SYNTHETIC STUDIES TOWARD LIPOIC ACID, OTHER BIOLOGICALLY ACTIVE COMPOUNDS AND DEVELOPMENT OF SOME USEFUL SYNTHETIC METHODOLOGIES

BY

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Synthetic Studies Toward Lipoic acid, Other Biologically active compounds and Development of some useful synthetic methodologies

A THESIS

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BY

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INDIA

MAY 2005

DEDICATED

TO MY BELOVED

PARENTS

DECLARATION

I here by declare that the research work embodied in this thesis has been carried out at National Chemical Laboratory, Pune under the supervision of **Dr. Subhsh P. Chavan**, Scientist E-II, Division of Organic Chemistry: Technology, National Chemical Laboratory, Pune – 411 008. This work is original and has not been submitted part or full, for any degree or diploma of this or any other University.

May 2005

Cherukupally Praveen

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CERTIFICATE

*The research work presented in thesis entitled "**Synthetic studies toward Lipoic acid and Other Biologically active compounds and Development of some useful synthetic methodologies**" has been carried out under my supervision and is a bonafide work of **Mr. Cherukupally Praveen**. This work is original and has not been submitted for any other degree or diploma of this or any other University.*

May 2005
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(Dr. Subhash P. Chavan)
Research Supervisor

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Cherukupally Praveen

ABBREVIATIONS

Ac	-	Acetyl
Ac_2O	-	Acetic anhydride
AcOH	-	Acetic acid
AIBN	-	2,2'-Azobisisobutyronitrile
BF_3:OEt_2	-	Boron trifluoride diethyl ether complex
H_3B:SMe_2	-	Borane dimethyl sulfide complex
BH_3:THF	-	Borane tetrahydrofuran complex
Bn	-	Benzyl
BnBr	-	Benzyl bromide
Boc	-	*tert*-Butoxy carbonyl
$(Boc)_2O$	-	Di-*tert*-butyl dicarbonate
*n*BuLi	-	*n*-Butyl lithium
nBu_3SnH	-	*n*-Tributyltin hydride
*m*CPBA	-	*m*-Chloroperbenzoic acid
CSA	-	Camphorsulphonic acid
DBU	-	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	-	Dicyclohexylcarbodiimide
DEAD	-	Diethyl azodicarboxylate
DIBAL-H	-	Diisobutylaluminium hydride
DIPEA	-	Diisopropyl ethylamine
DMF	-	*N*,*N*-Dimethylformamide
DMP	-	2,2-Dimethoxypropane
DMSO	-	Dimethyl sulfoxide
Et	-	Ethyl
Et_3N	-	Triethylamine
Et_2O	-	Diethyl ether
EtOAc	-	Ethyl acetate
EtOH	-	Ethanol
HOBt	-	1-Hydroxybenzotriazole hydrate

Im	-	Imidazole
LAH	-	Lithium aluminium hydride
LDA	-	Lithium diisopropylamine
LiHMDS	-	Lithium hexamethyl disiloxane
Me	-	Methyl
MeI	-	Methyl iodide
MeOH	-	Methanol
Ms	-	Methanesulfonyl
MsCl	-	Methanesulfonyl chloride
NaOAc	-	Sodium acetate
NMO	-	*N*-Methylmorpholine *N*-oxide
PCC	-	Pyridinium chlorochromate
Pd/C	-	Palladium on Carbon
$Pd(OH)_2/C$	-	Palladium hydroxide on Carbon
Ph	-	Phenyl
Piv	-	Trimethylacetyl (pivaloyl)
PivCl	-	Trimethylacetyl chloride
PMB	-	*p*-Methoxybenzyl
PMB-Br	-	*p*-Methoxybenzyl bromide
PMB-Cl	-	*p*-Methoxybenzyl chloride
Py	-	Pyridine
TBAF	-	Tetra-*n*-butylammonium fluoride
TBAI	-	Tetra-*n*-butylammonium iodide
TBS	-	*tert*-Butyldimethylsilyl
TBSCl	-	*tert*-Butyldimethylsilyl chloride
TBSOTf	-	*tert*-Butyldimethylsilyl trifluoromethanesulphonate
Tf_2O	-	Trifluoromethanesulphonic anhydride
THF	-	Tetrahydrofuran
TIPS	-	Triisopropylsilyl
TMS	-	Trimethylsilyl

*p*TSA	-	*p*-Toluenesulfonic acid
TsCl	-	*p*-Toluenesulfonyl chlori

GENERAL REMARKS

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

ABSTRACT

The thesis entitled **"Synthetic Studies Toward Lipoicacid, Other Biologically active compounds and Development of some useful synthetic methodologies"** consists of three chapters.

Chapter 1: Describes a brief introduction to the Sharpless asymmetric dihydroxylation, Claisen orthoester rearrangement and synthesis of Lipoic acid and is divided into two sections.

Chapter 2: Deals with the Stereoselective synthesis of piperidine and pyrrolidine Alkaloids and is divided into three sections.

Chapter 3: Describes the Stereoselective synthesis of microcarpalide and some Biologically active compounds and is divided into two sections.

Chapter 1: describes a brief introduction to the Sharpless asymmetric dihydroxylation and synthesis of Lipoic acid and is divided into two sections.

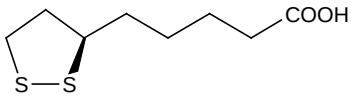
Section A: **Sharpless asymmetric dihydroxylation:**

This section gives a brief introduction to Sharpless asymmetric dihydroxylation (SAD) reaction and Claisen orthoester rearrangement. Catalytic asymmetric reactions provide an especially practical entry into the chiral world due to their economical use of asymmetric inducing agents. Asymmetric epoxidation and asymmetric dihydroxylation reactions have evolved as most powerful methods for enantioselective oxidation of olefins. While the former reaction requires the presence of a directing functional group in the substrate (allylic alcohols), the dihydroxylation process does not need any directing functional group in the substrate.

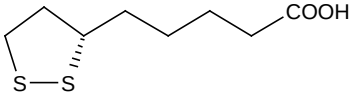
Sharpless asymmetric dihydroxylation has evolved as one of the most powerful and convenient method for the synthesis of biologically active compounds. This section covers the development of SAD reaction from stoichiometric to catalytic version, the mechanism,

reaction conditions and varied ligands used along with the recent applications to the synthesis of bioactive compounds. In our synthetic strategy, we have employed hydroxy lactones as the versatile intermediates for the synthesis of many biologically active compounds.

Section B: **Enantioselective Synthesis of *R*-(+)-α and *S*-(-)-α- Lipoic acid.**



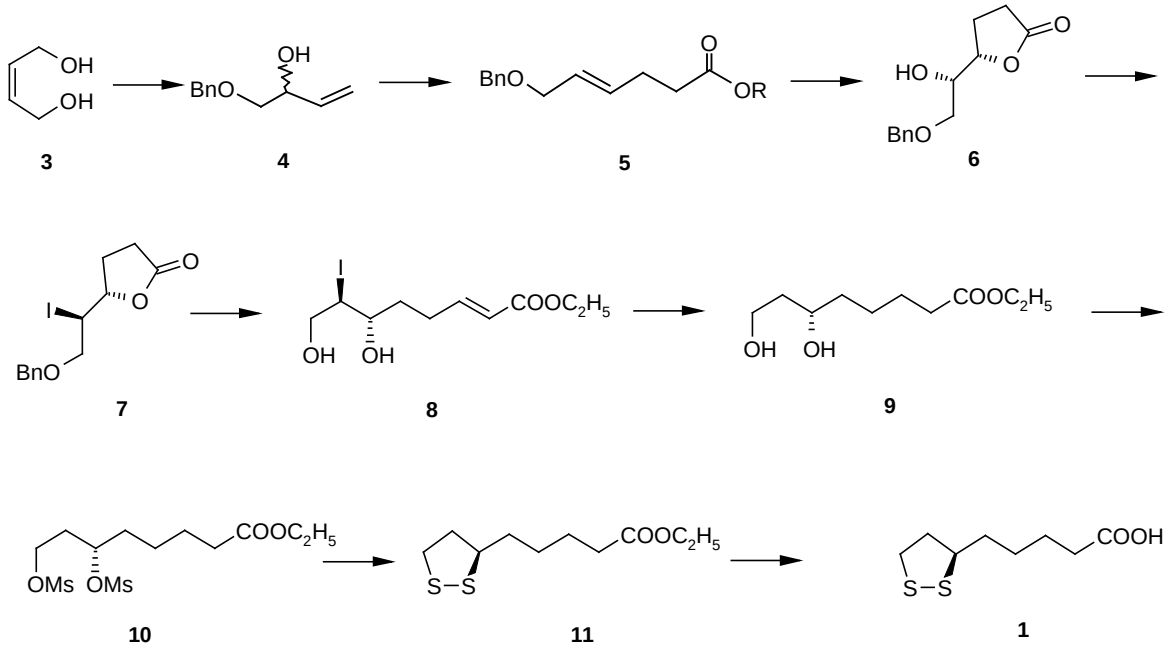
R-(+)-α-Lipoic acid (**1**)



S-(-)-α-Lipoic acid (**2**)

α-Lipoic acid is an important protein-bound coenzyme and growth factor found in plant and animal tissues as well as in microorganisms. α-Lipoic acid was first isolated by Reed and coworkers in 1950 and characterized as the cyclic disulphide 5-[3-(1,2-dithiolanyl)]-pentanoic acid. The absolute configuration of the natural α-(+)-lipoic acid was confirmed as *R* by the synthesis of its unnatural (-)-antipode from *S*-malic acid by Golding. Lipoic acid is an important and powerful biological anti-oxidant that can directly scavenge free radicals and protect cells from oxidative damage. Lipoic acid and its derivatives are highly active as anti HIV and anti-tumour agents. The *R*-(+)-enantiomer is much more effective than the *S*-(-)-enantiomer at enhancing insulin-stimulated glucose transport and non-oxidative and oxidative glucose metabolism.

Scheme 1



3 **4** **5** **6** **7** **8** **9** **10** **11** **1**

As outlined in Scheme **1**, the desired monoprotected allylic alcohol **4** was prepared in 2 steps from the inexpensive and readily available *cis*-2-butene-1, 4-diol **3** according to the literature procedure. Johnson Claisen orthoester rearrangement of the allylic alcohol **4** with the triethyl orthoacetate in the presence of catalytic propionic acid at 140 ^{o}C gave the γ,δ-unsaturated ester **5**. Sharpless asymmetric dihydroxylation employing AD-mix-α and *in situ* cyclization of the γ, δ-unsaturated ester **5** furnished the hydroxy lactone **6.** Enantiomerically pure hydroxy lactone **6**, the versatile intermediate for our synthesis, was treated with triphenyl phosphine, iodine and imidazole to give the iodo lactone **7**. Reduction of the lactone using DIBAL-H at –78 ^{o}C followed by *in situ* two-carbon Wittig reaction gave the unsaturated ester **8**. Removal of the benzyl protection, removal of iodine and reduction of the double bond was achieved in one pot using W2 Raney nickel in the presence of hydrogen at room temperature and pressure for 24 h to give the diol **9**.

The diol **9**, a well-known intermediate for the synthesis of (+)-lipoic acid, was treated with mesyl chloride to deliver the dimesylate **10**. The dimesylate on reacting with Na_2S and elemental sulphur in DMF at 90 ^{o}C for 24 h gave the ethyl lipoate **11**, which on hydrolysis with 1M ethanolic KOH gave the *R*-(+)-α-lipoic acid.

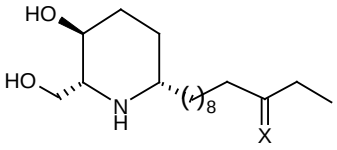
Having accomplished the synthesis of natural *R*-(+)-lipoic acid we turned our attention to synthesize unnatural *S*-(-)-lipoic acid. Accordingly we prepared the enantiomer of hydroxy

lactone **5**, by using AD-mix-β and then the same sequence of reactions as used to synthesize *R*-(+)-α-lipoic acid.

In summary both *R*-(+)-α- and *S*-(-)-α-lipoic acid were synthesized efficiently from the readily available cis-2-butene-1,4-diol as the commom achiral precursor.

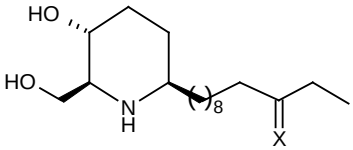
Chapter 2: This deals with the Stereoselective synthesis of piperidine and pyrrolidine Alkaloids and is divided into three sections.

Section A: **A concise and stereoselective synthesis of (+)- and (-)- deoxoprosophylline**



(+)-Prosophylline (**1**, X = O)

(+)-Deoxoprosophylline (**2**, X = H_2)

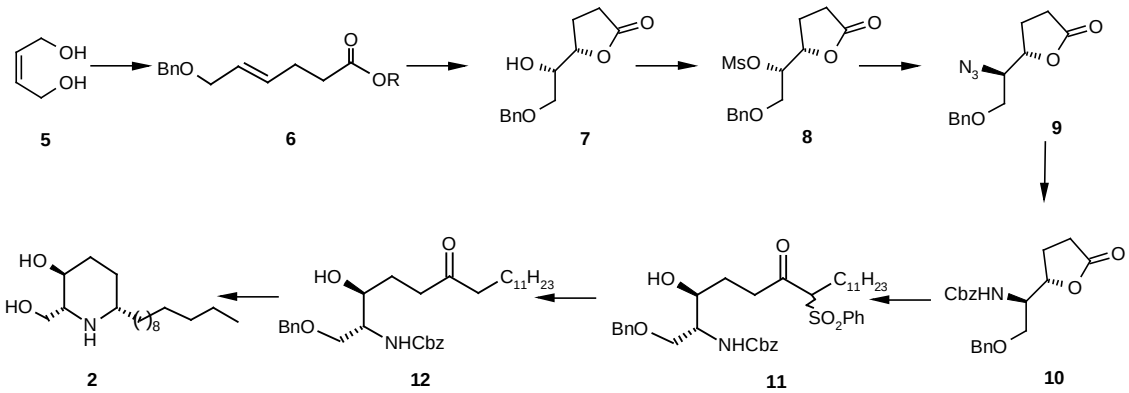


(-)-Prosophylline (**3**, X = O)

(-)-Deoxoprosophylline (**4**, X= H_2)

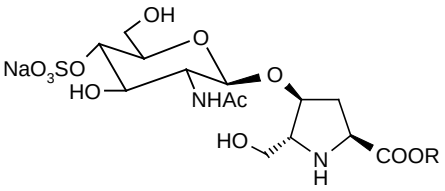
Multifunctionalized piperidine alkaloids possessing the 2,6-disubstituted piperidin-3-ol skeleton have been found abundantly in nature. Prosopis alkaloids, one of the subgroup of these piperidine alkaloids, were isolated from *Prosopis africana* Taub. Structurally, these compounds possessing a polar head group and a hydrophobic aliphatic tail can be considered as cyclic analogues of the membrane lipid spingosine. Besides their interesting structural features, these polysubstituted piperidine alkaloids exhibit a variety of pharmacological properties, such as anaesthetic, analgesic and antibiotic activities.

Scheme 1

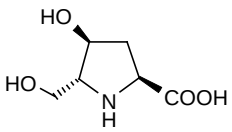


As shown in Scheme **1,** Sharpless asymmetric dihydroxylation employing AD-mix-α and *in situ* cyclization of the γ, δ-unsaturated ester **6** furnished the hydroxy lactone **7.** Mesylation of the hydroxy lactone **7** and displacement of the mesylate with NaN_3 in DMF at 90 ^oC gave the azido lactone **9**. The azide was reduced to the amine by using triphenylphosphine and water and the resulting amine was protected as its Cbz derivative by using CbzCl, TEA in presence of a catalytic amount of DMAP. Opening of the lactone of **10** was achieved by using $C_{12}H_{25}SO_2Ph$ and *n*-BuLi. Desulphonylation of **11** using 6% Na-Hg and Na_2HPO_4 at –10 ^oC gave the ketone **12.** Removal of the protecting groups and cyclization of the ketone **12** using catalytic $Pd(OH)_2$ and H_2 in a one pot reaction, afforded (+)-deoxoprosophylline **2** in 76% yield. Having accomplished the synthesis of natural **2**, we turned our attention towards the synthesis of its enantiomer. Accordingly, γ, δ-unsaturated ester **6** was transformed in a similar fashion to afford (-)-deoxoprosophylline **4** following a similar sequence however, using AD-mix-β.

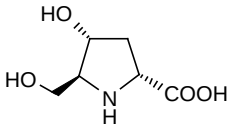
Section B: **An efficient stereoselective synthesis of (-) and (+)- Bulgecinine.**



15 Bulgecin A : R = $NHCH_2CH_2SO_3H$
16 Bulgecin B : R = $NHCH_2CH_2COOH$



(-)- Bulgecinine **13**

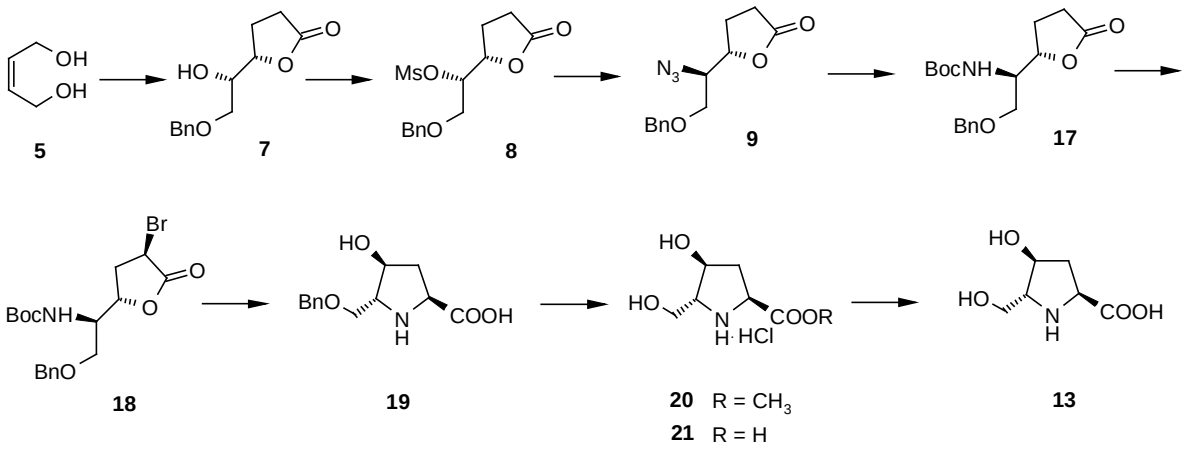


(+)- Bulgecinine **14**

Bulgecinine (**13**) an aminoacid constituent of naturally occurring antibiotic glycopeptides called bulgecins (**15**, **16**), isolated from *Pseudomonas acidophila* and *Pseudomonas mesoacidophila*. Bulgecins although devoid of antibacterial activity, induce characteristic morphological change called bulge formation in the cell wall of Gram-negative bacteria in co-operation with β-lactam antibiotics. As a result of bulge formation, the activity of these antibiotics was effectively enhanced and the bacteria are

killed at lower *β*-lactam concentrations. The structure of the (-)-bulgecinine (**13**) had been determined chemically and crystalographycally to be (2*S*, 4*S*, 5*R*)-4-hydroxy-5-hydroxymethyl proline.

Scheme 2

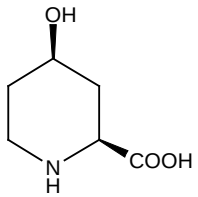


As outlined in scheme 2, the enantiomerically pure hydroxylactone **7**, the versatile intermediate for our synthesis was obtained in four steps from cis-2-butene-1,4-diol **5**, in which Johnson Claisen orthoester rearrangement and Sharpless asymmetric dihydroxylation was used as the key steps to install the requisite chirality. Mesylation of the hydroxy lactone **7** using MsCl and Et_3N in the presence of a catalytic amount of DMAP gave the mesylated lactone **8**. Displacement of the mesylate with NaN_3 at 90 ^oC in DMF gave the azidolactone **9**. Catalytic hydrogenation of the azido lactone over 10 % Pd/C in ethylacetate in the presence of Boc_2O gave the Boc protected lactone **17**. Now the challenging task in our synthesis was to introduce the bromine stereoselectively at C-2 of the lactone **17**. This was achieved by using LiHMDS, Et_3N, and NBS at –78 ^oC for 2h. The major isomer **18** along with its diastereomer (9:1 ratio) was separated by silicagel column chromatography. The conditions developed by Oppolzer were adapted to convert the major isomer (2*R*, 4*S*, 5*R*)-**18** in to the (2*S*, 4*S*, 5*R*)-**19** using the following sequence of reactions. Accordingly the lactone **18** on refluxing in DCM with 10 mol. equivalent of CF_3COOH for 3 h followed by evaporation of the solvent, dissolving the residue in 0.1 N $Ba(OH)_2$ keeping the mixture at pH 9 for 3 h, acidification to the pH 1, stirring the aqueous solution with Amberlite-IR-120 ion exchange resin for 24 h,

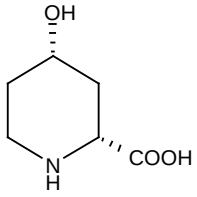
filtration, washing the resin with distilled water (until the clear solution with $AgNO_3$), stirring of the resin with 6 N aqueous NH_4OH solution for 3 h and filtration gave the benzyl protected (2*S*, 4*S*, 5*R*)- (-)-bulgecinine **19**. Removal of the benzyl protection was performed using Pd/C in methanolic HCl under normal hydrogen pressure and at room temperature to deliver a mixture of (-)-bulgecinine hydrochloride **20** and its methyl ester. This mixture was subjected to basic hydrolysis using 1M NaOH to deliver the pure (-)- bulgecinine. Accordingly we also prepared (+)-bulgecinine following the same sequence of reactions from the apposite enantiomer of hydroxylactone **7.**

In summary (+)-and (-)-bulgecinine were synthesized in an efficient overall yield of 43% in 7 steps from the hydroxylactone **7**, which in turn was obtained from the readily available *cis*-2-butene-1,4-diol.

Section C: **Synthetic studies towad (2S, 4R)-4-Hydroxy Pipecolic Acid.**

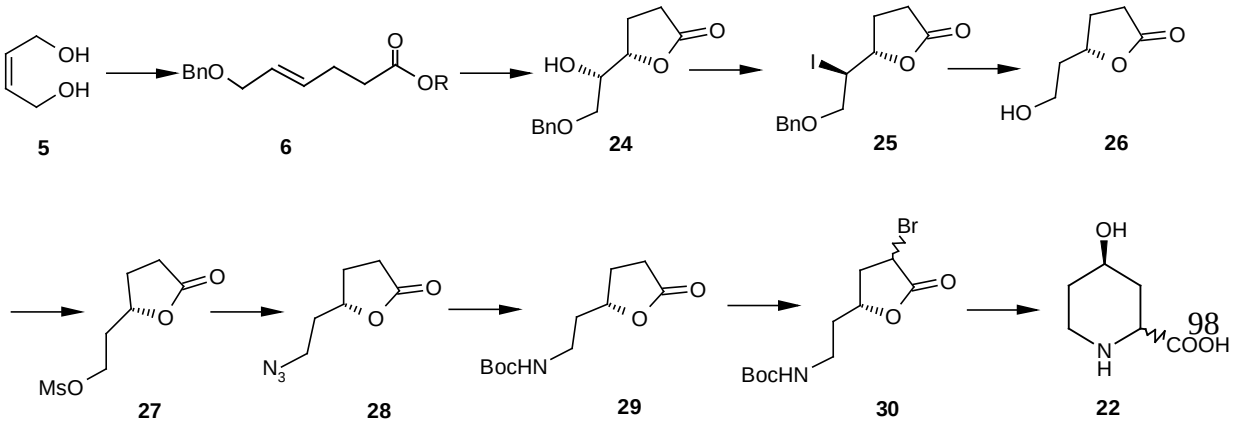


(2S, 4R)-4-Hydroxy Pipecolic Acid (**22**)



(2R, 4S)-4-Hydroxy Pipecolic Acid (**23**)

(2*S*, 4*R*)-4-Hydroxy Pipecolic Acid, a naturally occurring aminoacid isolated from leaves of *Calliandra pittieri* and S*trophantus scandeus*, is a constituent of certain cyclodepsipeptide antibiotics such as Virginiamycin S_2. (-)-Pipecolic acid served as a building block in a recent synthesis of Palinavir, a potent peptidomimetic based HIV protease inhibitor.



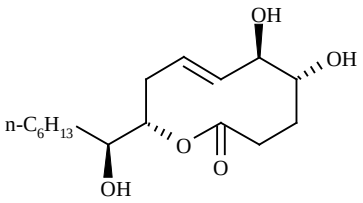
Scheme 3

The hydroxylactone intermediate **24** was obtained from the γ, δ-unsaturated ester **6** by using Sharpless asymmetric dihydroxylation in which AD-mix-α was used to install the requisite chirality. Treatment of **24** with triphenyl phosphine, iodine and imidazole to give the iodo lactone **25**. Removal of benzyl protection and removal of iodine was performed by using W2 Raney nickel. Mesylation of hydroxyl group and displacement of the mesylate with NaN_3 gave the azidolactone **28**. Catalytic hydrogenation of the azido lactone over 10 % Pd/C in ethylacetate in the presence of Boc_2O gave the Boc protected lactone **29**. Introduction of bromine at C-2 of the lactone gave the mixture of bromolactones, which was converted into diastereomeric pipecolic acids.

In conclusion our present synthesis is giving a mixture of diastereomeric pipecolic acids. However by slight modifications it may be possible to get the pure (2*S*, 4*R*)-4-Hydroxy Pipecolic Acid

Chapter 3: Describes the Stereoselective synthesis of microcarpalide and some biologically active comounds and is divided into two sections.

Section A: **Stereoselective synthesis of (-)- microcarpalide.**



1

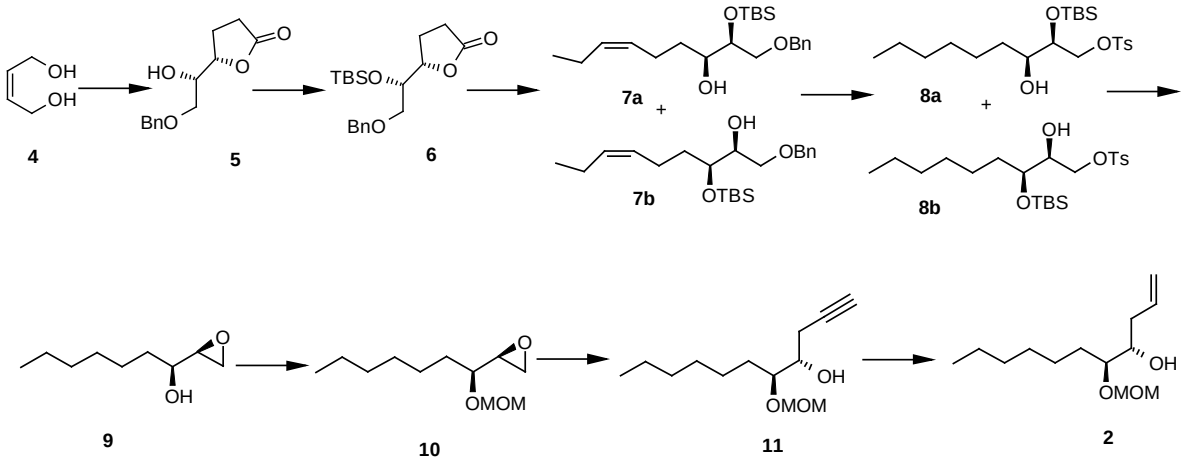
Microcarpalide (**1**) has been recently isolated from the fermentation broths of an unidentified endophytic fungus growing on the bark of tropical tree *Ficus microcarpa*. Hemscheidt and co-workers named this ten-membered cytotoxic lactone as microcarpalide, which shows remarkable antimicrofilament activity.

Our strategy is a convergent approach, that combines the fragments **2** and **3** via esterification followed by Ring-closing metathesis approach. The olefinic acid fragment **3** was obtained from the hydroxy lactone **12**, and its enantiomeric hydroxy lactone **5** was used for

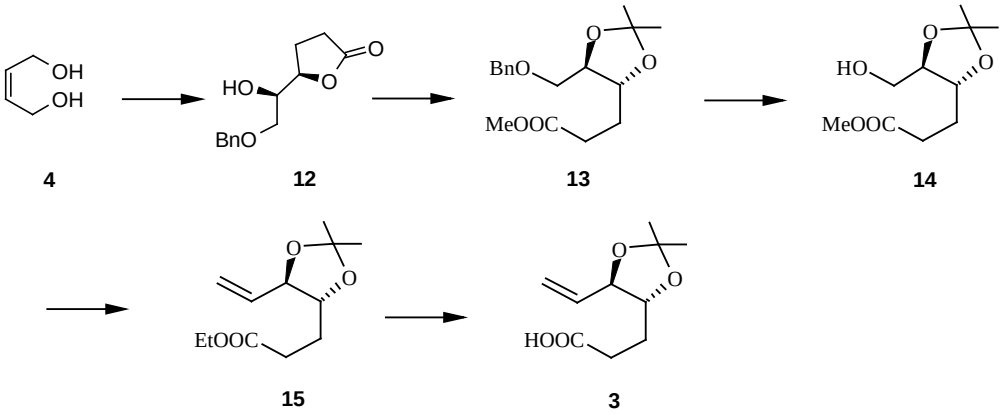
the synthesis of olefinic alcohol Fragment **2**. Both the enantiomeric lactones were obtained from the cis-2-butene-1,4-diol using Claisen orthoester rearrangement and Sharpless asymmetric dihydroxylation as the key steps.

The synthesis of alcoholic fragment **2** was commenced with the TBDMS protection of hydroxylactone **5**. DIBAL-H reduction and subsequent three carbon Wittig homologation of the resulting lactol gave the mixture of compounds **7a** and **7b** in almost 1:1 ratio, due to the silyl group migration. Removal of the benzyl protection and reduction of double bond was performed by using 10% Pd/C in methanol under H_2 atmosphere. Selective tosylation of primary hydroxyl group using tosyl chloride and pyridine for 24 hrs delivered the mixture of **8a** and **8b**. This mixture on treatment with 1M TBAF solution in dry THF gave the epoxy alcohol **9.** The epoxy alcohol was protected as its methoxymethyl (MOM) ether and the resultant epoxide **10** on treating with an excess lithium acetalide and partial hydrogenation using Lindlar's catalyst gave the corresponding olefinic fragment **2**.

Scheme 1



Construction of the acid fragment **3** began with the dimethoxy propane mediated ring opening of hydroxylactone **12** in presence of catalytic *p*TSA using methanol as a solvent to

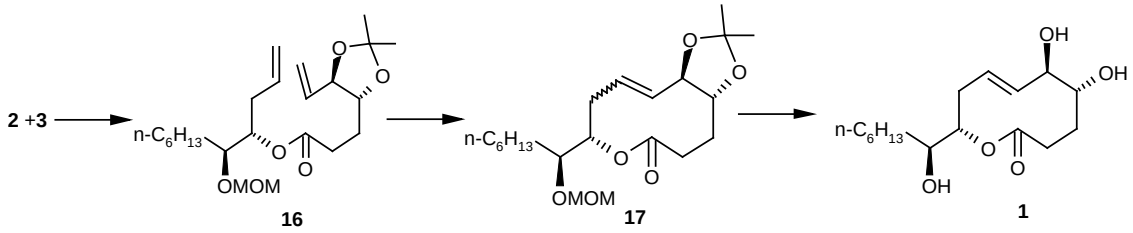


deliver the acetonide protected ester **13**. Removal of the benzyl protection with 10% Pd/C under H_2 atmosphere furnished alcohol **14**. Swern oxidation and subsequent one carbon homologation with methylene triphenyl phosphorane in dry THF at –20 ^{o}C gave the olefinic ester **15**. Saponification of ester **15** with KOH in THF:methanol:water (2:2:1) afforded the desired acid fragment **3**.

Scheme 2

Having accomplished the synthesis of both the fragments **2** and **3**, it remained to couple the two fragments and achieve crucial macrocyclization using RCM. The union of the two fragments **2** and **3** was achieved by using DCC to furnish the diene ester **16**. Treatment of diene ester **16** with the Grubb's first generation catalyst under highly diluted degassed conditions gave the ten-membered lactone as E and Z isomers in 67:33 ratio. The desired *E* isomer could be separated by column chromarography from *Z* isomer. Subjection of compound **17** for global deprotection gave the microcarpalide **1**.

Scheme 3

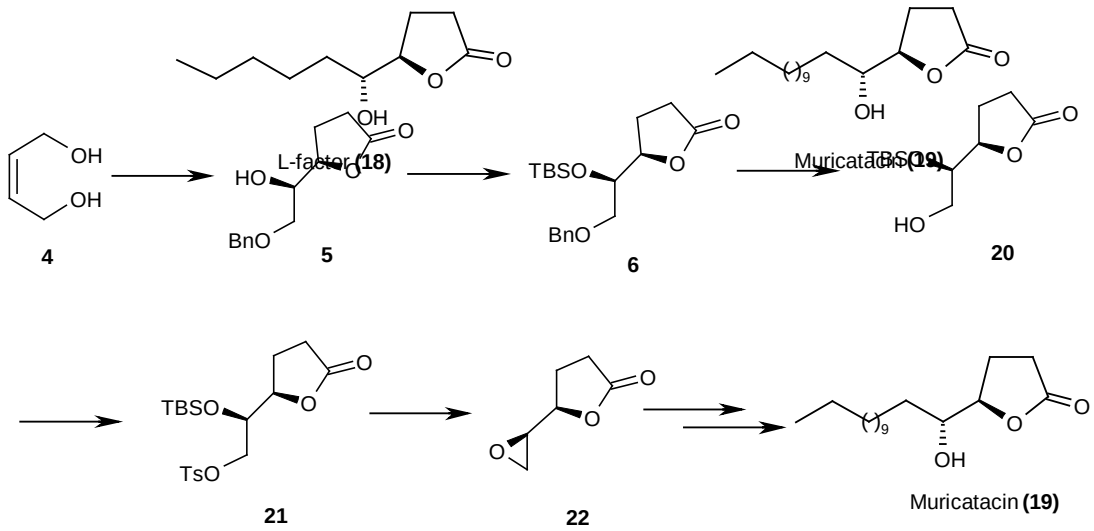


In conclusion we have achieved a highly convergent and efficient synthesis of (-)-microcarpalide.

Section B: **A versatile and flexible route for the synthesis of biologically active compounds from hydrxy butyrolactone as the key synthon.**

A number of related hydroxylated γ- lactones have been reported from microbial sources. Muricatacin **19** isolated from the seeds of *Annona muricata* has a dodecyl side chain, whereas L-factor **18** which was isolated from *Streptomyces griseus* has a pentyl Side chain. L- factor exhibits an autoregulatory role, controlling the formation of aerial mycelia and production of the anthracycline antibiotic leukaemomycin.

Scheme 4



Scheme 5

As reported earlier the hydroxylactone **5** was obtained in 4 steps from *cis*-2-butene-1, 4-diol **4**. TBS protection of hydroxyl group and removal of benzyl protection delivered the TBS protected compound **21**, which on reaction with 1 M TBAF gave the epoxide **22**, the well known intermediate for the synthesis of muricatacin.

In conclusion we have chosen hydroxylactone **5** as the versatile intermediate for the synthesis of biologically active compounds.

SECTION A

1.1 SHARPLESS ASYMMETRIC DIHYDROXYLATION

Introduction

Chemistry is an ancient science. It has existed for centuries although not always in the precise and well-defined sense as we know it now. Before the twentieth century, chemistry was just a collection of empirical observations, but since then it has metamorphosed into an advancing, burgeoning field of discipline-central to many sciences. Owing to the combined efforts of the giant scientists of the last few centuries, the basic properties of matter are now well studied and understood. Equipped, as we are now, with what can be called a rather clear understanding of the behavior of atoms and molecules, we have to advance further. The major challenges that a modern organic chemist faces include utilization of the wealth of knowledge to design reactions that are difficulty or not at all realized by the traditional methods and design of reactions that give different or even opposite selectivity to that previously known. In other words, the scientist has to “direct” or “control” reactions to proceed as per his will.

The availability of efficient methods for achieving absolute stereo selectivity via catalytic process in the production of enantiomerically rich compounds is of considerable current interest because a small amount of catalyst can produce the large amounts of enantiomerically enriched product. Catalytic asymmetric reactions provide an especially practical entry into the chiral world due to their economical use of asymmetric inducing agents.[1] In the last two decades, many powerful asymmetric reactions have emerged as a result of the growing need to develop efficient synthesis of biologically active compounds.[2] Increasingly severe economic and environmental constraints force the synthetic community to think about novel procedures and synthetic concepts to optimize efficiency.

Among the catalytic transformations the introduction of oxygen occupies an important place. The fact that traditional oxygenation reactions often use stoichiometric amounts of hazardous and poisonous oxidizing agents clearly indicates the need for the development of catalytic systems in which the active oxidant formed in minor amounts and recycled by a non-toxic and non-explosive reoxidant.

Especially oxidation of carbon-carbon double bonds occupies an important place among the oxygen transfer reactions.[3] Catalytic epoxidation and Sharpless dihydroxylation reactions have been the central focus of research for the past years. Epoxidation of olefins can be achieved by a number of transition metal complexes[4] and other oxidants like peracids,[5] dioxiranes,[6] hydrogen peroxide,[5] and molecular oxygen.[5] The efficient procedure for the epoxidation of allyl alcohols was developed by Sharpless *et al*,[7] which has the first practical and reliable asymmetric reaction.

Olefins can be employed to prepare the diols in a single oxidation reaction. The use of OsO_4[8] or alkaline $KMnO_4$ to accomplish this reaction has been known for many years. Due to the toxicity and cost of OsO_4 a catalytic versions of this reaction is preferred.[9] Last decade an asymmetric version of this reaction has been developed[10] and because of enormous work on these two reactions Barry K Sharpless was awarded a share of 2001 Nobel prize in chemistry.

The asymmetric dihydroxylation work arose from the pioneering work on the stoichiometric reaction of OsO_4 with olefins, Criege[11] showed that pyridine accelerates the rate of osmium tetroxide dihydroxylation of alkenes by co-ordination to metal complexes. In a similar work professor Bill Griffith[12] also observed that tertiary amines and bicyclic tertiary amines accelerates the dihydroxylation reactions. By modifying the reaction conditions the same catalytic system is able to convert olefins in a single reaction into the corresponding amino alcohols,[13] which are an important class of compounds used in pharmaceuticals, chiral auxiliaries and ligands in asymmetric synthesis.

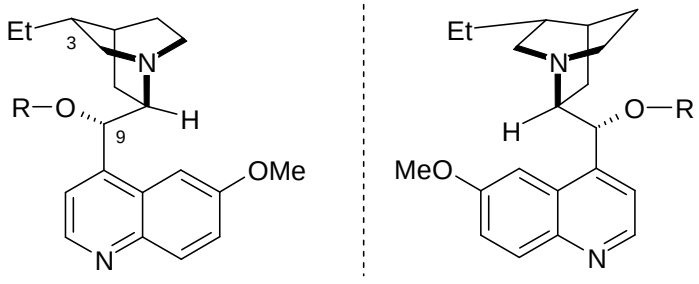
Among the so far known catalytic oxidation reactions the osmium tetraoxide catalyzed asymmetric dihydroxylation following Sharpless protocol, represents a benchmark reaction when it comes to generality and selectivity. Catalytic variants of this reaction which employ relatively inexpensive reagents for the re-oxidation of the osmium (VI) glycolate products, greatly enhance its synthetic utility.[8] Inorganic co-oxidants such as sodium or potassium chlorate[14a] or hydrogen peroxide,[14b,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,[15] or *N*-methylmorpholine *N*-oxide (NMO) (Upjohn Process).[16] Tsuji *et al*.[17] 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.[18] It was found that the binding constant of a ligand is extremely sensitive to the steric hindrance near the reacting center. Consequently, quiniclidine derivatives were used instead of pyridines for further investigations due to their intrinsically higher affinity for OsO_4.[19] Moderate to good enantiomeric excess using acetate esters of cinchona alkaloids as chiral ligands was obtained.[18]

Apart from the cinchona alkaloid catalyzed asymmetric dihydroxylation a number of recent methods employ chiral monodentate[20] and bidentate diamine ligands[21] for the asymmetric osmylation of olefins. 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[21] (**Figure 1**).

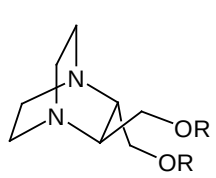
(a) Cinchona alkaloid ligands for asymmetric dihydroxylation under *Catalytic* Conditions[18,22,24,25]



Dihydroquinidine (R = H)
DHQD

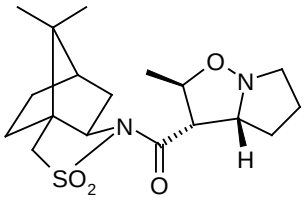
Dihydroquinine (R = H)
DHQ

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



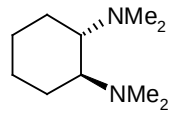
R = *t*-$BuPh_2Si$

Hirama *et al.*[20]

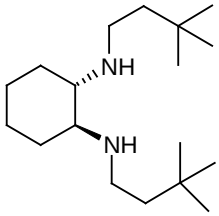


Murahashi *et al.*[21n]

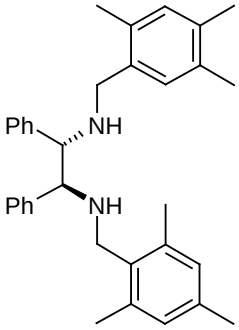
(c) Chiral diamine ligands for AD under *stoichiometric* conditions



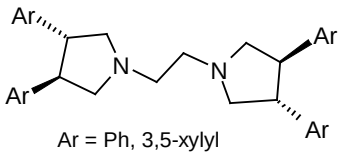
Snyder *et al.*[21m]



Hanessian *et al.*[21c]

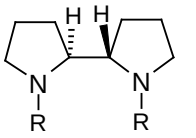


Corey *et al.*[21d]



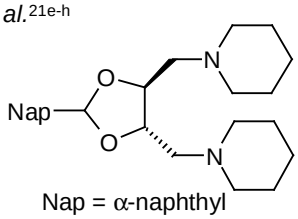
Ar = Ph, 3,5-xylyl

Tomioka *et al.*[21e-h]



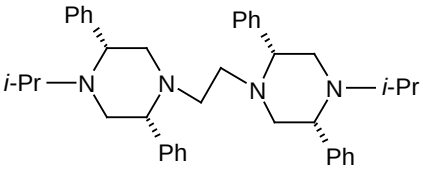
R = neohexyl

Hirama *et al.*[21j,k]



Nap = α-naphthyl

Narasaka *et al.*[21l]



Fuji *et al.*[21i]

Figure 1. Some ligands for AD reaction.[18,21]

Development of Asymmetric Dihydroxylation: Stoichiometric to catalytic version:

Initially, the asymmetric dihydroxylation using the derivatives of cinchona alkaloids was performed under stoichiometric conditions. The first catalytic version of the asymmetric

dihydroxylation was based on the Upjohn process, using *N*-morpholine-*N*-oxide (NMO) as the stoichiometric re-oxidant. However, the enantiomeric excess of the diol products obtained under these catalytic conditions was lower than that produced by the stoichiometric reaction. The origin of this discrepancy was found to be the presence of second catalytic cycle.[22] (**Figure 2**), which exhibited only low or no enantio selectivity. Wai[23] discovered a partial remedy in slow addition of the olefin. Kwong[24] found that the participation of second catalytic cycle can be virtually eliminated by performing the reaction under two-phase conditions with $K_3Fe(CN)_6$ as the stoichiometric re-oxidant. Under these conditions there is no oxidant other than OsO_4 in the organic layer, in contrast to the homogeneous NMO conditions. Since the actual osmylation takes place in this layer, the resulting osmium (VI) monoglycolate ester undergoes hydrolysis, releasing the diol and the ligand to the organic and Os (VI) to the aqueous layer before its regeneration can occur, and consequently entry of the osmium glycolate into the second cycle is prevented (**Figure 3**).

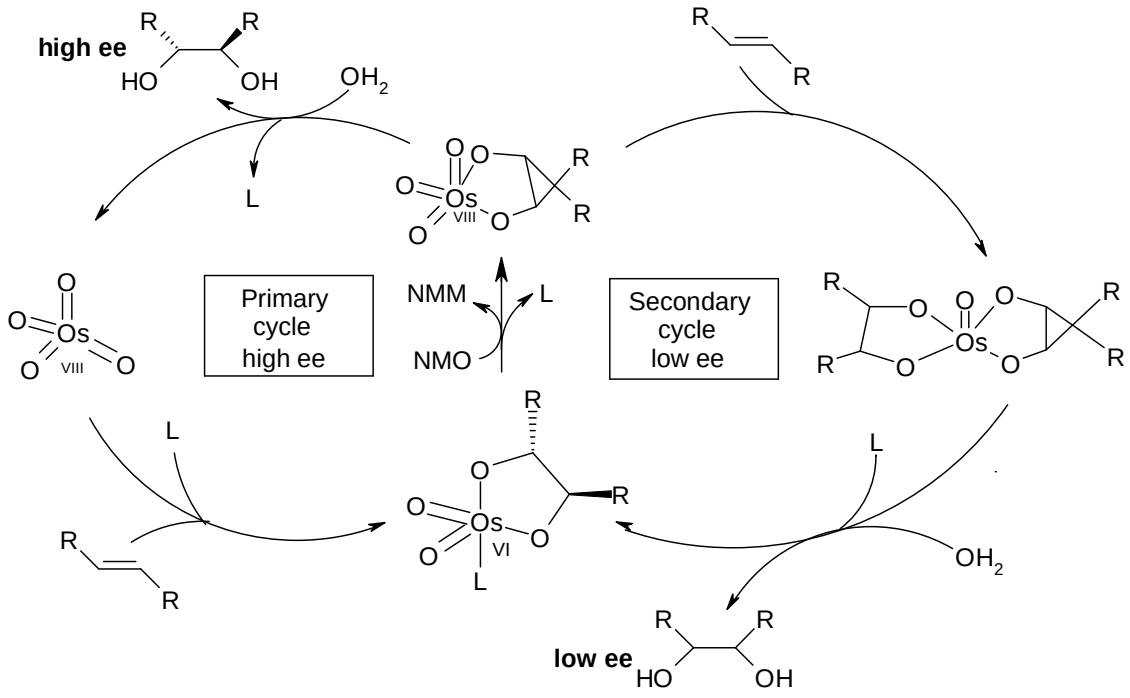


Figure 2. Two Catalytic Cycles for the AD Reaction using NMO as the Co-oxidant.[22]

Sharpless *et al.*[25] 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.[26] 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.

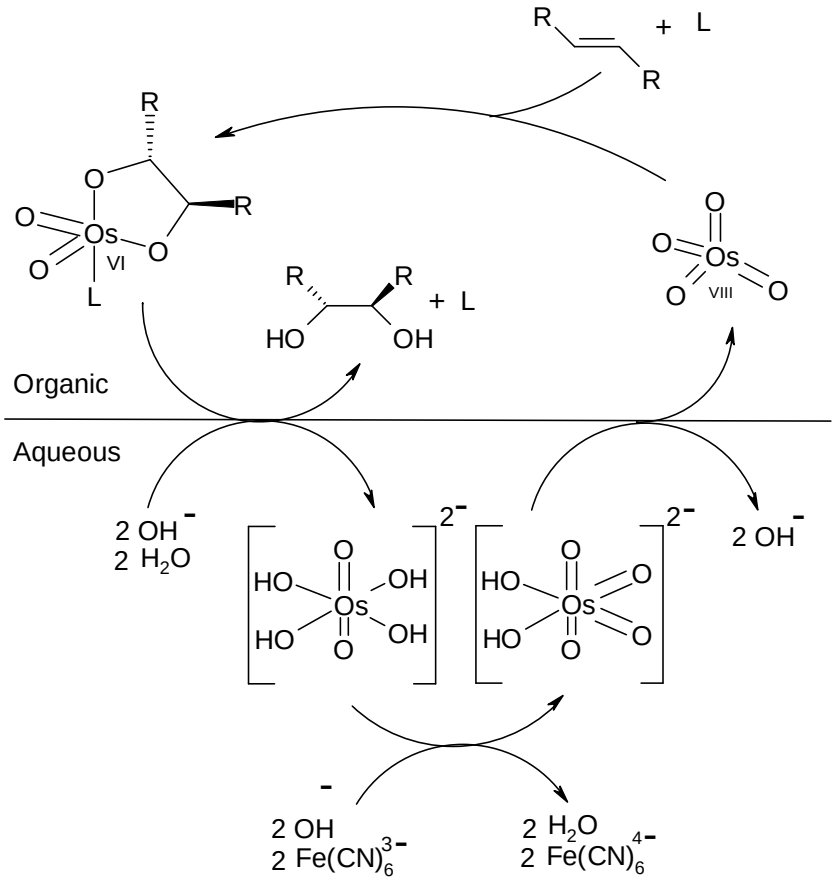


Figure 3. Catalytic Cycle of the AD Reaction with $K_3Fe(CN)_6$ as the Co-oxidant.[24]

The discovery of ligands with two independent cinchona alkaloid units by Hartung[25] (phthalazine core) and Crispino[27] (diphenylpyrimidine core) attached to a heterocylic spacer, has led to a considerable increase in both the enantioselectivity and the scope of the reaction (**Figure 4**)

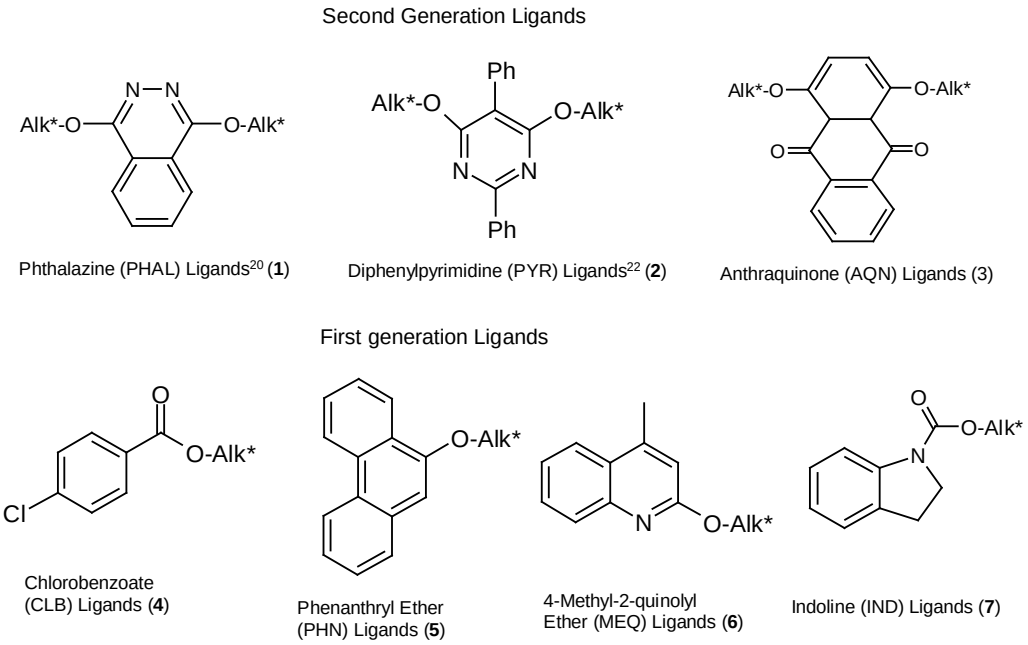


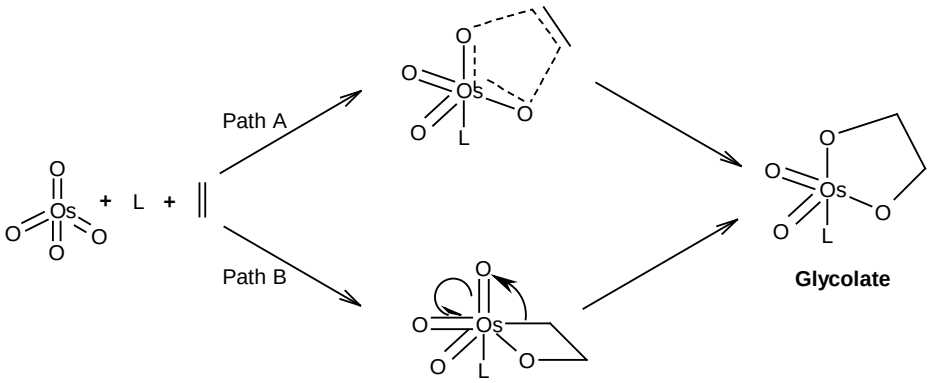
Figure 4. The latest generation of "dimeric" PHAL and PYR ligands and their predecessors (Alk* = DHQD or DHQ, see Fig. 1a)

Due to these improvements it is now possible to obtain high enantioselectivities with a broad range of alkenes.

Mechanism of Asymmetric Dihydroxylation:

The osmium catalized dihydroxylation reaction has been the center of extensive mechanistic investigations and two different mechanisms have been suggested. Boseken[28a] and Criegee[10] originally proposed a concerted [3+2] pethway (**Scheme 3, Path A**), while Sharpless et al.[28b] and Jorgensen et al.[28c] 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.

The recent observation of a nonlinear Erying relationship between enantiomeric excess and temperature[26] is consistent with Criegee's one-step [3+2] mechanism, but it can be



explained by a reaction pathway with at least two selectivity determining steps having different importance 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 there are energetically accessible minima on the potential energy surface.[29]

Scheme 3. Schematic presentation of the concerted [3+2] mechanism[28a] (Path A) and stepwise osmaoxetane mechanism[28b,,c](Path B).

Emperical Rules for Predicting the Face Selectivity

Despite the mechanistic uncertainties, the face selectivity of the dihydroxylation can reliably be predicted using an empirical 'mnemonic device' (**Scheme 4**).[30] The plane of the olefin is divided into four quadrants and the substituents are placed into three quadrants according to a simple set of rules. The SE quadrant is sterically inaccessible and, with few exceptions, no substituent other than hydrogen can be placed here. The NW quadrant, lying diagonally across from the SE quadrant, is slightly more open and the NE quadrant appears to be quite spacious. The SW quadrant is special in that its preferences are ligand-dependent. Even though this SW quadrant normally accepts the largest group, especially in the case of PYR ligands, it is especially attractive for aromatic groups in the case of PHAL ligands.[30c] An

olefin, which is placed into this plane according to the above constraints, receives the two OH groups from above, i.e. from the β-face, in the case of DHQD derived ligands and from the bottom, i.e. from the α-face, in the case of DHQ derivatives.

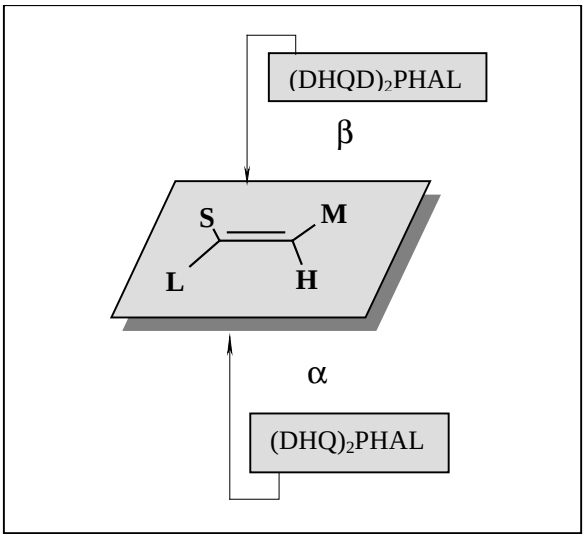


Fig. 5: ***Mnemonic diagram*** *(S = small group, L = large group, M = medium group, H = proton).*

Predictions for 1,1-disubstituted olefins using the empirical mnemonic device are not always unambiguous,[31] since it may be difficult to judge which of the two substituents prefer the attractive, SW quadrant. Along with steric size, the properties of the substituents have also to be taken into account and compared with the ligand-specific preferences for the SW quadrant. PHAL ligands show the following preferences for the SW quadrant.[30c,31,32]

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

Recent studies have revealed that oxygenated residues[31,33] have very small preferences for ligands binding pocket (SW quadrant). Studies with 1,1-disubstituted olefins have shown that pyrimidine (PYR) ligands have very different preferences for SW quadrant[30c,32] and the steric size of a substituent is much more important than in the PHAL system.

Thus, the following preference is observed:

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

A few exceptions mostly for terminal olefins have appeared in recent years. The AD of certain *ortho*-substituted allyl benzenes in the presence of PHAL ligands have been shown

to give facial selectivities opposite to those predicted by the mnemonic device.[34] Furthermore, *trans*-olefins in the same series react with the expected face selectivity even with the PHAL ligands; thereby demonstrating that exceptions are so far limited to the class of terminal olefins. Thus, the mnemonic device is a simple tool for predicting the facial selectivity of the AD reaction. However, reliable predictions require the intrinsic preference of each ligand to be taken into account. Thus, the SW quadrant is especially attractive for aromatic groups in the PHAL systems, while aliphatic groups are preferred in the PYR systems. PYR ligands are, therefore the ligands of choice for aliphatic and/or sterically congested olefins, while PHAL ligands are better for aromatic substrates. These simple rules allow the prediction of the face selectivities even in difficult cases and very few exceptions are known.

Reaction Conditions

Catalytic asymmetric dihydroxylation is performed in a 1:1 mixture of water and *t*-BuOH. The olefin concentration in the *t*-BuOH/water mixture is usually 0.1 M.[25] While the reaction is normally run under basic conditions (K_2CO_3, pH 12.2, aq. layer),[35] it is possible to buffer the system with 3 equivalents of $NaHCO_3$ (pH 10.3, aq. layer). Buffering of the reaction has a beneficial effect on the yield when base-sensitive substrates are used or base-sensitive products are formed. Normally the reaction is performed with 3 equivalents of $K_3Fe(CN)_6$ as the re-oxidant. The key reagents used are the Os reagent and the ligands. Only 0.2 to 0.4 mol% of Os reagent, either OsO_4 or the nonvolatile $K_2OsO_2(OH)_4$ is added. The ligand concentration is 1 mol%. However it can be dropped in some cases without much loss in enantioselectivity. For e.g. stilbene still gives 96% ee when 1/100 of 1 mol% of $(DHQD)_2$-PHAL is used as compared to the 99.8% ee obtained under normal conditions.[25] Alternatively, the amount of OsO_4 can be increased to 1 mol% for accelerating the reaction rate of relatively unreactive olefins. Additionally, the ligand can be recovered especially when large-scale reactions are carried out. For the PHAL ligands, the combined organic layers are extracted with 3% aq. H_2SO_4 saturated with K_2SO_4 (ca. 40 mL/1 g of ligand), followed by a second extraction of the organic solution with saturated K_2SO_4 (ca. 40 mL/1 g of ligand). The ligand enters the aqueous phase as the hydrogen sulfate salt and the solution can be reused directly for the subsequent AD reactions without further purification. However, the amount of K_2CO_3

in the subsequent reaction should be increased in order to neutralize excess H_2SO_4 and also to release the ligand salt as its free base. Additionally, the amount of water should be decreased by the volume of aqueous ligand solution added to the reaction mixture.

Since most substrates require very similar reaction condition, it is possible to use premix of all reactants. These are available commercially as 'AD-mixes' such as AD-mix-β [$(DHQD)_2PHAL$] and AD-mix-α [$(DHQ)_2PHAL$]. 1 kg of AD-mix contains $K_3Fe(CN)_6$ (699.6 g), K_2CO_3 (293.9 g), ligand (5.52 g) and $K_2OsO_2(OH)_4$ (1.04 g). The standard AD procedure calls for 1.4 g of this AD-mix per mmol of olefin. One equivalent of $MeSO_2NH_2$ should be added for all substrates other than terminal olefins to enhance hydrolysis of the osmate (VI) ester and hence the rate of catalytic turnover.

The Cinchona Alkaloid Ligands and their Substrate Preferences

Phthalazine (PHAL) ligands (1)

The phthalazine ligands are most widely used, due to their ready availability and their broad substrate scope.[30b] This ligand class is used in the AD-mix formulation. PHAL ligands react especially well when aromatic groups are present, and remarkably high enantioselectivities are observed when the aromatic substituents appear in certain optimal locations/patterns.[30a] One such case is *trans*-stilbene for which the enantioselectivity is as high as 99.8%.[36] However, PHAL ligands give inferior results with aliphatic olefins, especially if they are branched near the double bond or if they have very small substituents.

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

Pyrimidine (PYR) ligands (2)

The pyrimidine ligands (**2**) complement the phthalazine ligands (**1**) and they are the ligands of choice for olefins with sterically demanding substituents.[27] Both PHAL and PYR ligands are useful for tetrasubstituted olefins.

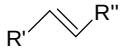
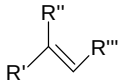
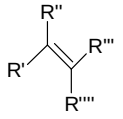
Anthraquinone (AQN) ligands (3)

The anthraquinone ligands are especially well suited for almost all olefins having aliphatic substituents.[37] Even diols derived from allyl halides or allyl alcohols can now be obtained with satisfactory enantiomeric purity, thereby giving access to valuable chiral building blocks. The AQN derivatives are the ligands of choice for the AD reaction, except for olefins with aromatic or sterically demanding substituents.

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.[39] However, in certain cases better results are obtained with the new second generation ligands.[37,38,4]

Table 1. Recommended ligands for each olefin class.

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

Recent Applications of Sharpless Asymmetric Dihydroxylation (AD) Reaction in Organic Synthesis

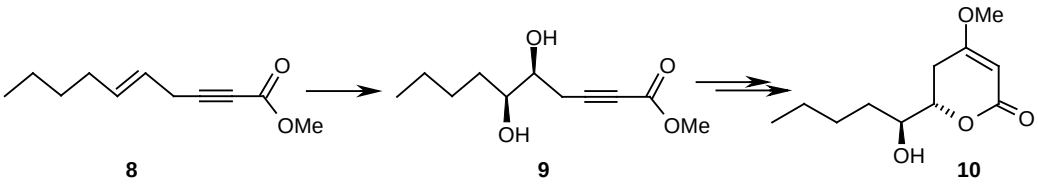
The Sharpless asymmetric dihydroxylation is ideally suited for the preparation of chiral building blocks for asymmetric synthesis, due to its wide scope and excellent enantioselectivity. By using Sharpless asymmetric dihydroxylation reaction we can synthesize the required enantiomer. The dihydroxylation reaction offers some important advantages over the use of sugars as chiral building blocks in enantioselective synthesis. The enantiospecific syntheses from the chiral pool require an elaborate protecting group strategy. However with AD, the diol can be carried through the synthesis "masked" as an olefin, ready to be released at any point.

Asymmetric Dihydroxylation is not limited to a certain number of standard starting materials. Any olefin can be regarded as a substrate. Thus, the synthetic strategy is left almost entirely to the imagination of the chemist and not restricted by the availability of certain starting materials.

The synthetic community immediately realized the potential utility of this methodology as a result, during last two decades numerous biologically active compounds were synthesized using Sharpless asymmetric dihydroxylation.

Most of the synthetic applications of SAD are covered in the Sharpless review on Dihydroxylation. Some of the recent applications are documented below.

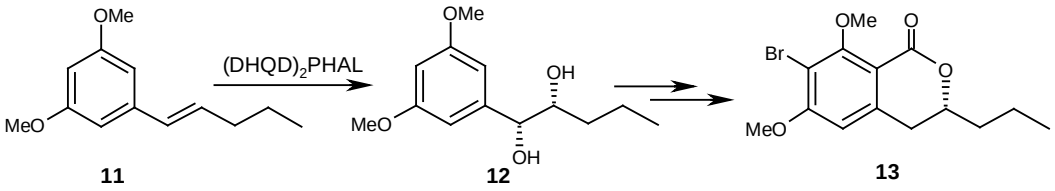
1. An efficient synthesis of (-)-pestalotin **10**[41] was achieved through the SAD reaction of enyne **8.** (**Scheme 2**).



8 **9** **10**

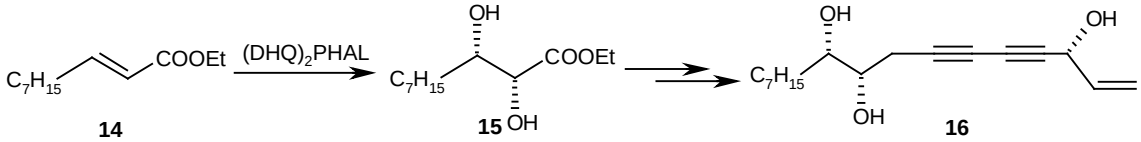
Scheme 1

2. Kitahara *et al*. has employed SAD to synthesize Hiburipyranone **13**,[42] a cytotoxic metabolite of a marine sponge. (**Scheme 3)**



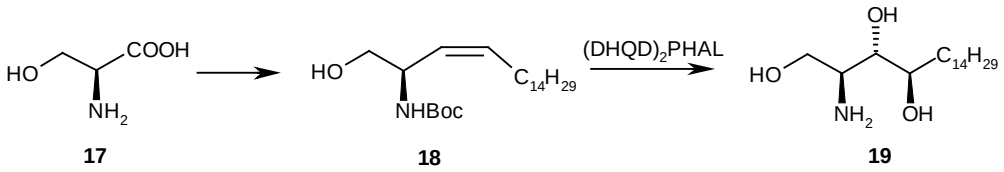
Scheme 3

3. Panaxytriol **16**[43] an anti tumour agent was prepared using SAD as the key step. (**Scheme 4**)



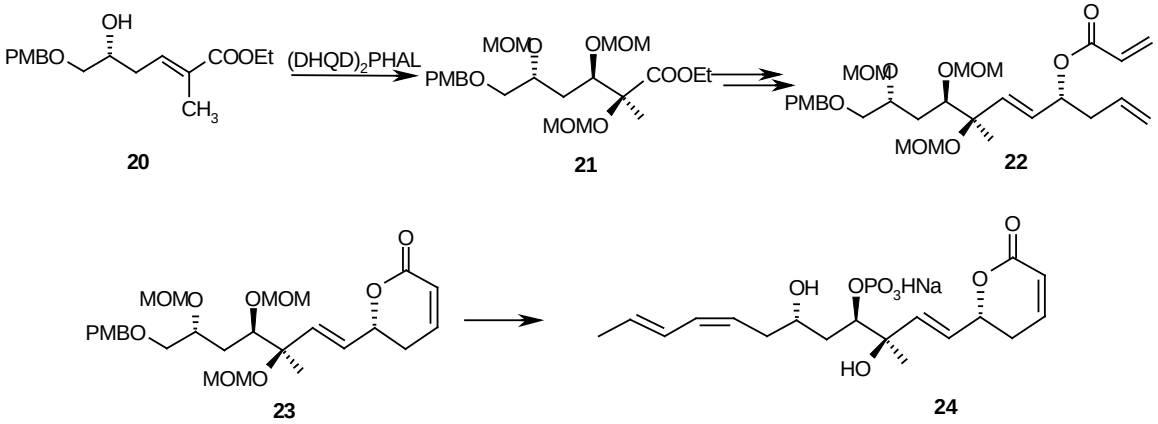
Scheme 4

4. Phytosphingosine **19**[44] was synthesized by employing SAD reaction of olefin **17**. (**Scheme 5)**



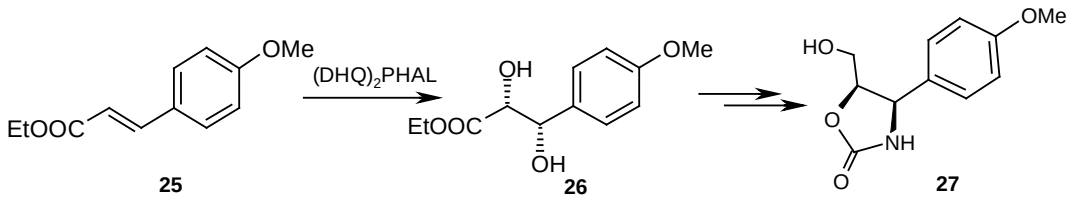
Scheme 5

5. The synthesis of C1-C12 fragment of fostriecin **23**[45] has been achieved using SAD and Ring Closing Metathesis. (**Scheme 6)**



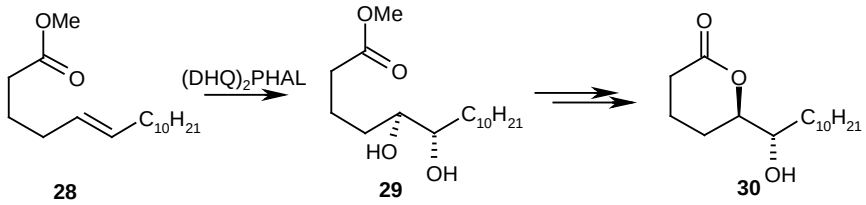
Scheme 6

6. Cytoxazole **27**[46] has been synthesized employing SAD as the key step. (**Scheme 7)**



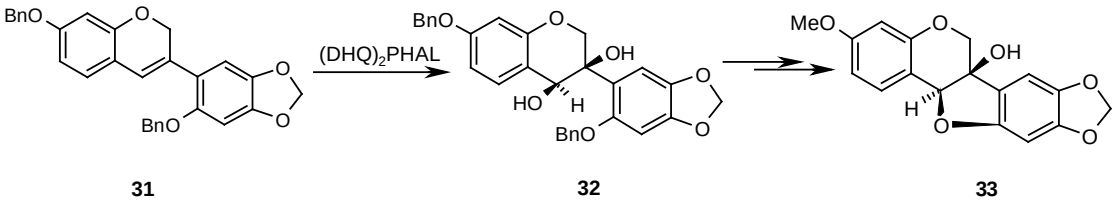
Scheme 7

7. An efficient synt6hesis of *erythro*-(-)-6-acetoxy-5-hexadecanolide **30**[47] was achieved using SAD. (**Scheme 8**)



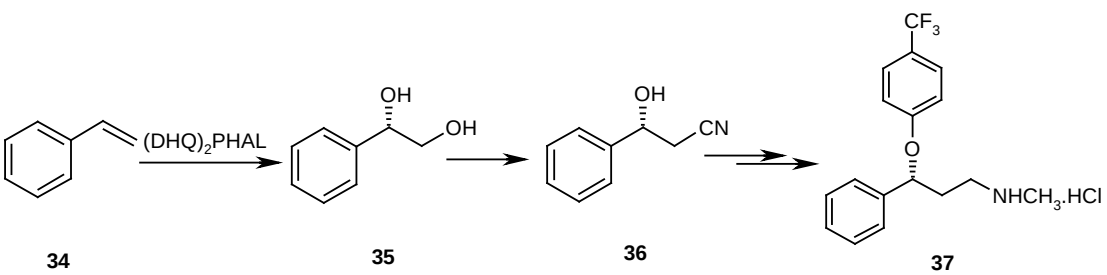
Scheme 8

8. Similarly (+)-pisatin **33**[48] has been synthesized using SAD. (**Scheme 9**)



Scheme 9

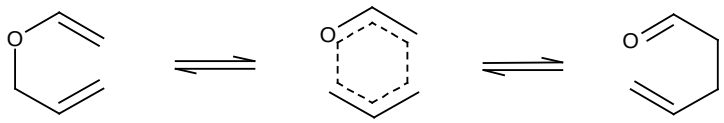
9. Norfluoxetine and Fluoxetine[49] important drugs for psychiatric disorders are synthesized using SAD. (**Scheme 10**)



Scheme 10

1.12 A brief account on Claisen Rearrangement

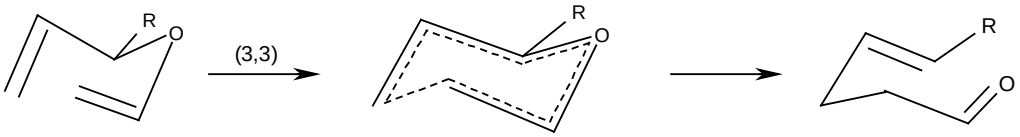
The Claisen rearrangement was discovered in 1912 and its mechanism was proposed in the 60's, just as Cope rearrangement which involves a similar [3,3]-sigmatropic rearrangement.[50] The Claisen rearrangement is the highly stereo selective [3,3]-sigmatropic rearrangement of allyl vinyl ethers **38** into carbonyl compounds **39**. The majority of these rearrangements require high temperatures (100-350 ^{o}C), although numerous examples of catalytic synthesis are also known.[51] The common feature of all [3,3]-sigmatropic rearrangements is a six-membered transition state with a delocalised electronic structure.



38 **39**

Figure 1

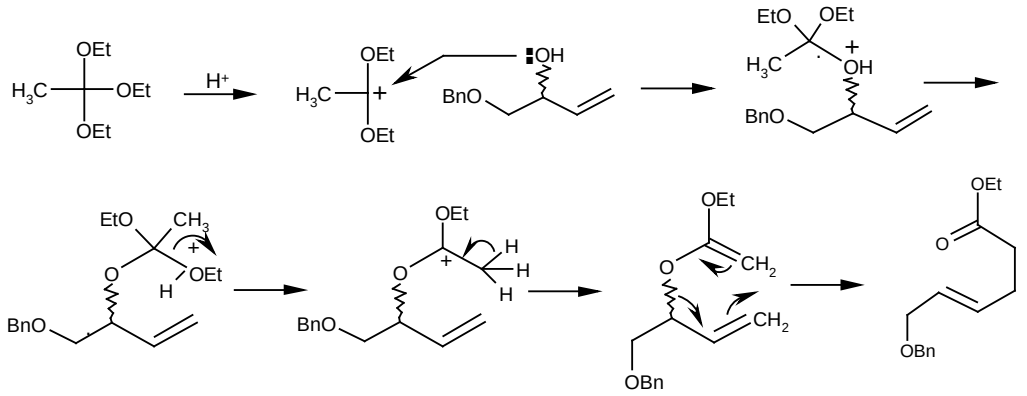
From the kinetic point of view, a chair conformation is preferred, which makes it possible to predict the stereochemical course of the reaction.[52,53] Thus, the Claisen rearrangement provides a means of introducing functionality in a stereo and regio-specific manner, while at the same time fixing the geometry about the newly formed carbon-carbon bond. In the Claisen rearrangement the resulting double bond strongly favours the trans (*E*)-geometry. This is because the substituent prefers an equitotial position on the chair transition state.



40 **41**

Figure 2

Mechanism of Orthoester Claisen Rearrangement:



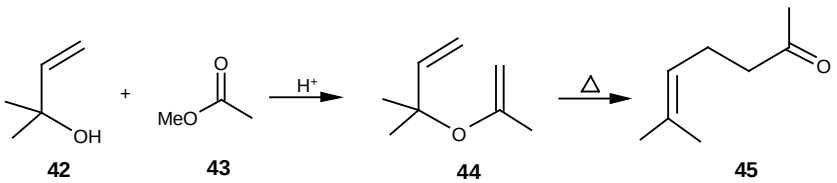
Scheme 11

Types of [3,3]-sigmatropic rearrangements:

Sigmatropic rearrangements have proven very useful in the synthesis of fragrance and flavour compounds.[55,55,56] Depending on the parent substances utilized, there exists a number of modifications, which have found a vast number of applications.[57]

Allyl Vinyl Ether Claisen Rearrngement:

The terpenoids are the largest and important group of compounds, which may be obtained by Claisen rearrangements. A key intermediate in the synthesis of many fragrances

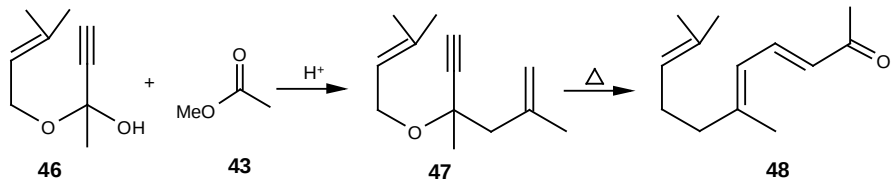


42 **43** **44** **45**

2-methyl-2-hepten-6-one is prepared by using Claisen rearrangement.[58]

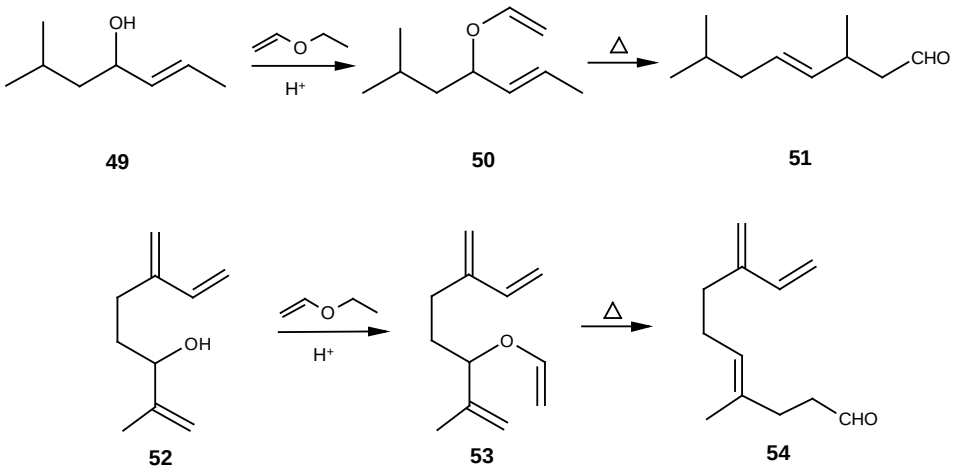
Scheme 12

In a similar way, pseudoionone **48** was prepared by using Claisen rearrangement.[59]



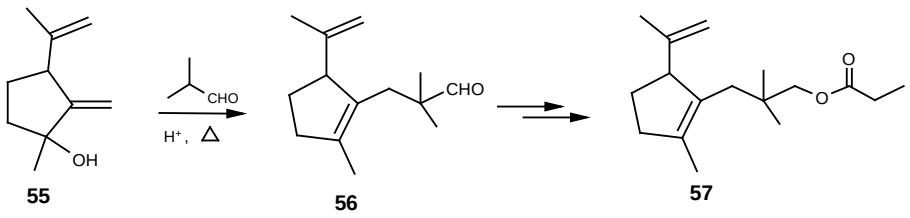
Scheme 13

Claisen rearrangement was also used for the synthesis of isoprenoid compounds.[60,61]



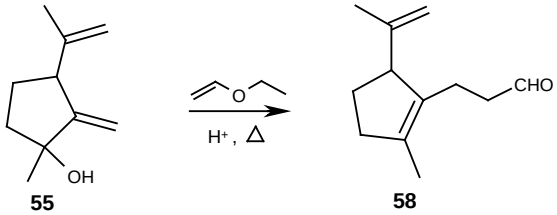
Scheme 14

The Claisen rearrangement can be also applied to alicyclic systems. Cyclomusk (BASF) **57** was prepared from alcohol **55**, which has a very interesting fruity, musky odor with a sandalwood note.[62]



Scheme 15

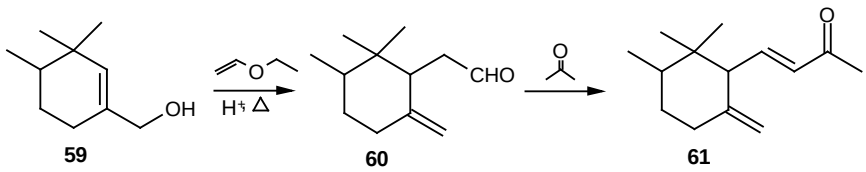
Alcohol **55** was also converted to β, γ-unsaturated aldehyde **58**, which was an important



intermediate for the synthesis of fragrant oils.[63]

Scheme 16

Another interesting application of the Claisen rearrangement is the synthesis of γ-irone **61**.[63]



59 **60** **61**

Scheme 17

Eschenmoser-Claisen rearrangement, Johnson-Claisen rearrangement, Ireland-Claisen rearrangement:

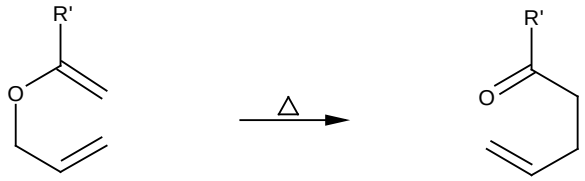
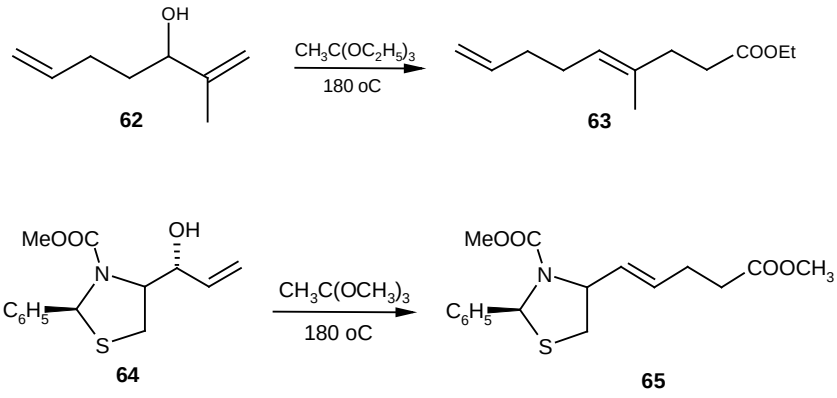


Figure 3

When R^1 = OR, the reaction is referred to as Johnson-Claisen rearrangement. Johnson *et al*[64] first reported the transformation of allylic alcohols into the corresponding γ, δ-unsaturated esters. Since the discovery, many useful applications of this rearrangement have been reported.[65]

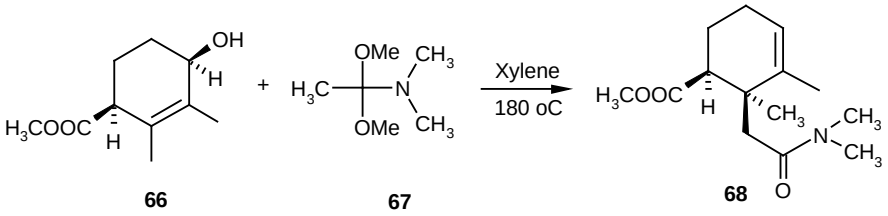


62 **63**

64 **65**

Scheme 18

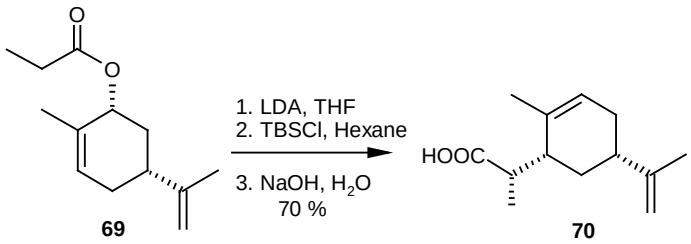
When $R^1 = NR_2$, the reaction referred to as Eschenmoser-Claisen rearrangement. Meerwin, Eschenmoser *et al* prepared γ, δ-unsaturated amides by the exposure of allylic alcohol **66** to an amide acetal **68**.[66]



66 **67** **68**

Scheme 19

When $R^1 = OSiR_3$ or OLi, the reaction referred to as Ireland-Claisen rearrangement.[67] R. E. Ireland invented this reaction in the 1970 and is widely used since. The resulted double bond shows *E* selectivity for the same reason as described earlier.



69 **70**

Scheme 20

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SECTION B
ENANTIOSELECTIVE SYNTHESIS OF *R*-(+)-α AND *S*-(-)-α-LIPOIC ACID

Introduction:

The synthesis of chiral molecules is of immense importance to the pharmaceutical industry. The main reason for this is that the biological properties of two enantiomers are in

principle different. Given that one enantiomer may exhibit enhanced therapeutic properties over the other, and an understanding in vivo *activity of both enantiomers is frequently a prerequisite for regulatory approval, the provision of a single enantiomer is often essential.*

Lipoic acid (**1**) was first isolated in 1951 by Reed and his co-workers[1] at the university of Texas in Austin. The first purified sample of lipoic acid was 30 mg of yellow crystals that were extracted from 100 kg of liver residue. The substance was known as α-lipoic acid (or) ALA. Some scientists believed the substance should be named thioctic acid because it contained two sulfur atoms (theion in Greek) and eight carbon atoms (octo in Greek). Ultimately, ALA was given the name lipoic acid because of its ability to dissolve in lipids.

Alpha lipoic acid is not considered to be a vitamin because it is assumed that it can be synthesized by the body in small amounts from essential fattyacids. Although alpha lipoc acid is found in foods, such as liver and yeast, there are no foods rich enough in alpha lipoic acid to serve as good sources.

Lipoic acid works at the cellular level to help essential substances for metabolism to enter the mitochondria. Lipoic acid is a powerful and well-known antioxidant. An increase in the amount of lipoic acid increases the amount of cellular fuel that is burned. This generates a greater energy reserve for the body that is available for growth, tissue repair and muscle development.

Many success stories have been reported from the treatment of sick livers with lipoic acid. In 1977 a couple was dying of liver failure after eating poisonous mushrooms. The attending physician was told that they would certainly die and to make it as comfortable as possible for them. However, the physician had read about a new experimental drug lipoic acid, which had successfully promoted liver growth in Europe. Within days after administering lipoic acid the couple was back at home in good health with fully functioning and regenerated livers. Since that time lipoic acid has been proposed as preventive against a variety of health conditions including aging, diabetes, cancer and cardiovascular disease.

Alpha lipoic acid does not accumulate in tissues and therefore does not have any toxicity in the amounts usually taken. Because it is distributed through the tissues, it is useful in a wide variety of conditions. It is particularly protective of the brain, which is the most sensitive of organs to free radical damage and the eye. However, animal experiments have

shown that this protective effect is highly dependent upon the timing and the form of administration.

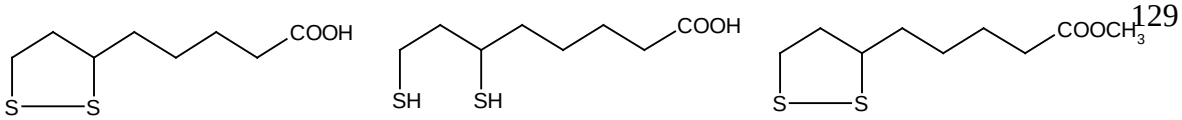
As part of the glycolytic pathway, alpha lipoic acid both stimulates insulin activity and reduces insulin resistance. It has been shown to enhance the burning of glucose in obese laboratory animals. There is no doubt that alpha lipoic acid is an important component in the production of energy from carbohydrates. It is involved through the complex multienzyme process, which catalyzes glucose in to energy. One study of adult diabetic patients showed that alpha lipoic acid increased the cellular uptake and oxidation (burning) of glucose by about 50 percent. This is important for athletes as well as for the overweight. The efficient burning of glucose is essential for the normal production of energy in the muscles, and impaired muscle metabolism have been found in the brain.

The reduction of alpha lipoic acid (**1**) in to dihydrolipoic acid (**2**) and the role of alpha lipoic acid in the production of glutathione appeal to be normal functions of alpha lipoic acid in the body. These are two of its several vitamin like physiologic functions. Alpha lipoic acid is unique in that, like vitamin C, it is effective as an antioxidant in water based tissues such as the blood, and yet as dihydro lipoic acid also is effective in protecting non-water based tissues like fatty tissues and membranes, a role it shares with vitamin E.

Thus alpha lipoic acid and dihydrolipoic acid together function as a universal anti oxidants, meaning an antioxidant that quenches free radicals in both lipid and water-soluble positions of tissues and cells. Lipoic acid and dihydrolipoic acids are extremely powerful quenchers of hydroxyl, singlet-oxygen, peroxy nitrite and other free radicals. We could also call lipoic acid a “broad spectrum” antioxidant because of its activity in aqueous and lipid phases.

Free radicals are associated with the development of artherosclerosis, lung disease and neurological disorders as well as being implicated in chronic inflammation, such as that found with rheumatoid arthritis and inflammatory bowel disease. Smog and many other sources of environmental toxins either are themselves (or) lead to the creation of free radicals in the body.

Under normal conditions, lipoic acid produced in our body along with what is derived from our diet is thought to meet our needs. However, under conditions of oxidative stress, the



available lipoic acid may not adequate enough to provide optimal protection. Those who are not meat-eaters particularly are more vulnerable. Red meat is a relatively good source of lipoic acid.

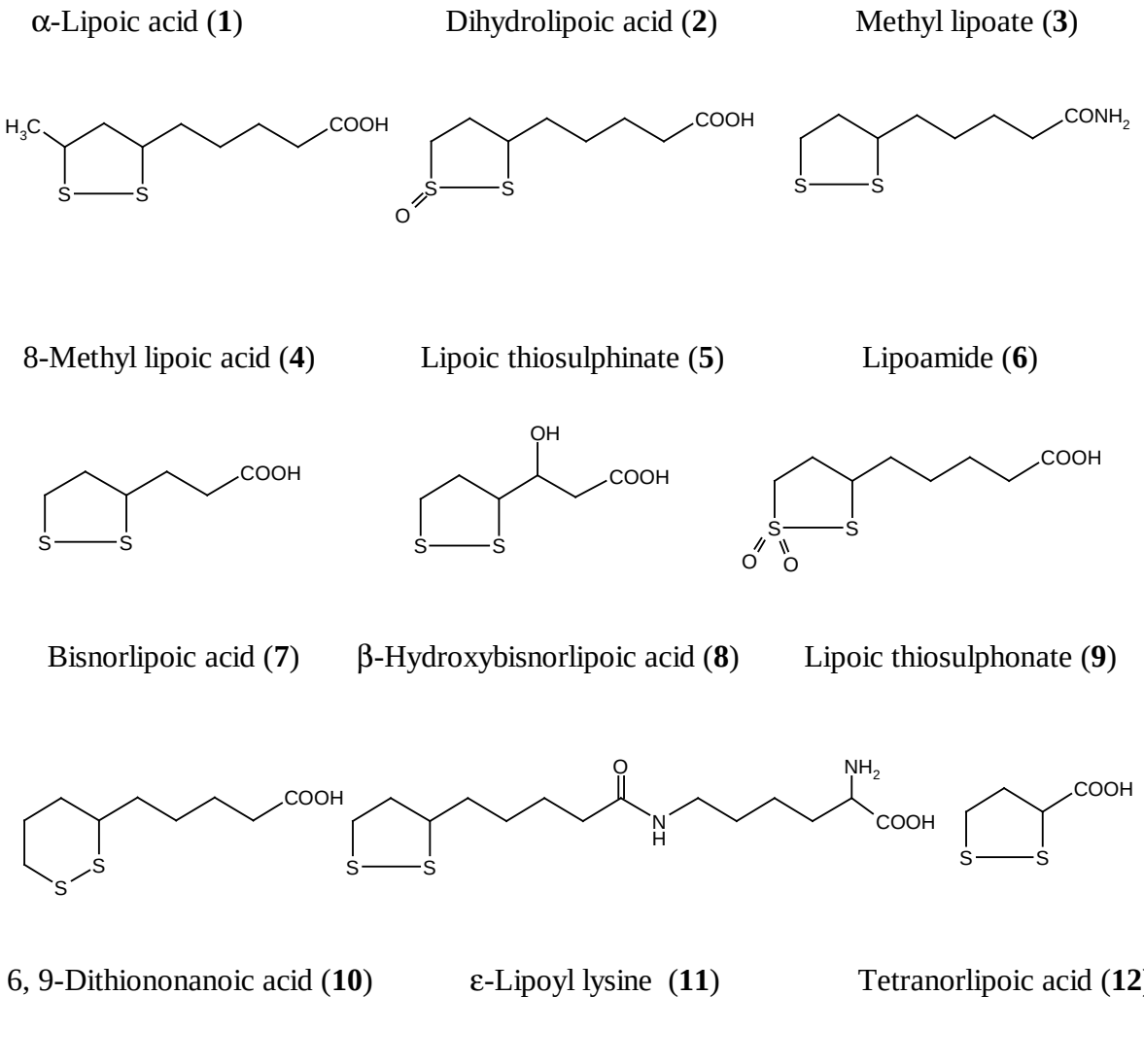


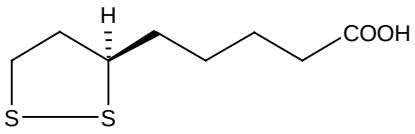
Figure 1. The structure of α-Lipoic acid and some of its related products.

Structure:

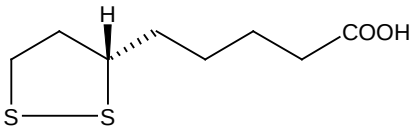
Lipoic acid is known by a variety of different names. Officially, it is known as lipoic acid (or) 1, 2-dithiolane-3-pentanoic acid. Unofficially, it has been known as α-lipoic acid, 6,

8-thiooctic acid, 5-(1, 2-dithiolan-3-yl)-valeric acid (or) 5, 3-(1, 2-dithiolanyl)-pentatonic acid.

α-Lipoic acid (**1**)



R-(+)-α-Lipoic acid (**1a**)



S-(-)-α-Lipoic acid (**1b**)

Figure-2

Lipoic acid is a molecule containing eight carbon atoms, two sulfur atoms, a 1, 2-dithiolane ring and a carboxylic acid group. The three position of the ring structure is a chiral centre.

There are two forms of lipoic acid i.e. *R* and *S*, *R* being the natural and pharmacologically more important form. For theraphy purposes lipoic acid is often used as racemic material because the (*S*)-enantiomer shows no significant biological side effects.

Mode of Biological Action of α-Lipoic Acid

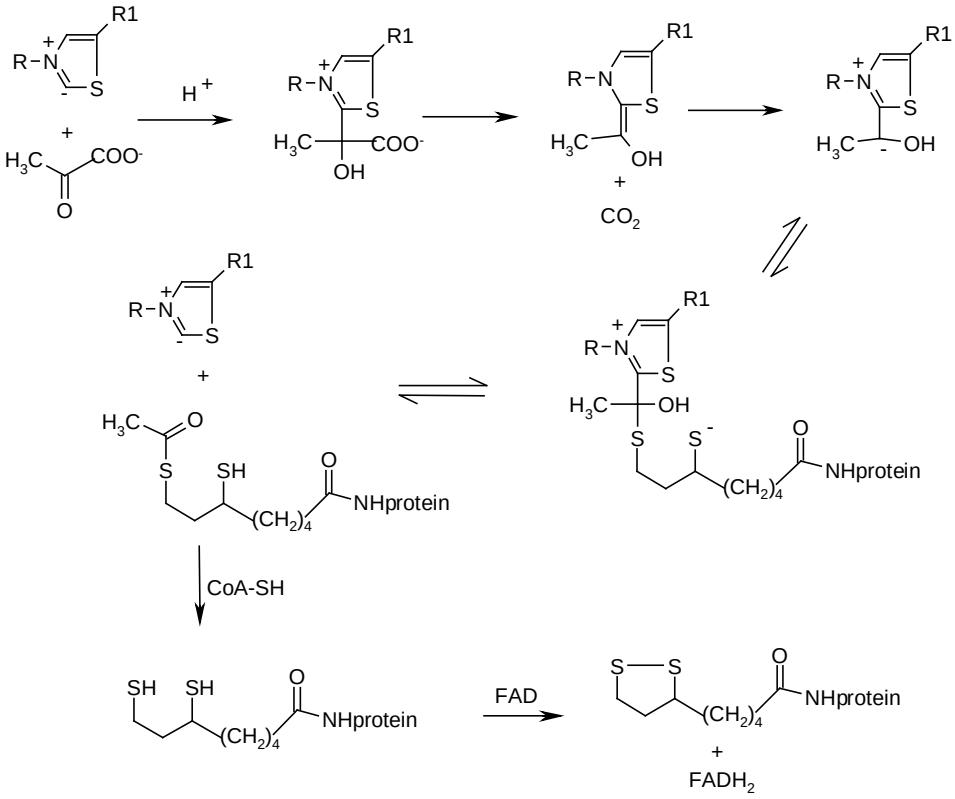
The complete oxidation of pyruvate during aerobic glycolysis takes place by tricarboxylic acid (TCA) cycle. Pyruvate undergoes oxidative decarboxylation before it enters TCA cycle.

The coenzymes required for the overall oxidative decarboxylation of pyruvate are thiamine pyrophosphate (TPP), nicotinamide adenine dinucleotide (NAD), α-lipoic acid, coenzyme A and flavin adenine dinucleotide (FAD).[2] The stages involved in this complex process are shown in scheme 1.

Thiamine pyrophosphate interacts with lipoic acid to form an addition complex which subsequently gets cleaved to form acyl lipoic acid complex and TPP is regenerated. The acetyl group, now present as a thioester, is then transferred from acyl lipoic acid to coenzyme-A to

form acyl-CoA by the acetyl-transfer enzyme system. Finally, the reduced lipoic acid moiety is reoxidised by the interaction with FAD and the cycle is completed. The acyl-CoA then enters the TCA cycle. FAD is regenerated by interaction with NAD^+ in the electron transport system.

The hydrophobic interaction and the metal ion coordinating ability[3] of the molecule which helps the free passage of the compound in various tissues are the factors which are responsible for the high biological activity of lipoic acid. α-Lipoic acid offers metal ions two different binding sites, the carboxylate group and the disulfide linkage. The carboxylate group dominates the coordinating properties of this ligand towards metal ions but a disulfide-metal ion interaction is still possible, and under sterically favoured conditions, may become very important. This could be true under enzymic conditions when the carbonyl group is no longer free but in the form of amide-linked to the protein. Further, the lipoyl moiety is ideally suited to undergo hydrophobic ligand-ligand interaction in the mixed ligand complexes due to the presence of valeric acid side chain.



Scheme 1

Alpha Lipoic Acid: It's Role in Human Health:

α-lipoic acid has been shown to have significant physiological as well as pharmacological properties.[3] There is no doubt that alpha lipoic acid have an important role in Human Health.[4]

- Alpha lipoic acid functions as a universal antioxidant and free radical scavenger.[5]
- Alpha lipoic acid is a co-enzyme associated with α-keto acid dehydrogenation.[6,9]
- Recycles both Fat and Water-soluble antioxidant vitamins.[7]
- Improves sugar metabolism and energy production. (i. e. controls diabetes).[8]
- α-lipoic acid acid has been used as a therapeutic agent in a number of conditions related to liver.[10]
- α-lipoic acid appears to have the potential to slow the process of aging.[11]
- α-lipoic acid significantly reduces inflammation and it also acts as an antitumour agent.[12]
- α-lipoic acid is an effective inhibitor of human immuno deficiency virus (HIV) replication.[13]
- α-lipoic acid has been found beneficial against radiation injury, smoking, heavy metal poisoning and chagas disease.[14]

Apart from the pharmacological importance, α-lipoic acid also finds its use in cosmetic preparations. α-Lipoic acid and its derivatives are used in skin lotions, ointments and creams as skin-whitening cosmetics.[15] Also, α-lipoic acid and its derivatives are used in hair tonics to control dandruff and stimulate hair growth.[16]

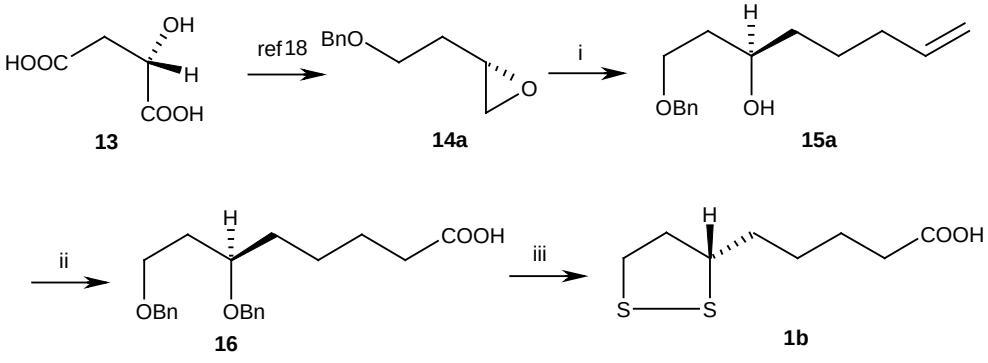
Finally, it is truly amazing how a relatively small and simple molecule like lipoic acid could have such a profound effect on so many diverse systems and functions in our body. It is thus becomes readily apparent that maintaining adequate alpha lipoic acid status is crucial for our long-term health and well being.

Review of Literature:

Reed and co-workers reported the isolation of α-lipoic acid in 1951 from liver residue. The chemical structure of α-lipoic acid was determined in the early 1950's and its absolute configuration was confirmed to be *R* in 1983, when Golding synthesized the complementary enantiomer from *S*-malic acid. It clearly indicates that scientists considered lipoic acid as small molecule and after knowing the biological activity and pharmaceutical importance the scientific community was attracted by its synthesis as a result a number of (±)-α-lipoic acid and optically active lipoic acids have been documented in the literature.[17-30]

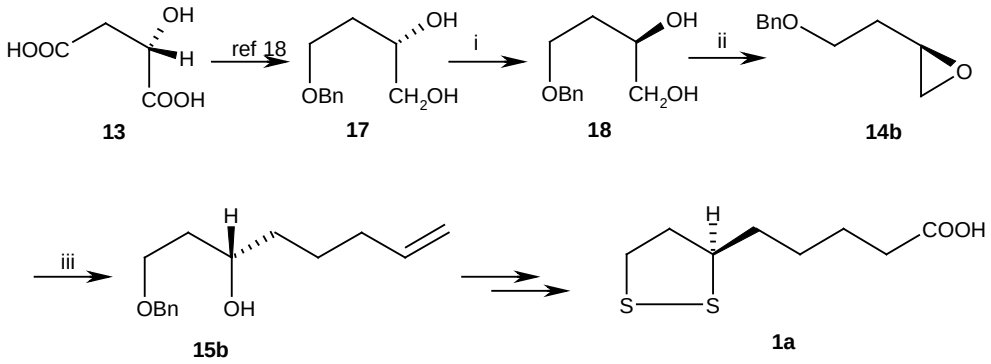
Golding *et al* (1983, Scheme-2),[17a] (1988, Scheme-3)[17b]

Golding and co-workers have utilized epoxide **14a** as the chiral precursor, which was prepared by known procedure from *S*-malic acid. Opening of epoxide with but-3-enyl magnesium chloride catalysed by lithium chloro cuprate delivered the compound **15a**. Protection of the free hydroxyl group as benzyl ether followed by hydroboration and oxidation gave the acid **16**. Esterification of acid **16** and removal of benzyl protection gave ester, which on mesylation followed by treatment of dimesylated compound with Na_2S, sulfur in DMF and final ester hydrolysis delivered *S*-lipoic acid.



Scheme 2. *Reagents and conditions:* (i) CH_2=$CH_2CH_2CH_2MgCl$, Li_2CuCl_4 (cat), THF; (ii) (a) $PhCH_2Br$, NaH, THF; (b) $HBSia_2$, THF, aq. HO_2-; (c) PDC, DMF; (iii) (a) MeOH-HCl; (b) Pd/C, H_2; (c) $MeSO_2Cl$, Et_3N; (d) Na_2S, S, DMF; (e) aq. NaOH.

In an another approach Golding and Brookes synthesized enantiomer of epoxide **14a** for the synthesis of *R*-Lipoic acid. They used the same starting material i.e *S*- malic acid but inverted the configuration of hydroxyl group to prepare the epoxide **14b**. Epoxide **14b** was converted in to *R*-Lipoic acid following the same sequence of reactions used in the earlier

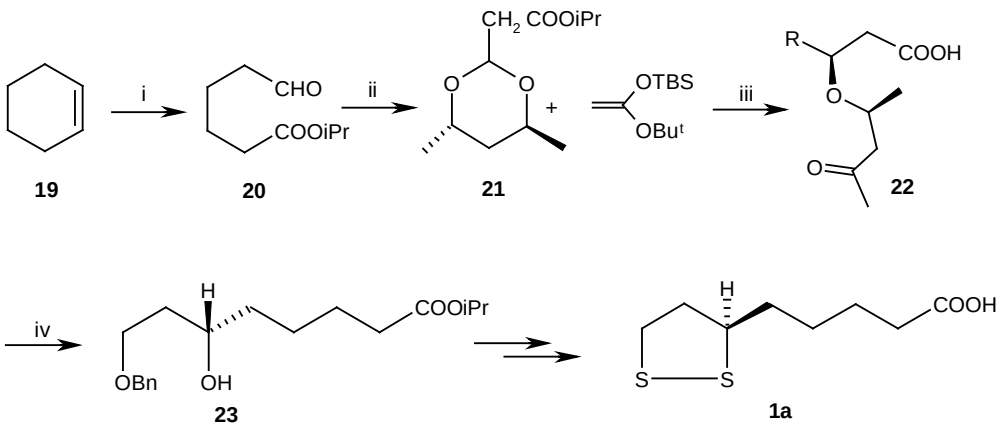


approach.

Scheme 3: ***Reagents and conditions***: (i) (a) $MeSO_2Cl$, Et_3N; (b) KOAc, Ac_2O; (c) K_2CO_3, MeOH; (ii) (a) PhCHO, H^+; (b) NBS, $ClF_2CCCl_2F_2$; (c) NaOH, $HOCH_2CH_2OH$; (iii) Scheme 2 conditions.

Elliott *et al* (1985, Scheme-4)[19]

Elliott and co-workers have reported the first synthesis of *R*-(+)-lipoic acid using highly diastereoselective $TiCl_4$ calalyzed aldol-type coupling of chiral acetal **21** with 1-*t*-butyldimethyl silyloxy ethane . The coupling product on hydrolysis followed by oxidation

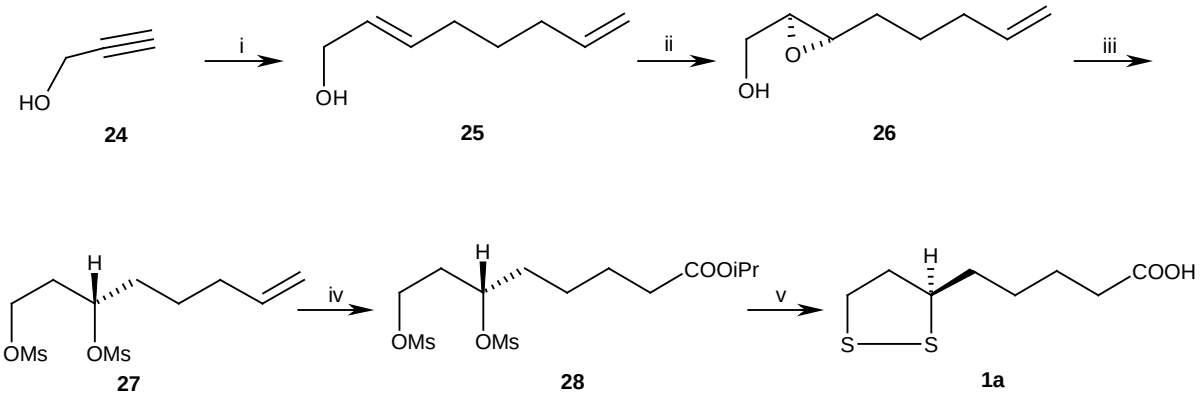


Scheme 4. *Reagents and conditions:* (i) (a) O_3, ^{i}PrOH, -78 ^{o}C, Ac_2O, Et_3N; (ii) (2*S*, 4*S*)-pentane-2, 4-diol, *p*-TSA, Benzene; (iii) (a) $TiCl_4$, CH_2Cl_2, -78 ^{o}C; (b) TFA, H_2O; (c) Jones oxidation; (iv) Piperidinium acetate, benzene, reflux, 97 %; (b) BH_3.THF, then 4 M aq. KOH, 82 %.

with Jones reagent gave acid **22**. Removal of the chiral auxiliary by β-elimination followed by hydroboration delivered the diol ester **23**. The diol ester was converted in to *R*-(+)-lipoic acid by using Goldings Procedure.

Sutherland *et al* (1986, Scheme 5)[20]

Sutherland and co-workers employed the alkylation of lithiodianion of propargyl alcohol in liquid ammonia solution with 6-bromohex-1-ene followed by dissolving metal reduction to deliver the allyl alcohol **25**. Sharpless asymmetric epoxidation of allyl alcohol **25** gave the (2*S*, 3*S*)-epoxy alcohol **26**. Reduction of **26** with Red-Al and mesylation of the resulting diol to deliver the dimesylate **27**. Ruthenium tetroxide oxidation of the terminal

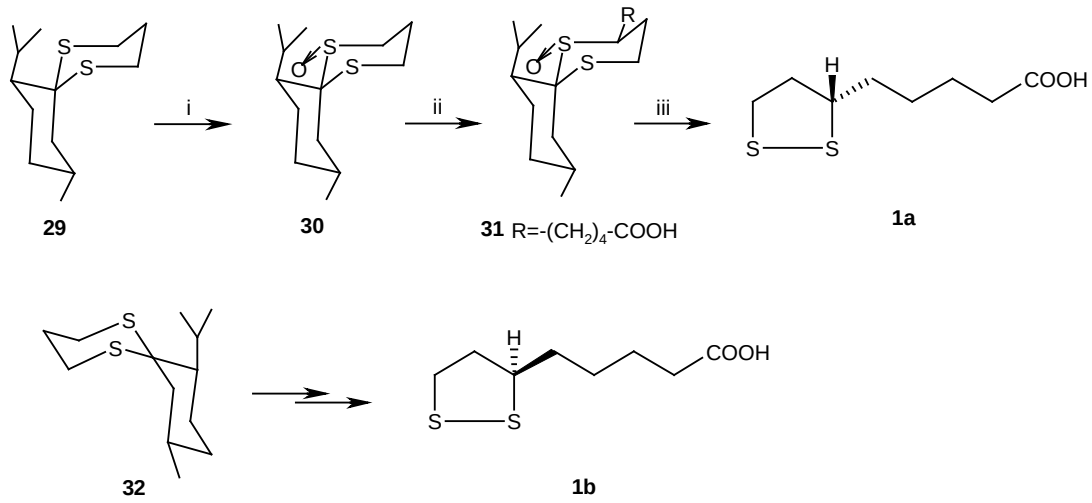


double bond of **27** and final disulfide displacement of acid **28** delivered the *R*-(+)-Lipoic acid.

Scheme 5. *Reagents and conditions:* (i) Na, liq. NH_3, $Br(CH_2)_3CH=CH_2$; (ii) L-(+)-diisopropyl tartarate, $Ti(OPr^{i})_4$, TBHP, CH_2Cl_2, -20 ^{o}C; (iii)(a) Red-Al, THF; (b) $MeSO_2Cl$, Et_3N, CH_2Cl_2; (iv) RuO_4 (v) Na_2S, S, DMF.

Ravindranathan *et al* (1987, Scheme 6)[21]

Ravindranathan's approach involves the formation of 1, 3-dithiane **29** from 1, 3-propane dithiol and L-menthone. Regio selective oxidation of dithiane **29** afforded sulfoxide **30**. Stereo selective alkylation of **30** followed by hydrolytic cyclization afforded *R*-(+)-lipoic acid. In the similar manner *S*-lipoic acid prepared by using D-menthone. In their approach they recovered the starting menthones in almost quantitative yield. This is the shortest and probably the best synthesis for both the enantiomers of lipoic acid.

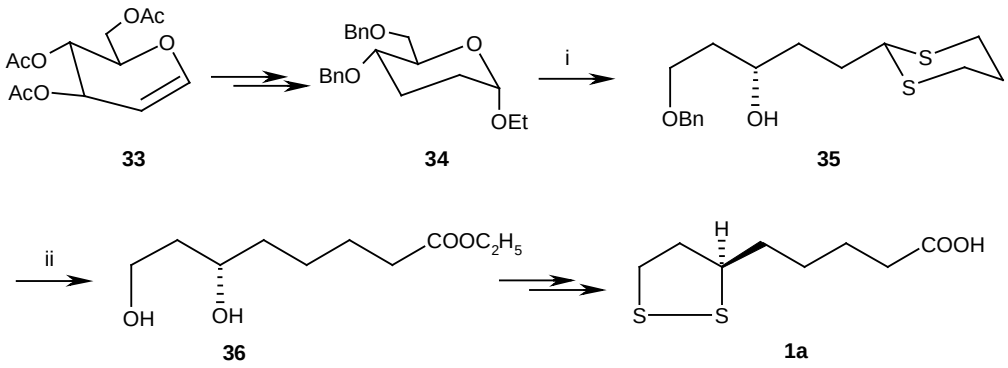


Scheme 6. *Reagents and conditions:* (i) $NaIO_4$, MeOH, 0 ^oC; (ii) LDA, TMEDA, THF, $Br(CH_2)_4CO_2Li$, -78 ^oC; (iii) aq. HCl, benzene.

Rama Rao *et al* (**1986**,[22a]**1987**[22b], **1987**[22c], **1987**[22d]) **Schemes 7-10**, respectively.

Rama Rao and co-workers have reported four different routes for the synthesis of lipoic acid.

In Rama Rao's first synthesis D-glucose was converted in to 4, 6-di-o-benzyl derivative through 3, 4, 6-tri-o-acetyl-D-glucal by known procedure. Treatment of **34** with propane dithiol followed by xanthate formation and tri-n-butyl hydride mediated reductive -

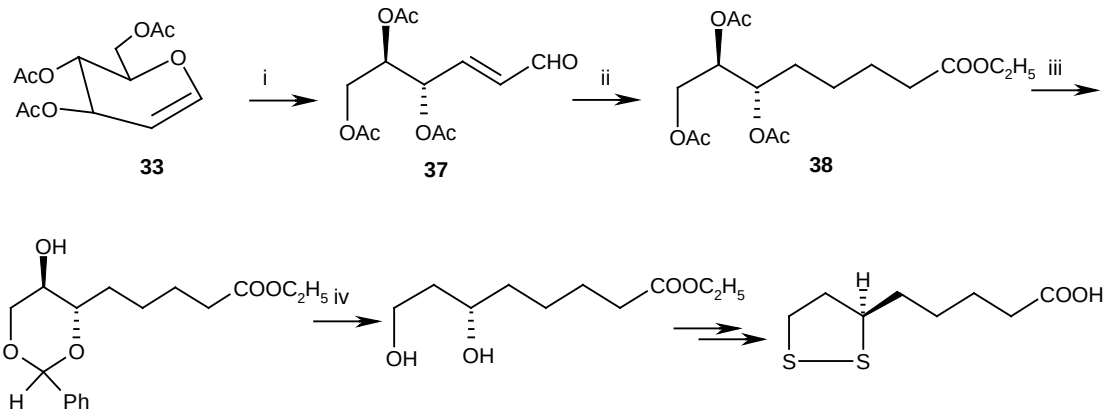


33 **34** **35** **36** **1a**

Scheme 7. *Reagents and conditions:* (i) (a) 1, 3-propane dithiol, $BF_3.Et_2O$, CH_2Cl_2; (b) NaH, CS_2, MeI; (c) n-Bu_3SnH, AIBN; (ii) (a) HgO, $BF_3.OEt_2$; (b) Ph_3P=CHCOOEt (c) H_2, Raney Ni.

-removal afforded dithiane derivative **35**. Sequential dithiane deprotection, two carbon wittig olefination, hydrogenation using Raney nickel delivered the diol **36**. The diol **36** was converted into lipoic acid following the known procedure.

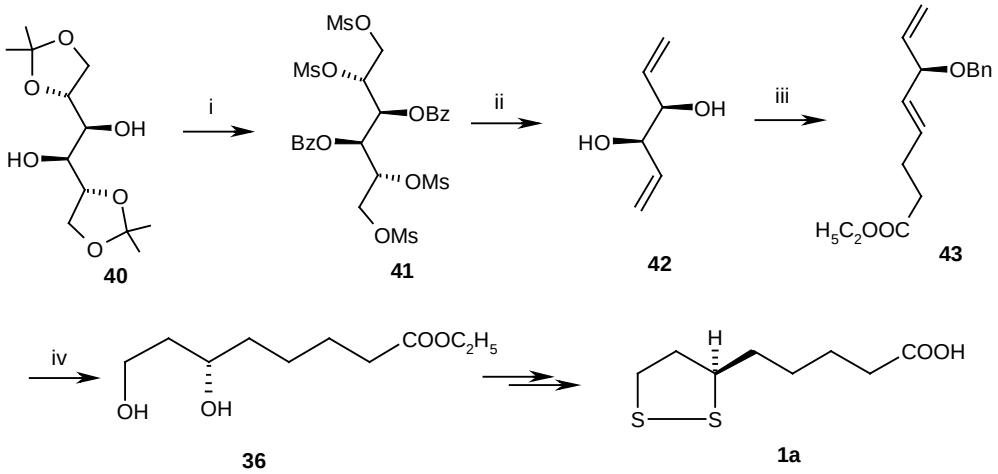
In Rama Rao's second approach tri-o-acetyl-D-glucal was converted to unsaturated aldehyde **37** using mercurous ion catalyzed ring opening. Sequential hydroxy group protection, two carbon Wittig homologation and hydrogenation gave the tri acetate **38**. Deacetylation and protection of 6, 8-hydroxyl groups with benzaldehyde dimethyl acetal gave the benzylidene protected compound **39**. Deoxygenation of the free hydroxyl group followed by removal of benzylidene protection gave the diol **36**, which was converted to lipoic acid.



