*. **1996**, *61*, 3055; (c) For a review on asymmetric dihydroxylation, see: Kolb, H. C.; VanNiewenhze, M. S.; Sharpless, K. B. *Chem. Rev*. **1994**, *94*, 2483.
12. For reviews on cyclic sulfites/sulfates, see: (a) Lohray, B. B. *Synthesis* **1992**, 1035; (b) Byun, H. S.; He, L.; Bittman, R. *Tetrahedron* **2000**, *56*, 7051.

13. Barrero, A. F.; Herrador, M. M.; Haïdour, A.; Altarejos, J.; Arteaga, P.; Chahboun, R.; *Tetrahedron Lett.* **1995**, *36*, 2649.
14. (a) Ohtani, I.; Kusumi, T.; Ishitsuka, M. O.; Kakisawa, H. *Tetrahedron Lett.* **1989**, *30*, 3147; (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H.; *J. Am. Chem. Soc.* **1991**, *113*, 4092.
15. Zhang, X.; Da, S.; Zhang, C.; Xie, Z.; Li, Y.; *Tetrahedron Lett.* **2006**, *47*, 507.
16. S. E. Schaus, B. D. Brandes, J. F. Larrow, M. Tokunaga, K. B. Hansen, A. E. Gould, M. E. Furrow, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 1307.
17. For reviews on the Swern oxidation, see: (a) T. T. Tidwell, *Synthesis* **1990**, 857; (b) T. T. Tidwell, *Org. React.* **1990**, *39*, 297.

CHAPTER 3

ENANTIOSELECTIVE SYNTHESIS OF HYDROXYORNITHINE AS A CORE UNIT OF BIOLOGICALLY ACTIVE NATURAL PRODUCTS: (2*R*,3*R*)- AND (2*S*,3*S*)-β-HYDROXYORNITHINE & PROTECTED (2*S*,4*R*)-4-HYDROXYORNITHINE

ENANTIOSELECTIVE SYNTHESIS OF (2R,3R)- AND (2S,3S)-β-HYDROXYORNITHINE

3.1.1. Introduction

β-Hydroxy-α-aminoacids are an important class of compounds, due to their presence in nature as primary metabolites themselves (threonine, serine, 4-hydroxyproline) and as components of more complex natural compounds. β-Hydroxyornithines **1a–d** serve as intermediates in the synthesis of important natural products like β-lactams and amino polyols[1] and as biosynthetic precursors to both the β-lactamase inhibitor clavulanic acid **2** and the anticancer agent, acivicin **3**.[2] Proclavaminic acid **4** has been recognized as the biosynthetic precursor of clavulanic acid **2**, a potent inhibitor of bacterial β-lactamase (Fig. 1).

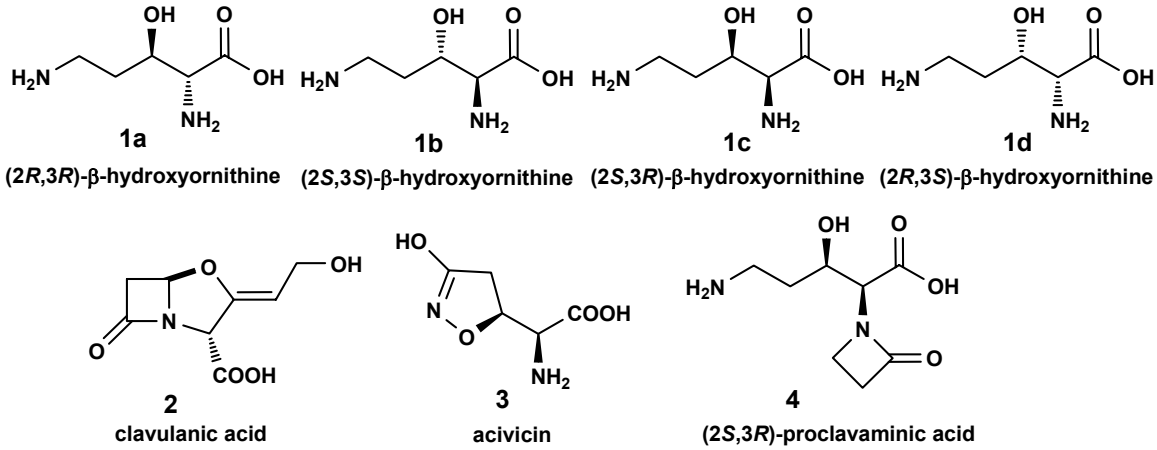


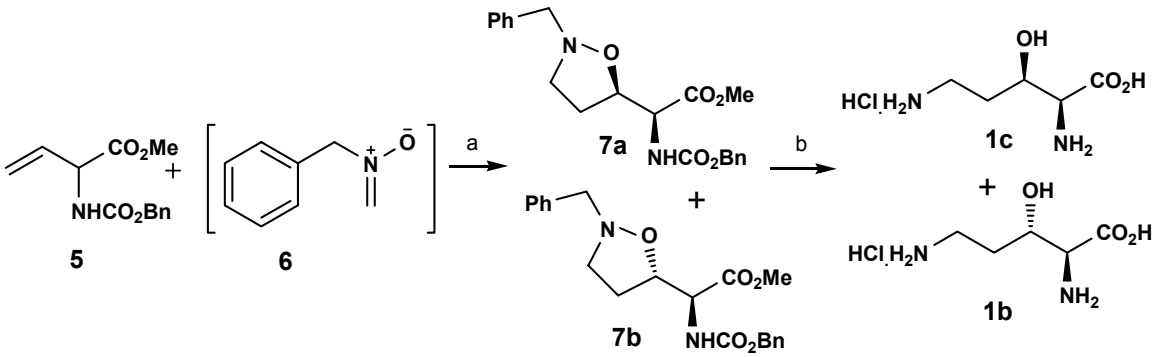
Figure 1.

3.1.2. Review of Literature

Various methods for the synthesis of β-hydroxyornithine in its different stereoisomeric forms mainly based on auxiliary supported or chiral pool approaches have been documented in the literature. A detailed report of these syntheses is described below.

Keszler, D. A. *et al.* (1987)[3]

Keszler, D. A. and co-workers synthesized (2*S*,3*R*)- and (2*S*,3*S*)-β-hydroxyornithine based on a [3+2] cycloaddition of a suitable nitrone with the protected L-vinyl glycine. As shown in Scheme 1, the dipolar cycloaddition of protected (*S*)-vinylglycine **5** and nitrone **6** which was generated in situ from *N*-benzylhydroxylamine and paraformaldehyde afforded a 92% yield of **7a-b** in a diastereomer ratio of 1.6:l. Hydrolysis of **7a-b** with 6N HCl, however, gave the acids **1b** and **1c** in almost quantitative yield, which were separable by flash chromatography.



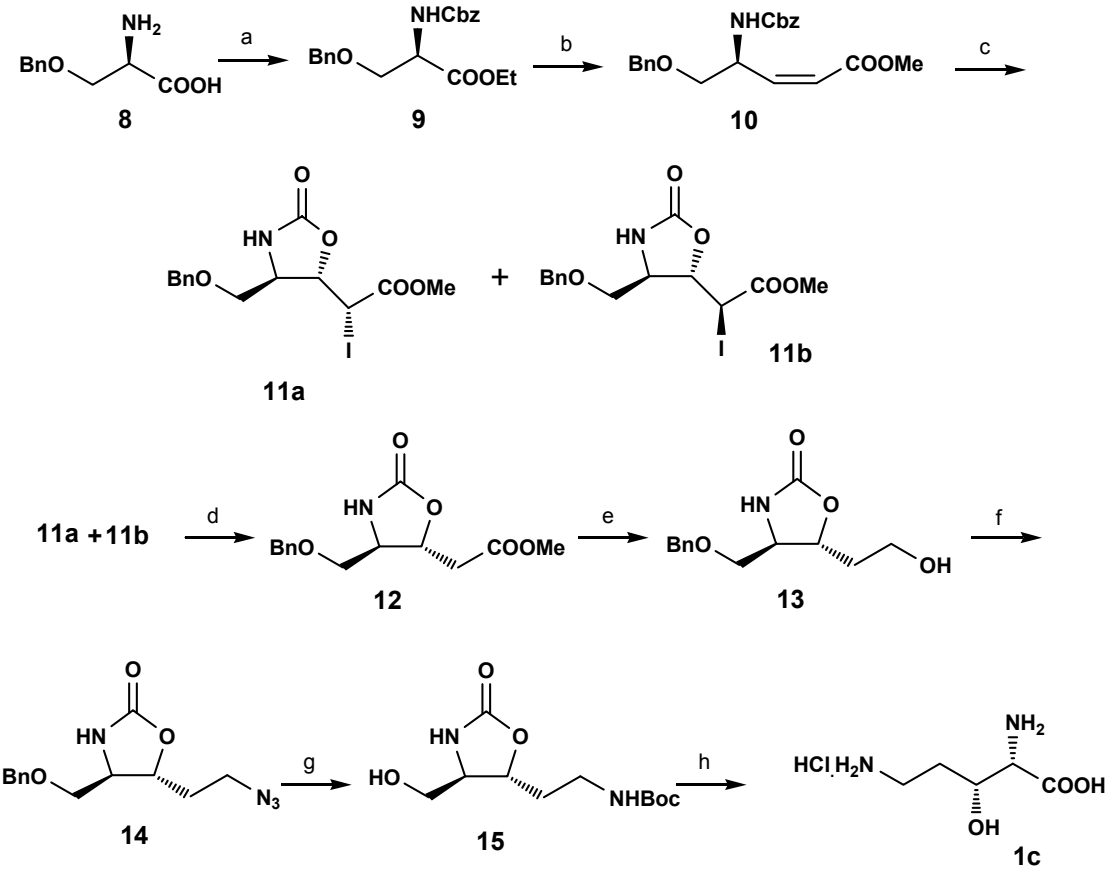
Scheme 1. *Reagents and conditions*: (a) paraformaldehyde, 4Å molecular sieves, C_6H_6, 85 ^oC, 12 h, 92%; (b) H_2/Pd-C, 24 h, 6N HCl, 78%.

Zappia, G. *et al* . (1993).[4]

Zappia, G. and co-workers synthesized (2*S*,3*R*)-*threo*-3-hydroxyornithine **1c** using a highly stereoselective iodocyclocarbamation of the chiral *Z*-olefin **10** prepared from D-serine. *O*-benzyl-D-serine **8** was converted into ethyl ester **9** which was reduced at -78°C with DIBAL-H to corresponding α-amino aldehyde and converted into the *Z*-olefin **10** by modified Still's procedure. *Z*-Olefin **10** was subjected to the iodocyclocarbamation to give a mixture of the two *trans*-oxazolidin-2-ones **11a** and **11b** in a ratio of 15:1.

The two *trans*-oxazolidin-2-ones **11a** and **11b** was converted into the oxazolidin-2-one **12** which on LAH reduction followed by its conversion into azide gave compound **14**. One pot deprotection of benzyl group, reduction of azide group to amine and Boc protection were carried out with H_2/Pd-C in the presence of Boc_2O to afford the alcohol **15**. Amino

alcohol **15** was oxidised with the Jone's reagent followed by acid hydrolysis to give the target compound **1c** in excellent yield.

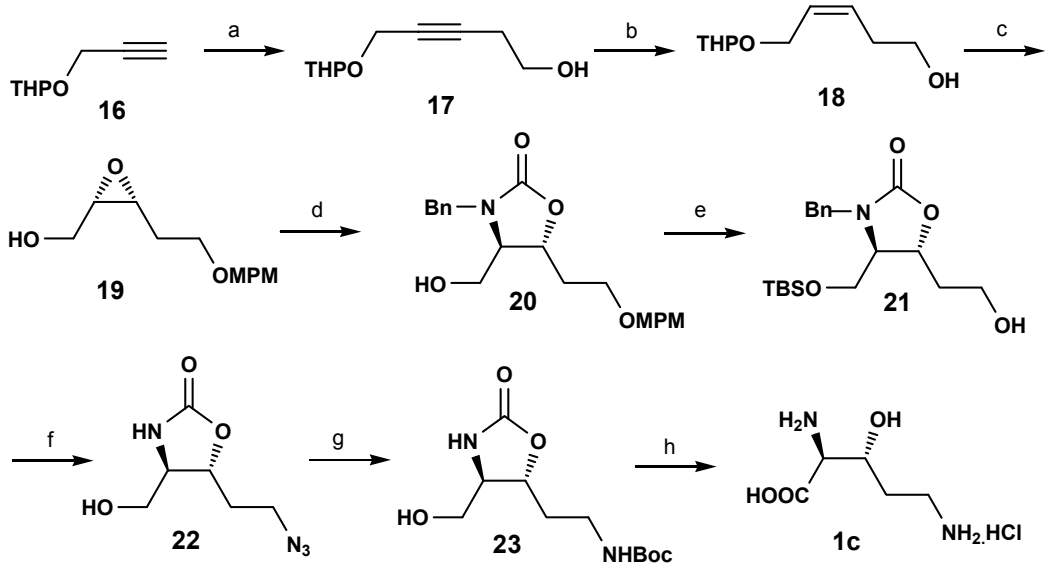


Scheme 2. *Reagents and conditions*: (a) i) Cbz_2O, 1N NaOH, dioxane; ii) EtOCOCl, NMM, DMAP, CH_2Cl_2, 0 ^oC. (b) i) DIBAL-H, toluene, -78 ^oC; ii) $(CF_3CH_2O)_2POCH_2$-COOMe, 18 crown 6, $(TMS)_2NK$, THF, -78 ^oC. (c) I_2 (3 eq.), CH_3CN or I_2 (3 eq.), AgOTf (2 eq.), $NaHCO_3$, CH_3CN. (d) *n*-Bu_3SnH, AIBN, benzene, reflux; (e) $LiAlH_4$ 1M in THF, 0 ^oC. (f) i) MsCl, Et_3N, DMF; ii) NaN_3, DMF, 85 ^oC. (g) H_2/Pd-C, Boc_2O, EtOAc. (h) i) Jone's reagent ii) 6N, HCl, reflux.

Gurjar, M. K. *et al.* (1997)[5]

Gurjar, M. K. *et al.* synthesized (2*S*,3*R*)-β-hydroxyornithine **1c** started from propargyl alcohol **16**. Sharpless asymmetric epoxidation and C_2 directed ring opening reaction with benzyl isocyanate compound **19** afforded 2-oxazolidinone derivative **20** which on TBS protection and MPM group removal with DDQ gave compound **21**. Benzyl group deprotection of **21** and conversion of free -OH into azide *via* the corresponding mesylate

and TBS group deprotection furnished the free alcohol **22**. Catalytic reduction of azido group and Boc protection afforded **23** which on Jone's oxidation and on treatment with 6N HCl gave β-hydroxyornithine **1c** in good yield.



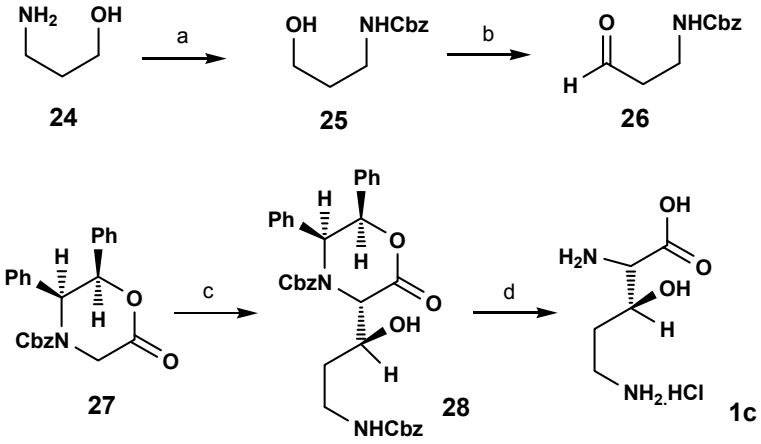
Scheme 3. *Reagents and conditions*: (a) i) $LiNH_2$, ethylene oxide, THF, -33 ^oC; (b) i) Pd-Nickel, H_2, EtOH; ii) NaH, MPMBr, THF; iii) HCl, MeOH; (c) (+)-DIPT, $Ti(OPr^i)_4$, TBHP, Molecular sieves, CH_2Cl_2, -20 ^oC; (d) i) BnNCO, Et_3N, CH_2Cl_2, NaH, THF; ii) TBDMSCl, Et_3N, CH_2Cl_2; iii) DDQ, CH_2Cl_2-H_2O; (f) i) Na/Liq. NH_3; ii) MsCl, Et_3N, CH_2Cl_2; iii) NaN_3, DMF, 90 ^oC; (g) Pd-C/ H_2, EtOH, Boc_2O, Et_3N; (h) i) Jone's oxidation ii) 6N HCl.

Williams R. M. *et al.* (2001)[6]

Williams R. M. and co-worker reported asymmetric syntheses of (2*S*,3*S*)- and (2*R*,3*R*)-β-hydroxyornithine **1a-b** in six steps and 46% overall yield. The key step in this synthesis involved an aldol reaction between a chiral glycine boron enolate and (3-oxo-propyl)-carbamic acid benzyl ester.

In order to arrive at the desired hydroxy amino acid, an aldol reaction between the benzyloxycarbonyl protected 3-aminopropanal **26** and the chiral oxazinone **27** resulted into benzyloxycarbamate **28**. Thus, treatment of **25** under Dess–Martin periodinane conditions afforded (3-oxo-propyl)-carbamic acid benzyl ester **26** which on addition to lactone **27**, provided the expected aldol product **28** in 69% yield. Hydrogenolysis of the

benzyloxycarbonyl groups as well as the chiral auxiliary was achieved by treatment of **28** with palladium chloride and hydrogen to afford (2*S*,3*S*)-β-hydroxyornithine **1a** in 68% yield.



Scheme 4. *Reagents and conditions*: (a) Cbz_2O, MeOH, 10% Et_3N, 99%; (b) Dess-Martin, 98%; (c) Bu_2BOTf, Et_3N, CH_2Cl_2, aldehyde **26**, 69%; (d) i) H_2, $PdCl_2$, EtOH, THF, 25 ^oC ii) NH_4OH, 68%.

3.2.3. Present work:

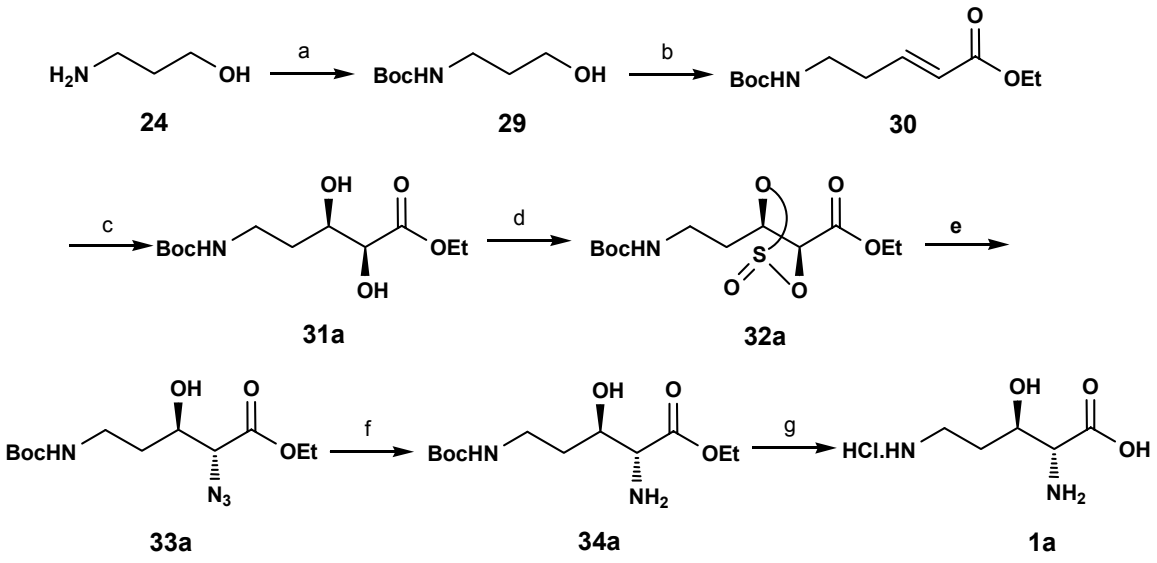
Objective:

The advent of Sharpless asymmetric dihydroxylation (AD)[7] greatly facilitated the synthesis of optically active dihydroxy compounds that serve as important synthons to a vast array of natural products. In continuation of our ongoing research towards syntheses of naturally occurring bioactive compounds employing asymmetric dihydroxylation approach we further aimed towards developing a concise and general protocol for the synthesis of various enantiomers of hydroxyornithine. This section discloses a new approach for an efficient and short synthesis of (2*R*,3*R*)- and (2*S*,3*S*)-β-hydroxyornithine **1a–b** using Sharpless asymmetric dihydroxylation and regioselective nucleophilic opening of a cyclic sulfite as the key steps.

3.2.4. Results and Discussion:

The detailed synthetic strategy involving AD and regiospecific opening of cyclic sulfite by nucleophile as key steps is illustrated in Scheme 5.

The synthesis of β-hydroxyornithine **1a-b** started from the commercially available 3-aminopropanol **24** as illustrated in Scheme 5. Amino group protection of **24** with $(Boc)_2O$ led to compound **29** in 94% yield which was oxidised to the aldehyde under Swern conditions[8] and subsequently treated with (ethoxycarbonylmethylene)triphenyl-phosphorane in dry THF to furnish the Wittig product **30** in 88% yield.



Scheme 5. *Reagents and conditions*: (a) Boc_2O, NaOH, 1,4-dioxane, H_2O, 0 ^oC-rt; then $KHSO_4$, 3 h, 94%; (b) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^oC to -60 ^oC, 2 h ; (ii) Ph_3P=CHCOOEt, dry THF, rt, 24 h, 88%; (c) $(DHQD)_2PHAL$, OsO_4, $CH_3SO_2NH_2$, K_3FeCN_6, K_2CO_3, *t*-BuOH:H_2O (1:1), 24 h, 0 ^oC, 95%; (d) $SOCl_2$, Et_3N, 30 min, 97%; (e) NaN_3, dry DMF, 60 ^oC, 20 h, 93%; (f) 10% Pd-C, H_2, EtOAc, rt, 98%; (g) 6N HCl, reflux, 6 h, 88%;

The IR spectrum of **30** showed the ester carbonyl absorption at 1718 cm^{-1} and olefin C=C stretching at 1655 cm^{-1}. The ^1H NMR spectrum gave olefin protons at δ 5.88 (doublet of triplet, one proton) with the coupling constant J = 1.52, 15.79 Hz, and at δ 6.82-6.97 (multiplet, one proton) indicating *trans*-olefin. Subsequent treatment of olefin **30** with osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of $(DHQD)_2PHAL$ under Sharpless asymmetric conditions[7] gave the diol **31a** in 95% yield with 98% ee. For the measurement of enantiomeric excess, the diol **31a** was converted into

its dibenzoate derivative. The enantiomeric purity of the dibenzoate was estimated to be 98% by chiral HPLC analysis using Cyclobond I beta 25 cm, 4.6 mm, HPLC-Cartridge (R.R.-Whelk-01), MeOH-H_2O, wavelength 254 nm, 1.0 mL/min. $[\alpha]_D^{25}$ +15.89 (*c* 1.00, $CHCl_3$). The IR spectrum of **31a** showed hydroxyl absorption at 3340 cm^{-1} and ester carbonyl at 1751 cm^{-1}. The ^1H NMR indicated absence of olefin protons. The chiral protons appeared at δ 4.01 (dt, *J* = 10.1, 3.5 Hz, 1H), and 4.07 (d, *J* = 2.4 Hz, 1H). The chiral carbons appeared at δ 69.8 and 73.7 in the ^{13}C NMR spectrum. The diol **31a** was then treated with thionyl chloride and Et_3N to give the cyclic sulfite **32a** in 97% yield. The IR spectrum of **31a** indicated the absence of hydroxyl groups. The synthetic strategy shown in Scheme 5 was based on the presumption that the nucleophilic opening of cyclic sulfite **32a** would occur in a regiospecific manner at the α-carbon atom. Indeed, the cyclic sulfite reacted with NaN_3 with apparent complete selectivity for attack at C-2 to furnish the azido alcohol **33a** in 93% yield. The carbonyl group must be responsible for the increased reactivity of the α-position.[9] Hydrogenation of azido alcohol **33a** with 10% Pd-C led to the amino alcohol **34a** in 98% yield. Finally, concomitant deprotection of the Boc group and ester hydrolysis were carried out with 6N HCl to furnish **1a** in excellent yield; $[\alpha]_D^{25}$ -21.32 (c 0.47, 6N HCl), {lit.[6] $[\alpha]_D^{25}$ -20.20 (c 0.47, 6N HCl)}. The physical and spectroscopic data were in full agreement with the literature.[6]

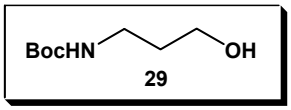
In a similar way (2*S*,3*S*)-β-hydroxyornithine **1b** was synthesized using $(DHQ)_2PHAL$ ligand in the Sharpless asymmetric dihydroxylation step and following a series of reactions analogous to those shown in Scheme 5.

3.2.5. Conclusion

In conclusion, a practical, short and highly enantioselective synthesis of (2*R*,3*R*)- and (2*S*,3*S*)-β-hydroxyornithine has been achieved employing Sharpless asymmetric dihydroxylation and cyclic sulfite methodology as the key steps. The merits of this synthesis are high enantioselectivity with high yielding reaction steps. The synthetic strategy described has significant potential for further extension to other stereoisomers via double inversion at the α-carbon.

3.2.6. Experimental Section

***tert*-Butyl 3-hydroxypropylcarbamate (29).**



A solution of di-*tert*-butyldicarbonate (6.39 g, 6.72 mL, 29.29 mmol) in dioxane (20 mL) is added to an ice cold solution of 3-aminopropanol **24** (2.0 g, 26.63 mmol) in 1N NaOH (2.13 g in 20 mL H_2O) by means of an addition funnel. The two phase mixture is stirred at 5 ^oC for 30 min, then allowed to warm to room temperature over 2.5 h at which TLC analysis shows the reaction to be complete. The mixture is concentrated to half its original volume at 35 ^oC, cooled in an ice bath, acidified to pH 2-3 by the slow addition of 1N $KHSO_4$ and then extracted with EtOAc (3 x 50 mL). The combined extracts are dried over Na_2SO_4, filtered and concentrated and purified by silica gel column chromatography (EtOAc/petroleum ether, 1:9) to give **29** as a pale yellow oil.

Yield: 3.27 g, 94%

Mol. Formula: $C_8H_{17}NO_3$

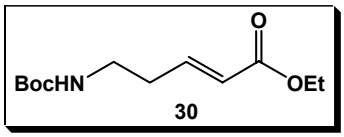
IR (neat, cm^{-1}): ν_{max} 3368, 2978, 1685, 1508, 1366

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44 (s, 9H), 1.60-1.72 (m, 2H), 2.58 (brs, 1H), 3.29 (q, J = 5.68, 11.62 Hz, 2H), 3.66 (t, J = 5.69 Hz, 2H), 4.81 (brs, 1H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 28.2, 32.4, 36.9, 59.1, 79.18, 156.9 ppm.

Analysis Calcd.: C, 54.84; H, 9.78; N, 7.99%; **Found:** C, 55.36; H, 9.11; N, 7.98%.

(*E*)-Ethyl 5-(*tert*-butoxycarbonylamino)pent-2-enoate (30).



To a solution of oxalyl chloride (4.37 g, 3.00 mL, 34.44 mmol) in dry CH_2Cl_2 (50 mL) at -78 ^oC was added dropwise dry DMSO (5.56 g, 5.02 mL, 71.17 mmol) in CH_2Cl_2 (10 mL). After 30 min, alcohol **29** (4.0 g, 22.95 mmol) in CH_2Cl_2 (20 mL) was added over 10 min giving copious white precipitate. After stirring for 1 h at -78 ^oC the reaction mixture was brought to -60 ^oC and Et_3N (10.22 g, 14.08 mL, 101.02 mmol) was added slowly and

stirred for 30 min allowing the reaction mixture to warm to room temperature. The reaction mixture was then diluted with water (50 mL) and CH_2Cl_2. The organic layer was separated and washed with water and brine, dried (Na_2SO_4) and passed through short pad of celite. The filtrate was concentrated to give the aldehyde as pale yellow oil, which was used as such for the next step without purification.

To a solution of (ethoxycarbonylmethylene)triphenyl phosphorane (8.79 g, 25.23 mmol) in dry THF (20 mL) was added a solution of the above aldehyde in dry THF (10 mL). The reaction mixture was stirred at room temperature for 24 h. It was then concentrated and purified by silica gel column chromatography (EtOAc/petroleum ether, 1:9) to give olefin **30** as pale yellow oil.

Yield: 4.89 g, 88%

Mol. Formula: $C_{12}H_{21}NO_4$

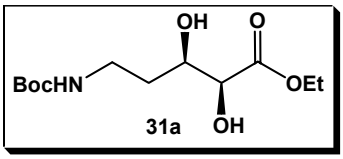
IR (neat, cm^{-1}): ν_{max} 3370, 2978, 1718, 1655, 1521, 1367, 1252

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (t, J = 7.07 Hz, 3H), 1.44 (s, 9H), 2.41 (dq, J = 1.51, 6.69, 13.64 Hz, 2H), 3.27 (t, J = 6.69 Hz, 2H), 4.33 (q, J = 7.07, 14.27 Hz, 2H), 5.88 (dt, J = 1.52, 15.79 Hz, 1H), 6.82-6.97 (m, 1 H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 28.0, 32.5, 38.7, 59.9, 78.8, 122.9, 145.3, 155.6, 165.9 ppm.

Analysis Calcd.: C, 59.24; H, 8.70; N, 5.76%; **Found:** C, 59.51; H, 8.88; N, 5.81%.

(2*S*,3*R*)-Ethyl 5-(*tert*-butoxycarbonylamino)-2,3-dihydroxypentanoate (31a)



31a

To a mixture of $K_3Fe(CN)_6$ (10.19 g, 30.95 mmol), K_2CO_3 (4.28 g, 30.95 mmol), $(DHQD)_2PHAL$ (8 mg, 1 mol%) in *t*-BuOH/H_2O (1:1, 100 mL) at 0 °C was added osmium tetroxide (0.43 mL, 0.1 M solution in toluene, 0.4 mol%), followed by methanesulfonamide (981 mg, 10.31 mmol). After stirring for 2 min at 0 °C, the olefin **30** (2.5 g, 10.31 mmol) was added in one portion. The reaction mixture was stirred at 0°C for 24 h and then quenched with solid sodium sulfite (5 g). The stirring was continued for additional 15 min and then the solution was extracted with EtOAc (3 x 20 mL). The

combined extracts were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography purification (EtOAc/petroleum ether, 1:4) of the crude product gave **31a** as a white solid.

Yield: 2.71 g, 95%

Mol. Formula: $C_{12}H_{23}NO_6$

Mp: 178 ^oC

31a $[\alpha]_D^{25}$: +15.89 (*c* 1.0, $CHCl_3$)

31b $[\alpha]_D^{25}$: -16.31(*c* 1.0, $CHCl_3$)

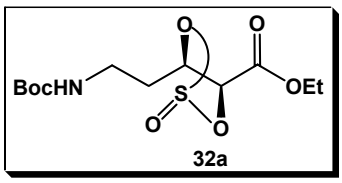
IR (neat, cm^{-1}): ν_{max} 3340, 2972, 1751, 1681, 1524, 1214

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (t, *J* = 7.1 Hz, 3H), 1.45 (s, 9H), 1.59-1.95 (m, 2H), 2.92 (br s, 2H), 3.11-3.27 (m, 1H), 3.37-3.51 (m, 1H), 4.01 (dt, *J* = 10.1, 3.5 Hz, 1H), 4.07 (d, *J* = 2.4 Hz, 1H) 4.29 (dq, *J* = 2.53, 7.2, 14.40 Hz, 2H), 4.83 (brs, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 28.2, 33.8, 37.1, 61.7, 69.8, 73.7, 79.4, 156.8, 173.1 ppm.

Analysis Calcd.: C, 51.97; H, 8.36; N, 5.05%; **Found:** C, 51.89; H, 8.33; N; 5.08%.

Compound 32a:



32a

To a solution of diol **31a** (2.75 g, 9.28 mmol) in dry CH_2Cl_2 (10 mL) was added Et_3N (1.88 mg, 2.59 mL, 18.56 mmol). The mixture was cooled in an ice bath and thionyl chloride (1.32 g, 0.81 mL, 11.13 mmol) added dropwise. The reaction mixture was stirred for 30 min and then quenched by adding water (10 mL). The phases were separated and aqueous phase extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated. Silica gel column chromatography purification (EtOAc/petroleum ether, 1:4) of the crude product gave sulfite **32a** as a colorless liquid.

Yield: 2.90 g, 97%

Mol. Formula: $C_{12}H_{21}NO_7S$

32a $[\alpha]_D^{25}$: +83.34 (*c* 1.0, $CHCl_3$)

32b $[\alpha]_D^{25}$: -39.66 (*c* 1.0, $CHCl_3$)

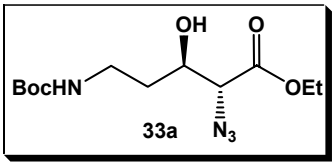
IR (neat, cm^{-1}): ν_{max} 3456, 3020, 2982, 1760, 1709, 1507, 1216

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.34 (t, *J* = 7.20 Hz, 3H), 1.45 (s, 9H), 1.73-1.2.27 (m, 4H), 3.36 (t, *J* = 6.45 Hz, 2H), 4.31 (dq, *J* = 2.90, 7.20, 14.27 Hz, 1H), 4.55-4.79 (m, 1 H), 5.06-5.27 (m, 1 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.7, 28.0, 32.3, 34.9, 36.8, 62.4, 79.0, 80.0, 81.1, 84.1, 155.8, 166.5, 166.8 ppm.

Analysis Calcd.: C, 44.71; H, 6.25; N, 4.35%; **Found:** C, 44.68; H, 6.21; N, 4.39%.

(2*R*,3*R*)-Ethyl 2-azido-5-(*tert*-butoxycarbonylamino)-3-hydroxypentanoate (33a):



To a solution of cyclic sulfite **32a** (2.0 g, 6.20 mmol) in dry DMF (10 mL) was added NaN_3 (1.21 g, 18.60 mmol) under argon. The reaction mixture was stirred at 60 °C for 20 h under argon. The solvent was removed under reduced pressure and to the residue, was added 20% aq. H_2SO_4:Et_2O (1:1, 10 mL) and stirred at room temperature for 12 h. Excess $NaHCO_3$ was added to it and the reaction mixture was stirred for 20 min and then extracted with ether (3 x 20 mL). The organic layer was separated and passed through celite and silica gel bed. Removal of solvent afforded the crude product as a dark yellow oil which was purified on a silica gel column using petroleum ether:EtOAc (3:1) as eluent to give **33a.**

Yield: 1.74 g, 93%

Mol. Formula: $C_{12}H_{21}N_4O_5$

33a $[\alpha]_D^{25}$: +8.3 (*c* 1.0, $CHCl_3$)

33b $[\alpha]_D^{25}$: -7.2 (*c* 1.0, $CHCl_3$)

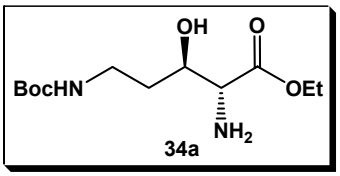
IR (neat, cm^{-1}): ν_{max} 3389, 2980, 2109, 1689, 1520, 1253

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33 (t, *J* = 7.2 Hz, 3H), 1.44 (s, 9H), 1.59-1.85 (m, 2H), 3.10-3.24 (m, 1H), 3.46 (brs, 1H), 3.77 (d, *J* = 3.1 Hz, 1H), 3.98-4.19 (m, 1H), 4.28 (q, *J* = 7.2 Hz, 2H) 4.86 (brs, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9, 28.1, 34.3, 36.6, 61.8, 65.8, 69.4, 79.5, 156.9, 169.1 ppm.

Analysis Calcd.: C, 47.83; H, 7.02; N, 18.59%; **Found:** C, 47.70; H, 7.35; N; 18.51%.

(2*R*,3*R*)-Ethyl 2-amino-5-(*tert*-butoxycarbonylamino)-3-hydroxypentanoate (34a)



34a

To a solution of azide **33a** (1.50 g, 4.97 mmol) in ethyl acetate (10 mL) was added Pd/C (75 mg). The resulting solution was stirred under hydrogen atmosphere at room temperature until disappearance of the azido alcohol as monitored by TLC. The reaction mixture was filtered through a celite pad to remove the catalyst and the filtrate was concentrated in vacuo. Silica gel column chromatography of the crude product using EtOAc/pet ether (1:1) as eluent gave **1a** as a colorless syrup liquid.

Yield: 1.34 g, 98%

Mol. Formula: $C_{12}H_{23}N_2O_5$

1a $[\alpha]_D^{25}$: +3.15 (*c* 1.0, $CHCl_3$)

1b $[\alpha]_D^{25}$: -4.2 (*c* 1.0, $CHCl_3$)

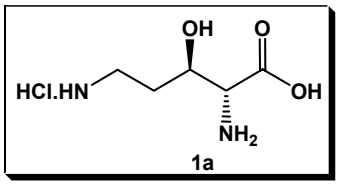
IR (neat, cm^{-1}): ν_{max} 3492, 2979, 1747, 1704, 1244

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (t, *J* = 7.07 Hz, 3H), 1.43 (s, 9H), 1.58-1.89 (m, 2H), 3.03 (brs, 3H), 3.25-3.54 (m, 2H), 3.63-4.03 (m, 1H), 4.23 (q, *J* = 6.69, 13.77 Hz, 2H), 4.92-5.14 (m, 1H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 28.1, 34.5, 37.9, 61.4, 64.2, 66.8, 78.7, 155.7, 171.1 ppm.

Analysis Calcd.: C, 52.35; H, 8.42; N, 10.17%; **Found:** C, 52.41; H, 8.38; N, 10.21%.

(2*R*,3*R*)-β-Hydroxyornithine (1a)



1a

To the compound **34a** (1.00 g, 3.63 mmol), 6N HCl (5 ml) was added and refluxed under stirring for 6 h. The reaction mixture was concentrated under vacuum and the residue was dissolved in the minimum amount of water (0.5 ml). The pH of the solution was adjusted to 6.5 with NH_4OH. To this solution ethanol was added, which resulted into recrystalization of the crude product to afford the amino acid **1a** in pure form.

Yield: 473 mg, 88%

Mp: 231 °C (lit.[6] mp 232 °C).

1a $[\alpha]_D^{25}$:-21.32 (*c* 0.47, 6N HCl), {lit.[6] $[\alpha]_D^{25}$ -20.20 (*c* 0.47, 6N HCl)}

1b $[\alpha]_D^{25}$: +23.66 (*c* 0.50, 6N HCl), {lit.[6] $[\alpha]_D^{25}$ +24.10 (*c* 0.56, 6N HCl)}

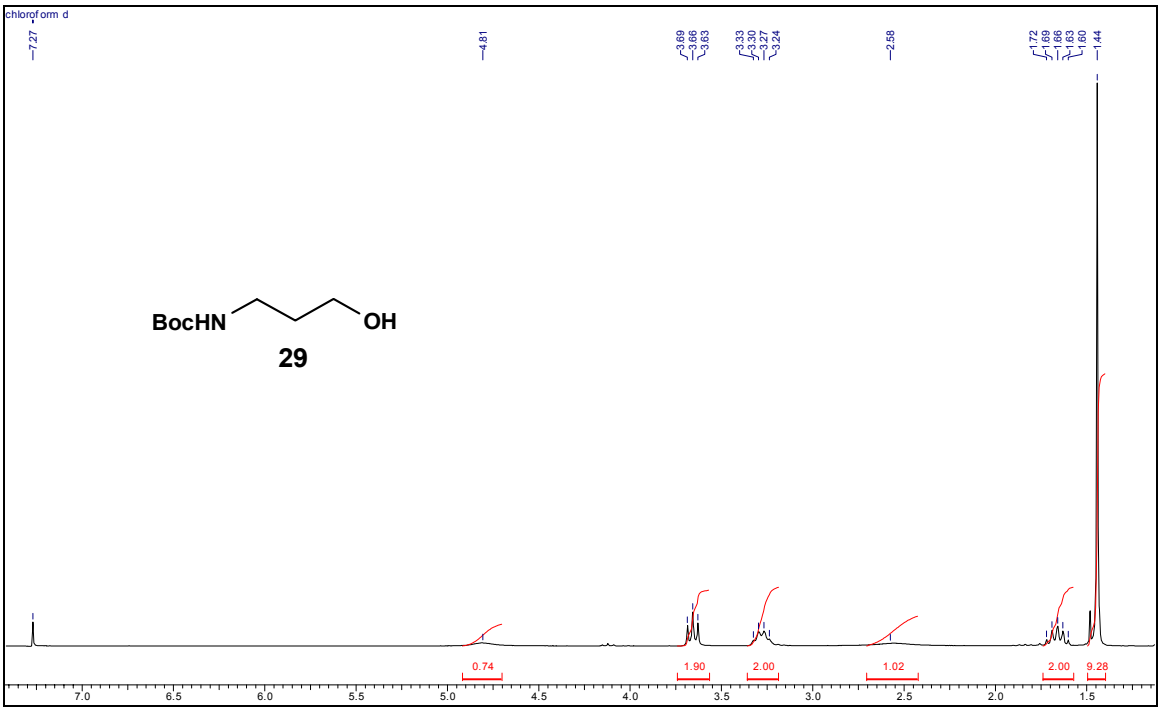
IR ((NaCl, 1% KBr, cm^{-1}): ν_{max} 3074, 1612, 1576, 1529, 1508, 1431, 1358, 1325, 1180, 1065, 1032

^{1}H NMR (200 MHz, D_2O): δ 1.77-2.09 (m, 2H), 3.03-3.20 (m, 2H), 3.97 (dd, *J* = 3.15, 26.14 Hz, 1H), 4.22 (dt, *J*=3.91, 14.52 Hz, 1H) ppm.

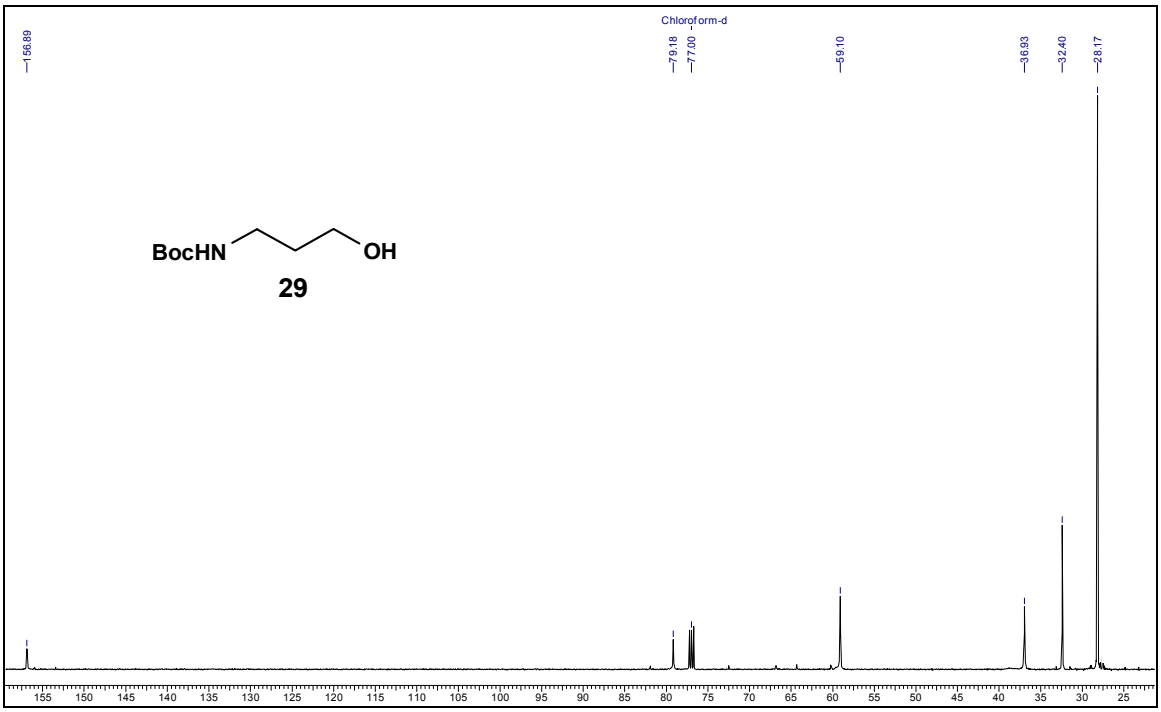
^{13}C NMR (50 MHz, $CDCl_3$): δ 30.0, 37.2, 59.1, 64.8, 68.4, 154.7, 171.1 ppm.

3.2.7 Spectra

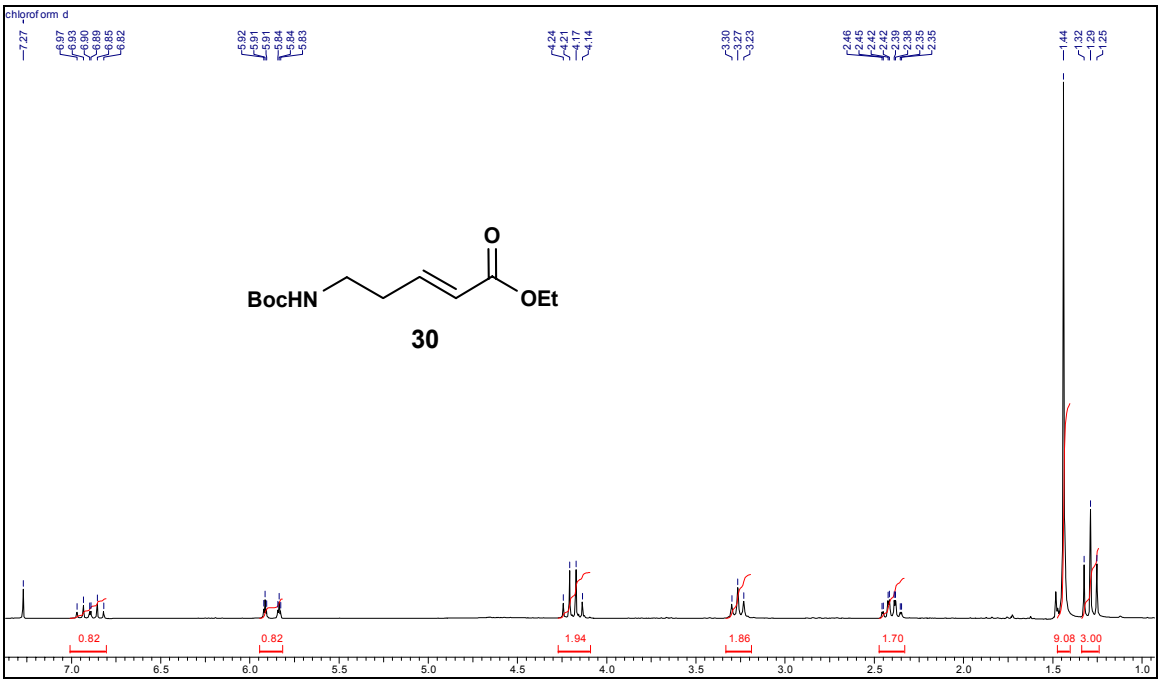
1. ^{1}H and ^{13}C NMR spectra of **29**
2. ^{1}H and ^{13}C NMR spectra of **30**
3. ^{1}H and ^{13}C NMR spectra of **31a**
4. ^{1}H and ^{13}C NMR spectra of **32a**
5. ^{1}H and ^{13}C NMR spectra of **33a**
6. ^{1}H and ^{13}C NMR spectra of **34a**
7. ^{1}H and ^{13}C NMR spectra of **1a**



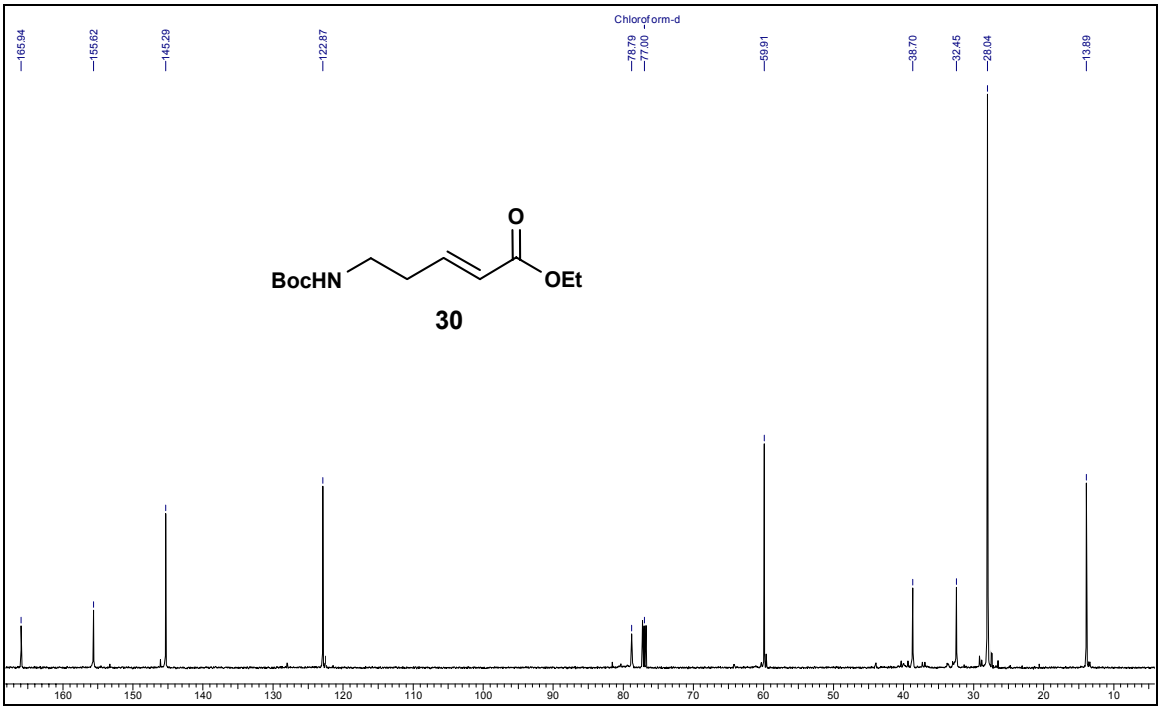
☞ ^{1}H NMR of the compound 29 in $CDCl_3$



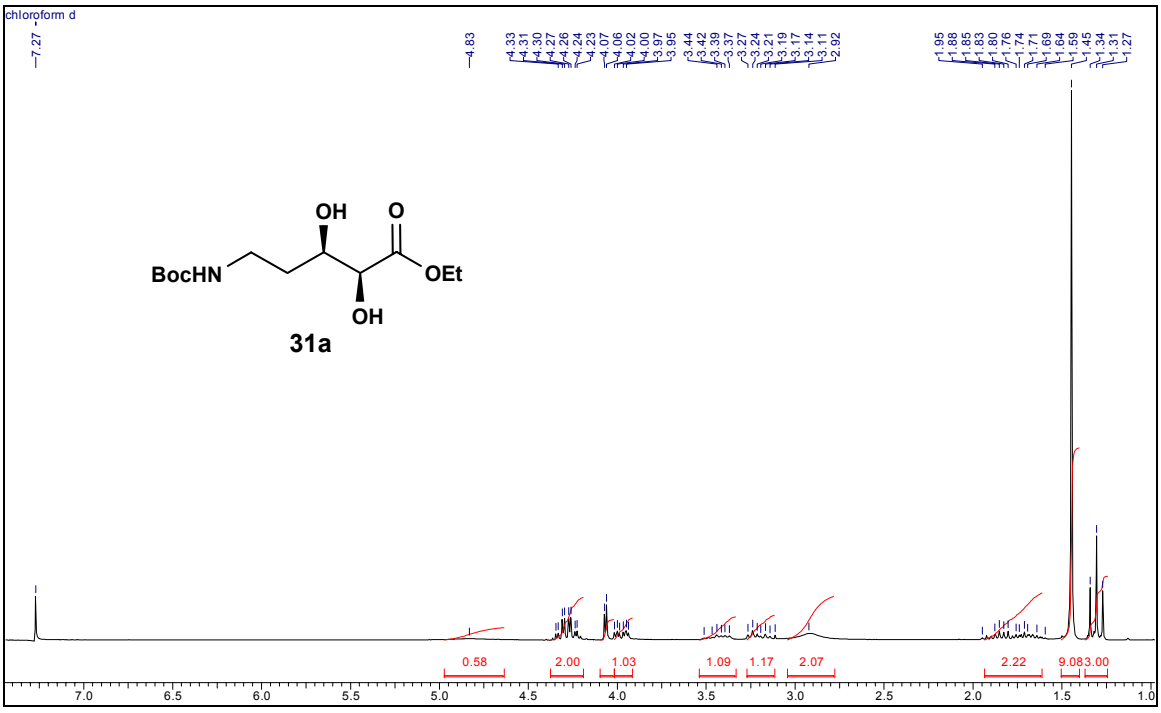
☞ ^{13}C NMR of the compound 29 in $CDCl_3$



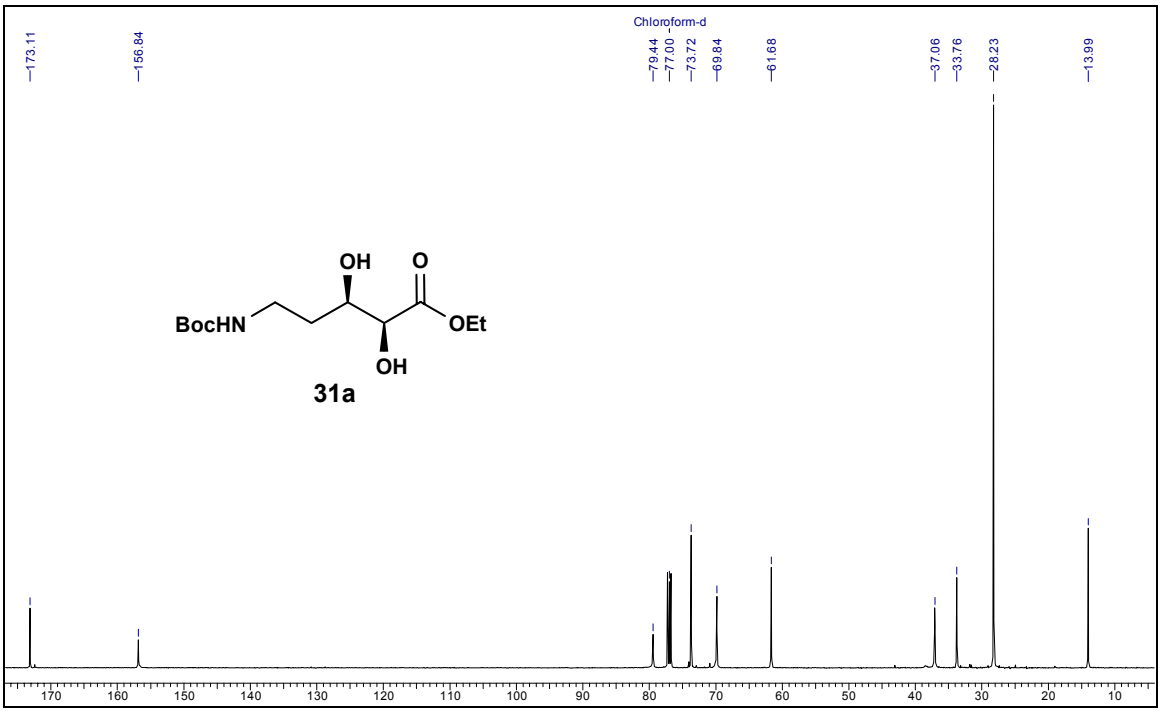
☞ ^{1}H NMR of the compound 30 in $CDCl_3$



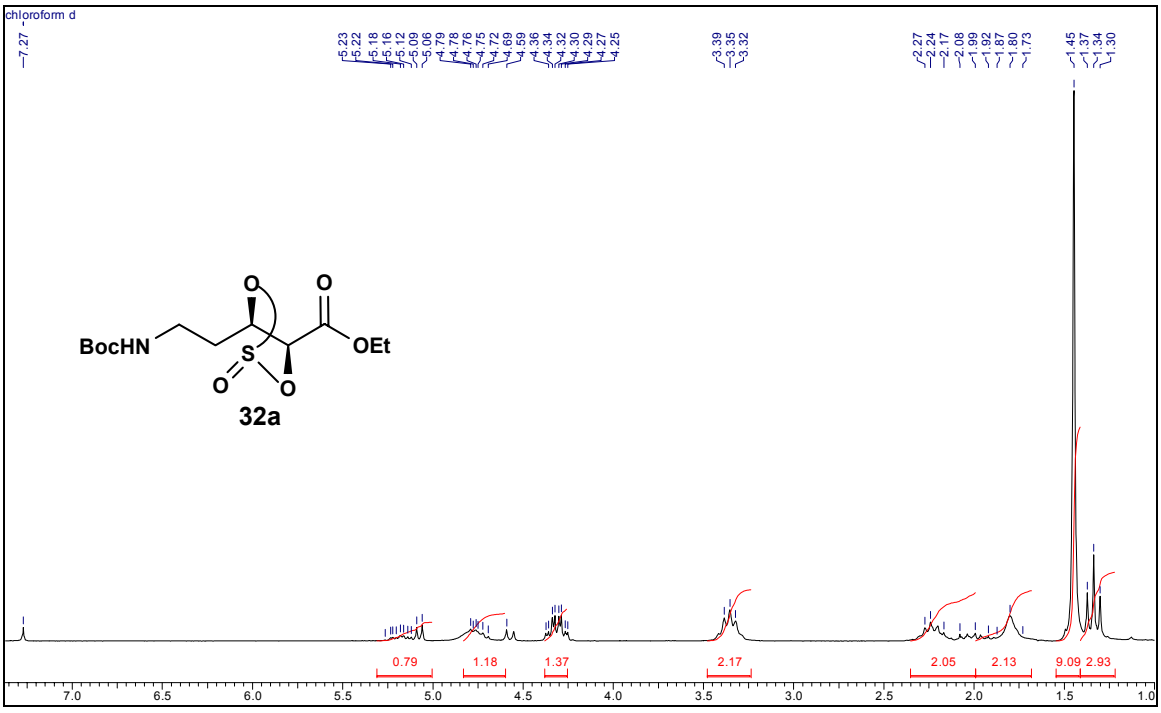
☞ ^{13}C NMR of the compound 30 in $CDCl_3$



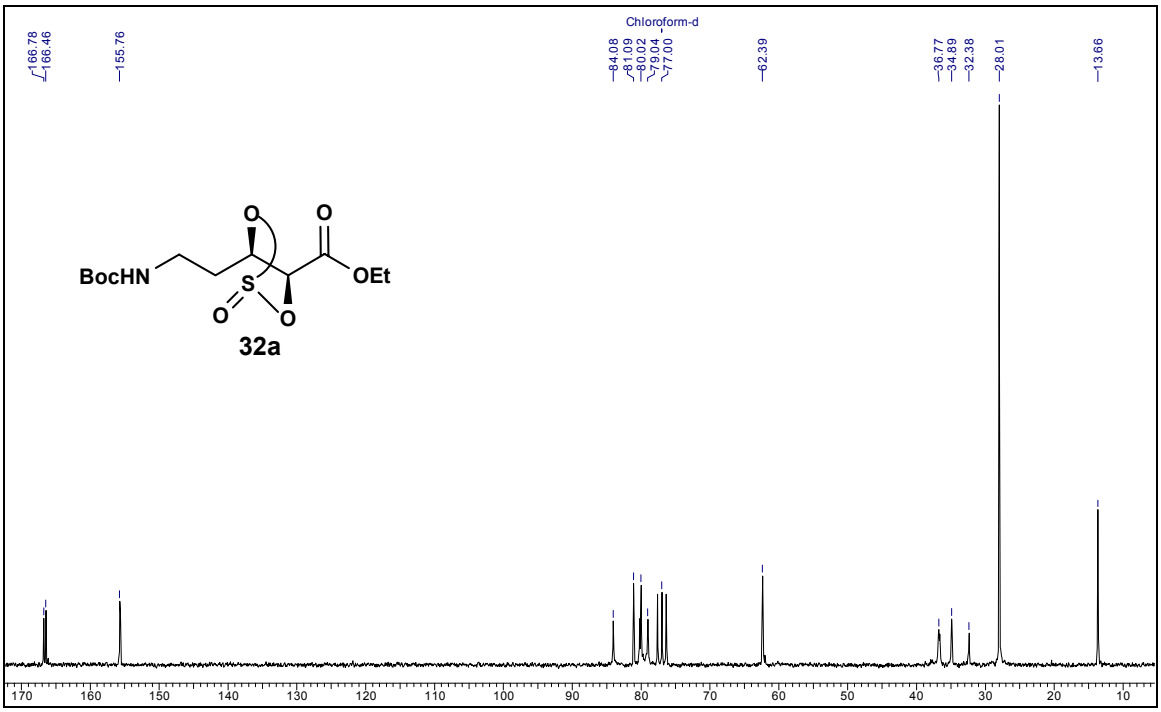
☞ ^{1}H NMR of the compound 31a in $CDCl_3$



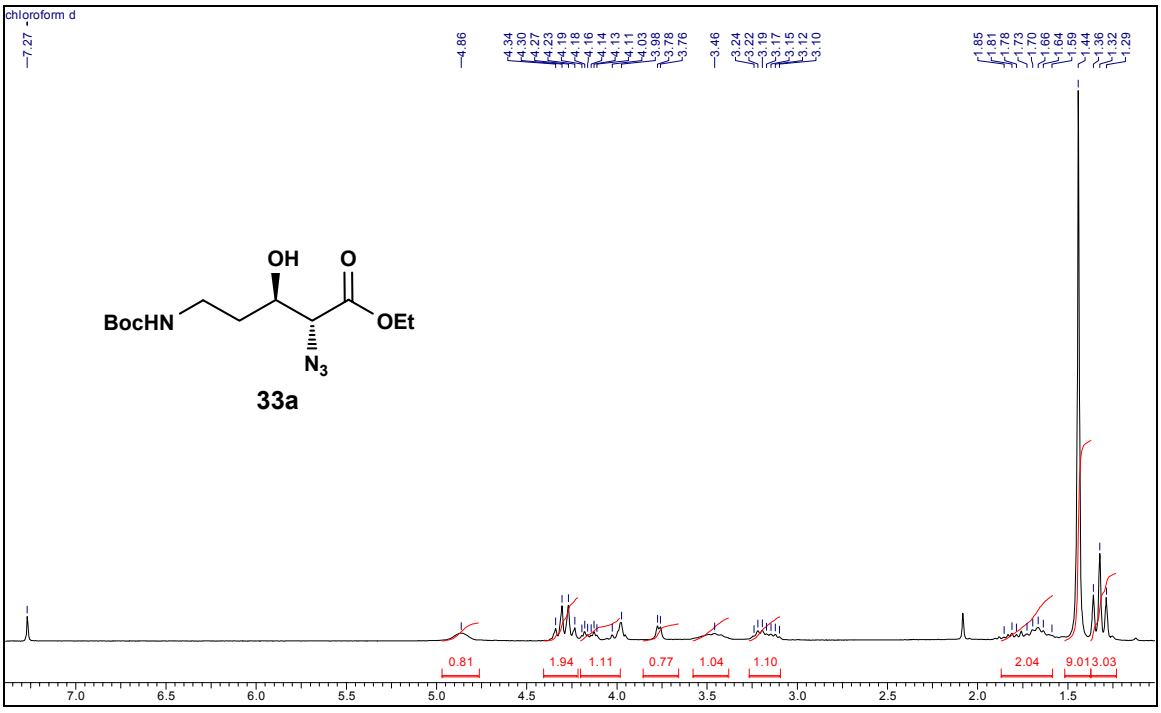
☞ ^{13}C NMR of the compound 31a in $CDCl_3$



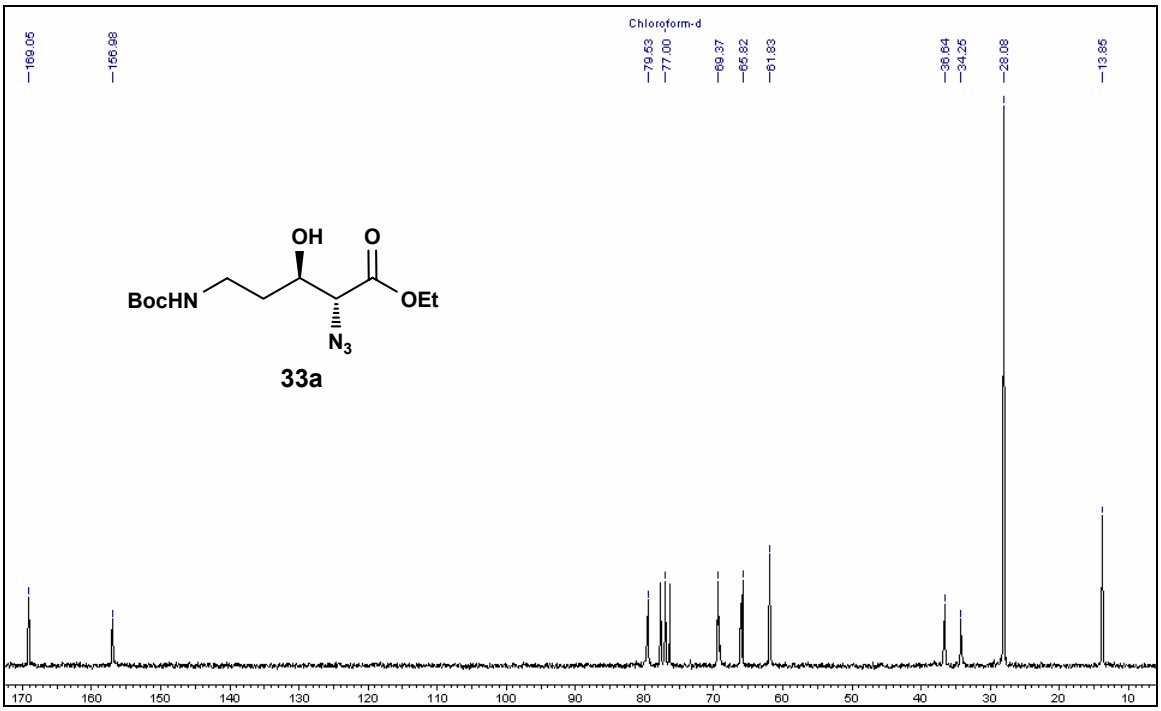
☞ ^{1}H NMR of the compound 32a in $CDCl_3$



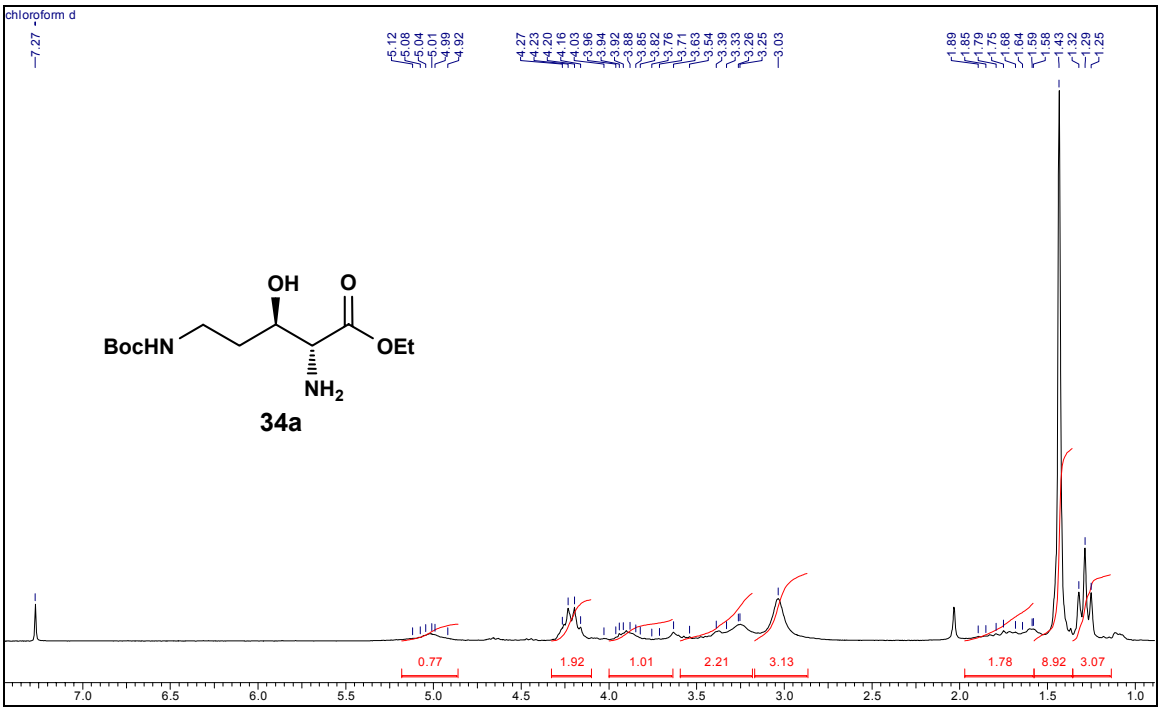
☞ ^{13}C NMR of the compound 32a in $CDCl_3$



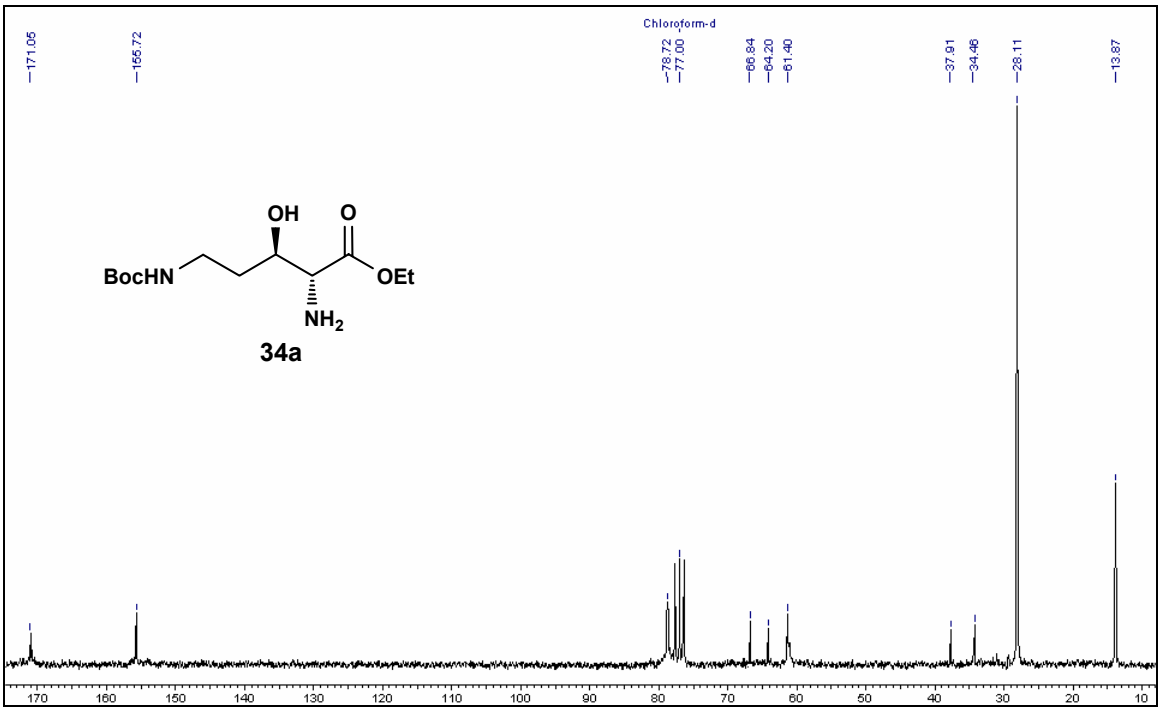
☞ ^{1}H NMR of the compound 33a in $CDCl_3$



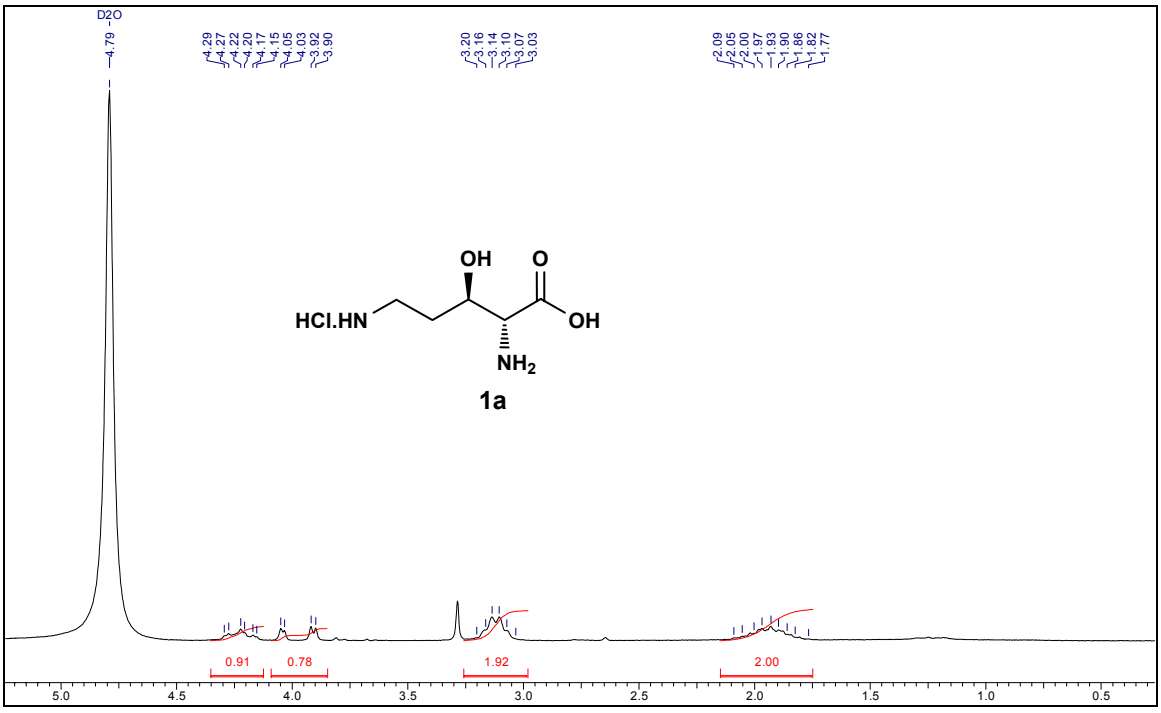
☞ ^{13}C NMR of the compound 33a in $CDCl_3$



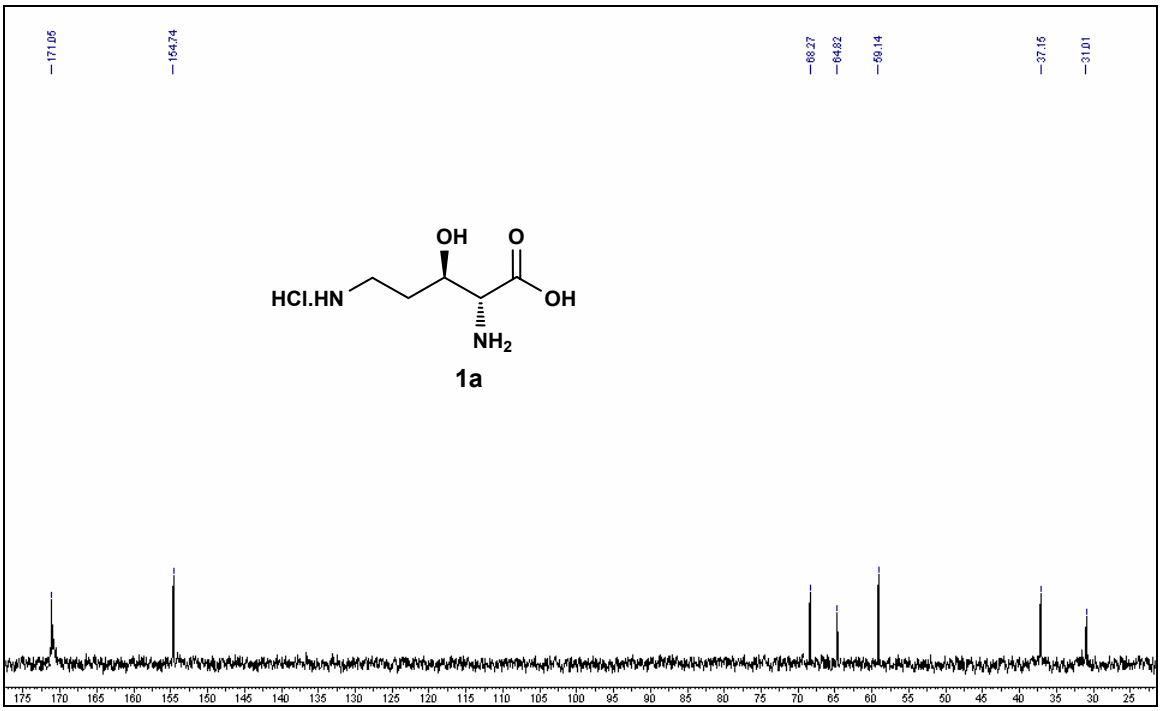
☞ ^{1}H NMR of the compound 34a in $CDCl_3$



☞ ^{13}C NMR of the compound 34a in $CDCl_3$



☞ ^{1}H NMR of the compound 1a in D_2O



☞ ^{13}C NMR of the compound 1a in D_2O

3.2 SECTION B

A CONCISE SYNTHESIS OF PROTECTED (2*S*,4*R*)-4-HYDROXYORNITHINE

3.2.1. Introduction

4-Hydroxyornithine **35a-b** is a nonproteinogenic amino acid found abundantly in Nature. It is a component of marine organism[10] and plants,[11] as well as a constituent of a number of peptide natural products, such as the antifungal lipopeptides echinocandin and pneumocandin,[12] the K 582 type antibiotics,[13] macrocyclic antibiotics such as the biphenomycin A and B **36a-b**,[14] the β-lactam antibiotic clavalanine **37**[15] and polyoxin M.[16] Related 4-hydroxylated α-amino acid, (2*S*,4*S*,6*R*)-4-hydroxy-5-phenylsulfinyl-norvaline **38** has also been identified as a key component of ustiloxin A and B,[17] a family of cyclic peptides with potent antimitotic activity (Fig. 2).[18]

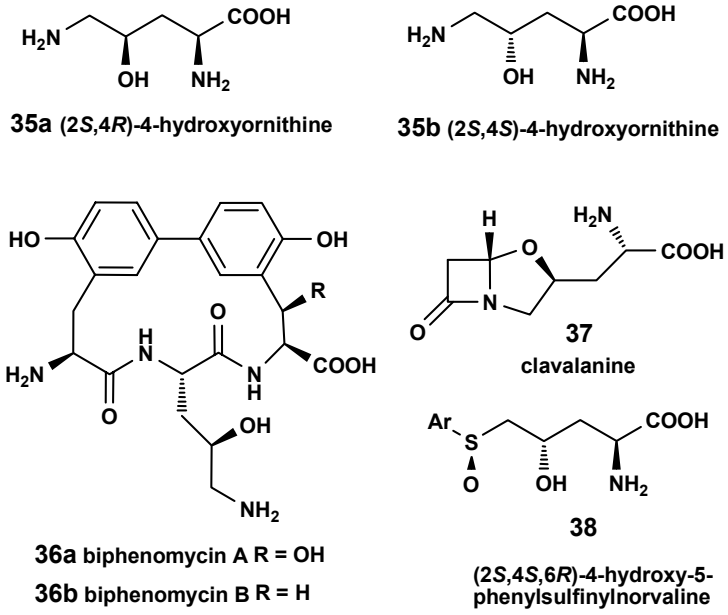


Figure 2.

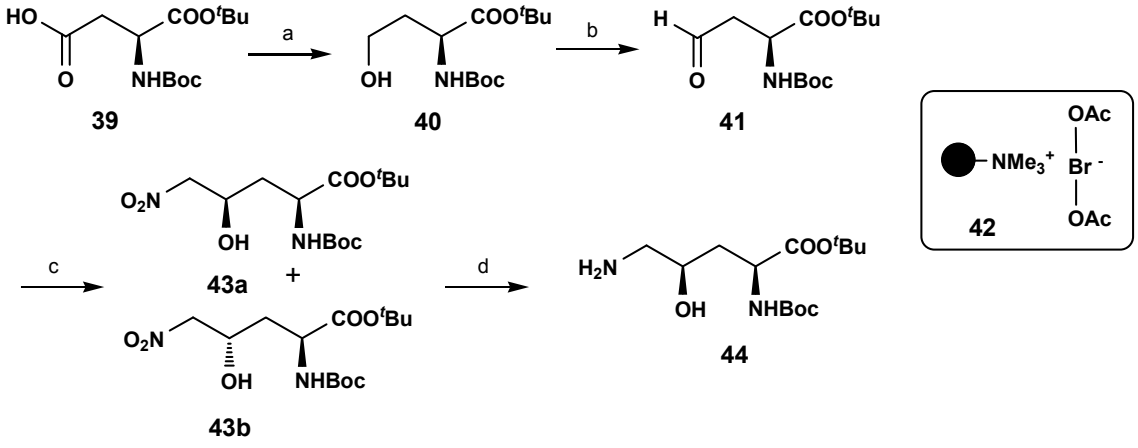
3.2.2. Review of Literature

Various methods for the synthesis of 4-hydroxyornithine including stereoselective approaches have been reported in the literature.[19] So far only five asymmetric synthesis of 4-hydroxyornithine was reported. A detailed report of recent syntheses is described below.

Rudolph J. *et al.* (2001)[20]

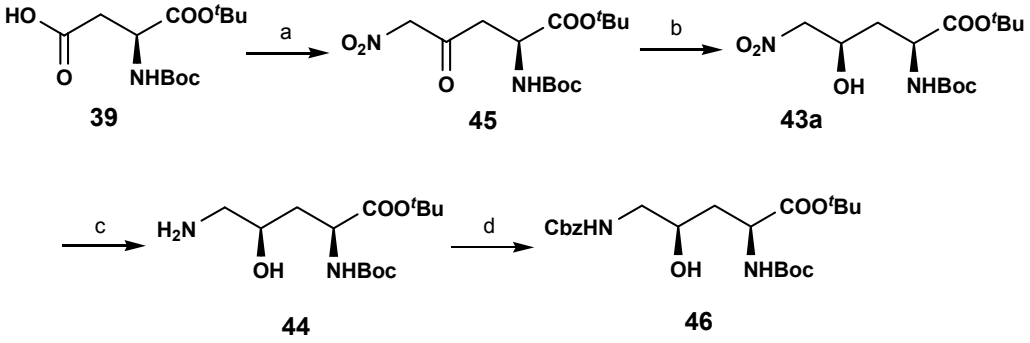
Joachim Rudolph and co-workers synthesized (2*S*,4*R*)-4-hydroxyornithine **35a** starting from diprotected L-aspartic acid, the scaffold of the target compound is constructed in a three-step approach: an efficient α-nitroketone formation through acylation of nitromethane is followed by a diastereoselective reduction of the resulting ketone. In the last step, the nitro group is reduced to furnish the (2*S*,4*R*)-4-hydroxyornithine.

The synthesis started from commercially available (*S*)-*N*-Boc-aspartic acid *tert*-butyl ester **39** which was reduced to the homoserine derivative **40** followed by oxidation to the semialdehyde **41.** Henry reaction of compound **41** gave the (2*S*,4*R*)-diastereomer (erythro) (**43a**) and (2*S*,4*S*)-diastereomer (threo) (**43b**) in a 2:3 ratio (Scheme 6).



Scheme 6. *Reagents and conditions:* (a) NMM, ClCOOEt, THF; $NaBH_4$, H_2O, 92%; (b) polymer-bound bromite **42** complex, catalytic TEMPO, 95%; (c) CH_3NO_2, NaOEt (5%), EtOH, 15%.(d) i) separation of diastereoisomer ii) reduction.

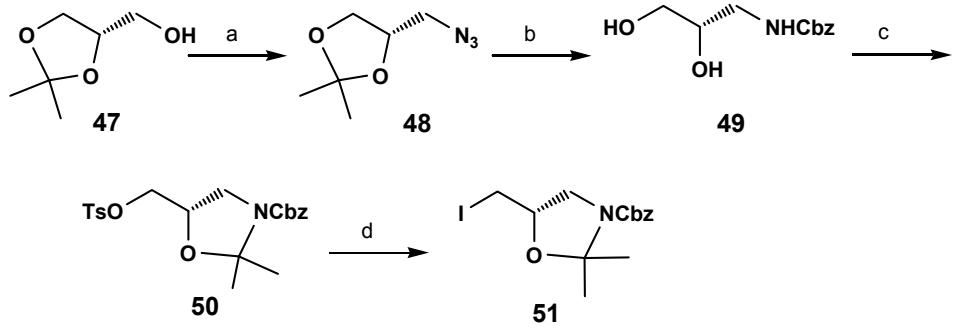
Because of the unfavorable diastereoselectivity and yield of the nitroaldol reaction, they turned to a different strategy for C-C-coupling which would involve the generation of an α-nitroketone. (*S*)-*N*-Boc-aspartic acid *tert*-butyl ester **39** was transformed to the nitroketone **45** and reduction of the keto group with L-Selectride gave rise to a 85:15 mixture in favor of the desired erythro compound **43a** (= (2*S*,4*R*)-diastereomer). In the last step of the sequence, the nitro group was reduced to furnish the vicinal amino alcohol function of the *tert*-butyl (2*S*,4*R*)-*N*-Boc-4-hydroxyornithinate **46** (Scheme 7).



Scheme 7. *Reagents and conditions:* (a) CDI (1.05 equiv), THF, rt; CH_3NO_2 (10 equiv), *t*-BuOK (1.1 equiv), rt, 96%; (b) L-Selectride, THF, -78 °C, 52%; (c) catalytic Pd/C, $NH_4^+HCOO^-$, -10 °C; (d) *Z*-OSu, DIPEA, DMF, rt, (51%, two steps).

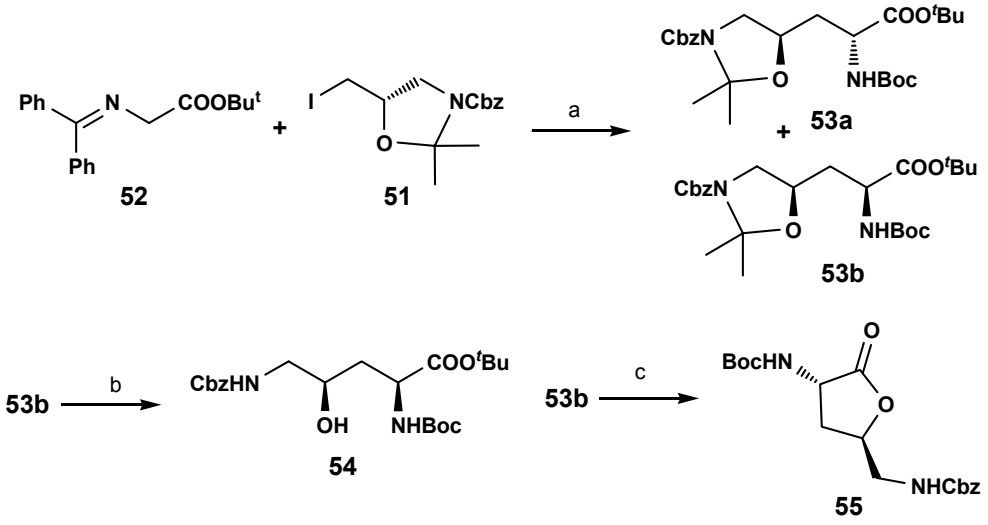
Zhu, J. *et al.* (2003)[21]

Jieping Zhu and co-workers synthesized orthogonally protected (2*S*,4*R*)- and (2*S*,4*S*)-4-hydroxyornithine starting from (*S*)-1,2-*O*-isopropylideneglycerol **47,** which on tosylation followed by nucleophilic displacement of tosylate with sodium azide provided azido derivative **48.** Hydrogenolysis under acidic conditions provided an amino diol that was chemoselectively *N*-acylated to give carbamate **49**. Regioselective tosylation of the primary hydroxy group afforded **49**, which was subsequently converted into iodide **51** *via* a classical two-step sequence (Scheme 8).