39 **36** **1a**

Scheme 8. *Reagents and conditions:* (i) (a) $HgSO_4$, H^+, Dioxane; (b) Ac_2O, Pyridine; (ii) (a) Ph_3P=CHCOOEt; (b) H_2, Raney Ni; (iii) (a) NaOEt, EtOH; (b) $PhCH(OMe)_2$, H^+; (iv) (a) Thiocarbonyl diimidazole, THF; (b) n-Bu_3SnH, AIBN; (c) H_2, Pd/C.

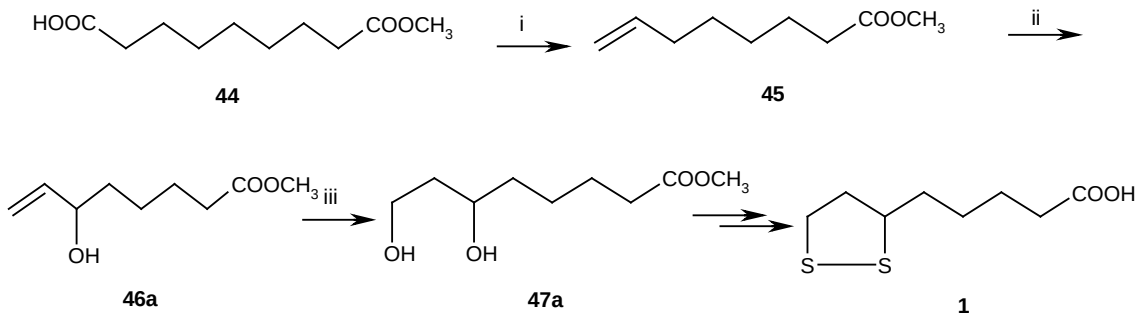
The third synthesis involves the utilization of mannitol diacetonide as a chiral precursor. Benzoyl protection of the hydroxyl groups followed by isopropylidene group



deprotection and mesylation gave the tetra mesylate **41**. Treatment of **41** with sodium Iodide and Zinc dust followed by debenzoylation gave (3*R*, 4*R*)-1, 2-divinyl glycol **42**. Selective protection of hydroxyl group and claisen-ester rearrangement of the resultant monoprotected benzyl ether delivered the compound **43**. Sequential hydroboration, oxidation and reduction of the double bond gave the known diol **36** which was converted in to *R*-(+)-lipoic acid.

Scheme 9. *Reagents and conditions:* (i) (a) PhCOCl, Pyridine; (b) 50 % aq. AcOH (c) $MeSO_2Cl$, Et_3N, CH_2Cl_2; (ii) (a) NaI, Zn, DMF, Reflux; (b) NaOMe (iii) (a) Bu_2SnO, Toluene, Reflux; (b) 1.2 eq $PhCH_2Br$, DMF, 100 ^oC; (c) $CH_3CH(OEt)_3$, Propionic acid (cat), 145 ^oC; (iv) (a) 9-BBN, OH^-/H_2O_2; (b) H_2, Pd/C.

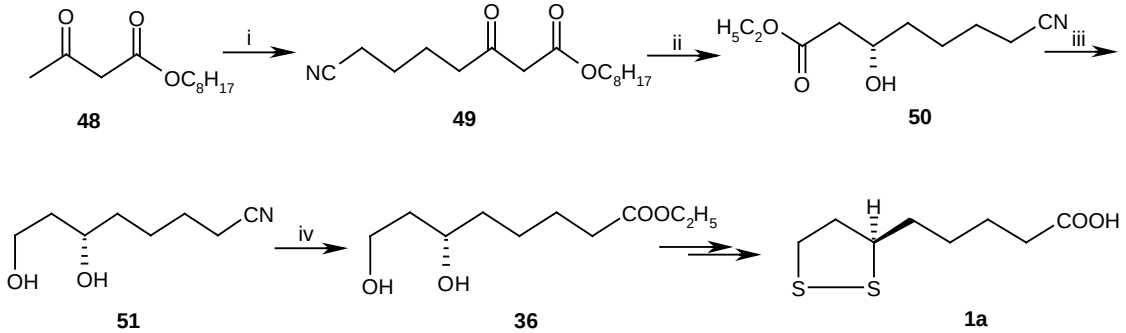
In the fourth synthesis Rama Rao *et al* employed highly regioselective Sharpless allylic oxidation of the olefin **45** with TBHP and SeO_2 to deliver the compound **46a**. Hydroboration, oxidation of olefinic compound **46a** delivered the known diol which by a series of known reactions converted in to (±)-α-lipoic acid.



Scheme 10. *Reagents and conditions:* (i) $Pb(OAc)_4$, $CuSO_4$, Benzene; (ii) TBHP, SeO_2, CH_2Cl_2; (iii) B_2H_6-THF, NaOOH.

Gopalan and Jacobs (1989, Scheme 11)[23]

Gopalan and Jacobs have utilized highly enantio selective yeast reduction of β-keto ester **49** as the key step to deliver the compound **50**. Reduction of ester **50** with $LiBH_4$ in THF at room temperature gave the diol **51**. The diol was converted in to diol ester **36** by using ethanol in presence of acid. By a series of known reactions diol ester **36** was converted in to

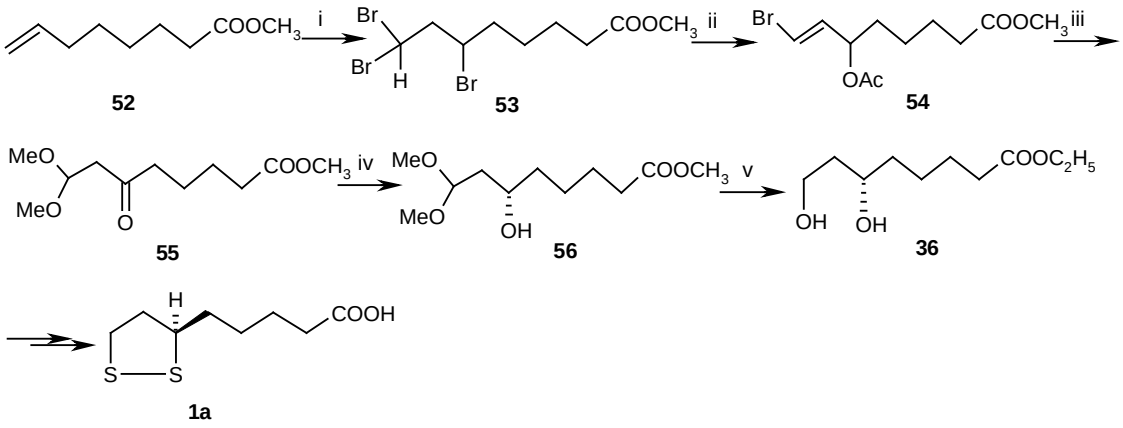


R-(+)-lipoic acid.

Scheme 11. *Reagents and conditions:* (i) (a) NaH, THF, HMPA, 0 ^{o}C; (b) nBuLi, $I(CH_2)_3CN$; (ii) Baker's Yeast (iii) $LiBH_4$, THF, 0 ^{o}C; (iv) EtOH, H^+, Reflux.

Bhalerao *et al* (1990, Scheme 12)[24]

Balerao and co-workers have used copper catalyzed bromoform addition to alkene **52** to give methyl-6, 8, 8-tribromooctonoate **53**, which on treatment with potassium acetate and

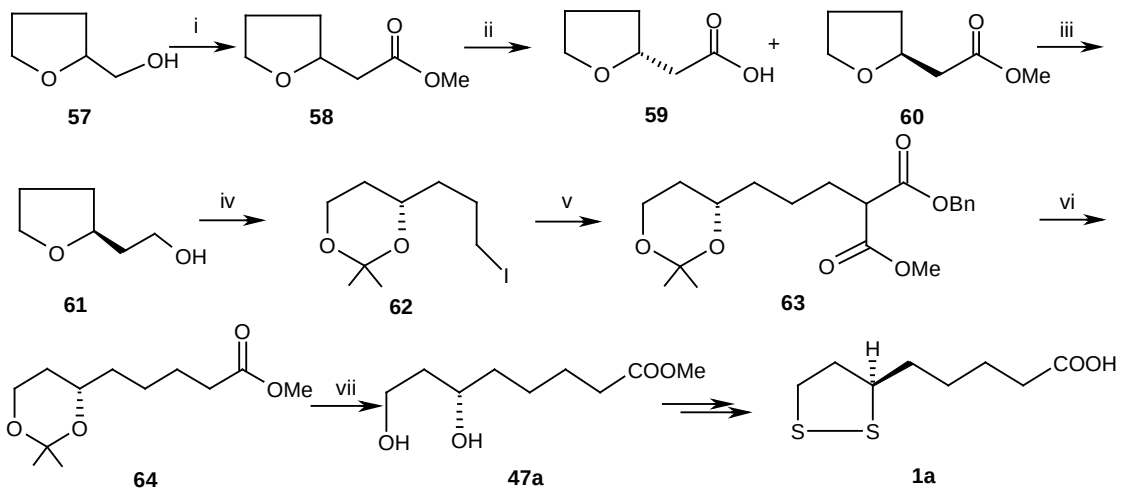


Scheme 12. *Reagents and conditions:* (i) Cu, $CHBr_3$, 80 %; (ii) KOAc, 18-crown-6, DMF; (iii) (a) K_2CO_3, MeOH then PCC, 68 %; (b) Triton B, MeOH; (iv) Baker's Yeast, pH 4.5-5; (v) H_3PO_4, Acetone then $NaBH_4$.

18-crown-6 in DMF gave compound **54**. Hydrolysis, Oxidation followed by treatment with triton-B gave the keto acetal **55**. The keto acetal **55** was reduced enantioselectively by baker's yeast to give compound **56**, which on treatment with H_3PO_4 in acetone followed by $NaBH_4$ reduction resulted in the formation of diol **36**. The diol was converted in to *R*-(+)-lipoic acid in a similar fashion reported earlier.

Iyengar's approach (1996, Scheme 13)[25]

Iyenger and Laxmi have employed selective hydrolysis of methyl 2-(tetrahydro-2-furyl) acetate **58** using lipase as the key step. On lipase hydrolysis, *R*-isomer undergoes hydrolysis but *S*-isomer did not under go hydrolysis. So the *S*-ester was then reduced with $LiAlH_4$ to give the compound **61**. Regioselective opening of **61** with TMSCl, NaI in acetone gave iodo acetonide **62**. Alkylation of **62** with benzyl methyl malonate gave the compound **63**. Compound **63** on debenzylation, decarboxylation followed by hydrolysis in acidic condition furnished the diol ester **47a**. Following the same procedure reported earlier the diol

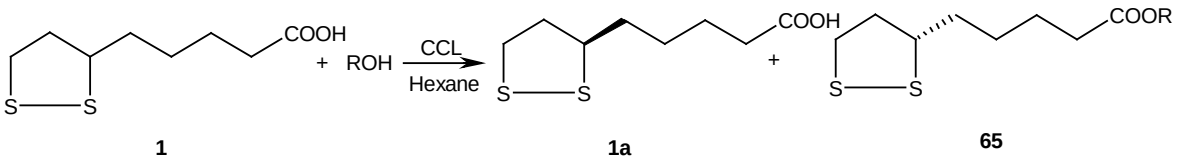


ester was converted to *R*-(+)-lipoic acid.

Scheme 13. *Reagents and conditions:* (i) (a) TsCl, KOH, 93 %; (b) KCN, 74 %; (c) KOH, 93 %; (d) MeOH, H^+; (ii) Liphase/Phosphate buffer (iii) $LiAlH_4$, ether, 84 % (iv) TMSCl, NaI, acetone; (v) Benzyl methyl malonate, NaH, THF, 25 %; (vi) (a) Pd/C, H_2, 98 % (b) 160 ^oC, 95%; (vii) MeOH, H^+, 98 %.

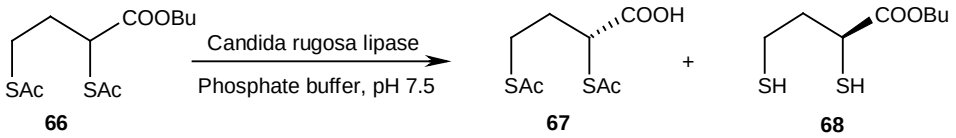
Fadnavis *et al* (1997, Scheme 14),[26a] (1998, Scheme 15)[26b]

Fadnavis and Koteshwar have utilized lipase catalyzed enantioselective esterification of racemic α-lipoic acid to deliver the *R*-(+)-lipoic acid. In presence of lipase of candida rugosa only *S*-isomer is converted to it's corresponding ester.

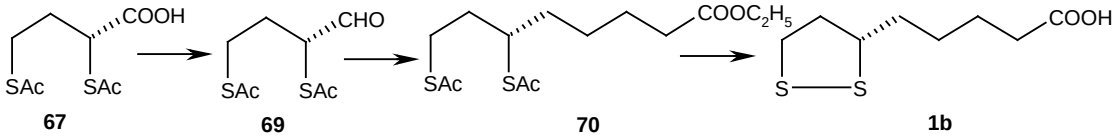


1 **1a** **65**

In an another approach Fadnavis and co-workers have synthesized *R* and *S* isomers of lipoic acid using lipase catalyzed regio and stereospecific hydrolysis of *n*-butyl ester of 2, 4-dithioacetyl butanoic acid **66**. Hydroboration **67** followed by PCC oxidation resulted in the formation of aldehyde **69**. Aldehyde on four carbon Wittig homologation and subsequent hydrogenation with Wilkinson's catalyst gave the ethyl ester **70**. Hydrolysis of **70** with wheatgerm lipase followed by treatment with oxidative enzyme mushroom tyrosinase in the same pot gave *S*-(-)-lipoic acid. Simultaneously *R*-(+)-lipoic acid was obtained in a similar fashion starting with **68**, after acetylation.



66 **67** **68**

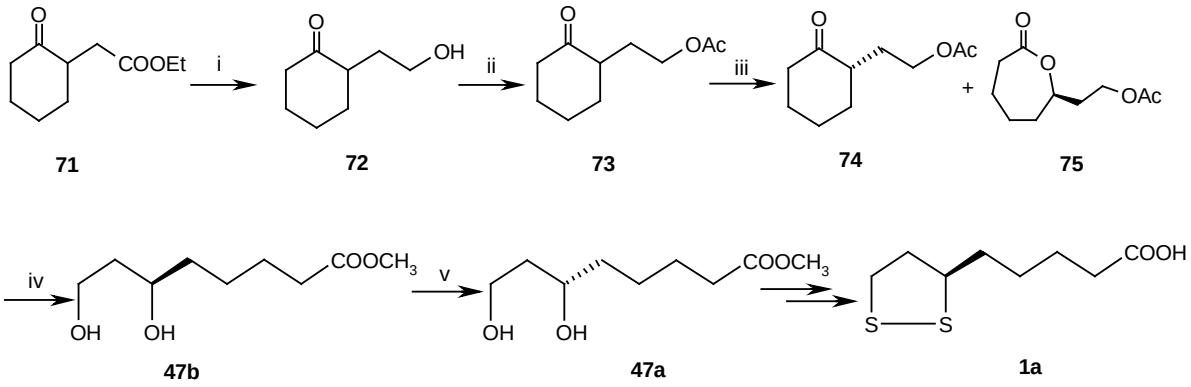


67 **69** **70** **1b**

Scheme 15. *Reagents and conditions:* (i) (a) BH_3.DMS, 0 ^oC; (b) PCC (ii) (a) $Br^-{}^+PPh_3(CH_2)_3COOEt$, NaHMDS, -78 ^oC; (b) $(PPh_3)_3RhCl$, H_2; (iii) (a) Wheatgerm Lipase, pH 7.0; (b) Tyrosinase.

Adger *et al* (1997, Scheme 16)[27]

Adger and co-workers regio and enantioselectively converted 2-(2-acetoxy ethyl) cyclohexanone **73** in to the lactone **75**, using monooxygenase enzyme. The lactone was converted in to diol **47b** using sodium methoxide in methanol. The stereochemistry at C-6 was inverted by using Mitsunobu reaction. Hydrolysis of benzoate ester delivered the known

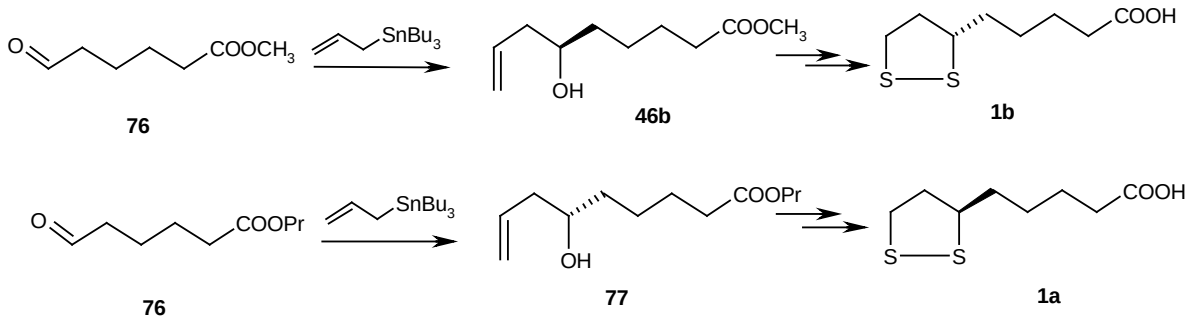


diol ester **47a** which by a series of known reactions was converted in to *R*-(+)-lipoic acid.

Scheme 16. *Reagents and conditions:* (i) (a) Ethylene glycol, *p*-TSA, Toluene; (b) $LiAlH_4$, Ether, 0-25 ^oC; (ii) Ac_2O, Pyridine, DMAP then HCl, MeOH; (iii) 2-Oxo-Δ^3-4, 5, 5-trimethyl cyclopentenyl acetyl-Co A. monooxegenase, NADPH, G-6-P, G-6-PDH; (iv) NaOMe, MeOH; (v) (a) p-$NO_2C_6H_4COOH$, PPh_3, DEAD, THF; (b) K_2CO_3, MeOH.

Zimmer *et al* (2000, Scheme 17)[28]

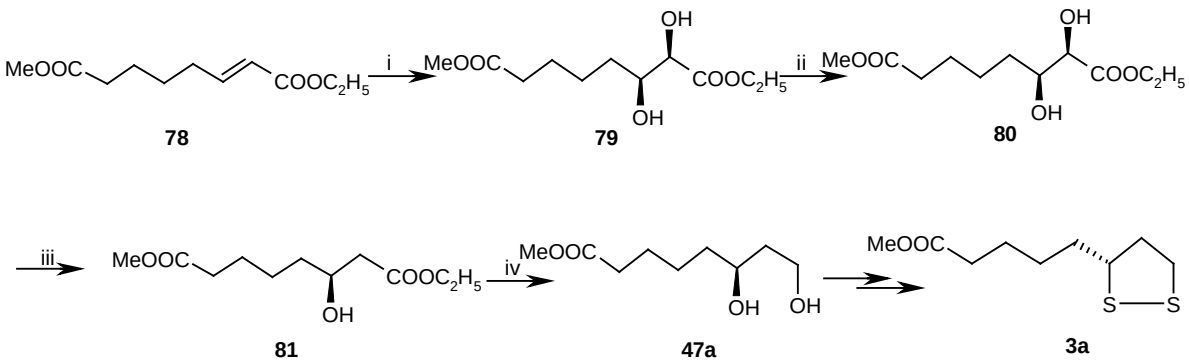
Zimmer and co-workers have employed calalytic asymmetric allyl stannation reaction as the key step to deliver the required stereochemistry. In the presence of 0.2 equivalents of (*S*)-BINOL, 0.2 eq. of $Ti(O^iPr)_4$ and 4 A^o molecular sieves the aldehyde **76** and allyl tributyl stannane provided *R*-alcohol **46b** with 98 % enantiomeric excess. The homoallylic alcohols could be converted in to lipoic acid by known methods.



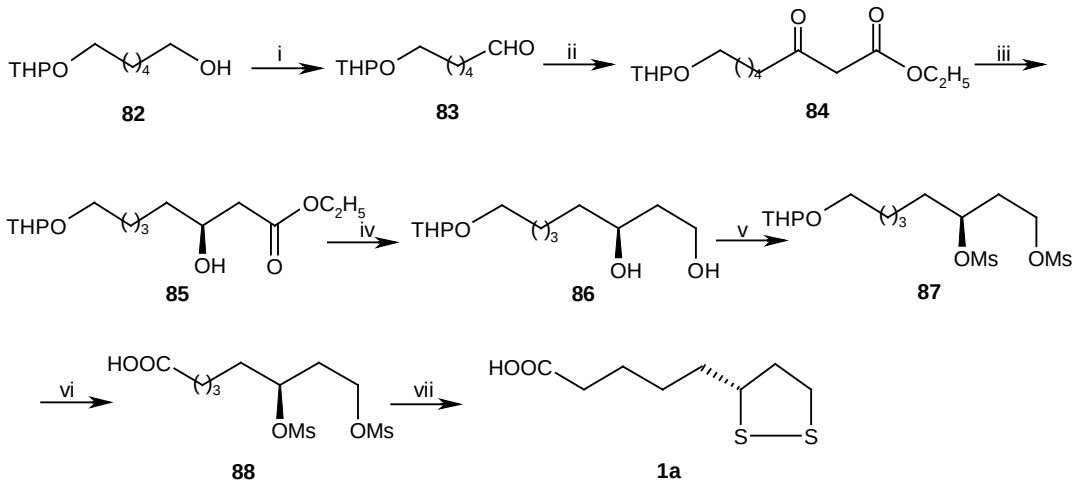
Scheme 17: *Reagents and conditions:* (i) (*S*)-BINOL (0.2 eq), $Ti(OPr^i)_4$ (0.2 eq), CH_2Cl_2, 2 days, 75 %, 98 % ee. (ii) (*R*)-BINOL (0.2 eq), $Ti(OPr^i)_4$ (0.1 eq), CH_2Cl_2, 6 days, 89 %, 98 % ee.

Sudalai *et al* (2001, Scheme 18 &19)[29]

Sudalai and co-workers employed Sharpless asymmetric dihydroxylation and Ruthenium catalyzed asymmetric hydrogenation reactions to get the β-hydroxy esters **81** and **85** respectively. These esters are the precursors for the synthesis of *R*-(+)-lipoic acid.



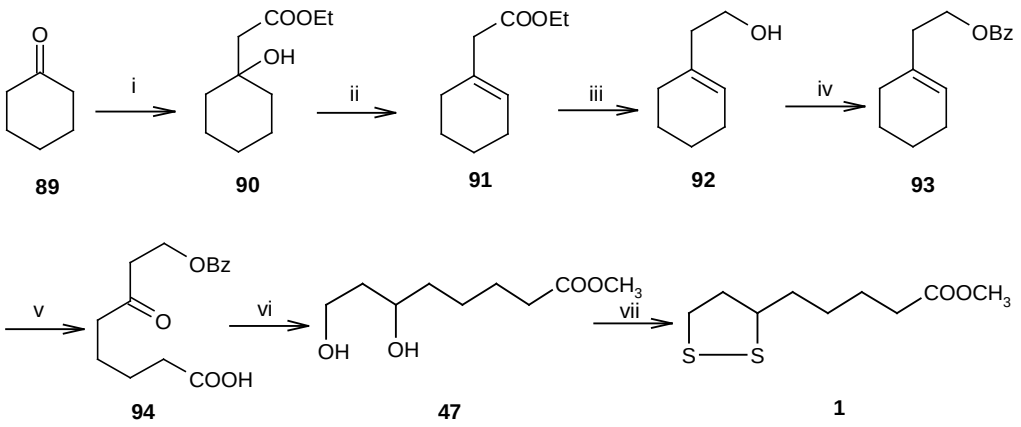
Scheme 18. *Reagents and conditions:* (i) OsO_4, $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, 0 ^oC, 95 %; (ii) (a) $SOCl_2$, Et_3N, CH_2Cl_2, 0 ^oC, 9 h; (b) $RuCl_3$ (cat), $NaIO_4$, 85 %; (iii) $NaBH_4$, DMAC, 20 % H_2SO_4, 63 %; (iv) $NaBH_4$, Et_3N, MeOH;DMF (2:1), AcOH, 0 ^oC, 5h.



Scheme 19. *Reagents and conditions:* (i) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, 75 %; (ii) (a) N_2CHCO_2Et, CH_2Cl_2, $SnCl_2$, 1 h, 85 %; (or) Zn, $BrCH_2CO_2Et$, Benzene, 4 h then PCC, CH_3CO_2Na, CH_2Cl_2, 4 h, 65 %; (iii) H_2 (400 Psi), MeOH, (S)-BINAP-Ru(II), 6h, 90 %; (iv) $NaBH_4$, $CuSO_4$, EtOH, 7h: (v) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 ^oC, 6 h; (vi) *p*-TSA, MeOH, 10 h; (b) PCC, CH_2Cl_2, 3 h and then Ag_2O, NaOH, 1 h, 62 %; (vii) $Na_2S.9H_2O$, DMF, HCl, 28 h, 45 %.

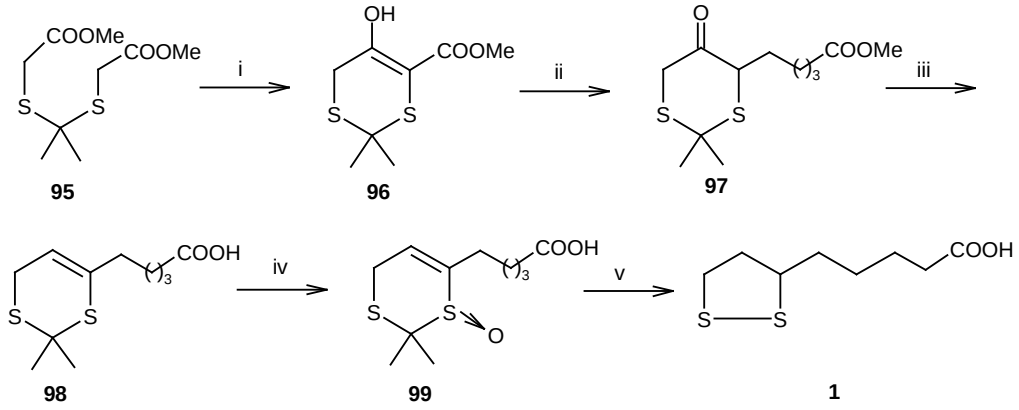
Chavan's synthesis (2005, Schemes 20, 21)[30a, 30b]

*Recently in our group, the synthesis of lipoic acid has been achieved by using modified Reformatsky reaction (**scheme 20**).*[30] *The elimination of the alcohol to furnish selectively the β, γ-unsaturated ester is another feature of this synthesis. Reformatsky reaction with chloroester was carried out on cyclohexanone to furnish alcohol ester **90**, which was then set for elimination using thionyl chloride and pyridine. The β, γ-ester thus obtained was then reduced using DIBAL-H. The alcohol **92** formed, was then protected using benzoyl chloride to give benzoate ester **93**, which was then subjected to ozonolysis followed by Jones oxidation to furnish ketoacid **94**. The reduction of ketoacid **94**, followed by esterification, furnished diol ester **47**. The diol ester **47** was then converted into methyl lipoate by known protocol.*



Scheme 20. *Reagents and conditions:* (i) Zinc, $ClCH_2COOEt$, benzene-ether (1:1), reflux, 65 %; (ii) $SOCl_2$, pyridine, DCM, 86 %; (iii) DIBAL-H, DCM, -78 ^oC, 65 % ; (iv) BzCl, Et_3N, DCM, 92 %; (v) (a) O_3, DCM; (b) Jones reagent, 85 %; (vi) (a) $NaBH_4$, MeOH, 90 %; (b) CH_2N_2, ether; (c) NaOMe, MeOH, 91 %; (vii) (a) $MeSO_2Cl$, Et_3N, (b) Na_2S, S, DMF, 60 % for 2 steps.

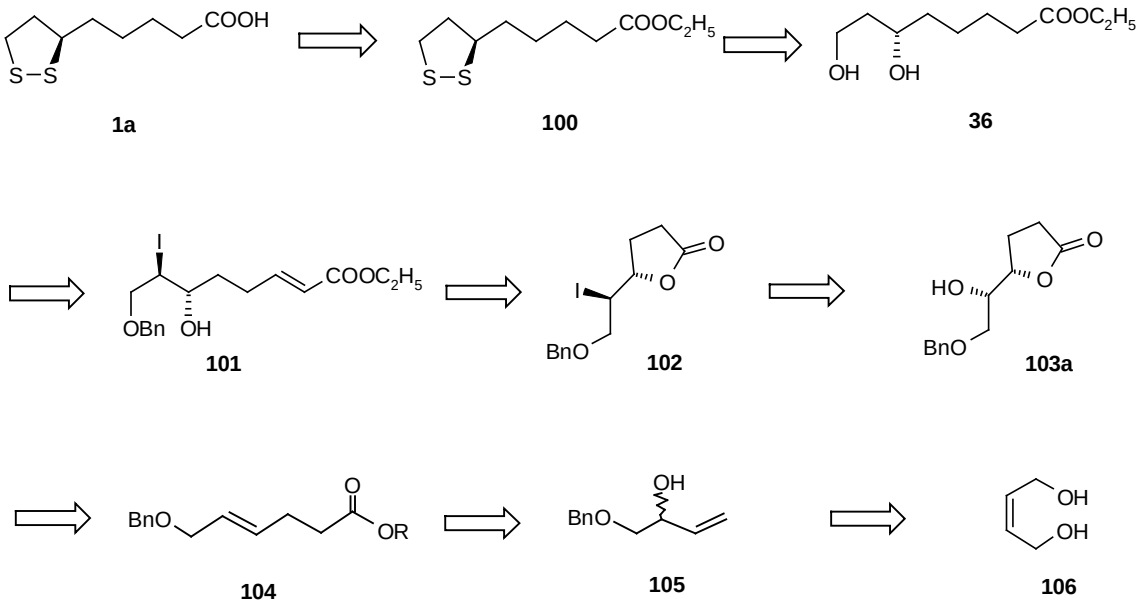
In another approach Chavan *et al* accomplished (±)-lipoic acid synthesis by using diester **95**, which was readily prepared in two steps from thioglycolic acid. Subjection of diester **95** to Dieckmann condensation delivered the β-keto ester **96** which exists in enolic form. Phase transfer catalysed alkylation of **96** followed by decarboxylation gave the ester **97**. The keto ester was converted into olefin acid **98** by treating with tosyl hydrazone followed by refluxing in presence of NaOH. Sequential reduction of double bond, oxidation to mono sulfoxide and final hydrolytic cyclization of **99** afforded (±)-lipoic acid.



Scheme 21. *Reagents and conditions:* (i) NaH, THF, 60 ^{o}C, 3 h, 86 %; (ii) (a) K_2CO_3, $Br(CH_2)_4COOCH_3$, Bu_4NHSO_4, THF, rt; (b) DMSO, NaCl, H_2O, 140 ^{o}C; (iii) (a) $TsNHNH_2$, MeOH, rt, 67 % ; (b) NaOH (2 equiv), ^{i}PrOH, Reflux, 84 %; (iv) (a) Et_3SiH, TFA, 0 ^{o}C, rt, 73 %; (b) $NaIO_4$, MeOH, 0 ^{o}C, 2 h, 68 %; (v) aq. HCl:Benzene (1:1), 50 ^{o}C, 7 h, 69 %.

Present work

The efficient synthesis of complex molecules such as natural and pharmaceutical important products is still a challenge in synthetic organic chemistry. Primarily, the key compounds with a defined constitution and defined stereogenic properties have to be generated. Such intermediates serve as starting materials for further synthetic efforts to produce the desired targets. Our ongoing programme on the synthesis of biologically active compounds and development of novel synthetic methodologies, we found that hydroxy lactone is the valuable synthon for the construction of many challenging synthetic targets.

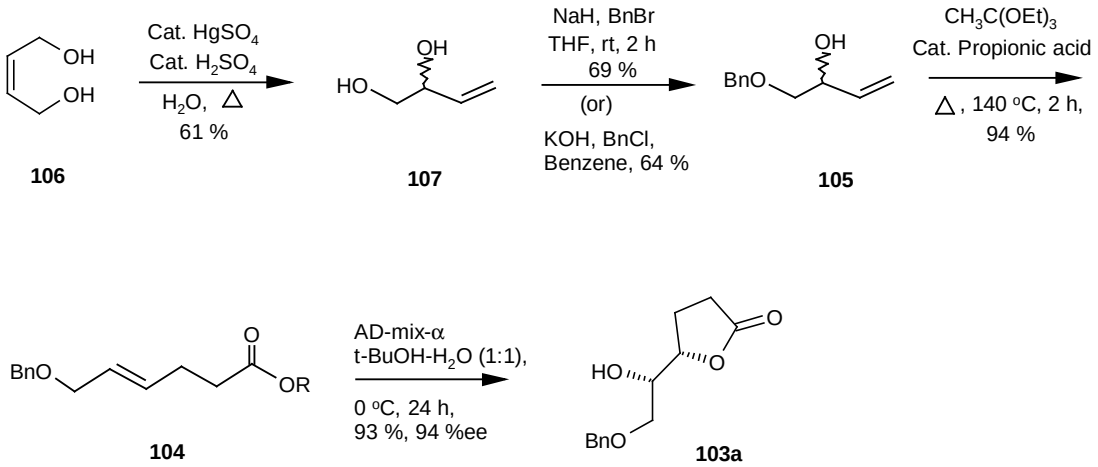


Scheme 22

The retrosynthetic analysis for the enantioselective synthesis of *R*-(+)-lipoic acid is depicted in **Scheme 22**. It was envisaged that a simple basic hydrolysis could be used to form **1a** from the ethyl lipoate **100**, and this in turn should be available from diol ester **36**. The diol ester **36** could be obtained from the iodo lactone, which could be easily prepared in one step from the hydroxy lactone **103a**. The stereocenters of **103a** can be set by Sharpless

Asymmetric Dihydroxylation reaction of β, δ-unsaturated ester **104**. The β, δ-unsaturated ester could be readily obtained from allyl alcohol **105** by a Claisen Orthoester rearrangement, which can be synthesized from *cis*-2-butene-1, 4-diol by a known procedure.

The synthesis starts from *cis*-2-butene-1, 4-diol a relatively in expensive starting material. As shown in **scheme 23**, the commercially available *cis*-2-butene-1, 4-diol **106** was isomerized in to 3-butene-1, 2-diol **107** by refluxing in water in presence of catalytic $HgSO_4$ and conc. H_2SO_4 (cat). Selective mono protection of the primary hydroxyl group as benzyl ether was achieved by using each one equivalent of sodium hydride and benzyl bromide in anhydrous THF. In an another method primary hydroxyl was selectively protected by refluxing 3-butene-1, 2-diol in anhydrous benzene by using 1.1 equivalent of KOH and 1 equivalent of benzyl chloride for 6 hrs. In the ^{1}H-NMR spectrum the peaks corresponds to benzyl group indicates the formation of benzyl protection, and the analysis and IR data are in good agreement with the literature data.

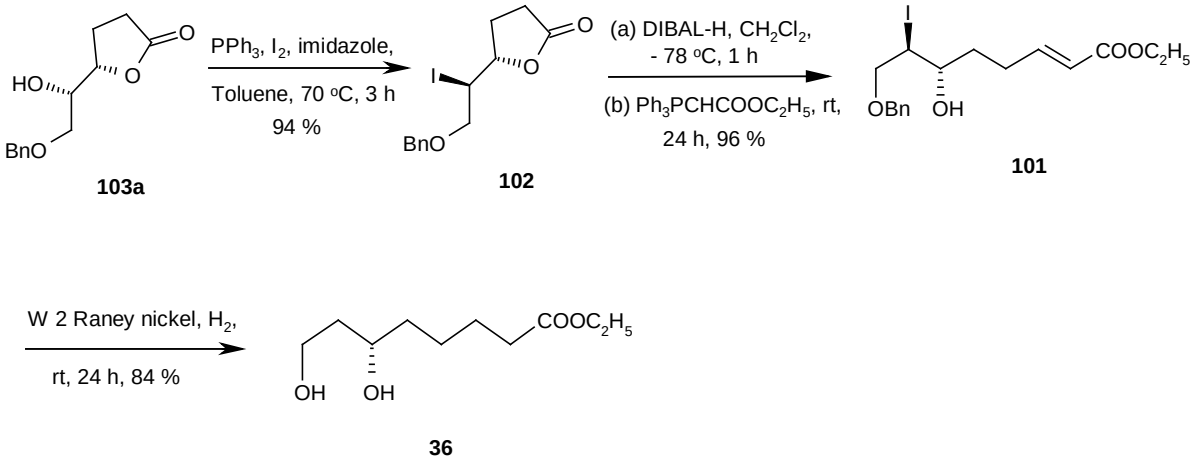


Scheme 23

Monoprotected allyl alcohol **105** was subjected to Johnson-Claisen rearrangement using triethyl orthacetate in the presence of catalytic amount of propionic acid at 140 ^{o}C to afford β, γ-unsaturated ester **104** in 94 % yield. In the IR spectrum sharp peak at 1740 cm^{-1} indicated the formation of ester. In the ^{1}H-NMR spectrum the multiplet at δ 5.8 corresponding

for two protons indicated the presence of internal double bond. In the ^{13}C-NMR spectrum the peak at δ 172.5 confirmed the presence of ester carbonyl and ^{1}H, ^{13}C-NMR, analysis data were in good agreement with the proposed structure.

Having the compound **104**, in hand the next concern was the stereoselective synthesis of hydroxy lactone **103a** with the desired stereochemistry. Thus β, γ-unsaturated ester **104** was subjected to Sharpless asymmetric dihydroxylation using AD-mix α. The IR spectrum of **103a** showed absorption at 3434 cm^{-1}for hydroxyl group and 1778 cm^{-1}for the γ-lactone carbonyl. The ^{1}H-NMR spectrum revealed disappearance of proton signals in the olefinic region and the proton signals corresponding to the ethyl group. This indicated that dihydroxylation and *in situ* cyclization had taken place in one pot. It was further confirmed by the ^{13}C NMR spectrum, which showed the peaks at δ 73.1 and 79.9 and deshielded carbonyl peak at δ 177.7. The enantiopurity of the hydroxylactone was estimated to be in excess of 94 % using chiral HPLC analysis. (Chiralcel OD, 80:20, hexane:^{i}PrOH, 1 mL /min, 254 nm).



103a **102** **101** **36**

Scheme 24

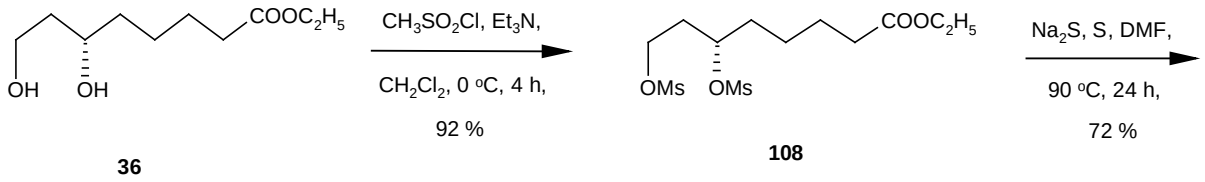
Treatment of the hydroxy lactone **103a** with PPh_3, Iodine and imidazole in anhydrous toluene at 70 ^{o}C for 3 h smoothly delivered the iodolactone **102**. In the IR spectrum hydroxyl

absorption was absent. In the H^1-NMR spectrum the proton signal corresponds to CH-I was deshielded from δ 3.84 in to δ 4.31. In the ^{13}C-NMR spectrum an upfield shift of CH-I carbon from δ 71.9 to δ 34.0 was observed. This clearly indicates the formation of iodolactone and the spectral and elemental analysis data were in good agreement with the proposed structure.

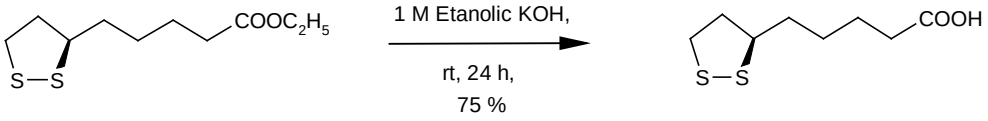
Having accomplished the synthesis of the compound **102**, our next concern was to reduce the lactone to lactal and two-carbon homologation to give the required compound **101**. Accordingly, iodolactone **102** was reduced using DIBAL-H at –78 ^{o}C, followed by *in situ* two-carbon Wittig reaction with ethoxy carbonyl methylene triphenyl phosphorane gave the unsaturated ester **101** in 96 % yield. In the IR spectrum hydroxyl absoption was observed at 3436 cm^{-1}. In the ^{1}H-NMR spectrum signals corresponding to olefinic protons were observed at δ 5.8 and δ 6.96 as doublet of triplets. The high coupling constant values J = 15.65 indicating the presence of trans double bond. Along with the trans compound a small amout of cis olefin, was also observed but since the next step was to reduce the double bond no attempt was made to separate them. The ^{13}C-NMR spectrum revealed the corresponding carbonyl peak at δ 166.1 corresponding to the α, β-unsaturated ester. The spectral data is in good agreement with the proposed structure.

The next immediate concern was the transformation of iodo ester **101** into the corresponding diol ester **36**. Thus removal of the benzyl protection removal of iodine and reduction of the double bond was efficiently achieved in a single step using W2 Raney nickel under an atmosphere of H_2 at room temperature and normal pressure for 24 h delivered the diol ester **36**. The IR spctrum of **36** revealed the presence of a hydroxyl absorption at 3439 $cm^{-1}$and carbonyl absorption at 1735 cm^{-1}. The ^{1}H-NMR spectrum showed the disappearance of benzylic and olefinic protons and the signal corresponds to CH-I was shielded from δ 4.2 to δ 1.6. In the ^{13}C-NMR spectrum disappearance of signals corresponding to benzyl group and olefinic carbons and the appearance of the deshielded carbonyl peak from δ 166.1 to δ 173.7 indicate the formation of the diol ester **36**. ^{1}H-NMR, ^{13}C-NMR, IR and elemental analysis values were in good agreement with the literature data.

The diol **36** is the well known intermediate for the synthesis of *R*-(+)-Lipoic acid and was converted in to the final target molecule by a series of reactions. Accordingly treatment of diol **36** with MsCl and Et_3N in anhydrous CH_2Cl_2 at 0 ^oC provided dimesylate in 92 % yield. The IR spectrum indicates the absence of hydroxyl absorption. In the ^{1}H-NMR



36 **108**



100 **1a**

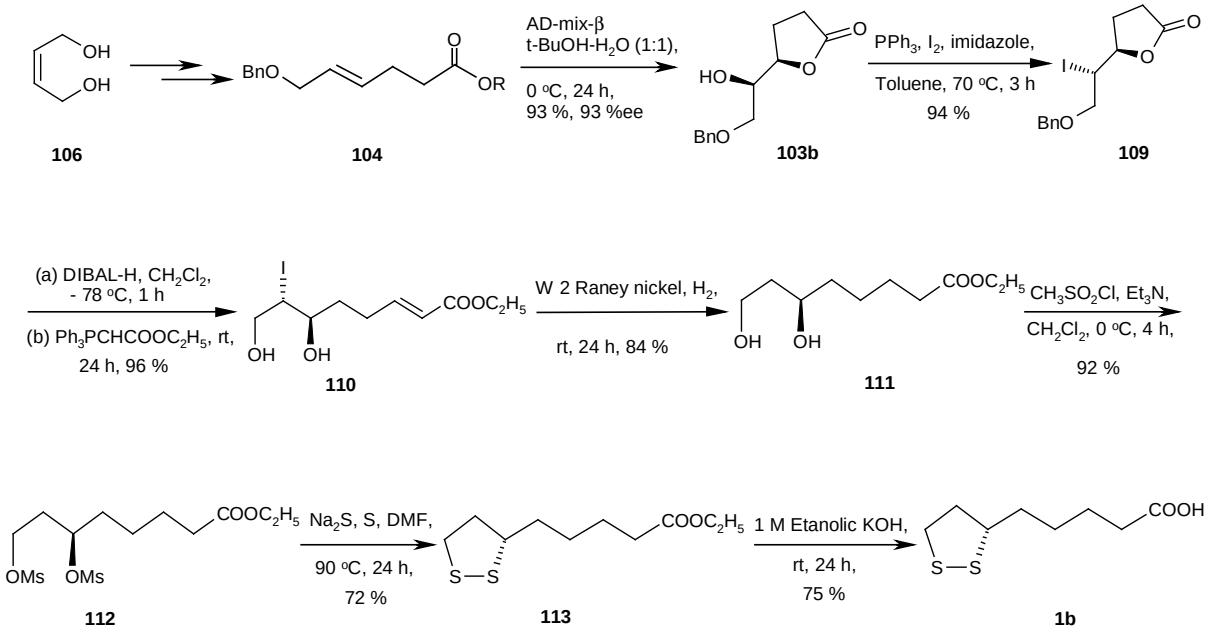
spectrum appearance of two singlets at δ 3.06 and δ 3.07 integrating for 6 protons indicated the formation of dimesylated compound **108**. The structure was further confirmed by ^{13}C-NMR and elemental analysis and all the data were in good agreement with the literature data. The $[\alpha]_D$ + 17.6 (*c* = 1, $CHCl_3$) obtained for **108** was in accordance with the reported value. $[\alpha]_D$ + 17.6 (*c* = 1, $CHCl_3$)[22a]

Scheme 25

The dimesylate **108** on reaction with sodiun sulfide nonahydrate and sulfur in anhydrous DMF at 90 ^oC for 24 h afforded ethyl lipoate **100** in 72 % yield. The ^{1}H-NMR spectrum indicated the presence of signals at δ 3.11 (m) and δ 3.54 (m) for H-8, 8[1] and H-6 respectively. The upfield shift of the signals for these protons was expected because of shielding effect of sulfur atom. In the ^{13}C-NMR spectrum disappearance of signals corresponding to mesyl groups indicated the formation of ethyl lipoate **100**. The observed data was in good agreement with the literature data. $[\alpha]_D$ + 64.7 (*c* = 0.5, $CHCl_3$) obtained for **101** is in accordance with the reported value. $[\alpha]_D$ + 61 (*c* = 0.3, $CHCl_3$) [22a]

Finally hydrolysis of ethyl lipoate **100** with 1 M KOH solution in ethanol at room temperature for 24 h afforded *R*-(+)-lipoic acid in 75 % yield. In the ^{1}H-NMR spectrum disappearance of signals corresponding to ethyl group indicated the formation of hydrolyzed product. This was further confirmed by ^{13}C-NMR and elemental analysis. The synthetic lipoic acid thus obtained showed the rotation $[\alpha]_D$ +106.29 (c=1, benzene) which was in good agreement with the literature data. $[\alpha]_D$ + 104 (*c* = 0.88, benzene)[1]

In a similar way we prepared the unnatural antipode *S*-(α)-lipoic acid was also prepared which shows an optical rotation $[\alpha]_D$ - 102 (c = 0.9, benzene). The same sequence of reactions was followed for the synthesis of *S* isomer except the use of AD-mix-β in place of AD-mix-α in the crucial Dihydroxylation reaction, which fixes the stereochemistry of the resultant compound. (**Scheme 26**). The spectral data were the same as described for *R*-(+)-lipoic acid.



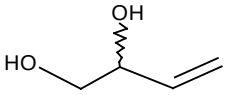
Scheme 26

Conclusion:

In summary both *R*-(+)-α and *S*-(-)-α-lipoic acid were synthesized efficiently from the readily available starting material. Sharpless asymmetric dihydroxylation and Claisen orthoester rearrangement were used as the key steps. The synthetic strategy employed has significant potential for further extension to the synthesis of many other biologically active compounds.

Experimental:

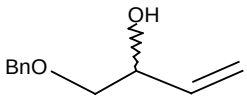
i) (±)-3-Butene-1, 2-diol (107)



Procedure: A mixture of 2-butene-1, 4-diol **106** (80 g, 90.9 mmol), water (35 mL), catalytic amount of concentrated sulphuric acid (0.5 mL) and mercuric sulphate (0.36 g) was heated under reflux. After 1.5 h the reaction mixture was cooled to 0 ^{o}C and neutralized with 10 % sodium hydroxide to pH 7. The contents of the flask were distilled by using a 12' vigreaux fractionating column. The first fraction boiled between 38-43 ^{o}C/15 mm contained water, second fraction collected between 78-90 ^{o}C/15 mm contained 3-butene-1, 2-diol **107** (49 g, 61 %) as a colourless syrup and subsequently, third fraction obtained had traces of unreacted starting material at 110-115 ^{o}C/15mm.

Appearance	:	Colourless syrup
Yield	:	61 %

Molecular Formula	:	$C_4H_8O_2$
B.P	:	85 ^oC /15 mm
IR ($CHCl_3$, cm^{-1})	:	3456, 1621
^1H NMR ($CDCl_3$, 200MHz)	:	δ 3.45 (dd, *J* = 10.56, 7.71 Hz, 1H), 3.63 (dd, *J* = 11.49, 3.28 Hz, 1H), 3.94 (s, 2H, OH), 4.22 (m, 1H), 5.18 (dt, *J* = 10.56, 1.52 Hz, 1H), 5.32 (dt, *J* = 17.31, 1.52 Hz, 1H), 5.81 (ddd, *J* = 17.31, 10.56, 5.56 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50MHz)	:	δ 66.0, 73.2, 116.3, 136.6.
Elemental analysis	:	Analysis calcd. for $C_4H_8O_2$: C, 54.52; H, 9.15. Found: C, 54.34; H, 9.42.



ii) (±)-1-Benzyloxy-3-butene-2-diol (105)

To a solution of **107** (6 g, 68.18 mmol) in anhydrous THF (100 mL) was added sodium hydride (3.27 g, 68.18 mmol, 50 % dispersion in oil) under nitrogen atmosphere. The reaction mixture was cooled to –20 ^oC and then benzyl bromide (11.68 g, 68.18 mol) in anhydrous THF (50 mL) was added dropwise for 30 min at the same temperature. After stirring at room temperature for 5 h, the reaction mixture was concentrated, diluted with CH_2Cl_2, washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue thus obtained was purified by silica gel column chromatography with EtOAc-light petroleum (1:2) as an eluent to afford **105** (8.4 g, 69 %) as colourless syrup.

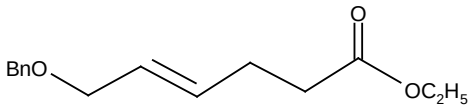
(or)

To a solution of **107** (5 g, 56.8 mmol) in anhydrous benzene (100 mL) were added KOH (3.5 g, 62.5 mmol) and benzyl chloride (6.5 mL, 56.8 mmol) and the reaction mixture was heated under reflux for 6 h. After completion of the reaction, the reaction mixture was diluted with water, extracted with EtOAc (2 x 60 mL) and the combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure.

The residue was chromatographed on silicagel using EtOAc-light petroleum (1: 2) as an eluent to afford **105** (6.47 g, 64 %) as colourless syrup.

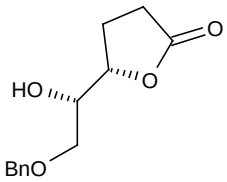
Appearance	:	Colourless syrup
Molecular Formula	:	$C_{11}H_{14}O_2$
Yield	:	69 %.
IR ($CHCl_3$, cm^{-1})	:	3450, 2400, 1731, 757.
^1H NMR ($CDCl_3$, 200MHz)	:	δ 2.55 (broad, 1H, OH), 3.37 (dd, *J* = 9.86, 7.71 Hz, 1H), 3.55 (dd, *J* = 9.86, 3.42 Hz, 1H), 4.35 (m, 1H), 4.58 (s, 2H), 5.20 (dt, *J* = 10.26, 1.47 Hz, 1H), 5.37 (dt, *J* = 17.09, 1.47 Hz, 1H), 5.84 (ddd, *J* = 17.09, 10.26, 5.86 Hz, 1H), 7.20-7.31 (m, 5H).
^{13}C NMR ($CDCl_3$, 50MHz)	:	δ 71.0, 72.9, 73.9, 115.6, 127.4, 128.1, 136.8, 137.6.
Elemental analysis	:	Analysis calcd. for $C_{11}H_{14}O_2$: C, 74.12; H, 7.92. Found: C, 74.36; H, 7.73.

iii) (4*E*)-Ethyl-6-Benzyloxy hexanoate (104)



Procedure: A mixture of compound **105** (3.5 g, 19.66 mmol), Propionic acid (cat) and triethyl orthoacetate (6.37 g, 39.32 mmol) was heated at 140 ^oC for 2 h with distillate removal of ethanol. After completion of the reaction the reaction mixture was quenched with water and extracted with CH_2Cl_2 (2 x 50 mL) and the combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel using EtOAc-light petroleum (1:10) as an eluent to afford **104** (4.57 g, 94 %) as colourless syrup.

Appearance	:	Colourless syrup
Molecular Formula	:	$C_{15}H_{20}O_3$
Yield	:	94 %.
IR ($CHCl_3$, cm^{-1})	:	2995, 1740, 1180, 965
^1H NMR ($CDCl_3$, 500MHz)	:	1.26 (t, *J* = 7.18, 3H), 2.40 (s, 4H), 3.97 (d, *J* = 5.66, 2H), 4.13 (q, *J* = 7.18, 2H), 4.49 (s, 2H), 5.66-5.71 (m, 2H), 7.32-7.35 (m, 5H).
^{13}C NMR ($CDCl_3$, 50MHz)	:	δ 14.1, 27.4, 33.6, 59.9, 70.3, 71.7, 127.5, 128.1, 131.8, 138.3, 172.3.
MS (ESI, Solv.: MeOH + H_2O + CH_3COONH_4)	:	m/z = 266.04 ($M+NH_4^+$).
Elemental Analysis	:	Analysis calcd. for $C_{15}H_{20}O_3$: C, 72.54; H, 8.12. Found: C, 72.38; H, 8.24.



iv) 6-(Benzyloxy)-2,3-dideoxy-L-threo-hexano-1,4-lactone (103a)

To a mixture of $K_3Fe(CN)_6$ (11.94 g, 36.29 mmol), K_2CO_3 (5.01 g, 36.29 mmol) and $(DHQ)_2PHAL$ (0.094 g, 0.12 mmol) in t-BuOH-H_2O (1:1, 120 mL) cooled at 0 ^oC was added osmium tetroxide (0.81 mL, 0.1 M solution in toluene, 0.4 mol %) followed by methane sulfonamide (1.15 g, 12.09 mmol). After stirring for 5 min at 0 ^oC, the olefin **104** (3 g, 12.09 mmol) was added in one portion. The reaction mixture was stirred at 0 ^oC for 24 h and then quenched with solid sodium sulfite (6 g). The stirring was continued for an additional 45 min and then the solution was extracted with EtOAc (3 x 30 mL). The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under

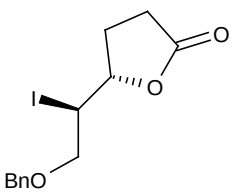
reduced pressure. The residue was chromatographed on silica gel using EtOAc-light petroleum (1:2) as an eluent to afford **103 a** (2.68 g, 94 %) as a white solid.

(or)

To a solution of AD-mix α (16.93 g) in t-BuOH-H_2O (1:1, 120 mL) at 0 ^oC was added methane sulfonamide (1.15 g, 12.09 mmol) and stirred at the same temperature. After stirring for 5 min, the olefin **104** (3 g, 12.09 mmol) was added in one portion. The reaction mixture was stirred at 0 ^oC for 24 h and then quenched with solid sodium sulfite (6 g). The stirring was continued for an additional 45 min and then the solution was extracted with EtOAc (3 x 30 mL). The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel using EtOAc-light petroleum (1:2) as an eluent to afford **103a** (2.68 g, 94 %) as a white solid.

Appearance	:	White solid
Molecular Formula	:	$C_{13}H_{16}O_4$
Yield	:	94 %.
M. P.	:	115-116 ^oC (White solid).
$[\alpha]_D$	:	+ 40.59 (*c* = 1, $CHCl_3$)
IR ($CHCl_3$, cm^{-1})	:	3434, 1778, 1720, 1216, 758.
^1H NMR ($CDCl_3$, 200MHz)	:	δ 2.25 (m, 2H), 2.48 (m, 2H), 2.69 (m, 1H), 3.59 (m, 2H), 3.84 (m, 1H), 4.57 (m, 3H), 7.33-7.43 (m, 5H).
^{13}C NMR ($CDCl_3$, 125MHz)	:	δ 23.4, 28.1, 70.6, 71.6, 73.1, 79.9, 127.5, 128.1, 137.5, 177.7.
MS (ESI, Solv.: MeOH + H_2O + CH_3COONH_4)	:	m/z = 254.05 ($M+NH_4^+$).
Elemental Analysis	:	Analysis calcd. for $C_{13}H_{16}O_4$: C, 66.13; H, 6.83. Found: C, 66.36; H, 6.92.

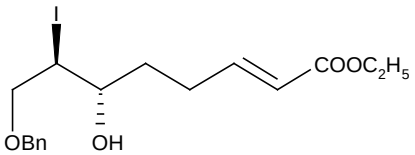
v) 5-Iodo-6-(Benzyloxy)-2,3,5-trideoxy-D-*erythro*-hexano-1,4-lactone (102)



A mixture of **103a** (2.5 g, 10.59 mmol), PPh_3 (5.55 g, 21.18 mmol), imidazole (0.72 g, 10.59 mmol) and I_2 (5.37 g, 21.18 mmol) was stirred under nitrogen in anhydrous toluene (40 mL) at 70 ^oC for 3 h. After completion of the reaction (TLC) the reaction mixture was diluted with EtOAc, washed with 20% aq. $Na_2S_2O_3$ solution, water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified on silica gel by eluting with light petroleum: EtOAc (4:1) to afford **102** (3.44 g, 94 %) as colourless syrup.

Appearance	:	Colourless syrup
Molecular Formula	:	$C_{13}H_{15}O_3I$
Yield	:	94 %.
IR ($CHCl_3$, cm^{-1})	:	3020, 2400, 1731, 757.
$[\alpha]_D$	:	- 19.77 (*c* = 1, $CHCl_3$)
^1H NMR ($CDCl_3$, 200MHz)	:	δ 2.04 (m, 1H), 2.42 (m, 1H), 2.49 (m, 2H), 3.72 (dd, *J* = 10.56 Hz, 5.87 Hz, 1H), 3.83 (dd, *J* = 10.56 Hz, 5.08 Hz, 1H), 4.31 (m 1H), 4.55 (m, 3H), 7.32 (m, 5H).
^{13}C NMR ($CDCl_3$, 50MHz)	:	δ 27.6, 28.4, 34.0, 71.4, 72.9, 78.8, 127.4, 128.2, 137.3, 175.7.
Elemental Analysis	:	Analysis calcd. for $C_{13}H_{15}O_3I$: C, 45.10; H, 4.37; I, 36.66. Found: C, 45.28; H, 4.40; I, 36.42.

vi) Ethyl (6S, 7R)-7-iodo-6,8-dihydroxy oct-2-enoate (101).

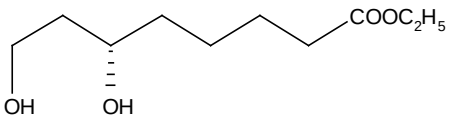


To a solution of **102** (2.0 g, 5.78 mmol) in anhydrous CH_2Cl_2 (25 mL) was added 1.6 M DIBAL-H solution in toluene (4.3 mL, 8.09 mmol) at –78 ^oC . After stirring for 1 h at –78 ^oC absolute MeOH (4.3 mL) was added to the reaction mixture and was allowed to attain the room temperature. To the above reaction mixture was added ethyl triphenyl phosphoranylidene acetate (4.02 g, 11.56 mmol) in anhydrous CH_2Cl_2 at room temperature

and stirred for 16 h at the same temperature. The reaction mixture was diluted with water, extracted with EtOAc (2 x 30 mL) and the combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc-light petroleum (1:4) as an eluent to afford **101** (2.3 g, 96 %) as colourless oil.

Molecular Formula	:	$C_{17}H_{23}O_4I$
Yield	:	96 %.
B. P.	:	Colourless liquid
IR ($CHCl_3$, cm^{-1})	:	3406, 1724, 1654.
$[\alpha]_D$	:	- 24.67 (c = 1, $CHCl_3$)
^1H NMR ($CDCl_3$ + CCl_4, 200MHz)	:	δ 1.29 (t, *J* = 7.05 Hz, 3H), 1.70 (m, 1H), 1.90 (m, 1H), 2.38 (m, 2H), 2.97 (broad, 1H), 3.65-3.91 (m, 3H), 4.20 (m, 3H), 4.56 (s, 2H), 5.8 (dt, *J* = 15.65, 1.57 Hz, 1H), 6.96 (dt, *J* = 15.65, 6.65 Hz, 1H), 7.32 (m, 5H).
^{13}C NMR ($CDCl_3$+CCl_4, 50MHz)	:	δ 14.1, 28.0, 33.9, 37.8, 59.8, 72.5, 72.9, 73.2, 121.5, 127.5, 127.4, 128.3, 137.0, 148.1, 166.1.
Elemental Analysis	:	Analysis calcd. for $C_{17}H_{23}O_4I$: C, 48.81; H, 5.54; I, 30.39. Found: C, 48.62; H, 5.74; I, 30.12.

vii) Ethyl (*S*)-6, 8-dihydroxy octanoate (36)

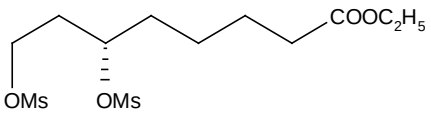


To a solution of **101** (0.92 g, 2.20 mmol) in adsolute ethanol (15 mL) was added W2 Raney nickel (2.5 g) and the mixture was flushed with H_2 for 5 min. After stirring under an atmosphere of hydrogen at room temperature for 24 h, the reaction mixture was filtered through a pad of celite and the solvent was concentrated under reduced pressure. The residue

was purified by silica gel column chromatography using EtOAc-light petroleum (2:1) as an eluent to afford diol **36** (0.37 g, 84 %) as colourless syrup.

Appearance	:	Colourless syrup
Molecular Formula	:	$C_{10}H_{20}O_4$
Yield	:	87 %.
IR ($CHCl_3$, cm^{-1})	:	3378, 2950, 2868
^1H NMR ($CDCl_3$, 200MHz)	:	δ 1.23 (t, *J* = 7.32 Hz, 3H), 1.28-1.40 (m, 6H), 1.56-1.64 (m, 2H), 2.26 (t, *J* = 7.32 Hz, 2H), 3.36 (m, 1H), 3.58-3.65 (m, 4H), 4.08 (q, *J* = 7.32, 2H).
^{13}C NMR ($CDCl_3$, 50MHz)		14.2, 24.8, 25.2, 29.1, 32.9, 34.2, 60.1, 66.7, 72.1, 173.7.
Elemental Analysis	:	Analysis calcd. for $C_{10}H_{20}O_4I$: C, 58.79; H, 9.87. Found: C, 58.53; H, 9.72.

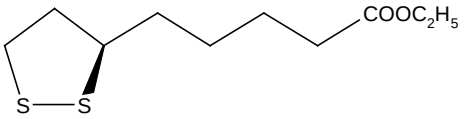
viii) **Ethyl (*S*)-6, 8-dimesyloxy octanoate (108)**



To a solution of the diol **36** (0.35 g, 1.71 mmol) in anhydrous CH_2Cl_2 (12 mL) were added Et_3N (1.19 mL, 8.57 mmol), MsCl (0.30 mL, 3.94 mmol) at 0 ^oC and stirred for 4 h at the same temperature. The reaction mixture was poured into aqueous sodium hydrogen carbonate and extracted with CH_2Cl_2 (2 x 15 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude oily compound was purified by silica gel column chromatography using EtOAc-light petroleum (2:3) as an eluent to afford 6, 8 dimesylate **108** (0.57 g, 92 %) as colourless syrup.

Appearance	:	Lighht yellow oil
Molecular Formula	:	$C_{12}H_{24}O_8S_2$
Yield	:	92 %.
IR ($CHCl_3$, cm^{-1})	:	3030, 1735, 1170.
$[\alpha]_D$		+ 17.6 (*c* = 1, $CHCl_3$)
^1H NMR	:	δ 1.24 (t, *J* = 7.33 Hz, 3H), 1.33-1.49 (m, 4H), 1.60-1.76
($CDCl_3$ + CCl_4, 200MHz)		(m, 4H), 2.28 (t, *J* = 7.33, 2H), 3.06 (s, 3H), 3.07 (s, 3H), 4.10 (q, *J* = 7.33 Hz, 2H), 4.24 (dd, *J* = 11.72, 5.86 Hz, 1H), 4.37 (dd, *J* = 10.99, 2.93 Hz, 1H), 4.80-4.86 (m, 1H).
^{13}C NMR	:	δ 14.3, 24.4, 24.5, 28.5, 30.9, 31.4, 34.0, 37.7, 38.7, 60.1,
($CDCl_3$+CCl_4, 50MHz)		69.4, 78.8, 173.2.
Elemental Analysis	:	Analysis calcd. for $C_{12}H_{24}O_8S_2$: C, 39.98; H, 6.71; S, 17.79. Found: C, 39.74; H, 6.82; S, 17.56.

ix) Ethyl R-(+)-Lipoate or [Ethyl (5R)-5-(1,2-dithiolan-3yl) Pentanoate] (100)

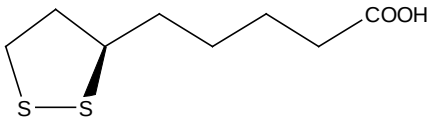


A mixture of dimesylate **108** (0.56 g, 1.55 mmol), finely powdered sodium sulfide nonahydrate (0.41 g, 1.78 mmol) and sulfur (0.05 g , 1.78 mmol) in anhydrous DMF (5 mL) were heated at 85-90 ^oC for 24 h. The reaction mixture was diluted with cold water, extracted with EtOAc (2 x 20 mL) and the combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc-light petroleum (2:8) as an eluent to afford **100** (0.26 g, 72 %) as light yellow oil.

Appearance	:	Light yellow oil
Molecular Formula	:	$C_{10}H_{18}O_2S_2$
Yield	:	87 %.
IR ($CHCl_3$, cm^{-1})	:	3020, 2400, 1731, 757.

$[\alpha]_D$	:	+ 64.7 (*c* = 0.5, $CHCl_3$)
^1H NMR ($CDCl_3$ + CCl_4, 200MHz)	:	δ 1.25 (t, *J* = 7.34 Hz, 3H), 1.42-1.72 (m, 6H), 1.87 (m, 1H), 2.29 (t, *J* = 7.34 Hz, 2H), 2.44 (m, 1H), 3.11 (m, 2H), 3.54 (m, 1H), 4.13 (q, *J* = 7.34 Hz, 2H).
^{13}C NMR ($CDCl_3$+CCl_4, 50MHz)	:	δ 14.3, 24.6, 28.7, 34.0, 34.6, 38.4, 40.1, 56.2, 60.1, 173.1
Elemental Analysis	:	Analysis calcd. for $C_{10}H_{18}O_2S_2$: C, 51.24; H, 7.74; S, 27.36. Found: C, 51.43; H, 7.52; S, 27.14.

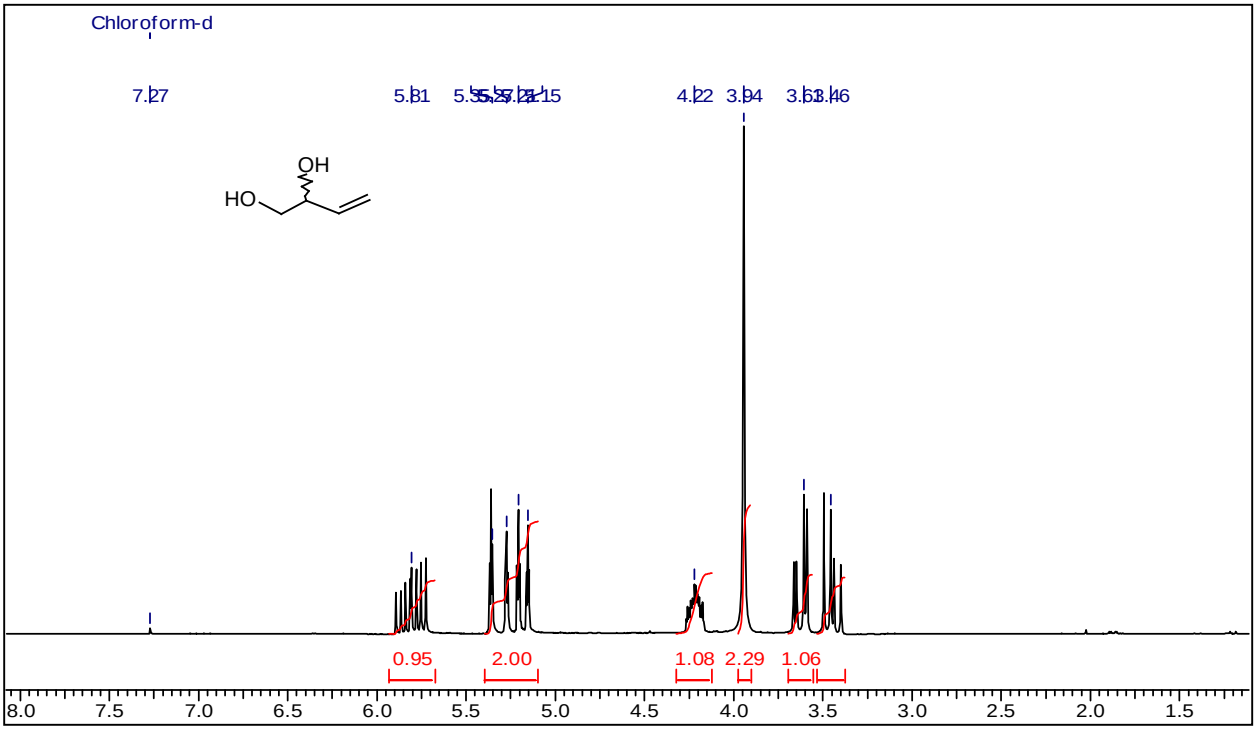
R-(+)-Lipoic acid or [(5R)-5-(1,2-dithiolan-3yl) Pentanoic acid] (1a).



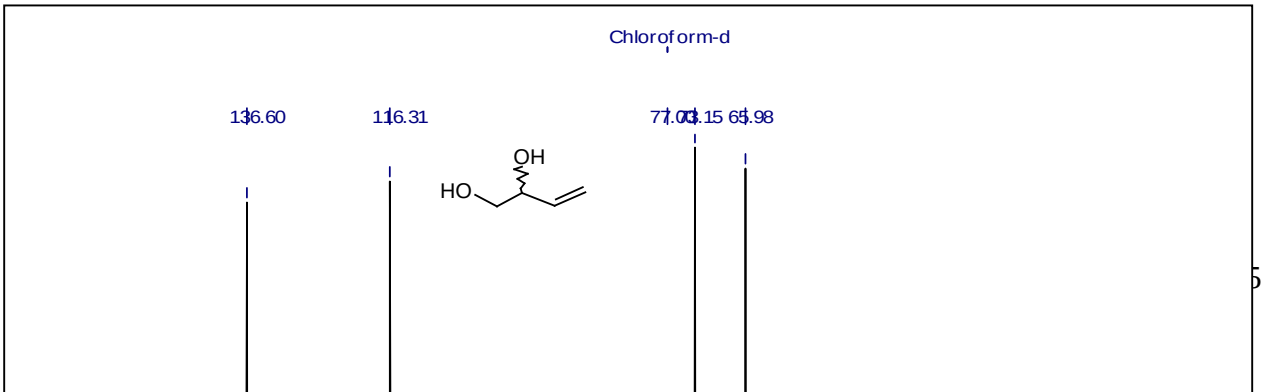
To a solution of **100** (0.25 g, 1.06 mol) in absolute ethanol (7 mL) was added 0.1 M ethanolic KOH (8 mL) in the dark and under nitrogen atmosphere. After stirring for 24 h, ethanol was evaporated and the aqueous solution was washed with light petroleum to remove the impurities. The aqueous layer was acidified to pH 1 by the addition of 2 N HCl and then extracted with ether (3 x 12 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography using EtOAc-light petroleum (1:2) as an eluent to afford lipoic acid **1a** (0.26 g, 72 %) as a,light yellow residue.

Appearance	:	Light yellow residue
Molecular Formula	:	$C_8H_{14}O_2S_2$
Yield	:	75 %.
M. P.	:	48 ^oC

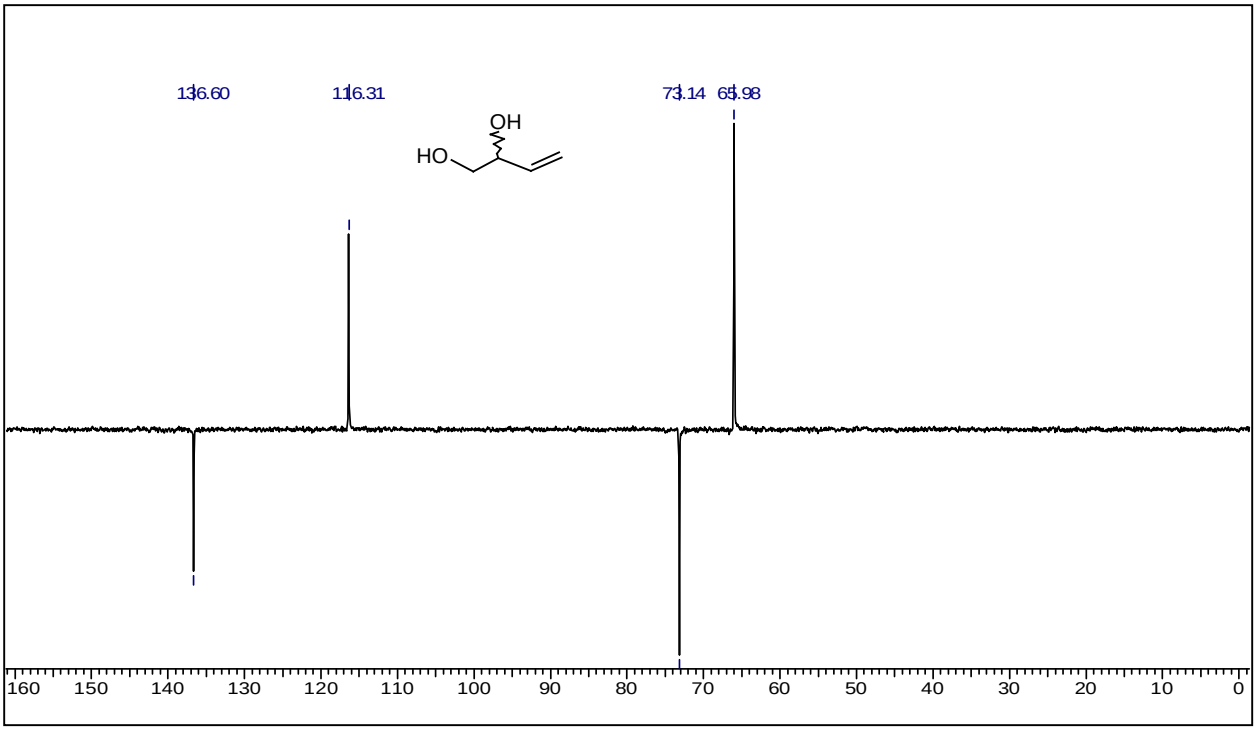
IR ($CHCl_3$, cm^{-1})	:	3018, 2934, 1701.
$[\alpha]_D$	:	+ 106.29 (*c* 1, Benzene)
^1H NMR ($CDCl_3$ + CCl_4, 200MHz)	:	δ 1.52-1.62 (m, 2H), 1.68-1.76 (m, 4H), 1.91 (m, 1H), 2.37 (t, *J* = 7.05 Hz, 2H), 2.63 (m, 1H), 3.18 (m, 2H), 3.55 (m, 1H).
^{13}C NMR ($CDCl_3$+CCl_4, 50MHz)	:	δ 24.4, 28.7, 33.9, 34.7, 38.5, 40.2, 56.2, 179.8
Elemental Analysis	:	Analysis calcd. for $C_8H_{14}O_2S_2$: C, 46.56; H, 6.84; S, 31.08. Found: C, 46.72; H, 6.91; S, 30.23.



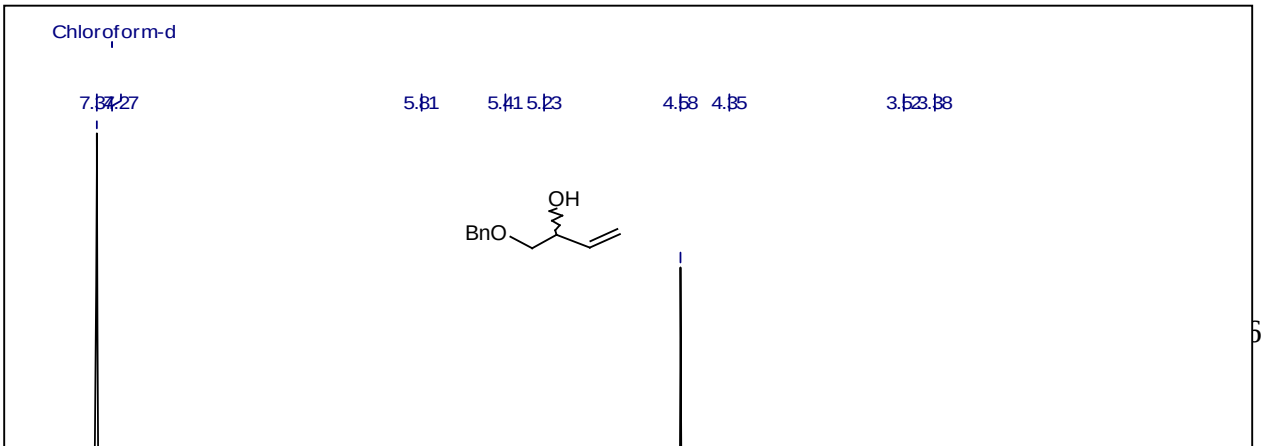
^1H NMR Spectrum of compound 107 in $CDCl_3$



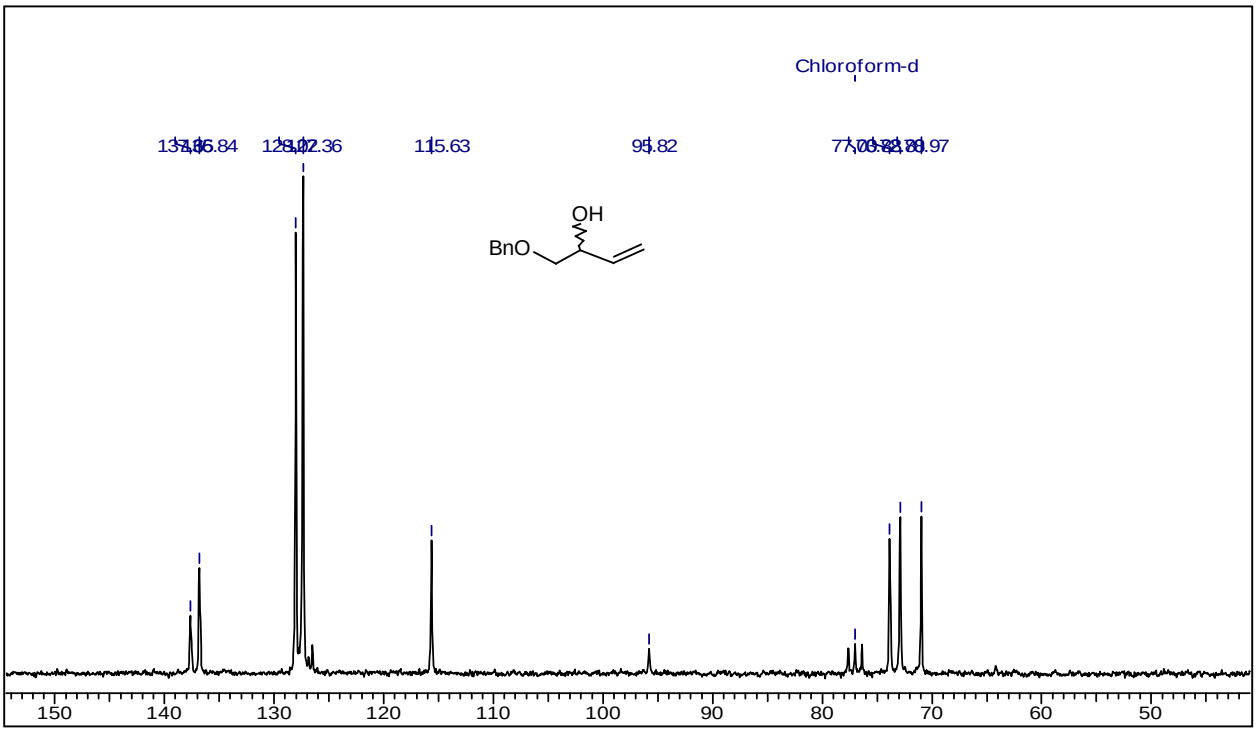
^{13}C NMR Spectrum of compound 107 in $CDCl_3$



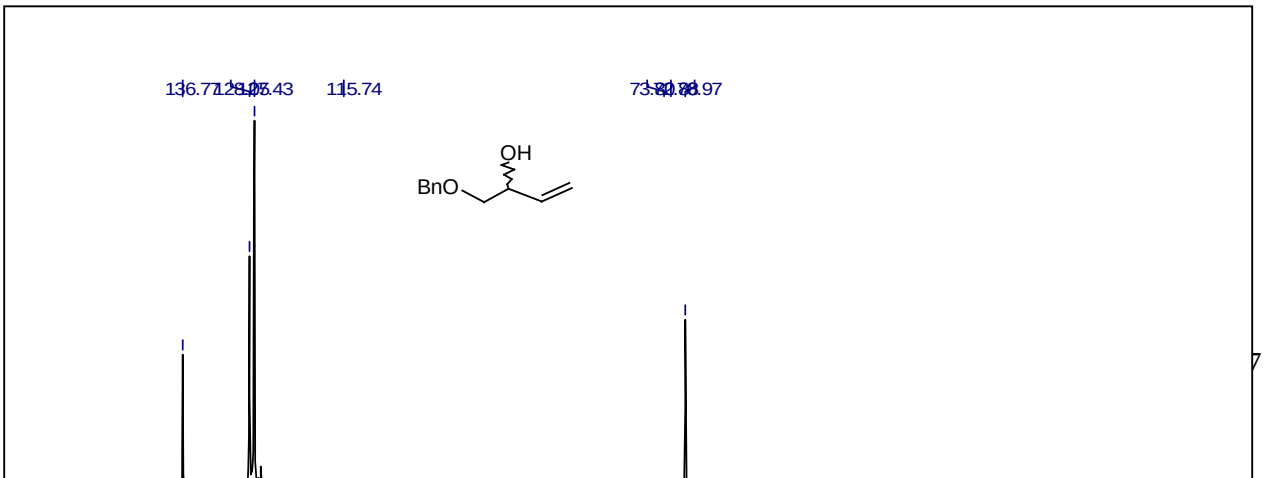
^{1}H NMR Spectrum of compound 107 in $CDCl_3$



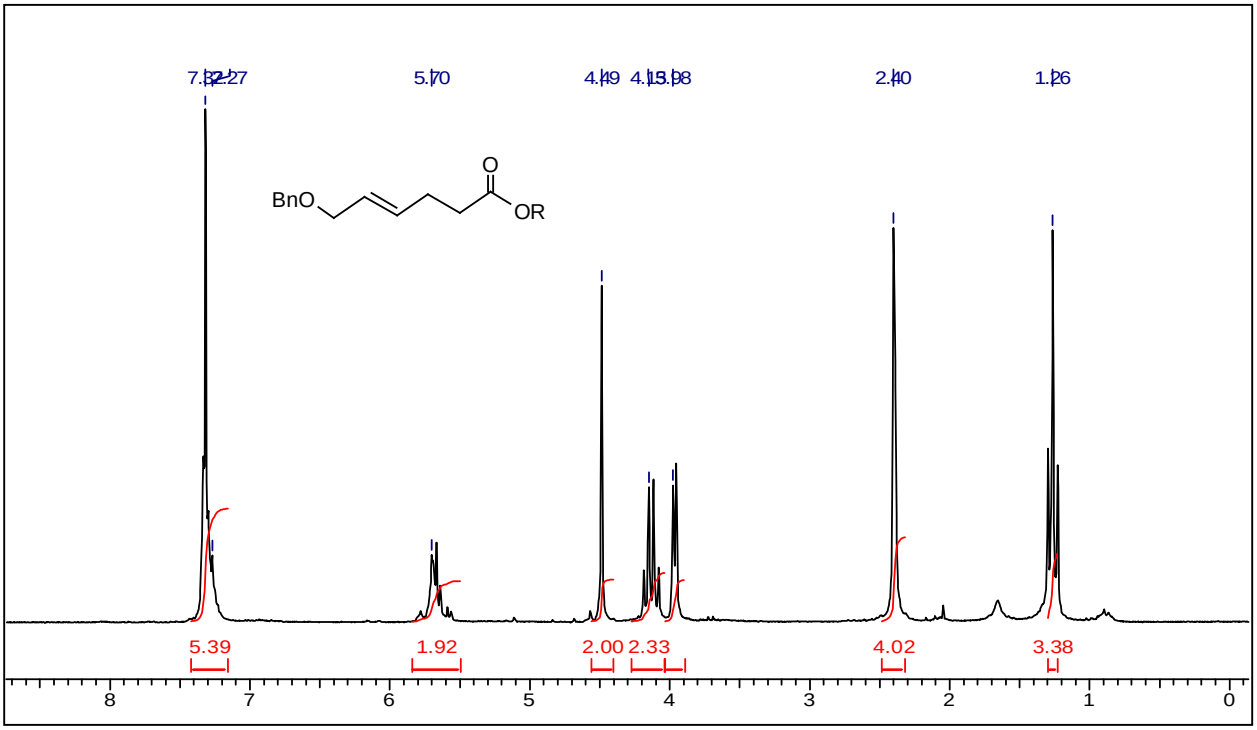
^{1}H NMR Spectrum of compound 105 in $CDCl_3$ + CCl_4



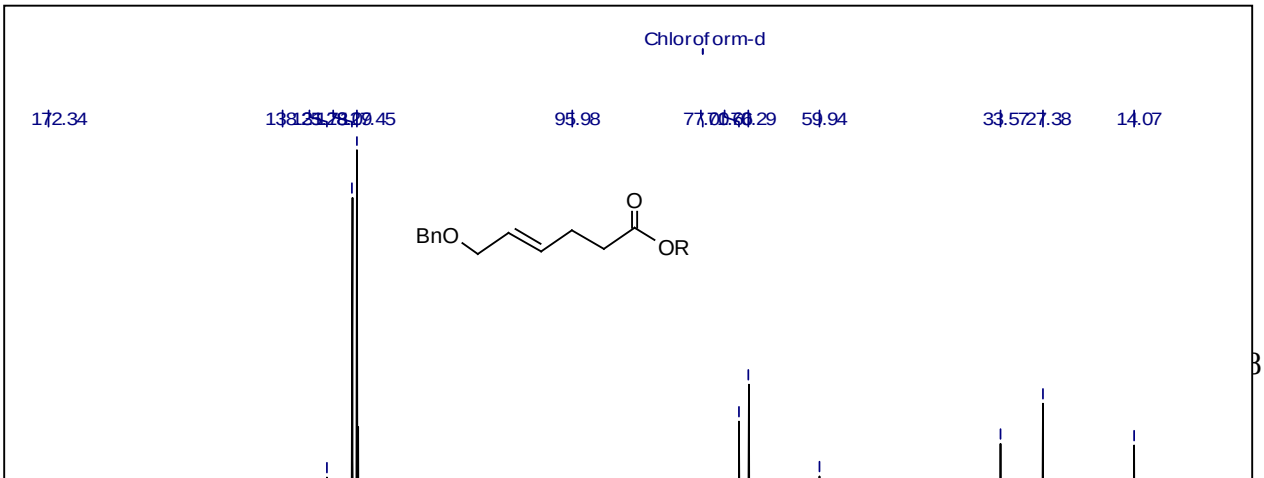
^{13}C NMR Spectrum of compound 105 in $CDCl_3$ + CCl_4



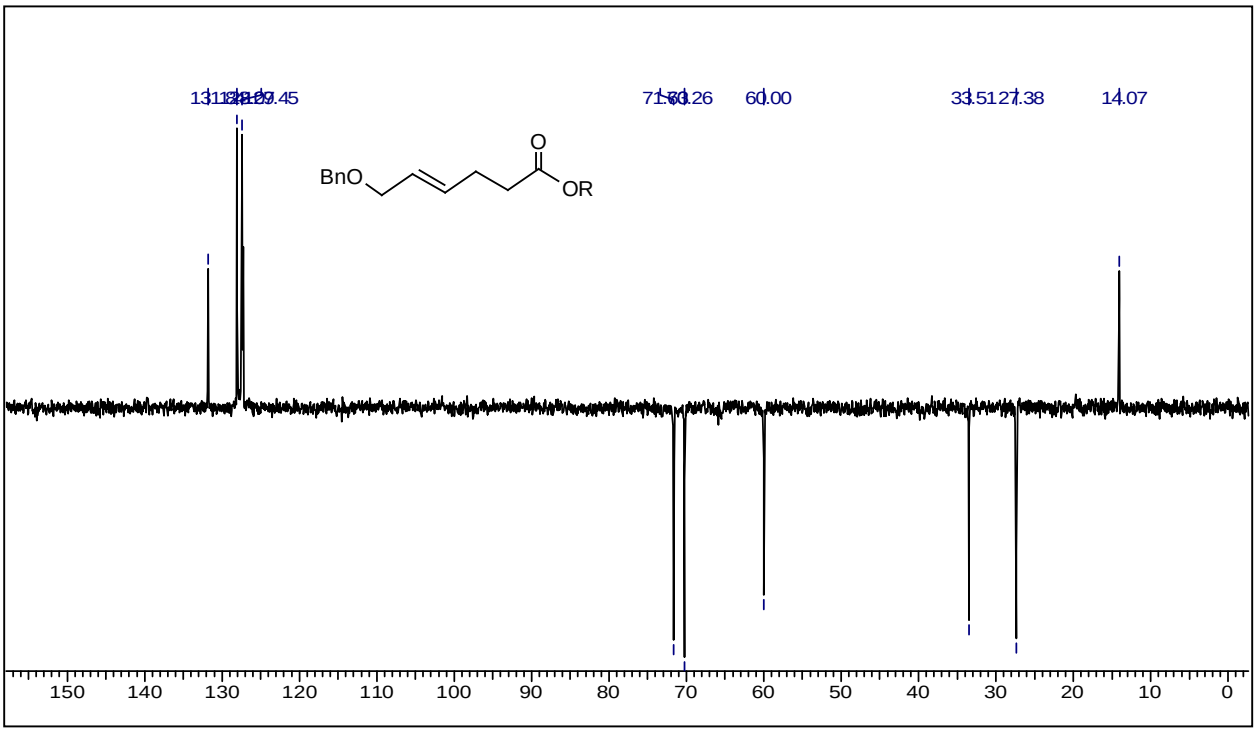
DEPT NMR Spectrum of compound 105 in $CDCl_3$ + CCl_4



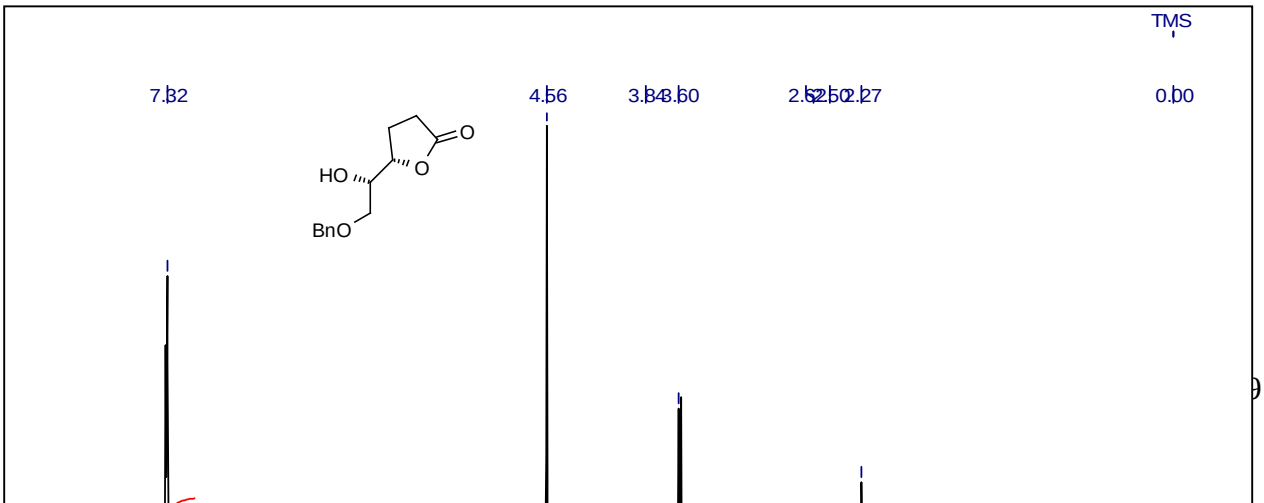
^{1}H NMR Spectrum of compound 104 in $CDCl_3$ + CCl_4



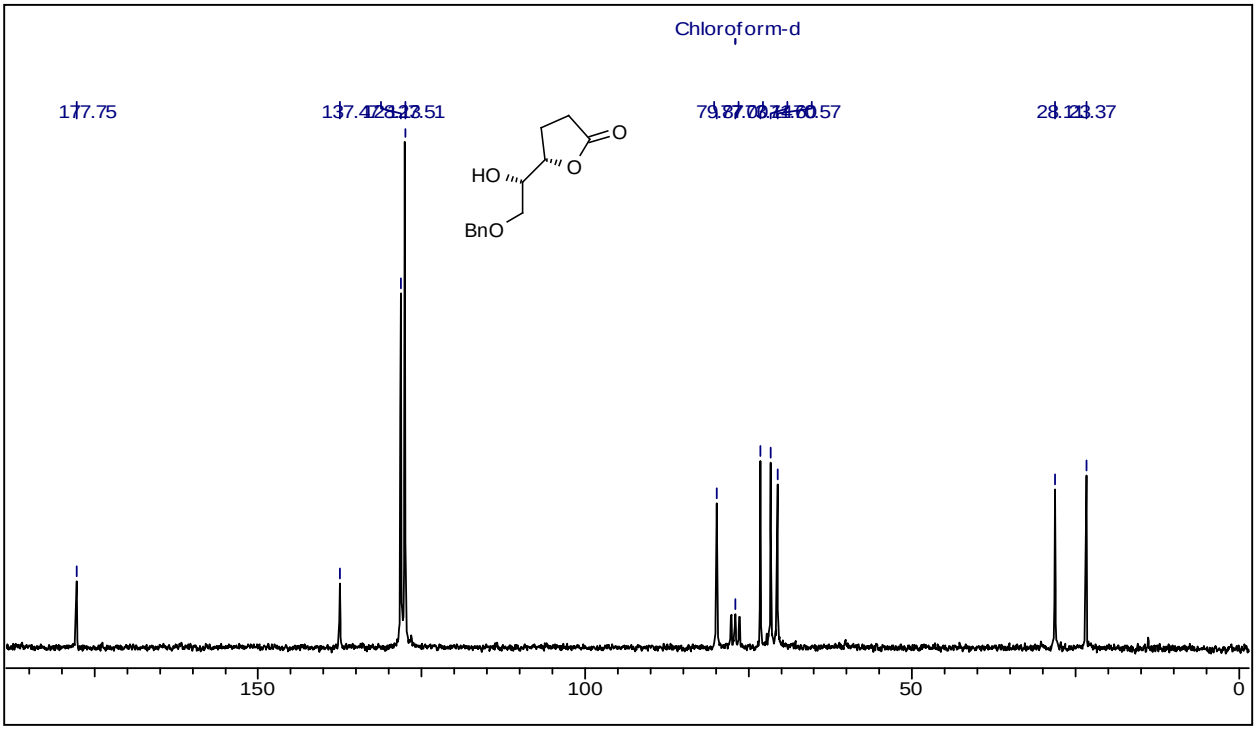
^{13}C NMR Spectrum of compound 104 in $CDCl_3 + CCl_4$



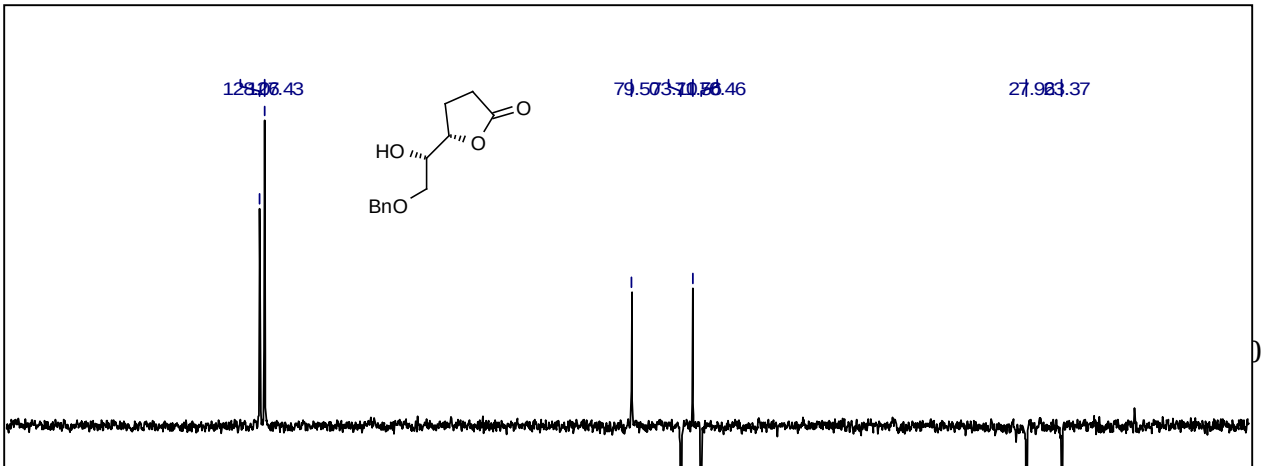
DEPT NMR Spectrum of compound 104 in $CDCl_3 + CCl_4$



^{1}H NMR Spectrum of compound 103a in $CDCl_3$

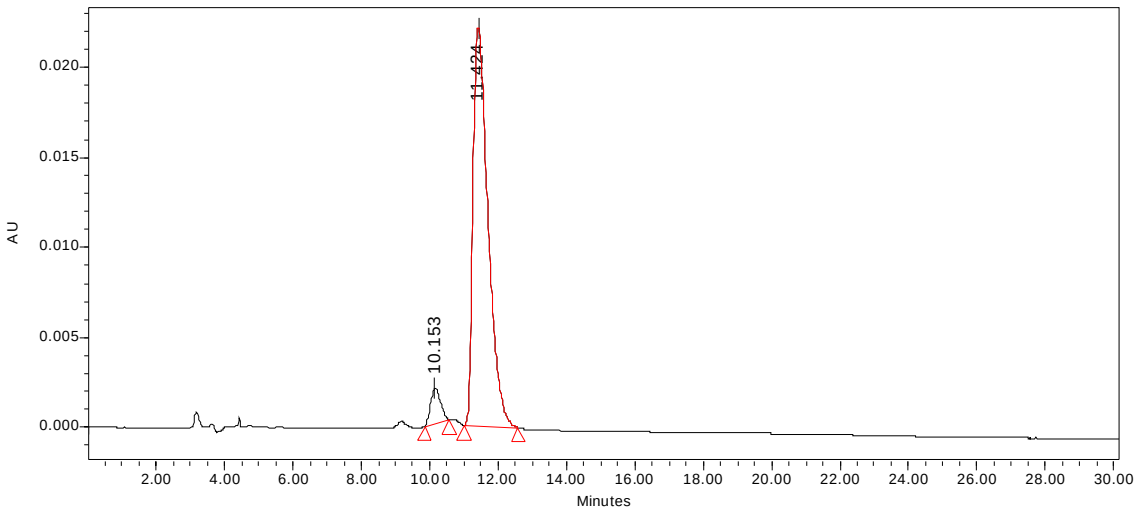


^{13}C NMR Spectrum of compound 103a in $CDCl_3$



DEPT NMR Spectrum of compound 103a in $CDCl_3$

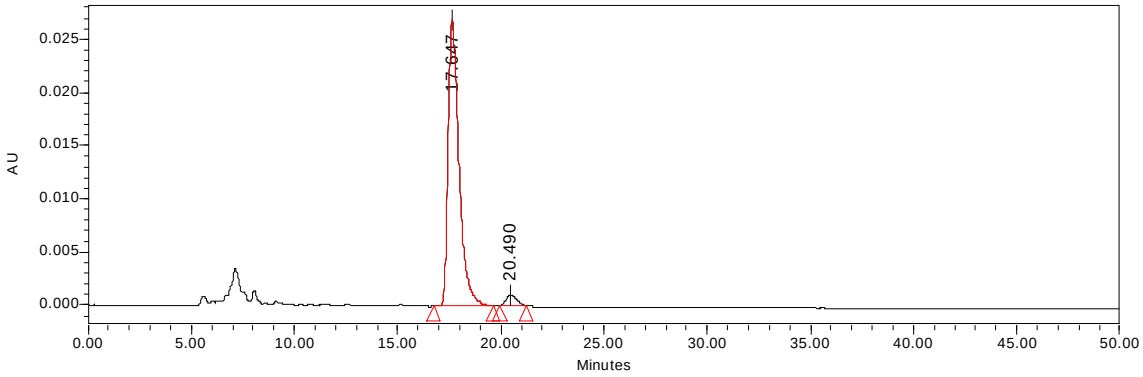
HPLC of Compound 103b



	Name	Retention Time	Area	% Area	Height	Int Type	Amount	Units	Peak Type	Codes
1		10.153	38328	3.36	1981	bB			Unknown	
2		11.424	1009240	96.74	22129	Bb			Unknown	

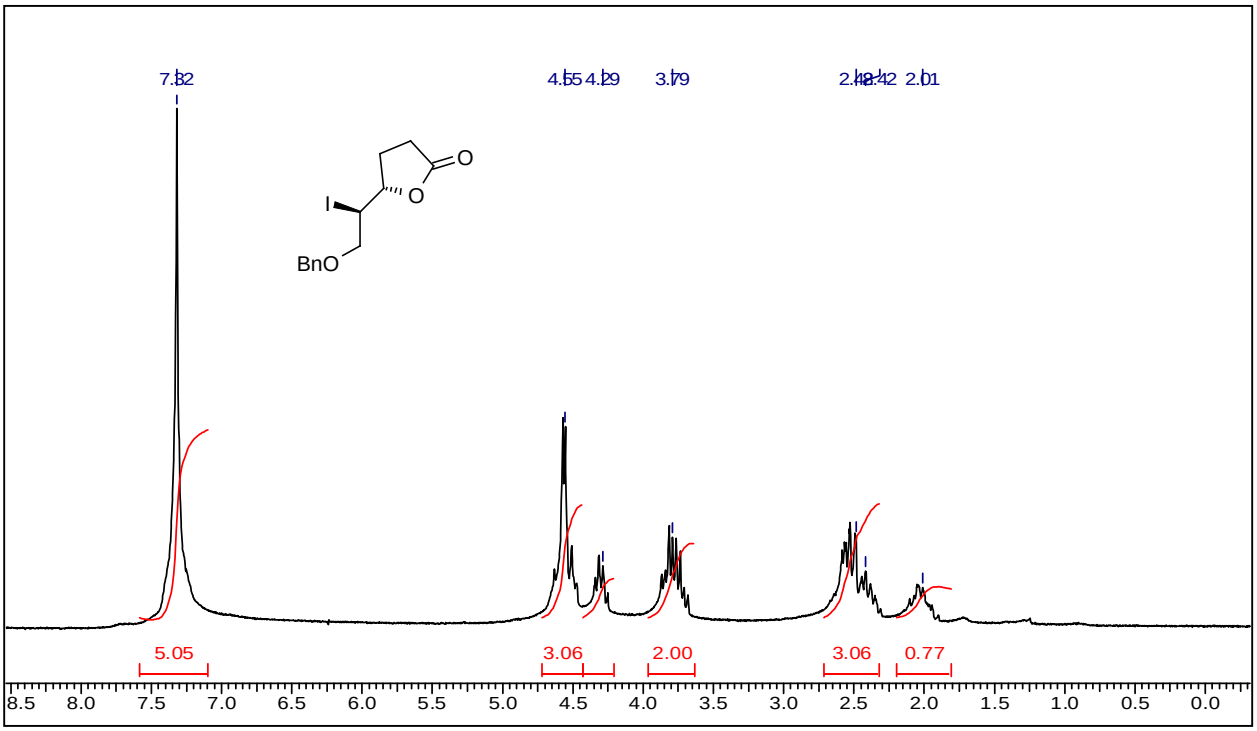
Column : Chiracel OD (4.6mm ID x 25cm L), 10um Column no.-OD00CE-CC054
Mobile Phase : Pet.Ether : Isopropanol (80:20) Spectrochem
Flow : 0.5 ml/min
Wavelength : 254nm

HPLC of Compound 103a

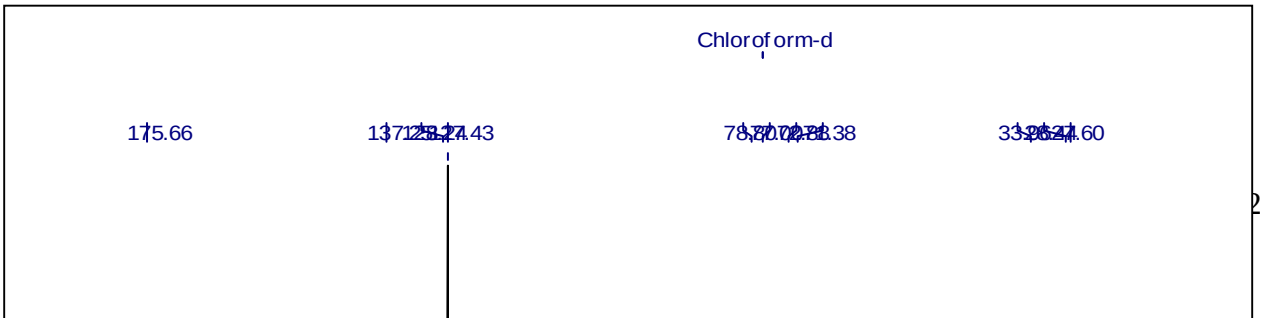


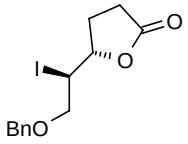
	Name	Retention Time	Area	% Area	Height	Int Type	Amount	Units	Peak Type	Codes
1		17.647	1005420	96.91	26968	bb			Unknown	
2		20.490	35314	3.19	986	bb			Unknown	

Column : Chiracel OD (4.6mm ID x 25cm L), 10um Column no.-OD00CE-CC054
Mobile Phase : Pet.Ether : Isopropanol (80:20) Spectrochem
Flow : 1.0 ml/min
Wavelength : 254nm

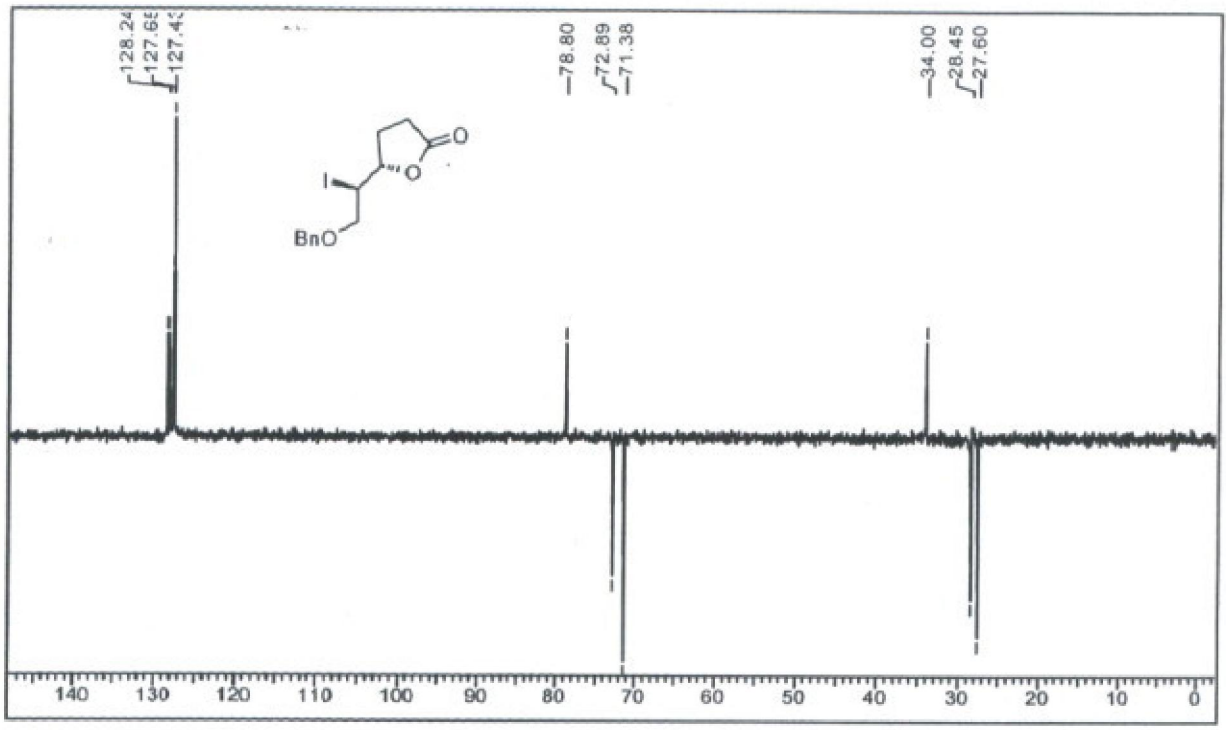


^{1}H NMR Spectrum of compound 102 in $CDCl_3$ + CCl_4

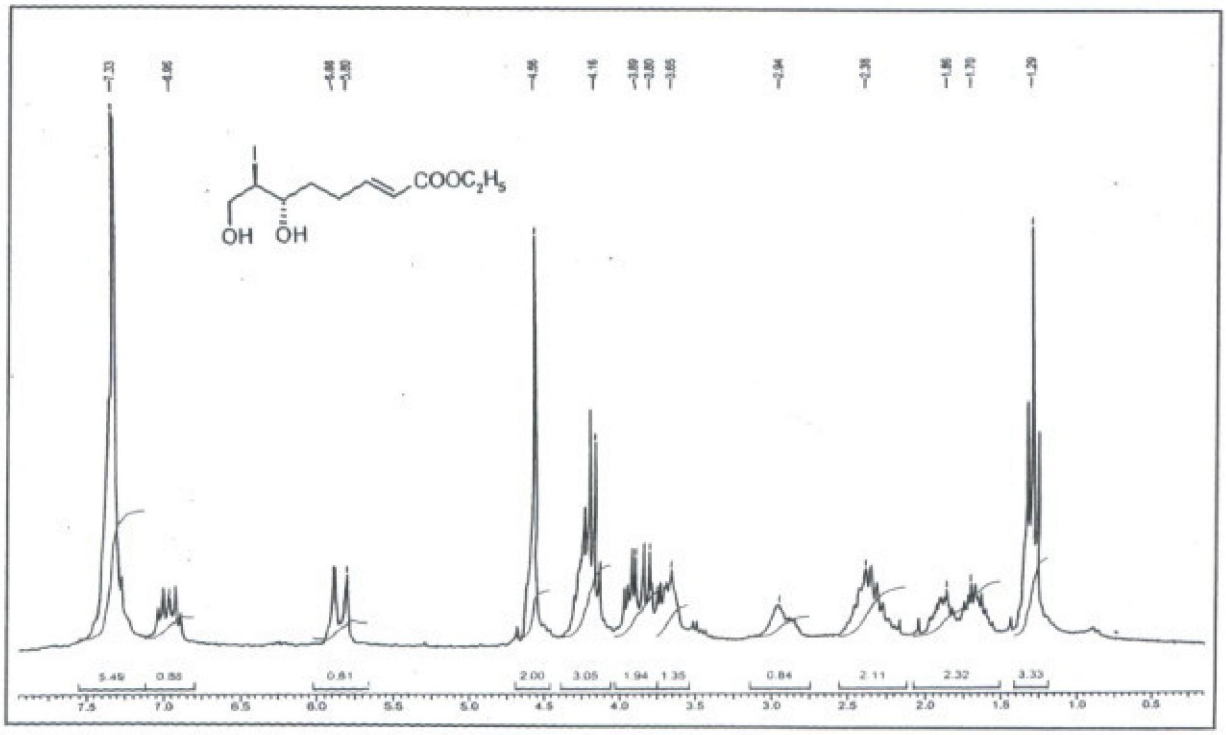




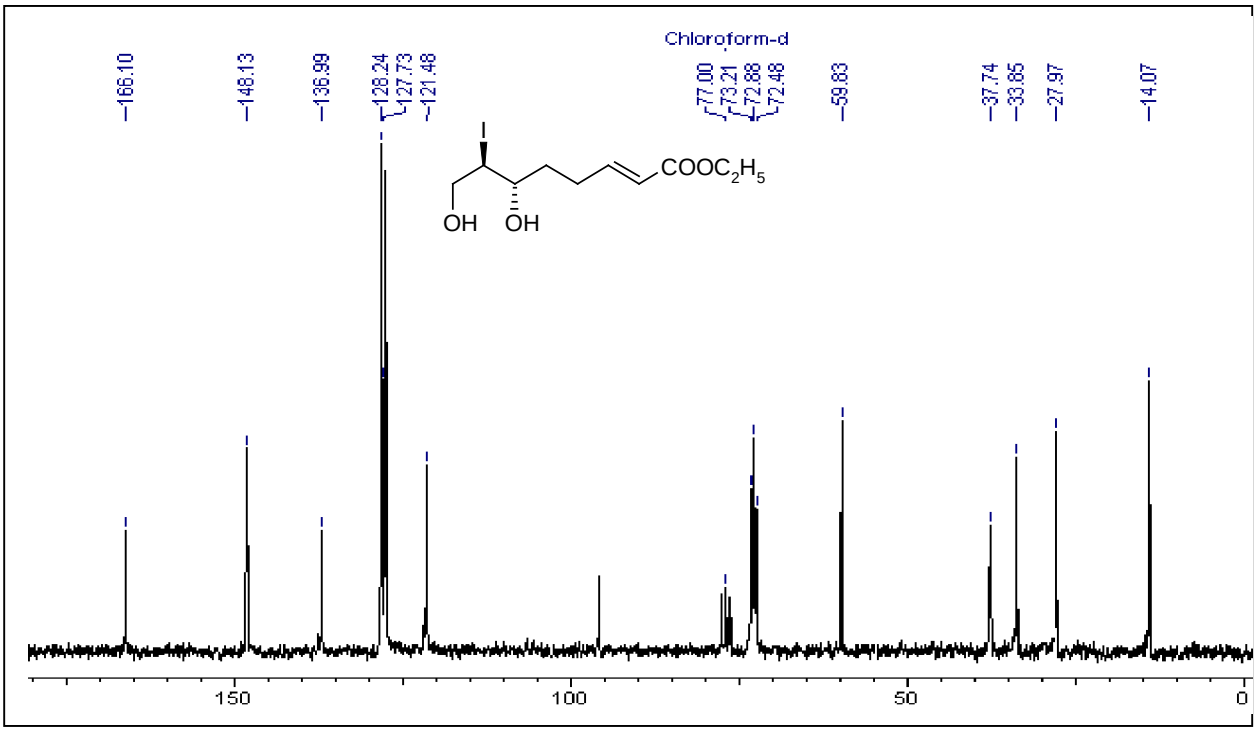
^{13}C NMR Spectrum of compound 102 in $CDCl_3$ + CCl_4



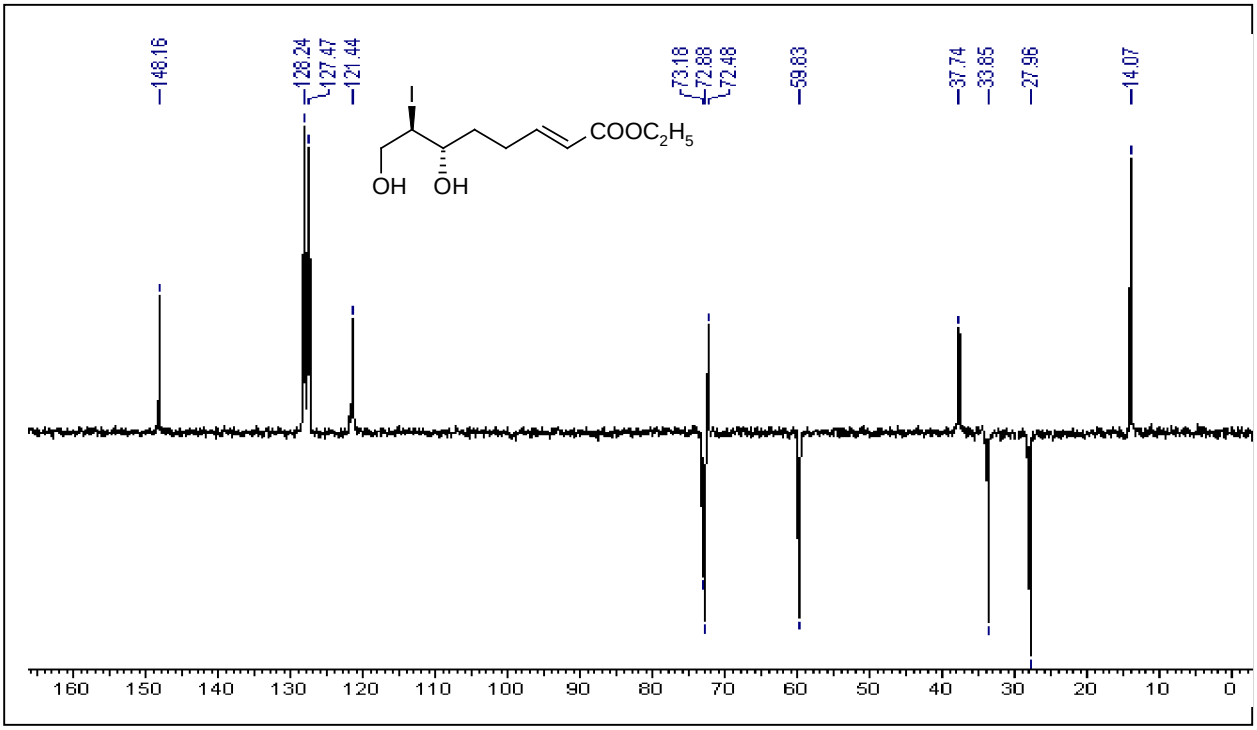
DEPT NMR Spectrum of compound 102 in $CDCl_3$ + CCl_4



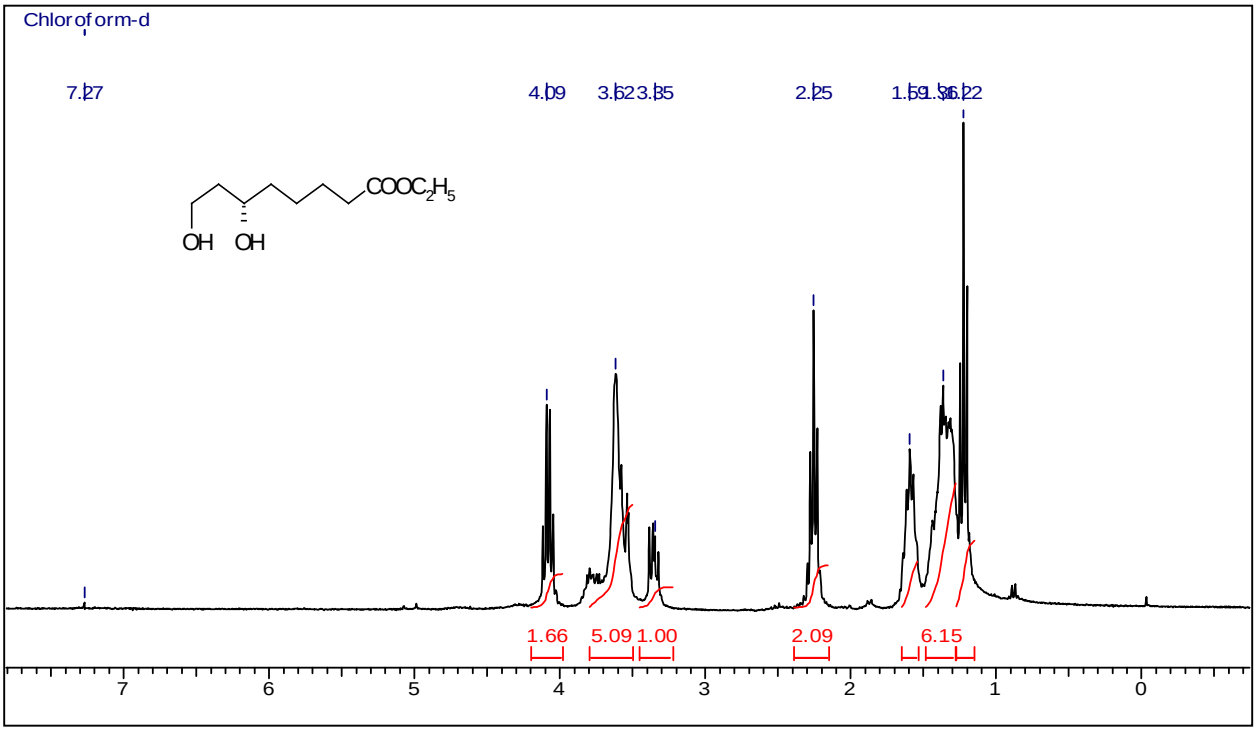
^{1}HNMR Spectrum of compound 101 in $CDCl_3$ + CCl_4



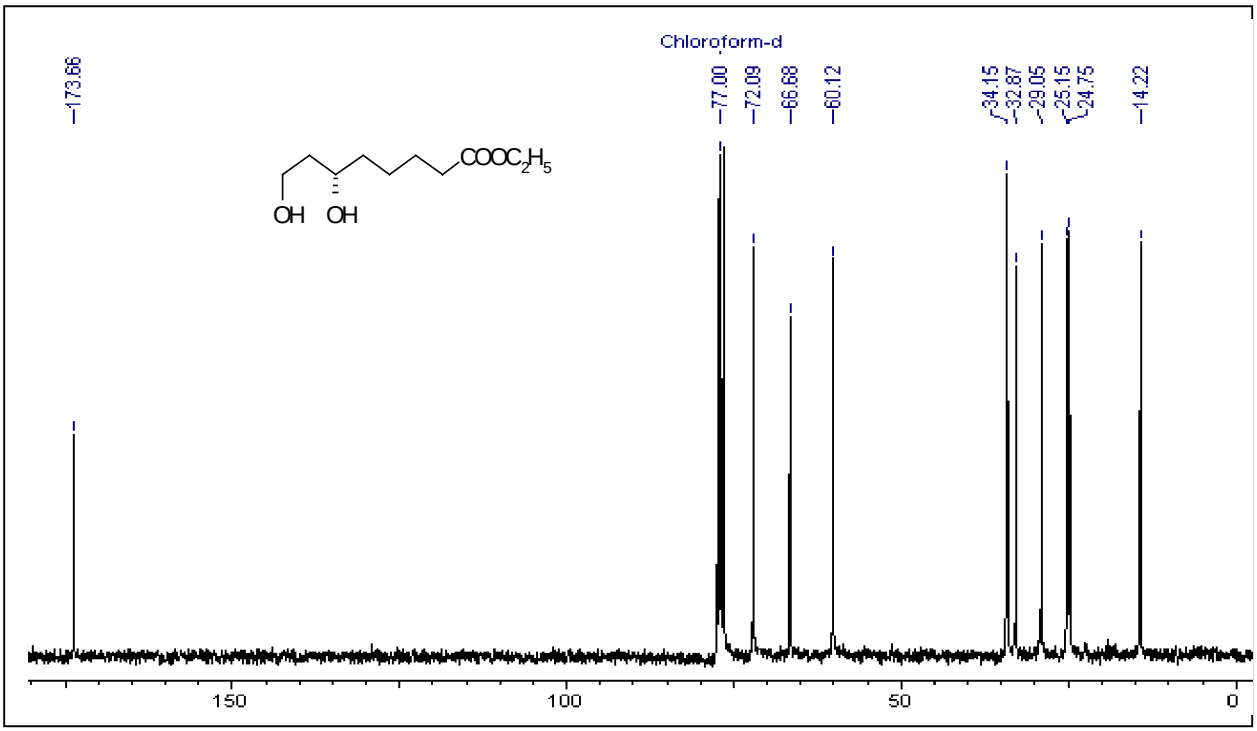
^{13}C NMR Spectrum of compound 101 in $CDCl_3$ + CCl_4



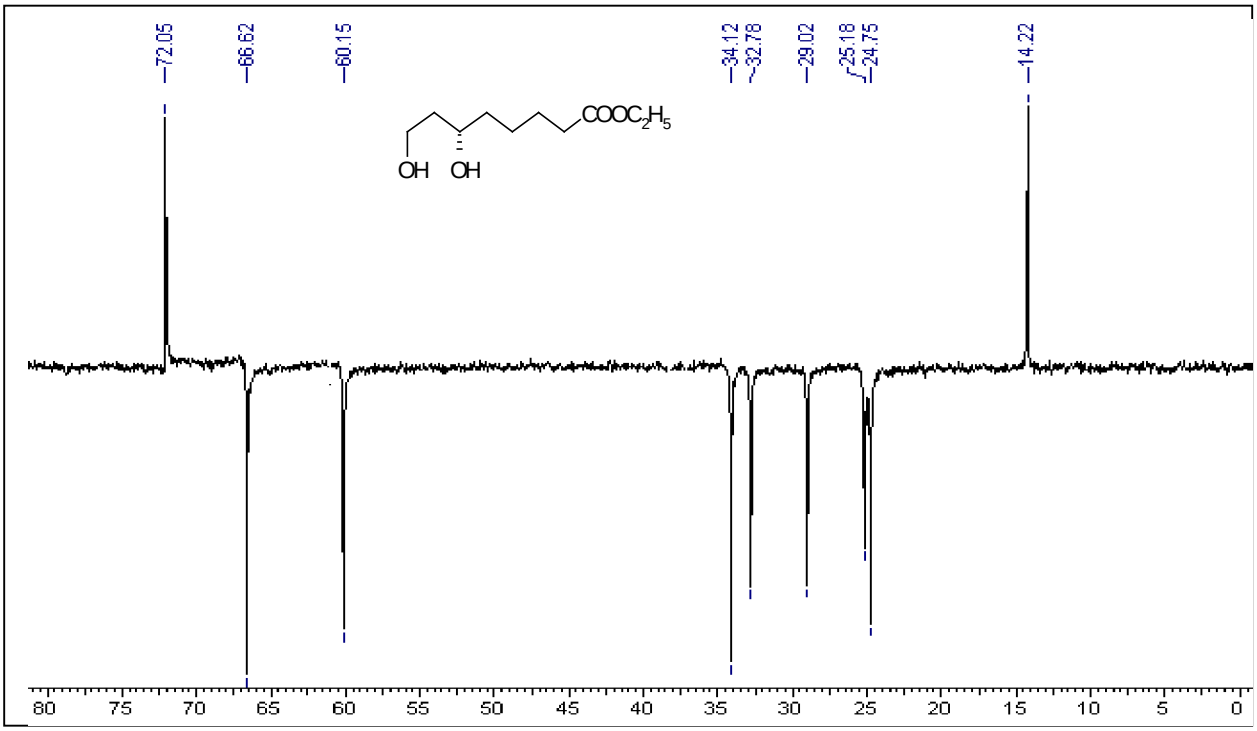
DEPT NMR Spectrum of compound 101 in $CDCl_3$ + CCl_4



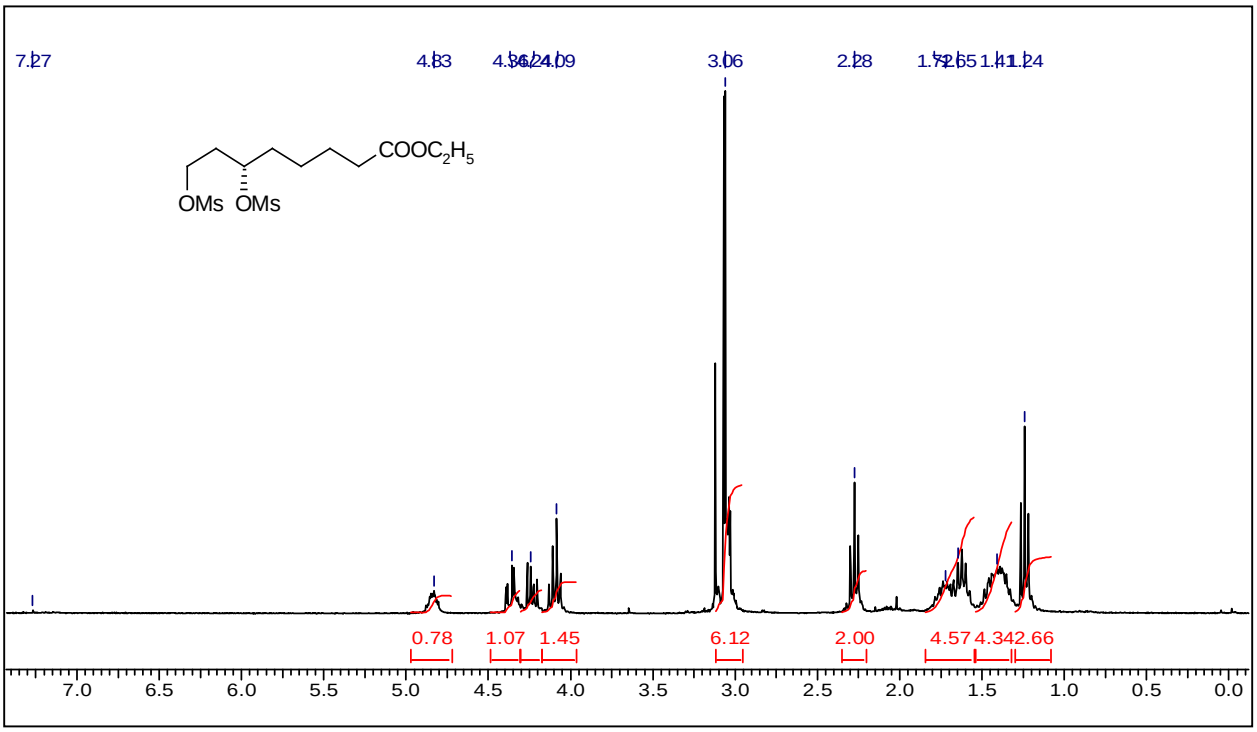
^{1}H NMR Spectrum of compound 36 in $CDCl_3$ + CCl_4



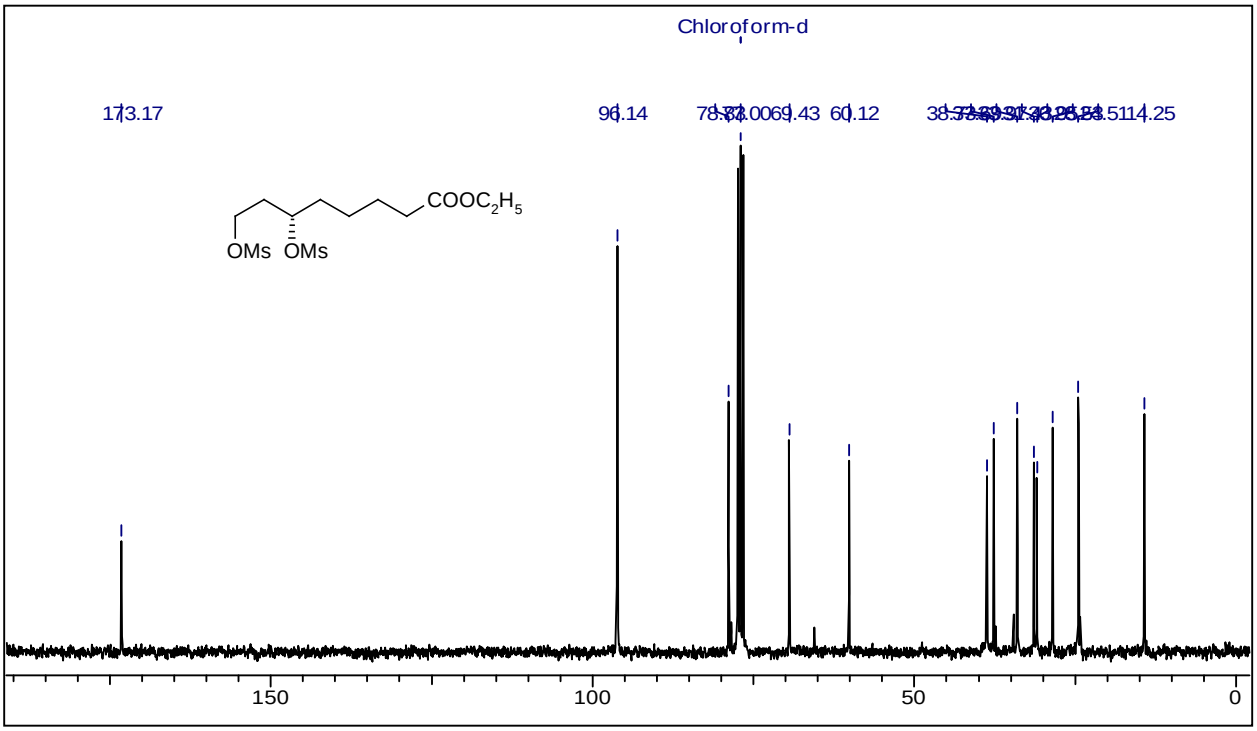
^{13}C NMR Spectrum of compound 36 in $CDCl_3$ + CCl_4



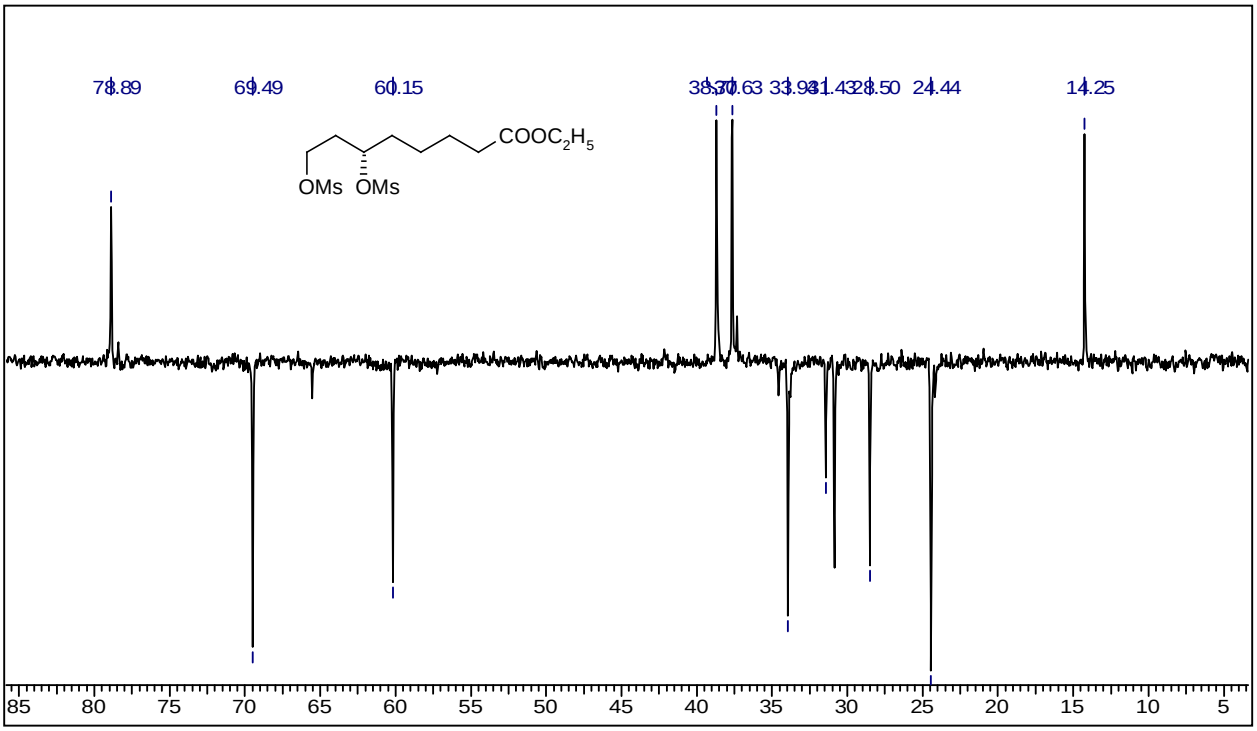
DEPT NMR Spectrum of compound 36 in $CDCl_3$ + CCl_4



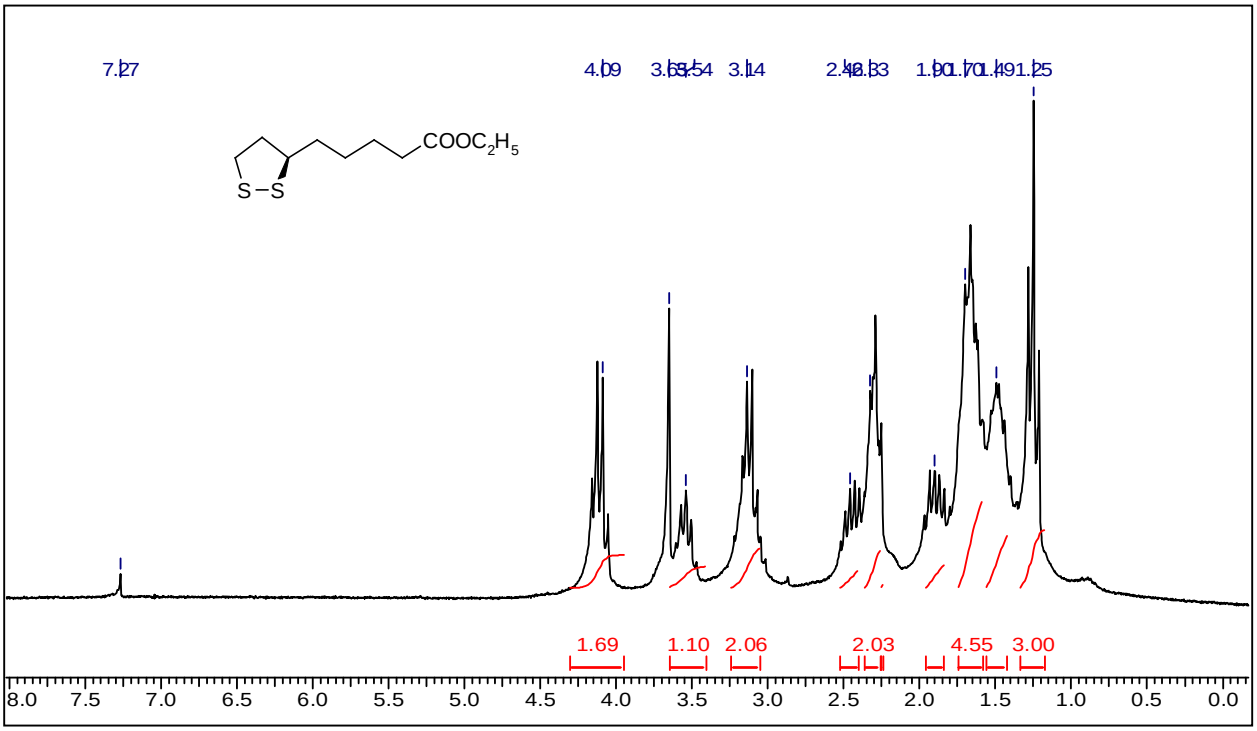
^{1}H NMR Spectrum of compound 108 in $CDCl_3$ + CCl_4



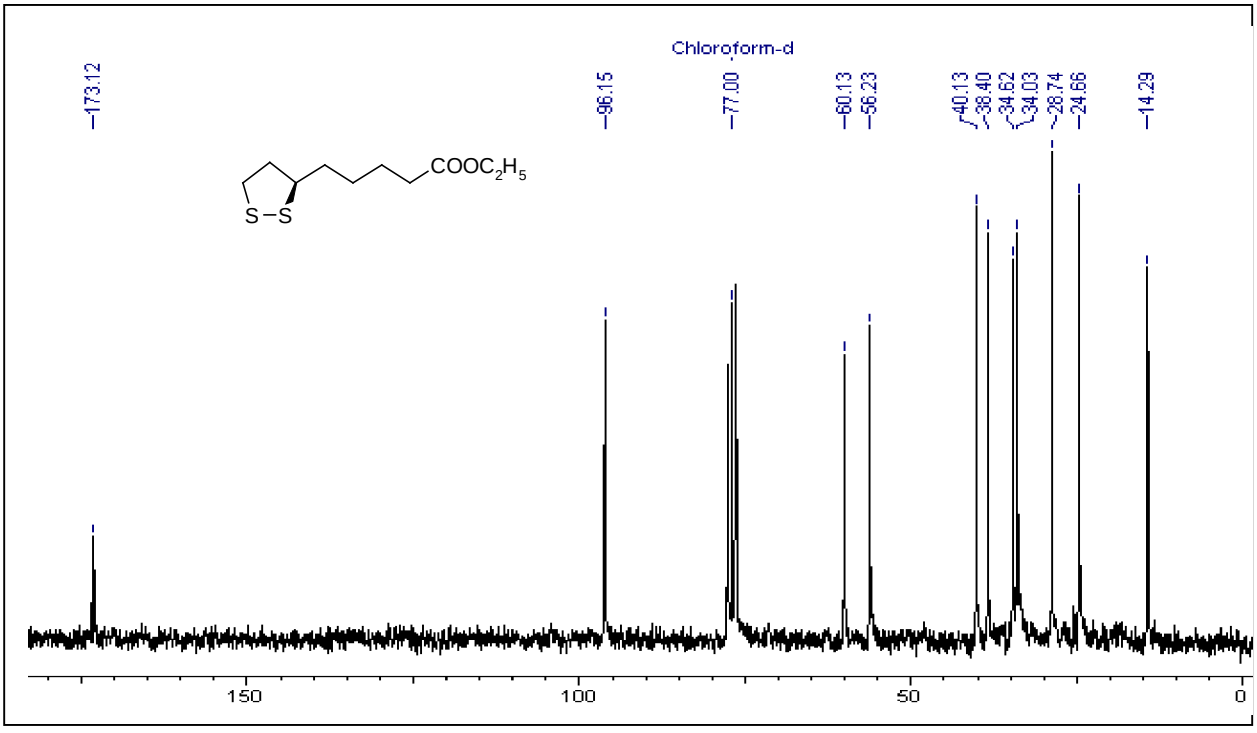
^{13}C NMR Spectrum of compound 108 in $CDCl_3$ + CCl_4



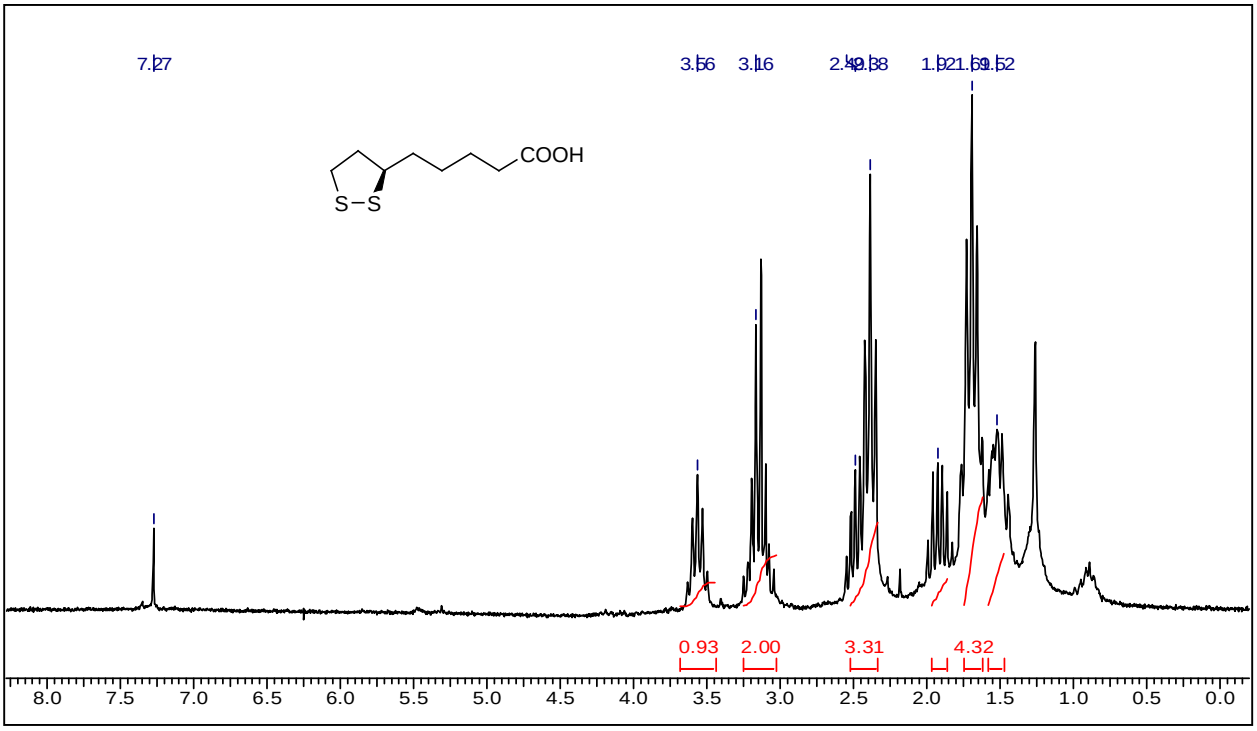
DEPT NMR Spectrum of compound 108 in $CDCl_3$ + CCl_4



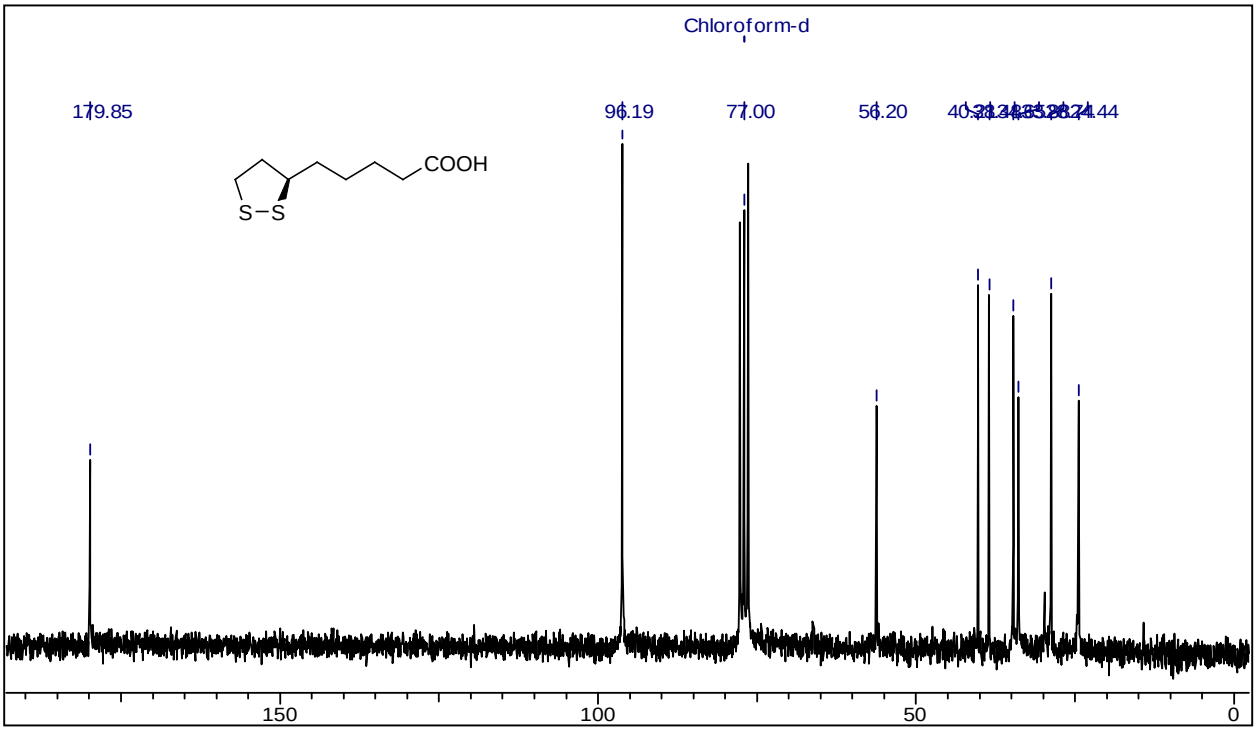
^{1}H NMR Spectrum of compound 100 in $CDCl_3$ + CCl_4



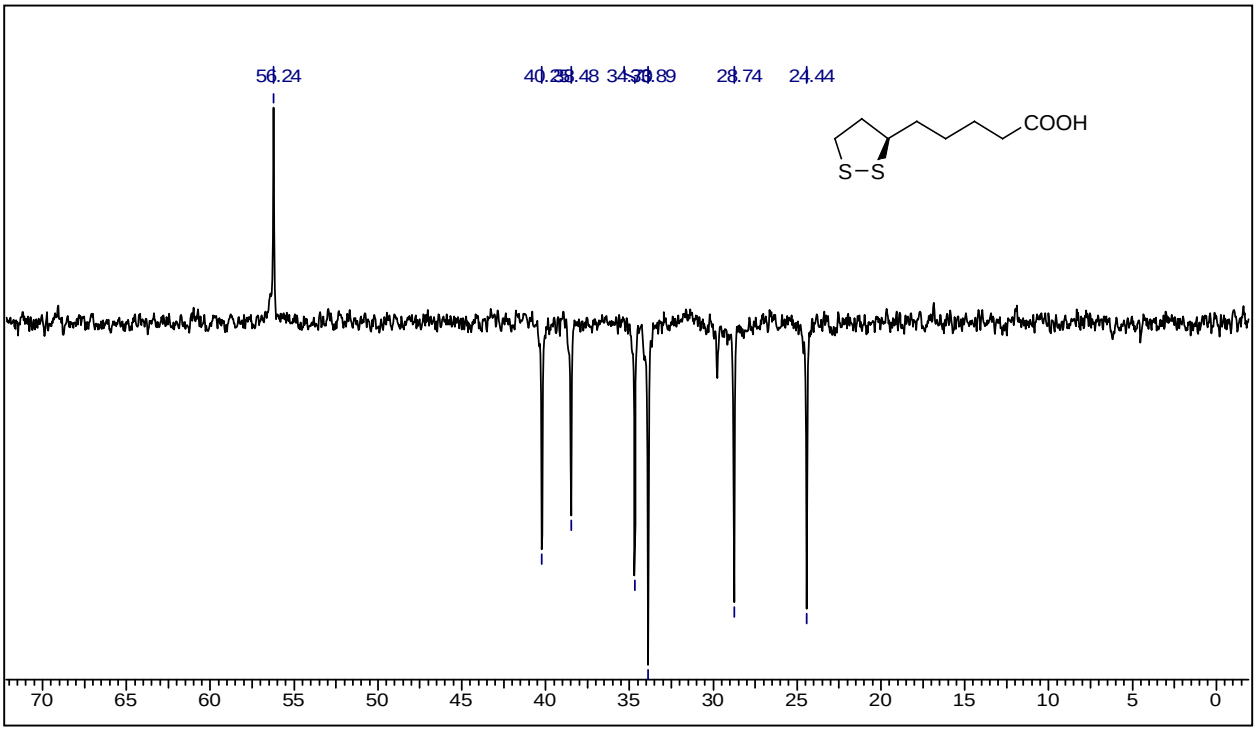
^{13}C NMR Spectrum of compound 100 in $CDCl_3 + CCl_4$



^{1}H NMR Spectrum of compound 1a in $CDCl_3 + CCl_4$



^{13}C NMR Spectrum of compound 1a in $CDCl_3$ + CCl_4



DEPT NMR Spectrum of compound 1a in $CDCl_3$ + CCl_4

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SECTION A

A CONCISE AND STEREOSELECTIVE SYNTHESIS OF (+)- AND (-)-DEOXOPROSOPHYLLINE

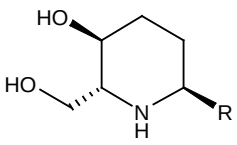
Introduction:

The piperidine ring system is one of the most common motifs found in numerous natural products, drugs and drug candidates. It was recently pointed out by Watson *et al.*[1] that the piperidinic structure was mentioned in over 12000 compounds in clinical or pre-clinical studies from July 1988 through December 1998. Accordingly, the important bioactivities of piperidines have stimulated the development of new approaches and considerable synthetic effort has been devoted to the preparation of these compounds,[2] in particular with respect to enantiomerically selective synthesis. Especially multifunctionalized piperidine alkaloids and their synthetic analogs are the focus of great interest in the pharmaceutical industry because they exhibit an extensive range of biological activities.

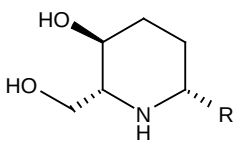
Prosopis alkaloids, one of the subgroup of these piperidine alkaloids, were found to contain a 2, 6-disubstututed 3-piperidinol framework with a long aliphatic appendage at the 6-position. Seven piperidine alkaloids (+)-Prosopinine (**1**), (+)-Prosopine (**2**), (+)-Deoxoprosopinine (**3**), (±)-Prosophylline (**4**), (+)-Deoxoprosophylline (**5**), (-)-

Deoxoprosophinine (**6**), (-)-Deoxoprosophylline (**7**) were isolated from the leaves of the West African savanna tree *Prosopis africana* Taub.[3]

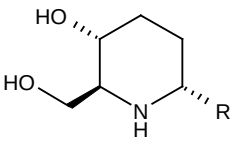
Structurally, these compounds possessing a polar head group with a configuration of the 1, 3-diol unit similar to those in deoxynojirimycin (**26**), a potent glucosadase inhibitor[4] and potentially valuable therapeutic agent for diabetes mellitus, hyperlipoproteinemia, cancer and arthritis.[5] The lipophilic tail portion, which resembles the membrane lipid sphingosine (**8**).[6] Because of these dual physiologically important structural features mentioned above, these polysubstituted piperidine alkaloids exhibits a wide variety of physiological properties[7] including analgesic, anaesthetic and antibiotic activity.[8] The reduction analogues of prosophylline and prosopinine such as deoxoprosophylline and deoxoprosopinine also displays similar biological properties.[9]



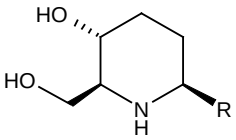
1. R = $(CH_2)_9COCH_2CH_3$
(+)- Prosopinine
2. R = $(CH_2)_{10}CH(OH)CH_3$
(+)- Prosopine
3. R = $C_{12}H_{25}$
(+)- Deoxoprosopinine



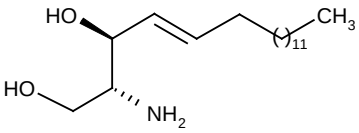
4. R = $(CH_2)_9COCH_2CH_3$
(±)-Prosophylline
5. R = $C_{12}H_{25}$
(+)- Deoxoprosophylline



6. R = $C_{12}H_{25}$
(-)- Deoxoprosopinine

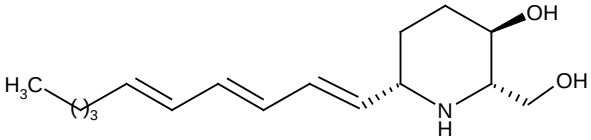


7. R = $C_{12}H_{25}$
(-)- Deoxoprosophylline



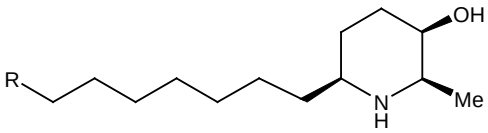
Spingosine (**8**)

Micropine (**9**) is a similar type of alkaloid isolated from *Microcos philippinensis.*[10]

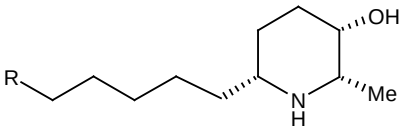


Micropine (**9**)

Like prosopis alkaloids Cassia alkaloids Cassine (**10**), Spectaline (**11**), Azimic acid (**12**) and Carpamic acid (**13**) were isolated from *Cassia excelsa* and *Cassia carnavalis* are found to contain a similar 2, 6-disubstituted 3-piperidinol skeleton.[11]

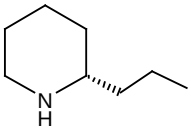


R = $(CH_2)_3COMe$; Cassine (**10**)

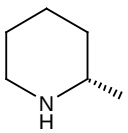


R = $(CH_2)_7COOH$; Spectaline (**11**)
R = COOH; Azimic acid (**12**)
R = $(CH_2)_2COOH$; Carpamic acid (**13**)

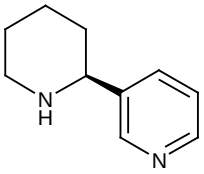
The family of chiral 2-substituted piperidines[12] like Conine (**14**), Pipecoline (**15**), Anabasine (**16**), Anatabine (**17**), β-conhydrine (**18**), Pipecolic acid (**19**), Baikiain (**20**) and Sedamine (**21**) also have a blend of physiologically important structural features. Conine (**14**), one of the simplest alkaloids and one of the poisonous alkaloid isolated from *Conium macalatum L*. Sedamine (**21**) was the first piperidine alkaloid isolated from *Sedem acre*[13] and was obtained later from a number of sedum species.[14]



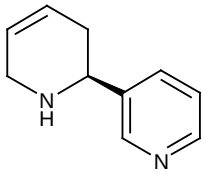
(*S*)-Conine (**14**)



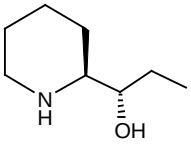
(*S*)-Pipecoline (**15**)



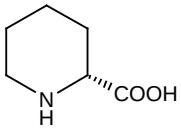
(*S*)-Anabasine (**16**)



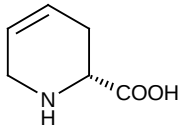
(*S*)-Anatabine (**17**)



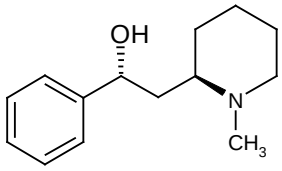
(-)-Conhydrine (**18**)



(*S*)-Pipecolicacid (**19**)

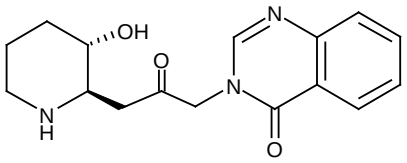


(*S*)-Baikiain (**20**)

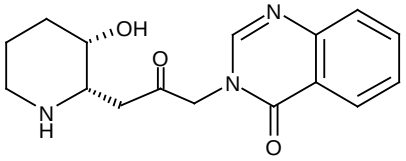


(+)-Sedamine (**21**)

(+)-Febrifugine (**22**) and (+)-isofebrifugine (**23**) are the potent antimalarial alkaloids isolated from *Dichroa febrifuga Lour*.[15] (+)-Febrifugine (**22**) exhibits comparable activity in vivo to the clinically used drug chloroquine.[15d,e]

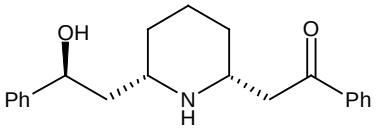


(+) - Febrifugine (**22**)

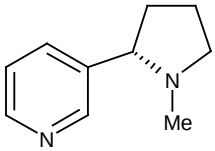


(+) - isofebrifugine (**23**)

2,6-Disubstituted piperidines represent a subclass of naturally occurring alkaloids that have also been the targets of many synthetic efforts due to their wide range of pharmacological activities. (-)- Lobeline (**24**) was one of the important alkaloid isolated from the herb *Lobelia inflanta*.[16] The plant was also known as Indian tobacco because the American Indian tobacco because the American Indians smoked the dried leaves to obtain the effects of (**24**) on the central nervous system (CNS). (-)-Lobeline was considered as nicotinic agonist as it resembles nicotine (**25**) in pharmacological activities.[17]

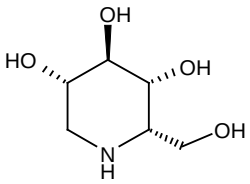


(-) - Lobeline (**24**)

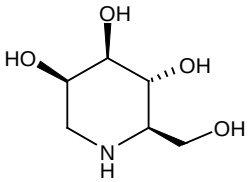


(-) - Nicotine (**25**)

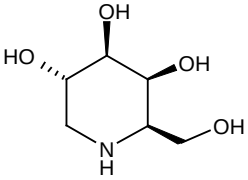
Polyhydroxylated piperidines (so called aza sugars, due to the N atom replacing the ring oxygen atom in the sugar) and their analogs have attracted a great deal of attention in recent years. Many representatives, such as 1-deoxynojirimycin (**26**), 1-deoxymannojirimycin (**27**), 1-deoxygalactostatin (**28**), 3-*epi*-fagomine (**29**), and fagomine (**30**) exibit significant biological properties as potent inhibitors of glycosidases and glycosyltransferases. The indazolidine alkaloids swainsonine and castanospermine are very important alkaloids which possess potent activities towards α-mannosidase and β-glucosidase.[18] The therapeutic importance of polyhydroxylated piperidines as new agents for the treatment of diseases related to metabolic disorders involving carbohydrates, such as diabetes, cancer and viral infections[19] has led to a great deal of interest amongst synthetic chemists.



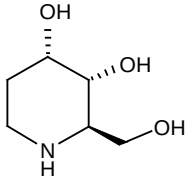
1- Deoxynojirimycin (**26**)



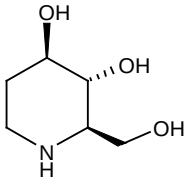
1- Deoxymannojirimycin (**27**)



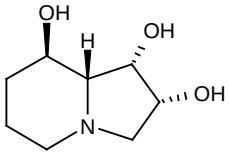
1- Deoxygalactostatin (**28**)



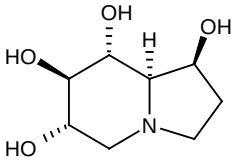
3-*epi*-Fagomine (**29**)



Fagomine (**30**)



Swainsonine (**31**)



Castanospermine (**32**)

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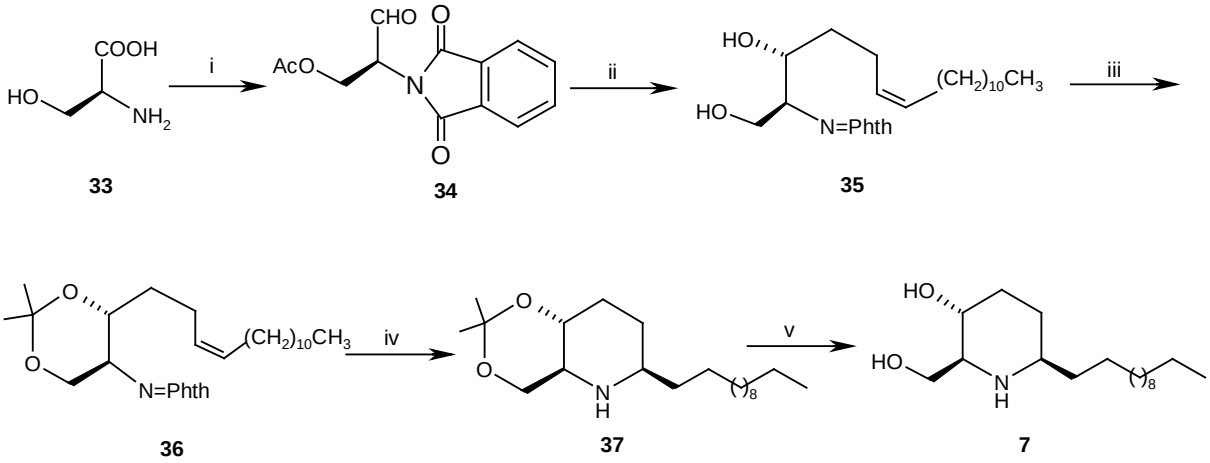
Review of Literature:

Along with the interesting structural features, these compounds and their synthetic analogs shows significant biological properties. Due to the importance of these alkaloids, a great deal of effort has been devoted to the synthesis of these alkaloids.[20-22]

Among the synthetic routes reported for deoxoprosophylline, the strategy often used is to employ either sugars or amino acids as the chiral pool starting materials. Some of the important literature syntheses are given below.

Takahashi *et al* (1980, Scheme-1)[23]

Takahashi and co-workers have synthesized 2*S*-3-acetoxy-2-phthalimido propanal **34** from L-serine by known procedure. Grignard reaction of **34** with (*Z*)-3-pentadecenyl bromide gave mixture of diastereomers, in which the major isomer was hydrolyzed and protected as acetonide derivative **36**. Phthaloyl deprotection and aminomercuration of compound **36** with $Hg(OAc)_2$ followed by demercuration with $NaBH_4$ giving two diastereomeric piperidine acetonides **35** and its C-6 epimer. Finally acid hydrolysis of acetonide 37 afforded (-)-



33 **34** **35** **36** **37** **7**

deoxoprosophylline.

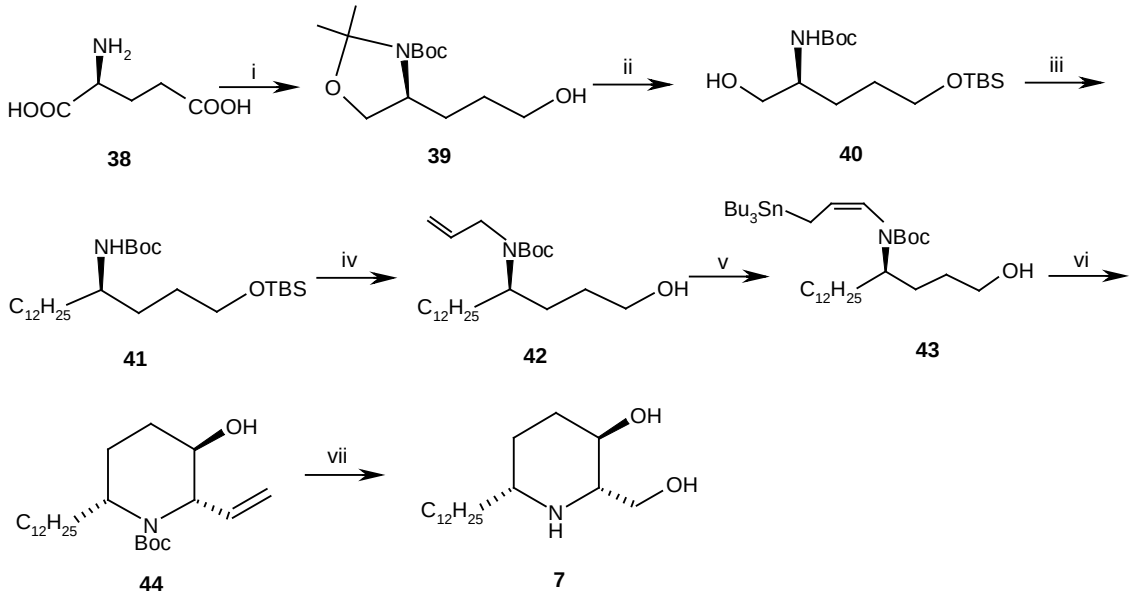
Scheme 1

Scheme 1. *Reagents and conditions:* (i) ref 24; (ii) (*Z*)-$CH_3(CH_2)_{10}CH{=}CHCH_2CH_2Br$, Mg, THF-Ether (2:1), -70 ^oC to -40 ^oC; (iii) (a) HCl, MeOH, reflux; (b) 2,2-dimethoxy propane, *p*-TSA (iv) (a) $NH_2.NH_2.H_2O$; (b) $Hg(OAc)_2$, MeOH, rt; (c) $NaBH_4$; (v) HCl, MeOH, reflux.

Yamamoyo *et al* (1997, Scheme-2)[25]

In Yamamoto's approach L-glutamic acid was converted to alcohol **39** by known procedure. Protection of the hydroxyl as TBS ether and selective deprotection of *N*, *O*-acetal gave compound **40**. Tosylation of **40** followed by alkylation with $C_{11}H_{23}Li$/CuI furnished the compound **41**. Allylation and subsequent desilylation of **41** gave **42**, which on treatment with sec-BuLi/TMEDA followed by the reaction of corresponding allylic anion with n-Bu_3SnCl afforded the allyl stannane derivative **43**. Oxidation of **43** followed by Lewis acid catalyzed cyclization gave **44** and it's C-2 epimer. Ozonolysis of **44** followed by $NaBH_4$ reduction and N-Boc deprotection gave (-)-deoxoprosophylline.

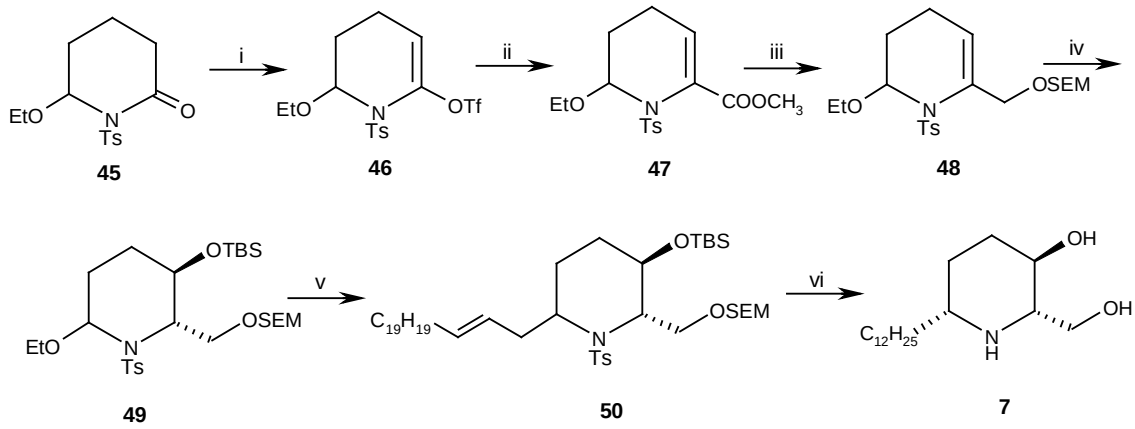
Scheme 2



Scheme 2. *Reagents and conditions:* (i) Ref. 26; (ii) (a) TBSCl, imidazole, CH_2Cl_2, rt, 100 %; (b) $PdCl_2(CH_3CN)_2$, CH_3CN, reflux, 98 %; (iii) (a) TsCl, Et_3N, DMAP, CH_2Cl_2, 98 %; (b) $C_{11}H_{23}Li$, CuI, Et_2O, -35 ^oC, 82 %; (iv) (a) Allyl bromide, KH, THF, 0 ^oC-rt, 92 %; (b) TBAF, THF, RT, 74 %; (v) Sec. BuLi, TMEDA, THF, -78 ^oC then n-Bu_3SnCl, -78 ^oC-rt, 61 %; (vi) (a) SO_3, Pyridine, DMSO, Et_3N, CH_2Cl_2, 0 ^oC, 92 %; (b) $MgBr_2.OEt_2$, CH_2Cl_2, 0 ^oC, 72 %; (vii) (a) O_3, MeOH, -78 ^oC then $NaBH_4$, -78 ^oC-rt; (b) 6 N HCl, Dioxane, reflux.

Speckamp *et al* (1997, Scheme-3)[27]

In Speckamp's approach piperidone derived enol triflate **46** on methoxy carbonylation gave ester **47**. Selective 1, 2-reduction of ester **47** gave an alcohol, which was protected as SEM ether **48**. Hydroboration of **48** followed by oxidative work up with trimethylamine *N*-oxide afforded alcohol, which was protected as TBS ether **49**. Introduction of 12-carbon chain in one step was straightforward by the generation of *N*-tosyliminium ion. Hydrogenation of olefin **50**, followed by deprotection of the hydroxy and amino groups gave (-)-deoxoprosophylline.

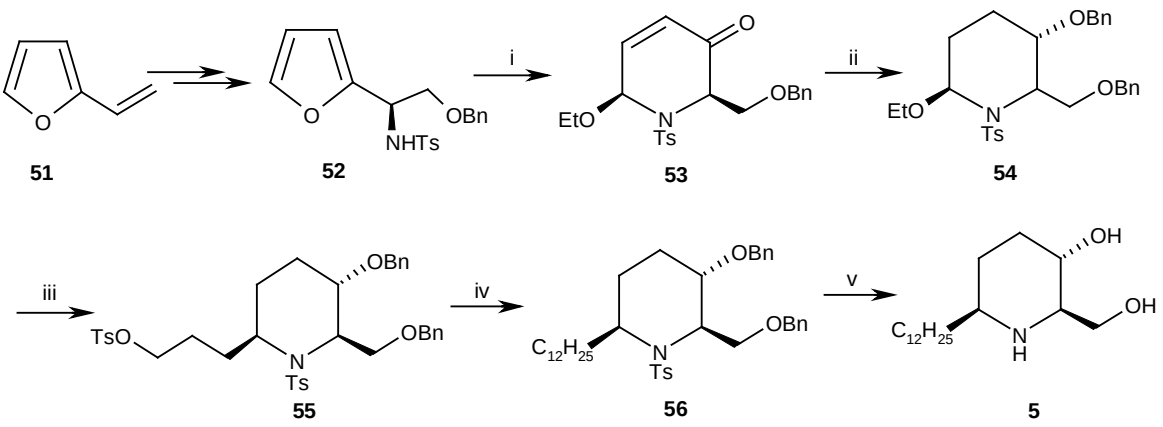


Scheme 3

Scheme 3. *Reagents and conditions:* (i) Comin's procedure, ref 28; (ii) $Pd(AsPh_3)_4$, CO, MeOH, DMF; (iii) (a) DIBAL-H, THF, 70 %; (b) SEMCl, Et^iPr_2N, CH_2Cl_2, 80 %; (iv) (a) BH_3.THF, -78 ^oC then Me_3NO, 85 %; (b) TBSOTf, 2,6-Lutidine, CH_2Cl_2, 92 %; (v) $C_9H_{19}CH(SiMe_3)CH{=}CH_2$, $BF_3.OEt_2$, -78 ^oC, 55 %; (vi) (a) Pd/C, H_2, MeOH; (b) HCl (0.4 M in MeOH), 75 % (two steps) (c) Na/NH_3, 75 %.

Zhou *et al* (1998, Scheme-4)[29]

Zhou and co-workers converted α-furyl ethylene **51** into α-furyl amine derivative **52** in five steps. Treatment of **52** with *m*-CPBA and the resultant dihydropyridone hydroxyl group was protected to give the compound **53**. Reduction of keto group followed by protection of the hydroxyl group as benzyl ether gave compound **54**. Treatment of **54** with allyl trimethyl silane followed by hydroboration and tosylation delivered **55**. Treatment of **55** with Grignard reagent afforded compound **56**. Deprotection of hydroxyl and amino groups delivered (+)-deoxoprosophylline **5**.

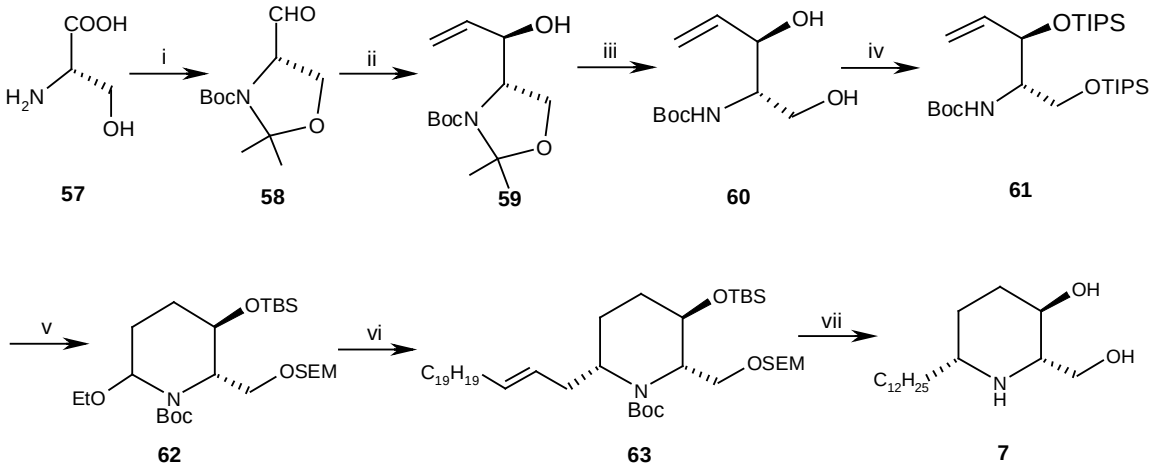


Scheme 4

Scheme 4. *Reagents and conditions:* (i) (a) *m*-CPBA, CH_2Cl_2, rt, 82 %; (b) $CH(OEt)_3$, $BF_3.OEt_2$, 4 A^o Molecular sieves, THF, 0 ^{o}C, 97 %; (ii) (a) $NaBH_4$, MeOH, 0 ^{o}C, 88 %; (b) BnBr, NaH, THF, rt, 85 %; (iii) (a) Allyltrimethylsilane, $TiCl_4$, CH_2Cl_2, -78 ^{o}C, 67 %; (b) $BH_3.SMe_2$, THF, NaOH, H_2O_2, 45 %; (c) Ts-Im, NaH, THF, 0 ^{o}C, 87 %; (iv) $C_9H_{19}MgBr$, Li_2CuCl_4, THF, 0 ^{o}C, 68 %; (v) (a) 10 %Pd/C, H_2, EtOH, 84 %; (b) Na/NH_3, -78 ^{o}C, 46 %.

Ojima *et al* (1998, Scheme-5)[30]

Ojima and Vidal have utilized *S*-Garner's aldehyde **58**, which on reaction with vinylmagnesium bromide afforded mixture of alcohols (6:1 ratio), which were separated to give the desired allyl alcohol **59**. Removal of the acetonide group followed by protection of hydroxyl groups as TIPS ether gave compound **61**. Rh-BIPHEPHOS complex catalyzed cyclo hydrocarbonylation of **61** at 65 ^{o}C and 4 atm CO and H_2 (1:1) in ethanol afforded the key intermediate **62**, which on reaction with allyl silane in the presence of $BF_3.OEt_2$ at –78 ^{o}C gave compound **63**. Compound **63** on Sequential hydroxyl group deprotection, hydrogenation and N-Boc deprtection delivered (-)-deoxoprosophylline **7**. They have also synthesized (+)-Prosopinine starting from *R*-Garner's aldehyde using almost the same reaction sequence.

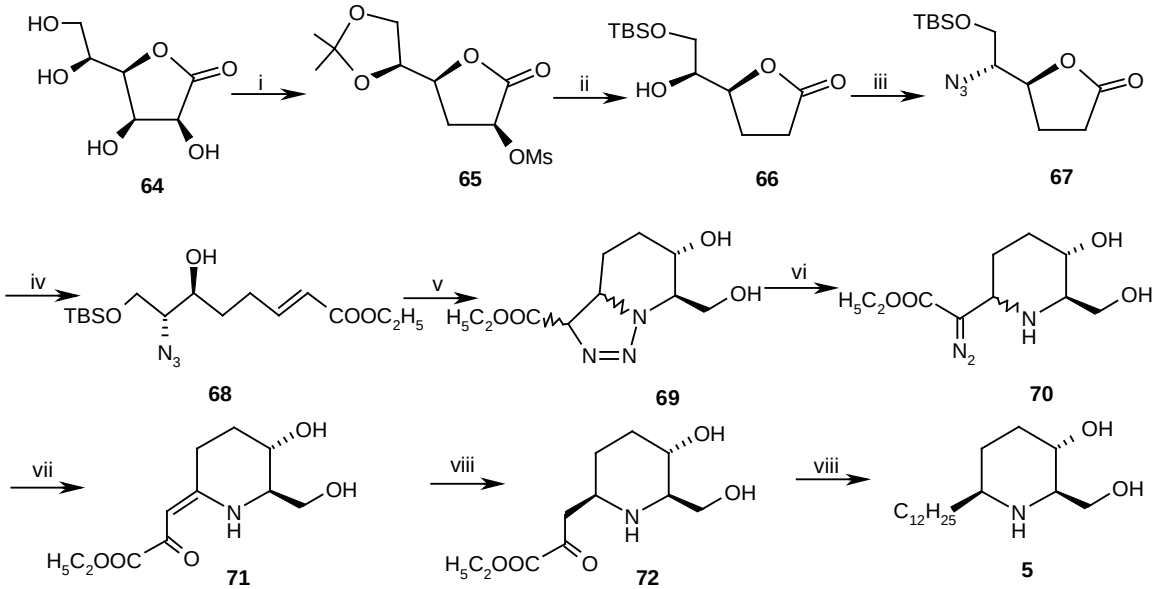


Scheme 5

Scheme 5. *Reagents and conditions:* (i) ref 31; (ii) Vinylmagnesium bromide, 77 %; (iii) *p*-TSA, MeOH, 95 %; (iv) TIPSCl, imidazole, DMF, 83 %; (v) $Rh(acac)(CO)_2$ (1 mol %), BIPHEPHOS (2 mol %), H_2/CO (1/1, 4 atm), EtOH, 65 ^oC, 96 %; (vi) $C_9H_{19}CH(SiMe_3)CH{=}CH_2$, $BF_3.Et_2O$, -78 ^oC, (vii) (a) TBAF, THF; (b) Pd/C, H_2; (c) CF_3COOH, CH_2Cl_2.

Herdeis *et al* (1999, Scheme-6)[32]

Herdies and Telser have synthesized α-mesylated lactone from L-gulanolactone **64** by known methods. Conversion of mesyl to Iodo followed by sequential halogenation, acetonide



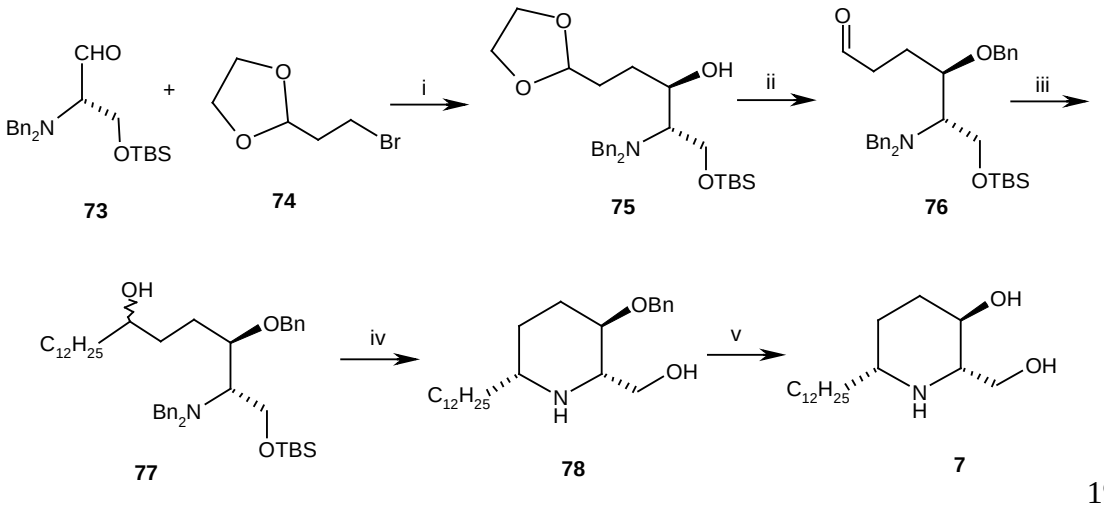
Scheme-6

Scheme 6. *Reagents and conditions:* (i) ref 33; (ii) (a) NaI, Acetone, reflux, 92 %; (b) H_2, Et_3N, 10 % Pd/C, 82 %; (c) Conc HCl, $^{i}PrOH$, 96 %; (d) TBSCl, Et_3N, DMAP, DMF, 99 %; (iii) (a) MsCl, Et_3N, CH_2Cl_2, 79 %; (b) NaN_3, DMPU, 70 ^{o}C, 65 %; (iv) (a) DIBAL-H, THF, -78 ^{o}C, 69 %; (b) Ph_3P=CHCOOEt, Toluene, rt; (v) Toluene, rt, 4 days, 98 %; (vi) Et_3N, CH_2Cl_2, 96 %; (vii) (a) $Rh_2(OAc)_4$, 97 %; (b) H_2, 10 %Pd/C, EtOH, 71 %; (viii) (a) TBSCl, imidazole, DMF, 84 %; (b) Dibal-H, n-Pentane, -78 ^{o}C, 66 %; (c) $Ph_3P^{+}(CH_2)_4CH_3\ Br^{-}$, LiHMDS, THF, 79 %; (d) H_2, 10 % Pd/C, EtOH, 93 %; (e) HCl, EtOH, 15 min, 6 N KOH, 87 %.

deprotection and selective protection of resultant diol as its TBS derivative delivered the lactone **66**. Conversion of hydroxy compound to azide **67** followed by DIBAL-H reduction and 2-carbon Wittig homologation delivered the α, β-unsaturated ester **68**, which on keeping at room temperature gave the triazole **69** as a diastereomeric mixture. Triazole **69** was converted into urethane derivative **71**, which on hydrogenation gave the piperidine **72** with the required stereochemistry. Sequential hydroxy protection, DIBAL-H reduction, Wittig homologation, hydrogenation and final hydrolysis delivered the (+)-deoxoprosophylline.

Zhu's approach (2001, Scheme-7)[34]

Zhu and Jourdant have synthesized compound **73** by a nucleophilic addition of Grignard reagent **74** (Buchi Grignard reagent) with serine aldehyde **75**. Protection of the secondary alcohol as its benzyl ether followed by acidic hydrolysis of dioxolane gave the aldehyde **76**. Reaction of aldehyde **76** with dodecyl magnesium bromide afforded alcohol **77**. Swern oxidation and catalytic transfer hydrogenolysis provided O-benzyl deoxoprosophylline



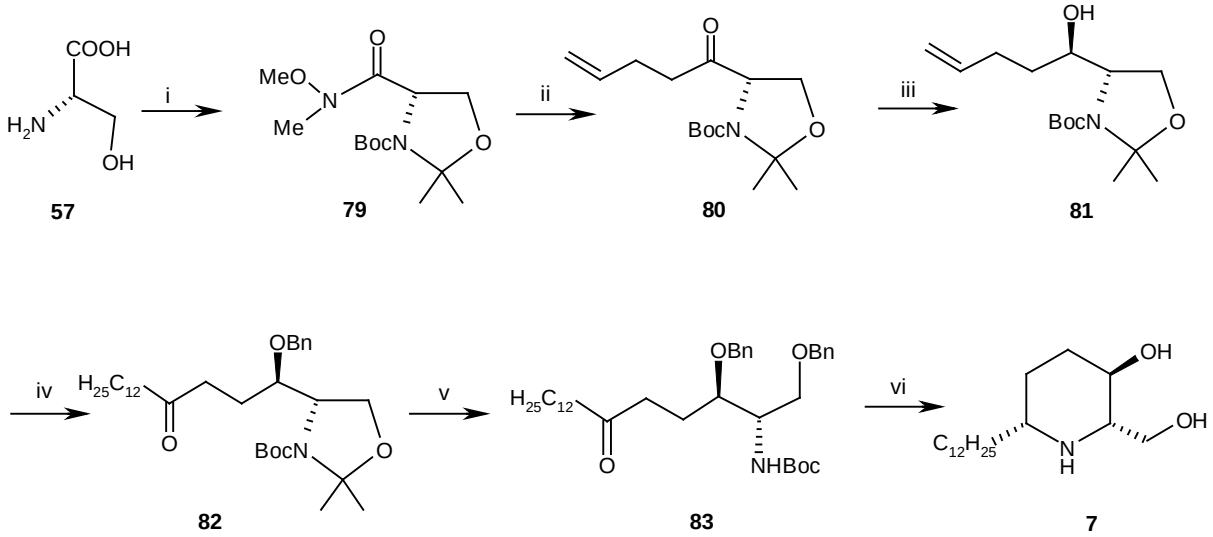
73 **74** **75** **76** **77** **78** **7**

78, which on debenzylation gave the (-)-deoxoprosophylline **7**.

Scheme 7. *Reagents and conditions:* (i) THF, rt, 86 %; (ii) (a) NaH, BnBr, TBAI, THF, 0 ^{o}C to rt, 85 %; (b) 3 N HCl, THF; (c) TBSCl, imidazole, DMF, rt, 90 %; (iii) $C_{12}H_{25}MgBr$, THF, 70 ^{o}C, 80 %; (iv) (a) DMSO, $(COCl)_2$ then Et_3N, 84 %; (b) $Pd(OH)_2$, Cyclohexene, EtOH, reflux; (v) Pd/C, MeOH, 73 %.

Apurba Datta *et al* (2001, Scheme-8)[35]

Datta and co-workers have utilized Weinreb amide **79** which on grignard reaction with 3-butenyl magnesium bromide afforded the ketone **80**. $ZnBH_4$ mediated chelation controlled reduction of ketone **80** gave the *anti* amino alcohol **81**. Protection of the free hydroxyl group as its benzyl ether followed by oxidative cleavage of double bond afforded the aldehyde, which on Grignard reaction with dodecyl magnesium bromide and subsequent oxidation gave the ketone **82**. Selective hydrolysis of acetonide and protection of hydroxyl as benzyl ether gave ketone **83**. Treatment of ketone **83** with formic acid followed by hydrogenation delivered (-)-deoxoprosophylline **7**.



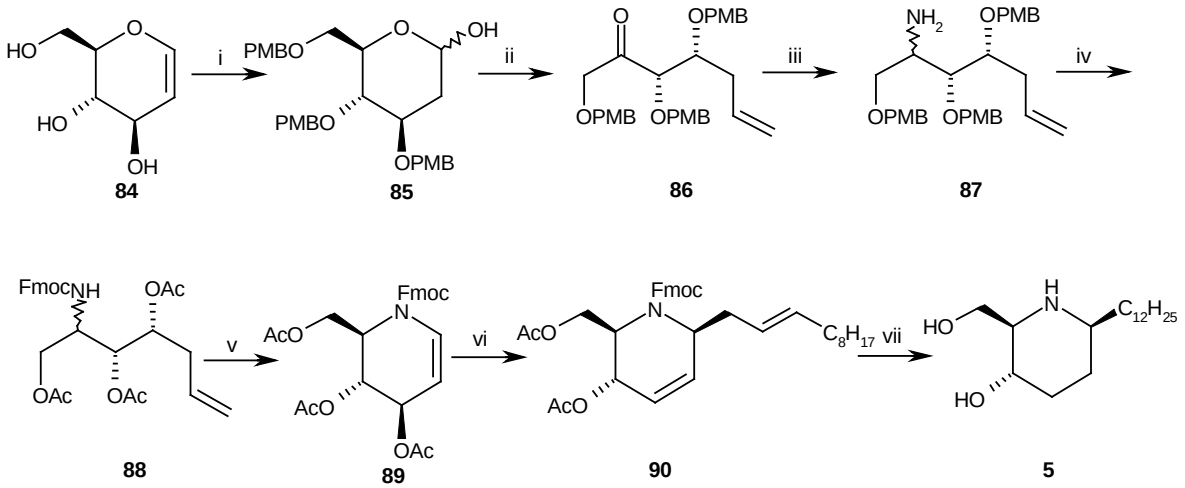
Scheme 8

Scheme 8. *Reagents and conditions:* (i) Ref. 36 b; (ii) CH_2=$CH(CH_2)_2MgBr$, THF, 0 ^{o}C, 76 %; (iii) $Zn(BH_4)_2$, Et_2O, Benzene, 70 %; (iv) (a) NaH, BnBr; (b) OsO_4, $NaIO_4$; (c) $C_{12}H_{25}MgBr$; (d) 2-Iodoxy

benzoic acid; (v) (a) 80 % AcOH in H_2O; (b) BnBr, Ag_2O; (vi) (a) HCOOH; (b) $Pd(OH)_2$, H_2, EtOH-HCl.

Shipman *et al* (2002, Scheme-9)[36]

Shipman and co-workers have utilized D-glucal **84** as the chiral starting material.. Protection of the hydroxyl groups followed by hydration of double bond gave hemiacetal **85**. Wittig olefination of **85** followed by TPAP oxidation of the resulting secondary alcohol gave ketone **86**, which was converted in to amine **87**. Ozonolytic cleavage of the terminal double bond, followed by dehydration of the hemiacetal gave 3, 4, 6-tri-O-acetylimino glucal **89**. Addition of 3-(trimethyl silyl) dodecec-1-ene to 6 smoothly gave piperidine **90** after Fmoc deprotection. Hydrogenation of **90** followed by removal of the acetate groups delivered (+)-deoxoprosophylline **5**.

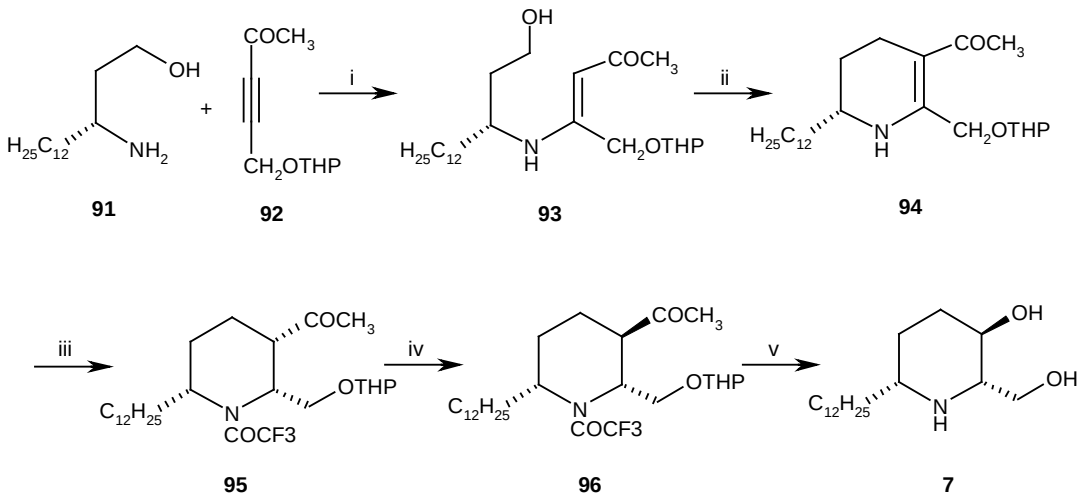


Scheme 9

Scheme 9. *Reagents and conditions:* (i) (a) NaH, PMBCl, DMF; (b) $Hg(OAc)_2$, THF-H_2O, then $NaBH_4$; (ii) (a) $Ph_3P{=}CH_2$, Toluene; (b) TPAP, NMO, 4 A^o molecular sieves, CH_2Cl_2; (iii) (a) $NH_2OH.HCl$, Pyridine, EtOH, 60 ^oC; (b) $LiAlH_4$, Et_2O, RT; (iv) (a) Fmoc-Cl, K_2CO_3, THF-H_2O (3:1); (b) CF_3COOH, CH_2Cl_2; (c) Ac_2O, Pyridine, rt; (v) (a) O_3, -78 ^oC, CH_2Cl_2, then Me_2S, RT; (b) $(COCl)_2$, Et_3N, DMF; (vi) (a) $BF_3.Et_2O$, CH_2Cl_2, $CH_2{=}CHCH(SiMe_3)C_9H_{19}$, - 60 ^oC, 3h; (b) Piperidine, CH_2Cl_2, rt, 1 h; (vi) (a) H_2, Pt/C, EtOH, 1.5 h; (b) LiOH, THF-H_2O, 2.5 h.

Dawei Ma *et al* (2003, Scheme-10)[37]

Dawei Ma and Nan Ma have prepared chiral amino alcohol **91** following Davies procedure.[38] Michael addition of **91** to the alkynone **92** gave the enamine **93**, which on treatment with PPh_3 and CCl_4 followed by refluxing in acetonitrile afforded cyclic enamine **94**. Hydrogenation of **94** gave the corresponding piperidine, which was protected with tri fluoro acetic anhydride to provide the amide **95**. Epimerization of the 3-acetyl group of **95** was achieved by treating with DBU to deliver compound **96**. Treatment of **96** with trifluoro peracetic acid afforded the Baeyer-Villiger product, which was hydrolysed to deliver the (-)-deoxoprosophylline **7**.



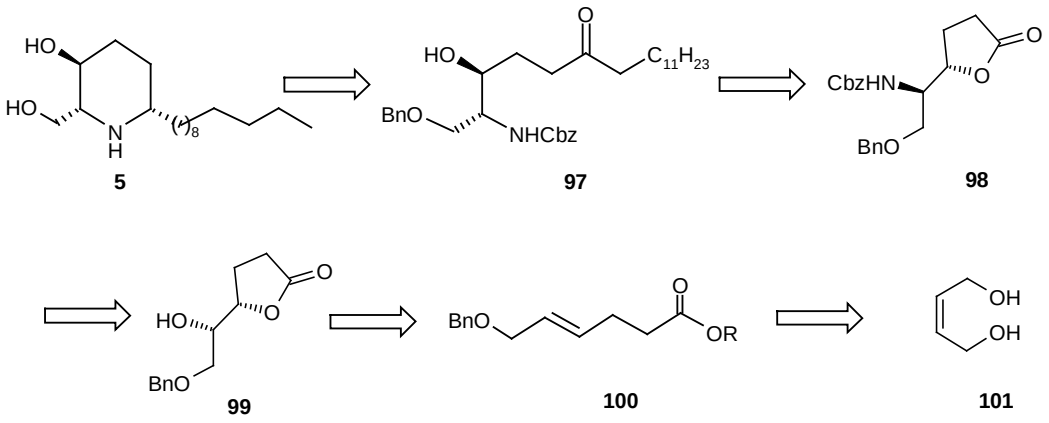
Scheme 10

Scheme 10. *Reagents and conditions:* (i) DMF, rt, 82 %; (ii) (a) PPh_3, CBr_4, Et_3N, CH_2Cl_2; (b) Et_3N, CH_3CN, Reflux, 76 %; (iii) (a) PtO_2, H_2, AcOH; (b) $(CF_3CO)_2O$, Et_3N, DMAP; (iv) DBU, THF, rt, 87 %; (v) (a) 95 % H_2O_2, $(CF_3CO)_2O$, NaH_2PO_4, CH_2Cl_2; (b) HCl-MeOH, 45 %.

Present work:

Although several synthesis of both (+)- and (-)-deoxoprosophylline are documented in the literature through varied synthetic routes, most involve a large number of steps or employing a chiral pool starting material. However, it is still desirable to develop a general strategy that provides a common pivotal intermediate from which 2,3,6-trisubstituted piperidines with desired stereochemistry can be readily derived. With this in mind, we envisaged establishing a versatile methodology for the synthesis of an enantio pure 2,6-disubstituted piperidine-3-ol framework starting from commercially available *cis*-2-butene-1, 4-diol.

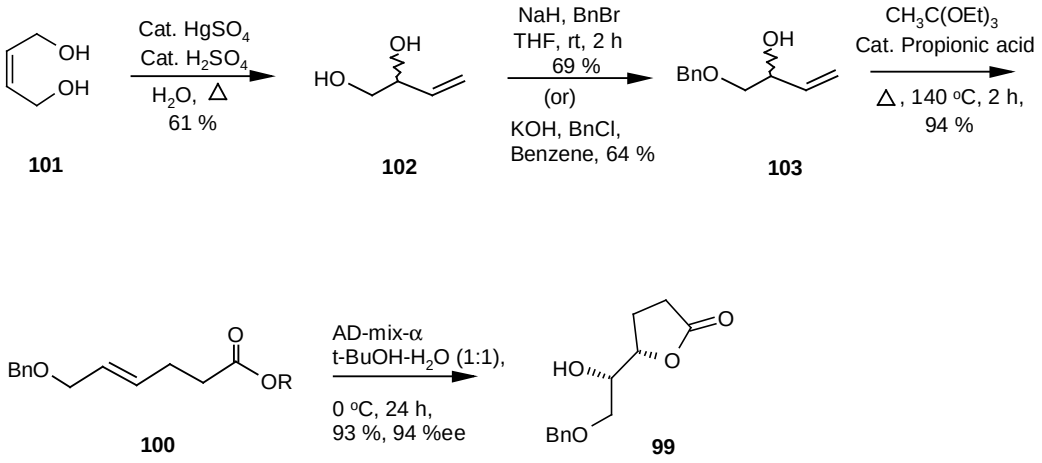
The retrosynthetic analysis for the stereoselective synthesis of (+)-deoxoprosophylline is depicted in **scheme 11**. It was envisaged that simple one step hydrogenation could be used to form the target molecule from the ketone **97**. The ketone **97** could be obtained from Cbz lactone **98**, which in turn could be derived from hydroxy lactone **99**. The hydroxy lactone **99**, is the versatile intermediate for our synthesis could be obtained from *cis*-2-butene-1, 4-diol.



Scheme 11: **Retrosynthetic analysis**

The synthesis of (+)- deoxoprosophylline commenced from *cis*-2-butene-1, 4-diol **101** as shown in scheme **11.** The commercially available *cis*-2-butene-1, 4-diol was converted into

monoprotected allyl alcohol **103**, which on Claisen orthoester rearrangement and Sharpless asymmetric dihydroxylation delivered the hydroxy lactone **99** with the required stereochemistry. The enantiopurity of the hydroxy lactone was estimated to be in excess of 94 % using chiral HPLC analysis. (Chiralcel OD, 80:20, hexane:^{i}PrOH, 1 mL /min, 254 nm).



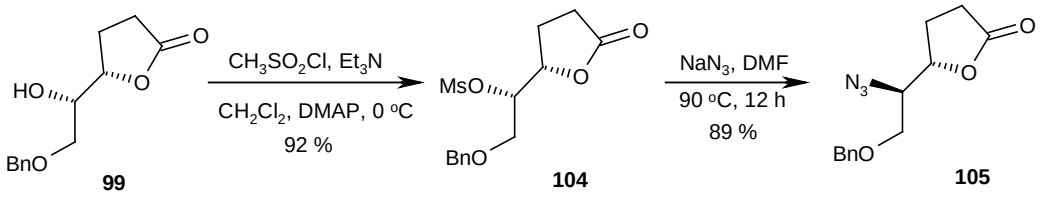
101 **102** **103** **100** **99**

Scheme 12

Having the key synthon **99** in hand, our next concern was to convert it into azido lactone **105**. Thus treatment of hydroxy lactone **99** with mesyl chloride and Et_3N in anhydrous CH_2Cl_2 at 0 ^{o}C provided mesylate **104** in 92 % yield. In the IR spectrum disappearance of hydroxyl absorption was observed. In the ^{1}H-NMR spectrum the singlet at δ 3.06 integrating for three protons and a downfield shift of CH-OMs proton from 3.83 to 4.83 indicating the formation of mesylate **104**. All the spectral data were in good agreement with the structure **104**.

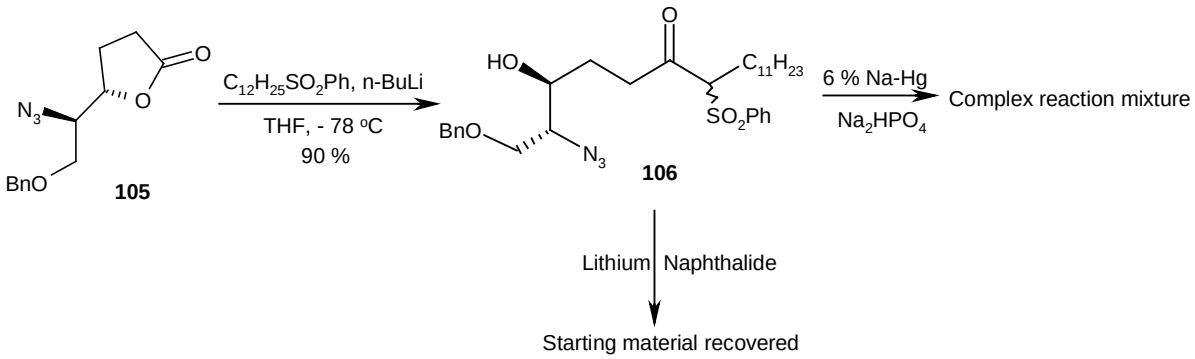
Nucleophilic displacement of the mesylate **104** was carried out with NaN_3 in anhydrous DMF at 90 ^{o}C for 16 h to deliver the azido lactone **105** in 89 % yield. The IR spectrum showed strong absorption at 2106 and 1783 cm^{-1}. In the ^{1}H-NMR spectrum disappearance of singlet at δ 3.06 and an upfield shift of CH-N_3 proton from δ 4.83 to δ 3.79 was observed. It was further supported by ^{13}C-nmr spectra, which showed disappearance of

corresponding mesyl resonance at δ 38.6. All the spectral data including elemental analysis data were also in good agreement with the assigned structure **105**.



Scheme 13

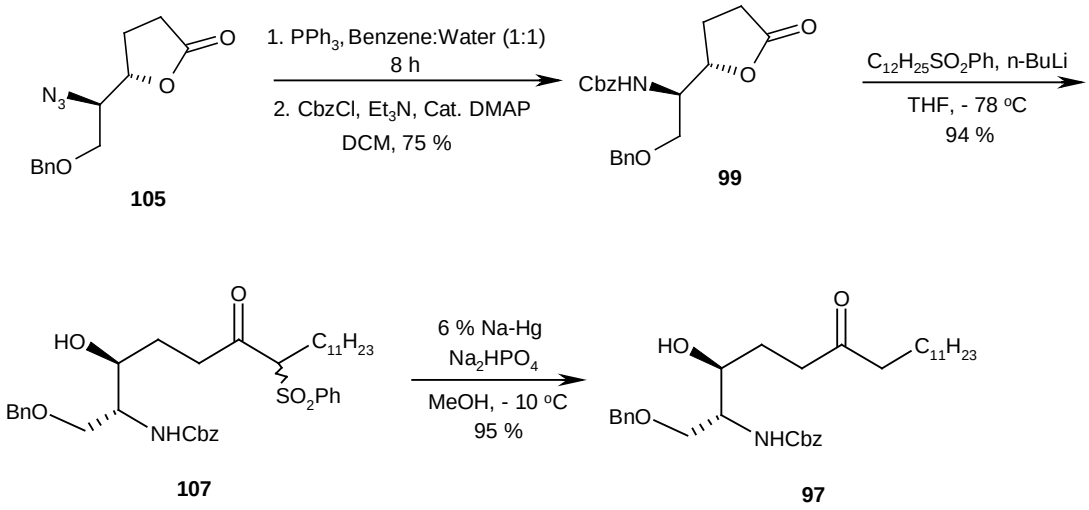
Having had the azidolactone **105** in hand, our next concern was to open the azidolactone with respective alkyl side chain and cyclize the resultant keto azide. Thus opening of azidolactone **105** was achieved by using $C_{12}H_{25}SO_2Ph$ and n-BuLi at – 78 °C to deliver the compound **106** as a 1:1 diastereo mixture. The next immediate concern was desulphonylation of compound **106**. For the desulfonylation use of lithium naphthalenide led to the recovery of the starting material. Next Na-Hg was tried for the desulfonylation. Attempted desulphonation, employing Na-Hg led to the formation of complex reaction mixture.



As the desulphonylation of **106** gave unforeseen problems, the azidolactone **105** was converted into Cbz lactone **98**. Thus the azide was reduced to amine using triphenylphosphine and water and the resulting amine was protected as its cbz derivative using CbzCl, TEA in

presence of a catalytic amount of DMAP to yield **98**. In the IR spectrum disappearance of strong absorption at 2106 cm^{-1} was observed indicating the absence of azide. The ^{1}H-NMR, ^{13}C-NMR, elemental analysis data were ion good agreement with the structure **98**.

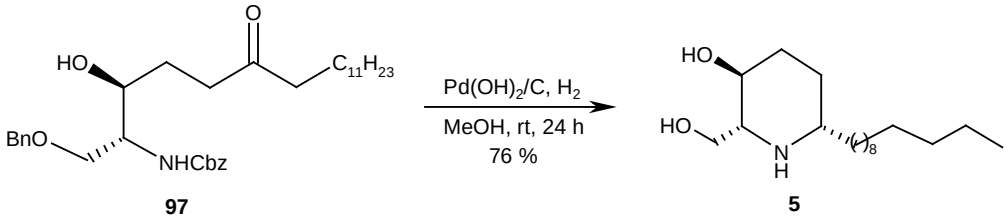
Next the Cbz lactone was opened by using $C_{12}H_{25}SO_2Ph$ and n-BuLi at – 78 ^{o}C to deliver the compound **107** in 94 % yield as a 1:1 mixture of two diastereomers at the C-7 position. The benzene sulfonyl moiety of **107** was successfully removed with 6 % Na-Hg and Na_2HPO_4 in MeOH at - 10 ^{o}C to give **97** in 95 % yield. In the IR spectrum of **97** strong carbonyl absorption at 1709 cm^{-1} was observed. The ^{1}H-NMR, ^{13}C-NMR, elemental analysis data were in good agreement with the structure **97**.



105 **99** **107** **97**

Scheme 14

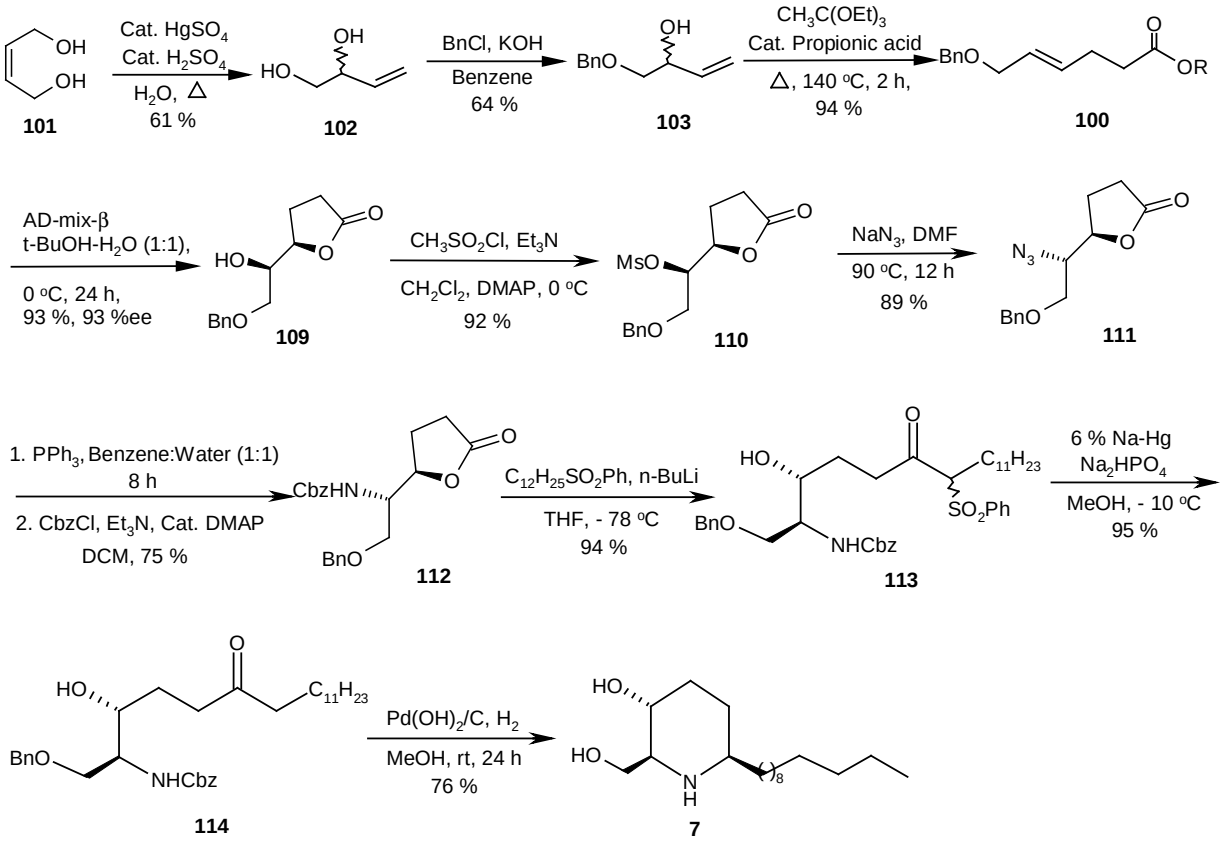
Finally removal of the protecting groups and cyclization of the ketone **97** was achieved in one pot reaction by using $Pd(OH)_2$ and H_2 to deliver the (+)-deoxoprosophylline **5** having mp 85-86 ^{o}C (lit 83 ^{o}C)[33] in 76 % yield. In the IR spectrum disappearance of carbonyl absorption was observed. The $[\alpha]_D$ + 13.5 (c = 0.3, $CHCl_3$) obtained for **5** is in good agreement with the reported value $[\alpha]_D$ + 13 (c = 0.22, $CHCl_3$)[33]. The structure was of **5** further confirmed by ^{1}H, ^{13}C-NMR and all the spectral data were in good agreement with the literature data.



97 **5**

Scheme 15

Having accomplished the synthesis of (+)- deoxoprosophylline **5**, we turned our attention towards the synthesis of its enantiomer *i.e* (-)- deoxoprosophylline **7**. Accordingly *cis*-2-butene-1, 4-diol **101** was transformed in a similar fashion to afford (-)-deoxoprosophylline **7** following a similar sequence however, using AD-mix-β in the crucial Sharpless asymmetric dihydroxylation of β, γ-unsaturated ester **100**.



Scheme 16

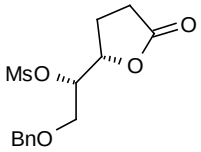
Conclusion:

In conclusion (+)- and (-)-deoxoprosophylline were efficiently synthesized from readily available *cis*-2-butene-1,4-diol. The present synthesis of (+)- and (-)-deoxoprosophylline having an overall yield of 37% in 8 steps starting from the known allyl alcohol **99** is better than earlier reported syntheses. By using Sharpless asymmetric

dihydroxylation as the key step, we have demonstrated that both enantiomers of deoxoprosophylline can be readily accessed.

Experimental:

6-Benzyloxy-2,3-dideoxy-5-mesyloxy-L-threo-hexano-1,4-lactone (104)

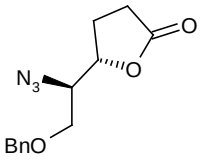


To a solution of **99** (1.5 g, 6.35 mmol) in anhydrous CH_2Cl_2 (20 mL) at 0 ^oC were added Et_3N (1.33 mL, 9.53 mmol), MsCl (0.54 mL, 6.99 mmol) and DMAP (cat). The reaction mixture was stirred for 5 h and then poured into aqueous sodium hydrogen carbonate and extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude oily compound was purified by silica gel column chromatography using EtOAc-light petroleum (3:7) as an eluent to afford **104** (1.83 g, 92 %) as light yellow oil.

Appearance	**:**	**Light yellow oil**
Molecular Formula	**:**	**$C_{14}H_{18}O_6S$**
Yield	**:**	**92 %.**
IR ($CHCl_3$, cm^{-1})	**:**	**1781, 1608, 1174.**
$[\alpha]_D$	**:**	**+ 8.31 (*c* = 1, $CHCl_3$)**
^{1}H NMR ($CDCl_3$, 500MHz)	**:**	**δ 2.26 (m, 1H), 2.36 (m, 1H), 2.46 (ddd, *J* = 16.95, 10.08, 6.41 Hz, 1H), 2.67 (ddd, *J* = 16.95, 9.62, 6.41 Hz, 1H), 3.06 (s, 3H), 3.71 (dd, *J* = 10.57 Hz, 3.67 Hz, 1H), 3.83 (dd, *J* = 10.54 Hz, 7.34 Hz, 1H), 4.65 (m, 2H), 4.68 (ddd, *J* = 8.25, 5.54, 3.27 Hz, 1H), 4.80 (m, 1H), 7.32 (m, 5H).**
^{13}C NMR	**:**	**δ 23.6, 27.3, 38.6, 68.5, 73.4, 77.5, 81.7, 127.7, 127.9,**

($CDCl_3$, 125MHz)		**128.4, 136.9, 176.0.**
MS (ESI, Solv.: MeOH + H_2O + CH_3COONH_4)	**:**	**m/z = 332.05 ($M+NH_4^+$).**
Elemental Analysis	**:**	Analysis calcd. for $C_{14}H_{18}O_6S$: C, 53.49; H, 5.77; S, 10.19. Found: C, 53.62; H, 5.86, 10.38.

5-Azido-6-benzyloxy-2,3,5-trideoxy-D-*erythro*-hexano-1,4-lactone (105)



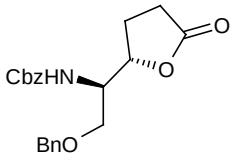
To a solution of **104** (1.8 g, 5.73 mmol) in anhydrous DMF (15 mL) was added sodium azide (0.74 g, 11.46 mmol) and the reaction mixture was stirred at 80 ^oC for 16 h. After completion of the reaction the reaction mixture was cooled to room temperature, diluted with water and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc-light petroleum (3:7) as an eluent to afford **105** (1.24 g, 89 %) as colourless oil.

Appearance	**:**	**Colourless oil**
Molecular Formula	**:**	**$C_{13}H_{15}O_3N_3$**
Yield	**:**	**89 %.**
IR ($CHCl_3$, cm^{-1})	**:**	**2106, 1783, 1250, 1110.**
$[\alpha]_D$	**:**	**- 16.61 (*c* = 1, $CHCl_3$)**
^{1}H NMR ($CDCl_3$ + CCl_4, 500MHz)	**:**	**δ 2.12 (m, 1H), 2.23 (m, 1H), 2.44-2.59 (m, 2H), 3.62 (dd, *J* = 10.08, 6.41Hz, 1H), 3.66 (dd, *J* = 10.08, 4.58 Hz, 1H), 3.79 (q, *J* = 5.82 Hz, 1H), 4.55 (m, 3H), 7.32 (m, 5H).**
^{13}C NMR ($CDCl_3$+CCl_4, 125MHz)	**:**	**δ 23.1, 27.6, 63.0, 68.9, 73.1, 77.6, 127.3, 127.6, 128.2, 137.1, 175.2.**

MS (ESI, Solv.: MeOH + H_2O + CH_3COONH_4) : **m/z = 279.05 ($M+NH_4^+$).**

Elemental Analysis : Analysis calcd. for $C_{13}H_{15}O_3N_3$: C, 59.75; H, 5.79; N, 16.08. Found: C, 59.56; H, 5.84, 16.19.

6-Benzyloxy-5-(benzyloxycarbonylamino)-2,3,5-trideoxy-D-erythro-hexano-1,4-lactone (98)



To a solution of **106** (1.6 g, 6.13 mmol) in benzene-water (9:1, 10 mL) was added PPh_3 (2.41 g, 9.19 mmol) and the reaction mixture was stirred at 45 ^oC for 8 h. After completion of the reaction, the solvent was removed on rotavapour under reduced pressure and the resultant residue was used as such for the next reaction.

To the crude and dried reaction mixture in anhydrous CH_2Cl_2 were added Et_3N (2.56 mL, 18.39 mmol), CbzCl (1.32 mL, 9.19 mmol) and DMAP (cat) at 0 ^oC, and stirred for 12 h at room temperature. The reaction mixture was quenched water and extracted with EtOAc (2 x 30 mL), the combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc-light petroleum (3:7) as an eluent to afford **98** (1.69 g, 75 %) as white solid.

Appearance : **White solid**

Molecular Formula : **$C_{21}H_{23}O_5N$**

Yield : **75 %.**

M. P. : **126 ^oC**

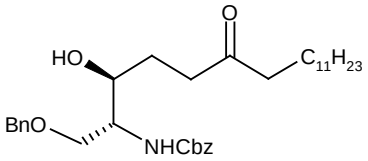
IR ($CHCl_3$, cm^{-1}) : **3020, 1775, 1609, 1114, 758.**

$[\alpha]_D$: **- 7.80 (*c* = 1, $CHCl_3$)**

^1H NMR : **δ 2.12 (m, 2H), 2.36 (m, 1H), 2.45 (m, 1H), 3.48 (dd, *J***

($CDCl_3$ + CCl_4, 500MHz)		**= 9.16, 3.21 Hz, 1H), 3.69 (d, *J* = 8.71 Hz, 1H), 3.78 (t, *J* = 8.71 Hz, 1H), 4.39 (d, *J* = 11.52 Hz, 1H), 4.43 (d, *J* = 11.52 Hz, 1H), 4.47 (m, 1H), 4.98 (d, *J* = 11.52 Hz, 1H), 5.02 (d, *J* = 11.52 Hz, 1H), 5.27 (d, *J* = 9.17 Hz, 1H, -NH), 7.17-7.27 (m, 10H).**
^{13}C NMR ($CDCl_3$+CCl_4, 50MHz)	**:**	**δ 24.6, 27.9, 53.6, 67.0, 68.7, 73.5, 78.2, 127.7, 128.1, 128.4, 136.1, 137.4, 156.1, 176.3.**
MS (ESI, Solv.: MeOH + H_2O + CH_3COONH_4)	**:**	**m/z = 387.05 ($M+NH_4^+$).**
Elemental Analysis	**:**	Analysis calcd. for $C_{21}H_{23}O_5N$: C, 68.27; H, 6.27; N, 3.79. Found: C, 68.26; H, 6.19, N, 3.86.

(2R, 3S)-1-Benzyloxy-2-(benzyloxycarbonylamino)-3-hydroxy-octadecane-6-one (97)



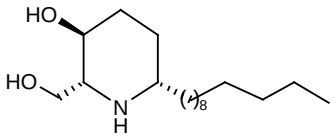
To a solution of sulphone **108** (2.51 g, 8.10 mmol) in anhydrous THF cooled to 0 ^oC was added 1.6 M *n*-BuLi solution in hexane (10 mL, 16.20 mmol). After stirring for 10 min, the reaction mixture was cooled to –78 ^oC, and then a solution of 9 (1.5 g, 4.05 mmol) in anhydrous THF was added drop wise. After stirring at – 78 ^oC for 1 h, the reaction mixture was quenched with sat. NH_4Cl and poured in to water (10 mL). After extraction with EtOAc (2 x 20 mL), the combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc-light petroleum (3:7) as an eluent to afford **107** (2.58 g, 94 %) as a syrup.

To a solution of **107** (2.2 g, 3.23 mmol) in anhydrous MeOH were added 6 % Na-Hg (0.45 g) and Na_2HPO_4 (0.46 g, 3.23 mmol) at –10 ^oC and stirred at the same temperature.

After 1.5 h, the reaction mixture was quenched with sat. NH_4Cl and poured in water (10 mL). After extraction with EtOAc (2 x 25 mL), the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc-light petroleum (2:8) as an eluent to afford **97** (1.65 g, 95 %) as a white solid.

Appearance	**:**	**White solid**
Molecular Formula	**:**	**$C_{33}H_{49}O_5N$**
Yield	**:**	**95 %.**
M. P.	**:**	**136 ^oC (White solid).**
IR ($CHCl_3$, cm^{-1})	**:**	**3445, 1709, 1607.**
$[\alpha]_D$	**:**	**- 8.76 (*c* = 1, $CHCl_3$)**
^1H NMR ($CDCl_3$ + CCl_4, 200MHz)	**:**	**0.86 (t, *J* = 6.5 Hz, 3H), 1.2-1.4 (m, 18H), 1.52-1.75 (m, 4H), 2.33 (m, 2H), 2.56 (m, 3H), 3.57-3.80 (m, 4H), 4.45 (s, 2H), 5.55 (s, 2H), 5.48 (d, *J* = 8.57 Hz, 1H, -NH), 7.25-7.32 (m, 10H).**
^{13}C NMR ($CDCl_3$+CCl_4, 50MHz)	**:**	**δ 14.2, 22.7, 23.9, 24.5, 27.8, 29.4, 29.6, 31.9, 39.0, 42.9, 54.3, 66.8, 68.9, 72.6, 73.6, 127.8, 128.1, 128.0, 136.43, 137.4, 156.2, 211.2**
MS (ESI, Solv.: MeOH + H_2O + CH_3COONH_4)	**:**	**m/z = 539.04 ($M+NH_4^+$).**
Elemental Analysis	**:**	Analysis calcd. for $C_{33}H_{49}O_5N$: C, 73.43; H, 9.15; N, 2.59. Found: C, 73.68; H, 9.32, 2.74.

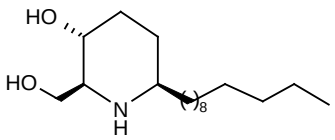
(+)-Deoxoprosophylline (5) :



To a solution of **97** (0.25 g, 0.46 mmol) in anhydrous MeOH was added $Pd(OH)_2$ (0.02 g) and the mixture was degassed with argon and flushed with H_2 for 5 min. After stirring under an atmosphere of H_2 for 24 h at room temperature, the mixture was filtered through a pad of celite and the solvent was concentrated under reduced pressure. The residue was purified on silica gel with MeOH-CH_2Cl_2 (1:9) as an eluent to afford **5** (0.10 g, 76 %) as white solid.

Appearance	**:**	**White solid**
Molecular Formula	**:**	**$C_{18}H_{37}O_2N$**
Yield	**:**	**76 %.**
M. P.	**:**	**85-86 ^oC**
IR ($CHCl_3$, cm^{-1})	**:**	**3417, 2980, 2880.**
$[\alpha]_D$		**+ 13.5 (*c* = 0.3, $CHCl_3$)**
^1H NMR ($CDCl_3$ + CCl_4, 200MHz)	**:**	**δ 0.88 (t, *J* = 6.5 Hz, 3H), 1.26 (m, 24H), 1.72-1.79 (m, 1H), 2.02-2.06 (m, 1H), 2.54-2.58 (2H, m), 2.98 (broad, 3H), 3.47 (dt, *J* = 10.1, 4.3 Hz, 1H), 3.71 (dd, *J* = 10.9, 5.1 Hz, 1H), 3.83 (dd, *J* = 10.9, 4.3 Hz, 1H).**
^{13}C NMR ($CDCl_3$+CCl_4, 50MHz)	**:**	**δ 14.2, 22.8, 26.3, 29.4, 29.7, 29.8, 30.8, 32.0, 33.8, 36.4, 56.2, 63.4, 63.9, 69.8.**
MS (ESI, Solv.: CH_3CN + H_2O + CH_3COONH_4)	**:**	**m/z = 300.05 (M+1).**
Elemental Analysis	**:**	Analysis calcd. for $C_{18}H_{37}O_2N$: C, 72.19; H, 12.45; N, 4.68. Found: C, 72.16; H, 12.24, 4.88.

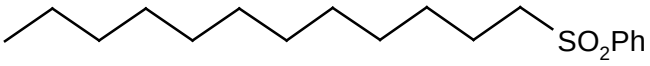
(-)-Deoxoprosophylline (7)



Compound **7** was prepared by following the same procedure for compound **5.**

Appearance	**:**	**White solid**
Molecular Formula	**:**	**$C_{18}H_{37}O_2N$**
Yield	**:**	**76 %.**
M. P	**:**	**89-90 ^oC**
$[\alpha]_D$	**:**	**-12.2 (*c* = 0.3, $CHCl_3$)**
^{13}C NMR	**:**	**δ 14.1, 22.7, 26.1, 29.4, 29.7, 29.8, 31.9, 33.3, 35.4, 56.7,**
($CDCl_3$+CCl_4, 50MHz)		**62.7, 63.5, 69.7.**

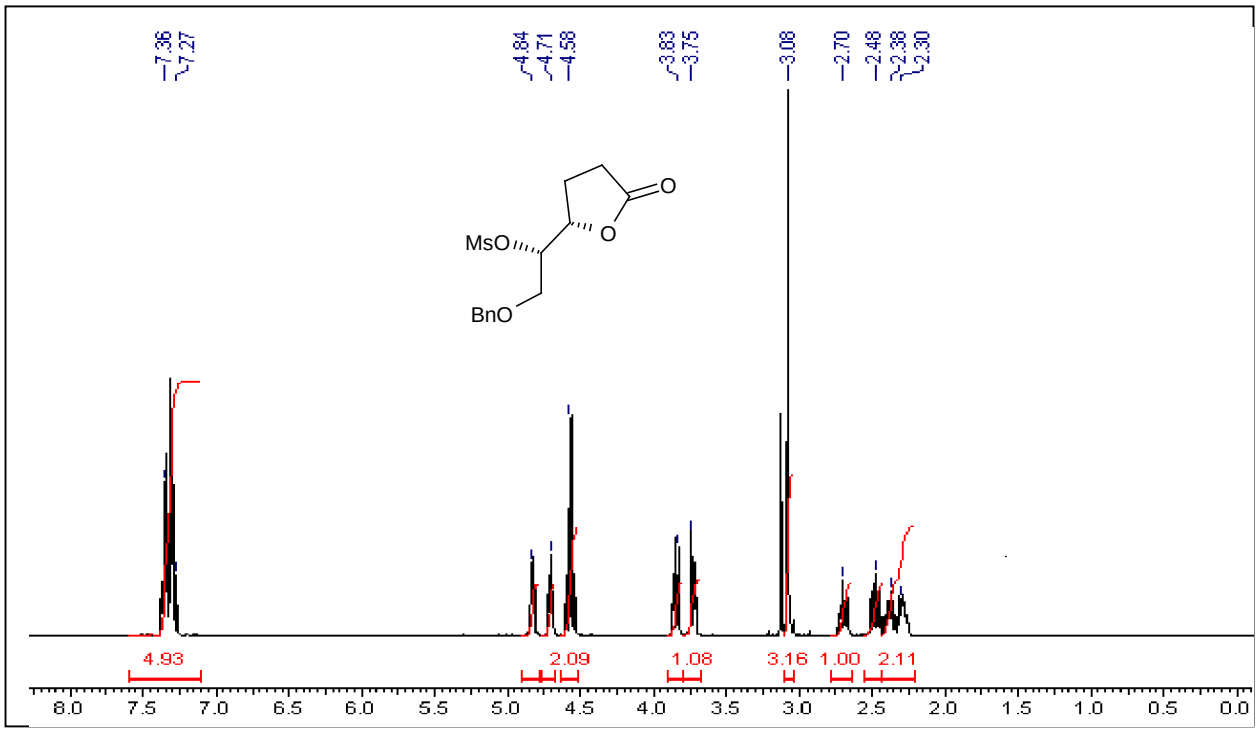
Dodecyl phenyl sulphone (108)



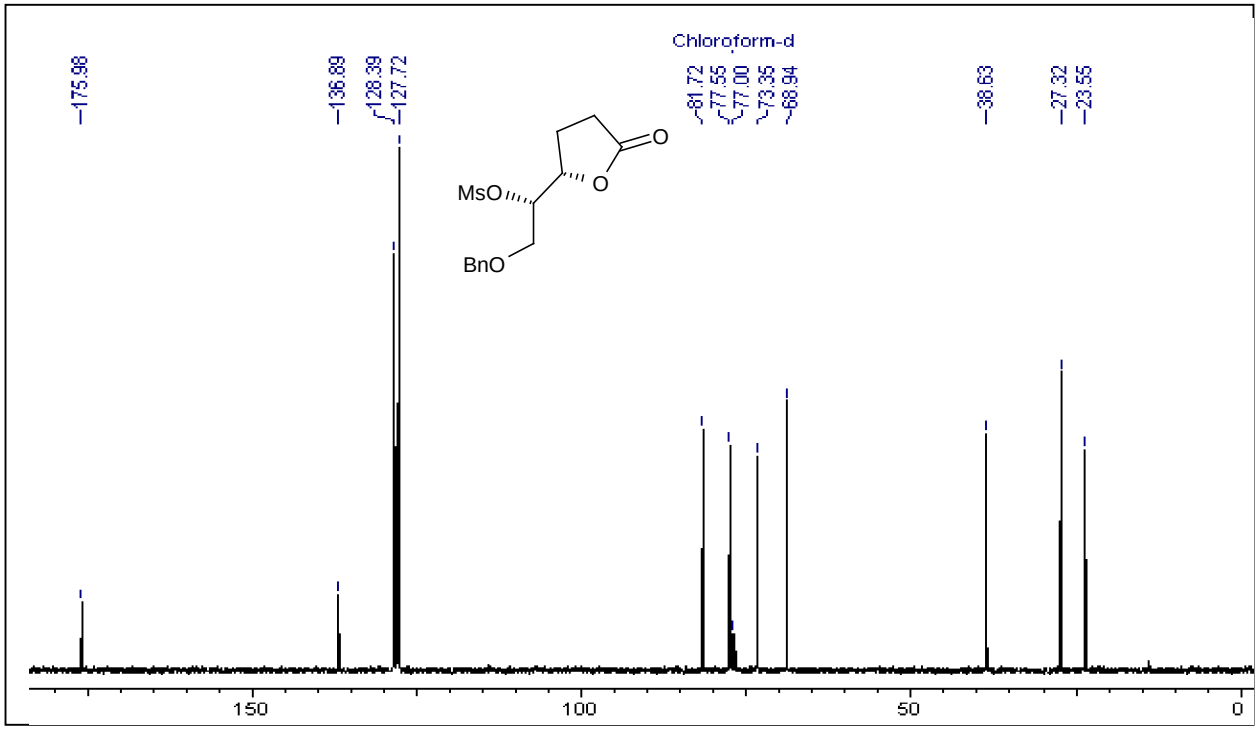
To a solution of benzenesulfinic acid sodium salt (1.74 g, 10.59 mmol) in anhydrous MeOH (20 mL) was added 1-bromo dodecane (2.5 mL, 9.62 mmol). The reaction mixture was refluxed for 24 h, and then cooled to room temperature and the solvent was evaporated. The crude reaction mixture was diluted with water (20 mL), and extracted with EtOAc (2 x 25 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography using EtOAc-light petroleum (1:9) as an eluent to afford **108** (2.62 g, 88 %) as white crystalline solid.