Scheme 8. *Reagents and conditions*: (a) i) TsCl, pyridine, r.t., 93%; ii) NaN_3, DMSO, 100 °C, 99%; (b) i) H_2, Pd/C, MeOH–HCl (10%); ii) CbzCl, $NaHCO_3$, H_2O-dioxane, r.t., 94%; (c) i) TsCl, pyridine, r.t., 85%; ii) 2,2-dimethoxypropane, acetone, $BF_3{\cdot}OEt_2$, r.t., 73%; (d) NaI, acetone, reflux, 85%.

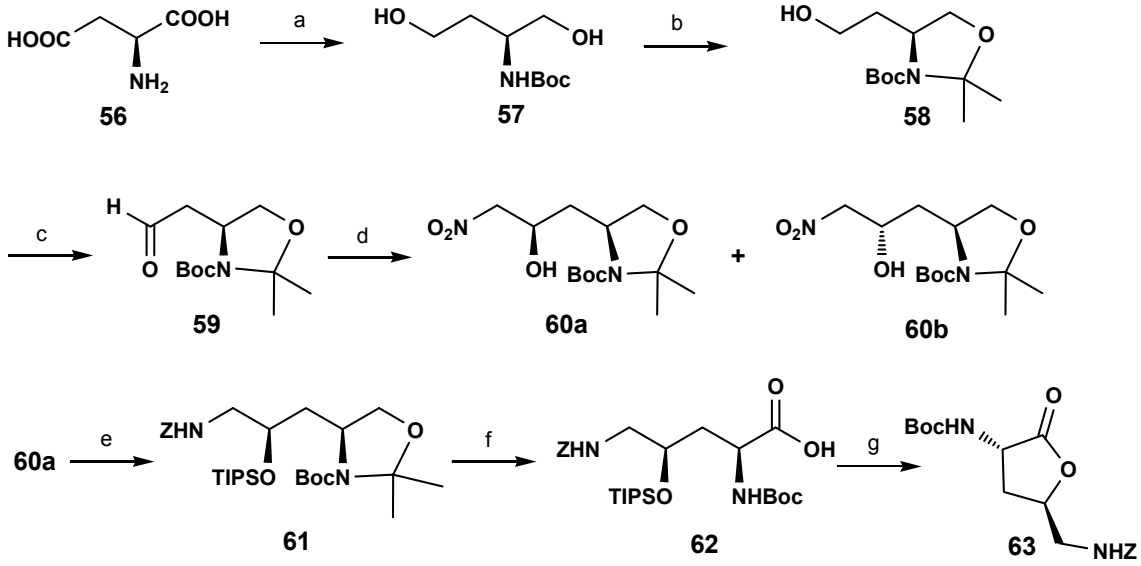
Alkylation of **52** with iodide **51** was carried out using *O*-(9)-allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide as catalyst under Corey's conditions (CsOH, 0.56 M in CH_2Cl_2) to give two diastereomers **53a** and **53b.** Selective hydrolysis of oxazolidine function of **53b** with *p*-TsOH followed by *N*-Boc formation led to ester **54**. On the other hand, treatment of **53b** with 5 N HCl provided the γ-lactone that was *N*-protected to afford **55** in 72% yield (Scheme 9).



Scheme 9. *Reagents and conditions*: (a) Corey's catalyst, $CsOH.H_2O$, -50 °C –rt, 68%; (b) i) catalytic *p*-TsOH, MeOH, r.t.; ii) Boc_2O, K_2CO_3, H_2O–dioxane (55% for two steps); (c) 5 N HCl, $CHCl_3$, r.t., Boc_2O, K_2CO_3, H_2O–dioxane (72% for two steps).

Paintner, F. F. *et al.* (2005).[22]

Franz F. Paintner and co-workers synthesized both orthogonally protected (2*S*,4*R*)- and (2*S*,4*S*)-4-hydroxyornithine **35a-b**. The approach is based on bis(oxazoline) copper(II)-complex-catalyzed diastereoselective Henry reactions of nitromethane with the homoserine-derived aldehyde. The synthesis started from aldehyde **59** prepared from known literature procedure, which was subjected to nitroaldol (Henry) reaction with nitromethane using Shibasaki's well-established heterobimetallic (*S*)-BINOL catalyst to give nitro alcohols **60a** and **60b.** Protection of the hydroxyl group as a TIPS ether and reduction of the nitro group was accomplished using ammonium formate as a hydrogen source and palladium on carbon as catalyst to afford the corresponding amine, which was transformed with (*Z*)-OSu/NEt_3) to compound **61** in 84% overall yield (three steps). Selective hydrolysis of the *N*,*O*-acetal using ethylene glycol/CSA (THF, 50 °C, 2 days) and final oxidation of the amino alcohol was best accomplished with TEMPO/NaOCl/$NaClO_2$ to give the desired carboxylic acid **62**. The absolute configuration of product **35a** was established to be (2*S*,4*R*) by subsequent transformation into the known *γ*-lactone **63** (Scheme 10).



Scheme 10. *Reagents and conditions*: (a) ref. 23; (b) i) 2,2-DMP, TsOH cat. ii) wet silica gel, CH_2Cl_2, 92%; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -60 °C, 97%; (d) $MeNO_2$, Shibasaki's catalyst (e) i) TIPSOTf, 2,6-lutidine, CH_2Cl_2; ii) HCO_2NH_4, Pd-C, MeOH; iii)

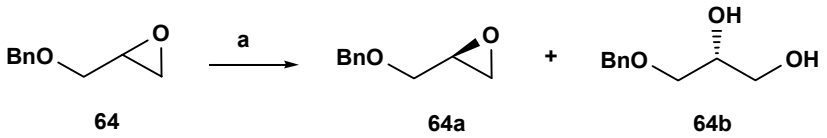
Z-OSu, Et_3N, CH_2Cl_2, (84%, three steps); (f) i) $(CH_2OH)_2$, CSA cat., THF, 50 °C; ii)TEMPO cat., NaOCl cat., $NaClO_2$, MeCN, buffer pH 6.7, (80%, two steps); (g) AcOH, H_2O, THF, 60 °C, 51%.

3.2.3. Present work:

Objective:

The stereoselective synthesis of 1,3-amino alcohol arrays is one of the most important topics in organic chemistry because of the ubiquity of 1,3-amino alcohol in various biologically active natural products and drugs. Thus, numerous strategies for their synthesis have been developed with great success. With the development of an efficient approach to the asymmetric synthesis of β-hydroxyornithine using Sharpless asymmetric dihydroxylation and cyclic sulfite chemistry,[24] we further became interested in developing a general protocol for the synthesis of 4-hydroxyornithines. In continuation, we herein describe a new and feasible route to 4-hydroxyornithines **35a-b** using Jacobsen's hydrolytic kinetic resolution (HKR) as the key step.

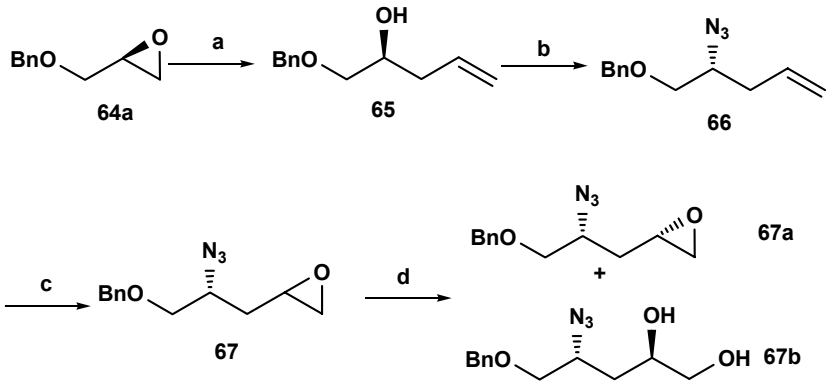
Results and Discussion:



Scheme 11. *Reagents and conditions:* (a) (*R,R*)-Salen-Co^{III}.(OAc) (0.5 mol%), dist. H_2O (0.55 equiv), 0 ^oC, 14 h, (47% for **64a**, 43% for **64b**).

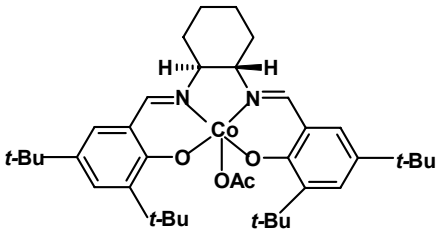
As illustrated in Scheme 11, racemic benzyl glycidol **64** was subjected to Jacobsen's HKR[25] using (*R,R*)-Salen-Co^{III}.OAc as the catalyst to give (*S*)-benzyl glycidol **64a** as a single enantiomer $[\alpha]_D^{25}$ + 8.63 (*c* 0.40, EtOH)}. {lit[26] $[\alpha]_D^{25}$ + 7.82 (*c* 0.40, EtOH)}, which was easily isolated from the more polar diol **64b** by distillation.

With enantiomerically pure epoxide **64a** in hand our next aim was to construct the *syn*-1,3-amino-alcohol. To establish the second stereogenic centre with the required stereochemistry, it was thought worthwhile to examine stereoselective epoxidation of a



Scheme 12. *Reagents and conditions* (a) Vinylmagnesium bromide, CuI, THF, -20 ^{o}C, 12 h, 88%; (b) (i) MsCl, Et_3N, DMAP, 0 ^{o}C-rt, 1.5 h; (ii) NaN_3, DMF, 70 ^{o}C, 9 h, 91%; (c) *m*CPBA, CH_2Cl_2, 0 ^{o}C-rt, 10 h, 96%, ds, *syn*:*anti*/ 1:1.18; (d) (*S,S*)-Salen Co^{III}**.** OAc (0.5 mol %), distd. H_2O (0.55 equiv.), THF, 0 °C, 14 h, (41% for **67a**, 43% for **67b**).

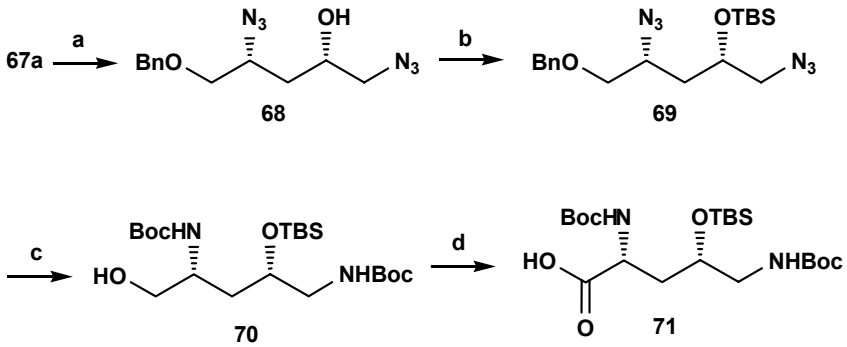
homoallylic azide (Scheme 12). Thus, (*S*)-benzyl glycidol **64a** was treated with vinylmagnesium bromide in the presence of CuI to give the homoallylic alcohol **65** in 88% yield. The IR spectrum of **65** gave broad hydroxyl absorption at 3410 cm^{-1}. The ^{1}H NMR spectrum of **65** gave olefin peaks at 5.74-5.94 (multiplet, one proton), 5.12-5.19 (multiplet, one proton), 5.08 (triplet, one proton). Compound **65** was then converted into its *O*-mesyl derivative, which on treatment with sodium azide in dry DMF furnished azide **66** with the desired inverted stereochemistry. The IR spectrum of **66** gave azide absorption at 2103 cm^{-1}. Compound **66** was then subjected to *m*-CPBA epoxidation, the epoxide **67** thus obtained was found to be a mixture of two diastereomers in almost equal amounts (*syn*:*anti*/ 1:1.18). The two diastereomers could not be differentiated on TLC. In order to improve the diastereoselectivity, we attempted the HKR method as depicted in Scheme 12. Thus HKR was performed on **67** with the (*S,S*)-Salen Co^{III}.OAc complex (0.5 mol%) (Figure 3) and water (0.55 eq) in THF (0.55 equiv) to afford epoxide **67a** as a single diastereoisomer (as determined from ^{1}H and ^{13}C NMR spectral analyses) in 41% yield and diol **67b** in 43% yield. The IR spectrum of **67a** gave azide absorption at 2115 cm^{-1}. The epoxide peaks appeared at δ 3.02-3.11 (multiplet, one proton), 2.84 (t, J = 4.04 Hz, one proton), 2.53 (doublet of doublet, J = 2.78, 5.05 Hz, one proton).



(*S,S*)-Salen Co(III).OAc complex

Figure 3.

The ring opening of epoxide **67a** was carried out with NaN_3 to give the diazido alcohol **68** in 92% yield (Scheme 13). Hydroxyl protection of **68** with *tert*-butyldimethylsilyl chloride and imidazole in the presence of a catalytic amount of DMAP afforded the silyl ether **69** in 97% yield. Concomitant one-pot deprotection of benzyl group, reduction of both the azide groups and Boc protection of the resulting diamine was carried out with $H_2/Pd(OH)_2$, Boc_2O to give the alcohol **70** in 86% yield. Finally, amino alcohol **70** was oxidized with TEMPO/NaOCl/$NaClO_2$ to furnish the desired protected amino acid **71** in excellent yield.



Scheme 13. *Reagents and conditions* (a) NaN_3, NH_4Cl, DMF, 50 ^oC, 14 h, 92%; (b) TBS-Cl (TBS=*tert*-butyldimethylsilyl), imidazole, DMAP, CH_2Cl_2, 0 ^oC-rt, 4 h, 97%; (c) 20% $Pd(OH)_2/C$, H_2, Boc_2O, EtOAc, 12 h, 86%; (d) TEMPO, NaOCl, $NaClO_2$, CH_3CN, 82%.

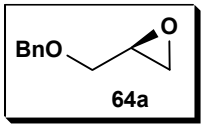
3.2.5. Conclusion

In conclusion, we have developed a short approach to protected (2*S*,4*R*)-4-hydroxyornithine in high enantio- and diastereomeric excess using Jacobsen's HKR as the key step. The *syn*- and *anti*-configuration of the 1,3-amino-alcohol moiety can be manipulated simply by changing the Jacobsen's catalyst in the hydrolytic kinetic resolution

step. The target compound **71** has been synthesized from **64** in 9 steps and in 9.32% overall yield. The synthetic strategy described here has significant potential for stereochemical variations and further extension to other stereoisomers, and analogues, e.g. (2*S*,4*S*,6*R*)-4-hydroxy-5-phenylsulfinyl-norvaline **38**.

3.2.6. Experimental Section

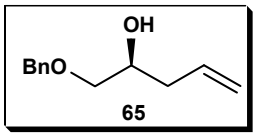
(*S*)-2-((Benzyloxy)methyl)oxirane (64a):



The racemic benzyl glycidol (±)-**64** was resolved to chiral epoxide (*S*)-**64a** in high enantiomeric excess by the HKR method as a single enantiomer which was easily isolated from the more polar diol **64b** by distillation following a literature procedure.[25]

$[\alpha]_D^{25}$ + 8.63 (*c* 0.40, EtOH)}. {lit[25a] $[\alpha]_D^{25}$ + 7.82 (*c* 0.40, EtOH)}.

(*S*)-1-(Benzyloxy)pent-4-en-2-ol (65):



To a stirred solution of **64a** (4.00 g, 24.38 mmol) and CuI (464 mg, 2.44 mmol) in dry THF (30 mL), was added over 30 min a 1 M solution of vinylmagnesium bromide in THF (4.80 g, 36.56 mmol, 36.56 ml, 1M solution in THF) dropwise at -20 °C and stirred for 12 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 Et_2O (3 x 30 mL), the combined ethereal extracts were washed with brine (20 mL) and dried (Na_2SO_4). Evaporation of the solvent and silica gel column chromatographic purification (EtOAc/ petroleum ether 1:20) of the crude product gave **65** as a colorless oil.

Yield: 4.12 g, 88%

Mol. Formula: $C_{12}H_{16}O_2$

$[\alpha]_D^{25}$: + 1.52 (c 1.16, $CHCl_3$)

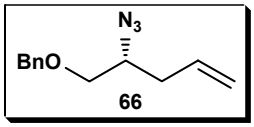
IR (neat, cm^{-1}): ν_{max} 3410, 3010, 2931, 1670, 1243

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.63 (brs, 1H), 2.26 (t, J = 6.95 Hz, 2 H), 2.36 (d, J = 3.54 Hz, 1H), 3.39 (dd, J = 7.45, 9.48 Hz, 1 H), 3.50-3.62 (m, 1 H), 3.83-4.04 (m, 1 H), 4.58 (s, 1 H), 5.08 (t, J = 1.26 Hz, 1 H), 5.12-5.19 (m, 1 H), 5.74-5.94 (m, 1 H), 7.31-7.39 (m, 5 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 37.8, 69.6, 73.2, 73.8, 115.50, 127.6, 128.3, 134.1, 137.8 ppm.

Analysis Calcd.: 74.97; H, 8.39%; **Found:** 74.88; H, 8.56%.

(*R*)-2-Azidopent-4-enyloxy)methyl)benzene (66):



To an ice-cold stirred solution of **65** (4.0 g, 20.80 mmol) and triethylamine (2.5g, 3.48 mL, 8.58 mmol) in anhydrous CH_2Cl_2 (50 mL) was added dropwise methanesulfonyl chloride (2.62 g, 1.77 mmol) over 15 min. The resulting mixture was allowed to warm up to room temperature and stirred for 1.5 h. After diluting with 50 mL CH_2Cl_2, the solution was washed with water (3 x 25 mL), brine, dried over Na_2SO_4 and concentrated to give the crude mesylated product. This was used for the next step without further purification.

To a solution of above mesylated product of **65** in dry DMF (20 mL) was added portion wise NaN_3 (4.05 g, 62.41 mmol) and the resulting suspension was stirred for 9 h at 70 °C. After cooling the orange solution to room temperature, Et_2O (25 mL) and H_2O (25 mL) were added and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. Silica gel column chromatography purification (R_f = 0.30, petroleum ether) of the crude product gave azide **66** as a yellowish liquid.

Yield: 4.17 g, 91%

Mol. Formula: $C_{12}H_{15}N_3O$

$[\alpha]_D^{25}$: + 6.31 (c 1.00, $CHCl_3$)

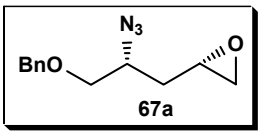
IR ($CHCl_3$, cm^{-1}): ν_{max} 2959, 2103, 1655, 1216.

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.32 (dt, J = 1.39, 6.94 Hz, 2H), 3.46-3.67 (m, 3H), 4.58 (s, 2H), 5.11 (t, J = 1.27 Hz, 1H), 5.15-5.21 (m, 1H), 5.70-5.91 (m, 1H), 7.30-7.38 (m, 5H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 35.2, 60.9, 72.1, 72.3, 118.25, 127.5, 127.7, 128.3, 133.4, 137.7 ppm.

Analysis Calcd.: C, 66.34; H, 6.96; N, 19.34%; **Found:** C, 66.41; H, 6.82; N, 19.39%.

(*S*)-2-(*R*)-2-Azido-3-(benzyloxy)propyl)oxirane (67a)



To a stirred solution of olefin **66** (3.80 g, 17.24 mmol) in CH_2Cl_2 (20 mL) at 0 ^oC was added *m*-CPBA (50%) (7.14 g, 20.69 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 **67** (3.91 g, 96%) as a colorless liquid in two diastereomers in almost equal amounts (*syn*:*anti*/ 1:1.18).

A solution of epoxide **67** (3.75 g, 15.87 mmol) and (*S,S*)-salen-Co(III)-OAc (52 mg, 0.08 mmol) in THF (0.1 mL) was stirred at 0 ^oC for 5 min, and then distilled water (16 μmL, 8.73 mmol) was added. After stirring for 24 h, it was concentrated and purified by silica gel column chromatography using pet ether: EtOAc (19:1) to afford **67a** (1.54 g, 41%) as a pale yellow color liquid. Continued chromatography with pet ether/EtOAc (3:2) provided the diol **67b** (1.73 g, 43%) as a yellow liquid as a single diastereomer.

Yield: 1.54 g, 41%

Mol. Formula: $C_{12}H_{15}N_3O_2$

$[\alpha]_D^{25}$: +49.93 (*c* 1.00, $CHCl_3$)

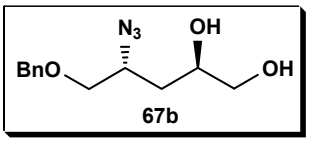
IR (neat, cm^{-1}): ν_{max} 2922, 2105, 1601, 1453, 1272

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.48-1.61 (m, 1H), 1.75-1.89 (m, 1H), 2.53 (dd, J = 2.78, 5.05 Hz, 1H), 2.84 (t, J = 4.04 Hz, 1H), 3.02-3.11 (m, 1H), 3.53 (dd, J = 7.07, 9.85 Hz, 1H), 3.66 (dd, J = 3.91, 6.31 Hz, 1H), 3.75-3.88 (m, 1H), 4.59 (s, 2H), 7.30-7.38 (m, 5H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 34.3, 47.2, 49.2, 59.4, 72.6, 73.2, 127.4, 127.7, 128.3, 137.6 ppm.

Analysis Calcd.: C, 61.79; H, 6.48; N, 18.01%; **Found:** C, 61.58; H, 6.67; N, 17.69%.

(2*R*,4*R*)-4-Azido-5-(benzyloxy)pentane-1,2-diol (67b):



67b

Yield: 1.73 g, 43%

Mol. Formula: $C_{12}H_{17}N_3O_3$

$[\alpha]_D^{25}$: + 25.86 (c 1.00, $CHCl_3$)

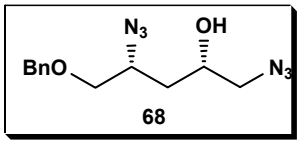
IR (neat, cm^{-1}): ν_{max} 3436, 2968, 2932, 2852, 2102, 1656, 1379, 1265, 1206

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.50-1.75 (m, 2 H), 2.24 (brs, 1H), 2.77-2.99 (m, 1 H), 3.40-3.56 (m, 1 H), 3.58-3.70 (m, 3 H), 3.74-3.95 (m, 2 H), 4.59 (s, 2 H), 7.32-7.39 (m, 5 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 33.8, 56.9, 66.0, 69.5, 72.4, 73.3, 127.5, 127.8, 128.4, 137.4 ppm.

Analysis Calcd.: C, 57.36; H, 6.82; N, 16.72%; **Found:** C, 57.54; H, 6.77; N, 16.69%.

(2*S*,4*R*)-1,4-Diazido-5-(benzyloxy)pentan-2-ol (68):



68

To a stirred solution of **67a** (1.00 g, 12.18 mmol) in dry DMF (20 mL), was added portion wise NaN_3 (2.40 g, 18.27 mmol) and NH_4Cl (2.40 g, 18.27 mmol) and the resulting suspension was stirred for 14 h at 50 °C. After cooling the orange solution to room temperature, Et_2O (25 mL) and H_2O (25 mL) were added and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over Na_2SO_4

and the solvent was removed under reduced pressure. Silica gel column chromatography purification (R_f = 0.30, petroleum ether) of the crude product gave diazide **68** as a yellowish liquid.

Yield: 1.1 g, 92%

Mol. Formula: $C_{12}H_{16}N_6O_2$

$[\alpha]_D^{25}$: + 39.08 (c 0.50, $CHCl_3$)

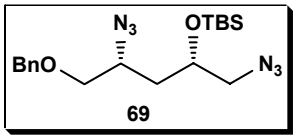
IR (neat, cm^{-1}): ν_{max} 3410, 2902, 2103, 1666, 1216

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.53-1.62 (m, 2 H), 2.37 (d, J = 4.93 Hz, 1 H), 3.22-3.68 (m, 4 H), 3.83-4.06 (m, 2 H), 4.60 (s, 2 H), 7.30-7.43 (m, 5 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 35.2, 57.1, 58.2, 67.3, 72.9, 73.3, 127.5, 127.8, 128.4, 137.5 ppm.

Analysis Calcd.: C, 52.16; H, 5.84; N, 30.42%; **Found:** C, 52.20; H, 5.75; N, 30.39%.

(2*S*,4*R*)-1,4-diazido-5-(benzyloxy)pentan-2-yloxy)(*tert*-butyl)dimethylsilane (69):



69

To a stirred solution of alcohol **68** (0.8 g, 2.81 mmol) in CH_2Cl_2 (10 mL) was added imidazole (0.23 g, 3.38 mmol). To this solution *t*-butyldimethylchlorosilane (0.47 g, 3.09 mmol) was added at 0 ^oC and reaction was stirred at room temperature for 4 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2 (3 x 20 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 (19:1) as eluent provided **69** as a colorless liquid.

Yield: 1.1 g, 97%

Mol. Formula: $C_{18}H_{30}N_6O_2Si$

$[\alpha]_D^{25}$: + 20.06 (c 0.76, $CHCl_3$)

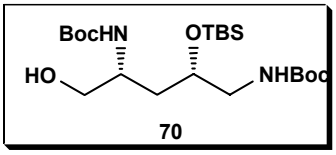
IR (neat, cm^{-1}): ν_{max} 2966, 2101, 1644, 1216

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.15 (s, 6 H), 0.93 (s, 9 H), 1.49-1.69 (m, 2 H), 3.12 (dd, J = 4.30, 12.51 Hz, 1 H), 3.38 (dd, J = 4.67, 12.63 Hz, 1 H), 3.46-3.81 (m, 3 H), 3.96-4.06 (m, 1 H), 4.60 (s, 2 H), 7.31-7.43 (m, 5 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -5.1, -4.3, 17.9, 25.8, 36.0, 57.1, 57.9, 68.3, 73.3, 73.5, 73.7, 127.5, 127.7, 128.4, 137.7 ppm.

Analysis Calcd.: C, 55.36; H, 7.74; N, 21.52%; **Found:** C, 55.33; H, 7.88; N, 21.29%.

(2*S*,4*R*)-1,4-Diamino-di(*tert*-butylcarbamate)-5-(benzyloxy)pentan-5-ol)(*tert*-butyl)dimethylsilane (70):



To a solution of azide **69** (0.2 g, 0.5 mmol) in ethyl acetate was added 20% $Pd(OH)_2/C$ (50 mg) and Boc_2O (0.3 mL, 1.3 mmol). The resulting solution was stirred under hydrogen atmosphere for 12 h at room temperature until disappearance of the azido alcohol as monitored by TLC. The reaction mixture was filtered through a celite pad to remove the catalyst and the filtrate was concentrated in vacuo. Silica gel column chromatography of the crude product using EtOAc/pet ether (3:7) as eluent gave **70** (0.24 g) as a colorless liquid.

Yield: 194 mg, 86%

Mol. Formula: $C_{21}H_{44}N_2O_6Si$

$[\alpha]_D^{25}$: + 20.89 (c 1.00, $CHCl_3$)

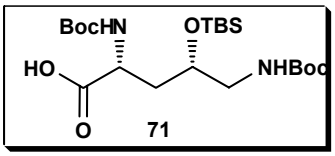
IR ($CHCl_3$, cm^{-1}): ν_{max} 3390, 3020, 2958, 2931, 2858, 1737, 1643, 1521, 1473, 1463, 1394, 1216

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.10 (s, 6 H), 0.91 (s, 9 H), 1.44 (s, 18 H), 1.60-1.75 (m, 2 H), 3.18 (t, J = 5.81 Hz, 2 H), 3.61 (m, 4 H), 3.13 (q, J = 7.20, 14.27 Hz, 1 H), 4.75 (brs, 1 H), 5.25 (brs, 1 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -5.0, -4.6, 17.9, 25.8, 28.3, 35.6, 50.0, 63.4, 68.7, 79.5, 156.1 ppm.

Analysis Calcd.: C, 56.22; H, 9.88; N, 6.24%; **Found:** C, 56.35; H, 9.69; N, 6.28%.

Protected (2*S*,4*R*)-4-hydroxyornithine (71)



A catalytic amount of TEMPO (4 mg, 0.02 mmol) was added to a solution of alcohol **70** (100 mg, 0.22 mmol) in MeCN (2 mL) and sodium phosphate buffer pH 6.7 (1 mL). The mixture was heated to 35 ^{o}C, 2.0 M $NaClO_2$ (0.5 mL) and diluted bleach (100 μl, 0.006 mmol free chlorine) were added simultaneously over 1 hour (**Caution** ! Do not mix bleach and $NaClO_2$ before being added to the reaction mixture). The reaction mixture was stirred at 35 ^{o}C for another 4.5 hour then cooled to room temperature, H_2O (5 mL) was added and the pH was adjusted to 8-9 with 4M NaOH. Then the mixture was poured into cold 0.5 Na_2SO_3 (10 mL). After 30 min the mixture was extracted with EtOAc (3 x 10). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in *vacuo*. The crude reaction product was purified by flash chromatography on silica gel (*n*-hexane/EtOAc 6:4 + 0.5 % HOAc) to afford **71** as a thick syrup liquid.

Yield: 84 mg, 82%

Mol. Formula: $C_{21}H_{42}N_2O_7Si$

$[\alpha]_D^{25}$: +38 (*c* 0.50, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 3346, 2910, 1716, 1453

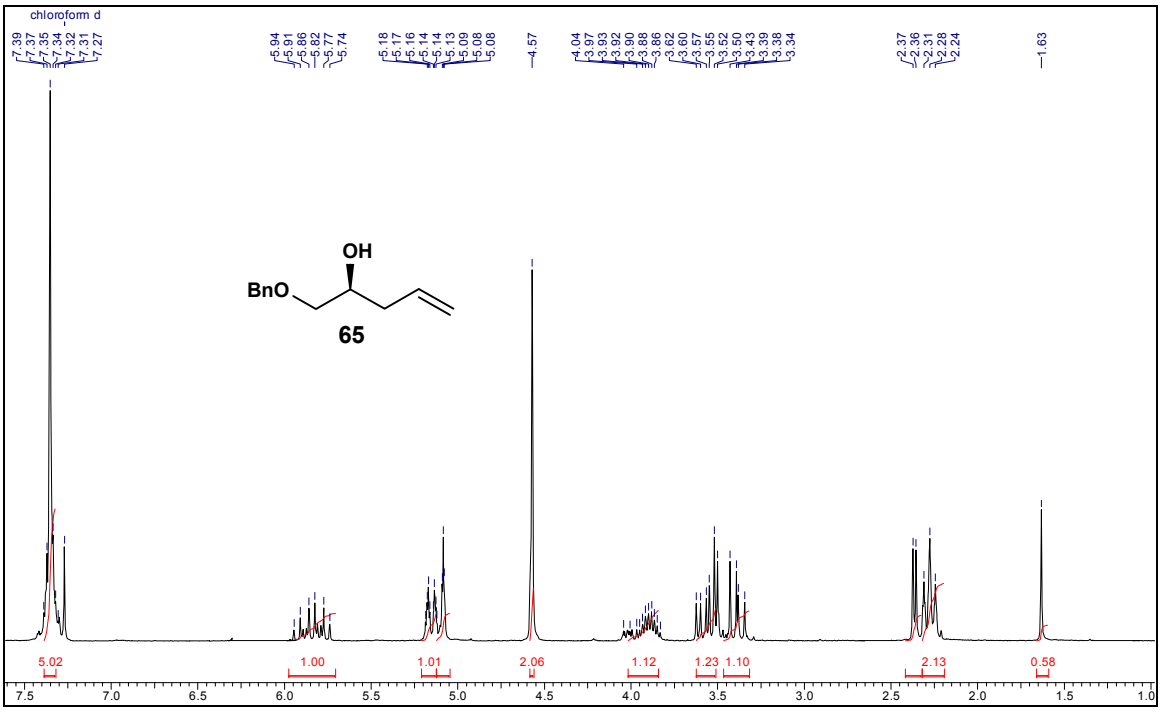
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.08 (s, 6H), 0.88 (s, 9H), 1.45 (s, 18H), 1.75-1.82 (m, 2H), 2.62-2.89 (m, 1H), 3.61-3.81(m, 1H), 3.98-4.38 (m, 2H), 4.31-4.62 (m, 1H), 5.49-5.74 (m, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -5.1, -4.7, 14.1, 18.0, 22.7, 28.3, 31.9, 42.5, 65.2, 66.3, 80.4, 163.3 ppm.

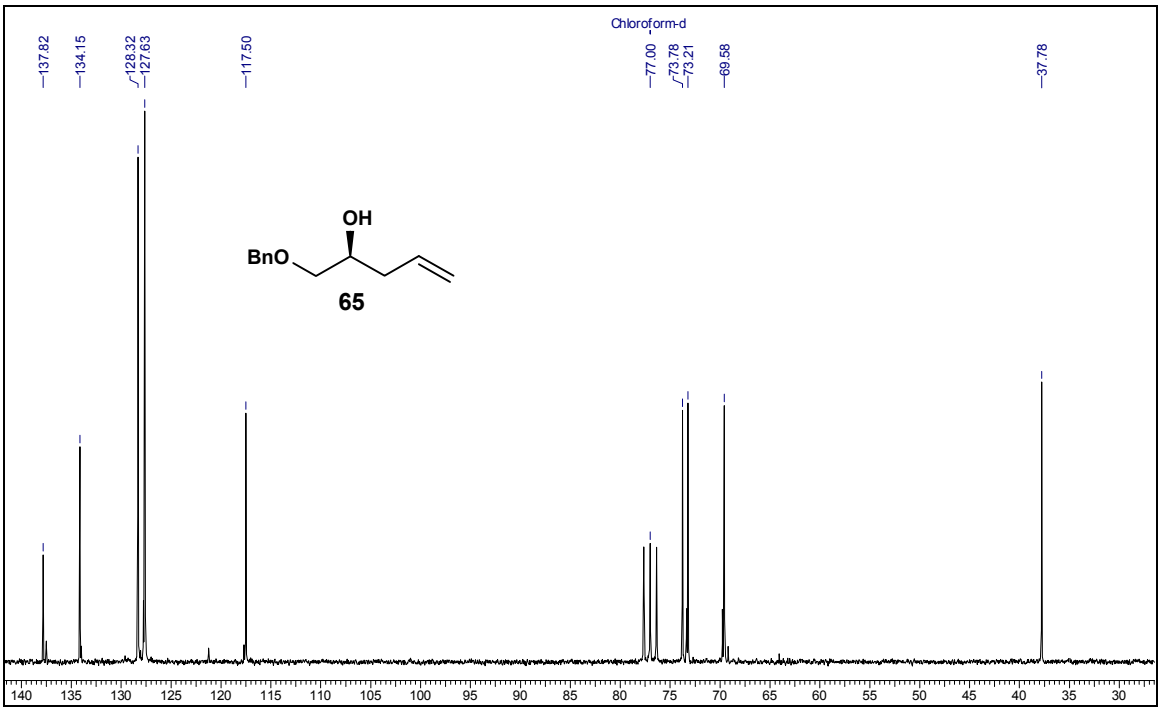
Analysis Calcd.: C, 54.52; H, 9.15; N, 6.05%; **Found:** C, 54.25; H, 9.37; N, 5.75%.

3.2.7 Spectra

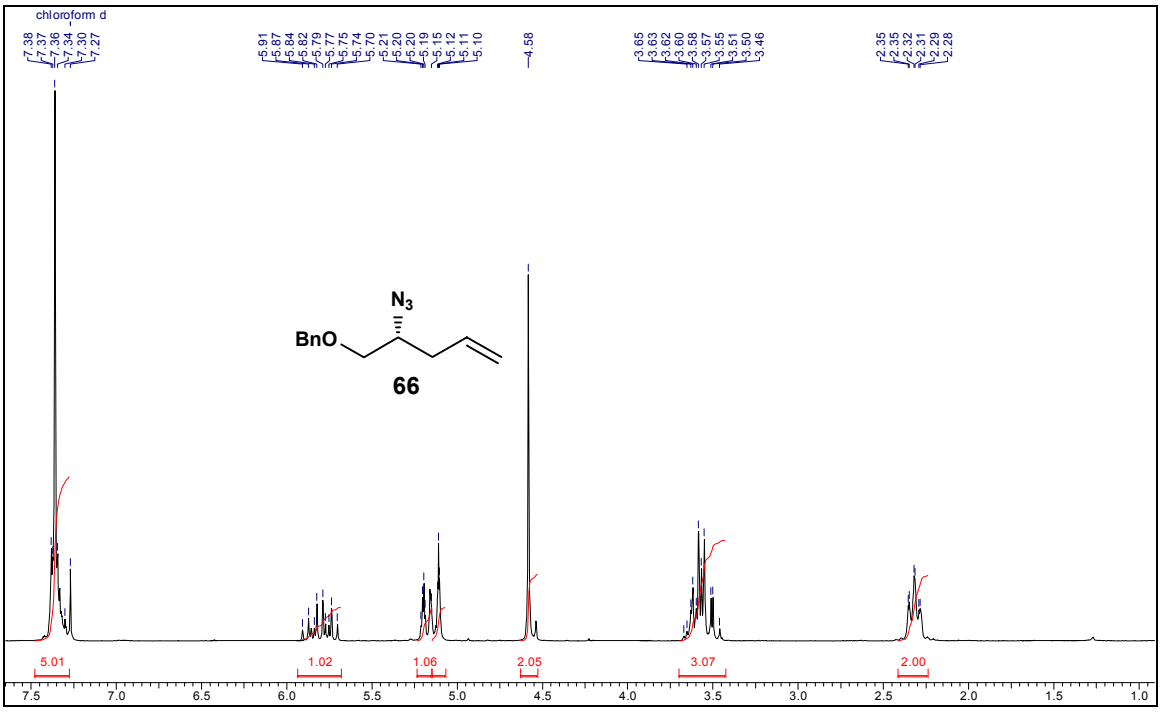
1. ^{1}H and ^{13}C NMR spectra of **65**
2. ^{1}H and ^{13}C NMR spectra of **66**
3. ^{1}H and ^{13}C NMR spectra of **67a**
4. ^{1}H and ^{13}C NMR spectra of **67b**
5. ^{1}H and ^{13}C NMR spectra of **68**
6. ^{1}H and ^{13}C NMR spectra of **69**
7. ^{1}H and ^{13}C NMR spectra of **70**
8. ^{1}H and ^{13}C NMR spectra of **71**



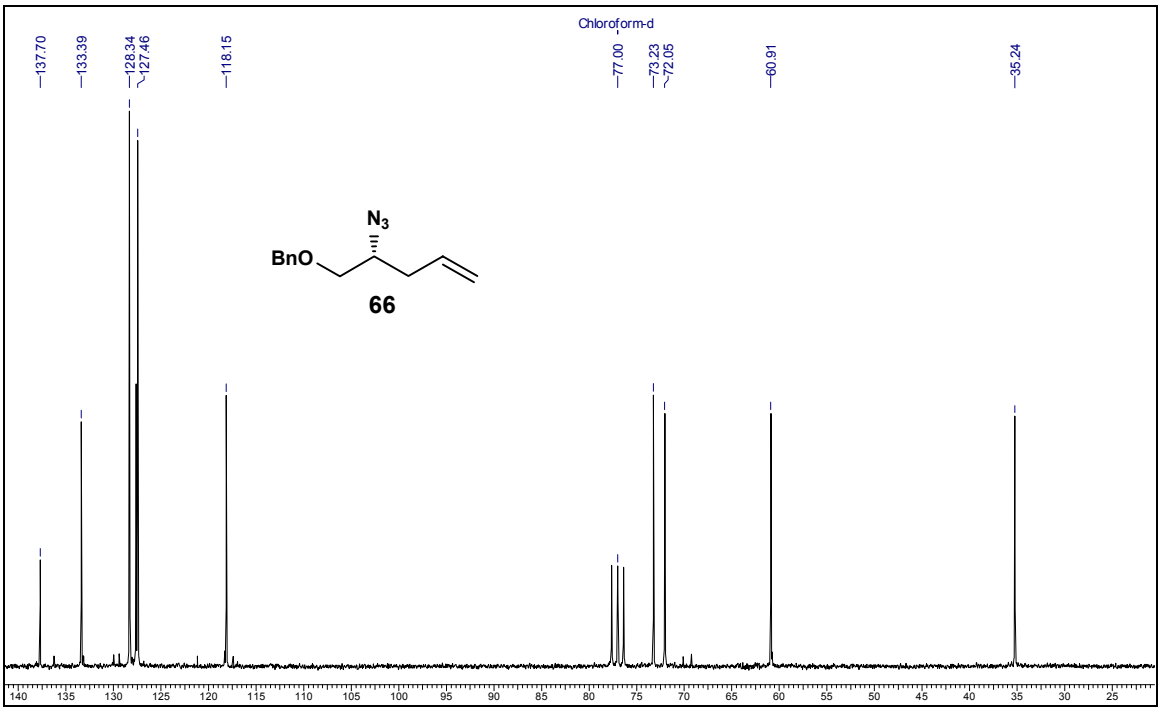
☞ ^{1}H NMR of the compound 65 in $CDCl_3$



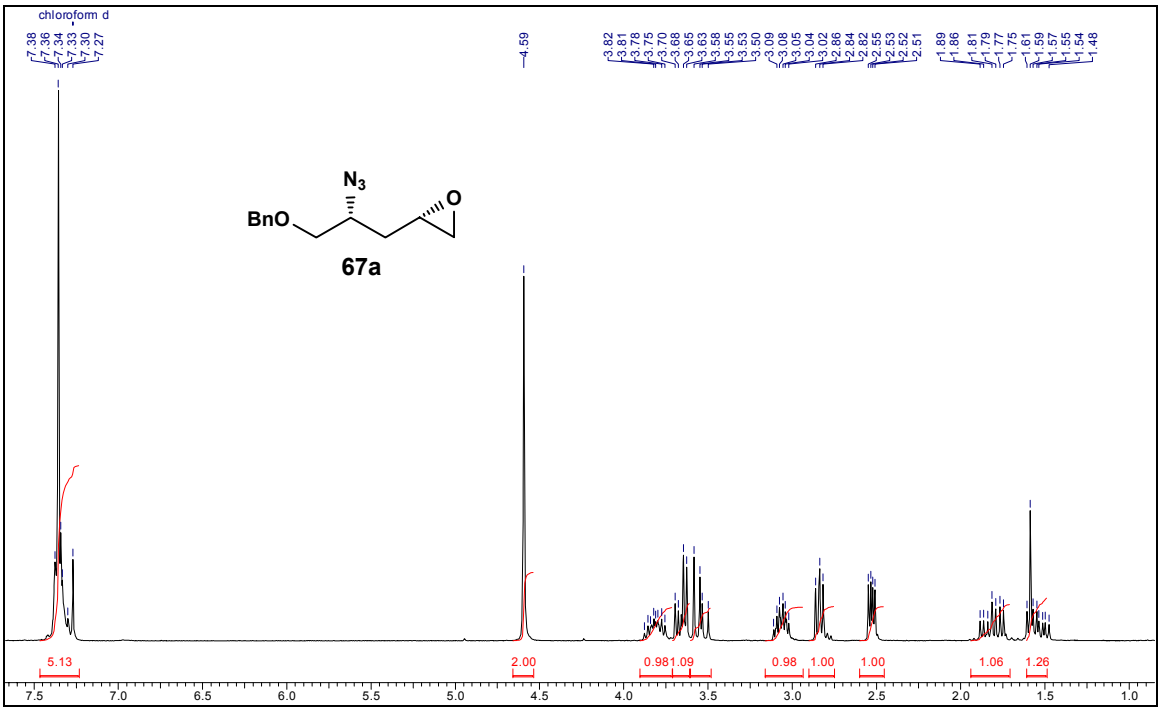
☞ ^{13}C NMR of the compound 65 in $CDCl_3$



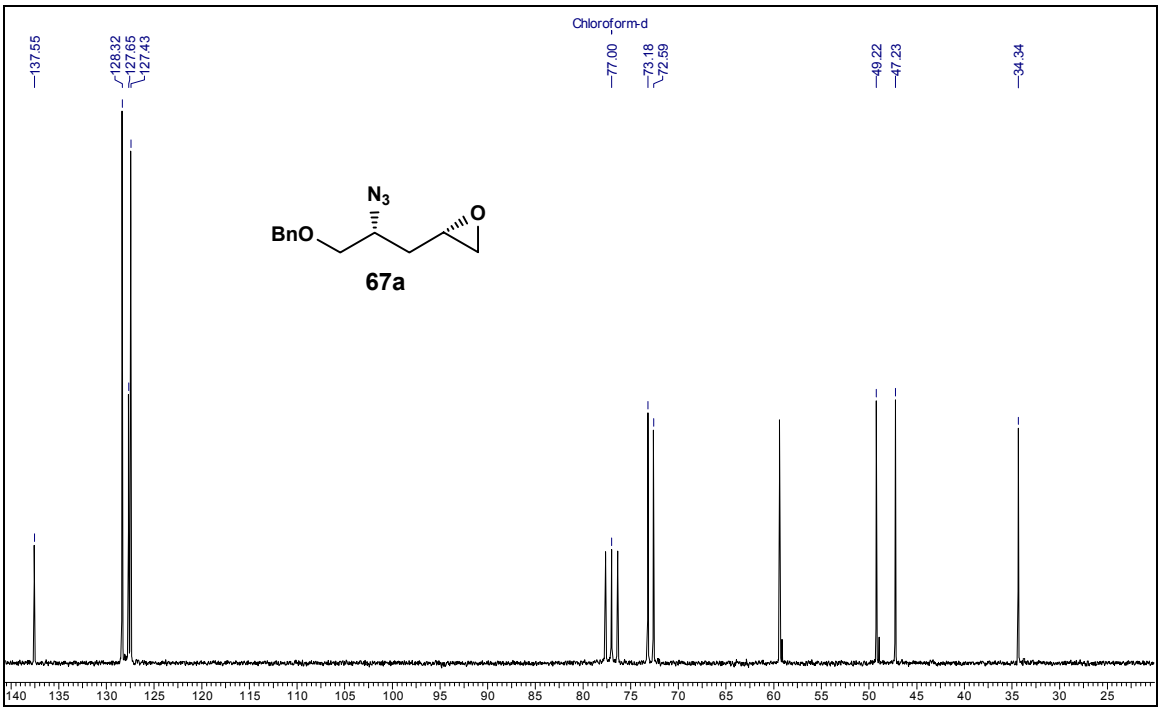
☞ ^{1}H NMR of the compound 66 in $CDCl_3$



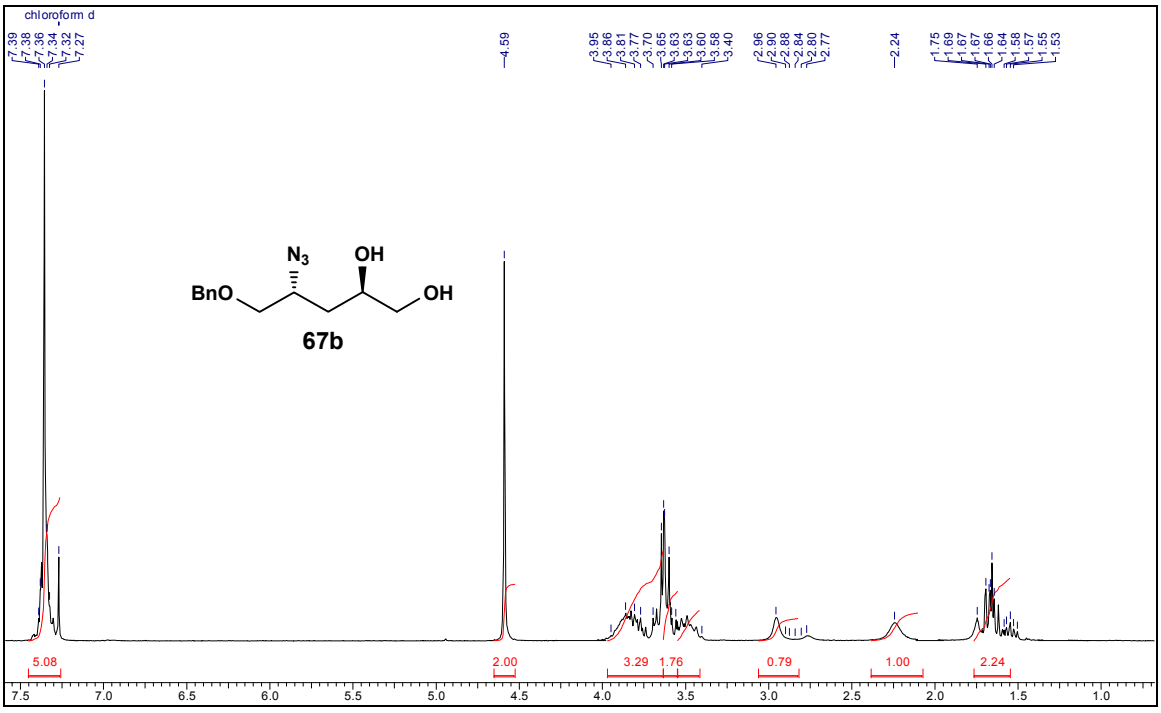
☞ ^{13}C NMR of the compound 66 in $CDCl_3$



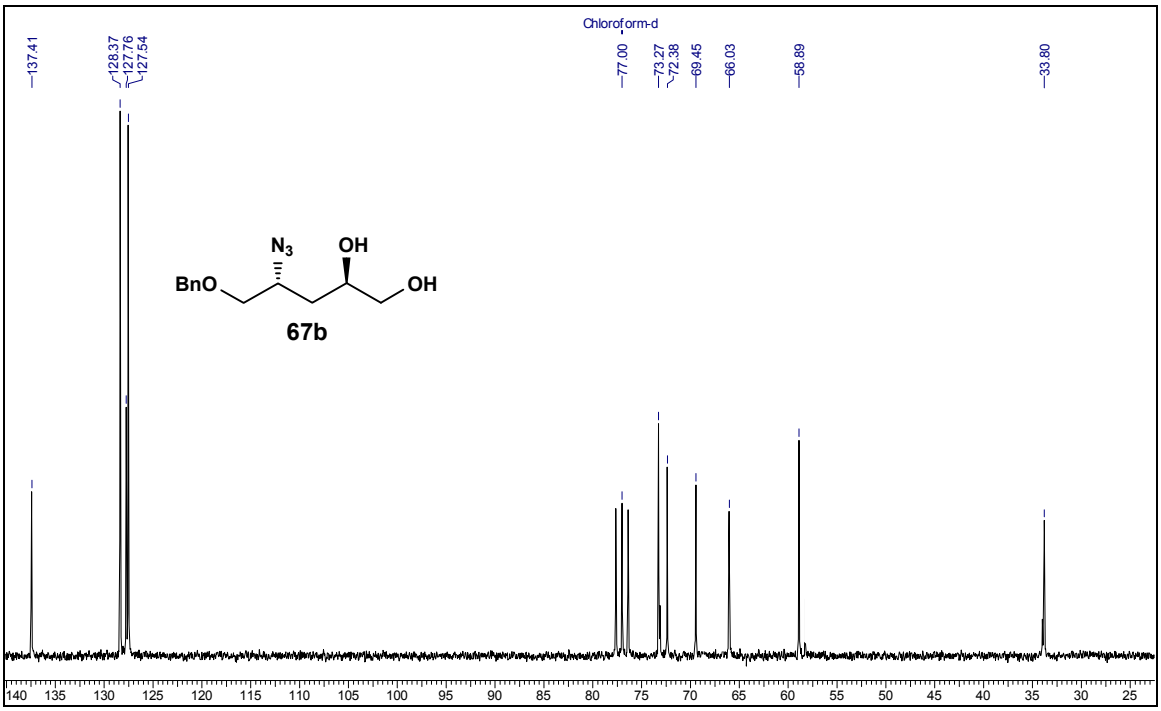
☞ ^{1}H NMR of the compound 67a in $CDCl_3$



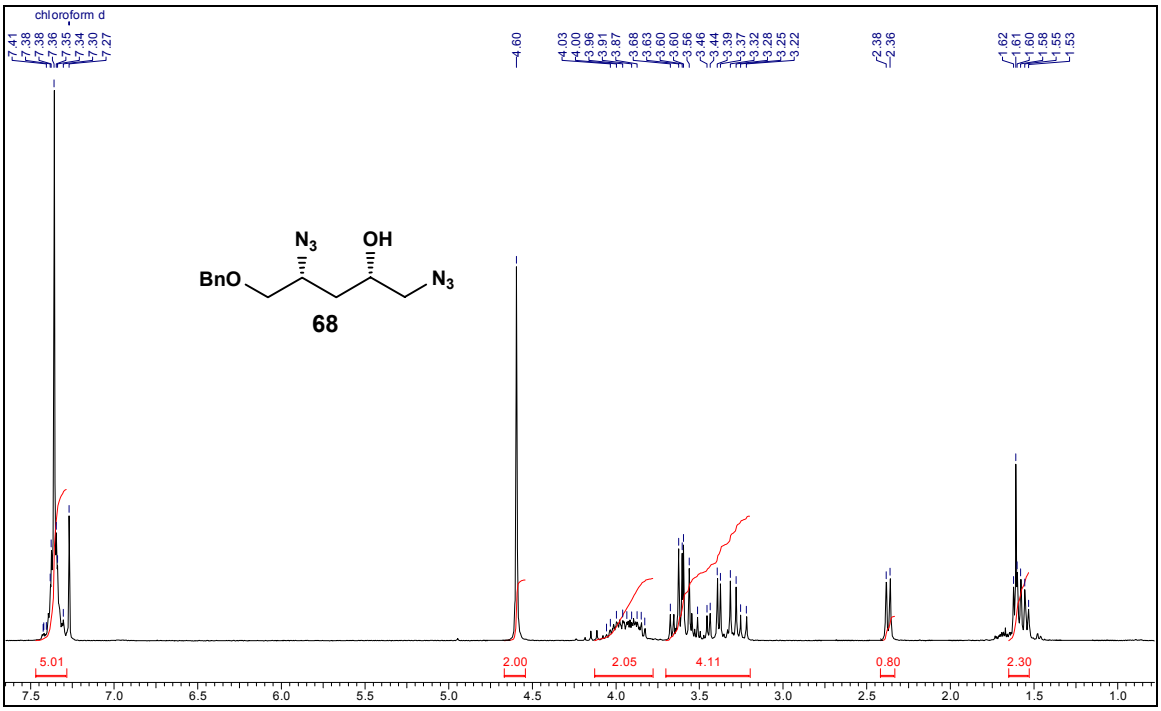
☞ ^{13}C NMR of the compound 67a in $CDCl_3$



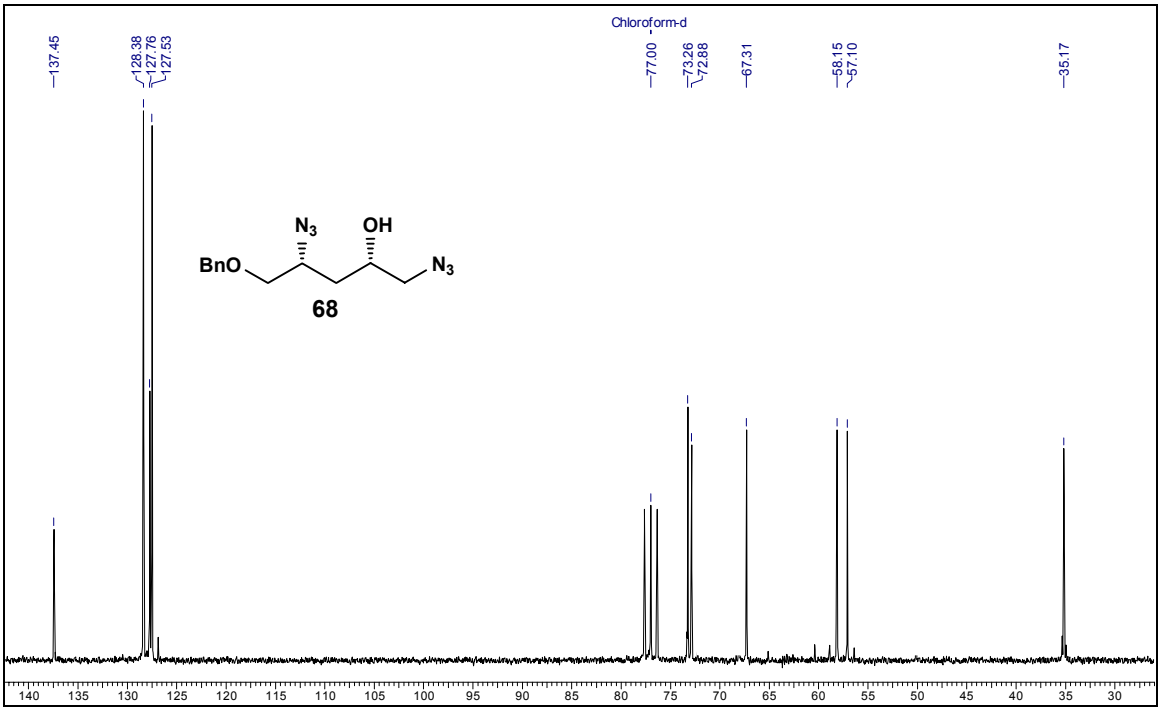
☞ ^{1}H NMR of the compound 67b in $CDCl_3$



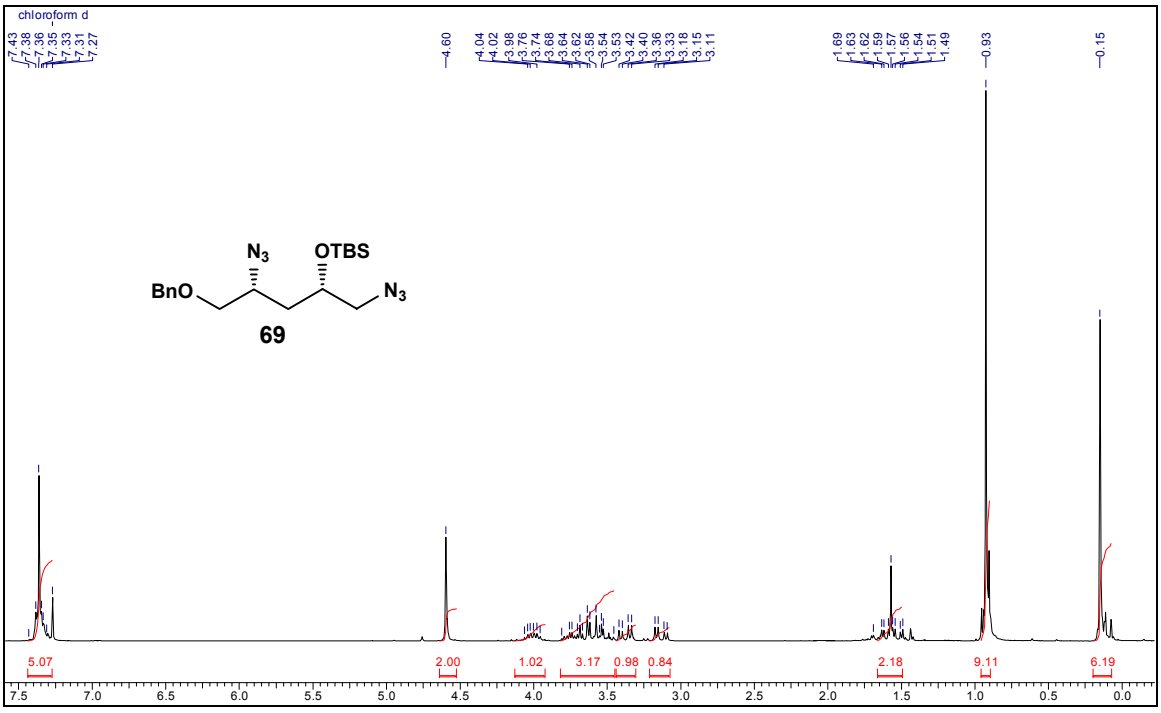
☞ ^{13}C NMR of the compound 67b in $CDCl_3$



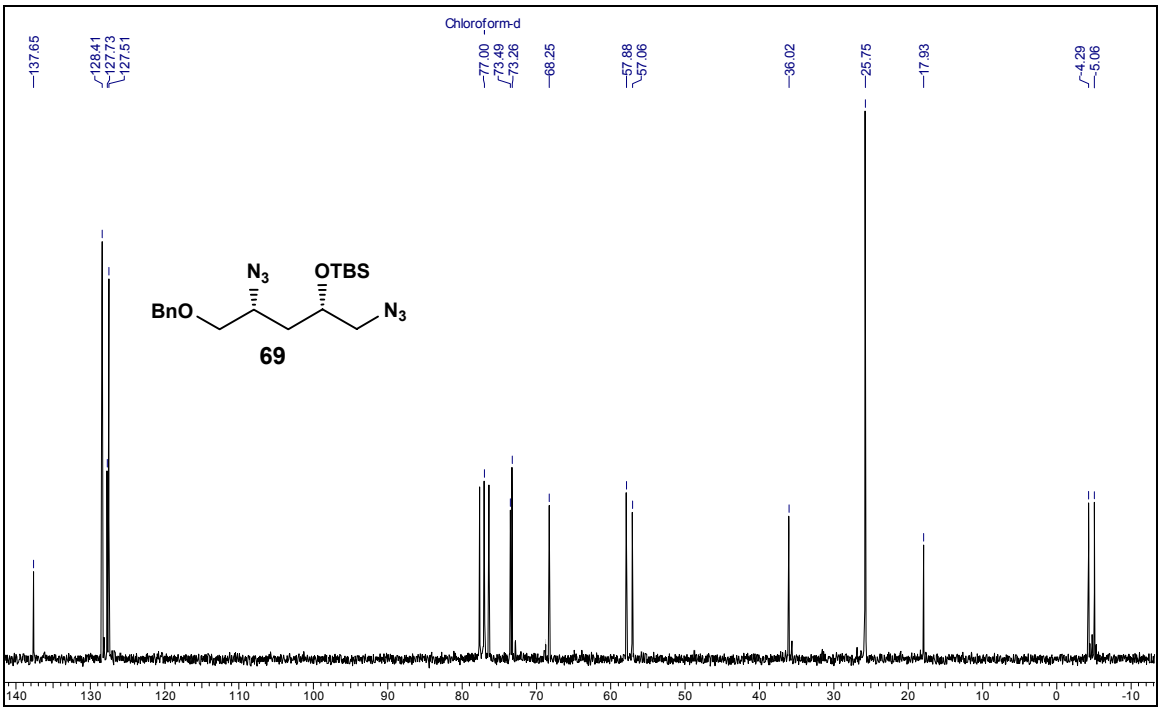
☞ ^{1}H NMR of the compound 68 in $CDCl_3$



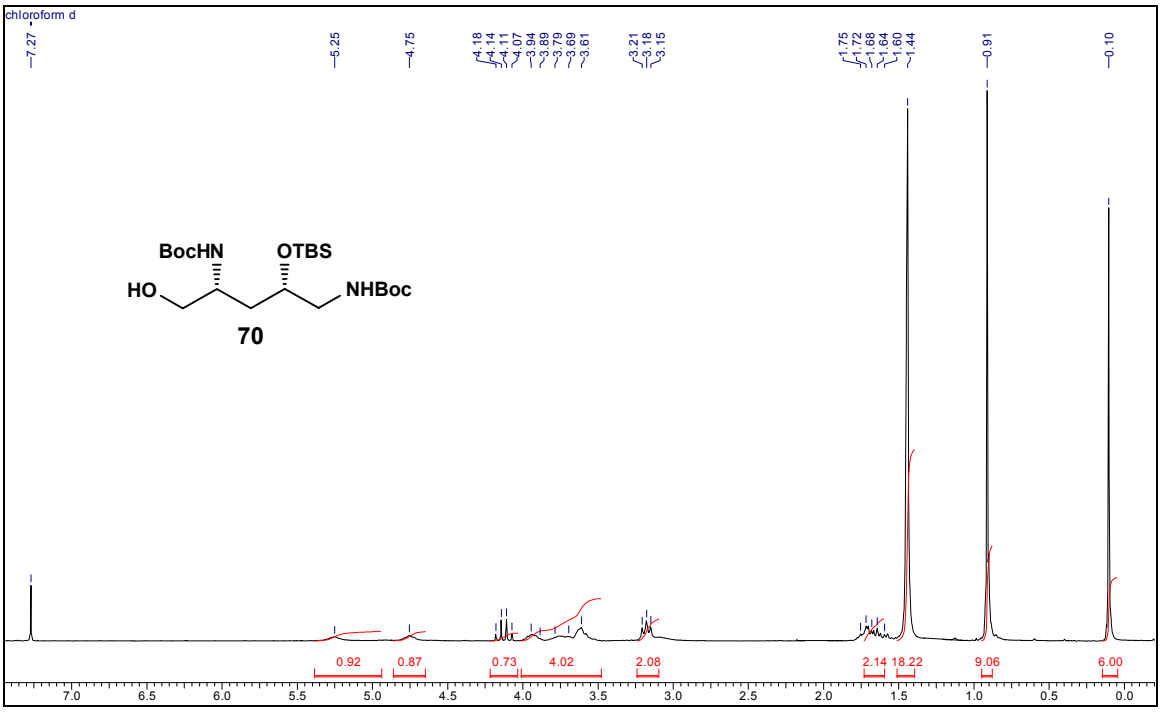
☞ ^{13}C NMR of the compound 68 in $CDCl_3$



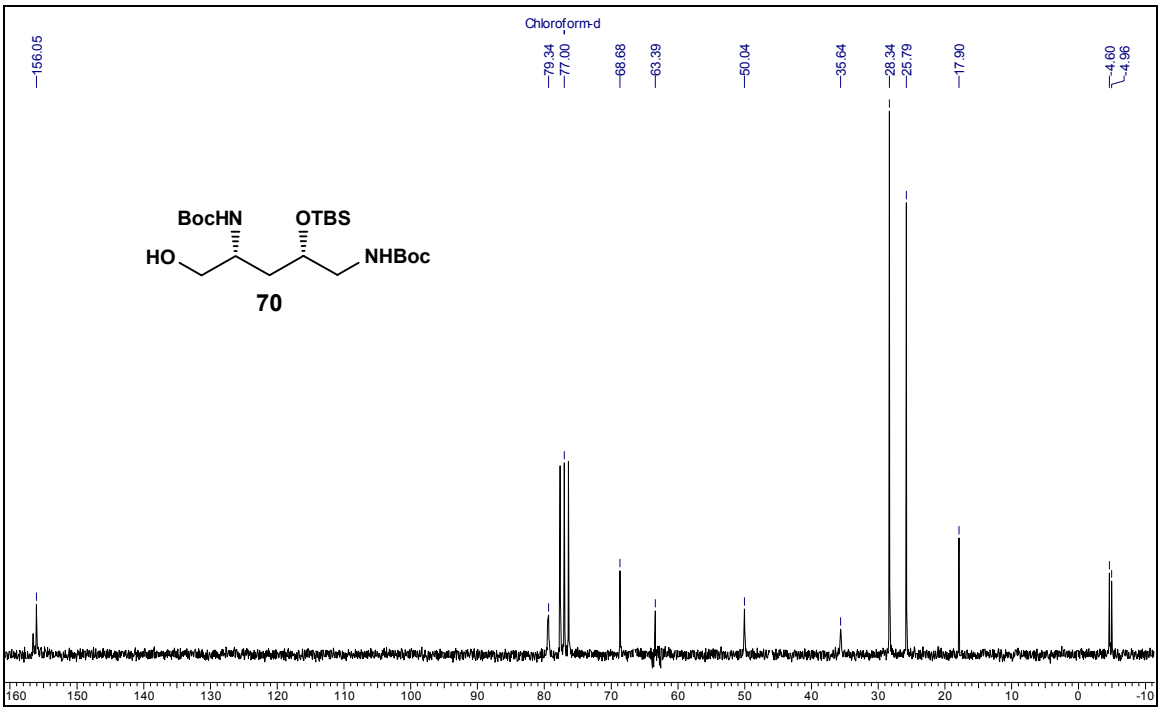
☞ ^{1}H NMR of the compound 69 in $CDCl_3$



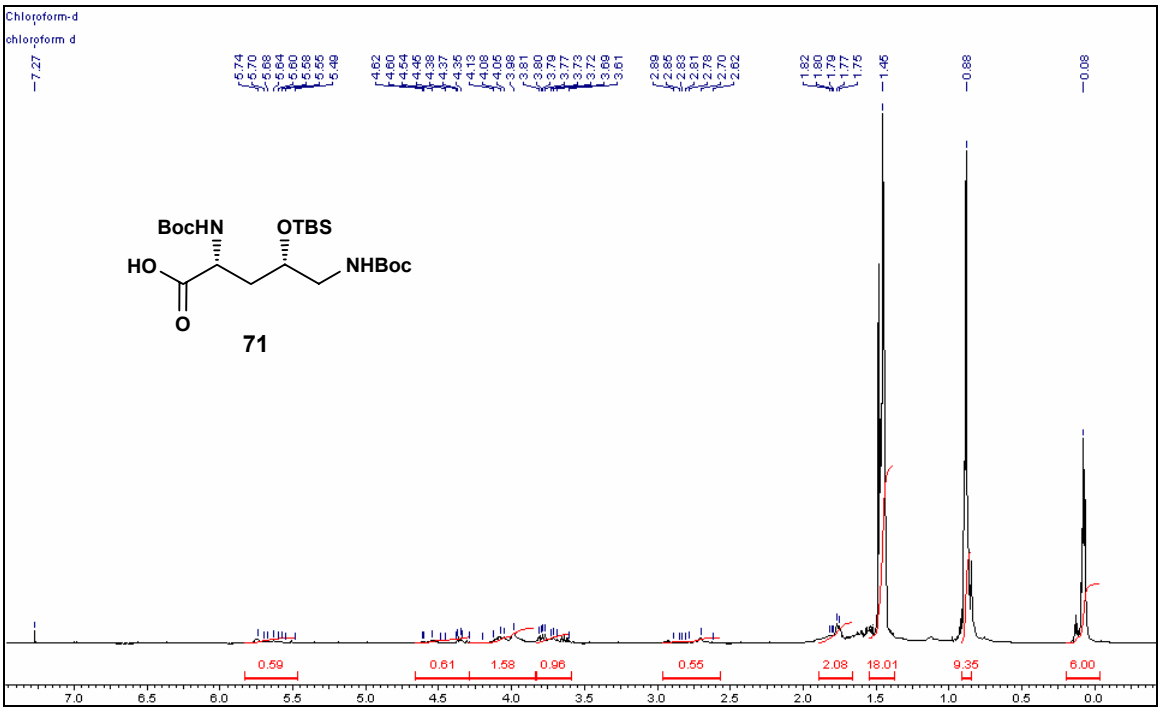
☞ ^{13}C NMR of the compound 69 in $CDCl_3$



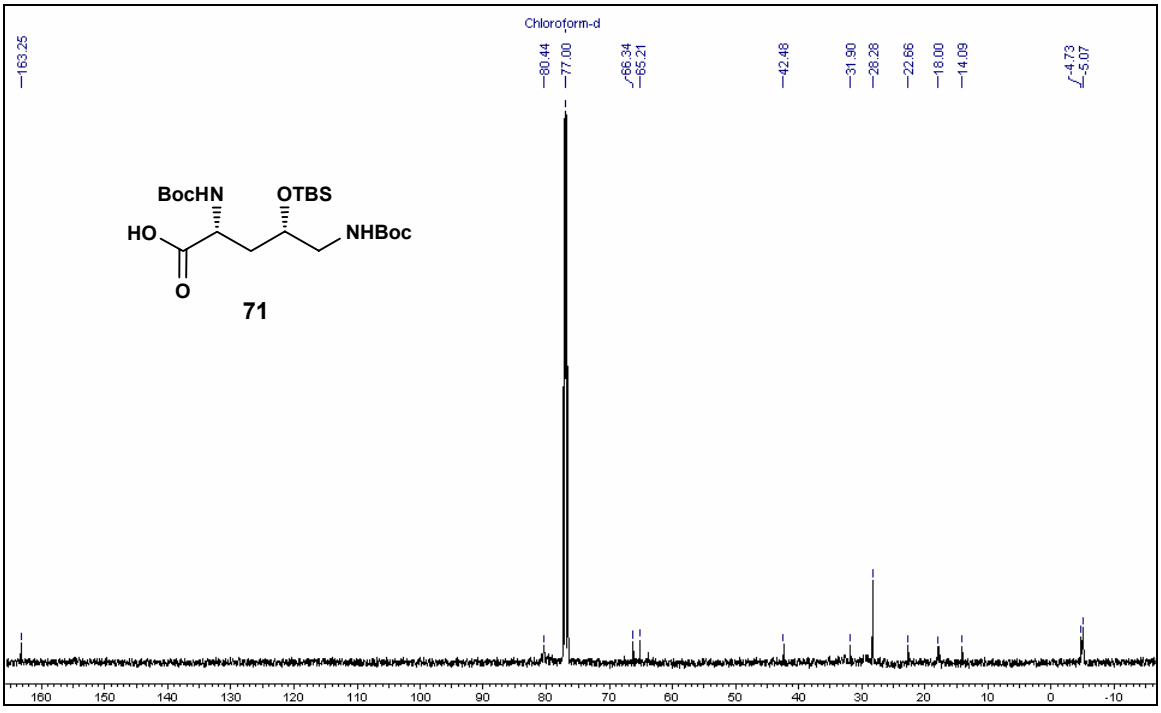
☞ ^{1}H NMR of the compound 70 in $CDCl_3$



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



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



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

3.3 REFERENCES

1. (a) Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis. Construction of Chiral Molecules Using Amino Acids*, J. Wiley and Sons, New York **1987**. (b) Miller, M. J. *Acc. Chem Res.* **1986**, *19*, 49-56 and references therein.
2. (a) Elson, S. W.; Baggaley, K. H.; Gillett, J.; Holland, S.; Nicholson, N. H.; Sime, J. T.; Woroniecki, S. R. *J. Chem. Soc., Chem. Commun.* **1987**, 1736–1738. (b) Baldwin, J. E.; Adlington, R. M.; Bryans, J. S.; Bringhen, A. O.; Coates, J. B.; Crouch, N. P.; Lloyd, M. D.; Schofield, C. J.; Elson, S. W.; Baggaley, K. H.; Cassels, R.; Nicholson, N. *J. Chem. Soc., Chem. Commun.* **1990**, 617–619.
3. Wityak, S. J.; Gould, S. J.; Hein S. J.; Keszler, D. A. *J. Org. Chem.* **1987**, *52*, 2179–2183.
4. Di Giovanni, M. C.; Misiti D.; Zappia, G. *Tetrahedron* **1993**, *49*, 11321-11328.
5. Rao, V. B.; Krishna, U. M.; Gurjar, M. K. *Synth. Commun.* **1997**, *27*, 1335–1345.
6. DeMong, D. E.; Williams, R. M. *Tetrahedron Lett.* **2001**, *42*, 183-185.
7. (a) Becker, H.; Sharpless, K. B. *Angew Chem., Int. Ed.* **1996**, *35*, 448-451. (b) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483-2547. (c) Torri, S.; Liu, P.; Bhuvaneswari, N.; Amatore, C.; Jutand, A. *J. Org. Chem.* **1996**, *61*, 3055-3060.
8. For reviews on the Swern oxidation, see: (a) Tidwell, T. T.; *Synthesis* **1990**, 857-870. (b) Tidwell, T. T. *Org. React.* **1990**, *39*, 297-572.
9. Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*; 3rd ed.; New York: Harper & Row, 1987; p. 321 and references therein.
10. (a) Fujita, Y. *Bull. Chem. Soc. Jpn.* **1959**, *32*, 439; (b) Makisumi, S. *J. Biochem.* **1961**, *49*, 284.
11. (a) Bell, E. A.; Tirimanna, A. S. L. *Nature* **1963**, *197*, 901. (b) Bell, E. A.; Tirimanna, A. S. L. *Biochem. J.* **1964**, *91*, 356.
12. Denning, D. W. *J. Antimicrob. Chemother.* **1997**, *40*, 611.
13. Kondo, S.; Meguriya, N.; Mogi, H.; Aota, T.; Miura, K.; Fujii, T.; Hayashi, I.; Makino, K.; Yamamoto, M.; Nakajima, N. *J. Antibiot.* **1980**, *33*, 533.
14. Ezaki, M.; Iwami, M.; Yamashita, M.; Hashimoto, S.; Komori, T.; Umehara, K.; Mine, Y.; Kohsaka, M.; Aoki, H.; Imanaka, I. *J. Antibiot.* **1985**, *38*, 1453.

15. (a) Pruess, D. L.; Kellett, M. *J. Antibiot.* **1983**, *36*, 208. (b) Evans, R. H. Jr.; Ax, H.; Jacoby, A.; Williams, T. H.; Jenkis, E.; Scannell, J. P. *J. Antibiot.* **1983**, *36*, 213. (c) Muller, J.-C.; Toome, V.; Pruess, D. L.; Blount, J. F.; Weigele, M. *J. Antibiot.* **1983**, *36*, 217.
16. Shiro, Y.; Kato, K.; Fujii, M.; Idab, Y.; Akitaa, H.; *Tetrahedron* **2006**, *62*, 8687 and references therein.
17. (a) Koiso, Y.; Natori, M.; Iwasaki, S.; Sato, S.; Sonoda, R.; Fujita, Y.; Yaegashi, H.; Sato, Z. *Tetrahedron Lett.* **1992**, *33*, 4157. (b) Koiso, Y.; Morisaki, N.; Yamashita, Y.; Mitsui, Y.; Shirai, R.; Hashimoto, Y.; Iwasaki, S. *J. Antibiot.* **1998**, *51*, 418. (c) Koiso, Y.; Li, Y.; Iwasaki, S.; Hanaoka, K.; Kobayashi, T.; Sonoda, R.; Fujita, Y.; Yaegashi, H.; Sato, Z. *J. Antibiot.* **1994**, *47*, 765. (d) Morisaki, N.; Mitsui, Y.; Yamashita, Y.; Koiso, Y.; Shirai, R.; Hashimoto, Y.; Iwasaki, S. *J. Antibiot.* **1998**, *51*, 423.
18. For recent use of this versatile chiral building block, see: Catalano, J. G.; Deaton, D. N.; Furfine, E. S.; Hassell, A. M.; McFayden, R. B.; Miller, A. B.; Miller, L. R.; Shewchuk, L. M.; Willard, D. H.; Whright, L. L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 275.
19. (a) Talbot, G.; Gaudry, R.; Berlinguet, L. *Can. J. Chem.* **1956**, *34*, 911. (b) Mizusaki, K.; Makisumi, S. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 470. (c) Jackson, R. F. W.; Wood, A.; Wythes, M. J. *Synlett* **1990**, 735. (d) Hausler, J. *Liebigs Ann. Chem.* **1992**, 1231. (e) Jackson, R. F. W.; Rettie, A. B.; Wood, A.; Wythes, M. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1719. (f) Girard, A.; Greck, C.; Genet, J. P. *Tetrahedron Lett.* **1998**, *39*, 4259. (g) Mues, H.; Kazmaier, U. *Synthesis* **2001**, 487.
20. Rudolph, J.; Hannig, F.; Theis, H.; Wischnat, R. *Org. Lett.* **2001**, *3*, 3153.
21. (a) Schmidt, U.; Meyer, R.; Leitenberger, V.; Stabler, F.; Lieberknecht, A. *Synthesis* **1991**, 409. (b) Lepine, R.; Carbonnelle, A.-C.; Zhu, J. *Synlett* **2003**, 1455.
22. Paintner, F. F.; Allmendinger, L.; Bauschke, G.; Klemann, P.; *Org. Lett.* **2005**, *7*, 1423.
23. Ksander, G.; de Jesus, R.; Yuan, A.; Ghai, R. D.; Trapani, A.; McMartin, C.; Bohacek, R. *J. Med. Chem.* **1997**, *40*, 495.
24. Pandey, S. K.; Kumar, P. *Tetrahedron Lett.* **2006**, *47*, 4167.
25. (a) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2002**, *124*, 1307. (b) Hansen,

T. V.; Vaagen, V.; Partali, V.; Anthonsen, H. W.; Anthonsen, T. *Tetrahedron: Asymmetry* **1995**, *6*, 499.

26. Hansen, T. V.; Vaagen, V.; Partali, V.; Anthonsen, H. W.; Anthonsen, T. *Tetrahedron: Asymmetry* **1995**, *6*, 499.

CHAPTER 4

EFFICIENT AND VERSATILE APPROACH TO ENANTIOPURE PIPERIDINE ALKALOIDS: (+)-α- AND (-)-β-CONHYDRINE & (-)-DEOXOPROSOPININE AND (+)-DEOXOPROSOPHYLLINE

STEREOSELECTIVE SYNTHESES OF (+)-α- AND (-)-β-CONHYDRINE FROM L-ASPARTIC ACID

4.1.1. Introduction

Alkaloid mimics with a nitrogen in the ring, including naturally occurring and synthetic monocyclic and bicyclic derivatives, constitute a realm of important functional molecules which have drawn considerable attention by virtue of their potent and varied biological activities. A search of the chemical and patent literatures reveal thousands of references concerning this simple ring system, both in clinical and pre-clinical states. Due to the extension of life expectancy in industrial countries, neurological disorderes, like Alzheimer's or Parkinson's disease pose an important public health problem. Thus, the discovery of effective agents for the treatment of these pathologies is one of the major challenges in medicine for the future.

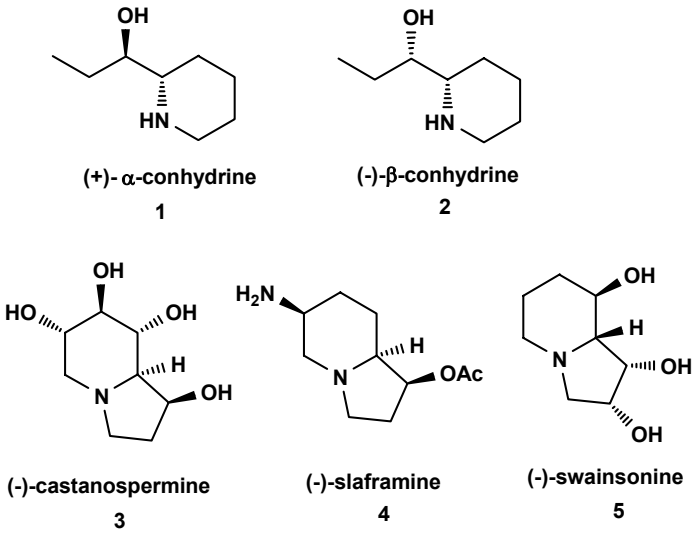


Figure 1.

Biologically active alkaloids containing a 2-(1-hydroxyalkyl)piperidine unit are abundant in nature.[1] (+)-α-Conhydrine **1** and (-)-β-conhydrine **2**, are two such alkaloids isolated from the seeds and leaves of the poisonous plant *Conium maculatum* L. (Figure 1).[2] The indolizidine alkaloids such as (-)-castanospermine **3**, (-)-slaframine **4** and (-)-swainsonine **5**

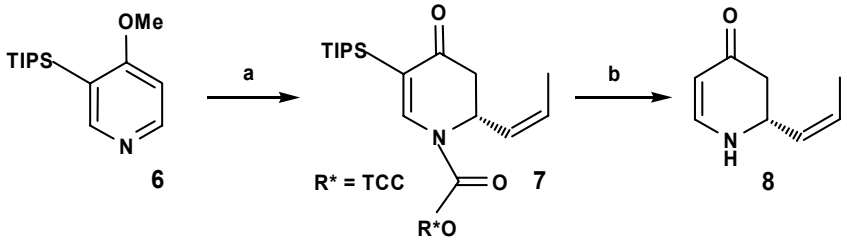
contain a similar structural pattern and are known to exhibit potent glycosidase inhibitor, antiviral and antitumor properties.[3]

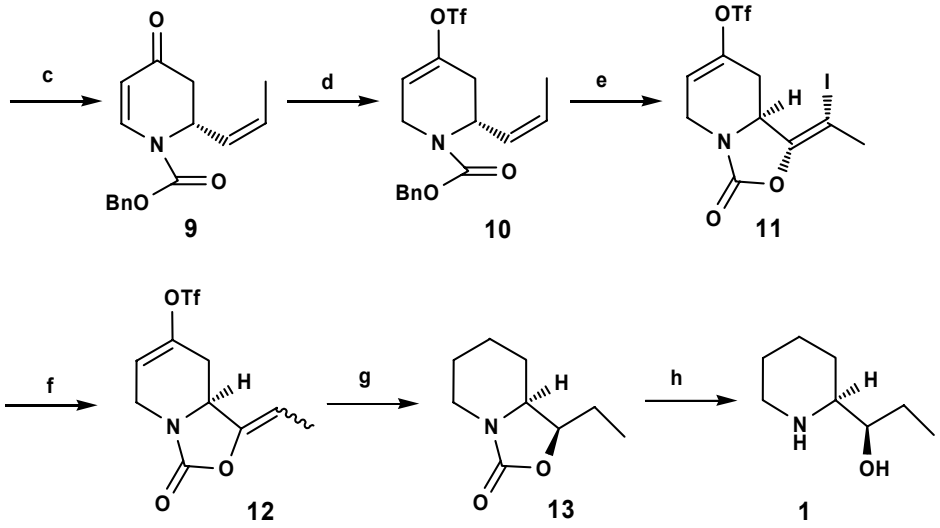
4.1.2 Review of Literature

Various methods for the synthesis of (+)-α- and (-)-β-conhydrine mainly based on auxiliary-supported or chiral pool approaches have been documented in the literature.[4] We have also recently reported the enantioselective synthesis of (-)-α-conhydrine via cyclic sulfate methodology employing Sharpless asymmetric dihydroxylation as the source of chirality.[5] Some of the recent syntheses of (+)-α- and (-)-β-conhydrine are described below.

Comins, D. L. *et al*. (2000) [4c]

Daniel L. Comins and his co-workers have developed an iodocyclocarbamation procedure for the stereoselective preparation of (+)-α-conhydrine **1**. *Cis*-propenyl magnesium bromide was added to a mixture of 4-methoxy-3-(triisopropyl)pyridine and chloroformate of (-)-TCC to give **7**. One-pot removal of the chiral auxiliary and TIPS groups gave enantiopure dihydropyridone **8**. Treatment of **8** with benzyl chloroformate provided the intermediate **9**. Conjugate addition of **9** with L-selectride followed by addition of *N*-(5-chloro-2-pyridyl)triflimide afforded vinyl triflate **10** which was subjected to the iodocyclocarbamation reaction to give **11**. Dehydrohalogenation of **11** was carried out to afford a enol carbamate **12**. Catalytic hydrogenation of **12** from the convex face gave the desired oxazolidinone **13** which was hydrolyzed to afford **1** (Scheme 1).

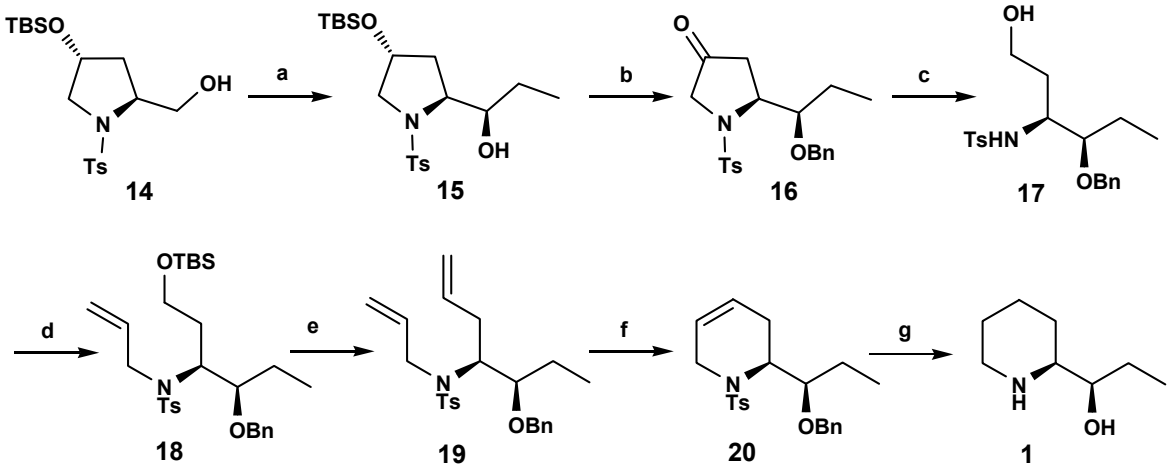




Scheme 1 : *Reagents and conditions* **:** (a) (-)-TCCOCOCl, C_3H_5Cl, H_3O^+, 78%; (b) i) NaOMe, MeOH, reflux; ii) 10% HCl, 80%; (c) *n*-BuLi, BnOCOCl, 85%; (d) L-selectride, *N*-(5-chloro-2-pyridyl)triflimide, 80% ; (e) Li_2CO_3, I_2, CH_3CN, 70% ; (f) DBU, THF, rt, 2 h, 99% ; (g) H_2, PtO_2, Li_2CO_3, iodine, EtOAc, 78% ; (h) KOH, EtOH, reflux, 79%. TCC = (1*R*,2*S*)-2-(1-methyl-1-phenylethyl)cyclohexanol

Chang M-Y. *et al*. (2006)[6]

Meng-Yang Chang and co-worker reported the synthesis of α-conhydrine **1** from prolinol **14** as illustrated in Scheme 2. Prolinol **14** on Swern oxidation followed by Grignard addition afforded compound **15** as a single isomer at -78 ^oC. The diastereoselective addition occurred in favor of the *anti* isomer through a chelated intermediate. Subsequently, alcohol **15** was converted to *O*-benzyl derivative followed by desilylation, and oxidation to afford ketone **16**. Baeyer–Villiger reaction of ketone **16** followed by reduction of the corresponding regioisomer provided amino-alcohol **17**. Compound **18** was synthesized *via* silylation of compound **17** and *N*-allylation of the resultant product. Compound **18** was subjected to desilylation, oxidation, and Wittig olefination to furnish the diene **19**. To build up the piperidine skeleton, diene **19** was subjected to a ring-closing metathesis employing Grubbs' second generation catalyst, the expected piperidine ring **20** was obtained. Finally, synthesis of α-conhydrine **1** was accomplished *via* hydrogenation and desulfonation.

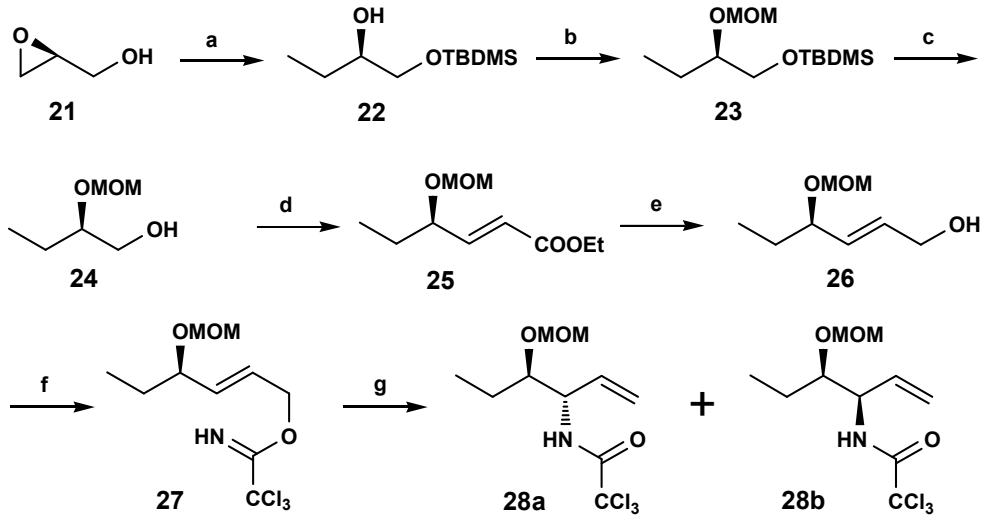


Scheme 2: *Reagents and conditions* **:** (a) i) Swern oxidation ii) EtMgBr, THF, 90%; (b) i) NaH, BnBr 88%; ii) TBAF, THF, 92%; iii) PCC, DCM, 83%; (c) i) *m*CPBA, Na_2CO_3 82%; ii) LAH, THF, 94%; (d) i) TBSCl, Imidazole, 96%; ii) NaH, allyl bromide, 97%; (e) i) TBAF, THF, 99%; ii) PCC, DCM, 87%; iii) $Ph_3P{=}CH_2$, 82%; (f) Grubb's 2nd generation catalyst, 92%; (g) i) H_2, Pd/C, EtOAc, 94%; (h) Na/Hg, MeOH, 80%.

Sutherland, A. *et al*. (2007)[7]

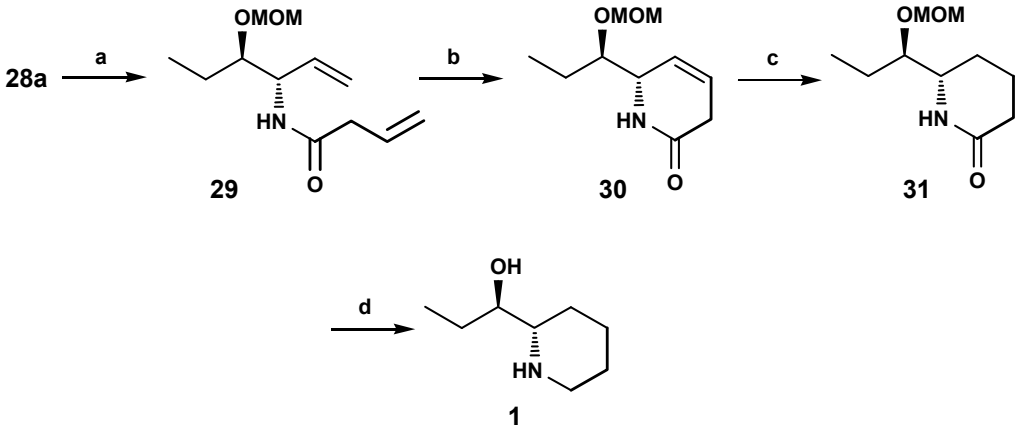
Andrew Sutherland and co-worker reported the synthesis of (+)-α-conhydrine **1** from allylic alcohol **26** (Scheme 3). (*S*)-Glycidol **21** was protected as the *tert*-butyldimethylsilyl ether followed by regioselective ring opening of the epoxide using a copper-catalyzed Grignard reaction to give **22** in excellent yield. Formation of the MOM-ether **23** using Hunig's base and bromomethyl methyl ether and then removal of the silyl-ether using TBAF afforded alcohol **24**. A one-pot Swern oxidation/Horner-Wadsworth-Emmons (HWE) reaction gave *E*-α,β-unsaturated ester **25** which on reduction using DIBAL-H afforded the required *E*-allylic alcohol **26** in 95% yield.

The allylic trichloroacetimidate **27** was prepared using a catalytic amount of DBU and trichloroacetonitrile which on Aza-Claisen rearrangement using bis-(acetonitrile)-palladium(II) chloride (10 mol %) as the catalyst furnished the *erthyro*- and *threo*- allylic trichloroamides **28a** and **28b** in 55% yield over the two steps in a 16:1 ratio. Hydrolysis of **28a** followed by acylation with 3-butenoyl chloride gave **29** which on ring-closing metathesis using Grubbs' first-generation catalyst led to the unsaturated δ-lactam **30**.



Scheme 3: *Reagents and conditions***:** (a) i) TBDMSCl, Imidazole, THF, 88%; ii) MeMgBr, CuBr.SMe_2, THF, 90%; (b) MOMBr, $EtN(i\text{-}Pr)_2$, CH_2Cl_2, 83%; (c) TBAF, THF, 59%; (d) i) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2; ii) $(EtO)_2POCH_2CO_2Et$, DBU, LiCl, MeCN, 86%; (e) DIBAL-H, Et_2O, 95%; (f) Cl_3CCN, DBU, CH_2Cl_2; (g) $PdCl_2(MeCN)_2$, toluene, **28a:28b**/16:1, 55%.

Finally, hydrogenation of the alkene, reduction of the lactam with borane-THF, and deprotection of the hydroxyl group under acidic conditions gave (+)-α-conhydrine **1** in 42% yield over the three steps (Scheme 4).



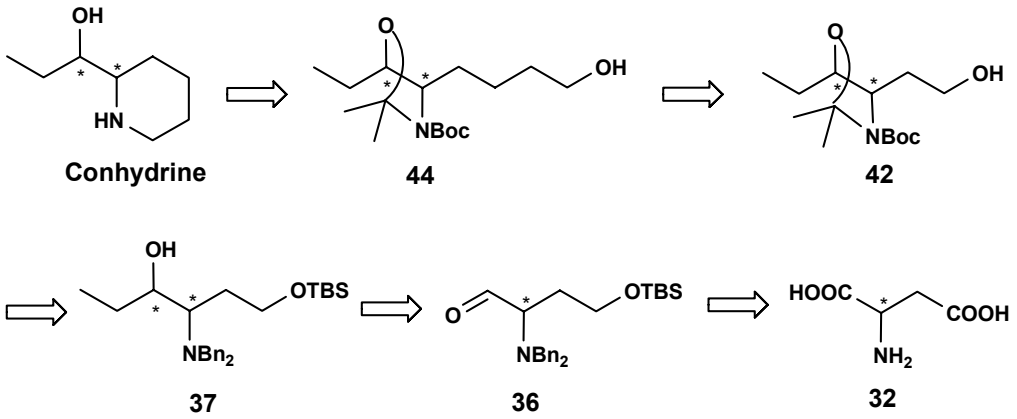
Scheme 4: *Reagents and conditions***:** (a) i) 2M NaOH ; ii) $ClCOCH_2CH{=}CH_2$, Et_3N, CH_2Cl_2, 52%; (b) Grubbs' I, CH_2Cl_2, 100%; (c) H_2, 10% Pd/C, EtOAc, 100%; (d) i) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2; ii) $(EtO)_2POCH_2CO_2Et$, DBU, LiCl, MeCN, 86%; (e) i) BH_3.THF ; ii) 6M HCl, 42%.

4.1.3. Present work:

Objective

Hydroxylated piperidines represent a stuctural unit frequently found in many biologically active alkaloids. Various methods for the synthesis of (+)-α- and (-)-β-conhydrine mainly based on auxiliary-supported or chiral pool approaches have been documented in the literature. In continuation of our research program aimed towards syntheses of bioactive compounds we became interested in developing a general route capable of providing not only the target molecules **1** and **2** but also their other stereoisomers. Herein we describe a new and convenient synthesis of (+)-α- and (-)-β-conhydrine employing the stereoselective addition of ethylmagnesium bromide or diethylzinc to an aldehyde as the key step.

Our synthetic approach for the synthesis of conhydrine was envisioned *via* the synthetic route as shown in Scheme 5. The amino aldehyde derivative **36** was visualized as a synthetic intermediate from which both (+)-α- and (-)-β-conhydrine could be synthesized by the stereoselective addition of an organometallic reagent and subsequent synthetic manipulation. The amino aldehyde **36** in turn could be derived from aspartic acid **32** through standard synthetic transformations.

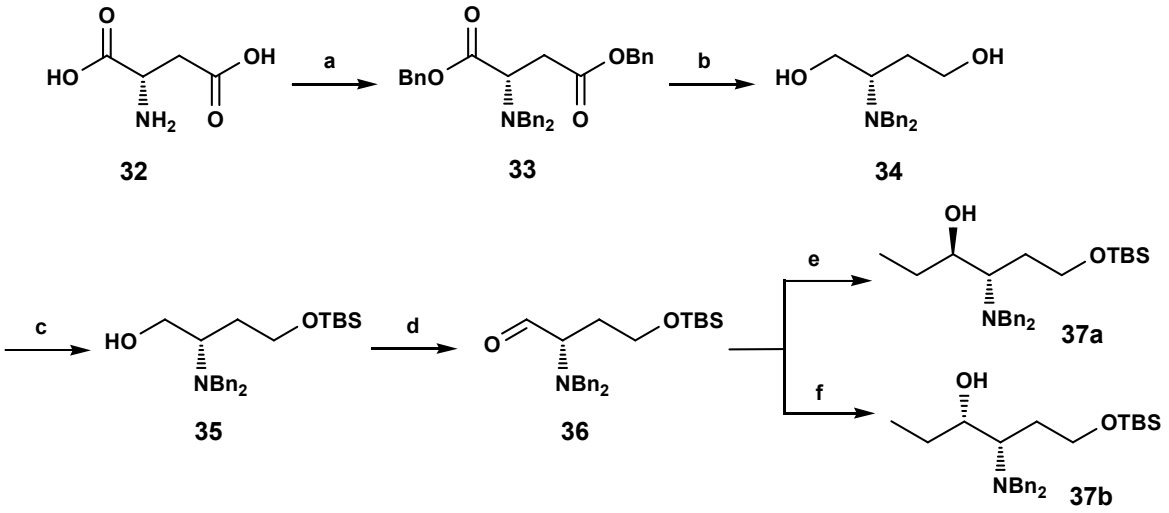


Scheme 5. Retrosynthetic route to conhydrine

4.1.4. Results and discussion:

The syntheses of (+)-α-conhydrine **1** and (-)-β-conhydrine **2** started from commercially available L-aspartic acid **32** as illustrated in Scheme 6. L-Aspartic acid **32** was first

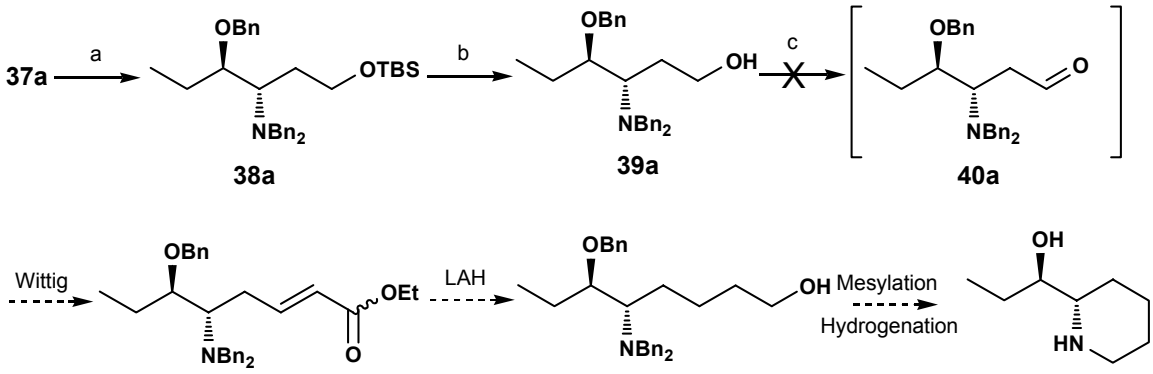
converted to an amino aldehyde derivative **36** following a literature procedure.[8] The aldehyde **36** was subjected to Grignard reaction with ethylmagnesium bromide to afford the amino alcohol **37a** as a single diastereomer in 73% yield, $[\alpha]_D^{20}$ +10.9 (c 1.0, $CHCl_3$), {lit.[9] $[\alpha]_D^{20}$ +10.7 (c 1.0, $CHCl_3$)}. The diastereoselectivities of non-chelated **37a** and chelated product **37b** were determined by ^{1}H NMR spectroscopy and also by comparison with the literature data. The formation of *anti*-**37a** as a single isomer is in agreement with a non-chelated model.[10] On the contrary when **36** was treated with diethylzinc, it led to the formation of *syn*-**37b** as a single isomer in 76% yield, $[\alpha]_D^{20}$ +28.2 (c 1.0, $CHCl_3$), {lit.[9] $[\alpha]_D^{20}$ +28.3 (c 1.0, $CHCl_3$)}. The diastereoselective addition of diethylzinc occurs in favor of the *syn* isomer through a chelated intermediate which is in accordance with a reported observation.[11]



Scheme 6. *Reagents and conditions:* (a) $C_6H_5CH_2Br$, K_2CO_3, H_2O, ^oC, 4 h, 76%; (b) $LiAlH_4$, THF, 0 ^oC, 1 h, 71%; (c) TBSCl, Imidazole, CH_2Cl_2, 0 ^oC to rt, 4 h, 66%; (d) $(COCl)_2$, DMSO, dry CH_2Cl_2, -78 ^oC, Et_3N, -60 ^oC, 1h; (e) EtMgBr, dry Et_2O, 0 ^oC, 2 h, 73%. (f) Et_2Zn, toluene, 0 ^oC, 8 h, 76%.

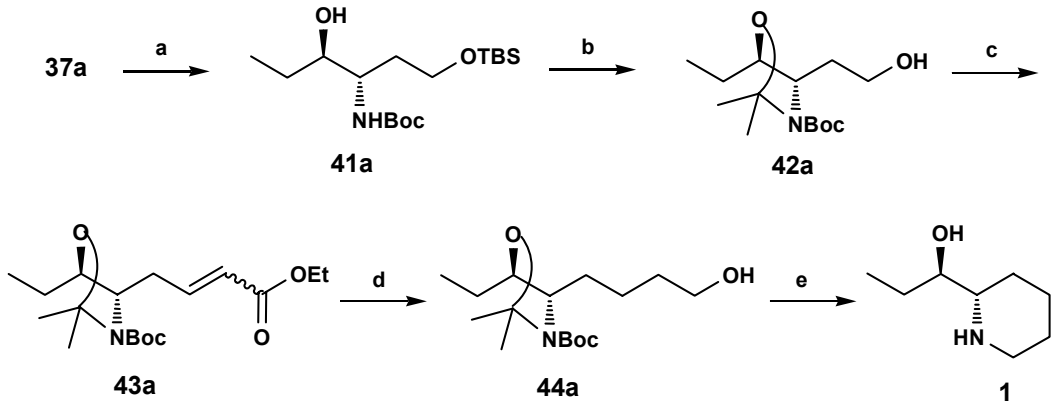
Our next aim was to carry out the two-carbon homologation of **37a** *via* Wittig reaction. To this end, we first proceeded with protection of the hydroxyl group of **37a** as its benzyl derivative **38a** followed by removal of the TBS group to give the corresponding alcohol **39a**. The resultant alcohol obtained was then subjected to oxidation under Swern

conditions, however, it gave a complex mixture which indicated that the β-amino-γ-hydroxy aldehyde **40a** formed during oxidation was unstable due to the dibenzylamino moiety[11] and which decomposed by retro-condensation to the corresponding amine and unsaturated aldehyde (Scheme 7).



Scheme 7. *Reagents and conditions:* (a) BnBr, NaH, 0 ^{o}C-rt, 4 h, 85%; (b) TBAF, 0 ^{o}C, 2 h, 96%; (c) Swern oxidation.

Further, in order to achieve the synthesis of target compounds **1** and **2** from **37a-b** we required a suitable amino protecting group for further synthetic manipulation (Scheme 8).



Scheme 8. *Reagents and conditions*: (a) $H_2/Pd(OH)_2$, Boc_2O, EtOAc, 12 h, 83% (b) 2,2-DMP, *p*-TsOH, CH_2Cl_2, 0 ^{o}C-rt, 1 h, 87% (c) (i) $(COCl)_2$, DMSO, dry CH_2Cl_2, -78 ^{o}C, Et_3N, -60 ^{o}C, 1h (ii) Ph_3P=CHCOOEt, dry THF, rt, 24 h, 96% (d) $LiAlH_4$, dry THF, rt, 4 h, 78% (e) (i) MsCl, Et_3N, -78 ^{o}C, 1h, (ii) CF_3COOH, dry DCM, 88%.

To this end, compound **37a** was subjected to debenzylation by hydrogenation using $Pd(OH)_2$[12] followed by protection of the amino group with $(Boc)_2O$ to afford compound **41a** in 83% yield. The presence of 9 protons for Boc group at δ 1.44 as singlet in the ^1H NMR spectrum showed the formation of **41**. The successive protection as the acetonide using 2,2-dimethoxypropane in the presence of catalytic amount of *p*-TSA and concomitant deprotection of the TBS group afforded **42a** in 87% yield. The IR spectrum of **42a** showed the hydroxyl absorption peak at 3422 cm^{-1}. Compound **42a** was oxidized to the aldehyde by Swern oxidations,[13] and subsequently treated with (ethoxycarbonylmethylene)triphenyl-phosphorane in dry THF at room temperature to furnish the Wittig product **43a** in 96% yield with an *E:Z* ratio of 95:5. The *E:Z* ratio of compound **43a** was determined from the ^1H NMR spectrum. The olefin and ester reduction of **43a** was carried out in a single step with $LiAlH_4$ to give the corresponding alcohol **44a** in excellent yield. The IR spectrum of **44a** showed the hydroxyl absorption peak at 3444 cm^{-1} and ^1H NMR spectrum revealed absence of olefinic peaks. Alcohol **44a** was subjected to cyclization using methanesulfonyl chloride and triethylamine followed by deprotection of the Boc group to furnish (+)-α-conhydrine **1**, $[\alpha]_D^{20}$ +8.9 (c 0.85, EtOH), {lit. [4c] $[\alpha]_D^{20}$ +9.0 (c 0.85, EtOH).

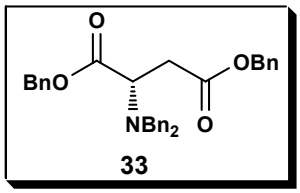
(-)-β-Conhydrine **2** was synthesized from **37b** following an analogy of those reactions as shown in Scheme 8, $[\alpha]_D^{20}$ –34.8 (*c* 0.4, $CHCl_3$), {lit. [4f] $[\alpha]_D^{20}$ –34.1 (*c* 0.4, $CHCl_3$)}. The physical and spectroscopic data of **1** and **2** were in full agreement with the literature data.[4c,f]

4.1.5. Conclusion

In conclusion, practical and stereocontrolled syntheses of (+)-α-conhydrine and (-)-β-conhydrine has been achieved from L-aspartic acid. The synthetic strategy described has significant potential for further extension of the 2-(1-hydroxyalkyl)piperdine unit and to the other isomers, (-)-α-conhydrine and (+)-β-conhydrine from D-aspartic acid.

4.1.6 Experimental Section

(*S*)-Dibenzyl 2-(dibenzylamino)succinate (33):



33

To a solution of L-aspartic acid **32** (5.0 g, 37.56 mmol) in aqueous K_2CO_3 (20%) was slowly added benzyl bromide (41.76 g, 24.42 mmol) at rt. The mixture was stirred at 100 ^oC for 4 h. After being cooled to rt, the reaction mixture was extracted with ether and the organic layer was dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (petroleum ether-EtOAc 97:3) to give **33** as colorless oil. IR and NMR data were in agreement with those previously reported.[8a]

Yield: 14.10g, 76%

Mol. Formula: $C_{32}H_{31}NO_4$

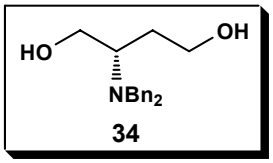
$[\alpha]_D^{25}$: -60.72 (c 1.00, $CHCl_3$) {lit[8a] -63.00 (c 1.00, $CHCl_3$)}

IR (neat, cm^{-1}): ν_{max} 3063, 3030, 2848, 1732, 1454, 1158

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.67 (dd, *J* = 7.05, 15.66 Hz, 1H), 2.90 (dd, *J* = 7.83, 15.65 Hz, 1H), 3.49 (d, *J* = 13.69 Hz, 2H), 3.75 (d, *J* = 13.69 Hz, 2H), 3.92 (t, *J* = 7.04 Hz, 1H), 4.88 (d, *J* = 12.13 Hz, 1H), 5.05 (d, *J* = 4.70 Hz, 1H), 5.11 (d, *J* = 4.70 Hz, 1H), 5.23 (d, *J* = 12.52 Hz, 1H), 7.14-7.39 (m, 20 H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 35.0, 54.7, 57.9, 66.3, 66.4, 72.0, 127.1, 127.5, 127.7, 128.1, 128.3, 128.4, 128.5, 128.8, 135.6, 135.7, 138.7, 170.2, 171.2 ppm.

(*S*)-2-(Dibenzylamino)butane-1,4-diol (34):



34

To a stirred solution of **33** (10.0 g, 20.26 mmol) was added $LiAlH_4$ (2.31, 60.78 mmol) at 0 ^oC. The temperature was allowed to warm to rt. After 1 h saturated Na_2SO_4 was added, followed by saturated $NaHCO_3$ and Et_2O. The organic layer was dried (Na_2SO_4) and

evaporated and the residue was purified by flash chromatography (petroleum ether-EtOAc 2:3) to give **34** as a thick colorless syrupy liquid. IR and NMR data were in agreement with those previously reported.[8a]

Yield: 4.10g, 71%

Mol. Formula: $C_{18}H_{23}NO_2$

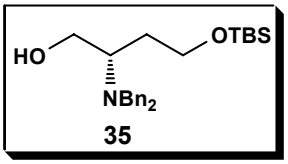
$[\alpha]_D^{25}$: +19.56 (c 1.00, $CHCl_3$) {lit[8a] +17 (c 1.00, $CHCl_3$)}

IR (neat, cm^{-1}): ν_{max} 3368, 3028, 2932, 1708, 1602, 1217

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (t, *J* = 7.05 Hz, 1 H), 1.42-1.54 (m, 1H), 1.88-2.18 (m, 2H), 2.58-3.19 (m, 3H), 3.52-3.79 (m, 6H), 7.10-7.42 (m, 10H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 28.9, 53.4, 57.3, 60.8, 61.1, 126.7, 127.0, 128.3, 128.9, 139.0 ppm.

(*S*)-2-(*N*,*N*-Dibenzylamino)-4-[(*tert*-butyldimethylsilyl)oxyl-1-butanol (35).



To a stirred solution of alcohol **34** (4.0 g, 14.02 mmol) in CH_2Cl_2 (50 mL) was added imidazole (1.15 g, 16.82 mmol). To this solution *t*-butyldimethylchlorosilane (2.32 g, 15.42 mmol) was added at 0 ^oC and reaction was stirred at room temperature for 4 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2 (3 x 20 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 (19:1) as eluent provided **35** as a colorless liquid. IR and NMR data were in agreement with those previously reported.[8a]

Yield: 3.70 g, 66%

Mol. Formula: $C_{24}H_{37}NO_2Si$

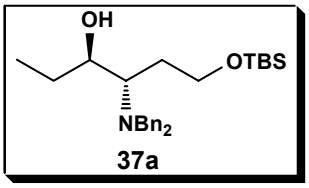
$[\alpha]_D^{25}$: +38.45 (c 1.00, $CHCl_3$) {lit[8a] +43 (c 1.00, $CHCl_3$)}

IR (neat, cm^{-1}): ν_{max} 3431, 3018, 2858, 1603, 1215

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.06 (s, 6H), 0.90 (s, 9H), 1.37-1.59 (m, 1H), 1.96-2.12 (m, 1H), 2.93-3.05 (m, 1H), 3.41-55 (m, 4H), 3.58 (t, *J* = 6.26 Hz, 2H), 3.83 (d, *J* = 13.30 Hz, 2H), 7.25-7.46 (m, 10H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ -5.5, 18.2, 25.8, 28.7, 53.2, 56.5, 60.9, 61.1, 127.0, 128.3, 128.9, 139.3 ppm.

(3*R*,4*S*)-6-(*tert*-Butyldimethylsilyloxy)-4-(dibenzylamino)hexan-3-ol (37a):



To a solution of oxalyl chloride (0.71 g, 0.5 mL, 5.63 mmol) in dry CH_2Cl_2 (10 mL) at -78 °C was added dropwise DMSO (0.88 g, 0.80 mL, 11.26 mmol) in CH_2Cl_2 (5 mL) over 15 min. The reaction mixture was stirred for 30 min and a solution of **35** (1.5 g, 3.75 mmol) in CH_2Cl_2 (10 mL) was added dropwise over 15 min. The reaction mixture was stirred for 30 min at -78 °C and 30 min at -60 °C and then Et_3N (1.67 g, 2.30 mL, 16.51 mmol) in CH_2Cl_2 (5.00 mL) was added dropwise and stirred for 1 h. The reaction mixture was poured into saturated solution of $NaHCO_3$ (20 mL) and the organic layer separated. The aqueous layer was extracted with ether (3 x 10 mL) and the combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated to give the crude aldehyde **36**. This was used for the next step without further purification.

A freshly generated Grignard (EtMgBr) prepared from EtBr (0.62 g, 5.70 mmol) and Mg (0.14 g, 5.70 mmol) solution in diethyl ether (10 mL) at 0 °C was added dropwise to a solution of amino aldehyde **36** (1.51 g, 3.80 mmol) in diethyl ether (10 mL). After stirring at this temperature for 1 h, saturated NH_4Cl (40 mL) was added and the mixture was extracted with diethyl ether (2 x 15 mL). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4 and the solvent evaporated under vacuum. After flash chromatography (silica gel: hexane/ EtOAc, 15:1), the compound *anti*-**37a** was obtained as a colorless oil. IR and NMR data were in agreement with those previously reported.[9]

Yield: 1.17 g, 73%

Mol. Formula: $C_{26}H_{41}NO_2Si$

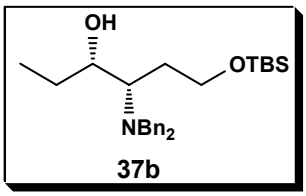
37a $[\alpha]_D^{25}$: +10.95 (c 1.00, $CHCl_3$) {lit[9] +10.7 (c 1.00, $CHCl_3$)}

IR (neat, cm^{-1}): ν_{max} 3394, 2930, 2956, 1723, 1216, 758

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.04 (s, 3H), 0.06 (s, 3H), 0.80 (br s, 12H), 1.16-1.48 (m, 3 H), 1.66-2.21 (m, 2 H), 2.66-2.77 (m, 1H), 3.53 (d, *J* = 13.70 Hz, 2 H), 3.54-3.66 (m, 1 H), 3.73 (d, *J* = 14.09 Hz, 2 H), 3.76-3.92 (m, 1 H), 7.21-7.51 (m, 10H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ -5.5, 10.1, 18.1, 25.8, 27.7, 28.6, 54.7, 59.3, 62.3, 72.9, 126.8, 128.1, 128.7, 139.9 ppm.

(3*S*,4*S*)-6-(*tert*-Butyldimethylsilyloxy)-4-(dibenzylamino)hexan-3-ol (37b):



37b

A solution of amino aldehyde **36** (1.5 g, 3.79 mmol) in anhydrous toluene (50 mL) at 0 °C (ice bath) under argon was added dropwise to 6 mL of 1M solution of diethylzinc in hexane (7.58 mmol, 2 equiv.). The mixture was stirred at 0 °C until the reaction was finished (TLC), and then quenched with aqueous saturated solution of ammonium chloride (50 mL). The organic layer was separated and the aqueous phase was extracted with diethyl ether (3 x 15 mL). The combined organic layers were washed with brine, and dried with anhydrous Na_2SO_4. The solvents were eliminated under vacuum and the residue was purified by flash chromatography (silica gel, hexane/EtOAc, 25:1), the compound *syn*-**37b** was obtained as a colorless oil. IR and NMR data were in agreement with those previously reported.[9]

Yield: 1.22 g, 76%

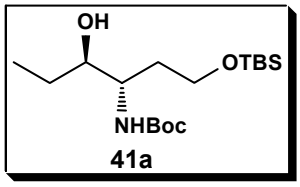
Mol. Formula: $C_{26}H_{41}NO_2Si$

37b $[\alpha]_D^{25}$: +29.17(c 1.00, $CHCl_3$) {lit[9] +28.3 (c 1.00, $CHCl_3$)}

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.14 (s, 6H), 0.97 (br s, 12H), 1.13-1.33 (m, 2H), 1.55-1.74 (m, 2 H), 1.99-2.12 (m, 1H), 2.56-2.64 (m, 1 H), 3.50 (d, *J* = 13.19 Hz, 2 H), 3.77 (d, *J* = 6.60 Hz, 2 H), 3.90 (d, *J* = 13.19 Hz, 2 H), 4.45 (brs, 1H), 7.21-7.41 (m, 10H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ -5.5, 9.9, 18.2, 25.9, 26.5, 29.4, 54.1, 59.4, 61.8, 71.8, 127.0, 128.2, 129.0, 139.1 ppm.

***tert*-Butyl (3*S*,4*R*)-1-(*tert*-butyldimethylsilyloxy)-4-hydroxyhexan-3-ylcarbamate (41a)**



To a solution of amino alcohol **37a** (1.0 g, 2.33 mmol) in ethyl acetate was added 20% $Pd(OH)_2/C$ (50 mg) and Boc_2O (0.56 g, 0.60 mL, 2.57 mmol). The resulting solution was stirred under hydrogen atmosphere for 12 h at room temperature until disappearance of the starting material as monitored by TLC. The reaction mixture was filtered through a celite pad to remove the catalyst and the filtrate was concentrated in vacuo. Silica gel column chromatography of the crude product using EtOAc/pet ether (3:7) as eluent gave **41a** as a colorless liquid.

Yield: 0.675 g, 83%

Mol. Formula: $C_{17}H_{37}NO_4Si$

41a $[\alpha]_D^{25}$: +12.98 (c 1.00, $CHCl_3$)

41b $[\alpha]_D^{25}$: -15.31 (c 1.00, $CHCl_3$)

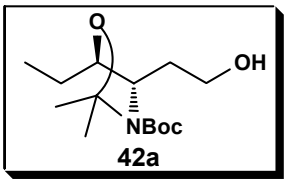
IR (neat, cm^{-1}): ν_{max} 3443, 3412, 2959, 2931, 1694, 1673, 1504, 1366, 1253

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.08 (s, 6H), 0.91 (s, 9H), 0.99 (t, *J* = 7.33 Hz, 3H), 1.44 (s, 9H), 1.48-1.58 (m, 2 H), 1.69-1.81 (m, 3H), 3.41-3.56 (m, 1 H), 3.73 (t, *J* = 5.87 Hz, 3 H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ -5.7, 10.3, 18.0, 25.7, 26.5, 28.2, 31.4, 53.2, 59.9, 66.1, 75.3, 79.0, 128.0, 156.0 ppm.

Analysis Calcd.: C, 58.75; H, 10.73; N, 4.03%; **Found:** C, 58.88; H, 10.69; N, 4.10%.

(4*R*,5*R*)-*tert*-Butyl 5-ethyl-4-(2-hydroxyethyl)-2,2-dimethyloxazolidine-3-carboxylate (42a):



To a solution of amino alcohol **41a** (0.60 g, 1.73 mmol) in dry DCM (10 mL) was added 2,2-dimethoxy propane (0.20 g, 0.25 mL, 1.90 mmol) and *p*-TsOH (20 mg). The reaction mixture was stirred at 0 °C to room temperature for 1 h. A pinch of $NaHCO_3$ was added and stirred for 15 min. The reaction mixture was passed through a pad of silica gel. The filtrate was concentrated and distilled to give **42a** as a colorless liquid.

Yield: 410 mg, 87%

Mol. Formula: $C_{14}H_{27}NO_4$

42a $[\alpha]_D^{25}$: -17.32 (c 1.00, $CHCl_3$)

42b $[\alpha]_D^{25}$: -8.69 (c 1.00, $CHCl_3$)

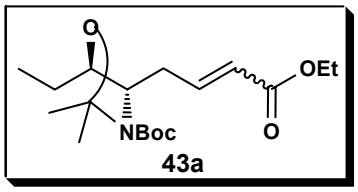
IR (neat, cm^{-1}): ν_{max} 3422, 2959, 1694, 1664, 1216

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98 (t, *J* = 7.33 Hz, 3H), 1.25-1.84 (m, 20H), 3.5 (t, *J* = 11.72 Hz, 1H), 3.62-3.77 (m, 1H), 3.98 (q, *J* = 5.13, 11.73 Hz, 1H), 4.15 (dt, *J* = 4.40, 11.72 Hz, 1H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 10.1, 21.6, 24.8, 25.7, 27.8, 28.1, 29.4, 31.9, 55.2, 57.9, 78.0, 80.6, 92.4, 153.9 ppm.

Analysis Calcd.: C, 61.51; H, 9.96; N, 5.12%; **Found:** C, 61.48; H, 10.01; N, 5.07%.

(4*S*,5*R*)-*tert*-Butyl -4-(3-(ethoxycarbonyl)allyl)-5-ethyl-2,2-dimethyloxazolidine-3-carboxylate (43a)



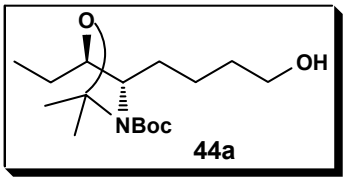
43a

To a solution of oxalyl chloride (0.28 g, 0.19 mL, 2.19 mmol) in dry CH_2Cl_2 (10 mL) at -78 °C was added dropwise DMSO (0.34 g, 0.31 mL, 4.39 mmol) in CH_2Cl_2 (2 mL) over 15 min. The reaction mixture was stirred for 30 min and a solution of **42a** (0.4 g, 1.46 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 15 min. The reaction mixture was stirred for 30 min at −78 °C and 30 min at −60 °C and then Et_3N (0.65 g, 0.90 mL, 46.60 mmol) in CH_2Cl_2 (1.00 mL) was added dropwise and stirred for 1 h. The reaction mixture was poured into saturated solution of $NaHCO_3$ (10 mL) and the organic layer separated. The aqueous layer was extracted with ether (3 x 10 mL) and the combined organic layers

were washed (brine), dried (Na_2SO_4) and concentrated to give the crude aldehyde. This was used for the next step without further purification.

To a solution of (ethoxycarbonylmethylene)triphenyl phosphorane (617 mg, 1.79 mmol) in dry THF (5 mL) was added a solution of the above aldehyde in dry THF (2 mL). The reaction mixture was stirred at room temperature for 24 h. It was then concentrated and purified by silica gel column chromatography (EtOAc/petroleum ether, 1:9) to give olefin **43a** as a pale yellow oil (3.27 g, 93%) with an *E:Z* ratio of 95:5 and both *E:Z* olefin used directly for the next step.

(4*S*,5*R*)-*tert*-Butyl 5-ethyl-4-(4-hydroxybutyl)-2,2-dimethyloxazolidine-3-carboxylate (44a):



44a

A suspension of $LiAlH_4$ (20 mg, 0.53 mmol) in anhydrous THF (4 mL) was stirred for 5 min at 0 °C, and a solution of **43a** (150 mg, 0.44 mmol) in THF (2 mL) was then added dropwise. The mixture was stirred for 2 h at 0 °C and for 2 h at room temperature. Excess $LiAlH_4$ was destroyed by slow addition of 10% aq NaOH (0.5 mL) and EtOAc (5 mL). The white precipitate was filtered through a pad of neutral alumina and washed with MeOH (3 x 10 mL). The filtrate was concentrated and the residue was purified by silica gel column chromatography to give **44a** as a colourless solid (103 mg, 78%).

Yield: 103 mg, 78%

Mol. Formula: $C_{16}H_{31}NO_4$

44a $[\alpha]_D^{25}$: -3.92 (c 1.00, $CHCl_3$)

44b $[\alpha]_D^{25}$: +7.21 (c 1.00, $CHCl_3$)

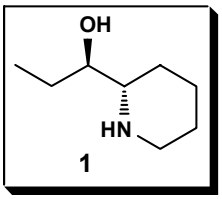
IR (neat, cm^{-1}): ν_{max} 3444, 3010, 2978, 1685, 1394, 1216

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98 (t, *J* = 7.32 Hz, 3H), 1.29 (t, *J* = 7.20 Hz, 2H), 1.46-2.34 (m, 21 H), 3.41-3.76 (m, 1H), 3.85-3.93 (m, 2H), 4.19 (q, *J* = 7.20, 14.27 Hz, 1 H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 10.6, 14.0, 18.4, 21.7, 24.8, 28.2, 32.4, 59.9, 62.2, 79.7, 92.3, 118.8, 129.6, 138.9, 144.7, 167.1 ppm.

Analysis Calcd.: C, 63.75; H, 10.37; N, 4.65%; **Found:** C, 63.68; H, 10.22; N, 4.60%.

(*R*)-1-((*S*)-Piperidin-2-yl)propan-1-ol: (+)-α-conhydrine (1)



To a stirred solution of compound **44a** (95 mg, 0.32 mmol) in dry CH_2Cl_2 (5 mL) was added methanesulfonyl chloride (0.03 mL, 0.32 mmol) at –78 ^oC and then triethyl amine (0.25 mL, 1.83 mmol) was added dropwise. After the mixture was stirred at -78 ^oC for 1 h, aqueous ammonium chloride (2 mL) was added. The mixture was warmed to room temperature and diluted with CH_2Cl_2 (5 mL), washed with brine, and dried over Na_2SO_4. The solvent was removed, and the residue was purified by flash chromatography using EtOAC/pet ether (4:6) to give mesylated product as a colorless liquid.

To the above mesylated product in dry CH_2Cl_2 (2 mL) was added trifluoroacetic acid in catalytic amount. The reaction mixture was stirred at room temperature for 12 h and then saturated aq. $NaHCO_3$ added and mixture extracted with dichloromethane (3 x 5 mL). The combined organic layers were washed with brine and dried over Na_2SO_4 and concentrated under reduced pressure to near dryness. The crude product was purified by silica gel column chromatography using CH_3OH/CH_2Cl_2 (1:10) as eluent to give **1** as solid compound. The physical and spectroscopic data of **1** were in full agreement with the literature data.[5c]

Yield: 40 mg, 88%

Mol. Formula: $C_8H_{17}NO$

M. P.: 120 ^oC (lit[4c] 121 ^oC)

1 $[\alpha]_D^{25}$: +7.97 (c 0.85, EtOH) {lit[4c] +9.0 (c 0.85, EtOH)}

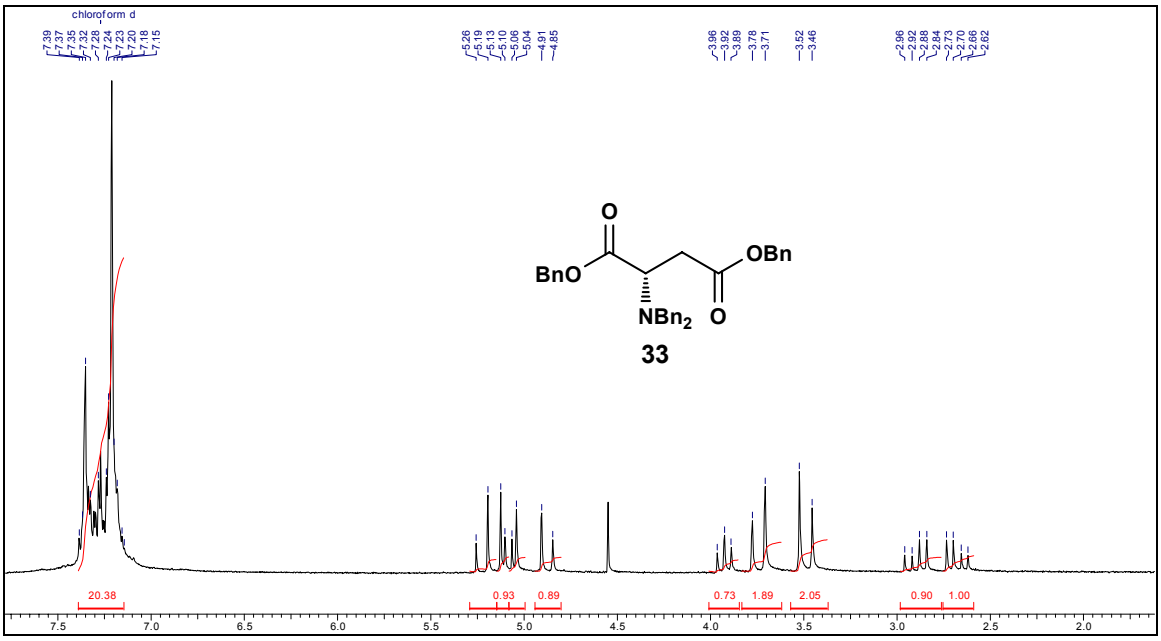
2 $[\alpha]_D^{25}$: $[\alpha]_D^{20}$ -34.8 (*c* 0.4, $CHCl_3$), {lit.[4f] $[\alpha]_D^{20}$ –34.1 (*c* 0.4, $CHCl_3$)}

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.99 (t, *J* = 6.94 Hz, 3H), 1.26 (s, 2H), 1.44-1.49 (m, 6H), 1.57-1.94 (m, 1H), 2.05-2.37 (m, 2H), 3.39-4.05 (m, 2H), 4.49-5.20 (m, 1H) ppm.

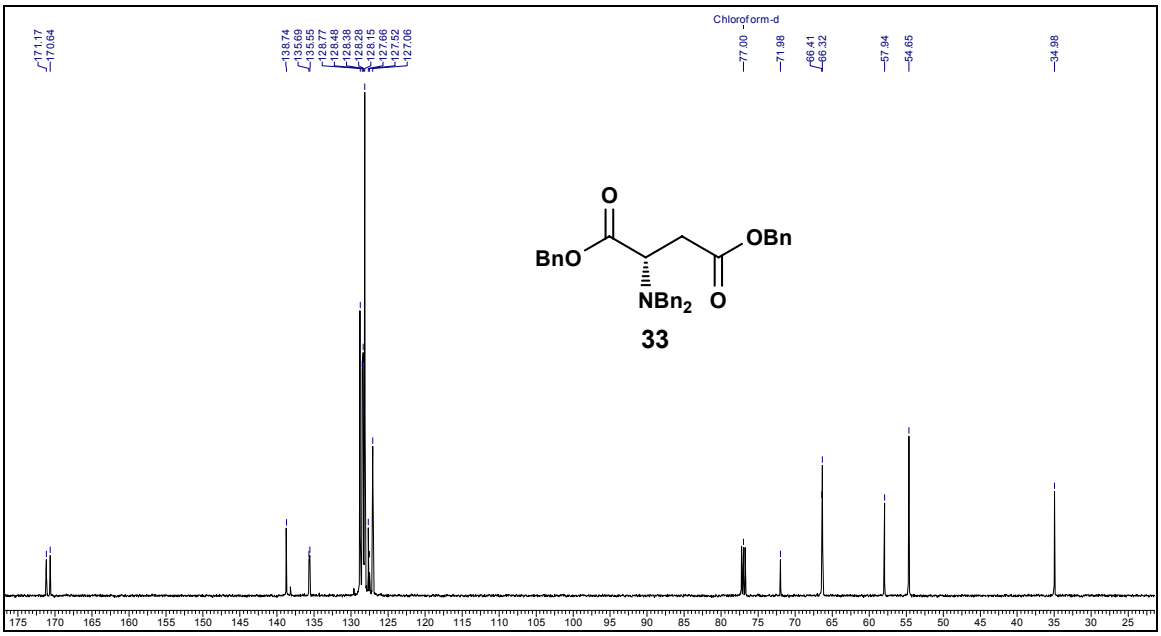
^{13}C NMR (75 MHz, $CDCl_3$): δ 10.4, 24.4, 25.9, 26.9, 44.0, 54.5, 70.7 ppm.

4.1.7 Spectra

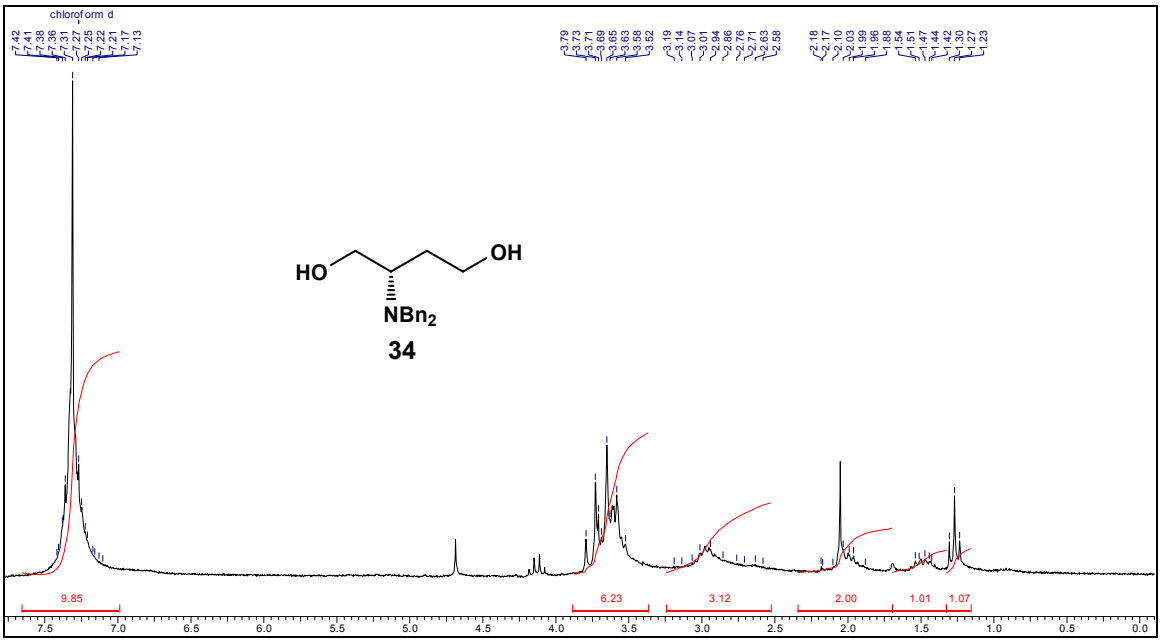
1. ^{1}H and ^{13}C NMR spectra of **33**
2. ^{1}H and ^{13}C NMR spectra of **34**
3. ^{1}H and ^{13}C NMR spectra of **35**
4. ^{1}H and ^{13}C NMR spectra of **37a**
5. ^{1}H and ^{13}C NMR spectra of **37b**
6. ^{1}H and ^{13}C NMR spectra of **41a**
7. ^{1}H and ^{13}C NMR spectra of **42a**
8. ^{1}H and ^{13}C NMR spectra of **44a**
9. ^{1}H and ^{13}C NMR spectra of **1**



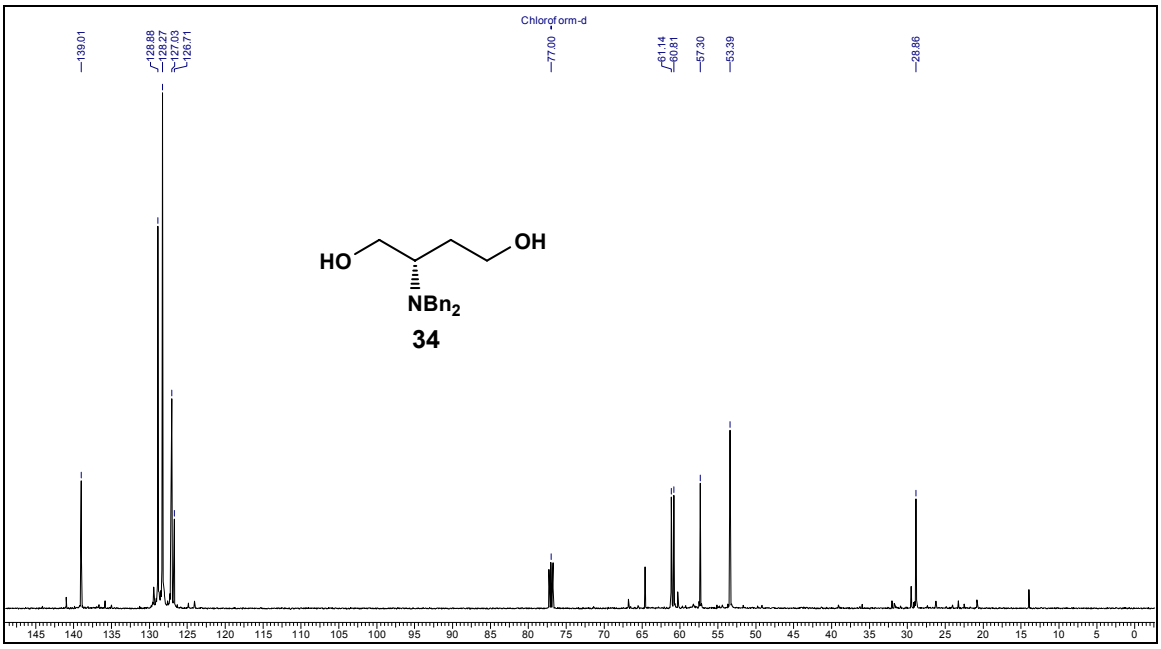
☞ ^{1}H NMR of the compound 33 in $CDCl_3$



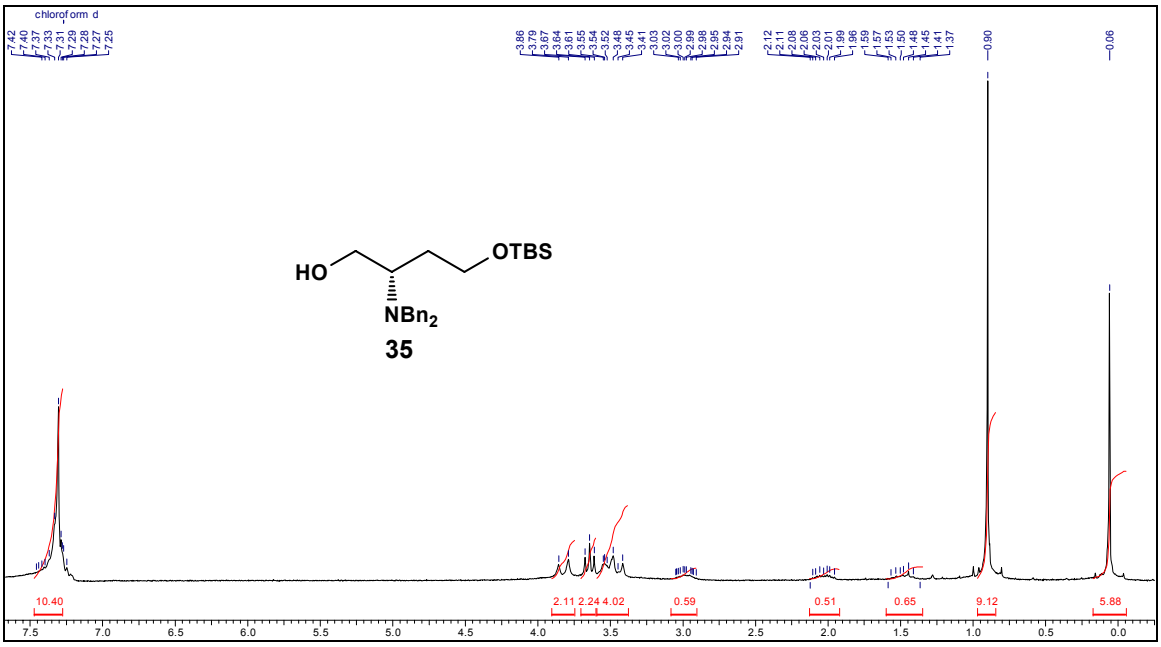
☞ ^{13}C NMR of the compound 33 in $CDCl_3$



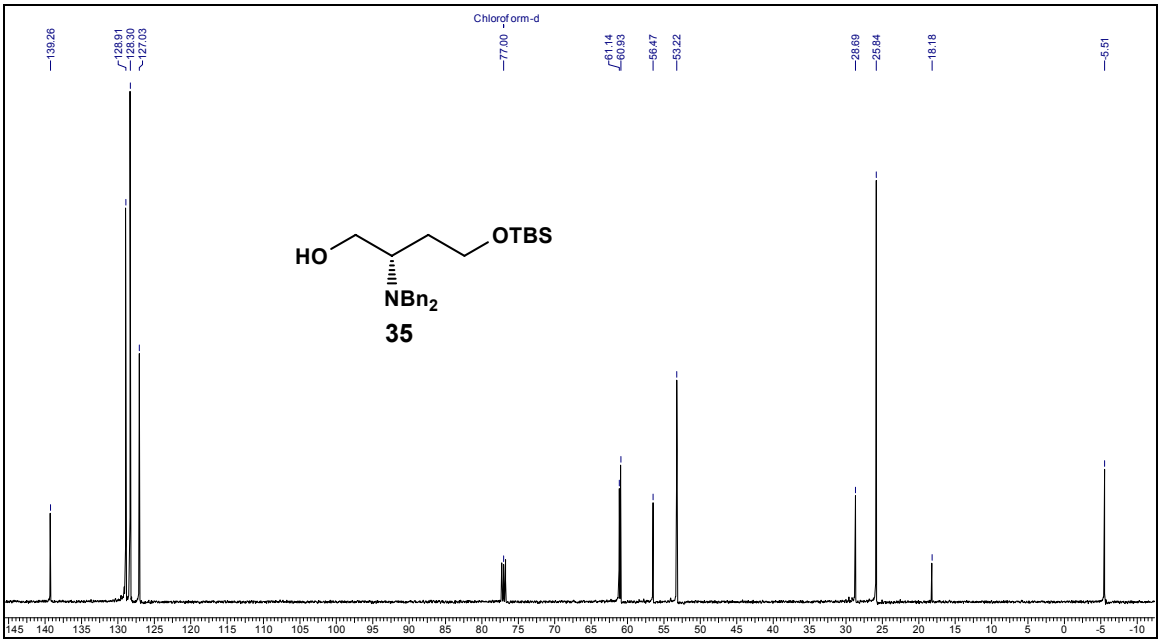
☞ ^{1}H NMR of the compound 34 in $CDCl_3$



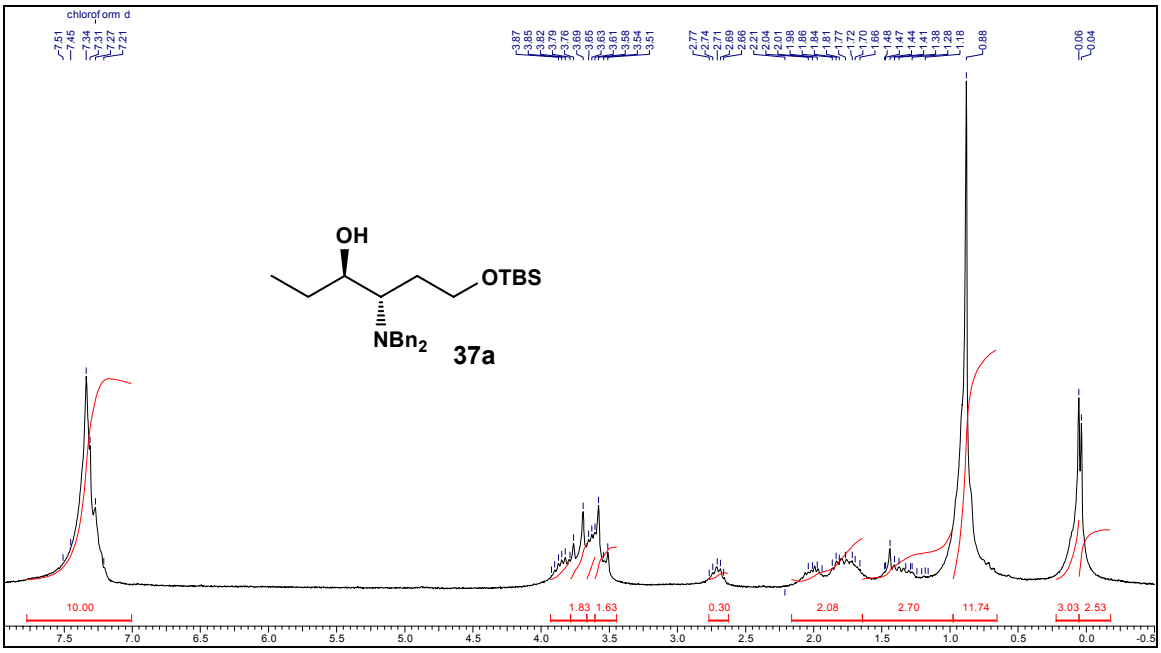
☞ ^{13}C NMR of the compound 34 in $CDCl_3$



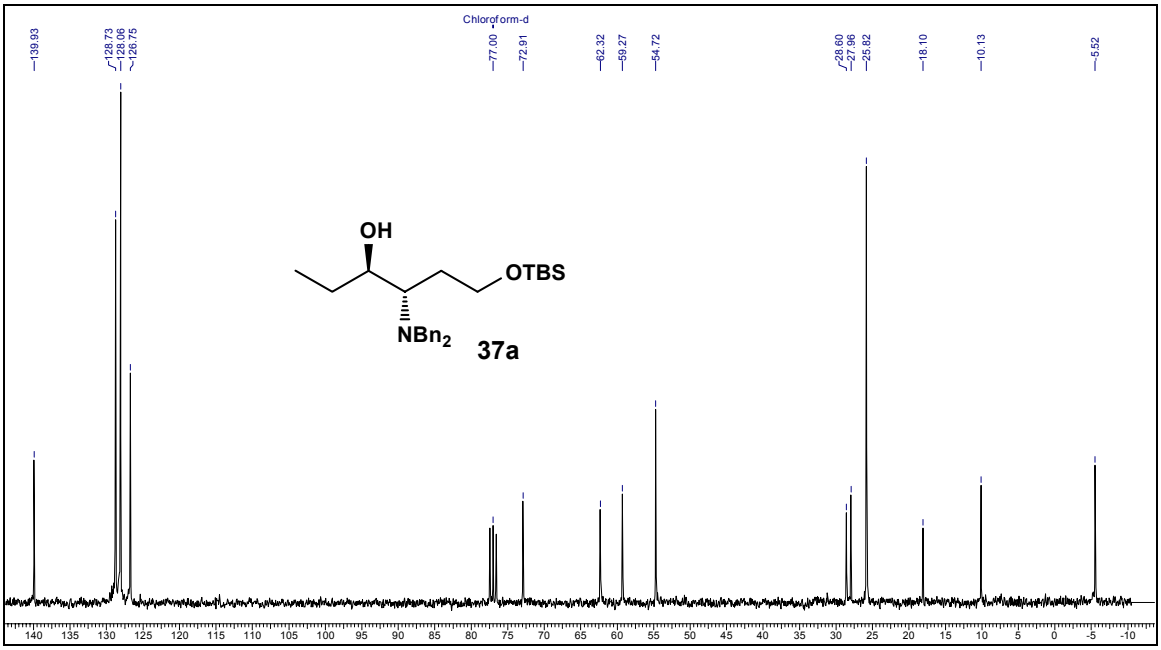
☞ ^{1}H NMR of the compound 35 in $CDCl_3$



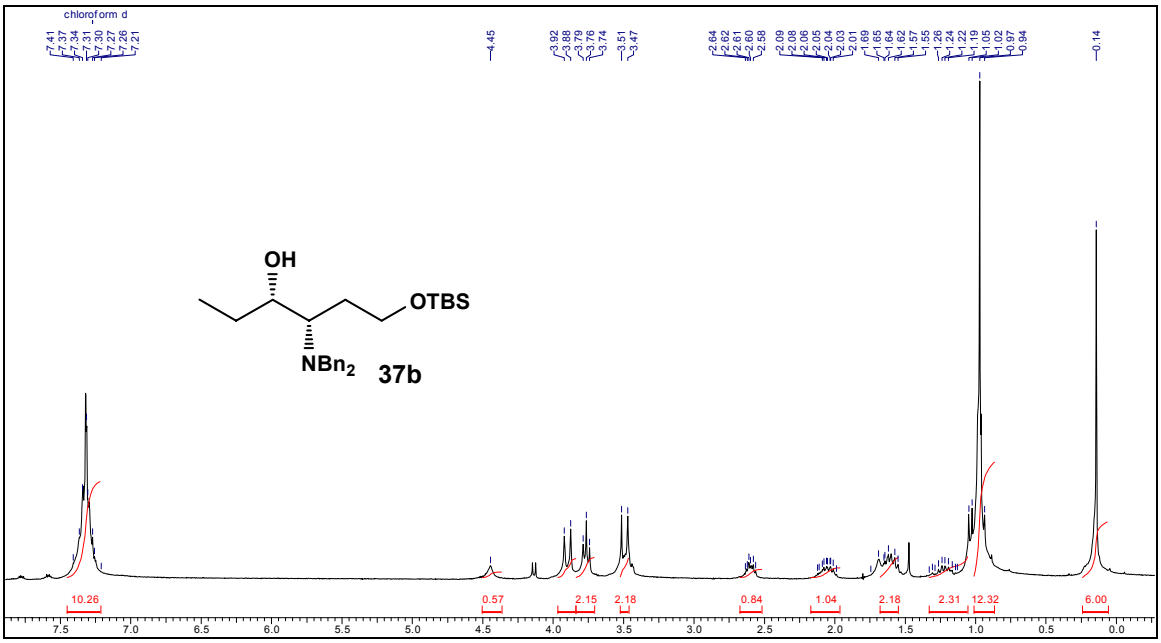
☞ ^{13}C NMR of the compound 35 in $CDCl_3$



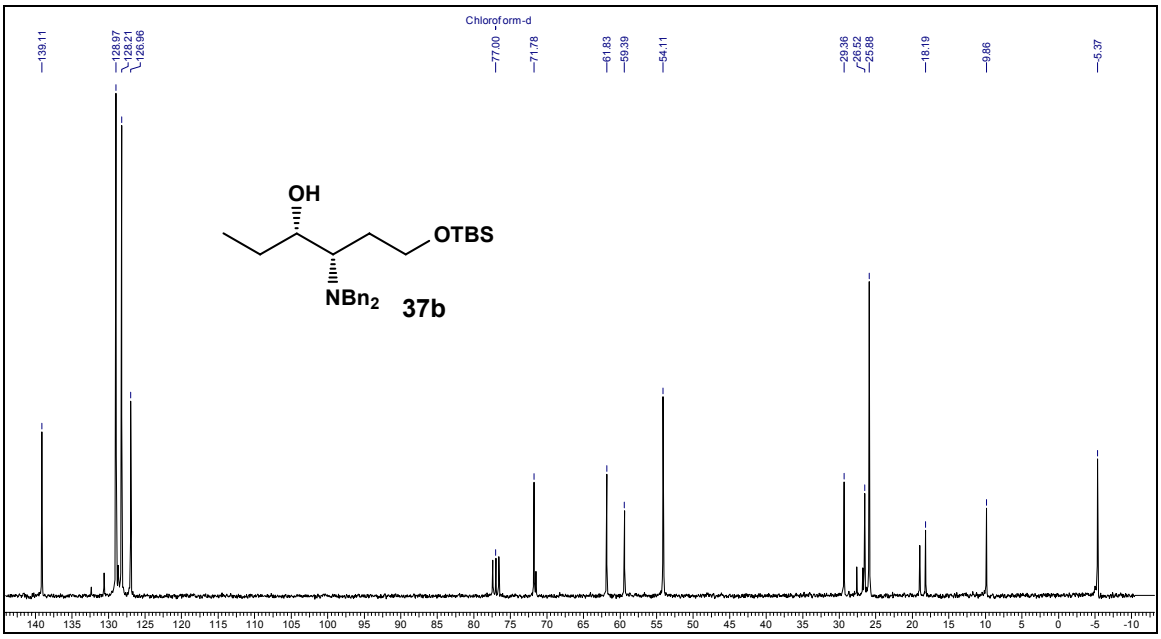
☞ ^{1}H NMR of the compound 37a in $CDCl_3$



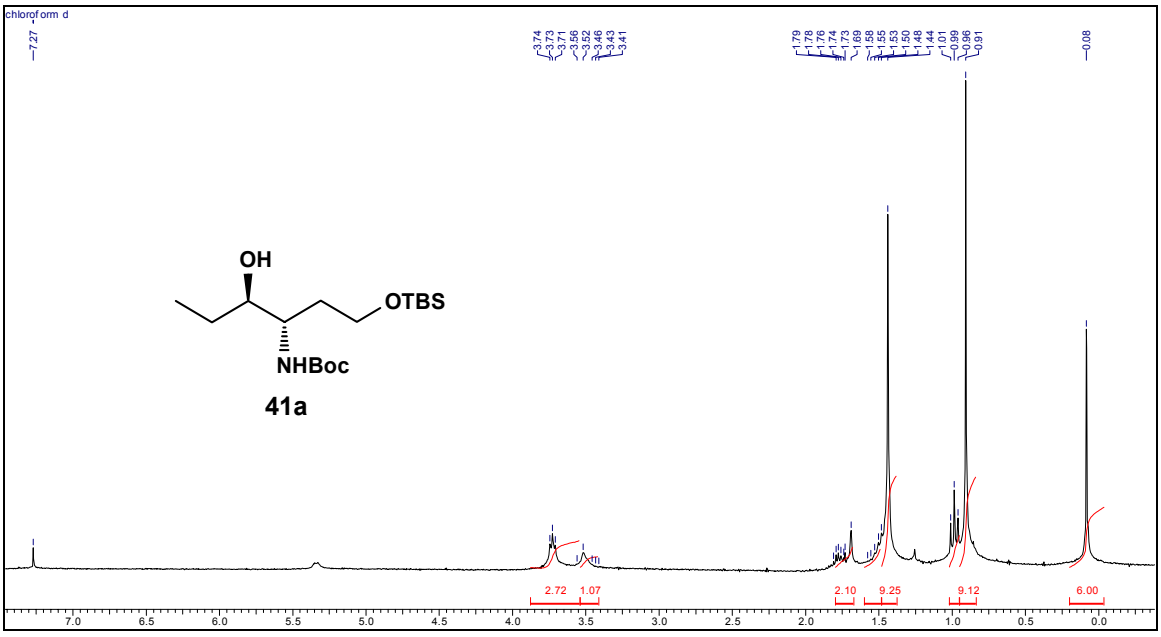
☞ ^{13}C NMR of the compound 37a in $CDCl_3$



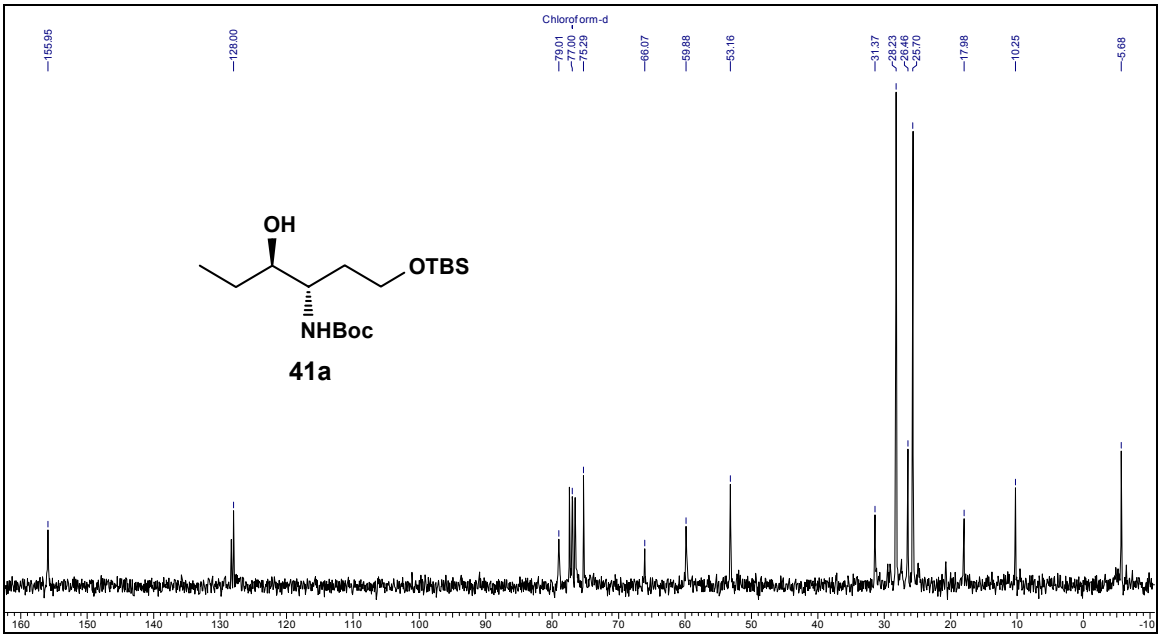
☞ ^{1}H NMR of the compound 37b in $CDCl_3$



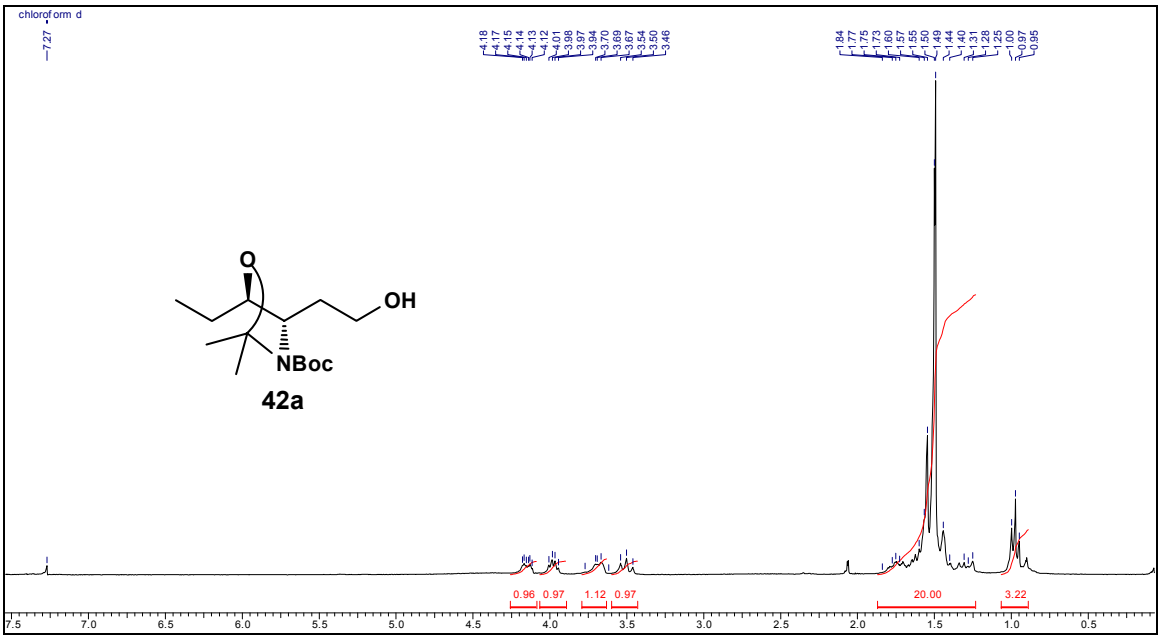
☞ ^{13}C NMR of the compound 37b in $CDCl_3$



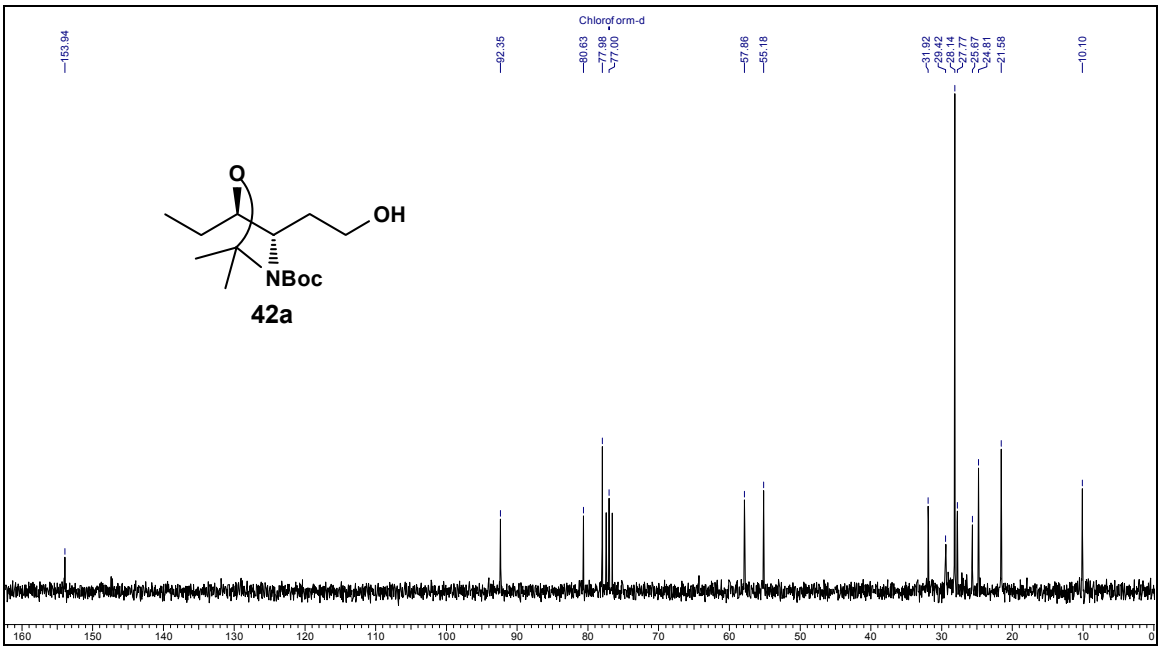
☞ ^{1}H NMR of the compound 41a in $CDCl_3$



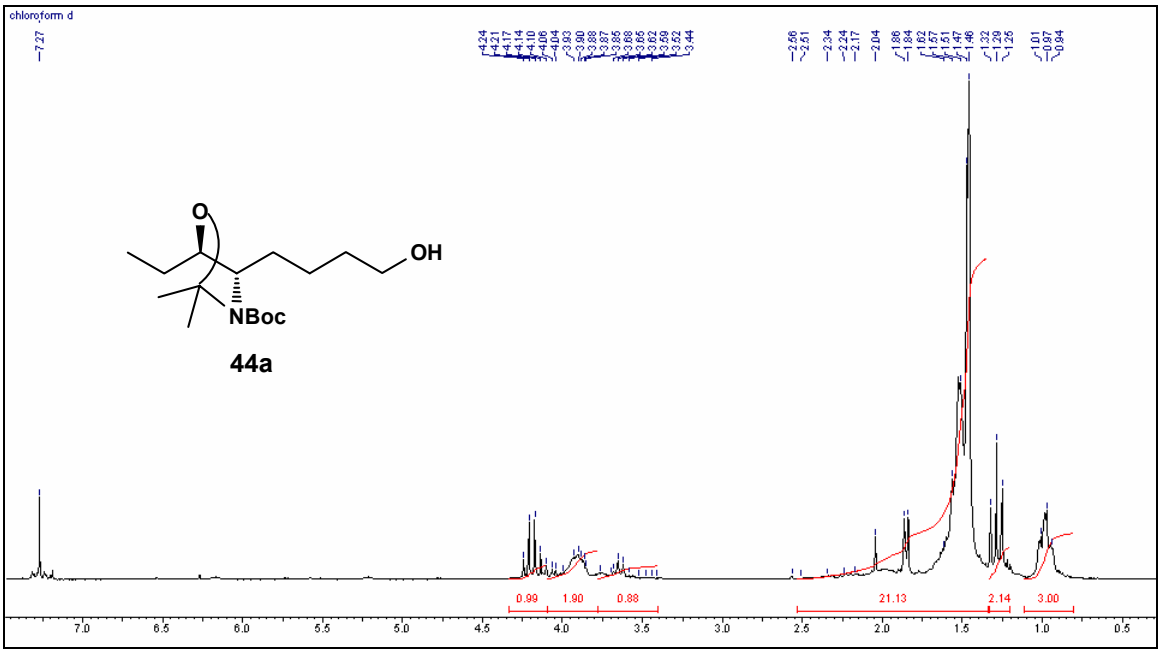
☞ ^{13}C NMR of the compound 41a in $CDCl_3$



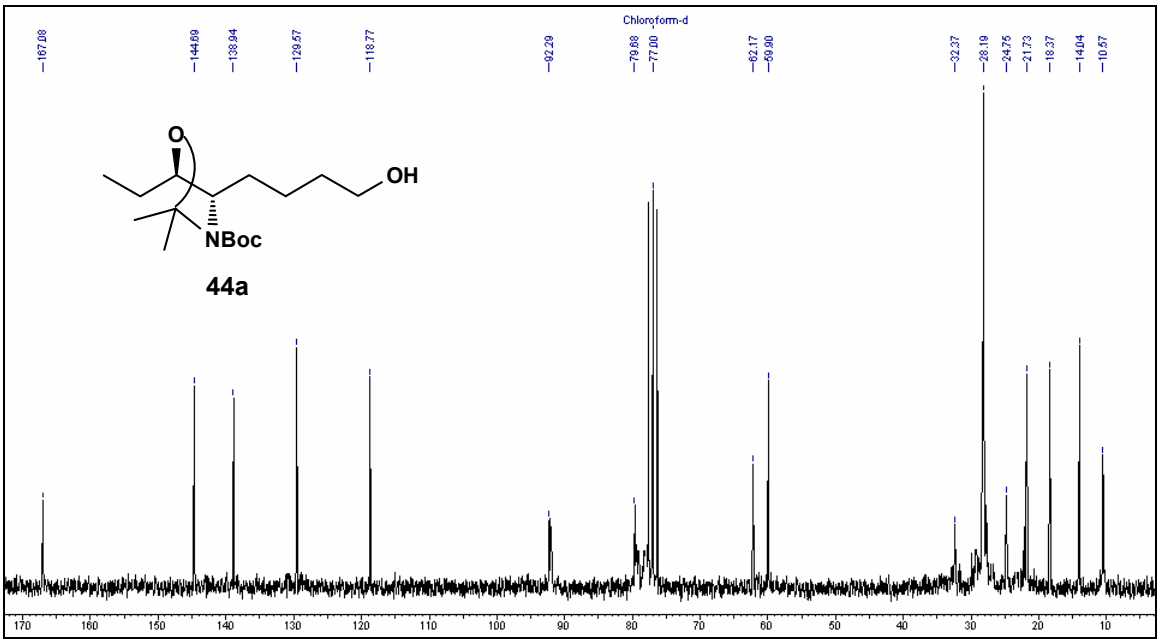
☞ ^{1}H NMR of the compound 42a in $CDCl_3$



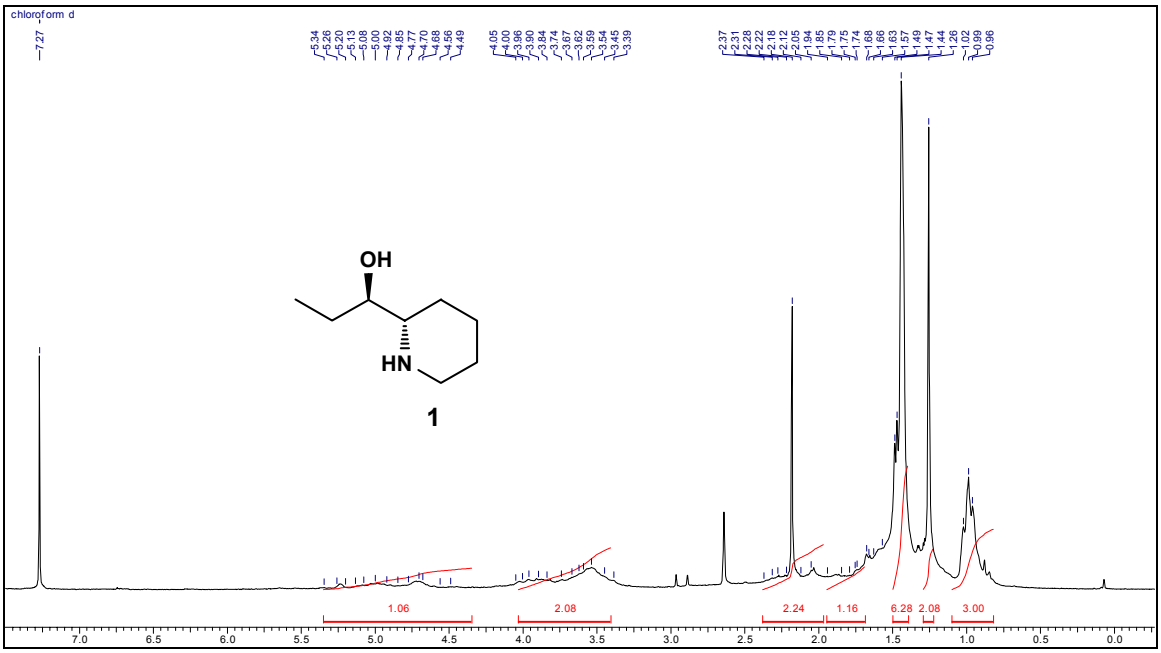
☞ ^{13}C NMR of the compound 42a in $CDCl_3$



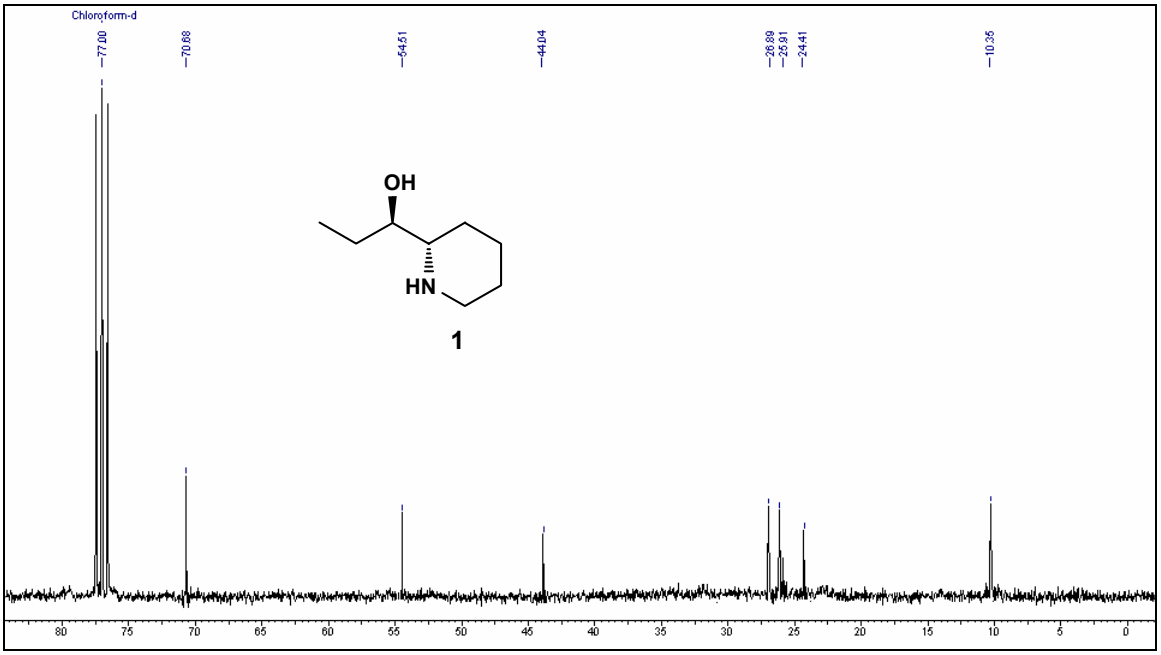
☞ **^{1}H NMR of the compound 44a in $CDCl_3$**



☞ **^{13}C NMR of the compound 44a in $CDCl_3$**



☞ ^{1}H NMR of the compound 1 in $CDCl_3$



☞ ^{13}C NMR of the compound 1 in $CDCl_3$

4.2 SECTION B

AN EFFICIENT AND VERSATILE APPROACH TO ENANTIOPURE 2,6-DISUBSTITUTED PIPERIDIN-3-OL: CONCISE SYNTHESIS OF (-)-DEOXOPROSOPININE AND (+)-DEOXOPROSOPHYLLINE

4.2.1. Introduction

Naturally occurring alkaloids containing multi-functionalised piperidine rings are found abundantly in nature and many of them exhibit biological acitivity of medicinal interest.[14] Prosopis alkaloids, one of the sub groups of these piperidine alkaloids, were isolated from the leaves of *Prosopis afrikana* Taub, containing 2,6-disubstituted piperidin-3-ol piperidine framework such as prosopinine **44, 48**, prosophylline **46, 50,** and their deoxo analogues deoxoprosopinine **45**, **49,** deoxoprosophylline **47**, **51** respectively (Figure 2).[15] These alkaloids exhibit antibiotic, anesthetic, analgesic and CNS stimulating properties.

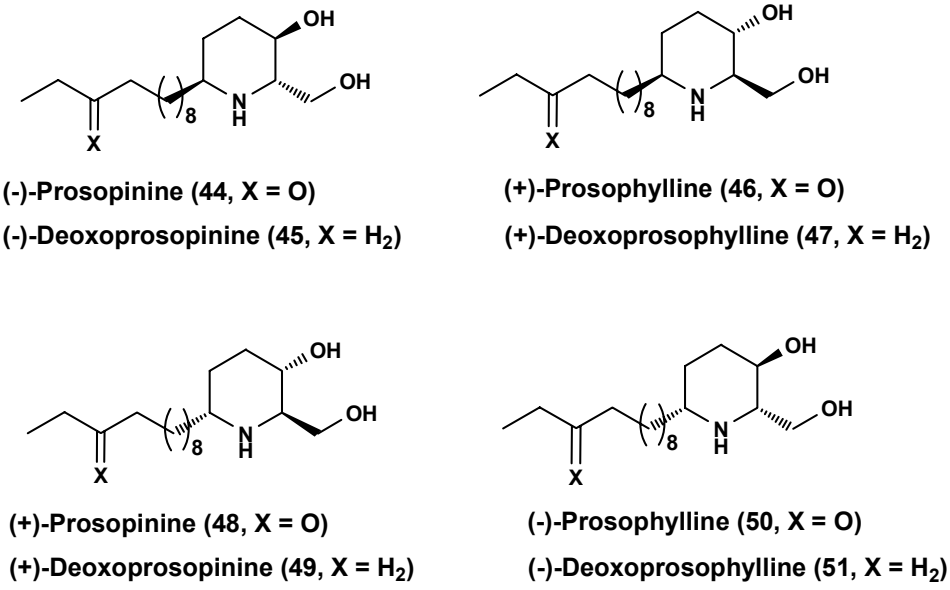


Figure 2

These alkaloids have attracted considerable interest as synthetic targets. At one end of these molecules is the polar head group with a configuration of the 1,3-diol unit similar to

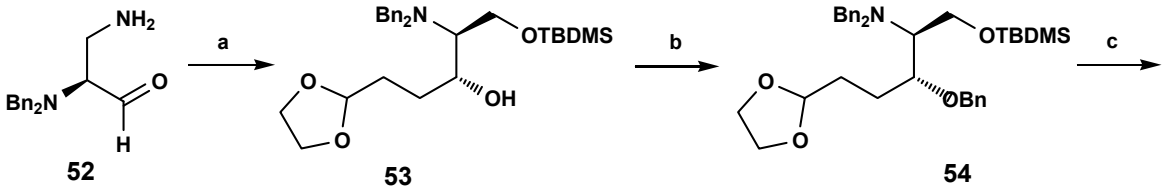
those in deoxynojirimycin, a potent a-glucosidase I and II inhibitor, while the lipophilic tail resembles the membrane lipid sphingosine.