Molecular Formula	**:**	**$C_{18}H_{30}O_2S$**
Yield	**:**	**88 %.**

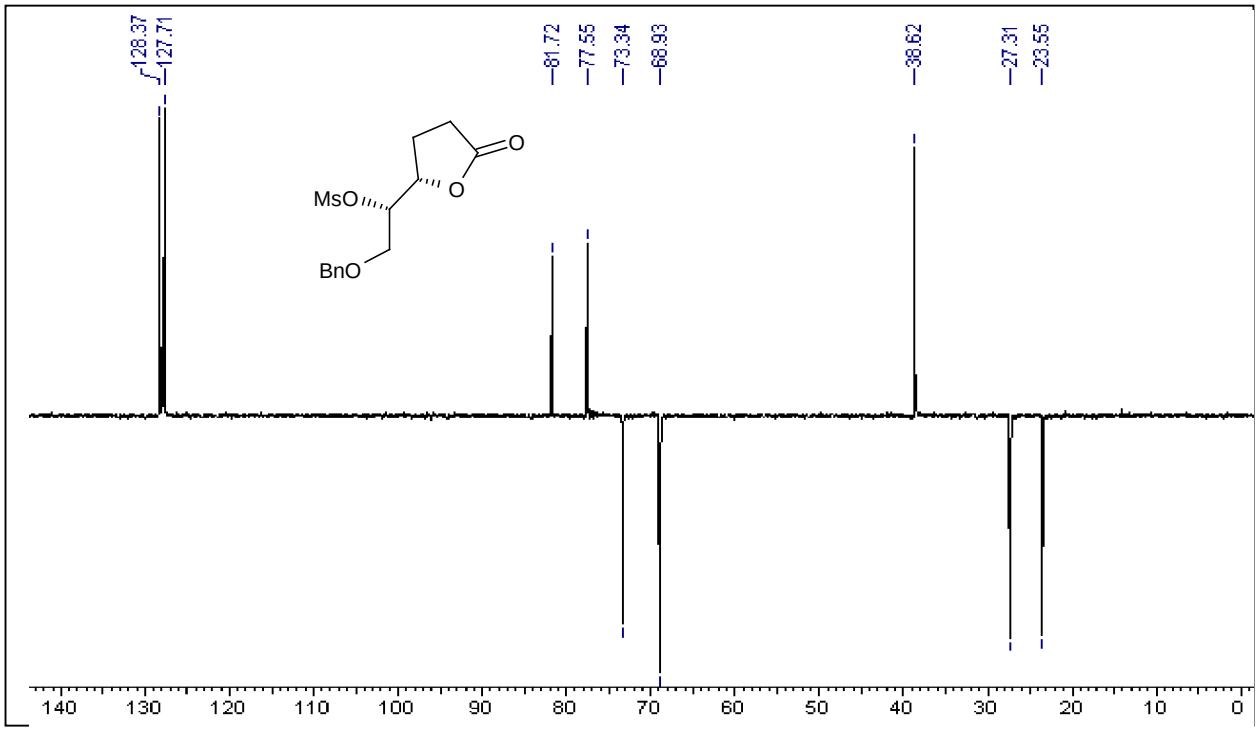
M. P.	**:**	**64 ^{o}C (White solid).**
IR ($CHCl_3$, cm^{-1})	**:**	**1316, 1303, 1288, 1144.**
^{1}H NMR ($CDCl_3$ + CCl_4, 200MHz)	**:**	**δ 0.88 (t, *J* = 6.6 Hz, 3H), 1.21-1.41 (m, 18H), 1.70 (m, 2H), 2.05 (m, 2H), 7.60 (m, 3H), 7.88 (m, 2H).**
^{13}C NMR ($CDCl_3$+CCl_4, 50MHz)	**:**	**δ 13.92, 22.5, 28.1, 28.8, 29.1, 29.4, 31.7, 56.1, 127.8, 129.0, 133.2, 139.4**
Elemental Analysis	**:**	Analysis calcd. for $C_{18}H_{30}O_2S$: C, 69.62; H, 9.74; S, 10.32. Found: C, 69.76; H, 9.48, 10.21.



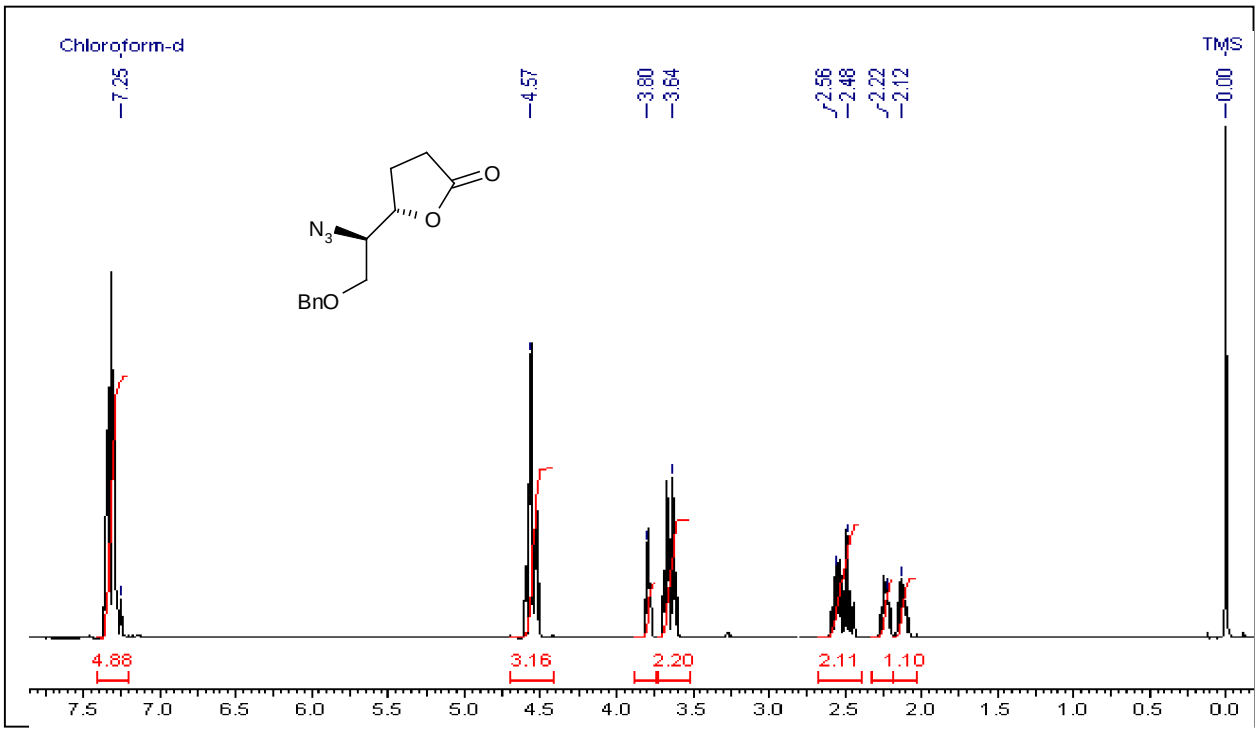
^{1}H NMR Spectrum of compound 104 in $CDCl_3$



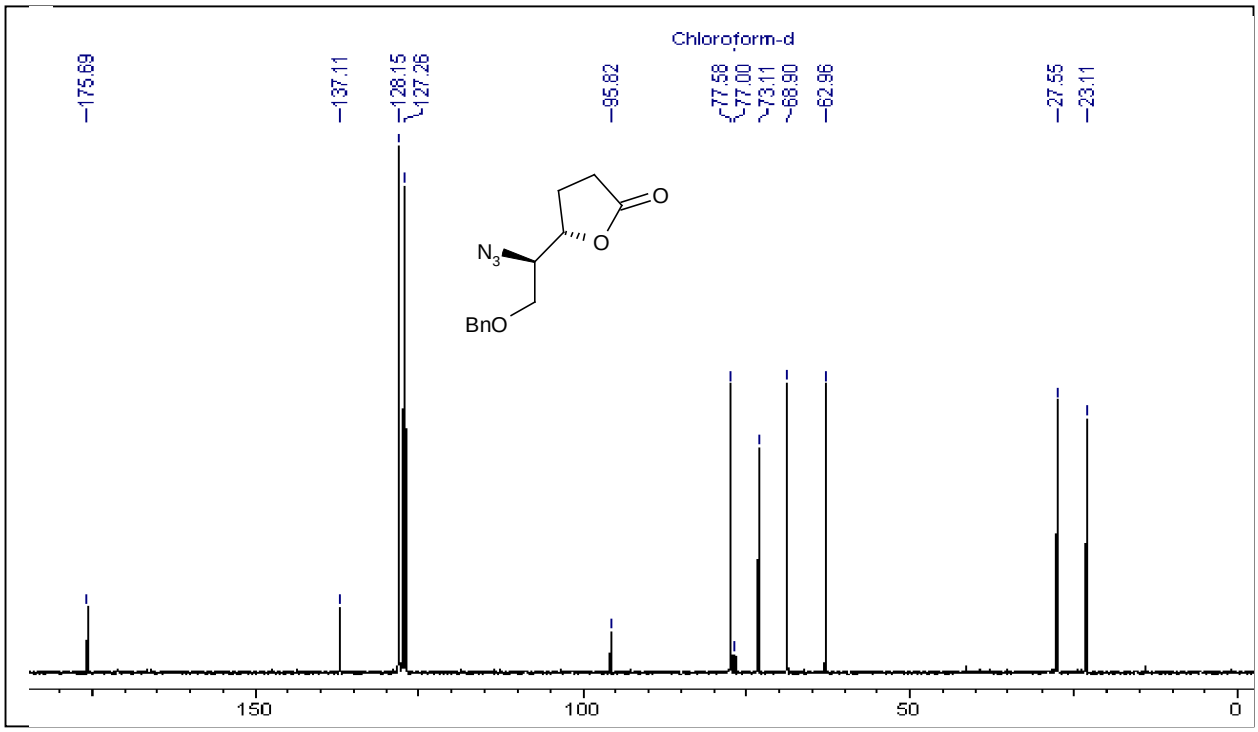
^{13}C NMR Spectrum of compound 104 in $CDCl_3$



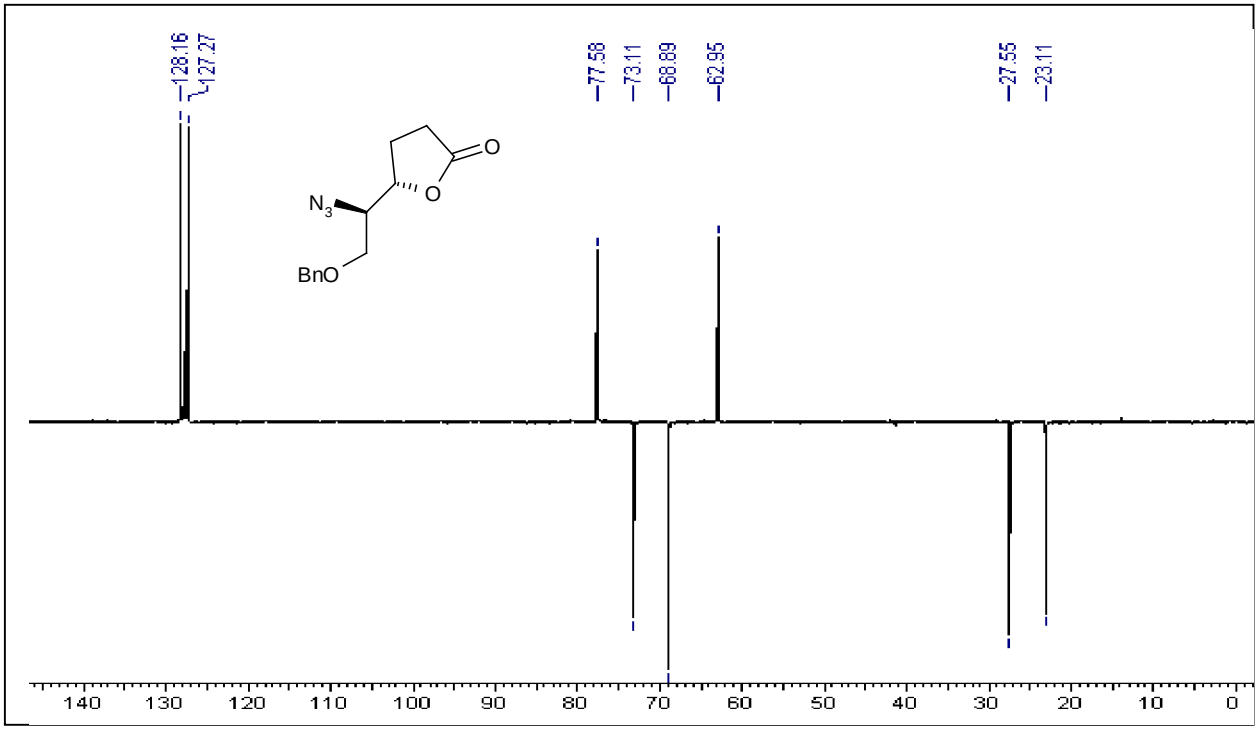
DEPT NMR Spectrum of compound 104 in $CDCl_3$ + CCl_4



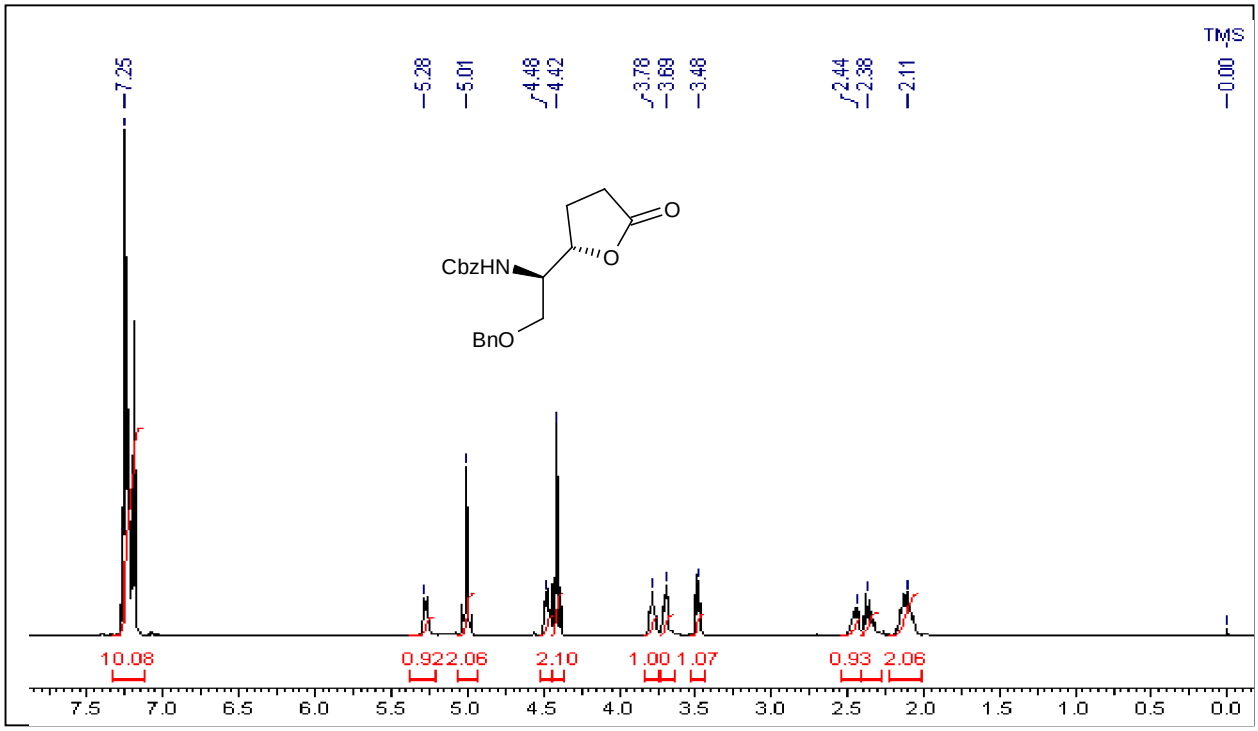
^{1}H NMR Spectrum of compound 105 in $CDCl_3$ + CCl_4



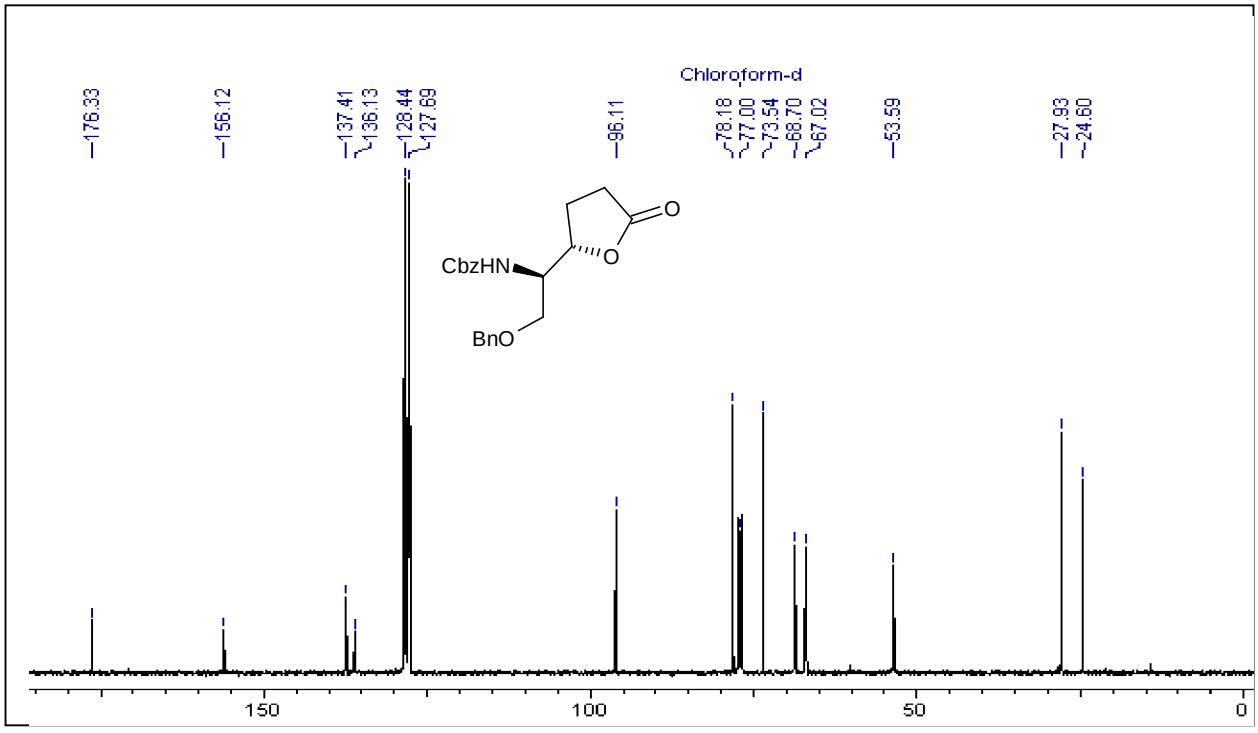
^{13}C NMR Spectrum of compound 105 in $CDCl_3$ + CCl_4



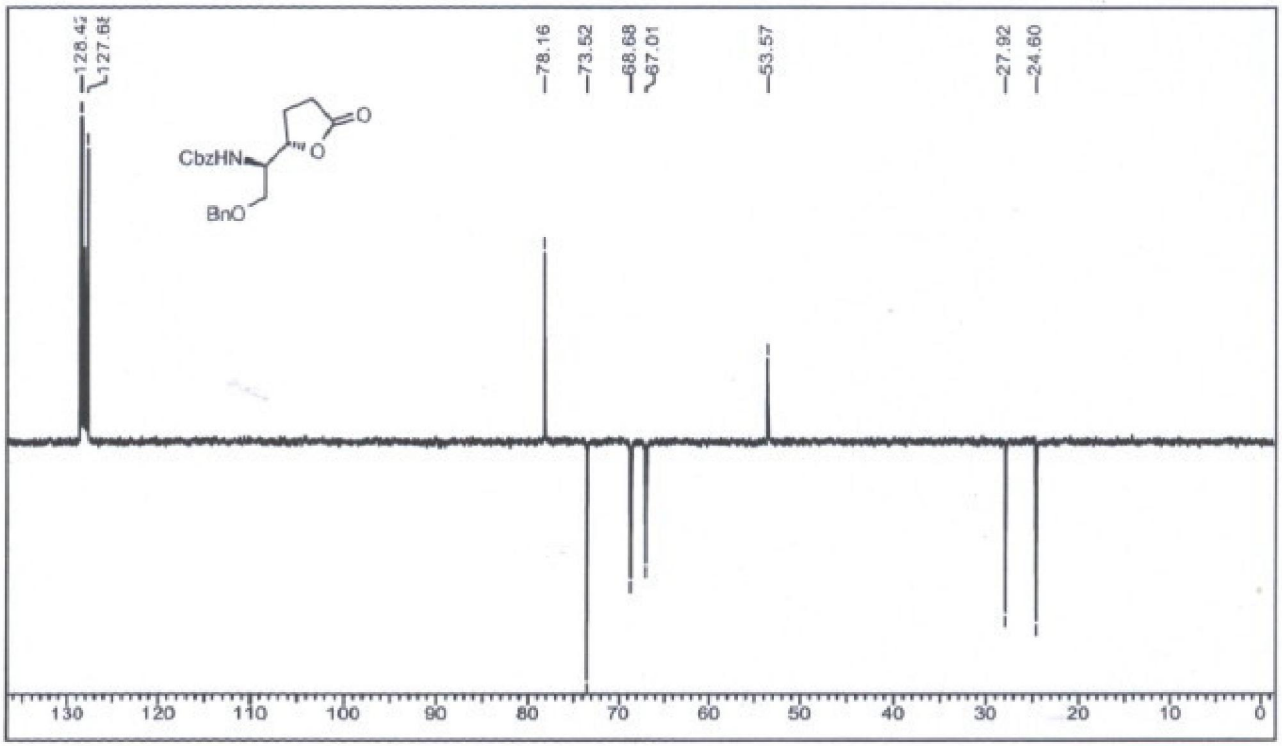
DEPT NMR Spectrum of compound 105 in $CDCl_3$ + CCl_4



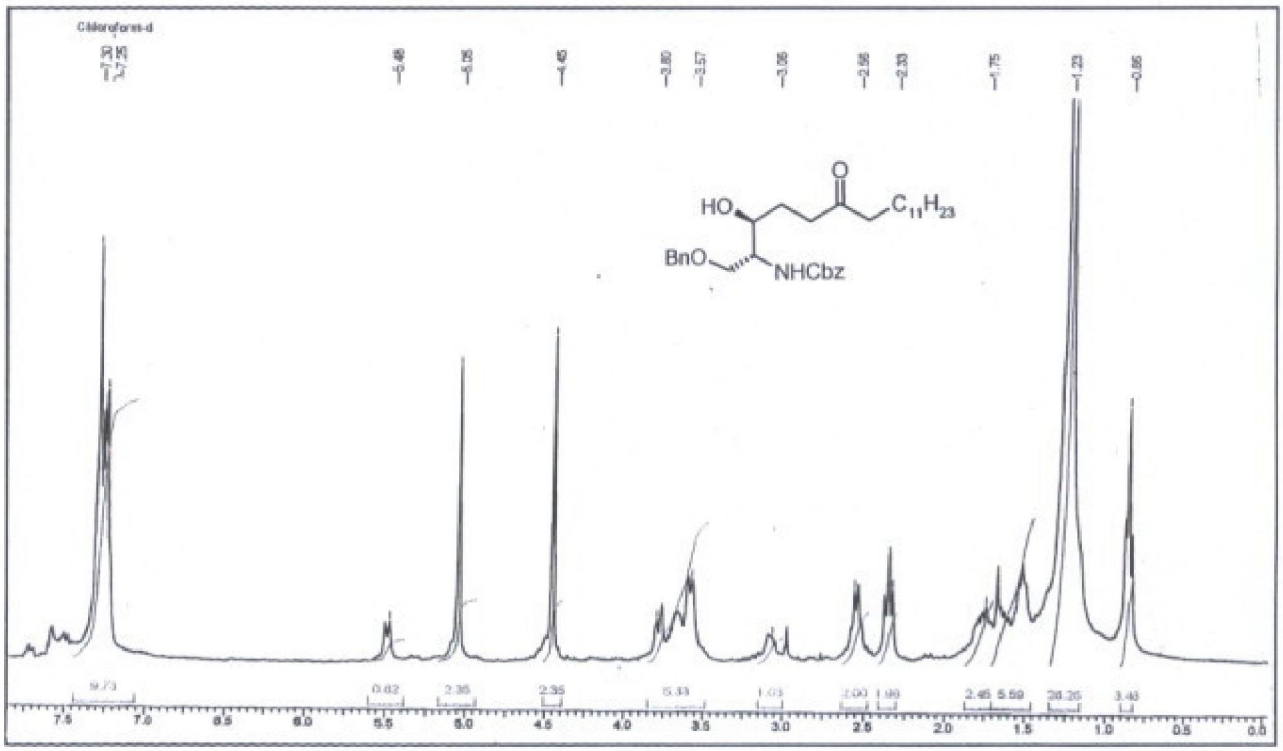
^{1}H NMR Spectrum of compound 98 in $CDCl_3$ + CCl_4



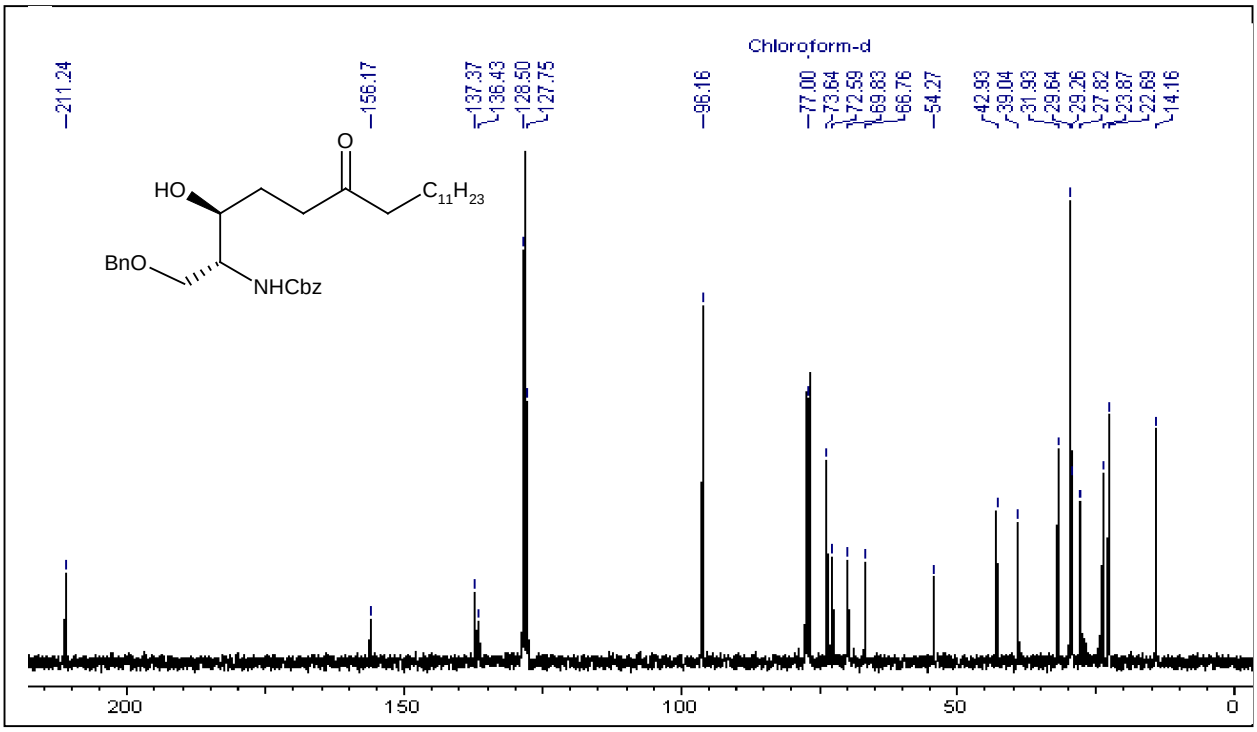
^{13}C NMR Spectrum of compound 98 in $CDCl_3$ + CCl_4



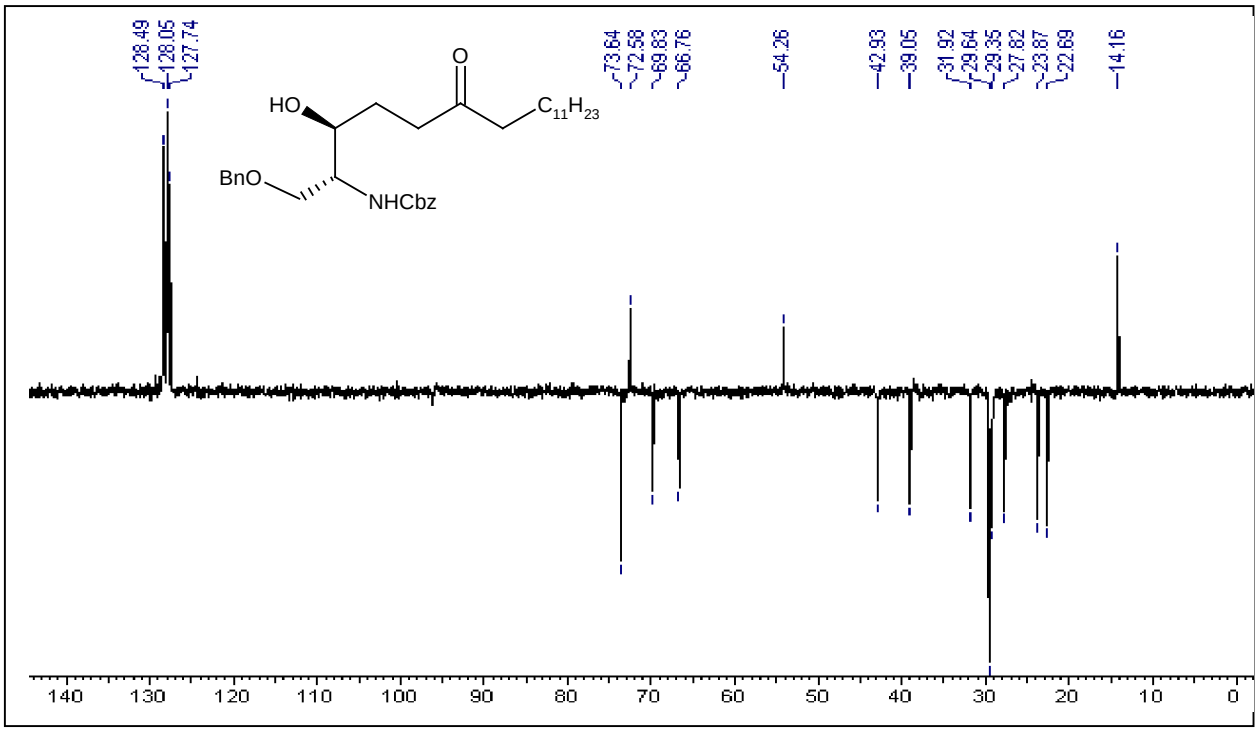
DEPT NMR Spectrum of compound 98 in $CDCl_3 + CCl_4$



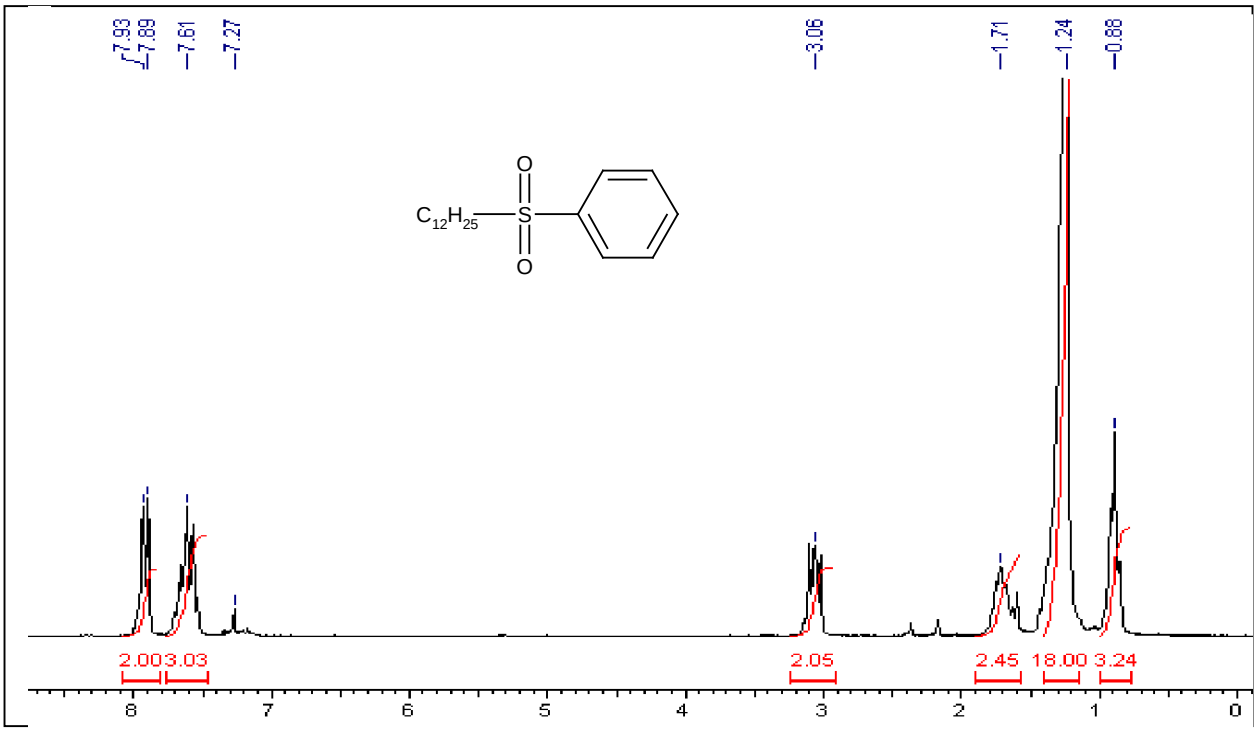
^{1}H NMR Spectrum of compound 97 in $CDCl_3 + CCl_4$



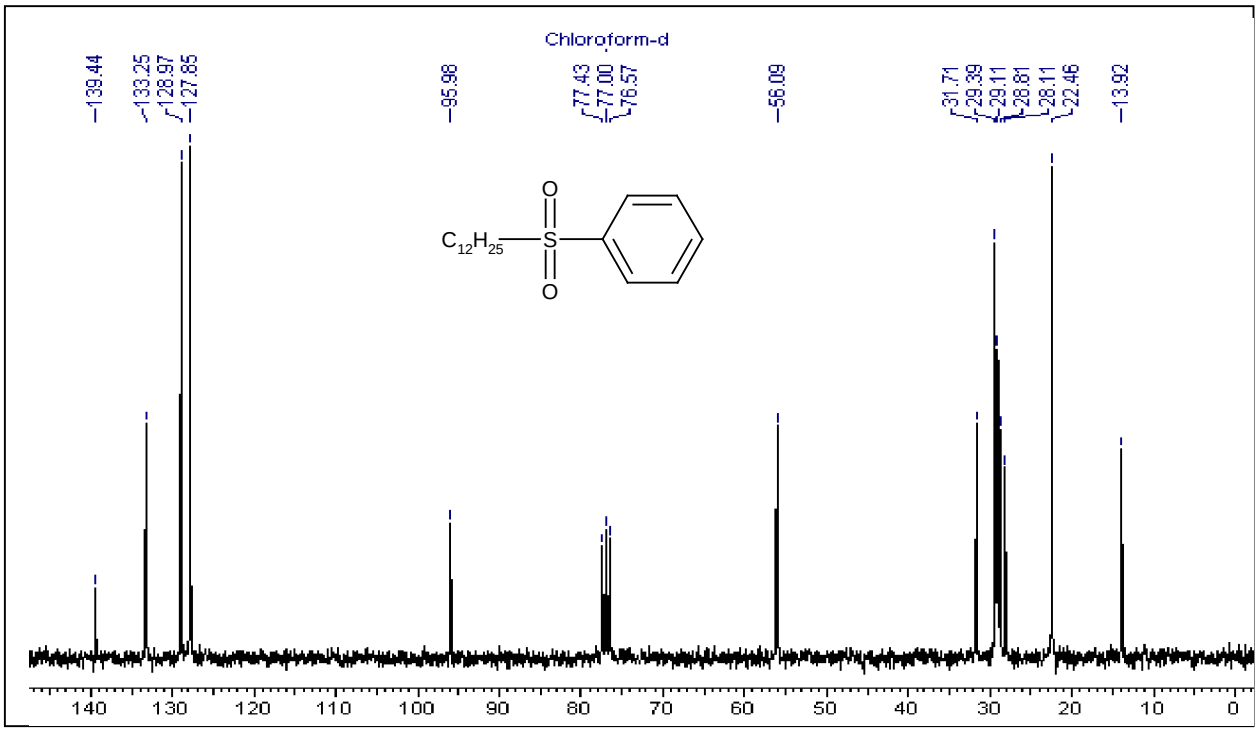
^{13}C NMR Spectrum of compound 97 in $CDCl_3$ + CCl_4



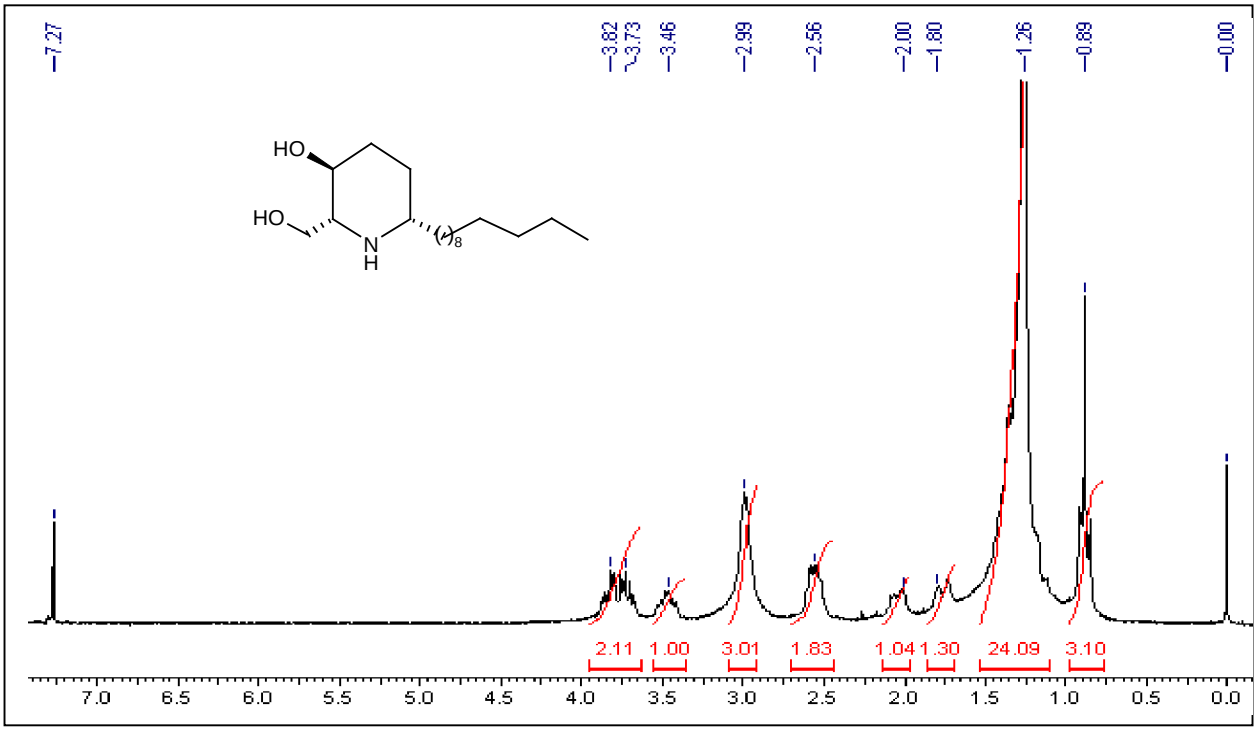
DEPT NMR Spectrum of compound 97 in $CDCl_3$ + CCl_4



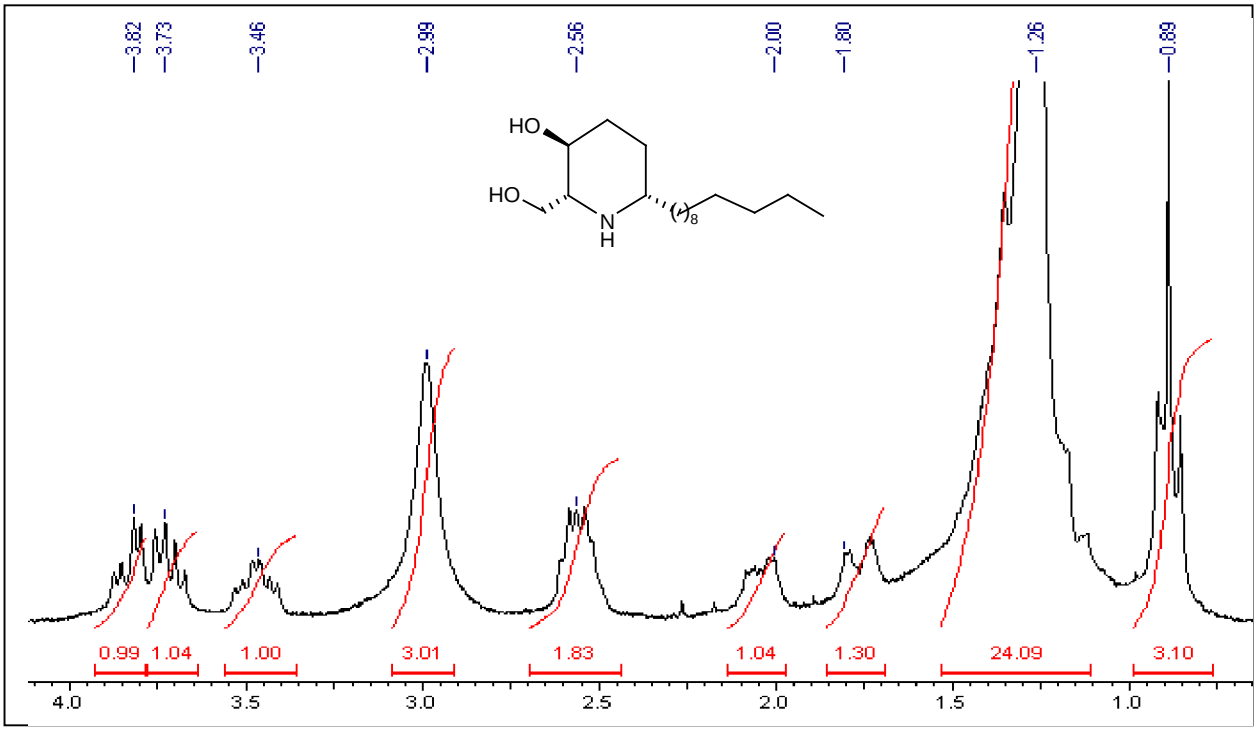
^{1}H NMR Spectrum of compound 108 in $CDCl_3$ + CCl_4



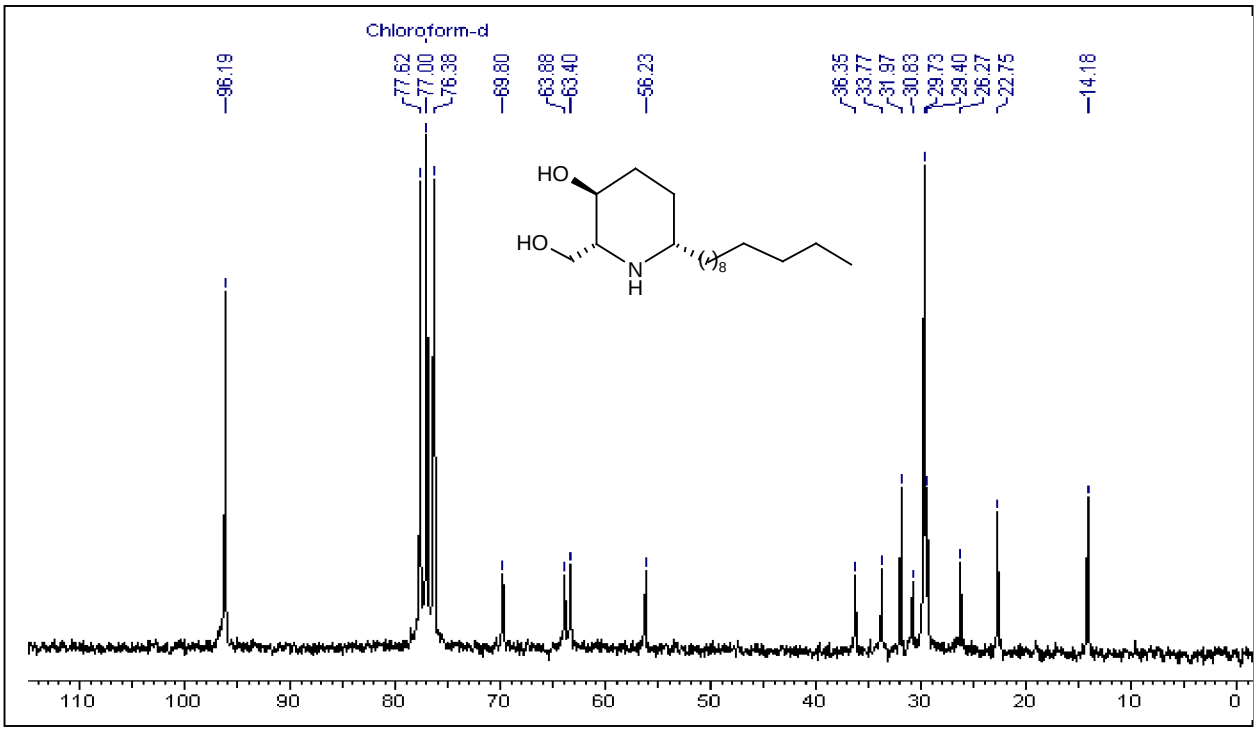
^{13}C NMR Spectrum of compound 108 in $CDCl_3$ + CCl_4



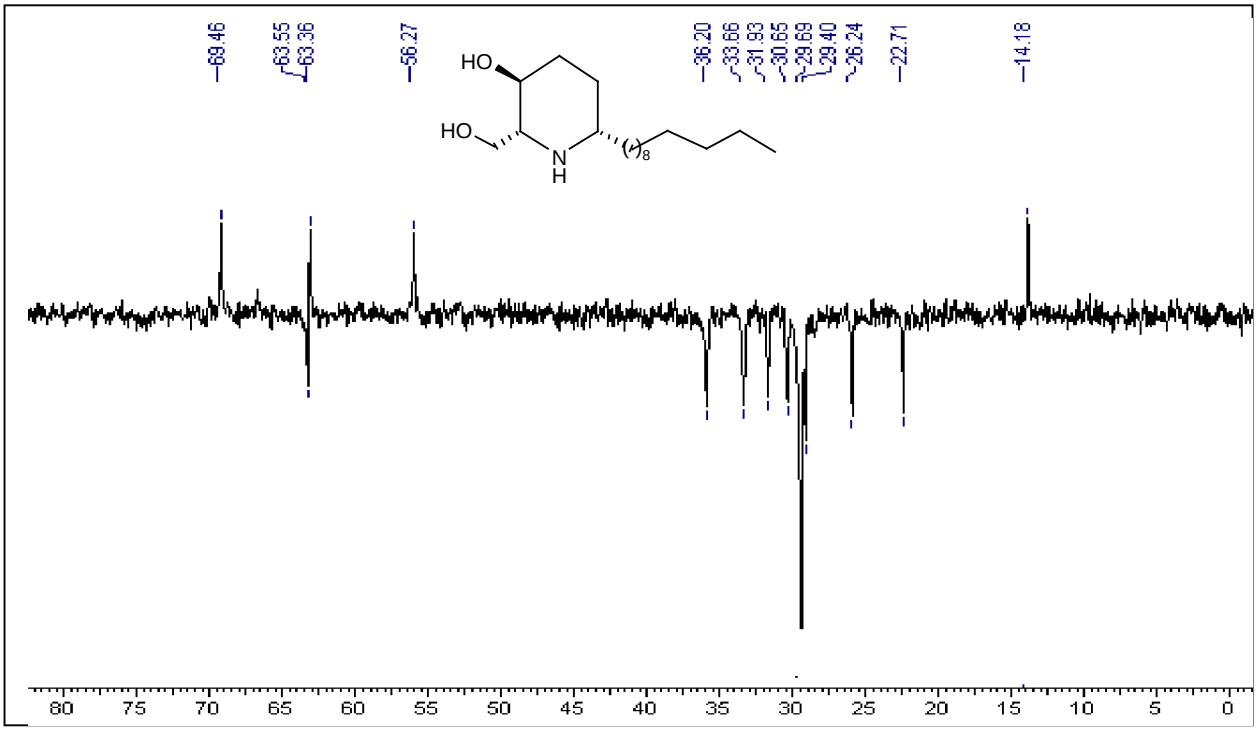
^{1}H NMR Spectrum of compound 5 in $CDCl_3$



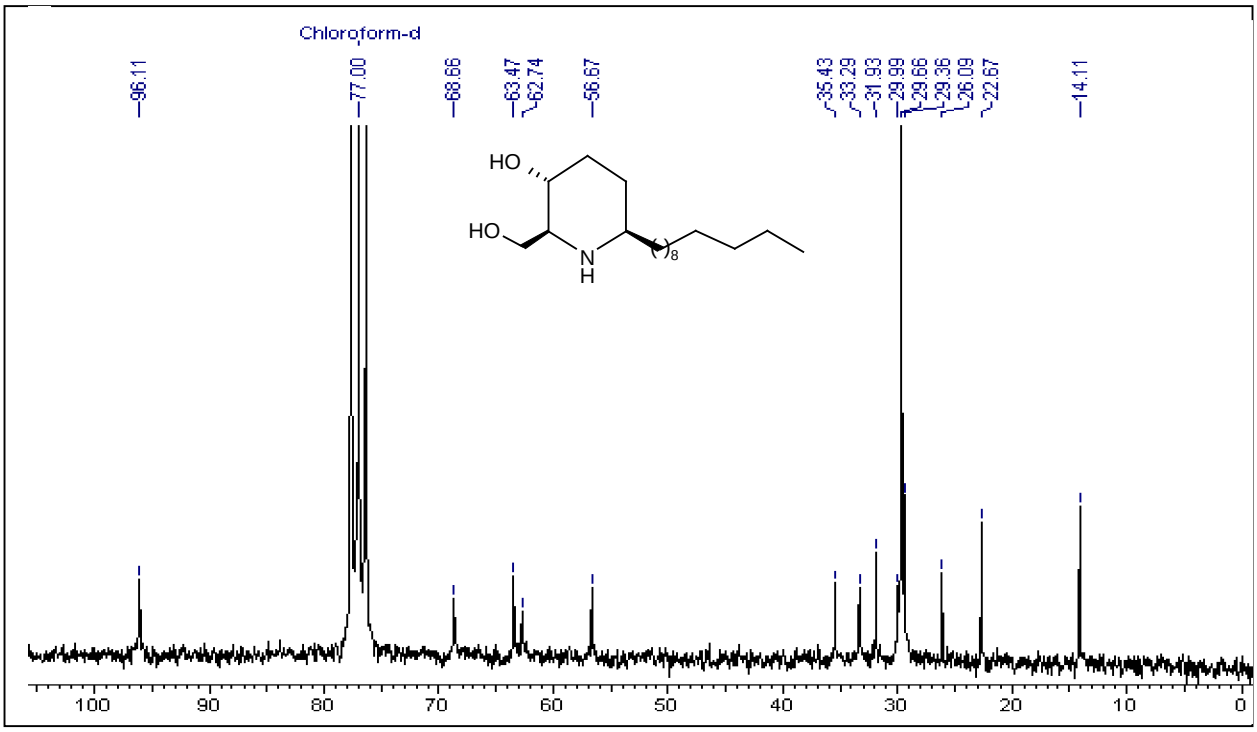
^{1}H NMR Spectrum of compound 5 in $CDCl_3$



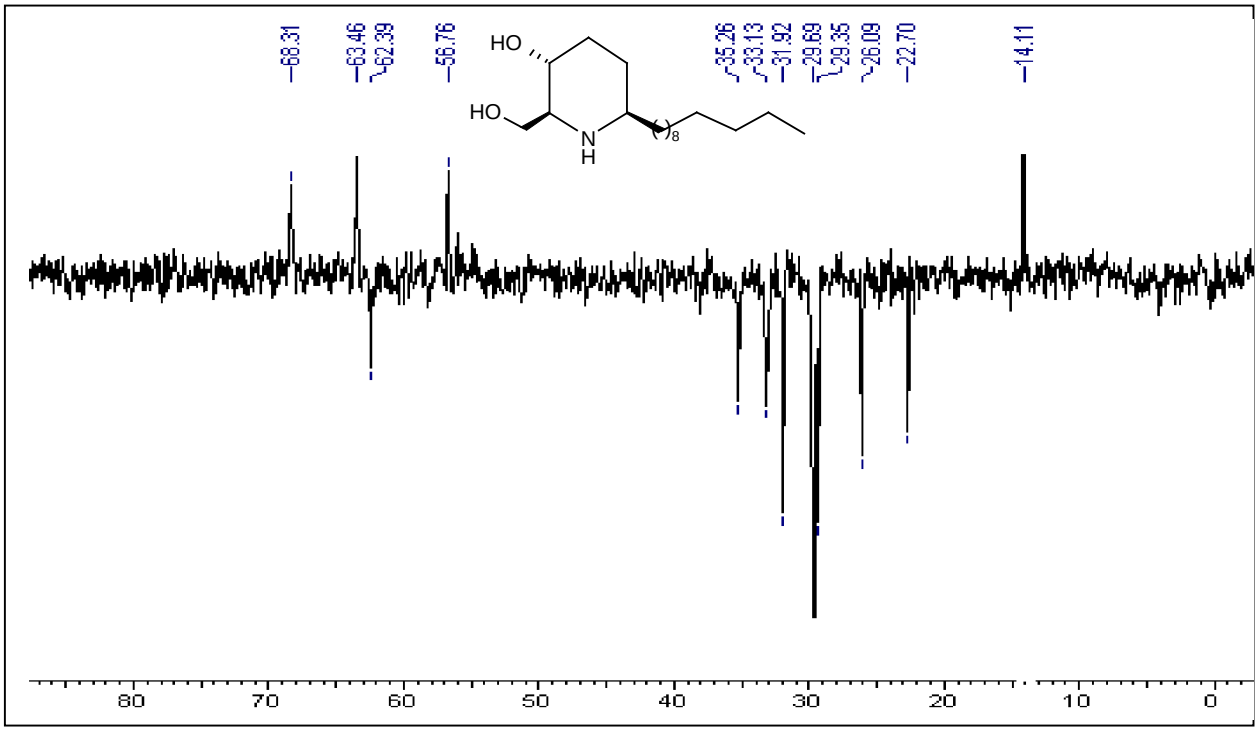
^{13}C NMR Spectrum of compound 5 in $CDCl_3$



DEPT NMR Spectrum of compound 5 in $CDCl_3$



^{13}C NMR Spectrum of compound 7 in $CDCl_3$



DEPT NMR Spectrum of compound 7 in $CDCl_3$

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SECTION B

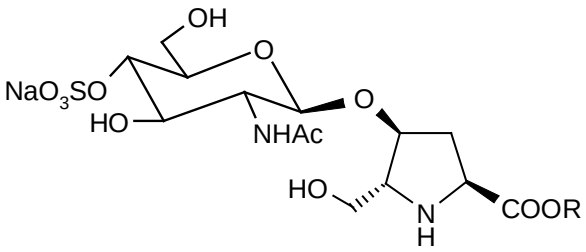
AN EFFICIENT STEREOSELECTIVE SYNTHESIS OF (2*S*,4*S*,5*R*)-(-)- AND (2*R*,4*R*,5*S*)-(+)-BULGECININE

Introduction:

Pyrrolidines are naturally ubiquitous, biologically important substances which display diverse structural and stereochemical features.[1] Not surprisingly, these alkaloids have been accorded considerable attention from synthetic chemists and an impressive range of new methodology has resulted, most recently in the area of asymmetric synthesis.

Among the pyrrolidine alkaloids, proline, hydroxy proline and their derivatives is of importance because they are the key constituents of bioactive molecules and are useful building blocks for asymmetric synthesis.[2-4] In peptides these cyclic aminoacids confer rigidity on the protein, which influences cell recognition events.[5] Replacement of proteinogenic amino acids with cyclic aminoacids has been used in structure-activity studies and in the search for new peptidomimetics that have improved pharmacological profiles as well as resistance to the protease enzymes.[6]

The bulgecins A (**1**), B (**2**) and C (**3**) are a group of potent β-lactam synergists produced during the fermentation of *Pseudomonas acidophila* and *P. mesoacidophila*.[7] These natural products, although devoid of antibacterial activity, induce characteristic morphological changes called bulge formation, in the cell wall of Gram negative bacteria in co-operation with β-lactam antibiotics. As a result of bulge formation, the activity of these antibiotics is effectively enhanced and the bacteria are killed at lower β-lactam concentrations.

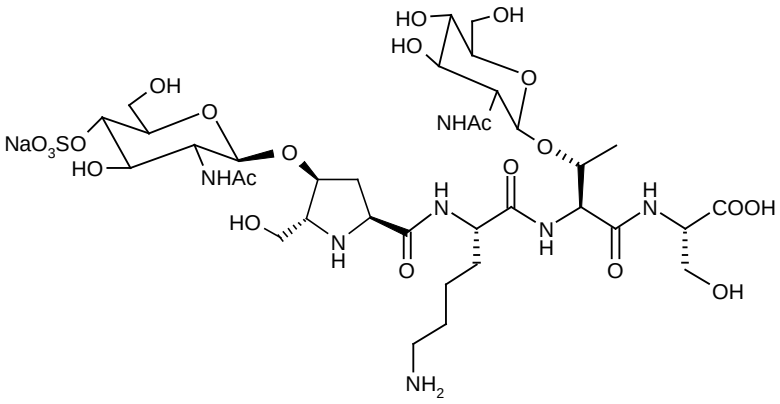


1 Bulgecin A : R = $NHCH_2CH_2SO_3H$

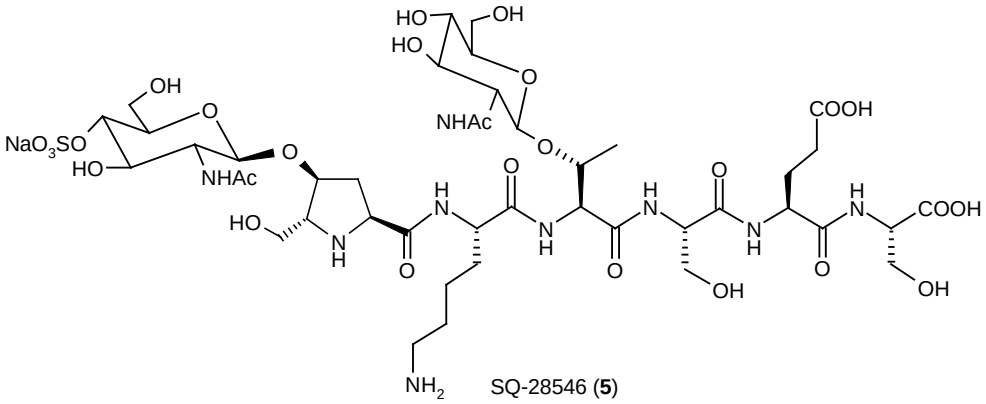
2 Bulgecin B : R = $NHCH_2CH_2COOH$

3 Bulgecin C : R = OH

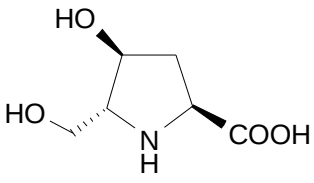
Recently, *Chromobacterium violaceum* has been shown to produce two structurally related glycopeptide sulfates, SQ-28504 (**4**) and SQ-28546 (**5**).[8] These substances are also β-lactam antibiotic potentiators. They contain (-)-bulgecinine **6**, which is a hydroxy proline derivative and has an antibiotic effect, as the common aglycon moiety.



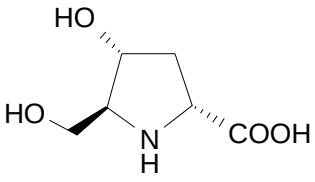
SQ-28504 (**4**)



SQ-28546 (**5**)

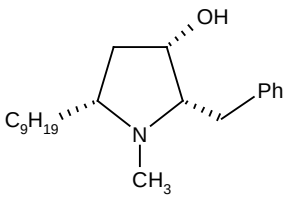


(-)-Bulgecinine (**6**)

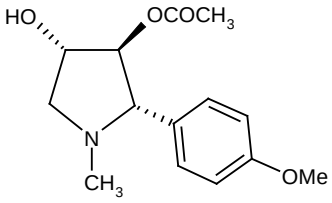


(+)-Bulgecinine (**7**)

(+)-Preussin (**8**) is a naturally occurring pyrrolidene alkaloid isolated from the fermentation of *Aspergillus ochraceus* and *Preussia sp*. Which by comparison to anisomycin (**9**) has a significant broader spectrum anti fungal activity.[9, 10]

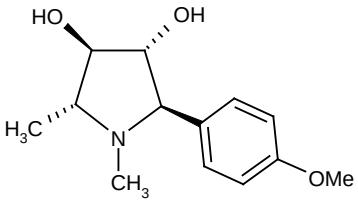


(+)-Preussin (**8**)

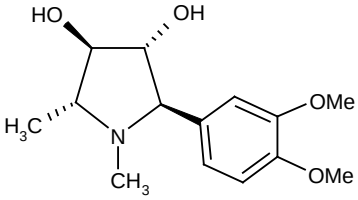


Anisomycin (**9**)

(-)-Codonopsinine 1 (**10**) and (-)-Codonopsine 2 (**11**) are the complex pyrrolidine alkaloids isolated from *Codonopsis clematidea* that display antibiotic activity and hypotensive activity without effecting the central nervous system in animal tests.[11] These two molecules contain the four contiguous stereocenters around a pyrrolidine ring in all trans arrangement.

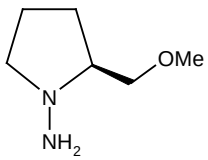


(-)- Codonopsinine 1 (**10**)

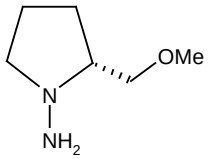


(-)- Codonopsinine 2 (**11**)

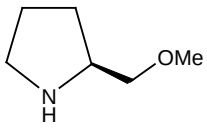
*Pyrrolidine derived chiral auxiliaries like SAMP (**13**), RAMP (**14**), SMP (**15**), RMP (**16**) have been frequently used in the synthesis of many optically active biologically important natural products.*[12]



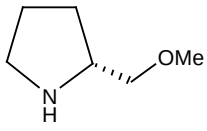
SAMP (**12**)



RAMP (**13**)



SMP (**14**)



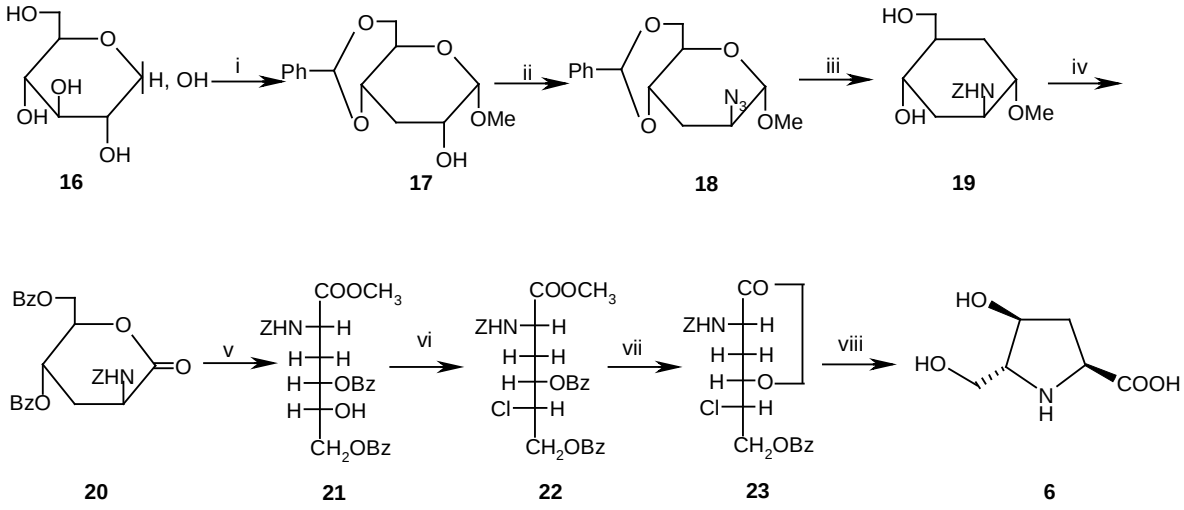
RMP (**15**)

Review of literature:

As a consequence of their biological effects and structural novelty, the bulgecins have been the subject of synthetic investigations. The bulgecin aglycon bulgecinine (**6**) has been synthesized from D-glucose, D-glucuronic acid, pyroglutamic acid and an L-allylglycine derivative. Additionally, Shiba and co-workers have reported the synthesis of bulgecin A (**1**) and two analogues.

Shiba *et al* (1985, Scheme-1)[13]

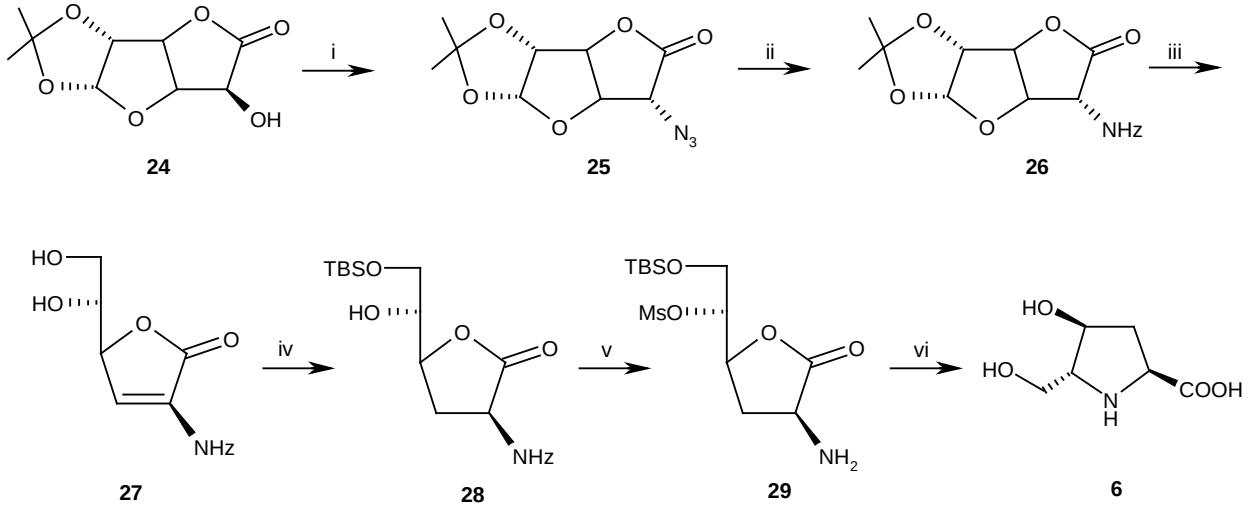
Shiba and co-workers have synthesized 3-deoxy-D-glucose derivative **17** from D-glucose according to the reported procedure.[14] The free hydroxy group of **17** was then substituted with azide group via tosylate. Reduction of the azide group, 4, 6-benzylidene deprotection and *in situ* protection of amine with *N*-benzyloxy carbonyloxy succinamide gave compound **19**. Sequential benzoyl protection, hydrolysis and oxidation gave the δ-lactone **20**. δ-Hydroxyl group freed by methanolysis of **20**, and was chlorinated with PPh_3 and CCl_4 accompanied by an inversion of the configuration on δ-carbon atom. Hydrogenolysis of compound **22** under acidic conditions gave the γ-lactone **23**. Final cyclization with saturated $Ba(OH)_2$ solution gave the (-)-bulgecinine.



Scheme 1. *Reagents and conditions:* (i) ref 14; (ii) (a) TsCl, pyridine, 88 %; (b) NaN_3, DMF, 73 %; (iii) (a) H_2, Pd black, MeOH (containing 1 eq HCl); (b) *N*-benzyloxy carbonyloxy succinamide, Et_3N, MeOH, 92 %; (iv) (a) BzBr, NaOH, DMF, 61 %; (b) Conc. HCl, AcOH, 66 %; (c) PDC, CH_2Cl_2, 59 %; (v) MeOH, reflux; (vi) PPh_3, CCl_4, 43 %; (vi) H_2, Pd black, MeOH, Conc. HCl; (viii) Sat. $Ba(OH)_2$, pH 9.0, 75 %.

Fleet *et al* (1986, Scheme-2)[15]

In Fleet's approach isopropylidene glucoronolactone **24** was treated with trifluoro methane sulphonic anhydride to form the triflate, which on treatment with NaN_3 gave the azide **25**. Hydrogenation of the azide followed by protection of amine as its Cbz devivative gave the compound **26**. Treatment of compound **26** with sodium methoxide followed by sodium borohydride reduction gave unsaturated diol **27**. Protection of the primary alcohol as TBS ether, followed by hydrogenation and then reprotection of amine as carbamate gave the compound **28**. Mesylation of **28** followed by Cbz group deprotection gave the compound **29**. Sequential treatment of **29** with bicarbonate and dilute acid gave after purification by ion exchange chromatography furnished (-)-bulgecinine **6**.



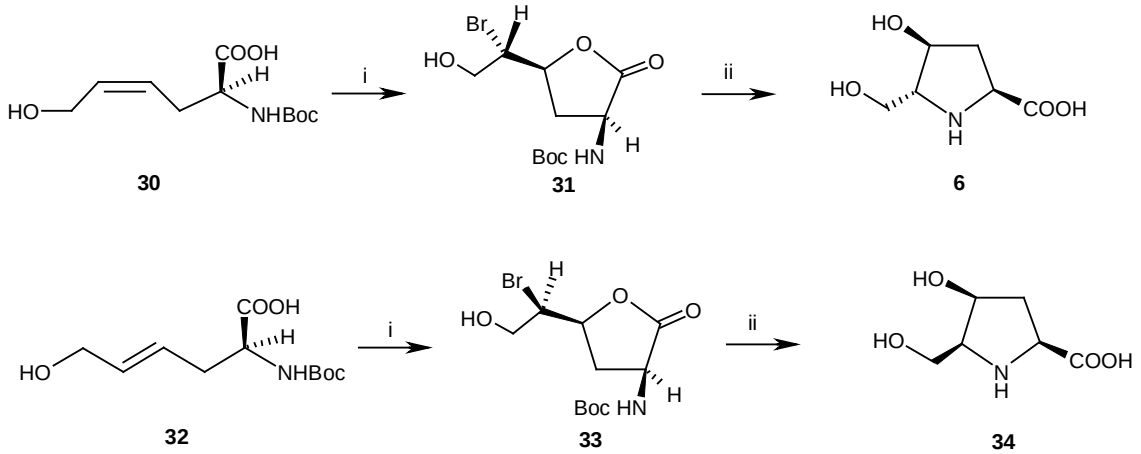
24 25 26 27 28 29 6

Scheme 2. *Reagents and conditions:* (i) (a) $(CF_3SO_2)_2O$, pyridine, - 30 ^oC, CH_2Cl_2; (b) NaN_3, DMF, - 20 ^oC; (ii) H_2, 10 % Pd/C, EtOAc; then CbzCl, $NaHCO_3$, EtOAc/H_2O; (iii) NaOMe/MeOH, 0 ^oC, 1 min then $NaBH_4$, MeOH, 0 ^oC, 5 min; (iv) (a) TBSCl, Et_3N, DMF, CH_2Cl_2, DMAP; (b) Pd black, H_2, EtOAc, pyridine, 20 ^oC, 24 h; then CbzCl, $NaHCO_3$, EtOAc/H_2O, 1 h; (v) $MeSO_2Cl$, pyridine,

DMAP, 20 °C, 24 h; then 10 % Pd/C, EtOAC-EtOH; (vi) $NaHCO_3$, $EtOH/H_2O$, rt, 12 h; then 2 N HCl, THF, rt, 4 h.

Ohfune *et al* (1986, Scheme-3)[16]

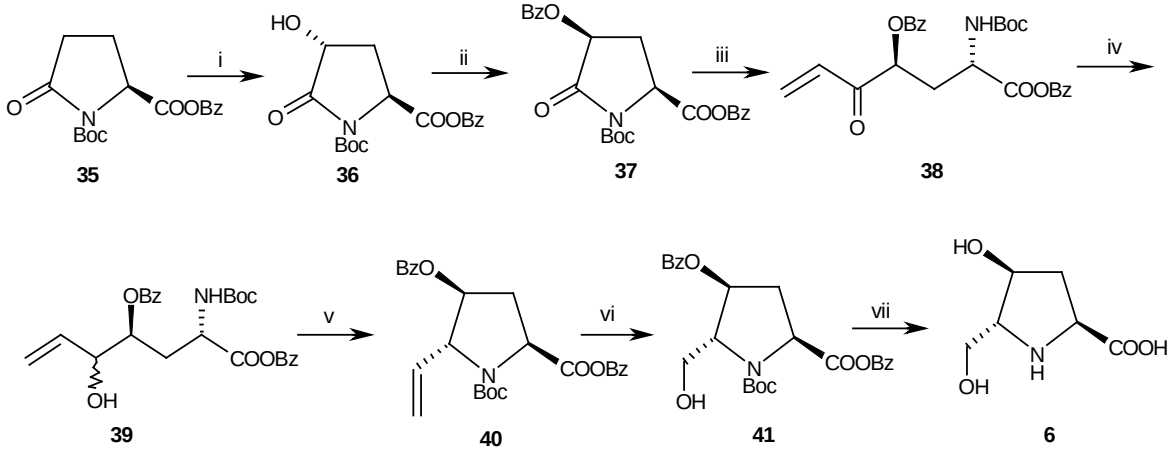
Ohfune and co-workers have employed electrophilic lactonization strategy of 2-amino-4-pentenoic acid derivatives **30**, **32** for the synthesis of the useful chiral intermediates (**31**, **33**) as a masked erythro 1, 3-amino hydroxyl system. Deprotection of Boc group of **31** followed by treatment with 0.1 N $Ba(OH)_2$ delivered the (-)-bulgecinine **6**.



Scheme 3. *Reagents and conditions:* (i) NBS, THF; (ii) (a) TFA, CH_2Cl_2; (c) 0.1 N $Ba(OH)_2$, *p*H = 9.

Nozoe *et al* (1988, Scheme-4)[17]

Nozoe and co-workers have employed regio and diastereoselective hydroxylation of



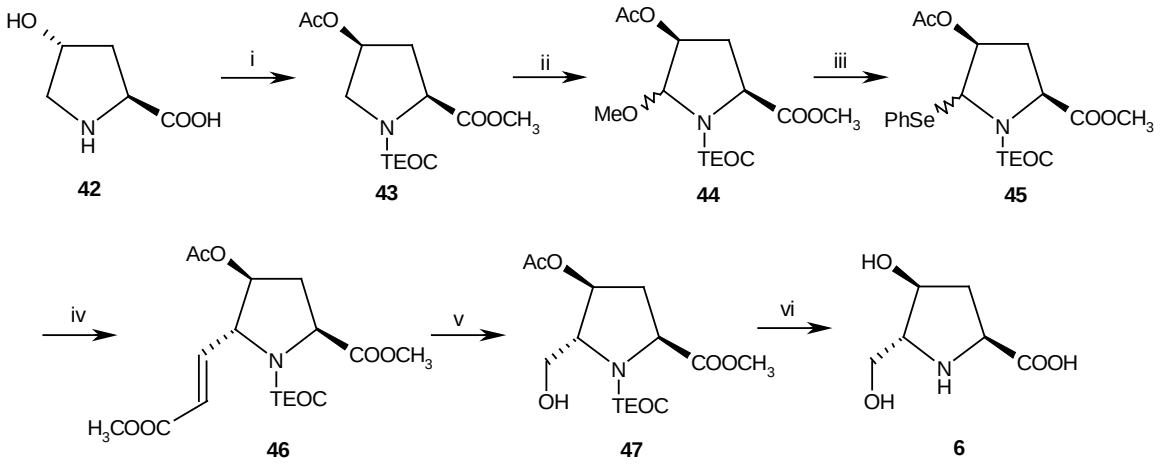
the *N*-1-butoxy carbonyl-L-pyroglutamate **35** to afford the 4*R*-hydroxy pyroglutamate **36**,

Scheme 4. *Reagents and conditions:* (i) LiHMDS, 2-toluenesulfonyl 3-phenyloxazilidine, THF, - 78 ^{o}C; (ii) PhCOOH, DEAD, PPh_3, THF, - 20 ^{o}C; (iii) Vinyl magnesium bromide, THF, - 40 ^{o}C; (iv) $NaBH_4$, $CeCl_3$, MeOH, - 20 ^{o}C, (v) MsCl, Et_3N, CH_2Cl_2, 0 ^{o}C, SiO_2; (vi) O_3, MeOH, - 78 to 0 ^{o}C; (vii) 1 N NaOH, MeOH, rt; TFA, PhOMe, 0 ^{o}C, Dowex 50 w, 1 N Pyridine.

which on Mitsunobu's reaction with benzoic acid gave the benzyloxy pyroglutamate **37**. Treatment of **37** with vinyl magnesium bromide gave the enone **38**, which on reduction using $NaBH_4.CeCl_3$ gave the alcohol **39**. Mesylation of **5** and adsorption of the crude mesylate on silicagel gave the cyclized product **40**. Ozonolysis of **40** followed by $NaBH_4$ reduction gave the ester **41**. Hydrolysis of ester **41** followed by deprotection with trifluoroacetic acid gave the (-)-bulgecinine **6**.

Barrett *et al* (1990, Scheme-5)[18]

Barrett and Pilipauskas have utilized 4-hydroxy proline **42** as a chiral precursor. Sequential esterification, amine protection and Mitsunobu reaction gave the acetate **43**. Anodic oxidation of **43** gave the 5-methoxy compound **44**, which on acetolysis and subsequent phenylselenation gave the compound **45**. Irradiation of the acetonide **45** in the presence of methyl (*Z*)-or (*E*)-2-(tributyl stannyl) acrylate in benzene gave the radical substituted product **46**. Ozonolysis of the α, β-unsaturated ester **46** followed by a reductive



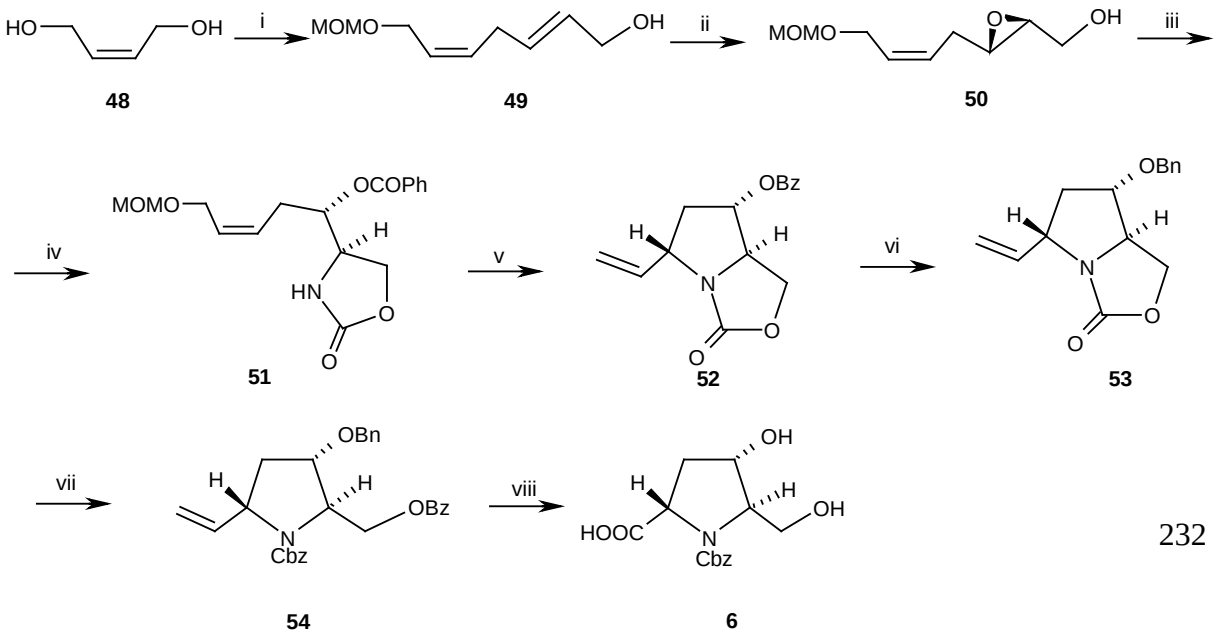
(TEOC = *O* -(2-(trimethylsilyl)ethyl)carbamate)

work up afforded the compound **47** which on deprotection gave the (-)-bulgecinine **6**.

Scheme 5. *Reagents and conditions:* (i) (a) $SOCl_2$, MeOH, 100 %; (b) TEOC-N_3, Et_3N, CH_3CN, 90 %; (c) PPh_3, DEAD, AcOH, THF, 65 %; (ii) Et_4NOTs, MeOH, graphite electrodes, 5.5 F mol^{-1}, then Ac_2O, Et_3N, CH_2Cl_2, 64 %; (iii) (a) Ac_2O, AcOH, H_2SO_4 (cat), 77 %; (b) PhSeH, TsOH (cat), 86 % (iv) (*E*)-(or) (*Z*)-$MeO_2CCH{=}CHSn(Bu)_3$, $(Bu_3Sn)_2$, 250 W sun lamp, Pyrex filter, 67 %; (v) O_3, MeOH-CH_2Cl_2, $NaBH_4$, 83 %; (vi) NaOH, MeOH, then TBAF, 50 %.

Momose *et al* (1992, Scheme-6)[19]

Momose and co-workers have utilized *cis*-2-butene-1, 4-diol **48** as the achiral precursor. Mono protection of **48** and subsequent treatment with mesyl chloride gave the allyl chloride which on C-C coupling reaction with propargyl alcohol followed by reduction with lithium aluminium hydride gave the compound **49**. Asymmetric epoxidation of **49** gave the 2, 3-epoxy alcohol **50**, which on treatment with benzoyl isocyanate followed by cyclization over potassium carbonate afforded oxazolidinone **51**. The intramolecular cyclization with bis(acetonitrile)palladium(II)chloride (30 mol %) gave an oxazolidinone **52**, which on debenzoylation followed by benzyl protection gave the compound **53**. Compound **53** on Oxazolidone ring cleavege, *N*-benzyloxy carbonylation and *O*-benzoylation afforded the pyrrolidine **54**. Sequential ozonolysis, oxidation, debenzylation and acid hydrolysis gave the

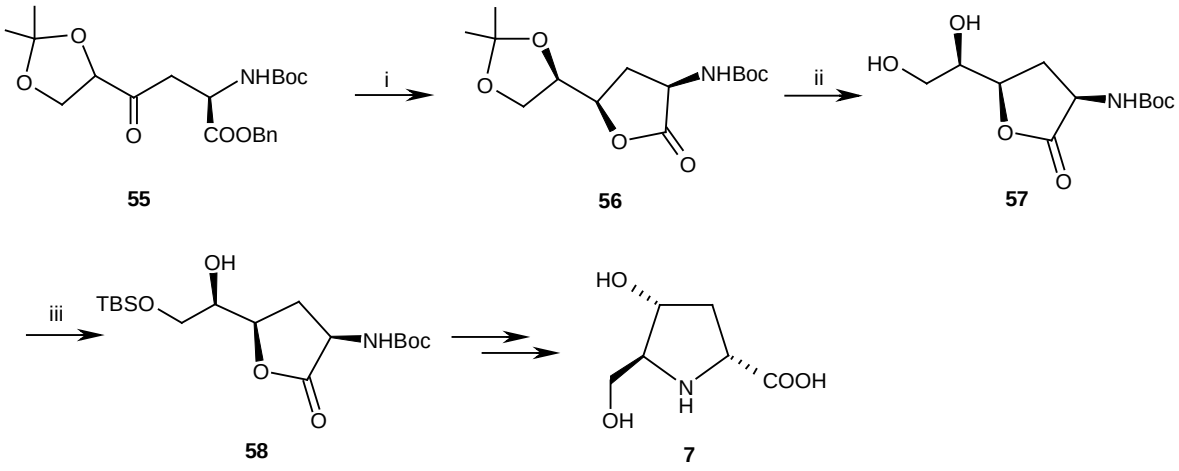


(-)-bulgecinine **6**.

Scheme 6. *Reagents and conditions:* (i) (a) MOMCl, NaH, THF, 64 %; (b) MsCl, Pyridine, 87 %; (ii) (a) Propargyl alcohol, DBU, CuI, $NH_2OH.HCl$, Phenothiazine, THF-HMPA, 60 ^oC, 60 %; (b) $LiAlH_4$, Et_2O, 76 %; (iii) L-DIPT, Ti(*i*-PrO)$_4$, TBHP, 23 ^oC, 57 %; (iv) (a) Benzoyl isocyanate, $(CH_2Cl)_2$; (b) K_2CO_3, CH_3CN, 93 % (for two steps); (v) 30 mol % $PdCl_2(MeCN)_2$, THF, rt; (vi) (a) 1 N KOH, MeOH, rt, 86%; (b) BnBr, NaH, 96 %; (vii) (a) 1N KOH, MeOH, Reflux, 100 %; (b) CbzCl, $NaHCO_3$, H_2O-CH_2Cl_2, 90 %; (c) BzCl, Pyridine, THF, 97 %; (viii) (a) O_3 then Me_2S, 99 %; (b) $KMnO_4$, *t*-BuOH, 80 %; (ix) (a) H_2, Pd/C, 81 %; (b) 5 N HCl, MeOH, Reflux, 64 %.

Jackson *et al* (1993, Scheme-7)[20]

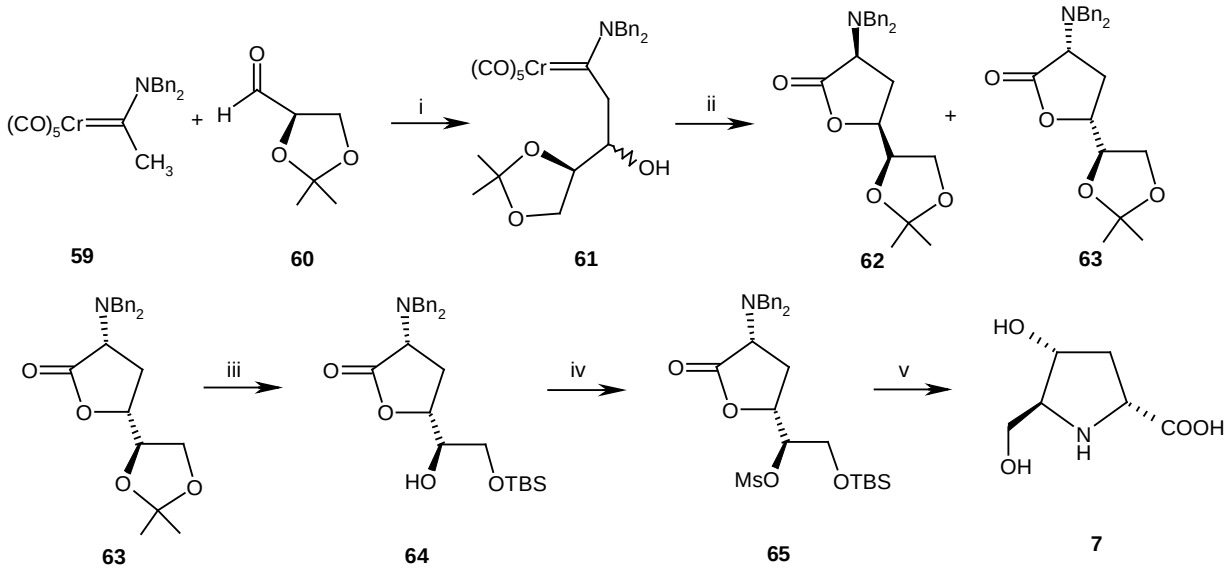
Jackson and Rettle have reduced 4-oxoamino acid **55** with high diastereo selectivity to get the trans lactone **56**. Removal of the isopropylidene acetal and selective protection of the primary hydroxyl group gave the hydroxy lactone **58**, which was the enantiomer of the Fleet's synthesis intermediate for the synthesis of (+)-bulgecinine **7**. Compound **58** was transformed in to (-)-bulgecinine **6** by known procedure.



Scheme 7. *Reagents and conditions:* (i) L-Selectride®, THF, - 78 ^{o}C, 8 h; (ii) I_2 in MeOH (1 %), rt, 48 h; (iii) TBSCl, Et_3N, DMAP, DCM/DMF.

Hegedus *et al* (1994, Scheme-8)[21]

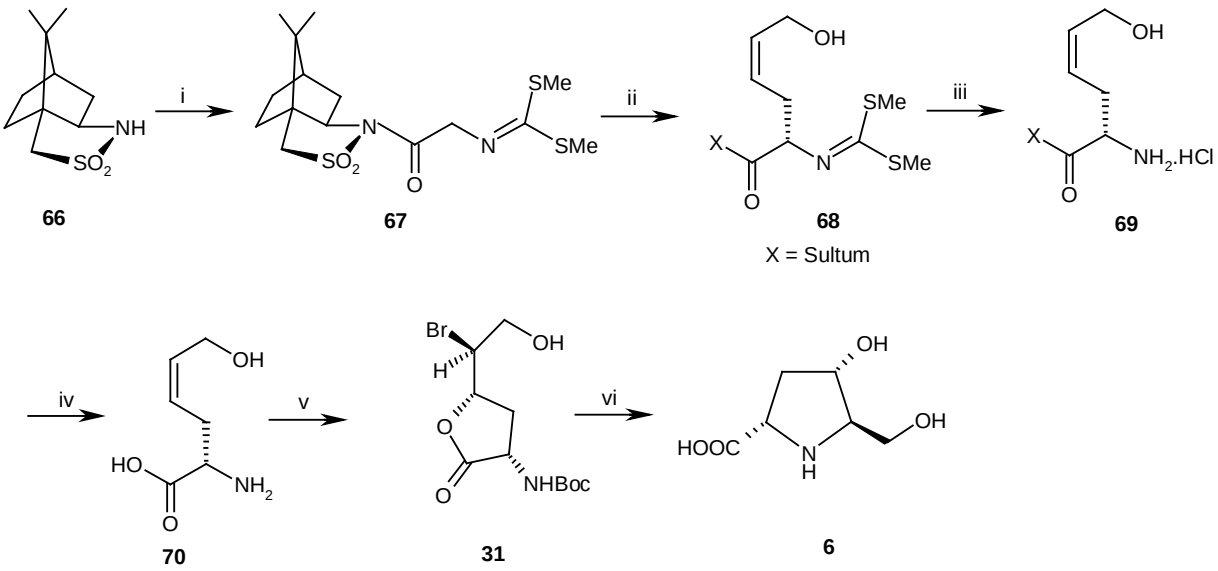
Hegedus and Schmeck have employed aldol and photocyclization reactions as the key steps in the synthesis of (+)-bulgecinine. The aldol reaction of chromium(dibenzyl amino) methylcarbene complex **59** with *R*-glyceraldehyde acetonide gave two aldol products in 1:1 ratio. Irradiation of this crude reaction mixture produced two lactones **62** and **63** in 1:1 ratio. Acetonide deprotection of **63** followed by selective primary hydroxyl protection and mesylation of the remaining hydroxyl group delivered compound **65**. Debenzylation, cyclization and final TBS deprotection gave the (+)-bulgecinine **7**.



Scheme 8. *Reagents and conditions:* (i) *n*-BuLi, -78 ^{o}C, 2 h, 87 %; (ii) hν, CO, 79 %; (iii) 1 N HCl, CH_2Cl_2, MeOH, 96 %; (iv) TBSCl, Et_3N, DMAP, CH_2Cl_2, 82 %; (v) MsCl, Et_3N, DMAP, 94 %; (vi) (a) H_2, $Pd(OH)_2$; (b) $NaHCO_3$, MeOH; (c) 5 % HCl, THF, 65 % (for two steps).

Oppolzer *et al* (1994, Scheme-9)[22]

Oppolzer and co-workers have utilized asymmetric alkylation of glycyl sultum **67**, which was readily prepared by Me_3Al mediated acylation of sultum **66** with methyl *N*-[bis(methylthio)methylidene] glycinate. Asymmetric alkylation followed by sequential mild acidic hydrolysis and saponification gave compound **70**. Boc protection and NBS reaction gave the lactone **31**, which on Boc deprotection and final cyclization provided (-)-bulgecinine **6**.

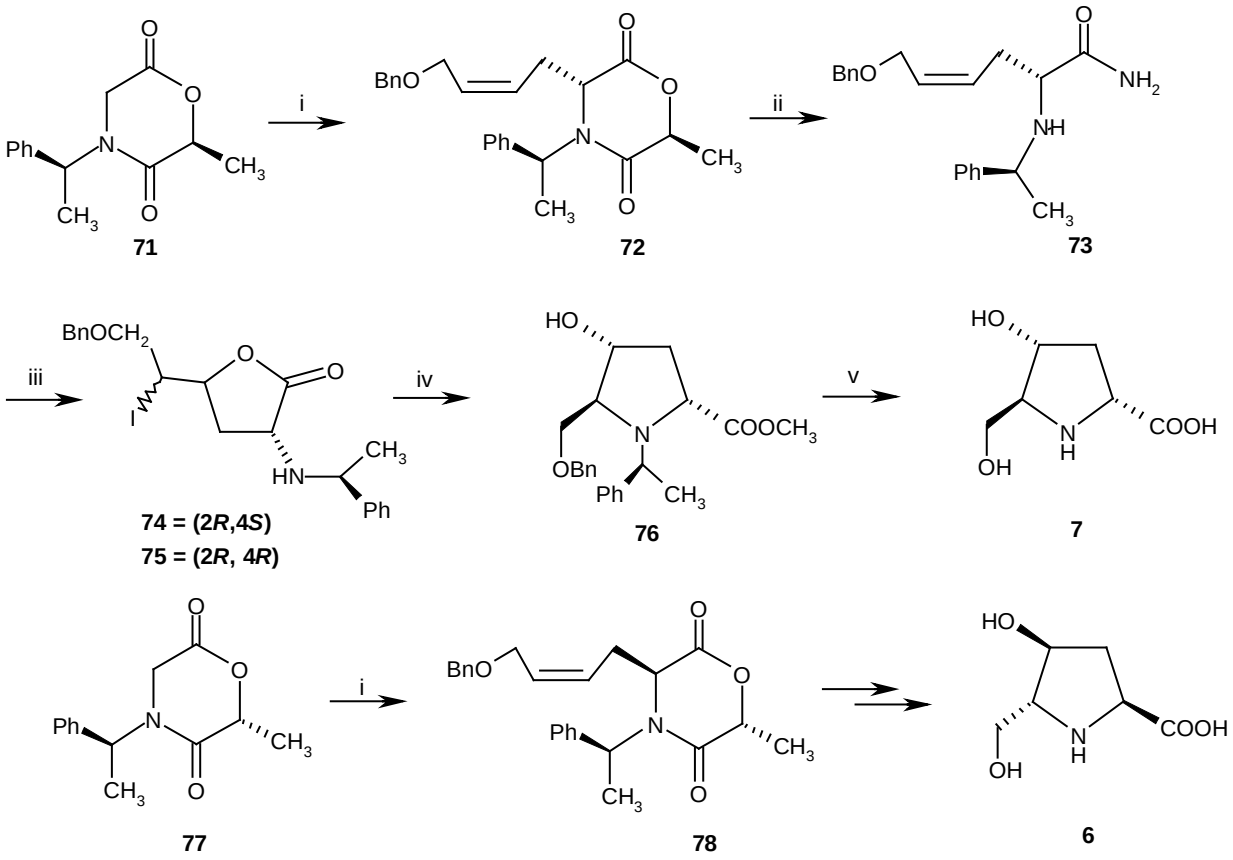


Scheme 9. *Reagents and conditions:* (a) Me_3Al, Toluene; (b) $MeO_2CCH_2N{=}C(SMe)_2$, 86 %; (ii) *n*-BuLi, THF, (*Z*)-(*t*-Bu)$Me_2SiOCH_2CH{=}CHCH_2Br$; (iii) 0.5 N HCl, THF, rt; (iv) aq. LiOH, THF, rt; (v) $(Boc)_2O$, $NaHCO_3$, Dioxane-H_2O (1:1), rt, 24 h then NBS; (vi) CF_3COOH, CH_2Cl_2, 60 ^oC, 3h; (b) aq. $Ba(OH)_2$, *p*H 9.0, 24 h.

Sandri *et al* (1996, Scheme-10)[23]

Sandri and co-workers have utilized the highly stereo controlled alkylation of chiral morpholidones **71** and **77** for the synthesis of (+) and (-)-bulgecinine. The alkylation of synthon **71** occurs with total 1, 4-trans induction to deliver the compound **72**. Conversion of **72** into the amide **73** was achieved under very mild conditions. The iodolactonization of amide **73** occurred with a relatively good *cis* selectivity affording diastereomeric iodolactones **74** and **75** in 1:4 mole ratio. Cyclization of **75** in alkaline medium gave 7**6**, which on

hydrogenolysis and ester hydrolysis delivered the (+)-bulgecinine. In a similar manner (-)-bulgecinine was prepared from (6*R*)-**77**. Sandri and co-workers in their successive paper investigated improvement in the stereoselectivity during iodolactonization.[24]

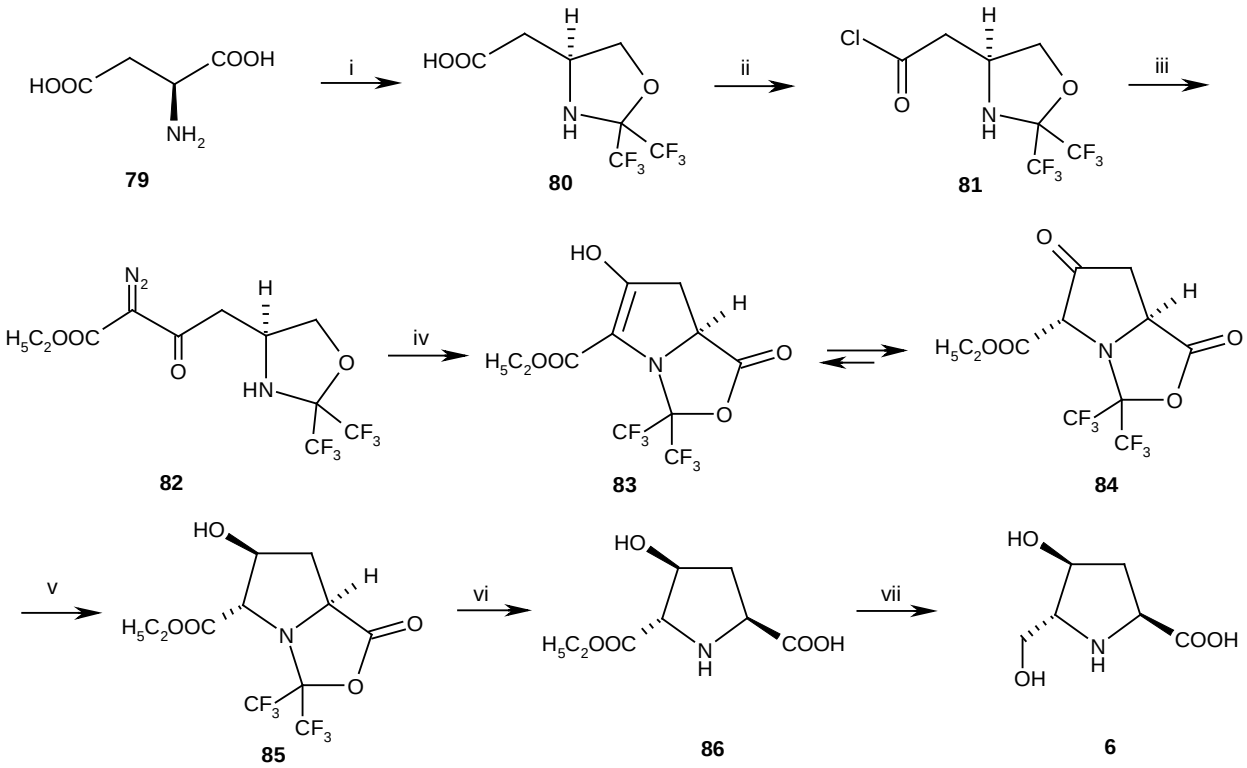


Scheme 10. *Reagents and conditions:* (i) 1 M LiHMDS, THF, - 45 °C, then (*Z*)-$BnOCH_2CH{=}CHCH_2X$; (ii) NH_3, EtOH, rt; (iii) I_2 in THF-H_2O; (iv) Na_2CO_3, MeOH, rt; (v) (a) H_2, $Pd(OH)_2$, MeOH; (b) 1 N NaOH, MeOH, rt.

Burger *et al* (1997, Scheme-11)[25]

Burger and co-workers have used *S*-aspartic acid as the chiral precursor. Reaction of aspartic acid with hexa fluoro acetone in dimethyl sulfoxide gave the compound **80**, which on treatment with thionyl chloride gave the acid chloride **81**. Treatment of **81** with ethyl diazo acetate gave the α-diazo carbonyl compound **82**. Compound **82** on catalytic reaction with

$[Rh(OAc)_2]_2$ followed by $NaBH_3CN$ reduction gave the diastereomeric lactones which were separated by flash column chromatography. On treatment with 2-propanol/water at room temperature followed by regioselective reduction of ester group delivered the (-)- bulgecinine **6**.

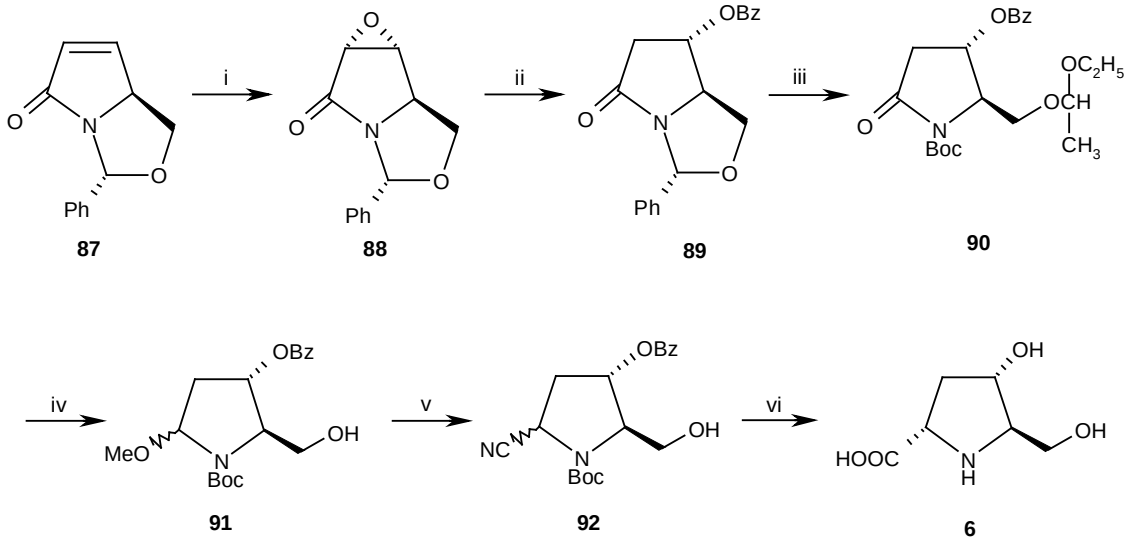


Scheme 11. *Reagents and conditions:* (i) $(CF_3)_2CO$, DMSO, 86 %; (ii) $SOCl_2$, 84 % (iii) $N_2CHCOOCH_2CH_3$, 90 %; (iv) $[Rh(OAc)_2]_2$, $CHCl_3$, rt; (v) $NaBH_3CN$, 2-propanol, 0 ^oC,; (vi) H_2O, ^iPrOH, rt, 92 % (vii) $LiBHEt_3$, THF, 0 ^oC, 44 %.

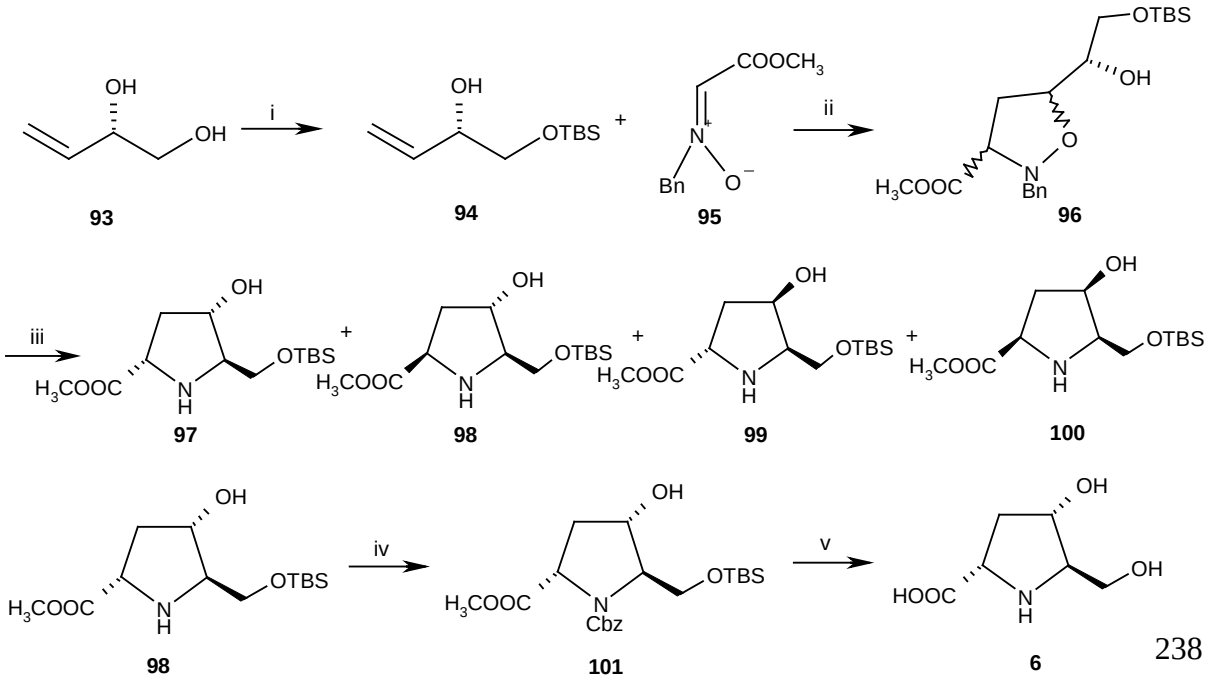
Langlois *et al* (1997, Scheme-12)[26]

Langlois and Panday have utilized γ-lactam **87** as the chiral pool starting material, which was easily prepared from *S*-pyroglutaminol. Diastereospecific epoxidation of **87** followed by cleavage of oxirane with SmI_2 gave the alcohol, which was protected as benzoate **89**. Acidic hydrolysis of oxazolidine ring followed by protection of hydroxyl and amino groups gave the compound **90**. DIBAL-H reduction of **90** followed by treatment with

methanol in presence of catalytic *p*-TSA gave the compound **91**, which on reaction with TMSCN delivered the compound **92**. Hydrolysis of nitrile group and deprotection of Boc group was achieved by using 6 N HCl to deliver the (-)-bulgecinine **6**.



Scheme 12. *Reagents and conditions:* (i) *t*-BuOOH, K_2CO_3, *n*-Bu_4NF, DMF, 75 %; (ii) (a) SmI_2, THF, MeOH, 95 %; (b) PhCOCl, CH_2Cl_2, Et_3N, 100 %; (iii) CF_3COOH, THF, H_2O, 91 %; (b) CH_2=CHOEt, H^+, 89 %; (c) $(Boc)_2O$, DMAP, 100 %; (iv) (a) DIBAL-H, hexane, THF, 95 %; (b) MeOH, H^+; (v) Me_3SiCN, $SnCl_4$, CH_2Cl_2, 50 %; (vi) HCl, 100 %.



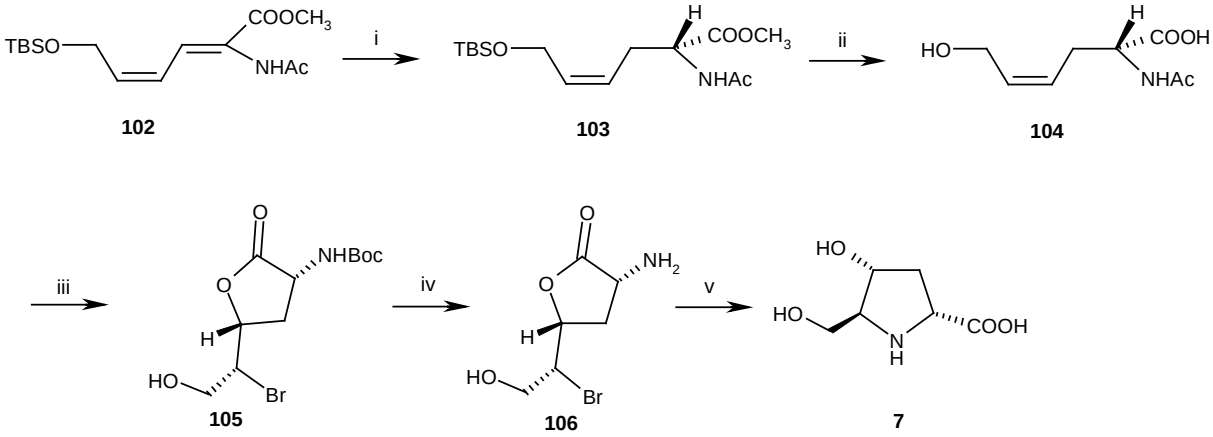
Ohta *et al* (1997, Scheme-13)[27]

Scheme 13. *Reagents and conditions:* (i) Toluene, reflux; (ii) (a) MsCl, Et_3N, CH_2Cl_2, 0 ^oC; (b) H_2, $Pd(OH)_2/C$, MeOH, rt; (iii) CbzCl, Na_2CO_3, MeOH, H_2O, 0 ^oC; (iv) TBAF, THF, rt; (v) 6 N HCl, Reflux.

Ohta and co-workers have utilized 1, 3-dipolar cycloaddition reaction as the key step. Mono protected chiral allyl alcohol **94** was chosen as a dipolarophile and was prepared from compound **93**. 1, 3-Dipolar cycloaddition reaction of nitrone **95** with the chiral allyl alcohol **94** proceeded in refluxing toluene to give a mixture of stereoisomers of oxazolidine **96**, which was mesylated without purification and the resultant mesylated products were subjected to hydrogenolysis to get the diastereomeric pyrrolidines. These pyrrolidines are separated by preparative thin layer chromatography and compound **98** was converted into (-)-bulgecinine **6**.

Burk *et al* (1998, Scheme-14)[28]

Burk and co-workers have employed highly regio and enantioselective catalytic hydrogenation reaction of α, β, γ, δ-unsaturated ester to deliver the compound **103**. Compound **103** on sequential treatment with $(Boc)_2O$, hydrazine, HF in pyridine, LiOH gave the compound **104**. Treatment of **104** with NBS to gave the desired bromolactone **105** and its diastereomer in 9:1 ratio. The key intermediate **105** on Oppolzer's reaction conditions was transformed in to (+)-bulgecinine **7**.

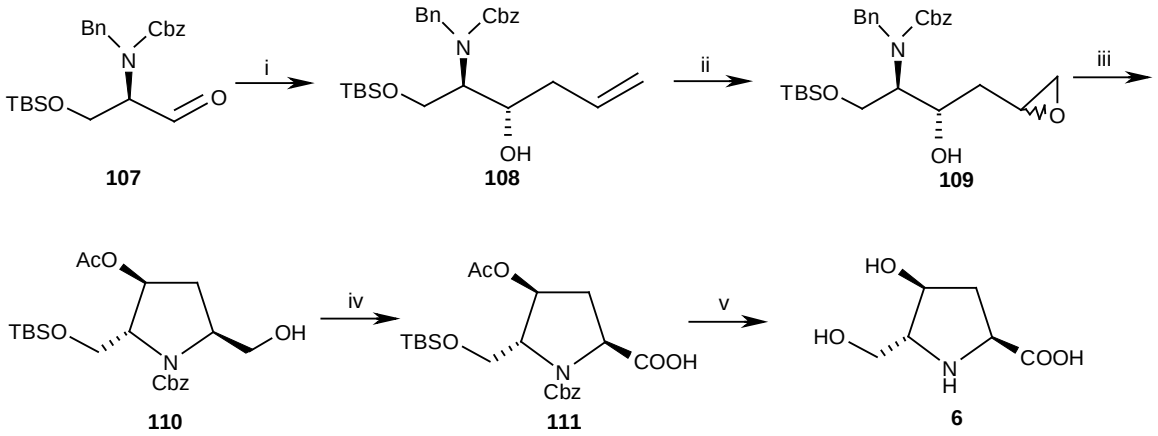


102 **103** **104** **105** **106** **7**

Scheme 14. *Reagents and conditions:* (i) [((*R*, *R*)-Et-DUPHOS)-Rh]OTf, S/C = 500/1, MeOH, 60 Psi, H_2, 2 h, (99.3 % ee of *R*) (ii) (a) $(Boc)_2O$, DMAP, THF, 24 h then N_2H_4, MeOH-THF (1:1), 4 h, 92 %; (b) HF-Pyridine, CH_2Cl_2, 91 %; (c) 0.5 M LiOH/THF (4:1), 91 %; (iii) NBS, THF, 0 ^oC, 5 min; (iv) (a) CF_3COOH, CH_2Cl_2, 40 ^oC, 3 h; (b) 0.1 N $Ba(OH)_2$, rt, 3 h, 80 %.