4.2.2. Review of Literature

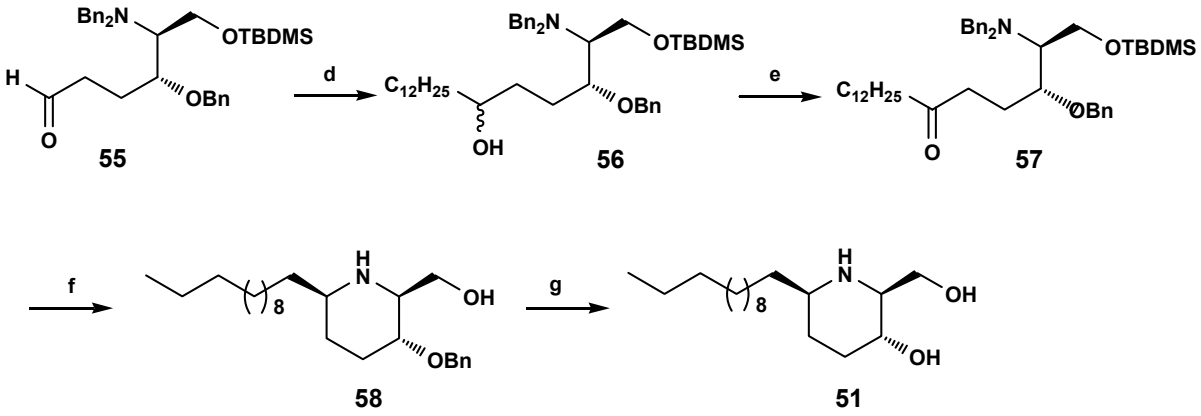
Various syntheses of this class of compounds have been reported. While majority of the syntheses of deoxoprosopinine and deoxoprosophylline employ chiral pool starting materials such as sugars and amino acids and involve many steps,[16,17] the literature describing a general synthetic strategy to construct the 2,6-disubstituted piperidin-3-ols framework is rather scarce. Some of the recent syntheses of deoxoprosopinine and deoxoprosophylline are described below.

Zhu, J. *et al.* (2001)[17e]

Jieping Zhu and co-workers synthesized (−)-deoxoprosophylline **51** by using a highly diastereoselective intramolecular reductive amination of ω-oxo amino diol as a key step (Scheme 9). Addition of Buchi's Grignard reagent, prepared in situ from the corresponding bromide, to the aldehyde **52** afforded the amino diol **53** in excellent yield and diastereoselectivity (*anti*/*syn* =15/1). Protection of the secondary alcohol as benzyl ether followed by acidic hydrolysis of dioxolane gave the aldehyde **55**. Reaction of aldehyde **55** with an excess of dodecylmagnesium bromide afforded alcohol **56** as a mixture of two diastereomers in a 1:1 ratio. Swern oxidation of alcohol **56** afforded ketone **57** which under catalytic transfer hydrogenolysis conditions developed recently by Bajwa and co-workers afforded a chemoselective *N*-debenzylation compound **58** which, without purification was *O*-debenzylated to afford (−)-deoxoprosophylline **51**.



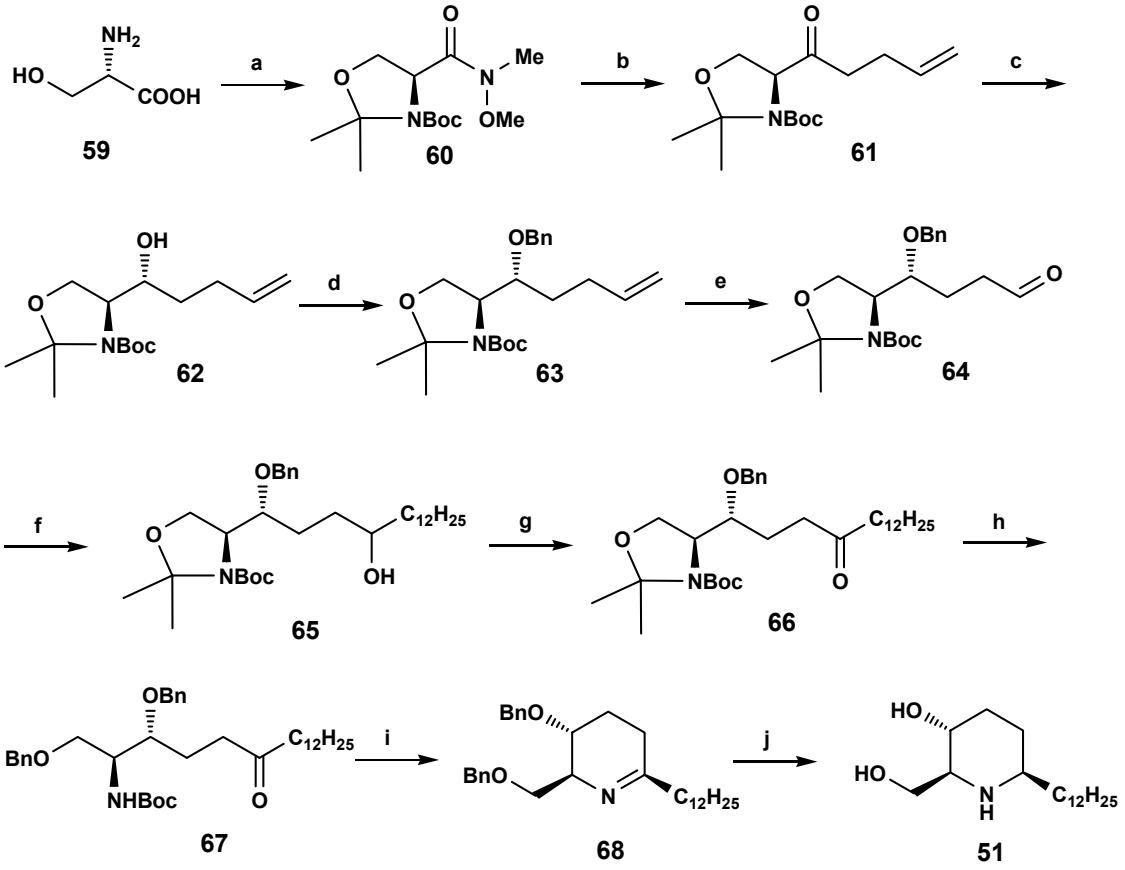
52 53 54



Scheme 9. *Reagents and conditions*: (a) $C_5H_9O_2Br$, Mg, THF, room temperature, then **52**, 86%; (b) NaH, BnBr, TBAI, THF, 0 °C, then room temperature, 85%; (c) (i) 3N HCl–THF; ii) TBDMSCl, imidazole, DMF, room temperature, 90%; (d) $C_{12}H_{25}Br$, Mg, dibromoethane, THF, then **55**, 70 °C, 80%; (e) DMSO, $(COCl_2)$ then Et_3N, 84%; (f) $Pd(OH)_2$, cyclohexene, EtOH, reflux, (g) Pd/C, MeOH, 73%.

Datta, A. *et al.* (2001)[17f]

Apurba Datta and co-workers synthesized (−)-deoxoprosophylline **51** utilizing the amino acid L-serine as a chiral pool starting material (Scheme 10). Grignard reaction of the Weinreb amide **60** (prepared from L-serine **51** *via* known procedure[18]) with 3-butenylmagnesium bromide afforded the ketone derivative **61** which on zinc borohydride $[Zn(BH_4)_2]$-mediated chelation-controlled reduction furnished the amino alcohol derivative **62** with *anti* selectivity. Protection of the free hydroxy group of the *anti*-amino alcohol **62** as its benzyl ether derivative **63**, followed by oxidative degradation of the double bond under standard conditions cleanly afforded the aldehyde **64.** Grignard reaction of the aldehyde **64** with dodecylmagnesium bromide furnished the adduct **65** which on oxidation afforded the corresponding ketone **66.** Selective hydrolysis of the acetonide linkage and benzyl protection of the primary hydroxy group yielded the open chain ketone **67**. Treatment of this δ-amino ketone with 96% formic acid resulted in simultaneous *N*-Boc-deprotection and cyclodehydration to form the expected piperidine derivative **68** in 78% yield. Finally, hydrogenation of the imine double bond and reductive removal of the benzyl protecting groups under standard conditions completed the synthesis of (-)-deoxyprosophylline **51**.

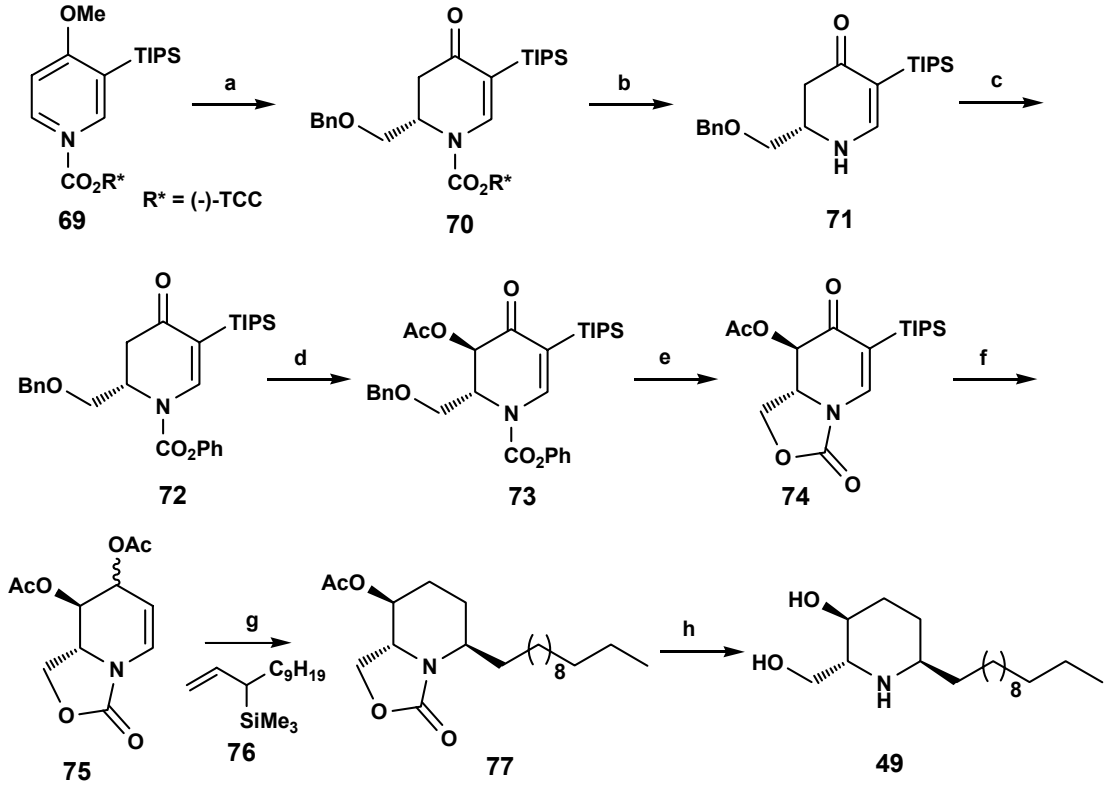


Scheme 10. *Reagents and conditions*: (a) ref. 18; (b) C_4H_7MgBr, THF, 0 ^oC, 76%; (c) $Zn(BH_4)_2$, Et_2O-C_6H_6, 76%; (d) NaH, BnBr, 97%; (e) i) OsO_4, ii) $NaIO_4$ (on silica gel), 92%; (f) $C_{12}H_{25}MgBr$, 80%; (g) 2-Iodoxybenzoic acid, 91%; (h) i) 80% AcOH in H_2O; ii) BnBr, Ag_2O, 85%; (i) HCO_2H, 78%; (j) Palladium hydroxide, H_2, EtOH-HCl, 72%.

Comins, D. L. *et al.* (2001)[161]

Daniel L. Comins and co-workers started the synthesis of (+)-deoxoprosopinine **49** from 1-acylpyridinium salt **69** which was treated with higher order cyanocuprate to afford dihydropyridone **70** in 70% yield (Scheme 11). Reaction of compound **70** with sodium methoxide followed by aqueous acid provided dihydropyridone **71** in quantitative yield which on *N*-Acylation with *n*-BuLi and phenyl chloroformate afforded 94% yield of enantiopure carbamate **72**. Treatment of **72** with $Pb(OAc)_4$ afforded **73** in 57% yield. Cyclization of **73** was effected by a one-pot procedure involving cleavage of the benzyl ether and formation of a formate ester *via* refluxing formic acid and subsequent treatment

with ammonia in MeOH at 0 °C to afford **74** in 73% yield. The allylic acetate **75** was generated in 98% yield by selective 1,2-reduction of enone **74** and subsequent acylation. Lewis acid promoted addition of allylsilane **76** to the *N*-acyliminium ion (generated in situ from **74** and $BF_3.Et_2O$) afforded **77** after catalytic hydrogenation of the diene intermediate. Finally, saponification in aqueous NaOH of both the acetate ester and the oxazolidinone ring afforded (+)-deoxoprosopinine **49** in 85% yield.

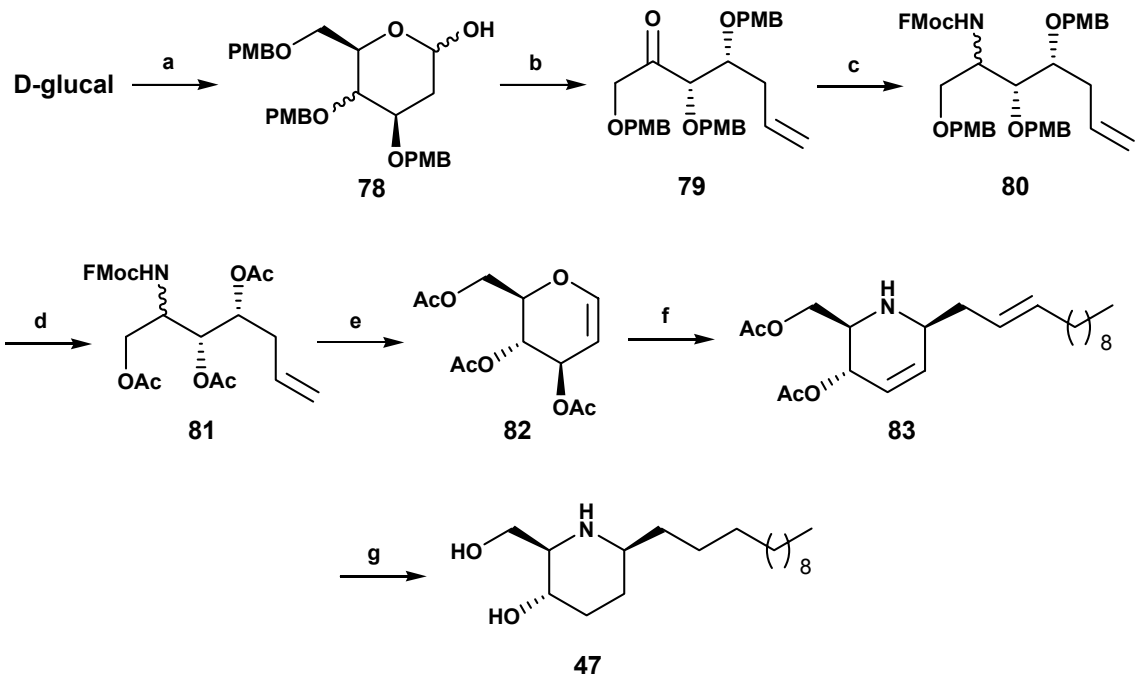


Scheme 11. *Reagents and conditions*: (a) i) $BnOCH_2(2\text{-Th})Cu(CN)Li_2$, THF, -78 °C; ii) 10% HCl, 70%; (b) i) NaOMe, MeOH, reflux; ii) HCl, *i*-PrOH, 100%; (c) *n*-BuLi, PhOCOCl, THF, -78 °C, 94%; (d) $Pb(OAc)_4$, toluene, reflux, 57%; (e) HCO_2H, reflux, 3.5 h; then NH_3, MeOH, 0 °C, 73%; (f) i) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, -40 °C; ii) Ac_2O, Et_3N, DMAP, CH_2Cl_2 (98%, two steps). (g) i) $BF_3.Et_2O$, CH_2Cl_2, -78 °C, **76**; ii) H_2, Pt/C, EtOH (71%, two steps). (h) NaOH, EtOH, 140 °C, 85%.

(-)-TCC = (1*R*,2*S*)-2-(1-methyl-1-phenylethyl)cyclohexanol.

Shipman, M. *et al.* (2003)[17g,h]

Michael Shipman and co-workers reported the synthesis of (+)-deoxoprosophylline **47** from chiral pool starting material D-glucal. Protection of the hydroxy groups as *p*-methoxybenzyl ethers followed by hydration of the double bond gave hemiacetal **78**. Wittig olefination with methylenetriphenylphosphorane followed by TPAP oxidation of the resulting secondary alcohol furnished ketone **79**, which was converted into amine **80** by reduction of the corresponding oxime. The PMB ether protecting groups was converted to acetates and triacetate **81** was subjected to ozonolytic cleavage of the terminal double bond followed by dehydration of the resulting hemiacetal using oxalyl chloride to afford **82** in good yield. Addition of 3-(trimethylsilyl)dodec-1-ene to **82** smoothly gave piperidine **83** which on hydrogenation followed by removal of the acetate groups afforded (+)-deoxoprosophylline **47** (Scheme 12).

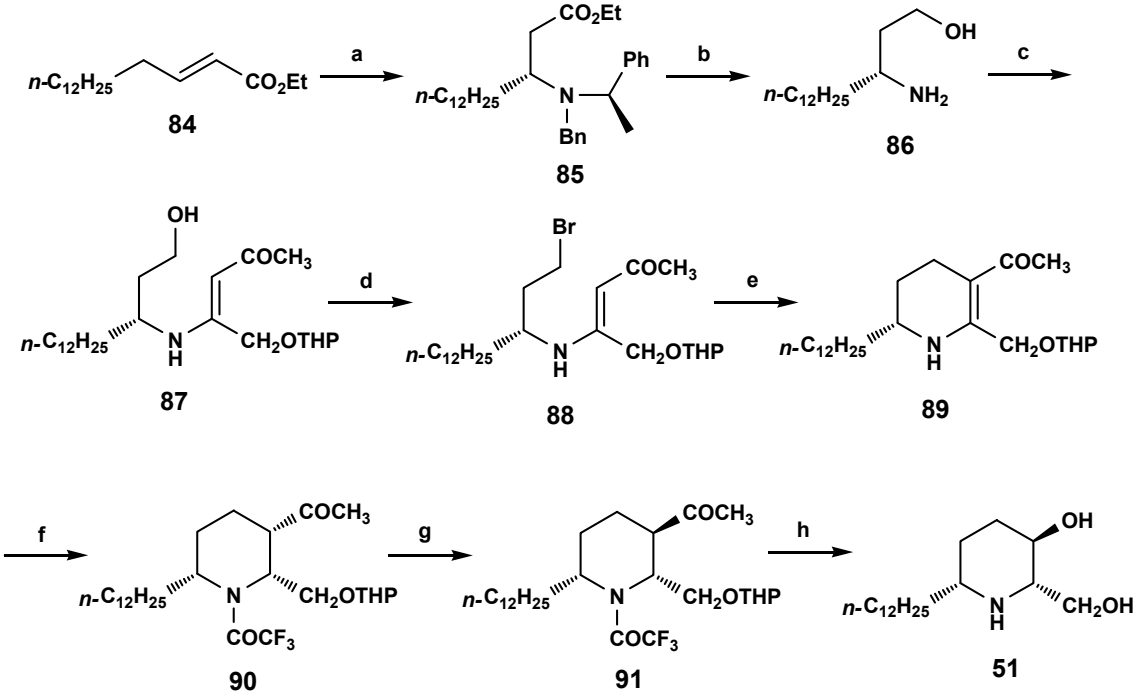


Scheme 12. *Reagents and conditions*: (a) i) NaH, PMBCl, DMF; ii) $Hg(OAc)_2$, THF–H_2O then $NaBH_4$, 51%; (b) i) $Ph_3P{=}CH_2$, toluene; ii) TPAP, NMO, 4 Å sieves, CH_2Cl_2, 69%; (c) i) $HONH_2$.HCl, pyridine, EtOH, 60 °C; ii) $LiAlH_4$, Et_2O, rt,; iii) FmocCl, K_2CO_3, THF–H_2O (3:1); (d) i) CF_3CO_2H, CH_2Cl_2; ii) Ac_2O, pyridine, rt, 54% two steps; (e) i) O_3, -78 °C, CH_2Cl_2 then Me_2S, rt; ii) $(COCl)_2$, Et_3N, DMF, CH_2Cl_2; (f) i) $BF_3{\cdot}Et_2O$, CH_2Cl_2,

$H_2CNCH_2CH(Si\text{-}Me_3)(CH_2)_8CH_3$, -60 to 0 °C, 3 h, 78%; ii) piperidine, CH_2Cl_2, rt, 1 h; (g) i) H_2, Pt/C, EtOH, 1.5 h; ii) LiOH, THF–H_2O, 2.5 h, 51%.

Ma, D. *et al.* (2003)[17i]

Dawei Ma and co-workers reported the synthesis of (-)-deoxoprosophylline **51** from the olefin **84.** β-Amino ester **85** obtained using Davies' procedure was subjected to LAH reduction to convert into corresponding alcohol, which on hydrogenolysis provided the desired γ-amino alcohol **86**. The Michael addition of **86** to the alkynone produced the enamine **87** which on treatment with triphenylphosphine and carbon tetrabromide assisted by triethylamine followed by reflux in acetonitrile afforded the cyclic enamine **88→89**. PtO_2-catalyzed hydrogenation of **89** afforded the corresponding saturated piperidine, which was protected with trifluoroacetic anhydride to provide the amide **90**. Epimerization of the 3-acetyl group of **90** under the action of DBU produced its thermodynamically more stable isomer **91**. Treatment of **91** with trifluoroperacetic acid afforded the Baeyer–Villiger oxidation product which was hydrolyzed with 6N HCl in methanol to remove all protecting groups to afford the (−)-deoxoprosophylline **51** (Scheme 13).

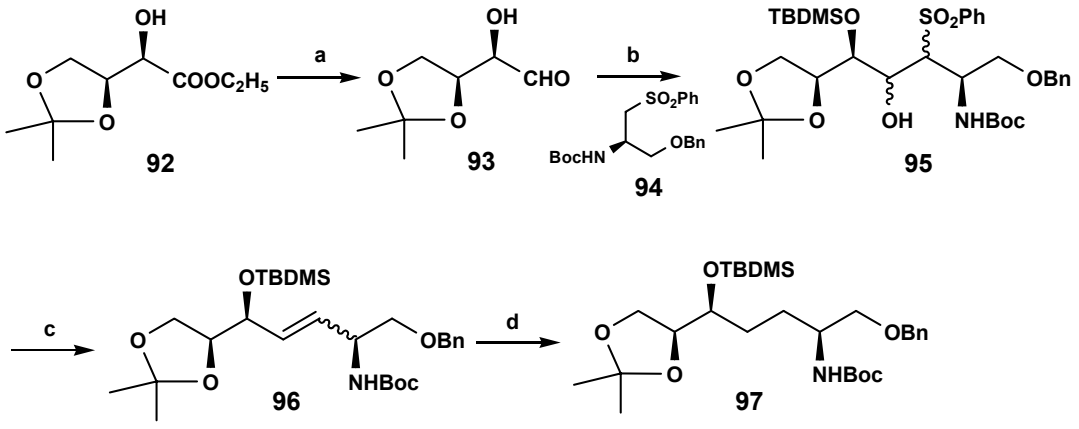


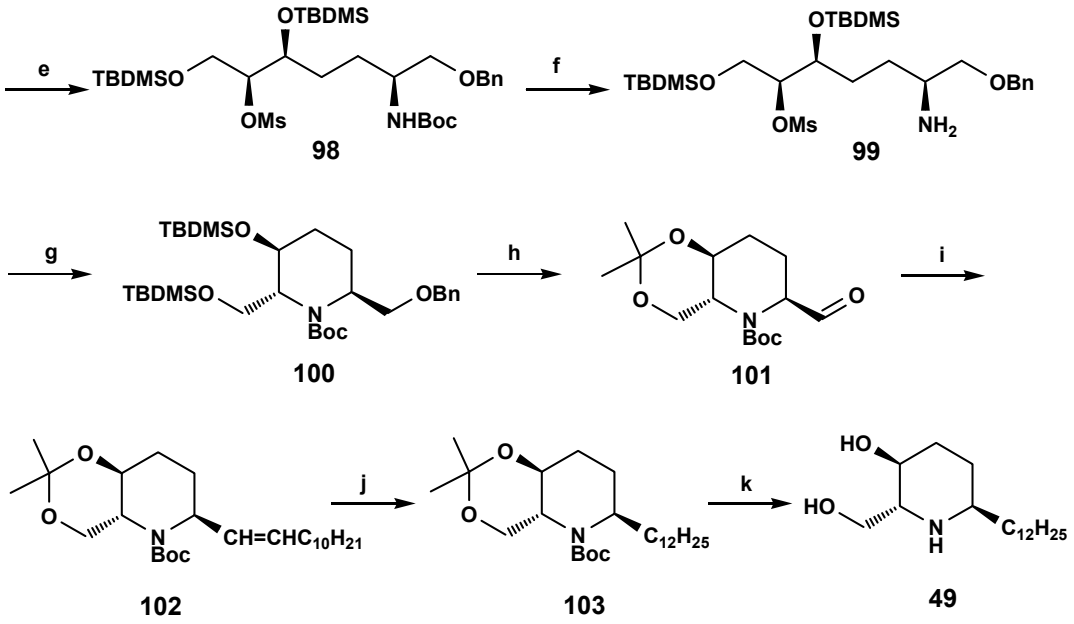
Scheme 13. *Reagents and conditions*: (a) *n*-BuLi, THF, 88%; (b) i) LAH, THF, 0 ^oC-rt, ii) $Pd(OH)_2/H_2$, MeOH, 89%; (c) $C_8H_{14}O_3$, DMF, rt, 82% (d) $TPP/CBr_4/Et_3N$, CH_2Cl_2, rt,

68%; (e) Et_3N, MeCN, reflux, 76%; (f) i) PtO_2/H_2, HOAc; ii) $(CF_3CO)_2O/Et_3N$, DMAP, 76%; (g) DBU/THF, rt, 87%; (h) i) 95% $H_2O_2/(CF_3CO)_2O$, Na_2HPO_4, CH_2Cl_2; ii) HCl/MeOH, 45%.

Sasaki, N. A. *et al.* (2004)[16m]

Andre Sasaki and co-workers reported synthesis of enantiopure 2,6-disubstituted piperidin-3-ol featuring Julia olefination and intramolecular *N*-alkylation using two key steps (Scheme 14). The synthesis commenced with the preparation of aldehyde **93** prepared from L-ascorbic acid derivative **92**. The coupling of the dianion prepared from chiral sulfone **94** with aldehyde **93** went smoothly to furnish hydroxysulfone **95** as a mixture of two diastereoisomers. Reduction of hydroxysulfone **95** gave the *E*-alkene **96** in 78% yield. Selective saturation of the double bond with retention of the benzyl and the TBDMS silyl ether functions under mild hydrogenation conditions afforded compound **97** which was transformed into mesylate **98** *via* a standard three-step sequence. Removal of the *N*-Boc group under mild conditions and refluxing a solution of **99** in methanol in the presence of *i*-Pr_2NEt for 48 h afforded piperidine **100** in 92% yield. The amine group of **100** was then subjected to Boc_2O protection, TBAF mediated deprotection of silyl ether, acetonide formation, removal of benzyl ether under hydrogenolysis conditions and Swern oxidation afforded aldehyde **101** which on Wittig reaction furnished alkene **102** in 87% overall yield. Catalytic hydrogenation of **102** followed by the simultaneous removal of the 1,3-diol protecting group and Boc group (1 N HCl in MeOH) provided (+)-deoxoprosopinine **49** in 74% overall yield.



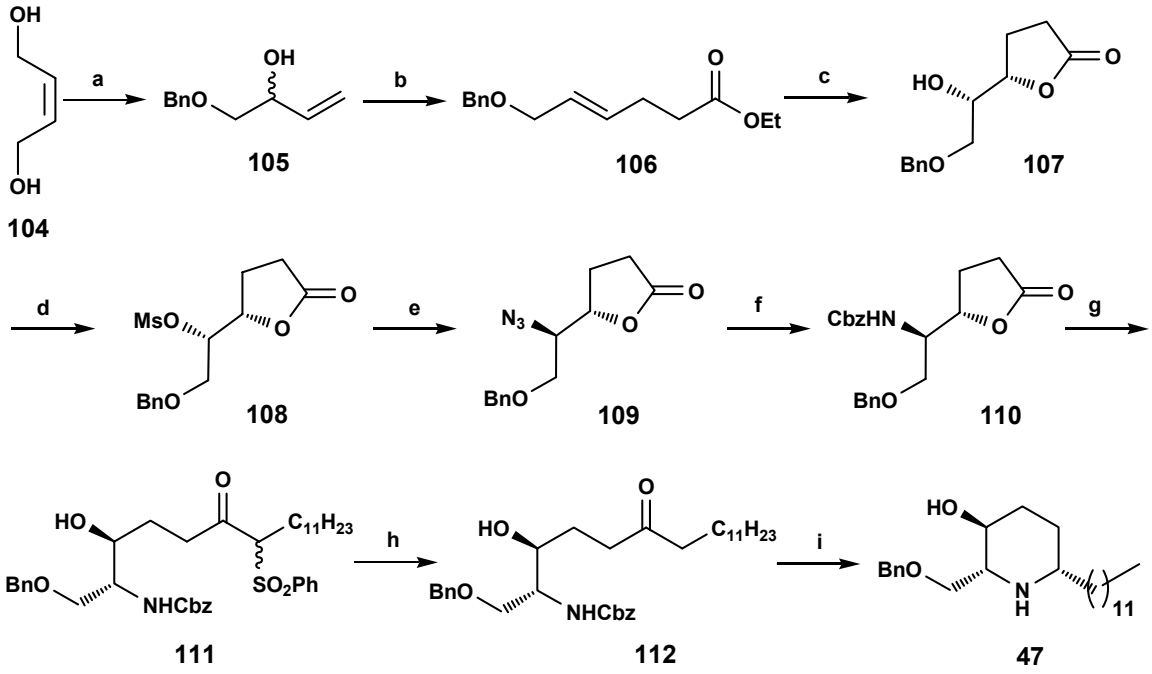


Scheme 14. *Reagents and conditions*: (a) i) TBDPSCl, imidazole, DMF, 0 °C, 15 min; rt, 3 h; ii) $LiBH_4$, MeOH, Et_2O, 0 °C, 3 h, 95% for two steps; iii) $(COCl)_2$, DMSO, CH_2Cl_2, -70 °C, 20 min; Et_3N, -70 °C, 1 h, 100%; (b) *n*-BuLi (2.2 equiv), THF, -70 °C, 30 min; **94**, -70 °C, 4 h, 83%; (c) 6% Na-Hg, Na_2HPO_4, MeOH, 0 °C, 2 h, 72%; (d) H_2, 10% Pd-C, NH_4OAc, MeOH, rt, 24 h, 100%; (e) i) HOAc-H_2O (4/1), rt, overnight, 93%; ii) TBDMSCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, 2 h, 100%; iii) MsCl, Et_3N, DMAP, CH_2Cl_2, -20 to 0 °C, 2 h 99%; (f) i) *i*Pr_2NEt, MeOH, reflux, 48 h, 92%; ii) Boc_2O, Et_3N, DMF, rt, overnight, 99%; (g) Bu_4NF, THF, 0 °C, 10 min; rt, 1 h, 100%; (h) i) 2,2-dimethoxypropane, TsOH, acetone, rt, 2 h, 93%; ii) H_2 (1 atm), 20% $Pd(OH)_2$-C, EtOAc, rt, 2 h, 96%; iii) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, 15 min; Et_3N, 0 °C, 1 h, 100%; (i) $Ph_3PC_{11}H_{23}Br$, KHMDS, THF, -78 °C, 10 min; 0 °C, 1 h; compound **101**, -78 °C, 20 min; 0 °C, 5 h, 87%; (j) H_2 (1 atm), 20% $Pd(OH)_2$-C, EtOAc, rt, overnight, 99%; (k) 1 N HCl-MeOH, rt, 24 h, 79%.

Chavan, S. P. *et al.* (2004) [17j]

From our laboratory Subhash P. Chavan and co-workers reported the syntheses of (+)- and (-)-deoxoprosophylline **47, 51** from the *cis*-2-butene-1,4-diol in which the Sharpless asymmetric dihydroxylation was used as the key step (Scheme 15). Monoprotected allylic alcohol **105** was prepared from the *cis*-2-butene-1,4-diol **104** according to the literature

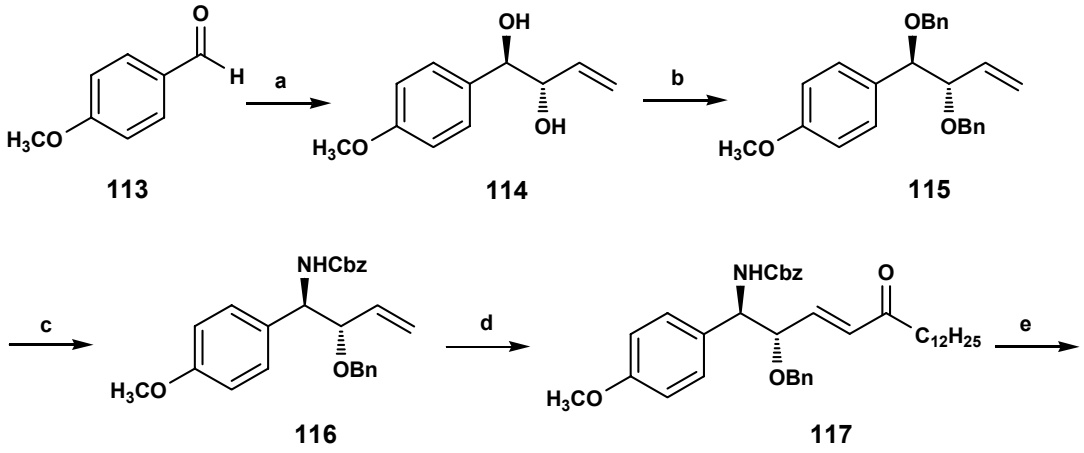
procedure[19] and was subjected to Claisen rearrangement with triethyl orthoacetate in the presence of catalytic propionic acid at 140 ^{o}C to give the, α,β-unsaturated ester **106**. Sharpless asymmetric dihydroxylation and in situ cyclization of the α,β-unsaturated ester **106** furnished the hydroxy lactone **107**. Mesylation and displacement of the mesylate with NaN_3 furnished the azido lactone **109** which was reduced to the amine and was protected as its Cbz derivative **110**. Opening of the lactone of **110** and desulfonylation of **111** using 6% Na–Hg and Na_2HPO_4 at -10 ^{o}C afforded the ketone **112**. Removal of the protecting groups and cyclization of the ketone **112** using catalytic $Pd(OH)_2/H_2$ led to the target compound (+)-deoxoprosophylline **47** in 76%yield.

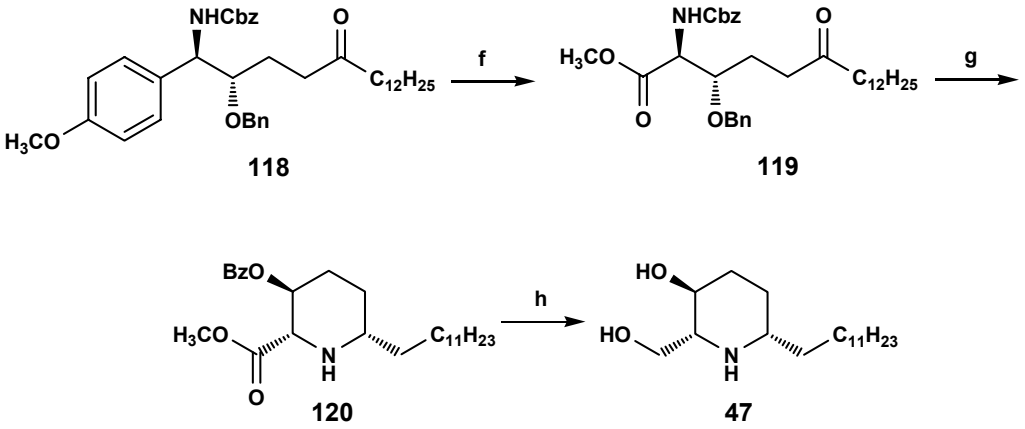


Scheme 15. *Reagents and conditions*: (a) ref. 19; (b) $CH_3C(OEt)_3$, cat. propionic acid, 140 ^{o}C, 2 h, 94%; (c) AD-mix-α, $CH_3SO_2NH_2$, *t*-BuOH:H_2O (1:1), 24 h, 0 ^{o}C, 95%, 93% ee; (d) CH_3SO_2Cl, Et_3N, DCM, 92%; (e) NaN_3, DMF, 90 ^{o}C, 89%; (f) i) TPP, H_2O, C_6H_6, 8 h, ii) CbzCl, Et_3N, cat. DMAP, DCM, 75% for two steps; (g) $C_{12}H_{25}SO_2Ph$, *n*-BuLi, THF, -78 ^{o}C, 2 h, 94%; (h) 6% Na–Hg, Na_2HPO_4, CH_3OH, -10 ^{o}C, 95%; (i) 20% $Pd(OH)_2/C$, H_2, CH_3OH, rt, 24 h, 76%.

Jung, Y. H. *et al.* (2007)[171]

Young Hoon Jung and co-workers reported stereoselective synthesis of (+)-deoxoprosophylline **47** from *p*-anisaldehyde. Key steps in the synthesis include the stereoselective amination of *anti*-1,2-dibenzyl ether using chlorosulfonyl isocyanate, intermolecular olefination, and Pd-catalyzed intramolecular cyclization (Scheme 16). *p*-Anisaldehyde **113** was converted into *anti*-1,2-diol **114** according to the literature procedure.[20] Treatment of the diol **114** with benzyl bromide and sodium hydride gave *anti*-1,2-dibenzyl ether **115** which was subjected to the regioselective and diastereoselective CSI reaction in toluene solution at -78 ^{o}C for 24 h, followed by desulfonylation with aqueous 25% sodium sulfite solution to give the desired *anti*-1,2-amino alcohol **116** with high diastereoselectivity (*anti:syn* = 49:1, 98% ds) in 90% yield. Cross-metathesis of **116** with pentadec-1-en-3-one using Hoveyda 2nd Grubbs catalyst provided (*E*)-α,β-unsaturated ketone **117** which was then hydrogenated to afford **118** in 70% yield. Oxidation of **118** with $RuCl_3$ and $NaIO_4$ gave the intermediate carboxylic acid which on treatment with diazomethane furnished the desired methyl ester **119**. Removal of the Cbz group by palladium-catalyzed hydrogenolysis and simultaneous intramolecular cyclization afforded piperidine **120** in 83% yield. Finally, reduction of ester **120** with $LiAlH_4$ in THF and removal of the benzoate group using 8N KOH in MeOH furnished (+)-deoxoprosophylline **47**.

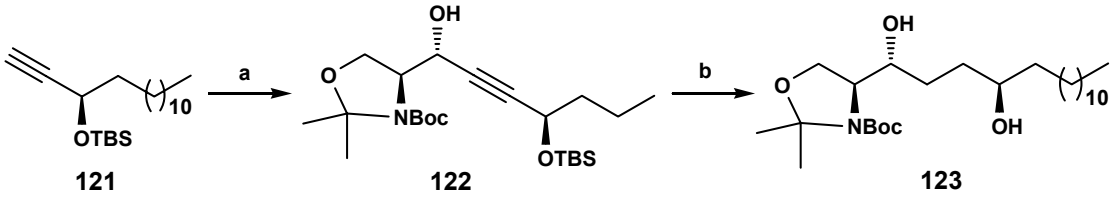


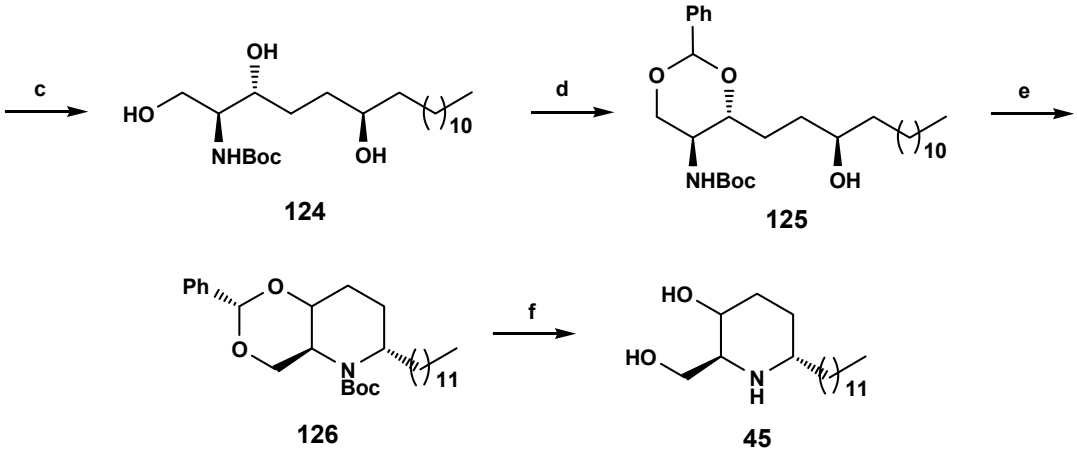


Scheme 16. *Reagents and conditions*: (a) ref. 20; (b) NaH, BnBr, THF/DMF (1:1), 11 h; (c) i) CSI, Na_2CO_3, toluene, -78 ^oC, 24 h; ii) 25% Na_2SO_3, 24 h; (d) Hoveyda 2nd Grubbs catalyst, toluene, 80 ^oC, 48 h; (e) PtO_2, H_2, EtOAc, 2 h; (f) i) cat. $RuCl_3$, $NaIO_4$, $H_2O/CH_3CN/EtOAc$ (2:1:1), 4 h; ii) CH_2N_2, Et_2O, 0 ^oC, 1 h; (g) 10% Pd/C, H_2, MeOH, 24 h; (h) (i) LAH, THF, 12 h; (ii) 8 N KOH, MeOH, reflux, 10 h.

Mori, K. *et al.* (2007)[17m]

Kenji Mori and co-workers reported (-)-deoxoprosopinine **45** and (-)-deoxoprosophylline **51** by intramolecular cyclization to generate a piperidine ring (Scheme 17). Coupling of (*S*)-Garner's aldehyde with (*R*)-3-*tert*-butyldimethylsilyl(TBS)oxy-1-pentadecyne **121** was executed as reported previously to give **122.**[21] After removal of the TBS protecting group of **122**, the resulting alkyne diol was hydrogenated over a palladium catalyst to give 6-hydroxylated dihydrosphingosine derivative **123**. Treatment of **123** with aqueous acetic acid afforded triol **124** which was protected as benzylidene acetal **125** and was mesylated to the precursor for cyclization to give crystalline **126.** Finally, removal of the benzylidene protective group with methanolic hydrogen chloride was followed by treatment with sodium hydroxide to give (-)-deoxoprosopinine **45**.





Scheme 17. *Reagents and conditions*: (a) ref. 21; (b) i) TBAF, THF, 99%; ii) H_2, $Pd(OH)_2/C$, EtOAc, 86%; (c) AcOH–H_2O (8:2), 94%; (d) $PhCH(OMe)_2$, PPTS, CH_2Cl_2, 89%; (e) i) MsCl, C_5H_5N, 0 ^oC; ii) NaH, THF, reflux, 89% (2 steps); (f) (i) HCl in MeOH; (ii) NaOH, H_2O, 72%.

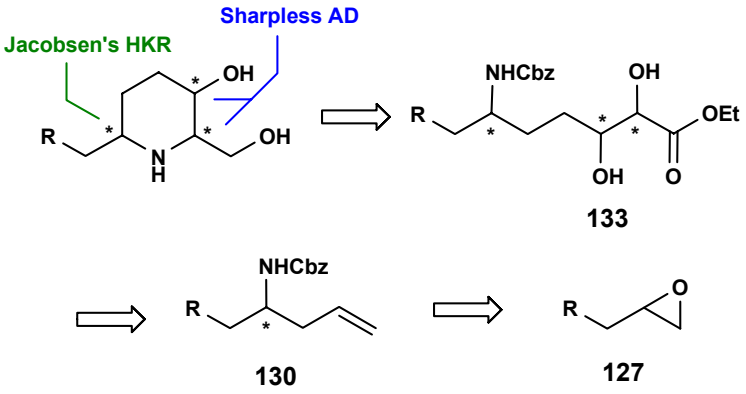
4.2.3. Present work:

Objective:

2,6-Disubstituted piperidin-3-ols alkaloids have attracted considerable interest as synthetic targets. Various syntheses of this class of compounds have been reported, the literature describing a general synthetic strategy to construct the 2,6-disubstituted piperidin-3-ols framework is rather scarce. Therefore, it is highly desirable to develop a general and enantiopure synthetic route that provides a common pivotal intermediate from which piperidin-3-ol derivatives with desired stereochemical variations can be synthesized. As part of our ongoing program towards asymmetric synthesis of biologically active natural products,[22] we became interested in developing a simple and flexible route to 2,6-disubstituted piperidin-3-ols. Here we present an enantioselective synthesis of (-)-deoxoprosopinine and (+)-deoxoprosophylline as a representative examples for a general synthetic strategy to all 2,6-disubstituted piperidin-3-ols.

Our synthetic approach for the synthesis of 2,6-disubstituted piperidin-3-ol framework was envisioned *via* the synthetic route as shown in Scheme 18. The amino-diol derivative **133** was visualized as a synthetic intermediate from which prosopinine, prosophylline and their deoxo analogues could be synthesized. The amino-diol **133** could be obtained from the

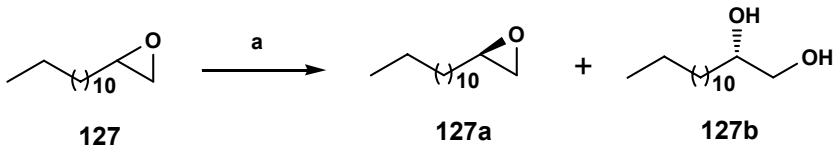
homoallylic amino derivative **130** by two carbon homologation and Sharpless asymmetric dihydroxylation which in turn could be easily synthesized from the enantiomerically pure terminal epoxide, prepared from racemic epoxide **127** by means of Jacobsen's HKR.



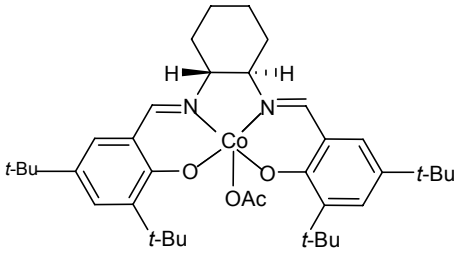
Scheme 18. Retrosynthetic analysis of 2,6-disubstituted piperidin-3-ol framework.

4.2.4. Results and Discussion:

The synthesis of (-)-deoxoprosopinine and (+)-deoxoprosophylline started from commercially available racemic 1,2-epoxytetradecane **127** which was subjected to Jacobsen's HKR using (*R*,*R*)-(salen)Co^{III}.OAc catalyst (Fig. 3) to give (*R*)-1,2-epoxytetradecane **127a** as a single enantiomer,[23] which was easily isolated from the more polar diol **127b** by distillation (Scheme 19).



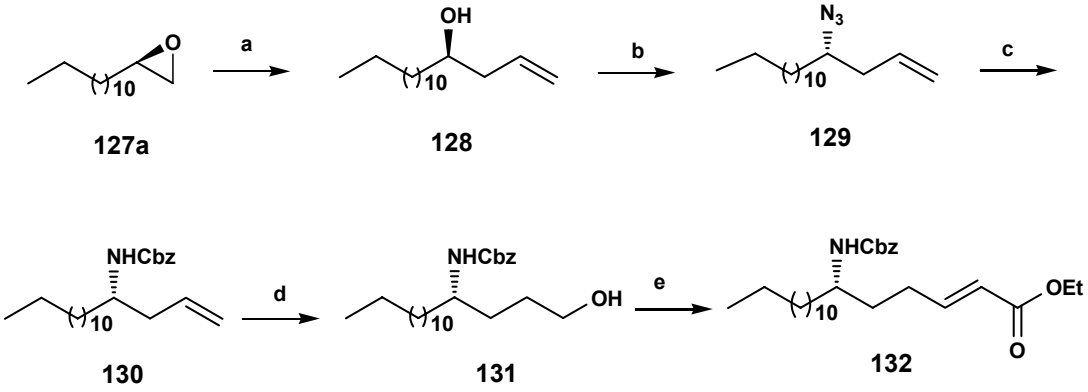
Scheme 19. *Reagents and conditions:* (a) (*R,R*)-Salen-Co^{III}.(OAc) (0.5 mol %), distd. H_2O (0.55 equiv), 0 ^oC, 24 h, (41% for **127a**, 43% for **127b**).



(*R*,*R*)-Salen Co^{III}. OAc Complex

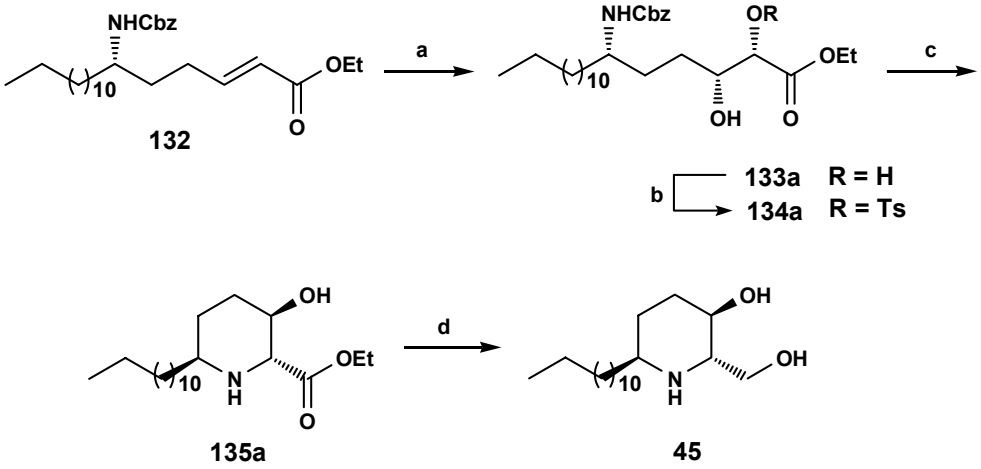
Figure 3.

With enantiomerically pure (*R*)-1,2-epoxytetradecane **127a** in hand, we then subjected it to copper-catalyzed (CuI) regioselective opening with vinylmagnesium bromide to give the homoallylic alcohol **128** in excellent yield. The IR spectrum of **128** gave broad hydroxyl absorption at 3454 cm^{-1}. The ^1H NMR spectrum of **128** gave olefin peaks at 5.10 (triplet, one proton), 5.14-5.20 (multiplet, one proton), 5.72-5.93 (multiplet, one proton). The free hydroxyl group of **128** was converted into *O*-mesylate, which on nucleophilic displacement with sodium azide in dry DMF afforded compound **129** in 93% yield. The IR spectrum of **129** showed strong azide absorption at 2102 cm^{-1}. The azide **129** was subjected to Staudinger reaction[24] and converted into amine which on Cbz protection with



Scheme 20. *Reagents and conditions:* (a) Vinylmagnesium bromide, CuI, THF, -78 ^oC, 12 h, 94%; (b) i) MsCl, Et_3N, dry CH_2Cl_2, 2 h; ii) NaN_3, dry DMF, 45 °C, 93%; (c) i) PPh_3, THF/H_2O (6:1), rt, 12 h; ii) benzyl chloroformate, Na_2CO_3, 1,4-dioxane/H_2O (1:1), 0 ^oC-rt, 90% (two step, one pot); (d) i) $BH_3.SMe_2$, THF, 0 °C - rt, 3 h; ii) 2NaOH, H_2O_2, 0 °C - rt, 6 h, 87%; (e) i) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, 30 min, Et_3N, -60 °C, 30 min. (ii) $Ph_3P{=}CHCO_2Et$, THF, rt., 24 h, 96%.

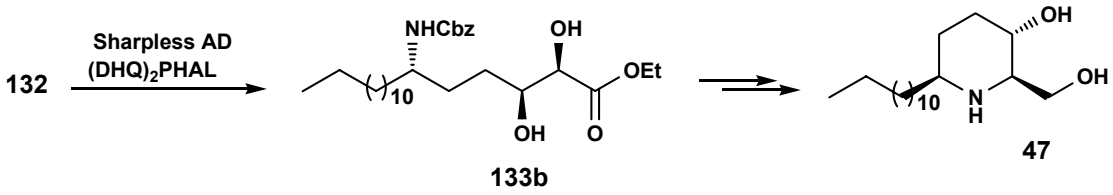
benzyl chloroformate led to **130** in 90% yield (two steps, one pot). The IR spectrum of **68** showed absence of azide absorption. The ^{1}H NMR spectrum of **130** gave benzylic five proton peaks at 7.24-7.47 as multiplet. The compound **130** was then subjected to hydroboration–oxidation reaction to afford the alcohol **131** in 87% yield. The IR spectrum of **131** gave broad hydroxyl absorption at 3318 cm^{-1}. With substantial amount of **131** in hand, our next aim was to carry out the two-carbon homologation by means of Wittig reaction in order to generate the *trans*-olefin required for AD reaction. To this end, compound **131** was oxidised to the aldehyde under Swern conditions,[13] followed by subsequent treatment with (ethoxycarbonylmethylene) triphenylphosphorane in dry THF at room temperature to furnish the *trans*-Wittig product **132** in excellent yield (Scheme 20). The IR spectrum of **132** showed the ester carbonyl absorption at 1717 cm^{-1} and olefin C=C stretching at 1685 cm^{-1}. The ^{1}H NMR spectrum gave olefin protons at δ 5.82 (doublet) with the coupling constant J = 15.62 Hz and δ 6.88 (multiplet) indicating the *trans*-olefin. The dihydroxylation of olefin **132** with osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of $(DHQD)_2PHAL$ under the Sharpless asymmetric conditions[25] gave the diol **133a** in 97% yield as a single diastereoisomer. The diastereoselectivity was determined from ^{1}H and ^{13}C NMR spectral data. The IR spectrum of **133a** showed hydroxyl absorption at 3434 cm^{-1} and ester carbonyl at 1719 cm^{-1}. The ^{1}H NMR indicated absence of olefin protons. The chiral carbons appeared at δ 72.3 and 73.4 in the ^{13}C NMR spectrum. Regioselective monotosylation[26] of this diol with tosyl chloride (TsCl) resulted in the α-tosylate **134a** in excellent yield**.** Concomitant deprotection of Cbz



Scheme 21. *Reagents and conditions:* (a) $(DHQD)_2PHAL$, OsO_4 (0.4 mol%), K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, *t*-BuOH/H_2O, 1:1, 0 °C, 24 h, 97%; (b) TsCl, Et_3N, CH_2Cl_2, 5 °C, 72 h, 88%; (c) 20% $Pd(OH)_2/C$, H_2, EtOAc, rt., 12 h, 97%; (d) $LiAlH_4$, THF, 0 °C - rt, 2 h, 86%.

and nucleophilic displacement of α-tosylate on hydrogenation with $Pd(OH)_2$ led to the cyclized product **135a** in 97% yield. Finally, reduction of **135a** with $LiAlH_4$ produced (-)-deoxoprosopinine **45** in excellent yield (Scheme 21).

In a similar way, as illustrated in Scheme 22, (+)-deoxoprosophylline **47** was synthesized using $(DHQ)_2PHAL$ in the Sharpless asymmetric dihydroxylation step and following series of reactions analogous to those shown in Scheme 21.



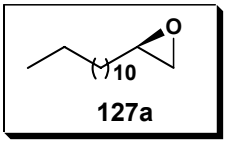
Scheme 22. Synthesis of **(**+)-deoxoprosophylline **47.**

4.2.5. Conclusion

In conclusion, a simple, flexible and highly efficient route to 2,6-disubstituted piperidin-3-ol has been developed employing Jacobsen's HKR and Sharpless asymmetric dihydroxylation as the key steps. Its usage is illustrated by the total synthesis of (-)-deoxoprosopinine and (+)-deoxoprosophylline. The merits of this synthesis are high enantio- and diastereoselectivity with high yielding reaction steps. The synthetic strategy described has significant potential for stereochemical variations at C-2, C-3 and C-6 positions and further extension to other stereoisomers, and analogues.

4.2.6. Experimental Section

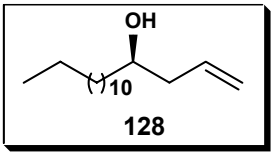
(*R*)-1,2-Epoxytetradecane (127a)



127a

The racemic 1,2-epoxytetradecane **127** was resolved with Jacobsen's HKR catalyst (*R*,*R*)-(salen)Co^{III}.OAc to give (*R*)-1,2-epoxytetradecane **127a** in high enantiomeric excess (>99%), which was easily isolated from the more polar diol **127b** by distillation, following a literature procedure.[23a] $[\alpha]_D^{25}$ + 7.29 (neat) ; {lit.[23a] $[\alpha]_D^{23}$ + 7.30 (neat)}.

(*R*)-Hexadec-1-en-4-ol (128)



128

Vinylmagnesium bromide (4.64 g, 35.32 mmol, 35.32 mL, 1 M solution in THF) was added dropwise to a stirred solution of **127a (**5.00 g, 23.54 mmol) and CuI (897 mg, 4.71 mmol) in dry THF (50 mL) over 40 min at –78 °C and stirred for 12 h. The mixture was warmed to 0 °C, before it was quenched with a saturated NH_4Cl solution (30 mL). The layers were separated, the aqueous layer extracted with Et_2O (3 x 40 mL), the combined ethereal extracts were washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification by silica gel column chromatography (R_f = 0.40, EtOAc/petroleum ether, 1:25) of the crude product gave **128** as a white solid.

Yield: 5.32 g, 94%

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

M. P.: 64 ^oC

$[\alpha]_D^{25}$: + 1.66 (*c* 0.76, $CHCl_3$)

IR (neat, cm^{-1}): ν_{max} 3454, 3019, 2928, 1640, 1466, 1215

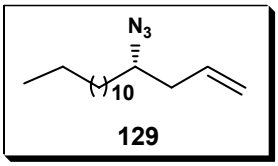
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.83 Hz, 3H), 1.23-1.59 (m, 23H), 2.30 (t, *J* = 7.07 Hz, 2H), 3.27-3.47 (m, 1H), 5.10 (t, *J* = 1.25 Hz, 1H), 5.14-5.20 (m, 1H), 5.72-5.93 (m, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 22.7, 25.6, 29.3, 29.5, 29.6, 31.9, 36.8, 41.9, 70.7, 118.0, 134.9 ppm.

MS (ESI) *m*/*z*: 241 $[M + H]^+$

Analysis Calcd.: C, 79.93; H, 13.42%; **Found:** C, 79.88; H, 13.40%.

(*S*)-4-Azidohexadec-1-ene (129)



129

To an ice-cold stirred solution of **128** (4.5 g, 18.72 mmol) and triethylamine (2.08 mL, 2.87 mL, 20.59 mmol) in anhydrous CH_2Cl_2 (75 mL) was added dropwise methanesulfonyl chloride (2.35 g, 1.59 mL, 20.59 mmol) over 15 min. The resulting mixture was allowed to warm up to room temperature and stirred for 2 h. After diluting with 100 mL CH_2Cl_2, the solution was washed with water (3 x 50 mL), brine, dried over Na_2SO_4 and concentrated to give the crude mesylated product. This was used for the next step without further purification.

To a solution of above mesylated product of **128** in dry DMF (40 mL) was added portion wise NaN_3 (2.43 g, 37.42 mmol) and the resulting suspension was stirred for 24 h at 45 °C. After cooling the orange solution to room temperature, Et_2O (50 mL) and H_2O (50 mL) were added and the aqueous layer was extracted with Et_2O (3 x 40 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. Silica gel column chromatography purification (R_f = 0.30, petroleum ether) of the crude product gave azide **129** as a yellowish liquid.

Yield: 4.62 g, 93%

Mol. Formula: $C_{16}H_{31}N_3$

$[\alpha]_D^{25}$: -16.06 (*c* 1.00, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} , 2855, 2103, 1643, 1466, 1215

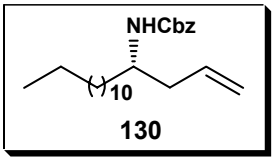
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, *J* = 5.91 Hz, 3H), 1.27-1.58 (m, 22H), 2.31 (t, *J* = 6.71 Hz, 2H), 3.24-3.39 (m, 1H), 5.11 (t, *J* = 1.24 Hz, 1H), 5.14-5.20 (m, 1H), 5.72-5.93 (m, 1H) ppm**.**

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 22.7, 26.0, 29.3, 29.5, 29.7, 31.9, 33.9, 38.8, 62.3, 117.9, 134.0 ppm.

MS (ESI) *m*/*z*: 266 $[M + H]^+$

Analysis Calcd.: C, 72.40; H, 11.77; N, 15.83%; **Found:** C, 72.43; H, 11.68; N, 15.88%.

(*S*)-Benzyl hexadec-1-en-4-ylcarbamate (130)



130

To a solution of azide **129** (4.50 g, 16.95 mmol) in THF (30 ml)/ water (4.5 ml) was added PPh_3 (5.34 g, 20.34 mmol) and mixture was stirred at room temperature for 12 h. The mixture was concentrated and then 1,4-dioxane (25 mL)/ water (25 mL) and Na_2CO_3 (2.72 g, 25.69 mmol) were added and stirred for another 10 min. at 0 ^oC. To this ice cold solution, benzyl chloroformate (3.21 g, 2.69 mL, 18.84 mmol) was added and mixture stirred overnight at 0 ^oC to room temperature. The solvent was evaporated at reduced pressure and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine, water, dried (Na_2SO_4) and concentrated. Silica gel column chromatography purification (R_f = 0.40, EtOAc/petroleum ether, 1:9) of the crude product gave compound **130** as a white solid.

Yield: 5.70 g, 90%

Mol. Formula: $C_{24}H_{39}NO_2$

M. P.: 106 ^oC

$[\alpha]_D^{25}$: -15.91 (*c* 1.00, $CHCl_3$)

IR (neat, cm^{-1}): ν_{max} 3438, 3019, 2928, 1716, 1510, 1215

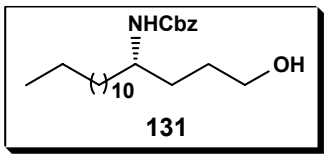
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.05 Hz, 3H), 1.18-1.71 (m, 22H), 2.11-2.35 (m, 2H), 3.56-3.80 (m, 1H), 4.38-4.72 (m, 1H), 5.04-5.10 (m, 4H), 5.67-5.88 (m, 1H), 7.24-7.47 (m, 5H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 22.6, 25.8, 29.3, 29.4, 29.6, 31.9, 34.5, 39.4, 50.6, 66.4, 117.7, 127.9, 128.4, 134.2, 136.6, 155.9 ppm.

MS (ESI) *m*/*z*: 392 $[M + NH_4]^+$

Analysis Calcd.: C, 77.16; H, 10.52; N, 3.75%; **Found:** C, 77.20; H, 10.55; N, 3.80%.

(*S*)-Benzyl 1-hydroxyhexadecan-4-ylcarbamate (131)



131

To a solution of **130** (3.25 g, 8.70 mmol) in dry THF (40 mL) at 0 °C under argon atmosphere was added BH_3.DMS (0.73 g, 0.88 mL, 9.57 mmol, 2 M solution in THF) and the reaction mixture was allowed to warm to room temperature and stirred for 3 h. The reaction flask was cooled to 0 °C and then a solution of NaOH (696 mg, 17.4 mmol) in EtOH/H_2O (2:1, 15 mL), followed by H_2O_2 (2.96 mL, 26.10 mmol, 30% w/v solution in water) were added drop wise over 15 min. It was then allowed to stir at room temperature for 6 h. The product was taken up in EtOAc and the aqueous layer extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine, water, dried (Na_2SO_4) and concentrated. Silica gel column chromatography purification (R_f = 0.30, EtOAc/petroleum ether, 4:6) of the crude product gave alcohol **131** as a white solid.

Yield: 2.96 g, 87%

Mol. Formula: $C_{24}H_{41}NO_3$

M. P.: 111-112 ^oC

$[\alpha]_D^{25}$: –6.87 (*c* 1.00, $CHCl_3$)

IR (neat, cm^{-1}): ν_{max} 3318, 3019, 2922, 1685, 1540, 1463, 1377

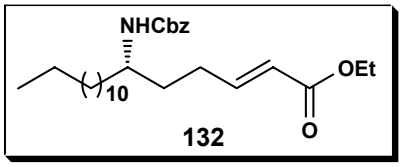
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.79 Hz, 3H), 1.16-1.64 (m, 27H), 1.74 (brs, 1H), 3.67 (t, *J* = 6.08 Hz, 3H), 5.10 (s, 2H), 7.33-7.38 (m, 5H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 22.6, 25.8, 28.8, 29.3, 29.6, 31.8, 35.5, 51.1, 62.4, 66.5, 127.9, 128.4, 136.6, 156.3 ppm.

MS (ESI) *m*/*z*: 392 $[M + H]^+$

Analysis Calcd.: C, 73.61; H, 10.55; N, 3.58%; **Found:** C, 73.65; H, 10.50; N, 3.60%.

(*S*,*E*)-Ethyl 6-(benzyloxycarbonylamino)octadec-2-enoate (132)



132

To a solution of oxalyl chloride (1.12 g, 0.78 mL, 8.82 mmol) in dry CH_2Cl_2 (20 mL) at - 78 °C was added dropwise DMSO (1.42 g, 1.29 mL, 18.22 mmol) in CH_2Cl_2 (5 mL) over 15 min. The reaction mixture was stirred for 30 min and a solution of **131** (2.3 g, 5.88 mmol) in CH_2Cl_2 (15 mL) was added dropwise over 15 min. The reaction mixture was stirred for 30 min at - 78 °C and 30 min at - 60 °C and then Et_3N (2.61 g, 3.61 mL, 25.86 mmol) in CH_2Cl_2 (5 mL) was added dropwise and stirred for 1 h. The reaction mixture was poured into saturated solution of $NaHCO_3$ (50 mL) and the organic layer separated. The aqueous layer was extracted with ether (3 x 20 mL) and the combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated to give the crude aldehyde. This was used for the next step without further purification.

To a solution of (ethoxycarbonylmethylene)triphenyl phosphorane (2.25 g, 6.47 mmol) in dry THF (20 mL) was added a solution of the above aldehyde in dry THF (5 mL). The reaction mixture was stirred at room temperature for 24 h. It was then concentrated and purified by silica gel column chromatography (R_f = 0.40, EtOAc/petroleum ether, 1:9) to give olefin **132** as a white solid.

Yield: 2.59 g, 96%

Mol. Formula: $C_{28}H_{45}NO_4$

M. P.: 116 ^oC

$[\alpha]_D^{25}$: + 3.27 (*c* 0.50, $CHCl_3$)

IR (neat, cm^{-1}): ν_{max} 3311, 2923, 2853, 1717, 1682, 1543, 1464, 1263

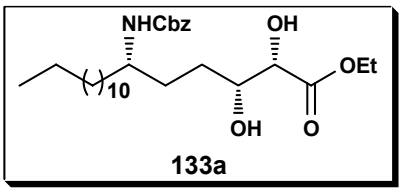
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.83 Hz, 3H), 1.26-1.68 (m, 27H), 2.26 (q, *J* = 7.09 Hz, 15.12 Hz, 2H), 3.57-3.72 (m, 1H), 4.19 (q, *J* = 7.10 Hz, 14.60 Hz, 2H), 4.48 (d, *J* = 9.13 Hz, 1H), 5.10 (s, 2H), 5.82 (d, *J* = 15.62 Hz, 1H), 6.88-6.99 (m, 1H) 7.31-7.38 (m, 5H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 14.1, 22.6, 25.7, 28.6, 29.2, 29.5, 31.8, 33.8, 35.3, 51.0, 60.0, 66.4, 121.4, 127.9, 128.4, 136.5, 148.3, 156.0, 166.4 ppm.

MS (ESI) *m*/*z*: 460 $[M + H]^+$

Analysis Calcd.: C, 73.16; H, 9.87; N, 3.05 %; **Found:** C, 73.20; H, 9.81; N, 3.10%

(2*R*,3*S*,6*S*)-Ethyl 6-(benzyloxycarbonylamino)-2,3-dihydroxyoctadecanoate (133a)



133a

To a mixture of $K_3Fe(CN)_6$ (2.15 g, 6.53 mmol), K_2CO_3 (902 mg, 6.53 mmol), $(DHQD)_2PHAL$ (17 mg, 1 mol%) in *t*-BuOH/H_2O (1:1, 20 mL) at 0 °C was added osmium tetroxide (0.09 mL, 0.1 M solution in toluene, 0.4 mol%), followed by methanesulfonamide (207 mg, 2.18 mmol). After stirring for 5 min at 0 °C, the olefin **132** (1.0 g, 2.18 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 24 h and then quenched with solid sodium sulfite (2.0 g). The stirring was continued for additional 15 min and then the solution was extracted with EtOAc (3 x 20 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated. Silica gel column chromatography purification (R_f = 0.50, EtOAc/petroleum ether, 6:4) of the crude product gave **133a** as a white crystal solid (single diastereomer).

Yield: 1.04 g, 97%

Mol. Formula: $C_{28}H_{47}NO_6$

M. P.: 137 ^oC

$[\alpha]_D^{25}$: +6.90 (*c* 1.00, $CHCl_3$)

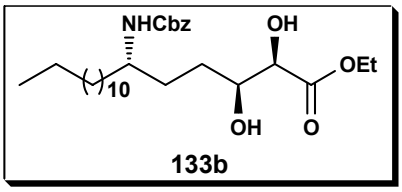
IR (neat, cm^{-1}): ν_{max} 3434, 3018, 2927, 1719, 1508, 1216

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, *J* = 5.95 Hz, 3H), 1.26-1.70 (m, 29H), 2.27 (brs, 2H), 3.62-3.71 (m, 1H), 3.91 (d, *J* = 6.45 Hz, 1H), 4.06 (d, *J* = 1.61 Hz, 1H), 4.29 (q, *J* = 6.72 Hz, 13.70 Hz, 2H), 4.55 (d, *J* = 8.87 Hz, 1H), 5.10 (s, 2H), 7.32-7.38 (m, 5H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 22.6, 25.8, 29.2, 29.6, 29.8, 31.4, 31.8, 35.5, 51.1, 61.8, 66.4, 72.3, 73.4, 127.9, 128.4, 136.5, 156.2, 173.4 ppm.

MS (ESI) *m*/*z*: 516 $[M + Na]^+$

Analysis Calcd.: C, 68.12; H, 9.60; N, 2.84 %; **Found:** C, 68.17; H, 9.58; N, 2.80%



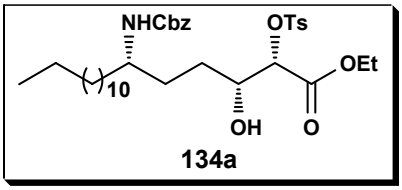
133b

133b $[\alpha]_D^{25}$: –3.53 (*c* 1.00, $CHCl_3$)

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.62 Hz, 3H), 1.26-1.77 (m, 29 H), 2.42 (brs, 2H), 3.59-3.79 (m, 1H), 3.85-3.91 (m, 1H), 4.05 (d, *J* = 2.25 Hz, 1H), 4.29 (q, *J* = 7.03 Hz, 14.33 Hz, 2H), 4.60 (d, *J* = 8.15 Hz, 1H), 5.10 (s, 2H), 7.31-7.41 (m, 5H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 22.5, 25.8, 29.2, 29.5, 31.8, 35.4, 51.2, 61.7, 66.5, 72.7, 73.4, 127.9, 128.3, 136.5, 156.4, 173.3 ppm.

(2*R*,3*S*,6*S*)-Ethyl 6-(benzyloxycarbonylamino)-3-hydroxy-2-(tosyloxy)octadecanoate (134a)



134a

To a one-neck round-bottomed flask were added the diol ester **133a** (580 mg, 1.18 mmol), dry CH_2Cl_2 (10 mL) and Et_3N (178 mg, 0.25 mL, 1.76 mmol). The flask was placed in an ice water bath and allowed to equilibrate for 10-30 min, at which time the *p*-toluene sulfonyl chloride (224 mg, 1.18 mmol) was added in one portion using a solid addition funnel. The flask was fitted with a serum cap and placed in a refrigerator (5 ^oC) for 72 h. The mixture was then concentrated to afford a paste, which was dissolved in Et_2O. The organic phase was washed three times with a 1 N aqueous HCl solution, once with a saturated aqueous $NaHCO_3$ solution, and once with brine, dried over Na_2SO_4, and concentrated to afford the crude product mixture, which was purified by flash column chromatography (R_f = 0.45, EtOAc/petroleum ether, 4:6) to give **134a** as a thick viscous liquid.

Yield: 670 mg, 88%

Mol. Formula: $C_{35}H_{53}NO_8S$

$[\alpha]_D^{25}$: -8.10 (*c* 1.00, $CHCl_3$)

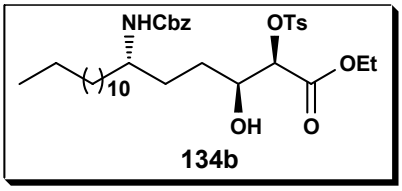
IR (neat, cm^{-1}): ν_{max} 3433, 2927, 1718, 1508, 1215

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 5.88 Hz, 3H), 1.19 (t, *J* = 6.63 Hz, 3H), 1.23-1.63 (m, 25H), 1.85 (brs, 1H), 2.44 (s, 3H), 3.50-3.61 (m, 1H), 3.95-4.07 (m, 1H), 4.12 (q, *J* = 7.21 Hz, 14.17 Hz, 2H), 4.48 (d, *J* = 9.34 Hz, 1H), 4.79 (d, *J* = 3.36 Hz, 1H), 5.10 (s, 2H), 7.31-7.37 (m, 7H), 7.82 (d, *J* = 8.40 Hz, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.8, 14.1, 21.6, 22.6, 25.8, 28.7, 29.0, 29.3, 29.6, 30.9, 31.8, 35.4, 50.8, 60.4, 62.0, 65.5, 71.3, 79.9, 128.0, 128.4, 129.7, 132.9, 136.6, 145.2, 156.2, 167.2 ppm.

MS (ESI) *m*/*z*: 670 $[M + Na]^+$

Analysis Calcd.: C, 64.89; H, 8.25; N, 2.16%; **Found:** C, 64.83; H, 8.29; N, 2.13%



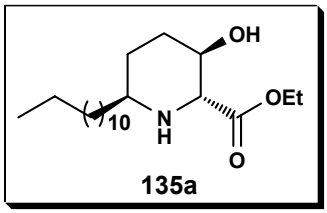
134b

134b $[\alpha]_D^{25}$: +7.12 (*c* 1.00, $CHCl_3$)

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.68 Hz, 3H), 1.16-1.77 (m, 29H), 2.05 (brs, 1H), 2.43 (s, 3H), 3.54-3.70 (m, 1H), 4.00-4.07 (m, 1H), 4.13 (tq, *J* = 1.23 Hz, 6.98 Hz, 14.39 Hz, 2H), 4.60 (d, *J* = 9.29 Hz, 1H), 4.85 (d, *J* = 2.84 Hz, 1H), 5.10 (s, 2H), 7.29-7.56 (m, 7H), 7.84 (d, *J* = 8.72 Hz, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.8, 14.0, 21.6, 22.6, 25.8, 28.7, 29.3, 29.5, 29.6, 31.8, 35.6, 51.0, 60.3, 61.9, 66.6, 71.9, 79.6, 127.9, 128.1, 128.4, 129.7, 132.9, 136.5, 145.1, 156.5, 167.2 ppm.

(2S,3S,6S)-Ethyl 6-dodecyl-3-hydroxypiperidine-2-carboxylate (135a)



135a

A solution of **134a** (620 mg, 2.54 mmol) in EtOAc (15 mL) in the presence of 20% $Pd(OH)_2$ at room temperature was subjected to hydrogenation at atmospheric pressure for

12 h. The catalyst was removed by filtration through Celite, and the solvent was evaporated to dryness. The residue was purified by flash column chromatography on silica gel (R_f = 0.40, MeOH/ CH_2Cl_2, 1:9) to give compound **135a**.

Yield: 313 mg, 97%

Mol. Formula: $C_{20}H_{39}NO_3$

M. P.: 96 ^oC

$[\alpha]_D^{25}$: +5.65 (*c* 0.60, $CHCl_3$)

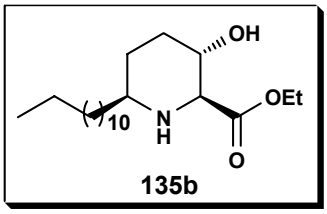
IR (neat, cm^{-1}): ν_{max} 3583, 3436, 3019, 2928, 1725, 1519, 1455, 1215

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.07 Hz, 3H), 1.26-1.79 (m, 30H), 2.11 (brs, 1H), 2.65-2.74 (m, 1H), 3.58 (d, *J* = 4.06 Hz, 1H), 4.11-4.17 (m, 1H) 4.21 (q, *J* = 7.12 Hz, 13.86 Hz, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 14.2, 22.6, 26.1, 28.0, 29.3, 29.5, 29.6, 31.8, 35.8, 51.6, 60.8, 61.5, 65.5, 172.2 ppm.

MS (ESI) *m/z*: 342 $[M + H]^+$

Analysis Calcd.: C, 70.33; H, 11.51; N, 4.10%; **Found:** C, 70.35; H, 11.48; N, 4.12 %



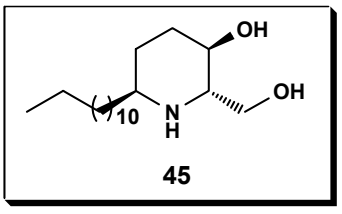
135b

135b $[\alpha]_D^{25}$: +2.47 (*c* 0.60, $CHCl_3$)

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.52 Hz, 3H), 1.11-1.43 (m, 27H), 1.70-1.78 (qd, *J* = 3.27 Hz, 12.79 Hz, 1H), 2.07-2.16 (m, 2H), 2.45-2.70 (m, 2H), 3.17 (d, *J* = 9.36 Hz, 1H), 3.59-3.73 (m, 1H), 4.26 (dq, *J* = 3.38 Hz, 7.19 Hz, 14.18 Hz, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 22.5, 26.0, 29.2, 29.5, 29.6, 30.6, 31.8, 32.3, 36.3, 56.0, 61.3, 64.6, 69.2, 172.6 ppm.

(2*S*,3*R*,6*S*)-6-Dodecyl-2-(hydroxymethyl)piperidin-3-ol: (-)-Deoxoprosopinine (45)



45

A suspension of $LiAlH_4$ (42 mg, 1.10 mmol) in anhydrous THF (10 mL) was stirred for 5 min at 0 °C, and a solution of **135a** (250 mg, 0.73 mmol) in THF (5 mL) was then added dropwise. The mixture was stirred for 1 h at 0 °C and for 1 h at room temperature. Excess $LiAlH_4$ was destroyed by slow addition of 10% aq NaOH (0.5 mL) and EtOAc (5 mL). The white precipitate was filtered through a pad of neutral alumina and washed with MeOH (3 x 15 mL). The filtrate was concentrated and the residue was purified by silica gel column chromatography (R_f = 0.30, MeOH/CH_2Cl_2, 2:8) to give **45** as a colourless solid.

Yield: 190 mg, 86%

M. P.: 90 °C, [Lit.[16a] 89.5-90 °C]

$[\alpha]_D^{25}$: -15. 81 (*c* 0.30, $CHCl_3$), [Lit[16a] $[\alpha]_D^{25}$ -14.7 (*c* 0.30, $CHCl_3$)

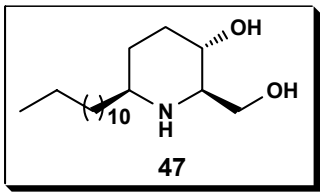
IR (neat, cm^{-1}): ν_{max} 3267, 2922, 2852, 1639, 1465, 1376

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 5.80 Hz, 3H), 1.26-1.77 (m, 24H), 2.66 (brs, 3 H), 2.74-2.83 (m, 1H), 2.86 (q, *J* = 5.59 Hz, 12.73 Hz, 1H), 3.51-3.61 (m, 1H), 3.66 (dd, *J* = 3.66 Hz, 7.12 Hz, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 22.6, 26.1, 29.3, 29.6, 29.7, 30.0, 31.9, 33.3, 35.5, 36.4, 62.2, 63.4, 68.2 ppm.

MS (ESI) *m/z*: 300 $[M + H]^+$

(2*R*,3*S*,6*S*)-6-Dodecyl-2-(hydroxymethyl)piperidin-3-ol: (+)-Deoxosoprosophylline (4)



47

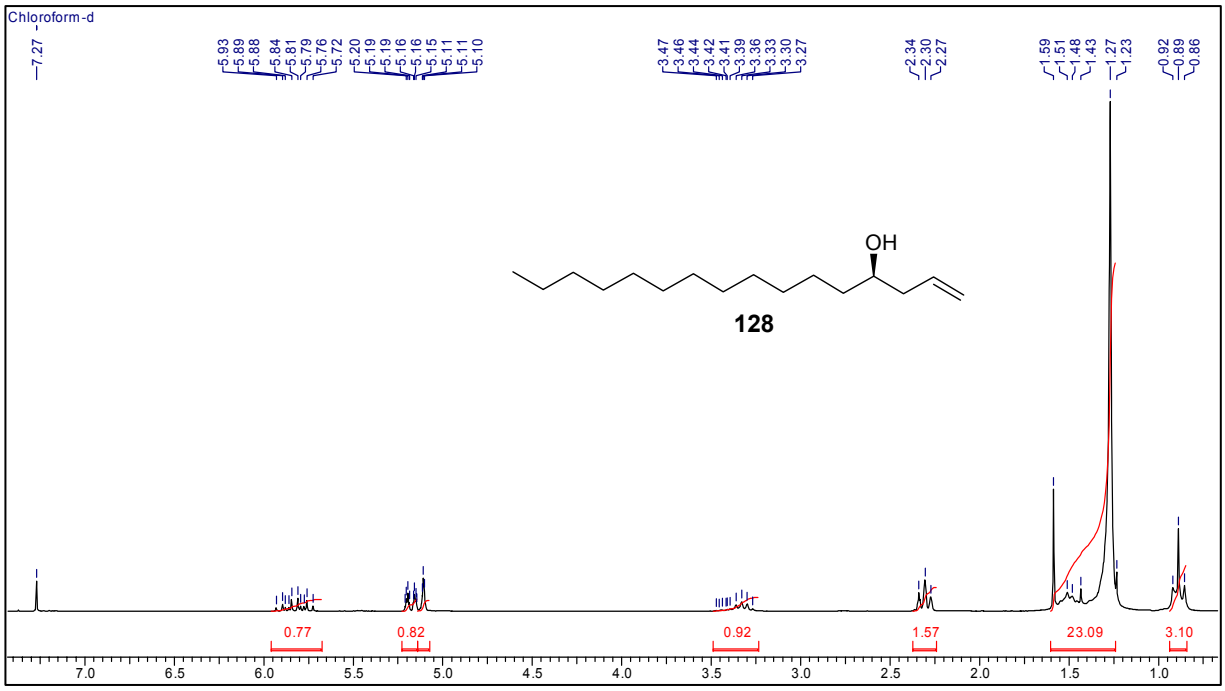
$[\alpha]_D^{25}$: $[\alpha]_D^{25}$ +13.86 (*c* 0.22, $CHCl_3$) [Lit[17g,h] $[\alpha]_D^{24}$ +12.50 (*c* 0.22, $CHCl_3$).]

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.65 Hz, 3H), 1.26-1.51 (m, 24H), 1.81 (dd, *J* = 2.65 Hz, 12.66 Hz, 1H), 1.96-2.15 (m, 2H), 2.53-2.66 (m, 2H), 3.33 (brs, 3H), 3.57 (dt, *J* = 4.36 Hz, 9.97 Hz, 1H), 3.84 (dt, *J* = 4.66 Hz, 12.58 Hz, 2H) ppm.

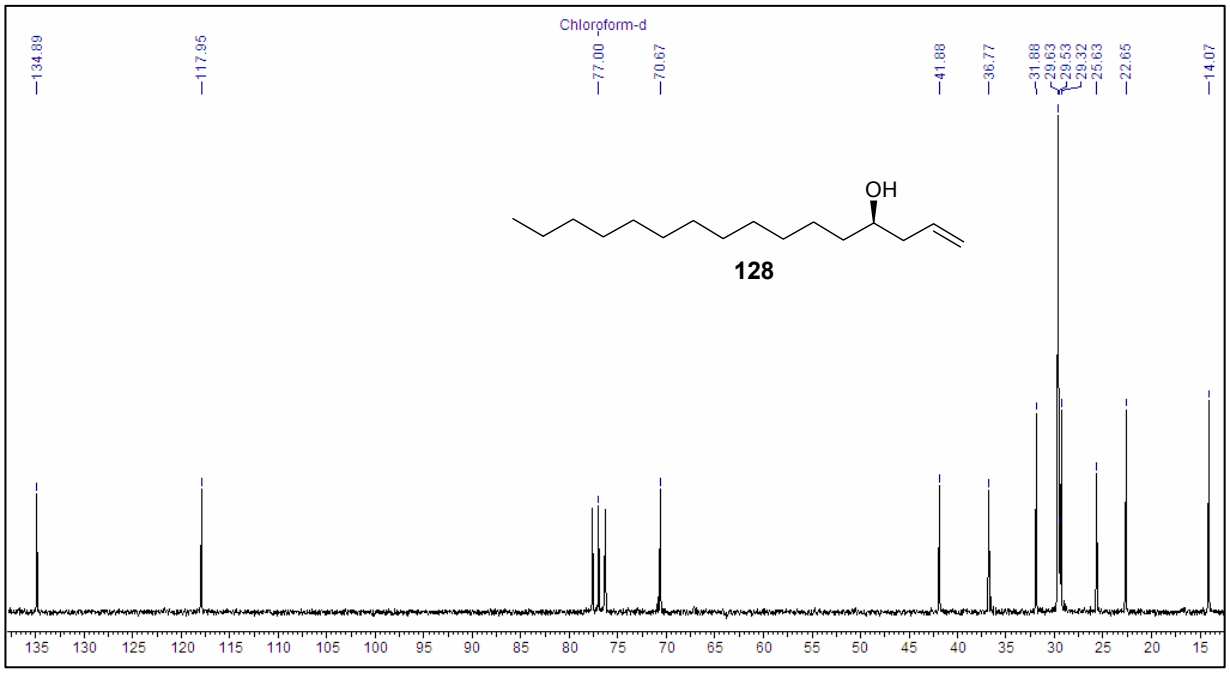
^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 22.6, 26.1, 29.3, 29.6, 29.7, 30.0, 31.9, 33.3, 35.5, 36.4, 62.2, 63.4, 68.2 ppm.

4.2.7 Spectra

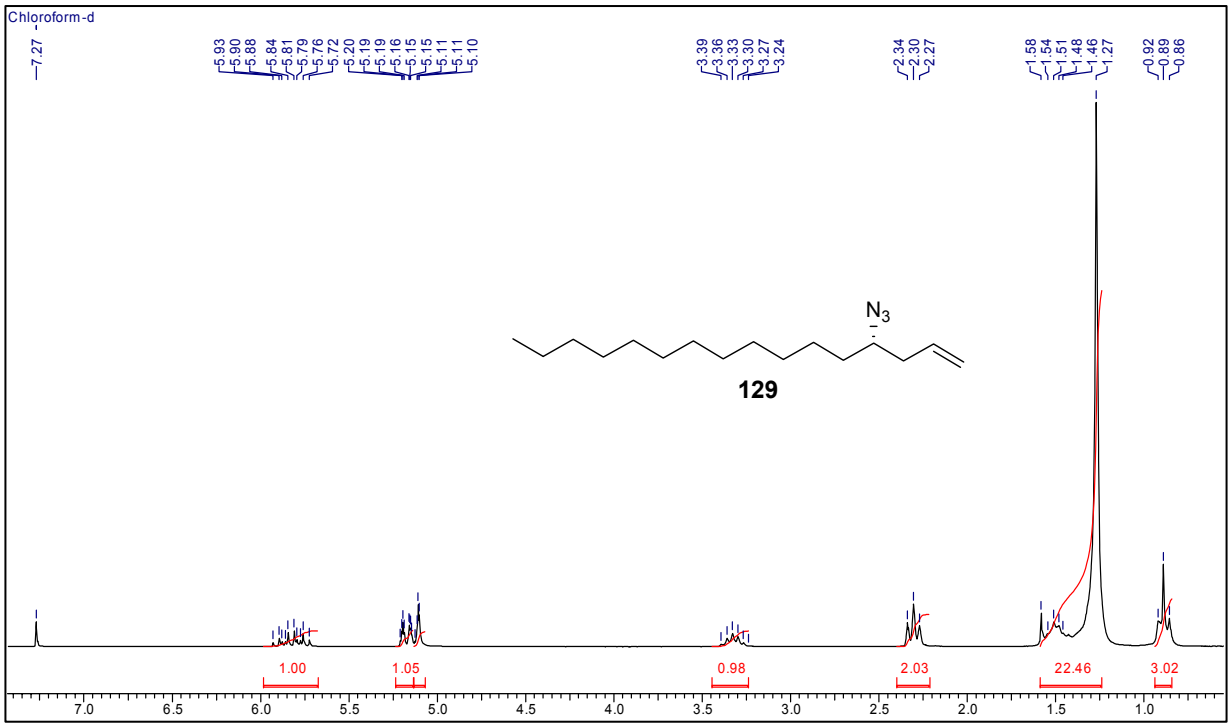
1. ^{1}H and ^{13}C NMR spectra of **128**
2. ^{1}H and ^{13}C NMR spectra of **129**
3. ^{1}H and ^{13}C NMR spectra of **130**
4. ^{1}H and ^{13}C NMR spectra of **131**
5. ^{1}H and ^{13}C NMR spectra of **132**
6. ^{1}H and ^{13}C NMR spectra of **133a**
7. ^{1}H and ^{13}C NMR spectra of **134a**
8. ^{1}H and ^{13}C NMR spectra of **135a**
9. ^{1}H and ^{13}C NMR spectra of **45**
10. ^{1}H and ^{13}C NMR spectra of **133b**
11. ^{1}H and ^{13}C NMR spectra of **134b**
12. ^{1}H and ^{13}C NMR spectra of **135b**
13. ^{1}H and ^{13}C NMR spectra of **47**



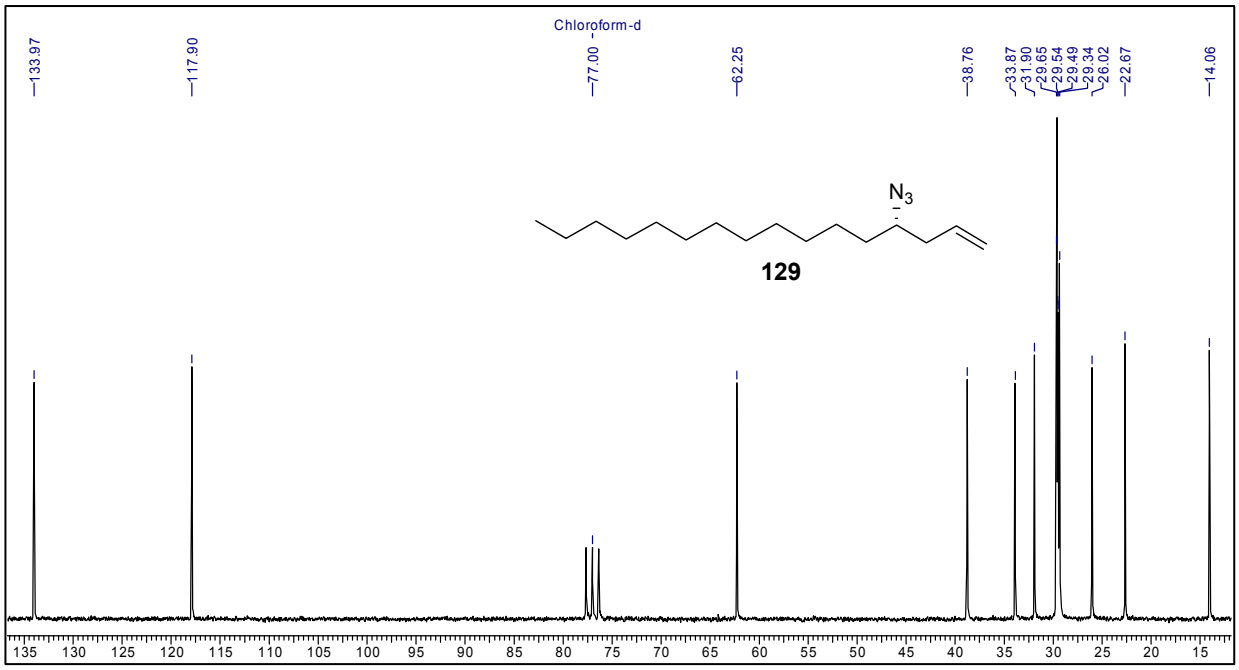
☞ ^{1}H NMR of the compound 128 in $CDCl_3$



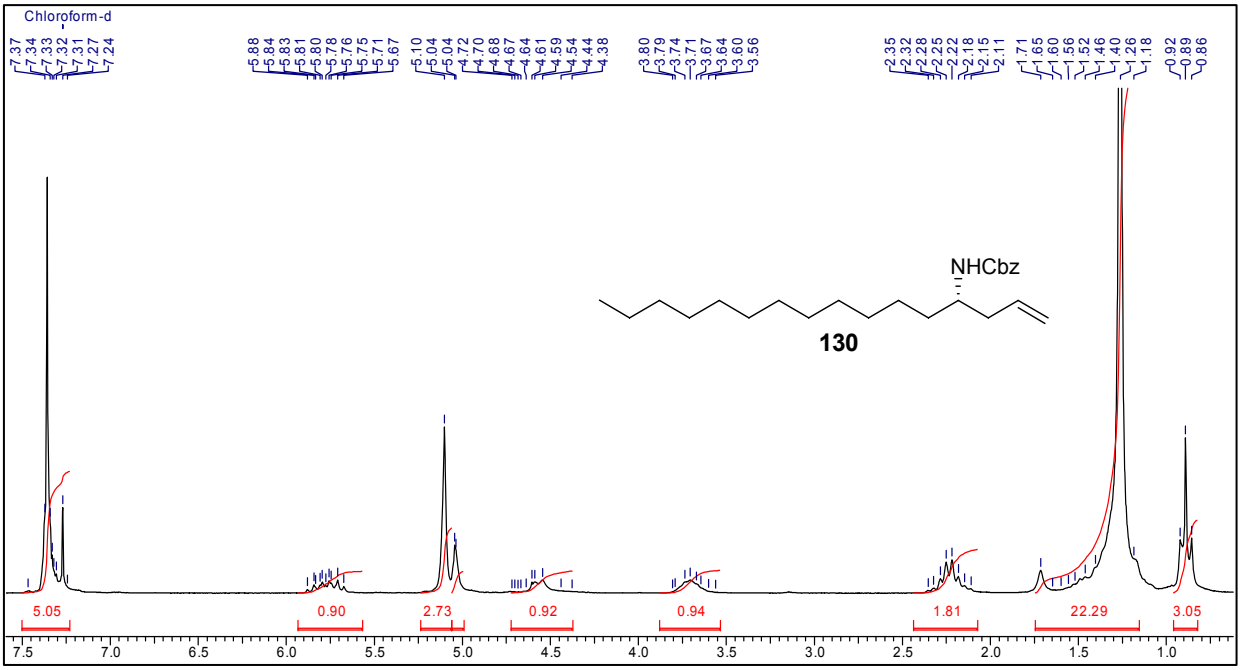
☞ ^{13}C NMR of the compound 128 in $CDCl_3$



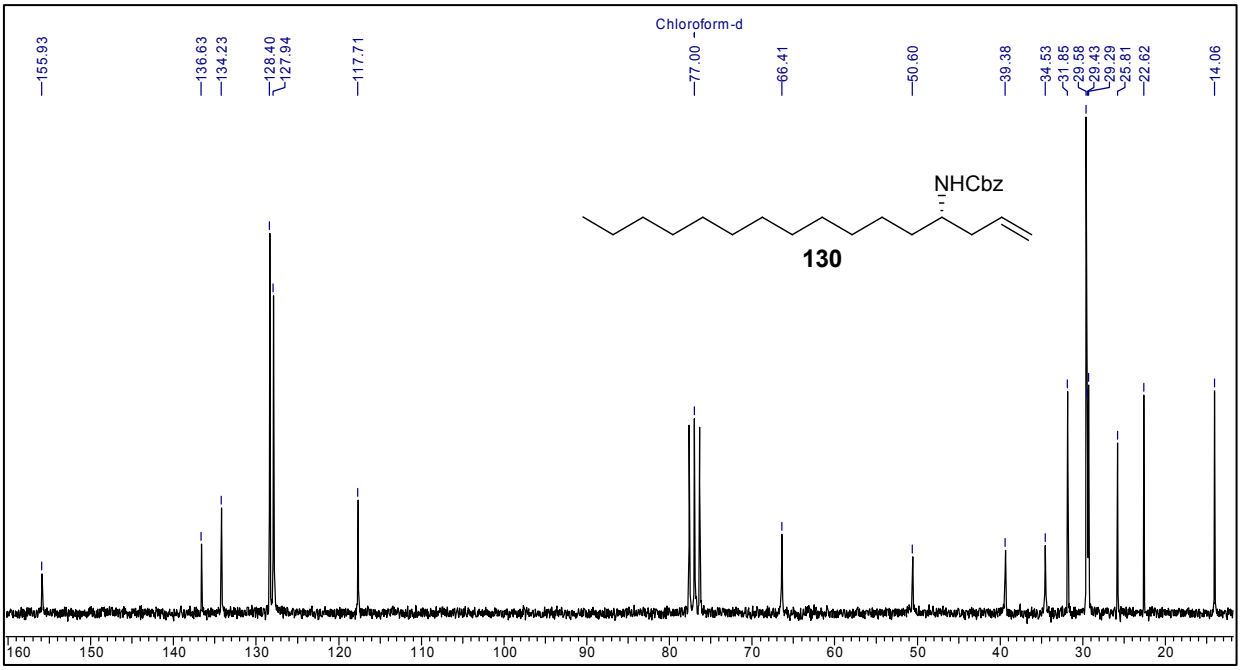
☞ ^{1}H NMR of the compound 129 in $CDCl_3$



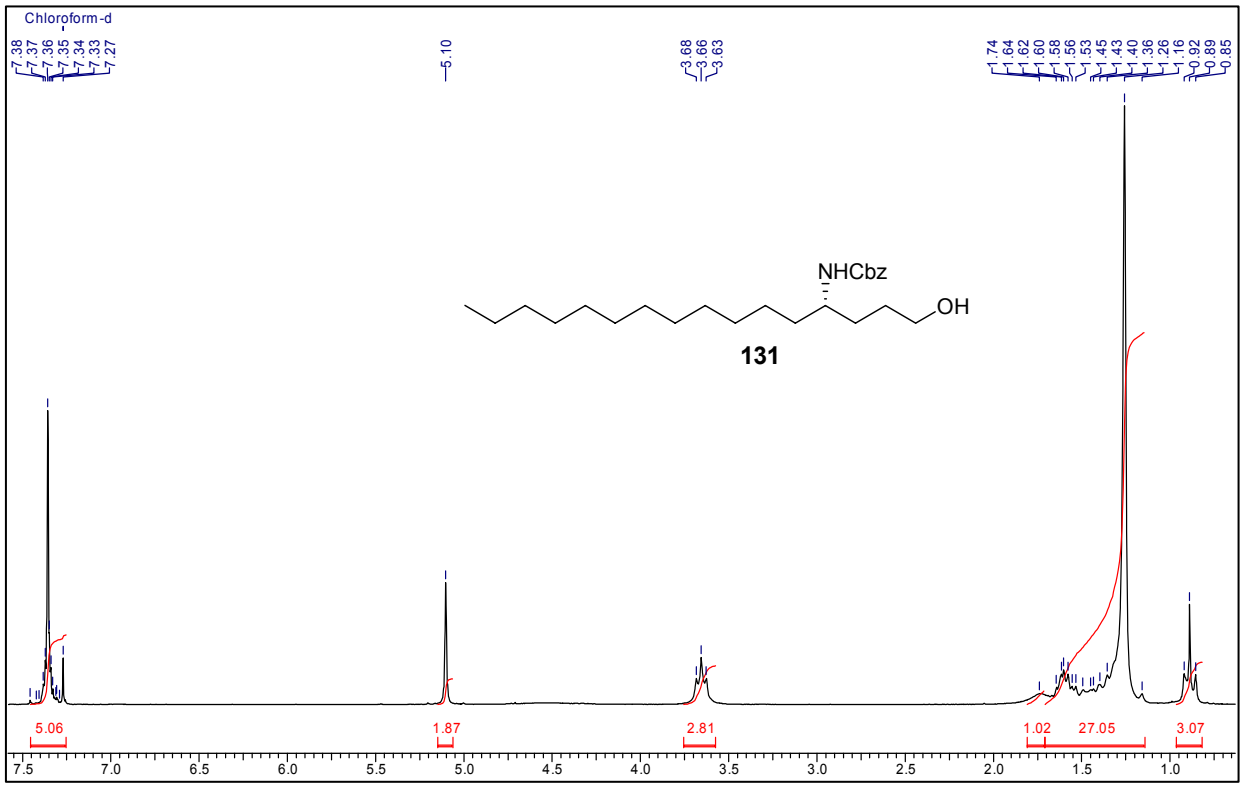
☞ ^{13}C NMR of the compound 129 in $CDCl_3$



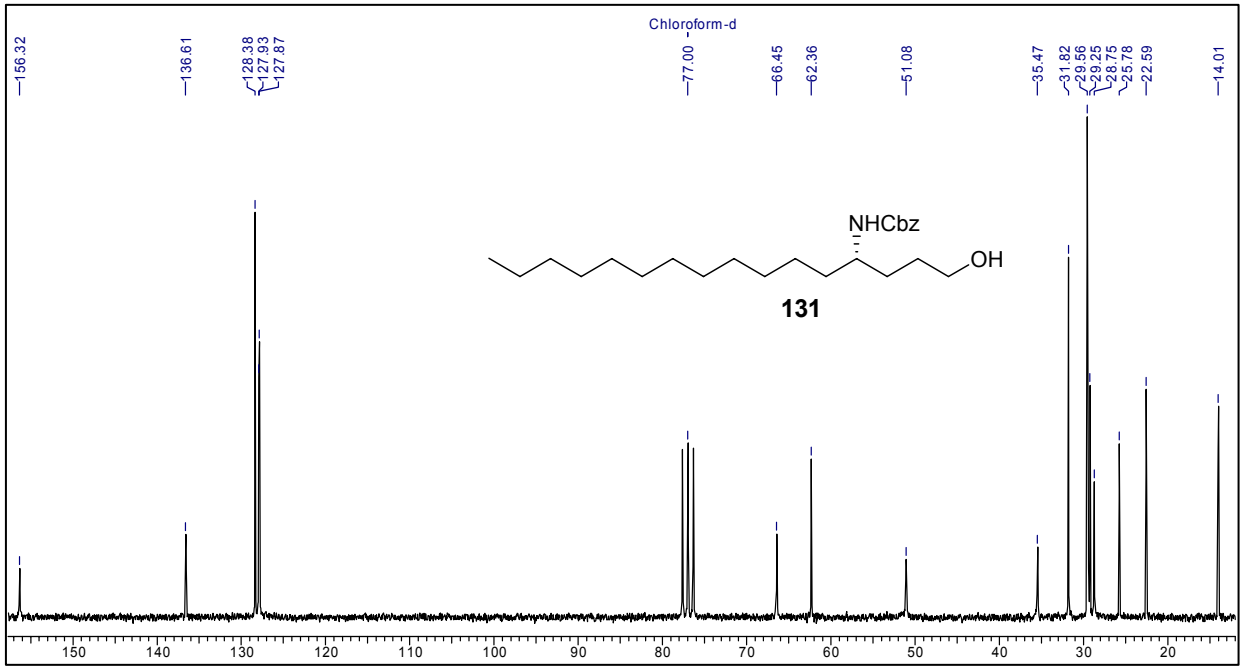
☞ ^{1}H NMR of the compound 130 in $CDCl_3$



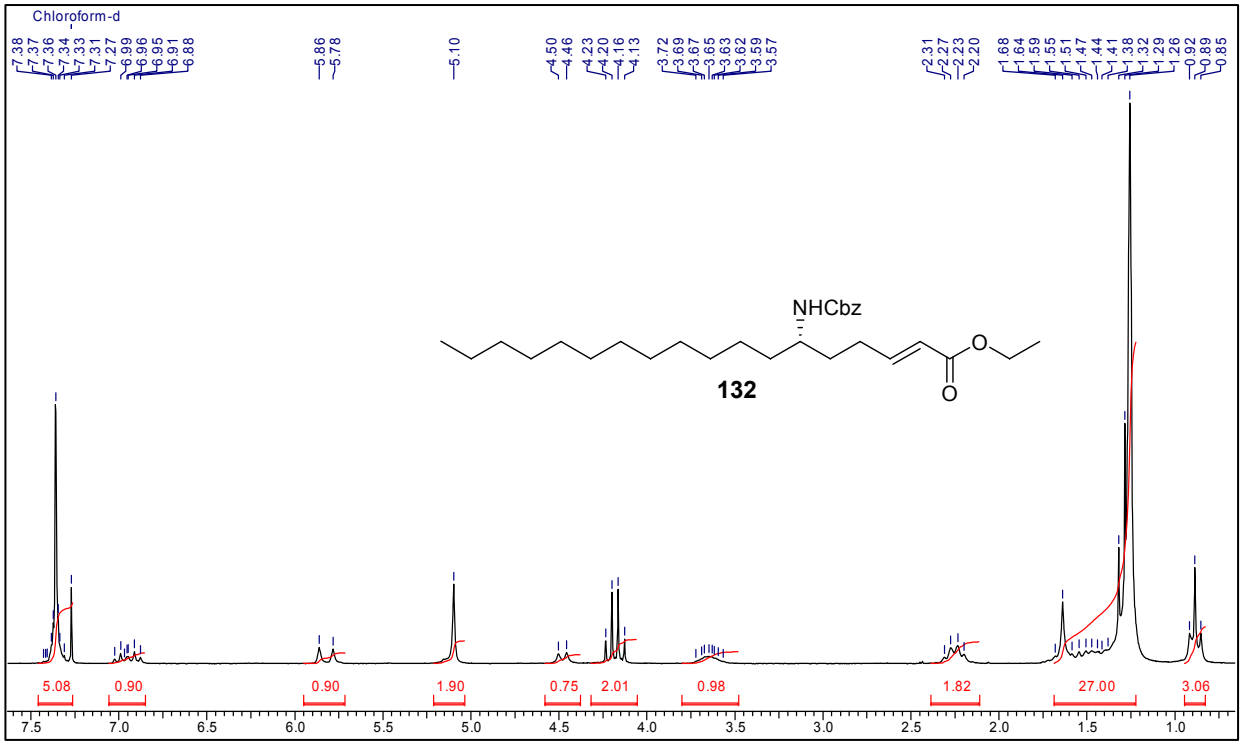
☞ ^{13}C NMR of the compound 130 in $CDCl_3$



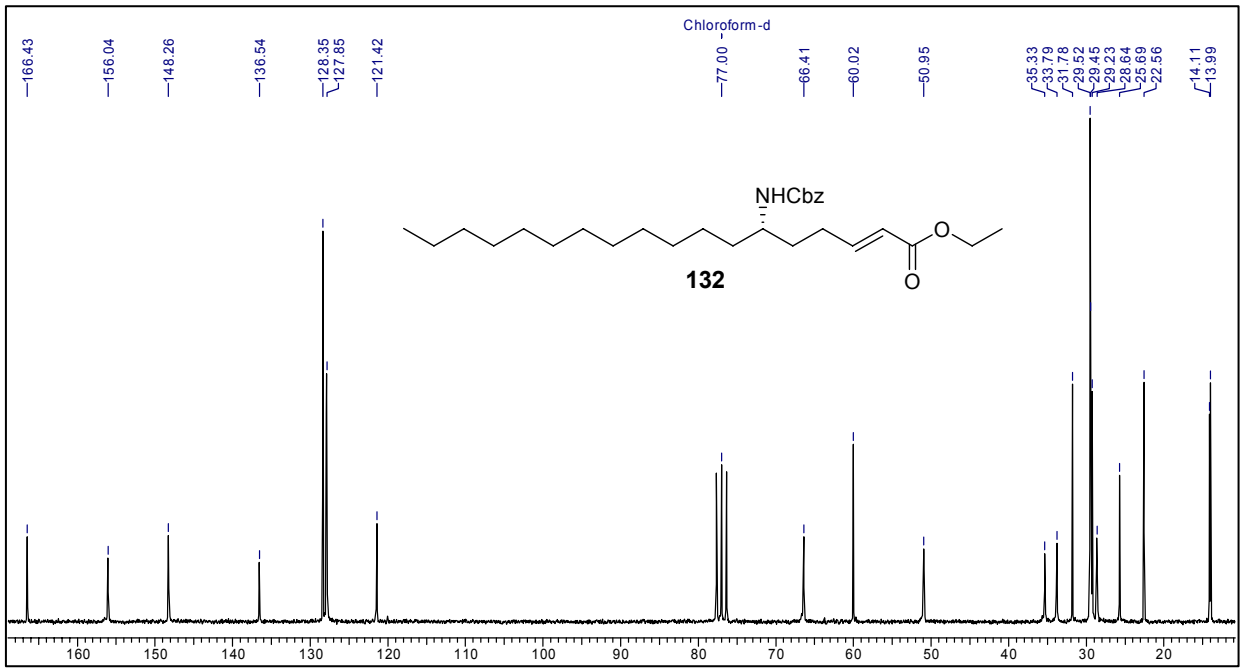
☞ ^{1}H NMR of the compound 131 in $CDCl_3$



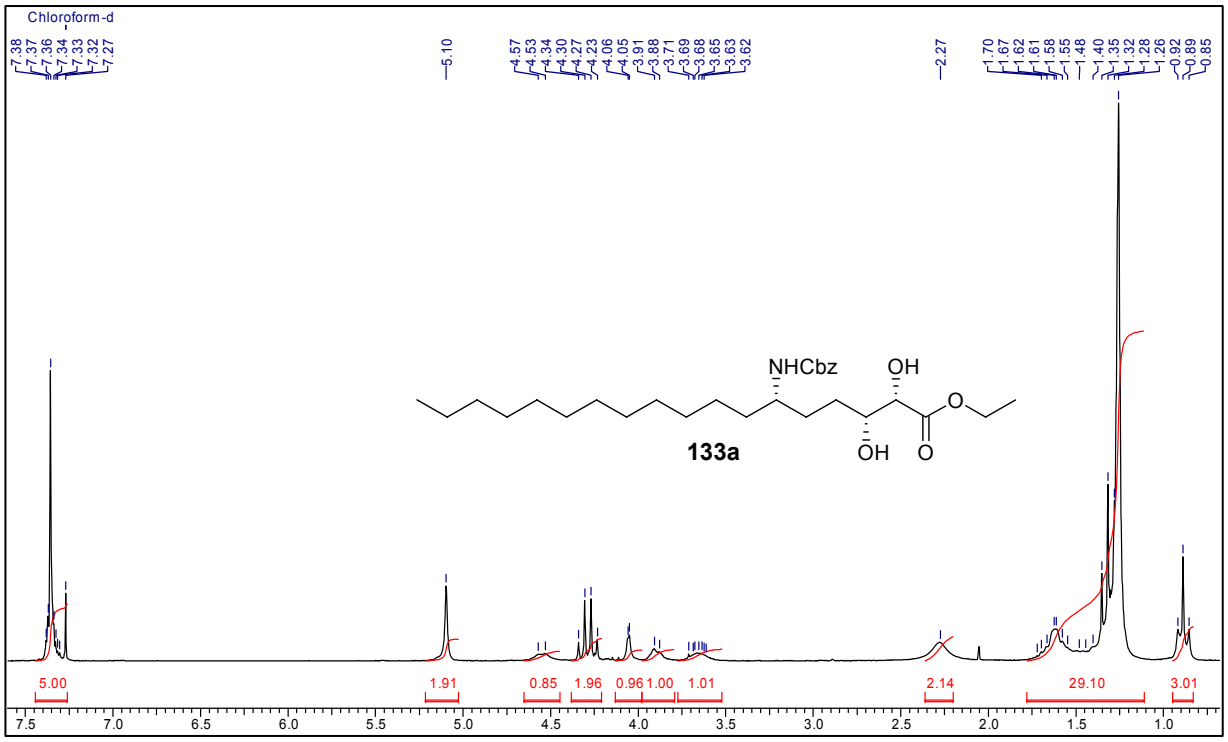
☞ ^{13}C NMR of the compound 131 in $CDCl_3$



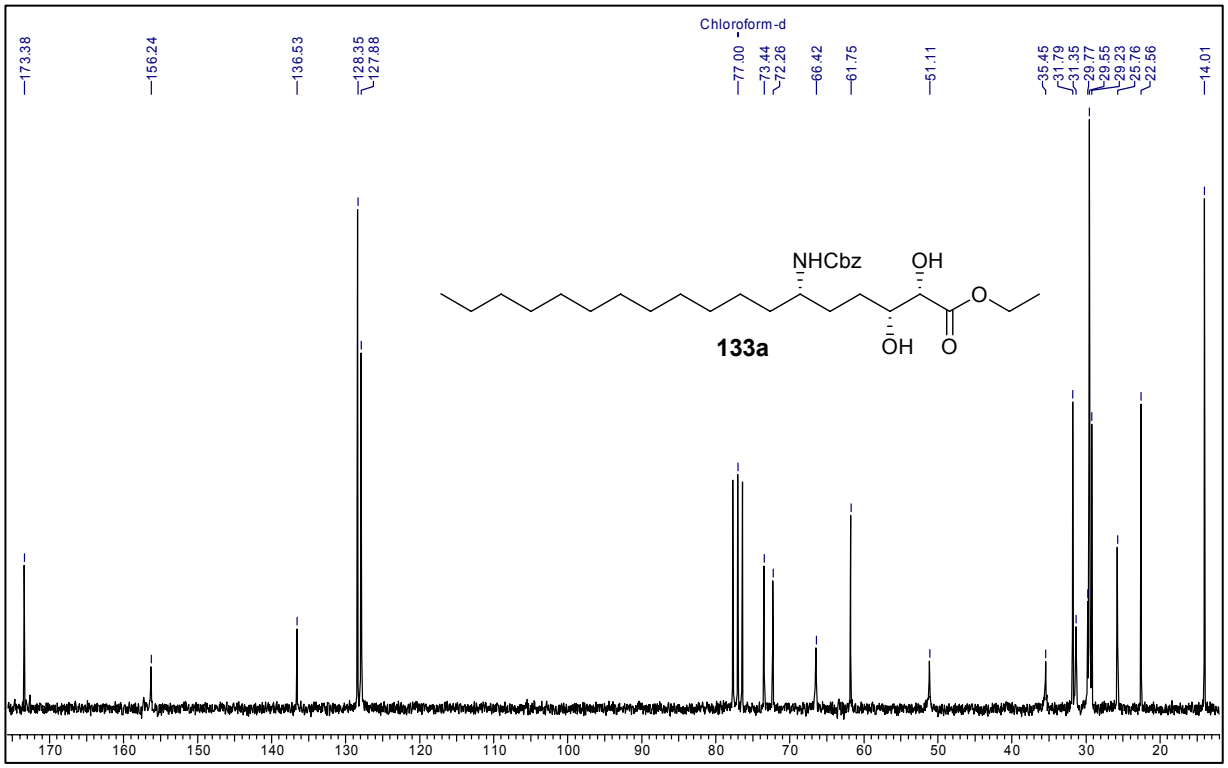
☞ **^{1}H NMR of the compound 132 in $CDCl_3$**



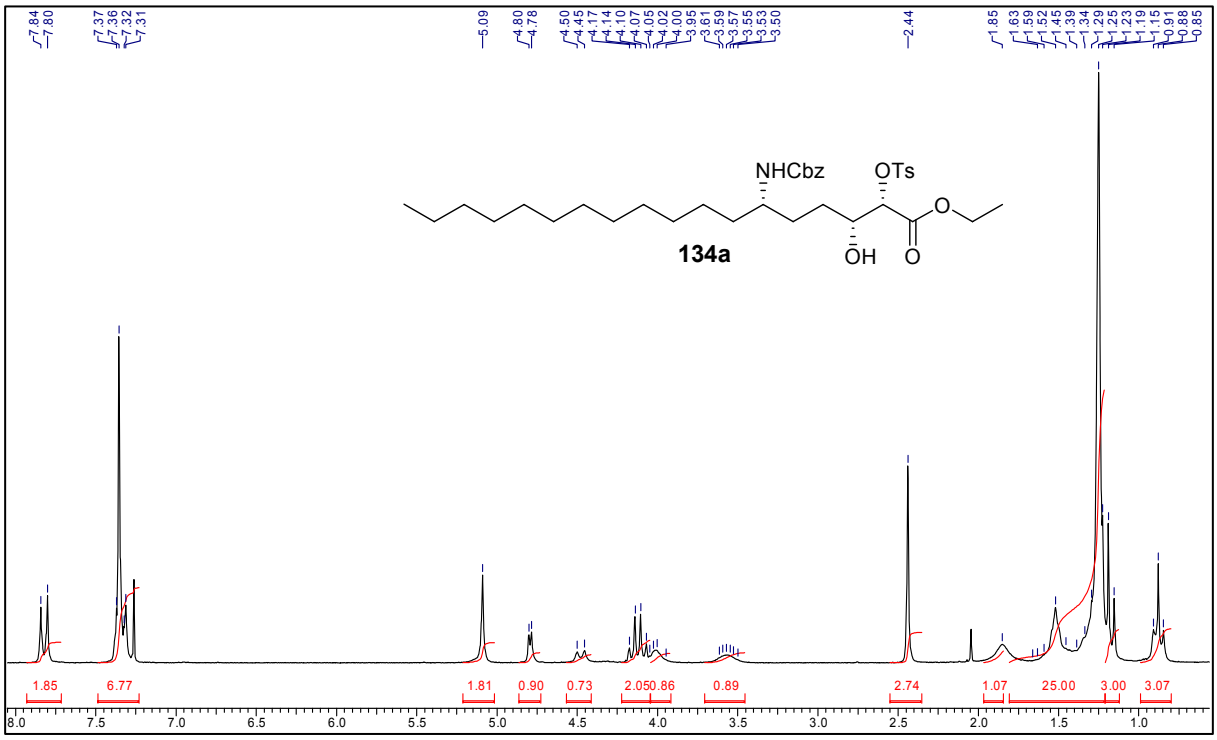
☞ **^{13}C NMR of the compound 132 in $CDCl_3$**



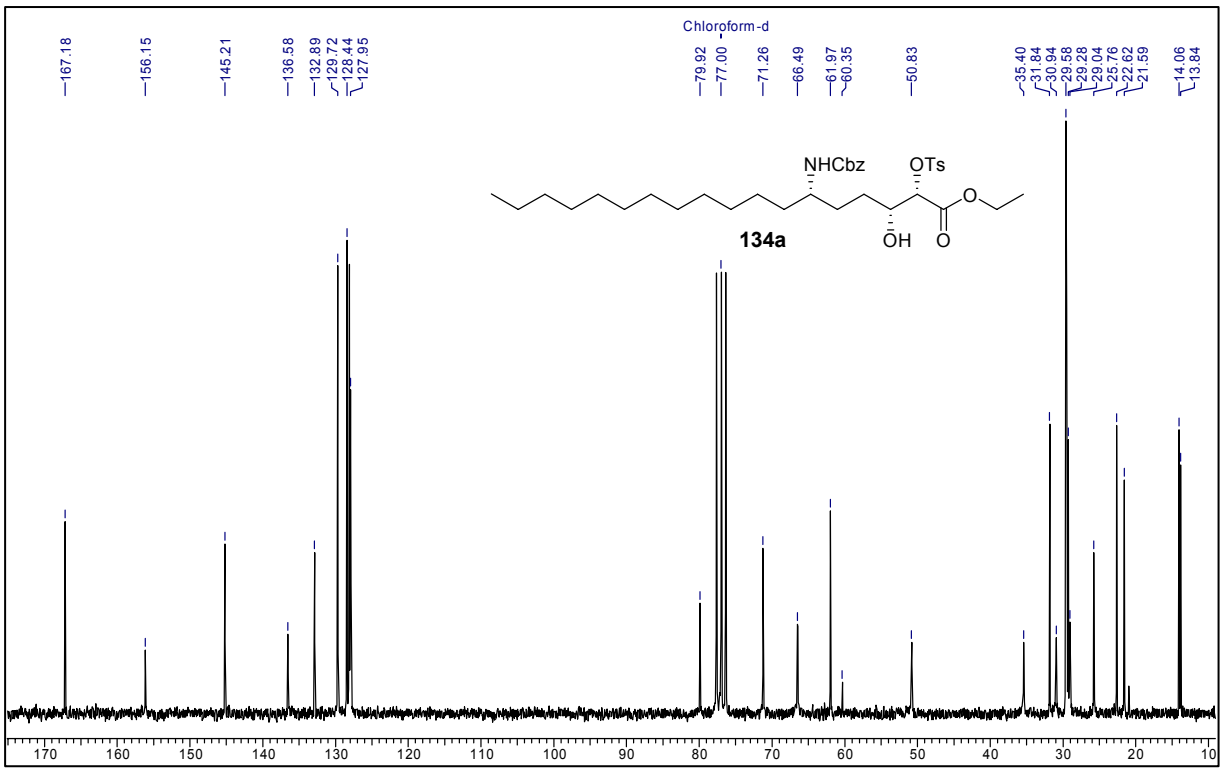
☞ ^{1}H NMR of the compound 133a in $CDCl_3$



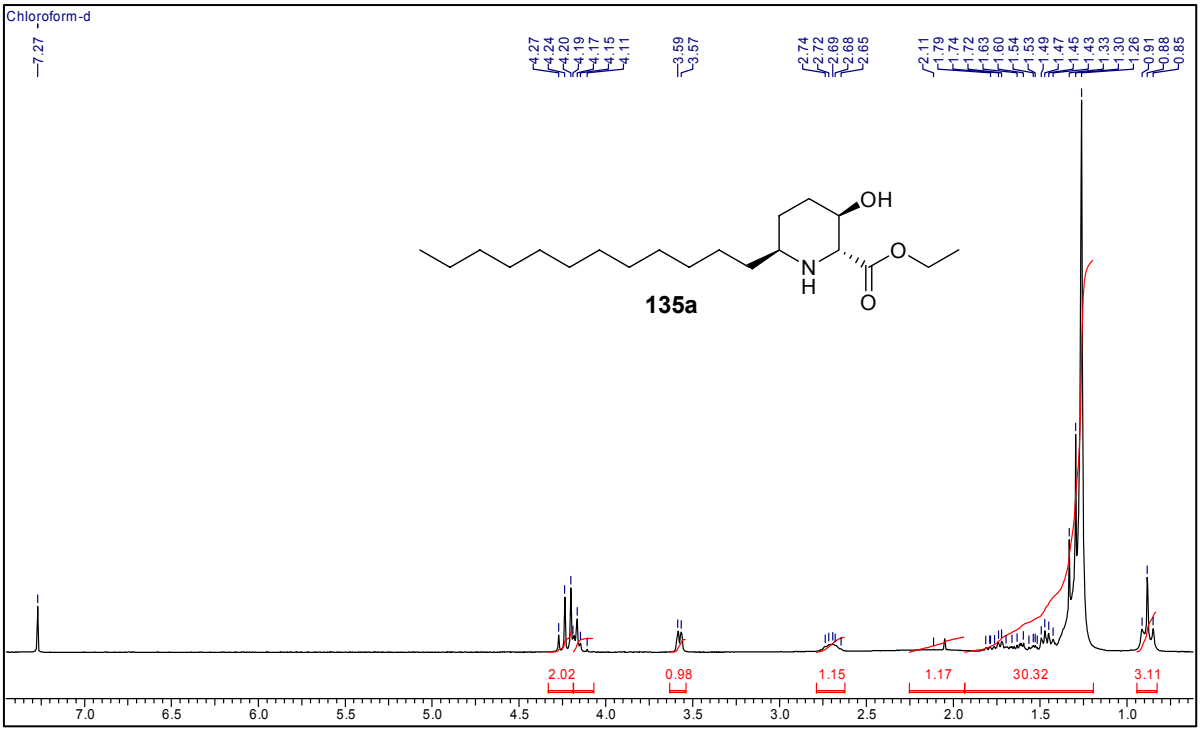
☞ ^{13}C NMR of the compound 133a in $CDCl_3$



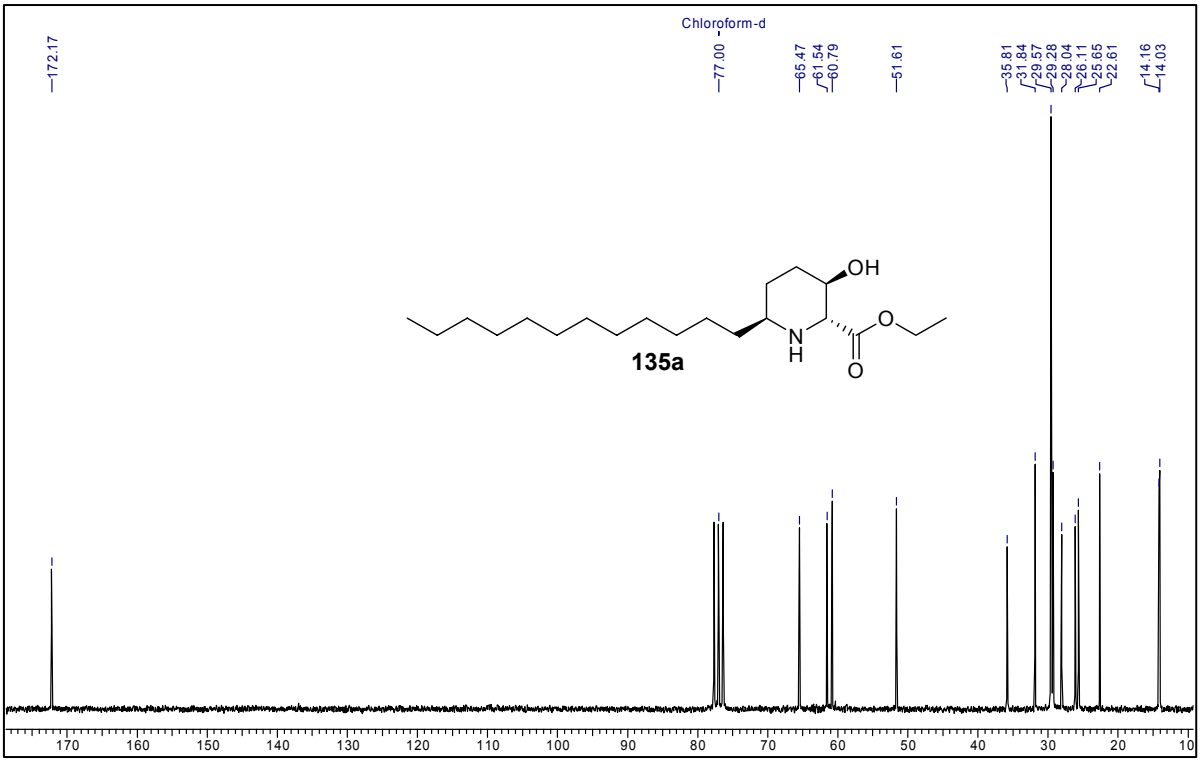
☞ ^{1}H NMR of the compound 134a in $CDCl_3$



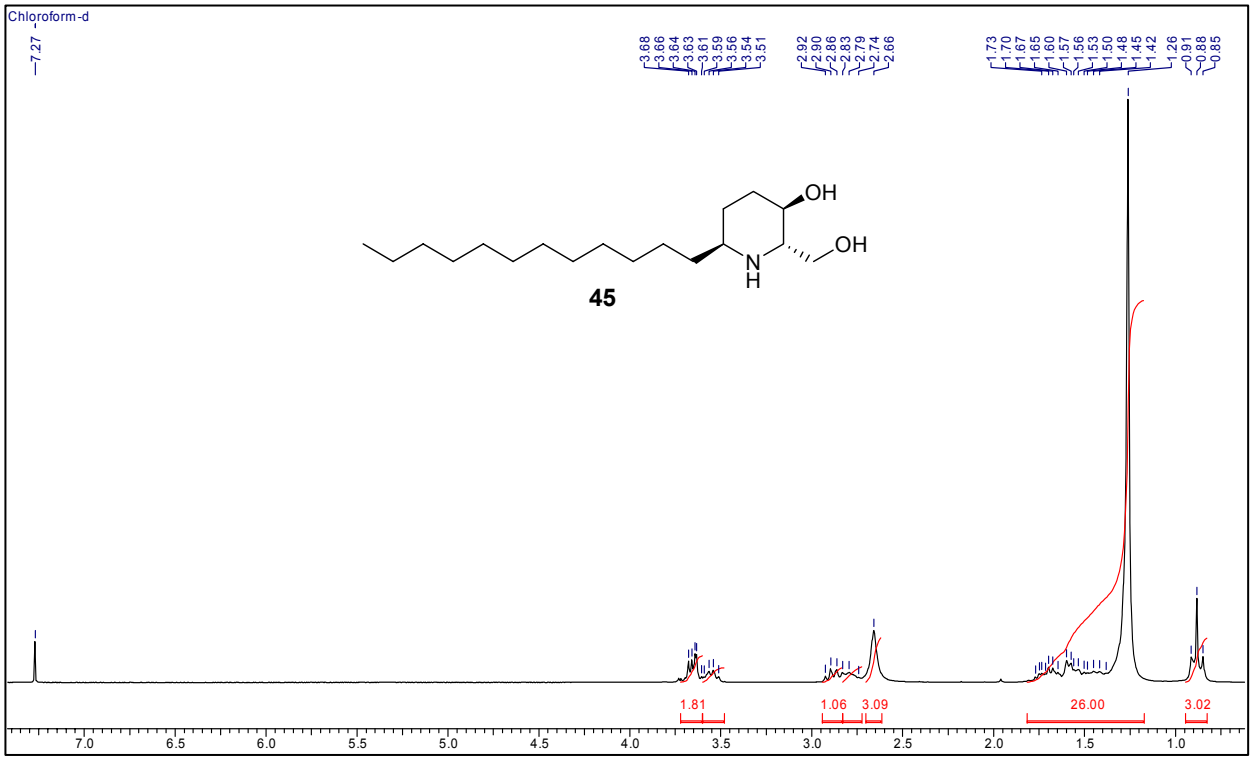
☞ ^{13}C NMR of the compound 133a in $CDCl_3$



☞ ^{1}H NMR of the compound 135a in $CDCl_3$

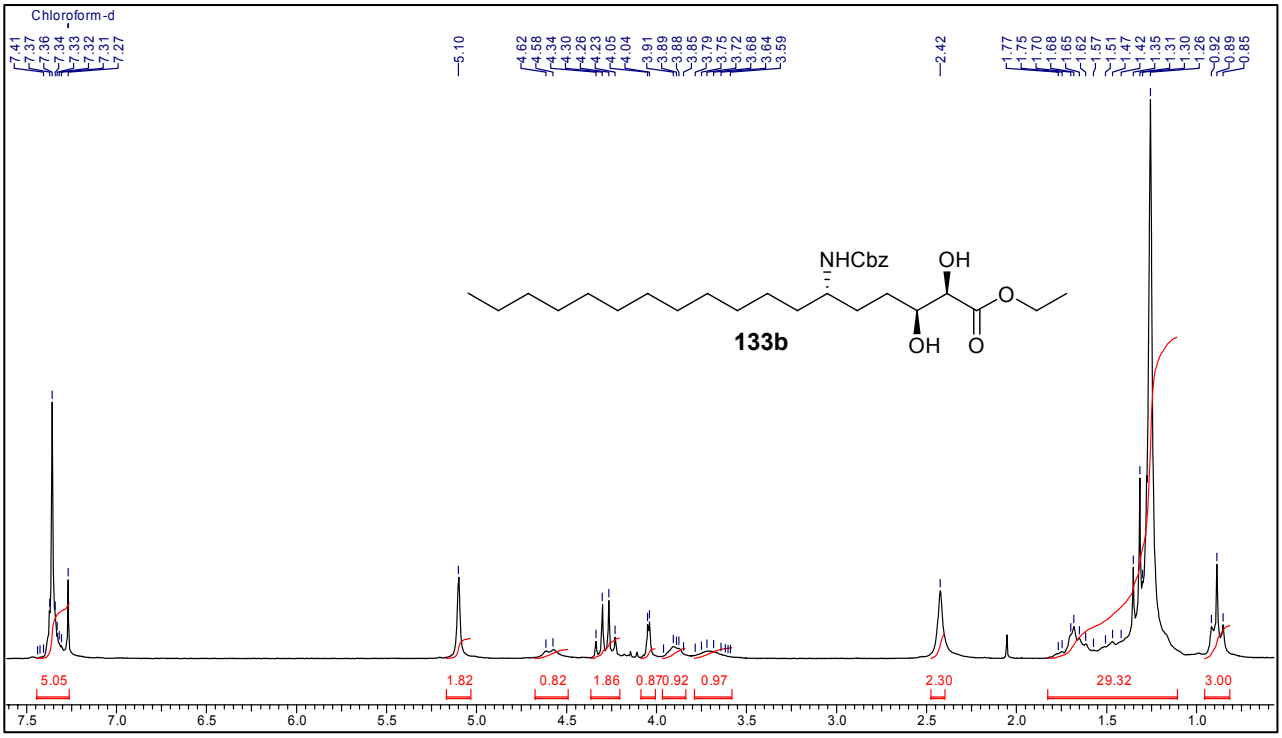


☞ ^{13}C NMR of the compound 135a in $CDCl_3$

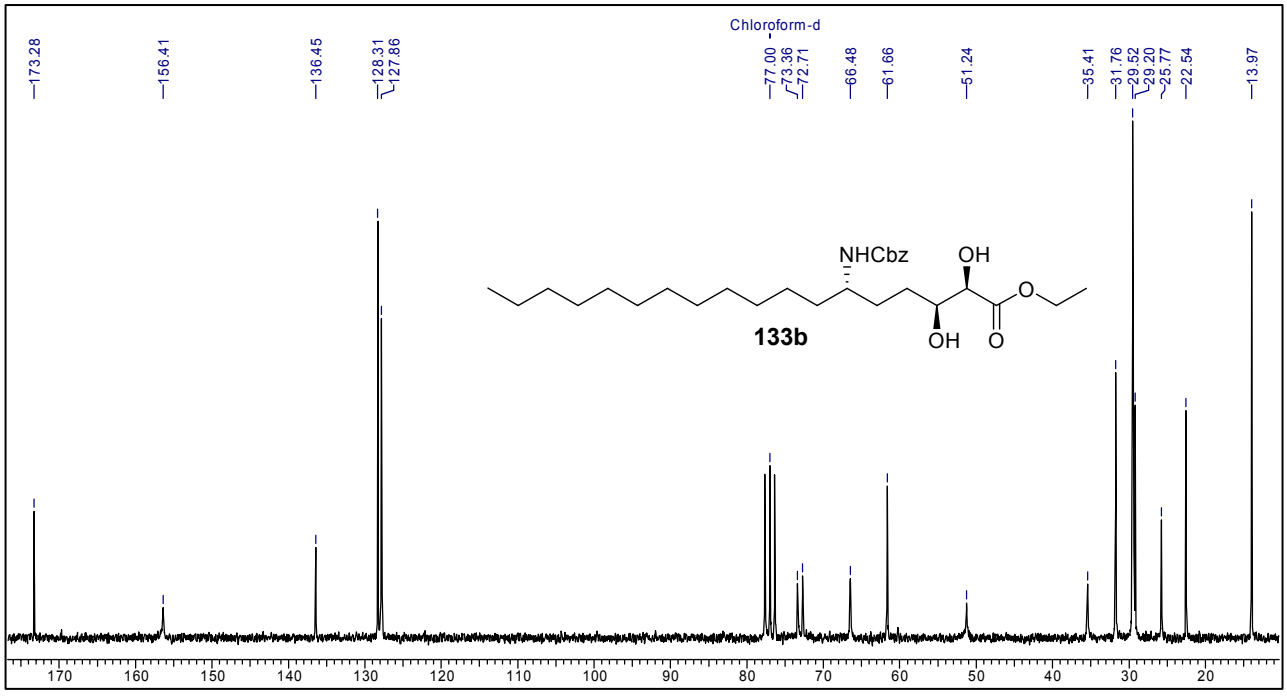


☞ ^{1}H NMR of the compound 45 in $CDCl_3$

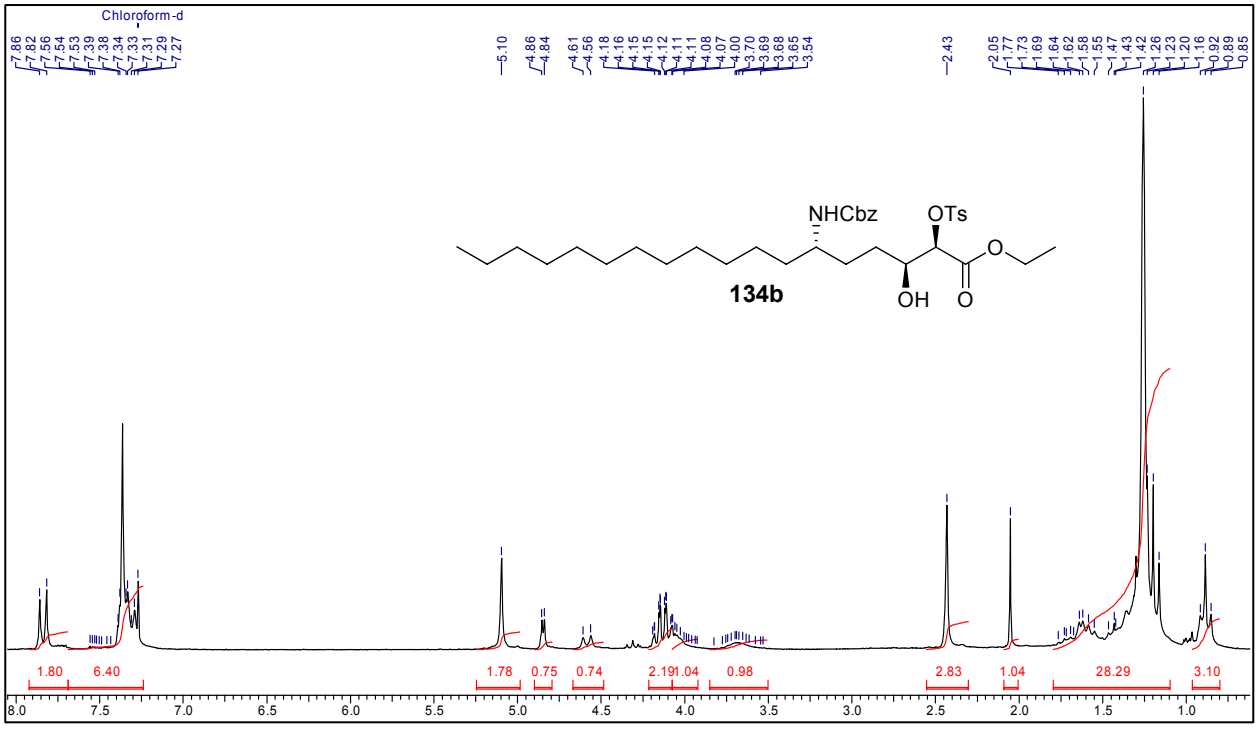
☞ ^{13}C NMR of the compound 45 in $CDCl_3$



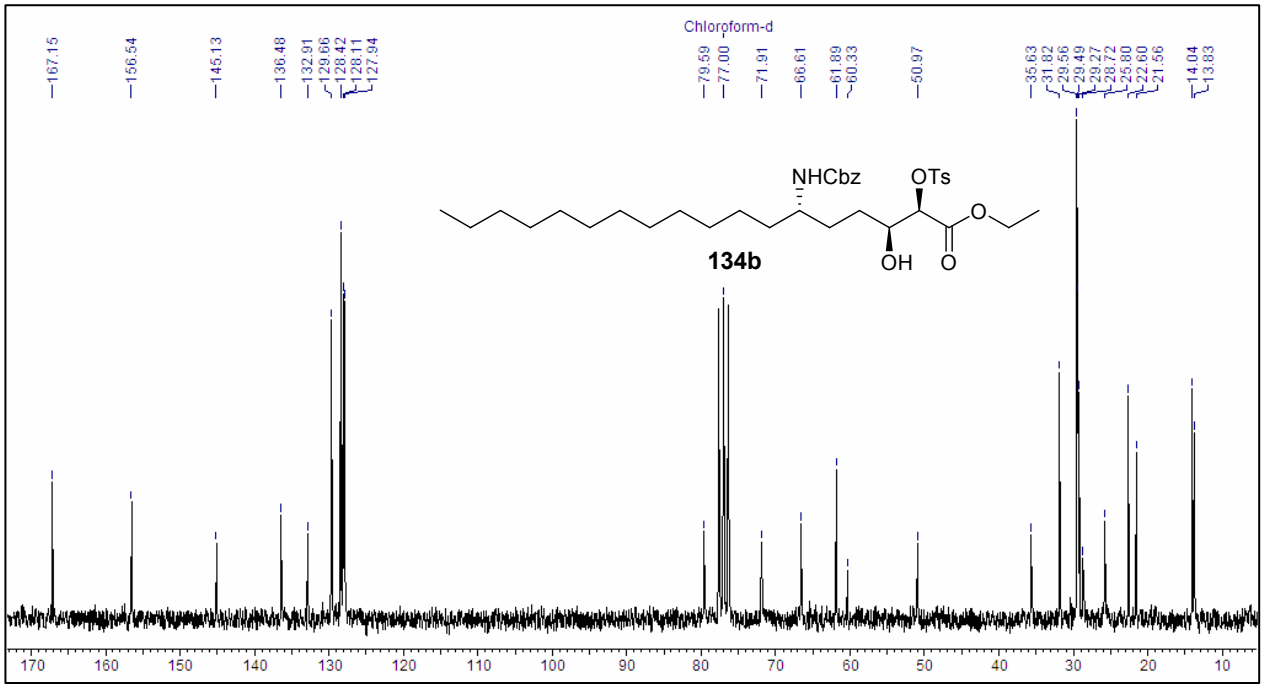
☞ ^{1}H NMR of the compound 133b in $CDCl_3$



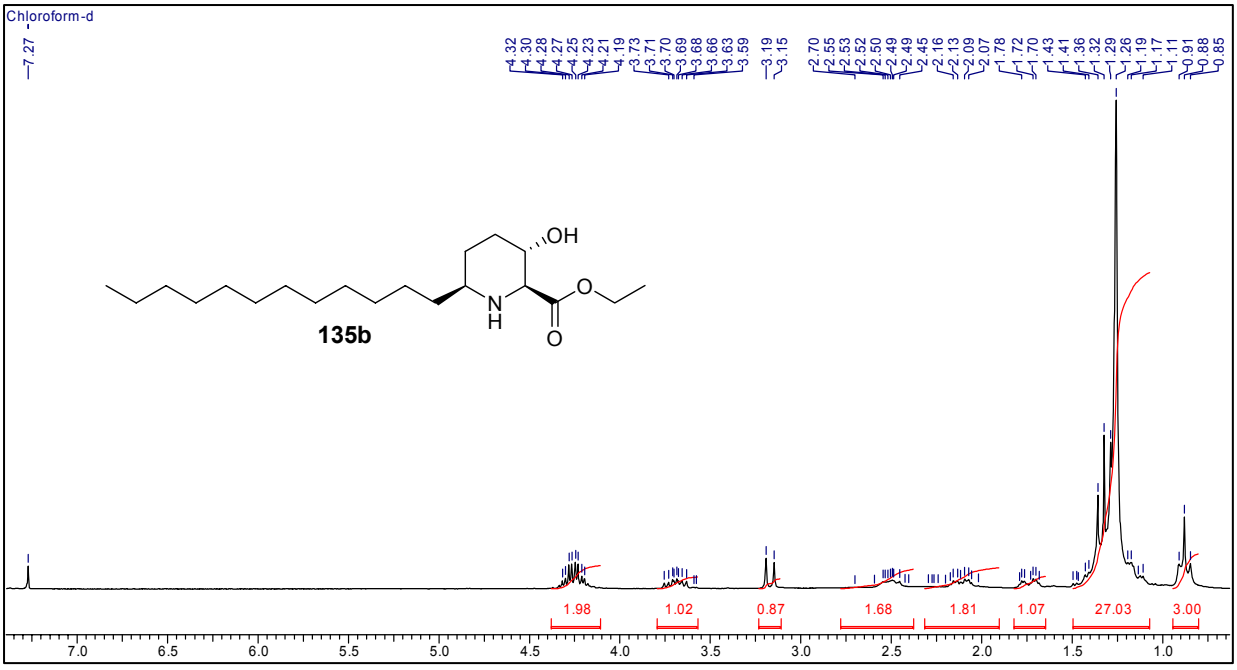
☞ ^{13}C NMR of the compound 133b in $CDCl_3$



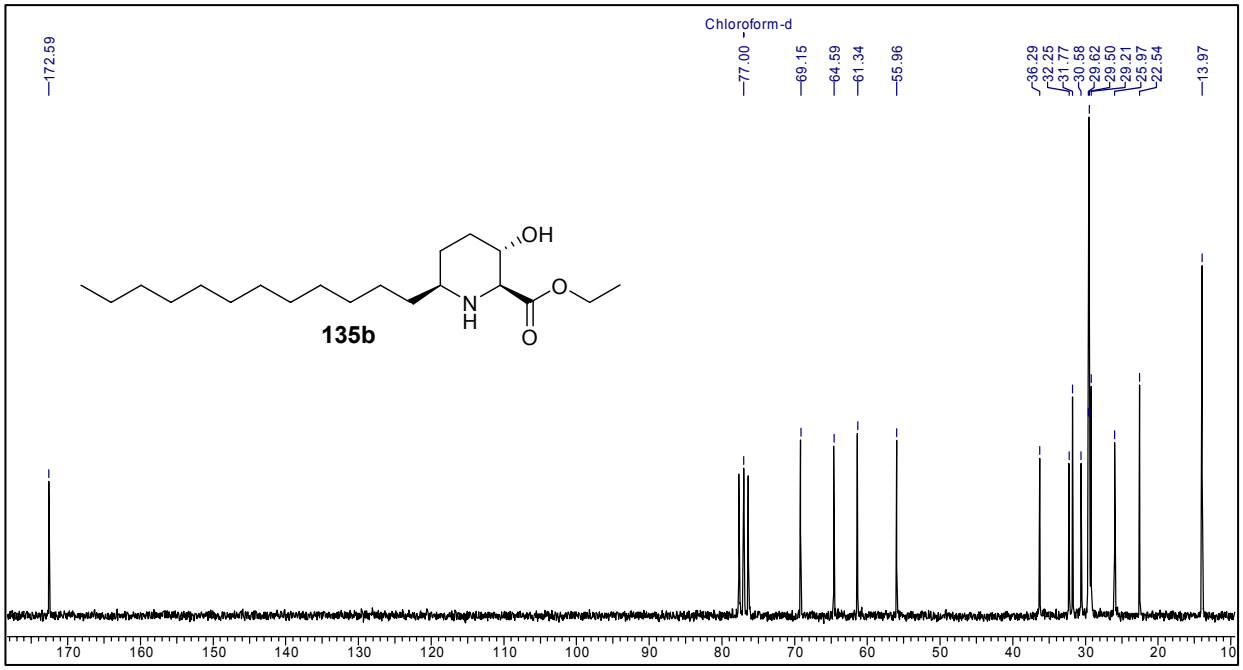
☞ ^{1}H NMR of the compound 134b in $CDCl_3$



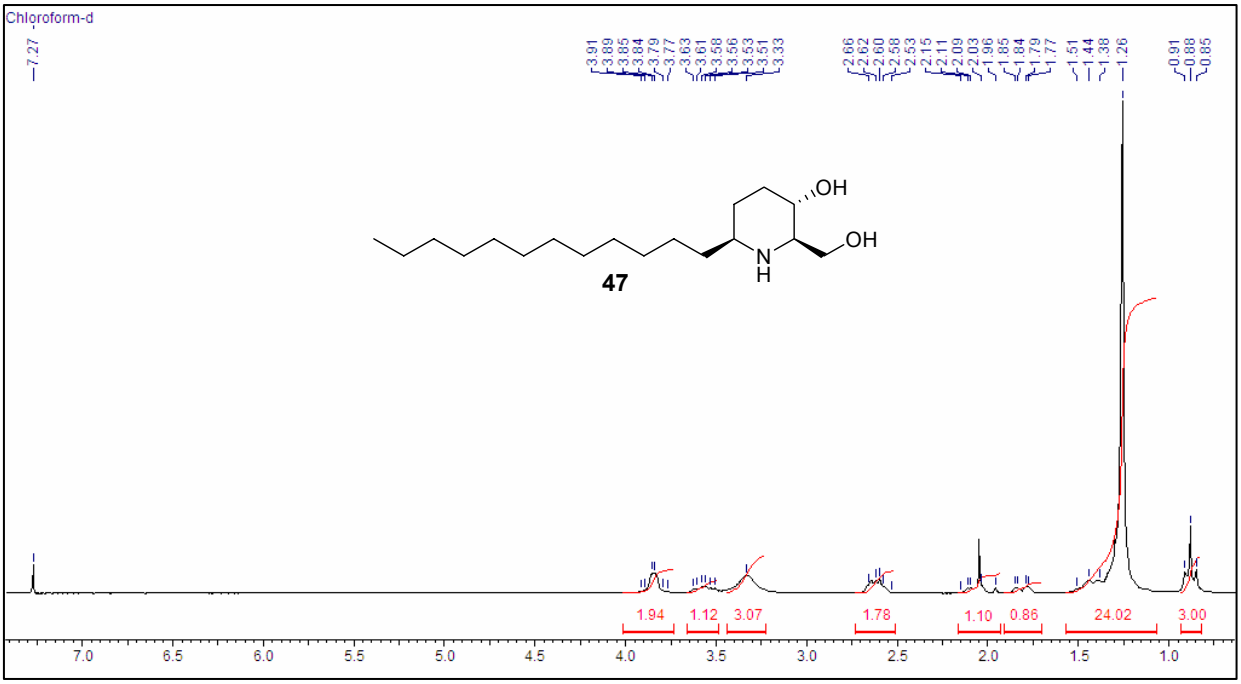
☞ ^{13}C NMR of the compound 134b in $CDCl_3$



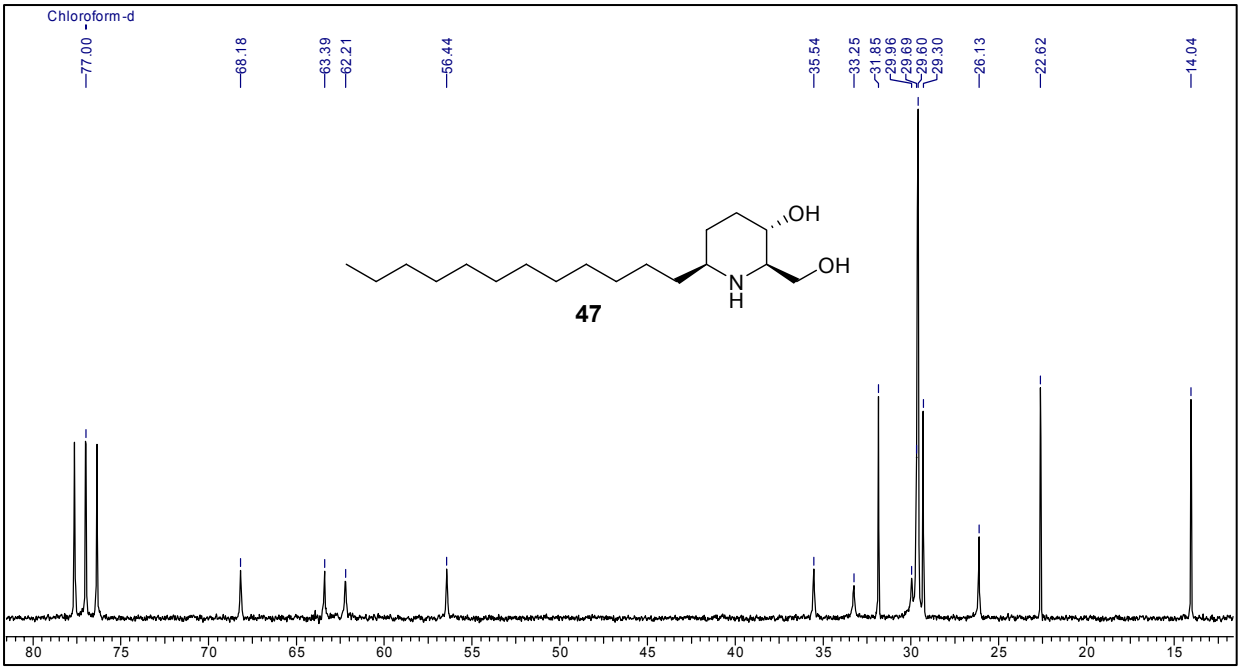
☞ ^{1}H NMR of the compound 135b in $CDCl_3$



☞ ^{13}C NMR of the compound 135b in $CDCl_3$



☞ ^{1}H NMR of the compound 47 in $CDCl_3$



☞ ^{13}C NMR of the compound 47 in $CDCl_3$

4.3 REFERENCES

1. Casiraghi, G.; Zanardi, F.; Rassu, G.; Spanu, P. *Chem. Rev*. **1995**, *95*, 1677.
2. Wertheim, T. *Liebigs Ann. Chem*. **1856**, *100*, 328.
3. (a) Elbein, A. D.; Molyneux, R. J.; Alkaloids: chemical and biological perspective: Pelletier, S.W., Ed.; Wiley:NewYork, **1986**; Vol. *5*, *pp* 1-54; (b) Comins, D. L.; Kuethe, J. T.; Hong, H.; Lakner, F. J. *J. Am. Chem. Soc.* **1999**, *121*, 2651; (c) Kuethe, J. T.; Comins, D. L. *Org. Lett*. **1999**, *1*, 1031.
4. (a) Ratovelomanana, V.; Royer, J.; Husson, H. P. *Tetrahedron Lett*. **1985**, *26*, 3803-3806; (b) Masaki, Y.; Imaeda, T.; Nagata, K.; Oda, H.; Ito, A. *Tetrahedron Lett*. **1989**, *30*, 6395; (c) Comins, D. L.; Williams, A. L. *Tetrahedron Lett*. **2000**, *41*, 2839; (d) Guerreiro, P.; Ratevelomanana-Vidal, V.; Genet, J. P. *Chirality* **2000**, *12*, 408; (e) Agami, C.; Couty, F.; Rabasso, N. *Tetrahedron Lett*. **2000**, *41*, 4113; (f) Agami, C.; Couty, F.; Rabasso, N. *Tetrahedron* **2001**, *57*, 5393; (g) Enders, D; Nolte, B.; Raabe, G.; Runsink, J. *Tetrahedron:Asymmetry* **2002**, *13*, 285.
5. (a) Kandula, S. V.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 1957; (b) Kandula, S. V.; Kumar, P. *Tetrahedron:Asymmetry* **2005**, *16*, 3268.
6. Chang, M-Y.; Kunga, Y-H.; Chen, S.-T. *Tetrahedron* **2006**, *62*, 10843.
7. Jamieson, A. G.; Sutherland, A. *Org. Lett*. **2007**, *9*, 1609.
8. (a) Gmieir, P.; Junge, D.; Kartner, A. *J. Org. Chem.* **1994**, *59*, 6766; (b) Oestreich, M.; Frohlich, R.; Hoppe, D.; *Tetrahedron Lett*. **1998**, *39*, 1745.
9. Andres, J. M.; Munoz, E. M.; Pedrosa, R.; Perez-Encabo, A.; *Eur. J. Org. Chem.* **2003,** 3387.
10. (a) Reetz, M. T. *Chem. Rev*. **1999**, *99*, 1121; (b) Reetz, M. T. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1531.
11. Andres, J. M.; deElena, N.; Pedrosa R.; *Tetrahedron* **2000,** *56*, 1523.
12. Yoshida, K.; Nakajima, S.; Wakamatsu, T.; Ban, Y.; Shibasaki, M. *Heterocycles* **1988**, *27*, 1167.
13. For reviews on the Swern oxidation, see: (a) Tidwell, T. T.; *Synthesis* **1990**, 857. (b) Tidwell, T. T. *Org. React.* **1990**, *39*, 297.
14. For reviews that include piperidine alkaloids, see: (a) Ayer, W. A.; Habgood, T. E. In *The Alkaloids*; Manske, R. H., Ed.; Academic Press: London, **1968**; Vol. 11, p 492. (b) Strunz, G. M.; Findlay, J. A. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New

York, **1985**; Vol. 26, pp 89. (c) Foder, G. B.; Colasanti, B. The Pyridine and Piperidine Alkaloids; Chemistry and Pharmacology. In *Alkaloids: Chemical and Biological Perspectives*: Pelletier, S. W., Ed.; Wiley: New York, **1985**; Vol. 3, pp 1. (d) Numata, A.; Ibuka, T. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, **1987**; Vol. 31, pp 193 and references therein. (e) Schneider, M. J. Pyridine and Piperidine Alkaloids: An Update. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: Oxford, **1996**; Vol. 10, pp 155. (f) Wang, C. J.; Wuonola, M. A. *Org. Prep. Proced. Int.* **1992**, *24*, 585. (g) Laschat, S.; Dickner, T.; *Synthesis* **2000**, 1781. (h) Weintraub, P. M.; Sabd, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953. Analgesic, antibiotic and anaesthetic properties: (i) Bourrinet, P.; Quevauviller, A. C. R. *Soc. Biol.* **1968**, *162*, 1138. (j) Bourrinet, P.; Quevauviller, A. *Ann. Pharm. Fr.* **1968**, *26*, 787.

15. Prosopis alkaloids from the leaves, stems, and roots of *Prosopis africana*: (a) Ratle, G.; Monseur, X.; Das, B. C.; Yassi, J.; Khuong- Huu, Q.; Goutarel, R. *Bull. Soc. Chim. Fr*. **1966**, 2945. (b) Khuong-Huu, Q.; Ratle, G.; Monseur, X.; Goutarel, R. *Bull. Soc. Chim. Belg*. **1972**, *81*, 425, 443.
16. Previous asymmetric synthesis of deoxoprosopinine, see: (a) Saitoh, Y.; Moriyama, Y.; Takahashi, T. *Tetrahedron Lett*. **1980**, *21*, 75. (b) Saitoh, Y.; Moriyama, Y.; Hirota, H.; Takahashi, T.; Khuong-Huu, Q. *Bull. Chem. Soc. Jpn*. **1981**, *54*, 488. (c) Ciufolini, M. A.; Hermann, C. W.; Whitmire, K. H.; Byrne, N. E. *J. Am. Chem. Soc*. **1989**, *111*, 3473. (d) Tadano, K.; Takao, K.; Nigawara, Y.; Nishino, E.; Takagi, I.; Maeda, K.; Ogawa, S. *Synlett* **1993**, 565. (e) Takao, K.; Nigawara, Y.; Nishino, E.; Takagi, I.; Maeda, K.; Tadano, K.; Ogawa, S. *Tetrahedron* **1994**, *50*, 5681. (f) Yuasa, Y.; Ando, J.; Shibuya, S. *Tetrahedron: Asymmetry* **1995**, *6*, 1525. (g) Yuasa, Y.; Ando, J.; Shibuya, S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 793. (h) Kadota, I.; Kawada, M.; Muramatsu, Y.; Yamamoto, Y. *Tetrahedron Lett.* **1997**, *38*, 7469. (i) Kadota, I.; Kawada, M.; Muramatsu, Y.; Yamamoto, Y. *Tetrahedron: Asymmetry* **1997**, *8*, 3887. (j) Agami, C.; Couty, F.; Mathieu, H. *Tetrahedron Lett*. **1998**, *39*, 3505. (k) Agami, C.; Couty, F.; Lam, H.; Mathieu, H. *Tetrahedron* **1998**, *54*, 8783. (l) Comins, D. L.; Sandelier, M. J.; Grillo, T. A. *J. Org. Chem.* **2001**, *66*, 6829. (m) Wang, Q.; Sasaki, N. A. *J. Org. Chem.* **2004**, *69*, 4767. (n) For an asymmetric synthesis of *epi*-deoxoprosopinine, see: (i) Enders, D.; Kirchhoff, J. H. *Synthesis* **2000**, 2099. (ii)

Felpin, F. X.; Boubekeur, K.; Lebreton, J.; *Eur. J. Org. Chem.* **2003**, 4518. (iii) Wei, B. G.; Chen, J.; Huang, P. Q. *Tetrahedron* **2006**, *62*, 190.

17. Previous asymmetric synthesis of deoxoprosophylline, see: (a) ref. 3. a, b, d, e, i, h. (b) Ojima, I.; Vidai, E. S. *J. Org. Chem.* **1998**, *63,* 7999. (c) Herdeis, C.; Telser, J. *Eur. J. Org. Chem.* **1999**, 1407. (d) Yang, C.; Liao, L.; Xu, Y.; Zhang, H.; Xia, P.; Zhou, W. *Tetrahedron: Asymmetry* **1999**, *10*, 2311. (e) Jourdant, A.; Zhu, J. *Tetrahedron Lett.* **2001**, *42*, 3431. (f) Datta, A.; Ravikumar, J. S.; Roy, S. *Tetrahedron* **2001**, *57*, 1169. (g) Dransfield, P. J.; Gore, P. M.; Shipman, M.; Slawin, A. M. Z. *Chem. Commn.* **2002**, 150. (h) Dransfield, P. J.; Gore, P. M.; Prokeš, I.; Shipman, M.; Slawin, A. M. Z. *Org. Biomol. Chem.* **2003**, *1*, 2723. (i) Ma, N.; Ma, D. *Tetrahedron: Asymmetry* **2003**, *14*, 14036. (j) Chavan S. P.; Praveen, C. *Tetrahedron Lett.* **2004**, *45*, 421. (k) Jourdant, A.; Zhu, J. *Heterocycles* **2004**, *64*, 259. (l) Kim, I. S.; Ryu, C. B.; Li, Q. R.; Zee, O. P.; Jung, Y. H. *Tetrahedron Lett.* **2007**, *48*, 6258. (m) Fuhshuku, K-i.; Mori, K. *Tetrahedron: Asymmetry* **2007**, *18*, 2104.
18. Campbell, A. D.; Raynham, T. M.; Taylor, R. J. K. *Synthesis* **1998**, 1707.
19. Ramarao, A. V.; Bose, D. S.; Gurjar, M. K.; Ravindranathan, T. *Tetrahedron* **1989**, *45*, 7031.
20. (a) Kim, I. S.; Oh, J. S.; Zee, O. P.; Jung, Y. H. *Tetrahedron* **2007**, *63*, 2622; (b) Kim, I. S.; Ji, Y. J.; Jung, Y. H. *Tetrahedron Lett.* **2006**, *47*, 7289.
21. Masuda, Y.; Mori, K. *Eur. J. Org. Chem.* **2005**, 4789.
22. (a) Pandey, S. K.; Kandula, S. V.; Kumar, P. *Tetrahedron Lett.* **2004**, *45*, 5877. (c) Pandey, S. K.; Kumar, P. *Tetrahedron Lett.* **2005**, *46*, 4091. (d) Pandey, S. K.; Kumar, P. *Tetrahedron Lett.* **2005**, *46*, 6625. (e) Kumar, P.; Naidu, S. V. *J. Org. Chem.* **2005**, *70*, 4207. (f) Kumar, P.; Naidu, S. V.; Gupta, P. *J. Org. Chem.* **2005**, *70*, 2843. (g) Kumar, P.; Bodas, M. S. *J. Org. Chem.* **2005**, *70*, 360. (h) Kumar, P ; Gupta, P.; Naidu, S. V. *Chem. Eur. J.* **2006**, *12*, 1397. (i) Kumar, P.; Naidu, S. V. *J. Org. Chem.* **2006**, *71*, 3935. (j) Pandey, S. K.; Kumar, P. *Tetrahedron Lett.* **2006**, *47*, 4167. (h) Pandey, S. K.; Kumar, P. *Eur. J. Org. Chem.* **2007**, 369.
23. (a) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307. (b) For a review on application of HKR, see: Kumar, P.; Naidu, S. V.; Gupta, P. *Tetrahedron* **2007**, *63*, 2745.

24. Staudinger, H.; Meyer, J. *Helv. Chim. Acta.* **1919**, *2*, 635.

25. (a) Becker, H.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1996**, *35*, 448. (b) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev*. **1994**, *94*, 2483. (c) Torri, S.; Liu, P.; Bhuvaneswari, N.; Amatore, C.; Jutand, A. *J. Org. Chem.* **1996**, *61*, 3055.

26. Fleming, P. R.; Sharpless K. B. *J. Org. Chem.* **1991**, *56*, 2869.

CHAPTER 5

ENANTIOSELECTIVE SYNTHESES OF THE NATURALLY OCCURRING LACTONES: *ISO*-CLADOSPOLIDE B, CLADOSPOLIDE B & (-)-COLLETOL

5.1 SECTION A

TOTAL SYNTHESIS OF *ISO*-CLADOSPOLIDE B AND CLADOSPOLIDE B

5.1.1. Introduction

The novel hexaketide compounds *iso*-cladospolide B **1** and cladospolide B **2** were isolated from the fungal isolate I96S215.[1] Cladospolide A **3**, cladospolide B **2** along with cladospolide C **4** were also isolated from the soil fungi *Cladosporium tenuissimum*, whose culture filtrate showed plant growth retardant activity towards rice seedlings. Cladospolide B **2** is inhibitory to shoot elongation of rice seedlings (*Oryza sativa* L.) without damaging the cells.[2] Recently cladospolide D **5** isolated from *Cladosporium sp.* FT-0012 whose configuration remains to be fully determined, was shown to exhibit antimicrobial activity against *Mucor racemosus* and *Pyricularia oryzae* with IC_{50} values of 0.15 and 29 μg ml^{-1}, respectively.[3]

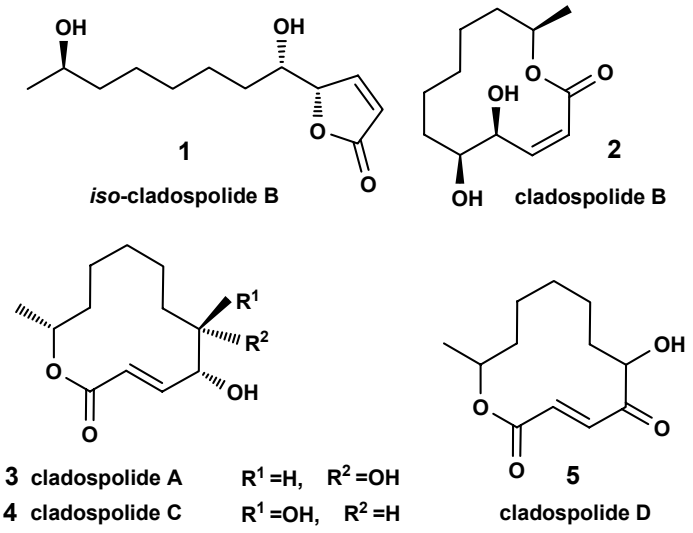


Figure 1.

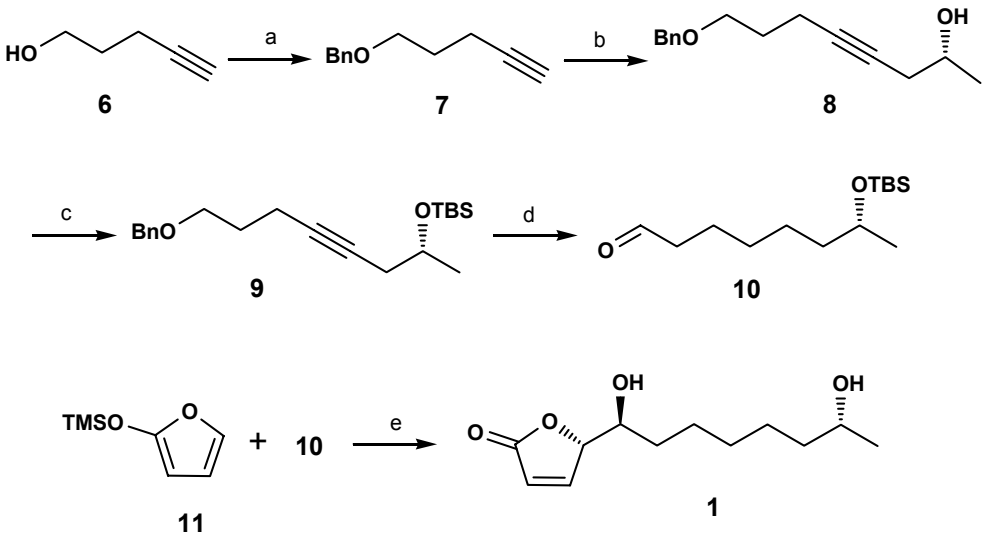
5.1.2. Review of Literature

The absolute configuration of the three stereogenic centres (4*S*,5*S*, and 11*R*) of *iso*-cladospolide B **1** was determined by Figadere *et al.* who also accomplished its synthesis

for the first time.[4] Very recently Banwell *et al.* reported the first total synthesis of cladospolide B using a chemoenzymatic sixteen-step synthesis *via* a ring-closing metathesis and photorearrangement of an *E* isomer.[5] The synthesis of *iso*-cladospolide B **1** and cladospolide B **2** reported in the literature is described below.

Figade`re, B. *et al.* (2001)[4]

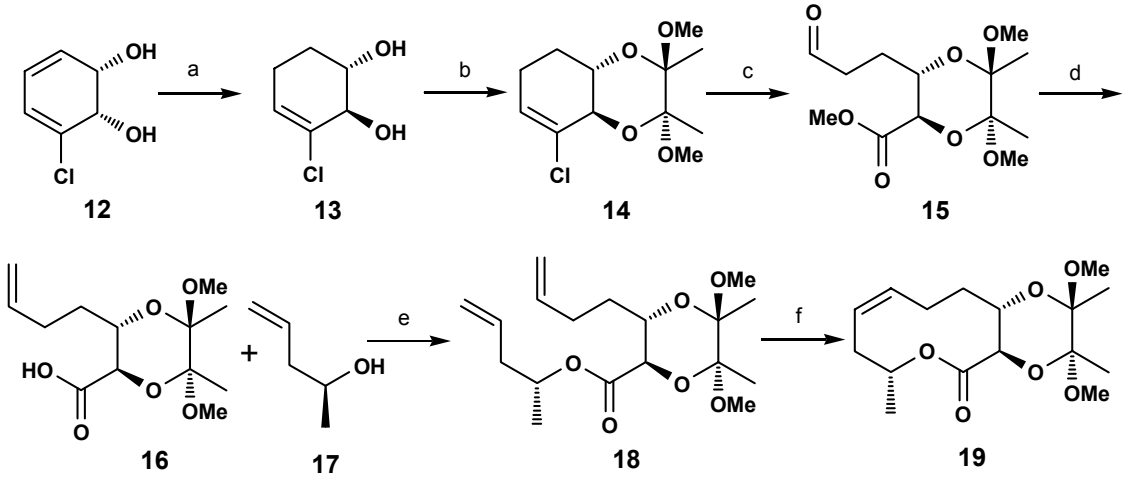
Bruno Figade`re and co-workers reported the first synthesis and also assigned the absolute configurations of the three stereogenic centers of **1**. Pent-4-yn-1-ol **6** was protected as benzyl ether **7**, then metallation of the latter with *n*-butyllithium at −78°C in THF followed by additions of (*R*)-propylene oxide and $BF_3{\cdot}OEt_2$, led to the homopropargyl alcohol **8** in 56% yield. Secondary hydroxyl group of **8** was protected as silyl ether; hydrogenation followed by Swern oxidation afforded desired aldehyde **10** in 81% yield. Aldehyde **10** was then treated at −78°C in CH_2Cl_2 by **11** in the presence of $BF_3{\cdot}OEt_2$ to afford *iso*-cladospolide **1** (Scheme 1).

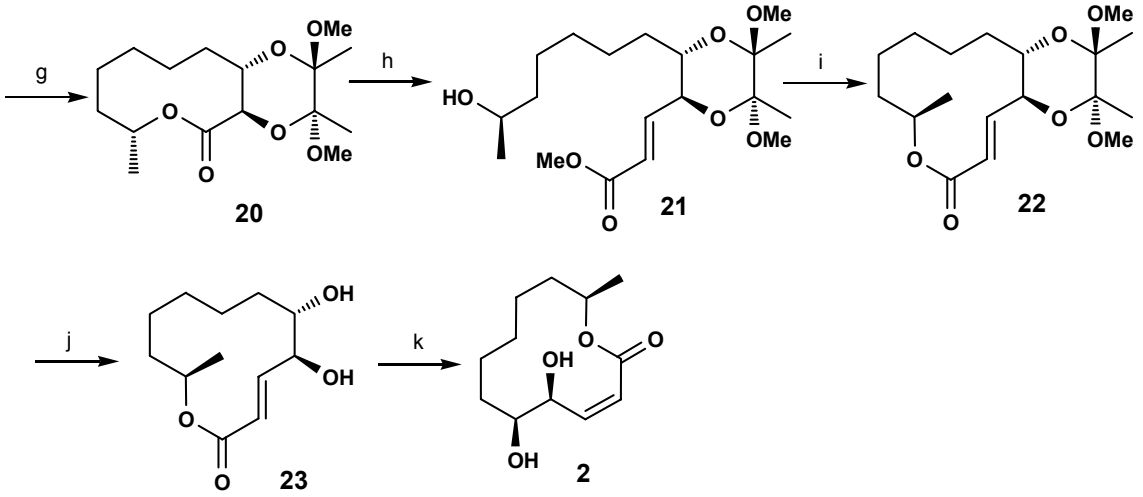


Scheme 1. *Reagents and conditions*: (a) NaH, BnBr, Bu_4NBr, THF, 71%; (b) *n*-BuLi, -78 °C, 1 h then (*R*)-propylene oxide (1.2 equiv), $BF_3.OEt_2$ (1.1 equiv), -78 °C, 3 h, 56%; (c) TBDMSCl, imidazole, DMAP, DMF, r.t., 3 h, 97%; (d) i) H_2, Pd/C, toluene, 82%; ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -60 °C, 81%; (e) i) TMSOF **11**, CH_2Cl_2, −78°C, $BF_3.OEt_2$; ii) HF, THF, 60%.