Jurczak *et al* (2001, Scheme-15)[29]

Jurczak and Krasinski have employed the allylation of aldehyde **107** under Barbier conditions to get the anti-adduct **108** with high diastereoselectivity. Epoxidation of **109** with $VO(acac)_2$,/*t*-BuOOH furnished diastereomeric epoxides **109**. Sequential treatment of this mixture with Ac_2O, Pd/C, CbzCl gave chromarographically separable pyrrolidines **110** and its



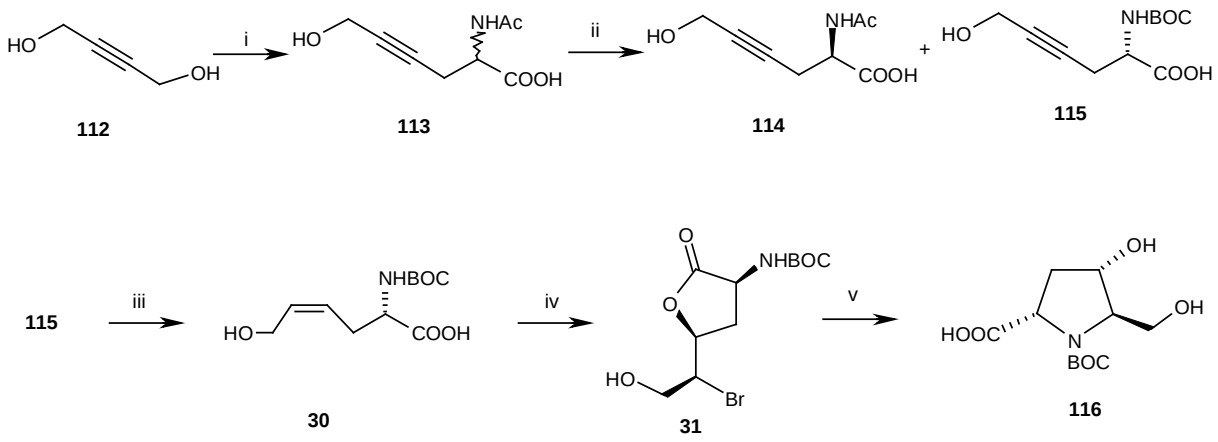
diastereomer. The major isomer **110** was then transformed into (-) bulgecinine **6**.

Scheme 15. *Reagents and conditions:* (i) Allyl bromede, Zn, Sat.NH_4Cl, THF, rt; (ii) *t*-BuOOH, $VO(acac)_2$, CH_2Cl_2, rt; (iii) (a) Ac_2O, Pyridine, DMAP, rt; (b) H_2, 5 % Pd/C, MeOH, rt; (c) CbzCl, CH_2Cl_2, sat. $NaHCO_3$, rt; (iv) $NaIO_4$, $RuCl_3$ (cat), CH_3CN:CCl_4:H_2O (2:2:3), 0 ^oC; (v) (a) 3 N HCl, THF, reflux; (b) H_2, 5 % Pd/C, MeOH, rt.

Holt *et al* (2002, Scheme-16)[30]

Holt and co-workers employed L-acylase and D-acylase enzymes for the synthesis on both isomers of bulgecinine. Conversion of 2-butyne-1, 4-diol **112** in to the racemic *N*-acetyl acid **113** was achieved by a series of reactions. Treatment of **113** with L-acylase at 65 0 ^oC

and at *p*H 7 gave a mixture of *S*-amino acid **115** and unreacted *R*-*N*-acetyl acid **114**. Hydrogenation of **115** with lindlar catalyst gave the *cis*-olefin **30**, which was converted in to *N*-Boc protected bulgecinine by a series of reported reactions.

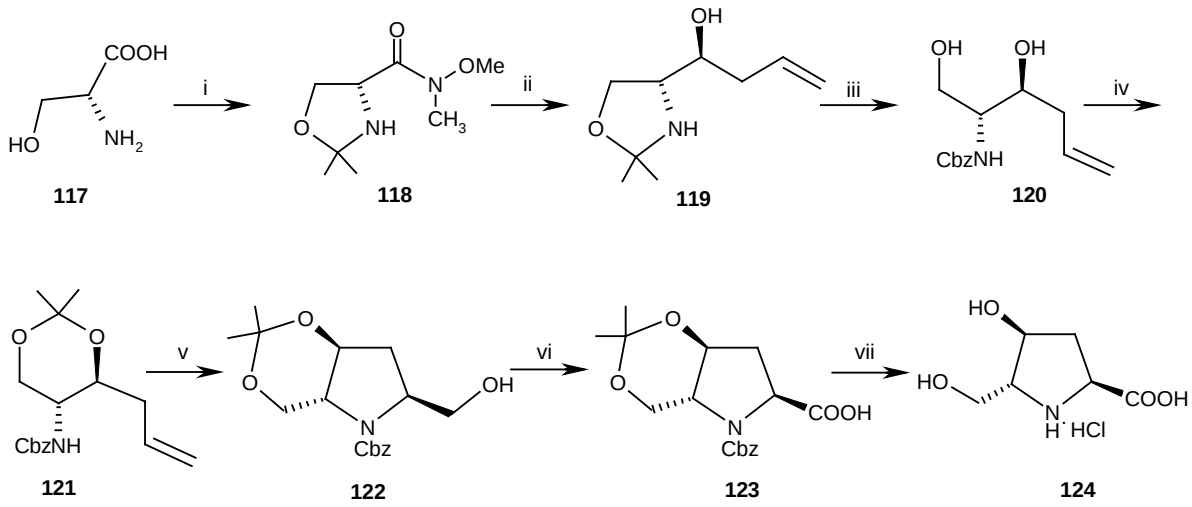


Scheme 16. *Reagents and conditions:* (i) (a) BzCl, Pyridine, CH_2Cl_2, rt; (b) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 ^oC; (c) LiBr, Acetone, 15 ^oC, (ii) (a) Diethyl acetamido malonate, KO^tBu, THF, Reflux; (b) NaOH, MeOH, Reflux then Conc. HCl, Reflux; (iii) L-acylase (200 u/g substrate), 30 mm KH_2PO_4, pH 7, 65 ^oC, then $(Boc)_2O$, NaOH, pH 10; (iv) *n*-acylase (40 u/g substrate), aq. NaOH to adjust pH 8, rt then $(Boc)_2O$, NaOH, pH 10; (v) 10 % wt Lindlar catalyst, MeOH, 1 bar H_2, 20 ^oC, (vi) NBS, THF, -10 0 ^oC, 20 min; (vii) (a) TsOH-H_2O, EtOAc, rt, 1 h; (b) H_2O, 1 M LiOH to pH 9, rt, 16 h; (c) $(Boc)_2O$, THF, 1 M LiOH to pH 9.

Datta *et al* (2004, Scheme-17)[31]

Datta and Khalaf have prepared *N*, *O*-acetonide protected Weinreb amide derivative **118** from the readily available D-serine. Reaction of **118** with allyl magnesium bromide followed by treatment with $Zn(BH_4)_2$ in presence of $CeCl_3.7H_2O$ gave the *anti* amino alcohol derivative **119**. Deprotection of the *N*, *O*-acetonide linkage and reprotection of the resulting 1, 3 diol **120** afforded *O*, *O*-acetonide derivative **121**. Treatment of **121** with $Hg(OAc)_2$ followed by oxidative demercuration gave the compound **122**. Oxidation of primary hydroxyl group to

carboxylic acid and its subsequent esterification gave the methyl ester **123**, which on global deprotection with aq. HCl gave THE hydrochloride salt of (-)-bulgecinine **6**.

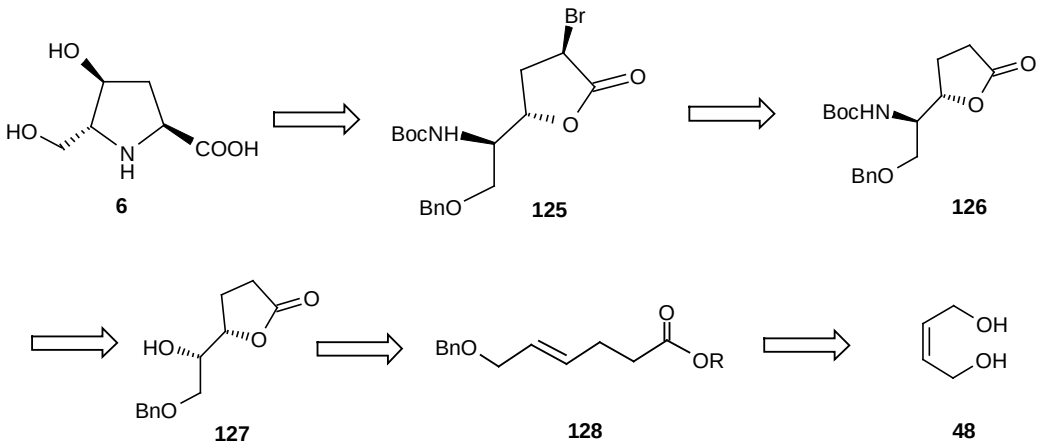


Scheme 17. *Reagents and conditions:* (i) ref 32; (ii) Allyl magnesium bromide, -78 ^{o}C, 100 %, (b) $Zn(BH)_4$, Et_2O, $CeCl_3.7H_2O$, MeOH, -10 ^{o}C, 88 %; (iii) AcOH-H_2O (3:1), 92 %; (iv) 2,2-dimethoxy propane, CSA, Acetone, 92 %; (v) (a) $Hg(OAc)_2$, CH_3CN, Δ; (b) O_2, $NaBH_4$, DMF, rt, 65; (vi) (a) DMP, then $NaClO_2$, NaH_2PO_4: (b) CH_2N_2, 71 %; (vii) aq. HCl, Reflux, 94 %.

Present work:

Although several syntheses of both (+)- and (-)-bulgecinine have documented in the literature through varied synthetic routes, most involve a large number of steps or employing a chiral pool starting material. Herein we planned to synthesize the target compound **6**, employing the Sharpless asymmetric dihydroxylation as the key step and thereby inducing the desired chirality, starting from cheap achiral source.

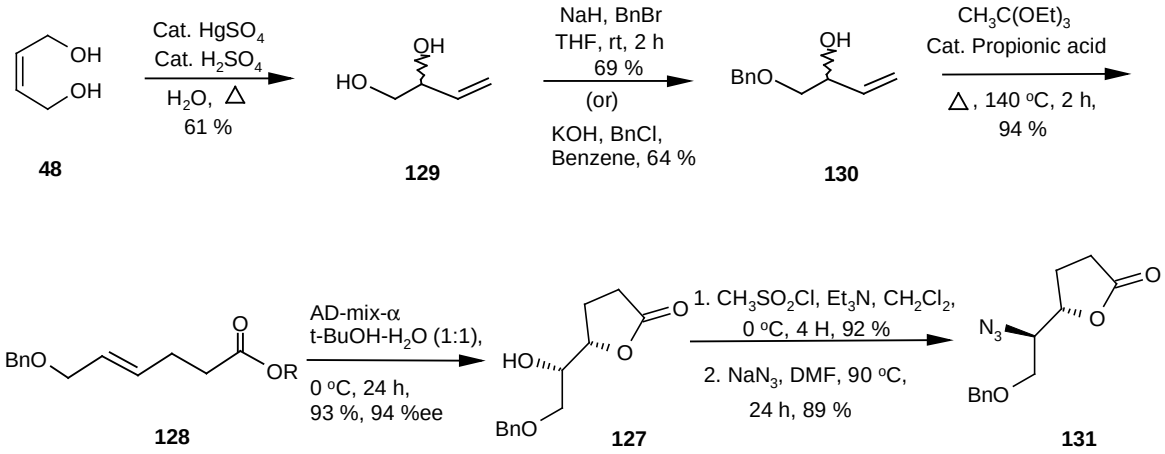
The retrosynthetic analysis for the stereoselective synthesis of (-)-bulgecinine is depicted in **scheme 18**. It was envisaged that simple two-step sequence, *i.e* cyclization and removal of benzyl protection could be used to form the target molecule from the bromo lactone **125**. The bromolactone **125** could be obtained from the hydroxy lactone **127**, the versatile intermediate for our synthesis could be obtained from *cis*-2-butene-1, 4-diol.



Scheme 18: **Retrosynthetic analysis**

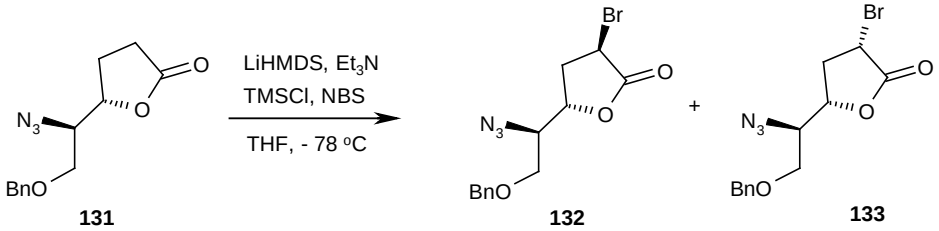
The synthesis of (-)- bulgecinine commences from *cis*-2-butene-1, 4-diol **48** as shown in scheme **19.** The commercially available *cis*-2-butene-1, 4-diol was converted into monoprotected allyl alcohol **130**, which on Claisen orthoester rearrangement and Sharpless

asymmetric dihydroxylation delivered the hydroxy lactone **127** with the required stereochemistry. The enantiopurity of the hydroxy lactone was estimated to be in excess of 94 % using chiral HPLC analysis. (Chiralcel OD, 80:20, hexane:^{i}PrOH, 1 mL /min, 254 nm). Mesylation followed by displacement of mesylate with NaN_3 delivered the azidolactone **131**.



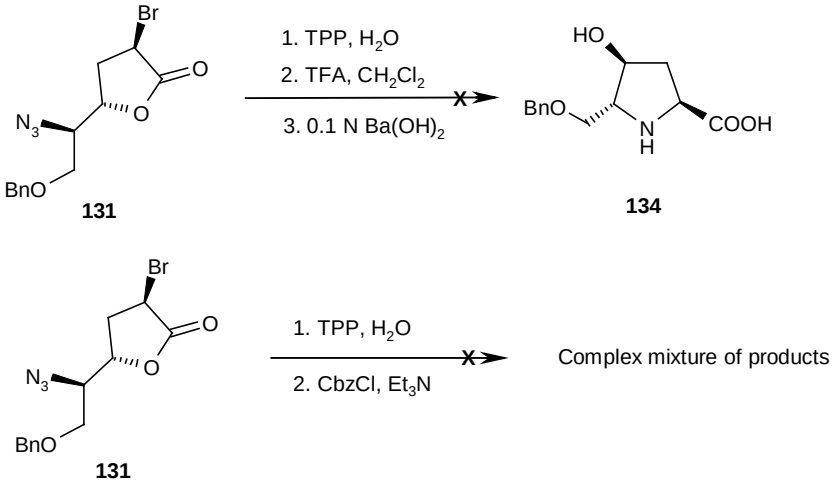
Scheme 19

Having the azidolactone **131** in hand, the challenging task in our synthesis was to introduce the bromine stereoselectively at C-2 of the lactone **131**. Accordingly reaction of the lactone with LiHMDS, Et_3N, and NBS at –78 ^{o}C for 2 h gave the mixture of **132** and **133**. The major isomer **132** along with its diastereomer **133** (2:1 ratio) was separated by silica gel column chromatography. The ^{1}H-NMR, ^{13}C-NMR data of **132**, **133** and NOESY of **133** were in good agreement with the proposed structures. The next immediate concern was to reduce the azide to amine and cyclize the resultant amine to deliver the final target.



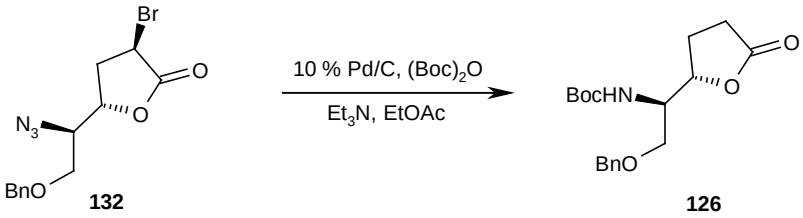
Scheme 20

Accordingly the bromo azide **132** was reduced by using triphenyl phosphine, water to deliver the crude amine, which on subsequent cyclization under Oppolzer's conditions should give the protected bulgecinine. Unfortunately the required product could not obtained using this route. Even the crude amine on reaction with CbzCl did not deliver the Cbz protected compound.



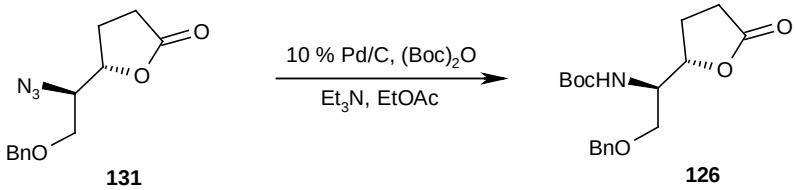
Scheme 21

Next attemp was to reduce the azide by using Pd/C in presence of $(Boc)_2O$. In this reaction along with the Boc protection debromination had taken place.



Scheme 22

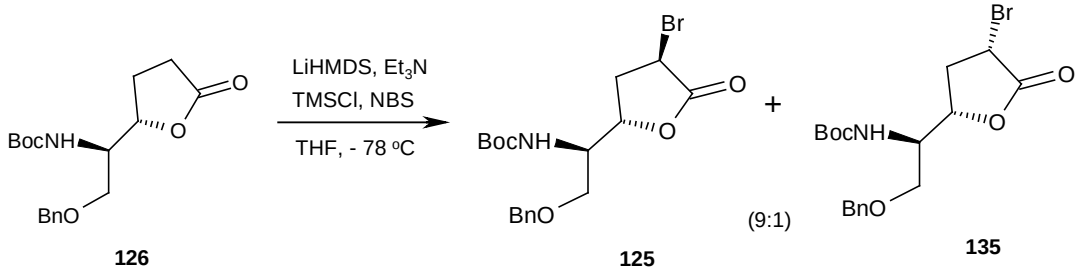
Thus, we turned our attention to reduce the azide **131** and protect it as its Boc derivative **126**. Accordingly the azide on reaction with Pd/C in EtOAc in presence of $(Boc)_2O$ and Et_3N delivered the Boc protected lactone **126**. In the IR spectrum disappearance of strong



absorption at 2106 cm-1 was observed. The ^{1}H-NMR, ^{13}C-NMR data and Elemental analysis data were in good agreement with the structure **126**.

Scheme 23

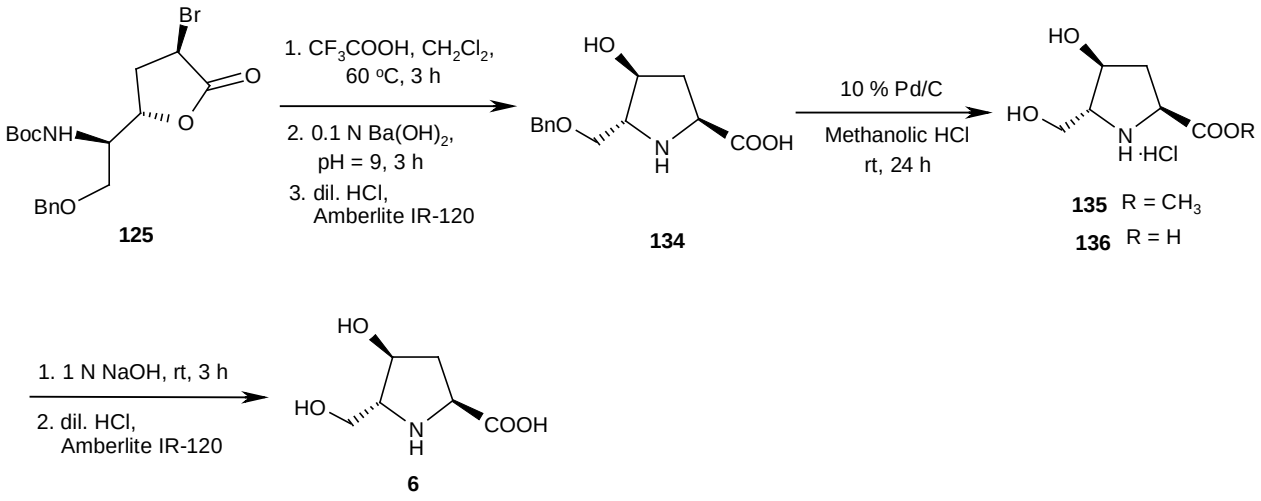
The introduction of bromine stereoselectively at C-2 of Boc lactone **126** was achieved by using the same conditions as used previously for the azido lactone **131**. Interestingly highter diastereoselectivity (9:1) was observed for the Boc lactone **126**. The required major isomer **125** was separated by silicagel column chromatography. The ^{1}H-NMR, ^{13}C-NMR data and elemental analysis data were in good agreement with the assigned structure **125**.



126 **125** **135**

Scheme 24

Now the cyclization of bromo lactone was remained to deliver the protected bulgecinine **134**. The conditions developed by Oppolzer[6] were adapted to convert the major isomer (2*R*,4*S*,5*R*)-**125** into the (2*S*,4*S*,5*R*)-**134** using the following sequence of reactions. The lactone **125** was refluxed in DCM with 10 mol. equivalents of CF_3COOH for 3 h followed by evaporation of the solvent.



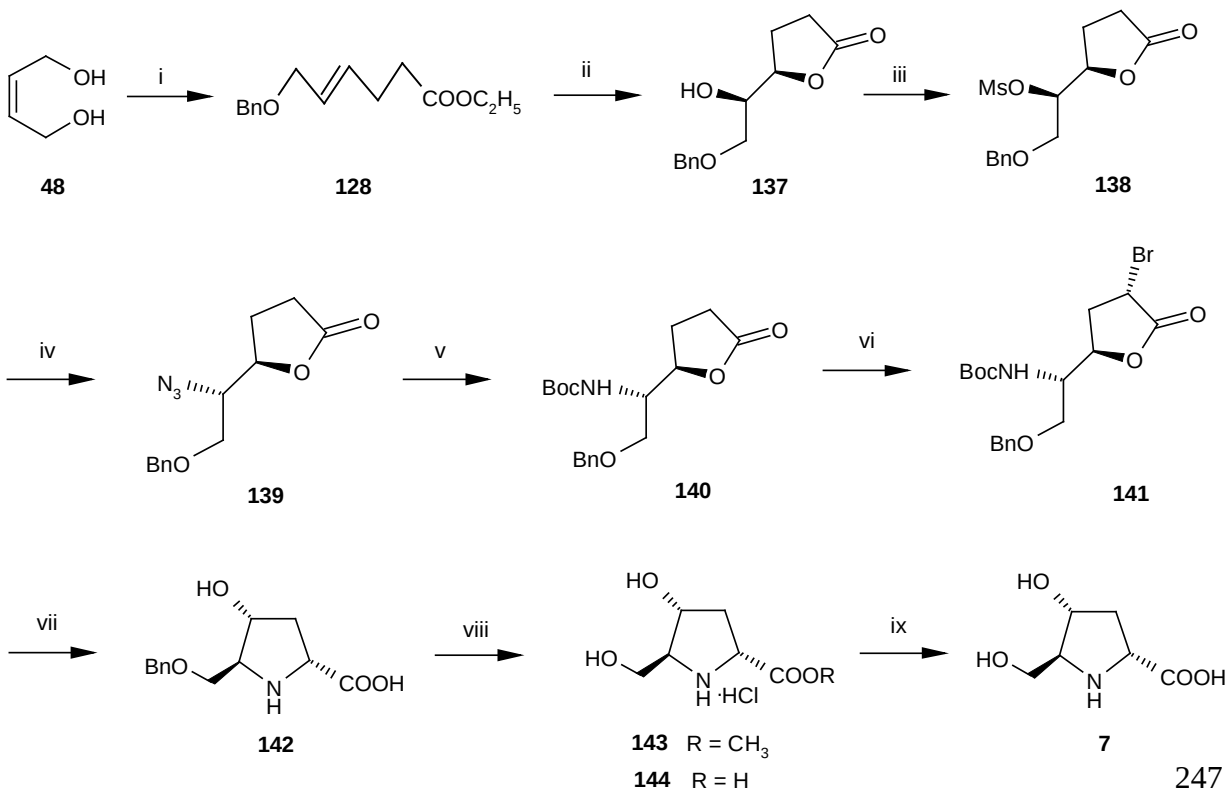
125 **134** **135** R = CH_3 **136** R = H **6**

Scheme 25

The residue was then dissolved in 0.1 N $Ba(OH)_2$ and the mixture maintained at pH 9 for 3 h. Acidification to pH 1, stirring the aqueous solution with Amberlite-IR-120 ion exchange resin for 24 h, filtration, washing the resin with distilled water (until it showed clear solution with $AgNO_3$ to test the complete removal of Cl^-), stirring the resin with 6 N aqueous NH_4OH solution for 3 h and filtration gave the benzyl protected (2*S*,4*S*,5*R*)-(-)-bulgecinine **134**.

Finally removal of the benzyl protection was performed using Pd/C in methanolic HCl under normal hydrogen pressure and at room temperature to deliver a mixture of (-)-bulgecinine hydrochloride **135** and its methyl ester **136**. This mixture was subjected to basic hydrolysis using 1M NaOH to deliver (-)-bulgecinine **6**. Our synthetic (-)-bulgecinine **6** showed the rotation $[\alpha]_D$ - 13.3 (c = 0.9, H_2O) is in good agreement with the literature data.

Accordingly we also prepared (+)-bulgecinine **7** following the same sequence of reactions from the opposite enantiomer of hydroxylactone **127**, which was prepared from the γ, δ-unsaturated ester **128** using AD-mix-β. The synthetic (+)-bulgecinine **7** showed the



rotation $[\alpha]_D$ + 12.5 (c = 0.9, H_2O) which is in good agreement with the literature data.

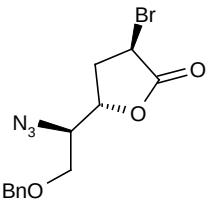
Scheme 26

Scheme 26: *Reagents and Conditions*: (i) (a) $HgSO_4$, H_2SO_4, H_2O, reflux; (b) BnCl, KOH, Benzene, reflux; (c) $CH_3C(OEt)_3$, cat. propionic acid, 140 ^oC, 2 h, 94%; (ii) AD-mix-β, $CH_3SO_2NH_2$, *t*-BuOH:H_2O (1:1), 24 h, 0 ^oC, 95%, 93% ee; (iii) CH_3SO_2Cl, Et_3N, DMAP, DCM, 0 ^oC, 4 h, 92%; (iv) NaN_3, DMF, 90 ^oC, 24 h, 89%; (v) H_2, 10% Pd/C, Et_3N, Boc_2O, EtOAc, rt, 2 h, 88%; (vi) LiHMDS, TMSCl, Et_3N, NBS, THF, -78 ^oC, 2 h, 65%; (vii) i. CF_3COOH, DCM, 60 ^oC, 3 h, ii. 0.1N $Ba(OH)_2$, pH = 9, 3 h; iii. dil. HCl, Amberlite IR-120, 24 h; iv. 6N NH_4OH (aq), 3 h; (viii) 10% Pd/C, methanolic HCl, rt, 24 h; (ix) 1M NaOH, RT, 92% (over three steps).

Conclusion:

In conclusion (+)- and (-)-bulgecinine were efficiently synthesized from the readily available *cis*-2-butene-1,4-diol using Sharpless asymmetric dihydroxylation as the key step. High enantio selectivity in Sharpless Asymmetric dihydroxylation and good diastereo selectivity in bromination reaction has been achieved.

Experimental:

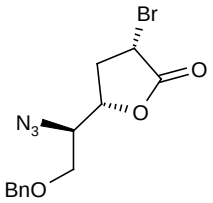


(2*R*, 4*S*, 5R)-5-Azido-6-Benzyloxy-2-Bromo-hexane-4-olide (132)

Procedure: To a solution of **131** (0.4 g, 1.53 mmol) in anhydrous THF (15 mL) were added LiHMDS (1.0 M solution in THF) (1.68 mL, 1.68 mmol), Et_3N (0.23 mL, 1.68 mmol) and NBS (0.3 g, 1.68 mmol) at – 78 ^oC and stirred for 2 h at the same temperature. The reaction mixture was quenched with sat. NH_4Cl and extracted with EtOAc (2 x 25 mL). The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed on silicagel using EtOAc-light petroleum ether (9:1) as an eluent to afford **132** (0.3 g, 57 %) and **133** (0.15 g, 29 %).

Appearance	**:**	**Colourless oil**
Yield	**:**	**57 %**
Molecular Formula	**:**	**$C_{13}H_{14}N_3O_3Br$**
^{1}H NMR ($CDCl_3$ + CCl_4,	**:**	**δ δ 2.45 (ddd, *J* = 14.86, 5.87, 2.73, 1H), 2.66-2.81 (m, 1H), 3.60-3.75 (m, 2H), 3.96-4.04 (m, 1H), 4.47-4.52 (m,**

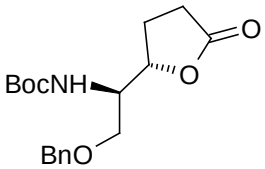
200MHz)		**4H), 4.60-4.66 (m, 2H), 4.84 (m, 1H), 7.25-7.45 (m, 5H).**
^{13}C NMR	**:**	**δ 35.1, 37.7, 62.2, 68.7, 73.5, 77.2, 127.6, 128.0, 128.5,**
($CDCl_3$+CCl_4, 50 MHz)		**137.0, 171.4.**
Elemental analysis	**:**	Anal. Calcd for $C_{13}H_{14}N_3O_3Br$; C, 45.88; H, 4.11; N, 12.35; Br, 23.23 %. Found: C, 45.64; H, 4.18; N, 12.16; Br, 23.42 %.



(2*S*, 4*S*, 5*R*)-5-Azido-6-Benzyloxy-2-Bromo-hexane-4-olide (133)

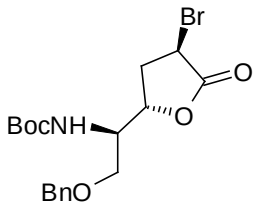
Appearance	**:**	**Colourless oil**
Molecular Formula	**:**	**$C_{13}H_{14}N_3O_3Br$**
Yield	**:**	**29 %.**
^{1}H NMR	**:**	**δ 2.44-2.56 (m, 1H), 2.72-2.90 (m, 1H), 3.62-3.75 (m,**
($CDCl_3$+CCl_4, 200 MHz)		**2H), 3.82-3.95 (m, 1H), 4.50-4.58 (m, 4H), 7.25-7.45 (m, 5H).**
^{13}C NMR	**:**	**δ 35.0, 36.5, 62.4, 68.8, 73.7, 76.4, 127.7, 128.1, 128.6,**
($CDCl_3$+CCl_4, 50 MHz)		**137.1, 171.4.**
Elemental analysis	**:**	Anal. Calcd for $C_{13}H_{14}N_3O_3Br$; C, 45.88; H, 4.11; N, 12.35; Br, 23.23 %. Found: C, 45.72; H, 4.24; N, 12.26; Br, 23.12 %.

6-Benzyloxy-5-(*t*-Butoxycarbonylamino)-2,3,5-trideoxy-D-erythro-hexano-1,4-lactone (126)



Procedure: To a solution of **131** (1.5 g, 5.74 mmol) in EtOAc were added Et_3N (0.88 mL, 6.32 mmol), $(Boc)_2O$ (1.45 mL, 6.32 ml) and 10 % Pd/C (0.05 g). After stirring under an atmosphere of H_2 for 4 h at normal temperature and pressure, the reaction mixture was concentrated under reduced pressure and the residue was purified by silica giel column chromatography using light petroleum ether:EtOAc (3:1) as an eluent to afford pure **126** (1.69 g, 88 %) as a colourless viscous oil.

Appearance	:	**Colourless viscous oil**
Yield	:	**88 %**
Molecular Formula	:	**$C_{18}H_{25}NO_5$**
IR ($CHCl_3$, cm^{-1})	:	**3119, 1776, 1605, 1445, 758.**
$[\alpha]_D$	:	**+ 1.87 (*c* = 1, $CHCl_3$)**
^1H NMR ($CDCl_3$ + CCl_4, 200MHz)	:	**δ 1.39 (s, 9H), 2.15 (m, 2H), 2.43 (m, 2H), 3.50 (dd, *J* = 9.4, 3.5 Hz, 1H), 3.68-3.80 (m, 2H), 4.45-4.56 (m, 3H), 5.10 (d, *J* = 9.4 Hz, 1H), 7.28 (m, 5H).**
^{13}C NMR ($CDCl_3$+CCl_4, 50 MHz)	:	**δ 24.4, 27.8, 28.1, 52.9, 68.8, 73.3, 78.5, 79.6, 127.5, 128.2, 137.5, 155.3, 176.2.**
Elemental analysis	:	Anal. Calcd for $C_{18}H_{25}NO_5$; C, 64.46; H, 7.51; N, 4.17%. Found: C, 64.38; H, 7.32; N, 4.08%.



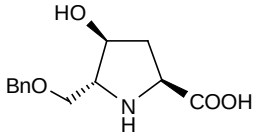
(2*R*, 4*S*, 5R)-6-Benzyloxy-2-Bromo-5-(t-Butoxycarbonylamino)-hexane-4-olide (125)

Procedure: To a solution of **126** (0.6 g, 1.79 mmol) in anhydrous THF (20 mL) were added LiHMDS (1.0 M solution in THF) (1.98 mL, 1.98 mmol), Et_3N (0.27 mL, 1.98 mmol) and NBS (0.35 g, 1.98 mmol) at – 78 ^oC and stirred for 2 h at the same temperature. The reaction mixture was quenched with sat. NH_4Cl and extracted with EtOAc (2 x 25 mL). The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, filtered and

concentrated under reduced pressure. The residue was chromatographed on silicagel using EtOAc-light petroleum (8:2) as an eluent to afford **125** (0.48 g, 65 %) as a colourless oil.

Molecular Formula	:	**$C_{18}H_{24}NO_5Br$**
Yield	:	**65 %.**
$[\alpha]_D$	:	**+ 10.50 (*c* = 1, $CHCl_3$).**
^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz)	:	**δ 1.36 (s, 9H), 2.42 (ddd, *J* = 8.2, 5.9, 2.3 Hz, 1H), 2.68 (m, 1H), 3.52 (dd, *J* = 9.8, 3.5 Hz, 1H), 3.80 (m, 2H), 4.42 (dd, *J* = 6.6, 2.3 Hz, 1H), 4.51 (m, 2H), 4.78 (m, 1H), 5.10 (d, *J* = 9 Hz, 1H), 7.26 (m, 5H).**
^{13}C NMR ($CDCl_3$+CCl_4, 50 MHz)	:	**δ 28.3, 36.8, 38.3, 52.8, 68.7, 73.5, 77.5, 80.0, 127.7, 128.4, 137.4, 155.3, 171.6**
Elemental analysis	:	Anal. Calcd for $C_{18}H_{24}NO_5Br$; C, 52.18; H, 5.83; N, 3.37; Br, 19.28%. Found: C, 52.07; H, 5.97; N, 3.36; Br, 19.06%.

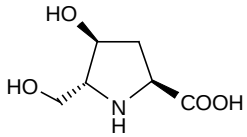
(2*S*, 4*S*, 5R)-5-Benzyloxymethyl-hydroxy-proline (134)



Procedure: To a solution of **125** (0.35 g, 0.845 mmol) in anhydrous CH_2Cl_2 (15 mL) was added trifluoro acetic acid (0.65 mL, 10 mol eq) and the mixture was refluxed for 3 h. The solvent was removed under reduced pressure and the residue thus obtained was then dissolved in 0.1 N $Ba(OH)_2$ and the mixture maintained at pH 9 for 3 h. Acidification to pH 1, stirring the aqueous solution with Amberlite-IR-120 ion exchange resin for 24 h, filtration, washing the resin with distilled water (until it showed clear solution with $AgNO_3$ to test the complete removal of Cl^-), stirring the resin with 6 N aqueous NH_4OH solution for 3 h and filtration gave the benzyl protected (2*S*,4*S*,5*R*)-(-)-bulgecinine **134** (0.2 g, 96 %) as white solid

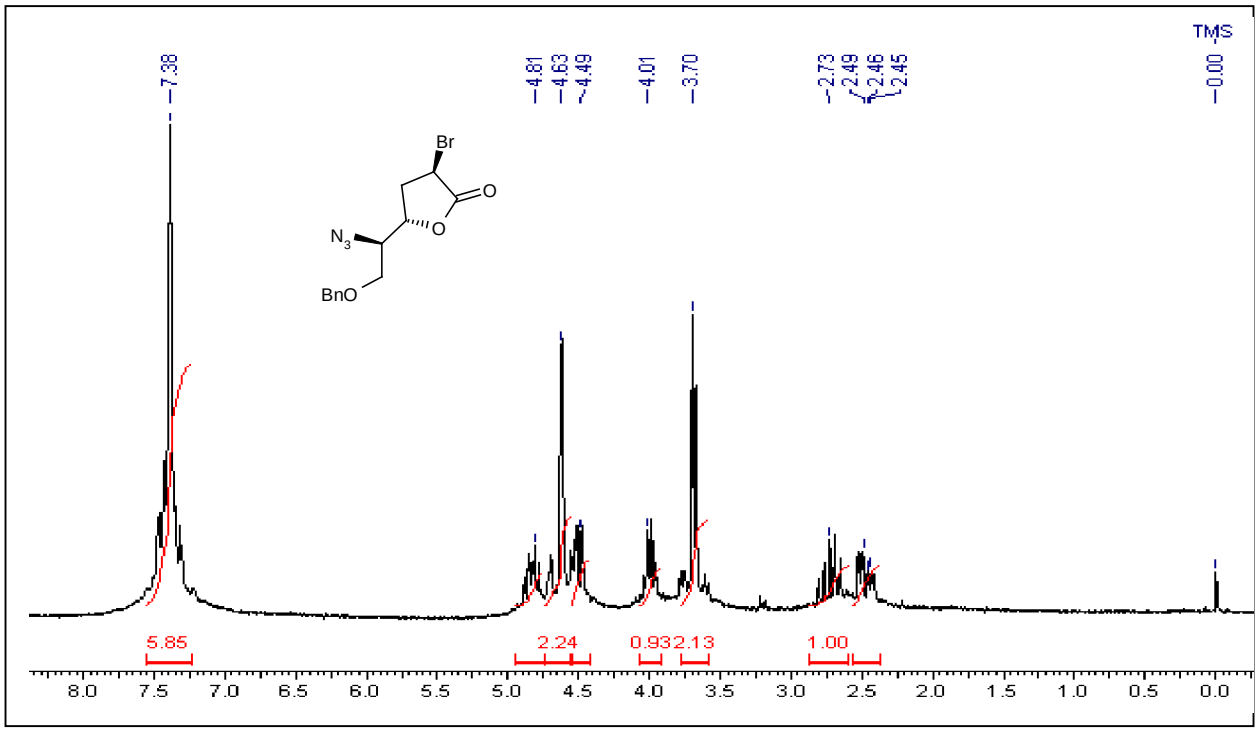
Appearance	:	**White solid**
Molecular Formula	:	**$C_{13}H_{17}NO_4$**
Yield	:	**96 %.**
M P.	:	**192 ^{o}C**
$[\alpha]_D$	:	**- 8.09 (*c* = 1, H_2O)**
^{1}H NMR (D_2O, 200MHz)	:	**δ 2.11 (ddd, *J* = 14.1, 6.2, 4.3 Hz, 1H), 2.51 (ddd, *J* = 14.1, 9.0, 5.8 Hz, 1H), 3.56-3.71 (m, 3H), 4.06 (dd, *J* = 9.0, 6.6 Hz, 1H), 4.23 (m, 1H), 4.49 (m, 2H), 7.32 (m, 5H).**
^{13}C NMR (D_2O, 50MHz)	:	**δ 36.2, 59.1, 64.8, 65.7, 70.6, 72.8, 128.0, 128.4, 136.7, 173.6.**
Elemental Analysis	:	Anal. Calcd for $C_{13}H_{17}NO_4$; C, 62.14; H, 6.81; N, 5.57%. Found: C, 62.02; H, 6.92; N, 5.49%.

(2*S*, 4*S*, 5R)-4-hydroxy-5-hydroxymethyl-proline [(-)-Bulgecinine] (6)

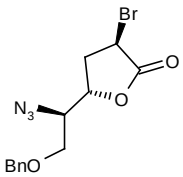


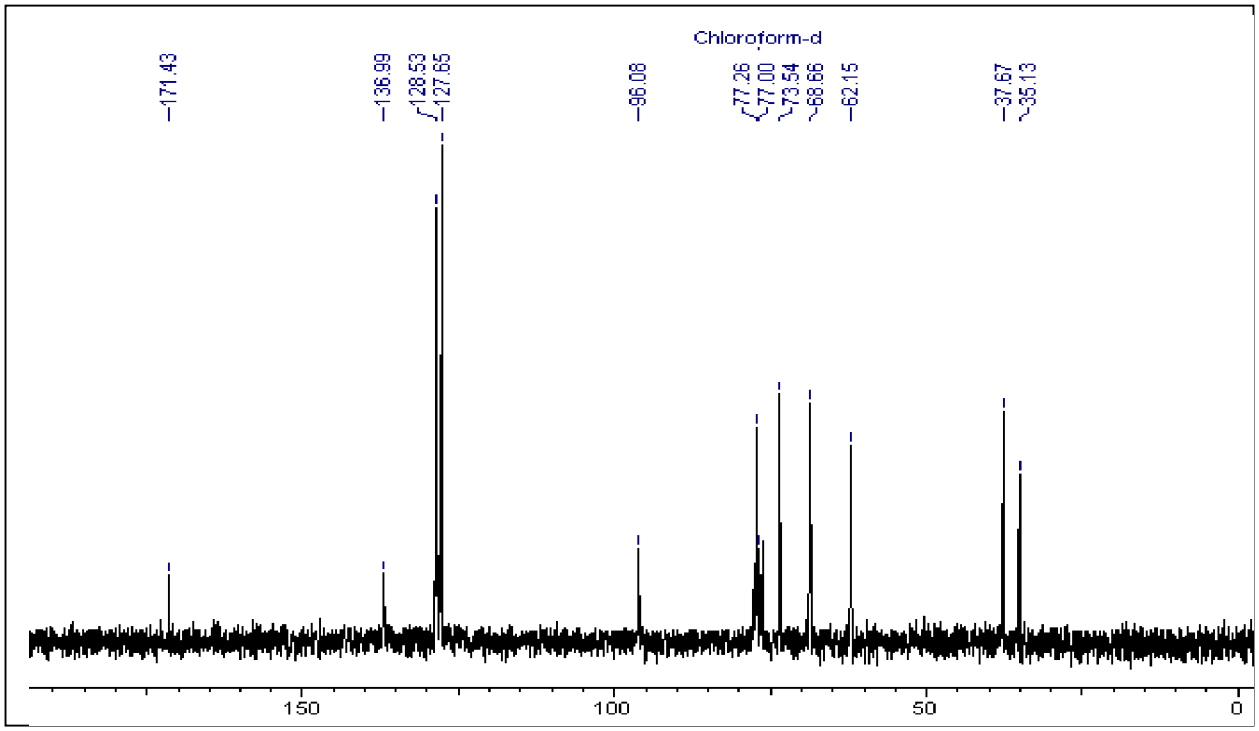
Procedure: To a solution of **134** (0.2 g, 0.79 mmol) in anhydrous methanolic HCl (8 mL) was added 10 % Pd/C and the mixture was flushed with H_2 for 5 min. After stirring under an atmosphere of hydrogen at room temperature for 24 h, the reaction mixture was filtered through a pad of celite and the solvent was concentrated under reduced pressure. The residue contained (-)-bulgecinine and its methyl ester. Subjection of this mixture to basic hyhrolysis using 1 N NaOH followed by acidification to pH 1, stirring the aqueous solution with Amberlite-IR-120 ion exchange resin for 24 h, filtration, washing the resin with distilled water (until it showed clear solution with $AgNO_3$ to test the complete removal of Cl^-), stirring the resin with 6 N aqueous NH_4OH solution for 3 h and filtration gave (2*S*,4*S*,5*R*)-(-)-bulgecinine **6** (0.13 g, 96 %) as white solid**.**

Appearance	**:**	**White solid**
Molecular Formula	**:**	**$C_6H_{11}NO_4$**
Yield	**:**	**96 %.**
M. P.	**:**	**179 ^oC**
$[\alpha]_D$	**:**	**- 13.3 (c = 0.9, H_2O)**
^1H NMR (D_2O, 200MHz)	**:**	**δ 2.11 (ddd, *J* = 14.5, 6.3, 4.6 Hz, 1H), 2.58 (ddd, *J* = 14.5, 9.0, 5.9 Hz, 1H), 3.56-3.71 (m, 3H), 4.06 (dd, *J* = 9.0, 6.6 Hz, 1H), 4.34 (m, 1H).**
^{13}C NMR (D_2O, 50MHz)	**:**	**δ 37.2, 59.2, 60.5, 66.2, 71.7, 174.7.**
Elemental Analysis	**:**	Anal. Calcd for $C_6H_{11}NO_4$; C, 44.72; H, 6.83; N, 8.69 %. Found: C, 44.68; H, 6.96; N, 8.42 %.

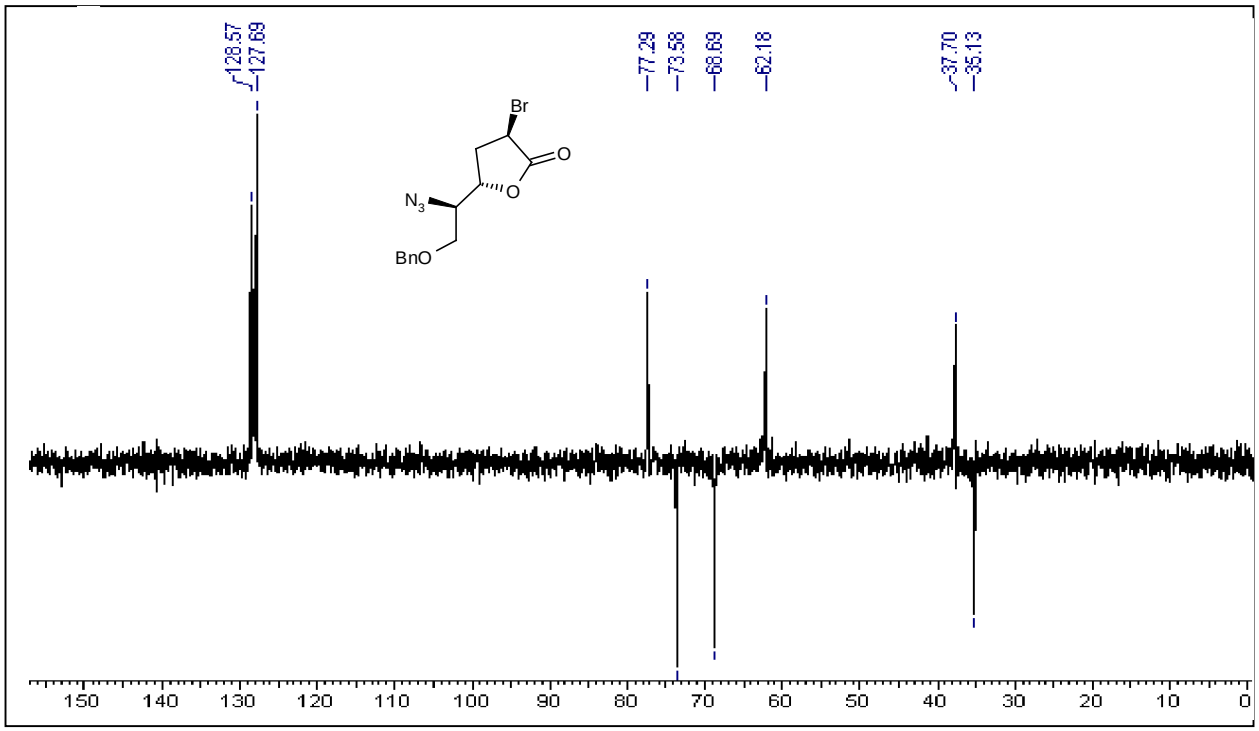


^1H NMR Spectrum of compound 132 in $CDCl_3$ + CCl_4

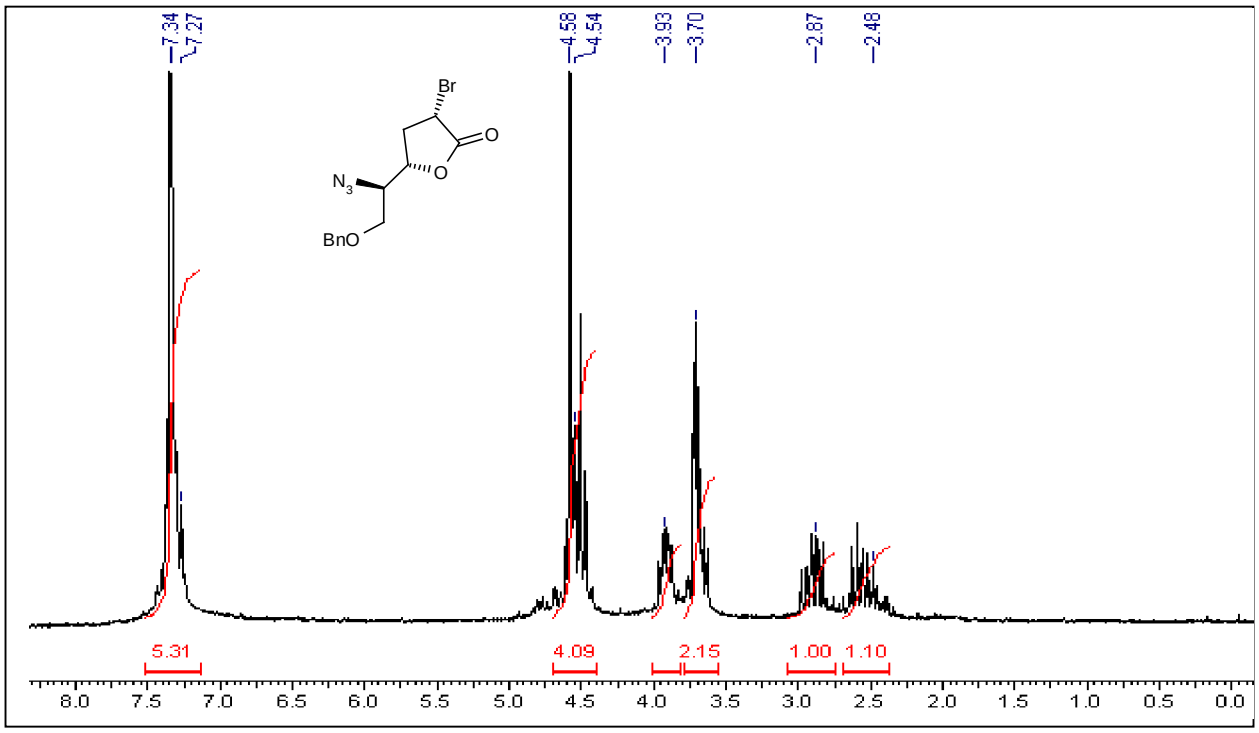




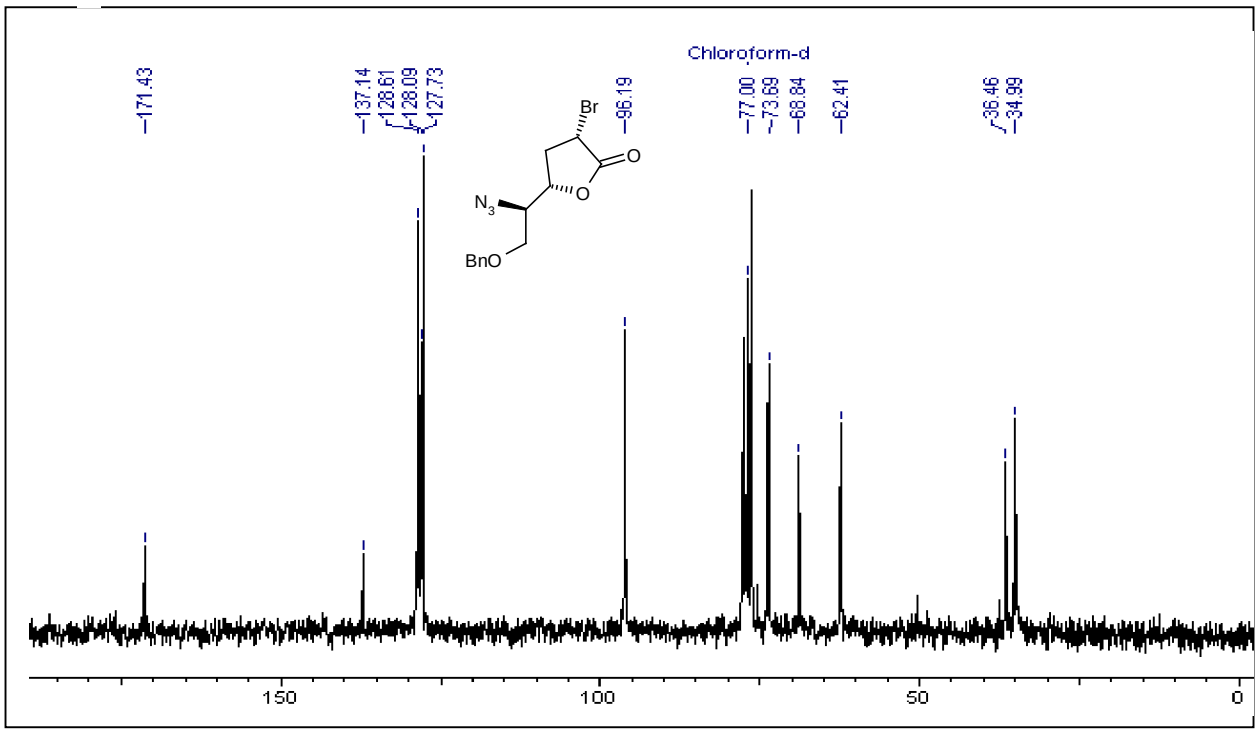
^{13}C NMR Spectrum of compound 132 in $CDCl_3$ + CCl_4



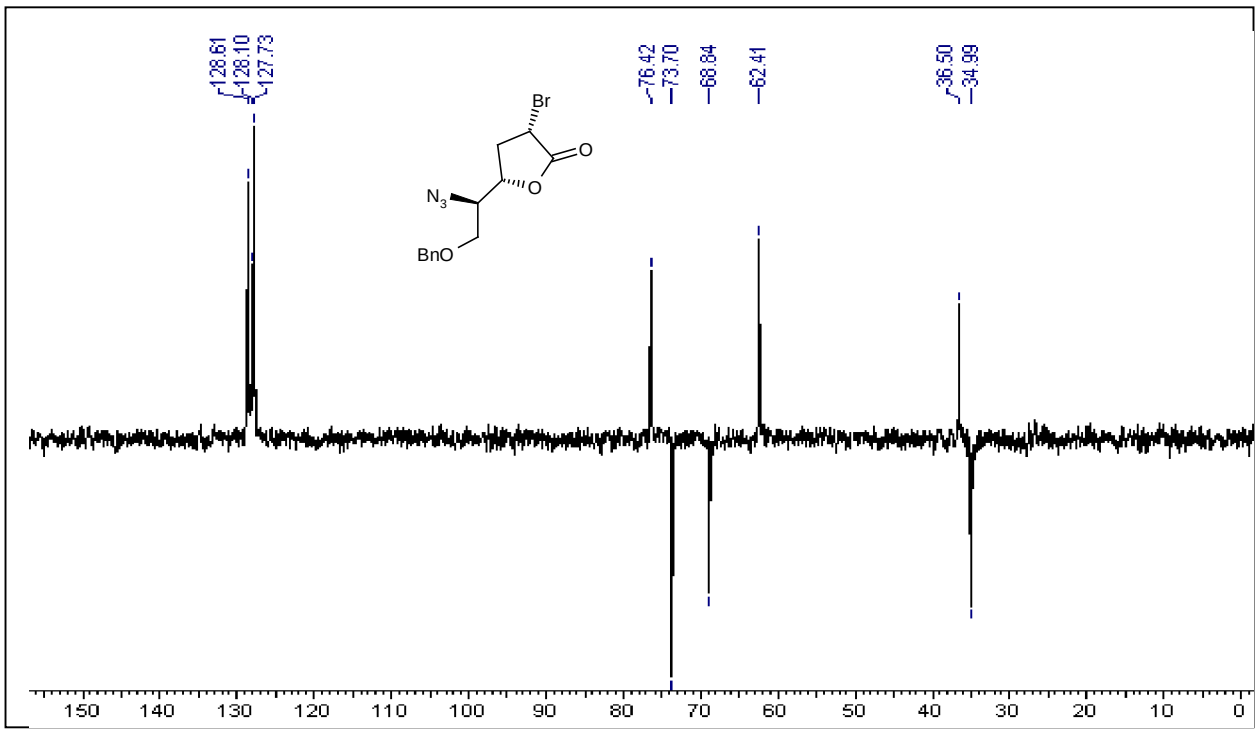
DEPT NMR Spectrum of compound 132 in $CDCl_3$ + CCl_4



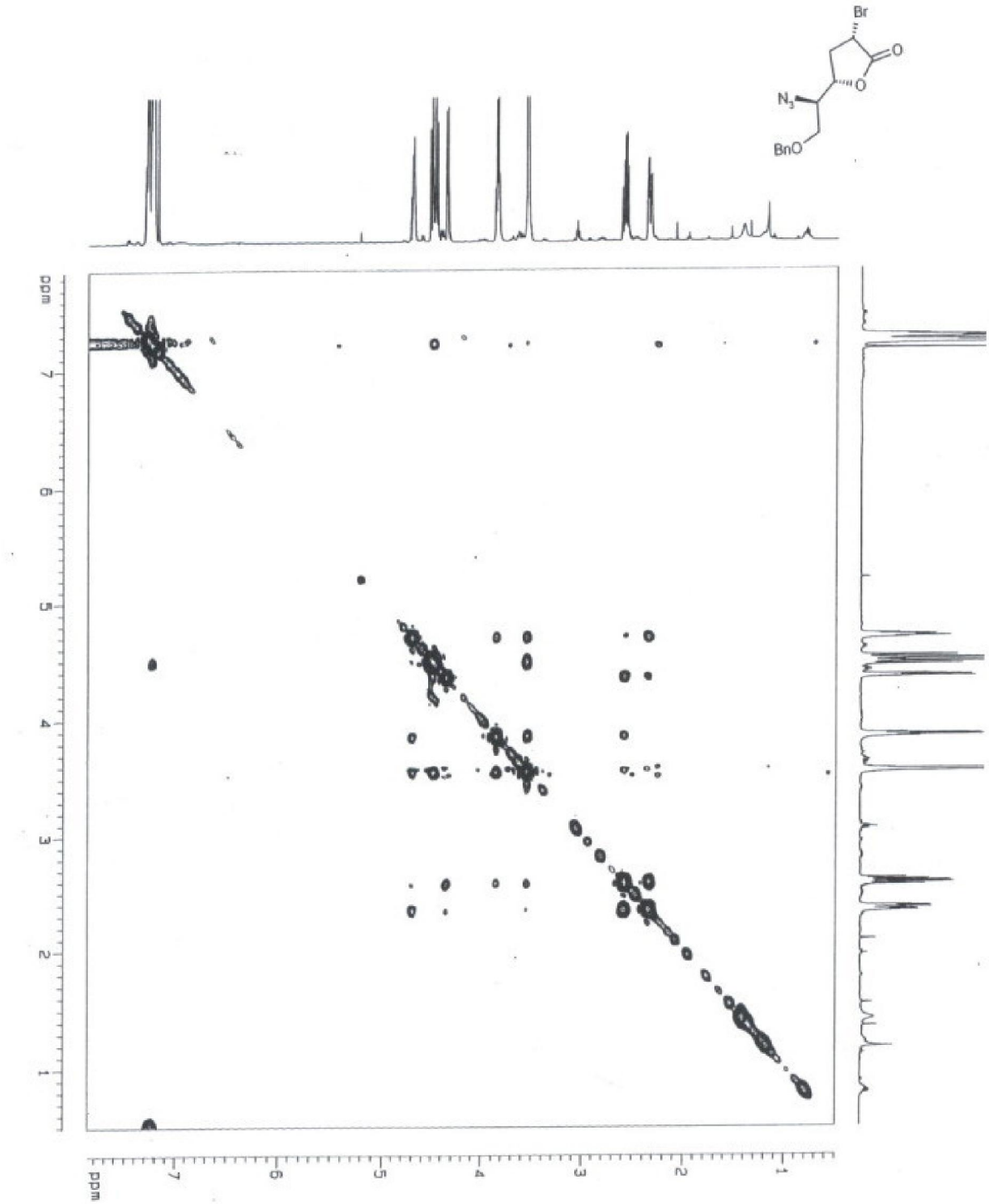
^{1}H NMR Spectrum of compound 133 in $CDCl_3$ + CCl_4



^{13}C NMR Spectrum of compound 133 in $CDCl_3$ + CCl_4



DEPT NMR Spectrum of compound 133 in $CDCl_3$ + CCl_4



C.H.PRAVEEN
BROMO AZIDE
NOESY

Current data Parameters
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EXPNO 66
PROCNO 1

F2 - Acquisition Parameters
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Time 12.27
INSTRUM spect
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PULPROG noesyld
TD 1024
SOLVENT CDCl3
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DS 16
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FIDRES 3.800684 Hz
AQ 0.1388064 sec
RG 181
DW 135.000 usec
DE 6.00 usec
TE 300.0 K
d0 0.00000300 sec
D1 2.00000000 sec
d8 1.00000000 sec
in0 0.00013880 sec

======== CHANNEL f1 ========
NUC1 1H
P1 8.80 usec
PL1 -2.00 dB
SFO1 500.1321484 MHz

F1 - Acquisition parameters
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FIDRES 14.403877 Hz
SW 7.373 ppm

F2 - Processing parameters
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SSB 0
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GB 0.014
PC 1.40

F1 - Processing parameters
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WDW QSINE
SSB 2
LB 0.00 Hz
GB 0

2D NMR plot parameters
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CY1 15.00 cm
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F2PH1 0.494 ppm
F2HI 247.12 Hz
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F1HI 3934.44 Hz
F1PH1 0.494 ppm
F2HI 247.12 Hz
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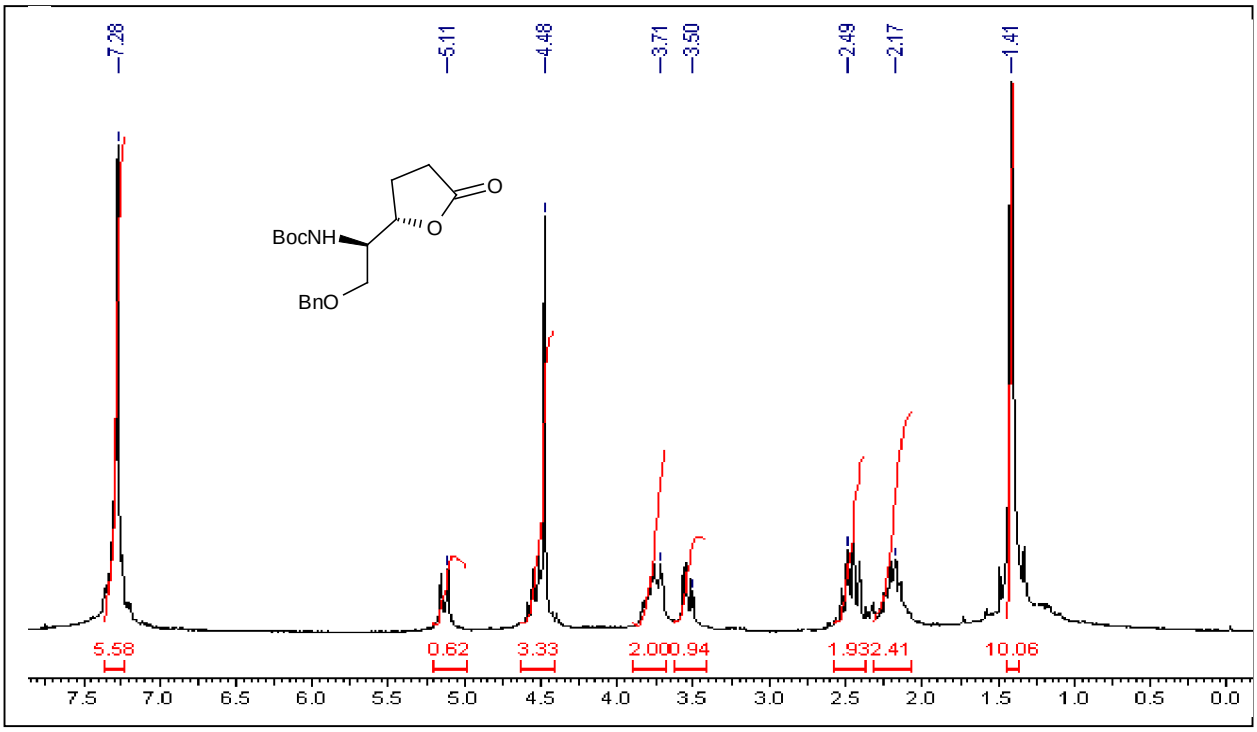
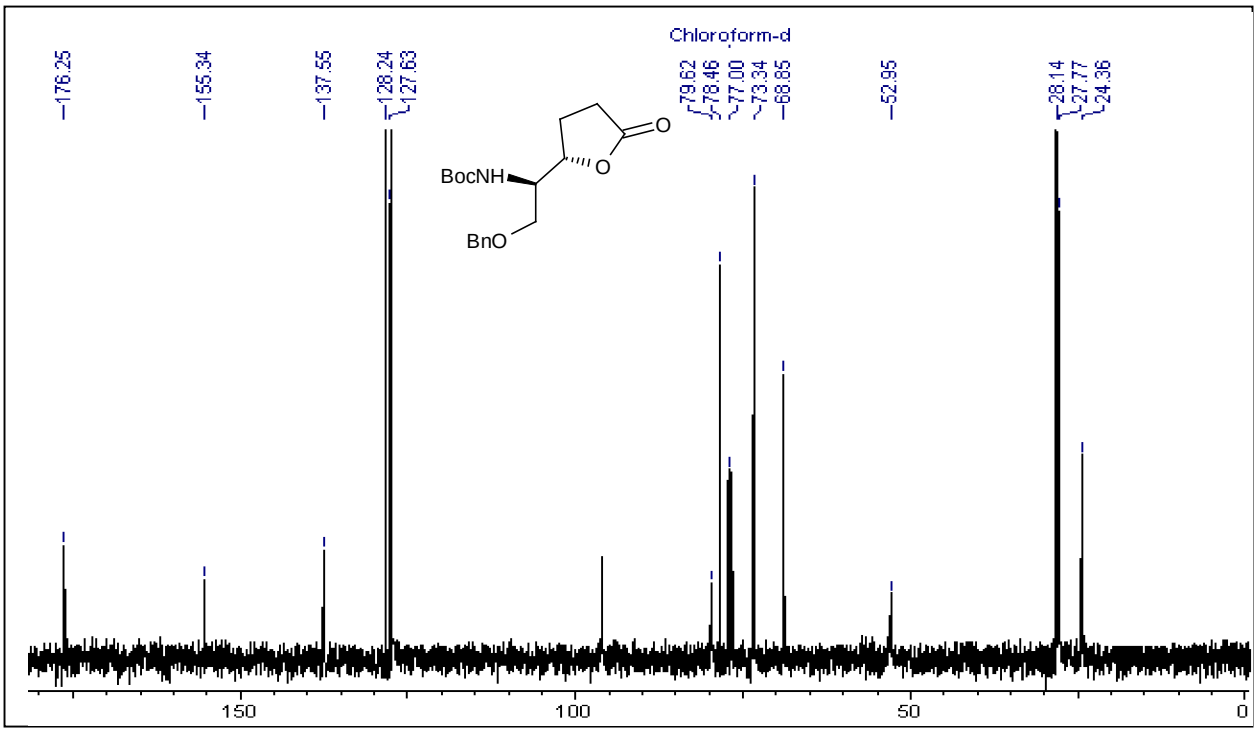
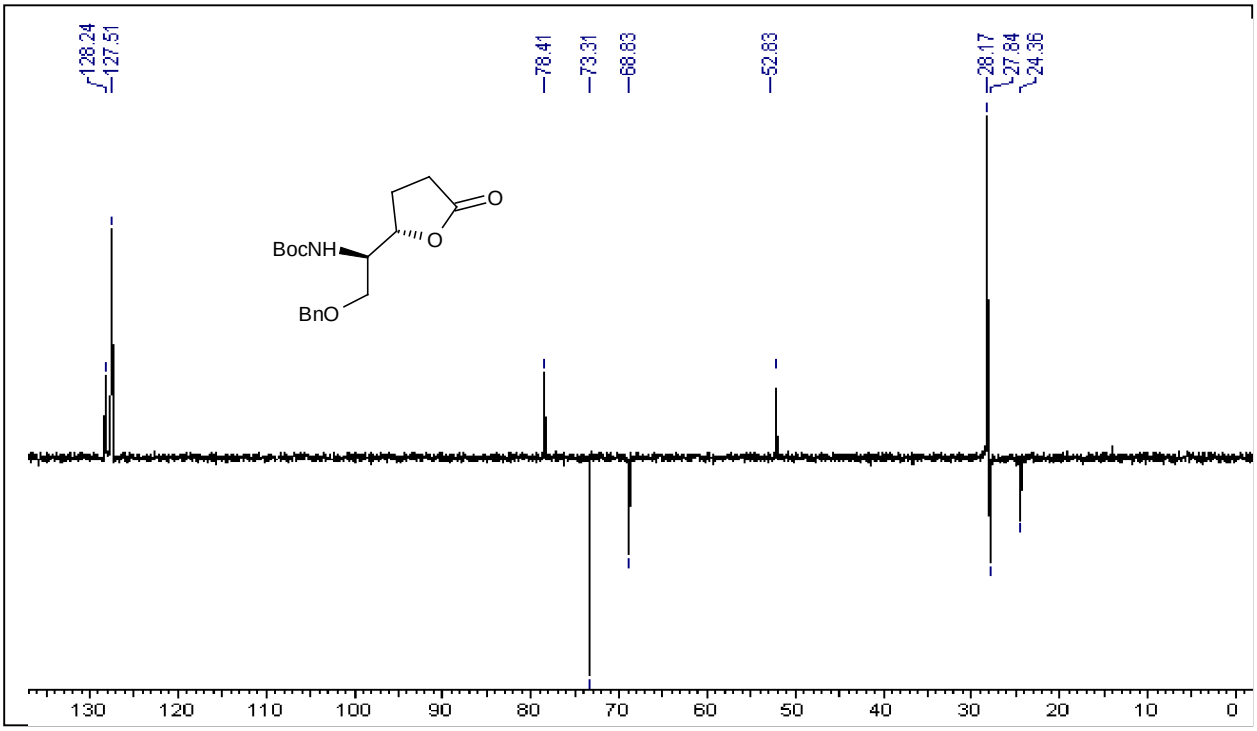
F1PPMCM 0.49151 ppm/cm
F1HZCM 245.82106 Hz/cm



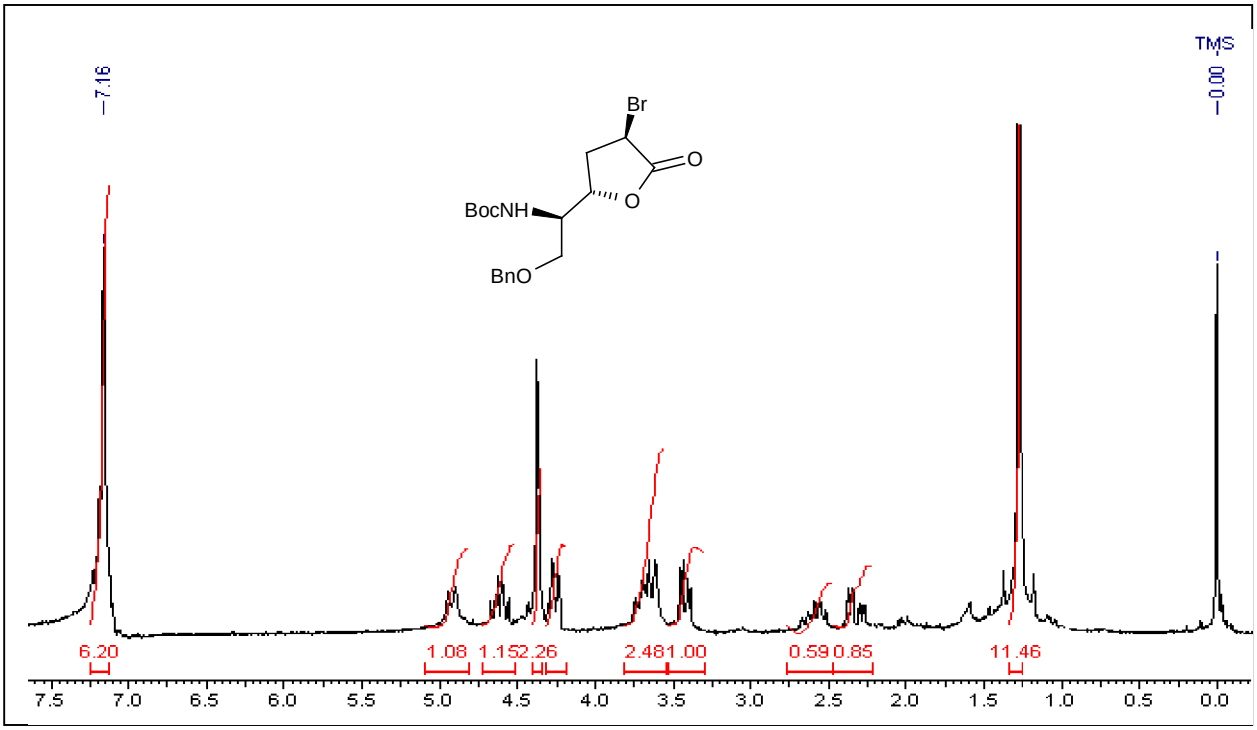
^{1}H NMR Spectrum of compound 126 in $CDCl_3$ + CCl_4



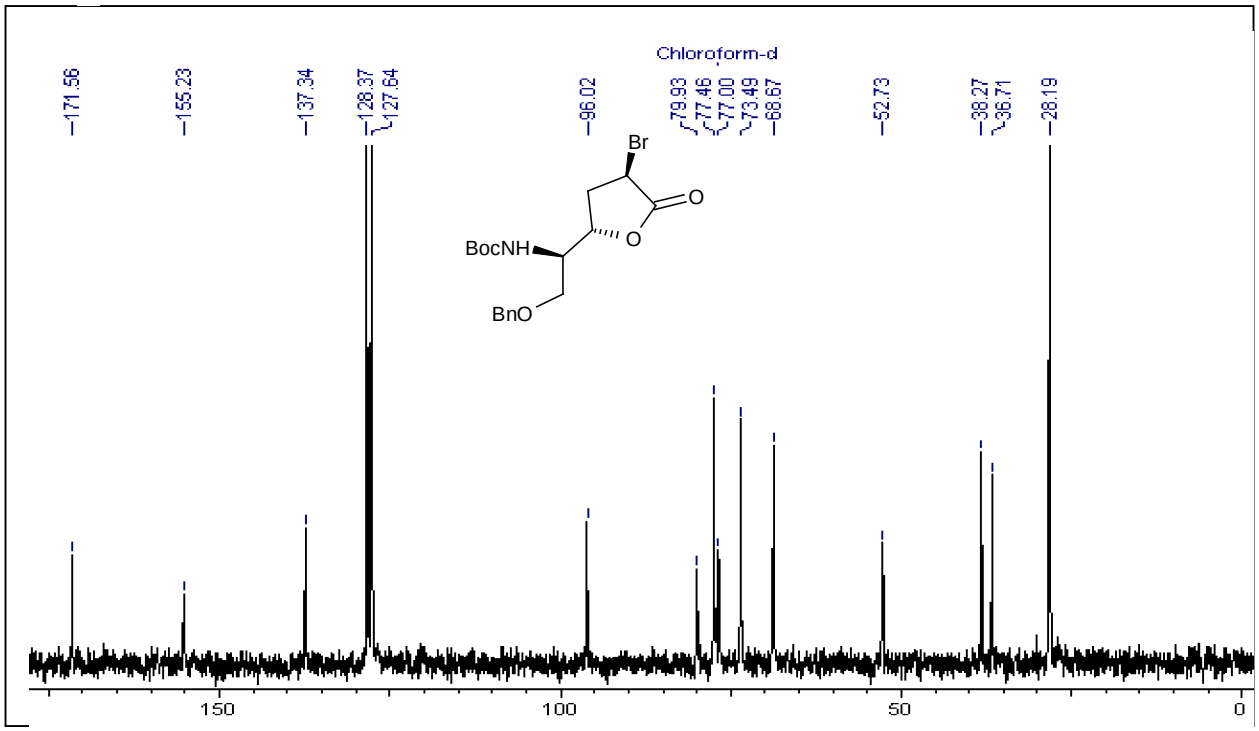
^{13}C NMR NMR Spectrum of compound 126 in $CDCl_3$ + CCl_4



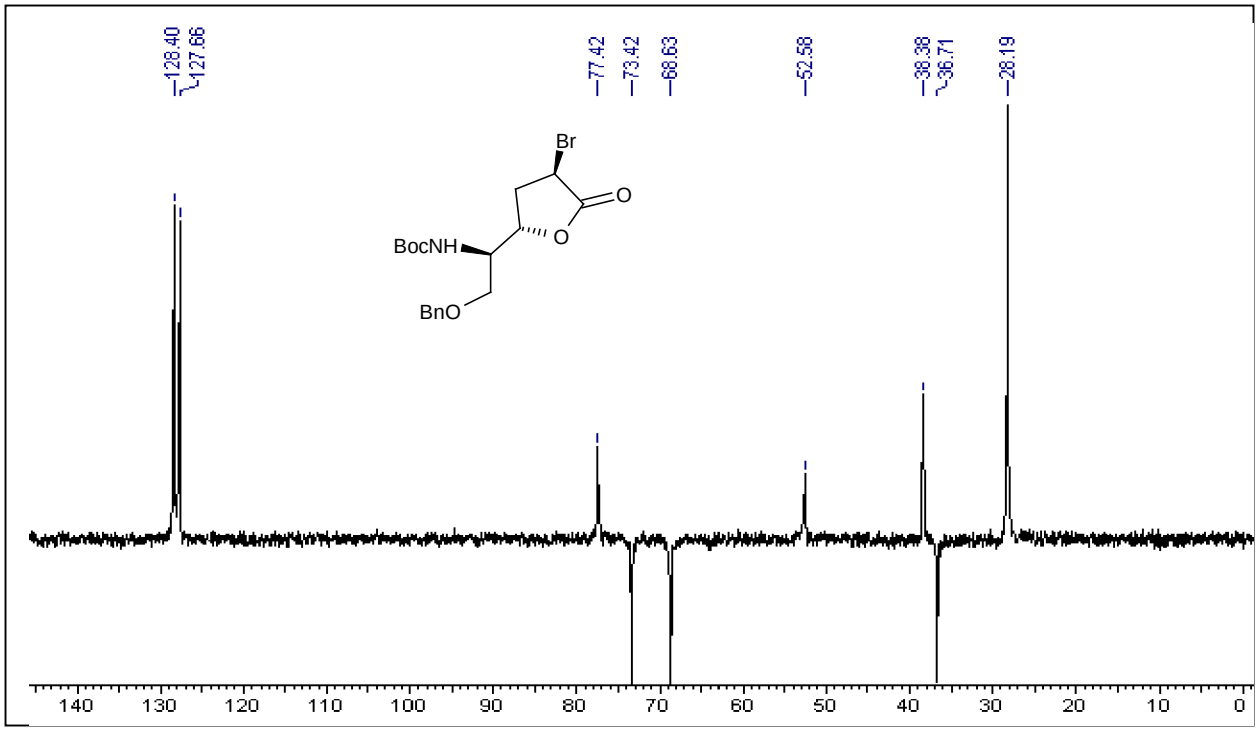
DEPT NMR Spectrum of compound 126 in $CDCl_3$ + CCl_4



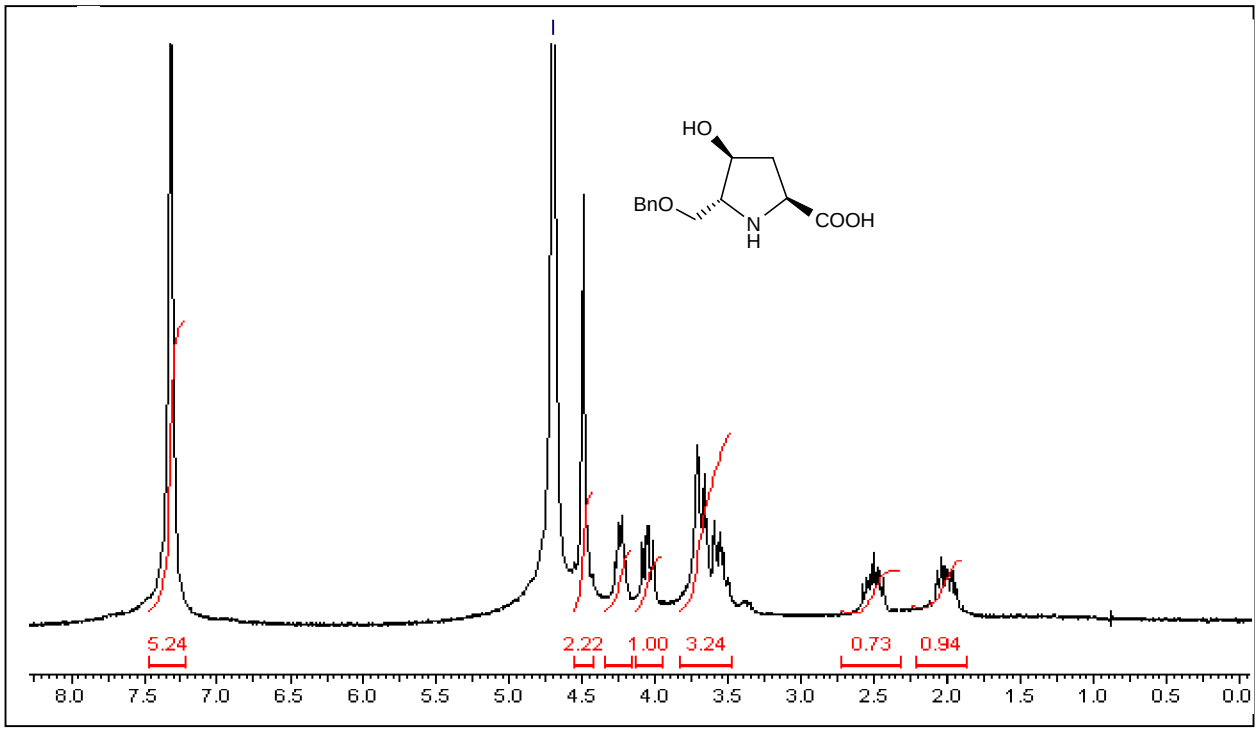
^{1}H NMR Spectrum of compound 125 in $CDCl_3$ + CCl_4



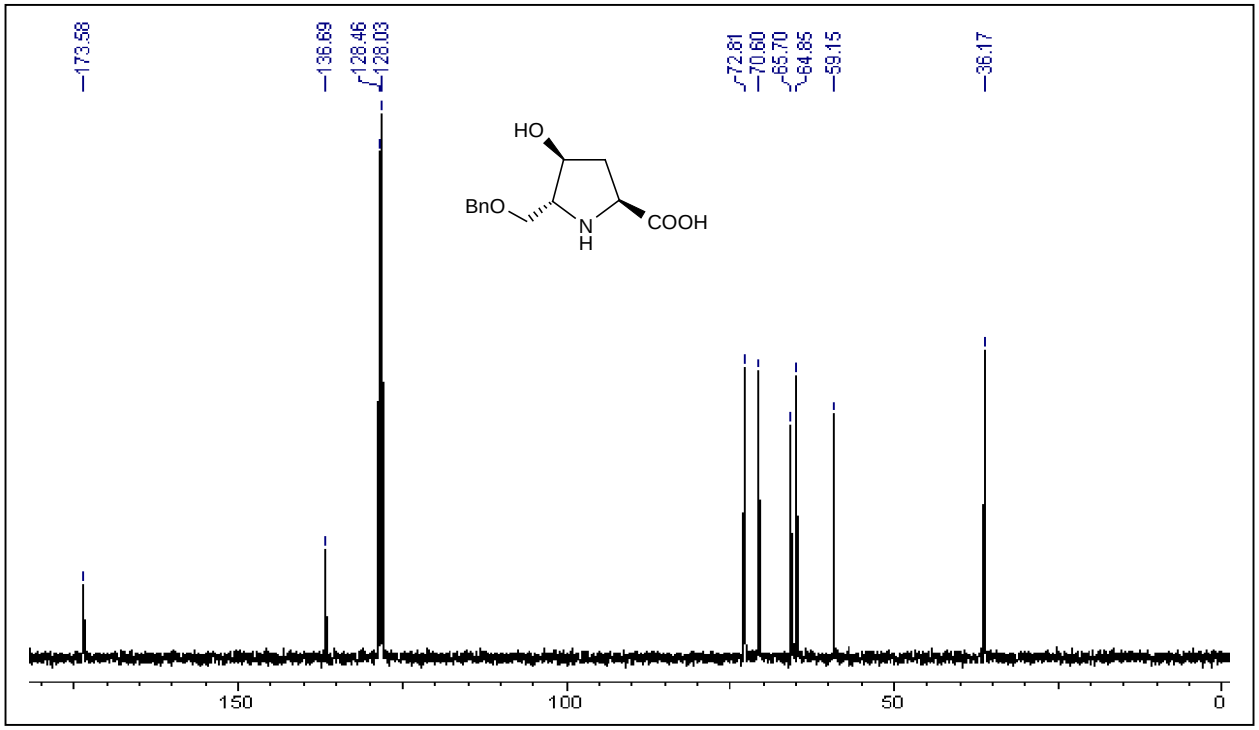
^{13}C NMR Spectrum of compound 125 in $CDCl_3$ + CCl_4



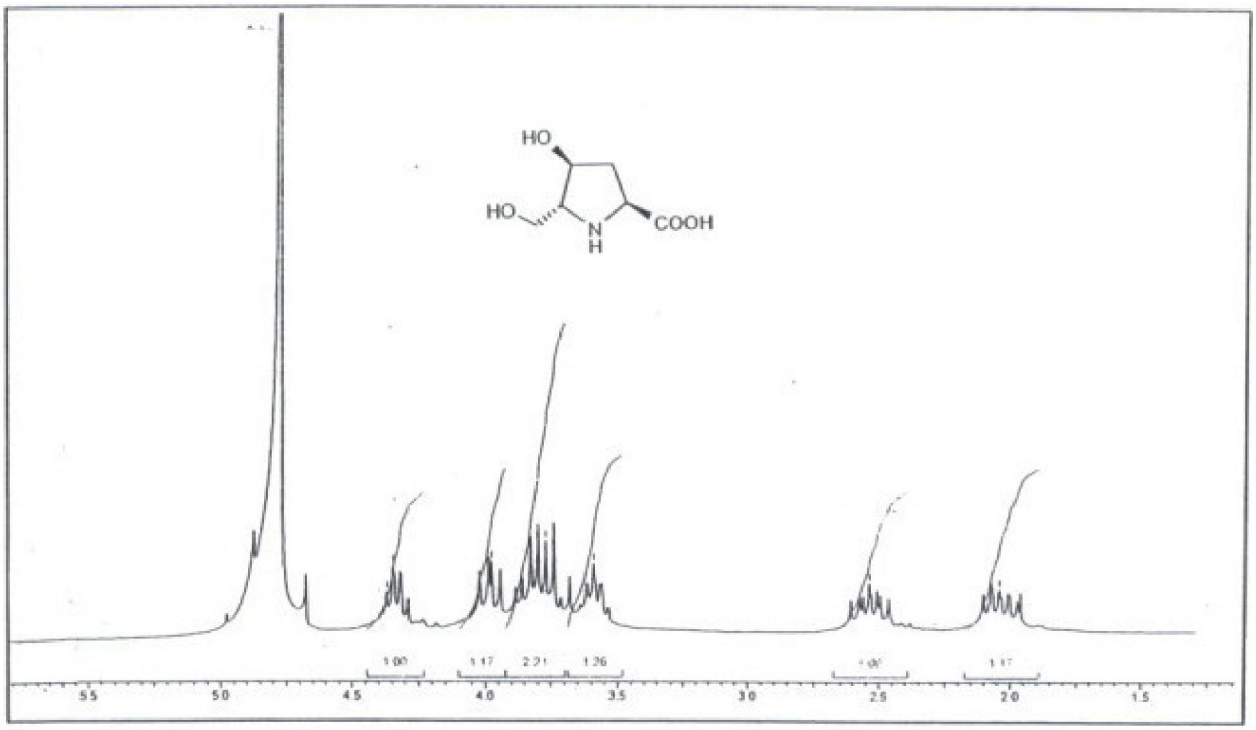
DEPT NMR Spectrum of compound 125 in $CDCl_3$ + CCl_4



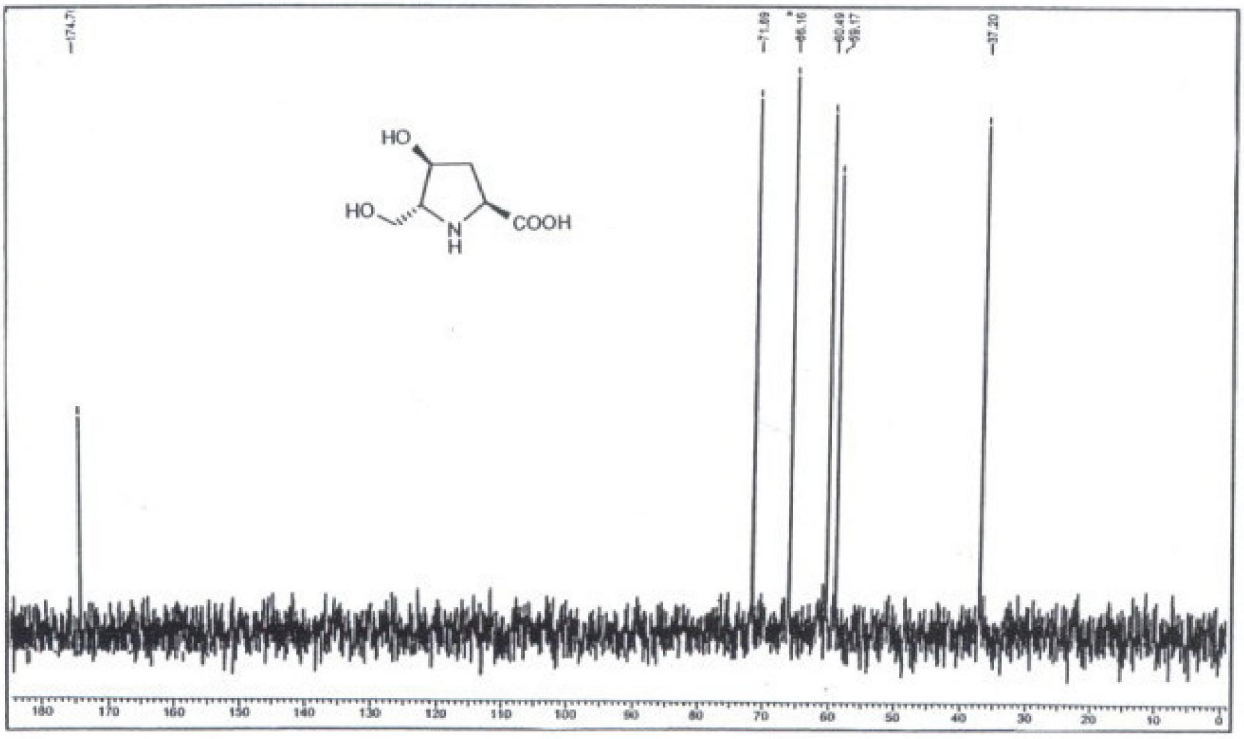
^{1}H NMR Spectrum of compound 134 in D_2O



^{13}C NMR Spectrum of compound 134 in D_2O



^{1}H NMR Spectrum of compound 6 in D_2O



^{13}C NMR Spectrum of compound 6 in D_2O

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SECTION C

STUDIES TOWARD THE SYNTHESIS OF (2*S*, 4*R*)-4 HYDROXY PIPECOLIC ACID

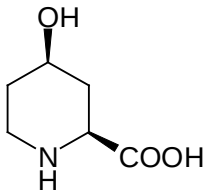
Introduction:

The piperidine ring continues to be a common moiety in pharmaceutical research. A search of the chemical and patent literature reveals thousands of references to this simple ring system in clinical and preclinical research. The synthesis of piperidine and related alkaloids are synthetically interesting targets because they can be used as building blocks for the preparation of peptides or peptidomimetic structures with biological activity.[1] In particular, incorporation of cyclic amino acids based on proline or pipecolic acid with well-defined structural properties into peptides leads to useful model compounds for studying peptide conformation and protein folding.[2] In addition, these substitutions often go along with improved pharmacological profiles in pharmacologically relevant peptides.[3] Derivatives of proline and pipecolic acid have been used as constrained analogues of proteinogenic amino acids[4] and as rigid modules to constrain peptide conformation.[5]

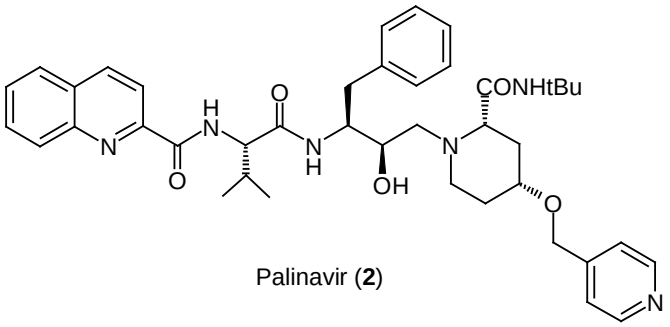
Pipecolic acid, the next higher homolog of proline, has generated considerable attention as a proline analog. The compound not only can serve as an analog of proline, but it has utility in the area of constrained amino acids, especially in combination with proline of opposite chirality in the *N*-terminal position. Substitution of the six-membered ring by any side chain moiety found in natural amino acids yields a constrained, chimeric amino acid. By holding the side chain and the backbone in a limited number of conformations, active analogs of biologically active peptides containing this unusual amino acid can provide valuable insights into the conformational requirements of ligand binding.

Pipecolic acid derivatives oxygenated at the 4-position are naturally occurring, nonproteogenic α-amino acids. The naturally occurring (2*S*, 4*R*)-4-hydroxypipecolic acid *cis*-4-hydroxy-2-piperidinecarboxylic acid, (-)-**1** has been isolated from leaves of *Calliandra*

pittieri and *Strophantus scandeus*.[6] It was also identified as a constituent of cyclopeptide antibiotics, such as virginiamycin S_2.[7] Compound **1** has served as a building block for the preparation of NMDA receptor antagonists, in which the six-membered pipecolic acid ring was used as a rigid scaffold for the construction of conformationally restricted analogs.[8] Furthermore, (-)-**1** has served as a building block in a recent synthesis of palinavir (**2**), a potent peptidomimetic-based HIV protease inhibitor.[9] Also, substituted D- and L-pipecolic acids have been used as key intermediates in the synthesis of different types of other piperidine natural products.[10] For these reasons, *cis*-4-hydroxypipecolic acid **2** is an



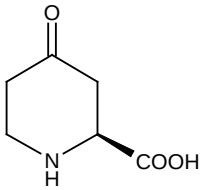
(2S, 4R)-Pipecolic acid (**1**)



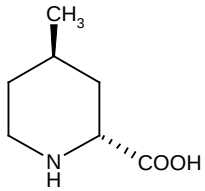
Palinavir (**2**)

interesting target molecule for synthesis.

The 4-oxo derivative **3** is a constituent of peptidolactone antibiotics isolated from *streptomyces* strains.[11] (2*R*,4*R*)-Methylpipecolic acid **4** is a key component for the preparation of a highly selective thrombin inhibitor.[12]



4-Oxopipecolic acid (**3**)



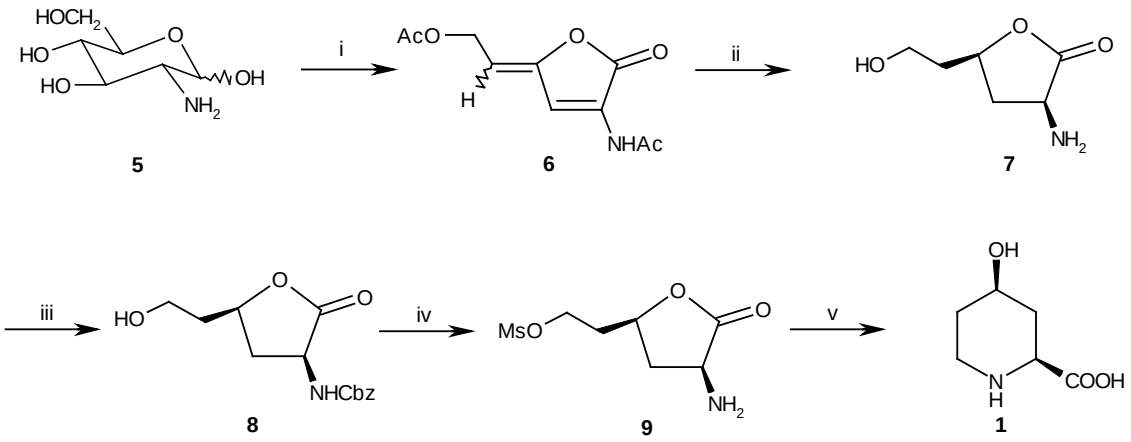
(2*R*, 4*R*)-Methylpipecolic acid (**4**)

Review of literature

A literature search of 2, 4-disubstituted piperidines revealed a paucity of interest in both clinical and preclinical development. The added synthetic difficulties and potentially heightened development costs of this substitution pattern could be the reason for the inactivity in this area of synthesis and drug discovery. Several racemic and a few enantioselective synthesis of **2** have been documented in the literature. Some of these are described below.

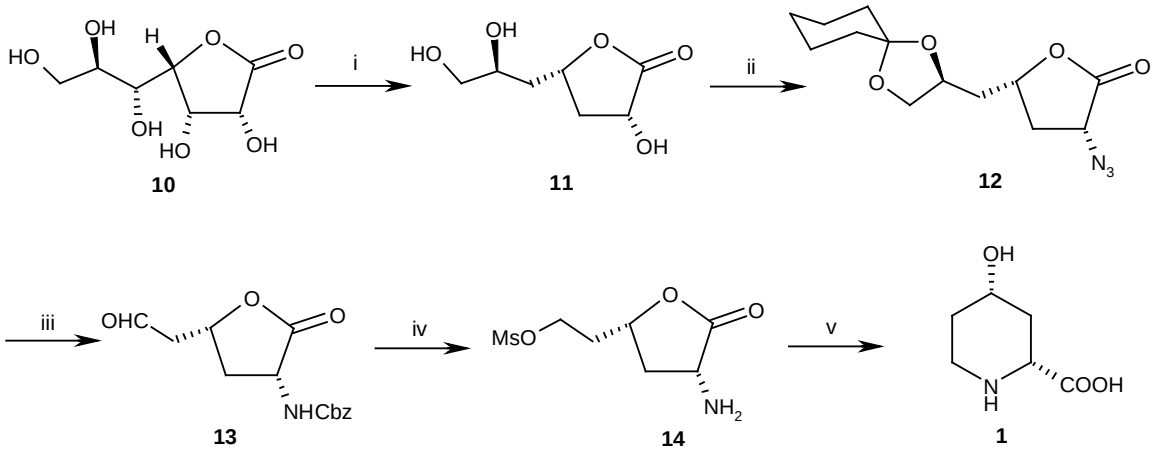
Varela *et al* (1993, 1999, Scheme 1, 2)[13, 15]

Valera and co-workers have converted D-glucosamine **5** in to the unsaturated lactone **6** in three steps. Diastereoselective hydrogenation and deacetylation of **6** delivered the amine **7**, which was protected as its Cbz derivative **8**. Mesylation, Cbz group deprotection and final basic hydrolysis delivered the (-)-Pipecolic acid.



Scheme 1: ***Reagents and conditions:*** (i) ref 14; (ii) (a) Pd/C, H_2 (15 psi); (b) aq. HCl; (iii) (a) CbzCl; (iv) (a) MsCl, Pyridine, CH_2Cl_2; (b) H_2, Pd/C (or) $(CH_3)_3SiI$; (v) aq. KOH

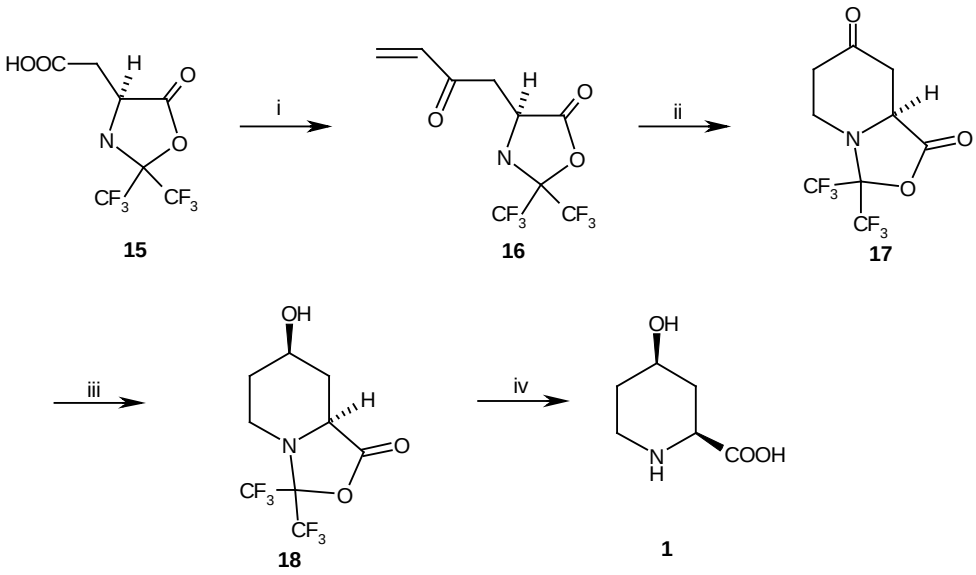
In an another approach Valera and co-workers have converted D-glucoheptono-1, 4-lactone **10** in to lactone **11** by benzoylation followed by β-elimination and diastereoselective hydrogenation. Sequential protection of diol, convertion of free hydroxy to azide group delivered the compound **12**. Compound **12** was converted in to aldehyde **13** by a series of reactions. Chemoselective reduction, mesylation and final basic hydrolysis delivered the (+)-pipecolic acid.



Scheme 2: ***Reagents and conditions:*** (i) Ref 16; (ii) (a) TsCl, Pyridine; (b) NaN_3, DMF; (iii) (a) H_2, Pd; (b) CbzCl; (c) H_3O^+; (d) $NaIO_4$; (iv) (a) $NaBH_3CN$; (b) MsCl; (c) H_2, Pd; (d) aq. KOH.

Burger *et al* (1995, Scheme 3)[17]

Burger and co-workers have utilized L-ascorbic acid as homochiral precursor, which on reaction with hexafluoroacetone delivered the protected compound **15**. Compound **15** on reaction with thionyl chloride gave the acid chloride, which was coupled with vinyl trimethyl tin in presence of palladium catalyst to deliver the enone **16**. Michael addition (6-endo trig) of the enone **16** gave the protected 4-oxo-L-pipecolic acid **17**. Reduction of compound **17** with

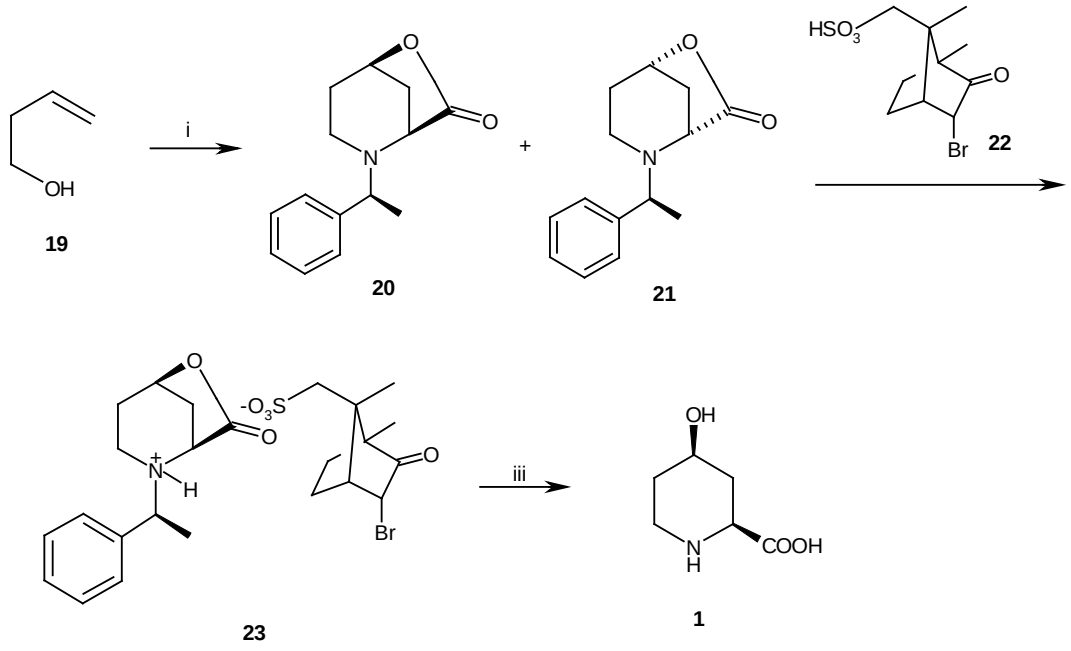


$NaBH_4$ followed by deprotection delivered the *cis* 4-hydroxy-L-pipecolic acid.

Scheme 3: ***Reagents and conditions:*** (i) (a) $SOCl_2$, reflux, 84 %; (b) CH_2=$CHSnMe_3$, $PhCH_2Pd(PPh_3)_2Cl$, dimethoxy ethane, 67 %; (ii) $BF_3.OEt_2$, benzene, reflux, 60 %; (iii) C_6H_5OH, $NaBH_4$, 80 %; (iv) $H_2O/^iPrOH$, 100 %

Beaulieu *et al* (1996, Scheme 4)[18]

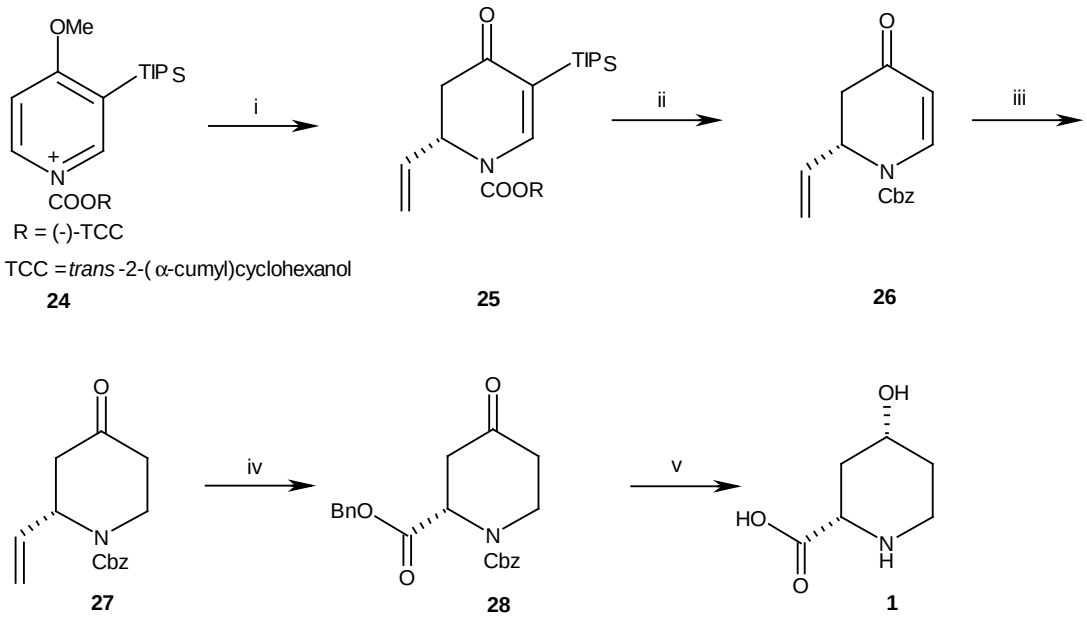
Beaulieu and co-workers have converted homo allylic alcohol in to diastereomeric lactones, from which the (2*S*, 4*R*) isomer was crystalized by using sulphonic acid **22**. Neutralization of the salt **23** with NH_4OH, followed by sequential hydrogenation and hydrolysis delivered the (2*S*, 4*R*)-pipecolic acid.



Scheme 4: ***Reagents and conditions:*** (i) (a) TsCl, Et_3N; (b) (*S*)-$PhCH_2(CH_3)NH_2$; (c) Glyoxalic acid, H_2O, CH_3CN, reflux; (ii) NH_4OH, 99 %; (iii) (a) H_2, $Pd(OH)_2$; (b) 6 N HCl, reflux; (c) Ion exchange resin (88 % for 3 steps)

Comins *et al* (2000, Scheme 5)[19]

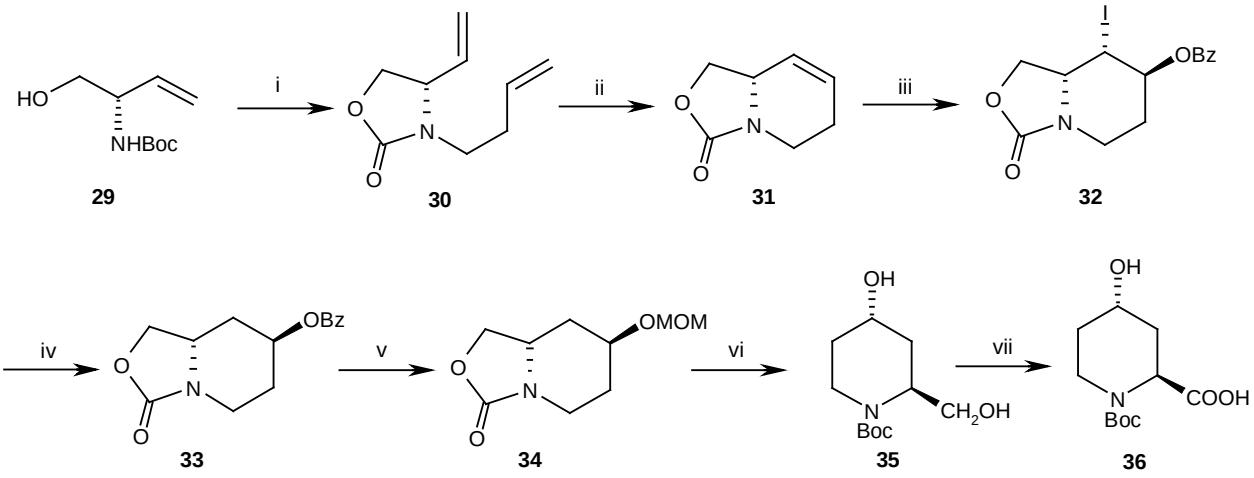
In Comin's approach chiral 1-acyl pyridinium salt **24** was converted in to dihydro pyridone **25** by the addition of vinyl magnesium bromide. Compound **25** on reaction with sodium methoxide followed by aqueous acid provided amine, which was protected as its Cbz derivative **26**. Conjugate addition of dihydropyridone **26** provided compound **27**, which on oxidative cleavage with ozone and subsequent esterification gave the ester **28**. Stereo selective reduction of C-4 keto group and removal of the protecting groups delivered the (-)-pipecolic acid.



Scheme 5: ***Reagents and conditions:*** (i) (a) Vinyl magnesium bromide; (b) H_3O^+, 78 %; (ii) (a) NaOMe, MeOH; (b) 10 % HCl, 89 %; (c) *n*-BuLi, BnOCOCl, 98 %; (iii) Zn, AcOH, 94 %; (iv) (a) O_3, Jones oxidation; (b) Sat. $NaHCO_3$, Bu_4NI, BnBr, CH_2Cl_2, 59 %; (v) H_2, Pd/C, EtOH, 98 %; (b) K-Selectride, 93 %.

Johnson *et al* (2001, Scheme 6)[20]

In Johnson's approach serine derivative **29** was converted in to oxazolidinone **30**, which on ring closing metathesis delivered the compound **31**. Compound **31** on subjection to Prevost reaction conditions delivered the iodo benzoate **32**, which on dehalogenation delivered the compound **33**. Protecting group exchange, hydrolysis of oxazolidinone ring followed by Boc protection gave the piperidine alcohol **34**. Oxidation of **34** using a two step Dess-Martin, $NaClO_2$ process delivered the protected trans-pipecolic acid **35**.

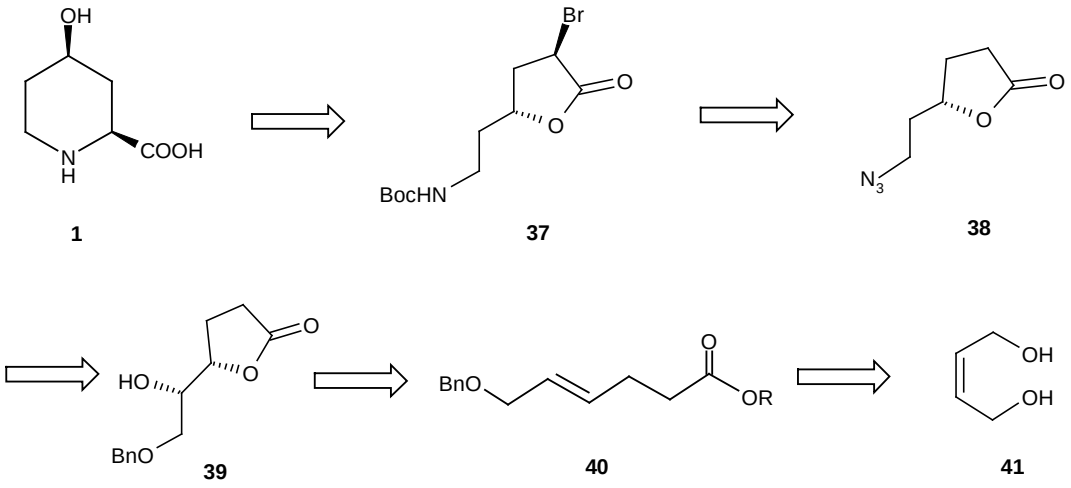


Scheme 6: ***Reagents and conditions:*** (i) (a) NaH, THF; (b) NaH, 4-bromo-1-butene, LiI, DMF; (ii) Grubb's catalyst, CH_2Cl_2; (iii) I_2, Silver benzoate, Benzene; (iv) Raney Ni, THF/MeOH; (v) (a) KCN, MeOH-H_2O (9:1); (b) MOM-Cl, Hunig's base, CH_2Cl_2; (vi) (a) 3 N NaOH, MeOH-H_2O (9:1), reflux, 24 h; (b) $(Boc)_2O$, EtOAc; (vii) Dess-Martin, THF; (b) $NaClO_2$, NaH_2PO_4.