Banwell, M. G. *et al.* (2005)[5]

Martin G. Banwell and co-workers reported a sixteen-step first synthesis of the twelve-membered macrolide cladospolide B **2** from the microbially-derived *cis*-1,2-dihydrocatechol **12** *via* ring-closing metathesis (RCM), Wadsworth–Horner–Emmons reaction, Yamaguchi lactonisation and photo-rearrangement as the key steps. The synthesis started from compound **12** which was converted into **13** by known procedure[6] and was protected as the corresponding *bis*-acetal **14** using protocols developed by Frost and Ley. Chloroalkene **14** was subjected to ozonolytic cleavage and after reductive work-up with dimethyl sulfide the aldehydic ester **15** was obtained which on Wittig methylenation and saponification furnished acid **16**. Esterification of acid under Mitsunobu conditions with the enantiomerically pure secondary alcohol **17** afforded the doubly-unsaturated ester **18** which was subjected to a RCM reaction using Grubbs' second-generation catalyst to afford *Z* isomer of lactone **19.** The lactone **19** on hydrogenation, DIBAL-H reduction, and Wadsworth–Horner–Emmons reaction furnished *E*-configured α, β-unsaturated ester **21.** Saponification of ester **21** and Yamaguchi lactonisation in refluxing toluene afforded the macrolide **22** in 62% yield. Removal of the *bis*-acetal protecting group (**22**→**23**) with $TiCl_4$ and photo irradiatation of *E* isomer **23** led to the target compound in a 4:1 mixture of compounds **23** (57% recovery) and cladospolide B **2** (31% at 43% conversion).



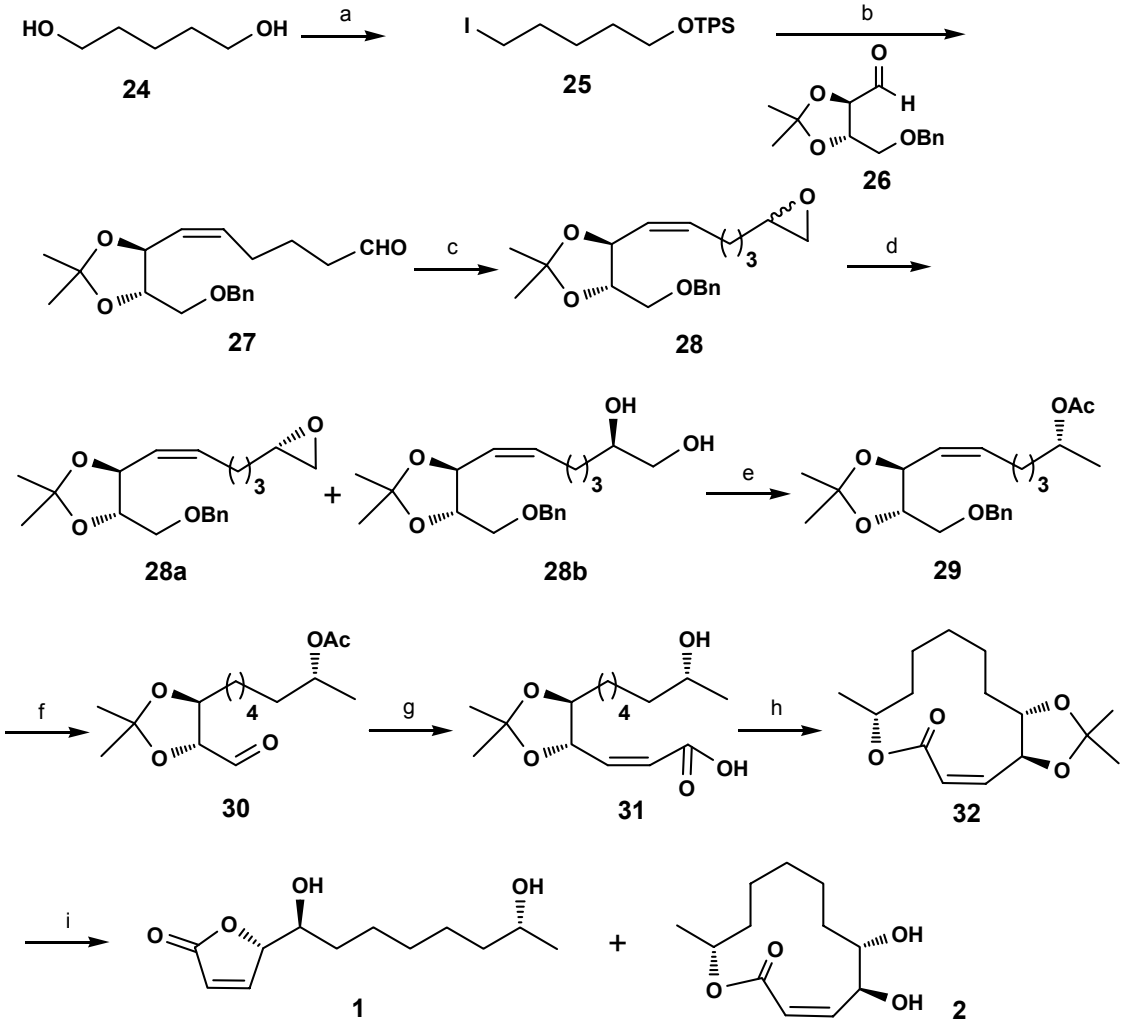


Scheme 2. *Reagents and conditions*: (a) ref. 6 (b) $[CH_3C\text{-}(OMe)_2]_2$, (+)-camphorsulfonic acid, reflux, 24 h, 92%; (c) i) O_3, pyridine, MeOH, -78 ^oC, 1 h; ii) Me_2S, -78 ^oC to 18 ^oC, 2 h (d) i) $H_2C{=}PPh_3$, THF, 0 to 18 ^oC, 1 h; ii) NaOH, EtOH, H_2O, 18 ^oC, 1 h; (e) diethyl diazodicarboxylate, Ph_3P, PhMe, 0 to 18 ^oC, 16 h, 91%; (f) Grubb's I cat., DCM, 18 ^oC, 16 h, 66%; (g) H_2, Pd on C, EtOH, 18 ^oC, 16 h, 86%; (g) i) DIBAL-H, PhMe, -78 ^oC, 0.5 h; ii) trimethylphosphonoacetate, NaH, THF, 0 to 18 ^oC, 1 h, 79%; (h) NaOH, EtOH, H_2O, 18 ^oC, 16 h; (i) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, PhMe, 112 ^oC, 2 h, (two steps 62%); (j) $TiCl_4$, DCM, 94%; (k) *hv*, C_6H_6, 31%.

Sharma, G. V. M. *et al.* (2006)[7]

G. V. M. Sharma and co-workers recently reported the synthesis and also determined the absolute stereochemistry of *iso*-cladospolide B **1** and cladospolide B **2**. Of the three stereogenic centres, the C-4/C-5 *vic*-diol was obtained from tartaric acid while the C-11 stereocentre was created by Jacobsen's method (Scheme 3). The diol **24** on mono TBDPS protection followed by treatment with Ph_3P and I_2, afforded phosphonium salt **25** (80%). Wittig olefination of the known aldehyde **26**[8] with phosphonium salt **25** afforded olefin which on desilylation, followed by Swern oxidation furnished aldehyde **27**. One carbon extension on **27** with trimethylsulfoxonium iodide afforded the diastereoisomeric epoxides **28**. Kinetic resolution of epoxide **28** under Jacobsen reaction conditions[9] using the (*S*,*S*)-catalyst gave epoxide **28a** (40%) and diol **28b** (42%). Reductive opening of epoxide **28a**

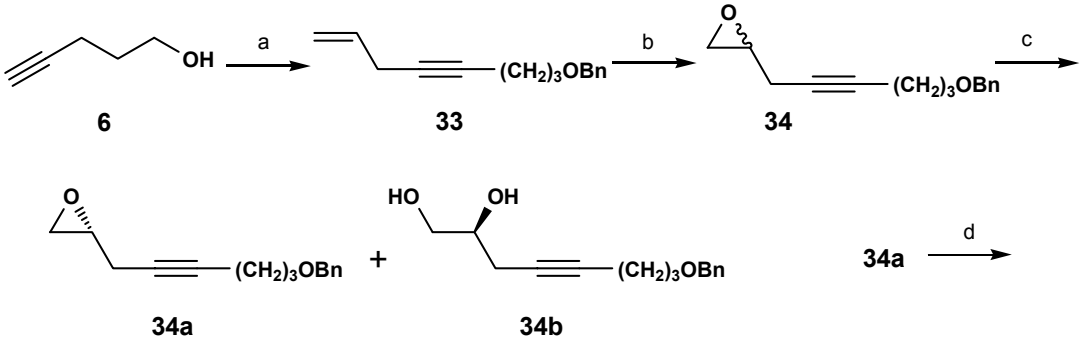
with LAH and acetylation afforded **29** which on catalytic hydrogenation followed by oxidation furnished aldehyde **30**. Wittig reaction of aldehyde **30** with $Ph_3P{=}CHCO_2Me$ in MeOH afforded α, β-unsaturated ester with *cis*-geometry which on base catalysed deprotection of both the ester functionalities furnished *seco*-acid **31**. The *seco*-acid **31** was subjected to macrolactonisation under Yamaguchi reaction conditions[10] to give macrolide **32** which on acetonide deprotection with aq. AcOH afforded (4*S*,5*S*,11*R*)-butenolide **1** (25%) and (4*S*,5*S*,11*R*)-macrolide **2** (55%) as a separable mixture of isomers.

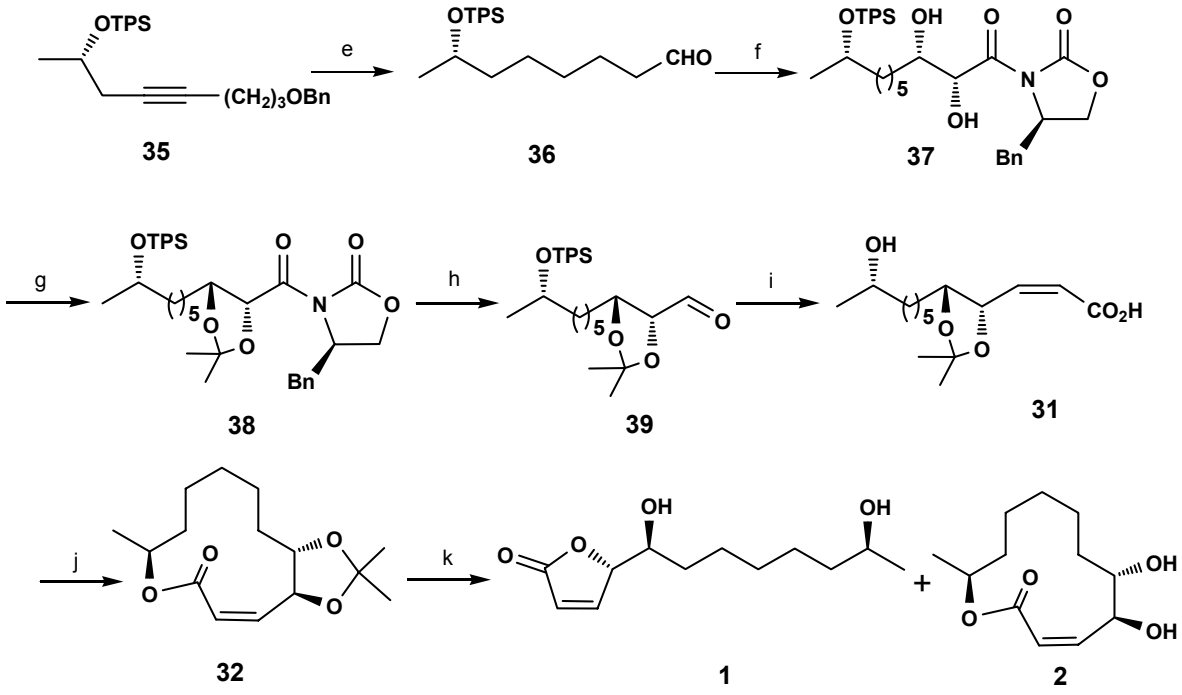


Scheme 2. *Reagents and conditions*: (a) i) TBDPSCl, imidazole, CH_2Cl_2, 0 ^oC, 12 h; ii) I_2, Ph_3P, imidazole, toluene, rt, 30 min; (b) i) Ph_3P, toluene, reflux, 24 h; ii) *n*-BuLi, dry THF, 0 ^oC, 2 h; (c) i) TBAF, dry CH_2Cl_2, 12 h; ii) $(COCl)_2$ dry DMSO, Et_3N, CH_2Cl_2, -78 ^oC, 2 h; iii) TMSOI, *t*-BuOK, dry DMSO, 0 ^oC, 1 h; (d) *S,S*-Jacobsen catalyst, H_2O, rt, 12 h; (e) i) LAH, dry THF, 0 ^oC, 1 h; ii) AcCl, Et_3N, DMAP, CH_2Cl_2, 0 ^oC, 2 h; (f) i) H_2, Pd/C,

EtOAc, rt, 12 h; ii) Swern oxidation; (g) i) $Ph_3P{=}CHCO_2Me$, MeOH, 0 ^oC, 2 h; ii) 4 N NaOH, MeOH, rt, 4 h; (h) 2,4,6-trichlorobenzoyl chloride, Et_3N, CH_2Cl_2, DMAP, toluene, reflux, 24 h; (i) i) 80% aq AcOH, 70 ^oC, 1 h and ii) $TiCl_4$, dry CH_2Cl_2, 0 ^oC, 2 h.

Carmeli and co-workers[11] reported the isolation of *iso*-cladospolide-B **1** from a different *Cladosporium sps.* and determined the absolute stereochemistry of **1** as 4*S*,5*S*,11*S* by Riguera's method and circular dichroism. G. V. M. Sharma and co-workers again attempted the first synthesis of *iso*-cladospolide-B **1** with (4*S*,5*S*,11*S*) configuration *via* different strategy (Scheme 4).[12] The alcohol **6** on benzyl protection followed by coupling with allyl bromide gave **33**, which on further treatment with *m*-CPBA furnished racemic epoxide **34**. Kinetic resolution of racemic epoxide **34** with *R,R*-Jacobsen's catalyst afforded chiral epoxide **34a** and diol **34b**. Reduction of epoxide **34a** with LAH followed by silylation of carbinol furnished ether **35** which on catalytic hydrogenation and IBX oxidation furnished aldehyde **36.** Reaction of aldehyde **36** with *R*-chiral auxiliary furnished **37** which on *p*-methoxybenzyl group removal followed by acetonation of diol, reduction with $LiBH_4$ and IBX oxidation afforded aldehyde **39**. The aldehyde **39** on Wittig olefination in MeOH, furnished *cis*-product which on base catalysed hydrolysis of methyl ester followed by desilylation afforded *seco*-acid **31**. Macrolactonisation of **31** under Yamaguchi reaction conditions furnished macrolide **32** in 66% yield, which on acetonide deprotection with $TiCl_4$ furnished cladospolide B **2** as the exclusive product in 85% yield, while exposure of **32** to aq. AcOH (60%) gave *iso*-cladospolide **1** (11*S*) and cladospolide-B **2** in 20% and 52% yields, respectively.



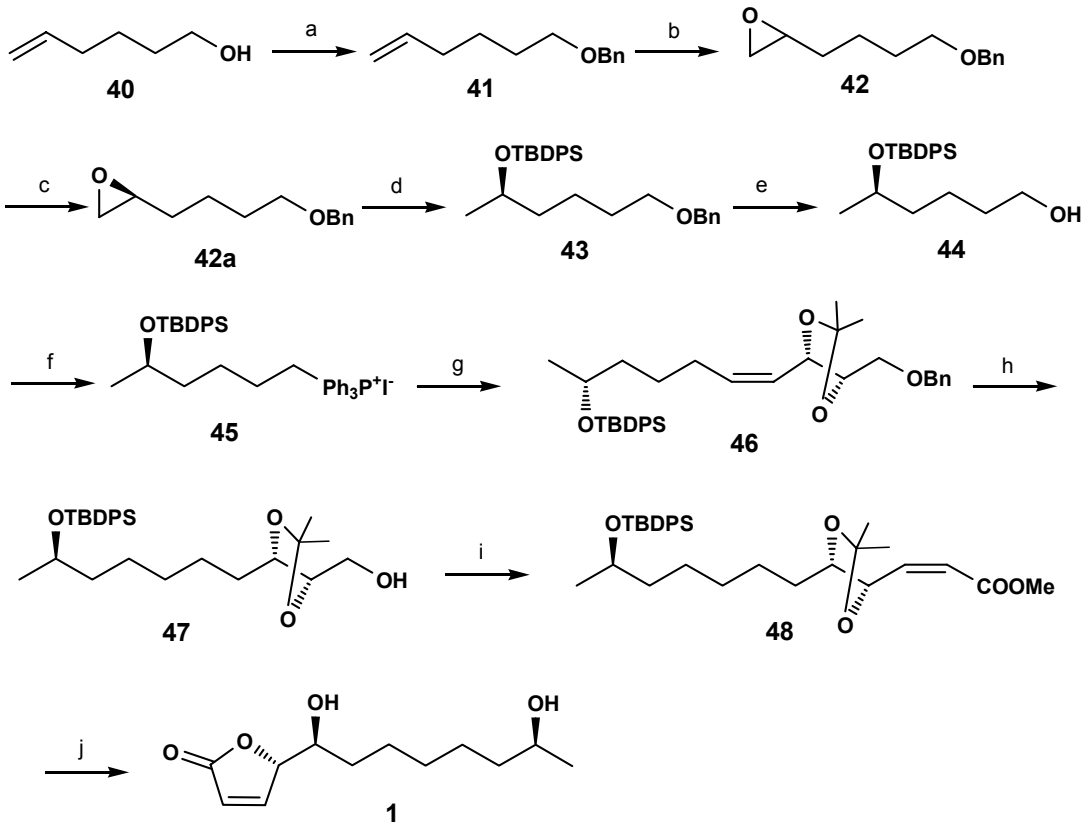


Scheme 4. *Reagents and conditions*: (a) i) NaH, BnBr, THF, 0 ^{o}C-rt, 5 h; ii) allyl bromide, CuI, K_2CO_3 and TBAI, DMF, rt, 12 h; (b) *m*-CPBA, CH_2Cl_2, rt, 10 h; (c) *R,R*-Jacobsen's catalyst, H_2O, rt, 12 h; (d) i) LAH, THF, 0 ^{o}C-rt, 5 h; ii) TBDPSCl, imidazole, CH_2Cl_2, 0 ^{o}C–rt, 3 h; (e) i) 10% Pd/ C, MeOH, H_2, 12 h; ii) IBX, DMSO, 0 ^{o}C-rt, 5 h; (f) (*R*)-chiral auxiliary (I), Bu_2BOTf, DIPEA, CH_2Cl_2, 0 to -78 ^{o}C, 4 h; (g) 2,2-DMP, CSA, 0 ^{o}C-rt, 30 min; (h) $LiBH_4$, THF-H_2O (2:1), 0 ^{o}C-rt, 3 h; (i) i) Ph_3P=CHCOOMe, MeOH, 0 ^{o}C-rt, 2 h; ii) 4 N NaOH, MeOH, 0 ^{o}C-rt, 4 h; iii) HF-pyridine, THF, 0 ^{o}C-rt, 12 h; (j) 2,4,6-trichlorobenzoyl chloride, THF, Et_3N, 0 ^{o}C-rt, 8 h, DMAP, toluene, reflux, 20 h; (k) i) $TiCl_4$, CH_2Cl_2, 0 ^{o}C-rt, 2 h, 85% exclusive **2**; ii) 80% AcOH, rt, 12 h, **1** in 20% and **2** in 52%.

Yadav, J. S. *et al.* (2006)[13]

J. S. Yadav and co-worker accomplished the stereoselective total synthesis of *iso*-cladospolide B **1** using Jacobsen's hydrolytic kinetic resolution as the key step (Scheme 5). The synthesis of **1** started with 5-hexen-1-ol **40** which was protected as its benzyl ether **41** and *m*-chloroperoxybenzoic acid (*m*CPBA) epoxidation afforded the racemic oxirane **42**. The oxirane **42** was hydrolyzed employing (*S,S*)-Salen.III.Co.(OAc) catalyst to give the chiral epoxide **42a**. The epoxide was reduced with LAH, silyl ether protection and

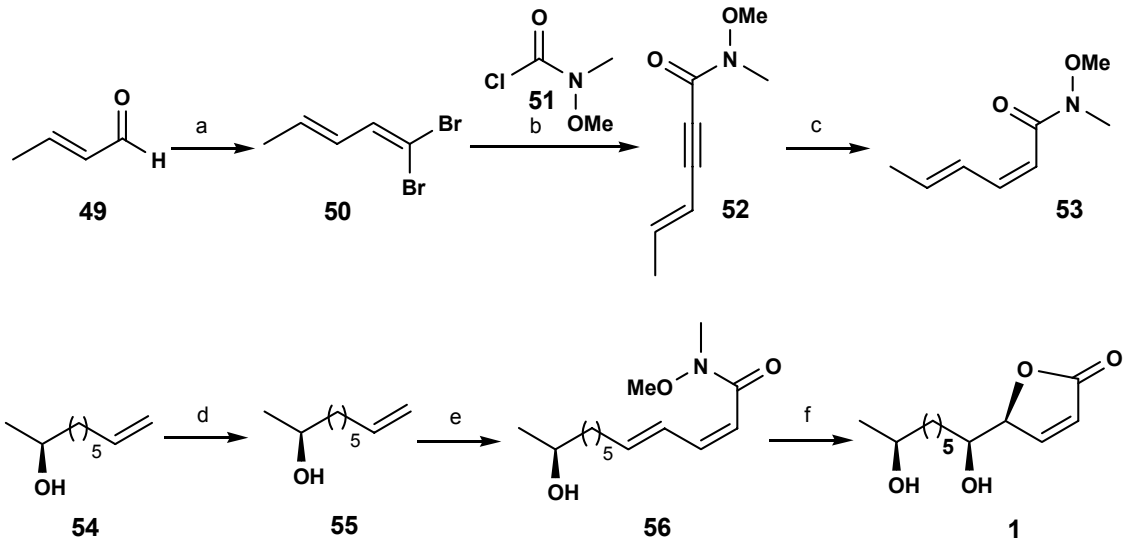
debenzylation afforded alcohol **44**. The alcohol was converted into the corresponding phosphorane salt **45**, with the intention of using this as one of the components in a Wittig reaction with **26** to afford **46**. The compound **46** on hydrogenation furnished saturated alcohol **47** which on Swern oxidation followed by modified Wadsworth–Emmons reaction provided the intermediate **48** exclusively. The intermediate **48** upon one-pot desilylation, deacetonization and lactonization using 3% HCl in methanol afforded *iso*-cladospolide B **1**.



Scheme 5. *Reagents and conditions*: (a) NaH, BnBr, THF, 3 h, 0 °C-r.t., 96%; (b) *m*-CPBA, CH_2Cl_2, 2 h, 84%; (c) Jacobsen resoln. 45%, 98% ee; (d) i) LAH, THF, 30 min, 94%; ii) TBDPSCI, imidazole, CH_2Cl_2, 4 h, 0 °C-r.t., 92%; (e) Pd/C, EtOAc, 12 h, 96%; (f) i) I_2, TPP, imidazole, benzene, 1 h, 96%; ii) TPP, benzene, reflux,16 h, 90%; (g) **36**, *n*-BuLi, THF, 2 h, 68%; (h) Pd/C, H_2 atm., 92%; (i) i) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78 °C, 90%; ii) $MeO_2CCH_2P(O)(OCH_2CF_3)_2$, NaH, THF, 0 °C to –78 °C, 85%; (j) 3% HCl in MeOH, 75%.

Cossy, J. *et al.* (2007)[14]

Very recently, Janine Cossy and co-worker accomplished the total synthesis of (–)-*iso*-cladospolide B **1** using chemoselective cross metatheses and asymmetric dihydroxylations as the key steps (Scheme 6). The synthesis started from crotonaldehyde **49** which on treatment under Fuchs–Corey conditions afforded dibromodiene **50** which was converted into acetylenic amide **52** in one pot *via* the acetylide intermediate which was generated in situ by treatment of **50** with *n*-BuLi, followed by the addition of the Weinreb chloroacetamide **51** (85% yield). After a selective hydrogenation, **53** was isolated in 82% yield. The Grignard reagent prepared from 6-bromohexene **54** was added to (*S*)-propylene oxide to afford alcohol **55** which on cross-metathesis with **53** in the presence of Grubbs–Hoveyda catalyst [Ru]-I furnished dienamide **56.** Sharpless dihydroxylation of dienamide **56** with modified AD-mix β[15] afforded (–)-*iso*-cladospolide B **1** in 68% yield.



Scheme 6. *Reagents and conditions*: (a) PPh_3, CBr_4, CH_2Cl_2, 30 min, 94%; (b) **52**, *n*-BuLi (2 equiv), -78 °C to -20 °C, 85%; (c) H_2 (1 atm), Pd (Lindlar's cat.), EtOAc, quinoline, 0 °C, 150 min, 82%; (d) i) Mg, Et_2O, ii) CuI, –30 °C, (*S*)-propylene oxide, 65%; (e) **54**, Grubbs–Hoveyda catalyst [Ru]-I (5 mol%)**,** CH_2Cl_2, 18 h**,** 57%; (f) modified AD-mix β, 68%.

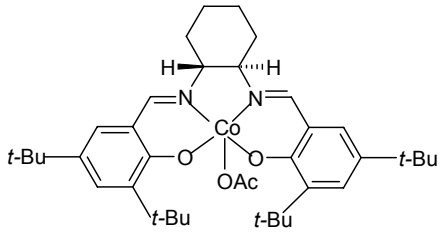
5.1.3. Present work:

Objective:

iso-Cladospolide B **1** and cladospolide B **2** have attracted a great deal of interest among synthetic organic chemists worldwide as an attractive synthetic target due to their interesting biological properties. As part of our research programme aimed at developing enantioselective syntheses of naturally occurring lactones[16] we became interested in devising an efficient route to **1** and **2** and present study describes our successful endeavors towards the total synthesis of *iso*-cladospolide B **1** and cladospolide B **2** from commercially available propylene oxide employing hydrolytic kinetic resolution (HKR), Sharpless asymmetric dihydroxylation (AD) and Yamaguchi macrolactonization as the key steps.

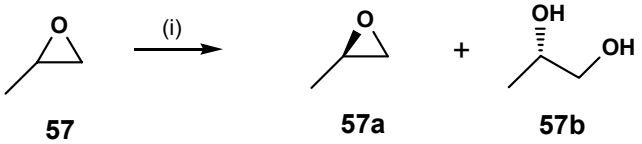
5.1.4. Results and Discussion:

Propylene oxide **57** was subjected to Jacobsen's HKR using (*R,R*)-Salen-Co-(OAc) catalyst (Figure 2) to give *R*-propylene oxide **57a** as a single isomer $[\alpha]_D^{25}$ +11.7 (neat) {lit[9] for (*S*)- propylene oxide $[\alpha]_D^{25}$ -11.6 (neat)}, which was easily isolated from the more polar diol **57b** by distillation (Scheme 7)



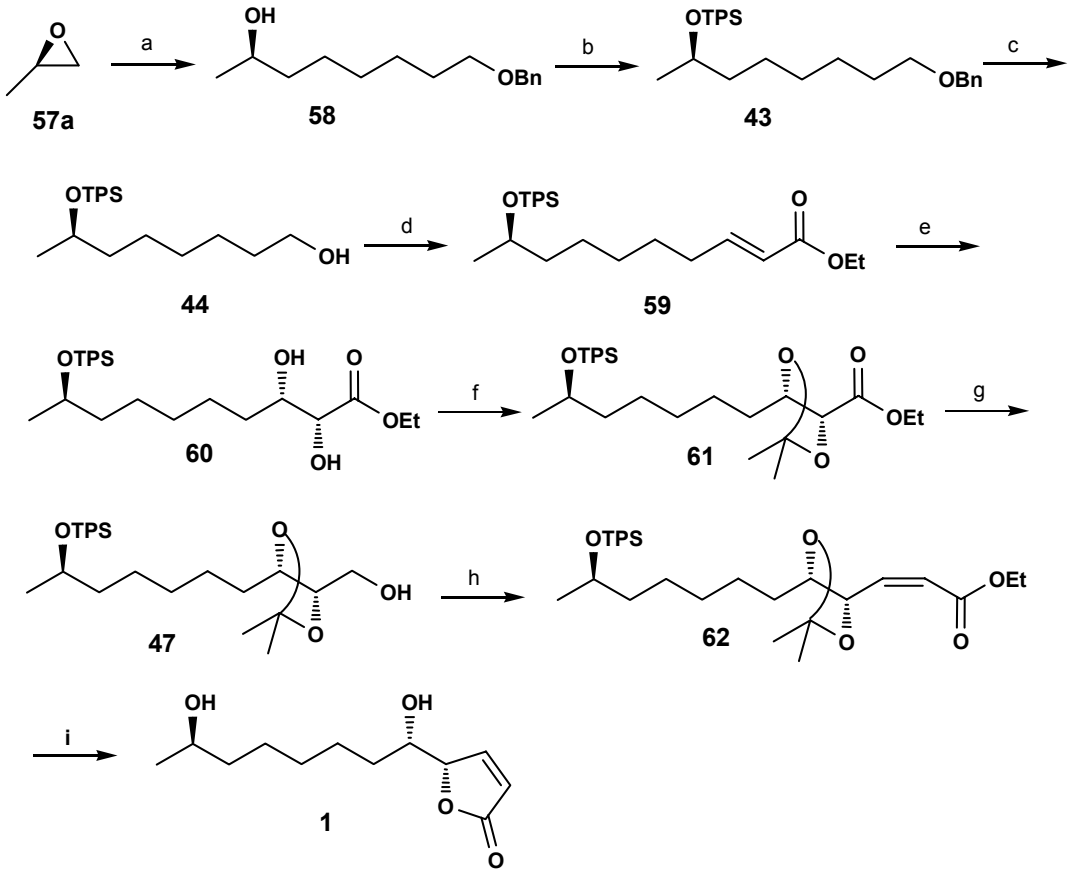
(*R,R*)-SalenCo(III) OAc complex

Figure 2.



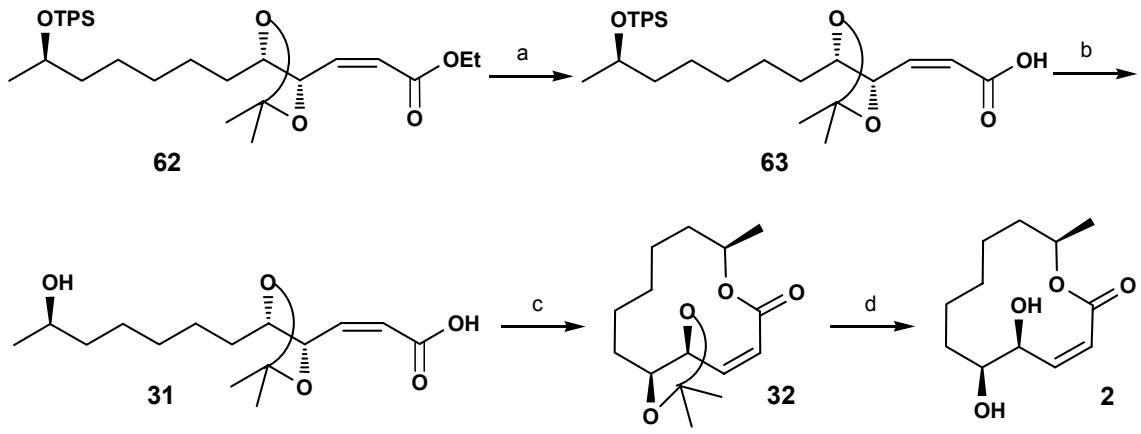
Scheme 7. ***Reagents and conditions:*** (i) (*R,R*)-Salen-Co-(OAc) (0.5 mol%), dist. H_2O (0.55 eq), 0 ^oC, 14 h, (46% for **57a**, 45% for **57b**)

With enantiomerically pure propylene oxide **57a** in hand, we then subjected it to copper-catalyzed (CuI) regioselective opening with the Grignard reagent, derived from benzyl protected bromopentanol to furnish alcohol **58** in 77% yield (Scheme 8). Hydroxyl protection of **59** with *tert*-butyldiphenylsilyl chloride and imidazole in the presence of a catalytic amount of DMAP afforded the silyl ether **43** in 95% yield which on debenzylation using H_2-Pd/C furnished the alcohol **44** in 91% yield. Compound **44** was



Scheme 8. ***Reagents and conditions:*** (a) $C_6H_5CH_2O(CH_2)_5MgBr$, CuI, THF, -78 ^oC, 12 h, 77%; (b) TBDPSCl, imidazole, DMAP, DMF, 0 ^oC, 2 h, 95%; (c) H_2-Pd/C, EtOAc, rt, 91%; (d) (i) $(COCl)_2$, DMSO, CH_2Cl_2, -78 ^oC, Et_3N, -65 ^oC, 1 h (ii) $Ph_3P{=}CHCO_2Et$, THF, reflux, 6 h, 92%; (e) $(DHQ)_2PHAL$ (1 mol%), 0.1M OsO_4 (0.4 mol%), K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, *t*-BuOH/H_2O 1:1, 0 ^oC, 24 h, 94%; (f) 2,2-DMP, *p*-TSA (cat.) CH_2Cl_2, 2 h, 89%; (g) $LiAlH_4$, THF, 0 ^oC-rt, 3 h, 85%; (h) (i) $(COCl)_2$, DMSO, CH_2Cl_2, -78 ^oC, Et_3N, , -65 ^oC, 1 h (ii) $Ph_3P{=}CHCO_2Et$, MeOH, -78 ^oC, 24 h, 82%; (i) 3% MeOH/HCl, 0 ^oC-rt, 5 h, 77%.

then oxidized to the corresponding aldehyde by Swern oxidation[17] and subsequently treated with (ethoxycarbonylmethylene)triphenylphosphorane in dry THF to furnish the Wittig product **59** in 92% yield. The IR spectrum of **59** showed the ester carbonyl absorption at 1712 cm^{-1} and olefin C=C stretching at 1664 cm^{-1}. The ^1H NMR spectrum gave olefin protons at δ 5.80 (doublet of triplet) and 6.88-7.02 (multiplet) with the coupling constant J = 1.51, 15.54 Hz indicating *trans*-olefin. The olefin **59** was treated with osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of $(DHQ)_2PHAL$ under Sharpless asymmetric conditions[18] to give the diol **60** in 94% yield with 96% de. The diastereoselectivity was determined from ^{13}C NMR spectral data. The IR spectrum of **60** showed hydroxyl absorption at 3410 cm^{-1} and ester carbonyl at 1713 cm^{-1}. The ^1H NMR indicated absence of olefin protons. Treatment of diol **60** with 2,2-dimethoxypropane in the presence of a catalytic amount of *p*-TSA gave compound **61**, which on subsequent reduction using $LiAlH_4$ provided the alcohol **47** in excellent yield. The acetonide methyl protons appeared at δ 1.47 (doublet) in the ^1H NMR spectrum and typical quaternary carbon of acetonide appeared at 110.6 in the ^{13}C NMR spectrum in compound **61**. The alcohol **47** was oxidized to the aldehyde under Swern conditions and subsequently treated with (ethoxycarbonylmethylene)triphenylphosphorane in dry methanol at -78 ^oC for 24 h to give the Wittig product **62** in 82% yield with a *Z:E* ratio of 85:15, the isomers of which could easily be separated by silica gel column chromatography. The *Z:E* ratio of compound **62** was determined from the ^1H NMR spectrum of the crude product. The IR spectrum of **62** showed the ester carbonyl absorption at 1723 cm^{-1} and olefin C=C stretching at 1655 cm^{-1}. The ^1H NMR spectrum gave olefin protons at δ 5.93 (doublet, one proton) with coupling constant J = 11.8 Hz and 6.13 (doublet of doublet, one proton) with coupling constant J = 8.7, 11.8 Hz indicating *cis*-olefin. Finally, deprotection of the acetonide and TPS groups and concomitant cyclization of the olefin **62** was achieved in one-pot using 3% methanolic HCl to furnish the target molecule, *iso*-cladospolide B **1** in 77% yield; $[\alpha]_D^{25}$ -105.3 (*c* 0.23, MeOH), {lit.[4] $[\alpha]_D^{25}$ -105.0 (*c* 0.23, MeOH)}. The physical and spectroscopic data were in full agreement with the literature.



Scheme 9. ***Reagents and conditions:*** (a) LiOH, MeOH/H_2O (3:2), 0 ^oC-rt; (b) TBAF, CH_2Cl_2, 0 ^oC-rt, (88%, two steps); (c) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, then DMAP, benzene, 86%; (d) CF_3COOH, THF/H_2O, 0 ^oC, 1 h, 88%.

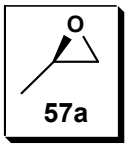
The synthesis of cladospolide B **2** started from the olefin **62** as illustrated in Scheme 9. Ester hydrolysis of **62** with LiOH furnished acid **63** which on TPS deprotection using TBAF led to the *seco*-acid **31** in 88% (two steps) yield. Macrolactonization of **31** under Yamaguchi conditions provided the lactone **32** in excellent yield, which on subsequent cleavage of the acetonide afforded the target molecule **2** in 88% yield; $[\alpha]_D^{25}$ -164.3 (*c* 0.10, MeOH), {lit.[5] $[\alpha]_D^{25}$ -162.0 (*c* 0.10, MeOH)}. The physical and spectroscopic data were in full agreement with the literature.[5]

5.1.5. Conclusion

In conclusion, a practical and enantioselective synthesis of *iso*-cladospolide B **1** and cladospolide B **2** has been achieved employing Jacobsen's HKR, a Sharpless asymmetric dihydroxylation and Yamaguchi macrolactonization as the key steps. The merits of this synthesis are high enantio- and diastereoselectivity with high yielding reaction steps. The synthetic strategy described has significant potential for further extension to other stereoisomers and analogues of *iso*-cladospolide B and cladospolide B.

5.1.6. Experimental Section

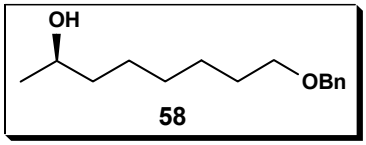
(*R*)-Propylene oxide (57a).



The racemic propylene oxide **57** was resolved to (*R*)-propylene oxide (**57a** in high enantiomeric excess by the HKR method following a literature procedure.[9]

$[\alpha]_D^{25}$: +11.7 (neat), lit.[9] $[\alpha]_D^{25}$ –11.6 (neat) (for (*S*)-propylene oxide).

(*R*)-8-(Benzyloxy)octan-2-ol (58)



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 –78 ^oC and vigorously stirred, and freshly prepared Grignard reagent from benzyl protected bromopentanol (9.96 g, 38.74 mmol) and Mg (0.941 g, 38.79 mmol) was injected to it. A solution of propylene oxide **57a** (1.5 g, 25.82 mmol) in THF (10 mL) was added slowly to the above reagent, and the mixture was stirred at –78 ^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 product which on distillation provided homoallylic alcohol **58** as a colorless liquid.

Yield: 4.7 g, 77%

Mol. Formula: $C_{15}H_{24}O_2$

$[\alpha]_D^{25}$: + 9.78 (c 1.0, $CHCl_3$) {Lit.[13] + 9.5 (c 1.8, $CHCl_3$)}

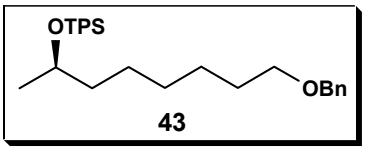
IR (neat, cm^{-1}): ν_{max} 3428, 2935, 2857, 1608, 1454, 1102

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.19 (d, *J*= 6.19 Hz, 3 H), 1.27-1.66 (m, 11 H), 3.48 (t, *J* = 6.45 Hz, 2 H), 3.72-3.87 (m, 1 H), 4.51 (s, 2 H), 7.29-7.37 (m, 5 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 23.6, 26.7, 29.3, 29.6, 32.6, 41.7, 70.2, 72.7, 127.5, 128.2, 138.5 ppm.

Analysis Calcd.: C, 76.23; H, 10.24%; **Found:** C, 76.31; H, 10.19%.

((*R*)-8-(Benzyloxy)octan-2-yloxy)(*tert*-butyl)diphenylsilane (43)



To a stirred solution of alcohol **58** (4.0 g, 16.92 mmol) in dry DMF (50 mL) and imidazole (1.27 g, 18.61 mmol) at 0 °C was added TBDPSCl (5.58 g, 5.21 mL, 20.31 mmol) and DMAP (cat.) dropwise and the reaction was stirred at 0 ^{o}C for 2 h. The reaction mixture was quenched with H_2O (50 mL) and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layer was washed with brine (2 x 40 mL) and dried over anhydrous Na_2SO_4. The solvent was concentrated under reduced pressure and the residue was purified by column chromatography (EtOAc–hexane, 5%) to give **43**.

Yield: 7.63 g, 95%

Mol. Formula: $C_{31}H_{42}O_2Si$

$[\alpha]_D^{25}$: + 14.21 (c 1.0, $CHCl_3$) {Lit.[13] + 11.74 (c 2.1, $CHCl_3$)}

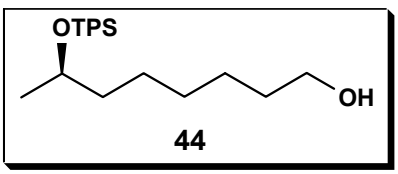
IR (neat, cm^{-1}): ν_{max} 2931, 2857, 1589, 1427, 1361, 1111

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.04-1.07 (m, 12 H), 1.22-1.61 (m, 10 H), 3.45 (t, J = 6.57 Hz, 2 H), 3.76-3.91 (m, 1 H), 4.51 (s, 2 H), 7.31-7.42 (m, 11 H), 7.69 (dd, J = 2.27, 7.70 Hz, 4 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 19.2, 23.2, 25.1, 26.1, 27.0, 29.4, 29.6, 39.3, 69.5, 70.4, 72.8, 127.3, 127.4, 127.5, 128.3, 129.4, 134.5, 134.8, 135.8, 138.6 ppm.

Analysis Calcd.: C, 78.43; H, 8.92%; **Found:** C, 78.39; H, 9.01%.

(*R*)-7-(*tert*-Butyldiphenylsilyloxy)octan-1-ol (44)



A solution of benzyl compound **43** (7.5 g, 15.88 mmol) in EtOAc (45 mL) was mixed with Pd/C (10% mol) and stirred for 12 h under hydrogen atmosphere. The catalyst was removed by filtration and the solvent was evaporated to give a residue that was purified by column chromatography (EtOAc–hexane, 20%) to afford the pure **44**.

Yield: 5.53 g, 91%

Mol. Formula: $C_{24}H_{36}O_2Si$

$[\alpha]_D^{25}$: + 12.48 (c 1.0, $CHCl_3$) {Lit.[13] + 8.25 (c 1.1, $CHCl_3$)}

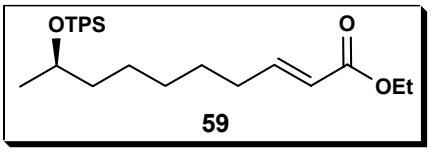
IR (neat, cm^{-1}): ν_{max} 3351, 2931, 2857, 1589, 1472, 1427, 1110, 1057

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.06 (brs, 12 H), 1.23-1.52 (m, 10 H), 3.62 (t, J = 6.57 Hz, 2 H), 3.76-3.91 (m, 1 H), 5.31 (brs, 1 H), 7.33-7.46 (m, 6 H), 7.69 (d, J = 7.33 Hz, 4 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 19.2, 23.1, 25.1, 25.6, 27.0, 29.3, 32.6, 39.3, 62.7, 69.5, 127.4, 129.3, 134.6, 134.9, 135.8 ppm.

Analysis Calcd.: C, 74.94; H, 9.43%; **Found:** C, 75.02; H, 9.51%.

(*R*,*E*)-Ethyl 9-(*tert*-butyldiphenylsilyloxy)dec-2-enoate (59)



59

To a solution of oxalyl chloride (2.48 g, 1.7 mL, 19.50 mmol) in dry CH_2Cl_2 (50 mL) at -78 ^oC was added dropwise dry DMSO (3.15 g, 2.9 mL, 39.00 mmol) in CH_2Cl_2 (10 mL). After 30 min, alcohol **44** (5.0 g, 13.00 mmol) in CH_2Cl_2 (20 mL) was added over 10 min giving copious white precipitate. After stirring for 1 h at -78 ^oC the reaction mixture was brought to -60 ^oC and Et_3N (5.80 g, 8.0 mL, 57.20 mmol) was added slowly and stirred for 30 min allowing the reaction mixture to warm to room temperature. The reaction mixture was then diluted with water (50 mL) and CH_2Cl_2. The organic layer was separated and washed with water and brine, dried (Na_2SO_4) and passed through short pad of celite. The filtrate was concentrated to give the aldehyde as pale yellow oil, which was used as such for the next step without purification.

To a solution of (ethoxycarbonylmethylene)triphenyl phosphorane (7.37 g, 21.19 mmol) in dry THF (20 mL) was added a solution of the above aldehyde in dry THF (10 mL). The

reaction mixture was stirred at reflux for 6 h. It was then concentrated and purified by silica gel column chromatography (EtOAc/petroleum ether, 1:9) to give olefin **59** as pale yellow oil.

Yield: 5.41 g, 92%

Mol. Formula: $C_{28}H_{40}O_3Si$

$[\alpha]_D^{25}$: + 19.18 (c 1.0, $CHCl_3$)

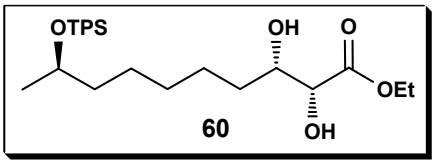
IR (neat, cm^{-1}): ν_{max} 2932, 2858, 1712, 1664, 1589, 1216, 1110

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.06 (brs, 12 H), 1.23-1.45 (m, 11 H), 2.15 (q, J = 7.83, 14.40 Hz, 2 H), 3.76-3.91 (m, 1 H), 4.21 (q, J = 7.08, 14.28 Hz, 2 H), 5.80 (dt, J = 1.51, 15.54 Hz, 1 H), 6.88-7.02 (m, 1 H), 7.34-7.44 (m, 6 H), 7.69 (m, 4 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 19.2, 23.2, 24.8, 27.0, 27.9, 29.0, 32.0, 31.2, 59.9, 69.4, 121.3, 127.3, 129.4, 134.6, 134.9, 135.8, 149.2, 166.6 ppm.

Analysis Calcd.: C, 74.29; H, 8.91%; **Found:** C, 74.31; H, 8.97%.

(2*R*,3*S*,9*R*)-Ethyl 9-(*tert*-butyldiphenylsilyloxy)-2,3-dihydroxydecanoate (60)



60

To a mixture of $K_3Fe(CN)_6$ (11.24 g, 34.13 mmol), K_2CO_3 (4.72 g, 34.13 mmol), $(DHQ)_2PHAL$ (90 mg, 1 mol%) in *t*-BuOH/H_2O (1:1, 110 mL) at 0 °C was added osmium tetroxide (0.50 mL, 0.1 M solution in toluene, 0.4 mol%), followed by methanesulfonamide (1.08 mg, 11.37 mmol). After stirring for 2 min at 0 °C, the olefin **59** (5.15 g, 11.38 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 24 h and then quenched with solid sodium sulfite (10 g). The stirring was continued for additional 15 min and then the solution was extracted with EtOAc (3×30 mL). The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography purification (EtOAc/petroleum ether, 1:4) of the crude product gave **60** as a colourless liquid.

Yield: 5.54 g, 94%

Mol. Formula: $C_{28}H_{42}O_5Si$

$[\alpha]_D^{25}$: +6.68 (c 1.0, $CHCl_3$)

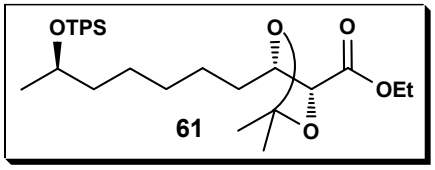
IR (neat, cm^{-1}): ν_{max} 3410, 2932, 1713, 1653, 1609, 1590, 1216

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.06 (s, 9H), 1.07 (t, J = 5.9 Hz, 3H), 1.18–1.58 (m, 13H), 2.10 (br s, 2H), 3.76–3.90 (m, 2H), 4.06 (d, J = 2.0 Hz, 1H), 4.30 (q, J = 7.2 Hz, 2H), 7.32–7.47 (m, 6H), 7.66–7.71 (m, 4H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 19.2, 23.2, 25.1, 25.6, 27.0, 29.4, 33.6, 39.2, 61.9, 69.4, 72.5, 73.1, 127.3, 129.3, 134.5, 134.8, 135.8, 173.7 ppm.

Analysis Calcd.: C, 69.10; H, 8.70%; **Found:** C, 69.04; H, 8.73%.

(4*R*,5*S*)-Ethyl 5-((*R*)-6-(*tert*-butyldiphenylsilyloxy)heptyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (61)



61

To a solution of amino alcohol **60** (2.5 g, 5.14 mmol) in dry DCM (25 mL) was added 2,2-dimethoxy propane (0.60 g, 0.70 mL, 5.65 mmol) and catalytic amount of *p*-TsOH (20 mg). The reaction mixture was stirred at 0 °C to room temperature for 2 h. A pinch of $NaHCO_3$ was added and stirring was continued for additional 15 min and then the solution was extracted with EtOAc (3 x 20 mL). The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography purification (EtOAc/petroleum ether, 5%) of the crude product gave **61** as a colourless liquid.

Yield: 2.41 g, 89%

Mol. Formula: $C_{31}H_{46}O_5Si$

$[\alpha]_D^{25}$: + 12.65 (c 1.0, $CHCl_3$)

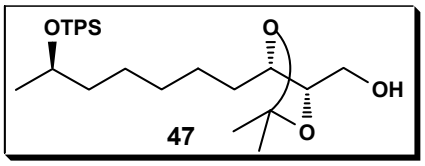
IR (neat, cm^{-1}): ν_{max} 2934, 2859, 1751, 1428, 1373, 1216, 1110

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.05 (brs, 12H), 1.18–1.39 (m, 10H), 1.47 (d, J = 4.80 Hz, 6H), 1.58-1.76 (m, 3H), 3.76–3.88 (m, 1H), 4.10 (s, 2H), 4.25 (q, J = 7.20, 14.41 Hz, 2H), 7.32–7.43 (m, 6H), 7.67 (d, J = 5.8 Hz, 4H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 19.1, 23.1, 25.0, 25.6, 26.9, 29.4, 33.4, 39.2, 61.1, 79.0, 79.1, 110.6, 127.3, 129.3, 134.4, 134.7, 135.7, 170.9 ppm.

Analysis Calcd.: C, 70.68; H, 8.80%; **Found:** C, 70.71; H, 8.79%.

(4*S*,5*S*)-5-[(*R*)-6-(*tert*-Butyldiphenylsilyloxy)heptyl]-2,2-dimethyl-1,3-dioxolan-4-yl}methanol (47)



A suspension of $LiAlH_4$ (190 mg, 5.01 mmol) in anhydrous THF (5 mL) was stirred for 5 min at 0 °C, and a solution of **61** (2.20 g, 4.18 mmol) in THF (4 mL) was then added dropwise. The mixture was stirred for 2 h at 0 °C and for 1 h at room temperature. Excess $LiAlH_4$ was destroyed by slow addition of 10% aq. NaOH (0.4 mL) and EtOAc (5 mL). The white precipitate was filtered through a pad of neutral alumina and washed with MeOH (3 x 15 mL). The filtrate was concentrated and the residue was purified by silica gel column chromatography to give **47** as a colorless liquid.

Yield: 1.72 g, 85%

Mol. Formula: $C_{29}H_{44}O_4Si$

$[\alpha]_D^{25}$: + 21.11 (c 1.0, $CHCl_3$)

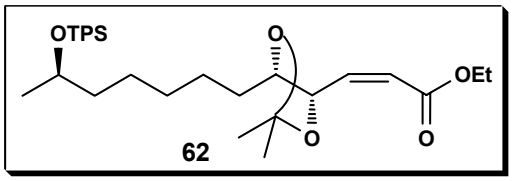
IR (neat, cm^{-1}): ν_{max} 3438, 3010, 2933, 1658, 1427, 1215, 1109

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.05 (brs, 12H), 1.18–1.82 (m, 16H), 1.70 (brs, 1H), 3.40–4.11 (m, 1H), 7.33–7.47 (m, 6H), 7.69 (d, J = 6.31 Hz, 4H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 19.2, 23.1, 25.0, 25.9, 26.9, 27.3, 29.6, 32.9, 39.2, 62.0, 69.4, 81.5, 108.4, 127.3, 129.3, 134.5, 134.8, 135.8 ppm.

Analysis Calcd.: C, 71.85; H, 9.15%; **Found:** C, 71.91; H, 9.11%.

(*Z*)-Ethyl-3-{(4*S*,5*S*)-5-[(*R*)-6-(*tert*-butyldiphenylsilyloxy)hept-1-enyl]-2,2-dimethyl-1,3-dioxolan-4-yl}acrylate (62)



To the solution of oxalyl chloride (0.50 g, 3.90 mL) in dry CH_2Cl_2 (15 mL) at –78 °C, was added DMSO (0.61 g, 0.55 mL) slowly *via* syringe and the reaction was stirred for 10 min. The alcohol **47** (1.26 g, 2.60 mmol) in dry CH_2Cl_2 (10 mL) was then added dropwise at -78 °C. After 2 h, Et_3N (1.16 g, 1.60 mL, 11.43 mmol) was added slowly and the reaction mixture was allowed to come to 0 °C over 30 min. The reaction mixture was diluted with H_2O (30 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layer was washed with brine (2 x 30 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude aldehyde which was used directly for the next step.

To a solution of (ethoxycarbonylmethylene)triphenyl phosphorane (1.09 g, 3.12 mmol) in dry MeOH (5 mL) was added a solution of the above aldehyde in dry MeOH (2 mL). The reaction mixture was stirred -78 ^oC for 24 h. It was then concentrated and purified by silica gel column chromatography (EtOAc/petroleum ether, 1:9) to give *cis*-olefin **62** as a pale yellow oil.

Yield: 1.18 g, 82%

Mol. Formula: $C_{33}H_{48}O_5Si$

$[\alpha]_D^{25}$: +29.22 (*c* 1.0, $CHCl_3$)

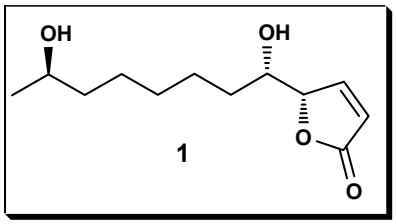
IR (neat, cm^{-1}): ν_{max} 3071, 2932, 1723, 1655, 1589, 1462, 1378, 1191

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.05 (s, 9H), 1.14-1.37 (m, 12H), 1.44 (s, 6H), 1.51-1.65 (m, 4H), 3.64-3.90 (m, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 5.27 (t, *J* = 8.6 Hz, 1H), 5.93 (d, *J* = 11.8 Hz, 1H), 6.13 (dd, *J* = 11.7, 8.7 Hz, 1H), 7.32-7.46 (m, 6H), 7.66-7.70 (m, 4H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 19.2, 23.1, 25.0, 26.0, 27.0, 29.6, 31.9, 39.3, 60.3, 69.4, 76.0, 80.9, 109.1, 122.9, 127.3, 129.3, 134.5, 134.8, 135.8, 145.5, 165.3 ppm.

Analysis Calcd.: C, 71.70; H, 8.75%; **Found:** C, 71.66; H, 8.74%.

(*S*)-5-((1*S*,7*R*)-1,7-dihydroxyoctyl)furan-2(5H)-one; *iso*-cladospolide B (1)



To a solution of amino alcohol **50** (60 mg, 1.09 mmol) was added 3% MeOH/HCl. The reaction mixture was stirred at 0 ^{o}C to room temperature for 5 h. To the reaction mixture pinch of $NaHCO_3$ and the stirring was continued for additional 15 min and then the solution was extracted with EtOAc (3 x 10 mL). The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography purification (EtOAc/petroleum ether, 1:4) of the crude product gave **1** as colorless syrup.

Yield: 19 mg, 77%

Mol. Formula: $C_{12}H_{20}O_4$

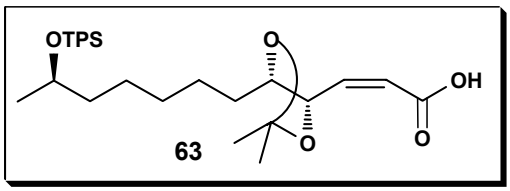
$[\alpha]_D^{25}$: -105.3 (c 0.23, MeOH) {Lit.[4] -105 (c 0.23, MeOH)}

IR (neat, cm^{-1}): ν_{max} 3437, 2932, 2871, 1745, 1462, 1329, 1165, 1097, 1040

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.20 (d, J = 6.19, 3H), 1.26-1.60 (m, 10H), 1.86-2.21 (m, 2 H), 3.66-3.88 (m, 2H), 4.99 (d, J = 2.65 Hz, 1H), 6.20 (dd, J = 2.02, 5.81 Hz, 1 H), 6.47 (dd, J = 1.52, 5.81 Hz, 1 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 23.1, 25.1, 29.4, 33.6, 39.2, 69.4, 72.5, 86.1, 122.8, 153.3, 173.7 ppm.

(*Z*)-3-((4*S*,5*S*)-5-((*R*)-6-(*tert*-Butyldiphenylsilyloxy)heptyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylic acid (63):



To the ester **62** (500 mg, 0.90 mmol) dissolved in MeOH (10 mL) and H_2O (6.67 mL) was added $LiOH.H_2O$ (0.11 g, 2.71 mmol) and stirred at 0 ^{o}C to room temperature for 5 h. The reaction mixture was further diluted with H_2O (5 mL) and stirred for 30 min then concentrated by rotary evaporator to quarter of its volume. The mixture was acidified with 1 M HCl (pH 3) and the reaction mixture was extracted with EtOAc (3 x 10 mL). The

combined organic layer was washed with brine (2 x 10 mL) and dried over anhydrous Na_2SO_4, filtered, evaporated and the crude product was purified by column chromatography (EtOAc–hexane, 35%) to yield pure **63**.

Yield: 427 mg, 90%

Mol. Formula: $C_{31}H_{44}O_5Si$

$[\alpha]_D^{25}$: + 5.75 (c 0.50, $CHCl_3$)

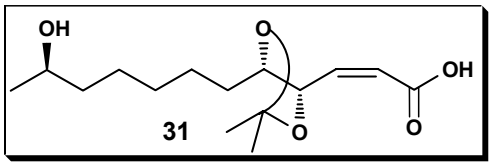
IR (neat, cm^{-1}): ν_{max} 2966, 2831, 1730, 1644, 1216, 1115

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.05 (brs, 12H), 1.22-1.60 (m, 16H), 3.48 (d, J = 8.46 Hz, 1H), 3.67-3.87 (m, 2H), 5.22 (t, J = 7.71 Hz, 1H), 5.96 (dd, J = 0.88, 11.75 Hz, 1H), 6.26 (dd, J = 8.46, 11.75 Hz, 1H), 7.32-7.42 (m, 6H), 7.66-7.70 (m, 4H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 19.2, 23.2, 25.1, 25.9, 27.0, 27.3, 29.6, 31.8, 39.3, 69.5, 76.0, 80.9, 109.4, 127.7, 129.4, 134.5, 134.9, 135.8, 147.6 ppm.

Analysis Calcd.: C, 70.95; H, 8.45%; **Found:** C, 70.75; H, 8.56%.

(*Z*)-3-((4*S*,5*S*)-5-((*R*)-6-Hydroxyheptyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylic acid (31):



To the acid **63** (400 mg, 7.59 mmol) dissolved in THF was added TBAF (0.22 g, 0.84 mmol) and stirred at r.t. for 24 h. The reaction mixture was further diluted with H_2O (10 mL) and stirred 0 ^oC to room temperature for 5 h. The reaction mixture was quenched with water (10 mL) and then the solution was extracted with EtOAc (3 x 10 mL). The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography purification (EtOAc/petroleum ether, 4:1) of the crude product gave **31** as colorless syrup.

Yield: 280 mg, 98% (two steps 88%).

Mol. Formula: $C_{15}H_{26}O_5$

$[\alpha]_D^{25}$: + 6.25 (c 0.75, $CHCl_3$)

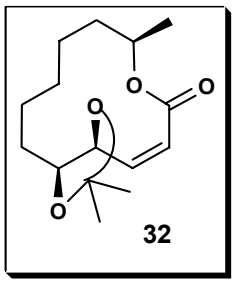
IR (neat, cm^{-1}): ν_{max} 3468, 2971, 2832, 1727, 1654, 1589, 1462, 1370, 1108

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.19 (d, J = 1.27, 6.19 Hz, 3H) 1.30-1.67 (m, 15H), 2.08 (d, J = 11.24 Hz, 1H), 3.70-3.94 (m, 2H), 5.28 (tt, J = 1.14, 8.34, 9.48 Hz, 1H), 5.47-5.66 (m, 2H), 5.96 (dt, J = 1.14, 11.75 Hz, 1H), 6.25 (dd, J = 5.89, 11.87 Hz, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 23.0, 25.1, 26.9, 27.2, 29.3, 31.4, 31.6, 38.7, 68.1, 76.0, 80.8, 109.3, 122.5, 141.1, 158.7 ppm.

Analysis Calcd.: C, 62.91; H, 9.15%; **Found:** C, 62.85; H, 9.05%.

Macrolactone 32:



32

To a solution of *seco* acid **31** (120 mg, 0.42 mmol) in THF (4 mL) were added Et_3N (0.88 mL, 0.63 mmol) and 2,4,6-trichlorobenzoyl chloride (153 mg, 0.1 mL, 0.63 mmol) and the reaction mixture was stirred for 2 h at room temperature under argon atmosphere and then diluted with toluene (150 mL). The resulting reaction mixture was added dropwise to a solution of DMAP (230 mg, 1.89 mmol) in toluene (20 mL) at 80 ^oC over 1 h and the mixture was stirred for additional 1 h under reflux. The reaction mixture was washed with aq. citric acid solution and brine. The organic layer was dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using pet ether/EtOAc (3:2) as eluent provided the lactone **32** as a light yellow color syrupy liquid.

Yield: 96 mg, 86%

Mol. Formula: $C_{15}H_{24}O_4$

$[\alpha]_D^{25}$: -33.06 (c 0.50, $CHCl_3$)

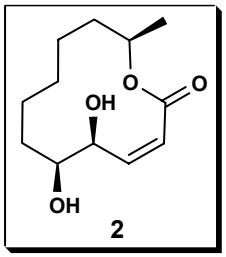
IR (neat, cm^{-1}): ν_{max} 2965, 2811, 1745, 1644, 1575, 1450, 1110

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.14-1.39 (m, 9H), 1.44 (d, J = 2.65 Hz, 6H) 1.58-1.96 (m, 4H), 3.59-3.95 (m, 1H), 4.04 (q, J = 8.59, 16.62 Hz, 1H), 4.92-5.07 (m, 1H), 6.24 (d, J = 11.65 Hz, 1H), 6.79 (dd, J = 8.5, 11.87 Hz, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 19.2, 23.2, 25.1, 25.9, 27.0, 33.3, 73.8, 76.0, 80.9, 109.4, 122.5, 147.6, 170.0 ppm.

Analysis Calcd.: C, 67.14; H, 9.01%; **Found:** C, 67.22; H, 8.98%.

Synthesis of Cladospolide B (2)



2

To the above the lactone **32** (45 mg, 0.17 mmol) in THF/H_2O, 4:1 (4 mL) was added trifluoroacetic acid in catalytic amount. The reaction mixture was stirred at 0 ^oC for 1 h and then saturated aq. $NaHCO_3$ added and mixture extracted with dichloromethane (3 x 5 mL). The combined organic layers were washed with brine and dried over Na_2SO_4 and concentrated under reduced pressure to near dryness. The crude product was purified by silica gel column chromatography to give **2** as a colorless solid.

Yield: 33 mg, 88%

$[\alpha]_D^{25}$: $[\alpha]_D^{25}$ -164.3 (*c* 0.10, MeOH), {lit.[5] $[\alpha]_D^{25}$ -162.0 (*c* 0.10, MeOH)}

M. P. : 99 ^oC (lit.[5] 98-102 ^oC **)**

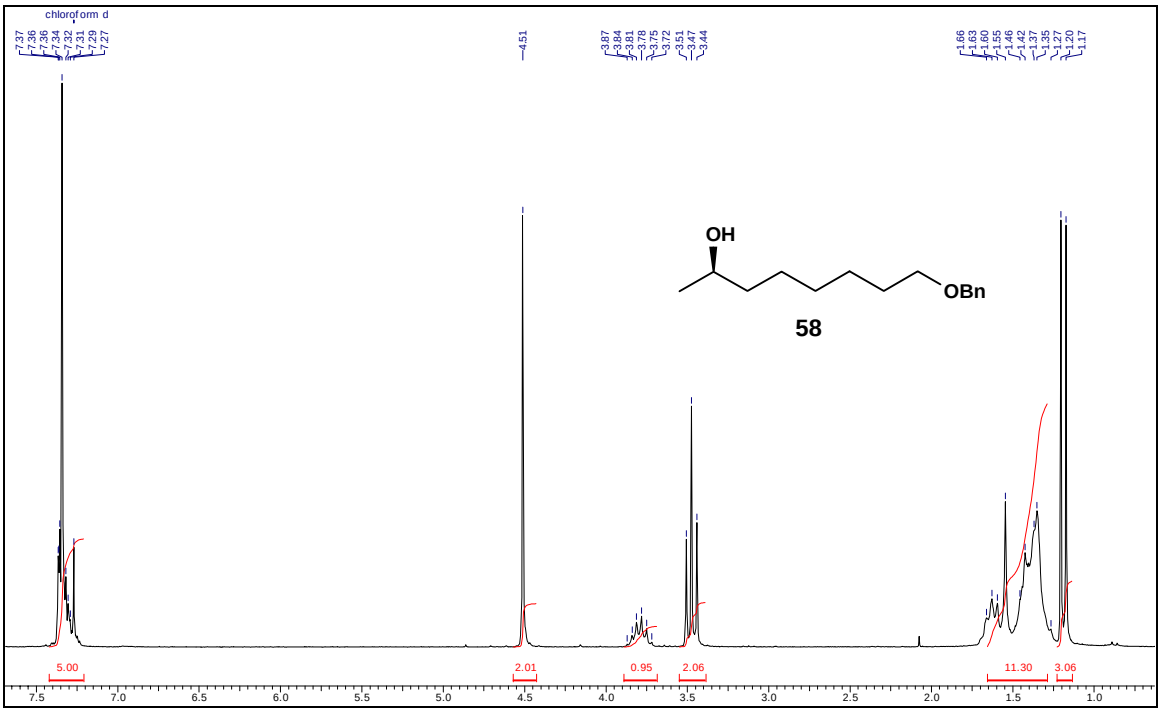
IR (KBr, cm^{-1}): ν_{max} 2940, 1716, 1630, 1347, 1282, 1075

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.25-1.65 (m, 13H), 3.64-3.87 (m, 1H), 4.98-5.18 (m, 2 H), 5.95 (d, *J* = 11.88 Hz, 1H), 6.14 (dd, *J* = 8.75, 11.87 Hz, 1H) ppm.

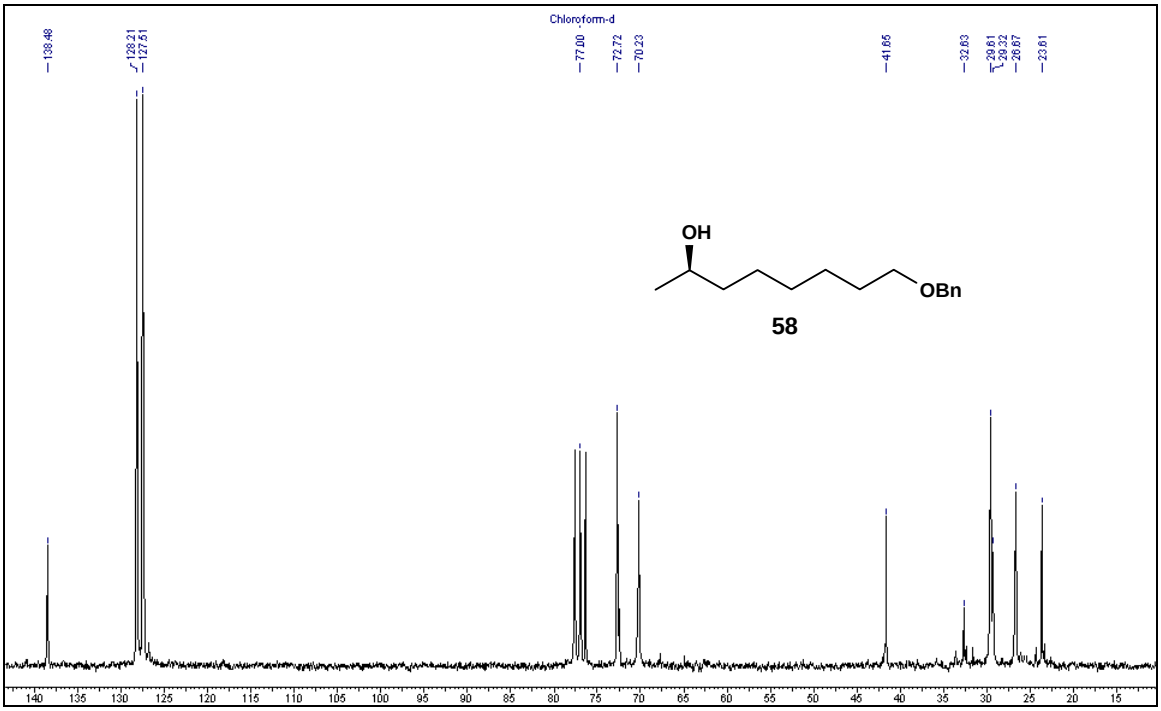
^{13}C NMR (50 MHz, $CDCl_3$): δ 19.2, 21.6, 24.8, 25.8, 30.7, 32.5, 69.4, 72.2, 74.7, 121.3, 149.2, 166.6 ppm.

5.1.7 Spectra

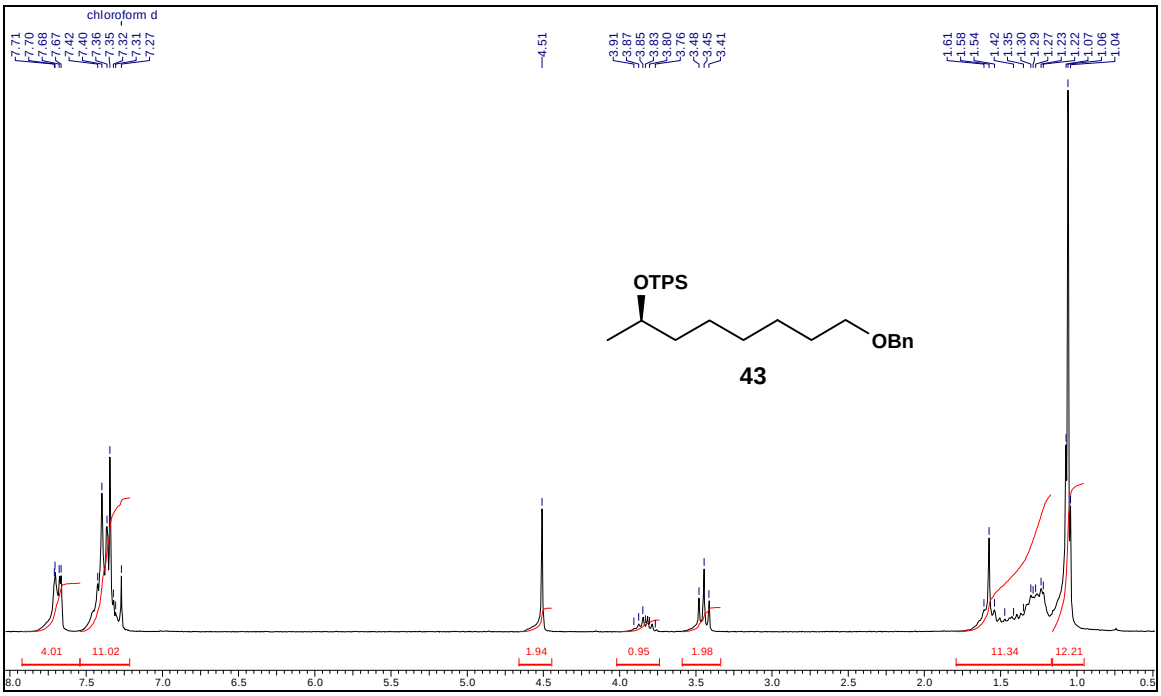
1. ^{1}H and ^{13}C NMR spectra of **58**
2. ^{1}H and ^{13}C NMR spectra of **43**
3. ^{1}H and ^{13}C NMR spectra of **44**
4. ^{1}H and ^{13}C NMR spectra of **59**
5. ^{1}H and ^{13}C NMR spectra of **60**
6. ^{1}H and ^{13}C NMR spectra of **61**
7. ^{1}H and ^{13}C NMR spectra of **47**
8. ^{1}H and ^{13}C NMR spectra of **62**
9. ^{1}H and ^{13}C NMR spectra of **1**
10. ^{1}H and ^{13}C NMR spectra of **63**
11. ^{1}H and ^{13}C NMR spectra of **31**
12. ^{1}H and ^{13}C NMR spectra of **32**
13. ^{1}H and ^{13}C NMR spectra of **2**



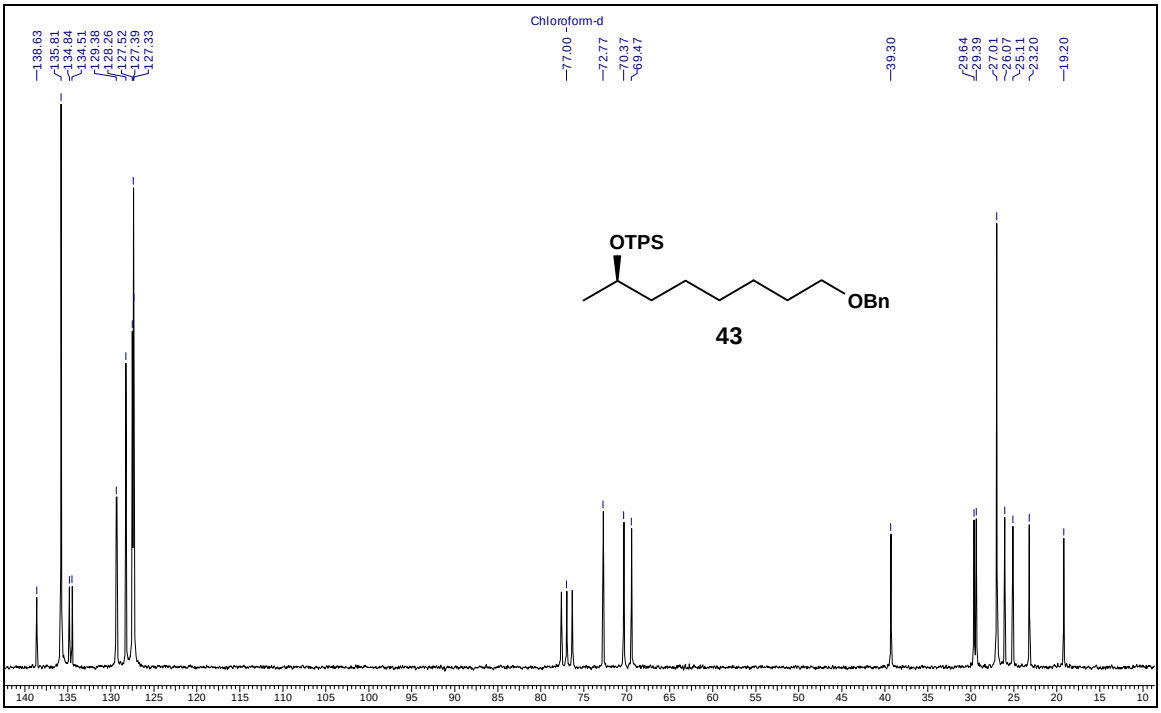
☞ ^{1}H NMR of the compound 58 in $CDCl_3$



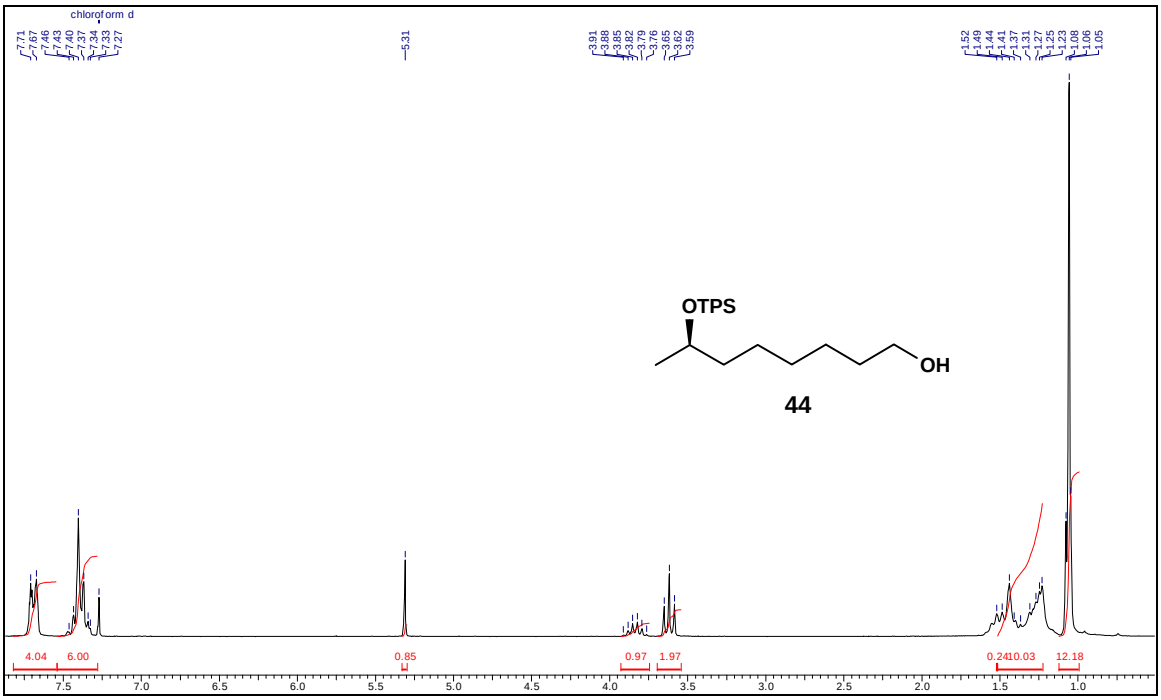
☞ ^{13}C NMR of the compound 58 in $CDCl_3$



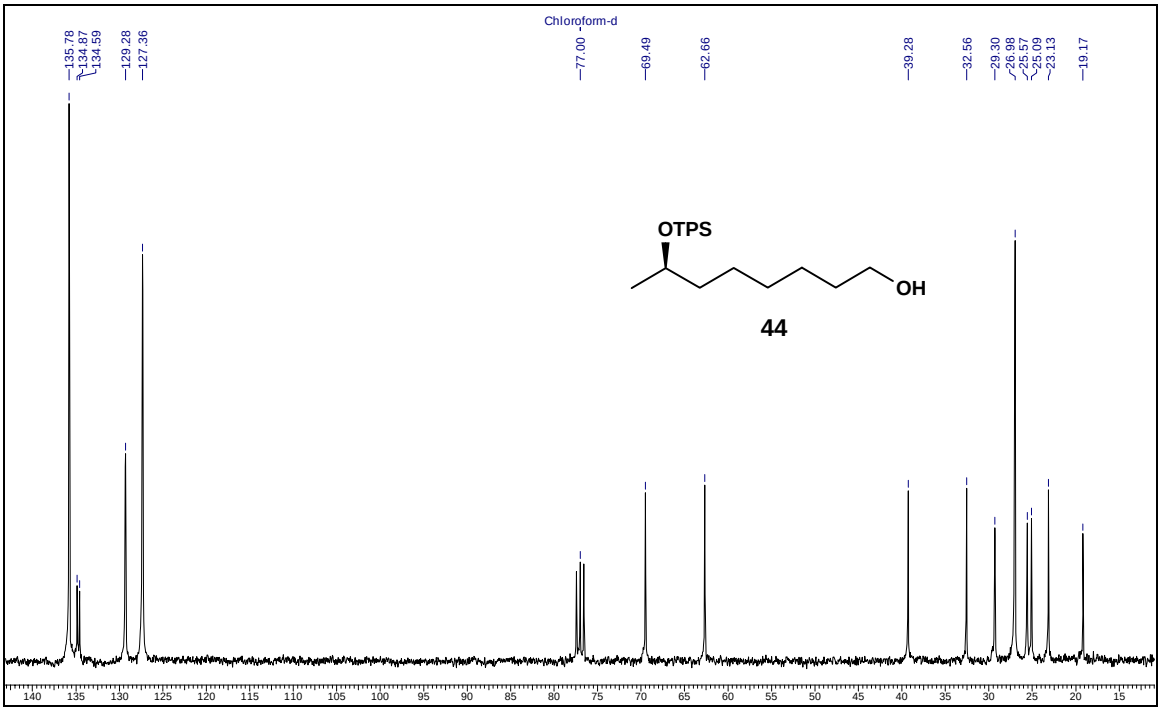
☞ ^{1}H NMR of the compound 43 in $CDCl_3$



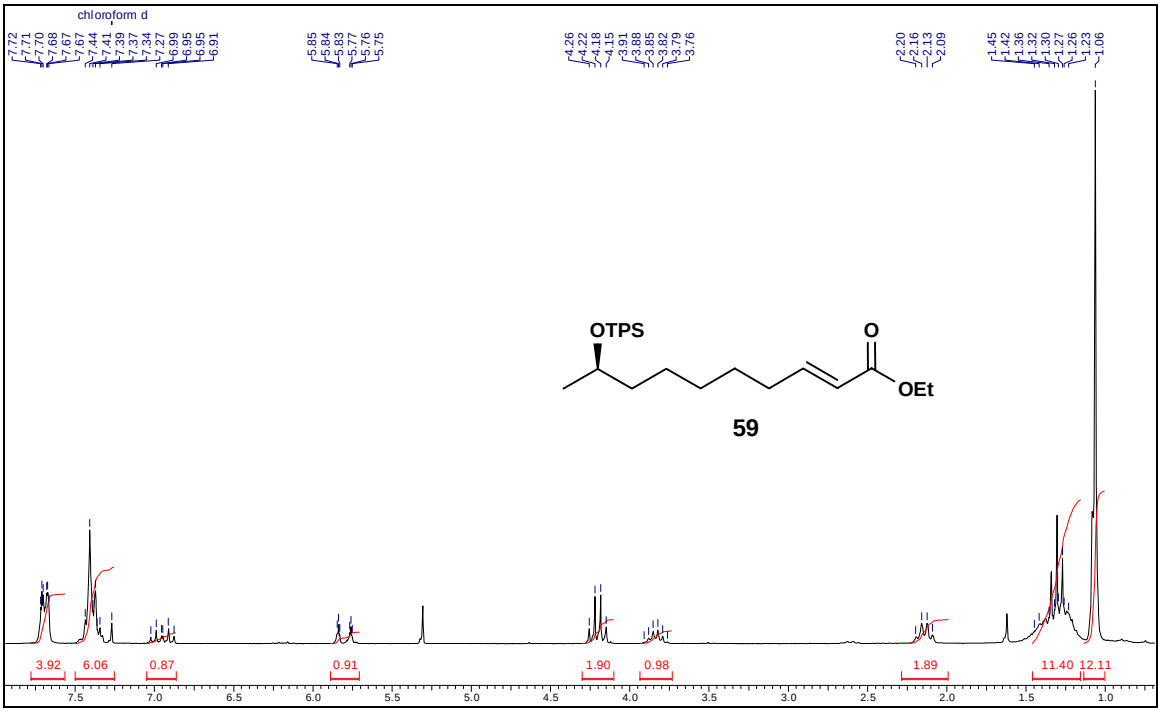
☞ ^{13}C NMR of the compound 43 in $CDCl_3$



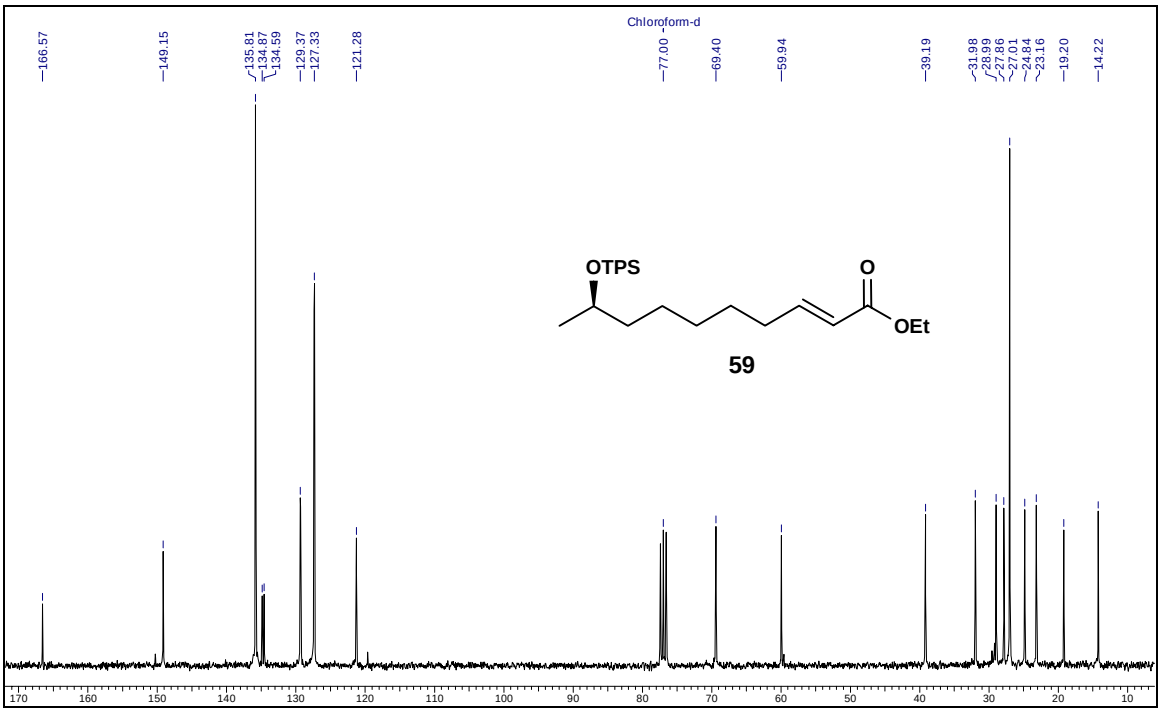
☞ ^{1}H NMR of the compound 44 in $CDCl_3$



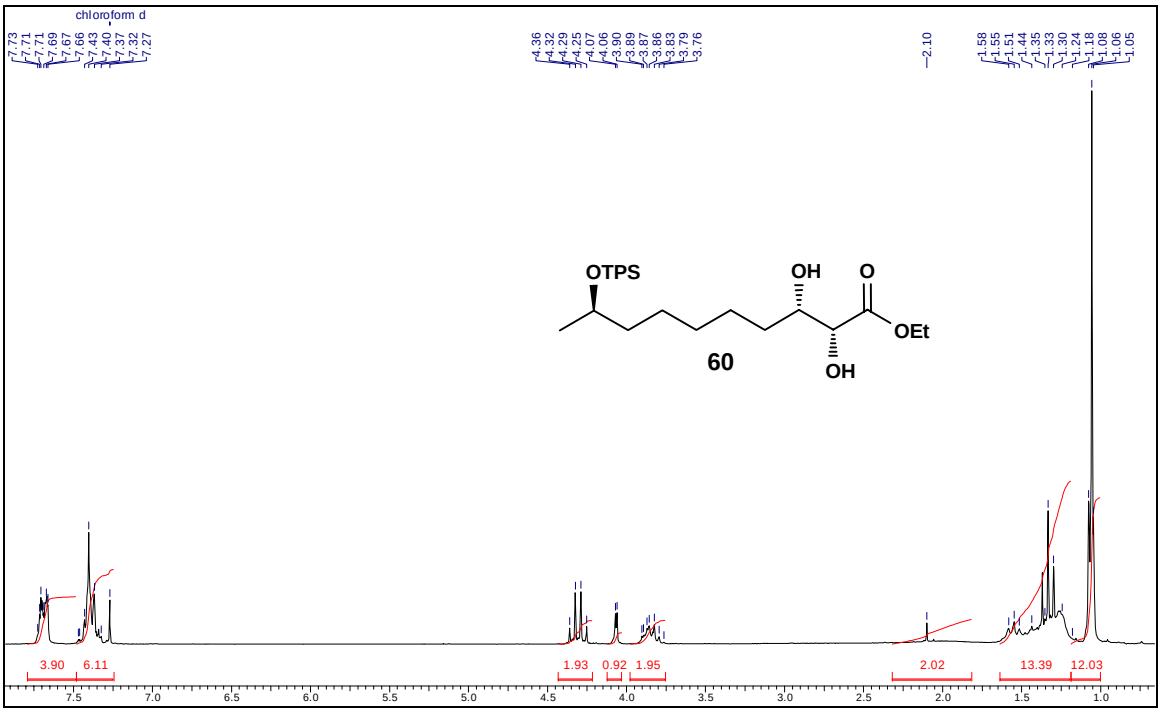
☞ ^{13}C NMR of the compound 44 in $CDCl_3$