Present work:

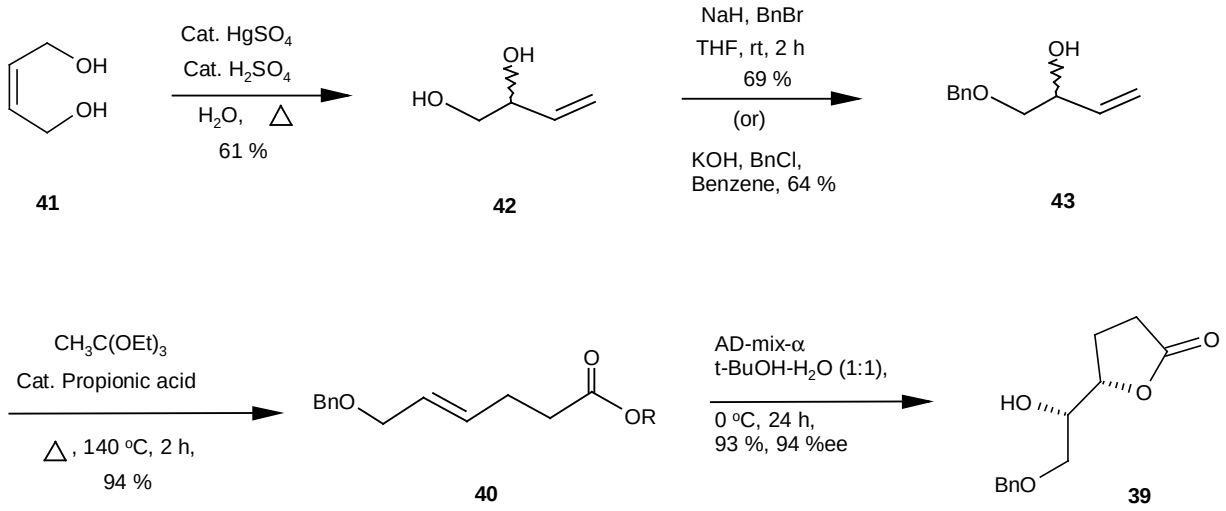
Although several syntheses of both (-)-pipecolic acids and (+)-pipecolic acids are documented in the literature through varied synthetic routes, most involve a large number of steps or employing a chiral pool starting material. Herein we planned to synthesize the target compound **1**, employing the Sharpless asymmetric dihydroxylation as the key step and thereby inducing the desired chirality, starting from cheap achiral source.

The retrosynthetic analysis for the stereoselective synthesis of (-)-pipecolic acid is depicted in **scheme 7**. It was envisaged that a simple basic hydrolysis could be used to form target molecule from the bromo lactone **37**. The bromolactone **37** could be obtained from the azidolactone **38**, which *inturn* could be obtained from the hydroxy lactone **39**, the versatile intermediate for our synthesis. The hydroxy lactone could be obtained from *cis*-2-butene-1, 4-diol **41**.



Scheme 7: **Retrosynthetic analysis**

The synthesis of (-)-pipecolic acid commences from *cis*-2-butene-1, 4-diol **41** as shown in scheme **8.** The commercially available *cis*-2-butene-1, 4-diol was converted into monoprotected allyl alcohol **43**, which on Claisen orthoester rearrangement and Sharpless asymmetric dihydroxylation delivered the hydroxy lactone **39** with the required stereochemistry.



Treatment of the hydroxy lactone **39** with PPh_3, Iodine and imidazole in anhydrous toluene at 70 ^oC for 3 h smoothly delivered the iodolactone **44**. In the IR spectrum hydroxyl absorption was disappeared. In the ^{1}H-NMR spectrum the proton signal corresponds to CH-I was deshielded from δ 3.84 in to 4.31. In the ^{13}C-NMR spectrum an up field shift of CH-I carbon from δ 71.9 to 34.0 was observed.

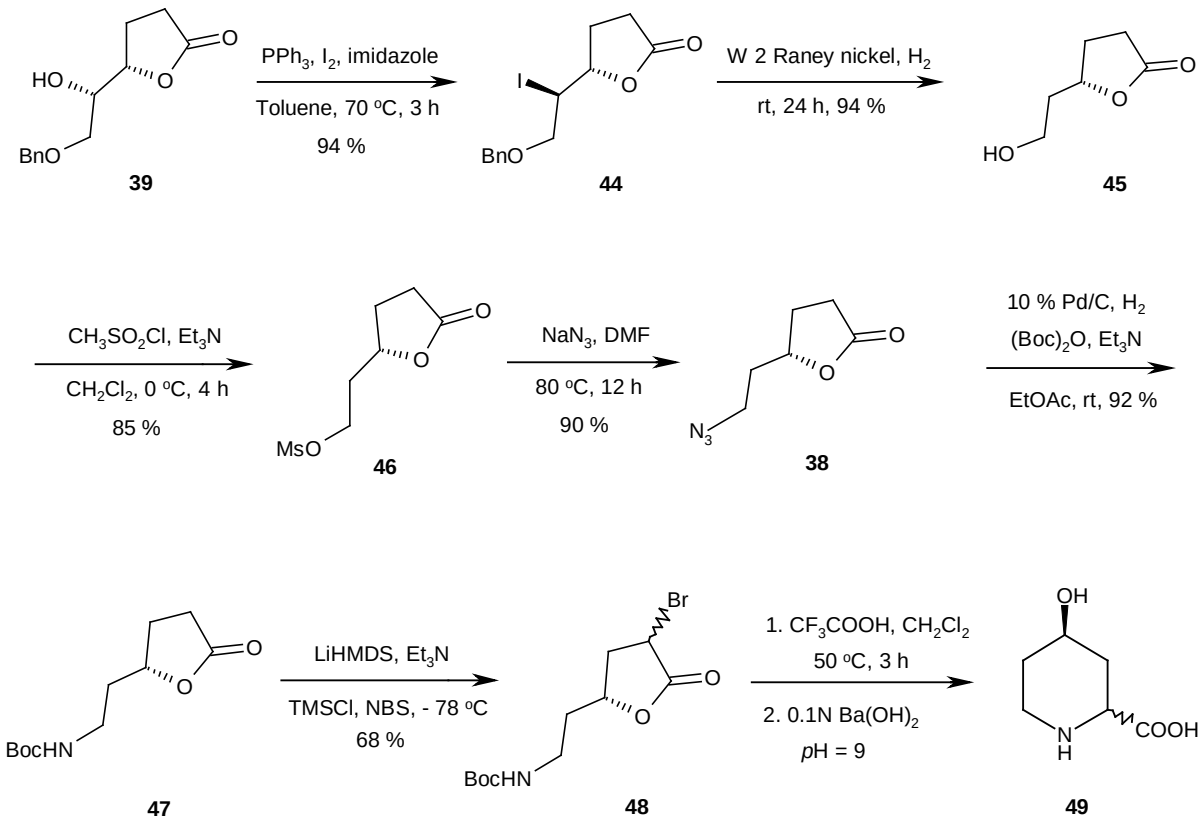
The iodolactone on reaction with W2 Raney nickel under an atmosphere of H_2 at room temperature and normal pressure for 24 h delivered the lactone **45**, formed by reductive deiodination and debenzylation in the same pot. The IR spectrum of **45** revealed the presence of hydroxyl absorption at 3446 cm^{-1} and carbonyl absorption at 1779 cm^{-1}. The ^{1}H-NMR

spectrum showed the disappearance of benzylic protons. ^{13}C-NMR and elemental analysis data were in good agreement with the assigned structure **45**.

Lactone **45** on reaction with mesylchloride and Et_3N in anhydrous CH_2Cl_2 at 0 ^oC provided the mesylate **45** in 85 % yield. In the IR spectrum disappearance of hydroxyl absorption was observed. The ^{1}H-NMR spectrum showed the singlet at δ 3.09 integrating for three protons. ^{13}C-NMR and elemental analysis data were in good agreement with the structure **46**.

Nucleophilic displacement of the mesylate **46** with NaN_3 in anhydrous DMF at 80 ^oC for 12 h gave the azide **38** in 90 % yield. The IR spectrum showed strong absorption at 2116 cm^{-1}. The ^{1}H-NMR spectrum showed disappearance of singlet at δ 3.09 and ^{13}C-NMR and elemental analysis data were in good agreement with the structure **38**.

The azido lactone on reaction with 10 % Pd/C under an atmosphere of H_2 in presence of $(Boc)_2O$ and Et_3N in EtOAc delivered the Boclactone **47**. The IR specrtrum showed the disappearance of strong absorption at 2116 cm^{-1}. In the ^{1}H-NMR spectrum the peaks corresponding to Boc group was observed. ^{13}C-NMR and elemental analysis data were in good agreement with the structure **47**.



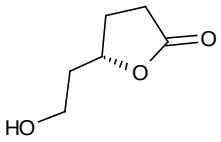
Having the Boclactone **47** in hand, our next concern was to introduce the bromine stereoselectively at C-2 of the lactone **47**. Accordingly reaction of lactone **47** with LiHMDS, Et_3N, and NBS at –78 °C for 2 h delivered the unseparable mixture of diastereomeric bromolactones. Subjection of this mixture to Oppolzer's conditions delivered the mixture of diastereomeric 4-hydroxypipecolic acids.

Conclusion:

In conclusion our present synthesis is giving a mixture of diastereomeric pipecolic acids. However by slight modifications it may be possible to get the pure (2*S*, 4*R*)-4-Hydroxy Pipecolic Acid.

Experimental:

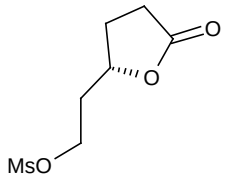
(4*R*)-6-Hydroxy-hexane-4-olide (45)



To a solution of **44** (1.8 g, 5.20 mmol) in absolute ethanol (20 mL) was added W2 Raney nickel (3.5 g) and the mixture was flushed with H_2 for 5 min. After stirring under an atmosphere of hydrogen at room temperature for 24 h, the reaction mixture was filtered through a pad of celite and the solvent was concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc-light petroleum (3:2) as an eluent to afford **45** (0.63 g, 94 %) as colourless syrup.

Appearance	**:**	**Colourless viscous oil**
Molecular Formula	**:**	**$C_6H_{10}O_3$**
Yield	**:**	**94 %.**
IR ($CHCl_3$, cm^{-1})	**:**	**3446, 1779, 751.**
^1H NMR ($CDCl_3$ + CCl_4, 200MHz)	**:**	**δ 1.61-1.81 (m, 3H), 2.13-2.26 (m, 1H), 2.29-2.38 (m, 2H), 3.50 (t, J = 6.27 Hz, 2H), 3.99 (broad, 1H), 4.48 (m, 1H).**
^{13}C NMR ($CDCl_3$+CCl_4, 50MHz)	**:**	**δ 27.4, 28.1, 37.6, 57.7, 78.0, 177.3.**
Elemental Analysis	**:**	Anal. Calcd for $C_6H_{10}O_3$; C, 55.38; H, 7.69 %. Found: C, 55.32; H, 7.78 %.

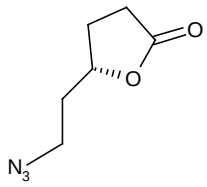
(4*R*)-6-Mesyloxy-hexane-4-olide (46)



To a solution of **45** (0.5 g, 3.84 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0 ^oC were added Et_3N (1.07 mL, 7.68 mmol), MsCl (0.33 mL, 4.23 mmol) and DMAP (cat). The reaction mixture was stirred for 6 h and then poured into aqueous sodium hydrogen carbonate and extracted with CH_2Cl_2 (2 X 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude oily compound was purified by silica gel column chromatography using EtOAc-light petroleum (4:6) as an eluent to afford **46** (0.76 g, 85 %) as light yellow oil.

Appearance	**:**	**Light yellow oil**
Molecular Formula	**:**	**$C_7H_{12}O_5S$**
Yield	**:**	**85 %.**
IR ($CHCl_3$, cm^{-1})	**:**	**3018, 2328, 1782, 761.**
^1H NMR ($CDCl_3$ + CCl_4, 200MHz)	**:**	**δ 1.72-1.82 (m, 3H), 2.21-2.29 (m, 1H), 2.32-2.44 (m, 2H), 3.56 (t, J = 6.17 Hz, 2H), 3.09 (s, 3H), 4.72 (m, 1H).**
^{13}C NMR ($CDCl_3$+CCl_4, 50MHz)	**:**	**δ 27.5, 28.2, 37.2, 38.7, 58.2, 78.1, 177.4.**
Elemental Analysis	**:**	Anal. Calcd for $C_7H_{12}O_5S$; C, 40.38; H, 5.77; S, 15.38 %. Found: C, 40.42; H, 5.86; N, 15.44 %.

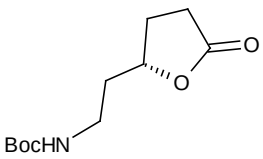
(4*R*)-6-Azido-hexane-4-olide (38)



To a solution of **46** (0.7 g, 3.36 mmol) in anhydrous DMF (10 mL) was added sodium azide (0.44 g, 6.72 mmol) and the reaction mixture was stirred at 85 ^{o}C for 18 h. After completion of the reaction the reaction mixture was cooled to room temperature, diluted with water and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc-light petroleum (4:6) as an eluent to afford **38** (0.47 g, 90 %) as colourless oil.

Appearance	**:**	**Colourless oil**
Molecular Formula	**:**	**$C_6H_9O_2N_3$**
Yield	**:**	**90 %.**
IR ($CHCl_3$, cm^{-1})	**:**	**2116, 1779.**
^{1}H NMR ($CDCl_3$ + CCl_4, 200MHz)	**:**	**δ = 1.72-1.92 (m, 3H), 2.28-2.38 (m, 1H), 2.48-2.58 (m, 2H), 3.48 (t, *J* = 6.05 Hz, 2H), 4.57 (m, 1H),**
^{13}C NMR ($CDCl_3$+CCl_4, 50MHz)	**:**	**δ 27.5, 28.2, 34.6, 47.4, 77.2, 176.0.**
Elemental Analysis	**:**	Anal. Calcd for $C_6H_9O_2N_3$; C, 46.45; H, 5.80; N, 27.09 %. Found: C, 46.62; H, 5.82; N, 27.34.

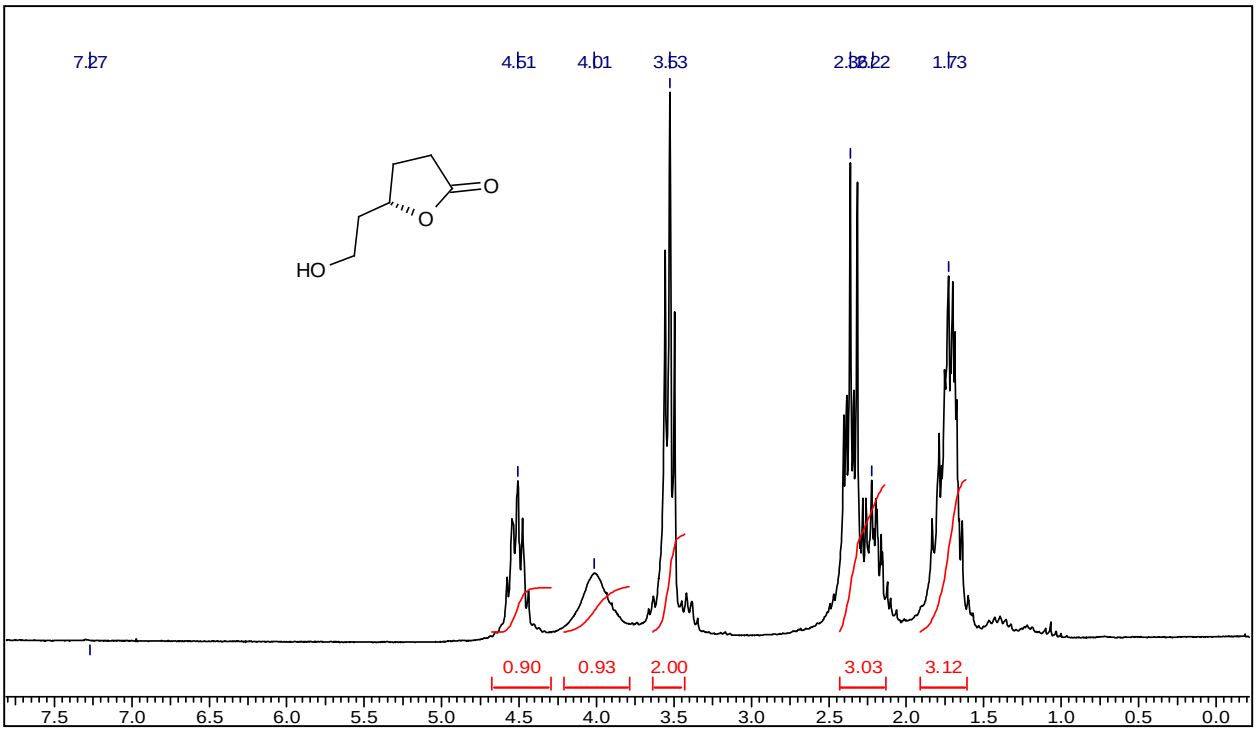
(4*R*)-6-tert-Butyloxycarbonylamino-hexane-4-olide (47)



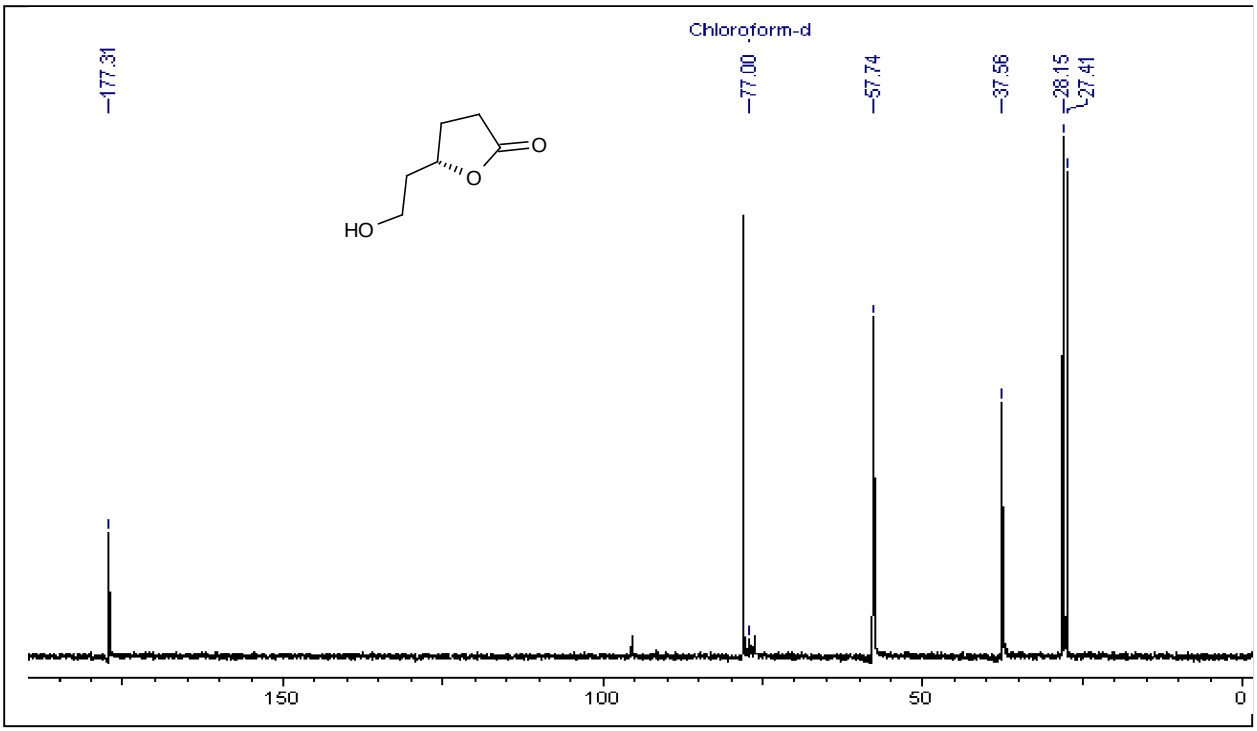
To a solution of **38** (0.6 g, 3.87 mmol) in EtOAc were added Et_3N (0.59 mL, 4.25 mmol), $(Boc)_2O$ (1.02 mL, 4.25 mmol) and 10 %Pd/C (0.02 g). After stirring under an atmosphere of

H_2 for 3 h at normal temperature and pressure, the reaction mixture was concentrated under reduced pressure and the residue was purified by silica giel column chromatography using light petroleum ether:EtOAc (3:2) as an eluent to afford pure **47** (0.81 g, 92 %) as colourless syrup.

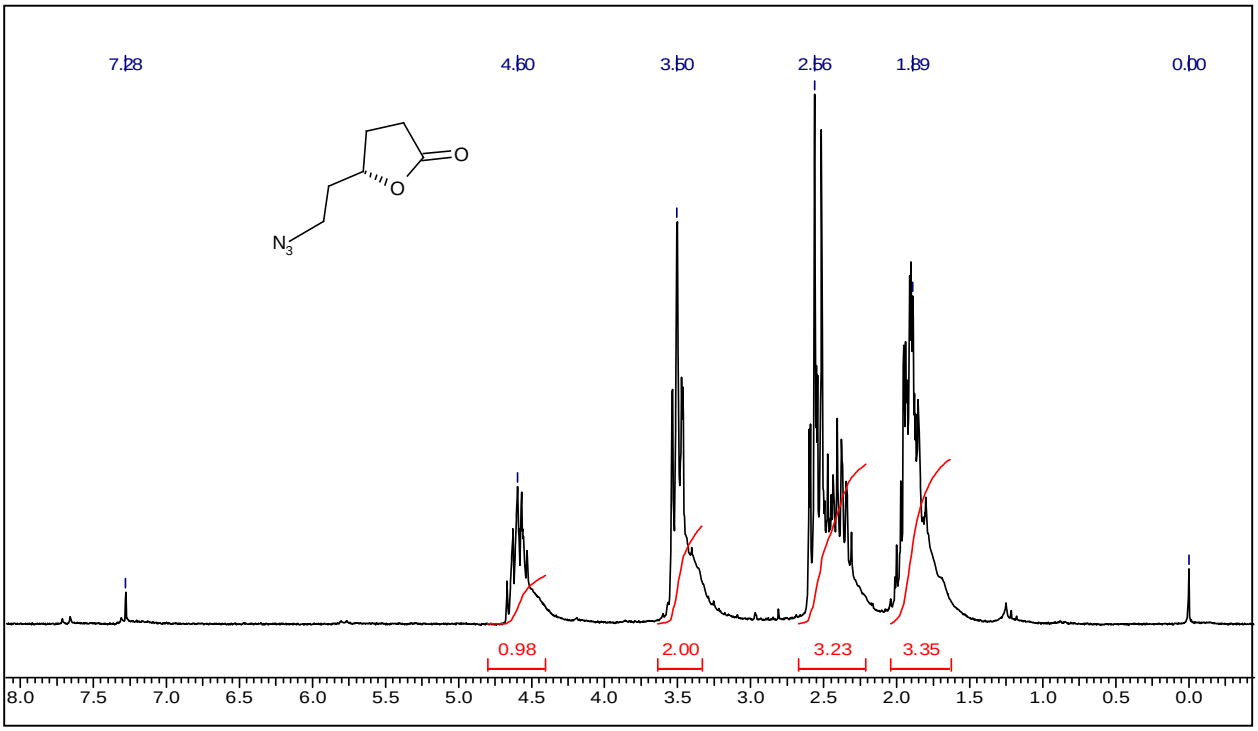
Appearance	**:**	**Colourless viscous oil**
Molecular Formula	**:**	**$C_{11}H_{19}O_4N$**
Yield	**:**	**92 %.**
IR ($CHCl_3$, cm^{-1})	**:**	**3042, 1776, 1602, 759.**
$[\alpha]_D$	**:**	**+ 42. 47 (*c* = 1, $CHCl_3$)**
^1H NMR ($CDCl_3$ + CCl_4, 200MHz)	**:**	**1.41 (s, 9H), 1.75-1.93 (m, 3H), 2.32-2.38 (m, 1H), 2.48-2.53 (m, 2H), 3.25 (m, 2H), 4.52 (m, 1H), 4.80 (broad, 1H).**
^{13}C NMR ($CDCl_3$+CCl_4, 50MHz)	**:**	**δ = 27.8, 28.2, 28.3, 35.7, 37.1, 78.6, 78.8, 155.7, 176.3.**
Elemental Analysis	**:**	Anal. Calcd for $C_{11}H_{19}O_4N$; C, 57.64; H, 8.29; N, 6.11 %. Found: C, 57.58; H, 6.23; N, 6.29 %.



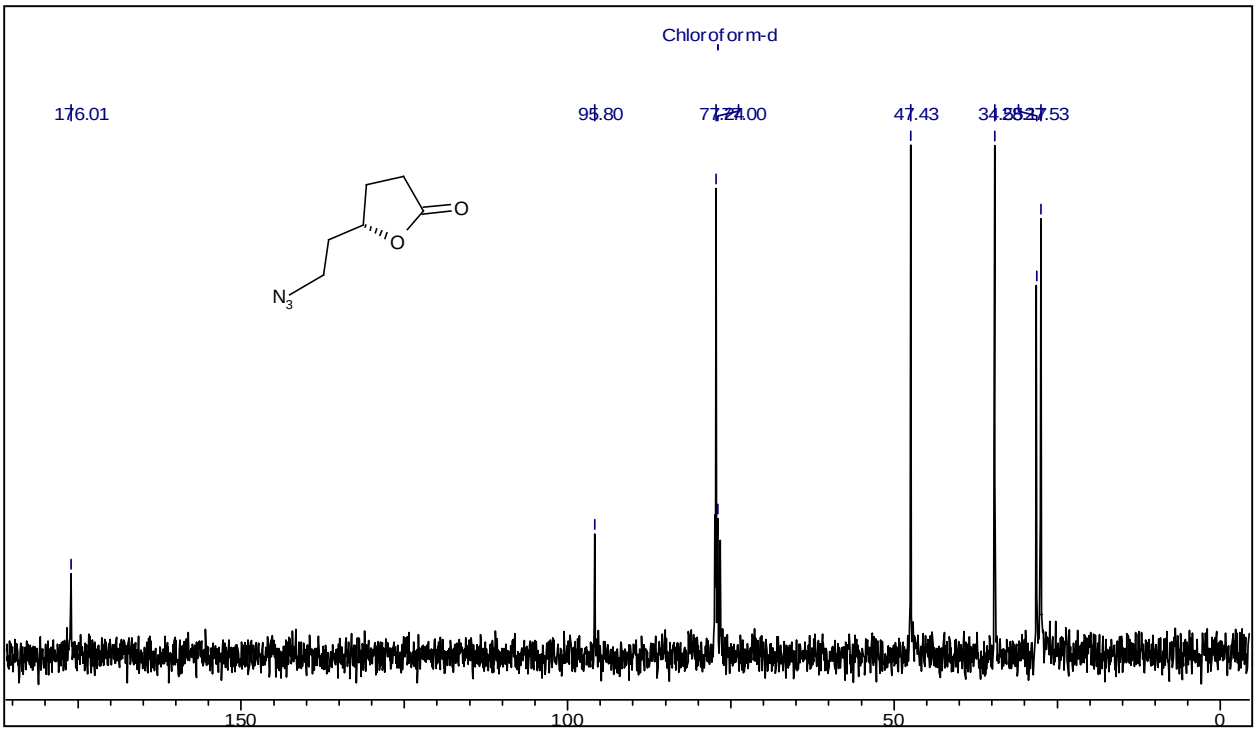
^{13}C NMR Spectrum of compound 45 in $CDCl_3$ + $CDCl_3$



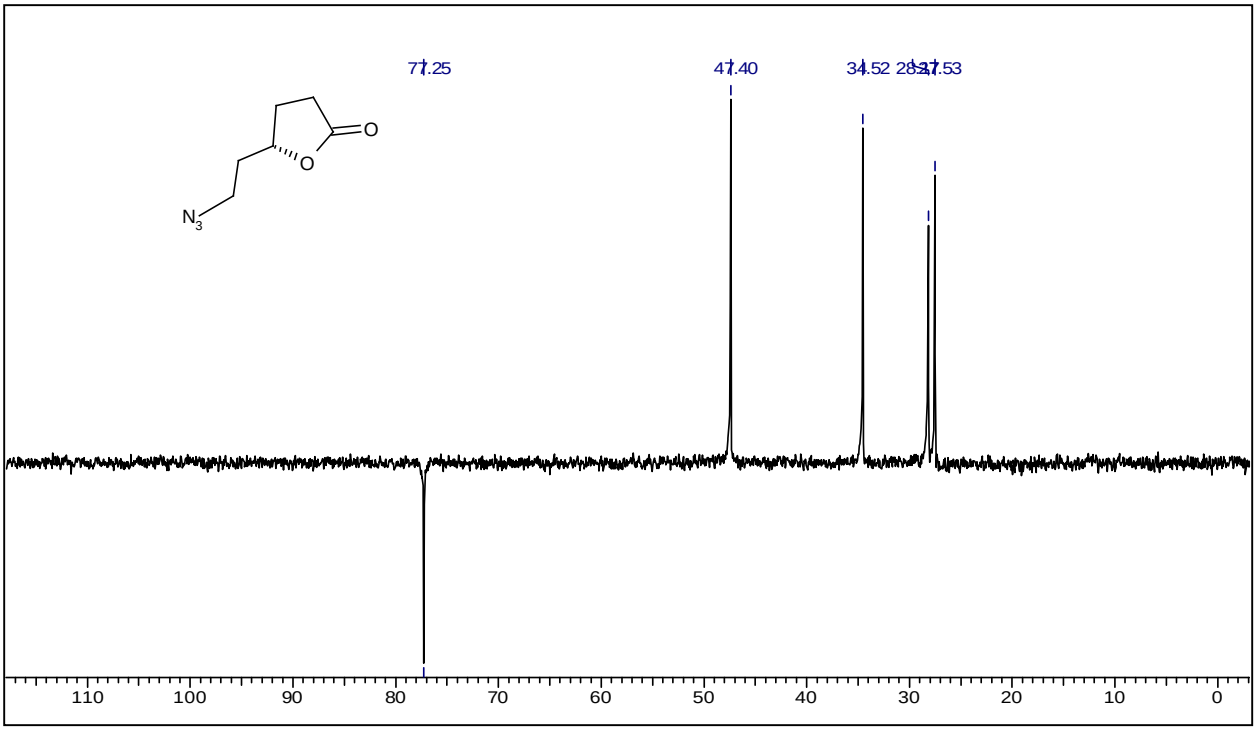
^{13}C NMR Spectrum of compound 45 in $CDCl_3$ + $CDCl_3$



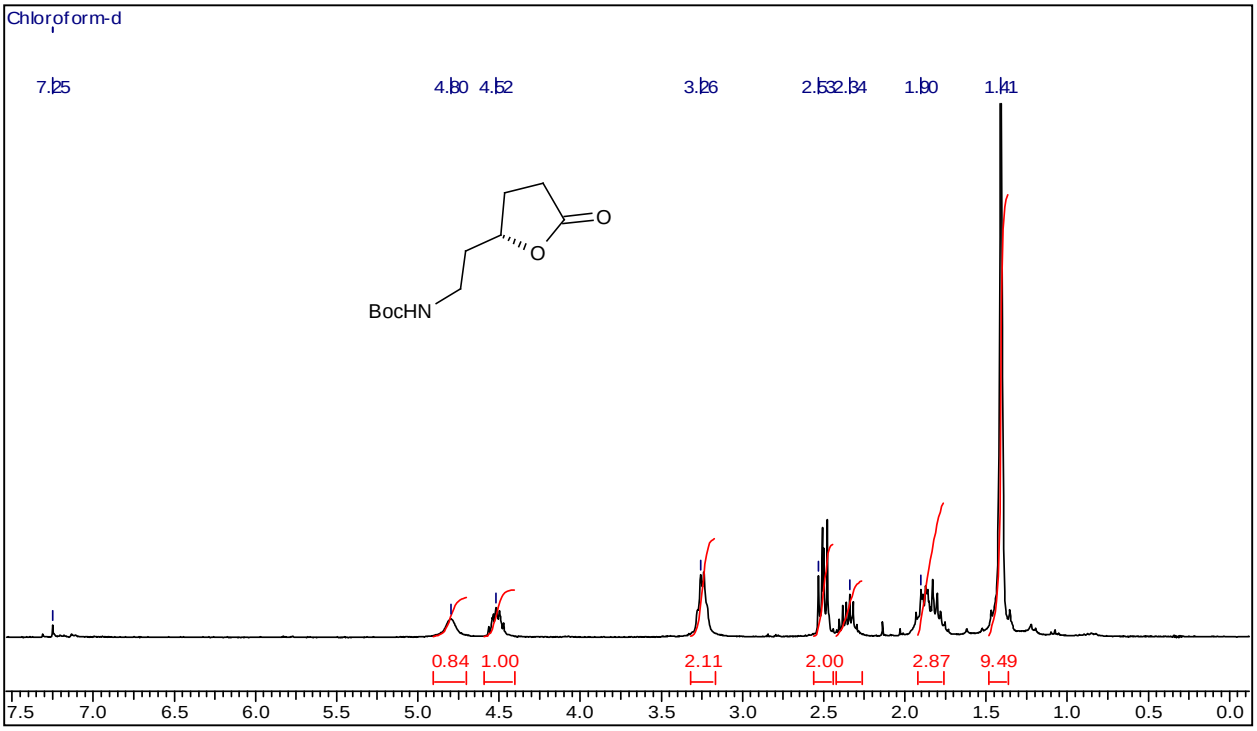
^{1}H NMR Spectrum of compound 38 in $CDCl_3$ + CCl_4



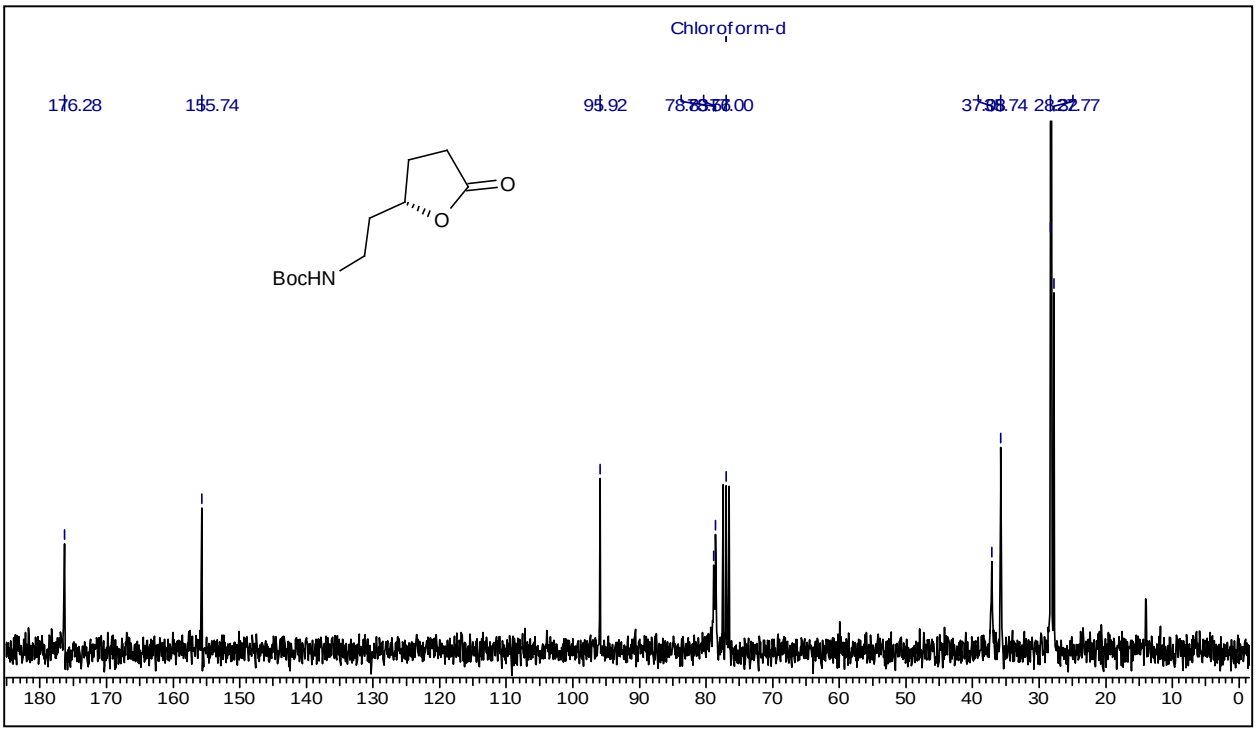
^{13}C NMR Spectrum of compound 38 in $CDCl_3$ + CCl_4



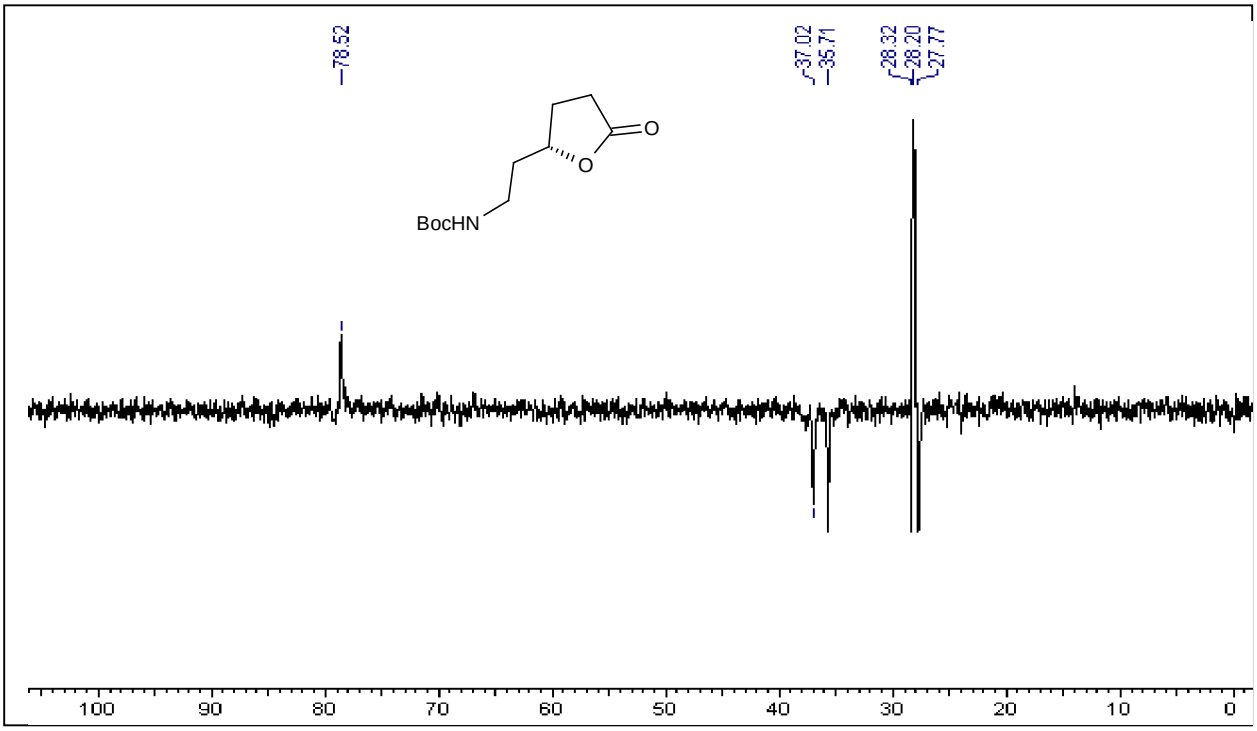
DEPT NMR Spectrum of compound 38 $CDCl_3$ + CCl_4



^{1}H NMR Spectrum of compound 47 in $CDCl_3$ + CCl_4



^{13}C NMR Spectrum of compound 47 in $CDCl_3$ + CCl_4



DEPT NMR Spectrum of compound 47 in $CDCl_3$ + CCl_4

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1. (a) Gante, J. *Angew. Chem.* **1994**, *106*, 1780–1802; *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699–1720; (b) Giannis, A.; Kolter, T. *Angew. Chem.* **1993**, *105*, 1303–1326; *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244–1267; (c) Hruby, V. J.; Li, G.; Haskell-Luevano, C.; Shenderovich, M. *Biopolymers* **1997**, *43*, 219–266.
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3. For example see: Smith, A. B., III; Benowitz, A. B.; Sprengeler, P. A.; Barbosa, J.; Guzman, M. C.; Hirschmann, R.; Schweiger, E. J.; Bolin, D. R.; Nagy, Z.; Campbell, R. M.; Cox, D. C.; Olson, G. L. *J. Am. Chem. Soc.* **1999**, *121*, 9286–9298.
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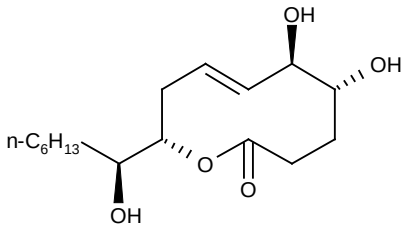
SECTION A

STEREOSELECTIVE SYNTHESIS OF (-)- MICROCARPALIDE

Introduction:

Macrocyclic marine natural products continue to provide a rich source of structurally diverse anti tumor agents with significant therapeutic potential.[1] Recently, a number of novel and stereo chemically complex macrolides, having a large macrolactone (22-to 44-membered) ring that interacts with the actin cytoskeleton have been isolated from different fungal and marine sources. Many molecules, which are of fungal as well as marine origin shown promising effect on the disruption of microfilaments of carcinomal cells, which consists mainly a protein actin. Owing to their potent anti tumor activities, these compounds, for example the aplyronines, also have potential for preclinical development in cancer chemotherapy.

In recent years the secondary metabolites from endophytic fungi have been receiving great deal of attention, because of peculiar structures with specific biological activities. Along this line, microcarpalide[2] (**1**) has been recently characterized as a new secondary metabolite produced by an endophytic fungus (so far unidentified) isolated from the bark of the tropical tree *Ficus microcarpa* L. Bioassay-guided purification of fermentation broths using immunofluorescence microscopy to test anticytoskeletal activity led to the isolation of microcarpalide displaying a remarkable disrupting action on actin microfilaments,[2] to which the structure **1** was assigned.



1

Microcarpalide (**1**) represents a novel alkyl-substituted nonenolide structurally related to a family of phytotoxins such as achaetolide,[3a] pinolidoxin,[3b,3c] putaminoxins[4a] and herbarumins,[4b] from which it differs in the hydroxylation pattern and the double bond position within the 10-membered lactone, as well as in the length of the side chain at C-10. At concentrations of 0.5–1 μg mL^{-1}, microcarpalide (**1**) was found to disrupt actin microfilaments in approximately 50% of A-10 cells (from rat smooth muscle); moreover, it displayed a weak cytotoxicity to mammalian cells, thus making it an attractive tool for studying cell motility and metastasis, and a potential lead structure to develop new anticancer drugs.[5]

Medium ring compounds in general

Medium ring compounds (those having a ring size in the range (8 to 11)[6] are becoming increasingly important in organic chemistry, as they are contained in an ever-growing number of natural products. Hydrocarbons, as well as heterocyclic compounds (ethers, lactones, amines, amides) have been isolated, and a number of reviews have already been published.[7]

These compounds have specific characteristics which had been recognized by at the beginning of this century,[8] and it was soon observed that they were much more difficult to synthesize by cyclization methods than other cyclic compounds including macrocyclic compounds (ring sizes >12). These difficulties are caused by the fact that the formation of these cyclic compounds are disfavoured by entropy as well as enthalpy[8]

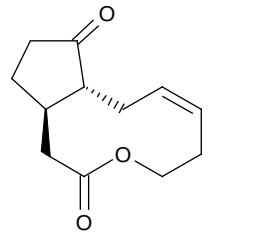
The pioneering work of Hunsdiecker and Erlbach reported the yields obtained in the reaction of ω-bromo alkanoic acids with potassium carbonate to give the corresponding lactones.[9] Good yields were observed in the preparation of five- to eight- and twelve- to eighteen-membered ring lactones. The yield of the nine-membered ring lactone was almost zero. This work was subsequently reinvestigated and developed by the Illuminati group.[10] They measured with great precision the rate of lactone formation in the ring sizes 3 to 23 by reaction of ω-bromoalkanoic acids with a base (KOH or diisopropylethylamine) in 21% aqueous DMSO.

In medium ring lactones, stereoelectronic factors can, however decrease the strain energy slightly. Lactones can exist in *Z* (or *syn)* and *E* (or *anti)* forms. The *syn* form is in

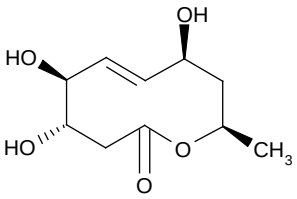
general more stable than the *anti* form (2-8 kcal/mole). For lactones with a ring sizes of at least 7 the rings are forced into the disfavored *anti* conformation. In 8- and 9-membered ring lactones, an equilibrium *syn anti* conformation was observed, while in 10- and 11-membered ring lactones (and macrolactones), the *syn* form is normal.[11]

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

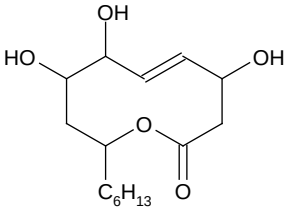
Natural products containing a medium ring lactone framework are found in plants, insects (pheromones) and bacteria (antibiotics); they can have a terrestrial, fungal or a marine origin. In the present context the emphasis was made only on 10-membered lactones. The oldest natural product possessing an oxecan-2-one framework would appear to be the jasmine ketolactone (**2**), a component of the essential oil of *Jasminum grandiflorium* isolated in 1942,[12] whose structure was confirmed twenty years later.[13]



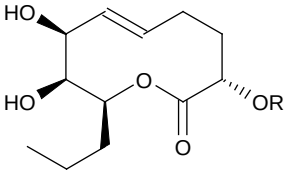
Jasmine ketolactone (**2**)



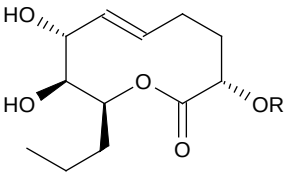
Tuckolide (**3**)



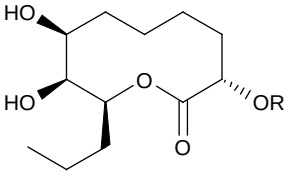
Achaetolide (**4**)



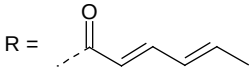
Pinolidoxin (**5**)



Epipinolidoxin (**6**)



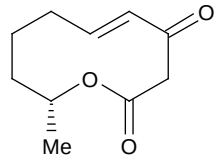
Dihydropinolidoxin (**7**)



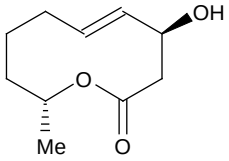
More recently, tuckolide (**3**) was isolated as metabolite of the Canadian tuckahoe, the sclerotium of *Polyporus tuberaster*, a subterranean fungus.[14] Achaetolide (**4**), a compound with a very similar structure, was also isolated from the fungus, *Achaetomium cristalliferum*.[15a] Pinolidoxin (**5**), a phytotoxin (anthraenose of pea) was produced by the

fungus *Aschochyta pinodes*.[15b] Subsequently, three new metabolites of this fungus were found: epi-(**6**),and dihydropinolidoxins (**7**).[15c]

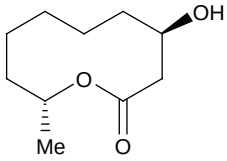
Diplodialides A, B, C and D (**8-11**), the metabolites of the phytopathogenic fungus *Diplodia pinea*, have more simple structures than pinolidoxine derivatives.[16] Diplodialide A (**8**) has been reported to be a steroid hydroxylase inhibitor. Another phytopathogenic fungus, *Pyrenophora teres*, produces metabolites, pyrenolides A, B and C (**12-14**), which have similar structures to the diplodialides.[17a] These compounds show inhibitory activity against fungi.[17b]



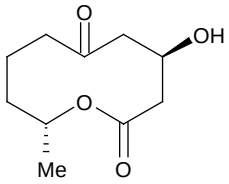
Diplodialide A (**8**)



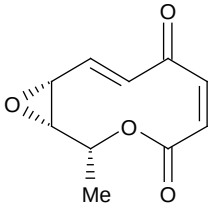
DiplodialideB (**9**)



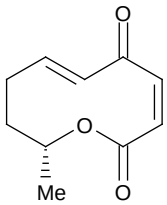
Diplodialide C (**10**)



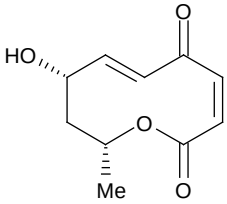
Diplodialide D (**11**)



Pyrenolide A (**12**)

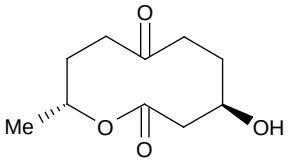


Pyrenolide B (**13**)

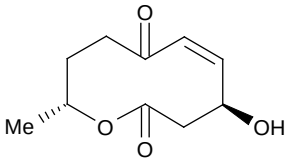


Pyrenolide C (**14**)

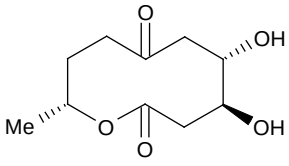
Two other similar structures, cephalosporolides B and C (**16, 17**), are metabolites of the fungus *Cephalosporium aphidicola*.[18a] Another interesting metabolite, thiobiscephalosporolide A (**18**), was isolated during the fermentation of *Cephalosporium a.* and found to be a dimeric 10-membered ring lactone.[18b] On degradation, it led to a compound which is a regioisomer of diplodialide D (**11**). The biogenesis of these different compounds has been discussed recently.[18c]



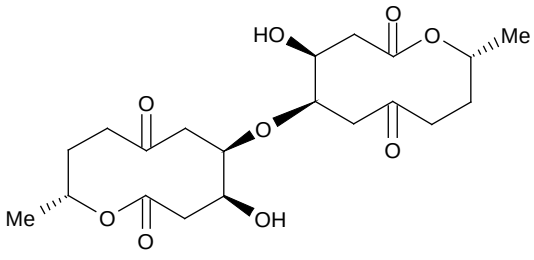
Cephalosporolide A (**15**)



Cephalosporolide B (**16**)

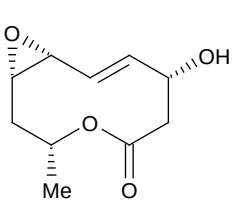


Cephalosporolide C (**17**)

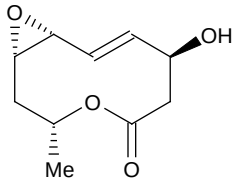


Thiobiscephalosporolide A (**18**)

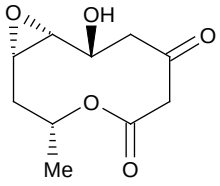
Various oxygenated oxecan-2-ones, decarestrictines A-J (**19-30**), were formed during the fermentation of *Penicillium simplicissimum*.[19] These compounds show important inhibitory effects on cholesterol biosynthesis.[20] Decarestritine D (**24**) is similar to tuckolide, and its isolation was published simultaneously.



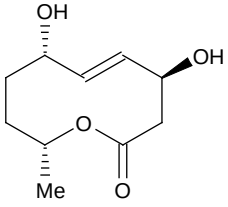
A_1 (**19**)



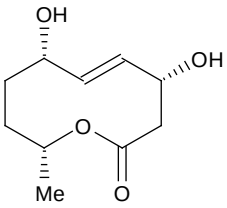
A_2 (**20**)



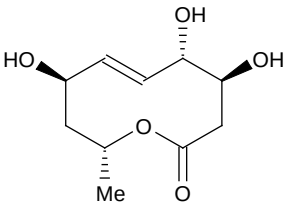
B (**21**)



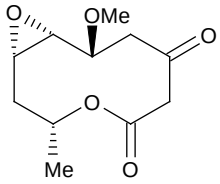
C_1 (**22**)



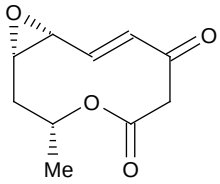
C_2 (**23**)



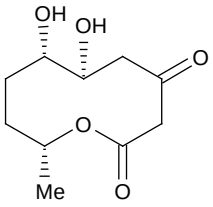
D (**24**)



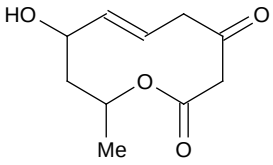
E (**25**)



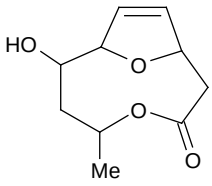
F (**26**)



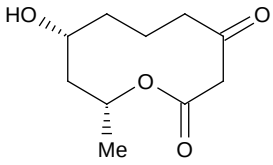
G (**27**)



H (**28**)

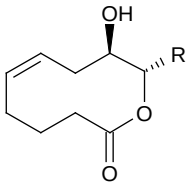


I (**29**)

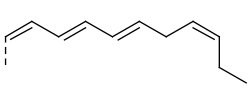


J (**30**)

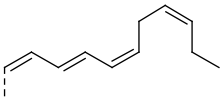
Metabolites of *Didenmum moseleyi* (Herdman), a tunicate living in the sea in Japan, didemnilactones A and B (**31, 32**), and neodidemnilactone, were also found to be 10-membered ring lactones.[21] These compounds exhibit weak binding activity to leukotriene B_4 receptors in human polymorphonuclear leukocyte membrane fractions. Ascidiatrienolides A, B, and C,[22a] (**34-36**) whose structures were recently reinvestigated,[22b] were found in marine ascidian *(Didemnum candidum)* and corresponded to oxidation products of C20 fatty acid.



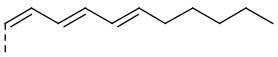
R =



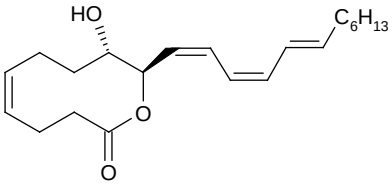
Didemnilactone A (**31**)



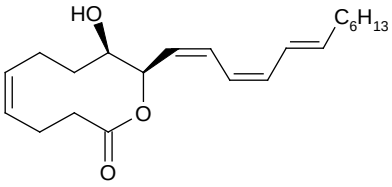
Didemnilactone B (**32**)



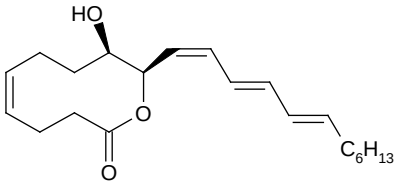
Neodidemnilactone A (**33**)



Ascidiatrienolide A (**34**)

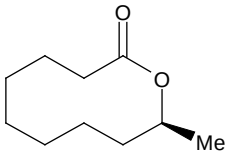


Ascidiatrienolide B (**35**)

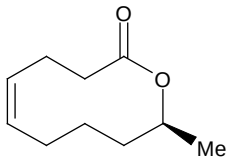


Ascidiatrienolide C (**36**)

The metastemal gland secretion of the common eucalypt longicom, *Phoracantha semipunctata* contains two lactones as major components, phoracantholide I (**37**) and phoracantholide J (**38**).[23]

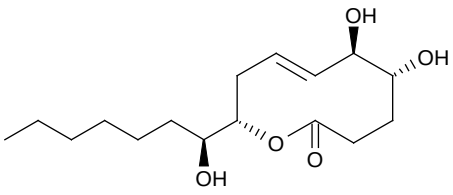


Phoracantholide I (**37**)

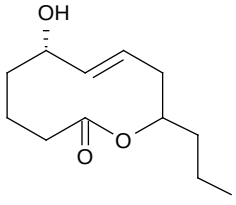


Phoracantholide J (**38**)

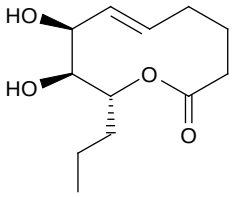
Microcarpalide[2] (**1**) represents novel alkyl-substituted nonenolide structurally related to a family of phytotoxins such as achaetolide[15a] (**4**), pinolidoxin[15b] (**5**), putaminotoxins[24a] (**39**) and herbarumins[24b] (**40**), from which it differs in the hydroxylation pattern and the double bond position within the 10-membered lactones, as well as in the length of the side chain at C-10.



Microcarpalide (**1**)



Putaminoxin (**39**)



Herbarumin (**40**)

Ring Closing Metathesis: a brief view

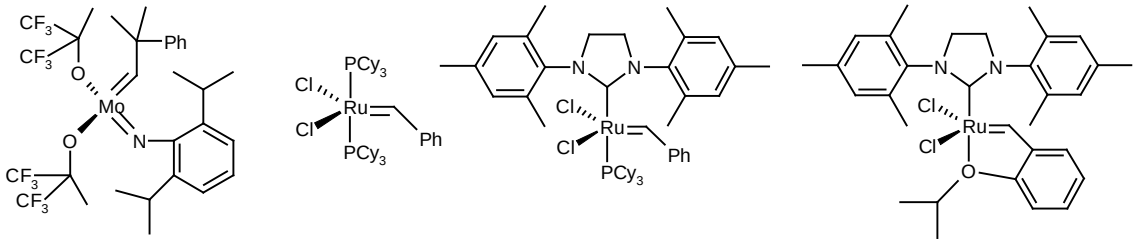
During the last ten years ring-closing metathesis (RCM)[55] has been developed into a powerful method for the preparation of both carbocyclic and heterocyclic ring systems. In particular, medium and large rings can be very effectively constructed, and thus RCM became a reliable tool for natural product synthesis.

The word metathesis describes the interchange of covalent bonds between two molecules. In olefin chemistry it refers to the redistribution of carbon-carbon double bonds between two alkenes.

Olefin metathesis catalyzed by metal carbene complexes has been known in polymer chemistry for about 40 years. However, the reaction has been limited to simple, unfunctionalized olefins. After development of new catalysts by Schrock and Grubbs this became useful in organic synthesis and synthetic community immediately realized the potential utility of this methodology.

The metathesis can be devided into an intramolecular (ring closing), inter molecular (cross olefin metathesis) and ring-opening metathesis polymerization. Ring closing metathesis (RCM), in which two olefins (unsubstituted or substituted) undergo ring closure with formal loss of ethylene. It has received a great deal of attention in recent years for the synthesis many biologically active compounds from acyclic diene precursors.

Although a number of titanium and tungsten catalysts have been developed for metathesis and related reactions, the Schrock's catalyst (**129**), Grubbs' 1st and 2nd generation catalysts (**130** and **131**), and Hoveyda-Grubbs catalyst (**132**) have greatly attracted the attention of synthetic chemists because of their high reactivity and commercial availability.



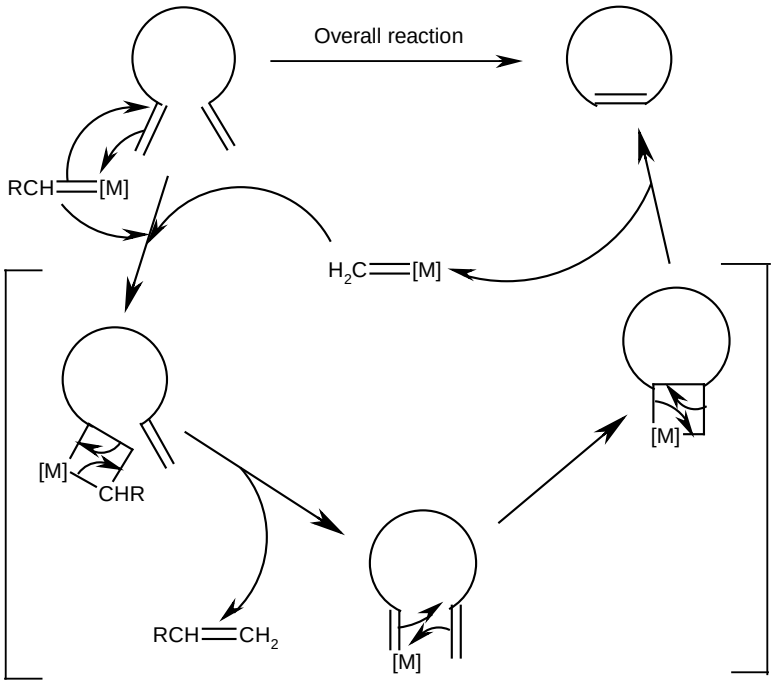
Schrock's catalyst (**129**) | Grubbs' 1st generation catalyst (**130**) | Grubbs' 2nd generation catalyst (**131**) | Hoveyda-Grubbs catalyst (**132**)

Leading metathesis catalysts

RCM Mechanism:

The postulated mechanism involves an iterative process of [2+2] cycloaddition and cycloreversion between the olefins, metal alkylidene and metallocyclobutane species (**Scheme 42**). The initial retro-type intermolecular [2+2] cycloaddition between the catalyst and one of the olefins of diene leads to the incorporation of the metal alkylidene in the

Scheme 42: Ring Closing Metathesis mechanism



substrate. The

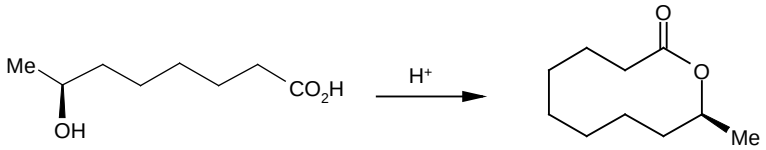
second cycloaddition takes place in a facile intramolecular fashion and ring opening of resulting metallocyclobutane leads to the cycloalkene and regeneration of the metal carbene, which takes up another diene molecule and acts in same fashion. In the first turn of the cycle, the volatile nature of the alkene by-product (the gaseous ethene in most cases) tends the reaction to proceed forward thermodynamically.

The construction of a 10-membered ring is by using ring closing metathesis was first reported bu Furstner and Muller in 1997 for the synthesis of Jasmine ketolactone (**2**). Furstner also synthesized herbarumin I and herbarumin II by using RCM strategy.[56]

Preparation of medium ring lactones

Lactonisation of ω-hydroxyalkanoic acids: Direct cyclisation

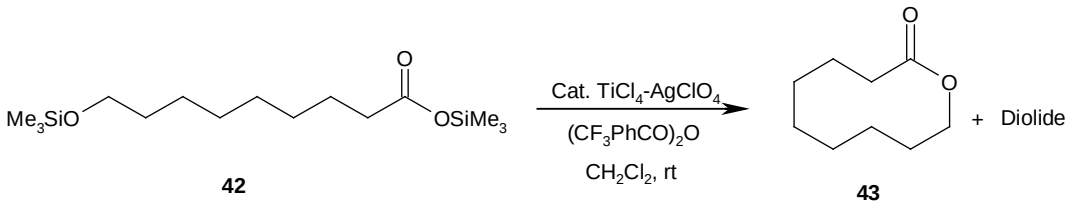
A number of reviews have been published on the subject of cyclisation methods and the synthesis of macrolides. However, only a few containing information about medium ring lactones are available.[25] Stoll and Rouve's was prepared Phoracantholide I (**37**) in 60 % yield by acid catalyzed lactonisation.[26]



41 **37**

Scheme 1

Recently, Mukaiyama and coworkers[27] have reported a new activation method based on the lactonisation of silyl ω-siloxyalkanoate using p-trifluoromethylbenzoic anhydride and a catalytic amount of a mixture of $TiCI_4$ and $AgC1O_4$. In the specific case of medium ring lactones, low yields were obtained (0 % for the 8 and 9-membered ring lactones; 33 % for the decanolide) except for the formation of the undecanolide (70 %).

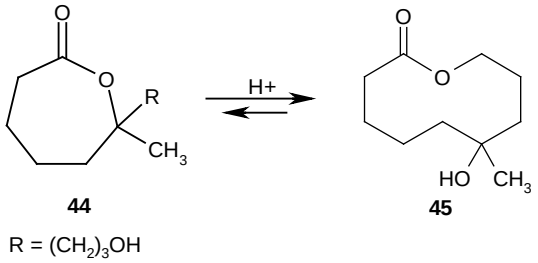


42 **43**

Scheme 2

Translactonisation method

In this method, first introduced by Corey and coworkers,[28] a hydroxy lactone is subjected to the action of a catalytic amount of acid to give a thermodynamically more stable hydroxylactone.

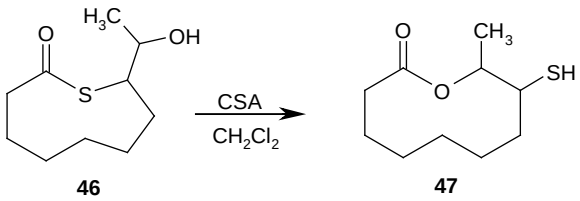


44 **45**

R = $(CH_2)_3OH$

Scheme 3

Since medium ring lactones are less stable than other lactones, it should be, *a priori*, difficult to obtain medium ring lactones by this technique. Corey showed that the seven-membered ring lactone can be transformed to a ten-membered ring lactone. In a subsequent work, Vedejs and coworkers[29] have shown that, starting with thiolactones, such an isomerisation can indeed take place. For example, a nine-membered ring thiolactone was transformed in good yield to a ten-membered ring lactone (70% yield) even though equilibrium between these two lactones was observed.

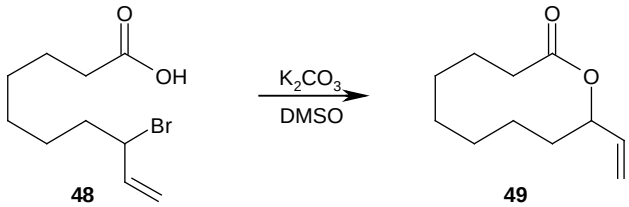


46 **47**

Scheme 4

Cyclisation of ω-haloalkanoic acids and related compounds

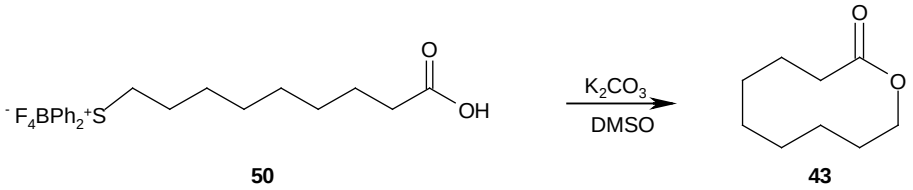
The cyclisation of ω-haloalkanoic acids induced by a base such as K_2CO_3 or NaOH is one of the oldest methods available for the preparation of medium ring lactones. Hunsdiecker reported the formation 10-and 11-membered ring lactones in good yields by the reaction of the corresponding bromoalkanoic acids with potassium carbonate.[9]



48 **49**

Scheme 5

However employing *O*-methanesulfonyl derivatives in this cyclisation was found to be favourable, and 10- and 11-membered ring lactones were obtained in approximately 50% yields.[30] The superiority of *O*-methanesulfonyl derivatives was also recognised by Vedejs in the syntheses of fulvine,[31] crispatine,[31] and monocrotaline.[32]

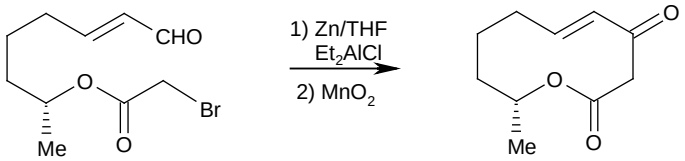


50 **43**

Scheme 6

Electrophile- Induced cyclisations

Intramolecular Reformatsky reaction promoted by Et_2A1C1 was found to induce the ring closure and give an unsaturated 10-membered ring lactone, which on oxidation gave diplodialide A[33] (**8**).

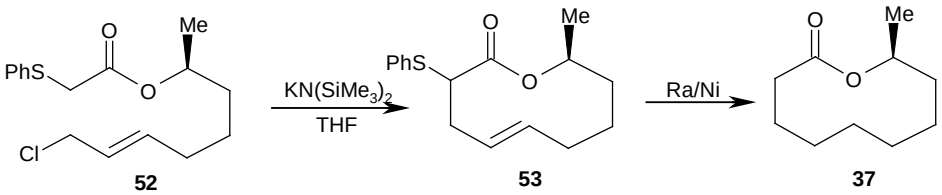


51 **8**

Scheme 7

Nucleophile-induced cyclisation

Tsuji and coworkers have shown that lactone formation could take place by carbon-carbon bond formation *via* the intramolecular alkylation of a carbanion generated from phenylthioacetate.[34] This strategy was applied to the preparation of a ten-membered ring



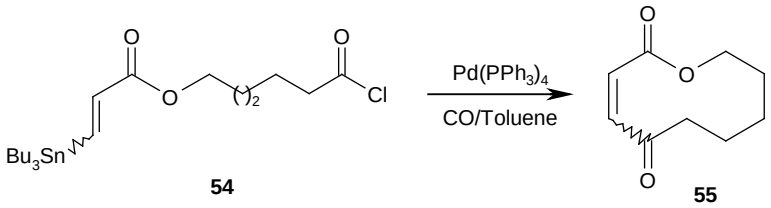
52 **53** **37**

lactone, which could be transformed into phoracantholide I (**37**).

Scheme 8

Palladium metal-induced cyclizations

Work in this field was pioneered by Trost who observed that stabilized anions react intramolecularly with acylic acetates in the presence of $Pd(PPh_3)_4$ and 1,2-diphenylphosphinoethane to give medium ring lactones.[35a] Recently, Baldwin and coworkers reported the intramolecular Pd(0)-catalysed coupling of acid chloride and β-stannylalkenoate in the presence of CO as a new route to 10-20-membered ring lactones. For the medium lactones, low yields were observed.[35b]

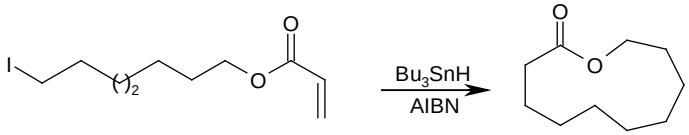


54 **55**

Scheme 9

Radical-induced cyclisations

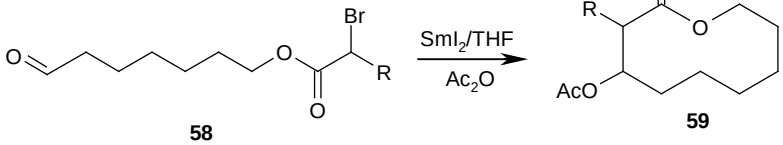
Porter reported that treatment of 10-iodoalkyl acrylate with tributyltin hydride and AIBN in benzene led to the formation of a 11-membered ring lactone in low yield (15-25%).[36]



56 **57**

Scheme 10

Cyclisation of ω-oxoalkenyl α-bromoalkanoates induced by SmI_2 has been reported to lead in high yields (76-92%) to 9-11-membered ring lactones.[37a] Macrolides were also formed with the same efficiency. This method was applied to the preparation of ferrulactone .[37b]



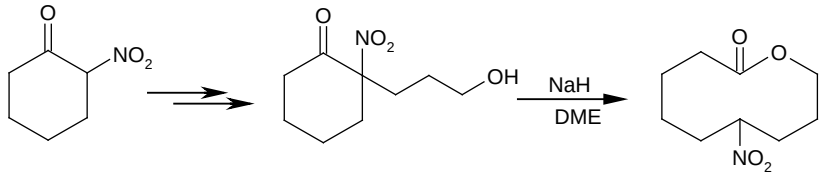
58 **59**

Scheme 11

Ring Expansion Methods

Hesse-Cookson approach

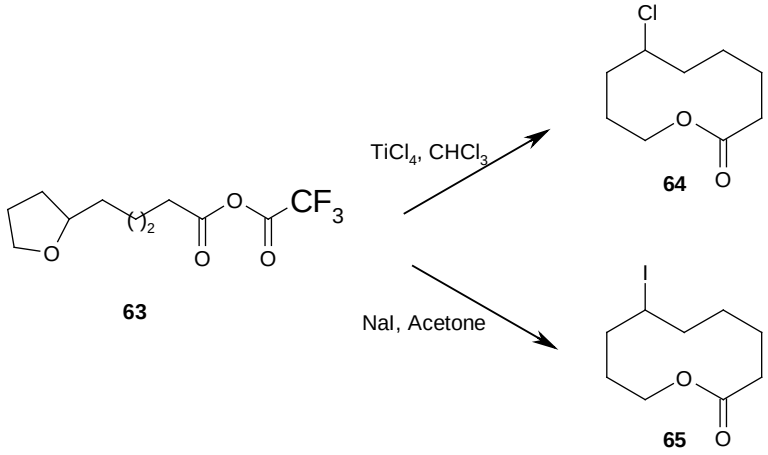
In this strategy, the chain bearing the alcohol is on the same carbon as the electron with drawing group. It was soon determined by Cookson[38] and Hesse[39] that the best electron-withdrawing group for this reaction was NO_2 group. Cookson showed that this method could be applied to the preparation of 10- and 11-membered ring lactones with excellent yields (76-78%), while Hesse applied this approach to the synthesis of phoracantholide I (**40**).



60 **61** **62**

Scheme 12

Recently, Grayson and Roycroft reported that reaction of 5-(tetrahydro-2-furyl) pentanoic trifluoroacefic anhydride with a Lewis acid ($TiCl_4$) or NaI in acetone leads to the formation of halolactones.[40]



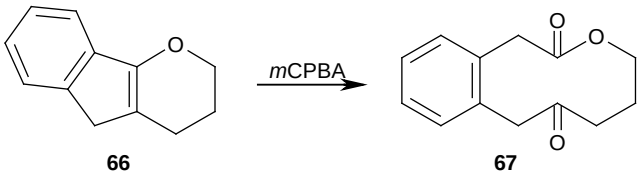
63 **64** **65**

Scheme 13

Ring expansion by Activated carbon-carbon double bond

Oxidative cleavage of C-C double bond is one of the method for the formation of 10- and 11-membered ring lactones.[41] The mixture of ruthenium tetraoxide-sodium metaperiodate[42a] and Corey's reagents, PCC, and PDC,[42b] were also found to be effective for this oxidative cleavage.

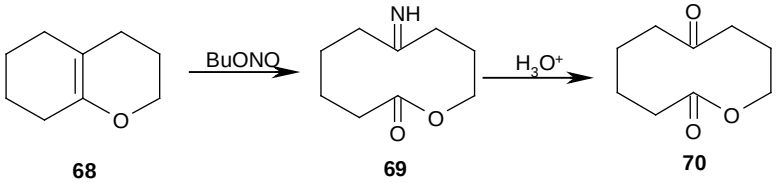
meta-Chloroperbenzoic acid was the reagent of choice for this cleavage, although ozone could be also used. Benzo-medium ring lactones have been prepared in good yields using this procedure.[43a]



66 **67**

Scheme 14

Mahajan showed some years later that n-butylnitrite was an excellent alternative reagent for this cleavage.[43b]

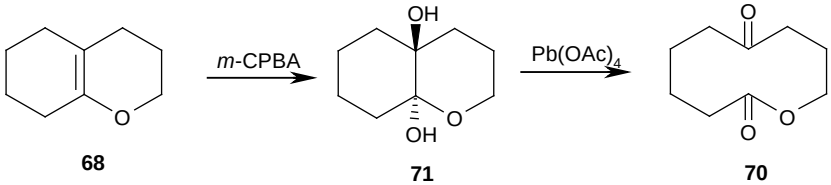


68 **69** **70**

Scheme 15

Ionic cleavage of bicyclic hemiketals

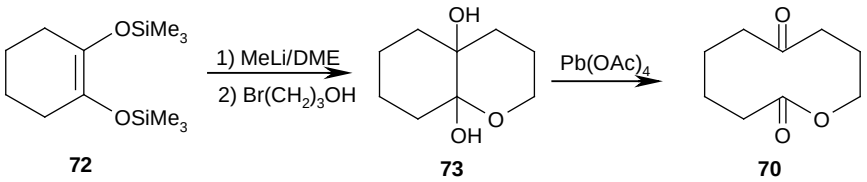
The first approach using this method was published by Borowitz, who reported the cleavage of a bicyclic *trans* 1,2-diol with lead tetra acetate[44a]



68 **71** **70**

Scheme 16

Wakamatsu and coworkers showed that bicyclic *cis* 1,2-diols, formed by alkylation of 1,2-enediolates with 3-bromo-l-alkanols, can also undergo to the same fragmentation.[44b] The application of this to the synthesis of diplodialides A and C (**11**, **13**) was reported.[44c]



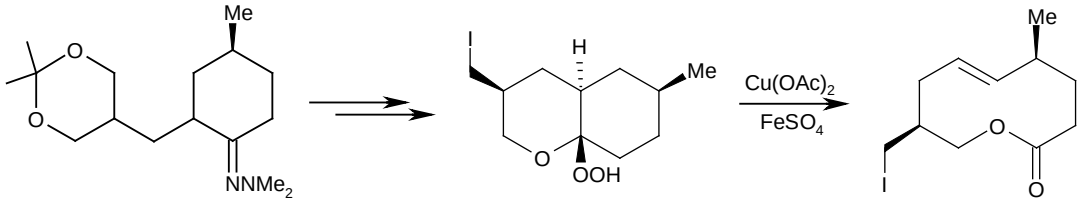
72 **73** **70**

Scheme 17

Posner used the same strategy to cleave bicyclic hemiketals, which were formed by sequential Michael reaction of enals or enones. Application of the reaction to the preparation of phoracantholide (**37**) was reported.[45]

Radical cleavage of bicyclic hemiketals

Schreiber and coworkers have reported the preparation of perhemiacetals which, when treated with a mixture of $FeSO_4$ and $Cu(OAc)_2$, gave the corresponding lactones.[46]



74 **75** **76**

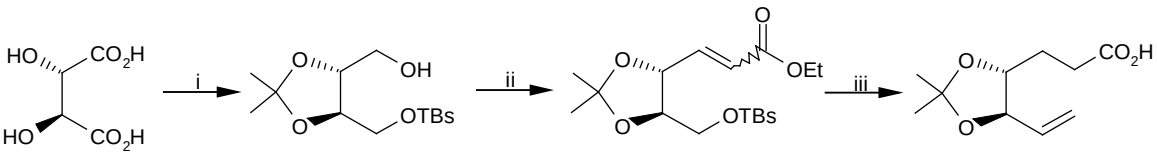
Scheme 18

Review of Literature:

Microcarpalide acts as a strong microfilament disrupting agent and shows weak cytotoxicity to mammalian cells. Because of the large difference between the effective concentration for the microfilament activity and the cytotoxicity, it is thought that this compound will be an effective tool for the studies of cell motility and metastasis. Owing to such peculiar biological activity and abundance of stereochemistry have stimulated enormous interest in the synthesis of this molecule, which are briefly described.

Marco *et al* (2002)[47]

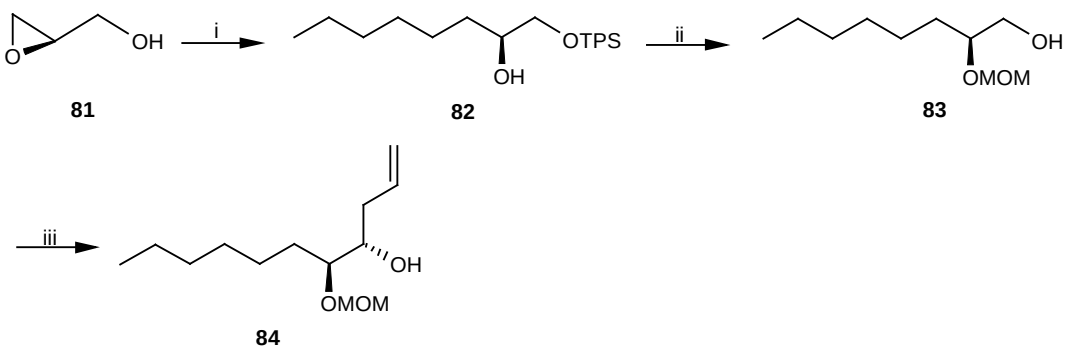
Marco and co-workers have reported the first total synthesis of (-)-Microcarpalide by using RCM as the key step. The diene ester required for RCM cyclization reaction was prepared by coupling of an olefinic acid and olefinic alcohol fragments which were prepared stereo selectively from (*S*, *S*)-tartaric acid and (*R*)-glycidol. (Scheme **19** & **20**)



77 **78** **79** **80**

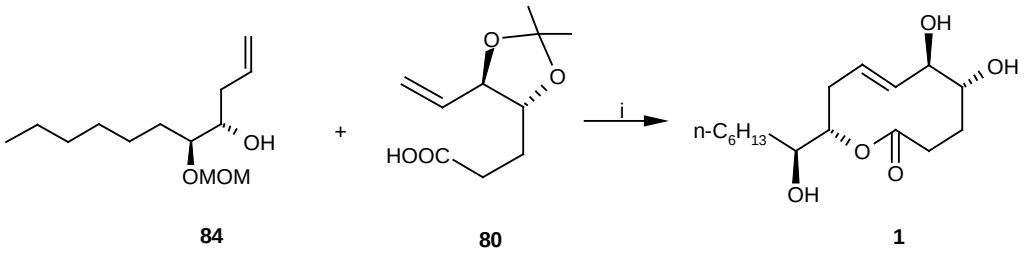
Scheme 19

Scheme 19: *Reagents and conditions*: (i) (a) 2,2-Dimethoxy propane, *p*-TsOH; (b) LAH, Et_2O, reflux; c) TBDMSCl, NaH, THF; (ii) (a) $(COCl)_2$, DMSO, Et_3N, -70 °C; (b) $Ph_3P{=}CHCO_2Et$, DMF, rt; (iii) (a) H_2, Pd/C, EtOH, rt; (b) TBAF, THF, rt; (c) $(COCl)_2$, DMSO, Et_3N, -72 °C; (d) $Ph_3P{=}CH_2$, n-BuLi, THF, -20 °C - rt; (e) KOH-MeOH-H_2O, rt.



Scheme 20

Scheme 20: *Reagents and conditions*: (i) (a) TPSCl, Et_3N, DMAP, CH_2Cl_2, 18 h, 93 %; (b) $CH_3(CH_2)_4MgBr$, CuI, THF, - 30 ^oC, 87 %; (ii) (a) MOMCl, Et_3N, DMAP, CH_2Cl_2, rt, 18 h, 87 %; (b) TBAF, THF, 5 h, rt, 93 %; (iii) (a) $(COCl)_2$, DMSO, CH_2Cl_2, -78 ^oC, 30 min then *N*, *N*-diisopropyl ethyl amine, 2 min at – 78 ^oC, then rt; (b) $Bu_3SnCH_2CH=CH_2$, $MgBr_2.Et_2O$, 3 A^o MS, CH_2Cl_2, 3 h at – 78 ^oC then 1.5 h at – 40 ^oC, 60 % for 2 steps.

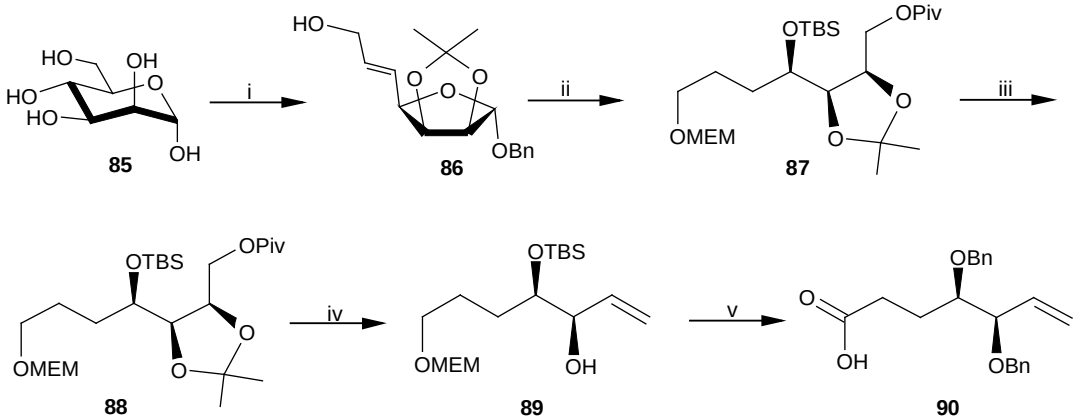


Scheme 21

Scheme 21: *Reagents and conditions*: i) (a) DCC, DMAP, Et_2O; (b) $(Cl_2(PCy_3)_2Ru=CHPh)$, CH_2Cl_2, reflux; (c) BF_3:Et_2O, $(CH_2SH)_2$, CH_2Cl_2, 0 ^oC, 1 h, 76 %.

Gurjar *et al* (2003)[48]

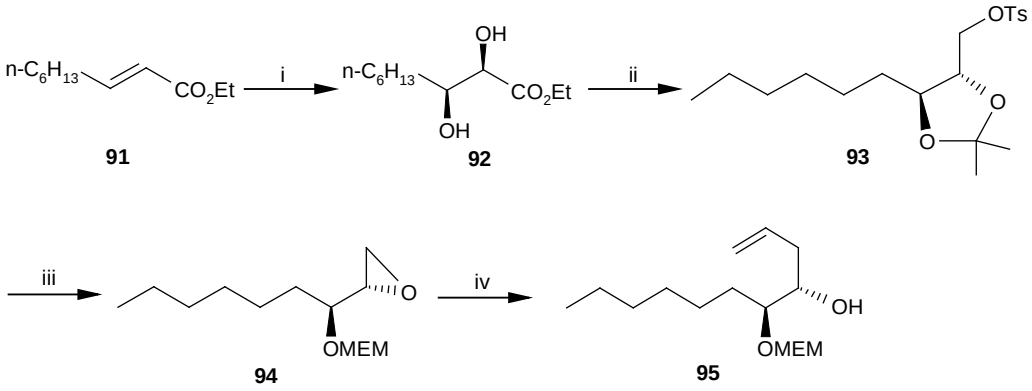
Gurjar and co-workers have synthesized (-)-microcarpalide by using RCM as the key step. For the preparation of olefinic acid fragment D-mannose was used as the chiral pool starting material and the Sharpless Asymmetric Dihydroxylation was used to prepare olefinic



alcohol fragment.

Scheme 22

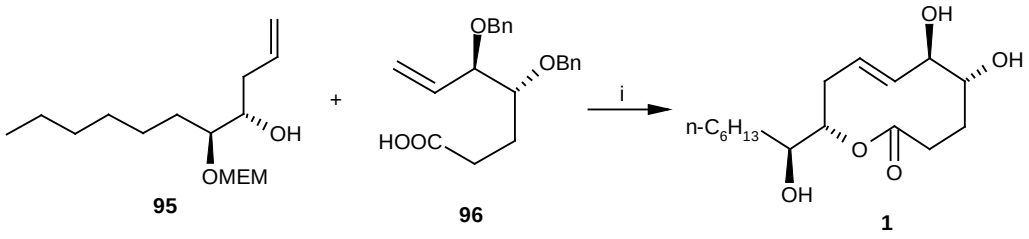
Scheme 22. *Reagents and conditions*: (i) Ref. 49; (ii) (a) MEM-Cl, $^{i}Pr_2NEt$, CH_2Cl_2, rt, 10 h; (b) H_2, 10% Pd/C, MeOH, 6 bar, 60 °C, 4 h; (c) $LiAlH_4$, THF, rt, 1 h, 71% for three steps; (ii) (a) $(CH_3)_3CCOCl$, pyridine, 0 °C–rt, 91%; (b) TBSCl, DMF, imidazole, rt, 4 h, 90 %; (iii) (a) DIBAL-H, CH_2Cl_2, −78 °C, 1 h, 89%; (b) I_2, PPh_3, imidazole, ether–benzene (2:1), rt, 1.5 h, 86%; (c) Zn, ethanol, reflux, 1.5 h, 96%; (iv) (a) *n*-$Bu_4N^+F^-$, THF, rt, 1 h, 85%; (b) NaH, BnBr, DMF, 0 °C–rt, 88 %; (c) PPTS, *t*-BuOH, 80 °C, 1.5 h, 85%; (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 1 h; (e) $NaClO_2$,



DMSO, NaH_2PO_4, rt, 1.5 h, 83% for two steps.

Scheme 23

Scheme 23. *Reagents and conditions*: (i) AD-mix-α, *t*-BuOH, H_2O, 0 °C, 10 h, 94%; (ii) (a) 2,2-dimethoxypropane, *p*-TsOH, CH_2Cl_2, 1.5 h, 96%; (b) DIBAL-H, CH_2Cl_2, −78 °C, 1 h, 97%; (c) *p*-TsCl, pyridine, 0 °C–rt, 96%; (iii) (a) conc. HCl (cat.), MeOH, 3 h, 87%; (b) K_2CO_3 (1.5 equiv.), MeOH, rt, 1.5 h, 85%; (c) MEM-Cl, $^{i}Pr_2NEt$, CH_2Cl_2, rt, 4 h, 91 %; (iv) (a) LiCCH: ethylenediamine, DMSO, rt, 12 h, 86 %; (b) H_2, Pd/$BaSO_4$, quinoline, benzene, 1 bar, rt, 0.5 h, 91%.

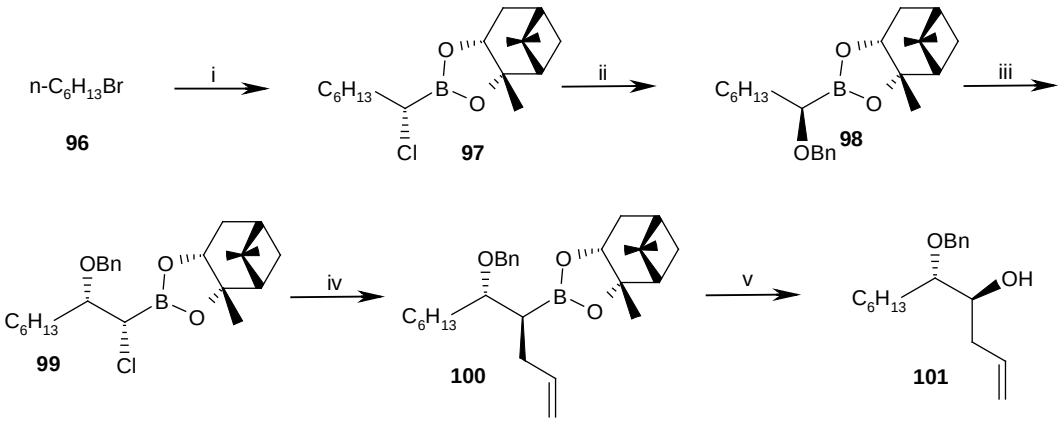


Scheme 24

Scheme 24: *Reagents and conditions*: (i) (a) DCC, DMAP, Et_2O; (b) $(Cl_2(PCy_3)_2Ru{=}CHPh)$, CH_2Cl_2, reflux; (c) $TiCl_4$, CH_2Cl_2, 0 °C.

Prati *et al* (2004)[50]

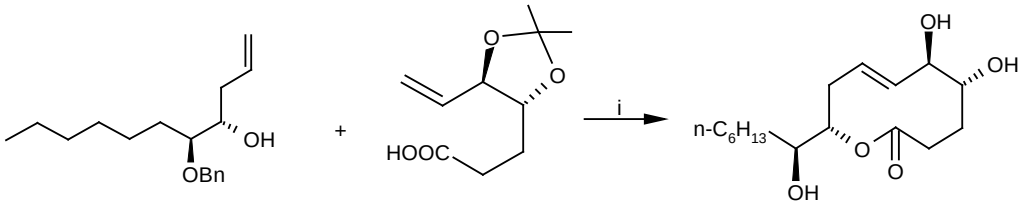
Prati and co-workers have used the same RCM reaction reaction for the ring formation. The alcohol fragment was synthesized from n-bromahexane through a seven-step sequence entailing two consecutive stereoselective homologation of chiral boronic esters as strategic transformations for the sequential insertion of two stereo centers with the final *S* absolute configuration, using (+)-pinanediol as the chiral director (**Scheme 25**). The acid fragment was prepared by using literature procedure.



Scheme 25

Scheme 25: *Reagents and conditions*: (i) (a) Mg, Et_2O, $(MeO)_3B$, reflux; (b) (1*S*,2*S*,3*R*,5*S*)-(+)-pinanediol, Et_2O, rt; (c) Cl_2CHLi, THF, -100 °C; ii) $C_6H_5CH_2OH$, n-BuLi, THF, -78 °C; iii) (a) Cl_2CHLi, $ZnCl_2$,THF, -100 °C; iv) allylmagnesium bromide, THF, -78 °C; v) H_2O_2, NaOH, THF, 0 °C.

As shown in Scheme **25**, the alcohol fragment was synthesized from n-bromohexane utilizing the stereo selective homologations of chiral boronic esters as strategic transformation for the sequential insertion of two stereo centers having *S*-configuration, using the (+)-pinanediol as the chiral director.



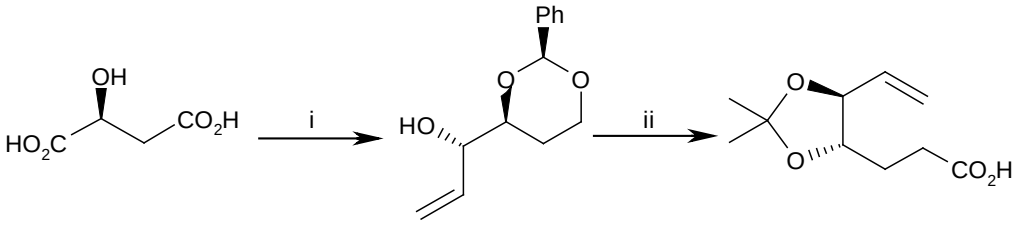
101 **80** **1**

Scheme 26

Scheme 26: *Reagents and conditions*: (i) (a) DCC, DMAP, Et_2O; (b) $(Cl_2(PCy_3)_2Ru=CHPh)$, CH_2Cl_2, reflux; (c) $TiCl_4$, CH_2Cl_2, 0 °C.

Banwell's Synthesis (2004)[51]

Banwell *et al* in 2004 reported the synthesis of enatiomer of (-) microcarpalide, once again using RCM as the key reaction. A chiral pool approach for the preparation of the acid component from (*S*)-malic acid (**102**) was executed using well established reactions.

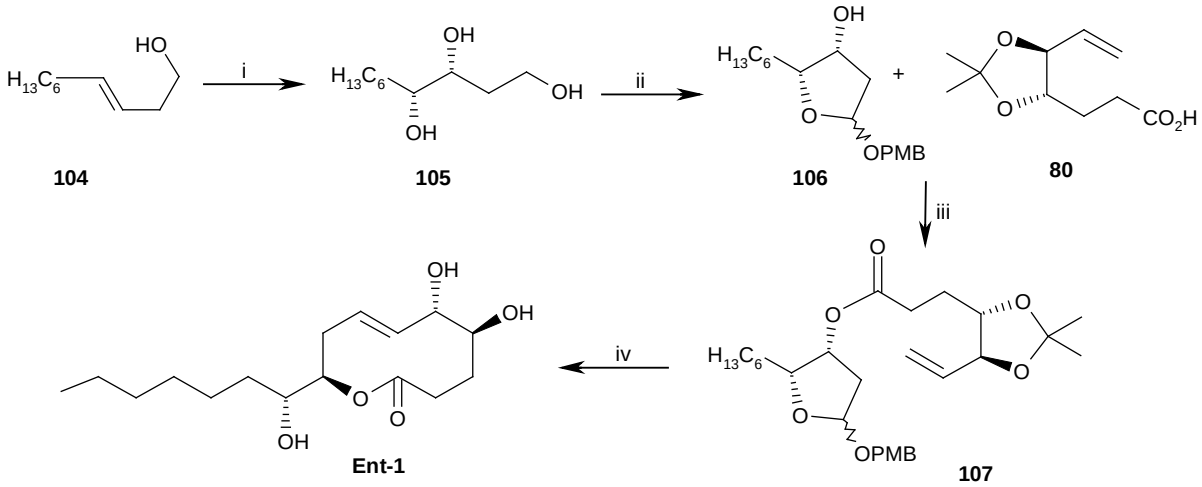


102 **103** **80**

Scheme 27

Scheme 27: *Reagents and conditions*: (i) (a) BH_3-DMS, $B(OMe)_3$, THF; (b) PhCHO, $(MeO)_3CH$, TFA, CH_2Cl_2; (c) 4-Ac*N*-TEMPO, $PhI(OAc)_2$, CH_2Cl_2; (d) $(CH_2{=}CH)_2Zn$, THF, -50 °C; (ii) (a) 1 M aq. HCl, THF; (b) *p*-TSCl, Py, DMAP; (c) KCN, DMF, 60 °C; (d) KOH, MeOH-H_2O.

Sharpless asymmetric dihydroxylation of a homoallyl alcohol **104** has been used in the preparation of the second fragment. The difference in the approach of Banwell is that they have coupled both the fragment in advance before constructing the olefin of the alcohol fragment.

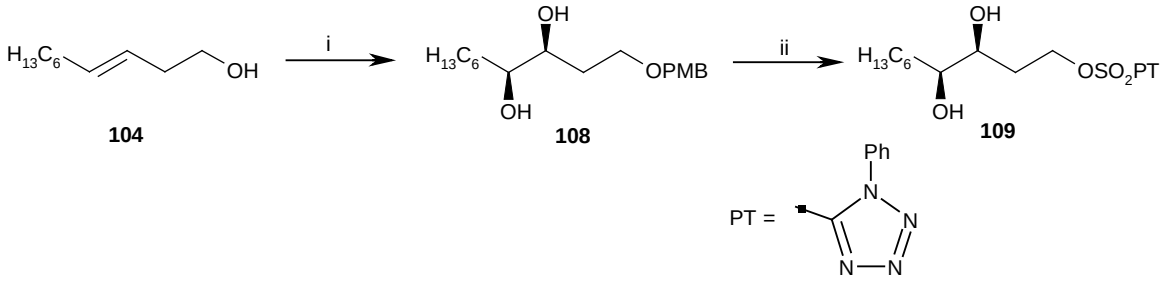


Scheme 28

Scheme 28: *Reagents and conditions*: (i) AD-mix-β, $MeSONH_2$, t-BuOH-H_2O, 0 °C; ii) (a) 2,2-DMP, *p*-TSOH, CH_2Cl_2; (b) 4-AcN-TEMPO, $PhI(OAc)_2$, CH_2Cl_2; (c) AcOH-H_2O-THF, 50 °C; (d) PMB-OH, *p*-TSOH, CH_2Cl_2; (iii) DCC, DMAP, CH_2Cl_2; iv) (a) DDQ, THF; (b) $Ph_3P{=}CHCO_2Me$, toluene, 0 °C; (c) MOM-Cl, DIPEA, CH_2Cl_2; (d) Grubbs 2nd gen. Cat., $CH_2{=}CH_2$, CH_2Cl_2; (e) ($Cl_2PCy_3Ru{=}CHPh$), CH_2Cl_2, 40 °C; (f) $(CH_2SH)_2$, $BF_3.Et_2O$, CH_2Cl_2.

Kitahara *et al* (2004)[52]

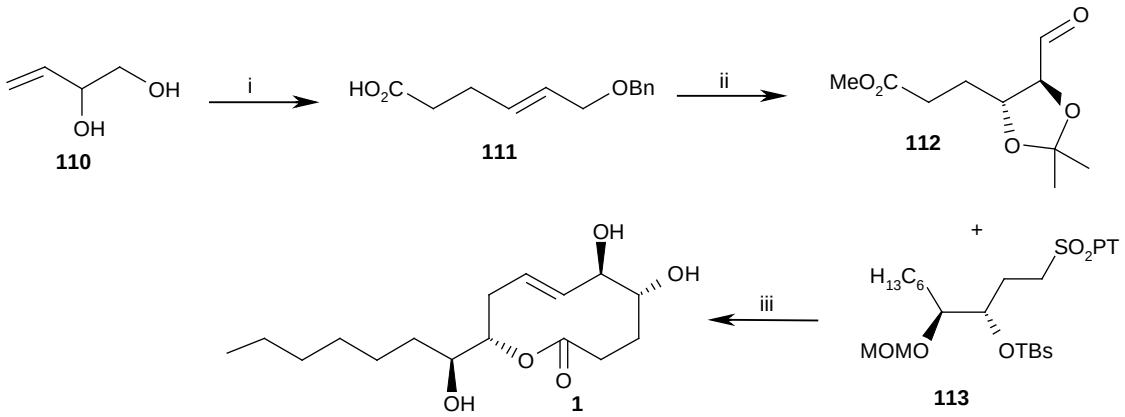
Kitahara and Ishigami accomplished the synthesis of (-)-microcarpalide employing the Julia olefination and macrolactonization. Synthesis of sulphone fragment required for the Julia olefination reaction was obtained starting from 3-decenol **104** as shown in the **Scheme 29**.



Scheme 29

Scheme 29: *Reagents and conditions:* (i) (a) PMBCl, NaH, TBAB, THF, reflux; (b) AD-mix-α, t-BuOH, H_2O; (ii) (a) DDQ, CH_2Cl_2; (b) MOMCl, DIPEA, CH_2Cl_2; (c) AcOH, H_2O, THF; (d) PTSH, PPh_3, DIAD, THF; (e) $(NH_4)_6Mo_7O_{24}.4H_2O$, EtOH; (f) TBSOTf, 2,6-lutidine, CH_2Cl_2.

As depicted in the **Scheme 30**, the synthesis of aldehyde fragment started from diol **110**. Sharpless asymmetric dihydroxylation reaction of acid **111** furnished the corresponding diol in 60 % ee. After having the key coupling partners **112** and **113** in hand Julia olefination reaction was employed for the formation of trans olefin, followed by Yamaguchi protocol for the ring closure lactonisation and the deprotection led to the formation of microcarpalide **1.**



Scheme 30

Scheme 30: *Reagents and conditions*: (i) (a) BnBr, NaH, TBAI, THF; (b) $MeC(OMe)_3$, $EtCO_2H$, 140 °C; (c) LiOH, THF, H_2O; ii) (a) AD-mix-β, t-BuOH, H_2O; (b) 2,2-DMP, HCl, acetone; (c) H_2, Pd/C, *i*-PrOH; (d) 4-MeO-TEMPO, KBr, NaOCl, $NaHCO_3$, CH_2Cl_2; iii) (a) KHMDS, 18-Crown-6, -108 °C; (b) TBAF, THF; (c) LiOH, THF; (d) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, DMAP, C_6H_6; (e) $BF_3.Et_2O$, $(CH_2SH)_2$, CH_2Cl_2.

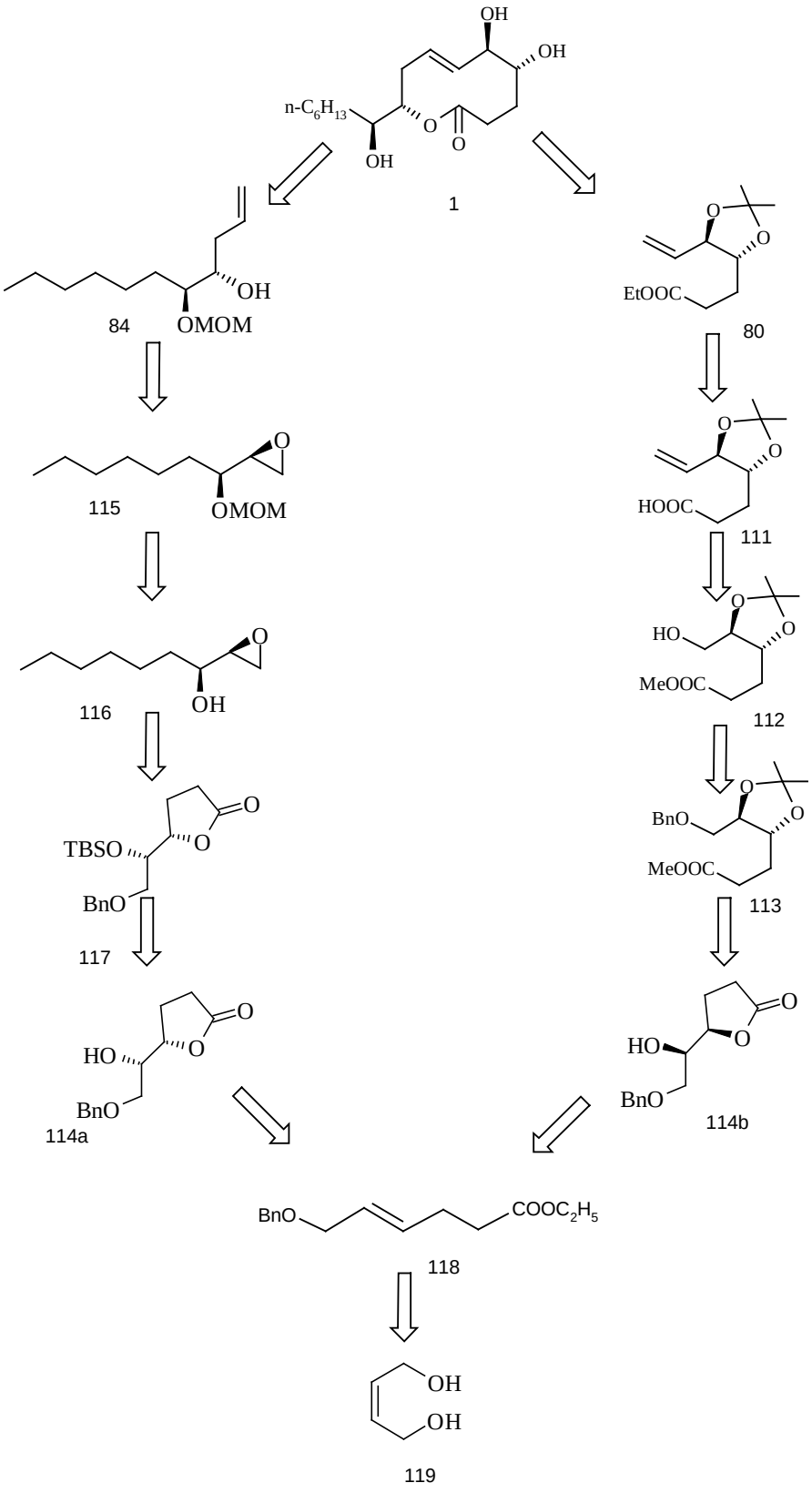
Present Work:

Microcarpalide acts as a strong microfilament disrupting agent and shows weak cytotoxicity to mammalian cells. Most of the syntheses of microcarpalide described earlier have used chiral precursors, chiral auxiliaries (or) involve a large number of steps (or) costly chiral materials. Hence, a practical route for the construction of this molecule is still desirable. With the completion of the synthesis of molecules described in the earlier chapters employing Sharpless asymmetric dihydroxylation, we found that the hydroxy lactones **114a** & **114b** are the versatile intermediates for the synthesis of many biologically active compounds. Using these versatile intermediates we planned to develop a new synthesis of microcarpalide.

Our retro synthetic analysis posited a macrocyclization by way of a ring closing metathesis to form the olefin (**Scheme 12**). This would allow for a simple esterification as the fragment coupling event and breaks the target into two fragments **84** and **80**. Thus the key fragment **84** would be synthesized either by opening of epoxide **115** with vinyl magnesium bromide (or) in two step process by lithium acetalide opening followed by reduction of acetelinic compound with lindlar's catalyst. The MOM epoxide **115** would be obtained simply by protection of hydroxy epoxide **116**. A careful observation revealed that the epoxide **116** could be obtained from hydroxy lactone **114a** by a series of transformations.

Fragment **80** would be synthesized from compound **111** by simple ester hydrolysis, which in turn was obtained from compound **113**. Compound **113** could be obtained by acetonide mediated opening of hydroxy lactone **114b**.

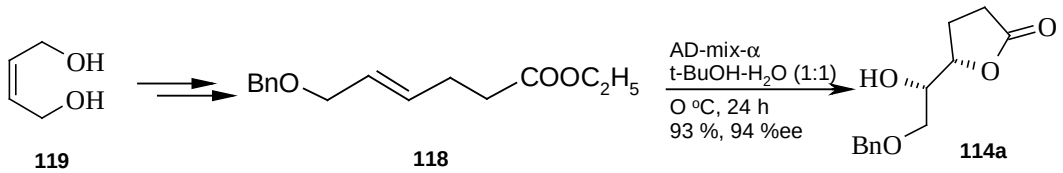
The key intermediates in our synthesis the hydroxylactones **114a** and **114b** were obtained from commercially available *cis*-2-butene-1, 4-diol by a series of reactions discussed in the earlier chapters.



Scheme 31: Retrosynthesis

Synthesis of Fragment 84:

Retro synthetic analysis outlined in **Scheme 31** identified compound **114a** as one of the potential synthetic intermediate for the construction of fragment **84**. The synthesis began with commercially available *cis*-2-butene-1, 4-diol (**119**), which was converted into β, γ-unsaturated ester **118**. The Sharpless asymmetric dihydroxylation of β, γ-unsaturated ester **118** using $(DHQ)_2PHAL$ as the chiral ligand and catalytic OsO_4 gave the hydroxy lactone **114a** in 94 % yield. The enantiopurity of the hydroxylactone was estimated to be in excess of 94 % using chiral HPLC analysis. (Chiralcel OD, 80:20, hexane:^{i}PrOH, 1 mL /min, 254 nm).

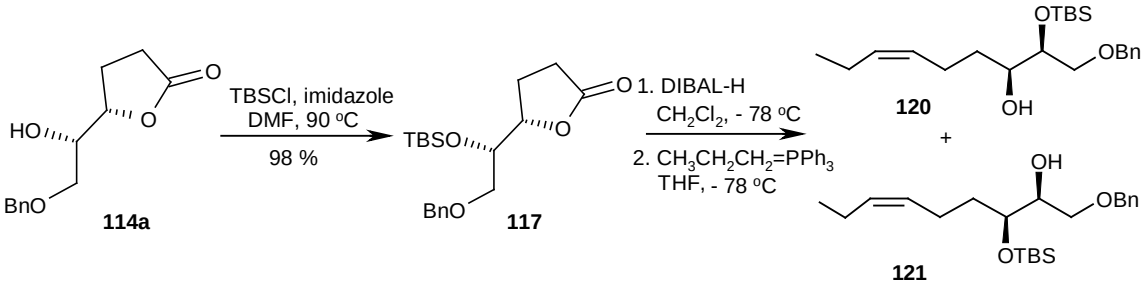


119 **118** **114a**

Scheme 32

Treatment of hydroxy lactone **114a** with TBSCl, imidazole in anhydrous DMF at 80 ^{o}C for 24 h smoothly delivered the TBS protected compound **117**. In the IR spectrum hydroxyl absorption was absent indicating the conversion of OH to its silyl derivative. In the ^{1}H-NMR spectrum signals corresponding to TBS group was observed at δ 0.09, 0.10 and at δ 0.89. The ^{13}C-NMR data and elemental analysis data were in good agreement with the proposed structure.

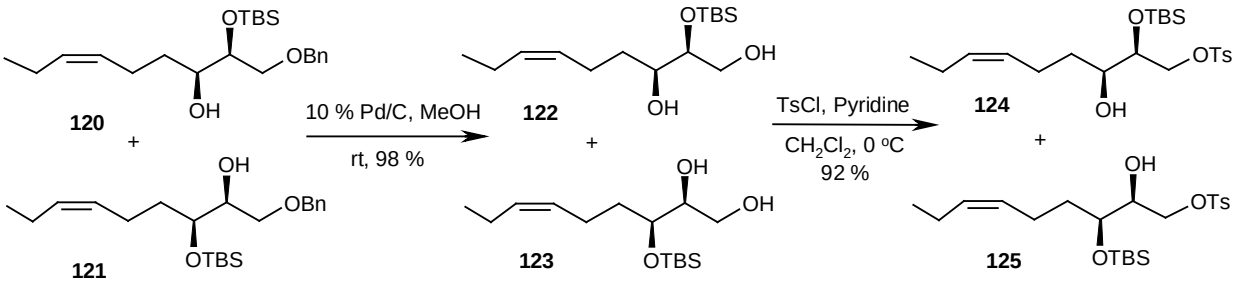
Having the compound **117** in hand, our next concern was to reduce the lactone into lactol and subsequent three-carbon homologation. Accordingly, the lactone **117** was reduced using 1.6 M DIBAL-H at – 78 ^{o}C to deliver the crude lactol, which on reaction with propylenetriphenyl phosphorane gave the mixture of compound **120** and **121** in almost 1:1 ratio, due to the TBS group migration, as an inseparable mixture. In the IR spectrum the hydroxyl absorption was observed at 3469 cm^{-1}. In the ^{1}H-NMR spectrum signals corresponding to olefinic protons were observed at δ 5.26-5.30 as multiplet. The ^{13}C-NMR spectrum showed disappearance of carbonyl resonance. The ^{13}C-NMR spectrum also confirmed the presence of two compounds **120** and **121** in almost equal ratio and all the data were in good agreement with the proposed structures.



Scheme 33

In the Wittig reaction use of different bases like LiHMDS, NaHMDS, ^{t}BuOK also resulted in the formation of products **120** and **121** as a mixture in almost the same ratio. Since this TBS group was to be removed at later stages and was not expected to create problem in our synthesis, we proceeded further with this mixture.

Hydrogenation of the mixure of **120** and **121** using 10 % Pd/C in MeOH under an atmosphere of H_2 and at room temperature delivered the mixture of diols **122** and **123**. In the ^{1}H-NMR spectrum disappearance of benzylic and olefinic protons was observed. The ^{1}H-NMR, analysis data is in good agreement with the proposed structure.

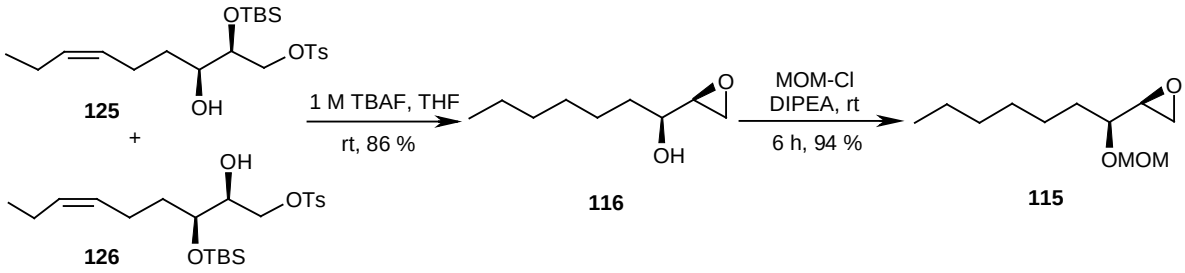


Scheme 34

Having the mixture of compounds **122** and **123** in hand, our immediate concern was to convert this mixture into epoxy alcohol **116**. Thus selective protection of the primary hydroxyl was achieved by using tosyl chloride and pyridine in anhydrous CH_2Cl_2 at 0 ^{o}C for 24 h in 92 % yield. The ^{1}H-NMR of **124** and **125** showed aryl methyl group at 2.46 (singlet) and aromatic protons at δ 7.31 and δ 7.81 as doublets (J = 8.27). The TBS deprotection with

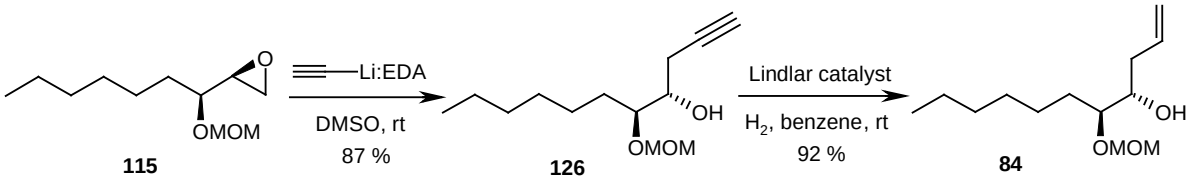
1M TBAF solution in anhydrous THF led to *in situ* epoxidation in one pot. In the ^{1}H-NMR spectrum disappearance of the signals corresponding to the TBS and tosyl group were observed. The characteristic resonance's due to the terminal epoxy protons were observed at δ 2.70 (double-doublet, J = 4.93, 2.78 Hz), δ 2.80 (double-doublet, J = 4.93, 4.17 Hz), and at δ 2.96 as a double-triplet J = 6.77, 2.78 Hz. The elemental analysis data and ^{13}C-NMR data were in good agreement with the structure **116**.