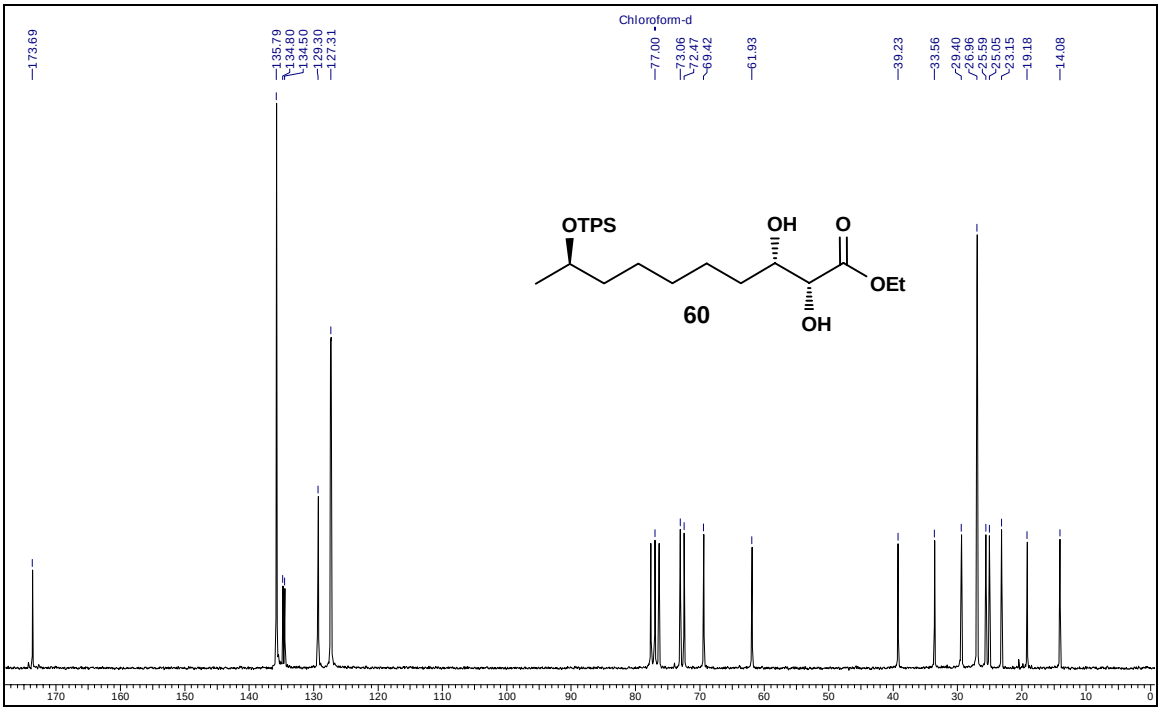
☞ ^{1}H NMR of the compound 59 in $CDCl_3$



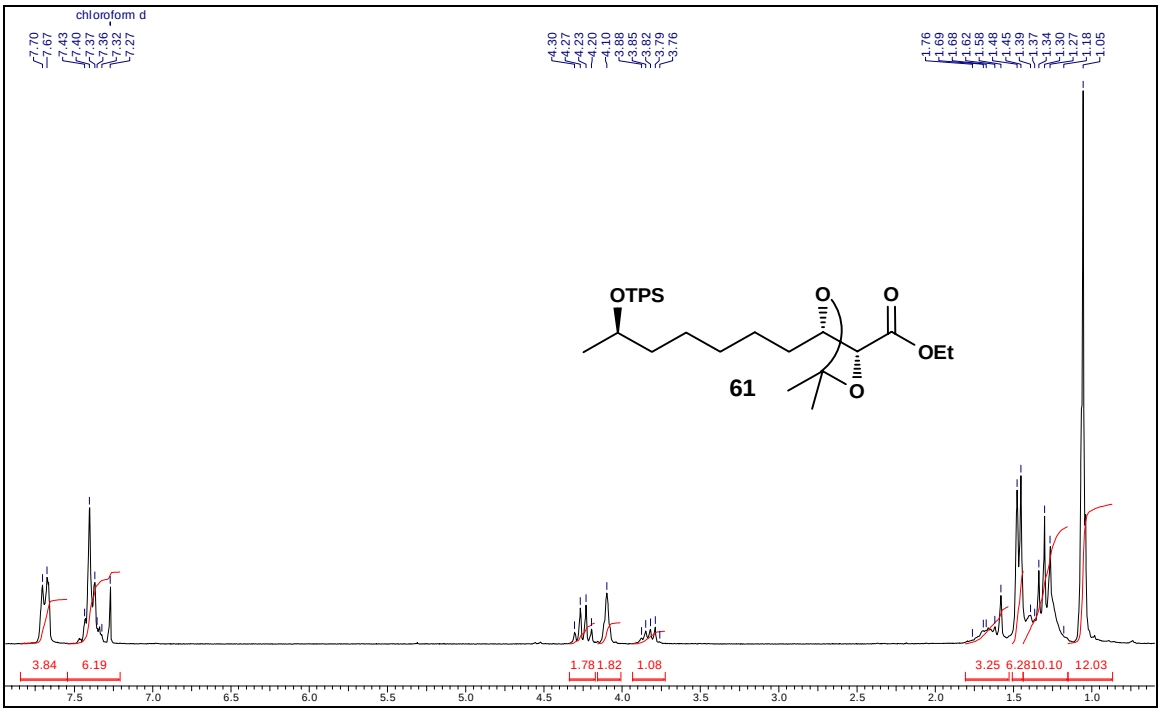
☞ ^{13}C NMR of the compound 59 in $CDCl_3$



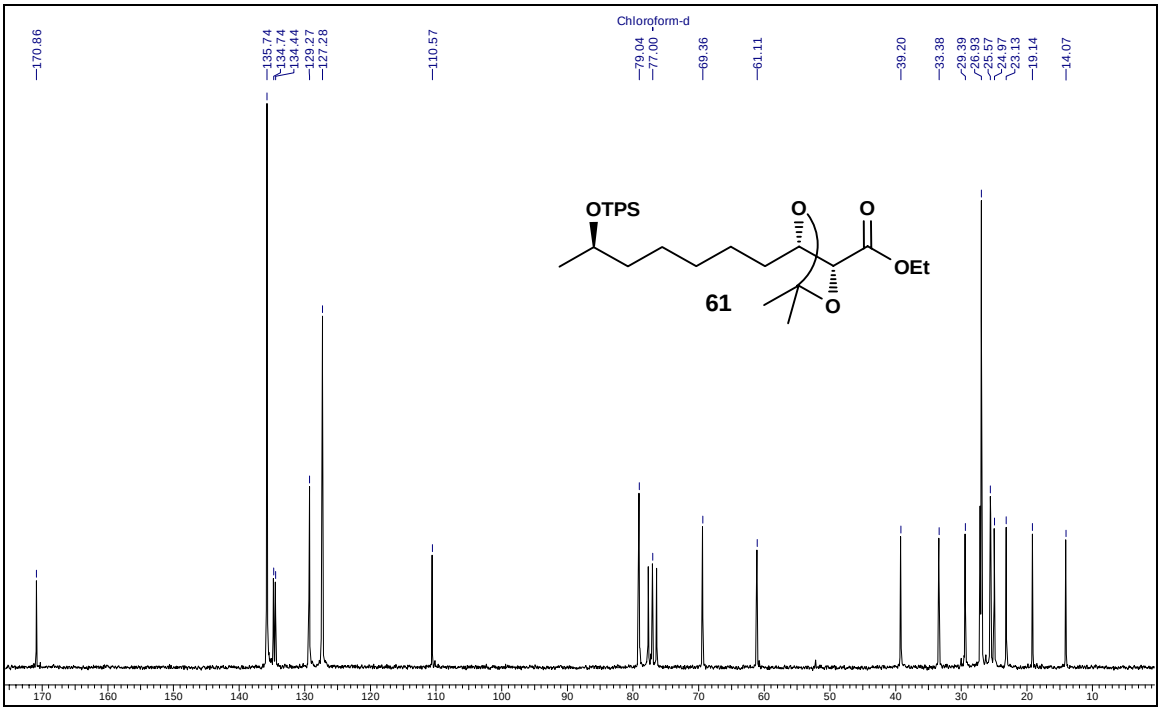
☞ ^{1}H NMR of the compound 60 in $CDCl_3$



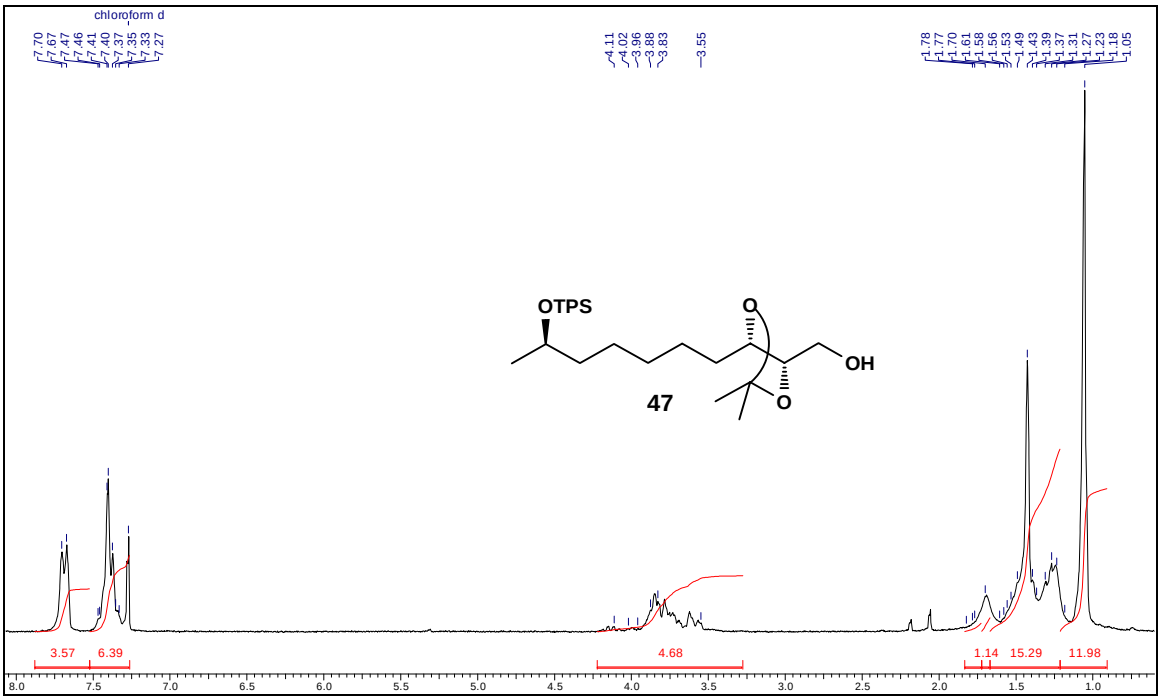
☞ ^{13}C NMR of the compound 60 in $CDCl_3$



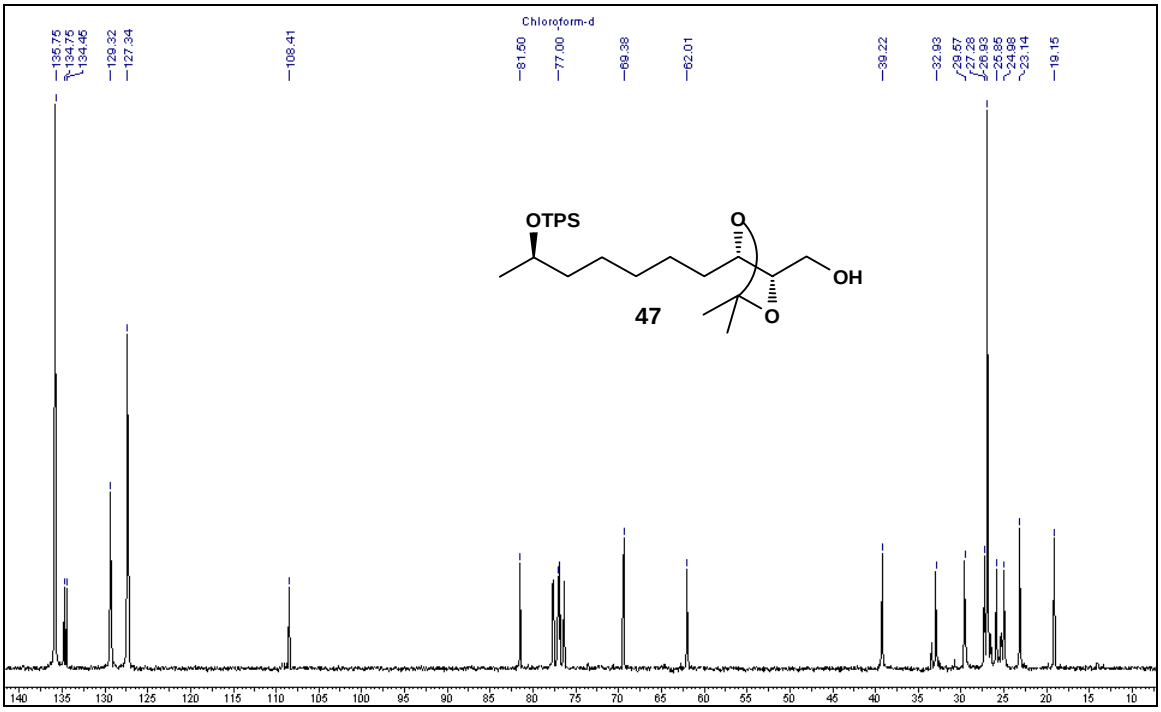
☞ ^{1}H NMR of the compound 61 in $CDCl_3$



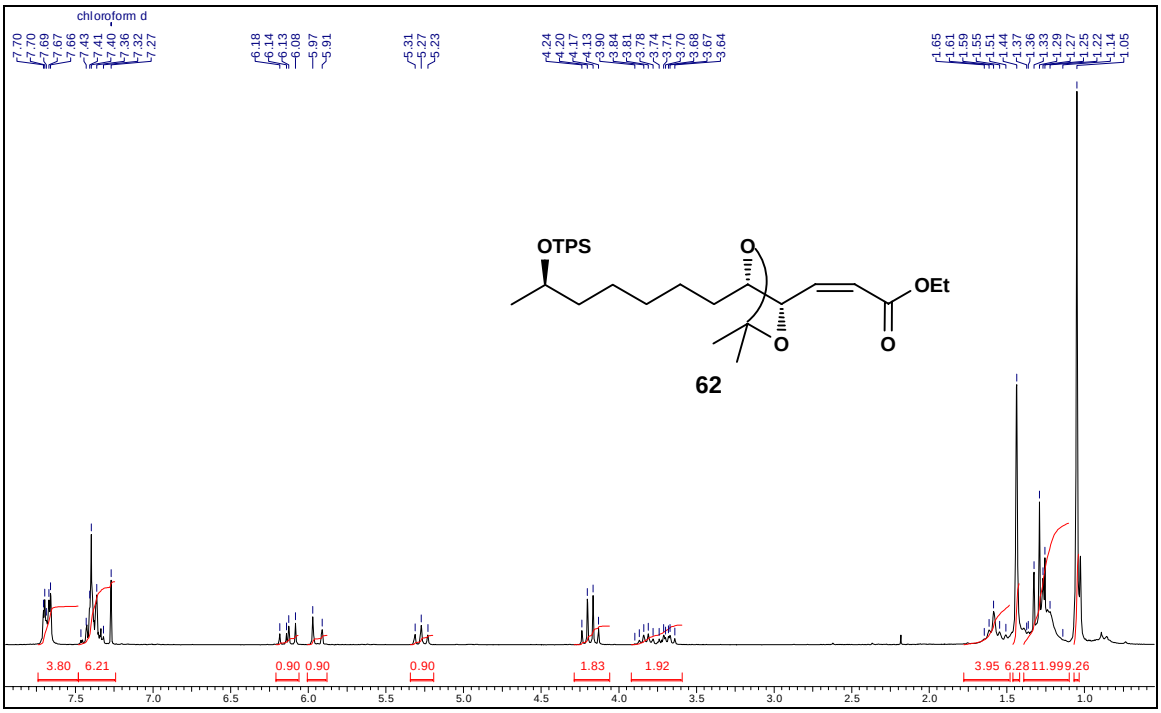
☞ ^{13}C NMR of the compound 61 in $CDCl_3$



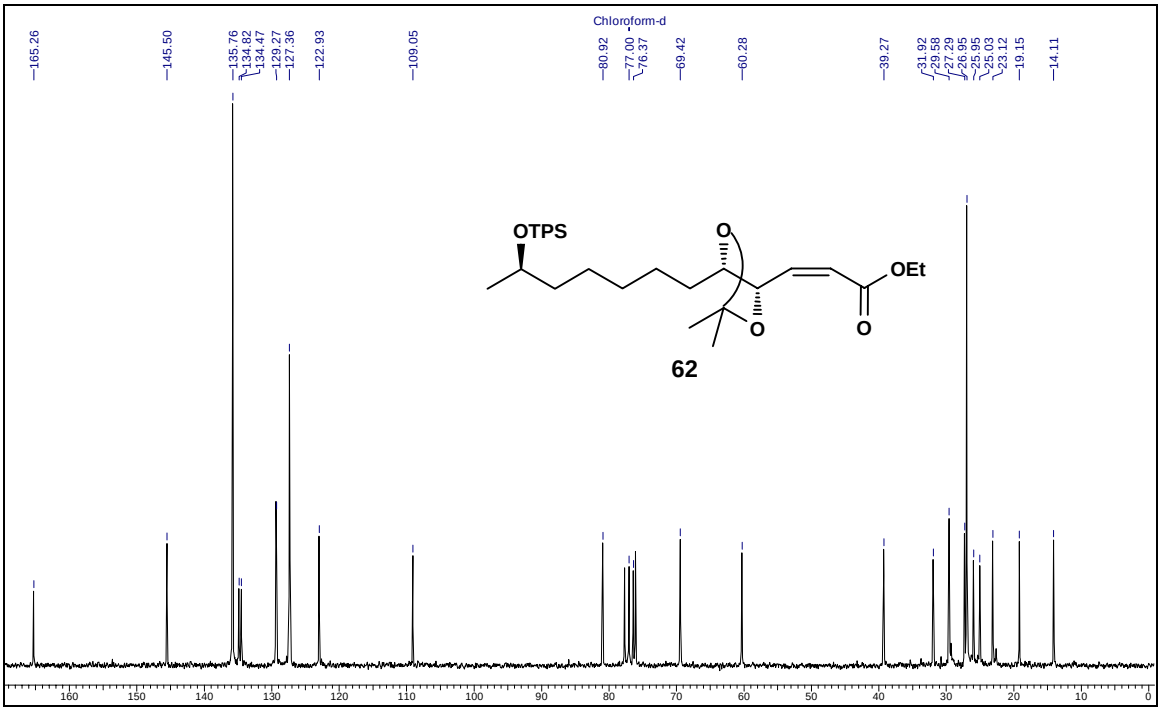
☞ ^{1}H NMR of the compound 47 in $CDCl_3$



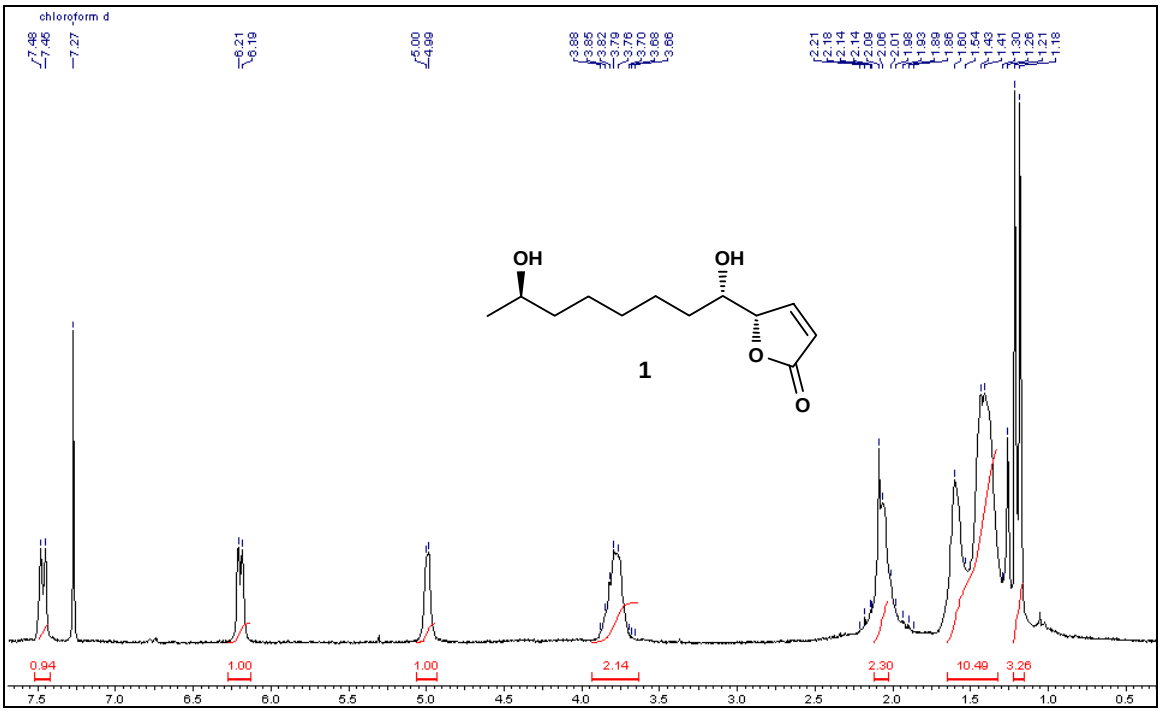
☞ ^{13}C NMR of the compound 47 in $CDCl_3$



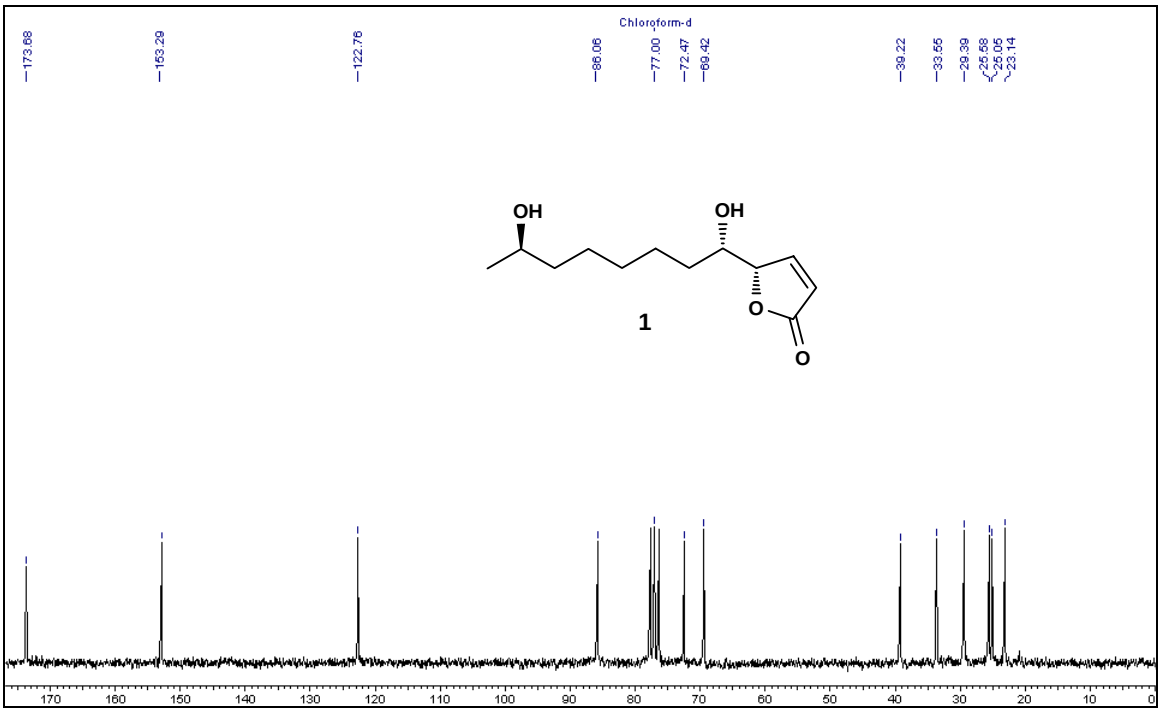
☞ ^{1}H NMR of the compound 62 in $CDCl_3$



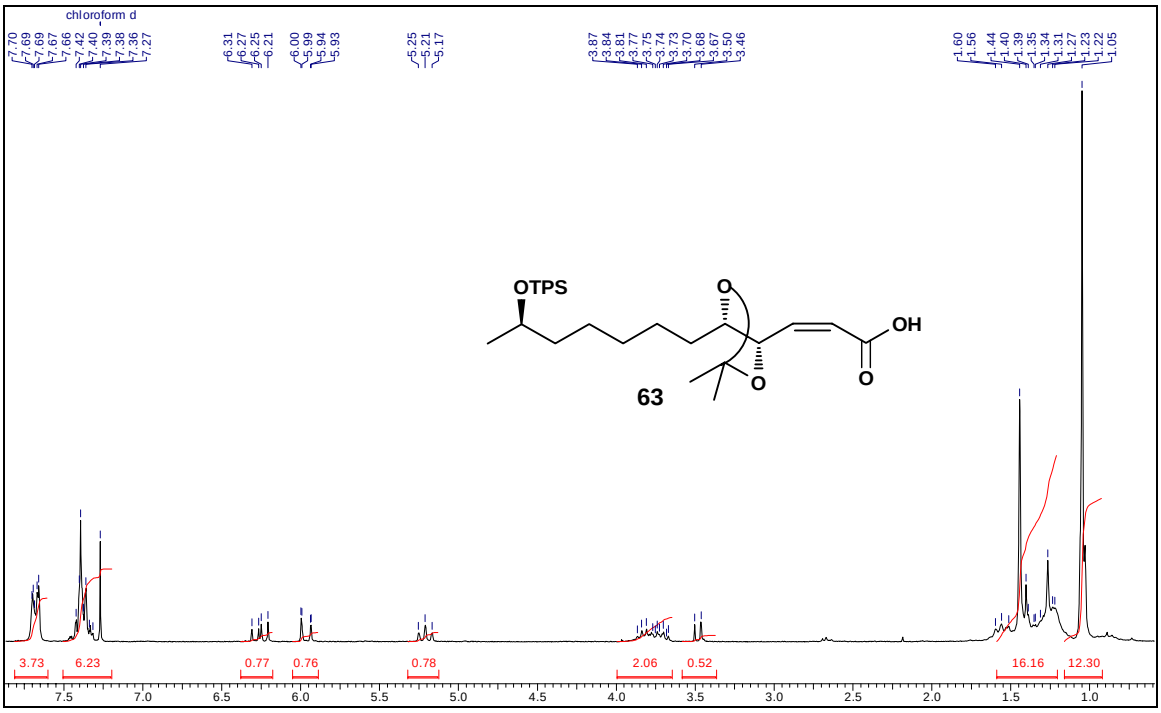
☞ ^{13}C NMR of the compound 62 in $CDCl_3$



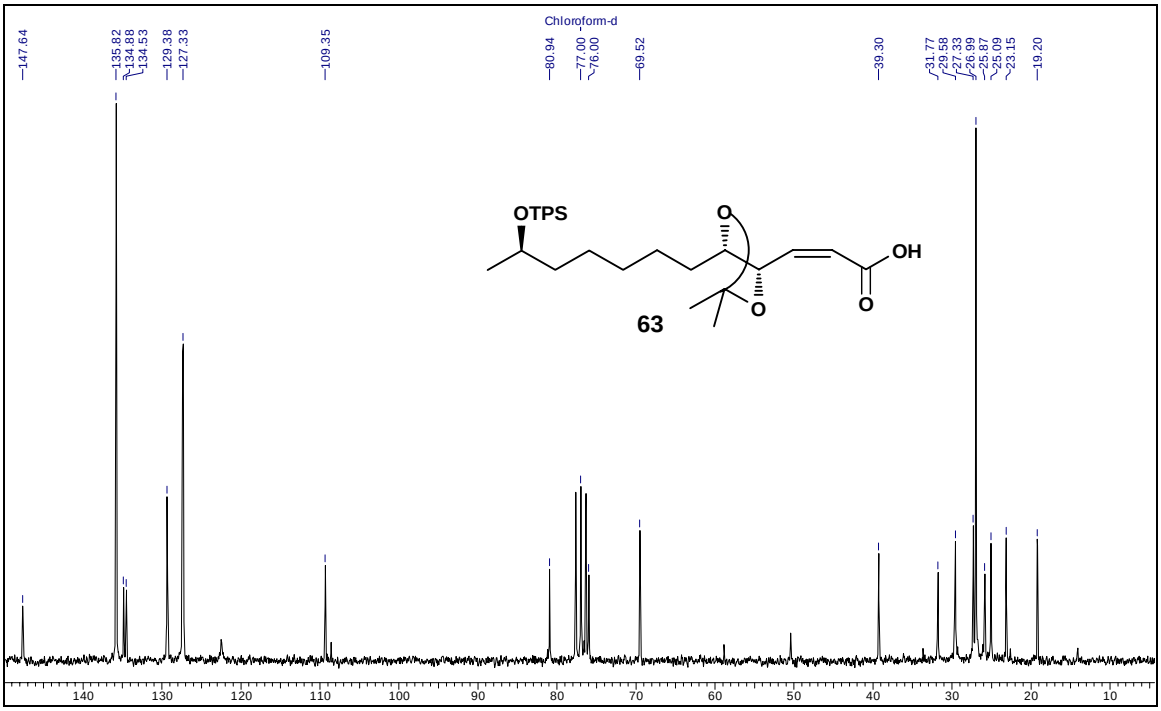
☞ **^{1}H NMR of the compound 1 in $CDCl_3$**



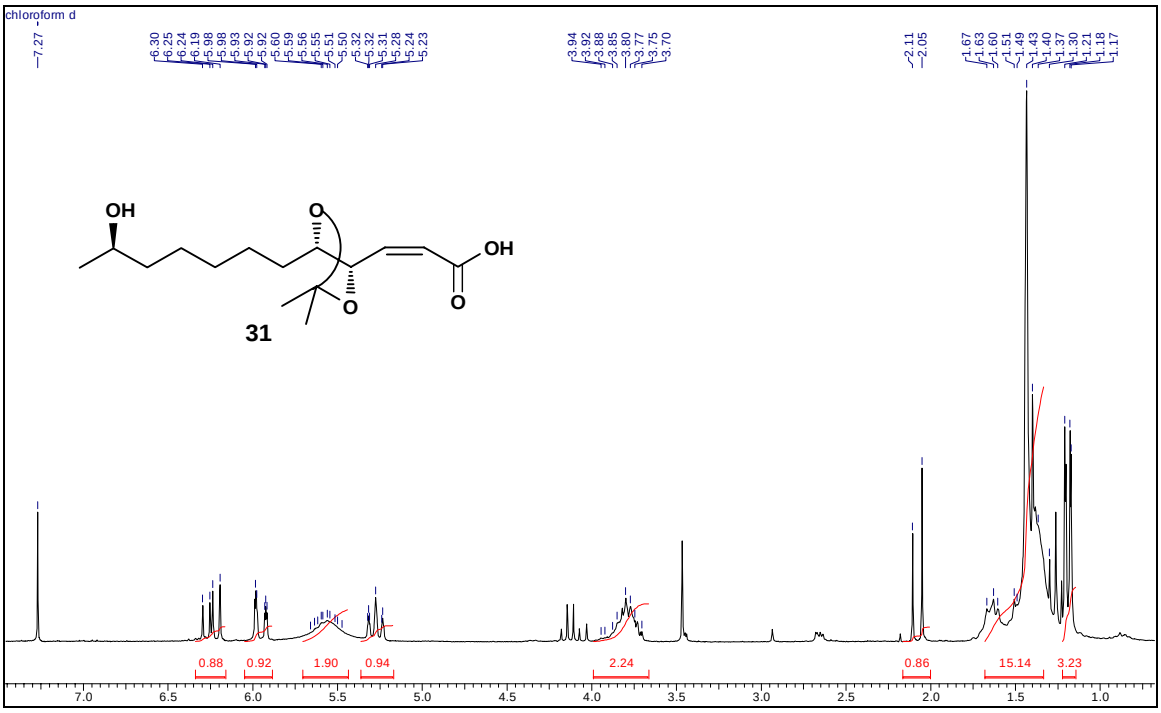
☞ **^{13}C NMR of the compound 1 in $CDCl_3$**



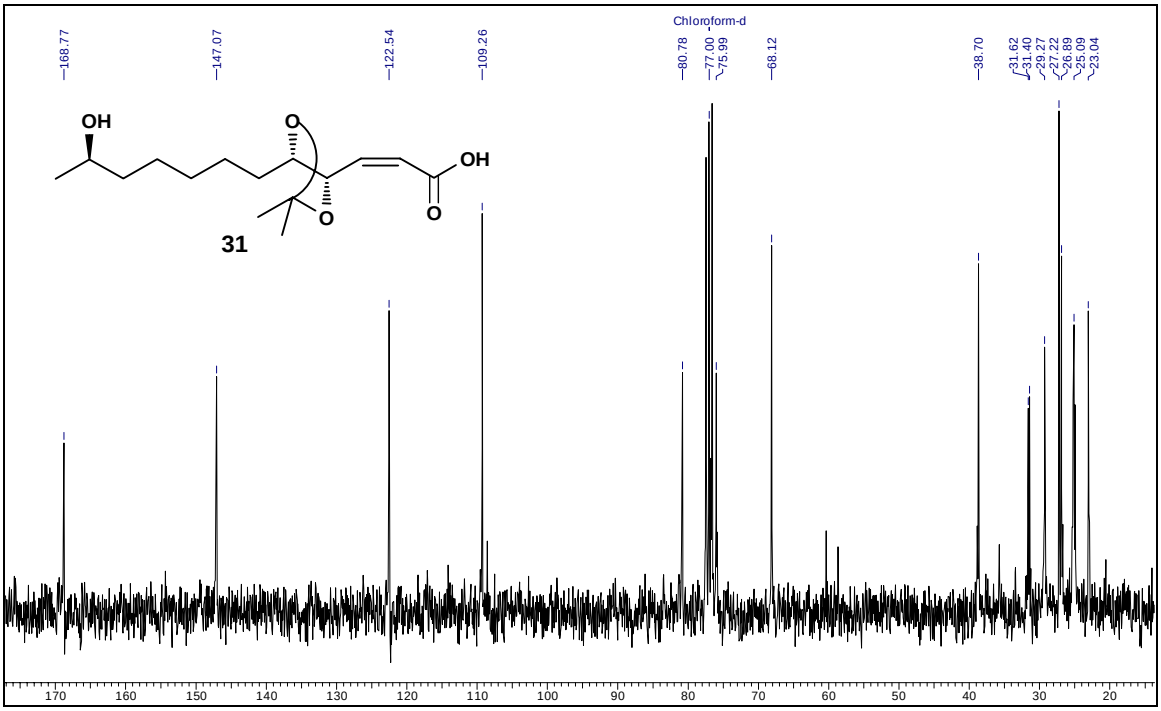
☞ ^{1}H NMR of the compound 63 in $CDCl_3$



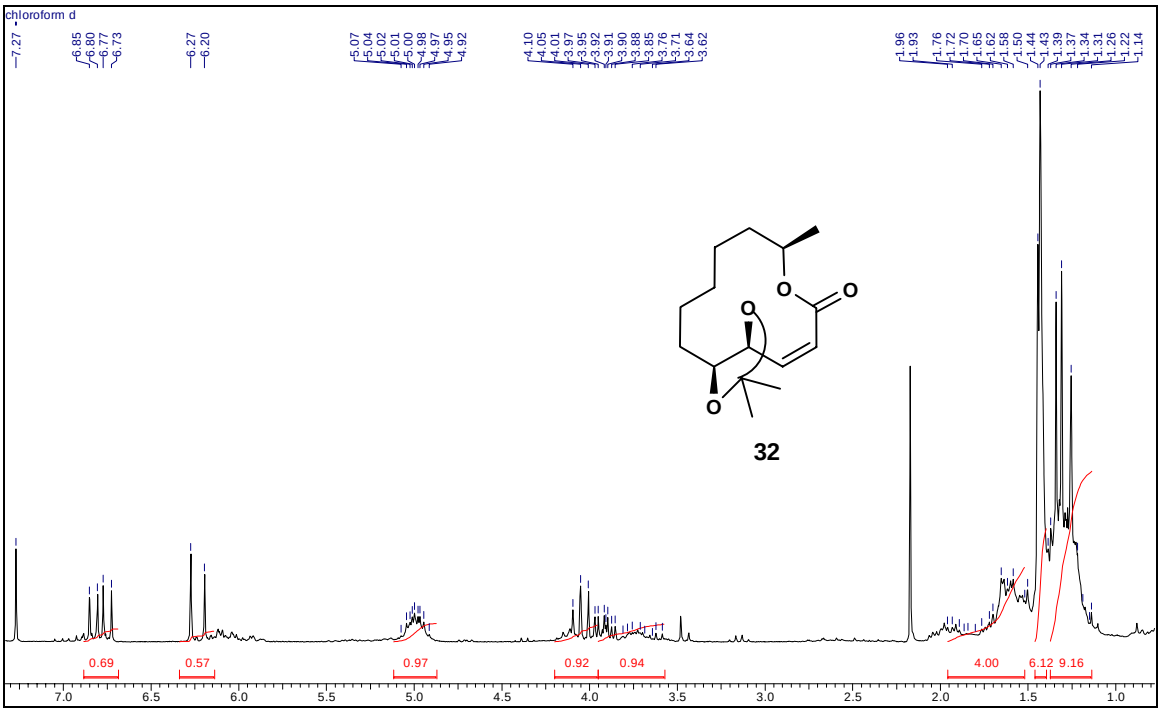
☞ ^{13}C NMR of the compound 63 in $CDCl_3$



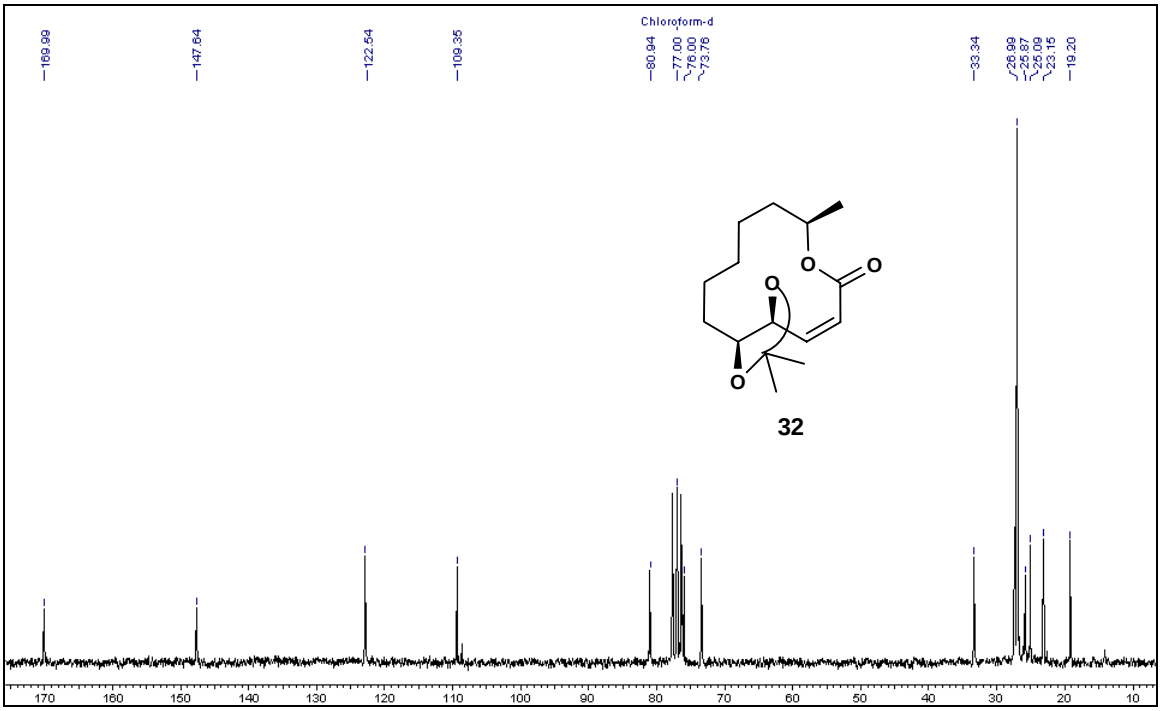
☞ ^{1}H NMR of the compound 31 in $CDCl_3$



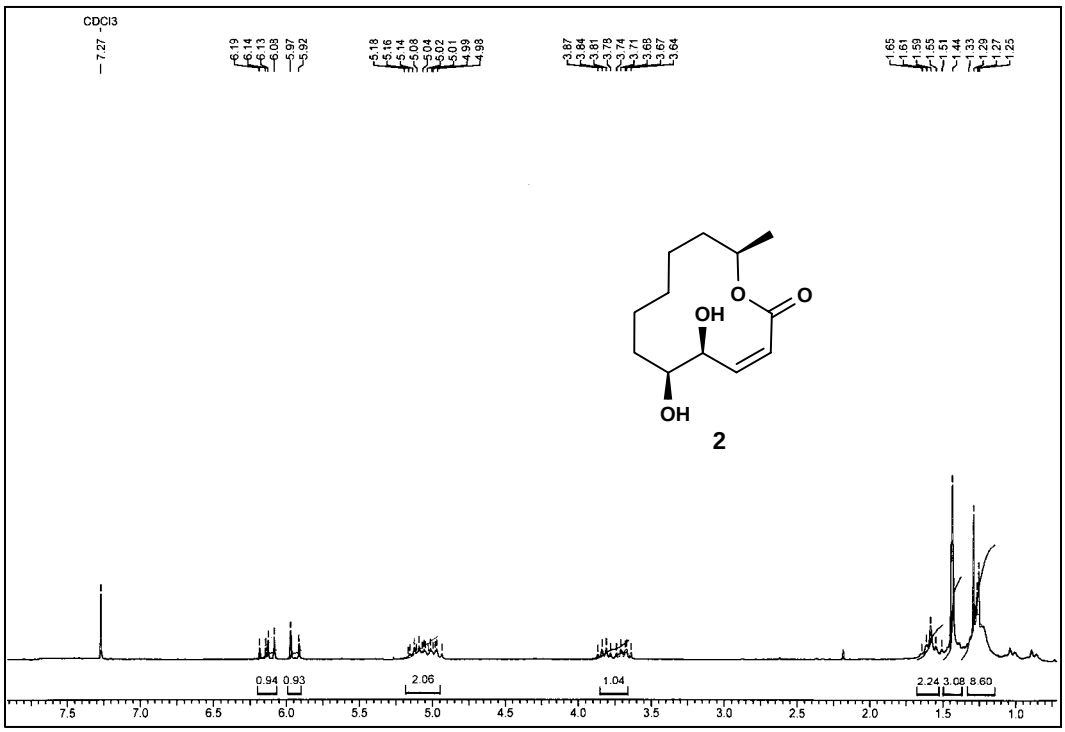
☞ ^{13}C NMR of the compound 31 in $CDCl_3$



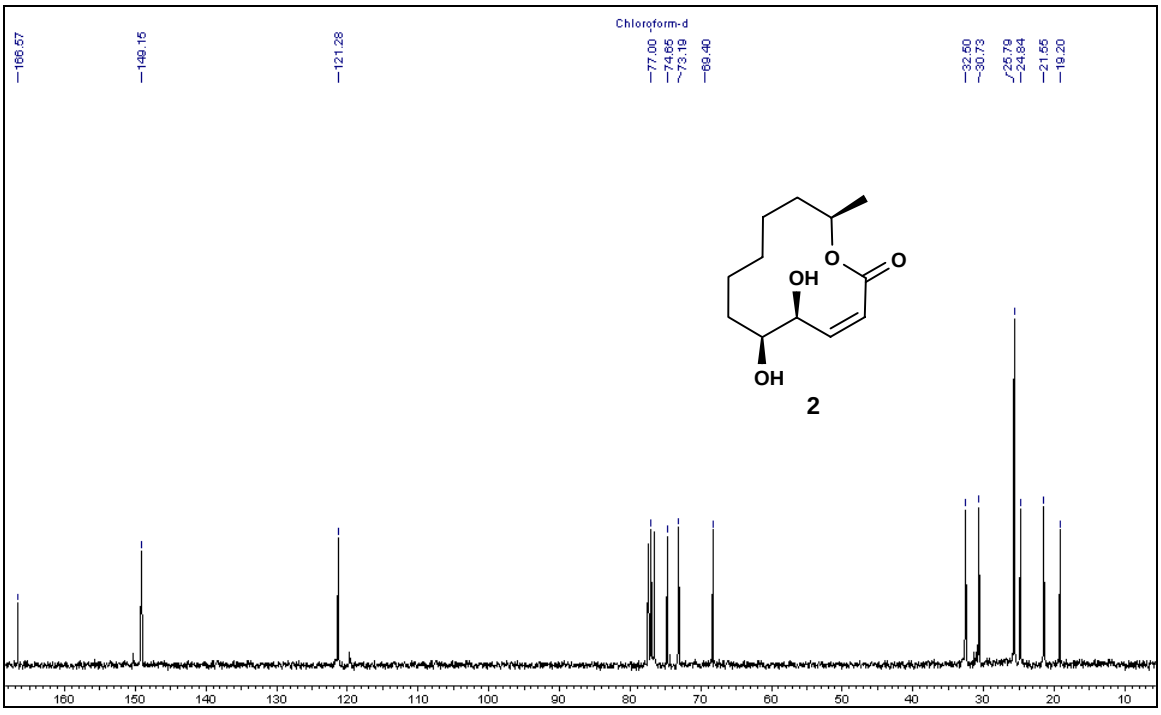
☞ **^{1}H NMR of the compound 32 in $CDCl_3$**



☞ **^{13}C NMR of the compound 32 in $CDCl_3$**



☞ **^{1}H NMR of the compound 2 in $CDCl_3$**



☞ **^{13}C NMR of the compound 2 in $CDCl_3$**

5.2 SECTION B

FORMAL TOTAL SYNTHESIS OF (-)-COLLETOL

5.2.1. Introduction

(-)-Colletol **64,** a 14-membered unsymmetrical bis-macrolactone, was isolated from the fermentation broth of *Collectotrichum capsici* in 1973 along with related bis-lactones colletodiol **65**, colletallol **66** and colletoketol **67** (Fig. 3).[19] More recently, two related 14-membered bis-lactones were isolated from the aerobic fermentation of cultures of *Cytospora* sp. ATCC 20502, these being the structurally isomeric grahamimycin A **67** and grahamimycin A_1 **68**.[20] It was later realized that the structures of colletoketol and grahamimycin A were identical.[21] These macrolactones can result from a biosynthesis *via* the macrodiolide colletotriene **69.**[22] This class of macrolactone has been a synthetic target of considerable interest due to its promising biological activity and unique structure with an array of functionalities.

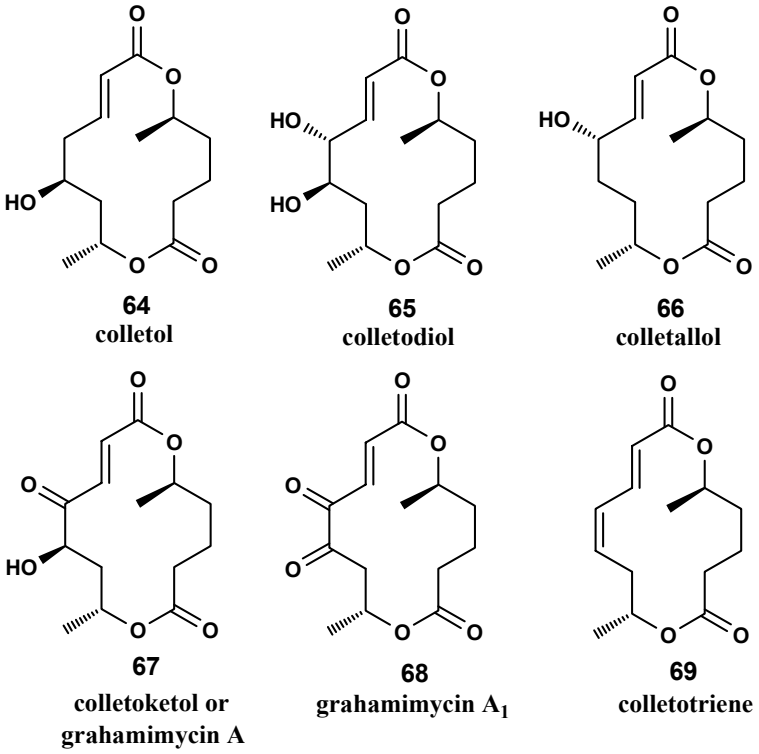


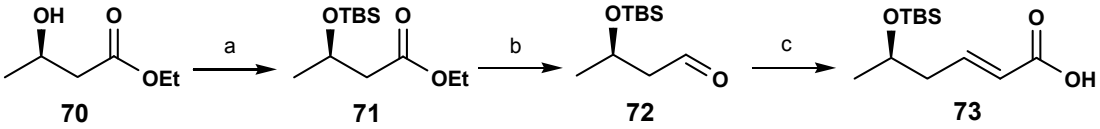
Figure 3.

5.2.2. Review of Literature

Various methods for the synthesis of (-)-Colletol **64** mainly based on auxiliary-supported or chiral pool approaches have been documented in the literature.[23] Some of the recent syntheses of (-)-Colletol **64** are described below.

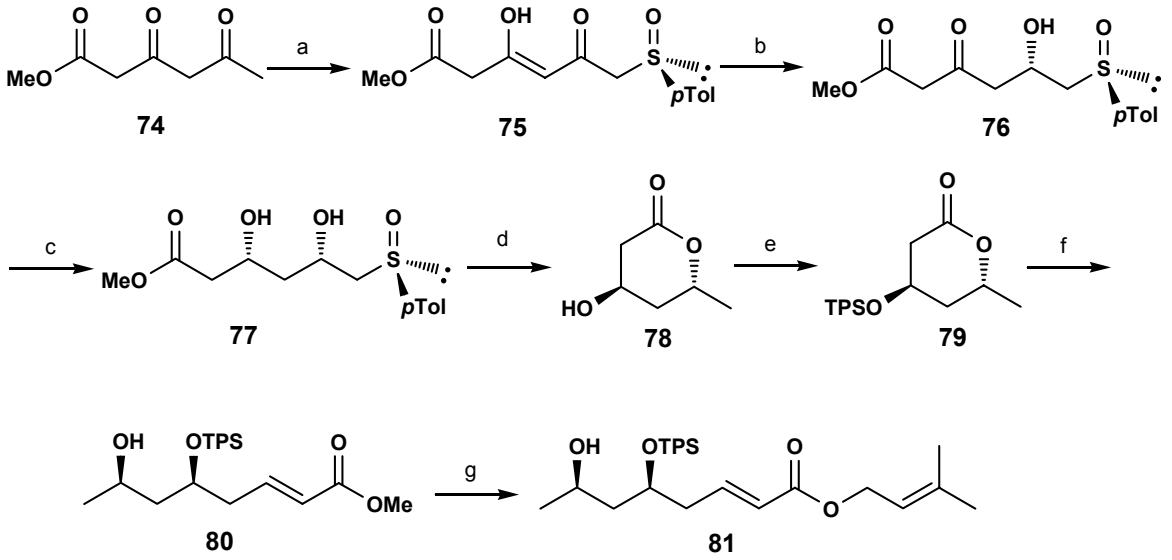
Solladie, G. *et al.* (2000)[23d]

Guy Solladie and co-workers accomplished the enantioselective synthesis of (–)-colletol **64** in which chiralty induced by chiral sulfoxides. Hydroxy ester **70** was protected as its TBDMS ether, reduced with diisobutylaluminum hydride (DIBAL-H), and oxidized with pyridinium chlorochromate to give aldehyde **72** in 56% overall yield (Scheme 10). This aldehyde was then allowed to react with stabilized trimethyl phosphonoacetate to give ester which was hydrolyzed to the corresponding acid **73.**



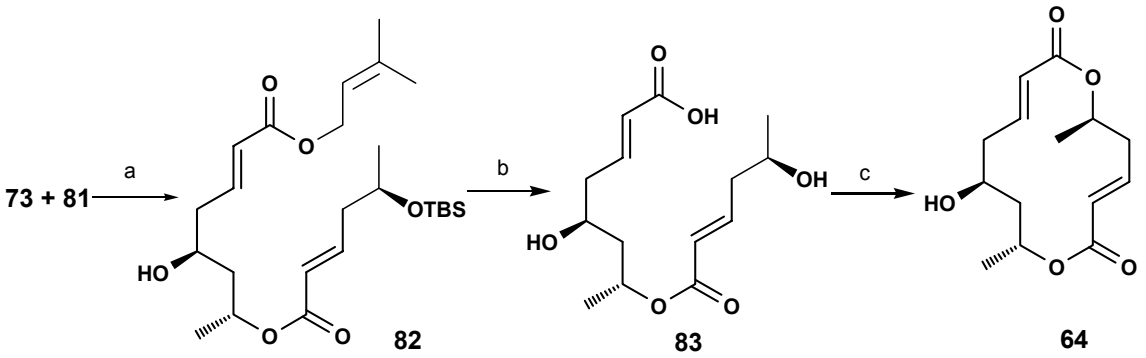
Scheme 10. *Reagents and conditions*: (a) TBDMSCl, imidazole, 98%; (b) i) DIBAL-H, ether/pentane, 70%; ii) PCC, AcONa, CH_2Cl_2, 81%; (c) i) $(MeO)_2POCH_2CO_2Me$, 86%; ii) $LiOH.H_2O$, THF, 98%.

Dioxo ester **74** was obtained in one step by a known procedure[24] which on condensation with (2)-menthyl (*S*)-*p*-toluenesulfinate afforded (*R*)-β,δ-dioxo sulfoxide **75** (Scheme 11). The δ carbonyl was entirely enolized and reduction with DIBAL-H gave only the diastereomer **76** which was reduced with $Et_2BOMe/NaBH_4$ to give the *syn*-diol **77**. Desulfurization with Raney nickel and lactonization of the corresponding hydroxy ester afforded the β-hydroxy lactone **78** which on protection with *tert*-butyldiphenylsilyl chloride, reduction with DIBAL and addition of a triphenylphosphorane furnished vinylic ester **80** in 80% yield. The vinylic ester **80** was *trans*-esterified with 3-methyl-2-buten-1-ol (prenol) in the presence of a catalytic amount of 1-chloro-3-hydroxytetrabutyl distannoxane to furnish prenyl ester **81.**



Scheme 11. *Reagents and conditions*: (a) NaH, *t*-BuLi, (2)-menthyl (*S*)-*p*-toluenesulfinate, 80%; (b) DIBAL-H, THF, 60%; (c) EtBOMe, $NaBH_4$, 99%; (d) i) Raney Ni, ii) $ZnCl_2$, THF, 62%; (e) TBDPSCl, imidazole, 87%; (f) i) DIBAL-H, toluene, 87%; ii) $Ph_3P{=}CHCO_2Me$, CH_3CN, 80%; (g) prenol, $ClSnBu_2OSnBu_2OH$, 79%.

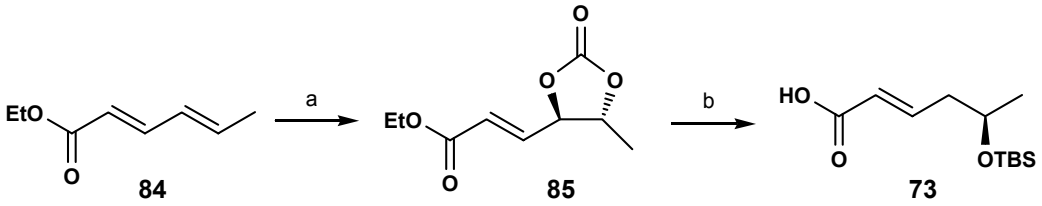
Esterification of **73** with **81** using 2,4,6-trichlorobenzoyl chloride gave **82** in 70% yield (Scheme 12). Removal of the allylic moiety using iodine in cyclohexane followed by deprotection of the TBDMS ether gave hydroxycarboxylic acid **83** in 71% overall yield. Finally, lactonization with 2,4,6-trichlorobenzoyl chloride and deprotection of the TBDPS group with tetrabutylammonium fluoride in benzoic acid gave (-)-colletol **64** in 81% yield.



Scheme 12. *Reagents and conditions*: (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, 70%; (b) i) I_2, cyclohexane; ii) PPTS, EtOH, 71%; (c) i) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene; ii) TBAF, THF, PhCOOH, 81%.

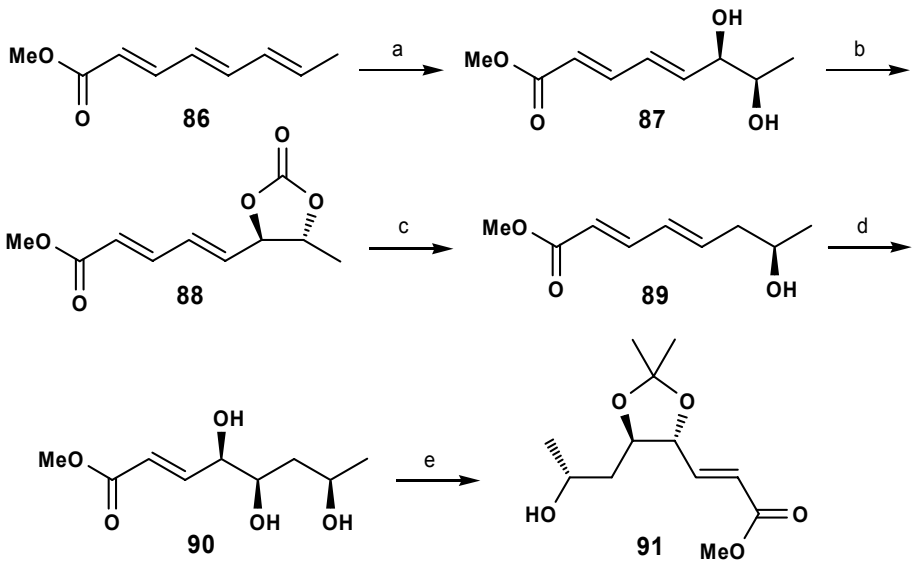
O'Doherty, G. A. *et al.* (2002)[23e]

George A. O'Doherty and co-workers reported the synthesis of (-)-colletol **64** using Sharpless asymmetric dihydroxylation as the key step. The Sharpless dihydroxylation of ethyl sorbate **84** yielded the diol which was converted into cyclic carbonate **85** (Scheme 13). Treatment of **85** with a catalytic amount of palladium and triphenylphosphine afforded δ-hydroxyester which was protected as the TBS-ether followed by ester hydrolysis to furnish **73**.



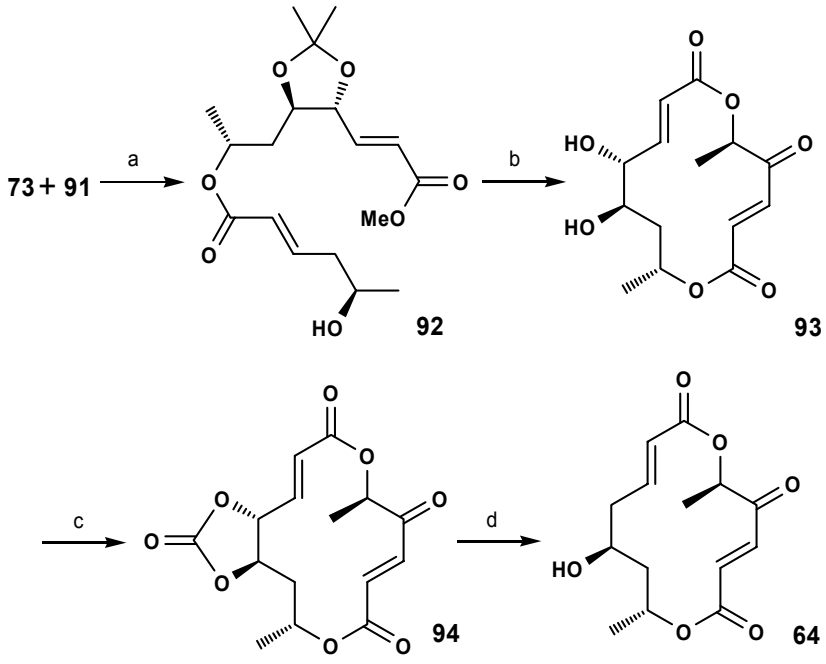
Scheme 13. *Reagents and conditions*: (a) i) AD mix-β, 82%; ii) $(CH_3CO)_2CO$, Py/CH_2Cl_2, 88%; (b) i) HCOOH/Et_3N, 2.5% $Pd_2(dba)_3.CHCl_3$, 6.3% PPh_3, THF, 66 ^oC, 92%; ii) TBSCl, Et_3N, iii) LiOH, THF/H_2O 82% (two steps);

Treatment of triene **86** with asymmetric dihydroxylation conditions gave diol which was converted into cyclic carbonate **88**. Treatment of **88** with a catalytic amount of palladium and triphenylphosphine afforded δ-hydroxy ester **89**. The asymmetric dihydroxylation of **89** produced triol **90** which on protection as the acetonide to furnish acetonide **91** (Scheme 14).



Scheme 14. *Reagents and conditions*: (a) AD mix-β, 82%; (b) $(CH_3CO)_2CO$, Py/CH_2Cl_2, 88%; (c) i) HCOOH/Et_3N, 2.5% $Pd_2(dba)_3.CHCl_3$, 6.3% PPh_3, THF, 66 ^oC, 92%; (d) AD mix-β, 82%; (e) *p*-TsOH, 2,2-DMP, acetone, 24 h, 54%.

Alcohol **91** was esterified with acid **73** using 2,4,6-trichlorobenzoyl chloride and removal of the TBS group afforded compound **92** in 79% yield. Hydrolysis of methyl ester of **92** furnished hydroxy acid which on macrolactonization and deprotection, furnished colletodiol **93**. Treatment of colletodiol **93** with triphosgene yielded the cyclic carbonate which on palladium-catalyzed reduction afforded (-)-colletol **64** (Scheme 15).

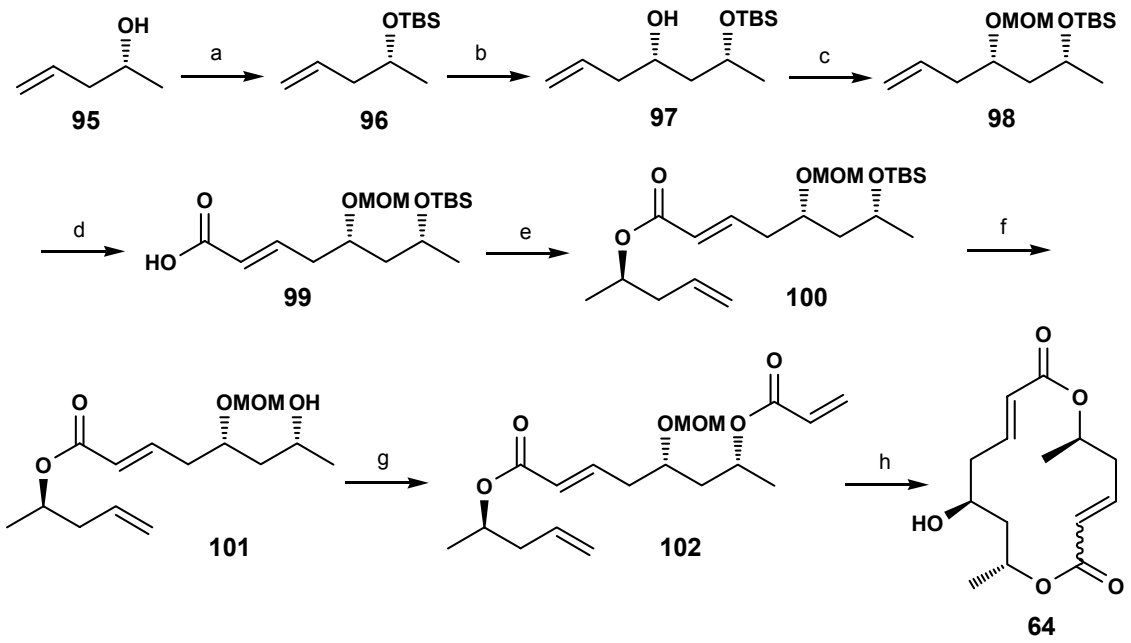


Scheme 15. *Reagents and conditions*: (a) i) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, 70%; ii) TBAF, $PhCO_2H$, 61%; (b) i) $LiOH.H_2O$, THF/H_2O, 79%; ii) DCC/DMAP, iii) Dowex/MeOH, 86%; (c) i) $(CH_3CO)_2CO$, Py/CH_2Cl_2, 90%; (d) HCOOH/Et_3N, 2.5% $Pd_2(dba)_3.CHCl_3$, 6.3% PPh_3, THF, 66 ^oC, 82%

BouzBouz, S. *et al.* (2006)[23f]

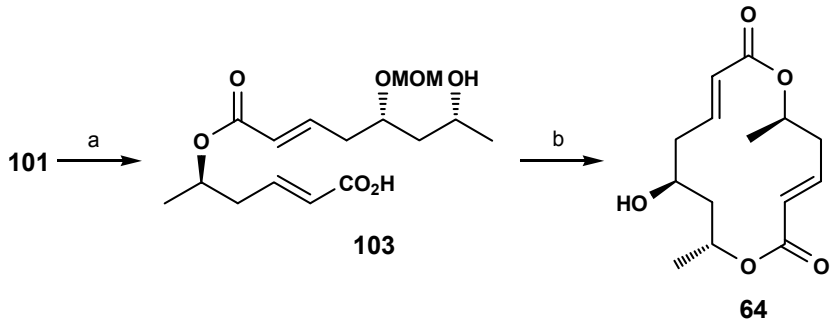
Samir BouzBouz and co-workers accomplished the synthesis of (-)-colletol **64** from (*R*)-pent-4-en-2-ol by using enantioselective allyltitanations to control the stereogenic centers at C5 and cross-metathesis, ring-closing metathesis reactions to control the configuration

of the double bonds (Scheme 16). After protection of the hydroxy group of (*R*)-pent-4-en-2-ol **95**, the silyl ether **96** was oxidatively cleaved to produce an aldehyde which was directly treated with the optically active (*R*,*R*)-allyltitanium complex and transformed to the *syn* 1,3-diol **97**. After protection of the hydroxy group, the resulting compound **98** was involved in a CM reaction with acrylic acid in the presence of the Hoveyda-Grubbs catalyst and transformed to the *E*-unsaturated carboxylic acid **99** with an *E*/*Z* ratio of 20/1. In order to introduce the non-activated olefin, carboxylic acid **99** was treated with (*R*)-**95** under the Yamaguchi's conditions to afford ester **100**. Ester **100** was then converted to alcohol **101** which was esterified using acryloyl chloride and the obtained unsaturated ester **102** was subjected to the Hoveyda-Grubbs catalyst (HG) and deprotection led to the inseparables (-)-colletol **64** and its (*E,Z*)-isomer in 77% yield in a ratio of 2.8/1.



Scheme 16. *Reagents and conditions*: (a) TBSOTf, 2.6-lutidine, CH_2Cl_2 , -78 °C, 95 %; (b) i) OsO_4, NMO, $NaIO_4$, Acetone/H_2O, 25 °C; ii) (*R*,*R*)-allyltitanium complex, ether -78 °C, 3 h, 78%; (c) MOMCl, *i*Pr_2NEt CH_2Cl_2, 25 °C, 90%; (d) Acrylic acid (3eq.), Hoveyda-Grubbs catalyst, (HGcat.) (5mol%) CH_2Cl_2, 25 °C, 82%; (e) 2,4,6-$Cl_3C_6H_3COCl$, Et_3N, toluene, 25 °C, DMAP, toluene, 72%; (f) NH_4F, MeOH, 65 °C, 83%; (g) Acryloyl chloride, *i*Pr_2NEt, CH_2Cl_2, -78 °C, 92%; (h) HGcat. (5 mol%), CH_2Cl_2 (10-3M), 25°C, 72h, 32%; ii) HCl (2N), THF, 25°C, 77%.

Due to the non-stereoselective RCM, compound **101** has been transformed to acrylic acid **103** in order to achieve a macrolactonization. The obtained *seco*-acid **103** was macrolactonized under the Yamaguchi's conditions to afford the macrolactone, which after treatment with HCl was converted to (-)- colletol **64** (Scheme 17).



Scheme 17. *Reagents and conditions*: (a) Acrylic acid (3eq.), HGcat (5mol%), CH_2Cl_2, 25 °C, 78%; (b) i) 2,4,6-$Cl_3C_6H_3COCl$, Et_3N, toluene, 25 °C, DMAP, toluene, 110 °C, 60%; ii) HCl (2N), THF, 25 °C, 79%.

5.2.3. Present work:

Objective:

The promising biological activity and the unique structure of the 14-membered unsymmetrical bis-macrolactones make them attractive synthetic targets and therefore there have been several synthesis of (-)-colletol **64** in recent past. As part of our research programme aimed at developing enantioselective syntheses of naturally occurring lactones[16] we have also accomplished the formal synthesis of (-)-colletol **64** from commercially available propylene oxide employing Jacobsen's HKR and Yamaguchi coupling as the key steps.

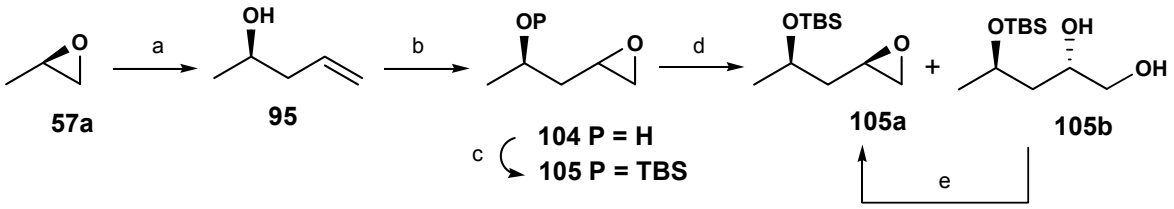
5.2.4. Results and Discussion:

Synthesis of acid fragment 108 (Scheme 18, 19)

In designing a route to (-)-colletol **64** we chose commercially available racemic propylene oxide as an appropriate starting material. As shown in Scheme 7, propylene oxide **57** was

subjected to Jacobsen's HKR using (*R*,*R*)-salen-Co-OAc catalyst (Fig. 2) to give (*R*)-propylene oxide **57a** as a single isomer.

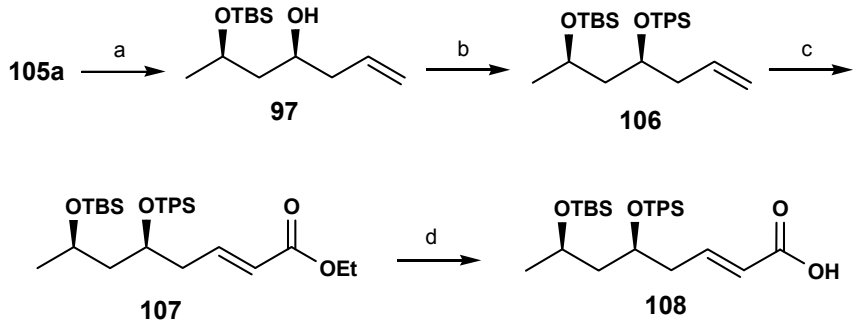
(*R*)-Propylene oxide **57a** was treated with vinylmagnesium bromide in the presence of CuI to give the homoallylic alcohol **95** in excellent yield. Previously, in our group we have explored the stereoselective outcome of the epoxidation reaction with and without hydroxyl group protection. Toward this end the hydroxyl group of homoallylic alcohol **95** was first protected as the TBS ether, followed by epoxidation with *m*-CPBA. The epoxide thus obtained was found to be a mixture of two diastereomers (*anti:syn*/3:1). The desired *syn* isomer **105a** was obtained only as a minor component. However, when epoxidation was carried out on alcohol **95** followed by hydroxy protection as the TBS–ether, the epoxide was formed in favor of the desired *syn* isomer **105a** (*syn:anti*/1.2:1). The two diastereoisomers could not be differentiated on TLC.[25]



Scheme 18. *Reagents and conditions*: (a) vinylmagnesium bromide, THF, CuI, -20 ^{o}C, 12 h, 87%; (b) *m*-CPBA, CH_2Cl_2, 0 ^{o}C to rt, 4 h, 96%; (c) TBDMSCl, imidazole, CH_2Cl_2, 0 ^{o}C to rt, 4 h, 95%; (d) *R*,*R*-salen-Co-(OAc) (0.5 mol%), dist. H_2O (0.55 eq), 0 ^{o}C, 24 h, (46% for **105a**, 45% for **105b**) (e) ref. 25.

In order to improve the diastereoselectivity, we attempted the hydrolytic kinetic resolution method (HKR) as depicted in Scheme 18. Thus, the HKR was performed on **105** with (*R*,*R*)-salen-Co-OAc complex (0.5 mol %) and water (0.55 equiv) in THF (0.55 equiv) to afford the epoxide **105a** as a single stereoisomer (as determined from the ^{1}H and ^{13}C NMR spectral analysis) in 46% yield and the diol **105b** in 45% yield. Epoxide **105a** could easily be separated from the more polar diol **105b** through silica gel column chromatography. The diol **105b** was converted into epoxide **105a** *via* chemoselective pivalalation, mesylation follwed by base treatment.[25] The opening of epoxide **105a** with vinylmagnesium bromide in the presence of CuI in THF at -20 ^{o}C furnished the

homoallylic alcohol **97** in 89% yield (Scheme 19). The IR spectrum of **97** gave broad hydroxyl absorption at 3436 cm^{-1}. The ^1H NMR spectrum of **97** gave olefin peaks at δ 5.06-5.15 (multiplet, two proton), 5.74-5.86 (multiplet, one proton). Hydroxyl protection of **97** with *tert*-butyldiphenylsilyl chloride and imidazole in the presence of a catalytic amount of DMAP afforded the silyl ether **106** in 96% yield. The IR spectrum of **106** showed absence of hydroxyl group. The olefin **106** was oxidized to aldehyde in the presence of OsO_4 and $NaIO_4$[26] followed by reaction with (ethoxycarbonylmethylene)-triphenylphosphorane in dry THF at room temperature to furnish the *trans*-olefin **107** in 92% yield. The IR spectrum of **107** showed the ester carbonyl absorption at 1712 cm^{-1} and olefin C=C stretching at 1661 cm^{-1}. The ^1H NMR spectrum gave olefin protons at δ 6.72 (doublet of triplet, one proton) with the coupling constant J = 1.26, 15.66 Hz, and at δ 6.81-7.01 (multiplet, one proton) indicating *trans*-olefin. The ester **107** was hydrolyzed to afford the corresponding acid **108** in excellent yield.

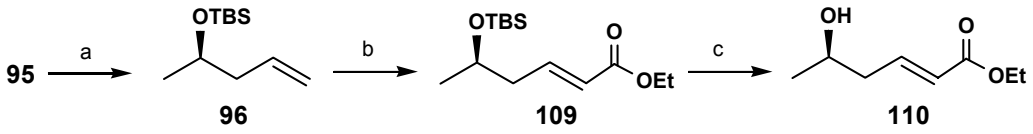


Scheme 19. *Reagents and conditions*: (a) vinylmagnesium bromide, THF, CuI, -20 ^oC, 12 h, 89%; (b) TBDPSCl, imidazole, DMAP, DMF, 0 ^oC, 2 h, 96%; (c) (i) OsO_4, $NaIO_4$, 2,6-Lutidine, 1,4-Dioxane: H_2O (3:1), 0 ^oC; (ii) $Ph_3P{=}CHCO_2Et$, THF, rt, 24 h, 92% from two steps; (d) $LiOH.H_2O$, THF/H_2O (3:2), 0 ^oC-rt, 6 h, 92%.

Synthesis of alcohol fragment 110 (Scheme 20):

The protection of hydroxy group of **96** as TBS ether furnished the olefin **96** in 96% yield. The ^1H NMR spectrum of **96** gave olefin peaks at δ 5.00-5.10 (multiplet, two proton), 5.82 (doublet, one proton) with coupling constant J = 8.1 Hz. The IR spectra of **96** showed absence of hydroxyl absorption. The olefin was oxidized to aldehyde in the presence of

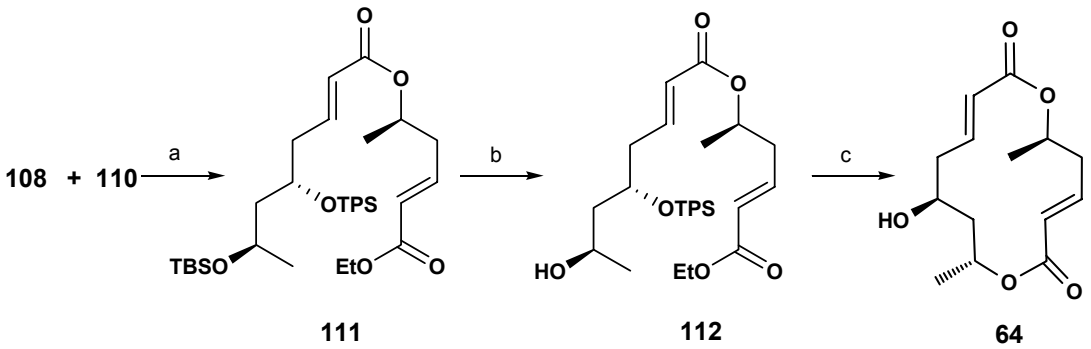
OsO_4 and $NaIO_4$ followed by reaction with (ethoxycarbonylmethylene)triphenyl-phosphorane in dry THF at room temperature to furnish the *trans*-olefin **109** in 92% (two steps) yield. The IR spectrum of **109** showed the ester carbonyl absorption at 1708 cm^{-1} and olefin C=C stretching at 1664 cm^{-1}. The ^1H NMR spectrum gave olefin protons at δ 5.84 (doublet of triplet) with the coupling constant J = 1.34, 15.66 Hz and δ 6.88-7.03 (multiplet) indicating *trans*-olefin. The TBS group was deprotected to give alcohol **110** in 96% yield. The IR spectra of **110** showed presence of hydroxyl absorption at 3378 cm^{-1}.



Scheme 20. *Reagents and conditions*: (a) TBSCl, CH_2Cl_2, 0 ^oC to rt, 4 h, 96%; (b i) OsO_4, $NaIO_4$, 2,6-Lutidine, 1,4-Dioxane: H_2O (3:1), 0 ^oC; (ii) $Ph_3P{=}CHCO_2Et$, THF, rt, 24 h, 92% from two steps; (c) TBAF, THF, 0 ^oC-rt, 1 h, 96%;

Formal total synthesis of (-) colletol (Scheme 21)

Having obtained both the fragments alcohol **110** and acid **108** in substantial amount we required to couple them and achieve the synthesis of target compound by synthetic manipulations. Thus, both the fragment were subjected to esterification under Yamaguchi



Scheme 21. *Reagents and conditions*: (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, then DMAP, benzene, 88%; (b) *p*-TsOH (cat.), CH_2Cl_2, 0 ^oC-rt, 1 h, 96% (c) ref. 23c.

coupling conditions to furnish **111** in 88% yield (Scheme 21). The TBS ether of **111** was cleaved by PPTS in EtOH to afford alcohol **112** in 96% yield. Transformation from **112** to

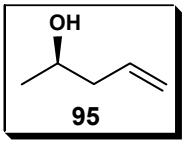
the target molecule **64** can easily be accomplished by ester hydrolysis, Yamaguchi macrolactonization and TPS deprotection following the literature procedure.[23c]

5.2.5. Conclusion

In conclusion, a formal total synthesis of (-)-colletol with high enantioselectivity has been developed in which all the stereocentres were established by Jacobsen's hydrolytic kinetic resolution. The synthetic strategy described here has significant potential for further extension to the synthesis of all the isomers of (-)-colletol and other 14-membered unsymmetrical bis-macrolactone.

5.2.6. Experimental Section

(*R*)-Pent-4-en-2-ol (95).



A round bottomed flask was charged with copper (I) iodide (2.63 g, 13.78 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 ^{o}C and vigorously stirred, and vinylmagnesium bromide (1M in THF, 206 mL, 206.75 mmol) was injected to it. A solution of propylene oxide **57a** (8 g, 13.78 mmol) in THF (10 mL) was added slowly to the above reagent, and the mixture was stirred at –20 ^{o}C for 12 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated to afford the crude product which on distillation provided homoallylic alcohol **95** as a colorless liquid.

Yield: 10.31g, 87%

Mol. Formula: $C_5H_{10}O$

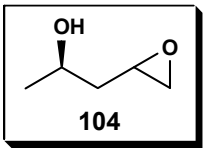
$[\alpha]_D^{25}$: -8.16 (c 0.9 $CHCl_3$) lit.[27] $[\alpha]_D^{24}$- 9.84 (*c* 3.2, Et_2O).

IR ($CHCl_3$, cm^{-1}): ν_{max} 3428, 2975, 1641, 1376, 1432, 1113, 909.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.21 (d, *J* = 6.19, 3H), 1.80 (s, 1H), 2.09-2.35 (m, 2H), 3.86 (dq, *J* = 1.13, 6.06, 12.25 Hz, 1H), 5.08-5.12 (m, 1H), 5.15-5.19 (m, 1H), 5.72-5.93 (m, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 22.4, 43.41, 66.8, 117.3, 134.7 ppm.

(2*R*)-1-(Oxiran-2-yl)propan-2-ol (104).

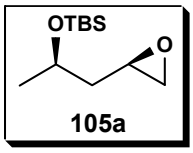


To a stirred solution of olefin **95** (7.5 g, 87.08 mmol) in CH_2Cl_2 (70 mL) at 0 ^oC was added *m*-CPBA (50%) (33 g, 95.79 mmol). The reaction mixture was stirred at room temperature for 10 h and quenched by saturated $NaHCO_3$ solution, extracted with CH_2Cl_2, washed with sat. $NaHCO_3$ and brine, dried (Na_2SO_4), concentrated and purified by silica gel column chromatography using pet ether/EtOAc (9:1) as eluent to yield the epoxide **104** as a colorless liquid in diastereomeric mixture (1.1:1).

Yield: 8.54 g, 96%.

$[\alpha]_D^{25}$: -7.71 (*c*, 0.50, $CHCl_3$)

***tert*-Butyldimethyl((*R*)-1-((*R*)-oxiran-2-yl)propan-2-yloxy)silane (105a).**



To a stirred solution of alcohol **104** (3 g, 29.37 mmol) in CH_2Cl_2 (25 mL) was added imidazole (2.3 g, 35.25 mmol). To this solution *t*-butyl dimethylchlorosilane (4.87 g, 32.31 mmol) was added at 0 ^oC and reaction was stirred at room temperature for 4 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 (19:1) as eluent provided **105** as a colorless liquid (6.04 g, 95%).

A solution of epoxide **105** (5.5 g, 25.41 mmol) and (*R,R*)-Salen-Co(III)-OAc (0.084 g, 0.13 mmol) in THF (0.3 mL) was stirred at 0 ^{o}C for 5 min, and then distilled water (251 μL, 13.97 mmol) was added. After stirring for 24 h, it was concentrated and purified by silica gel column chromatography using pet ether/EtOAc (19:1) to afford **105a (**2.53g, 46%) as a yellow color liquid. Continued chromatography with pet ether/EtOAc (3:2) provided the diol **105b** as a brown color liquid as a single diastereomer.

Yield: 2.53 g, 46%

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

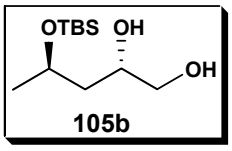
$[\alpha]_D^{25}$: -7.71 (*c*, 0.50, $CHCl_3$) {lit.^{25} $[\alpha]_D^{24}$ - 11.4 (*c* 0.67, $CHCl_3$)}.

IR ($CHCl_3$, cm^{-1}): ν_{max} 3017, 2983, 2878, 2096, 1658, 1466

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.09 (s, 3H), 0.89 (s, 9H), 1.23 (q, *J* = 7.83, 13.90 Hz, 4H), 1.57-1.70 (m, 1H), 2.47 (dd, *J* = 2.66, 5.06 Hz, 1H), 2.77 (dt, *J* = 0.51, 4.55 Hz, 1H), 2.99-3.08 (m, 1H), 4.04 (q, *J* = 5.94, 12.0 Hz, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.98, -4.5, 18.0, 23.7, 25.8, 42.4, 46.7, 49.6, 66.6 ppm.

(2*S*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)pentane-1,2-diol (105b)



105b

Yield: 2.48g, 45%

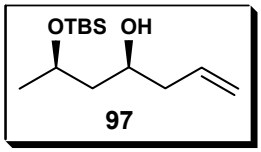
Mol. Formula: $C_{11}H_{26}O_3Si$

$[\alpha]_D^{25}$: +36.6 (*c* 1.00, $CHCl_3$)

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.10 (s, 6H), 0.92 (s, 9H), 1.20-1.29 (m, 3H), 1.41-1.82 (m, 2H), 2.13 (brs, 2H), 3.42-3.71 (m, 2H), 3.99-431 (m, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -5.08, -4.60, 17.85, 23.0, 25.7, 40.5, 66.9, 67.0, 69.0 ppm.

(4*S*,6*R*)-6-(*tert*-Butyldimethylsilyloxy)hept-1-en-4-ol (97).



97

A round bottomed flask was charged with copper(I)iodide (198 mg, 1.04 mmol), gently heated under vaccum and slowly cooled with a flow of argon and THF (10 mL) was added. This suspension was cooled to –20 ^{o}C, stirred and vinylmagnesium bromide (1M in THF, 15.61 mL, 15.61 mmol) was added to it. A solution of epoxide **105a** (2.25 g, 10.41 mmol) in THF (20 mL) was added to the above reagent and the mixture was stirred at –20 ^{o}C for 1 h. After consumption of starting material, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl. The water layer was extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated. Purification of crude product by silica gel column chromatography using pet ether/EtOAc (9:1) as eluent afforded **97** as a colorless liquid.

Yield: 2.26 g, 89%

Mol. Formula: $C_{13}H_{28}O_2Si$

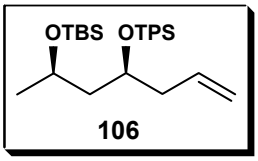
$[\alpha]_D^{25}$: –34.5 (*c* 0.80, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3436, 2858, 1640, 1448, 1376, 1260, 1075.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.11 (s, 3H), 0.12 (s, 3H), 0.90 (s, 9H), 1.19 (d, *J* = 6.07 Hz, 2H), 1.21-1.25 (m, 1H), 1.53-1.74 (m, 2H), 2.18-2.26 (m, 2H), 2.51 (brs, 1H), 3.74-3.89 (m, 1H), 4.00-4.19 (m, 1H), 5.06-5.15 (m, 2H), 5.74-5.86 (m, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.9, -4.0, 17.8, 24.4, 25.8, 41.9, 45.0, 69.7, 70.5, 117.2, 134.8 ppm.

(5*S*,7*R*)-5-allyl-2,2,7,9,9,10,10-heptamethyl-3,3-diphenyl-4,8-dioxa-3,9-disilaundecane (106)



To a stirred solution of alcohol **97** (1.5 g, 6.14 mmol) in dry DMF (50 mL) and imidazole (501 mg, 7.36 mmol) at 0 °C was added TBDPSCl (1.86 g, 1.73 mL, 6.75 mmol) and DMAP (cat.) dropwise and the reaction was stirred at 0 ^{o}C for 2 h. The reaction mixture was quenched with H_2O (50 mL) and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layer was washed with brine (2 x 40 mL) and dried over anhydrous Na_2SO_4. The

solvent was concentrated under reduced pressure and the residue was purified by column chromatography (EtOAc–hexane, 5%) to give **106**.