Next the free hydroxyl group of **116** was protected as its MOM ether **115** using MOMCl and DIPEA in anhydrous CH_2Cl_2 for 6 h. In the IR spectrum of **115** absence of hydroxyl absorption was observed. In the ^{1}H-NMR spectrum, appearance of singlet at δ 3.36 integrates for three protons and at δ 4.62 doublet, J = 6.6 Hz and at δ 4.64 doublet, J = 6.65 Hz integrating each for one proton indicated the formation of MOM-ether **115**. The ^{1}H-NMR, ^{13}C-NMR, elemental analysis were in accordance with the structure **115**.



Scheme 35

As ring opening reaction of oxirane **115** with vinyl magnesium bromide gave the problem, it was decided to make the fragment **84** by two step process. Accordingly, treatment of oxirane **115** with lithium acetylide-EDA complex[53] in anhydrous DMSO at room temperature smoothly delivered the acetylide **126** in 87 % yield. In the IR spectrum, hydroxyl absorption at 3444 cm^{-1} was observed. In the ^{1}H-NMR spectrum triplet at δ 2.07 (J = 2.65) was attributed to acetylenic proton while propargylic methylene protons resonated as doublet of double doublet at δ 2.48.

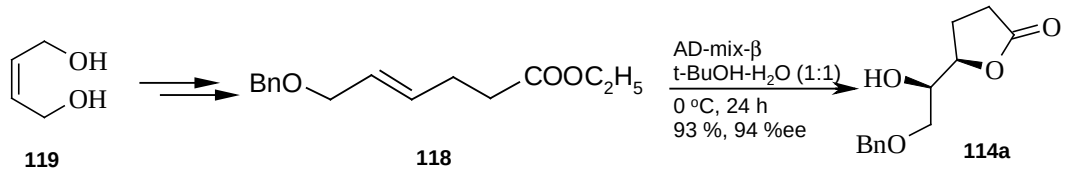


Scheme 36

Partial hydrogenation of the triple bond of **126** was carried out by hydrogenation using Lindlar's catalyst at normal pressure and temperature for 0.5 h to deliver the key fragment **84** in excellent yield (92 %). In the ^{1}H-NMR spectrum of **126**, the signals corresponds to olefinic protons were observed at δ 5.06, 5.12 and δ 5.18 as multiplets. The ^{13}C-NMR spectrum indicated peaks at δ 117.2, δ 134.9 for olefinic protons.^{13}C-NMR, ^{1}H-NMR and elemental analysis data were in good agreement with the structure **84**.

Synthesis of Fragment 80:

Construction of acid fragment **80** began with **114b**, the antipode of **114a** by the dimethoxy propane mediated ring opening of hydroxylactone **114b**, which in turn was obtained from the β, δ–unsaturated ester **118** by Sharpless asymmetric dihydroxylation using $(DHQD)_2PHAL$ as chiral ligand and catalytic OsO_4 in 94 % yield. The enantiopurity of the hydroxylactone was estimated to be in excess of 93 % using chiral HPLC analysis. (Chiralcel OD, 80:20, hexane:^{i}PrOH, 0.5 mL /min, 254 nm).

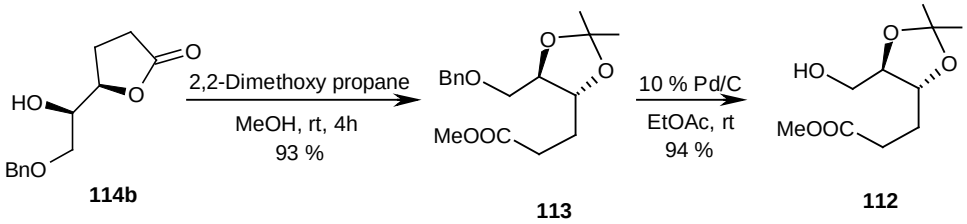


119 **118** **114a**

Scheme 37

Thus hydroxylactone **114b** on reaction with 2, 2-dimethoxy propane in anhydrous MeOH in presence of catalytic amount of *p*-TSA smoothly delivered the acetonide ester **113** in 94 % yield. The IR spectrum indicates the absence of hydroxyl absorption and presence of ester carbonyl absorption at 1739 cm^{-1}. In the ^{1}H-NMR spectrum signals at δ 1.38, 1.40 and at δ 3.67 each integrates for three protons corresponds to the acetonide and methyl ester protons was observed. The ^{13}C-NMR, elemental analysis were in accordance with the structure **113**. The deprotection of benzyl group of **113** was achieved by subjecting compound **113** to hydrogenolysis in ethyl acetate in presence of 10 % Pd/C under normal pressure and temperature to deliver the debenzylated compound **112** in 94 % yield. In the IR spectrun

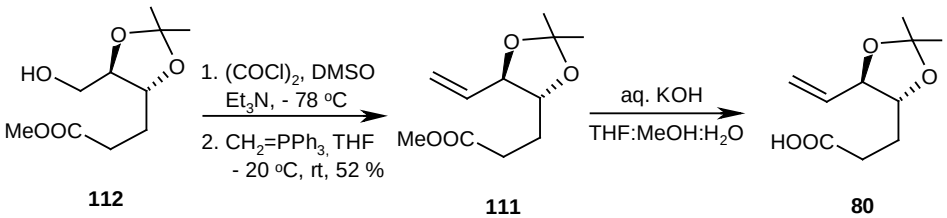
hydroxyl absorption was observed at 3437 cm^{-1}. ^{1}H-NMR, ^{13}C-NMR, analysis data were in good agreement with the structure **112**.



114b **113** **112**

Scheme 38

Having the compound **112** in hand, our next concern was to oxidize the hydroxyl function to aldehyde and subsequent one carbon Wittig reaction and finally the ester hydrolysis. The oxidation of hydroxyl ester **112** was achieved by using oxaloyl chloride and DMSO at – 78 ^{o}C for 45 min to deliver the crude aldehyde[54] which was immediately subjected to Wittig reaction with methylene triphenyl phosphorane in anhydrous THF at –20 ^{o}C to furnish the olefinic ester **111**. In the ^{1}H-NMR spectrum the proton signals corresponding to olefinic region was observed at δ 5.24 (d, *J* = 10.20, 1H), at δ 5.32 (d, *J* = 16.84, 1H) and at δ 5.74 (ddd, *J* = 16.84, 10.20, 7.26, 1H). The analysis and ^{13}C-NMR values are in good agreement with the proposed structure **111**.



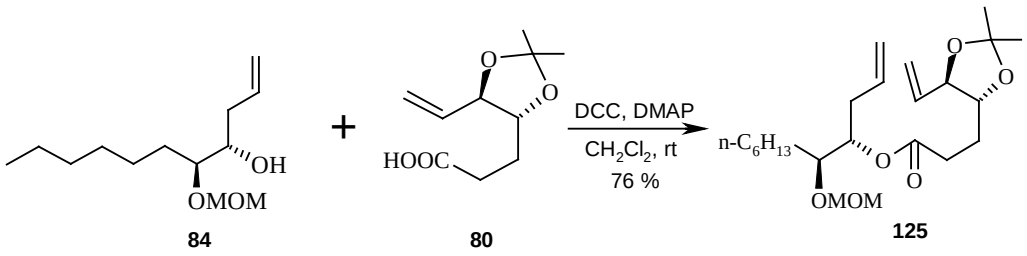
112 **111** **80**

Scheme 39

Finally hydrolysis of methyl ester **111** with KOH in THF: MeOH: H_2O (2:2:1) afforded the desired acid fragment **80**. In the ^{1}H-NMR spectrum disappearance of peak corresponds to the methyl ester group was observed. ^{1}H-NMR, ^{13}C-NMR, elemental analysis data were in good agreement with the literature data.

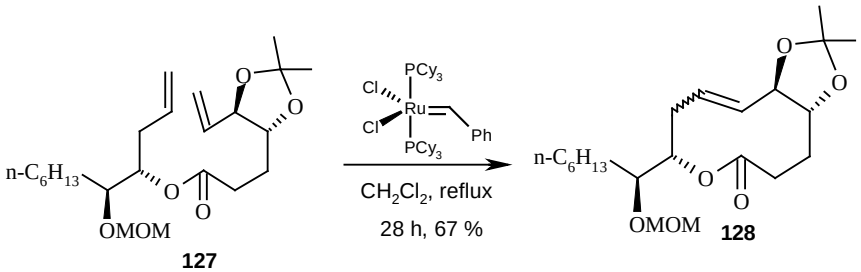
Coupling reaction between Fragment 84 and 80:

Having accomplished the synthesis of both the advanced fragments **84** and **80**, it remained to couple the two fragments and achieve the crucial macrocyclization using RCM. The coupling reaction of fragment **84** and **80** was performed by using DCC in the presence of catalytic DMAP in anhydrous CH_2Cl_2 for 18 h gave the ester **127** in 76 % yield. In the IR spectrum ester carbonyl absorption was observed at 1744 cm^{-1}. The ^{1}H-NMR, ^{13}C-NMR spectra and elemental analysis data were in good agreement with the literature data. The $[\alpha]_D$ + 4.1 (*c* = 1, $CHCl_3$) obtained for **127** is in accordance with the reported value. $[\alpha]_D$ + 4.2 (*c* = 1, $CHCl_3$).



Scheme 40

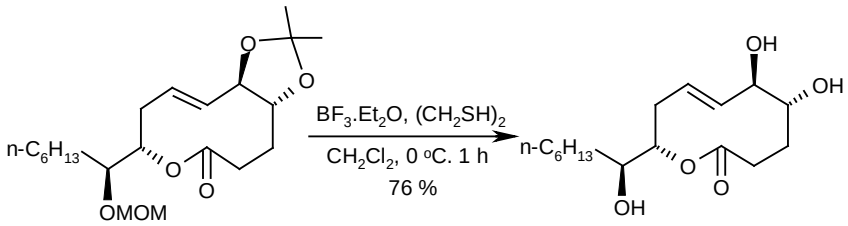
Ring closing metathesis reaction of **127** with Grubb's first generation catalyst (Cl_2Pcy_3Ru=CHPh) in highly diluted degassed CH_2Cl_2 under reflux for 28 h provided the ten-membered lactones as a mixture of 2:1 *E*/*Z* mixture from which the *E*-isomer was isolated by means of column chromatography on silica gel. The ^{1}H-NMR spectrum matched well with the reported spectral data by Marco and co-workers. The ^{13}C-NMR, elemental analysis data were in good agreement with the literature values. The $[\alpha]_D$ – 17.6 (c = 0.5, $CHCl_3$) is in accordance with the reported value. – 18.1 (c = 0.6, $CHCl_3$).



Scheme 41

Removal of protecting groups

Treatment of *E*-**128** with $BF_3.OEt_2$, ethane dithiol at 0 ^oC resulted in the simultaneous removal of both the acetonide and MOM groups, affording a single product whose spectral data matched with those reported by Hemscheidt *et al*[12c] for the natural product **1**. The $[\alpha]_D$ – 22.3 (c = 0.4, MeOH) is in accordance with the reported value. – 22 (c = 0.67, MeOH).



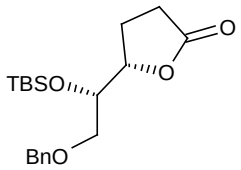
128 **1**

Scheme 46

Conclusion:

In summary, total synthesis of the microfilament disrupting agent microcarpalide (**1**), a secondary metabolite produced by an endophytic fungus, has been accomplished. Formation of the required 10-membered lactone was achieved by using RCM. The approach described here is highly convergent, in which and the two key fragments were obtained from the same starting material *cis*-2-butene-1, 4-diol. Finally global deprotection of protective groups was achieved by employing reported conditions, thus completing the total synthesis of microcarpalide.

Experimental



6-Benzyloxy-5-(*tert*-butyldimethylsilyloxy)-2,3-dideoxy-L-threohexano-1,4-lactone (117)

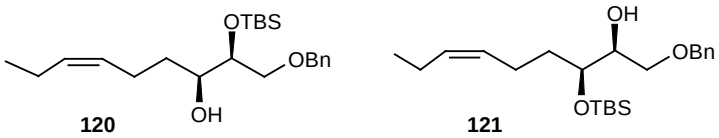
TBDMSCl (0.95 g, 6.98 mmol) was added to a mixture of **114a** (1.5 g, 6.35 mmol) and imidazole (0.65 g, 9.53 mmol) in anhydrous DMF (15 mL) and stirred at 90 ^{o}C for 24 h. After completion of the reaction, the reaction mixture was diluted with water, extracted with EtOAc (3 x 20 mL). The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc-light petroleum (1:4) as an eluent to afford **117** (2.17 g, 98 %) as a colourless syrup.

Appearance	:	Colourless Syrup
Molecular Formula	**:**	**$C_{19}H_{30}O_4Si$**
Yield	**:**	**98 %.**
$[\alpha]_D$	**:**	**+ 49.82, (*c* = 1, $CHCl_3$)**
IR ($CHCl_3$, cm^{-1})	**:**	**1779, 1175, 777**
^{1}H NMR ($CDCl_{34}$, 200MHz)	**:**	**δ 0.09 (s, 3H), 0.10 (s, 3H), 0.89 (s, 9H), 2.22-2.54 (m, 4H), 3.56 (m, 2H), 3.85 (m, 1H), 4.55 (m, 2H), 4.75 (ddd, *J* = 7.83, 5.48, 2.74 Hz, 1H), 7.32-7.37 (m, 5H).**
^{13}C NMR	**:**	**δ -5.1, -4.7, 17.8, 23.3, 25.5, 28.1, 70.1, 73.2, 73.3, 79.8,**

($CDCl_3$, 50MHz) **127.4, 128.2, 137.8, 176.9.**

Elemental Analysis : Analysis calcd. for $C_{19}H_{30}O_4Si$: C, 65.10; H, 8.62. Found: C, 65.24; H, 8.81.

(2*S*, 3*S*, 6*Z*)-1-Benzyloxy-2-(*tert*-butyldimethylsilyloxy)-3-hydroxy-6-nonene (120) and



120 **121**

(2*S*, 3*S*, 6*Z*)-1-Benzyloxy-3-(*tert*-butyldimethylsilyloxy)-2-hydroxy-6-nonene (121).

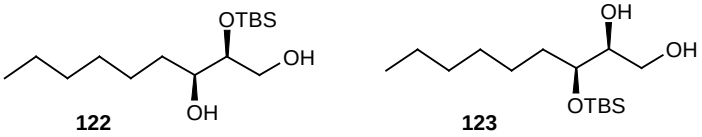
To a solution of **117** (2.08 g, 5.95 mmol) in anhydrous CH_2Cl_2 (25 mL) was added 1.6 M DIBAL-H solution in toluene (4.1 mL, 6.54 mmol) at – 78 ^oC . After stirring for 1 h at –78 ^oC absolute MeOH (4 mL) was added to the reaction mixture and was allowed to attain the room temperature. The reaction mixture was diluted with water, extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. and the crude lactol was used as such for the next reaction.

To a suspension of *n*-propyl (triphenyl) phosphonium bromide (6.87 g, 17.85 mmol) in anhydrous THF (15 mL) was added 1.6 M BuLi in hexane (7.5 mL, 11.9 mmol) at –20 ^oC under nitrogen atmosphere, and the mixture was allowed to warm to room temperature. After being stirred for further 40 min at room temperature the reaction mixture was cooled to –78 ^oC and a solution of the above crude lactol in anhydrous THF was added dropwise and continued the stirring for 1 h at the same temperature. The reaction mixture was quenched with sat. NH_4Cl solution and poured in ether and stirred for 5 min and then filtered through a short pad of celite. After evaporation of the solvent the residue was purified by silica gel column chromatography using EtOAc-light petroleum (2:8) as an eluent to afford **120 &121** (1:1)(1.61 g, 72 %) as colourless oil.

Appearance	**:**	**Colourless oil**
Molecular Formula	**:**	**$C_{22}H_{38}O_3Si$**
Yield	**:**	**72 %.**
IR ($CHCl_3$, cm^{-1})	**:**	**3469, 2956, 1092, 775**
^1H NMR ($CDCl_3$, 200MHz)	**:**	**δ 0.08 (m, 6H), 0.88 (m, 12H), 1.49-2.38 (m, 7H), 3.48-3.76 (m, 4H), 4.52 (d, *J* = 4.70 Hz, 2H), 5.38 (m, 2H), 7.33-7.39 (m, 5H).**
Elemental Analysis	**:**	Analysis calcd. for $C_{19}H_{30}O_4Si$: C, 69.79; H, 10.11. Found: C, 69.74; H, 10.26.

(2*S*, 3*S*)-2-(*tert*-butyldimethylsilyloxy)-nonane-1,3-diol (122) and

(2*S*, 3*S*)-3-(*tert*-butyldimethylsilyloxy)-nonane-1,2-diol (123).



122 **123**

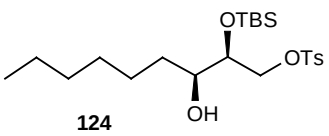
To the mixture of **121** and **122** (1.56 g, 4.12 mmol) in MeOH (15 mL) was added 10 % Pd/C (0.05 g) and the mixture was degassed with argon and flushed with H_2 for 5 min. After stirring under an atmosphere of H_2 for 6 h at room temperature, the reaction mixture was filtered through a pad of celite and the solvent was concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc-light petroleum (1:2) as an eluent to afford **122 &123** (1.14 g, 96 %) as colourless syrup.

Appearance	**:**	**Colourless Syrup**
Molecular Formula	**:**	**$C_{15}H_{34}O_3Si$**
Yield	**:**	**96 %.**
IR ($CHCl_3$, cm^{-1})	**:**	**3438 cm^{-1}**
^1H NMR	**:**	**0.09 (m, 6H), 0.9 (m, 12H), 1.27-1.60 (m, 11H), 2.42**

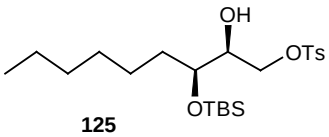
($CDCl_3$, 200MHz) **(broad, 1H), 3.58-3.68 (m, 4H).**

Elemental Analysis : Analysis calcd. for $C_{15}H_{34}O_3Si$: C, 62.01; H, 11.79. Found: C, 62.12; H, 11.66.

(2*S*, 3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-hydroxy-(4-methyl)-1-benzene sulfonate (124) and (2*S*, 3*S*)-3-(*tert*-butyldimethylsilyloxy)-2-hydroxy-(4-methyl)-1-benzene sulfonate (124)



124



125

To the mixture of diols **122 &123** (1.05 g, 3.62 mmol) in anhydrous CH_2Cl_2 (15 mL) were added pyridine (0.58 mL, 7.24 mmol) and TsCl (0.72 g, 3.80 mmol) at 0 ^oC and stirred for 24 h at same temperature. After completion of the reaction, the reaction mixture was quenched with water, washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc-light petroleum (2:8) as an eluent to afford mixture of **123 &124** (1.47 g, 92 %) as colourless oil.

Appearance : **Colourless oil**

Molecular Formula : **$C_{22}H_{40}SO_5Si$**

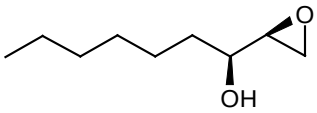
Yield : **92 %.**

B. P. : **Colourless Oil.**

^{1}H NMR ($CDCl_3$, 200MHz) : **0.02-0.09 (m, 6H), 0.81-0.86 (m, 12H), 1.26-1.61 (m, 10H), 2.46 (s, 3H), 3.31-3.42 (m, 3H), 3.71-3.98 (m, 1H), 4.42-4.56 (m, 1H), 7.37 (d, *J* = 8.27, 2H), 7.81 (d, *J* = 8.27, 2H).**

Elemental Analysis : Analysis calcd. for $C_{22}H_{40}SO_5Si$: C, 59.42; H, 9.06; S, 7.20. Found: C, 59.62; H, 9.14, S, 7.16.

1-oxiranyl-heptan-1-ol (116)



To the mixture of tosylates **123 &124** (1.45 g, 3.26 mmol) in anhydrous THF was added 1M solution of TBAF in THF (4.89 mL, 4.89 mmol) at 0 ^oC and was stirred at room temperature for 6 h. After completion of the reaction, solvent was removed on rotavapour under reduced pressure and the resulted residue was purified by silica gel column chromatography using EtOAc-light petroleum (2:8) as an eluent afforded pure epoxide **116** (0.438 g, 86 %) as colourless syrup.

Appearance : **Colourless Syrup**

Molecular Formula : **$C_9H_{18}O_2$**

Yield : **86 %.**

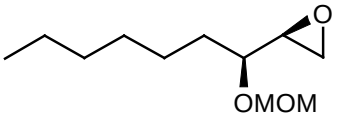
$[\alpha]_D$: **+ 4.07 (*c* = 2.1, $CHCl_3$)**

^{1}H NMR (CDCl$_3$, 200MHz) : **δ 0.86 (t, *J* = 6.78 Hz, 3H), 1.27-1.38 (m, 8H), 1.57 (m, 2H), 1.90 (broad, 1H), 2.70 (dd, *J* = 4.93, 2.78 Hz, 1H), 2.82 (dd, *J* = 4.93, 4.17 Hz, 1H), 2.96 (ddd, *J* = 6.77, 2.78 Hz, 1H), 3.42 (q, *J* = 5.69, 1H).**

^{13}C NMR (CDCl$_3$, 50MHz) : **δ 13.7, 22.4, 25.1, 29.1, 31.6, 34.1, 45.1, 55.5, 71.7.**

Elemental Analysis : Analysis calcd. for $C_9H_{18}O_2$: C, 68.31; H, 11.47. Found: C, 68.56; H, 11.41.

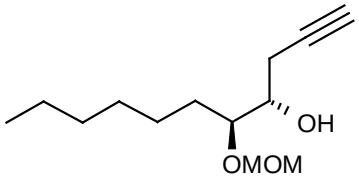
2-(1-methoxymethoxy-heptyl)-oxirane (115)



To a solution of **116** (0.8 g, 5.06 mmol) in anhydrous CH_2Cl_2 (15 mL) at 0 ^oC were added DIPEA (1.31 mL, 7.59 mmol), MOM-Cl (0.49 g, 6.07 mmol) and stirred for 6 h at room temperature. After completion of the reaction, the reaction mixture was diluted with water and extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude oily compound was purified by silica gel column chromatography using EtOAc-light petroleum ether (1:4) as an eluent to afford **115** (0.94 g, 94 %) as colourless syrup.

Appearance	**:**	**Colourless Syrup**
Molecular Formula	**:**	**$C_{11}H_{22}O_3$**
Yield	**:**	**92 %.**
IR ($CHCl_3$, cm^{-1})	**:**	**2941, 1615, 1132.**
$[\alpha]_D$	**:**	**- 63.61 (*c* = 1, $CHCl_3$).**
^{1}H NMR ($CDCl_3$ + CCl_4, 200MHz)	**:**	**δ 0.86 (t, *J* = 6.65 Hz, 3H), 1.26-1.34 (m, 8H), 1.52-1.62 (m, 2H), 2.48 (dd, *J* = 4.69, 2.74 Hz, 1H), 2.73 (t, *J* = 4.69 Hz, 1H), 2.92 (dt, *J* = 6.65, 2.74 Hz, 1H), 3.20 (q, *J* = 6.65 Hz, 1H), 3.36 (s, 3H), 4.62 (d, *J* = 6.66 Hz, 1H), 4.64 (d, *J* = 6.65 Hz, 1H).**
^{13}C NMR ($CDCl_3$ + CCl_4, 50MHz)	**:**	**δ 13.9, 22.5, 25.3, 29.2, 31.6, 32.2, 43.4, 54.5, 55.3, 77.8, 95.4.**
Elemental Analysis	**:**	Analysis calcd. for $C_{11}H_{22}O_3$: C, 65.31; H, 10.95. Found: C, 65.42; H, 10.84.

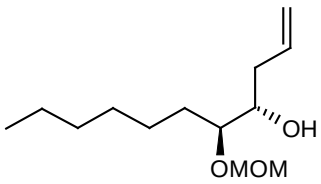
(4*S*, 5*S*)-4-Hydroxy-5-(2-methoxy methoxy)-undeca-1-yne (126)



To a solution of **115** (0.45 g, 2.22 mmol) in DMSO (3 mL) at 0 °C was added lithium acetylide-EDA complex (0.31 g, 3.34 mmol) in one portion. The reaction mixture was stirred at 0 °C for 30 min and over night at room temperature. The excess of reagent was quenched with sat. ammonium chloride and extracted with EtOAc, washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography by eluting with light petroleum ether: EtOAc (7:3) to afford **126** (0,44 g, 87 %) as colourless oil.

Appearance	:	**Colourless syrup**
Molecular Formula	:	**$C_{13}H_{24}O_3$**
Yield	:	**87 %.**
$[\alpha]_D$	:	**+ 41.35 (*c* = 1, $CHCl_3$).**
^{1}H NMR ($CDCl_3$, 200MHz)	:	δ **0.91 (t, *J* = 6.70 Hz, 3H), 1.31-1.38 (m, 8H), 1.56-1.68 (m, 2H), 2.07 (t, *J* = 2.65 Hz, 1H), 2.48 (ddd, 7.32, 4.67, 2.65 Hz, 2H), 3.01 (broad, 1H), 3.45 (s, 3H), 3.62 (m, 1H), 3.74 (m, 1H), 4.75 (m, 2H).**
^{13}C NMR ($CDCl_3$, 50MHz)	:	δ **13.9, 22.5, 23.5, 25.1, 29.2, 30.7, 31.6, 55.8, 70.1, 70.2, 80.7, 81.0, 96.9.**
Elemental Analysis	:	Analysis calcd. for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.52; H, 10.68.

(4*S*, 5*S*)-4-Hydroxy-5-(2-methoxy methoxy)-undeca-1-ene (84)

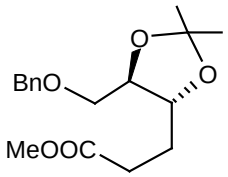


Compound **126** (0.4 g, 1.75 mmol), Lindlar catalyst (10 mg) and quinoline (cat) in benzene (10 mL) were stirred under hydrogen atmosphere at normal temerature and pressure

for 30 min. The catalyst was through a pad of celite and the solvent was concentrated under reduced pressure. The residue extracted with ethyl acetate (2 x 15 mL). The combined organic fractions were washed with 1N HCl, water, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with light petroleum ether: EtOAc (7:3) to give **84** (0.37 g, 92 %) as clear oil.

Appearance	:	**Colourless Syrup**
Molecular Formula	:	**$C_{13}H_{26}O_3$**
Yield	:	**92 %.**
$[\alpha]_D$	:	**+ 28.84 (*c* = 1, $CHCl_3$)**
^{1}H NMR ($CDCl_3$, 200MHz)	:	**δ 0.89 (t, *J* = 6.8 Hz, 3H), 1.22-1.38 (m, 8H), 1.46-1.62 (m, 2H), 2.12-2.39 (m, 2H), 2.71 (d, *J* = 4.0 Hz, -OH, 1H), 3.32-3.39 (m, 1H), 3.40 (s, 3H), 3.56 (m, 1H), 4.67 (s, 2H), 5.06 (m, 1H) 5.12 (m, 1H), 5.86 (m, 1H).**
^{13}C NMR ($CDCl_3$, 50MHz)	:	**δ 14.0, 22.5, 25.1, 29.3, 30.8, 31.7, 37.8, 55.7, 72.0, 82.4, 97.0, 117.2, 134.9 ppm.**
Elemental Analysis	:	Analysis calcd. for $C_{13}H_{26}O_3$: C, 67.78; H, 11.38. Found: C, 67.72; H, 11.14.

(4*R*, 5*R*)-6-Benzyloxy-4, 5-(isopropylidenedioxy)hexanoic acid methyl ester (113)

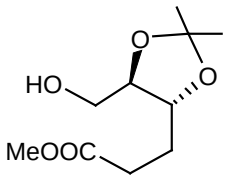


To a solution of **114b** (1.2 g, 5.08 mmol) in anhydrous MeOH (20 mL) was added 2, 2-dimethoxy propane (0.94 mL, 7.62 mmol), catalytic amount of *p*-TSA and stirred at room temperature for 4 h. After completion of the reaction the reaction mixture was concentrated under reduced pressure and the residue was extracted with EtOAc (2 x 25 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and

concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc-light petroleum (1:9) as an eluent to afford **113** (1.45 g, 93 %) as colourless syrup.

Appearance	:	**Colourless syrup**
Molecular Formula	:	**$C_{17}H_{24}O_5$**
Yield	:	**94 %.**
$[\alpha]_D$	:	**+ 20.33 (*c* = 1, $CHCl_3$)**
IR ($CHCl_3$, cm^{-1})	:	**1739, 1370, 1090.**
^{1}H NMR ($CDCl_3$, 200MHz)	:	**δ 1.38 (s, 3H), 1.40 (s, 3H), 1.76-2.04 (m, 2H), 2.34-2.62 (m, 2H), 3.58 (m, 2H), 3.67 (s, 3H), 3.84 (m, 2H), 4.58 (s, 2H), 7.33-7.38 (m, 5H).**
^{13}C NMR ($CDCl_3$, 50MHz)	:	**δ 26.8, 27.0, 28.1, 30.1, 51.2, 70.4, 73.3, 77.4, 79.5, 108.7, 127.4, 128.2, 137.9, 173.3.**
Elemental Analysis	:	Analysis calcd. for $C_{17}H_{24}O_5$: C, 59.98; H, 9.28. Found: C, 59.73; H, 9.42.

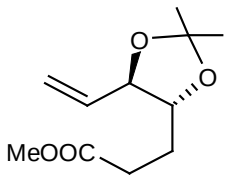
(4*R*, 5*R*)-6-Hydroxy-4, 5-(isopropylidenedioxy)hexanoic acid methyl ester (112)



To a solution of **113** (1.4 g, 4.54 mmol) in EtOAc was added 10 % Pd/C (0.04 g) and stirred for 4 h under H_2 atmosphere at normal temperature and pressure. The mixture was filtered through a pad of celite and the solvent was concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc-light petroleum (1:1) as an eluent to afford **112** (0.93 g, 94 %) as colourless syrup.

Appearance	:	**Colourless syrup**
Molecular Formula	:	**$C_{10}H_{18}O_5$**
Yield	:	**94 %.**
$[\alpha]_D$	:	**+ 23.6 (*c* = 1, $CHCl_3$)**
IR ($CHCl_3$, cm^{-1})	:	**3437, 1731, 1410.**
^1H NMR ($CDCl_3$ + CCl_4, 200MHz)	:	**δ 1.38 (s, 6H), 1.82-1.94 (m, 2H), 2.22 (broad, 1H), 2.42-2.52 (m, 2H), 3.62 (dd, *J* = 11.73, 2.94 Hz, 1H), 3.68 (s, 3H), 3.72-3.80 (m, 2H), 3.88 (dt, *J* = 11.0, 8.1, 2.93 Hz, 1H).**
^{13}C NMR ($CDCl_3$+CCl_4, 50MHz)	:	**δ 26.9, 27.1, 28.0, 30.2, 51.3, 61.9, 76.3, 81.1, 108.6, 173.3.**
Elemental Analysis	:	Analysis calcd. for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found: C, 55.32; H, 8.16.

(4*R*, 5*R*)-4,5-(Isopropylidenedioxy)hept-6-enoic acid methyl ester (111)



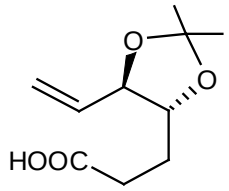
A solution of DMSO (0.88 mL, 12.36 mmol) in anhydrous CH_2Cl_2 (2 mL) was added dropwise to a solution of $(COCl)_2$ (0.54 mL, 6.18 mmol) in anhydrous CH_2Cl_2 (15 mL) under argon atmosphere at –78 ^oC. The mixture was stirred for 10 min and then a solution of **112** (0.9 g, 4.12 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise. After 45 min Et_3N (2.3 mL, 16.5 mmol) was added and then it was allowed to attain room temperature. The reaction mixture was diluted with water, extracted with CH_2Cl_2, washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give crude aldehyde, which was used as such for the next reaction.

To a suspension of methyl(triphenyl)phosphoniumiodide (5.0 g, 12.36 mmol) in anhydrous THF (15 mL) was added 1.6 M BuLi in hexane (5.16 mL, 8.25 mmol) at –20 ^oC under nitrogen atmosphere, and the mixture was allowed to attain room temperature. After

being stirred for further 40 min at room temperature the reaction mixture was re cooled to – 20 ^{o}C and a solution of crude aldehyde obtained above in anhydrous THF (18 mL) was added dropwise. The reaction mixture was stirred for 30 min at – 20 ^{o}C and then 2 h at room temperature. The reaction mixture was poured in ether and stirred for 5 min then filtered through a short pad of celite. After evaporation of the solvent the residue was purified by silica gel column chromatography using EtOAc-light petroleum ether (2:8) as an eluent to afford **111** (0.46 g, 52 %) as light yellow syrup.

Appearance	**:**	**Light yellow syrup**
Molecular Formula	**:**	**$C_{11}H_{18}O_4$**
Yield	**:**	**52 %.**
$[\alpha]_D$	**:**	**+ 0.5 (*c* = 1, $CHCl_3$)**
IR ($CHCl_3$, cm^{-1})	**:**	**1725, 1642.**
^{1}H NMR ($CDCl_3$ + CCl_4, 200MHz)	**:**	**1.33 (s, 6H), 1.74-2.02 (m, 2H), 2.32-2.42 (m, 2H), 3.62 (m, 4H), 3.93 (t, *J* = 6.4 Hz, 1H), 5.24 (d, *J* = 10.20 Hz, IH), 5.32 (d, *J* =16.84 Hz, 1H), 5.74 (ddd, *J* =16.84, 10.20, 7.26 1H).**
^{13}C NMR ($CDCl_3$+CCl_4, 50MHz)	**:**	**26.8, 26.9, 27.2, 30.7, 51.6, 79.8, 82.4, 108.9, 119.3, 135.0, 174.2.**
Elemental Analysis	**:**	Analysis calcd. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.46. Found: C, 61.42; H, 8.36.

(4*R*, 5*R*)-4, 5-(Isopropylidenedioxy)hept-6-enoic acid (80):

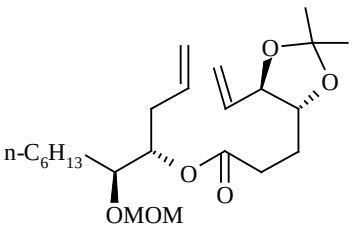


To a solution of **111** (0.4 g, 1.87 mmol) in 12 mL of THF-MeOH (1:1) was added added aqueous KOH (0.5 g in 3 mL water) and stirred at room temperature for 20 h. After

consumption of the starting material the mixture was poured in to a mixture of ether and water (30 mL, 1:1) and was then acidified to pH 4 by the addition of 2 N HCl. The aqueous layer was extracted with ether (3 x 20 mL), and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc-light petroleum (4:6) as an eluent to afford **80** (0.32 g, 87 %) as colourless syrup.

Appearance	:	**Colourless oil.**
Molecular Formula	:	**$C_{10}H_{16}O_4$**
Yield	:	**87 %.**
$[\alpha]_D$	:	**- 7.1 (*c* = 1, $CHCl_3$)**
IR ($CHCl_3$, cm^{-1})	:	**3418, 1706.**
^{1}H NMR ($CDCl_3$, 200MHz)	:	**δ 1.38 (s, 6H), 1.72-2.04 (m, 2H), 2.38-2.57 (m, 2H), 3.69 (dt, *J* = 8.2, 3.9 Hz, 1H), 3.97 (dd, *J* = 8.2, 7.2 Hz, 1H), 5.28 (ddd, *J* = 10.2, 1.5, 0.8 Hz, IH), 5.39 (ddd, *J* = 17.2, 1.5, 0.8 Hz, 1H), 5.79 (ddd, *J* = 17.2, 10.2, 7.3 Hz, 1H).**
^{13}C NMR ($CDCl_3$, 50MHz)	:	**δ 26.5, 26.9, 27.1, 30.4, 79.5, 82.4, 108.8, 119.2, 135.1, 178.6 ppm.**
Elemental Analysis	:	Analysis calcd. for $C_{10}H_{16}O_4$; C, 59.98; H, 8.05. Found: C, 59.72; H, 7.97.

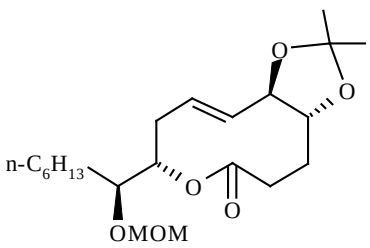
(4*R*, 5*R*)-4,5-(Isopropylidenedioxy)hept-6-enoicacid,
(1'*S*, 1''*S*)-1'-(1''-(2-methoxymethoxy)-3'-butenyl ester (127)



To a solution of compounds **84** (0.09g, 0.45 mmol), **80** (0.103, 0.45 mmol) and DMAP (5 mg) in anhydrous CH_2Cl_2 (2mL) was added DCC (0.093 g, 0.45 mmol). The reaction mixture was stirred at room temperature for 15 h, filtered and evaporated under reduced pressure to afford a residue, which on purification by silica gel column chromatography eluting with light petroleum: EtOAc (7:3) afforded **127** (0.14 g, 76 %) as colourless oil.

Appearance	**:**	**Colourless oil**
Molecular Formula	**:**	**$C_{23}H_{40}O_6$**
Yield	**:**	**76 %.**
$[\alpha]_D$	**:**	**+ 4.1 (*c* = 1, $CHCl_3$)**
IR ($CHCl_3$, cm^{-1})	**:**	**2926, 1744, 1240.**
^{1}H NMR ($CDCl_3$, 200MHz)	**:**	**0.89 (t, *J* = 6.9 Hz, 3H), 1.28-1.34 (m, 8H), 1.40 (s, 6H), 1.50 (m, 2H), 1.82 (m, 1H), 1.95 (m, 1H), 2.34-2.52 (m, 4H), 3.39 (s, 3H), 3.59 (m, 1H), 3.70 (td, *J* = 8.3, 3.4 Hz, 1H), 3.99 (t, *J* = 7.9 Hz, 1H), 4.69 (ABq, *J* = 3.4 Hz, 2H), 5.07 (m, 2H), 5.09 (dd, *J* = 17.6, 1.6 Hz, 1H), 5.26 (d, *J* = 10.4 Hz, 1H), 5.37 (d, *J* = 17.6 Hz, 1H), 5.77 (m, 2H).**
^{13}C NMR ($CDCl_3$, 50MHz)	**:**	**δ: 14.0, 22.5, 25.3, 26.8, 26.9, 27.2, 29.3, 30.5, 30.7, 31.7, 34.6, 55.8, 73.7, 78.1, 79.5, 82.4, 96.7, 108.8, 117.6, 118.9, 133.9, 135.2, 172.5 ppm.**
Elemental Analysis	**:**	Analysis calcd. for $C_{23}H_{40}O_6$; C, 66.95; H, 9.78. Found: C, 66.62; H, 10.04.

(5*R*, 6*R*, 7*E*, 10*S*)-10-[(1'*S*)-1'-(2-methoxymethoxy)-5,6-isopropylidenedioxy-3,4,5,6,9,10-

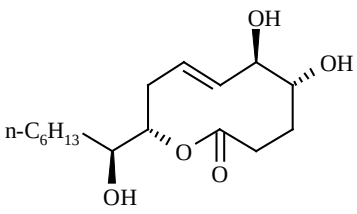


hexahydro-2*H*-oxecin-2-one (128)

To a solution of **127** (0.12 g, 0.29 mmol) in freshly distilled degassed anhydrous CH_2Cl_2 (120 mL) was added Grubb's first generation catalyst (48 mg, 0.058 mmol). The reaction mixture was refluxed for 28 h under an atmosphere of argon. After complete disappearance of the starting material, the solvent was concentrated on rotavapour under reduced pressure and the brown residue was purified by chromatography on silica gel using light petroleum ether:EtOAc (3:7) afforded pure **128** (0.074 g, 67 %) as colourless oil.

Appearance	**:**	**Colourless syrup**
Molecular Formula	**:**	**$C_{21}H_{36}O_6$**
Yield	**:**	**67 %.**
$[\alpha]_D$	**:**	**- 17.6 (*c* = 0.5, $CHCl_3$)**
IR ($CHCl_3$, cm^{-1})	**:**	**2927, 1731, 1032.**
^{1}H NMR ($CDCl_3$, 200MHz)	**:**	**0.89 (t, *J* = 7.0 Hz, 3H), 1.24-1.36 (m, 8H), 1.41 (s, 6H), 1.60 (m, 2H), 1.96-2.06 (m, 2H), 2.28-2.64 (m, 4H), 3.42 (s, 3H), 3.62 (m, 2H), 3.93 (t, *J* = 8.8 Hz, 1H), 4.69 (m, 2H), 4.95 (ddd, *J* = 8.8, 3.8, 2.5 Hz, 1H), 5.35 (dd, *J* = 15.8, 9.4 Hz, 1H), 5.78 (ddd, *J* = 15.8, 11.4, 4.7 Hz, 1H).**
^{13}C NMR ($CDCl_3$, 50MHz)	**:**	δ 14.0, 22.6, 25.3, 25.4, 26.9, 27.1, 29.4, 30.5, 30.8, 31.7, 34.2, 56.0, 73.6, 79.3, 79.8, 84.4, 96.5, 108.8, 129.4, 130.1, 171.7.
Elemental Analysis	**:**	Analysis calcd. for $C_{21}H_{36}O_6$; C, 65.59; H, 9.43. Found: C, 65.3; H, 9.32

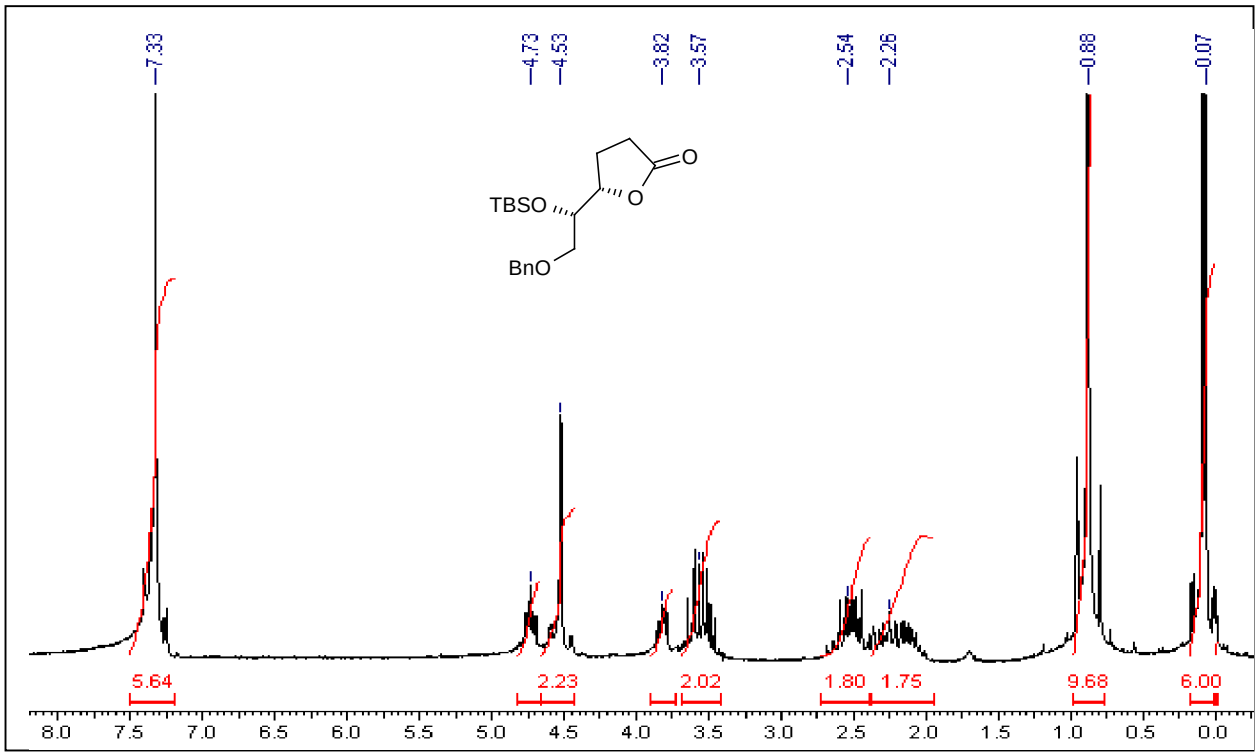
(5*R*, 6*R*, 7*E*, 10*S*)-5, 6-Dihydroxy-10-[(1'*S*)-1'-hydroxyheptyl]-3,4,5,6,9,10-hexahydro-



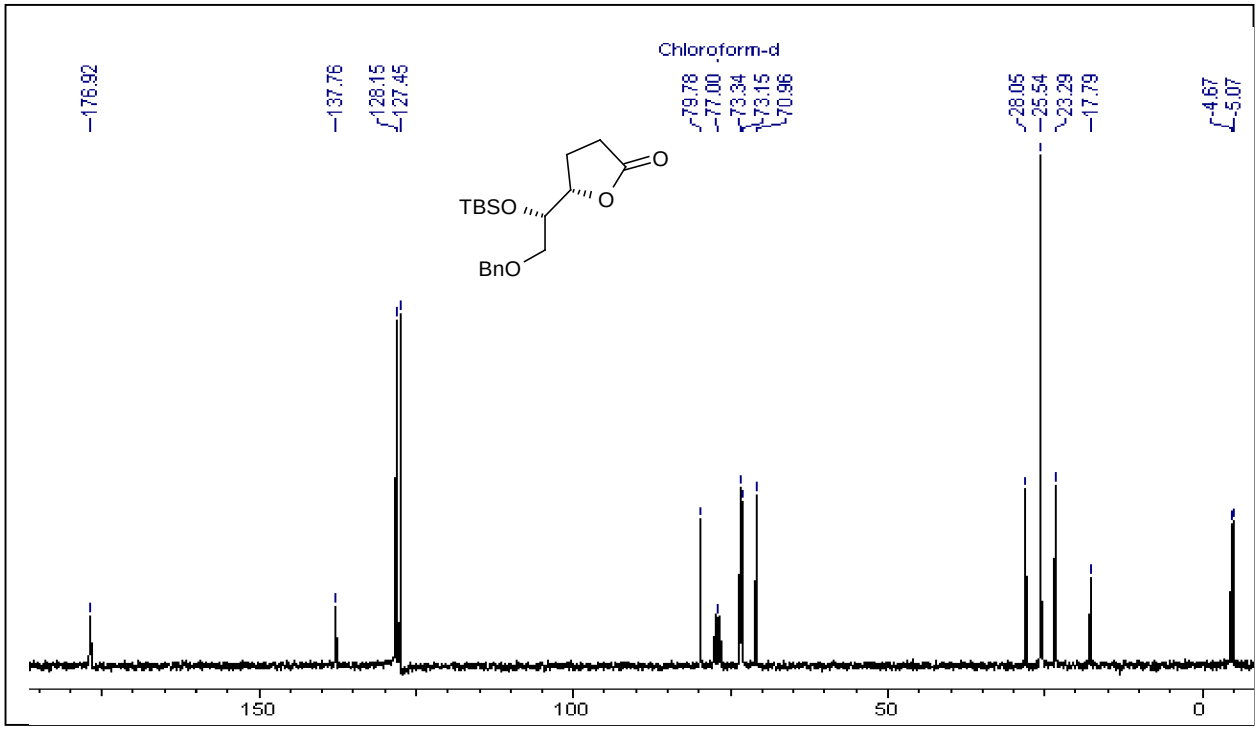
2*H*-oxecin-2-one. (Microcarpalide 1)

To a solution of **128** (0.065, 0.169 mmol) in anhydrous CH_2Cl_2 were added $BF_3.Et_2O$ (0.021 mL, 0.169 mmol) and ethane dithiol (0.06 mL, 0.676 mmol) at 0 ^oC under argon atmosphere. The reaction mixture was stirred at 0 ^oC for 1 h then quenched with sat. $NaHCO_3$ and extracted with ether (3 x 15 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc-light petroleum ether (9:1) as an eluent to afford pure **1** (0.05 g, 76 %) as colourless oil.

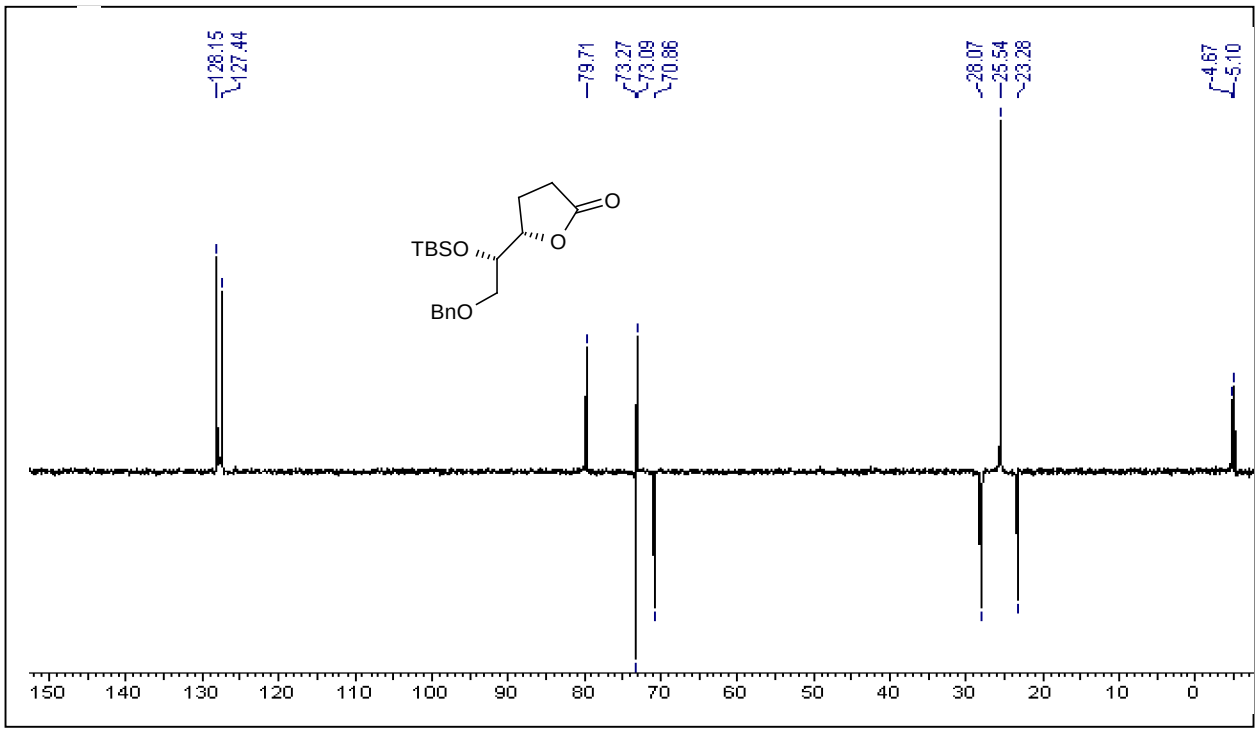
Appearance	**:**	**Colourless oil**
Molecular Formula		**$C_{16}H_{28}O_5$**
Yield	**:**	**76 %.**
$[\alpha]_D$	**:**	**- 22.3 (*c* = 0.4, MeOH)**
IR ($CHCl_3$, cm^{-1})	**:**	**3020, 2400, 1731, 757.**
^{1}H NMR (CD_3CN, 500MHz)	**:**	**δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.28–1.32 (m, 8H), 1.54–1.59 (m, 3H), 2.04 (ddd, *J* = 15.2, 10.6, 6.2 Hz, 1H), 2.27 (ddd, *J* = 14.7, 10.6, 1.4, 1H), 2.24–2.30 (m, 2H), 2.61 (dd, *J* = 14.7, 9.2 Hz, 1H), 3.38 (s, 3H), 3.54–3.56 (m, 2 H), 3.67–3.78 (m, 4H), 4.07 (br. d, *J* = 4.5 Hz, 1H), 4.47 (d, *J* = 11.9 Hz, 1H), 4.48 (d, *J* = 12.5 Hz, 1H), 4.54 (d, *J* = 11.9 Hz, 1H), 4.65 (d, *J* = 12.5 Hz, 1H), 4.78–4.81 (m, 2H), 5.15 (dt, *J* = 9.2, 4.6 Hz, , 1 H), 5.64 (dd, *J* = 15.8, 2.1 Hz, 1H), 5.64–5.73 (m, 1 H).**
^{13}C NMR (CD_3CN, 50MHz)	**:**	δ 14.0, 22.6, 25.0, 29.4, 31.2, 31.7, 36.1, 59.0, 67.4, 71.3, 71.5, 71.8, 78.2, 95.4, 126.5, 127.2, 127.5, 127.6, 128.3, 128.4, 131.7, 138.5, 138.8, 175.17.
Elemental Analysis	**:**	Analysis calcd. for $C_{16}H_{28}O_5$; C, 63.97; H, 9.40. Found: C, 64.12; H, 9.28.



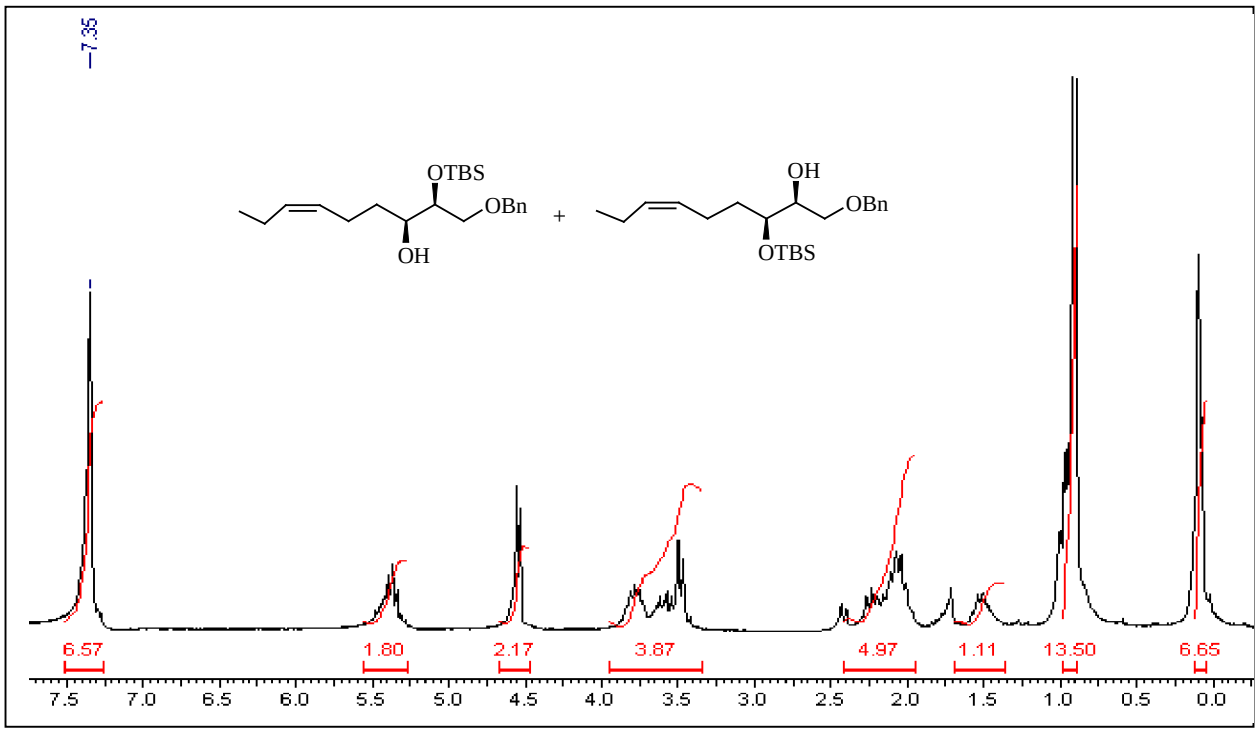
^{1}H NMR Spectrum of compound 117 in $CDCl_3$



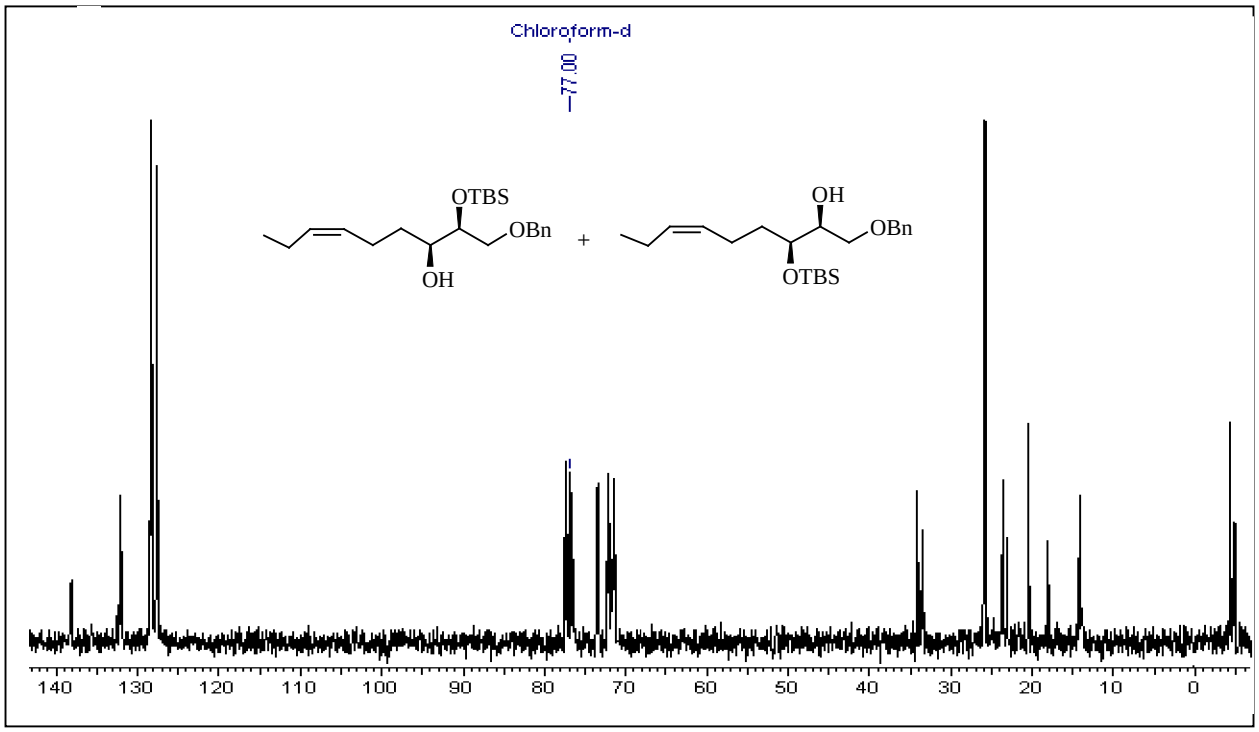
^{13}C NMR Spectrum of compound 117 in $CDCl_3$



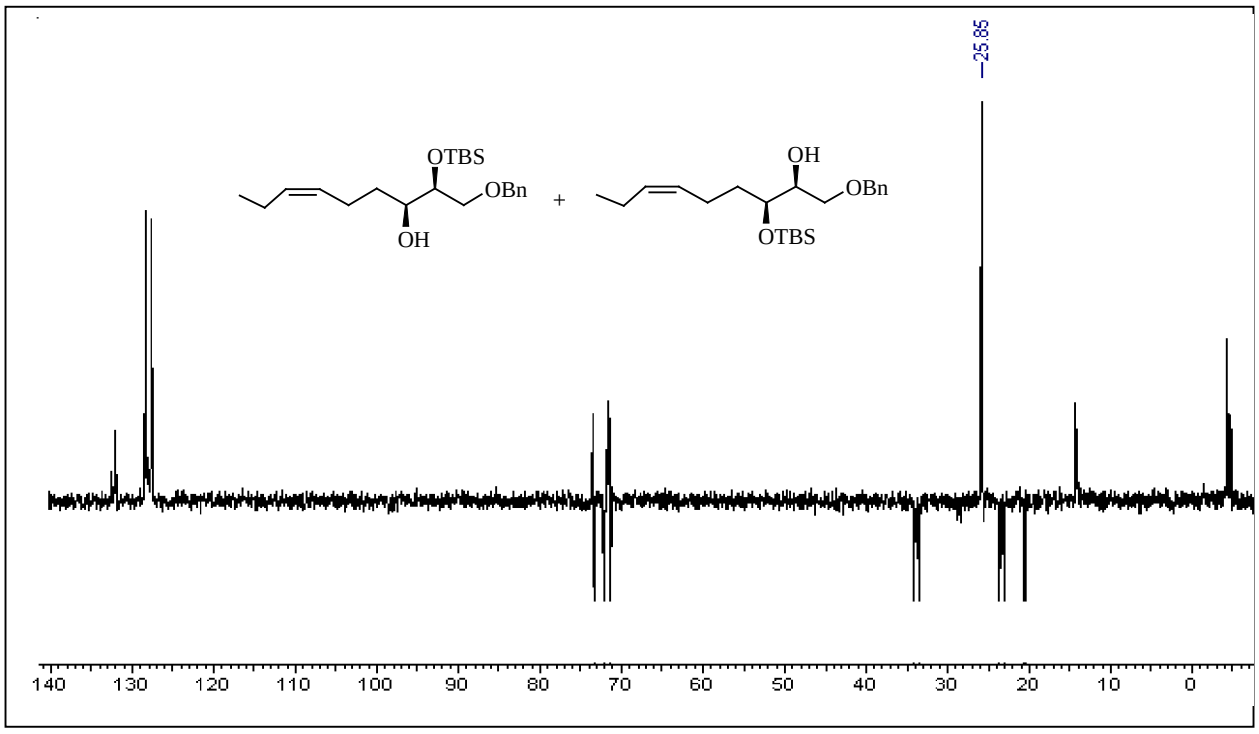
DEPT NMR Spectrum of compound 117 in $CDCl_3$



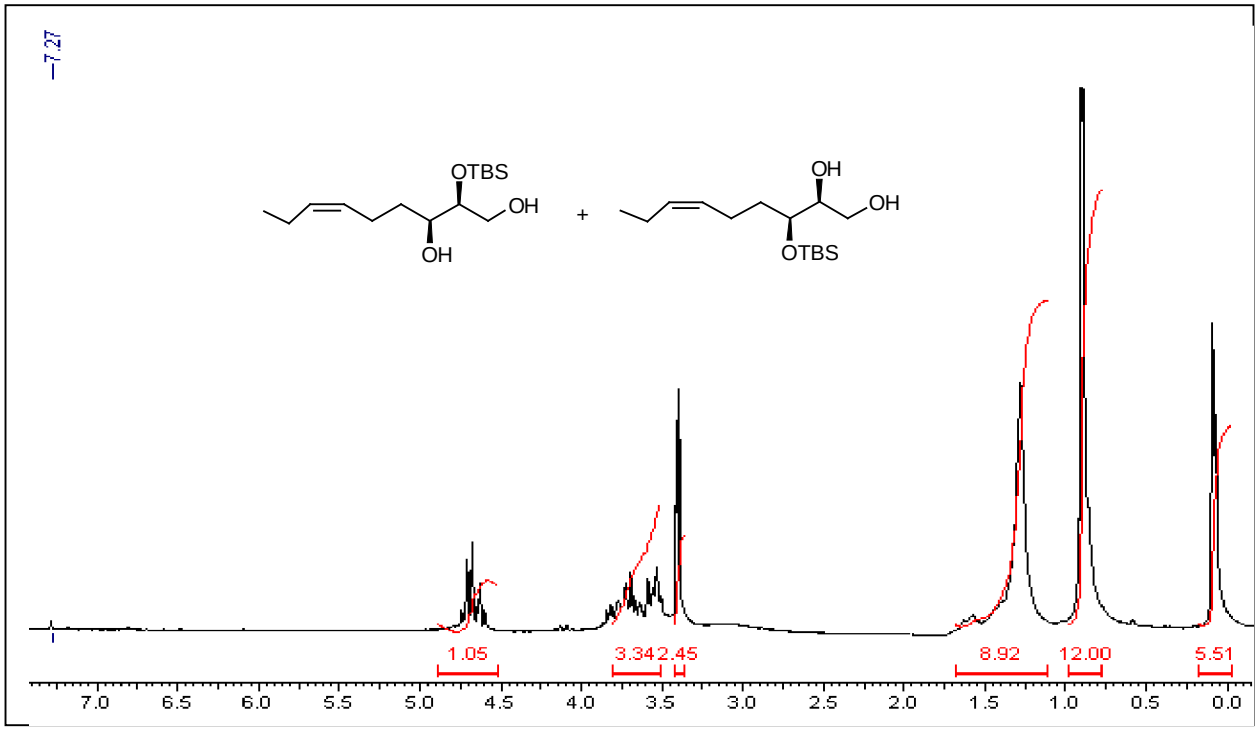
^{1}H NMR Spectrum of compound 120 & 121 in $CDCl_3$



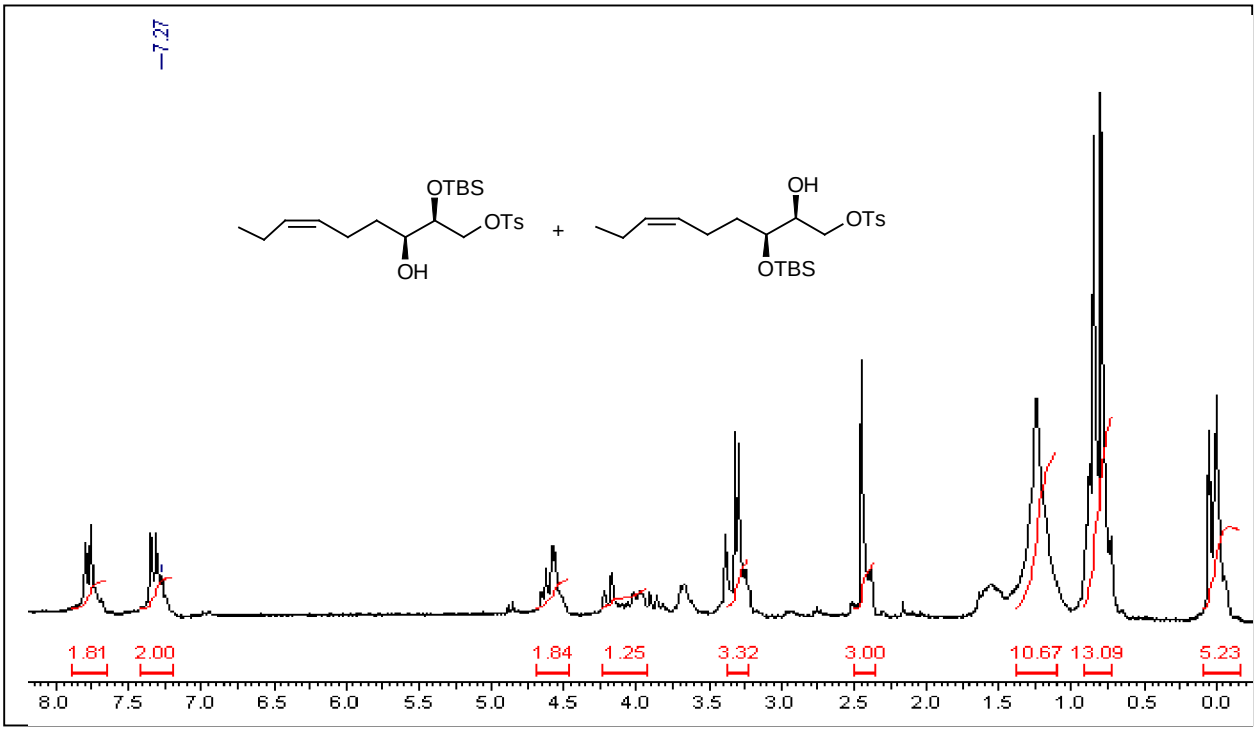
^{13}C NMR Spectrum of compound 120 & 121 in $CDCl_3$



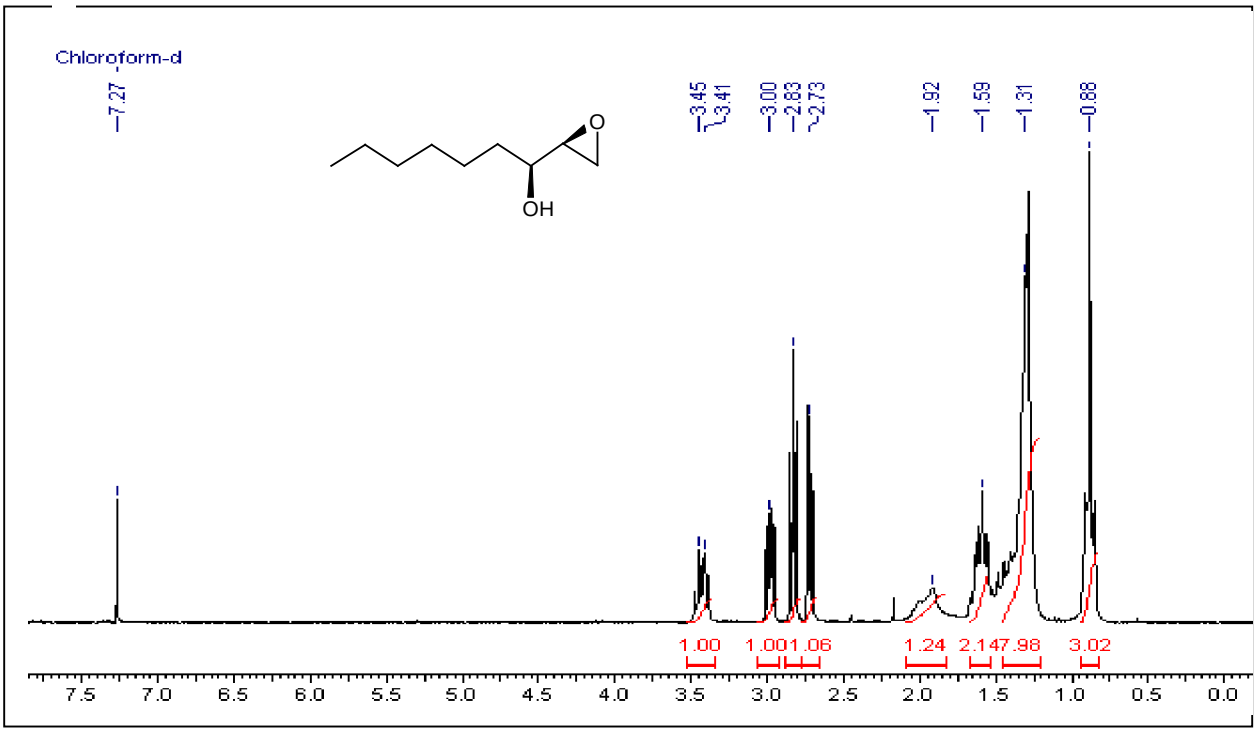
DEPT NMR Spectrum of compound 120 & 121 in $CDCl_3$



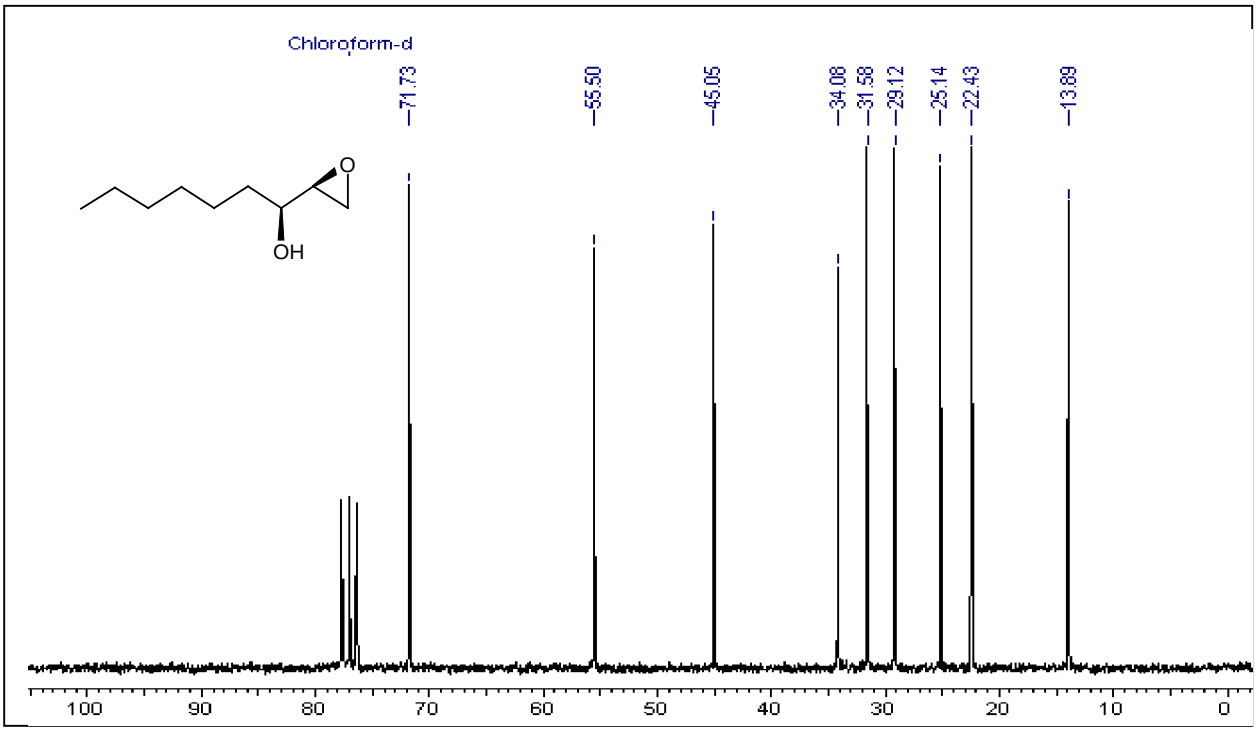
^{1}H NMR Spectrum of compound 122 & 123 in $CDCl_3$



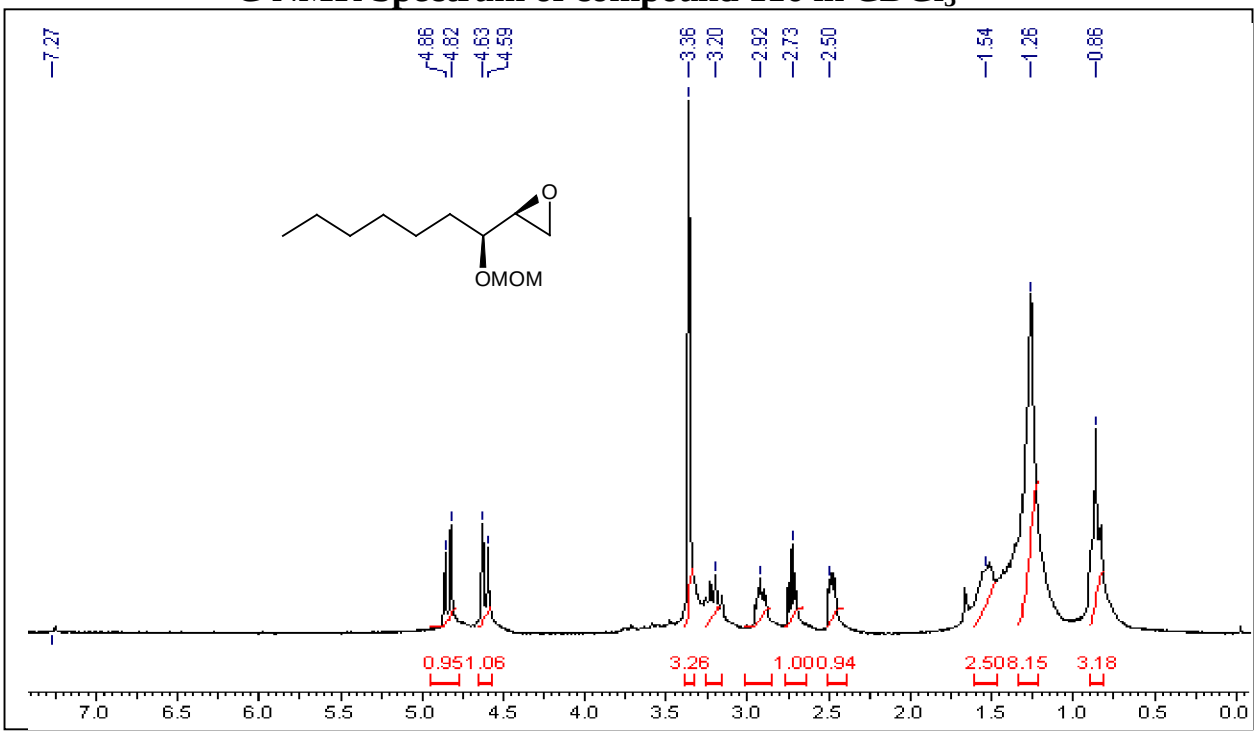
^{1}H NMR Spectrum of compound 124 & 125 in $CDCl_3$



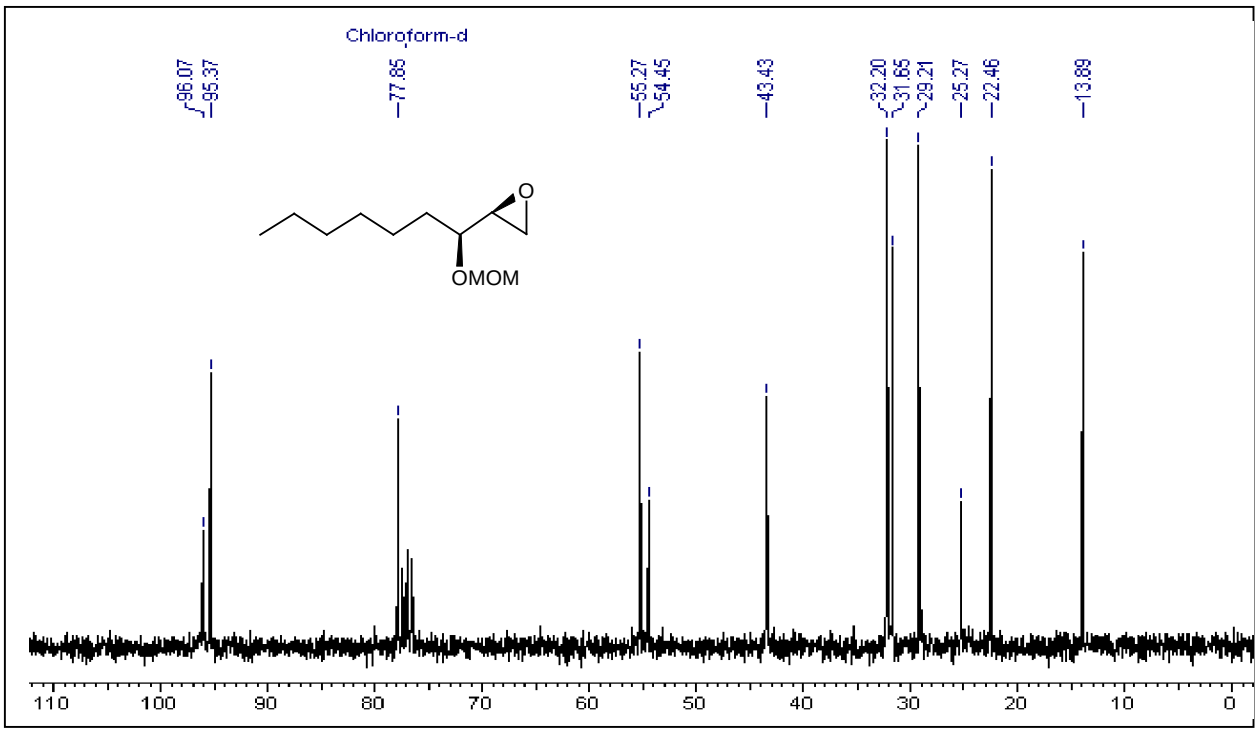
^{1}H NMR Spectrum of compound 116 in $CDCl_3$



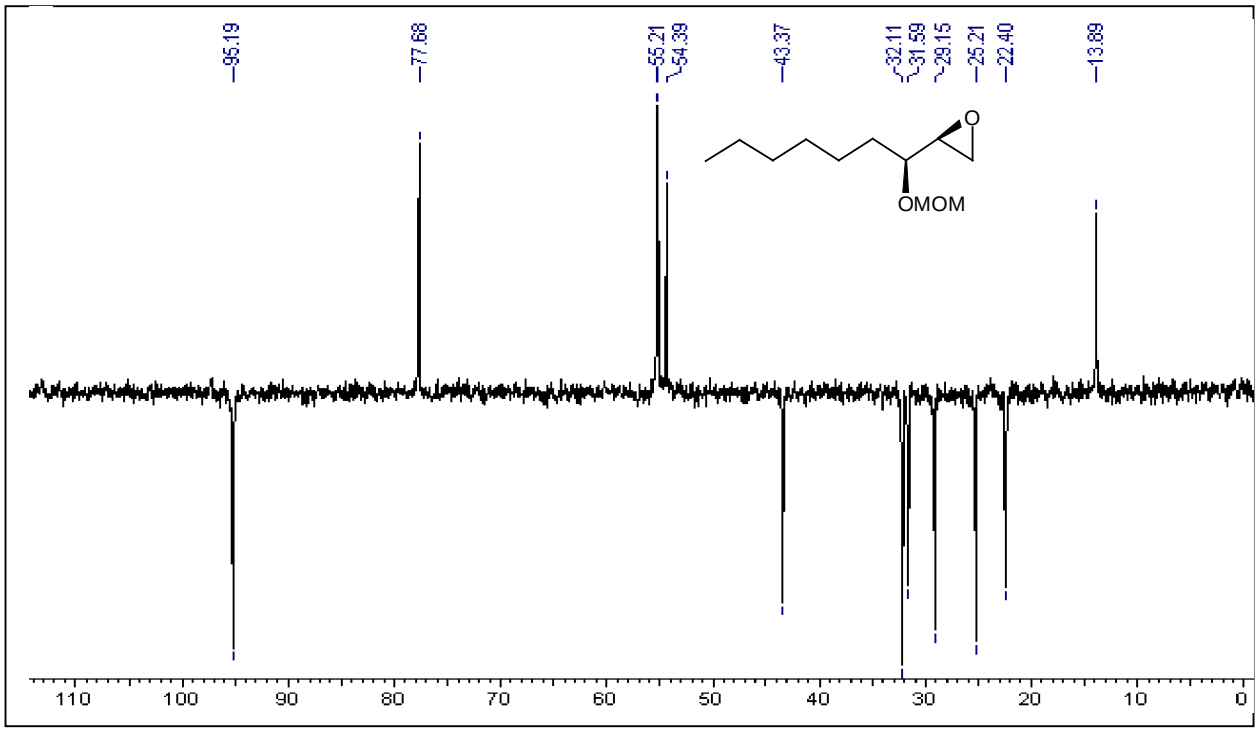
^{13}C NMR Spectrum of compound 116 in $CDCl_3$



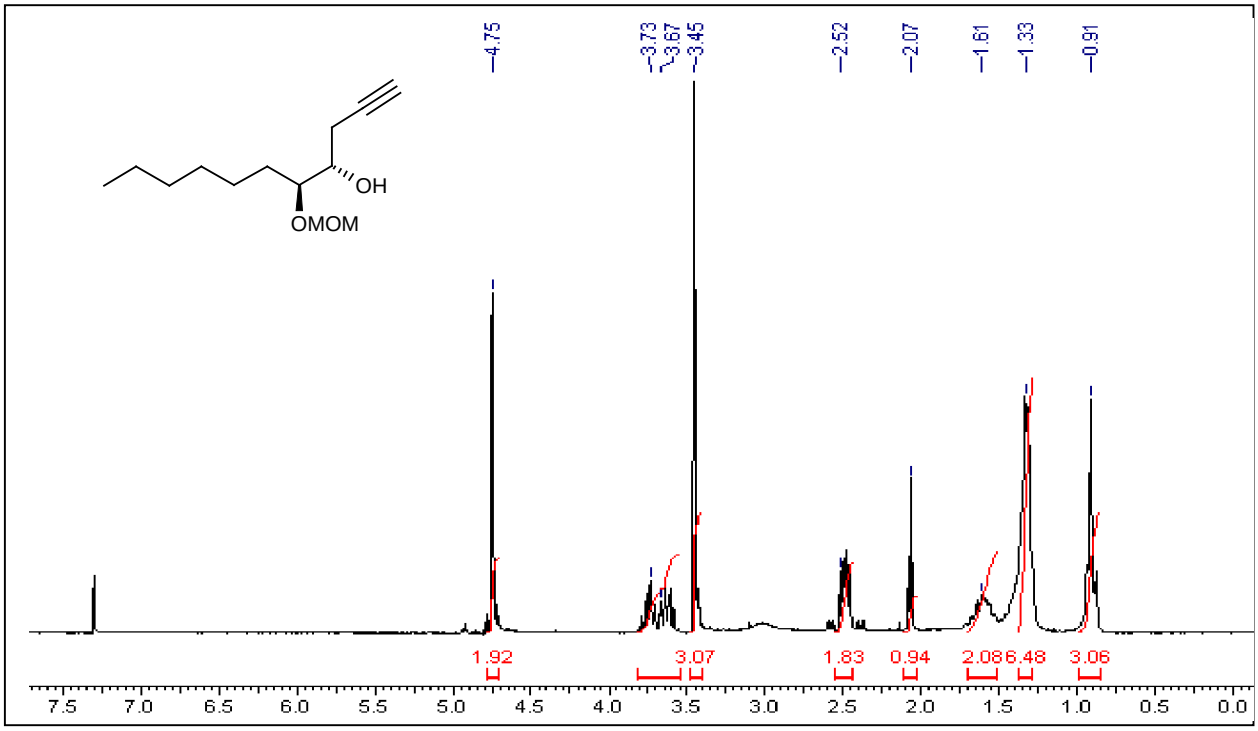
^{1}H NMR Spectrum of compound 115 in $CDCl_3$ + CCl_4



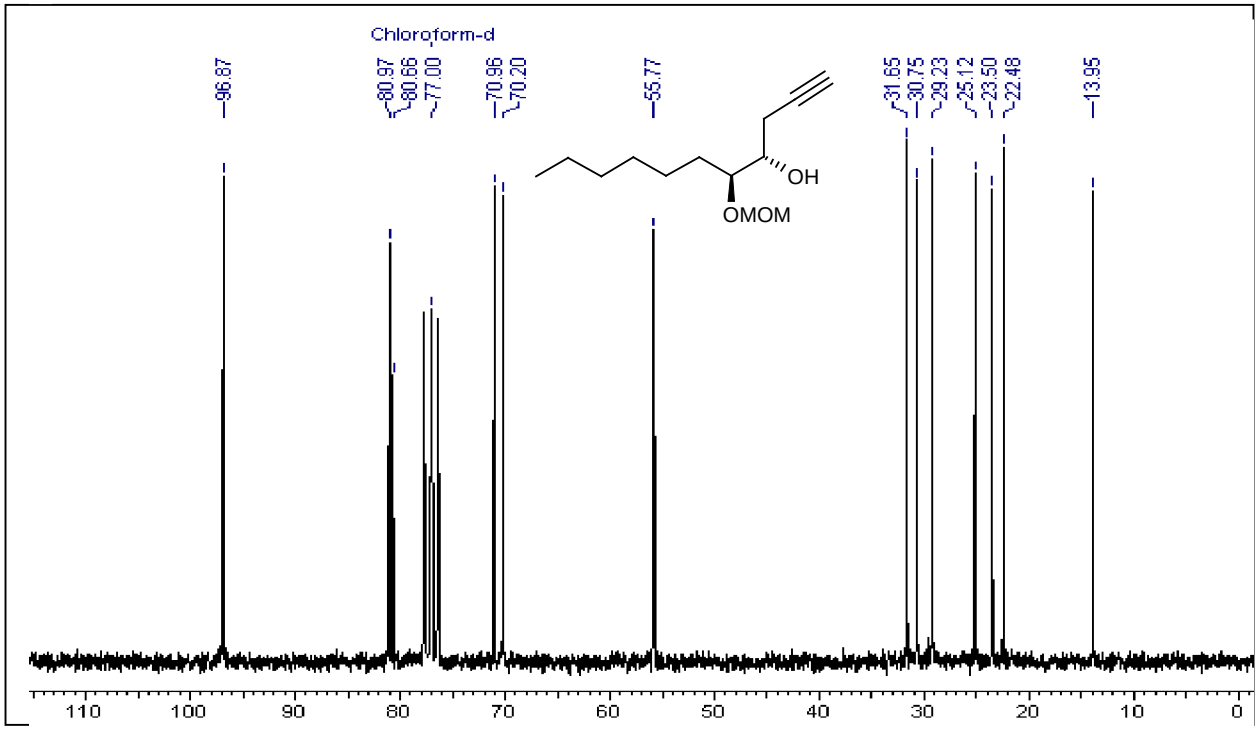
^{13}C NMR Spectrum of compound 115 in $CDCl_3$ + CCl_4



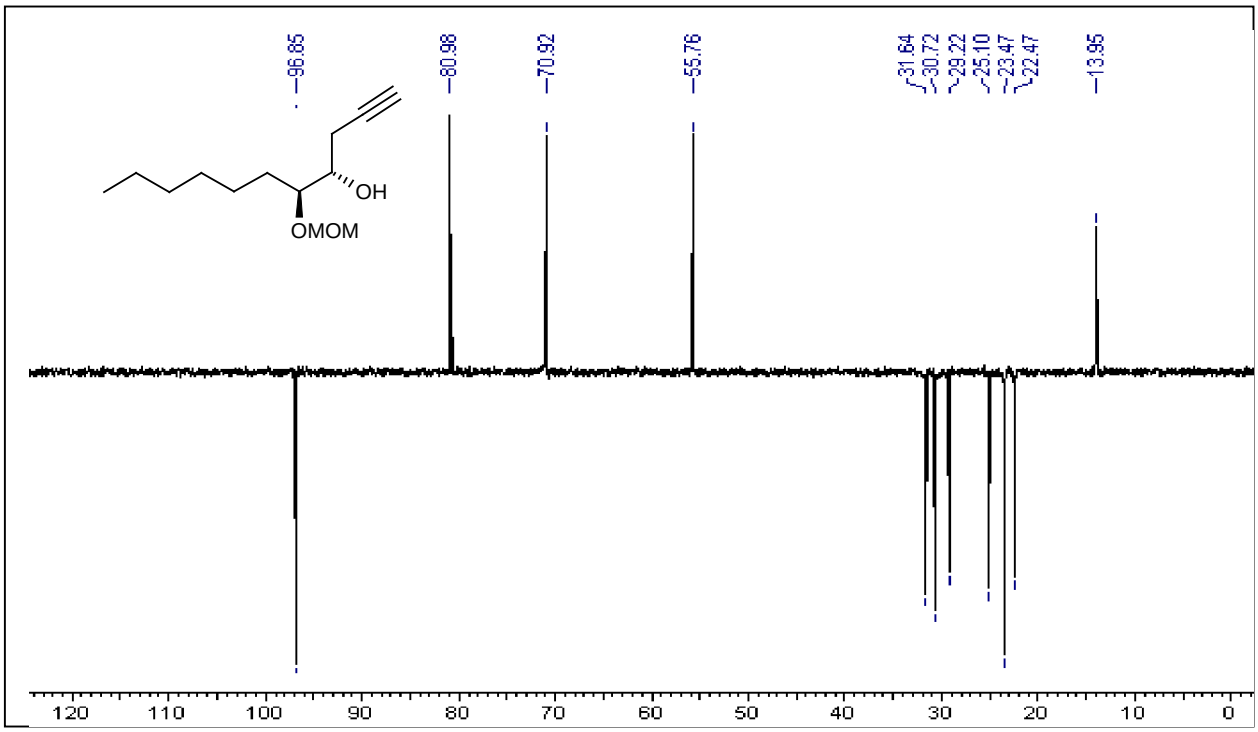
DEPT NMR Spectrum of compound 115 in $CDCl_3$ + CCl_4



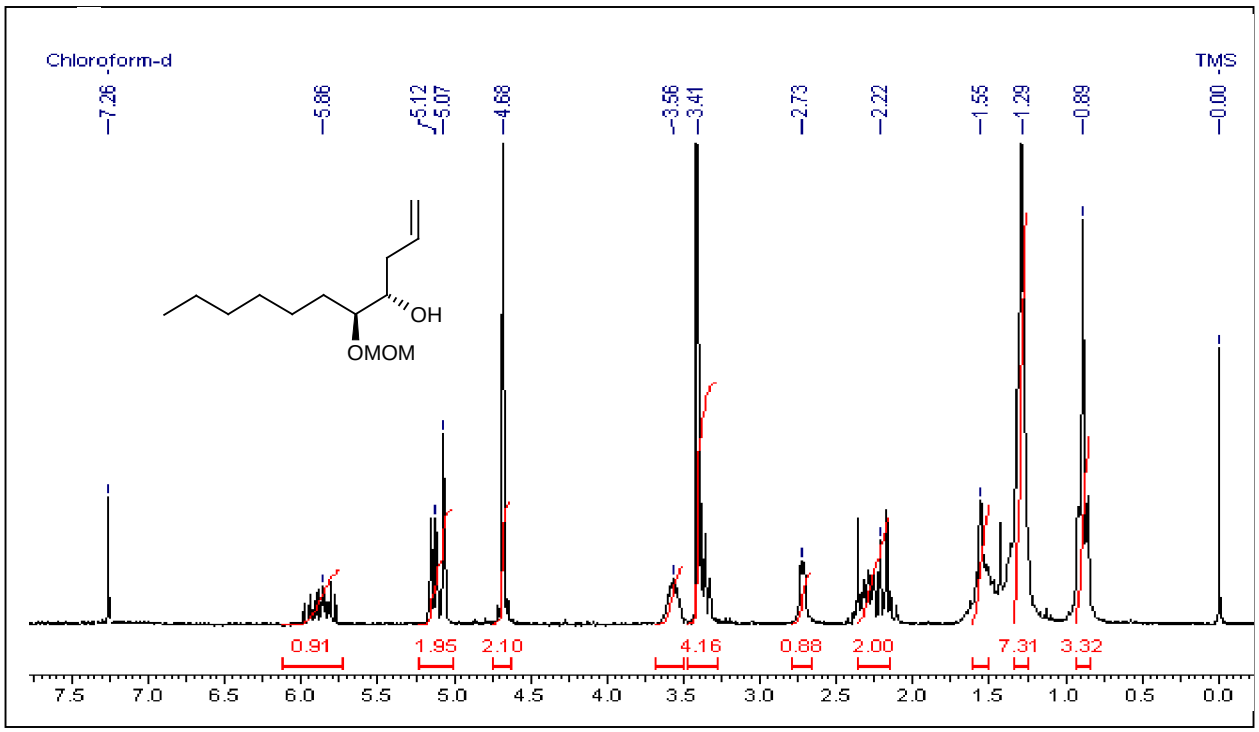
^{1}H NMR Spectrum of compound 126 in $CDCl_3$



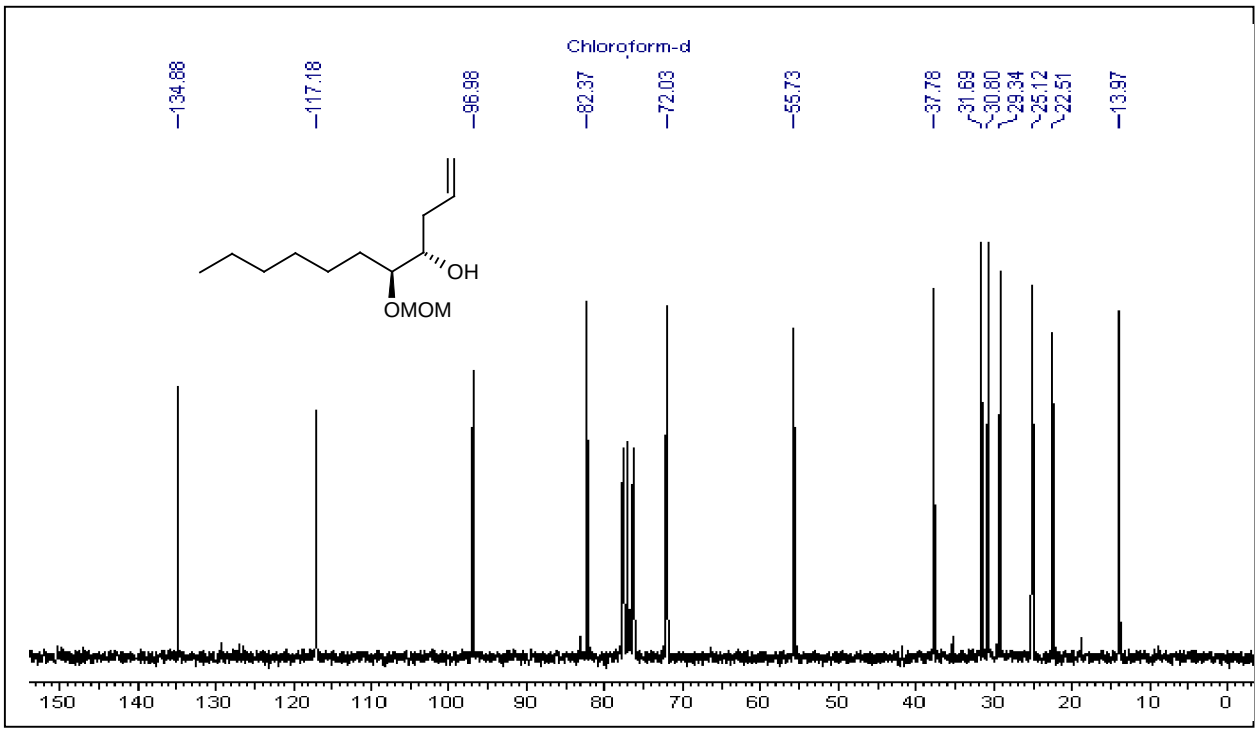
^{13}C NMR Spectrum of compound 126 in $CDCl_3$



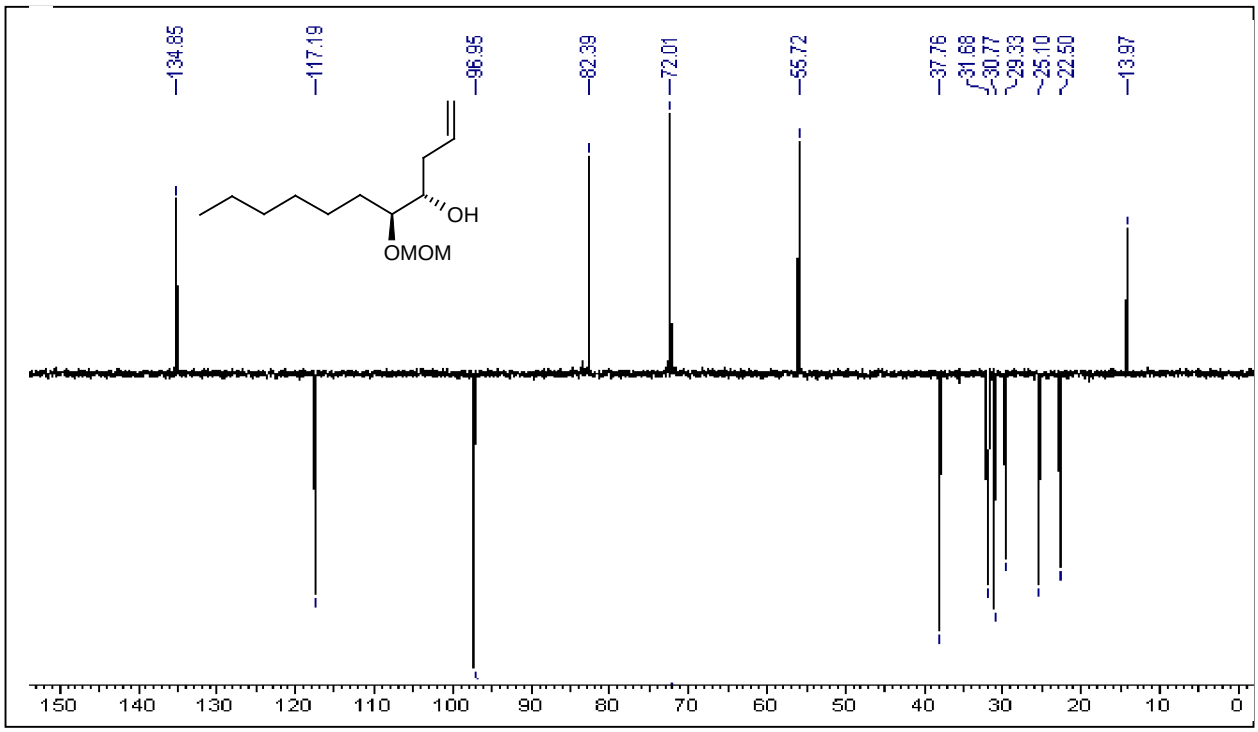
DEPT NMR Spectrum of compound 126 in $CDCl_3$



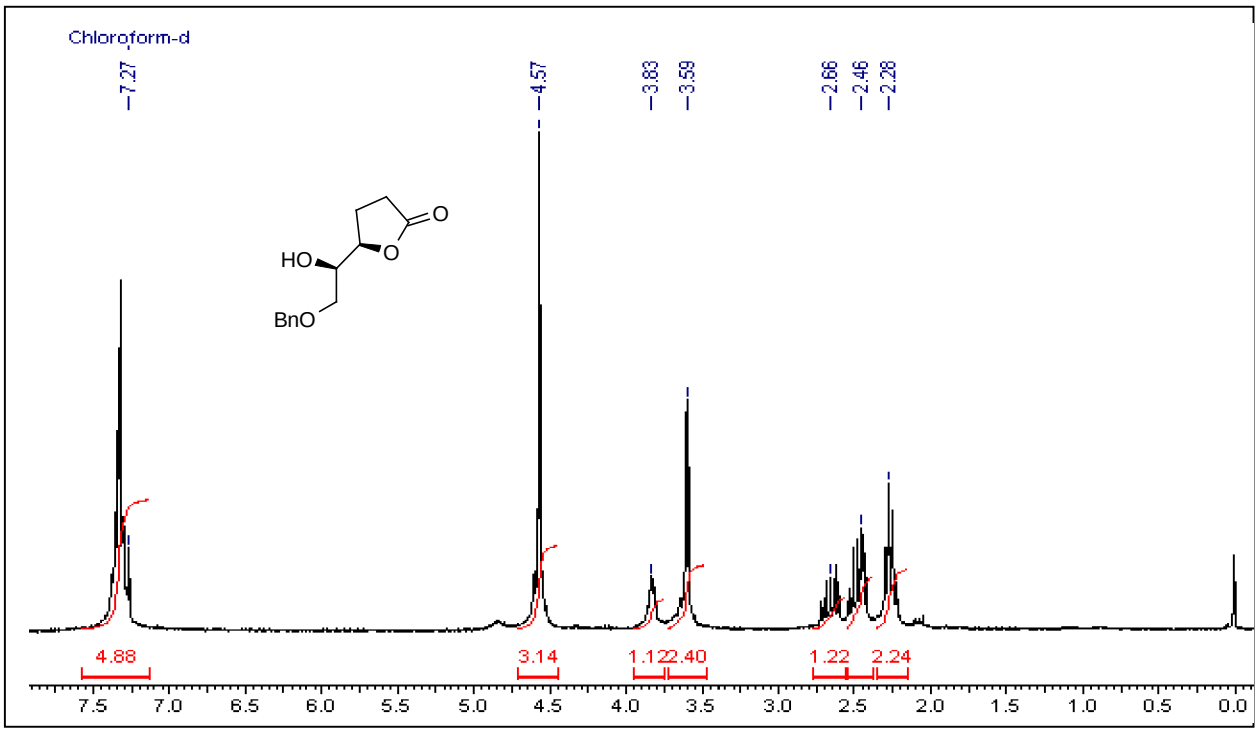
^{1}H NMR Spectrum of compound 84 in $CDCl_3$



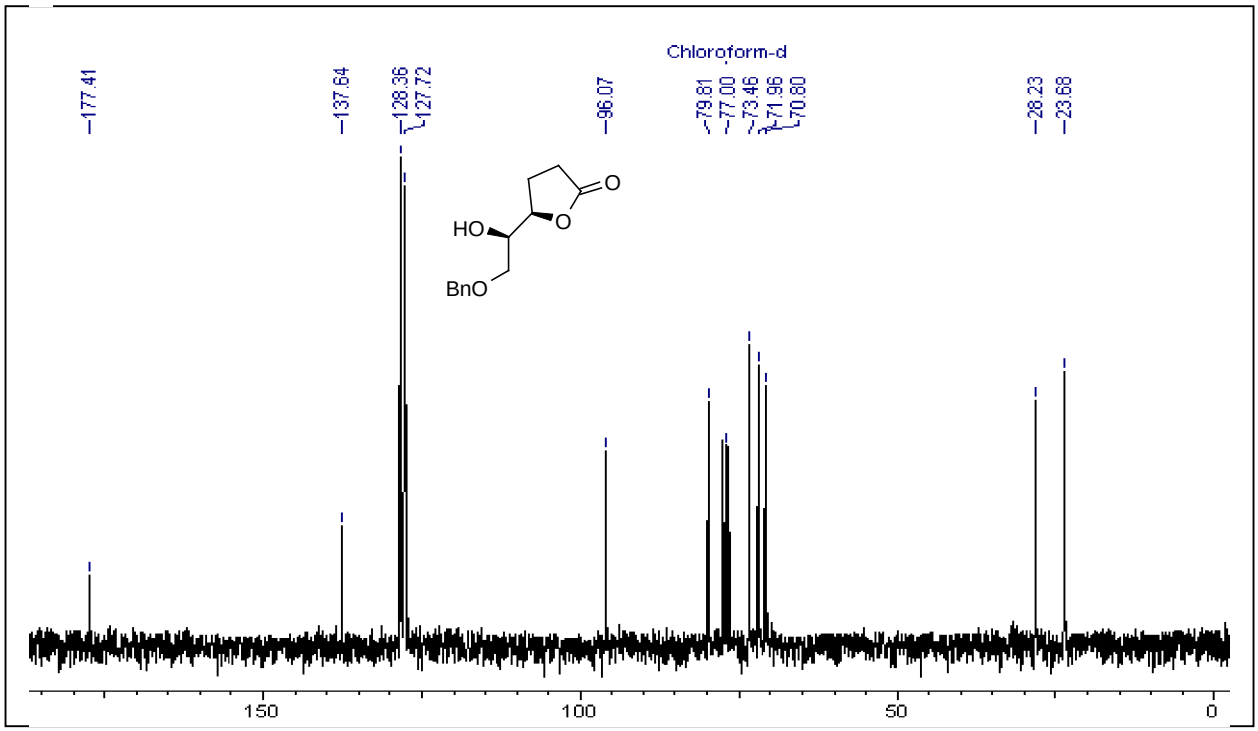
^{13}C NMR Spectrum of compound 84 in $CDCl_3$



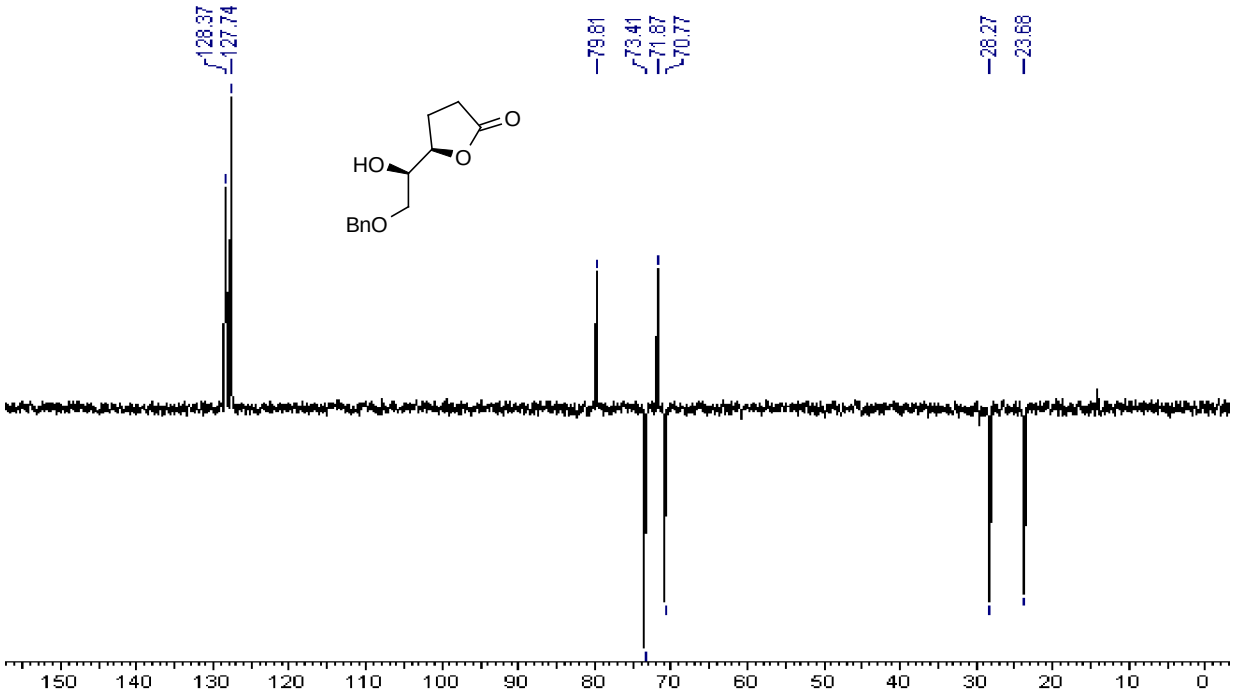
DEPT NMR Spectrum of compound 84 in $CDCl_3$



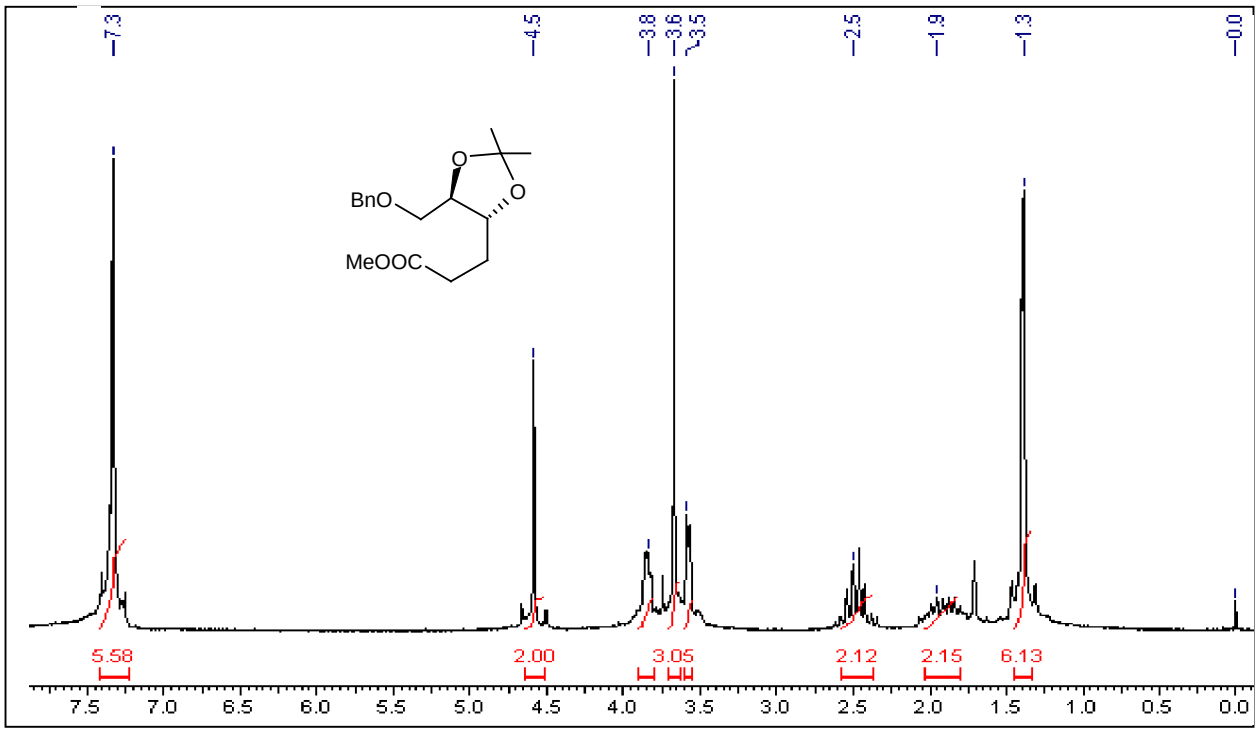
^{1}H NMR Spectrum of compound 114 b in $CDCl_3$ + CCl_4



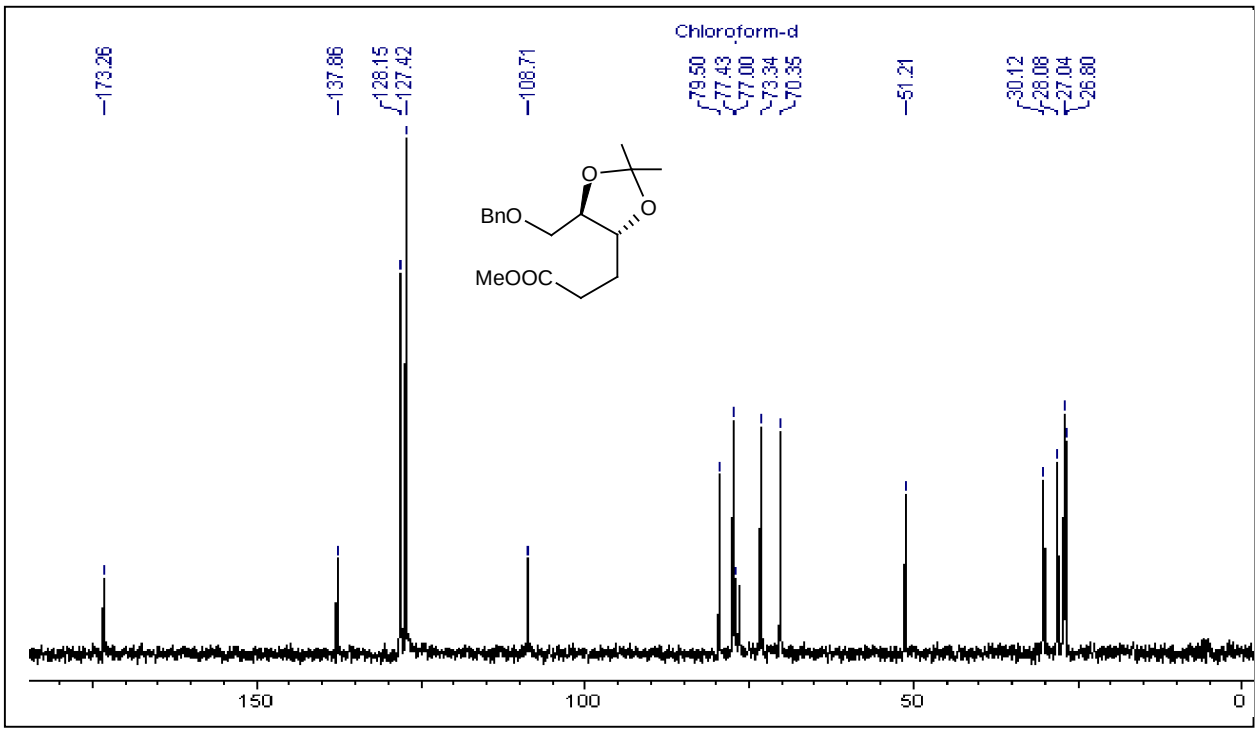
^{13}C NMR Spectrum of compound 114 b in $CDCl_3$ + CCl_4