Yield: 2.84 g, 96%

Mol. Formula: $C_{29}H_{46}O_2Si_2$

$[\alpha]_D^{25}$: +8.07 (c 0.68 $CHCl_3$)

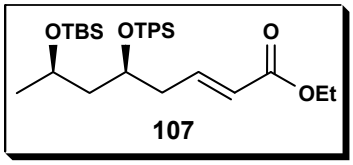
IR ($CHCl_3$, cm^{-1}): ν_{max} 3020, 2972, 2921, 2892, 1646, 1541, 1215

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.01 (d, *J* = 6.06 Hz, 3H), 0.1 (d, *J* = 3.40 Hz, 3H), 0.82 (s, 9H), 0.91 (s, 9H), 1.13-1.20 (m, 1H), 1.28 (d, *J* = 5.94 Hz, 2H), 1.44-1.55 (m, 1H), 1.64-1.80 (m, 1H), 2.15-2.33 (m, 1H), 3.21-3.37 (m, 1H), 3.82-4.05 (m, 2H), 4.85-4.88 (m, 1H), 4.94-5.01 (m, 1H), 5.64-5.85 (m, 1H), 7.32-7.43 (m, 6H), 7.66-7.73 (m, 4H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.8, -4.3, 18.0, 19.4, 22.3, 23.7, 25.8, 27.1, 39.1, 41.1, 46.1, 65.8, 68.6, 70.4, 117.0, 127.4, 127.5, 127.7, 129.5, 134.7, 135.9 ppm.

Analysis Calcd.: C, 72.14; H, 9.60%; **Found:** C, 72.04; H, 9.66%.

(5*S*,7*R*,*E*)-ethyl 7-(*tert*-butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxy)oct-2-enoate (107)



107

To a solution of compound **106** (1.5 g, 3.11 mmol) in dioxane-water (3:1, 20 mL) were added 2,6-lutidine (0.72 mL, 6.21 mmol), OsO_4 (0.1M solution in toluene, 0.8 mL, 0.06 mmol) and $NaIO_4$ (2.66 g, 6.21 mmol). The reaction was stirred at 25 ^oC for 3 hours. After the reaction was complete, water (10 mL) and CH_2Cl_2 (20 mL) were added. The organic layer was separated, and the water layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layer was washed with brine and dried (Na_2SO_4) to give crude aldehyde which was used as such for the next step without further purification.

To a solution of (ethoxycarbonylmethylene)triphenylphosphorane (1.3 g, 3.75 mmol) in dry THF (15 mL) was added a solution of the above aldehyde in dry THF (5 mL). The reaction mixture was stirred at room temperature for 24 h. It was then concentrated and

purified by silica gel column chromatography using petroleum ether/EtOAc (8.5:1.5) as eluent to afford the α,β-unsaturated olefin **107** as a pale yellow liquid.

Yield: 1.58 g, 92%

Mol. Formula: $C_{32}H_{50}O_4Si_2$

$[\alpha]_D^{25}$: +12.23 (c 0.82 $CHCl_3$)

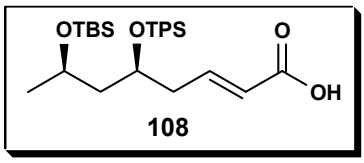
IR ($CHCl_3$, cm^{-1}): ν_{max} 3056, 3019, 2962, 2916, 1712, 1661, 1472, 1463

^{1}H NMR (200 MHz, $CDCl_3$): δ -0.04 (s, 3H), 0.00 (s, 3H), 0.80 (s, 9H), 0.95 (dd, *J* = 4.42, 8.46 Hz, 2H), 1.06 (s, 9H), 1.29 (t, *J* = 7.07 Hz, 3H), 1.53-1.78 (m, 3H), 2.23-2.37 (m, 2H), 3.83-4.01 (m, 2H), 4.18 (q, *J* = 7.07, 14.27 Hz, 2H), 5.72 (dt, *J* = 1.26, 15.66 Hz, 1H), 6.81-7.01 (m, 1H), 7.32-7.44 (m, 6H), 7.59-7.69 (m, 4H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.9, -4.3, 14.2, 17.9, 19.3, 23.8, 25.8, 27.0, 39.3, 46.3, 60.1, 65.6, 69.7, 123.6, 127.5, 129.6, 133.9, 134.0, 145.4, 166.3 ppm.

Analysis Calcd.: C, 69.26; H, 9.08%; **Found:** C, 69.31; H, 9.11%.

(5*S*,7*R*,*E*)-7-(*tert*-butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxy)oct-2-enoic acid (108)



108

To the ester **107** (1.2 g, 2.16 mmol) dissolved in MeOH (10 mL) and H_2O (6.67 mL) was added $LiOH.H_2O$ (266 mg, 6.49 mmol) and stirred at 0 ^oC to room temperature for 6 h. The reaction mixture was further diluted with H_2O (5 mL) and stirred for 30 min then concentrated by rotary evaporator to quarter of its volume. The mixture was acidified with 1 M HCl (pH 3) and the reaction mixture was extracted with EtOAc (3 x 10 mL). The combined organic layer was washed with brine (2 x 10 mL) and dried over anhydrous Na_2SO_4, filtered, evaporated and the crude product was purified by column chromatography (EtOAc–hexane, 35%) to yield pure **108**.

Yield: 1.05 g, 92%

Mol. Formula: $C_{30}H_{46}O_4Si_2$

$[\alpha]_D^{25}$: +26.87 (c 0.50 $CHCl_3$)

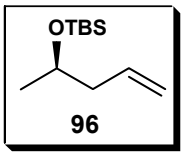
IR ($CHCl_3$, cm^{-1}): ν_{max} 2972, 1717, 1680, 1475, 1449

^{1}H NMR (200 MHz, $CDCl_3$): δ -0.06 (d, *J* = 10.99 Hz, 3H), 0.00 (s, 3H), 0.80 (s, 9H), 0.95 (t, *J* = 5.8 Hz, 3H), 1.07 (s, 9H), 1.24-1.32 (m, 1H), 1.51-1.81 (m, 2H), 2.36 (q, *J* = 5.31, 11.75 Hz, 2H), 3.62-4.05 (m, 2H), 5.75 (dd, *J* = 2.91, 15.67 Hz, 1H), 6.98-7.15 (m, 1H), 7.33-7.44 (m, 6H), 7.63-7.73 (m, 4H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.9, -4.3, 14.2, 17.9, 19.3, 23.8, 25.8, 27.0, 39.3, 46.3, 60.1, 65.6, 69.7, 123.6, 127.5, 129.6, 133.9, 134.0, 145.4, 166.27 ppm.

Analysis Calcd.: C, 68.39; H, 8.80%; **Found:** C, 68.42; H, 8.79%.

(*R*)- *tert*-Butyldimethyl-(pent-4-en-2-yloxy)-silane (96).



To a stirred soluion of alcohol **95** (2.5 g, 29.03 mmol) in CH_2Cl_2 (25 mL), imidazole (2.37, 34.83 mmol) was added. To this solution *t*-butylchlorodimethyl silane (4.81 g, 31.92 mmol) was added at 0 ^oC and reaction was stirred at room temperature for 4 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 **96**.

Yield: 5.58 g, 96%

$[\alpha]_D^{25}$: -11.87 (c 1.00 $CHCl_3$) {lit.[16g] $[\alpha]_D^{28}$ –14.46 (*c* = 1.8, $CHCl_3$)}

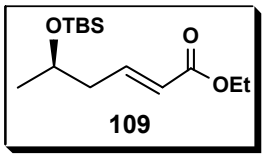
Mol. Formula: $C_{11}H_{24}OSi$

IR ($CHCl_3$, cm^{-1}): ν_{max} 3088, 2929, 2896, 1642, 1255, 1129

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.06 (s, 6H), 0.91 (s, 9H), 1.14 (d, *J* = 6.06 Hz, 3H), 2.19 (dq, *J* = 1.01, 5.81, 11.88 Hz, 1H), 3.21-3.37 (m, 1H), 3.92-4.04 (m, 1H), 5.00-5.10 (m, 2H), 5.82 (d, *J* = 8.1 Hz, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.7, -4.5, 18.1, 23.4, 25.9, 44.3, 68.6, 116.5, 135.6 ppm.

(*R*,*E*)-Ethyl 5-(*tert*-butyldimethylsilyloxy)hex-2-enoate (109).



To a solution of compound **96** (2 g, 9.98 mmol) in dioxane-water (3:1, 20 mL) were added 2,6-lutidine (2.28 mL, 19.96 mmol), OsO_4 (0.1M solution in toluene, 0.4 mL, 0.20 mmol) and $NaIO_4$ (8.53 g, 39.92 mmol). The reaction was stirred at 25 ^oC for 3 hours. After the reaction was complete, water (5 mL) and CH_2Cl_2 (10 mL) were added. The organic layer was separated, and the water layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layer was washed with brine and dried (Na_2SO_4) to give crude aldehyde which was used as such for the next step without further purification.

To a solution of (ethoxycarbonylmethylene)triphenylphosphorane (4.22 g, 12.10 mmol) in dry THF (20 mL) was added a solution of the above aldehyde in dry benzene (5 mL). The reaction mixture was stirred at room temperature for 24 h. It was then concentrated and purified by silica gel column chromatography using petroleum ether/EtOAc (8.5:1.5) as eluent to afford the α,β-unsaturated olefin **109** as a pale yellow liquid.

Yield: 2.50 g, 92%.

Mol. Formula: $C_{14}H_{28}O_3Si$

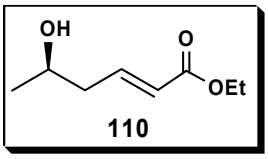
$[\alpha]_D^{25}$: -5.11 (*c* 0.50, $CHCl_3$){lit.[28] $[\alpha]_D^{16g}$ -9.5 (*c* 1.00, $CHCl_3$)}

IR ($CHCl_3$, cm^{-1}): ν_{max} 3016, 2957, 2931, 2858, 1708, 1664, 1583, 1376, 1216, 1089

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.88 (s, 9H), 1.17 (d, *J* = 6.06 Hz, 3H), 1.29 (t, *J* = 7.07 Hz, 3H), 2.32 (tt, *J* = 1.13, 7.20 Hz, 2H), 3.85-4.0 (m, 1H), 4.19 (q, *J* = 7.20, 14.28 Hz, 2H), 5.84 (dt, *J* = 1.34, 15.66 Hz, 1H), 6.88-7.03 (m, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.9, -4.6, 14.2, 18.0, 23.7, 25.7, 42.4, 60.1, 67.6, 123.1, 146.0, 166.4 ppm.

(*R*,*E*)-ethyl 5-hydroxyhex-2-enoate (110)



To the ester **109** (1.0 g, 3.67 mmol) dissolved in THF was added TBAF (1.06 g, 1.25 mL, 4.04 mmol) and stirred at r.t. for 6 h. The reaction mixture was further diluted with H_2O

(10 mL) and stirred 0 ^{o}C to room temperature for 1 h. The reaction mixture was quenched with water (10 mL) and then the solution was extracted with EtOAc (3 x 10 mL). The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography purification (EtOAc/petroleum ether, 4:1) of the crude product gave **110** as colorless syrup.

Yield: 510 mg, 88%

Mol. Formula: $C_8H_{14}O_3$

$[\alpha]_D^{25}$: -19.07 (*c* 0.86, $CHCl_3$)

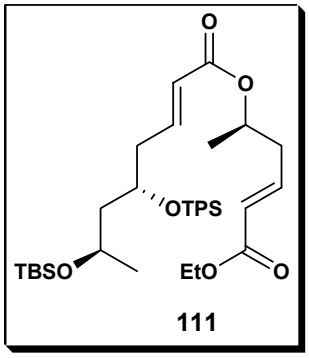
IR (neat, cm^{-1}): ν_{max} 3378, 2975, 2932, 1638, 1583, 1422, 1375, 1227, 1129

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.24 (d, *J* = 5.43 Hz, 3H), 1.29 (t, *J* = 7.20 Hz, 3H), 1.81 (brs, 1H), 2.37 (dt, *J* = 1.39, 7.45 Hz, 2H), 3.89-4.05 (m, 1H), 4.19 (q, *J* = 7.20, 14.27 Hz, 2H), 5.90 (dt, *J* = 1.52, 15.66 Hz, 1H), 6.85-7.04 (m, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 22.9, 41.6, 60.2, 66.4, 123.4, 145.4, 166.5 ppm.

Analysis Calcd.: C, 60.74; H, 8.92%; **Found** C, 60.68; H, 8.88%

(5*S*,7*R*,*E*)-((*R*,*E*)-6-Ethoxy-6-oxohex-4-en-2-yl) 7-(*tert*-butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxy)oct-2-enoate (111):



111

To a solution of acid **108** (100 mg, 0.20 mmol) in THF, was added triethyl amine (0.04 mL, 0.18 mmol) and 2,4,6-trichlorobenzoyl chloride (0.1 mL, 0.28 mmol) under nitrogen atmosphere at 0 ^{o}C and the reaction mixture was allowed to stir under this condition for 1 h. To this, alcohol **110** (30 mg, 0.20 mmol) in THF (2 mL) and catalytic amount of 4-dimethyl aminopyridine (DMAP) were added successively at 0 ^{o}C. Stirring was continued for additional 20 h at rt. The reaction mixture was quenched with water and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were thoroughly washed with

saturated sodium bicarbonate solution, brine, dried (Na_2SO_4), and concentrated to afford the crude product which was purified by silica gel column chromatography using ethyl acetate: light petroleum (1:9) to afford the ester **111** as a colorless syrupy liquid.

Yield: 110 mg, 88%

Mol. Formula: $C_{38}H_{58}O_6Si_2$

$[\alpha]_D^{25}$: +19.57 (*c* 0.92, $CHCl_3$)

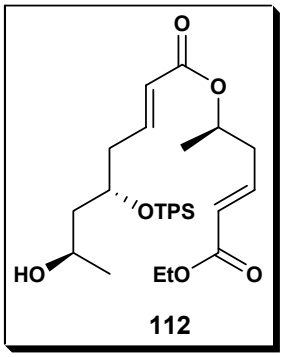
IR ($CHCl_3$, cm^{-1}): ν_{max} 2935, 1716, 1680, 1475, 1320, 1216, 1144, 1110

^{1}H NMR (200 MHz, $CDCl_3$): δ -0.04 (s, 3H), 0.00 (s, 3H), 0.80 (s, 9H), 0.89-0.99 (m, 3H), 1.06 (s, 9H), 1.07 (d, *J* = 4.68 Hz, 3H), 1.22-1.32 (m, 5H), 1.49-1.62 (m, 2H), 2.28-2.36 (m, 1H), 2.41-2.53 (m, 1H), 3.80-4.02 (m, 2H), 4.19 (q, *J* = 7.07, 14.15 Hz, 2H), 4.91-5.10 (m, 1H), 5.70 (dt, *J* = 1.26, 15.67 Hz, 1H), 5.88 (dt, *J* = 1.26, 15.67 Hz, 1H), 6.77-7.02 (m, 2H), 7.33-7.46 (m, 6H), 7.65-7.75 (m, 4H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.9, -4.3, 14.2, 17.9, 19.3, 19.6, 23.7, 25.8, 26.5, 27.0, 46.3, 60.3, 65.6, 68.9, 69.6, 124.1, 127.5, 129.6, 134.8, 135.8, 143.6, 145.8, 165.6, 166.1 ppm.

Analysis Calcd.: C, 68.42; H, 8.76%; **Found** C, 68.48; H, 8.71%.

(5*S*,7*R*,*E*)-((*R*,*E*)-6-Ethoxy-6-oxohex-4-en-2-yl)5-(*tert*-butyldiphenylsilyloxy)-7-hydroxyoct-2-enoate (112)



112

To a solution of ester **111** (100 mg, 0.15 mmol) in DCM, was added catalytic amount of *p*TsOH and the resulting mixture was stirred for 1 h at room temperature. The reaction mixture was then hydrolyzed with satd. brine (10 mL), the solvent was evaporated, and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were

dried (Na_2SO_4) and the solvent was evaporated. The crude product was purified by column chromatography on silica gel to give **112** as a colorless thick syrupy liquid.

Yield: 80 mg, 96%

Mol. Formula: $C_{32}H_{44}O_6Si$

$[\alpha]_D^{25}$: +9.57 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3410, 2935, 1727, 1690, 1466, 1322, 1216

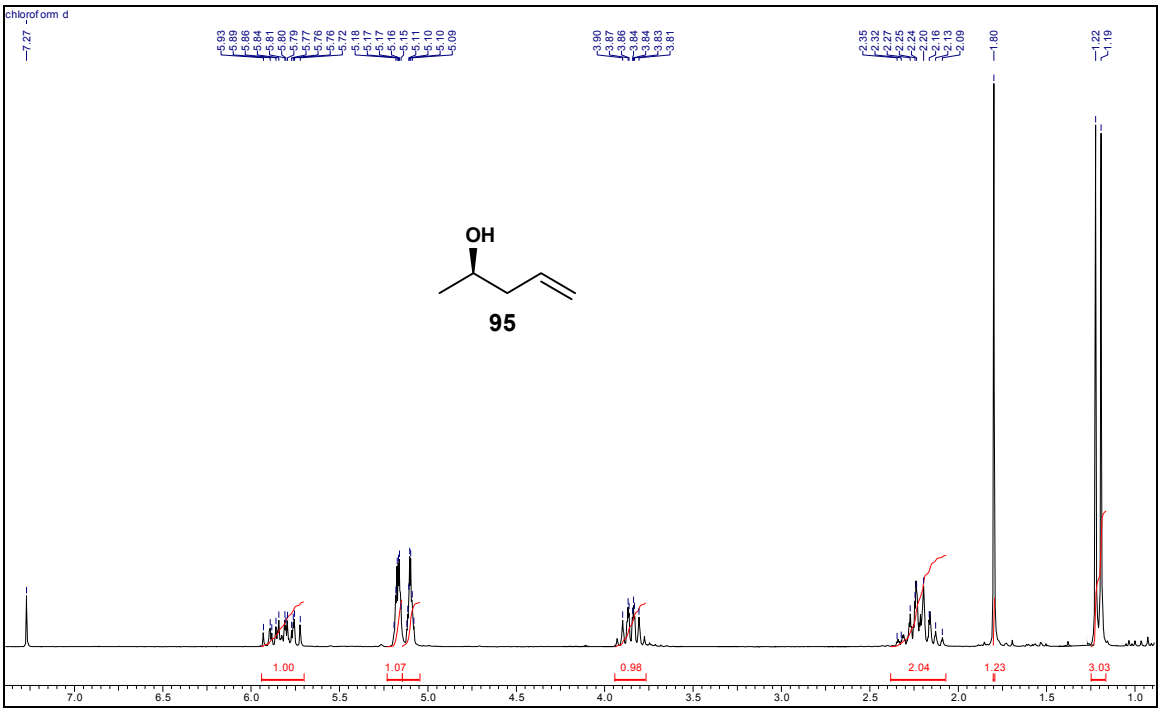
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.06 (s, 9H), 1.17-1.33 (m, 8H), 1.43-1.82 (m, 3H), 2.18-2.53 (m, 5H), 3.91-4.10 (m, 2H), 4.22 (dq, *J* = 2.52, 14.27 Hz, 2H), 4.96-5.11 (m, 1H), 5.59 (dt, *J* = 1.26, 15.67 Hz, 1H), 5.87 (dt, *J* = 1.26, 15.67 Hz, 1H), 6.67-7.05 (m, 2H), 7.35-7.49 (m, 6H), 7.65-7.74 (m, 4H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.2, 19.2, 19.6, 23.6, 26.9, 38.3, 40.0, 41.8, 45.2, 60.3, 66.0, 69.9, 71.8, 123.7, 124.1, 127.6, 129.8, 133.1, 133.7, 136.8, 143.5, 144.9, 165.5, 166.1 ppm.

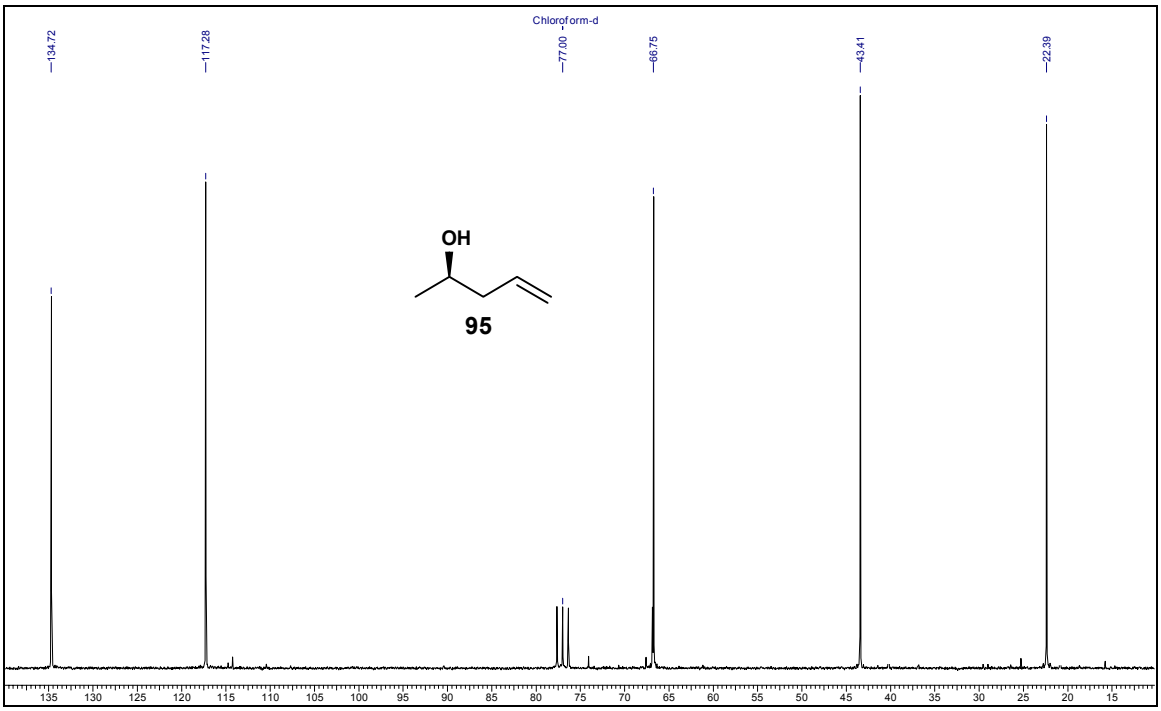
Analysis Calcd.: C, 69.53; H, 8.02%; **Found** C, 69.48; H, 8.10%.

5.2.7 Spectra

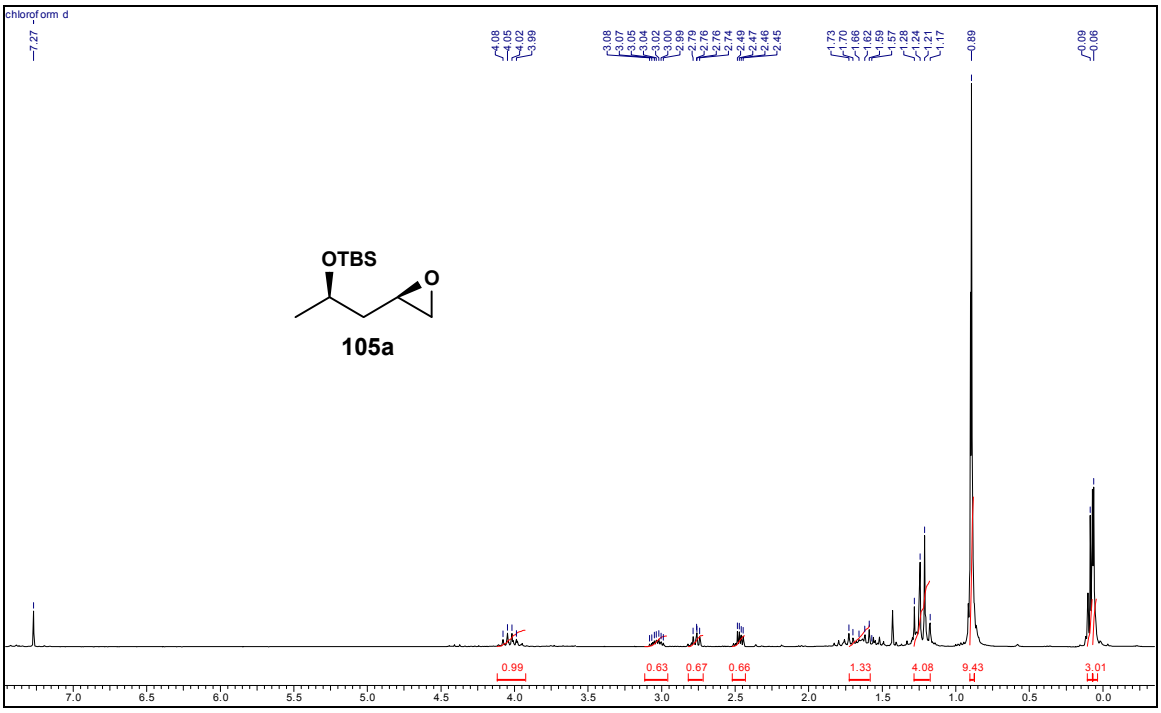
1. ^{1}H and ^{13}C NMR spectra of **95**
2. ^{1}H and ^{13}C NMR spectra of **105a**
3. ^{1}H and ^{13}C NMR spectra of **105b**
4. ^{1}H and ^{13}C NMR spectra of **97**
5. ^{1}H and ^{13}C NMR spectra of **106**
6. ^{1}H and ^{13}C NMR spectra of **107**
7. ^{1}H and ^{13}C NMR spectra of **108**
8. ^{1}H and ^{13}C NMR spectra of **96**
9. ^{1}H and ^{13}C NMR spectra of **109**
10. ^{1}H and ^{13}C NMR spectra of **110**
11. ^{1}H and ^{13}C NMR spectra of **111**
12. ^{1}H and ^{13}C NMR spectra of **112**



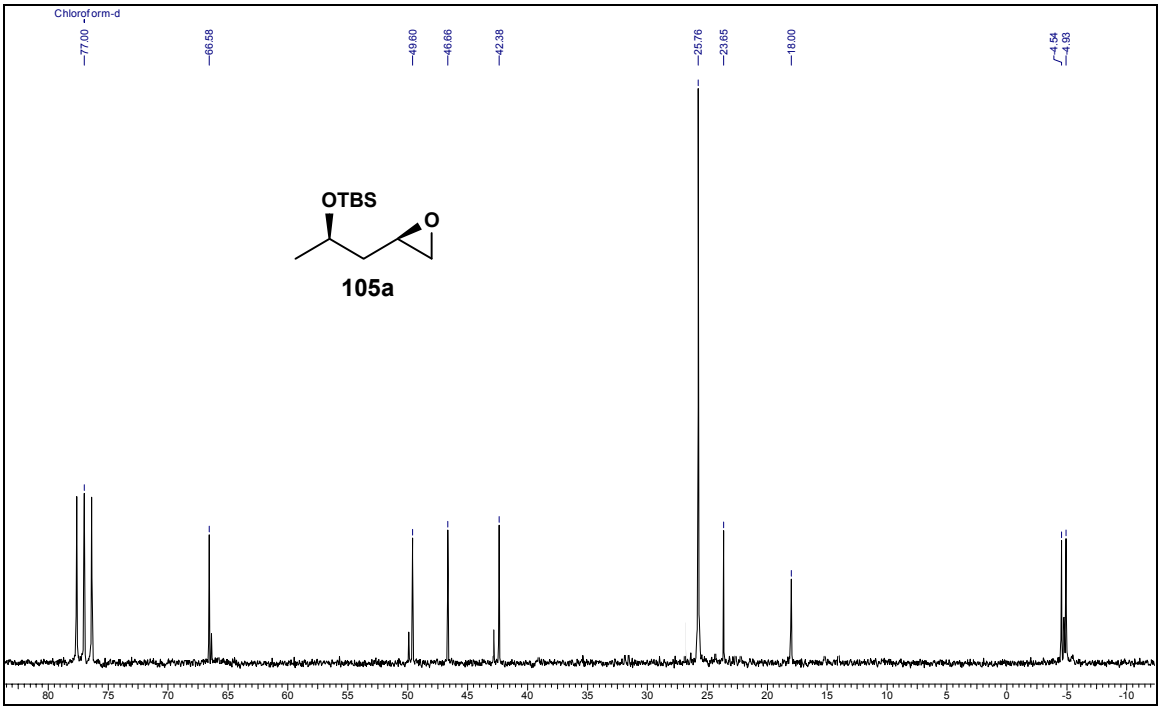
☞ ^{1}H NMR of the compound 65 in $CDCl_3$



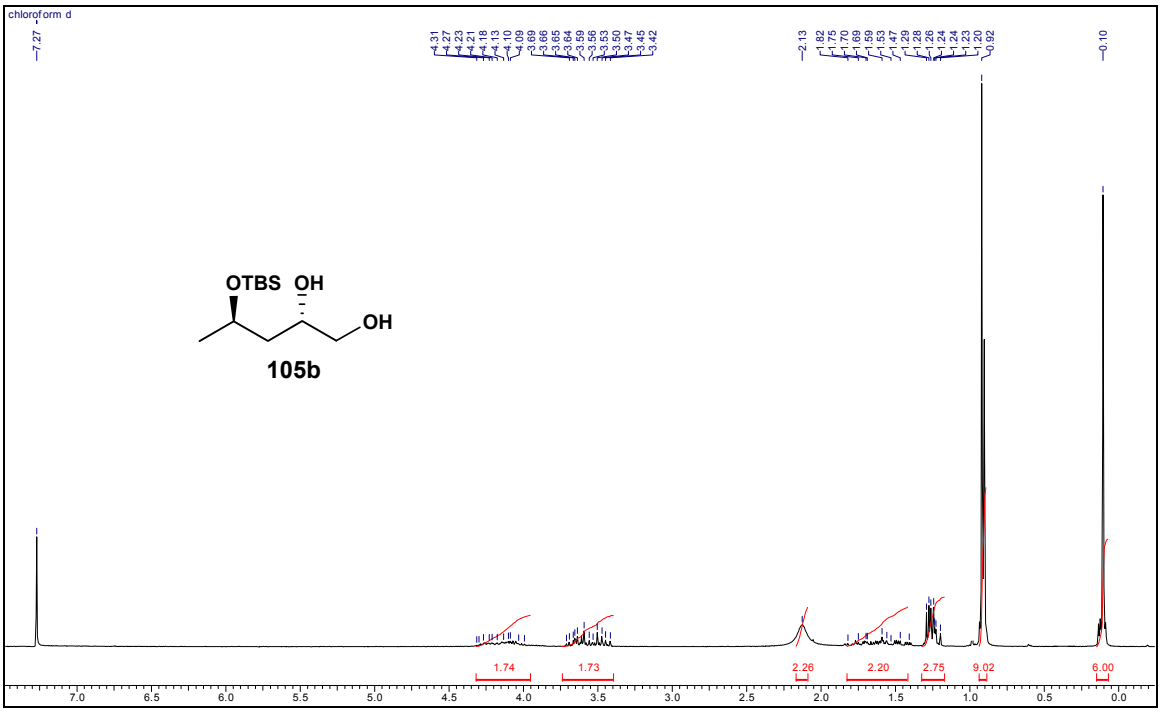
☞ ^{13}C NMR of the compound 95 in $CDCl_3$



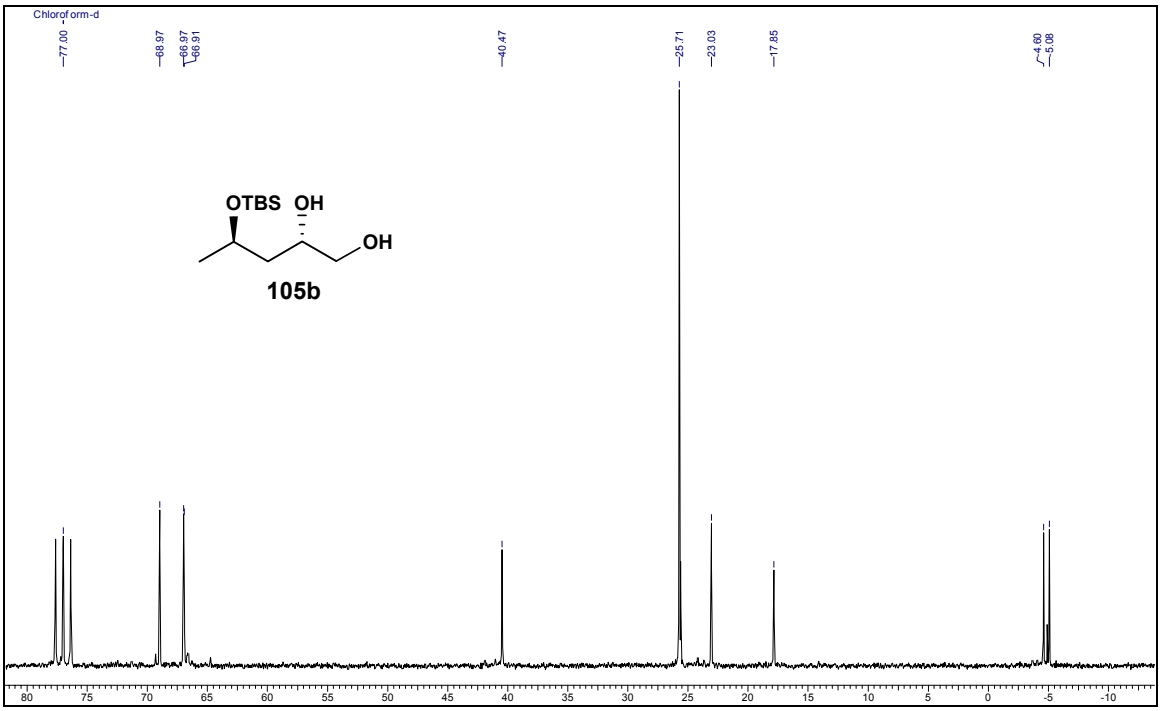
☞ ^{1}H NMR of the compound 105a in $CDCl_3$



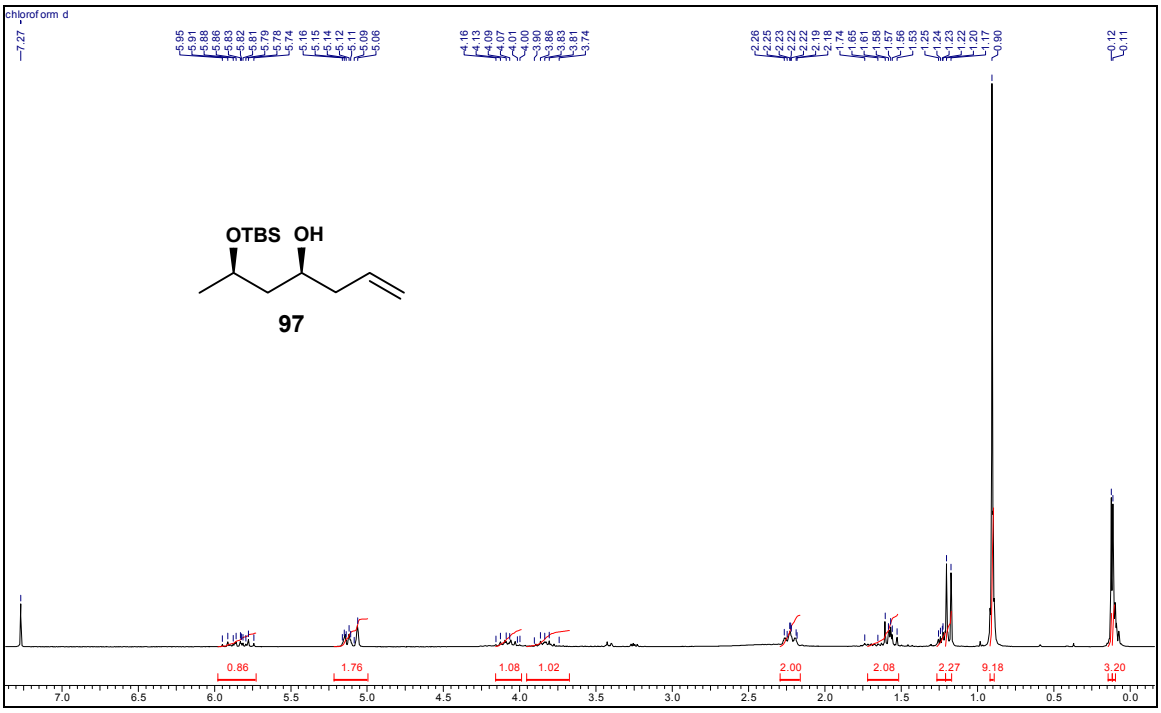
☞ ^{13}C NMR of the compound 105a in $CDCl_3$



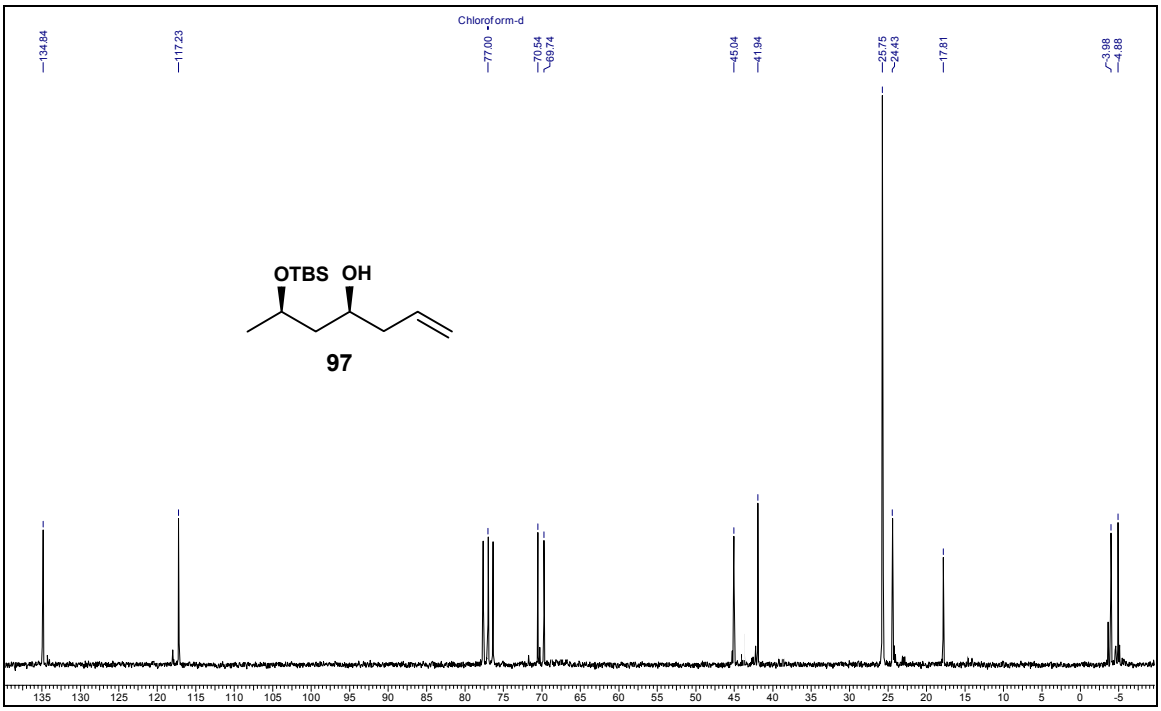
☞ ^{1}H NMR of the compound 105b in $CDCl_3$



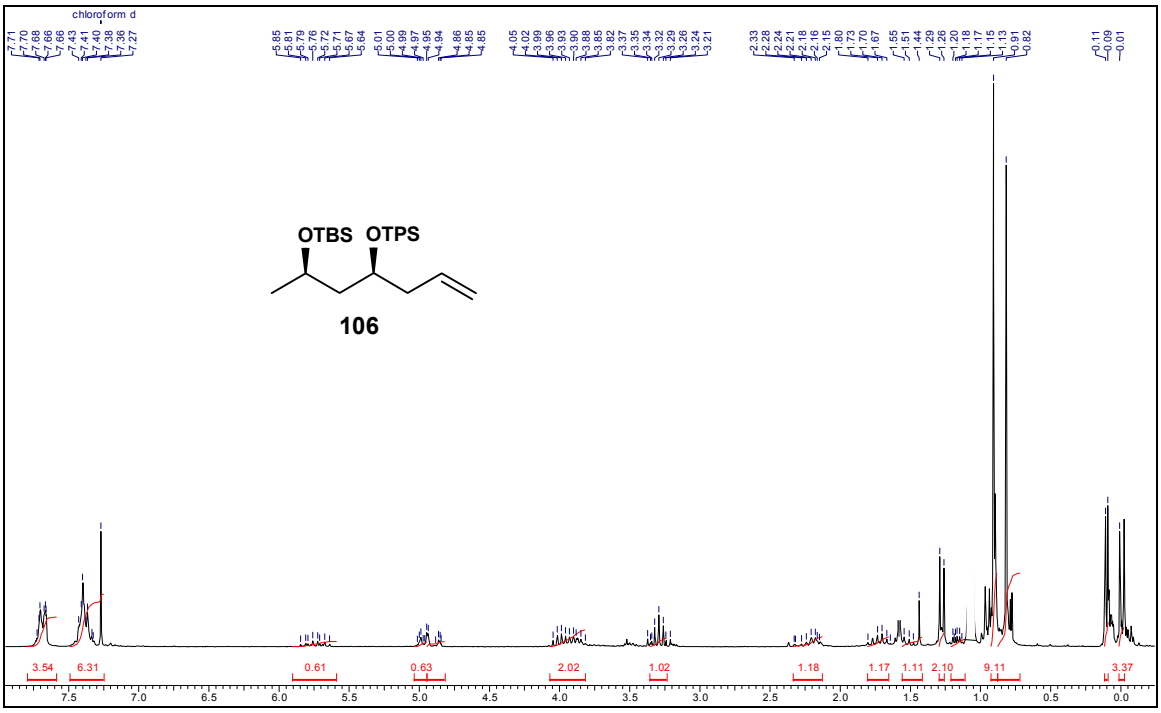
☞ ^{13}C NMR of the compound 105b in $CDCl_3$



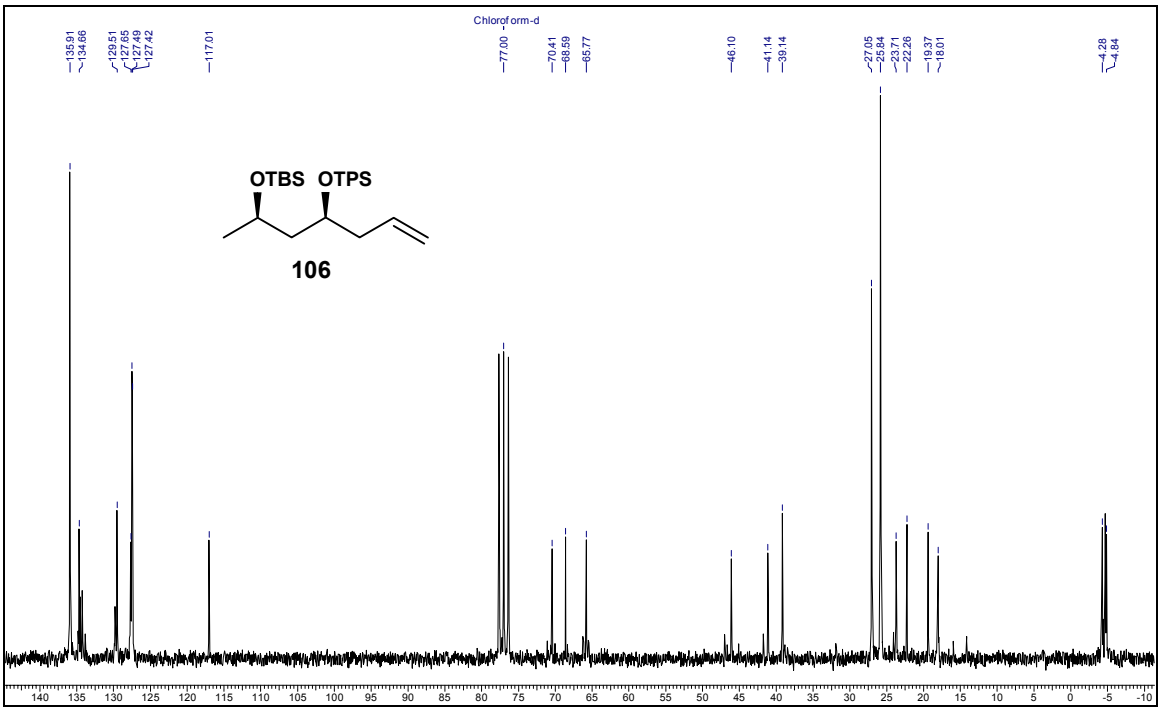
☞ ^{1}H NMR of the compound 97 in $CDCl_3$



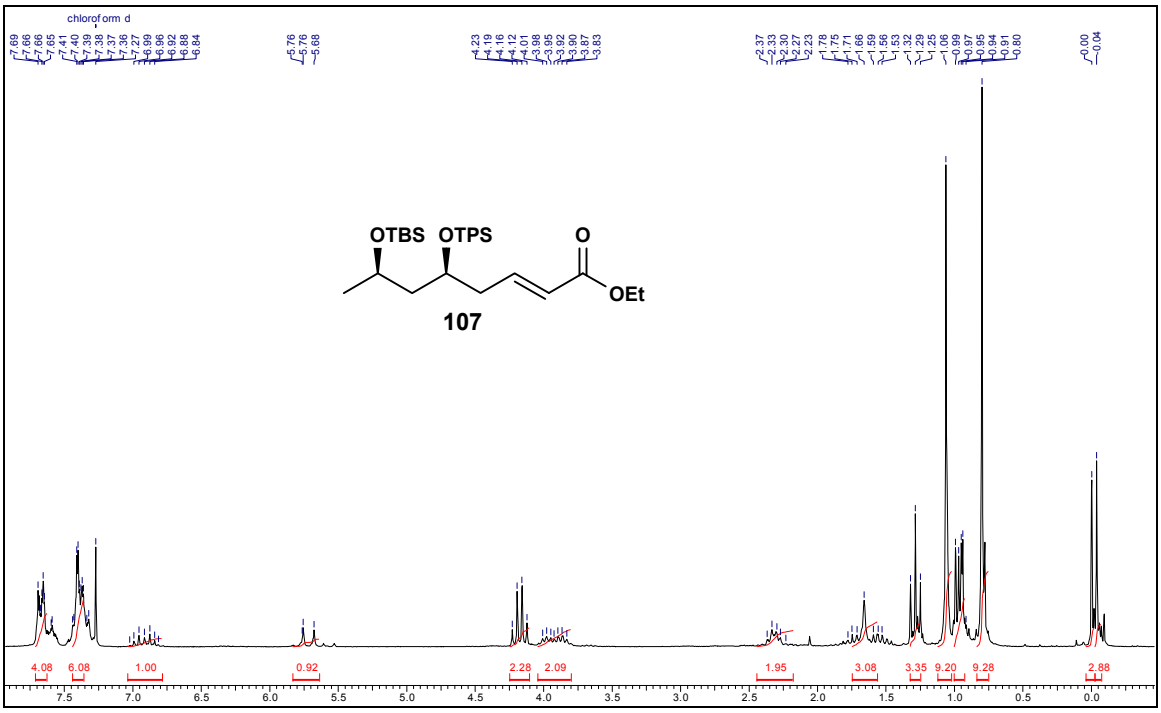
☞ ^{13}C NMR of the compound 97 in $CDCl_3$



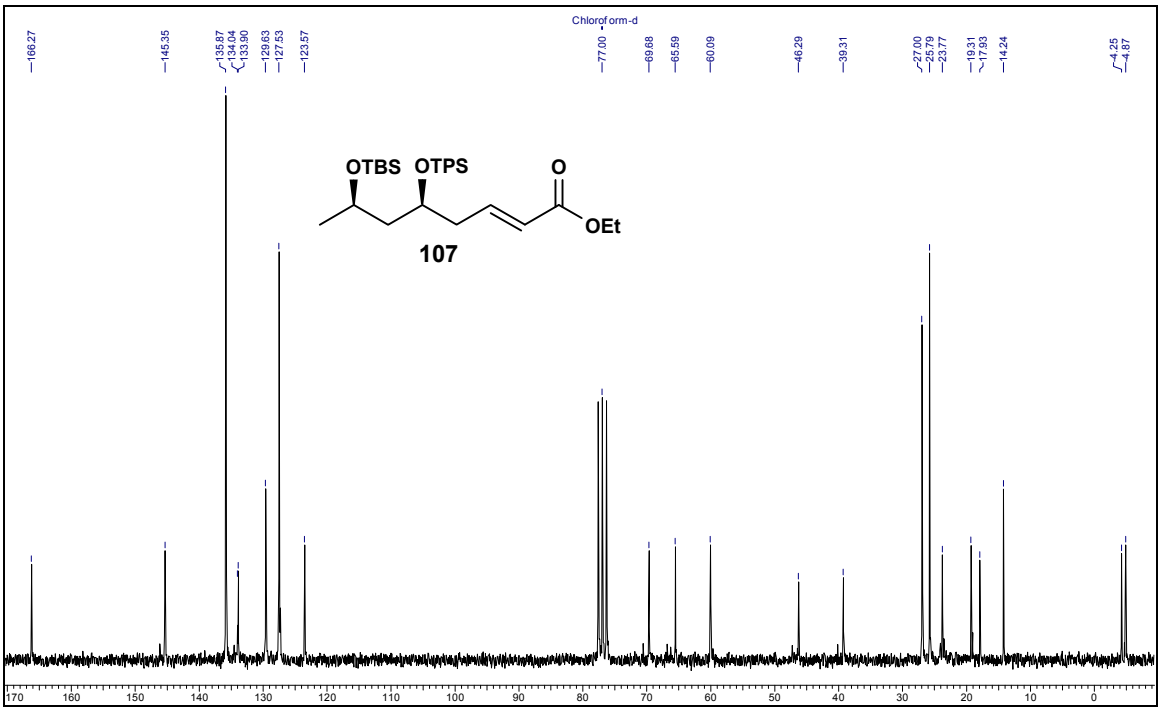
☞ ^{1}H NMR of the compound 106 in $CDCl_3$



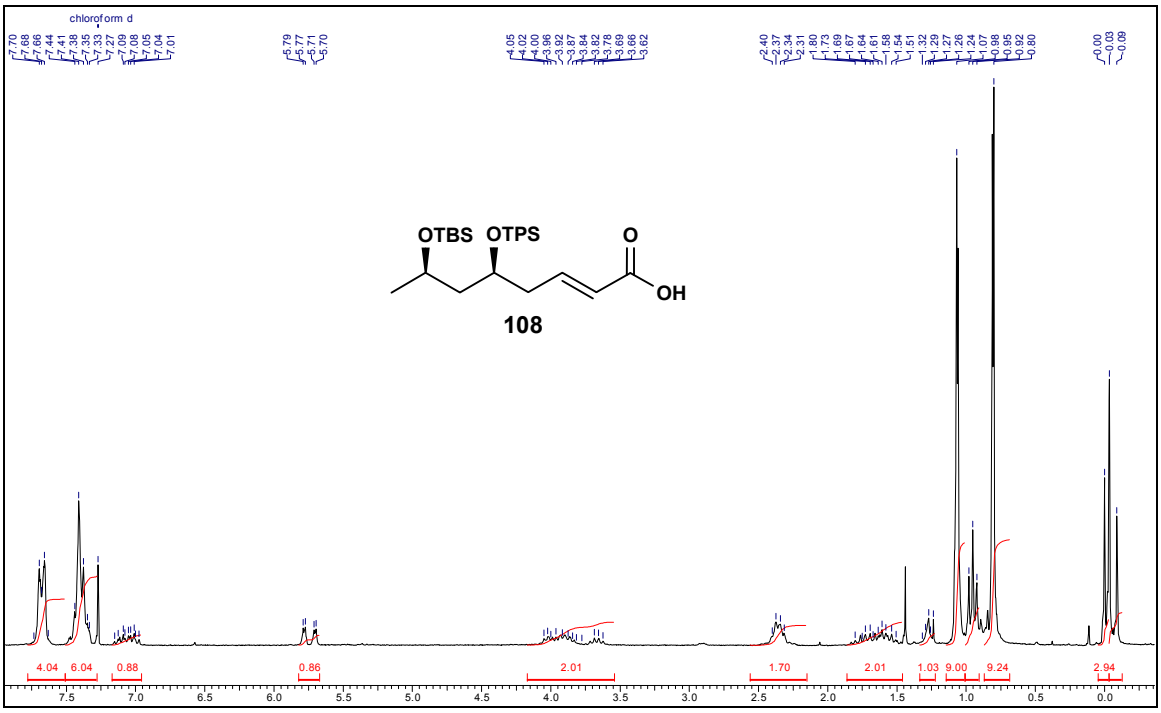
☞ ^{13}C NMR of the compound 106 in $CDCl_3$



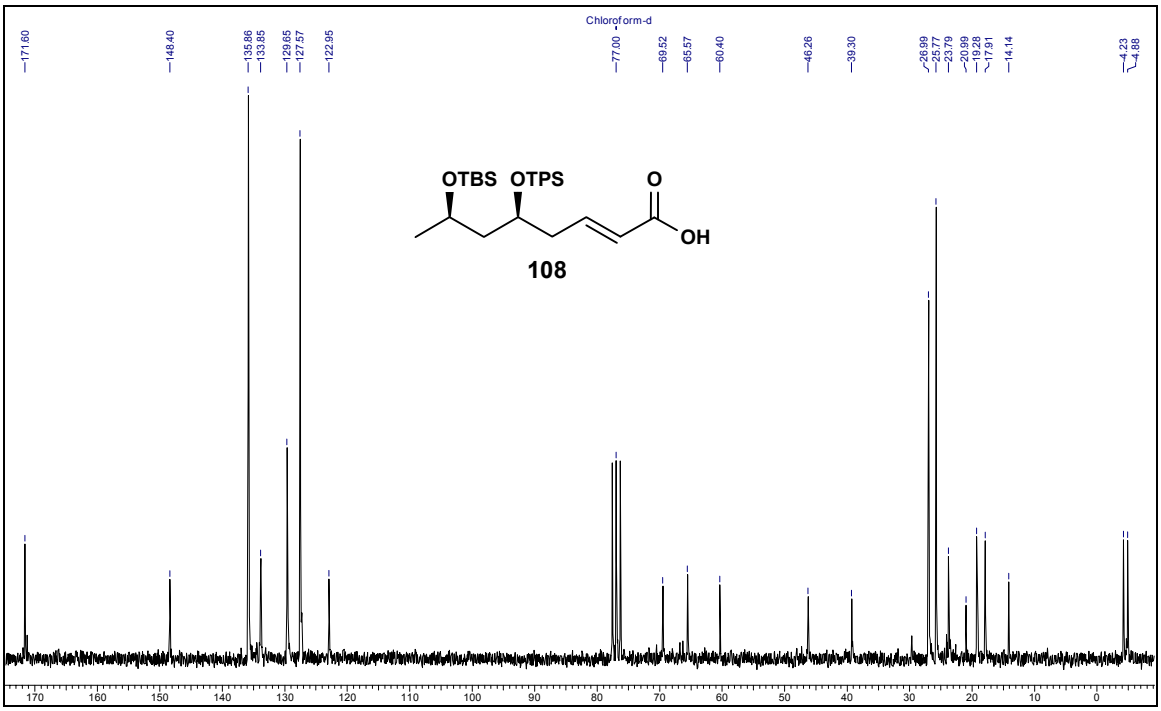
☞ ^{1}H NMR of the compound 107 in $CDCl_3$



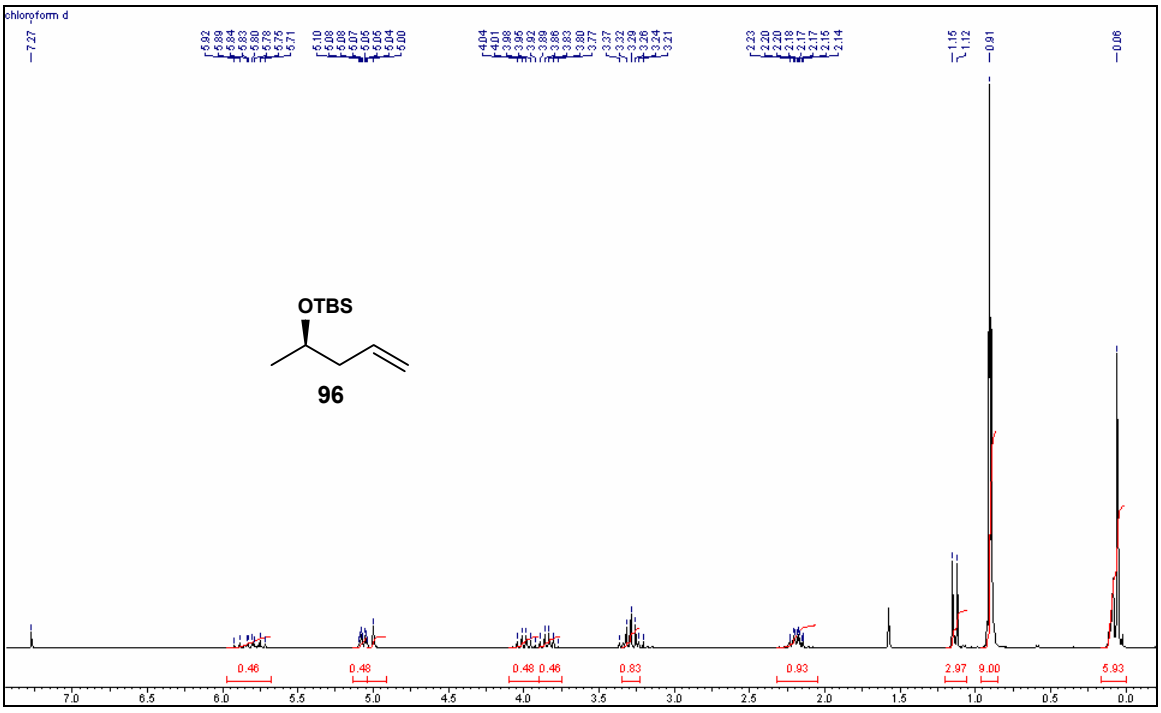
☞ ^{13}C NMR of the compound 107 in $CDCl_3$



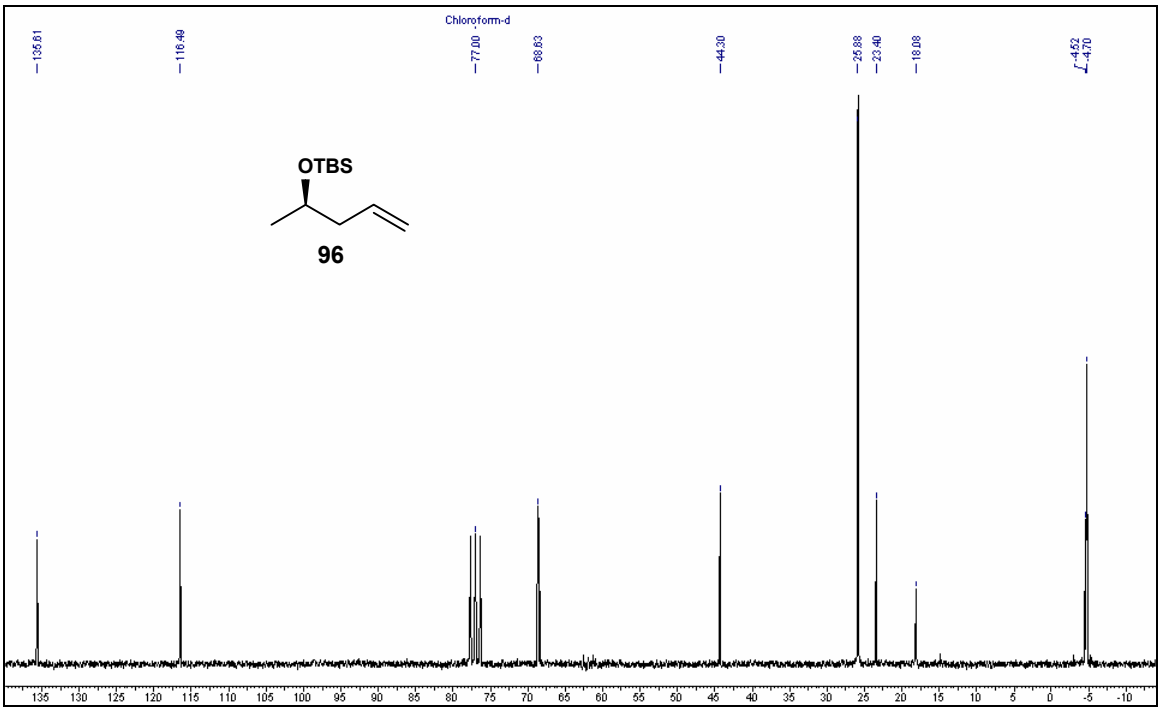
☞ ^{1}H NMR of the compound 107 in $CDCl_3$



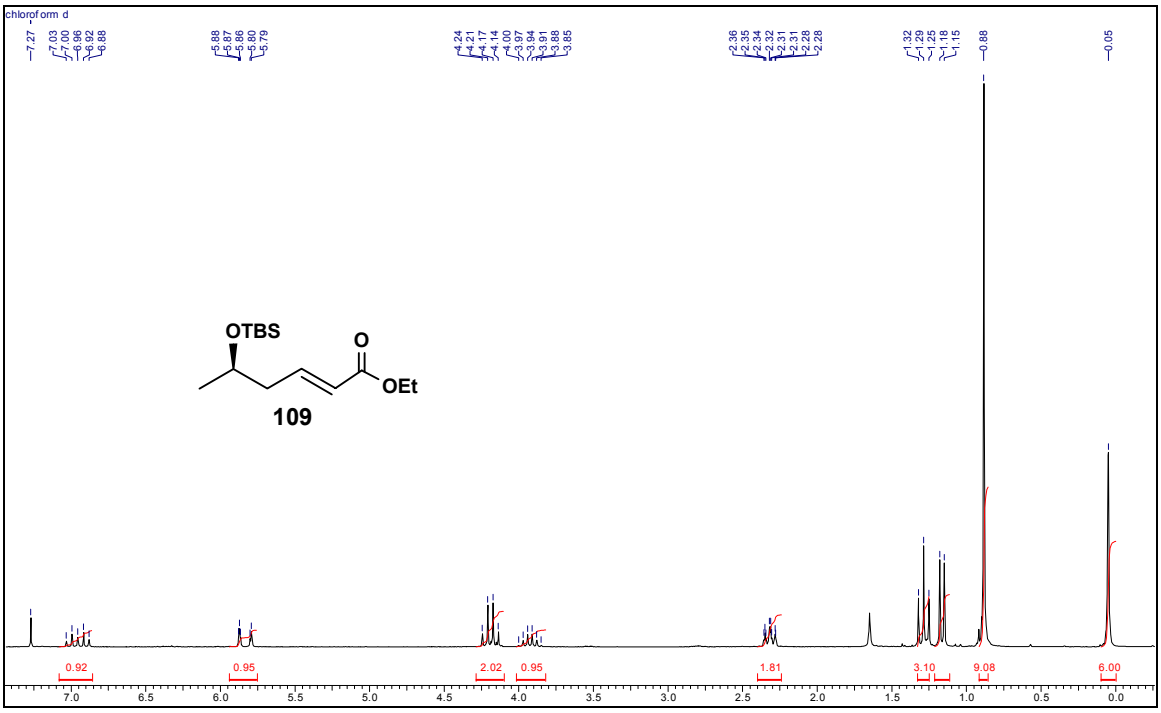
☞ ^{13}C NMR of the compound 108 in $CDCl_3$



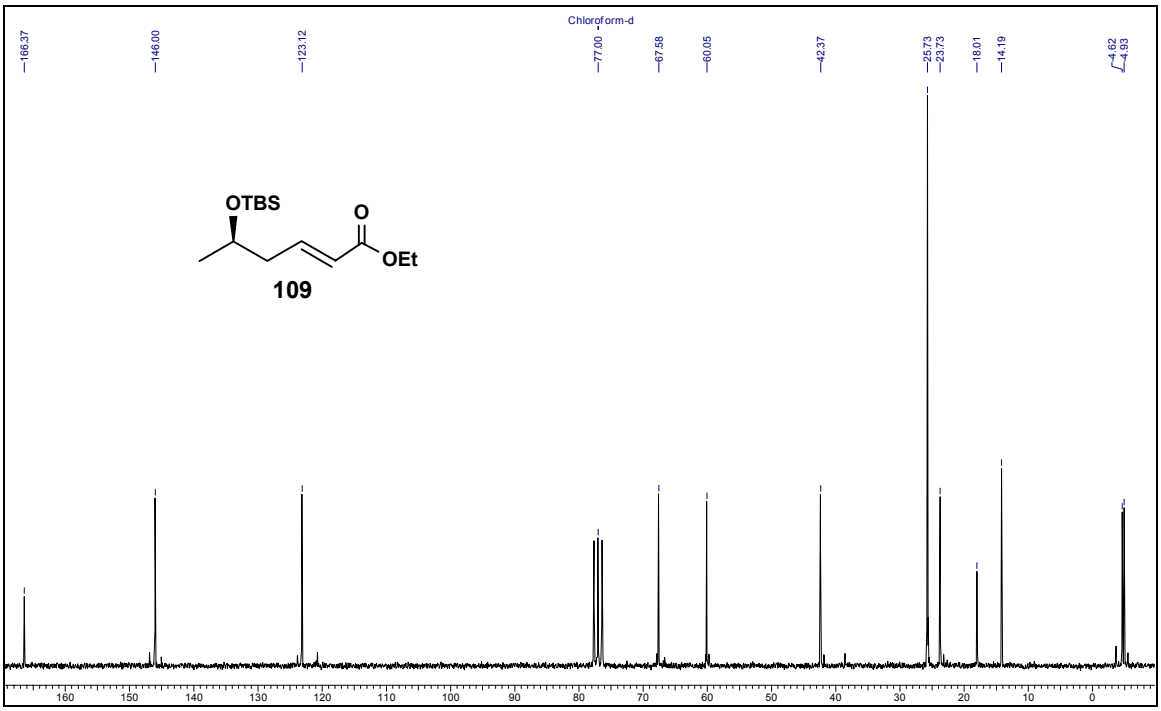
☞ ^{1}H NMR of the compound 96 in $CDCl_3$



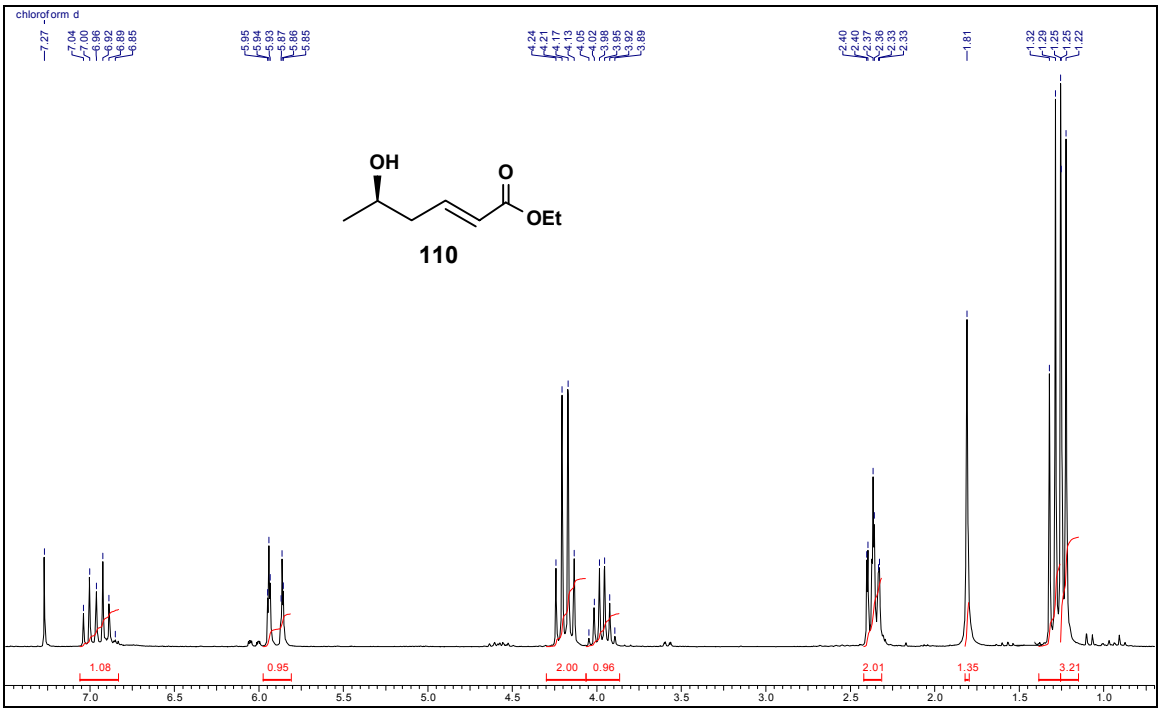
☞ ^{13}C NMR of the compound 96 in $CDCl_3$



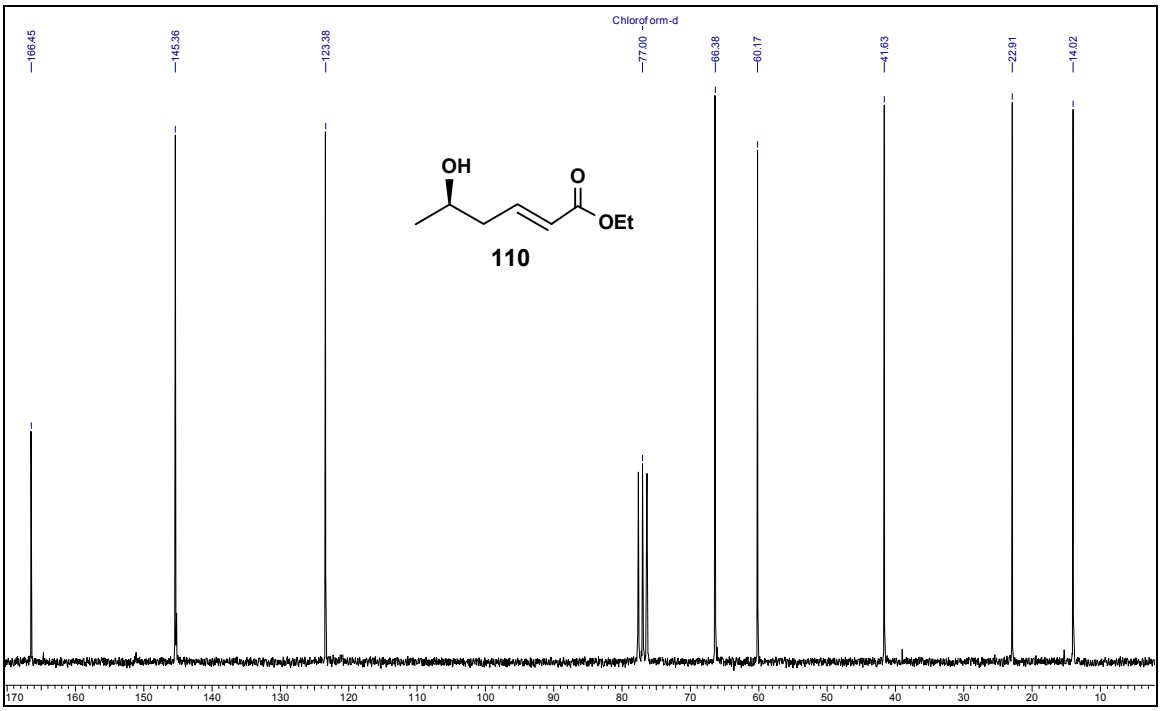
☞ ^{1}H NMR of the compound 109 in $CDCl_3$



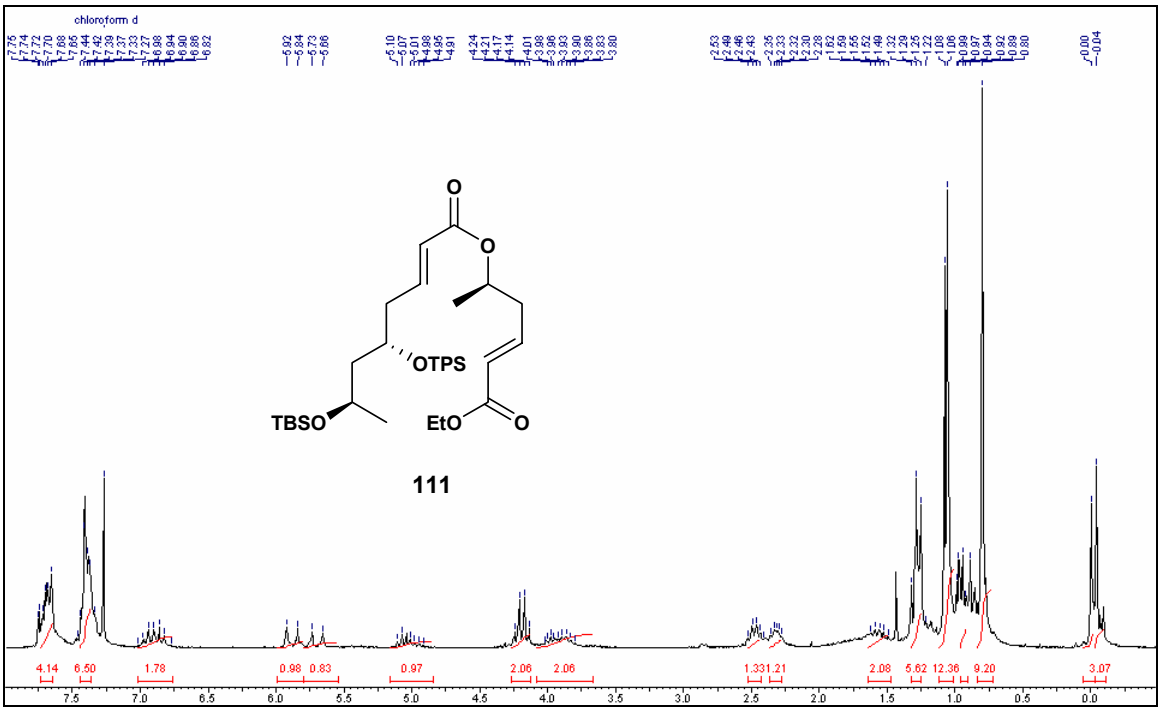
☞ ^{13}C NMR of the compound 109 in $CDCl_3$



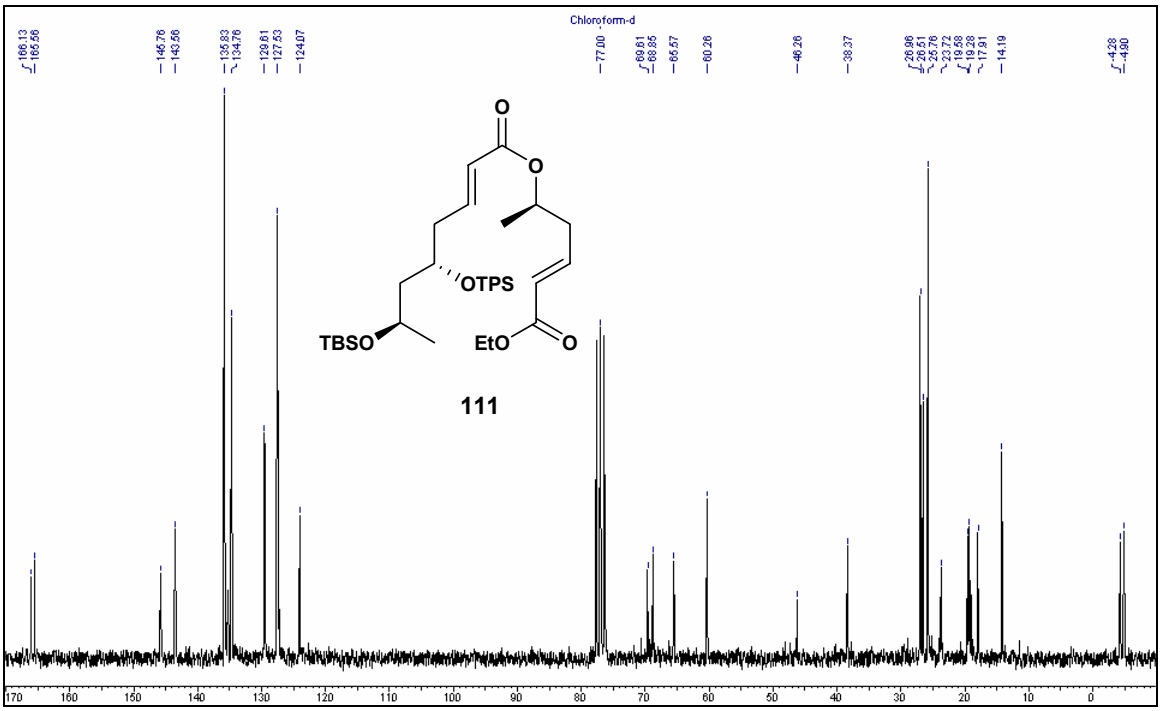
☞ ^{1}H NMR of the compound 110 in $CDCl_3$



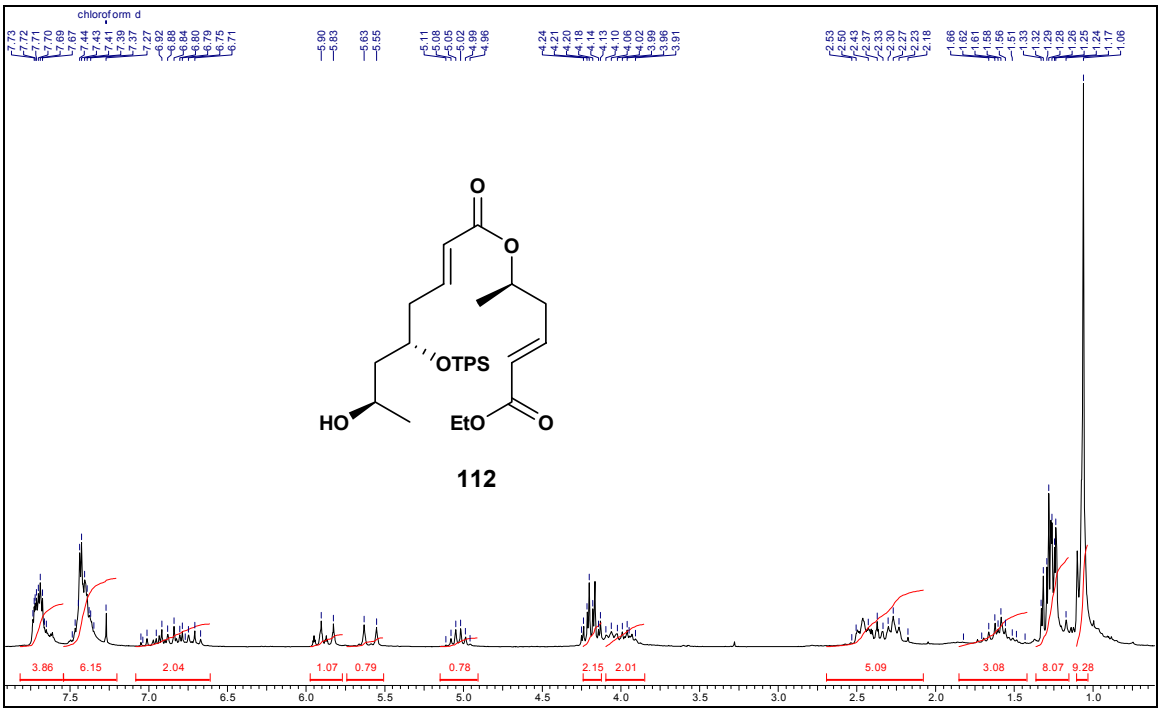
☞ ^{13}C NMR of the compound 110 in $CDCl_3$



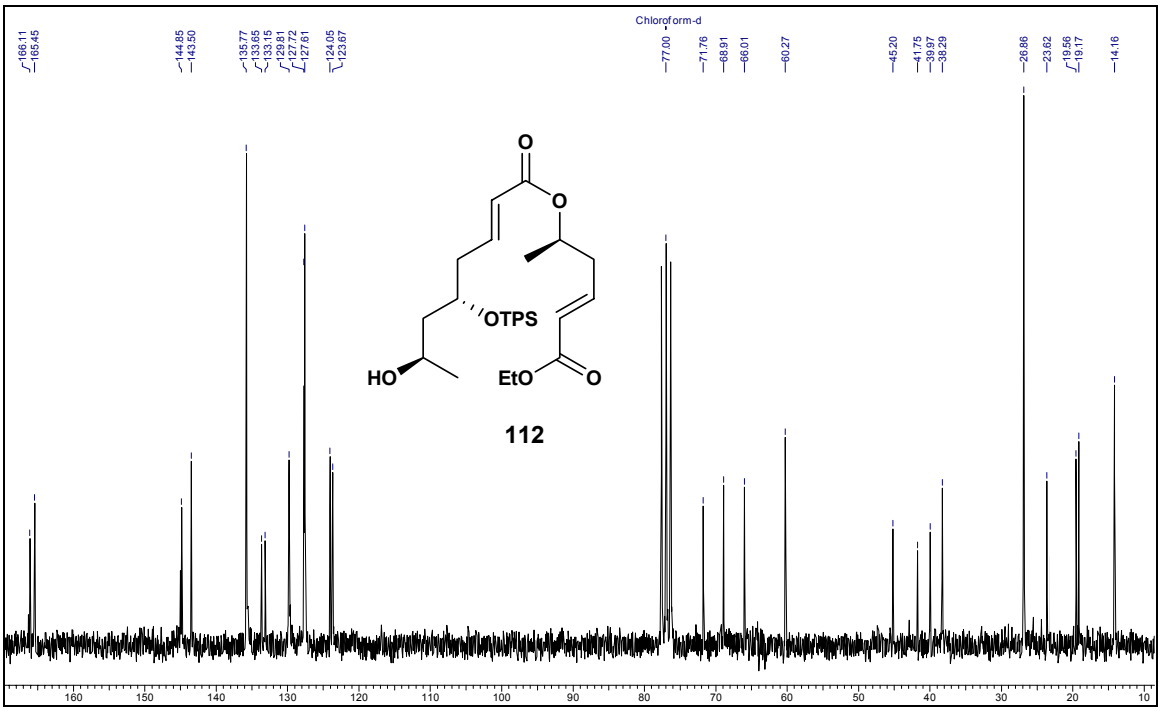
☞ ^{1}H NMR of the compound 111 in $CDCl_3$



☞ ^{13}C NMR of the compound 111 in $CDCl_3$



☞ ^{1}H NMR of the compound 112 in $CDCl_3$



☞ ^{13}C NMR of the compound 112 in $CDCl_3$

5.3 REFERENCES

1. Cameron, J. S.; Abbanat, D.; Bernan, V. S.; Maiese, W. M.; Greenstein, M.; Jompa, J.; Ireland, C. M. *J. Nat. Prod.* **2000**, *63*, 142.
2. (a) Hirota, H.; Hirota A.; Sakai, H.; Isogai A.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2147-2148. (b) Hirota, A.; Sakai, H.; Isogai, A. *Agric. Biol. Chem*. **1985**, *49*, 731-735. (c) Fujii, Y. Fukuda, A.; Hamasaki, T.; Ichimoto, I.; Nakajima, H. *Phytochemistry* **1995**, *40*, 1443.
3. Zhang, H.; Tomoda, H.; Tabata N.; Miura H.; Namikoshi, M.; Yamaguchi, Y.; Masuma, R.; Omura S. *J. Antibiot.* **2001**, *54*, 635.
4. Franck, X.; Araujo, M. E.; Jullian, J.-C.; Hocquemiller, R.; Figade're, B. *Tetrahedron Lett*. **2001**, *42*, 2801.
5. Austin, K. A. B.; Banwell M. G.; Loong, D. T. J.; Rae, D.; Willis, A. C. *Org. Biomol. Chem.* **2005**, *3*, 1081.
6. Banwell, M. G.; Edwards, A. J.; Loong, D. T. J. *Arkivoc*, **2004**, 53.
7. Sharma, G. V. M.; Janardhan Reddy, J.; Laxmi Reddy, K. *Tetrahedron Lett.* **2006**, *47*, 6531.
8. Inch, T. D. J. *Carbohydr. Chem.* **1967**, 45.
9. Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2002**, *124*, 1307.
10. Inanaga, J.; Hirata, K.; Sacki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
11. Gesner, S.; Cohen, N.; Ilan, M.; Yarden, O.; Carmeli, S. *J. Nat. Prod.* **2005**, *68*, 1350.
12. Sharma, G. V. M.; Janardhan Reddy, J.; Laxmi Reddy, K. *Tetrahedron Lett.* **2006**, *47*, 6537
13. Srihari, P.; Vijaya Bhasker, E.; Harshavardhan, S. J.; Yadav, J. S. *Synthesis* **2006**, 4041.
14. Ferrié, L. ; Reymond, S.; Capdevielle, P.; Cossy, J. *Synlett* **2007**, 2891.
15. Hermitage, S. A.; Murphy, A.; Nielsen, P.; Roberts, S. M. *Tetrahedron* **1998**, *54*, 13185.
16. (a) Fernandes, R. A.; Kumar, P. *Eur. J. Org. Chem.* **2002**, 2921. (b) Kandula, S. V.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 6149. (c) Gupta, P.; Naidu, S. V.; Kumar, P. *Tetrahedron Lett.* **2004**, *45*, 849. (d) Naidu, S. V.; Gupta, P.; Kumar, P. *Tetrahedron*

Lett. **2005**, *46*, 2129. (e) Kumar, P.; Naidu, S. V.; Gupta, P. *J. Org. Chem.* **2005**, *70*, 2843. (f) Kumar, P.; Naidu, S. V. *J. Org. Chem.* **2005**, *70*, 4207. (g) Gupta, P.; Kumar, P. *Eur. J. Org. Chem.* **2008**, 1195.

17. For reviews on the Swern oxidation, see: (a) Tidwell, T. T.; *Synthesis* **1990**, 857-870. (b) Tidwell, T. T. *Org. React.* **1990**, *39*, 297.
18. (a) Becker, H.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1996**, *35*, 448. (b) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (c) Torri, S.; Liu, P.; Bhuvaneswari, N.; Amatore, C.; Jutand, A. *J. Org. Chem.* **1996**, *61*, 3055.
19. (a) MacMillan, J.; Pryce, R. J. *Tetrahedron Lett.* **1968**, 5497; (b) MacMillan, J.; Simpson, T. J. *J. Chem. Soc., Perkin Trans.* 1 **1973**, 1487.
20. Gurusiddaiah, S.; Ronald, R. C. *Antimicrob. Agents Chemother.* **1981**, *19*, 153.
21. (a) O'Neill, J. A.; Simpson, T. J.; Willis, C. L. *J. Chem. Soc.*, *Chem. Commun.* **1993**, 738. (b) Keck, G. E.; Boden, E. P.; Wiley, M. R. *J. Org. Chem.* **1989**, *54*, 896.
22. Munoz, D. C.; Passey, S. C.; Simpson, T. J.; Willis, C. L.; Campbell, J. B.; Rosser, R. *Aust. J. Chem.* **2004**, *57*, 645.
23. (a) Keck, G. E.; Murry, J. A. *J. Org. Chem.* **1991**, *56*, 6606; (b) Shimizu, I.; Omura, T. *Chem. Lett.* **1993**, 1759; (c) Sharma, G. V. M.; Raja Rao, A. V. S.; Murthy, V. S. *Tetrahedron Lett.* **1995**, *36*, 4117; (d) Solladie´, G.; Gressot, L.; Colobert, F. *Eur. J. Org. Chem.* **2000**, 357; (e) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2002**, *4*, 4447. (f) BouzBouz, S.; Cossy, J. *Tetrahedron Lett.* **2006**, *47*, 901.
24. Batelaan, J. G. *Synth. Commun.* **1976**, *6*, 81.
25. Gupta, P.; Naidu, S. V.; Kumar, P. *Tetrahedron Lett.* **2005**, *46*, 6571.
26. Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217.
27. Reddy, M. V. R.; Yucel, A. J.; Ramachandran, P. V. *J. Org. Chem.* **2001**, *66*, 2512.