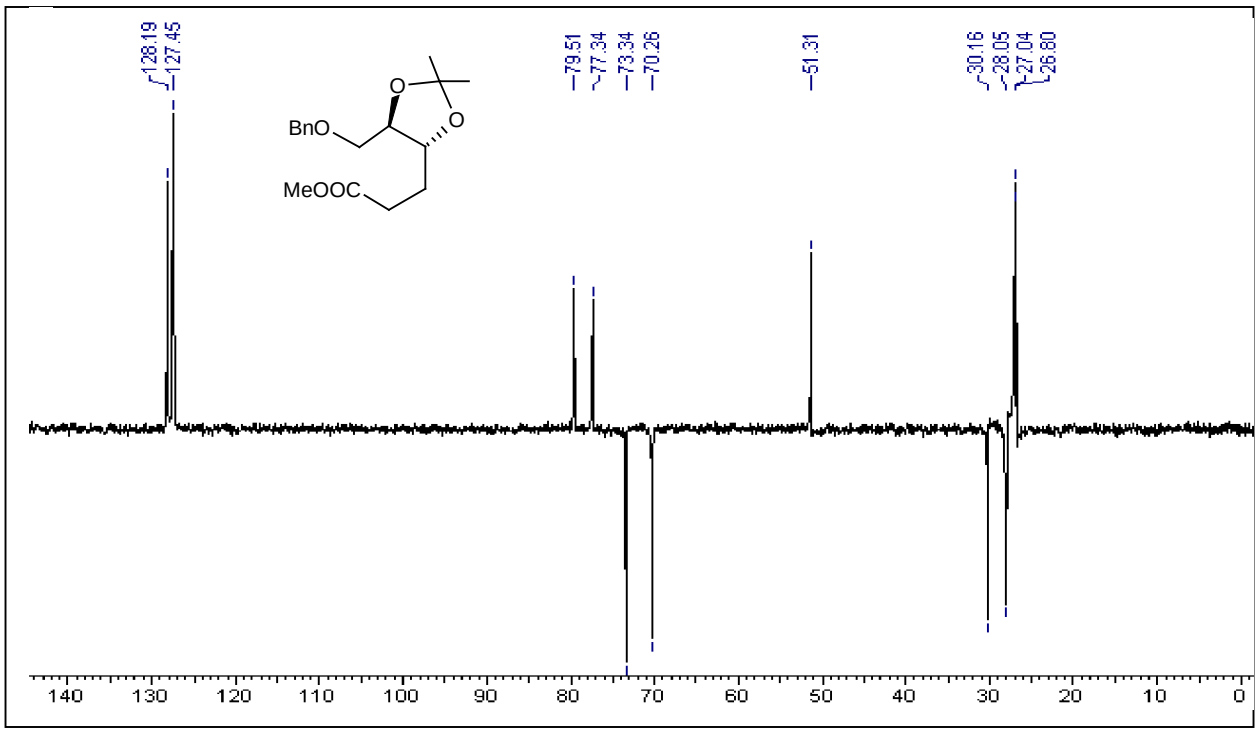
DEPT NMR Spectrum of compound 114 b in $CDCl_3$ + CCl_4



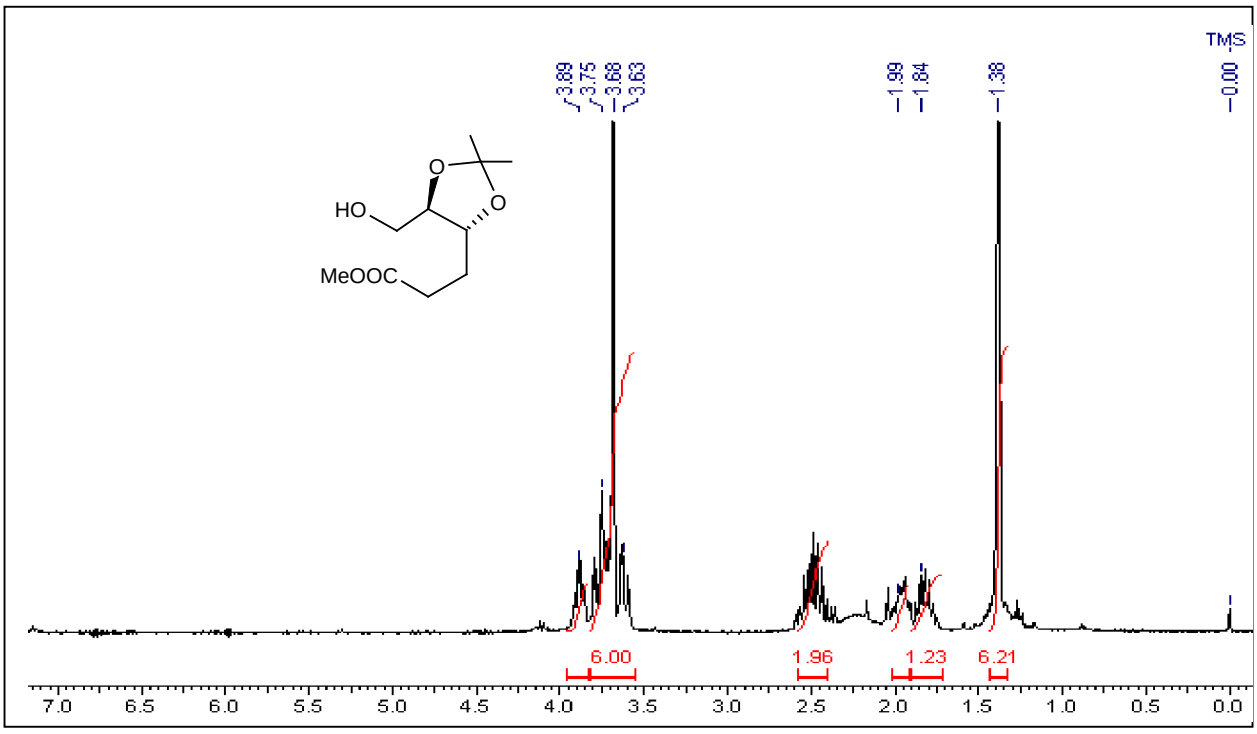
^{1}H NMR Spectrum of compound 113 in $CDCl_3$



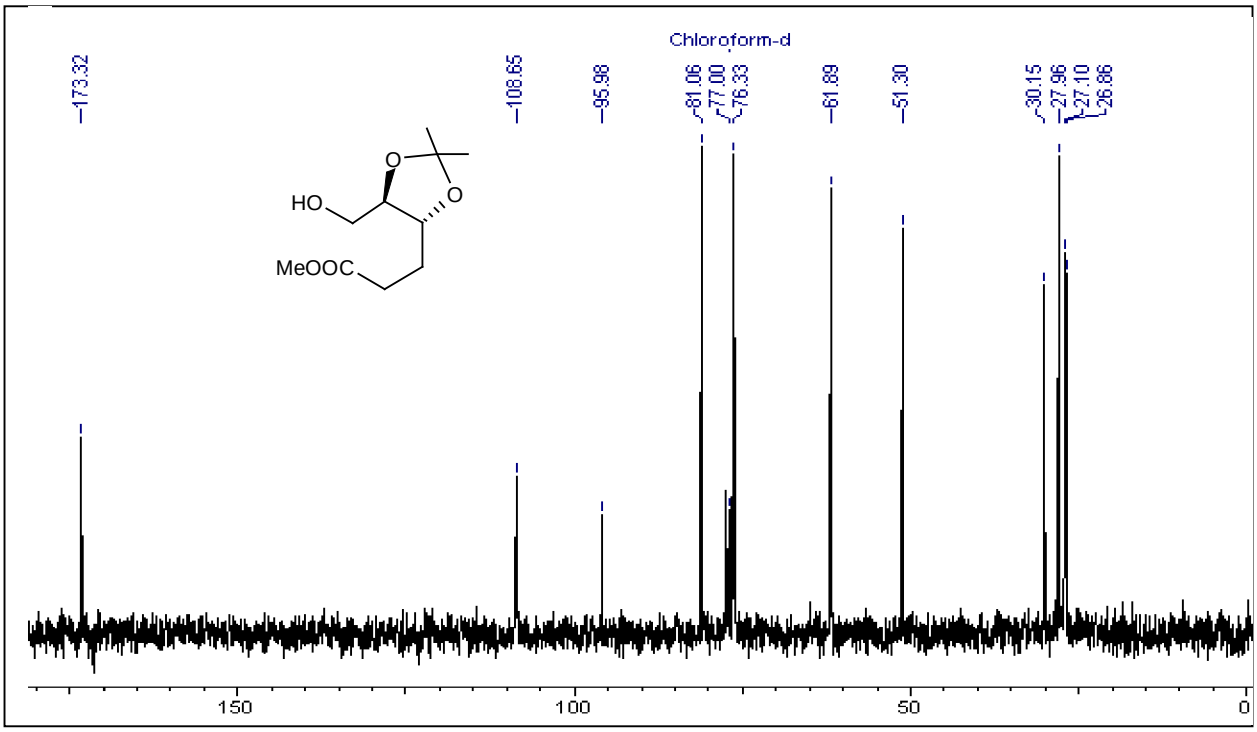
^{13}C NMR Spectrum of compound 113 in $CDCl_3$



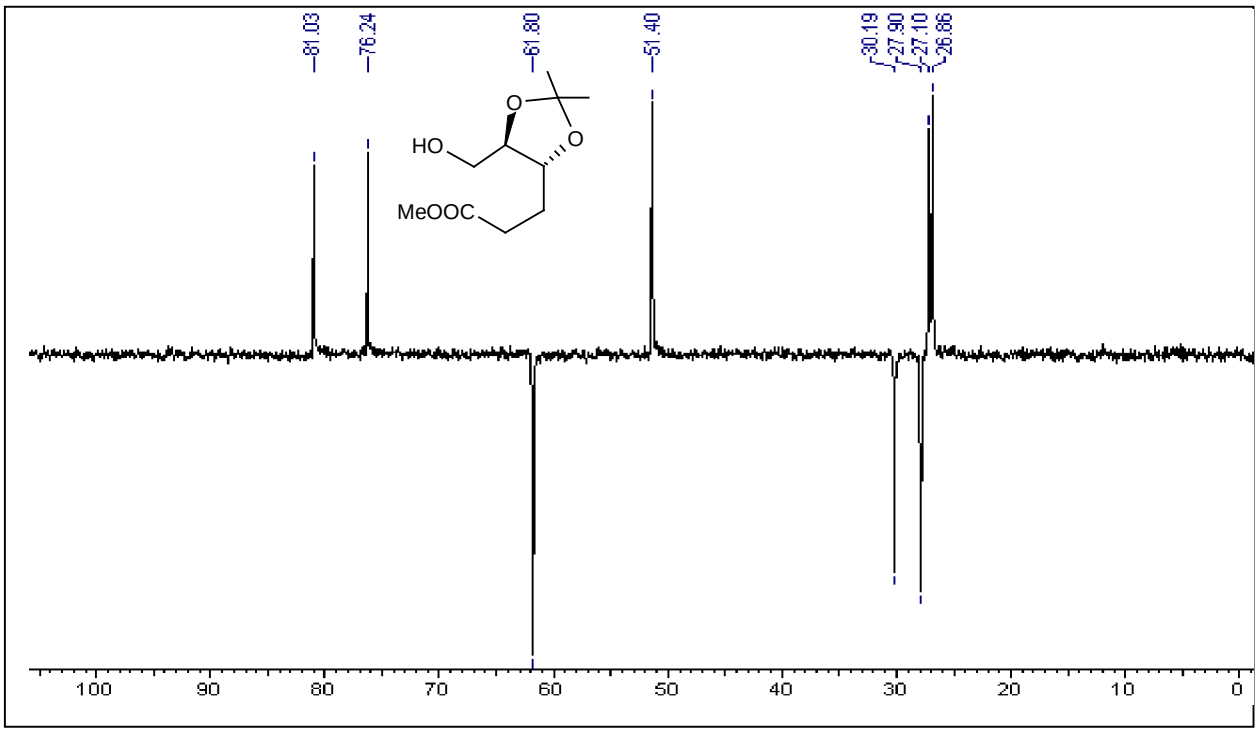
DEPT NMR Spectrum of compound 113 in $CDCl_3$



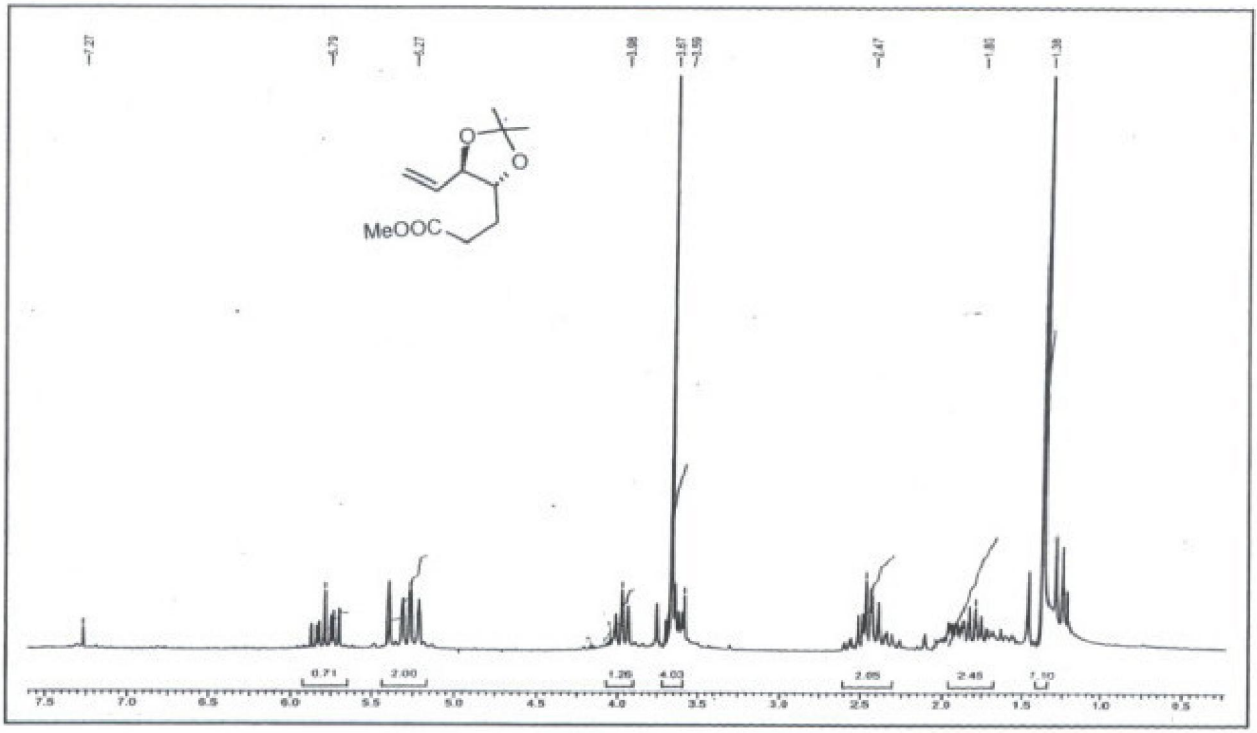
^{1}H NMR Spectrum of compound 112 in $CDCl_3$ + $CDCl_3$



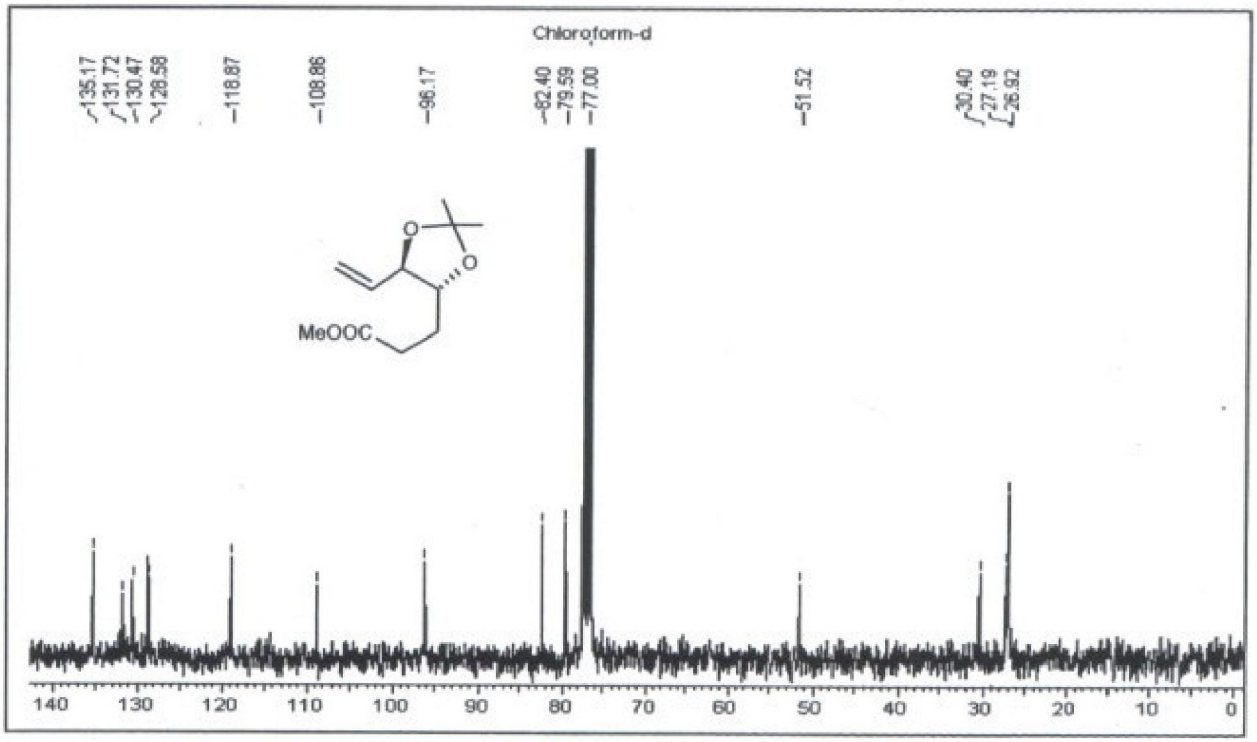
^{13}C NMR Spectrum of compound 112 in $CDCl_3$ + $CDCl_3$



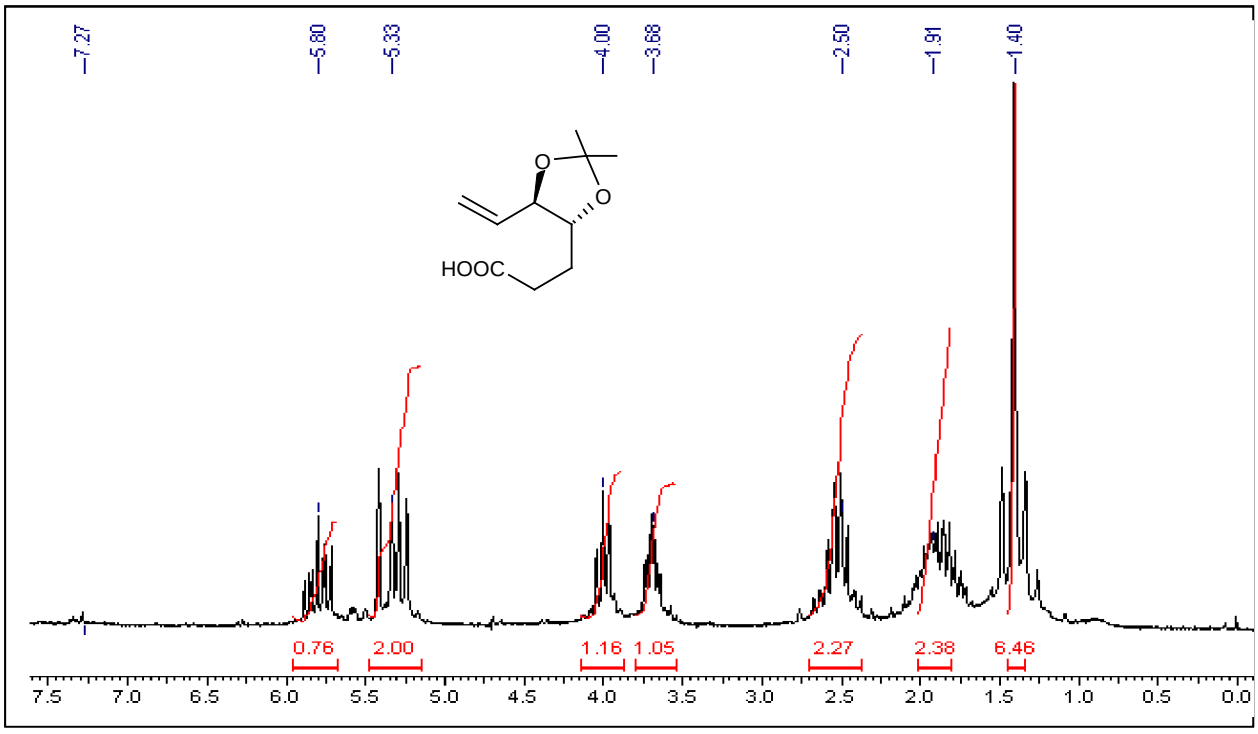
DEPT NMR Spectrum of compound 112 in $CDCl_3$ + $CDCl_3$



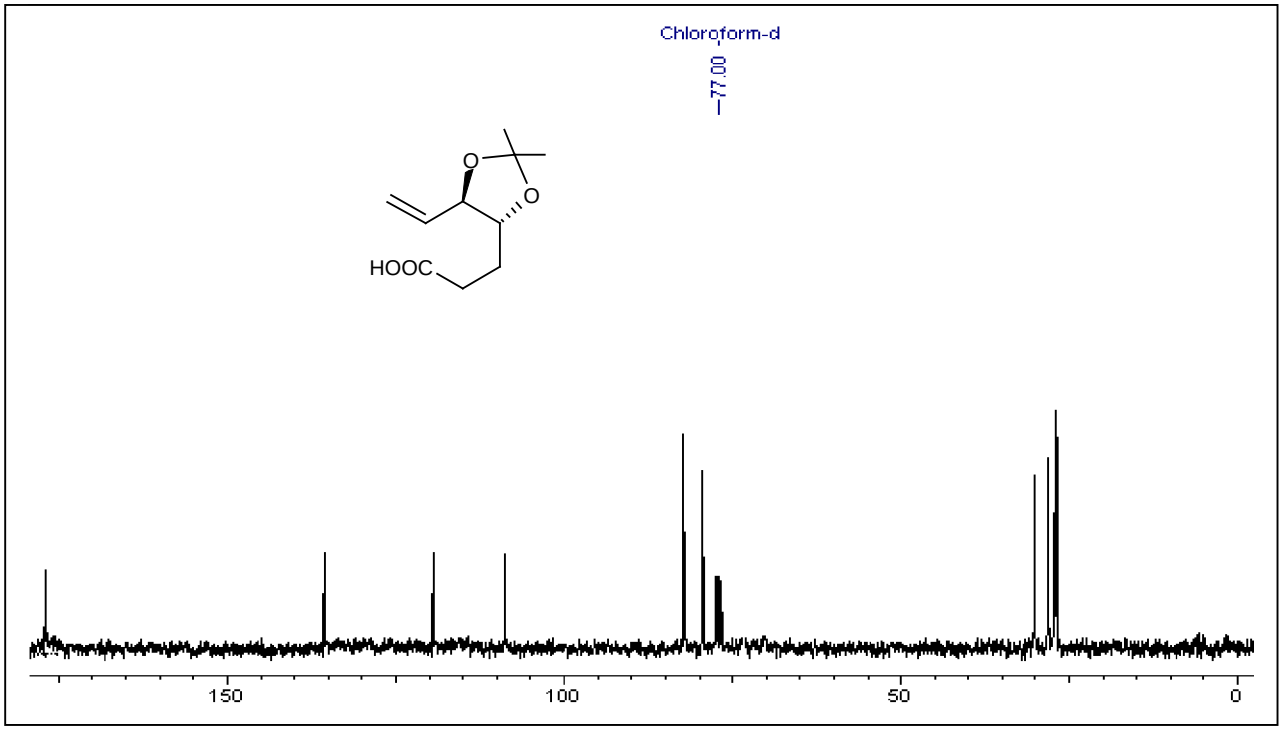
^{1}H NMR Spectrum of compound 111 in $CDCl_3 + CCl_4$



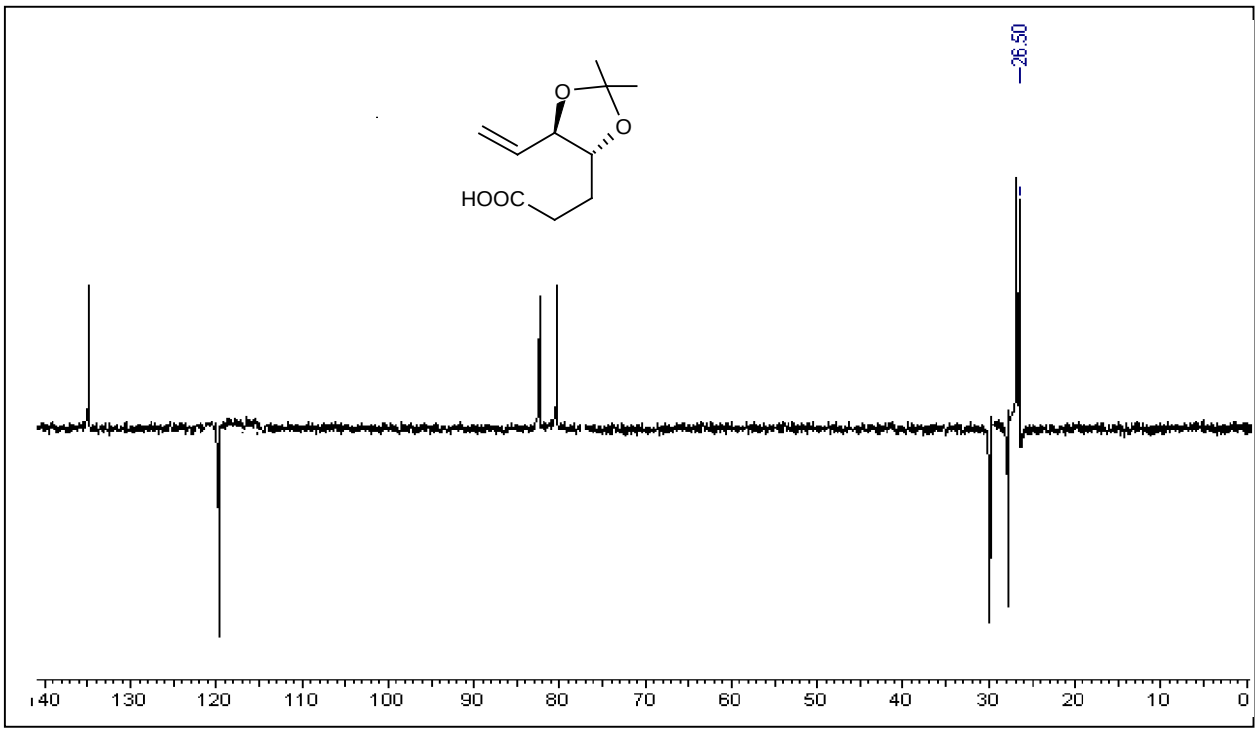
^{13}C NMR Spectrum of compound 39 in $CDCl_3 + CCl_4$



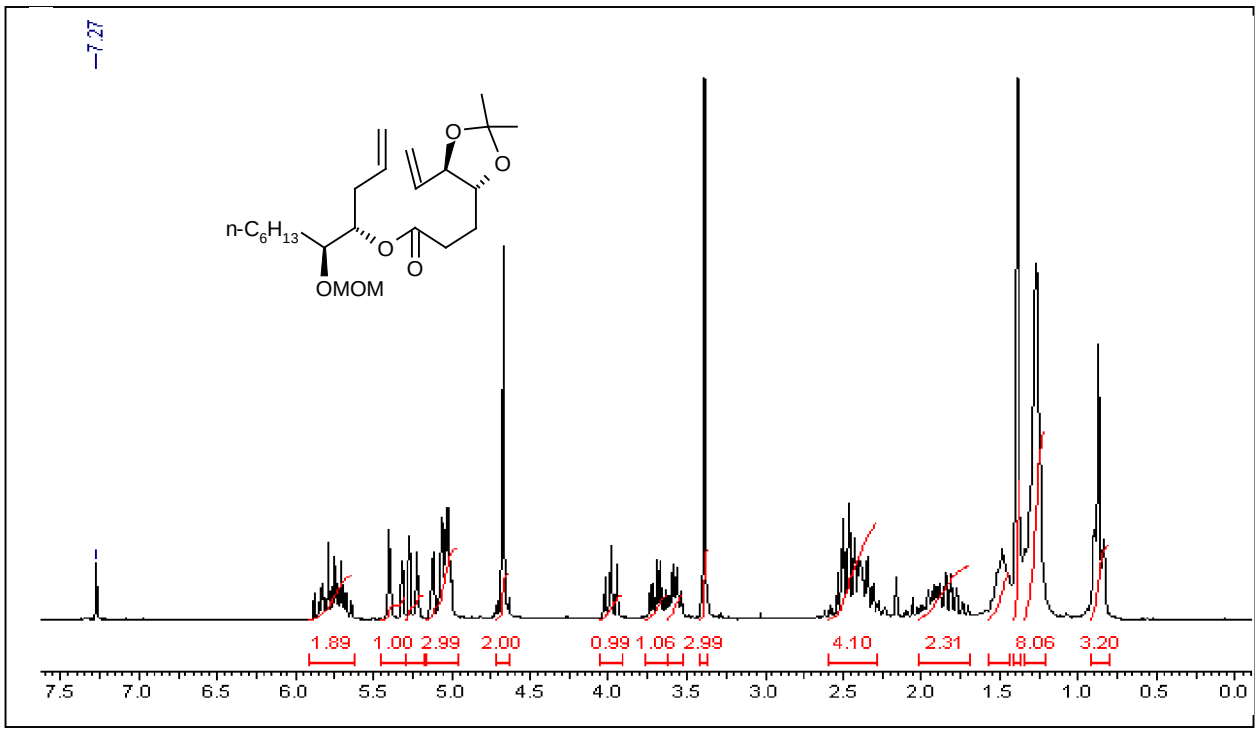
^{1}H NMR Spectrum of compound 80 in $CDCl_3$



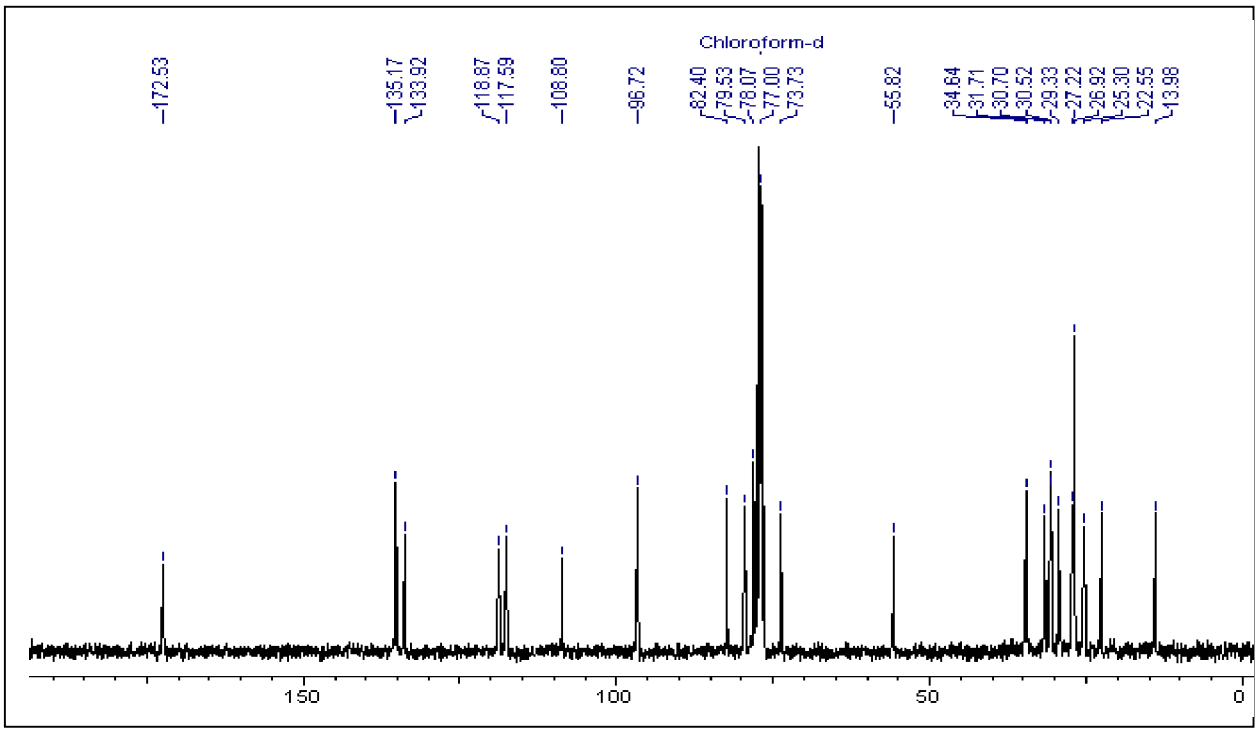
^{13}C NMR Spectrum of compound 80 in $CDCl_3$



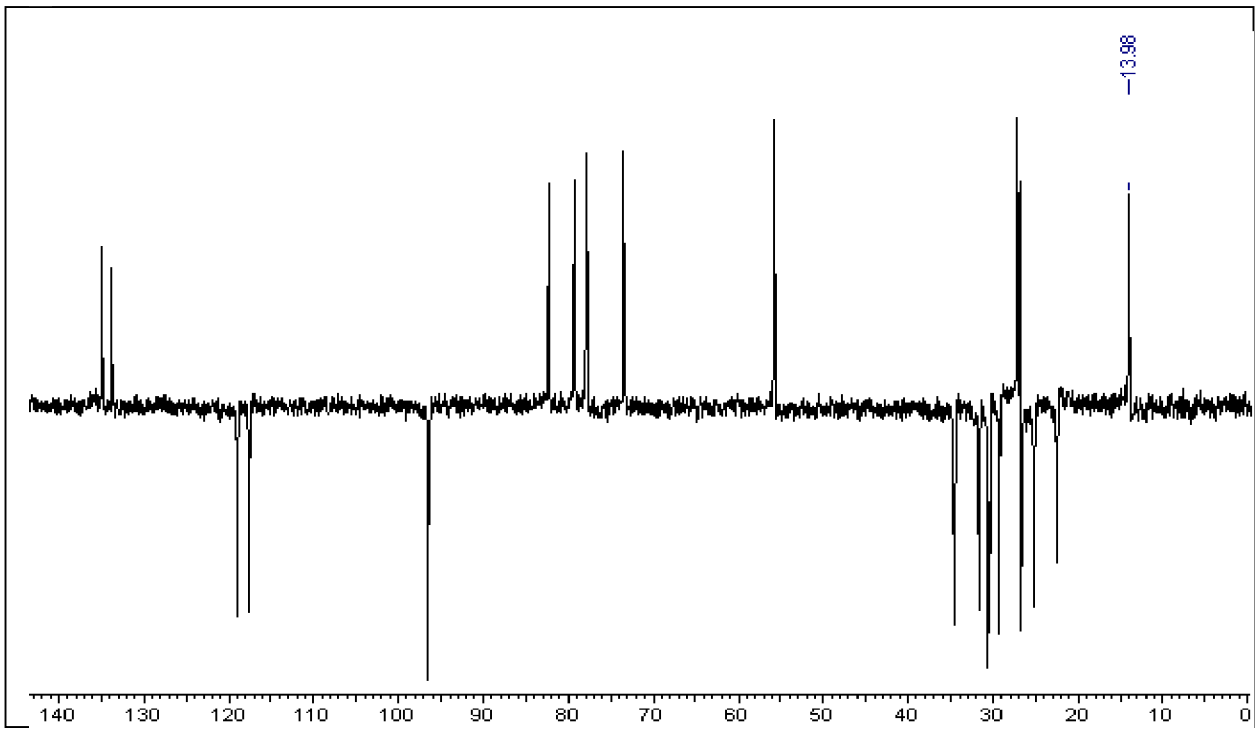
DEPT NMR Spectrum of compound 80 in $CDCl_3$



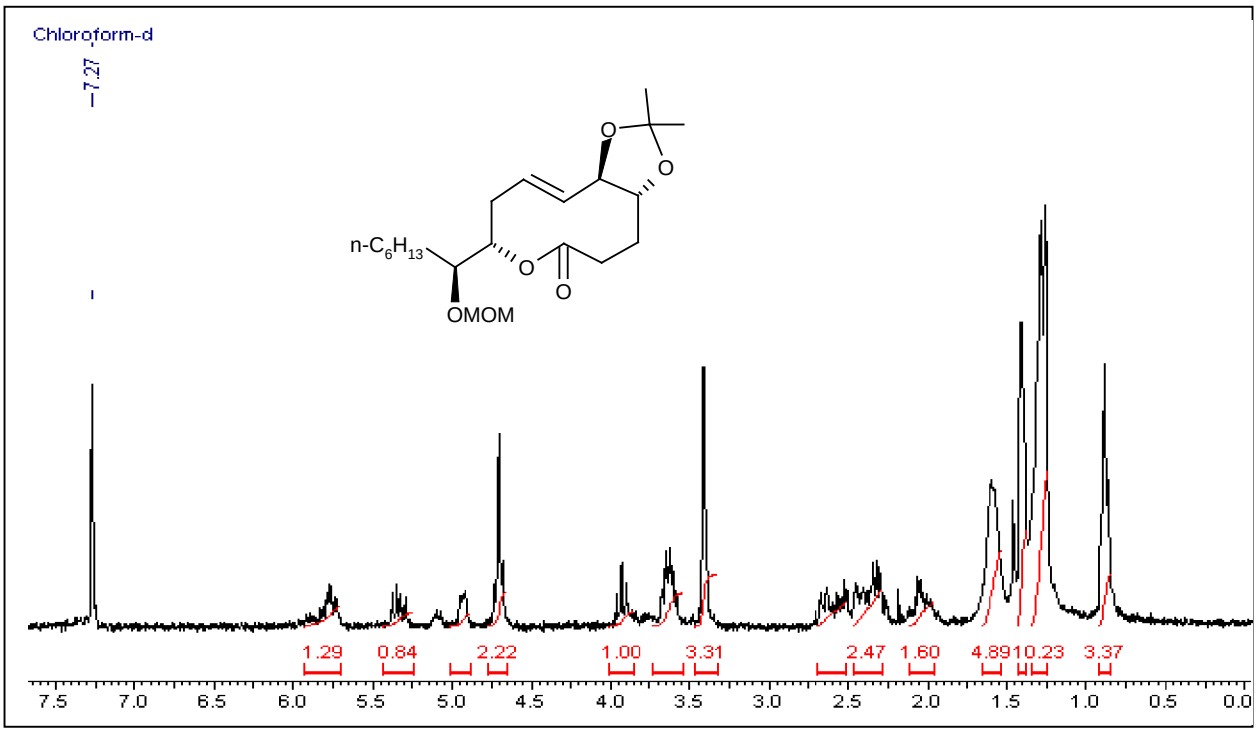
^{1}H NMR Spectrum of compound 125 in $CDCl_3$



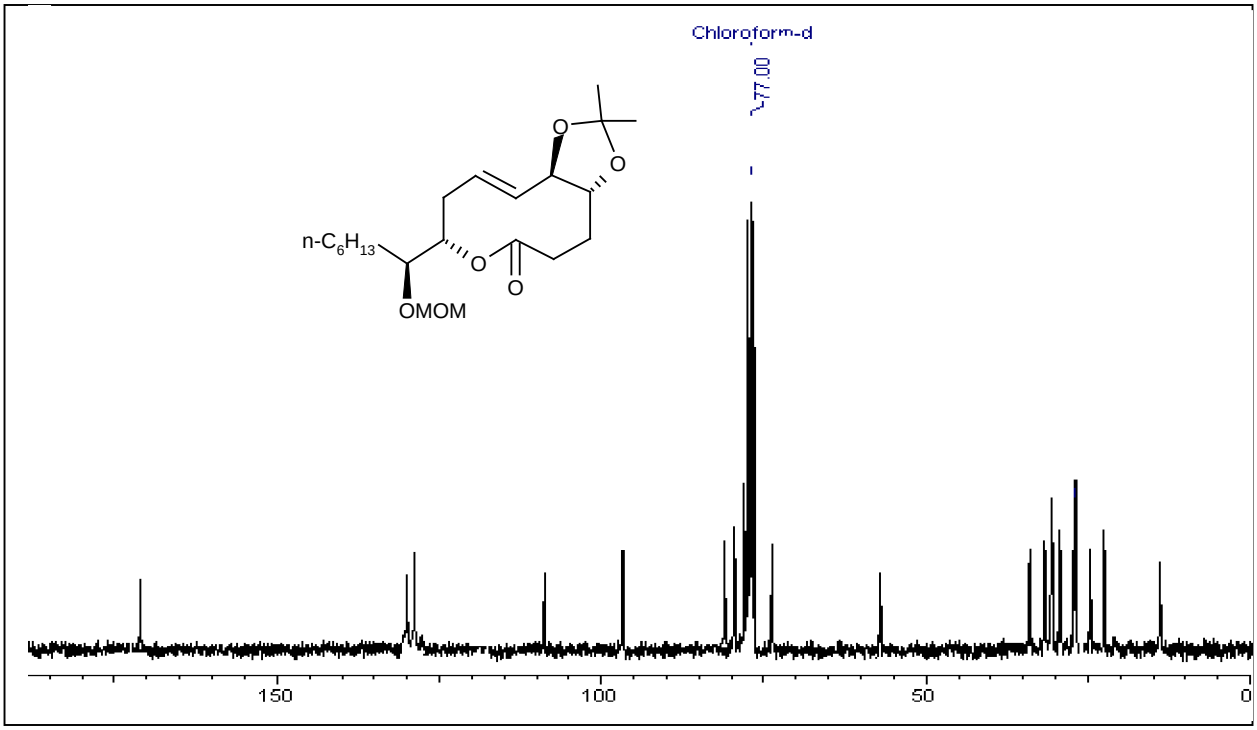
^{13}C NMR Spectrum of compound 125 in $CDCl_3$



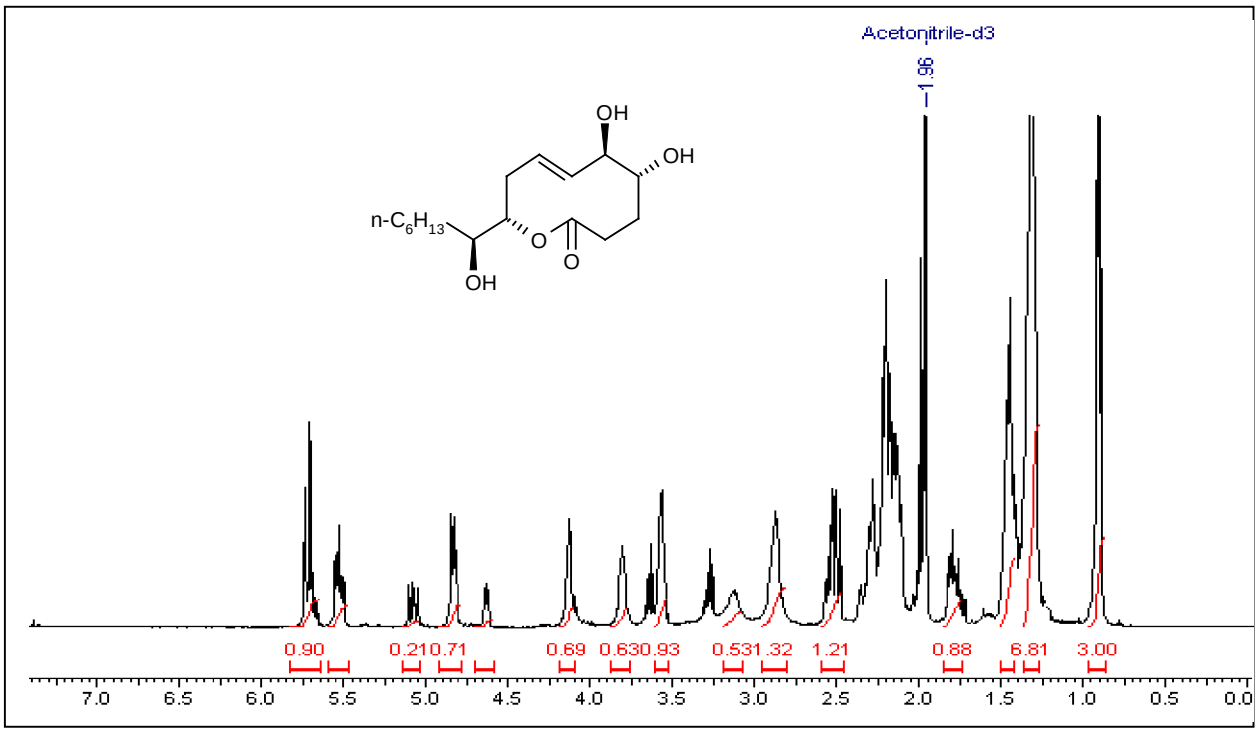
DEPT NMR Spectrum of compound 38 in $CDCl_3$



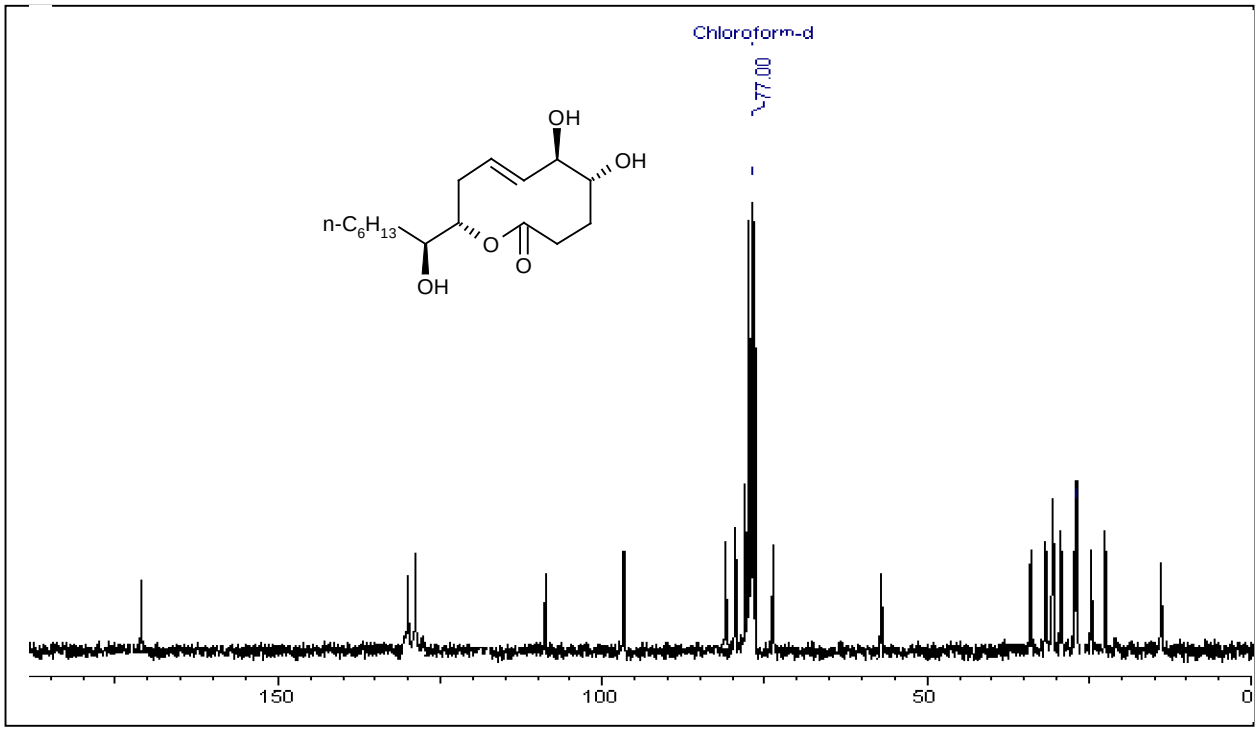
^{1}H NMR Spectrum of compound 128 in $CDCl_3$



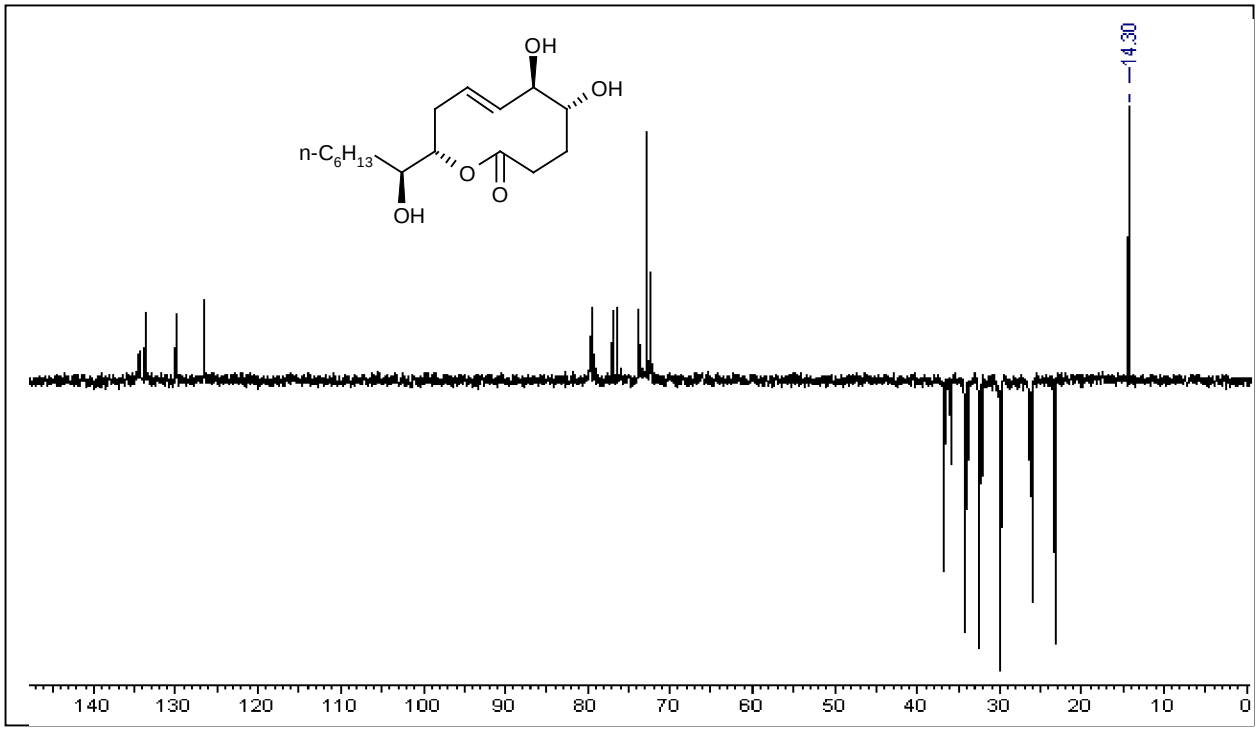
^{13}C NMR Spectrum of compound 128 in $CDCl_3$



^{1}H NMR Spectrum of compound 1 in CD_3CN



^{13}C NMR Spectrum of compound 1 in CD_3CN



DEPT NMR Spectrum of compound 1 in CD_3CN

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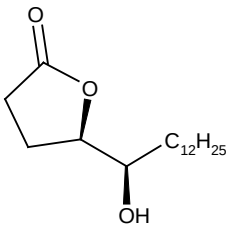
SECTION B

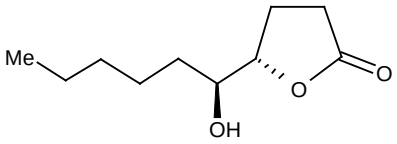
A VERSATILE AND FLEXIBLE ROUTE FOR THE SYNTHESIS OF BIOLOGICALLY ACTIVE COMPOUNDS FROM HYDROXY BUTYROLACTONE AS THE KEY SYNTHON

Introduction:

Chiral hydroxylactones occupy an important position as bio-active molecules and useful synthetic intermediates in total synthesis. One such group of hydroxylactones comprises the 5-hydroxyalkylbutan-4-olides viz. muricatacin **1**. These are widely found in nature and show diverse biological properties. Some of these compounds are known to have insect antifeedant activity[1] and are cytotoxic to human tumor cells.[2] The short chain homologues are important flavor constituents in wine, sherry, and tobacco smoke.[3] These are also found in microbial metabolite cultures of *Erwinia quernica*[4] and *Streptomyces griseus*.[5] Many of these butanolides are often used as synthons in the synthesis of complex and biologically important natural products.[6] These have been used as precursors to HIV-1 protease inhibitors.[7] One such molecule that has attracted much attention since its isolation was (-)-muricatacin **1**.



Muricatacin (**1**)



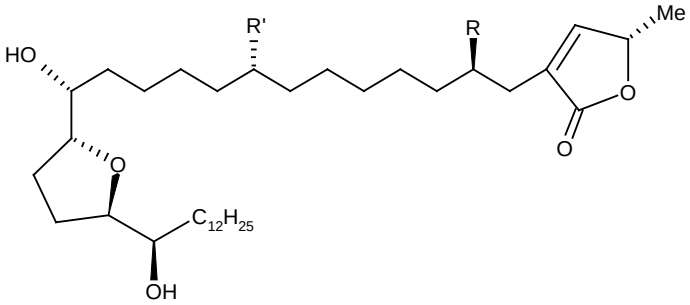
L-factor (**2**)

Muricatacin was isolated from the seeds of *Anona muricata* L. (annonaceae),[8] commonly known as sour soup or guanabana, and is grown commercially as a fruit crop throughout the tropical regions of the world. This plant as well as others in the family of annonaceae are a source of many annonaceous acetogenins that are known to have anti-tumor properties.[2] Both enantiomers of **1** are found in nature. The isolated material is a mixture of the two, the (-)-(*R*,*R*)-enantiomer **1** being predominant (e.e. of ca. 25% based on optical rotation). It has been shown to be cytotoxic towards human tumor cells. Biological studies revealed that the length of the side chain is very crucial. Decreasing the length of the alkyl side chain led to decreased activity but increasing the chain length did not show any increase in activity. Both (+)- and (-)-muricatacin have the same activity.

A similar compound L-factor **2**, was isolated from Streptomyces griseus and was thought to have an autoregulatory role,[9] controlling the formation of aerial mycelia and production of the anthracycline antibiotic leukaemycin, although this activity was

subsequently shown[10] to be due to contamination with trace amounts of the true regulatory molecule, A-factor. The reported biological activity for L-factor **2** prompted synthetic efforts to produce all the four diastereomers.[11]

Muricatacin **1**, probably a product of oxidative cleavage of its monotetrahydrofuranic acetagenin congeners[12] **4**-**9**. Muricatacin is a member of the hydroxy lactone class of compounds that are notable[13] for their biological activity and as building blocks in the synthesis of complex biologically active compounds.[14]



4. R = R' = OH, Annonacin

5. R = OH, R' = OH, Annonacinone

6. R = H, R' = OH, Corrosolin

7. R = H, R' = O, Corrosolone

8. R = OH, R' = H, Murisolin

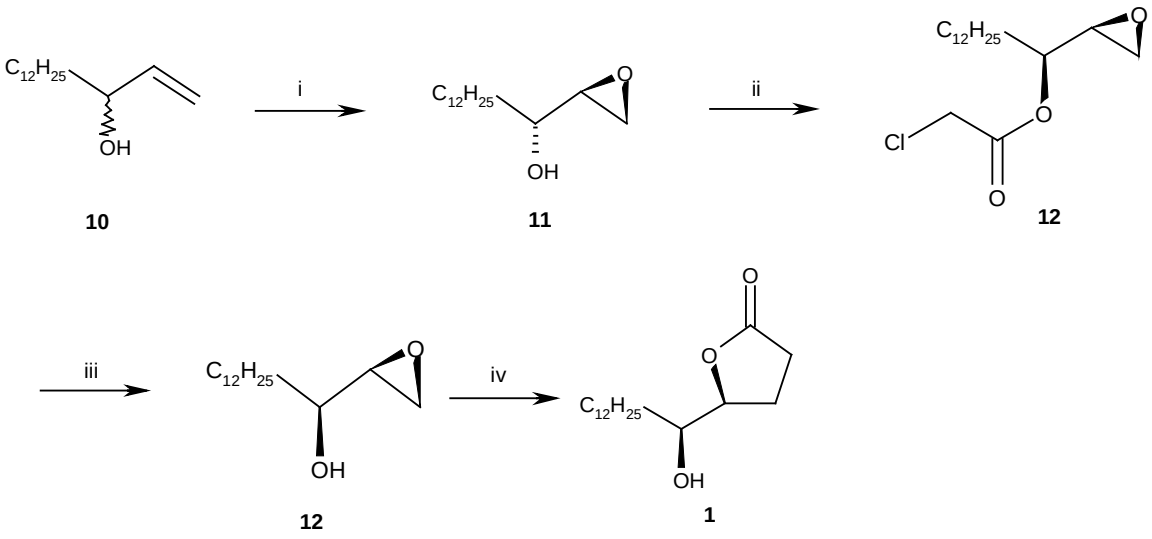
9. R = R' =H, Solamin

Review of literature:

Muricatacin is biologically active showing cytotoxicity in KB and VERO cell lines. It has stimulated a great deal of attention due to its biological activity and many synthesis have been reported in the literature,[15] some of which are given below.

Bessodes *et al* (1993, Scheme-1)[16]

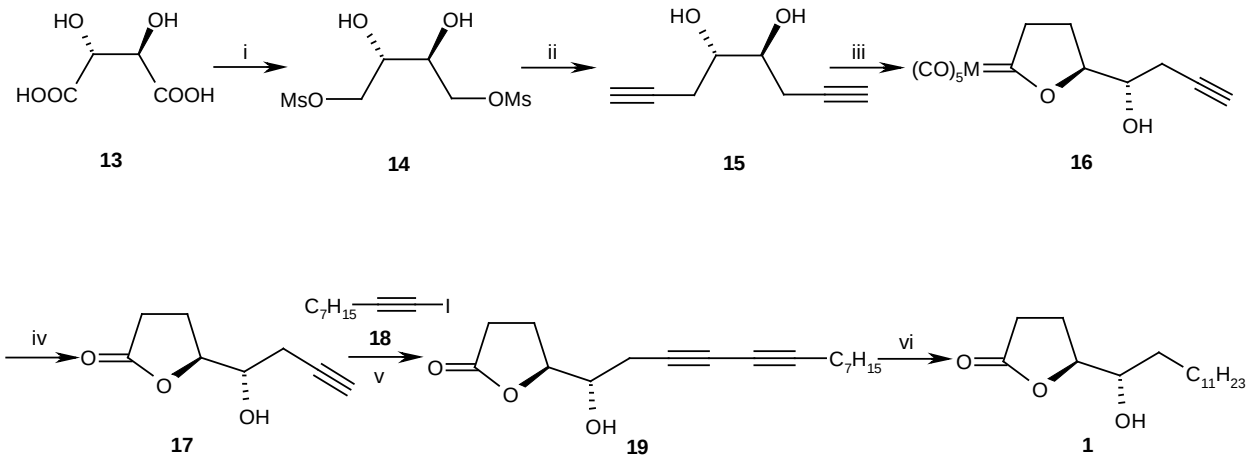
*In Bessodes approach allyl alcohol **10** was converted in to the chiral epoxide **11** using Sharpless epoxidation procedure. The stereochemistry of the free hydroxy group was inverted by the Mitsunobu reaction, using chloroacetic acid. Dilithioacetate opening of epoxide **12** gave the intermediate lithium carboxylate which upon acidification delivererd the (+)-muricatacin.*



Scheme 1. *Reagents and conditions:* (i) $Ti(O^iPr)_4$, D-isopropyl tartarate, TBHP, CH_2Cl_2, - 20 ^oC; (ii) DEAD, Ph_3P, $ClCH_2COOH$, benzene, rt; (iii) MeONa (1 %), MeOH; (iv) (a) $LiCH_2COOLi$, THF, reflux; (ii) H^+.

Quayle *et al* (1995, Scheme-2)[17]

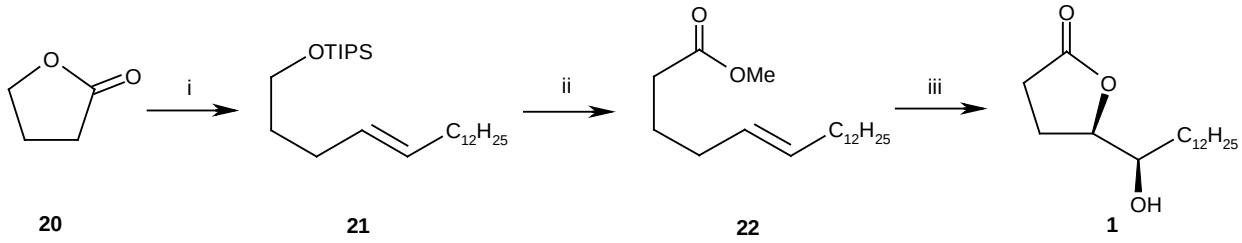
*Quayle et al have utilized L-(+)-tartaric acid **13** as a chiral starting material, which was converted in to dimesylate **14** by known procedure. Treatment of dimesylate with lithium acetylide ethylenediamine complex gave the bis-acetylide which on reaction with $Cr(CO)_5$ gave the γ-butyrolactone **17**. Coupling of acetylide **17** with acetylene iodide **18** using Wityak's procedure followed by hydrogenation delivered the (+)-muricatacin.*



Scheme 2. *Reagents and conditions:* (i) ref 18; (ii) Lithium acetylide-EDA complex, DMSO, 0 ^{o}C, 87 %; (iii) $Cr(CO)_5$, THF (or) $W(CO)_5$, THF; (iv) CAN, acetone, 20 ^{o}C, 74 %; (v) $(Ph_3P)_2PdCl_2$, CuI, DIPA, THF, 45 ^{o}C, 82 %; (vi) H_2, 10 % Pd/C, EtOAc, 20 ^{o}C, 16 h, 74 %.

Couladouros *et al* (1999, Scheme-3)[19]

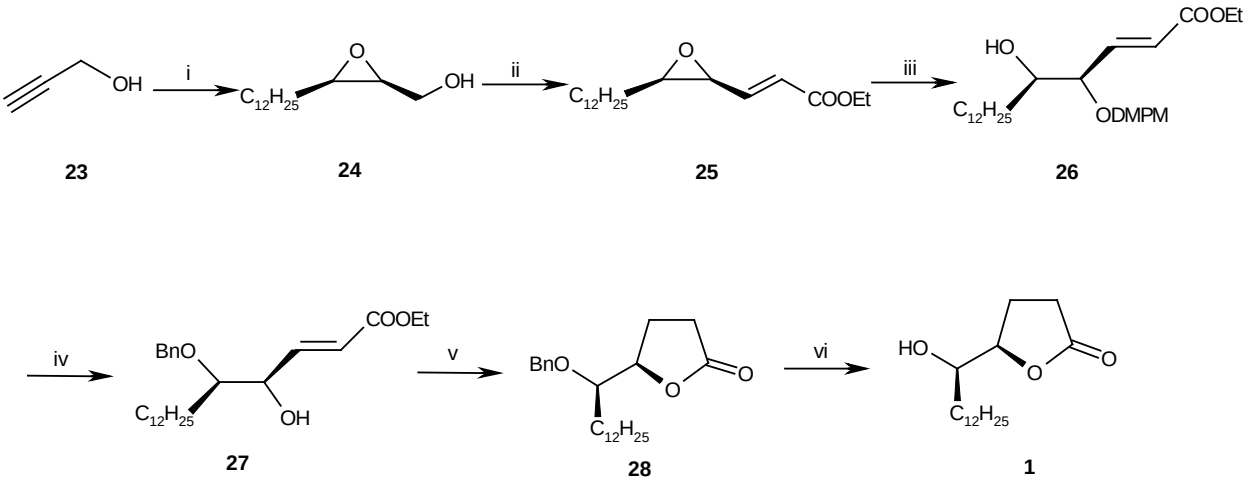
*In Couladouros approach γ-butyrolactone **20** was converted in to olefin **21** by a three step sequence. Jones oxidation resulted in the deprotection of the silyl group followed by the oxidation of the resultant alcohol in to the acid, which was protected as its methyl ester **22**. Final Sharpless asymmetric dihydroxylation using AD-mix-β delivered the (-)-muricatacin.*



Scheme 3. *Reagents and conditions:* (i) (a) DIBAL-H, 93 %; (b)TPSCl, 84 %; (c) $C_{13}H_{27}Ph_3P^{+}Br^{-}$, *sec*-BuLi, - 78 ^{o}C, 84 %; (ii) (a) Jones oxidation, 25 ^{o}C, 12 h, 89 %; (iii) AD-mix-β, 92 %.

Mioskowski *et al* (1999, Scheme-4)[20]

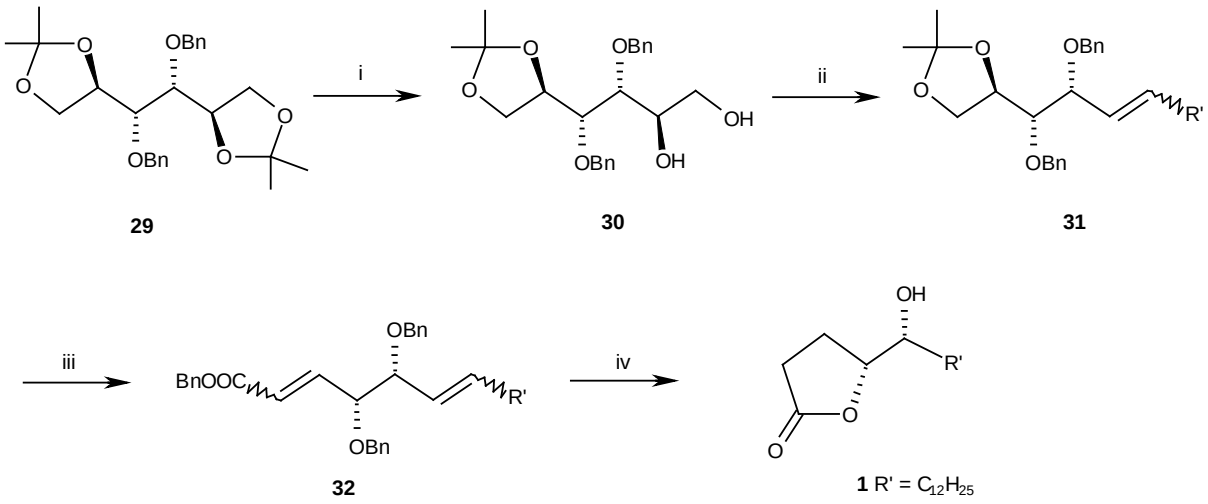
Mioskowski *et al* have prepared (2*S*, 3*R*)-2, 3-epoxy pentadecanol **24** from propargylic alcohol **23** by known procedure. Oxidation of the alcohol **24** followed by two-carbon homologation gave the α, β-unsaturated ester **25**. Treatment of **25** with 3, 4-dimethoxy benzyl alcohol (DMPMOH) gave the alcohol **26**, which was converted in to compound **27** by protection, deprotection sequence. Sequential hydrogenation (P-2 nickel catalyst), lactonization and deprotection of the benzyl group delivered the (-)-muricatacin.



Scheme 4. *Reagents and conditions:* (i) ref 21; (ii) (a) SO_3.Pyridine, Et_3N, CH_2Cl_2, DMSO; (b) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF; (iii) DMPMOH, $BF_3.OEt_2$, CH_2Cl_2; (iv) (a) NaH, BnBr, DMF; (b) DDQ, CH_2Cl_2, H_2O; (v) (a) $Ni(OAc)_2$, $NaBH_4$, EtOH; (b) *p*-TSOH, C_6H_6; (vi) H_2, Pd/C, EtOH

Singh *et al* (2002, Scheme-5)[22]

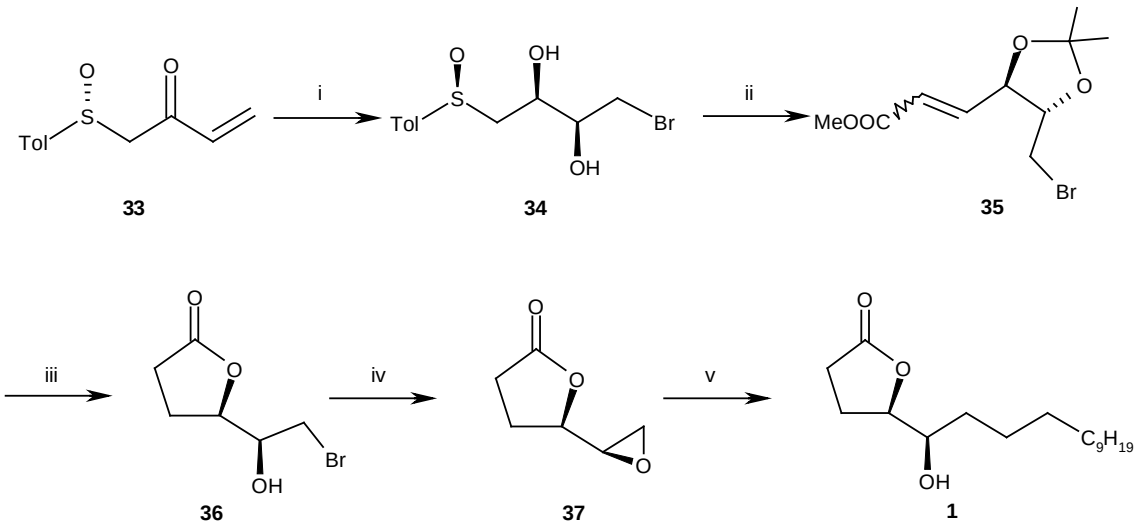
Singh and co-workers have selectively hydrolised diacetonide benzy ether **29** to deliver the diol **30**. The diol on oxidative cleavage and Wittig homologation delivered the olefin **31**. The selective acetonide deprotection, oxidative cleavage of the resultant diol followed by two-carbon Wittig homologation delivered the compound **32** as a mixture of cis and trans isomers. Hydrogenation followed by cyclization gave the (-)-muricatacin **1**.



Scheme 4. *Reagents and conditions:* (i) AcCl, MeOH, 0 ^{o}C, 5 min, 88 %; (ii) (a) $Pb(OAc)_4$, CH_2Cl_2, rt, 3 h; (b) R'$CH_2Ph_3P^+Br^-$, n-BuLi, THF, 0 ^{o}C, 12 h, 65 %; (iii) (a) CF_3COOH, THF-H_2O (4:1), 65 ^{o}C, 6 h, 85-95 %; (b) $Pb(OAc)_4$, CH_2Cl_2, rt, 3 h; (c) $BnO_2CCH_2Ph_3P^+Br^-$, *n*-BuLi, THF, 0 ^{o}C, 12 h; (iv) (a) H_2, 10 % Pd/C, EtOH, rt, 12 h; (b) *p*-TSA, Toluene, 70 ^{o}C, 1 h.

Raghavan *et al* (2003, Scheme-6)[23]

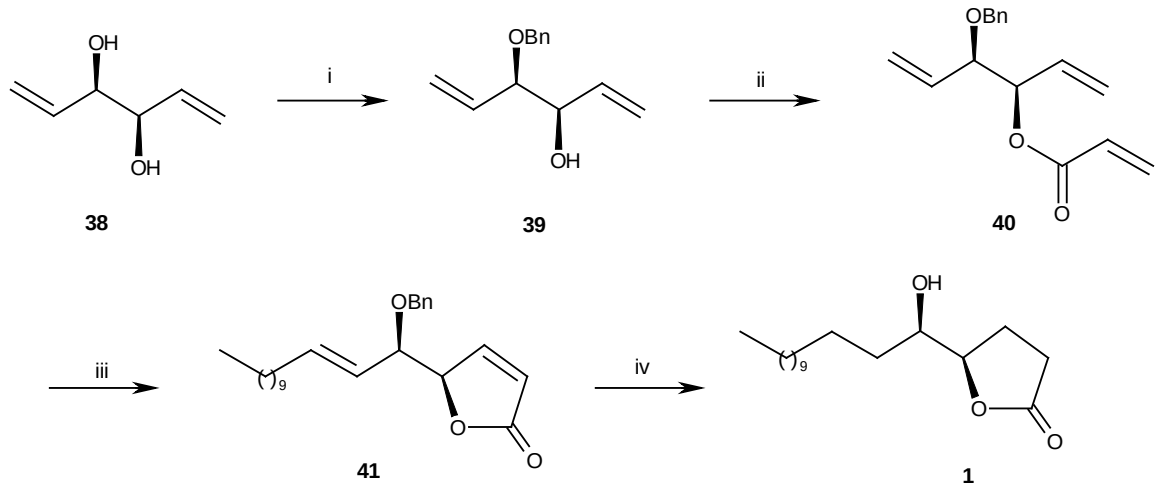
Raghavan and co-workers have transformed keto sulfoxide **33** in to bromohydrin by diastereoselective reduction and sulfoxide directed chirality transfer by NBS reaction. Protection of diol as acetonide followed by Pummerer reaction delivered the aldehyde, which on two-carbon Wittig homologation gave the mixture of *cis* and *trans* olefins in 1:1 ratio. Hydrogenation followed by cyclisation delivered the bromolactone **36**, which on treatment with Ag_2O delivered the epoxide **37**. Finally grignard reaction of epoxide delivered the (-)-muricatacin **1**



Scheme 6. *Reagents and conditions:* (i) (a) DIBAL-H, THF, - 78 ^{o}C, 93 %; (b) NBS, H_2O, Toluene, rt, 81 %; (ii) (a) 2, 2-DMP, cat. CSA, acetone, rt, 92 %; (b) TFAA, Et_3N, CH_2Cl_2, 0 ^{o}C, 15 min. then aq. $NaHCO_3$; (c) Ph_3P=CHCOOMe, PhH, rt; (iii) (a) H_2, Pd/C, EtOAc, rt, 94 %; (b) cat. CSA, MeOH, rt, 84 %; (iv) Ag_2O, CH_3CN, rt, 81 %; (v) $C_{12}H_{25}MgBr$, Li_2CuCl_4, THF, 72 %.

Quinn *et al* (2004, Scheme-7)[24]

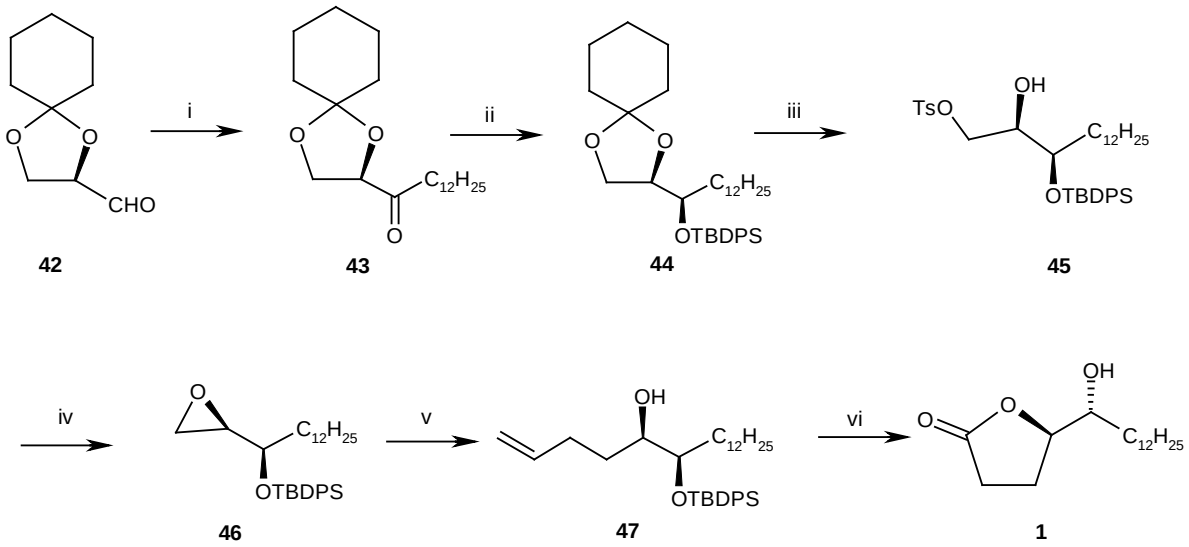
*Quinn and co-workers have desymmetrized the diol **38** by mono benzylation of the stannylene acetal of **38** to deliver the compound **39**. Acetylation of the free hydroxyl group with acryloyl chloride provided triene **40**. Treatment of triene **40** with 10 mol % the Grubb's second generation catalyst in presence of 1-dodecene gave the compound **41**, which on hydrogenation gave the (-)-muricatacin.*



Scheme 7. *Reagents and conditions:* (i) Bu_2SnO, Bu_4NI, PhH, H_2O, BnBr, 84 %; (ii) $CH_2{=}CH_2COCl$, $^{i}Pr_2NEt$, CH_2Cl_2, 83 %; (iii) Grubb's catalyst (10 mol %), 1-dodecene (5 eq), PhH, 80 ^{o}C; (iv) H_2, Pd/C, EtOH, 82 %.

Chattopadhyay *et al* (2005, Scheme-8)[25]

Chattopadhyay and Dhotare have prepared the compound **44** by a series of reactions. Deketalization followed by selective protection of primary hydroxyl gave the tosylate **45**, which on reaction with K_2CO_3 delivered the epoxide **46**. Regioselective ring-opening of the epoxide **46** with allylmagnesium bromide produced **47**. Following the known procedure compound 46 was converted in to (-)-muricatacin **1**.

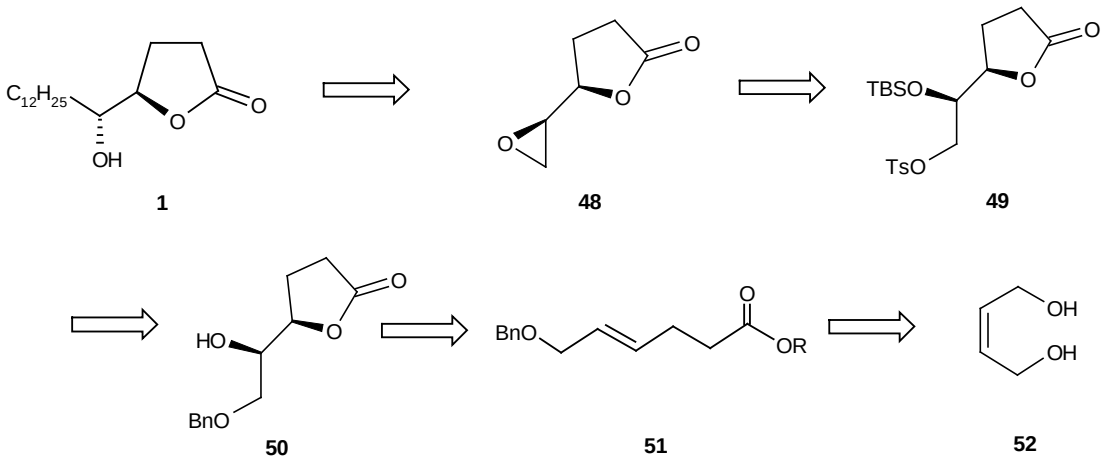


Scheme 8. *Reagents and conditions:* (i) (a) $C_{12}H_{25}MgBr$, 0 ^{o}C, 76 %; (b) PCC, rt, 75 %; (ii) (a) $LiAlH_4$, THF, 0 ^{o}C, 94 %. (or) $NaBH_4$, MeOH, 0 ^{o}C, 89 %; (b) TBDPSCl, Imidazole, rt; (iii) CF_3COOH, H_2O, 0 ^{o}C, 88 %; (b) *p*-TosCl, Py, 0 ^{o}C; (iv) K_2CO_3, MeOH, rt, 85 %; (v) allylMgBr, CuBr, - 40 ^{o}C to rt, 78 %; (vi) O_3, MeOH, NaOH, - 15 ^{o}C, 75 %; (b) TBAF, THF, rt, 72 %.

Present work:

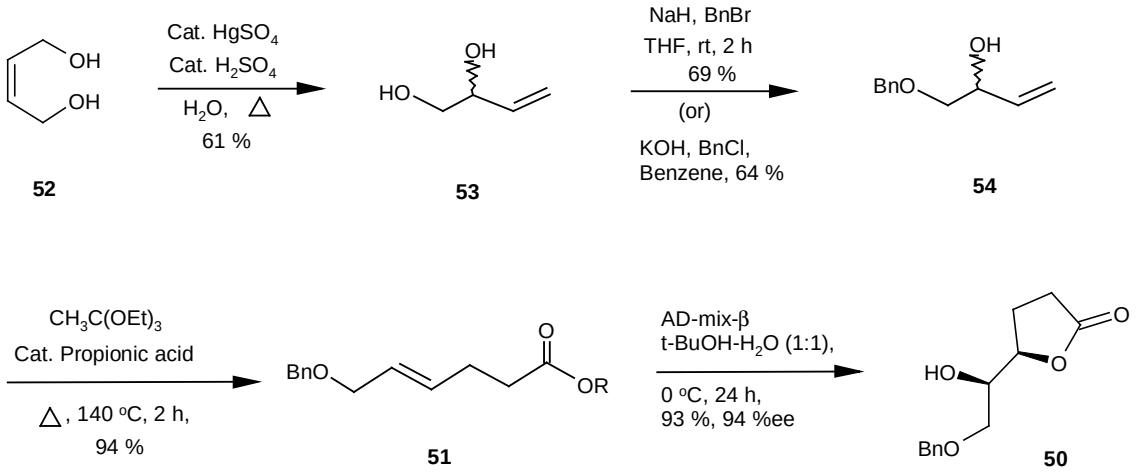
Although several syntheses of both (+)- and (-)-Muricatacin are documented in the literature through varied synthetic routes, most involve a large number of steps or employing a chiral pool strategy. Herein we planned to synthesize the target compound **1**, employing the Sharpless asymmetric dihydroxylation as the key step and thereby inducing the desired chirality, starting from cheap achiral source.

The retrosynthetic analysis for our planned synthesis of (-)-muricatacin is depicted in **scheme 9**. The epoxide **37**, the precursor to the (-)-muricatacin, could be obtained from the tosylate **48**, which in turn could be obtained from the hydroxy lactone **49**, the versatile intermediate for our synthesis could be readily obtained from *cis*-2-butene-1, 4-diol **51**.



Scheme 9: **Retrosynthetic analysis**

The synthesis of (-)- muricatacin commences from *cis*-2-butene-1, 4-diol **51** as shown in scheme **10.** The commercially available *cis*-2-butene-1, 4-diol **51** was converted into monoprotected allyl alcohol **53**, which on Claisen orthoester rearrangement and Sharpless asymmetric dihydroxylation delivered the hydroxy lactone **49** with the required stereochemistry.



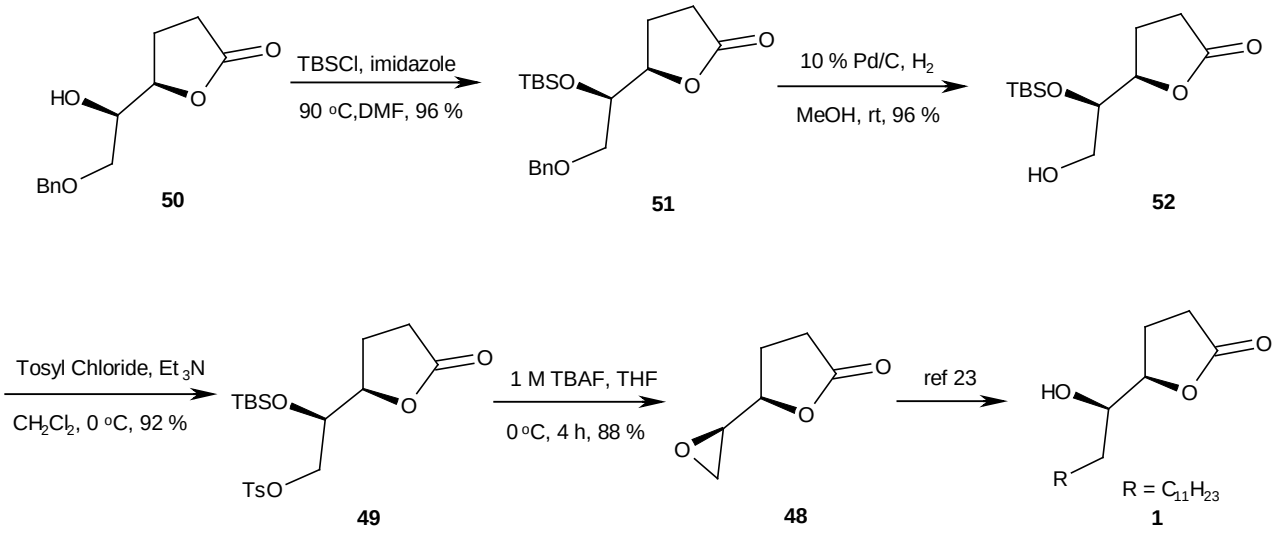
52 53 54 51 50

Scheme 10

Hydroxylactone **49** on treatment with TBSCl, imidazole in anhydrous DMF at 80 ^{o}C for 24 h delivered the TBS protected lactone **53**. Hydrogenation of lactone **53** using 10 % Pd/C in MeOH under H_2 atmosphere gave the debenzylated product **54**. The IR spectrum of **54** shows the hydroxyl absorption at 3434 cm^{-1}. In the ^{1}H-NMR spectrum benzylic protons was disappeared indicating the removal of benzyl group. ^{13}C-NMR and elemental analysis data were in good agreement with the structure **54**.

The next immediatwe concern was the transformation of compound **54** in to the epoxide **37**, which is the known intermediate for the synthesis of muricatacin. Thus treatment of **54** with tosyl chloride and Et_3N in presence of catalytic DMAP at 0 ^{o}C gave the tosylate **48**. The IR spectrum showed the disappearance of hydroxyl absorption. ^{1}H-NMR, ^{13}C-NMR and elemental analysis data were in good agreement with the structure **48**.

Compound **48** on reaction with 1 M TBAF solution in THF at 0 ^{o}C for 4 h delivered the epoxide **37**. The ^{1}H-NMR spectrum showed the disappearance of signals corresponding to TBS group and tosyl group. ^{1}H-NMR, ^{13}C-NMR and elemental analysis data were in good agreement with the literature data. Our synthetic epoxide showed an optical rotation $[\alpha]_D$ -27.8 (*c* = 1.2, $CHCl_3$) is in accordance with the literature data.[23] The epoxide can be converted in to the (-)-muricatacin according to the literature procedure.

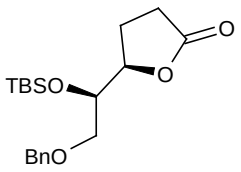


Conclusion:

In conclusion a formal synthesis of (-)-muricatacin has been achieved from the readily available starting material.

Experimental

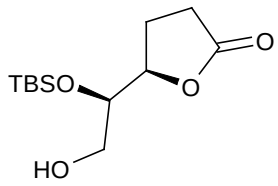
(4*R*, 5*R*)-5-tert-Butyldimethylsilyloxy-6-Benzyloxy-hexane-4-olide (53)



TBDMSCl (0.95 g, 6.98 mmol) was added to a mixture of **49** (1.5 g, 6.35 mmol) and imidazole (0.65 g, 9.53 mmol) in anhydrous DMF (15 mL) and stirred at 90 ^{o}C for 24 h. After completion of the reaction, the reaction mixture was diluted with water, extracted with EtOAc (3 x 20 mL). The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc-light petroleum (1:4) as an eluent to afford **53** (2.08 g, 98 %) as colourless syrup.

Appearance	:	Colourless Syrup
Molecular Formula	**:**	**$C_{19}H_{30}O_4Si$**
Yield	**:**	**98 %.**
$[\alpha]_D$	**:**	**- 47.67, (*c* = 1, $CHCl_3$)**
IR ($CHCl_3$, cm^{-1})	**:**	**1772, 1167, 757**
^{1}H NMR ($CDCl_3$ + CCl_4, 200MHz)	**:**	**δ 0.09 (s, 3H), 0.10 (s, 3H), 0.89 (s, 9H), 2.24-2.56 (m, 4H), 3.58 (m, 1H), 3.86 (m, 1H), 4.56 (m, 2H), 4.74 (ddd, *J* = 7.92, 5.6, 2.9 Hz, 1H), 7.32-7.37 (m, 5H).**
^{13}C NMR ($CDCl_3$+CCl_4, 50MHz)	**:**	**δ -5.1, -4.7, 17.8, 23.3, 25.5, 28.1, 70.1, 73.2, 73.3, 79.8, 127.4, 128.2, 137.8, 176.9.**
Elemental Analysis	**:**	Analysis calcd. for $C_{19}H_{30}O_4Si$: C, 65.10; H, 8.62. Found: C, 65.08; H, 8.86.

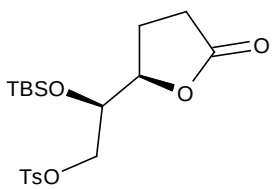
(4*R*, 5*R*)-5-tert-Butyldimethylsilyloxy-6-hydroxy-hexane-4-olide (54)



To a solution of **53** (2.4 g, 5.20 mmol) in adsolute ethanol (25 mL) was added W2 Raney nickel (3.2 g) and the mixture was flushed with H_2 for 5 min. After stirring under an atmosphere of hydrogen at room temperature for 24 h, the reaction mixture was filtered through a pad of celite and the solvent was concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc-light petroleum (2:3) as an eluent to afford **54** (1.68 g, 96 %) as colourless syrup.

Appearance	**:**	**Colourless syrup.**
Molecular Formula	**:**	**$C_{12}H_{24}O_4Si$**
Yield	**:**	**96 %.**
IR ($CHCl_3$, cm^{-1})	**:**	**3434, 1778, 1465, 1080.**
^1H NMR ($CDCl_3$ + CCl_4, 200MHz)	**:**	**δ 0.09 (s, 3 H), 0.10 (s, 3 H), 0.89 (s, 9H), 2.22-2.54 (m, 4H), 3.56 (m, 2H), 3.85 (m, 2H), 4.81 (m, 1H).**
^{13}C NMR ($CDCl_3$+CCl_4, 50MHz)	**:**	**δ - 4.9, -4.7, 17.8, 23.5, 25.6, 28.5, 62.7, 74.4, 80.0, 177.5**
Elemental Analysis	**:**	Analysis calcd. for $C_{12}H_{24}O_4Si$: C, 58.53; H, 9.75. Found: C, 58.68; H, 9.72.

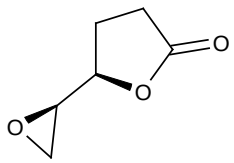
(4*R*, 5*R*)-5-tert-Butyldimethylsilyloxy-6-tosyloxy-hexane-4-olide (48)



To a solution of **54** (0.6 g, 2.44 mmol) in anhydrous CH_2Cl_2 (15 mL) at 0 ^oC were added Et_3N (0.68 mL, 4.88 mmol), TsCl (0.51 g, 2.68 mmol) and DMAP (cat). The reaction mixture was stirred for 6 h and then poured into cold water and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure.. The crude oily compound was purified by silica gel column chromatography using EtOAc-light petroleum (1:3) as an eluent to afford **48** (0.51 g, 92 %) as colourless oil.

Appearance	**:**	**Colourless Oil**
Molecular Formula	**:**	**$C_{19}H_{30}O_6SSi$**
Yield	**:**	**92 %.**
IR ($CHCl_3$, cm^{-1})	**:**	**1780, 1345, 826.**
^1H NMR ($CDCl_3$ + CCl_4, 200MHz)	**:**	**δ 0.11 (s, 6 H), 0.86 (s, 9H), 2.04-2.13 (m, 1H), 2.27-2.37 (m, 1H), 2.41-2.55 (m, 5 H), 3.90-4.06 (m, 3H), 4.61 (ddd, *J* = 8.06, 5.13, 2.20 Hz, 1 H), 7.36 (d, *J* = 8.06 Hz, 2H), 7.78 (d, *J* = 8.06 Hz, 2H).**
^{13}C NMR ($CDCl_3$+CCl_4, 50MHz)	**:**	**δ - 4.9, -4.6, 17.9, 21.7, 23.3, 25.7, 28.0, 69.4, 72.0, 78.8, 127.9, 130.0, 132.5, 145.1, 176.4.**
Elemental Analysis	**:**	Analysis calcd. for $C_{19}H_{30}O_6SSi$: C, 57.0; H, 7.50; S, 8.0.. Found: C, 57.12; H, 7.59; S, 8.16.

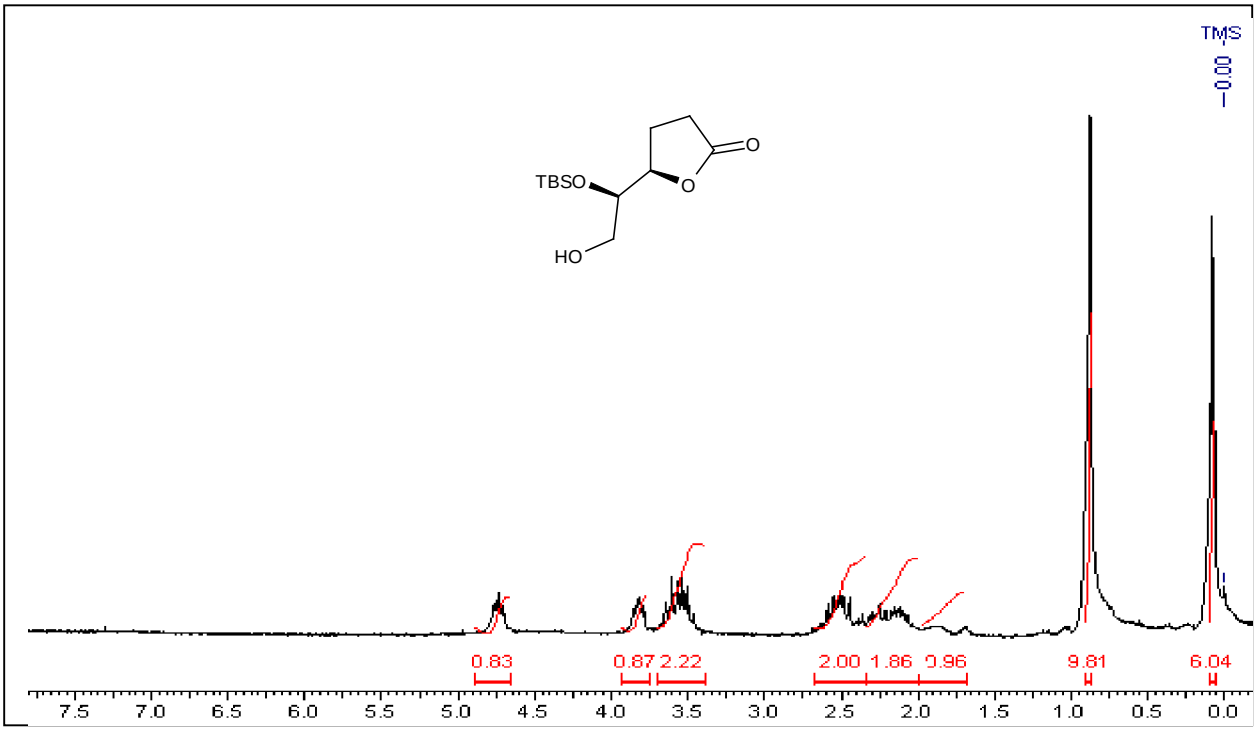
5-[(2*R*)-Oxiran-2-yl]-5*R*-2*H*, 3*H*, 4*H*-2-furanone(37)



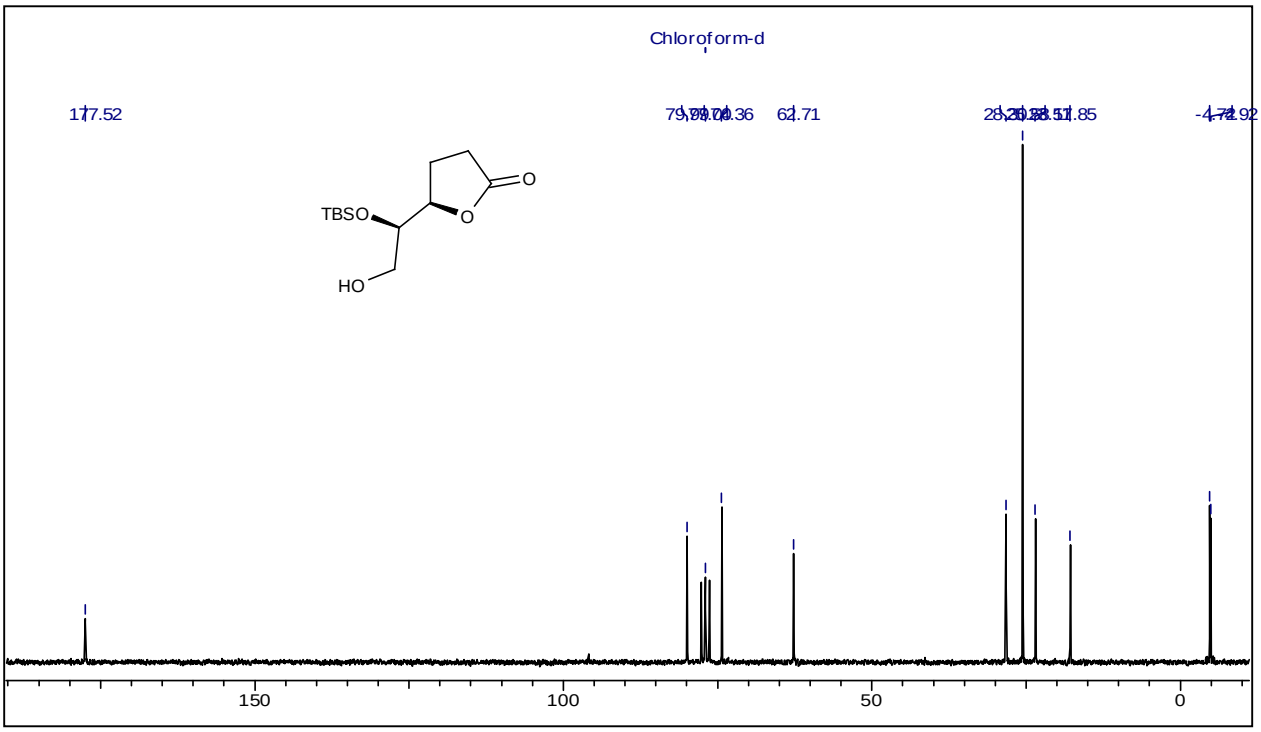
To a solution of **48** (0.8 g, 2.0 mmol) in anhydrous THF (10 mL) at 0 ^oC was added 1 M TBAF solution THF (3 mL, 3.0 mmol) and the stirring was continued for 4 h at room

temperature. After completion of the reaction the reaction mixture was diluted with water and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc-light petroleum (2:3) as an eluent to afford **37** (0.22 g, 88 %) as colourless oil.

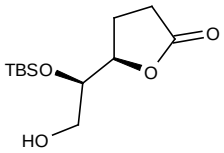
Appearance	**:**	**Colourless oil**
Molecular Formula	**:**	**$C_6H_8O_3$**
Yield	**:**	**88 %.**
IR ($CHCl_3$, cm^{-1})	**:**	**1776, 757.**
$[\alpha]_D$	**:**	**- 27.8 (*c* = 1.2, $CHCl_3$), lit $[\alpha]_D$ - 28.6 (*c* = 1.64, $CHCl_3$).**
^1H NMR ($CDCl_3$ + CCl_4, 200MHz)	**:**	**δ 2.28-2.34 (m, 1 H), 2.42 (m, 1 H), 2.46-2.52 ((m, 1 H), 2.64 (m, 1 H), 2.78-2.86 (m, 2H), 3.16 (m, 1H), 4.62 (m, 1 H).**
^{13}C NMR ($CDCl_3$+CCl_4, 50MHz)	**:**	**δ 24.9, 27.6, 43.7, 53.0, 76.9, 176.2.**
Elemental Analysis	**:**	Analysis calcd. for $C_6H_8O_3$: C, 56.25; H, 6.25. Found: C, 56.46; H, 6.12.



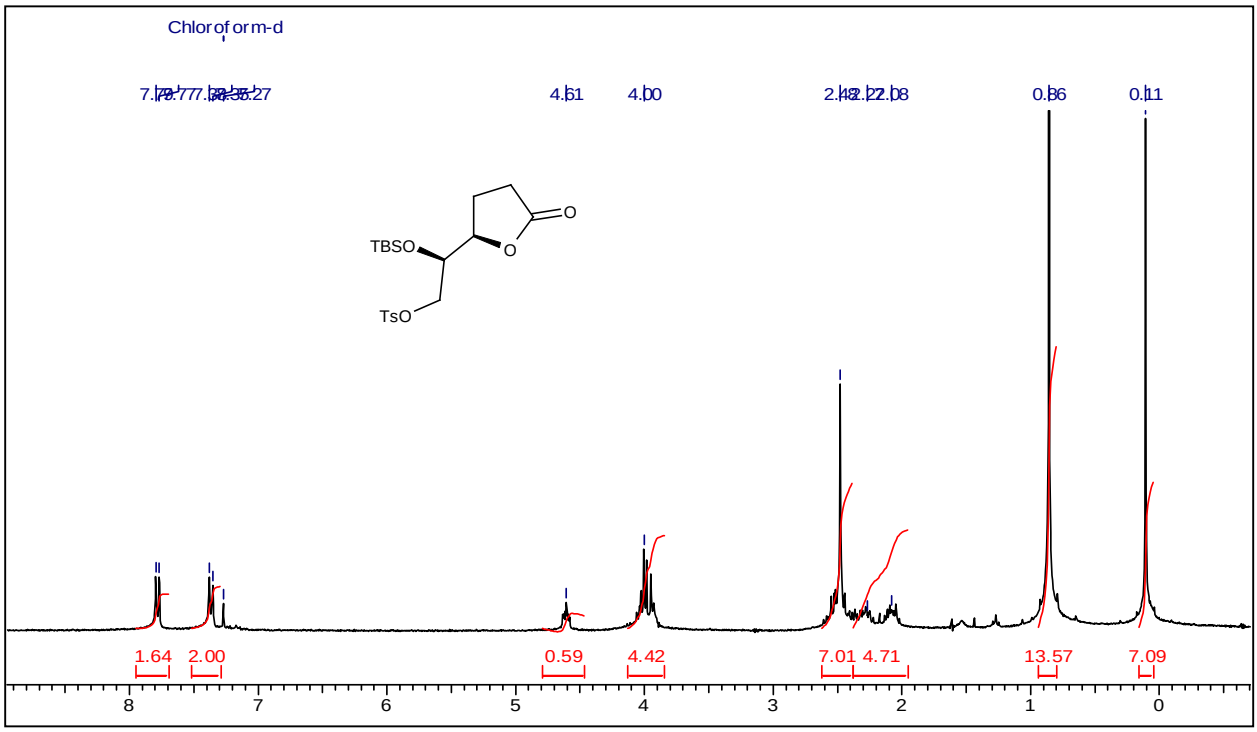
^{1}H NMR Spectrum of compound 52 in $CDCl_3$



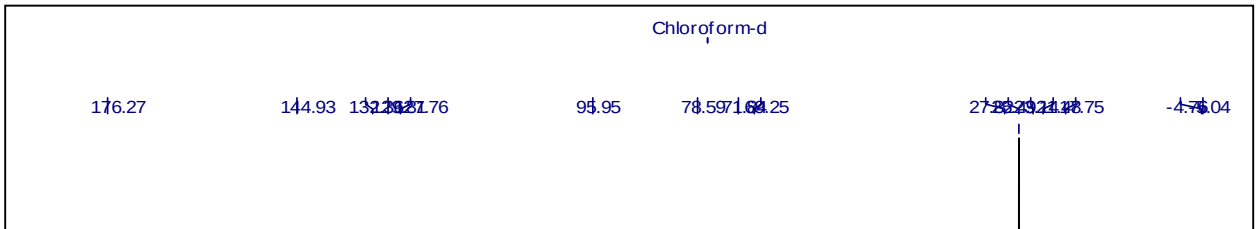
^{13}C NMR Spectrum of compound 52 in $CDCl_3$

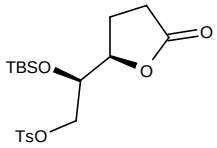


DEPT NMR Spectrum of compound 34 in $CDCl_3$

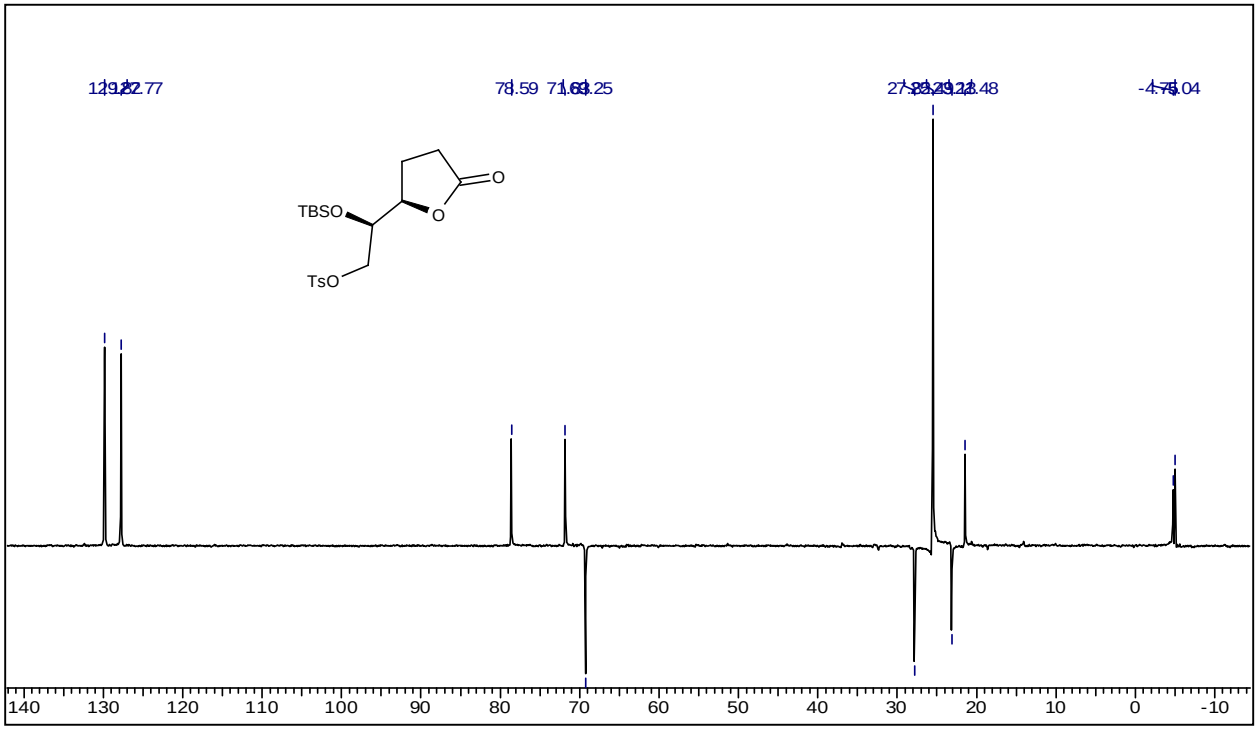


^1H NMR Spectrum of compound 49 in $CDCl_3$ + CCl_4

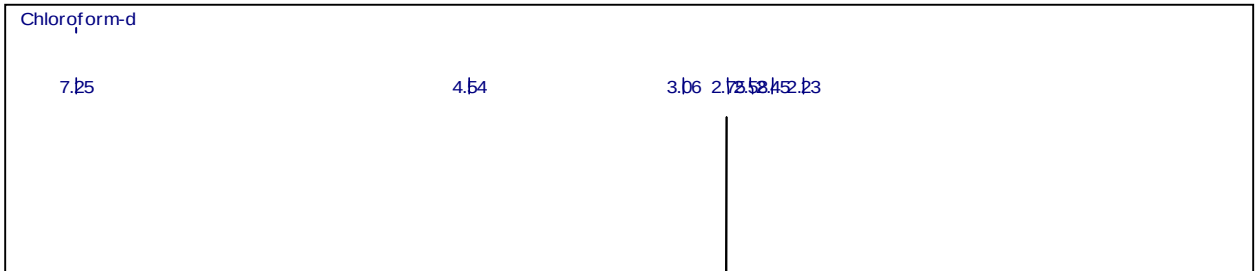


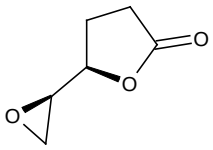


^{13}C NMR Spectrum of compound 49 in $CDCl_3 + CCl_4$

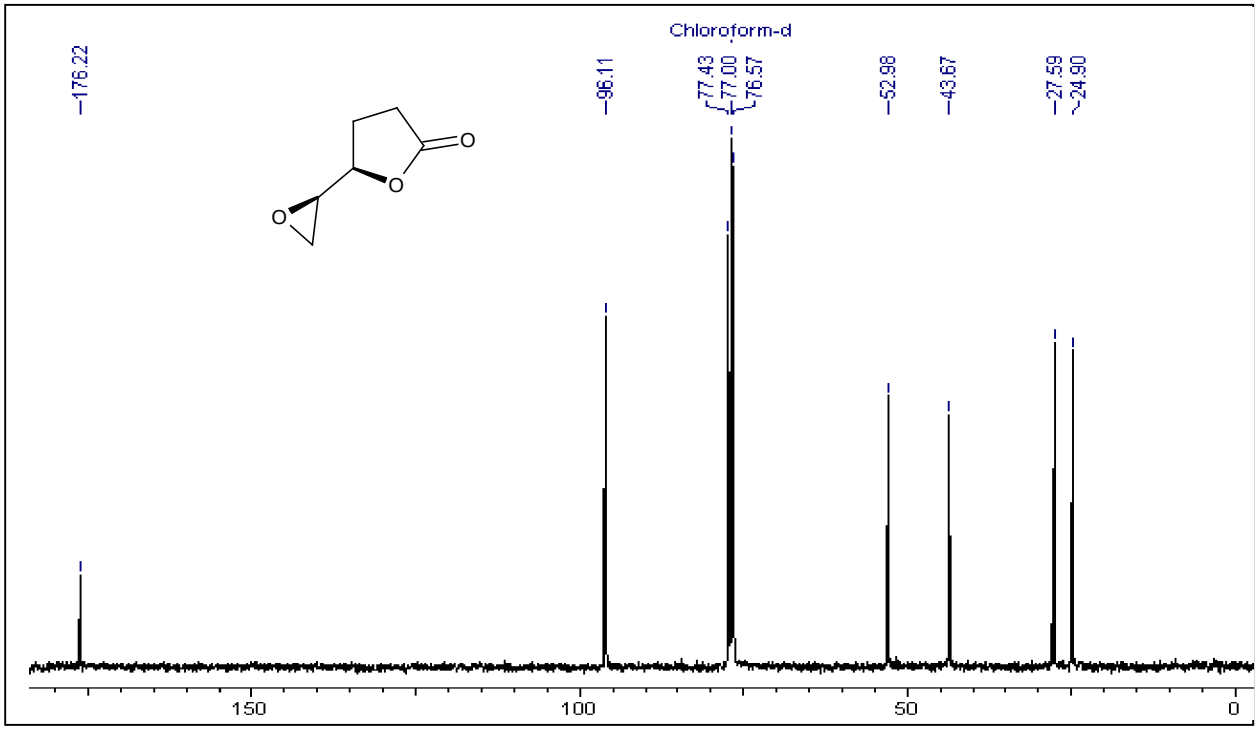


DEPT NMR Spectrum of compound 49 in $CDCl_3 + CCl_4$

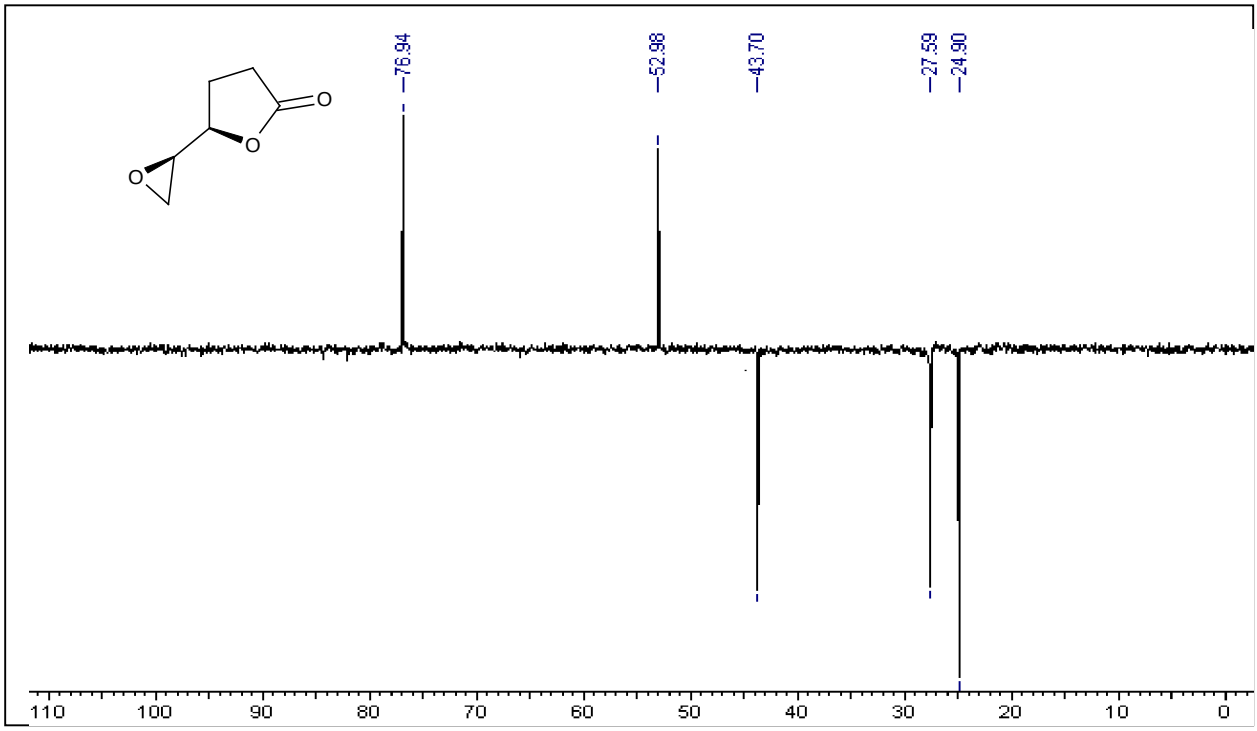




^{1}H NMR Spectrum of compound 378 in $CDCl_3$ + CCl_4



^{13}C NMR Spectrum of compound 37 in $CDCl_3$ + CCl_4



DEPT NMR Spectrum of compound 37 $CDCl_3$ + CCl_4

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List of Publications

1. Titanosilicate (TS-1) Catalyzed Oxidation of Aromatic Aldehydes to Esters. Subhash P. Chavan*, Shubhada W. Dantale, Chitra A. Govande, Meenakshi S. Venkatraman, **Cherukupally Praveen** *Synlett* **2002**, 267-268.

2. A concise and stereo selective synthesis of (+) and (–)-Deoxoprosophylline. Subhash P. Chavan and **Cherukupally Praveen** *Tetrahedron Lett*. **2004**, *45*, 421-423.

3. Enantioselective synthesis of *R*-(+)-α and *S*-(–)-α-lipoic acid. Subhash P. Chavan, **Cherukupally Praveen**, G. Ramakrishna and U. R. Kalkote *Tetrahedron Lett*. **2004**, *45*, 6027-6028.

4. An efficient stereoselective synthesis of (2*S*, 4*S*, 5*R*)-(–) and (2*R*, 4*R*, 5*S*)-(+)-Bulgecinine. Subhash P. Chavan, **Cherukupally Praveen**, Pallavi Sharma and U. R. Kalkote *Tetrahedron Lett*. **2005**, *46*, 439-441.

5. Stereoselective synthesis of (–)-microcarpalide. Subhash P. Chavan, and **Cherukupally Praveen** *Tetrahedron Lett*. **2005**, *47*, 1939-1941.